

Meningococcal Disease and Travel

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Invasive meningococcal disease, in both endemic and epidemic forms, is the cause of significant morbidity and mortality worldwide. Despite all advances in therapy, the fatality rate of meningococcal meningitis remains unacceptably high, between 5% and 10%, and a similar proportion suffers long-term neurological sequelae. Prevention of this rapidly fatal disease is of paramount importance. The use of the available internationally licensed meningococcal vaccines would be indicated for individuals with medical conditions that increase the risk of the disease and for travelers to high-risk countries. In the last 2 years, there has been a shift in the epidemic pattern of meningococcal disease during the Hajj (pilgrimage) season, with predominance of *Neisseria meningitidis* serogroup W135. Recent changes have been made in the policy issued by the Saudi Ministry of Health (Riyadh, Saudi Arabia), which requires visitors from all over the world arriving for purposes of *umra* and *Hajj* to show evidence of vaccination against meningitis with the quadrivalent meningococcal vaccine.

THE DISEASE AND SYMPTOMS

Invasive meningococcal disease, in both endemic and epidemic forms, is the cause of significant morbidity and mortality worldwide. Epidemics of meningitis were recorded decades before the discovery of the causative agent, *Neisseria meningitidis*, by Weichselbaum in 1887 [1]. Many epidemics occurred in Europe and America from 1837–1887. From the beginning of the twentieth century, the disease was also reported in Africa and during the years 1934–1941, it swept the whole area north of the equator and south of the Sahara “meningitis belt” (Lapeyssonnie; figure 1) [1]. Now the disease is endemic in many countries, and international travelers may be at risk of acquiring the disease during travel and can act as a reservoir for international spread of certain epidemic strains of the disease [3].

The meningococcus is a gram-negative, oxidase-positive, aerobic diplococcus. Pathogenic strains have a highly antigenic polysaccharide capsule which forms the basis for the major serogrouping. Isolates from patients with meningococcal disease belong almost exclusively to 5 of the 13 recognized *N. meningitidis* serogroups: A, B, C, W135, and Y [4]. Meningitis can be further divided into types, subtypes, and immunotypes

according to outer membrane proteins and lipo-oligosaccharides [5]. Most patients with meningococcal disease acquire their invading strain from an asymptomatic carrier: the bacteria lodge in the nose and throat of a patient and are spread through face-to-face contact, including coughing, sneezing, kissing, and the sharing of drinks, foods, and cigarettes [6]. The risk of invasive disease depends on age, functional or anatomic asplenia, host immune defense mechanisms, and bacterial virulence factors. Individuals with deficiencies of any of the complement components are highly susceptible to meningococcal infections [7]. After an incubation period of 2–10 days, initial symptoms may be similar to those of viral upper respiratory tract infections and can include fever and a general malaise. These symptoms may be followed by intense headache, nausea and vomiting, stiff neck, and maculopapular, purpuric, or petechial rash. Delirium and coma often appear. Occasional fulminant cases exhibit sudden prostration, ecchymoses, and shock. [8, 9]

