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MENINGOCOCCAL INVASIVE DISEASE

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Meningococcal Invasive Disease is a disease caused by the systemic invasion by the bacteria *Neisseria meningitidis*, also known as meningococcus.

Microbiology

Neisseria meningitidis is a Gram-negative diplococcus with a "coffee bean" appearance. Most *Neisseria*, inhabit mucous membranes of warm-blooded hosts. They are aerobic, non-motile, do not form spores and grow best at 37ºC. Growth is best in moist and CO_2 rich environment. They are oxidase-positive and catalase-positive.

A major virulence factor is the capsular polysaccharide. There are 13 capsular polysaccharides: A, B, C, D, H, I, K, L, X, Y, Z, W135 and 29E. Most human infections are due to A, B, C, Y or W135. Many *N.meningitidis* are non-groupable.

There is a high frequency of antigenic variation in the outer membrane protein and capsular switching. Numerous techniques have been used to "type" *N.meningitidis* and identify clonal groups: Multi-locus sequence typing (MLST); restriction fragment length polymorphism (RFLP); pulse field gel electrophoresis (PFGE); ribo typing; polymerase chain reaction (PCR).

Virulent clones are characterized by high transmission rates and high rates of disease after introduction in a susceptible population. Virulent clones are found in asymptomatic carriers and rarely cause diseases. Eventually circulating virulent clonal groups undergo genetic diversification via transformation and various selective environmental pressures. These clones disappear and may re-emerge at a later date.

Epidemiology

Incidence: There are between 50 and 100 cases of meningococcal invasive diseases reported yearly in Louisiana. The incidence rate ranges from one to two per 100,000 per year. This incidence is similar to U.S. incidence. The seasonal trend in the number of cases in Louisiana shows a high peak during the first quarter of the year (January to March), during which approximately 50% of the cases reported during the year occur. Infants (newborn to one-year-old) have the highest occurrence of new cases of meningococcal meningitis, at ten per 100,000. However all age groups are at risk, particularly young adults and the elderly.

Serogroups B, C, and Y are the major causes of meningococcal disease in the U.S. as in Louisiana, 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 one 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 older than 11 years of age, 75% are caused by serogroups C, Y, or W-135, which are included in vaccines available in the United States.
Sporadic /Outbreaks: In the U.S., more than 98% of cases of meningococcal disease are sporadic. However, since 1991, the frequency of localized outbreaks has increased. Also in Louisiana, most cases

are sporadic. In the past, U.S. outbreaks have occurred in semi-closed communities, including child care centers, colleges and military recruit camps. In spite of the scarcity of outbreaks, the public perception is that outbreaks are a major risk.

Meningococci are common colonizers of the upper respiratory tract (about 1% to 5% of healthy people are carriers at any time). Meningococci are transmitted, when a person coughs, sneezes, or speaks and sends droplets containing meningococci into the air, with other people inhaling the bacteria. The bacteria enters the nose or throat and multiplies locally. If the immune system of the recipient is temporarily weakened, the bacteria may invade the blood, meninges or lung. The host factors that protect carriers from developing invasive disease are:

1-Specific functional antibodies
2-Intact complement system
3-Normal reticuloendothelial function

Risk factors: Persons who have deficiencies in the terminal common complement pathway (C3, C5-9), and those with anatomic or functional asplenia are at increased risk for acquiring meningococcal disease. Antecedent viral infection, household crowding, chronic underlying illness, and both active and passive smoking also are associated with increased risk for meningococcal disease. During outbreaks, bar or nightclub patronage and alcohol use also have been associated with higher risk for meningococcal disease.

Meningococcal Disease and College Students: Multiple studies have been conducted in the U.S. and the United Kingdom concerning the risk for meningococcal disease among college students. The risk for meningococcal disease among U.S. college students was higher for those who resided in dormitories than for those residing in other types of accommodations. Overall incidence among college students usually is similar to or somewhat lower than that observed among persons in the general population of similar age. Cases of meningococcal disease occurred nine to 23 times more frequently among students living in dormitories than among those living in other types of accommodations. U.S. surveillance data from the 1998-1999 school year indicated that the overall rate of meningococcal disease among undergraduate college students was lower than the rate among persons aged 18 to 23 years who were not enrolled in college (0.7 and 1.4 per 100,000 population, respectively). Rates were somewhat higher among freshmen (1.9 per 100,000 population).

Among the approximately 600,000 freshmen living in dormitories, rates were higher (5.1 per 100,000 population) than among any age group in the population other than children younger than two years of age.

In the United Kingdom, rates of meningococcal disease were higher among university students than among non-students of similar age. Regression analysis indicated that the main risk factor was catered hall accommodations (the U.K. equivalent of U.S. dormitories). A recent study conducted in the United Kingdom demonstrated a rapid increase in carriage rates of meningococci among university students in the first week of the fall semester, although rates of disease peaked later in the academic year.

The incubation period is one to ten days, usually less than four days. The disease usually develops within a few days of initial colonization.

Clinical Description

The onset often is abrupt with fever, chills, malaise, prostration, and a rash that initially may be macular, maculopapular, or petechial.

The signs and symptoms of meningococcal meningitis are indistinguishable from signs and symptoms of acute meningitis caused by other meningeal bacterial pathogens. Common symptoms of meningitis include headache, nausea and often vomiting, stiff neck and photophobia.

Less common manifestations include pneumonia, febrile bacteremia and conjunctivitis. Complications are arthritis, myocarditis, pericarditis and endophthalmitis.

The fulminant cases (Waterhouse-Friderichsen syndrome) are characterized by purpura, disseminated intravascular coagulation, shock and coma. Death may follow within several hours, despite appropriate therapy.

