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Control of epidemic meningococcal disease. WHO practical guidelines. 2nd edition

World Health Organization
Emerging and other Communicable Diseases,
Surveillance and Control

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PREFACE

The present Guidelines for the control of epidemic meningococcal disease are a revised and updated version of the Guidelines published in 1995 (see page ix) which was acknowledged by the health care personnel world-wide. The present edition results from an initiative of the WHO Regional Office for the Eastern Mediterranean (EMRO) and the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC), WHO Headquarters and was prepared by an editorial working group in a meeting held in Alexandria, EMRO in January 1997. The revision reflects the increasing concern for cerebrospinal meningitis in the Region and elsewhere.

The 1995 edition of the Guidelines reflected primarily the pattern of epidemic meningitis in the sub-Saharan "meningitis belt" area of Africa. This revised edition retains the emphasis on rapid detection and control of epidemic meningococcal disease, but also reflects the epidemiological situation of this disease as well as the factors affecting its spread in countries of the Eastern Mediterranean Region.

The revision took into account the experience gained in case management, prevention and control of meningococcal disease in the Eastern Mediterranean Region. Although the Guidelines follow the format of the first edition they have been expanded to include viral meningitis, a comprehensive case definition, and indicators for early warning of a possible meningococcal epidemic. The list of drugs recommended for treatment and chemoprophylaxis has been adapted to regional conditions.

These Guidelines provide comprehensive information on epidemiology and standard techniques for diagnosis, treatment, prevention and control of meningococcal disease both in its epidemic and endemic forms. The editorial group hopes that they meet the needs of physicians, laboratory workers and health care administrators.

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The views expressed in the Guidelines are solely the responsibility of the WHO Working Group.*

Many practical and logistical advice presented in the annexes are inspired by the handbook of "**Médecins sans Frontières**" on the management of epidemic meningitis.

The development of the Guidelines was sponsored jointly by **WHO** and the **Fondation Marcel Mérioux** and co-sponsored by the **French League for the Prevention of Infectious Diseases**.

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INTRODUCTION

Meningococcal disease is a contagious disease caused by the meningococcus (*Neisseria meningitidis*), a Gram-negative bacterium. There are two clinical forms of meningococcal disease. **Meningococcal meningitis** is the more common entity, especially during epidemics; outcome is good if appropriately treated. In contrast, **meningococcal septicaemia**, in which bacteria are found in the blood stream, is less common but highly fatal, even when actively treated. Cases in which both meningitis and septicaemia occur simultaneously are usually regarded as cases of meningitis.

Meningococcal meningitis, commonly designated as cerebrospinal meningitis, is the only form of bacterial meningitis which causes epidemics. Epidemics can occur in any part of the world. However, the largest epidemics occur mainly in the semi-arid areas of sub-Saharan Africa, designated the African “meningitis belt”.

Apart from epidemics, meningococcal meningitis occurs sporadically throughout the world, with seasonal variations, and accounts for a variable proportion of *endemic bacterial meningitis*. In non-epidemic conditions, only laboratory investigation of cerebrospinal fluid (CSF), obtained by lumbar puncture, can reliably differentiate meningococcal meningitis from other types of bacterial meningitis.

The purposes of these practical guidelines are to help health personnel and health authorities, at any level:

- to update current knowledge about meningococcal disease;
- to detect and control epidemics of meningococcal disease as early as possible, especially in areas such as developing countries where epidemic meningitis raises particular difficulties;
- to strengthen the capacity for emergency response to epidemics of meningococcal disease.

EPIDEMIOLOGY OF DISEASE DUE TO *NEISSERIA MENINGITIDIS*

AGENT - *Neisseria meningitidis*

- Gram-negative diplococcus
- capsular polysaccharide antigens differentiate serogroups (A, B, C, X, Y, Z, 29-E, and W135)
- serogroups A, B, and C associated with epidemics
- subtyping identified certain strains (clones) associated with increased virulence and epidemic potential (e.g. serogroup A, III-1; serogroup B, ET-5)

RESERVOIR

- humans
- asymptomatic carriage in nasopharynx common

MODE OF SPREAD

- person-to-person by direct contact with respiratory droplets of infected people
- most cases acquired through exposure to asymptomatic carriers, relatively few through direct contact with patients with meningococcal disease

HOST FACTORS

- risk of invasive disease due to *N. meningitidis* higher in children, decreases with age
- all humans susceptible, but disease risk higher in persons with terminal complement deficiency, splenectomy

INCUBATION PERIOD

- 1-10 days, usually <4 days
-

1. MAGNITUDE OF THE PROBLEM

Neisseria meningitidis was first identified as the causative agent of bacterial meningitis by Weichselbaum in 1887. However, clinical meningococcal disease was described by Vieusseux in 1805 during an outbreak in the vicinity of Geneva, Switzerland. During the 20th century, major outbreaks were noted during World War I and World War II. On the African continent epidemic meningitis has been known to occur for a long time. It was reported from the West coast of Africa by G. William in 1909 and has occurred from then onwards. In the Sudan, cerebrospinal meningitis has been present from time immemorial. However, the disease probably did not appear in the Northern savanna of Africa before the 1880s.

Since World War II, epidemic meningitis caused by group A meningococcus has been infrequent in developed countries with a temperate climate, whereas meningococcal disease in its epidemic form has periodically continued to devastate sub-Saharan territories of Africa. At least 340,000 cases with 53,000 deaths occurred in the 10-year period 1951-1960 in the countries of this region (estimated total population of 35 million).

1.1 REVIEW OF EPIDEMICS SINCE THE 1970s

The word "epidemic", used in the context of meningococcal disease, may refer to different events throughout the world. In comparison to explosive epidemics occurring in the African meningitis belt, European epidemics and recent epidemics in the Americas are rather moderate, since their highest incidence is usually lower than the endemic incidence in African countries. Thus, epidemic conditions can be defined, for a given country, as an unacceptable incidence rate requiring emergency control measures.

Geographical distribution

While the largest epidemics of meningococcal disease affect mainly sub-Saharan African countries within the meningitis belt, epidemic meningococcal disease has become a worldwide problem and can affect any country regardless of climate (Figure 1, Table 1).

Figure 1. Major epidemics of meningococcal meningitis in 1971-1997

Map 2. Major outbreaks of meningococcal meningitis, 1971-1997
Carte 2. Principales épidémies de méningite à méningocoques, 1971-1997

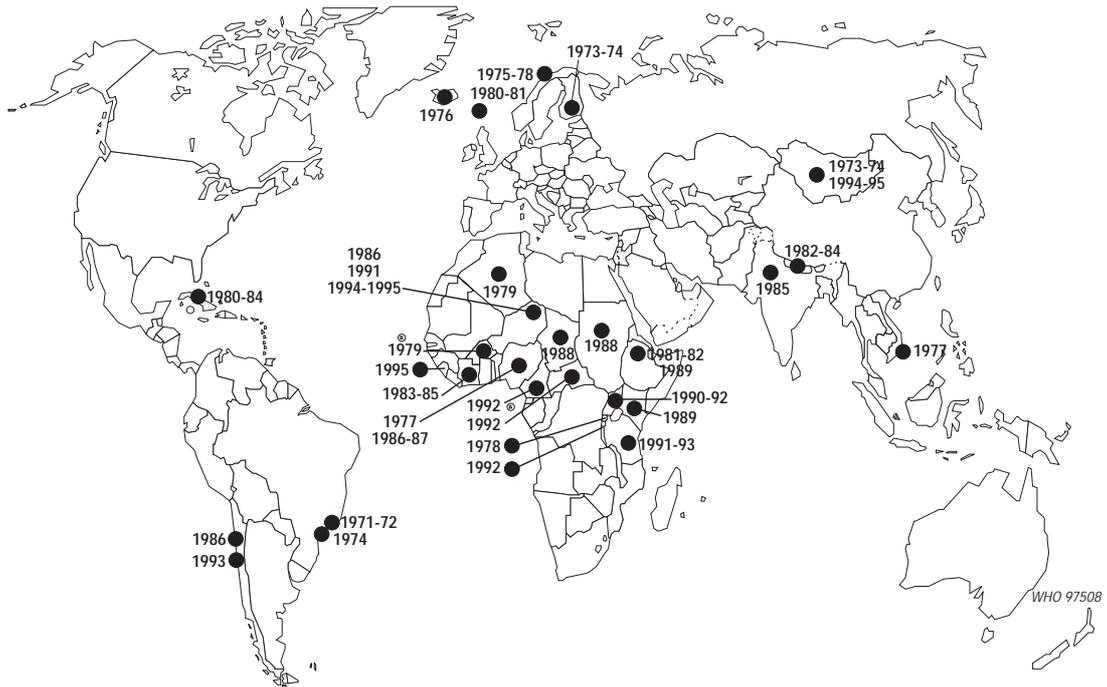


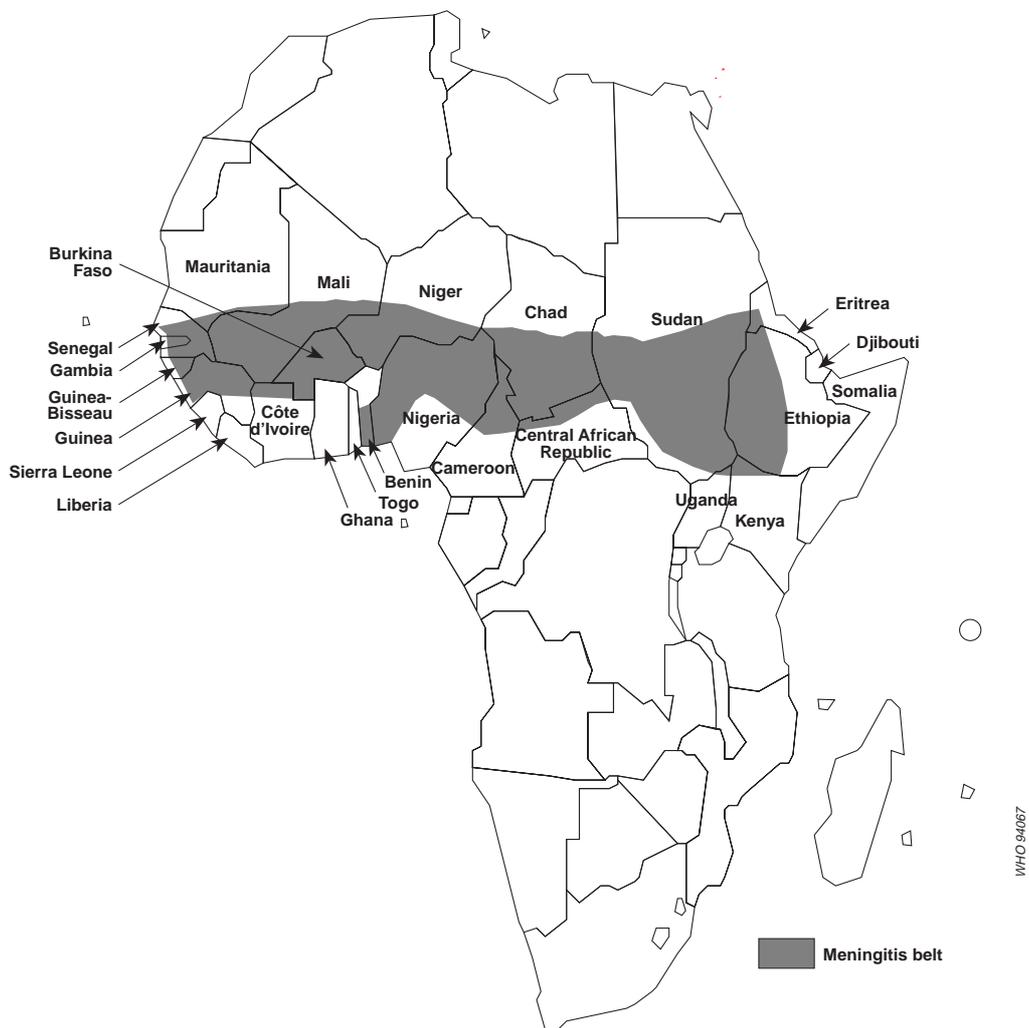
Table 1. Epidemics of meningococcal disease, 1970-1996

COUNTRY AREA	YEAR	NO. OF CASES	ATTACK RATE per 100,000 pop.	CFR	SERO-GROUP
EUROPE					
Finland	1973-74*	1,300	14.6*	4.3	A
Norway (North)	1975*-78	404	23.9*	13.7	B
Iceland	1976	86	37.7	10.3	B
Faroe Islands	1980-81*	74	95.0*	NA	B
SOUTH AND CENTRAL AMERICA					
Chile, Iquique	1986	46	31.2	NA	B
Brazil, Sao Paulo	1971-72	2,005	11	NA	C
Brazil, Sao Paulo	1974	30,555	370.0	NA	A
Cuba	1980-84*	NA	14.4*	14.9	B
ASIA					
Mongolia	1973-74	NA	141.0 -194.0*	11.8	A
Viet Nam, Ho Chi Minh	1977	1,015	>20.0	27.4	C
Nepal, Kathmandu	1983	875	103.0	10.9	A
AFRICA					
Nigeria, Zaria	1977	1,257	360.0	8.3	A
Rwanda, Ruhengeri,	1978	1,182	223.0	4.8	A
Kigombe	1978	248	729.0	NA	A
Burkina Faso,					
Diapaga	1979	539	517.0	10.2	C
Côte d'Ivoire					
Boundiali	1983	414	207.0	NA	A
Ferkessedougou	1985	251	217.0	8.5	A
Korhogo	1985	367	92.0	8.5	A
Chad, N'Djamena	1988	4,542	826.0	9.5	A
Sudan	1988	32,016	133.0	NA	A
Ethiopia	1989	41,139	83.0	3.9	A
Addis Ababa	1989	7,000	420.0	NA	A
Kenya, Nairobi	1989	3,800	250.0	9.4	A
Burundi, Ruyigi	1992	1,615	608.0	8.0	A
Burkina Faso	1996	42,129		10.0	A
	1997	22,305		11.3	A
Mali	1996	7,254		11.5	A
	1997	11,228		10,1	A
Niger	1995	26,738			A
	1996	16,145		9.9	A
Nigeria	1996	108,568		11.2	A

* Peak attack rate per 100,000. CFR=Case-fatality rate. NA = Not available.

The African meningitis belt (Figure 2), initially characterized by Lapeyssonnie and then revised, extends from Ethiopia in the East, to Senegal in the West, mainly within the range of 300 mm to 1,100 mm annual rainfall. In this area sporadic infections occur in seasonal annual cycles while large-scale epidemics occur at greater intervals with irregular patterns. The countries within the meningitis belt are Benin, Burkina Faso, Northern Cameroon, Chad, Ethiopia, The Gambia, Ghana, Mali, Niger, Northern Nigeria, Senegal and Sudan. In the meningitis belt countries, the estimated incidence for the 20-year period 1970-1992 was about 800,000 cases.

