



Safety and immunogenicity of a hexavalent DTwP-IPV-HB-PRP~T vaccine versus separate DTwP-HB-PRP~T and IPV vaccines in healthy infants in India



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ABSTRACT

Background: Multivalent vaccines containing whole-cell pertussis (wP) antigens combined with established diphtheria (D), tetanus (T), hepatitis B (HB), *Haemophilus influenzae* type b (Hib), and inactivated poliomyelitis (IPV) antigens allow the provision of a high-quality, affordable DTwP-IPV-HB-PRP~T vaccine.

Methods: Phase I/II, randomized, active-controlled, open-label study in healthy toddlers (Cohort I) and infants (Cohort II). Toddlers in Cohort I who had completed primary series D, T, P, HB, Hib, and polio vaccination received a booster dose of DTwP-IPV-HB-PRP~T (N = 30) or DTwP-HB-PRP~T + IPV (N = 15) vaccines at 15–18 months of age. After satisfactory review of safety data in Cohort I, infants in Cohort II received DTwP-IPV-HB-PRP~T (N = 100) or DTwP-HB-PRP~T + IPV (N = 50) at 6–8, 10–12, and 14–16 weeks of age. All infants in Cohort II had received previous oral polio and HB vaccines per country recommendations.

Results: Booster and primary series vaccinations were well tolerated with no clinically significant differences between vaccine groups. Most adverse events were mild and resolved spontaneously; there were no vaccine-related serious adverse events and no deaths. In both vaccine groups, anti-D, anti-T, anti-HB, anti-Hib, and anti-polio 1, 2, and 3 seroprotection was 100% post-booster and post-primary series. For the pertussis antigens, booster response rate was > 86% in both groups. For the primary series, vaccine response rate was slightly higher for DTwP-IPV-HB-PRP~T than DTwP-HB-PRP~T + IPV for anti-PT (80.2% and 70.8%) and anti-FHA (81.3% and 68.8%), slightly lower for anti-PRN (72.5% and 81.3%), and similar in each group for anti-FIM (95.6% and 97.9%).

Conclusions: This study demonstrated a good safety and immunogenicity profile of the hexavalent DTwP-IPV-HB-PRP~T vaccine for infant primary series vaccination at 6–8, 10–12, and 14–16 weeks of age and booster vaccination at 15–18 months of age and supported progression to the next development phase.

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Introduction

Pediatric vaccines that incorporate several antigens in a single administration facilitate high vaccine coverage and compliance. Such vaccines are used routinely globally and have been critical in achieving dramatic decreases in the global incidence of childhood diseases such as diphtheria (D), tetanus (T), pertussis, hepatic

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tis B (HB), *Haemophilus influenzae* type b (Hib) infection, and polio [1,2].

A pentavalent vaccine containing D, T, whole cell pertussis (wP), HB, and Hib antigens (SHAN5[®]) was licensed in India by Sanofi Healthcare India Private Limited (SHIPL) (formerly Shanta Biotechnics Private Ltd) in March 2014 and pre-qualified by the World Health Organization (WHO) in April of the same year. It is currently licensed in >20 countries globally with approximately 150 million doses having been administered. The inactivated poliomyelitis vaccine (IPV) SHANIPV[™] was licensed in India in 2015 on the basis of the international licenses of Imovax Polio manufactured by the parent company of SHIPL (Sanofi Pasteur).

To support the objective of the Global Polio Eradication Initiative outlined in the last edition of its 2019–2023 Endgame Strategic Plan [3] and in alignment with market needs [4] SHIPL developed SHAN6[™], a fully liquid, ready-to-use, wP-IPV hexavalent vaccine (DTwP-IPV-HB-PRP~T vaccine) by combining the SHAN5 and SHANIPV antigens. The D, T, wP, HB, Hib, and IPV antigens contained in SHAN6 have been extensively evaluated in prior clinical development. The D, T, and wP antigens are the same as those included in SHAN5 with the exception of thiomersal preservative [5] and the wP antigen is derived from the historical *Bordetella pertussis* seed strains used by Sanofi Pasteur for its established DTwP trivalent (DTCoq[®]), DTwP-IPV quadrivalent (TETRACoq[®]), and pentavalent DTwP-IPV//Hib (PENTACOq[®]) vaccines [6–8]; the HB antigen is *Hansenula polyporpha*-derived and is the same as the HB component of Sanofi Pasteur's Hexaxim[™] (an aP-containing hexavalent vaccine also licensed as Hexyon[™] and Hexacima[™]) [9] produced using its manufacturing facility in Argentina [10]; the Hib component is produced by SHIPL in India by the conjugation of purified capsular polysaccharide (PRP) provided by Sanofi Pasteur France and used in Hexaxim with tetanus toxoid carrier protein from SHIPL [5]; and the trivalent IPV is also used in Hexaxim and IMOVAX[®] Polio and bulk is supplied by Sanofi Pasteur France, with formulation, filling, and packaging steps conducted at SHIPL. The Hib and IPV components are also used in Sanofi Pasteur's well-established aP-containing pentavalent vaccine, Pentaxim[®] [11]. Good primary series safety and immunogenicity have previously been demonstrated for Hexaxim and Pentaxim in a 6, 10, 14 week schedule in India [12,13] and South Africa [14,15].

The development of a wP-containing hexavalent vaccine in addition to existing acellular pertussis (aP)-containing vaccines was considered important to offer a high-quality vaccine at a cost that is affordable for developing countries. Since the antigens included in SHAN6 have been approved and marketed as either established standalone or combination vaccines, robust immunogenicity was expected for each antigen. The primary objective of the present study was therefore to evaluate the safety profile of the new hexavalent vaccine in a Phase I/II stepwise trial design approach. Assessment of immunogenicity was included as secondary objectives.

Materials and methods

Study design and participants

This was a Phase I/II, randomized, active-controlled, open-label study conducted in toddlers (Cohort I) and infants (Cohort II) at 4 sites in India (Clinical Trials Registry India Number CTRI/2016/11/007434). The study protocol and one amendment were approved by the institutional ethics committee of each study site and the study was performed according to local and national regulations and was consistent with the standards established by the Declaration of Helsinki and compliant with the International

Council for Harmonization guidelines for Good Clinical Practice. An informed consent form was signed by each participant's parents or legally acceptable representatives before enrolment into each study. The study was conducted between November 2016 and October 2017.

