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Immunogenicity and safety of fully liquid $DTaP_5$-IPV-Hib compared with $DTaP_3$-IPV/Hib when both coadministered with a heptavalent pneumococcal conjugate vaccine (PCV7) at 2, 3, 4, and 12 to 18 months of age: A phase III, single-blind, randomised, controlled, multicentre study☆

Emmanuel Grimprel[a,*], Jacek Wysocki[b], Florence Boisnard[c], Stéphane Thomas[c], Grace Mwawasi[d], Donna Reynolds[d]

[a] Hôpital Armand Trousseau and Université Pierre et Marie Curie Paris VI, Paris, France
[b] Poznań University School of Medical Sciences and Regional Center for Mother and Child Healthcare, Poznań, Poland
[c] Sanofi Pasteur MSD S.N.C., Lyon, France
[d] Sanofi Pasteur Limited, Toronto, Canada

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ABSTRACT

This study compared immunogenicity and safety of $DTaP_5$-IPV-Hib to $DTaP_3$-IPV/Hib coadministered with PCV7 at 2, 3, and 4 months (primary series) and a fourth-dose booster at 12–18 months of age. Seroprotection rates for $DTaP_5$-IPV-Hib were high (noninferior to $DTaP_3$-IPV/Hib for the primary series) for antigens common to both vaccines and PCV7 antigens. Geometric mean concentration (GMC) for Hib antibodies were higher in the $DTaP_5$-IPV-Hib group than the $DTaP_3$-IPV/Hib group after the primary series and booster dose; GMCs or titers for other antigens were generally similar between groups after the primary series and booster dose. Safety profiles were similar between groups.

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, 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 advantages of a fully liquid formulation over vaccines that require reconstitution include ease of use by healthcare providers, a reduction in errors caused by reconstitution, and a resultant increase in coverage.

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]. 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 fourth-dose booster in the second year of life in Canada [4,5], Mexico [6,7], Taiwan [8,9], and the Philippines [10].

This is the first clinical trial in which $DTaP_5$-IPV-Hib has been coadministered with a heptavalent pneumococcal vaccine (PCV7), and provides safety and immunogenicity data after concomitant usage. Owing to the growing complexity of pediatric vaccine schedules, coadministration of recommended vaccines in clinical trials helps to address the potential for interference of antibody response to study vaccines [11]. This trial also directly compared the safety and immunogenicity of $DTaP_5$-IPV-Hib to a licensed pentavalent

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* Corresponding author at: Hôpital Armand Trousseau, Urgences Pédiatriques, 26 Avenue du Dr. Arnold Netter, 75012 Paris, France. Tel.: +33 1 44 73 62 20; fax: +33 1 44 73 69 85.
E-mail address: emmanuel.grimprel@trs.aphp.fr (E. Grimprel).

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$DTaP_3$-IPV/Hib vaccine using a primary series administered at 2, 3, and 4 months of age and a fourth-dose booster at 12–18 months of age.

2. Methods

This clinical trial was a phase III, single-blind, randomised, controlled, multicentre study conducted in 53 sites in France and 12 sites in Poland (ClinicalTrials.gov Accession #NCT00343421). The study was conducted in compliance with the Declaration of Helsinki. The study protocol and informed consent forms were approved by the institutional ethics committee at each study site. Parent(s) or legal guardian(s) of all participants provided written consent prior to initiation of any study-specific procedures.

2.1. Participants

At study entry, eligible participants were 55–75 days old and born at full term of pregnancy (>37 weeks). Other eligibility requirements can be found at ClinicalTrials.gov. [12]

2.2. Vaccines

The following vaccines were administered in the study: fully liquid $DTaP_5$-IPV-Hib combined vaccine [13], $DTaP_3$-IPV/Hib combined vaccine (Infanrix-IPV®+Hib; GlaxoSmithKline) [14], and PCV7 (Prevenar®; Wyeth Lederle Vaccines S.A.) [15]. $DTaP_3$-IPV/Hib combined vaccine comprises a liquid formulation of $DTaP_3$-IPV that is used to reconstitute the freeze-dried Hib component.

$DTaP_5$-IPV-Hib 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 polysaccharide PRP covalently bound to 20 μg of tetanus toxoid protein carrier per 0.5-mL dose. $DTaP_3$-IPV/Hib contains diphtheria toxoid (≥25 Lf), tetanus toxoid (≥10 Lf), PT (25 μg), FHA (25 μg), PRN (8 μg), and IPV and PRP in the same amounts as $DTaP_5$-IPV-Hib in a 0.5 mL dose. PCV7 consists of capsular antigens of *Streptococcus pneumoniae* individually conjugated to a mutant diphtheria protein (CRM_{197}). The product composition of PCV7 is available in the summary of product characteristics [15].