Occult bacteremia: Among young, nontoxic-appearing children aged three to 36 months with temperatures of 39°C or more and no clear source, approximately 2% to 3% have occult bacteremia. Of these bacteremias, approximately 90% are caused by *S. pneumoniae*, 5% by nontyphoidal *Salmonella* sp., and 1% by *N. meningitidis*. Most children with occult pneumococcal bacteremia improve spontaneously, but approximately 25% of untreated patients have persistent bacteremia or develop new focal infections, including 3% to 6% who develop meningitis. Occult meningococcal bacteremia, although rare, has frequent complications, including meningitis in approximately 40% and death in approximately 4%.

Febrile, young children at risk for occult bacteremia require a careful clinical evaluation and close follow-up. A strategy for obtaining blood cultures and empirically administering antibiotics on the basis of an increased ANC, in addition to close clinical follow-up, may be effective in reducing the frequency and severity of uncommon but adverse sequelae.

Disability: Meningococcal invasive disease also causes substantial morbidity: about 10% to 20% of survivors have sequelae (e.g., neurologic disability, limb loss and hearing loss).

Mortality: Despite the continued sensitivity of meningococcus to multiple widely available antibiotics, including penicillin, the case-fatality ratio for meningococcal disease is 10% to 15%.

Surveillance

Meningococcal invasive disease is a reportable condition. Do not report colonization: meningococci identified in the upper respiratory tract or sputum.

Case Definition

Clinical description: Meningococcal disease manifests most commonly as meningitis and/or meningococcemia that may progress rapidly to purpura fulminans, shock and death. However, other manifestations might be observed.

Laboratory criteria for diagnosis
Isolation of *Neisseria meningitidis* from a normally sterile site (e.g., blood or cerebrospinal fluid [CSF] or, less commonly, joint, pleural, or pericardial fluid)

Case classification

Probable: a case with a positive antigen test in CSF, or Gram-negative diplococcic, or clinical purpura fulminans in the absence of a positive blood culture

Confirmed: a clinically compatible case that is laboratory-confirmed

Positive antigen test results from urine or serum samples are unreliable for diagnosing meningococcal disease.

Laboratory Tests

Examination of the spinal fluid collected from a spinal tap is useful for the etiologic diagnosis of a meningitis (Table 1).

Table 1: Spinal fluid examination for bacterial and aseptic meningitis

CSF	Normal	Bacterial Meningitis	Aseptic Meningitis
Opening Pressure	70-180 mm H_2O	Normal to increased	Usually normal
Protein	15-45 mg/dL	Increased	Normal to increased
Glucose	45-80 mg/dL	Decreased	Normal to decreased
WBC Count	0-10	25 to 10 x 10^3	5 to 2 x 10^3
Predominant Cells	Mononuclear	Polymorphonuclear	Lymphocytes
Gram stain	Negative	May be positive	Negative

Source: AMA

A Gram stain of a CSF specimen, petechial or purpuric scraping and buffy coat smear of blood may show a Gram-negative diplococcus.

Cultures of blood and cerebrospinal fluid (CSF) are indicated for patients with suspected invasive meningococcal disease. Other sites that could be cultured are: a petechial or purpuric scraping, synovial fluid and other body fluid specimens. Because meningococci can be part of the nasopharyngeal flora, isolation of meningococci from the upper respiratory tract site is not diagnostic.

Bacterial antigen detection in CSF supports the diagnosis of a probable case if the clinical illness is consistent with meningococcal disease. Antigen detection offers rapidity in diagnosis and specificity, provided that organisms containing cross-reacting antigens are not involved (e.g., *E. coli* K1 and group B streptococci). False-negative results occur commonly; in one series, almost half of the patients with meningococcal meningitis had negative tests. Positive antigen results from serum and urine samples are unreliable for diagnosing meningococcal disease.

A serogroup-specific polymerase chain reaction test to detect *N. meningitidis* from clinical specimens is under development in the United States.

Serologic diagnosis is not used for the diagnosis of invasive meningococcal disease.

After cultures are done by the initial health care facility and isolation of *N. meningitides* is made, forward the isolate to the Louisiana State Lab for serogrouping (without cost), even if the referring laboratory has already determined the serogroup. This will ensure that the isolates will be available in the event further subtyping becomes necessary during an outbreak investigation. If necessary, consult with the state laboratory - Bacteriology Section for transport and handling. The organism produces a polysaccharide capsule which protects the meningococci from human host defenses and is used for differentiation in serogroups. Serogroups A, B, C, Y and W-135 are responsible for invasive disease. Serogroups B, C and Y each account for approximately 30% of reported cases in Louisiana.

Pulsed Field Gel Electrophoresis (PFGE) techniques are performed to be more specific for the same serogroup strain. If necessary, consult with the State Lab Bacteriology Section for transport and handling and the Infectious Disease Epidemiology (IDEpi) Section for further consultation.

Case Investigation

The purpose of investigation is to confirm cases, to differentiate between the serogroups of meningococci, to prevent transmission by identifying those most at risk, and recommending appropriate prophylaxis.

Contact the physician or hospital to confirm the diagnosis by obtaining a clinical summary, results of CSF examination (cell count, percentage of types of leucocytes, glucose and protein), CSF Gram stain, blood and CSF culture, and CSF antigen detection. Request the physician or hospital to send the culture on the suspected case to the state laboratory for serogrouping.

A case investigation would not be warranted on the basis of a simple suspicion of meningitis or of bacterial meningitis of unknown origin. However, a case investigation should be instituted for cases meeting the probable definition and should not be delayed pending final confirmation.

Identify all close contacts of the case for the prior seven days. Close contacts are defined as

- household members
- child care center classmates, nursery school contacts
- personnel who resuscitated, intubated, or suctioned the patient before antibiotics were begun
- people who had intimate contact with the patient's oral secretions: Those who have been exposed to oral secretions of a case, such as occurs as a result of kissing or sharing of food and drink (same plate or same cup), or using same toothbrush.

Do not include casual contacts: There is no evidence that casual contact places a person at any increased risk of developing the disease. These casual contacts include:

- classroom (other than child care center)
- elementary or secondary school class mates
- school bus
- office co-worker
- healthcare worker with casual contact (for example, entering the patient room, taking vital signs).

