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Immunogenicity and reactogenicity of co-administered tetanus–diphtheria–acellular pertussis (Tdap) and tetravalent meningococcal conjugate (MCV4) vaccines compared to their separate administration☆

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ABSTRACT

In the United States, co-administration of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine and tetravalent meningococcal conjugate vaccine (MCV4) is recommended in adolescents. In this clinical study, 1341 adolescents received Tdap (*Boostrix*® GlaxoSmithKline) and MCV4 (*Menactra*®, Sanofi-Pasteur) simultaneously or sequentially one month apart. Co-administration of Tdap + MCV4 was well tolerated and immunogenic, resulting in high levels of antibodies against diphtheria, tetanus, pertussis and meningococcal serogroup A,C,W-135 and Y antigens. The data provide support for current recommendations for co-administration of Tdap and MCV4 vaccines at the same office visit.

1. Introduction

Booster vaccination of adolescents against pertussis was introduced into the United States' routine immunization program in 2005 [1]. A single dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is recommended for all adolescents 11–12 years of age, and for catch-up vaccination of 13–18 year olds if they have not received a Td vaccine within the last 5 years. In the same year, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of adolescents 11–12 years of age against meningococcal disease [2]. This recommendation was extended in 2007 to include catchup vaccination of 13–18 years olds [3]. In adolescents, immunization against meningococcal disease is provided through administration of a single dose of meningococcal vaccine, either tetravalent meningococcal serogroups A, C, Y and W-135 diphtheria toxoid conjugate vaccine (MCV4; *Menactra*®, Sanofi-Pasteur) or the recently approved meningococcal (groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine (MenACWY-CRM; *Menveo*®, Novartis). Based on studies examining simultaneous and sequential administration of Td and MCV4 vaccines, the American Academy of Pediatrics recommends that both the Tdap and MCV4 vaccines should be administered at the same office visit. If co-administration is not feasible, the vaccines are recommended to be given sequentially, with at least one month separating each vaccination [4].

The Tdap vaccine *Boostrix*® (GlaxoSmithKline Biologicals [GSK], Rixensart, Belgium) is licensed in the US as a single-dose booster vaccination for adolescents and adults between 10 and 64 years of age. *Boostrix*® contains the same antigens as GSK's pediatric DTaP vaccine (*Infanrix*®), but in reduced quantities. Efficacy of *Infanrix*® in preventing pertussis (as defined by the World Health Organization) was demonstrated in a household contact study in Germany [5], and in a National Institutes of Health-sponsored efficacy study conducted in Italy [6].

Both Tdap vaccine and the MCV4 vaccine used in this study contain diphtheria toxoid, and concerns about the potential for increased reactogenicity following their sequential administration have been raised [1]. The present study was undertaken to evaluate immunogenicity and safety of co-administered Tdap and MCV4, relative to their sequential administration, in adolescents.

2. Methods

2.1. Study design and subjects

This Phase IV study (GSK study identifier 105753; NCT00282295, www.clinicaltrials.gov) was conducted in 24

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centers in the US between 25 January 2006 and 8 August 2006.

Subjects were healthy adolescents 11–18 years of age who had completed routine childhood vaccination against tetanus, diphtheria and pertussis. Subjects were excluded from participation if they had received their DTP booster (fifth dose) or a Td vaccine within the previous 5 years, or if they had previously been vaccinated against meningococcal disease. Subjects were also excluded if they had received any other investigational or non-registered drug or vaccine within 30 days of study entry; if they had a history of allergic reactions to any vaccine component; if after a previous dose of pertussis vaccine they had experienced clinically significant reactions including encephalopathy, hypotonic–hyporesponsive episodes or abnormal crying, seizures or temperature ≥40.5 °C (105 °F); if they had any progressive neurologic disorder, uncontrolled epilepsy or progressive encephalopathy; acute disease at the time of vaccination; or if they had received immunoglobulins and/or any blood products within the three months before, or their planned administration during, the study. Pregnant or lactating women, and women planning to conceive during the study were also ineligible.

In order to compare both possible sequential vaccination schemes for Tdap and MCV4 to co-administration, subjects were randomized (1:1:1) into one of three groups, all of whom received vaccination with Tdap and MCV4 vaccines. The vaccines were either administered simultaneously in separate limbs (group Tdap + MCV4); or one month apart: Tdap followed one month later by MCV4 (group Tdap → MCV4), or, MCV4 followed one month later by Tdap (group MCV4 → Tdap).

The study was open label with respect to simultaneous or sequential vaccination. Subjects receiving simultaneous vaccination with Tdap and MCV4 were not told which vaccine was injected into which arm. Vaccination in the sequential groups was observer blind. Neither the subjects in the sequential groups nor study site personnel involved in the clinical evaluation of study subjects knew which vaccine was given at any time. Vaccines were prepared and administered by study site staff, who were not otherwise involved in the clinical evaluation of subjects.

