Annu. Rev. Med. 2004. 55:333–53
doi: 10.1146/annurev.med.55.091902.103612
First published online as a Review in Advance on Oct. 20, 2003

OPPORTUNITIES FOR CONTROL OF MENINGOCOCCAL DISEASE IN THE UNITED STATES*

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Key Words *Neisseria meningitidis*, epidemiology, chemoprophylaxis, meningococcal vaccines, meningococcal diagnostics

■ **Abstract** The United States currently has relatively low rates of meningococcal disease caused by *Neisseria meningitidis*. Serogroups Y, C, and B are most common. Although most cases are sporadic, a minority are associated with outbreaks. Pediatric populations have disproportionately higher rates of disease, but nearly two thirds of all cases occur in persons aged 15 years and older. The major challenge to control of domestic meningococcal disease is the absence of a vaccine to prevent sporadic cases spanning many age groups. The quadrivalent A/C/Y/W-135 meningococcal polysaccharide vaccine is licensed in the United States, but because of its limited efficacy in children under two years of age, it is recommended for high-risk groups and outbreak response rather than routine childhood immunization. New conjugate meningococcal vaccines have successfully reduced endemic disease in the United Kingdom, and similar vaccines promise to have a dramatic impact on the burden of meningococcal disease in the United States.

INTRODUCTION

The epidemiology of meningococcal disease in the United States has undergone a tremendous shift over the past hundred years. In the first half of the twentieth century, large, explosive "cerebrospinal meningitis epidemics" raged periodically, with primary attack rates as high as 310 per 100,000 population and case fatality ratios approaching 70% (1–3). Mortality rates dropped with the advent of sulfonamide antibiotics, but major epidemics in both civilian and military populations

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recurred during World War II troop mobilizations (4). These regular meningococcal disease epidemics disappeared from the United States in the postwar period (5). Since the 1950s, the United States has experienced low and relatively stable rates of endemic meningococcal disease at 1–2 per 100,000 population (5). Superimposed on this background rate, the meningococcus causes occasional outbreaks within organizations or communities. This pattern of predominantly endemic disease overlaid with infrequent outbreaks is also observed in other industrialized nations (6). In the United States, the major challenge to control of meningococcal disease is the absence of a vaccine to prevent sporadic cases. Because of their limited efficacy in young children, meningococcal polysaccharide vaccines are recommended for high-risk groups and outbreak response rather than routine childhood immunization (7). However, new conjugate meningococcal vaccines have successfully reduced endemic disease in the United Kingdom, and similar vaccines promise to have a dramatic impact on the burden of meningococcal disease in the United States.

Microbiology

Meningococcal disease is caused by the encapsulated Gram-negative diplococcus *Neisseria meningitidis*. The meningoccal capsule consists of chemically distinct polysaccharides that can be classified antigenically into at least 13 serogroups (A, B, C, H, I, K, L, W-135, X, Y, Z, Z′, 29E), five of which cause the vast majority of disease (A, B, C, Y, W-135). Meningococci are further distinguished by serotype and serosubtype based on the outer membrane proteins (OMPs) PorB and PorA, which lie within the meningococcal outer membrane beneath the polysaccharide capsule. Other OMPs include Opa (class 5), Opc (class 5c), and transferrin binding proteins (Tbps). The serogroup A, C, Y, and W-135 polysaccharide capsules elicit serogroup-specific bactericidal antibody responses (8, 9), which correlate with protection against serogroup A and serogroup C disease (10). These polysaccharide moieties form the basis of the quadrivalent serogroup A/C/Y/W-135 meningococcal polysaccharide vaccine. In contrast, the serogroup B polysaccharide capsule is poorly immunogenic, probably because of its similarity to polysialosyl glycopeptides expressed on the surface of developing neural cells, which induce self-tolerance (11). Therefore, vaccine strategies against serogroup B meningococci have focused on OMPs (12).

