EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Infanrix hexa

diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/000296/P46/131

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 15.07.2019, the MAH submitted a completed paediatric study for Infanrix hexa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study DTPA (BOOSTRIX)-048 PRI (201330 - EUDRACT Number: 2014-001117-41) ' A phase IV, open-label, non-randomised, multicentre study to assess the immunogenicity and safety of Infanrix hexa administered as primary vaccination in healthy infants born to mothers given Boostrix during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047] is part of a clinical development program. Study Boostrix-048 is the second study of the clinical development program, and the final study BOOSTRIX-049 is still ongoing. Study Boostrix-048 is the subject of this PAM, whereas BOOSTRIX-049 CSR is expected to be submitted by March 2020 as a variation. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Infanrix hexa is composed of DTPa-HBV-IPV and Hib vaccines. Hib vaccine was to be reconstituted before use with the liquid DTPa-HBV-IPV component.

Formulation of DTPa-HBV-IPV vaccine:
Diphteria Toxoid (DT) >=30IU; Tetanus Toxoid (TT) >=40IU; Pertussis Toxoid (PT)=25µg; Filamentous Haemagglutinin (FHA)=25µg; Pertactin (PRN)=8µg; Hepatitis B surface antigen (HBsAg)=10µg; Inactivated Poliovirus type 1 (Mahoney strain)=40DU; Inactivated Poliovirus type 2 (MEF-1 strain)=8DU; Inactivated Poliovirus type 3 (Saukett strain)=32DU; Aluminium=700µg Al3+

Formulation of Hib vaccine:
Haemophilus influenzae type b polysaccharide (PRP)=10µg; TT (as carrier protein) ~=25µg; Aluminium as salts=0.12 mg

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study DTPA (BOOSTRIX)-048 PRI (201330 - EUDRACT Number: 2014-001117-41) ' A phase IV, open-label, non-randomised, multicentre study to assess the immunogenicity and safety of Infanrix hexa administered as primary vaccination in healthy infants born to mothers given Boostrix during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047].'

2.3.2. Clinical study

Study DTPA (BOOSTRIX)-048 PRI: ` A phase IV, open-label, non-randomised, multicentre study to assess the immunogenicity and safety of Infanrix hexa administered as primary vaccination in healthy infants born to mothers given Boostrix during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047].

Description

The study was a Phase IV, open-label, non-randomised, uncontrolled, multi-centre, multi-country study with 2 parallel groups to evaluate the immunogenicity and safety of Infanrix hexa given in a primary schedule to all infants born to pregnant women who participated in study 116945 [DTPA (BOOSTRIX)-047], in which the mothers received a single dose of Boostrix either during pregnancy or immediately post-delivery.

The study was initiated on January 22th 2016 and completed on March 7th 2018.

Methods

Objective(s)

1. Primary:

- To assess the immunological response to Infanrix hexa in terms of seroprotection status for diphtheria, tetanus, hepatitis B, poliovirus and Hib antigens, and in terms of vaccine response to the pertussis antigens, 1 month after the last dose of the primary vaccination in infants born to mothers vaccinated with Boostrix during pregnancy or immediately post-delivery.

A seroprotected subject was a subject whose antibody concentration/titre was greater than or equal to the level defining clinical protection.
A seropositive subject was a subject whose antibody concentration/titre was greater than or equal to the assay cut-off defined in the study.
Vaccine response to the PT, FHA and PRN antigens, was defined as:

- *Appearance of antibodies in subjects who were initially seronegative (i.e., with concentrations <cut-off value).*
- *At least maintenance of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e., with concentrations ≥cut-off value).*

2. Secondary:

- To assess persistence of antibodies against diphtheria, tetanus and pertussis antigens, before the first dose of Infanrix hexa in infants born to mothers vaccinated with Boostrix during pregnancy or immediately post-delivery.
- To assess the immunological response to Infanrix hexa and Prevenar 13 in terms of antibody concentrations or titres against all antigens, 1 month* after the last dose of the primary vaccination in infants born to mothers vaccinated with Boostrix during pregnancy or immediately post-delivery.
- To assess the immunological response to Infanrix hexa in terms of seropositivity rates against pertussis antigens, 1 month after the last dose of the primary vaccination in infants born to mothers vaccinated with Boostrix during pregnancy or immediately post-delivery.
- To assess the safety and reactogenicity of Infanrix hexa and Prevenar 13 in terms of solicited and unsolicited adverse events (AEs) and serious adverse events (SAEs).

**In some countries/regions with an Infanrix hexa 3-dose vaccination schedule, Prevenar 13 could have been administered as 2-dose or 3-dose primary vaccination schedule (according to the routine national immunisation schedule). In such an instance, the evaluation was to be performed 1 month after the last Infanrix hexa dose regardless of Prevenar 13 vaccination. In the countries/regions with an Infanrix hexa 2-dose schedule, Prevenar 13 was co-administered at the same time as Infanrix hexa.*

Study design

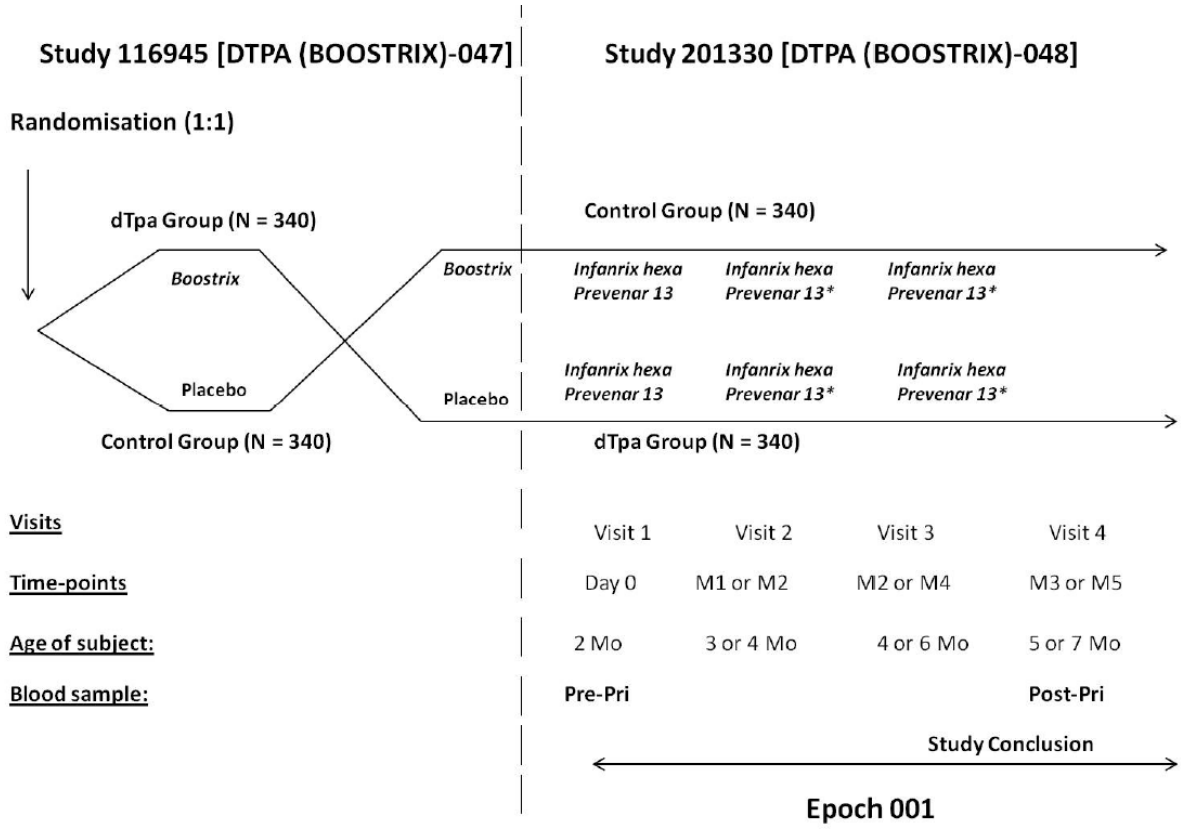
Phase IV, open-label, non-randomised, multi-centric, multi-country study conducted in Australia, Canada, Czechia, Finland, Italy and Spain, with 2 parallel groups.

Subjects were to receive either 3 doses of Infanrix hexa co-administered with Prevenar 13 at 2, 4 and 6 months or 2, 3 and 4 months (Figure 1), either 2 doses of Infanrix hexa co-administered with Prevenar 13 at 3 and 5 months or 2 and 4 months (Figure 2), depending on the immunisation schedule of the country.

The intended duration of the study was approximately 3 months, per subject, for subjects vaccinated according to the 2 and 4, the 3 and 5 or the 2, 3 and 4 months schedule and approximately 5 months, per subject, for those vaccinated according to 2, 4 and 6 months schedule.

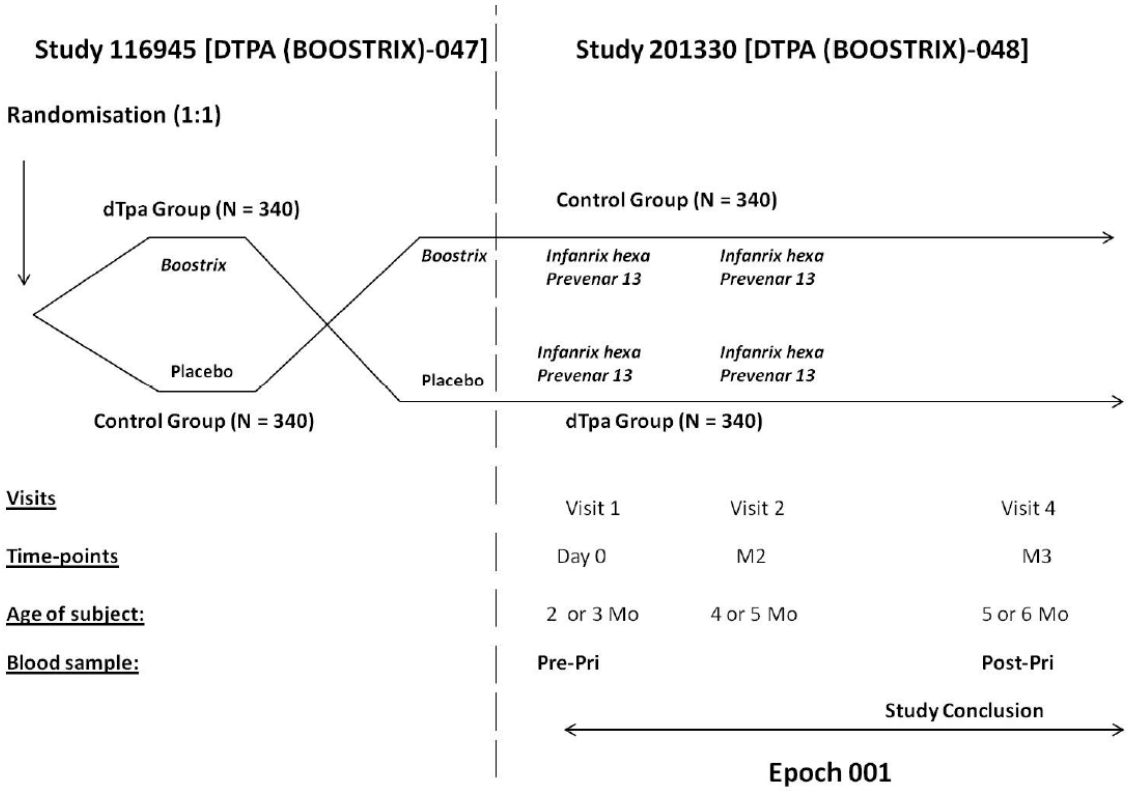
Blood samples were to be drawn from all subjects at the indicated timepoints (Figure 1, Figure 2).

An independent data monitoring committee was established to oversee the safety of subjects enrolled in the clinical study 116945 [DTPA (BOOSTRIX)-047] (pregnant women), 201330 [DTPA (BOOSTRIX-048 PRI (infants) and 201334 [DTPA (BOOSTRIX)-049 BST 048].



N=Maximum number of subjects that were planned to be enrolled.
M=Month, Mo=age in months
Timepoints were numbered based on the different vaccination schedules. D0, M1, M2 and M3 timepoints reflected for subjects who were to be vaccinated according to the 2, 3 and 4 month schedule while D0, M2, M4 and M5 timepoints reflected for subjects who were to be vaccinated according to the 2, 4 and 6 month schedule.
* In some countries/regions with an *Infanrix hexa* 3-dose schedule, *Prevenar 13* was given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.
Pre-Pri=Blood sample was to be collected before the first dose of the primary vaccination course.
Post-Pri=Blood sample was to be collected 1 month after the last dose of the primary vaccination course.

Figure 1. Study design diagram for infants receiving a 3-dose schedule of Infanrix hexa



N=Maximum number of subjects that were to be enrolled.
M=Month, Mo=age in months
Pre-Pri=Blood sample was to be collected before the first dose of the primary vaccination course.
Post-Pri=Blood sample was to be collected 1 month after the last dose of the primary vaccination course.
Subjects were to be vaccinated either at 2 and 4 months of age or 3 and 5 months of age, according to the routine national immunisation schedule.

Figure 2. Study design diagram for infants receiving a 2-dose schedule of Infanrix hexa

Study population /Sample size

Healthy infants as established by medical history and clinical examination, born to mothers who participated in study 116945 [DTPA (BOOSTRIX)-047] and who were at 6-14 weeks of age (including 6 weeks and up to and including 14 weeks and 6 days of age) at the time of the first vaccination. Infants were divided in 2 groups in the study as follows:

1. dTpa Group: This group consisted of infants born to mothers belonging to the dTpa group in study 116945 [DTPA (BOOSTRIX)-047], who received a single dose of Boostrix during pregnancy and a dose of placebo immediately post-delivery. All subjects in this group received Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.

2. Control Group: This group consisted of infants born to mothers belonging to the control group in study 116945 [DTPA (BOOSTRIX)-047], who received a single dose of placebo during pregnancy and a dose of Boostrix immediately post-delivery. All subjects in this group received Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.

The target was to enrol a maximum of 680 eligible subjects aged 6-14 weeks (approximately 340 subjects in each group).

Treatments

Formulation and characteristics of the study vaccine are presented in Table 1. The dosage and administration of study vaccine is given in Table 2.

