Paul-Ehrlich-Institut
Federal Institute for
Vaccines and Biomedicines

Doc. Ref.: CMDh/220/2006, Rev2
November 2012

Mutual Recognition Procedure

Type II group of variations
Preliminary Variation Assessment Report - updated

Boostrix
Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content)

Boostrix Polio
Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content)

DE/H/xxxx/WS/161

Marketing Autorisation Holder:

GlaxoSmithKline Biologicals

Date: 27 September 2016

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ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	Boostrix Boostrix Polio
Name of the active substance (INN, common name):	Boostrix: Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed, reduced antigen(s) content) Boostrix Polio: Diphtheria, tetanus, pertussis (acellular, component) and poliomyelitis (inactivated) vaccine (adsorbed, reduced antigen(s) content)
Pharmaco-therapeutic group (ATC code)	Boostrix: J07AJ52 Boostrix Polio: J07CA02
Pharmaceutical form(s) and strength(s)	Suspension for injection

Procedure number	DE/H/xxxx/WS/161
Member States concerned	DE, AT, BE, BG, CY, CZ, DK, EE, EL, ES, FI, FR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK

RMS contact person	**Name:** [redacted]
Names of the assessors	**Clinical:** **Name(s):** [redacted] **Clinical:** **Name(s):** [redacted]

Nature of change/s requested	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinincal, clinical or pharmacovigilance data; type II

I. RECOMMENDATION

Based on the review of the data on safety (and efficacy), the RMS considers that the variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for Boostrix and Boostrix Polio for the following proposed changes:

to update the PI of Boostrix and Boostrix Polio with inclusion of human safety data in the 'pregnancy' section from:

- The post-authorisation safety study (PASS) with Boostrix listed in the RMP dated on November 2013, hereafter referred to as the Pertussis in Pregnancy Safety (PIPS) study.
- The GSK pregnancy US registry for Boostrix and spontaneous reports of pregnancy cases for Boostrix and Boostrix Polio.
- The publications of studies that assessed the safety of Boostrix use during pregnancy.

is approvable.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

The MAH considers that the Product Information (PI) of Boostrix and Boostrix Polio should be revised to inform the Prescribers and Health Care Practitioners of the data currently available when administering Boostrix and Boostrix Polio to pregnant women.
Therefore, the purpose of the current application is to update the PI of Boostrix and Boostrix Polio with inclusion of human safety data in the "pregnancy" section from:

- The post-authorisation safety study (PASS) with Boostrix listed in the RMP dated on November 2013, hereafter referred to as the **Pertussis in Pregnancy Safety (PIPS)** study.
- The **GSK pregnancy US registry** for Boostrix and spontaneous reports of pregnancy cases for Boostrix and Boostrix Polio.
- The **publications** of studies that assessed the safety of Boostrix use during pregnancy.

To support this approach, National consultations were performed in 2014 with the Paul-Ehrlich Institute (PEI) in Germany, the Medicines and Healthcare products Regulatory Agency (MHRA) in UK and the Federal Agency for Medicines and Health Products (FAMHP) in Belgium.

In addition, the Company took the opportunity:

- to further align the SmPC, labelling and Package leaflet in accordance with the QRD template version 3 for MRP/DCP procedure,
- to combine the SmPC of the pre-filled syringe and vial presentations,
- to correct minor editorial changes.

The RMS (PEI) has agreed to receive the updated RMP's by end of July, 2016. This would allow the Company to update RMP's for Boostrix and Boostrix Polio after the submission of all planned label updates that are impacting the above mentioned vaccines.

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

The applicant provided human safety data for use of Boostrix in pregnant women originating from

- Post-authorization safety study (PASS), hereafter referred to as Pertussis in Pregnancy Study (PIPS),
- GSK pregnancy US registry for Boostrix and spontaneous reports of pregnancy cases for Boostrix and Boostrix Polio,
- Publications of studies that assessed the safety of Boostrix administered to pregnant women.

The applicant has planned a series of randomized controlled trials in which infants born to mothers vaccinated with Boostrix during pregnancy will receive three primary doses of Infanrix hexa plus a booster dose in the 2nd year of life. [redacted] B

Please note that the PIPS study with Boostrix used during pregnancy submitted within the current procedure did not disclose any efficacy or immunogenicity data.

However, the applicant provided an evaluation of efficacy/ immunogenicity of Boostrix/ Boostrix Polio/ dTap use during pregnancy based on a literature review.

Besides, the MAH has planned a series of 3 randomized controlled trials in which infants born to mothers vaccinated with Boostrix during pregnancy will receive 3 primary doses and one booster dose of Infanrix hexa. Potential interference with other routinely/ concomitantly administered infant vaccines will be evaluated. [redacted] B

III.1.1 Clinical efficacy

Published studies on the efficacy of dTpa vaccination during pregnancy in preventing pertussis in infants:

A full review of the literature was conducted on 22 September 2015, covering articles published from 2010 to 2015. The search strategy used was Boostrix/Boostrix Polio/dTpa/Pertussis vaccine/Tetanus vaccine/Diphtheria vaccine combined with the following keywords: Pregnancy and outcomes, maternal immunization, efficacy, effectiveness, safety, adverse effects and immune response. Only peer-reviewed publications with results of original research on safety, effectiveness and immune interference of maternal immunization for pertussis were selected. Unpublished abstracts (unless with critical relevant safety data) and publications with only immunology data and reviews were excluded.

An overview of the study design, population and objectives for each study is presented in Table 1.

Among the 18 publications listed in Table 1, 8 were identified as the most relevant for estimating the effectiveness and impact of maternal immunization (Amirthalingam, 2014; Dabrera, 2015; Vizzotti, 2015) and the potential immune interference with infant primary vaccination (Hardy-Fairbanks, 2013; Munoz, 2014; Ladhani, 2015; Maertens, 2016; Hoang, 2016). These studies were briefly described below.

Table 1 Overview of published studies selected from the literature review (Source: Table 2, Clinical Overview)

Lead Author	Study design Total study period Vaccine (in bold)	Study population	Study objective
Amirthalingam G The Lancet 2014	Vaccine effectiveness (VE) study (Screening Method). dTpa coverage in pregnant women was estimated using both national coverage data and Clinical Practice Research Datalink (CPRD) data. Cases were identified using laboratory confirmed hospital admissions for pertussis in infants (aged <3 months) occurring in England between Jan 1 2008 and Sept 30 2013. VE effectiveness estimates relate to the period October 2012 to September 2013. **Note: only *Repevax* was used in the UK routine schedule during the study period.**	Data used approximate the general population in England (the final VE calculations included 82 confirmed infant pertussis cases)	To estimate the effectiveness of maternal pertussis vaccination against pertussis in English infants aged <3 months.
Dabrera G CID 2015	Vaccine effectiveness (VE) study (case-control method) during the period October 2012 to July 2013. Cases were laboratory confirmed pertussis cases in infants aged <8 weeks at onset. Family doctors of each case were asked to identify healthy infants born consecutively after the case in each practice, to act as controls. The mothers vaccination status was determined by telephone and questionnaire. **Note: only *Repevax* was used in the UK routine schedule during the study period.**	Cases (n=58) and controls (n=55) identified in England and Wales	To estimate the effectiveness of maternal pertussis vaccination in protecting infants against laboratory-confirmed pertussis infection (Primary objective). To determine if maternal pertussis vaccination was associated with shorter length of hospital stay among infant pertussis cases aged <8 weeks (Secondary objective)
Datwani H Vaccine 2015	Retrospective study using the VAERS (Vaccine Adverse Event Reporting System) database was searched for reports of chorioamnionitis following receipt of any US licensed vaccine in the US. July 1990 to February 2014 **Note: dTpa brand name is not specified.**	841 out of 3,389 pregnancy reports in VAERS met the search criteria for chorioamnionitis. dTpa vaccination was associated with 8 of these reports.	To describe reports of chorioamnionitis in the VAERS database following receipt of any US licensed vaccines following identification of chorioamnionitis as a possible safety signal in pregnant women vaccinated with dTpa (Kharbanda et al 2014).
Donegan, K BMJ 2014	Retrospective, observational safety cohort study using the UK Clinical Practice Research Datalink (CPRD) using women who received a pertussis vaccination during pregnancy and a matched historical unvaccinated control group of pregnant women. October 2012 to March 2013	Data used approximate the general UK population and include 20,074 pregnant women who routinely received pertussis vaccine.	To examine the safety of pertussis vaccination in pregnancy. Adverse events were identified from clinical diagnoses during pregnancy, with additional data from the matched child record identified through mother-child linkage. The

