Prevalence of Serum Bactericidal Antibody to Serogroup C *Neisseria meningitidis* in England a Decade after Vaccine Introduction

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Serogroup C meningococcal disease incidence and carriage declined rapidly in the United Kingdom after infant serogroup C conjugate vaccination was introduced in 1999, with catch-up vaccination for children under 18 years. Antibody levels and effectiveness waned quickly in children vaccinated at 2, 3, and 4 months of age. Therefore, in 2006, the current revised schedule of doses at 3, 4, and 12 months was introduced. This study assessed age-specific protection in 2009 compared with data from historical prevaccination and early postvaccination studies. Rabbit complement serum bactericidal antibody (SBA) was measured in anonymously banked serum samples collected in England in 2009 ($n = 1,174$), taking titers of ≥ 8 as protective. Age-stratified proportions of SBA titers that were ≥ 8 and geometric mean titers were compared. SBA titers varied markedly by birth cohort and time since vaccination. Overall, 35% of samples (95% confidence interval [CI], 33 to 38%) had titers that were ≥ 8. Only in cohorts eligible for catch-up vaccination did the majority of individuals have protective antibody levels. Antibody levels were higher in children eligible for vaccination at primary and secondary school ages, compared to those eligible below the age of 5 years. In those eligible for completed vaccination under the current schedule, protective levels were very modest and there was no evidence of superiority to cohorts that were eligible for the previous schedule. This supports a need for older childhood or adolescent booster vaccination in those previously eligible for vaccination during the infant, toddler, or preschool periods, to maintain direct protection and potentially enhance population immunity.

In 1999, the United Kingdom was the first country to introduce meningococcal serogroup C conjugate (MCC) vaccines, incorporating these into the routine childhood immunization schedule at 2, 3, and 4 months of age. During 2000, a phased catch-up campaign was implemented for young people up to the age of 18 years; this was later extended to 24 years of age. The MCC vaccine had an early and marked impact on the incidence of serogroup C disease (16). Within the first 2 years, there was an overall reduction in incidence of 87% in the targeted age groups and there was a decrease in attributable deaths from 67 in 1999 to 5 in 2001 (2). A reduction in the prevalence of nasopharyngeal serogroup C meningococcal carriage in adolescents was observed 1 year following the introduction of the MCC vaccine (14), providing a basis for indirect protection (herd immunity). Reduced carriage rates were sustained (13), and there was an estimated 67% fall in the attack rate in the unvaccinated population, presumably due to this herd immunity (19). By 2002, the overall direct vaccine effectiveness was estimated at well over 90% (19).

Despite the success of the MCC program, there is evidence that individual protection is short-lived, particularly following routine infant immunization. Field effectiveness of the initial 3-dose vaccination schedule (given at ages 2, 3, and 4 months) was shown to wane rapidly (22), and serological studies found that only 36% of children were still protected (defined as a serum bactericidal antibody [SBA] titer of ≥ 8, with rabbit complement) 18 months after infant vaccination (20, 23). In 2006, the immunization schedule was adjusted such that MCC vaccine is now given at ages 3, 4, and 12 months. The expectation was that the booster dose in toddlers would provide improved and extended individual protection. Disease incidence rates have remained at very low levels, with the UK Health Protection Agency (HPA) reporting fewer than 40 laboratory-confirmed cases per year in England and Wales since 2005 up until 2010 (11).

