Impact of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial

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Abstract

Background: Meningococcal conjugate vaccines protect individuals directly, but may also confer herd protection by interrupting carriage transmission. This Phase III observer-blind, randomised, controlled study evaluated the effects of meningococcal quadrivalent glycoconjugate (MenACWY-CRM) or serogroup B (4CMenB) vaccination on meningococcal carriage rates in 18-24 year-old adults.

Methods: University students from ten sites in England were randomised (1:1:1, block size of three) to receive two doses one month apart of Japanese Encephalitis vaccine (controls), 4CMenB, or one dose of MenACWY-CRM then placebo. Participants and outcome-assessors were blinded to treatment arm. Meningococci were isolated from oropharyngeal swabs collected before vaccination and at five scheduled intervals over one year. Primary analyses were cross-sectional carriage one month after each vaccine course; secondary analyses included comparisons of carriage at any time point after primary analysis until study termination. Reactogenicity and adverse events were monitored throughout the study.

Findings: 2954 subjects were randomised (control, n=987; 4CMenB, n=979; MenACWY-CRM, n=988); approximately one-third of each group was positive for meningococcal carriage at study entry. By one month, there was no significant difference in carriage between controls and 4CMenB (Odds Ratios (OR), 1·2 [95%CI: 0·8–1·7]) or MenACWY-CRM (OR, 0·9 [95%CI: 0·6–1·3]) groups. From three months after dose two, 4CMenB vaccination resulted in significantly lower carriage of any meningococcal strain (18·2% [95%CI: 3·4–30·8] carriage reduction) and capsular groups BCWY (26·6% [95%CI: 10·5–39·9] carriage reduction) compared to control vaccination.

Significantly lower carriage rates were also observed in the MenACWY-CRM group compared with controls: 39·0% [95%CI: 17·3-55·0] and 36·2% [95%CI: 15·6-51·7] carriage reduction for serogroups Y and CWY, respectively. Study vaccines were generally well tolerated, with elevated rates of transient local injection pain, and myalgia, in the 4CMenB group. No safety concerns were identified.

Interpretation: MenACWY-CRM and 4CMenB vaccines reduced meningococcal carriage rates over 12 months post-vaccination and, therefore, may affect transmission where widely implemented. [ClinicalTrials.gov, NCT01214850]

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Introduction

It is estimated that there are 0·5–1·2 million episodes of meningococcal disease every year causing 50,000–135,000 deaths worldwide.[1,2] *Neisseria meningitidis* colonises the nasopharynx and is transmitted via large-droplet spread. Asymptomatic carriage is highest among adolescents, associated with social behaviours such as bedroom-sharing, smoking, kissing, and attending bars and clubs.[3–6] The most important disease-associated serogroups are A, B, C, W, and Y, with X being a recent concern in Africa.[7] Post-implementation analyses of population-scale vaccination programmes reveal that meningococcal serogroup C conjugate (MCC) vaccines provide benefit not only by direct protection of vaccinated individuals, but more importantly also through the interruption of transmission (i.e., herd protection),[8–10] a factor that enhances public health impact and cost-effectiveness.[11]

In addition to quadrivalent glycoconjugate vaccines against *s*erogroups A, C, W, and Y such as MenACWY-CRM (Menveo®, NVS, Siena, Italy), a multi-component serogroup B meningococcal vaccine, 4CMenB (Bexsero®, NVS, Siena, Italy) has recently been licensed in the European Union, Australia and Canada. 4CMenB contains Neisseria Heparin Binding Antigen (subvariant 1.2) fused with accessory protein 953, Neisserial adhesin A (subvariant 3.1), factor H binding protein (subvariant 1.1) fused with accessory protein 936, and the outer membrane vesicle (OMV) from *N meningitidis* strain NZ98/254 (OMV NZ) derived from the MeNZB vaccine.[12,13]

We report the findings from a study conducted to evaluate the effect of 4CMenB and MenACWY-CRM vaccination on meningococcal carriage rates in university students in England.

Methods

This was a randomised, observer-blind, controlled Phase III study at ten study centres in England, conducted in accordance with the provisions of the Declaration of Helsinki (1996) and the International Conference on Harmonization Guidelines for Good Clinical Practice. The National Research Ethics Service approved the study protocol. All participants gave informed consent. This trial is registered with ClinicalTrials.gov, number NCT01214850.

