Randomised 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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ABSTRACT

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 or TT-conjugated MenACWY vaccine in teenagers primed with different MCC vaccines at pre-school age.

Methods: 93 teenagers (16-19 years), who were previously randomised at age 3-6 years to receive single-dose MCC-CRM or MCC-TT, were randomised 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: Pre-boosting, MCC-TT-primed teenagers had significantly higher MenC SBA titers than those MCC-CRM-primed (p=0.02). Post-boosting, both MenACWY vaccines induced protective SBA titers to all four serogroups in most participants (≥98% at 1 month and ≥90% by 9 months post-boost). The highest MenC SBA titers were seen in those MCC-TT-primed and MenACWY-TT boosted (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~5,500). The estimated post-booster 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.

INTRODUCTION

As meningococcal serogroup C (MenC) disease occurs primarily in infants and teenagers, the introduction of MenC conjugate (MCC) vaccination into the U.K. immunisation 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 since persistent serum bactericidal antibody (SBA) determines long-term efficacy (8). To extend antibody persistence, in 2006 the immunisation schedule was restructured to two priming MCC doses in infancy, using vaccines conjugated to either tetanus toxoid (TT) (NeisVac-C®) or a diphtheria toxin variant, CRM197 (CRM) (Menjugate® or Meningitec®); and a booster at 12 months of age using Menitorix® (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 vaccinees and help ensure maintenance of herd protection in the UK. However, it remains unclear how the different vaccines used in the childhood immunisation schedule would affect booster responses in teenagers. Response to MCC booster given at 12 months of age depends on the primary vaccine given, with post-booster 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 post booster 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 randomised 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 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 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 randomised 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) (Figure 1). Healthy volunteers from that cohort who were still locally available, eligible, and provided written consent, were grouped by primary vaccine and randomised 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 modelling of antibody decline by time since booster. Seroprotected proportions (SBA titers ≥8), ≥4-fold rises in SBA titer, SBA geometric mean titers (GMTs), and IgG geometric mean concentrations (GMCs) were calculated. Pre-boost antibody levels were compared by primary vaccine using a Kruskal-Wallis test, while normal errors regression modelling was used to analyse post-vaccination measurements (see further details in Supplemental Digital Content 1 (SDC-1)). Antibody data were modelled 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% 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 due to 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 the current study were similar to those who did not, with respect to age at preschool

vaccination and the proportions that received each of the three primary MCC vaccines, while gender proportions differed (38.7% male among current study participants, compared to 52.1% among non-participants, p=0.02). The primary response to MCC vaccine in the original study was similar between the current study participant subset and non-participants (Table S1 in SDC-2).

MenACWY conjugate vaccines were provided by the manufacturers. Novartis MenACWY contains capsular oligosaccharides conjugated to CRM197 (15), while 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 authorised 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 (Figure 1), aged 16-19 years, with a period of 12-14 years between primary (preschool) and booster (teenage) vaccination. Pre-boost, 1-month post-boost, and persistence blood samples were provided by 93, 92 and 91 participants, respectively.

Pre-boost serology: Teenagers who were randomised 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 confidence intervals overlapped with the

MCC-CRM-primed groups (Table 1). Individual-level data from the original preschool study was accessed to compare historical post-primary titers (after MCC vaccination ≥12 years previously) with corresponding pre-MenACWY booster titers obtained in the current study. Whilst most individual SBA titers had waned since priming, post-primary and pre-boost SBA titers (Figure 2) were positively associated (rank correlation r = 0.45 with all data or 0.57 excluding two participants with post-primary titer <8). Notably, 73% (11/15) of the highest initial responders (SBA titer ≥8192) still had titers ≥8 over a decade later, compared with 25% (6/24) of those with more moderate post-primary titers (64-4096).

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

Post-boost MenC serology: One month post-booster, 100% of participants achieved protective serogroup-specific SBA responses against all four meningococcal serogroups, except for 2% for MenY in those boosted with MenACWY-CRM (Table 2). When categorised 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, 21600 for Menjugate, Meningitec and NeisVac-C, respectively); whereas MenACWY-CRM-boosted individuals showed no difference (p=0.81) by primary vaccine (GMT ~ 11100, 13000, 11100 for Menjugate, Meningitec and NeisVac-C, respectively) (Figure 3; and see Table S2 in SDC-3). Comparisons across the six study arms, based on non-overlapping 95% CIs, showed no further remarkable post-booster variations (Figure 3). To compare the 1-month teenage post-booster responses observed in this study with the responses to primary childhood vaccination measured in the original study, logged (teenage) post-boost titers were modelled on logged (original) post-primary titers, taking account of the primary and booster vaccines received. Associations between post-primary and post-boost 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 ELISA). In contrast to IgG, SBA responses showed comparatively less variability and generally higher post-boost relative to post-primary titers (see Figure S1 in SDC-4).

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 post booster time points the SBA GMTs for Menjugate, Meningitec and NeisVac-C were 983, 583, and 2702, respectively, for teenagers boosted with MenACWY-TT; compared to 2139, 2323, and 3128 for those boosted with MenACWY-CRM (see Table S3 in SDC-5). 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).

Post-boost serology for other antigens: For MenA, one 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 Figure 3 b-d). Understandably, only MenACWY-TT increased tetanus IgG levels while MenACWY-CRM boosted diphtheria antibody (see SDC-6 (Table S4), and SDC-7 (Table S5)).

Kinetics: Antibody decline over time was modelled as log-titer against log-time, for both SBA (Figure 4) and IgG (see SDC-8 (Figure S2)). 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 Men W (0.58-0.69); both declining more rapidly than Men A, 0.84 (0.79-0.91) and Men Y, 0.80 (0.75-0.85).

Tolerability and safety: None of four serious adverse events (SAE) was investigator-assessed as causally vaccine-related. Of three that occurred in the MenACWY-CRM group, one was an incident case of ulcerative colitis onset ~20 weeks after vaccination, and was stably managed as an out-patient. The other two involved brief hospitalisation (one for transient disorientation following suspected spiked social drinks, and the other for severe tonsillitis); both fully recovered. The only SAE in the GSK MenACWY-TT group was a hospital-treated case of appendicitis. No participant withdrew from the study, but two were lost to follow-up (Figure 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 two (CRM or TT-conjugated) MenACWY booster vaccines, in teenagers who had been primed with a CRM 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 four serogroups which were sustained through 9-month follow-up, demonstrating for the first time that either CRM or TT-conjugated MenACWY vaccines induce lasting protective immune responses in teenagers primed at pre-school 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 post-booster differences may not be important for effectiveness. Secondarily, this study also enabled observation of novel long-term MenC post-primary antibody persistence data at 12-14 years after pre-school priming, providing possibly the lengthiest primary persistence estimates available for this age-group.