The study was conducted according to Good Clinical Practice and in accordance with the Declaration of Helsinki. The protocol and associated documents were reviewed and approved by ethics committees at each study center. Written informed consent was obtained from the parents/guardians of subjects less than 18 years of age before study entry. Subjects 18 years of age provided their own written informed consent. Written assent was also required from subjects younger than 18.

2.2. Study vaccines and administration

A single 0.5 mL dose of Tdap (*Boostrix*®, GlaxoSmithKline) contained: 2.5 Lf diphtheria toxoid (D); 5 Lf tetanus toxoid (T); 8 μg pertussis toxoid (PT); 8 μg filamentous hemagglutinin (FHA); 2.5 μg pertactin (PRN); with ≤0.39 mg aluminum hydroxide. One 0.5 mL dose of MCV4 (*Menactra*®, Sanofi Pasteur) contained 4 μg each of meningococcal serogroup polysaccharides A, C, W-135 and Y, conjugated to 48 μg diphtheria toxoid. Neither vaccine contained preservative. Injections were given intramuscularly into the deltoid using a 22–25 gauge needle, 1–1.5 in. long. In the group receiving simultaneous vaccinations, Tdap was given in the left arm and MCV4 in the right arm. In the sequential administration groups, all vaccinations were given in the left arm.

2.3. Assessment of immunogenicity

Blood samples were collected from all subjects prior to and approximately one month after each vaccination. Sera were stored at −20 °C until analysis at GSK's laboratories, using assays with standardized and validated procedures, and with adequate controls.

Standardized enzyme-linked immunosorbent assays (ELISA) were used to determine serum concentrations of antibodies against diphtheria, tetanus, PT, FHA, and PRN. Antibody concentrations ≥0.1 IU/mL against diphtheria and tetanus toxoids were considered indicative of seroprotection [7,8]. Antibody concentrations ≥5 ELISA units (EL U/mL) against PT, FHA, and PRN, which represented the cut-off for these assays, were pre-specified to indicate seropositivity [9,10].

Antibody levels against meningococcal antigens A, C, W-135 and Y were determined by a serum bactericidal assay based on the CDC protocol [11] using baby rabbit complement. Titers were expressed as the reciprocal of the dilution resulting in 50% inhibition of bactericidal activity. A titer of 8 represented the cut-off of each assay [12,13].

2.4. Assessment of reactogenicity

Subjects were given a diary card at the first visit on which they were asked to record local symptoms (pain, redness and swelling at the injection site) and general symptoms (fatigue, fever [oral temperature ≥37.5 °C or 99.5 °F], gastrointestinal symptoms and headache) that occurred during a 4-day follow-up period (Days 0–3) after each vaccination.

Intensity of solicited symptoms was graded on a scale of 0 (absent) to 3. Grade 3 symptoms were defined for redness and swelling as diameter ≥50 mm; for fever, as temperature ≥39.0 °C (≥102.2 °F); and for pain and all other adverse events, as preventing normal daily activities.

Subjects who experienced a large injection site reaction, defined as swelling with diameter >100 mm at the injection site, diffuse swelling of the injected arm that interfered with or prevented normal activities, or diffuse swelling of the injected arm that involved the shoulder, elbow or chest, were instructed to contact the study site immediately for evaluation. Specific pages for recording of large swelling event data were included in the case report form for completion by the investigator.

All other (unsolicited) adverse events were recorded for 31 days after each vaccine dose. Serious adverse events occurring within 31 days of the final vaccination were recorded. Adverse event symptom intensity was graded by the investigator on a scale of 0–3, where 'Grade 0' was absent and 'Grade 3' referred to symptoms that prevented normal activity.

2.5. Statistical analysis

The primary study objective was to demonstrate non-inferiority, with respect to immune responses, of co-administered Tdap and MCV4 vaccines to those of separately administered vaccines. Immune responses were evaluated in terms of geometric mean antibody concentrations/titers (GMCs/GMTs) and percentages of subjects with booster responses to pertussis antigens and vaccine responses to meningococcal antigens. Booster responses for pertussis antigens were defined as post-vaccination antibody levels ≥20 EL U/mL in subjects who were seronegative (<5 EL U/mL) prior to vaccination, a 4-fold rise in antibody level for subjects with pre-vaccination antibody levels between 5 EL U/mL and 20 EL U/mL, and a 2-fold rise in antibody level for subjects with pre-vaccination antibody levels ≥20 EL U/mL. Vaccine responses for meningococcal antigens were defined as a post-vaccination antibody titer of at least 32 for subjects with pre-vaccination antibody titers below the assay cut-off of 8, and a 4-fold rise in antibody titer for subjects with pre-vaccination titers of at least 8.

Groups were compared by calculating the 2-sided standardized asymptotic 95% CI for group differences in the percentage of