

Antibody persistence following administration of a hexavalent DTwP-IPV-HB-PRP~T vaccine versus separate DTwP-HB-PRP~T and IPV vaccines at 12–24 months of age and safety and immunogenicity of a booster dose of DTwP-IPV-HB-PRP~T in healthy infants in India

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ABSTRACT

Background: The combination of whole-cell pertussis (wP) antigens with established diphtheria (D), tetanus (T), hepatitis B (HB), *Haemophilus influenzae* type b (Hib), and inactivated poliomyelitis (IPV) antigens provides a high-quality DTwP-IPV-HB-PRP~T vaccine. This study evaluated a DTwP-IPV-HB-PRP~T booster coadministered with measles, mumps, and rubella (MMR) vaccine.

Methods: Phase II, open-label, randomized study. Healthy toddlers who had previously completed a DTwP-IPV-HB-PRP~T or separate DTwP-HB-PRP~T and IPV primary vaccination series received a DTwP-IPV-HB-PRP~T booster vaccine at 12–24 months of age. All participants had also received 1 or 2 doses of measles-containing vaccine between primary vaccination and enrolment (N = 100 and N = 6, respectively). Those who had received 1 prior measles-containing vaccine received an MMR dose either concomitantly (N = 50) or 28 days after (N = 50) the DTwP-IPV-HB-PRP~T booster. Immunogenicity was evaluated using validated assays and safety by parental reports.

Results: Pre-booster vaccination, 100.0% participants showed antibody persistence after DTwP-IPV-HB-PRP~T or DTwP-HB-PRP~T and IPV for anti-T (≥ 0.01 IU/mL), anti-Hib (≥ 0.15 µg/mL), and anti-polio 3 (≥ 8 1/dil) and at least 95.8% of participants for anti-D (≥ 0.01 IU/mL), anti-HB (≥ 10 mIU/mL), and anti-polio 1 and 2 (≥ 8 1/dil). For the pertussis antigens, pre-booster antibody persistence (≥ 2 EU/mL) ranged from 88.6 to 88.7% (anti-PT), 91.4–98.6% (anti-FHA), 69.0–74.3% (anti-PRN), and 97.1–97.2% (anti-FIM). For the booster response, seroprotection based on either the primary series or measles-containing vaccination regimen was 100.0% for anti-D and anti-T (≥ 0.01 IU/mL and ≥ 0.10 IU/mL), anti-HB (≥ 10 mIU/mL and ≥ 100 mIU/mL), anti-Hib (≥ 0.15 µg/mL and ≥ 1 µg/mL) and anti-polio 1, 2, and 3 (≥ 8 1/dil), and for the pertussis antigens booster response ranged from 88.6 to 91.8% (anti-PT), 91.1–95.9% (anti-FHA), 88.6–93.9% (anti-PRN), and 95.9–98.6% (anti-FIM). There were no safety concerns in any group.

Conclusions: This study showed good antibody persistence of the DTwP-IPV-HB-PRP~T vaccine and good immunogenicity and safety of a booster dose given with MMR in the second year of life.

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Introduction

The widespread and routine use of pediatric combination vaccines has been pivotal in the control of childhood diseases including diphtheria (D), tetanus (T), pertussis, hepatitis B (HB), *Haemophilus*

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influenzae type b (Hib) infections, and poliomyelitis [1]. To maintain immunity against these diseases a 3-dose primary series followed by a booster vaccination in the second year of life is required, and can be achieved using either co-administration of monovalent, trivalent, tetravalent, or pentavalent vaccines or administration of a single hexavalent vaccine, according to local regulations and available vaccines. The inclusion of several antigens in a single vaccine can lead to improved compliance to increasingly complex pediatric vaccination schedules.

A pentavalent vaccine containing D, T, whole cell pertussis (wP), HB, and Hib antigens (SHAN5[®]) was licensed for primary series vaccination in India by Shanta Biotechnics Private Ltd (SBPL) in March 2014. It was pre-qualified by the World Health Organization (WHO) in April of the same year and is currently licensed in 22 countries globally with approximately 150 million doses having been administered. The coadministration of pentavalent vaccines such as SHAN5 with the oral polio vaccine (OPV) or inactivated poliovirus vaccine (IPV), can ensure the delivery of primary series and booster vaccination against D, T, pertussis, HB, Hib, and poliomyelitis, which are recommended in Indian infants at 6, 10–14 weeks of age (D, T, pertussis, HB, Hib, and polio) and at 16–18 months of age (D, T, pertussis, Hib, and polio) [2].

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] Sanofi Healthcare India Private Ltd (SHIPL) has 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 HB, Hib, and IPV antigens contained in SHAN6 are based on those included in Sanofi Pasteur's acellular pertussis-containing DTaP-IPV//PRP~T pentavalent (Pentaxim[®]) [5] and DTaP-IPV-HB-PRP~T hexavalent (Hexaxim[®]) [6] vaccines and have consistently shown good safety and robust immunogenicity in clinical trials globally.

Data from the first clinical study for SHAN6 have recently been reported [7], in which an initial booster dose in a cohort of healthy toddlers aged 15–18 months and a subsequent primary vaccination series in a cohort of infants at 6–8, 10–12, and 14–16 weeks of age in India showed good safety and immunogenicity of the wP-containing hexavalent vaccine with no clinically important differences compared to participants who received separate wP-containing pentavalent antigen-matching (DTwP-HB-PRP~T: SHAN5) and standalone IPV (SHANIPV) vaccines. The present study was conducted to evaluate antibody persistence and the safety and immunogenicity of a DTwP-IPV-HB-PRP~T booster with or without the coadministration of measles, mumps, and rubella (MMR) vaccine given in the second year of life to toddlers who had received an infant primary series vaccination of either the DTwP-IPV-HB-PRP~T hexavalent vaccine or the antigen-matching pentavalent DTwP-HB-PRP~T + IPV vaccines in the previous clinical study.

Materials and methods

Study design and participants

This was a Phase II, open-label, randomized study conducted in toddlers at 4 sites in India (Clinical Trials Registry India Number CTRI/2018/04/013375). 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 the

study. The study was conducted between May 2018 and October 2018.