Vaccine carrier protein influence: In our original pre-school study, MCC-TT was the most immunogenic primary vaccine (12), and MCC-TT-primed individuals in the current study had significantly higher SBA titers prior to 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). Following booster vaccination, individuals who were both primed and boosted with a TT-conjugated vaccine had significantly higher post-boost 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 USA, only MenACWY-CRM or MenACWY-D (Menactra®, a diphtheria-based conjugate vaccine) are licensed and routinely recommended for both primary vaccination at age 11-12 years and booster at 16 years (23). Thus recent USA 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).

Post-booster and post-primary persistence: Post-booster 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 titre with time was limited by the small sample size of the study, particularly as the intended target size was not obtained due to 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) post-primary antibody persistence data in individuals primed at pre-school age. Approximately one-third to one-half of participants (depending on primary vaccine) were still putatively seroprotected, with significantly higher pre-boost 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

and CRM-conjugated MCC vaccine groups (29). Previous studies of post-primary 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 post-booster 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 UK. 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) infection in England are noted, and important local MenW transmission linked with imported infection has previously been documented (32).

Conclusion: Both MenACWY vaccines stimulated protective functional antibody titers against all serogroups in 16-19 year olds 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 UK.

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FIGURE LEGENDS

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

Figure 2. Comparison of post-primary and pre-boost MenC SBA titres: Meningococcal group C (MenC) serum bactericidal antibody (SBA) titers after the original primary vaccination at preschool age (post-primary, x-axis); compared with MenC SBA titers ≥12 years later (measured immediately before teenage booster vaccination) (pre-boost, y-axis). Correlation between post-primary and pre-boost 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 two individuals who had post-primary titers <8 in the original study).

Figure 3. Serogroup-specific meningococcal serum bactericidal antibody (SBA); before and 1 month after boosting with quadrivalent TT 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, *labelled as C-CRM 1*); Meningitec® (MCC-CRM, *labelled as C-CRM 2*); or NeisVac-C® (MCC-TT, labelled as C-TT). *Booster vaccines:* MenACWY-CRM (Menveo®, Novartis, *labelled as ACWY-CRM*) or MenACWY-TT (Nimenrix®, GSK, *labelled as ACWY-TT*). **Panels (from the top): *Upper panel:*** MenC. ***Second from the top:*** MenW. ***Third from the top:*** MenA. ***Lower panel:*** MenY.

Figure 4: Decline in titers of serogroup-specific meningococcal (MenA, MenC, MenW, or MenY) serum bactericidal antibody (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: ***Upper left panel:*** MenC 0.57 (0.53-0.62); ***upper right panel:*** MenW 0.63 (0.58-0.69); ***lower left panel:*** MenA 0.84 (0.79-0.91); and ***lower right panel:*** MenY 0.80 (0.75-0.85).

LIST OF SUPPLMENTAL DIGITAL CONTENT FILES

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Table 1: Serogroup-specific serum bactericidal antibody pre and post-booster vaccination, by primary vaccine

		n				Proportion with SBA titer ≥8 (95% CI)					SBA geometric mean titers (GMT) (95% CI)				
		Pre boost	1 month post-boost			Pre boost	1 month post-boost		6 months post-boost	9 months post-boost	Pre boost	1 month post-boost		6 months post-boost	9 months post-boost
	Primary vaccine	Pre-boost	1 month post-boost	6 months post-boost	9 months post-boost	% ≥8	% ≥8	% ≥4-fold SBA	% ≥8	% ≥8	GMT	GMT	(*n*-fold) rise	GMT	GMT
Men C	*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)
A	*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)
W	*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)
Y	*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); NeisVac-C® (MCC-TT).

Table 2: Serogroup-specific serum bactericidal antibody pre and post-booster vaccination, by booster vaccine

		n				Proportion with SBA titer ≥8 (95% CI)					SBA geometric mean titers (GMT) (95% CI)				
						Pre boost	1 month post-boost		6 months post-boost	9 months post-boost	Pre	1 month post-boost		6 months post-boost	9 months post-boost
	Booster vaccine	Pre-boost	1 month post-boost	6 months post-boost	9 months post-boost	% ≥8	% ≥8	% ≥4-fold	% ≥8	% ≥8	GMT	GMT	(*n*-fold) rise	GMT	GMT
Men C															
	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)
A															
	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)
W															
	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)
Y															
	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)

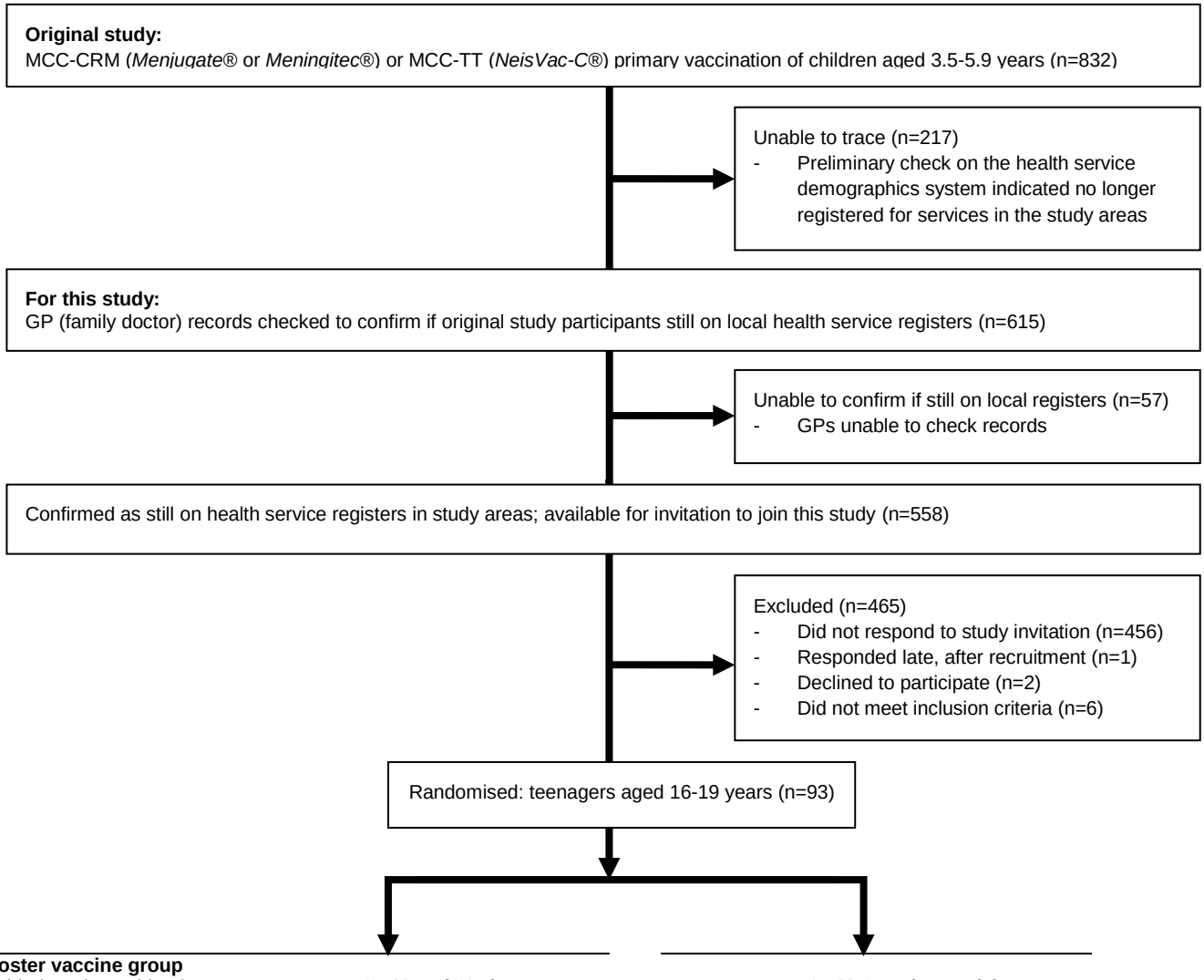
Table 3: Seroroup-specific IgG pre and post-booster vaccination, by booster vaccine

