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Updated Recommendations for Use of Meningococcal Conjugate Vaccines --- Advisory Committee on Immunization Practices (ACIP), 2010

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On October 27, 2010, the Advisory Committee on Immunization Practices (ACIP) approved updated recommendations for the use of quadrivalent (serogroups A, C, Y, and W-135) meningococcal conjugate vaccines (Menveo, Novartis; and Menactra, Sanofi Pasteur) in adolescents and persons at high risk for meningococcal disease. These recommendations supplement the previous ACIP recommendations for meningococcal vaccination (*1*,*2*). The Meningococcal Vaccines Work Group of ACIP reviewed available data on immunogenicity in high-risk groups, bactericidal antibody persistence after immunization, current epidemiology, vaccine effectiveness (VE), and cost-effectiveness of different strategies for vaccination of adolescents. The Work Group then presented policy options for consideration by the full ACIP. This report summarizes two new recommendations approved by ACIP: 1) routine vaccination of adolescents, preferably at age 11 or 12 years, with a booster dose at age 16 years and 2) a 2-dose primary series administered 2 months apart for persons aged 2 through 54 years with persistent complement component deficiency (e.g., C5--C9, properidin, factor H, or factor D) and functional or anatomic asplenia, and for adolescents with human immunodeficiency virus (HIV) infection. CDC guidance for vaccine providers regarding these updated recommendations also is included.

Rationale for Adding a Booster Dose to the Adolescent Schedule

The goal of the 2005 ACIP meningococcal immunization recommendations was to protect persons aged 16 through 21 years, when meningococcal disease rates peak. At that time, vaccination was recommended at age 11 or 12 years rather than at age 14 or 15 years because 1) more persons have preventive-care visits at age 11 or 12 years, 2) adding this vaccine at the 11 or 12 year-old visit would strengthen the pre-adolescent vaccination platform, and 3) the vaccine was expected to protect adolescents through the entire period of increased risk. Meningococcal conjugate vaccines were licensed in 2005 based on immunogenicity (because a surrogate of protection had been defined) and safety data. After licensure, additional data on bactericidal antibody persistence, trends in meningococcal disease epidemiology in the United States, and VE have indicated many adolescents might not be protected for more than 5 years. Therefore, persons immunized at age 11 or 12 years might have decreased protective immunity by ages 16 through 21 years, when their risk for disease is greatest.

Meningococcal disease incidence has decreased since 2000, and incidence for serogroups C and Y, which represent the majority of cases of vaccine-preventable meningococcal disease, are at historic lows. However, the peak in disease among persons aged 18 years (Figure) has persisted, even after routine vaccination was recommended in 2005. In the 2009 National Immunization Survey-Teen, 53.6% of adolescents aged 13 through 17 years had received a dose of meningococcal vaccine (*3*). From 2000--2004 to 2005--2009, the estimated annual number of cases of serogroups C and Y meningococcal

disease decreased 74% among persons aged 11 through 14 years but only 27% among persons aged 15 through 18 years. Cases of meningococcal disease caused by serogroups C and Y among persons who were vaccinated with meningococcal conjugate vaccine have been reported. An early VE analysis that modeled expected cases of disease in vaccinated persons estimated a VE of 80%--85% up to 3 years after vaccination (*4*). In 2010, CDC received 12 reports of serogroup C or Y meningococcal disease among persons who had received a meningococcal conjugate vaccine. The mean age of these persons was 18.2 years (range: 16 through 22 years). The mean time since vaccination was 3.25 years (range: 1.5--4.6 years). Five of these 12 persons had an underlying condition that might have increased their risk for meningococcal disease (CDC, unpublished data, 2010).