Carriage and Immunity

Meningococci colonize the human nasopharynx, which is the organism's only natural reservoir. Asymptomatic carriage of both pathogenic and nonpathogenic strains is relatively common, yet few carriers develop invasive disease. In the United States, baseline meningococcal carriage rates are 5%–10% (13). The duration of carriage ranges from weeks to months (14). Transmission occurs through direct contact with respiratory droplets from colonized individuals. Increased carriage rates can be observed in crowded settings, such as military barracks (15). Meningococcal carriage is an immunizing event, resulting in the development of

serogroup-specific protective antibody (16). Adolescents and young adults have the highest meningococcal carriage rates; children and infants more frequently carry the nonpathogenic species *Neisseria lactamica*, which may be an important means of acquiring cross-protective immunity (14, 17). The classic studies of Goldschneider et al. found that the age-dependent risk of meningococcal disease correlated with carriage and naturally acquired immunity to meningococcus (10, 16). Infants in the first month of life have a moderate rate of disease because they are protected by transplacentally derived maternal antibodies (16, 18). As this protective immunity wanes, meningococcal disease risk increases, with rates peaking at 3–4 months of age (10, 18). As children gradually become exposed to meningococci and *N. lactamica* through nasopharyngeal carriage, and to antigenically similar enteric flora such as *E. coli* K1 and K92 (19, 20), they develop bactericidal antibody and have lower disease rates. By adulthood, 65%–85% of individuals possess bactericidal antibody against meningococci and consequently remain at low disease risk (10). Age-related waning of natural immunity may contribute to increased meningococcal disease rates observed in persons aged 65 years and older (21).

Clinical Features

In a small proportion of carriers, meningococci invade the mucosa and proliferate in the bloodstream, causing invasive disease. Invasive meningococcal disease encompasses three common clinical forms: meningitis, meningococcal bacteremia, and pneumonia. Meningitis (meningeal infection), observed in ~50% of invasive meningococcal infections, is characterized by abrupt onset of fever, headache, and neck stiffness, sometimes with nausea, vomiting, photophobia, and altered mental status (21). Meningococcal bacteremia (bloodstream infection) occurs in 40% of invasive disease cases, and a subset exhibit clinical signs of meningococcemia, or fulminant meningococcal sepsis (21, 22). Key signs of meningococcemia are sudden onset of fever and a petechial or purpuric rash. The clinical course is characterized by hemodynamic instability leading to shock, diffuse intravascular coagulation, and death; case fatality ratios have been reported to range from 18% to 53% (23). Meningococcal pneumonia occurs in ~6% of invasive disease cases (21). In contrast to the other clinical forms of meningococcal disease, pneumonia primarily affects older patients and results in case fatality ratios below 10% (24, 25). Despite presumed improvements in clinical care since the 1970s, case fatality ratios for all meningococcal infections have remained relatively stable between 9% and 12% (5). Between 8 and 19% of survivors suffer from serious sequelae such as deafness, neurologic deficits, or limb loss (22, 23, 26).

Risk Factors

Risk factors for meningococcal disease can be categorized into organism characteristics that promote virulence; environmental conditions that facilitate exposure to meningococci; and host factors that increase bacterial colonization, invasion, and survival in the bloodstream (22). Meningococcal virulence determinants include

capsular polysaccharide, adhesins, nutrient-acquisition factors, and the ability to release outer membrane vesicles containing endotoxin (27). In the environment, crowded living conditions are likely to facilitate respiratory droplet transmission of meningococci (28–32). Black race (21, 33) and low socioeconomic status (2, 3, 34), both linked to higher rates of meningococcal disease, may also be considered environmental risk factors, in that they are presumably markers for increased exposure to high-transmission settings. Risk factors that likely influence meningococcal colonization or invasion include include active or passive smoking (30, 32, 35, 36) and recent *Mycoplasma pneumoniae* or viral upper respiratory tract infections (30, 37, 38). Meningococci may be better able to attach to and penetrate nasopharyngeal mucosa that have been damaged by other pathogens or by tobacco smoke (30, 32, 35, 36).

Risk factors related to host immune defense include age (10, 16), chronic illness (30), and rare immune deficiencies (39–41). Natural immunity is acquired with age, and this inverse relationship between age and susceptibility is thought to explain high rates of meningococcal disease in children aged less than two years (10, 16). Chronic underlying illness may reduce humoral immune defense (30). Rare host immune deficiencies, such as late component complement deficiency (39), properdin deficiency (40), and asplenia (41), also favor the proliferation of meningococci in the bloodstream, the former two by interfering with classical and alternative pathways for complement-mediated lysis. However, because these conditions are rare, persons with these known risk factors account for only a small fraction of meningococcal disease cases (42).

EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE IN THE UNITED STATES

Each year, 2400–3000 cases of meningococcal disease occur in the United States (21, 43). Approximately 97% of cases are sporadic and represent background endemic disease; the remaining 3% are associated with outbreaks (21, 43). Meningococcal disease is seasonal, with incident cases peaking in December and January (21). Both passive and active surveillance systems are used to monitor meningococcal disease, a reportable disease in the United States. In the passive National Notifiable Diseases Surveillance System (NNDSS), state health departments collect and transmit weekly reports of cases to the Centers for Disease Control and Prevention (CDC) through the National Electronic Telecommunications System for Surveillance (44).

