MENINGOCOCCAL
GUIDELINES
Introduction

In January 2005, a tetravalent meningococcal polysaccharide-protein conjugate vaccine (MCV4) was licensed by the Food and Drug Administration for use among persons 11-55 years of age. This article reviews meningococcal disease and updates healthcare providers in Virginia on the current meningococcal vaccination recommendations.

*Neisseria meningitidis*

*Neisseria meningitidis*, or meningococcus, is an aerobic gram-negative diplococcus. Meningococci are classified using serological methods based on antigens to the organisms’ polysaccharide capsule. Thirteen antigenically and chemically distinct polysaccharide capsules have been described. Almost all invasive meningococcal 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 disease in sub-Saharan Africa but is rarely isolated in the United States. In addition, some strains, often those found to cause asymptomatic nasopharyngeal carriage, are not groupable and do not have a capsule.

Meningococci are transmitted by droplet aerosol or direct contact with secretions from the nose or throat of colonized or infected persons. The bacteria attach to and multiply on the mucosal cells of the nasopharynx. In a small proportion (<1%) of colonized persons the organism penetrates the mucosal cells and enters the bloodstream (a recent upper respiratory tract infection may be a contributing factor). The incubation period of meningococcal disease is 3-4 days, with a range of 2-10 days. Disease progression can be extremely rapid.

Clinical Features

Meningitis is the most common presentation of invasive meningococcal disease (49% of cases). Meningeal infection is similar to other forms of acute purulent meningitis, characterized by a sudden onset of fever, headache, and stiff neck often with nausea, vomiting, photophobia, and altered mental status.

Meningococcal sepsis (meningococcemia) occurs without meningitis in 33% of invasive meningococcal infections. This condition is characterized by an 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 (9% of cases), arthritis (2%), otitis media (1%), and epiglottitis (<1%).

The case-fatality rate for invasive meningococcal disease is 10%-14%, even with appropriate antibiotic therapy. The case-fatality rate of meningococcemia may reach 40%. Up to 20% of survivors have permanent sequelae such as hearing loss, neurologic deficits or loss of a limb.
Occurrence

Meningococcal disease occurs worldwide in both endemic and epidemic form. Humans are the only natural reservoir of the meningococcus, and up to 10% of adolescents and adults are asymptomatic transient carriers of mostly non-pathogenic *N. meningitidis*.

Risk factors for the development of invasive meningococcal disease include antecedent viral infection, household crowding, deficiencies in the terminal common complement pathway, functional or anatomic asplenia, and both active and passive smoking. Family members of a person with meningococcal disease are at an increased risk of infection. In the United States, blacks and persons of low socioeconomic status have been consistently at higher risk although race and socioeconomic status are likely markers for other factors (e.g., household crowding). Persons with HIV infection are probably at an increased risk. Cases of invasive meningococcal disease, including at least two fatal cases, have been reported among microbiologists working with *N. meningitidis* isolates. In addition, recent studies have shown that college freshmen living in dormitories are at a moderately increased risk of acquiring meningococcal disease. However, overall, U.S. college students are not at a higher risk for meningococcal disease than other people of similar age. During outbreaks, bar or nightclub patronage and alcohol use have been associated with higher risk for meningococcal disease.

Trends in the United States

Approximately 2,500 to 3,000 cases of meningococcal disease are reported each year in the United States (0.8-1.3 cases per 100,000 population). In 2002, an estimated 150 deaths due to meningococcal disease occurred in the U.S. In Virginia, 24 cases (including two deaths) were reported in 2004, the lowest number of cases in over 15 years and 45% below the five year mean of 44 cases per year. While meningococcal infections can occur throughout the year, the incidence is highest in the late winter (peak: December/January) and early spring (Figure 1).

Nationwide, infants (persons less than 12 months of age) have the highest risk of disease from *N. meningitidis*. Incidence of disease declines in early childhood, increases during adolescence and early adulthood, then declines among older adults (Figure 2). The proportion of cases among adolescents and young adults has increased in recent years. During 1992-1998, 28% of reported cases were in persons 12-29 years of age.

