REDUCING THE IMPACT OF MENINGOCOCCAL DISEASE IN ADOLESCENTS AND YOUNG ADULTS

FACULTY
William Schaffner, MD, Chairman
Lee H. Harrison, MD
Sheldon L. Kaplan, MD
Elizabeth Miller, MD
Walter A. Orenstein, MD
Georges Peter, MD
Nancy E. Rosenstein, MD

Release Date: July 2005
Expiration Date: July 2007
Estimated Time to Complete Activity: 1.5 hours
FACULTY

William Schaffner, MD, Chairman
Professor and Chair, Department of Preventive Medicine
Professor of Medicine (Infectious Diseases)
Vanderbilt University School of Medicine
Nashville, Tennessee

Lee H. Harrison, MD
Professor of Medicine
Infectious Diseases Epidemiology Research Unit
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Sheldon L. Kaplan, MD
Professor and Vice Chairman for Clinical Affairs
Department of Pediatrics
Baylor College of Medicine
Houston, Texas

Elizabeth Miller, MD
Head of the Immunisation Department
Communicable Disease Surveillance Centre
Health Protection Agency Centre for Infections
London, England

Walter A. Orenstein, MD
Director, Vaccine Policy and Development
Associate Director, Emory Vaccine Center
Emory University School of Medicine
Atlanta, Georgia

Georges Peter, MD
Professor, Department of Pediatrics
Brown Medical School
Founding Director, Division of Pediatric Infectious Diseases
Rhode Island Hospital
Providence, Rhode Island

Nancy E. Rosenstein, MD
Chief, Meningitis and Special Pathogens Branch
Division of Bacterial and Mycotic Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia
Target Audience
Primary care physicians, pediatricians, infectious disease specialists, college health professionals and public health officials responsible for or interested in communicable diseases.

Statement of Need
Meningococcal disease causes substantial morbidity and mortality. Cyclic trends in disease epidemiology suggest that persons across many age groups may be at increased risk of disease and severe complications, including death. U.S. immunization policy and recommendations changed following approval of a conjugate meningococcal vaccine for use in persons aged 11 to 55 years. All physicians and public health officials interested in communicable diseases should be aware of the new recommendations by the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices and the scientific data that provide rationale for an immunization strategy designed to lessen the burden of meningococcal disease.

Educational Format
This activity was developed by the faculty based on a literature review and personal knowledge and expertise about meningococcal disease.

Evaluation and Exam
A course evaluation form and self-assessment examination at the end of this monograph will provide participants with the opportunity to critique the program content and method of delivery, identify future educational needs and possible bias in the presentation materials and complete the self-assessment examination to receive CME credits.

Accreditation
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) by the National Foundation for Infectious Diseases (NFID). NFID is accredited by the ACCME to provide Continuing Medical Education (CME) for physicians. NFID takes responsibility for the content, quality and scientific integrity of the CME activity.

NFID designates this CME activity for a maximum of 1.5 credits toward the AMA Physician’s Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent on the educational activity.

OBJECTIVES
After completing the monograph, physicians will be able to:

• Discuss the epidemiology of meningococcal disease in terms of age, serogroup and geographic distribution;
• Describe clinical presentations of meningococcal disease;
• Outline U.S. immunization recommendations;
• Compare features of conjugate and polysaccharide vaccines.
Commercial Support
This CME activity is made possible by an unrestricted educational grant from sanofi pasteur to the National Foundation for Infectious Diseases.

Financial Disclosures
Lee H. Harrison, MD, has a financial interest/relationship with sanofi pasteur in the form of research support, consulting, and speaking fees.

Sheldon L. Kaplan, MD, has a financial interest/relationship with sanofi pasteur in the form of a research grant, stipend and/or fellowship.

Elizabeth Miller, MD, has a financial interest/relationship with Chiron, Wyeth Pharmaceuticals and Baxter in the form of provision of meningococcal surveillance reports for submission to licensing authorities.

Walter A. Orenstein, MD, has no significant financial interests or relationships to disclose in relation to this program.

Georges Peter, MD, has no significant financial interests or relationships to disclose in relation to this program.

Nancy E. Rosenstein, MD, has no significant financial interests or relationships to disclose in relation to this program.

William Schaffner, MD, has no significant financial interests or relationships to disclose in relation to this program.

Disclaimer
Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient’s condition, possible contraindications or dangers in use, review of any applicable manufacturer’s product information and comparison with recommendations of other authorities.

Release date: July 2005
Expiration date: July 2007
INTRODUCTION

Following approval of the first conjugate vaccine against meningococcal disease, the Centers for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) has broadened its meningococcal disease vaccination recommendations.\(^1\)

The ACIP recommends routine vaccination of young adolescents with the meningococcal conjugate vaccine at the pre-adolescent health care visit (11-12 years of age). For those persons who have not previously received the meningococcal conjugate vaccine, ACIP recommends vaccination before high-school entry (approximately 15 years of age). Routine vaccination is also recommended for college freshmen living in dormitories. By 2008, the goal will be routine vaccination of all adolescents beginning at 11 years of age.