From 1996 through 2001, the average annual incidence of meningococcal disease reported to NNDSS varied greatly by state, ranging from 0.6 per 100,000 population in Delaware to 2.8 per 100,000 population in Oregon (Figure 1). Regional variation in meningococcal disease was also apparent, with elevated rates detected in the Pacific Northwest, midwestern Mississippi Valley, and South. The higher disease rates in the Pacific Northwest were probably due to the well-documented

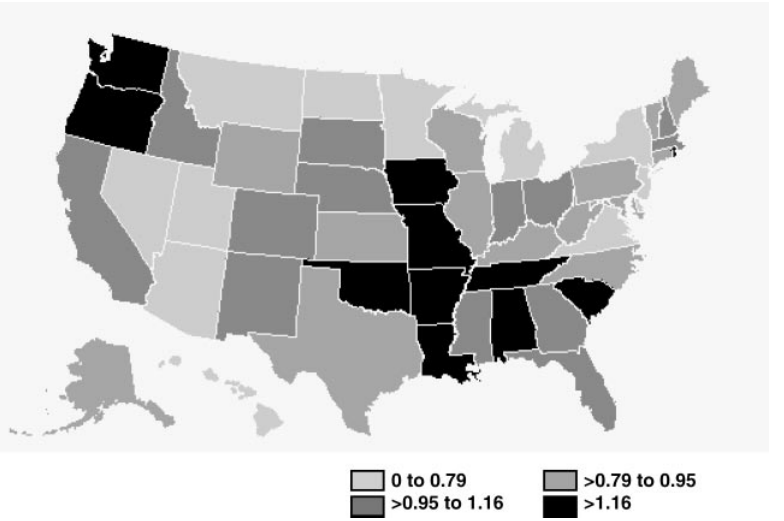

Figure 1 Distribution of mean annual meningococcal disease incidence rates in the United States, 1996–2001. Incidence rates per 100,000 population per year are averaged for the years 1996–2001 by state. Shading represents rate quartiles. Confirmed (clinically compatible illness with isolation of *N. meningitidis* from a normally sterile site) and probable (clinically compatible cases with positive antigen test in cerebrospinal fluid or clinical purpura fulminans in the absence of a positive blood culture) cases are included. Sources: National Notifiable Diseases Surveillance System and US Census Bureau.

epidemic of serogroup B meningococcal disease in Oregon and neighboring areas of Washington, which was first detected in 1993 (45, 46). Low-incidence states were concentrated in the Northeast, along the Canadian border, and in the Southwest. The factors governing clustering of high- and low-incidence states deserve further investigation, although these crude rates are not adjusted for differing age and race structures of the underlying state populations.

As a complement to the passive NNDSS system, CDC coordinates active laboratory-based surveillance for invasive meningococcal disease as part of the Emerging Infections Program through Active Bacterial Core surveillance (ABCs) (47). Participating surveillance sites collect data from all patients with sterile site *N. meningitidis* isolates, allowing detection of trends in causative meningococcal serogroup and accurate estimation of age-specific incidence rates. From 1996 through 2001, the largest proportion of meningococcal disease cases was due to serogroup Y (39%), followed by serogroup C (31%) and serogroup B (23%) (Figure 2). The increasing proportion of serogroup Y has been previously noted in the United States (21), whereas serogroups B and C predominate in Canada and Europe (6, 48). Persons with serogroup Y meningococcal disease were more likely to be older, to be black, to have chronic underlying illnesses, and to present

