

## POLICY STATEMENT

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

Committee on Infectious Diseases

## Prevention and Control of Meningococcal Disease: Recommendations for Use of Meningococcal Vaccines in Pediatric Patients

**ABSTRACT.** Two peaks in the incidence of invasive meningococcal disease (IMD) occur in pediatric patients: infants younger than 1 year and adolescents 15 to 18 years of age. Although the incidence of IMD is highest in infants, the case-fatality rate is highest in adolescents (~20%). Epidemiologic studies also have demonstrated increased risk of IMD among college freshman living in dormitories compared with other college students and similarly aged persons in the general population. At least 75% of cases of IMD in 11- to 18-year-olds are caused by serogroups A, C, Y, and W-135; thus, IMD potentially is preventable by immunization with quadrivalent meningococcal vaccines. Meningococcal A, C, Y, W-135 conjugate vaccine (MCV4) was licensed in 2005 for use in people 11 to 55 years of age. On the basis of data indicating increased risk of meningococcal disease and fatality among certain adolescents and college students, the American Academy of Pediatrics recommends administration of MCV4 to young adolescents (at the 11- to 12-year visit), students entering high school or 15-year-olds, and college freshmen who will be living in dormitories. For pediatric patients 11 years and older who are at increased risk of meningococcal disease, MCV4 also is recommended. The purposes of this statement are to provide the rationale for routine use of MCV4 in adolescents and to update recommendations for use of the meningococcal polysaccharide vaccine in pediatric patients. *Pediatrics* 2005;116:496–505; *meningococcal disease*.

ABBREVIATIONS. IMD, invasive meningococcal disease; CDC, Centers for Disease Control and Prevention; AAP, American Academy of Pediatrics; MPSV4, tetravalent meningococcal (A, C, Y, W-135) polysaccharide vaccine; FDA, Food and Drug Administration; MCV4, tetravalent meningococcal (A, C, Y, W-135) conjugate vaccine; SBA, serum bactericidal activity; rSBA, serum bactericidal assay using baby rabbit serum; GMT, geometric mean titer; Td, adult-type diphtheria and tetanus toxoids; OMP, outer membrane protein.

## BACKGROUND INFORMATION

Each year, 1400 to 3000 cases of invasive meningococcal disease (IMD) occur in the United States, reflecting the 5- to 7-year cycles in incidence.<sup>1</sup> Although the annual incidence of IMD is relatively low, ranging from 0.5 to 1.1 per 100 000 population (Centers for Disease Control and Prevention [CDC]), case-fatality rates and sequelae among

survivors are appreciable. Death occurs in ~10% to 14% of cases, and significant sequelae including limb or digit amputation, skin scarring, neurologic disabilities, and hearing loss occur in 11% to 19% of cases.<sup>2</sup> Although only a portion of these cases present clinically as meningitis, *Neisseria meningitidis* has become the leading cause of bacterial meningitis in children after the dramatic reductions in the incidence of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b infections achieved after introduction of conjugate vaccines for these pathogens.

The incidence of IMD in pediatric patients has 2 peaks. The highest incidence of meningococcal disease is in infants younger than 12 months, but a second, lower peak occurs during adolescence.<sup>2</sup> Adolescents 15 years or older are more likely than infants and children to have meningococemia without meningitis (40% vs 20%, respectively), shock at presentation (69% vs 27%, respectively), and a fatal outcome (22.5% vs 4.6%, respectively).<sup>3</sup> Not surprisingly then, adolescents have the highest case-fatality rate (estimated at ~20%) of any age group. Survivors at any age are at risk of permanent sequelae.

The American Academy of Pediatrics (AAP) previously recommended tetravalent meningococcal (A, C, Y, W-135) polysaccharide vaccine (MSPV4 [Menomune-A/C/Y/W-135; Sanofi Pasteur, Swiftwater, PA]) for use in certain high-risk children and adolescents, including travelers to countries with epidemic or hyperendemic meningococcal disease, for people who have certain medical conditions (terminal complement component deficiencies and anatomic or functional asplenia), and for control of meningococcal disease outbreaks attributable to strains in the vaccine.<sup>4</sup> Previous AAP guidelines for college freshmen have emphasized education about meningococcal disease and the availability of a meningococcal vaccine without recommending routine use of meningococcal polysaccharide vaccine.<sup>5</sup>

The new tetravalent meningococcal (A, C, Y, W-135) conjugate vaccine (MCV4 [Menactra; Sanofi Pasteur]), licensed by the Food and Drug Administration (FDA) on January 14, 2005, for use in people 11 to 55 years of age, should become an important addition to existing meningococcal disease-preventive measures. This statement provides the recommendations of the AAP for prevention and control of meningococcal disease in pediatric patients through

immunization with MPSV4 as well as the new MCV4. More detailed information regarding contemporary epidemiology of IMD, evaluation and management of suspected outbreaks of IMD, cost-effectiveness analyses for meningococcal vaccines, and recommendations for use of meningococcal vaccines and chemoprophylaxis in adults can be found in the statement of the Advisory Committee on Immunization Practices of the CDC.<sup>2</sup>

### EPIDEMIOLOGY OF IMD

The overall case-fatality rate of IMD in children and adults in the United States is 10% to 14%.<sup>2</sup> From 1991 to 2002, the highest incidence of IMD in the United States (9.2 per 100 000) was among infants younger than 1 year (Fig 1); the rate among adolescents 11 to 19 years of age (1.2 per 100 000) also was higher than that for the general population. Thirty-eight percent of IMD cases were observed in infants and children younger than 11 years, but adolescents had the highest case-fatality rate (~20%).

