CE 1.0 Pharmacology and 1.5 ANCC Contact Hours

Meningococcal Disease

Vaccines–Who's at Risk and the Future

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Meningococcal disease is a serious life-threatening infection that impacts all ages and can cause meningococcemia, meningococcal meningitis, and Waterhouse-Friderichsen hemorrhagic adrenalitis. Meningococcemia has a case fatality of 10% to 15%, with nearly 20% of cases experiencing neurological injury or amputation despite aggressive care. Meningitis is the most common invasive meningococcal disease expression followed by bacteremia. Less common is meningococcal pneumonia and more rarely septic arthritis.[1]

While many assume that outbreaks are rare, they are not. Global outbreaks particularly in Africa, Norway, Cuba, Chile, and New Zealand have involved thousands of persons and some outbreaks last years. While endemic disease is often sporadic and related to multiple clones, epidemics are more likely related to virulent clones that become dominate in the epidemic area.[2] *Neisseria meningitidis* serogroups A, B, C, Y, X, and W are primarily responsible for disease across the world. As locations of outbreaks vary, new virulent clones continue to emerge within serogroups.[3,4]

In the United States, meningococcal disease is most common among infants and children younger than 5 years, adolescents and young adults 16 to 21 years old, and adults older than 65 years. The most prevalent serogroups are B, C, and Y. Although overall rates of meningococcal disease have declined, meningococcal serogroup B (MenB) remains the most common source of disease, accounting for approximately half of all patients aged 17 to 22 years. Infection can present as otitis media and epiglottitis, and mortality can be as high as 40% in patients with septicemia.[4] Survival of infection may include scarring of skin, hearing loss, limb loss, and cognitive disabilities in up to 50% of cases. [3]

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In the United States, 4 meningococcal vaccines are available, differentiated by the type and number of serogroups the vaccine protects against. Meningococcal conjugate vaccines Menactra (Sanofi Pasteur Inc, Swiftwater, Pennsylvania) and Menveo (Novartis, Cambridge, Massachusetts) provide protection against 4 serogroups (A, C, W, Y). Serogroup B meningococcal vaccines (Trumenba [Pfizer, Philadelphia, Pennsylvania] and Bexsero [GlaxoSmithKline, Research Triangle Park, North Carolina]) are monovalent recombinant protein vaccines and provide protection only against MenB.[5] Table 1 describes available meningococcal vaccines for the United States.[6–10]

Meningococcal Conjugate Vaccine

Meningococcal infection is at an all-time low, related to the routine use of meningococcal conjugate vaccines. Meningococcal disease (serogroups C, Y, W) has decreased 80% for persons aged 11 to 19 years. However, in age groups not routinely vaccinated with conjugate vaccines, similar declines have not occurred, suggesting that meningococcal conjugate vaccines provide protection for the vaccinated but may not help the unvaccinated via herd immunity.[5]

Children aged 11 to 12 years should be vaccinated with a meningococcal conjugate vaccine, and a booster is recommended at age 16 years to provide the greatest protection during the period of highest risk of meningococcal disease. Adolescents who receive the first dose at age 13 through 15 years, a booster should be provided at age 16 through 18 years, before the high-risk period. Adolescents who receive their first dose of meningococcal conjugate vaccine at or after age 16 years do not require a booster dose.[6]

Adults with the following factors should also receive a meningococcal conjugate vaccine[6]:

- complement component deficiency
- taking Soliris (Alexion Pharmaceuticals, New Haven, Connecticut)
- functional or anatomic asplenia
- human immunodeficiency virus infection

Table 1. Available Meningococcal Vaccines in the United States and Resources for Use[a,6–10]

Vaccine	Injection (Intramuscular) Properties	Use	Pharma
Trumenba[b,c] MenB-FHbp vaccine Approved by FDA October 2014	3-Dose schedule: 0, 1-2, and 6 mo 2-Dose schedule: 0, 6 mo. If the second dose is administered earlier than 6 mo after the first dose, a third dose should be administered at least 4 mo after the second dose.	Prevent invasive disease by *Neisseria meningitidis* serogroup B. Approved for persons aged 10–25 y Safety/effectiveness has *not* been established in children aged <10 y Effectiveness of the two2dose schedule against diverse *N meningitidis* serogroup strains has not been confirmed	Pfizer Wyeth Pharmaceuticals (Philadelphia, Pennsylvania)
Bexsero[b,c] MenB-4C vaccine Approved by FDA January 2015	Two doses at least 1 mo apart	Prevent invasive disease by *N meningitides* serogroup B. Approved for persons aged 10–25 y. Effectiveness against diverse serogroup B strains has not been confirmed	GlaxoSmithKline Biologicals, Inc (Research Triangle Park, North Carolina)
Menactra[c,d] Meningococcal conjugate vaccine	A single booster can be given to persons aged 15–55 y at risk of meningococcal disease if at least 4 y have elapsed since the last dose	Prevent invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y, and W-135 Does not prevent *N meningitidis* serogroup B disease	Sanofi Pasteur Inc (Swiftwater, Pennsylvania)
Menveo[c,d] Meningococcal conjugate vaccine	Children 2 through 5 years of age at continued high risk of disease a second dose may be provided 2 mo after the first dose	Prevent invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y, and W-135. Does not prevent N meningitidis serogroup B disease	Novartis Vaccines and Diagnostics (Cambridge, Massachusetts) GlaxoSmithKline

