Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices, 2015

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At its June 2015 meeting, the Advisory Committee on Immunization Practices (ACIP) recommended that adolescents and young adults aged 16–23 years may be vaccinated with a serogroup B meningococcal (MenB) vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. This report summarizes the deliberations of ACIP, the rationale for its decision, and recommendations for use of MenB vaccines in adolescents and young adults. Two MenB vaccines have recently been licensed by the Food and Drug Administration (FDA) for use in the United States and approved for use in persons aged 10–25 years: MenB-FHbp (Trumenba, Wyeth Pharmaceuticals, Inc.) and MenB-4C (Bexsero, Novartis Vaccines). Both MenB vaccines were licensed based on statutory regulations for accelerated approval (*1*), which enabled FDA to approve the MenB vaccines for serious or life-threatening diseases based on safety and demonstration that vaccine effectiveness, as measured by bactericidal antibody responses with assays using several MenB test strains that were representative of prevalent strains in the United States, is reasonably likely to predict clinical benefit. As a requirement for accelerated approval, confirmatory studies in the postmarketing period will be conducted to verify and further describe the effectiveness of the vaccines against an extended number of MenB strains that represent a broader diversity of endemic disease. Additional postlicensure safety data are also needed and will be reviewed by ACIP as they become available.

Recommendations for routine use of vaccines in children, adolescents, and adults are developed by the Advisory Committee on Immunization Practices (ACIP). ACIP is chartered as a federal advisory committee to provide expert external advice and guidance to the Director of the Centers for Disease Control and Prevention (CDC) on use of vaccines and related agents for the control of vaccine-preventable diseases in the civilian population of the United States. Recommendations for routine use of vaccines in children and adolescents are harmonized to the greatest extent possible with recommendations made by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetricians and Gynecologists (ACOG). Recommendations for routine use of vaccines in adults are harmonized with recommendations of AAFP, ACOG, and the American College of Physicians (ACP). ACIP recommendations approved by the CDC Director become agency guidelines on the date published in the Morbidity and Mortality Weekly Report (MMWR). *Additional information is available at http://www.cdc.gov/vaccines/acip.*

Methods

The ACIP Meningococcal Vaccines Work Group reviewed the immunogenicity and safety data from seven clinical trials of MenB-FHbp (*2*–*5*) (Pfizer, unpublished data) and five clinical trials of MenB-4C (*6*–*10*) during monthly teleconferences. The work group evaluated the available published and unpublished data and evidence regarding meningococcal disease epidemiology in the United States, carriage, cost-effectiveness, immunogenicity, and safety. Based on a literature search and consultation with the manufacturers, these studies represent all known clinical trials and evidence for these two vaccines. A summary of the data reviewed and Work Group discussions was presented to ACIP, and recommendations for use of MenB vaccines in adolescents and young adults were approved by ACIP at its June 24, 2015, meeting (meeting minutes are available at http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html).

The type and quality of evidence supporting the use of MenB vaccines in adolescents and young adults, including college students, was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (*11*,*12*) (Table 1).

Epidemiology of Serogroup B Meningococcal Disease Among Adolescents and Young Adults, Including College Students

ACIP reviewed the burden of serogroup B meningococcal disease among adolescents, young adults, and college students. Meningococcal disease is a rare but serious illness and each case is life-threatening. The United States is currently experiencing a historic low in meningococcal disease incidence (0.18 per 100,000 among persons of all ages) (CDC, unpublished data, 2013), and the incidence of disease has declined for all meningococcal serogroups, including serogroup B, a serogroup not included in the quadrivalent (serogroups A, C, W, Y) meningococcal conjugate vaccines. The incidence of serogroup B meningococcal disease is stable and low in

adolescents and young adults aged 11-23 years, with approximately 50 to 60 cases and five to 10 deaths reported annually; the majority (>80%) of these cases occur in older adolescents and young adults aged 16–23 years (CDC, unpublished data). Seven outbreaks of serogroup B meningococcal disease have occurred on college campuses since 2009 (range = 2–13 cases), resulting in 41 cases and three deaths. Whereas several outbreaks of serogroup B meningococcal disease have occurred in recent years on college campuses, during 2009–2013, the estimated incidence of serogroup B meningococcal disease in college students aged 18–23 years (0.09 per 100,000) was similar to, or lower than, the incidence in all persons aged 18–23 years (0.14 per 100,000), and non-college students aged 18–23 years (0.21 per 100,000) (CDC, unpublished data).