Certain patients are at increased risk of IMD, including patients with deficiency of the terminal complement pathway (C5-C9) or C3 and patients with anatomic or functional asplenia (ie, sickle cell disease). Healthy children also can be at increased risk of meningococcal disease if they are traveling to or living in areas outside the United States where IMD is hyperendemic or epidemic or if they are involved in a confirmed outbreak.

In the United States, more than 98% of cases of IMD in children and adults are sporadic, but since 1991, the frequency of localized outbreaks has increased, especially in schools.<sup>6</sup> The proportion of meningococcal disease caused by serogroup Y has increased from 2% in 1989–1991<sup>7</sup> to 37% in 1997–2002.<sup>2</sup> Currently, serogroups B, C, and Y are the major causes of IMD in the United States, each being responsible for approximately one third of all cases. The proportion of cases caused by each serogroup varies by age group; more than half of cases among infants younger than 1 year are caused by serogroup B, for which no vaccine is licensed or available in the United States.<sup>8</sup> Seventy-five percent of all cases of

meningococcal disease in people 11 to 18 years of age are caused by serogroups (A, C, Y, or W-135) included in currently available vaccines.<sup>2</sup> The incidence of IMD caused by these vaccine-preventable serotypes peaks in people 18 years of age (1.8 per 100 000), is beginning to increase substantially at 15 years of age, and decreases by 19 years of age (Fig 2).

Three studies conducted in the United States address the risk of meningococcal disease among college students.<sup>9–11</sup> Each study demonstrated that the risk of meningococcal disease was higher in college students who reside in dormitories than in other college students. The earliest of these reports described a low overall incidence of meningococcal disease in college students (1 per 100 000 population per year), but IMD occurred 9 to 23 times more frequently in students residing in dormitories than in students residing in other types of accommodations.<sup>11</sup> In the second study, which was a retrospective, cohort investigation conducted in Maryland for the period of 1992–1997, the overall incidence of IMD in college students was similar to the incidence in the US population of people the same age (1.74 vs 1.44 per 100 000, respectively), but rates were significantly higher among students living in dormitories compared with students living off campus (3.2 vs 0.96 per 100 000;  $P = .05$ ).<sup>10</sup> Finally, US surveillance data from the 1998–1999 school year suggested that the overall rate of meningococcal disease among undergraduate college students was lower than the rate among people 18 to 23 years of age who were not enrolled in college (Table 1; 0.7 vs 1.5 per 100 000, respectively). Among the ~600 000 freshmen who lived in dormitories during this period, the rate (5.1 per 100 000) was higher than any age group in the population other than children younger than 2 years but lower than the threshold of 10 per 100 000 recommended for initiating meningococcal immunization campaigns.<sup>9</sup>

Although ample data define the risk for IMD among certain college students, there are no studies among adolescents in living circumstances that may be similar to college dormitories (boarding schools, “sleep-away” camps, etc). In the absence of data establishing increased risk, adolescents in these cir-

**Fig 1.** Burden of disease (percentage of cases) and rates of invasive meningococcal disease (all serogroups) in the United States, 1991–2002, according to age (CDC, Active Bacterial Core surveillance).<sup>2</sup> The solid line correlates with rate per 100 000 population, and bars correlate with burden of disease.

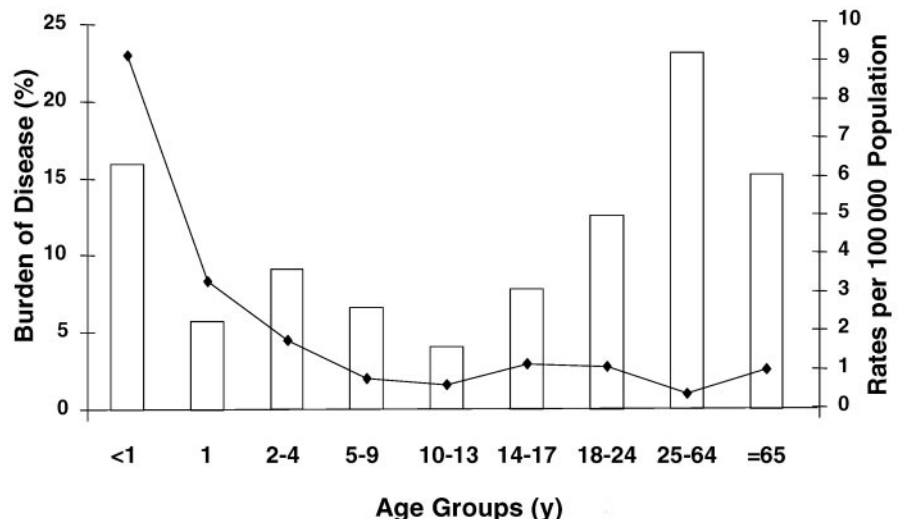


Fig 2. US rates of meningococcal disease (A, C, Y, and W-135) in 11- to 30-year-olds, 1991–2002 (CDC, Active Bacterial Core surveillance).<sup>2</sup>

