

Serogroup C Meningococcal Glycoconjugate Vaccine in Adolescents: Persistence of Bactericidal Antibodies and Kinetics of the Immune Response to a Booster Vaccine More Than 3 Years after Immunization

Matthew D. Snape,¹ Dominic F. Kelly,¹ Penny Salt,^{1,3} Sarah Green,¹ Claire Snowden,^{1,4} Linda Diggle,¹ Astrid Borkowski,⁵ Ly-mee Yu,² E. Richard Moxon,¹ and Andrew J. Pollard¹

¹Oxford Vaccine Group, Department of Paediatrics, and ²Centre for Statistics in Medicine, University of Oxford, Oxford, ³The Whittington Hospital National Health Service Trust, London, and ⁴Faculty of Medicine, University of Leicester, Leicester, United Kingdom; and ⁵Novartis Vaccines, Marburg, Germany

(See the editorial commentary by Harrison on pages 1395–7)

Background. The persistence of protection from meningococcal disease following immunization with serogroup C meningococcal (MenC) glycoconjugate vaccines in infancy is short-lived. The duration of protective immunity afforded by these vaccines in other at-risk age groups (i.e., adolescents and young adults) is not known. We evaluated the persistence of bactericidal antibodies following immunization with a MenC glycoconjugate vaccine (MenCV) in adolescents and the kinetics of immune response to a meningococcal AC plain polysaccharide vaccine (MenPS) challenge or a repeat dose of MenCV.

Methods. We conducted a randomized comparative trial of 274 healthy 13–15-year-olds from whom a total of 4 blood samples were obtained (prior to administration of a dose of MenPS or MenCV, again on 2 further occasions at varying times from days 2–7 after vaccination, and finally on day 28 after vaccination. The correlate of protection was a serum bactericidal assay titer ≥ 8 (with a serum bactericidal assay using human complement).

Results. A serum bactericidal assay using human complement titer ≥ 8 was observed in 75% of participants at baseline (mean age, 14.5 years; mean time since routine MenCV vaccination, 3.7 years). No increase in serum bactericidal assay geometric mean titers was detected until day 5 after administration of MenPS. Geometric mean titers following administration of MenCV were significantly higher than those observed following administration of MenPS, at days 5, 7, and 28.

Conclusions. This study showed sustained levels of bactericidal antibodies for at least 3 years after immunization of adolescents with MenCV. After challenge of immunized adolescents with MenPS, there was no increase in serum bactericidal assay observed until day 5 after vaccination, indicating that immunological memory may be too slow to generate protection against this potentially rapidly invasive organism.

The rate of invasive meningococcal disease is highest in children <1 year of age, but it increases again among teenagers [1]. Accordingly, countries such as the United Kingdom, Ireland, Spain, and Canada, which incorporate the 3 serogroup C meningococcal (MenC) gly-

coconjugate vaccines into their routine infant immunization schedules, have also undertaken mass immunization campaigns in which a single dose is offered to older children and adolescents [2].

The MenC glycoconjugate vaccines have been highly effective in preventing MenC disease [2]; however, preliminary surveillance data in England and Wales suggest a waning of effectiveness from 1 year after 3-dose priming in infancy [3]. This is accompanied by rapid waning of the level of protective in serum of children, as measured by the serum bactericidal assay (SBA) [4, 5]. Similarly, a trend toward a decrease in effectiveness and in SBA geometric mean titers (GMTs) has been observed

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Reprints or correspondence: Dr. Matthew Snape, Clinical Research Fellow, Oxford Vaccine Group, Dept. of Paediatrics, University of Oxford, Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Old Rd., Headington, Oxford, OX3 7LJ (matthew.snape@paediatrics.ox.ac.uk).

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Table 1. Characteristics of randomization groups.

Group	Vaccine	Blood sampling days
1	MenPS	0, 2, 6, 28
2	MenPS	0, 4, 6, 28
3	MenPS	0, 3, 7, 28
4	MenPS	0, 5, 7, 28
5	MenCV	0, 3, 7, 28
6	MenCV	0, 5, 7, 28

NOTE. MenPS, meningococcal serogroup A and C plain polysaccharide vaccine; MenCV, meningococcal serogroup C glycoconjugate vaccine.

following a single dose of vaccine at 1–3 years of age [3, 6].

In contrast, preliminary data suggest that the effectiveness of the MenC glycoconjugate vaccines in adolescents may be maintained at 90% >1 year after immunization [3]. Also, 95% of adolescents had “protective” SBA titers 1 year after immunization [7]. There are, however, no published data on the persistence of immunity beyond 1 year after immunization in this age group.

