Meningococcal Disease

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Meningococcal disease is an acute, severe illness caused by the bacterium *Neisseria meningitidis*. A leading cause of bacterial meningitis and sepsis in the United States, *N. meningitidis* can also cause pneumonia and focal disease, such as septic arthritis. As of August 2020, five meningococcal vaccines are licensed and available in the United States: three quadrivalent (serogroups A, C, W, and Y) conjugate meningococcal vaccines and two recombinant serogroup B vaccines.

Meningococcal Disease

- A leading cause of bacterial meningitis and sepsis in U.S.
- As of August 2020, five meningococcal vaccines licensed in U.S.

Neisseria meningitidis

N. meningitidis, or meningococcus, is an aerobic, gram-negative bacterium, closely related to *N. gonorrhoeae* and to several typically nonpathogenic *Neisseria* species, such as *N. lactamica*.

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

Meningococci are classified into serogroups based on the structure of the polysaccharide capsule. Twelve antigenically and chemically distinct polysaccharide capsules have been described and the polysaccharide capsule determines the serogroup labeling. Almost all reported cases of invasive disease worldwide are caused by one of six serogroups: A, B, C, W, X, and Y. The relative importance of each serogroup depends on factors such as geographic location and patient age. Some strains are nongroupable and do not express capsule; these strains are most commonly associated with asymptomatic nasopharyngeal carriage rather than invasive disease.

Neisseria meningitidis

- Aerobic, gram-negative bacterium
- Outer membrane surrounded by polysaccharide capsule important for pathogenicity
- 12 antigenically and chemically distinct polysaccharide capsules that determine serogroup labeling have been described
- Almost all invasive disease caused by serogroups A, B, C, W, X, and, Y
- Relative importance of serogroups depends on factors such as geographic location and age

Pathogenesis

Meningococci are transmitted person-to-person by respiratory droplets or secretions from persons with asymptomatic colonization or meningococcal disease. The bacteria attach to and multiply in the mucosal cells of the nasopharynx and oropharynx and, in a small proportion (much less than 1%) of persons, penetrate the mucosal cells and enter the bloodstream. The bacteria can then spread through the blood to cause systemic disease and cross the blood-brain barrier into the cerebrospinal fluid (CSF) to cause meningitis.

Meningococcal Disease Pathogenesis

- Bacteria attach to and multiply in nasopharynx and oropharynx
- In <1% of persons, bacteria enter bloodstream
  - Can cause systemic disease and meningitis

Meningococcal Disease Clinical Features

- Incubation period 3 to 4 days (range, 1 to 10 days)
- Meningitis is the most common presentation of invasive disease (~50% of U.S. cases)
  - Sudden onset of fever, headache, stiff neck, nausea, vomiting, photophobia, altered mental status
- Meningococcal septicemia (30% of cases)
  - Abrupt onset of fever, chills, cold hands and feet, severe aches or pain, vomiting, diarrhea, rash
- Bacteremic pneumonia (15% of cases)
- Meningococci occasionally cause noninvasive infections
- Risk factors for invasive disease
  - Persistent complement component deficiencies
  - Functional or anatomic asplenia
  - HIV infection
  - Travel to or residence in a country where disease is hyperendemic or epidemic
  - Exposure during an outbreak
  - Microbiologists who routinely work with isolates of *N. meningitidis*
  - Household crowding
  - Smoking
  - Antecedent viral upper respiratory infection

Clinical Features

The incubation period of meningococcal disease is typically 3 to 4 days, with a range of 1 to 10 days. Meningitis is the most common presentation of invasive meningococcal disease and is found in about 50% of cases in the United States. Symptoms are similar to those seen in other forms of bacterial meningitis, and typically include sudden onset of fever, headache, and stiff neck, often accompanied by other symptoms, such as nausea, vomiting, photophobia (eye sensitivity to light), and altered mental status. Meningococci can be isolated from the blood in up to 75% of persons with meningitis.

Meningococcal septicemia (bloodstream infection or meningococcemia) occurs without meningitis in about 30% of invasive meningococcal infections. This condition is characterized by abrupt onset of fever; chills; cold hands and feet; severe aches or pain in the muscles, joints, chest, or abdomen; vomiting; diarrhea; and a petechial or purpuric rash often associated with hypotension, shock, acute adrenal hemorrhage, and multiorgan failure. An additional 15% of U.S. cases present with bacteremic pneumonia; this is the most common presentation in adults over 65 years of age. Other syndromes involving isolation of meningococci from normally sterile body sites, such as septic arthritis, can also occur.

