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Immunogenicity and safety of MenACWY-TT, a meningococcal conjugate vaccine, co-administered with routine childhood vaccine in healthy infants: A phase III, randomized study

Ghassan Dbaibo [a], Juan Carlos Tinoco Favila [b], Magali Traskine [c], Archana Jastorff [c], Marie Van der Wielen [c,*]

[a] Center for Infectious Diseases Research, Department of Pediatrics and Adolescent Medicine, American University of Beirut, Riad El Solh, Beirut 1107-2020, Lebanon
[b] Hospital General de Durango, Durango, Mexico
[c] GSK, Wavre, Avenue Fleming 20 (W23), 1300 Wavre, Belgium

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ABSTRACT

Background: Invasive meningococcal disease has a high burden in young children, particularly during infancy. We investigated the immunogenicity and safety of a quadrivalent meningococcal conjugated vaccine (MenACWY-TT) co-administered with routine vaccines in healthy infants.
Methods: In this phase IIIb study (NCT01340898) conducted in 2 centers in Lebanon and Mexico, 750 infants were randomized (2:1:1) to receive MenACWY-TT according to 3 schedules: 3+1 (at ages 2, 4, 6 and 15–18 months; group ACWY3+1); 1+1 (at 6 and 15–18 months; group ACWY1+1) or single-dose at 15–18 months (group ACWY1). All infants received PHiD-CV and DTPa-IPV/Hib at ages 2, 4, 6, 15–18 months. Immune responses to MenACWY-TT were assessed by rSBA and hSBA at 7 months (groups ACWY3+1, ACWY1+1) and pre- and post-vaccination at 15–18 months of age (all groups). Immune responses to co-administered vaccines, reactogenicity and safety were also evaluated.
Results: Immunogenicity of MenACWY-TT at 1 month post-primary vaccination was demonstrated in group ACWY3+1: the lower limit of the 95% confidence interval for the percentage of infants with rSBA titers ≥8 was >80% for each serogroup. At 7 months of age, ≥93.9% of MenACWY-TT-primed infants had rSBA titers ≥8. Post-MenACWY-TT vaccination at age 15–18 months, ≥96.3% of participants in all groups had rSBA titers ≥8, regardless of the number of doses received previously. The percentage of infants with hSBA titers ≥4 were ≥87.2% and ≥89.7% at post-primary and booster/single-dose vaccination, respectively. Immune responses to PHiD-CV and DTPa-IPV/Hib did not seem impacted by co-administration with MenACWY-TT in infancy. The incidence of all adverse events was similar among groups. Serious adverse events were reported for 63/750 children in all groups; none were considered vaccine-related by investigators.
Conclusion: Primary vaccination with 3 or 1 dose(s) of MenACWY-TT when co-administered with routine pediatric vaccines in infants is immunogenic and well-tolerated.

1. Introduction

Invasive meningococcal disease (IMD) is a life-threatening condition which, if left untreated, can lead to a case fatality ratio of up to 50% [1].

IMD is caused by different serogroups of *Neisseria meningitidis*, 6 of those (MenA, MenB, MenC, MenW, MenX and MenY) being responsible for the majority of IMD cases [1], although epidemiology varies greatly geographically. MenA and MenC are more prominent in Asia, MenB and MenC in Europe, Australia and South America, while in North America, MenB, MenC and MenY prevalence is higher [2–4]. In the African meningitis belt, MenW is the most common serogroup following a decrease in MenA prevalence [1–3], and MenC [5,6] and MenX [7] also emerging as serious causes of meningitis.

The incidence of IMD remains high, with more than 1.2 million cases per year reported worldwide [2]. Children aged <5 years are at particular risk of IMD, and the highest rate of disease is recorded in infants, while a second, lower peak is observed in adolescents [8,9]. While treatment of IMD may be complex, with the choice

* Corresponding author at: GSK Vaccines, Avenue Fleming 20, B-1300 Wavre, Belgium.
E-mail addresses: gdbaibo@aub.edu.lb (G. Dbaibo), jctinoco@prodigy.net.mx (J.C. Tinoco Favila), magali.x.traskine@gsk.com (M. Traskine), archana.m.jastorff@gsk.com (A. Jastorff), marie.x.van-der-wielen@gsk.com (M. Van der Wielen).

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of antibiotics depending on age and local resistance rates [10], the disease is preventable and several vaccines are currently available [11]. Three quadrivalent meningococcal conjugate vaccines using diphtheria toxoid (MenACWY-DT; *Menactra*, Sanofi Pasteur), non-toxic diphtheria cross-reacting mutant CRM_{197} (MenACWY-CRM; *Menveo*, GSK), or tetanus toxoid (MenACWY-TT; *Nimenrix*, Pfizer) as carrier proteins are approved for use in different age groups, including infants [12].

MenACWY-TT was first licensed in 2012 in Europe and Canada for individuals ≥2 years of age followed by an extension of its indication as of 6 weeks of age in Europe [13–15]. Recently, the vaccine was prequalified by the World Health Organization [16]. Co-administration of MenACWY-TT with routine pediatric vaccines at 2, 3, 4 and 12 months of age or 2, 4 and 12 months of age was shown to induce adequate immune responses, as measured by serum bactericidal antibody assays with human (hSBA) and rabbit (rSBA) complement, with an acceptable safety profile in a European population [17].