Figure 2. African meningitis belt



The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate border lines for which there may not yet be full agreement.

In the 1960s, meningococcal disease constituted a permanent public health problem in some countries of the tropical zone, particularly those located in the African meningitis belt. However, it was considered to be no longer a serious problem in most European and North American countries.

Since 1970, epidemics have occurred all over the world. Meningococcal disease increased in a number of countries of the Americas, Asia and Europe, with a pattern characterized by recurrent epidemics and persistent sporadic disease. A significant increase in incidence was observed in Italy, Portugal, Spain and Yugoslavia in 1970-1971, in Belgium (1971-1972), in Argentina (1974), United Kingdom (1974-1975) and France (1973 and 1978). Outbreaks of meningococcal meningitis were reported in Finland, Mongolia and in former USSR (1973-1974), in Norway (from 1975 throughout the 1980s), in Algeria and Chile (1979), in Viet Nam and Rwanda (1977-1978). Recurrent outbreaks have been reported in Brazil since 1971.

In the 1980s, an epidemic wave of meningococcal disease spread over vast territories in Asia (India, Nepal) and in Africa (Figure 1). Approximately 1,500 cases of meningococcal meningitis occurred in the Kathmandu Valley, Nepal, in 1982-1984 with an annual attack rate of 103 cases per 100,000 population. In 1985, New Delhi experienced an outbreak after a lapse of almost 20 years. A total of 6,133 cases were reported. The overall case-fatality rate was 13%, the highest occurring in children under one year of age (25.5%). An epidemic of group B meningococcal disease occurred in Cuba in 1982-1984 and in Chile in 1986 and 1993. There was a substantial increase in reported meningococcal disease in Africa in 1996. The total number of meningitis cases reported during the period January-October 1996 was 188,341 of which nearly 20,000 were fatal. These figures are strongly influenced by the outbreaks which affected Burkina Faso, Mali, Niger and Nigeria.

Extension outside the traditional meningitis belt in Africa

From the early 1980s, epidemics of meningococcal disease occurred throughout the meningitis belt in Benin, Burkina Faso, Chad, The Gambia, Ghana, Mali, Niger, Nigeria, Senegal and Togo, culminating in severe epidemics in Ethiopia and Sudan in 1987-1989 (Figure 1). More than 30,000 cases were reported in Sudan in 1988, the year of peak incidence, and over 40,000 cases in Ethiopia in 1989.

The epidemic wave then spread in West Africa, including Niger (more than 25,000 cases notified in 1995, more than 16,000 cases in 1996), Northern Nigeria (more than 105,000 reported cases in 1996), Burkina Faso (more than 40,000 reported cases in 1996, more than 20,000 in 1997) and Mali (more than 7,000 reported cases in 1996, more than 10,000 in 1997).

However, in the same period, outbreaks of meningococcal disease reached other African countries. The epidemics seen towards the end of the 1980s and the early 1990s in Burundi, Central African Republic, Kenya, Rwanda, Uganda, United Republic of Tanzania, and Zambia are examples of the spread of the disease outside its usual boundaries. If this is a truly new feature of the epidemiology of meningococcal disease, it could be due to climate change with subsequent extension of drought areas, and/or increased mobility of the population whether by voluntary travel, through warfare or refugee movements. The outbreaks may also reflect the introduction of a new meningococcal strain into susceptible populations.

Epidemiology of meningitis in countries in the Eastern Mediterranean Region

The situation of meningococcal meningitis in the Eastern Mediterranean Region varies considerably from one country to the other (Table 2). Apart from Sudan which falls within the meningitis belt, the disease is endemic in many countries, particularly North African countries, e.g. Egypt, Morocco and Tunisia. Following the return of pilgrims in August 1987 many countries in the Region faced an unusual spread of meningococcal infection. In Sudan and Yemen, the 1987 introduction developed into epidemic spread in the meningitis season of 1988. This widespread introduction caused limited outbreaks in some other countries of the Region. Since the early 1990s some countries particularly Egypt, Saudi Arabia and Sudan, have been practising preventive vaccination, mainly directed to high-risk groups. Since then, these countries have not faced any unusual occurrence of meningococcal meningitis.

Periodicity and seasonality of the epidemics

Most countries within the meningitis belt, such as Burkina Faso, Chad, Ghana, Mali and Sudan, have suffered large outbreaks every 8-12 years during the past 50 years (Figure 3). Since the 1980s, these cycles have not been observed, particularly in regions with extensive communication and mixing of populations. In such regions, the intervals between epidemics have become shorter and more irregular.

In numerous other countries, no evident periodicity has been observed. Nevertheless, three outbreaks have occurred in Norway during the 20th century, approximately every 30-40 years (Figure 4). Epidemics of meningococcal disease occur in the same period of the year as the seasonal upsurge observed in non-epidemic conditions: in winter-spring in temperate zones; in the dry season in tropical countries.

Epidemic patterns

Major African epidemics expand rapidly, reaching their peak within weeks and, in the absence of vaccination, can last for several months (Figure 5). There is often a characteristic pattern of meningococcal disease: a local outbreak

Table 2. Cases of meningococcal disease reported in the Eastern Mediterranean Region, 1986-1996

Country	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
Afghanistan	331	218	388	426							
Bahrain	34	27	5	4	4	0	10	1	2	0	
Cyprus	3	2	5	0	2	0	0	1	0	4	5
Djibouti		64	68	22	31	5					
Egypt	824	998	3,327	3,894	2,986	1,646	1,165	896	800	671	
Iran (Islamic Rep. of)	676	565	711	709	500	546	281	322	306	156	337
Iraq	1,415	1,010	1,814	2,559		5,792	4,534	3,923	3,427	3,138	131
Jordan	47	71	78	110	58	29	39	45	35	44	27
Kuwait	6	26	17	21	15	4	6	7	6	9	
Lebanon								5			
Libyan Arab Jamahiriya	4	6	5	14	28	15	25	68			
Morocco	629	720	1,348	1,802	826	529	226	405	462	341	
Oman	7	126	41	33		27	7	15			
Pakistan	6,048	5,927	5,918	4,481	5,309	5,143	5,505			6,621	
Palestinian Self-Rule Areas	0	1	0	12	11	2	4	2			
Qatar	2	13	1	0	1	0	1				
Saudi Arabia	59	1,841	305	92	101	74	88	52	30	58	
Somalia	16		22	106							
Sudan	452	443	32,016	7,051	1,326	737	716	1,147	397	372	301
Syrian Arab Rep.	393	506	510	614	478	232	443	285	371	404	
Tunisia	992	1,557	699	580	459	430	451	422	325	278	
United Arab Emirates	73	248	108	45	73	62	36	47			
Yemen	682		8,211	4,264			646	433			
Total	12,642	14,305	55,593	26,585	12,199	15,299	14,191	8,076	6,247	12,151	1,821

in one city of a rural region may presage a more widespread and intense epidemic. A large widespread epidemic can follow the local outbreak during the second year of the cycle and incidence rates remain elevated during the following 1-2 years with successive seasonal outbreaks separated by remissions. Such a profile, observed at the provincial or national level, may result from the

Figure 3. Annual number of cases of meningitis, Burkina Faso, 1940-1993

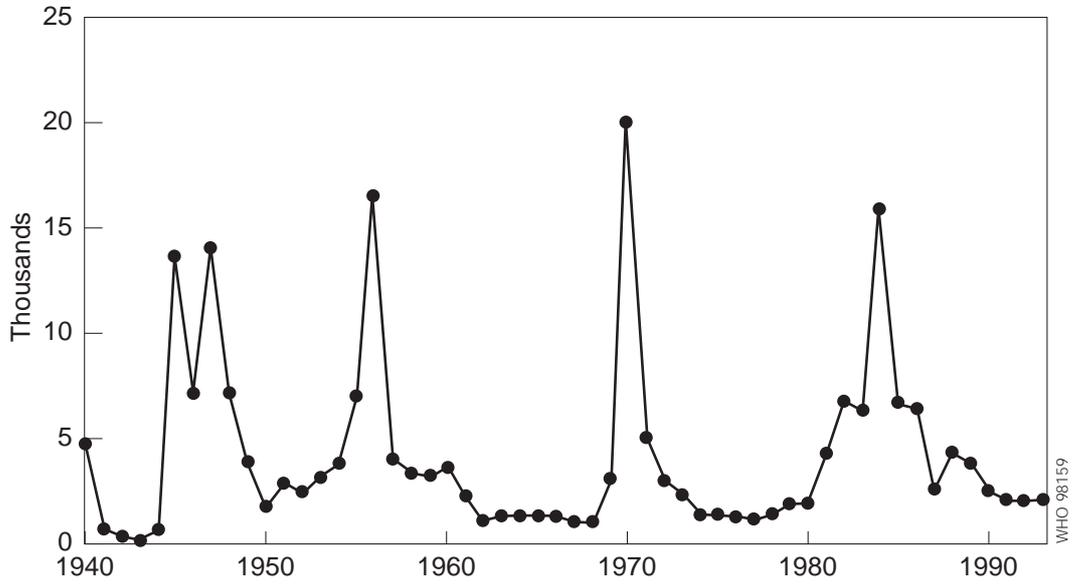


Figure 4. Officially recorded cases and deaths of meningococcal disease, Norway, 1935-1993

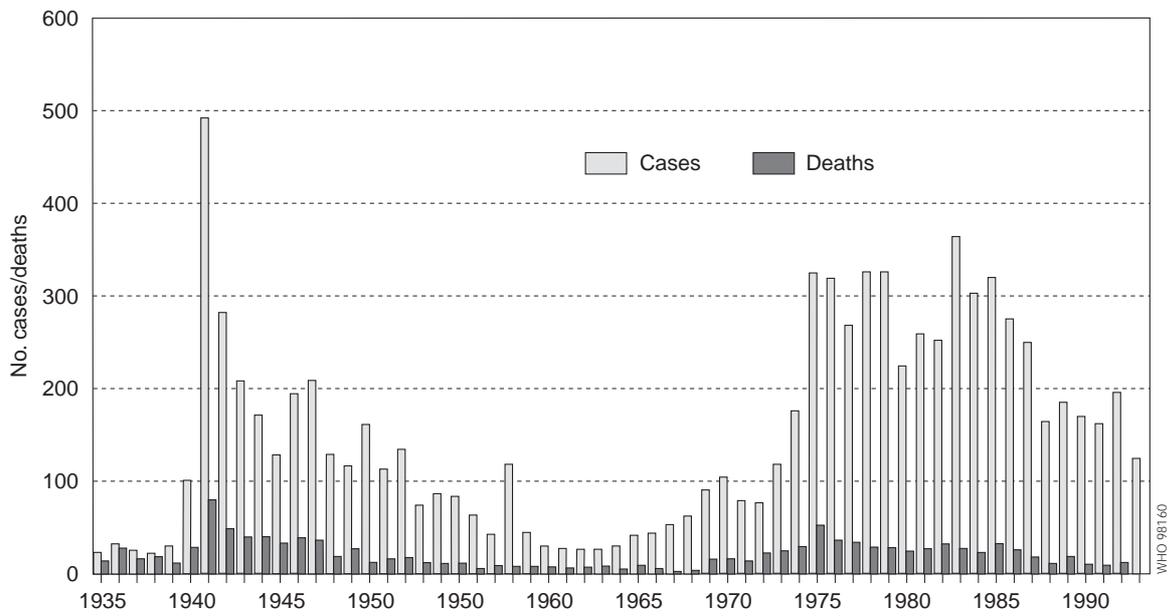


Figure 5. Monthly incidence of meningococcal meningitis, Burkina Faso

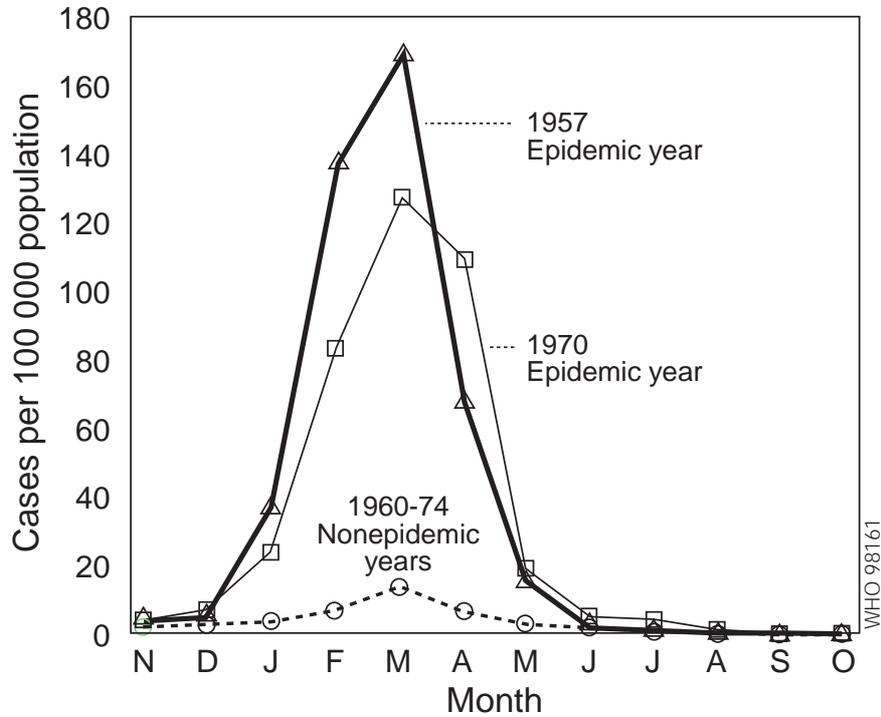
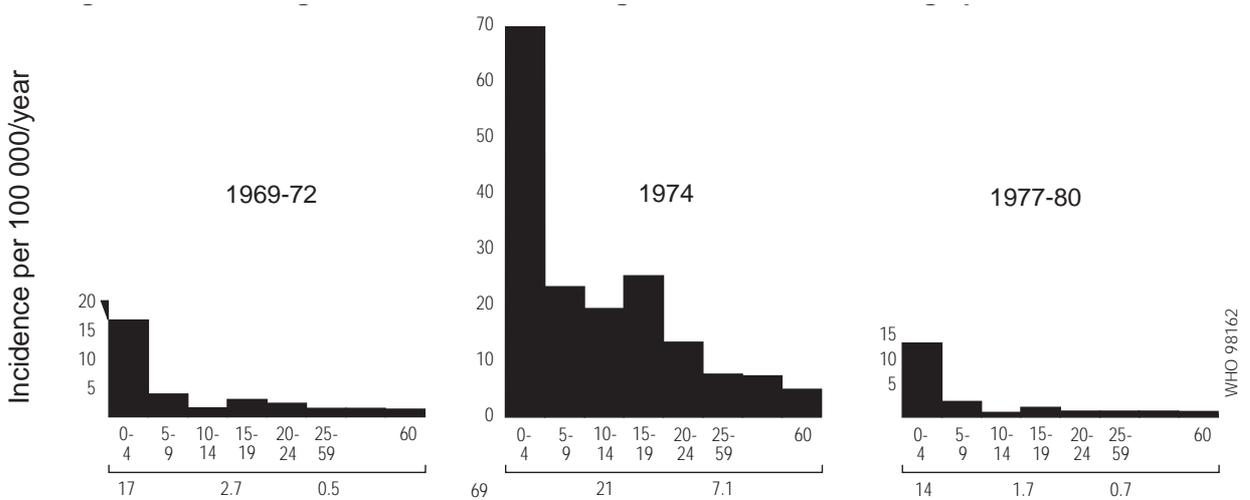


Figure 6. Shift in age distribution of meningococcal disease during epidemics in Finland



combination of a number of local outbreaks, spreading from place to place throughout the country, in particular along the transport axes. Many epidemics last for 6 months or more in warm countries without marked seasons.