According to the Indian Academy of Pediatrics (IAP) Immunization Timetable [2], a measles or measles-containing vaccine should be administered at 9 months of age and an MMR vaccine in the second year of life. The study population consisted of healthy toddlers aged 12–24 months of age who had previously received a complete primary vaccination series of hexavalent DTwP-IPV-HB-PRP~T vaccine or separate DTwP-HB-PRP~T and IPV vaccines administered at 6–8, 10–12, and 14–16 weeks of age [7] and who had additionally received either one (at 9 months of age: Group A and Group B) or two (at 9 and 12–24 months of age: Group C) doses of measles-containing vaccine between completion of the primary series and enrolment into the present study.

All subjects received a DTwP-IPV-HB-PRP~T booster vaccination. Group A included subjects who received a second dose of MMR vaccine concomitantly with the DTwP-IPV-HB-PRP~T vaccine (ie, coadministration of MMR and DTwP-IPV-HB-PRP~T), whereas in Group B subjects received a second dose of MMR vaccine 28 days after the DTwP-IPV-HB-PRP~T (ie, sequential administration of MMR vaccine after the DTwP-IPV-HB-PRP~T booster). Group A and Group B (ie, subjects who had previously received a single MMR dose) were randomized in a 1:1 ratio to receive the second MMR dose either concomitantly with the DTwP-IPV-HB-PRP~T booster or sequentially after the DTwP-IPV-HB-PRP~T booster. Group C included a smaller group of subjects who had already (ie, prior to inclusion) received two doses of MMR vaccine (ie, the DTwP-IPV-HB-PRP~T booster was administered after the MMR doses).

The main exclusion criteria were the receipt of any vaccine containing D, T, wP, aP, HB, Hib, or IPV antigens in the second year of life; previous (in the 4 weeks before enrolment) or planned participation in another clinical study; receipt of any vaccine in the preceding 4 weeks or planned receipt of any vaccine within 28 days post-study vaccination (with the exception of oral poliovirus vaccine received during national immunization days); known hypersensitivity to any vaccine component; any chronic illness that could interfere with study conduct or completion; congenital or acquired immunodeficiency or receipt of immunosuppressive therapy; receipt of blood products in the 30 days prior to inclusion or planned during the study; history of D, T, P, Hib, HB, or poliomyelitis infection; history of human immunodeficiency virus or hepatitis C infection; known thrombocytopenia, bleeding disorder, or receipt of anticoagulants in the 3 weeks prior to inclusion; acute illness or febrile illness on the day of vaccination; any known contraindication to further vaccination with a pertussis vaccine.

The study vaccines were administered by intramuscular injection into the anterolateral area of the thigh (DTwP-IPV-HB-PRP~T vaccine) or by subcutaneous injection into the upper and outer quadrant of the deltoid muscle (MMR vaccine [Groups A and B only]).

Study vaccines

The hexavalent DTwP-IPV-HB-PRP~T vaccine (SHAN6[™], batch number HPCU0117, expiry date August 2019) was manufactured by SHIPL and supplied as a liquid, sterile suspension for injection in 5 mL vials containing 10 doses. Each 0.5 mL dose contained ≥ 30 IU D-toxoid, ≥ 60 IU T-toxoid, ≥ 4 IU whole-cell pertussis, 10 μ g 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 antigen units of poliovirus type 1 (Mahoney strain), type 2 (MEF-1 strain), and type 3 (Saukett strain), respectively, and ≤ 1.25 mg aluminum phosphate.

The MMR vaccine (TRESIVAC[®], Serum Institute of India Pvt Ltd, batch number 013N6113B, expiry date April 2019) was live atten-

uated, pre-qualified by the World Health Organization. It was supplied as a lyophilized powder (≥ 1000 cell culture infectious dose 50% [CCID50] measles virus, ≥ 5000 CCID50 mumps virus per dose, and ≥ 1000 CCID50 rubella virus per dose) that was reconstituted to obtain a homogenous suspension prior to administration as a single 0.5 mL dose.

Reactogenicity and safety

Participants were observed at the study site for 30 min after vaccination to assess immediate unsolicited adverse events (AEs). Subsequently, parent(s)/legal representative(s) used diary cards for 7 days to record the duration and intensity of solicited injection site reactions (tenderness, erythema, swelling) (for DTwP-IPV-HB-PRP~T only, i.e. not collected for MMR vaccination) and solicited systemic reactions (fever ≥ 38.0 °C by the axillary route), vomiting, crying abnormal, drowsiness, appetite lost, irritability) (see Table 1 for definition of Grade 3 for solicited reactions). All solicited AEs were automatically considered to be related to the vaccination (adverse reactions). Unsolicited AEs were recorded using diary cards for 28 days after vaccination. Unsolicited injection site AEs were considered to be related to the vaccination and the Investigator assessed unsolicited systemic AEs for causality. Serious adverse events (SAEs) were collected throughout the study and the Investigator assessed their causality.

Serology

Blood samples (approximately 3–5 mL) were collected pre-vaccination and 28 days post-vaccination for determination of antibodies to all antigens (anti-D, anti-T, anti-pertussis toxin [PT], anti-filamentous hemagglutinin [FHA], anti-pertactin [PRN], and anti-fimbriae 2/3 [FIM], anti-Hib, anti-HB, anti-polio 1, anti-polio 2, and anti-polio 3). No analysis for anti-MMR vaccine-induced antibodies was performed.

Anti-D (IU/mL), anti-T (IU/mL), anti-PT (EU/mL), anti-FHA (EU/mL), anti-PRN (EU/mL), anti-FIM (EU/mL) antibody concentrations were measured by a multiplexed chemiluminescence assay using the Meso Scale Discovery platform (DTP-ECL) [8], anti-HB (mIU/mL) antibody concentrations by enzyme linked immunosorbent assay (ELISA) using a commercially available kit (VITROS, Ortho Clinical Diagnostics, United Kingdom), anti-PRP (μ g/mL) antibody concentrations by radioimmunoassay, and anti-poliovirus antibody titers by micro metabolic testing (MIT) against wild-type poliovirus strains [9,10].