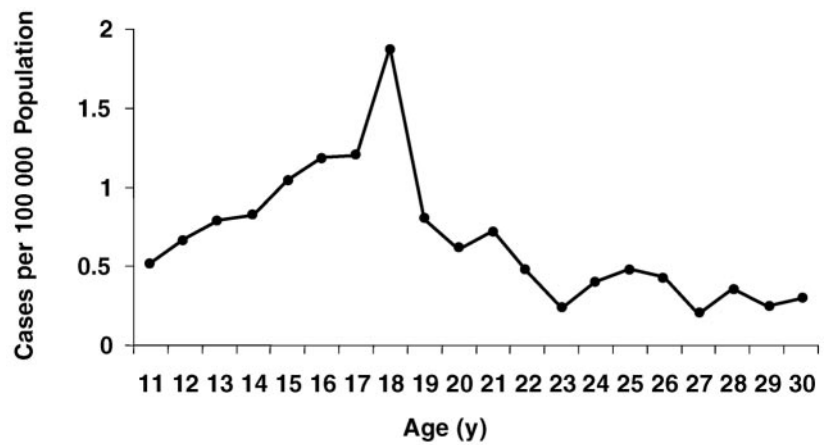


TABLE 1. Rates of Meningococcal Disease in the United States (September 1998 to August 1999<sup>9</sup>)

Age Group	No. of Cases	Population	Rate per 100 000
All 18- to 23-y-olds	304	22 070 535*	1.4
18- to 23-y-olds, nonstudents	211	14 579 322*†	1.4
All college students	96	14 897 268†	0.6
Undergraduates	93	12 771 228†	0.7
Freshmen‡	44	2 285 001†	1.9
Dormitory residents	48	2 085 618‡§	2.3
Freshmen living in dormitories†	30	591 587‡§	5.1

\* 1998 Census data.

† National Center for Education Statistics, US Department of Education, 1996–1997.

‡ First-time freshman defined as student's first enrollment in any postsecondary education.

§ National College Health Risk Behavior Survey, United States, 1995.

cumstances should be immunized only if they fall into a recommended group by age or underlying medical condition.

In 2000, the Advisory Committee on Immunization Practices and AAP Committee on Infectious Diseases<sup>1,5</sup> concluded that college students who live in dormitories are at increased risk of meningococcal disease relative to other people their age. They recommended that college students and their parents be informed by health care professionals of the risks of meningococcal disease and potential benefits of immunization with MPSV4, that college and university health services facilitate implementation of educational programs concerning meningococcal disease and availability of immunization services, and that the vaccine be made available to those requesting immunization. As of August 2004, 31 states have adopted legislation requiring colleges to provide information on risks of meningococcal disease to matriculating students and students residing on campus. Eleven of those states mandate immunization of students living on campus unless an immunization waiver is provided.

#### MENINGOCOCCAL VACCINES

There are 2 meningococcal vaccines licensed for use in children and adults. Menomune-A/C/Y/W-135 (MPSV4) was licensed in 1981 for use in children older than 2 years as well as adults and has been recommended by the AAP for use in these children only if they are at increased risk of meningococcal disease.<sup>4</sup> Menactra (MCV4) was licensed in 2005 for use in children 11 years and older and adults

through 55 years of age. Currently, MCV4 is being considered for licensure by the FDA for use in children 2 to 10 years of age.

#### Meningococcal Polysaccharide Vaccine

##### Vaccine Composition and Administration

Each dose of MPSV4 consists of 50 µg each of the 4 (A, C, Y, and W-135) purified meningococcal capsular polysaccharides. MPSV4 (Menomune-A/C/Y/W-135) is available in single-dose (0.5-mL) and multiple-dose (5-mL) vials. MPSV4 is administered subcutaneously as a single 0.5-mL dose. MPSV4 can be administered concomitantly with other vaccines at different anatomic sites.<sup>12,13</sup> Protective concentrations of antibodies usually are achieved within 7 to 10 days of immunization.<sup>14</sup>

##### Immunogenicity and Efficacy

MPSV4 (Menomune-A/C/Y/W-135) was licensed in the United States in 1981 on the basis of safety and immunogenicity data. Immunogenicity of this vaccine was compared with immunogenicity of an existing bivalent A and C meningococcal polysaccharide vaccine, which had demonstrated 97% efficacy against serogroup A and 90% efficacy against serogroup C meningococcal disease in military recruits.<sup>15</sup> The immunologic criterion used for licensing was an increase in serum bactericidal activity (SBA) of fourfold or greater in 90% of adults 3 to 4 weeks after immunization.