Table 1. Study vaccines

Treatment name	Vaccines name	Formulation	Presentation	Number of doses	Lot number
Infanrix hexa	DTPa-HBV-IPV	DT>=30IU; TT>=40IU; PT=25µg; FHA=25µg; PRN=8µg; HBsAg=10µg; Inactivated Poliovirus type 1 (Mahoney strain)=40DU; Inactivated Poliovirus type 2 (MEF-1 strain)=8DU; Inactivated Poliovirus type 3 (Saukett strain)=32DU; Aluminium=700µg Al3+	The DTPa-HBV-IPV component was presented as a turbid white suspension in a pre-filled syringe.	2 or 3**	AC21B548B/ AHIBD107A AC21B548B/ AHIBVD014D AC21B551A/ AHIBVD052A AC21B557C/ AHIBD086E AC21B604A/ AHIBD159B AC21B614A/ AHIBD165C AC21B617B/ AHIBD195C AC21B623A/ AHIBD183C
	Hib	PRP=10µg; TT~=25µg Aluminium as salts=0.12 mg	The lyophilised Hib component was presented as a white pellet in a glass vial; it was to be reconstituted before use with the liquid DTPa-HBV-IPV component.		
Prevenar 13	*Prevenar 13*	PS1=2.2µg CRM197; PS3=2.2µg CRM197; PS4=2.2µg CRM197; PS5=2.2µg CRM197; PS6A=2.2µg CRM197; PS6B=4.4µg CRM197; PS7F=2.2µg CRM197; PS9V=2.2µg CRM197; PS14=2.2µg CRM197; PS18C=2.2µg CRM197; PS19A=2.2µg CRM197; PS19F=2.2µg CRM197; PS23F=2.2µg CRM197; $AlPO_4$=125µg Al3+	Suspension for injection in a pre-filled syringe	2 or 3 ***	DEXTA533AZ DEXTA539AZ DEXTA549AZ DLOCA154A DLOCA157A DLOCA158A DLOCA159A DLOCA161A

The volume of vaccines to be administered was 0.5 mL for both *Infanrix hexa* (after reconstitution) and *Prevenar 13*.
**In some countries, *Infanrix hexa* was given as a 2-dose schedule at 2 and 4 months of age or at 3 and 5 months of age. In other countries *Infanrix hexa* was given as a 3-dose schedule at 2, 4 and 6 months of age or at 2, 3 and 4 months of age as recommended by the routine immunisation programme.
****Prevenar 13* was administered at the same schedule as *Infanrix hexa* except in some countries/regions with an *Infanrix hexa* given as a 3-dose schedule where *Prevenar 13* was given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.

Table 2. Dosage and administration

Type of contact and timepoint	Volume to be administered	Study group	Treatment name	Route[1]	Site	Side
Visit 1 (Day 0), Visit 2 (Month 2), Visit 3 (Month 4)* Or Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2)**	0.5 mL	dTpa Group and Control Group	*Infanrix hexa*	IM	Thigh	Right
Visit 1 (Day 0), Visit 2 (Month 2), Visit 3 (Month 4)* Or Visit 1 (Day 0), Visit 2 (Month 2)† Or Visit 1 (Day 0), Visit 2 (Month 1), Visit 3 (Month 2)**	0.5 mL	dTpa Group and Control Group	*Prevenar 13*	IM	Thigh	Left
Visit 1 (Day 0), Visit 2 (Month 2)***	0.5 mL	dTpa Group and Control Group	*Infanrix hexa*	IM	Thigh	Right
Visit 1 (Day 0), Visit 2 (Month 2)***	0.5 mL	dTpa Group and Control Group	*Prevenar 13*	IM	Thigh	Left

[1] IM=Intramuscular
*For subjects vaccinated with *Infanrix hexa* at 2, 4 and 6 months of age
** For subjects vaccinated with *Infanrix hexa* at 2, 3 and 4 months of age
*** For subjects vaccinated with *Infanrix hexa* at 2 and 4 months of age or at 3 and 5 months of age. These subjects were to receive *Prevenar 13* at the same vaccination schedule.
† In some countries/regions with an *Infanrix hexa* 3-dose schedule, *Prevenar 13* was given as a 2-dose schedule at 2 and 4 months of age as a part of the routine immunisation programme.

Outcomes/endpoints

1. Primary endpoints:

Immunogenicity with respect to components of Infanrix hexa.

- Anti-diphtheria (anti-D), anti-tetanus (anti-T), anti-hepatitis B surface antigen (anti-HBs), anti-poliovirus types 1, 2 and 3 and anti-polyribosyl-ribitol phosphate (anti-PRP) seroprotection status, 1 month after the last dose of primary vaccination.

A seroprotected subject was a subject whose antibody concentration/titre was greater than or equal to the level defining clinical protection. The following seroprotection thresholds were applicable:
- Anti-D antibody concentrations ≥0.1 IU/mL.
- Anti-T antibody concentrations ≥0.1 IU/mL.
- Anti-HBs antibody concentrations ≥10 mIU/mL.
- Anti-poliovirus types 1, 2 and 3 antibody titres ≥8 ED50.
- Anti-PRP antibody concentrations ≥0.15 µg/mL.

- Vaccine response to pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) antigens, 1 month after the last dose of primary vaccination.

Vaccine response to the PT, FHA and PRN antigens, was defined as:

- Appearance of antibodies in subjects who were initially seronegative (i.e., with concentrations < assay cut-off value).
- At least maintenance of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e., with concentrations ≥ assay cut-off value).

The assay cut-off value was 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.

2. Secondary endpoints:

- Persistence of antibodies before the first dose of Infanrix hexa:
  Anti-D and anti-T seroprotection status, anti-PT, anti-FHA, anti-PRN seropositivity status and antibody concentrations.
- Immunogenicity with respect to components of Infanrix hexa and Prevenar 13:
  Anti-D, anti-T, anti-poliovirus types 1, 2 and 3, anti-HBs, anti-PRP, anti-PT, anti-FHA, anti-PRN and anti-pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) antibody concentrations or titres, 1 month after the last dose of primary vaccination.

  A concentration of immunoglobulin G (IgG) anti-pneumococcal capsular polysaccharide antibodies of ≥ 0.35 µg/mL measured by ELISA at 1 month after primary immunisation was recommended as the protective threshold and as the basis for licensing Pneumococcal Conjugate Vaccine.
- Immunogenicity with respect to components of Infanrix hexa:
  Anti-PT, anti-FHA, anti-PRN antibody seropositivity status, 1 month after the last dose of primary vaccination.
- Solicited local and general AEs:
  Occurrence of solicited local/general AEs during the 4-day (Days 0-3) follow-up period aftereach vaccination.
- Unsolicited AEs:
  Occurrence of unsolicited AEs during the 31-day (Days 0-30) follow-up period after each vaccination.
- All SAEs:
  Occurrence of SAEs from first vaccination dose to study end.

Statistical Methods

The primary analyses of immunogenicity were based on the according to protocol (ATP) cohort while the primary analyses of safety were based on the total vaccinated cohort (TVC). All analyses in this study were descriptive.

Analysis of immunogenicity:

For each group, antigens and at each timepoint, a blood sample result was available:
- Seropositivity rates and seroprotection rates were calculated with exact 95% CI.
- The geometric mean concentration/titre (GMC/GMT) with 95% CI was tabulated for antibodies against each antigen.
- The vaccine response rates to PT, FHA and PRN (with exact 95% CI) were calculated.

Analysis of safety:

- The percentage of doses and of subjects with at least 1 local AE (solicited or unsolicited), with at least 1 general AE (solicited or unsolicited) and with any AE (solicited or unsolicited) during the 4-

day (Days 0-3) solicited follow-up period was tabulated with exact 95% CI after each vaccine dose and overall. The same calculations were done for AEs (solicited or unsolicited) rated as grade 3 in intensity, for symptoms (solicited or unsolicited) leading to medical advice and for symptoms (solicited or unsolicited) assessed as causally related to vaccination.

- The percentage of doses and of subjects reporting each individual solicited local and general AE during the 4-day (Days 0-3) solicited follow-up period was tabulated after each vaccine dose and overall, with exact 95% CI. The same calculations were done for each individual solicited AE rated as grade 3 in intensity and for each individual solicited symptom assessed as causally related to vaccination.
- All computations mentioned above were done for grade ≥2 (solicited AEs only) and grade 3 AEs, for AEs considered related to vaccination (general AEs only), for grade 3 AEs considered related to vaccination (general AEs only) and for AEs that resulted in a medically attended visit.
- Occurrence of fever and related fever were reported per 0.5°C cumulative temperature increments as well as the occurrence of grade 3 fever (>39.0°C axillary temperature) with causal relationship to vaccination.
- The verbatim reports of unsolicited AEs were reviewed by a physician and the signs and symptoms were coded according to Medical Dictionary for Regulatory Activities (MedDRA). Every verbatim term was matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31-day (Days 0-30) follow-up period after any dose with its exact 95% CI was tabulated by group, and by Preferred Term. Similar tabulation was done for unsolicited AEs rated as grade 3, for unsolicited AEs with causal relationship to vaccination and AEs/SAEs leading to withdrawal from the study.
- The percentage of subjects who received concomitant medication and antipyretic medication during the 4-day (Days 0-3) follow-up period and the 31-day (Days 0-30) follow-up were tabulated (with exact 95% CI) after each vaccine dose and overall.
- All SAEs reported from first vaccination dose up to study end were described in detail.

Assessor's comment

Methods are overall acceptable.

Primary and secondary objectives and endpoints are relevant. The seroprotection thresholds proposed as associated with clinical protection against diphtheria, tetanus, hepatitis B, poliomyelitis, *Haemophilus influenzae type b* and *Streptococcus pneumoniae* infections are appropriate. The definition of vaccine response to pertussis antigens is acknowledged and further discussed in the results' section.

Results

Recruitment/ Number analysed

A total of 601 subjects fulfilled the criteria to participate in this follow-up study of DTPA (BOOSTRIX)-047. These subjects were vaccinated with the study vaccines and comprised the TVC. Of the 601 subjects, 9 subjects were withdrawn from the study mainly because of migration/moving from study area (n=4) and consent withdrawal (n=3). Hence, 592 subjects comprised the ATP cohort for safety.

Further, a total of 50 subjects were withdrawn from the ATP cohort for safety, leaving 542 subjects evaluable for the ATP cohort for immunogenicity (Table 3).

Table 3. Number of subjects enrolled into the study as well as excluded from ATP analysis with reasons for exclusion (All enrolled subjects)

	Total			dTpa Group		Control Group	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	601			296		305	
Total vaccinated cohort	**601**		**100**	**296**		**305**	
Randomisation failure (code 1050)	1	1		0	0	1	1
Randomisation code broken at the investigator site (code 1060)	2	2		1	1	1	1
Study vaccine dose not administered according to protocol (code 1070)	2	2		2	2	0	0
Vaccine temperature deviation (code 1080)	4	5		2	3	2	2
ATP cohort for safety	**592**		**98.5**	**291**		**301**	
Protocol violation (inclusion/exclusion criteria) (code 2010)	7	8		4	5	3	3
Non-compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	11	11		4	4	7	7
Non-compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	8	9		3	4	5	5
Essential serological data missing (code 2100)	24	29		12	16	12	13
ATP cohort for immunogenicity	**542**		**90.2**	**268**		**274**	

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
Note: Subjects may have more than 1 elimination code assigned
n=number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s=number of subjects with the elimination code assigned
%=percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
All eliminations from the primary study 116945 [DTPA(BOOSTRIX)-047] were carried forward for this follow up study except for the visit specific elimination codes (2090, 2100 and 2120).

Assessor's comment

Similar proportion of subjects were withdrawn from the ATP cohort for safety and for immunogenicity in both groups. ATP cohort for safety consists of 98.3 and 98.7% of the total vaccinated cohort for dTpa and control groups, respectively. ATP cohort for immunogenicity consists of 90.5 and 89.8% of the total vaccinated cohort for dTpa and control groups, respectively. This is acceptable.

Baseline data

The demographic characteristics for the TVC is presented in Table 4.

Overall for both the groups, the average age of subjects was 8.8 months (±1.7). Of the 601 subjects, 47.4% were females, 92% belonged to the white Caucasian/European heritage. A total of 12.1% of subjects were given a 2-dose schedule, while majority of the subjects (87.9%) received the study

vaccines as a 3-dose schedule. More than 50% of the subjects' mothers received Boostrix during 27-32 gestational weeks of the foetus.

The demographic characteristics of the ATP cohort for immunogenicity were similar to the TVC.

Table 4. Summary of demographic characteristics (Total Vaccinated Cohort)

		dTpa Group N=296		Control Group N=305		Total N=601	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age [week] at vaccination dose: 1	Mean	8.7	-	8.9	-	8.8	-
	SD	1.6	-	1.8	-	1.7	-
	Q1	8.0	-	8.0	-	8.0	-
	Median	9.0	-	9.0	-	9.0	-
	Q3	9.0	-	9.0	-	9.0	-
Gender	Female	141	47.6	144	47.2	285	47.4
	Male	155	52.4	161	52.8	316	52.6
Geographic Ancestry	African Heritage/African American	4	1.4	9	3.0	13	2.2
	Asian-East Asian Heritage	2	0.7	0	0.0	2	0.3
	Asian-South East Asian Heritage	3	1.0	0	0.0	3	0.5
	White-Arabic/North African Heritage	1	0.3	3	1.0	4	0.7
	White-Caucasian/European Heritage	268	90.5	285	93.4	553	92.0
	Other	18	6.1	8	2.6	26	4.3
Dose schedule	2-dose schedule	32	10.8	41	13.4	73	12.1
	3-dose schedule	264	89.2	264	86.6	528	87.9
Maternal age group	18-24Y	7	2.4	12	3.9	19	3.2
	25-34Y	187	63.2	188	61.6	375	62.4
	35-45Y	102	34.5	105	34.4	207	34.4
Gestational week of foetus at dose 1 of maternal vaccination	27-32W	174	58.8	179	58.7	353	58.7
	33-36W	121	40.9	126	41.3	247	41.1
	Above 36W	1	0.3	0	0.0	1	0.2
Country	Australia	20	6.8	18	5.9	38	6.3
	Canada	68	23.0	76	24.9	144	24.0
	Czechia	35	11.8	36	11.8	71	11.8
	Finland	21	7.1	31	10.2	52	8.7
	Italy	8	2.7	6	2.0	14	2.3
	Spain	144	48.6	138	45.2	282	46.9

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
N=total number of subjects; n=number of subjects in a given category; Value=value of the considered parameter
SD=standard deviation; %=n/Number of subjects with available results x 100; Q1=Quartile 1; Q3=Quartile 3
2-dose schedule=subjects who received 2-dose of *Infanrix hexa* at 2,4 months of age or 3,5 months of age, co-administered with *Prevenar 13*.
3-dose schedule=subjects who received 3-dose of *Infanrix hexa* at 2,3,4 months of age or 2,4,6 months of age, co-administered with *Prevenar 13*. *Prevenar 13* could be administered as 2-dose or 3-dose primary vaccination schedule (according to the routine national immunisation schedule of the country)

Assessor's comment

Demographic characteristics are appropriately balanced between groups.

Efficacy results

1. Immune responses to Diphtheria and Tetanus toxoids (Table 5, Table 6):

   - At 1 month after the subjects received last dose of Infanrix hexa, the percentage of subjects seroprotected against diphtheria and tetanus (anti-D and anti-T antibody concentrations ≥0.1 IU/mL) was 100% in both groups (Primary objective).
   - Before the first dose of Infanrix hexa primary vaccination, the maternal antibodies against diphtheria and tetanus were found to be persistent in the subjects and it was observed that subjects in dTpa group had higher antibody concentrations when compared to the subjects in control group.
   - At 1 month after the subjects received the last dose of Infanrix hexa, all subjects in the dTpa group presented lower anti-D GMCs when compared to the control group. Consequently, the percentage of subjects that was ≥ 1.0 IU/ml was lower in the dTpa group when compared to the control group.

