In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

BOOSTRIX® (TETANUS TOXOID, REDUCED DIPHTHERIA TOXOID AND ACELLULAR PERTUSSIS VACCINE, ADSORBED)

PREGNANCY REGISTRY

CUMULATIVE REPORT

03 MAY 2005 THROUGH 02 AUGUST 2014

1 SUMMARY

Although there is no evidence of teratogenicity from reproductive toxicology studies of *Boostrix*, GlaxoSmithKline (GSK) manages this registry as part of an ongoing program of safety monitoring. Women judged to be at risk of tetanus, diphtheria, and pertussis may be exposed to *Boostrix* before or during pregnancy. This registry is considered essential because of the potential for exposure during pregnancy and the unknown risks to pregnancy of any new chemical entity.

The purpose of this Registry is to detect and describe any abnormal pregnancy outcomes, including teratogenicity, in females intentionally or unintentionally exposed to *Boostrix* during their pregnancies The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the lack of data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing effort to assess the safety of *Boostrix*. The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance. Following new European Union Pharmacovigilance legislation, pregnancy registries are to be considered as Post Approval Safety Studies (PASS). The ongoing Registry has therefore been converted into a PASS.

The *Boostrix* pregnancy registry was and will be maintained by Vaccine Clinical Safety and Pharmacovigilance in GSK.

The Registry requires voluntary, prospective reporting of eligible pregnancies by patients and HCPs. Patient confidentiality is strictly maintained. The intent of the Registry is to prospectively collect data describing exposure to *Boostrix* immediately before or during pregnancy, potential confounding factors (such as exposure to other medications, infections, family history of congenital anomalies, etc), and information related to the outcome of the pregnancy.

This 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 (e.g. foetal ultrasound, serum markers). Because the outcome of the pregnancy is unknown when the prenatal exposure is reported, follow-up to determine the pregnancy outcome is required. Prospective reporting of ongoing pregnancies prior to knowledge of the pregnancy outcome reduces bias and permits estimation of the risk of birth defects.

Retrospective reports, data acquired after the outcome of the pregnancy is known or after the detection of a congenital malformation on prenatal test, are also reported. However, retrospective reports are likely to be biased toward the reporting of more unusual and unfavorable outcomes and are less likely to be representative of the general population [Mitchell, 1988 and Wilcox, 1984]. Therefore, the inclusion of such reports for calculation of probability (risk) of birth defects is inappropriate. The purpose of summarizing the retrospective reports is to assist in the detection of any unusual patterns that may exist among the reported birth defects.

Pregnancy and birth outcomes in infants born to women who did or did not receive Tdap vaccine during pregnancy were assessed in a retrospective cohort study [Shakib, 2013]. The study, ending in 2009, was performed before Tdap administration during pregnancy was recommended (From May 2005 through August 2009). The authors concluded that there was no increase in adverse outcomes in infants born to women receiving Tdap compared to infants of women in the control group.

In 2011, the Advisory Committee on Immunization Practices (ACIP) reviewed published and unpublished data from the Vaccine Adverse Event Reporting System, Sanofi Pasteur (Adacel) and GSK (*Boostrix*) pregnancy registries, and small studies [Talbot, 2010; Gall, 2011] investigating the administration of combined reduced antigen content tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnancy [CDC, 2011a]. ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events (AEs) and outcome in pregnant women who received Tdap and that the few serious AEs reported were unlikely to have been caused by the vaccine. Both tetanus- and diphtheria-toxoid vaccines (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic [Silveria, 1995; Czeizel, 1999]. From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks gestation is preferred to minimize the risk for any low-frequency AEs and the possibility that any spurious association might appear causative [CDC, 2013a; Terranella, 2013].

No clinical data on the safety or immunogenicity of the use of *Boostrix* during pregnancy or lactation have been generated. It is generally accepted that inactivated vaccines pose no risk to the pregnant or lactating woman [CDC, 2011d]. In the absence of supporting data, *Boostrix* should only be administered to pregnant women when clearly needed, and when the possible benefit outweighs the possible risks to the fetus. In the US, Tdap vaccination is recommended by ACIP in each pregnancy [CDC, 2013a].

As of 02 Aug 2014, 644 US prospective pregnancy reports had been received in the Registry and 78 after the conversion of the Registry into a PASS became effective.

Among the prospective reports received after the Registry became a PASS, one (1.3%) was lost to follow-up and the77 others were ongoing (98.7%).

2 INTRODUCTION

GlaxoSmithKline maintains a *Boostrix* Pregnancy Registry. The purpose of this Registry is to detect any major teratogenic effect in pregnancies intentionally or

unintentionally exposed to *Boostrix*. The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the lack of data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing program to assess the safety of *Boostrix* in pregnant women. This is a prospective, voluntary, observational, program of enhanced pharmacovigilance. Patient confidentiality is strictly maintained. The purpose of the Registry is to prospectively collect data describing exposure to *Boostrix* before or during pregnancy, potential confounding factors (such as exposure to other medications, infections, family history of congenital anomalies, etc), and information related to the outcome of the pregnancy. The Registry is intended to provide an early signal of potential risks in advance of results from formal epidemiologic studies. Registry data are used to supplement animal toxicology studies and to assist clinicians in weighing the potential risks and benefits of treatment for individual patients.

The *Boostrix* Pregnancy Registry is maintained by Vaccine Clinical Safety and Pharmacovigilance in GSK. The Registry began at the time of US approval on 3 May 2005. This analysis includes data from all Registry cases received from spontaneous post-marketing sources in the United States.

To increase the rate of pregnancy registration (accrual), a web page (http://pregnancyregistry.gsk.com/boostrix.html) has been created with instructions for enrolling patients in the Registry. In addition, GSK had requested that the FDA post a link to this web page on their Pregnancy Registry Website. In response to a 2008 request from FDA to facilitate enrollment, GSK initiated a dedicated toll-free telephone number [redacted] at which US-based callers can receive assistance in the registration of pregnancies. Notice of this new toll-free number was posted on the GSK web page in January 2009; the new toll-free number was added to the United States Prescribing Information in early 2009. It is unknown what, if any, effects these measures will have on Registry enrollment.

On 01 April 2014, this Pregnancy Registry has been re-classified as a post-authorization safety study (PASS) to collect data on pregnancy outcomes and new-born health status outcomes following vaccination with *Boostrix* during pregnancy. These data are reviewed periodically to identify any signals where the use of the vaccine might be associated with adverse events.

3 METHODS

3.1 Registration and follow-up

Reporting of exposed pregnancies is voluntary. Since the initiation of the Registry in 2005, GSK has taken several measures to increase the rate of pregnancy registration (accrual). A GSK Registry web page (http://pregnancyregistry.gsk.com/twinrix.html) was created on 07 March 2007 with instructions for enrolling patients in the Registry and GSK has requested that the FDA post a link to this web page on their Pregnancy Registry Website In response to a 2008 request from FDA to facilitate enrollment, GSK initiated a dedicated toll-free number [redacted] where callers can receive assistance in the registration of pregnancies. Notice of this new toll-free number was posted on the GSK web page in January 2009; the new toll-free number was added to the United States Prescribing Information in early 2009. The Prescribing Information

and GSK Registry website each give a brief summary of the purpose and intent of the Registry, along with telephone and fax contact information. It is unknown what, if any, effects these measures have on Registry enrollment.

When the pregnancy is reported prospectively, the Registry collects registration data from the reporter through telephone interview or a short registration form. For a pregnancy report to be considered eligible for registration, certain data must be available. The required data include:

- Documentation that *Boostrix* was administered $\leq$ 28 days before or 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 to be obtained so that the pregnancy outcome can be ascertained.

Follow-up is sought by telephone contact or a form mailed to the health professional. Information about maternal events throughout the pregnancy, pregnancy outcome, and neonatal health is requested. Additional follow-up is not sought from subsequent healthcare providers.

A report of an exposure is closed when clear information is received about exposure to *Boostrix* and pregnancy outcome determination, or when the patient is lost to follow-up. A patient is considered to be lost to follow-up when the Registry does not receive the minimum information, or if the reporting healthcare provider can no longer locate the patient.

