

# Antibody Persistence after Serogroup C Meningococcal Conjugate Immunization of United Kingdom Primary-School Children in 1999–2000 and Response to a Booster: A Phase 4 Clinical Trial

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**Background.** After immunization with serogroup C meningococcal (MenC) conjugate vaccine, antibody responses and vaccine effectiveness are sustained in adolescents, in contrast to rapid waning in young children. We investigated the persistence of serum bactericidal antibody (SBA) titers in children 6 years after immunization with MenC vaccine (primed between 2 months and 6 years of age). The response to a *Haemophilus influenzae* type b–MenC conjugate (Hib–MenC) booster was also measured.

**Methods.** A phase 4 clinical trial was conducted among 250 healthy 6–12-year-old children. SBA titers were measured before, 1 month after, and 1 year after Hib–MenC administration. The correlate of protection was an SBA titer of  $\geq 8$ .

**Results.** An SBA titer of  $\geq 8$  was observed in 61 (25% [95% confidence interval {CI}, 20%–30%]) of 244 participants (mean age, 9.1 years; mean interval since MenC immunization, 6.75 years). The proportion with an SBA titer of  $\geq 8$  and the SBA geometric mean titer increased with age, from 12% (95% CI, 4%–23%) to 48% (95% CI, 29%–67%) and from 2.90 (95% CI, 2.11–3.99) to 17.20 (95% CI, 6.80–43.5), respectively, from a mean age of 7.0 to 12.1 years. One month after the Hib–MenC booster, all participants had an SBA titer of  $\geq 8$ , which was sustained in 99.6% at 1 year.

**Conclusions.** As a result of waning antibody, the majority of 6–12-year-old children in the United Kingdom have inadequate serological protection against MenC. The persistence of MenC immunity and the response to a Hib–MenC booster is dependent on age at priming. A booster was highly effective in this cohort and could sustain population immunity against MenC disease.

**Trial registration.** Current Controlled Trials (<http://www.controlled-trials.com>) identifier: ISRCTN72858898.

The introduction of serogroup C meningococcal (MenC) conjugate vaccine in the United Kingdom in 1999 was a great success [1, 2]. A massive catch-up campaign targeted all children and young adults from 2 months to 18 years (later extended to 24 years) of age. As part of the simultaneous introduction of MenC vaccine into

the routine infant immunization schedule, a single dose of MenC vaccine was administered to those 1–18 years of age, 2 doses were administered to children 5–11 months of age, and 3 doses were administered to infants at 2, 3, and 4 months of age. Vaccine coverage of  $>90\%$  was achieved for routine infant immunization, and  $\sim 85\%$  was achieved in the catch-up cohort [3]. Post-licensure surveillance revealed high rates of vaccine efficacy among teenagers and toddlers [4], a substantial reduction in carriage [5], and a resultant increase in herd immunity [6]. MenC disease rates declined dramatically among both immunized and unimmunized individuals, and the beneficial effects with respect to population protection have been sustained and accentuated over time [5].

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**Table 1. Study Design and Number of Enrolled Participants**

Group	Age at MenC vaccine priming	No. of priming doses of MenC vaccine	Approximate interval since MenC vaccine priming, years	Approximate age at enrollment, years	No. of enrolled participants
1	≤6 months	3	6	6–7	55
2	5–11 months	2	6	7	28
3	1–2 years (12–23 months)	1	6	7–8	54
4	2–3 years (24–35 months)	1	6	8–9	30
5	3–4 years (36–47 months)	1	6	9–10	27
6	4–5 years (48–59 months)	1	6	10–11	27
7	5–7 years (60–83 months)	1	6	11–12	29
Total					250

**NOTE.** MenC, serogroup C meningococcal.

However, additional postlicensure surveillance revealed that despite short-term immunogenicity in all age groups [7], MenC vaccine effectiveness wanes rapidly in children <3 years of age [3] and is associated with a reduction in the proportion of children with a serum bactericidal antibody (SBA) titer above the accepted correlate of protection (serological protection). Persistence of an adequate postimmunization SBA titer rather than the demonstration of an anamnestic response to subsequent antigen challenge is now regarded as the key to the maintenance of individual protection against the rapid invasion of MenC [8].

