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Safety and immunogenicity of fractional dose intradermal injection of two quadrivalent conjugated meningococcal vaccines

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ABSTRACT

Background: Vaccination with conjugated meningococcal vaccines is the best way to prevent invasive meningococcal disease. Changes in serogroup epidemiology have led to the inclusion of quadrivalent vaccines in the national immunization programs of several countries, but vaccines are frequently in short supply. Intradermal administration has the potential to increase vaccine availability through dose reduction, without sacrificing efficacy. It has never before been investigated for glycoconjugate meningococcal vaccines.

Methods: Different fractional doses of two quadrivalent meningococcal conjugate vaccines (MenACWY-CRM_{197} (Menveo®) and MenACWY-TT (Nimenrix®)) were administered intradermally to sequential groups of 4 participants, according to an adaptive dose escalation design, starting at 1/10th of the original dose. Booster doses were given after 4–6 months based on interim serology results using a multiplex bead-based assay (MIA). Final analyses were based on serum bactericidal antibody titers (rSBA).

Results: A total of 12 subjects were enrolled (average 25 years old, range 19–48). MenACWY-CRM_{197} became unavailable during the course of the study and was only evaluated for a 1/10th dose. This dose resulted in less than complete seroprotection for serogroup A but complete protection against the other serogroups. MenACWY-TT was evaluated for a 1/10th and 1/5th dose level. Both fractional doses of MenACWY-TT resulted in complete seroprotection against all vaccine serogroups. Geometric mean titers 1 month after vaccination were lower and decayed faster in the MenACWY-CRM_{197} group. Adverse events were mild and there were no serious adverse events.

Conclusion: Fractional intradermal vaccination against meningococcal disease with quadrivalent conjugate vaccine appears to be safe and effective in our small dose finding study. Tetanus toxoid conjugated vaccine (Nimenrix®) shows a trend towards higher antibody levels compared to CRM_{197}-conjugated vaccine (Menveo®). The 1/5th fractional dose of MenACWY-TT appears to result in higher antibody levels than does the 1/10th dose. These results can be used for a larger non-inferiority study.

This trial was registered in clinicaltrials.gov under NCT01782066.

1. Introduction

Neisseria meningitidis is a major cause of invasive bacterial infections globally. Virulent strains of *N. meningitidis* have a polysaccharide capsule, which is the major virulence factor for this bacterium. There are 13 diverse polysaccharide capsules, but only A, B, C, W, X and Y commonly cause invasive infections. The polysaccharide capsule of *N. meningitidis* induces a protective antibody response and there is an inverse correlation between the incidence of invasive meningococcal disease and the age-related acquisition of serum bactericidal antibodies [1]. Vaccination is generally accepted as the best way to prevent invasive meningococcal disease caused by serotypes A, C, Y, and W [2]. In recent years, 2 quadrivalent conjugate vaccines (Menveo®, MenACWY-CRM_{197} and Nimenrix®, MenACWY-TT) have been registered in Europe to replace the unconjugated (quadrivalent) polysaccharide vaccine.

Although serogroup A was a common cause of invasive meningococcal disease (IMD) in Europe up to the 1950s, it has now disappeared [3,4]. In 2002, after an outbreak of IMD caused by serogroup C, MenC-TT was added to the Dutch National Immunization Program after a mass vaccination campaign with a coverage of 94%. The decline in serogroup C disease is mainly attributable to the use of conjugated meningococcal group C vaccines [5]. In recent years, the rise of serogroup W from South

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America to the UK and now to the rest of Europe has been the most notable change in European meningococcal epidemiology [6]. This had led several countries to include or consider including a quadrivalent meningococcal vaccine into their national immunization program to replace the meningococcal C vaccines. Recently, the UK and Australia have included a quadrivalent meningococcal vaccine and the UK was the first country to include meningococcal B vaccine (Bexsero®) in the national immunization program [7].

Normally, vaccines are administered into the muscle (intramuscular administration, IM). However, the skin (dermis) contains a much higher density of antigen presenting dendritic cells than does muscle [8]. The skin lymphatic system is extensively organized into several plexus systems, which aids efficient transport of antigen presenting dendritic cells to the regional lymph nodes [9]. As a consequence, a lower vaccine dose introduced directly into the dermis (intradermal administration, ID) might be sufficient to achieve a protective immune response. This principle has already been demonstrated for rabies, yellow fever, inactivated polio and seasonal influenza vaccine [10].

In this dose-finding trial we investigated the safety and immunogenicity of intradermal administration of fractional dose MenACWY-CRM$_{197}$ and MenACWY-TT. It is the first study of intradermal use of a conjugated vaccine.

