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Immunogenicity and safety of the quadrivalent meningococcal vaccine MenACWY-TT co-administered with a combined diphtheria-tetanus-acellular pertussis vaccine versus their separate administration in adolescents and young adults: A phase III, randomized study

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ABSTRACT

Background: This study evaluated the immunogenicity and safety of quadrivalent meningococcal conjugate vaccine using tetanus (T) toxoid as carrier protein (MenACWY-TT) co-administered with combined diphtheria-tetanus-acellular pertussis vaccine (Tdap) versus their separate administration in adolescents and young adults.

Methods: In this phase III, randomized, partially-blind study (NCT01767376), healthy 11–25-year-olds (N = 660) were randomized (1:1:1) to receive MenACWY-TT and Tdap at Month 0 (Co-ad group), MenACWY-TT at Month 0 and Tdap at Month 1 (ACWY_Tdap group) or Tdap at Month 0 and MenACWY-TT at Month 1 (Tdap_ACWY group). Immune responses to MenACWY-TT were measured by serum bactericidal assay using rabbit complement (rSBA). Anti-diphtheria (D), anti-tetanus (T), anti-pertussis toxin (PT), anti-filamentous hemagglutinin (FHA) and anti-pertactin (PRN) antibody concentrations were assessed using enzyme-linked immunosorbent assays. Non-inferiority of immunogenicity was assessed using pre-defined clinical criteria. Safety was also evaluated.

Results: Non-inferiority of immunogenicity of MenACWY-TT and Tdap when co-administered versus their separate administration was demonstrated in terms of rSBA geometric mean titers (GMTs) for 4 meningococcal serogroups and of the percentage of participants with antibody concentrations >1 IU/ml for D and T. Among the pertussis antigens, non-inferiority criteria for geometric mean concentrations (GMCs) were reached for PT, but not met for FHA and PRN. Across all groups, ≥93.2% of participants had vaccine responses to each meningococcal serogroup, ≥99.1% were seroprotected against T and D, and ≥85.5% had booster responses to each pertussis antigen. Robust increases in antibody GMTs/GMCs

Abbreviations: AE, adverse event; ATP, according-to-protocol; CI, confidence interval; D, diphtheria; ELISA, enzyme-linked immunosorbent assay; FHA, filamentous hemagglutinin; GMC, geometric mean concentration; GMT, geometric mean titer; HibMenCY-TT, *Haemophilus influenzae* -MenC/Y conjugate vaccine; IMD, invasive meningococcal disease; IU, international units; Lf, limit of flocculation; LL, lower limit; MenA, serogroup A; MenC, serogroups C; MenW, serogroup W; MenY, serogroups Y; MenACWY-TT, quadrivalent serogroups A, C, W and Y conjugate vaccine using tetanus toxoid as carrier protein; MMRV, measles-mumps-rubella-varicella vaccine; NOCI, new onset of chronic illness; PRN, pertactin; PT, pertussis toxin; rSBA, serum bactericidal assay using rabbit complement; SAE, serious adverse event; T, tetanus; Tdap, combined diphtheria-tetanus-acellular pertussis vaccine; Tdap-HBV-IPV/Hib, combined diphtheria-tetanus-acellular pertussis -hepatitis B-inactivated polio-Hib vaccine; TVC, total vaccinated cohort.

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were observed for all antigens between pre-and post-vaccination. Both vaccines had clinically acceptable safety profiles.
Conclusion: Immune responses to MenACWY-TT and to the T and D antigens from Tdap were not impacted by their co-administration. The lower antibody concentrations observed against the pertussis components may be of limited clinical relevance since robust anti-pertussis booster responses were observed. This study supports concurrent administration of the 2 vaccines in adolescents.

1. Introduction

Despite the availability of meningococcal conjugate vaccines, invasive meningococcal disease (IMD) remains a significant global cause of morbidity and mortality [1–3]. Although most cases are caused by serogroups A (MenA), MenB, MenC, MenW, MenX, or MenY [3], IMD epidemiology and serogroup distribution vary largely by region [4]. In America, Europe and Australia, MenB and MenC are the most common [4], with both MenY and MenW prevalence increasing lately in Europe and Latin America [3,5] while the emergence of MenW was also reported in Australia [6]. In Africa and Asia, MenA causes most IMD cases [4]. However, implementation of mass vaccination programs with serogroup A meningococcal conjugate vaccine has led to a significant decrease of IMD caused by MenA in Africa [7].

