

Prospects for Vaccine Prevention of Meningococcal Infection

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INTRODUCTION	142
HISTORY	142
CLINICAL ASPECTS OF MENINGOCOCCAL INFECTION	143
EPIDEMIOLOGIC ASPECTS OF MENINGOCOCCAL INFECTION	144
Meningococcal Serogroups	144
Risk Factors for Infection	145
Meningococcal Carriage	146
Changing Epidemiology in the United States	146
MOLECULAR CHARACTERIZATION OF <i>N. MENINGITIDIS</i>	147
CAPSULAR SWITCHING AND OTHER ANTIGENIC VARIATION	147
MENINGOCOCCAL VACCINES	148
Polysaccharide Vaccines	148
Meningococcal Conjugate Vaccines	149
Meningococcal Conjugate Vaccines in the United States	149
Cost-Effectiveness	150
Current Recommendations and Future Prospects for the Use of Meningococcal Vaccines in the United States	151
Monitoring the Impact of the New Conjugate Vaccine	153
Serogroup B Vaccines	153
Other Vaccine Approaches	154
PREVENTION IN THE DEVELOPING WORLD	155
FUTURE PROSPECTS	155
ACKNOWLEDGMENTS	155
REFERENCES	155

INTRODUCTION

Neisseria meningitidis is a leading cause of bacterial meningitis and other invasive bacterial infections, both in the United States and worldwide (244, 300, 314). The role of the meningococcus as a cause of bacterial meningitis has become more pronounced in recent years with the declines in meningitis caused by *Haemophilus influenzae* type b and *Streptococcus pneumoniae* because of the introduction of new conjugate vaccines, *Listeria* because of efforts to reduce the contamination of food with *L. monocytogenes*, and group B streptococcus because of the use of intrapartum chemoprophylaxis in selected women (3, 312, 341, 384).

N. meningitidis is a gram-negative diplococcus that is a strict human pathogen. It most commonly causes asymptomatic nasopharyngeal carriage but on occasion causes invasive disease (10, 58, 150). A striking feature of the meningococcus is that much of its genetic variability is achieved through genetic recombination, which gives the organism the ability to rapidly acquire new traits in response to selective pressures (100, 101, 190, 357). In recent years, there have been changes in the epidemiology of meningococcal disease and new opportunities for vaccine prevention. The purpose of this paper is to review

these developments. More extensive general reviews of the clinical manifestations and therapy of meningococcal disease and bacterial meningitis can be found elsewhere (10, 354, 355).

HISTORY

The first definitive recognition of epidemic meningitis in the United States occurred in Medfield, Massachusetts, in 1806, 1 year after its first description in Geneva (73, 74, 367). This first American account vividly describes some of the nine fatal cases that occurred during an outbreak in March 1806 and the treatments that were utilized: “At first it was thought advisable to evacuate the stomach and bowels, and to exhibit bark and wine as speedily and freely as possible. This mode was followed in the three first cases that received medical advice, in all which it was found ineffectual: the patients seemed to sink faster after each evacuation” (73). In the case of a 15-month-old child (presented as originally printed): “on account of the *very violent puffation* discovered at the fontanel, about an ounce of blood was taken from the jugular vein; the effect was unfortunate; the child seemed to fail faster, even from this small depletion, and died within twelve hours from the attack” (74).

In 1886, Hirsch described “epidemic cerebro-spinal meningitis” throughout Europe, Africa, Asia, and the Americas, as well as some of the epidemiologic features of meningococcal disease (171). The organism was first isolated from cerebro-spinal fluid of patients with meningitis and named “*Diplococcus intracellularis meningitidis*” by the Austrian pathologist and

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bacteriologist Anton Weichselbaum (375). Asymptomatic carriage was first described in 1896 in Europe and subsequently correlated with meningococcal incidence (48, 198).

In the early part of the 20th century, the American physician Simon Flexner reported on the use of antimeningococcal serum therapy, first in an animal model and subsequently in humans, demonstrating that intrathecal administration reduced the mortality of meningococcal meningitis (111–114). In 1915, a serogrouping scheme was proposed that separated meningococcal isolates into types I to IV (later changed to the letter-based nomenclature that is used today), which eventually was adopted in the United States (140, 365).

There were vivid descriptions of meningococcal epidemics that occurred in the late 1920s in Milwaukee and Detroit; no data on the serogroups responsible were provided (124, 254). The use of serum therapy fell by the wayside in the 1930s with the advent of sulfonamide therapy for treatment of meningococcal infection (318, 319). In a report from the Surgeon General in 1930, rates of meningococcal meningitis were reported for the United States, with rates that are much higher than those of today (386). For example, rates of 18 to 59 per 100,000 population were reported for the mountain states and 16 per 100,000 for New York City, versus rates of around 0.5 to 1.5 per 100,000 in more recent years. The advice that was given in this report included “maintenance of high standards of bodily vigor, sterilization of dishes and eating utensils, and optimum of fresh air and sunshine for carriers and convalescents.” The value of meningococcal prophylaxis in both reducing meningococcal carriage and preventing disease in military personnel was described in 1943 (202). The subsequent appearance of clinically significant sulfonamide resistance created a renewed interest in meningococcal vaccines (239, 311).

CLINICAL ASPECTS OF MENINGOCOCCAL INFECTION

Clinical syndromes caused by *N. meningitis* are many and include meningitis, with or without meningococcemia; relatively mild bacteremia, fulminant meningococcemia, meningococcal meningitis, pneumonia, and septic arthritis, as well as other presentations (10). The case fatality is around 12% but varies widely by clinical presentation. Meningococcemia without meningitis is the most deadly of the meningococcal syndromes (163). Permanent sequelae are common among survivors of meningococcal infection (93, 95). Definitive diagnosis requires the isolation of *N. meningitidis* from a normally sterile body fluid or the detection of meningococcal DNA by PCR (36, 71, 87, 259, 321).

Therapy requires the prompt administration of antibiotics following the collection of appropriate diagnostic specimens. The therapy of choice is penicillin or ampicillin because the meningococcus remains susceptible to these agents in the United States. A small percentage of isolates from the United States have intermediate susceptibility to penicillin (MIC of 0.1 to 1.0 $\mu\text{g/ml}$) but the clinical significance of this is not clear (183, 301). Penicillin resistance has been reported in Spain and is mediated by changes in penicillin binding proteins (20, 52). Other appropriate antibiotics for the treatment of invasive meningococcal infection include ceftriaxone or cefotaxime, antibiotics that are frequently used for empirical therapy of bacterial meningitis. In the patient with penicillin and cephalosporin allergy, chloramphenicol is an alternative agent.

Chloramphenicol resistance, mediated by a chloramphenicol acetyltransferase, has been reported in 11 serogroup B strains in France and Vietnam (129). Although chloramphenicol is rarely used for the treatment of meningococcal infection in the United States, it is commonly used in developing countries as a single dose in oil (170, 389). An analysis of a collection of 33 serogroup A isolates collected in 1963 and 1998 from nine African countries failed to reveal chloramphenicol resistance (348).

Treatment of meningococcal infection also requires supportive care for complications such as vascular collapse, adult respiratory distress syndrome, and disseminated intravascular coagulation. Although there are limited data on the use of activated protein C in meningococcal infection, its use is appropriate if the exclusion criteria of the Protein C Worldwide Evaluation in Severe Sepsis trial are utilized (5, 19, 247, 291). However, this agent should not be used in pediatric severe sepsis. A recent randomized, double-blind, placebo-controlled trial of activated protein C stopped enrollment because of concerns over both safety and efficacy, including an increase in the rate of central nervous system bleeding (www.fda.gov/medwatch/SAFETY/2005/xigris_dearHCP_4-21-05.htm, last accessed 12 December 2005). In addition, the manufacturer recently notified healthcare professionals that among adults with single organ dysfunction and recent surgery, all-cause mortality was higher with the activated protein C group compared to with a placebo (www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Xigris, last accessed 12 December 2005) (1, 261).

The administration of corticosteroids in patients with sepsis or bacterial meningitis remains controversial (80, 344, 354). In one study, patients with pneumococcal but not meningococcal meningitis appeared to benefit from steroid therapy, although the study did not have a sufficient sample size to demonstrate efficacy for specific pathogens other than *S. pneumoniae* (80). There is some suggestion that low-dose steroids may be beneficial in sepsis and a clinical trial is under way to definitively address this issue (216, 241).

The estimated incidence of meningococcal infection among household contacts of a sporadic case is around 0.4%, 500- to 800-fold higher than in the general population (236). Observational data suggest that chemoprophylaxis is effective in reducing secondary disease. In a study conducted by the Centers for Disease Control and Prevention (CDC), none of 693 household contacts of a meningococcal case who received appropriate chemoprophylaxis developed meningococcal disease, compared with 5 of 1,179 (0.424%) contacts who received no drugs or those felt to be ineffective (236, 237). Chemoprophylactic agents that can be used to prevent secondary cases among adult contacts of patients with meningococcal infection include rifampin, single-dose intramuscular ceftriaxone, or single-dose oral ciprofloxacin; the first two agents can also be used in children (65, 83, 92, 130, 180, 277, 284, 315, 316, 325). These agents generally decrease nasopharyngeal carriage by 90 to 95%. There is also evidence that azithromycin may be effective in eradicating meningococcal carriage (131, 139) but this drug is not a recommended regimen in the United States (28, 65). Rifampin-resistant strains are seen commonly with the persistence of meningococcal carriage despite rifampin chemoprophylaxis (160, 180, 249, 353, 376). Chemoprophylaxis should be administered as soon as possible after the onset of

the index case and is considered to be of little or no value beyond 14 days.

