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Antibody persistence and booster response 68 months after vaccination at 2–10 years of age with one dose of MenACWY-TT conjugate vaccine ☆

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ABSTRACT

Background: We evaluated antibody persistence up to 68 months (M) post-vaccination with a quadrivalent meningococcal serogroups A, C, W and Y tetanus toxoid conjugate vaccine (MenACWY-TT) or a licensed monovalent MenC conjugate vaccine (MenC-CRM$_{197}$) and subsequent booster responses to MenACWY-TT in healthy European children.

Methods: In the initial study (NCT00674583), healthy children, 2–10 years of age, were randomized to receive a single dose of either MenACWY-TT or MenC-CRM$_{197}$. In the follow-up study, we present the persistence at 32, 44, 56, and 68 M post-vaccination, overall and stratified by age (2–5 and 6–10 years), and the immunogenicity and safety of MenACWY-TT administered to all study participants at M68 post-primary vaccination.

Results: At M68, 33.3% (age group 2–5 years) and 47.1% (age group 6–10 years) of the children vaccinated with MenACWY-TT, and 50.0% (age group 2–5 years) and 75.9% (age group 6–10 years) vaccinated with MenC-CRM$_{197}$ retained titers $\geq$1:8 for MenC, as assessed by a serum bactericidal assay using rabbit complement (rSBA). In the MenACWY-TT recipients, the percentages of children retaining rSBA titers $\geq$1:8 for MenA, MenW, and MenY were 81.7%, 47.3% and 66.7% in age group 2–5 years and 91.8%, 58,8% and 76.5% in age group 6–10 years, respectively. The booster dose induced robust responses (100% for all serogroups) and was well-tolerated.

Conclusions: Antibody persistence (rSBA titers $\geq$ 1:8) for serogroups A, W and Y was observed in more than 50.0% of the children 68 M after receiving one dose of MenACWY-TT; for MenC, antibody persistence was observed in more than one third of MenACWY-TT and more than half of MenC-CRM$_{197}$ recipients. Vaccination with a booster dose of MenACWY-TT induced robust immune responses for all serogroups.

1. Introduction

Invasive meningococcal disease (IMD) caused by the bacterium *Neisseria meningitidis* is associated with high morbidity and mortality [1–3]. Infants and children younger than 5 years of age have the highest incidence of IMD. Until recently, meningococcal serogroups B (MenB) with 68.0% of IMD cases and C (MenC) with 17.0% were the most prevalent in Europe [4,5] with estimates from Germany (2002–2010) and France (2012) showing that MenC was responsible for 25.0% [6] and 27.0% [7] of confirmed IMD cases, respectively. However, epidemiological data from 2010 onwards demonstrate an increased total number and proportion of serogroup Y IMD cases (up to 50.0%) in various European regions such as the Scandinavian countries and Switzerland [2,8]. Until recently,

Abbreviations: AEs, adverse events; ATP, according-to-protocol; CIs, confidence intervals; GI, gastrointestinal; GMTs, geometric mean titers; hSBA, serum bactericidal activity assay using human complement; IMD, invasive meningococcal disease; M, month; MenB, meningococcal serogroup B; MenC, meningococcal serogroup C; MenACWY-TT, quadrivalent meningococcal serogroups A, C, W and Y tetanus toxoid conjugate vaccine; MenC-CRM, monovalent MenC conjugate vaccine; NOCI, new onset of chronic illness; rSBA, serum bactericidal assay using rabbit complement; SAEs, serious adverse events; TT, tetanus toxoid; TVC, total vaccinated cohort.

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serogroups A and W were not frequently detected in Europe, but remained important causes of epidemic IMD in Africa, Asia and Latin America [7,9] However, the incidence of serogroup W disease has been rising in several European countries, underscoring a potential risk in Europe [10–14]. In view of these epidemiological data, vaccination against multiple serogroups is considered the best strategy to protect individuals against a broader range of IMD in a single injection.

MenC conjugate vaccines are effective in preventing IMD in infants and young children, and were associated with a reduction of MenC nasopharyngeal carriage [15]. MenC vaccine is marketed in Europe, Canada, Australia, and Latin America and was introduced in the national childhood vaccination schedule for children in the second year of life in several European countries [16] such as, in Germany in 2006 [6] and in France in 2010 [17].

Currently, three quadrivalent meningococcal conjugate vaccines (MenACWY) are available: MenACWY-DT (*Menactra*, Sanofi Pasteur Inc.), MenACWY-CRM (*Menveo*, GSK) and MenACWY-TT (*Nimenrix*, Pfizer). In Europe, MenACWY-CRM and MenACWY-TT are licensed for children aged ≥2 years, and as of 6 weeks, respectively [18,19].

Previous clinical studies have shown that MenACWY-TT is immunogenic and well-tolerated in toddlers, children, adolescents, and adults. Non-inferiority of MenACWY-TT compared to a licensed quadrivalent plain polysaccharide vaccine was shown in two previous studies conducted in children 2–10 years of age [20,21]. Booster vaccination in toddlers and adolescents has been shown to elicit robust memory responses [22–24].

