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Recommendations for Serogroup B Meningococcal Vaccine for Persons 10 Years and Older

COMMITTEE ON INFECTIOUS DISEASES

This policy statement provides recommendations for the prevention of serogroup B meningococcal disease through the use of 2 newly licensed serogroup B meningococcal vaccines: MenB-FHbp (Trumenba; Wyeth Pharmaceuticals, a subsidiary of Pfizer, Philadelphia, PA) and MenB-4C (Bexsero; Novartis Vaccines, Siena, Italy). Both vaccines are approved for use in persons 10 through 25 years of age. MenB-FHbp is licensed as a 2- or 3-dose series, and MenB-4C is licensed as a 2-dose series for all groups. Either vaccine is recommended for routine use in persons 10 years and older who are at increased risk of serogroup B meningococcal disease (category A recommendation). Persons at increased risk of meningococcal serogroup B disease include the following: (1) persons with persistent complement component diseases, including inherited or chronic deficiencies in C3, C5–C9, properdin, factor D, or factor H or persons receiving eculizumab (Soliris; Alexion Pharmaceuticals, Cheshire, CT), a monoclonal antibody that acts as a terminal complement inhibitor by binding C5 and inhibiting cleavage of C5 to C5A; (2) persons with anatomic or functional asplenia, including sickle cell disease; and (3) healthy persons at increased risk because of a serogroup B meningococcal disease outbreak. Both serogroup B meningococcal vaccines have been shown to be safe and immunogenic and are licensed by the US Food and Drug Administration for individuals between the ages of 10 and 25 years. On the basis of epidemiologic and antibody persistence data, the American Academy of Pediatrics agrees with the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention that either vaccine may be administered to healthy adolescents and young adults 16 through 23 years of age (preferred ages are 16 through 18 years) to provide short-term protection against most strains of serogroup B meningococcal disease (category B recommendation).

abstract

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DOI: 10.1542/peds.2016-1890

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they do not have a financial relationship relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: AAP COMMITTEE ON INFECTIOUS DISEASES. Recommendations for Serogroup B Meningococcal Vaccine for Persons 10 Years and Older. *Pediatrics.* 2016;138(3): e20161890

INTRODUCTION

There are 12 known serogroups of *Neisseria meningitidis*, as determined by antigens of the *N meningitidis* polysaccharide capsule. Six serogroups (A, B, C, W, X, and Y) are responsible for invasive human disease. Serogroups A and X are currently rare in the United States. Before October 2014, 4 vaccines were licensed for the prevention of meningococcal disease: 2 quadrivalent meningococcal conjugate vaccines (MenACWY [Menveo; Novartis, Siena, Italy] and Menactra [Sanofi Pasteur; Swiftwater, PA]), a bivalent meningococcal conjugate vaccine (serogroups C and Y) combined with a *Haemophilus influenzae* type b conjugate vaccine (MenHibrix; GlaxoSmithKline; Brentford, United Kingdom), and a quadrivalent meningococcal polysaccharide vaccine (Menomune; Sanofi Pasteur). In October 2014, the first serogroup B meningococcal vaccine, MenB-FHbp (Trumenba; Wyeth Pharmaceuticals, a subsidiary of Pfizer, Philadelphia, PA), was licensed. The second serogroup B meningococcal vaccine, MenB-4C (Bexsero; Novartis Vaccines; Siena, Italy), was licensed in January 2015. Both vaccines are licensed for use in persons 10 through 25 years of age. MenB-FHbp is administered as a 3-dose series for those at increased risk of serogroup B meningococcal disease and as a 2-dose series for those not at increased risk (Table 1). MenB-4C is administered as a 2-dose series for all groups. On February 26, 2015, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended the routine use of MenB vaccines in persons 10 years and older at increased risk of serogroup B meningococcal disease (category A recommendation*). On June 24, 2015, the ACIP stated that healthy adolescents and young adults 16 through 23 years of age (preferred ages, 16 through 18 years) who are not at increased risk of serogroup B meningococcal disease may be considered for vaccination with an MenB vaccine to provide short-term protection against most strains of serogroup B meningococcal disease (category B recommendation), but routine immunization is not recommended. The age groups reflected in the recommendation were determined by epidemiologic and antibody persistence data.

*Category A recommendations are made for all persons in an age- or risk factor–based group. Category B recommendations are made for individual clinical decision-making.

