Randomized Trial to Compare the Immunogenicity and Safety of a CRM or TT Conjugated Quadrivalent Meningococcal Vaccine in Teenagers who Received a CRM or TT Conjugated Serogroup C Vaccine at Preschool Age

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Background: Protection after meningococcal C (MenC) conjugate (MCC) vaccination in early childhood is short-lived. Boosting with a quadrivalent vaccine in teenage years, a high-risk period for MenC disease, should protect against additional serogroups but might compromise MenC response. The carrier protein in the primary MCC vaccine determines the response to MCC booster in toddlers, but the relationship between primary vaccine and booster given later is unclear. This study compared responses to a CRM-conjugated or tetanus toxoid (TT)-conjugated MenACWY vaccine in teenagers primed with different MCC vaccines at preschool age.

Methods: Ninety-three teenagers (16–19 years), who were previously randomized at age 3–6 years to receive single-dose MCC–CRM or MCC–TT, were randomized to receive either MenACWY–CRM or MenACWY–TT booster. Serum bactericidal antibodies (SBA, protective titer ≥8) were measured before, 1 month and 6 or 9 months after boosting.

Results: Preboosting, MCC–TT-primed teenagers had significantly higher MenC SBA titers than those MCC–CRM-primed ($P = 0.02$). Postboosting, both MenACWY vaccines induced protective SBA titers to all 4 serogroups in most participants (≥98% at 1 month and ≥90% by 9 months postboost). The highest MenC SBA titers were seen in those MCC–TT-primed and MenACWY–TT-boosted [geometric mean titer (GMT) ~ 22,000] followed by those boosted with MenACWY–CRM irrespective of priming (GMT ~ 12,000) and then those MCC–CRM-primed and MenACWY–TT-boosted (GMT ~ 5500). The estimated postbooster MenC SBA decline beyond 1 month was ~40% as time since booster doubles. Both vaccines were well tolerated with no attributable serious adverse events.

Conclusion: Both MenACWY vaccines safely induced protective sustained antibody responses against all targeted serogroups in MCC-primed teenagers.

Key Words: meningococcal, vaccine, teenagers, antibody, randomized trial

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As meningococcal serogroup C (MenC) disease occurs primarily in infants and teenagers, the introduction of MenC conjugate (MCC) vaccination into the UK immunization schedule in 1999 was complemented by a catch-up vaccination campaign to 18 years of age.[1] This led to rapid and marked reductions in disease incidence,[1] attributable deaths[2] and carriage,[3,4] with evidence of herd protection.[5] However, poor antibody persistence was observed in infants and young children,[6,7] raising concerns about sustained protection because persistent serum bactericidal antibody (SBA) determines long-term efficacy.[8] To extend antibody persistence, in 2006, the immunization schedule was restructured to 2 priming MCC doses in infancy, using vaccines conjugated to either tetanus toxoid (TT; NeisVac-C; Thetford, Norfolk, UK) or a diphtheria toxin variant, cross-reacting material (CRM) 197 (Menjugate, Novartis, Siena, Italy; or Meningitec, formerly Nuron Biotech) and a booster at 12 months of age using Menitorix (GlaxoSmithKline, Rixensart, Belguim) [MCC–TT plus *Haemophilus influenza* type b (Hib)]. Despite this, antibody persistence remained poor.[9]

To ensure protective antibody through the teenage years, which is a high-risk period for disease and carriage,[4] a teenage MCC booster dose was introduced from 2013[10] to directly protect vaccines and help ensure maintenance of herd protection in the United Kingdom. However, it remains unclear how the different vaccines used in the childhood immunization schedule would affect booster responses in teenagers. Response to MCC booster given at 12 months of age depends on the primary vaccine given, with postbooster MenC SBA titers higher in children primed with MCC–TT than those primed with MCC–CRM.[9] In children primed with MCC–TT, Hib–MCC–TT or MCC–CRM, and then given MCC–TT at age 13–14 months, the MenC-protected proportion (SBA titers ≥8) at 5 years postbooster was highest in those primed with MCC–TT.[11] Better understanding of these interactions between priming and booster vaccines and carrier proteins would help further inform meningococcal vaccination policy, but this has not previously been studied in teenagers.

To investigate this, we identified a cohort of teenagers who were randomized to receive either MCC–TT (NeisVac-C) or MCC–CRM (Meningitec or Menjugate) at age 3.5–6 years during a trial conducted before the national introduction of MCC in 1999[12] and were thus ideally suited to assess the response to a CRM-conjugated or TT-conjugated booster given in the teenage years. Moreover, an alternative to boosting with MCC vaccines would be to use quadrivalent conjugate vaccines offering additional benefit in

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protection from serogroups A, Y and W. In view of recent evidence of increased W disease,[13] a policy of boosting with a MenACWY vaccine was considered, but there were concerns about possible interference with the C-specific response.[14] Therefore, this trial assessed and compared the immunogenicity and safety of either a CRM-conjugated (MENVEO, Novartis, Siena, Italy) or TT-conjugated (NIMENRIX, GlaxoSmithKline, Rixensart, Belgium) MenACWY vaccine in teenagers who received either MCC–TT or MCC–CRM during a primary vaccination study 12–14 years earlier. The main aim was to evaluate the role of MCC primary vaccine carrier proteins on responses to MenACWY vaccine in teenagers.

METHODS

Participants were recruited from a cohort of teenagers in Hertfordshire and Gloucestershire, England, who were randomized to receive a single dose of MCC between 3.5 and 5.9 years of age, during a previous study between January 1998 and May 2000[12] (Fig. 1). Healthy volunteers from that cohort who were still locally available, eligible and provided written consent were grouped by primary vaccine and randomized to receive either CRM-conjugated or TT-conjugated MenACWY booster. Sera were collected before, 28 days after and either 6 or 9 months after booster to allow modeling of antibody decline by time since booster. Seroprotected proportions (SBA titers ≥8), ≥4-fold rises in SBA titer, SBA geometric mean titers (GMTs) and immunoglobulin (IgG) geometric mean concentrations (GMCs) were calculated. Preboost antibody levels were compared by primary vaccine using a Kruskal–Wallis test, whereas normal errors regression modeling was used to analyze postvaccination measurements (see further details in Supplemental Digital Content 1, http://links.lww.com/INF/C165). Antibody data were modeled as log-titer against log-time to assess decline over time using a fixed effects model to allow for decline in individual responses, as previously described.[9] The aim of the trial was to estimate the percentages of subjects achieving protective antibody levels in each treatment group with 95% confidence interval (CI) widths ≤±10% (assumed observed percentage ≥90%), needing a sample size of 50 in each study group. However, it was acknowledged from the outset that recruitment was unpredictable because of the strictly restricted pool of potential participants drawn from a specific previous study cohort. The eventual numbers recruited were lower than aimed, with corresponding effects on estimates precision and detectable differences. The subset of children who participated in this study were similar to those who did not, with respect to age at preschool vaccination and the proportions that received each of the 3 primary MCC vaccines, whereas gender proportions differed (38.7% male among this study participants, compared with 52.1% among nonparticipants, $P = 0.02$). The primary response to MCC vaccine in the original study was similar between this study participant subset and nonparticipants (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/C166).