3.2 Classification of Outcomes

This Registry uses the term ‘birth defects’ for outcomes sometimes referred to as ‘congenital anomalies’. For purposes of analysis, pregnancy outcomes are dichotomized according to the presence or absence of birth defects. The latter group is further categorized as: 1) live births, 2) spontaneous abortions (i.e., pregnancy losses) and 3) induced abortions.

This Registry adopts a definition of a child with a birth defect as any live or stillborn neonate with a structural or chromosomal abnormality diagnosed before 6 years of age. The Registry employs a conservative approach of including all morphologic anomalies, including minor ones, as birth defects.

To provide consistency in the definitions of major defects in this Registry, CDC MACDP criteria are used for the classification of defects [CDC, 2008; Correa-Villasenor 2003]. Some of the conditions excluded from the MACDP criteria for major structural defects may actually have major clinical, functional, or genetic significance. Therefore, minor malformations not appearing in the CDC inclusion list may be classified as birth defects in this Registry. In addition, CDC guidelines disqualify as defects those findings that are present in infants delivered at less than 36 weeks of gestation and are attributable to prematurity itself, such as a patent ductus

arteriosus or inguinal hernias. Infants with infectious conditions (e.g., neonatal sepsis) or isolated biochemical abnormalities (e.g., hyperbilirubinemia) are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized congenital abnormality. All other congenital abnormalities are included in the 'birth defects' category, regardless of whether the neonate is delivered alive, including structural defects in neonates delivered prior to 20 weeks of gestation or weighing less than 500 g.

3.3 Exclusions

For this Registry, emphasis is placed on prospective registration of pregnancies. Although the Registry encourages reporting of all known prenatal exposures to *Boostrix*, not all reports are appropriate for inclusion in the analysis of data. Retrospective reports from patients and healthcare providers are also received in the Registry. These outcomes are reported and are helpful for detecting a possible pattern of defects. However, because there is no denominator from which risk can be calculated, these reports are excluded from the analysis.

3.4 Analysis

Pregnancy outcomes include spontaneous abortion (pregnancy loss before 20 weeks gestation), fetal deaths/stillbirths (loss at or after 20 weeks gestation), elective/therapeutic abortions, and live births. Gestational weeks are counted from the date of the last menstrual period. The second trimester is considered to begin at week 14, and the third trimester begins at week 28. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories.

Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration during pregnancy. Reports of multiple exposures (i.e., multiple administrations of *Boostrix*) during a pregnancy are classified by the earliest trimester of exposure. When exposure occurs before and after conception, the exposure is classified by the dose administered after conception.

The majority of spontaneous abortions occur early in pregnancy [Wilcox, 1981; Wilcox, 1983; Ellish, 1996]. If spontaneous abortions were to be evaluated as an outcome of interest, it would be essential to enroll pregnancies as soon as possible after vaccination with *Boostrix*. Because enrollment and recognition of pregnancy would occur at various times, it would be virtually impossible to meaningfully evaluate the effects of *Boostrix* on pregnancy loss [Kennedy, 2004].

The risk in the general population of all birth defects meeting CDC criteria is approximately 3% (1 of 33) of live births [Centers for Disease Control and Prevention, 2013b]. The estimated risk cited in the medical literature varies because of differences in case definitions, populations sampled and ascertainment methods. The Collaborative Perinatal Project, using a broader case definition and prospective ascertainment, reports a frequency of 5% to 7% [Chung, 1975]. Most major structural defects originate during the first trimester of pregnancy, which is the critical time for organogenesis [Centers for Disease Control and Prevention, 2013b]. For such defects, exposures occurring in the second or third trimester are not likely to be causally associated. However, for the sake of completeness and to enable the assessment of

possible increases in the frequency of birth defects, all defects will be included in the periodic summary reports of this Registry.

Studies have shown that the risk of spontaneous abortion is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 10% to 22% [Wilcox, 1981; Wilcox, 1983; Wilcox, 1988; Fenster, 1997; Windham, 1997; Khattak, 1999; Anderson, 2000; Osborn, 2000].

Criteria for review of a specific individual report include:

- Is the timing of the vaccination with *Boostrix* commensurate with the ontogenetic development of the organ(s) affected by the abnormalities?
- Is there another known or likely cause (e.g., pre-existing genetic or chromosomal defect or exposure to a known teratogen)?
- Is the congenital abnormality not previously described (i.e., is it new to medical science)?
- Is there a unique constellation of defects (i.e., is there a new syndrome)?

Criteria for review of aggregate data include:

- Is there a deviation from the expected frequency of all defects indicating an increase in the overall risk of defects?
- Is there a deviation from the expected frequencies of individual defects?
- Is there uniqueness (e.g., a pattern) of the abnormalities that is suggestive of a common etiology?

While the Registry is to be limited to prospective reports, some pregnancy exposures are reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports. In general, retrospective notification of outcomes following exposure to drugs or vaccines is biased toward reporting the severe and unusual cases and is not reflective of the general experience with the drug. Information about the total number of exposed pregnancies, i.e., the pool of exposures from which the retrospective reports arise, is unknown; therefore, incidences of outcomes cannot be calculated from these data.

Calculation of risk of spontaneous pregnancy losses overall should not be attempted and cannot be compared to the incidence in the general population because pregnancies in this Registry are reported at variable and, occasionally, imprecise times. Also, pregnancy losses occurring early in gestation may not be recognized and/or reported.

In 2011, the US was the first country to recommend the use of Tdap in pregnant women who had previously not been vaccinated with Tdap in adulthood and this advice has been updated to recommend offering women Tdap in every pregnancy irrespective of the patient's prior history of vaccination with Tdap [Centers for Disease Control and Preventionbelow, 2013]. The optimal timing for Tdap administration was proposed at 27 weeks through 36 weeks gestation [CDC, 2012]. Following the initial recommendation in the US by the ACIP on June 22, 2011 [CDC,

2011], temporary immunization programmes for pregnant women with a Tdap combination vaccine have been implemented in the UK, New Zealand, Israel, Mexico, Brazil, Colombia, Uruguay, Panama, Costa Rica and Argentina [Joint Committee on Vaccination and Immunization (JCVI, 2012; Pharmaceutical Management Agency (PHARMAC), 2012; Ministerio de Saludde Salud, 2012; TAG, 2013]. Since 2013, vaccination during pregnancy is also recommended in Belgium between the 24th and 32nd week of pregnancy [CSS, 2013].

Since 01 April 2014 the Pregnancy registry has been converted into a Post Autorization Safety Study (PASS) to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with *Boostrix* during pregnancy. These data are reviewed periodically to identify any signals where the use of the vaccine might be associated with adverse events.

3.5 Potential Biases

This Registry is a prospective cohort study. Active enrollment of a valid internal comparison group is not feasible. Therefore, background risks from existing, external systems (e.g., the National Birth Defects Prevention Network and the National Center for Health Statistics) are used. The potential limitations of comparisons between Registry and background data depend upon the event(s) being compared and will be discussed on an ad hoc basis in the relevant periodic Registry reports.

Potential sources of biases are described below:

- As reporting of pregnancies is voluntary, it is possible that even among prospectively-reported pregnancies there could be bias in type of pregnancies which are reported. For example, high-risk pregnancies may be more likely to be reported.
- The calculation of risk, which does not include spontaneous abortions or voluntary terminations for which no defects have been reported, may introduce bias. It is unknown what proportions of these pregnancies consist of potentially normal outcomes versus congenital abnormalities. GSK attempts to obtain information on anomalies detected at the time of the outcome, but this may not be known to the reporting physician.
- 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.

4 DATA

4.1. Prospective reports received from the Registry and PASS

Considering that since April 1st, 2014 this Registry has been converted into a PASS the analysis has been performed including cases coded as spontaneous cases untill March 31st, 2014 and as post marketing cases from April 1st, 2014 to August 2nd, 2014. As of 31 March 2014, 644 pregnancies involving exposure to *Boostrix* in the United States had been prospectively reported since the initiation of this pregnancy

registry on 03 May 2005, out of which 642 received as “Parent case”. Among these 642 pregnancies four hundred eighty-two (482) were lost to follow-up, five considered unknown, seventy six (76) pregnancies were ongoing at the time of last contact. Seventy-four (74) live infants were born without birth defects. There were two reports of spontaneous abortions; one at seven weeks gestation with exposure to *Boostrix* during the first trimester and one at four weeks gestation with exposure to *Boostrix* during first trimester. Three live infants were born with reported birth defects; of which two mothers were exposed during the second trimester and one during the third trimester. The three cases are described below.