Long-term protection against IMD was suggested to be related to the presence of circulating antibodies [25]. Antibody persistence data after infant/toddler vaccination with multivalent meningococcal conjugate vaccines are currently available up to 5 years post-vaccination [23,24,26,27]. These studies have shown that serum antibody levels elicited by meningococcal conjugate vaccines wane over time, especially at younger ages, suggesting that a booster dose may be warranted [23–25,28–32]. Given the inverse relationship between waning antibodies and long-term protection, a booster dose of MenC conjugate vaccine during the second year of life was introduced in the United Kingdom in 2006 following infant vaccination [25] (replaced by the MenACWY conjugate vaccine in 2015 [33]). Due to the success of the MenC vaccination program and herd protection of infants, in 2016 the schedule was revised and currently a primary dose is. given at 12 months of age with a booster dose of MenACWY at 14 years of age [34]. In the United States, one dose of MenACWY conjugate vaccine is recommended for 11–12 year olds followed by a booster dose at 16 years of age [35].

Serum bactericidal activity against the four *Neisseria meningitidis* serogroups is determined using human or rabbit complement. As the human source is scarce, rabbit complement is more frequently used. A correlation between the two assays, in particular for serogroups A, W and Y is a matter of debate [36–38]. To assess the value of each assay in our settings, we have decided to use both complement sources.

The primary phase of this study (NCT00674583) conducted in children 2–10 years of age demonstrated non-inferiority of MenACWY-TT versus a commonly used monovalent MenC conjugate vaccine (MenC-CRM; *Menjugate*, GSK) in terms of vaccine response to MenC, assessed by a serum bactericidal assay using rabbit complement (rSBA-MenC) [39]. The aim of this follow-up study was to evaluate for the first time (1) persistence to MenACWY-TT and *Menjugate* and (2) persistence in this age group of functional antibodies up to 68 M after primary vaccination and immunogenicity and safety of a MenACWY-TT booster dose administered at 68 M, in order to facilitate vaccination recommendations for a booster dose.

2. Material and methods

2.1. Study design and children

This phase III, open, controlled study (NCT01266993) was conducted in 16 centers in Germany and 8 centers in France between January 2011 and May 2014. In the initial study (NCT00674583), healthy children, 2–10 years of age, were randomized to receive a single dose of either MenACWY-TT (ACWY-TT group) or MenC-CRM_{197} (MenC-CRM group). Immunogenicity data at M1 post-vaccination have been already published [39]. We present here the persistence at 32, 44, 56, and 68 M post-vaccination, overall and stratified by age (2–5 years and 6–10 years), and the immunogenicity and safety one month after booster vaccination of MenACWY-TT administered to all study participants at M68. The vaccine composition of MenACWY-TT has been previously described [39].

Exclusion criteria in the persistence phase included vaccination with a meningococcal vaccine against serogroup A, C, W or Y outside of the primary study and history of meningococcal disease. In the booster phase of the study, all eligible primed children received a single booster dose of MenACWY-TT. Additional criteria applicable to the booster phase can be found in the supplements.

The study protocol and associated documents were reviewed and approved by local ethics committees. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. We obtained informed consent from the parent or guardian of each child before performing any study-specific procedures (for country specific details see supplements).

This study is registered at http://www.clinicaltrials.gov NCT01266993. A summary of the protocol is available at http://www.gsk-clinicalstudyregister.com (GSK study ID 113977).

2.2. Study objectives

The primary objective was to evaluate the long-term persistence of the immunogenicity of MenACWY-TT at M32, M44, M56, and M68 in terms of percentages of children with rSBA antibody titers ≥1:8 for all serogroups.

The secondary objectives were: (1) to evaluate the long-term persistence of the immunogenicity of MenACWY-TT at M32, M44, M56, and M68 overall and stratified by age; (2) to evaluate the immunogenicity of a booster vaccination given at M68 in terms of percentages of children with: (i) rSBA (antibody titers ≥1:8, ≥1:128, and geometric mean titers [GMTs]) at one month post-booster vaccination; and (ii) human complement (hSBA) (antibody titers ≥1:4, ≥1:8 and GMTs) at one month post-booster vaccination for all serogroups; and (3) to evaluate the immunogenicity of a booster vaccination in terms of the percentage of children with rSBA vaccine responses for all serogroups at one month post-booster vaccination.

The safety and reactogenicity of MenACWY-TT were evaluated with respect to (1) local and general solicited symptoms during the 4-day period (Days 0–3) following vaccination; (2) unsolicited serious and non-serious adverse events (AEs) and new onset of chronic illness (NOCI) (e.g. autoimmune disorders, asthma, type I diabetes and allergies) during the 31-day period (Days 0–30) following vaccination.

2.3. Immunogenicity assessments

Blood samples were collected at each persistence and the booster timepoints and functional anti-meningococcal activity was determined by rSBA and hSBA assays, based on the Centers for Dis-