The Telemark Meningococcal Project

1987-2007

Twenty years experience of preventing secondary cases of meningococcal disease by identification and eradication of the disease–causing strain of *Neisseria meningitidis* in close contacts of patients with primary meningococcal disease

Master Degree Diploma in Public Health

Bjørn-Erik Kristiansen

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Institute of Community Medicine

University of Tromsø

Norway

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Acknowledgements

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Bjørn-Erik Kristiansen,

Porsgrunn, June 10th, 2008

Introduction

Meningococcal disease

Meningococcal disease is caused by the bacterium *Neisseria meningitidis* and presents as septicaemia, meningitis or by a combination of septicaemia and meningitis (1, 2, 3). More seldom, meningococcal disease occurs as an entity called chronic meningococcemia characterised by fever, rash and arthritis (4). The overall fatality rate of meningococcal disease is approximately 10 %, but in septicaemia the fatality rate may reach 30 % (5, 6, 7, 8, 9, and 10).

Bacteriology, immunity and typing methods

N. meningitidis is identified by microscopy of gram stained specimens and standard biochemical tests applied on pure culture (11). The bacterium may be classified into serogroups based on antigenic differences in the capsular polysaccharides. There are at least 10 different serogroups the most commonly occurring denoted A, B, C, Y, and W135 (11, 12). The serogroup classification is important because the capsular polysaccharides of serogroup A, C, Y and W135 are highly antigenic and exposure by invasive disease, carriage or by vaccination stimulates the formation of bactericidal antibodies which are correlated with protection against (13, 14, 15, 16, 17). There exist vaccines against these four serogroups (18, 19). The serogroup B polysaccharide is not immunogenic in humans, probably because it is expressed on brain cell in the foetus and is therefore a part of “self” (20)

Meningococci can further be divided into serotypes and sero-subtypes based on immunogenic differences in proteins of the cell wall's outer membrane. The Norwegian group B meningococcus mainly has the serotype 15:P1.16 (21, 22). Vaccines have been made against the serotype antigens. A nation-wide study was performed in Norway nearly 20 years ago. The vaccine was safe, but had only 57 % protection and protection lasted for only 6 months (23, 24).

Chromosomal DNA fingerprinting. The first genetic method, chromosomal DNA fingerprinting, was developed by our group at The University of Tromsø in the early eighties (13, 25, 26, 27, 28, 29). The method uses restriction endonucleases recognising unique DNA fragments of 6 base pairs, to cleave chromosomal DNA into fragments with a mean length of approximately 4000 base pairs. The fragments are separated according to length, by gel electrophoresis followed by staining. The resulting band pattern consists of approximately 50 different bands, and each strain has its unique band pattern, comparable to the bar codes printed on almost every items that are sold today (Fig. 1). The method is laborious and takes 2 days to perform after having obtained pure culture of the bacterium.

PCR amplicon restriction endonuclease analyses (PCR AREA). PCR AREA was developed by us (21, 30, 31, 32). The method is rapid, can be performed in one day, and may be applied on non-pure growth of the meningococcus on primary plates. DNA is extracted and a PCR procedure is performed using primers from the gene (*fol*P) coding for sulphonamide resistance which is a marker for virulence (31, 32). The 950 base pairs – large PCR product is further cleaved by restriction endonuclease resulting in a band pattern that is

unique for each bacterial strain (Fig. 2). The PCR AREA is therefore convenient for the rapid recognition of a disease-causing strain in close contacts. By applying the same PCR method on cerebrospinal fluids from patients with meningococcal meningitis, we were able to develop the first PCR based method for diagnosis of bacterial meningitis (33).

MLST typing. However, for classification of the genus N. meningitidis, the MLST (multilocus sequence typing) has been internationally accepted as the present gold standard (34, 35, 36). Also other variants of genetic typing methods have been published (36, 37, 38)

Carriage of meningococci

N. meningitidis is part of the normal flora and most people will during their lives be a transient carrier of the bacterium (39, 40, 41). The carrier state will last for up to 1 year. During carriage the host will produce bactericidal antibodies which will protect against invasive disease (17). Carriage of meningococci may therefore be looked upon as "nature's vaccine" against meningococci. Consequently, carriage of meningococci should never be terminated by chemoprophylaxis unless it is a disease-causing strain. These natural occurring antibodies appear around the age of 16, and increases in amount with age (13). There is an inverse relation between the protective antibodies and the age specific incidence of meningococcal disease (Fig 2). Approximately 10 % of a normal population will carry N. meningitidis at a given time. It has been shown by us (13) and in a study from the Oslo area (39), that approximately 90 % of the carrier strains are never found in patients and may be regarded as non-virulent. The remaining 10 % of the carrier strains possess a DNA fingerprint indistinguishable from bacteria isolated from patients and may

be regarded as virulent strains. Carriers of these strains are probably the source of meningococcal disease. These carriers are at risk of developing meningococcal disease themselves or may become chronic asymptomatic carriers spreading the bacterium to susceptible persons.

Measures for preventing the spread of meningococcal disease.

Since there exist no vaccines against serogroup B meningococci, the first case of group B meningococcal disease in a community cannot be prevented. Other measures to prevent the disease from spreading must be applied. The classical way of stopping an infection by identification of the causative agent and stopping its spreading route, may be applied. Consequently, it will be necessary to identify the person(s) carrying the disease-causing strain and eradicate the disease-causing strain before it spread further. Eradication of the disease-causing strain by chemoprophylaxis may be obtained. Chemoprophylaxis is treating a person with a short course of antibiotics to remove a potential hazardous microorganism from a a person without symptoms of disease. Rifampicin or ciprofloxacin for 2 days are most commonly used for chemoprophylaxis of meningococcal disease, and have in systematic reviews, been shown to prevent secondary cases (42, 43, 44, 45, 46, 47, 48, 49, 50). Penicillin, which is the first choice for treating patients with invasive meningococcal disease, does nor eradicate meningococci from the throat because of its poor penetration to the mucosal surface (51). Most countries apply the use of chemoprophylactic treatment of all close contacts of the primary patient to prevent spread of the infection (46, 47, 48, 49, 50). The pitfall of this strategy is overuse of antibiotics because most (< 5 %) close contacts do not carry the disease-causing strain (53). Overuse increases the risk of inducing bacterial

resistance. The Norwegian group B meningococcus which is highly virulent, has developed sulphonamide resistance, probably due to overuse of this drug (6, 7, 22).

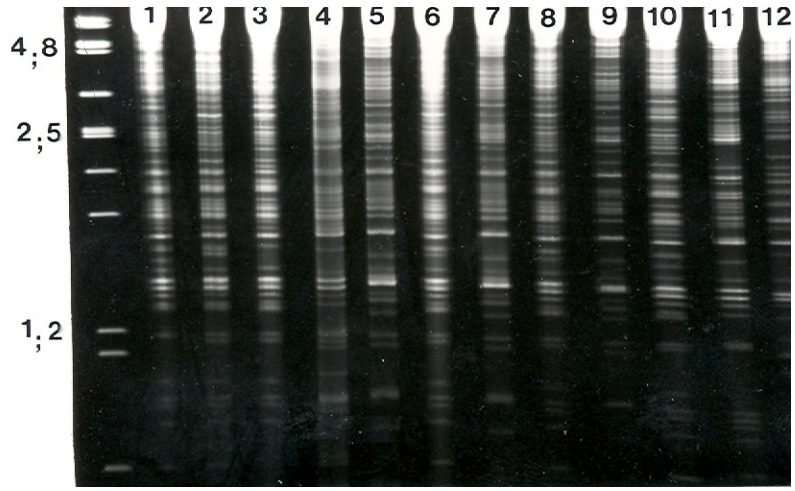


Figure 1. Fingerprint of meningococcal chromosomal DNA

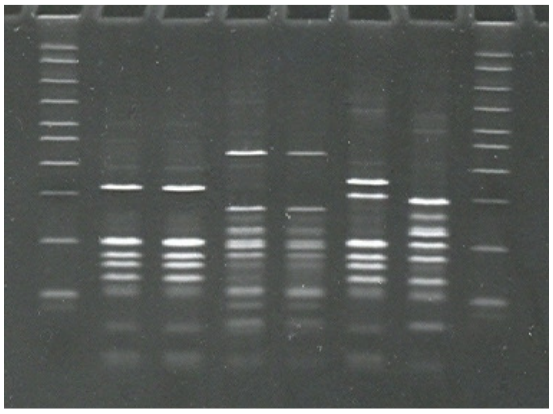


Figure 2. PCR amplicon restriction endonuclease analysis, PCRAREA

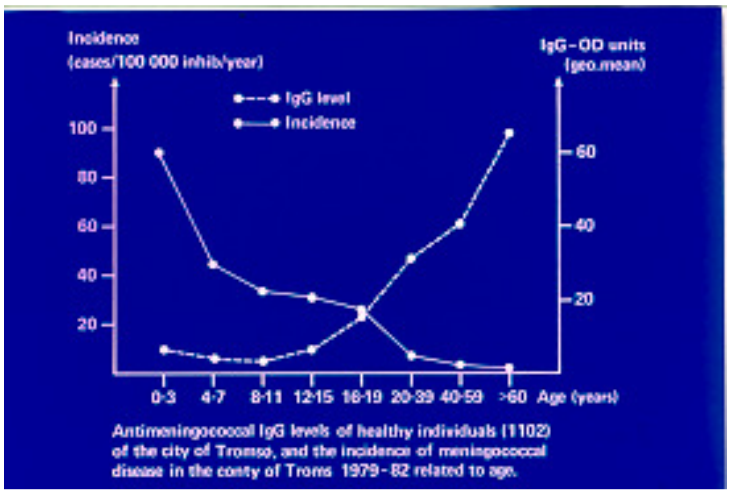


Figure 3. Plot of age specific incidence of meningococcal disease versus antibody level (from refr. 13)

The Norway recommendations for preventing spread of meningococcal disease (54) are not aimed at eradicating the disease-causing strain from the contacts, but at protect family members at the highest risk of contracting secondary infection. The patient's family members (household members) below 16 years of age are defined as having invasive infection regardless of clinical symptoms. They are kept at home from school or kindergarten and are treated with penicillin orally for 7 days. . However, the efficacy of this strategy is disputed as it has been documented (51) that household members below 15 years may develop invasive disease after penicillin treatment has stopped. The reason is that the disease-causing strain has not been eradicated and therefore may infect susceptible person following the stop of penicillin treatment. The Norwegian strategy has been criticized (48, 53) for not aiming at eradication of the disease-causing strain from the environment.

Epidemiology of meningococcal disease

Meningococcal disease occurs mostly as sporadic cases in western countries, but may cause local outbreaks (2, 3, 55, 56). Endemics of meningococcal disease may occur which was the case in Norway during the period from 1974 until the late eighties (6, 56, Fig. 4). However, in the African meningococcal belt (Fig. 5), endemics are almost an annual event (2, 55, 58). The reasons may be that the mucosal surfaces of the airways are dried out making people susceptible to infections, poor health condition and low vaccine coverage. Of the 550.000 cases of meningococcal disease occurring worldwide per year, approximately 500.000

occur in Africa (57), mainly caused by the serogroup A or W135 meningococci (57, 58).