Meningococci also occasionally cause noninvasive infections such as conjunctivitis or urethritis. Noninvasive illness due to meningococci is not nationally notifiable and the incidence is unclear. Throughout this chapter, risk factors and demographics described apply only to invasive, reportable meningococcal disease cases and the term *meningococcal disease* refers to *invasive meningococcal disease*. The overall case-fatality ratio of meningococcal disease is 10% to 15%, even with appropriate antibiotic therapy, and can be higher in persons with meningococcemia. As many as 20% of survivors have permanent sequelae, such as hearing loss, neurologic damage, or loss of a limb.

In the United States, incidence of meningococcal disease is highest among infants younger than age 1 year, followed by children age 1 through 4 years. A second peak of disease incidence is found in young adults 17 through 21 years of age. Incidence increases again in adults older than 85 years of age.

Risk factors for the development of meningococcal disease include persistent complement component deficiencies (including use of a complement component inhibitor, eculizumab [Soliris®] or ravulizumab-cwvz [Ultomiris]), functional or anatomic asplenia, HIV infection, travel to or residence in a country where meningococcal disease is hyperendemic or epidemic, and exposure during an outbreak of meningococcal disease. Microbiologists who routinely work with isolates of *N. meningitidis* are also at risk. In

addition, household crowding, active and passive smoking, and antecedent viral upper respiratory infection have been associated with meningococcal disease transmission.

Laboratory Testing

Meningococcal disease is diagnosed by culture of *N. meningitidis* from a normally sterile site (e.g., blood, CSF) or purpuric lesions. Meningococcal disease may also be diagnosed through detection of *N. meningitidis*-specific nucleic acid in a specimen obtained from a normally sterile site using a validated polymerase chain reaction (PCR) assay. Although culture remains the gold standard for diagnosis of meningococcal disease, PCR is useful for detection of *N. meningitidis* from clinical samples, particularly when a patient was treated with antibiotics prior to specimen collection. Identification of gram-negative diplococci identified in a sterile site specimen strongly suggests *N. meningitidis* but is not confirmatory.

Once the diagnosis of meningococcal disease has been confirmed, the serogroup should be identified through slide agglutination or real-time PCR. Laboratories that cannot perform serogrouping should transfer the isolate or specimen to a reference laboratory, such as their state public health laboratory. Several new commercial multiplex PCR assays capable of simultaneously testing a single specimen for an array of pathogens have become available (e.g., FilmArray® Blood Culture Identification Panel and FilmArray® Meningitis/Encephalitis Panel by PCR from ARUP Laboratories). While these assays can rapidly identify *N. meningitidis* species, most do not determine serogroup. Thus, laboratories should continue to perform simultaneous culture and use validated, specific, real-time PCR assays capable of detecting and differentiating meningococcal serogroups. Otherwise, additional steps need to be taken, including performing a reflex culture or, at a minimum, retaining a clinical specimen for further testing at a public health laboratory.

Molecular typing using whole genome sequencing (WGS) can provide useful epidemiologic information, particularly if an outbreak of meningococcal disease is suspected.

Serologic testing (e.g., enzyme immunoassay) for antibodies to meningococcal antigens is not validated for clinical use in the United States. Serologic testing should not be used to establish the diagnosis of meningococcal disease or to determine whether a patient should receive a meningococcal vaccination.

Medical Management

Empiric therapy with broad-spectrum antibiotics (including a third-generation cephalosporin) should be started promptly when meningococcal disease is suspected, ideally after appropriate cultures are obtained.

Once *N. meningitidis* infection has been confirmed, treatment may be continued with penicillin, ampicillin, cefotaxime, or ceftriaxone. However, because there have been recent reports of penicillin-resistant, β-lactamase-producing *N. meningitidis* serogroup Y cases in the United States, healthcare providers should ascertain susceptibility of meningococcal isolates to penicillin before using penicillin or ampicillin for treatment.

Antimicrobial Chemoprophylaxis

Antimicrobial Chemoprophylaxis

- Primary means for prevention of sporadic meningococcal disease
- Close contacts of infected persons: Household members, childcare center contacts, anyone directly exposed to patient's oral secretions during the 7 days before symptom onset
- Administer as soon as possible, ideally less than 24 hours after identification of index patient

In the United States, the primary means for prevention of sporadic meningococcal disease is antimicrobial chemoprophylaxis of close contacts of infected persons. Close contacts include household members, childcare center contacts, and anyone directly exposed to the patient's oral secretions (e.g., through kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management) during the 7 days before symptom onset. Healthcare personnel should receive chemoprophylaxis if they were managing an airway or were exposed to respiratory secretions of a patient with meningococcal disease.