Penicillin, despite being effective for the treatment of meningococcal infection (10), is ineffective for the eradication of carriage when given orally as penicillin V because it does not achieve sufficient concentrations in tears and saliva to eradicate carriage (118, 173). Intramuscular procaine penicillin is also ineffective (14, 163). Other antibiotics that have been found to be ineffective in eliminating nasopharyngeal carriage include benzathine penicillin, ampicillin, erythromycin, tetracycline, chloramphenicol, and cephalexin (77, 307).

Mass chemoprophylaxis to control large meningococcal epidemics is not recommended (28). However, chemoprophylaxis can be considered for smaller outbreaks in well defined populations, such as a school, or for small serogroup B outbreaks, for which no vaccine is available in the United States (180, 397).

EPIDEMIOLOGIC ASPECTS OF MENINGOCOCCAL INFECTION

Meningococcal Serogroups

Discussions of meningococcal epidemiology and prevention necessarily include meningococcal serogroups. Pathogenic strains of *N. meningitidis* have a polysaccharide capsule, which serves as a major virulence factor for this organism. Unencapsulated strains, frequently found in the nasopharynx of asymptomatic carriers, rarely cause invasive disease (68, 172, 370). The biochemical composition of the capsule determines the serogroup of the strain. Although there are 13 different polysaccharide types, only 5, A, B, C, W-135, and Y are common causes of invasive disease. The serogroup A capsule is composed of *N*-acetyl-D-mannosamine-1-phosphate (89). The capsules of serogroups B, C, W-135, and Y are composed of sialic acid. Through genetic recombination, *N. meningitidis* has the ability to undergo capsular switching, which is discussed further below.

Knowledge of the serogroup distribution of strains causing invasive infection is important information needed for vaccine formulation because most meningococcal vaccines are serogroup specific. As will be discussed later in this review, the two meningococcal vaccines that are available in the United States include serogroups A, C, W-135, and Y. Serogroup A, which continues to be responsible for most of the major meningococcal epidemics worldwide, has largely disappeared as a cause of infection in the United States (317, 346, 390, 391). Serogroup A epidemics occur in 8- to 10-year cycles in the meningitis belt of sub-Saharan Africa and only during the dry season. These epidemics can be devastating, with incidence rates approaching 1%, 1,000-fold higher than the rate in the United States. Even between epidemics, the incidence of meningococcal infection in sub-Saharan Africa is much higher than the endemic disease incidence in the United States and other developed countries (151, 152). There are also occasional serogroup C outbreaks in Africa, as well as relatively infrequent disease caused by other serogroups (29, 51, 82). Interestingly, meningococcal carriage in this setting is not seasonal, suggesting ongoing transmission of *N. meningitidis* during the rainy season despite a low incidence of invasive disease (34).

The absence of serogroup A infection in the United States has occurred despite the fact that epidemic serogroup A strains have been introduced into the United States relatively recently (245). The last known outbreak of serogroup A meningococcal infection in the United States occurred in 1975 among residents of a skid row community in Seattle, Wash. (72, 104). Outbreaks of serogroup A infection were also seen in Finland during the 1970s and in Moscow as late as the 1990s (2, 225, 265). It is not known why there is virtually no serogroup A disease in the United States but immunity caused by cross-reactive antibodies to other organisms has been proposed as a possible mechanism (105, 159, 293). In a recent study, only about a quarter of preimmunization sera from North Americans participating in meningococcal vaccine trials had anti-serogroup A bactericidal titers of $\geq 1:4$ and most of the bactericidal antibodies present were against noncapsular antigens (7). There were high concentrations of anticapsular antibody, but they were not bactericidal.

Serogroup B accounts for a substantial proportion of cases in the United States and many other parts of the world and accounts for about half of invasive infections in infants in the United States (299). Because group B polysaccharide is poorly immunogenic in humans, group B vaccines cannot be based on capsular polysaccharide. The lack of serogroup B immunogenicity is believed to be because of immunologic cross-reactivity with fetal neural antigens (107, 108, 392). This molecular mimicry raises safety issues because of the potential of serogroup B polysaccharide vaccines to elicit autoreactive antibodies. In addition, it has greatly complicated vaccine development for serogroup B because, based on noncapsular antigens, the population of organisms causing invasive infection is genetically quite diverse (304).

In addition to the endemic disease caused by serogroup B strains, there have been serogroup B outbreaks in many parts of the world, including Oregon, many parts of Europe, Latin America, and New Zealand (16, 56, 57, 64, 86, 227, 263, 303, 364, 374). In contrast to outbreaks of endemic disease, serogroup B outbreaks tend to be clonal, which has allowed the development of outer membrane vesicle vaccines that target the outbreak strain (255).

Serogroup C is a major cause of endemic disease in North America and Europe and since the 1990s has caused multiple outbreaks in schools and in the community (42, 106, 182, 383, 397). The bulk of these infections are caused by a group of highly related strains referred to as the sequence type (ST) 11/enzyme type (ET) 37 clonal complex.

Serogroup W-135 accounts for only a small proportion of cases in the United States and, until recently, had never been known to cause outbreaks. In 2000, a W-135 outbreak occurred in Saudi Arabia during the annual Hajj pilgrimage (79, 229, 275, 335–337). The outbreak strain spread to multiple other countries and caused a large epidemic in Burkina Faso in 2002. Serogroup Y, which in recent years has accounted for a substantial proportion of cases in the United States, has classically been associated with pneumonia and the military (199, 326). In a study of 58 meningococcal pneumonia cases, around 45% of cases were caused by serogroup Y (387). However, only 15% of serogroup Y cases are associated with pneumonia (278). As outlined below, the incidence of serogroup Y disease increased remarkably during the 1990s (128, 184, 299) and is the pre-

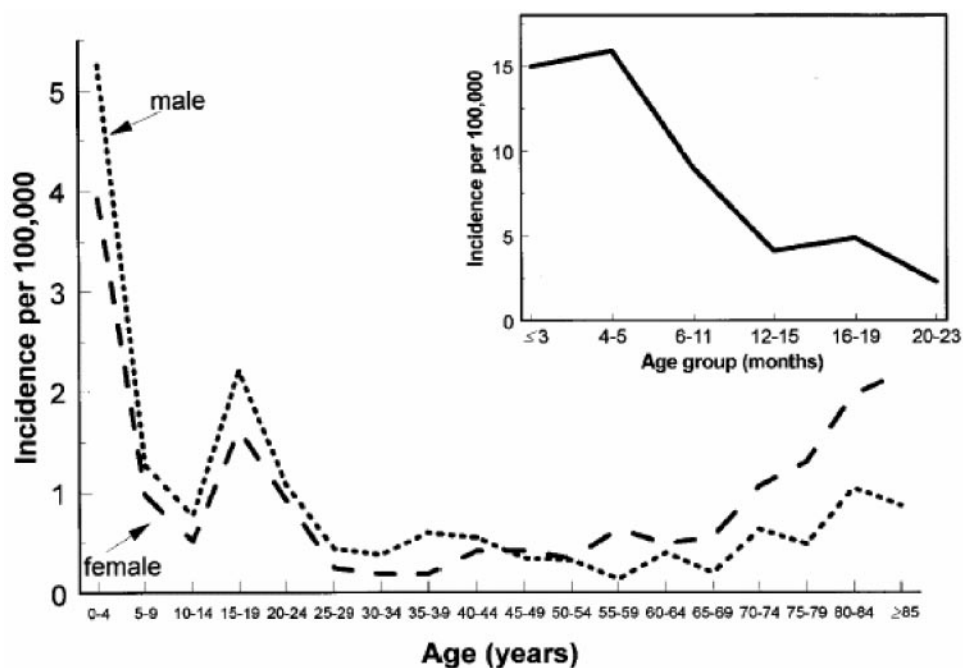


FIG. 1. Race-adjusted rates of meningococcal disease by age group and gender in California, Georgia, Maryland, Tennessee, Connecticut, Minnesota, and Oregon, 1992 to 1996. (Reprinted from reference 299 with permission of the University of Chicago Press.)

dominant cause of invasive infection in the elderly. Strains with other serogroups, such as serogroup X, are uncommon causes of invasive disease but can occasionally cause small outbreaks (88).