Most epidemics result in a shift in the age distribution of cases. In sporadic conditions, the highest rates occur in young children. During epidemics there may be a broader peak in incidence, with older children, teenagers and young adults also affected. A wide age distribution appears to be a characteristic of meningococcal epidemics (Figure 6). In a recent epidemic in Nairobi, Kenya, the average age of patients was 18 years and the highest age-specific attack rate occurred in those aged 20-29 years.

The attack rate of epidemic meningococcal disease is usually in the range of 10 to 1,000 per 100,000. In major African epidemics, the nationwide attack rate ranges from 100 to 800 per 100,000 population (Table 1), but the local attack rate in affected villages or cities may exceed 1,000 cases per 100,000 persons. Conversely, during the epidemics which occurred in the 1970s in Finland and Norway the annual incidence was only 15-25 per 100,000 population. The ratio between epidemic and mean endemic incidence rates is generally higher in developing countries than in developed.

1.2 RISK FACTORS FOR EPIDEMICS

Risk factors for invasive disease and for outbreaks are not completely understood. A combination of conditions (environment, host and organism) are necessary for an epidemic to occur. These include: immunological susceptibility of the population (perhaps due to loss of herd immunity to the prevalent strain), special climatic conditions (dry season, dust storm), low socio-economic status and transmission of a virulent strain. Acute respiratory tract infections may also contribute to the development of meningococcal disease epidemics.

Serogroups, serotypes of the meningococcus

The risk of epidemic meningococcal disease differs between serogroups. Serogroups A, B and C can cause outbreaks. Other serogroups (groups D, E29, X, W135, Y and Z) have so far not been associated with outbreaks.

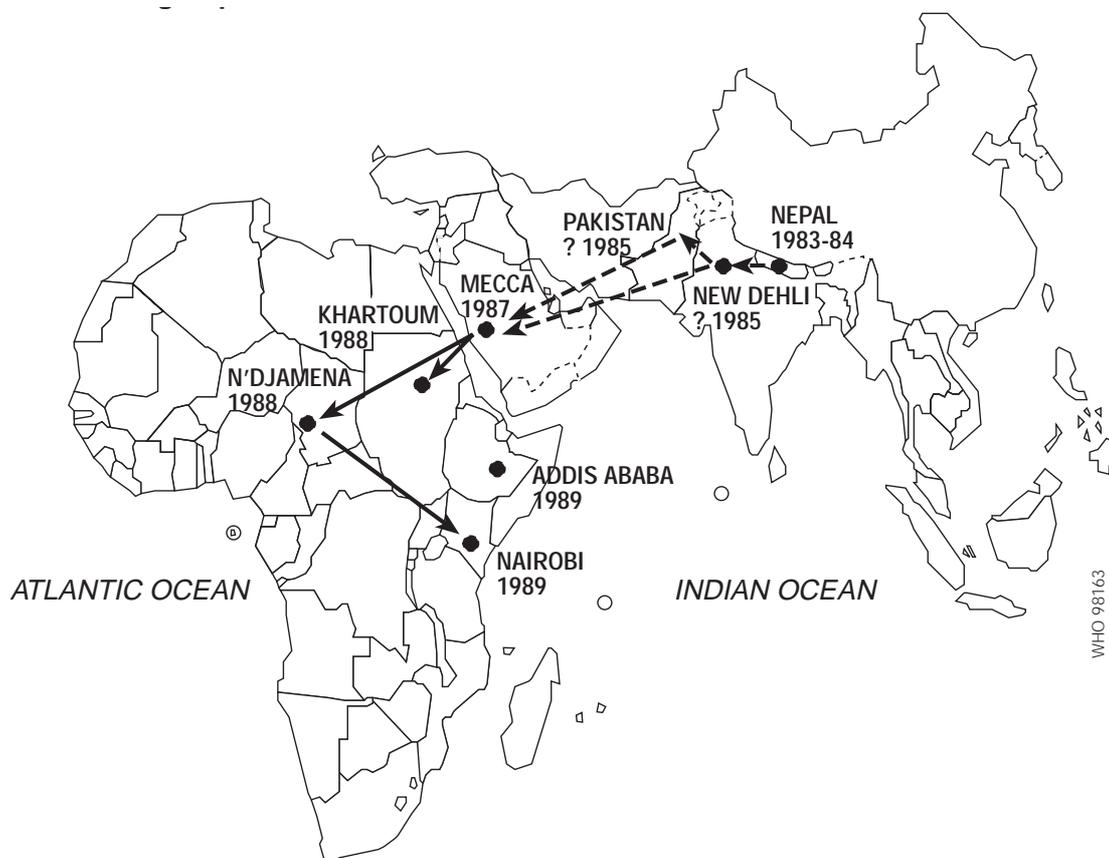
Serogroup A meningococcus has historically been the main cause of epidemic meningococcal disease and still dominates in Africa during both endemic and epidemic periods. Elsewhere the major and most explosive epidemics of meningococcal meningitis have also been almost exclusively associated with serogroup A, as in Brazil (1974), North America and Europe prior to the mid-1950s, Finland (1974), Nepal (1983-1985), Rwanda (1978), Saudi Arabia (1987), Sudan and Ethiopia (1988-1989), Kenya, Uganda and Burundi (1989-1992), United Republic of Tanzania, or in West Africa especially in Burkina Faso and Mali (1995-1997), Niger and Nigeria.

Serogroup B, generally associated with sporadic disease, may cause some upsurges or outbreaks as in Norway (mid-1970s), Cuba (1982-1984), Chile (1986, 1993), Brazil (1989) and Oregon, USA (1994).

Serogroup C, like serogroup A, has been responsible for large outbreaks in Brazil (1972-1974), Viet Nam (1977-1978), Northern Nigeria (1975), Burkina Faso and Mali (1979).

Certain strains of meningococci may be more virulent and more likely than others to cause outbreaks and/or epidemics. Recent technological developments have made it possible to trace the spread of epidemic meningococcal strains using subtyping by electrophoretic isoenzyme typing. Figure 7 shows the spread of an epidemic strain of *N. meningitidis* serogroup A, designated as epidemic clonal group III-1. This particular strain was involved in epidemics in Burkina Faso, Burundi, Chad, Ethiopia, Guinea, Kenya, Niger, Nigeria, Nepal, Saudi Arabia, Sudan and United Republic of Tanzania.

**Figure 7. Intercontinental spread of serogroup A
Neisseria meningitidis clonal group III-1**



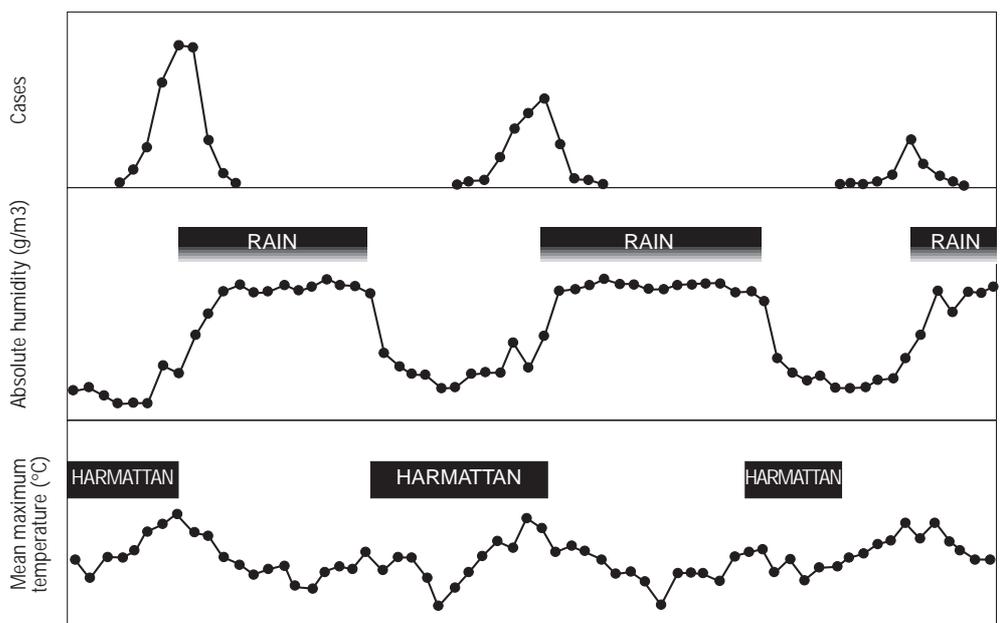
Nasopharyngeal carriage

Neither the meningococcal carriage rate nor the serogroup specific carriage rate can be used to predict epidemics. Carriage rates, which can range between 1% and 50%, vary with age, socioeconomic status, and with the predominant strain circulating in the area, but do not seem to vary with season or herd immunity. Although an increasing carrier rate could increase the risk of illness occurring in nonimmune persons, there is no constant or close relationship between the carrier rate and the incidence of disease. In the course of serogroup A meningococcal epidemics, carriage rates often increase. However, surveillance for nasopharyngeal carriage is not recommended as a useful public health tool.

Waning immunity

Humoral immunity is an essential factor in the prevention of meningococcal disease. Natural infection (disease or nasopharyngeal carriage) protects against disease caused by the same serogroup. The risk of acquiring meningococcal disease decreases with age. Waning herd immunity to a particular strain in a population may be necessary for an outbreak to occur and loss of herd immunity against group A meningococci may contribute to the regularity of epidemic cycles in sub-Saharan Africa. Development of herd immunity due to widespread carriage should limit meningococcal transmission, and may help to end an epidemic wave.

Figure 8. Relation of seasonal climatic factors to hospital admissions for meningococcal disease in Zaria, Nigeria, during 1977-1979



Environmental factors

Climatic factors play an important role in the seasonal upsurge of meningococcal disease. In sub-Saharan Africa the spread of infection may be enhanced by drought and dust storm; meningococcal epidemics generally stop with the onset of the rains (Figure 8). Low absolute humidity and dust may enhance meningococcal invasion by damaging the mucosal barrier directly or by inhibiting mucosal immune defences. Unfavourable climatic conditions may lead to the crowding of people in poorly ventilated dwellings, where spread of virulent meningococci is optimal.

Demographic factors

Travel and migration facilitate the circulation of virulent strains inside a country or from country to country. The gathering of susceptible people is an important risk factor for outbreaks, as exemplified in military communities where many outbreaks have occurred, particularly among new recruits. Large population movements, such as a pilgrimage, play a major role in the spread of infection and disease. The outbreak which occurred in Mecca in 1987, at the end of the pilgrimage period, caused more cases among pilgrims than among the Saudi population. In many countries, returning pilgrims caused the occurrence of cases of meningococcal meningitis in their immediate communities. In some countries the occurrence of epidemics (Chad 1988, Morocco 1989, Sudan 1988) may have been provoked by the introduction of a virulent strain of serogroup A meningococcus imported by returning pilgrims. Other large population displacements, e.g. those of refugees, may pose similar risks.

Socioeconomic factors

As shown in several outbreaks, poor living conditions and overcrowded housing are linked with a higher incidence of meningococcal disease.

Concurrent infections

Upper respiratory tract infections may contribute to some meningococcal outbreaks. The association between acute respiratory infections and meningococcal disease has been found both in temperate and tropical climates. During a group A meningococcal epidemic in Chad in 1988, patients with meningococcal meningitis were about 23 times more likely than matched control patients to have nasopharyngeal shedding of respiratory pathogens, including *Mycoplasma hominis*, adenoviruses, parainfluenza viruses, rhinoviruses and respiratory syncytial virus.

1.3 MENINGOCOCCAL MENINGITIS AS PART OF BACTERIAL MENINGITIS

Excluding epidemics, at least 1.2 million cases of bacterial meningitis are estimated to occur each year and 135,000 of these patients die. Approximately 500,000 of the cases and 50,000 deaths are due to the meningococcus. In non-epidemic conditions, meningococci cause 10-40% of cases of purulent meningitis.

Endemic meningococcal disease

In most countries of the world, endemic attack rates of meningococcal disease range from <1 to 5 per 100,000 population. In the sub-Saharan arid area, the incidence rate between epidemics varies greatly and may be over 20 per 100,000. The annual incidence may vary substantially from year to year in the same country, in the absence of epidemics.

Seasonal factors also contribute to the epidemiology of endemic meningococcal disease, in particular in areas with marked seasons. In the northern hemisphere, including subtropical countries, a seasonal upsurge in meningococcal disease occurs in winter and spring, beginning in December-January and culminating in March-April. Between two-thirds and fourth-fifths of cases occur in the first six months of the year. The peak resembles that of disease due to many bacteria and viruses which are spread by the respiratory route.

During non-epidemic conditions, meningococcal disease is most common in children under school age: 50-60% of cases occur in children 3 months to 5 years old. However, cases are also seen in teenagers and young adults under 25-30 years of age. In countries within the meningitis belt the maximum incidence is usually found among children aged 5 to 10 years. Young people living in closed communities, such as boarding-school pupils and military recruits, are affected more than other individuals. The incidence among recruits is at least 4-10 times higher than in the general population.

Household contacts of patients with meningococcal disease have a risk of acquiring disease of approximately 500-800 times the age-specific incidence in the general population. The secondary attack rate for household contacts is estimated around 4 cases per 1,000 contacts.

Bacterial meningitis caused by other agents

Neisseria meningitidis, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b represent the triad responsible for over 80% of all cases of bacterial meningitis. Other bacteria causing the disease include Gram-negative rods (especially *Escherichia coli*), streptococci (other than *S. pneumoniae*), *Listeria monocytogenes*, and staphylococci.

