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Adolescent meningococcal serogroup A, W and Y immune responses following immunization with quadrivalent meningococcal A, C, W and Y conjugate vaccine: Optimal age for vaccination

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ABSTRACT

Background: Recently the incidence of meningococcal serogroup Y (MenY) and in particular serogroup W (MenW) invasive disease has risen in several European countries, including the Netherlands. Adolescents are a target group for primary prevention through vaccination to protect against disease and reduce carriage and induce herd protection in the population. The present study assessed MenA, MenW and MenY antibody levels in adolescents up to one year following primary vaccination with quadrivalent MenACWY-PS conjugated to tetanus toxoid (MenACWY-TT).

Methods: In this phase IV, open-label study, healthy 10-, 12- and 15-year-olds received the MenACWY-TT vaccine. Blood samples were collected before, 1 month and 1 year after the vaccination. Functional antibody levels against MenA, MenW and MenY were measured with serum bactericidal assay using baby rabbit complement (rSBA). MenA-, MenW-, and MenY-PS specific IgG, IgG1 and IgG2 levels were measured using fluorescent-bead-based multiplex immunoassay.

Results: The quadrivalent MenACWY-TT vaccine elicited robust antibody responses against MenA, MenW and MenY, and the majority (94%) of the participants maintained rSBA titers ≥128 one year after the vaccination against all three serogroups. After one year, higher MenW rSBA GMTs were observed in the 12- and 15-year-olds compared to the 10-year-olds, while rSBA GMTs against MenA and MenY were similar between age groups. Furthermore, those participant who showed SBA titer ≥8 at baseline, also had higher antibody levels one year after vaccination as compared to participants with rSBA titer <8 at baseline.

Conclusion: The MenACWY-TT vaccine induces robust protective primary immune responses up to one year after vaccination. Our results suggest that persistence of individual protection increases with the age at which a primary quadrivalent MenACWY-TT vaccination is administered. Our results indicate that 12 or 15 years seems a more optimal age for a primary quadrivalent MenACWY-TT vaccination to protect against the rapid increase of MenW disease.

1. Introduction

Neisseria meningitidis, a gram-negative diplococcus bacterium, is a commensal of the human upper respiratory tract (nasopharynx) but may cause devastating disease after entering the blood stream [1], which may result in invasive meningococcal disease (IMD) with a mortality rate of 10% and serious sequelae in a substantial number of survivors.

The worldwide epidemiology of IMD is unpredictable due to its cyclical fluctuation over time. Incidence rate of IMD varies between 0.5 (North America) up to 1000 per 100,000 population in epidemic

Abbreviations: CI, confidence interval; GMC, geometric mean concentration; GMT, geometric mean titer; IMD, invasive meningococcal disease; MEC-U, Medical research Ethics Committees United; MenA, meningococcal serogroup A; MenC, meningococcal serogroup C; MenCC, meningococcal serogroup C conjugated vaccine; MenW, meningococcal serogroup W; MenY, meningococcal serogroup Y; MIA, multiplex immunoassay; PS, polysaccharide; rSBA, serum bactericidal assay using baby rabbit complement; T0, before the study vaccination; T1, 1 month after the study vaccination; T2, 1 year after the study vaccination; TT, tetanus toxoid; UK, United Kingdom.

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years in Africa [2,3]. Based on the capsular polysaccharide, meningococci can be classified into 12 serogroups [1,4]. Six serogroups (A, B, C, W, X and Y) cause most IMD, and are geographically distributed differently around the world [5], with meningococcal serogroup A (MenA) predominating in Africa and meningococcal serogroup B (MenB) and C (MenC) in many other regions [2]. In Europe, IMD is mainly caused by MenB and MenC [6]. The annual incidence rate of IMD in the Netherlands declined from 4.5 per 100,000 population in 2001 to 0.18 in 2014. This was mainly due to a gradual natural decline of the number of MenB cases [7], next to a rapid decline MenC IMD after the mass campaign in 2002 vaccinating all children between age 1 and 19 with conjugate (MenCC) vaccine [8]. However, increases of meningococcal serogroup Y (MenY) IMD have been described in certain regions of Europe, especially in Scandinavian countries and the UK [9,10]. A steep increases of meningococcal serogroup W (MenW) IMD have been observed in the UK, South America, and Australia [6,11–14], resulting in the introduction of a MenACWY-PS conjugate vaccine in adolescents [15,16]. Also in the Netherlands, a small increase in IMD caused by MenY has been observed over the last years but MenW has increased rapidly since the end of 2015 and is now responsible for 50/151 (33%) of all IMD cases in 2016 as compared to 1% in 2014 [Personal communication A. van der Ende].

Adolescents are a main target group for meningococcal vaccination, not only to protect this age group against IMD but also to reduce carriage and induce herd protection in the population, since adolescents represent the age group with the highest meningococcal carriage prevalence [3,17–19]. The aim of the present study was to assess the optimal age to vaccinate with the quadrivalent MenACYW conjugate vaccine. To this aim, MenA, MenW and MenY bactericidal titers, IgG and IgG subclasses up to one year following primary vaccination with quadrivalent MenACWY-PS conjugated to tetanus toxoid (MenACWY-TT) at the age of 10, 12 and 15 years were compared.

