

CLINICAL PRACTICE

Prevention of Meningococcal Disease

Pierce Gardner, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A previously healthy 18-year-old college freshman presented to an emergency department with acute onset of fever and headache. He was listless and in distress. His temperature was 40.0°C, his pulse was 140 per minute, his blood pressure was 70/40 mm Hg, and his respirations were 35 per minute. Petechiae were noted over his thorax. Meningococcal septicemia was suspected (and subsequently confirmed by the growth of *Neisseria meningitidis* serogroup C isolated from blood). Despite the prompt administration of antibiotics and other support, the patient's illness was fulminant and he died 12 hours after the onset of the symptoms. Should he have previously received meningococcal vaccine, and what measures should be taken to protect his close contacts and his community?

THE CLINICAL PROBLEM

From the Department of Medicine and the Graduate Program in Public Health, Stony Brook University School of Medicine, Stony Brook, NY.

N Engl J Med 2006;355:1466-73.
Copyright © 2006 Massachusetts Medical Society.

In the United States, the occurrence of a death from meningococcal disease is devastating to the family and the community of the person who died and elicits a strong demand for preventive measures from clinicians and the public health sector. Preventive strategies include antimicrobial chemoprophylaxis for close contacts of patients with invasive meningococcal disease and, in certain circumstances, immunization of the community with meningococcal vaccine.

EPIDEMIOLOGY OF *NEISSERIA MENINGITIDIS*

Neisseria meningitidis commonly colonizes the nasopharynx in humans and is transmitted by direct contact with large-droplet respiratory secretions. In a 32-month community-based study, *N. meningitidis* was isolated from 18% of persons from whom serial specimens were obtained.¹ Colonization may be transient, intermittent, or long-term, and the prevalence may increase in the presence of conditions such as concomitant upper respiratory tract infection, crowded living conditions, and smoking.² Colonization induces an immunologic response to *N. meningitidis* (as do certain organisms in the enteric flora that have cross-reacting antigens), so that by young adulthood, the majority of people in the United States have measurable antibody to the pathogenic serogroups of *N. meningitidis* (A, B, C, Y, and W-135).³⁻⁵

Invasive meningococcal disease is most often manifested by the development of meningitis or meningococcemia. The disease occurs most commonly in persons who are seronegative and have newly acquired *N. meningitidis*.⁶ Entry into a new environment of crowded conditions (such as an educational institution or a military training camp) is the classic high-risk setting. For example, in a study of a military base involving 492 recruits,³ 13 recruits were initially seronegative and subsequently became colonized with *N. meningitidis*; invasive meningococcal disease developed in 5 of them within 10 days after colonization was detected. Given

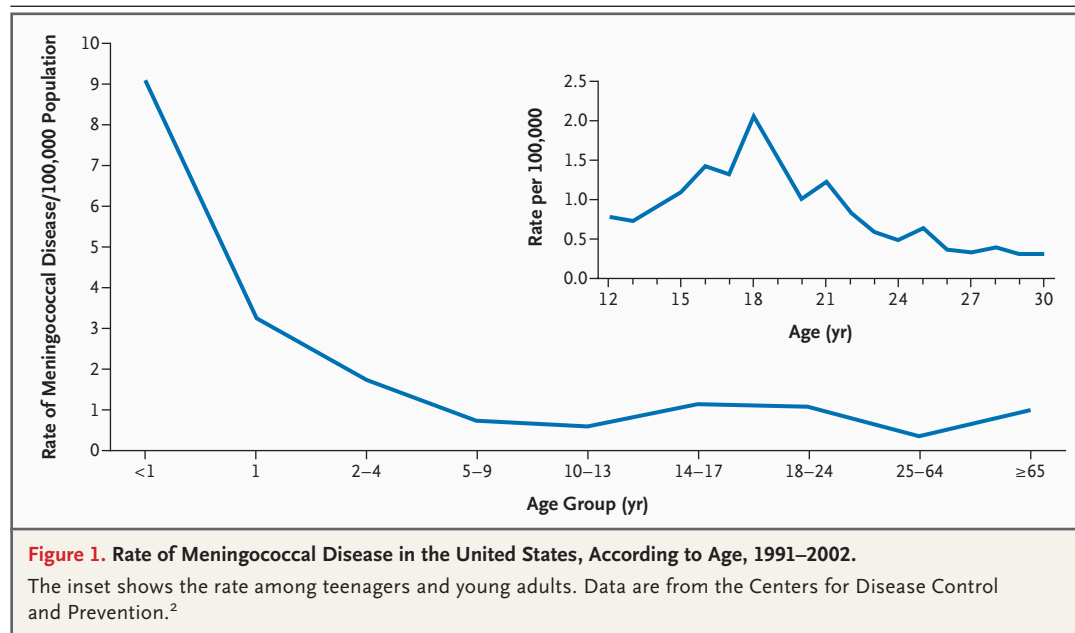
the short interval between the acquisition of the organism and clinical infection, the immediate focus of prevention is prompt chemoprophylaxis for close contacts of a patient with invasive meningococcal disease.