For travelers, antimicrobial chemoprophylaxis should be considered for any passenger who had direct contact with respiratory secretions from an index patient or for anyone seated directly next to an index patient on a prolonged flight (i.e., one lasting more than 8 hours), or within one seat in any direction on a flight of any duration if the index patient was coughing or vomiting on the flight. Any case of meningococcal disease in a person who has recently traveled should be reported to the local quarantine station to determine whether an air travel contact investigation is indicated.

Chemoprophylaxis is not recommended for close contacts of patients with evidence of *N. meningitidis* only in nonsterile sites (e.g., oropharyngeal, endotracheal, conjunctival). Reports of secondary cases after close contact with persons with noninvasive pneumonia or conjunctivitis are rare; there is no evidence of substantive excess risk. Furthermore, there is no indication to treat persons who are asymptomatic nasopharyngeal carriers.

Because the rate of secondary disease for close contacts is highest immediately after onset of disease in the index patient, antimicrobial chemoprophylaxis should be administered as soon as possible, ideally less than 24 hours after identification of the index patient. Conversely, chemoprophylaxis administered

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

Rifampin, ciprofloxacin, and ceftriaxone are 90% to 95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are all acceptable antimicrobial agents for chemoprophylaxis. Because there have been recent reports of ciprofloxacin-resistant, β-lactamase-producing *N. meningitidis* serogroup Y cases in the United States, clinicians and public health staff should consider obtaining antimicrobial susceptibility testing of meningococcal isolates to inform prophylaxis decisions if their state has reported a case of meningococcal disease caused by ciprofloxacin-resistant strains within the past 2 years. Clinicians should report suspected chemoprophylaxis failures to their public health departments. Systemic antimicrobial therapy for meningococcal disease with agents other than ceftriaxone or other third-generation cephalosporins might not reliably eradicate nasopharyngeal carriage of *N. meningitidis*. If other agents have been used for treatment, the patient should receive chemoprophylactic antibiotics for eradication of nasopharyngeal carriage before being discharged from the hospital.

Epidemiology

Occurrence

Meningococcal disease occurs worldwide. Incidence rates vary by serogroup and geography.

Reservoir

Humans are the only natural reservoir of meningococcus. At any given time, about 10% of adolescents and adults are asymptomatic nasopharyngeal carriers of *N. meningitidis*. Many of these carried strains are nongroupable (not encapsulated) and unlikely to cause disease in most people.

Transmission

Primary mode is by respiratory droplet spread or by direct contact with respiratory secretions.

Temporal Pattern

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

Meningococcal Disease Epidemiology

- Reservoir
  - Human
- Transmission
  - Respiratory droplets or direct contact with respiratory secretions
- Temporal pattern
  - Peaks in late winter and early spring
- Communicability
  - Generally limited

Communicability

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

Meningococcal Disease Secular Trends in the United States

- In 2018, 329 total cases reported (0.10 per 100,000 population)
- Serogroups B and C major causes of meningococcal disease
- Proportion of cases caused by each serogroup varies by age group
- Outbreaks account for 5% of reported cases

Secular Trends in the United States

Incidence of meningococcal disease in the United States has declined annually following a peak in the late 1990s. In 2018, 329 total cases were reported in the United States, representing an incidence of 0.10 per 100,000 population. Serogroups B and C are the major causes of meningococcal disease in the United States, each being responsible for approximately 25% to 40% of cases; serogroups W and Y, along with nongroupable meningococci, are each responsible for another 5% to 15%. The proportion of cases caused by each serogroup varies by age group. Approximately 60% of disease among children and young adults under 24 years of age is caused by serogroup B. In particular, among individuals 18 to 24 years of age, college students have more than three times the risk of serogroup B meningococcal disease as similarly aged people not attending college. Meanwhile, serogroups C, W, or Y cause about 60% of all cases of meningococcal disease among persons 24 years of age and older.

In the United States, meningococcal outbreaks account for about 5% of reported cases (i.e., 95% of cases are sporadic). An outbreak is defined as 2–3 outbreak-associated cases (e.g., cases of the same serogroup unless found to be genetically unrelated by molecular typing methods) in an organization (e.g., school, college, correctional facility) during a three-month period, or multiple outbreak-associated cases with an incidence of meningococcal disease that is above the expected incidence in a community during a three-month period. During 2010 through 2018, multiple serogroup B outbreaks among university students and serogroup C outbreaks among men who have sex with men were reported. Other communities and organizations, including populations experiencing homelessness and correctional facilities, also experienced outbreaks during this time.

Meningococcal Vaccines

Characteristics

Meningococcal Polysaccharide Vaccine

As of 2017, meningococcal polysaccharide vaccine (Menomune) is no longer available in the United States.