Seroprevalence studies have proven valuable in improving our understanding of population immunity and can crucially complement disease surveillance. Serological surveillance has been utilized for a considerable time in the United Kingdom to inform vaccine policy for several diseases, such as measles (10) and infection with *Haemophilus influenzae* type b (24). Therefore, the aim of this study was to assess the population levels of immunity in England to serogroup C meningococci, using measurements of specific functional antibody levels in age-stratified sera. Specific study objectives were to assess the current age-stratified levels of population immunity to the infection (measured approximately 10 years after vaccine introduction), to compare the current immunity levels to historical time points before and shortly after vaccine introduction, and to determine whether the change in vaccine schedule (introduction of a booster dose at age 12 months) has had a beneficial effect. The study's findings also provide population data for subsequent mathematical modeling to guide future decisions on MCC vaccine scheduling in the United Kingdom.
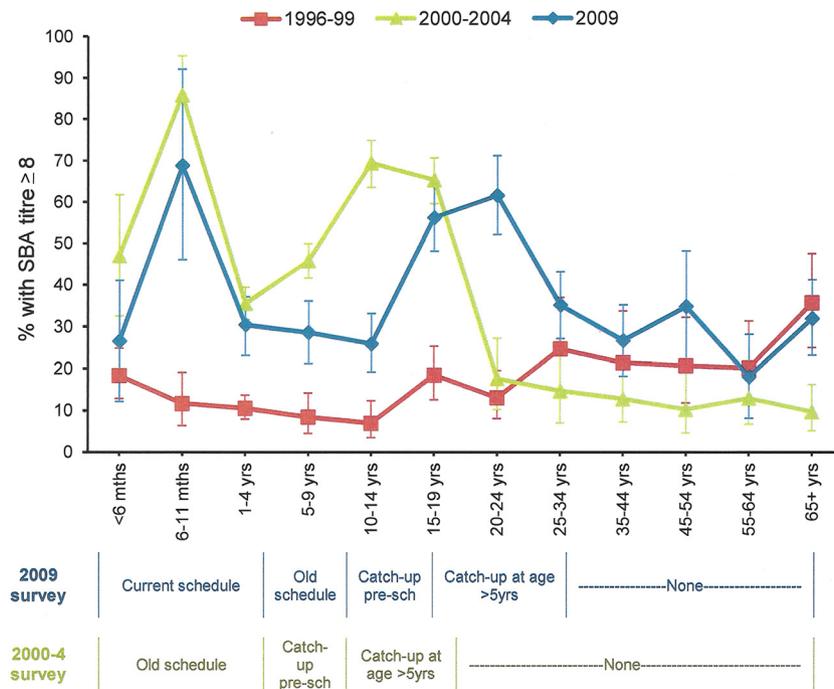
FIG 1 Seroprotection against serogroup C meningococci measured by proportions with serum bactericidal antibody (SBA) titers of ≥8. Shown is a comparison of current levels (2009) with the periods before (1996 to 1999) and shortly after (2000 to 2004) vaccine introduction. The applicable vaccine schedules to each age band at the time of the two postvaccine surveys are shown below the graphs. pre-sch, preschool.

MATERIALS AND METHODS

Source of sera. Serum samples were obtained from the HPA Seroepidemiology Unit. The Unit maintains a depository of anonymized residual sera from routine diagnostic testing at participating laboratories. There is no record of the indication for blood testing, but immunocompromised individuals are not included. The age and sex of the anonymous donors and year of collection are collated on the database, as well as the location of the source laboratory (17). Sera collected in 2009 were used for this study, it being approximately 10 years since the introduction of MCC vaccine in England.

Serological methods. The age-specific susceptibility to serogroup C meningococcal infection was estimated by measuring the levels of standardized SBA, using baby rabbit complement (Pel-Freeze Incorporated, Rodgerson, AZ) to serogroup C *Neisseria meningitidis* strain C11 (C:16: P1.7-1,1) as previously described (15). Assays were conducted at the laboratory of the HPA Vaccine Evaluation Unit, Manchester. SBA titers were expressed as the reciprocal of the final serum dilution giving ≥50% killing at 60 min. Titers of ≥8 were taken as the putative protective level of protection against disease (4). Titers of <4 were assigned a value of 2 for computational purposes, being half of the value of the lowest limit of detection.