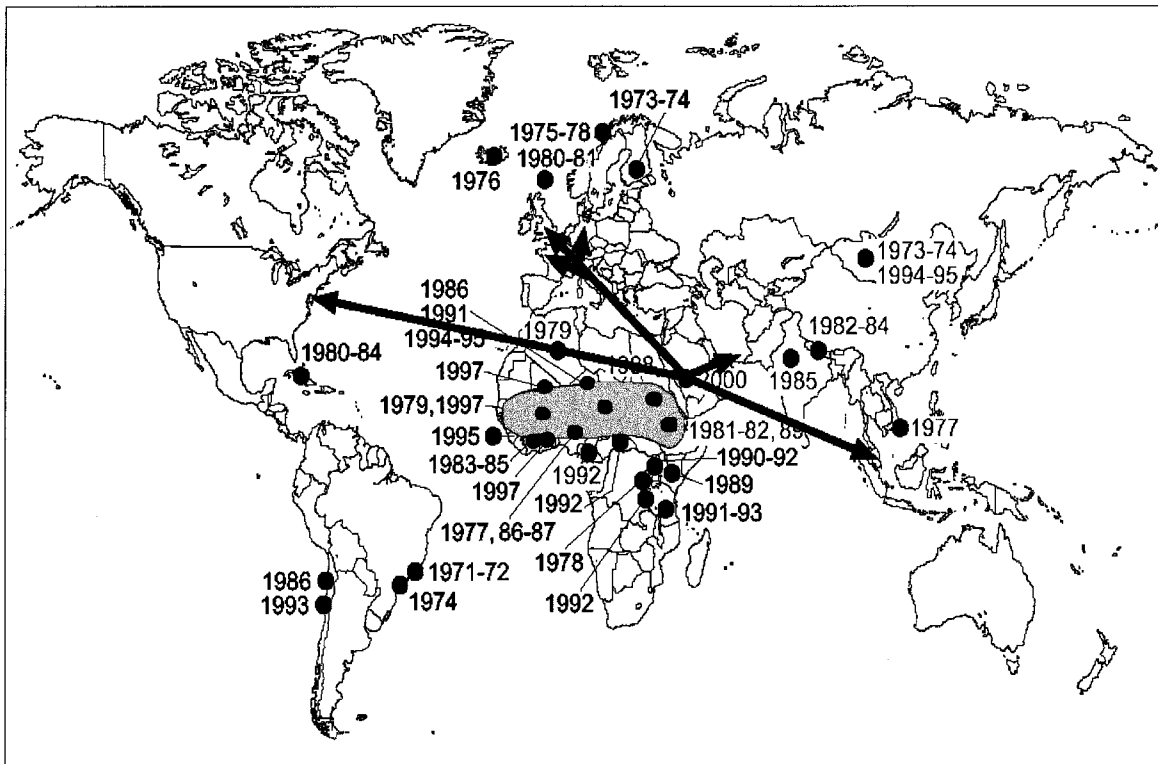
Meningococcal disease usually presents as meningitis in 80%–85% of cases, whereas in the remaining 15%–20% cases, it presents with pure septicemia without meningitis. Less common presentations include pneumonia, pericarditis, conjunctivitis, urethritis, and arthritis [10]. Even with timely antibiotic therapy, the case fatality rate (CFR) of meningococcal meningitis is between 5% and 10% [11, 12], and a similar proportion suffers long-term neurological sequelae. CFRs for septicemia can, however, be as high as 70% in developing countries and 19% in developed countries. It has been estimated that in

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■ Meningitis belt (Lapeyssonnie), main transmission December to June

Figure 1. Major outbreaks of meningococcal meningitis, 1971–2000. From Steffen and Dupont [2].

Third World countries >310,000 persons per year suffer from infections caused by *N. meningitidis*, resulting in 35,000 deaths [13].

Definitive diagnosis of meningococcal infection requires the isolation of *N. meningitidis* from a sterile body site, usually the blood or CSF. In suspected cases of meningococcal meningitis, CSF culture may give the highest yield, 94%, followed by blood culture, 50% [14]. The yield of Gram stain and culture of petiacheal skin lesion for *N. meningitidis* is ~70%. Newer, faster technologies utilizing PCR on the CSF have shown promising results, with sensitivity and specificity as high as 91% [15]. This area is rapidly developing, and it is hoped that this technology will be of particular value in patients who received parenteral antibiotics prior to presentation and will assist in rapid identification of meningococcal serogroups and subtypes [16, 17]. Studies using bacterial antigen detection method on the CSF can give rapid results and have been shown to be more sensitive in meningococcal meningitis caused by serogroups A and C than in serogroup B disease. Despite reports of resistance to penicillin G, sulfonamide, rifampin, and tetracycline, high-level resistance to penicillins through β -lactamase production is still extremely rare [18]. Recent reports documented the emergence of high-level chloramphenicol resistance in *N. meningitidis* isolates from Southeast Asia, where injectable chloramphenicol is

used commonly to treat meningitis [19]. At present, penicillin and ampicillin are the drugs of choice for *N. meningitidis*, and ceftriaxone or cefotaxime could be used as alternatives in case of severe illness [18]. In addition to antibiotic therapy, patients with poor prognostic signs or imminent shock need immediate fluid resuscitation, prompt start of mechanical ventilation, and transfer to a fully equipped intensive care unit.