Risk Factors for Infection

There are specific host factors that increase the risk of invasive meningococcal infection because only a minute fraction of nasopharyngeal carriers of *N. meningitidis* develop clinical disease. Although the incidence in the United States tends to range between 0.5 to 1.5 cases per 100,000 per year, the incidence varies substantially by age, with infants having the highest incidence (Fig. 1) (299). Lack of serum bactericidal antibody (SBA) titers has been known for decades to be one of the key host factors associated with an increased risk (136, 137). For reasons that are not known, the risk is higher among males until around age 45 years, at which time the risk becomes higher among women (299). Black race and lower socioeconomic status have been associated with an increased risk, but whether race per se actually increases the risk is doubtful (163, 184, 299). Functional or anatomic asplenia; deficiencies or genetic polymorphisms in components of the innate immune system, such as terminal complement components, properdin, Toll-like receptor 4, and mannose-binding lectin; and human immunodeficiency virus infection have all been associated with an increased risk (94, 103, 119, 175, 203, 271, 306, 327, 331). Variation in the plasminogen-activator inhibitor 1 (PAI-1) gene has been associated with increased susceptibility to meningococcal septic shock, but not an overall risk of meningococcal disease (382). In studies in Atlanta, Ga., and Maryland, underlying medical conditions were uncommon among adolescents and young adults but frequent among persons over 24 years old (168, 331). Predisposing conditions in those studies

included human immunodeficiency virus infection, congestive heart failure, malignancy, diabetes mellitus, organ transplantation, and corticosteroid use.

There are also a variety of environmental and behavioral risk factors for meningococcal infection. Concomitant upper respiratory infection has been associated with an increase risk of carriage and invasive disease in some settings (54, 162, 201, 246, 256, 395). For example, an outbreak among five middle school students on the same school bus in rural Virginia was associated with a severe outbreak of influenza B (162). Possible mechanisms for this association include disruption of the respiratory epithelium with subsequent facilitation of invasion of *N. meningitidis* and increased transmission because of coughing. Clearly, climactic conditions influence the risk of infection. In sub-Saharan Africa, epidemic meningococcal infection typically starts during the dry season, when it typically is hot, dusty, and arid, and ends with the onset of the rainy season (153).

Crowding has been shown to increase the risk of meningococcal infection. During World War II, two thirds of all meningococcal infections occurred during initial training among troops with under 3 months of service (47). Active and passive smoking has been associated with meningococcal disease and meningococcal carriage in most (70, 110, 178, 179, 340) but not all studies (44). Bar patronage was also been associated with the risk of infection during a university outbreak (179). Transmission of serogroup C meningococcal disease during a small outbreak in Maryland appears to have occurred during a party (106).

Several studies of the risk of meningococcal disease in college students yielded similar results (44, 125, 166). In a study in Maryland from 1992 to 1997, 4-year-college students living on campus had an over threefold increased risk relative to the

off-campus population (166). In a multistate study involving one school year, freshmen living in dormitories had the highest risk (44). In the two studies, 86 and 68%, respectively, of cases of disease in college students were caused by serogroups that are included in the quadrivalent polysaccharide and conjugate vaccines. University students in the United Kingdom have high rates of meningococcal infection, but most infections in that setting were caused by serogroup B strains (251, 252). Permanent sequelae are common among college students surviving meningococcal infection (95). There have been numerous reports of laboratory-acquired meningococcal infection, mostly among microbiologists manipulating the organism on an open laboratory bench (27, 61, 62, 258, 267).

Meningococcal Carriage

The meningococcus is a commensal organism that is found naturally only in humans. It most commonly causes asymptomatic nasopharyngeal carriage and only relatively rarely causes invasive infection. The prevalence of carriage varies by study but is generally highest in adolescents and young adults (55, 58, 195).

Carriage can change substantially over time in populations. For example, in a cross-sectional study of carriage rates among university students during the first week of the school term in the United Kingdom, carriage increased from 6.9% on day 1 to 23.1% on day 4 (252). Carriage is transient in some individuals, is intermittent in others, and can last for many months in others (8, 330). Meningococcal carriage typically produces a bactericidal antibody response against capsular and noncapsular antigens, making it an immunizing event (137, 191). Accordingly, most invasive disease occurs within 2 weeks of the acquisition of a new strain because if carriage persists beyond that time period, an antibody response to the colonizing strain has already occurred.

The likelihood that invasive infection will occur following nasopharyngeal colonization is highly dependent on the strain that is acquired and on environmental and host factors discussed below. Meningococci found in the nasopharynx are genetically quite diverse, whereas the strains causing invasive disease are much more genetically restricted (195).

Newer molecular subtyping methods have allowed for an improved understanding of the dynamics of meningococcal carriage. Multilocus enzyme electrophoresis (MEE) and, more recently, multilocus sequence typing (MLST) have been the primary methods that have been used to study carriage dynamics (57, 222). These approaches have revealed striking differences in the dynamics between strains. Some common causes of invasive disease, such as ET-37/ST-11 serogroup C strains, are rarely found in the nasopharynx. In a study in Georgia, no ET-37 carriers were found in 1,816 students from a county in Georgia with a high incidence of serogroup C infection (195). On the other hand, serogroup Y ST-23/ET-508 complex strains are both a common cause of invasive disease and frequently found in asymptomatic carriers. Many carried meningococci do not express polysaccharide capsule and therefore are not pathogenic (195).

Meningococcal carriage has important implications for vaccine prevention because newer conjugate vaccines exert substantial herd immunity effects through reductions in acquisition of nasopharyngeal carriage (discussed below).

Changing Epidemiology in the United States

Up until around the end of World War II, the overall incidence of meningococcal infection in the United States was as high as 14 cases per 100,000 population per year (163). Since then, however, the incidence has tended to fluctuate between around 0.5 to 1.5 cases per 100,000 population per year. Although improvements in socioeconomic status are an oft-cited explanation for this dramatic change in the epidemiology of meningococcal infection, in reality the reasons for the change are not known.

There is marked seasonal variation, with the incidence in summer months typically around one third the incidence during the peak season, which generally occurs in the first 3 months of the year. In addition to the seasonal variation that occurs with meningococcal infection, over the past 40 years the incidence has tended to vary in 15- to 20-year cycles (145). Most recently, meningococcal incidence peaked in the United States during the 1990s at an overall incidence of around 1.7 per 100,000 with the subsequent decline in the late 1990s and early 2000s to around 0.5 (Nancy Rosenstein, personal communication, 30 March 2005; www.cdc.gov/abcs/).

There are also major fluctuations in serogroup distribution. This is important because designing a vaccine based on the serogroup distribution from one point in time could potentially lead to the exclusion of potentially important serogroups. For example, serogroup Y was relatively common in some populations during the 1970s but, during 1989 to 1991, only 2% of infections were caused by this serogroup (128, 184). By the mid-1990s, over a third of infections were caused by serogroup Y (299). In Maryland, the increase in serogroup Y infection occurred mostly among children <15 years old and adults over 25 years (231). In addition, serogroup C infection also increased during the 1990s. Serogroup W-135 was more common in previous years than it is now (17, 128, 299).

The incidence of meningococcal infection is age specific, with infants having the highest rates of disease (184, 299). Typically, the incidence among adolescents and young adults is low (184). However, in the 1990s, the incidence increased substantially in this group (Fig. 1). In Oregon, the increase was caused by a serogroup B clone whereas elsewhere in the United States, the increase was caused in large part by serogroup C (86, 166, 299). In addition, the case-fatality rate in adolescents and young adults has historically been low (18, 331). However, in a study of the increased incidence in 15 to 24 years in Maryland during the 1990s, the case-fatality rate was unusually high at 22.5%, higher than among children <15 years old (4.6%) and adults 25 years old and over (16.5%). The frequently fatal outcome in 15- to 24-year-olds was a result of the severe nature of the infection in this age group: 69% presented with hypotension, 40% presented with meningococemia without meningitis (the most severe meningococcal clinical syndrome), 35% with renal dysfunction, and 40% with thrombocytopenia. Nearly half of infections in this age group were caused by serogroup C strains and 83% were caused by serogroups included in the quadrivalent polysaccharide and conjugate vaccines, indicating that infection in this age group is mostly vaccine preventable.

Meningococcal outbreaks also increased beginning in the early 1990s with a total of 76 identified between mid-1994 and

mid-2002 throughout the United States (42, 106, 182, 383, 397). Some outbreaks were community based and there were 13 college outbreaks, 19 primary and secondary school outbreaks, and 9 outbreaks in nursing homes. Most of these were caused by serogroup C *N. meningitidis* but serogroup B and Y outbreaks also occurred. Meningococcal polysaccharide vaccine was frequently used to control the outbreaks that were caused by serogroup C and Y strains.

MOLECULAR CHARACTERIZATION OF *N. MENINGITIDIS*

An understanding of meningococcal epidemiology and the issues related to vaccine prevention requires knowledge of the molecular epidemiologic characteristics of the organism. A common molecular tool for characterizing *N. meningitidis* is MLST, which involves DNA sequencing of segments of seven housekeeping genes (222). Housekeeping genes are utilized because they are generally not under selective pressure for rapid change and therefore can be used to assess the genetic background of this organism. MLST has widely replaced MEE, although meningococcal strains are often referred to by both their sequence type and enzyme type (292). For example, ST-11 strains, responsible for most of the serogroup C disease in the United States and elsewhere, are often also referred to as ET-37 (189).