This document describes meningococcal disease epidemiology and disease burden among children, adolescents and young adults in the U.S. It also discusses prevention strategies for meningococcal disease, with a focus on recommended use of the quadrivalent conjugate meningococcal vaccine. An overview of the meningococcal conjugate vaccination program in the United Kingdom, implemented in 1999, provides an example of the benefits of widespread conjugate immunization across a population.

Meningococcal disease is a potentially life-threatening infection caused by the bacterium *Neisseria meningitidis*. It affects 1,400 to 2,800 persons in the U.S. annually.\(^1\) Most cases are sporadic; less than 5% occur in outbreaks.\(^2,3\) Incidence is highest in children less than 2 years of age, but approximately 50% of cases occur in those over 15 years. Temporal and geographic peaks have been noted, however, in various age groups. A study in Maryland found that in the 1990s, 30% of cases occurred in adolescents and young adults.\(^4\) During the same period (1991 to 2002), 13% to 14% of disease countrywide was in persons 11 to 18 years of age (CDC. Unpublished data).\(^2\) The annual disease rate generally ranges from 0.9 to 1.5 cases per 100,000, but clearly the overall and age-specific incidence rates are markedly cyclical.

### Meningococcal Disease Immunization Recommendations

In addition to the ACIP, other important groups have issued recommendations regarding meningococcal disease vaccination. These may be reviewed at the following Web addresses:

**Advisory Committee on Immunization Practices**
www.cdc.gov/mmwr/PDF/rr/rr5407.pdf

**American Academy of Family Physicians**
www.aafp.org/x34406.xml

**American Academy of Pediatrics**
www.cispimmunize.org/pro/pdf/aapmengpolicy.pdf

**American College Health Association**
www.acha.org/projects_programs/men.cfm

Meningococcal disease is associated with an overall case fatality rate of 10% to 14%.\(^1\) Fatality rates can vary widely, however, depending on prevalence of the disease, the nature of the infection and societal conditions.\(^5\) Case fatality rates generally increase with age,\(^6\) but again, aberrations have been noted. During a decade-long span ending in 2002, CDC surveillance reported fatality rates of 12% in those aged 10 to 17 years and 14% in those aged 14 to 24 years (CDC. Unpublished data).\(^2\) Beyond mortality, meningococcal disease is also associated with substantial long-term morbidity. Of those who survive, 11% to 19% have permanent sequelae, such as hearing loss, brain damage, renal failure or limb amputation.\(^1,7,8\)
Five clinically relevant meningococcal serogroups, A, B, C, Y and W-135, are responsible for nearly all disease worldwide. Currently, serogroups B, C and Y cause the majority of U.S. infections; serogroup A is extremely rare in the U.S. and W-135 causes a very small proportion of infections. However, serogroup distribution has changed over time. Serogroup Y caused only 2% of U.S. cases in the early 1990s but 39% of cases from 1996 to 2001 (this specific change appears to be confined to the U.S. thus far). Serogroup distribution also varies by age. Serogroup B is the most common serogroup in infants, serogroup C is most common in adolescents and young adults and serogroup Y causes the majority of cases in those aged 65 years and older. Similar fluctuations in serogroups are seen worldwide.

A quadrivalent conjugate meningococcal vaccine (MCV4), approved for use in persons aged 11 to 55 years (Menactra®, sanofi pasteur), is a key addition to existing meningococcal disease prevention measures. Like the polysaccharide vaccine, which has been licensed in the United States since 1978, the quadrivalent conjugate offers protection against four serogroups of *N. meningitidis* (A, C, Y, W-135), the bacteria that cause meningococcal disease. Successful conjugate vaccine technology, however, offers additional benefits compared with polysaccharide vaccines, including improved duration of protection, induction of immunologic memory, booster responses and reduction in nasopharyngeal bacterial carriage.

Routine vaccination is also recommended for groups that have elevated risk. These groups include microbiologists who are routinely exposed to isolates of *N. meningitidis*; persons who travel to or reside in countries in which *N. meningitidis* is epidemic; military recruits; and those with complement deficiency or functional or anatomic asplenia. In addition to these groups, all other adolescents and college students who wish to reduce their risk of meningococcal disease may elect to be vaccinated.