Sampling and statistical methods. Samples were selected from a range of age bands that were intended to fit with the various vaccine schedules since introduction of the serogroup C meningococcal vaccine and also to enable comparison with previous studies as described below. Therefore, the selection target was to obtain about 100 samples from each of the following age bands: <1 year, 1 to 3 years, 4 to 6 years, 7 to 10 years, 11 to 14 years, 15 to 19 years, 20 to 23 years, 24 to 27 years, 28 to 40 years, 41 to 64 years, and ≥65 years. The sample size target was chosen to achieve reasonable precision around the 95% confidence intervals (95% CIs) of proportions with SBA titers of ≥8 within the strata of interest. For example, a 50% proportion would have 95% CI of 40 to 60%. To achieve these numbers, all samples in the <1-year age group and a random selection of samples within each age, gender, and region stratum were tested. Propor-

tions of sera with SBA titers above the putative protective cutoff (≥8) were determined, along with exact binomial 95% CIs of proportions. Geometric mean titers (GMTs) were also calculated with 95% CIs. Information on individual immunization status was not available in this anonymous sample collection. In lieu of this, and as coverage with each schedule has been high, the age of each serum donor in years and months was used to estimate the vaccination schedule they would have been eligible for (16). Protection was then compared according to the applicable vaccination schedule by age and, within this, over time.

Comparison with previous studies. Results from this serosurvey (using samples collected in 2009) were compared with historical data from two previously published, similarly designed studies of age-specific profiles for the prevaccine (1996 to 1999) (21) and earlier post-vaccine-introduction (2000 to 2004) (23) periods. Both of these previous studies were conducted using the same source of sera and the same serological methods conducted in the same laboratory as the present study.

Ethical approval. The HPA Seroepidemiology Unit holds ethical approval (05/Q0505/U5) to carry out serological surveillance in support of the National Immunization Programme for England and Wales, issued by the Joint University College London/University College London Hospitals (UCL/UCLH) Committees on the Ethics of Human Research.

RESULTS

In the 2009 survey, results were available for 1,174 samples, of which 415 (35%; 95% CI, 33 to 38%) had evidence of seroprotection (shown by attaining putatively protective SBA titers of ≥8).

The data were first categorized into the same age-bands used in our two previous similarly designed surveys of samples taken prior to MCC introduction (in 1996 to 1999) and shortly after introduction of MCC (in 2000 to 2004) (21, 23) (Fig. 1). This showed that protective levels were similar in those aged 0 to 4 years in 2009 compared with 2000 to 2004, but strikingly, the secondary peak of high levels seen in adolescent age groups in 2000 to 2004 (repre-

TABLE 1 Proportions of samples with protective levels of antibody by birth cohort and vaccination schedule

Vaccination schedule for birth cohort	Yr/period of birth	Estimated vaccine coverage (%)	2000–2004 survey			2009 survey		
			n	Proportion (%) with SBA titer ≥ 8 (95% CI)	GMT (95% CI)	n	Proportion (%) with SBA titer ≥ 8 (95% CI)	GMT (95% CI)
Current routine schedule								
No vaccination yet (age <3 mo at time of sampling)	2009	NA[a]	NA			27	25.9 (11–46)	4.8 (3–9)
Incomplete (below age for 3rd dose)	2009	93	NA			23	56.5 (34–77)	25.9 (10–70)
3, 4, and 12 mo	2006–2008	92	NA			133	31.6 (24–40)	7.0 (5–10)
Old routine schedule (2, 3, and 4 mo)	2004–2005	91	11 (2004 only)			63	30.2 (19–43)	5.7 (4–9)
	2001–2003	90	272	44.9 (39–51)	13.9 (11–18)	76	29.0 (19–41)	4.8 (3–7)
	1999–2000	89	341	35.8 (31–41)	8.1 (7–10)	53	17.0 (8–30)	3.7 (2–6)
Single–dose catch–up for various birth cohorts at vaccine introduction in 1999–2000								
Catch–up in 2nd yr of life	1998	85	165	33.9 (27–42)	8.3 (6–12)	32	15.6 (5–33)	3.4 (2–6)
Toddler/preschool catch–up	1995–1997	76	392	41.1 (36–46)	12.6 (10–16)	101	31.7 (23–42)	7.2 (5–11)
Primary school catch–up	1990–1994	86–89	266	71.4 (66–77)	104.2 (74–147)	132	56.1 (47–65)	27.5 (18–43)
Secondary school catch–up	1982–1989	60–88	394	65.0 (60–70)	89.7 (66–122)	165	55.8 (48–63)	28.3 (19–42)
None (most persons >18 yr not included in catch–up)	Pre–1982	NA	550	12.5 (10–16)	3.4 (3–4)	369	27.1 (23–32)	6.1 (5–7)
Total			2,391	41.2 (39–43)	15.26 (14–17)	1,174	35.4 (33–38)	8.9 (8–10)