MenACWY conjugate vaccines were provided by the manufacturers. Novartis MenACWY contains capsular oligosaccharides conjugated to CRM197,[15] whereas GSK MenACWY is conjugated to TT.[16–18] Primary vaccines used in the original study were previously described.[12] Reactions were monitored via telephone, self-completed diary and enquiry at study visits. The trial was authorized by the UK Medicines and Healthcare products Regulatory Authority and conducted in accordance with the Helsinki Declaration (2008). It was registered with the clinical trials registration site www.ClinicalTrials.gov (identifier NCT01192997).

RESULTS

A total of 93 teenagers were enrolled (Fig. 1), aged 16–19 years, with a period of 12–14 years between primary (preschool) and booster (teenage) vaccination. Preboost, 1-month postboost and persistence blood samples were provided by 93, 92 and 91 participants, respectively.

Preboost Serology

Teenagers who were randomized for primary vaccination with MCC–TT had significantly higher MenC SBA GMT than those primed with either of the MCC–CRM primary vaccines ($P = 0.02$). Also, a relatively greater proportion of them still had protective SBA titer, although CIs overlapped with the MCC–CRM-primed groups (Table 1). Individual-level data from the original preschool study was accessed to compare historical postprimary titers (after MCC vaccination ≥12 years previously) with corresponding pre-MenACWY booster titers obtained in this study. Although most individual SBA titers had waned since priming, postprimary and preboost SBA titers (Fig. 2) were positively associated (rank correlation $r = 0.45$ with all data or 0.57 excluding 2 participants with postprimary titer <8). Notably, 73% (11 of 15) of the highest initial responders (SBA titer ≥8192) still had titers ≥8 over a decade later, compared with 25% (6 of 24) of those with more moderate postprimary titers (64–4096).

Participants had raised tetanus and diphtheria antibody levels, which was as anticipated because vaccines against both are included in UK routine immunization schedules.

Postboost MenC Serology

One month postbooster, 100% of participants achieved protective serogroup-specific SBA responses against all 4 meningococcal serogroups, except for 2% for MenY in those boosted with MenACWY–CRM (Table 2). When categorized by primary vaccine (Table 1), there was also 100% seroprotection in all categories, except for 3% for MenY in those primed with MCC–TT. Therefore, a limited number of MCC–TT-primed individuals who received CRM-conjugated booster did not achieve MenY seroprotection. Protected proportions were similar whether gauged by the ≥8 titer threshold or conservatively by ≥128 (not shown). SBA titers showed evidence of an interaction between the primary vaccine and the booster given ($P = 0.03$). This appeared to arise from MenACWY–TT generating significantly ($P < 0.001$) higher SBA titers in those primed with MCC–TT (GMT ~ 6400, 4800, 21,600 for Menjugate, Meningitec and NeisVac-C, respectively); whereas MenACWY–CRM-boosted individuals showed no difference ($P = 0.81$) by primary vaccine (GMT ~ 11,100, 13,000, 11,100 for Menjugate, Meningitec and NeisVac-C, respectively; Fig. 3 and see Table, Supplemental Digital Content 3, http://links.lww.com/INF/C167). Comparisons across the 6 study arms, based on nonoverlapping 95% CIs, showed no further remarkable postbooster variations (Fig. 3). To compare the 1-month teenage postbooster responses observed in this study with the responses to primary childhood vaccination measured in the original study, logged (teenage) postboost titers were modeled on logged (original) postprimary titers, taking account of the primary and booster vaccines received. Associations between postprimary and postboost MenC antibody for both SBA and IgG levels were weak and not statistically significant ($r = 0.27$, $P = 0.26$ for SBA; $r = 0.21$, $P = 0.09$ for IgG enzyme-linked immunosorbent assay). In contrast to IgG, SBA responses showed comparatively less variability and generally higher postboost relative to postprimary titers (see Fig., Supplemental Digital Content 4, http://links.lww.com/INF/C168).

Beyond the 1-month time point, MCC–TT-primed participants had significantly higher MenC SBA GMTs than those MCC–CRM-primed if boosted with MenACWY–TT ($P = 0.01$) but not MenACWY–CRM ($P = 0.50$). Pooling together the 6-month and 9-month postbooster time points, the SBA GMTs for Menjugate, Meningitec and NeisVac-C were 983, 583 and 2702, respectively,