- One female was exposed to *Boostrix* at 19 weeks gestation. The physician reported that the baby had an unspecified congenital anomaly.
- One female neonate, who’s mother was exposed to *Boostrix* during the second trimester, was diagnosed with plagiocephaly at the age of two months. Family history included occipital deformational plagiocephaly. The outcome of the plagiocephaly was reported as unknown.
- One male neonate, who’s mother was exposed to *Boostrix* during the third trimester, was diagnosed at birth with a mild left foot ligament deformity, which was considered unrelated to *Boostrix* by the reporting physician. The reporter indicated that additional follow-up information will not be provided.

Exposure to *Boostrix* in the 155 pregnancy reports with known outcomes occurred during the first (n=23), second (n=22), third trimesters (n=69), and exposure data unknown (n=41).

Out of 644 pregnancies, two (2) have been reported as “Child cases” describing exposure during the second and the first trimester, respectively, with outcome unknown in the first case and live infant with no apparent congenital anomaly in the second.

As of 01 April 2014 this registry has been converted into a PASS. The number of pregnancies prospectively reported involving exposure to *Boostrix* in United States includes 78 cases retrieved from 01 April 2014 to 02 August 2014. One was lost to follow-up and in all the remaining 77 the pregnancies were ongoing at the time of reporting.

Among these, one case was considered serious due to a “near death experience” reported by a consumer. The subject was exposed to *Boostrix* at 7 months of pregnancy, and at an unspecified time after vaccination the subject experienced a near-death experience. No clinical or diagnostic details are available and the event was not medically verified. The case was reported as resolved.

4.2 Description of reports received from other countries

In addition to the prospective reports of pregnancy received from the United States, for completeness GSK’s spontaneous reporting system provides the Registry with prospective reports of *Boostrix*-exposed pregnancies from other countries. Cumulatively, sixty seven reports were received from the 03 May 2005 to the 31 March 2014 from the following countries: Argentina (n=5), Australia (n=14), Belgium (n=6), Brazil (n=23), Canada (n=1), Colombia (n=1), Germany (n=4),

Ireland (n=1), Israel (n=1), Republic of Korea (n=4), Netherlands (n=1), New Zealand (n=3), Sweden (n=1) and Switzerland (n=2).

Of these sixty-seven reports, exposure was reported as during the first trimester (n=16), second trimester (n=5), third trimester (n=11), unknown (n=30) and an unspecified time prior to conception (n=5).

Three pregnancies were reported to be ongoing, forty two were lost to follow-up and twenty pregnancies reported with the outcome as a 'normal' delivery. The remaining two reports concern a spontaneous abortion and a live infant with a congenital anomaly, respectively described below:

- A 12-year-old female subject received unspecified dose of *Boostrix* and was not aware that she was pregnant. Approximately 1 week after vaccination with *Boostrix*, the subject perfomed a pregnancy test and was found to be pregnant for 3 weeks. At 6 weeks of pregnancy, the subject experienced spontaneous abortion.
- A 34-year-old who was exposed to *Boostrix* vaccine during the third trimester. Approximately 5 days after vaccination to *Boostrix*, the subject delivered a live male diagnosed with a congenital anomaly. The neonate, born via a normal vaginal delivery was diagnosed with trigonocephaly. Subsequently, the neonate underwent surgical correction.

As of 01 April 2014 this registry has been converted into a PASS. From April 1st 2014 to August 2nd 2014 nine spontaneous cases have been prospectively reported from outside US, of which one was lost to follow-up and eight are ongoing pregnancies.

4.3 Description of reports received from clinical trials

For completeness pregnancy reports received from clinical trials were also reviewed. As of 02 August 2014, fifteen pregnancy exposures during clinical trials were reported in US. Seven subjects were exposed to the vaccine before conception, three during the first trimester and in the remaining five cases time of exposure was not reported.

Six pregnancies reported a live infant born without any apparent congenital anomaly, seven subjects were lost to follow-up and the remaining two cases were spontaneous abortions without any apparent congenital anomaly, described here below:

- Six months after the 1st dose of Blinded vaccine, a 27-year-old subject underwent spontaneous abortion after 9 weeks of pregnancy. The investigator causality was unknown at the time of reporting.
- Seven days after the 1st dose of blinded vaccine, a 28-year-old subject was reported to be pregnant. Abstinence was used as contraception method at time of the study start. The subject was exposed to the vaccine during 1st trimester of pregnancy. 16 days after the 1st dose of blinded vaccine and after 6 weeks of pregnancy, the subject experienced a miscarriage/spontaneous abortion. The investigator considered that there was no reasonable possibility that the miscarriage may have been caused by investigational product.

An Investigator Sponsored Study (ISS) is ongoing in New-Zeeland, until the 02 August 2014, 23 cases have been received.

4.4 Description of retrospective reports received from the Registry

For completeness pregnancy reports received retrospectively were also reviewed.

During the period 03 May 2005 to 31 March 2014, a total of thirteen retrospective pregnancy reports from the Registry were received in US. Eight reports included a live infant and two subjects were lost to follow-up. One included a live infant with congenital anomaly, describing the case of a 31-year-old woman that received *Boostrix* a Flu vaccine and Adacel during first trimester, and that delivered a neonate born with pulmonary hypertension and arterial venous malformation. The remaining two reports pertained to one spontaneous abortion at eight weeks gestation with exposure to *Boostrix* during the first trimester, and one infant delivered at an unspecified gestational age and diagnosed at birth with pulmonary hypertension and arterial venous malformation. The infant died while hospitalized; the cause of death was not provided and it was unknown whether an autopsy was performed.

In addition three retrospective cases have been reported as Child cases in literature article (Yenlik, 2012), In one the child was born without any apparent congenital anomaly One case described 15-year-old mother who received an unspecified dose of *Boostrix* and a non-GSK HPV vaccine at 8 weeks of gestation. After unspecified weeks of gestation, the neonate was delivered and experienced gastroschisis. The third case described a neonate who was exposed during unspecified trimester and experienced laryngotracheomalacia after delivery at unspecified gestational age. No other information is available.

During the period 03 May 2005 to 31 March 2014, six retrospective reports were received from outside the United States: two from Belgium, one from Brazil, one from Germany, one from South Korea and one from Switzerland.

Exposure to *Boostrix* in the six pregnancy reports with known outcomes occurred during the second trimester of pregnancy (n=3), third trimester (n=2) and before the conception (n=1).

Of the six reports, 3 pregnancies were reported with the outcome as a ‘live infant born without apparent congenital anomaly’. The three remaining cases are described below.

- A 36 or 37-year-old female subject was exposed to vaccine at 35 weeks gestation. At unknown time after vaccination with *Boostrix*, the subject went to the hospital for her routine follow up visit and the foetal ultrasound examination revealed some abnormal findings. The subject was hospitalized and the physician decided to perform emergency caesarean -section. The neonate was born with pleural effusion and cardiomegaly.
- A 25-year-old female subject received unspecified dose of *Boostrix* at 30 weeks and 3 days of gestation. One day after vaccination with *Boostrix* she experienced influenza like syndrome and 5 days after vaccination, the subject discovered that her baby wasn't moving anymore and an intra-uterine death was diagnosed (gestational age 31 weeks and 4 days) No macroscopic abnormalities in foetus, placenta or umbilical cord were observed. The placenta with membranes and

umbilical cord of 349 grams was investigated. The conclusions were: low funiculitis, small focal choriamnionitis and no particular abnormalities in the placenta.

- A 34-year-old female subject received unspecified dose of *Boostrix* in second trimester of pregnancy and 14-19 days after vaccination she experienced late abortion.

Five additional cases have been reported as Child case: one in Switzerland concerning a live infant born with a congenital anomaly after the mother was exposed during the first trimester, two in Belgium, in both the mothers were exposed during the third trimester and the live infants did not present any apparent congenital anomaly. One case was received from United Kingdom describing the occurrence of solitary kidney in a premature female neonate whose 38-year-old mother was vaccinated with *Boostrix* and also erroneously received 2 doses of Influenza vaccine during 3rd trimester. One case was reported in Germany concerning a child (multigravida pregnancy) born with foetal vitium cordis after the mother was exposed to *Boostrix* before conception.

