

CONCISE COMMUNICATION

Meningococcal C Polysaccharide Vaccine Induces Immunologic Hyporesponsiveness in Adults That Is Overcome by Meningococcal C Conjugate Vaccine

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Widespread use of meningococcal AC polysaccharide (MACP) vaccines has raised concerns about induction of hyporesponsiveness to C polysaccharide. Whether meningococcal C conjugate (MCC) vaccine overcomes any immunologic refractoriness following MACP vaccination in adults was investigated. University students vaccinated 6 months previously with MACP vaccine were randomized to receive MACP or MCC vaccine, and antibody responses were compared with those of previously unvaccinated students receiving MACP or MCC vaccine. In students primed with MACP vaccine, MCC vaccine induced significantly higher IgG and serum bactericidal antibody levels than did a second dose of MACP vaccine. Responses to a second dose of MACP vaccine were significantly lower than to the first dose. Previous receipt of MACP vaccine reduced serum bactericidal antibody but not IgG responses to MCC vaccine compared with those in previously unvaccinated students. This confirms that MACP vaccine induces immunologic hyporesponsiveness to C polysaccharide in adults, but this can be overcome with MCC vaccine. Repeated vaccination with MACP vaccine may be ineffective, and MCC vaccines should provide better long-term protection.

Increases in the incidence of serogroup C meningococcal disease in regions of Europe and North America, with associated media attention and public anxiety, have led to mass immunization campaigns with meningococcal AC (or ACW-135Y) polysaccharide (MACP) vaccines. Although these have proved effective in the short term [1], concerns have been raised about the induction of immunologic hyporesponsiveness to C polysaccharide by MACP vaccines [2, 3]. This has been clearly demonstrated among infants and toddlers [3–5], age groups in whom meningococcal C polysaccharide vaccines are poorly im-

munogenic and not protective [6]. The extent to which this occurs in older children and adults, who normally respond well to polysaccharide vaccine, is unclear. It is not known whether hyporesponsiveness will affect susceptibility to meningococcal C disease in the long term.

Meningococcal C conjugate (MCC) vaccines have been developed that are immunogenic in infants and toddlers [3, 4, 7] and are expected to be available in the near future. In populations among whom mass immunization with MACP vaccine has occurred and the introduction of MCC vaccines is being considered, an important question is whether previous polysaccharide vaccine will impair the response to subsequent MCC vaccine. We investigated whether MACP vaccine induces immunologic refractoriness to subsequent meningococcal C polysaccharide in adults and whether this can be overcome by MCC vaccine.

Subjects and Methods

Study population. The study population comprised 190 students who had received a single dose of MACP vaccine as part of outbreak control measures at Southampton and Salford Universities in late 1997. They were randomized to be revaccinated with either MACP or MCC vaccine 6 months later. Two nonrandomized control groups of previously unvaccinated students attending the same universities were also included; 91 students received a single

Received 20 August 1999; revised 29 October 1999; electronically published 14 January 2000.

Presented in part: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 1999.

Written informed consent was obtained from all subjects, and the study protocol was approved by the Public Health Laboratory Service, Southampton and South West Hampshire Authority, and the Salford and Trafford Health Authority ethics committees.

This study was supported by the UK Department of Health (grant VCA/9/3).

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The Journal of Infectious Diseases 2000;181:761–4

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0022-1899/2000/18102-0053\$02.00

Table 1. Serogroup C-specific serum bactericidal antibody (SBA) and IgG antibody levels before and after dose of meningococcal C polysaccharide (MACP) or conjugate vaccine (MCC) in students previously vaccinated with MACP vaccine and in unvaccinated students.