Widespread conjugate meningococcal vaccination should decrease the risk of meningococcal disease in adolescents and adults. Expectations for conjugate vaccines are based on recent experience. In the U.K., widespread use of conjugate meningococcal C vaccines has led to sharp decreases in meningococcal C disease (which was responsible for 30% to 40% of cases in the U.K.), reduction in bacterial carriage and consequent reduction in incidence in unimmunized persons. In the U.S., universal use of conjugate *Haemophilus influenzae* type b (Hib) and pneumococcal vaccines has led to sharp decreases in meningitis cases caused by these bacteria. Because of these immunization successes, meningococcal disease is now the most common cause of bacterial meningitis among children over 2 years of age, adolescents and young adults in the U.S.

Several factors make meningococcal disease a matter of public health importance. First, it is a communicable disease associated with notable morbidity and mortality. Second, isolated meningococcal cases and outbreaks often cause serious medical and social stress in communities and are associated with increased costs—both economic and social. Finally, each case of meningococcal disease requires a public health response (i.e., identification of close contacts for prophylaxis).
N. Meningitidis is a commensal bacterium of the human nasopharynx that infrequently causes invasive disease. Up to 10% to 30% of adolescents and young adults and 19% to 39% of adult males (military recruits) are asymptomatic, transient nasopharyngeal carriers of N. meningitidis, although most carry nonpathogenic strains. Asymptomatic carriage rates in young children are much lower (< 2%). Some carriers develop protective antibodies against the organism. In a minority of exposed individuals, N. meningitidis penetrates the nasopharyngeal mucosa, reaches the bloodstream and causes systemic disease.

The rate of meningococcal disease in the U.S. generally varied between 0.9 and 1.5 cases per 100,000 persons for 4 decades. Although meningococcal disease occurs throughout the year, incidence peaks in late winter and early spring. Rates of meningococcal disease are highest in infancy with a second spike in incidence in adolescence, with a peak at around 18 years of age (Figure 1).

The distribution of serogroups causing meningococcal disease (A, B, C, Y, W-135) varies over time and by geographic location. From 1988 through 1991, most U.S. cases of meningococcal disease were caused by serogroups B and C, with serogroup Y accounting for only 2% of cases. More recently (1996 through 2001), serogroup Y disease caused the largest proportion of cases (39%), followed by serogroup C (31%) and serogroup B (23%).

Although serogroup W-135 is relatively uncommon in the U.S. and was not previously known to cause outbreaks, it played a major role in an outbreak during the Hajj pilgrimage to Mecca in 2000. Four cases of W-135 meningococcal disease were identified in pilgrims returning to the U.S. from Saudi Arabia and their close contacts.

Serogroup A was a common cause of U.S. epidemics early in the last century, but has been rare since World War II. Serogroups A and C continue to predominate throughout Asia and Africa, with serogroup A remaining the major cause of meningococcal disease in sub-Saharan Africa (the “meningitis belt”). Even so, serogroup W-135 was responsible for a large meningitis outbreak in Burkina Faso in 2002. The diversity in geographic distribution of meningococcal serogroups causing disease, while unexplained, is important given the ease and frequency of travel and potential exposure to serogroups other than those common to one’s region of residence.

Overall, serogroups B, C and Y cause a substantial proportion of disease across all ages, but specific distribution varies by age group. Recent U.S. data (2002) show that infants and toddlers experience a higher proportion of serogroup B disease than older age groups (Figure 2). Among young adults (18 to 34 years old), serogroup C is the most common (48% of cases) and in those 65 years and older, serogroup Y is most common (62%). In a
prospective surveillance study of U.S. college students with meningococcal infection during the 1998–1999 school year, serogroup C was the most common (48% of isolates for which serogroup data were available), followed by B, Y and W-135 (28%, 19% and 1%, respectively).\textsuperscript{23}

**N. meningitidis** is an aerobic, gram-negative diplococcus. The bacterium has an outer membrane that is surrounded by a protective polysaccharide capsule. Thirteen antigenically and chemically unique polysaccharide capsules have been identified and form the basis of serogroup classification of the organism. Five serogroups — A, B, C, Y and W-135 — cause nearly all cases of invasive meningococcal disease.

The cyclic nature of disease and changing distribution of serogroups, combined with frequency of travel worldwide, underscore the need for a prevention strategy that incorporates all major serogroups.