Until the availability of conjugate vaccines, *Haemophilus influenzae* type b (Hib) has been the most common cause of bacterial meningitis in childhood outside epidemic periods. In several countries where Hib vaccines have recently entered the routine infant immunization schedule, Hib meningitis has nearly been eliminated. The annual incidence of Hib meningitis is about 1-3 per 100,000 population. However, the age-specific incidence rate among children under 5 years of age is much higher, ranging from 20-60 cases per 100,000 per year. Ninety percent of patients with Hib meningitis are under 5 years of age and the peak age group affected is 6-11 months. The case-fatality rate in Hib meningitis is approximately 5-20%. Sequelae occur in approximately 10-30%, the most common being hearing loss.

The annual incidence of meningitis caused by *S. pneumoniae* is 1-2 per 100,000 population in most developed countries. Developing countries have higher incidence rates, up to 20 per 100,000. In temperate climates, incidence is higher in the cold season than in the warm season. The highest incidence is found in children under 2 years of age. Incidence decreases in the subsequent age groups to a low level in young adults but again increases in the elderly. The case-fatality rate in pneumococcal meningitis is several times higher than in meningococcal or Hib meningitis. More than half of pneumococcal meningitis patients have one or more complications. Of special concern are hearing problems which often are bilateral and profound.

Although epidemics of meningococcal disease attract much public attention, endemic bacterial meningitis causes substantial illness and death, as well as persistent neurological defects, particularly among infants and young children. Throughout the world, bacterial meningitis may be the most important cause of acquired deafness.

1.4 VIRAL MENINGITIS

Viruses are the main causes of acute aseptic meningitis syndrome defined as acute meningitis with CSF lymphocytic pleocytosis for which there is no apparent cause after initial evaluation and routine staining and culture of CSF. The disease is rarely serious and recovery is usually complete. There are no specific treatment or specific control measures.

Viral meningitis occurs world-wide in sporadic and epidemic forms. The incidence during non-epidemic conditions is rarely known. Seasonal variations can be observed and depend on the causative agent. Enteroviruses are the most common cause of epidemics of viral meningitis and they occur in general in late summer or early winter periods, affecting mainly infants and young children.

Mumps virus is another important agent of viral meningitis in non-immunized populations. Outbreaks of aseptic meningitis in late winter may be due mainly to mumps. The most affected in these outbreaks are children in the age group 5-9 years.

Arboviral meningitis outbreaks, e.g. West Nile virus may occur under special favouring conditions (Romania 1996) such as periods of increased vector activity.

Recently (1994-1996) outbreaks of enteroviral meningitis occurred in some countries in the Eastern Mediterranean Region which caused great concern among the public as they coincided with the vast wave of meningococcal outbreaks in Africa and the increased public awareness of the disease. Lack of diagnostic capabilities early in the outbreak intensified this concern. Such outbreaks should be investigated rapidly to allow an early distinction from epidemics of meningococcal disease which are more serious and require specific control measures.

2. THE DISEASE

2.1 HOW TO RECOGNIZE AND CONFIRM MENINGOCOCCAL DISEASE

Acute purulent meningitis is the usual form of meningococcal infection. Since the diagnosis of meningitis is ultimately based on evaluation of the cerebrospinal fluid (CSF), a lumbar puncture is indicated whenever such a diagnosis is seriously considered. Meningococcal septicaemia, sometimes fulminating, can occur independently, or in association with meningitis.

Symptoms and signs

Acute meningitis is characterized by a sudden onset of intense headache, fever, nausea, vomiting, photophobia and stiff neck. In addition, neurological signs can be observed, such as lethargy, delirium, coma, and/or convulsions. However, infants may have illness without sudden onset and stiff neck.

Meningococcal septicaemia is difficult to recognize outside an epidemic: abrupt onset, fever and shock occur irregularly, petechial rash or purpura may not be obvious initially and meningeal symptoms are usually absent.

Physical examination should include an examination for:

- meningeal rigidity: stiff neck, Kernig's or Brudzinski's signs;
- neurological signs such as decreased awareness; localizing neurological symptoms are unusual;
- purpura, sometimes extensive and necrotic, usually localized in the extremities, or generalized, cutaneous or mucosal (conjunctival) are often associated with meningococcal disease; purpura is a basic symptom of meningococcaemia;
- blood pressure and symptoms of shock; shock associated with purpura indicates fulminating meningococcaemia, the most severe form of meningococcal disease;
- focal infection such as arthritis, pleuritis or pneumonia, pericarditis, episcleritis.

In infants (under one year of age), the clinical signs of meningitis are often atypical and may be difficult to recognize. The onset is not always rapid. In addition to fever, inconsolable irritability and screaming, failure to feed, vomiting, lethargy, convulsions or hypotonia may be presenting features. Stiff neck may be absent, bulging fontanelle may be observed.

Lumbar puncture and CSF examination

Lumbar puncture is necessary to confirm the diagnosis of purulent meningitis and to identify the meningococcus (and exclude other common causative pathogens, such as pneumococcus and *H. influenzae*).

Lumbar puncture must be done as soon as meningitis is suspected, prior to starting antibacterials. It requires minimal expertise, but careful asepsis is necessary. Fundoscopic examination to rule out papilloedema should be performed when feasible but should not be a prerequisite for lumbar puncture.

Cerebrospinal fluid is usually turbid or purulent (but may occasionally be clear or bloody). Basic routine examination feasible in most laboratories consists of:

- a) measurement of white blood cell count: white cell count is usually above 1,000 cells/mm³ (<3 in normal CSF) with >60% polymorphonuclears;
- b) measurement of protein level: >0,80 g/l (<0.60 g/l in normal CSF);
- c) Gram stain, showing Gram-negative diplococci (intra- or extracellular) in 80% of cases not previously treated (Annex 1). If Gram stain is not feasible, it can be replaced by methylene blue stain.

Additional investigations performed on CSF usually include:

- measurement of glucose concentration (<0,40 g/l);
- bacterial culture on appropriate media (Mueller-Hinton or chocolate agar) and identification and serogrouping of *Neisseria meningitidis*;
- rapid antigen detection techniques, able to identify directly, not only meningococcal infection, but also the causative serogroup; latex agglutination is the procedure most commonly used (Annex 2);

Neisseria meningitidis or meningococcus is a Gram-negative diplococcus, non-motile, non-sporulating, usually encapsulated and pilated.

- The meningococcus is a fragile organism, susceptible to cold and drying. It is cultivated on enriched media, such as Mueller-Hinton or chocolate agar.
- Capsular polysaccharide antigens differentiate nine serogroups. Serogrouping is performed either after culture, by agglutination on colonies, or directly on CSF, by latex agglutination.
- Subtyping using new sophisticated procedures is carried out only in some reference laboratories (See Annex 12 for WHO Collaborating Centres).

other techniques are coagglutination, countercurrent immunoelectrophoresis, and ELISA;

- antibiogram testing of sensitivity to antibacterials.

Other laboratory investigations

Blood cell counts may show an increase of polymorphonuclear cells. In severe purpuric cases marked thrombocytopaenia may be observed along with signs of disseminated intravascular coagulopathy.

Blood cultures are often positive (in 30% of cases or more). When purpura is present, microscopic direct examination and culture of a specimen of pus or tissue fluid (collected by needle aspiration) may be useful when haemoculture cannot be performed.

Differential diagnosis

In endemic situations, acute meningitis or meningoencephalitis is associated with purulent or cloudy CSF only in a minority of cases (around a third). More often, the CSF is clear, and acute meningitis is due to one of numerous viral agents. Occasionally other bacteria (*Mycobacterium tuberculosis*, spirochetes) or fungi (*Cryptococcus*) cause acute meningitis. The latter is especially important in patients with HIV infection.

Since cloudy CSF is a sign of bacterial meningitis, lumbar puncture is essential. Meningococcal septicaemia is more difficult to distinguish from other acute febrile illnesses, particularly in the absence of petechial rash. **The association of acute fever, purpura and shock is very suggestive of meningococcal disease.**

Improved disease surveillance and case reporting of meningococcal disease must be based on the use of a standard case definition for meningococcal meningitis. Three levels of diagnosis (suspected, probable, or confirmed) are shown in Chapter 3.2.

2.2 HOW TO MANAGE PATIENTS WITH MENINGOCOCCAL DISEASE

Principles

- Meningococcal disease (either meningitis or septicaemia) is potentially fatal and should always be viewed as a **medical emergency**.
- **Admission to a hospital** or health centre is necessary for diagnosis (lumbar puncture and CSF examination) and for treatment.
- Antimicrobial therapy is essential and should be combined with supportive treatment.
- As contagiousness of patients is moderate and disappears quickly following antimicrobial treatment, **isolation of the patient is not necessary**

Antimicrobial therapy

Timing

Antimicrobial treatment must be instituted as soon as possible. Lumbar puncture should be performed, if possible, prior to the administration of antibiotics, which should be given immediately after the puncture, without waiting for laboratory results. Treatment of a suspected case of meningococcal disease with an antibiotic should not be delayed when lumbar puncture cannot be done on initial presentation. If the lumbar puncture yields blood but the clinical picture suggests meningitis, then antimicrobial treatment should be initiated immediately. This is the case also if the CSF looks clear but the symptoms and signs are suggestive of meningococcal septicaemia; initiation of antimicrobial therapy without any delay may be life-saving.

Choice of antimicrobials

Many antimicrobials are active against meningococci *in vitro*, but only those that penetrate sufficiently the cerebrospinal space and are affordable should be used. Either parenteral *penicillin* or *ampicillin* is the drug of choice. *Chloramphenicol* is a good and inexpensive alternative. The third-generation cephalosporins, *ceftriaxone* and *cefotaxime*, are excellent alternatives but are considerably more expensive. On the other hand, *ceftriaxone* can be administered once a day and for as short a period as two days (Table 3); this should be taken into account when comparing the total costs of treatment with this antibiotic, with a 5-day regimen of ampicillin. Although oral *cotrimoxazole* (trimethoprim-sulfamethoxazole) is inexpensive and has good CSF penetration, sulfa resistant strains have become common and sulfa drugs are not recommended unless sulfa sensitivity testing has been done. In unfavourable conditions, the drug of choice is oily chloramphenicol.

Route of administration

The intravenous route is recommended. However a series of clinical studies have shown the use of intramuscular chloramphenicol in oil to be as efficacious as intravenous ampicillin for meningococcal disease. Penetration of chloramphenicol into the cerebrospinal space is good even after oral administration. In patients where the intramuscular (IM) or intravenous (IV) route is not possible oral administration is acceptable. Higher than normal doses are then advisable (Table 3).

Duration of therapy

A seven-day course is still the rule for the treatment of meningococcal disease (beyond the neonatal period) in most developed countries. However there is good evidence that for meningococcal meningitis a four-day course of penicillin G is as effective as any longer course of antimicrobials. The long-acting form of chloramphenicol has also been shown to be effective.

Table 3. Antimicrobials to treat bacterial meningitis

Agent (generic name)	Route	Dose adults	Dose children	Duration (1) (days)	Cost (2)
Penicillin G	IV	3-4 MU q. 4-6 h	400,000 U/kg	≥ 4	low
Ampicillin or Amoxicillin	IV	2-3 g q. 6 h	250 mg/kg	≥ 4	moderate
Amoxicillin	oral	2-3 g q. 6 h	250 mg/kg	≥ 4	high
Chloramphenicol	IV	1 g q. 8-12 h	100 mg/kg	≥ 4	moderate
Chloramphenicol (oily)	IM	3 g single dose	100 mg/kg	1-2	low
Cefotaxime	IV	2 g q. 6 h	250 mg/kg	≥ 4	very high
Ceftriaxone	IV	1-2 g q. 12-24 h	50-80 mg/kg	≥ 4	very high
Ceftriaxone	IM	1-2 g single dose	50-80 mg/kg	1-2	high

(1) Duration of treatment of meningococcal disease: conventional - at least 4 days; short - single dose 1 or 2 days.

(2) Cost of full treatment (conventional or short): low: US\$ < 10; moderate: US\$ 10-50; high: US\$ 50-250; very high: US\$ >250 (when infusion is required, the cost of material and solution should be added).

IV = Intravenous.

IM = Intramuscular.

In non-epidemic conditions, initial antimicrobial therapy should be effective against the three major causes of bacterial meningitis until bacteriological results are available (Table 4).

Table 4. Initial empiric antibacterial therapy for presumed bacterial meningitis (therapy to be initiated after lumbar puncture)

Age group	Probable pathogens	Antibiotic therapy	
		First choice	Alternative
<u>IN EPIDEMIC SITUATIONS</u>			
All age groups	<i>N. meningitidis</i>	Penicillin G	Ampicillin Chloramphenicol Ceftriaxone
<u>IN NON-EPIDEMIC SITUATIONS</u>			
Adults and children 5 years of age	<i>S. pneumoniae</i>	Penicillin G	Ampicillin or Amoxicillin Chloramphenicol Ceftriaxone or Cefotaxime
Children 1 month - 5 years of age	<i>H. influenzae</i> <i>S. pneumoniae</i> <i>N. meningitidis</i>	Ampicillin or Amoxicillin (1)	Chloramphenicol Ceftriaxone or Cefotaxime
Neonates	Gram-negative bacteria Group B streptococci Listeria	Ampicillin and Gentamycin	Ceftriaxone or Cefotaxime (2) Chloramphenicol (at reduced doses)

(1) If *H. influenzae* is highly resistant to ampicillin, chloramphenicol should be given with ampicillin.

(2) No effect on Listeria.

Supportive therapy

Fluid and electrolyte balance should be monitored and fluid replaced accordingly. If the patient is unconscious or vomits, and if an intravenous line cannot be placed, a nasogastric tube should be inserted.

When required, anticonvulsants (*diazepam*) or antiemetics may be administered by an appropriate route.

Increased intracranial pressure probably plays a key role in meningitis mortality. When facilities are available, barbiturate anaesthesia with the use of a ventilator seems the best way of decreasing the pressure. Routine use of dexamethasone cannot be recommended for treatment of meningococcal meningitis at this time.

Severe forms of the disease including coma, shock and purpura fulminans should be treated in an intensive care unit or by well-trained physicians.

Feeding by the oral or nasogastric route to maintain nutritional status, and nursing care, including prevention of bedsores, are important components of supportive care.

Simplified management in unfavourable conditions

In most developing countries, health facilities lack material, drugs, and laboratory equipment. More and more frequently, patients or their families are required to pay for drugs and laboratory examinations. Thus, even in non-epidemic conditions, patient management must be simplified.

Furthermore, when an epidemic occurs in any country, the flood of patients can result in worsened problems, and overwhelm personnel and facilities. As soon as an epidemic has been confirmed, case management should be simplified to achieve the maximal benefit with the minimal cost.

While lumbar puncture with Gram staining (or latex agglutination) is generally recommended for each case, the degree of investigative activity should be adjusted to prevailing conditions. When the prevalence of meningococcal disease is high and laboratory capacities cannot match the demand, plain visual examination of CSF gives some useful information.