In Cohort I, healthy toddlers aged 15–18 months who had completed a primary infant series vaccination against D, T, P, HB, Hib, and polio were eligible for inclusion. In Cohort II, healthy infants aged 6–8 weeks, born at full-term (≥ 37 weeks), with birth weight ≥ 2.5 kg, who had received a birth dose of oral poliovirus vaccine (OPV), HB vaccine, and Bacillus Calmette-Guérin (BCG) vaccine ≥ 4 weeks prior to the first study vaccination were eligible for inclusion. The main exclusion criteria in both groups were recent (in the 4 weeks prior to the first vaccination) or planned participation in another clinical study; known hypersensitivity to any vaccine component; any chronic illness that could interfere with study conduct or completion; receipt of blood products in the 30 days prior to inclusion or planned during the study; history of diphtheria, tetanus, pertussis, Hib, HB, or poliovirus infection; personal/maternal history of human immunodeficiency virus, HB or hepatitis C infection; known thrombocytopenia, bleeding disorder, or receipt of anticoagulants in the 3 weeks prior to inclusion; history of seizures; acute illness or febrile illness on the day of vaccination. Additionally, participants were excluded for receipt of immunosuppressive therapy for more than 2 consecutive weeks in the past 3 months (Cohort I) or for more than 2 consecutive weeks (Cohort II), any planned vaccination in the 4 weeks following study vaccination or booster dose scheduled in the second year of life (Cohort I), planned receipt of any other non-study vaccine from 8 days before to 8 days after each study vaccination or previous vaccination (other than the birth dose of OPV, HB, and BCG vaccines) or planned receipt of any D, T, P, HB, Hib, or poliomyelitis vaccine other than the study vaccines in the 4 weeks following study vaccination (Cohort II).

In Cohort I, 45 toddlers were randomized in a 2:1 ratio using permuted blocks and stratified by site to receive a single dose of either the fully liquid hexavalent vaccine (DTwP-IPV-HB-PRP~T) or separately administered DTwP-HB-PRP~T and IPV vaccines at 15–18 months of age. After independent review by a Data Safety Monitoring Board (DSMB) of the safety data from Cohort I, 30 infants in Cohort II were randomized in a 2:1 ratio to receive either the DTwP-IPV-HB-PRP~T vaccine or separately administered DTwP-HB-PRP~T and IPV vaccines at 6–8, 10–12, and 14–16 weeks of age. A further 120 infants were enrolled in Cohort II following review of the first dose safety data by the DSMB from the first 30 infants in Cohort II.

Study vaccines were administered by intramuscular injection into the anterolateral aspect of the left thigh (DTwP-IPV-HB-PRP~T or DTwP-HB-PRP~T vaccines) and right thigh when applicable (IPV vaccine).

Study vaccines

The hexavalent DTwP-IPV-HB-PRP~T vaccine (SHAN6, batch number HPCK0216, expiry date January 2018) was manufactured by SHIPL and supplied as a liquid, sterile suspension for injection in a single dose vial. Each 0.5 mL dose contained ≥ 30 IU D-toxoid, ≥ 60 IU T-toxoid, ≥ 4 IU whole-cell *B. pertussis* organisms, 10 μ g rDNA HB surface antigen (HBsAg), 12 μ g Hib purified capsular polysaccharide conjugated to 20–40 μ g tetanus toxoid carrier protein, 40, 8 and 32 D antigen units of poliovirus type 1 (Mahoney strain), type 2 (MEF-1 strain), and type 3 (Saukett strain), respectively, and 0.625 mg aluminum phosphate as adjuvant.

The pentavalent DTWP-HB-PRP~T vaccine (SHAN5, batch number PLK033B15, expiry date September 2017) was manufactured by SHIPL and supplied as a liquid, sterile suspension for injection in a 10 dose vial. Each 0.5 mL dose contained ≥ 30 IU D-toxoid, ≥ 60 IU T-toxoid, ≥ 4 IU whole-cell *B. pertussis* organisms, 10 μ g Hib purified capsular polysaccharide conjugated to 20–40 μ g tetanus toxoid carrier protein, 10 μ g rDNA HB surface antigen (HBsAg), and 0.625 mg aluminum phosphate as adjuvant.

The IPV vaccine (SHANIPV, batch number IPQ002A16, expiry date December 2017) was manufactured by SHIPL and supplied as a liquid, sterile suspension for injection in a 5 dose vial. Each 0.5 mL dose contained 40, 8 and 32 D antigen units of poliovirus type 1 (Mahoney strain), type 2 (MEF-1 strain), and type 3 (Saukett strain), respectively.

Reactogenicity and safety

Participants were observed at the study site for 30 min after each vaccination to assess immediate unsolicited adverse events (AEs). Subsequently, parent(s)/legal representative(s) used diary cards for 7 days after each vaccination to record the duration and intensity (Grade 1 [mild] to 3 [severe]) of solicited injection site reactions (tenderness, erythema, swelling) and solicited systemic reactions (fever, vomiting, crying abnormal, drowsiness, appetite lost, irritability) reactions. All solicited reactions were automatically considered to be related to the vaccination. For temperature measurement the axillary route was preferred.

Unsolicited AEs were recorded using diary cards for 28 days after each vaccination. All unsolicited injection site AEs were automatically considered to be related to the vaccination and the Investigator assessed unsolicited systemic AEs for causality and intensity (Grade 1, no interference with activity; Grade 2, some interference with activity; Grade 3, significant - prevents daily activity).

Serious adverse events (SAEs) and AEs of special interest (anaphylaxis/hypersensitivity, convulsions [including febrile convulsion], and hypotonic hyporesponsive episodes) were collected throughout the study and the Investigator assessed their causality.

Table 1
Summary of serological assessments by antigen, assay, laboratory, and cohort.

	Cohort I		Cohort II	
	Assay (LLOQ)	Laboratory	Assay (LLOQ)	Laboratory
Diphtheria	ELISA (NovaTec) (0.01 IU/mL ^a)	QDI	ELISA (NovaTec) (0.01 IU/mL ^a)	QDI
	DTP-ECL (0.007 IU/mL)	GCI	DTP-ECL (0.007 IU/mL)	GCI
Tetanus	ELISA (IBL) (0.0004 IU/mL ^b)	QDI	ELISA (IBL) (0.0004 IU/mL ^b)	QDI
	DTP-ECL (0.01 IU/mL)	GCI	DTP-ECL (0.01 IU/mL)	GCI
Pertussis				
PT	DTP-ECL (4 EU/mL)	GCI	DTP-ECL (4 EU/mL)	GCI
FHA	DTP-ECL (3 EU/mL)	GCI	DTP-ECL (3 EU/mL)	GCI
PRN	DTP-ECL (4 EU/mL)	GCI	DTP-ECL (4 EU/mL)	GCI
FIM	DTP-ECL (4 EU/mL)	GCI	DTP-ECL (4 EU/mL)	GCI
HB	ELISA (VITROS) (5 mIU/mL)	QDI	ELISA (VITROS) (5 mIU/mL)	QDI
Hib	ELISA (Binding Site) (0.11 μ g/mL ^a)	QDI	ELISA (Binding Site) (0.11 μ g/mL ^a)	QDI
Polio	MIT (4 1/dil)	GCI	MIT (4 1/dil)	GCI

See text for abbreviations.

^a Analytical sensitivity.

^b Refers to limit of detection.

Serology

Blood samples (approximately 3–5 mL) were collected in Cohort I pre-vaccination and 28 days post-vaccination, and in Cohort II pre-first vaccination and 28 days post-third vaccination for determination of antibodies to all antigens (anti-D, anti-T, anti-pertussis, anti-Hib, anti-HB, anti-polio 1, anti-polio 2, and anti-polio 3).

Assays were performed at either Quest Diagnostics India Pvt Ltd (QDI) (Delhi, India) or Sanofi Pasteur's Global Clinical Immunology (GCI) laboratory (Swiftwater, PA, USA).