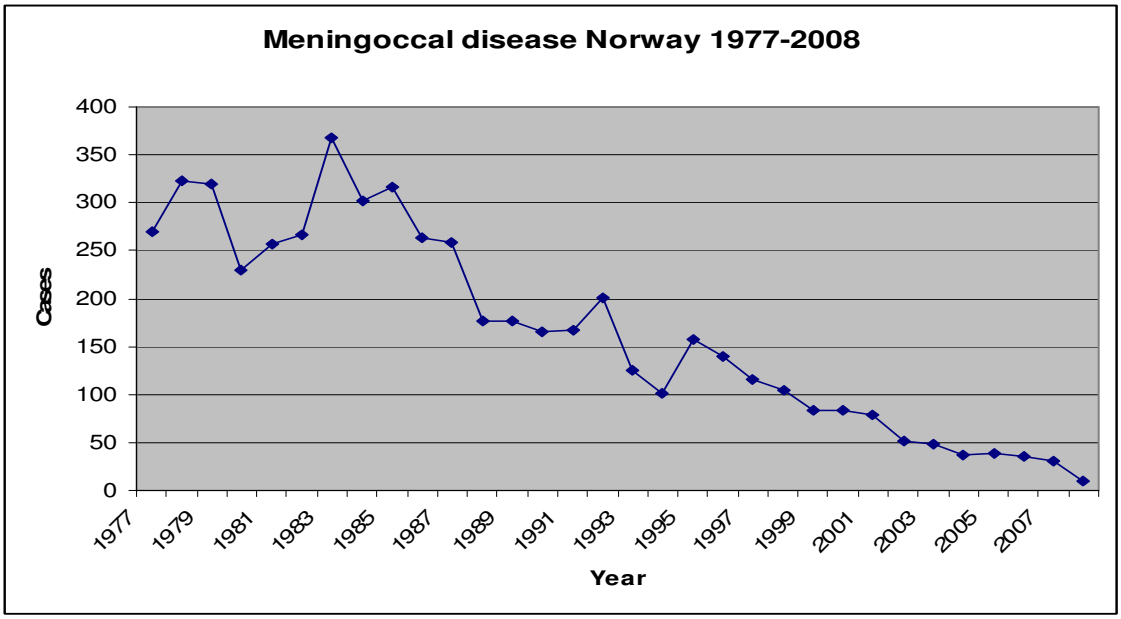
Meningococcal disease in the county of Telemark before the Telemark Meningococcal Project

The background for the Telemark Meningococcal Project was the large number of secondary cases that occurred in Telemark during the period from 1984 to 1987. During these 4 years there were a total of 43 cases of meningococcal cases of which five were the primary cases for 12 bacteriologically verified and 4 suspected secondary cases of meningococcal disease (42). The prevalence of secondary cases of all cases was therefore nearly 30 %. At Notodden it was a large outbreak with a total of 8 cases all associated with one particular high-school. The first case appeared in March 1986 and the final in November 1986 causing widespread concern and anxiety and high consumption of antibiotics, prescribed by desperate local physicians. We had developed DNA typing methods that enabled the rapid and reliable identification of the disease - causing strain of N. meningitidis (13, 25, 26). The situation following the occurrence of a primary case of meningococcal disease is schematically visualized in Fig. 6. There will be three variants of carriers:

- Carriers of non-virulent meningococci
- Carriers of virulent meningococci
- Non-carriers

Carriers of the disease-causing strain should be identified and the bacterium eradicated. r in subclinical meningococcal infections (59, 60, 61, 62, 63). In this

Figure 4. Cases of meningococcal disease in Norway 1977-2008 (figures from National Inst of Public Health, Oslo, refr.56)



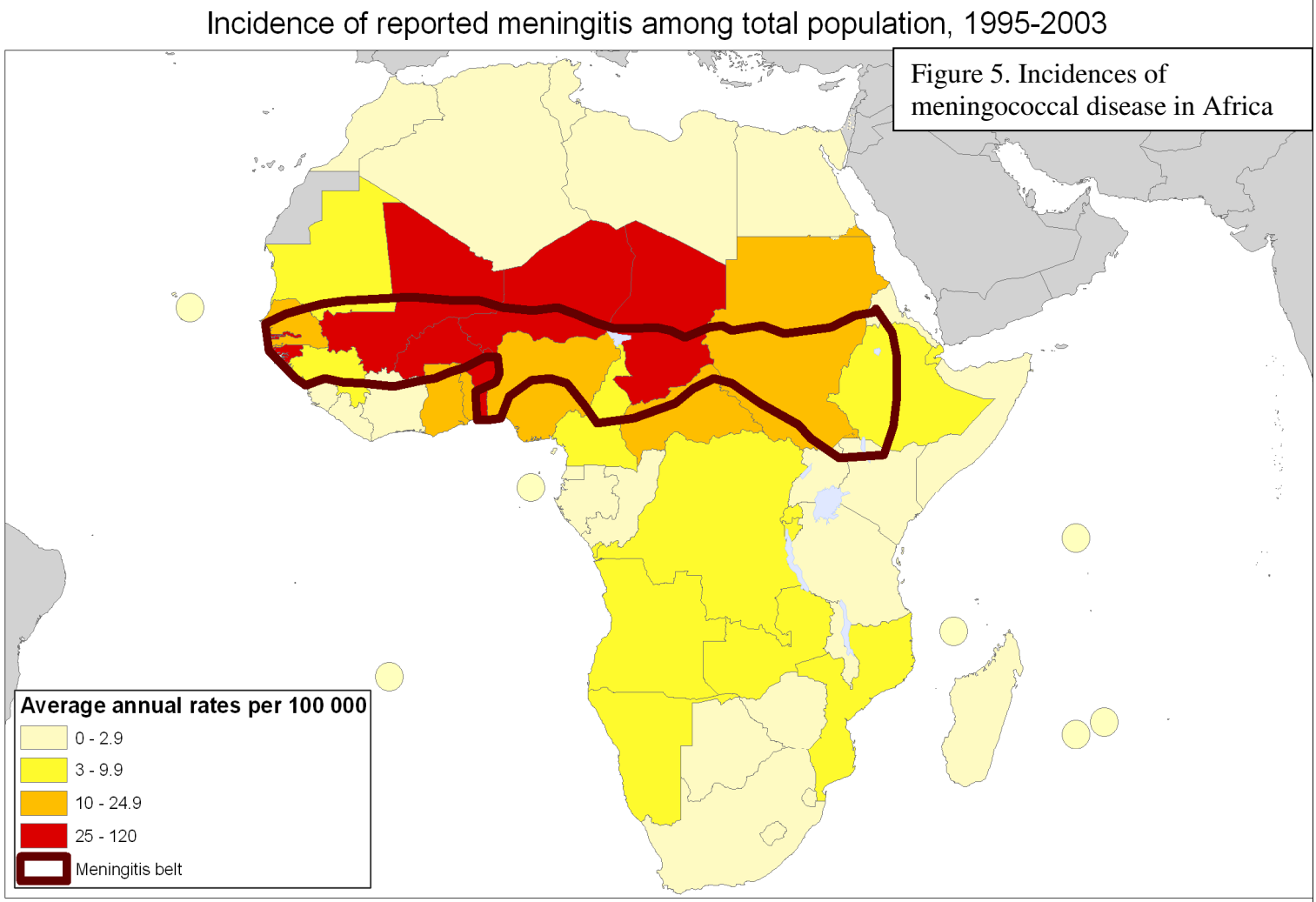
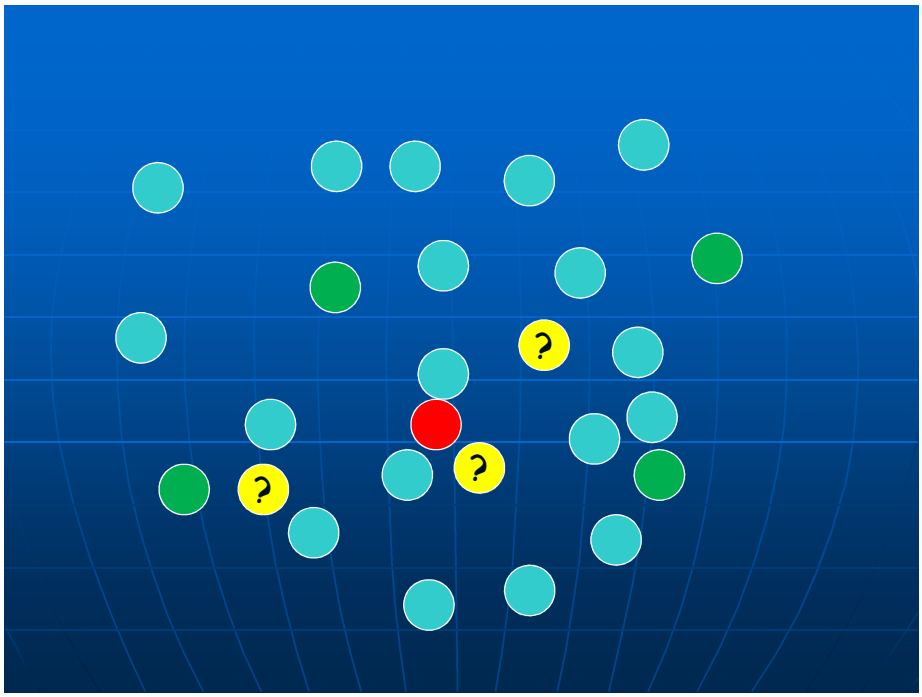


Figure 5. Incidences of meningococcal disease in Africa

study we report the 20-years experiences with the Telemark Meningococcal Project and we try to evaluate:

1. if the interventions of the Telemark Meningococcal Project may have prevented secondary infection;
2. which of the contacts has the highest risk of carrying the disease-causing strain; and
3. the costs of the Project.

Figure 6. A theoretical model for the spread of the disease-causing strain at the time a case of meningococcal disease occurs in a population (red). There are persons carrying the disease-causing strain (yellow), contacts carrying other strains of meningococci (green) as well as non-carriers (turquoise). The aim of the Meningococcal Project of Telemark is to identify the contacts carrying the disease-causing strain (yellow) and to treat these with rifampicin to eradicate it from the affected population



Materials and Methods

Organization of the project.

In 1987, the County Health Officer of the County of Telemark (165.000 inhabitants) distributed the recommendations for the Telemark Meningococcal Project to all local community infection control physicians, general practitioners, departments of medicine and paediatrics at all four hospitals of Telemark, and to the private medical microbiology laboratory of Telelab which served as the official microbiology laboratory for all hospitals, institutions and outpatients clinics in all Telemark (Appendix A). These guidelines were developed through the collaboration between consultants of the Departments of medicine and paediatrics at the Telemark Central Hospital, the consultant at Telelab and a local community infection control physician. The recommendations contained detailed information on:

- the pre-hospital and hospital collection of specimens for bacterial diagnosis, clinical diagnosis and treatment of meningococcal disease,
- diagnostic procedures to be applied and information to be given to the local physician by the microbiology laboratory,
- procedures for identifying close contacts of patients,
- sampling of throat cultures from close contacts and registration of their relation to the patient, age and sex and telephone number in case of need for chemoprophylactic treatment
- schemes for chemoprophylactic treatment with rifampicin of contacts who carry the disease-causing strain

- post-treatment bacterial control of contacts carrying the disease-causing strain.
- information policy to the public by meetings, press-releases, and letters to family and affected community.

Interventions undertaken by the Telemark Meningococcal Project.

Typically, when a case of meningococcal disease was suspected by the consulting general practitioner, the patient was immediately admitted to hospital after blood culture and throat samples were collected. When the transport time exceeded 30 minutes, the patient was given penicillin intramuscularly or intravenously. On admission in hospital blood samples including blood culture, throat samples as well as cerebrospinal fluid were collected and sent immediately to the laboratories. At the Telelab AS, the specimens were cultured on appropriate media and a gram stained specimen was prepared for microscopic examination. The Telemark Meningococcal Project was initiated by the microbiologist on:

- the finding of gram negative diplococci in the gram stained cerebrospinal fluid specimen (Day 0) or,
- growth of gram negative diplococci in blood culture (Day 1) or,
- growth of oxydase positive, gram negative diplococci on plates incubated with cerebrospinal fluid (Day 1) or,
- growth of serogroup B meningococci from the throat without growth from blood or from the cerebrospinal fluid in patients who had been given penicillin before admission and who presented on admission with fever, neck stiffness and/or petecchial bleedings (Day 1).

Upon confirmation of meningococci in specimen(s) from the patient, the microbiologist on duty (either of two) shall:

- inform the doctor on duty at the hospital and collect information on the patient (address, family members, whether working, in school, kindergarten or at home, which persons have slept in the same room as the patient during the preceding 2 weeks, kissing contacts)
- alarm the local infectious disease control physician and define who are close contacts from whom throat sampling shall be performed, plan throat sampling and information meeting (Day 1 or 2)

In every case there was held an information meeting for family, contacts, and other persons affected by the outbreak with the attendance of both the microbiologist and the local infection disease control physician. Figure 7 shows a review of how the sampling of close contacts is performed. The throat specimens were plated immediately after collection and data of each contact was collected. Upon arrival back to the laboratory the specimens were incubated and the plates read the days thereafter (Day 2 or 3), and meningococci identified on Day 3 or 4. DNA fingerprinting was performed on Day 3 or 4. In 1995, the method for identification disease-causing strains was changed to the PCR AREA method developed by us (30). The PCR AREA method enables the identification of the disease-causing strain to be obtained on Day 2 or 3 (Table 1). Information of whom were carriers of the disease-causing strain was given by the microbiologist to the local infection control physician, who was responsible for starting chemoprophylactic treatment with rifampicin. Rifampicin was made available from the hospital pharmacy (Appendix A). All contacts who carried the disease-

causing strain were controlled with culture 7-10 days following chemoprophylaxis.