Quadrivalent Meningococcal Conjugate (Serogroups A, C, W, Y) Vaccines

Three quadrivalent meningococcal conjugate vaccines are licensed for use in the United States: MenACWY-D (Menactra), MenACWY-CRM (Menveo), and MenACWY-TT (MenQuadfi). The combination Hib and bivalent meningococcal conjugate vaccine, Hib-MenCY (MenHibrix), is no longer available in the United States.

Menactra is approved for use in persons age 9 months through 55 years, Menveo is approved for use in persons age 2 months through 55 years, and MenQuadfi is approved for use in persons age 2 years or older. Menveo is prepared using media containing yeast extracts. Quadrivalent meningococcal conjugate vaccines are administered by intramuscular injection and do not contain an adjuvant, antibiotic, or preservative, although formaldehyde is added during the manufacturing process.

Serogroup B Meningococcal Vaccines

Two recombinant serogroup B meningococcal (MenB) vaccines are licensed for use in the United States: MenB-FHbp (Trumenba) and MenB-4C (Bexsero).

Trumenba and Bexsero are approved for use in persons age 10 through 25 years and are administered by intramuscular injection. Each dose of Trumenba and Bexsero contain aluminum as an adjuvant. Bexsero contains kanamycin as an antibiotic. Neither Trumenba nor Bexsero contain a preservative. The tip caps of prefilled syringes of Bexsero contain latex.

Meningococcal Vaccines

- Quadrivalent Meningococcal Conjugate Vaccines
  - MenACWY-D (Menactra)
  - MenACWY-CRM (Menevo)
  - MenACWY-TT (MenQuadfi)
- Serogroup B Meningococcal Vaccines
  - MenB-FHbp (Trumenba)
  - MenB-4C (Bexsero)

Meningococcal Vaccine Characteristics

- Quadrivalent Meningococcal Conjugate Vaccines
  - Administered by intramuscular injection
  - Do not contain an adjuvant, antibiotic, or preservative
- Serogroup B Meningococcal Vaccines
  - Administered by intramuscular injection
  - Contain aluminum as an adjuvant
  - MenB-4C (Bexsero) contains kanamycin as an antibiotic and its prefilled syringes contain latex

Vaccination Schedule And Use

Meningococcal Conjugate Vaccines

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with MenACWY vaccine for all adolescents at age 11 through 18 years, with the first dose at age 11 or 12 years and a booster dose at age 16 years. For adolescents who receive the first dose at age 13 through 15 years, a one-time booster dose should be administered, preferably at age 16 through 18 years. Healthy persons who receive their first routine dose of MenACWY vaccine at or after age 16 years do not need a booster dose unless they become at

Meningococcal Vaccination Schedule

- Quadrivalent Meningococcal Conjugate Vaccines
  - 1 dose at age 11 or 12 years
  - Booster dose at age 16 years
  - Healthy persons who receive first dose at or after age 16 years do not need a booster dose unless they become at increased risk for meningococcal disease
  - Schedule for persons at increased risk for meningococcal disease varies by risk group and age (see tables)
- Serogroup B Meningococcal Vaccines
  - Recommended for persons age 10 years or older who are at increased risk of serogroup B meningococcal disease (see tables)
    - 2-dose series of Bexsero at 0 and 1 month or
    - 3-dose series of Trumenba at 0, 1–2, and 6 months
  - Shared clinical decision making for adolescents age 16 through 23 years

increased risk for meningococcal disease. Routine vaccination of healthy persons who are not at increased risk for meningococcal disease is not recommended after age 21 years.

ACIP also recommends vaccination for persons age 2 months or older at increased risk for meningococcal disease due to serogroups A, C, W, or Y. This recommendation includes:

- Persons with persistent complement component deficiencies, including persons taking eculizumab or ravulizumab-cwvz
- Persons who have functional or anatomic asplenia, including sickle cell disease
- Persons with HIV infection
- Microbiologists who are routinely exposed to isolates of *N. meningitidis*
- Persons identified by public health officials to be at increased risk during a meningococcal disease outbreak due to serogroup A, C, W, or Y
- Persons who travel to or reside in countries where meningococcal disease is endemic or hyperendemic, including the "meningitis belt" of sub-Saharan Africa or the Kingdom of Saudi Arabia during the annual Hajj and Umrah pilgrimages

Infants and children who received Hib-MenCY and are traveling to areas with high endemic rates of meningococcal disease are not protected against serogroups A and W and should receive age-appropriate MenACWY vaccine.

MenQuadfi, but not Menactra or Menveo, is licensed for use in adults age 56 years or older. However, any of these vaccines can be used to vaccinate people in this age group who are recommended to receive quadrivalent meningococcal vaccine because of increased risk for meningococcal disease.