Commercial enzyme linked immunosorbent assay (ELISA) kits were used at QDI to measure anti-D (NovaTec Immunodiagnostica GmbH, Germany), anti-T (IBL International GmbH, Germany), anti-HB (VITROS, Ortho Clinical Diagnostics, United Kingdom), and anti-Hib (Binding Site Ltd, United Kingdom) antibody concentrations.

At GCI, a validated MesoScale Discovery Multiplexed Electro Chemoluminescence (DTP-ECL) immunoassay [16,17] was used to measure anti-D, anti-T, and anti-pertussis (anti-pertussis toxin [PT], anti-filamentous hemagglutinin [FHA], anti-pertactin [PRN], and anti-fimbriae 2/3 [FIM]) antibodies. Poliovirus neutralizing antibody titers were measured at GCI by micro metabolic inhibition testing (MIT) against wild type strains.

Table 1 summarizes the serological assessments for each antigen by assay (ELISA [NovaTec, IBL, VITROS, Binding Site], DTP-ECL, or MIT), laboratory (QDI or GCI), and cohort.

Statistical analyses

No statistical hypotheses were tested and all evaluations were descriptive. The sample size was chosen for the identification of common AEs with a total of 30 participants in the DTWP-IPV-HB-PRP~T group in Cohort I allowing for the detection of an AE occurring with a frequency of 10% or more and a total of 100 participants in the DTWP-IPV-HB-PRP~T group in Cohort II allowing for the detection of an AE occurring with a frequency of 3% or more, each using the rule of three [18] and with 95% probability. A drop-out rate of approximately 5% (Cohort I) and 10% (Cohort II) was

assumed for the immunogenicity assessment and overall sample sizes were 45 participants for Cohort I and 150 participants for Cohort II.

Seroprotection was defined as anti-D antibody ≥ 0.01 IU/mL, anti-T ≥ 0.01 IU/mL, anti-HBs ≥ 10 mIU/mL, anti-Hib ≥ 0.15 μ g/mL, and anti-polio 1, 2, and 3 titers ≥ 8 1/dil. For pertussis responses, booster responses (for anti-PT, anti-FHA, anti-PRN, and anti-FIM) for Cohort I were defined in participants with pre-booster concentrations $< 4 \times$ LLOQ as post-booster concentrations $\geq 4 \times$ pre-booster concentrations, and in participants with pre-booster concentrations $\geq 4 \times$ LLOQ as post-vaccination titers $\geq 2 \times$ pre-booster concentrations. Vaccine responses for Cohort II participants were defined as in participants with pre-vaccination concentrations $< 4 \times$ LLOQ as post-vaccination concentrations $\geq 4 \times$ pre-vaccination concentrations, and in participants with pre-vaccination concentrations $\geq 4 \times$ LLOQ as post-vaccination titer \geq pre-vaccination concentrations. The lower limits of quantification (LLOQ) for each assay are shown in Table 1.

Data were also presented for the following thresholds: anti-D ≥ 0.1 and ≥ 1.0 IU/mL, anti-T ≥ 0.1 and ≥ 1.0 IU/mL, anti-HB ≥ 100 mIU/mL, anti-Hib ≥ 1.0 μ g/mL. The percentage of participants with a ≥ 4 -fold rise in anti-PT, anti-FHA, anti-PRN, and anti-FIM antibody titers are presented post-vaccination in Cohort I and post-third vaccination in Cohort II. Additionally, geometric mean concentrations (GMCs: anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, anti-FIM, anti-HB, anti-Hib) geometric mean titers (GMTs: anti-polio 1, 2, and 3), and the ratio of post/pre-vaccination (Cohort I) and post-primary/pre-primary (Cohort II) are presented for all antigens.

Data are presented with their 95% confidence intervals (CIs), calculated using the exact binomial distribution (Clopper-Pearson method) [19] for proportions and the normal approximation method for GMCs and GMTs.

The safety analysis set (SafAS) population was used for all safety analyses (participants who received at least one vaccination) and the Full analysis set (FAS) was used for the immunogenicity analyses (participants who received at least one vaccination and analyzed according to the randomization).

The statistical analyses were done under the responsibility of Sanofi Pasteur's biostatistics group using SAS[®] software, Version 9.4 (SAS Institute, Cary, NC, USA).

Results

Participants studied

In Cohort I, a total of 45 participants were randomized to receive a single dose of either DTwP-IPV-HB-PRP~T (N = 30) or DTwP-HB-PRP~T + IPV (N = 15) (Fig. 1). In each group the male:female ratio (50:50 and 40:60), mean \pm SD age (16.4 \pm 1.0 and 16.3 \pm 1.0 months), and mean \pm SD weight (9.58 \pm 1.16 and 9.07 \pm 1.09 kg) were similar.

In Cohort II, a total of 150 participants were randomized to receive three doses of either DTwP-IPV-HB-PRP~T (N = 100) or DTwP-HB-PRP~T + IPV (N = 50) (Fig. 1). In each group the male:female ratio (51:49 and 50:50), mean \pm SD age at first vaccination (6.3 \pm 0.53 and 6.2 \pm 0.51 months), and mean \pm SD birth weight (2.94 \pm 0.33 and 3.02 \pm 0.37 kg) were similar.

All participants in Cohort I completed the study; in Cohort II, 91/100 participants (DTwP-IPV-HB-PRP~T) and 48/50 participants (DTwP-HB-PRP~T + IPV) completed the study (Fig. 1).

Safety and tolerability

There were no immediate AEs (i.e. within 30 min after any vaccination) in Cohort I or Cohort II.

In Cohort I, the overall incidence of participants with at least one solicited injection site or solicited systemic reaction was slightly higher for DTwP-IPV-HB-PRP~T (96.7% and 90.0%) than DTwP-HB-PRP~T + IPV (86.7% and 80.0%) (Table 2). In each group the most common solicited injection site reaction was tenderness (93.3% and 73.3%); the most common solicited systemic reactions were irritability for DTwP-IPV-HB-PRP~T (70.0%) and fever for DTwP-HB-PRP~T + IPV (73.3%). Grade 3 injection site reactions were only reported by 2 participants in the DTwP-IPV-HB-PRP~T group and 1 participant in the DTwP-HB-PRP~T + IPV group; no Grade 3 solicited systemic reactions were reported. Most solicited injection site reactions resolved spontaneously within 3 days. Unsolicited AEs occurred in 10% of participants in the DTwP-IPV-HB-PRP~T group and none in the DTwP-HB-PRP~T + IPV group. None was rated as Grade 3 in intensity. In the DTwP-IPV-HB-PRP~T group, 3 participants (6.7%) reported unsolicited AEs: 2 episodes of injection site nodule in 2 participants that were Grade 1 in intensity, related to the study vaccine, and which resolved within 3 weeks without medication, and a single episode of rectal abscess and staphylococcal infection in another participant that was not related to the study vaccine. The rectal abscess and staphylococcal infection resolved after hospitalization and so was classed as SAEs but not considered to be related to vaccination. No AE of special interest was reported in either cohort.