Time point, parameter	1st dose MACP vaccine (n = 214)	MACP vaccine after previous MACP vaccine (n = 86)	MCC vaccine after previous MACP vaccine (n = 83)	1st dose MCC vaccine (n = 86) in naive subjects
Before vaccination				
SBA GMT (95% CI)	NA	139 (83–231)	99 (61–161)	6 (4–8)
No. (%) with SBA titer <8	NA	12 (14)	15 (18)	60 (70)
No. (%) with SBA titer <32	NA	23 (27)	26 (31)	71 (83)
IgG GMC (95% CI)	NA	14.9 (10.7–20.6)	17.9 (13.8–23.1)	2.41 (1.6–3.6)
After vaccination				
SBA GMT (95% CI)	614 (449–840)	220 (136–355)	663 (446–987)	1336 (908–1966)
No. (%) with SBA titer <8	12 (5.6)	6 (7)	1 (1)	0
No. (%) with SBA titer <32	20 (9.2)	16 (19)	3 (3.6)	3 (3.4)
IgG GMC (95% CI)	27.7 (23.5–32.6)	16.9 (12.4–23)	35.3 (28.3–43.9)	32.2 (24.0–43.2)

NOTE. CI, confidence interval; GMC, geometric mean concentration; GMT, geometric mean titer; NA, not applicable.

dose of MCC vaccine at the same time as the groups received their boosters, and 214 subjects were historical controls who received a single dose of MACP vaccine during the Salford outbreak and for whom postvaccination sera were available. There were 66 students in the historical control group who were subsequently revaccinated with either MACP ($n = 35$) or MCC ($n = 31$) vaccines and had sera available after each vaccination.

Study vaccines and reactogenicity assessment. The MACP vaccine (Mengivac A+C; Pasteur Mérieux Sérums et Vaccins, Lyon, France) contained 50 μg each of serogroups A and C polysaccharide. Different batches were used in the outbreak control and revaccination. The MCC vaccine (Wyeth Lederle Vaccines and Pediatrics, Philadelphia) contained 10 μg of meningococcal C oligosaccharide linked to 15 μg of CRM₁₉₇ mutant diphtheria toxin. The vaccines were administered by intramuscular injection in the arm. Reactogenicity was assessed by means of a 7-day health diary recording local reactions, temperatures, and systemic symptoms and an interview at 4–6 weeks after immunization. No reactogenicity data were obtained for the historical control group.

Blood samples and serologic analysis. Blood samples were taken before and 4–6 weeks after immunization; postvaccination sera in the historical control group were taken at 6–8 weeks. Sera were tested for IgG antibodies to serogroup C polysaccharide by standardized ELISA and for serum bactericidal antibodies (SBAs) to C11 meningococcal strain (phenotype C:16:P1.7^a,1) by use of standardized protocols, as described elsewhere [7, 8]. SBA titers were expressed as the reciprocal of the final serum dilution giving $\geq 50\%$ killing at 60 min. Pooled baby rabbit serum (Pel-Freeze, Rodgeron, AZ) was used as an exogenous complement source in the SBA. For this assay, the SBA titer that correlates with protection is not known. Previously, a titer of $\geq 1 : 8$ has been used [7], although a more conservative titer of $\geq 1 : 32$ was suggested at a recent World Health Organization meeting regarding meningococcal assay standardization (R. Borrow, personal communication). Therefore, the percentage of subjects with titers higher than both of these levels was calculated for each group.

Statistical analysis. Antibody levels were log-transformed, and geometric mean concentrations for IgG levels and SBA geometric mean titers (GMTs) were calculated with 95% confidence intervals (CIs). Antibody responses were compared between groups by Stu-

dent's t test. A paired t test was used to compare SBA responses for subjects who had sera available at each time point. Proportions of subjects with antibody concentrations below putative protective levels and proportions with local reactions were compared by use of χ^2 and Fisher's exact tests, when appropriate. Correlation between antibody levels and fold rise was calculated by use of Pearson's correlation coefficient.

Results

Of the 190 students who had previously received MACP vaccine, 97 and 93 received a further dose of MACP and MCC vaccines, respectively (median interval since initial vaccination, 29 weeks for both groups). Pre- and postvaccination blood samples were obtained from 169 subjects (85 men, 84 women; median age, 19 years; range, 18–25). Ninety-one previously unvaccinated subjects (25 men, 66 women; median age, 21 years; range, 18–25) received a single dose of MCC vaccine, with paired pre- and postvaccination sera available for 86. The historical group ($n = 214$) had a median age of 19 years (range, 18–25).

The vaccines were well tolerated, with no vaccine-attributable severe adverse events. In students vaccinated with MCC vaccine, the incidences of erythema and swelling ≥ 2.5 cm in diameter at the injection site (13% and 5%, respectively) were the same for subjects primed with MACP vaccine and previously unvaccinated controls. Only 2 subjects, both MCC recipients, had fevers $>38^\circ\text{C}$ within 7 days of vaccination.

