Meningococcal Disease

Meningococcal disease is an acute, potentially severe illness caused by the bacterium *Neisseria meningitidis*. Illness believed to be meningococcal disease was first reported in the 16th century. The first definitive description of the disease was by Vieusseux in Switzerland in 1805. The bacterium was first identified in the spinal fluid of patients by Weichselbaum in 1887.

*Neisseria meningitidis* is a leading cause of bacterial meningitis and sepsis in the United States. It can also cause focal disease, such as pneumonia and arthritis. *N. meningitidis* is also a cause of epidemics of meningitis and bacteremia in sub-Saharan Africa. The World Health Organization has estimated that meningococcal disease was the cause of 171,000 deaths worldwide in 2000.

The first monovalent (group C) polysaccharide vaccine was licensed in the United States in 1974. A quadrivalent polysaccharide vaccine was licensed in 1978. Meningococcal conjugate vaccine has been licensed in United Kingdom since 1999 and has had a major impact on the incidence of type C meningococcal disease. A quadrivalent conjugate vaccine was first licensed in the United States in 2005.

*Neisseria meningitidis*

*N. meningitidis*, or meningococcus, is an aerobic, gram-negative diplococcus, closely related to *N. gonorrhoeae*, and to several nonpathogenic *Neisseria* species, such as *N. lactamica*. The organism has both an inner (cytoplasmic) and outer membrane, separated by a cell wall. The outer membrane contains several protein structures that enable the bacteria to interact with the host cells as well as perform other functions.

The outer membrane is surrounded by a polysaccharide capsule that is necessary for pathogenicity because it helps the bacteria resist phagocytosis and complement-mediated lysis. The outer membrane proteins and the capsular polysaccharide make up the main surface antigens of the organism.

Meningococci are classified by using serologic methods based on the structure of the polysaccharide capsule. Thirteen antigenically and chemically distinct polysaccharide capsules have been described. Some strains, often those found to cause asymptomatic nasopharyngeal carriage, are not groupable and do not have a capsule. Almost all invasive disease is caused by one of five serogroups: A, B, C, Y, and W-135. The relative importance of each serogroup depends on geographic location, as well as other factors, such as age. For instance, serogroup A is a major cause of
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**Pathogenesis**

Meningococci are transmitted by droplet aerosol or secretions from the nasopharynx of colonized persons. The bacteria attach to and multiply on the mucosal cells of the nasopharynx. In a small proportion (less than 1%) of colonized persons, the organism penetrates the mucosal cells and enters the bloodstream. The bacteria spread by way of the blood to many organs. In about 50% of bacteremic persons, the organism crosses the blood–brain barrier into the cerebrospinal fluid and causes purulent meningitis. An antecedent upper respiratory infection may be a contributing factor.

**Clinical Features**

The incubation period of meningococcal disease is 3 to 4 days, with a range of 2 to 10 days.

Meningitis is the most common presentation of invasive meningococcal disease and results from hematogenous dissemination of the organism. Meningeal infection is similar to other forms of acute purulent meningitis, with sudden onset of fever, headache, and stiff neck, often accompanied by other symptoms, such as nausea, vomiting, photophobia (eye sensitivity to light), and altered mental status. Meningococci can be isolated from the blood in up to 75% of persons with meningitis.

Meningococcal sepsis (bloodstream infection or meningococcemia) occurs without meningitis in 5% to 20% of invasive meningococcal infections. This condition is characterized by abrupt onset of fever and a petechial or purpuric rash, often associated with hypotension, shock, acute adrenal hemorrhage, and multiorgan failure.

Less common presentations of meningococcal disease include pneumonia (5% to 15% of cases), arthritis (2%), otitis media (1%), and epiglottitis (less than 1%).

The case-fatality rate of invasive meningococcal disease is 9% to 12%, even with appropriate antibiotic therapy. The fatality rate of meningococcemia is up to 40%. As many as 20% of survivors have permanent sequelae, such as hearing loss, neurologic damage, or loss of a limb.

Risk factors for the development of meningococcal disease include deficiencies in the terminal common complement
pathway and functional or anatomic asplenia. Persons with HIV infection are probably at increased risk for meningococcal disease. Certain genetic factors (such as polymorphisms in the genes for mannose-binding lectin and tumor necrosis factor) may also be risk factors.

