Meningococcal group C polysaccharide-protein conjugate vaccines (MCV) prime infants and children for memory anticapsular responses upon subsequent exposure to unconjugated polysaccharide. The objective of this study was to determine whether MCV primes vaccine-naive adults and adults previously vaccinated with meningococcal polysaccharide vaccine (MPSV) for memory antibody responses. Meningococcal vaccine-naive adults were randomized to receive either MCV (MCV/naïve group) (n = 35) or pneumococcal conjugate vaccine (PCV) (PCV/naïve group) (n = 34). Participants with a history of receiving MPSV were given MCV (MCV/MPSV group) (n = 26). All subjects were challenged 10 months later with one-fifth of the usual dose of MPSV (10 µg of each polysaccharide). Sera were obtained before the conjugate vaccination and before and 7 days after the MPSV challenge and assayed for immunoglobulin G (IgG) anticapsular antibody concentrations and bactericidal titers. The MCV/naïve group had 7- to 10-fold-higher serum IgG and bactericidal responses after the MPSV challenge than the PCV/naïve group (P < 0.001). The increases (n-fold) in anticapsular antibody concentrations in the MCV/naïve group were greatest in subjects with antibody concentrations of ≥2 µg/ml before the challenge (geometric mean increase [n-fold] of 8.3 versus 1.1 in subjects with concentrations of >2 µg/ml before the challenge; P < 0.0001). Only 3 of 11 MCV-vaccinated subjects who had received MPSV before enrollment and who had antibody concentrations of ≥2 µg/ml before the polysaccharide challenge showed more-than-twowfold increases in anticapsular antibody concentration or bactericidal titer after the challenge. MCV vaccination of meningococcal vaccine-naïve adults primes for robust memory antibody responses. There was no evidence of induction of memory by MCV in adults previously vaccinated with MPSV.

MATERIALS AND METHODS

Study design. Healthy adults ages 18 to 30 years were eligible to enroll in a phase 2, partially randomized, controlled, single-center study to evaluate the safety and immunogenicity of a meningococcal group C conjugate vaccine that is licensed in Canada and Europe (Menjugate; Chiron Vaccines). A dose of the vaccine consists of 10 µg of meningococcal group C oligosaccharide conjugated to the nontoxic mutant diphtheria toxin CRM 197 protein carrier, which was administered with 1 mg of aluminum hydroxide. Subjects were recruited from the San Francisco Bay area. Individuals who had never received a meningococcal vaccine were randomized to receive either an intramuscular dose of MCV (MCV/naïve group) or, as a control, a U.S.-licensed 7-valent pneumococcal polysaccharide-CRM197 conjugate vaccine (PCV) (PCV/naïve group) (Prevnar; Wyeth Lederle). Individuals who had previously received MPSV at least 6 months prior to enrollment were assigned to a third group and were given a dose of MCV (MCV/MPSV group). Ten months later, all participants were given a subcutaneous challenge consisting of 0.1 ml (one-fifth of the regular dose) of the licensed quadrivalent meningococcal polysaccharide vaccine (Menomune; Sanofi-Pasteur), which is equivalent to 10 µg of each of the four polysaccharides. The lower dose served as an immunologic probe to evaluate memory antibody responses to group C polysaccharide (defined as higher antibody responses in the MCV/naïve group compared with the responses of the control PCV/naïve group) (11). The data reported herein were obtained from serum samples collected upon enrollment (prior to the conjugate vaccination) and 10 months later (before the MPSV challenge), as well as 7 days after the MPSV challenge.

The protocol was approved by the Institutional Review Board of the Children's Hospital and Research Center at Oakland.

Serology. All serologic studies were performed blindly on coded serum samples at Chiron Vaccines (Emeryville, CA). IgG group C anticapsular antibody was measured by a modified enzyme-linked immunosorbent assay that incorporated a chaotropic agent in the serum-diluting buffer to favor the detection of higher-avidity anticapsular antibodies, which was performed as previously described (12). Serum bactericidal activity was measured using extrinsic human complement as previously described (18). For statistical analyses, antibody concentrations or titers that were less than the lower limit of detection were assigned values half that of the lower limit (i.e., 0.2 µg/ml for group C anticapsular IgG concentration).
concentrations <0.4 μg/ml and a bactericidal titer of 1:2 for sera with titers of <1:4). The respective geometric means of the antibody concentrations or titers and associated two-sided 95% confidence intervals (CIs) were computed from the log (base 10) values. Statistical comparisons were all two tailed. Because of heterogeneity in the serum antibody concentrations at the time of enrollment for subjects previously vaccinated with MPSV, the subjects in that group were stratified based on MPSV immunization 3 years or 3 years prior to enrollment.

