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Quadrivalent meningococcal (MenACWY-TT) conjugate vaccine or a fourth dose of *H. influenzae–N. meningitidis* C/Y conjugate vaccine (HibMenCY-TT) is immunogenic in toddlers who previously received three doses of HibMenCY-TT in infancy

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ABSTRACT

Background: Immunogenicity and safety of a single dose of MenACWY-TT or a fourth dose of HibMenCY-TT were evaluated in the second year of life in HibMenCY-TT-primed toddlers.
Methods: Healthy infants were randomized (5:1) and primed at 2, 4 and 6 months of age with HibMenCY-TT and diphtheria–tetanus–acellular pertussis–hepatitis B-inactivated poliovirus (DTaP–HBV–IPV) vaccine; or Hib-TT and DTaP–HBV–IPV (control). Recipients of HibMenCY-TT + DTaP–HBV–IPV were re-randomized (2:2:1) to receive MenACWY-TT at 12–15 months and DTaP at 15–18 months; MenACWY-TT co-administered with DTaP at 15–18 months; or HibMenCY-TT at 12–15 months and DTaP at 15–18 months. Controls received DTaP only at 15–18 months due to Hib conjugate vaccine shortage. Serum bactericidal activity using human complement (hSBA) and safety were assessed one month after meningococcal vaccination.
Results: After vaccination with MenACWY-TT at 12–15 months or MenACWY-TT + DTaP at 15–18 months, all subjects previously primed for serogroups C/Y had hSBA ≥1:8 for these serogroups. At least 96.1% also had hSBA ≥1:8 for serogroups A/W. All subjects in the HibMenCY-TT group had hSBA ≥1:8 for serogroups C/Y. All pre-defined statistical criteria for meningococcal immunogenicity were satisfied. All vaccination regimens had acceptable safety profiles.

Abbreviations: 95% CI, 95 percent confidence interval; ACIP, Advisory Committee on Immunization Practices; AE, adverse event; ATP, according-to-protocol; Coadco, administration treatment group who received MenACWY-TT + DTaP at the fourth dose visit (15/18 months of age) DTaPcombined diphtheria–tetanus–acellular pertussis vaccine; DTaP–HBV–IPV, combined diphtheria–tetanus–acellular pertussis–hepatitis B-inactivated poliovirus vaccine; GMT, geometric mean antibody titers; Hib-MenCY-TT, meningococcal serogroup C and Y conjugate vaccine combined with *Haemophilus influenzae* type b conjugate vaccine; Hib-TT, *Haemophilus influenzae* type b conjugate vaccine; hSBA, serum bactericidal activity using human complement source; IMDi, nvasive meningococcal disease; MenACWY-DT, quadrivalent serogroups A, C, W and Y conjugate vaccine with all serogroups conjugated to the diphtheria toxoid carrier protein; MenACWY-CRM$_{197}$, quadrivalent serogroups A, C, W and Y conjugate vaccine with all serogroups conjugated to CRM-197 (mutant diphtheria toxoid); MenACWY-TT, quadrivalent serogroups A, C, W and Y conjugate vaccine with all serogroups conjugated to the tetanus toxoid carrier protein; SAEs, erious adverse event; PRN, pertactin; TT, tetanus toxoid; US, United States.

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Conclusion: Children primed with three doses of HibMenCY-TT who then received a single dose of MenACWY-TT or a fourth dose of HibMenCY-TT had robust increases in hSBA titers for serogroups C/Y. These data provide support that MenACWY-TT, given with or without the fourth scheduled dose of DTaP could be administered as an alternative to a fourth dose of HibMenCY-TT in the second year of life. This study (110870/110871) is registered at www.clinicaltrials.gov NCT00614614.

1. Introduction

Invasive *Neisseria meningitidis* infection causes severe disease with approximately 10% mortality even when appropriate antibiotics and supportive therapy are administered [1]. In the United States (US) the majority of invasive meningococcal disease (IMD) is caused by serogroups B, C and Y [2]. While serogroups A and W are more rarely detected in the US, they are important causes of disease outbreaks in many regions worldwide, including Latin America [3–6]. Infants <1 year of age have the highest incidence of IMD (5.38 cases per 100,000 population; 1998–2007 US data) [2]. Therefore, in order to impact IMD in US infants and children, meningococcal conjugate vaccines need to be effective from early ages [7].