[a]*Pediatric considerations are not fully described in the table.*
[b]*Serogroup B meningococcal (MenB) vaccine.*
[c]*Always check prescribing insert before dosing.*
[d]*Meningococcal conjugate vaccine.*

- working as a microbiologist routinely exposed to *N meningitidis*
- traveling or residing in countries where meningococcal disease is common
- member of a group identified at increased risk because of a serogroup A, C, W, or Y meningococcal disease outbreak
- first-year college student living in a residence hall
- military recruit

Serogroup B Meningococcal Vaccine

Adolescents and young adults (16–23 years of age) may also be vaccinated with a MenB vaccine, preferably at 16 through 18 years of age. However, the Centers for Disease Control and Prevention (CDC) recommends that certain adolescents and young adults should be vaccinated if identified as at increased risk or with medical conditions such as complement component deficiencies, taking Soliris (Alexion Pharmaceuticals), and functional or anatomic asplenia (including sickle cell disease).[6]

Adults should receive the MenB vaccine if they have functional or anatomic asplenia or are part of a population identified to be at risk related to a MenB disease outbreak. Finally, any microbiologist routinely exposed to *N meningitidis* should also be vaccinated with a booster of meningococcal conjugate vaccine every 5 years if exposure risk continues. Check the CDC Web site for specific infant and children recommendations for meningococcal vaccinations (https://www.cdc.gov/vaccines/vpd/mening/hcp/who-vaccinate-hcp.html).[6]

Considerations

Meningococcal vaccines should not be administered to persons with a history of severe allergic response after a previous dose or allergy to any vaccine component. Meningococcal conjugate vaccines may be given to pregnant women at increased risk of serogroup A, C, W, or Y meningococcal disease. However, MenB vaccines should be avoided in pregnant or lactating women and given only to women who are at increased risk of MenB disease and who decide, after talking with their care provider, that the benefits of receiving the vaccine outweigh any risks. At this time, there are limited data regarding the use of MenB vaccines in pregnant or lactating women.[6]

The Advisory Committee on Immunization Practices (ACIP) recommends either the MenB-FHbp (Trumenba) or the MenB-4C (Bexsero); ACIP has no product preference for MenB vaccine.[11] However, these vaccines are not interchangeable, and same product must be used for all doses in the series. Dosing schedules have been modified

since 2015; therefore, always check the package insert. At this time, MenB-FHbp has a 2-dose or 3-dose series depending on the risk of exposure and susceptibility to MenB disease. For persons at high risk of meningococcal disease and during MenB disease outbreaks, ACIP recommends 3 doses of MenB-FHbp be administered at 0, 1 to 2, and 6 months. For healthy adolescents, not at increased risk, ACIP recommends 2 doses of MenB-FHbp at 0 and 6 months. MenB-4C vaccination requires a 2-dose series in all cases. Any adverse events should be reported to the Vaccine Adverse Event Reporting System at 1-8900-822-7967 or online at https://vaers.hhs.gov.[11]

Serogroup B Vaccines Moving Forward

Meningococcal outbreaks (defined as ≥2 cases) are rare. Ninety-eight percent of cases are sporadic and occur in situations of persons living in close contact such as dormitories or prisons. Thirty percent of US meningococcal infections are MenB meningitis.[4]

Prior to the access to broad-spectrum meningococcal B vaccines Bexsero and Trumenba, strain-specific vaccines were created to control outbreaks. No vaccine was available in the United States in 2013 when the FDA allowed the European MenB-4C vaccine to be used after the CDC filed an Investigational New Drug application for MenB outbreaks at 2 universities. Bexsero was used with more than 90% of the 5000 at-risk students receiving the 2 doses with no further infections after the vaccination program. In a second university outbreak, the CDC applied for another Investigational New Drug for 20 000 at-risk students. Again, no safety concerns were identified during the vaccination program.[3] Since 2013, a total of 8 additional outbreaks have occurred in the United States, with approximately 35 students experiencing infection at 9 universities, which resulted in immediate mass vaccinations and prophylactic antibiotics for those with close contact.[1]