		IgG geometric mean concentrations (GMC) (ug/mL) (95% CI)							
		Pre-boost		1 month post-boost			6 months post-boost		9 months post-boost
	Booster vaccine	*n*	*GMC*	*n*	*GMC*	*(n-fold) rise in GMC*	*n*	*GMC*	*n*	*GMC*
Men C									
	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)
A									
	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)
W									
	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)
Y									
	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)

Table 4: Serogroup-specific IgG pre and post-booster vaccination, by primary vaccine and across all study groups

			IgG geometric mean concentrations (GMC) (ug/mL) (95% CI)									
	Booster vaccine	***Primary vaccine***	**Pre-boost**		**1 month post-boost**			**6 months post-boost**		**9 months post-boost**	
			n	***GMC***	***n***	***GMC***	***n-fold rise in GMC***	***n***	***GMC***	***n***	***GMC***
Men C	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)
A	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)
W	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)
Y	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)

FIGURE 1



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 2

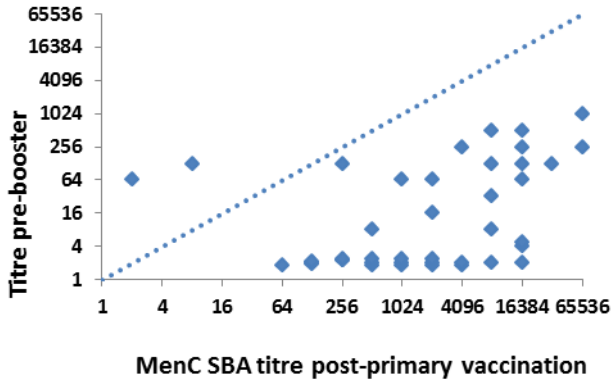
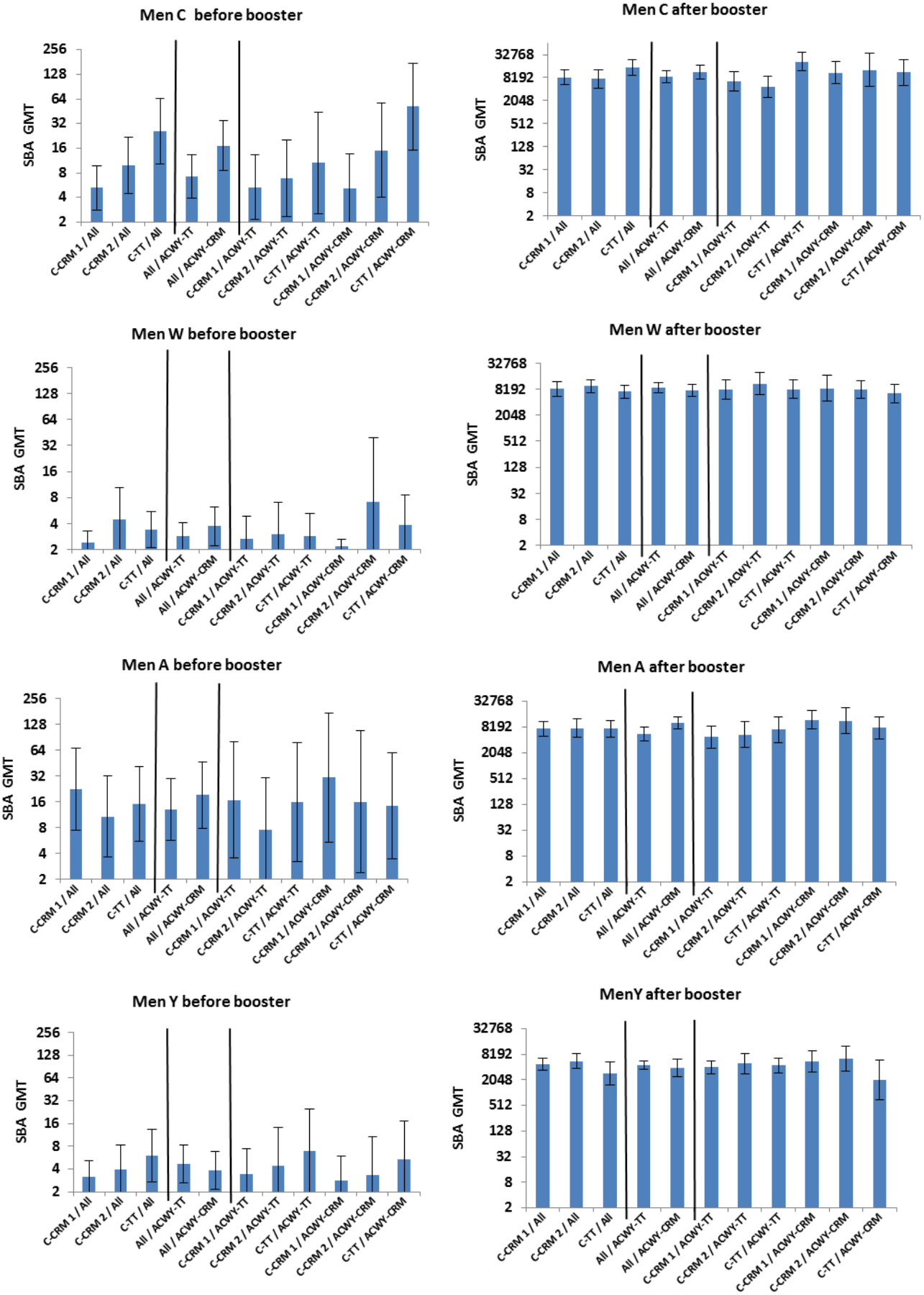
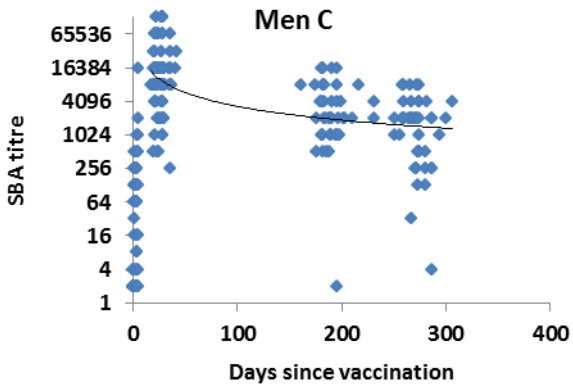
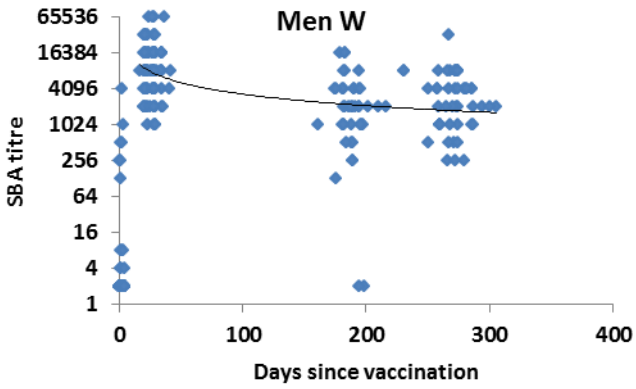