**Figure 2:**
Serogroup Distribution of Invasive Meningococcal Disease by Age Group in the U.S. — Active Bacterial Core Surveillance 2002

Source: ABCs\textsuperscript{2}
TRANSMISSION OF *N. MENINGITIDIS* occurs by droplet aerosolization (e.g., coughing or sneezing) or direct contact with secretions from the nasopharynx of colonized persons. Whether the organism remains a colonizer of the nasopharynx or crosses the mucosal barrier and gains access to the bloodstream, central nervous system and/or other organs depends on both specific bacterial virulence factors (e.g., fimbriae, polysaccharide capsule, IgA protease) and host defense mechanisms (e.g., mucosal epithelium, secretory IgA, serum antibody, ciliary activity, complement, blood-brain barrier).²⁴

Various medical conditions increase the risk of developing meningococcal disease. Persons with immature or dysfunctional humoral immunity are most susceptible to meningococcal infection.²⁵,²⁶ Immune defects that predispose to meningococcal disease include functional or anatomical asplenia, deficiency of properdin and mannose-lectin binding protein and terminal complement components.²⁷-²⁹ Antecedent respiratory tract infection also has been associated with increased risk of meningococcal disease.³⁰,³¹ Finally, evidence indicates genetic risk factors may increase susceptibility to meningococcal infection.³²,³³

Increased risk of meningococcal infection among military recruits and college freshmen living in dormitories is likely a consequence of crowded living conditions. Likewise, certain environmental factors have been shown to increase the risk of meningococcal disease. The infection rate (secondary infection) is 500- to 800-fold greater in household contacts exposed to a person who has a sporadic meningococcal infection than in the general population.³⁴ Increased risk of meningococcal infection among military recruits³⁵ and college freshmen living in dormitories²³ is likely a consequence of crowded living conditions.

In the U.S., higher rates of meningococcal disease have been observed in black persons and persons of low socio-economic status, which are likely surrogate risk markers (e.g., for household crowding and exposure to tobacco smoke) rather than inherent genetic risk factors for disease.³⁶ Active smoking and passive exposure to tobacco smoke increase the risk of illness, most likely by increasing the creation and dissemination of respiratory droplets or compromising the respiratory mucosa as a barrier to microbial invasion.³⁷ During outbreaks, bar or nightclub attendance and alcohol consumption have been identified as risk factors for infection.³⁸-⁴⁰

Once *N. meningitidis* enters the nasopharynx, the organism attaches to and multiplies on nonciliated epithelial cells. Some exposed individuals become asymptomatic nasopharyngeal carriers of *N. meningitidis*,¹³,¹⁴ which is an immunizing event. In less than 1% of colonized persons, *N. meningitidis* penetrates the nasopharyngeal mucosa and causes a systemic infection.¹⁷ In the bloodstream, the organism can rapidly produce and release endotoxin, which stimulates cytokine production and the alternative complement pathway.⁷ In about half of bacteremic persons, *N. meningitidis* crosses the blood-brain barrier into the cerebrospinal fluid (CSF), and meningitis follows.
The quadrivalent meningococcal conjugate vaccine (MCV4, Menactra®) is recommended for routine vaccination (Table 1) of young adolescents at the pre-adolescent health care visit (11-12 years of age). For those persons who have not previously received MCV4, vaccination is recommended before high-school entry (approximately 15 years of age). Also, if not previously vaccinated, routine vaccination is recommended for college freshmen living in dormitories. Finally, other adolescents and college students who wish to decrease their risk for meningococcal disease may elect to receive the vaccine.

The ACIP recommends catch-up vaccination at approximately 15 years of age as an effective strategy to reduce meningococcal disease incidence among adolescents and young adults. The routine vaccination recommendation at 11-12 years of age might strengthen the role of the pre-adolescent visit and have a positive effect on vaccine coverage among adolescents. A routine visit at 11-12 years of age to assess immunization status and other preventive services is recommended by the ACIP, American Academy of Pediatrics (AAP), American Academy of Family Physicians (AAFP) and the American Medical Association (AMA).

Routine meningococcal vaccination is also recommended for persons in specific risk groups. These are microbiologists routinely exposed to isolates of N. meningitidis; military recruits; persons who travel to, or reside in countries in which N. meningitidis is hyperendemic or epidemic; persons with terminal complement component deficiencies; and those who have anatomic or functional asplenia. HIV patients who wish to decrease their risk of meningococcal disease may elect to be vaccinated.

Conjugate Versus Polysaccharide Vaccine
Vaccination with MCV4 is preferred for all persons in the age range for which it is approved, 11 to 55 years, because of the benefits it should provide compared with polysaccharide vaccine (Table 2). Immunogenicity data show MCV4 induces antibody levels at least as good as the polysaccharide vaccine. Both vaccines include protection against four of the five strains (A, C, Y and W-135) that cause the majority of cases worldwide. Neither includes protection against serogroup B disease (see box, “About Serogroup B Vaccines”).

Although the vaccines are equally immunogenic, MCV4, which is administered intramuscularly (versus subcutaneous injection of the polysaccharide vaccine) is more reactogenic. MCV4 is expected to have a duration of protection of at least 8 years compared with 3 to 5 years for the polysaccharide vaccine. Ongoing studies will provide specific data about duration of protection in the coming years.

