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CME REVIEW ARTICLE

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Epidemiology and prevention of meningococcal disease

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OBJECTIVES

1. *To review the historical, microbiologic and clinical aspects of meningococcal disease.*
2. *To understand the epidemiology of meningococcal disease in the United States and Africa.*
3. *To outline therapeutic options in the treatment and prophylaxis of meningococcal disease, particularly in view of increasing antibiotic resistance.*
4. *To review the use of currently available vaccines and the development of more immunogenic and effective vaccines.*

More than two decades have passed since the development of the first successful polysaccharide vaccines for the prevention of group A and C meningococcal disease. Since then additional polysaccharide vaccines have been developed for serogroups Y and W135. These vaccines are poorly immunogenic in infants and small children and have a limited duration of protection in children. Substantial progress in the field of immunology has enhanced our ability to make polysaccharide antigens immunogenic in infants. Because disease caused by *Neisseria meningitidis* continues to cause substantial morbidity and mortality, particularly in the developing countries of the African meningitis belt, it is important that these advances be applied to the production of new effective meningococcal vaccines that could be incorporated into routine infant immunization programs. Although individual host risk factors such as complement component deficiencies have been described, risk factors for epidemic disease remain poorly understood. This review will focus on the epidemiology and prevention of meningococcal disease with an emphasis on the epidemiology of meningococcal disease in Africa and the progress in vaccine development in recent years.

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MICROBIOLOGY

Epidemic spinal meningitis was first described by Vieusseux in the area around Geneva, Switzerland, in the spring of 1805.[1] *N. meningitidis*, initially isolated from cerebrospinal fluid (CSF) by Weichselbaum[2] in 1887, is a Gram-negative diplococcus distinguished from *Neisseria gonorrhoeae* by its ability to ferment both maltose and glucose; the gonococcus ferments only glucose. The meningococcus is classified on the basis of its capsular polysaccharides, outer membrane proteins (OMPs) and lipopolysaccharides. Capsular polysaccharides are classified into 12 serogroups: A, B, C, X, Y, Z, W135, 29E(Z'), H, I, K and L.[3] Unique serotypes are defined on the basis of antigenic differences in the class 2 and 3 OMPs, whereas differences in the Class 1 OMPs determine subtypes.[4,5] There are currently more than 20 serotypes and at least 10 class 1 subtypes. Thus B:15:P1.16 represents serogroup B, serotype 15 and subtype P1.16. The 11 lipopolysaccharide immunotypes are defined by heterogeneity in the lipopolysaccharides of the cell membrane.

CLINICAL SYNDROMES

Infection with the meningococcus results in one of four major clinical conditions. The most common is asymptomatic nasopharyngeal carriage. Humans are the only known carriers of the meningococcus and serve as reservoirs for continued transmission. The organism is spread from person to person by intimate contact with oral secretions or exposure to respiratory droplets. Natural immunity develops as the result of asymptomatic carriage, typically 2 weeks after nasopharyngeal infection begins.[6] Baseline carriage prevalence rates in the United States range from 5 to 11%, and the median duration of carriage in two studies ranged from 8.5 to 9.6 months.[7,8] Factors thought to increase the carriage rate include crowded conditions such as those existing in military barracks,[9] coincident viral infections[10] and cigarette smoking.[11] A case-control study in England showed no difference in meningococcal carriage rates associated with household crowding, housing conditions, frequency of physical exercise or upper respiratory illnesses between patients and controls.[11] There was a significantly increased risk of meningococcal carriage among active smokers and among persons exposed to smokers (passive smoking).[11] During the first World War the prevalence of carriage was thought to be an indicator of invasive disease, with epidemics occurring when the carriage rate exceeded 20%. Attempts to modify the carriage rate by isolating carriers and patients proved ineffective. During World War II the United States Army undertook massive carriage studies of all military recruits. These findings were summarized in a review by Aycock and Mueller[12] who found that "... the incidence of the disease is greater in recruits than in seasoned troops, greater in the military than in civilian populations and greater in winter than in summer, despite the fact that the carrier rate appears to be the same in all."

Meningococci are occasionally grown from blood cultures in the absence of classic findings of meningococcemia. This "benign bacteremia" is discovered when blood cultures are obtained as part of the evaluation of fever; frequently no antibiotic therapy has been initiated and the patient has improved by the time the positive cultures are noted.

Meningitis, the most common pathologic presentation, manifests with the classic findings of fever, headache and stiff neck. Meningeal infection is the result of hematogenous dissemination of the organism. Laboratory evaluation of the CSF shows an elevated number of white blood cells (predominantly polymorphonuclear leukocytes) usually in the hundreds or thousands per ml. The CSF glucose concentration is low (<50 mg/dl), and the protein is elevated. Mortality despite optimal antimicrobial treatment and supportive care remains about 5% in children younger than 5 years of age and 10 to 15% in adults.

Meningococcemia is the most severe form of infection: patients may present with a petechial or purpuric rash, hypotension, disseminated intravascular coagulation, and multiorgan failure. The condition is often fulminant, with death occurring 12 to 48 hours after presentation. The case-fatality rate ranges from 15 to 30%. Poor prognostic findings include shock, coma, acidosis, seizures, disseminated intravascular coagulation and thrombocytopenia.[13]

Other forms of meningococcal disease such as purulent arthritis, pericarditis and endophthalmitis[14] are less common and are the result of metastatic infection during the bacteremic phase. Meningococcal conjunctivitis is uncommon, found in 2% of children (21 of 1030) with bacterial conjunctivitis in one series; however, 29% (6 of 21) of the children went on to develop systemic disease.[15]

EPIDEMIOLOGY

Endemic or sporadic meningococcal disease incidence rates in developed countries are 1 to 3/100 000 persons, whereas endemic rates in many developing countries range from 10 to 25/100 000 persons.[16–20] In a multistate surveillance project conducted between 1989 and 1991 in the United States, the average annual incidence of meningococcal disease was 1.1/100 000; 46% of cases occurred in children ≤2 years of age, and the highest age-specific incidence was in children younger than 4 months of age. The incidence did not differ significantly between males and females.[21] Meningococci of serogroups B and C accounted for most of the endemic disease in the United States; of 261 meningococcal isolates available for serogrouping, 46% were group B and 45% were group C.[21]