2. Methods

2.1. Study design

Open-label uncontrolled randomized intervention study. The study was performed with 2 vaccines: MenACWY-CRM$_{197}$ (Menveo®) and MenACWY-TT (Nimenrix®). An adaptive dose escalation rule based on interim analyses of safety and immunogenicity was used to increase the fractional vaccine dosage as the study progressed. A minimum of 8 and a maximum of 16 subjects per vaccine could be included, based on discussions with experts on dose escalation studies. Inclusion started at the fractional 1/10th dose level and dose escalation was limited to a 1/5th fractional dose. Subjects were randomly assigned to dose level and vaccine in groups of 4 subjects each. All subjects followed the same schedule: primary vaccination with a fractional dose and blood sampling on day 0 followed by blood sampling on day 27–29, and after 4–6 months on days 0 and 7 and 27–29 after revaccination. No IM control arm was included because the study was not intended to compare ID administration to IM; the goal was to establish an immunogenic dose that could be assessed against IM administration in a subsequent much larger comparative trial.

Due to insufficient immunogenicity after the highest dose (1/5th fractional dose) according to the interim serological analysis using a multiplex immunoassay (MIA), the study was amended and a booster dose of a single intradermal injection was added with the same fractional dose as previously received by the subject. Because MenACWY-CRM$_{197}$ (Menveo®) became unavailable in the Netherlands during the study, this vaccine was only evaluated in the primary 1/10th dose level. All subjects, including those who initially received MenACWY-CRM$_{197}$ (Menveo®), were boostered with MenACWY-TT (Nimenrix®).

2.2. Vaccination

Two quadrivalent conjugated meningococcal vaccines were used: MenACWY-CRM$_{197}$ (Menveo®, GSK, lot No. M11026) and MenACWY-TT (Nimenrix®, Pfizer, lot No. A90CA001E). Both vaccines consist of capsular oligosaccharides of 4 meningococcal serogroups conjugated to a bacterial carrier protein.

For the 1/5th fractional dose, 0.1 mL of the original vaccine formulation was injected intradermally. Because the quality measures for intradermal vaccination are standardized on a 0.1 mL injectable volume, the 1/10th fractional dose was also administered in a 0.1 mL volume (achieved by adding twice the amount of diluent). The vaccine doses were injected into the skin on the dorsal side of the forearm using disposable Beckton Dickinson U-100 Micro-Fine™ insulin syringes with integrated 29G needle.

2.3. Vaccine safety

Adverse events were solicited for 7 days after primary and booster vaccination using a paper diary provided to each subject. Adverse events were also checked by telephone interview 7 days after the primary vaccination. Furthermore, an independent data and safety monitoring board (DMSB) was established, because this study involved the first trial of intradermal injection of conjugated polysaccharide vaccine. Due to very limited local reactogenicity after primary vaccination, even in those subjects who were seroprotected against MenC at inclusion, the DSMB was discontinued for the booster doses.

2.4. Study population and inclusion criteria

Subjects were recruited through advertisements in Leiden University buildings. Volunteers between 18 and 65 years old were included if they were in good health, willing and able to adhere to the study regimen and provide informed consent. Exclusion criteria were a known previous quadrivalent meningococcal vaccination, previous meningococcal infection, allergy to any of the vaccine components, close contact with a person known to be Neisseria positive within the last 60 days, (family) history of Guillain-Barré Syndrome, known or suspected immune deficiency either congenital or acquired, administration of blood products in the last 3 months, use of anticoagulants, pregnancy, refusal to use contraceptives during the study period, fever, acute infectious disease other than seasonal cold, and participation as a subject in another trial in the last 3 months. An incentive of 45 euros was provided to all subjects who completed the primary vaccination and a further 45 euro after the booster phase.

2.5. Immunogenicity analysis

Serology was performed at the National Institute of Public Health and the Environment (RIVM, Bilthoven, the Netherlands). The immunogenicity and antibody persistence against MenACWY polysaccharides were initially assessed by fluorescent-bead-based multiplex immunoassay (MIA) during the study, as previously described [11,12].

Gold standard serology was performed at the end of the study by measuring the level of specific functional antibodies for each serogroup using an in-house serum bactericidal antibody assay (SBA) with baby rabbit complement (Pelfreez, ref#360160) and MenA, MenC, MenW and MenY strains 3125, C11, MP01240070, S-1975, respectively. The bactericidal titer was defined as the dilution of the test serum that resulted in $\geq$50% killing after 60 min incubation with a titer of $\geq$8 as correlate of protection and the more conservative threshold of $\geq$128 for long term protection [13–18].

2.6. Statistics

No formal sample size calculation was performed, as only a proof of principle was required. Sample sizes for dose finding studies are usually small. The adaptive design allowed for dose switching at interim analysis, which optimized the use of subjects.

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