65536
16384
4096
1024
256
64
16
4
1
Titre pre-booster
1
4
16
64
256
1024
4096
16384
65536
MenC SBA titre post-primary vaccination

FIGURE 3


Men C before booster
Men C after booster
Men W before booster
Men W after booster
Men A before booster
Men A after booster
Men Y before booster
MenY after booster
SBA GMT
C-CRM 1 / All
C-CRM 2 / All
C-TT / All
All / ACWY-TT
All / ACWY-CRM
C-CRM 1 / ACWY-TT
C-CRM 2 / ACWY-TT
C-TT / ACWY-TT
C-CRM 1 / ACWY-CRM
C-CRM 2 / ACWY-CRM
C-TT / ACWY-CRM


Men C
SBA titre
65536
16384
4096
1024
256
64
16
4
1
0
100
200
300
400
Days since vaccination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SBA titre
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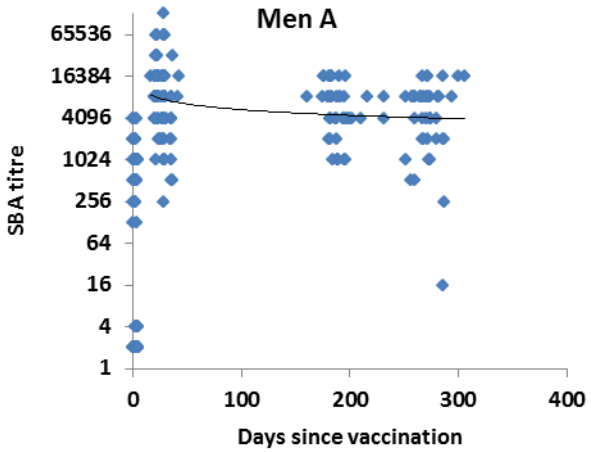
100
200
300
400
Days since vaccination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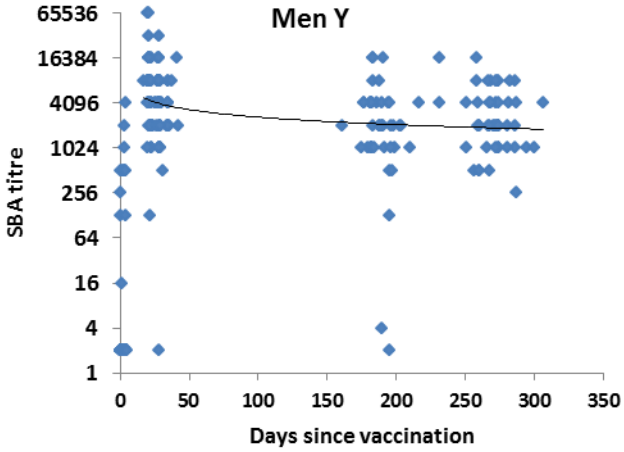
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4
1
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150
200
250
300
350
Days since vaccination

SUPPLEMENTAL DIGITAL CONTENT 1 – SUPPLEMENTAL TEXT

Supplemental to:

Randomized trial to compare immunogenicity and safety of a CRM and TT conjugated quadrivalent meningococcal vaccine in teenagers who received a CRM or TT conjugated serogroup C vaccine at preschool age.

David A. Ishola, Nick Andrews, Pauline Waight, Chee Yung, Jo Southern, Xilian Bai, Helen Findlow, Mary Matheson, Anna England, Bassam Hallis, Jamie Findlow, Ray Borrow, Elizabeth Miller. Public Health England, Immunization Department, Centre for Infectious Disease Surveillance and Control, 61 Colindale Avenue, London NW9 5EQ, UK. Tel +44 (0)20 83277434. Fax +44 (0)20 83277404.

SUPPLEMENTAL DIGITAL CONTENT – METHODS

Participants: From the original cohort of 832 pre-school age children who took part in a previous study between 1998 and 2000, a preliminary check on the health service demographics system suggested that 615 were still registered with GPs for health services in Hertfordshire and Gloucestershire, England (see Figure 1 in main article). Study vaccine research nurses and partners from the regional primary care research network (PCRN) contacted GPs to check their records. For 57 individuals, the records were inaccessible as GP configurations had either changed or their GPs were not able to participate in the checking process. Those who were confirmed to still be registered were invited to join this study, and eligible respondents were enrolled after providing fully informed written consent. Teenagers who received an MCC vaccine during the preschool study, but no further MCC vaccination thereafter, and no other vaccine within the 3 months preceding enrolment, were included. Exclusion criteria included immunosuppression, pregnancy, significant medical illness, antibiotic use within 14 days of enrolment, previous confirmed invasive meningococcal disease, and any other contraindication as per routine practice guidelines in the UK national immunisation guidance "Green Book"[1]. Study formal procedures commenced in June 2012 and recruitment took place between July and

[1] Department of Health, England. Meningococcal meningitis and septicaemia (Updated 11 April 2014). In: Salisbury D, Ramsay M, eds. Immunisation against infectious disease: the Green Book (chapter 22). London: Crown copyright 2013; Open Government Licence v 2.0. URL: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/302904/Green_Book_Chapter_22_v2_5.pdf (accessed 14 August 2014).