Between 1985 and 1992 a clonal serogroup C meningococcal strain (defined by multilocus enzyme electrophoresis) designated ET-15 has been associated with an increase in both the incidence and mortality of invasive meningococcal disease in Canada.[22] This clonal strain and four other closely related strains have also been implicated in a marked increase in the number of serogroup C outbreaks in the United States since 1991.[23] These strains are part of a larger but genetically related complex of strains (ET-37) responsible for small outbreaks and sporadic disease on several continents in the 1980s.[24]

Ongoing surveillance shows that fewer than 1% of meningococcal isolates in the United States are serogroup A.* The United States has not experienced a major epidemic of meningococcal disease since 1945. In contrast large epidemics of meningococcal disease, pri-

* Centers for Disease Control and Prevention, unpublished data.

marily caused by serogroup A, continue to occur in other parts of the world and account for the major morbidity and mortality of this pathogen.

MENINGOCOCCAL DISEASE IN AFRICA

Epidemics of meningococcal disease continue throughout the world, although nowhere have recurrent epidemics caused more morbidity than in the countries forming the meningitis belt of sub-Saharan Africa. Originally defined by Lapeyssonnie[25] as the region bordered on the north by the 300-mm isohyet or precipitation band, the belt extends southward to the 1100-mm isohyet. The region initially described by Lapeyssonnie consisted of portions of 10 countries: Burkina Faso, Ghana, Togo, Benin, Niger, Nigeria, Chad, Cameroon, Central African Republic and the Sudan. Greenwood[26] later suggested that the belt be expanded both east and west to include portions of Ethiopia, Mali, Guinea, Senegal and The Gambia. These 15 countries form the expanded meningitis belt (Fig. 1).

In this region epidemic attack rates have approached 1000/100 000 (1%). In 1988 more than 57 000 cases of meningococcal disease were reported from the African continent; in 1989 the number of cases increased to over 70 000, with more than 40 000 of these cases reported from Ethiopia (World Health Organization, unpublished data). Because reporting is often delayed and incomplete, this figure likely represents a substantial underestimate of the actual number of cases. The magnitude of the problem in the meningitis belt is illustrated by the fact that although only 42% of the population of Africa resides in the countries of the meningitis belt, over 80% of the total number of cases of meningococcal disease for both 1988 and 1989 were reported from these 15 countries.

FIG. 1. Map of the African meningitis belt (adapted from Lapeyssonnie[25] and Greenwood.[26]

The medical and economic impact of meningococcal epidemics is substantial. Essential services and personnel must be diverted to cope with the outbreak, and costs for antibiotics, vaccine, vehicles and fuel strain limited health budgets.

To evaluate the epidemiology of meningococcal disease in Africa, we analyzed historical reports of epidemics from 1919 to 1955 and data provided to the World Health Organization from 1955 to 1989 to calculate the country wide incidence of reported meningitis (World Health Organization, unpublished data; the Directorate, Epidemiology, Department of National Health and Population Development, Republic of South Africa, unpublished data).[27–30] Census estimates were obtained from the United Nations World Population Prospects, 1988.[31] These data have obvious limitations. Reporting sensitivity varies by country and by time, and in some countries a large part of the population is outside of the meningitis belt. We arbitrarily defined an epidemic as a reported rate ≥100/100 000. Thirty-four epidemics occurred during the observation period. The median duration of an epidemic was 1 year (range, 1 to 6 years).

Table 1 shows the number of years for which data were available from 1919 to 1989, the maximum and minimum annual rates and the mean annual incidence for each of the 15 countries in the meningitis belt. Missing values were not included in the calculation of the mean. Figure 2 displays the annual incidence (rates per 100 000) in 8 countries of the meningitis belt.

The observation by Lapeyssonnie[25] that epidemics recur in 8- to 12-year cycles is not confirmed by these data (e.g. Niger). Although a pattern of epidemics every 8 to 12 years has been noted in Burkina Faso[32] and is apparent in Senegal, consistent cyclic patterns are not present in most countries included in the meningitis belt. To evaluate this observation further we examined

TABLE 1. Meningococcal meningitis in Africa: annual incidence, 1919 to 1989

Country	Years Data Available	Rates/100 000 Population		
		Maximum	Minimum	Mean
Gambia	40	158.5	2.0	23.58
Senegal	58	459.0	0.0	25.90
Guinea	40	28.0	0.0	4.29
Mali	59	238.0	0.0	28.11
Burkina Faso	62	399.0	0.0	72.33
Ghana	60	249.5	0.0	22.85
Togo	55	962.0	0.0	34.67
Benin	59	331.5	0.0	21.47
Niger	57	449.0	0.0	76.17
Nigeria	54	174.5	0.0	16.93
Cameroon	63	55.0	0.0	10.88
Chad	53	497.5	0.5	49.15
Central African Republic	39	28.0	0.0	11.62
Sudan	49	554.5	1.0	50.20
Ethiopia	40	98.0	0.0	6.75