Given the high rates of colonization with *N. meningitidis*, invasive meningococcal disease is surprisingly uncommon in the United States. Approximately 2500 cases (0.5 to 1.1 per 100,000 population) occur annually. The case fatality rate is approximately 10%, and substantial sequelae occur in about 11 to 19% of survivors (mainly because of neurologic damage and complications resulting from disseminated intravascular coagulation).² The highest rate of disease occurs among the very young (Fig. 1), but 62% of cases occur in individuals 11 years of age or older. Factors that increase colonization, such as an antecedent upper respiratory tract infection, household crowding, and both active and passive smoking, are associated with an increased risk of meningococcal disease.² Disease rates are higher among the poor and among black persons,² although these increases are attributable to other risk factors. Other groups at increased risk for invasive meningococcal infection include persons with anatomical or functional asplenia or a deficiency in the terminal common complement pathway (C3 and C5 to C9), microbiologists routinely exposed to *N. meningitidis*, and travelers to regions where meningococ-

cal disease is epidemic or hyperendemic, such as Saudi Arabia or sub-Saharan Africa.⁷

Of the five pathogenic serogroups of *N. meningitidis* (A, B, C, Y, and W-135), those dominant in the United States are B, C, and Y, each accounting for approximately one third of the total cases, with B overrepresented among young children and Y overrepresented among the elderly.²

Sporadic cases of meningococcal disease account for more than 98% of cases.² Outbreaks (defined as 3 or more cases of the same serogroup but not among persons in close contact with one other, occurring within 3 months of one other and resulting in an attack rate of greater than 10 cases per 100,000 population) are uncommon but are highly disruptive to the community and to health care systems. Of 76 outbreaks identified in the United States during an 8-year period, approximately 34% were community based and approximately 65% occurred in colleges and universities, primary and secondary schools, and nursing homes.² Students recently arrived at college who are living in dormitories have modestly elevated rates of meningococcal disease (5.1 per 100,000 population), but after the first year, the rates are no longer elevated and the overall rate among all undergraduate college students (0.7 per 100,000 population) is lower than that among persons of similar age who are not enrolled in college (1.4 per 100,000 population).²



STRATEGIES AND EVIDENCE

ANTIMICROBIAL CHEMOPROPHYLAXIS

The most urgent priority for prevention after a case of meningococcal disease has been identified is to treat the patient's close contacts with an effective antimicrobial agent to eradicate potential colonization by *N. meningitidis*. The definition of "close contact" is not precise, but it is intended to include persons who have had prolonged (8 hours or more) contact while in close proximity (3 ft is the general limit for large-droplet spread) to the patient or who have been directly exposed to the patient's oral secretions (e.g., through prolonged face-to-face contact, mouth-to-mouth resuscitation, kissing, or management of an endotracheal tube) within 1 week before the onset of the patient's symptoms until 24 hours after appropriate antimicrobial therapy has been initiated. Such persons typically include members of the household and roommates, persons at a child-care center, and others who have had prolonged exposure to the infected patient (e.g., travelers on an airplane seated next to the patient for more than 8 hours).⁸ Classmates and coworkers are not included unless they meet the criteria for close contact. Close contacts who have previously received meningococcal vaccination should still be given chemoprophylaxis, because the vaccines do not confer 100% protection and immunity wanes with time.

