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Safety and immunogenicity of a four-component meningococcal group B vaccine (4CMenB) and a quadrivalent meningococcal group ACWY conjugate vaccine administered concomitantly in healthy laboratory workers

Jamie Findlow[a,*], Xilian Bai[a], Helen Findlow[a], Emma Newton[a], Ed Kaczmarski[a], Elizabeth Miller[b], Ray Borrow[a,c]

[a] Public Health England, Public Health Laboratory, Manchester, Manchester Medical Microbiology Partnership, PO Box 209, Clinical Sciences Building II, Manchester Royal Infirmary, Manchester M13 9WZ, UK
[b] Immunisation Department, Health Protection Services, Public Health England, Colindale, London NW9 5EQ, UK
[c] University of Manchester, Inflammation Sciences Research Group, School of Translational Medicine, Stopford Building, Manchester M13 9PL, UK

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ABSTRACT

Safety precautions for laboratory staff working with meningococci should primarily rely on laboratory procedures preventing exposure to aerosols containing viable meningococci. Despite this, vaccination is a key component of protection in the occupational setting. In the UK in 2009, there were no licensed vaccines for meningococcal capsular group B or conjugate vaccines for capsular groups A, C, W and Y. We therefore undertook a Phase II trial in laboratory workers to investigate the safety and immunogenicity of a four component group B vaccine (4CMenB) and a quadrivalent group A, C, W and Y conjugate vaccine (ACWY-CRM).

Enrolment was open to staff aged 18–65 years at the Public Health Laboratory, Manchester who may have had a potential occupational exposure risk to meningococci. 4CMenB was administered at 0, 2 and 6 months in the non-dominant arm and ACWY-CRM concomitantly at 0 months in the dominant arm. Pre- and post-vaccination blood samples were taken and analysed by the serum bactericidal antibody (SBA) assay against A, C, W and Y strains and a panel of seven diverse group B strains. Diary cards were used to record any local and systemic reactions following each vaccination.

In total, 38 staff were enrolled and received initial vaccinations with 31 completing the trial per protocol. Both vaccines were proven safe, with local reactogenicity being more commonly reported following 4CMenB than ACWY-CRM. High proportions of subjects had putative protective SBA titres pre-vaccination, with 61–84 and 61–87% protected against A, C, W and Y strains and diverse MenB strains, respectively. Post-vaccination, SBA titres increased with 95–100 and 90–100% of subjects with protective SBA titres against A, C, W and Y strains and diverse MenB strains, respectively.

These data suggest that 4CMenB and ACWY-CRM are safe when administered concomitantly and have the potential to enhance protection for laboratory workers.

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1. Introduction

Invasive meningococcal disease (IMD) caused by the Gram-negative bacterium *Neisseria meningitidis* remains a significant cause of morbidity and mortality in many countries. In the general population, the greatest burden of disease is observed in infants, young children and adolescents. Asplenia and complement deficiency are specific risk factors irrespective of age [1]. As transmission of meningococci occurs via the aerosol/respiratory route, laboratory workers handling live meningococcal cultures in clinical, reference or research facilities have a potential occupational exposure risk. This is supported by a number of reports of probable/laboratory acquired cases [2] and a UK study which estimated laboratory workers to have a 184-fold increased risk of acquiring IMD compared to the general population [3].

* Corresponding author. Tel.: +44 0161 701 5303; fax: +44 0161 276 6792.
E-mail addresses: jamie.findlow@phe.gov.uk (J. Findlow), xilian.bai@phe.gov.uk (X. Bai), helen.findlow@phe.gov.uk (H. Findlow), emma.newton@phe.gov.uk (E. Newton), ed.kaczmarski@phe.gov.uk (E. Kaczmarski), elizabeth.miller@phe.gov.uk (E. Miller), ray.borrow@phe.gov.uk (R. Borrow).

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Although protection of laboratory workers from IMD should principally rely on physical control measures to prevent exposure and acquisition [2], vaccination is an important form of defence. In Europe, the first quadrivalent (A, C, W and Y) glycoconjugate vaccine was licensed in 2010 [4] and a vaccine to provide protection against capsular group B strains was licensed in 2013 [5]. It is therefore now possible to implement an occupational vaccination programme designed to achieve protection against the five most prevalent capsular groups: A, B, C, W and Y which collectively account for almost all cases of disease [6]. The potential risk of disease in laboratory workers is longitudinal and therefore booster vaccinations are necessary to sustain protective antibody concentrations. The concern of immunological hyporesponsiveness induced by bivalent (A and C) and quadrivalent (A, C, W and Y) plain polysaccharide vaccines [7–10] has historically, complicated re-vaccination recommendations. The ability of glycoconjugate vaccines such as the monovalent MenC vaccines to overcome and not induce immunological hyporesponsiveness has resulted in these becoming the preferred option in groups requiring repeat vaccination [2].