The proportion of disease caused by different serogroups has also changed during the last 15 years. From 1988 to 1991, most cases of meningococcal disease in the United States were due to either serogroup B or C; serogroup Y accounted for only 2% of cases. Currently, serogroups B, C, and Y each cause approximately one-third of cases. In addition, the proportion of cases caused by each serogroup varies by age group. Among infants, more than half of meningococcal infections are caused by serogroup B, for which no vaccine is available in the U.S. However, 75% of all cases of meningococcal disease among persons 11 years of age or older are caused by serogroups C, Y, or W-135 (all of which are included in both available vaccines).

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 500-1,000 cases per 100,000 population. In the United States, meningococcal outbreaks account for less than two percent of reported cases (i.e., more than
98% of cases are sporadic), although the frequency of localized outbreaks has increased since 1991.

_Meningococcal Vaccines_

**Meningococcal Polysaccharide Vaccine (MPSV4)**

The tetravalent A, C, Y, W-135 polysaccharide vaccine (Menomune™, Sanofi Pasteur, Inc., Swiftwater, PA) was licensed in 1981 and until recently was the only formulation available in the United States. Each dose consists of 50 μg of each of the four purified bacterial capsular polysaccharides. The vaccine contains lactose as a stabilizer and is available in single- and 10-dose vials (50-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 as a preservative.

The characteristics of MPSV4 are similar to other polysaccharide vaccines (e.g., pneumococcal polysaccharide vaccine). Since bacterial polysaccharides, including those in the capsule of _N. meningitidis_, are T-cell-independent antigens, they stimulate mature B-lymphocytes but not T-lymphocytes. This leads to relatively short-term protection, does not induce an anamnestic response, does not cause the sustainable reduction of nasopharyngeal carriage of _N. meningitidis_ that would create ‘herd immunity’, and cannot be boosted with subsequent vaccinations. In addition, the response to the vaccine is age-dependent, resulting in poor immunogenicity in children less than two years of age. Overall, this limits the effectiveness of polysaccharide vaccines.

Following vaccination with MPSV4, a protective level of antibody is usually achieved within 7-10 days. Among infants and children less than five years of age, measurable levels of antibodies against serogroups A and C polysaccharides decrease substantially during the first three years following a single dose of vaccine. In 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 three years, the efficacy of the serogroup A vaccine in children less than five years of age may decrease markedly. In one study, efficacy declined from greater than 90% to less than 10% three years after vaccination among children who were less than four years of age when vaccinated.

Improved vaccine efficacy has not been demonstrated among persons who receive multiple doses of MPSV4. In fact, recent serologic studies have reported that multiple doses of serogroups A and C polysaccharide vaccine might cause immunologic hyporesponsiveness (i.e., a reduced antibody response after subsequent challenge with the same polysaccharide antigen) to serogroups A and C polysaccharide, although the clinical relevance of this finding is unknown.

For both children and adults, MPSV4 is administered _subcutaneously_ as a single 0.5 mL dose. The vaccine can be administered at the same time as other vaccines but should be given at a different anatomic site.

Adverse reactions to MPSV4 are generally mild. The most frequent complaints are local reactions such as pain and redness at the injection site. These reactions last for 1-2 days and occur in 5%-10% of recipients. Systemic reactions such as headache and malaise are reported in
2%-5% of recipients, and low grade fever occurs in up to 3% of vaccines. Severe reactions to polysaccharide meningococcal vaccine are uncommon.

A severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose of meningococcal polysaccharide vaccine is a contraindication to the receipt of further doses. A moderate or severe acute illness is reason to defer routine vaccination but a minor illness is not. Pregnancy, breastfeeding and immunosuppression are not contraindications to vaccination. MPSV4 should be shipped in insulated containers and stored at refrigerator temperature [2-8°C (35-46°F)]. The vaccine must not be exposed to freezing temperature. Single dose vials of MPSV4 must be used within 30 minutes of reconstitution. Multidose vials must be discarded 35 days after reconstitution. Providers should consult the drug package insert for additional information as needed.