TABLE 1 Increased Risk Groups Recommended for the Different Meningococcal Vaccines

MenACWY	MenB
Complement deficiency[a]	Complement deficiency[a]
Anatomic/functional asplenia[b]	Anatomic/functional asplenia[b]
Outbreak[c]	Outbreak[c]
Microbiologists[d]	Microbiologists[d]
Travelers[e]	
First-year college students[f]	
Military recruits	

Sources: refs 1–4.

[a] Inherited or chronic deficiencies of C3, C5–C9, properdin, factor D, or factor H or those receiving eculizumab.

[b] Includes sickle cell disease.

[c] The CDC defines outbreaks and those at risk.[5]

[d] Only microbiologists who routinely work with *N meningitidis*.

[e] To areas with hyperendemic or epidemic meningococcal disease.

[f] Unvaccinated or inadequately vaccinated first-year college students who live in residence halls.

Previous meningococcal vaccines have relied on the polysaccharide antigens from serogroups A, C, W, and Y. Protein conjugation of these polysaccharide antigens enhanced immunogenicity. However, the polysaccharide capsule of *N meningitidis* serogroup B is poorly immunogenic, even among those who experience serogroup B meningococcal disease.[6] The immunochemical structure of the serogroup B meningococcal polysaccharide is similar to human glycoproteins, including certain intracellular adhesion molecules.[6] The induction of antibodies to serogroup B meningococcal polysaccharide capsular antigens might result in unacceptable adverse events. For theoretical safety reasons, a serogroup B meningococcal vaccine was designed to contain nonpolysaccharide antigens. MenB-FHbp is a bivalent vaccine consisting of 2 different recombinant lipidated factor H binding protein (FHbp) antigens, one from FHbp subfamily A and one from FHbp subfamily B. MenB-4C is a multicomponent vaccine consisting of 3 recombinant proteins from *N meningitidis* (FHbp, neisserial adhesion A [NadA], and neisserial heparin binding antigen protein [NHBA]) and an outer membrane vesicle containing Por A P.14 (New Zealand epidemic strain N298/254).

Although in 2015 meningococcal disease caused by any serogroup in the United States was rare, invasive meningococcal disease is a serious illness. Each case can be life-threatening. The United States currently is experiencing historically low levels of meningococcal disease caused by all serogroups, with an incidence of 0.18 per 100 000 population (CDC, unpublished data, 2013). The incidence of meningococcal disease caused by all serogroups has declined. Serogroup B disease incidence has declined despite the fact that serogroup B is not contained in any of the existing conjugate polysaccharide meningococcal vaccines. Approximately 50 to 60 cases of serogroup B meningococcal disease occur annually in adolescents and young adults 11 through 24 years of age in the United States.

A majority of these (80%) occur in individuals 16 through 23 years of age (CDC, unpublished data). Despite a number of recent outbreaks on college campuses, the incidence of serogroup B meningococcal disease in college students (0.09 per 100 000) is similar to or lower than the incidence in all 18- through 23-year-olds (0.14 per 100 000) and noncollege students (0.21 per 100 000) (CDC, unpublished data). A routine adolescent MenB vaccine recommendation would be estimated to prevent 15 to 29 cases and 2 to 5 deaths per year, assuming that all eligible persons were immunized. A recommendation for routine MenB vaccination of college students only is estimated to prevent 10 cases and 1 death per year (CDC, unpublished data).