The efficacy of a shortened course of antimicrobial therapy has special relevance during epidemics. The great majority of patients can be treated with a single dose of long-acting oily chloramphenicol or ceftriaxone, when available and affordable (doses are listed in Annex 3). For patients who do not improve rapidly, an additional dose of the same antimicrobial is recommended 48 hours later.

Outcome

In meningococcal meningitis the case-fatality rate usually is around 10% among patients who are appropriately treated. In meningococcal septicaemia, the case-fatality rate may exceed 50%.

Few data on permanent sequelae of bacterial meningitis are available. In The Gambia, 12% of patients who survived meningococcal meningitis were left with a moderate or severe neurological abnormality. Hearing impairment was the most frequent sequela (6%). Many permanent sequelae remain undetected. It is thus recommended that, whenever possible, hearing should

be tested (with bilateral audiometry) one to three months later, or at the earliest age the child is able to cooperate sufficiently. In addition, if possible, a developmental assessment should be performed a year later to detect any subsequent mental handicap in the child.

2.3 HOW TO PREVENT MENINGOCOCCAL DISEASE

Meningococcal disease is potentially preventable through vaccination and/or chemoprophylaxis in special circumstances.

Prevention of transmission

Transmission of *N. meningitidis* occurs from person to person, usually from a nasopharyngeal carrier rather than from a patient, through contact with respiratory droplets or oral secretions. The prevalence of nasopharyngeal carriage is variable, and does not correlate with the risk of an outbreak. Contagiousness rapidly disappears in patients after starting antibiotic therapy. Since the meningococcus is relatively susceptible to temperature changes and desiccation, the organism is not transmitted through shared equipment or material. Thus:

- neither isolation of the patient nor disinfection of the room, bedding or clothes are necessary;
- identification of carriers by nasopharyngeal culture is not recommended. Carriage studies are not useful in predicting an outbreak, or in guiding decisions about prophylaxis.

Vaccination

Four specific antigens related to serogroups A, C, Y and W135 are currently available. They are distributed in freeze-dried form, injectable by IM route, either as bivalent AC vaccine, or quadrivalent A, C, Y, W135 vaccine, containing 50 µg of each antigen (Annex 4).

Meningococcal A, C, Y, W135 vaccines are based on capsular polysaccharide antigens and induce a T cell-independent immune response which is age dependent. In adults and in children above 4 years of age, a single dose induces a rapid rise of antibodies and protection within 10 days in over 85% of recipients. Protection lasts for at least one year and often several years longer. The response is poorer in infants and young children.

The group A vaccine is more immunogenic than some other polysaccharide vaccines and it can induce an appreciable antibody concentration even in 3-month-old infants.

These polysaccharide vaccines are generally very well tolerated but may induce some mild adverse reactions (local pain and swelling, fever and malaise) in 10-20% of recipients, for the 2-3 days following the vaccination.

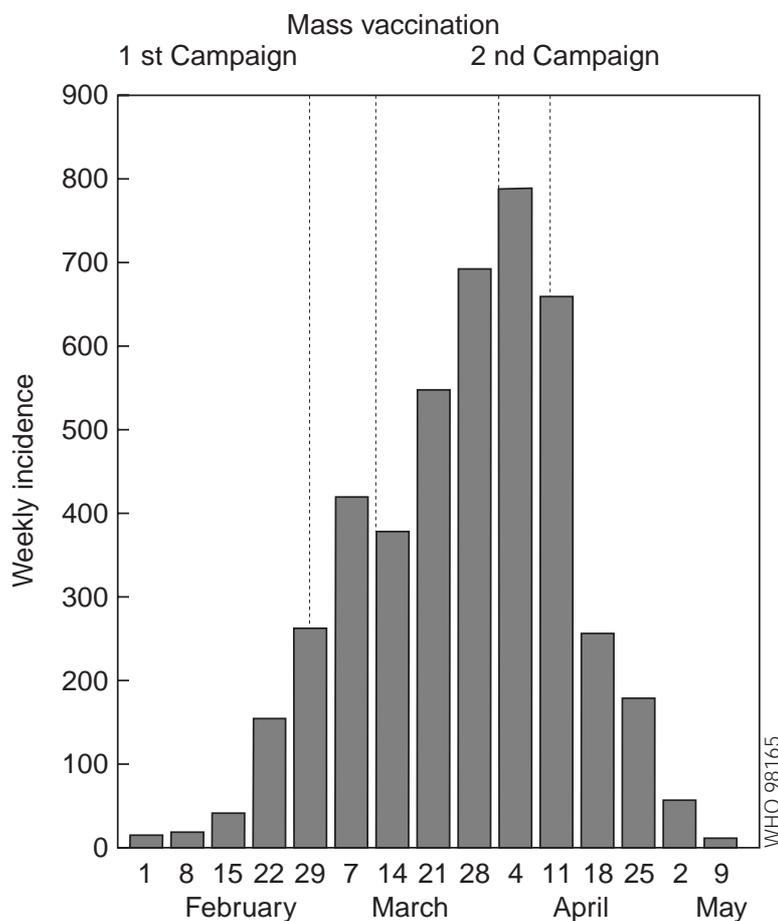
Meningococcal polysaccharide vaccines are not routinely used in early childhood because of their general lack of efficacy in infants and young children. In some countries, recruits are routinely vaccinated with A-C vaccine, at the beginning of military service.

To prevent secondary cases around a sporadic case of meningococcal disease, vaccine is used in some countries for close contacts of patients with meningococcal disease due to A, C, Y, or W serogroups.

To halt epidemics due to A and C serogroups, meningococcal vaccines are very effective. When used in rapid mass campaigns, vaccination can contain an outbreak within two-three weeks (Figure 9).

New vaccines against the meningococcus are being developed. Serogroup B outer membrane protein vaccines have been developed and tested in Brazil, Chile, Cuba, Iceland and Norway. To date, the efficacy of these products has varied, and significant clinical efficacy in young children (i.e. <4 years of age) has not been demonstrated. Investigational serogroup A and C meningococcal conjugate vaccines (polysaccharide combined with a protein carrier) are

Figure 9. Weekly incidence of cerebrospinal meningitis during the epidemic in N'Djamena, Chad, 1988



undergoing clinical trials in Africa, Europe, and the United States. If new conjugate vaccines are proven to be protective in infants and young children, meningococcal vaccination could be integrated into the infant Expanded Programme on Immunization (EPI) schedule in areas at high risk of meningococcal disease.

Chemoprophylaxis

Chemoprophylaxis has been considered for control of meningococcal disease but it has several limitations, and its use should be limited to **special circumstances** [see below]. The aim of chemoprophylaxis is to prevent secondary cases by eliminating nasopharyngeal carriage. To be effective in preventing secondary cases, chemoprophylaxis must be initiated as soon as possible (i.e. not later than 48 hours after diagnosis of the case).

Chemoprophylaxis is only effective in eradicating nasopharyngeal carriage when systemic antibiotics are used. Topical chemoprophylaxis and topical (pharyngeal) disinfection are of no value. Among potentially useful agents, the antibiotic most often recommended is *rifampicin*, administered in a two-day course. *Ciprofloxacin* (single oral dose) and *ceftriaxone* (single IM dose) are very efficient but expensive. Alternatives are a five-day course of *spiramycin* (well tolerated) or *minocycline* (which frequently provokes dizziness). *Penicillins* (*oracillin*, IM *extencillin* or other long-acting penicillins) and *chloramphenicol* are not recommended since they are ineffective.

Table 5. Antimicrobials for chemoprophylaxis of meningococcal disease

Generic name	Dose adults	Dose children	Route	Duration	Cost
Rifampicin	600 mg/12h.	10 mg/kg/12h.	oral	2 days	moderate
Spiramycin	1 mg/12h.	25 mg/kg/12h.	oral	5 days	moderate
Ciprofloxacin	500 mg	-	oral	single dose	high
Ceftriaxone	250 mg	-	IM	single dose	high

IM = Intramuscular.

Special circumstances for which chemoprophylaxis is appropriate:

In non-epidemic settings, chemoprophylaxis should be restricted to close contacts of a case, which are defined as:

- household members (i.e. persons sleeping in the same dwelling as the case);
- institutional contacts who shared sleeping quarters (i.e. for

boarding-school pupils, roommates; for military camps, persons sharing a barracks);

- nursery school or childcare centre contacts (i.e. children and teachers who share a classroom with the case);
- others who have had contact with the patient's oral secretions through kissing or sharing of food and beverages.

In addition, in areas where household contacts routinely receive prophylaxis, chemoprophylaxis should also be given to the patient with meningococcal disease upon discharge from the hospital, provided the patient's illness was treated with an agent (e.g. penicillin) which does not eliminate the organism from the nasopharynx.

Mass chemoprophylaxis to prevent/control epidemics is not recommended.

3. HOW TO DETECT AND CONFIRM AN OUTBREAK OR EPIDEMIC OF MENINGOCOCCAL DISEASE

3.1 EPIDEMIC VERSUS ENDEMIC DISEASE

Detecting an epidemic of meningococcal disease requires the differentiation of the pattern of cases occurring from the usual, or endemic, pattern observed in the region. Epidemic meningitis occurs when attack rates are substantially higher than baseline. *Neisseria meningitidis* is the only pathogen associated with epidemics of meningitis. During meningococcal epidemics in sub-Saharan Africa, attack rates can exceed 1% (or 1,000/100,000) in the affected area, but in other parts of the world attack rates during an epidemic may be much lower.

The magnitude of disease during meningococcal epidemics makes them easy to recognize in retrospect. Since intervals between epidemics vary greatly, even in a given area, the occurrence of an epidemic is not predictable anywhere in the world.

Although there are several potential risk factors for meningococcal epidemics (Chapter 1.2), no one factor is sufficient to explain why an epidemic is occurring or where one is likely to occur next. For this reason, early warning systems for meningococcal epidemics are based on information on the occurrence of meningococcal disease, rather than on changes in the prevalence of potential risk factors.

For the early recognition of epidemic disease, an EARLY WARNING SYSTEM should be designed to:

- detect an epidemic early enough for preventive efforts to have an impact;
- detect localized epidemics and widespread epidemics;
- be appropriate for local conditions.

3.2 PLANNING AND IMPLEMENTATION OF AN EARLY WARNING SYSTEM

The foundation of epidemic recognition is effective surveillance. Timely and sensitive reporting systems are difficult to achieve in any setting and are particularly challenging in areas with limited resources. Logistics of meningitis surveillance need to be tailored to local conditions, but the ability of early warning systems to detect the emergence of an epidemic is completely dependent on the effectiveness of surveillance.

Surveillance of meningococcal disease is essentially targeted at meningitis, since septicaemia is much less frequent and more difficult to recognize and confirm, especially in poorly equipped health facilities. Meningitis surveillance should therefore be based on a simple case definition that can be implemented in any health care setting, such as the following:

**STANDARD CASE DEFINITION OF
MENINGOCOCCAL MENINGITIS¹**

1. Suspected case of acute meningitis²
 - sudden onset of fever (>38.5 °C rectal or 38.0 °C axillary)

WITH

 - stiff neck

In patients under one year of age, a suspected case of meningitis occurs when fever is accompanied by a bulging fontanelle
2. Probable case of bacterial meningitis³
 - suspected case of acute meningitis as defined above

WITH

 - turbid CSF
3. Probable case of meningococcal meningitis³
 - suspected case of either acute or bacterial meningitis as defined above

WITH

 - Gram stain showing Gram-negative diplococcus

OR

 - ongoing epidemic

OR

 - petechial or purpurral rash
4. Confirmed case⁴
 - suspected or probable case as defined above

WITH EITHER

 - positive CSF antigen detection for *N. meningitidis*

OR

 - positive culture of CSF or blood with identification of *N. meningitidis*

¹ This case definition allows the detection of cases of meningococcal septicaemia.

² Often the only diagnosis that can be made in dispensaries (peripheral level of health care).

³ Diagnosed in health centres where lumbar punctures and CSF examination are feasible (intermediate level).

⁴ Diagnosed in well-equipped hospitals (provincial or central level).

Reporting mechanisms must be tailored to local conditions, but effective reporting systems must incorporate several common features for the early recognition of epidemics.

Collection of information

The quantity of information reported must balance the need for simplicity (to increase efficiency of the system) and the need to collect sufficient data for reporting to be useful. Two approaches can be integrated (a) a minimal quantity of data can be reported from all health sites (e.g. new cases and deaths by week) and (b) more extensive data can be reported from selected referral health centres.

At each health facility level, a consultation log book should be maintained for notifiable diseases and include for each suspected case of acute meningitis: age, sex, address, date of onset, date of consultation, treatment received and mode of diagnosis: (a) clinical; (b) CSF; (c) CSF culture or antigen detection. This registry is the basis for appropriate regular tabulation of the number of acute meningitis cases to be reported.

Documenting the age of cases is useful, both in distinguishing endemic disease from epidemics, and in determining the age groups at highest risk, to whom vaccination efforts could be targeted.

The most up-to-date census data for population groups (by region and age group whenever possible) should be available to permit calculation of attack rates by both area and age group.

Reporting of information

Regular reporting from community-based treatment facilities to regional centres, and from regional centres to a central level of the public health system is essential. Reporting should be on a weekly or daily basis. The absence of cases should also be reported ("zero reporting") on a weekly basis, to permit public health personnel to distinguish an area that is truly unaffected from one in which the communication system has failed.

Meningitis reporting is most feasible if it can be incorporated into weekly reporting of notifiable diseases as defined by health authorities on a single report form. Year-round weekly reporting of a limited number of notifiable diseases could include meningitis cases, most of which would occur during the winter-spring season.

Mode of reporting

Reporting should be rapid and reliable. Cases may be reported by radio, telephone, telegram, facsimile, or courier; different methods might be appropriate for various facilities within one system. Arrangement for use of available means of communication should be made in advance. All other informal sources of information (travellers, merchants, religious leaders, etc.) should be taken into account and all rumours verified.

Seasonal enhancement of supervision

Supervision of reporting should be enhanced in the high-incidence season.

Regular data review

Reliable disease reporting only can be translated into early control measures if data are analysed and interpreted regularly (on a weekly basis). At any level, the person responsible for data review should be designated early.

Data review and decision making should be decentralized when compatible with local structures, to permit early identification of an outbreak and rapid response. For this purpose, training of peripheral health workers based on simple principles of using data for decision making should be continuously updated.

Weekly rates of disease should be calculated in a given area, defined preferably at the district level. These rates should be compared with the previous week's attack rates and with rates during the same period in the 3-5 previous years (in non-epidemic years). Simple computer software programmes are now widely available to undertake this activity (Annex 5).

Regular feedback of summary data (newsletters, epidemiological bulletins, etc.) from the central or provincial to peripheral levels should be implemented. It may stimulate the participation of health personnel involved in the reporting.

