FINAL CLINICAL STUDY REPORT

A single centre, open-label, randomised clinical trial to investigate meningococcal serogroup A, C, W-135 and Y saccharide specific B cell response to a primary and a booster dose of the meningococcal ACWY conjugate vaccine and to a primary dose of the ACWY polysaccharide vaccine followed by a booster dose of the meningococcal ACWY conjugate vaccine administered to adult volunteers

Protocol Number:	OVG 2007/04
Ethics Approval:	Oxfordshire Research Ethics Committee OxREC Ref: 09/H0606/20
Investigational products:	**Menveo** –*Neisseria meningitidis* serogroups A, C,W &Y conjugate vaccine containing meningococcal serogroups A,C,W &Y polysaccharides conjugated to CRM_{197} Manufactured by: Novartis Vaccines, PL 10592/0217, First authorisation 19/12/2005 **ACWYVax** - *Neisseria meningitidis* serogroups A, C,W &Y polysaccharide vaccine containing meningococcal serogroups A,C,W &Y polysaccharides Manufactured by: GlaxoSmithKline, PL 10592/0301, Renewal of authorisation 23/06/2008
Indication:	Prophylaxis for *N. meningitidis* serogroups A, C, W & Y infection
Sponsor	University of Oxford
Developmental Phase:	Phase III
Study Initiation Date:	02/04/2009
Study Completion Date:	26/10/2010
Investigator:	Professor Andrew Pollard
Date of the report:	20/04/2012
Author of the report:	Dr Maheshi Ramasamy

Contents

1. List of Abbreviations, and Definitions of Terms

Abbreviation	Definition
AE	adverse event
ANCOVA	Analysis of covariance
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine
cDNA	complementary deoxyribonucleic acid
CI	Confidence interval
CRF	case report form
ELISA	enzyme-linked immunosorbent assay
ELISpot	Enzyme linked immunosorbant spot assay
FDC	Follicular dendritic cells
FOB	Follicular B cells
GCP	Good Clinical Practice
GMC	Geometric mean count
GMT	Geometric mean titre
GP	General Practitioner
GSK	Glaxo Smith Kline (UK)
Hib	*Haemophilus influenzae* type b
HIV	Human immunodeficiency virus
hSBA	human complement serum bactericidal activity
ICH	International Conference on Harmonization
Ig(G,M,A,D)	Immunoglobulin (G,M,A,D)
IgG	immunoglobulin class G
IM	intramuscular(ly)
ITT	intention to treat
MBC	Memory B cell
Men(A,C,W,Y)	Neisseria meningitidis serogroup A,C,W,Y
MenACWY-CRM	Protein–polysaccharide conjugate meningococcal A, C, W-135 and Y vaccine
MenACWY-PS	Plain polysaccharide meningococcal A, C, W-135 and Y vaccine
mL	millilitre
mL	Millilitre
mRNA	messenger ribonucleic acid
non-CTIMP	non-clinical trials of an investigational medicinal product
OVG	Oxford Vaccine Group
OxREC	Oxfordshire Research Ethics Committee

PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PIIL	Paediatric Infection & Immunity Laboratory
PP	Per-protocol
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SBA	Serum bactericidal activity
SD	Standard deviation
TD	Thymus dependent
TI	Thymus independent
TLR	Toll-like receptors

2. Study administrative structure

2.1. Principal investigator

Andrew J Pollard FRCPCH PhD,
Professor of Paediatric Infection & Immunity
University of Oxford,
Oxford, United Kingdom

2.2. Study Site

Oxford Vaccine Group,
Department of Paediatrics, University of Oxford
Centre for Vaccinology and Tropical Medicine,
Churchill Hospital, Old Road, Headington,
Oxford, United Kingdom

2.3. Staff involved in the conduct of the study

The trial was administered by employees of The Oxford Vaccine Group, Department of Paediatrics, University of Oxford. Study monitoring was administered by employees of the Oxford Vaccine Group, Department of Paediatrics, University of Oxford.

Monitors examined the study files on a periodic basis and performed verification of source documentation for each participant.

Table 1 lists persons whose participation materially affected the conduct of the study.

Table 1 Staff and Responsibilities

Activity	**Name**
Principle Investigator	Prof Andrew Pollard
Investigators	Dr Matthew Snape, Dr Dominic Kelly
Study Monitors	Rebecca Beckley, Emma Godfrey, Simon Kerridge
Laboratory Assays	Dr Maheshi Ramasamy, Dr Elizabeth Clutterbuck, Jaclyn Barel, Amber Thompson
Research Doctors	Dr Maheshi Ramasamy, Dr Theresa Nickells
Research Nurses	Mushiya Mpelembue, Kathryn Haworth
Clinical Trials Assistants	Emma Godfrey, Rebecca Beckley
Administration	Shirley Ashmore, Saima Khalid

Table 2 lists the laboratories which performed immunological assays for the study.

Table 2 Central Laboratories for Immunological Assays

Immunological Assay	**Central Laboratory**
Serum Bactericidal Assay	Novartis Vaccines & Diagnostics Emil-von-Behring-Staβe 76 35041 Marburg Germany
Serum separation, ELISpot, cDNA preparation	Paediatric Infection and Immunity Laboratory Centre for Clinical Vaccinology and Tropical Medicine Churchill Hospital Oxford, UK
Parallel sequencing	Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge. CB10 1SA UK

3. Protocol synopsis

Neisseria meningitidis is a globally important cause of meningitis and septicaemia. The primary approach to the control of meningococcal disease remains effective vaccination programmes in susceptible populations. In the absence of a serogroup B vaccine, quadrivalent vaccines against serogroups ACW-135 and Y offer the broadest possible protection against meningococci. Protection induced by these vaccines relies on anti-capsular polysaccharide antibodies.