Certain individuals are known to have an increased susceptibility to invasive meningococcal disease.[1] These individuals are currently recommended to be vaccinated with a quadrivalent meningococcal conjugate vaccine (MenACWY).[1] Many, but not all, of these groups are also at increased risk of invasive disease attributable to *N meningitidis* serogroup B (Table 1). Persons with persistent complement component deficiencies, including inherited or chronic deficiencies in C3, C5–C9, properdin, factor D, or factor H, have up to a 10 000-fold increased risk of meningococcal disease and can experience recurrent disease.[1,2] Individuals receiving eculizumab (Soliris; Alexion Pharmaceuticals, Cheshire, CT), a monoclonal antibody that binds to C5 and inhibits the terminal portion of the complement pathway, are at increased risk of invasive meningococcal disease, including serogroup B meningococcus.[3] Eculizumab is approved for the treatment of atypical hemolytic-uremic syndrome and paroxysmal nocturnal hemoglobinuria.[3] Five of 326 subjects (1.5%) in clinical trials of eculizumab developed invasive meningococcal disease despite previous immunization with a meningococcal vaccine.[3] The package insert does not describe the serogroups of these 5 meningococcal infections.[3] However, serogroup B meningococcal disease in eculizumab recipients has been described. Persons with functional or anatomic asplenia, including sickle cell disease, appear to be at increased risk of invasive meningococcal disease and have a higher case fatality rate (40%–70%) from meningococcal disease than healthy populations.[4] The increased risk of meningococcal infection in patients with asplenia is less than that for invasive pneumococcal disease.[1] Data describing immune responses to MenB vaccines in populations with complement deficiency and asplenia have not yet been published. Microbiologists who routinely work with *N meningitidis* have an attack rate of 13 per 100 000. This attack rate in microbiologists is several-fold higher than that in the general population.[1] Because microbiologists are not in the pediatric age range, recommendations for microbiologists will not be included in recommendations from the American Academy of Pediatrics (AAP) but are included in the ACIP recommendations.

The vast majority of all cases of meningococcal disease occurring in the United States are sporadic (97%–98%). However, outbreaks of meningococcal disease continue to occur and often receive media attention because of the severity of invasive meningococcal disease. In recent years, outbreaks of serogroup B meningococcal disease have occurred on several different college campuses. Data from 2 recent outbreaks on college campuses (spring 2013 through spring 2014) noted a 200- to 1400-fold increase in risk of meningococcal disease among students at these colleges during the outbreak period (CDC, unpublished data).

A comparison of risk groups for the quadrivalent meningococcal conjugate vaccine and the recently licensed serogroup B meningococcal vaccines is presented in Table 1. Persons at increased risk and for whom administration of the quadrivalent meningococcal vaccine (MenACWY) is recommended but for whom the serogroup B meningococcal vaccine is not recommended routinely include the following: (1) persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, (2) first-year college students living in residence halls, and (3) military recruits. Serogroup B meningococcal vaccine is currently not recommended for travel to any area of the world.[1] College students have a lower risk of serogroup B meningococcal disease than the general population of a similar age (college students compared with 18- through 23-year-olds: 0.09 per 100 000 and 0.14 per 100 000, respectively).

The safety and immunogenicity of both serogroup B meningococcal vaccines (MenB-4C and MenB-FHbp) have been evaluated in numerous published clinical trials[7–16] (and in unpublished data[†]). Both vaccines appear to provide

[†]Unpublished data from the following sources: Safety and Immunogenicity of Novartis Meningococcal B Vaccine Formulated With OMV Manufactured at Two Sites, in Healthy Adolescents Aged 11–17 Years; T Vesikari et al. Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 Meningococcal Group B Vaccine Administered Concomitantly With Tdap-IPV Vaccine to Healthy Adolescents. (Clinical Trials Registration: NCT01323270); Safety, Tolerability, and Immunogenicity of MCV4, Tdap Vaccine When Administered Concomitantly in Healthy Subjects Aged ≥10 to <13 Years; Safety and Tolerability of a Meningococcal Serogroup B Bivalent Recombinant Lipoprotein (rLP2086) Vaccine Given in Healthy Subjects Aged ≥10 to <26 Years; T Vesikari et al. Meningococcal Serogroup B Bivalent rLP2086 Vaccine Elicits Broad and Robust Serum Bactericidal Responses in Healthy Adolescents; and Open Label Safety and Immunogenicity in Meningococcal Laboratory Workers.

short-term immunogenicity in healthy populations.[7–16] Studies on vaccine efficacy are not available. Licensure was based on the ability of the vaccines to elicit detection of bactericidal antibody that is presumed to indicate protection. Studies regarding antibody persistence are limited. Immunogenicity studies in populations at increased risk of invasive meningococcal disease have not been completed. MenB-FHbp has been administered concomitantly with the following: quadrivalent human papillomavirus (HPV) vaccine (Gardasil; Merck & Co, Kenilworth, NJ)[16] but not 9-valent HPV vaccine; with MenACWY (unpublished data); with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap) vaccine (Adacel; Sanofi Pasteur [unpublished data]); and with Tdap/inactivated poliovirus vaccine (Repevax; Sanofi Pasteur [this vaccine is not licensed in the United States; unpublished data]). Immune responses were noninferior for HPV-6, HPV-11, and HPV-16[16] and for MenACWY and tetanus, diphtheria, and pertussis antigens (unpublished data) when MenB-FHbp was administered concomitantly. For HPV-18, noninferiority criteria (lower bound of the 95% confidence interval of geometric mean titer [GMT] ratio >0.67) were not met for the GMT ratio at 1 month after the third quadrivalent HPV vaccination (lower bound of 95% confidence interval for GMT ratio was 0.62); however, for each HPV vaccine type, more than 99% of subjects achieved seroconversion.[16]