Among the retrospective post marketing cases none has been reported in US from 01 April 2014 to 02 August 2014.

CONCLUSIONS

The number of pregnancies and outcomes accrued in this Registry since May 2005 represents a sample of insufficient size for reaching reliable and definitive conclusions about the risk, to pregnant females or their *in utero* offspring, of vaccination with *Boostrix* during pregnancy. In addition this Pregnancy Registry do not correspond to a "registry" from a pharmacoepidemiological viewpoint since they don't register all cases of pregnancy exposure to *Boostrix* since they are based on voluntary reporting.

As of 02 Aug 2014, 644 US prospective pregnancy reports had been received in the Registry and 78 after the conversion of the Registry into a PASS became effective.

Among the prospective reports received in the Registry, 482 (74.8%) were lost to follow-up, six (0.9%) were reported with unknown outcome, and 76 (11.8%) pregnancies were ongoing at the time of last contact. In 75 cases (11.7%), a live infant was born without birth defects. Two spontaneous abortions (0.3%) were reported; one at seven weeks gestation and one at four weeks, both with exposure to *Boostrix* during the first trimester. Three pregnancies ended with a live infant (0.5%) with birth defects. Of these, two mothers were exposed during the second and one during the third trimester of pregnancy.

Among the prospective reports received after the Registry became a PASS, one (1.3%) was lost to follow-up and the77 others were ongoing (98.7%).

Pregnancy outcome	Since 03May2005 to 02 Aug2014	Prospective cases Number

		Timing of exposure in pregnancy				
	Tot=644 in US	Before conception	1st trimester	2nd trimester	3rd trimester	Unknown
lost to follow-up	482		21	56	322	83
unknown	6		1	2		3
ongoing	153	1	12	15	86	39
live infant was born without birth defects	75		11	11	40	13
spontaneous abortions	2		2			
live infants with birth defects	3			2	1	

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before initiation of the study.

GSK plans to continue the Registry for 5 years. Summary reports will be written annually and will be submitted with the Periodic Benefit-Risk Evaluation Report for *Boostrix* if applicable. A final report will be written and submitted after 5 years. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

Summary results of observational studies that are designed to inform the safety or effectiveness, including cost-effectiveness, of GSK vaccines/products as used in ordinary clinical practice are publicly registered within 8 months of completion of the analysis.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis.

REFERENCES

Anderson AN, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *British Medical Journal* 2000;320:1708-1712.

CDC, 2012: source Website:.cdc.gov/pertussis/clinical/treatment.html Accessed 20 September 2013.

CDC. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months --- Advisory Committee on Immunization Practices (ACIP), 2011. MMWR; 60(41);1424-1426.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for persons aged 0 through 18 years and adults aged 19 years and older--United States, 2013: MMWR Surveill Summ. 2013 Feb 1;62 Suppl 1:1.

Centers for Disease Control and Prevention (CDC). Birth Defects and Genetic Diseases Branch 6-digit code for reportable congenital anomalies. Revised 2008. Internet site: cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf.

Centers for Disease Control and Prevention (CDC). Birth defects. Internet site: cdc.gov/ncbddd/birthdefects/facts.html. Accessed: 27 November 2013(b).

Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization ractices (ACIP). MMWR Recomm Rep. 2011(d); 60(2): 1-64.

Centers for Disease Control and Prevention (CDC). Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months - Advisory Committee on Immunization Practices (ACIP), 2011. MMRW. 2011(a); 60(41): 1424-1426.

Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. MMWR. 2013(a); 62(7): 131-135.

Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations: Reports from the Collaborative Perinatal Project. Birth Defects Original Article Series 1975; Vol. 11, No. 10.

Conseil Supérieur de la Santé (CSS). Fiches de vaccination éditées par le CSS (CSS 9110). Vaccination anticoquelucheuse ; vaccination de l'adulte (2013) http://health.belgium.be/eportal/Aboutus/relatedinstitutions/SuperiorHealthCouncil/publications/factsheetsvaccination/13038500_FR?ie2Term=center&ie2section=9130&fodnlang=fr ; accessed on 25 November 2013

Correa-Villasenor A, Cragan J, Kucik J, O'Leary L, Siffel C, Williams L. The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the Centers for Disease Control and Prevention. Birth Defects Research (Part A) 2003;67:617-24.

Czeizel AE, Rockenbauer M. Tetanus toxoid and congenital abnormalities. Int J Gynecol Obstet. 1999; 64: 253-258.

Ellish NJ, Saboda K, O'Connor J, et al. A prospective study of early pregnancy loss. Hum. Reprod. 1996; 11: 406-12.

Fenster L, Hubbard AE, Windham GC, Waller KO, Swan SH. A prospective study of work-related physical exertion and abortion. *Epidemiology* 1997;8:66-74.

Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheriapertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol. 2011; 204: 334.e-5.

Joint Committee on Vaccination and Immunization (JCVI). JVCI meeting on pertussis immunization: August 2012. Draft minutes of discussions on the immunization of pregnant women against pertussis. Published 28 September 2012. http://transparency.dh.gov.uk/2012/09/28/jcvi-pertussis/ ; accessed on 08 August 2013.

Kennedy DL, Uhl K, Kweder SJ. Pregnancy exposure registries. Drug Safety. 2004; 27: 215-228.

Khattak S, K-Moghtader G, McMartin K, Barrera M, Kennedy D, Koren G. Pregnancy outcome following gestational exposure to organic solvents. *Journal of the American Medical Association* 1999;281:1106-1109.

Ministerio de Salud, Presidencia de la Nación, alert dated 25 January 2012. Whooping Cough: Increased cases and deaths. Internet site: msal.gov.ar/images/stories/alertas_epidemiologia/2012/alerta-1-tos-convulsa-2012.pdf; accessed on 28 August 2013.

Mitchell AA, Cottler LB, Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. *American Journal of Epidemiology* 1988;123:670-676.

New Zealand Pharmaceutical Management Agency (PHARMAC). Decision to amend the diphtheria, pertussis and tetanus vaccine (Boostrix) listing, 12 December 2012. Internet site: pharmac.govt.nz/2012/12/12/; accessed on 28 August 2013.

Osborn JF, Cattaruzza MS, Spinelli A. Risk of spontaneous abortion in Italy, 1978-1995, and the effect of maternal age, gravity, marital status, and education. *American Journal of Epidemiology* 2000;151:98-105.

Shakib JH, Korgenski K, Sheng X, Varner MW, Pavia AT, Byington CL. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: Pregnancy and infant health outcomes. J Pediatrics. 2013; 163: 5 (1422-1426.e4).

Silveria CM, Caceres VM, Dutra MG, Lopes-Camelo J, Castilla EE. Safety of tetanus toxoid in pregnant women: a hospital-based case-control study of congenital anomalies. Bull World Health Organ. 1995; 73: 605-608.

Talbot EA, Brown KH, Kirkland, KB, Baughman AL, Halperin SA, Broder KP. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine. 2010; 28: 8001-8007.

Technical Advisory Group (TAG) on Vaccine-preventable Diseases. Vaccination: a shared responsibility. Quito, Ecuador 3-5 July 2013.

Terranella A, Asay GR, Messonnier ML, Clark TA, Liang JL. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis. Pediatrics. 2013; 131(6): e1748-1756.

Wilcox AJ, Horney LF. Accuracy of spontaneous abortion recall. *American Journal of Epidemiology* 1984;120:727-733.

Wilcox AJ, Treloar AE, Sandler DP. Spontaneous abortion over time: comparing occurrence in two cohorts of women a generation apart. *American Journal of Epidemiology* 1981;114:548-553.

Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Sclatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early ls of pregnancy. *New England Journal of Medicine* 1988;319:189-194.

Wilcox AJ. Surveillance of pregnancy loss in human populations. *American Journal of Industrial Medicine* 1983;4:285-291.

Windham GC, Von Behren J, Fenster L, Schaefer C, Swan SH. Moderate maternal alcohol consumption and risk of spontaneous abortion. *Epidemiology* 1997;8:509-514.

Yenlik A. Zheteyeva Adverse event reports after tetanos toxoid, reduced diphteria toxoid, and acellular pertussis vaccines in pregnant woman. Am J Obstet Gynecol 2012;207:59.e1-7.