Study population

Eligible participants were healthy males and females attending university, aged 18–24 years, who were available for all scheduled visits with no history of serogroup B meningococcal vaccination, meningococcal disease or contact with it, significant infection of any nature within the previous seven days, or use of antibiotics within 72 hours of enrolment. Pregnant women, nursing mothers, females of childbearing age who did not use acceptable birth control, people with chronic disease, impairment/alteration of the immune system (including immunosuppressive therapy), or history of severe allergic reactions after vaccinations were excluded.

Interventions

Subjects were randomised to three arms – controls, 4CMenB and MenACWY-CRM groups. The control group received two doses of Japanese encephalitis vaccine (IXIARO® [Intercell, Vienna, Austria]). The 4CMenB group received two doses of recombinant MenB vaccine (Bexsero®;

NVS). The MenACWY-CRM group received one dose of MenACWY-CRM vaccine (Menveo®; NVS) then a dose of placebo (containing 1·5 mg aluminium hydroxide) one month later.

Subjects were observed for 30 minutes after each vaccination for any immediate reactions. Subjects recorded adverse events (AEs) and serious AEs (SAEs) via a paper diary throughout the study. All AEs and SAEs were judged by an investigator as not related, possibly related, or probably related to study vaccination. A subset of subjects in each group recorded solicited local and systemic reactions, as well as other indicators of reactogenicity (i.e. use of analgesic or antipyretic), via a separate paper diary for a seven day period following each vaccination.

From study Day 1 to study termination there were six clinic visits over 12 months. All subjects had oropharyngeal swabs collected at every visit. *N meningitidis*-positive samples were identified by culture and biochemical confirmation. Isolates were further characterised by genogroups, serogroups and sequence types. Isolates were serogrouped and reported here as combined or individual serogroups. All non-serogroupable meningococci were then assessed by PCR[14] and reported here as combined or individual capsular (caps) groups. CapsB isolates were classified into sequence types (STs) by multilocus sequence typing and reported here as strains that belong to STs associated with invasive disease in the UK, or all STs. Strains that were 'disease associated' were pre-defined in the analysis plan as those with matching ST or clonal complex to those found to cause invasive disease in the UK between 2006 and 2010.

Outcomes

The primary outcomes were carriage prevalence of (1) capsB strains belonging to STs associated with invasive disease one month after the two-dose series of either 4CMenB or control vaccination, and (2) serogroup ACWY strains at one month after a single dose of MenACWY-CRM or control vaccination.

Predefined secondary outcomes included: assessment of vaccine impact on carried meningococcal strains, including all capsular group ABCWY (capsABCWY) strains and all capsB strains; assessment of vaccine impact across multiple aggregate timepoints and impact on new acquisition of meningococcal strains; and assessment of vaccine impact on carriage in students with known risk factors for high transmission – younger subjects, smokers, and subjects enrolling early in the university year. A group-unblinded interim analysis was performed after all subjects had completed their third study visit.

The study required 850 evaluable subjects/arm (assuming 15% drop-out rate) and a carriage prevalence of ≥20% for each of the primary outcomes to have sufficient power (89% each outcome) to detect a 30% relative difference in carriage prevalence. Calculations were performed with NQuery version 6·01 (two group continuity corrected chi-square test, two-sided alpha=0·05).

Safety assessments included the incidence of selected indicators of reactogenicity reported within a seven-day period following each vaccination, as well as the incidence of unsolicited AEs and SAEs reported throughout the study period.

Randomisation and masking

Subjects were randomised in a 1:1:1 ratio into three arms using a validated computer-generated random allocation list provided by NVS. Fourteen enrolled subjects were not randomised to any of the arms due to protocol deviations; these subjects did not receive any study vaccinations. To maintain study masking, subjects and investigative site personnel were blinded to group assignment until the conclusion of the study. Study vaccines were prepared and administered by unblinded personnel who did not participate in any outcome assessments; study vaccines were prepared out of the view of subjects and those persons assessing outcomes. Unblinding of subjects following completion of visit five was permitted for those individuals who required immunizations for travel to JE- or MenACWY-endemic areas.