The immunogenicity and efficacy of serogroup A and C meningococcal polysaccharide vaccines are

established. Serogroup A polysaccharide vaccine induces antibodies in some children as young as 3 months of age, although an immune response comparable to that in adults is not achieved until 4 to 5 years of age; serogroup C polysaccharide vaccine is poorly immunogenic in children younger than 24 months. Serogroup A and C polysaccharide vaccines have demonstrated estimated clinical efficacies of more than 85% in school-aged children and adults and are useful in controlling outbreaks.<sup>16,17</sup> Serogroup Y and W-135 polysaccharide vaccines are safe and immunogenic in children older than 2 years and adults, and although clinical efficacy has not been documented, immunization with these polysaccharide vaccines induces high titers of serum bactericidal antibodies, a correlate of protection. The antibody responses to each of the 4 polysaccharides in the tetravalent polysaccharide vaccine are serogroup-specific and independent. Serogroup C polysaccharide vaccine can cause immunologic hyporesponsiveness (reduced antibody response after reimmunization with the same polysaccharide antigen), but the biological significance of this observation is unclear.<sup>18</sup>

#### *Duration of Protection*

In children 2 to 5 years of age, measurable concentrations of antibodies against group A and C polysaccharides decrease substantially during the first 3 years after a single dose of vaccine.<sup>19</sup> Although vaccine-induced protection likely persists in school-aged children and adults for at least 3 years, the efficacy of the group A vaccine administered to children younger than 5 years may decrease markedly within this period of time. In one study, group A vaccine efficacy in children immunized at younger than 4 years decreased from more than 90% to less than 10%; in children given vaccine at older than 4 years of age, vaccine efficacy was 67% 3 years later.<sup>20</sup>

#### *Precautions and Contraindications*

MPSV4 has been used extensively in mass-immunization programs as well as in the military and among international travelers. Adverse reactions to MPSV4 generally are mild; the most frequent reaction is pain and redness at the injection site lasting for 1 or 2 days. Estimates of the incidence of such local reactions have varied, ranging from 4% to 56%. Transient fever occurs in up to 5% of vaccine recipients in some studies but is less common in older children and adults. Most studies report the rate of systemic allergic reactions (eg, urticaria, wheezing, and rash) as 0.0 to 0.1 per 100 000 vaccine doses.<sup>21</sup> Anaphylaxis has been documented in less than 0.1 per 100 000 vaccine doses.<sup>22</sup>

### **Meningococcal Conjugate Vaccines**

#### *Theoretic Advantage of MCV4*

Bacterial polysaccharides, including those comprising the capsule of *N meningitidis*, are T-cell-independent antigens. T-cell-independent antigens do not elicit a memory response. They stimulate mature B lymphocytes but not T lymphocytes, thus inducing a response that is neither long lasting nor character-

ized by anamnestic response after subsequent challenge with the same polysaccharide antigen.<sup>23</sup> Meningococcal polysaccharide vaccines, therefore, have several inherent limitations. Meningococcal polysaccharide vaccines do not confer long-lasting immunity and do not elicit a sustainable reduction of nasopharyngeal carriage of *N meningitidis* to result in herd immunity.<sup>24</sup>

Conjugation (covalent coupling) of polysaccharide to a protein carrier that contains T-cell epitopes changes the expression of the immune response to the polysaccharide from T-cell independent to T-cell dependent, resulting in an improved primary response to the polysaccharide and a strong anamnestic response at reexposure.<sup>25</sup> Both conjugate *H influenzae* type b and conjugate *S pneumoniae* vaccines introduced for mass infant immunization in the United States in 1990 and 2000, respectively, have been successful in reducing the incidence of disease caused by serotypes contained in the vaccines.<sup>1</sup> In addition, both vaccines decrease asymptomatic carriage of the respective bacteria, thus protecting unimmunized individuals through a herd-immunity effect.<sup>1</sup>

#### *Meningococcal Serogroup C Conjugate Vaccine in the United Kingdom*

In November 1999, 3 monovalent serogroup C conjugate vaccines were introduced in the United Kingdom during a national immunization campaign. A routine 3-dose infant immunization series began at the same time as a mass catch-up campaign targeting all children between 12 months and 17 years of age.<sup>26</sup> By 2001–2002, vaccine coverage in the United Kingdom was estimated at 80% in infants, 84% in toddlers, 76% in preschoolers, and 87% in school-aged children.<sup>27</sup> Effectiveness of the meningococcal group C conjugate vaccines within the first year of immunization ranged from 88% to 98% in different age groups.<sup>28</sup> Because the vaccine campaign was initiated in 1999, duration of protection data are not yet available. However, effectiveness among infants who received 3 doses of vaccine at 2, 3, and 4 months of age decreased by 81% after only 1 year.<sup>28</sup> Although the number of cases remains low, likely in part because of vaccine-induced herd immunity, this study raises important questions about the meningococcal vaccine schedule and the need for a booster dose in infants. Carriage rates of group C meningococci in the United Kingdom decreased by 66% during the campaign; incidence of IMD decreased by 67% in unimmunized children 1 to 17 years of age, demonstrating the ability of the conjugate vaccine to elicit herd immunity.<sup>27</sup>

#### *Vaccine Composition and Administration*

MCV4 is a tetravalent meningococcal conjugate vaccine (Menactra) that contains capsular polysaccharides from serogroups A, C, Y, and W-135 (4  $\mu$ g each) conjugated to 48  $\mu$ g of diphtheria toxoid. MCV4 is available only in single-dose (0.5-mL) vials; vaccine is administered as a single 0.5-mL dose. Protective concentrations of antibodies are achieved within 8 days of immunization.