Although short-term protection against invasive disease caused by encapsulated bacteria is known to be conferred by vaccine-induced antibody, sustained protection has been attributed to immunological memory—the rapid increase of antibody on rechallenge with an antigen months to years after priming with a glycoconjugate vaccine [8]. However, recent studies indicate that invasive disease may occur despite evidence of priming in immunized children who subsequently have *Haemophilus influenzae* type b [9] or MenC [10] disease. One potentially important factor is the rapidity of antibody response following exposure to the pathogen in individuals in whom prior antibody levels did not afford protection.

The only data on the kinetics of this response for MenC comes from a study of 18 adults who were immunized with a combined serogroup A and C meningococcal glycoconjugate vaccine and who were subsequently challenged with a vaccine containing the MenC plain polysaccharide capsule (MenPS; as a surrogate of exposure to the organism) [11]. No increase in MenC-specific IgG was detected at day 3 after administration of MenPS; however, a significant increase in both MenC-specific IgG and SBA titer was detected on day 7. No data on the kinetics of the response between days 3 and 7 are available, nor has this response been studied in younger age groups.

Given the importance of prevention of meningococcal disease in the adolescent age group, we studied both the persistence of bactericidal antibody after a single dose of a MenC glycoconjugate vaccine and the kinetics of the antibody response to a MenC polysaccharide antigenic challenge (vaccination with MenPS). A comparative arm of the study was used to assess the immunogenicity of a booster dose of a MenC glycoconjugate vaccine and to compare the kinetics of the immune response to a MenC glycoconjugate vaccine and MenPS.

METHODS

Study design and vaccines. A phase IV, open-label, randomized comparative trial was conducted from September 2003 to June 2004 in Oxfordshire and Buckinghamshire, United Kingdom. Ethical approval was received from the Research Ethics Committees of Oxfordshire (approval number CO2.328) and Mid and South Buckinghamshire (approval number NC1165/703).

Invitation letters addressed to both the student and the student's parent(s) were sent via participating schools. The inclusion criterion was healthy 13–15 year olds who were vaccinated with a single dose of Menjugate (Chiron Vaccines), a meningococcal serogroup C-CRM₁₉₇ glycoconjugate vaccine (hereafter referred to as MenCV), in the 1999–2000 UK mass immunization campaign. Previous immunization status was determined by reference to the centralized immunization records of the relevant Child Health Computer departments. Exclusion criteria included immunosuppression, pregnancy, significant medical illness, antibiotic use within 14 days of enrollment, and previous confirmed invasive meningococcal disease.

Subject numbers were prospectively randomized in blocks of 6 according to a computer-generated blocked randomization scheme that allocated equal numbers of subjects to the 6 groups (table 1). Following a detailed telephone discussion, written consent was obtained from parents, and eligible adolescent subjects were assigned a subject number. Assent was taken from the student on the day of their study visit (conducted at the participant's school). The identity of the assigned treatment group was concealed by means of an opaque envelope until the point of enrollment.

Participants randomized to groups 1, 2, 3, or 4 received the plain polysaccharide serogroup A and C meningococcal vaccine

Table 2. Demographic characteristics of enrolled participants.

Characteristic	Group						All
	1	2	3	4	5	6	
No. of participants	44	44	46	47	47	46	274
No. of male patients/no. of female patients	26/18	17/27	21/25	22/25	22/25	19/27	127/147
Mean age, years \pm SD	14.0 \pm 0.7	14.0 \pm 0.7	13.9 \pm 0.8	14.0 \pm 0.8	14.0 \pm 0.6	14.0 \pm 0.8	14.0 \pm 0.8