Few data on the long-term persistence of postimmunization SBA titers in children immunized with MenC vaccine are available. Waning serological protection has been shown in infants [9] and in 2-year-old children [10]. In contrast, sustained SBA titers above the correlate of protection [11, 12] and high effectiveness [3] are found in older children immunized with MenC vaccine at 6–15 years of age. However, there are no published data, to our knowledge, addressing either the long-term (>5 years) persistence of MenC SBA titers in children in the United Kingdom with a documented history of MenC immunization or the response to a booster dose of MenC vaccine in this age cohort.

We measured MenC SBA titers and immunoglobulin G (IgG) concentrations in 250 children aged 6–12 years of age who had been immunized 6 years previously between 2 months and 6 years of age in the United Kingdom MenC mass immunization campaign. We also assessed the memory response at 1 month and the persistence of antibody at 1 year after a *Haemophilus influenzae* type b–MenC conjugate (Hib–MenC) booster by measuring MenC SBA titers and IgG concentrations at these additional time points.

## METHODS

**Study design and participants.** We conducted an open-label phase 4 study in Oxfordshire, United Kingdom, from Septem-

ber 2006 through July 2008. The primary objective was to evaluate the persistence of MenC SBA in participants aged 6–12 years of age who had received primary MenC vaccination during the 1999–2001 United Kingdom MenC mass immunization campaign. Children were recruited after parents responded to a letter sent to all parents of children in the target age group. Only healthy children who had received all United Kingdom scheduled immunizations (including 2 catch-up vaccinations: MenC vaccine in 1999–2000 and a Hib booster in 2003) were enrolled. Children were excluded if they had a previous diagnosis of confirmed or suspected meningitis; were previously exposed to or infected with MenC or Hib; had previously had an anaphylactic reaction to vaccine components; had any acute or chronic infection; had received antibiotics during the past 7 days; had a temperature  $\geq 38^{\circ}\text{C}$  during the past 3 days; had received blood products during the past 3 months; had a serious disease, bleeding disorder, immune dysfunction, or genetic anomaly; were born at <36 weeks' gestation; or had received doses of Hib or MenC vaccines in addition to those given in accordance with the routine United Kingdom immunization schedule or catch-up campaigns. Ethical approval was obtained from the Oxfordshire Research Ethics Committee (06/Q1605/100). The study was registered at <http://www.controlled-trials.com> (ISRCTN72858898).

Participant's individual MenC immunization history was verified from medical records or centralized immunization records. Children were stratified into 7 groups on the basis of their MenC immunization history (age of child at receipt of MenC vaccine during the United Kingdom 1999–2001 mass immunization campaign) and age at enrollment (Table 1). Developmentally appropriate information was provided to the participant, and written informed consent was obtained from their parent or legally authorized representative. A 10-mL blood sample was obtained and all participants received a single dose of the Hib–MenC booster (Menitorix; GlaxoSmithKline Vaccines), administered intramuscularly into the deltoid with a 23-gauge,

25-mm needle. In the United Kingdom at enrollment, this vaccine was licensed for use in children from 2 months of age. Additional blood samples were collected 1 month and 1 year after administration of the Hib-MenC booster.

**Serological responses.** MenC SBA assays, using baby rabbit complement, were done by the Vaccine Evaluation Unit, Manchester, United Kingdom, using standard protocols [13]. The reference strain was C11 (C:16:P1.7-1,1), and SBA titers were expressed as the reciprocal of the final serum dilution yielding 50% or greater killing at 60 min. An SBA titer of at least 8 was used as the serological correlate of protection. SBA titers <4 were assigned a value of 2.

The MenC polysaccharide-specific IgG concentration in serum was determined using an enzyme-linked immunosorbent assay at the Oxford Vaccine Group, University of Oxford, as described elsewhere [14]. Laboratory staff at both laboratories were blinded to the participants' age and group allocation.