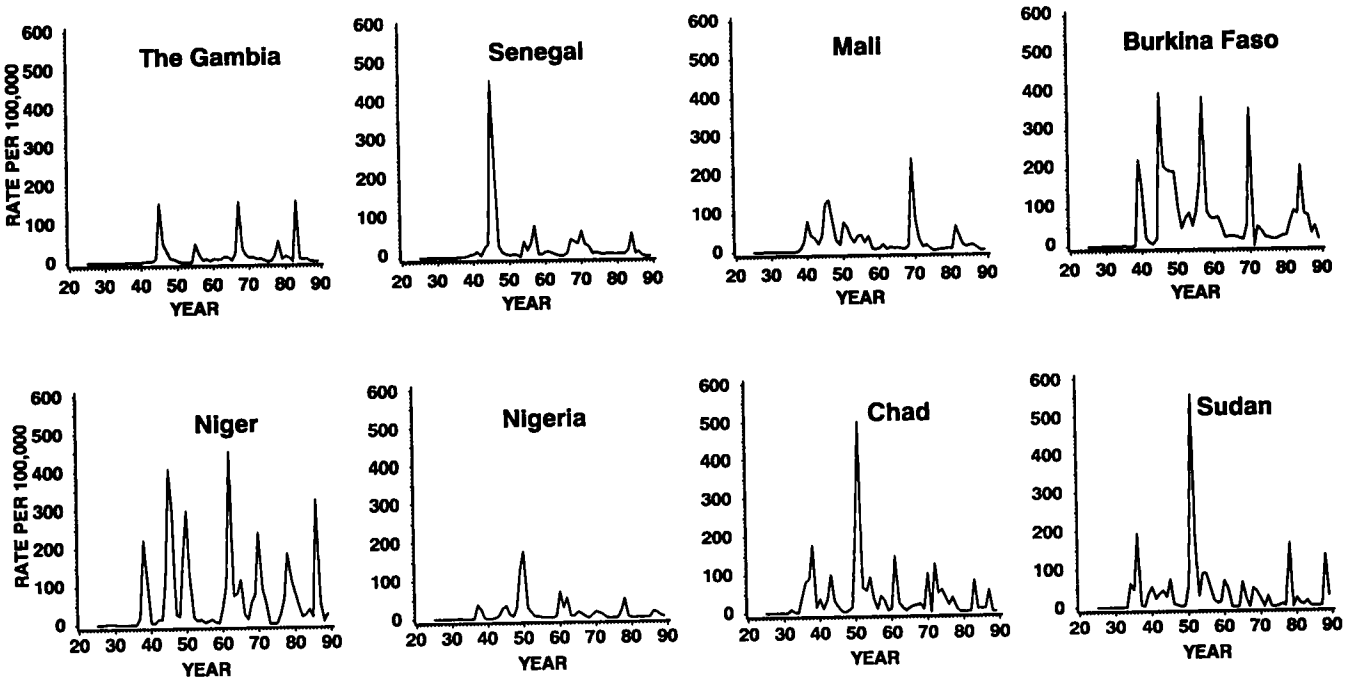

FIG. 2. Meningitis rates (per 100 000 persons) in selected countries of the African meningitis belt.

the intervals between epidemics. The mean interval between epidemics was defined as the period ≥1 year, beginning with the year after an epidemic and extending through the year before the next epidemic. The median interval between epidemics in the meningitis belt was 9 years (range, 2 to 25 years). However, Figure 3 shows that interepidemic intervals varied widely. Almost 70% of epidemic intervals are 12 years or less; 9 (41%) intervals are less than 8 years. Thus although populations in the meningitis belt experience recurrent epidemics of a magnitude unmatched in most areas of the world, predictable cycles of epidemic disease are uncommon.

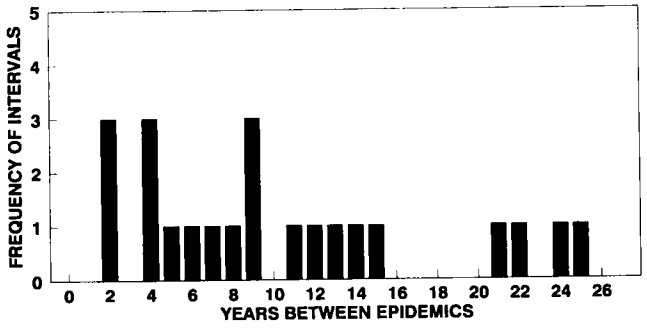

FIG. 3. Periodicity of epidemics from 1919 to 1989 in 15 countries of the African meningitis belt. An epidemic was defined as an annual rate ≥100/100 000 persons. An interval was defined as the period ≥1 year, beginning with the year after an epidemic and extending through the year before the next epidemic. Terminal intervals were not included. Twenty-two intervals are shown. The median interval between epidemics was 9 years (range, 2 to 25 years).

ORGANISM CHARACTERISTICS

The reasons for recurrent epidemic disease in the meningitis belt of Africa are unclear. One variable that may effect the occurrence of epidemic disease is the introduction of a virulent organism. An example of a highly related meningococcal clonal group causing intercontinental spread of group A epidemics is demonstrated by the spread of the III-1 clonal strains. First noted in China in the early and mid-1960s,[33] strains of this clonal complex appeared in Nepal in 1983, in Saudi Arabia in 1987, in Chad and the Sudan in 1988,[34, 35] in Ethiopia and Kenya in 1988 to 1989[33, 36] and in Uganda in 1989 to 1990 (Uganda Ministry of Health, unpublished data).* Group A meningococcal disease in northern Tanzania[37] suggests the continued spread of this clonal group outside the usual boundaries of the meningitis belt.

The 1987 epidemic in Saudi Arabia was associated with the Haj, the annual Moslem pilgrimage to Mecca. Eight primary cases of meningococcal disease occurred in Hajis from the United States, an attack rate of 640/100 000. Carriage of the epidemic strain was found in 11% of those returning on flights from Mecca, illustrating how widespread dissemination of an epidemic strain can occur.[38] No secondary cases of group A meningococcal disease were reported in the United States after the Haj.

After the 1987 Haj epidemic the Saudi Ministry of Health required all future Hajis to show evidence of meningococcal vaccination before being allowed to enter the Kingdom during the Haj. In 1990 fewer than 20 cases of meningococcal disease occurred during the

Haj, although one American Haji who had not been vaccinated became ill on the return flight from Mecca; the meningococcus isolated was a serogroup A strain in the III-1 clonal complex, suggesting the persistent circulation of this clone in the region.

INDIVIDUAL SUSCEPTIBILITY

The risk of meningococcal disease decreases with increasing age. During the multistate surveillance project in the United States from 1989 to 1991, 49% of invasive meningococcal disease occurred in children ≤2 years of age.[21] In contrast to endemic disease the average age of patients increases during epidemics. In Finland the ratio of case patients older than 4 years of age to those younger than the age of 4 increased more than 3-fold when epidemic years were compared with pre- and postepidemic years.[39] The reason for this age shift is unclear. It may represent a more global risk factor such as environmental conditions, the introduction of a more virulent clone, the dissemination of an infectious cofactor or the lack of population immunity.