RESULTS

The vaccines were generally well tolerated. No serious adverse events were noted. Table 1 summarizes the demographic information for the subjects in all of the vaccine groups. Although the subjects in the MCV/MPSV group who received MPSV 3 years or more prior to enrollment were slightly younger than the subjects in the other groups, there were no other differences among the vaccine groups. Table 2 summarizes the IgG anticapsular antibody concentrations as measured by enzyme-linked immunosorbent assay. Ten months after the conjugate vaccine immunization (immediately before the MPSV challenge dose), the serum IgG anticapsular antibody concentrations were higher in the groups immunized with MCV than those of controls given PCV (P < 0.0001). Compared with controls primed with PCV, MCV immunization of the meningococcal vaccine-naïve group primed for memory IgG antibody responses (i.e., geometric mean antibody concentrations postimmunization that were more than eightfold higher than those of controls). The groups immunized with MPSV before enrollment and given a dose of MCV had higher geometric mean antibody concentrations after the

### Table 1. Demographics of the sample

| Group           | No. of subjects | Median age (range) | % Females | % Caucasians |
|-----------------|-----------------|--------------------|-----------|--------------|
| MCV/naïve       | 35              | 29 (20–49)         | 66        | 63           |
| PCV/naïve       | 34              | 29.5 (19–51)       | 68        | 68           |
| MCV/MPSV <3 yrs prior | 14          | 29.5 (19–46)       | 36        | 64           |
| MCV/MPSV ≥3 yrs prior | 12         | 22.5 (19–39)       | 75        | 50           |

a. Median interval between MPSV immunization and enrollment, 1 year (range, 1 to 2 years).

b. Median interval between MPSV immunization and enrollment, 3.5 years (range, 3 to 11 years).

### Table 2. Serum IgG group C anticapsular responses

| Group           | No. of subjects | Pre-conjugate | Pre-MPSV | Post-MPSV |
|-----------------|-----------------|---------------|----------|-----------|
| MCV/naïve       | 35              | 0.4 A (0.2–0.6) | 2.2 B (1.0–4.6) | 6.1 C (3.6–10.2) |
| PCV/naïve       | 34              | 0.3 (0.2–0.3)  | 0.2 D (0.2–0.3) | 0.5 E (0.3–0.9)  |
| MCV/MPSV <3 yrs prior | 14         | 4.9 F (1.8–13.4) | 7.7 G (2.8–21.0) | 7.5 H (2.9–19.5) |
| MCV/MPSV ≥3 yrs prior | 12        | 0.9 I (0.3–2.3) | 2.3 J (0.6–8.4) | 4.1 K (1.5–11.7) |

a. For comparison between A and B, P < 0.0001; for comparison between F and G, P = 0.2; for comparison between I and J, P = 0.006; for comparison between B and C, P < 0.0001; for comparison between D and E, P < 0.002; for comparison between G and H, P = 0.9; for comparison between J and K, P < 0.02 (paired t test). For comparison between C and E, P < 0.0001; for comparison between E and H, P < 0.0001; for comparison between E and K, P = 0.0002 (unpaired t test).

MPSV challenge at 10 months than the meningococcal vaccine-naïve control group primed with PCV (P < 0.001). However, as described below, induction of immunologic memory in subjects previously given MPSV was difficult to evaluate based on the geometric mean antibody concentrations.

Figure 1 shows the individual antibody concentrations of each subject after the MPSV challenge in relation to the respective antibody concentrations immediately before the chal-
more-than-twofold increases, which were not different from those observed in the PCV/naïve control group. None of the 15 subjects with >2 μg/ml of serum antibody before the polysaccharide challenge had more-than-twofold increases in antibody after the challenge.