Lead Author	Study design Total study period Vaccine (in bold)	Study population	Study objective
	Note: only *Repevax* was used in the UK routine schedule during the study period.		primary event of interest was stillbirth (intrauterine death after 24 weeks gestation).
Hoang, HTT Vaccine 2016	Randomized, controlled study conducted in Vietnam. Pregnant women received either a dTpa vaccine or a tetanus only vaccine between 19 and 35 weeks' gestational age. Study conducted in 2013 **Note: Women in the dTpa group received *Adacel***	*Adacel* (n=52) Tetanus vaccine as control (n=51) Infants received primary series of *Infanrix hexa* (EPI: month 2-3-4).	To assess the effect of adding a pertussis component to the tetanus vaccination, in the pregnancy immunization program in Vietnam.
Hardy-Fairbanks AJ Pediatr Infect Dis J 2013	Observational cohort study investigating antibody levels to pertussis in infants in dTpa vaccinated **(Adacel in any trimester)** and unvaccinated pregnant mothers. Serum samples used relate to pregnant mothers vaccinated with dTpa in 2006 and unvaccinated pregnant mothers delivering between March 2008 and February 2009.	*Adacel* (n=16) Control (n=54) Infants received primary series and booster dose of diphtheria, tetanus, and acellular pertussis (DTPa) and other vaccines.	To investigate pertussis antibody concentrations in infants at birth and at intervals during the first 18 months of life following maternal dTpa vaccination during pregnancy.
Judy A American Journal of Obstetrics and Gynecology 2015 (Poster presentation)	Retrospective study conducted at a US medical center evaluating women who had been vaccinated with a dTpa vaccine postpartum (PP) or antepartum (AP). June 2008 to May 2012 **Note: dTpa brand name is not specified.**	dTpa antepartum (n=877) dTpa postpartum (n=837)	To compare neonatal and obstetric outcomes among women receiving postpartum dTpa vaccination to women receiving antepartum dTpa vaccination.
Kharbanda EO JAMA 2014	Retrospective, observational cohort vaccine safety study using administrative health care databases from two California Vaccine Safety Datalink (VSD) sites in pregnant women who received a pertussis vaccine and a matched historical unvaccinated control group. January 2010 to November 2012. **Note: vaccination with *Boostrix* or *Adacel* (the majority of dTpa doses administered to pregnant women were Adacel).**	US women from the Californian region with singleton pregnancies (26,229 women vaccinated with dTpa (*Adacel* or *Boostrix*) and 97,265 women who did not receive dTpa during pregnancy)	To evaluate whether maternal dTpa vaccination during pregnancy is associated with increased risks of adverse obstetric events or adverse birth outcomes.
Ladhani S.N. Clin Infect Dis 2015	Observational antibody prevalence study investigating responses to primary immunization in infants born to **women routinely vaccinated with dTpa-IPV (Repevax)** and recruited Dec 2012 – July 2014. Post vaccination responses are compared to those in a historical comparator group of infants recruited 2011-2012 whose mothers were not vaccinated with dTpa.	141 children born to UK women routinely vaccinated with *Repevax* during pregnancy. The historical comparator group consisted of 246 infants recruited from the same geographical areas.	To assess antibody responses to primary immunization in infants born to UK women who received *Repevax* in pregnancy (includes infant primary response to pertussis vaccine antigen plus various other antigens featuring in the primary series in vaccines conjugated to TT or CRM)

Lead Author	Study design Total study period Vaccine (in bold)	Study population	Study objective
Maertens K Vaccine 2016	Prospective, controlled cohort study in pregnant women and their infants conducted in Belgium. **Pregnant women were vaccinated with *Boostrix*** at a mean gestational age of 28.6 weeks. A control group of pregnant women received placebo. February 2012 to September 2014	*Boostrix* (n=57) Placebo (42) Infants received primary series of Infanrix hexa (2, 3, 4 months).	To measure the influence of vaccination of pregnant women with *Boostrix* on the titer and duration of the presence of maternal antibodies in the infants and to assess possible interference with infant immune responses.
Morgan JL Obstet Gynecol. 2015	Retrospective cohort study using electronic medical records at a single institution in Texas investigating pregnancy outcomes in mothers who accepted (n=7,152) or declined (n=226) dTpa at 32 weeks of gestation following the 2012 ACIP guidelines on dTpa use in pregnancy June 2013 to July 2014 **Note: dTpa brand name is not specified.**	US pregnant women in Dallas County, Texas, vaccinated with dTpa (n=7,152).	To evaluate pregnancy outcomes of women who received tetanus, diphtheria, and acellular pertussis (dTpa) vaccination at or after 32 weeks of gestation. Outcomes from consecutive pregnancies during which the mother received dTpa were also analyzed.
Munoz FM JAMA 2014	Phase I, randomized, double-masked, placebo-controlled clinical trial conducted in the US. **Pregnant women received dTpa (*Adacel*)** or placebo at 30-32 weeks gestation with cross-over dTpa immunization postpartum. 2008 to 2012	*Adacel* n=33 Placebo n=15	To evaluate the safety and immunogenicity of dTpa immunization during pregnancy and its effect on infant responses to diphtheria and tetanus toxoids and acellular pertussis (dTpa) vaccine.
Shakib JH J Pediatr. 2013	Retrospective, observational cohort study in women aged 12-45 yrs who received dTpa during pregnancy (n=138) and their infants and compared with unvaccinated mother-infant pairs (n=552). May 2005 to August 2009 **Note: dTpa brand name is not specified.**	Pregnant women in Utah, USA (vaccinated with dTpa at Intermountain Healthcare facilities)	To assess pregnancy and birth outcomes in infants born to women who did or did not receive tetanus, diphtheria, acellular pertussis (dTpa) vaccine during pregnancy
Sukumaran L Obstet Gynecol. 2015	Retrospective cohort study of pregnant women aged 14–49 years in the Vaccine Safety Datalink. Medically attended acute events (fever, any acute reaction) and adverse birth outcomes (preterm delivery, low birth weight, small for gestational age) were compared in women receiving concomitant dTpa and influenza vaccine (n=8,464) and women receiving sequential vaccination (n=28,380). January 2007 to November 2013 **Note: vaccine brands are not specified.**	US pregnant women identified in the Vaccine Safety Datalink database.	To evaluate the safety of coadministering tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (dTpa) and influenza vaccines during pregnancy by comparing adverse events after concomitant and sequential vaccination.
Sukumaran L JAMA 2015	Retrospective cohort study in 29,155 pregnant women aged 14 through 49 years using data from 7 Vaccine Safety Datalink sites in California, Colorado, Minnesota, Oregon, Washington, and Wisconsin. Women received dTpa in pregnancy following a prior tetanus-containing vaccine less than 2 years before, 2 to 5 years before, and more than 5	US pregnant women identified in the Vaccine Safety Datalink database.	To determine whether receipt of dTpa vaccine during pregnancy administered in close intervals from prior tetanus-containing vaccinations is associated with acute adverse events in mothers and adverse birth outcomes

Lead Author	Study design Total study period Vaccine (in bold)	Study population	Study objective
	years before. January 1, 2007 to November 15, 2013. **Note: dTpa brand name is not specified.**		in neonates.
Vizzotti C. Vaccine 2015	An analysis and summary of Argentinian national routine surveillance data following the introduction of dTpa for pregnant women in the National Immunization Schedule (Feb 2012). Data up to the end of 2014 are presented. **Note: dTpa vaccine used for pregnant women alternated between *Boostrix* and *Adacel*.**	National routine surveillance in Argentina. Reflects ~1.2 million doses of dTpa given during pregnancy.	To share the experience with dTpa maternal immunization from the perspective of a middle-income country, and provide insight into the impact on epidemiological trends for pertussis and safety of routine dTpa vaccination following its use in this context in Argentina.
Wang M Pharmacoepidemiology and Drug Safety 2011 (Poster presentation)	Retrospective study of 539 reports from the **Sanofi Pasteur's *Adacel* pregnancy registry** of which 49 were Phase IV study reports, 10 were retrospective spontaneous reports and 480 were prospective spontaneous reports. June 2005 to January 2011.	*Adacel* (n=539)	To describe the pregnancy outcome and safety of *Adacel* vaccine administered during the pregnancy.
Zheteyeva YA Am J Obstet Gynecol 2012	Retrospective study of the Vaccine Adverse Event Reporting System (VAERS) database in the US to search for reports of pregnant women who received dTpa. January 2005 to June 2010 **Note: vaccination of pregnant women with *Boostrix* or *Adacel* (the majority of dTpa doses administered to pregnant women were *Adacel*).**	US pregnant women vaccinated with dTpa identified in the VAERS database *Boostrix* (n=20) *Adacel* (n=95) Unknown (n=17)	To characterize reports to the VAERS of pregnant women who received tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (dTpa).