In clinical trials, both MenB vaccines were safe, with few serious adverse events (all resolved without sequelae).[7–16] There were no deaths considered to be related to either vaccine. Local and systemic adverse events noted in clinical trials are included in Table 2.[7–16]

TABLE 2 Local and Systemic Adverse Events Reported in Clinical Trials for MenB-4C and MenB-FHbp

Adverse Event	MenB-4C (Bexsero), %	MenB-FHbp (Trumenba), %
Severe pain at injection site	20–29	5–8
Fever ≥38%	1–5	2–8
Headache (severe)	4–6	1
Fatigue (severe)	4–6	1–4
Muscle pain (severe)	12–13	1–3
Joint pain (severe)	2	1
Use of antipyretic medication	NA	17– 28

Sources: refs 7–16; unpublished data. NA, not applicable.

Both MenB vaccines were licensed for use in the United States under an accelerated approval pathway. Both vaccine manufacturers are required to conduct postmarketing studies to confirm effectiveness against a panel of diverse meningococcal group stains. Important data, including duration of immunogenicity, the proportion of serogroup B meningococcal strains covered by each vaccine in different geographic areas, and other data needed to provide guidance for recommendations for MenB vaccines, are not yet available. Theoretical concerns exist regarding autoimmune disease after receipt of a vaccine containing FHbp antigen.[17] Additional postlicensure safety data are also needed and will be reviewed by the ACIP and the AAP as they become available.

RECOMMENDATIONS

1. Persons 10 years and older at increased risk of meningococcal disease should receive an MenB vaccine routinely (category A recommendation for all 3 of the following groups):
   (a) persons with persistent complement component deficiencies, including inherited or chronic deficiencies in C3, C5–C9, properdin, factor D, or factor H or those receiving eculizumab;
   (b) persons with anatomic or functional asplenia, including sickle cell disease; and
   (c) healthy persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak (defined by local health department on the basis of CDC criteria[5]); these persons should receive an MenB vaccine series if their treating health care providers, in consultation with their local health or state departments, determine they are appropriate candidates on the basis of CDC criteria.[5]
2. An MenB vaccine series is not routinely recommended, but it may be administered to adolescents and young adults 16 through 23 years of age to provide short-term protection against diverse strains of serogroup B meningococcal disease (category B recommendation). If an MenB vaccine is administered, the preferred age for MenB vaccination is 16 through 18 years of age. This age preference is based on limited data on antibody persistence and the peak ages of invasive serogroup B meningococcal disease.

The MenB vaccines are routinely recommended for individuals at increased risk of disease (category A recommendation) but not for low-risk adolescents and young adults in the age range for which the vaccines are licensed (Table 1). Instead, a permissive or category B recommendation was made for low-risk individuals. The ACIP recommendation for MenB vaccine in low-risk adolescents

TABLE 3 Summary of Cost-effectiveness Analysis of Different Strategies for Adolescent Vaccination, United States

Strategy	Cases Prevented, *n*	Deaths Prevented, *n*	NNV to Prevent Cases	NNV to Prevent Deaths	Cost by QALY, $
Series at 11 years	15	2	203 000	1 512 000	$8 700 000
Series at 16 years	28	5	107 000	788 000	$4 100 000
Series at 18 years	29	5	102 000	638 000	$3 700 000
College students	9	1	368 000	2 297 080	$9 400 000

Sources: ref 5; unpublished data, key model assumptions presented at ACIP meeting, June 2015; and methods described in MacNeil et al.[18] NNV, number needed to vaccinate; QALY, quality-adjusted life-year.