There are numerous advantages of MLST over previously used meningococcal molecular subtyping methods, including that the results are highly objective and portable, allowing for direct comparison of results across laboratories worldwide through the Internet (188). However, MLST also is generally not sufficiently discriminatory for outbreak investigations, and for that purpose other approaches, such as MLST in combination with outer membrane protein gene sequencing, pulsed-field gel electrophoresis, sequencing of 16S rRNA genes, and multilocus variable-number tandem repeat analysis, have been used (99, 276, 305, 393).

There are several meningococcal outer membrane proteins that are important both for molecular epidemiologic characterization of strains and because outer membrane proteins are frequent components of serogroup B vaccines. Susceptibility to meningococcal infection is determined in part by SBAs to these proteins. One of these, PorA, is an immunogenic porin that is the basis of the meningococcal serosubtyping (98, 120). *porA* genotyping is accomplished through DNA sequencing of variable regions 1 and 2, which is more sensitive than serosubtyping for detecting PorA variability (233). This is an important issue because a single amino acid change in PorA has been associated with an increased incidence of meningococcal infection (232). PorA can be variably expressed and the *porA* gene has been shown to be deleted from some clinically relevant strains (360–362, 388). PorB, also an immunogenic porin, is the basis of meningococcal serotyping, and an individual strain has either a class 2 or class 3 protein (123, 358).

Meningococcal immunotypes are based on lipooligosaccharide serotypes (120, 300, 352). There are only 13 immunotypes, indicating that there is less antigenic variability in meningococcal lipopolysaccharide than the outer membrane protein antigens described above. Meningococcal strains usually have two lipopolysaccharide determinants, but there can be multiple

ones (120). The generally accepted nomenclature for describing these characteristics of meningococcal strains lists serogroup, serotype, serosubtype and immunotype, separated by colons (e.g., B:15:P1.7,16:L3,7,9).

CAPSULAR SWITCHING AND OTHER ANTIGENIC VARIATION

The meningococcus employs a variety of mechanisms to change rapidly, particularly in the face of selective pressure, such as natural or vaccine-induced immunity. *N. meningitidis* achieves genetic change primarily through horizontal gene transfer, which allows it to acquire large sequences of DNA, presumably during cocolonization of the human nasopharynx with at least two strains (213, 223). The organism is also able to undergo gene conversion, which is essentially autologous recombination, a mechanism also used by *N. gonorrhoeae* (9, 176). For example, Pile, a major component of the meningococcal pilus, is encoded by the *pilE* gene. Immediately upstream from *pilE* are eight truncated pseudogene homologs, referred to as *pilS* or silent pilin genes, because they are not directly expressed. The meningococcal pilus aids the organism in binding to human cells (300). The *pilE* homologs contain a portion of the semivariable region and almost all or all of the hypervariable region of *pilE*. Gene conversion is therefore a mechanism that allows recombination that does not require DNA from another organism, resulting in antigenic change in the face of immunologic pressure. The organism is also able to vary its phenotype through phase variation and variable gene expression, which often occurs through slipped-strand mispairing of variable-number tandem repeat regions, and the use of insertion elements (67, 89, 309, 332).

Capsular switching, by which the capsular phenotype of the organism changes, is one such mechanism. Increasing evidence suggests that outbreaks of meningococcal infection can be initiated or sustained through capsular switching, presumably allowing escape from natural immunity against the original serogroup (4, 196, 334, 369). Capsular switching, which occurs through horizontal gene transfer, is usually detected by identifying strains that are highly related genetically by, for example, MLST, MEE, and/or pulsed-field gel electrophoresis, but express different capsular polysaccharides. In one example, the boyfriend of a 16-year-old girl who died of serogroup B meningococcal infection was colonized in the nasopharynx with an otherwise indistinguishable serogroup C strain (369).

Another example of an apparent capsular switch occurred in the Pacific Northwest in the 1990s. In the face of a major increase in serogroup B infections in Oregon and adjacent counties in Washington caused by strains of the ET-5 complex, strains of this complex that were serogroup C were noted (86, 334). These strains were identical by several genetic markers to the predominant serogroup B ET-5 complex strains. The B to C switch in capsular expression was likely caused by horizontal gene transfer of polysialyltransferase, which is involved in capsule synthesis, a phenomenon that has also been demonstrated *in vitro* by cocultivation of a serogroup W-135 donor strain and a serogroup B recipient (126).

Capsular switching can lead to major changes in meningococcal epidemiology. For example, until recently serogroup W-135 strains had never been known to cause an outbreak.

However, this serogroup caused a worldwide outbreak that started during the 2000 annual Hajj pilgrimage to Mecca (229, 275, 335, 336). The outbreak was caused by a serogroup W-135 clone that was genetically related to a virulent serogroup C clone. This suggested that a capsular switch had occurred but, since this strain was found in archived isolates, the switch would have likely occurred years before the onset of the outbreak. Because of a previous Hajj-related serogroup A epidemic, many pilgrims had been immunized with a bivalent serogroup A/C polysaccharide vaccine, providing an optimal setting for this serogroup W-135 clone to emerge.

The major concern about capsular switching is that it could occur as a result of vaccine-induced immunity, particularly in the face of vaccines that do not include protection against all of the important meningococcal serogroups. However, this has not yet been noted following the introduction of serogroup C conjugate vaccines in the United Kingdom.

Antigenic shift in noncapsular antigens has also been shown to occur and was associated with increasing incidence of serogroup C and serogroup Y *N. meningitidis* in Maryland (167). For serogroup Y, the changes involved recombination events in the genes encoding PorA, PorB, and FetA. For serogroup C, the changes involved FetA and deletions of the gene that encodes PorA.

MENINGOCOCCAL VACCINES

Polysaccharide Vaccines

The development of a pneumococcal vaccine six decades ago demonstrated the feasibility of vaccine prevention of invasive encapsulated bacterial diseases (221). Purified polysaccharide vaccines for serogroups A and C *N. meningitidis* were developed several decades later. Early vaccines were poorly immunogenic apparently because the polysaccharides that were used were of low molecular weight, whereas vaccines made from polysaccharide with a molecular weight over 100,000 had excellent immunogenicity (12, 141, 143, 144).

The immunogenicity of meningococcal vaccines is also influenced by O-acetylation. The serogroup A polysaccharide is 70 to 95% O acetylated at carbon 3 and acetylation occurs via the *mycC* gene (158, 185, 205). In a study using pre- and postimmunization sera from humans vaccinated with polysaccharide vaccine, the majority of antibodies to the serogroup A polysaccharide involved O-acetyl epitopes. In one study in mice, immunization with a de-O-acetylated conjugate vaccine led to a 32-fold lower level of SBA titers than immunization with a similar O-acetylated product (21). Serogroups C, W-135, and Y also have various degrees of O-acetylation, although the implications for polysaccharide immunogenicity for these serogroups is not known (38, 215). For serogroup C, expression of O-acetylation can be downregulated by phase variation involving slipped-strand mispairing (67).

Until recently, the only meningococcal vaccine licensed for use in the United States was an A/C/W-135/Y polysaccharide vaccine (MPSV4), known as Menomune, manufactured by Sanofi Pasteur. In other countries, both monovalent and other combinations of capsular polysaccharides have been used. All four components of MPSV4 have been shown to be immunogenic in adults and older children. Vaccine efficacy (clinical

protection demonstrated in a randomized controlled field trial) and effectiveness (clinical protection demonstrated in observational postlicensure studies) have been demonstrated for the serogroup A and C components. Serogroup A polysaccharide has some immunogenicity as early as 3 months of age, albeit not as much as in older children and adults, and serogroup C polysaccharide is poorly immunogenic in children under 2 years old (133, 264). The immunogenicity of the serogroup W-135 and Y components has been demonstrated when given alone, combined, and together with the A and C components as a tetravalent vaccine (6, 11, 50, 155, 156, 206, 368). MPSV4 is immunogenic in anatomically asplenic persons whose spleens were removed because of nonlymphoid tumors or trauma (243, 302). In persons with terminal complement deficiency, the vaccine is immunogenic and appears to provide some clinical protection, presumably by opsonic antibodies (91, 271).

The efficacy/effectiveness of the serogroup C and serogroup A components has been demonstrated for adults and school-aged children (13, 46, 47, 132, 265, 298, 371, 372). In military recruits, who historically have been at high risk of meningococcal infection, the short-term efficacy of the serogroup C component was found to be 89.5% (13, 46, 47, 132). The effectiveness of C polysaccharide in 2- to 29-year-olds during an outbreak in Texas was 85% (298). During a serogroup A outbreak in Egypt in the early 1970s, efficacy in school-aged children was 89% (371, 372). There are no efficacy data for the serogroup W-135 and serogroup Y components; vaccine licensure was based on immunogenicity data.

