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Review article

Prevention of Meningococcal Infection in the United States: Current Recommendations and Future Considerations

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A B S T R A C T

Neisseria meningitidis is a common cause of bacterial meningitis and septicemia that can lead to permanent sequelae or death. *N meningitidis* is classified into serogroups based on the composition of the capsular polysaccharide, with serogroups A, B, C, W, X, and Y recognized as the major disease-causing organisms. The unpredictability of infection coupled with the poor prognosis for some patients suggests immunization as an effective preventive strategy. Importantly, four of the six disease-causing serogroups (A, C, Y, and W) may be prevented with available quadrivalent capsular polysaccharide–protein conjugate vaccines; these vaccines have been successfully implemented into immunization programs in the United States. Unfortunately, quadrivalent conjugate vaccines are not effective against serogroup B, now the most common cause of invasive meningococcal disease. Two recombinant protein vaccines recently were licensed for prevention of serogroup B disease. Recommendations for use of these serogroup B vaccines in the United States have been made by the Advisory Committee on Immunization Practices. This article will discuss all available meningococcal vaccines, current recommendations for use, lessons learned from previous experiences, and future considerations, with the hope of further understanding how use of these vaccines may help reduce incidence of meningococcal disease in the United States.

Neisseria meningitidis, an exclusively human pathogen, is a major cause of invasive meningococcal disease (IMD), most often manifesting as septicemia with or without meningitis that can lead to death within 24–48 hours of symptom onset [1]. IMD incidence is highest in infants and children (<5 years old), adolescents and young adults (16–21 years old), and the elderly (≥65 years old) [2]. The case:fatality ratio of IMD generally ranges from approximately 10%–20% [1–6]. Moreover, nearly 20% of survivors experience significant sequelae including limb loss, hearing loss, chronic pain, skin scarring, and neurologic deficits [7].

Most cases of IMD are sporadic, but they can be associated with outbreaks, making them highly unpredictable [8,9]. The volatile nature of disease is emphasized by the four meningococcal serogroup B (MnB) outbreaks occurring at universities in the United States since 2013. The sometimes poor prognosis of infected patients, coupled with the unpredictability of disease onset and progression, suggests an urgent need for implementing effective prevention.

Person-to-person transmission can be interrupted by either chemoprophylaxis (i.e., antibiotic administration) or immunoprophylaxis (i.e., immunization). Prophylaxis with antibiotics, such as rifampin, quinolones, or ceftriaxone, are used to prevent

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Table 1
U.S. licensed meningococcal vaccines and current ACIP recommendations

Vaccine	Licensure (age; year)	ACIP recommendation, dose:population			
		General population			High-risk groups[a]
		Category	Primary	Booster	
MenACWY vaccines					
MenACWY-D (Menactra; Sanofi Pasteur)	2–55 years; 2005 9–23 months; 2011	A	One dose [2]: age 11–12 years or 13–18 years if not previously immunized Catch-up: age 19–21 years for those who have not received a dose after age 16 years.	One dose: if first dose before age 16 years	Two doses, 12 weeks apart: age 9–23 months (Menactra).[b,c,d] Four doses at 2, 4, 6, and 12 months: age 2–23 months (Menveo [26]).[b,c,d,e] Two doses, 8–12 weeks apart: age 2–55 years, not immunized previously.[d,e] One dose: age 2–55 years, not immunized previously [26].[b,c,f,g]
MenACWY-CRM (Menveo; GlaxoSmithKline)	2–55 years; 2010 ≥2 months; 2013	A			
MenCY vaccines					
Hib-MenCY-TT (MenHibrix; GlaxoSmithKline)	6 weeks–18 months; 2012	A	N/A	N/A	Four doses at 2, 4, 6, and 12–15 mo: age 2–18 mo [2].[c,d,e]
MenB vaccines					
Bivalent rLP2086 (Trumenba; Pfizer Inc)	10–25 years; 2014	B	Two–three doses: age 16–23 years, in consultation with health care provider [27].[h]	N/A	Two–three doses: age ≥10 years [28].[c,d,e,g]
4CMenB (Bexsero; GlaxoSmithKline)	10–25 years; 2015	B			

ACIP = Advisory Committee on Immunization Practices; N/A = not applicable.
[a] Individuals remaining at increased risk of meningococcal disease should receive an MenACWY booster 3 or 5 years after completing the primary immunization at age 2 months–6 years or ≥7 years, respectively. Boosters should be repeated every 5 years thereafter.
[b] Individuals traveling to locations or who are residents of countries where meningitis is hyperendemic or epidemic.
[c] Community outbreaks caused by a vaccine serogroup.
[d] Individuals with persistent complement deficiencies, including those being treated with eculizumab (Solaris).
[e] Individuals with functional or anatomic asplenia (including sickle cell disease).
[f] Individuals who are first-year college students aged ≤21 years living in residential housing.
[g] Microbiologists who routinely work with *Neisseria meningitidis* isolates.
[h] 4CMenB is licensed as a two-dose series, with doses administered ≥1 month apart; Bivalent rLP2086 is licensed as a three-dose series, with the second and third doses administered 1-2 and 6 months after the first dose. In addition to the three-dose schedule for bivalent rLP2086, recently the Food and Drug Administration has approved a two-dose series (0 and 6 months); the choice of schedule depends on the risk of exposure and the patient's susceptibility to disease.

secondary cases in individuals in close contact with an infected patient [10,11]; detailed guidelines for their use already are described [12]. This review will focus on immunization as a preventive strategy, with an in-depth discussion of the available meningococcal vaccines in the United States, current recommendations for their use, lessons learned from previous experiences, and future considerations.

Assessment of Meningococcal Vaccine Effectiveness

Because of the low incidence of IMD in the United States, generally <1 per 100,000 persons [13], large-scale Phase 3 vaccine efficacy studies are not feasible because of financial and logistic difficulties. Therefore, alternative in vitro functional assays that mimic the main mechanism of protection observed in vivo were developed to assess the potential efficacy of a meningococcal vaccine in a population. Specifically, complement-dependent bactericidal activity of antibodies derived from the serum of individuals after immunization with meningococcal antigens is used as a surrogate (or correlate) of protection [14]. This correlate is measured with an assay referred to as a serum bactericidal antibody assay and is performed using human complement (hSBA) [2]. hSBA assays are the U.S. Food and Drug Administration's (FDA's) accepted standard for estimating efficacy of a meningococcal vaccine; an hSBA titer of ≥1:4 is considered protective [14–17]. This threshold has been shown to correlate with effectiveness in postlicensure studies [18], and hSBA titers are used to demonstrate protection across meningococcal serogroups [14,19,20].

Vaccines Available for the Prevention of Invasive Meningococcal Disease

Serogroup A, C, W, and Y vaccines

Neisseria meningitidis is classified into serogroups based on the composition of their capsular polysaccharides (CPSs) [6,21], with serogroups designated as A, B, C, W, X, and Y attributed to almost all cases of life-threatening, sporadic, and endemic disease globally [21–25]. Until recently, meningococcal vaccines approved in the United States only protected against IMD caused by four of the six disease-causing serogroups of *N meningitides*: A, C, W, and Y.

Four different meningococcal vaccines containing purified CPSs alone or CPSs conjugated to a carrier protein are licensed in the United States for the prevention of IMD caused by serogroups A, C, W, and Y (Table 1). The quadrivalent CPS vaccine MPSV4 (Menomune [Meningococcal Polysaccharide Vaccine, Groups A, C, W, and Y combined]; Sanofi Pasteur Inc., Swiftwater, Pennsylvania) has been available since the 1970s for use in individuals