Individual host factors that predispose to invasive meningococcal disease have been well-described. The most well-known are deficiencies in the complement system,[40–42] in particular deficiencies of the terminal complement components (C5 to C8).[43–49] More recently meningococcal disease has been documented in persons with deficiencies of C2,[50] C3,[44] homozygous C4b[51] and C9.[52–54] Kindreds in which properdin, a component of the alternative pathway, is absent or dysfunctional have been shown to be at increased risk for meningococcal disease.[55–57]

Meningococcal infection in persons with properdin deficiency is associated with a case-fatality rate of 75%[57] compared with 2.9% in persons with deficiencies of the terminal complement components.[40] The lower case-fatality rate in persons with terminal complement deficiencies contrasts sharply with the overall case-fatality rate of 12 to 17%.* The reason for this is not clear but may reflect an ascertainment bias, because those with fulminant disease and early death are less likely to undergo complement testing.

Anecdotal reports have found an association of meningococcal disease and IgM deficiency[58] and IgG2 subclass deficiency.[59] Data are insufficient to ascribe a causal relationship, although immunoglobulin subclass deficiency, particularly IgG2 and IgG4, is associated with a failure to respond to a polysaccharide vaccine.[60] Although both complement and immunoglobulin abnormalities may increase an individual's risk for invasive disease, the prevalence of these conditions is too low to account for widespread epidemic disease.

POPULATION SUSCEPTIBILITY

The curious geographic and meteorologic boundaries of the African meningitis belt have prompted studies of the role of climate as a factor in these epidemics. Within the meningitis belt, the incidence of disease is greatest during the dry season between December and June, with disease incidence increasing markedly in January and returning to normal monthly levels in late June when the rainy season starts.[25, 26] Several theories to explain this seasonal pattern have been proposed, including changes in social behavior during the dry season when agricultural activity decreases. However, as pointed out by Greenwood,[26] this does not explain the simultaneous seasonal outbreaks in large urban centers where social activities are not as greatly influenced by farming.

Studies in Africa show that rates of carriage do not change seasonally. Carriage continues throughout the wet months despite dramatic seasonal fluctuations in the rates of invasive disease.[61–63] Carriage studies of both civilian and military populations during the last epidemic in the United States also showed no seasonal variation despite a clear seasonal pattern of invasive disease.[12] Similar observations have been made in the United Kingdom.[64] Although a clearly demonstrable seasonal pattern in the incidence of invasive meningococcal disease exists, temperature and humidity appear to have a negligible impact on the prevalence of carriage.

Certain infectious agents may increase the risk of bacterial disease by transiently suppressing the immune response. *In vitro* abnormalities have been demonstrated in the function of lymphocytes, monocytes, macrophages[65] and neutrophils[66] after viral infection. Investigators have found an association between bacterial meningitis and *Mycoplasma* infection[67, 68] as well as infection with a number of viruses including influenza, adenovirus, parainfluenza and respiratory syncytial virus.[10, 67, 68] These studies must be interpreted with caution. Two of the studies were conducted in the setting of small outbreaks or sporadic disease; only one was performed in the course of a large scale epidemic.[68] Also confirmation of infection with *Mycoplasma* and viral agents was often serologically based, and polyclonal antibody increases may be seen after severe bacterial infection. Finnish investigators[69] found what they considered to be nonspecific increases in *Mycoplasma* antibody titers after bacterial meningitis.

Infectious agents such as enteric bacteria may induce cross-reacting IgA antibodies. These antibodies, which are unable to fix complement, competitively inhibit the binding of bactericidal IgG and IgM antibodies to the meningococcus.[70] Griffiss[71] has theorized that it is the slow fecal-oral spread of these enteric organisms that determines the time-space characteristics of an epidemic and respiratory droplet transmission of the meningococcus that determines the magni-

tude. One might hypothesize that the seasonal fluctuations in the prevalence and transmission of these enteric organisms, followed by changes in the host immune response to the meningococcus, account for the seasonal pattern of invasive disease. Few data, however, support this hypothesis. During an investigation of an outbreak of meningococcal disease in the Pacific Northwest, Filice et al.[72] could isolate cross-reacting bacteria (*Bacillus pumilus* and *Streptococcus faecalis*) from only three individuals in the study. None of these persons were nasopharyngeal carriers of the meningococcus or had invasive disease.

Finally certain bacteria, including viridans streptococci, have been shown to inhibit the growth of the group A meningococcus *in vitro*. Epidemiologically it has been shown that there is an inverse relationship between the risk of meningococcal carriage or disease and the prevalence of these organisms in the nasopharynx.[72]

The role of temperature, humidity and infectious cofactors has been difficult to establish, although it seems plausible that the changing prevalence of infection and carriage of a number of organisms, including bacteria and viruses, may influence the microenvironment inhabited by the meningococcus and may increase the susceptibility of the host. The role of infectious agents as cofactors in the development of invasive meningococcal disease deserves further study.

THERAPY

Serum therapy was the first successful treatment of meningococcal disease. In 1913 Flexner[73] published a report of 1294 patients treated with direct subdural injections of serum. Mortality compared with that of historical controls decreased from 70 to 90% to 31%. The discovery of sulfa in the 1930s and its success in treating meningococcal disease represented a major advance and replaced serum therapy as the treatment of choice. With the development of sulfa resistance in the 1950s, penicillin became the antibiotic of choice for invasive meningococcal disease. Penicillin-resistant strains of meningococci (minimum inhibitory concentration, MIC 0.1 to 1.28 μg/ml) have been reported from Spain,[74] England,[75] South Africa,[76] Canada[77] and the United States;[78, 79] disease caused by these partially resistant meningococci may be associated with a higher complication rate.[80] The penicillin-resistant isolates from Spain were susceptible to ceftriaxone.[81] Ceftriaxone and other third generation cephalosporins such as cefotaxime and ceftazadime are active against Gram-negative bacteria and achieve high CSF concentrations. Although these antimicrobial drugs have increased the number of therapeutic choices, cost limits their extensive use. For meningococcal disease in most countries they are not needed.