Figure 2 summarizes the geometric mean increases (n-fold) in antibody concentrations of the different groups after the MPSV challenge. The data are stratified based on serum antibody concentrations of ≤2 μg/ml and >2 μg/ml prior to MPSV challenge. Among subjects with concentrations of ≤2 μg/ml prior to challenge, those in the MCV/naïve group had a greater geometric mean increase (n-fold) after the polysaccharide challenge than in the other three groups (P < 0.05 for each comparison). Interestingly, the geometric mean increase (n-fold) after the MPSV challenge of subjects who had received MPSV ≥3 years before enrollment was higher than that of subjects who had received MPSV <3 years before enrollment (geometric mean increase [n-fold] of 2.8 versus 1.1, respectively; P = 0.03).

Table 3 summarizes the geometric mean serum bactericidal titers of the individual subjects in relation to the respective bactericidal titers present immediately before the MPSV challenge. The bactericidal antibody responses of the different groups paralleled the respective antcapsular antibody responses.

**DISCUSSION**

The antibody responses to unconjugated MPSV are thought to be relatively T-cell independent, and immunization does not prime for memory antibody responses. In contrast, meningococcal polysaccharide-protein conjugate vaccines are immunogenic for all ages. In infants (2, 6, 15, 20) and young children (18, 23), group C meningococcal conjugate vaccines also prime for the ability to respond with serum IgG memory antibody responses upon subsequent exposure to unconjugated MPSV.

In previous studies, it has been difficult to determine whether adults immunized with polysaccharide-protein conjugate vaccines are primed for memory responses, in part because antibody responses of vaccine-naïve adults to a first dose of polysaccharide vaccine are characteristic of memory antibody responses (rapid rises in serum antibody and class switched to IgG with hypermutation of variable regions) (1, 16), probably as a result of natural priming. For example, pneumococcal conjugate vaccine primes infants and young children for memory, yet several studies of adults did not

![Figure 2](image-url)  
**Figure 2.** Geometric mean severalfold increases (postchallenge/prechallenge) in relation to serum IgG antcapsular antibody concentrations prior to challenge with MPSV. Among subjects with ≤2 μg/ml of antibody immediately before the challenge, the statistical significance of the differences between the geometric mean (Geo. M.) severalfold increase of the MCV/naïve group versus the PCV/naïve group was a P value of <0.001, that versus the MCV/MPSV group that received MPSV <3 years prior to enrollment was a P value of <0.01, and that versus the MCV/MPSV group that received MPSV ≥3 years prior to enrollment group was a P value of <0.05. The MCV/MPSV group that received MPSV ≥3 years prior to enrollment also had higher responses to the challenge dose than the group that received MPSV <3 years before enrollment (P = 0.03). All other respective differences are not significant (P > 0.1).

**Table 3. Serum bactericidal antibody responses**

| Group               | No. of subjects | Preconjugate | Bactericidal antibody titer [1/GMT (95% CI)] | Pre-MPSV boost | Post-MPSV boost |
|---------------------|-----------------|--------------|---------------------------------------------|----------------|----------------|
| MCV/naïve           | 35              | 7.2 A (4.2–12.3) | 44.7 B (23.1–86.7) | 140.2 C (80.8–243.2) |
| PCV/naïve           | 34              | 8.2 (5.8–11.6) | 7.4 D (5.1–10.7) | 20.4 E (12.8–32.4) |
| MCV/MPSV <3 yrs     | 14              | 37.9 F (16.8–85.3) | 87.7 G (30.5–252.2) | 83.0 H (31.3–220.4) |
| MCV/MPSV ≥3 yrs     | 12              | 22.3 I (8.8–56.7) | 67.1 J (23.5–191.9) | 111.7 K (54.2–230.3) |

*For comparison between A and B, P < 0.0001; for comparison between F and G, P = 0.07; for comparison between I and J, P = 0.02; for comparison between B and C, P < 0.0001; for comparison between D and E, P < 0.0001; for comparison between G and H, P = 0.7; for comparison between J and K, P < 0.05 (paired t test). For comparison between C and E, P < 0.0001; for comparison between E and H, P < 0.004; for comparison between E and K, P = 0.0003 (unpaired t test). GMT, geometric mean titer.
demonstrate an induction of immunologic memory after pneumococcal conjugate vaccination (22, 27).