Family members of an infected person are at increased risk for meningococcal disease. Antecedent upper respiratory tract infection, household crowding, and both active and passive smoking also are also associated with increased risk. In the United States, African Americans and persons of low socioeconomic status have been consistently at higher risk; however, race and low socioeconomic status are likely markers for differences in factors such as household crowding rather than risk factors. During outbreaks, bar or nightclub patronage and alcohol use have also been associated with higher risk for disease.

Cases of invasive meningococcal disease, including at least two fatal cases, have been reported among microbiologists. These persons have worked with \textit{N. meningitidis} isolates rather than patient specimens.

**Laboratory Diagnosis**

Invasive meningococcal disease is typically diagnosed by isolation of \textit{N. meningitidis} from a normally sterile site. However, sensitivity of bacterial culture may be low, particularly when performed after initiation of antibiotic therapy. A Gram stain of cerebrospinal fluid showing gram-negative diplococci strongly suggests meningococcal meningitis.

Kits to detect polysaccharide antigen in cerebrospinal fluid are rapid and specific, but false-negative results are common, particularly in serogroup B disease. Antigen tests of urine or serum are unreliable.

Serologic testing (e.g., enzyme immunoassay) for antibodies to polysaccharide may be used as part of the evaluation if meningococcal disease is suspected but should not be used to establish the diagnosis.

**Medical Management**

The clinical presentation of meningococcal meningitis is similar to other forms of bacterial meningitis. Consequently, empiric therapy with broad-spectrum antibiotics (e.g., third-generation cephalosporin, vancomycin) should be started promptly after appropriate cultures have been obtained.

Many antibiotics are effective for \textit{N. meningitidis} infection, including penicillin. Few penicillin-resistant strains of meningococcus have been reported in the United States. Once \textit{N. meningitidis} infection has been confirmed, penicillin alone is recommended.
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Epidemiology

Occurrence
Meningococcal disease occurs worldwide in both endemic and epidemic form.

Reservoir
Humans are the only natural reservoir of meningococcus. As many as 10% of adolescents and adults are asymptomatic transient carriers of *N. meningitidis*, most strains of which are not pathogenic (i.e., strains that are not groupable).

Transmission
Primary mode is by respiratory droplet spread or by direct contact.

Temporal Pattern
Meningococcal disease occurs throughout the year, however, the incidence is highest in the late winter and early spring.

Communicability
The communicability of *N. meningitidis* is generally limited. In studies of households in which a case of meningococcal disease has occurred, only 3%–4% of households had secondary cases. Most households had only one secondary case. Estimates of the risk of secondary transmission are generally 2–4 cases per 1,000 household members at risk. However, this risk is 500–800 times that in the general population.

Secular Trends in the United States
Prior to 2000, an estimated 1,400 to 2,800 cases of meningococcal disease occurred each year in the United States, a rate of 0.5 to 1.1 per 100,000 population. The proportion of meningococcal cases caused by serogroup Y increased from 2% during 1989 through 1991 to 37% during 1997 through 2002. Serogroups B, C, and Y are the major causes of meningococcal disease in the United States, each being responsible for approximately one third of cases. The proportion of cases caused by each serogroup varies by age group. Among infants younger than 1 year of age, more than 50% of cases are caused by serogroup B, for which no vaccine is licensed or available in the United States. Of all cases of meningococcal disease among persons 11 years of age or older, 75% are caused by serogroups C, Y, or W-135.

Meningococcal disease incidence has decreased since 2000, and incidence of serogroups C and Y, which represent the majority of cases of vaccine-preventable meningococcal
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Meningococcal disease, are at historic lows. However, a peak in disease incidence among persons 18 to 21 years of age has persisted, even after routine vaccination of adolescents was recommended in 2005. From 2000–2004 to 2005–2009, the estimated annual number of cases of serogroups C and Y meningococcal disease decreased 74% among persons aged 11 through 14 years but only 27% among persons aged 15 through 18 years.

Cases of meningococcal disease caused by serogroups C and Y among persons who were vaccinated with meningococcal conjugate vaccine have been reported. In 2010, CDC received 12 reports of serogroup C or Y meningococcal disease among persons who had received a meningococcal conjugate vaccine. The mean age of these persons was 18.2 years (range: 16 through 22 years). The mean time since vaccination was 3.25 years (range: 1.5–4.6 years). Five of these 12 persons had an underlying condition that might have increased their risk for meningococcal disease.