Table 1 summarizes the antimicrobial regimens recommended by the Centers for Disease Con-

trol and Prevention (CDC) for prophylaxis on the basis of their efficacy (90 to 95%) in eradicating nasopharyngeal carriage of *N. meningitidis* and the almost complete absence of secondary cases among close contacts who have received antimicrobial chemoprophylaxis.² Preliminary evidence suggests that azithromycin may be similarly effective,¹⁰ although confirmatory data are needed.

Ideally, chemoprophylaxis should be started within 24 hours after the index case has been identified, although diminishing levels of benefit may still be realized even with delays of up to 2 weeks.² Chemoprophylaxis after 2 weeks adds little benefit, presumably because the development of protective immunity in response to the colonizing *N. meningitidis* obviates the need for antimicrobial agents. Despite heavy community pressure to "do something" immediately in response to a death from meningococcal disease, mass chemoprophylaxis in those who have not been in close contact with an infected person is unwarranted and is not recommended. However, in limited settings (e.g., a single school) in which cases of infection continue to occur, broad chemoprophylaxis may be considered.¹¹ In such settings, all targeted persons should receive chemoprophylaxis at the same time in order to avoid "ping-pong" reinfection.

MENINGOCOCCAL VACCINES

Vaccination is recommended to provide preexposure immunity in populations such as college students, adolescents, and other persons at an in-

Table 1. Regimens of Chemoprophylaxis against Meningococcal Disease.*

Medication	Dose for Children		Dose for Adults
	Age, <1 mo	Age ≥1 mo	
Rifampin (Rifadin, Merrell; Rimactane, Ciba-Geigy) †	5 mg/kg of body weight every 12 hr orally for 2 days	10 mg/kg of body weight every 12 hr orally for 2 days	600 mg every 12 hr orally for 2 days
Ciprofloxacin (Cipro, Bayer) ‡	—	—	500 mg orally once
Ceftriaxone (Rocephin, Roche)	125 mg once IM	125 mg once IM	250 mg once IM (for those ≥15 yr of age)

* Data are from the CDC.² IM denotes intramuscular.

† Rifampin is not recommended for pregnant women because of teratogenicity in studies in animals. Because this drug could decrease the reliability of oral contraceptives, patients should consider using alternative contraceptive measures while receiving rifampin.

‡ Ciprofloxacin is not usually recommended for persons younger than 18 years of age or for pregnant or lactating women, because studies in animals have shown it causes cartilage damage in immature animals. The drug can be used for chemoprophylaxis in children when no acceptable alternative is available. There have been no reports of irreversible adverse effects in cartilage or age-associated adverse events among children and adolescents.⁹

Table 2. Persons at Increased Risk for Meningococcal Disease for Whom Immunization Is Recommended.*

College freshmen living in dormitories
Microbiologists routinely exposed to <i>Neisseria meningitidis</i>
Populations in which an outbreak of meningococcal disease occurs
Military recruits
Persons with increased susceptibility (those with anatomical or functional asplenia or a terminal complement deficiency)
Travelers to regions where <i>N. meningitidis</i> is hyperendemic (e.g., sub-Saharan Africa and Saudi Arabia) or epidemic†

* The Advisory Committee on Immunization Practices also makes permissive recommendations for other persons not recognized as being at increased risk but who may elect to be vaccinated. Such persons include adolescents not covered in the initial rounds of immunization at the age of 11 years or on entry into high school, college students other than freshmen living in dormitories, and persons infected with the human immunodeficiency virus. The recommendations do not specifically address other groups among whom an increased prevalence of meningococcal disease has been noted, including black persons, persons of low socioeconomic status, those living in crowded conditions, and smokers. Data are from the CDC.²

† Travelers may consult the CDC online (at www.cdc.gov/travel) or call the CDC Travelers' Health Automated Information Line (at 877-FYI-TRIP).