In children at increased risk for meningococcal disease, Menactra should be given either before or at the same time as DTaP to avoid interference with the immune response to meningococcal vaccine. In addition, because of the high risk for invasive pneumococcal disease, children with functional or anatomic asplenia or HIV infection should not be vaccinated with Menactra before age 2 years to avoid interference with the immune response to pneumococcal conjugate vaccine (PCV13). If Menactra is used in persons of any age with asplenia or HIV, it should not be administered until at least 4 weeks after completion of all PCV13 doses. There are no similar constraints on Menveo or MenQuadfi administration. Booster vaccination is recommended for persons who remain at increased risk of meningococcal disease. If the most recent dose was received at younger than 7 years, a booster dose should be given after

3 years. If the most recent dose was received at age 7 years or older, a booster dose should be administered after 5 years and every 5 years thereafter as long as the person remains at increased risk for meningococcal disease.

Menactra, Menveo, or MenQuadfi can be administered at the same visit as other indicated vaccines with one exception. In persons with anatomic or functional asplenia and/or HIV infection, Menactra and pneumococcal conjugate vaccine (PCV13) should not be administered simultaneously.

If the liquid C-W-Y component of Menveo is administered alone (without using it to reconstitute the lyophilized A component), revaccination may not be needed. Serogroup A disease is rare in the United States, so revaccination is not necessary if the person does not plan to travel outside the United States. However, the person should be revaccinated with a properly reconstituted dose of Menveo, or a dose of Menactra or MenQuadfi if they are traveling internationally, especially if traveling to Africa. There is no minimum interval between the incomplete dose given in error and the repeat dose.

Serogroup B Meningococcal Vaccines

ACIP recommends MenB vaccine for persons 10 years of age or older who are at increased risk of serogroup B meningococcal disease. This recommendation includes persons with persistent complement component deficiencies, including persons taking eculizumab or ravulizumab; persons who have anatomic or functional asplenia, including sickle cell disease; microbiologists who are routinely exposed to isolates of *N. meningitidis*; or anyone identified by public health officials to be at increased risk because of a serogroup B meningococcal disease outbreak. In persons at increased risk for serogroup B meningococcal disease, ACIP recommends either a 2-dose series of Bexsero at 0 and 1 month (or longer), or a 3-dose series of Trumenba at 0, 1 to 2, and 6 months. See the tables on pages 241-242 for details on ACIP MenB vaccine recommendations for persons at increased risk for meningococcal disease. If the second dose of Bexsero or Trumenba dose is given earlier than the recommended interval, then the dose should be repeated at least 4 weeks after the last dose. However, if the second dose of Trumenba is administered at an interval of 6 months or more, a third dose does not need to be administered. If the third dose of Trumenba is administered earlier than 4 months after the second dose, the dose should be repeated at least 4 months after the last dose.

ACIP also recommends adolescents age 16 through 23 years receive MenB vaccine for short-term protection against most strains of serogroup B meningococcal disease based on shared clinical decision-making. The preferred age for vaccination is 16 through 18 years. In healthy adolescents, either a 2-dose series of Bexsero at 0 and 1 month (or longer) or a 2-dose series of

Trumenba at 0 and 6 months may be used. If the second dose of Bexsero is given earlier than the recommended interval, the dose should be repeated at least 4 weeks after the last dose. If the second dose of Trumenba is administered earlier than 6 months after the first dose, a third dose should be administered at least 4 months after the second dose.

Persons who have completed a MenB primary series and who become or remain at increased risk for meningococcal disease are recommended to receive booster vaccination. For persons 10 years of age or older with complement deficiency, complement inhibitor use, asplenia, or who are microbiologists routinely exposed to isolates, ACIP recommends a booster dose one year following completion of a MenB primary series followed by booster doses every 2 to 3 years thereafter, for as long as increased risk remains. For persons 10 years of age or older determined by public health officials to be at increased risk during a serogroup B outbreak, ACIP recommends a one-time booster dose if it has been at least one year since completion of the primary series. (A booster interval of at least six months may be considered by public health officials depending on the specific outbreak, vaccination strategy, and projected duration of elevated risk). Serogroup B meningococcal vaccine may be administered simultaneously or at any interval with other live or inactivated vaccines, including meningococcal conjugate vaccines.

Trumenba and Bexsero are not interchangeable. The same serogroup B meningococcal vaccine brand must be used for all doses of the series. If doses of both brands have been

administered to the same patient, the provider should ensure that the patient receives a complete series of either brand and ignore any doses of the other brand. The next dose of the selected brand should be given no sooner than the recommended interval after the previous dose of the same brand AND at least 4 weeks after the last (or only) dose of the other brand.