All assays were performed at Sanofi Pasteur's Global Clinical Immunology (GCI) laboratory (Swiftwater, PA, USA).

Statistical analyses

No statistical hypotheses were tested and all evaluations were descriptive. The sample size was based on the primary vaccination series study and as many toddlers as possible who had completed the primary series were enrolled for booster vaccination. In the primary series study, 150 infants were enrolled, and so the expected sample size for the booster study was at least 100 toddlers.

Safety and immunogenicity data were analyzed for Group A (DTwP-IPV-HB-PRP~T administered concomitantly with MMR) and Group B + C (combined for DTwP-IPV-HB-PRP~T not administered concomitantly with MMR). Additionally, immunogenicity data were analyzed according to the vaccine previously received during the primary series (DTwP-IPV-HB-PRP~T or DTwP-HB-PRP~T + IPV).

Seroprotection was defined as anti-D antibody ≥ 0.01 IU/mL, anti-T ≥ 0.01 IU/mL, anti-HB ≥ 10 mIU/mL, anti-Hib ≥ 0.15 μ g/mL, and anti-polio 1, 2, and 3 titers ≥ 8 1/dil. The lower limits of quan-

tification (LLOQ) for anti-D, anti-T, anti-HB, anti-Hib, and anti-polio were 0.005 IU/mL, 0.01 IU/mL, 5 mIU/mL, 0.06 μ g/mL, and 4 1/dil, respectively. Vaccine response (for anti-PT, anti-FHA, anti-PRN, and anti-FIM) was defined in subjects with pre-booster concentration $< 4 \times$ LLOQ as post-booster concentration $\geq 4 \times$ pre-booster concentration, and in subjects with pre-booster concentration $\geq 4 \times$ LLOQ as post-booster titer $\geq 2 \times$ pre-booster concentration. The LLOQ for the pertussis antigens was 2 EU/mL (in an earlier study an LLOQ of 4 EU/mL [anti-PT, anti-PRN, and anti-FIM] or 3 EU/mL [anti-FHA] was used [7]).

Data are 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 post-vaccination in anti-PT, anti-FHA, anti-PRN, and anti-FIM antibody concentrations are also presented. 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 are presented for all antigens.

Data are presented with their 95% confidence intervals (CIs), calculated using the exact binomial distribution (Clopper-Pearson method) [11] 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 the DTwP-IPV-HB-PRP~T vaccination) and the Full analysis set (FAS) was used for the immunogenicity analyses (participants who received the DTwP-IPV-HB-PRP~T 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 9.2 or later (SAS Institute, Cary, NC, USA).

Results

Participants studied

A total of 106 participants who had previously completed the primary series vaccinations were enrolled. Of these, 50 participants were randomized to Group A (co-administration of DTwP-IPV-HB-PRP~T booster with MMR), 50 participants were randomized to Group B (sequential administration of MMR 28 days after DTwP-IPV-HB-PRP~T booster), and 6 participants had already received two measles-containing vaccinations before enrolment (Group C) (Fig. 1a). For the immunogenicity assessments according to the primary series vaccine(s) received, in all groups combined, 71 participants had received a primary vaccination series of DTwP-IPV-HB-PRP~T and 35 participants had received DTwP-HB-PRP~T + IPV (Fig. 1b). One participant in Group A, who had previously received DTwP-IPV-HB-PRP~T in the primary series, discontinued from the study (voluntary withdrawal not due to an AE).

There was a similar number of male and female participants in each group (overall 52% male), and at the time of vaccination mean \pm SD age (Group A: 15.7 ± 0.9 months, Group B: 15.7 ± 0.9 , and Group C: 16.7 ± 1.0 months) and mean \pm SD weight (Group A: 9.7 ± 1.0 kg, Group B: 9.8 ± 1.5 kg, and Group C: 10.3 ± 1.4 kg) were similar in each group.

Safety and tolerability

There were no immediate adverse reactions (i.e. within 30 min post-vaccination). The overall incidence of solicited injection site and systemic reactions was similar in Group A and Group B + C, with the incidence of Grade 3 reactions being slightly higher in Group A than Group B + C (24.0% versus 17.9% of participants and 6.0% versus 1.8% of participants for solicited injection site

Table 1
Immediate, solicited, unsolicited, and serious adverse events during the study

Participants with at least one:	Group A (N=50)			Group B+C (N=56)		
	n/M	%	(95% CI)	n/M	%	(95% CI)
Immediate unsolicited AE	0/50	0.0	(0.0;7.1)	0/56	0.0	(0.0;6.4)
Solicited reaction	45/50	90.0	(78.2;96.7)	48/56	85.7	(73.8;93.6)
Grade 3 ^a	15/50	30.0	(17.9;44.6)	11/56	19.6	(10.2;32.4)
Solicited injection site reaction	40/50	80.0	(66.3;90.0)	44/56	78.6	(65.6;88.4)
Grade 3	12/50	24.0	(13.1;38.2)	10/56	17.9	(8.9;30.4)
Tenderness	38/50	76.0	(61.8;86.9)	44/56	78.6	(65.6;88.4)
Erythema	14/50	28.0	(16.2;42.5)	14/56	25.0	(14.4;38.4)
Swelling	19/50	38.0	(24.7;52.8)	26/56	46.4	(33.0;60.3)
Solicited systemic reaction	39/50	78.0	(64.0;88.5)	47/56	83.9	(71.7;92.4)
Grade 3 ^a	3/50	6.0	(1.3;16.5)	1/56	1.8	(0.0;9.6)
Fever	29/50	58.0	(43.2;71.8)	30/56	53.6	(39.7;67.0)
Vomiting	6/50	12.0	(4.5;24.3)	3/56	5.4	(1.1;14.9)
Crying abnormal	9/50	18.0	(8.6;31.4)	12/56	21.4	(11.6;34.4)
Drowsiness	14/50	28.0	(16.2;42.5)	8/56	14.3	(6.4;26.2)
Appetite lost	19/50	38.0	(24.7;52.8)	17/56	30.4	(18.8;44.1)
Irritability	24/50	48.0	(33.7;62.6)	34/56	60.7	(46.8;73.5)
Unsolicited AE	5/50	10.0	(3.3;21.8)	5/56	8.9	(3.0;19.6)
Unsolicited AR	0/50	0.0	(0.0;7.1)	0/56	0.0	(0.0;6.4)
AE leading to study discontinuation	0/50	0.0	(0.0;7.1)	0/56	0.0	(0.0;6.4)
SAE	0/50	0.0	(0.0;7.1)	1/56	1.8	(0.0;9.6)
Death	0/50	0.0	(0.0;7.1)	0/56	0.0	(0.0;6.4)