2.3. Study design

At study entry, healthy infants were randomly assigned in a 1:1 ratio to receive $DTaP_5$-IPV-Hib coadministered with PCV7 (Group A) or $DTaP_3$-IPV/Hib coadministered with PCV7 (Group B). A single 0.5-mL dose of $DTaP_5$-IPV-Hib or $DTaP_3$-IPV/Hib was administered IM into the anterolateral aspect of the thigh at 2, 3, and 4 months (primary series). A fourth-dose was administered between 12 and 18 months of age (booster dose) in the deltoid muscle. PCV7 was coadministered IM into the contralateral limb.

Sera were obtained within 7 days before the first dose to assess prevaccination antibodies to pertussis antigens (PT, FHA, PRN, and FIM). Sera were also obtained 28–42 days after Dose 3, within 7 days before booster Dose 4, and 28–42 days after Dose 4 to assess antibody responses elicited by all test vaccine antigens and PCV7 pneumococcal antigens.

2.4. Endpoints

The primary immunogenicity endpoints were the proportion of participants achieving seroprotective titers and seroresponses to vaccine antigens 1 month (28–42 days) after receiving Dose 3. The antibody seroprotective endpoints included PRP ≥0.15 μg/mL, diphtheria toxoid ≥0.01 IU/mL, tetanus toxoid ≥0.01 IU/mL, poliovirus types 1, 2, and 3 ≥1:8 dilution, and pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F ≥0.35 μg/mL. Antibody seroresponse to pertussis antigens was defined as the proportion of participants achieving antibody concentrations at or above the assay lower limit of quantitation (LLOQ; PT > 4 EU/mL, FHA > 3 EU/mL, PRN > 4 EU/mL, and FIM > 4 EU/m) when baseline concentrations were below LLOQ or maintenance of the baseline antibody concentration in those who were initially above the LLOQ. The secondary immunogenicity endpoints were the assessment of geometric mean concentrations (GMCs) or geometric mean titers (GMTs) of antibodies against antigens in the test vaccines and PCV7 vaccine after the primary series and after the booster dose; proportion of participants achieving seroprotective titers to PRP (≥1 μg/mL), diphtheria toxoid (≥0.1 IU/mL), and tetanus toxoid (≥0.1 IU/mL) 1 month (28–42 days) after receiving Dose 3 in the primary series and 1 month (28–42 days) after receiving booster Dose 4; and booster response rates for pertussis antigens after the Dose 4 booster. The pertussis booster response rates were defined as ≥4-fold increase in antibody concentration if the pre-booster dose was <4x LLOQ, otherwise ≥2-fold increase).

Safety endpoints included the frequency of solicited injection site reactions and solicited systemic reactions and data were collected using a diary card for 7 days after each vaccination. Additional safety endpoints included the frequency of unsolicited adverse events (AEs; reported within 28 days after each injection) and serious adverse events (SAEs; reported at any time during the study). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.0. The intensity of solicited injection site reactions was rated as Grade 1 (minor tenderness 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 hour; Grade 3: ≥6 episodes per hour or requiring parenteral hydration), abnormal crying (inconsolable crying without a reason; Grade 1: <1 h duration; Grade 2: 1–3 h duration; Grade 3: >3 h duration), drowsiness (Grade 1: sleepier than usual or less interested in surroundings; Grade 2: not interested in surroundings or did not wake up for a meal; Grade 3: sleeping most of the time or difficulty waking), lost appetite (Grade 1: eating less than normal; Grade 2: missed 1 or 2 feedings completely; Grade 3: refuses ≥3 feedings or refused most feedings), and irritability (Grade 1: easily consolable; Grade 2: requiring increased attention; Grade 3: inconsolable).

2.5. Serologic evaluations

Antibodies to diphtheria toxin were measured by the ability of the test sera to protect Vero cells from a diphtheria toxin challenge. Antibodies to tetanus toxoid and pertussis antigens (PT, FHA, PRN, and FIM) were assessed by enzyme-linked immunosorbent assay (ELISA). Antibodies to poliovirus antigens were measured by microbiological neutralization in Vero cells. Antibodies to PRP were assessed by a Farr-type radioimmunoassay (RIA). Response to PCV7 was determined by measurement of antibodies to pneumococcal polysaccharides specific for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F by ELISA.

Pneumococcal antibody assessments were performed by validated assay at Professor D. Goldblatt's Laboratory, Institute of Child Health, University College, London, UK. All other assessments were