Chloramphenicol, usually considered a bacteriostatic agent, is bactericidal against the meningococcus and achieves high concentrations in the CSF.[82] It remains an excellent alternative to penicillin for the treatment of meningococcal disease. Several studies have suggested that a single injection of a suspension of chloramphenicol in oil could successfully treat patients with meningococcal meningitis.[83–85] A controlled trial by Wali et al.[86] showed that a single injection of chloramphenicol in oil was as effective as a 5-day course of crystalline and procaine penicillin, providing an acceptable treatment option in areas where access to medical care is limited. Chloramphenicol in oil is not effective in the treatment of pneumococcal meningitis and great care should be exercised in the empiric application of this drug. Single dose therapy with chloramphenicol in oil should be reserved for the treatment of diagnostically confirmed cases of meningococcal meningitis or treatment of suspected cases in the setting of a documented meningococcal epidemic. In the latter setting patients should receive careful follow-up to document a satisfactory response, because meningitis caused by the pneumococcus will continue to occur.

Data on the use of adjunctive corticosteroids in the treatment of meningococcal meningitis are limited. The number of individuals with meningococcal disease in one study was too small to assess clinical efficacy.[87] In a second study 267 patients with meningococcal meningitis were randomized to receive steroid or placebo treatment. No difference in the frequency of neurologic side effects was observed in the 251 survivors.[88]

PREVENTION: CHEMOPROPHYLAXIS

The role of antibiotics in eliminating carriage is limited to those persons with an increased risk of developing invasive disease. Household contacts exposed to a case of meningococcal disease have a 500- to 800-fold[89] to 3000- to 4000-fold[90] increased risk of developing invasive disease. Whereas earlier studies showed that 70 to 80% of secondary cases occurred within 14 days of the primary case,[89, 91] a recent report from England noted that 9 (53%) of 17 secondary cases occurred 5 to 39 weeks after the primary case.[92]

Current recommendations of the Advisory Committee on Immunization Practices are that household members, day-care center contacts and persons exposed to the oral secretions of the patient should receive prophylaxis.[93] Unless the organism is known to be susceptible to sulfadiazine, the antibiotic of choice is rifampin (600 mg every 12 hours for adults, 10 mg/kg every 12 hours for children 1 month of age and older and 5 mg/kg every 12 hours for children less than 1 month of age for 2 days).[93] Minocycline 100 mg orally twice daily for 3 days or ceftriaxone 250 mg intramuscularly[94] are acceptable alternative agents. Rifampin

should not be given to pregnant women because of its potential teratogenicity. Minocycline, in addition to causing vestibular toxicity, discolors teeth and should not be used for pregnant women or children.

Chemoprophylaxis is not appropriate for epidemic control because of the multiple sources of exposure and prolonged duration of risk. For example during the 1987 Haj epidemic, carriage rates for pilgrims returning to the United States were similar in those who did and did not report using rifampin prophylaxis (14% *vs.* 10%, respectively).[38] Furthermore a study of chemoprophylaxis during the same outbreak showed substantial acquisition of carriage in the control population, suggesting that the apparent prophylaxis failures were caused by recolonization with the epidemic strain.[94]

IMMUNITY

In the late 1960s Goldschneider et al.[95] showed that the incidence of meningococcal disease correlates inversely to the level of serum bactericidal activity against the meningococcus. In military recruits studied prospectively, 51 of 54 persons with meningococcal disease lacked bactericidal antibody to the disease-producing strain as well as the heterologous strains of meningococci. The lack of bactericidal activity of these sera could be corrected by the addition of purified gamma-globulin but was not enhanced by exogenous complement.[95]

Natural immunity follows both disease and nasopharyngeal carriage. Kayhty et al.[96] found that among children older than 1.5 years, 85% with group A disease and 90% with group C disease developed a 4-fold or greater increase in antibody levels and/or a high specific antibody level, defined as an acute or convalescent antibody concentration exceeding the 99th percentile of that found in the general population. However, serologic studies of group A meningococcal infection should be interpreted with caution. Nonspecific 4-fold increases in antibody to group A meningococcus occurred in 22.5% of infections with other bacteria such as *Haemophilus influenzae* type b, group C meningococcus and *Streptococcus pneumoniae*.[96]

Carriage of the meningococcus results in increased bactericidal antibody to the carriage isolate and to heterologous meningococcal strains in 92 and 87% of carriers, respectively.[6] Increases in titers of IgG, IgM and IgA antimeningococcal antibodies usually occur within 2 weeks of the onset of carriage.[6] Serum bactericidal activity consists of antibodies directed against both specific capsular polysaccharides as well as non-polysaccharide epitopes that are not serogroup-specific. Absorption studies have shown that the majority of serum bactericidal activity consists of group-specific antibodies.[6]

Antibodies directed against common neisserial antigens other than the serogroup-specific polysaccharide may be important for protection in young infants. Whereas immunity in neonates is the result of transplacental transfer of maternal IgG, carriage of nonpathogenic *Neisseria*, such as *Neisseria lactamica*, is thought to produce protective antibody in young children.[6, 97] Carriage of *N. lactamica* increases steadily from birth to 18 months of age, when the point prevalence in one study reached 21%.[97]

In 1943 Thomas et al.[98] noted that the bactericidal activity of undiluted convalescent serum was diminished against the patient's own strain of meningococcus. In addition the bactericidal activity of fresh, normal serum for a susceptible strain of meningococcus could be inhibited by the addition of this convalescent serum. Griffiss later demonstrated that the inhibition of bactericidal activity in convalescent serum was caused by blocking IgA[70] and that blocking IgA was present in acute phase serum as well.[99] The role of blocking IgA antibody in the pathogenesis of infection remains uncertain.

Vaccination with any of the meningococcal polysaccharides induces marked increases in serum IgA levels, particularly IgA2, 14 days after immunization.[100] Similar increases in salivary IgA antibody levels are not seen. The functional importance of this response is not clear. IgA antibodies opsonize bacteria poorly.[101] However, IgA2 antibody molecules are resistant to proteases elaborated by *N. meningitidis*[102] as well as *H. influenzae* and *S. pneumoniae*,[103] suggesting some role for these antibodies in the immune defense to encapsulated bacteria.