**Statistical analysis.** The primary objective of the present study was to determine the proportion of participants (in total and in each group) who had an SBA titer of  $\geq 8$  six years after immunization with MenC vaccine; 95% confidence intervals (CIs) were calculated using the binomial exact method. In addition, SBA geometric mean titers (GMTs) were calculated for each group. Each titer measured was logarithmically transformed for analysis. Two-sided 95% CIs were constructed by back-transformation of the CI for the mean of the logarithmically transformed assay results, computed using the Student *t* distribution.

Secondary objectives for this study included assessment of IgG geometric mean concentrations (GMCs) 6 years after receipt of MenC vaccine (baseline). In addition, the proportion of participants with an SBA titer of  $\geq 8$  and an SBA titer of  $\geq 128$  as well as SBA GMTs and IgG GMCs 1 month and 1 year after administration of the Hib-MenC booster were calculated; 95% CIs were calculated as described above. All antibody concentrations were log-transformed for analysis.

Analysis of variance was used to compare baseline concentrations (ie, assessment of persistence of antibodies 6 years after priming) between groups. Comparisons between groups 1 month and 1 year after boosting were done using analysis of covariance, adjusting for baseline measures. The  $\chi^2$  test was used to compare protection rates.

All enrolled participants were included in the demographic analysis. Analysis was conducted on all available data. However, participants were excluded from the analysis for inappropriate enrollment (Figure 1). Decisions with respect to exclusion of participants from the analysis were made a priori. Sensitivity analyses were also conducted with all participants included and with those who had a protocol violation excluded. Results remained consistent with the overall conclusion.

Data were analyzed using Excel 2007 software (Microsoft

Office), Stata software (version 10; StataCorp), and SAS software (version 9.1).

## RESULTS

Of the 13,103 families approached, 1586 responded; 459 provided favorable responses and were assessed for eligibility. Of 250 enrolled participants, 249 received the Hib-MenC booster; 244 (98%) were included in the analysis, and 230 (92%) completed all study visits (Table 1 and Figure 1).

The mean age at enrollment was 9.1 years; age ranged from 6.4 (group 1) to 12.6 (group 7) years. The mean age at primary MenC immunization ranged from 0.2 (group 1) to 5.8 (group 7) years, and the mean interval since MenC immunization was 6.75 years (standard deviation, 0.36 years). There was a trend toward MenC immunization to have been done slightly more recently in older age groups (range, 5.94–7.25 years) (Table 2).