[a] NA, not applicable.

senting those eligible for catch-up vaccination from primary school age forwards) has shifted into the older age groups. Thus, levels in those aged 5 to 9 and 10 to 14 years in 2009 are lower than in 2000 to 2004, although still higher than in the prevaccine study. Among the adults, seroprotection levels had seemed to decline following vaccine introduction. The latest survey, however, shows seroprotection levels that are very similar to those of the prevaccine era.

In further analysis according to vaccine schedule (Table 1), cohorts that were eligible for single-dose catch-up vaccination at the outset of the MCC program in 1999 and 2000 showed declining levels of antibody in all age groups. The percentage decline in GMTs from 2000 to 2004 to 2009 was highest in the cohorts with the highest initial levels, with the GMTs declining from 89.7 (95% CI, 66 to 122) (n = 394) to 28.3 (95% CI, 19 to 42) (n = 101) in those eligible for vaccination at secondary school, from 104.2 (95% CI, 74 to 147) (n = 266) to 27.5 (95% CI, 18 to 43) (n = 132) in those eligible for primary school vaccination, and from 12.6 (95% CI, 10 to 16) (n = 392) to 7.2 (95% CI, 5 to 11) (n = 165) in those eligible for preschool vaccination (Table 1). Seroprotection levels remained much higher in those who were eligible for vaccination at primary or secondary school age (born between 1982 and 1994 and approximately between 6 and 18 years old at the time of the catch-up campaign) compared to those eligible for toddler/preschool single-dose catch-up vaccination (born in 1995 to 1997 and 3 to 5 years old during that period). Protection was especially low in children born in 1998, who were eligible for the single catch-up vaccine dose in early 2000 and were approximately 1 year old then.

Those 4 to 10 years old at sampling in 2009 (born in 1999 to

2005) had eligibility for routine vaccination with infant doses only (before the addition of a booster to the schedule in 2006). Only about a quarter of these subjects had protective antibody levels (26.0%; 95% CI, 20 to 33%).

Children born between 2006 and 2008 (approximately 1 to 3 years old when sampled), who were eligible for the current routine schedule of two infant primary doses plus a booster at age 12 months, also had only modest seroprotection, with less than one-third showing a protective SBA titer (31.6%; 95% CI, 24 to 40%). The youngest groups (infants born in 2009, up to 11 months old at sampling) showed notable seroprotection levels, but as they were either yet to commence or to complete their vaccination under the current schedule, they were not readily comparable to other groups.

GMTs followed a similar pattern to that described for proportions of seroprotection (Table 1 and Fig. 2), across all of the vaccinated and the older unvaccinated age groups. GMT levels remained relatively high for those targeted for catch-up vaccination as older children than those who were eligible for the routine schedules. Similar to the seroprotection proportions, high GMTs in infants of 2000 to 2004 fell sharply—as seen in the comparator 5- to 9-year-old band of 2009.