     There was no significant difference observed in the GMC values for anti-T in both study groups.
   - At 1 month after the subjects received the last dose of Infanrix hexa, the percentage of subjects that had anti-D ≥ 1.0 IU/ml was lower for infants that received the study vaccines as a 2-dose schedule when compared to the infants that received the study vaccines as a 3-dose schedule. This difference was more important in the dTpa group. Nevertheless, the percentage of subjects seroprotected against diphtheria was 100%, whatever the vaccine regimen.

     The percentage of subjects that had anti-T ≥ 1.0 IU/ml was lower for infants that received the study vaccines as a 2-dose schedule when compared to the infants that received the study vaccines as a 3-dose schedule, but to a less extend than for the anti-D Ab. No difference was observed between dTpa and control groups. The percentage of subjects seroprotected against tetanus was 100%, whatever the vaccine regimen.
   - Maternal age and gestational week of foetus at dose 1 in maternal study did not interfere with the diphtheria and tetanus responses.

Table 5. Overall percentage of subjects with anti-D and anti-T Ab concentration ≥ to the assay cut-off, 0.1 IU/ml, 1.0 IU/ml and GMC, before the first and 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥ Assay cut-off*				≥ 0.1 IU/mL				≥ 1 IU/mL				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-D antibody	dTpa Group	Pre-Pri	242	215	88.8	84.2	92.5	200	82.6	77.3	87.2	69	28.5	22.9	34.6	0.423	0.354	0.506
		Post-Pri	264	264	100	98.6	100	264	100	98.6	100	202	76.5	70.9	81.5	1.747	1.598	1.910
	Control Group	Pre-Pri	252	143	56.7	50.4	62.9	110	43.7	37.4	50.0	10	4.0	1.9	7.2	0.089	0.076	0.103
		Post-Pri	271	271	100	98.6	100	271	100	98.6	100	250	92.3	88.4	95.1	2.746	2.502	3.015
anti-T antibody	dTpa Group	Pre-Pri	242	240	99.2	97.0	99.9	240	99.2	97.0	99.9	209	86.4	81.4	90.4	2.152	1.925	2.406
		Post-Pri	266	266	100	98.6	100	266	100	98.6	100	227	85.3	80.5	89.4	2.347	2.135	2.582
	Control Group	Pre-Pri	253	242	95.7	92.4	97.8	225	88.9	84.4	92.5	44	17.4	12.9	22.6	0.378	0.330	0.434
		Post-Pri	271	271	100	98.6	100	271	100	98.6	100	230	84.9	80.0	88.9	2.278	2.069	2.508

dTpa Group = Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group = Infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.
*Assay cut-off is 0.057 IU/mL for anti-diphtheria, 0.043 IU/mL for anti- tetanus
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Pri = blood sample collected before the first dose of the primary vaccination course
Post-Pri = blood sample collected 1 month after the last dose of the primary vaccination course

Table 6. Percentage of subjects with anti-D and anti-T Ab concentration ≥ to the assay cut-off, 0.1 IU/ml and 1.0 IU/ml and GMC, before the first dose and 1 month after the last dose of the primary vaccination - by dose schedule (ATP cohort for immunogenicity)

					≥ Assay cut-off*				≥ 0.1 IU/mL				≥ 1 IU/mL				GMC		
							95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-D antibody	dTpa Group	2 dose schedule	Pre-Pri	22	22	100	84.6	100	22	100	84.6	100	4	18.2	5.2	40.3	0.520	0.340	0.796
			Post-Pri	27	27	100	87.2	100	27	100	87.2	100	7	25.9	11.1	46.3	0.739	0.599	0.911
		3 dose schedule	Pre-Pri	220	193	87.7	82.6	91.8	178	80.9	75.1	85.9	65	29.5	23.6	36.0	0.415	0.342	0.503
			Post-Pri	237	237	100	98.5	100	237	100	98.5	100	195	82.3	76.8	86.9	1.927	1.764	2.106
	Control Group	2 dose schedule	Pre-Pri	34	22	64.7	46.5	80.3	17	50.0	32.4	67.6	0	0.0	0.0	10.3	0.102	0.069	0.151
			Post-Pri	34	34	100	89.7	100	34	100	89.7	100	26	76.5	58.8	89.3	1.531	1.147	2.043
		3 dose schedule	Pre-Pri	218	121	55.5	48.6	62.2	93	42.7	36.0	49.5	10	4.6	2.2	8.3	0.087	0.074	0.102
			Post-Pri	237	237	100	98.5	100	237	100	98.5	100	224	94.5	90.8	97.0	2.987	2.717	3.283
anti-T antibody	dTpa Group	2 dose schedule	Pre-Pri	22	22	100	84.6	100	22	100	84.6	100	12	54.5	32.2	75.6	1.352	1.050	1.739
			Post-Pri	27	27	100	87.2	100	27	100	87.2	100	16	59.3	38.8	77.6	1.339	1.027	1.746
		3 dose schedule	Pre-Pri	220	218	99.1	96.8	99.9	218	99.1	96.8	99.9	197	89.5	84.7	93.3	2.254	2.002	2.538
			Post-Pri	239	239	100	98.5	100	239	100	98.5	100	211	88.3	83.5	92.1	2.501	2.266	2.761
	Control Group	2 dose schedule	Pre-Pri	34	33	97.1	84.7	99.9	30	88.2	72.5	96.7	1	2.9	0.1	15.3	0.294	0.214	0.403
			Post-Pri	34	34	100	89.7	100	34	100	89.7	100	20	58.8	40.7	75.4	1.209	0.950	1.540
		3 dose schedule	Pre-Pri	219	209	95.4	91.8	97.8	195	89.0	84.1	92.9	43	19.6	14.6	25.5	0.393	0.338	0.457
			Post-Pri	237	237	100	98.5	100	237	100	98.5	100	210	88.6	83.9	92.4	2.494	2.258	2.756

dTpa Group = Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group = Infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.
2 dose schedule = subjects who received 2 doses of Infanrix hexa at 2,4 months of age or 3,5 months of age, co-administered with Prevenar 13.
3 dose schedule = subjects who received 3 doses of Infanrix hexa at 2,3,4 months of age or 2,4,6 months of age, co-administered with Prevenar 13.

Prevenar 13 could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule of the country).
*Assay cut-off is 0.057 IU/mL for anti-diphtheria, 0.043 IU/mL for anti- tetanus
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Pri = blood sample collected before the first dose of the primary vaccination course
Post-Pri = blood sample collected 1 month after the last dose of the primary vaccination course

Assessor's comment

All subjects were seroprotected (cut-off ≥ 0.1 IU/ml) against diphtheria and tetanus 1 month after primary vaccination with Infanrix hexa, independently of the time of vaccination of the mother, maternal age and dose schedule of infant's vaccination.

As expected, higher percentages of infants born from mothers vaccinated during pregnancy were seroprotected before the primary vaccination (dTpa group) when compared to the infants born from mothers vaccinated post-delivery (control group). These higher percentages were also observed when considering the threshold associated with long term protection (≥ 1.0 IU/ml, for both anti-D and anti-T Ab). This is reflected by the difference in GMT between both groups.

Percentages of infants achieving the cut-off of ≥ 1.0 IU/ml anti-T Ab and anti-T GMT post-primary vaccination were similar between groups. This was not the case for the immune response to diphtheria toxoid. A trend for lower percentage of infants achieving the cut-off of ≥ 1.0 IU/ml anti-D Ab and lower anti-D GMT were observed in the dTpa group when compared to the control group. This trend was more marked for infants receiving the primary vaccination in a 2-dose schedule when compared to those receiving a 3-dose schedule. Whether this can be due to the infant's pre-vaccination status and therefore a blunting of the infant's immune response due to mothers' vaccination during pregnancy is not known.

Overall, lower percentages of infants achieving the cut-off of ≥ 1.0 IU/ml anti-D and anti-T Ab were observed after a 2-dose schedule compared to a 3-dose schedule. However, 100% of the infants were seroprotected against diphtheria and tetanus, whatever the dose regimen. In addition, as discussed during the scientific advice conducted in June 2019, the small sample size for the 2-dose schedule does not allow to draw meaningful conclusions from the comparison between the two schedules, as the analysis is not powered to generate statistically significant results.

2. Immune response to HBs antigen (Table 7):

   - At 1 month after the subjects received the last dose of Infanrix hexa, the percentage of subjects seroprotected against hepatitis B (anti-HBs antibody concentration ≥10 mIU/mL) was >98% of subjects in both groups (Primary objective).
   - At 1 month after the subjects received the last dose of Infanrix hexa, there was no significant difference observed in the GMC values for anti-HBs in both groups. The percentages of subjects achieving anti-HBs Ab titers ≥100 mIU/mL were similar between groups.
   - Maternal age and gestational week of foetus at dose 1 in maternal study did not interfere with anti-HBs Ab level 1 month post-primary vaccination.
   - Vaccine regimen (2 vs 3 doses) did not interfere with anti-HBs Ab level observed 1 month post-primary vaccination.

Table 7. Overall percentage of subjects with anti-HBs antibody concentration ≥ to the assay cut-off, 10 mIU/mL, 100 mIU/mL and GMC, 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥6.2 mIU/mL				≥10 mIU/mL				≥100 mIU/mL				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-HBs	dTpa Group	Post-Pri	253	252	99.6	97.8	100	251	99.2	97.2	99.9	237	93.7	89.9	96.3	1322.8	1116.7	1567.0
antibody	Control Group	Post-Pri	263	262	99.6	97.9	100	259	98.5	96.2	99.6	254	96.6	93.6	98.4	1339.2	1132.8	1583.3

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
GMC=geometric mean antibody concentration calculated on all subjects; N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value; 95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course

Assessor's comment

Percentages of infants that were seroprotected (cut-off ≥ 10 mIU/ml) against Hepatitis B 1 month after primary vaccination with Infanrix hexa were high, independent of the time of vaccination of the mother, the mother's maternal age and the dose schedule of infant's vaccination. Percentages of subjects mounting an Ab response ≥ 100 mIU/ml and GMT were similar between groups suggesting that maternal immunization does not interfere with the infant's vaccine induced-protection against Hepatitis B.

3. Immune responses to poliovirus types 1, 2 and 3 (Table 8 and Table 9):

- At 1 month after the subjects received the last dose of Infanrix hexa, the percentage of subjects seroprotected against poliovirus types 1, 2 and 3 (anti-poliovirus types 1, 2 and 3 antibody titres ≥8 ED50) was >95% of subjects in both groups (primary objective).
- At 1 month after the subjects received the last dose of Infanrix hexa, there was no significant difference observed in the GMT values for anti-poliovirus types 1, 2 and 3 in both groups.
- Maternal age and gestational week of foetus at dose 1 in maternal study did not interfere with for anti-poliovirus types 1, 2 and 3 Ab level observed 1 month post-primary vaccination.
- At 1 month post-primary vaccination, a trend for lower anti-poliovirus types 1, 2 and 3 GMT was observed in 2-dose schedule vaccine recipients compared to the infants that received the study vaccines according to a 3-dose schedule. Consequently, slightly lower percentages of infants seroprotected against poliovirus types 1, 2 and 3 were observed (with larger 95% CI).

Table 8. Overall percentage of subjects with anti-poliovirus type 1, 2, and 3 Ab concentrations ≥ 8 and GMT, 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥8 ED50				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Polio 1 antibody	dTpa Group	Post-Pri	237	233	98.3	95.7	99.5	432.1	351.8	530.9
	Control Group	Post-Pri	244	242	99.2	97.1	99.9	489.9	402.6	596.0
anti-Polio 2 antibody	dTpa Group	Post-Pri	241	239	99.2	97.0	99.9	424.6	342.7	526.2
	Control Group	Post-Pri	245	235	95.9	92.6	98.0	388.4	306.3	492.6
anti-Polio 3 antibody	dTpa Group	Post-Pri	230	228	99.1	96.9	99.9	730.6	596.5	894.9
	Control Group	Post-Pri	237	236	99.6	97.7	100	775.6	645.9	931.3

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
GMT=geometric mean antibody titre calculated on all subjects; N=number of subjects with available results; n/%=number/percentage of subjects with titre equal to or above specified value; 95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit; Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course.

Table 9. Percentage of subjects with anti-poliovirus type 1, 2 and 3 Ab titer above or equal to 8 and GMC titre, 1 month after the last dose of primary vaccination - by dose schedule (ATP cohort for immunogenicity)

					≥ 8 ED50				GMT		
							95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
anti-Polio 1 antibody	dTpa Group	2 dose schedule	Post-Pri	20	17	85.0	62.1	96.8	59.6	27.2	130.6
		3 dose schedule	Post-Pri	217	216	99.5	97.5	100	518.7	425.7	632.0
	Control Group	2 dose schedule	Post-Pri	31	29	93.5	78.6	99.2	102.1	54.8	190.1
		3 dose schedule	Post-Pri	213	213	100	98.3	100	615.5	509.6	743.4
anti-Polio 2 antibody	dTpa Group	2 dose schedule	Post-Pri	23	21	91.3	72.0	98.9	137.7	57.8	328.1
		3 dose schedule	Post-Pri	218	218	100	98.3	100	478.2	385.6	593.1
	Control Group	2 dose schedule	Post-Pri	31	24	77.4	58.9	90.4	47.2	21.8	101.9
		3 dose schedule	Post-Pri	214	211	98.6	96.0	99.7	527.2	422.1	658.4
anti-Polio 3 antibody	dTpa Group	2 dose schedule	Post-Pri	22	22	100	84.6	100	180.8	85.1	384.2
		3 dose schedule	Post-Pri	208	206	99.0	96.6	99.9	846.9	692.3	1036.0
	Control Group	2 dose schedule	Post-Pri	27	27	100	87.2	100	169.6	99.5	289.1
		3 dose schedule	Post-Pri	210	209	99.5	97.4	100	943.0	788.0	1128.6

dTpa Group = Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group = Infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.
2 dose schedule = subjects who received 2 doses of Infanrix hexa at 2,4 months of age or 3,5 months of age, co-administered with Prevenar 13.
3 dose schedule = subjects who received 3 doses of Infanrix hexa at 2,3,4 months of age or 2,4,6 months of age, co-administered with Prevenar 13.
Prevenar 13 could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule of the country).
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Post-Pri = blood sample collected 1 month after the last dose of the primary vaccination course

Assessor's comment

Percentages of infants that were seroprotected (cut-off ≥ 8 ED50) against poliovirus types 1, 2 and 3 1 month after primary vaccination with Infanrix hexa were high, independent of the time of vaccination of the mother and the mother's maternal age (at least for 25-34y and 35-45y sb-groups, no interpretation possible for 18-24y sub-group since n= 6).

No meaningful conclusions can be drawn on the difference of GMT and percentage of seroprotected infants between 2- and 3-dose vaccines regimen.