and young adults is based on the very low incidence of serogroup B meningococcal disease in persons who are not at high risk and lack of availability of certain data that would be valuable in developing policy. For these reasons, the ACIP determined that there were insufficient data to make a routine recommendation that all adolescents be vaccinated with an MenB vaccine. The AAP also considered the difficulty of delivering multiple vaccine doses to adolescents, the cost of the vaccine series, and the unfavorable cost-effectiveness evaluation (ACIP meeting, unpublished data, June 2015; methods described in MacNeil et al[18]; Table 3) while developing these recommendations. This restrictive recommendation allows treating clinicians to determine which adolescents and young adults might receive benefit from receiving a series of one of the MenB vaccines. If the clinician and family discuss the MenB vaccine and the MenB vaccine is not administered, the discussion and decision should be documented in the patient's health record.

Specific epidemiologic data or guidelines are not available to assist treating clinicians to determine who should receive the MenB vaccine series. Estimates from the CDC indicate that fewer than 60 cases of meningococcal B disease occur each year in the United States among young persons between 11 and 21 years of age. Universal vaccination of the annual cohort of 4 million persons at 16 or 18 years of age would prevent an estimated maximum of 28 cases. Universal vaccination of all college students is estimated to prevent, at most, 10 cases and 1 death. Except during outbreaks, the available data do not suggest an increased rate of MenB disease among college students relative to non–college students of the same age group.[19]

Pediatricians are encouraged to discuss the availability of the MenB vaccines with families. Discussion should include the low incidence of MenB disease and the unknown efficacy of the vaccines (licensure was based on the ability of the vaccines to induce a presumed concentration of protective antibodies). MenACWY vaccine administration is recommended for college freshman because of increased invasive meningococcal disease attributable to serogroups in the conjugate meningococcal vaccine in college students, particularly in college freshmen living in residence halls; however, this is not the case for serogroup B meningococcal disease. This apparent dichotomy in the incidence of the different meningococcal serogroups in college students is not understood. Colleges and universities may recommend or even require the MenB vaccine for students. The treating clinician should discuss the benefits, risks, and costs with patients and their families and then work with them to determine what is in their best interest.

When used, MenB vaccine should be administered as either a 2-dose series of MenB-4C or as a 3-dose series of MenB-FHbp. A 2-dose series of MenB-FHbp was recently licensed by the Food and Drug Administration. The 2-dose series of MenB-FHbp should be administered at day 0, and the second dose should be administered no sooner than 6 months after the first dose. The 2-dose series of Men-FHbp should not be used for persons at increased risk of meningococcal B disease (Table 1 lists persons at increased risk) or for persons for whom immediate protection is optimal. The inclusion of the 2-dose series of MenB-FHbp in formal recommendations will be made in conjunction with the ACIP of the CDC when additional data are available, including longer-term antibody persistence after a 2-dose series. On the basis of available data and expert opinion, either MenB vaccine may be administered concomitantly with other vaccines indicated for this age, but at a different anatomic site, if feasible. The first dose of MenB-4C should be administered at day 0, and the second dose should be administered ≥1 month later; the 3-dose series of MenB-FHbp should be administered on a 0-, 1- to 2-, and 6-month schedule. Because there are no data on the interchangeability of the 2 MenB vaccines and each vaccine uses very different protein antigens, the same vaccine must be used for all doses to complete the full series. Providers need to communicate to patients which product was given so that the same vaccine is used for subsequent doses.

PRECAUTIONS AND CONTRAINDICATIONS

Before administering MenB vaccines, treating clinicians should consult the package insert for a

full list of precautions, warnings, and contraindications. Pregnancy and breastfeeding are precautions, because neither vaccine has been evaluated in these situations. A severe allergic reaction to a previous dose of MenB vaccine or any of its components is a contradiction. Adverse events occurring after the administration of any vaccine should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted to VAERS online, by fax, or by mail. Additional information about VAERS is available by telephone (1-800-822-7963) or online (http://vaers.gov).

ABBREVIATIONS

AAP: American Academy of Pediatrics
ACIP: Advisory Committee on Immunization Practices
CDC: Centers for Disease Control and Prevention
FHbp: factor H binding protein
GMT: geometric mean titer
HPV: human papillomavirus
Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed
VAERS: Vaccine Adverse Event Reporting System

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Pediatrics 2016;138;
DOI: 10.1542/peds.2016-1890 originally published online August 29, 2016;

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