Between the ages of 1 and 3 years, antibody levels were similar in children eligible for vaccination according to both the old schedule (doses at 2, 3, and 4 months) and the current schedule (3, 4, and 12 months). At the ages of 1, 2, and 3 years, respectively, GMT measurements in the 2000-to-2004 survey were 13.7 (95% CI, 9 to 20) (n = 138), 7.5 (95% CI, 5 to 11) (n = 109), and 5.7 (95% CI, 4 to 8) (n = 83), compared to 13.1
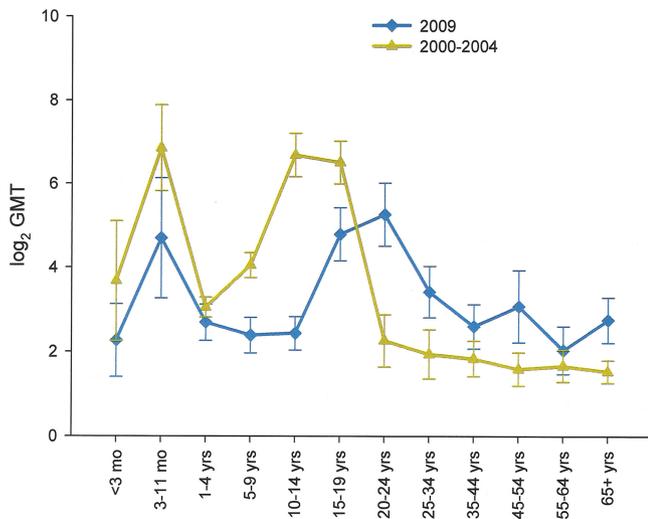
FIG 2 Geometric mean titer (GMT) of serum bactericidal antibody (SBA) against group C meningococci. Shown are current levels (2009) compared with the period shortly after vaccine introduction (2000 to 2004).

(95% CI, 7 to 25) ($n = 49$), 6.1 (95% CI, 3 to 11) ($n = 51$), and 3.3 (95% CI, 2 to 5) ($n = 33$) in 2009.

Within a year and around 2 years after vaccination, antibody levels were comparable to or higher than those in children eligible for a single-dose catch-up in the second year of life (without having been primed as infants) and those eligible for the booster at age 12 months. In the 1998 birth cohort (eligible for single-dose catch-up in 2000 and sampled in 2001), the GMT was 4.7 (95% CI, 2 to 9) ($n = 40$). This compared with 6.1 (95% CI, 3 to 11) ($n = 51$) in the 2007 birth cohort (eligible for the 12-month booster in 2008 and sampled in 2009). Around 2 years after vaccination, the levels in the catch-up group (born in 1998, eligible for a single-dose catch-up in 2000, and sampled in 2002) were higher (13.4; 95% CI, 7 to 26; $n = 43$) than in those eligible for the current routine schedule (born in 2006, eligible for the 12-month booster in 2007, and sampled in 2009) (3.3; 95% CI, 2 to 5; $n = 33$).

DISCUSSION

This report presents the results of a cross-sectional survey of SBA to serogroup C *N. meningitidis* in England, carried out a decade after the introduction of MCC vaccination in 1999. The findings of this study suggest that protective antibody levels have declined markedly in all immunized cohorts since the time of vaccination. The proportions with seroprotective antibody levels remain much higher in those eligible for catch-up vaccine at primary or secondary school age (from approximately 5 years) than in those eligible as toddlers or at preschool age (between 1 and 4 years). The aging of these cohorts over time explains the shift seen in the age group with peak antibody levels between 2000 to 2004 and 2009. This is probably mainly due to the higher antibody levels achieved in those vaccinated at an older age—there was no clear evidence of a higher rate of decline of antibody in those vaccinated earlier in childhood. Furthermore, there was no evidence that the extended routine vaccination schedule has had any substantial impact on sustaining seroprotection. Neither seroprotected proportions nor SBA GMT levels were significantly higher in those eligible for the booster dose after 12 months than in those eligible for infant doses

only, at the equivalent age. This suggests that the introduction of a booster dose has had a very limited short-term benefit over the previous schedule. In addition, children vaccinated under the current routine schedule achieve similar GMT levels to those eligible for catch-up vaccination in the second year of life, suggesting that the priming vaccination in infancy does not improve the longer-term persistence of antibody from the 12-month dose.