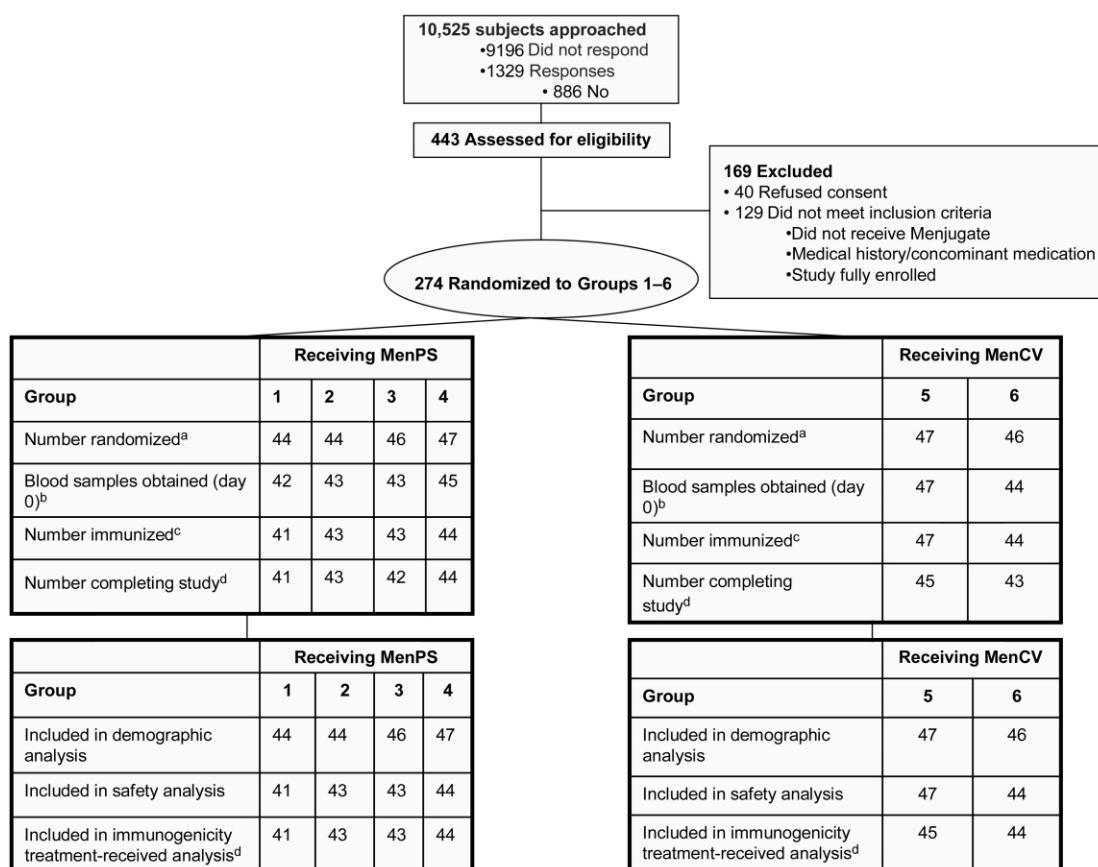


Figure 1. Flow chart for recruitment into the study, randomization to groups 1–6, and inclusion in demographic, safety, and treatment-received immunogenicity analyses. ^aFour subjects were reallocated from the groups to which they were originally randomized because of logistical issues. Inadvertent administration of meningococcal serogroup C glycoconjugate vaccine (MenCV) rather than meningococcal serogroup A and C plain polysaccharide vaccine (MenPS) led to 1 subject each being reallocated from group 1 to group 5 and from group 3 to group 5; administration of MenPS rather than MenCV led to 1 subject being reallocated from group 5 to group 3. Inability to conduct a study visit on the allocated day led to 1 subject being reallocated from group 2 to group 4. The numbers per group shown are those following this reallocation. ^bSubjects were randomized but did not provide a blood sample at day 0 for the following reasons (by group): group 1, 1 subject was receiving oral antibiotics (OAB), and 1 subject did not have a confirmed previous vaccination with Menjugate (Chiron Vaccines; MNC); group 2, 1 MNC; group 3, 2 did not assent (DNA), 1 OAB; group 4, 1 DNA, 1 OAB; and group 6, 2 DNA. ^cSubjects were randomized and provided a blood sample but did not receive a vaccination for the following reasons (by group): group 1, 1 subject DNA; and group 4, 1 subject DNA. ^dSubjects did not complete the study for the following reasons (by group): group 3, 1 lost to follow-up; group 5, 1 OAB (treatment commenced on day 0 following enrollment, so subject was, therefore, withdrawn from the study), 1 withdrawal of assent (WOA); and group 6, WOA. Although not completing the study, 2 subjects (1 in group 3 and 1 in group 6) were able to be included in the treatment-received analysis, because at least 1 postvaccination blood sample was available for analysis. Subjects included in the treatment-received analysis are not included in the analysis for any blood sampling time points at which they did not provide an interpretable blood sample. In addition to the above, exclusions from the per-protocol analysis were made for the following subjects: group 1, 1 subject was determined to not have received Menjugate (serum bactericidal assay [SBA] and ELISA assays excluded for all samples obtained), 1 subject received the Bacille Calmette-Guérin vaccine (SBA assay excluded for sample 4), 1 subject's blood sample was obtained outside time lines (SBA and ELISA excluded for sample 4); group 2, no exclusions; group 3, 1 subject's blood sample was obtained outside time lines (SBA and ELISA assays excluded for sample 4); group 4, 1 subject OAB (SBA assay excluded for sample 4); group 5, 1 subject OAB (SBA assay excluded for sample 4); and group 6, 1 subject's blood sample was obtained outside time lines (SBA and ELISA assays excluded for sample 4).

MenPS (Meningivac; Aventis Pasteur MSD), whereas persons randomized to groups 5 or 6 received MenCV. A one-fifth dose of MenPS was used in preference to a full dose of MenPS (50 μ g) so that all volunteers would receive an equal dose of meningococcal serogroup C polysaccharide (10 μ g); furthermore, a smaller dose of MenPS has a lower reactogenicity profile than the full-dose of this vaccine [12]. Both vaccines were admin-

istered intramuscularly into the left deltoid using a 23-gauge, 25-mm needle. Blood samples of up to 10 mL were obtained prior to vaccination, twice more in the week after vaccination (the timing of venesection being determined by their group allocation) (table 1) and at days 26–34 after vaccination.