Bacteriological methods

Specimens from the patients (blood, cerebrospinal fluid and nasopharynx*)* and from the close contacts (nasopharynx) were cultured on standard media and incubated in 10% CO_2 overnight as described (11). Growth of oxydase positive colonies was gram stained for gram negative diplococcic. On growth of pure culture, meningococci were identified by degradation of glucose and maltose, but not of sucrose, lactose or tributyrine. Sulphonamide susceptibility was tested by the e-test, and serogrouping was performed using antibodies against the different serogroups in a slide-agglutination test (11). DNA fingerprinting and later PCR AREA for strain identification was performed as published (25, 30). All strains of meningococci were frozen at – 70^0C.

Databases and statistical calculations.

The data for the patients and for the contacts were first written into Dbase III +. For the statistical calculations the Dbase III + files were imported and converted into SPSS 15.0 for Windows (SPSS UK, Ltd., 2006). Relative risks and chi-square test were performed according to Jekel et al (64).

Table 1. Steps in the Telemark Meningococcal Project from the day of microbial verification of meningococcal disease (Day 0) until bacterial control after chemoprophylaxis using either the DNA fingerprint method or the PCR AREA for strain verification

Day	DNA fingerprinting (1987-94)	PCR AREA (1995-2007)
Day 0	Identification of gram negative diplococci in CSF	Identification of gram negative diplococci in CSF
	Information to hospital consultant	Information to hospital consultant
	Alarm to local infectious disease control physician	Alarm to local infectious disease control physician
	Identification of close contacts	Identification of close contacts
	Planning of information meeting and throat sampling	Planning of information meeting and throat sampling
Day 1	Information meeting for affected population	Information meeting for affected population
	Throat specimen sampling of close contacts	Throat specimen sampling of close contacts
	Plating and incubation	Plating and incubation
Day 2	Reading plates. Spreading for pure culture	Reading plates. DNA extraction of oxydase positive growth
		Identification of disease-causing strain from PCR AREA pattern
		Information to carriers of disease-causing strain
		Start of chemoprophylactic chemotherapy with rifampicin
Day 3	Identification of meningococci	
	Extraction and cleavage of DNA from meningococci	
	Start electrophoresis of DNA fragment	
Day 4	Identification of disease-causing strain from DNA fingerprint pattern	
	Information to carriers of disease-causing strain	
	Start of chemoprophylactic chemotherapy with rifampicin	
Day 11-14	Bacterial control of contacts with disease-causing strain	Bacterial control of contacts with disease-causing strain

Figure 7 (row by row from top left): plates and spatula needed for collection of nasopharynx samples, teaching close contacts how to say ”AAAAA” before collection of specimens, samples are collected using one single cotton swab which are rolled over both tonsils and nasopharynx mucosa, collection of sample by the microbiologist, incubation of plates, spreading culture for purification, growth of meningococci on chocolate plate, degradation of sugars for identification of meningococci, extraction of DNA, PCR AREA band pattern

Results

Patients

During the study period from November 1, 1987 until October 31, 2007, there were 66 cases of bacteriologically verified meningococcal disease in the county of Telemark. There was no secondary case of meningococcal disease. All 66 cases were primary cases with no link to each other.

Age. The mean age of the patients was 16,6 years ranging from 0 – 79 years (SD 22,3).

Figure 8. Age distribution of the 66 primary cases of meningococcal disease in Telemark 1987-2007

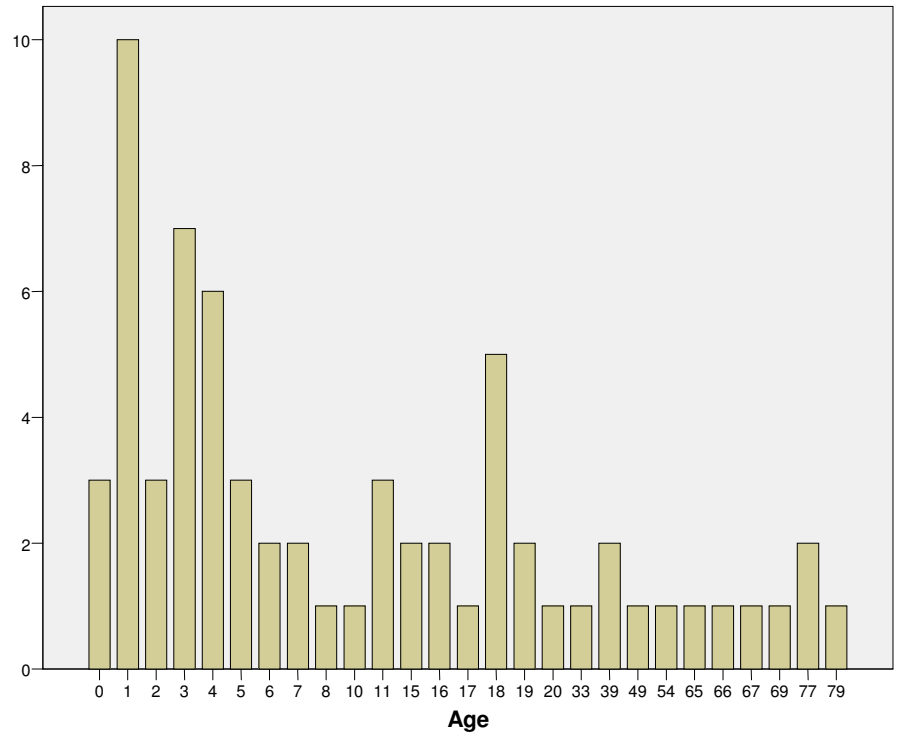


Table. 2. Age distribution of the 66 patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	3	4,5	4,5	4,5
	1	10	15,2	15,2	19,7
	2	3	4,5	4,5	24,2
	3	7	10,6	10,6	34,8
	4	6	9,1	9,1	43,9
	5	3	4,5	4,5	48,5
	6	2	3,0	3,0	51,5
	7	2	3,0	3,0	54,5
	8	1	1,5	1,5	56,1
	10	1	1,5	1,5	57,6
	11	3	4,5	4,5	62,1
	15	2	3,0	3,0	65,2
	16	2	3,0	3,0	68,2
	17	1	1,5	1,5	69,7
	18	5	7,6	7,6	77,3
	19	2	3,0	3,0	80,3
	20	1	1,5	1,5	81,8
	33	1	1,5	1,5	83,3
	39	2	3,0	3,0	86,4

Table 2 and Fig. 1 both show the age distribution of the 66 patients. The age-specific prevalence was highest in the youngest age group. Thirty-four (51,5 %) of the patients were six years of age or younger. There is also a high number of patients at 18 and 19 years of age (10, 6 %). Only 18,2 % of the patients were above 20 years of age.

Sex. Forty-one (62,1 %) of the 66 patients were males and 25 (37,9 %) were females (Table3).

Table 3. Sex distribution of the 66 patients

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Men	41	62,1	62,1	62,1
	Women	25	37,9	37,9	100,0
	Total	66	100,0	100,0	

Sources of material for isolation of N. meningitidis. Meningococci were isolated in blood culture from 48 % of the patients, from the cerebrospinal fluid in 39,4 5 of the patients (patients with meningitis), and from nasal or nasopharyngeal specimens in 12,1 % of the patients. The latter patients had all clinical signs of septicaemia (petecchial bleedings) and/or meningitis (neck-stiffness), but in whom culture from blood and cerebrospinal fluid failed due to antibiotic treatment before collecting clinical specimens.

Table 4. Sources of material for the isolation of N.meningitidis. BK= blood culture, HA= nasopharyngeal specimen, NE= nose, CSF= cerebrospinal fluid

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	BK	32	48,5	48,5	48,5
	HA	7	10,6	10,6	59,1
	NE	1	1,5	1,5	60,6
	SP	26	39,4	39,4	100,0

Clinical outcome. A total of 5 (7,6 %) of the patients died. The age of those who died (Fig. 9) was higher (mean 31,8 years, CI = 9,9 – 73,6) than in those who survived (mean 15,3 years, CI = 9,9 – 20,7). Three out of 41 (7, 3 %) males died and 2 (8 %) out of 25 females had a fatal outcome.

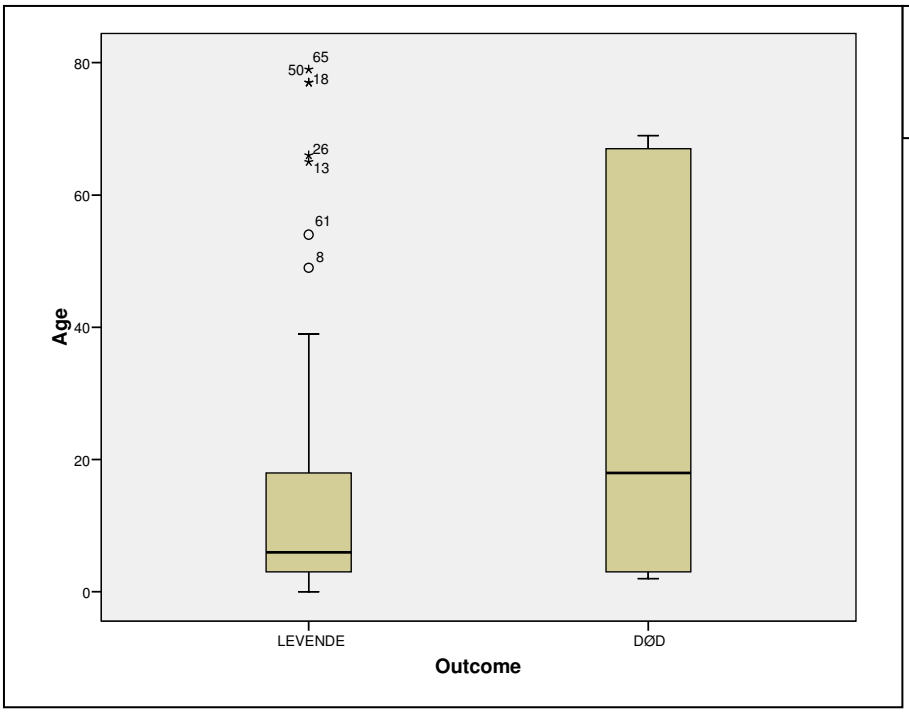


Figure 9. Age of patients who died and in patients who survived

Annual number of cases. The annual numbers of bacteriologically verified cases are shown in Table 5. The annual numbers of notified cases to the Norwegian notification system for infectious diseases (MSIS, National Institute of Public Health, Oslo) are shown in the same table. The discrepancy between the annual figures may be due to the fact that both suspected and verified cases are notifiable to the National Institute of Public Health.

Year	Verified	Notified
1987*	3	3
1988	8	10
1989	2	2
1990	6	7
1991	7	8
1992	7	9
1993	2	2
1994	3	2
1995	3	4
1996	7	8
1997	4	4
1998	3	3
1999	2	2
2000	3	3
2001	2	2
2002	2	2
2003	1	1
2004	0	0
2005	1	1
2006	0	0
2007	0	0
Total	66	73

*from November 1

Table 5. Annual number of bacteriological verified (Telelab AS) and notified cases (National Inst Public Health, Oslo) of systemic meningococcal disease in the County of Telemark 1987 - 2007

Serogroup distribution of disease-causing strains. Table 6 shows that the predominant serogroup among the 66 case strains was the serogroup B causing disease in almost 65 % of the patients. Serogroup C was isolated from approximately 25 % of the patients.

Table 6. Distribution of serogroups among the disease-causing meningococcal strains from the 66 patients

		Group	Percent	Valid Percent	Cumulative Percent
Valid	A	1	1,5	1,5	1,5
	B	42	63,6	63,6	65,2
	C	17	25,8	25,8	90,9
	W135	2	3,0	3,0	93,9
	Y	4	6,1	6,1	100,0

Close contacts

A total of 2252 close contacts of the 66 patients were identified and included. In two (3 %) out of the 66 patients, no close contacts were identified. The disease-causing strain was isolated from close contacts of 37 (56, 1 %) out of the 66 patients; in 29 (43, 9 %) cases, no close contact colonized with the disease-causing strain was detected. The mean number of close contacts per patient was 34, 1 (range 0-198, SD 33,9). There were 1151 (51, 1 %) female and 1101 (48, 9 %) male contacts.