**Meningococcal Conjugate Vaccines (MCV4)**

Conjugation (i.e., covalent coupling) of polysaccharide to a protein carrier that contains T-cell epitopes changes the nature of the immune response from T-cell independent to T-cell-dependent, leading to a significant primary response among infants and a strong anamnestic response at re-exposure. Both conjugate *Haemophilus influenzae* type b (Hib) and conjugate *Streptococcus pneumoniae* vaccines (introduced for mass infant immunization in the U.S. in 1990 and 2000, respectively) have substantially reduced the incidence of disease caused by vaccine preventable serotypes.

Efforts to produce a conjugated meningococcal vaccine have yielded MCV4, a tetravalent meningococcal conjugate vaccine (Menactra™, Sanofi Pasteur, Inc., Swiftwater, PA) licensed for use in persons 11-55 years of age in the United States as of January 2005. A 0.5-mL single dose of vaccine contains 4 µg each of capsular polysaccharide from serogroups A, C, Y, and W-135 conjugated to 48 µg of diphtheria toxoid.

MCV4 is available only in single-dose vials. MCV4 was licensed on the basis of findings indicating that it was comparable to MPSV4 in terms of immunogenicity and safety (i.e., demonstrated noninferiority).

For both children and adults, MCV4 is administered **intramuscularly** as a single 0.5 mL dose. The vaccine can be administered at the same time as other vaccines but should be given at a different anatomic site.

Adverse reactions to MCV4 are similar to those of MPSV4 and are also generally mild. The most frequent are local reactions such as pain and redness at the injection site. A severe allergic (anaphylactic) reaction to a vaccine component or following a prior dose of meningococcal conjugate vaccine is a contraindication to the receipt of further doses. A moderate or severe acute illness is reason to defer routine vaccination, but a minor illness is not. Data are not available at this time on the safety of MCV4 during pregnancy.

As with MPSV4, MCV4 should be shipped in insulated containers. Vaccine should be stored at refrigerator temperature [2-8 °C (35-46 °F)] and must not be exposed to freezing temperature. Providers should consult the drug package insert for additional information as needed.
**Recommendations for Use of Meningococcal Vaccines**

In general, the use of MCV4 is preferred among persons 11-55 years of age; if MCV4 is unavailable, MPSV4 is an acceptable alternative. Use of MPSV4 is recommended among children 2-10 years of age and persons 56 years of age or older. MPSV4 and MCV4 are both available through the Vaccines for Children (VFC) Program.

**Routine Vaccination of Adolescents**
The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of young adolescents (defined as persons 11-12 years of age) with MCV4 at the preadolescent healthcare visit. For those adolescents who have not previously received MCV4, ACIP recommends vaccination before high school entry (at approximately 15 years of age) as an effective strategy to reduce meningococcal disease incidence among adolescents and young adults. Other adolescents who wish to decrease their risk for meningococcal disease may elect to receive MCV4.

Adolescents who receive their first dose at age 13 through 15 years should receive a booster dose at age 16 through 18 years. The minimum interval between doses of MCV4 is 8 weeks. Adolescents who receive a first dose after their 16th birthday do not need a booster dose unless they become at increased risk for meningococcal disease. Persons aged 19 through 21 years are not recommended routinely to receive MCV4. MCV4 may be administered up to age 21 years as catch-up vaccination for those who have not received a dose after their 16th birthday. Healthcare personnel should use every opportunity to provide the booster dose when indicated, regardless of the vaccine brand used for the previous dose or doses.

**Other Populations at Increased Risk**

Vaccination is recommended for the following populations considered to be at an increased risk for invasive meningococcal disease:

- College freshmen living in dormitories (Note: In Virginia, all new full-time students at any public four-year college or university must be vaccinated against meningococcal disease or must sign a waiver refusing the vaccine);
- Microbiologists who are routinely exposed to isolates of *N. meningitidis*;
- Military recruits;
- Persons who travel to or reside in countries where *N. meningitidis* is hyperendemic or epidemic, particularly if contact with the local population will be prolonged. Vaccination is especially recommended for those visiting the parts of sub-Saharan Africa known as the “meningitis belt” during the dry season (December-June). Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj;
- Persons who have terminal complement component deficiencies; and,
- Persons who have anatomic or functional asplenia.