The major limitation of this study lies in the use of banked anonymous serum samples from the HPA Seroepidemiology Unit, which lack information on the actual vaccination status of the individuals that the samples were obtained from. However, this disadvantage is mitigated by the generally high vaccine coverage in England (25), and this form of convenience sampling has been shown to provide similar results to more conventional random sampling approaches (12). In addition, this particular serum bank has proven to be a valuable resource for a variety of infections, supporting research and contributing to successful vaccine policy interventions in the United Kingdom (17). As the United Kingdom was the first country where MCC vaccination was introduced, these data from the population longest exposed to the vaccine will strengthen the evidence base underpinning national policy decisions on vaccination in England and elsewhere.

This study's findings are consistent with previous evidence of poor antibody persistence following MCC vaccination in young children (5, 9). Separately, Snape and colleagues, in an observational study of people 11 to 20 years old who were previously immunized between the ages of 6 and 15 years, found that antibody levels remain higher some years after immunization at an older age (20). Data from The Netherlands also suggest that higher levels of serological protection are associated with vaccination above the age of 5 years (8). Furthermore, Perrett and colleagues observed rapid decline of serological protection in children vaccinated below the age of 5 years (18). This concords with findings by Campbell et al. that in children vaccinated under the routine infant schedule, effectiveness declines significantly after the first year (6). It has been postulated that age-dependent vaccine responses may be due to greater immune maturation with increasing age (20); although prior exposure to meningococci may also contribute to the better response. An additional explanation may relate to the previous exposure history of children offered vaccination at school age in 1999. Subsequent cohorts will have experienced limited opportunity to become exposed to serogroup C infection and therefore respond as if completely naïve.

Although the incidence of serogroup C disease is currently very low (11), and modeling studies suggest that indirect protection is likely to persist for some time (6), the proportion of the childhood population without individual protection is increasing each year. There is therefore a clear need to consider introducing a booster dose in older childhood. This study suggests that this dose should be given at age 5 years or above. Further evidence from clinical trials of MCC booster doses given to children 6 to 12 years of age showed that although responses were good across all age groups, there was an age-dependent trend whereby the best boost responses occurred among the 12-year-olds (18). The response in older children may depend, however, on age, prior exposure, and choice of vaccine used. For example a better booster response to Menitorix (containing a tetanus MenC conjugate) has been shown in those primed with tetanus conjugates in infancy (3). Such studies would need to be repeated in older age groups and may also consider boosting with quadrivalent conjugate vaccines

that also offer protection against serogroups A, Y, and W135. Such vaccines are now licensed, although the burden of disease due to these other serogroups in this age group is also currently very low (11). In the United States, quadrivalent vaccine is currently recommended for routine use at ages 11 to 12 years, followed by a second dose at 16 years, aiming for optimal protection in the critical high-risk period of the late teen years (1).

Boosting at or after 12 years of age in the United Kingdom would offer the potential additional advantage of alignment with existing routinely scheduled vaccines, such as the tetanus, diphtheria, and polio (Td/IPV) booster, currently offered to young people between ages 13 and 18, or the human papillomavirus (HPV) vaccine, currently available to girls 12 to 13 years old. Giving the booster in adolescence might also ensure that antibody levels remain high going into the secondary peak risk period for meningococcal disease in the late teen years and early twenties. These age groups are also those that represented the peak in carriage in the prevaccine era (7), and therefore, delaying booster vaccination until adolescence has potential to provide a larger herd immunity benefit.

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