In the United States, meningococcal outbreaks account for less than 5% of reported cases (95%–97% of cases are sporadic). However, since 1991, the frequency of localized outbreaks has increased. Most of these outbreaks have been caused by serogroup C. Since 1997, localized outbreaks caused by serogroups Y and B have also been reported. See http://www.cdc.gov/mmwr/PDF/rr/rr4605.pdf for additional information on the evaluation and management of meningococcal outbreaks.

Large outbreaks of serogroup A meningococcal disease occur in the African “meningitis belt,” an area that extends from Ethiopia to Senegal. Rates of endemic meningococcal disease in this area are several times higher than in industrialized countries. In addition, outbreaks occur every 8–12 years with attack rates of 500–1000 cases per 100,000 population.

Meningococcal Vaccines

Characteristics

Meningococcal Polysaccharide Vaccine (MPSV4)
The first meningococcal polysaccharide vaccine was licensed in the United States in 1974. The current quadrivalent A, C, Y, W-135 polysaccharide vaccine (Menomune, sanofi pasteur) was licensed in 1978. Each dose consists of 50 mcg of each of the four purified bacterial capsular polysaccharides. The vaccine contains lactose as a stabilizer.

MPSV4 is administered by subcutaneous injection. The vaccine is available in single-dose and 10-dose vials. Fifty-dose vials are no longer available. Diluent for the single-dose vial is sterile water without preservative. Diluent for the 10-dose vial is sterile water with thimerosal added as a preservative.
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Preservative. After reconstitution the vaccine is a clear colorless liquid.

No vaccine is available in the United States for serogroup B.

**Meningococcal Conjugate Vaccine (MCV4)**

Two meningococcal conjugate vaccines are licensed in the United States.

Menactra (sanofi pasteur) was licensed in 2005. The vaccine contains *N. meningitidis* serogroups A, C, Y and W-135 capsular polysaccharide antigens conjugated to diphtheria toxoid protein. Each 0.5-mL dose of vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 mcg each of meningococcal A, C, Y, and W-135 polysaccharides conjugated to approximately 48 mcg of diphtheria toxoid protein carrier. Menactra is approved for use in persons 9 months through 55 years of age. It is administered by intramuscular injection. Menactra is supplied as a liquid in a single-dose vial and does not contain a preservative or an adjuvant.

Menveo (Novartis) was licensed in the United States in 2010. Menveo consists of two components: 10 µg of lyophilized meningococcal serogroup A capsular polysaccharide conjugated to CRM_{197} (MenA) and 5 µg each of capsular polysaccharide of serogroup C, Y, and W135 conjugated to CRM_{197} in 0.5 mL of phosphate buffered saline, which is used to reconstitute the lyophilized MenA component before injection. Menveo is approved for use in persons 2 through 55 years of age. It is administered by intramuscular injection. It does not contain a preservative or an adjuvant.

**Immunogenicity and Vaccine Efficacy**

**Meningococcal Polysaccharide Vaccine**

The characteristics of MPSV4 are similar to other polysaccharide vaccines (e.g., pneumococcal polysaccharide). The vaccine is generally not effective in children younger than 18 months of age. The response to the vaccine is typical of a T-cell independent antigen, with an age-dependent response, and poor immunogenicity in children younger than 2 years of age. In addition, little boost in antibody titer occurs with repeated doses; the antibody which is produced is relatively low-affinity IgM, and “switching” from IgM to IgG production is poor.

A protective level of antibody is usually achieved within 7–10 days of vaccination. Among infants and children younger than 5 years of age, the level of antibody against serogroup A and C polysaccharide decreases substantially during the first 3 years following a single dose of vaccine. In
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healthy adults, antibody levels also decrease, but antibodies are detectable as long as 10 years after vaccination. Although vaccine-induced protection likely persists in school-aged children and adults for at least 3 years, the efficacy of the group A vaccine in children younger than 5 years of age may decrease markedly within this period. In one study, efficacy declined from more than 90% to less than 10% 3 years after vaccination among children who were younger than 4 years of age when vaccinated. Efficacy was 67% among children who were older than 4 years of age at vaccination.

Meningococcal Conjugate Vaccine
The approval of Menactra was based on studies that compared the serologic response to a single dose to the response of persons of similar age who received a single dose of meningococcal polysaccharide vaccine. In these studies a similar proportion of recipients achieved at least a fourfold rise in serum bactericidal antibody titer assay following MCV4 as those who received MPSV4. The proportion of recipients in each group that achieved a titer of 1:128 (the titer considered to predict protection) was more than 98% in both groups.