Bacterial findings. The number of close contacts carrying a strain of N.meningitidis was 302 (13, 4 %). Other oxydase positive diplococcal species (Moraxella catarrhalis and Neisseria lactamica*)* were found in 243 (10, 8 %) contacts (Table 7). Of the 302 isolates of *N.meningitidis,* 70 (23,2 %) were identical to the disease-causing strain (Table 8). The carriage rate of the disease-

Table 7. Bacterial species isolated from the nasopharynx of 2252 close contacts. M.CA= *Moraxella catarrhalis*, N.LA= *Neisseria lactamica*, N.MC= *Neisseria meningitidis*,

		Frequency	Percent	Valid Percent	Cumulative Percent
Neg		1707	75,8	75,8	75,8
	M.CA	79	3,5	3,5	79,3
	N.LA	164	7,3	7,3	86,6
	N.MC	302	13,4	13,4	100,0
	Total	2252	100,0	100,0	

causing strain among all close contacts was 3, 1 % (70/2252). The carriage rate of non-disease causing meningococci among all close contacts was 10, 3 %. Of the 70 close contacts who carried a disease-causing strain, 26 were females (37, 1 %) and 44 (62,9 %) were males. Among the 232 who carried a non-disease causing meningococcal strain, 103 (44,4 %) were females and 129 (55,6 %) were males.

In whom could the disease-causing strain be found?

The close contacts were divided into 20 contact groups according to their relation to the patient (Table 8). Groups 1-17 consists of persons who had direct contacts with the patient (primary contacts). Whenever a primary contact was shown to carry a disease-causing strain, his or hers kissing contacts and household-members were also screened for meningococci colonization. These contacts were defined as secondary contacts and were categorized into contact group 18. Tertiary contacts (contact group 19) were household-members and kissing contacts of secondary contacts that carried the disease-causing strain and finally, quartary contacts (contact group 20) were similarly related to tertiary contacts. The 6 first groups of contacts are household - members or kissing contact. In these 6 groups, containing 210 persons, the prevalence of the disease-causing strain was 13,3 % whereas the prevalence of non-disease causing meningococci was 7,6 %, giving a total prevalence of meningococcal carriage of 20,9 %. Among the remaining 1917 primary contacts the carrier rate of the disease-causing strain in the nasopharynx was 1, 8 % and of non-disease-causing isolates 10, 7 %.

Figure 10. The result of the environmental study in a kindergarten following a case of meningococcal septicemia in a 2 years old girl (red circle) diagnosed on Sept. 11 (!). On Day 1 (Sept. 12), we identified two other children in the kindergarten carrying the same disease-causing strain (red triangles) as well as one adult employee (red squares). Further investigations of these three contacts revealed that the mother and grandmother of one child and the teenage son of the adult employee harbored the disease-causing strain. By extended studies of these person's household-members and kissing contacts, no more carriers of the disease-causing strain was revealed. All carriers of the disease-causing strain were given rifampicin with good effect

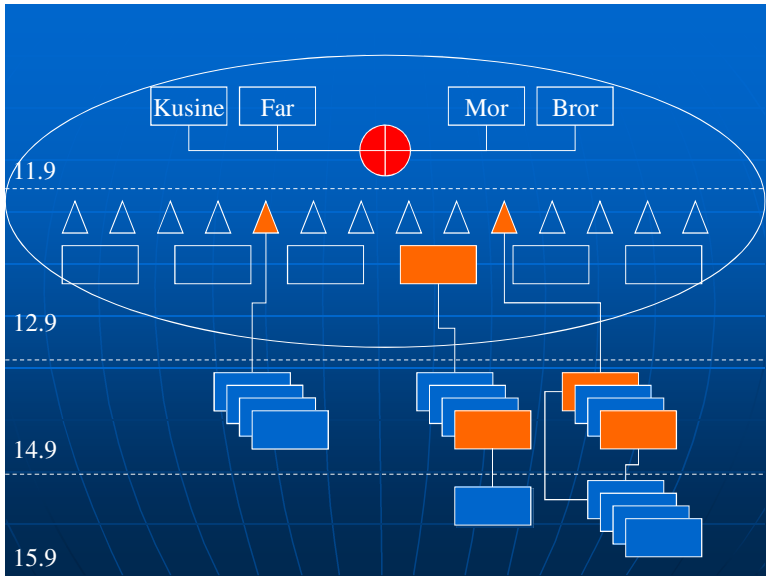


Figure 11. A summary of the finding of disease-causing strain in primary, secondary, tertiary and quartary contacts of patients with meningococcal disease

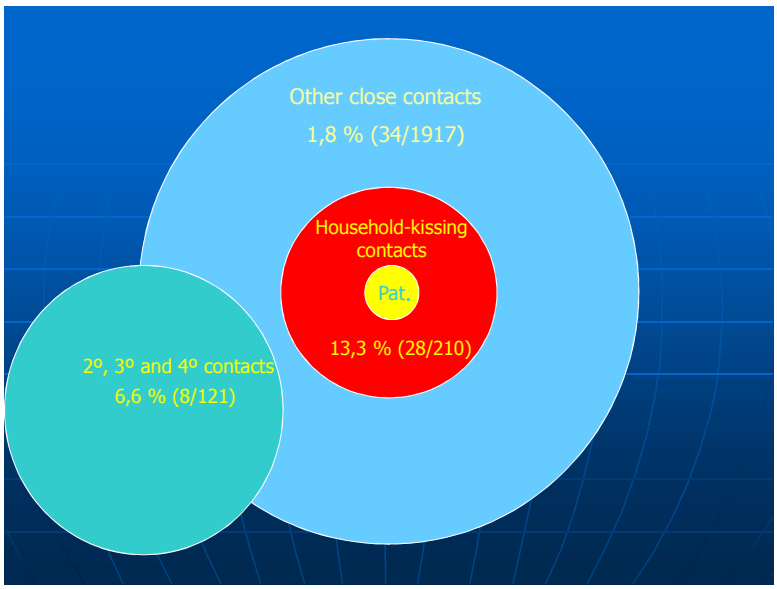


Table 8. The number of contacts in different groups according to relation to the patient. "Identical" denotes a contact carrying a disease causing strain of N. meningitidis, and "Different" denotes carriage of a strain that is different from the disease-causing strain.

Contact group	Relation to the patient	Frequency	Percent	Identical	Identical %	Different	Different %
1	Fathers	49	2,2	6	12,2	3	6,1
2	Mothers	51	2,3	6	11,8	3	5,9
3	Sisters	37	1,6	3	8,1	1	2,7
4	Brothers	39	1,7	7	17,9	3	7,7
5	Kissing contacts	10	0,4	4	40,0	0	0,0
6	Others	24	1,1	2	8,3	6	25,0
	Sum household members	**210**	**9,3**	**28**	**13,3**	**16**	7,6
7	Grandparents	56	2,5	4	7,1	6	10,7
8	Playmates family	116	5,2	2	1,7	20	17,2
9	Playmates	286	12,7	6	2,1	48	16,8
10	Nursery employees	114	5,1	2	1,8	4	3,5
11	Childminders	6	0,3	1	16,7	1	16,7
12	Other family	214	9,5	5	2,3	37	17,3
13	Classmates	342	15,2	5	1,5	48	14,0
14	Children at nursery	421	18,7	2	0,5	11	2,6
15	Teachers	65	2,9	0	0,0	3	4,6
16	Colleagues	3	0,1	0	0,0	2	66,7
17	Others	294	13,1	7	2,4	25	8,5
	Sum other primary contacts	**1917**	**85,1**	**34**	**1,8**	**205**	**10,7**
	Total close contacts	**2127**	**94,4**	**62**	**2,9**	**221**	**10,4**
18	Secondary contacts	86	3,8	5	5,8	9	10,5
19	Tertiary contacts	16	0,7	3	18,8	2	12,5
20	Quartary contacts	19	0,8	0	0,0	0	0,0
	Sum	**2248**	**99,8**	**70**	**3,1**	**232**	10,3
	Missing	4	0,2				
	Total	**2252**	**100**	**70**	**3,1**	**232**	**10,3**

In the secondary carriers, the carriage rate of the disease-causing strain was 5, 8 %, among tertiary contacts 18, 8 % and in quartary contacts 0 %.

Odds Ratio for being a carrier of the disease-causing strain. From Table 8 it can be calculated that the Odds Ratio (OR) for carrying the disease-causing strain being a house-member or a kissing contact (contact groups 1-6) is 8, 52. These contacts, therefore, have 8, 52 times higher risk than other primary contacts, to carry the disease-causing strain. The chi-square value was calculated to 15, 31 which gives shows that the difference in Odds Ratio is statistical significant at $p < 0, 0005$ level with one degree of freedom (*df*=1). Furthermore, the attributable risk percentage in the exposed (AR %) can be calculated from the formula:

AR % = Risk (exposed) – Risk (unexposed)/Risk (exposed) X 100

where "exposed" are the household-members and kissing contacts, and "non-exposed" are other primary contacts. The AR % is (13,3 – 1,8)/13,3 X 100 = 86,5 %, which means that of the total risk of carrying the disease-causing strain, being a household-member or a kissing contact, 86,5 % of the risk stems from being in contact groups 1-6, the remaining risk being caused by other factors.

Discussion

Cost – benefit estimates and cost utility analyses

The costs of the Project are mainly linked to the laboratory analyses. The flow-chart for the procedures leading from sampling and culture to conclusive "identity" or "not-identity" for the nasopharyngeal specimens from all 2252 contacts, is shown in Fig 12. Each procedure has its own price determined by the Ministry of Health. Hence, it is possible to estimate the total costs of the Project. All prices and costs are given in 2007 - values. The total costs of the project are estimated to 660.000 NOK (Table 9A). What has been gained by this money? A saving of the Project is the hospitalization cost of the persons who were prevented from contracting meningococcal disease. How many cases were prevented by our interventions? The number of cases of meningococcal that may have been prevented by the Project can be calculated from the expected prevalence of secondary cases. Given that 66 is the number of primary cases, the expected total number of cases is 66 plus the expected number of secondary cases. In the literature, the prevalence of secondary infections is reported to vary between <2 % (65) and 30 % (42) with 10 % reported from all Norway (66). Given a prevalence of secondary cases at 2 %, the expected number of cases is 67,3; hence 1 secondary infection may have been prevented. Given a prevalence of secondary infection at 10 % (66), the total number of expected cases is 73, 3, consequently, 7 secondary cases may have been prevented.

The calculations for hospitalization costs are performed according to instructions given by the Norwegian Social- and Health Directorate (67). There is a unit price

presently at 33647 NOK. Each diagnosis is given a Diagnosis Related Group (DRG) point according to estimated costs for that particular diagnosis (laboratory tests, X-ray procedures, treatment procedures and drugs). According to this system, meningococcal disease has three different cost categories or DRG points:

- Infections in the central nervous system: 2, 21 points.
- Septicemia below 17 years of age: 2,44 points
- Septicemia in patients 17 years of age or older: 1,94

The savings of hospitalization costs varied from approximately 82.000 NOK (1 secondary case prevented) to approximately 470.000 NOK (7 patients prevented, Table 9B). It was assumed that of the 7 patients that may have been prevented, 3 had septicemia and were below 17 years, 3 had meningitis, and one patient was above 17 years and had septicemia. The saving in hospitalization costs, therefore was less than the costs of the Project (660.000 NOK).

But in addition to saving costs for hospitalization, which can be said to be the cost-benefit effect of the Project, the patients who may have been prevented from contracting disease, may also benefit by not having its health related life quality reduced following meningococcal disease. In the worst case meningococcal disease may be fatal, and 30 % of those with septicemia die (10), the overall mortality is 10 %. Consequently, there may be a benefit from the Project that cannot be measured in money, prevention of reduced health quality of life. This may be called the cost – utility effect and can be measured by cost – utility analyses. We apply the QALY (quality adjusted life years) principles to calculate

the improvement in health related quality of life that is assumed to be gained from our interventions. Our calculations are based on some assumptions:

- The life-expectancy of patients who survive meningococcal disease is not shortened
- There is a small, but significant risk for patients who recover from meningococcal disease to get permanent sequelae (68, 69, 70), the most common being psycho-social, physical and orthopedic problems and some few cases with epilepsy, hearing loss and blindness.
- Patients who contract meningococcal disease had no reduction in health related quality of life before contracting meningococcal disease
- All patients who may have been prevented survived with no fatal case.