Safety evaluation. Each participant was observed for 15 min after vaccination and was asked to complete a diary for 1

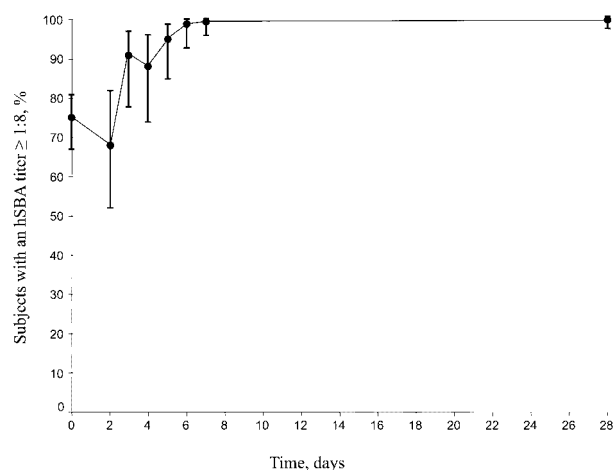


Figure 2. Proportion of volunteers from groups 1–4 with human complement serum bactericidal assay (hSBA) titers ≥ 8 determined for serum samples obtained on various days after administration of a plain polysaccharide meningococcal vaccine. Bars, 95% CIs.

week after immunization, recording daily sublingual temperature values and all local and systemic adverse events. Information on adverse events was actively obtained by study staff at each of the follow-up visits.

Serological responses. Serum samples were analyzed for MenC SBA titers using human complement SBA (hSBA) at the laboratory of Chiron Vaccines (Marburg, Germany). Laboratory staff were blinded to the participant's study group. The test strain was C11 (phenotype C:16:P1.7:L3, 7, 9a,(1)). hSBA titers were expressed as the reciprocal serum dilution yielding $\geq 50\%$ killing after 90 min. An hSBA titer ≥ 8 was used to indicate a very conservative measure of protection. ELISAs were performed at the same laboratory to measure the concentration of MenC-specific IgG.

Statistical analysis. All students who were allocated a randomization number were included in the demographic data, even if, at the first study visit, they withdrew their assent to continue in the study or did not meet the inclusion criteria. These students were then excluded from further analyses.

Participants who received a study vaccine and who provided a sufficient serum sample at some time point following vaccination were included in a treatment-received analysis, the primary analysis for immunogenicity. A per-protocol analysis for immunogenicity was also conducted.

The primary objective of this study was to determine hSBA GMTs and the percentage of participants with an hSBA titer ≥ 8 (and their associated 95% CIs) at days 2–7 after vaccination with MenPS. The analysis was descriptive, and no formal calculations of study power were conducted for this objective.

The secondary objectives for this study were to assess the hSBA GMT and geometric mean antibody concentration measured by ELISA (ELISA GMC) and the associated 95% CI for

the following populations: all vaccine recipients (at day 0), all recipients of MenPS and MenCV (analyzed separately for values at both day 0 and day 28 after vaccination), and groups 1–6 (analyzed separately for all days on which blood samples were obtained). In addition, the ratios of hSBA GMTs and ELISA GMCs (and associated 95% CIs) in recipients of MenCV and MenPS at comparable time points after immunization were calculated. Participants in group 3 were, therefore, compared with participants in group 5, and those in group 4 were compared with those in group 6. The null hypothesis for this comparison was that the hSBA GMTs that were observed following vaccination with MenCV would be less than one-half of those observed following vaccination with MenPS. To correct for variations in baseline values between groups, the proportional increase in hSBA GMT from day 0 to days 3, 5, 7, and 28 after vaccination was calculated and compared among recipients of MenCV and MenPS. In addition, a post hoc analysis was performed by 1 of the authors (L.Y.), who was blinded to the initial results. A mixed-effect model was used to compare the groups, adjusting for baseline hSBA GMT, within subject-time and group-time interaction.

A safety analysis was performed, using the χ^2 test, on data from all study participants who received a study vaccine, to enable comparison of the proportions of MenCV and MenPS recipients with adverse reactions to the vaccine. Data were analyzed using SAS software, version 9.1 (SAS Institute).