There are limited data on the duration of protection of MPSV4. Serum antibody levels decline significantly in infants and children <5 years old but in healthy adults antibodies can still be detected after 10 years (12, 133, 194, 207, 398). However clinical protection wanes over time in both children and adults. In a study involving three yearly vaccine effectiveness studies in Burkina Faso, the estimate of effectiveness of the serogroup A polysaccharide vaccine at 1, 2, and 3 years following immunization in children 4 years old and over was 85, 74, and 67%, respectively. Among children under 4 years old, effectiveness was estimated to be 100, 52, and 8%, respectively (283).

The routine use of meningococcal polysaccharide vaccine in U.S. military recruits has virtually eliminated the outbreaks that were common in the military in the prevaccine era and disease caused by vaccine serogroups is uncommon (46, 47). Despite the utility of the MPSV4 in selected populations, there are major limitations that have restricted its widespread use, including lack of immunogenicity in infants, lack of immunologic memory and booster response, and relatively short duration of protection. Studies of serogroup A polysaccharide vaccines have shown no discernible impact on carriage (35, 43, 154). Although there is some evidence suggesting that meningococcal polysaccharide vaccines may have some short-term impact on serogroup C nasopharyngeal carriage at 3 to 6 weeks after vaccination (142, 333), polysaccharide vaccines in general are not considered to provide substantial herd immunity (145).

Meningococcal polysaccharide vaccines have been shown to induce immunologic hyporesponsiveness. In this phenomenon, the antibody response in persons previously immunized with the meningococcal polysaccharide vaccine is less than that in persons receiving a first dose (135, 138, 146, 217, 218). It occurs

in all age groups but is most profound in children under 2 years old. The duration of the hyporesponsiveness is unknown but can be present for 2 to 5 years. It is postulated to be due to terminal differentiation of B cells stimulated by more than one dose of polysaccharide vaccine (76). However, the clinical significance of hyporesponsiveness is not known.

Meningococcal polysaccharide vaccines have been used extensively for decades and are considered safe. Adverse reactions, such as injection site pain and erythema, are common but usually mild (206, 310). Transient fever can also occur in up to 5% of vaccinees (134, 264). Severe adverse reactions are rare. Systemic allergic responses occur at a rate of 0 to 1 case per million doses administered and anaphylaxis occurs at a rate of <1 case per million doses (264, 295, 394).

Meningococcal Conjugate Vaccines

Meningococcal conjugate vaccines, in which meningococcal polysaccharide is covalently linked to a carrier protein, are typically T-cell dependent, which confers major immunologic improvements over polysaccharide vaccines (208, 209, 329). The carrier proteins used for meningococcal conjugate vaccines have included tetanus toxoid protein, diphtheria toxoid, and diphtheria cross-reactive material (CRM)₁₉₇. Meningococcal conjugate vaccines have been in development for several decades but have only recently started coming to market (22–24). One of the major advantages is immunogenicity in infants, which protects the age group with the highest incidence. Other advantages include induction of immunologic memory, a booster response, and the ability to overcome the immune hyporesponsiveness that is induced by the polysaccharide vaccine (290). Serogroup C meningococcal conjugate vaccines also reduce carriage of *N. meningitidis* in the nasopharynx, which leads to a decrease in transmission to unvaccinated persons (224, 280). *Haemophilus influenzae* type b and pneumococcal conjugate vaccines have dramatically changed the epidemiology in children of infection caused by these organisms, whereas polysaccharide vaccines have limited immunogenicity and effectiveness in young children (33, 90, 96, 164, 165, 169, 308, 323, 384).

The huge public health impact of the herd immunity effect afforded by conjugate vaccines has been appreciated over the past 15 years based on experiences with *Haemophilus influenzae* type b, pneumococcal, and serogroup C meningococcal conjugate vaccines. For *Haemophilus influenzae* type b, there was a huge reduction among infants under 1 year old when the *Haemophilus influenzae* type b conjugate vaccine was licensed for use in children 18 months and over (3, 250). More recently, the heptavalent pneumococcal conjugate vaccine in children has led to a major decline in the incidence of invasive pneumococcal infection in adults (384).

The experience with serogroup C conjugate vaccines in the United Kingdom has been illustrative of the potential impact of meningococcal conjugate vaccines in other countries. There is very little serogroup Y infection in the United Kingdom. In late 1999, faced with high rates of serogroup C infection, an intensive immunization program with three serogroup C conjugate vaccines was implemented. A schedule of doses at 2, 3, and 4 months of age was introduced into the routine infant immunization schedule and, in addition, there was a catch-up

campaign among children under 18 years old (240). Vaccine coverage rates were impressive at around 90% for infants and 85% in the catch-up campaign.

There has been evidence for high vaccine effectiveness (240, 279) and a herd immunity effect (224, 280). Since the introduction of serogroup C conjugate vaccines in the United Kingdom, there has been an approximately two-thirds drop in nasopharyngeal carriage of serogroup C *N. meningitidis* among 15- to 17-year-olds, as well a similar reduction in serogroup C meningococcal incidence among the unvaccinated population of all ages (224, 280). There are three serogroup C conjugate vaccines that are licensed in the United Kingdom, Europe, and Australia (28). A meningococcal C conjugate vaccine was recently reported to be effective in Quebec, Canada, with an estimated effectiveness of 98.6% (84, 85).

In a recent follow-up study in the United Kingdom, there was no longer evidence for clinical protection in infants immunized at 2, 3, and 4 months of age more than 1 year after immunization despite evidence for continued protection in all other age groups that were targeted for immunization (349). These data must be interpreted with caution because the upper bound of the 95% confidence interval was such that true effectiveness in this group could have been as high as 71%. Nonetheless, this follow-up study raises doubts about the duration of protection of this immunization schedule in infants in the absence of a booster dose. These data also raise questions about the role of immunologic memory in protection in the absence of protective antibody levels. They also underscore the need for continued active surveillance for meningococcal disease after the licensure of a new vaccine.

Meningococcal Conjugate Vaccines in the United States

A monovalent serogroup C vaccine would be suboptimal for use in the United States given the importance of serogroup Y infection in this country. In January 2005, a quadrivalent meningococcal conjugate vaccine (MCV4) was licensed by the U.S. Food and Drug Administration (FDA) for 11- to 55-year-olds (Menactra, manufactured by Sanofi Pasteur). A single dose of MCV4 contains 4 µg each of the A, C, Y, and W-135 polysaccharides conjugated to 48 µg of diphtheria toxoid (Table 1). Licensure was based on immunologic noninferiority to the polysaccharide vaccine; there have been no efficacy trials of this vaccine.

In a randomized controlled trial of 881 healthy 11- to 18-year-olds, the proportion of subjects who had SBA titers of <1:8 that subsequently developed an SBA titer of >1:32 28 days after MCV4 or MPSV4 immunization was similar for both vaccines and nearly 100% for all four serogroups (28, 197) (Table 2). In a randomized controlled trial of 2,378 adults 18 to 55 years old, the criteria for noninferiority were also achieved (Table 2). In a follow-up of persons immunized at the ages of 14 to 21 years, the antibody titers 3 years later were higher for all serogroups among those who had received the tetravalent conjugate versus those who had received the tetravalent polysaccharide vaccine, although the differences were significant only for serogroups A and W-135, suggesting superior persistence of antibody with the conjugate vaccine (28).

Although not licensed for this age group, in 2- to 3-year-olds MCV4 was more immunogenic for all four serogroups than

TABLE 1. Characteristics of meningococcal polysaccharide and conjugate vaccines, both manufactured by Sanofi Pasteur, licensed in the United States

Vaccine	Trade name	Type	Yr licensed	Basis for licensure	Serogroups covered	Dose and route of administration	Amt of polysaccharide of each serogroup antigen (μg)	Available form(s)
Polysaccharide	Menomune	Purified polysaccharide	1981	Safety and immunogenicity	A, C, W-135, Y	0.5 ml, subcutaneous	50	Single-dose vials, ten-dose vials
Conjugate	Menactra	Polysaccharide covalently linked to diphtheria toxoid	2005	Safety and immunogenicity	A, C, W-135, Y	0.5 ml, intramuscular	4	Single-dose vials

MPSV4 (147–149). There also was persistence of antibodies for at least 2 to 3 years with MCV4 in children immunized at 2 to 3 years of age, although a large proportion of immunized children had SBA titers of $<1:4$, suggesting a lack of protection and the need for a booster dose.

There is evidence that the quality of the antibody response induced by conjugate vaccines is superior to the response induced by polysaccharide vaccine. In children 2 years old, the serogroup C antibodies produced following immunization with MCV4 were of higher avidity to capsular polysaccharide than those produced with the serogroup C polysaccharide vaccine and there was increasing avidity (avidity maturation) over 6 months with the former but not the latter (147). In an infant rat model of meningococcal bacteremia, antibodies in sera from unimmunized adults of higher avidity were associated with greater protection among persons with low SBA titers ($<1:4$) than antibodies with lower avidity (377). Avidity maturation is a marker of priming for memory, which was confirmed in children who received the quadrivalent conjugate vaccine at 2 to 3 years old when immunized 2 years later with polysaccharide (28, 149). The vaccine manufacturer recently filed an application with the FDA to obtain approval for the new conjugate vaccine for 2- to 10-year-olds.