It is estimated that approximately 15 to 29 cases and two to five deaths could be prevented annually with a routine adolescent MenB vaccination program administered at age 11, 16, or 18 years (Table 2). A recommendation for college students only is estimated to prevent approximately nine cases and one death annually (Table 2).

MenB Vaccine Immunogenicity and Safety

Evaluation of vaccine effectiveness against all serogroup B meningococcal strains is difficult because the strains are antigenically and genetically diverse. Efficacy studies designed to assess clinical disease outcomes would be the clearest demonstration of the benefit of MenB vaccines to prevent meningococcal B disease; however, such studies would be difficult to conduct because of the low prevalence and sporadic occurrence of disease in the United States. Vaccine effectiveness of MenB-FHbp and MenB-4C, for purposes of U.S. licensure, was inferred based on an immunologic marker of protection, serum bactericidal activity with human complement (hSBA) as measured by assays using selected meningococcal serogroup B strains. Immunogenicity was assessed as the proportion of subjects who achieved a fourfold or greater increase in 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) (*13*). The lower limit of quantification was defined as the lowest amount of the antibody in a sample that can be reliably quantified.

TABLE 1. Summary of evidence for MenB-FHbp and MenB-4C vaccination of healthy adolescents and young adults, including college students — United States

Outcome	Evidence type*	
	MenB-FHbp	MenB-4C
Benefits		
Short-term immunogenicity	2	2
Persistence in immunogenicity	4	3
MenB immunogenicity with concomitant vaccination	2	†
Harms		
Serious adverse events	2	2
Serious adverse events following concomitant vaccination	2	†

* Evidence type: 2 = moderate level of evidence; 3 = low level of evidence; 4 = lowest level of evidence.
† Not assessed because of lack of available data.

Both MenB-FHbp and MenB-4C vaccines contain components that include factor H binding protein. In two animal models, antibodies measured after MenB-4C vaccination have been noted to be cross-reactive with human factor H (*14,15*). However, it is not known if auto-antibodies to factor H develop in humans after vaccination with MenB-FHbp or MenB-4C and, if auto-antibodies are generated postvaccination, whether they are of clinical significance. FDA reviewed safety data from six MenB-4C clinical trials and seven MenB-FHbp clinical trials, which included approximate totals of 3,100 and 4,500 vaccine recipients, respectively. For most participants who reported an autoimmune condition, the onset of symptoms consistent with the diagnosis existed before the first vaccination (*16,17*). Theoretically, onset of autoimmune-disease-related symptoms could be delayed well beyond vaccination and postlicensure safety surveillance will be important to detect any potential safety signals.

MenB-FHbp

MenB-FHbp consists of two purified recombinant lipidated factor H binding protein (FHbp) antigens. One antigen from

TABLE 2. Potential cases and deaths prevented and cost-effectiveness of different strategies for MenB vaccination of adolescents and young adults, including college students, by age — United States

Age at MenB series	Cases prevented	Deaths prevented	NNV* to prevent case	NNV to prevent death	Cost per QALY (million $)
11 yrs	15	2	203,000	1,512,000	8.7
16 yrs	28	5	107,000	788,000	4.1
18 yrs	29	5	102,000	638,000	3.7
College student	9	1	368,000	2,297,000	9.4

Abbreviations: MenB = meningococcal B vaccine; NNV = number needed to vaccinate; QALY = quality-adjusted life years.
Sources: Unpublished data, ACIP meeting June 2015. Key model assumptions were presented at the June 2015 ACIP meeting. Methods described in Shepard CW, Ortega-Sanchez IR, Scott RD 2nd, Rosenstein NE. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. Pediatrics 2005;115:1220–32.

each FHbp subfamily (A and B) is included in the vaccine. MenB-FHbp is licensed as a 3-dose series, with the second and third doses administered 2 and 6 months, respectively, after the first dose.