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 Grade 3 solicited injections site and systemic reactions were defined as follows: tenderness, cries when injected limb is moved or the movement of the injected limb is reduced; erythema and swelling, a diameter of ≥ 5 cm; fever, temperature >39.5 °C; vomiting, ≥ 6 episodes/day; crying abnormal crying, >3 hours; drowsiness, sleeping most of the time or difficult to wake up; appetite lost, missed ≥ 3 meals or refused most meals; irritability, inconsolable

and systemic reactions, respectively). The most common solicited injection site reaction in each group was tenderness (76.0% and 78.6% in Group A and Groups B + C, respectively) and the most common solicited systemic reaction in Group A was fever (58.0%, versus 53.6% in Groups B + C) and in Groups B + C was irritability (60.7%, versus 48.0% in Group A) (Table 1).

The incidence of unsolicited AEs within 28 days after vaccination was similar in Group A (10.0%) and Group B + C (8.9%). The most commonly reported were pyrexia in Group A (6.0%) and either infections and infestations (3.6%) or skin and subcutaneous tissue disorders (3.6%) in Groups B + C. None was considered to be related to vaccination and most resolved spontaneously within 2 weeks.

There was one SAE (nephrotic syndrome that required hospitalization), which occurred in a 16 month old girl in Group B and was not considered to be related to vaccination. No AEs led to any discontinuation, and there were no AEs of special interest or deaths.

Immunogenicity

Antibody persistence

Prior to the booster vaccination, 100.0% of participants who had received a primary vaccination series of either DTwP-IPV-HB-PRP~T or DTwP-HB-PRP~T + IPV had antibody persistence for anti-T (≥ 0.01 IU/mL), anti-Hib (≥ 0.15 µg/mL), and anti-polio 3 (≥ 8 1/dil) and at least 95.8% of participants for anti-D (≥ 0.1 IU/mL), anti-HB (≥ 10 mIU/mL), and anti-polio 1 and 2 (≥ 8 1/dil). For the *Bordetella pertussis* antigens, pre-booster antibody persistence (≥ 2 EU/mL) was similar in each group (according to the primary series vaccination) and ranged from 88.6 to 88.7% (anti-PT), 91.4–98.6% (anti-FHA), 69.0–74.3% (anti-PRN), and 97.1–97.2% (anti-FIM) (Table 4). Pre-booster antibody levels were similar in Group A and Group B + C (Table 2) to those described by primary series vaccination. Pre-booster (GMCs) (anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, anti-FIM, anti-HB, and anti-Hib) and GMTs (anti-polio 1, 2, and 3) were similar in each group (Table 3 and Table 5).

Booster response according to MMR booster vaccine(s) received (Group A and Groups B + C)

Post-DTwP-IPV-HB-PRP~T booster, 100.0% of participants in Group A and Group B + C had titers above pre-defined thresholds for anti-D and anti-T (≥ 0.01 IU/mL and ≥ 0.1 IU/mL), anti-HB (≥ 10 mIU/mL and ≥ 100 mIU/mL), anti-Hib (≥ 0.15 µg/mL and ≥ 1 µg/mL) and anti-polio 1, 2, and 3 (≥ 8 1/dil). For the pertussis antigens, the post-booster response was similar in each group, with 98.0–100.0% of participants having titers ≥ 2 EU/mL and the vaccine response ranging from 89.3 to 91.8% (anti-PT), 91.1–95.9% (anti-FHA), 92.9–93.9% (anti-PRN), and 95.9–96.4% (anti-FIM) (Table 2). The increase in GMCs for anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, and anti-FIM was generally similar in each group, and the increase in anti-PRP GMC (22.1 for Group A versus 10.8 for Groups B + C) and anti-polio 1, 2, and 3 GMTs (respectively, 3.78, 26.8, and 9.35 for Group A and 2.44, 12.7, and 4.44) was slightly higher in Group A than Groups B + C (Table 3).

Booster response according to the primary series vaccine(s) received (DTwP-IPV-HB-PRP~T or DTwP-HB-PRP~T + IPV)

Post-DTwP-IPV-HB-PRP~T booster, 100.0% of participants in each primary series vaccine group (DTwP-IPV-HB-PRP~T or DTwP-HB-PRP~T + IPV primary series) had titers above pre-defined thresholds for anti-D and anti-T (≥ 0.01 IU/mL and ≥ 0.10 IU/mL), anti-HB (≥ 10 mIU/mL and ≥ 100 mIU/mL), anti-PRP (≥ 0.15 µg/mL and ≥ 1 µg/mL) and anti-polio 1, 2, and 3 (≥ 8 1/dil). Additionally, 100.0% of participants who had received DTwP-IPV-HB-PRP~T as the primary vaccination series had anti-PT, anti-FHA, anti-PRN, and anti-FIM antibodies ≥ 2 EU/mL; for those who had received a primary vaccination series of DTwP-HB-PRP~T + IPV, 100.0% had anti-FHA and anti-PRN antibodies ≥ 2 EU/mL and 97.1% had anti-PT and anti-FIM antibodies above this threshold. Vaccine response for the pertussis antigens was similar in each group, ranging from 88.6 to 91.4% (anti-PT), 91.4–94.3% (anti-FHA), 88.6–95.7% (anti-PRN), and 91.4–98.6% (anti-FIM) (Table 4). The increase in GMCs for anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, anti-FIM, and GMTs for anti-polio 1, 2, 3 was generally similar in