In Cohort II after any vaccination, the overall incidence of participants with at least one injection site reaction was similar for DTwP-IPV-HB-PRP~T (79.8%) and DTwP-HB-PRP~T + IPV (81.6%); for solicited systemic reactions the incidence was slightly higher for DTwP-IPV-HB-PRP~T (82.8%) than DTwP-HB-PRP~T + IPV (73.5%). In each group the most common injection site reaction was tenderness and the most common solicited systemic reaction was irritability (Table 1). Grade 3 injection site and systemic reactions were reported by 29.3% and 5.1% of participants in the DTwP-IPV-HB-PRP~T group and 10.2% and 4.1% of participants in the DTwP-HB-PRP~T + IPV group. Generally, the incidence of solicited injection site and systemic reactions either reduced or stayed similar after each subsequent vaccination. The overall incidence of unsolicited AEs was slightly higher for DTwP-HB-PRP~T + IPV (20.0%) than DTwP-IPV-HB-PRP~T (14.0%), with most in each group being Grade 1 in intensity, occurring later than 14 days post-vaccination, and lasting < 14 days. Of these, episodes of injection site discoloration, indentation, induration, and nodule were considered to be related to vaccination in the DTwP-IPV-HB-PRP~T group and none was considered to be related to vaccination in the DTwP-HB-PRP~T + IPV group. In 1 participant, two episodes of vaccine-related induration after the first and second dose led to discontinuation of the participant from the study. Two participants experienced SAEs, which were not related to the study vaccine: episodes of gastroenteritis, dehydration, septic shock, and hepatic ischemia in a 4 month old girl who had received 3 doses of DTwP-IPV-HB-PRP~T and which resolved within 4 days after hospitalization (the participant remained in the study), and congenital heart disease with congestive cardiac failure in a 3 month old boy who had received 2 doses of DTwP-IPV-HB-PRP~T and which resolved within 142 days after hospitalization (the participant was discontinued from the study).

There were no vaccine-related SAEs and no deaths in either cohort during the study.

Immunogenicity

Cohort I

Pre-vaccination, anti-D ≥ 0.01 IU/mL, anti-T ≥ 0.01 , anti-HB ≥ 10 mIU/mL, anti-Hib ≥ 0.15 μ g/mL, and anti-polio 1, 2, and 3 antibody titers ≥ 8 1/dil were all $> 93\%$ in each group, and all increased to 100.0% post-vaccination (Table 3). The results

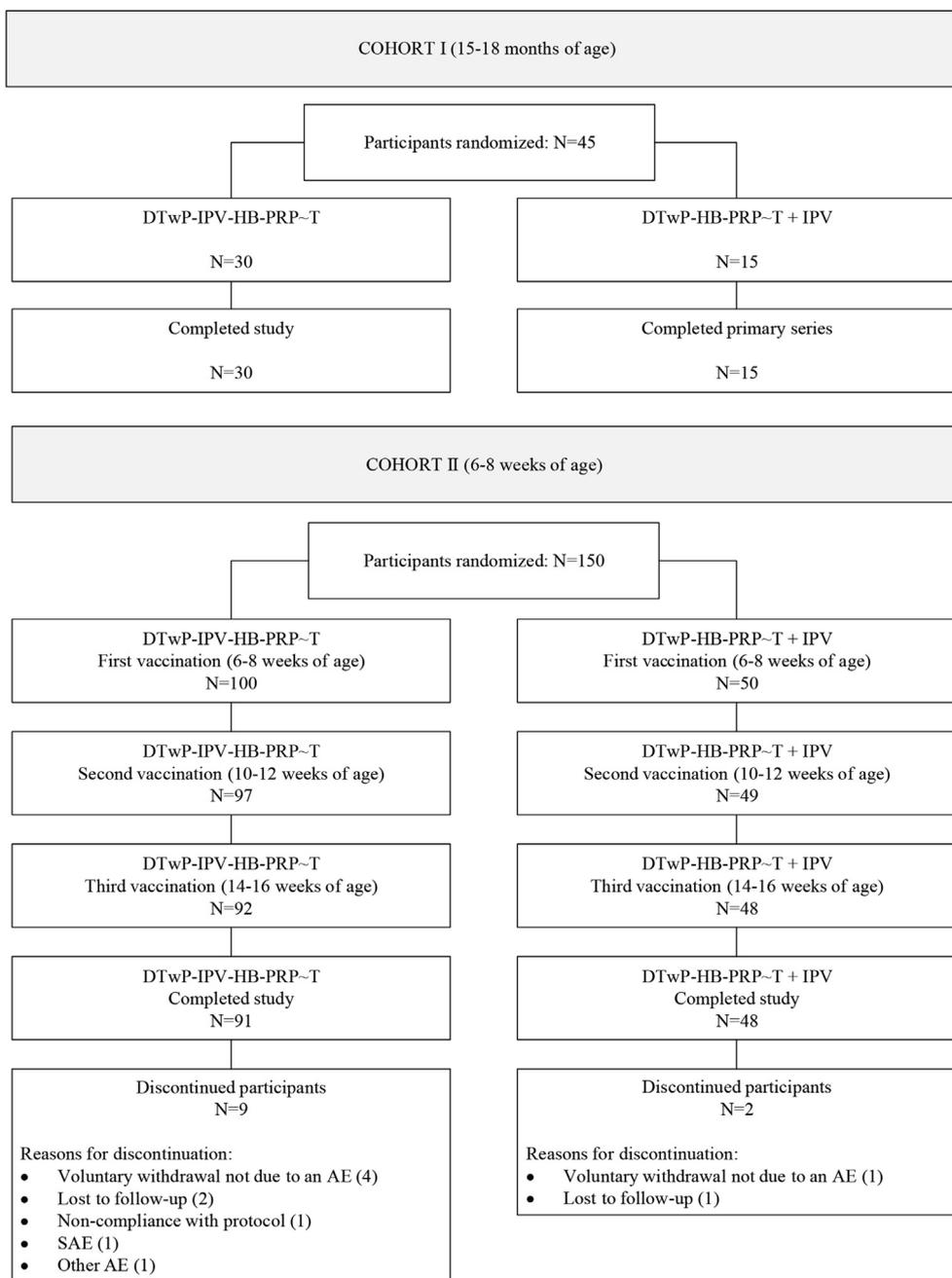


Fig. 1. Disposition of study participants.

obtained using ELISA or DTP-ECL were similar. Additionally, all other pre-defined thresholds for these antigens increased to 100.0% post-vaccination in each group. For pertussis responses (anti-PT, anti-FHA, anti-PRN, and anti-FIM) there was little difference between groups pre-vaccination and the post-vaccination vaccine response (anti-PT, anti-FHA, anti-PRN, and anti-FIM) was strong with little difference between groups (ranging from 86.7% [anti-PRN] in both groups to 96.7% [anti-FHA and anti-FIM] for DTwP-IPV-HB-PRP~T and 100.0% [anti-FIM] for DTwP-HB-PRP~T + IPV). Geometric mean concentrations and GMTs (Table 5) showed some differences between groups, with post-vaccination anti-T GMC and anti-polio 1, 2, and 3 GMTs being slightly higher for DTwP-HB-PRP~T + IPV and anti-wP, GMCs being slightly higher for DTwP-IPV-HB-PRP~T.

Cohort II

Pre-primary vaccination seroprotection rates and other pre-defined thresholds for anti-D, anti-T, anti-HB, anti-Hib, and anti-IPV (Table 4), as well as GMCs and GMTs (Table 6), were generally similar in each group.