A case-control study evaluating the VE of meningococcal conjugate vaccine was begun in January 2006 (ACIP meeting, October 2010). Because Menactra was the only licensed vaccine until February 2010, the preliminary results are estimates for Menactra only; no data are available regarding the effectiveness of Menveo. As of October 1, 2010, 108 case-patients and 158 controls were enrolled in the effectiveness study. The overall VE estimate in persons vaccinated 0--5 years earlier was 78.0% (95% confidence interval [CI] = 29%--93%). VE for persons vaccinated less than1 year earlier was 95% (CI = 10%--100%), VE for persons vaccinated 1 year earlier was 91% (CI = 10%--101%), and VE for persons vaccinated 2 through 5 years earlier was 58% (CI = -72%--89%). Although the CIs around the point estimates are wide, the ACIP Work Group concluded that VE wanes.

The ACIP Work Group also concluded that serologic data are consistent with waning immunity. Three characteristics of conjugate vaccines are believed to be important for establishing long-term protection against a bacterial pathogen: memory response, herd immunity, and circulating antibody (*5*). Recent data from the United Kingdom indicate that although vaccination primes the immune system, the memory response after exposure might not be rapid enough to protect against meningococcal disease. After initial priming with a serogroup C meningococcal conjugate vaccine (MenC), a memory response after a booster dose was not measurable until 5--7 days later (*6*). The incubation period for meningococcal disease usually is less than 3 days. Although herd immunity has been an important component associated with long-term protection with MenC vaccine in the United Kingdom and other countries, immunization coverage has increased slowly in the United States, and to date no evidence of herd immunity has been observed (ACIP meeting, October 2010). Therefore, the Work Group concluded that circulating bactericidal antibody is critical for protection against meningococcal disease. The Work Group took into consideration the proportion of subjects with bactericidal antibody levels above thresholds considered protective, depending on the assay used, evaluating antibody persistence in five studies (Table 1). Although each study tested a small number of vaccine recipients, the Work Group concluded that the studies found sufficient evidence to indicate that approximately 50% of persons vaccinated 5 years earlier had bactericidal antibody levels protective against meningococcal disease. Therefore, more than 50% of persons immunized at age 11 or 12 years might not be protected when they are at higher risk at ages 16 through 21 years.

Two studies evaluated the response after a booster dose of Menactra at 3 and 5 years after the primary vaccination (*7*; ACIP meeting, June 2009). At both 3 and 5 years after the first dose, the booster dose elicited substantially higher geometric mean antibody titers (GMT), compared with the titers elicited by a primary dose. Using a complement serum bactericidal activity (SBA) assay and baby rabbit complement (brSBA) as a measure of immune response, a booster dose administered 5 years after the first dose elicited a GMT for serogroup C of 23,613, compared with 9,045 among subjects administered a primary dose (ACIP meeting, October 2010). As expected with conjugate vaccines, the first dose primes the immune system to have a strong response to the booster dose. Local and systemic reactions to the booster were comparable to those in persons receiving a first dose. The duration of protective antibody after the booster dose is not known but is expected to last through age 21 years for booster doses administered at ages 16 through 18 years.

Optimizing meningococcal vaccination. Despite the current low burden of meningococcal disease, the ACIP Work Group agreed that because of mounting evidence of waning immunity by 5 years postvaccination, vaccinating adolescents with a single dose at age 11 or 12 years is not the best strategy for protection through age 21 years. The Work Group considered two other options for optimizing protection: moving the dose from age 11 or 12 years to age 14 or 15 years or vaccinating at age 11 or 12 years and providing a booster dose at age 16 years. Although a single dose at age 14 or 15 years likely would protect most adolescents through the higher risk period at ages 16 through 21 years, the opportunities to administer vaccine at age 14 or 15 years might be more limited. Data indicate that as adolescents grow older, they are less likely to visit a health-care provider for preventive care (*8*). Adding a booster dose to the recommended schedule would provide more opportunities to increase vaccination coverage, while persons aged 11 through 13 years would continue to be protected. An economic analysis comparing the three adolescent vaccination strategies concluded that administering a booster dose has a cost per quality-adjusted life year similar to that of a single dose at age 11 years or age 15 years but is estimated to prevent twice the number of cases and deaths (CDC, unpublished data, 2010).