Serogroup C-specific IgG and SBA responses for each group are shown in table 1. There were no significant differences in antibody responses between men and women in any group. High SBA and IgG levels were induced by the initial dose of MACP vaccine. Antibody levels had fallen substantially 6 months after vaccination, although the majority remained above putative protective levels (SBA titer of ≥ 8) [7]. After revaccination with MACP vaccine, there was a small increase in SBA GMTs ($P < .001$) but no significant increase in IgG

antibody levels ($P = .22$). SBA GMTs and IgG geometric mean concentrations were significantly lower after a second dose of MACP vaccine than after a single dose in historical controls ($P < .001$ for both). Similar results (figure 1) occurred in the subset of 35 students revaccinated with MACP who also had sera available after the initial dose of MACP vaccine. SBA GMT following the first dose was 380 (95% CI, 174–833), versus 107 (95% CI, 53–219) after the second dose ($P < .001$). There was poor correlation between antibody levels before revaccination with MACP vaccine and fold rise in antibodies after revaccination ($r^2 = .02$ for IgG and $.12$ for SBA). Only 6 of 12 subjects with SBA titers < 8 before revaccination had titers increase to ≥ 8 after vaccination.

In subjects primed with MACP vaccine, SBA titers and IgG levels increased significantly following MCC vaccination and were significantly greater than in students receiving a second dose of MACP vaccine ($P < .001$ for both IgG and SBA). Compared with previously unvaccinated students receiving their first dose of MCC vaccine, there was no difference in IgG levels ($P = .62$), but SBA GMT following MCC vaccination was significantly lower ($P = .013$) in subjects previously vaccinated with MACP. The number of subjects achieving putative protective SBA titers (≥ 8) after MCC vaccination was similar in each group. All MACP-primed subjects ($n = 15$) with SBA titers < 8 before revaccination had their titers increase to ≥ 8 after MCC vaccination, although 1 subject with an SBA titer of 8 had the titer fall to 4.

Discussion

This study has demonstrated a reduced antibody response to a second full dose of MACP vaccine in adults revaccinated 6 months after the initial dose. There was no effect of previous MACP vaccine on the IgG response to MCC vaccine, although SBA titers were lower. Immunologic hyporesponsiveness following receipt of meningococcal C polysaccharide is well documented in young children [3–5]. It has also been reported in adults primed with serogroup A polysaccharide vaccines containing trace amounts of C polysaccharide [9] and in a small group of 5 adults who were revaccinated with 0.02 of the recommended dose of MACP vaccine, in whom hyporesponsiveness was still evident at 4 years [10]. This is the first report of hyporesponsiveness to C polysaccharide in adults receiving 2 full doses of vaccine. This hyporesponsiveness did not appear to be due to persistently high antibody levels, because there was poor correlation between levels before revaccination and subsequent antibody fold rise, and only 50% of subjects with SBA titers < 8 were able to mount an antibody response. Although the comparison of nonrandomized groups may be a source of bias, the confirmation of the hyporesponsiveness in 36 subjects for whom sera were available after first and second doses of MACP vaccine would indicate that this is a true phe-