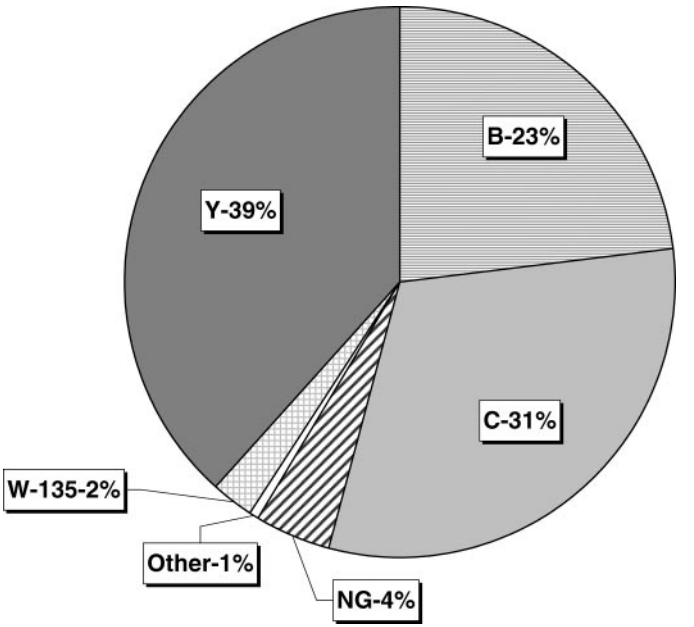

Figure 2 Serogroup distribution among meningococcal isolates received from participating Active Bacterial Core surveillance sites (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New York, Tennessee), 1996–2001. NG = nongroupable. Analysis excludes Oregon because of its unusual serogroup B meningococcal disease epidemic.

with meningococcal pneumonia (21, 49). Serogroup A was notably absent and serogroup W-135 was rare in this US population, yet both have recently caused major meningococcal epidemics in Africa (50, 51). Following the 2000 serogroup W-135 outbreak associated with the Hajj in Saudi Arabia, serogroup W-135 cases were detected among a few pilgrims returning to the United States and their close contacts (52, 53). Nevertheless, serogroup W-135 meningococcal disease rates have not increased in the United States (CDC, unpublished data). Importantly, approximately one fourth of US meningococcal cases were caused by the non–vaccine-preventable B serogroup.

Because the population under active ABCs surveillance is defined, these data can also be used to generate national age-specific meningococcal disease incidence rates and disease burden (Figure 3). As has been historically observed, in 1996–2001, children under two years of age had the highest age-specific incidence of meningococcal disease (5.5 per 100,000 population), followed by children aged 2–4 years. However, children under five years accounted for only 25% of the total disease burden. Although pediatric populations had disproportionately higher rates of disease, nearly two thirds of all meningococcal disease cases occurred in adolescents and adults aged 15 years and older. Consistent with previous data,

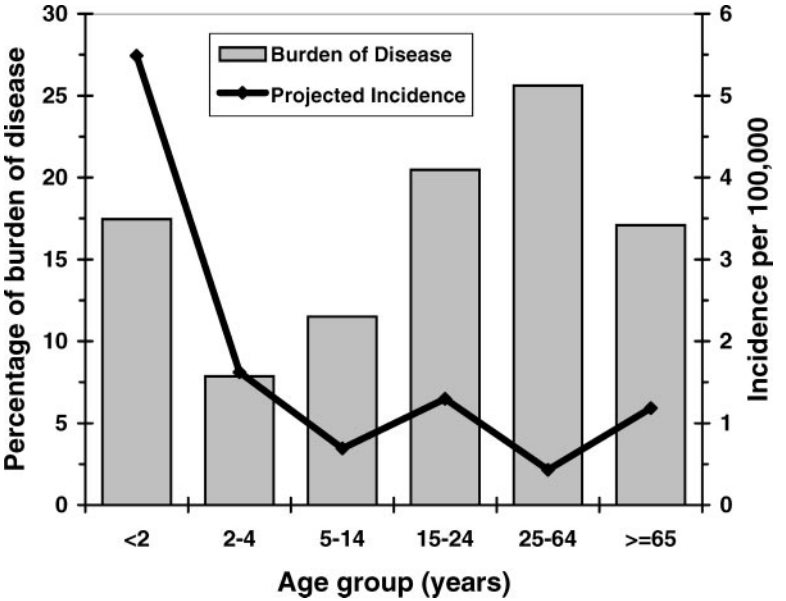

Figure 3 Age-specific annual incidence rates and burden of meningococcal disease, race-adjusted and projected to US population from Active Bacterial Core surveillance (ABCs) data, 1996–2001. ABCs sites included California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee; aggregate population under surveillance ranged from 24.1 million in 1996 to 35.4 million in 2001.

slightly elevated rates of disease were observed in adolescents and young adults aged 15–24, and in adults over 65 years (21). Therefore, primary prevention strategies for the United States must consider the dispersed disease burden that spans many age groups.