ACIP meningococcal vaccine recommendations for persons at increased risk for meningococcal disease (age 2 through 23 months)

Age	Risk Group	MenACWY primary series	MenACWY booster dose	MenB vaccine recommendation*	MenB booster dose*
2–23 months	• Asplenia • HIV infection	Menactra: Not recommended MenQuadfi: Not recommended Menveo: • 1st dose at 8 weeks: 4-dose series at 2, 4, 6, and 12 months • 1st dose at 7–23 months: 2 doses at least 12 weeks apart, with 2nd dose at age 1 year or older	Recommended for individuals at continued risk.†	No recommendation	No recommendation
	• Complement deficiency • Outbreak • Travel	MenQuadfi: Not recommended Menactra: • 9–23 months: 2 doses at least 12 weeks apart *or* Menveo: • 1st dose at 8 weeks: 4-dose series at 2, 4, 6, and 12 months • 1st dose at 7–23 months: 2 doses at least 12 weeks apart, with 2nd dose at age 1 year or older	Recommended for individuals at continued risk.†	No recommendation	No recommendation

*Note that MenB-FHbp and MenB-4C are not interchangeable; the same vaccine should be used for all doses, including booster doses.

†Revaccination with meningococcal conjugate vaccine is recommended after 3 years for children who received their last dose at <7 years of age. Revaccination is recommended after 5 years for people who received their last dose at ≥7 years of age, and every 5 years thereafter for people at continued risk.

ACIP meningococcal vaccine recommendations for persons at increased risk for meningococcal disease (age 2 through 9 years)

Age	Risk Group	MenACWY primary series	MenACWY booster dose	MenB vaccine recommendation*	MenB booster dose*
2–9 years	• Asplenia[†] • HIV infection[†] • Complement deficiency	2 doses at least 8 weeks apart	Recommended for individuals at continued risk.[§]	No recommendation	No recommendation
	• Outbreak • Travel	1 dose	Recommended for individuals at continued risk.[§]	No recommendation	No recommendation

*Note that MenB-FHbp and MenB-4C are not interchangeable; the same vaccine should be used for all doses, including booster doses.

[†]Menactra must be administered at least 4 weeks after completion of PCV13 series.

[§]Revaccination with meningococcal conjugate vaccine is recommended after 3 years for children who received their last dose at <7 years of age. Revaccination is recommended after 5 years for people who received their last dose at ≥7 years of age, and every 5 years thereafter for people at continued risk.

ACIP meningococcal vaccine recommendations for persons at increased risk for meningococcal disease (age 10 years or older)

Age	Risk Group	MenACWY primary series	MenACWY booster dose	MenB vaccine recommendation*	MenB booster dose*
≥10 years	• Asplenia[†] • Complement deficiency	2 doses at least 8 weeks apart	Recommended for individuals at continued risk.[§]	Trumenba: 3-dose series at 0, 1–2, and 6 months or Bexsero: 2-dose series at least 1 month apart	For individuals who remain at increased risk of serogroup B disease, a single dose of MenB vaccine is recommended 1 year after completion of the primary vaccination series and every 2-3 years thereafter
	HIV infection[†]	2 doses at least 8 weeks apart	Recommended for individuals at continued risk.[§]	No recommendation	No recommendation
	Microbiologist	1 dose	Recommended for individuals at continued risk.[§]	Trumenba: 3-dose series at 0, 1–2, and 6 months or Bexsero: 2-dose series at least 1 month apart	For individuals who remain at increased risk of serogroup B disease, a single dose of MenB vaccine is recommended 1 year after completion of the primary vaccination series and every 2-3 years thereafter
	Outbreak	1 dose	Recommended for individuals at continued risk.[§]	Trumenba: 3-dose series at 0, 1–2, and 6 months or Bexsero: 2-dose series at least 1 month apart	For individuals who were previously vaccinated and identified as being at increased risk during an outbreak, a single dose of MenB vaccine is recommended if it has been ≥1 year since MenB primary series completion (≥6 month interval might also be considered by public health professionals).
	Travel	1 dose	Recommended for individuals at continued risk.[§]	No recommendation	No recommendation

*Note that MenB-FHbp and MenB-4C are not interchangeable; the same vaccine should be used for all doses, including booster doses.

[†]Menactra must be administered at least 4 weeks after completion of PCV13 series.

[§]Revaccination with meningococcal conjugate vaccine is recommended after 3 years for children who received their last dose at <7 years of age. Revaccination is recommended after 5 years for people who received their last dose at ≥7 years of age, and every 5 years thereafter for people at continued risk.