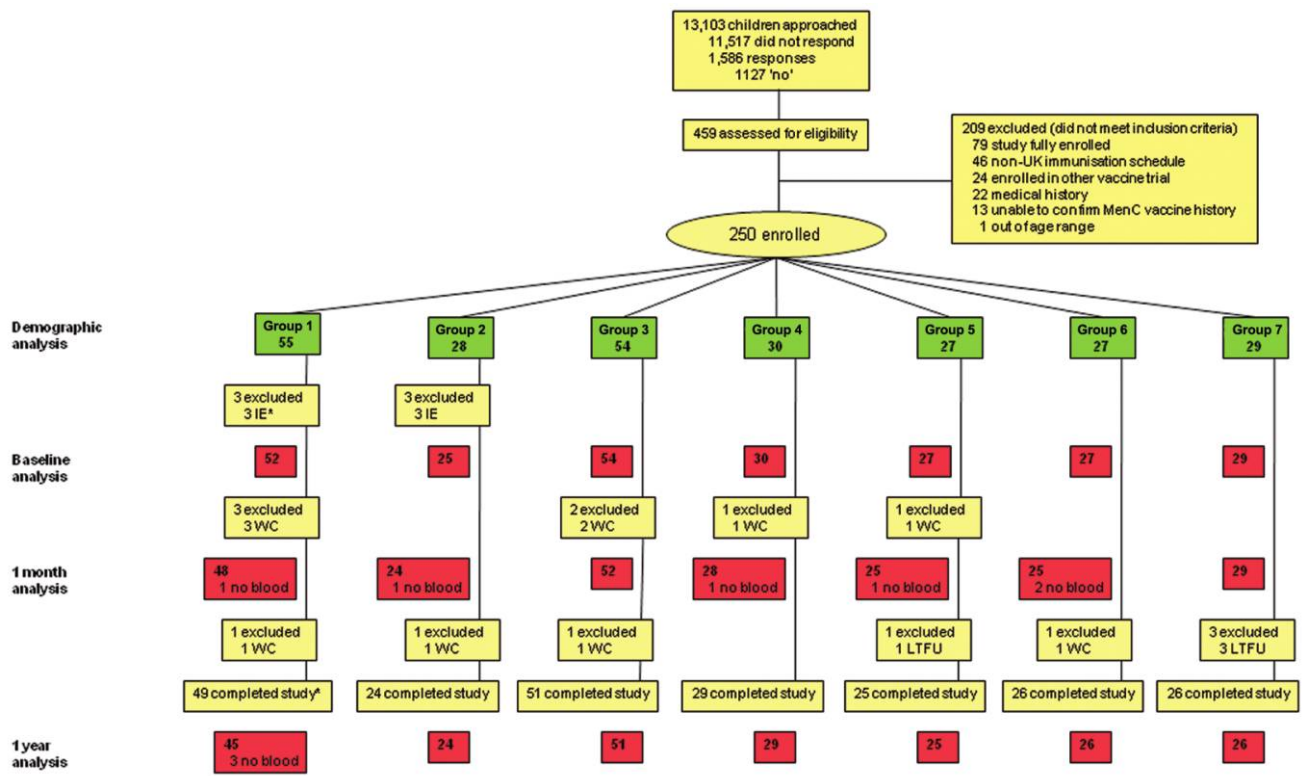
**Primary objective.** The proportion of participants with an SBA titer of  $\geq 8$  and SBA GMTs 6 years after MenC immunization (baseline) were calculated by age group (Table 3). Overall, 61 (25% [95% CI, 20%–30%]) of 244 participants had an SBA titer of  $\geq 8$  (range, 12% [95% CI, 4%–23%] in group 1 to 48% [95% CI, 29%–67%] in group 7; test for trend across groups,  $P < .001$ ). Antibody levels differed by age: an SBA titer of  $\geq 8$  was found in 13% (95% CI, 5%–21%) of participants in groups 1 and 2; 27% (95% CI, 19%–34%) in groups 3–6; and 48% (95% CI, 29%–67%) in group 7. There was strong evidence of a trend toward increasing SBA GMTs with age at MenC priming ( $P < .001$ ).

**Secondary objectives.** There were similar age-related differences in IgG GMCs at baseline (range, 0.20  $\mu\text{g}/\text{mL}$  in group 1 to 0.59  $\mu\text{g}/\text{mL}$  in group 7, respectively) (Table 3). Age-dependent immune memory responses were observed 1 month after the Hib-MenC booster; all participants had an SBA of  $\geq 128$  and a high SBA GMT (range, 4077–16,005). Anamnestic IgG GMC responses were evident, although the trend across the age groups was not significant.

One year after the Hib-MenC booster, 224 (99.6%) of 225 participants still had an SBA titer above the serological correlate of protection and age-dependent responses persisted, as evidenced by only 87% (95% CI, 73%–95%) of group 1 participants having an SBA titer of  $\geq 128$ , compared with 100% (95% CI, 87%–100%) of group 7 participants. SBA GMTs and IgG GMCs increased across the age groups (test for trend,  $P < .001$  and  $P = .03$ , respectively).

## DISCUSSION

The present study shows that vaccine-induced immunity is not sustained after immunization of young children with MenC vaccine. Specifically, only one-quarter of 6–12-year-old children had persistent SBA titers above the serological correlate of protection (ie, SBA titer of  $\geq 8$ ). Furthermore, long-term persis-