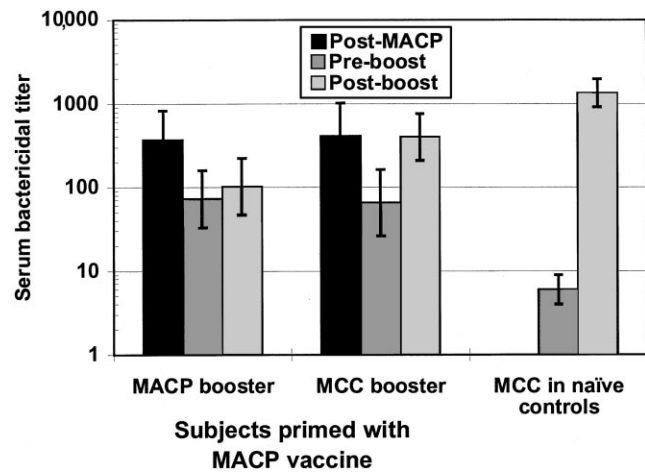


Figure 1. Serogroup C-specific serum bactericidal antibody geometric mean titers with 95% confidence intervals following initial meningococcal AC polysaccharide vaccine and before and after meningococcal AC polysaccharide (MACP; $n = 35$) or meningococcal C conjugate (MCC; $n = 31$) revaccination 6 months later in healthy adults for whom sera were available at each time point. Geometric mean titers of serum bactericidal antibodies before and after MCC vaccination in previously unvaccinated (naïve) adults ($n = 86$) are also shown for comparison.

nomenon. Variation in the immunogenicity of different batches of vaccines can also occur, but it is unlikely to be responsible for the magnitude of the effect seen in this study. Persistence of this hyporesponsiveness will be assessed in students being revaccinated 12 months after their initial MACP vaccination. The mechanism of this hyporesponsiveness to C polysaccharide is not known; however, it has not been reported with repeated doses of *Haemophilus influenzae* type b or serogroup A meningococcal polysaccharide vaccines [4, 11].

We found that MCC vaccine is able to overcome the hyporesponsiveness induced by previous polysaccharide vaccine in adults. The IgG antibody responses in MACP-primed adults were similar to those of previously unvaccinated adults receiving MCC vaccine. This reassuring finding illustrates the different immunologic properties of conjugate vaccines that are able to recruit T cell help. The reduction in the magnitude of the SBA response suggests the production of lower-avidity antibody as a result of MACP priming. This will be further investigated by assessing the high-avidity IgG antibody responses [12] and IgG avidity maturation over time. Despite this reduction in SBA, 99% of MACP-primed subjects achieved putative protective SBA titers. Further information is required to determine whether immunologic priming for memory is intact and whether there is a greater effect in children. Data for 13 Gambian children suggest adequate priming for memory [13], but further studies are required, particularly in countries such as Canada and Spain, where mass immunization campaigns with

MACP vaccines involving young children have been conducted. In the event of widespread introduction of MCC vaccine, our study shows that previous immunization with MACP vaccine should not affect either the immunogenicity or the reactogenicity profile in older age groups.

Meningococcal C polysaccharide vaccines are effective in preventing meningococcal C disease in older children and adults in the short term [1]. Vaccinating persons in high-risk situations (e.g., outbreaks) with MACP vaccine provides protection until functional antibody levels decline. The demonstration of subsequent hyporesponsiveness to MACP vaccine means that vaccinating low-risk persons (e.g., primary schoolchildren) may reduce the effectiveness of revaccination in a high-risk situation (e.g., school outbreak). Furthermore, it raises the theoretical concern that such persons may be unable to mount a protective antibody response if later exposed to serogroup C organisms and may be at increased risk of developing meningococcal disease [3, 10]. Although the use of MACP vaccine has been restricted in the United Kingdom, we have recently documented 6 laboratory-confirmed meningococcal C infections in persons within 2 years of MACP vaccine given during community outbreaks [14, 15] (E. Kaczmarek, unpublished data). Whereas these cases may reflect the failures expected with any vaccine, our finding of hyporesponsiveness in adults to the C polysaccharide supports continued restriction of use of MACP vaccine to groups at immediate increased risk. For adults requiring revaccination against meningococcal C disease, MCC vaccines are safe and should offer better protection. The superior immunogenicity of MCC vaccines and their ability to prime for memory suggests that they will be the preferred vaccine for use in outbreak control, particularly in countries with endemic meningococcal C disease.

Acknowledgments

We thank study nurses Anne Sesay, Rosemary Atwell, Debbie Hull, and Lista McArthur for their help in recruitment and follow-up; Southampton University Health Service and University of Salford Medical Centre for providing administrative assistance; Graham Jones (Southampton Public Health Laboratory) for organizing sample collection and storage; Nick Andrews (Public Health Laboratory Service Statistics Unit) for providing statistical advice; and Wyeth Lederle Vaccines and Pediatrics for providing vaccine. We also thank Jo Southern, Pauline Kaye, and Joan Vurdien for study administration and data management and David Salisbury (Department of Health) for his support of the study.

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