Immunogenicity and Vaccine Effectiveness

Meningococcal Conjugate Vaccines

In clinical trials, the immunogenicity of MenACWY vaccines was assessed as seroconversion rates, defined as achieving a seroresponse at a predefined serum bactericidal antibody level for each serogroup, or the proportion of participants with a fourfold or greater increase in bactericidal antibody to each serogroup. An evaluation of MenACWY-D effectiveness (VE) in U.S. adolescents demonstrated that the overall effectiveness is 69% (51 to 80%). Effectiveness was 77% (57 to 88%) for serogroup C and 51% (1 to 76%) for serogroup Y. Effectiveness waned over time; VE was 79% (49 to 91%) within 1 year of vaccination, 69% (44 to 83%) 1 to 2 years after vaccination, and 61% (25 to 79%) 3 to 8 years after vaccination. These results, along with antibody persistence data showing waning immunity 3 to 5 years following a single dose, informed the ACIP recommendation for a booster dose in adolescents at age 16 years following a primary dose at age 11 or 12 years.

Serogroup B Meningococcal Vaccines

For both Trumenba and Bexsero, antibody responses were measured by serum bactericidal activity using human complement against selected meningococcal serogroup B strains. Immunogenicity was assessed as the proportion of subjects who achieved a fourfold or greater increase in serum bactericidal activity using human complement (hSBA) titer for each of the serogroup B strains tested, and the proportion of subjects who achieved a titer greater than or equal to the lower limit of quantification of the assay for all strains (composite response).

In a multicenter study conducted among adolescents age 11 to 17 years in the United States, 81% of subjects who received Trumenba and concomitant quadrivalent HPV vaccine (4vHPV) had a composite response, and 84% of subjects who received Trumenba with saline had a composite response.

In a randomized, controlled trial in the United Kingdom among college students age 18 to 24 years, 88% of recipients of both doses of Bexsero had a composite response at one month following the second dose. At 11 months after the second dose, 66% of recipients had a composite response. In a randomized, controlled trial in Australia and Canada among adolescents age 11 to 17 years, 63% of recipients had a composite response one month after the second dose.

Meningococcal Vaccine Efficacy

- Quadrivalent Meningococcal Conjugate Vaccines
  - 69% effective in U.S. adolescents
  - Effectiveness wanes over time
- Serogroup B Meningococcal Vaccines
  - Multicenter study demonstrated 84% of adolescents receiving Trumenba with saline had composite response
  - In a randomized, controlled trial 88% of college students receiving 2 doses of Bexsero had a composite response after 1 month; 66% at 11 months

Meningococcal Vaccines Contraindications and Precaution

- Contraindication
  - Severe allergic reaction to vaccine component or following prior dose
  - Severe allergic reaction after any of the following*:
    - A previous dose of Menactra, Menveo, or MenQuadfi
    - Any component of Menactra, Menveo, or MenQuadfi vaccines
    - Any other meningococcal, diphtheria toxoid-, tetanus toxoid-, or CRM_{197}-containing vaccine
- Precaution
  - Moderate or severe acute illness
  - Latex sensitivity (Bexsero only)

*Contraindication for MenACWY vaccines

Meningococcal Vaccine Safety

- Quadrivalent Meningococcal Conjugate Vaccines
  - Injection site pain, erythema
  - Irritability, drowsiness, myalgia, headache, fatigue, sleepiness, malaise
- Serogroup B Meningococcal Vaccines
  - Injection site pain, induration, erythema, swelling
  - Headache, fatigue, myalgia, arthralgia

Contraindications and Precautions to Vaccination

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

Vaccination with MenACWY vaccine is contraindicated for persons who have had a severe allergic reaction (e.g., anaphylaxis) after any the following:

- A previous dose of Menactra, Menveo, or MenQuadfi
- Any component of Menactra, Menveo, or MenQuadfi vaccines
- Any other meningococcal, diphtheria toxoid-, tetanus toxoid-, or CRM_{197}-containing vaccine.

After reviewing safety studies, ACIP voted in 2010 to remove a history of Guillain-Barré syndrome (GBS) as a precaution for vaccination with any MenACWY vaccine including Menactra. However, a history of GBS continues to be listed as a precaution in the package insert for Menactra.

For both Bexsero and Trumenba, severe allergic reaction (e.g., anaphylaxis) after a previous dose or to any vaccine component is a contraindication for vaccination. Latex sensitivity is listed as a precaution for Bexsero because the tip caps of the prefilled syringes contain natural rubber latex. Menveo is prepared using media containing yeast extracts.

Vaccination during Pregnancy

To date, no randomized clinical trials have been conducted to evaluate use of MenACWY or MenB vaccines in pregnant or lactating women. MenACWY vaccines are recommended for lactating women if otherwise indicated. ACIP recommends that Bexsero or Trumenba vaccination of pregnant women should be deferred unless the woman is at increased risk and, after consultation with her health care provider, the benefits of vaccination are considered to outweigh the potential risks.