EPIDEMIOLOGY

Meningococcal disease occurs as both endemic and epidemic disease in most parts of the world, with significant implications for morbidity and mortality. The worldwide incidence of meningococcal meningitis probably exceeds 100,000 cases per year. Although the majority of these cases occur in explosive epidemics in sub-Saharan African countries within the meningitis belt, small-epidemic meningitis is a worldwide problem and can affect any country [1]. Among the different serogroups of *N. meningitidis*, serogroups A, B, and C account for up to 90% of the disease [4]. During the 1990s, the frequency of outbreaks of meningococcal disease has increased in many developed countries, with serogroup C disease most noticeable, especially among teenagers and young adults, particularly in the United States and Canada [20, 21]. Recent studies have identified cer-

tain behaviors—such as secondhand or active smoking, visits to crowded, poorly ventilated bars, and intimate kissing—are important risk factors for meningococcal serogroup C infection during outbreaks [22, 23]. In most European and many Latin American countries, serogroup B is the most prevalent [24].

Historically, serogroup A has been the most common cause of epidemic and endemic meningococcal disease in sub-Saharan Africa. Elsewhere, the most explosive epidemics of meningococcal meningitis have also been almost exclusively associated with serogroup A, as in Nepal (1983–85) and Saudi Arabia (1987; figure 1) [25, 3]. To date, the risk factors for epidemic meningococcal disease have not been completely understood. It is believed, however, that an outbreak will occur where the presence of a virulent strain of *N. meningitidis* exists in an immunologically susceptible population and the climate is optimal (dry season). Virulent strains of *N. meningitidis* most often express capsules of serogroups A, B, C, Y, and, sometimes, W135. By contrast, isolates of asymptomatic nasopharyngeal carriers are nongroupable or express X, Z, or 29 E capsular serogroup. Invasive meningococcal isolates also have specific serotype and subtype proteins and lipo-oligosaccharide immunotypes. Most epidemic and endemic cases of meningococcal disease are caused by a limited number of genetically defined clonal groups that have been referred to as “hyperinvasive lineage.” The reason for the greater virulence of these lineages remains unknown [26, 27]. The concomitant presence of viral respiratory tract infection or *Mycoplasma pneumoniae* infection in the population will increase the chance of the epidemic [7, 28]. In most countries worldwide, the endemic attack rate of meningococcal diseases ranges from 1 to 5 cases per 100,000 population. This risk is much higher in sub-Saharan African countries, where it reaches close to 20 cases per 100,000 population. These rates vary from year to year in the same country. In the United States, epidemic-associated meningococcal disease accounts for only 2% of cases each year [29]. Therefore, the majority of outbreaks of meningococcal disease in the United States and other developed countries are endemic.

The latest reported cumulative incidence of meningococcal disease in the United States was 0.7 cases per 100,000, in 1998. The incidence was highest in infants, and the most common serogroups were C, B, and Y (35%, 32%, and 26%, respectively) [11].

RISK FOR TRAVELERS

Data on the true risk of meningococcal infection for travelers are rare, but it is accepted that the risk to travelers is generally low and cases are rare. Risk increases as the length of stay in risk areas and the level of contact with local populations increases.

Meningococcal disease has a special significance in the King-

dom of Saudi Arabia. Each year during the *Hajj*, ~2 million people from >140 countries worldwide gather in the holy cities of Mecca and Medina in Saudi Arabia. Despite the best efforts of local health authorities, a large outbreak of meningococcal meningitis occurred in 1987 among *Hajjis* (figure 1). The disease rapidly spread to *Hajjis* of all nationalities participating in the pilgrimage and to the Saudi indigenous population [3]. Outbreaks were eventually reported in other Persian Gulf states. In Qatar, 15 cases alone were seen in a 21-day period following the *Hajj* [30]. As with other epidemics in the “meningitis belt,” serogroup A was responsible. Electrophoretic enzyme typing revealed that the meningococcus has been brought to the Middle East by *Hajjis* from Nepal [3].