Polysaccharide ACWY vaccines consist of pure capsular polysaccharide from each of the four serogroups and have been in widespread use since the late 1970's. However, polysaccharide vaccines are poorly immunogenic in young children, have no effect on carriage and do not provoke long lasting immune response[1]. Newer conjugate vaccines consist of capsular oligosaccharides chemically linked to a protein carrier. Conjugation of a polysaccharide to a protein carrier allows the recruitment of cognate T cell help with subsequent exposure to antigen provoking a potentiated antibody response and immunological memory. This study compared the immune responses to a quadrivalent ACWY polysaccharide vaccine (MenACWY-PS), and a quadrivalent ACWY conjugate vaccine (MenACWY-CRM) containing capsular oligosaccharides of serogroups A, C ,W-135 & Y conjugated to a CRM_{197} mutant diphtheria toxoid carrier.

Persistent functional antibody is thought to be pivotal in immunity against disease caused by potentially rapidly invasive meningococci. As free antibody has a half-life of 3 weeks[2], persistent antibody levels must be maintained by continuous secretion from plasma cells. Long-lived plasma cells have been demonstrated in mice but not humans[3]. However, memory B cells have been shown to persist in humans for years after antigen exposure[4]. An alternative explanation for antibody persistence is that plasma cells are constantly generated from existing antigen specific memory B cells. Meningococcal-specific of functional antibody and the degree of the booster response up to one year later[5]. Also, a prior study has shown that conjugate serogroup C vaccination induces persisting memory cells in infants in contrast to serogroups C polysaccharide[6]. Quantification of the memory and plasma cell responses, alongside SBAs, to MenACWY-PS and MenACWY-CRM may provide important information as to which vaccine generates long term protection.

Vaccine-induced hyporesponsiveness is the inability to mount a booster response of at least the same magnitude as that produced to the priming dose. Previous vaccination meningococcal polysaccharide vaccine has been shown to impair antibody responses to subsequent meningococcal polysaccharide[7,8] or conjugate vaccines[9] . The design of the clinical trial allows investigation of the phenomenon of polysaccharide induced hyporesponsiveness in quadrivalent meningococcal vaccines at the level of memory B cell and plasma cell responses.

Serogroup A meningococcal capsules are chemically distinct from those of the other serogroups. Plain serogroup A polysaccharide vaccines show unexpected immunogenicity in young infants[10,11] The trial investigates whether group A polysaccharides are handled by the immune system in the same way as other serogroup polysaccharides.

Previous studies have shown that the human humoral response to specific antigens is restricted in diversity within the individual and across populations with a limited number of antibody encoding variable region genes being utilised.[12,13] A new technology ('parallel sequencing') permits the assessment of large numbers of gene sequences in short periods of time from a single sample. This study will investigate the antibody genes used in defined populations of B cells in response to conjugate and polysaccharide vaccines.

4. Study Design

Participants were randomised on a 1:1 basis to receive either two doses of MenACWY-CRM conjugate one month apart (Group I), or a single dose of MenACWY-PS polysaccharide followed by a dose of MenACWY-CRM conjugate one month later (Group II). An overview of the study design is shown in **Table 3** below.

Table 3 Overview of study design

	V1 Day 0	**V2 Day 7**	**V3 Day 28**	**V4 Day 35 (V3+7)**	**V5 Day 56 (V3+28)**
Group I 75 participants	MenACWY-CRM conjugate		MenACWY-CRM conjugate		
Group II 75 participants	MenACWY-PS polysaccharide		MenACWY-CRM conjugate		
Assays	SBA Memory BC	SBA Plasma cells	SBA Memory BC	SBA Plasma cells	SBA Memory BC

5. Ethical conduct of the study

5.1. Ethics Committee

Prior to study commencement, the Investigator provided the Oxfordshire Research Ethics Committee C and the Sponsor with all appropriate material, including the protocol, informed consent form, other written participant information and advertising material. The trial was only initiated once written OxREC C approval had been received by the Investigator and Sponsor. The Investigator submitted all subsequent protocol amendments to the OxREC C and the Sponsor.

5.2. GCP compliance

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004), in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 and regulatory requirements in accordance with the United Kingdom's MHRA Medicines for Human Use (Clinical Trials) Regulations, 2004.

The study was conducted in accordance with procedures identified in the protocol which was reviewed and approved by the OxREC. The study was conducted by scientifically and medically qualified persons. Standard Operating Procedure (SOPs) were used at all clinical and laboratory sites. Regular monitoring was performed according to ICH GCP. Following written SOPs, the monitors verified that the clinical trial was conducted and data generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The Investigator site provided direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

5.3. Subject Information and Consent

Written informed consent, in accordance with the principles of the Declaration of Helsinki, ICH-GCP, and applicable UK regulations, was obtained from each participant prior to entering the participant into the trial. A copy of the signed informed consent form was provided to the participant and a copy was kept by the Investigator in the participant's clinical trial record.