All close contacts should receive antibiotic prophylaxis. Chemoprophylaxis can eliminate nasopharyngeal carriage of close contacts and therefore reduce their risk of developing invasive disease, BUT chemoprophylaxis does NOT prevent contacts from subsequently acquiring the infection, and chemoprophylaxis does NOT treat infection in those incubating disease.

Educate contacts on disease transmission and encourage them to take all dosages of the antibiotic. Explain that since the prophylactic antibiotic does not cure incubating disease, anyone developing signs and symptoms (fever) should see their physician.

The index case also should receive chemoprophylaxis before hospital discharge unless the infection was treated with ceftriaxone or cefotaxime, both of which are effective in nasopharyngeal eradication of *N. meningitidis.*

Close observation of contacts is recommended; they should be evaluated promptly if a febrile illness develops. Exposed individuals who develop a febrile illness should seek prompt medical evaluation even if they received an adequate prophylaxis. Prophylaxis does NOT cure incubating disease.

Day Care Center:
If a case of Meningococcal meningitis is associated with a child care center, notify the IDEpi Section and follow these recommendations:

1-Contact the owner/director of the child care or private baby-sitter to notify him/her of the case and to determine if any other cases have occurred.

2- Prepare a list of all children and adults attending the center.

3-Arrangements will need to be made to insure that all children and employees receive appropriate chemoprophylaxis and clinical surveillance. Have the child care owner/director send a letter home to the parents notifying them of the situation and indicating the need for prophylactic treatment with rifampin. (See sample letter Page 17).

4-Make arrangements to provide chemoprophylaxis (usually rifampin in this case) to child care contacts. Prophylaxis must be given as soon as possible, therefore it is of vital importance to coordinate and collaborate the necessary information as soon as notification of an exposure has occurred. Provision of rifampin with dosage instructions will insure appropriate prophylaxis of all contacts.

Schools:
When a case of meningococcal disease occurs in a school (other than a child care center), it is not

necessary for school officials to send notices home to the parents of asymptomatic children to suggest that they seek prophylaxis. Such actions are unwarranted and are often responsible for creating community confusion and panic. In the event that rumors have been spreading among school children, their parents and the media, school officials might feel that it is necessary to inform the community. In this case the points important to make are:

1-There is case in the school; however, there is no outbreak and outbreaks are an exception nowadays

2-The classmates and other school children are NOT at higher risk of acquiring the disease than anyone else in the community

3-If anyone should experience flu-like signs and symptoms, they should be evaluated by a physician. More than likely these would be the results of an infection by some other microorganism.

4-Provide the Office of Public Health (OPH) phone number.

Chemoprophylaxis

Rifampin, ceftriaxone and ciprofloxacin are appropriate drugs for chemoprophylaxis in adults.

Ciprofloxacin administered to adults in a single oral dose also is effective in eradicating meningococcal carriage. A single 500-mg oral dose of ciprofloxacin is a reasonable alternative to the multidose rifampin regimen. It is often preferred because of its single dose administration. At present, ciprofloxacin is not recommended for people younger than 18 years of age, or for pregnant women and lactating women. A recent international consensus report has concluded that ciprofloxacin can be used for chemoprophylaxis of children when no acceptable alternative therapy is available.

Ceftriaxone given in a single intramuscular dose was administered (125 mg for children and 250 mg for adults) is as effective as oral rifampin. Ceftriaxone has the advantage of ease of administration, which increases compliance and is safe for use during pregnancy. Rifampin is not recommended for pregnant women.

Rifampin is administered twice daily for two days (600 mg every 12 hours for adults, 10 mg/kg of body weight every 12 hours for children older than one month of age and 5 mg/kg every 12 hours for infants younger than one month of age). Where mass prophylaxis has been used, rifampin-resistant strains have quickly developed. Between 10% to 25% of contacts treated with rifampin will eventually become recolonized with rifampin-resistant strains. Repeated and unjustified use of rifampin among medical personnel would result in increasing in-hospital circulation of rifampin resistant meningococci. Rifampin is the drug of choice for most children. It is not recommended during pregnancy; however, in tuberculosis patients who were pregnant and had received rifampin, no teratogenic effects were noted. Rifampin changes the color of urine to reddish-orange and is excreted in tears and other body fluids; it may cause permanent discoloration of soft contact lenses. Because the reliability of oral contraceptives may be affected by rifampin therapy, consideration should be given to using alternate contraceptive measures while rifampin is being administered (Table 2).

Table 2: Dosages, Age Groups and Duration for Rifampin, Ciprofloxacin and Ceftriaxone

Drug	Age Group	Dosage	Duration
Rifampin	Children <1mo	5mg/kg q12hr	2 days
	Children ≥1 mo	10mg/kg q12hr	2 days
	Adults	600mg q12hrs	2 days
Cipro	Adults >18yr	500mg	Stat
Ceftriaxone	Children <18 yr	125mg	Stat IM
	Adults	250mg	Stat IM

Some experts recommend a two-day course of azithromycin dihydrate, which has been shown to be effective for eradication.

The health department does not provide chemoprophylaxis to individuals and/or families. They should be referred to their private physician or charity hospital. In some instances, OPH may arrange to provide prophylaxis (Contact the Regional Medical Director).

Infected people are not considered contagious after 24 hours of appropriate antimicrobial therapy. After discharge from the hospital, they pose no risk to classmates and may return to school.

Chemoprophylaxis administered more than 14 days after onset of illness in the index case-patient is probably of limited or no value. Oropharyngeal or nasopharyngeal cultures are not helpful in determining the need for chemoprophylaxis and may unnecessarily delay institution of this preventive measure.

Contact During Flight

There are no changes to the infectiousness criterion for an airplane CI (the infectious period for a person with meningococcal disease is defined as seven days before onset until 24 hours after the start of appropriate antibiotics). For travelers with meningococcal disease who were not coughing or vomiting during the flight, the contact zone remains one seat on either side of the ill traveler (not crossing the aisle), and the eight-hour minimum "gate-to-gate" travel time remains in effect.