4. Immune responses to *Haemophilus influenzae type b* PRP (Table 10 and Table 11):

   - The percentage of subjects seroprotected against Hib (anti-PRP antibody concentration ≥0.15 µg/mL) was >94% of subjects in both groups (primary objective).
   - At 1 month after the subjects received the last dose of Infanrix hexa, there was no significant difference observed in the GMC values for anti-PRP in both groups.
   - Maternal age and gestational week of foetus at dose 1 in maternal study did not interfere with for anti-Hib Ab level observed 1 month post-primary vaccination.
   - At 1 month after the subjects received the last dose of Infanrix hexa, a trend for lower anti-Hib GMT was observed in the 2-dose schedule vaccine recipients compared to the infants that received the study vaccines according to a 3-dose schedule. Consequently, slightly lower percentages of infants seroprotected against *Haemophilus influenzae type b* were observed.

Table 10. Overall percentage of subjects with anti-PRP Ab concentration ≥assay cut-off, 0.15 µg/ml, 1.0 µg/ml and GMC, 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥0.066 µg/mL				≥0.15 µg/mL				≥1 µg/mL				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP antibody	dTpa Group	Post-Pri	266	262	98.5	96.2	99.6	255	95.9	92.7	97.9	172	64.7	58.6	70.4	1.862	1.554	2.231
	Control Group	Post-Pri	271	264	97.4	94.8	99.0	256	94.5	91.0	96.9	177	65.3	59.3	71.0	1.717	1.428	2.064

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
GMC=geometric mean antibody concentration calculated on all subjects
N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course

Table 11. Percentage of subjects with anti-PRP Ab concentration ≥ assay cut-off, 0.15 µg/ml, 1.0 µg/ml and GMC, 1 month after the last dose of the primary vaccination - by dose schedule (ATP cohort for immunogenicity)

					≥ 0.066 µg/mL				≥ 0.15 µg/mL				≥ 1 µg/mL				GMC		
							95% CI				95% CI				95% CI			95% CI	
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PRP antibody	dTpa Group	2 dose schedule	Post-Pri	27	24	88.9	70.8	97.6	23	85.2	66.3	95.8	10	37.0	19.4	57.6	0.575	0.333	0.990
		3 dose schedule	Post-Pri	239	238	99.6	97.7	100	232	97.1	94.1	98.8	162	67.8	61.5	73.7	2.126	1.766	2.559
	Control Group	2 dose schedule	Post-Pri	34	30	88.2	72.5	96.7	27	79.4	62.1	91.3	12	35.3	19.7	53.5	0.522	0.287	0.949
		3 dose schedule	Post-Pri	237	234	98.7	96.3	99.7	229	96.6	93.5	98.5	165	69.6	63.3	75.4	2.037	1.695	2.449

dTpa Group = Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group = Infants born to mothers belonging to the Control group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received Infanrix hexa co-administered with Prevenar 13 according to the routine national immunisation schedule.
2 dose schedule = subjects who received 2 doses of Infanrix hexa at 2,4 months of age or 3,5 months of age, co-administered with Prevenar 13.
3 dose schedule = subjects who received 3 doses of Infanrix hexa at 2,3,4 months of age or 2,4,6 months of age, co-administered with Prevenar 13.
Prevenar 13 could be administered as 2-doses or 3-doses primary vaccination schedule (according to the routine national immunisation schedule of the country).
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Post-Pri = blood sample collected 1 month after the last dose of the primary vaccination course

Assessor's comment

Percentages of infants that were seroprotected (cut-off ≥ 0.15 µg/ml) against *Haemophilus influenzae type b* 1 month after primary vaccination with Infanrix hexa were high, independent of the time of vaccination of the mother and the mother's maternal age (at least for 25-34y and 35-45y sub-groups, no interpretation possible for 18-24y sub-group since n= 5-7).

No meaningful conclusions can be drawn on the difference of GMT and percentage of seroprotected infants between 2- and 3-dose vaccines regimen (small sample size).

5. Immune responses to *Bordetella pertussis* antigens (PT, FHA, PRN) (Table 13 and Table 13):

- The vaccine response rate observed in dTpa group was 77.1% for anti-PT, 39.6% for anti-FHA and 37.5% for anti-PRN. The vaccine response rate observed in control group was 99.2% for anti-PT, 94.8% for anti-FHA and 90% for anti-PRN (primary objective).
- Before the first dose of Infanrix hexa primary vaccination, the maternal antibodies against pertussis antigens were found to be persistent in the subjects and it was observed that subjects in dTpa group had higher antibody concentrations when compared to the subjects in control group. In the dTpa group, >90% of subjects had anti-pertussis antibodies greater than or equal to the assay cut-off whereas ≤83% of subjects had anti-pertussis antibodies greater than or equal to the assay cut-off in the control group. Pre-vaccination GMC were always higher in the dTpa group.
- Overall, at 1 month after the subjects received the last dose of Infanrix hexa, all subjects in dTpa group developed anti-pertussis Ab above or equal to the assay cut-off but presented lower GMC values when compared to control group.
- Vaccine schedule (2 versus 3 doses) did not interfere with the percentages of subjects that mount Ab titers above or equal to the assay cut-off. However, GMC were always lower for subjects vaccinated with a 2-dose regimen when compared to those vaccinated with a 3-dose regimen.
- At 1 month post-primary vaccination, maternal age did not interfere with anti -PT, -FHA and -PRN Ab level. A trend for lower anti-PRN GMC in the 25-34y sub-group compared to 35-45y sub-group in the dTap group was however observed.
- At 1 month post-primary vaccination, gestational week of foetus at dose 1 in maternal study did not interfere with anti -PT, -FHA and -PRN Ab level. A trend for lower anti-FHA GMC in the 27-32W sub-group compared to 33-36W sub-group in the dTap group was however observed.

Table 12. Overall percentage of subjects with anti-PT, anti-FHA and anti-PRN antibody concentration ≥the assay cut-off, and GMC before the first dose and 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥Assay cut-off*				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
anti-PT antibody	dTpa Group	Pre-Pri	242	218	90.1	85.6	93.5	11.9	10.3	13.6
		Post-Pri	266	266	100	98.6	100	32.7	30.2	35.3
	Control Group	Pre-Pri	253	88	34.8	28.9	41.0	2.2	2.0	2.5
		Post-Pri	271	271	100	98.6	100	54.7	51.0	58.6
anti-FHA antibody	dTpa Group	Pre-Pri	242	242	100	98.5	100	88.3	77.7	100.4
		Post-Pri	266	266	100	98.6	100	68.5	63.5	73.9
	Control Group	Pre-Pri	253	210	83.0	77.8	87.4	6.6	5.7	7.7
		Post-Pri	271	271	100	98.6	100	103.5	95.6	112.1
anti-PRN antibody	dTpa Group	Pre-Pri	242	231	95.5	92.0	97.7	70.5	56.1	88.5
		Post-Pri	266	266	100	98.6	100	60.5	54.2	67.6
	Control Group	Pre-Pri	253	151	59.7	53.4	65.8	4.5	3.7	5.4
		Post-Pri	270	269	99.6	98.0	100	92.0	81.6	103.6

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
*Assay cut-off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA,2.187 IU/mL for anti-PRN
GMC=geometric mean antibody concentration calculated on all subjects
N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
Pre-Pri=blood sample collected before the first dose of the primary vaccination course
Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course

Table 13. Overall percentage of subjects with vaccine response for anti-PT, anti-FHA and anti-PRN Ab, 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				Vaccine response			
						95% CI	
Antibody	Group	Pre-Pri*status	N	n	%	LL	UL
anti-PT antibody (IU/mL)	dTpa Group	S-	24	24	100	85.8	100
		S+	216	161	74.5	68.2	80.2
		Total	240	185	77.1	71.2	82.2
	Control Group	S-	163	163	100	97.8	100
		S+	88	86	97.7	92.0	99.7
		Total	251	249	99.2	97.2	99.9
anti-FHA antibody (IU/mL)	dTpa Group	S-	0	-	-	-	-
		S+	240	95	39.6	33.4	46.1
		Total	240	95	39.6	33.4	46.1
	Control Group	S-	43	43	100	91.8	100
		S+	208	195	93.8	89.5	96.6
		Total	251	238	94.8	91.3	97.2
anti-PRN antibody (IU/mL)	dTpa Group	S-	11	11	100	71.5	100
		S+	229	79	34.5	28.4	41.0
		Total	240	90	37.5	31.4	44.0
	Control Group	S-	101	101	100	96.4	100
		S+	149	124	83.2	76.2	88.8
		Total	250	225	90.0	85.6	93.4

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
S-=Initially seronegative subjects (antibody concentration below assay cut-off for anti-PT, anti-FHA, anti-PRN); S+=Initially seropositive subjects (antibody concentration above assay cut-off for anti-PT, anti-FHA, anti-PRN); Total=subjects either seropositive or seronegative at pre-vaccination; N=number of subjects with pre- and post-vaccination results available; n(%)=number(percentage) of subjects with booster response; 95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit; *Pre-Pri=blood sample collected before the first dose of the primary vaccination course; Note: The assay cut-off was 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, and 2.187 IU/mL for anti-PRN.
Vaccine response to PT, FHA and PRN antigens is defined as: For subjects with pre-vaccination antibody concentration below the assay cut-off, post-vaccination antibody concentration equal or above the assay cut-off; For subjects with pre-vaccination antibody concentration equal or above the assay cut-off, post-vaccination antibody concentration equal or above the pre-vaccination antibody concentration.

Assessor's comment

Results and interpretation of immune responses to pertussis antigens were recently shared and discussed with the Belgian and the German Regulatory Authorities during a Scientific-Technical Advice meeting that took place on 3 June 2019.

It was agreed with the Company that the vaccine seroresponse rate could be underestimated for infants born from dTpa vaccinated mothers compared to the group of infants born from unvaccinated mothers. Post-hoc analysis were presented during the scientific advice to support the hypothesis that the pertussis vaccine response elicited by primary vaccination is masked by the persistence of antibodies acquired through maternal immunisation (also presented in the cover statement document).

A more appropriate way (than seroresponse rate) to study a potential effect of maternal immunization (MI) on infant's vaccination is to compare the GMC induced by the primary vaccination in the dTpa and in the control groups. As such, lower GMC were observed for anti-PT, anti-FHA and anti-PRN antibodies in the dTPa group. 95% CI were not overlapping for all three antigens. These findings clearly demonstrate a blunting effect of the MI on infant vaccine-induced antibody responses.

Findings of the study BOOSTRIX-048 are in line with those of other studies that have assessed the persistence of the blunting of pertussis response after the primary and the booster vaccination administered around 12 months of age (Hardy-Fairbanks 2013, Munoz 2014, Maertens 2016, Halperin 2018, Barug 2019). Overall, all these publications show a trend for lower GMC of pertussis antigens-specific Ab in infants born from dTap vaccinated mothers during the pregnancy compare to unvaccinated or post-partum vaccinated mothers. This is true for post-primary vaccination and post-boost vaccination. The blunting of the majority of the antigen-specific Ab responses observed post-primary vaccination was still observed post-boost. None of these studies have assessed the vaccine efficacy of MI in protecting infants from pertussis disease in parallel.

Several studies assess the vaccine efficacy/effectiveness (VE) of MI in preventing pertussis in young infants. Overall, MI does protect infants from pertussis disease before primary vaccination (Amirthalingam, Baxter, Becker-Dreps, Bellido-Belasco, Marshall - communication in the 12th international symposium on Bordetella). Although the duration of the (additional) protection of MI varies across studies, no deleterious effect of MI was evidenced during and/or shortly after the primary vaccination (up to 5-6 months of age).

Nevertheless, in the absence of correlate of protection (CoP), the observed blunting of the pertussis response is difficult to interpret in term of clinical relevance.

As for the immune response to other vaccine antigens, the small sample size for the 2-dose schedule does not allow to draw meaningful conclusions from the comparison between the two schedules, as the analysis is not powered to generate statistically significant results. Influence of maternal age and gestational week of foetus at dose 1 in maternal study on the infant's vaccine-induced response should be confirmed in larger studies before to drawn any conclusion.

6. Immune responses to Prevenar 13 (Table 14):

   - Overall, at 1 month after the subjects received the last dose of Prevenar 13, all subjects in both groups developed anti-pneumococcal (anti-PnPS) antibodies for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. In both groups, >92% of subjects presented antibodies above or equal to the assay cut-off and >74% of subjects presented antibodies ≥0.35 µg/mL. However a trend for lower SPR is observed for 5 out of 13 serotypes (4, 5, 6B, 9V and 23F). GMTs induced in dTap group are generally slightly lower than those induced in the control group.
   - Overall, maternal age and gestational week of foetus at dose 1 in maternal study did not interfere with anti-PnPS Ab level. The sample size was small for the maternal age 18-24y sub-group
   - Vaccine regimen (2 vs 3 doses) did not interfere with anti-PnPS Ab level. Sample size was small for the 2-dose schedule sub-group.

Table 14. Overall percentage of subjects with anti-pneumococcal serotypes Ab concentration ≥ to the assay cut-off, 0.35 µg/ml and GMC, 1 month after the last dose of the primary vaccination (ATP cohort for immunogenicity)

				≥Assay cut-off*				≥0.35 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PnPS 1 antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	222	95.7	92.2	97.9	1.61	1.43	1.80
	Control Group	Post-Pri	237	237	100	98.5	100	227	95.8	92.4	98.0	1.92	1.73	2.14
anti-PnPS 3 antibody (ECL)	dTpa Group	Post-Pri	232	228	98.3	95.6	99.5	173	74.6	68.5	80.0	0.54	0.49	0.60
	Control Group	Post-Pri	237	235	99.2	97.0	99.9	181	76.4	70.4	81.6	0.60	0.55	0.67
anti-PnPS 4 antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	214	92.2	88.0	95.3	1.20	1.07	1.35
	Control Group	Post-Pri	237	236	99.6	97.7	100	228	96.2	92.9	98.2	1.56	1.40	1.75
anti-PnPS 5 antibody (ECL)	dTpa Group	Post-Pri	226	218	96.5	93.1	98.5	199	88.1	83.1	92.0	1.09	0.96	1.24
	Control Group	Post-Pri	234	224	95.7	92.3	97.9	214	91.5	87.1	94.7	1.27	1.13	1.43
anti-PnPS 6A antibody (ECL)	dTpa Group	Post-Pri	232	228	98.3	95.6	99.5	221	95.3	91.7	97.6	2.16	1.89	2.47
	Control Group	Post-Pri	237	234	98.7	96.3	99.7	226	95.4	91.8	97.7	2.59	2.27	2.95
anti-PnPS 6B antibody (ECL)	dTpa Group	Post-Pri	232	215	92.7	88.5	95.7	185	79.7	74.0	84.7	1.37	1.12	1.68
	Control Group	Post-Pri	237	223	94.1	90.3	96.7	200	84.4	79.1	88.8	1.44	1.20	1.73
anti-PnPS 7F antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	229	98.7	96.3	99.7	2.39	2.15	2.65
	Control Group	Post-Pri	237	237	100	98.5	100	236	99.6	97.7	100	2.67	2.43	2.93
anti-PnPS 9V antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	212	91.4	87.0	94.7	1.33	1.19	1.50
	Control Group	Post-Pri	237	237	100	98.5	100	227	95.8	92.4	98.0	1.64	1.47	1.83
anti-PnPS 14 antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	229	98.7	96.3	99.7	5.70	4.99	6.52
	Control Group	Post-Pri	237	235	99.2	97.0	99.9	233	98.3	95.7	99.5	6.57	5.71	7.56
anti-PnPS 18C antibody (ECL)	dTpa Group	Post-Pri	232	229	98.7	96.3	99.7	220	94.8	91.1	97.3	1.61	1.42	1.82
	Control Group	Post-Pri	237	235	99.2	97.0	99.9	223	94.1	90.3	96.7	1.79	1.59	2.01
anti-PnPS 19A antibody (ECL)	dTpa Group	Post-Pri	232	227	97.8	95.0	99.3	216	93.1	89.0	96.0	1.61	1.43	1.82
	Control Group	Post-Pri	237	232	97.9	95.1	99.3	227	95.8	92.4	98.0	2.01	1.78	2.27