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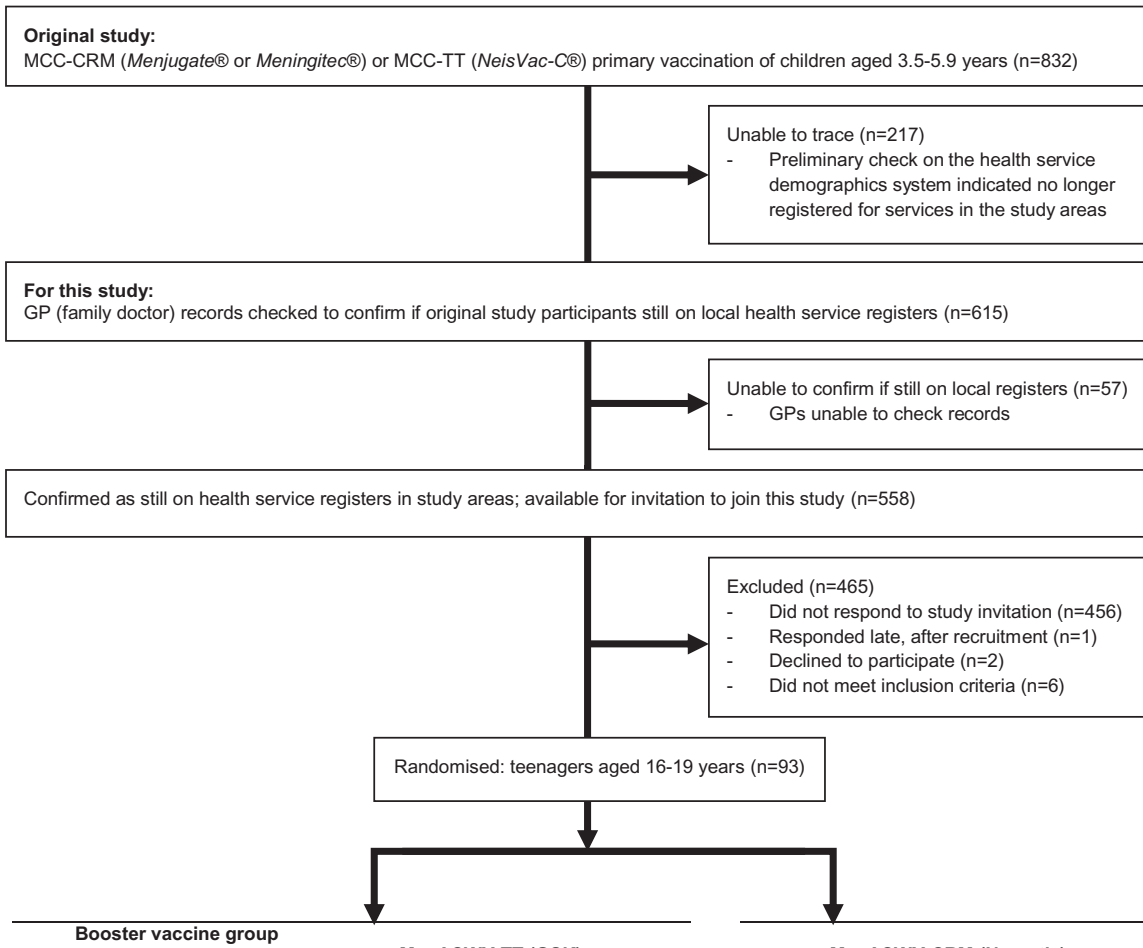

Booster vaccine group *(provided pre-boost blood sample and received allocated booster)*	**MenACWY-TT (GSK)** n = 46			**MenACWY-CRM (Novartis)** n = 47		
Priming vaccine received *(during original study)*	*(MCC-CRM) Menjugate® n=17*	*(MCC-CRM) Meningitec® n=14*	*(MCC-TT) NeisVac-C® n=15*	*(MCC-CRM) Menjugate® n=16*	*(MCC-CRM) Meningitec® n=12*	*(MCC-TT) NeisVac-C® n=19*
Provided 1-month post-boost blood sample	n=17	14	15	n=16	12	18 (1 lost to follow-up; relocated)
Provided final post-boost blood sample (All included in analysis)	n=17	14	15	n=16	11 (1 lost to follow-up; loss of contact)	18

FIGURE 1. Study participants and progression flow chart (CONSORT diagram).

for teenagers boosted with MenACWY–TT; compared with 2139, 2323 and 3128 for those boosted with MenACWY–CRM (see Table, Supplemental Digital Content 5, http://links.lww.com/INF/C169). Overall this meant that Novartis MenACWY–CRM vaccine gave significantly higher MenC titers than MenACWY–TT ($P = 0.02$, adjusted for primary vaccination and time since vaccination) (1.97-fold difference, 95% CI: 1.10–3.53).

Postboost Serology for Other Antigens

For MenA, 1 month after booster, MenACWY–CRM induced significantly higher SBA titers than MenACWY–TT (Table 1; $P = 0.02$, adjusted for primary vaccination); but this difference was not significantly sustained at further follow-up. MenW and MenY antibodies did not differ significantly between booster vaccine groups or by other comparisons (Tables 1–4 and Fig. 3B–D). Understandably, only MenACWY–TT increased tetanus IgG levels, whereas MenACWY–CRM boosted diphtheria antibody (see Tables, Supplemental Digital Content 6 and 7, http://links.lww.com/INF/C170 and http://links.lww.com/INF/C171).

Kinetics

Antibody decline over time was modeled as log-titer against log-time, for both SBA (Fig. 4) and IgG (see Fig., Supplemental Digital Content 8, http://links.lww.com/INF/C170). Fold change in SBA titers as time doubles (beyond day 28) was estimated at 0.57 for MenC (95% CI: 0.53–0.62) and 0.63 for MenW (0.58–0.69); both declining more rapidly than MenA, 0.84 (0.79–0.91) and MenY, 0.80 (0.75–0.85).

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TABLE 1. Serogroup-Specific Serum Bactericidal Antibody Prebooster and Postbooster Vaccination, by Primary Vaccine