Hardy-Fairbanks et al. Pediatr Infect Dis J. 32:1257; 2013:

This is an observational cohort study in which pertussis antibodies were measured in infants born to dTap (Adacel)-vaccinated (n=16) and unvaccinated pregnant mothers (n=54). Anti-pertussis (PT, FHA, PRN) antibody concentrations in infant serum were higher in the vaccinated group than in the control group. This persisted until administration of the first infant DTaP dose. After the primary series, slightly decreased immune responses were seen in infants of the dTap group, however, this did not persist following booster dose.

The study had some limitations, in particular administration of different infant DTaP vaccines to the control infants and different follow-up periods in the 2 cohorts.

Munoz et al. J Am Med Assoc 17:1760, 2014:

This randomized, placebo-controlled study was conducted in the US to assess maternal antibody transfer in infants born to dTap-vaccinated pregnant women. Adacel (n=33) or placebo (N=15) was administered at 30-32 weeks gestation with crossover immunization postpartum.
After the primary vaccination course, antibody concentrations in infants of women vaccinated during pregnancy were lower for PT, FHA and FIM (up to -48%) compared to infants of postpartum-vaccinated women; the difference was statistically significant for FHA. However, no significant difference in infant antibody levels was seen following the booster dose at 13 months of age for pertussis antigens, indicating no evidence of (long-term) immune interference.

Ladhani et al. Clin Infect Dis 61:1637, 2015:

The observational antibody prevalence study investigated antibody responses to primary vaccination of infants (N=141) born to UK women vaccinated during pregnancy with Repevax. The infant's immune responses to Pediacel and concomitant vaccine antigens were compared to those of a historical cohort of infants (N=246) born to mothers not vaccinated during pregnancy and primary vaccinated using the same vaccines and schedules.
Infants of dTpa-vaccinated mothers had high pertussis antibody concentrations at pre-immunization; their anti-PT antibody concentration significantly increased post-primary immunization whereas their anti-FHA and anti-FIM antibody concentrations significantly decreased. Compared to infants of unvaccinated mothers, anti-PT, anti-FHA and anti-FIM antibodies were significantly lower at post-primary vaccination. Antibodies to diphtheria and some pneumococcal antigens were also lower although most infants achieved protective thresholds. Antibodies to tetanus and Hib were higher. Antibody levels were not measured in the 2nd year of life since no DTaP booster was given. The authors thus concluded that that antenatal pertussis immunization resulted in high infant pre-immunization antibody concentrations, but blunted subsequent responses to pertussis vaccine. In countries with no pertussis booster until school age, continued monitoring of protection against pertussis thus is indicated.

Maertens et al. Vaccine 34:142, 2016:

The authors studied anti-pertussis antibody titres in infants born to mothers (N=57) vaccinated with Boostrix during pregnancy at 29 weeks (mean, SD 2.8 weeks) gestational age. A control group (N=42)of pregnant women not vaccinated during pregnancy was included. No randomization was performed. Infants of vaccinated women had much higher antibody levels against all vaccine antigens during the first 2 months of life compared to control infants. After primary vaccination, antibody GMCs against diphtheria toxoid and PT were significantly lower in infants of the Boostrix group than in control infants although higher than at pre-vaccination. For FHA and pertactin, antibody GMCs decreased in the vaccine

group from pre-vaccination to post-vaccination, however, at post-vaccination, levels were high and in the same range as those of the control group.

Accessor's comment:
The authors meanwhile published a follow-up study on booster data measured in toddlers following the booster dose at 15 months of age (Maertens et al., Vaccine 34:3613, 2016). At 1 month post-dose booster dose, infants in both groups showed high and protective antibody levels against PT, FHA, and PRN. However, anti-PT GMCs were still significantly lower in the vaccine group compared to the infants whose mothers were not vaccinated during pregnancy.

Hoang et al. Vaccine 34:151; 2016:

The immune response of pregnant women and their infants vaccinated with Adacel (N=52) or a tetanus vaccine as control (N=51) between 19 and 35 weeks' gestational age was investigated. Infants of Adacel-vaccinated mothers had significantly higher GMC against pertussis antigens than those of the control group up to pre-vaccination time point at 2 months of age. Following primary vaccination, infants of the Adacel group showed a further increase in antibody titers against D, T and pertussis antigens, however, anti-diphtheria and anti-PRN GMCs were significantly lower than in control group infants albeit reaching high levels in both groups (i.e., above protection threshold).

Amirthalingam et al. Lancet 384:1521; 2014:

This study confirmed effectiveness of vaccination during pregnancy by comparison of data on laboratory-confirmed cases and hospital admissions for pertussis in infants before and after implementation of the maternal immunization program in 2012 (total observational period: January 2008 to September 2013). The immunization program offered Repevax to all pregnant women between 28 and 38 weeks gestation. It was set up in response to a significant pertussis outbreak that began in 2011 and extended into 2012 (peak: October 2012). For the first 9 months of 2013 compared to the same period in 2012, the greatest proportionate fall in confirmed cases (72 vs. 328, -78%) and in hospital admissions (140 vs. 440, -68%) was recorded in infants younger than 3 months. Vaccine coverage in pregnant women from 1-Oct-2012 to 3-Sep-2013 was 64%; vaccine effectiveness based on 82 confirmed pertussis cases in infants younger than 3 months was 91%. VE dropped to 38% if mothers were vaccinated between 6 days before and up to 13 days after delivery suggesting that the protection was mainly due to placental transfer of antibodies.

Dabrera et al. Clin Infect Dis 60:333; 2015

This is another vaccine effectiveness study analyzing the impact of maternal immunization with Repevax on infant pertussis infection in UK during the national pertussis outbreak. The case-control study was conducted in England and Wales between October 2012 and July 2013. Cases (N=58) were infants aged <8 weeks with confirmed pertussis infection, controls (N=55) were healthy infants born consecutively after the case in each practice. Mothers of 10 cases (17%) and of 39 controls (71%) were vaccinated during pregnancy, resulting in an unadjusted VE of 91% (95%CI: 77-97%) and an adjusted VE of 93% (CI: 81-97%).

Vizzotti et al. Vaccine 33:6413;2015:

The authors published national surveillance data from Argentina on the impact of a universal dTap vaccination strategy for pregnant women from 20 weeks gestation on, starting in February 2012 with a high vaccination coverage (up to 67% in 2013). Data showed 87% decrease in absolute pertussis mortality, 70% decrease in the overall pertussis fatality rate and 84% decrease in pertussis fatality rate in infants < 2 months. In 2014, the lowest number of deaths due to pertussis (n=6) was recorded in Argentina since 40 years, representing a 92% reduction compared to 2011.

Assessor's comment:
Literature data demonstrate that pertussis vaccination of mothers during pregnancy results in high infant anti-pertussis antibody levels and thereby provides highly effective protection against disease to infants between birth and start of primary immunization responses. Data also indicate that maternal antibody concentrations result – to variable extent – in measurable blunting of the infant's primary immune response to pertussis, diphtheria and/or CRM-conjugated antigens. It remains unknown whether this blunting effect is of clinical relevance. However, antibody levels generally were above protective thresholds following primary immunization. Thus, it can be assumed that infants of vaccinated mothers are protected against diseases following primary vaccination at least until booster time point.

Limited data also indicate that antibody interference was either not seen or was very limited following the booster dose in the 2nd year of life.

III.1.2 Clinical safety

III.1.2.1 Pertussis in pregnancy safety study (PIPS)

The observational PIPS study was launched in February 2014 was sponsored by the University of Auckland, New Zealand, and funded by The local District Health Board (DHB) of Canterburg and GSK Biologicals. New Zealand had experienced a large pertussis epidemic 2011 to 2013 and, in response to this, the New Zealand's Ministry of Health recommended the use of a dTpa vaccine during pregnancy in 2012.