				≥Assay cut-off*				≥0.35 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PnPS 19F antibody (ECL)	dTpa Group	Post-Pri	232	232	100	98.4	100	230	99.1	96.9	99.9	2.57	2.35	2.82
	Control Group	Post-Pri	237	237	100	98.5	100	233	98.3	95.7	99.5	3.24	2.92	3.60
anti-PnPS 23F antibody (ECL)	dTpa Group	Post-Pri	230	224	97.4	94.4	99.0	182	79.1	73.3	84.2	0.86	0.74	0.99
	Control Group	Post-Pri	236	229	97.0	94.0	98.8	203	86.0	80.9	90.2	1.02	0.88	1.17

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (BOOSTRIX)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
*Assay cut-off is 0.080 µg/mL for Anti-pneumococcal serotypes 1, 0.075 µg/mL for Anti-pneumococcal serotypes 3, 0.061 µg/mL for Anti-pneumococcal serotypes 4, 0.198 µg/mL for Anti-pneumococcal serotypes 5, 0.111 µg/mL for Anti-pneumococcal serotypes 6A, 0.102 µg/mL for Anti-pneumococcal serotypes 6B, 0.063 µg/mL for Anti-pneumococcal serotypes 7F, 0.66 µg/mL for Anti-pneumococcal serotypes 9V, 0.160 µg/mL for Anti-pneumococcal serotypes 14, 0.111 µg/mL for Anti-pneumococcal serotypes 18C, 0.199 µg/mL for Anti-pneumococcal serotypes 19A, 0.163 µg/mL for Anti-pneumococcal serotypes 19F, 0.073 µg/mL for Anti-pneumococcal serotypes 23F
GMC=geometric mean antibody concentration calculated on all subjects
N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
Post-Pri=blood sample collected 1 month after the last dose of the primary vaccination course

Assessor's comment

A trend for higher GMC of Ab specific to most of the serotypes was observed for the control group compared to the dTpa group. However, percentages of subjects achieving the cut-off of 0.35 µg/ml, considered as the protective threshold, were generally high but were slightly lower for 5 out of 13 serotypes. Percentage of subjects achieving anti-PnPS3 Ab ≥0.35 µg/ml were the lowest (74.6 and 76.4%) and were lower than the one presented in the SmPC of Prevenar 13 (98.2%). Whether this is due to the study population or the infanrix hexa co-administration should be clarified.

Safety results

1. During the 4-day (Days 0-3) period following each Infanrix hexa primary vaccination co-administered with Prevenar 13 (overall/subject):

- Any AE: The overall incidence of at least 1 AE (solicited/unsolicited) reported for subjects was 98% and 95.4% in dTpa group and control group, respectively.
- Solicited local AE:
    - The most frequently reported local AE solicited for Infanrix hexa primary vaccination was redness and was reported in 62.9% and 61.1% of subjects dTpa group and control group, respectively.
    - The most frequently reported local AE solicited for Prevenar 13 was redness and was reported in 55.6% and 56.1% of subjects in dTpa group and control group, respectively.

- Grade 3 solicited local AE:
    - The most commonly reported grade 3 local AEs solicited for Infanrix hexa primary vaccination in dTpa group was redness, reported in 3.4% of subjects and in control group was redness and pain reported in 4.6% of subjects, respectively.
    - The most commonly reported grade 3 local AEs solicited for Prevenar 13 in dTpa group was pain, reported in 3.1% of subjects and in control group was swelling, reported in 3.6% of subjects, respectively.
- Solicited general AE: The most frequently reported solicited general AE was irritability/fussiness and was reported for 86.7% and 84.8% of subjects in dTpa group and control group, respectively.
- Grade 3 solicited general AE: Irritability/fussiness was also the most frequently reported grade 3 solicited general AE and was reported for 12.2% of subjects in both groups.

2. During the 31-day (Days 0-30) period following each Infanrix hexa primary vaccination co-administered with Prevenar 13 (overall/subject):
    - Unsolicited AEs: Overall, at least 1 unsolicited AE was reported for 54.4% and 56.7% of subjects in dTpa group and control group, respectively. Of which, most commonly reported AE was upper respiratory tract infection reported in 12.2% and 10.8% of subjects in dTpa group and control group, respectively.
    - Grade 3 unsolicited AEs: At least 1 grade 3 unsolicited AE was reported for 5.1% and 5.9% of subjects in dTpa group and control group, respectively. Of which, most common AEs that were reported per group were teething in dTpa group (1.4%) and pyrexia in control group (1.0%).
    - Causally related unsolicited AEs: At least 1 causally related unsolicited AE was reported for 3.7% and 4.3% of subjects in dTpa group and control group, respectively. Of which, most common AEs that were reported per group were vomiting and mass at the injection site in dTpa group (1%); bruise at the injection site and increase in body temperature in control group (0.7%).
    - Grade 3 causally related unsolicited AEs: There were no grade 3 causally related unsolicited AEs reported during the study period.
3. Throughout the study period:
    - SAEs: There were no fatal cases reported in this study. At least 1 SAE was reported for 2.4% of subjects in the dTpa group and for 5.6% of subjects in the control group, respectively. There were no SAEs reported with causal association to vaccination.
    - Withdrawals due to AEs/SAEs: A single subject in the dTpa group was withdrawn from the study after Visit 1 due to the SAEs – intestinal hemorrhage and cow's milk allergy. The investigator however, considered that there was no reasonable possibility that intestinal hemorrhage and cow's milk allergy may have been caused by the vaccination.

Assessor's comment

Infanrix hexa and Prevenar 13 were well tolerated. Overall, Infanrix hexa induces a slightly higher number of solicited local AE.

The safety profile of the Infanrix hexa and Prevenar 13 co-administration is acceptable and similar between groups.

2.3.3. Discussion on clinical aspects

The study was a Phase IV, open-label, non-randomised, uncontrolled, multi-centre, multi-country study to evaluate the immunogenicity and safety of Infanrix hexa given in a primary schedule to all infants born to pregnant women who participated in study BOOSTRIX-047, in which the mothers received a single dose of Boostrix either during pregnancy (dTpa group) or immediately post-delivery (control group). Infanrix hexa was administered with Prevenar 13 in a 2- or 3- dose schedule according to the country of enrolment.

The study is part of a clinical data generation plan consisting of 3 studies that document the maternal vaccination during the third trimester of pregnancy with Boostrix (BOOSTRIX-047), and the impact thereof on the response to the infant primary vaccination (BOOSTRIX-048) and toddler booster vaccination (BOOSTRIX-049). Clinical data of BOOSTRIX-049 study will be available in January 2020.

Clinical protection against diphtheria, tetanus, hepatitis B, poliomyelitis, *Haemophilus influenzae type b* and *Streptococcus pneumoniae* infections were defined by their serological correlates of protection. The seroprotection thresholds were ≥0.1 IU/mL for anti-D and anti-T antibody concentrations, ≥10 mIU/mL for anti-HBs antibody concentrations, ≥8 ED50 for anti-poliovirus types 1, 2 and 3 antibody titres, ≥0.15 µg/mL for anti-PRP antibody concentrations and ≥ 0.35 µg/mL for anti-PnPS Ab concentrations.

At 1 month after the last dose of Infanrix hexa, 100% of the subjects of both groups were seroprotected against diphtheria and tetanus, >98% against Hepatitis B, >95% against poliovirus type 1, 2 and 3, and >94% against *Haemophilus influenzae type b* infections. The percentages of subjects achieving the protective threshold of 0.35 µg/ml against *Streptococcus pneumoniae* infection were generally high (ranging from 74.6% to 99.6%).
A trend for a lower percentage of infants achieving the cut-off associated with long term protection against diphteria (≥ 1.0 IU/ml anti-D Ab) and lower anti-D GMT were however observed in the dTpa group when compared to the control group. This suggests that MI might affect the induction of the immune memory. However, data from study BOOSTRIX-049 that were further presented suggest that the generation of immune memory in both groups is adequate. The decreased GMC would not imply an impact on clinical protection since all the subjects achieved the cut-off associated with short term protection (≥ 1.0 IU/ml) and >99% of the toddlers achieved the cut-off associated with long term protection (≥ 1.0 IU/ml). Additionally, regular booster vaccinations are generally recommended.
Similarly, a trend for lower GMC of Ab specific to most of the serotypes of *Streptococcus pneumoniae* was observed for the dTpa group compared to the control group, both at post-primary and post-booster vaccination timepoints. The lower percentages of subjects achieving the cut-off of 0.35 µg/ml observed in the dTap group for 5 out 13 serotypes when compared to the control group post-primary vaccination was not observed anymore post-boost. Indeed, study BOOSTRIX-049 results demonstrate that comparable percentage of subjects had Ab titers ≥ 0.35 µg/ml 1 month post-boost in both groups, suggesting that the subjects of both groups are comparatively able to mount an anamnestic response. Thus, the observed (slight) interference of MI on infant's Ab concentration post-primary and post-booster vaccination is not likely to be clinically relevant.
Maternal age and gestational week of foetus at dose 1 in maternal study generally did not interfere with vaccines-induced seroprotection. Conversely, the 2-dose regimen generally induced lower GMT/GMC with the exception of anti-Hbs Ab concentration that were comparable between both regimens. However, the small sample size for the 2-dose schedule does not allow to draw meaningful conclusions from the comparison between the two schedules, as the analysis is not powered to generate statistically significant results.

Results and interpretation of immune responses to pertussis antigens are more difficult to interpret since there is currently no correlate of vaccine protection. Results were already shared and discussed with the Belgian and the German Regulatory Authorities during a Scientific-Technical Advice meeting (June 2019). Criteria defining seroresponse were not ideal, particularly for infants with high level of specific Ab pre-vaccination. Comparison of GMC induced by the primary vaccination between both the dTpa and the control groups is more relevant. Lower GMC were observed for anti-PT, anti-FHA and anti-PRN antibodies in the dTPa group. 95% CI were not overlapping for all three antigens. Even if MI doesn't prevent the infants from developing a response to the primary vaccination, these findings clearly demonstrate a blunting effect of the MI on infant vaccine-induced antibody responses. One month post-booster vaccination, lower GMC were still observed for anti-PT and anti-FHA antibodies in the dTPa group (BOOSTRIX-049 study) when compared to the control group. The data also suggest that infants of both groups developed an immune memory against *B. pertussis*. Longer-term memory responses still need to be investigated. The results observed in both studies are in line with those found in the literature.

Of note, the entire results of the BOOSTRIX-049 study will be submitted in January 2020 and assessed at that time.

Several observational studies indicate effectiveness of the MI strategy in protecting neonates of <2-3 months of age against pertussis disease. Both effectiveness studies and UK epidemiological data suggest that there is no deleterious effect of MI during and/or shortly after the infant's vaccination. However, in the absence of CoP, it is difficult to estimate the clinical relevance of the blunting of pertussis responses and the 'real' (long-term) impact of MI for the infants. At present, the Infanrix hexa SmPC does not contain any information about the blunting effect observed when a child born to a vaccinated mother receives a primo-vaccination with Infanrix hexa. The VWP considered that it could be appropriate to add a subsection in section 5.1 of the SmPC for Infanrix hexa under a heading of *Infant immune responses following maternal immunisation* (or similar). The section could shortly describe the observed effect on infant GMCs for pertussis antigens. However, the VWP recommended to postpone such SmPC revision until the final data from the booster study BOOSTRIX-049 are submitted for assessment, at which time the overall dataset will be available.

Influence of maternal age, gestational week of foetus at dose 1 in maternal study and dose schedule on the infant's pertussis-induced response should be confirmed in larger studies before to draw any conclusion.

Finally, both vaccines were generally well tolerated. The safety profile was similar whatever the time of mother's vaccination (during or post-pregnancy). An update of the section 4.8 would be proposed by the Company as part of a variation in March 2020.

3. CHMP overall conclusion and recommendation

In the present study, infants born from mother either vaccinated during pregnancy (dTpa group) or post-delivery (control group) were vaccinated with Infanrix hexa and Prevenar 13 (according to a 2- or 3-dose schedule).
Immunogenicity results demonstrated that maternal immunization (MI) does not interfere with the vaccine-induced (short term) seroprotection against diphtheria, tetanus, Hepatitis B, poliovirus type 1, 2 and 3, *Haemophilus influenzae type b* and, in some extent, *Streptococcus pneumoniae*.
A slight blunting effect was however observed for diphtheria and *Streptococcus pneumoniae* induced-immune responses post-primary and post-booster vaccination (in terms of GMT). However, 1 month after the booster dose, >99% of the subjects of dTpa group achieved the anti-D Ab threshold

associated with long-term protection and comparable percentage of subjects had anti-PnPs Ab titers ≥ 0.35 µg/ml in both groups. It is thus unlikely that the observed interference is clinically relevant.

In line with the literature, a blunting effect of the MI on infant vaccine-induced pertussis antibody responses was also observed (at both post-primary and post-booster vaccination timepoints). Currently, limited surveillance data of UK (2017 and 2018) does not suggest an increase in pertussis incidence due to MI in young children. In the absence of CoP, it is however difficult to estimate the clinical relevance of this blunting of pertussis responses and the 'real' (long-term) impact of MI for the infants.

At present, the Infanrix hexa SmPC does not contain any information about the blunting effect observed when a child born to a vaccinated mother receives primo-vaccination with Infanrix hexa. For the sake of transparency, it could be appropriate to add a subsection in section 5.1 of the SmPC for Infanrix hexa. The section could shortly describe the observed effect on infant GMCs for pertussis antigens. Such SmPC revision should be postponed until the final data from the booster study BOOSTRIX-049 are submitted for assessment, at which time the overall dataset will be available.

Both vaccines were generally well tolerated. The safety profile was similar whatever the time of mother's vaccination (during or post-pregnancy).

The longer-term data will be submitted the 10th of January 2020 (BOOSTRIX-049 study). The Company committed to submit a variation in March 2020 in which the outcome of the three maternal vaccination studies dTpa-047, -048 and -049 will be discussed. A draft label update will be proposed as part of this variation.

☒ **Fulfilled:**

The MAH provided the requested clarifications. The VWP recommendations were included in the report.