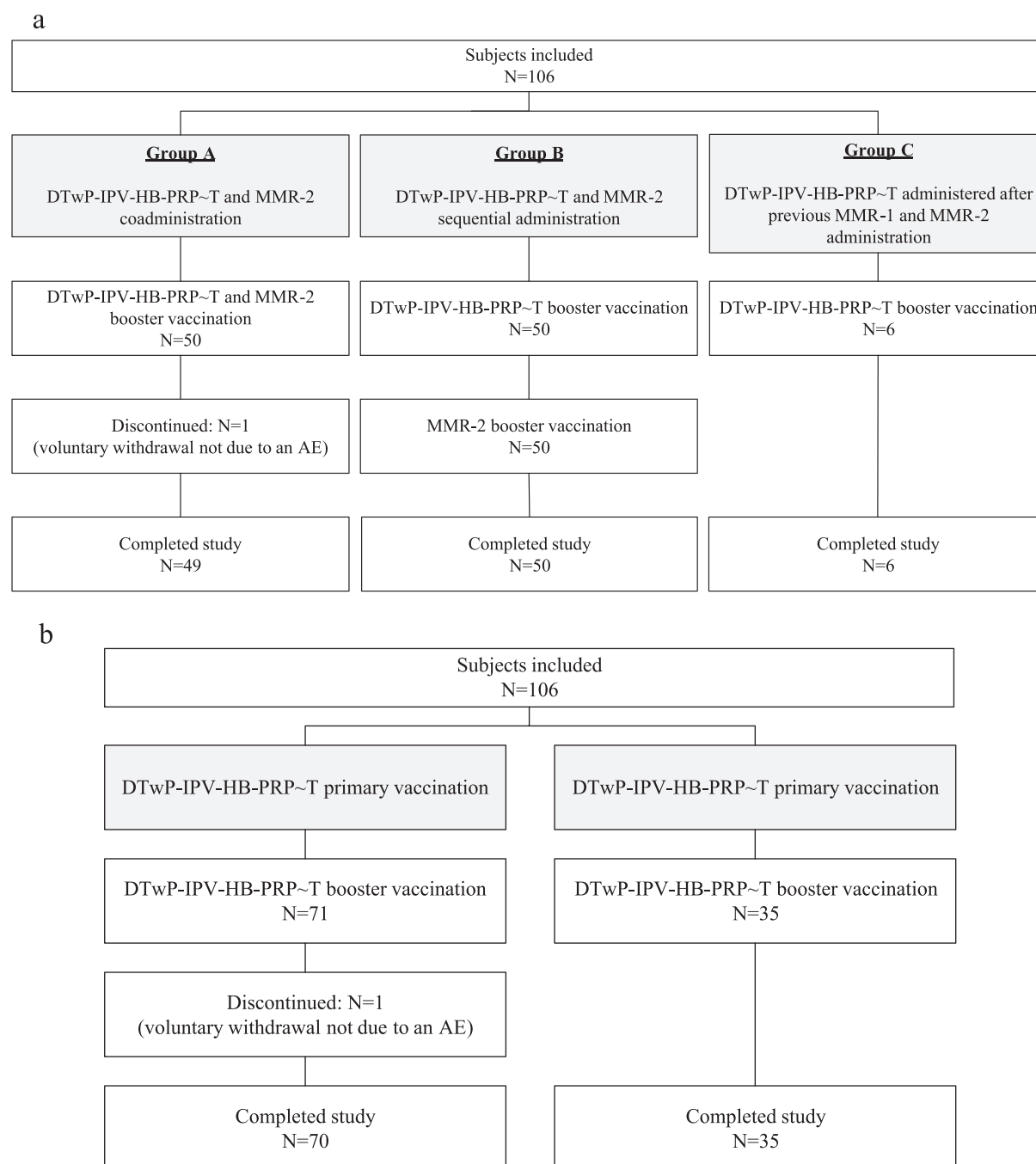


Fig. 1. Disposition of study participants. **Fig. 1a** Disposition according to MMR booster vaccine(s) received concomitantly (Group A) or not concomitantly (Group B and Group C) (for safety and immunogenicity analyses). MMR-1, first dose of MMR vaccine; MMR-2, second dose of MMR vaccine. **Fig. 1b** Disposition according to primary series vaccine (s) received (for immunogenicity analyses only).

each group, and the increase in anti-HB and anti-PRP GMCs was slightly higher for participants who had received DTwP-HB-PRP~T + IPV as the primary vaccination series (Table 5).

Discussion

This study provides the first data for antibody persistence up to the second year of life (around 15–16 months of age) following a primary series of the hexavalent DTwP-IPV-HB-PRP~T vaccine compared to separate administration of DTwP-HB-PRP~T + IPV, and the first safety and immunogenicity data for the DTwP-IPV-

HB-PRP~T vaccine administered in the second year of life following a primary vaccination series of the same vaccine or antigen-matched vaccines.

There were no safety concerns associated with booster administration of the hexavalent vaccine, which showed a safety profile that was comparable to shown previously for this vaccine [7] and in-line with that expected for wP-containing vaccines of this type [12–16]. All participants showed good antibody persistence prior to the booster vaccination and the booster vaccination resulted in a strong anamnestic response to all antigens with no clinically relevant differences in the immune response between those who had received a primary vaccination series of DTwP-IPV-HB-

Table 2

Seroprotection and seroresponse rates pre- and post-booster vaccination for Group A (concomitant MMR and DTwP-IPV-HB-PRP~T) and Group B+C (not concomitant MMR and DTwP-IPV-HB-PRP~T) (FAS).