Studies in military recruits conducted in the United States in the 1960s demonstrated that naturally acquired bactericidal antibodies measured by SBA confer protection from IMD. SBA titers of  $\geq 1:4$  using human serum as an exogenous complement source (hSBA) are considered to be the correlate of protection against serogroup C meningococcal disease.<sup>29</sup> This correlate of protection was used in the recent licensure of monovalent serogroup C meningococcal conjugate vaccines in the United Kingdom without the requirement for clinical efficacy trials.<sup>30</sup> However, immunogenicity data supporting the use of these conjugate vaccines were generated by a serum bactericidal assay using baby rabbit serum (rSBA), rather than human serum, as an exogenous complement source.

Additional evaluation of rSBA threshold values were performed by using vaccine efficacy estimates from postlicensure surveillance in the United Kingdom. Postlicensure surveillance data suggested that an rSBA 4 weeks after immunization of  $\geq 1:8$  was most consistent with the observed protective effect.<sup>31</sup> On the basis of these efficacy estimates, rSBA titers of  $< 1:8$  were proposed to be predictive of susceptibility to IMD. The proportion of responders in various clinical trials of meningococcal C conjugate vaccines and on the group C seroprevalence study conducted before introduction of group C conjugate vaccines also provide evidence that rSBA titers of  $\geq 1:8$  correlate with short-term protection.<sup>32</sup> There exist little or no similar data linking immune response to efficacy for serogroups A, Y, or W-135.

MCV4 was licensed on the basis of demonstrated noninferiority to MPSV4 for immunogenicity and safety. MPSV4 had been licensed on the basis of efficacy against serogroup A and C meningococcal disease in military recruits.<sup>33</sup> The primary criterion in determining immunogenic noninferiority of MCV4 to MPSV4 was the percentage of adolescents and adults who had an increase in SBA of fourfold or greater after receiving MCV4 compared with the percentage of those after MPSV4 was used. However, for licensure of MCV4, an rSBA of  $\geq 1:128$  was considered as "protective," because it would not only predict short-term but also long-term clinical efficacy.

A randomized, controlled trial compared the immunogenicity of MCV4 and MPSV4 in adolescents 11 to 18 years of age 28 days after immunization. A similar percentage of subjects achieved at least a fourfold increase in rSBA titers in the MCV4 and MPSV groups (Table 2). The percentage of adolescents with at least a fourfold increase in rSBA was highest for serogroup W-135 (96.7% for MCV4; 95.3% for MPSV4) and lowest for serogroup Y (81.8% for MCV4; 80.1% for MPSV4). The percentage of subjects achieving an rSBA geometric mean titer (GMT) of  $\geq 1:128$  was higher than 98% for all meningococcal serogroups in both MCV4 and MPSV4 recipients.<sup>34</sup>

*Duration of Protection and Reimmunization*

Unlike MPSV4, the duration of protection after MCV4 is not known but is expected to be longer than 3 years; additional studies will be needed to confirm this. More data are anticipated to become available within the next 5 years to guide recommendations regarding reimmunization for people who were immunized previously with MCV4. Reimmunization with MCV4 is indicated for adolescents 11 years and older previously immunized with MPSV4 if they remain at high risk of IMD (eg, people residing in areas in which disease is epidemic). In children 2 to 10 years of age immunized with MPSV4, antibody concentrations decrease rapidly over 2 to 3 years. If indications continue to exist for immunization, use of MCV4 may be considered within 3 to 5 years if adolescents are 11 years or older.<sup>4</sup>

To date, the only data concerning reimmunization with MCV4 come from a study in which 76 adolescents previously immunized with MCV4 and 77 adolescents previously immunized with MPSV4 were compared with 88 age-matched vaccine-naive adolescents.<sup>34</sup> rSBA was measured in sera from these adolescents before (day 0) and 8 and 28 days after immunization with MCV4 (Table 3). Adolescents initially immunized with MCV4 had higher rSBA GMT before reimmunization than adolescents initially immunized with MPSV4; this difference reached statistical significance for serogroup A ( $P < .001$ ) and W-135 ( $P < .001$ ) but not for serogroups C and Y. In addition, a higher percentage of adolescents initially immunized with MCV4 had protective rSBA titers of  $\geq 1:128$  compared

**TABLE 2.** Response of Adolescents to Meningococcal Vaccines 28 Days After Immunization According to Serogroup

Age Group	$\geq 4$ -Fold Increase in rSBA Titer		rSBA GMT		% Subjects With rSBA $\geq 1:128^*$	
	MCV4, % (95% CI)	MPSV4, % (95% CI)	MCV4, GMT	MPSV4, GMT	MCV4	MPSV4
Adolescents (11–18 y)†						
A	92.7 (89.8–95.0)	92.4 (89.5–94.8)	5483.2	3245.7	99.8	100.0
C	91.7 (88.7–94.2)	88.7 (85.2–91.5)	1924.4	1638.9	98.8	98.4
Y	81.8 (77.8–85.4)	80.1 (76.0–83.8)	1322.3	1228.3	99.5	99.3
W-135	96.7 (94.5–98.2)	95.3 (92.8–97.1)	1407.2	1545.0	98.6	98.8

CI indicates confidence interval.