4. Additional clarification requested to the MAH

1. The MAH is invited to clarify whether the lower percentage of subjects achieving anti-PnPS3 Ab ≥0.35 µg/ml (74.6 and 76.4%) in study BOOSTRIX-048 when compared to the percentage presented in the SmPC of Prevenar 13 (98.2%) is due to the study population or the Infanrix hexa co-administration.
2. In principle the risk of blunting of infants' pertussis, diphtheria and *Streptococcus pneumoniae* responses should be added in the SmPC of Infanrix-hexa in the section 4.4. The MAH should discuss a proposal.
3. Further data would be useful in the context of a variation before any conclusion on product information amendments is made. Immunogenicity data of the studies BOOSTRIX-048 and BOOSTRIX-049 should be added in section 5.1 of the SmPC, upon assessment. An update of the section 4.8 with the safety data of both studies is also required. It is understood from previous scientific advices that the MAH commits to submit the data from studies 047, 048 and 049 as variations to the MA in 2020. The MAH should discuss their plans to submit any data in the near future.

MS comments

Comments were received from MS1 and MS2.

MS1 agrees with the Rapporteur's assessment and conclusions of the Rapporteur are endorsed. It is agreed with the Rapporteur that the observed data, including the blunting effect of the MI on infant vaccine-induced pertussis antibody responses should be presented in the SmPC.

MS2 does not endorse the CHMP Rapp AR and recommends the critical issue of adding a comment to the SPC on maternal immunisation blunting antibody responses in infants is referred to the Vaccine Working Group.

In the comparative assessment of rates of seroprotective antibody (Ab) or vaccine responses the lower limit (LL) of the 95% confidence interval (CI) is preferred.
High rates of seroprotection or vaccine response are achieved for each component of Infanrix hexa after primary vaccination with evidence of higher rates with 3 vs 2 dose schedule of primary vaccination for example for Diphtheria, Tetanus, Polio & Hib.
Maternal immunisation with Boostrix is associated with blunting of the Ab response in infants to specific homologous Pertussis (vaccine responses & GMCs) & Diphtheria antigens (GMCs), and heterologous Polio (lower GMTs for 2 of 3 polio viruses) & Pneumococcal (seroprotection rates [5 of 13 serotypes show >/= 4% point lower rates of Ab >/=0.35 µg/mL] & lower GMCs for 13/13 serotypes) vaccine antigens.

The association of maternal immunisation with Boostrix or TdaP in pregnancy with blunting of Ab responses in infants is reported for specific matching vaccine antigens, and potential mechanisms are being explored although the clinical relevance of this phenomenon is unclear (Vono et al 2019 https://doi.org/10.1016/j.celrep.2019.07.047).
More controversially, blunting of Ab responses to heterologous vaccine antigens (polio and pneumococcal) as well as specific homologous (diphtheria and pertussis) vaccine responses is also reported in a recent small study by Zimmermann 2019,https://doi.org/10.1016/j.eclinm.2019.06.010). Neither the potential mechanism nor clinical relevance of this observation is clear.

The MS2 does not support the Rapp's proposal to include a comment like the statement in Boostrix / Boostrix-IPV, shown for reference in brackets below:
(SmPC Section 4.6 Fertility, pregnancy and lactation

Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with Boostrix [-IPV] during pregnancy. The clinical relevance of this observation is unknown.)
The MS2 suggests that the Rapp's proposal has wide implications for the vaccination of infants and their mothers with potential relevance to many vaccines. Therefore, this issue should be referred to the Vaccine Working Group for discussion before a precedent is established.

Rapporteur's position

The position of MS2 is acknowledged. The issue on the blunting effect of various antigen immune responses following maternal immunization has indeed wide implication. The issue will therefore be referred to the VWP. The AR was updated according to the comment received.

Proposed Questions to the VWP:

Maternal immunization (MI) with Boostrix is associated with blunting of immune responses to homologous antigens (pertussis antigens and diphteria toxoid) and to some extent, to heterologous antigens (pneumococcal antigens). The clinical relevance of this observation is unknown.

Does the VWP agree with this association between MI with Boostrix and blunting of (i) homologous and (ii) heterologous antigens-induced immune responses in infants?

Does the VWP consider that the blunting of specific immune responses is linked to a specific vaccine or to a class product effect?

Does the VWP consider that this blunting effect should be reflected in the Infanrix SmPC? Could a wording be proposed?

Does the VWP consider that the unknown clinical relevance of the blunted immune responses in infants needs to be further studied by the MAH and how?

Does the VWP has any other comments with regards to the data assessed in this procedure?

Proposed Timetable to incorporate the VWP discussion:

submission 19/11/2019
start date 20/11/2019
assessment report 27/11/2019
comments 02/12/2019
updated AR 05/12/2019
opinion 12/12/2019

MAH responses to Request for supplementary information

1. **The MAH is invited to clarify whether the lower percentage of subjects achieving anti-PnPS3 Ab ≥0.35 µg/ml (74.6 and 76.4%) in study BOOSTRIX-048 when compared to the percentage presented in the SmPC of Prevenar 13 (98.2%) is due to the study population or the Infanrix hexa co-administration.**

The Company presented the results of the response to pneumococcal serotype 3 observed in the toddlers included in the BOOSTRIX-049 study. Similarly to those observed in the BOOSTRIX-048 study, these results indicate that no difference was observed between both groups of vaccinees (dTpa and control groups). Thus, results of both studies indicate that the maternal immunisation (MI) did not impact the proportion of the infants achieving the seroprotection threshold for this pneumococcal serotype.

Whether or not the co-administration of DTPa combination vaccines in general or Infanrix hexa in particular with Prevenar 13 led to low immune response to pneumococcal serotype 3 is difficult to ascertain. Indeed, at the time of the authorisation of Prevenar 13, vaccination of infants with DTPa-combination vaccines was the standard of care in most EU countries and in the US. To the knowledge of the Company, no clinical trials in infants were performed in which Prevenar 13 was given without co-administration of a DTPa (or DTPw)-combination vaccine. In the European and US pivotal non-inferiority trials conducted to support the registration of Prevenar 13, DTPa-combination vaccines were always co-administered.

A table (Table 15) listing the different co-administration studies (GSK and non-GSK) that were conducted with Prevenar 13 and different DTPa combination vaccines was presented. Results of the studies were briefly presented.

Table 15. Listing of clinical studies from different MA holders, for which results were discussed

Study	Marketing Authorization Holder	Reference
Prevenar 13 study 006	Pfizer	Kieninger et al. 2010 Prevenar 13 EPAR
Prevenar 13 study 004	Pfizer	Yeh et al. 2010 Prevenar 13 EPAR
Prevenar 13 studies 008, 009, 3000, 003, 501, 3005 and 3007	Pfizer	Prevenar 13 EPAR
DTPa-HBV-IPV-124 DTPa-HBV-IPV-125 BST124	GSK	Vesikari, 2017
SPNG-003	GSK	Prymula, 2014
Hib-097	GSK	Klein, 2017
Hib-MenCY-TT-016	GSK	Klein, 2018
Vaxelis study V419-006	MCM Vaccine B.V.	Block et al, 2017
Hexaxim/ Hexacima/ Hexyon study A3L39	Sanofi	Vesikari et al (2017b)

Overall, for all studies taken together, the percentage of subjects with anti-PnPS3 ≥0.35 µg/ml (or 0.2 µg/ml depending of the assay cut-off) ranged between 63.5% and 99.6% one month post primary vaccination.

This is appropriately reflected in the Prevenar 13 SmPC that includes results of both Prevenar 13 004 and 006 studies: "For serotype 3, the percentages of Prevenar 13 recipients with serum IgG ≥ 0.35 µg/ml were 98.2% (study 006) and 63.5% (study 004). "

In conclusion, the Company considers that it is unlikely that the lower anti-PnPS3 response observed in BOOSTRIX-048 is specific to the co-administration with Infanrix hexa or to the study population. Rather, the lower percentage of subjects equal to or above the 0.35 µg/ml threshold for anti-PnPS3 in study BOOSTRIX-048, is likely due to an inherent variability in the response to PnPS3 that has been observed by GSK as well as by other manufacturers when Prevenar 13 is co-administered with DTPa-combination vaccines and other vaccines.

Assessor's comment

The Company appropriately clarified that the results of the serological response to pneumococcal serotype 3 observed in the study BOOSTRIX-048 are acceptable. The results of the various studies discussed by the Company indicate that there is a variability in the response to PnPS3 when Prevenar 13 is co-administered with DTPa-combination vaccines and other vaccines, ranging from 63.5% to 99.6%.

Point resolved

2. In principle the risk of blunting of infants' pertussis, diphtheria and *Streptococcus pneumoniae* responses should be added in the SmPC of Infanrix-hexa in the section 4.4. The MAH should discuss a proposal.

The Company does not consider it appropriate to describe blunting of infants' pertussis, diphtheria and *Streptococcus pneumoniae* responses as a risk related to maternal immunization with dTpa in the Special warnings and precautions for use section of the Infanrix hexa SmPC. On the contrary, the Company considers that any description of blunting in the section 4.4 could be interpreted by health

care professionals as a precaution for use of dTpa vaccination during pregnancy and such an interpretation would be counterproductive to the efforts done in multiple countries in different geographical regions to implement MI against pertussis in order to protect young infants against pertussis disease between birth and the start of the primary vaccination.

The EMA guideline on the SmPC (revision 2, 2009), section 4.4 Special warnings and precautions for use, describes the following: "Information on a specific risk should be given in section 4.4 only when the risk leads to a precaution for use or when healthcare professionals have to be warned of this risk."

The Company does not consider that there is any evidence of clinical relevance of the observed immune interference of MI with the response to the primary and booster vaccinations in infants and toddlers. On the contrary, the Company considers that all the information currently available supports the position that blunting does not lead to an increased risk of pertussis disease in infants and toddlers. The Company provided several supportive information that are summarized below.

Immunogenicity data from studies dTpa-048 and dTpa-049

Since the submission of the Clinical Study Report for study dTpa-048 under Article 46 of the Regulation (EC) 1901/2006, as amended, the statistical analysis of study dTpa-049 has become available. Key data related to infants' pertussis, diphtheria and *Streptococcus pneumoniae* responses from studies dTpa-048 and -049 were provided and discussed.

Immune responses to Diphtheria toxoid (Table 16)

Post-primary vaccination with Infanrix hexa, lower diphtheria antibody concentrations were observed for infants and toddlers born to mothers vaccinated with dTpa as compared to controls.

At the post-booster timepoint, all subjects in both study groups had seroprotective antibody titres ≥0.1 IU/ml. Additionally, 99.1% and 100% of the toddlers in the dTpa and control groups respectively had antibody titres ≥1.0 IU/ml.

A comparable fold-increase in GMCs from the pre- to the post-booster timepoints was observed in both groups (30-fold for the dTpa group and 26-fold for the control group), showing that an adequate and comparable immune memory for diphtheria was generated in both groups.

At 1 month after the booster dose, a lower GMCs value for anti-D antibodies was still observed in the dTpa group when compared to the control group. Based on modelling data, even much bigger differences in the GMCs are not expected to change the seroprotection rates in the long term (Cheuvart, 2004).

Table 16. Overall percentage of subjects with anti-D Ab concentration ≥ 0.1 IU/ml and ≥1.0 IU/ml and GMC, before and after the booster dose (ATP cohort for immunogenicity)

				≥0.1 IU/mL				≥1 IU/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-D antibody	dTpa Group	Pre-Bst	223	181	81.2	75.4	86.1	10	4.5	2.2	8.1	0.207	0.184	0.234
		Post-Bst	221	221	100	98.3	100	219	99.1	96.8	99.9	6.114	5.577	6.703
	Control Group	Pre-Bst	244	220	90.2	85.7	93.6	27	11.1	7.4	15.7	0.322	0.285	0.363
		Post-Bst	247	247	100	98.5	100	247	100	98.5	100	8.402	7.694	9.174

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (*BOOSTRIX*)-047] where mothers received dTpa during pregnancy.
Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (*BOOSTRIX*)-047] where mothers received placebo during pregnancy.
All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.
GMC=geometric mean antibody concentration calculated on all subjects; N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
Pre-Bst=blood sample collected before the booster dose in infants
Post-Bst=blood sample collected 1 month after the booster dose in infants
Data source: DTPA (*BOOSTRIX*)-049 BST 048 (201334) Statistical Analysis Report (27-Aug-2019)

Assessor's comment

Results of the study BOOSTRIX-049 indicate that 100% of the subjects of both groups were sero-protected 1 month after the booster dose. Almost 100% of the subjects of both groups had Ab titers above the threshold associated with long term protection (≥ 1.0 IU/ml). The results also suggest the generation of a comparable immune memory in both groups. Therefore, the lower anti-D GMT observed in the dTpa group when compared to the control group 1 month post-primary (and post-boost) would not imply an impact on clinical protection.

The clinical study report of BOOSTRIX-049 study will be submitted in January 2020 and the overall results will be assessed at that time.

Immune responses to Streptococcus pneumoniae (Table 17)

As assessed in the initial report, a trend for higher GMCs of Ab specific to most of the serotypes was observed for the control group compared to the dTpa group. However, percentages of subjects achieving the cut-off of 0.35 µg/ml, considered as the protective threshold, were generally high but were slightly lower for 5 out of 13 serotypes. The Company considered that this trend was only seen for serotypes 4 and 19F and that the percentage of subjects with antibody concentrations above the seroprotective threshold of 0.35 µg/ml was similar in both groups.

Post-booster vaccination, comparable percentages of subjects with antibody concentrations above the seroprotective threshold were observed between the two study groups, for all serotypes.

Post-booster vaccination, GMTs induced in dTap group were generally slightly lower than those induced in the control group.