BOOSTRIX® (TETANUS TOXOID, REDUCED DIPHTHERIA TOXOID AND ACELLULAR PERTUSSIS VACCINE, ADSORBED)

PREGNANCY REGISTRY

PASS STUDY No. 201327

CUMULATIVE REPORT

03 MAY 2005 THROUGH 02 AUGUST 2015

1 INTRODUCTION

Although there is no evidence of teratogenicity from reproductive toxicology studies of *Boostrix*, GlaxoSmithKline (GSK) manages this registry as part of an ongoing program of safety monitoring. This registry is considered essential because of the potential for vaccine exposure during pregnancy.

The purpose of this Registry is to detect and describe any adverse pregnancy outcomes, including teratogenicity in pregnancies intentionally or unintentionally exposed to *Boostrix*. The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the limited data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing program to assess the safety of *Boostrix* in pregnant women.

This is a prospective, voluntary, observational, program of enhanced pharmacovigilance. Patient confidentiality is strictly maintained. The purpose of the Registry is to prospectively collect data describing exposure to *Boostrix* within 28 days before pregnancy or anytime during pregnancy, potential confounding factors (such as exposure to other medications, infections, family history of congenital anomalies, etc), and information related to the outcome of the pregnancy. The Registry is intended to provide an early signal of potential risks in advance of results from formal epidemiologic studies. Registry data are used to supplement animal toxicology studies and to assist clinicians in weighing the potential risks and benefits of treatment for individual patients.

The *Boostrix* Pregnancy Registry is maintained by Vaccine Clinical Safety and Pharmacovigilance in GSK. This analysis includes data from all Registry cases received from spontaneous and post-marketing sources in the United States. The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance at the time of US approval. Following new European Union Guidelines on Good Pharmacovigilance Practice (Module VIII), which became into effect on 2 July 2012, Pregnancy Registries are to be considered Post Approval Safety Studies (PASS). On 01 April 2014, this Pregnancy Registry has been re-classified as a post-authorization safety study (PASS) to collect data on pregnancy outcomes and new-born health status outcomes following vaccination with *Boostrix* during pregnancy. These data are reviewed periodically to identify any signals where the use of the vaccine might be associated with adverse events. Of note, the searches actually done in GSK safety database for *Boostrix* Pregnancy registry (Post-marketing cases) are based on the study e-track number (201327) since its conversion to PASS study.

To increase the rate of pregnancy registration (accrual), a web page (http://pregnancyregistry.gsk.com/boostrix.html) has been created with instructions for enrolling patients in the Registry. In addition, GSK had requested that the FDA post a link to this web page on their Pregnancy Registry Website. In response to a 2008 request from FDA to facilitate enrolment, GSK initiated a dedicated toll-free telephone number [redacted] at which US-based callers can receive assistance in the registration of pregnancies. Notice of this new toll-free number was posted on the GSK web page in January 2009; the new toll-free number was added to the United

States Prescribing Information in early 2009. It is unknown what, if any, effects these measures will have on Registry enrolment.

This report contains a description of all prenatal exposures to *Boostrix* in the United States (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 (e.g. foetal ultrasound, serum markers). Because the outcome of the pregnancy is unknown when the prenatal exposure is reported, follow-up to determine the pregnancy outcome is required. Prospective reporting of ongoing pregnancies prior to knowledge of the pregnancy outcome reduces bias and permits estimation of the risk of birth defects and other adverse pregnancy outcomes. Retrospective reports, which are reported in this periodic update, are data acquired after the outcome of the pregnancy is known or after the detection of a congenital malformation on prenatal test. However, retrospective reports are likely to be biased toward the reporting of more unusual and unfavorable outcomes and are less likely to be representative of the general population [Mitchell, 1988 and Wilcox, 1984]. Therefore, the inclusion of such reports for calculation of probability (risk) of adverse pregnancy outcomes is inappropriate. The purpose of summarizing the retrospective reports is to assist in the detection of any unusual patterns that may exist among the reported outcomes.

Pregnancy and birth outcomes in infants born to women who did or did not receive Tdap vaccine during pregnancy have been assessed in a retrospective cohort study [Shakib, 2013]. The study, ending in 2009, was performed before Tdap administration during pregnancy was recommended (From May 2005 through August 2009). The authors concluded that there was no increase in adverse outcomes in infants born to women receiving Tdap compared to infants of women in the control group.

In 2011, the Advisory Committee on Immunization Practices (ACIP) reviewed published and unpublished data from the Vaccine Adverse Event Reporting System, Sanofi Pasteur (Adacel) and GSK (*Boostrix*) pregnancy registries, and small studies [Talbot, 2010; Gall, 2011] investigating the administration of combined reduced antigen content tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnancy [CDC, 2011a]. ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events (AEs) and outcome in pregnant women who received Tdap and that the few serious AEs reported were unlikely to have been caused by the vaccine. Both tetanus- and diphtheria-toxoid vaccines (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic [Silveria, 1995; Czeizel, 1999]. From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks gestation is preferred to minimize the risk for any low-frequency AEs and the possibility that any spurious association might appear causative [CDC, 2013a; Terranella, 2013].

It is generally accepted that inactivated vaccines pose no risk to the pregnant or lactating woman [CDC, 2011d]. In the absence of supporting data, *Boostrix* should only be administered to pregnant women when clearly needed, and when the possible benefit outweighs the possible risks to the fetus. In the US, Tdap maternal immunization is recommended by ACIP [CDC, 2013a].

In addition, following the New Zealand Ministry of Health's recommendation to use Tdap during pregnancy an observational study was launched in February 2014, sponsored by the University of Auckland. This is a three-component observational PASS study that will collect data both retrospectively and prospectively. Data for all pregnant women and their infants in New Zealand between 2009 and 2013 will be obtained and pertussis vaccine exposure during pregnancy verified (part one). Two sub-studies will actively follow mothers who received Tdap during pregnancy with one also following their infants for one year after birth (Part two and three). Preliminary results were reported for study part 2 and study part 3 of the EPI-PERTUSSIS-025 VS NZ SUPP (201024), and are briefly presented in this report; no particular trend or safety concern was identified from the review of the SAEs from the PIPS study 2 and 3 Preliminary Maternal Outcomes reports.

Currently, there are 4 clinical trials planned to evaluate the use of *Boostrix* in pregnant women; those studies are further presented in section 4 of this report. However, there are currently no available data regarding the immunogenicity of *Boostrix* in pregnant women, the effectiveness of IgG transplacental antibody transfer to neonates, and the subsequent safety and immunogenicity of the routine pediatric vaccination schedule in such infants.

3 METHODS

3.1 Registration and follow-up

Reporting of exposed pregnancies is voluntary. Since the initiation of the Registry in 2005, GSK has taken several measures to increase the rate of pregnancy registration (accrual). A GSK Registry web page (http://pregnancyregistry.gsk.com/twinrix.html) was created on 07 March 2007 with instructions for enrolling patients in the Registry and GSK has requested that the FDA post a link to this web page on their Pregnancy Registry Website In response to a 2008 request from FDA to facilitate enrolment, GSK initiated a dedicated toll-free number [redacted] where callers can receive assistance in the registration of pregnancies. Notice of this new toll-free number was posted on the GSK web page in January 2009; the new toll-free number was added to the United States Prescribing Information in early 2009. The Prescribing Information and GSK Registry website each give a brief summary of the purpose and intent of the Registry, along with telephone and fax contact information. It is unknown what, if any, effects these measures have on Registry enrolment.

When the pregnancy is reported prospectively, the Registry collects registration data from the reporter through telephone interview or a short registration form. For a pregnancy report to be considered eligible for registration, certain data must be available. The required data include:

- Documentation that *Boostrix* was administered within 28 days before pregnancy or anytime during pregnancy;
- Confirmation that the pregnancy is being prospectively reported;
- Confirmation that the subject is a US resident (US case);
- Identification of a healthcare provider (name, address, and telephone number);

- A patient identifier that will allow follow-up to be obtained so that the pregnancy outcome can be ascertained.

Follow-up is sought by telephone contact or a form mailed to the health professional. Information about maternal events throughout the pregnancy, pregnancy outcome, and neonatal health is requested. Additional follow-up is not sought from subsequent healthcare providers.