The immunogenicity and safety of MenB-FHbp in adolescents and young adults were evaluated in seven clinical trials: five randomized controlled trials and two open-label studies (*2–5,16,18*) (Pfizer, unpublished data). In a multicenter trial conducted in the United States, persons aged 11–17 years were randomly assigned to one of three groups: group 1 received MenB-FHbp and quadrivalent human papillomavirus vaccine (4vHPV [Gardasil, Merck and Co.]); group 2 received MenB-FHbp and saline; and group 3 received 4vHPV and saline.

One month following the third dose, 81.0% (95% confidence interval [CI] = 78.0%–83.7%) of subjects in group 1 and 83.9% (CI = 81.1%–86.4%) of subjects in group 2 had a composite response to all four strains tested (*2,18*). One month following the second of 3 doses, approximately 50% of the subjects in each study group had a composite response to all four strains. In studies conducted in Europe among persons aged 11–18 years, the hSBA responses in subjects who received MenB-FHbp according to the same schedule were similar to hSBA antibody responses in subjects in the U.S. study (*3,18*).

Evaluation of concomitant administration of MenB-FHbp with vaccines routinely administered to adolescents in the United States or Europe occurred in three trials. Subjects received MenB-FHbp coadministered with 4vHPV, quadrivalent meningococcal conjugate vaccine (MenACWY [Menactra, Sanofi Pasteur]), tetanus-diphtheria-acellular pertussis vaccine (Tdap, [Adacel, Sanofi Pasteur]), or tetanus-diphtheria-acellular pertussis-inactivated polio (Tdap/IPV [Repevax, Sanofi Pasteur]) vaccines, depending on the study population in the trial. Except for the antibody response to HPV type 18, no immunogenic interference was observed for serogroup B or concomitant vaccine antigens (HPV types 6, 11, 16, MenACWY, tetanus, diphtheria, pertussis, and IPV antigens) when MenB-FHbp was administered concomitantly (*4,5*). For HPV type 18, noninferiority criteria (lower bound of the CI of the geometric mean titer ratio >0.67) were not met for the geometric mean titer ratio at 1 month after the third 4vHPV dose (lower bound of the CI for the geometric mean titer ratio was 0.62); however, for each HPV vaccine type, ≥99% of subjects achieved seroconversion.

Antibody persistence through 48 months after dose 3 for MenB-FHbp was evaluated in a clinical trial (Pfizer, unpublished data). The data demonstrate an initial rapid decline in antibodies after vaccination followed by a flattening out of the antibody curve at approximately 6 months after the third dose. At 48 months, >50% of vaccinated subjects continued to demonstrate hSBA titers greater than or equal to the lower limit of quantification against three of the four strains tested (Pfizer, unpublished data).

In seven clinical trials (*2–5*) (Pfizer, unpublished data), a total of 9,808 subjects received at least 1 dose of MenB-FHbp; four subjects reported seven serious adverse events that were considered by the study investigator to be related (or possibly related) to the vaccine.* All vaccine-related serious adverse events resolved without sequelae. No increased risk for any specific serious adverse event considered to be clinically significant was identified in any of the studies. No deaths were considered to be related to MenB-FHbp. The most common solicited adverse reactions observed in the 7 days after receipt of MenB-FHbp in the clinical trials were pain at the injection site (≥85%), fatigue (≥40%), headache (≥35%), myalgia (≥30%), and chills (≥15%) (*18*).

MenB-4C

MenB-4C consists of three recombinant proteins (neisserial adhesion A [NadA], factor H binding protein [FHbp] fusion protein, and neisserial heparin binding antigen [NHBA] fusion protein) and outer membrane vesicles (OMVs) containing outer membrane protein PorA serosubtype P1.4. MenB-4C is licensed as a 2-dose series, with doses administered at least 1 month apart, although in some studies, MenB-4C doses were administered up to 6 months apart. No data are available following 3 doses of MenB-4C in a North American population.