\* Protective titer: SBA  $\geq 1:128$ .

† Number of adolescents in MCV4 group = 423 and in MPSV4 group = 423.

**TABLE 3.** Comparison of rSBA According to Serogroup in Reimmunized\* and Naive 14- to 21-Year-Olds Given MCV4<sup>34</sup>

Immune Status	Day 0			Day 8 After MCV4			Day 28 After MCV4		
	MCV4 Primed (n = 76)	MPSV4 Primed (n = 77)	Naive (n = 88)	MCV4 Primed (n = 76)	MPSV4 Primed (n = 77)	Naive (n = 88)	MCV4 Primed (n = 76)	MPSV4 Primed (n = 77)	Naive (n = 88)
rSBA GMT									
A	1082	171	84	9393	4406	12936	4326	3271	6399
C	211	109	43	18113	1196	7453	8192	665	2955
Y	592	380	211	12808	2896	7053	5846	2327	4366
W-135	447	120	22	9566	1921	5657	4612	1578	2955
Subjects With rSBA $\geq$ 1:128, %†									
A	94.7	70.1	58.0	100.0	100.0	100.0	100.0	100.0	100.0
C	71.1	57.1	45.5	100.0	92.1	98.9	100.0	100.0	100.0
Y	96.1	83.1	74.7	100.0	97.4	100.0	100.0	100.0	100.0
W-135	83.1	67.5	28.4	100.0	100.0	100.0	100.0	100.0	100.0

\* Reimmunized = primed 3 years previously with MCV4 or MPSV4.

† Protective titer.

with adolescents initially immunized with MPSV4 (Table 3). Vaccine-naïve adolescents had low rSBA before immunization compared with adolescents who had received MCV4 or MPSV4 previously.

Response to reimmunization with MCV4 also was assessed by determining the percentage of adolescents initially immunized with MCV4 or MPSV4 with rSBA titers of  $\geq$ 1:128 before (day 0) and 8 and 28 days after administration of MCV4 and with vaccine-naïve controls. All adolescents in each of the 3 groups achieved rSBA titers of  $\geq$ 1:128 28 days after MCV4 (Table 3). Subjects initially primed with MCV4 achieved higher rSBA GMTs compared with vaccine-naïve controls for all serogroups except serogroup A.

#### Concomitant Administration of MCV4 and Other Vaccines

Among adolescents 11 to 18 years of age, a randomized, controlled trial evaluated the immunogenicity and safety of MCV4 administered concomitantly with tetanus and diphtheria toxoids absorbed for adult use (Td; Sanofi Pasteur) versus Td administered concomitantly with placebo and then MCV4 administered 28 days later. Concomitant administration of Td and MCV4 did not adversely affect immune response to antigens in either vaccine.<sup>34</sup> When MCV4 and Td were administered concomitantly, antibody response to diphtheria antigen 28 days after immunization was greater (diphtheria GMT: 120.9 IU/mL) than when Td and MCV4 were administered sequentially 28 days apart (diphtheria GMT: 8.4 IU/mL 28 days after Td dose).

#### Safety

Among adolescents 11 to 18 years of age, safety of administering MCV4 and MPSV4 was assessed in 2 randomized, controlled trials.<sup>34</sup> The percentage of subjects reporting systemic adverse events was similar in both groups (Table 4). Approximately half of the adolescents experienced at least 1 systemic adverse reaction, but less than 5% experienced at least 1 severe systemic reaction. Fever was reported by 3.4% to 5.1% of adolescents who received MCV4 and by 2.5% to 3.0% of adolescents who received MPSV4, a difference that was not significant.

Local adverse reactions were more common among adolescents who received MCV4 than among adolescents who received MPSV4 (Table 5). Of adolescents who received MCV4, 13.1% to 16.9% reported pain that limited movement in the arm of injection, compared with 2.6% to 3.9% of adolescents who received MPSV4. These differences in frequency of local reactions could be attributable in part to different methods of administering the 2 vaccines (MCV4 is administered intramuscularly; MPSV4 is administered subcutaneously). The frequency of local adverse reactions reported after MCV4 administration was similar to that reported after Td administration, which, like MCV4, is given intramuscularly.<sup>34</sup>

#### Precautions and Contraindications

Immunization with MCV4 is contraindicated among people known to have hypersensitivity to any

**TABLE 4.** Percentage of Adolescents 11 to 18 Years of Age Reporting Systemic Adverse Reactions 0 to 7 days After Immunization With MCV4 or MPSV4

Reaction	Immunized With MCV4, %		Immunized With MPSV4, %	
	Study 1 (n = 439)	Study 2 (n = 2265)	Study 1 (n = 441)	Study 2 (n = 970)
Any systemic adverse reaction	57.2	55.1	51.9	48.7
Any severe systemic adverse reaction	3.9	4.3	4.1	2.6
Fever				
$\geq$ 38°C	3.4	5.1	2.5	3.0
$\geq$ 39°C	0.7	0.6	0.2	0.4

Systemic adverse reactions in study 1 included fever, headache, fatigue, anorexia, vomiting, diarrhea, or rash. In study 2, systemic reactions included fever, headache, fatigue, malaise, chills, arthralgia, anorexia, vomiting, diarrhea, seizures, or rash.<sup>34</sup>