Study design:
The PIPS study represents a 3-component observational PASS study. A comparative group was omitted because maternal vaccination with Boostrix was part of the immunization calendar. Data were to be collected retrospectively in study part 1 and prospectively in parts 2 and 3. Part 1 enrolled a large cohort comprising all New Zealand women pregnant between 2009 and 2013. Parts 2 and 3 actively followed mothers who received Boostrix during pregnancy (parts 2 and 3) with a follow-up of their infants for up to 1 year of age in part 3.

Part 2 was set up in general practices and antenatal clinics in various New Zealand areas; part 3 was implemented in the Canterbury region only.

The applicant submitted **parts 2 and 3 study reports within this variation** whereas part 1 study data will be available in Q3 2016.

Objectives:
Primary objective, part 2:
To follow up a subgroup of women who received Boostrix during pregnancy for a period of one month after vaccine administration and to document health outcomes for vaccinees for this period.

Primary objective, part 3:
To describe adverse events in women who were administered Boostrix under the DHB program and to describe outcomes for their infants.

Secondary objective, part 3:
To evaluate infants of mothers vaccinated with Boostrix during pregnancy who have symptoms consistent with pertussis or who have had significant contact with a proven case.

Methodology:
All pregnant women

- (**Part 2**:) vaccinated with Boostrix **between 28 and 38 weeks gestation** at any participating general practice or antenatal clinic in New Zealand or
- (**Part 3**:) 18-40 years of age vaccinated with Boostrix **between 30 and 36 weeks gestation** at any participating general practice in Canterbury

represented the study population.

Pregnant women were recruited regardless of their medical and gynaecological history and participants with high-risk pregnancies were included.

During the influenza season some participants were co-administered an influenza vaccine dose.

Inclusion criteria (beside those mentioned before):

- Compliant with routine antenatal care, including at least one ultrasound early in pregnancy;
- For whom associated information on vaccine/s given including batch number was obtainable.

Exclusion criteria:

- Vaccination outside gestational age window or delivery prior to being contacted by the study team

Nurses from participating practices and clinics provided pregnant women just vaccinated with a Summary Information Sheet about the study. If women consented to be contacted, they were provided further information sheets including consent form and subsequently were contacted by the study team. If consent was not given the reason for decline was recorded. Patients were also provided plastic tools for measuring maximum diameter of local reactions and diary cards for recording AEs.

Referrals of pregnant women were obtained between 30-Jan to 30-June 2014 (**part2**) and between 30-Sep 2012 and 30-June 2014 (**part 3**), respectively.

Safety data were collected by the study team

- (**Part 2**:) via telephone interviews at 48-72h and 1 month post-vaccination.
- (**Part 3**:) via telephone interviews at 48-72h and 7-14 days post-vaccination and via (postal) questionnaire at 1 month post-vaccination; infants of participating women were followed up at 6 weeks, 3-7 months and (partly) up to 1 year of age (through routine medical checks).

Endpoints:
The safety endpoints (i.e. injection site reactions, fever and AEs) were collected based on Brighton Collaboration Definitions and Guidelines. Any cases of stillbirth, foetal death, elective abortion or other significant pregnancy outcomes that occurred during the period of active data collection were reported within 24 hours of notification. Events related to labour and delivery were separated from those related to pregnancy and, together with infant outcomes, were classified as adverse event (AE) or serious adverse event (SAE) using an algorithm based on the indications of foetal/infant distress. AEs and SAEs from study parts 2 and 3 were pooled.

The way AEs were reported in Study part 3 was slightly different from the way they were reported in study part 2. In Study 3, a CARM (New Zealand Center for Adverse Reactions Monitoring) report was sent if the participant reported more than one symptom (e.g., not just a sore arm, but a cluster of symptoms), sought advice from a health professional (e.g., midwife or doctor), had symptoms that were reported within 4-weeks post-vaccination and that had no obvious explanations, took time off work or was hospitalised. In Study 2, no judgement was made and all events that were adverse were reported.

The investigators considered the biological plausibility, possible alternative etiologies and timing of onset proximal to vaccination to assess if an adverse event was likely to be attributable to vaccination.

Study 3 was underway before the decision was made to merge results and there were some differences in the way data were collected. A number of variables, e.g., induration, were collected in Study 2 but not Study 3.

All maternal and infant safety outcomes were descriptive only.

Assessor's comment:
The lack of a comparator group and the collection of events (almost) exclusively by telephone contact were constraints of the study.

Results

A total of 793 pregnant women with a median age of 32 years consented to participate in the study, 326 of 363 referred patients in study 2 (90%) and 467 of 710 patients (66%) in study 3.

Overall, participants were predominantly NZ European, but Study 2 was more ethnically diverse. The participants were not considered fully representative of the general population of New Zealand, ethnically and socioeconomically. There was an underrepresentation of Maori and Pacific women who have higher risk pregnancies than the European ethnicity. According to the applicant, this was likely related to the difference in health seeking behaviour between these populations.

Table 2 Demographic characteristics of participants

	Study 2 (N=326) n (%)	Study 3 (N=467) n (%)	Total (N=793) n (%)
Ethnicity			
NZ European	180 (55.2)	403 (86.3)	583 (73.5)
Māori	37(11.3)	18 (3.9)	55 (6.9)
Pacific Island	32 (9.8)	2 (0.4)	34 (4.3)
Asian	69 (21.2)	34 (7.3)	103 (13.0)
Middle Eastern/Latin American/African	8 (2.5)	10 (2.1)	18 (2.3)
Age Category			
19 years or less	7 (2.1)	5 (1.1)	12 (1.5)
20–24 years	33 (10.1)	32 (6.9)	65 (8.2)
25–29 years	78 (23.9)	102 (21.8)	180 (22.7)
30–34 years	129 (39.6)	178 (38.1)	307 (38.7)
35–39 years	66 (20.2)	114 (24.4)	180 (22.7)
40 years or more	13 (4.0)	36 (7.7)	49 (6.2)
Co-administered flu vaccine			
Yes	157 (48.2)	64 (13.7)	221 (27.9)
Medical History/Pre-existing conditions			
None noted	266 (81.6)	385 (82.4)	651 (82.1)
Diabetes	14 (4.3)	15 (3.2)	29 (3.7)
Asthma	14 (4.3)	10 (2.1)	24 (3.0)
Pregnancy related conditions	3 (0.9)	13 (2.8)	16 (2.0)
Cardiovascular	2 (0.6)	10 (2.1)	12 (1.5)
Atopy	1 (0.3)	3 (0.6)	4 (0.5)
Cancer	1 (0.3)	1 (0.2)	2 (0.3)
Chronic Renal Disease	1 (0.3)	-	1 (0.1)
Chronic Respiratory Disease	-	1 (0.2)	1 (0.1)
Other	23 (7.1)	29 (3.7)	52 (6.6)
Declined to answer	1 (0.3)	-	1 (0.1)

Source: Table 3, PIPS Maternal Outcomes Report

Injection side reactions

Pain was the most commonly reported injection site reaction with 79% of participants reporting mild or moderate pain and 2.6% reported severe pain. The study part 2 subjects reported pain of higher intensity, later onset and longer time until resolution. This was likely related to ethnic differences and reporting methods.

Swelling and erythema rates were < 8% with less than 1% of participants reporting a size >5 cm diameter. Induration was collected in study part 2 only and was reported by 12% of participants.