Protective levels of antimeningococcal antibody have not been established. Finnish investigators[104] suggested that meningococcal-specific antibody levels in excess of 2 μg/ml were protective. Currently an international effort is under way to develop a standardized enzyme-linked immunosorbant assay for measurement of antibodies to the group A and C capsular polysaccharides.[105]

PREVENTION: VACCINES

Efforts to develop a successful vaccine against the meningococcus began in the early 1900s;[25] field trials of early whole cell vaccines yielded mixed but generally poor results.[106] Failure of the early whole cell vaccines may have been the result of degradation of the polysaccharide; to be consistently antigenic, polysaccharides must have molecular weights >100 000.[107, 108] In addition endotoxin contamination led to severe pyrogenic reactions, limiting the amount of vaccine that could be administered. Gotschlich et al.[109, 110] developed the first consistently immunogenic polysaccharide vaccines for the group A and C meningococci in the late 1960s. Field trials of the group C polysaccharide vaccine in military recruits showed an 87% reduction in meningococcal disease; this protection was limited to

serogroup C.[111] The efficacy of the group C vaccine is age-specific; no protection was observed in children younger than 24 months old.[112]

Successful efficacy trials for the group A meningococcal polysaccharide vaccine took place in Finland[104, 113] and Egypt[114] in the mid-1970s. Vaccine was well-tolerated with serious side effects occurring in less than 2% of recipients. The investigators theorized but could not prove that vaccination of 40% of the population appeared to decrease the incidence rate of disease in the entire population.[104, 113] They speculated that this population immunity may be a result of a decrease in transmission from case patients and to a decrease in carriage. The effect of the vaccine on nasopharyngeal carriage is controversial. Although one study showed that group C vaccine reduced carriage of the meningococcus,[115] subsequent investigators have been unable to show a lasting effect of vaccine on carriage rates.[38, 116, 117] Unfortunately carriage rates in the Finnish studies were too low to assess the impact of the group A vaccine.

In one trial the group A polysaccharide vaccine appeared to be protective in a population of infants and young children 3 months to 5 years of age when examined as a group.[104] However, the numbers of infants under 1 year of age included in the trial were small, making it impossible to assess efficacy in this age group. Additionally cases were not reported by age, precluding estimates of age-specific vaccine efficacy. Finally antibody response after initial administration of vaccine was limited in children younger than 18 months of age. Second doses of vaccine given 3 months after the initial vaccination appeared to induce antibody responses comparable to those produced by the primary vaccination administered at that age. Thus no booster effect was apparent with the second dose. Other studies of United States children suggest that a booster effect may be seen with group A but not group C polysaccharide vaccine.[118]

Meningococcal serogroup Y and W135 polysaccharide vaccine are both safe and immunogenic;[119-121] no efficacy studies exist for these two vaccines.

A number of factors including age, nutritional status, coexistent malaria infection and lymphoid malignancies affect antibody response to the polysaccharide vaccine. Of these age is the most critical. Maturation of the humoral immune response to polysaccharide antigens is progressive and considered complete at 60 months. Heterogeneous antibody responses to different polysaccharide antigens are seen depending on the age of child. For example the *H. influenzae* type b polysaccharide antigen (polyribosyl-ribose phosphate) has limited immunogenicity in children younger than 16 months of age;[122] polysaccharides from pneumococcal serotypes 3 and 8 are highly immunogenic from the age of 6 months, yet pneumococcal serotypes 6A, 14, 19F and 23F, the most common causes of invasive pneumococcal disease in the pediatric age group, are poorly immunogenic in children younger than 5 years of age.[123] Antibody response to the meningococcal serogroup A polysaccharide is limited in children younger than 1 year of age.[104] The group C polysaccharide induces a weak antibody response in children younger than 1 year of age; no booster effect was demonstrated.[118] The limited response to the meningococcal polysaccharide antigens in the very young precludes incorporation of these vaccines into routine childhood immunization programs.

The production of antibody in response to a number of polysaccharide antigens, including the group A meningococcal polysaccharide, was markedly decreased in an animal model of vitamin A deficiency.[124] The impact of a selective, critical nutritional deficiency such as vitamin A deficiency and antibody response to meningococcal polysaccharides in humans has not been studied. Indirect data from two human studies in children have shown that vitamin A supplementation dramatically reduces overall mortality, particularly mortality associated with diarrhea, convulsions, measles and symptoms associated with other infections.[125, 126] Reductions in mortality were evident within all age groups. Further studies will be needed to determine the impact of vitamin A supplementation on disease-specific morbidity and mortality.

Malaria infection transiently impairs the humoral immune response to a number of vaccines. The response to the group C meningococcal vaccine, however, remains depressed up to 1 month after malaria infection in children.[127] When Nigerian children younger than 2 years of age were protected against malaria infection with chloroquine, a significant increase in antibody titers to both the group A and group C meningococcal polysaccharide vaccines was observed compared with that in children not treated with chloroquine.[128] No significant difference in response between the two groups was noted for a variety of other vaccines including diphtheria, pertussis, tetanus, measles and *Bacillus Calmette-Guérin* (BCG). These data suggest that control of malaria could enhance the immune response to meningococcal polysaccharide antigens in an age group where the vaccine is marginally immunogenic.

Individual host factors may limit antibody response to the meningococcal polysaccharide vaccines. Individuals with asplenia caused by trauma, immune thrombocytopenic purpura and nonlymphoid tumors respond to a bivalent A/C vaccine almost as well as controls, whereas those with lymphoid tumors respond poorly.[129] Late complement component-deficient individuals appear to respond to the tetravalent meningococcal

vaccine. *In vitro* studies suggest that antibodies mediate meningococcal killing in both a complement- and phagocytic-dependent manner; in late complement component deficient individuals antibody-mediated phagocyte killing may be crucial.[130, 131] An immunodeficiency syndrome characterized by recurrent sinopulmonary infections and the absence of an IgG response to polysaccharide vaccines has been described.[132]

No data are available on the immunogenicity of meningococcal vaccine in persons infected with the human immunodeficiency virus. Antibody response to the pneumococcal polysaccharide vaccine is decreased both in persons with acquired immunodeficiency syndrome and those with asymptomatic human immuno deficiency virus infection compared with noninfected controls. Although blunted, the response may still be protective.[133, 134] The quantitative antibody response to a conjugate (protein-polysaccharide) *H. influenzae* type b vaccine (HbOC: polyribosylribitol phosphate (PRP) conjugated with a mutant diphtheria protein, CRM_{197}) was significantly greater than that seen with the polysaccharide (PRP) vaccine alone in asymptomatic human immunodeficiency virus-infected adult men.[135]

Early studies of the group A and C polysaccharide vaccines showed a persistent antibody response measured by indirect hemagglutination and fluorescent antibody testing up to 18 months after immunization in a group of laboratory workers.[136] Duration of immunity, however, is also a function of age. West African children vaccinated at 4 years of age and older have sustained protection against the group A meningococcus for 3 years; those vaccinated with a single dose before the age of 4 show a rapid decrease in vaccine efficacy over 3 years.[137] No long term studies of vaccine efficacy exist and current recommendations are that high risk persons be revaccinated every 3 to 5 years.