The safety of MCV4 and MPSV4 was similar in 11- to 55 year-olds (28). However, fever of $\geq 38^\circ\text{C}$ was slightly higher with the conjugate than with the polysaccharide vaccine for

both 11- to 18-year-olds (5.1 and 3.0%, respectively) and 18 to 55-year-olds (1.5 and 0.5%, respectively). For both of these age groups, local reactivity was higher for the conjugate vaccine. The frequency of local adverse reactions reported after the administration of MCV4 is in line with what has been reported after the tetanus-diphtheria vaccine (115, 116). In children 2 to 10 years old, systemic reactions in the two groups were similar for the conjugate and polysaccharide vaccines. Two other studies examined concomitant administration of MCV4 with tetanus diphtheria vaccine and another with typhoid vaccine, vaccines that are commonly given to adolescents and travelers, respectively, and found that there was no immunologic interference (115, 116, 197).

There are studies of other meningococcal conjugate vaccines that demonstrate solid immunogenicity in infants, immunologic memory, and the booster phenomenon (37, 66, 97, 204, 219, 220, 234, 235, 285–289, 356). An exception to this was that one of the earliest serogroup A conjugate vaccines, a bivalent A/C product, failed to induce immunologic memory, while the C component did, suggesting a failure to elicit a T-cell-dependent response to the group A component of the conjugate vaccine (204, 356).

Cost-Effectiveness

Determining the precise cost-effectiveness of meningococcal vaccines is problematic because there are many factors that are

TABLE 2. Subjects with ≥ 4 -fold rise in SBA after vaccination^a

Age group and serogroup	% of subjects showing fourfold or greater increase in rSBA titer (95% confidence interval)		rSBA GMT		% of subjects achieving rSBA GMT ≥ 128	
	MCV4	MPSV4	MCV4	MPSV4	MCV4	MPSV4
11–18 yr ^b						
A	92.7 (89.8–95.0)	92.4 (89.5–94.8)	5,483	3,246	99.8	100.0
C	91.7 (88.7–94.2)	88.7 (85.2–91.5)	1,924	1,639	98.8	98.4
Y	81.8 (77.8–85.4)	80.1 (76.0–83.8)	1,322	1,228	99.5	99.3
W-135	96.7 (94.5–98.2)	95.3 (92.8–97.1)	1,407	1,545	98.6	98.8
18–55 yr ^c						
A	80.5 (78.2–82.6)	84.6 (82.3–86.7)	3,897	4,114	99.8	99.9
C	88.5 (86.6–90.2)	89.7 (87.8–91.4)	3,231	3,469	98.8	98.5
Y	73.5 (71.0–75.9)	79.4 (76.9–81.8)	1,750	2,449	97.0	98.5
W-135	89.4 (87.6–91.0)	94.4 (92.8–95.6)	1,271	1,871	97.1	98.5

^a Percentage of subjects achieving a fourfold rise or greater in serum bactericidal activity by using baby rabbit complement (rSBA), rSBA geometric mean titer (GMT) of >128 , and rSBA GMT, 28 days after vaccination with meningococcal conjugate vaccine (MCV4) and meningococcal polysaccharide vaccine (MPSV4). (Reprinted from reference 28.) Source: Food and Drug Administration (115, 116).

^b $N = 423$ in the MCV4 group and 423 in the MPSV4 group.

^c $N = 1,280$ in the MCV4 group and 1,098 in the MPSV4 group.

TABLE 3. Recommended use of vaccines for persons not vaccinated previously^a

Population group	Recommendations for indicated age group (yr)				
	<2	2-10	11-19	20-55	>55
General population	Not recommended	Not recommended	Single dose of MCV4 is recommended at age 11 to 12 yr (at preadolescent assessment visit) or at high school entry (at approximately age 15 yr)	Not recommended	Not recommended
Groups at increased risk College freshmen living in dormitories Certain travelers ^b Certain microbiologists ^c Certain populations experiencing outbreaks of meningococcal disease ^d Military recruits Persons with increased susceptibility ^e	Not usually recommended ^a	Single dose of MPSV4	Single dose of MCV4 is preferred (MPSV4 is an acceptable alternative)	Single dose of MCV4 is preferred (MPSV4 is an acceptable alternative)	Single dose of MPSV4

^a Meningococcal polysaccharide vaccine (MPSV4) (two doses, 3 months apart) can be considered for children aged 3 to 18 months to elicit short-term protection against serogroup A disease (a single dose should be considered for children aged 19 to 23 months). Reprinted from reference 28.

^b Persons who travel to or in areas where *Neisseria meningitidis* is hyperendemic or epidemic are at increased risk of exposure, particularly if contact with the local population will be prolonged. Vaccination is especially recommended to those visiting the "meningitis belt" of sub-Saharan Africa during the dry season (December to June), and vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj. Advisories for travelers are available at <http://www.cdc.gov/travel/outbreaks.htm>, <http://www.cdc.gov/travel>, or by calling CDC's Travelers' Health Hotline at (877) FYI-TRIP (toll-free).

^c Microbiologists who are routinely exposed to isolates of *N. meningitidis* should be vaccinated.

^d The use of vaccination in outbreak settings has been described previously (59).

^e Includes persons who have terminal complement component deficiencies and persons with anatomic or functional asplenia.

difficult to incorporate into analysis. In addition to direct medical costs from the acute episode, other factors include the costs of long-term sequelae; the costs to society of meningococcal outbreaks, including the outbreak investigation, providing antibiotic chemoprophylaxis, and providing a meningococcal vaccine; the costs of litigation (192, 193, 380); and the cost of disruption in schools, other institutions, and the community. In addition, cost-benefit analyses of meningococcal conjugate vaccines have generally failed to take the potential substantial impact of herd immunity into account, a major limitation given the demonstrated impact of conjugate vaccines on the incidence of disease in unimmunized persons (3, 224, 280, 384). Despite these limitations, cost-effectiveness analyses performed for the United States suggest that the cost per prevented outcome is relatively high but not out of line with that of other accepted life-saving interventions (322, 342).

Several studies evaluated the cost-effectiveness of immunizing college students with the polysaccharide vaccine. The costs to society of immunizing of freshmen living in dormitories were estimated, assuming a duration of protection of 4 years and vaccine efficacies of 80 and 90%. The cost for each case prevented ranged from US\$600,000 to US\$1.8 million and the cost for each death prevented ranged from US\$7 million to US\$20 million (320). This study took into account some of the costs of long-term disease-related sequelae but not some of the other factors outlined above. The results of this study were in line with a previous study on the cost-effectiveness of immunizing college students (181). For immunizing 11-year-olds, the

estimated cost per case prevented was US\$633,000, cost per death prevented was US\$5 million, and cost per year-life saved was US\$122,000 (28). In the United Kingdom, the cost per life-year saved for immunizing 0- to 17-year-olds was estimated to be £6,259, or approximately US\$12,000 (350).

Current Recommendations and Future Prospects for the Use of Meningococcal Vaccines in the United States

As of the beginning of 2005, two meningococcal vaccines are available in the United States, MCV4 and MPSV4, and new recommendations for the use of both have recently been published (28). The characteristics of the two vaccines are shown in Table 1.

Routine immunization of adolescents with MCV4 is now recommended, either at 11 to 12 years of age or before high school entry (Table 3) (28). Adolescents outside of these groups may elect to be vaccinated. Sufficient amounts of vaccine to cover these age groups will not be available for the next several years, so vaccine shortages are anticipated during this period.

Other high-risk groups are also recommended for routine immunization (Table 3). The conjugate vaccine is preferred in persons 11 to 55 years old. According to the Advisory Committee on Immunization Practices (ACIP) recommendations, the polysaccharide vaccine should be used in persons 2 to 10 and over 55 years old because MCV4 is not licensed for these age groups. However, providers may choose to use MCV4

off-label in some situations. For example, in the case of an 8-year-old who received the polysaccharide vaccine and requires another meningococcal immunization because of continued high risk, use of MCV4 would avoid the problem of hyporesponsiveness, in addition to providing other benefits inherent to conjugate vaccines. It is anticipated that the age indications for the conjugate vaccine will be expanded in the near future. For example, the manufacturer has a supplemental application pending with the FDA to include children 2 to 10 years old, and several manufacturers are working on vaccines for infants. The groups that should be routinely immunized include college freshmen living in dormitories, microbiologists who are routinely exposed to meningococcal isolates, military recruits, persons who reside in or travel to geographic locations with hyperendemic or epidemic meningococcal disease, persons with terminal complement deficiency, and persons with anatomic or functional asplenia (102, 119, 271). Elective immunization can also be undertaken for other college students, persons with human immunodeficiency virus infection, and adults 20 to 55 years old. Either of the two vaccines can be used for the control of outbreaks caused by vaccine-preventable serogroups (28, 59) but, again, in some settings off-label use of MCV4 could be considered.