November 2012. For antibody persistence measurements, participants were randomised in order of inclusion using a computer-generated list, to either 6 or 9 months follow-up, with final study visits in August 2013. Participants completed a health diary to record oral temperature and any local or systemic reactions daily for the week following vaccination. Reactions and events were further monitored by vaccine research nurses during a telephone follow-up on the 8th day post-vaccination; and by directly enquiring from participants at each study visit.

Regulation: The trial was approved by the North West 3 NHS Research Ethics Committee (Reference 11/H1002/6) and conducted in accordance with the Helsinki Declaration (2008 amendment), the 1996 International Committee for Harmonisation Guidelines for Good Clinical Practice, and the 2004 EU Clinical Trial Directive. The supplementary section provides further information on participants, regulation, vaccines, serology, and analyses. After gaining all regulatory approvals, appropriate local research governance permissions in Hertfordshire and Gloucestershire were obtained. The trial EudraCT Number is 2010-022505-18. It was registered on the public website, www.ClinicalTrials.gov (identifier NCT01192997), and adopted and registered on the National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio database (ID 10242).

Vaccines: Novartis MenACWY (Menveo®) was licensed by the European Medicine Agency (EMeA) in 2009, and currently indicated for use from 2 years of age and above. It has 10 µg of MenA oligosaccharide; and 5 µg of each of MenC, W and Y, with a total *Corynebacterium diphtheriae* CRM197 protein content of 32.7-45.8 µg per dose. GSK MenACWY was an investigational product during preparation for this

study. It became licensed [2] (as Nimenrix®) just before study commencement, but the already provided pre-licensure batch was used. It had 5 µg oligosaccharide of each of the four serogroups, and a total tetanus toxoid content of ~44 µg per dose.

Serology: After blood sample collection, sera were separated and testing for tetanus and diphtheria antitoxin performed at Public Health England (PHE) Microbiology Services laboratories at Porton Down; aliquots were transported on dry ice to the PHE Vaccine Evaluation Unit, Manchester, for meningococcal antibody measurements. Laboratory staff remained unaware of participants' study groups. Sera were tested for serogroup-specific IgG antibodies using a standardised enzyme-linked immunosorbent assay (ELISA) protocol. They were tested for serogroup-specific SBA using a standardized assay incorporating serum from 3-4 week old rabbits as the exogenous complement source. The target meningococcal strains used were MenC C11, MenW M01.240070, and MenY M00.241125 (S1975), MenA M99.243594. SBA titers were expressed as the reciprocal serum dilutions yielding ≥50% killing after 60 min. Diphtheria and tetanus-specific antibodies (IgG) were quantified using standardized ELISAs with the National Institute for Biological Standards and Control (NIBSC) National Diphtheria reference serum 00/496 and the first International Tetanus reference serum 26/488.

[2] European Medicines Agency (2012). EPAR-summary for the public: Nimenrex (EMA/CHMP/136315/2012). URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002226/WC500127665.pdf (accessed 14 August 2014)

Statistics: Outcomes were measured at three time points; pre-booster, 28 days post-boost, and either 6 or 9 months post-boost. The proportion of participants with serogroup A, C, W and Y-specific SBA titers ≥8 and ≥128 (not shown); as well as SBA geometric mean titers (GMTs) were calculated with 95% confidence intervals (95% CIs) at each time point. Proportions with ≥4-fold rises in SBA titer from baseline (results not shown) and geometric mean (*n*-fold) rises in SBA titer from baseline were also calculated with 95% CIs. Similarly, serogroup-specific IgG geometric mean concentrations (GMCs) were calculated with 95% CIs at each time point, along with geometric mean rises (*n*-fold) in concentration from the baseline. For antibody responses to the vaccine carrier proteins, GMCs of antibody to TT and diphtheria toxin, as well as proportions with specific IgG concentration ≥0.1 IU/mL, were calculated with 95% CIs at each time point (CIs not shown). SBA titers below the lower detection limit of 4 were assigned a value of 2 for computational purposes, and antibody titers were log-transformed for geometric mean calculations. The 95% CIs were calculated for each of the groups as well as overall by the three primary vaccines and overall by the two trial vaccines. Comparisons between boosters and by primary vaccination overall were done at a 5% significance level. Post-boost measurements were compared by primary vaccine and by booster vaccine, with multivariable normal errors regression on logged antibody levels, adjusting for pre-vaccination titers and time from vaccination to blood sample, and testing for interactions. Previously-reported post-primary antibody responses from the original study were compared with pre-booster antibody responses from the current trial, by regression of logged post-primary (original study) titers on logged teenage (current study) pre-boost titers, taking account of between-group differences in primary

vaccine and booster vaccine. Comparisons across the 6 arms were by non-overlapping 95% CIs, being a conservative approach (equivalent to a $P < 0.01$ approximately) to allow for the high numbers of possible comparisons.

SUPPLEMENTAL DIGITAL CONTENT – RESULTS

The male/female distribution was 16 /30 (MenACWY-TT group) and 20/27 (MenACWY-CRM group). The median 1, 6 and 9-month post-booster intervals to blood sampling were 27 (range 17-42), 273 (251-306), and 189 (161-231) days, respectively. All were included in analysis as they were within pre-set time point limits. Per-protocol analysis only was carried out since there was no difference to modified intention-to-treat data. For all antigen group comparisons, age and gender were not associated with responses and not included in the models.

LEGENDS TO SUPPLEMENTAL FIGURES

Supplemental Figure S1. Meningococcal group C serum bactericidal antibody (SBA) (***upper panel***, n=40) and IgG (***lower panel***, n=81). Antibody titers after the original primary vaccination with a meningococcal C conjugate vaccine at pre-school age (post-primary, x-axis), were compared to titers one month after teenage booster vaccination (1-month post-boost, y-axis). Trend lines were fitted. Regression of logged post-boost on post-primary titers, allowing for primary and booster vaccines, showed weakly positive association for both SBA and IgG, but neither reached statistical significance (SBA p=0.26; IgG p=0.09).

Supplemental Figure S2. Decline in meningococcal serogroup-specific IgG titers over time, after teenage booster vaccination, with fitted trend lines. Fold titer changes per doubling time

since day 28 (and 95% CI) estimated from a fixed effects model were as follows: ***Upper left panel:*** MenC IgG 0.61 (0.58-0.64); ***Upper right panel:*** MenW 0.67 (0.64-0.71); ***Lower left panel:*** MenA 0.66 (0.62-0.7); and ***lower right panel:*** MenY 0.78 (0.74-0.82).