Since 1987, the health authorities of Saudi Arabia have implemented 2 preventive strategies to prevent further outbreaks: (1) compulsory vaccination requirements with the bivalent A and C vaccine for all pilgrims and (2) annual vaccination campaigns for all local populations living in high-risk areas (pilgrimage sites) or among high-risk groups [31]. This was coupled with compulsory administration of oral ciprofloxacin to pilgrims coming from the sub-Saharan African belt, in an attempt to reduce carriage rate. Those measures controlled the epidemic meningococcal disease during the following few years. Despite providing the vaccine free to everyone locally and enforcing the requirements of compulsory vaccination for international *Hajjis*, sporadic, small outbreaks of meningococcal disease continued to occur in Mecca (the actual site of *Hajj*) and Jidda (the main point of entry to the holy places), mainly these outbreaks were due to *N. meningitidis* serogroup A in 1992 and serogroup W135 in 1993, and occurred mainly among people who did not receive the vaccine [32–34]. The most common reason mentioned for not being vaccinated by both case patients and control patients was lack of knowledge about the disease [32, 33]. Education campaigns were introduced and made for successful control of serogroup A meningococcal disease. Review of all cases of meningococcal disease at the hospitals in Mecca during the period 1988–97 revealed that 431 (89.2%) of 483 cases were due to strains of serogroup A, 31 (6.4%) to serogroup W135, 16 (3.3%) to serogroup C, and 5 (1%) to serogroup B [35]. In February 1999, because there was no evidence of ongoing epidemic meningococcal disease in the Kingdom of Saudi Arabia, the US Centers for Disease Control and Prevention (CDC) changed its recommendation and lifted the vaccination requirements for people traveling to Saudi Arabia [36]. Coinciding with the *Hajj* pilgrimage during March 2000, an outbreak of meningococcal disease was identified by the health authorities of Saudi Arabia, where >300 cases of *N. meningitidis* serogroup W135 were reported in Saudi Arabia and 9 other countries among the *Hajj* pilgrims or their close contacts [37–39]. This was the first large outbreak of serogroup W135 meningococcal disease, which is a relatively uncommon

cause of meningococcal epidemic. This outbreak indicated a shift in the epidemic pattern of meningococcal disease during the *Hajj* and highlighted the need to revise the vaccination policy for the future *Hajj* seasons and consider utilizing the quadrivalent A/C/Y/W135 vaccine instead of the bivalent one. Attempts by the local health authority to make the quadrivalent meningococcal vaccine available for the year 2000 *Hajj* season were unsuccessful, because of a shortage of vaccine supply. Although only a small number of cases of meningococcal meningitis appeared in Mecca during the 2001 *Hajj* week, >109 cases of meningococcal meningitis (predominantly *Hajj* pilgrims from outside the Kingdom of Saudi Arabia), including 35 deaths, were reported cumulatively during the period 9 February–22 March 2001 [40]. More than 50% of these cases were confirmed to be the result of *N. meningitidis* serogroup W135. To address the significance of pharyngeal carriage among returning pilgrims, the CDC performed a study this year to assess the pharyngeal colonization among *Hajjis* and non-*Hajjis* before and after returning from Saudi Arabia, to verify the need to administer a prophylactic decolonizing agent to the returning *Hajjis* to prevent meningococcal meningitis outbreak among their close contacts. Among returning passengers, carriage of serogroup W135 was similar among pilgrims and nonpilgrims (0.8% vs. 0.9%; $P = .98$) [41]. On the basis of the low rate of carriage in the study population, prophylactic antibiotics were not recommended for returning *Hajjis*.

The changing pattern of meningococcal disease during the last 2 years, has prompted the Ministry of Health in the Kingdom of Saudi Arabia to change the policy for meningococcal vaccination for the upcoming *Hajj* season (2002), whereby all local population at risk will be vaccinated with the quadrivalent vaccine. The requirement for vaccination of pilgrims for year 2002 has also been changed to quadrivalent meningococcal vaccine. All international health authorities have been officially notified of this recent change [42]. The concern about the compliance of all 1–1.5 million *Hajjis* with the compulsory vaccination requirement will be magnified because the vaccine supply for next year might not be sufficient. This concern is also being considered for local Saudis who fail to get vaccinated or let their vaccinations lapse beyond the effective period. In Saudi Arabia, strict legislation is being implemented, whereby only local *Hajjis* with valid vaccination certificates are allowed to enter the holy places. It is hoped that the enforcement of the vaccination strategies will raise the immunity level among people performing the *Hajj* and prevent the spread of meningococcal disease.