DIAGNOSTIC TECHNIQUES USEFUL IN CHARACTERIZING MENINGOCOCCAL DISEASE

The current US confirmed case definition for meningococcal disease requires isolation of *N. meningitidis* from a sterile site, typically blood or cerebrospinal fluid (CSF) but occasionally joint, pleural, or pericardial fluid. In cases of meningococcemia, aspirates or skin biopsies of purpura or petechiae can also yield meningococci (54). As an adjunct to culture, latex agglutination testing can rapidly detect meningococcal polysaccharide antigens in CSF and provide serogroup identification. Although commercial latex agglutination kits detect *N. meningitidis* capsular antigens with high sensitivity and specificity among culture-confirmed cases (55), these tests appear to have low sensitivity when Gram stain and culture of CSF are

negative (56, 57). Ultrasound has been reported to enhance the sensitivity of latex agglutination testing for *N. meningitidis* (58).

Determination of the meningococcal serogroup becomes critically important in the context of investigating suspected meningococcal disease outbreaks, because public health actions differ for vaccine-preventable and non–vaccine-preventable serogroups. Patients with suspected meningitis often receive parenteral antibiotics prior to lumbar puncture, which interfere with culture confirmation. This has prompted the development of nonculture meningococcal diagnostics (59). Polymerase chain reaction (PCR) assays can detect meningococcal-specific nucleic acid sequences in CSF and blood. Most involve an initial screening reaction to confirm meningococcal infection and a subsequent reaction to determine serogroup. The first PCR test amplifies the meningococcal-specific capsular transport gene *ctrA*; specimens that test positive are subjected to the second test, which distinguishes serogroup B, C, Y, and W-135 alleles of the *siaD* sialyltransferase gene (60–63). These techniques have been adapted to a fully automated TaqMan system (64) that allows the rapid, sensitive, and specific confirmation of meningococcal etiology as well as identification of the main disease-causing serogroups. A LightCycler PCR system has also recently been developed that detects and genogroups A, B, C, Y, and W-135 meningococci within a few hours (65). Because of its different polysaccharide biosynthesis pathway, serogroup A capsule is detected by PCR amplification of the *sacC* gene in this system (65). In England and Wales, 36% of meningococcal disease cases are confirmed by PCR alone (64). Similar technology is being evaluated in the United States.

Both phenotypic and genotypic methods have been used to investigate meningococcal diversity and global epidemiology. Serogrouping, serotyping, and serosubtyping are phenotypic methods that require specialized reagents for serologic discrimination of variant meningococcal surface structures—namely, capsular polysaccharide (serogroup) and porin proteins PorB (serotype) and PorA (serosubtype). Multilocus enzyme electrophoresis (MEE) is the established phenotyping technique for analyzing the temporal and geographic distribution of meningococcal strains across the world. MEE detects allelic variants of conserved metabolic enzymes revealed through electrophoretic mobility differences on starch gels (66). Although labor-intensive and time-consuming, this phenotypic subtyping method has been used to classify meningococci into electrophoretic types (ETs) and to identify hypervirulent lineages (67). For example, serogroup B meningococci of the ET-5 complex were shown to have caused an epidemic in Norway that was first detected in 1974 and lasted through 1991 (67, 68). This clonal complex spread across Europe and South America in the 1980s. In the United States, ET-5 strains were subsequently associated with the serogroup B meningococcal disease epidemic in Oregon from 1992 through 1996 (46). MEE has also demonstrated that meningococci from a different clonal lineage, the ET-37 complex, have caused serogroup C outbreaks in the United States (69).

MEE has been used for two decades for meningococcal subtyping, but the technique is restricted to a few reference laboratories, and its results are difficult to

standardize between groups. Molecular genotyping techniques are increasingly being explored to classify disease isolates both in the localized outbreak setting and within the global context of meningococcal disease (70). Pulsed-field gel electrophoresis (PFGE) can be a valuable short-term molecular subtyping tool to determine whether isolates from different individuals in a suspected outbreak represent the same strain. This technique exploits the rapid evolution of variability in restriction enzyme sites within the meningococcal genome, and thus can distinguish unrelated sporadic disease isolates with multiple PFGE patterns from an outbreak clone. A retrospective analysis of PFGE profiles within serogroup C outbreaks in the United States demonstrated that isolates were not identical but had a very high degree of similarity (>95% pattern relatedness), and this knowledge would have provided additional evidence for public health action (69). PFGE can also discriminate among highly diverse serogroup B meningococci (71, 72). In contrast to its utility for serogroup C outbreaks, however, PFGE is not as frequently employed for investigating serogroup B meningococcal disease because of the organism's great diversity (69).