We studied co-administration of MenACWY-TT with a pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV; *Synflorix*, GSK) and a combined diphtheria, tetanus, acellular pertussis, inactivated polio and *H. influenzae* type b vaccine (DTPa-IPV/Hib; *Infanrix-IPV*/Hib, GSK) in healthy infants from Lebanon and Mexico. The 3+1 primary-booster schedule at 2, 4, 6 and 15–18 months of age was designed to align with the priming schedule of other routine infant vaccines used in several countries across the world. This study also evaluates a 1+1 schedule, as well as a single dose in toddlers.

2. Methods

2.1. Study design and participants

This phase IIIb, open, controlled, randomized study was conducted between January 2012 and October 2015 in 2 centers in Lebanon and Mexico.

Infants were randomized (2:1:1) into 3 groups to receive MenACWY-TT according to different schedules. Two groups received a 3-dose (at 2, 4 and 6 months of age; group ACWY3+1) or a 1-dose (6 months of age; group ACWY1+1) primary schedule followed by a booster dose at age 15–18 months. Group ACWY1 received a single dose at 15–18 months of age and served as control. As part of the study, all participants received DTPa-IPV/Hib and PHiD-CV at 2, 4, 6 and 15–18 months of age, according to national immunization programs (NIPs) (Fig. 1). The trial included a primary vaccination phase (up to 7 months of age), a booster phase (14–19 months of age) and a 6-month extended safety follow-up (Fig. 1).

Participants were healthy infants aged 6–12 weeks at enrollment, born after a gestation period of ≥36 weeks. Text S1 presents full inclusion/exclusion criteria.

Treatment allocation was performed at the investigators' site using an internet-based system, using a minimization algorithm accounting for center. All personnel in charge of laboratory testing were blinded to the treatment.

Vaccines were administered intramuscularly, into the upper-left (MenACWY-TT), upper-right (PHiD-CV) or lower-right (DTPa-IPV/Hib) anterolateral thigh; vaccine compositions are detailed in Text S2.

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from each participant's parent/guardian prior to enrollment. The protocol and informed consent forms were reviewed and approved by an Independent Ethics Committee or Institutional Review Board at each center. The study is registered at www.clinicaltrials.gov (NCT01340898) and a protocol summary is available at http://www.gsk-clinicalstudyregister.com/114858.

2.2. Study objectives

The primary objective was to demonstrate that MenACWY-TT is immunogenic in infants after 3 primary doses, in terms of rSBA antibodies to each meningococcal serogroup. The following statistical criterion, which was considered clinically relevant, was used: the lower limit (LL) of the 2-sided 95% confidence interval (CI) for the percentage of infants with rSBA titers ≥8 for each serogroup should be ≥80%.

Secondary objectives evaluated the immune responses to MenACWY-TT vaccination at 1 month post-primary vaccination (groups ACWY3+1 and ACWY1+1) and pre- and 1 month post-booster/single dose (all groups), in terms of percentage of children with titers above pre-specified thresholds, geometric mean titers (GMTs) and booster/vaccine response measured by rSBA and hSBA (subset of participants). The post-primary immunogenicity of co-administered vaccines and post-booster anti-tetanus immune response and immunogenicity of PHiD-CV in subsets of participants, safety and reactogenicity were also assessed.

2.3. Immunogenicity assessment

Approximately 5 mL of blood were collected from all participants, post-primary and pre- and post-booster/single dose vaccination (Fig. 1).

Antibody titers for each meningococcal serogroup were determined by rSBA and hSBA (in a randomized subset), with pre-specified thresholds for seropositivity of 8 and 4, respectively [18–21] (Table S1).

rSBA/hSBA booster and vaccine response to MenACWY-TT in previously-primed groups and group ACWY1, respectively, was defined as a post-vaccination titer of ≥32 (rSBA)/≥8 (hSBA) for initially seronegative participants or as a ≥4-fold increase for initially seropositive participants.

Immune responses to co-administered vaccines was assessed in randomized exclusive subsets of 25% of participants by neutralization (for polio) or enzyme-linked immunosorbent assay (all other antigens), using the thresholds presented in Table S1.

2.4. Safety and reactogenicity assessment

Solicited local and general symptoms (days 0–7) and unsolicited adverse events (AEs) (days 0–30) were recorded by parents on diary cards post-each vaccination and graded by intensity.

Serious AEs (SAEs) and new onset of chronic illnesses were recorded throughout the study.

2.5. Statistical analyses

The target sample size for the evaluation of the primary objective was 300 infants in group ACWY3+1. Assuming a drop-out/non-evaluable rate of 20% post-primary vaccination, a total target sample size of 750 infants was calculated for enrollment. The power to meet the primary confirmatory objective was 99.4%, computed by assuming 90% of evaluable infants will have post-primary vaccination rSBA titers ≥8 for each serogroup.

Analyses were performed separately for the primary and booster phases. Safety was assessed in the primary and booster total vaccinated cohorts, which included all participants with ≥1 primary and booster dose(s) with any of the study vaccines, respectively. Immunogenicity was evaluated in all children or different

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