Three quadrivalent meningococcal conjugate vaccines are currently available [8]: MenACWY-TT (*Nimenrix*, Pfizer) using tetanus (T) toxoid as carrier protein, which is indicated for individuals from the age of 6 weeks in Europe [9,10]; MenACWY-DT (*Menactra*, Sanofi Pasteur Inc.) with diphtheria (D) toxoid as carrier protein [11], for individuals aged 9 months to 55 years in the United States (US) [12]; and MenACWY-CRM_{197} (*Menveo*, GSK), using diphtheria CRM_{197} protein as carrier protein, for individuals from the age of 2 years in Europe [13], Canada and Australia [14], and for infants from 2 months up to 55 years in the US [15,16].

While IMD incidence is highest in young children with a second peak in 12–19-year olds [4], meningococcal carriage and transmission are the most important in adolescents [17]. Therefore, in addition to the primary vaccination schedule in infants and toddlers, routine meningococcal vaccination is increasingly recommended in many countries for adolescents [17]. However, vaccine coverage is not easy to attain in this age group [18]. Since a combined diphtheria-tetanus-acellular pertussis vaccine is also given routinely during adolescence in many countries, its co-administration with MenACWY-TT may increase vaccination coverage [19].

This study evaluated the immunogenicity and safety of MenACWY-TT and tetanus toxoid-reduced-diphtheria toxoid-acellular pertussis vaccine (Tdap; *Boostrix*, GSK) when co-administered compared to their separate administration in adolescents/young adults from the Dominican Republic, Germany and South Korea. In the Dominican Republic and Germany, IMDs are mainly caused by MenB and MenC, and increases in MenW and MenY incidences have been reported [3,5,20,21]. In South Korea, epidemiological data are limited [7,22,23], but a recent study on meningococcal carriage showed that MenB followed by MenC are the most common serogroups [24]. Targeted vaccination of adolescents may confer direct protection against peaks in disease incidence in this age group, as well as reduce transmission and render herd protection.

2. Methods

2.1. Study design and participants

This phase III, randomized, controlled study was conducted between January 2013 and January 2014 in 1 center in the Dominican Republic, 7 centers in Germany, and 7 centers in the Republic of Korea.

Healthy 11–25-year-olds were randomly assigned (1:1:1) to the Co-ad (receiving MenACWY-TT and Tdap at Month 0), ACWY_Tdap (receiving MenACWY-TT at Month 0 and Tdap at Month 1) and Tdap_ACWY (receiving Tdap at Month 0 and MenACWY-TT at Month 1) groups (Supplementary Fig. S1). Treatment allocation was performed at the investigators' site using an internet-based randomization system, with a minimization algorithm accounting for center and age stratum (11–17 and 18–25 years). The study was partially-blind as the Co-ad group had only 1 vaccination visit. The composition of the vaccines is detailed in the Supplementary Text S1. MenACWY-TT was administered intramuscularly in the left deltoid, and Tdap in the left deltoid when given alone and the right deltoid when co-administered with MenACWY-TT.

Exclusion criteria included history of meningococcal disease, previous vaccination against *N. meningitidis,* and vaccination with Tdap-containing vaccines within 5 years preceding the study. A detailed list of exclusion criteria can be found in Supplementary Text S2. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent/assent was obtained from each participant or participant's parent/guardian prior to enrolment, as applicable. The study protocol and informed consent were reviewed and approved by an Independent Ethics Committee or Institutional Review Board at each center. The study is registered at www.clinicaltrials.gov (NCT01767376). A protocol summary is available at http://www.gsk-clinicalstudyregister.com (study 116705).

2.2. Objectives

The co-primary objectives were assessed in a hierarchical manner to demonstrate: (1) the non-inferiority of MenACWY-TT co-administered with Tdap compared to MenACWY-TT given alone in terms of geometric mean titers (GMTs) against MenA, MenC, MenW and MenY as assessed by serum bactericidal assay using baby rabbit complement (rSBA); the non-inferiority of Tdap co-administered with MenACWY-TT compared to Tdap given alone in terms of (2) the percentage of participants with post-vaccination concentration >1 IU/ml for D and T and (3) geometric mean concentrations (GMCs) for PT, FHA and PRN.

Secondary objectives evaluated the percentages of participants with rSBA titers $\geq$1:8 and $\geq$1:128 and vaccine responses for each meningococcal serogroup, anti-D and anti-T antibody GMCs, and booster responses to PT, FHA and PRN; compared the immunogenicity of MenACWY-TT when given before and after Tdap, and of Tdap when given before and after MenACWY-TT; and assessed the reactogenicity and safety of the study vaccines.

2.3. Immunogenicity assessment

Blood samples were collected at Months 0 and 1 in the Co-ad group, and at Months 0, 1 and 2 in the ACWY_Tdap and Tdap_ACWY groups (Supplementary Fig. S1).

Functional anti-MenA, -MenC, -MenW and MenY antibodies were measured by rSBA at the Public Health England laboratory