The approval of Menveo was based on a comparison of serum bactericidal antibody responses to immunization with Menveo to those following immunization with Menactra. The response to Menveo was found to be non-inferior to the response to Menactra in all age groups that were studied (2 through 55 years).

When MCV4 vaccine was licensed in 2005 it was believed that a single dose would provide protection for at least 10 years. Since that time serologic data have become available that show a significant decline in antibody 3 to 5 years after vaccination, although few cases among vaccinated persons have been reported. ACIP believes the serologic data are sufficiently compelling to recommend revaccination for persons at highest risk of meningococcal disease.

Data indicate that the immune response to a single dose of meningococcal conjugate vaccine is not sufficient in persons with persistent complement component deficiency (e.g., C5–C9, properdin, factor H, or factor D deficiency) or asplenia. Persons with these conditions should receive a 2-dose primary series administered 2 months apart.

Vaccination Schedule And Use
Meningococcal Polysaccharide Vaccine
Routine vaccination of civilians with MPSV4 is not recommended. Use of MPSV4 should be limited to persons older than 55 years of age, or when MCV4 is not available.
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**Meningococcal Conjugate Vaccine**

ACIP recommends routine vaccination of persons with MCV4 vaccine at 11 or 12 years of age, with a booster dose at 16 years of age. After a booster dose of meningococcal conjugate vaccine, antibody titers are higher than after the first dose and are expected to protect adolescents through the period of increased risk through 21 years of age. For adolescents who receive the first dose at 13 through 15 years of age, a one-time booster dose should be administered, preferably at age 16 through 18 years. Healthy persons who receive their first routine dose of meningococcal conjugate vaccine at or after age 16 years do not need a booster dose. Routine vaccination of healthy persons who are not at increased risk for exposure to *N. meningitidis* is not recommended after age 21 years. A booster dose is not recommended for healthy persons 22 years of age or older even if the first dose was administered at 11 through 15 years of age.

Children 9 through 23 months of age with persistent complement component deficiency, who are traveling to or residents of countries where meningococcal disease is hyperendemic or epidemic, and who are in a defined risk group during a community or institutional meningococcal outbreak should receive a 2-dose series of Menactra brand MCV4, 3 months apart. Because of their high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should be vaccinated with MCV4 beginning at age 2 years to avoid interference with the immunologic response to the infant series of pneumococcal conjugate vaccine (PCV). The minimum interval between doses is 8 weeks.

Meningococcal vaccination is recommended for persons at increased risk for meningococcal disease, including microbiologists who are routinely exposed to isolates of *N. meningitidis*, military recruits, and persons who travel to and U.S. citizens who reside in countries in which *N. meningitidis* is hyperendemic or epidemic, particularly countries in the sub-Saharan Africa “meningitis belt.” Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj. Information concerning geographic areas for which vaccination is recommended can be obtained from the CDC Travelers Health website at http://www.cdc.gov/travel. These high-risk persons should be revaccinated every 5 years as long as their increased risk continues.

Persons who received the first dose of MCV4 or MPSV4 before 7 years of age and remain at increased risk for meningococcal disease should be revaccinated 3 years after the first dose. Persons who received a dose of MCV4 or MPSV4 at 7 years of age or older and remain at increased risk for meningococcal disease should be revaccinated 5 years after their previous dose.
Persons with persistent complement component deficiency, and persons with functional or anatomic asplenia should receive a 2-dose primary series administered 2 months apart and a booster dose every 5 years.

HIV infection is not currently considered to be an indication for MCV4 vaccination by itself. However, some persons with HIV infection should receive MCV4 for other indications, such as adolescents or international travel. Persons with HIV infection who are vaccinated with MCV4 should receive 2 doses at least 8 weeks apart. Persons with complement component deficiency, functional or anatomic asplenia or HIV infection who have already received 1 dose of MCV4 should receive a second dose at the earliest opportunity.

The minimum interval between MCV4 doses is 8 weeks. Although doses separated by 8 weeks can both be counted as valid it is preferable to use a longer interval between doses, 3 to 5 years if possible.

MCV4 can be administered at the same visit as other indicated vaccines. All vaccines should be given at separate sites with separate syringes.

Both MCV4 and MPSV4 are recommended for use in control of meningococcal outbreaks caused by vaccine-preventable serogroups (A, C, Y, and W-135). An outbreak is defined by the occurrence of at least three confirmed or probable primary cases of serogroup C meningococcal disease during a period of 3 months or less, with a resulting primary attack rate of 10 or more cases per 100,000 population.