Multi-locus sequence typing (MLST) employs a similar rationale to MEE's, but entails sequencing seven conserved "housekeeping" genes and classifying allelic differences into sequence types. The main advantage of MLST is its reliance on standard molecular biology techniques, which enables different laboratories to document and compare their results quite readily; typing results can be deposited in a public database accessible by the Internet (http://neisseria.org/nm/typing/mlst). The congruence between MLST sequence types and MEE electrophoretic types has been established for some hypervirulent lineages of meningococci (70). However, a recent comparison of meningococcal subtyping methods revealed that MLST may not discriminate between sporadic and outbreak isolates as well as a newer technique, 16S ribosomal RNA gene sequencing (73). Different combinations of classical and molecular subtyping techniques may be appropriate for public health investigations and population genetic studies of meningococci.

CHEMOPROPHYLAXIS TO PREVENT MENINGOCOCCAL DISEASE

Persons who have close contact with meningococcal disease patients are at substantially increased risk for acquiring carriage and disease (74–76). Among close contacts, household members of index cases have a dramatically elevated risk of acquiring disease compared to the general population in industrialized countries, with relative risk estimates ranging from 500 to 1200 (77–80). The secondary attack rate among this exposed group has been estimated at 2–4 per 1000 exposed persons (77, 78). Rates of secondary disease also appear somewhat elevated among daycare attendees (80) and schoolchildren (81). One study in the United Kingdom estimated secondary disease among health care workers to be 0.8 per 100,000 persons, a small absolute risk but 25 times greater than in the general population (82).

Systemic antibiotics can eradicate nasopharyngeal carriage of meningococci among contacts of sporadic cases and thus prevent secondary disease. Consequently, the US Advisory Committee on Immunization Practices (ACIP) (7) and the Red Book (83) recommend antimicrobial chemoprophylaxis for close contacts of meningococcal disease cases. Approximately 70% of secondary cases occur within seven days of disease onset in the index case, necessitating prompt antibiotic administration, ideally within 24 h of identifying the case (7, 79, 80). Antibiotic chemoprophylaxis is unlikely to be helpful after 14 days. Anecdotal evidence suggests widespread implementation of these recommendations. Since secondary cases are rare, chemoprophylaxis represents the most significant means of prevention of meningococcal disease in the United States.

In serogroup C meningococcal outbreaks, mass chemoprophylaxis is not often considered because of the existence of effective polysaccharide vaccines with longer duration of protection. However, because of the lack of a serogroup B vaccine, mass chemoprophylaxis has been employed to control organization-based serogroup B meningococcal outbreaks. In an evaluation of rifampicin administered prophylactically to 900 students in a school outbreak of serogroup B disease, meningococcal carriage was reduced by 85%, and no further cases were detected (84). However, rifampicin-resistant meningococcal isolates rapidly emerged, although they did not cause disease (84). Mass chemoprophylaxis appears most effective in focal serogroup B outbreaks in small, well-defined populations such as schools (84), rather than in community-wide serogroup B outbreaks of longer duration (85). An analysis of school-based meningococcal disease clusters lent further support to the potential utility of chemoprophylaxis in school settings (81). Within these school clusters, one third of subsequent cases appeared within two days of disease onset in the index case. Thus, even when an organization-based outbreak is caused by a vaccine-preventable serogroup, antibiotic distribution may be a more timely intervention than vaccination, because protective antibodies take 7–10 days to develop after vaccination. The potential benefit of mass chemoprophylaxis in these settings needs to be weighed against the possible emergence of antibiotic resistance, rare adverse events associated with chemoprophylaxis, and the logistic difficulties of prophylaxis campaigns (84).

Antimicrobial Agents for Chemoprophylaxis

Current ACIP guidelines recommend rifampicin, ciprofloxacin, or ceftriaxone as chemoprophylactic agents because of their demonstrated efficacy in eradicating meningococcal carriage (Table 1) (7). A two-day regimen of rifampicin is effective in clearing carriage but is unsuitable for pregnant women because of its teratogenicity (84, 86). A single dose of ciprofloxacin can eradicate carriage (87, 88), but it is not generally recommended for pregnant and lactating women and children under 18 years owing to findings of cartilage damage in animal models (89). However, ciprofloxacin has been used to eradicate carriage in Malawian children without adverse events (90). Ceftriaxone is also effective as a single dose, but it must

TABLE 1 Antibiotics recommended by the US Advisory Committee on Immunization Practices for chemoprophylaxis against meningococcal disease (7)

Generic name (References)	Adult dose	Pediatric dose	Route	Duration	Antimicrobial resistance documented?
Rifampicin (84, 86)	600 mg/12 h	10 mg/kg/12 h	oral	2 days	Yes
Ciprofloxacin (87, 88)	500 mg	—	oral	Single dose	No
Ceftriaxone (91)	250 mg	125 mg	IM	Single dose	No

be administered parenterally (91). More recently, a single dose of azithromycin was shown to eradicate carriage of meningococci in a cohort of Egyptian nursing students (92); further validation of these results in a pediatric population (e.g., mass chemoprophylaxis in a school) could expand the battery of meningococcal chemoprophylactic agents for specific outbreak settings.