A report of an exposure is closed when clear information is received about exposure to *Boostrix* and pregnancy outcome determination, or when the patient is lost to follow-up. A patient is considered to be lost to follow-up when the Registry does not receive the minimum information, or if the reporting healthcare provider can no longer locate the patient.

3.2 Classification of Outcomes

This Registry uses the term 'birth defects' for outcomes sometimes referred to as 'congenital anomalies'. Pregnancy outcomes include spontaneous abortion (pregnancy loss before 20 weeks gestation), fetal deaths/stillbirths (loss at or after 20 weeks gestation), elective/therapeutic abortions and live births. The presence or absence of birth defects is evaluated within each of the preceding outcome categories.

This Registry adopts a definition of birth defect as any structural or chromosomal abnormality diagnosed before 6 years of age. The Registry employs a conservative approach of including all morphologic anomalies, including minor ones, as birth defects.

To provide consistency in the definitions of major defects in this Registry, CDC MACDP criteria are used for the classification of defects [CDC, 2008; Correa-Villasenor 2003]. Some of the conditions excluded from the MACDP criteria for major structural defects may actually have major clinical, functional, or genetic significance. Therefore, minor malformations not appearing in the CDC inclusion list may be classified as birth defects in this Registry. In addition, CDC guidelines disqualify as defects those findings that are present in infants delivered at less than 36 weeks of gestation and are attributable to prematurity itself, such as a patent ductus arteriosus or inguinal hernias. Infants with infectious conditions (e.g., neonatal sepsis) or isolated biochemical abnormalities (e.g., hyperbilirubinemia) are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized congenital abnormality. All other congenital abnormalities are included in the 'birth defects' category, regardless of whether the neonate is delivered alive, including structural defects in neonates delivered prior to 20 weeks of gestation or weighing less than 500 g.

3.3 Exclusions

For this Registry, emphasis is placed on prospective registration of pregnancies. Although the Registry encourages reporting of all known prenatal exposures to *Boostrix*, not all reports are appropriate for inclusion in the analysis of data. Retrospective reports from patients and healthcare providers are also received in the Registry. These outcomes are reported and are helpful for detecting a possible pattern

of defects. However, there is no denominator from which risk can be calculated for the retrospective reports.

In addition, cases originating from US (inclusion criteria) will be analysed and subdivided between prospective and retrospective reports in the context of this yearly pregnancy registry update.

3.4 Analysis

Gestational weeks are counted from the date of the last menstrual period. The second trimester is considered to begin at week 14, and the third trimester begins at week 28. The presence or absence of birth defects or other abnormalities is evaluated within each of the pregnancy outcome categories described in section 3.2.

Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for exposures within 28 days before pregnancy with no subsequent administration during pregnancy. Reports of multiple exposures (i.e., multiple administrations of *Boostrix*) during a pregnancy are classified by the earliest trimester of exposure. When exposure occurs before and after conception, the exposure is classified by the dose administered after conception.

The majority of spontaneous abortions occur early in pregnancy [Wilcox, 1981; Wilcox, 1983; Ellish, 1996]. If spontaneous abortions were to be evaluated as an outcome of interest, it would be essential to enroll pregnancies as soon as possible after vaccination with *Boostrix*. Because enrollment and recognition of pregnancy would occur at various times, it would be virtually impossible to meaningfully evaluate the effects of *Boostrix* on pregnancy loss [Kennedy, 2004].

The risk in the general population of all birth defects meeting CDC criteria is approximately 3% (1 of 33) of live births [Centers for Disease Control and Prevention, 2013b]. The estimated risk cited in the medical literature varies because of differences in case definitions, populations sampled and ascertainment methods. The Collaborative Perinatal Project, using a broader case definition and prospective ascertainment, reports a frequency of 5% to 7% [Chung, 1975]. Most major structural defects originate during the first trimester of pregnancy, which is the critical time for organogenesis [Centers for Disease Control and Prevention, 2013b]. For such defects, exposures occurring in the second or third trimester are not likely to be causally associated. However, for the sake of completeness and to enable the assessment of possible increases in the frequency of birth defects, all defects will be included in the periodic summary reports of this Registry.

Studies have shown that the risk of spontaneous abortion is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 10% to 22% [Wilcox, 1981; Wilcox, 1983; Wilcox, 1988; Fenster, 1997; Windham, 1997; Khattak, 1999; Anderson, 2000; Osborn, 2000].

Criteria for review of a specific individual report include:

- ✓ Is the timing of the vaccination with *Boostrix* commensurate with the ontogenetic development of the organ(s) affected by the abnormalities?

- ✓ Is there another known or likely cause (e.g., pre-existing genetic or chromosomal defect or exposure to a known teratogen)?
- ✓ Is the congenital abnormality not previously described (i.e., is it new to medical science)?
- ✓ Is there a unique constellation of defects (i.e., is there a new syndrome)?

Criteria for review of aggregate data include:

- ✓ Is there a deviation from the expected frequency of all defects indicating an increase in the overall risk of defects?
- ✓ Is there a deviation from the expected frequencies of individual defects?
- ✓ Is there uniqueness (e.g., a pattern) of the abnormalities that is suggestive of a common etiology?

While the Registry is to be limited to prospective reports, some pregnancy exposures are reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports. In general, retrospective notification of outcomes following exposure to drugs or vaccines is biased toward reporting the severe and unusual cases and is not reflective of the general experience with the drug. Information about the total number of exposed pregnancies, i.e., the pool of exposures from which the retrospective reports arise, is unknown; therefore, incidences of outcomes cannot be calculated from these data.

Calculation of risk of spontaneous pregnancy losses overall should not be attempted and cannot be compared to the incidence in the general population because pregnancies in this Registry are reported at variable and, occasionally, imprecise times. Also, pregnancy losses occurring early in gestation may not be recognized and/or reported.

In 2011, the US was the first country to recommend the use of Tdap in pregnant women who had previously not been vaccinated with Tdap in adulthood and this advice has been updated to recommend offering women Tdap in every pregnancy irrespective of the patient's prior history of vaccination with Tdap [Centers for Disease Control and Prevention, 2013]. The optimal timing for Tdap administration was proposed at 27 weeks through 36 weeks gestation [CDC, 2012]. Following the initial recommendation in the US by the ACIP on June 22, 2011 [CDC, 2011], temporary immunization programmes for pregnant women with a Tdap combination vaccine have been implemented in the UK, New Zealand, Israel, Mexico, Brazil, Colombia, Uruguay, Panama, Costa Rica and Argentina [Joint Committee on Vaccination and Immunization (JCVI, 2012; Pharmaceutical Management Agency (PHARMAC), 2012; Ministerio de Salud, 2012; TAG, 2013]. Since 2013, vaccination during pregnancy is also recommended in Belgium between the 24th and 32nd week of pregnancy [CSS, 2013].

3.5 Potential Biases

This Registry is a prospective cohort study. Active enrolment of a valid internal comparison group is not feasible. Therefore, background risks from existing, external

systems (e.g., the National Birth Defects Prevention Network and the National Center for Health Statistics) are used. The potential limitations of comparisons between Registry and background data depend upon the event(s) being compared and will be discussed on an ad hoc basis in the relevant periodic Registry reports.

Potential sources of biases are described below:

As reporting of pregnancies is voluntary, it is possible that even among prospectively-reported pregnancies there could be bias in type of pregnancies which are reported. For example, high-risk pregnancies may be more likely to be reported.

The calculation of risk, which does not include spontaneous abortions or voluntary terminations for which no defects have been reported, may introduce bias. It is unknown what proportions of these pregnancies consist of potentially normal outcomes versus congenital abnormalities. GSK attempts to obtain information on anomalies detected at the time of the outcome, but this may not be known to the reporting physician.

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.

4 DATA

Until 31 March 2014, a total of 660 pregnancies involving exposure to *Boostrix* in the US had been prospectively and retrospectively reported since the initiation of this pregnancy registry on 03 May 2005 (spontaneous reports). As of 01 April 2014 this registry has been converted into a PASS. The number of post-marketing reports involving exposure to *Boostrix* during pregnancy in United States includes 248 prospective and retrospective reports retrieved from 01 April 2014 to 02 August 2015.