		n				Proportion with SBA Titer ≥8 (95% CI)					SBA GMT (95% CI)				
						Preboost	1 Mo Postboost		6 Mo Postboost	9 Mo Postboost	Preboost	1 Mo Postboost		6 Mo Postboost	9 Mo Postboost
	Primary Vaccine	Preboost	1 Mo Postboost	6 Mo Postboost	9 Mo Postboost	% ≥8	% ≥8	% ≥4-fold SBA	% ≥8	% ≥8	GMT	GMT	n-Fold Rise	GMT	GMT
MenC	Menjugate	33	33	16	17	24 (11–42)	100 (89–100)	100 (89–100)	100 (79–100)	94 (71–100)	5 (3–10)	8366 (5430–12889)	1592 (870–2914)	2896 (1609–5214)	739 (269–2027)
	Meningitec	26	26	13	12	42 (23–63)	100 (87–100)	100 (87–100)	92 (64–100)	100 (74–100)	10 (4–22)	7562 (4288–13336)	764 (386–1511)	971 (278–3390)	1085 (495–2378)
	NeisVac-C	34	33	16	17	53 (35–70)	100 (89–100)	97 (84–100)	100 (79–100)	100 (80–100)	26 (10–64)	15064 (9294–24414)	659 (230–1885)	3922 (2391–6434)	2222 (1367–3613)
MenA	Menjugate	33	33	16	17	39 (23–58)	100 (89–100)	97 (84–100)	100 (79–100)	100 (80–100)	22 (7–67)	7532 (5040–11256)	336 (113–997)	5547 (3791–8117)	3341 (1438–7761)
	Meningitec	26	26	12	12	27 (12–48)	100 (87–100)	92 (75–99)	100 (74–100)	100 (74–100)	11 (4–32)	7767 (4769–12648)	724 (221–2376)	3251 (1681–6287)	5793 (3350–10015)
	NeisVac-C	34	33	16	17	32 (17–51)	100 (89–100)	85 (68–95)	100 (79–100)	100 (80–100)	15 (5–41)	7532 (4883–11618)	471 (143–1551)	5793 (3562–9420)	3932 (2136–7240)
MenW	Menjugate	33	33	16	17	6 (1–20)	100 (89–100)	100 (89–100)	94 (70–100)	100 (80–100)	2 (2,3)	8366 (5579–12545)	3462 (1978–6061)	1722 (588–5045)	2222 (1129–4374)
	Meningitec	26	26	11	12	15 (4–35)	100 (87–100)	96 (80–100)	100 (72–100)	100 (74–100)	4 (2–11)	9613 (6728–13735)	2160 (858–5438)	1162 (471–2867)	2299 (1205–4386)
	NeisVac-C	34	33	16	16	12 (3–27)	100 (89–100)	100 (89–100)	94 (70–100)	100 (79–100)	3 (2–6)	7222 (5174–10081)	2091 (1277–3426)	1722 (569–5215)	2435 (1432–4142)
MenY	Menjugate	33	33	16	17	9 (2–24)	100 (89–100)	97 (84–100)	100 (79–100)	100 (80–100)	3 (2–5)	4745 (3453–6520)	1526 (764–3051)	3158 (1758–5675)	2222 (1466–3367)
	Meningitec	26	26	13	12	12 (2–30)	100 (87–100)	100 (87–100)	92 (64–100)	100 (74–100)	4 (2–8)	5640 (3789–8395)	1448 (593–3538)	1410 (462–4306)	2580 (1609–4139)
	NeisVac-C	34	33	16	17	21 (9–38)	97 (84–100)	91 (76–98)	94 (70–100)	100 (80–100)	6 (3–14)	2927 (1588–5396)	471 (172–1291)	1166 (396–3437)	2222 (1200–4113)

Primary vaccines: Menjugate, Meningitec (both MCC–CRM) and NeisVac-C (MCC–TT).

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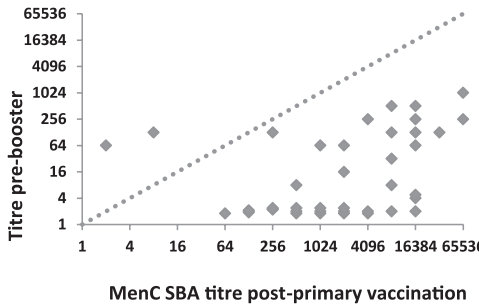

FIGURE 2. Comparison of postprimary and preboost MenC SBA titers: MenC SBA titers after the original primary vaccination at preschool age (postprimary, *x*-axis); compared with MenC SBA titers ≥12 years later (measured immediately before teenage booster vaccination; preboost, *y*-axis). Correlation between postprimary and preboost titers, $r = 0.45$, n = 41 (all teenagers who had MenC SBA results from the original study) or $r = 0.57$, n = 39 (excluding the 2 individuals who had postprimary titers <8 in the original study).

Tolerability and Safety

None of the 4 serious adverse events was investigator-assessed as causally vaccine-related. Of 3 that occurred in the MenACWY–CRM group, 1 was an incident case of ulcerative colitis onset ~20 weeks after vaccination and was stably managed as an out-patient. The other 2 involved brief hospitalization (1 for transient disorientation following suspected spiked social drinks and the other for severe tonsillitis); both fully recovered. The only serious adverse event in the GSK MenACWY–TT group was a hospital-treated case of appendicitis. No participant withdrew from the study, but 2 were lost to follow-up (Fig. 1). Participant diary-reported solicited symptoms indicated an overall similar level of reactogenicity between the booster vaccines. The more severe grades of reactions were generally rare, although some appeared to be more often reported with either MenACWY–CRM (redness and muscle pain) or MenACWY–TT (tiredness).

DISCUSSION

Key Findings

This study compared meningococcal serogroup-specific responses to 2 (CRM-conjugated or TT-conjugated) MenACWY booster vaccines, in teenagers who had been primed with a CRM-conjugated or TT-conjugated MCC vaccine at 3–6 years of age. The primary objective was to examine the relationships between childhood priming and teenage boosting with the different meningococcal antigen carrier proteins used in UK-licensed vaccines. Both booster vaccines induced high SBA levels against all 4 serogroups, which were sustained through 9-month follow-up, demonstrating for the first time that either CRM-conjugated or TT-conjugated MenACWY vaccines induce lasting protective immune responses in teenagers primed at preschool age, regardless of the primary MCC vaccine received. In a persistent interaction effect, MenACWY–TT stimulated higher MenC SBA titers in those primed with MCC–TT than MCC–CRM-primed individuals. At follow-up, MenACWY–CRM elicited significantly higher MenC antibody titers after adjusting for primary vaccine and time since vaccination. Given the strong and persistent responses to both vaccines, the postbooster differences may not be important for effectiveness. Second, this study also enabled observation of novel long-term MenC postprimary antibody persistence data at 12–14 years after

TABLE 2. Serogroup-Specific Serum Bactericidal Antibody Prebooster and Postbooster Vaccination, by Booster Vaccine