Rationale for 2-Dose Primary Series for Persons with a Reduced Response to a Single Dose

Evidence supporting the need for a 2-dose primary meningococcal vaccine series for the small number of persons at increased risk for meningococcal disease was reviewed. Data indicated that SBA could be increased with 2 doses, 2 months apart. For persons who are asplenic or have HIV infection, a 2-dose primary series improves the initial immune response to vaccination. A 2-dose primary series in patients with persistent complement component deficiency will help achieve the high levels of SBA activity needed to confer protection in the absence of effective opsonization.

The complement pathway is important to preventing meningococcal disease, and *Neisseria meningitidis* is the primary bacterial pathogen affecting persons with late component complement (LCCD) or properidin deficiency. Although persons with LCCD are able to mount an overall antibody response equal to or greater than complement-sufficient persons after vaccination with quadrivalent meningococcal polysaccharide vaccine (MPSV4), antibody titers wane more rapidly in persons with complement component deficiency, and higher antibody levels are needed for other clearance mechanisms such as opsophagocytosis to function (*9,10*). Asplenic persons are at increased risk for invasive infection caused by many encapsulated bacteria, including *N. meningitidis*. Moreover, the mortality rate is 40%--70% among these persons when they become infected with *N. meningitidis*. Asplenic persons achieve significantly lower geometric mean SBA titers than healthy persons after vaccination with meningococcal C conjugate vaccine, with 20% not achieving brSBA titers ≥1:8. This proportion was reduced to 7% when a second dose of vaccine was administered to nonresponders 2 months later, suggesting a booster might be effective in achieving higher circulating antibody levels and improving immunologic memory (*11*).

Patients with HIV infection likely are at increased risk for meningococcal disease, although not to the extent that they are at risk for invasive *Streptococcus pneumoniae* infection. The risk to persons with HIV infection also is not as great as to persons with complement component deficiency or asplenia. One study has investigated the response rates to a single dose of meningococcal conjugate vaccinate among HIV-infected adolescents. Response to vaccination measured by brSBA titers ≥1:128 was 86%, 55%, 73%, and 72% for serogroups A, C, Y, and W-135, respectively. Response rates were significantly lower among patients with a CD4+ T-lymphocyte percentage of <15% or viral loads >10,000 copies/mL (*12*).

The immunogenicity and safety of a 2-dose primary series has not been studied in older children and adults. However, Menactra and Menveo have been studied following administration as a 2-dose primary series in infants and young children. Infants vaccinated with a 2-dose primary series of Menactra at ages 9 months and 12 through 15 months achieved high antibody titers after the second dose. Administration

of 2 doses of Menveo 2 months apart to children aged 2 through 5 years was associated with a similar rate of adverse events as a single dose (*13*).

Recommendation for Routine Vaccination of Persons Aged 11 Through 18 Years

ACIP recommends routine vaccination of persons with quadrivalent meningococcal conjugate vaccine at age 11 or 12 years, with a booster dose at age 16 years. After a booster dose of meningococcal conjugate vaccine, antibody titers are higher than after the first dose and are expected to protect adolescents through the period of increased risk through age 21 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, before the peak in increased risk. Persons who receive their first dose of meningococcal conjugate vaccine at or after age 16 years do not need a booster dose. Routine vaccination of healthy persons who are not at increased risk for exposure to *N. meningitidis* is not recommended after age 21 years.