In 2009, a quadrivalent (A, C, W and Y) glycoconjugate vaccine using a CRM carrier protein (ACWY-CRM) and the four component vaccine for capsular group B strains (4CMenB) were undergoing licensure review and in pre-licensure development, respectively. Both had acceptable safety profiles and proven immunogenicity [1,4]. We therefore undertook a single group phase II trial to evaluate the safety and immunogenicity of a single dose of ACWY-CRM and three 4CMenB doses in staff that may be at potential occupational exposure to meningococci. This trial incorporated the first evaluation of the concomitant administration of ACWY-CRM and 4CMenB and provided the potential of broader protection than that afforded by the vaccination programme in place at that time.

2. Materials and methods

2.1. Study population and schedule

Enrolment into this open-label phase II trial was open to adult (18–65 years of age) laboratory staff from the Public Health Laboratory, Manchester who were considered to be at potential occupational exposure to meningococci and provided written informed consent. Potential occupational exposure was defined as routine handling of live meningococcal cultures, which included both scientific staff and support staff. At enrolment, this incorporated a greater range of staff than were then scheduled to receive occupational meningococcal vaccination which was limited to scientific staff. During the course of this trial, ACWY-CRM gained licensure in Europe [4].

Exclusion criteria included known or suspected pregnancy, serious chronic disease (as evaluated by the trial clinician which would include progressive neurological disease or seizure disorder), bleeding diathesis or any other condition associated with prolonged bleeding time, history of severe allergic reactions after previous vaccinations, hypersensitivity to any vaccine component or receipt of another investigational agent within 90 days prior to enrolment or before completion of safety follow-up period.

MenACWY-CRM (Novartis Vaccines and Diagnostics, Siena, Italy) [4], from a single lot (Lot: X38D28N1Z) and 4CMenB (Novartis Vaccines and Diagnostics) [1], from a single lot (Lot: X79P45I1O) were administered to the deltoid muscle of the non-dominant and dominant arms, respectively at visit 1. Second and third doses of 4CMenB were administered at three and six months, respectively. Vaccination was deferred if the oral temperature measured was >38 °C or if there was acute illness on the day of vaccination. Subsequent immunisations were also delayed if any contradictions specified in the initial exclusion criteria were developed or any convulsions, neurological disturbances experienced following previous doses.

Blood samples were taken before and following each vaccination at months 0 (visit 1), 2 (visit 2), 3 (visit 3), 6 (visit 4) and 7 (visit 5).

2.2. Serology

Serum samples were assayed in the Vaccine Evaluation Unit at the Public Health England (PHE), Manchester, using a multiplexed fluorescent bead assay to quantify IgG antibody concentrations to A, C, W and Y polysaccharides [11]. Functional antibody activity against A, C, W and Y was determined in the serum bactericidal antibody (SBA) assay as previously described [12] utilising target strains presented in Table 1. Baby rabbit sera (Pel-Freeze Incorporated, Rodgerson, AZ, USA) was used as the exogenous complement source (rSBA) as recommended by the World Health Organization [13] in the standardised assay [12]. rSBA titres were expressed as the reciprocal of the final serum dilution giving 50% killing at 60 min. For computational purposes, rSBA titres lower than the serum starting dilution of 4 were assigned a value of 2. As baby rabbit complement is unsuitable for group B target strains, functional antibody activity against seven diverse strains (Table 1) was determined using human serum (Sera Laboratories International Ltd, UK) as the exogenous complement source (hSBA) as previously described [14]. hSBA titres were calculated as rSBA titres, with the exception that titres lower than the serum starting dilution of 2 were assigned a value of 1.

2.3. Correlates of protection

For group C, an rSBA titre of ≥8 is the putative protective titre which was shown to predict short-term clinical protection against disease in the UK [15,16]. The more discriminatory rSBA titre of ≥128 reliably predicts a hSBA titre of ≥4 [16], the accepted hSBA correlate of protection for group B [17,18]. Although an anti-capsular Ig concentration of ≥2 μg/mL has historically been used for group A [19], there are currently no established SBA correlates for groups A, W and Y; therefore, the group C rSBA correlate was applied in line with previous studies [20].

2.4. Safety

Following each vaccination, subjects were monitored for 30 min. Subjects were provided with a ruler and thermometer on enrolment to enable the completion of a health diary, for seven days recording and measuring oral temperature and any local reactions. Any visits to a doctor, systemic reactions (including headache and nausea) or any medication taken were also recorded in the diary. Severe reactions were classified as any local reaction >100 mm and any pain level which resulted in an inability to perform normal daily activities.

2.5. Analyses

All immunogenicity results gained were used in the analysis. For IgG antibody concentrations, geometric mean concentrations (GMCs) with 95% confidence intervals (95% CI) were calculated at each time point. For SBA results, geometric mean titres (GMTs) with 95% CI and proportions of subjects achieving rSBA titres ≥8 and ≥128 and hSBA titres ≥4 were calculated at each time point. Due to the small sample sizes, immunogenicity analysis did not include any formal statistical analysis.