### Table 1: Recommendations for Use of Meningococcal Conjugate Vaccine *

- **At the pre-adolescent health care visit (11-12 years old)**
- **At high-school entry (approximately 15 years old), if not previously vaccinated with MCV4**
- College freshmen living in dormitories
- Microbiologists routinely exposed to isolates of N. meningitidis
- Military recruits
- International travelers and citizens residing in endemic or hyperendemic areas
- Persons with anatomic or functional asplenia
- Persons with terminal complement component disorders

* Approved for use in persons aged 11 to 55 years
Source: CDC
In fact, extensive post-licensure evaluation of MCV4 will be ongoing. Data collected in the coming years will provide vaccine-specific information and will shape future recommendations. The hope is that this conjugate vaccine provides benefits similar to other conjugate vaccines.

Conjugate technology changes the nature of the immune response from T-cell independent to T-cell dependent. This leads to benefits not seen with polysaccharide vaccines, including induction of immunologic memory, booster responses and reduction in nasopharyngeal bacterial carriage. Reduction in asymptomatic carriage rates, if widespread, leads to protection of unvaccinated individuals through a herd immunity effect. These benefits have been demonstrated with use of a monovalent meningococcal conjugate C vaccine in the U.K. and widespread Hib and pneumococcal conjugate vaccination in the U.S. (discussed below). Data on similar benefits are not yet available on MCV4.

### Table 2: Comparison: Conjugate and Polysaccharide Meningococcal Disease Vaccines

<table>
<thead>
<tr>
<th></th>
<th>Conjugate (Menactra®)</th>
<th>Polysaccharide (Menomune®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity*</td>
<td>82% to 97%</td>
<td>80% to 95%</td>
</tr>
<tr>
<td>Duration of protection</td>
<td>&gt; 8 years†</td>
<td>3-5 years</td>
</tr>
<tr>
<td>Administration</td>
<td>Intramuscular injection</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Safety</td>
<td>Generally mild adverse reactions; mainly pain, redness and induration at injection site, headache, fatigue and malaise.</td>
<td>Generally mild adverse reactions; most frequent is pain and redness at injection site. Severe reaction uncommon.</td>
</tr>
<tr>
<td>Induction of immunologic memory‡</td>
<td>Expected</td>
<td>No</td>
</tr>
<tr>
<td>Booster responses‡</td>
<td>Expected</td>
<td>No</td>
</tr>
<tr>
<td>Reduction in nasopharyngeal bacterial carriage‡</td>
<td>Expected</td>
<td>No</td>
</tr>
<tr>
<td>Herd immunity‡</td>
<td>Expected under some vaccination strategies</td>
<td>No</td>
</tr>
<tr>
<td>Cost§</td>
<td>$82</td>
<td>$86</td>
</tr>
</tbody>
</table>

* Measured as ≥ four-fold rises in antibody titers in adolescents; † Based on CDC model, ongoing evaluation is expected to provide direct data in three to five years; ‡ Assumptions based on demonstrated benefits of other conjugate vaccines; § Retail cost to physicians.

Sources: CDC1, CDC unpublished data.

### About Serogroup B Vaccines

*In clinical trials, most candidate vaccines against serogroup B polysaccharide have not stimulated protective immunity in humans.*42 Research has focused on noncapsular antigens as vaccine candidates. For example, an outer-membrane protein serogroup B vaccine, licensed for use in New Zealand in 2004, was designed to match and combat an outbreak of serogroup B disease ongoing throughout the 1990s. However, this approach does not address the diversity of outer-membrane proteins that cause sporadic serogroup B disease or geographic variations.43-44
The quadrivalent meningococcal polysaccharide vaccine (Menomune®, sanofi pasteur) continues to be recommended in children aged 2 to 10 years and adults older than 55 years who are at increased risk of infection. The polysaccharide vaccine is also an acceptable alternative for persons aged 11 to 55 years if MCV4 is unavailable.

Both vaccines are recommended for control of meningococcal disease outbreaks, with the conjugate vaccine preferred for those aged 11 to 55 years. Revaccination may be indicated for those who previously received the polysaccharide vaccine if they remain at high risk for infection and are aged 11 to 55 years.

Benefits of Other Conjugate Vaccines
Non-meningococcal conjugate vaccines, including Hib and a 7-valent pneumococcal, are routinely used in the U.S. Before introduction of the vaccine, Hib disease was the leading cause of bacterial meningitis in children younger than 5 years. Incidence of invasive Hib disease has declined more than 99% since vaccine licensure. Similarly, rates of invasive pneumococcal disease in children younger than 2 years have declined 70% to 80% since vaccine licensure in 2000. Conjugate pneumococcal vaccination also appears to have a substantial herd immunity effect. While the vaccine is used only in children, disease rates have declined among adults. For the serotypes included in the vaccine, disease incidence decreased in those aged 20 to 39 years, 40 to 64 years and 65 years and older by 46%, 20% and 29%, respectively (CDC. Unpublished data).