Vaccine Safety

Meningococcal Conjugate Vaccines

In clinical trials of Menactra, the most common injection-site reactions were pain (31% to 69%) and erythema (3% to 43%). The most common systemic reactions in infants and children were irritability and drowsiness; in adolescents and adults the most common were myalgia, headache, and fatigue. Most symptoms were mild-to-moderate and resolved within three

days. The Vaccine Adverse Event Reporting System (VAERS) received 13,075 reports for Menactra from 2005 through June 2016, during which time over 70 million Menactra doses were distributed. The most commonly reported adverse events were injection site erythema, fever, and headache. Reported adverse events were consistent with the findings from pre-licensure studies, and no new safety concerns were identified. A cohort study in which 1.4 million doses of Menactra were administered found that Menactra vaccination was associated with a small risk of syncope and medically-attended fever but identified no new safety concerns.

In clinical trials of Menveo, the most common injection-site reactions were pain (8% to 54%) and erythema (12% to 39%). The most common systemic reactions in infants and toddlers were irritability and sleepiness. The most common in children were irritability, myalgia, headache, and sleepiness. In adolescents and adults, myalgia, headache, and fatigue were the most common. Most symptoms were mild-to-moderate and resolved within three days. VAERS received 2,614 reports for Menveo from 2010 through 2015, during which time 8.2 million Menveo doses were distributed. The most commonly reported adverse events were consistent with the findings from pre-licensure studies, and no new safety concerns were identified. In a postlicensure cohort study in which approximately 49,000 individuals aged 11 to 21 years received Menveo, an increased risk of Bell's palsy during the 84 days following vaccination was observed when Menveo was administered simultaneously with other vaccines but not when Menveo was administered alone. However, this finding was based on only eight patients, several of whom had other conditions or infections that might precede Bell's palsy. The importance of this finding is uncertain.

In clinical trials of MenQuadfi, the most common injection-site reaction after the primary dose in all age groups was pain (26% to 45%). The most common systemic reactions were myalgia, headache, and malaise. Solicited adverse reactions following a booster dose in adolescents and adults were comparable to those observed following primary vaccination. MenQuadfi was not yet in use at the time of this publication and postlicensure vaccine safety evaluations will be performed.

Serogroup B Meningococcal Vaccines

In clinical trials of Trumenba, the most common local reactions were injection site pain (72% to 93%), induration (21% to 37%), and erythema (10% to 24%). The most common systemic reactions were headache (27% to 67%), fatigue (30% to 66%), myalgia (21% to 40%), and arthralgia (11% to 33%). Most symptoms were mild-to-moderate and resolved within five days. VAERS received 1,719 reports for Trumenba from 2014 through June 2018. The most commonly reported adverse events were fever, headache, and injection site pain. Reported adverse

events were consistent with the findings from pre-licensure studies, and no new safety concerns were identified. Adverse events following Trumenba were also evaluated during a mass vaccination campaign on a university campus in which over 10,000 doses were administered; rates of injection site pain, fatigue, myalgia, fevers, and chills were similar to those reported during clinical trials.

In clinical trials of Bexsero, the most common local reactions were injection site pain (82% to 98%), erythema (35% to 68%), swelling (26% to 47%), and induration (10% to 48%). The most common systemic reactions were headache (21% to 65%), fatigue (18% to 73%), myalgia (17% to 75%), and arthralgia (8% to 42%). VAERS received 1,470 reports for Bexsero from 2015 through June 2018. The most commonly reported adverse events were injection site pain, fever, and headache; transient decreased mobility of the arm where Bexsero was injected was also disproportionately reported. Otherwise, reported adverse events were consistent with the findings from pre-licensure studies, and no new safety concerns were identified. Adverse events following Bexsero were also evaluated during several mass vaccination campaigns in the United States and Canada. The most commonly reported adverse events were consistent with findings based on clinical trial data (e.g., fever, injection site pain, arm pain), and 0.88 syncopal events per 1,000 persons were observed in the U.S. evaluation.

Vaccine Storage and Handling

MMenACWY (Menactra, Menveo and MenQuadfi) and MenB (Bexsero and Trumenba) should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Whenever possible, the lyophilized and liquid components of Menveo should be stored together.

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

Manufacturer package inserts contain additional information. For complete information on storage and handling best practices and recommendations, please refer to CDC's Vaccine Storage and Handling Toolkit, https://www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf.

Surveillance and Reporting of Meningococcal Disease

Meningococcal disease is a reportable condition in all states. Healthcare personnel should immediately report any case of invasive meningococcal disease to local and state health departments. This is essential so that antimicrobial chemoprophylaxis can be rapidly administered to close contacts of the case. For guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the Manual for the Surveillance of Vaccine-Preventable Diseases, https://www.cdc.gov/vaccines/pubs/surv-manual/chapters.html.

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