Post-primary series vaccination GMCs increased for anti-D, anti-PT, anti-FHA, anti-PRN, anti-FHA, anti-HB, and anti-Hib and were generally similar for each group whereas the post-vaccination increase in anti-polio 1, 2, and 3 GMTs were higher for DTwP-IPV-HB-PRP~T than DTwP-HB-PRP~T + IPV (Table 6). Anti-T GMCs decreased slightly post-vaccination as the result of the very high pre-existing maternal antibodies. Anti-D ≥ 0.01 IU/mL, anti-T ≥ 0.01 and ≥ 0.10 , anti-HB ≥ 10 mIU/mL, anti-Hib ≥ 0.15 μ g/mL, and anti-polio 1, 2, and 3 ≥ 8 1/dil antibody

Table 2
Immediate, solicited, unsolicited, and serious adverse events during the study.

Participants with at least one:	DTwP-IPV-HB-PRP~T			DTwP-HB-PRP~T + IPV		
	n/M	%	(95% CI)	n/M	%	(95% CI)
COHORT I						
Immediate unsolicited AE	0/30	0.0	(0.0;11.6)	0/15	0.0	(0.0;21.8)
Solicited reaction	29/30	96.7	(82.8;99.9)	13/15	86.7	(59.5;98.3)
Solicited injection site reaction	29/30	96.7	(82.8;99.9)	11/15	73.3	(44.9;92.2)
Tenderness	28/30	93.3	(77.9;99.2)	11/15	73.3	(44.9;92.2)
Erythema	14/30	46.7	(28.3;65.7)	3/15	20.0	(4.3;48.1)
Swelling	18/30	60.0	(40.6;77.3)	6/15	40.0	(16.3;67.7)
Solicited systemic reaction	27/30	90.0	(73.5;97.9)	12/15	80.0	(51.9;95.7)
Fever	15/30	50.0	(31.3;68.7)	10/15	66.7	(38.4;88.2)
Vomiting	3/30	10.0	(2.1;26.5)	0/15	0.0	(0.0;21.8)
Crying abnormal	13/30	43.3	(25.5;62.6)	6/15	40.0	(16.3;67.7)
Drowsiness	6/30	20.0	(7.7;38.6)	5/15	33.3	(11.8;61.6)
Appetite lost	15/30	50.0	(31.3;68.7)	5/15	33.3	(11.8;61.6)
Irritability	21/30	70.0	(50.6;85.3)	5/15	33.3	(11.8;61.6)
Unsolicited AE	3/30	10.0	(2.1;26.5)	0/15	0.0	(0.0;21.8)
Unsolicited AR	2/30	6.7	(0.8;22.1)	0/15	0.0	(0.0;21.8)
AE leading to study discontinuation	1/30	3.3	(0.1;17.2)	0/15	0.0	(0.0;21.8)
SAE	0/30	0.0	(0.0;11.6)	0/15	0.0	(0.0;21.8)
Death	0/30	0.0	(0.0;11.6)	0/15	0.0	(0.0;21.8)
COHORT II^a						
Immediate unsolicited AE	0/100	0.0	(0.0;3.6)	0/50	0.0	(0.0;7.1)
Solicited reaction	87/99	87.9	(79.8;93.6)	42/49	85.7	(72.8;94.1)
Solicited injection site reaction	79/99	79.8	(70.5;87.2)	40/49	81.6	(68.0;91.2)
Tenderness	77/79	77.8	(68.3;85.5)	38/49	77.6	(63.4;88.2)
Erythema	38/99	38.4	(28.8;48.7)	16/49	32.7	(19.9;47.5)
Swelling	60/99	60.6	(50.3;70.3)	28/49	57.1	(42.2;71.2)
Solicited systemic reaction	82/99	82.8	(73.9;89.7)	36/49	73.5	(58.9;85.1)
Fever	51/99	51.5	(41.3;61.7)	26/49	53.1	(38.3;67.5)
Vomiting	21/99	21.2	(13.6;30.6)	8/49	16.3	(7.3;29.7)
Crying abnormal	23/99	23.2	(15.3;32.0.8)	5/49	10.2	(3.4;22.2)
Drowsiness	41/99	41.4	(31.6;51.8)	15/49	30.6	(18.3;45.4)
Appetite lost	42/99	42.4	(32.5;52.8)	14/49	28.6	(16.6;43.3)
Irritability	61/99	61.6	(51.3;71.2)	28/49	57.1	(42.2;71.2)
Unsolicited AE	14/100	14.0	(7.9;22.4)	10/50	20.0	(10.0;33.7)
Unsolicited AR	3/100	3.0	(0.6;8.5)	0/50	0.0	(0.0;7.1)
AE leading to study discontinuation	2/100	2.0	(0.2;7.0)	0/50	0.0	(0.0;7.1)
SAE	2/100	2.0	(0.2;7.0)	0/50	0.0	(0.0;7.1)
Death	0/100	0.0	(0.0;3.6)	0/50	0.0	(0.0;7.1)

n, number of participants; N, number of participants in group; M, number of participants with available data; AE, adverse event; AR, adverse reaction; SAE, serious adverse event.

^a Data for Cohort II are after any vaccination.

titers all increased to 100.0% in each group post-primary series vaccination (Table 3). Vaccine response was slightly higher for DTwP-IPV-HB-PRP~T than DTwP-HB-PRP~T + IPV for anti-PT (80.2% and 70.8%), anti-FHA (81.3% and 68.8%), slightly lower for DTwP-IPV-HB-PRP~T than DTwP-HB-PRP~T + IPV for anti-PRN (72.5% and 81.3%), and similar in each group for anti-FIM (95.6% and 97.9%). The results for anti-D and anti-T obtained using ELISA or DTP-ECL were similar.

Discussion

This study is the first to evaluate the safety and immunogenicity of the fully liquid DTwP-IPV-HB-PRP~T vaccine compared to its active control, antigen-matched vaccines (pentavalent DTwP-HB-PRP~T and standalone IPV). As such, the study was designed to administer the vaccines in a step-down manner, initially as a single dose to toddlers aged to 15–18 months (Cohort I) to establish

safety before proceeding to a 3-dose primary vaccination series in infants aged 6–8, 10–12, and 14–16 weeks (Cohort II).

No safety concerns were observed in Cohort I and so participants in Cohort II were enrolled and received the primary series vaccination as planned. The low incidence of transient vaccine-related nodules reported following DTwP-IPV-HB-PRP~T was within the expected range for DTwP-containing vaccines [20] and was not considered to be of clinical importance, and no vaccine-related SAEs were reported. Overall, in each cohort, the hexavalent vaccine showed a similar safety profile to the comparator DTwP-HB-PRP~T and standalone IPV vaccines and the safety profile was in-line with that reported for other wP-containing hexavalent and pentavalent vaccines in India and elsewhere [5,21–23].

The responses to each antigen in both Cohort I and Cohort II were robust and similar between vaccine groups in terms of seroprotection to D, T, HB, Hib, and polio 1, 2, and 3, and it was noted that in Cohort II pre-vaccination anti-T titers were already elevated due to pre-natal maternal tetanus vaccination. Overall, the

Table 3
Seroprotection and seroresponse rates pre- and post-vaccination (Cohort I) (FAS).