The 2017 changes to the meningococcal disease protocol only apply to cases in which the ill traveler was reported to have been coughing or vomiting during the flight. The contact zone for vomiting is determined based on the location of the traveler when vomiting occurred (i.e., the default assumption is that vomiting occurred in the seat, but if vomiting occurred in the aisle, then a zone in the area where the vomiting occurred would be included and may cross the aisle; vomiting that occurred in the bathroom does not change the contact zone). There is no minimum flight duration to trigger a CI.

In all cases where a meningococcal disease CI is warranted, additional exposure information obtained during the case investigation (e.g., the ill traveler changed seats during the flight) could justify modifying the contact zone. Airplane CIs will still be conducted up to 14 days after the flight exposure.

Outbreak Management

Since the early 1990s, outbreaks of meningococcal disease have occurred with increasing frequency in the United States. During July 1994 to June 2002, a total of 76 outbreaks were identified (annual median: ten; range: four to 16), including 48 (63%) outbreaks caused by serogroup C, 19 (25%) by serogroup B and nine (12%) by serogroup Y. These outbreaks occurred in 32 states and involved 247 patients (accounting for less than 2% of total cases of meningococcal disease in the U.S. during this period). Of the 76 outbreaks, 26 (34%) were community-based and accounted for 53% of all outbreak related cases. Of the 50 (65%) outbreaks that were organization-based: 13 **(**26%**)** occurred in colleges; 19 (38%) in primary and secondary schools; nine (18%**)** in nursing homes. Vaccination campaigns (using an average of 2,500 doses of MPSV4* per outbreak) were conducted in 34 outbreaks (30 of which were caused by serogroup C and four by serogroup Y).

The following only applies when there is an outbreak, NOT for a single case

Outbreaks are characterized by increased rates of disease among persons who may have a common organizational affiliation or who live in the same community, yet do not have close contact. An outbreak is defined by the occurrence of three or more confirmed, or probable cases of identical serogroup

**see page 12*

meningococcal disease during a period of less than or equal to three months, with a resulting primary attack rate of at least ten cases per 100,000 population. For calculation of this threshold, population-based rates are used and not age-specific attack rates. Outbreaks are extremely rare in Louisiana.

A primary case is a case that occurs in the absence of previous known close contact with another case-patient. A secondary case is defined as one that occurs among close contacts of a primary case-patient more than 24 hours after onset of illness in the primary case-patient. If two or more cases occur among a group of close contacts with onset of illnesses separated by less than 24 hours, these cases are considered to be co-primary.

Close contacts**.** Close contacts of a patient who has meningococcal disease include: 1) household members; 2) child-care center contacts; 3) persons directly exposed to the patient's oral secretions (e.g., by kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management).

An organization-based outbreak is defined as the occurrence of three or more confirmed or probable cases during a period of greater than or equal to three months in persons who have a common affiliation but no close contact with each other, resulting in a primary disease attack rate of at least ten cases per 100,000 persons. In instances where close contact has occurred, chemoprophylaxis should be administered to close contacts. Organization-based outbreaks have recently occurred in schools, universities and correctional facilities. Investigation of organization-based outbreaks may reveal even closer links between patients than suggested by initial reports.

A community-based outbreak is defined as the occurrence of three or more confirmed or probable cases during a period of less than or equal to three months among persons residing in the same area who are not close contacts of each other and who do not share a common affiliation, with a primary attack rate of at least ten cases per 100,000 population. Community-based outbreaks have occurred in towns, cities and counties. Distinguishing whether an outbreak is organization-based or community-based is complicated by the fact that, in some instances, these types of outbreaks may occur simultaneously.

The population at risk is defined as a group of persons who, in addition to close contacts, are considered to be at increased risk for meningococcal infection when compared with historical patterns of disease in the same population or with the risk for disease in the general U.S. population. This group is usually defined on the basis of organizational affiliation or community of residence. The population at risk is used as the denominator in calculations of the disease attack rate.

Attack Rate and Decision To Vaccinate: For a primary attack rate to be calculated, all confirmed cases of the same serogroup should be summed; secondary cases should be excluded and each set of co-primary cases counted as one case. Because attack rates are calculated both to characterize the risk for disease among the general population and to determine whether overall rates have increased, related cases (secondary and co-primary) should not be included. From an epidemiologic perspective, secondary and co-primary cases can be considered as representing single episodes of disease with direct spread to one or more close contact(s), which is consistent with endemic disease.

If three or more cases have occurred either in an organization, or a community-based outbreak **during a period of less than three months** (starting at the time of the first confirmed or probable case), a primary attack rate should be calculated. Because of the limited number of cases typically involved and the seasonal patterns of meningococcal disease (more cases occur during fall than other times of the year), rate calculations should not be annualized. The following formula is used to calculate attack rates:

$$\text{Attack rate per } 100{,}000 = \frac{\text{(Number of definite and probable cases during a three-month period)}}{\text{(Number of population at risk)} * 100{,}000}$$

Vaccination of the population at risk should be considered if the attack rate is greater than **ten cases per 100,000 persons.**

The actual attack rate at which the decision to vaccinate is made varies. Public health personnel should consider the following factors:

1) completeness of case reporting and number of possible cases of meningococcal disease for which bacteriologic confirmation or serogroup data are not available;

2) occurrence of additional cases of meningococcal disease after recognition of a suspected outbreak (e.g., if the outbreak occurred two months previously and if no additional cases have occurred, in which case vaccination might be unlikely to prevent additional cases of meningococcal disease);

3) logistic and financial considerations.

Serogroup B Outbreaks:

Meningitidis serogroup B accounts for approximately half of all meningococcal cases among persons aged 17-22 years in the U.S. and caused four more recent outbreaks (2015) in college settings. Two MenB vaccines, MenB-FHbp (Trumenba, Wyeth Pharmaceuticals, Inc.) and MenB-4C (Bexsero, Novartis Vaccines) were recently licensed in the United States. Although there are no current recommendations for general use of MenB vaccines, the Advisory Committee on Immunization Practices(ACIP) recommends use of MenB vaccines in persons aged older or equal to 10 years at increased risk for serogroup B meningococcal disease, including in outbreak settings. **The Center for Disease Control and Prevention's interim guidance suggests consideration of vaccination during outbreaks in which two or more primary cases of *N. meningitidis* serogroup B are reported in organizations of more than 5,000 persons within a six-month period**.