Deciding when an epidemic is occurring

In the Eastern Mediterranean Region one of the following three indicators can be used as an early warning of a possible meningococcal epidemic: 1) two-to-three-fold increase in cases compared with the same month in previous years; 2) doubling of the number of meningitis cases from one week to the next for a period of three weeks; 3) an increasing proportion of patients 5 years of age and older (in endemic conditions, the majority of cases occur in infants and young children).

REQUIREMENTS FOR AN EARLY WARNING SYSTEM

- Health facility registry
- Census data
- Regular daily/weekly reporting, including weekly zero reporting
- Seasonal enhancement of supervision of reporting
- Communication network
- Regular data review for:
 - calculating attack rates
 - preparing graphs

3.3 RAPID ASSESSMENT OF A SUSPECTED EPIDEMIC OF MENINGOCOCCAL DISEASE

When a suspected outbreak is reported, it is important to determine rapidly whether a true outbreak is occurring. This requires sending a rapid assessment team to the field. Such a team should ideally include an epidemiologist, and/or a clinician, a microbiologist and/or a laboratory technician, preferably experienced in meningitis. They should report promptly to local decision makers. Provision of reliable transport for this team should be given high priority. This team has to answer three questions:

- Is it meningococcal disease?
- Is there a true outbreak of meningococcal disease?
- What is the current size and geographical limit of the outbreak?

If the area experiencing high rates of suspected cases does not have laboratory diagnostic capability, the investigation team dispatched to the affected area should obtain specimens for laboratory confirmation. The team should bring appropriate materials for diagnostics, including spinal needles, latex agglutination material, and transport media, because confirmation of the etiology of meningitis in a suspected epidemic is essential for planning control measures (Annex 6).

Investigation of suspected cases

Investigation of suspected cases should include collection of cerebrospinal fluid (CSF).

Visual inspection of fluid from cases usually reveals cloudy fluid, but this is also characteristic of bacterial meningitis due to other pathogens.

If possible, Gram stain should be done on site (Annex 1), Gram stain may help distinguish meningococcal from other types of meningitis.

RESPONSIBILITIES OF A RAPID ASSESSMENT TEAM

- investigate previously reported meningococcal disease cases
- establish or confirm diagnosis by investigation of new cases
- obtain CSF for: direct examination, Gram stain, latex agglutination, and culture
- implement a working case definition
- quantify cases by time, place and personal characteristics (e.g. age group)
- assess local treatment protocols
- assess local human and material resources for treatment and prevention

Latex agglutination permits rapid detection of meningococcal antigen in field conditions by trained personnel (Annex 2). Latex agglutination kits can be used to establish the diagnosis of disease due to group A or group C meningococcus (serogroups associated with outbreaks that are preventable with polysaccharide vaccine) as well as other common causes of bacterial meningitis (pneumococcus, *H. influenzae* b). Information on kits appears in Annex 7. If latex agglutination is not available to the investigation team, CSF should still be collected for transport to a provincial or central laboratory for testing, since the stability of the antigen permits testing at a later time. If possible, CSF for subsequent antigen testing should be transported in sterile vials. Refrigeration of the sample is not essential, provided the specimen has been kept in a sterile container, but should be used for specimens destined for antigen testing.

Confirmation of isolates by culture is usually more difficult to arrange in the field but can be important to determine antibiotic resistance patterns and for subsequent subtyping of epidemic strains. Cerebrospinal fluid collected in the field for culture should be transported in appropriate transport media (Annex 8) and kept at 37 °C during transport to a laboratory with capability to perform cultures. The meningococcus is extremely fragile, susceptible to heat, cold, and direct sunlight, and undergoes autolysis in CSF. If no transport media is available, CSF specimens should be transported in a sterile container at body temperature. Under extremely hot conditions, it may be necessary to transport CSF specimens in a cool box (as close to 37 °C as possible). Specimens for culture should **not** be refrigerated. If the occurrence of cases of meningitis is documented by laboratory studies, then the team should investigate the possible outbreak by reviewing dispensary logbooks and clinical records to collect data on cases and outcome. Cases should be described in terms of time (date of onset of case), place (village, neighbourhood of residence of case), and personal characteristics (e.g. age, sex). The appropriateness of treatment protocols in operation should be evaluated and the team should assess the materials available for case management (e.g. antibiotics, needles, and syringes).

COLLECTION OF CEREBROSPINAL FLUID FOR:

- visual inspection
- Gram stain
- latex agglutination
- culture

Once the field team has investigated a potential outbreak, the information needs to be reviewed at the next appropriate health level, where these data can be correlated with information from other areas and with population, or

denominator, data. The number of probable and confirmed cases in an area can be used to determine the attack rate for the preceding three months, and to assess whether a meningococcal epidemic is occurring or imminent. Indicators of an epidemic include:

- an attack rate at least 5-fold higher than that observed during previous years in the same area, or if data for the same area are not available, an attack rate at least 5-fold higher than rates in similar areas of the country;
- an attack rate of probable and confirmed meningococcal disease surpassing 5 cases per 100,000 population.

To determine whether epidemic rates of disease indicate a need for vaccination, it is critical that serogroup information confirms that the majority of diagnosed cases are due to vaccine-preventable serogroups, usually serogroup A or serogroup C.

Attack rates should be applied to the population of a district. Estimation of attack rates in an entire country, or for populations of several million, will usually fail to detect local epidemics, or will detect such epidemics too late for vaccination to have an impact on the course of the epidemic.

In addition to estimating attack rates, investigation of a suspected epidemic of meningococcal meningitis should include calculation of the proportion of cases resulting in death (case-fatality rate, or CFR). Very high CFRs (>20%) suggest problems in case management and indicate the need to review treatment routines. Very low CFRs (<5%) may indicate “overdiagnosis” but could also occur if severe cases did not reach treatment facilities. Review of clinical data on cases as well as any information from the community on recent deaths outside treatment centres can help to distinguish these two explanations.

It is difficult to generalize the need for various control measures when small populations—such as schools, refugee camps, or villages—experience high rates of disease. The decision to vaccinate when group A or C meningococcal disease occurs in such settings should be based on the number of potential cases that could be prevented, the expected duration of increased risk (e.g. whether the epidemic is recognized near the end of the high incidence season, whether students are about to disperse for vacation), the availability of medical services to manage any new cases, and the resources available.

Information from the field investigation of a suspected meningococcal outbreak should be used to calculate attack rates within a region for specific age groups (e.g. <5 years old, 5-14, 15-29, 30-44, etc.). If the age distribution of the local population is not available, estimates can be made using a theoretical age distribution for a developing country (see below). On the basis of this evaluation, a decision must be made regarding whether or not a pre-established plan of action for meningococcal epidemics should be implemented.

**HYPOTHETICAL AGE DISTRIBUTION OF POPULATION
IN A DEVELOPING COUNTRY**

Age group in years	% of total population
0 - 4	17
5 - 14	28
5 - 29	28
30 - 44	15
>45	12

Identifying the age groups with the highest rates of disease can help guide vaccination plans. Focusing vaccination campaigns on geographical areas and age groups with the highest rates of disease can permit rapid coverage of the highest-risk populations and save resources.

4. HOW TO PLAN FOR AND RESPOND TO AN EPIDEMIC

4.1 A NATIONAL/PROVINCIAL CRISIS COMMITTEE

In areas where meningitis epidemics are frequent, it is appropriate to have an established committee responsible for meningococcal disease that meets on a regular basis. This committee could be a part of a national/provincial advisory committee in charge of emergency preparedness and response for epidemics and possibly for other disasters. It should be activated promptly if an epidemic is suspected.

Where such a committee does not already exist, a meningitis crisis committee should be rapidly formed, once an epidemic is identified.

Meetings should initially be held frequently (daily if possible), and once response efforts are underway and surveillance data suggest that additional areas are not experiencing increased disease occurrence, meetings can be held less frequently (weekly). The central committee is essential to eliminate duplication of efforts and to coordinate appropriate distribution of personnel and resources. It is crucial that the committee have the authority to implement emergency measures. Working links should be established between the Ministry of Health, national relief organizations, WHO, UNICEF, UNHCR, UNDP, NGOs, bilateral and intergovernmental agencies as appropriate.

WHO SHOULD BE INCLUDED IN THE CRISIS COMMITTEE?

- The committee may consist of representatives from:
- Ministry of Health (including personnel from the office of communicable diseases and the central administration)
- referral hospital for meningitis
- reference laboratory
- other hospitals in the affected area(s)
- head of national logistic and drug supply
- community health programmes
- Expanded Programme on Immunization (EPI)
- mobile immunization teams
- non-governmental organizations (NGOs) involved in health care
- technical assistants as needed

ROLE OF THE CRISIS COMMITTEE

- plan control strategies
 - define populations at risk
 - develop policies and sustain executive structures with clear responsibilities for emergency health response
 - assign specific responsibilities to individuals or units for epidemic detection and response
 - establish procedures to rapidly mobilize mass immunization programmes.
 - identify the important resources needed for rapid epidemic response, and update information on these resources at local and national levels
 - estimate the requirements to control the epidemic (drugs, vaccine, human resources, transport, financial resources)
 - establish procedure for accessing funds
 - identify and ensure that competent laboratory support remains available in the country
 - coordinate communication with and education of the health care community and the general public
 - supervise and coordinate implementation and achievement of control measures
 - evaluate and follow up the results, adjust strategy if necessary, draw up the post-epidemic review
-

Health authorities in neighbouring provinces, districts or cities should be informed of local disease activity so that the spread of epidemic disease to other areas can be monitored. Health care personnel within the region should be kept informed of the extent of the epidemic and about appropriate case management, reporting procedures, and vaccination plans.

During the 1980s and 1990s, meningococcal epidemics have spread across country borders within a given season or from one year to the next. These occurrences underscore the importance of keeping regional agencies (e.g. WHO) and neighbouring countries informed of new epidemic activity, in order to stimulate enhanced monitoring of diseases in areas with increased risk of future epidemics.

4.2 INFORMING THE PUBLIC

Once an epidemic of meningococcal disease has been recognized, there is likely to be widespread media attention and public concern. Therefore, it is important early in the outbreak to begin efforts to accurately inform the community about the outbreak to avoid panic. These efforts should continue during the epidemic.

REACHING THE PUBLIC

- Radio
- Television
- Newspapers
- Meetings with health personnel, community and political leaders
- Posters
- Fliers
- Presentations at markets, health centres, schools, women's groups, religious centres

The media can help to increase awareness among health workers and educate the community about early symptoms that may be related to disease in the outbreak. Media information for the public should emphasize how the disease is spread, that antibiotic therapy is effective in treating the disease, where to go for treatment, that cases could be cured more often than not if early treatment is sought, and, if vaccination is to be undertaken, where and when the community should report to receive immunizations. Local beliefs about disease transmission should be explored and any misconceptions addressed. A close collaboration between the media and health authorities is necessary throughout an epidemic.

4.3 PLANNING AN APPROPRIATE EMERGENCY RESPONSE

Case management during an epidemic

During epidemics of confirmed meningococcal disease, case management needs to be simplified to permit the health system to respond to rapidly expanding numbers of cases. It may be necessary to create temporary treatment facilities to handle overflow from established treatment centres. Such facilities need to be appropriately staffed, supplied, and incorporated into the reporting system.

Diagnosis and reporting of new cases should be based on the standard case definition (Section 3.1). As the flood of patients during epidemics could make the routine use of lumbar puncture to confirm meningitis impossible, every suspected case of meningitis should be considered and treated as one of meningococcal meningitis. Patients with septicaemia can be difficult to identify, in the absence of meningeal symptoms. Special attention should be given to a search for a purpurial rash among all patients with acute fever.

During epidemics, simplified treatment protocols are appropriate (Section 2.2). Drug shortages, logistical constraints, and high admission rates often force changes in the standard treatment protocols. Recent trials confirm the efficacy of using a single intramuscular dose of long-acting chloramphenicol in oil suspension for meningococcal meningitis, which can greatly simplify management of large numbers of cases (Annex 3). Most patients improve within 24-48 hours. A second dose should be given within 48 hours in patients who show no signs of clinical improvement. Appropriate dosages are given in Annex 3. Ordering appropriate quantities of oily chloramphenicol can be based on the age distribution of cases. In areas where meningococcal epidemics are frequent, it may be useful to keep a stock of oily chloramphenicol and injection material for use during an epidemic before additional supplies arrive. If chloramphenicol in oil is not available, any of the antibiotics listed in Table 3 could be used pending arrival of additional supplies.

Vaccination

A mass vaccination campaign, if appropriately carried out, is able to halt an epidemic of meningococcal disease due to serogroups A or C within weeks. To plan and implement such campaigns, speed is essential since time is needed to obtain and distribute vaccine. Therefore, a programme for acquiring vaccine should be established before an epidemic occurs. The advisory committee should decide early the extent of the population who will be vaccinated, in order to estimate the number of doses of vaccine that will be needed.

Factors that need to be considered are the geographical distribution of cases, the age-specific attack rates, and the resources available.

Vaccination will be concentrated in the area where the epidemic is maximal.

If vaccine supplies and administrative support are not limited, mass vaccination of the entire population should be considered. If resources are limited, it may be necessary to restrict vaccination to the age groups most at risk (as identified through the process described in Section 3.3), namely those with the highest attack rates or accounting for the largest proportion of cases.

It is reasonable to offer early vaccination to personnel involved in management of the epidemic and health care providers in the affected area, regardless of age.

Since meningococcal vaccine against serogroup A is safe and may be of some benefit in infants as young as three months it is reasonable to offer the vaccine even to infants during an epidemic.

Once a decision has been made to vaccinate, vaccine supplies should be investigated (Annex 4) and in conditions where it is necessary, NGOs and other agencies should be contacted to determine how purchase of vaccine and injection material can be arranged. Some groups involved in emergency assistance provide kits that include all materials and equipment needed for mass immunization (Annex 9).

HOW MANY DOSES OF VACCINE SHOULD BE ORDERED FOR THE CAMPAIGN?

For an estimated population of about 50,000

Target population <30 years of age (~70% of total population)	x0.7	= 35,000
Goal coverage 100%	x1.0	= 35,000
Number of doses to administer (1 per person)	x1	= 35,000
Number of doses needed, assuming wastage (~17%)	x1.17	= 40,950
Number of doses needed assuming need for a reserve (~25%)	x1.25	= 51,875

Approximately 52,000 doses should be ordered. With 50 doses per vial, ~1 040 vials will be needed.

It will usually be necessary to organize a mass vaccination campaign outside the routine EPI. Vaccine can be administered using either mobile vaccination teams or fixed vaccination stations, usually set up at existing health centres or other community facilities.