Based on the literature reporting sequelae, we estimate that the reduction in health associated QALY in patients recovering from meningococcal disease to be 0, 2 on a range from 0 - 1 where 1 represents no reduction in health-related life quality and = is death. Given that the age of the prevented cases corresponds to the mean age of the 66 patients (17 years), their remaining life span can be calculated by means of the calculator that is found on the homepage of Statistisk Sentralbyrå (http://www.ssb.no/vis/emner/02/02/10/dode/art-2008-04-10-01.html). If the patients is a woman at 17 years of age, she will have a life-expectancy of 82 years (and 2 months) living in Telemark. Being a male at 17 years of age, the life-expectancy is 77 years (76 years and 9 months). As more than 60 % of the patients are males, the calculations of QALY at the 2 % prevalence level will be done for a male and at the 10 % prevalence level (7 secondary cases prevented) for 3 females and 4 males. The QALY can be calculated by the formulas:

$$([[TF * (H1 - H0)] * NF] + [TM * (H1 - H0)] * NM]])_{2\ \%\text{prevalence}}$$

$$([[TF * (H1 - H0)] * NF] + [TM * (H1 - H0)] * NM]])_{10\ \%\ \text{prevalence}}$$

where H1 is the health quality without contracting secondary disease which is assumed to have the value "1", H0 is the quality of life after recovering from secondary disease and is set to "0, 8", TF (65 years) is the remaining life expectancy for females at 17 years of age, and TM (60 years) for males at 17 years of age, living in Telemark, NF is the number of female patients who were prevented, and NM the number of males prevented from secondary infection.

$$(65 * 0{,}2 * 0 + 60 * 0{,}2 * 1)_{2\ \%\ \text{level}} = 0 + 12 = 12\ \text{QALYS}$$

$$(65 * 0{,}2 * 3 + 60 * 0{,}2 * 4)_{10\ \%\ \text{level}} = 29 + 48 = 77\ \text{QALYS}$$

Given a prevalence of secondary infections between 2 % and 10 %, the health quality gain from the Project are in the magnitude of from 12 – 77 QALYS.

The Telemark Meningococcal Project may have additional positive effects that are difficult to measure. The affected population is offered immediate oral and written information on meningococcal disease which may lead to quicker response once a secondary case occurs. Moreover, information and the fact that something active is done (bacterial testing), may prevent much of the anxiety that always follows the footsteps of meningococcal disease. The local health system which is under significant pressure in this case, gets active support from the Specialist Health Care System. Local physicians have expressed a relief in their situation as a

consequence of the Project. There are less telephones and visits than before the Project.

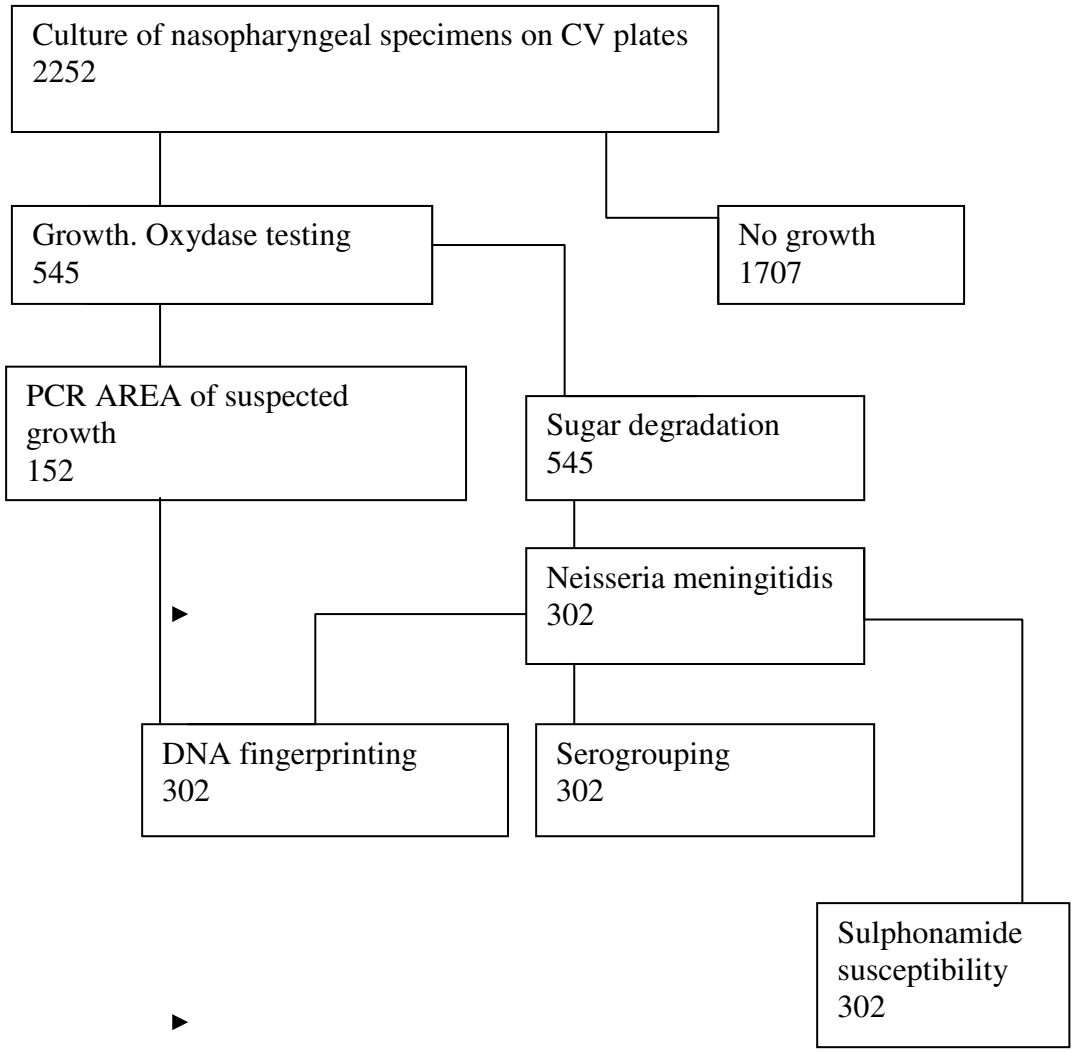


Figure 12. Flow-chart for processing nasopharynx samples from close contacts according to the recommendations of the Telemark Meningococcal Project (Appendix B). The figures represent the number of each procedure being performed

Table 9A. Estimates of the costs of the Project. The costs are mainly linked to the laboratory procedures.

Procedure	Price (NOK)	No of tests	Total (NOK)
Culture of meningococci	83	2252	186916
Oxydase testing	38	545	20710
Gram staining	38	545	20710
Sugar fermentation	38	545	20710
Sulphonamide susceptibility testing	38	302	11476
Agglutination (3 serogroups)	114	302	34428
DNA fingerprinting, alone (until 1994)	909	150	136350
DNA fingerprinting in combination with PCR AREA (from 1995)	909	152	138168
PCR AREA (from 1995)	606	152	92112
Total costs of the Telemark Meningococcal Project			**661580**

Table 9B. Estimates of the costs of hospitalization of patients who were prevented from contracting secondary meningococcal disease by the intervention measures of the Project. At a level of 2 % prevalence of secondary infection, the estimated number of prevented cases is 1, and at the level of 10 %, 7 cases are prevented (see Discussion)

			At 2 % prevalence level		At 10 % prevalence level	
Diagnosis Related Group	Unit price	DRG points	No. patients	Costs (NOK)	No. patients	Costs (NOK)
20. Infection of CNS	33647	2,21	0	0	3	223079,61
416. Septicemia > 17 years of age	33647	1,94	0	0	1	0
417. Septicemia 17 years or younger	33647	2,44	1	82098,68	3	246296,04
Total cost of hospitalization of prevented cases				82098,68		469375,65

Does the Telemark Meningococcal Project prevent secondary cases?

During the Project period, there was no secondary case of meningococcal disease, but 66 bacteriological verified primary cases. A vital question is if this absence of secondary cases was a consequence of our intervention, or whether it can be explained by chance. As was discussed in the section above, the expected total number of cases of meningococcal disease is 66 X 100/98 = 67, 3 cases at a 2 % level of secondary cases. At the 10 % level, the expected number of total cases is 66 X 100/90 = 73, 3 cases. Consequently, the number of cases which could have been prevented by our interventions varies between 1, 3 and 7, 3 cases. At the 30 % level, the number of prevented cases would have been 28, 3. We find it not unlikely that these expected secondary cases have been prevented by our interventions. By applying the chi-square test on the differences between the number of cases that were identified (66 cases), and the expected number of cases, calculations show that the numbers are too small to demonstrate any difference of statistical significance at the 2 % or 10 % level, respectively. Only at a level of 15 % prevalence of secondary cases, would the material allow the difference to be statistical significant. At the earlier reported level of 30 % prevalence from Telemark (42), the chi-square test shows a statistical significant difference at p = 0,012.

Does the Telemark Meningococcal Project influence the number of primary cases of meningococcal cases?

Previous studies from Norway show that only a few different virulent strains are causing meningococcal disease (21, 30). These clones probably circulate in the population constantly. By our interventions, the prevalence of these virulent clones may be reduced to such an extent that infecting chains are broken resulting in a reduction also of primary cases. The encounter between a virulent meningococcus and a susceptible host occurs less frequent because the virulent clone is "diluted" in the population; the "dilution" effect. This "dilution" effect is difficult to prove since it is known that there has been a decline in the incidence of meningococcal disease in all Norway during the last 20 years, probably caused by a rise in herd immunity against the circulating clones.

To try to answer the question whether the interventions of the Telemark Meningococcal Project also reduced the number of primary cases, we compared the development of incidence of meningococcal disease in Norway, Telemark and the neighbouring county of Vestfold (220.000 inhabitants) during three 10-years periods:

1. 1978-1987; the 10-years period immediately prior to the initiation of the Project
2. 1988-1997; the first 10-years period after the Project was started
3. 1998-2007; the second 10-years period after initiation of the Project

While the effect on secondary cases is assumed to have immediate effect on the occurrence of meningococcal disease, the "dilution" effect will probably appear after several years of eradicative interventions. The reason for the late effect is

that it takes time to eradicate the virulent clones enough to block the routes of spread. We hypothesize that a reduction in the mean annual incidence from the first 10-years period to the second 10-years period after the project was started, has two explanations:

- An increase in herd immunity leading to a general decline affecting also neighbouring counties
- The "dilution" effect caused by systematic and thorough eradication of virulent clones of the Project

The "dilution" effect can only be seen in Telemark, and the decrease in meningococcal disease occurrence shall be more pronounced in Telemark than in neighbouring counties. We therefore compared the incidences of meningococcal disease in Telemark with that of neighbouring counties of Vestfold, Buskerud and Aust-Agder (Table 10 and Fig. 13) in the two 10-years periods after the Project was started. Fig. 14 shows a map of the region. The incidence of meningococcal disease in Telemark is constantly lower than in all Norway and in Vestfold during the last 10-years period of the Project (1998-2007). As can be seen from Fig. 15 and Table 11 , the mean annual incidence in Telemark in the first 10-years period of the Project (1988-1997) was 3, 52 cases/100.000 inhabitants (CI 2, 13 – 4, 91), and in the second 10-years period the mean annual incidence was 0, 86 (CI 0, 34 – 1, 38). Since the confidence intervals do not overlap, the fall in the mean annual incidence is statistically significant. No statistical reduction in incidence was seen in Vestfold during the same periods Table 11, Fig. 15), nor in the two other neighbouring counties (data not shown). Consequently, it is tempting to speculate that the interventions in our Project may have contributed to the

significant fall in meningococcal disease incidence seen in Telemark from the period 1987-1996 to 1997 – 2007.