The Investigator ensured that the participant's anonymity was maintained. The participant was identified only by initials and a participant's ID (enrolment) number on the CRF. All documents are being stored securely and kept in strict confidence in compliance with the Data Protection Act.

6. Regulatory approval

Initial approval was obtained from OXREC C on 2nd April 2009. An overview of subsequent substantial amendments is listed in Table 4 below.

Table 4 Overview of substantial amendments to the study protocol

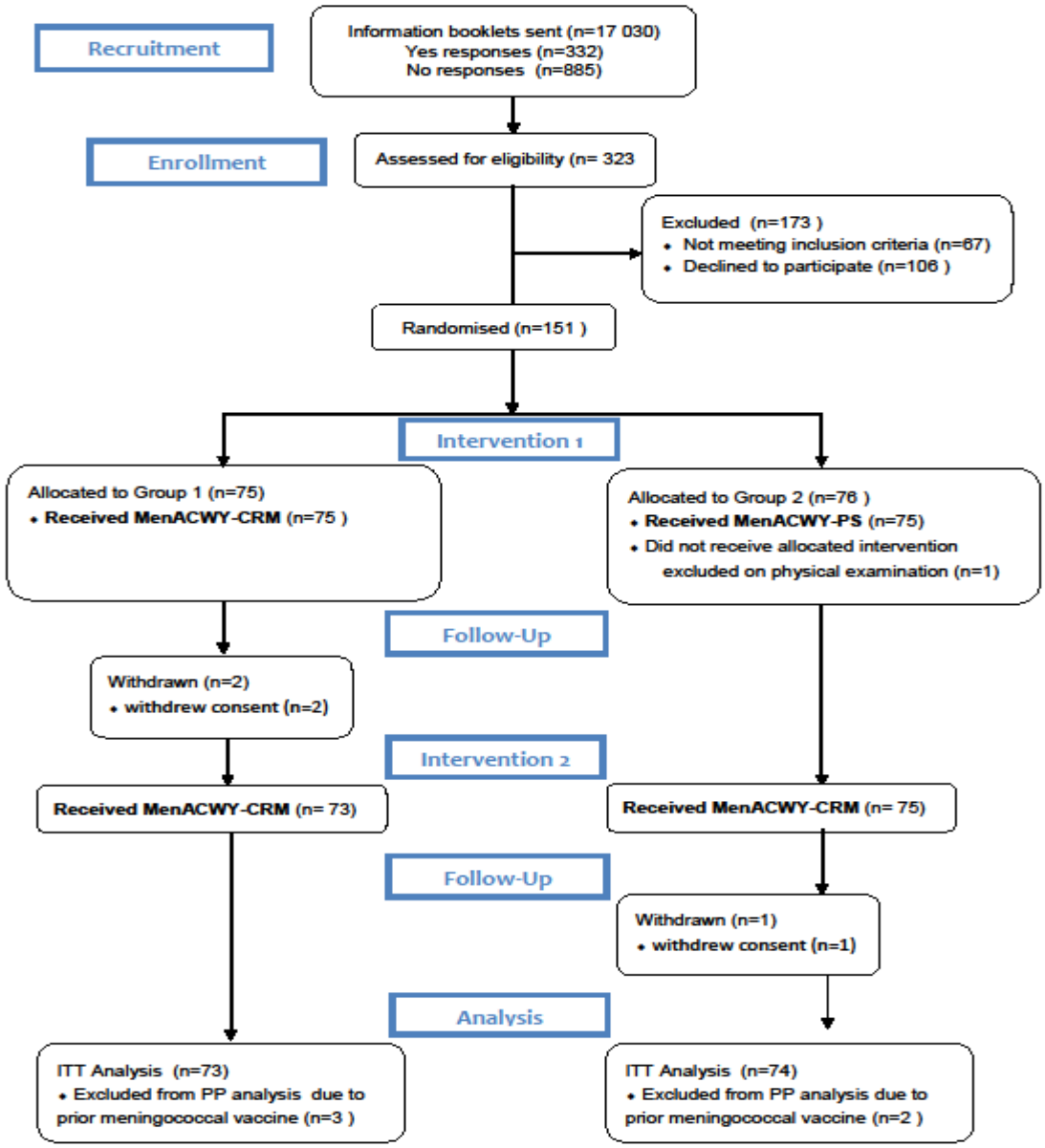
Amendment number	Date of submission	Summary of amendment	Date of approval
1	22nd April 2009	breast-feeding included as an exclusion criterion	20th May 2009
2	8th May 2009	updated study timelines, formal confirmation of prior vaccination status with participants' GPs and a broader recruitment strategy	18th June 2009
3	17th September 2009	broader recruitment strategy and updated study timelines	5th December 2009
4	26th November 2009	increase in the upper age limit of participants and a planned interim analysis	16th December 2009
5	7th July 2010	licensure of the IMP Menveo and updated travel immunisation advice to participants	6th August 2010

7. Study participants

7.1. Recruitment

Recruitment for the study occurred between June 2009 and October 2010. The positive response rate was 2% and the exclusion rate was 21%. The main reason for exclusion was prior receipt of a meningococcal vaccine. The flow of participants through the study is shown in **Figure 1** below.

Figure 1 CONSORT diagram of flow of participants through study



7.2. Participant characteristics

The baseline characteristics of the participants are shown in **Table 5** below.