As part of the outbreak response, ciprofloxacin chemoprophylaxis should be provided to persons who are potentially exposed to oral secretions from either of primary case(s). Additionally provide education on signs and symptoms of meningococcal disease and safe hygiene practices to prevent transmission. If a vaccination campaign is indicated, the group designated to be administered vaccine is called the vaccination group. In some instances, the vaccination group will be the same as the population at risk; however, in other instances, these groups may differ. For example, in an organization-based outbreak at a university in which all cases have occurred among undergraduates rather than graduate students, faculty or other staff, undergraduates may be the vaccination group. In community-based outbreaks, cases often occur in persons within a narrow age range (e.g., only in persons younger than 30 years of age). Because the available vaccine is probably not effective in children younger than two years of age, these children are not usually included in the vaccination group; the vaccination group may be that portion of the population at risk who are two-to-29 years of age. For control of outbreaks, vaccination administered before or during the seasonal peak (i.e., fall and winter months) is more likely to prevent cases than vaccination administered during lower incidence periods (i.e., spring and summer).

Outbreak Control

Meningococcal vaccine is recommended for the control of outbreaks, which often affects older children and adults, for whom vaccination is effective. The benefit of vaccination for control of outbreaks is difficult to assess because the pattern of disease occurrence is unpredictable and the numbers of cases are usually small.

Outbreaks have occurred in organizations and communities.

In a community-based outbreak, identifying groups most likely to benefit from vaccination is more difficult because communities include a broad range of ages among whose risk for disease and vaccine efficacy vary. Thus, the recommendations for evaluation and management of organization-based and community-based outbreaks are considered separately.

Ten Steps to Control an Outbreak

1-Establish a diagnosis of meningococcal invasive disease

Only confirmed and probable cases should be considered in the characterization of a suspected outbreak. Cases not fulfilling these criteria should be excluded from consideration.

2-Administer chemoprophylaxis to appropriate contacts.

Chemoprophylaxis should be administered to close contacts of patients. Administering chemoprophylaxis to persons who are not close contacts of patients has not been effective in preventing community outbreak-associated cases and usually is not recommended. Neither oropharyngeal nor nasopharyngeal cultures for *N. meningitidis* are useful in deciding who should receive chemoprophylaxis, or when investigating suspected outbreaks.

3-Enhance surveillance, save isolates and review historical data.

OPH relies on passive surveillance for meningococcal disease, which may result in delayed or incomplete reporting of cases. When an outbreak is suspected, potential reporting sites (hospitals) should be alerted and encouraged to report new cases promptly. Reporting sites also should send all *N. meningitidis* isolates to the state laboratory until investigation of the suspected outbreak is completed. This action will ensure availability of isolates for confirmation of serogroup and application of other methods for subtyping. Information on the serogroup of *N. meningitidis* isolates is needed to fulfill criteria for confirmed and probable case definitions. This information should be obtained promptly with all meningococcal disease case reports.

Overall and serogroup-specific meningococcal disease rates for previous years in the same or comparable population(s) should be reviewed. These data should be compared with data currently reported for the population being evaluated to characterize both the geographic extent and magnitude of the outbreak.

4-Investigate links between cases.

In addition to demographic information, collect age-appropriate information concerning each patient (e.g., close contact with other case-patients, day care attendance, participation in social activities, participation in sports activities and affiliation with organizations). This information will help identify secondary and co-primary cases and also may reveal links between cases that will help define the population at risk.

5-Subtyping.

Subtyping of *N. meningitidis* isolates is done in Louisiana by using pulsed-field gel electrophoresis (PFGE) of enzyme-restricted DNA fragments. PFGE may provide information that will be useful in determining whether a group of cases represents an outbreak. Outbreaks usually are caused by closely related strains. Subtyping data can allow identification of an “outbreak strain” and aid in better defining the extent of an outbreak.

If strains from a group of patients are unrelated by subtyping, the group of cases most likely does not represent an outbreak. Although subtyping is potentially useful, it is time consuming and can be done only in specialized reference laboratories. In addition, results can sometimes be difficult to interpret. Initiation of outbreak-control efforts should not be delayed until subtyping results are available.

Exclude secondary and co-primary cases. To calculate a primary disease attack rate, all confirmed and probable cases should be summed; secondary cases should be excluded and each set of co-primary cases counted as one case. Because the purpose of calculating attack rates is both to characterize the risk for disease among the general population and to determine whether overall rates have increased, related cases (i.e., secondary and co-primary cases) should not be included. Epidemiologically, secondary and co-primary cases can be considered as representing single episodes of disease with direct spread to one or more close contact(s), which is consistent with endemic disease. Because the risk for acquiring meningococcal disease is 500 to 800 times greater among close contacts of case-patients than among the total population, chemoprophylaxis is recommended for these persons. Because secondary and co-primary cases occur infrequently, they should represent a small portion of outbreak-associated cases in the United States.

6-Determine if the suspected outbreak is organization- or community-based.

Epidemiologic and laboratory investigations can reveal common affiliations among case-patients. Potential affiliations can be organizational, with all or most of the patients attending a particular day care center, school, or university or belonging to a sports team or club. Alternatively, common affiliations can be geographic (e.g., residing in the same town, city, or county). Of the 21 U.S. outbreaks identified between 1980 and mid-1993, 11 (52%) were organization-based and ten (48%) were community-based. Eight (73%) of the 11 organization-based outbreaks occurred in schools. If a common organizational affiliation other than community can be identified, the outbreak is termed organization-based; otherwise, it is considered to be community-based.

7-Define population at risk and determine its size.