Table 3 Number and percentage of participants reporting pain after Boostrix injection

Pain	Study 2 (N=326) n (%)	Study 3 (N=467) n (%)	Total (N=793) n (%)
None	56 (17.2)	90 (19.3)	146 (18.4)
Mild, still able to move arm normally	163 (50.0)	184 (39.4)	347 (43.8)
Moderate, hurts to move or to touch	90 (27.6)	189 (40.5)	279 (35.2)
Severe, unable to move arm	17 (5.2)	4 (0.9)	21 (2.6)
Onset of pain	(N=270)	(N=377)	(N=647)
0–24 hours	201 (74.4)	342 (90.7)	543 (83.9)
25–48 hours	68 (25.2)	35 (9.3)	103 (15.9)
49–72 hours	1 (0.4)	-	1 (0.2)
Pain resolved by			
0–24 hours	30 (11.1)	131 (34.7)	161 (25.1)
25–48 hours	86 (31.9)	141 (37.4)	227 (35.4)
>49 hours	154 (57.0)	99 (26.3)	253 (39.5)
Missing	-	6 (1.6)	6 (0.9)

Source: Table 4, PIPS Maternal Outcomes Report

Table 4 Number and percentage of participants reporting swelling after Boostrix injection

Swelling	Study 2 (N=326) n (%)	Study 3 (N=467) n (%)	Total (N=793) n (%)
None	299 (91.7)	434 (92.9)	733 (92.4)
>0.0–<1.0 cm	13 (4.0)	20 (4.3)	33 (4.2)
>1.0–<2.5 cm	5 (1.5)	7 (1.5)	12 (1.5)
>2.5–<5.0 cm	8 (2.5)	4 (0.9)	12 (1.5)
>5.0–<10.0 cm	-	2 (0.4)	2 (0.3)
>10.0–<15.0 cm	1 (0.3)	-	1 (0.1)
	(N=27)	(N=33)	(N=60)
Onset of swelling	n (%)	n (%)	n (%)
0–24 hours	13 (48.1)	31 (93.9)	44 (73.3)
25–48 hours	14 (51.9)	2 (6.1)	16 (26.7)
Swelling resolved	n (%)	n (%)	n (%)
0–24 hours	7 (25.9)	7 (21.2)	14 (23.3)
25–48 hours	6 (22.2)	9 (27.3)	15 (25.0)
>49 hours	14 (51.9)	17 (51.5)	31 (51.7)

Source: Table 5, PIPS Maternal Outcomes Report

Table 5 Number and percentage of participants reporting erythema after Boostrix injection

Erythema	Study 2 (N=326) n (%)	Study 3 (N=467) n (%)	Total (N=793) n (%)
None	289 (88.7)	458 (98.1)	747 (94.2)
>0.0–<1.0 cm	22 (6.7)	3 (0.6)	25 (3.2)
>1.0–<2.5 cm	6 (1.8)	4 (0.9)	10 (1.3)
>2.5–<5.0 cm	7 (2.1)	1 (0.2)	8 (1.0)
>5.0–<10.0 cm	2 (0.6)	1 (0.2)	3 (0.4)
Onset of erythema	**(N=37) n (%)**	**(N=9) n (%)**	**(N=46) n (%)**
0–24 hours	19 (51.4)	8 (88.9)	27 (58.7)
25–48 hours	15 (40.5)	1 (11.1)	16 (34.8)
49–72 hours	3 (8.1)	-	3 (6.5)
Erythema resolved	**n (%)**	**n (%)**	**n (%)**
0–24 hours	12 (32.4)	1 (11.1)	13 (28.3)
25–48 hours	7 (18.9)	3 (33.3)	10 (21.7)
>49 hours	18 (48.6)	5 (55.6)	23 (50.0)

Source: Table 6, PIPS Maternal Outcomes Report

Table 6 Number and percentage of participants reporting induration after Boostrix injection

Induration (Study 2 data only, N=326)	n (%)
None	287 (88.0)
>0.0–<1.0 cm	21 (6.4)
>1.0–<2.5cm	12 (3.7)
>2.5–<5.0cm	6 (1.8)
Onset of induration after injection (N=39)	
0–24 hours	15 (38.5)
25–48 hour	22 (56.4)
49–72 hour	2 (5.1)
Induration resolved (N=39)	
0–24 hours	6 (15.4)
25–48 hours	11 (28.2)
>49 hours	22 (56.4)

Source: Table 7, PIPS Maternal Outcomes Report

Systemic events

Fever was reported by 2.1% of participants. Other than fever, systemic events included headache and dizziness, nausea and vomiting, fatigue and myalgia or arthralgia. Fatigue was the most frequently reported systemic symptom in 7.9% of participants. Other systemic AEs were common (reported for approximately 3% of the subjects). Almost all systemic events occurred in the 24 hours following

immunization supporting a causal role for the vaccine. Around one third of the subjects who reported a systemic event also received an influenza vaccine concomitantly.

The reactogenicity and safety profile of Boostrix in the PIPS study was in line with that observed in the randomized controlled clinical trial conducted in the US in pregnant women vaccinated with Repevax/Adacel [Munoz, 2014]. In this study, pain was reported in 76% of pregnant women, erythema and induration/swelling each in 9.1%, fever in 3.0%, whereas any systemic AEs were reported in 36.4% of subjects.

Overall the injection site reactions and systemic events reported in the PIPS study are also consistent with Boostrix' safety profile mentioned in the current SmPC for adults and adolescents aged 10 years and older. A few differences, e.g. higher rates for myalgia/ arthralgia and lower rates for headache and fatigue, can be explained by the variable methods of data collection.

Assessor's comment:
Altogether, Boostrix was well tolerated by the study population of New Zealand pregnant women. The rates and intensity of injection site reactions and systemic AEs seen in the PIPS study do not differ from those seen in other (non-pregnant) adults following dTap vaccination and are in the range of those mentioned in the SmPC for Boostrix and Boostrix Polio.

Table 7 Number and percentage of participants reporting fever and taking antipyretics or pain medication following Boostrix injection

Fever (N=793)	Study 2 (N=326) n (%)	Study 3 (N=467) n (%)	Total (N=793) n (%)
None reported	316 (96.9)	460 (98.5)	776 (97.9)
Fever	10 (3.1)	7 (1.5)	17 (2.1)
Onset of fever	(N=10)	(N=7)	N=17)
0–24 hours	10 (100.0)	4 (57.1)	14 (82.4)
25–48 hours	-	2 (28.6)	2 (11.8)
49–72 hours	-	1 (14.3)	1 (5.9)
Antipyretic or pain medication taken			
No	299 (91.7)	463 (99.1)	762 (96.1)
Yes	27 (8.3)	4 (0.9)	31 (3.9)
Fever within 24 hrs and co-administered influenza vaccine			
Yes	6 (1.8)	0 (0.0)	6 (0.8)

Source: Table 8, PIPS Maternal Outcomes Report

Table 8 Number and percentage of participants reporting systemic events and time on onset following Boostrix injection

	Study 2 (N=326)	Study 3 (N=467)	Total (N=793)
Headache/dizziness	n (%)	n (%)	n (%)
0–24 hours	12 (3.7)	16 (3.4)	27 (3.5)
All	13 (4.0)	17 (3.6)	30 (3.8)
Missing	1 (0.3)	-	1 (0.1)
Fatigue			
0–24 hours	22 (6.7)	36 (7.7)	58 (7.3)
All	24 (7.4)	39 (8.4)	63 (7.9)
Missing	4 (1.2)	-	4 (0.5)
Nausea/vomiting			
0–24 hours	11 (3.4)	8 (1.7)	19 (2.4)
All	12 (3.7)	9 (1.9)	21 (2.6)
Missing	1 (0.3)	-	1 (0.1)
Myalgia/Athralgia			
0–24 hours	4 (1.2)	17 (3.6)	21 (2.6)
All	5 (1.5)	19 (4.1)	24 (3.0)

Source: Table 9, PIPS Maternal Outcomes Report

SAEs in women and infants

A total of 31 pregnant women (3.9%) experienced SAEs, 23 of which occurred during pregnancy; and 8 SAEs were recorded during labor/ delivery in the newborn. The pregnancy SAEs were predominantly related to bleeding, premature delivery, and infection. All resulted in hospitalization and all but one occurred after 30 weeks gestation. None was considered by the investigator as related to vaccination.