Persons with human immunodeficiency virus (HIV) are likely at an increased risk for meningococcal disease although not to the extent that they are at risk for invasive *S.*
*pneumoniae* infection. While the efficacy of MCV4 among HIV infected patients is unknown, HIV-infected patients may elect to be vaccinated with MCV4.

**Adults 20-55 Years of Age**

In adults 20-55 years of age, MCV4 is safe, immunogenic, and likely provides relatively long-lasting protection against meningococcal disease caused by serogroups A, C, Y, and W-135. Since rates of meningococcal disease are low for this age group, and since vaccination will decrease but not eliminate risk, routine vaccination is not recommended. However, persons who wish to decrease their risk for meningococcal disease may elect to be vaccinated.

**Children <11 Years of Age and Adults >55 Years of Age**

MCV4 is not licensed for use among children aged less than 11 years of age or adults older than 55 years of age. However, it is likely that this or a similar vaccine will be licensed for younger age groups in the future.

Routine vaccination with MPSV4 is not recommended for children less than two years of age because it is relatively ineffective and offers a short duration of protection. Routine vaccination with MPSV4 is not recommended for children 2-10 years of age and adults older than 55 years of age except for those identified as being at increased risk for meningococcal disease.

**Outbreaks of Meningococcal Disease**

Both MPSV4 and MCV4 are appropriate for use in the control of meningococcal outbreaks caused by vaccine-preventable serogroups (A, C, W-135, and Y) of *N. meningitidis*. However, use of MCV4 is preferred if the population targeted for vaccination includes age groups for which MCV4 is licensed. Detailed recommendations on the evaluation and management of suspected outbreaks of meningococcal disease have been published previously [MMWR. 1997. 46(RR- 5):13-21].

**Public Health Response**

Overall, the communicability of *N. meningitidis* is relatively limited. In studies of households where a case of meningococcal disease has occurred, only 3%- 4% of households had additional cases (most with only a single additional case). As a result, the estimated occurrence of co-primary or secondary cases is 2-4 per 1,000 household members. This risk is 500-800 times that of the general population.

The potential severity of invasive meningococcal infections warrants that public health interventions focus on the rapid identification and management of at-risk individuals. Therefore, the *Regulations for Disease Reporting and Control* (Title 12 VAC 5-90-80) require that suspicion or confirmation of invasive *N. meningitidis* infections must be reported within 24 hours to the local health department by healthcare providers, directors of medical care facilities and directors of laboratories. Close contacts (e.g., household members; daycare center classmates; personnel who performed mouth-to-mouth resuscitation, intubated, or suctioned the patient before antibiotics were begun; and persons who had intimate contact with the patient’s oral secretions through kissing, sharing of food or drink, sharing cigarettes, etc.) are then identified.
by health department staff. These individuals are evaluated and, if appropriate, receive chemoprophylaxis and education.

In addition, laboratories are required by the Regulations for Disease Reporting and Control (Title 12 VAC 5-90-90) to submit the initial culture of a meningococcal infection to the Division of Consolidated Laboratory Services (state laboratory). This enables laboratory confirmation of the serogroup for monitoring trends as well as genotyping for linking suspected outbreaks.

Summary

While relatively rare in occurrence, invasive disease caused by *N. meningitidis* often leads to tragic consequences. In addition to the impact on the patient and family, this condition generates significant public anxiety and requires extensive public health follow-up to protect against additional cases. The introduction of a new, conjugated vaccine that may provide longer-lasting immunity may significantly reduce the risk of meningococcal disease in vulnerable populations and communities. In light of the new meningococcal vaccine recommendations, existing Virginia vaccination recommendations for college entry may need to be modified in the future.

Selected References


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