Table 5 Baseline characteristics of study participants

	Group 1	Group 2
Mean age in years (range)	50.9 (28-70)	49.5 (23-70)
Sex %female	64%	49%
Number of participants	75	75

8. Eligibility criteria

8.1. Inclusion Criteria:

The participants satisfied all the following criteria to be eligible for the study:

- Willing and able to give informed consent for participation after the nature of the study has been explained
- Male or Female, aged 18- 70 years inclusive
- In good health as determined by: medical history, history-directed physical examination and clinical judgment of the investigator
- Female participants of child bearing potential must be willing to ensure that they or their partner use effective contraception during the study and for 3 months thereafter
- Able (in the Investigator's opinion) and willing to comply with all study requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study.

8.2. Exclusion Criteria:

The participant could not enter the study if ANY of the following applied:

- Are unwilling or unable to give written informed consent to participate in the study;
- Have previously received any meningococcal vaccine
- Have previously been diagnosed with laboratory confirmed meningococcal disease;
- Have a history of any anaphylactic shock, asthma, urticaria or other allergic reaction after previous vaccinations or known hypersensitivity to any vaccine component;
- Have a known or suspected autoimmune disease or impairment /alteration of immune function
- Have a suspected or known HIV infection or HIV related disease;
- Have received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months
- Have a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time;
- Have any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives.

- Participation in another clinical trial investigating a vaccine, a drug, a medical device, or a medical procedure
- Pregnancy as confirmed by a positive pregnancy test
- Currently breast-feeding

9. Study vaccines

9.1. MenACWY-CRM Conjugate Vaccine

The investigational Novartis MenACWY Conjugate Vaccine was obtained by extemporaneous mixing just before injection of the lyophilized MenA component to be reconstituted with the MenCWY component. This vaccine was administered intramuscularly. After reconstitution Novartis MenACWY Conjugate Vaccine had the following composition per 0.5 mL of injectable solution:

Name of Ingredients	**Quantity per dose**
MenA-CRM_{197} conjugate	10 µg MenA, 12.5 – 33 µg CRM_{197}
MenC-CRM_{197} conjugate	5 µg MenC, 6.5 – 12.5 µg CRM_{197}
MenW-CRM_{197} conjugate	5 µg MenW, 3.3 – 10 µg CRM_{197}
MenY-CRM_{197} conjugate	5 µg MenY, 3.3 – 10 µg CRM_{197}
Sodium chloride	4.5 mg
Sucrose	12.5 mg
Sodium phosphate buffer	10 mM
Potassium dihydrogen phosphate	5 mM
WFI	Qs to 0.5 mL

Batch MenACWY X79P45I1E was used from 01/06/2009-01/12/2009 and batch MenACWY X79P45I1V was used from 01/12/2009 until the conclusion of the study.

9.2. MenACWY-PS Polysaccharide Vaccine

The ACWY polysaccharide vaccine, ACWY Vax (GSK Vaccines) was obtained by reconstituting the purified ACWY polysaccharides with the 0.5 ml solution. This vaccine was administered subcutaneously. After reconstitution the ACWY polysaccharide vaccine had the following composition per 0.5 mL of injectable solution:

Name of Ingredients	**Quantity per dose**
MenA purified polysaccharide	50 µg
MenC purified polysaccharide	50 µg
MenW purified polysaccharide	50 µg
MenY purified polysaccharide	50 µg

Batch ACWYVax lot A83CA066A was used for the duration of the study

9.3. Vaccine Accountability

The study vaccines MenACWY conjugate were supplied by Novartis Vaccines, in accordance with OVG SOP 001 Version 3 Receiving vaccine supplies. The study vaccine ACWY Vax, manufactured by GlaxoSmithKline, was sourced by the Oxford Vaccine Group from GlaxoSmithKline, UK. The vaccines were stored between +2 and +8°C within the OVG vaccine fridge at the CCVTM in accordance with the manufacturer's instructions and OVG SOP 002 'Clinical Trials Vaccine Storage'. All vaccine doses were accounted for within an accountability log. Unused vaccines were disposed of in accordance with OVG SOP 45 'Disposal of Vaccines' at the end of the trial.

9.4. Compliance with dosing regime

All vaccines were to be administered by the Investigator, recorded in the CRF and verified by a second team member. The study medication was at no time in the possession of the participant and compliance therefore was not an issue.

10. Study Objectives

10.1. Primary Objective

To determine whether meningococcal serogroup A specific serum bactericidal activity (SBA) geometric mean titres (GMTs) are significantly higher at 7 days after immunisation with MenACWY than 7 days after immunisation with MenACWY-PS.

10.2. Secondary Objectives

- To determine whether meningococcal serogroup C, W-135 and Y specific SBA GMTs are significantly higher at 7 days after immunisation with MenACWY than 7 days after immunisation with MenACWY-PS.

- To determine if response to the booster dose of MenACWY is greater than the response to a priming dose of MenACWY conjugate vaccine by comparing specific plasma cells, memory B cells and SBA GMTs 7 or 28 days after the initial dose with results 7 or 28 days after the booster dose (i.e. comparing Day 7 with Day 35 or Day 28 with Day 56 within Group 1 MenACWY conjugate arm only).