Statistical methods

Analysis of pharyngeal carriage was performed on the modified intention-to-treat (MITT) population, which included all enrolled subjects who received a study vaccination and provided at least one evaluable swab sample after baseline. The percentage of subjects with *N meningitidis* carriage and the associated 95% Clopper-Pearson confidence intervals (CIs) were tabulated by vaccine group and timepoint. Differences between vaccine and control groups were analysed using Pearson's chi-square test or Fisher's exact test, where appropriate. The percentage of subjects with new acquisition of *N meningitidis* carriage was calculated with two-sided 95% CI for each vaccine group and at each timepoint following vaccination. New acquisition of *N meningitidis* carriage was defined as the detection of an *N meningitidis* isolate that was undetected at baseline, once the subject received at least one dose of vaccine. The

odds ratios (ORs) of carriage at each visit were analysed by logistic regression, incorporating carriage status at baseline as a covariate for any post-baseline visit analyses; ORs, as measures of relative rates in the vaccine groups compared to the control group were calculated and the associated two-sided 95% CIs computed. The ORs of carriage for aggregate post-baseline visits were analysed using a generalised estimating equation (GEE) including baseline carriage status and significant risk factors as covariates. ORs and the associated two-sided 95% CIs were computed. Carriage reduction was calculated for the comparisons as (1 – OR) multiplied by 100. The duration of carriage/new acquisition was calculated by least square means (LSM) returned from a general linear model assuming normal-scale distribution of data; between group differences were adjusted by centre and group.

Role of the funding source

This investigator-initiated trial was funded, administered, and monitored by employees/representatives of NVS. The chief investigators drafted and then finalised the manuscript with editorial assistance funded by NVS. All authors reviewed and approved the final version. RCR, PMD, and R Borrow had full access to study data and hold final responsibility for publication submission.

Results

Overall, 2968 subjects were enrolled (21 September to 21 December 2010) and 2954 were randomised (figure 1). The demographic variables and baseline *N meningitidis* carriage rates were balanced across the treatment groups (table 1). No serogroup A *N meningitidis* was detected in any individual. Over 99% of the randomised subjects were included in the MITT analysis.

Control group characteristics

At study entry, 31% (303/986) of control subjects were nasopharyngeal carriers of *N meningitidis* (table 1). Among control subjects with swabs from all six study visits who were negative at baseline, monthly acquisition of *N meningitidis* was 18% (112/627) during the first month, declining to 2% (14/361 over 6 months) at month 12. (figure 2; supplementary table 1). Acquisition of any capsulated meningococci (capsBCWY) occurred in 10% (69/663) of non-carriers during the first month with lower rates thereafter. Acquisition was lowest for capsB, with 4% (26/715) acquiring within the first month of enrolment and low rates over subsequent visits (figure 2).

The mean duration of any meningococcal carriage in the control group was 202 (95% CI: 185–219) LSM days for all *N meningitidis,* 147 (95%CI: 113–182) LSM days for capsB, and 113 (95% CI: 87–138) LSM days for serogroups CWY (supplementary table 3).

Impact of 4CMenB vaccination

Overall carriage prevalence

One month following the second vaccination (primary endpoint) there was no significant difference between the 4CMenB and control groups in the prevalence of carriage of disease-associated STs of capsB (OR [95% CI], 1·2 [0·8−1·7]) (table 2). Considering all sampling points together from three months after second vaccination, there was no significant difference between the 4CMenB and control groups in carriage prevalence for all capsB (OR [95% CI]; 0·8 [0·6–1·1]) or disease-associated STs of capsB (OR [95% CI]; 0·9 [0·7–1·2]) (table 3). Significantly lower carriage prevalence was, however, observed for 4CMenB versus control group at any timepoint from three months after the second vaccination (visits 4–6) for all *N meningitidis*, capsBCWY, capsCWY, and serogroup CWY (table 3).

Acquisition, loss and duration of carriage in 4CMenB vaccinees

For the aggregate timepoint (visits 4–6), there was a non-significant trend toward lower acquisition of any *N meningitidis*, capsBCWY, and capsB in 4CMenB-vaccinated individuals, resulting in carriage reductions of 22.3% [95% CI: -5·2− 42·6%], 15·9% [95% CI: -17·3− 39·8%], and 28·6% (95% CI: -12−54·4%), respectively (table 4). Acquisition at individual timepoints is shown in supplementary table 1. There was no observed impact on the proportion of subjects losing carriage of all *N meningitidis*, capsBCWY, or capsB at any timepoint from three months after second vaccination (data not shown).