	Booster Vaccine	n			Proportion with SBA Titer ≥8 (95% CI)					SBA GMT (95% CI)				
					Preboost	1 Mo Postboost		6 Mo Postboost	9 Mo Postboost	Preboost	1 Mo Postboost		6 Mo Postboost	9 Mo Postboost
		Preboost	1 Mo Postboost	6 Mo Postboost	9 Mo Postboost	% ≥8	%≥4-fold	% ≥8	% ≥8	GMT	GMT	n-Fold Rise	GMT	GMT
MenC	MenACWY–TT	46	46	21	25	30 (18–46)	100 (92–100)	98 (88–100)	95 (76–100)	96 (80–100)	7 (4–13)	8701 (6008–12601)	1209 (631–2315)	1208 (565–2581)	1082 (562–2084)
	MenACWY–CRM	47	46	24	21	49 (34–64)	100 (92–100)	100 (92–100)	100 (86–100)	100 (84–100)	17 (9–35)	11585 (7560–17753)	735 (371–1457)	4216 (2727–6518)	1424 (737–2753)
MenA	ACWY–TT	46	46	21	25	30 (18–46)	100 (92–100)	91 (79–98)	100 (84–100)	100 (86–100)	13 (6–30)	5706 (4003–8134)	440 (177–1095)	4096 (2715–6180)	3191 (1741–5852)
	ACWY–CRM	47	46	23	21	36 (23–51)	100 (92–100)	91 (79–98)	100 (85–100)	100 (84–100)	19 (8–47)	10116 (7314–13992)	504 (194–1308)	5706 (3894–8361)	5513 (3468–8762)
MenW	ACWY–TT	46	46	21	24	7 (1–18)	100 (92–100)	100 (92–100)	100 (84–100)	100 (86–100)	3 (2–4)	8967 (6733–11943)	3170 (1997–5032)	1795 (989–3255)	2299 (1460–3620)
	ACWY–CRM	47	46	22	21	15 (6–28)	100 (92–100)	98 (88–100)	91 (71–99)	100 (84–100)	4 (2–6)	7597 (5586–10333)	2017 (1145–3555)	1360 (492–3754)	2337 (1370–3985)
MenY	ACWY–TT	46	46	21	25	17 (8–31)	100 (92–100)	100 (92–100)	95 (76–100)	100 (86–100)	5 (3–8)	4484 (3555–5655)	964 (492–1888)	1522 (759–3050)	2353 (1641–3372)
	ACWY–CRM	47	46	24	21	11 (4–23)	98 (88–100)	91 (79–98)	96 (79–100)	100 (84–100)	4 (2–7)	3915 (2390–6414)	1009 (468–2175)	1990 (896–4419)	2261 (1412–3622)

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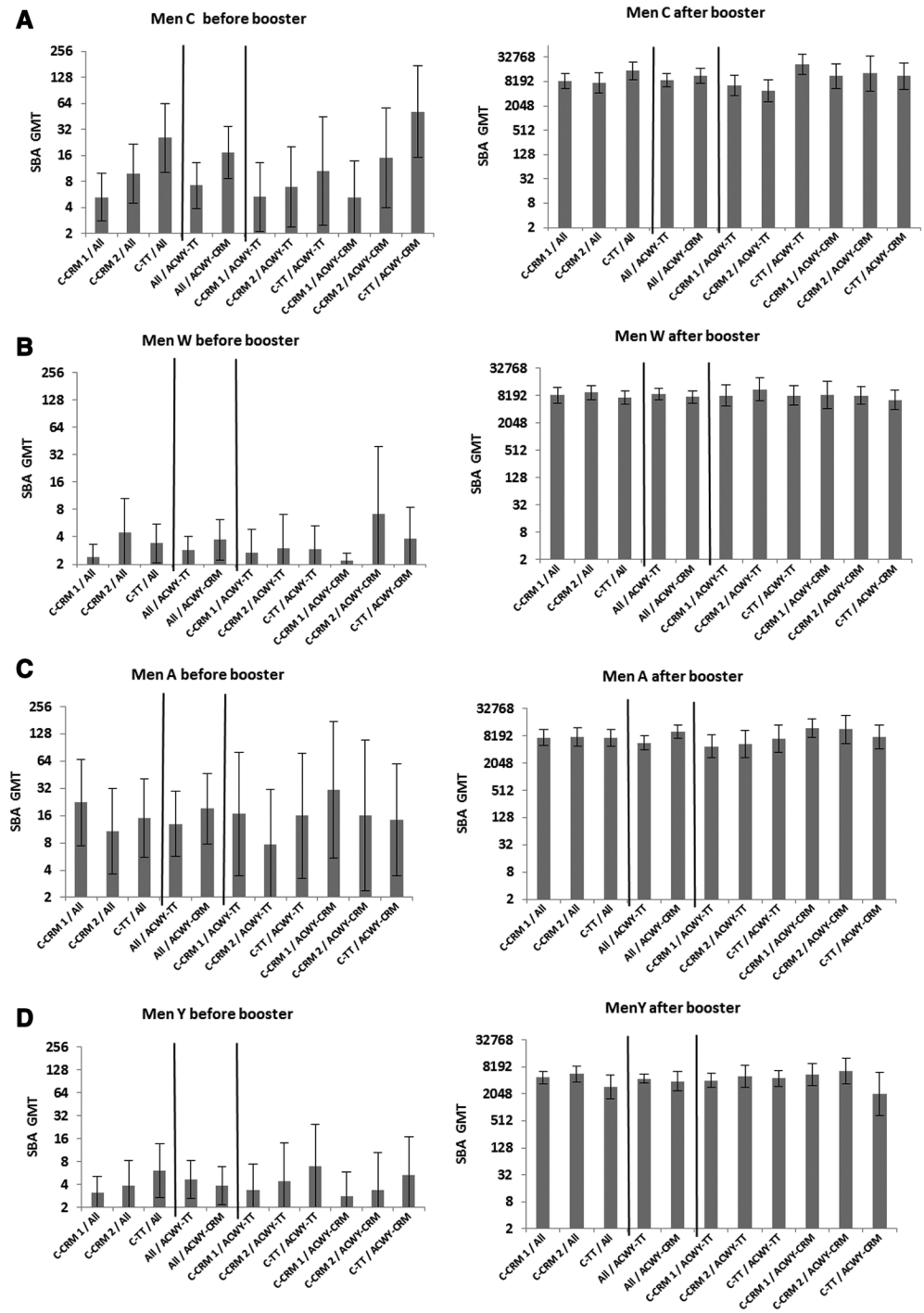

FIGURE 3. Serogroup-specific meningococcal SBA; before and 1 month after boosting with quadrivalent TT-conjugated or CRM-conjugated MenACWY vaccines, in teenagers who were primed in childhood with either a TT or CRM-conjugated meningococcal C conjugate (MCC) vaccine. Bars represent different combinations of vaccines (primary/booster); error bars represent 95% CI. The horizontal axis labels indicate the various combinations of prime and booster vaccines received. Priming vaccines: Menjugate (MCC–CRM, labeled as C-CRM 1); Meningitec (MCC–CRM, labeled as C-CRM 2) or NeisVac-C (MCC–TT, labeled as C-TT). Booster vaccines: MenACWY–CRM (Menveo, Novartis, labeled as ACWY-CRM) or MenACWY–TT (Nimenrix, GSK, labeled as ACWY-TT). Panels: (A) MenC; (B) MenW; (C) MenA and (D) MenY.

