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Safety and immunogenicity of fully liquid DTaP$_5$-IPV-Hib pediatric combination vaccine (Pediacel®) compared to DTaP$_3$-HBV-IPV/Hib (Infanrix® Hexa) when coadministered with heptavalent pneumococcal conjugate vaccine (PCV7) as a booster at 11–18 months of age: A phase III, modified double-blind, randomized, controlled, multicenter study☆

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ABSTRACT

This study compared the safety and immunogenicity of DTaP$_5$-IPV-Hib vaccine (followed by monovalent hepatitis B vaccine [HBV]) and DTaP$_3$-HBV-IPV/Hib vaccines, both coadministered with PCV7, as a fourth-dose booster in toddlers 11–18 months who had a hexavalent vaccine primary series. The fever rate within 4 days of DTaP$_5$-IPV-Hib was noninferior to DTaP$_3$-HBV-IPV/Hib. DTaP$_5$-IPV-Hib induced a marked immune response and had a similar safety and immunogenicity profile compared with DTaP$_3$-HBV-IPV/Hib. Fully liquid DTaP$_5$-IPV-Hib can be used as a booster after a hexavalent vaccine primary series; where required, a fourth dose of monovalent HBV can be administered after DTaP$_5$-IPV-Hib (NCT ID: NCT00355654).

1. Introduction

The fully liquid DTaP$_5$-IPV-Hib vaccine (Pediacel®; Sanofi Pasteur Limited, Toronto, Canada) is indicated to protect against infectious diseases caused by *Clostridium tetani*, *Corynebacterium diphtheriae*, *Bordetella pertussis*, *Haemophilus influenzae* type b (Hib), and poliovirus types 1, 2, and 3 for primary and booster vaccination of infants and toddlers. This licensed pentavalent vaccine contains five-component acellular pertussis antigens (aP$_5$), adsorbed diphtheria and tetanus toxoids, inactivated poliomyelitis vaccine (IPV), and a purified polyribosylribitol phosphate (PRP) capsular polysaccharide of *H. influenzae* type b conjugated to tetanus toxoid.

The safety and immunogenicity of DTaP$_5$-IPV-Hib after a three-dose primary series at 2, 3 and 4 months of age has been demonstrated in clinical studies conducted in the United Kingdom [1–3] and in France and Poland [4]. In addition, DTaP$_5$-IPV-Hib has been evaluated using a three-dose primary series (2, 4 and 6 months or 6, 10 and 14 weeks) and as a fourth-dose booster in the second year of life in Canada [5,6], Mexico [7,8], Taiwan [9,10], the Philippines [11], and France and Poland [4]. To date, no study has examined the safety and immunogenicity of DTaP$_5$-IPV-Hib vaccine administered as a fourth dose booster to toddlers who had received a primary series with a hexavalent vaccine. In addition, a direct comparison between the safety and immunogenicity of DTaP$_5$-IPV-Hib vaccine and DTaP$_3$-HBV-IPV/Hib (Infanrix® hexa; GlaxoSmithKline Biologicals, Rixensart, Belgium) vaccine has not been described for toddlers in this setting.

The incidence of fever, defined as body temperature ≥38.0 °C within 4 days of vaccination, has been reported to be 48–50% in studies conducted in Europe [12,13] using a fourth dose booster of a hexavalent vaccine, DTaP$_3$-HBV-IPV/Hib, concomitantly administered with the heptavalent pneumococcal conjugate vaccine (PCV7). Without PCV7 coadministration, the corresponding

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fever rate after $DTaP_3$-HBV-IPV/Hib vaccination was observed to be lower at 38.8% [12]. The primary objective of this study was to compare the rates of fever in two study groups: toddlers who received $DTaP_5$-IPV-Hib vaccine compared with toddlers who received a licensed hexavalent $DTaP_3$-HBV-IPV/Hib vaccine when both were administered as a fourth dose booster and coadministered with PCV7. In addition, the immune responses to all vaccine antigens were evaluated. A monovalent hepatitis B recombinant vaccine (HBV) was administered to $DTaP_5$-IPV-Hib recipients 1 month after $DTaP_5$-IPV-Hib vaccination. For vaccination schedules requiring a fourth dose of hepatitis B vaccine, the immune response to hepatitis B antigens is presented for both study groups.

2. Methods

This phase III, modified double-blind, randomized, controlled, multicenter study was conducted in Germany (NCT ID: NCT00355654; EudraCT ID: 2006-000898-30) from September 2006 to September 2007. A modified double-blind design was utilized since one of the vaccines ($DTaP_3$-HBV-IPV/Hib) required reconstitution; an unblinded member of the study team prepared and administered the study vaccines but was not involved in collection of other study data. Blinding was discontinued at the second visit to administer HBV to $DTaP_5$-IPV-Hib recipients. The study was conducted in compliance with the Declaration of Helsinki. The study protocol and informed consent forms were approved by the appropriate ethics committee for each study site. Written consent was obtained by parent(s) or legal guardian(s) for each participant prior to initiation of study-specific procedures. The manuscript was prepared following guidelines established by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

2.1. Participants

Eligible participants were toddlers, 11–18 months of age, who had received three doses of a hexavalent vaccine for their primary vaccination series within the first 9 months of life with the last vaccine dose administered at least 6 months before study vaccination. Participants were excluded if they had received a pneumococcal vaccine prior to study initiation. Hence, this study provided the first dose of PCV7 to the participants. Other eligibility requirements can be found at clinicaltrials.gov/ [14].