Recommendation for Persons Aged 2 Through 54 Years with Reduced Immune Response

Data indicate that the immune response to a single dose of meningococcal conjugate vaccine is not sufficient in persons with certain medical conditions. Persons with persistent complement component deficiencies (e.g., C5--C9, properidin, factor H, or factor D) or asplenia should receive a 2-dose primary series administered 2 months apart and then receive a booster dose every 5 years. Adolescents aged 11 through 18 years with HIV infection should be routinely vaccinated with a 2-dose primary series. Other persons with HIV who are vaccinated should receive a 2-dose primary series administered 2 months apart. All other persons at increased risk for meningococcal disease (e.g., microbiologists or travelers to an epidemic or highly endemic country) should receive a single dose.

CDC Guidance for Transition to an Adolescent Booster Dose

Some schools, colleges, and universities have policies requiring vaccination against meningococcal disease as a condition of enrollment. For ease of program implementation, persons aged 21 years or younger should have documentation of receipt of a dose of meningococcal conjugate vaccine not more than 5 years before enrollment. If the primary dose was administered before the 16th birthday, a booster dose should be administered before enrollment in college. The booster dose can be administered anytime after the 16th birthday to ensure that the booster is provided. The minimum interval between doses of meningococcal conjugate vaccine is 8 weeks.

No data are available on the interchangeability of vaccine products. Whenever feasible, the same brand of vaccine should be used for all doses of the vaccination series. If vaccination providers do not know or have available the type of vaccine product previously administered, any product should be used to continue or complete the series. Persons with complement component deficiency, asplenia, or HIV infection who have previously received a single dose of meningococcal conjugate vaccine should receive their booster dose at the earliest opportunity.

These updated meningococcal conjugate vaccine recommendations from ACIP have been summarized (Table 2). Additionally, a meningococcal conjugate vaccine information statement is available at http://www.cdc.gov/vaccines/pubs/vis/default.htm, and details regarding the routine meningococcal conjugate vaccination schedule are available at http://www.cdc.gov/vaccines/recs/schedules/default.htm#child. Adverse events after receipt of any vaccine should be reported to the Vaccine Adverse Event Reporting System at http://vaers.hhs.gov .

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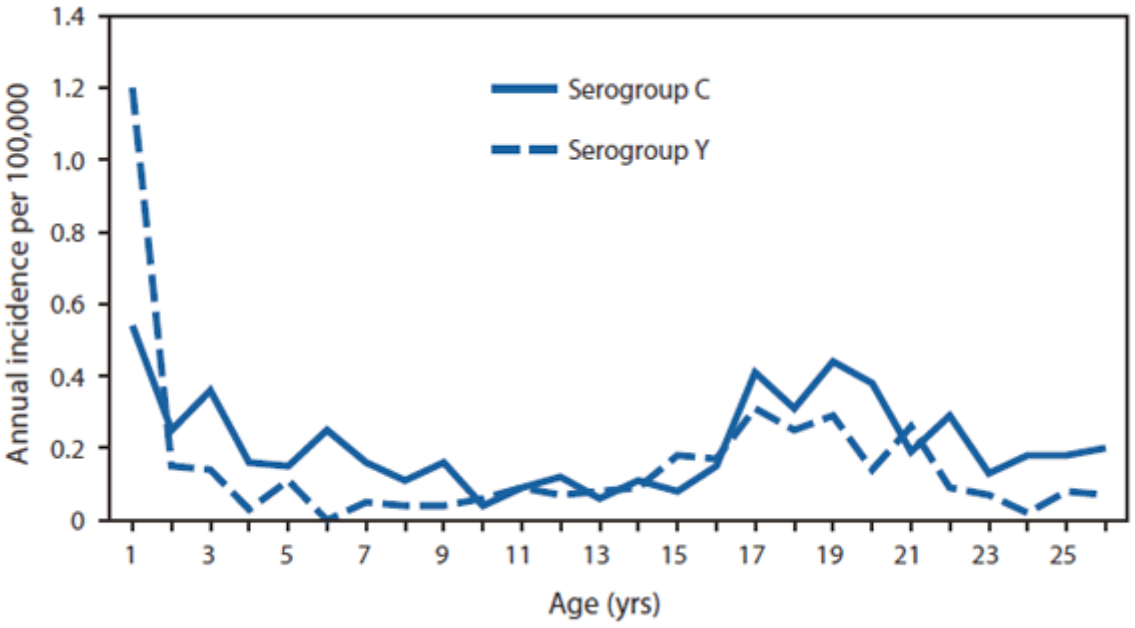
FIGURE. Annual incidence of meningococcal disease (serogroup C and serogroup Y), by age --- Active Bacterial Core surveillance (ABCs), United States, 1999--2008