**TABLE 5.** Percentage of Adolescents 11 to 18 Years of Age Reporting Local Adverse Reactions 0 to 7 days After Immunization With MCV4 or MPSV4

Reaction	Immunized With MCV4, %		Immunized With MPSV4, %	
	Study 1 (n = 438)	Study 2 (n = 2264)	Study 1 (n = 441)	Study 2 (n = 970)
Redness				
Any	12.1	10.9	6.1	5.7
≥1 inch	1.8	2.2	0.2	0.4
Swelling				
Any	14.4	10.8	5.4	3.6
≥1 inch	3.2	2.4	0.7	0.3
Induration				
Any	20.3	15.7	7.7	5.2
≥1 inch	3.7	2.8	0.5	0.5
Pain*				
Any	68.9	59.2	30.2	28.7
Moderate/severe	16.9	13.1	3.9	2.6

\* Pain: mild indicates that symptoms were present but arm movement was not affected; moderate, limits usual arm movement; severe, disabling.<sup>34</sup>

component of the vaccine, including diphtheria toxoid, and to dry, natural rubber latex, which is used in the vial stopper. Serious adverse events are rare in later allergic persons given vaccines from vials with rubber stoppers. Any adverse effect suspected to be associated with MCV4 vaccine should be reported to the Vaccine Adverse Events Reporting System (more information can be obtained by calling 800-822-7967 or by accessing the Web site at [www.vaers.org](http://www.vaers.org)).

#### *Cost of Meningococcal Vaccines*

Whether universal immunization of adolescents with tetravalent A, C, Y, W-135 meningococcal vaccine would result in a net cost or a net savings to society depends on IMD incidence, which varies by year, the rates of death or permanent sequelae, and the cost of immunization. A recent study from the CDC suggests that universal immunization of adolescents would be cost-effective.<sup>35</sup> However, variations in the epidemiology of and outcomes from IMD by region make it impossible to generate a precise estimate of the cost benefit. If, as expected, universal adolescent immunization with MCV4 becomes a reality in the next few years, more precise estimates should become available.

The total cost of immunizing a single adolescent with MCV4 includes direct and indirect costs. The direct costs include supplies (eg, vaccine [MCV4 = \$82.00 and MPSV4 = \$86.10 per dose], syringe with needle), personnel, and administrative expenses. Public and private insurers should be responsible for payment of costs for MCV4. MCV4 is included in the Vaccines for Children program. For private insurers, avoiding financial responsibility by transferring this to intermediate risk-bearing entities (eg, independent practice associations or other physician groups), individual physicians, or college health services will result in adolescents not being immunized in a timely fashion. Physicians incur significant administrative expenses when ensuring that adolescents are immunized with recommended vaccines in a timely fashion, including explaining risk and benefits of immunization to adolescents and parents; ordering, purchasing, storing, and administering the vaccine; recording immunizations in records; and other activities. Physicians

should receive reimbursement for expenses associated with each vaccine administration.

#### **FUTURE NEEDS**

MCV4 has been licensed on the basis of safety and short-term immunogenicity data in adolescents. Several postmarketing studies are planned, including a study to evaluate the duration of antibody responses in participants who received a single dose of MCV4 vaccine or MPSV4 vaccine 5 and 10 years earlier and a study to evaluate safety and immunogenicity when MCV4 is given concomitantly with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine. However, vaccine effectiveness and herd immunity based on the ability of MCV4 to alter transmission patterns cannot be predicted from immunogenicity data alone. Information on MCV4 effectiveness, duration of protection, and herd-immunity effects obtained from MCV4 evaluation studies will be indispensable in guiding prevention policies and formulating recommendations for immunization in other age groups.

MCV4 and other meningococcal conjugate vaccines may be licensed in the United States in the near future for use in other age groups, including children 2 to 10 years of age and infants. Such vaccines are undergoing clinical trials and are likely to be more immunogenic in infants and young children compared with MPSV4, which currently is the only meningococcal vaccine licensed in the United States for use in young children.

Because meningococcal serogroup B capsular polysaccharide is poorly immunogenic in humans, vaccine development has focused on common surface proteins, including the outer membrane proteins (OMPs) of specific epidemic strains.<sup>36</sup> OMP vaccines have shown good efficacy in older children and adults, but efficacy in infants and young children, in whom rates of disease are highest, has not been demonstrated. In addition, the variability in OMP strains causing endemic disease likely will limit their usefulness in the United States.<sup>37</sup>

Because of the potential limitations of these vaccines, other new approaches to meningococcal serogroup B vaccines are being pursued. With the recent sequencing of the serogroup B meningococcal ge-

nome, several new genes encoding putative membrane proteins have been identified, suggesting potential new targets for serogroup B vaccines. The availability of new meningococcal conjugate vaccines as well as the pursuit of new vaccine strategies should lead to substantial improvements in control and prevention of meningococcal disease in the United States and globally.