**Figure 1.** Study flow chart for recruitment, enrollment, and inclusion in demographic and immunogenicity analysis. Six participants (3 each from groups 1 and 2) were excluded from the analysis for inappropriate enrollment (IE) because their confirmed dates of serogroup C meningococcal (MenC) priming immunization fell outside of their group requirements (eg, group 1 participants must have received all 3 doses of MenC vaccine at  $\leq 6$  months of age, and group 2 participants must have received 2 doses of MenC vaccine between 5 and 11 months of age). One participant in group 1 (indicated by the asterisk) completed the study before being withdrawn for IE. Further exclusions from the per-protocol analysis were made for the following participants: in group 1, blood was drawn from 3 participants outside the time lines (sample 2 assays excluded), and 1 participant was receiving oral antibiotics at the 1-month visit (serum bactericidal antibody [SBA] assay excluded for sample 2); in group 2, blood was drawn from 1 participant outside the time lines (sample 2 assays excluded); in group 3, blood was drawn from 3 participants outside the time lines (sample 2 [ $n = 2$ ] and sample 3 [ $n = 1$ ] assays excluded); in group 4, blood was drawn from 1 participant outside the time lines (sample 3 assays excluded); in group 5, no exclusions; in group 6, blood was drawn from 2 participants outside the time lines (sample 2 assays excluded); and in group 7, blood was drawn from 1 participant outside the time lines (sample 2 assays excluded), and 2 participants were taking oral antibiotics at the 1-month visit (SBA assay excluded for sample 2). LTFU, lost to follow-up; no blood, no blood sample obtained at visit; WC, withdrawal of consent.

tence of functional antibody was dependent on age at primary immunization. To our knowledge, this is also the first study to assess the response to a booster MenC vaccine given  $>5$  years after priming.

Previous studies have shown a rapid waning of MenC SBA titers in infants. In the United Kingdom, 1 year after 3 doses of MenC vaccine given at 2, 3, and 4 months of age, 54% of children had an SBA titer of  $\geq 8$  [9, 15], declining to 12% by 4 years [9, 15]. In line with these findings, we found that 12% of participants in a similar age cohort (group 1) had an SBA titer of  $\geq 8$  six years after immunization. This figure is similar to the age-specific prevalence of SBA titers above the serological correlate of protection found in the United Kingdom prevaccine serosurvey [16]. This suggests that the nadir of bactericidal antibody decline is reached within 4 years after infant MenC immunization.

Antibody decline after immunization in toddlers appears to be less rapid. A previous study reported that 37% of children immunized at 2 years of age had SBA titers above the serological correlate of protection at 4 years of age [10]. Protection in this age cohort fell to 23% by 9 years of age in our study (group 4), suggesting that waning might continue in this age cohort through childhood. We found that a similar proportion of children had SBA titers above the correlate of protection (23%–33%) among those immunized at 1–4 years of age (groups 3–6) 6 years after immunization, suggesting that immune persistence after a single dose of MenC vaccine is not age dependent among preschool children.

In contrast to the poor persistence of functional antibody in infants and preschool children, Snape et al [12] reported that 4–5 years after immunization of 6–15-year-olds, most continued to have SBA titers above the correlate of protection; SBA

**Table 2. Demographic Characteristics of Enrolled Participants**

Characteristic	Group (age in months at MenC vaccine priming)						
	Group 1 (≤6)	Group 2 (5–11)	Group 3 (12–23)	Group 4 (24–35)	Group 5 (36–47)	Group 6 (48–59)	Group 7 (60–83)
Age at baseline, years							
Mean ± SD	7.04 ± 0.41	7.96 ± 0.16	8.26 ± 0.35	9.26 ± 0.44	10.27 ± 0.32	11.30 ± 0.36	12.09 ± 0.27
Range	6.37–7.88	7.68–8.24	7.65–9.08	8.23–10.08	9.42–10.68	10.51–11.89	11.50–12.59
No. of participants	55	28	54	30	27	27	29
Sex, no. (%)							
Male	31 (56.4)	12 (42.9)	31 (57.4)	15 (50.0)	17 (63.0)	18 (66.7)	11 (37.9)
Female	24 (43.6)	16 (57.1)	23 (42.6)	15 (50.0)	10 (37.0)	9 (33.3)	18 (62.1)
Race, no. (%)							
White	51 (92.7)	27 (96.4)	51 (94.4)	27 (90.0)	27 (100)	25 (92.6)	29 (100)
Asian	1 (1.8)	0 (0)	0 (0)	1 (3.3)	0 (0)	2 (7.4)	0 (0)
Black	2 (3.6)	0 (0)	1 (1.8)	1 (3.3)	0 (0)	0 (0)	0 (0)
Mixed	1 (1.8)	1 (3.6)	2 (3.7)	1 (3.3)	0 (0)	0 (0)	0 (0)
Age at first MenC immunization, mean years ± SD	0.21 ± 0.06	0.73 ± 0.12	1.45 ± 0.30	2.54 ± 0.33	3.60 ± 0.23	4.58 ± 0.30	5.83 ± 0.37
Age at last MenC immunization, mean years ± SD	0.39 ± 0.10	0.82 ± 0.14	NA	NA	NA	NA	NA
Interval since first MenC immunization, mean years ± SD	6.83 ± 0.37	7.22 ± 0.18	6.80 ± 0.25	6.71 ± 0.32	6.67 ± 0.20	6.72 ± 0.21	6.26 ± 0.17