Duration of carriage of any *N meningitidis* strains was comparable in 4CMenB and control groups (193 [95% CI: 176–210] and 202 [95% CI: 185–219] LSM days, respectively) but the 4CMenB group showed a trend towards lower duration of carriage of capsBCWY (143 [95% CI: 122–164] LSM days versus 162 [95% CI: 141–183] LSM days in control group), and all capsB (127 [95% CI: 92–162] LSM days versus 146 [95% CI: 112–180] LSM days in control group) than the control group (supplementary table 3).

<u>High risk groups</u>

When assessed at any timepoint from three months after the second vaccination, there were significantly lower carriage rates of all *N meningitidis* strains in the 4CMenB group when they had received their first vaccination <30 days after the start of the university term (OR [95% CI]; 0·7 [0·5–0·9]), if they were smokers (OR [95% CI]; 0·7 [0·5–1·0]) and if they were aged <21 years (OR [95% CI]; 0·8 [0·6–0·9]), (supplementary table 4). Similar findings were observed for capsBCWY (supplementary table 4). No significant difference in carriage rates was observed for these high-risk groups for capsB, including disease-associated STs.

Impact of MenACWY-CRM vaccination

<u>Overall carriage prevalence</u>

At one month following vaccination there was no significant difference between the MenACWY-CRM and control groups in the prevalence of carriage of serogroups CWY (combined) (OR [95% CI]; 0·9 [0·6–1·3]) (table 2). Taking all timepoints together after two months, significantly lower carriage rates were observed in the MenACWY-CRM group

compared with controls for all capsular and serogroups evaluated (table 5). The carriage reductions ranged from 36·2% (95% CI: 15·6-51·7) for serogroups CWY to 39% (95% CI: 17·3–55·0) for serogroup Y (table 5).

Acquisition, loss and duration of carriage

From two months after one dose of MenACWY-CRM, there was a trend but no statistically significant differences towards lower acquisition rates for serogroups CWY and serogroup Y in the MenACWY-CRM group than the control group (14·8% [95% CI: -22·7–40·9%] and 23% [95% CI: -14·6–48·3%] carriage reduction, respectively) (table 6). Notably, the MenACWY-CRM group had a significantly lower acquisition rate of serogroup Y than the control group (66·7% carriage reduction) at two months after one dose of MenACWY-CRM (data not shown). Acquisition at individual timepoints is shown in supplementary table 2.

A trend towards lower duration of carriage was observed in the MenACWY-CRM vaccination group compared with control for serogroups CWY (vaccination: 88 [95% CI: 62–114] LSM days; control: 113 [95% CI: 87–138] LSM days) and serogroup Y (vaccination: 86 [95% CI: 59–114] LSM days; control: 117 [95% CI: 91–144] LSM days; supplementary table 5). Similarly, the MenACWY-CRM vaccinated group showed a trend to lower duration of carriage compared with the control group for newly acquired serogroups CWY (vaccination: 90 [95% CI: 57–123] LSM days; control: 120 [95% CI: 89–151] LSM days) and serogroup Y (vaccination: 87 [95% CI: 52–122] LSM days; control: 120 [95% CI: 87–153] LSM days; supplementary table 5) strains.

High risk groups

In subjects at higher risk of carriage, the MenACWY group showed significantly lower carriage rates of serogroups CWY and serogroup Y among early vaccinated subjects (OR [95% CI]; 0·5 [0·3–0·8] for serogroups CWY; OR [95% CI]; 0·6 [0·4–1·0] for serogroup Y) and subjects aged <21 years (OR [95% CI]; 0·7 [0·5–1·0] for serogroups CWY; OR [95% CI]; 0·7 [0·5–1·0] for serogroup Y; supplementary table 6). No significant difference was observed among smokers.

Reactogenicity and safety

Of 2968 subjects enrolled in the study, 2943 (99%) were exposed to at least one study vaccination and contributed to the safety analyses. Solicited local and systemic reactions occurring within the seven-day period following each vaccination were analysed in a subset of subjects in each group (4CMenB, n=185 (19%); MenACWY-CRM: n=176 (18%); Control: n=182 (18%)). Rates of solicited local reactions after any vaccination were generally higher in the 4CMenB group, with overall lower reports of reactogenicity following the second vaccination as compared to the first vaccination within this group (supplementary table 7). Rates of solicited systemic reactions after any vaccination were similar across groups, with exception to myalgia, which was reported at a higher rate in the 4CMenB group. Across groups, the most commonly reported local and systemic reactions were injection site pain and myalgia, respectively. Overall, there was a low incidence of severe reactions across all groups.