Antigen	Threshold	Group A (N = 50)		Group B + C (N = 56)	
		Pre-booster	Post-booster	Pre-booster	Post-booster
Diphtheria	≥0.01 IU/mL	98.0 (89.4;99.9)	100.0 (92.7;100.0)	98.2 (90.4;100.0)	100.0 (93.6;100.0)
	≥0.10 IU/mL	78.0 (64.0;88.5)	100.0 (92.7;100.0)	82.1 (69.6;91.1)	100.0 (93.6;100.0)
	≥1.0 IU/mL	12.0 (4.5;24.3)	93.9 (83.1;98.7)	8.9 (3.0;19.6)	96.4 (87.7;99.6)
Tetanus	≥0.01 IU/mL	100.0 (92.9;100.0)	100.0 (92.7;100.0)	100.0 (93.6;100.0)	100.0 (93.6;100.0)
	≥0.10 IU/mL	98.0 (89.4;99.9)	100.0 (92.7;100.0)	98.2 (90.4;100.0)	100.0 (93.6;100.0)
	≥1.0 IU/mL	36.0 (22.9;50.8)	98.0 (89.1;99.9)	48.2 (34.7;62.0)	100.0 (93.6;100.0)
Pertussis PT	≥2 EU/mL	90.0 (78.2;96.7)	100.0 (92.7;100.0)	87.5 (75.9;94.8)	98.2 (90.4;100.0)
	≥4-fold rise ^a	NA	75.5 (61.1;86.7)	NA	75.0 (61.6;85.6)
	VR ^b	NA	91.8 (80.4;97.7)	NA	89.3 (78.1;96.0)
FHA	≥2 EU/mL	96.0 (86.3;99.5)	100.0 (92.7;100.0)	96.4 (87.7;99.6)	100.0 (93.6;100.0)
	≥4-fold rise ^a	NA	91.8 (80.4;97.7)	NA	83.9 (71.7;92.4)
	VR ^b	NA	95.9 (86.0;99.5)	NA	91.1 (80.4;97.0)
PRN	≥2 EU/mL	66.0 (51.2;78.8)	100.0 (92.7;100.0)	75.0 (61.6;85.6)	100.0 (93.6;100.0)
	≥4-fold rise ^a	NA	87.8 (75.2;95.4)	NA	89.3 (78.1;96.0)
	VR ^b	NA	93.9 (83.1;98.7)	NA	92.9 (82.7;98.0)
FIM	≥2 EU/mL	94.0 (83.5;98.7)	98.0 (89.1;99.9)	100.0 (93.6;100.0)	100.0 (93.6;100.0)
	≥4-fold rise ^a	NA	89.8 (77.8;96.6)	NA	85.7 (73.8;93.6)
	VR ^b	NA	95.9 (86.0;99.5)	NA	96.4 (87.7;99.6)
HB	≥10 mIU/mL	98.0 (89.4;99.9)	100.0 (92.7;100.0)	96.4 (87.7;99.6)	100.0 (93.6;100.0)
	≥100 mIU/mL	78.0 (64.0;88.5)	100.0 (92.7;100.0)	75.0 (61.6;85.6)	100.0 (93.6;100.0)
Hib	≥0.15 µg/mL	100.0 (92.9;100.0)	100.0 (92.7;100.0)	100.0 (93.6;100.0)	100.0 (93.6;100.0)
	≥1 µg/mL	94.0 (83.5;98.7)	100.0 (92.7;100.0)	94.6 (85.1;98.9)	100.0 (93.6;100.0)
Polio 1	≥8 1/dil	98.0 (89.4;99.9)	100.0 (92.7;100.0)	100.0 (93.6;100.0)	100.0 (93.6;100.0)
Polio 2	≥8 1/dil	98.0 (89.4;99.9)	100.0 (92.7;100.0)	100.0 (93.6;100.0)	100.0 (93.6;100.0)
Polio 3	≥8 1/dil	100.0 (92.9;100.0)	100.0 (92.7;100.0)	100.0 (93.6;100.0)	100.0 (93.6;100.0)

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

VR = vaccine response; NA = not applicable; NC = not calculated.

^a From pre-booster to post-booster.

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

Table 3

Geometric mean concentrations (GMCs) and geometric mean titers (GMTs) pre- and post-booster vaccination for Group A (concomitant MMR and DTwP-IPV-HB-PRP~T) and Group B + C (not concomitant MMR and DTwP-IPV-HB-PRP~T) (FAS).

Antigen		Group A (N = 50)		Group B + C (N = 56)	
		Pre-booster	Post-booster	Pre-booster	Post-booster
Diphtheria	GMC (IU/mL)	0.254 (0.179;0.360)	7.00 (5.02;9.77)	0.238 (0.173;0.327)	6.49 (4.86;8.67)
	Ratio ^a	NA	27.6 (19.2;39.7)	NA	27.3 (20.9;35.6)
Tetanus	GMC (IU/mL)	0.830 (0.563;1.22)	16.9 (13.2;21.7)	1.00 (0.695;1.45)	17.4 (13.6;22.2)
	Ratio ^a	NA	20.2 (12.8;32.1)	NA	17.3 (12.2;24.5)
Pertussis PT	GMC (EU/mL)	18.3 (11.8;28.1)	157 (116;212)	18.5 (12.3;27.7)	140 (97.8;199)
	Ratio ^a	NA	8.81 (5.76;13.5)	NA	7.55 (5.78;9.87)
FHA	GMC (EU/mL)	9.72 (6.86;13.8)	113 (88.1;144)	9.34 (7.03;12.4)	99.6 (76.9;129)
	Ratio ^a	NA	11.4 (8.52;15.3)	NA	10.7 (7.99;14.2)
PRN	GMC (EU/mL)	3.41 (2.39;4.88)	73.9 (56.5;96.5)	3.96 (3.01;5.21)	67.3 (52.6;86.1)
	Ratio ^a	NA	21.6 (14.7;31.5)	NA	17.0 (13.2;21.8)
FIM	GMC (EU/mL)	88.0 (55.7;139)	1427 (981;2075)	151 (113;200)	1753 (1455;2111)
	Ratio ^a	NA	16.0 (10.4;24.6)	NA	11.6 (8.49;16.0)
HB	GMC (mIU/mL)	335 (216;522)	13,884 (9495;20302)	366 (227;591)	13,528 (9074;20167)
	Ratio ^a	NA	41.3 (31.3;54.7)	NA	37.0 (26.9;50.7)
Hib	GMC (µg/mL)	10.5 (7.24;15.2)	231 (182;293)	15.0 (9.82;22.9)	163 (122;217)
	Ratio ^a	NA	22.1 (13.7;35.7)	NA	10.8 (6.64;17.7)
Polio 1	GMT (1/dil)	942 (611;1454)	3531 (2748;4536)	1448 (1056;1987)	3531 (2644;4714)
	Ratio ^a	NA	3.78 (2.45;5.82)	NA	2.44 (1.75;3.39)
Polio 2	GMT (1/dil)	161 (107;241)	4243 (3311;5439)	254 (185;350)	3238 (2478;4230)
	Ratio ^a	NA	26.8 (17.4;41.4)	NA	12.7 (9.51;17.0)
Polio 3	GMT (1/dil)	630 (426;932)	5917 (4464;7843)	1103 (779;1561)	4901 (3660;6563)
	Ratio ^a	NA	9.35 (5.68;15.4)	NA	4.44 (2.85;6.93)