- To compare the difference in response to a single dose of MenACWY conjugate vaccine in those who have received a previous dose of MenACWY-PS compared to those who have previously received no vaccine. (e.g. comparing Day 7 in the MenACWY conjugate group to Day 35 in the MenACWY-PS group and comparing Day 28 in the MenACWY conjugate group to Day 56 in the MenACWY-PS group).

- To compare the results of giving a booster dose of MenACWY conjugate vaccine to adults previously vaccinated with MenACWY-PS compared to those

vaccinated with MenACWY conjugate. (i.e. comparing Day 35 in both groups, and Day 56 in both groups)

- To determine whether the treatment effect (difference between MenACWY and MenACWY-PS) differs according to serogroup – specifically whether the serogroup A component of the vaccine behaves differently to that of the other serogroups (C, W135 and Y) 7 and 28 days after treatment.

- To investigate the effect of genetic polymorphisms on immune response to the MenACWY vaccine.

11. Endpoints and Outcome Measures

11.1. Primary endpoint

Meningococcal serogroup A specific SBA GMTs were measured at Day 7 (Visit 2) following the initial immunisation with MenACWY and MenACWY PS. SBAs were determined using human complement (hSBAs) and were performed at the laboratories of Novartis Vaccines, Marburg.

11.2. Secondary endpoints

- Meningococcal serogroup C, W-135 and Y SBAs were measured at days 0, 7, 28, 35 and 56 following the initial immunisation with MenACWY and MenACWY PS.

- Meningococcal serogroup A, C, W-135 and Y specific memory B cells were measured on days 0, 7, 28, 35 and 56.

- Meningococcal serogroup A, C, W-135 and Y specific plasma cells were measured on days 7 and 35 only.

12. Statistical Methods

Please see Appendix 1 – Statistical Report for an overview of statistical methods.

13. Safety

There were 9 AEs in Group 1 and 11 in Group 2, which are listed in **Table 6**. There was a single SAE in Group 2; a diagnosis of prostate cancer made in a participant who was known to have had a raised prostate specific antigen prior to enrolment in the study.

Table 6 Adverse events by group

Group	Adverse events (AEs)	Group	Adverse events (AEs)
1	Haematuria/Urinary tract infection	**2**	Gynaecomastia
1	Exacerbation of asthma	**2**	Urinary tract infection
1	Plantar fasciitis	**2**	Fracture fibula
1	Influenza	**2**	Coryzal symptoms
1	Mastalgia	**2**	Swollen fingers
1	High fasting blood sugar	**2**	Tiredness
1	Hypoglycaemia	**2**	Eye infection
1	Urinary tract infection	**2**	Tiredness
1	Diverticultis	**2**	Shingles
		2	Osteoarthritis exacerbation
		2	Lip haemangioma
		2	Prostate cancer (SAE)

14. Protocol Deviations

There were a total of 11 protocol violations (7 in Group 1 and 4 in Group 2), related to either prior meningococcal vaccination not disclosed at the time of enrolment or to visits being incorrectly timed for B cell assays. As specified in the protocol, participants were not excluded on account of these protocol violations. The primary objective was assessed using both intention to treat (ITT) and per protocol (PP) analyses. All other comparisons were made using ITT in accordance with the ICH Guidance on Statistical Principles for Clinical Trials.

15. Summary of scientific findings

Immunogenicity of MenACWY-CRM and MenACWY-PS

The primary objective of the study (Section 10.1) was to investigate if serogroup A specific hSBA GMTs were significantly higher 7 days after immunisation with MenACWY-CRM than 7 days after immunisation with MenACWY-PS. As shown in **Figure 1**, there were no statistically significant differences between the conjugate and the polysaccharide groups in meningococcal serogroup A,C, W or Y specific GMTs measured at day 7 with adjustment for baseline values at day 0.

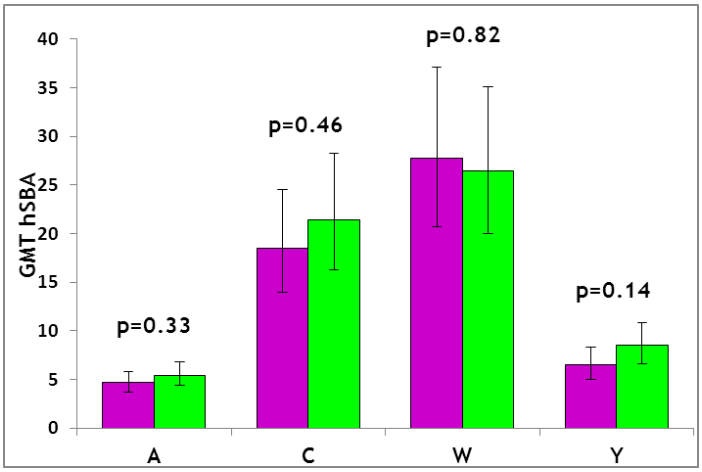


Figure 3 hSBA GMTs & 95% CI 7 days after vaccination with a single dose of conjugate (n=68-72) or a single dose of polysaccharide (n=73-74), ANCOVA with adjustment for baseline values at day 0.

Group 1	conjugate
Group 2	polysaccharide

At 28 days after the initial vaccination, there is a trend towards higher hSBA GMTs in the polysaccharide group to serogroups A , with statistically significant higher titres for serogroup C (**Figure 2**). However, for serogroup W, MenACWY-CRM generates higher SBA tires than MenACWY-PS.