VACCINES TO PREVENT MENINGOCOCCAL DISEASE

Meningococcal Polysaccharide Vaccines

The quadrivalent serogroup A/C/Y/W-135 polysaccharide vaccine (Menomune®) is the only meningococcal vaccine licensed in the United States. Although the vaccine is recommended for controlling serogroup A, C, Y, and W-135 meningococcal epidemics, it is not routinely used against endemic disease because of its immunologic shortcomings. The protective efficacy of serogroup C polysaccharide has been estimated at ~85% in both clinical trials and epidemic settings (93–95). However, the serogroup C polysaccharide does not induce strong or lasting immune responses in children under two years of age (96–98). Even in vaccinated adults, serogroup C serum bactericidal antibody levels decline markedly within two years of vaccination (99).

The serogroup A polysaccharide has a similarly high protective efficacy, between 89% and 100% in clinical trials (100, 101), and the vaccine has proven effective in controlling epidemics (102–104). Infants as young as three months develop antibodies to serogroup A polysaccharide (97, 105) and can develop short-term protection (101). However, the antibody response declines within 12 months to background levels (98), and the duration of protection against serogroup A disease appears short-lived in children and adults (99, 106). In children vaccinated before the age of four years, vaccine efficacy declines from 100% to 8% within three years; in children vaccinated after four years of age, the vaccine efficacy decreases from 85% to 67% over the same time period (106). The protective efficacy of the

serogroup Y and serogroup W-135 meningococcal polysaccharides has not been established, although immunogenicity has been demonstrated (9).

The utility of meningococcal polysaccharide vaccines is further restricted because they do not sustainably reduce meningococcal carriage (102, 107, 108) and therefore do not lead to herd immunity. Furthermore, repeated immunization with the serogroup A (109, 110) and serogroup C (111–113) polysaccharide has induced immunologic hyporesponsiveness in children and adults, although the clinical relevance of these findings is unknown.

In summary, plain meningococcal polysaccharide vaccine is not considered for routine use in the general population because of its poor immunogenicity in children, short duration of protection, and inability to induce herd immunity. Despite these limitations, in the United States the quadrivalent meningococcal polysaccharide vaccine is useful for certain high-risk groups, such as military recruits, laboratory workers exposed to *N. meningitidis*, persons with asplenia or complement deficiencies, and travelers to highly endemic or epidemic areas (7, 114). Freshmen living in dormitories have a modestly increased risk of invasive meningococcal disease (115, 116). Because studies demonstrated that 68% of cases in college students were vaccine-preventable, ACIP recommended that college freshmen, especially those who live in dormitories, receive education about meningococcal disease and the quadrivalent meningococcal vaccine (117).

Conjugate Meningococcal Polysaccharide Vaccines

Conjugate vaccine technology can overcome the immunologic limitations of meningococcal polysaccharide vaccines, which provoke T-cell–independent responses. When the capsular polysaccharide antigen is conjugated to a protein carrier, a T-cell–dependent host immune response develops, resulting in long-lasting protection and immunologic memory even in infants. This technology was first successfully exploited for the *H. influenzae* serotype b (Hib) conjugate vaccine, which has reduced the US burden of Hib disease by 99% in children less than five years of age (118). This remarkable decline can partly be attributed to herd immunity: Hib vaccine also reduces nasopharyngeal carriage in vaccinated individuals, thereby lowering disease transmission and indirectly benefiting unvaccinated individuals (118). A pneumococcal conjugate vaccine was licensed in February 2000 in the United States; it has already substantially reduced the rate of invasive disease caused by *Streptococcus pneumoniae* among toddlers and may also be reducing the rate in adults (119).