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TABLE 3. Serogroup-Specific IgG Prebooster and Postbooster Vaccination, by Booster Vaccine

		IgG geometric mean concentrations (GMC, μg/mL) (95% CI)							
		Preboost		1 Mo Postboost			6 Mo Postboost	9 Mo Postboost	
	Booster Vaccine	n	GMC	n	GMC	(n-fold) rise in GMC	n	GMC	n	GMC
MenC	MenACWY–TT	46	0.2 (0.2–0.3)	46	15.0 (10.9–20.4)	62.4 (42.9–90.6)	21	3.9 (2.5–6.1)	25	2.4 (1.7–3.5)
	MenACWY–CRM	47	0.4 (0.3–0.5)	46	20.2 (15.9–25.7)	56.2 (37.6–84)	24	6.8 (4.6–9.9)	21	2.6 (1.6–4.2)
MenA	MenACWY–TT	46	1.8 (1.3–2.6)	46	27.7 (17.1–44.6)	15 (10.1–22.1)	21	6.0 (2.9–12.6)	24	7.0 (3.6–13.5)
	MenACWY–CRM	47	1.3 (1.0–1.7)	46	44.1 (30.1–64.4)	34.2 (25.4–46.1)	24	17.5 (8.0–38.5)	21	9.1 (4.7–17.8)
MenW	MenACWY–TT	46	0.7 (0.5–1.0)	46	19.4 (13.7–27.4)	26.3 (18.1–38.3)	21	5.7 (2.9–11.4)	25	6.2 (4.1–9.3)
	MenACWY–CRM	47	0.7 (0.5–1.1)	46	16.9 (11.2–25.5)	23.6 (14.9–37.3)	23	4.8 (2.4–9.6)	21	4.1 (2.1–8.1)
MenY	MenACWY–TT	46	1.2 (0.9–1.6)	46	13.2 (9.0–19.4)	11.2 (8.1–15.5)	21	7.1 (3.8–13.4)	24	5.4 (3.3–9.0)
	MenACWY–CRM	47	0.8 (0.6–1.0)	46	9.0 (5.7–14.3)	11.6 (7.6–17.9)	22	3.8 (2.1–6.9)	21	5.0 (2.2–11.0)

preschool priming, providing possibly the lengthiest primary persistence estimates available for this age-group.

Vaccine Carrier Protein Influence

In our original preschool study, MCC–TT was the most immunogenic primary vaccine,[12] and MCC–TT-primed individuals in this study had significantly higher SBA titers before boosting. For those primed with either of the two MCC–CRM vaccines, the composite (Menjugate plus Meningitec) proportion that still retained seroprotection before boosting was 32% (95% CI: 21–46%), notably consistent with a UK serosurvey finding that 31.7% (23–42%) of those eligible for single-dose (mainly MCC–CRM) "catch-up" vaccination in England at toddler/preschool age had protective SBA titer after a decade.[19] After booster vaccination, individuals who were both primed and boosted with a TT-conjugated vaccine had significantly higher postboost SBA titers, whereas those primed with MCC–CRM responded equally to either booster. Previous studies of meningococcal vaccine boosting in teenagers have not been specifically designed to investigate priming and boosting with different carrier protein-conjugated vaccines. Rather, participants were both primed and boosted with the same conjugate, either MCC–CRM[20,21] or MCC–TT.[22] In the US, only MenACWY–CRM or MenACWY-D (Menactra, a diphtheria-based conjugate vaccine; Sanofi Pasteur, Swiftwater, PA) are licensed and routinely recommended for both primary vaccination at age 11–12 years and booster at 16 years.[23] Thus, recent US studies have mostly focused on CRM-conjugated rather than TT-conjugated vaccines.[24,25]

Postulations to explain the higher booster responses associated with TT-conjugated priming[9,11] include the suggestion that MCC–TT is inherently superior to MCC–CRM for primary vaccination[26] regardless of the booster vaccine–carrier combination, possibly because the de-O-acetylated polysaccharide of NeisVac-C is more immunogenic than the O-acetylated alternative.[27] This might explain why Menitorix (O-acetylated) boosting induces protective MenC responses in more NeisVac-C-primed than Menitorix-primed children.[11] Our data support neither the proposal that CRM-conjugated vaccines have inherently diminished immunogenicity[28] nor that priming and boosting with the same carrier protein is superior to priming and boosting with different carrier proteins.[9]

Postbooster and Postprimary Persistence

Postbooster kinetic analysis of MenC antibody persistence showed ~40% decline in antibody as time doubles, contrasting with two-thirds decline previously observed in children given Hib–MCC–TT booster in the second year of life.[9] Our analysis of decline in antibody titer with time was limited by the small sample size of the study, particularly as the intended target size was not obtained because of the restricted pool of original study participants that could be recruited. Notwithstanding, our findings are compatible with other data indicating shorter antibody persistence after vaccination in younger relative to older age-groups.[19,29] Others have, however, estimated a slower annual 23% decline (95% CI: 15–30) in odds of protection after Meningitec vaccination at age 13–45 months.[30]

This study also provided long-term (12–14 years) postprimary antibody persistence data in individuals primed at preschool age. Approximately one-third to one-half of participants (depending on primary vaccine) were still putatively seroprotected, with significantly higher preboost MenC titers in those primed with MCC–TT. The age at primary vaccination may be crucial for the differential effect, as 5-year persistence after priming in older age cohorts (6–15 years) did not significantly differ between TT-conjugated and CRM-conjugated MCC vaccine groups.[29] Previous studies of postprimary persistence in teenagers did not compare different vaccine carrier proteins and involved cohorts that were primed at older ages (≥9 years)[17,20] or younger (1–3 years)[30] (and therefore with different immunologic backgrounds) than our participants. Similar to the postbooster analysis, there are limitations in our primary persistence data as only a modest proportion of the original trial cohort could be included in this study, given the practical challenges of recruiting teenage participants from a previous childhood study of over a decade earlier. A third of the original group could not be contacted as they were no longer registered with local services or their records were inaccessible. But from the remainder, we obtained a distinctive study group who provided a unique opportunity to gain new information on long-term persistence and booster responses given different meningococcal vaccine carrier proteins.