Considering that since April 1st, 2014 this Registry has been converted into a PASS the analysis has been performed separately, including cases coded as spontaneous cases until March 31st, 2014 and then, as post marketing cases from April 1st, 2014 to August 2nd, 2015. Of note, difference in terms of spontaneous US pregnancy reports compared to last year update might be due to the fact that some cases were updated as regards their outcomes or corrected after follow-up data. It is important to note that the safety database from which data are retrieved is an in-house 'living' database and is subject to updates and corrections depending on information provided by GSK local country offices. These constant updates may result in discrepancies between consecutive queries of the safety database.

4.1. Prospective reports received from the US Registry/PASS

Reported cases until March 31st, 2014:

Until 31 March 2014, a total of 644 pregnancy reports involving exposure to *Boostrix* in the US had been prospectively reported since the initiation of this pregnancy registry on 03 May 2005.

Among the 644 prospective reports, 84 had a known outcome. Of the remaining 560 reports, 517 pregnancies were lost to follow-up or had an unknown outcome and 43 pregnancies were ongoing at the time of last contact.

Exposure to *Boostrix* for the 84 pregnancy reports with known outcomes occurred during the first (n=19), second (n=16), and third trimesters (n=49). Of these, there were:

- Seventy nine (79) live infants without apparent birth defects
- Two (2) reports of spontaneous abortions; one in a 30 years old patient at 7 weeks of gestation with exposure to *Boostrix* during the first trimester, and one in a 19 years old patient at 11 weeks of gestation with exposure to *Boostrix* during first trimester.
- Three (3) live infants were born with reported birth defects; of which 2 mothers were exposed during the second trimester and one during the third trimester. The 3 cases are briefly described below.

    - ✓ One 25 years old female was vaccinated with *Boostrix* at 19 weeks gestation. The physician reported that the baby had an unspecified congenital anomaly.
    - ✓ One 34-year-old female neonate, whose mother was vaccinated with *Boostrix* during the second trimester (5 month gestation), was diagnosed with plagiocephaly at the age of two months. The outcome of the plagiocephaly was reported as unknown.
    - ✓ One male neonate, who's 23-year-old mother was vaccinated with *Boostrix* during the third trimester (29 weeks gestation), was diagnosed at birth with a mild left foot ligament deformity, which was considered unrelated to *Boostrix* by the reporting physician.

Reported cases from April 1st, 2014 to August 2nd, 2015:

The number of pregnancies reported involving exposure to Boostrix in United States includes 246 prospective reports retrieved from 01 April 2014 to 02 August 2015.

Out of those 246 prospective pregnancy cases, there were 72 pregnancy reports with known outcomes, all reported live infant with no apparent congenital anomaly. Of the remaining 174 reports, 94 were lost to follow-up or had an unknown outcome and 80 were ongoing at the time of last contact.

Exposure to *Boostrix* in the 72 pregnancy reports with known outcomes occurred before pregnancy (n=1), during the second trimester (n=3), and third trimesters (n=67) respectively. In the remaining case, exposure to *Boostrix* occurred at an unspecified moment.

Of note, in one case, a patient of unspecified age experienced "apparent death"; she was vaccinated with *Boostrix* vaccine at 7 months of pregnancy (third trimester). At an unspecified time after vaccination the patient reported that she "nearly died" because she felt sick after vaccination. No clinical or diagnostic details are available and the event was not medically verified. The case was reported as resolved.

4.2 Description of retrospective reports received from the US Registry/PASS

For sake of completeness pregnancy reports received retrospectively were also reviewed and analyzed in this report.

Reported cases until March 31st, 2014:

During the period 03 May 2005 to 31 March 2014, a total of 16 retrospective pregnancy reports from the Registry were received in US. From these, 14 reports had a known pregnancy outcome and 2 subjects were lost to follow-up.

From the 14 known pregnancy outcomes:

- Nine (9) reports included a live infant without congenital anomaly.
- Two (2) reports of stillbirth reported without congenital anomaly; in one case, a 20 years old patient experienced placental abruption which ended with stillbirth around week 37 of gestation, a few hours after being exposed to Tdap vaccine, and in the second case, a 27 years old patient experienced stillbirth (46 days after being vaccinated with Tdap vaccine) around 22 week of gestation, unknown cause.
- Three (3) reports of live infant with congenital anomaly, of which one describing a 31-year-old woman that received *Boostrix,* and Adacel during first trimester, and who delivered a neonate born with pulmonary hypertension and arterial venous malformation, the neonate remained hospitalized and ultimately died of unknown cause. The second report pertained to one case describing a 15-year-old mother who received an unspecified dose of *Boostrix* and a non-GSK HPV vaccine at 8 weeks of gestation. After unspecified weeks of gestation, the neonate was delivered and presented gastroschisis. The third case described a neonate who was exposed to Tdap during unspecified trimester of pregnancy and who experienced laryngotracheomalacia after birth (unspecified gestational age). No other information is available.

Reported cases from April 1st, 2014 to August 2nd, 2015:

There have been 2 retrospective post marketing cases reported in US from 01 April 2014 to 02 August 2015.Those cases are summarized as follows;

In one case, the patient received *Boostrix* in Dec 2014 at week 3 of the pregnancy (first trimester of pregnancy), pregnancy is still ongoing. In the second case, the patient received *Boostrix* at week 28 of the pregnancy (third trimester of pregnancy); the pregnancy resulted in a live birth with no apparent congenital anomaly after 39 weeks gestation.

4.3 Description of reports received from other countries

In addition to the reports of pregnancy received from the United States, for sake of completeness, GSK's spontaneous reporting system also provides the Registry with reports of *Boostrix*-exposed pregnancies from other countries.

Cumulatively, there were 132 pregnancy reports (22 retrospective and 110 prospective) received until 02 Aug 2015 from the following countries: Argentina (n=12), Australia (n=19), Belgium (n=21), Brazil (n=25), Canada (n=1), Colombia (n=3), Costa Rica (n =1), Germany (n=7), Ireland (n=3), Israel (n=1), Republic of Korea (n=10), Netherlands (n=2), New Zealand (n=5), Saudi Arabia (n=1), Slovakia (n=1),Spain(n=2),Sweden (n=1), Switzerland (n=10), Thailand (n=1), United Kingdom (n= 6).

Reported Prospective Worldwide Cases until August 2nd, 2015

Among the 110 prospective pregnancies cases, 32 had a known outcome (30 live births, 1 spontaneous abortion without apparent congenital anomaly and 1case of live birth with a congenital anomaly, respectively described below). Of the remaining 78 reports, 52 pregnancies were lost to follow-up or had an unknown outcome, and 26 pregnancies were ongoing at the time of last contact.

Spontaneous abortion: 1 report:

In one case reported from Belgium, a12-year-old female patient was vaccinated with *Boostrix* and was not aware that she was pregnant. Her last menstrual period occurred on an unspecified date and estimated date of delivery was not provided. She was exposed to the vaccine during the first trimester. At 6 weeks of pregnancy, she experienced miscarriage. It was not explained whether it was a planned/induced termination or a spontaneous abortion.

Live infant with a congenital anomaly: 1 *report*

In one case reported from Belgium, a 34-year-old female patient who was exposed to *Boostrix* vaccine during the third trimester delivered a live male diagnosed with a congenital anomaly approximately 5 days after vaccination. The neonate, born via a normal vaginal delivery was diagnosed with trigonocephaly. Subsequently, the neonate underwent surgical correction.

Reported Retrospective Worldwide Cases until August 2nd, 2015:

Among the 22 retrospective pregnancies cases, 20 cases had a known outcome (11 live births, 1 case of spontaneous abortion without apparent congenital anomaly, 2 stillbirths and 6 cases of live birth with a congenital anomaly; those cases with adverse outcomes are respectively described below). Two (2) remaining reports were lost to follow-up.

- Spontaneous abortion: 1 report

A case reported from Germany described the occurrence of late abortion around 21 weeks of gestation in a 34-year-old female patient who was vaccinated with *Boostrix* 2 weeks before the abortion.

- Stillbirth: 2 reports

Both cases of stillbirth were reported from Belgium. In the first case, a 25-year-old female patient who was vaccinated with *Boostrix* around 30 weeks gestation discovered that her baby wasn't moving anymore and intra-uterine death was diagnosed 5 days after vaccination. She gave birth to a death male infant by vaginal delivery. No macroscopic abnormalities in foetus, placenta or umbilical cord were

observed. Additional examination of placenta revealed low funiculitis and focal choriamnionitis. It was also reported that1 day after *Boostrix* vaccination, the patient experienced influenza like syndrome.