The incidence of unsolicited AEs after any vaccination in the overall safety set were similar across groups (35-40%), with a majority of these AEs assessed as unrelated study vaccination

(supplementary table 8). For the study duration, the most commonly reported unsolicited AEs across groups were tonsillitis (3%) and urinary tract infection (2-3%). Across vaccine groups, a similar rate (2-3%) of subjects reported SAEs, with three subjects in the 4CMenB group reporting SAEs that were judged as at least possibly related to the study vaccine (dyspnoea, hand tremors, and acute thyroiditis occurring 2, 18, and 18 days post-vaccination, respectively). Premature withdrawals due to AEs were reported by 1% of subjects across vaccine groups.

Discussion

Over the one year period of follow-up, the MenACWY-CRM and 4CMenB vaccines significantly reduced carriage of *N meningitidis*. MenACWY-CRM impacted on carriage of vaccine serogroups whilst 4CMenB had a broad effect. The latter impact is not surprising, as although 4CMenB is characterized as a "MenB vaccine," antigens contained in the vaccine are present in, and able to induce bactericidal antibodies against, non-serogroup B strains as well.[15] However, neither vaccine exhibited any immediate impact on carriage one month after completion of the vaccine course, nor was the study able to demonstrate a specific impact of 4CMenB on carriage of capsB strains.

Evaluations in other clinical trials or early post-implementation studies after glycoconjugate vaccines have revealed positive effects on reduction of carriage several months or even years after vaccination.[16–19] As such, it is not clear whether the lack of significant difference after one month is unusual or, more likely, too early to accumulate sufficient acquisition events to demonstrate an impact. Post-glycoconjugate vaccination evaluations of pneumococcal carriage

similarly did not show any early impact and only at later timepoints were differences demonstrated. [20,21]

For MenACWY-CRM, significantly lower carriage rates were observed for serogroups CWY (36·2% carriage reduction) and serogroup Y (39·0% carriage reduction) specifically when assessed at any timepoint from two months after vaccination. Evaluation of acquisition of serogroups CWY and serogroup Y carriage suggests that the lower carriage rates result mainly from reduction in acquisition rather than increased carriage clearance among vaccinated individuals compared with controls. This is expected and consistent with results from other carriage studies where impact on acquisition is thought to be the mechanism by which vaccine-induced responses may impact on overall carriage. Reduction in carriage has been observed with a range of glycoconjugate vaccines including different pneumococcal vaccines, serogroup A and C meningococcal vaccines, and a *Haemophilus influenzae* type b vaccine (Hib).[18,22–27]

Similarly, although 4CMenB vaccination did not result in a significant reduction in carriage prevalence for capsB one month after vaccination, significant differences in carriage of *N meningitidis*, capsBCWY, capsCWY, serogroups CWY, capsY, and serogroup Y (18·2–29·6% carriage reduction) were observed when assessed at any timepoint from three months after second vaccination. Evaluations of impact of 4CMenB on specific STs associated with serogroup B (e.g., ST-41/44, ST32, ST269) did not reveal differences between groups although numbers of isolates were very small, which limits interpretation (data not shown). Whilst the effect of 4CMenB on disease–associated meningococci may contribute to herd protection, the potential broad additional effect on commensal *Neisseria* and non-disease-associated *N meningitidis*

cannot be predicted. Significant effects on carriage were observed both across the whole student population and also across sub-populations where acquisition rates are known to be highest, such as in smokers, early enrollers and younger students.

In 1999 the UK introduced MenC conjugate vaccination to all persons younger than 18 years, rapidly achieving a high coverage rate. Based on analyses of disease rates in unvaccinated 15–17 year olds before and after vaccine introduction, herd protection was quantified at 67% after one year,[28] increasing to 75% after two years, with an observed disproportionately high impact on carriage of the genotype associated with the UK epidemic in the 1990s.[18] Although the observed carriage impact in the present study appears modest, in the setting of a pathogen such as *N meningitidis*, with a relatively low estimated basic reproduction number (R0 ~ 1·36),[29] even a modest individual carriage impact may translate into a significant level of herd protection.

There are some limitations to the work described here. There was limited new acquisition of meningococcal strains, and in particular capsB strains, across the one year of study follow-up. It is generally agreed that glycoconjugate vaccines impact carriage through decreasing new acquisition and not eliminating existing carriage. As 4CMenB is a two-dose series and the highest acquisition was observed between the first two study visits, and because enrolment took place over a three month period, vaccines may have been administered too late to observe a maximal impact. Carriage among the university students in our study is consistent with others, with a peak during the late teenage years.[4] Thus, for greatest impact, a vaccine

programme might be initiated among early teens rather than university students as in this study.