Except for the military meningococcal vaccine is not routinely recommended in the United States for two reasons: (1) about 50% of meningococcal disease is caused by serogroup B, for which an effective vaccine is not currently approved; (2) in the most recently available surveillance data 46% of cases occurred in children 2 years of age or younger,[21] an age group in which vaccine provides only a limited period of protection. Vaccine should be targeted at specific groups with an increased risk of meningococcal disease. The Advisory Committee on Immunization Practices currently recommends immunization for certain high risk groups including those with late complement component deficiencies and those who are functionally or anatomically asplenic.[138] The United States military has successfully used meningococcal vaccine to prevent outbreaks of meningococcal disease in recruits, and Saudi Arabia has required vaccination for all Hajis since the 1987 outbreak, substantially reducing the number of cases in both populations.

The decision to use currently available vaccines in high risk populations and for epidemic control must be made by individual countries. National ongoing surveillance programs are crucial for establishing baseline sporadic disease incidence and for promptly detecting the onset of epidemics. In addition surveillance is useful for assessing the age distribution of disease and the meningococcal serogroups responsible for cases. National vaccination policies should be formulated on the basis of these data. A recent population-based analysis offers guidance in determining a threshold level of disease in African countries that would warrant initiating a vaccination campaign.[139]

VACCINES IN DEVELOPMENT

Despite the availability of meningococcal vaccines against four meningococcal serogroups, success in controlling endemic and epidemic disease has been limited for several reasons: (1) while group B meningococcus continues to cause most of the sporadic disease in the United States and epidemic disease in Brazil and Chile, no effective group B polysaccharide vaccine has been found; (2) current meningococcal polysaccharide vaccines produce only marginally protective antibody responses in young children; (3) duration of immunity is age-dependent and diminishes rapidly in children vaccinated before 4 years of age. Future vaccines must solve these three critical shortcomings of the current polysaccharide vaccines.

Attempts to develop an immunogenic group B polysaccharide vaccine have been unsuccessful.[4, 140] Although the group B polysaccharide induces an immunologic memory, a process probably mediated by B cells, it is incapable of evoking a humoral antibody response.[141] Even after natural infection with group B meningococcus, the immune response to the polysaccharide is poor.[142] Studies to identify specific immunogenic epitopes of the group B polysaccharide are in progress. Of concern, however, are the findings of Finne et al.[143] who have identified cross-reactivity between a monoclonal antibody to the group B polysaccharide capsule and certain fetal tissue glycoproteins. Additional study will be required to determine the implications of this finding on vaccine safety.

Jennings et al.[144–146] have shown that an *N*-propionylated group B polysaccharide conjugated to the tetanus toxoid induces bactericidal antibodies in mice directed against a noncapsular epitope of the group B meningococcus. These antibodies were bactericidal *in vitro* against homologous group B strains, but not group C meningococci. *In vivo* these antibodies protected mice against bacteremia with group B meningococci.

Efforts to elicit antibodies directed against group B polysaccharide using a polysaccharide from *Escherichia coli* K92 conjugated to a carrier protein have been reported.[147] Antibodies produced in this manner reacted with group B and C meningococci and *E. coli* K1. Further studies to evaluate the immunogenicity, the functional activity of the antibody and the safety of this product will be important.

The limited immunogenicity of the group B polysaccharide led to the study of noncapsular antigens such as OMPs as potential immunogens. OMPs of serotypes 6,[141] 2,[148] 2a[149] and 2b[150] all show varying levels of immunogenicity in humans and animals or protection in animal models. Vaccines containing serotypes 2b and 15 complexed with serogroup A, C, Y and W135 polysaccharides and serotype 2a complexed with group B polysaccharide produced serotype-specific antibodies in human volunteers.[151, 152]

A group B polysaccharide vaccine complexed with serotype 2 protein was examined in children 4 months to 5 years of age in South Africa in 1981; unfortunately the number of children enrolled was too small given the low incidence of disease in the unvaccinated group to draw any conclusions on vaccine efficacy.[153] Additional data on the clinical protection engendered by these vaccines have recently become available. An individually randomized controlled, double blind study of a meningococcal B:15:P1.3 OMP vaccine complexed with group C polysaccharide was conducted in Iquique, Chile, from 1987 to 1989 among 40 811 volunteers. Overall efficacy was 51%, although the 95% confidence intervals did not exclude zero.[154]

A field trial of a B:4:P1.15 OMP and high molecular weight protein complexed with the group C polysaccharide has been completed in Cuba. From 1987 to 1989, 106 000 students 10 to 14 years of age were randomized by school to receive vaccine or placebo; vaccine efficacy was 83%.[155] The OMP vaccine developed in Cuba was subsequently used for control of an outbreak of group B meningococcal disease in Sao Paulo, Brazil, in 1989 and 1990. A case-control study showed that estimated vaccine efficacy varied by age; no efficacy was shown in children vaccinated before 24 months of age, whereas in children vaccinated at 48 months, to 6 years of age the estimated efficacy was 74% (95% confidence interval, 16 to 92%).[147]

The Norwegians have developed and tested an OMP vaccine from a B:15:P1.7,16 *N. meningitidis* strain. The vaccine was evaluated in a blinded placebo-controlled efficacy trial conducted among 171 800 Norwegian secondary school students; students were randomly assigned by school. The efficacy was 57%, with a 95% lower confidence interval of 27.7%.[156]

The protective effect found in the efficacy studies of the Cuban and Norwegian vaccines provides the potential for control of epidemic disease caused by group B meningococcus. To compare these vaccines directly in the same population, the World Health Organization is currently undertaking a comparative immunogenicity and safety trial of the Cuban and Norwegian vaccines in secondary students in Iceland. Given the intermediate efficacy shown in the Norwegian trial and the questionable efficacy of the vaccines in young children, it appears premature to introduce these vaccines for prevention of endemic disease.