RESULTS

A total of 274 participants were randomized to 1 of 6 groups; demographic characteristic data were comparable among the 6 groups (table 2). Of the 274 participants enrolled in the study,

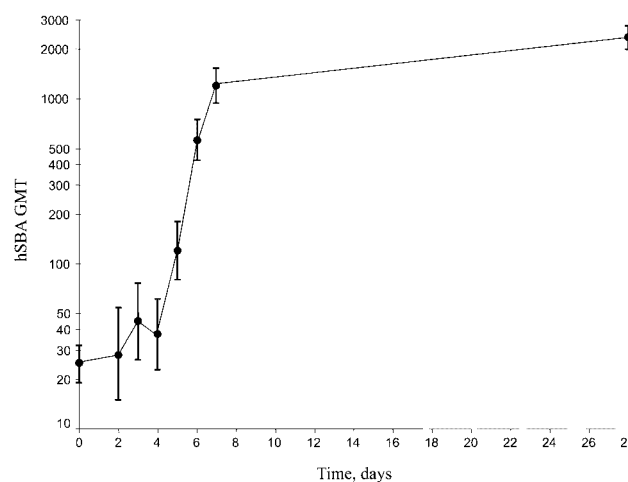


Figure 3. Geometric mean human complement serum bactericidal assay titers (hSBA GMTs) and 95% CIs (bars) of serum samples obtained from patients in groups 1–4 on various days after administration of a plain polysaccharide meningococcal vaccine.

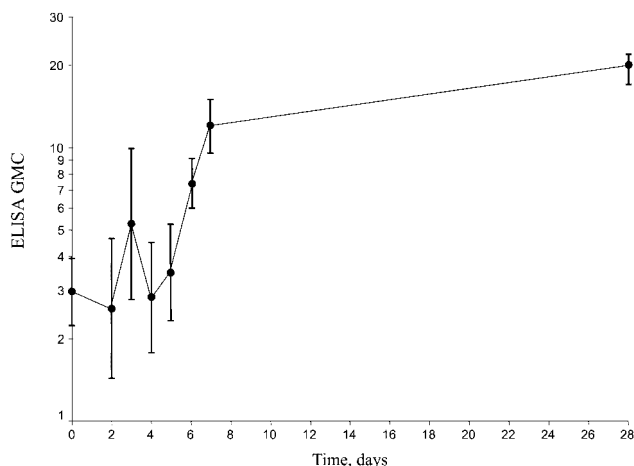


Figure 4. Geometric mean ELISA IgG concentrations (ELISA GMCs) and 95% CIs (bars) of serum samples obtained from patients in groups 1–4 on various days after administration of a plain polysaccharide meningococcal vaccine.

a total of 264 provided a blood sample at day 0, and 262 were vaccinated (figure 1). Two of these subjects provided no subsequent blood sample; therefore, a total of 260 participants were included in the treatment-received analysis for immunogenicity. One hundred seventy-one of these had been randomized to groups 1–4 (receiving MenPS), and 89 were randomized to groups 5 or 6 (receiving MenCV). The mean age of these 260 participants at the time of their prior MenCV vaccination in

the UK mass immunization campaign was 10.8 years (range, 9.1–12.5 years), and the mean time since routine vaccination with MenCV was 3.7 years (range, 3.2–4.3 years).

A total of 7 participants were excluded from the per-protocol immunogenicity analysis for at least 1 time point in the study (figure 1). The results of the per-protocol analysis were similar to the treatment-received analysis (results not shown).

Primary objectives. The percentage of participants with an hSBA titer ≥ 8 at each of the time points after vaccination with MenPS is shown in figure 2. hSBA GMTs and ELISA GMCs following vaccination with MenPS are shown in figures 3 and 4, respectively. No increase in hSBA GMT was detected until 5 days after administration of MenPS (SBA GMT day 0, 24.7 [95% CI, 18.9–32.3]; day 4, 37.9 [95% CI, 23.8–60.6]; and day 5, 120.8 [95% CI, 82.1–177.6]).

Secondary objectives. The MenC-specific hSBA GMT for all participants prior to repeat vaccination was 23.3 (95% CI, 18.9–28.6), and ELISA GMC was 3.0 $\mu\text{g/mL}$ (95% CI, 2.5–3.8). An hSBA titer ≥ 8 was measured in the serum samples of 74.6% of participants (95% CI, 69.3%–79.1%), whereas 83.9% of participants had an hSBA titer ≥ 4 (95% CI, 79.4–88.3).

All participants demonstrated an hSBA titer ≥ 8 at day 28 after vaccination. The hSBA GMTs observed 28 days following vaccination with MenCV (4979.4; 95% CI, 4205–5895.3) were higher than those observed following vaccination with MenPS (2370.9; 95% CI, 2008.8–2798.2) (figure 5). ELISA GMCs were similarly higher 28 days after vaccination with MenCV, com-