There are conflicting data on the ability of meningococcal conjugate vaccines to prime adults for meningococcal group C immunologic memory. Two studies of MCV-immunized adults attempted to infer priming for memory by measurement of group C antibody avidity maturation, a surrogate that has been useful in investigations of immunologic memory in infants and young children (4, 23). One study observed a significant increase in the anticapsular avidity index (i.e., avidity maturation) at 6 months (25), which was consistent with a memory response, while the second study reported a significant decrease (10). The lack of avidity maturation in some MCV-immunized adults may reflect maximal stimulation of memory B cells that had already undergone extensive hypermutation at 1 month after MCV vaccination. In a third study, adults immunized with an investigational group A plus group C meningococcal conjugate vaccine had memory group C antibody responses to a 1-μg challenge dose of MPSV given 4 to 5 years later (11). However, the sample sizes in this study were small, the results were of borderline statistical significance, the adults in the conjugate group had received different doses 4 to 5 years earlier, and the control group of vaccine-naive adults was recruited at the time of the MPSV challenge and therefore may have differed from the group of adults who received the conjugate vaccine 4 to 5 years earlier. Thus, there were confounding factors that could have affected the assessment of memory.

Keyserling et al. previously reported that group C antibody responses to a second dose of quadrivalent MCV in adolescents who had been immunized 3 years earlier were higher than responses in control adolescents who were given a first dose of MCV (14). Although boostable anticapsular antibody responses to repeated injections of MCV are consistent with an induction of immunologic memory, the data do not distinguish between the possible role of memory B cells induced by the polysaccharide component of the conjugate vaccine and that of T cells elicited by the diphtheria toxoid carrier on the booster anticapsular antibody responses observed after the second dose of MCV.

The present study was designed prospectively to assess the induction of memory to group C polysaccharide directly by measuring group C antibody responses to one-fifth (10 μg) of the usual dose of MPSV, which was given 10 months after a dose of MCV or PCV. Meningococcal vaccine-naive adults randomized to receive MCV showed much higher IgG anticapsular and bactericidal antibody responses to the polysaccharide challenge than those of meningococcal vaccine-naive adults randomized to receive the control polysaccharide conjugate vaccine that employed the same carrier protein (CRM197) as MCV. In both priming groups, nearly all subjects with ≥2 g/ml of antibody before the polysaccharide challenge showed minimal increases in serum antibody levels after the challenge. Therefore, evidence of priming by MCV was observed only in subjects with ≥2 μg/ml of antibody.

In previous studies, immunization with MPSV was associated with immune refractoriness to a second dose of MPSV (decreased group C antibody responses compared with the responses to a first dose of vaccine). This phenomenon has been observed in immunized infants, toddlers, older children (7–9, 13, 17, 18), and adults (11, 26). Several studies have also shown that MCV is immunogenic in children and adults who were previously immunized with MPSV (3, 5, 17, 28), although in general, their serum antibody responses to the conjugate vaccine (particularly bactericidal antibody) were lower than those of vaccine-naive subjects (3, 17, 26).

Less information is available on the possible influence of previous exposure to MPSV on priming by MCV for memory responses. In a study in The Gambia, memory group C antibody responses to MPSV were observed in 5-year-old chil-

FIG. 3. Serum bactericidal titers of individual subjects after MPSV challenge in relation to prechallenge titers. (A) MCV/ naïve group. (B) PCV/ naïve group. (C) MCV/MPSV subset that received MPSV <3 years prior to enrollment. (D) MCV/MPSV subset that received MPSV ≥3 years prior to enrollment. “n” refers to the number of subjects who had bactericidal titers below the limit of detection in sera obtained before and after the MPSV challenge.
dren who had been immunized with two doses of MPSV as infants and one dose of a group A plus group C conjugate vaccine given in the second year of life (19). In a second study in the United Kingdom, there was evidence of avidity maturation in serum samples obtained at 1 and 6 months after a dose of MCV in children previously immunized with MPSV (3). However, in two studies of adults who were immunized with MPSV and who were given a subsequent dose of MCV, there was no evidence of avidity maturation (10, 28).

In the present study, the adults who had been given MPSV before enrollment and who were immunized with MCV had IgG anticapsular antibody concentrations and bactericidal titers after the polysaccharide challenge that were higher than before enrollment and who were immunized with MCV had a dose of MCV, there was no evidence of avidity maturation. Immunization with MPSV and who were given a subsequent dose of MCV, there was no evidence of avidity maturation (10, 28).

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