Autodestruct syringes represent the current method of choice for conducting mass immunization campaigns. Multiple-use nozzle jet gun injectors can be used in situations in which large numbers of persons must be rapidly vaccinated with the same vaccine, the use of autodestruct needles and syringes is not practical, and health authorities judge that the public health benefit from the use of jet injector outweighs the potential risk of blood-borne disease transmission. Properly used jet injectors are safer than disposable syringes in situations where the improper disposal and reuse of needles and syringes occurs. Appropriate numbers of needles and syringes must be obtained.

A typical vaccination team would include: 1 supervisor, 2 nurses, 3-4 record clerks, 2-3 local community representatives, 1 technician responsible for the cold chain, and 1 driver. Such a team should be able to administer at least 1,000 doses a day using syringes and needles. Larger numbers of doses can be administered using jet injectors. Targets of the population vaccinated will depend on the population density and distances between the groups to be vaccinated. To ensure maximum number of vaccines per day, the subject flow through the vaccination centre should be carefully organized (Annex 10).

For persons with EPI vaccination cards, it is important to document that meningococcal vaccine has been administered. In populations where cards are not used, it is preferable to provide a vaccination card (Annex 11). These measures can prevent unnecessary confusion and are helpful in monitoring coverage, vaccine efficacy, and subsequent need for vaccination. Total numbers of persons vaccinated by area should be recorded on a daily basis, permitting revised estimates of the time needed to complete vaccination (as well as the adequacy of remaining vaccine supplies).

Vaccine storage and transport can usually be accomplished in conjunction with EPI facilities and personnel: freeze-dried meningococcal vaccine should be stored between 2 and 8 °C (not frozen). Freeze-dried vaccine stored at these temperatures remains usable for at least two years. Reconstituted vaccine should be refrigerated and remains stable up to five days. However, under field conditions, to maintain asepsis, remaining reconstituted vaccine should be discarded at the end of each working day. It is important to identify in advance adequate storage space for the vaccine. Fifty-dose vials, including solvent and packaging, require approximately 144 cm³ storage space at 2-8 °C.

Chemoprophylaxis

Chemoprophylaxis of contacts of meningitis patients is not warranted during an epidemic for several reasons. During epidemics large numbers of people qualify as close contacts and thus giving them prophylaxis would increase adverse effects. Mass prophylaxis is unlikely to be effective because of reinfection of asymptomatic persons. Effective chemoprophylactic regimens (e.g. rifampicin, ceftriaxone) are expensive and can divert resources from priority health programmes. In smaller clusters or outbreaks among closed populations (e.g. extended household, boarding schools) chemoprophylaxis may still be appropriate.

General measures

Although some uncertainty remains about the circumstances in which transmission of meningococci occur, it has been suggested that transmission may be enhanced when people are brought together in crowded situations

such as markets, social gatherings, or religious ceremonies. Therefore, some authorities have recommended that meningitis control should include closing markets and schools and discouraging social gatherings. However, the effectiveness of these measures has never been documented. The hypothetical risk of disease transmission is probably of less concern than the economic and social disruption caused by such measures.

4.4 SUSTAINING THE CONTROL PROGRAMME AND ENSURING FOLLOW UP

The crisis committee should continue to meet regularly throughout the course of the epidemic response. At these meetings, the following items should be reviewed:

- Incidence of disease by area and age: Is the area affected by the epidemic expanding? Are rates decreasing satisfactorily in vaccinated areas? Is the targeted age group sufficient?
- Case fatality by geographical area: Is case management appropriate or are additional treatment materials needed? Very high case-fatality rates (>20%) may represent problems in case management and suggest the need to review treatment routines.
- Supply of antimicrobials and injection materials: Are additional supplies needed?
- Vaccine supplies: Will more vaccine and injection material be needed?
- Transport needs: Are vehicles and fuel supplies adequate?

The end of the epidemic is defined by a weekly incidence rate decreased to the usual endemic level, for at least one month. It should be officially announced, and emergency measures could be lifted. However, enhanced postepidemic surveillance should be maintained, since the epidemic could reemerge during the next high incidence season, and reach areas not previously affected.

Postepidemic evaluation is recommended. It should include:

- sample survey on vaccine coverage (in different places and age groups);
- assessment of the emergency measures, such as case management, vaccination and logistic problems;
- an evaluation of the impact of the epidemic on the activity of health

structures and on the community;

- if new confirmed cases occur in vaccinated areas, a study could be carried out to evaluate vaccine effectiveness.

4.5 DOCUMENTING THE EPIDEMIC

A summary report on disease activity and the emergency response should be distributed after the epidemic to local personnel to provide feedback. The report should also be provided to international organizations such as WHO, and other interested parties. This is important for training and planning appropriate future responses. If the response was not optimal, evaluation of problem areas is needed to assure that epidemic management will be more effective in the future.

5. INTEREPIDEMIC PROPHYLAXIS

5.1 CONTAINMENT AROUND A PATIENT WITH MENINGOCOCCAL DISEASE, IN NON-EPIDEMIC CONDITIONS

The following measures are **not** appropriate and should be discouraged: isolation of the patient, study of nasopharyngeal carriage of meningococcus in contacts, closing affected schools or institutions or exclusion of siblings from school.

If available and affordable, chemoprophylaxis of close contacts (see section 2.3) can be used as soon as the meningococcus is recognized (Table 5). However it should be restricted to intimate contacts, namely people who have been eating and sleeping in the same dwelling as the patient. Health personnel are not at risk, even in the hospital, unless they have been in intimate contact with a patient, e.g. after providing mouth-to-mouth resuscitation. To be effective, chemoprophylaxis must be used rapidly. Mass chemoprophylaxis is not recommended.

Since protective antibodies induced by vaccination may not occur until 7-10 days, and the highest risk of secondary cases occurs within the week following a contact, chemoprophylaxis, not vaccination, remains the main measure to prevent secondary cases of meningococcal disease in sporadic conditions.

5.2 ROUTINE VACCINATION

Routine mass vaccination of infants is generally not recommended, even in areas at high risk of epidemics, because:

- the currently available meningococcal vaccines (polysaccharides A, C, Y, W135), used in children less than 18-24 months of age, are not immunogenic enough to provide long-lasting protection (especially for serogroup C) or require several subsequent doses if started at three months of age (for serogroup A);
- the feasibility of such vaccination is questionable. Due to their limited efficacy in young children, polysaccharide meningococcal vaccines cannot be integrated into the regular schedule of immunization within the EPI and other programmes for routine immunization of the population and are not considered cost-beneficial.

However, in some groups at risk for relatively short time periods, routine immunization has been recommended. In some countries, military recruits and travellers to Mecca and highly endemic countries are routinely vaccinated with bivalent polysaccharide A+C. Technical staff, likely to deal with laboratory samples containing meningococci, should also be vaccinated.

When new conjugate vaccines become available, a routine early meningococcal vaccination could be considered in hyperendemic areas, perhaps associated with immunization against *H. influenzae* b (Hib), and possibly integrated into the EPI schedule.

5.3 ADVICE TO TRAVELLERS

Vaccination with a single dose of A+C polysaccharide is recommended for travellers above 18 months of age going to an area experiencing an epidemic of meningococcal disease or to areas with a high rate of endemic meningococcal disease.

Since the epidemic of meningococcal disease that occurred in 1987 during the Hajj in Mecca, proof of vaccination against meningococcus has been required for the pilgrims to the Hajj or Umra, at their entry in Saudi Arabia.

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ANNEXES

TECHNIQUES FOR GRAM STAIN AND METHYLENE BLUE STAIN

Materials and Equipment:

Microscope
Centrifuge
Sterile centrifuge tubes with caps
Clean glass slides
Pipettes

Reagents:

A. Gram stain (Hucker modification)

1. Ammonium oxalate-crystal violet

a. Crystal violet (certified)	2 g
Dissolve in 95% ethyl alcohol	20 ml
b. Ammonium oxalate	0.8 g
Distilled water	80 ml

Mix solutions a. and b. Let stand overnight or until dye is dissolved.

Filter through coarse filter paper.

2. Gram's iodine

Iodine crystals	1 g
Potassium iodide	2 g
Distilled water	300 ml

Grinding the dry chemicals in a mortar with small additions of distilled water may be helpful in preparing the solution.

3. Decolorizer

95% ethyl alcohol

4. Counter stain

a. Safranin

Stock solution:

Safranin-O (certified)	2.5 g
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TECHNIQUES FOR GRAM STAIN AND METHYLENE BLUE STAIN

95% ethyl alcohol	100 ml
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Working solution:

Safranin stock solution	10 ml
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Distilled water	90 ml
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- b. Ziehl-Nielsen carbol-fuchsin (considered by many to be a more effective counter stain than safranin)

Basic fuchsin	0.3 g
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95% ethyl alcohol	10 ml
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Phenol crystals, melted	5 ml
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Distilled water	95 ml
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Dissolve the fuchsin in alcohol. Add the 5% phenol solution. Let stand overnight. Filter through paper.

Gram stain kits or individual reagents are also available commercially from several laboratory supply companies.

- B. Methylene blue stain (if Gram stain is not possible):

Methylene blue	0.3 g
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95% ethyl alcohol	30 ml
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Distilled water	100 ml
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Dissolve methylene blue in alcohol. Then add distilled water.

Handling of cerebrospinal fluid (CSF):

At least 20 drops (1 ml) of CSF should be collected in a sterile tube. Do not refrigerate but hold at room temperature before staining. Processing should take place as soon as possible after collection.

1. Centrifuge CSM at 2000 rpm for 10 minutes.
2. Draw off the supernatant and reserve for antigen detection, or other tests.
3. Use a drop of the sediment to make a smear on a glass slide. Air dry, and fix gently with heat by passing through a flame.
4. Stain the smear.

TECHNIQUES FOR GRAM STAIN AND METHYLENE BLUE STAIN

Gram stain:

- a. Flood the smear with ammonium oxalate-crystal violet and let stand for 1 minute.
- b. Rinse gently with tap water. Drain off excess water.
- c. Flood smear with Gram's iodine solution and let stand for 1 minute.
- d. Rinse with tap water as in step b.
- e. Decolorize with 95% ethanol (5-10 seconds may be enough).
- f. Counter stain with safranin 20-30 seconds or carbol-fuchsin 10-20 seconds.
- g. Rinse the slide with tap water and blot dry.

Methylene blue stain:

- a. Flood the smear with methylene blue solution and let stand for 1-3 minutes.
- b. Rinse and blot dry.

Results:

Examine the smear under oil-immersion with a microscope equipped with a bright-field condenser. Meningococci may occur intra- or extra-cellularly, and appear as Gram-negative, coffee-bean shaped diplococci.

GENERAL METHOD FOR PERFORMING LATEX AGGLUTINATION TESTS

Materials and equipment:

Latex kit (Annex 7)

Centrifuge

Water bath (boiling) or dry heat block at 100 °C

Slide- or serological rotator

Pipettes to deliver up to 50 µl

Handling of cerebrospinal fluid (CSF):

Follow the procedure outlined in Annex 1. For best results, test the supernatant of the centrifuged CSF sample (a minimum of 0.5 ml) as soon as possible. If immediate testing is not possible, the sample can be refrigerated (between 2 and 8 °C) up to several hours, or frozen at -20 °C for longer periods.

Storage of latex reagents:

Reagents should be kept refrigerated between 2 and 8 °C when not in use. Product deterioration occurs at higher temperatures, especially in tropical climates and test results may become unreliable before the kit's expiration date. Latex suspensions should never be frozen.

Performance of latex agglutination test:

1. Heat the CSF in a boiling water bath for 3-5 minutes.
2. Centrifuge the CSF for 10 minutes at 2000 rpm and collect the supernatant.
3. Shake the latex suspension gently until homogeneous.
4. Place one drop of each latex suspension on a ringed glass slide or a disposable card.
5. Add 30-50 µl of the CSF to each suspension.
6. Rotate by hand or on a rotator at 100 rpm for 2-10 minutes.

Reading the reaction:

Read under a bright light without magnification:

Negative reaction: the suspension remains homogeneous and slightly milky in appearance.

GENERAL METHOD FOR PERFORMING LATEX AGGLUTINATION TESTS

Positive reaction: within 10 minutes, agglutination (or visible clumping) of the latex particles occurs.

These instructions are typical for the detection of the soluble antigens of *Neisseria meningitidis*, and other bacterial agents of meningitis in body fluids, with the use of latex agglutination test kits. However, it is important to follow exactly the manufacturer's instructions for the kit you are using.

IM INJECTABLE OILY CHLORAMPHENICOL

Oily chloramphenicol is the optimal choice for health facilities with limited resources to deal with epidemics of meningococcal disease.

Advantages:

- active on most strains of meningococcus;
- good penetration of the blood/CSF barrier;
- effective on meningococcal meningitis (and other common bacterial meningitis);
- well-tolerated: haematological side-effects are unlikely at the prescribed low dosage;
- a single IM dose is effective in most cases (some patients may need a second dose 48 hrs later);
- can be used in ambulatory treatment;
- very stable, can be stored at ambient temperature;
- low cost.

Presentation:

- vials of 0.5 g - 2 ml

Dosage:

- 100 mg/kg; max 3 g
- according to age:

1-8	2-11	1-2	3-5	6-9	10-14	15+
weeks	months	years	years	years	years	years
0.25g	0.5g	1g	1.5g	2g	2g	3g
(1ml)	(2ml)	(4ml)	(6ml)	(8ml)	(10ml)	(12ml)

Directions:

- the oily suspension is rather thick and may be difficult to push through the needle;
- the dose can be divided in 2 parts to be injected in the 2 buttocks.

Commercial name:

- Chloramphenicol oily suspension IM produced by Astrapin, Pharmazeutische Präparate, Gewerbestrasse 1, D-55546 Pfaffen-Schwabenheim, Germany, tel +49 6701 93400, fax +49 6701 934017

VACCINE PRODUCT INFORMATION

VACCINE	ADDRESS
A+C Meningococcal vaccine	Pasteur Mérieux Connaught International 58, avenue Leclerc B.P. 7046 F-69348 Lyon Cedex 7 France Tel: +33 4 72 73 77 07 Fax: +33 4 72 73 78 30
Mecevax AC Menceva ACWY	SmithKline Beecham Biologicals 89, rue de l'Institut B-1330 Rixensart Belgium Tel: +32 2 656 87 54 Fax: +32 2 656 90 34
A+C Meningococcal vaccine	Institute of Immunology Rockefellerova 10 Zagreb Croatia Tel: +385 1 43 03 33 Fax: +385 1 27 72 78

PUBLIC DOMAIN COMPUTER SOFTWARE FOR EPIDEMIOLOGICAL INVESTIGATIONS

EPIINFO and EPIMAP: Software package for data entry and analysis of epidemiological data. Distributed by CDC and WHO.

COSAS: Software package for analysis of vaccine coverage surveys and programme evaluation. Distributed by WHO and EPICENTRE.