Using the same technology, serogroup A, C, Y, and W-135 polysaccharides have been conjugated to tetanus toxoid and CRM197 proteins. The safety and immunogenicity of bivalent A+C and monovalent C conjugate vaccines have been demonstrated among infants and adults in the United States, England, and Africa (120–123). Because of the relatively low burden of endemic meningococcal disease, clinical efficacy trials are difficult to implement in industrialized countries. In the United Kingdom, meningococcal serogroup C conjugate vaccines were

licensed based on immunologic data in 1999 and introduced in the routine infant immunization schedule (124). A mass "catchup" vaccination campaign also targeted all persons under the age of 18 years (124). The serogroup C vaccine efficacy was ~90% among all age groups, and two years after the introduction of the vaccine, serogroup C disease incidence declined 87% among vaccinees (125, 126). Moreover, carriage of serogroup C meningococci among teenagers decreased 66% within one year of vaccination (127), and disease decreased 34%–61% among unvaccinated individuals (125). Carriage of other meningococcal serogroups was unaffected (127).

These exciting results indicate that serogroup C conjugate vaccines provide serogroup-specific protection against meningococcal carriage and have at least a short-term impact on herd immunity, although the duration of this effect remains to be seen. In addition, the length of protection and need for a booster dose will need to be evaluated in all age groups, particularly in infants. Potential complications of the vaccine implementation strategy include the emergence of replacement disease due to other serogroups and the development of capsule switching, as has been documented for serogroups B and C (128, 129). Thus far, the United Kingdom has not reported either of these problems, although surveillance is ongoing (125). Several other countries in Europe, as well as Canada and Australia, are in the process of implementing serogroup C conjugate vaccine programs. A quadrivalent conjugate polysaccharide A/C/Y/W-135 vaccine has recently been shown to be safe and immunogenic in healthy adults and may eventually become available in the United States (130).

Serogroup B Vaccines

The serogroup B capsular polysaccharide is poorly immunogenic in humans because it resembles a self-antigen (11). However, because serogroup B *N. meningitidis* causes about one third of meningococcal disease in the United States (21) and can cause outbreaks (45, 46), a serogroup B vaccine is critical for long-term control. Serogroup B vaccine development has focused on subcapsular antigens, using preparations of outer membrane proteins (OMPs) from epidemic strains (12). OMP vaccines have been moderately useful in the control of native epidemics caused by the homologous vaccine strain, but they have had limited to no efficacy in young children and infants (131, 132). Moreover, OMP vaccines have failed to induce protective responses against heterologous serogroup B strains (133). Because of the diversity of OMPs associated with endemic disease, this approach may be best suited for the development of designer vaccines for outbreaks (134, 135).

Because OMP vaccines produce poor cross-protective immune responses and low efficacy in young children, novel serogroup B vaccine strategies are being explored. In 2000, the genome of a virulent serogroup B meningococcal strain was sequenced (136), and a functional screen of open reading frames yielded seven novel surface-exposed proteins with the potential to elicit bactericidal immune responses in mice (137). Further studies will determine whether any of these

proteins will be immunogenic and efficacious in humans, but this genome-based strategy is one of multiple approaches to serogroup B vaccine development (12).

PROSPECTS FOR THE CONTROL OF MENINGOCOCCAL DISEASE IN THE UNITED STATES

Although most meningococcal disease in the United States is endemic, meningococcal outbreaks often create public fear and panic and consequently command disproportionate attention and resources. Currently, two strategies exist for controlling meningococcal disease outbreaks: antimicrobial chemoprophylaxis and polysaccharide vaccines. Unfortunately, these approaches do not significantly reduce the overall burden of meningococcal disease. To accomplish this objective, new tools are needed.

Meningococcal conjugate vaccines will soon be available in the United States, but complicated questions remain about formulations, target age groups, and combinations with other vaccines. Serogroups A and W-135 are rare in the United States, but the occurrence of international outbreaks and the potential for imported disease suggest that the broadest possible vaccine formulation would be preferable. Use of conjugate vaccines in infants, toddlers, or adolescents could have a substantial impact on disease (138). If conjugate meningococcal vaccines reduce carriage and thus create herd immunity, immunizing adolescents, who have the highest carriage rates, might rapidly reduce transmission. Finally, because of the already crowded infant immunization schedule, multiple combination vaccines are being explored.

The significant presence of serogroup B disease also requires the development and implementation of serogroup B vaccines, which are likely to have different immunologic and epidemiologic properties from the conjugate protein-polysaccharide antigens. In the long run, serogroup-specific vaccines may not be the final solution, and the pendulum may shift toward common protein vaccines that protect against all pathogenic meningococcal serogroups (12). Improved surveillance and diagnostic techniques will become increasingly important to monitor trends in meningococcal disease epidemiology after the introduction of these much-anticipated vaccines in the United States.

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Volume 55, 2004

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