Table 10. Incidence of meningococcal disease in all Norway, in Telemark and in each of its neighbouring counties Buskerud, Vestfold and Aust.Agder 1978 – 2007 as well in these neighbouring counties together (BVAA). The cases are notified cases by the National Institute of Public Health, Oslo. No: number of cases, Popul: population in 100.000, Incid: incidence (No cases/100.000 inhabitants/year)

County		1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
All	No.	270	323	230	257	267	368	302	317	263	259	177	176	165	167	201	126	102	158	139	115	105	83	83	78	51	48	37	39	35	30
Norway	Popul	40,8	40,8	40,9	40,9	41,1	41,3	41,5	41,6	41,8	41,9	42	42,2	42,4	42,5	42,7	43	43,2	43,5	43,7	43,9	44,2	44,5	44,8	45	45,2	45,5	45,8	46,1	46,4	46,8
	Incid	6,6	7,9	5,6	6,3	6,5	8,9	7,3	7,6	6,3	6,2	4,2	4,2	3,9	3,9	4,7	2,9	2,4	3,6	3,2	2,6	2,4	1,9	1,9	1,7	1,1	1,1	0,8	0,8	0,8	0,6
Buskerud	No.	11	11	10	12	17	5	11	14	13	21	6	9	8	8	8	8	9	7	5	4	5	4	5	5	3	1	3	2	1	1
	Popul	2,1	2,1	2,1	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,3	2,3	2,3	2,3	2,3	2,3	2,3	2,3	2,3	2,4	2,4	2,4	2,4	2,4	2,4	2,5	2,5
	Incid	5,2	5,2	4,8	5,5	7,7	2,3	5	6,4	5,9	9,5	2,7	4,1	3,6	3,6	3,5	3,5	3,9	3	2,2	1,7	2,2	1,7	2,1	2,1	1,3	0,4	1,3	0,8	0,4	0,4
Vestfold	No.	15	19	19	18	11	16	18	21	20	14	11	5	5	8	6	5	3	1	9	5	5	7	2	5	4	2	2	4	3	3
	Popul	1,8	1,9	1,9	1,9	1,9	1,9	1,9	1,9	1,9	1,9	1,9	1,9	2	2	2	2	2	2	2	2,1	2,1	2,1	2,1	2,2	2,2	2,2	2,2	2,2	2,2	2,2
	Incid	8,3	10	10	9,5	5,8	8,4	9,5	11,1	10,5	7,4	5,8	2,6	2,5	4	3	2,5	1,5	0,5	4,5	2,4	2,4	3,3	1	2,3	1,8	0,9	0,9	1,8	1,4	1,4
Aust-	No.	3	1	1	4	2	3	1	3	2	1	4	5	3	5	7	4	4	6	7	0	3	0	5	2	1	2	0	2	1	3
Agder	Popul	0,9	0,9	0,9	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	Incid	3,3	1,1	1,1	4	2	3	1	3	2	1	4	5	3	5	7	4	4	6	7	0	3	0	5	2	1	2	0	2	1	1
BVAA	No.	29	31	30	34	30	24	30	38	35	36	21	19	16	21	21	17	16	14	21	9	13	11	12	12	8	5	5	8	5	7
	Popul	4,8	4,9	4,9	5,1	5,1	5,1	5,1	5,1	5,1	5,1	5,1	5,1	5,2	5,3	5,3	5,3	5,3	5,3	5,3	5,4	5,4	5,4	5,5	5,6	5,6	5,6	5,6	5,6	5,7	5,7
	Incid	6	6,3	6,1	6,7	5,9	4,7	5,9	7,5	6,9	7,1	4,1	3,7	3,1	4	4	3,2	3	2,6	4	1,7	2,4	2	2,2	2,1	1,4	0,9	0,9	1,4	0,9	1,2
Telemark	No.	6	3	3	9	5	17	6	8	14	14	10	2	7	8	9	2	2	4	8	4	3	2	3	2	2	1	0	1	0	0
	Popul	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,6	1,7	1,7	1,7	1,7	1,7	1,7	1,7	1,7
	Incid	3,8	1,9	1,9	5,6	3,1	10,6	3,8	5	8,8	8,8	6,3	1,3	4,4	5	5,6	1,3	1,3	2,5	5	2,5	1,9	1,3	1,8	1,2	1,2	0,6	0	0,6	0	0

Figure 13. Incidence of meningococcal disease in all Norway, and in the counties of Vestfold and Telemark 1978-2007

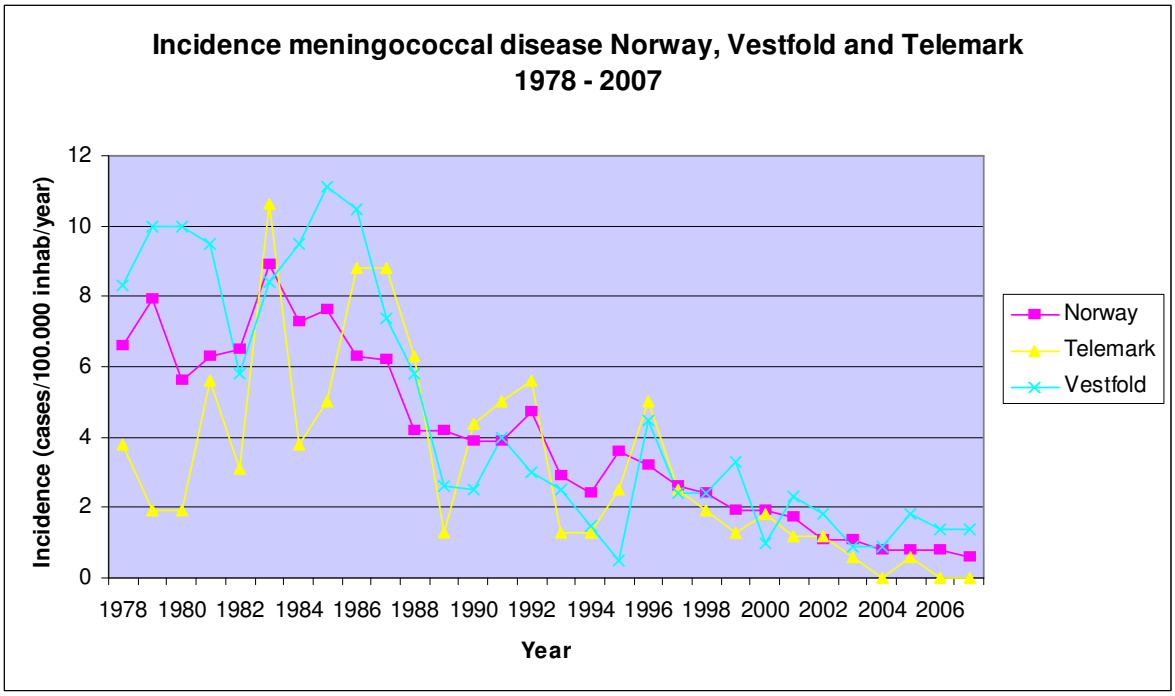
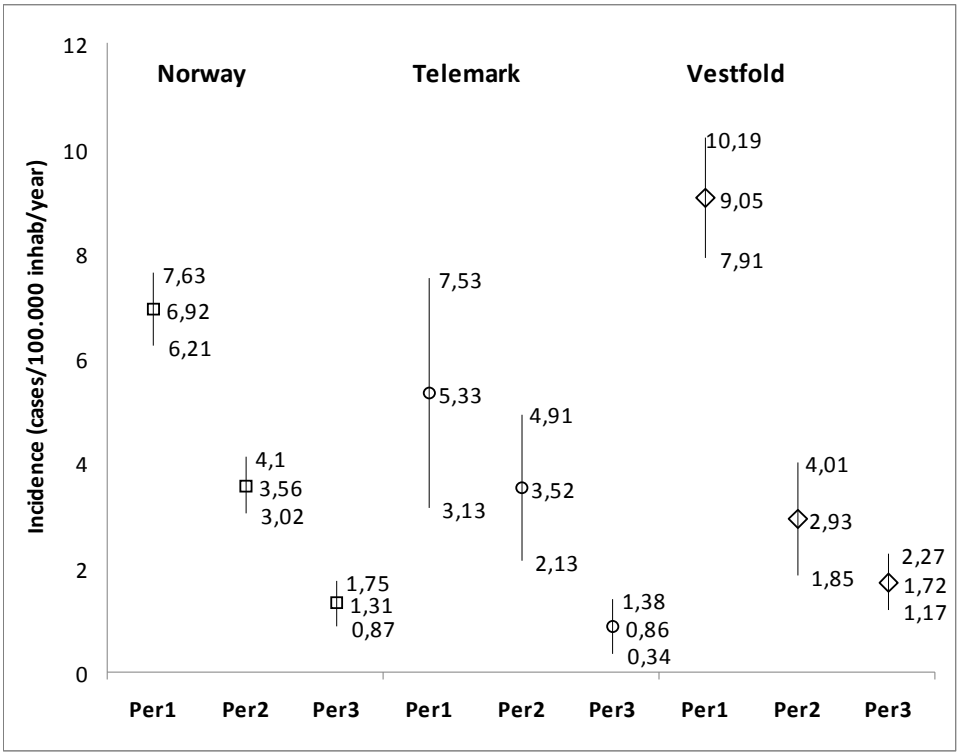


Figure 14. The county of Telemark and its surrounding counties. The closest contact is between Telemark (165.000 inhabitants) and Vestfold (220.000 inhabitants).

Table 11. Annual mean incidences with confidence intervals for meningococcal disease during three 10-years periods in Norway, Vestfold and Telemark 1978-2007

	1978-1987	1988-1997	1998-2007
All Norway			
Confidence level (95 %)	0,71	0,54	0,44
Upper confidence interval level	7,63	4,1	1,75
Mean	6,92	3,56	1,31
Lower confidence interval level	6,21	3,02	0,87
Telemark			
Confidence level (95 %)	2,2	1,39	0,52
Upper confidence interval level	7,53	4,91	1,38
Mean	5,33	3,52	0,86
Lower confidence interval level	3,13	2,13	0,34
Vestfold			
Confidence level (95 %)	1,14	1,08	0,55
Upper confidence interval level	10,19	4,01	2,27
Mean	9,05	2,93	1,72
Lower confidence interval level	7,91	1,85	1,17

Figure 15. Mean annual incidence and confidence intervals (CI) of meningococcal disease in three 10-yeras periods: Per 1: 1978-1987, Per 2: 1988-1997, Per 3: 1998-2007. The figures are notified cases to the National Inst Publ Health, Oslo



Conclusions

- There has been no secondary case of meningococcal disease in the county of Telemark after the Telemark Meningococcal Project was started in November 1987.
- It is not unlikely that the Project has prevented from 1 to 7 cases of secondary meningococcal infections.
- The prevalence of secondary cases was reduced from 30 % prior to the project (1984-87) to 0 % after the Project was started.
- The annual incidence of meningococcal disease in Telemark has been constantly lower in Telemark during the last 10 years compared to the incidence in all Norway and in Vestfold.
- There was a statistical significant fall in the mean annual incidence of notified meningococcal disease from the first 10-years period of the project (1988-97) to the second 10-years period (1998-2007). No statistical significant fall was seen in the neighboring counties of Vestfold, Buskerud or Aust-Agder.
- The risk of being a carrier of the disease-causing strain is highest among house-hold members and kissing contacts. The administration of chemoprophylaxis to these contacts once meningococcal disease occurs should be implemented in Norwegian recommendations.
- The costs of the Project are higher than what is saved hospitalization expenses for cases that may have been prevented.
- The Project may have saved from 12 – 99 quality adjusted life years (QALY)

- The Project should be continued and its recommendations implemented on a permanent basis for preventing meningococcal disease to spread in Telemark

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Appendix A. Historical documents including updated (2003) recommendations for the Telemark Meningococcal Project

Statens legemiddelkontroll
The Norwegian Medicines Control Authority

Avdeling/Seksjon/Kontor: Fako | Vår dato: 26.04.89 | Vår referanse:

Overlege Bjørn E. Kristiansen
A/S Telelab
Postboks 1868 Gulset
3701 SKIEN

Anne Birger Knapskog
Fylkeslegen i Telemark
3700 SKIEN

RIMACTAN - KLINISK UTPRØVNING (SLK nr 89-00755)

Vi viser til Deres melding om klinisk utprøvning av Rifampicin mottatt 8.3.89 samt til vårt brev av 7.4.89 og brev fra dr. Kristiansen datert 17.4.89.
Som jeg indikerte i vår telefonsamtale i går finner vi at prøvningsplanen ikke tilfredsstiller forskriftenes krav.
Dessuten er vi i tvil om man overhode kan forvente å få tilstrekkelig pasienttall innen rimelig tid fra aktuelt område (eller fra Norge som helhet) i og med at begge "meningokokksyklusene" indikerer tydelig avtagende frekvens.
I brev av 7. april 89 nevnes registreringsfritak som et alternativ til klinisk utprøvning. Rimactan er registrert, men kun til Tbc. Det er derfor ikke behov for registreringsfritak, men man rekvirerer Rimactan til 3 dagers behandling til den enkelte pasient etter avtale med Rikshospitalets apotek.
Noe fare for resistensutvikling ved 3 dagers behandling som kan ha betydning for Tbc-behandlingen synes ikke å foreligge.

Med vennelig hilsen
STATENS LEGEMIDDELKONTROLL
Egil Wickström
e.f.

Kopi: Bjørn Jøldal/Helsedirektoratet

b28lw31

Adresse: Sven Oftedals vei 6, N-0950 Oslo 9 | Telefon: Nasjonalt (02) 23 75 50, Internasj +47 2 23 75 50 | Telefax: (02) 23 74 64 | Telex: 72430 lmsn n, servicekode 050 | Bankkonto: 1600 40 70997 | Postgiro: 5 14 12 70

FYLKESLEGEN I TELEMARK
KONTOR: RÅDHUSGT 2. SKIEN
POSTADRESSE: POSTBOKS 730. 3701 SKIEN
TLF (03) 52 82 50 TELEFAX (03) 52 82 54

Rundskriv nr. 51/87

Jnr. 4951/87/ABK/KV

Helseetaten i kommunen
v/medisinsk-faglig ansvarlig lege

Ledende helsesøster

Sjukehusene i fylket

Skien, 30. desember 1987

MENINGOKOKKPROSJEKTET I TELEMARK

I Telemark har vi de siste årene hatt mange tilfelle av meningokokksjukdom, til dels som små epidemier. Det har vært et klart behov for fastere retningslinjer for hvordan helsetjenesten skal takle situasjonen når et meningokokktilfelle oppstår. Moderne DNA-fingerprinting teknikk har gitt oss et godt verktøy i det praktiske arbeidet. Foreløpig er det stort sett bare vårt eget mikrobiologiske laboratorium som bruker denne teknikken.