Antigen	Assay	Threshold	DTwP-IPV-HB-PRP~T (N = 30)		DTwP-HB-PRP~T + IPV (N = 15)	
			Pre-vaccination	Post-vaccination	Pre-vaccination	Post-vaccination
Diphtheria	ELISA (NovaTec)	≥0.01 IU/mL	100.0 (88.4;100.0)	100.0 (84.4;100.0)	100.0 (78.2;100.0)	100.0 (78.2;100.0)
		≥0.10 IU/mL	86.7 (69.3;96.2)	100.0 (84.4;100.0)	93.3 (68.1;99.8)	100.0 (78.2;100.0)
		≥1.0 IU/mL	13.3 (3.8;30.7)	100.0 (84.4;100.0)	6.7 (0.2;31.9)	100.0 (78.2;100.0)
Tetanus	ELISA (IBL)	≥0.01 IU/mL	100.0 (88.4;100.0)	100.0 (88.4;100.0)	100.0 (78.2;100.0)	100.0 (78.2;100.0)
		≥0.10 IU/mL	96.7 (82.8;99.9)	100.0 (88.4;100.0)	93.3 (68.1;99.8)	100.0 (78.2;100.0)
		≥1.0 IU/mL	13.3 (3.8;30.7)	100.0 (84.4;100.0)	6.7 (0.2;31.9)	100.0 (78.2;100.0)
Pertussis PT	DTP-ECL	≥4 EU/mL	90.0 (73.5;97.9)	100.0 (88.4;100.0)	73.3 (44.9;92.2)	100.0 (78.2;100.0)
		≥4-fold rise ^a	NA	93.3 (77.9;99.2)	NA	100.0 (78.2;100.0)
		Vaccine response ^b	NA	93.3 (77.9; 99.2)	NA	93.3 (68.1;99.8)
FHA	DTP-ECL	≥3 EU/mL	70.0 (60.6;85.3)	96.7 (82.8;99.9)	53.3 (26.6;78.7)	100.0 (78.2;100.0)
		≥4-fold rise ^a	NA	96.7 (82.8;99.9)	NA	93.3 (68.1;99.8)
		Vaccine response ^b	NA	96.7 (82.8;99.9)	NA	93.3 (68.1;99.8)
PRN	DTP-ECL	≥4 EU/mL	46.7 (28.3;65.7)	96.7 (82.8;99.9)	53.3 (26.6;78.7)	100.0 (78.2;100.0)
		≥4-fold rise ^a	NA	90.0 (73.5;97.9)	NA	93.3 (68.1;99.8)
		Vaccine response ^b	NA	86.7 (69.3;96.2)	NA	86.7 (59.5;98.3)
FIM	DTP-ECL	≥4 EU/mL	96.7 (82.8;99.9)	100.0 (88.4;100.0)	100.0 (78.2;100.0)	100.0 (78.2;100.0)
		≥4-fold rise ^a	NA	90.0 (73.5;97.9)	NA	100.0 (78.2;100.0)
		Vaccine response ^b	NA	96.7 (82.8;99.9)	NA	100.0 (78.2;100.0)
HB	ELISA (VITROS)	≥10 mIU/mL	93.3 (77.9;99.2)	100.0 (88.4;100.0)	100.0 (75.3;100.0)	100.0 (78.2;100.0)
		≥100 mIU/mL	86.7 (69.3;96.2)	100.0 (88.4;100.0)	84.6 (54.6;98.1)	100.0 (78.2;100.0)
Hib	ELISA (Binding Site)	≥0.15 µg/mL	96.7 (82.8;99.9)	100.0 (88.4;100.0)	93.3 (68.1;99.8)	100.0 (78.2;100.0)
		≥1 µg/mL	83.3 (65.3;94.4)	100.0 (88.4;100.0)	80.0 (51.9;95.7)	100.0 (78.2;100.0)
Polio 1	MIT	≥8 1/dil	96.7 (82.8;99.9)	100.0 (88.4;100.0)	100.0 (78.2;100.0)	100.0 (78.2;100.0)
Polio 2	MIT	≥8 1/dil	100.0 (88.4;100.0)	100.0 (88.4;100.0)	100.0 (78.2;100.0)	100.0 (78.2;100.0)
Polio 3	MIT	≥8 1/dil	100.0 (88.4;100.0)	100.0 (88.4;100.0)	100.0 (78.2;100.0)	100.0 (78.2;100.0)

Data are % (95% CI) participants with titer or concentration above threshold.

NA = not applicable; NC = not calculated.

^aFrom pre-primary to post-primary (Cohort II).

^b If pre-vaccination concentration < 4xLLOQ, then the post-vaccination titer was ≥ 4x the pre-vaccination concentration; if pre-vaccination concentration was ≥ 4xLLOQ, then the post-vaccination titer was ≥ 2x the pre-vaccination concentration.

immunogenicity data showed a strong response to each antigen following a 3-dose primary series of DTwP-IPV-HB-PRP~T in Indian infants, as well as following a single dose at 15–18 months of age.

The DTP-ECL assay has previously been validated for the analysis of antibody responses to *B. pertussis* vaccines [17]. Additionally, in our study, anti-D and anti-T antibody titers determined by ELISA were similar to those determined by DTP-ECL at GCI, supporting the use of DTP-ECL in future studies.

A limitation of the study is the open-label design, which could have introduced bias into the safety assessments as both the participants and investigators knew whether the investigational DTwP-IPV-HB-PRP~T vaccine or licensed DTwP-HB-PRP~T + IPV vaccines had been administered. However, based on diverse post-marketing experience over a long period of time with several products that use the same antigens, this is not considered to represent a major weakness.

In conclusion, the study demonstrated a good safety and immunogenicity profile of the hexavalent DTwP-IPV-HB-PRP~T vaccine when administered as an infant primary 3-dose vaccination series at 6–8, 10–12, and 14–16 weeks of age as well as when given to toddlers as a single booster dose and warrants further development in larger and statistically powered studies.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Clinical investigators involved in these studies (SP, MM, MDR, and APD) received fees from Sanofi Pasteur through their institutions for the conduct of these clinical studies, but did not receive any direct payment from Sanofi Pasteur in this regard. EJ, FN, and SM hold Sanofi stock. EJ, FN, and AM are employees of Sanofi Pasteur. DMP and EJ were employees of Sanofi Pasteur at the time of the study. BNP, SM, MVJ, SR, and SRJ are employees of Sanofi Healthcare India Private Ltd (SHIPL).

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Table 4
Seroprotection and seroresponse rates pre- and post-primary series vaccination (Cohort II) (FAS).