The immunogenicity and safety of MenB-4C in adolescents and young adults were evaluated in five clinical trials; three randomized controlled trials, one randomized uncontrolled trial, and one immunogenicity extension study (*6–10,17,19*). In a randomized controlled trial conducted in Chile, persons aged 11–17 years received 2 doses of MenB-4C 1, 2, or 6 months apart. One month following the second dose, 90%–94% of subjects had a composite response to all three strains tested, depending on the vaccination schedule administered; 77%–94% of subjects had an hSBA titer of ≥1:4 against all three strains tested at 18–24 months after the second dose, depending on the vaccination schedule administered (*9*).

In a randomized controlled trial conducted in the United Kingdom, a subset of enrolled subjects (university students aged 18–24 years) received 2 doses of MenB-4C vaccine 1 month apart. One month following the second dose, 88% (CI = 82%–93%) of subjects had a composite response to all three strains tested; 66% (CI = 58%–72%) of the subjects had a composite response to all three strains tested at 11 months

* The administration of the investigational vaccine and a serious adverse event were considered reasonably related in time and the serious adverse event could not be explained by causes other than exposure to the investigational vaccine. The reported serious adverse events included pyrexia (1), vomiting (1), vertigo (1), chills (1), headache (1), anaphylaxis (1), and neutropenia (1).

after the second dose (*8*). In a randomized uncontrolled trial conducted in Australia and Canada, persons aged 11–17 years received 2 doses of MenB-4C 1 month apart. One month following the second dose, 63% (CI = 57%–68%) of subjects had a composite response to all three strains tested (*7*,*19*).

In three clinical trials for which a control group was available, serious adverse events were assessed in 2,716 subjects who received at least 1 dose of MenB-4C and for whom safety data were collected through 6 months postvaccination (*6*,*8*,*10*). Five serious adverse events were considered by the study investigator to be related (or possibly related) to the vaccine.[†] Rates of serious adverse events were similar in the vaccine and the control groups. In addition, information about serious adverse events was collected during three vaccination campaigns in response to three outbreaks of serogroup B meningococcal disease (at two U.S. universities and in one region of Canada). A total of 59,091 participants in the vaccination campaigns received at least 1 dose of MenB-4C. Three serious adverse events were considered to be related (or possibly related) to the vaccine[§]; all resolved with no sequelae (CDC and Novartis, unpublished data). No deaths were considered to be related to MenB-4C in the clinical trials or campaigns. The most common solicited adverse reactions observed in the 7 days after receipt of MenB-4C in the clinical trials were pain at the injection site (≥83%), myalgia (≥48%), erythema (≥45%), fatigue (≥35%), headache (≥33%), induration (≥28%), nausea (≥18%), and arthralgia (≥13%) (*19*). Immunogenicity and safety data regarding MenB-4C when coadministered with vaccines routinely administered to U.S. adolescents are not available.

Summary of ACIP Deliberations and Rationale

The available data suggest that MenB vaccines might be an important step for controlling serogroup B meningococcal disease. Although current data suggest they will protect against the majority of currently circulating strains, these vaccines are not expected to provide protection against disease caused by all serogroup B strains circulating in the United States. Additional studies assessing breadth of strain coverage are ongoing, and ACIP will review results as they become available. Immune responses following MenB vaccination in the studies described were evaluated after completion of the primary immunization series, but no data are available on vaccine effectiveness against clinical disease endpoints or duration of protection against clinical disease. On the basis of the limited available data, no concerning patterns of serious adverse events have been reported for MenB vaccines; additional safety data and postlicensure safety surveillance data are needed and will be reviewed by ACIP as they become available. In addition, the potential impact of MenB vaccines on nasopharyngeal carriage and herd protection is inconclusive, as is the potential impact vaccine introduction might have on the population of *Neisseria meningitidis*.