CEIS (Computerized EPI Information System): Software package for the surveillance of vaccine-preventable diseases and vaccine programme activities. Distributed by WHO.

ANACOV: Software package for analysis of vaccine coverage surveys. Distributed by WHO and Centre International de l'Enfance (Paris).

ADDRESSES:

Centers for Disease Control and Prevention (CDC)
1600 Clifton Road, Atlanta, GA 30333, USA
Tel: +1 404 639 08 40
Fax: +1 404 639 08 41

EPICENTRE
8 rue Saint Sabin, F-75011 Paris, France
Tel: +33 1 40 21 28 48
Fax: +33 1 40 21 28 03

World Health Organization (WHO)
20 avenue Appia, CH-1211 Geneva 27, Switzerland
Tel: +41 22 791 26 60
Fax: +41 22 791 41 98
Telex: 415 416

CHECKLIST OF MATERIALS REQUIRED FOR FIELD INVESTIGATION

Necessary material:

- Graph paper
- Pens/pencils
- Pocket calculator
- Material for specimen collection (needles, syringes, sterile tubes, gloves, antiseptic agent)
- Transport media (e.g. trans-isolate media, Annex 8)
- Material for Gram stain (Annex 1)
- Latex agglutination kits (Annex 2)
- Population census data
- Area maps
- WHO manual
- Reliable transportation, fuel

Optional material:

- Cool box/ice pack
- Camera
- Portable computer*
- Bibliography
- Communication radio

- * Public domain software suitable for epidemiological investigations in Annex 5.

DIAGNOSTIC MATERIALS FOR *NEISSERIA MENINGITIDIS*

Latex agglutination

	SUPPLIERS	PRODUCT INFORMATION
Bactigen	Wampole Laboratories Cranbury, NJ 08512 USA Tel: +1 800 257 95 25 +1 609 655 60 00 Fax: +1 800 532 02 95	14M7 Meningitis Panel A,B,C,Y, W 135, Hib <i>S. pneumoniae</i> (14 types) 14N7 <i>N. meningitidis</i> A,B,C,Y, W135
Directigen	Becton-Dickinson Microbiology Systems Cockeysville, MD 21030 USA Tel: +1 410 584 89 66 Fax: +1 410 584 81 29	8523 60 Meningitis Combo Kit A,Y / C, W135/ B, <i>E. coli</i> K1/Hib/ <i>S. pneumoniae</i> / group B strep
	Becton-Dickinson Benelux Denderstraat 24 9440 Erembodegm Belgium Tel: +32 3 710 32 77 Fax: +32 3 710 32 90	8501-60 <i>N. meningitidis</i> Kit A,Y / C, W135 8555-60 <i>N. meningitidis</i> Kit Group B/ <i>E. coli</i> K1
Pastorex	Sanofi Diagnostics Pasteur 3 Bld. R. Poincaré - BP 3 92430 Marnes-La Coquette France Tel: +33 1 47 95 60 00 Fax: +33 1 47 41 91 33 Telex: 631293F	Pastorex Meningitis Kit 61701 for <i>N. meningitidis</i> A,C,B/ <i>E.coli</i> K1, Hib, <i>S. pneumoniae</i> , group B strep

DIAGNOSTIC MATERIALS FOR *NEISSERIA MENINGITIDIS*

	SUPPLIERS	PRODUCT INFORMATION
Slidex	Bio-Mérieux Marcy-l'Etoile 69260 Charbonnières-les-Bains France Tel: +33 4 78 87 21 03 Fax: +33 4 78 87 20 72 Telex: 330967	5880 2 Slidex méningite-Kit for <i>N. meningitidis</i> A,C, <i>S. pneumoniae</i> , Hib
Murex	Murex Diagnostics Inc. Customer Service Department 3075 Northwoods Circle Norcross, GA 30071, USA Tel: +1 770 662 06 60 Fax: +1 770 447 49 89 Murex Diagnostics, Central Temple Hill Dartford, Kent DA1 5LR United Kingdom Tel: +44 132 227 7711 Fax: +44 132 228 2572 Wellcome Scientific Office Apt. 5, 11 Orabi St. Tawfikea Square Cairo, Egypt Tel: +20 2 752167 Fax: +20 2 763522 Wellcome Nigeria Ltd. Oba Akran Ave. PMB 21099, Ikeja Nigeria Tel: +234 960 841 Telex: 26746 TABLOD-NG	ZL23 Wellcogen polyvalent <i>N. meningitidis</i> A/C/Y/W135 ZL24 <i>N. meningitidis</i> B ZL26 Bacterial meningitis antigen kit <i>N. meningitidis</i> A/C/Y/W135 B/ <i>E. coli</i> K1, group B strep <i>S. pneumoniae</i> , Hib

DIAGNOSTIC MATERIALS FOR *NEISSERIA MENINGITIDIS*

Serogrouping antisera

	SUPPLIERS	PRODUCT INFORMATION
Murex	Murex Diagnostics, Central Temple Hill Dartford, Kent DA1 5LR United Kingdom Tel: +44 132 227 7711 Fax: +44 132 228 2572	2 polyvalent sets of meningococcal agglutinating antisera Single antisera for meningococcus A,C, D,X,Y,Z, W135 (polyclonal), and Group B (monoclonal)
DIFCO	DIFCO Laboratories Detroit, MI 48232, USA Tel: + 1 313 462 85 00 Fax: + 1 313 462 85 17 DIFCO, UK P.O. Box 14B Central Avenue E. Molesey Surrey, KT8 0SE United Kingdom Tel: +44 181 979 9951 Fax: +44 181 979 2506	For <i>N. meningitidis</i> A, B, C, D, X,Y, Z, Z', W135 may be obtained singly or in 2 polyvalent sets

TRANS-ISOLATE MEDIUM: COMPOSITION AND PREPARATION

Trans-isolate medium is a biphasic medium that can be used for transporting cerebrospinal fluid for the isolation of meningococcus, *Haemophilus influenzae*, and *Streptococcus pneumoniae*.

Solid phase:	Activated charcoal (C5510, Sigma)	4 g
	Soluble starch	5 g
	Bacto-agar	20 g

Suspend in 1000 ml of 0.1 M MOPS buffer [3-(*N*-morpholino) propanesulfonic acid (Sigma)] which had been adjusted to pH 7.2. Heat to dissolve the starch and the agar. With mechanical stirring to keep charcoal in suspension, dispense 15 ml quantities in 60 ml Wheaton serum bottles. Cover the bottles with aluminium foil and autoclave in metal baskets at 121 °C for 20 minutes. Remove baskets from the autoclave and with bottles remaining in their baskets, allow to cool in a slanted position.

Liquid phase: Add 60 g tryptic soy broth (DIFCO), and 20 g gelatin to 1 litre of 0.1 M MOPS buffer adjusted to pH 7.2. Heat the medium to dissolve the gelatin and autoclave at 121 °C for 15 minutes. When cool, add 20 ml of sterile supplement B (DIFCO) for the isolation of *H. influenzae*. Dispense 15 ml of the broth aseptically into each of the bottles containing the solid phase. Seal with sterile rubber stoppers and aluminium caps.

For the isolation of meningococcus from potentially contaminated specimens, add 0.3 ml (1 per cent of the volume of the two phases) of sterile, reconstituted VCN (vancomycin-colistin-nystatin) inhibitor (BBL) per bottle (note that this combination of antimicrobials would preclude the recovery of pneumococcus and *Haemophilus*).

Alternatively, while transporting the CSF sample, substitute 60 ml serum bottles with 15 ml screw cap bottles and dispense the solid and liquid phases of the medium in 5 ml quantities and use the autoclavable permeable membrane screw caps for closing the bottles.

SOURCES OF KITS FOR MASS VACCINATION CAMPAIGNS

OXFAM

274 Baudary Road
Oxford OX2 7D7
United Kingdom
Tel: +44 1865 567 77
Fax: +44 1865 576 12

BIOFORCE

44, boulevard Lénine
F-69694 Venissieux Cedex
France
Tel: +33 4 78 67 32 32

Médecins Sans Frontières Logistique

14, rue de l'Argonne
F-33700 Mérignac
France
Tel: +33 5 56 13 73 73
Fax: +33 5 56 13 73 74

ORGANIZING A VACCINATION SESSION

Duration of the campaign

The campaign should be initiated promptly and completed as rapidly as possible in order to stop the progression of the epidemic.

The campaign should begin when all supplies, equipment and personnel are ready as interruption in the middle of a campaign may lead to rioting if the public becomes impatient.

Optimal conditions:

- perfectly organized circuit
- no delay in the registration
- no disruption of stock
- 6 to 8 hours work per day of on-site vaccination

One community health worker (CHW) (+2 assistants) can vaccinate 350 persons per hour, i.e. 2,000 to 2,800 per day

Duration of the campaign will be estimated by geographical site, transport time and number of health staff at hand.

Example: During vaccination against meningitis in Burundi in September-October 1992, the vaccination team consisted of:

- 9 CHW: 4 vaccinators and 5 CHW responsible for the reconstitution of the vaccine and loading of syringes;
- 4 literate people checking the data;
- 15 members of the community (ensuring communication with the population, transporting water, preparing arms for vaccination, distributing cards);
- 1 nurse responsible for supervision;
- 1 person responsible for logistics.

This team vaccinated 8 to 10,000 persons per 6-7 hour work day. Each vaccinator thus immunized an average of 6 persons per minute with ready-to-use syringes.

The experience of the campaign carried out in Guinea (1993) was similar.

ORGANIZING A VACCINATION SESSION

Site

Depending on the situation (e.g. rural or urban areas, refugee camps), health centres, schools, religious places, shade of a tree will be used as a site. The place must be easily accessible for everyone. To avoid confusion and mobs, there should be a large shaded waiting area. The vaccination areas should be protected (requiring ropes if the site is an open one). It is absolutely essential that there are two doors (entrance and exit) to avoid trampling; people must never exit via the entrance route.

Vaccination sites will be distributed geographically based on population density. Use of walkie-talkies improves the logistical organization and limits unnecessary movement.

Site organization

In an emergency situation, each member of the team has a specific part to play in the organization of the vaccination site and in the progress of the vaccination. Logistical organization is the key to a successful campaign.

Plan of vaccination site

- 1: sorting area, verification of age
- 2: distribution of vaccination information
- 3: completion of vaccination cards
- 4: vaccination stations
- 4bis: preparation of syringes
- 5: verifying vaccinations and directing to the exit
- 6: storage area

Areas must be separated by ropes if the vaccination campaign takes place in an open site. Waiting lines should be narrow and allow only one person at a time. Ropes must delimit areas and lines.

ORGANIZING A VACCINATION SESSION

Zone	Site	Equipment	Personnel	Tasks
Waiting area	Spacious and shady place	Sheet for the shade, tanks with drinkable water	Community volunteers	Keeping calm and order
Sorting area	After the waiting area	Ropes, stakes	Members of community	Verification of age and vaccinal status Information of side-effects
Registration	After shady zone Anticipate big space	Several tables, chairs, registers, vaccination cards, plastic envelopes, date stamps	Literate persons (school teachers)	Completion of vaccination cards (date, name, age)
Vaccination	After registration Spacious zone with waiting lines	Tables, chairs, vaccine supports, fridges, cold batteries, injection material, trays, water, soap	Community health workers trained in vaccination; facilitators	Dilution of vaccine Preparation of syringes Vaccination (0.5 ml/SC or IM)
Check out	In front of exit	Tables and chairs Data record forms Date stamps	Literate persons (school teachers)	Completion of the data sheet record according to age groups Stamping of vaccination cards Directing families to exit
Storage	Close to vaccination site Shaded	All cold chain equipment (fridges, deep freezers for ice packs, generators) or ice boxes	Supervisor Responsible for equipment and supplies	Handling vaccines Planification of needs

SC = Subcutaneous.

IM = Intramuscular.

ORGANIZING A VACCINATION SESSION

Social mobilization

Success of the campaign will be guaranteed by simple elements such as:

- adequate communication with the public
- good organization

Creation of a mobilization committee improves efficiency. The committee can include:

- political and administrative representatives
- neighbourhood representatives
- health authorities
- a police chief

Depending on the size of the epidemic and the location, information will be transmitted by:

- the media (radio, television)
- megaphones in the villages
- district chiefs
- community health workers in health centres
- religious leaders

The message will describe:

- the illness and its complications
- the importance to detect cases and their referral to a hospital
- the advantages of vaccination and absence of side-effects
- the age groups to be vaccinated
- the location and time of vaccinations
- the importance to bring one's EPI vaccination card

Evaluation

During the campaign:

Establishing a system for data recording to assess the number of persons vaccinated per day and the number of vaccine doses used.

ORGANIZING A VACCINATION SESSION

The data form will be completed daily and will permit the calculation of:

- approximate vaccine coverage:

$$\frac{\text{number of doses administered}}{\text{target population to be vaccinated}} \times 100$$

- percentage of vaccine utilization:

$$\frac{\text{number of doses administered}}{\text{number of doses used*}} \times 100$$

*number of opened vials x number of doses/vials

After the campaign:

- carry out a global assessment of the data recorded during the campaign
- evaluate the vaccination campaign, if necessary, by carrying out a "vaccine coverage survey"
- assess morbidity and case-fatality ratio
- evaluate cost (of treatment and vaccination campaign)

VACCINATION CARD

Place:

N°:

Name:

Father's name:

Mother's name:

Birth date:

Sex:

Address:

<i>Vaccine</i>	DATE			
	1st dose	2nd dose	3rd dose	Booster
BCG				
DTP				
POLIO				
MEASLES				
HEPATITIS B				
MENINGOCOCCAL				
OTHER VACCINES				

WHO COLLABORATING CENTRES FOR MENINGOCOCCAL INFECTIONS

WHO Collaborating Centre for Reference Research on
Meningococcal Infections:

Institut de Médecine tropicale du Service de Santé des Armées
Parc du Pharo, B.P. 46
F-13998 Marseille-Armées, France
Tel: +33 4 91 14 01 15
Fax: +33 4 91 14 44 77
E-mail: imtissa@gulliver.fr
Dr G. Martet

WHO Collaborating Centre for Control of Epidemic Meningitis
Centers for Disease Control and Prevention
Atlanta, GA 30333, USA
Tel: +1 404 639 42 71 or 639 22 15 (direct)
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E-mail: dcaugant@extern.vio.no
Dr D.A. Caugant

WHO COLLABORATING CENTRE FOR VIRUS DISEASES

(Including enteroviruses causing viral meningitis)

WHO Collaborating Centre for Reference and Research on Virus
Diseases:

Public Health Laboratory Service
Central Public Health Laboratory
61 Colindale Avenue
London NW9 5HT, United Kingdom
Tel: +44 181 200 44 00
Fax: +44 181 200 78 74
Dr P. Mortimer