På denne bakgrunn har fylkeslegen bestemt at det fra og med januar 1988 og foreløpig i 2 år skal kjøres et "Meningokokkprosjekt Telemark". Prosjektet er utformet i samarbeid med overlege Jon Steen-Johnsen ved Barneavdelingen-TSS, overlege Bjørn-Erik Kristiansen ved Telelab og kommunelege Tor Reiten, Seljord. Videre har overlege Gunnar Hopen ved Medisinsk avd.-TSS vært konsultert.

Vedlagt oversendes "Retningslinjer i forbindelse med tilfelle av meningokokksykdom i lokalmiljøet" utarbeidet av Tor Reiten og veiledning vedrørende "Oppsporing av den sykdomsfremkallende

FYLKESLEGEN I TELEMARK
KONTOR: RÅDHUSGT 2. SKIEN
POSTADRESSE: POSTBOKS 730. 3701 SKIEN
TLF (031) 52 82 50 TELEFAX (031) 52 82 54

Rundskriv nr. 52/87
Jnr. 4951/87/ABK/KV
Skien, 30. desember 1987

Legene i Telemark

MENINGOKOKKPROSJEKT TELEMARK

Fra og med januar 1988 og foreløpig i 2 år skal vi i Telemark ha et eget meningokokkprosjekt. Bakgrunnen er at vi de siste årene har hatt mange tilfelle av meningokokksjukdom i fylket. Prosjektet er utformet i samarbeid med overlegene Jon Steen-Johnsen og Bjørn-Erik Kristiansen og kommunelege Tor Reiten.

Helseetaten i kommunen (v/medisinsk-faglig ansvarlig lege) og sjukehusene i fylket har fått detaljert informasjon om prosjektet. Denne består av utførlige retningslinjer for hva som skal gjøres når et (mistenkt) tilfelle av meningokokksjukdom oppstår. Telelab har utarbeidet en veiledning vedrørende "Oppsporing av den sykdomsframkallende bakteriestammen i nærmiljøet ved utbrudd av meningokokksykdom".

Alle tilfelle av (mistenkt) meningokokksjukdom skal omgående meldes muntlig og skriftlig til den offentlige legen (kommunelegen).

Det er helseetaten i kommunen som har ansvaret for tiltakene. Innleggende lege dvs. den legen som diagnostiserer det mulige meningokokktilfellet, skal likevel med en gang:

1. Ta blodprøve av pasienten i blodkulturglass, eventuelt halsutstryk på bomullspinne fra tonsiller og bakre svelgvegg (Culturette).

bakteriestammen i nærmiljøet ved utbrudd av meningokokksykdom"
./. satt opp av Bjørn-Erik Kristiansen. Videre vedlegges en orientering som sendes alle legene i fylket.

Fylkeslegen ber om at disse retningslinjene følges ved alle tilfelle av meningokokksjukdom, både sikre og mistenkte tilfelle. Medisinsk-faglig ansvarlig lege i kommunen bes orientere helsepersonellet og gjøre de praktiske forberedelser, herunder utarbeide publikumsbrosjyre. Det er av største betydning at alle tilfelle omgående blir meldt til den offentlige legen både muntlig og skriftlig.

I slutten av februar d.å. blir det et dagsseminar hvor vi vil drøfte prosjektet nærmere. Innkalling blir sendt ut i nær framtid. På seminaret vil det også bli orientert om SIFF sitt meningokokkvaksineprosjekt som etter planen skal starte høsten 1988.

Med hilsen

Arne-Birger Knapskog

Vegard Høgli

FYLKESMANNEN I TELEMARK
HELSEAVDELINGEN

Til adressater i følge liste

DERES REF	VÅR REF VED SVAR	DATO
	03/2098/AJO/732.2	17. februar 2003

RETNINGSLINJER/PROSEDYRER VED MISTENKT MENINGOKOKKSYKDOM

Vi viser til tidligere rundskriv fra fylkeslegen i Telemark og møte 30.01.03 i helseavdelingen, der spørsmålet om et oppdatert rundskriv fra helseavdelingen burde sendes ut til kommunehelsetjenesten.

Forekomsten av meningokokksykdom er heldigvis kraftig redusert i Telemark, som i landet for øvrig. Sykdommen kan imidlertid ha fatal utgang dersom den ikke oppdages i tide og det er viktig med årvåkenhet omkring sykdomsbildet. Videre er det viktig å sanere smittekilde der hvor det foreligger utbrudd eller koprimære tilfeller.

Samarbeidet mellom Telelab og primærhelsetjenesten ved meningokokksykdom har vært svært nyttig. Det er både ønskelig og nødvendig at samarbeidet fortsetter. Vi vil her vise til spesialisthelsetjenestelovens bestemmelse om veiledningsplikt (§ 6-3) til primærhelsetjenesten.

Helseavdelingen har vurdert behovet for et revidert rundskriv og har funnet at prosedyrer for behandling av meningokokksykdom i Telemark bør utvikles i fagmiljøene, basert på Smittevernhåndbokas anbefalinger. Det er naturlig av smittevernansvarlig lege i helseregion Sør og smittevernlegene i kommunehelsetjenesten trekkes inn i utarbeidelsen av prosedyrene. Telelab og Telemark legeforenings prosedyregruppe bør kunne lage et utkast til prosedyrer på bakgrunn av gjeldene praksis.

Vi anser det derfor ikke som hensiktsmessig å lage et nytt rundskriv i helseavdelingen. Vi kan imidlertid være behjelpelig med å distribuere de reviderte prosedyrene til kommuner og helseforetak i regionen.

Vennlig hilsen

Arne Johannesen
fylkeslege

Astrid Irene Keltner
Rådgiver

Saksbehandler: Arne Johannesen

Postadresse
Statens hus. 3708 Skien
Besøksadresse
Rådhusg 2. 3724 Skien

Telefon
35 58 61 10

Telefaks
35 52 82 54

Organisasjonsnr
974 762 684

E-post
postmottak@fm-te stat no
Hjemmeside
www.fylkesmannen.no/telemark

MENINGOKOKKPROSJEKT TELEMARK

(Dokumentet finnes også på Telelab sin hjemmeside:
http://www.telelab.no/memimemen.htm)

Meningokokkprosjekt Telemark er et tillegg til nasjonale retningslinjer om behandling og forebyggelse av meningokokksykdom og skal ikke erstatte disse.

A. FORMÅL

- Å hindre at smitten sprer seg og at det oppstår nye tilfeller av meningokokksykdom i nærmiljøet til pasienter med meningokokksykdom.
- Å sikre at pasienter med mistenkt meningokokksykdom får stilt rask diagnose og at behandling igangsettes så tidlig som mulig.
- Å sikre at lokalmiljøet får tilstrekkelig kunnskap om sykdommen slik at evt nye tilfeller blir oppdaget raskt og at unødig angst og uro i miljøet forhindres..
- Å gi kommunehelsetjenesten spesialiststøtte ved utbrudd av meningokokksykdom med de store utfordinger dette fører med seg.

B. DEFINISJONER

- **Primærtilfellet**: det første tilfellet av meningokokksykdom i ett miljø
- **Koprimære tilfeller**: tilfeller av meningokokksykdom som oppstår innenfor 24 timer i det samme miljøet som hos primærtilfellet
- **Sekundærtilfeller**: tilfeller som skyldes smittespredning og som oppstår mer enn 24 etter primær tilfellet. Et sekundær tilfelle kan oppstå måneder etter primær tilfellet. Ved genetiske metoder kan det påvises også evt spredning til andre miljøer. Også slike tilfeller i nye miljøer vil være sekundærtilfeller.
- **Kjemoprofylakse**: behandling med antibakterielle midler (rifampicin eller ciprofloksasin) som dreper meningokokker på halsslimhinnen og dermed sanerer smittestoffet fra miljøet.
- **Antibiotikabehandling**: behandling med antibiotika (penicillin) som dreper meningokokker som har invadert til blod og spinalvæske, men som ikke nødvendigvis vil drepe meningokokker som befinner seg på halsslimhinnen. Antibiotikabehandling med penicillin vil ikke utrydde meningokokkbakterien fra halsslimhinnen og smitteveiene vil derfor ikke brytes.

C. REGELVERK OG NASJONALE RETNINGSLINJER

- Lov om vern mot smittsomme sykdommer (Smittevernloven) av 05.08.1994 nr. 55: *§ **2-3** Meldingsplikt for leger, § **3-1** Om legers plikt til å diagnostisere og behandle allmennfarlige sykdommer, § **3-5** Legens plikt til å foreta undersøkelse av smittede personer og §**3-6** Legens plikt til å foreta smitteoppsporing.*
- Forskrift om leger og annet helsepersonells melding og varsling av smittsomme sykdommer av 30.12. 1994 nr. 1224
- Forskrift om allmennfarlige og smittsomme sykdommer av 01.01.1995 nr 100
- Forskrift om stønad til dekning av utgifter til viktige legemidler og spesielt medisinsk utstyr av 18.04.97
- Retningslinjer for diagnose og behandling av systemisk meningokokksykdom, hoveddokument IK-2297 (og sammendrag beregnet på sykehusavdelinger som

behandler meningokokkpasienter – IK-2296), Helsedirektoratet, Statens institutt for folkehelse og Institutt for farmakoterapi, Oslo 1989
- Smittevern 5 - Smittevernhåndbok for kommunehelsetjenesten 2002 – 2003, Folkehelsa 2001
- MSIS-rapport uke 18 2002, Nasjonalt folkehelseinstitutt, Oslo

D. TILTAK VED MISTENKT MENINGOKOKKINFEKSJON I TELEMARK

1. KOMMUNEHELSETJENESTEN

INNLEGGENDE LEGE

1. Ved mistanke om meningokokksykdom skal pasienten innlegges i sykehus

2. Dersom transporttiden er lengre enn 30 minutter og pasienten har hudblødninger eller er medtatt, skal behandling inngangsettes før transport. Penicillin gis iv. Etter flg skjema (IK-2297):
    i. Barn under 2 år: 0,3 g (500.000 IE)
    ii. Barn 2-7 år: 0,6 g
    iii. Barn over 7 år og voksne: 1,2 g

3. Før antibiotika gis skal det tas en halsprøve til dyrkning. En bomullspinne strykes mot tonsillene og sendes med pasienten på transportmedium for videreforsendelse til Telelab. Det er også anbefalt at innleggende lege tar blodprøve på eget blodkulturmedium som lege på legevakt bør ha i legekofferten.

4. Legen bør om mulig følge pasienten til nærmeste sykehus.

5. Legen varsler kommunelegen ved mistanke om meningokokk sykdom.

KOMMUNELEGEN

1. Gi husstandsmedlemmer under 15 år **behandling** med penicillin etter nasjonale retningslinjer (Smittevern 5). Utgifter til antibiotika dekkes av Folketrygden.

2. Gi nærkontakter over 2 år gruppe A/C vaksine dersom sykdommen er forårsaket av meningokokkgruppene A eller C, eller gruppe A/C/Y/W135 vaksine dersom sykdom med gruppe Y eller W135 foreligger (Smittevern 5). Utgifter til vaksine dekkes av Folketrygden.

3. Ved bekreftet tilfelle av meningokokksykdom vil Telelab varsle telefonisk. Sammen med mikrobiolog fra Telelab utarbeides en liste over de nærkontaktene som det bør tas halsprøve til dyrkning fra. Slike nærkontakter kan være husstandsmedlemmer og andre som pasienten har sovet sammen med eller oppholdt seg i samme rom som i flere timer de siste 14 dagene før sykdommen oppsto, kyssekontakter, klassekamerater (men ikke skolelever utenfor klassen), voksne ansatte og barn i samme barnehage osv.

4. Organisere prøvetaking og informasjonsmøte. Mikrobiolog fra Telelab kommer og tar halsprøvene og deltar gjerne på informasjonsmøtet for familie, andre pårørende, skolelever, evt også for foreldre som det er naturlig å gi informasjon.