While the development of the meningococcal conjugate vaccine for serogroups A, C, W, and Y has produced very effective agents, vaccine development for MenB was more difficult related to the immunogenicity of the conjugates, which have significant potential to effect autoimmune disease. The polysaccharide is structurally like molecules found on human neuronal cells and thus can be identified as a human antigen.[12] These safety concerns for autoimmunity resulted in focusing on surface-exposed proteins present in a majority of MenB strains with limited immunologic variability to obtain the desired immune response.[3,4]

As recommendations regarding the use of MenB vaccines continue to emerge, the advantages of vaccinating adolescents on public health continue to be explored. Data described in Table 2 suggest that meningococcal conjugate and MenB vaccines produce an immune response that is protective against disease 1 month after completing the required series. However, evidence for effectiveness is limited because meningococcal disease is uncommon, and data describing immunity over time are limited.[5] While aggressive vaccinations during an outbreak appear to suggest an additional primary prevention effect, questions remain concerning the rate of immunogenicity, duration of protection, and the range of MenB subtypes covered by these high-cost vaccines.[4,5]

Table 2. Percent of Persons With Protective Immune Response 30 Days After Completion of Vaccine Series[5]

Vaccine	Adolescents	Adults
Menactra	Between 82% and 97%	Between 74% and 89%
Menveo	Between 75% and 96%	Between 69% and 94%
Bexsero	Between 63% and 94%	Between 63% and 94%
Trumenba	Between 81% and 84%	Between 81% and 84%

Also unknown is whether there is any reduction of colonization in asymptomatic carriers with vaccination. These issues are unknown because of the social and economic difficulties of research during mass vaccination events. What is known is that evidence suggests that MenB vaccination provides excellent protection in most persons against most strains of MenB in North America. The cost of the vaccine limits mass vaccinations in light of other vaccines needed for more prevalent illnesses. However, in outbreak settings such as universities and prisons, the vaccine appears to provide significant protection and perhaps herd immunity for persons while they live in these settings. Further research with more precise methods is needed to understand the epidemiology and pathway of meningococcal carriage and transmission.[1,13]

Clinical Implications

Although meningococcal disease outbreaks are rare, once they occur, they persist often for years without intervention. The morbidity and mortality risks of infection cannot be overstated. While early recognition is very important, prevention remains the ideal.[3]

Antibiotic prophylaxis has been shown to be effective in small closed settings. However, antibiotics fail in large outbreaks such as in university settings. Furthermore, evidence suggests that a significant percentage of persons die even with antibiotic treatment, and those who survive have significant morbidity. Finally, with increased vaccinations using the meningococcal conjugate vaccine, MenB infection is increasing.[3]

At-risk groups include children, adolescents, and men who have sex with men, as well as persons with component deficiency.[1] Limited evidence suggests that the prevalence of meningococcal carriage peaks in age 16 to 24 years. Asymptomatic meningococcal carriage promotes exchange

of genetic material. Increased carriage risk is related to social behaviors that result in close physical content and disease transmission and include frequent kissing, smoking, and night club attendance. Vaccination of adolescent and young adults provides protection for these groups with the highest carriage and protects the unvaccinated group as well.[13]

The next 5 years of experience with MenB vaccines will provide more information on the effects of the vaccines on carriage and immunity over time, which will drive how these vaccines will be used in the future.[13] In a recent study of 106 subjects from 4923 university students immunized with recommended 2 doses of MenB-4C during anoutbreak, serum samples were obtained at 1.5 to 2 months. Fifteen serum samples were also obtained from 52 unvaccinated students. Follow-up serum samples were obtained at 7 months from 42 vaccinated and 24 unvaccinated subjects. Efficacy of the vaccine was measured as serum bactericidal antibody. Findings indicated that MenB-4C elicited effective short-term protective titers. However, at 7 months, the protective titers were less than 40%, suggesting a booster dose may be needed to maintain protective titers.[14]

For now, there is no vaccine for the sixth meningococcal serogroup type (X).[4] Continuing research will add to knowledge regarding vaccine activity against all serogroups of *N meningitidis* with the continued goal of a universal multivalent vaccine for the world's health that is also cost effective.[1,14]

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