Areas other than Saudi Arabia and countries in the meningitis belt of sub-Saharan Africa that should be targeted for meningococcal prevention include those with current epidemics as identified in frequent updates published by the World Health Organization and CDC and areas in sub-Saharan Africa

outside of the traditional meningitis belt in which recent epidemics have occurred within the last 3 years.

PREVENTION

N. meningitidis is the leading cause of meningitis worldwide and a significant public health problem in most countries. Despite all the advances in the therapy, the CFR still remains unacceptably high (5%–10%). Recently published data on the CFR of meningococcal disease during outbreaks in Mecca in 1987–97 shows a higher rate, 16.7% [35]. Chemoprophylaxis may prevent secondary cases (among contacts of cases), but they comprise only 1%–2% of all meningococcal disease; hence, chemoprophylaxis is not considered an ideal method to control endemic and epidemic meningococcal disease. The worldwide distribution of *N. meningitidis* varies by serogroup. Serogroups A, B, and C cause >90% of meningococcal disease worldwide. Throughout Asia and Africa serogroups A and C predominate, whereas serogroups B and C are responsible for disease in Europe, North America, Latin America, Australia, and New Zealand. Serogroup Y has been on the rise in many countries, including the United States, Sweden, and Israel, and serogroup W135 has recently emerged as a problem in Saudi Arabia. These changes in serotype-specific disease are not clearly understood and could be attributed to immunologic changes in the general population or to the introduction of a new strain of *N. meningitidis* into populations [8]. The use of the available internationally licensed meningococcal vaccines would be indicated for disease control. Monovalent (A or C), bivalent (A and C), or quadrivalent (A, C, Y, and W135) meningococcal polysaccharide vaccines exist that are effective and safe for adults and children >2 years of age. In children >4 years of age, they give a protective antibody response that develops within 10–14 days and lasts for up to 3 years [21, 43, 44], though in adults antibodies against serogroups A and C polysaccharide have been detected as long as 10 years after vaccination.

The serogroup B polysaccharide is not immunogenic in humans and thus is unsuitable as a vaccine antigen [44]. The serogroups A and C polysaccharide vaccine induces a good immune response among older children and adults, with clinical efficacy as high as 85%–100% [45]. Although serogroup A polysaccharide vaccine can induce antibody in some infants as young as 3 months of age, serogroup C polysaccharide vaccine never gives any protective immunity in children <2 years of age. Despite the lack of efficacy data, it is believed that the serogroups Y and W135 polysaccharide vaccine is immunogenic in older children and adults. In general, the antibody response to the polysaccharide vaccine is age dependent, with very high efficacy in adults. With the exception of serogroup A, the polysaccharide vaccine elicits incomplete and short-lived protection in infants and preschool children. It is not clear why

meningococcal A vaccine is effective in infants >3 months of age, but the duration of protection is age dependent and declines rapidly within 1–2 years. Conjugated meningococcal vaccines have been shown to be more immunogenic in humans [46].

Published data are available only for serogroups A and C conjugate vaccine. Meningococcal group C conjugate vaccine uses the same technology as the *Haemophilus influenzae* type B conjugate vaccine. Conjugation of the serogroup C polysaccharide to a protein carrier switches the immune response from a thymus-independent to a thymus-dependent one.

Three meningococcal group C conjugate vaccines are licensed in the United Kingdom and have been used across all age groups, infants, toddlers, preschool children, teenagers, and young adults. The vaccine induced an improved primary antibody response in all age groups and, when compared with the polysaccharide vaccine, it also induced immunologic memory. Prior vaccination with polysaccharide vaccine did not seem to impair the induction of this immunologic memory. Experience with Hib conjugate vaccine suggests that the group C meningococcal conjugate vaccine is also likely to have a major effect on carriage of group C meningococci in the vaccinated and unvaccinated members of the population [47].