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

NA = not applicable; NC = not calculated.

^a Ratio of post-booster/pre-booster.

PRP~T or DTwP-HB-PRP~T + IPV, or in those who received the DTwP-IPV-HB-PRP~T booster coadministered with MMR compared to those who received MMR on a separate occasion. Although no prior data exist for the administration of the DTwP-

IPV-HB-PRP~T booster vaccine after the same vaccine given as an infant primary series, data for the administration of DTwP-IPV-HB-PRP~T to Indian infants in the second year of life [7] are comparable to those observed in the present study. In Cohort I of the

Table 4

Sero-protection and sero-response rates pre- and post-booster vaccination according to the primary series vaccine(s) (DTwP-IPV-HB-PRP~T or DTwP-HB-PRP~T + IPV) (FAS).

Antigen	Threshold	DTwP-IPV-HB-PRP~T primary series (N = 71)		DTwP-HB-PRP~T + IPV primary series (N = 35)	
		Pre-booster	Post-booster	Pre-booster	Post-booster
Diphtheria	≥0.01 IU/mL	98.6 (92.4;100.0)	100.0 (94.9;100.0)	97.1 (85.1;99.9)	100.0 (90.0;100.0)
	≥0.10 IU/mL	77.5 (66.0;86.5)	100.0 (94.9;100.0)	85.7 (69.7;95.2)	100.0 (90.0;100.0)
	≥1.0 IU/mL	9.9 (4.1;19.3)	95.7 (88.0;99.1)	11.4 (3.2;26.7)	94.3 (80.8;99.3)
Tetanus	≥0.01 IU/mL	100.0 (94.9;100.0)	100.0 (94.9;100.0)	100.0 (90.0;100.0)	100.0 (90.0;100.0)
	≥0.10 IU/mL	97.2 (90.2;99.7)	100.0 (94.9;100.0)	100.0 (90.0;100.0)	100.0 (90.0;100.0)
	≥1.0 IU/mL	39.4 (28.0;51.7)	100.0 (94.9;100.0)	48.6 (31.4;66.0)	97.1 (85.1;99.9)
Pertussis PT	≥2 EU/mL	88.7 (79.0;95.0)	100.0 (94.9;100.0)	88.6 (73.3;96.8)	97.1 (85.1;99.9)
	≥4-fold rise ^a	NA	74.3 (62.4;84.0)	NA	77.1 (59.9;89.6)
	VR ^b	NA	91.4 (82.3;96.8)	NA	88.6 (73.3;96.8)
FHA	≥2 EU/mL	98.6 (92.4;100.0)	100.0 (94.9;100.0)	91.4 (76.9;98.2)	100.0 (90.0;100.0)
	≥4-fold rise ^a	NA	90.0 (80.5;95.9)	NA	82.9 (66.4;93.4)
	VR ^b	NA	94.3 (86.0;98.4)	NA	91.4 (76.9;98.2)
PRN	≥2 EU/mL	69.0 (56.9;79.5)	100.0 (94.9;100.0)	74.3 (56.7;87.5)	100.0 (90.0;100.0)
	≥4-fold rise ^a	NA	90.0 (80.5;95.9)	NA	85.7 (69.7;95.2)
	VR ^b	NA	95.7 (88.0;99.1)	NA	88.6 (73.3;96.8)
FIM	≥2 EU/mL	97.2 (90.2;99.7)	100.0 (94.9;100.0)	97.1 (85.1;99.9)	97.1 (85.1;99.9)
	≥4-fold rise ^a	NA	90.0 (80.5;95.9)	NA	82.9 (66.4;93.4)
	VR ^b	NA	98.6 (92.3;100.0)	NA	91.4 (76.9;98.2)
HB	≥10 mIU/mL	95.8 (88.1;99.1)	100.0 (94.9;100.0)	100.0 (90.0;100.0)	100.0 (90.0;100.0)
	≥100 mIU/mL	76.1 (64.5;85.4)	100.0 (94.9;100.0)	77.1 (59.9;89.6)	100.0 (90.0;100.0)
Hib	≥0.15 µg/mL	100.0 (94.9;100.0)	100.0 (94.9;100.0)	100.0 (90.0;100.0)	100.0 (90.0;100.0)
	≥1 µg/mL	95.8 (88.1;99.1)	100.0 (94.9;100.0)	91.4 (76.9;98.2)	100.0 (90.0;100.0)
Polio 1	≥8 1/dil	98.6 (92.4;100.0)	100.0 (94.9;100.0)	100.0 (90.0;100.0)	100.0 (90.0;100.0)
Polio 2	≥8 1/dil	98.6 (92.4;100.0)	100.0 (94.9;100.0)	100.0 (90.0;100.0)	100.0 (90.0;100.0)
Polio 3	≥8 1/dil	100.0 (94.9;100.0)	100.0 (94.9;100.0)	100.0 (90.0;100.0)	100.0 (90.0;100.0)

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

VR = vaccine response; NA = not applicable; NC = not calculated.