The meningococcal serogroups C/Y vaccine, combined with *Haemophilus influenzae* type-b (HibMenCY-TT, *MenHibrix*™, GlaxoSmithKline Vaccines), is approved in the US as a four-dose series in infants. HibMenCY-TT is recommended by the Advisory Committee on Immunization Practices (ACIP) for use in infants and children at increased risk for IMD such as those with complement deficiencies or asplenia including sickle cell disease, and may be used as an alternative for routine vaccination against Hib [8]. Immunogenicity and safety of HibMenCY-TT was demonstrated in clinical trials conducted in infants and toddlers [9–16]. The quadrivalent serogroups A/C/W and Y meningococcal conjugate vaccine MenACWY-CRM_{197} (*Menveo*™, Novartis) is also approved in the US as a four-dose series in infants, and *Menactra*™ (MenACWY-DT, Sanofi Pasteur) is approved as a two-dose schedule in children aged 9–23 months. For children aged <2 years, both MenACWY-CRM_{197} and MenACWY-DT are recommended for use in those with complement deficiencies or exposure due to travel/residence in an endemic area and, in addition, MenACWY-CRM_{197} is recommended in those with asplenia including sickle cell disease [17,18].

GlaxoSmithKline Vaccines' MenACWY vaccine with all serogroups conjugated to tetanus toxoid (TT) (MenACWY-TT: *Nimenrix*™), is licensed as a single dose in Europe, but remains investigational in the US. One dose of MenACWY-TT is immunogenic and well tolerated in children from 12 months of age, adolescents and adults [19–26].

We investigated the safety and immunogenicity of MenACWY-TT when given as a booster dose for the C/Y antigens, and as a priming dose for the A/W antigens in toddlers 12–18 months of age who were primed with HibMenCY-TT and combined diphtheria–tetanus–acellular pertussis–hepatitis B and inactivated poliomyelitis vaccine (DTaP–HBV–IPV). The study also evaluated the co-administration of DTaP with MenACWY-TT (reported in [27]).

2. Methods

2.1. Study design

This Phase III, randomized, controlled study was conducted in 59 US centers between 09 December 2008 and 19 August 2010. The study protocol was approved by local or central ethics committees for each center. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki (1996 Somerset West). Written informed consent was obtained from each subject's parent/guardian prior to enrollment.

Healthy infants were enrolled and randomized 5:1 to vaccination at 2, 4 and 6 months of age with HibMenCY-TT and DTaP–HBV–IPV, or Hib-TT + DTaP–HBV–IPV (Table 1, Fig. 1). At 12–15 months of age (fourth dose phase), children vaccinated with HibMenCY-TT + DTaP–HBV–IPV were re-randomized (2:2:1) to receive MenACWY-TT at 12–15 months of age followed by DTaP at 15–18 months (MenACWY-TT group); MenACWY-TT co-administered with DTaP at 15–18 months of age (Coad group); or HibMenCY-TT at 12–15 months of age followed by DTaP at 15–18 months (HibMenCY-TT group). Hib-TT + DTaP–HBV–IPV-primed children were not re-randomized and received DTaP at 15–18 months of age (control group). Subjects in the Coad, MenACWY-TT and control groups did not receive Hib booster vaccination because of an ongoing shortage of Hib conjugate vaccine in the US at the time of study conduct [28]. The study was conducted prior to the availability of a meningococcal conjugate vaccine licensed in the US for use in children <2 years of age; therefore the control group did not receive meningococcal vaccination during the study. All subjects were permitted to receive routine vaccines recommended by ACIP.

The study was single-blind in the primary phase due to the different appearance of the vaccines. Prior to the fourth dose parents/guardians were informed of their primary vaccination group. Parents/guardians were aware of their treatment group in the fourth dose phase, due to the differing number of vaccines and serum sampling time points for the various treatment groups.

A randomization list was used to number the vaccines. Random assignment of the subjects for each study phase was performed using a central, web-based system which included a minimization procedure to ensure balanced allocation between groups at individual centers.

2.2. Study subjects and vaccines

Participants were healthy infants between 6 and 12 weeks of age, born after at least 36 weeks of gestation. Exclusion criteria included prior receipt of any blood product since birth or receipt of vaccines other than pneumococcal conjugate vaccine or human rotavirus vaccine within 30 days of dose-1. A birth dose of hepatitis B vaccine was allowed. A history of disease due to *N. meningitidis*, Hib, diphtheria, tetanus, pertussis, hepatitis B, or polio, or vaccination against any of these diseases performed outside of the study resulted in exclusion from both phases. Subjects included in the fourth dose phase were to have received all three primary vaccination doses.

One 0.5 ml dose of HibMenCY-TT contained 2.5 μg of Hib polyribosylribitol phosphate conjugated to TT, and 5 μg each of MenC polysaccharide and MenY polysaccharide conjugated to TT. One 0.5 ml dose of MenACWY-TT contained 5 μg of each meningococcal serogroup A/C/W and Y polysaccharide conjugated to TT. The lyophilized meningococcal vaccines were reconstituted with sterile saline for injection, and were administered intramuscularly into the left thigh or arm.

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