Antigen	Assay	Threshold	DTwP-IPV-HB-PRP~T (N = 100)		DTwP-HB-PRP~T + IPV (N = 50)	
			Pre-primary	Post-primary	Pre-primary	Post-primary
Diphtheria	ELISA (NovaTec)	≥0.01 IU/mL	45.0 (35.0;55.3)	100.0 (96.0;100.0)	52.0 (37.4;66.3)	100.0 (92.6;100.0)
		≥0.10 IU/mL	4.0 (1.1;9.9)	98.9 (94.0;100.0)	18.0 (8.6;31.4)	97.9 (88.9;99.9)
		≥1.0 IU/mL	0.0 (0.0;3.6)	69.2 (58.7;78.5)	0.0 (0.0;7.1)	62.5 (47.4;76.0)
Tetanus	ELISA (IBL)	≥0.01 IU/mL	66.0 (55.8;75.2)	100.0 (96.0;100.0)	70.0 (55.4;82.1)	100.0 (92.6;100.0)
		≥0.10 IU/mL	5.0 (1.6;11.3)	100.0 (96.0;100.0)	18.0 (8.6;31.4)	97.9 (88.9;99.9)
		≥1.0 IU/mL	0.0 (0.0;3.6)	80.2 (70.6;87.8)	0.0 (0.0;7.1)	79.2 (65.0;89.5)
Tetanus	DTP-ECL	≥0.01 IU/mL	100.0 (96.4;100.0)	100.0 (96.0;100.0)	100.0 (92.9;100.0)	100.0 (92.6;100.0)
		≥0.10 IU/mL	99.0 (94.6;100.0)	100.0 (96.0;100.0)	100.0 (92.9;100.0)	100.0 (92.6;100.0)
		≥1.0 IU/mL	86.0 (77.6;92.1)	73.6 (63.3;82.3)	82.0 (68.6;91.4)	83.3 (69.8;92.5)
Pertussis PT	DTP-ECL	≥0.01 IU/mL	100.0 (96.4;100.0)	100.0 (96.0;100.0)	100.0 (92.9;100.0)	100.0 (92.6;100.0)
		≥0.10 IU/mL	99.0 (94.6;100.0)	100.0 (96.0;100.0)	98.0 (89.4;99.9)	100.0 (92.6;100.0)
		≥1.0 IU/mL	83.0 (74.2;89.8)	81.3 (71.8;88.7)	82.0 (68.6;91.4)	91.7 (80.0;97.7)
FHA	DTP-ECL	≥4 EU/mL	43.0 (33.1;53.3)	92.3 (84.8;96.9)	56.0 (41.3;70.0)	89.6 (77.3;96.5)
		≥4-fold rise ^a	NA	75.8 (65.7;84.2)	NA	66.7 (51.6;79.6)
		Vaccine response ^b	NA	80.2 (70.6;87.8)	NA	70.8 (55.9;83.0)
PRN	DTP-ECL	≥3 EU/mL	88.0 (80.0;93.6)	100.0 (96.0;100.0)	88.0 (75.7;95.5)	100.0 (92.6;100.0)
		≥4-fold rise ^a	NA	51.6 (40.9;62.3)	NA	33.3 (20.4;48.4)
		Vaccine response ^b	NA	81.3 (71.8;88.7)	NA	68.8 (53.7;81.3)
FIM	DTP-ECL	≥4 EU/mL	13.0 (7.1;21.2)	94.5 (87.6;98.2)	18.0 (8.6;31.4)	100.0 (92.6;100.0)
		≥4-fold rise ^a	NA	82.4 (73.0;89.6)	NA	87.5 (74.8;95.3)
		Vaccine response ^b	NA	72.5 (62.2;81.4)	NA	81.3 (67.4;91.1)
HB	ELISA (VITROS)	≥4 EU/mL	54.0 (43.7;64.0)	98.9 (94.0;100.0)	70.0 (55.4;82.1)	97.9 (88.9;99.9)
		≥4-fold rise ^a	NA	87.9 (79.4;93.8)	NA	93.8 (82.8;98.7)
		Vaccine response ^b	NA	95.6 (89.1;98.8)	NA	97.9 (88.9;99.9)
Hib	ELISA (Binding Site)	≥10 mIU/mL	12.0 (6.4;20.0)	100.0 (96.0;100.0)	12.0 (4.5;24.3)	100.0 (92.6;100.0)
		≥100 mIU/mL	5.0 (1.6;11.3)	95.6 (89.1;98.8)	6.0 (1.3;16.5)	100.0 (92.6;100.0)
		≥0.15 µg/mL	54.0 (43.7;64.0)	100.0 (96.0;100.0)	54.0 (39.3;68.2)	100.0 (92.6;100.0)
Polio 1	MIT	≥1 µg/mL	20.0 (12.7;29.2)	98.9 (94.0;100.0)	24.0 (92.6;100.0)	100.0 (92.6;100.0)
		≥8 1/dil	80.8 (71.7;88.0)	100.0 (96.0;100.0)	67.3 (52.5;80.1)	100.0 (92.6;100.0)
		≥1 dil	70.0 (60.0;78.8)	100.0 (96.0;100.0)	66.0 (51.2;78.8)	100.0 (92.6;100.0)
Polio 2	MIT	≥8 1/dil	58.0 (47.7;67.8)	100.0 (96.0;100.0)	70.0 (55.4;82.1)	100.0 (92.6;100.0)
		≥1 dil	58.0 (47.7;67.8)	100.0 (96.0;100.0)	70.0 (55.4;82.1)	100.0 (92.6;100.0)
		≥1 dil	58.0 (47.7;67.8)	100.0 (96.0;100.0)	70.0 (55.4;82.1)	100.0 (92.6;100.0)

Data are % (95% CI) participants with titer or concentration above threshold.

NA = not applicable; NC = not calculated.

^a From pre-primary to post-primary (Cohort II).^b If pre-vaccination concentration < 4xLLOQ, then the post-vaccination titer was ≥ 4x the pre-vaccination concentration; if pre-vaccination concentration was ≥ 4xLLOQ, then the post-vaccination titer was ≥ 2x the pre-vaccination concentration.**Table 5**
Geometric mean concentrations (GMCs) and geometric mean titers (GMTs) pre- and post-vaccination (Cohort I) (FAS).