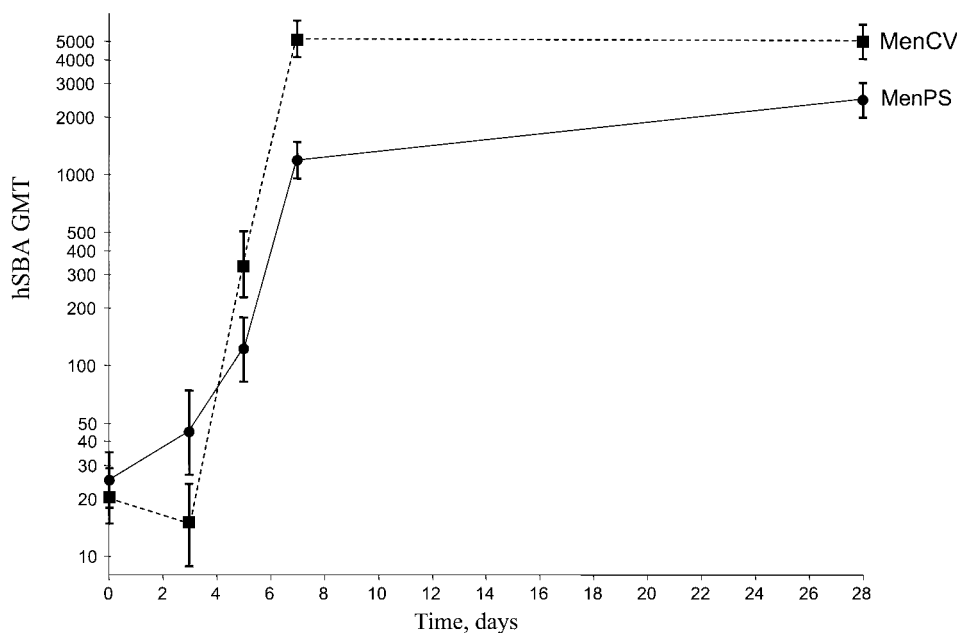


Figure 5. Geometric mean human complement serum bactericidal assay titers (hSBA GMTs) and 95% CIs (bars) of serum samples obtained on various days after administration of either a plain polysaccharide meningococcal vaccine (MenPS) or a monovalent glycoconjugate vaccine (MenCV). Data at day 0, day 7, and day 28 after vaccination are pooled from groups 3 and 4 (MenPS) and groups 5 and 6 (MenCV). Data at day 3 are from group 3 (MenPS) and group 5 (MenCV). Data at day 5 are from group 4 (MenPS) and group 6 (MenCV).

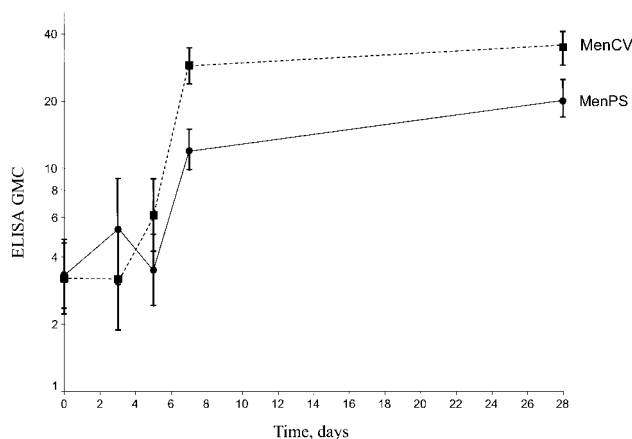


Figure 6. Geometric mean ELISA IgG concentrations (ELISA GMCs) and 95% CIs (bars) of serum samples obtained on various days after administration of either a plain polysaccharide meningococcal vaccine (MenPS) or a monovalent glycoconjugate vaccine (MenCV). Data at day 0, day 7, and day 28 after vaccination are pooled from groups 3 and 4 (MenPS) and groups 5 and 6 (MenCV). Data at day 3 are from group 3 (MenPS) and group 5 (MenCV). Data at day 5 are from group 4 (MenPS) and group 6 (MenCV).

pared with ELISA GMCs after vaccination with MenPS (35.7 [95% CI, 29.5–43.2] and 19.5 [95% CI, 17.1–22.3], respectively) (figure 6).

As with MenPS, no increase in hSBA GMT was observed until 5 days after vaccination with MenCV. The hSBA GMTs that were demonstrated following vaccination with MenCV were higher at days 5, 7, and 28, compared with those observed after vaccination with MenPS. By contrast, at day 3 after vaccination, hSBA GMTs observed in group 3 (receiving MenPS) were higher than those in group 5 (receiving MenCV), and the lower 95% CI of the ratio of hSBA GMT in group 5 compared with group 3 was <0.5 (0.33; 95% CI, 0.16–0.65). A trend toward a higher hSBA GMT was observed at day 0 in group 3 (hSBA GMT, 41; 95% CI, 24–69), compared with group 5 (hSBA GMT, 17; 95% CI, 11–27). To correct for this variation, the proportional increase in the hSBA GMT from day 0 to day 3 was calculated for group 3 (proportional increase in hSBA GMT, 1.04; 95% CI, 0.9–1.19) and for group 5 (proportional increase in hSBA GMT, 0.81; 95% CI, 0.67–0.99), and the ratio of these values were calculated (ratio of group 5 to group 3, 0.79; 95% CI, 0.59–1.05). Application of the mixed-effect model analysis yielded similar results, although the ratio of group 5 to group 3 at day 3 was 0.61 (95% CI, 0.42–0.89) (figure 7). Using this analysis, hSBA GMTs remained significantly higher at days 5, 7, and 28 following vaccination with MenCV.