We observed that both 4CMenB and MenACWY-CRM were generally well-tolerated, with no indications of safety concerns. While reactogenicity following any vaccination was overall higher in the 4CMenB group, the incidence of unsolicited AEs was similar across groups throughout the study period. Moreover, the rates of SAEs were low and similar across all vaccine groups.

In summary, results from pre-specified secondary analyses of this study support the conclusion that both MenACWY-CRM and 4CMenB have an impact on carriage and could provide a degree of herd protection against meningococcal disease if implemented in a campaign targeting a population (e.g., adolescents) where high transmission is known to occur. Although the study was not designed to provide precise estimates of herd protection, an estimate of individual carriage impact of 27% for 4CMenB (based on data from capsBCWY) and 36% for MenACWY-CRM (based on data from serogroup CWY) assumptions can be made; the impact of 4CMenB on capsB strains is less clear. An appropriate translation of this individual carriage impact estimate into herd protection will likely only be available after implementation of large scale vaccination programmes.

Panel: **Research in Context**

Systematic review

In addition to direct protection, the ability of a meningococcal vaccine to impact colonization and transmission of meningococci and, in turn, to provide indirect protective effects through herd protection, has important implications for evaluating the population impact and cost effective benefit of the vaccine. We searched PubMed with the MeSH terms “Neisseria” AND “vaccine” AND “randomized controlled trial” AND “impact” OR “evaluation” OR “effectiveness” to find papers published between 1970 (when meningococcal polysaccharides vaccines were first investigated) and March 19th 2014, that reported randomised controlled trials which investigated oropharyngeal carriage in human recipients of meningococcal vaccines. We searched Web of Science for articles that cited selected references. No such randomised controlled trials were identified, and no studies have previously investigated the effect of non-polysaccharide vaccines on meningococcal colonisation. Incorporation of monovalent meningococcal conjugate vaccines against serogroup C and serogroup A in mass vaccination programmes in the United Kingdom and sub-Saharan Africa, respectively, has resulted in significant reduction of cross-sectional pharyngeal carriage rates of the respective serogroup in those targeted populations;[18,27,28,30] however, the impact of vaccination with a quadrivalent meningococcal vaccine or a protein-based meningococcal vaccine such as 4CMenB on pharyngeal meningococcal carriage has not yet been clinically evaluated .[5, 10]

Interpretation

This is the first randomised controlled trial of oropharyngeal carriage rates of *Neisseria meningitidis* after meningococcal vaccination. These data suggest that 4CMenB or MenACWY-CRM are likely to provide individual protection against the acquisition of carriage of meningococci when evaluated over a broad time window after vaccination, and the scale of the effect can be used to aid in estimates of cost-effectiveness. This study was conducted in the United Kingdom in a population sub-group – young adults – with high rates of carriage and transmission, in order to provide a “proof of principle” that these

vaccines may provide herd protection, and data to guide implementation decisions wherever they may be made.

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Author contributions

RCR, R Borrow, and PMD conceived of and designed the study. RCR, DB, DRC, SNF, AF, SBG, PTH, DJML, AJP, DPJT, R Baziz, AG, TH, KRN, IOO, BM-A, KP, MDS, JW, SG, SJG, and MCJM conducted the study. All authors participated in the acquisition, analysis, and interpretation of the data. HW provided statistical evaluation. All authors reviewed and approved the final version for submission.

Declarations of interest

DT, HW, MM, and PMD are permanent employees of NVS. All other authors acted as chief or principal investigators for this NVS-sponsored trial conducted on behalf of their respective NHS Trusts and/or Universities, but received no personal payments from NVS for study conduct. RCR reports speaker fees and travel assistance from NVS to attend a meeting, outside the submitted work. SNF reports honoraria from NVS, Pfizer and Sanofi to attend conferences, paid to his

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Table 1: **Demographics, baseline characteristics and carriage**