Supplemental digital content: Table S1: Characteristics of current study participants, compared with individuals from the original study cohort who did not participate in this study

Factor		**Participants in current study (total n=93)**	**Non-participants in current study (total n=750)**	**p-value**
Age in years: Mean		4.32	4.28	0.22
Sex: Number of males (percentage)		36/93 (38.7%)	391/750 (51.1%)	0.02
Primary vaccine received in the original study	Menjugate®	33	282	0.79
	Meningitec®	26	184	
	NeisVac-C®	34	276	
Post-primary MenC antibody responses in the original study	SBA GMT (95% CI)	1114 (488-2542) [n=41]	1180 (965-1444) [n=376]	0.87
	IgG GMC, µg/mL (95% CI)	8.75 (6.64-11.53) [n=82]	8.55 (7.74-9.43) [n=618]	0.87

Supplemental digital content: Table S2: Serogroup-specific serum bactericidal antibody (SBA) geometric mean titres (GMT) pre and post-booster vaccination, across all study groups

			Pre boost		1 month post-boost			6 months post-boost		9 months post-boost	
	Booster vaccine	**Primary vaccine**	n	**GMT (95% CI)**	n	**GMT (95% CI)**	**(*n*-fold) rise in GMT (95% CI)**	n	**GMT (95% CI)**	n	**GMT (95% CI)**
MenC	MenACWY-TT	*Menjugate*	17	5 (2-13)	17	6414 (3604-11417)	1205 (467-3109)	8	1448 (724-2895)	9	697 (129-3765)
		Meningitec	14	7 (2-20)	14	4752 (2527-8935)	689 (250-1899)	7	420 (45-3956)	7	689 (261-1816)
		NeisVac-C	15	11 (3-44)	15	21619 (12144-38484)	2048 (426-9837)	6	3251 (1795-5888)	9	2389 (1194-4780)
	MenACWY-CRM	*Menjugate*	16	5 (2-14)	16	11094 (5580-22058)	2139 (937-4883)	8	5793 (2712-12370)	8	790 (173-3594)
		Meningitec	12	15 (4-57)	12	13004 (4786-35334)	861 (297-2496)	6	2580 (863-7714)	5	2048 (409-10247)
		NeisVac-C	19	51 (15-172)	18	11148 (5171-24034)	256 (64-1032)	10	4390 (1990-9682)	8	2048 (853-4918)
MenA	MenACWY-TT	*Menjugate*	17	17 (3-79)	17	4822 (2651-8769)	289 (64-1307)	8	4467 (2515-7932)	9	1756 (382-8069)
		Meningitec	14	8 (2-31)	14	5513 (2746-11068)	724 (130-4035)	7	2756 (1046-7265)	7	4522 (2075-9854)
		NeisVac-C	15	16 (3-79)	15	7132 (3546-14344)	446 (67-2975)	6	5793 (2125-15788)	9	4424 (1796-10894)
	MenACWY-CRM	*Menjugate*	16	31 (5-174)	16	12098 (7444-19663)	395 (68-2278)	8	6889 (3781-12550)	8	6889 (3781-12550)
		Meningitec	12	16 (2-109)	12	11585 (5667-23684)	724 (105-4983)	5	4096 (1050-15972)	5	8192 (2855-23506)
		NeisVac-C	19	14 (3-60)	18	7883 (4290-14483)	493 (90-2683)	10	5793 (2960-11336)	8	3444 (1191-9959)
MenW	MenACWY-TT	*Menjugate*	17	3 (1-5)	17	8192 (4873-13772)	3079 (1219-7776)	8	2233 (1018-4901)	9	1896 (770-4670)

		Meningitec	14	3 (1-7)	14	11026 (6165-19718)	3710 (1267-10865)	7	840 (194-3643)	7	2756 (1219-6231)
		NeisVac-C	15	3 (2-5)	15	8192 (4956-13541)	2830 (1717-4665)	6	3251 (991-10663)	8	2435 (882-6724)
	MenACWY-CRM	*Menjugate*	16	2 (2-3)	16	8555 (4274-17122)	3922 (1910-8055)	8	1328 (131-13468)	8	2656 (742-9503)
		Meningitec	12	7 (1-39)	12	8192 (5172-12977)	1149 (215-6154)	4	2048 (832-5040)	5	1783 (382-8313)
		NeisVac-C	19	4 (2-9)	18	6502 (3993-10587)	1625 (705-3750)	10	1176 (202-6848)	8	2435 (1240-4784)
MenY	MenACWY-TT	*Menjugate*	17	3 (2-7)	17	4096 (2868-5850)	1205 (464-3135)	8	2048 (959-4374)	9	2212 (1125-4350)
		Meningitec	14	4 (1-14)	14	4993 (2871-8684)	1131 (260-4924)	7	1024 (102-10330)	7	2497 (1357-4594)
		NeisVac-C	15	7 (2-25)	15	4493 (2991-6749)	645 (162-2568)	6	1625 (898-2944)	9	2389 (1039-5495)
	MenACWY-CRM	*Menjugate*	16	3 (1-6)	16	5547 (3132-9825)	1961 (648-5938)	8	4871 (1852-12813)	8	2233 (1163-4289)
		Meningitec	12	3 (1-11)	12	6502 (3362-12574)	1933 (612-6101)	6	2048 (1068-3925)	5	2702 (852-8575)
		NeisVac-C	19	5 (2-17)	18	2048 (684-6130)	362 (75-1739)	10	955 (153-5970)	8	2048 (643-6526)

Supplemental digital content: Table S3: MenC-specific serum bactericidal antibody (SBA) geometric mean titres (GMT): Composite 6 and 9-month post-booster data, by primary and booster vaccine, and across all study groups

Booster vaccine	Primary vaccine	n	GMT (95 %CI)
All	*Menjugate*	33	1433 (777-2642)
	Meningitec	25	1024 (511-2054)
	NeisVac-C	33	2927 (2077-4124)
GSK	All	46	1138 (706-1834)
Novartis	All	45	2541 (1696-3806)
MenACWY-TT	*Menjugate*	17	983 (413-2342)
	Meningitec	14	538 (189-1532)
	NeisVac-C	15	2702 (1757-4156)
MenACWY-CRM	*Menjugate*	16	2139 (853-5363)
	Meningitec	11	2323 (1102-4896)
	NeisVac-C	18	3128 (1793-5456)