Protection of all the OMP vaccines is likely to be serotype-specific and is the major limitation of this class of vaccines. Improving the usefulness of these vaccines will depend on incorporating multiple serotypes into one vaccine or finding an outer membrane protein common to multiple serotypes and capable of inducing cross-protective bactericidal antibodies.

Two major weaknesses of the currently licensed polysaccharide vaccines are their limited immunogenicity in infants and the limited duration of efficacy in young children. Similar limitations existed with the *H. influenzae* type b (Hib) polysaccharide vaccine. Covalent coupling of the polysaccharide antigen to a protein carrier to create a conjugate vaccine has been effective in preventing Hib disease and serves as a model for the development of similar conjugate vaccines against the meningococcus. HbOC, a conjugate Hib vaccine, is immunogenic[157] and effective[158] in preventing Hib disease in children younger 1 year of age. The antibody response is durable; over 80% of the infants had protective antibody levels at 24 months of age.[157] Because it is T cell-dependent, a booster effect is seen on revaccination.[157] The HbOC vaccine has been approved for administration to infants at 2, 4, 6 and 15 months of age in the United States. A second Hib conjugate vaccine (PRP-OMP) consisting of the Hib polysaccharide conjugated to a group B *N. meningitidis* outer membrane protein complex is also immunogenic, effective in children younger than 1 year of age, and has been approved for administration in the United States.[159] Incorporation of meningococcal vaccines that are immunogenic, are capable of eliciting a booster response and provide a durable antibody response into routine childhood immunization programs would greatly enhance control efforts, particularly in infants and young children.

Attempts to develop meningococcal conjugate vaccines have been ongoing since the late 1970s. Jennings and Lugowski[160] prepared water-soluble conjugates of the meningococcal group A, B and C polysaccharides and tetanus toxoid. These vaccines produced high levels of group A and C polysaccharide-specific bactericidal antibodies in rabbits and mice, animals that do not produce antibodies to the polysaccharides alone. The group B-tetanus toxoid conjugate, by contrast,

failed to elicit polysaccharide-specific antibodies in either animal. Beuvery et al.[161–163] also synthesized group A and C polysaccharide-tetanus toxoid conjugates. The conjugates were immunogenic in mice although antibody response to the polysaccharide portion of the group A conjugate was seen only after a booster dose, suggesting T cell-mediated antibody production.

The World Health Organization is sponsoring studies to develop a safe, immunogenic and effective conjugate of serogroup A and C meningococcal vaccines that would provide prolonged protection for infants and children. Several conjugate vaccines have undergone preclinical testing and the first human clinical trials are currently under way. This vaccine could be incorporated into routine childhood immunization programs in African countries targeted to children younger than 1 year of age. The short duration of protection and the limited efficacy in children younger than 2 years precludes the use of the currently available meningococcal polysaccharide vaccines in that age group.

Initial evaluation of the conjugates will require demonstration of immunogenicity in infants living in countries that experience epidemic disease. It will also be important to assess the duration of elevated antibody levels. Because of the unpredictable epidemic nature of group A disease, it would be difficult to design a prospective controlled trial to evaluate vaccine efficacy, and a control group of unvaccinated individuals would be unethical. The conjugate vaccines also require two to three doses at least 1 month apart to elicit protection in infants, making it impossible to vaccinate a population once an epidemic has begun. Because these vaccines are likely to be substantially more expensive than the currently available polysaccharide vaccine, efforts should be made to ensure rigorous evaluation of effectiveness, possibly through demonstration projects in areas with periodic epidemics. In addition continued research is needed to develop inexpensively produced vaccines effective against group A disease in young children.

Control of meningococcal disease will be contingent on a better understanding of the epidemiology of this organism, in particular those factors that lead to epidemic disease and to defining the populations at risk. Global control of meningococcal disease will depend on the continued development of vaccines that provide long lasting protection for populations at risk. Development of an effective group B vaccine remains a high priority for reducing disease in the Americas, where the group B meningococcus accounts for a substantial portion of disease. Incorporation of effective meningococcal conjugate vaccines into routine infant immunization programs in high risk populations such as those in the African meningitis belt will substantially reduce the morbidity and mortality of meningococcal disease in these areas.

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Multiple Choice Questions. Answer the following five questions by circling the letter of the correct answer.

1. The following attributes of the meningococcus are true:
   a. Nasopharyngeal carriage of the meningococcus leads to immunity.
   b. Meningococcal bacteremia is usually a benign condition.
   c. Meningococci remain universally susceptible to penicillin.
   d. Nasopharyngeal carriage is uncommon and, when present, is almost always associated with invasive disease.
   e. All of the above.
2. The following statements reflect the epidemiology of the meningococcus:
   a. The incidence of disease is highest in children younger than 5 years of age.
   b. Serogroups B and C are the most frequently isolated serogroups in the United States.
   c. Recurrent outbreaks in Africa have a unique geographic distribution.
   d. A new serogroup A clone has been responsible for most of the meningococcal disease in Africa in recent years.
   e. All of the above.
3. The following antibiotics are used in the treatment of meningococcal meningitis:
   a. High dose penicillin.
   b. Ceftriaxone.
   c. Chloramphenicol.
   d. Cephalexin.
   e. Erythromycin.
4. The following statements about currently available meningococcal vaccines are false:
   a. The vaccine is highly immunogenic in children younger than 2 years of age.
   b. The vaccine is recommended for asplenic individuals.
   c. Religious pilgrims to Jerusalem should be routinely immunized.
   d. Travelers to certain regions in Africa should be immunized.
   e. All of the above.
5. Future vaccines should include the following:
   a. Immunogenicity against serogroup B.
   b. Immunogenicity in children younger than 2 years of age.
   c. Efficacy in all age groups.
   d. Prolonged duration of protection.
   e. All of the above.

Correct Answers:
1. a
2. e
3. a, b, c
4. a and c
5. e