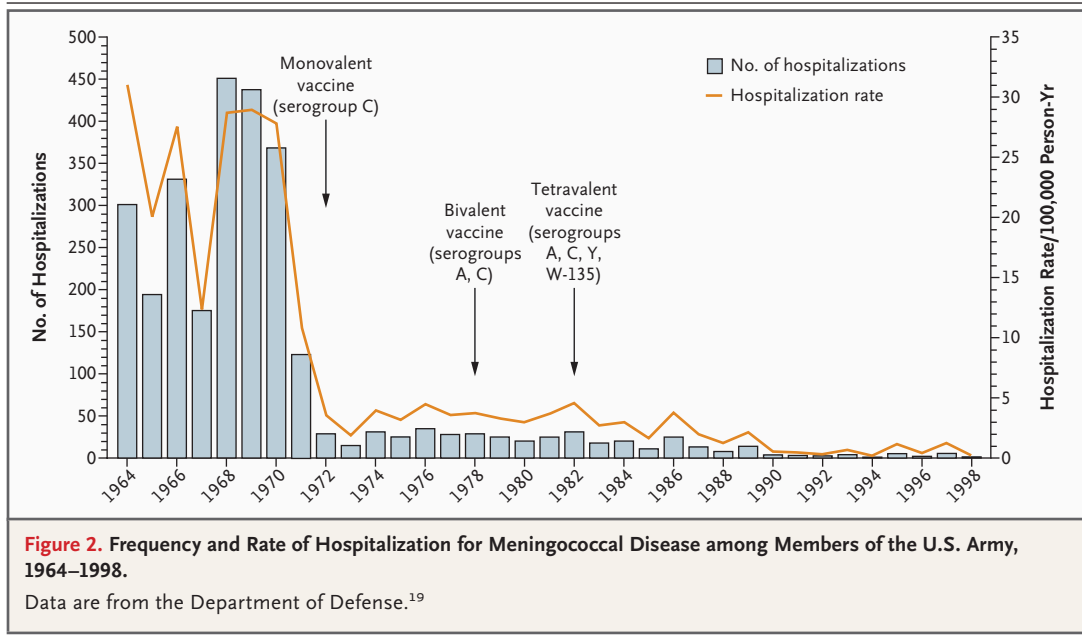
creased risk for meningococcal infection (Table 2). It is also used to control outbreaks caused by serogroups A, C, Y, and W-135 of *N. meningitidis*. Because protective levels of antibody are not achieved until 7 to 10 days after the primary immunization (the period of greatest vulnerability after close contact with an infected person), vaccination is not an essential component of immediate disease prevention for close contacts of patients with sporadic cases.

Two meningococcal vaccines, each containing antigens to serogroups A, C, Y, and W-135, are licensed for use in the United States. A major limitation of these vaccines is that neither provides immunity against serogroup B, which is responsible for approximately one third of cases of meningococcal disease. Both vaccines elicit protective levels of bactericidal antibody to all four serogroups in more than 97% of recipients (as measured at 28 days). Both vaccines can be given with other vaccines. Mild-to-moderate local reactions at the injection site and minor systemic symptoms (i.e., headache, fatigue, malaise, and low-grade fever) may occur after receipt of either vaccine.

The first vaccine, meningococcal polysaccharide vaccine (MPSV4 or Menomune, Sanofi Pasteur), has been available for more than 25 years.¹² It is approved for use in all age groups for which meningococcal vaccine is currently recommended. The vaccine is safe and offers protection of approximately 90 to 95% for a limited period. However, the vaccine has several limitations. The

duration of protection is short (1 to 3 years in children younger than 5 years of age^{13,14} and 3 to 5 years in adolescents and adults). Like other polysaccharide vaccines (e.g., against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b), it does not generate memory T cells, and attempts to boost protection with repeated vaccination may result in a diminished antibody response.^{15,16} Also, like other polysaccharide vaccines, this meningococcal vaccine does not prevent mucosal colonization and therefore does not provide herd immunity through interrupted transmission of *N. meningitidis*.^{17,18} These features make this vaccine a reasonable option for persons requiring protection for a limited time (travelers to an area of endemic disease, college freshmen, at-risk persons in community outbreaks) but limit its use in broad public health programs. The most impressive illustration of the protective effect of the polysaccharide meningococcal vaccines has been the experience of the U.S. Army, which in the early 1970s initiated the routine immunization of all recruits, thereby resulting in a sustained reduction in the incidence of meningococcal disease (Fig. 2).¹⁹

