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Immunogenicity and safety of one or two doses of the quadrivalent meningococcal vaccine MenACWY-TT given alone or with the 13-valent pneumococcal conjugate vaccine in toddlers: A phase III, open-label, randomised study

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ABSTRACT

Background: We evaluated the immunogenicity and safety of 1 and 2 doses of quadrivalent meningococcal serogroup A, C, W and Y tetanus toxoid-conjugate vaccine (MenACWY-TT) given alone or co-administered with 13-valent pneumococcal conjugate vaccine (PCV13) in toddlers.

Methods: In this phase III, open-label, controlled, multicentre study (NCT01939158), healthy toddlers aged 12–14 months were randomised into 4 groups to receive 1 dose of MenACWY-TT at month (M) 0 (ACWY_1), 2 doses of MenACWY-TT at M0 and M2 (ACWY_2), MenACWY-TT and PCV13 at M0 (Co-ad), or PCV13 at M0 and MenACWY-TT at M2 (PCV13/ACWY). Immune responses were assessed 1 month post-each vaccination. Solicited and unsolicited symptoms were recorded for 4 and 31 days post-each vaccination, respectively; serious adverse events (SAEs) and new onset of chronic illnesses (NOCIs) up to M9 from first vaccination.

Results: 802 toddlers were vaccinated. Post-dose 1 of MenACWY-TT, ≥92.8% of toddlers had rSBA titres ≥1:8, and ≥62.5% had hSBA titres ≥1:4 for each meningococcal serogroup. Post-dose 2 of MenACWY-TT, rSBA titres ≥1:8 were observed in ≥98.0% and hSBA titres ≥1:4 in ≥95.3% of toddlers. Percentages of toddlers with hSBA titres ≥1:4 were higher after 2 doses versus 1 dose of MenACWY-TT for MenW (97.1% versus 62.5–68.9%) and MenY (95.3% versus 64.3–67.6%). Non-inferiority of immune responses to co-administered MenACWY-TT and PCV13 over their separate administration was demonstrated.

Abbreviations: AE, adverse event; ATP, according-to-protocol; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; GMT, geometric mean titre; hSBA, human complement serum bactericidal antibody assay; MenACWY-TT, quadrivalent serogroups A, C, W and Y conjugate vaccine using tetanus toxoid as carrier protein; LL, lower limit; M, month; PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; rSBA, rabbit complement serum bactericidal antibody assay; SAE, serious adverse event; TT, tetanus toxoid.

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AEs incidence was comparable among groups. SAEs were reported for 4.9%, 5.1%, 5.5% and 7.5%, and NOCIs for 2.0%, 3.0%, 0.5% and 3.5% of toddlers in the ACWY_1, ACWY_2, Co-ad and PCV13/ACWY groups, respectively; 4 SAEs reported in 3 toddlers were vaccine-related. Two fatal vaccine-unrelated SAEs were reported.

Conclusion: MenACWY-TT was immunogenic when administered as a single dose at 12–14 months of age. A second dose in toddlers increased hSBA responses against MenW and MenY. MenACWY-TT and PCV13 can be co-administered without impairing the immunogenicity or safety profile of either vaccine.

1. Introduction

Invasive meningococcal disease and meningococcal meningitis caused by *Neisseria meningitidis* have their highest incidence in infants, with a second peak in adolescents and young adults [1,2]. The most important disease-causing serogroups are meningococcal serogroups A (MenA), MenB, MenC, MenW and MenY. Their prevalence varies geographically, with MenB, MenC and MenY being more prominent in the Americas and Europe, MenA and MenC in Asia, and MenA, MenC and MenW in Africa [3]. Increases in MenW incidence have been reported recently in the United Kingdom, South America and Australia [4–7].

Meningococcal infections can be prevented through vaccination [2,8]. Three quadrivalent meningococcal conjugate vaccines are currently available, using (i) diphtheria toxoid (*Menactra*, Sanofi Pasteur), (ii) non-toxic diphtheria cross-reacting mutant CRM_{197} (MenACWY-CRM_{197}; *Menveo,* GSK) or (iii) tetanus toxoid (MenACWY-TT; *Nimenrix*, Pfizer) as carrier proteins. MenACWY-TT has been approved for use as a single dose in individuals as of 12 months of age in Europe and Canada [9,10].