Antigen	Assay		DTwP-IPV-HB-PRP~T (N = 30)		DTwP-HB-PRP~T + IPV (N = 15)	
			Pre-vaccination	Post-vaccination	Pre-vaccination	Post-vaccination
Diphtheria	ELISA (NovaTec)	GMC (IU/mL)	0.296 (0.201;0.434)	2.40 (NC)	0.244 (0.152;0.390)	2.40 (NC)
		GMC post-/pre-dose	NA	8.12 (5.52;11.9)	NC	9.84 (9.15;15.8)
		GMC (IU/mL)	0.405 (0.293;0.560)	11.4 (8.52;15.3)	0.297 (0.186;0.474)	11.3 (7.95;16.1)
Tetanus	ELISA (IBL)	GMC post-/pre-dose	NA	28.2 (22.1;36.0)	NA	38.1 (26.7;54.4)
		GMC (IU/mL)	1.02 (0.681;1.54)	17.1 (12.6;23.3)	1.13 (0.690;1.85)	28.8 (23.6;35.2)
		GMC post-/pre-dose	NA	16.8 (11.4;24.7)	NA	25.5 (17.5;37.1)
Tetanus	DTP-ECL	GMC (IU/mL)	1.06 (0.737;1.51)	17.7 (14.3;21.9)	1.25 (0.815;1.91)	29.4 (22.5;38.3)
		GMC post-/pre-dose	NA	16.7 (12.0;23.4)	NA	23.5 (16.3;33.9)
		GMC (EU/mL)	21.0 (12.5;35.3)	217 (142;332)	16.8 (7.14;39.7)	180 (83.8;389)
FHA	DTP-ECL	GMC post-/pre-dose	NA	10.4 (7.47;14.4)	NA	10.7 (7.94;14.5)
		GMC (EU/mL)	4.76 (3.27;6.92)	59.3 (36.7;95.7)	3.24 (1.98;5.30)	59.4 (35.6;98.9)
		GMC post-/pre-dose	NA	12.5 (9.21;16.8)	NA	18.3 (11.2;29.9)
PRN	DTP-ECL	GMC (EU/mL)	4.35 (3.10;6.12)	66.0 (40.8;107)	4.16 (2.77;6.26)	65.4 (34.4;124)
		GMC post-/pre-dose	NA	15.2 (10.2;22.5)	NA	15.7 (10.0;24.7)
		GMC (EU/mL)	138 (78.5;242)	2230 (1610;3089)	114 (59.4;217)	1754 (1017;3024)
FIM	DTP-ECL	GMC post-/pre-dose	NA	16.2 (11.1;23.5)	NA	15.4 (10.2;23.2)
		GMC (mIU/mL)	384 (190;773)	9580 (5953;15418)	355 (143;877)	11,921 (9089;15635)
		GMC post-/pre-dose	NA	25.0 (14.2;43.9)	NA	34.4 (16.0;73.8)
Hib	ELISA (Binding Site)	GMC (µg/mL)	2.99 (1.81;4.95)	34.3 (30.2;28.8)	2.24 (0.953;5.27)	35.0 (28.3;43.3)
		GMC post-/pre-dose	NA	11.5 (6.72;19.5)	NA	15.6 (6.34;38.5)
		GMT (1/dil)	220 (143;340)	1867 (1323;2636)	268 (106;677)	2001 (1269;3157)
Polio 1	MIT	GMT post-/pre-dose	NA	8.47 (5.10;14.1)	NA	7.46 (2.85;19.6)
		GMT (1/dil)	441 (317;612)	2170 (1410;3340)	397 (238;661)	3822 (2386;6122)
		GMT post-/pre-dose	NA	4.92 (3.11;7.80)	NA	9.62 (4.51;20.5)
Polio 2	MIT	GMT (1/dil)	167 (103;271)	3214 (2287;4516)	223 (90.6;548)	6654 (4337;10208)
		GMT post-/pre-dose	NA	19.2 (10.9;33.9)	NA	29.9 (11.5;77.8)
		GMT (1/dil)	167 (103;271)	3214 (2287;4516)	223 (90.6;548)	6654 (4337;10208)

Data are geometric mean titer (GMT) or geometric mean concentration (GMC) (95% CI).

NA = not applicable; NC = not calculated.

Table 6
Geometric mean concentrations (GMCs) and geometric mean titers (GMTs) pre- and post-primary series vaccination (Cohort II) (FAS).

Antigen	Assay		DTwP-IPV-HB-PRP~T (N = 100)		DTwP-HB-PRP~T + IPV (N = 50)	
			Pre-primary	Post-primary	Pre-primary	Post-primary
Diphtheria	ELISA (NovaTec)	GMC (IU/mL)	0.010 (0.008;0.013)	1.22 (1.02;1.46)	0.015 (0.010;0.021)	1.14 (0.857;1.52)
		GMC post-/pre-dose	NA	115 (85.2;155)	NA	78.7 (43.7;142)
	DTP-ECL	GMC (IU/mL)	0.016 (0.013;0.020)	2.39 (1.94;2.96)	0.022 (0.015;0.033)	2.46 (1.76;3.44)
Tetanus	ELISA (IBL)	GMC post-/pre-dose	NA	141 (98.4;202)	NA	108 (54.7;213)
		GMC (IU/mL)	2.67 (2.24;3.18)	1.74 (1.48;2.04)	2.27 (1.65;3.13)	2.03 (1.64;2.51)
	DTP-ECL	GMC post-/pre-dose	NA	0.611 (0.482;0.775)	NA	0.914 (0.600;1.39)
Pertussis	DTP-ECL	GMC (IU/mL)	2.50 (2.06;3.04)	2.26 (1.89;2.71)	2.30 (1.65;3.21)	3.20 (2.42;4.24)
		GMC post-/pre-dose	NA	0.852 (0.641;1.13)	NA	1.41 (0.864;2.32)
	PT	GMC (EU/mL)	3.87 (3.24;4.63)	96.9 (66.3;142)	4.65 (3.63;5.95)	52.6 (30.4;91.1)
FHA	DTP-ECL	GMC post-/pre-dose	NA	25.5 (15.6;41.8)	NA	11.3 (5.54;23.0)
		GMC (EU/mL)	8.26 (6.70;10.2)	33.0 (28.0;39.0)	10.8 (8.09;14.4)	25.3 (20.3;31.6)
PRN	DTP-ECL	GMC post-/pre-dose	NA	4.00 (2.91;5.49)	NA	2.39 (1.52;3.77)
		GMC (EU/mL)	2.45 (2.18;2.74)	27.4 (21.8;34.5)	2.57 (2.18;3.02)	29.8 (24.0;36.9)
FIM	DTP-ECL	GMC post-/pre-dose	NA	11.1 (8.35;14.7)	NA	11.5 (8.81;15.0)
		GMC (EU/mL)	7.35 (5.38;10.0)	1080 (832;1404)	8.86 (6.26;12.5)	1001 (681;1472)
HB	ELISA (VITROS)	GMC post-/pre-dose	NA	136 (83.4;222)	NA	110 (60.1;203)
		GMC (mIU/mL)	4.18 (3.08;5.67)	1219 (912;1629)	4.03 (2.72;5.98)	974 (746;1271)
Hib	ELISA (Binding Site)	GMC post-/pre-dose	NA	303 (194;476)	NA	237 (137;409)
		GMC (μ g/mL)	0.240 (0.177;0.325)	21.1 (17.8;25.0)	0.247 (0.160;0.382)	19.0 (14.8;24.6)
Polio 1	MIT	GMC post-/pre-dose	NA	94.0 (65.1;136)	NA	80.3 (47.7;135)
		GMT (1/dil)	34.6 (24.6;48.5)	1327 (1031;1708)	19.2 (12.3;30.1)	587 (430;803)
Polio 2	MIT	GMT post-/pre-dose	NA	39.8 (26.8;59.2)	NA	32.4 (19.4;54.4)
		GMT (1/dil)	13.4 (10.3;17.4)	724 (547;959)	13.6 (9.25;20.1)	334 (248;452)
Polio 3	MIT	GMT post-/pre-dose	NA	58.4 (36.2;94.0)	NA	23.8 (13.1;43.3)
		GMT (1/dil)	18.7 (13.0;27.0)	1599 (1300;1966)	24.1 (14.6;39.7)	424 (322;558)
		GMT post-/pre-dose	NA	80.9 (49.5;132)	NA	16.8 (9.86;28.7)

Data are geometric mean titer (GMT) or geometric mean concentration (GMC) (95% CI).
NA = not applicable; NC = not calculated.

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