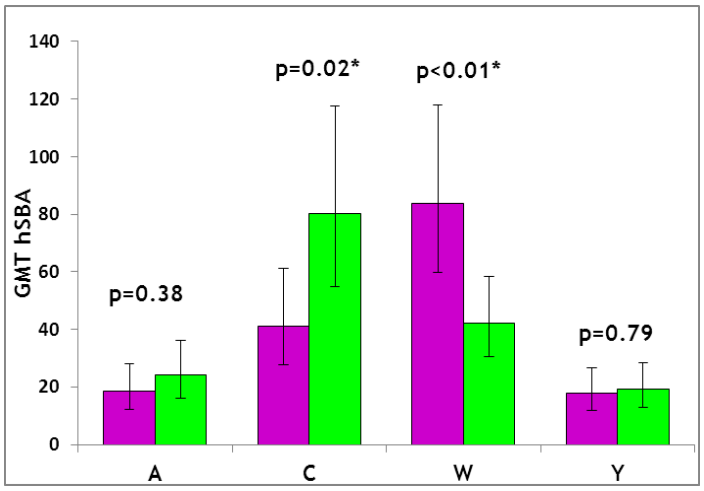


Figure 4 hSBA GMTS & 95%CI 28 days after vaccination with a single dose of conjugate (n=62-66) or a single dose of polysaccharide (n=68-70), ANCOVA with adjustment for baseline values. Note the difference in scale of the y axis from Figure 1.

Group 1	conjugate
Group 2	polysaccharide

Both quadrivalent vaccines are currently licensed in the UK as travel vaccines for individuals travelling to areas at risk of A,C W or Y meningococcal disease[14]. This finding suggests that there is no immediate advantage in using the newer, more expensive conjugate vaccine over the polysaccharide vaccine to provide short-term protection to those traveling to high risk areas at short notice.

15.1. MenACWY-PS induces plasma cells while MenACWY-CRM induces memory B cells

Plasma cell GMCs were compared between Group 1 and 2 at day 7 to assess the response to a single dose of either conjugate or polysaccharide. MenACWY-PS appears to generate a greater plasma cell response at 7 days than MenACWY-CRM across all four serogroups, though this is not statistically significant.

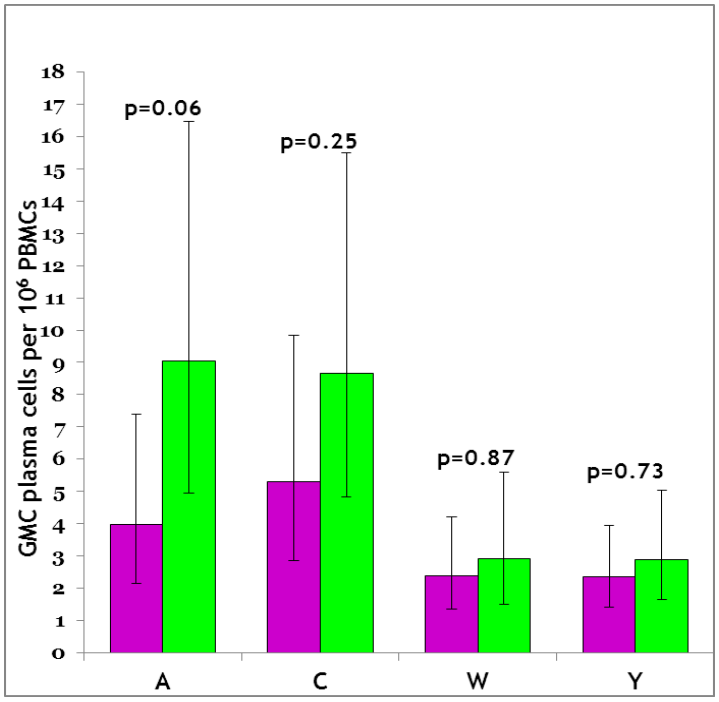


Figure 5 Plasma cell GMC & 95%CI 7 days after vaccination with MenACWY-CRM (n=47) or MenACWY-PS(n=50), independent 2 sample t tests.

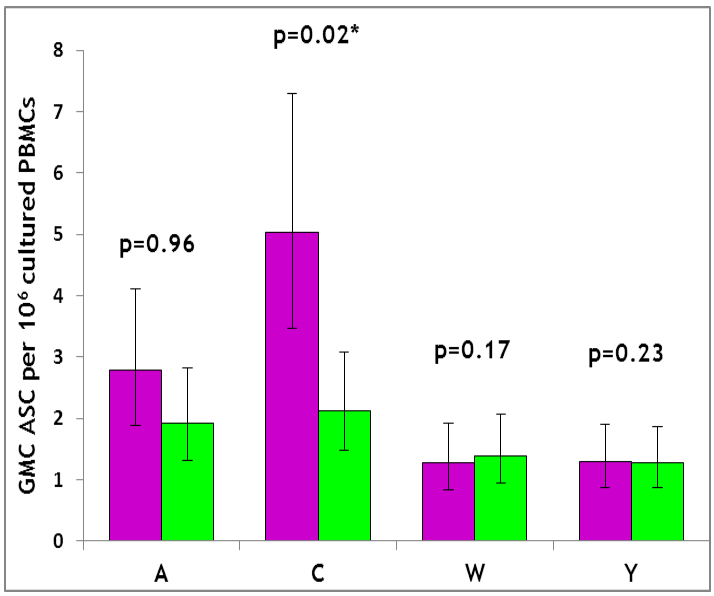


Figure 6 MBC GMCs & 95%CI 28 days after vaccination with a single dose of conjugate (n=49-55) or a single dose of polysaccharide (n=52-57), ANCOVA with adjustment for baseline values at day 0.