Table 9 SAEs among pregnant women - Study 2

Participant	Event	SAE definition	Onset post Tdap	Gestation at time of event (wks)
[redacted]	PV bleeding	Required hospitalisation	11d	30w
	Hypertension in pregnancy	Required hospitalisation	27d	40+w
	Pelvic pain, bacterial vaginitis	Required hospitalisation	9d	34w
	Cellulitis	Required hospitalisation	6d	38w
	Hypertension in pregnancy	Required hospitalisation	11d	34w
	Threatened labour and Group A strep infection	Required hospitalisation	20d	31w
	Bleeding	Required hospitalisation	24d	36w
	Maternal tachycardia	Required hospitalisation	16d	34w

C

Source: Table 12, PIPS Maternal Outcomes Report

Table 10 SAEs among pregnant women - Study 3

Participant	Event	SAE definition	Onset post Tdap	Gestation at time of event (wks)
[redacted]	Gestational diabetes & antenatal partum haemorrhage	Required hospitalisation	29d	34w
	Preterm labour	Required hospitalisation	1d	36w
	Preterm labour	Required hospitalisation	24d	36w
	Preterm labour	Required hospitalisation	7d	33w
	Exacerbation of pre-existing condition	Required hospitalisation	17d	36w
	Exacerbation of pre-existing condition	Required hospitalisation	7d	19w
	Preeclampsia	Required hospitalisation	8d	36w
	Preterm labour	Required hospitalisation	16d	36w
	Preterm labour	Required hospitalisation	19d	36w
	Preterm labour	Required hospitalisation	11d	33w
	Preterm labour	Required hospitalisation	19d	36w
	Vaginal bleeding	Required hospitalisation	21d	34w

C

Source: Table 13, PIPS Maternal Outcomes Report

The investigator provided brief narratives of every SAE during pregnancy. SAEs recorded were consistent with events generally anticipated in a pregnant population. The onset of each SAE was between 7 d and 29 d after Boostrix vaccination except for two patients who presented with pre-term labor or coronavirus infection, respectively, at 1 d-post-vaccination. No particular trend or safety concern emerged.

Among the 8 SAEs recorded in infants during labor/delivery there were 2 perinatal deaths, one of which was identified to be due to a congenital anomaly (trisomy 11q); the other was a stillbirth for which no specific cause could be identified.

Assessor's comment:
SAEs that occurred in pregnant women of the PIPS study were consistent to those generally anticipated in a pregnant population. From the narratives it can be inferred that none of the SAEs observed was related to previous vaccination with Boostrix.
Besides, there is no indication to assume that any of the SAEs observed in neonates during labor/ delivery was related to previous Boostrix vaccination of the mother.
However, Maori and Pacific people who more often have higher risk pregnancies than the European ethnicity were underrepresented in the PIPS study which might have resulted in a lower number of SAEs than would be expected from the whole New Zealand pregnant population presenting with up to 15% of pregnancies with obstetric complications.
Furthermore, study participants were recruited through attendance of primary health care units and chose to receive a dTap vaccine during pregnancy which further biased the study population.

Table 11 SAEs during labor and delivery - Study 2

Participant	Event	SAE definition	Onset post Tdap	Gestation at time of event (wks)
[redacted]	Cyanotic episodes in infant	Prolongation of existing hospitalisation	31d	39w
	Fetal death (trisomy 11q)	Resulted in death	10d	36w
	Fetal distress	Intervention to prevent permanent damage or death	11d	38w
	Fetal distress	Hospitalisation	23d	39w
	Fetal distress	Intervention to prevent permanent damage or death	37d	41w
	Fetal distress	Intervention to prevent permanent damage or death	18d	39w

C

Source: Table 14, PIPS Maternal Outcomes Report

Table 12 SAEs during labor and delivery - Study 3

Participant	Event	SAE definition	Onset post Tdap	Gestation at time of event (wks)
[redacted]	Concern for fetus	Admission to NICU and CPAP	28d	37w
	Perinatal death	Resulted in death	53d	40w

C

Source: Table 15, PIPS Maternal Outcomes Report

Follow-up of study 3 infants:

Infant outcomes included gestational age and weight at birth. Congenital anomalies were identified from routine 6-week medical checks or other sources. Growth parameters were also obtained from the 6-week check as well as routine health care nurse visits between 5 and 8 months of age.

There were 409 births recorded with 12 twins and 397 singleton infants. One infant was still born with no congenital abnormalities identified. Despite postmortem examination the reason for this stillbirth is unknown. The mother, however, had a history of previous stillbirth.

The mean gestational age at delivery was 39.1 weeks with 19 women delivering prior to 37 weeks gestation. The mean birth weight was 3490 grams. One infant weighed less than 1500 grams at birth and a further 8 infants weighed < 2500 grams. The rates of prematurity and low birth weight were within the range for the New Zealand population (Ministry of Health, 2015 http://www.health.govt.nz/publication/new-zealand-maternity-clinical-indicators-2013).

Follow up data were obtained on 403 infants, 340 of which through 12 months of age and 63 through 6 months of age. In 67 cases only maternal data were available. A total of 303 infants completed their 6-week check and 278 completed their 5-month check. 28 infants were withdrawn from the study.

Besides the stillbirth case, a total of 10 out of 403 newborns (2.5%) had one of the following reported medical events of significance or congenital abnormalities: gastroschisis, malrotation of bowel, benign neonatal myoclonus, hypospadias, subluxation right hip, perforated bowel, pyloric stenosis, hip dysplasia, right hand anomaly, and laryngomalacia. Of note, perforated bowel and benign neonatal myoclonus are not considered congenital anomalies based on CDC guideline.

Nine infants had contact with a confirmed pertussis case during the follow-up period. A total of 64 infants were reported to have had a cough for more than 10 days, 9 of which were tested negative for pertussis (PCR). None of the infants developed pertussis during the follow-up period.

Assessor's comment:
The rates of prematurity, low birth weight and other health outcomes are within the range for the New Zealand population. The single stillbirth of unknown cause is considered unrelated to maternal vaccination since temporal association was missing (vaccination 2 months before) and no significant immediate adverse event in the mother following vaccination was observed.

None of the infants developed pertussis during the follow-up period.

III.1.2.2 Post-marketing experience

The post-marketing safety evaluation of Boostrix was performed using the GSK worldwide safety database (Argus) and the US pregnancy registry. The post-marketing surveillance data for Boostrix Polio have been gathered from the GSK worldwide safety database (Argus).

Please note that the registered US formulation has a lower aluminium content (0.3 mg/dose).

The US pregnancy registry is a prospective, voluntary, observational, program of enhanced pharmacovigilance to collect data describing exposure to Boostrix (within 28 days before pregnancy or anytime during pregnancy), potential confounding factors and information related to the pregnancy and newborn outcomes following vaccination with Boostrix during pregnancy.

The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance at the time of US approval. Based on the new EU Guidelines on Good

Pharmacovigilance Practice (Module VIII), this Pregnancy Registry was re-classified on 01 April 2014 as a post-authorization safety study (PASS) to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Boostrix during pregnancy. To increase the rate of pregnancy registration (accrual), a web page (http://pregnancyregistry.gsk.com/boostrix.html) was created with instructions for enrolling patients in the Registry.

The US Registry report contains a description of all prenatal exposures to Boostrix in the US that were reported to GSK. Prospectively reported exposures are data acquired prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination. A follow-up to determine the pregnancy outcome is required. Prospective reporting of ongoing pregnancies reduces bias and permits estimation of the risk of birth defects and other adverse pregnancy outcomes. In contrast, retrospective reports, are data acquired after the outcome of the pregnancy is known or after the detection of a congenital malformation via prenatal test. Retrospective reports are more likely to be biased toward the reporting of more unusual and unfavorable outcomes.

When the pregnancy is reported prospectively, the Registry collects registration data from the reporter through telephone interview or a short registration form. The required data include:

- Documentation that *Boostrix* was administered within 28 days before or anytime during pregnancy;
- Confirmation that the pregnancy is being prospectively reported;
- Confirmation that the subject is a US resident;
- Identification of a healthcare provider (name, address, and telephone number);
- A patient identifier that will allow follow-up so that the pregnancy outcome can be ascertained.

Follow-up is sought via telephone contact or a form mailed to the health professional. Information about maternal events throughout the pregnancy, pregnancy outcome, and neonatal health is requested.

This Registry uses the term 'birth defects' for outcomes sometimes referred to as 'congenital anomalies'. The definition of birth defect encompasses any structural or chromosomal abnormality diagnosed before 6 years of age. All morphologic anomalies, including minor ones, were included.

Pregnancy outcomes were stratified by the trimester of exposure, with an additional stratum for exposures within 28 days before pregnancy with no subsequent administration during pregnancy. The second trimester is considered to begin at gestation week 14, and the third trimester begins at week 28. Reports of multiple exposures (i.e., multiple administrations of Boostrix) during a pregnancy were classified by the earliest trimester of exposure. When exposure occurs before and after conception, the exposure is classified by the dose administered after conception.

Potential bias: The US Registry is a prospective cohort study. Active enrollment of a valid internal comparison group is not feasible. As reporting of pregnancies is voluntary, thus, even among prospectively reported pregnancies there could be bias in type of pregnancies which are reported. E.g., high-risk pregnancies may be more likely to be reported. Those pregnancies that have reached estimated dates of delivery but for which outcome information was unobtainable are considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. All attempts are made to minimize this potential source of bias.