Table 17. Overall percentage of subjects with anti-pneumococcal serotypes Ab concentration ≥ 0.35µg/ml and GMC, before and after the booster dose (ATP cohort for immunogenicity)

				≥Assay cut-off*				≥0.35 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PnPS 1 antibody (ECL)	dTpa Group	Pre-Bst	211	196	92.9	88.5	96.0	61	28.9	22.9	35.5	0.22	0.19	0.24
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	3.22	2.88	3.60
	Control Group	Pre-Bst	232	214	92.2	88.0	95.3	91	39.2	32.9	45.8	0.27	0.24	0.30
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	3.64	3.28	4.04
anti-PnPS 3 antibody (ECL)	dTpa Group	Pre-Bst	211	122	57.8	50.8	64.6	8	3.8	1.7	7.3	0.08	0.07	0.09
		Post-Bst	208	208	100	98.2	100	165	79.3	73.2	84.6	0.59	0.53	0.65
	Control Group	Pre-Bst	232	147	63.4	56.8	69.6	12	5.2	2.7	8.9	0.10	0.09	0.11
		Post-Bst	235	235	100	98.4	100	187	79.6	73.8	84.5	0.62	0.57	0.69
anti-PnPS 4 antibody (ECL)	dTpa Group	Pre-Bst	209	189	90.4	85.6	94.1	28	13.4	9.1	18.8	0.15	0.13	0.16
		Post-Bst	208	208	100	98.2	100	207	99.5	97.4	100	2.91	2.54	3.33
	Control Group	Pre-Bst	232	215	92.7	88.5	95.7	63	27.2	21.5	33.4	0.19	0.17	0.22
		Post-Bst	234	234	100	98.4	100	232	99.1	96.9	99.9	3.28	2.89	3.72
anti-PnPS 5 antibody (ECL)	dTpa Group	Pre-Bst	211	163	77.3	71.0	82.7	100	47.4	40.5	54.4	0.33	0.29	0.37
		Post-Bst	204	204	100	98.2	100	204	100	98.2	100	2.66	2.39	2.97
	Control Group	Pre-Bst	229	182	79.5	73.7	84.5	124	54.1	47.5	60.7	0.34	0.31	0.38
		Post-Bst	229	228	99.6	97.6	100	227	99.1	96.9	99.9	2.81	2.52	3.14
anti-PnPS 6A antibody (ECL)	dTpa Group	Pre-Bst	211	196	92.9	88.5	96.0	112	53.1	46.1	60.0	0.38	0.33	0.43
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	9.07	8.05	10.22
	Control Group	Pre-Bst	232	219	94.4	90.6	97.0	146	62.9	56.4	69.2	0.44	0.39	0.50
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	9.49	8.45	10.67
anti-PnPS 6B antibody (ECL)	dTpa Group	Pre-Bst	211	175	82.9	77.2	87.8	96	45.5	38.6	52.5	0.29	0.25	0.33
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	7.83	6.82	8.98
	Control Group	Pre-Bst	232	205	88.4	83.5	92.2	115	49.6	43.0	56.2	0.33	0.29	0.38
		Post-Bst	236	236	100	98.4	100	235	99.6	97.7	100	8.00	7.06	9.06
anti-PnPS 7F antibody (ECL)	dTpa Group	Pre-Bst	211	210	99.5	97.4	100	147	69.7	63.0	75.8	0.49	0.44	0.54
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	5.00	4.55	5.50
	Control Group	Pre-Bst	232	232	100	98.4	100	175	75.4	69.4	80.8	0.56	0.51	0.61
		Post-Bst	235	235	100	98.4	100	235	100	98.4	100	4.96	4.50	5.48
anti-PnPS 9V antibody (ECL)	dTpa Group	Pre-Bst	211	203	96.2	92.7	98.3	71	33.6	27.3	40.5	0.26	0.23	0.29
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	3.74	3.35	4.16
	Control Group	Pre-Bst	232	225	97.0	93.9	98.8	106	45.7	39.2	52.3	0.32	0.28	0.36
		Post-Bst	235	235	100	98.4	100	235	100	98.4	100	3.91	3.52	4.35

				≥Assay cut-off*				≥0.35 µg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	value	LL	UL
anti-PnPS 14 antibody (ECL)	dTpa Group	Pre-Bst	211	201	95.3	91.5	97.7	184	87.2	81.9	91.4	0.97	0.85	1.11
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	10.36	9.22	11.64
	Control Group	Pre-Bst	232	223	96.1	92.8	98.2	206	88.8	84.0	92.5	1.19	1.04	1.37
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	11.62	10.34	13.06
anti-PnPS 18C antibody (ECL)	dTpa Group	Pre-Bst	211	168	79.6	73.5	84.8	42	19.9	14.7	25.9	0.19	0.17	0.21
		Post-Bst	208	208	100	98.2	100	207	99.5	97.4	100	3.23	2.86	3.65
	Control Group	Pre-Bst	232	190	81.9	76.3	86.6	79	34.1	28.0	40.5	0.23	0.21	0.26
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	3.57	3.21	3.98
anti-PnPS 19A antibody (ECL)	dTpa Group	Pre-Bst	211	148	70.1	63.5	76.2	86	40.8	34.1	47.7	0.32	0.27	0.37
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	7.90	7.06	8.83
	Control Group	Pre-Bst	232	172	74.1	68.0	79.6	118	50.9	44.2	57.5	0.37	0.32	0.43
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	8.68	7.82	9.63
anti-PnPS 19F antibody (ECL)	dTpa Group	Pre-Bst	211	183	86.7	81.4	91.0	104	49.3	42.4	56.2	0.37	0.32	0.43
		Post-Bst	208	208	100	98.2	100	208	100	98.2	100	7.66	6.84	8.57
	Control Group	Pre-Bst	232	202	87.1	82.1	91.1	143	61.6	55.0	67.9	0.47	0.41	0.55
		Post-Bst	236	236	100	98.4	100	236	100	98.4	100	8.63	7.75	9.62
anti-PnPS 23F antibody (ECL)	dTpa Group	Pre-Bst	210	160	76.2	69.8	81.8	33	15.7	11.1	21.4	0.14	0.12	0.16
		Post-Bst	207	206	99.5	97.3	100	203	98.1	95.1	99.5	2.07	1.83	2.34
	Control Group	Pre-Bst	229	191	83.4	77.9	88.0	58	25.3	19.8	31.5	0.19	0.16	0.22
		Post-Bst	235	235	100	98.4	100	232	98.7	96.3	99.7	2.38	2.10	2.69

dTpa Group=Infants born to mothers belonging to the dTpa Group in study 116945 [DTPA (*BOOSTRIX*)-047] where mothers received dTpa during pregnancy.

Control Group=Infants born to mothers belonging to the Control Group in study 116945 [DTPA (*BOOSTRIX*)-047] where mothers received placebo during pregnancy.

All subjects in this study received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule.

GMC=geometric mean antibody concentration calculated on all subjects

N=number of subjects with available results

n/%=number/percentage of subjects with concentration equal to or above specified value

95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit

Pre-Bst=blood sample collected before the booster dose in infants

Post-Bst=blood sample collected 1 month after the booster dose in infants

*Assay cut-off is 0.080 µg/mL for anti-pneumococcal serotypes 1, 0.075 µg/mL for anti-pneumococcal serotypes 3, 0.061 µg/mL for anti-pneumococcal serotypes 4, 0.198 µg/mL for anti-pneumococcal serotypes 5, 0.111 µg/mL for anti-pneumococcal serotypes 6A, 0.102 µg/mL for anti-pneumococcal serotypes 6B, 0.063 µg/mL for anti-pneumococcal serotypes 7F, 0.66 µg/mL for anti-pneumococcal serotypes 9V, 0.160 µg/mL for anti-pneumococcal serotypes 14, 0.111 µg/mL for anti-pneumococcal serotypes 18C, 0.199 µg/mL for anti-pneumococcal serotypes 19A, 0.163 µg/mL for anti-pneumococcal serotypes 19F, 0.073 µg/mL for anti-pneumococcal serotypes 23F

Assessor's comment

Comparable percentage of subjects had Ab titers ≥ 0.35 µg/ml 1 month post-boost. The threshold of ≥ 0.35 µg/mL is considered as a protective threshold. The results suggest that the subjects of both groups are comparatively able to mount an anamnestic response. Thus, the observed (slight) interference of MI on infant's Ab concentration post-primary and post-booster vaccination is not likely to be clinically relevant.

As stated above, results should be confirmed when the entire results of BOOSTRIX-049 study will be assessed in January 2020.

Immune responses to Bordetella pertussis antigens (PT, FHA, PRN) (Table 18)

In study dTpa-048, lower antibody concentrations against pertussis antigens were observed post-primary vaccination in infants born to mothers vaccinated with Boostrix during pregnancy.

At 1 month after the booster dose of Infanrix hexa in study dTpa-049, lower GMCs were observed in the dTpa group for anti-PT and anti-FHA when compared to the control group, but not for PRN.

A significant GMC-fold increase in antibodies against pertussis was observed from the pre- to the post-booster timepoint in the dTpa group (anti-PT: 11.9-fold, anti-FHA: 13.6-fold, anti-PRN: 48.4-fold), and similar ranges were observed in the control group (anti-PT: 12.7-fold, anti-FHA: 11.3-fold, anti-PRN: 27.3-fold). These data are aligned to those published by independent investigators.

Table 18. Studies dTpa-047, dTpa-048 and dTpa-049: overall percentage of subjects with anti-PT, anti-FHA and anti-PRN Ab concentration ≥ the assay cut-off, and GMC across all the time point (Adapted ATP cohort for immunogenicity)

					≥ Assay cut-off*				GMC		
							95% CI			95% CI	
Antibody	Group	Study	Timing	N	n	%	LL	UL	value	LL	UL
anti-PT	dTpa	DTPA-047	PRE	288	167	58.0	52.1	63.8	4.0	3.5	4.5
			PI(D30)	289	285	98.6	96.5	99.6	45.6	40.4	51.5
			PI(CORD)	290	286	98.6	96.5	99.6	46.9	41.2	53.3
		DTPA-048	Pre-Pri	242	218	90.1	85.6	93.5	11.9	10.3	13.6
			Post-Pri	266	266	100	98.6	100	32.7	30.2	35.3
		DTPA-049	Pre-Bst	223	153	68.6	62.1	74.6	4.4	3.8	5.0
			Post-Bst	221	220	99.5	97.5	100	52.4	46.9	58.4
	Control	DTPA-047	PRE	291	184	63.2	57.4	68.8	4.3	3.8	4.8
			PI(D30)	292	179	61.3	55.5	66.9	4.1	3.6	4.6
			PI(CORD)	292	201	68.8	63.2	74.1	5.5	4.8	6.3
		DTPA-048	Pre-Pri	253	88	34.8	28.9	41.0	2.2	2.0	2.5
			Post-Pri	271	271	100	98.6	100	54.7	51.0	58.6
		DTPA-049	Pre-Bst	244	201	82.4	77.0	86.9	6.3	5.5	7.1
			Post-Bst	247	247	100	98.5	100	80.3	73.3	88.1
anti-FHA	dTpa	DTPA-047	PRE	289	273	94.5	91.2	96.8	13.7	11.8	15.8
			PI(D30)	290	290	100	98.7	100	317.5	285.0	353.8
			PI(CORD)	291	291	100	98.7	100	366.1	329.0	407.3
		DTPA-048	Pre-Pri	242	242	100	98.5	100	88.3	77.7	100.4
			Post-Pri	266	266	100	98.6	100	68.5	63.5	73.9
		DTPA-049	Pre-Bst	223	215	96.4	93.1	98.4	11.2	9.6	13.1
			Post-Bst	221	221	100	98.3	100	152.5	136.3	170.6
	Control	DTPA-047	PRE	291	275	94.5	91.2	96.8	15.7	13.6	18.0
			PI(D30)	291	275	94.5	91.2	96.8	15.0	13.1	17.2
			PI(CORD)	292	282	96.6	93.8	98.3	22.7	19.7	26.2
		DTPA-048	Pre-Pri	253	210	83.0	77.8	87.4	6.6	5.7	7.7
			Post-Pri	271	271	100	98.6	100	103.5	95.6	112.1
		DTPA-049	Pre-Bst	244	241	98.8	96.4	99.7	16.5	14.4	18.8
			Post-Bst	247	247	100	98.5	100	187.2	172.7	202.9
anti-PRN	dTpa	DTPA-047	PRE	289	244	84.4	79.7	88.4	11.1	9.1	13.4
			PI(D30)	290	290	100	98.7	100	283.6	237.1	339.1
			PI(CORD)	290	289	99.7	98.1	100	301.8	250.9	362.9
		DTPA-048	Pre-Pri	242	231	95.5	92.0	97.7	70.5	56.1	88.5
			Post-Pri	266	266	100	98.6	100	60.5	54.2	67.6
		DTPA-049	Pre-Bst	223	187	83.9	78.4	88.4	6.9	5.8	8.2
			Post-Bst	220	220	100	98.3	100	333.9	285.4	390.7
	Control	DTPA-047	PRE	290	247	85.2	80.6	89.1	11.3	9.4	13.6
			PI(D30)	291	246	84.5	79.9	88.5	10.5	8.7	12.5
			PI(CORD)	291	256	88.0	83.7	91.5	14.6	12.1	17.7
		DTPA-048	Pre-Pri	253	151	59.7	53.4	65.8	4.5	3.7	5.4
			Post-Pri	270	269	99.6	98.0	100	92.0	81.6	103.6
		DTPA-049	Pre-Bst	244	213	87.3	82.5	91.2	9.6	8.3	11.2
			Post-Bst	247	247	100	98.5	100	262.3	230.9	298.1

Study DTPA-047:

dTpa Group: *Boostrix* during pregnancy + placebo post-delivery; Control Group: placebo during pregnancy + *Boostrix* post-delivery

Studies DTPA-048 and DTPA-049:

dTpa Group: infants born to mothers receiving *Boostrix* during pregnancy + placebo post-delivery in study DTPA-047; Control Group: infants born to mothers receiving placebo during pregnancy + *Boostrix* post-delivery in study DTPA-047. All subjects in these 2 studies received *Infanrix hexa* co-administered with *Prevenar 13* according to the routine national immunisation schedule (2- or 3-dose schedule in study DTPA-048 and one booster vaccination in study DTPA-049).
*Assay cut-off is 2.693 IU/mL for anti-PT, 2.046 IU/mL for anti-FHA, 2.187 IU/mL for anti-PRN
ATP=according-to-protocol; FHA=filamentous haemagglutinin; GMC=geometric mean antibody concentration calculated on all subjects; PRN=pertactin; PT=pertussis toxoid.
N=number of subjects with available results
n/%=number/percentage of subjects with concentration equal to or above specified value
95% CI=95% confidence interval; LL=Lower Limit, UL=Upper Limit
PRE = Pre-booster vaccination (pregnancy dose) blood sampling time-point
PI(D30) = Post-booster vaccination (pregnancy dose) blood sampling time-point, 1-month after booster dose
PI(CORD)=Cord blood sample at delivery post-pregnancy booster dose
Pre-Pri = blood sample collected before the first dose of the primary vaccination course
Post-Pri = blood sample collected 1 month after the last dose of the primary vaccination course
Pre-Bst = blood sample collected before the booster dose
Post-bst = blood sample collected 1 month after the booster dose
Data source: DTPA (*BOOSTRIX*)-049 BST 048 (201334) Report

Assessor's comment

Results of the study BOOSTRIX-049 suggest that infants of both groups developed an immune memory against *B. pertussis*. However, 1 month post-boost, lower anti-PT, -FHA and –PRN Ab GMCs were observed in the dTpa group when compared to the control group. The clinical relevance of this observation is unknown.

Even if data suggest that an immune memory was induced by the vaccination, it is not known for which duration and if the quality of the recall responses would be unaffected.

As stated above, the results of BOOSTRIX-049 study should be confirmed by the assessment of the entire results in January next year.

Epidemiological data on pertussis disease following the implementation of maternal immunization against pertussis

If the interference of maternal vaccination against pertussis with the response to paediatric vaccination against pertussis would be clinically relevant, one would expect to see over time an increased risk of pertussis disease in older infants and/or toddlers following the implementation of maternal immunization.

Epidemiological effectiveness studies have assessed the risk of pertussis disease following the completion of the primary immunization series.