Revaccination is indicated for persons who received the polysaccharide vaccine and remain at high risk for meningococcal infection (28). For children <4 years old at the time of first polysaccharide vaccine immunization, the ACIP recommends that revaccination be considered after 2 to 3 years. For older children and adults, ACIP recommends that revaccination be considered at 3 to 5 years. The ACIP recommends that for 11- to 55-year-olds, revaccination should be accomplished with the conjugate vaccine, whereas the polysaccharide vaccine should be used for persons 2 to 10 and over 55 years old. However, given the problem of hyporesponsiveness with repeated immunizations with the polysaccharide vaccine, off-label use of MCV4 beyond the 11- to 55-year-old age group could be considered. It is likely that the protective effect of the conjugate vaccine will be longer than that of the polysaccharide vaccine but the duration of protection is not yet known.

Both MCV4 and MPSV4 can be administered during minor acute illness, whether fever is present or not. Vaccination with either vaccine is contraindicated in persons with known hypersensitivity to any of the vaccine components or dry natural rubber latex. The polysaccharide vaccine can be administered to pregnant women if indicated but there are no data on the use of the conjugate vaccine in pregnancy (78, 210, 230). Both vaccines can be given concomitantly with other vaccines, as long as they are administered at a different anatomic site (15, 28). Protective antibody responses are generally present within 7 to 10 days (12, 39).

While a major advance on the road towards reducing the burden of meningococcal infection in the United States, the new ACIP recommendations are an interim measure because they provide for the use of conjugate vaccine only in 11- to 55-year-olds. As indicated previously, the highest incidence of meningococcal infection in the United States occurs in infants <1 year old, and it is anticipated that conjugate vaccines will be available for younger children in the next few years.

A recent CDC study analyzed the potential impact of a variety of different immunization strategies (212). Although

the study had limitations, such as assumptions of no herd immunity (which is unlikely) and duration of protection of 22 years (which is overly optimistic), the study provided insights into the relative contribution of targeting various age groups. Immunizing students at college entry would be expected to reduce total meningococcal cases and deaths by only 3 and 6%, respectively, after 10 years, which underscores the interim nature of the original college recommendation (63). Interestingly, immunizing infants with a three-dose schedule at 2, 4, and 6 months (28% reduction in cases and 25% reduction in deaths) was similar to a one-dose schedule at 12 months (24% reduction in cases and 25% reduction in deaths). A single dose at 11 years would have a disproportionate impact on deaths (21% reduction in cases and 35% reduction in deaths) because of the relatively high case fatality in adolescents and young adults (168). The highest impact is a combined strategy that targets several groups, with the highest impact being a strategy of immunizing infants, 11-year-olds, and students at college entry, with a 50% reduction in cases and 64% reduction in deaths. It is anticipated that when new vaccines are available for younger children, some type of combined strategy will be utilized.

During this interim period, there is a strong rationale for the strategy of targeting older children and adults for immunization. First, as mentioned above, adolescents have an unusually high case-fatality rate from meningococcal infection (168). In addition, over the past several years, adolescents and young adults have had an unusually high incidence of meningococcal disease (168, 299). The highest rates of nasopharyngeal carriage of *N. meningitidis* occur in adolescents, which suggests that immunizing this group could have a major herd impact on the incidence of disease in age groups not initially targeted for immunization (55, 58, 195). Although the focus of previous pediatric immunization efforts has not been in adolescents, there are a variety of other vaccines in the pipeline that will likely be used in this age group, such as acellular pertussis and human papillomavirus vaccines (117, 200). In fact, two acellular pertussis vaccines that also include tetanus and reduced diphtheria toxoids were recently licensed by the FDA, one for 10- to 18-year-olds (www.fda.gov/bbs/topics/ANSWERS/2005/ANS01354.HTML, last accessed 12 December 2005) and another for 11- to 64-year-olds (www.fda.gov/cber/products/tdapave061005.htm, last accessed 12 December 2005).

During the summer of 2005, there were five cases of Guillain-Barré syndrome (GBS) temporally associated with the administration of the MCV4 that were reported in the Vaccine Adverse Events Reporting System (60). All cases occurred in 17- to 18-year-olds with symptom onset between 14 and 31 days after MCV4 administration. One patient had had two prior episodes of GBS at ages 2 and 5 years 2 weeks after immunization with pediatric vaccines, and another patient had a mother with a history of GBS. One patient had a preceding illness compatible with an upper respiratory infection. There was tight geographic and temporal clustering of the cases: two cases occurred in Pennsylvania and one each in New York, New Jersey, and Ohio, and all occurred between 10 June and 25 July 2005. The cases involved four vaccine lots. The use of intravenous immunoglobulin and/or plasmapheresis in all of the patients precluded a serologic investigation of, for example, recent *Campy-*

lobacter infection; *Campylobacter jejuni* appears to trigger a substantial proportion of GBS cases (282, 338, 396).

The observed number of cases of GBS is similar to what would be expected given the background incidence of GBS in adolescents (60). In addition, the main components of the vaccine, meningococcal polysaccharide and diphtheria toxoid, have been used for years without any known association with GBS. However, given the temporal association with vaccine administration, the CDC, FDA, and others are investigating this issue to determine whether there is evidence of a causal relationship, if any, between MCV4 administration and GBS. In the meantime, CDC recommends no change in immunization strategy. For now, caregivers should advise adolescents and their guardians of this ongoing investigation as part of the informed consent process for MCV4 immunization. In addition, the use of MCV4 in persons with a history of GBS should be avoided.

Monitoring the Impact of the New Conjugate Vaccine

The Active Bacterial Core Surveillance (ABCs) network, which is funded by CDC and a component of the Emerging Infections Program network, has conducted active, population- and laboratory-based surveillance for invasive meningococcal infection in selected sites throughout the United States for over a decade (86, 166, 168, 269, 299, 313). The sensitivity of this surveillance network for culture-confirmed invasive meningococcal disease and the fact that bacterial isolates are available in the vast majority of cases makes the ABCs network an ideal infrastructure from which to launch the studies that will be needed to monitor the public health impact of the newly licensed vaccines. The importance of studying the impact of new meningococcal conjugate vaccines has been demonstrated in the United Kingdom (224, 279, 280, 349, 351).

During the year before the licensure of the new conjugate vaccines, an ABCs meningococcal working group began the development of protocols for studies to measure the impact of the vaccine. One study will examine the impact of the new vaccine on the acquisition of nasopharyngeal carriage in high school students at several ABCs sites. Although the study will look at the impact on carriage of *N. meningitidis* in general, it is powered to examine specifically the impact on serogroup Y strains, an issue that has not been previously studied with a conjugate vaccine. Another study will involve laboratory surveillance of *N. meningitidis* throughout the Emerging Infections Program network to determine if there are antigenic changes in the organism that result in escape from vaccine-induced immunity. Perhaps a worst-case scenario in that regard would be if the virulent ST-11 serogroup C clone, against which the new vaccine should be effective, were to undergo a capsular switch to serogroup B, with subsequent clonal expansion and its emergence as a major cause of invasive disease. Finally, observational studies of vaccine effectiveness are also planned, using a variety of study designs, including a case-control study and a study design referred to as the screening method (281). This portfolio of studies will provide information on the public health impact of the new conjugate vaccine, similar to what was done following licensure of serogroup C conjugate vaccines in the United Kingdom.

Serogroup B Vaccines

There is general misconception that there are no serogroup B vaccines. While there is no licensed product in the United States, there are a variety of serogroup B vaccines that have been used in special settings. However, the development of a comprehensive serogroup B vaccine has been a vexing problem that has not been accomplished despite decades of active research (31, 32, 40, 81, 121, 122, 174, 238, 266, 296, 297, 324, 339, 373, 399, 400). This is especially problematic because a substantial proportion of meningococcal disease in developed countries is caused by this serogroup. In the United States, serogroup B accounts for approximately a third of all invasive meningococcal infections and half of the cases in infants. In addition, serogroup B strains are a major cause of disease in many other parts of developed countries, as well as in developing countries. Therefore, a definitive solution to the prevention of meningococcal disease will not be possible until a serogroup B vaccine is available that is efficacious in infants, as well as older age groups.

The main reason that vaccine development for serogroup B has been much more difficult than for the other important serogroups is because of immunologic cross-reactivity between serogroup B polysaccharide and human neurologic tissue (108, 157, 392). This cross-reactivity has led to a hunt for alternative approaches to serogroup B vaccine development, most often using meningococcal outer membrane protein antigens.

Serogroup B disease occurs in two main epidemiologic patterns: endemic disease and prolonged outbreaks. Endemic serogroup B disease is caused by a very diverse group of strains, which complicates vaccine development. For example, one of the antigens that has been targeted for serogroup B vaccines is PorA, an immunogenic outer membrane protein that serves as the basis for the meningococcal serosubtyping system. PorA both is highly variable in strains causing endemic disease and plays a major role in eliciting strain-specific SBAs following nasopharyngeal carriage, invasive meningococcal infection, and serogroup B outer membrane vesicle immunization (177, 191, 262, 297, 339, 363). Therefore, serogroup B vaccines that use outer membrane vesicles must be polyvalent. In a study of the variability of endemic serogroup B strains from a variety of sites throughout the United States, it was found that 20 PorA types would have to be included in a serogroup B outer membrane vesicle vaccine to cover 80% of strains that cause endemic disease (347).