**NOTE:** Of the 244 participants included in the baseline immunogenicity analysis, 227 (93%) received primary vaccine(s) containing serogroup C meningococcal (MenC) capsular polysaccharide conjugated to a CRM<sub>197</sub> carrier protein, and 2 (1%) received primary vaccine(s) containing a tetanus toxoid carrier protein; for 15 (6%) of the 244, the type of carrier protein was unknown. NA, not applicable; SD, standard deviation.

**Table 3. Serogroup C Meningococcal (MenC) Serum Bactericidal Antibody (SBA) Titers and Immunoglobulin G (IgG) Antibody Concentrations at Baseline and at 1 Month and 1 Year after Immunization with a *Haemophilus influenzae* Type b–MenC Conjugate (Hib–MenC) Booster**

Category	Group (age in months at MenC vaccine priming)							P <sup>a</sup>
	Group 1 (≤6)	Group 2 (5–11)	Group 3 (12–23)	Group 4 (24–35)	Group 5 (36–47)	Group 6 (48–59)	Group 7 (60–83)	
SBA titer of ≥8								
Baseline								<.001
Proportion	6/52	4/25	14/54	7/30	9/27	7/27	14/29	
% (95% CI)	12 (4–23)	16 (4–36)	26 (15–40)	23 (10–42)	33 (16–54)	26 (11–46)	48 (29–67)	
1 month								...
Proportion	48/48	24/24	52/52	28/28	25/25	25/25	29/29	
% (95% CI)	100 (93–100)	100 (86–100)	100 (93–100)	100 (88–100)	100 (86–100)	100 (86–100)	100 (88–100)	.86 <sup>b</sup>
1 year								
Proportion	45/45	24/24	50/51	28/28	25/25	26/26	26/26	
% (95% CI)	100 (92–100)	100 (86–100)	98 (90–100)	100 (88–100)	100 (86–100)	100 (87–100)	100 (87–100)	
SBA titer of ≥128								
Baseline								.001
Proportion	3/52	2/25	6/54	3/30	6/27	1/27	11/29	
% (95% CI)	6 (1–16)	8 (1–26)	11 (4–23)	10 (2–26)	22 (9–42)	4 (0.9–19)	38 (21–58)	
1 month								...
Proportion	48/48	24/24	52/52	28/28	25/25	25/25	29/29	
% (95% CI)	100 (93–100)	100 (86–100)	100 (93–100)	100 (88–100)	100 (86–100)	100 (86–100)	100 (88–100)	
1 year								.02 <sup>b</sup>
Proportion	39/45	21/24	46/51	26/28	24/25	26/26	26/26	
% (95% CI)	87 (73–95)	88 (68–97)	90 (78–97)	93 (76–99)	96 (80–100)	100 (87–100)	100 (87–100)	