In organization-based outbreaks, cases are linked by a common affiliation other than a shared geographically delineated community. The population at risk is the group of persons who best represent that affiliation. For example, if the only association between patients was attending the same school or university, the population at risk would be all persons attending the school or university. Information concerning the size of the organization should be obtained from officials in the organization. In community-based outbreaks, there are no common affiliations among patients other than a shared, geographically defined community. The population at risk can be defined by the smallest geographically contiguous population that includes all (or almost all) case-patients. This population is usually a neighborhood, town, city, or county. The size of the population can be obtained from census information.

8-Calculate the attack rate.

If three or more cases have occurred in either an organization- or community-based outbreak in less than or equal to three months (starting at the time of the first confirmed or probable case), a primary disease attack rate should be calculated. Because of the small number of cases typically involved and the seasonal patterns of meningococcal disease, rate calculations should not be annualized for use in this algorithm. The following formula can be used to calculate this attack rate:

$$\text{Attack rate per } 100{,}000 = \frac{\text{(Number of definite and probable cases during a three-month period)}}{\text{(Number of population at risk)} * 100{,}000}$$

The actual attack rate at which the decision to vaccinate is made may vary. Public health personnel should consider the following factors:

a) completeness of surveillance and number of possible cases for which bacteriologic confirmation or serogroup data are not available;

b) occurrence of additional cases after recognition of a suspected outbreak (e.g., if the outbreak occurred two months previously and if no additional cases have occurred, vaccination may be unlikely to prevent additional cases);

c) logistic and financial considerations.

If an attack rate exceeds ten cases per 100,000 persons, vaccination of the population at risk should be considered.

9-Select the target group for vaccination.

In most organization-based outbreaks, the vaccination group may include the whole population at risk, provided all persons are older than two years of age. If a substantial proportion of patients are younger than two years of age and thus, not eligible to receive the current vaccine, patients younger than two years of age may be exclude, and if at least three case-patients remain, an attack rate should be recalculated. If after recalculation the attack rate is still more than ten cases per 100,000 persons, vaccination should be considered for some or all of the population at risk than is older than two years of age. In some organization-based outbreaks, a vaccination group larger than the population at risk may be designated. For example, in a high school in which all outbreak-associated cases occurred among students, authorities may decide to offer vaccine to staff. In community-based outbreaks, the vaccination group usually can be defined as a subset of the entire population at risk, based on a group older than two years of age (e.g.,

two- to-19 or two-to-29 years of age). This age range should contain all (or almost all) patients older than two years of age. If a large proportion of patients are younger than two years of age and probably will not be protected with the current vaccine, patients younger than two years of age may be excluded from calculation of an attack rate.

10-Select the target group for immunization

In some situations, the entire population older than two years of age, without other age restriction, might be the most appropriate vaccination group. For example, in a small town in which several cases have occurred among children older than two years of age and adults older than 29 years of age, it may be most appropriate to select all persons older than two years of age as the vaccination group. For larger populations, this decision would be costly in terms of finances and human resources; restricting the vaccination group to the persons in age groups with the highest attack rates may be more appropriate. Age-specific attack rates can be calculated by using the formula previously provided and restricting the numerator and denominator to persons within specific age groups (e.g., persons two- to-19 years of age). Many recent immunization programs have been directed at persons who are two-to-19 years of age or who are two-to-29 years of age.

Other Control Measures

Mass chemoprophylaxis (i.e., administration of antibiotics to large populations) **is not effective** in most settings in which community-based or organization-based outbreaks have occurred. Disadvantages of widespread administration of antimicrobial drugs for chemoprophylaxis include cost of the drug and administration, difficulty of ensuring simultaneous administration of chemoprophylactic antimicrobial drugs to large populations, side effects of the drugs and the emergence of resistant organisms. In most outbreak settings, these disadvantages outweigh the possible (and unproven) benefit in disease prevention. However, in outbreaks involving small populations (e.g., an outbreak in a small organization, such as a single school), administration of chemoprophylaxis to all persons within this population may be considered. If mass chemoprophylaxis is undertaken, it should be administered to all members at the same time.

In the United States, measures that have not been recommended for control of outbreaks include restricting travel to areas with an outbreak, closing schools or universities, or cancelling sporting or social events.

Educating communities, physicians and other health-care workers about meningococcal disease is an important part of managing suspected outbreaks.

Educational efforts should be initiated as soon as an outbreak is suspected.

Immunization

Meningococcal Tetravalent Polysaccharide Vaccine (MPSV)

MPSV4 is a tetravalent meningococcal polysaccharide vaccine (Menomune®-A, C, Y, W-135, manufactured by SanofiPasteur) available in the United States. Each dose consists of the four (A, C, Y, W-135) purified bacterial capsular polysaccharides. This vaccine has been used since the 1970s.

The immunogenicity and clinical efficacy of the serogroups A and C meningococcal vaccines have been well established. The serogroup A polysaccharide induces antibody response among certain children as young as three months of age, although a response comparable with that occurring in adults is not achieved until the age of four to five years; the serogroup C component is poorly immunogenic among recipients aged younger than 18 to 24 months. The serogroups A and C vaccines have demonstrated estimated clinical efficacies of greater than 85% among school-aged children and adults and are useful in controlling outbreaks. Serogroups Y and W-135 polysaccharides are safe and immunogenic among adults

and children older than two years of age. The antibody responses to each of the four polysaccharides in the tetravalent vaccine are serogroup specific and independent.

Persons whose spleens have been removed because of trauma, or nonlymphoid tumors and persons who have inherited complement deficiencies have acceptable antibody responses to polysaccharide meningococcal vaccine. 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 groups A and C polysaccharide. The clinical relevance of such hyporesponsiveness is unclear.

Duration of Protection: Among infants and children aged younger than five years, measurable levels of antibodies against groups A and C polysaccharides decreased substantially during the first three years after a single dose of vaccine; among healthy adults, antibody levels also decreased, but antibodies were still detectable less than ten years after vaccine administration.