The second vaccine, meningococcal conjugate vaccine A, C, Y, and W135 (MCV4 or Menactra, Sanofi Pasteur), was approved in January 2005 for use in persons 11 to 55 years of age. It contains the same antigens as those in the meningococcal polysaccharide vaccine conjugated to 48 μg of diphtheria toxoid.² This vaccine elicits an initial antibody



response that is similar to that of the polysaccharide vaccine but is more durable, and revaccination can elicit a rise in antibody level. By analogy to other conjugate vaccines, it is likely (but not yet proved) that this vaccine will provide more durable protection than the meningococcal polysaccharide vaccine and will reduce nasopharyngeal carriage, thereby interrupting the transmission of *N. meningitidis* and establishing herd immunity. In the United Kingdom, where since 1999 children 1 to 17 years of age have routinely received a serogroup C conjugate vaccine, serogroup C meningococcal disease has been almost totally eliminated among vaccine recipients and dramatically reduced among unvaccinated persons.^{20,21}

The advantages of the meningococcal conjugate vaccine have led the Advisory Committee on Immunization Practices (ACIP) of the CDC to broaden extensively its recommendations for use of meningococcal vaccines.² Whereas previous recommendations focused on short-term protection in certain persons and high-risk groups, the new recommendations seek to interrupt the transmission of *N. meningitidis* by immunizing all adolescents with the meningococcal conjugate vaccine, beginning with children 11 to 12 years of age, supplemented by a catch-up program at entry into high school (among those not previously immunized). If this strategy were fully implemented, the

immunization of all children 11 to 19 years of age would be accomplished by 2008. By extrapolation from the British experience with the conjugate meningococcal C vaccine, this strategy is predicted to reduce invasive meningococcal disease by 32%. The program will be expensive, however. Even assuming (generously) that some benefit may last for as long as 22 years, the estimated cost is \$633,000 per case averted and \$5.0 million per death prevented.²²

Either of these two vaccines is recommended for use in the control of outbreaks caused by *N. meningitidis* serogroups A, C, Y, and W-135.² Because of its superior booster effect, the conjugate vaccine is preferred when revaccination is indicated for persons who had previously received the meningococcal polysaccharide vaccine and who remain at increased risk. Long-term studies are needed to determine the need for boosters in those initially immunized with the meningococcal conjugate vaccine.

AREAS OF UNCERTAINTY

Many of the assumed advantages of the conjugate vaccine (long-term immunity, decreased nasopharyngeal carriage, and herd immunity) are based on experience with other conjugated polysaccharide vaccines and require confirmation. Because

62% of the cases of meningococcal disease in the United States occur in children younger than 11 years of age, a comprehensive approach to preventing meningococcal disease will need to address children younger than 11 years. Conjugated polysaccharide vaccines against *H. influenzae* type b and certain pneumococcal serogroups have been shown to be effective in inducing immunity in children as young as 6 months of age and in lessening the transmission of these pathogens to nonimmunized populations. Preliminary studies suggest that the conjugated meningococcal vaccines elicit protective immune responses in infants and young children, and the licensure of Menactra for use in young children is anticipated.²³ However, the lack of an effective vaccine for serogroup B meningococcus (the cause of more than 50% of cases among infants and young children) limits the potential effect of immunization strategies in infants and young children.

A theoretical concern is that a reduction in the transmission of certain serogroups of *N. meningitidis* by vaccination may lead to replacement by other serogroups not covered by the vaccine (especially serogroup B). This was not observed in the United Kingdom after the broad immunization of children with a serogroup C meningococcal vaccine. However, for both *H. influenzae* type b and the vaccine-related pneumococci, a modest degree of serogroup replacement has occurred since the implementation of routine pediatric immunization, and this possibility will need to be tracked for *N. meningitidis*.

Implementation of the plan for universal immunization of adolescents has been hampered by

logistical shortcomings in reaching adolescent populations and by vaccine shortages. One manufacturer produces both Menomune and Menactra, making the manufacture of the vaccines particularly vulnerable to production problems.