	4CMenB N=979	MenACWY-CRM N=988	Control N=987	Total N=2968[†]
Age (Years±SD)	19·9±1·6 (N=977)	19·9±1·6	19·8±1·6	19·9±1·6 (N=2966)
Males, n (%)	463 (47)	455 (46)	440 (45)	1369 (46)
Caucasian, n (%)	860 (88)	876 (89)	866 (88)	2610 (88)
Weight (kg±SD)	69·7±13·2 (n=973)	68·8±13·4 (n=985)	69·2±13·5 (n=986)	69·2±13·4 (n=2950)
Height (cm±SD)	172·6±9·4 (n=974)	172·5±9·4 (n=987)	172·0±9·4 (n=986)	172·4±9·4 (n=2953)
Smokers, n/N (%)*	159/974 (16)	161/983 (16)	143/984 (15)	463/2941 (16)
Carriage, n (%)	N=976	N=984	N=986	N=2946
N meningitidis	326 (33)	334 (34)	303 (31)	963 (33)
A (serogroupable)	0 (0)	0 (0)	0 (0)	0 (0)
B (all)	92 (9)	100 (10)	86 (9)	278 (9)
B (disease-associated)	78 (8)	84 (9)	72 (7)	234 (8)
B (all serogroupable)	66 (7)	73 (7)	57 (6)	196 (7)
C (all)	3 (0)	3 (0)	3 (0)	9 (0)
C (serogroupable)	1 (0)	1 (0)	0 (0)	2 (0)
W (all)	20 (2)	20 (2)	10 (1)	50 (2)
W (serogroupable)	15 (2)	15 (2)	4 (0)	34 (1)
Y (all)	70 (7)	67 (7)	68 (7)	205 (7)
Y (serogroupable)	54 (6)	42 (4)	45 (5)	141 (5)
CWY (all)	93 (10)	90 (9)	81 (8)	264 (9)
CWY (serogroupable)	70 (7)	58 (6)	49 (5)	177 (6)
N lactamica	7 (1)	5 (1)	5 (1)	17 (1)

*Number and percentage of smokers are from Day 1 visit. †Total includes the 14 enrolled subjects who were not randomised; the number of subjects for each site were as follows: Univ. of Sheffield Medical School (n=826); St. Georges Hospital (n=156); Nottingham University Hospital / NHS (n=319); Oxford Vaccine Group (n=263); South Tees Hospital Foundation (n=121); University of Manchester (n=255); Liverpool School of Tropical Medicine (n=501); University of Southampton (n=308); North Bristol NHS Trust (n=206); University of Surrey (n=13).

Table 2: **Pharyngeal carriage prevalence of disease-associated STs of capsB in 4CMenB and control groups and serogroups A, C, W or Y (combined) of *N meningitidis* in MenACWY-CRM and control groups (primary endpoints; MITT Population)**

	Percentage of subjects with carriage n/N (%; 95% CI)		Group difference % (95% CI)*	OR (95% CI)	Carriage Reduction,† % (95% CI)
	4CMenB (N=974)	**Control (N=984)**			
Day 1 (Baseline)	78/974 (8; 6–10)	72/984 (7; 6–9)	0.6 (−1·6–2·7)	NA	NA
1 month after 2nd vaccination	87/916 (9; 8–12)	75/928 (8; 6–10)	1·0 (−1·5–3·5)	1·2 (0·8–1·7)	−18·2 (−73·3–19·4)
	MenACWY-CRM (N=981)	**Control (N=984)**			
Day 1 (Baseline)	58/981 (6; 5–8)	49/984 (5; 4–7)	0 (−0·4–0·4)	NA	NA
1 month after vaccination	57/956 (6; 5–8)	58/947 (6; 5–8)	−1 (−2·8–0·8)	0·9 (0·6–1·3)	10·5 (−34·2–40·3)

*Vaccine group differences in proportions between vaccine and control groups were analyzed by using Pearson's chi-square test or Fisher's exact test where appropriate with center and treatment group in the model.

†Carriage Reduction = 100 × (1-OR)

NA=Not applicable

Table 3: **Odds Ratios (GEE model) for carriage prevalence of *N meningitidis* in 4CMenB and control groups at any timepoint from three months after second vaccination (visits 4 to 6) – MITT population**