Overall, 908 US pregnancy reports (890 prospective and 18 retrospective) had been received in the registry for Boostrix from 3 May 2005 until 2 August 2015, for which 171 had a known outcome.

Among the 644 prospective reports that had been prospectively reported until 31 March 2014, 84 had a known outcome with vaccination occurring during the first (n=19), second (n=16), and third trimester (n=49). Of these, 79 live infants were without apparent birth defects. There were 2 reports of spontaneous abortions during the first trimester of pregnancy and 3 reports of birth defects (one unspecified anomaly, one plagiocephaly and one mid foot ligament deformity) following exposure during the second or the third trimester.

A total of 246 pregnancies had been prospectively reported from 1April 2014 to 2 August 2015. Among these 246 cases, there were 72 pregnancy reports with known outcomes following exposure before pregnancy (n=1), in the 2nd trimester (n=3), 3rd trimester (n=67) or unspecified time point (n=1). For all cases a live infant with no apparent congenital anomaly was reported.

Pregnancy reports that were received retrospectively are summarized below:

Up to 31st March 2014 there were 16 respective reports with known pregnancy outcome for 14 cases. Among the 14 known outcomes, 9 live infants and 2 stillbirths were reported, one case due to placental disruption a few hours after vaccination at 37 w gestation, one with an unknown cause at 22 w gestation and 1 month-post exposure. Three reports specified live infants with a congenital anomaly (pulmonary hypertension and arteriovenous malformation; gastroschisis and laryngotracheomalacia) after vaccination in the 1st or at an unspecified trimester. The neonate with pulmonary hypertension died of unknown cause.

There were 2 retrospective reports from 1April 2014 to 2 August 2015, one from the 3rd trimester resulting in a live birth with no apparent congenital anomaly, one from the 1st trimester with pregnancy still ongoing at 2 Aug 2015.

Pregnancy reports from other (non-US) countries:

GSK worldwide safety database (Argus) provided 132 non-US pregnancy reports (22 retrospective and 110 prospective reports) that were received from 3 August 1999 to 2 August 2015.

Amongst 110 prospective cases, 32 had a known outcome: 30 live births, 1 spontaneous abortion without apparent congenital anomaly at 6 weeks gestation and 1 case of live birth with a congenital anomaly (trigonocephaly) at 5 days post-exposure during 3rd trimester). Of the remaining 78 prospective reports, 52 pregnancies were lost to follow-up or had an unknown outcome, and 26 pregnancies were still ongoing.

20 of 22 retrospective cases had a known outcome: 11 live births, 1 case of spontaneous abortion without apparent congenital anomaly (2 weeks after exposure at around 21 weeks), and 2 stillbirths without apparent congenital anomalies (5 days after exposure at 30 weeks with placenta showing focal chorioamnionitis and one case without further details following vaccination at 22 weeks gestation).

There were 6 cases of live birth with a congenital anomaly. The congenital anomalies were 1 case of pleural effusion and cardiomegaly (exposure at 35 weeks gestation), 2 cases of convulsions along with encephalitis or cardiopathy, respectively (exposure both in the 3rd trimester), 2 cases of unilateral renal agenesis (exposure during the 1st and 3rd trimester, respectively), and 1 case with vitium cordis (exposure time point not specified). Of note, pleural effusion, convulsions and encephalitis are not considered congenital anomalies based on CDC guidelines. Two remaining reports were lost to follow-up.

Worldwide pregnancy reports for Boostrix Polio:

GSK's worldwide database provided 108 pregnancy outcome reports for Boostrix Polio from December 2003 through 9 July 2015. There were 102 prospective reports with 3 spontaneous abortions, 3 elective terminations and 41 live infants, all without apparent congenital anomaly, one live infant with congenital anomaly, and 54 residual cases (lost to follow-up, unknown, ongoing). Among the 6 retrospective reports, there were 2 spontaneous abortions, 2 stillbirths, and 2 live births, all without apparent congenital anomaly.

Assessor's comment:

In the US pregnancy registry of Boostrix 94% of reports documented a live birth with no congenital anomaly. For 6 (3.5%) of the live born neonates a birth defect was reported. This risk of congenital anomaly is in line with the number reported in the general population of all birth defects, which is approximately 3% of live births (CDC 2016; http://www.cdc.gov/ncbddd/birthdefects/facts.html).

Generally, most cases of live birth with congenital anomalies were observed in retrospective reports which are more prone to bias towards reporting of severe and unusual cases.

In summary, analysis of GSK pregnancy safety database did not raise any safety concern for maternal or infant health following maternal vaccination.

III.1.2.3 Literature review regarding safety of dTpa vaccination during pregnancy

The applicant also provided a short literature review of published studies that analyzed the safety of dTap vaccination during pregnancy (for details, see Table 2).

Three non-randomized, controlled clinical trial has been conducted so far to assess the safety of vaccination with dTap vaccines (Boostrix or Adacel) during pregnancy and the health outcomes of newborns born to vaccinated mothers (Maertens, 2015; Munoz, 2014; Hoang, 2016). These preliminary assessments showed that maternal immunization with either Boostrix or Adacel during the 3rd trimester of pregnancy is safe and that the rates of AEs were in line with those observed in the control groups and in the PIPS study.

The safety of pertussis vaccination during pregnancy was also evaluated in several retrospective, observational studies conducted in dTpa-vaccinated pregnant women identified within large databases in the US and the UK and, whenever possible, the participants were compared with matched unvaccinated controls (Datwani, 2015; Donegan, 2014; Kharbanda, 2014; Morgan, 2015; Sukumaran, 2015a and b). The main objective was to determine whether immunization with a dTpa (-IPV) vaccine (Boostrix, Adacel or Repevax) was associated with an increased risk of adverse obstetric events or adverse birth or neonatal outcomes. These studies consistently did not identify any concerning patterns in maternal, infant or foetal outcomes with the exception of a small, yet significant increased risk for chorioamnionitis in one study with a relative risk of 1.19 (95% CI, 1.13 to 1.26) after adjusting for maternal age and comorbidities (Kharbanda, 2014). The authors emphasized that this finding should be interpreted with caution because no increased risk of preterm birth was observed, which is a major sequel of chorioamnionitis. The chorioamnionitis risk observed in the Kharbanda study may be due to residual confounding, in particular the presence of risk factors for chorioamnionitis, e.g., premature rupture of membranes, prolonged labor, lower genitourinary infections etc. In other, more recent studies, no increased risk for chorioamnionitis was found (Datwani, 2015; Morgan, 2015; Judy, 2015).

Overall, literature data confirmed the findings of the PIPS study and GSK pregnancy database evaluations that dTap vaccines are well tolerated and not associated with other safety outcomes that those commonly reported in the general (pregnant) female population.

Assessor's comment:

Since 2012 several countries have recommended vaccination against pertussis of all pregnant women using a dTpa vaccine during the third trimester of pregnancy. Vaccine effectiveness and impact on pertussis morbidity and mortality in infants born to dTpa-vaccinated mothers have demonstrated that this strategy is highly effective in preventing pertussis infection in young infants.

Safety data available from published controlled clinical trials and observational studies following (routine) implementation of dTpa vaccination during pregnancy did not reveal any concerning patterns in maternal, fetal or infant outcomes with the exception of a small, but significantly increased risk of chorioamnionitis in the study of Kharbanda et al. (JAMA 312:1897, 2014). The assessor agrees that a causative relation between vaccination and the few cases of chorioamnionitis is very unlikely since no increased rate of preterm birth was observed in the subjects of the Kharbanda study and since this risk of chorioamnionitis was neither found in other published observational studies, nor in the PIPS study. Thus, the small, albeit increased number of chorioamnionitis cases more likely was related to the increased incidence of risk factors for this condition in that cohort of pregnant women (see also Datwani et al., Vaccine 33:3110, 2015).

III.2 Product information

The Company considers that the **Boostrix** data can be used for the **Boostrix Polio** application as the antigens and components are the same besides the poliomyelitis antigens. With regard to the polio antigen, as with other inactivated vaccines and as reflected in the 'pregnancy' section of the SmPC, harm to the fetus is not anticipated.

Corresponding changes are proposed for Boostrix and Boostrix Polio PI (see below).