As of February 2006, the development of the Guillain-Barré syndrome in eight patients within 2 to 5 weeks after receipt of the conjugate vaccine has been reported to the Vaccine Adverse Event Reporting System of the CDC and the Food and Drug Administration (FDA).²⁴ This overall rate appears to be within the expected background incidence of the Guillain-Barré syndrome (1 to 2 cases per 100,000 population), but the timing is of concern and has prompted a warning included in the package insert for Menactra. The FDA and the CDC consider the evidence insufficient to establish a causal association or warrant a change in the vaccine recommendations at this time. However, the Guillain-Barré syndrome does not appear to be a concern in relation to the polysaccharide vaccine and pending further evaluation, some physicians may prefer to use the polysaccharide vaccine when options exist.

Worldwide, the pattern of the meningococcal serogroups responsible for disease varies greatly according to region. In sub-Saharan Africa, major epidemics of infection with serogroup A meningococcal disease are common and constitute a major public health threat; limited use of a serogroup A polysaccharide vaccine in programs of epidemic control has achieved limited results. The evaluation of a meningococcal A conjugate vaccine for both routine immunization and epidemic control is under way.

Table 3. Recommended Use of Meningococcal Vaccines in Previously Unvaccinated Persons.

General Population	Persons at Increased Risk
A single dose of meningococcal conjugate vaccine is recommended for persons 11–12 yr of age or on entry into high school (approximately 15 yr of age).	<p>A single dose of meningococcal conjugate vaccine is preferred in persons 11–55 yr of age.</p> <p>A single dose of meningococcal polysaccharide vaccine is recommended for persons 2–10 yr of age or ≥55 yr and is an acceptable alternative to meningococcal conjugate vaccine in patients 11–55 yr of age.</p> <p>Vaccination of persons younger than 2 yr of age is not recommended.*</p>

* Meningococcal polysaccharide vaccine may be used to elicit short-term protection against serogroup A disease in travelers to regions of endemic disease. For children 3 to 18 months of age, the vaccine is given in two doses 3 months apart, and in a single dose in children 19 to 23 months of age. Data are from the CDC.²

GUIDELINES

The recommendations of the ACIP for the use of meningococcal vaccines are summarized in Tables 2 and 3.²

CONCLUSIONS AND RECOMMENDATIONS

The rare but tragic case of death from meningococemia described in the vignette could have been prevented by immunization with either of the two meningococcal vaccines. The conjugate vaccine is currently recommended for use in adolescents and persons 11 to 55 years of age with disorders or exposures putting them at an increased risk for meningococcal disease. (Because the approval of the meningococcal conjugate vaccine is currently limited to use in persons of these ages, the meningococcal polysaccharide vaccine is preferred for persons 2 to 10 years of age and over 55 years of age.) Challenges to a comprehen-

sive program include the lack of coverage for serogroup B meningococcal disease by the current vaccines, vaccine shortages, logistical issues, and the high cost per case of illness or death prevented.

When a case of meningococcal disease occurs, close contacts should be given chemoprophylaxis, preferably within 24 hours after the identification of the infection. Immunization is not an important component of the acute care of contacts in the setting of newly diagnosed infection. However, the anxiety arising from a report of a case of meningococcal disease provides an opportunity to promote community compliance with current recommendations. Population-based immunization programs are warranted in the control of outbreaks of meningococcal disease involving infection with serogroups A, C, Y, and W-135.

No potential conflict of interest relevant to this article was reported.

I am indebted to David Lin, M.D., for his contribution to the research and for his wisdom.