Precautions and Contraindications: Meningococcal polysaccharide vaccines have been used extensively in mass vaccination programs as well as in the military and among international travelers. Adverse reactions to polysaccharide meningococcal vaccines are usually mild; the most frequent reaction is pain and redness at the injection site, lasting for one-to-two days. Estimates of the incidence of such local reactions have varied (range: 4% to 56%). Severe reactions to polysaccharide meningococcal vaccine are uncommon. The majority of studies report the rate of systemic allergic reactions (e.g., urticaria, wheezing, and rash) as zero-to-0.1 per 100,000 vaccine doses. Anaphylaxis has been documented among less than 0.1 per 100,000 vaccine recipients. Neurologic reactions (e.g., seizures, anesthesias and paresthesias) have also been observed infrequently.

Meningococcal Conjugate Vaccines: Advantages of Meningococcal Conjugate Vaccines

Bacterial polysaccharides, including those comprising the capsule of *N. meningitdis*, are T-cell–independent antigens. T-cell–independent antigens do not elicit a memory response; they stimulate mature B-lymphocytes but not T-lymphocytes, thus inducing a response that is neither long-lasting nor characterized by an anamnestic response after subsequent challenge with the same polysaccharide antigen.

Thus, meningococcal polysaccharide vaccines have inherent limitations. The serogroup C polysaccharide is poorly immunogenic among children younger than two years of age. The A polysaccharide induces antibody response in infants, but vaccine efficacy declines rapidly. Meningococcal polysaccharide vaccines do not confer long-lasting immunity; they also do not cause a sustainable reduction of nasopharyngeal carriage of *N. meningitdis* and therefore do not substantially interrupt transmission to elicit herd immunity. Finally, multiple doses of serogroups A and C polysaccharide vaccine might cause immunologic hyporesponsiveness to the groups A and C polysaccharide, although clinical implications of this phenomenon are unknown.

Conjugation (i.e., covalent coupling) of polysaccharide to a protein carrier that contains T-cell epitopes changes the nature of immune response to polysaccharide from T-cell– independent to T-cell–dependent, leading to a substantial primary response among infants and a strong anamnestic response at re-exposure. Both conjugate Hib and conjugate *S. pneumoniae* vaccines (introduced for mass infant immunization in the U.S. in 1990 and 2000, respectively) have reduced incidence of disease caused by vaccine preventable serotypes. In addition, both vaccines reduce asymptomatic carriage of respective bacteria, thus protecting unvaccinated persons through a herd immunity effect.

Meningococcal Tetravalent Conjugate Vaccine

MCV4 is a tetravalent meningococcal conjugate vaccine (Menactra™, manufactured by Sanofi Pasteur) that was licensed for use in the U.S. in 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.

Immunogenicity: Studies among U.S. military recruits conducted in the 1960s indicated that the absence of naturally acquired bactericidal antibodies, measured by a serum bactericidal antibody assay (SBA) using an intrinsic human complement source, was associated with susceptibility to meningococcal group C disease. SBA titers greater than four, using human serum as an exogenous complement source (hSBA), are considered the standard correlate of clinical protection against serogroup C meningococcal disease. In 1981, MPSV4 (Menomune®) was licensed in the U.S. on the basis of data on safety and immunogenicity. Immunogenicity of this vaccine was compared with that of the vaccine then licensed for use in the United States, A/C meningococcal polysaccharide vaccine, which had demonstrated 97% efficacy against serogroup A and 90% efficacy against serogroup C. The immunologic criterion used for licensing was a fourfold or greater rise in SBA among 90% of adults at three to four weeks after vaccination. As a result, in 2005, MCV4 (Menactra™) was licensed on the basis of findings indicating that it was not inferior to MPSV4 in terms of immunogenicity and safety (i.e., demonstrated non-inferiority). A primary criterion in determining immunogenic non-inferiority of the new vaccine was the percentage of vaccinees having a fourfold or greater increase in bactericidal antibody for MCV4 compared with MPSV4.

Routine Vaccination of Adolescents

In May 2005, the ACIP recommended routine vaccination of **young adolescents (aged 11 to 12 years) with MCV4 at the preadolescent health-care visit** (i.e., a visit to a health-care provider at age 11 to 12 years, at which time ACIP and other professional organizations recommend that persons aged 11 to 12 years receive appropriate vaccinations and other preventive services). Introducing a recommendation for MCV4 vaccination among persons 11 to 12 years of age might strengthen the role of the preadolescent health-care visit and have a positive effect on vaccine coverage during adolescence.

In June 2007, the ACIP recommended routine vaccination of **all persons aged 11 to 18 years** with one dose of MCV4 at the earliest convenience.

Other Populations at Increased Risk for Meningococcal Disease

Routine vaccination also is recommended for certain persons who have increased risk for meningococcal disease. Use of MCV4 is preferred among persons 11-to-55 years of age; however, use of MPSV4 is recommended among children two-to-ten years of age and persons older than 55 years of age. If MCV4 is unavailable, MPSV4 is an acceptable alternative for persons aged 11-to-55 years.

The following populations are at increased risk for meningococcal disease:

- college freshmen living in dormitories
- microbiologists who are routinely exposed to isolates of *N. meningitdis*
- military recruits
- persons who travel to or reside in countries in which *N. meningitdis* is hyperendemic or epidemic, particularly if contact with the local population will be prolonged
- persons who have terminal complement component deficiencies
- persons who have anatomic or functional asplenia.

Because of feasibility constraints in targeting freshmen in dormitories, colleges can elect to target their vaccination campaigns to all matriculating freshmen. The risk for meningococcal disease among non-freshmen college students is similar to that for the general population of similar age (age 18-to-24 years). However, the vaccines are safe and immunogenic and therefore can be provided to non-freshmen college students who want to reduce their risk for meningococcal disease.

For travelers, vaccination is especially recommended to 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. Advisories for travelers to

other countries will be issued when epidemics of meningococcal disease caused by vaccine-preventable serogroups are detected. Further information concerning geographic areas for which vaccination is recommended can be obtained from international health clinics for travelers and state health departments.