Supplemental digital content: Table S4: Tetanus antibody

		Geometric mean concentrations (GMC) (IU/mL) (95% CI)							
		Pre-boost		**1 month post-boost**		**6 months post-boost**		**9 months post-boost**	
Primary vaccine	**Booster vaccine**	***n***	***GMC***	***n***	***GMC***	***n***	***GMC***	***n***	***GMC***
Menjugate	All	33	1.04 (0.6-1.82)	32	3.85 (2.07-7.18)	16	2.68 (1.25-5.72)	17	1.8 (0.81-4.04)
Meningitec	All	25	0.93 (0.53-1.63)	25	3.8 (1.81-7.98)	11	3.1 (1.24-7.76)	12	1.44 (0.5-4.14)
NeisVac-C	All	33	1.76 (1.15-2.71)	32	4.89 (2.86-8.36)	16	3.07 (1.54-6.13)	17	3.46 (2.15-5.55)
all	MenACWY-TT	45	1.13 (0.73-1.76)	44	13.7* (10.2-18.4)	20	7.06 (4.61-10.83)	25	3.5 (2.14-5.73)
all	MenACWY-CRM	46	1.31 (0.88-1.96)	45	1.31 (0.88-1.95)	23	1.36 (0.82-2.24)	21	1.22 (0.63-2.37)
Menjugate	MenACWY-TT	17	0.88 (0.37-2.08)	16	11.66 (6.19-21.94)	8	6.73 (3.82-11.85)	9	2.07 (0.61-6.98)
Meningitec	MenACWY-TT	13	0.91 (0.45-1.83)	13	13.2 (7.38-23.6)	6	5.28 (1.52-18.31)	7	3.97 (1.85-8.53)
NeisVac-C	MenACWY-TT	15	1.82 (0.81-4.1)	15	16.8 (11.29-25)	6	10.09 (3.81-26.72)	9	5.4 (2.84-10.26)
Menjugate	MenACWY-CRM	16	1.24 (0.56-2.76)	16	1.27 (0.58-2.77)	8	1.06 (0.33-3.43)	8	1.55 (0.39-6.1)
Meningitec	MenACWY-CRM	12	0.95 (0.34-2.63)	12	0.98 (0.38-2.54)	5	1.64 (0.29-9.36)	5	0.35 (0.05-2.26)
NeisVac-C	MenACWY-CRM	18	1.72 (1.05-2.82)	17	1.65 (0.95-2.86)	10	1.5 (0.79-2.87)	8	2.09 (1.09-4)
		Proportions ≥0.1 IU/mL							
		Pre-boost		**1 month post-boost**		**6 months post-boost**		**9 months post-boost**	
		n	***% ≥0.1 IU/mL***	***n***	***% ≥0.1 IU/mL***	***n***	***% ≥0.1 IU/mL***	***n***	***% ≥0.1 IU/mL***

Menjugate	All	33	88	32	97	16	94	17	94
Meningitec	All	25	96	25	96	11	100	12	92
NeisVac-C	All	33	97	32	100	16	100	17	100
all	MenACWY-TT	45	91	44	100	20	100	25	96
all	MenACWY-CRM	46	96	45	96	23	96	21	95
Menjugate	MenACWY-TT	17	82	16	100	8	100	9	89
Meningitec	MenACWY-TT	13	100	13	100	6	100	7	100
NeisVac-C	MenACWY-TT	15	93	15	100	6	100	9	100
Menjugate	MenACWY-CRM	16	94	16	94	8	88	8	100
Meningitec	MenACWY-CRM	12	92	12	92	5	100	5	80
NeisVac-C	MenACWY-CRM	18	100	17	100	10	100	8	100

*p<0.001 vs MenACWY-CRM, normal errors regression, adjusting for primary vaccine.

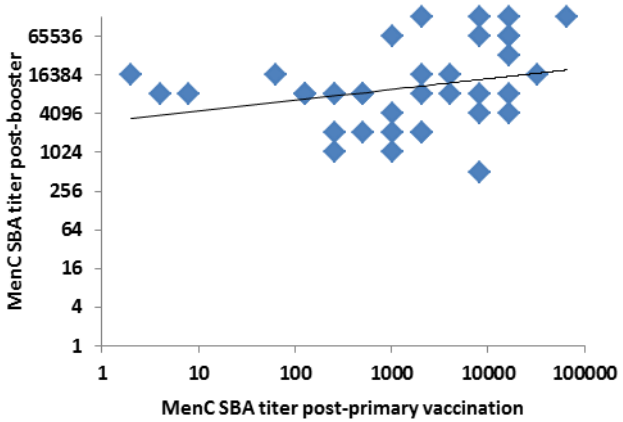
Supplemental digital content: Table S5: Diphtheria antibody

		Geometric mean concentrations (GMC) (IU/mL) (95% CI)							
		Pre-boost		**1 month post-boost**		**6 months post-boost**		**9 months post-boost**	
Primary vaccine	**Booster vaccine**	***n***	***GMC***	***n***	***GMC***	***n***	***GMC***	***n***	***GMC***
Menjugate	All	33	0.43 (0.25-0.73)	33	2.15 (0.9-5.18)	16	1.36 (0.46-4.01)	17	1.05 (0.36-3.05)
Meningitec	All	25	0.46 (0.27-0.81)	25	1.98 (0.74-5.28)	11	1.34 (0.34-5.22)	12	0.54 (0.18-1.63)
NeisVac-C	All	33	0.47 (0.3-0.72)	32	2.31 (0.99-5.37)	16	1.63 (0.56-4.71)	17	1.09 (0.44-2.69)
all	MenACWY-TT	45	0.29 (0.19-0.45)	45	0.28 (0.18-0.44)	20	0.33 (0.14-0.76)	25	0.24 (0.14-0.39)
all	MenACWY-CRM	46	0.7 (0.51-0.97)	45	16.38* (12.32-21.77)	23	5.24 (3.43-8.02)	21	4.36 (2.72-7)
Menjugate	MenACWY-TT	17	0.3 (0.13-0.68)	17	0.28 (0.12-0.64)	8	0.26 (0.09-0.77)	9	0.26 (0.07-1.04)
Meningitec	MenACWY-TT	13	0.31 (0.11-0.83)	13	0.32 (0.13-0.82)	6	0.67 (0.05-8.17)	7	0.17 (0.07-0.4)
NeisVac-C	MenACWY-TT	15	0.27 (0.14-0.52)	15	0.26 (0.13-0.51)	6	0.23 (0.04-1.38)	9	0.28 (0.15-0.51)
Menjugate	MenACWY-CRM	16	0.63 (0.31-1.3)	16	18.81 (12.72-27.82)	8	7.27 (3.72-14.21)	8	5 (2.27-11)
Meningitec	MenACWY-CRM	12	0.73 (0.45-1.18)	12	14.07 (6.21-31.88)	5	3.08 (0.65-14.49)	5	2.77 (0.67-11.43)
NeisVac-C	MenACWY-CRM	18	0.75 (0.44-1.27)	17	16.01 (10.16-25.22)	10	5.26 (2.65-10.44)	8	5.05 (1.98-12.9)
		Proportions ≥0.1 IU/mL							
		Pre-boost		**1 month post-boost**		**6 months post-boost**		**9 months post-boost**	
		n	***% ≥0.1 IU/mL***	***n***	***% ≥0.1 IU/mL***	***n***	***% ≥0.1 IU/mL***	***n***	***% ≥0.1 IU/mL***