The U.K. Experience: Monovalent Meningococcal Conjugate C Vaccine
Additional evidence comes from the U.K., where a comprehensive monovalent meningococcal conjugate C vaccine immunization program was implemented in 1999. Disease epidemiology in the U.K. differs from that in the U.S.; the U.K. sees very little serogroup Y disease and has a higher incidence of serogroup C infection. Widespread use of the monovalent conjugate C vaccine would be expected to have a greater relative impact in the U.K.

The U.K. program includes a routine 3-dose infant vaccination course (at 2, 3 and 4 months) with a single dose for children aged 12 months to 17 years (with a subsequent extension to 25 years of age). Immunization rates of about 85% in target groups resulted in an 81% reduction in serogroup C disease incidence within 18 months. While the vaccine was immunogenic in young infants, their immunity waned at about 1 year. Despite this, control of disease in all age groups has been excellent with disease incidence declining 67% in the unvaccinated population. This is attributable to the herd immunity arising from the marked reduction in nasopharyngeal carriage (a key feature of conjugate vaccines). Nasopharyngeal carriage rates decreased 66% among students aged 15 to 17 years. Surveillance has shown no evidence of serogroup replacement or development of capsular switching in the first 18 months in the U.K. MCV4 will be used much differently in the U.S. than the monovalent vaccine is used in the U.K. It is unclear if the current U.S. immunization strategy will yield a herd immunity benefit.
Meningitis and Meningococcemia

Meningococcal disease manifests most commonly as meningitis and/or meningococcal bacteremia. It is meningococcemia, however, a less common but more severe presentation (5% to 20% of cases) that is associated with the highest mortality rates and long-term sequelae. Meningococcemia often begins with a sudden onset of fever, malaise, myalgia and headache; seizures occur in 20% of cases. About half of patients (even more children and young adults) develop a prominent petechial or purpuric rash, primarily on the extremities. When present, a meningococcal rash can change and spread very rapidly. Meningococcemia may occur either with or without meningitis.

The more common clinical presentation, meningococcal meningitis, is often nonspecific. Early symptoms may mimic those of other more common but less serious diseases. Patients may present with sudden onset of fever, headache, meningismus and signs of cerebral dysfunction. However, the classic triad of headache, confusion and nuchal rigidity is not always evident. Wide variations in presentation can occur at all ages, and symptoms can progress and change rapidly during the course of the disease.

Infants and the elderly may not present with the classic symptoms and signs of meningococcal meningitis. Meningismus is absent in neonates and often in infants. One of the most important clues to a meningitis diagnosis in neonates is a change in affect or level of alertness. Clinical suspicion should also be raised by temperature instability, listlessness, high-pitched crying, lethargy, weak suck, refusal to eat, irritability, jaundice, vomiting, diarrhea presentations, progression and sequelae.

CASE REVIEW: 12-year-old male

A 12-year-old African-American boy was rushed to the emergency room by his parents at 5 p.m. on a Saturday after they found him unresponsive in the bathroom. Otherwise healthy, he had had two days of a non-productive cough accompanied by malaise, headache and intermittent nausea. He had been seen that morning by his physician who prescribed azithromycin for bronchitis. It had taken some time to fill the prescription and the boy received only one dose of the medication, which he promptly vomited just before he was discovered in the bathroom.

In the emergency department, the boy had no detectable blood pressure and required immediate intubation. A few petechial lesions were evident on the palms and soles of the feet, at the belt line and in the conjunctivae. When present, a meningococcal rash can change and spread very rapidly. Meningococcemia may occur either with or without meningitis.

Meningismus is absent in neonates and often in infants. One of the most important clues to a meningitis diagnosis in neonates is a change in affect or level of alertness. Clinical suspicion should also be raised by temperature instability, listlessness, high-pitched crying, lethargy, weak suck, refusal to eat, irritability, jaundice, vomiting, diarrhea

Teaching Points: Symptoms of meningococcemia can appear suddenly and progress rapidly. Even with rapid diagnosis and appropriate treatment, serious sequelae are possible; deafness being the most common one in children. Meningococcal rashes may appear at areas where pressure occurs from stockings, elastic or belts.
or respiratory distress. Elderly patients, especially those with multiple co-morbid diseases, may be afebrile or hypothermic, lethargic or exhibit reduced alertness and have variable signs of meningeal inflammation. Confusion is common, as is a prior or concurrent respiratory tract infection. A definitive diagnosis of meningococcal disease is based on isolation of *N. meningitidis* from a normally sterile site (e.g., blood; CSF; joint, pleural or pericardial fluid).