REFERENCES

- Greenfield S, Sheehy PR, Feldman HA. Meningococcal carriage in a population of "normal" families. *J Infect Dis* 1971; 123:67-73.
- Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005;54(RR-7):1-21.
- Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. II. Development of natural immunity. *J Exp Med* 1969;129:1327-8.
- Robbins JB, Myerowitz L, Whisnant JK, et al. Enteric bacteria cross-reactive with *Neisseria meningitidis* groups A and C and *Diplococcus pneumoniae* types I and II. *Infect Immun* 1972;6:651-6.
- Edwards EA, Devine LF, Sengbusch CH, Ward HW. Immunological investigations of meningococcal disease. III. Brevity of group C acquisition prior to disease occurrence. *Scand J Infect Dis* 1977;9:105-10.
- Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J Exp Med* 1969;129:1307-26.
- Health information for international travel 2005-2006. Atlanta: Centers for Disease Control and Prevention, 2005.
- Guidelines for the management of airline passengers exposed to meningococcal disease. Atlanta: Centers for Disease Control and Prevention, 2000. (Accessed September 11, 2006, at <http://www.cdc.gov/travel/menin-guidelines.htm>.)
- Burstein GR, Berman SM, Blumer JL, Moran JS. Ciprofloxacin for the treatment of uncomplicated gonorrhea in adolescents: does the benefit outweigh the risk? *Clin Infect Dis* 2002;35:Suppl 2:S191-S199.
- Girgis N, Sultan Y, Frenck RW Jr, El-Gendy A, Farid Z, Matezcun A. Azithromycin compared with rifampin for eradication of nasopharyngeal colonization by *Neisseria meningitidis*. *Pediatr Infect Dis J* 1998;17:816-9.
- Zangwill KM, Schuchat A, Riedo FX, et al. School-based clusters of meningococcal disease in the United States: descriptive epidemiology and case-control analysis. *JAMA* 1997;277:389-95.
- 1999 Drug topics red book. Montvale, NJ: Medical Economics, 1999.
- Reingold AL, Broome CV, Hightower AW, et al. Age-specific differences in duration of clinical protection after vaccination with meningococcal polysaccharide A vaccine. *Lancet* 1985;2:114-8.
- Lepow ML, Goldschneider I, Gold R, Randolph M, Gotschlich EC. Persistence of antibody following immunization of children with groups A and C meningococcal polysaccharide vaccines. *Pediatrics* 1977;60:673-80.
- Borrow R, Joseh H, Andrews N, et al. Reduced antibody response to revaccination with meningococcal serogroup A polysaccharide vaccine in adults. *Vaccine* 2000; 19:1129-32.
- MacLennan J, Obaro S, Deeks J, et al. Immune response to revaccination with meningococcal A and C polysaccharides in Gambian children following repeated immunization during early childhood. *Vaccine* 1999;17:3086-93.
- Hassan-King MK, Wall RA, Greenwood BM. Meningococcal carriage, meningococcal disease and vaccination. *J Infect* 1988;16:55-9.
- Moore PS, Harrison LH, Telzak EE, Ajello GW, Broome CV. Group A meningococcal carriage in travelers returning from Saudi Arabia. *JAMA* 1988;260:2686-9.
- Department of Defense. Meningococcal disease among soldiers, U.S. Army, 1964-1998. *Med Surveill Mon Rep* 2000; 6(1):2-3.
- Maiden MC, Stuart JM. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. *Lancet* 2002;359:1829-31.
- Ramsay M, Andrews NJ, Trotter CL, Kaczmarski EB, Miller E. Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. *BMJ* 2003;326:365-6.
- Shepard CW, Ortega-Sanchez IR, Scott RD II, Rosenstein NE. Cost-effectiveness of conjugate meningococcal vaccination

strategies in the United States. *Pediatrics* 2005;115:1220-32.
23. MacLennan J, Obaro S, Deeks J, et al. Immunologic memory 5 years after menin-

gococcal A/C conjugate vaccination in infancy. *J Infect Dis* 2001;183:97-104.
24. Update: Guillain-Barré syndrome among recipients of Menactra meningo-

coccal conjugate vaccine — United States, October 2005–February 2006. *MMWR Morb Mortal Wkly Rep* 2006;55:364-6.
Copyright © 2006 Massachusetts Medical Society.

CORRECTION

Prevention of Meningococcal Disease

Prevention of Meningococcal Disease . In the third paragraph under the heading "Epidemiology of *Neisseria meningitidis*" (page 1467), the fourth sentence should have read "The highest rate of disease occurs among the very young (Figure 1), but 62% of cases occur in individuals 11 years of age or older," rather than "The highest rates of disease occur among the very young (Fig. 1), and 62% of cases occur in children younger than 11 years of age." The text has been corrected on the *Journal's* Web site at www.nejm.org.