Menjugate	All	33	82	33	85	16	88	17	82
Meningitec	All	25	88	25	88	11	91	12	83
NeisVac-C	All	33	85	32	88	16	81	17	88
all	MenACWY-TT	45	73	45	73	20	70	25	72
all	MenACWY-CRM	46	96	45	100	23	100	21	100
Menjugate	MenACWY-TT	17	71	17	71	8	75	9	67
Meningitec	MenACWY-TT	13	77	13	77	6	83	7	71
NeisVac-C	MenACWY-TT	15	73	15	73	6	50	9	78
Menjugate	MenACWY-CRM	16	94	16	100	8	100	8	100
Meningitec	MenACWY-CRM	12	100	12	100	5	100	5	100
NeisVac-C	MenACWY-CRM	18	94	17	100	10	100	8	100

*p<0.001 vs MenACWY-TT, normal errors regression, adjusting for primary vaccine.

Figure S1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4096
1024
256
64
16
4
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10
100
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100000
MenC SBA titer post-primary vaccination

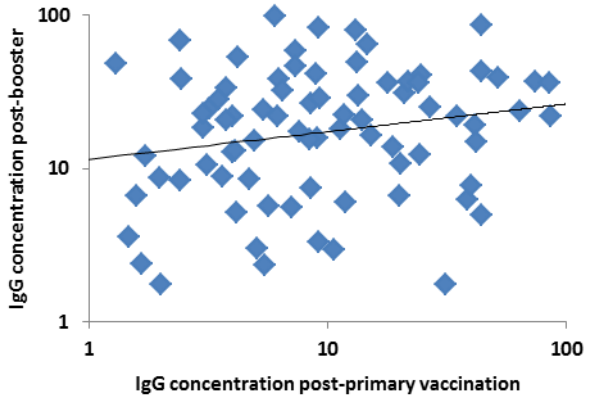
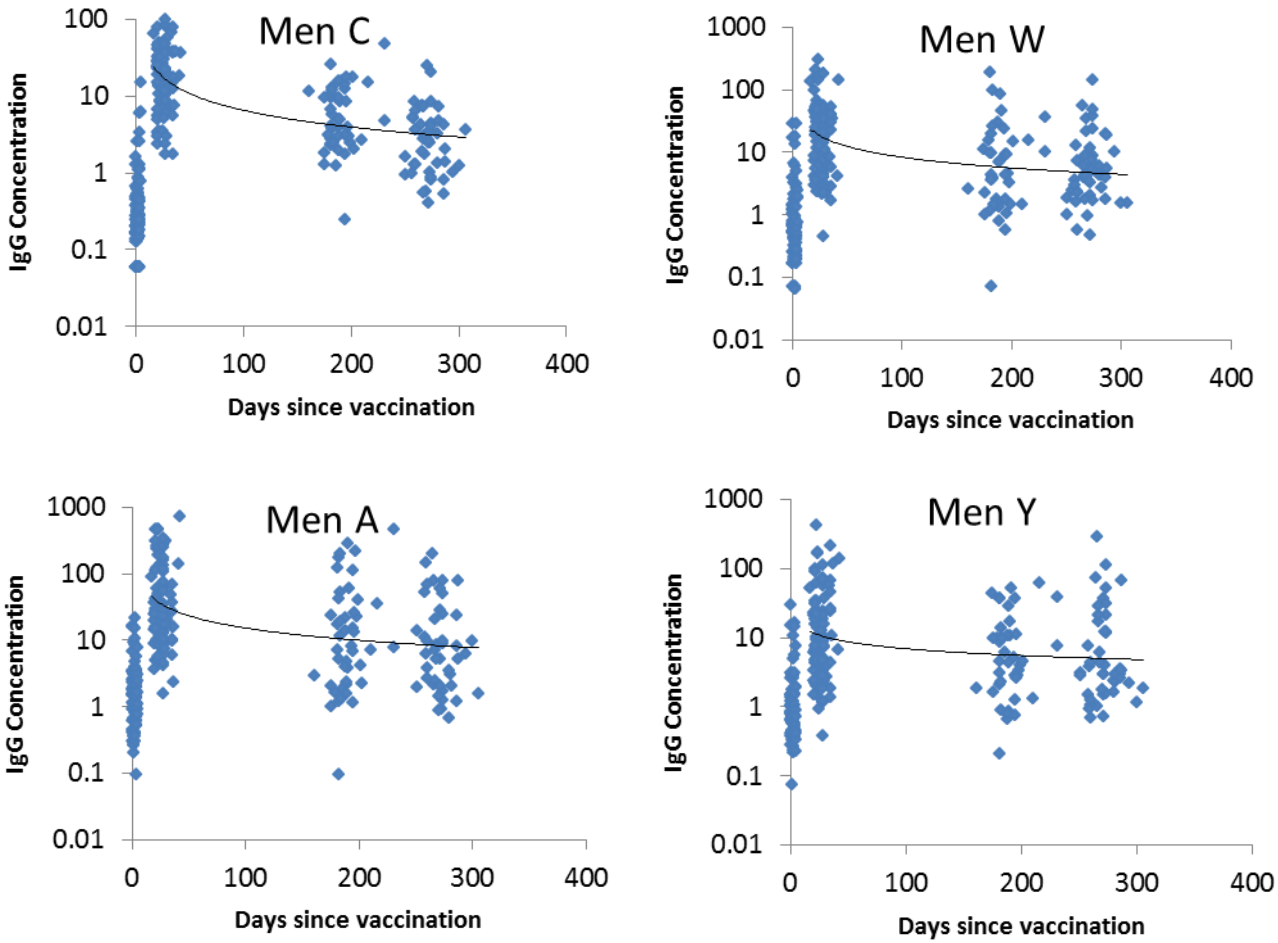

IgG concentration post-booster
100
10
1
1
10
100
IgG concentration post-primary vaccination

Figure S2


Men C
IgG Concentration
100
10
1
0.1
0.01
0
100
200
300
400
Days since vaccination
Men W
IgG Concentration
1000
100
10
1
0.1
0.01
0
100
200
300
400
Days since vaccination
Men A
IgG Concentration
1000
100
10
1
0.1
0.01
0
100
200
300
400
Days since vaccination
Men Y
IgG Concentration
1000
100
10
1
0.1
0.01
0
100
200
300
400
Days since vaccination