Meningococcal meningitis is fatal in approximately 10% of cases among the general population; the case fatality rate is as high as 53% in patients with meningococcemia. Factors associated with an increased mortality rate include recovery of an isolate from the bloodstream and serogroup C infection.

**Other Presentations**

Up to 15% of patients with meningococcal disease have pneumonia. Meningococcal pneumonia occurs primarily in older adults and is most commonly associated with serogroup Y or W-135 infection. Less common manifestations of disease (<2% of cases) include pericarditis, otitis media, epiglottitis and arthritis (Figure 3).

**Sequelae**

Even with appropriate therapy, systemic meningococcal infection can progress rapidly — often within hours of the first symptoms. Despite the susceptibility of *N. meningitidis* to penicillin and advances in medical care, 11% to 19% of patients who survive invasive meningococcal disease suffer from permanent sequelae, including hearing loss, neurologic or brain damage, renal failure and limb amputation.

**Prevention of Secondary Disease**

The primary method of preventing secondary meningococcal disease is antimicrobial prophylaxis of persons in close contact with an infected person (Table 3). Those

---

**Figure 3: Clinical Manifestations of Meningococcal Disease**

![Diagram showing the prevalence of various manifestations of meningococcal disease.]

**Table 3: Meningococcal Disease Prophylaxis Recommendations: High-Risk Contacts**

- **Household contact (especially young children)**
- **Child care or nursery school contact***
- **Direct exposure to secretions of index patient through kissing, sharing toothbrushes or eating utensils (markers of close social contact)***
- **Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation***
- **Frequently slept or ate in same dwelling as index patient***

* During 7 days before onset of illness

Source: AAP
most in need of chemoprophylaxis against meningococcal infection include household members, daycare center contacts and persons directly exposed to the oral secretions of a patient with invasive meningococcal infection. Antimicrobial prophylaxis of at-risk persons should be initiated within 24 hours after the index infection is identified, if possible.11

Oral rifampin and ciprofloxacin and parenteral ceftriaxone substantially reduce (by 90% to 95%) nasopharyngeal carriage of \textit{N. meningitidis} and are therefore recommended by the ACIP and the AAP for prophylaxis of meningococcal disease (Table 4).11–60 One study showed azithromycin is also effective in eradicating nasopharyngeal carriage.61 Persons with invasive meningococcal disease treated with agents other than ceftriaxone or other third-generation cephalosporins should also receive one of the chemoprophylactic antibiotics before hospital discharge.62

**Outbreak Control**

Given the devastating nature of meningococcal disease, sporadic cases often become the topic of front-page and TV news. Such cases elicit community fear and increased telephone calls and visits to treatment centers. Public
health departments are faced with assessing potential outbreaks, determining the need for and designing appropriate control procedures and fielding public inquiries. Requests for chemoprophylaxis and vaccination are common, even among those without close contact with infected persons.

The decision to implement mass vaccination is complicated. Such vaccination campaigns are expensive, require considerable public health effort and can create unwarranted public concern. Still, mass vaccination may be necessary to prevent the substantial morbidity and mortality associated with meningococcal disease. The CDC has issued guidelines, including criteria for deciding whether use of meningococcal vaccine is warranted (available at: www.cdc.gov/mmwr/pdf/rr/rr4605.pdf).

**Economic Impact and Cost Effectiveness**

An economic cost and benefit analysis of routine meningococcal vaccination at 11 years of age showed that costs associated with this intervention are high compared with many other recommended preventive measures. A similar analysis examining routine vaccination in college freshmen also highlighted the high cost of a widespread meningococcal vaccination program. Both analyses included a wide range of costs associated with each meningococcal disease case. The high end of these ranges demonstrates the potential for serious disease sequelae and even death that accompany each infection.

Although data about the economic impact of meningococcal disease are imperfect, older CDC data estimated the direct cost of meningococcal disease at $13,431 per case (1995 dollars). The estimated lifetime costs of sequelae ranged from $44,187 per case (hearing loss) to $864,980 (severe retardation). Indirect costs (lost productivity) were estimated to be $1 million per case. Preventing disease would avert these costs for the individual, families, health care providers, employers, health care payers and society.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age Group</th>
<th>Dosage and Route of Administration</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Adults</td>
<td>500 mg po</td>
<td>Single dose</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Children &lt; 15 yrs</td>
<td>125 mg IM 250 mg IM</td>
<td>Single dose Single dose</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Children &lt; 1 mo</td>
<td>5 mg/kg po q12h 10 mg/kg po q12h 600 mg po q12h</td>
<td>2 days 2 days 2 days</td>
</tr>
<tr>
<td></td>
<td>Children &gt; 1 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources: CDC, AAP
Meningococcal disease is a serious illness that can progress rapidly, resulting in substantial morbidity and mortality, even with appropriate treatment. U.S. immunization policy shifted with the availability of a quadrivalent conjugate meningococcal vaccine. The conjugate vaccine is approved for use in persons aged 11 to 55 years and recommended for routine vaccination of adolescents and college freshmen living in dormitories. Others at high risk and therefore recommended for vaccination include microbiologists routinely exposed to isolates of *N. meningitidis*, international travelers or U.S. citizens living in areas where *N. meningitidis* is endemic or hyperendemic, those with anatomic or functional asplenia or terminal complement component disorders and military recruits.