Although the signs and symptoms of IMD frequently are nonspecific, increasing awareness of meningococcal disease can result in people seeking medical care earlier and improved clinical outcome. In addition, educating adolescents and their parents about the benefits of receiving MCV4 is critical to prevention of a substantial number of cases of IMD. However, parents and adolescents must understand that MCV4 will not prevent all meningococcal disease, and at least 25% of cases in adolescents are caused by serogroup B.<sup>1</sup> Educating the general public about the benefits of being immunized with MCV4 may foster increased immunization coverage rates for adolescents and substantially decrease the burden of meningococcal disease in the United States.

#### RATIONALE FOR MENINGOCOCCAL VACCINE RECOMMENDATIONS

MCV4 offers advantages over MPSV4. First, it demonstrates a T-cell–dependent characteristic so that children given a second dose have an anamnestic or booster response not found after a second dose of MPSV4. Second, the elevated rSBA 3 years after MCV4 but not after MPSV4 immunization in adolescents suggests a longer duration of immunity than with MPSV4. Third, the experience in the United Kingdom with the monovalent meningococcal serogroup C conjugate vaccine demonstrating a reduction in nasopharyngeal carriage of that serogroup in immunized infants and children as well as herd immunity affecting nonimmunized children suggests that MCV4 also will have similar effects, although data will be necessary to demonstrate these characteristics. Finally, MCV4 should induce antibodies against most strains causing IMD among adolescents 11 years or older.

Because the initial supply of MCV4 will be limited for the next 2 to 3 years, initially only 2 cohorts can be recommended to be immunized routinely. The first cohort, young adolescents at the 11- to 12-year visit, was selected because this is the age at which a booster dose of Td already is recommended and when well visits to the pediatrician are more likely to occur than in older adolescents.<sup>2</sup> The AAP also emphasizes the importance of more pediatric patients of this age having well visits for preventive services other than immunization. A recommendation to immunize all 11- to 12-year-olds, therefore, not only is more likely to be feasible compared with older adolescents but also should be associated with enhancing the importance of the young adolescent visit. The second cohort, entering high school students or 15-year-olds, whichever comes first, was chosen on the basis of 2 factors: the peak IMD incidence and routine medical visits by adolescents 13 years and older. The peak incidence of disease occurs after 15 years of age, but less than 20% of adolescents 16

to 18 years of age have routine medical visits to pediatricians. Some states already have high school entry laws requiring certain vaccines. Once MCV4 supply is abundant, routine immunization of all adolescents likely will be recommended. Also, within 3 years, information on duration of immunity and need for reimmunization, if any, should become available. To date, the vaccine uptake by adolescents suggests that pediatricians should do everything possible to use other medical visits (eg, sports or camp preparticipation physical examinations or evaluations for minor illnesses such as upper respiratory tract infections) to ensure that recommended vaccines are administered.

#### RECOMMENDATIONS

1. Two cohorts of adolescents should be immunized routinely with MCV4: (1) young adolescents at the 11- to 12-year visit; and (2) adolescents at high school entry or 15 years of age, whichever comes first (both evidence grade I [see the Appendix]). Within 3 years, the goal will be routine immunization of all adolescents with MCV4 beginning at 11 years of age.
2. Adolescents should visit a health care professional at 11 to 12 years of age, when immunization status and other preventive services can be addressed. Subsequent annual visits throughout adolescence also are recommended.
3. Entering college students who plan to live in dormitories should be immunized with MCV4 routinely (evidence grade II-2).
4. People at increased risk of meningococcal disease should be immunized with MCV4 if they are at least 11 years of age, including
  - adolescents who have a terminal complement deficiency or adolescents who have anatomic or functional asplenia (evidence grade II-3); or
  - adolescents who travel to or reside in countries in which *N meningitidis* is hyperendemic or epidemic (CDC Travelers' Health Hotline 877-FYI-TRIP or online at [www.cdc.gov/travel](http://www.cdc.gov/travel)) (evidence grade II-3).
5. Because people with HIV infection are likely to be at higher risk of meningococcal disease, although not to the extent that they are at risk of invasive *S pneumoniae* infection, they may elect to be immunized with MCV4 if they are at least 11 years of age.
6. Children 2 to 10 years of age at increased risk of meningococcal disease (see recommendations 3 and 4) should be immunized with MPSV4, because MCV4 is not yet licensed for use in these children.
7. People who wish to decrease their risk of meningococcal disease may elect to receive MCV4 if they are 11 years or older.
8. For control of meningococcal outbreaks caused by vaccine-preventable serogroups (A, C, Y, or W-135), MPSV4 or MCV4 should be used for people 11 years or older (evidence grade II-2). MCV4 is preferred, but MPSV4 is acceptable. For children 2 to 10 years of age, MPSV4 should be used.
9. Immunization with MCV4 may be indicated for adolescents previously immunized with MPSV4. These people should be considered for reimmunization.

zation 3 to 5 years after receiving MPSV4 if they remain at increased risk of meningococcal disease.

10. Public and private insurers should be responsible for payment of costs of MCV4, its administration to adolescents for whom MCV4 is recommended, and administrative costs involved in providing vaccines to high-risk people.

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APPENDIX. US Preventive Services Task Force Rating System of Quality of Scientific Evidence<sup>38</sup>

I	Evidence obtained from at least 1 properly designed, randomized, controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferentially from >1 center or group
II-3	Evidence obtained from multiple time series with or without the intervention or dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s)
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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