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

For persons 11-to-55 years of age who have been previously vaccinated with MPSV4, revaccination with MCV4 is not indicated unless vaccination occurred three-to-five years previously and the person still remains at increased risk for meningococcal disease.

Adults Aged 20-to-55 Years

MCV4 is licensed for use among adults 20-to-55 years of age. It is safe, immunogenic and likely to provide relatively long-lasting protection against meningococcal disease caused by serogroups A, C, Y and W-135. The rates of meningococcal disease are low in this age group; vaccination will decrease but not eliminate risk. Therefore, routine vaccination is not recommended; however, persons who wish to decrease their risk for meningococcal disease may elect to be vaccinated.

Children Younger Than 11 Years of Age and Adults Older Than 55 Years of Age

MCV 4 is not licensed for use among children less than 11 years of age or adults older than 55 years. Routine vaccination with MPSV4 is not recommended for children younger than two years old because it is relatively ineffective and offers a short duration of protection. Routine vaccination with MPSV4 is not recommended for children two-to-ten years old and adults older than 55 years who are not identified as being at increased risk for meningococcal disease.

Revaccination

Revaccination might be indicated for persons previously vaccinated with MPSV4 who remain at increased risk for infection (e.g., persons residing in areas in which disease is epidemic), particularly children who were first vaccinated when younger than four years of age. Such children should be considered for revaccination after two-to-three years if they remain at increased risk. Although the need for revaccination among adults and older children after receiving MPSV4 has not been determined, antibody levels decline rapidly after two-to-three years and if indications still exist for vaccination, revaccination might be considered after five years. Repeated vaccination with serogroup A and C polysaccharide vaccine might induce immunologic hyporesponsiveness, although clinical implications of such hyporesponsiveness are not known.

Hyporesponsiveness to serogroup C polysaccharide can be overcome by vaccination with serogroup C conjugate vaccine. MCV4 is recommended for revaccination of persons 11 to 55 years of age; however, use of MSPV4 is acceptable. ACIP expects that MCV4 will provide longer protection than MPSV4; however, studies are needed to confirm this assumption. More data will likely become available within the next five years to guide recommendations on revaccination for persons who were previously vaccinated with MCV4.

Precautions and Contraindications

Recommended vaccinations can be administered to persons with minor acute illness (e.g., diarrhea or mild upper respiratory tract infection with or without fever). Vaccination should be deferred for persons with moderate or severe acute illness until the person's condition improves. Vaccination with MCV4 or MPSV4 is contraindicated among persons known to have a severe allergic reaction to any component of the vaccine, including dipththeria toxoid (for MCV4), or to dry natural rubber latex. Any adverse effect suspected to be associated with MCV4 or MPSV4 vaccine should be reported to the Vaccine Adverse

Event Reporting System (VAERS). Because both MCV4 and MPSV4 are inactivated vaccines, they may be administered to persons who are immunosuppressed as a result of disease or medications; however, response to the vaccine might be less than optimal. Studies of vaccination with MPSV4 during pregnancy have not documented adverse effects among either pregnant women or newborns. On the basis of these data, pregnancy should not preclude vaccination with MPSV4, if indicated. MCV4 is safe and immunogenic among non-pregnant persons 11 to 55 years of age, but no data are available on the safety of MCV4 during pregnancy. Women of childbearing age who become aware that they were pregnant at the time of MCV4 vaccination should contact their health-care provider or the vaccine manufacturer.

Waterhouse–Friderichsen Syndrome (WFS)

Some bacterial or viral infections may lead to massive hemorrhage into one or (usually) both adrenal glands. It is characterized by overwhelming infection leading to massive blood invasion, organ failure, coma, low blood pressure and shock, disseminated intravascular coagulation (DIC) with widespread purpura, rapidly developing adrenocortical insufficiency and death.

This is more commonly found with meningococcal invasive disease but may also be encountered in:

- *Haemophilus influenzae*
- *Pseudomonas aeruginosa*
- *Streptococcus pneumoniae* infections, a common bacterial pathogen typically associated with meningitis in the adult and elderly population.
- *Mycobacterium tuberculosis* could also cause WFS. Tubercular invasion of the adrenal glands could cause hemorrhagic destruction of the glands and cause mineralocorticoid deficiency.
- *Staphylococcus aureus* has recently also been implicated in pediatric WFS
- Cytomegalovirus can cause adrenal insufficiency, especially in the immunocompromised.

FOR DAY CARE CENTERS, (NOT FOR ELEMENTARY OR SECONDARY SCHOOLS)

Dear Parent,

Meningococcal meningitis is a bacterial infection that leads to the inflammation of the spinal cord and/or brain. The Louisiana Office of Public Health is aware of one probable case of meningococcal meningitis diagnosed in a child at the _____Day Care Center.

In accordance with the guidelines established by the Centers for Disease Control and Prevention and the American Academy of Pediatrics, the Louisiana Office of Public Health recommends that all children attending _____ Day Care Center receive antibiotic prophylaxis in order to reduce the risk of developing disease.

While antibiotic prophylaxis has been demonstrated to substantially decrease the risk of contracting meningococcal disease, it remains important for parents and guardians to observe their children for signs of illness. If your child complains of or develops any of the following symptoms, please seek medical advice:

- Fever
- Sore throat
- Nausea and vomiting
- Loss of appetite
- Lethargy (sluggishness, confusion, fatigue)
- Headaches
- Stiff neck
- Flat red rash on the trunk of body or extremities
- Intolerance to light and/or sound

The attached information sheet may address some of your questions and concerns. You may also contact the Office of Public Health at 1-800-256-2748 or the regional public health office at (___) ___-____, for any additional questions you might have. Please sign the form below and return it to the _____ Day Care director.

……

I have received the meningococcal disease notification and prophylaxis recommendations provided by the _____ Day Care Center and the Louisiana Office of Public Health.

Date _____

Parent's Signature _____