5. Dersom det påvises at en eller flere av nærkontaktene har den sykdomsfremkallende meningokokkbakterien i halsen, skal disse ha rifampicin. Rifampicin utleveres kun fra Sykehusapoteket i Skien. Telelab kan være behjelpelig med å skaffe dette til veie. Dosering:
    - < 1 år: 5mg/kg x 2 i 2 dager
    - 1-12 år: 10mg/kg x 2 i 2 dager
    - > 12 år: 600mg x 2 i 2 dager

    Nærkontakter som påvises å være smittebærer må behandles anonymt for ikke å bli stigmatisert i nærmiljøet.!

    Hos personer over 16 år kan ciprofloxacin 500 mg eller ofloxacin 400 mg som engangsdose brukes dersom rifampicin er vanskelig tilgjengelig (helger, høytider).

6. Dersom det påvises sykdomsfremkallende meningokokker hos en nærkontakt skal det tas halsprøve også av denne kontaktens husstandsmedlemmmer og kyssekontakt selv om disse ikke har hatt direkte kontakt med primærtilfellet.

7. Halsprøve til bakteriologisk kontroll av smittebærere skal tas 7-10 dager etter seponering. En bomullspinne strykes over begge tonsiller og bakre halsvegg og sendes Telelab på transportmedium.

8. Kommunelegen er ansvarlig for informasjon til nærmiljøet gjennom møter, skriv og pressemeldinger. Forslag til pressemelding og publikumsbrosjyre finnes under E. Utfyllende kommentarer.

9. Det er viktig at den lokale helsetjenesten signaliserer tilgjengelighet til alle som er engstelige.

2. TILTAK SOM SETTES IGANG VED SYKEHUS

1. Ved innleggelse av pasient med mistenkt meningokokksykdom skal sykehuslegen ta spinalvæskeprøve, blodkultur og halsprøve til bakteriologisk dyrkning og mikroskopi. Prøvene sendes til Telelab som ø.hjelp. Spinalpunksjon utføres ikke ved septisk sjokk eller tegn på økt intrakranialt trykk.

2. Adekvat behandling skal gis etter avdelingens retningslinjer.

3. Sykehuset skal varsle kommunelegen på pasientens hjemsted muntlig og skriftlig.

4. Der hvor det er mest hensiktsmessig kan sykehuslegen igangsette penicillinbehandling av pasientens husstandsmedlemmer under 15 år i henhold til nasjonale retningslinjer (Smittevern 5).). Kommunelegen skal varsles om dette.

5. Dersom husstandsmedlemmer av pasienten (mor, far, søsken ol) følger med pasienten til sykehuset kan sykehuslege etter samråd med Telelab ta halsprøve av disse til miljøundersøkelse.

6. Varsling til MSIS i hht nominativ meldeplikt, gruppe B sykdom.

3. TILTAK SOM SETTES IGANG VED AS TELELAB.

1. Prøver fra pasienten (fra innleggende lege og fra sykehuset) skal analyseres som ø.hj., også om natten og i helger. Prøvene sås ut og spinalvæske mikroskoperes.

2. Oppstart av Meningokokkprosjekt Telemark skjer ved mikrobiologiske påvisning av meningokokker i pasientprøve. Påvisning av meningokokker skjer ved:

    - Påvisning av gram negative diplokokker i spinalvæskeprøve ved mikroskopi
    - Påvisning av meningokokk DNA i spinalvæske ved PCR
    - Vekst av meningokokker fra blod og/eller spinalvæske
    - Vekst av meningokokker fra hals (NB. Kun dersom pasienten har kliniske symptomer på meningokokkinfeksjon)

3. Dersom meningokokker påvises varsler Telelab vakthavende lege ved sykehusavdelingen. Dersom pasientens familie er tilstede hos pasienten anbefaler Telelab at vakthavende sykehuslege tar halsprøve av disse og sende prøvene til Telelab.

4. Telelab varsler snarest kommunelegen for planlegging av miljøundersøkelse.

5. Sammen med kommunelegen i pasientens hjemkommune er lege ved Telelab med på å definere hvem som er pasientens nærkontakter og som det skal samles inn halsprøve fra.

6. Telelab bistår i innsamling av halsprøver og står til rådighet for kommunelegen ved informasjonsmøter i samband med miljøundersøkelse.

7. Sykdomsfremkallende meningokokker påvises ved:
    a. Halsprøvene fra nærkontaktene sås ut på CV skåler og inkuberes over natten ved 37^0 C i 10% CO_2.
    b. Skålene avleses. Ved vekst av oxydase positive kolonier med utseende og egenskaper som meningokokker, spres bakteriene på blod- og brunskål og den resterende vekst på CV skålen benyttes til å ekstrahere DNA for PCR AREA etter nærmere metode på laboratoriet.
    c. Spredningsskålene inkuberes til neste dag og det settes opp forgjæring, sulfaresistens og grupping etter nærmere metode. Dersom meningokokker påvises fryses de.
    d. DNA fra nærkontaktisolatene analyseres vha PCR AREA sammen med isolatet fra pasienten. Dersom det båndmønsteret som fremkommer ved PCR AREA av bærerisolatet er identisk med isolatet fra pasienten antas de to isolatene å tilhøre samme stamme

e. I visse situasjoner kan ulikheter i sulfafølsomhet mellom pasientstammen og bærerstammen bli brukt til å utelukke identitet.

8. Om det påvises sykdomsfremkallende meningokokker i halsen til en eller flere av nærkontaktene, skal mikrobiolog ved Telelab varsle kommunelegen umiddelbart slik at rifampicin profylakse (evt ciprofloxacin) kan startes opp.

9. Dersom den sykdomsfremkallende meningokokkbakterien påvises hos en eller flere nærkontakter, skal husstandsmedlemmene til disse bærerene og evt kyssekontakter tilbys halsprøve.

10. Telelab sender skriftlig rapport om resultatet av undersøkelsen til kommunelegen med kopi til sykehusavdeling.

E. UTFYLLENDE KOMMENTARER

1. INFORMASJON TIL NÆRMILJØET

A. BARNEHAGER – SKOLER

I barnehagemiljø og skolemiljø kan det være greit å sende brev med hjem til foreldrene. Skolen/barnehagen ordner med dette, men teksten på informasjonen til foreldrene bør godkjennes av kommunelegen. Eks.: "Vi har hatt et tilfelle av meningokokksykdom/ smittsom hjernehinnebetennelse ved skolen i ..... Helsetjenesten har gitt råd til skolen og iverksatt de tiltak som er nødvendige i tråd med gjeldende faglige retningslinjer. Familiemedlemmer som bor og spiser under samme tak som pasienten og som er under 15 år, skal få penicillinbehandling. Medelever til den syke skal være fritatt for kroppsøving i 1 uke. Skolen går ellers som normalt. Underskrift . Rektor/ansvarlig førskolelærer i barnehage etc."

B. PRESSEMELDING

Det er ingen grunn til å kontakte presse/radio i forbindelse med utbrudd av meningokokksykdom. På grunn av den store oppmerksomhet som utbrudd av denne sykdommen har fått i våre media synes det rett å være forberedt på at en kan bli kontaktet. Det er vanskelig å avvise journalister med bakgrunn i dårlig tid etc. (dårlig tid blir det alltid i forbindelse med utbrudd av meningokokksykdom). Vær derfor forberedt. Ha klart for deg at en nøktern pressemelding er mye bedre enn at journalisten "komponerer" noe ut fra spinkle opplysninger (rykter). Bruk pressemeldingen til å gi saklig informasjon.
Eks. på pressemelding:
"Vi har hatt et tilfelle av meningokokksykdom (hjernehinnebetennelse) i .... Pasienten er innlagt på sykehus. Gjeldende faglige retningslinjer i forbindelse med tilfeller av meningokokksykdom er satt i verk av helsetjenesten. Helsetjenesten i kommunen ber publikum kontakte legekontoret/legevakta dersom en har spørsmål i forbindelse med meningokokksykdommen/hjernehinnebetennelsen. Kontakt alltid legetjenesten ved uklare febersykdommer."

C. PUBLIKUMSBROSJYRE

I hver kommune bør det (på forhånd!) lages ei lita brosjyre som legges ut på legekontorenes venteværelser, helsestasjonene etc. når et tilfelle av meningokokksykdom har opptrådt.
Forslag til tekst i en brosjyre:
”Hver vinter/vår opplever vi tilfeller av meningokokksykdom (ofte kalt smittsom hjernehinnebetennelse). Folk er naturlig nok redde for å bli smitta av denne sykdommen. Sykdommen er dramatisk og skremmende, men angsten for sykdom/smitte blant folk blir lett et stort tilleggsproblem. Kunnskap om sykdommen og informasjon om forebyggende tiltak er viktige å kjenne til.

HVA ER MENIGOKOKKSYKDOM?
Sykdommen skyldes ofte en bakterie - meningokokk - som lager betennelse i hjernehinnene og/eller blodet. Pasienten får som regel høy feber, hodepine og kvalme. Stivhet i rygg og nakke kan også være vanlige symptomer. Pasienten blir også ofte uklar og virker mer syk enn det en vanligvis opplever ved influensalignende sykdom. Et rødt småprikkete utslett (små hudblødninger) er en svært viktig observasjon! De som er mest utsatt for denne type for meningokokksykdom er barn og ungdom.

HVORDAN SMITTER SYKDOMMEN?
Meningokokker (smittestoffet) finner en i halsen hos ca. 25 % av alle i en normalbefolkning. En regner med at barn i regelen blir smittet av en frisk voksen bærer. Hvorfor noen av disse bakteriene plutselig blir "sinte" og går til angrep, og hvem de går til angrep på, vet vi ikke nok om til å kunne sette inn mottiltak. Smittemåten er dråper fra nese og munn fra en bærer til nese og munn til den som blir syk. Meningokokkene kan ikke overleve særlig lenge utenfor kroppen. Meningokokksykdom er altså en etter måten lite smittsom sykdom. Langt mindre smittsom enn f.eks. de vanlige barnesykdommene.

TILTAK FOR Å HINDRE NYE TILFELLER:
Helsemyndighetene har kommet med nasjonale retningslinjer når det gjelder generelle forebyggende tiltak. Søsken, familie eller andre som bor sammen med pasienten og som er under 15 år, får penicillin og skal holde seg borte fra skole/barnehage i en uke. "Sosialkontakter", klassekamerater og barn i samme barnehagegruppe som den syke, blir tilrådd å unngå fysisk aktivitet i en uke. Dette er et tiltak for å hindre utbrudd av sykdommen hos eventuelt andre som kan være smitta i denne gruppa. Foreldrene bør være raske til å ta kontakt med lege/legevakt dersom en får mistanke om meningokokksykdom. Sykdommen kan utvikle seg raskt, og tidlig behandling er ofte avgjørende for hvorledes det går med pasienten.
Hvis du har spørsmål - ta gjerne kontakt med helsesøster/legekontoret, eventuelt legevakta utenom den vanlige kontortida.
Et lite råd til slutt:
Pass alltid på å ha et termometer som er i orden i huset. Febermåling bør gjøres før en kontakter lege dersom det er mulig. Kontakte helsetjenesten dersom du har spørsmål.”

2. FORHOLDET TIL NASJONALE RETNINGSLINJER

Meningokokkprosjekt Telemark er et tillegg til de nasjonale retningslinjer. Nasjonale anbefalinger slik de fremkommer i Smittevern 5 og IK-2297 skal derfor følges.

Hovedskillet mellom de nasjonale tiltak og Meningokokkprosjekt Telemark er at vi i Telemark i tillegg forsøker å fjerne den sykdomsfremkallende meningokokken fra miljøet. Dette kan ikke oppnås ved penicillinbehandling, for penicillin dreper ikke meningokokker som befinner seg på halsslimhinnen. Slik sanering kan bare skje gjennom kjemoprofylakse. I neste alle andre land enn Norge benyttes kjemoprofylakse, men da til alle nærkontakter. Vi i Telemark ønsker å begrense bruken av kjemoprofylakse bare til de få som virkelig har den sykdomsfremkallende meningokokken i halsen.

3. VITENSKAPELIGE PUBLIKASJONER OM MENINGOKOKKPROSJEKT TELEMARK.

Det er publisert en rekke artikler om Meningokokkprosjekt Telemark og det er per februar 2003 i gang et arbeide med å bearbeide alle resultatene fra de første 15 årene. Opplegget har ført til diskusjoner men har også gitt som resultat at de nyere norske retningslinjene (Smittevern 5) har blitt endret siden de opprinnelige retningslinjene fra 1977, slik at de nå er nærmere opplegget for Meningokokkprosjekt Telemark. Det åpnes nå for å bruke kjemoprofylakse (ved flere en ett tilfelle) og også bruk av miljøundersøkelser.

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