Contraindications and Precautions to Vaccination

For both MCV4 and MPSV4, a severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose of either vaccine is a contraindication to receipt of further doses. A moderate or severe acute illness is reason to defer routine vaccination, but a minor illness is not. Breastfeeding and immunosuppression are not contraindications to vaccination. Studies of vaccination with MPSV4 during pregnancy have not documented adverse effects among either pregnant women or newborns. No data are available on the safety of MCV4 during pregnancy. However, pregnancy is not considered to be a contraindication to either MPSV4 or MCV4.

Adverse Reactions Following Vaccination

Meningococcal Polysaccharide Vaccine

Adverse reactions to MPSV4 are generally mild. The most frequent are local reactions, such as pain and redness at the injection site. These reactions last for 1 or 2 days, and occur
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Meningococcal Conjugate Vaccine
Reported adverse reactions following MCV4 are similar to those reported after MPSV4. The most frequent are local reactions, which are reported in up to 59% of recipients. Fever (100°F–103°F) within 7 days of vaccination is reported for up to 5% of recipients. Systemic reactions, such as headache and malaise are reported in up to 60% of recipients with 7 days of vaccination. Less than 3% of recipients reported these systemic reactions as severe.

Vaccine Storage and Handling
Both MPSV4 and MCV4 should be shipped in insulated containers to prevent exposure to freezing temperature. Vaccine should be stored at refrigerator temperature (35°–46°F, [2°–8°C]). The vaccines must not be exposed to freezing temperature, and any vaccine exposed to freezing temperature should not be used.

Single-dose vials of MPSV4 must be used within 30 minutes of reconstitution, and multidose vials must be discarded 10 days after reconstitution.

The MenA (lyophilized) component of Menveo can only be reconstituted using the liquid C-Y-W135 component of Menveo. No other vaccine or diluents can be used for this purpose. The reconstituted vaccine should be used immediately, but may be held at or below 77°F (25°C) for up to 8 hours.

If the liquid C-Y-W135 component of Menveo is administered without using it to reconstitute the lyophilized A component revaccination may not be needed. Serogroup A disease is rare in the U.S. so revaccination is not necessary if the person does not plan to travel outside the U.S. However, the person should be revaccinated with either a properly reconstituted dose of Menveo or with Menactra if international travel anticipated, especially travel to Africa. There is no minimum interval between the incomplete dose given in error and the repeat dose.

Surveillance and Reporting of Meningococcal Disease
Invasive meningococcal disease is a reportable condition in most states. All healthcare personnel should report any case
of invasive meningococcal disease to local and state health departments.

**Antimicrobial Chemoprophylaxis**

In the United States, the primary means for prevention of sporadic meningococcal disease is antimicrobial chemoprophylaxis of close contacts of infected persons. Close contacts include household members, child care center contacts, and anyone directly exposed to the patient’s oral secretions (e.g., through kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management).

For travelers, antimicrobial chemoprophylaxis should be considered for any passenger who had direct contact with respiratory secretions from an index patient or for anyone seated directly next to an index patient on a prolonged flight (i.e., one lasting more than 8 hours). The attack rate for household contacts exposed to patients who have sporadic meningococcal disease was estimated to be four cases per 1,000 persons exposed, which is 500–800 times greater than the rate for the total population. In the United Kingdom, the attack rate among healthcare personnel exposed to patients with meningococcal disease was determined to be 25 times higher than among the general population.

Because the rate of secondary disease for close contacts is highest immediately after onset of disease in the index patient, antimicrobial chemoprophylaxis should be administered as soon as possible, ideally less than 24 hours after identification of the index patient. Conversely, chemoprophylaxis administered more than 14 days after onset of illness in the index patient is probably of limited or no value. Oropharyngeal or nasopharyngeal cultures are not helpful in determining the need for chemoprophylaxis and might unnecessarily delay institution of this preventive measure.

Rifampin, ciprofloxacin, and ceftriaxone are 90%–95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are all acceptable antimicrobial agents for chemoprophylaxis. Systemic antimicrobial therapy for meningococcal disease with agents other than ceftriaxone or other third-generation cephalosporins might not reliably eradicate nasopharyngeal carriage of *N. meningitidis*. If other agents have been used for treatment, the index patient should receive chemoprophylactic antibiotics for eradication of nasopharyngeal carriage before being discharged from the hospital.

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