^a From pre-booster to post-booster.^b If pre-vaccination concentration < 4xLLOQ, then the post-booster titer was ≥ 4x the pre-booster concentration; if pre-booster concentration was ≥ 4xLLOQ, then the post-booster titer was ≥ 2x the pre-booster concentration.**Table 5**

Geometric mean concentrations (GMCs) and geometric mean titers (GMTs) pre- and post-booster vaccination according to the primary series vaccine(s) (DTwP-IPV-HB-PRP~T or DTwP-HB-PRP~T + IPV) (FAS).

Antigen		DTwP-IPV-HB-PRP~T primary series (N = 71)		DTwP-HB-PRP~T + IPV primary series (N = 35)	
		Pre-booster	Post-booster	Pre-booster	Post-booster
Diphtheria	GMC (IU/mL)	0.237 (0.181;0.310)	6.34 (4.93;8.15)	0.263 (0.165;0.419)	7.57 (4.96;11.6)
	Ratio ^a	NA	26.8 (21.2;33.9)	NA	28.8 (17.9;46.3)
Tetanus	GMC (IU/mL)	0.762 (0.561;1.03)	15.4 (12.6;18.9)	1.34 (0.813;2.21)	21.2 (15.4;29.3)
	Ratio ^a	NA	20.2 (15.3;26.5)	NA	15.8 (8.22;30.5)
Pertussis PT	GMC (EU/mL)	20.9 (14.5;30.1)	163 (122;217)	14.2 (8.71;23.2)	121 (79.9;183)
	Ratio ^a	NA	7.93 (6.04;10.4)	NA	8.50 (5.18;14.0)
FHA	GMC (EU/mL)	9.28 (7.27;11.8)	110 (88.7;136)	10.0 (6.32;15.9)	97.9 (70.0;137)
	Ratio ^a	NA	11.7 (9.33;14.6)	NA	9.76 (6.41;14.9)
PRN	GMC (EU/mL)	3.67 (2.81;4.79)	69.8 (56.0;86.9)	3.73 (2.50;5.58)	71.3 (51.6;98.5)
	Ratio ^a	NA	18.9 (15.1;23.7)	NA	19.1 (11.6;31.4)
FIM	GMC (EU/mL)	116 (85.6;157)	1687 (1421;2001)	119 (69.9;203)	1419 (858;2347)
	Ratio ^a	NA	14.4 (10.5;19.8)	NA	11.9 (7.50;18.9)
HB	GMC (mIU/mL)	384 (247;597)	12,020 (8313;17380)	293 (193;445)	17,769 (12375;25513)
	Ratio ^a	NA	31.2 (24.2;40.1)	NA	60.7 (42.9;85.8)
Hib	GMC (µg/mL)	15.5 (10.9;22.0)	186 (147;237)	8.46 (5.36;13.3)	203 (146;282)
	Ratio ^a	NA	12.0 (7.78;18.5)	NA	24.0 (13.6;42.2)
Polio 1	GMT (1/dil)	1307 (930;1837)	4240 (3359;5333)	965 (640;1454)	2488 (1795;3338)
	Ratio ^a	NA	3.25 (2.27;4.65)	NA	2.54 (1.74;3.69)
Polio 2	GMT (1/dil)	218 (158;301)	3898 (3116;4876)	181 (118;277)	3262 (2350;4527)
	Ratio ^a	NA	18.0 (12.9;25.1)	NA	18.0 (11.6;27.9)
Polio 3	GMT (1/dil)	924 (667;1281)	5458 (4256;7001)	710 (452;1114)	5144 (3591;7368)
	Ratio ^a	NA	5.86 (3.86;8.88)	NA	7.25 (4.03;13.0)

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

NA = not applicable; NC = not calculated.

^a Ratio of post-booster/pre-booster.

previous study the DTwP-IPV-HB-PRP~T booster was administered alone, and so from the similarity of the results in the present study it would appear that its immunogenicity is not affected by the administration of MMR given either before, at the same time, or

after the DTwP-IPV-HB-PRP~T vaccine. Previous studies of aP-containing hexavalent and pentavalent vaccines with similar HB, Hib, and IPV antigens to those in the DTwP-IPV-HB-PRP~T vaccine provide useful comparisons for the antibody persistence and

booster response of these antigens. In particular, in South Africa antibody persistence at 15–18 months of age after a 6, 10, 14 week DTaP-IPV-HB-Hib primary series was robust for each antigen and co-administration of the DTaP-IPV-HB-Hib booster with an MMR-Varicella vaccine was safe and immunogenic [17]. Similarly, the antibody persistence and booster response of a DTaP-IPV/Hib vaccine in the second year of life were robust in an Indian infant population after a 6, 10, 14 week primary series [18].

The ECL assay used has been shown to perform better than commercially available assays developed for pertussis diagnostic purposes, which are not suited to the precise, accurate, and reproducible evaluation that is required in clinical trials. The rationale for the use of the ECL assay in assessing the vaccine responses elicited by wP vaccines has recently been described [19].

Limitations of the study include the open-label design (necessitated by the different number of injections), the small sample size, the lack of a control group with no MMR vaccination, no evaluation of the MMR response, and the lack of a control group with a booster of DTwP-HB-PRP~T + IPV.

In conclusion, the combination of established antigens can improve vaccination compliance and offers a high-quality, fully liquid wP-containing hexavalent vaccine. The study has shown good antibody persistence of the DTwP-IPV-HB-PRP~T vaccine and has demonstrated good safety and robust immunogenicity following a booster dose given with MMR in the second year of life, supporting its progression to Phase 3 clinical development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflicts of interest

Clinical investigators involved in these studies (SP, MM, MDR, and RS) 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. FN and AM are employees of Sanofi Pasteur. DMP and EJ were employees of Sanofi Pasteur at the time of the study and during manuscript development. BNP, SM, MJ, and SR are employees of Sanofi Healthcare India Private Ltd (SHIPL).

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