Booster Vaccine Policy

Our data address current policy considerations in the United Kingdom. The Joint Committee on Vaccination and Immunisation in 2012 recommended routine adolescent MCC booster vaccination but cautioned that "a serogroup Y-containing meningococcal vaccine should only be used if the available vaccines do not compromise the response to meningococcal C."[14] We observed no such compromise, as most participants achieved protective and persistent antibody levels against all serogroups. MenACWY–CRM induced significantly higher MenA SBA GMT, possibly because of its much higher MenA antigen content. Moderate recent increases in MenW[13] and MenY[13,31] infections in England are noted, and important local MenW transmission linked with imported infection has previously been documented.[32]

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TABLE 4. Serogroup-Specific IgG Prebooster and Postbooster Vaccination, by Primary Vaccine and Across All Study Groups

			IgG geometric mean concentrations (GMC, μg/mL) (95% CI)							
			Pre-boost		1 month post-boost			6 months post-boost		9 months postboost
	Booster Vaccine	Primary Vaccine	n	GMC	n	GMC	n-fold rise in GMC	n	GMC	n	GMC
MenC	All	Menjugate	33	0.3 (0.2–0.4)	33	17.3 (12.4–24.1)	63.3 (44.3–90.4)	16	6.4 (3.7–11.2)	17	2.3 (1.4–3.8)
		Meningitec	26	0.3 (0.2–0.4)	26	13.7 (9.1–20.7)	51.4 (32.6–81.0)	13	2.8 (1.6–5.1)	12	2.3 (1.1–4.9)
		NeisVac-C	34	0.4 (0.2–0.6)	33	21.1 (15.4–28.8)	61.9 (34.2–111.8)	16	7.0 (4.8–10.1)	17	2.8 (1.9–4.2)
	MenACWY–TT	Menjugate	17	0.3 (0.2–0.4)	17	13.5 (8.1–22.6)	49.5 (29.8–82)	8	4.6 (2.2–9.8)	9	2.4 (1.4–4.1)
		Meningitec	14	0.2 (0.1–0.5)	14	11.7 (6.3–21.7)	46.9 (25.2–87.3)	7	2.1 (0.8–5.5)	7	2.8 (0.9–8.8)
		NeisVac-C	15	0.2 (0.1–0.4)	15	21.1 (11.7–38.1)	105.8 (44.4–252.2)	6	6.4 (2.9–14.2)	9	2.2 (1.2–4.0)
	MenACWY–CRM	Menjugate	16	0.3 (0.1–0.5)	16	22.4 (14.5–34.6)	82.3 (48.4–139.7)	8	8.9 (3.5–22.7)	8	2.2 (0.8–6.5)
		Meningitec	12	0.3 (0.2–0.4)	12	16.6 (9.1–30.5)	57.1 (26.3–124.0)	6	4.1 (1.7–9.9)	5	1.8 (0.4–7.2)
		NeisVac-C	19	0.6 (0.3–1.1)	18	21.0 (14.6–30.1)	39.6 (17.3–90.2)	10	7.4 (4.5–12.1)	8	3.8 (2.1–6.7)
MenA	All	Menjugate	33	1.8 (1.3–2.5)	33	51.1 (31.8–82.2)	28 (18.0–43.4)	16	24.1 (12.1–47.8)	17	8.9 (3.9–20.5)
		Meningitec	26	1.2 (0.8–1.9)	26	18.6 (9.9–35.1)	15.0 (9.4–23.7)	12	4.2 (1.1–15.3)	12	4.1 (1.9–8.8)
		NeisVac-C	34	1.5 (1.0–2.3)	33	39.1 (24.0–63.8)	25.4 (16.2–39.7)	16	10.1 (4.1–24.7)	17	11.6 (5.2–25.7)
	MenACWY–TT	Menjugate	17	2.3 (1.4–3.8)	17	41.0 (18.3–91.7)	17.7 (8.4–37.5)	8	15.2 (5.5–42.2)	9	7.3 (2.1–25.4)
		Meningitec	14	1.4 (0.8–2.7)	14	14.5 (5.6–37.7)	10.2 (5.4–19.1)	7	4.0 (0.5–29.7)	7	2.8 (1.3–5.9)
		NeisVac-C	15	1.8 (0.8–4.0)	15	32.4 (13.8–76.0)	17.7 (8.4–37.4)	6	2.8 (1.4–5.6)	9	15.2 (3.7–61.8)
	MenACWY–CRM	Menjugate	16	1.4 (1.0–2.1)	16	64.6 (36.9–113.1)	45.3 (30.5–67.4)	8	38.1 (13.4–108.8)	8	11.2 (2.8–45.7)
		Meningitec	12	1.1 (0.6–2.0)	12	25.0 (9.8–63.9)	23.6 (12.0–46.1)	5	4.4 (0.4–50.4)	5	6.9 (1.0–48.4)
		NeisVac-C	19	1.3 (0.8–2.1)	18	45.7 (24.5–85.4)	34.2 (19.4–60.2)	10	21.7 (6.6–70.8)	8	8.9 (2.9–27.3)
MenW	All	Menjugate	33	0.6 (0.4–1.0)	33	18.7 (12.6–27.7)	30.2 (17.6–51.7)	16	6.2 (3.1–12.5)	17	4.7 (2.6–8.4)
		Meningitec	26	0.7 (0.5–1.0)	26	13.6 (8.0–23.3)	20.2 (10.6–38.4)	12	2.0 (0.8–5.1)	12	3.6 (1.9–6.8)
		NeisVac-C	34	0.9 (0.5–1.4)	33	21.9 (13.3–35.9)	24.3 (16.3–36.0)	16	8.9 (3.8–20.8)	17	7.4 (3.5–15.4)
	MenACWY–TT	Menjugate	17	0.8 (0.4–1.6)	17	17.3 (10.9–27.4)	21.8 (10.9–43.5)	8	4.2 (1.7–10.6)	9	6.6 (2.9–15.0)
		Meningitec	14	0.7 (0.5–1.0)	14	14.9 (7.5–29.8)	21.6 (9.9–47.3)	7	2.7 (0.9–8.3)	7	4.9 (2.4–10.2)
		NeisVac-C	15	0.7 (0.4–1.4)	15	28.0 (13.0–60.4)	39.2 (22.1–69.5)	6	20.2 (3.4–120.9)	9	6.9 (2.9–16.7)
	MenACWY–CRM	Menjugate	16	0.5 (0.2–1.0)	16	20.3 (10.0–41.3)	42.7 (17.7–102.9)	8	9.1 (2.7–31.2)	8	3.1 (1.2–8.4)
		Meningitec	12	0.7 (0.3–1.5)	12	12.2 (4.7–31.8)	18.7 (5.6–61.8)	5	1.3 (0.1–12.7)	5	2.2 (0.5–10.3)
		NeisVac-C	19	1.0 (0.5–2.1)	18	17.8 (8.8–35.9)	16.3 (9.7–27.4)	10	5.5 (2.1–14.6)	8	7.8 (1.8–34.9)
MenY	All	Menjugate	33	1.1 (0.8–1.6)	33	13.8 (8.6–22.1)	12.6 (7.8–20.5)	16	10.4 (5.3–20.4)	17	4.8 (2.3–10.1)
		Meningitec	26	0.8 (0.5–1.1)	26	7.3 (4.2–12.6)	9.5 (5.7–15.9)	11	2.5 (0.8–7.5)	12	2.6 (1.4–4.8)
		NeisVac-C	34	1.0 (0.7–1.5)	33	11.9 (6.8–20.7)	11.9 (7.7–18.3)	16	4.2 (2.4–7.3)	16	9.4 (3.9–22.6)
	MenACWY–TT	Menjugate	17	1.1 (0.6–1.9)	17	12.1 (7.0–20.8)	11.2 (6.4–19.6)	8	10.7 (3.1–37.1)	9	2.8 (1.9–4.1)
		Meningitec	14	1.0 (0.6–1.6)	14	8.2 (3.9–17.4)	8.4 (4.2–16.6)	7	3.1 (0.8–12.2)	7	4.4 (1.9–10.5)
		NeisVac-C	15	1.5 (0.8–3.1)	15	22.7 (10.3–50.1)	14.7 (8.3–26.1)	6	11.0 (5.0–24.0)	8	13.4 (3.9–46.5)
	MenACWY–CRM	Menjugate	16	1.1 (0.7–1.9)	16	15.8 (6.8–37.1)	14.4 (6.0–34.3)	8	10.1 (4.0–25.4)	8	8.8 (1.8–43.7)
		Meningitec	12	0.6 (0.3–1.0)	12	6.3 (2.4–16.1)	11.0 (4.4–27.2)	4	1.7 (0.1–46.0)	5	1.3 (0.9–1.8)
		NeisVac-C	19	0.7 (0.4–1.1)	18	6.9 (3.3–14.6)	10 (5.1–19.5)	10	2.4 (1.4–4.0)	8	6.6 (1.5–30.0)