	Percentage of positive samples, n (%)		OR (95% CI)	Carriage Reduction,[†] % (95% CI)
	4CMenB N=2489	**Control** N=2576		
All STs of capsB	233 (9·4)	262 (10·2)	0·8 (0·6–1·1)	15·6% (−11·0–35·9)
Disease-associated STs of capsB	214 (8·6)	237 (9·2)	0·9 (0·7–1·2)	12·6% (−15·9–34·1)
All *N meningitidis*	797 (32·0)	885 (34·4)	0·8 (0.7–1.0)	18·2% (3.4–30.8)
Capsular groups BCWY	449 (18·0)	539 (20·9)	0·7 (0·6–0·9)	26·6% (10·5–39·9)
Capsular groups CWY	216 (8·7)	277 (10·8)	0·7 (0·5–0·9)	29·6% (8·1–46·0)
Serogroups CWY	149 (6)	186 (7·2)	0·7 (0·5–1.0)	28·5% (2·8–47·5)
Capsular Y	178 (7·2)	228 (8·9)	0·7 (0·6–1·0)	25·1% (−0·2–44·0)
Serogroup Y	128 (5·1)	161 (6·3)	0·7 (0·5–1·0)	28·2% (−0·1–48·4)

"N" given for GEE results refers to total number of swab samples across visits.
OR and Carriage Reduction adjusted by treatment group, baseline status, and significant risk factors as identified within the multivariate model
[†]Carriage Reduction = 100 × (1-OR).

Table 4: **Percentage of subjects with new acquisition of pharyngeal carriage at 3, 5 or 11 months post second vaccination with 4CMenB versus controls (Pharyngeal carriage; subjects with all 6 swabs)**

	Percentage of subjects with carriage n/N (%; 95% CI)		Difference between Vaccine Groups (95% CI)	Odds Ratio (95%CI)	Carriage Reduction, % (95% CI)
	4CMenB	**Control**	**4CMenB**		
Any *N meningitidis*	105/410 (26; 21–30)	140/452 (31; 27–35)	−5% (−11%–1%)	0·8 (0·6–1·1)	22·3% (−5·2%–42·6%)
Capsular groups, BCWY	74/519 (14; 11–18)	91/551 (17; 14–20)	−2% (−7%–2%)	0·8 (0·6–1·2)	15·9% (−17·3%–39·8%)
All capsB	34/628 (5; 4–7)	50/674 (7; 6–10)	−2% (−5%–1%)	0·7 (0·5–1·1)	28·6% (−12·0%–54·4%)
Disease-associated capsB	34/638 (5; 4–7)	44/686 (6; 5–9)	−1% (−4%–1%)	0·8 (0·5–1·3)	17·9% (−30·3%–48·2%)

OR and Carriage Reduction adjusted by treatment group, baseline status, and significant risk factors as identified within the multivariate model

Table 5: **Odds Ratios (GEE Model) for carriage prevalence of *N meningitidis* in MenACWY-CRM and control groups at any timepoint after two months of one vaccine dose (Visits 3 to 6) (MITT Population)**

	Percentage of positive samples		OR (95% CI)	Carriage Reduction, % (95% CI)
	MenACWY-CRM n (%) N=3520	Control n (%) N=3504		
Capsular CWY	333 (9·5)	388 (11·1)	0·7 (0·6–0·9)	27·1 (6·9–42·9)
Serogroups CWY	193 (5·5)	260 (7·4)	0·6 (0·5–0·8)	36·2 (15·6–51·7)
Capsular Y	261 (7·4)	325 (9·3)	0·7 (0·6–1·0)	26·5 (4·1–43·7)
Serogroup Y	157 (4·5)	227 (6·5)	0·6 (0·5–0·8)	39·0 (17·3–55·0)

"N" given for GEE results refers to total number of swab samples across visits.
OR and Carriage Reduction adjusted by treatment group, baseline status, and significant risk factors as identified within the multivariate model

Table 6: **Percentage of subjects with new acquisition of pharyngeal carriage at 2, 4, 6 or 12 months post first dose/1, 3, 5 or 11 months post second vaccination with MenACWY-CRM versus controls (Pharyngeal carriage; subjects with all 6 swabs)**

	Percentage of subjects with carriage n/N (%; 95% CI)		Difference between Vaccine Groups (95% CI)	Odds Ratio (95%CI)	Carriage Reduction
	MenACWY-CRM	Control			
Serogroups CWY	59/712 (8; 6-11)	68/709 (10; 8-12)	−1% (−4%-2%)	0·9 (0·6-1·2)	14·8% (−22·7%-40·9%)
Serogroup Y	47/730 (6; 5-8)	59/719 (8; 6-10)	−2% (−5%-1%)	0·8 (0·5-1·2)	23·0% (−14·6%-48·3%)

OR and Carriage Reduction adjusted by treatment group, baseline status, and significant risk factors as identified within the multivariate model