In contrast, at day 28, serogroups A & C specific memory B cells showed an increase from baseline in response to MenACWY-CRM (Figure 4). No significant changes were seen in antigen specific memory B cells after MenACWY-PS.

15.2. Prior polysaccharide vaccine causes hyporesponsiveness to subsequent doses of conjugate vaccine

Hyporesponsiveness is defined as an attenuated response to subsequent antigenic challenge. The study showed that prior polysaccharide vaccination inhibited subsequent responses to a conjugate vaccine as measured at both at 7 days (data not shown) and 28 days after the conjugate vaccine. This confirms that MenACWY-PS induces hyporesponsiveness at the functional antibody level.

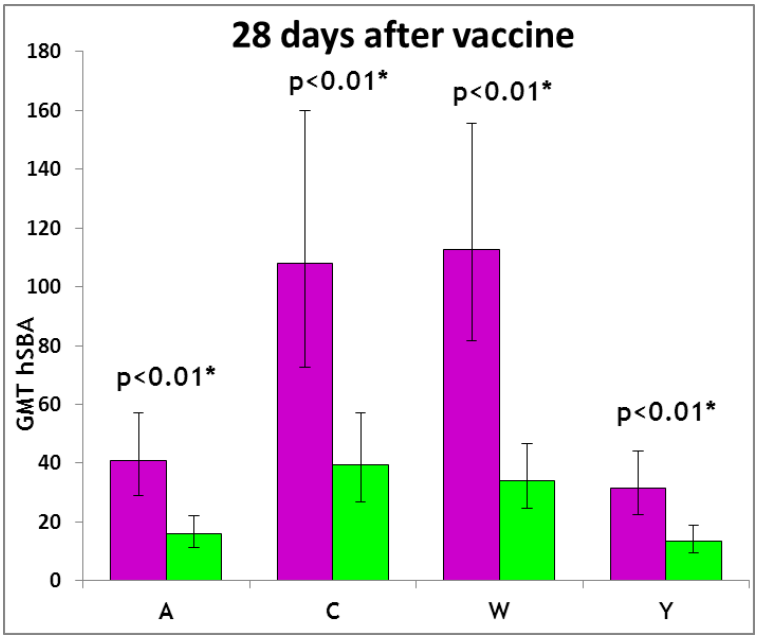


Figure 7 hSBA GMTs & 95% CI 28 days after a dose of MenACWY-CRM conjugate, with or without a prior dose of Men ACWY-PS polysaccharide, ANCOVA with adjustment for baseline pre-conjugate

Group 1	conjugate	
Group 2	polysaccharide	conjugate

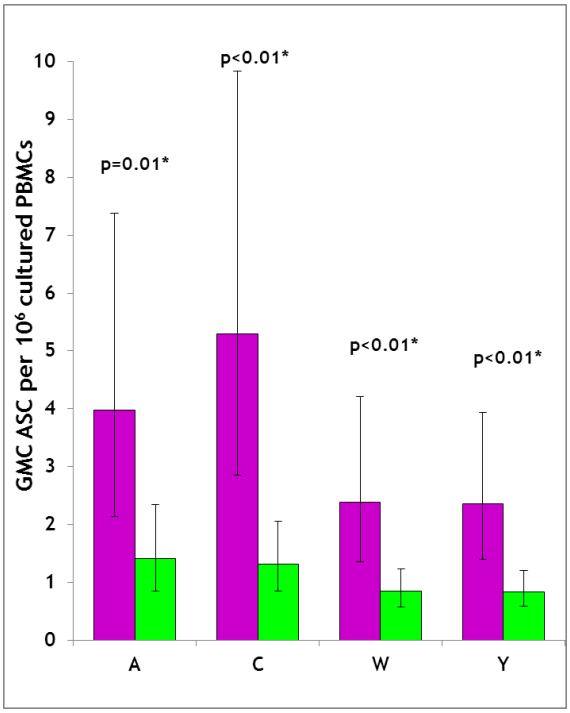


Figure 8 Plasma cell GMC and 95% CI, 7 days after a single dose of conjugate MenACWY-CRM with (N=47) or without (N=47) a prior dose of MenACWY-PS polysaccharide, independent 2 sample t tests

Group 1	conjugate	
Group 2	polysaccharide	conjugate

A between group comparison of plasma cell GMCs at day 35 in Group 2 and day 7 in Group 1 was made to assess the response to a single dose of conjugate, either with (Group 2) or without (Group 1) a prior dose of polysaccharide. This confirmed polysaccharide induced hyporesponsiveness at the plasma cell level