Primary vaccines: Menjugate, Meningitec (both MCC–CRM) and NeisVac-C (MCC–TT).

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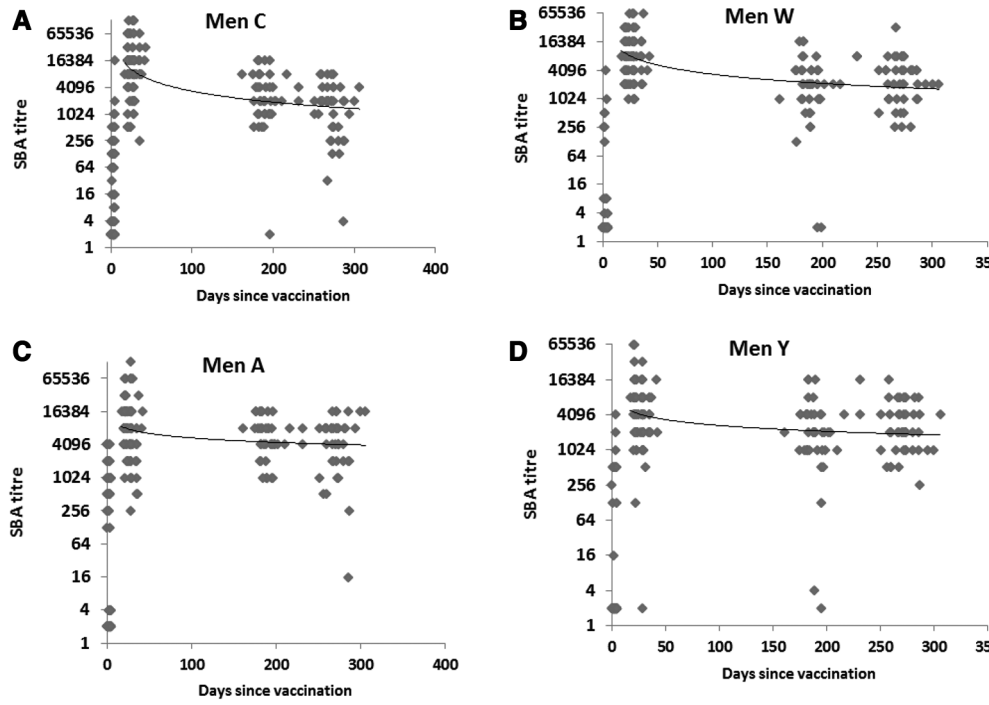

FIGURE 4. Decline in titers of serogroup-specific meningococcal (MenA, MenC, MenW or MenY) SBA over time, after teenage booster vaccination, with fitted trend lines. Fold IgG titer changes per doubling times from day 28 (and 95% CI) estimated from a fixed effects model were as follows: (A) MenC 0.57 (0.53–0.62); (B) MenW 0.63 (0.58–0.69); (C) MenA 0.84 (0.79–0.91) and (D) MenY 0.80 (0.75–0.85).

Conclusion

Both MenACWY vaccines stimulated protective functional antibody titers against all serogroups in 16–19 years old primed over a decade earlier, regardless of the primary MCC vaccine received. Individuals primed and boosted with TT-conjugated vaccine had higher MenC SBA titers, but overall titers were higher with MenACWY–CRM. Childhood MCC vaccine priming followed by teenage MenACWY boosting could be a suitable option to broaden meningococcal protection without compromise to MenC population immunity in the United Kingdom.

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