PorB and FetA, which are also outer membrane proteins, are also quite antigenically diverse (345, 347, 357). In a recent study of a limited number of selected meningococcal isolates, however, it was suggested that a only a limited number of PorA-FetA combinations would need to be included, given the constrained antigenic structuring of *N. meningitidis* outer membrane proteins (359). The potential utility of this approach will need to be validated with a larger collection of isolates. Further complicating the use of PorA-based vaccines is the fact that deletions of the *porA* gene have been reported, suggesting that vaccine escape could be achieved through this mechanism if PorA were the primary vaccine antigen (167, 360, 362).

Prolonged serogroup B outbreaks tend to be caused by a single clone and are therefore potentially more amenable to

TABLE 4. Studies of efficacy of outer membrane protein vaccines^a

Yr of vaccination	Vaccine strain and formulation	Location (no. vaccinated)	Age	Percent efficacy (95% confidence interval)
1987–1989	B:4:P1.15 C PS/alum	Cuba (106,000)	10–14 yr	83 (42–95)
1989–1990	B:4:P1.15 C PS/alum	São Paulo, Brazil (2.4 million)	3–23 mo 24–47 mo 4–7 yr	–37 (–100 to 73) 47 (–72 to 84) 74 (16 to 92)
1990	B:4:P1.15 C PS/alum	Rio de Janeiro, Brazil (1.6 million)	6–23 mo 24–47 mo 4–9 yr	41 (–96 to 82) 14 (–165 to 72) 71 (34 to 87)
1987–1989	B:15:P1.3 C PS/alum	Iquique, Chile (40,800)	1–4 yr 5–21 yr	–39 (–100 to 77) 70 (3 to 93)
1988–1991	B:15:P1.7.16 alum	Norway (171,800)	14–16 yr	57 (28 to NR)

^a Every study examined the efficacy of two doses of vaccine. The two Brazil studies were retrospective case-control studies. The remainder were prospective trials. The vaccines were outer membrane protein vesicles with the exception of the one used in Chile, which was purified outer membrane protein. C PS, serogroup C polysaccharide vaccine that is mixed with outer membrane protein or outer membrane protein vesicles. Alum preparations were Al(OH)₃. (Reprinted from reference 186 with permission from Elsevier.)

vaccine prevention. Oregon has experienced a prolonged serogroup B outbreak that began in the 1990s. The incidence of meningococcal infection caused by all serogroups was around 4.0 per 100,000 during the mid-1990s, substantially higher than the incidence in the rest of the United States. Sixty-five percent of disease was caused by serogroup B strains, most of which were caused by a single clone (B:15:P1.7,16) (86, 347).

There has also been a prolonged outbreak of serogroup B infection in New Zealand caused by another clone (B:4:P1.7b,4) that started in the early 1990s. Persons of Pacific Islands origin and the Maori have had very high rates of disease, with incidences of 45.6 and 20.6 per 100,000 population, respectively. The corresponding rates for infants <1 year old are 611 and 247, respectively (16). Given the prolonged nature of the outbreak and strikingly high incidence rates, in 2001 the government of New Zealand, in collaboration with Chiron Vaccines and the Norwegian Institute of Public Health, entered into an endeavor to develop, test, and manufacture an outer membrane vesicle vaccine which contains PorA and PorB, as well as lipopolysaccharide for the New Zealand strain (255). This vaccine received a provisional license in New Zealand in 2004 and is now being used widely in infants and children in that country.

The immunogenicity of a variety of outer membrane protein-based serogroup B vaccines has been studied. In an evaluation of three doses of a Cuban B:4:P1.15 vaccine and a Norwegian B:15:P1.7,16 vaccine in Chile, two-thirds or more of children and adults had at least a fourfold rise in SBA, as did at least 90% of infants (40). However, immunogenicity against the heterologous Chilean epidemic strain B:15:P1.7,3 was as expected less favorable, with no response among infants and only 31 to 35% and 37 to 60% of children and adults, respectively, having at least a fourfold rise in SBA. A Norwegian outer membrane vesicle vaccine made from a B:15:P1.7,16 strain was used to immunize 20 researchers who were at risk for laboratory-acquired infection three times at 2-month intervals (109). Three-quarters and 94% of subjects showed a fourfold increase in SBA titers after two and three doses, respectively.

Given the genetic diversity of PorA protein in serogroup B strains and the reduced immunogenicity against heterologous strains, investigators in the The Netherlands developed a genetically engineered vaccine that included six PorA proteins that accounted for 80% of disease-causing strains in the United Kingdom (53). Infants in the United Kingdom were immunized at 2, 3, and 4 months of age and then given a booster dose at 12 to 18 months old. After the third dose, 81% of infants had developed a fourfold rise in SBA to one of the six vaccine components, whereas the response to each of the other five was under 50%. This is suboptimal because the highest incidence of serogroup B meningococcal infection occurs among infants. Other the other hand, 78 to 95% of children had a fourfold rise in SBA between the pre-fourth- and post-fourth-dose sera.

Serogroup B outer membrane protein-based vaccines for control of clonal outbreaks have had modest success (Table 4) (31, 32, 40, 81, 186, 253, 324). For example, a vaccine made from a B:4:P1.15 strain given to 10- to 14-year-olds in Cuba was demonstrated to have an efficacy of 83% (324). Among 2- to 3-year-old children in São Paulo, Brazil, who received two doses of a vaccine against the same strain, effectiveness was estimated to be 47% (81). Unfortunately, none of the studies done to date have demonstrated clinical protection in infants, a major problem given the high rates of disease and the importance of serogroup B in this population. Also, although there are few data on the impact of serogroup B outer membrane protein vaccines on nasopharyngeal carriage of *N. meningitidis*, studies in Norway and Chile did not suggest an effect (30, 40).

Other Vaccine Approaches

Attempts have been made to make a polysaccharide-based serogroup B vaccine in which the polysaccharide has been chemically modified. One such candidate vaccine was recently shown to be poorly immunogenic in adults, suggesting that this may not be a fruitful approach (45). In addition, it is doubtful

that vaccine manufacturers will embrace the development of a vaccine that could even theoretically elicit antibodies that cross-react with human neural antigens.

One advance in the field of meningococcal vaccine development is the complete DNA sequencing of serogroup A, B, and C strains (260, 343) (www.sanger.ac.uk/Projects/N_meningitidis/seroC/seroC.shtml, last accessed 12 December 2005). Using reverse genetics, investigators have attempted to identify candidate antigens that could be used for a serogroup B vaccine (270). Monoclonal antibodies to one relatively conserved antigen among genetically diverse serogroup B strains were recently found to be protective in infant rats (379). Other promising antigens have also been identified based on this approach (69, 228, 378). Other antigens that have been explored with various degrees of success include neisserial surface protein A, transferrin-binding protein B, and another outer membrane protein referred to as H0.8 (25, 26, 49, 75, 226, 242, 381). Antigens of *N. lactamica*, a related *Neisseria* species that is also found as a commensal in the human nasopharynx, are also being explored as a possible meningococcal vaccine (41, 214, 248, 257). Detoxified lipooligosaccharide has also been explored as a potential vaccine candidate, as has a conserved inner-core lipooligosaccharide (272, 273, 366).

PREVENTION IN THE DEVELOPING WORLD

A comprehensive approach to vaccine prevention of meningococcal infection requires the development of a vaccine that can be used in developing countries (161). This necessitates an appropriately formulated vaccine that can be provided at low cost. Although conjugate vaccines are being used exclusively at present in developed countries, clearly their largest potential impact would be in sub-Saharan Africa, which continues to suffer from devastating serogroup A epidemics (274, 294, 390).

The Meningitis Vaccine Project was created in 2001 with a US\$70 million grant from the Bill and Melinda Gates Foundation (187, 328). The project, a collaborative effort between the World Health Organization and the Program for Appropriate Technology in Health, has the ultimate goal of ending epidemic meningococcal in sub-Saharan Africa. Currently, the project is working on serogroup A meningococcal vaccine that can be used to prevent and control epidemics. The project is working with a developing country vaccine manufacturer to develop a vaccine at a price of under US\$0.50 (<http://www.meningvax.org/files/essay-fmlaforce-0311.pdf>, last accessed 12 December 2005). Given the recent emergence of epidemic W-135 disease in Africa and elsewhere (79, 211) as well as outbreaks of serogroup X infection (88, 127), future vaccine development for Africa may need to include serogroups other than just serogroup A.

FUTURE PROSPECTS

Although substantial progress has been made with the recent licensure of the new conjugate vaccine, vaccine prevention of meningococcal infection still has a long way to go. Ultimately, we will need a vaccine in the United States that can be given to infants, the group with the highest incidence of disease. In addition, a vaccine against endemic serogroup B dis-

ease remains an elusive goal. However, with recent genomic and proteomic approaches, new antigens that hold promise have been discovered. Finally, affordable conjugate vaccines that can be used by developing countries, particularly in sub-Saharan Africa, must continue to be pursued.

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