In addition to the update of the pregnancy section, the MSH took the opportunity
- to align the SmPC and Package leaflet in accordance with the QRD template version 3 for MRP/DCP procedure,
- to combine the SmPC of pre-filled syringe and vial presentation and
- to correct minor editorial changes.

(regarding these changes please refer to separate PI documents)

III.2.1. Summary of Product Characteristics

B

(Changes are indicated below in red or ~~red struck through~~)

Boostrix: Section 4.6 Fertility, pregnancy and lactation

[redacted]

[redacted]

B

[redacted]

[redacted]

B

III.2.2. Package leaflet

Boostrix: Section 2, paragraph 'Pregnancy and breast-feeding'

[redacted]

IV. OVERALL CONCLUSION

PIPS study data showed that Boostrix is well tolerated and safe when administered to pregnant women in the 3rd trimester. The reactogenicity and safety profile found in pregnant women is in line with the current Boostrix SmPC for those aged 10 years and older, taking into account the study limitations.

The health outcomes for newborns and infants reflected those commonly reported in the general population of New Zealand. No particular trend or safety concern was identified from the review of the SAEs collected from the PIPS study parts 2 and 3 (maternal outcomes) and supplementary study part 3 (infant outcomes). None of the SAEs in the PIPS study were likely to be related to vaccination with Boostrix.

In addition, analysis of GSK pregnancy safety database and the US registry did not raise any safety concern for maternal or infant health. This is in line with (limited) published data on controlled clinical trials and observational studies that further advocate the administration of pertussis containing vaccines in the 3rd trimester of pregnancy.

Following responses to the request for supplementary information, the final changes to the PI are endorsed (see below).

V. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE MEMBER STATES

V.1 Points for clarification

V.1.1 Product information

(1) The UK endorses the need to amend section 4.6 of the SmPC for Boostrix and Boostrix Polio to reflect available clinical evidence on safety in pregnancy, and to make such use more permissive. This is important in the context of current national public health programmes. However, we question the need to limit this to 3rd trimester use. Although most current use, and safety data, is in the 3rd trimester, there is ongoing use in 2nd trimester. For instance, the UK recently adopted a national recommendation to offer pertussis vaccine (including Boostrix Polio) from the 2nd trimester (https://app.box.com/s/iddfb4ppwkmtjusir2tc/1/2199012147/66698939189/1) which was supported by a recent study by Eberhardt et al (http://www.ncbi.nlm.nih.gov/pubmed/26797213).

The existing wording in section 4.6 of the SmPCs is already permissive of use in pregnancy, but does not make reference to trimester. We are concerned that the proposed wording, particularly '*The use of Boostrix may be considered during the third trimester of pregnancy. Human data from prospective clinical studies on the use of Boostrix during the first and second trimester of pregnancy are not available*', actually now makes the SmPC more restrictive than it currently is, and excludes use in 2nd trimester. This may undermine confidence in use of the vaccine at a time when there will be important benefits, with no evidence of risk. We therefore ask that further consideration is given to the proposed wording.

Assessor's comment:

Although the publication by Eberhardt mentioned above refers to immunogenicity data, the objection is acknowledged.

However, the submitted data do not comprise (prospective) data on safety following vaccination in the 2nd trimester.

Unless additional safety data on 2nd trimester vaccination are available, the Assessor suggests to further update the SmPC by keeping the sentence that there are generally no safety concerns regarding pregnancy vaccination:

Safety data from a prospective observational study where Boostrix was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from post-marketing surveillance where pregnant women were exposed to Boostrix or to Boostrix Polio (dTpa-IPV vaccine) have shown no vaccine related adverse effect on pregnancy or on the health of the foetus/newborn child.

The use of Boostrix may be considered during the third trimester of pregnancy.

Human data from prospective clinical studies on the use of Boostrix during the first and second trimester of pregnancy are not available. However, as with other inactivated vaccines, it is not expected that vaccination with Boostrix harms the foetus at any trimester of pregnancy.

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 during pregnancy. The clinical relevance of this observation is unknown.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3).

Boostrix should only be used during pregnancy when the possible advantages outweigh the possible risks for the foetus.

(2) We suggest that an enclosure regarding vaccination during pregnancy (according to section 4.6 in the SmPC) "*The use of Boostrix Polio may be considered during the third trimester of pregnancy*" also in section 4.2 of the SmPC should be considered.

Assessor's comment:

This is acknowledged. Proposed wording, Section 4.2:

A single 0.5 ml dose of the vaccine is recommended.

Boostrix may be administered from the age of four years onwards.

The use of Boostrix may be considered during the third trimester of pregnancy (see section 4.6).

Boostrix should be administered in accordance with official recommendations and/or local practice regarding the use of vaccines that provide low (adult) dose diphtheria, tetanus and pertussis antigens.

(...)

(3) The sentence "*The frequency of possible side effects listed below is defined using the following convention*:" in section 4 of the package leaflets should be omitted, as the convention paragraph itself is proposed to be deleted.

(refer to SmPC for further details)

VI. ASSESSMENT OF THE RESPONSES TO THE MEMBER STATE(S) REQUEST FOR SUPPLEMENTARY INFORMATION

Question No. 1 - Labelling:

The UK endorses the need to amend section 4.6 of the SmPC for Boostrix and Boostrix Polio to reflect available clinical evidence on safety in pregnancy, and to make such use more permissive. This is important in the context of current national public health programmes. However, we question the need to limit this to 3rd trimester use. Although most current use, and safety data, is in the 3rd trimester, there is ongoing use in 2nd trimester. For instance, the UK recently adopted a national recommendation to offer pertussis vaccine (including Boostrix Polio) from the 2nd trimester (https://app.box.com/s/iddfb4ppwkmtjusir2tc/1/2199012147/66698939189/1) which was supported by a recent study by Eberhardt et al (http://www.ncbi.nlm.nih.gov/pubmed/26797213).
The existing wording in section 4.6 of the SmPCs is already permissive of use in pregnancy, but does not make reference to trimester. We are concerned that the proposed wording, particularly '*The use of Boostrix may be considered during the third trimester of pregnancy. Human data from prospective clinical studies on the use of Boostrix during the first and second trimester of pregnancy are not available*', actually now makes the SmPC more restrictive than it currently is, and excludes use in 2nd trimester. This may undermine confidence in use of the vaccine at a time when there will be important benefits, with no evidence of risk. We therefore ask that further consideration is given to the proposed wording.

Response:

The Company acknowledges the comment and proposes to update the EU SmPC according to the Assessor's proposal (insertions marked in ***bold/italic***):
"Human data from prospective clinical studies on the use of Boostrix during the first and second trimester of pregnancy are not available. ***However, as with other inactivated vaccines, it is not expected that vaccination with Boostrix harms the foetus at any trimester of pregnancy***."
In addition, also concerning section 4.6 of the SmPC, the Company would like to take the opportunity to simplify the wording of the statement below as follows (deletions are marked in **bold/strikethrough** and insertions marked in ***bold/italic***):
"~~**Boostrix should only be used during pregnancy when the possible advantages outweigh the possible risks for the foetus.**~~ ***The benefits versus the risks of administering Boostrix during pregnancy should be carefully evaluated.***"
The respective EU SmPCs were updated accordingly.

Question No. 2 - Labelling:

We suggest that an enclosure regarding vaccination during pregnancy (according to section 4.6 in the SmPC) "The use of Boostrix Polio may be considered during the third trimester of pregnancy" also in section 4.2 of the SmPC should be considered.

Response:

The Company agrees to include the proposed statement in section 4.2. of the EU SmPC.
Both EU SmPCs were updated accordingly.

Question No. 3 - Labelling

The sentence "The frequency of possible side effects listed below is defined using the following convention:" in section 4 of the package leaflets should be omitted, as the convention paragraph itself is proposed to be deleted.

Response:

The Company acknowledges the comment and proposes to correct the package leaflets by deleting the remaining sentence as proposed by the Assessor.
In addition, the Company would like to take the opportunity to correct a typographical error in section 4.8 of the EU SmPC of Boostrix Polio. The adverse reaction "gastrointestinal disorders" was mistakenly listed in the tabular listing of adverse reactions reported with Boostrix in subjects aged 10 - 76 years. This error was corrected in the proposed EU SmPC.

Assessor's comment:
All changes/ proposals to the SmPC of Boostrix/ Boostrix Polio are endorsed.

Annex:

FINAL SMPC VERSIONS OF BOOSTRIX AND BOOSTRIX POLIO

- Please refer to separate SmPC documents -