After reviewing the available data, ACIP supported consideration of vaccination of all adolescents rather than college students only, primarily because an important number of serogroup B meningococcal disease cases occurs in persons aged 18–23 years who are not attending college, and vaccinating college students only is estimated to prevent the fewest cases and deaths among all the options considered (Table 2). However, ACIP also acknowledges the impact that cases and outbreaks have on college campuses, both in terms of the cost for vaccination campaigns in response to these outbreaks as well as public concern. On the basis of the available antibody persistence data, ACIP concluded that a preference to administer the MenB series in later adolescence exists, preferably at

Summary

What is currently recommended?

The Advisory Committee on Immunization Practices recommends routine vaccination of all adolescents aged 11–18 years with a quadrivalent meningococcal conjugate vaccine (MenACWY). A single dose should be administered at age 11 or 12 years with a booster dose at age 16 years for persons who receive the first dose before age 16 years. Routine vaccination of certain persons at increased risk for meningococcal disease with MenACWY and serogroup B meningococcal (MenB) vaccine is also recommended.

Why are the recommendations being modified now?

Two serogroup B meningococcal vaccines were recently licensed by the Food and Drug Administration and approved for use in persons aged 10–25 years. The evidence supporting the use of MenB vaccines in adolescents and young adults was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation framework. The recommendation was designated as Category B (recommended for individual clinical decision making).

What are the new recommendations?

A MenB vaccine series may be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16–18 years.

[†] The administration of the investigational vaccine and a serious adverse event were considered reasonably related in time and the serious adverse event could not be explained by causes other than exposure to the investigational vaccine. The reported serious adverse events included tremor (1), dyspnea (1), acute thyroiditis (1), and juvenile arthritis (2).

[§] The administration of the investigational vaccine and a serious adverse event were considered reasonably related in time and the serious adverse event could not be explained by causes other than exposure to the investigational vaccine. The reported serious adverse events included rhabdomyolysis (1), anaphylaxis (1), and fever (1).

age 16–18 years, to maximize the likelihood that protection would last into the highest age-related risk period.

The current low prevalence of disease, coupled with the fact that important data for making policy recommendations for MenB vaccines are not yet available, resulted in ACIP determining that insufficient evidence exists to make a routine public health recommendation that all adolescents be vaccinated with MenB vaccine. Given the seriousness of meningococcal disease and the availability of licensed vaccines, ACIP agreed that sufficient evidence exists to encourage individual clinical decision making.

Recommendations

A MenB vaccine series may be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16–18 years (recommendation Category B).¶

MenB vaccine should either be administered as a 3-dose series of MenB-FHbp or a 2-dose series of MenB-4C. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses. On the basis of available data and expert opinion, MenB-FHbp or MenB-4C may be administered concomitantly with other vaccines indicated for this age, but at a different anatomic site, if feasible.

No randomized controlled clinical trials have been conducted to evaluate use of MenB vaccines in pregnant or lactating women. Vaccination should be deferred in pregnant and lactating women unless the woman is at increased risk (*20*), and, after consultation with her health care provider, the benefits of vaccination are considered to outweigh the potential risks.

Additional information for health care providers and parents can be found on the CDC website at http://www.cdc.gov/meningococcal.

In February 2015, ACIP recommended routine use (recommendation Category A)** of MenB vaccines in certain groups of persons at increased risk for serogroup B meningococcal disease, including during outbreaks of serogroup B meningococcal disease (*20*). College campuses that have recently experienced an outbreak of serogroup B meningococcal disease should continue to follow the recommendations for use of MenB vaccines in outbreak settings that recommend vaccination for persons aged ≥10 years.

Precautions and Contraindications

Before administering MenB vaccines, health care providers should consult the package insert for precautions, warnings, and contraindications (*18*,*19*). Adverse events occurring after 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 (1-800-822-7967) or online (https://vaers.hhs.gov).

¶ Category B recommendations are made for individual clinical decision making.

** Category A recommendations are made for all persons in an age- or risk-factor-based group.

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ACIP members (membership roster for July 2014–June 2015 available at http://www.cdc.gov/vaccines/acip); ACIP Meningococcal Vaccines Work Group.

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