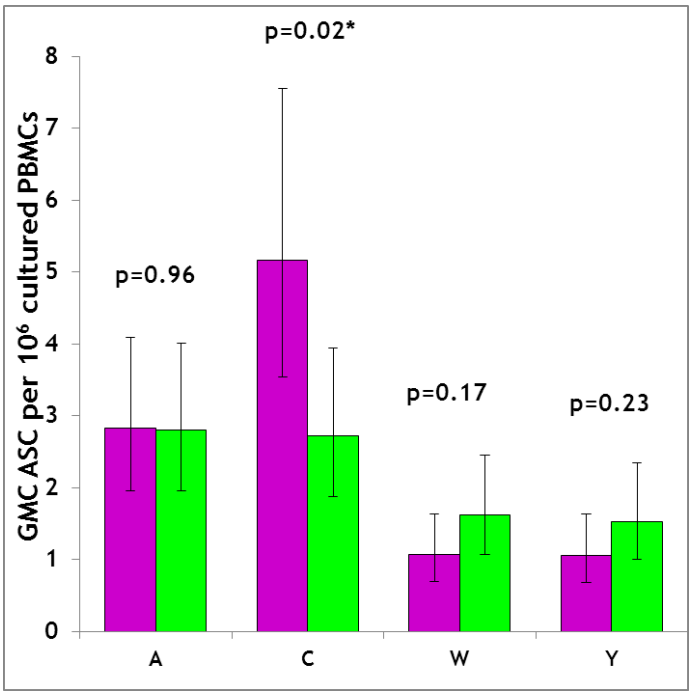
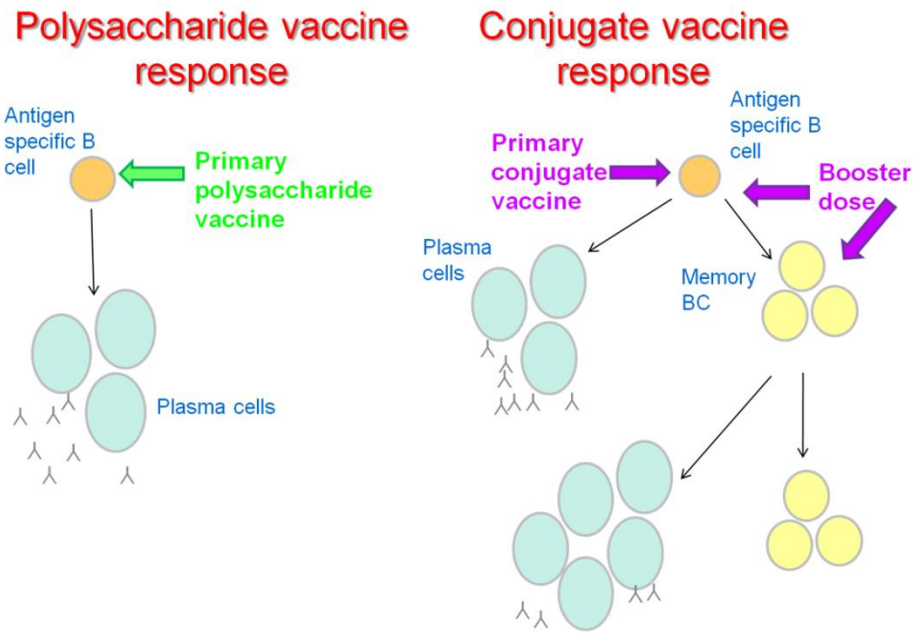


Figure 9 Memory B cell GMC & 95% CI 28 days after a dose of MenACWY-CRM conjugate, with (N=56-58) or without (N=57-58) a prior dose of Men ACWY-PS polysaccharide, ANCOVA with adjustment for baseline pre-conjugate

Hyporesponsiveness at the memory b cell level due to MenACWY-PS was only conclusively demonstrated for serogroup C.

Taken together, these results suggest that prior polysaccharide vaccination impairs the subsequent functional antibody response to conjugate vaccination via memory B cell and plasma cells. This supports the theory that polysaccharide vaccines drive terminal differentiation of pre-existing antigen specific memory B cells into short-lived antibody producing plasma cells without replenishment of the memory cell pool. Thus, subsequent plasma cell responses and the generation of further memory B cells in response to booster vaccine are impaired.

Figure 10 B cell responses to conjugate and polysaccharide vaccines



15.3. Serogroup A

In the various comparisons made across the B cell data, serogroup A does not appear to behave differently from the other three serogroups. This suggests that the Serogroup A component of the MenACWY-PS does act as a classical TI antigen, and not, as has been suggested, as a TD antigen.

15.4. Parallel sequencing

Further optimisation of the methods required for this procedure is ongoing. All remaining cellular samples have had their mRNA extracted and stored to be used in ongoing genetic analysis under the OVG 'Biobank' project (REC 10/H0504/25). This is consistent with the informed consent obtained from each participant at the outset of the study.

16. Discussion

This is the first study to compare MenACWY-CRM with MenACWY-PS, the only quadrivalent polysaccharide vaccine licensed outside of the Americas. The vaccines used in this study were safe, with no SAE's attributable to study vaccines.

Our findings suggest that MenACWY-CRM offers no advantage over MenACWY-PS for short-term immune protection. In addition we have demonstrated that MenACWY-PS induces hyporesponsiveness to a subsequent MenACWY-CRM booster.

Parallel sequencing is an innovative new method for assessing the antibody repertoire to vaccination. However, adapting clinical samples for analysis by this method is complex. Further method development is ongoing.

The functional antibody and B cell data are being prepared for a manuscript. Once this has been accepted by a suitable peer-reviewed journal, a copy of the article along with a covering letter explaining the findings in lay terms will be sent to all participants.

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18. Appendices

18.1. Patient information sheet

18.2. Patient consent form

18.3. Final statistical analysis report