Alternate Text: The figure above shows the annual incidence of meningococcal disease (serogroup C and serogroup Y) per 100,000 population, by age, according to the Active Bacterial Core surveillance (ABCs) in the United States, during 1999-2008. Incidence peaked at approximately 18 years.

TABLE 1. Summary of serogroup C bactericidal antibody persistence as determined by serum bactericidal activity (SBA) 2--5 years after vaccination with Menveo and/or Menactra

Age group (yrs) at vaccination	Years postvaccination	Serogroup C SBA	Vaccine	No. of vaccine recipients in study	% of recipients with protective antibody levels
11 through 18*	2	% hSBA ≥1:8	Menveo	273	62
			Menactra	185	58
11 through 18†	3	% hSBA ≥1:4	Menactra	52	35
			MPSV4	48	35
11 through 18§	3	% brSBA ≥1:128	Menactra	71	75
			MPSV4	72	60
2 through 10§	5	% brSBA ≥1:128	Menactra	108	55
			MPSV4	207	42
11 through 18§	5	% brSBA ≥1:128	Menactra	16	56
			MPSV4	10	60

Abbreviations: hSBA = SBA using human complement; brSBA = SBA using baby rabbit complement; MPSV4 = quadrivalent meningococcal polysaccharide vaccine.

* **Source:** Gill C, Baxter R, Anemona A, Ciavarro G, Dull P. Persistence of immune responses after a single dose of Novartis meningococcal serogroup A, C, W-135 and Y CRM-197 conjugate vaccine (Menveo) or Menactra among healthy adolescents. Human Vaccines 2010;6:881--7.

† **Source:** Vu DM, Welsch JA, Zuno-Mitchell P, Dela Cruz JV, Granoff DM. Antibody persistence 3 years after immunization of adolescents with quadrivalent meningococcal conjugate vaccine. J Infect Dis 2006;193:821--8.

§ **Source:** Proceedings of the Advisory Committee on Immunization Practices (ACIP) meeting, June 2009.

TABLE 2. Summary of meningococcal conjugate vaccine recommendations, by risk group --- Advisory Committee on Immunization Practices (ACIP), 2010

Risk group	Primary series	Booster dose
Persons aged 11 through 18 years	1 dose, preferably at age 11 or 12 years	At age 16 years if primary dose at age 11 or 12 years At age 16 through 18 years if primary dose at age 13 through 15

		years No booster needed if primary dose on or after age 16 years At age 16 years if primary dose at age 11 or 12 years
HIV-infected persons in this age group	2 doses, 2 months apart	At age 16 through 18 years if primary dose at age 13 through 15 years No booster needed if primary dose on or after age 16 years
Persons aged 2 through 55 years with persistent complement component deficiency* or functional or anatomical asplenia	2 doses, 2 months apart	Every 5 years At the earliest opportunity if a 1-dose primary series administered, then every 5 years
Persons aged 2 through 55 years with prolonged increased risk for exposure†	1 dose	Persons aged 2 through 6 years: after 3 years Persons aged 7 years or older: after 5 years§

Abbreviation: HIV = human immunodeficiency virus.

* Such as C5--C9, properidin, or factor D.

† Microbiologists routinely working with *Neisseria meningitidis* and travelers to or residents of countries where meningococcal disease is hyperendemic or epidemic.

§ If the person remains at increased risk.

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