Safety objectives. No vaccine-related serious adverse events were recorded in this study. Recorded rates of systemic and local reactions are displayed in table 3. The only differences in adverse events between the 2 groups were higher rates of in-

jection-site swelling and of analgesic or antipyretic use in the recipients of MenCV ($P = .04$ and $P = .01$, respectively).

DISCUSSION

This study provides evidence that MenCV induces sustained elevation of bactericidal antibodies after immunization of 10-year-old children. Specifically, we demonstrated that, 3.7 years after immunization with a single dose of MenCV, 75% of adolescents aged 13–15 years had an hSBA titer ≥ 8 . Furthermore, 84% of tested serum samples obtained from the participants in our study met or exceeded the widely accepted protective hSBA titer threshold of 1:4 [13]. Although our study design did not include a control group of age-matched, MenCV-naïve subjects, seroprevalence studies conducted in the United Kingdom prior to the introduction of the MenC glycoconjugate vaccines into the national immunization campaign suggest that seroprotection would only be observed in 20% of this population [14].

The contrast with the persistence of antibody observed in children immunized with the MenC glycoconjugate vaccines as infants or toddlers is marked. One year after receiving 3 infant doses (at 2, 3, and 4 months of age) of MenC-CRM₁₉₇ glycoconjugate vaccine, only 46% of recipients still had bactericidal antibody levels that were deemed protective, decreasing to 12% by 4 years after immunization [4]. Similarly, only 37% of 2-year-old children receiving a single dose of MenC-CRM₁₉₇ demonstrated “protective” SBA titers 2 years after immunization [6]. Comparison between previous MenC glycoconjugate

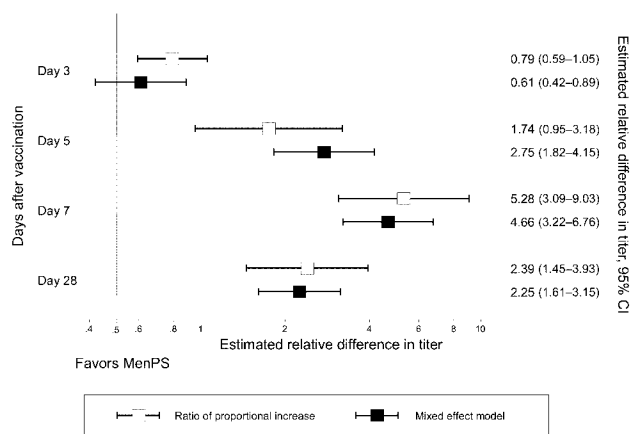


Figure 7. Mixed-effect model analysis and ratio of proportional increases of geometric mean human complement serum bactericidal assay titers (hSBA GMTs) of serum samples obtained on various days after administration of either a plain polysaccharide meningococcal vaccine (MenPS) or a monovalent glycoconjugate vaccine (MenCV). Data at day 7 and day 28 after vaccination are pooled from groups 3 and 4 (MenPS) and groups 5 and 6 (MenCV). Data at day 3 are from group 3 (MenPS) and group 5 (MenCV). Data at day 5 are from group 4 (MenPS) and group 6 (MenCV). Bars, 95% CIs.

Table 3. Summary of reactogenicity of meningococcal serogroup A and C plain polysaccharide vaccine (MenPS) and meningococcal serogroup C glycoconjugate vaccine (MenCV).

Adverse event	No. (%) of subjects receiving MenPS (n = 171)	No. (%) of subjects receiving MenCV (n = 91)
Local reactions		
Pain		
Any	157 (92)	88 (97)
Severe	71 (42)	48 (53)
Erythema		
Any	49 (29)	35 (38)
>50 mm	0	3 (3)
Induration		
Any	41 (24)	23 (25)
>50 mm	0	2 (2)
Swelling		
Any	22 (13)	13 (14)
>50 mm	1 (1)	5 (5) ^a
Systemic reactions		
Chills	25 (15)	11 (12)
Nausea	27 (16)	21 (23)
Malaise	67 (39)	42 (46)
Myalgia	67 (39)	34 (37)
Arthralgia	19 (11)	15 (16)
Headache	69 (40)	35 (38)
Fever (temperature, ≥38.5°C)	2 (1)	0
Use of analgesics or antipyretics	43 (25)	34 (37) ^b

^a $P = .04$ for χ^2 test of proportions between groups.

^b $P = .01$ for χ^2 test of proportions between groups.

vaccine studies in infants, toddlers, and adolescents suggests that the higher protective antibody levels in the adolescent age group is the result of both a higher hSBA GMT generated in response to a single dose of MenC glycoconjugate vaccine and to slower rates of decrease in bactericidal antibody titer [7, 8, 15].