Previous studies have shown that a single dose of MenACWY-TT is immunogenic with a clinically acceptable safety profile in infants [11], toddlers and children [12–16], and persistence of the immune response was observed up to 5 years post-vaccination [17–21]. However, data suggest that protection against MenW and MenY in toddlers who received their first dose of MenACWY-TT at 9 months might be improved by administration of a second dose at 12 months of age [12].

This study investigates the short-term (at 1 month post-vaccination) and long-term (at 1, 3, and 5 years post-vaccination) immune responses induced by 1 or 2 doses of MenACWY-TT in toddlers. The study long-term follow-up is ongoing; here, we report the short-term immunogenicity and safety data up to 9 months post-first vaccination. Since the recommended timing of vaccination could coincide with the administration of a booster dose of pneumococcal conjugate vaccine (PCV), according to paediatric immunisation programmes worldwide, we also aimed to determine whether co-administration of MenACWY-TT with the booster dose of the 13-valent PCV (PCV13; Prevnar/Prevenar 13, Pfizer) impacted the immunogenicity or safety of either of the vaccines.

2. Methods

2.1. Study design and participants

This phase III, randomised, open-label, controlled, multicentre study was conducted in Australia, Canada, Czech Republic, Panama, South Africa and Turkey. The study interventions were performed in the vaccination phase (October 2013 to February 2015) lasting up to 3 months from first vaccination. A 6 M extended safety follow-up was completed in August 2015.

Participants were healthy 12–14-month-olds at the time of first vaccination, with documented receipt of the full primary series of PCV13 and diphtheria, tetanus and pertussis-containing vaccines according to local recommendations at least 5 months prior to enrolment.

Toddlers were randomised (1:1:1:1) into 4 groups to receive 1 dose of MenACWY-TT at month [M] 0 (ACWY_1 group), 2 doses of MenACWY-TT at M0 and M2 (ACWY_2 group), 1 dose of MenACWY-TT co-administered with PCV13 at M0 (Co-ad group), or 1 dose of PCV13 at M0 and 1 dose of MenACWY-TT at M2 (PCV13/ACWY group).

Randomisation was performed using a web-based system, with a minimisation algorithm accounting for centre, country and number of PCV13 doses (2 or 3, received before study start) with equal weight. The open-label design was imposed by differences in the vaccines' appearance and vaccination schedules for each group, but the personnel in charge of laboratory testing were blinded to treatment.

One 0.5 mL-dose of MenACWY-TT contained 5 μg of each MenA, MenC, MenW and MenY polysaccharide conjugated to TT (total TT content ~44 μg). PCV13 composition was previously described [22]. At each vaccination, a 0.5 mL dose was administered intramuscularly in the left (MenACWY-TT) or right (PCV13) anterolateral thigh or deltoid.

The study was conducted in agreement with the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from parents/legally acceptable representatives prior to enrolment. The study protocol, amendments and informed consent forms were approved by independent ethics committees at each site. The study is registered at www.clinicaltrials.gov (NCT01939158) and a protocol summary is available at https://www.gsk-clinicalstudyregister.com (116892).

2.2. Objectives

The immunogenicity of 1 or 2 doses of MenACWY-TT was compared at 1 month following last vaccination, in terms of serum bactericidal activity using rabbit complement (rSBA) titres. Evaluation of the persistence of the immune response at years 1, 3 and 5 is still ongoing (exploratory primary objective). The same comparisons were performed in terms of serum bactericidal activity using human complement (hSBA) titres.

The non-inferiority of co-administration of MenACWY-TT and PCV13 versus administration of either MenACWY-TT or PCV13 alone was evaluated at 1 month following last vaccination with MenACWY-TT and PCV13, respectively (confirmatory primary objectives).

Other secondary objectives evaluated the immunogenicity, reactogenicity and safety of the study vaccines in all groups.

2.3. Assessments

Blood samples (~5 mL) were collected from toddlers at pre-vaccination, and 1 month post-each vaccination. Immune responses to MenACWY-TT were evaluated using rSBA and hSBA assays [23] and to PCV13 antigens by both 22F-inhibition

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