2. Methods

2.1. Study design and participants

This study was part of a phase IV, open-label, randomized, controlled trial conducted in a single center in the Netherlands which compared the immunogenicity between the monovalent MenC-TT and MenACWY-TT vaccine. The results of MenC antibody responses are reported in an accompanied manuscript [van Ravenhorst et al. Submitted]. In short, healthy 10-, 12- and 15-year-olds, previously immunized with single MenC-TT (NeisVac-C®, Pfizer) vaccine between 14 months and 3 years of age, were recruited from the surrounding area of Utrecht, The Netherlands. Exclusion criteria included a severe acute illness or fever at time of vaccination, the use of antibiotics within 14 days prior to enrolment, (chronic) illness or medication that could interfere with the study results in history or at time of vaccination, allergy to a vaccine component, history of IMD, multiple meningococcal vaccinations in the immunization history, other vaccinations 1 month prior to enrolment and pregnancy. All participants received the MenACWY-TT (Nimenrix®, Pfizer) vaccine. Venous blood samples using BD Vacutainer® serum separation tubes (catalogue number: 367955) were collected before (T0), 1 month (T1) and 1 year (T2) after the study vaccination.

This study was designed and conducted in accordance with the Good Clinical Practice guidelines established by the International Conference on Harmonization and with the Declaration of Helsinki. Ethical approval was obtained from the local ethics committee Medical research Ethics Committees United (MEC-U). Written informed consent was obtained from both parents or guardians and subjects aged ≥12 years before enrollment. This study was registered at the EU Clinical Trials database (EudraCT number: 2013-001823-38) and at the Dutch Trial Register (www.trialregister.nl; NTR4430).

2.2. Immunogenicity analysis

The functional antibodies were assessed using an in-house serum bactericidal antibody assay using baby rabbit complement (Pelfreez, ref#360160) (rSBA) [20]. The used MenA strain 3125, MenW strain MP01240070 and MenY strain S-1975 were kindly donated by the Vaccine Evaluation Unit, Public Health England, Manchester, UK. The MenA strain 3125 was used in this study because we aimed to assess vaccine induced immunity rather than natural immunity [21,22]. The bactericidal titer was defined as the dilution of the test serum that resulted in ≥50% killing after 60 min incubation with a titer of ≥8 as correlate of protection [23–25]. Functional antibody titers were also analyzed using the more conservative threshold of ≥128 [23]. MenA-, MenW-, and MenY-PS specific IgG levels were measured using the fluorescent-bead-based multiplex immunoassay (MIA) as previously described [26–28]. MenW- and MenY-PS specific IgG1 and IgG2 subclasses were also determined using the MIA.

2.3. Statistical analysis

All immunogenicity analyses were performed in the according to protocol (ATP) cohort as previously described [van Ravenhorst et al. Submitted]. GMTs and GMCs with two-sided 95% confidence intervals (CI) were calculated. Difference in antibody responses between the age groups were analyzed with linear regression analyses within each vaccine group, adjusting for baseline titers and concentrations. The p-values for the analyses between age groups were adjusted for 3 comparisons with the Bonferroni correction. Proportions with two-sided 95% CI of participants with an rSBA ≥8 and ≥128 were calculated using the Wilson score interval with continuity correction (http://vassarstats.net). Differences in proportions were tested with the Chi-square test. A p-value below 0.05 was considered statistically significant. Data were analyzed using SPSS statistics 22 (IBM) and GraphPad Prism 7.00.

3. Results

Baseline characteristics of participants are outlined in Supplementary Table 1. The MenACWY-TT vaccine was administered in 79/83 (95%), 79/82 (96%) and 78/81 (96%) of the 10-, 12-, and 15-year-olds, respectively [van Ravenhorst et al. Submitted]. Non-compliance with the blood sampling schedule was observed in 6/83 (7%), 2/82 (2%), and 3/81 (4%) for the 10-, 12-, and 15-year-olds, respectively.

3.1. rSBA titers against MenA, MenW and MenY

At baseline (T0) in all 3 age groups together, 43/223 (19.1%), 34/224 (15.1%) and 72/223 (32.0%) participants in the MenACWY-TT vaccine group had rSBA titers ≥8 against MenA, MenW and MenY, respectively. The 12-year-olds showed the highest MenA rSBA titers compared to the 10- and 15-year-olds (p-value 0.009 and 0.027, respectively; Fig. 1A and Table 1). For MenW and MenY, GMTs were similar between age groups (Fig. 1B, C and Table 1).

At one month (T1), GMTs increased considerably for MenA, MenW and MenY in all age groups (Fig. 1A–C and Table 1). For MenW and MenY, antibody GMTs in the 15-year-olds were higher compared to the 10-year-olds (p-value 0.027 and 0.045,

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