The constantly changing epidemiology, coupled with the ease and frequency of travel of U.S. citizens, suggests broad coverage against meningococcal serogroups is warranted. Although no vaccine against serogroup B is available currently, the quadrivalent meningococcal conjugate and polysaccharide vaccines both provide protection against the other four clinically relevant strains of *N. meningitidis* (A, C, Y, W-135). The conjugate vaccine is available for persons aged 11 to 55 years while the polysaccharide vaccine is approved for use in anyone aged 2 years or older and recommended for those aged 2 to 10 and 55 years and older.

Health care providers must also be aware of the variable and potentially fulminant clinical presentation of meningococcal disease. The difficulty of a quick and accurate diagnosis and the occurrence of substantial morbidity and mortality even with appropriate and rapid treatment are compelling reasons for a conjugate vaccine-based approach to the prevention of meningococcal disease.
REFERENCES


1. What percent of meningococcal disease cases in the U.S. are fatal?
   a) <4
   b) 4 to 6
   c) 6 to 10
   d) 10 to 14

2. What percent of meningococcal disease survivors experience permanent sequelae (e.g., hearing loss, brain damage, renal failure or limb amputation)?
   a) 4 to 7
   b) 8 to 10
   c) 11 to 19
   d) ≥20

3. What is the most common cause of bacterial meningitis in the U.S.?
   a) Haemophilus influenzae type b
   b) Neisseria meningitidis
   c) Staphylococcus aureus
   d) Streptococcus pneumoniae

4. Which serogroup, commonly responsible for U.S. epidemics a century ago, now rarely causes infection in this country?
   a) A
   b) C
   c) Y
   d) W-135

5. Which serogroup caused 2% of cases in the early 1990s, but nearly 40% by the end of the decade?
   a) A
   b) C
   c) Y
   d) W-135

6. Which factors affect whether *N. meningitidis* crosses the mucosal barrier and gains access to the bloodstream, CNS and other organs?
   a) Bacterial virulence
   b) Host defense mechanisms
   c) Neither A nor B
   d) Both A and B

7. Which symptom is absent in neonates with meningococcal meningitis?
   a) Change in affect or alertness level
   b) Fever
   c) Headache
   d) Meningismus

8. Incidence of invasive Hib disease has fallen by what percent following widespread uptake of the conjugate Hib vaccine?
   a) 50
   b) 70
   c) 90
   d) >99

9. Which benefit is *not* associated with use of the polysaccharide meningococcal vaccine?
   a) Highly effective in older children and adults
   b) Favorable safety profile
   c) Lifelong immunity
   d) Protection against serogroups A, C, Y and W-135

10. Conjugate vaccines are associated with which benefit(s) versus polysaccharide vaccines?
    a) Herd effect
    b) Improved duration of activity
    c) Induction of immunologic memory
    d) All of the above
CME EVALUATION

Your input is extremely important and valuable to us. Please take the time to complete the following evaluation giving us your assessment of this CME activity.

1. This content meets the educational objectives
   a) agree
   b) neutral
   c) disagree

2. Considering my experience, the material presented was
   a) satisfactory
   b) too elementary
   c) too technical

3. I gained information which will be useful to me
   a) agree
   b) neutral
   c) disagree

4. The format is clear, readable and useful
   a) agree
   b) neutral
   c) disagree

5. There was commercial bias in this activity
   a) yes
   b) no

If yes, please give examples:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Suggested topics for future issues or other comments about this publication:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Instructions for obtaining CME credits

To receive CME credits after reading the publication, complete the self-assessment examination, the CME evaluation, and your contact information. Return the examination and evaluation form, including your complete contact information, via fax to 301-907-0878 or by mail to:

NFID Office of CME
4722 Bethesda Avenue, Suite 750
Bethesda, Maryland 20814

No fee is required. Please allow 4-6 weeks for processing your certification. Inquiries may be directed by phone to 301-656-0003 ext. 19 or by e-mail to info@nfid.org Requests for credit must be received no later than November 2007.

Name: ___________________________ Degree: ___________________________
Title: ___________________________ Organization: _______________________
Street Address: ___________________ E-mail Address: ___________________
City: ___________________________ State: __________ Zip Code: ___________
Signature: ______________________ Date: _______________________

(Please print legibly or we will be unable to process your certificate.)