Amirthalingam 2016: The study was conducted by Public Health England (PHE) assessed the effectiveness of maternal dTpa-IPV vaccination to protect newborns and infants against pertussis disease in England. In infants below 3 months of age, maternal vaccination with dTpa-IPV was shown to be >90% effective to protect against pertussis. Further analysis suggested that high levels of protection are conferred to infants who have received their first dose of the primary series. After the third infant dose, the number of pertussis cases were too small to generate meaningful results and there was no longer evidence of protection from maternal immunization. However, importantly, the estimates remained above 0%, which according to the investigator indicates that there is no evidence

of greater risk of pertussis disease after the primary immunization, in those infants whose mothers received the dTpa vaccine during pregnancy.

Becker-Dreps 2018: The study was conducted in the United States and concluded that between 6 and 18 months of life, there were no differences in pertussis rates by receipt of prenatal dTpa vaccine, after adjustments in the analysis for the infant's DTPa receipt.

Baxter 2017: The study was conducted in the United States of infants born at Kaiser Permanente Northern California from 2010 to 2015. In this retrospective cohort study, the investigators estimated the effectiveness of maternal pertussis vaccination for protecting newborns against pertussis in the first 2 months of life and in the first year of life by accounting for each infant DTaP dose. The estimated maternal vaccination effectiveness was still at 65.9% (95% CI, 4.5 to 87.8) after the infants had 3 DTPa doses.

In England, maternal immunization with Tdap-IPV was implemented in 2012. With >70% MI vaccine coverage in 2017 and 2018, the number of pertussis disease cases in infants < 3 months of age in 2018 was the lowest since 1994. The number of cases in infants < 1 year of age was the lowest since 2010. In older infants (6-11 months of age), cases remained low since the 2012 epidemic peak and MI implementation. In children ≥ 1 year of age, the number of pertussis cases in 2018 was below the number of cases in 2017, with the exception of infants 1 to 4 years of age (15% increase, with 86 cases in 2018 versus 75 cases in 2017). According to Public Health England, the extension of the age range for oral fluid testing for pertussis diagnosis from 5 to <17 years to 2 to <17 years as of May 1, 2018 is likely to have contributed to this increase. Public Health England concluded that the low number of confirmed pertussis cases in older infants was consistent with protection from primary vaccination offered at 2, 3 and 4 months of age. As raised levels of pertussis persist in all age groups other than infants, the 2018 PHE surveillance report concludes that women should, therefore, continue to be encouraged to be immunised against pertussis at the optimal time during pregnancy in order to protect their babies from birth.

Although not confirmatory, these data further support the position that the interference of maternal immunization with the infant immune response to paediatric pertussis vaccination as apparent by GMC levels should not have a clinical impact.

In June 2019, the Joint Committee on Vaccination and Immunization (JCVI) concluded that the maternal programme has been highly successful, and that there has been a substantial impact on pertussis disease in England. The Committee noted also that it was reassured that blunting of the infant immune responses was not having any clinical impact and advised that the MI programme should continue as a routine programme.

Assessor's comment

As already indicated in the initial report, it is acknowledged that MI does protect infants from pertussis disease before primary vaccination and that no deleterious effect of MI was evidenced during and/or shortly after the primary vaccination. This is supported by both effectiveness studies and UK epidemiological data (from 2017 and 2018).

The increased number of cases in infants from 1 to 4 years in 2018 compared to 2017 is likely due to a modification of the cases detection. It is unlikely that is due to interference of MI but this cannot be proven with the data presented (since the PHE report presented the data from infants of 1 to 4 yoa and not from infants of 1 to 2 yoa only, i.e. born in 2017-2018) (PHE, annual report for 2018).

Nevertheless, the JCVI committee was reassuring regarding the absence of any clinical impact of the blunting of infants immune responses.

Upcoming PHE data in the following years and additional epidemiological data from countries where the vaccine coverage of pregnant women is high would help to further insight the potential impact on the protection against pertussis disease.

Overall Company conclusion on the need to describe a warning in section 4.4

Overall, the currently available evidence from clinical and epidemiological studies do not suggest the blunting to be of any clinical relevance. Any mention of this phenomenon in the section 4.4 Warnings and Precautions for use is therefore considered inappropriate by the Company. The Company shares the opinion of the member state reviewer (MS2 in the assessment report) that an update of this section may have wide implications for the vaccination of infants and their mothers with potential relevance to many vaccines. It may further lead to vaccination hesitance, leading to suboptimal protection of vaccine-preventable diseases.

Assessor's comment

It is agreed that the issue on the blunting effect of various antigen immune responses following maternal immunization has indeed wide implication. Overall, and in the absence of a CoP, it remains difficult to ascertain whether there is a (long-term) clinical impact of the observed blunting of the infant's immune responses.

The VWP considered that a warning in section 4.4 of the Infanrix hexa SmPC is not appropriate since Infanrix hexa is not given to pregnant women. However, the VWP considered that it could be appropriate to add a subsection in section 5.1 of the SmPC for Infanrix hexa under a heading of *Infant immune responses following maternal immunisation* (or similar). The section could shortly describe the observed effect on infant GMCs for pertussis antigens. Such SmPC revision should be considered by the MAH when the overall dataset will be available.

Blunting as a class effect and need for class labelling if update of section 4.4 imposed by authorities

If the authorities would disagree with the Company position that update of the Special warnings and precautions for use section 4.4 of Infanrix hexa is inappropriate and impose an update of the SmPC, the Company strongly insists that blunting is a class effect to be reflected using a class labelling wording across registered DTPa combination vaccines in Europe. Indeed, all available data on blunting resulting from MI indicate that the effect is independent of the combination of vaccines used for maternal and childhood immunisation (Maertens, 2016a; Maertens, 2016b; Munoz, 2014; Ladhani, 2015; Hoang, 2016; Maertens, 2016c; Halperin, 2018; Kent, 2016; Villareal Pérez, 2017; Hardy-Fairbanks, 2013; Rice, 2019, Barug, 2019). Importantly, there is no evidence suggesting that the interference is vaccine-product specific since blunting has been observed following primary and/or booster infant vaccinations, regardless of the vaccine brands used for MI and primary/booster series and importantly also without maternal vaccination as a natural phenomenon.

A full Company Position Paper detailing all currently available evidence with different products and concluding on blunting as a class effect is annexed to the current response document. Two independent experts reviewed this document and endorsed the Company's conclusion that blunting of the response to paediatric vaccination should not be considered as a product-specific phenomenon. Consequently, if the Authorities consider blunting to be of a real clinical concern to be highlighted to the Health Care Practitioners (HCP) through the SmPC, the only appropriate way to do so is to update the SmPCs of all the different DTPa combination vaccines that are registered across the EU, with

identical wording. The Company would insist that in such a case, this label update is to be implemented in a synchronized manner for all relevant products.

The Company further wants to highlight that to date GSK is the only manufacturer that has taken responsibility to generate robust data on the safety and immunogenicity of maternal dTpa vaccination, as well as on the potential impact on the response to paediatric vaccines, through manufacturer-sponsored clinical trials. Therefore, GSK is the only company that is obliged through the Article 46 of the paediatric regulation to have these data assessed by the EMA, with the potential request for a product-specific label update as a consequence. As blunting is observed across DTPa combination products following maternal immunization, GSK considers that such procedural reason would be an insufficient justification to limit the description of a warning to Infanrix hexa label only.

Assessor's comment

The position of the MAH is acknowledged. The VWP considers that it can reasonably be expected that the above-mentioned effect is not limited to maternal vaccination with Boostrix and that a similar effect can be expected for other vaccines containing pertussis antigens that would be suitable for pregnant women. However, the magnitude of the effect on infant immune responses could differ depending on the vaccine administered during pregnancy and the infant vaccine.

The assessors agree with the VWP.

3. **Further data would be useful in the context of a variation before any conclusion on product information amendments is made. Immunogenicity data of the studies BOOSTRIX-048 and BOOSTRIX-049 should be added in section 5.1 of the SmPC, upon assessment. An update of the section 4.8 with the safety data of both studies is also required. It is understood from previous scientific advices that the MAH commits to submit the data from studies 047, 048 and 049 as variations to the MA in 2020. The MAH should discuss their plans to submit any data in the near future.**

Study dTpa-049 will be submitted according to the Article 46 requirements of the Regulation (EC) 1901/2006, as amended, by the 10th of January 2020.

The Company further confirms that a variation for Infanrix hexa is being prepared for submission in March 2020. This variation will discuss the outcome of the three maternal vaccination studies dTpa-047, -048 and -049. A draft label update will be proposed as part of this variation. Also in March next year, a variation to update the Boostrix and Boostrix Polio SmPCs with the results of the same three studies will be submitted. Beyond these variations, no further submissions related to maternal vaccination are currently anticipated.

The Company also raised the limitations for the Company to generate further data concerning the clinical impact of blunting. This was already discussed and agreed during a consultation with the PEI (i.e. the Regulatory Authority of the Reference Member State (RMS) for Boostrix and Boostrix Polio in the MRP in Europe) in April 2018. Indeed, despite the occurrence of outbreaks, pertussis remains a relatively rare disease in countries with high pertussis vaccination rates. Hence drawing statistically powered conclusions concerning the effect of maternal pertussis vaccination on the epidemiology of pertussis disease in infants and children does not only require very large datasets at the population level, it also necessitates access to robust pertussis disease surveillance data and reported pertussis cases which are being collected on an ongoing basis by national and supranational health organisations such as Public Health England (PHE) and the European Centre for Disease Prevention and Control (ECDC). Therefore, the Company proposal was to monitor the independently generated scientific evidence by national and supranational health organisations who have access to large populations in order to get further insights on the effect of maternal vaccination with Boostrix/Boostrix Polio on the

pertussis disease epidemiology, i.e. by monitoring reports on pertussis vaccine effectiveness in the offspring and children from women vaccinated with dTpa during pregnancy and also the overall impact of pertussis MI within the well-established infancy immunization programs. This monitoring will be performed on publications from peer-reviewed journals and reports publicly available on public health organizations' websites. This monitoring plan is currently described in the Boostrix and Boostrix Polio RMPs in the section "Other forms of routine pharmacovigilance activities for blunting".

Assessor's comment

The MAH presented their plans of submission as required.

The MAH clarified that, due to pertussis epidemiology, no further data concerning the clinical impact of blunting will be generated. The MAH will rather monitor the scientific evidences generated by independent health organisations to gain further insights into the impact of MI, if any, on the protection of infants against pertussis. This proposal was agreed by the MS3 and is described in the RMPs of Boostrix and Boostrix Polio. This clarification is acknowledged and endorsed.

MS comments and VWP responses

Comment was received from MS3. The dossier was discussed at VWP.

MS3 comment

MS3 agrees with the Rapporteur's assessment.
We would like to stress the importance of the discussion TC on Monday and our view at the moment is to mention the results in the SmPC under 5.1 as no clinically relevant blunting is seen and thus a warning statement is not in order. Also, we are of the opinion that this is a class issue of the booster vaccines used in maternal immunization.

VWP responses

1. **Does the VWP agree with this association between MI with Boostrix and blunting of (i) homologous and (ii) heterologous antigens-induced immune responses in infants?**

The data suggest that maternal immunisation with dTpa during pregnancy result in some blunting of the GMCs against pertussis antigens following vaccination of infants with Infanrix hexa. This was observed after primary and booster doses. However, the VWP noted that the post-booster GMCs were higher than the post-primary GMCs in infants in the dTpa and control groups, suggesting that infants in both groups had to some extent been primed during the primary series. The VWP considered that it is unlikely that the effect observed on GMCs is clinically relevant.

The VWP also agreed that there is no indication that infant immune responses to the other antigens in Infanrix hexa are affected to any clinically important extent.

2. **Does the VWP consider that the blunting of specific immune responses is linked to a specific vaccine or to a class product effect?**

It can reasonably be expected that the above-mentioned effect is not limited to maternal vaccination with Boostrix and that a similar effect can be expected for other vaccines containing pertussis antigens that would be suitable for pregnant women. However, the magnitude of the effect on infant immune responses could differ depending on the vaccine administered during pregnancy and the infant vaccine.

3. **Does the VWP consider that this blunting effect should be reflected in the Infanrix SmPC? Could a wording be proposed?**

The VWP did not agree with the Rapporteur's proposal that a warning should be placed in section 4.4 of the Infanrix hexa SmPC. Infanrix hexa is not given to pregnant women (its antigen content is unsuitable for adults) and therefore the warning statement introduced into the various dTpa vaccines would be inappropriate for the Infanrix hexa SmPC.

The VWP considered that it could be appropriate to add a subsection in section 5.1 of the SmPC for Infanrix hexa under a heading of *Infant immune responses following maternal immunisation* (or similar). The section could shortly describe the observed effect on infant GMCs for pertussis antigens. However, the VWP recommended to postpone such SmPC revision until the final data from the booster study 049 are submitted for assessment, at which time the overall dataset will be available.

4. **Does the VWP consider that the unknown clinical relevance of the blunted immune responses in infants needs to be further studied by the MAH and how?**

The VWP did not consider that there is anything that the MAH could be requested to do to further investigate this effect.

It is agreed that important information on any possible impact of the blunting effect would come from ongoing routine surveillance for pertussis in countries that have introduced maternal immunisation against pertussis. These data cannot be generated by the MAH but published results should be reported in PSURs.

5. **Does the VWP has any other comments with regards to the data assessed in this procedure?**

The VWP is of the opinion that the current SmPC statements on blunting of immune responses in infants following maternal immunisation should be revised for Boostrix/Boostrix IPV and Covaxis/Repevax. The warning in section 4.4 for the latter vaccines, which appears in section 4.6 for the former vaccines, is so vague as to be totally unhelpful, and it misrepresents the evidence. Furthermore, inserting such a statement in 4.6 is not in line with the expected content of section 4.6 (safety of pregnancy) and the SmPC Guideline. These vaccines are not approved through the centralised route and it will be for the reference Member State (RMS) to initiate revisions, which could follow on from the MAH's planned variation to the Infanrix hexa SmPC in early 2020.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Infanrix hexa

Active substance: Active substance: Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Haemophilus type b (Hib) conjugate vaccine (adsorbed)

Study title	Study number	Date of completion	Date of submission of final study report
A Phase IV, observer-blind, randomised, cross-over, placebo-controlled, multicentre study to assess the immunogenicity and safety of a single dose of Boostrix in pregnant women.	BOOSTRIX-047 (EudraCT number: 2014-001119-38)	24 October 2017	N/A: Not in scope of Article 46 of the paediatric regulation No. 1901/2006 as it concerns the vaccination of pregnant women ≥ 18 years of age with *Boostrix*.
A phase IV, open-label, non-randomised, multicentre study to assess the immunogenicity and safety of Infanrix hexa administered as primary vaccination in healthy infants born to mothers given Boostrix during pregnancy or post-delivery in 116945 [DTPA (BOOSTRIX)-047].	BOOSTRIX-048 (EudraCT number: 2014-001117-41)	07 March 2018	July 2019
A phase IV, open-label, non-randomised, multi-centre study to assess the immunogenicity and safety of a booster dose of Infanrix hexa in healthy infants born to mothers vaccinated with Boostrix during pregnancy or immediately post-delivery.	BOOSTRIX-049 BST: 048 (EudraCT number: 2014-001120-30)	19 March 2019	March 2020