Possible reasons for the greater immunogenicity of MenCV in the older age group include maturational changes in the immune response during childhood [16, 17] or “priming” of the immune system by nasopharyngeal carriage of MenC, resulting in an anamnestic response to MenCV. The latter explanation appears to be unlikely, because cross sectional studies of carriage rates of MenC indicate low rates in children <10 years of age, increasing to only 0.45% at 15–17 years of age [18]. Similarly, significant “boosting” by postimmunization exposure to MenC is unlikely given the even-lower rates of nasopharyngeal carriage in the UK following the immunization campaign [18]. Priming or boosting may also result from mucosal carriage of an organism bearing a cross-reactive polysaccharide, such as *Escherichia coli* K92 [19].

Because of concerns regarding the waning of protection against MenC disease after priming in infancy, a combined *H. influenzae* type b–MenC glycoconjugate vaccine will be introduced into the United Kingdom immunization schedule for children 12 months of age [20]. Given that adolescents have the highest rates of carriage and contribute substantially to the transmission of meningococci [21], an alternative approach would be to immunize this older age group. The sustained immunogenicity described in this study suggests that such a policy could provide protection that is both direct (to the adolescents who were immunized) and indirect (to the younger age groups).

The kinetics of the immune response to antigenic challenge were assessed to better understand the relative contribution to vaccine efficacy of “resting” levels of bactericidal antibody and the anamnestic increase in bactericidal antibody. To this end, we have presumed that challenge with an intramuscular dose of MenPS mimics the antigenic exposure experienced by the human immune system following exposure to *Neisseria meningitidis* and that MenCV primes for immunological memory in the age groups we have studied, as it does in infants and 1–2-year-old children [6, 14]. Despite this (presumed) immunological memory, no increases in hSBA GMT or ELISA GMC were observed until day 5 after a MenPS antigenic challenge. Given that invasion usually occurs soon after acquisition [22], this delay implies that it is not possible to rely on the anamnestic response to colonization or revaccination to protect against rapidly invasive meningococcal infection. These observations, which are similar to those previously reported for *H. influenzae* type b [23], are supported by surveillance data for MenC disease recorded in both the United Kingdom [3] and Spain [24], countries that report higher rates of MenC glycoconjugate vaccine failures in cohorts with a low prevalence of serological evidence of protection.

Participants in this study, all of whom had been previously immunized with MenCV, received a dose of either MenPS or MenCV, both of which contained 10 μ g of serogroup C meningococcal polysaccharide. MenCV induced a significantly better immune response than did MenPS from day 5 after vaccination onwards. At day 3, the unadjusted data suggest a lower hSBA GMT following receipt of MenCV, compared with after receipt of MenPS. When adjusting for a trend to a lower hSBA GMT at day 0 in the MenCV group by either comparing the ratios of the proportional increase from day 0 to day 3 in the 2 relevant groups (as specified in the study protocol) or by application of a post hoc mixed-effect model analysis, this result becomes of borderline significance. The higher hSBA GMT observed following administration of MenCV from day 5 onwards raises the possibility that glycoconjugate vaccines may be more effective vaccines for the management of an outbreak of serogroup C meningococcal infection in a previously im-

munized population. However, the recommended dose of plain polysaccharide vaccine is 50 μg (which is likely to be more immunogenic than the 10- μg dose used in this study), thus limiting the direct comparisons that can be made between the usefulness of the 2 vaccines in this setting.

This study provides novel data on the persistence of bactericidal antibody after immunization with MenCV in the pre-adolescent age group and the kinetics of the antibody response directed at the MenC polysaccharide. Although the sustained elevation of these antibodies in the majority of adolescents following primary immunization against MenC in the United Kingdom is reassuring, the delayed increase in antibody after immune challenge highlights the importance of maintaining protective levels of antibody in populations whose postvaccination immunity has waned.

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Potential conflicts of interest. A.J.P. is an inventor on a patent application in the area of MenB vaccines. During the period 2004–2005, E.R.M. was a consultant to Chiron Vaccines on meningococcal disease and vaccine development. A.J.P. and E.R.M. act as chief investigators for clinical trials conducted on behalf of Oxford University that are sponsored by vaccine manufacturers (Aventis-Pasteur MSD, Chiron Vaccines, Glaxosmithkline, Sanofi-Aventis, and Wyeth Vaccines) and have received assistance to attend scientific meetings from Aventis Pasteur MSD, Chiron Vaccines, and Wyeth Vaccines. M.D.S. has received assistance to attend scientific meetings from Chiron Vaccines and Sanofi Pasteur and has spent a period of secondment at Chiron Vaccines (Siena, Italy). L.D. has received assistance to attend scientific meetings from Wyeth pharmaceuticals. A.B. is an employee of Chiron Vaccines (Marburg, Germany). All other authors: no conflicts.

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