SBA titer										
Baseline										
No. analyzed	52	25	54	30	27	27	29	29		<.001
GMT (95% CI)	2.90 (2.11–3.99)	3.29 (1.92–5.64)	4.98 (3.20–7.74)	4.81 (2.61–8.87)	9.10 (3.71–22.3)	4.32 (2.60–7.17)	17.2 (6.80–43.5)			
1 month										
No. analyzed	48	24	52	28	25	25	29	29		<.001 <sup>b</sup>
GMT (95% CI)	5312 (4077–6921)	5468 (4059–7365)	8526 (6335–11,475)	9742 (7512–12,634)	7331 (4905–10,958)	8422 (6366–11,142)	11,448 (8188–16,005)			
1 year										
No. analyzed	45	24	51	28	25	26	26	26		<.001 <sup>b</sup>
GMT (95% CI)	308 (204–465)	332 (190–580)	423 (286–626)	551 (337–902)	605 (406–901)	705 (512–970)	1302 (856–1978)			
IgG level										
Baseline										
No. analyzed	52	25	54	30	27	27	29	29		<.001
GMC, $\mu$ g/mL	0.20 (0.15–0.26)	0.26 (0.18–0.36)	0.21 (0.17–0.27)	0.24 (0.17–0.32)	0.39 (0.25–0.60)	0.32 (0.22–0.45)	0.59 (0.36–0.97)			.36 <sup>b</sup>
1 month										
No. analyzed	48	24	52	28	25	25	29	29		
GMC, $\mu$ g/mL	13.3 (10.5–16.8)	15.1 (11.5–19.9)	17.5 (13.6–22.5)	21.0 (17.1–25.9)	14.2 (10.6–19.2)	14.4 (11.4–18.2)	20.8 (14.5–29.8)			.03 <sup>b</sup>
1 year										
No. analyzed	45	24	51	28	25	26	26	26		
GMC, $\mu$ g/mL	1.42 (1.08–1.86)	1.28 (0.90–1.82)	1.5 (1.15–1.95)	1.53 (1.14–2.04)	1.46 (1.07–1.98)	1.82 (1.42–2.34)	3.80 (2.38–6.06)			

**NOTE.** Baseline indicates the blood sample collected at enrollment, before administration of a Hib-MenC booster; 1 month indicates 1 month after a Hib-MenC booster; and 1 year indicates 1 year after a Hib-MenC booster. CI, confidence interval; GMC, geometric mean concentration; GMT, geometric mean titer.

<sup>a</sup> Test for trend.

<sup>b</sup> Adjusted for baseline measures (log transformed).

titers of  $\geq 8$  were found in 79% of those immunized at 6–9 years of age (mean, 8.1 years) when measured at 11–13 years of age and in up to 88% of those immunized at 10–15 years of age when measured at 14–20 years of age. In our study, only 48% of children immunized at 5–6 years of age had SBA titers above the serological correlate of protection at 11–12 years of age. This suggests that there may be a maturation of immune responses to polysaccharide-protein antigens occurring around 5 years of age that leads to improved antibody persistence.

An estimate of vaccine effectiveness in children targeted in the United Kingdom MenC mass immunization campaign showed a similar pattern, with better and more persistent protection in children immunized at  $>3$  years of age [3]. Similarly, a recent seroprevalence study showed a significant difference in the persistence of SBA titers above the correlate of protection between children given MenC vaccine at 5–9 years of age and children given vaccine at 1–4 years of age (an SBA titer of  $\geq 8$  in 65% and 32%, respectively) [17]. In contrast to this serosurvey, our study enrolled only those children who had a documented MenC immunization history, had narrow criteria for group allocation on the basis of age at MenC priming, and had a narrow time interval since immunization. These strict conditions allowed persistence data to be accurately determined for each increment in age at priming immunization between infancy and 6 years of age in children in the United Kingdom.

The immune response to receipt of a MenC vaccine booster was dependent on age. Secondary immune responses (1 month and 1 year after boosting) paralleled postprimary persistent immune responses (baseline), suggesting that younger children were less well primed. Age-dependent differences in sustained antibody responses to priming and booster immunization with MenC vaccine may be explained by immune maturation. Immunization at an older age during childhood elicits a higher primary immune response than that induced in infants. The natural decline in circulating SBA titer with time also occurs faster in infants than in older children [3, 18]. The mechanisms behind these observations are thought to be related to interference by maternal antigens, immature intrinsic germinal center B cell reactions, and suboptimal microenvironmental factors in lymphoid tissue and bone marrow [19]. Booster or anamnestic responses are likely to be of a lower magnitude in young children, for whom fewer preexisting memory B cells are available for the secondary immune response.