INDICATIONS FOR MENINGOCOCCAL VACCINE IN TRAVELERS

In considering whether the meningococcal vaccination is to be of benefit for the international traveler, careful assessment of the known risk factors for disease acquisition must be made. This assessment includes the traveler's medical condition and the details of the planned trip as it relates to the destination of travel, the required vaccination of that country, duration of stay (high risk exists for long-term travelers) and the expected activities (high risk exists for high level of contact with local population [e.g., sharing crowded accommodation or transportation, working in the medical field with extensive patient contact]) [48–50].

Individuals should be vaccinated if they have underlying health problems recognized to increase the risk of acquiring meningococcal disease. Functional or anatomic asplenia, terminal complement deficiency, alcoholism, or any other immune-suppressing conditions all contribute to risk. Additionally, individuals <30 years of age traveling to countries of the African meningitis belt during the dry season (December–June) or countries in sub-Saharan Africa outside the meningitis belt (where outbreak of meningitis has been reported in the preceding 2–3 years) and individuals traveling to a recently identified area of epidemic meningitis by international health authorities [36–51]. A number of options for vaccines exist, including the quadrivalent polysaccharide vaccine, the only me-

ningococcal vaccine that is licensed and available in the United States. The choice of vaccine given will depend on knowledge of the predominant strains causing disease in the country of travel. In most industrialized countries, the common strains causing disease are serogroups B and C, and, except for the United States, Sweden and Israel, where the incidence of serogroup Y meningococcal disease is noted, the monovalent C or bivalent A and C vaccine could be used. In the United States, Sweden, and Israel, the quadrivalent vaccine is recommended. In Africa and Asia, serogroups A and C predominate and except for Saudi Arabia, where recent emergence of serogroup W135 has been noted, bivalent vaccine A and C can be used. The Saudi Ministry of Health (Riyadh, Saudi Arabia) has recently issued new policy which requires visitors from all over the world arriving for purposes of *umra* or for the *Hajj*, or for seasonal work, to show evidence of vaccination against meningitis issued not >3 years and <10 days before arrival in Saudi Arabia. Adults and children >2 years of age must receive 1 dose of the quadrivalent (A, C, Y, W135) vaccine, and children between 3 months and 2 years of age should be given 2 doses of the A vaccine with a 3-month interval between the 2 doses [42]. It is imperative that explanations of the limited efficacy of the vaccine against serogroup C be given to parents traveling with children <2 years of age, and consideration should be given to providing prophylactic medication to be administered only after contact with a case. "Significant contact" includes household members, day care center contacts, and exposure to patients oral secretions. Because the rate of secondary disease for close contact is highest during the first few days after onset of disease in the index patient, the chemoprophylactic agents should be given within the first 24 h. In children, rifampin is the chemoprophylactic agent of choice, and the dosing depends on the child's age. In children <1 month of age, the dosage is 5 mg/kg q12h for 2 days, whereas children >1 month of age should receive 10 mg/kg q12h for 2 days. The only other alternative chemoprophylaxis in children <15 years of age is ceftriaxone injection, where 125 mg is given as a single dose. In adult patients, in addition to the above, other alternatives include a single oral dose of a quinolones such as ciprofloxacin (500 mg) or ofloxacin (400 mg) or a single dose of a macrolide such as azithromycin (500 mg). Mass chemoprophylactic programs are not recommended to control large outbreaks, due to their cost, the logistic problems, and continuous multiple source exposures. Nevertheless, the lack of efficacy of polysaccharide vaccine in eradicating *N. meningitidis* carrier status, the poor compliance of the 2 million *Hajjis* performing the *Hajj* every year, and cases of meningitis among Saudis either returning from *Hajj* or their household contacts, compels the Saudi Ministry of Health to consider mass chemoprophylaxis to all local *Hajjis* before and after performing the *Hajj* next season 2002 (Ministry of Health, Saudi Arabia, personal com-

munication). It is hoped that data generated from this exercise will generate useful information on the cost effectiveness of mass chemoprophylaxis. Costly mass chemoprophylaxis will not be considered or justified in the near future when the conjugate vaccines containing A, C, W135, and Y (which is in early development) are licensed. Whether the new conjugate quadrivalent vaccine passes the test of time in inducing long-lasting immunity and mucosal antibody (which suggests that they may reduce carriage of all 4 *N. meningitidis* serogroups included in the vaccine) remains to be seen.

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