2.2. Vaccines

The following vaccines were administered in the study: fully liquid $DTaP_5$-IPV-Hib vaccine, $DTaP_3$-HBV-IPV/Hib (Infanrix® hexa; GlaxoSmithKline Biologicals, Rixensart, Belgium), PCV7 (Prevenar®; Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA), and hepatitis B virus recombinant vaccine (Engerix-B®; GlaxoSmithKline). All vaccines were to be maintained at 2–8 °C and 25 mm, 23 gauge needles were provided for administration.

A 0.5-mL dose of $DTaP_5$-IPV-Hib vaccine is composed of diphtheria (15 Lf; ≥30 IU) and tetanus toxoids (5 Lf; ≥40 IU) adsorbed to aluminum phosphate, 5 pertussis antigens (20 μg of pertussis toxoid [PT], 20 μg of filamentous haemagglutinin [FHA], 3 μg of pertactin [PRN], and 5 μg of fimbriae types 2 and 3 [FIM]), IPV (40 D antigen units poliovirus type 1 Mahoney, 8 D antigen units poliovirus type 2 MEF-1, and 32 D antigen units poliovirus type 3 Saukett), and 10 μg of *H. influenzae* type b capsular PRP covalently bound to 20 μg of tetanus toxoid protein carrier. $DTaP_3$-HBV-IPV/Hib contains diphtheria toxoid (≥25 Lf), tetanus toxoid (≥10 Lf), 3 pertussis antigens (aP_3) (PT (25 μg), FHA (25 μg), PRN (8 μg), hepatitis B surface antigen (HBsAg; 10 μg), and IPV and PRP in the same amounts as $DTaP_5$-IPV-Hib in a 0.5 mL dose. The PRP component (10 μg conjugated to 20–40 μg tetanus toxoid) of $DTaP_3$-HBV-IPV/Hib is supplied as a powder, which is reconstituted in a suspension containing all other vaccine components. The monovalent HBV contains 10 μg recombinant HBsAg (S protein) adsorbed per 0.5 mL dose. The product composition of PCV7 vaccine is available in the summary of product characteristics [15].

2.3. Study design

At study entry (Visit 1), participants were randomly assigned in a 1:1 ratio to receive $DTaP_5$-IPV-Hib coadministered with PCV7, followed by HBV 1 month later (Group A) or $DTaP_3$-HBV-IPV/Hib coadministered with PCV7 (Group B). A single 0.5-mL dose of $DTaP_5$-IPV-Hib (Lot C2415AA) or $DTaP_3$-HBV-IPV/Hib (Lots A21CA191A; A21CA192A; A21CA193A, A21CA175A, A21CA202A, A21CA254E and A21CA267C) was administered intramuscularly (IM) into the deltoid. A single dose of PCV7 (Lot 20587) was coadministered IM into the deltoid muscle of the opposite arm.

Visit 2 occurred 28 (+14) days later, when the participants were unblinded and Group A was vaccinated with HBV (Lot AHBVB105AK) IM into the deltoid muscle. Visit 3 occurred 28 (+14) days after Visit 2. Diary cards were provided to the parents/legal representatives to record data for the safety endpoints.

Immunogenicity endpoints were assessed in a subset of participants in both groups. Twenty study sites that anticipated enrolling a high number of participants were pre-selected to enroll participants into the immunogenicity subset. Sera for immunogenicity testing for all study vaccine antigens and PCV7 were collected pre-vaccination at Visit 1 and at Visit 2. Sera to assess the antibody response to the monovalent HBV were collected from participants in Group A at Visit 3.

2.4. Safety endpoints

The primary endpoint for analysis of safety was the rate of fever (body temperature ≥38.0 °C, preferably by the rectal route) reported within 4 days of $DTaP_5$-IPV-Hib + PCV7 or $DTaP_3$-HBV-IPV/Hib + PCV7 vaccination. Secondary safety endpoints were the incidence rate of Grade 3 fever (body temperature ≥39.6 °C) reported within 4 days of vaccination. Observational safety endpoints were the frequency of solicited injection-site reactions, solicited systemic reactions and extensive limb swelling (ELS) within 7 days after vaccination. ELS was defined as swelling extending from the injection site beyond one or both adjacent joints (i.e., elbow and/or shoulder) after administration of $DTaP_5$-IPV-Hib or $DTaP_3$-HBV-IPV/Hib, and required confirmatory assessment by the investigator.

Additional safety endpoints included the frequency of unsolicited adverse events (AEs; within 28 days after vaccination) and serious AEs (SAEs; any time during the study) [16]. Given that all participants were unblinded at Visit 2, safety data on solicited reactions and unsolicited AEs refer to events after vaccines received at Visit 1 (i.e., $DTaP_5$-IPV-Hib, $DTaP_3$-HBV-IPV/Hib, PCV7). All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.0. The data regarding use of antipyretics/analgesics on days 0–7 after vaccination was also gathered.

The intensity of solicited injection-site reactions (tenderness, erythema, swelling) was rated as Grade 1 (minor reaction upon touching, or redness or swelling from >0 to <2.5 cm), Grade 2 (cries and protests upon touching, or redness or swelling ≥2.5 and <5 cm), or Grade 3 (cries when injected limb is moved or movement is reduced, or redness or swelling ≥5 cm). Solicited systemic reactions included fever (Grade 1: ≥38.0 °C to 38.5 °C; Grade 2: ≥38.6 °C to 39.5 °C; Grade 3: ≥39.6 °C), vomiting (Grade 1: 1 episode per 24 h; Grade 2: 2–5 episodes per 24 h; Grade 3: ≥6 episodes per 24 h or requiring parenteral hydration), abnormal crying (inconsolable