Studies conducted before the introduction of MenC vaccine showed that there was no difference in the proportion of children 2–14 years of age with SBA titers above the correlate of protection (United Kingdom data) [16] and that nasopharyngeal carriage in children  $<10$  years of age was rare (Norwegian data) [20]. This implies that acquisition of natural immunity with age or “priming” from nasopharyngeal carriage are unlikely explanations for greater immune responses in older age

groups. Our study was designed to assess the persistence of antibody after MenC immunization rather than be a population-based seroepidemiological survey. Given that a vaccine coverage rate of  $\sim 85\%$  was achieved in the targeted cohorts [1], it is unlikely that our findings significantly overestimate the proportion with SBA titers above the correlate of protection in the population.

In response to concern about the rapid waning of protection against MenC disease after priming during infancy, in 2006 the United Kingdom introduced a Hib-MenC booster during the second year of life, and in 2007 Canada recommended this booster if priming occurred at  $<12$  months of age [21]. Of concern, recent data indicate that antibody also wanes rapidly after this booster during the second year of life, further supporting our observation that immune responses remain suboptimal in preschool children [22]. Our data suggest that at the end of 2009 most children in the United Kingdom aged 4–15 years were susceptible to invasive MenC disease and carriage—specifically those who either received MenC vaccine at  $<6$  years of age (group 2–7 cohort) in the 1999–2001 mass immunization campaign or received the infant schedule without a booster (group 1 cohort) from 1999 to 2006. In countries such as the Netherlands and Australia, which give only a single dose of MenC vaccine at 1 year of age (comparable to the group 3 cohort), our data suggest that only one-quarter may remain protected by 7 years of age. Therefore, without a booster the vast majority of adolescents (a highly susceptible age group in the prevaccine era) in these countries are likely to be susceptible to MenC disease.

We recently proposed that current population immunity in the United Kingdom is the result of both direct protection of young adults by their own vaccine-induced immunity (those immunized in the MenC mass immunization campaign in 1999–2001 when aged 6–24 years and now around 16–35 years) and indirect protection from herd immunity blocking transmission from immune adolescents and parents to susceptible adolescents and children [23]. Therefore, waning immunity is currently offset by herd immunity in all countries that used a catch-up campaign, and consequently there is now no significant disease in the cohorts of children described in this study whose immunity has waned. Dynamic transmission models of future MenC disease and carriage in the United Kingdom suggest that further boosting for population immunity is not urgent [24]. However, this situation is unlikely to remain static, because the susceptible cohort will again become the transmitting adolescents and parents. The excellent sustained booster responses demonstrated in primed 6–12-year-old children in this study provides evidence for preemptive strategies for sustaining population immunity. A timely MenC booster given at an older age (eg, with routine preschool or adolescent vaccines) could provide more-sustained protection that is both direct (to

the older child or adolescent who was immunized) and indirect (to the younger child). This strategy might also allow for the cost-effective removal of 1 or more infant doses.

A model that incorporated both herd immunity and waning immunity to determine the number of cases of meningococcal disease averted compared different immunization strategies based on Canadian epidemiology and found a 68% reduction in invasive meningococcal disease if MenC vaccine was given at 1 and 12 years of age and a 85% reduction if a quadrivalent meningococcal vaccine was used as the 12-year booster [25]. In April 2009, the National Advisory Committee on Immunization in Canada recommended that an adolescent dose of meningococcal conjugate vaccine (monovalent serogroup C or quadrivalent ACYW135) be incorporated into the routine schedule regardless of previous infant or toddler doses [21]. The data described here provide the first comprehensive evidence supporting the introduction of a booster dose of vaccine for cohorts of children who have been immunized with monovalent MenC vaccine before school age. Adolescent boosting should ensure sustained population immunity against this devastating disease and should now be considered in all countries that have introduced MenC vaccine into their routine childhood immunization schedules to prevent a resurgence of disease in the decades to come.

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