In the second case, a patient from unspecified age experienced intra-uterine death at an unknown date after receiving *Boostrix*. The pregnancy ended in a stillbirth around 22 weeks gestation with no apparent congenital anomaly. No additional details provided.

- Live infant with a congenital anomaly: 6 reports

The 6 retrospective reports outside US of live infant with a congenital anomaly are presented as follows;

- In one case reported from Korea, a 36 or 37-year-old female patient received unspecified dose of *Boostrix* during pregnancy at 35 weeks gestation. At unknown time after vaccination she went to the hospital and foetal ultrasound examination revealed some abnormal findings. Emergency caesarean section was performed and the neonate was born with pleural effusion and cardiomegaly.
- In a case reported from Belgium, a female patient of unspecified age was exposed to *Boostrix* between 28 to 32 weeks gestation. The pregnancy was normal and the neonate was delivered by vaginal delivery. A few hours later the neonate experienced convulsions and encephalitis. The reporting physician did not consider the events as related to the mother's vaccination with *Boostrix.*
- In another case reported from Belgium, a female patient of unspecified age was exposed to *Boostrix* during 36th week of pregnancy and delivered a full-term male baby. Around birth, the neonate experienced epilepsy (severe neonatal convulsions) and cerebral encephalopathy. The baby also presented cardiopathy (abnormal pulmonary venous return in the heart and inter auricular communication). He was treated with phenobarbitone. Persistent sequelae of encephalopathy with important peripheral and axial hypertonia were noted. The physician considered encephalopathy and epilepsy as possibly related to vaccination with *Boostrix*.
- In one case reported from Switzerland, a 28-year old female patient was exposed to Boostrix during the 1st trimester. At 38 weeks gestation, the neonate was delivered by vaginal delivery. The neonate was born with a congenital renal agenesis as he only had the right kidney. The regulatory authority reported that the event was possibly related to the mother's vaccination with *Boostrix*.
- In one case reported from United Kingdom, a 38 year old female patient, who received *Boostrix* in the third trimester of pregnancy, gave birth to a baby for whom no malformations or anomalies were diagnosed around birth. At six months age, the baby experienced urinary tract infection and was then found to have only one kidney.
- In one case of exposure to *Boostrix* during pregnancy reported from Germany, prenatal examinations revealed fetal vitium cordis (single ventricle, atrioventricular septum defect with double outlet right ventricle, and persistent left superior vena cava). Thirty minutes after birth at term, the neonate was

transferred to a neonatologic intensive care unit due to cyanotic condition and congenital vitium cordis. During the first hour of life, the baby was treated with Dinoprostone (Minprostin). Echocardiogram showed mesocarida with dextroversion, unbalanced atrioventricular canal with functional univentricular heart, double outlet right ventricle (DORV) with transposition of big vessels, pulmonary artery stenosis, duct of botallo patency with continuing shunt, pulmonary vena flow into left atrium, persistent left superior vena cava (LPVCS), small cross vena and mild AV valve insufficiency. He received alprostadil and vitamin K. According to verbal follow-up information the baby underwent surgery for vitium cordis and was in good condition.

4.4 Description of reports received from clinical trials

For completeness, pregnancy reports received from clinical trials were also reviewed. Until 02 August 2015, 28 pregnancy exposures throughout clinical trials involving *Boostrix* were reported worldwide.

Twenty- two (22) subjects were vaccinated before pregnancy and 6 during the first trimester of pregnancy.

Of these 28 reports, 15 resulted in a live infant without any apparent congenital anomaly, 4 resulted in spontaneous abortion without apparent congenital anomalies, 1 case was a case of elective termination and 8 subjects were lost to follow-up. In 4 out of the 5 pregnancy reports with an adverse outcome, vaccination occured well before pregnancy onset. Of note, within the 15 cases reported with “live infant born without any apparent congenital anomaly», there was 1 case in which the neonate was born prematurely and experienced neonatal respiratory distress syndrome.

The 5 cases reporting adverse pregnancy outcomes are briefly described here below:

- Six months after receiving *Boostrix* vaccine, a 17 years old patient was found to be pregnant via a serum pregnancy test. She experienced vaginal spotting for two weeks and vomiting. An obstetric ultrasound on 18 August 2003 revealed endometrial thickening and early intrauterine pregnancy. On the same day, after five weeks of gestation, the subject had a spontaneous abortion. The investigator considered there was no reasonable possibility that the spontaneous abortion may have been caused by the investigational product.

- Seven days after the Tdap vaccine, a 28-year-old patient was reported to be pregnant. Abstinence was used as contraception method at time of the study start. The subject was exposed to the vaccine during 1st trimester of pregnancy. 16 days after the 1st dose of blinded vaccine and after 6 weeks of pregnancy, the subject experienced a miscarriage/spontaneous abortion. The investigator considered that there was no reasonable possibility that the miscarriage may have been caused by investigational product.
- Six months after Tdap vaccine, a 27-year-old patient underwent spontaneous abortion after 9 weeks of pregnancy. The investigator causality was unknown at the time of reporting.

- Six months after the 1st dose of *Boostrix*, a 20-year-old patient experienced incomplete abortion after the 8 weeks of pregnancy. The subject was hospitalized and treated with Ringer lactate solution, ceftriaxone, ketorolac trometamol, ciprofloxacin, metronidazole and diclofenac. Curettage was done. The investigator considered that there was no reasonable possibility that the incomplete abortion may have been caused by the vaccinations previously administered to the patient (MenACWY-TT, *Boostrix* and *Cervarix*).
- Five months after the 2 dose of *Cervarix*, 6 months after the 1 dose of MenACWY-TT and 6 months after *Boostrix* this 18-year-old patient underwent elective abortion after 3 weeks of gestation. There was no report of any pathology of the foetus. The parents of the patient requested the abortion.

There are currently 4 clinical trials being planned to evaluate the use of *Boostrix* in pregnant women; this is due to the fact that multiple countries have recently instituted recommendations regarding the use of Tdap vaccine in pregnant women and given that the use of Boostrix in pregnant women has also been listed as a specific "Missing Information" in the Boostrix EU RMP (approved by EMA and PEI authorities); those studies are further presented below;

- ✓ [DTPA (BOOSTRIX)-047] (116945) :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.Primary objective of this study is to demonstrate that the maternally transferred antibodies against pertussis in the dTpa Group is superior to that in the Control Group in terms of geometric mean concentrations (GMCs) for the pertussis antibodies, in the cord blood sample. In addition, safety of a single dose of Boostrix in pregnant women, administered during 27-36 weeks of gestation,will be assessed in terms of the outcomes of pregnancy and pregnancy-related adverse events of interest/neonate-related events up to two months post-delivery.
- ✓ Infants born to mothers enrolled in study 047 will be followed-up in 2 separate clinical studies: DTPA (BOOSTRIX)-048 PRI (201330) and DTPA (BOOSTRIX)-049 BST: 048 (201334). Infants will be given the primary vaccination course of Infanrix hexa in DTPA (BOOSTRIX)-048 PRI study and a booster dose in the second year of life in DTPA (BOOSTRIX)-049 study in order to generate safety and immunogenicity data. The impact of maternal Boostrix vaccination on immune response of infants to primary and booster DTPa vaccination will also be evaluated in these studies. These studies will also collect SAE/AEs. Study 049 will assess safety of the booster dose of the same vaccines in the second year of life which also includes an assessment of the neurodevelopmental milestones.
- ✓ EPI-PERTUSSIS-037 VS BR (203153); A post-marketing, observational, retrospective, cohort study to assess the safety of BoostrixTM (Tdap) when administered during pregnancy in a maternal immunization program in Brazil. The aim of this retrospective study is thus to investigate any potential increased risks of specific pregnancy-related adverse events (AEs) and AEs in neonates following the routine maternal Boostrix vaccination during pregnancy. The AEs of interest are those reported more frequently in the literature as important markers of maternal and neonatal risks, for which a theoretical concern exists and from which it would be feasible to obtain the required data. The events that are more commonly reported in the third trimester of pregnancy have been chosen as

primary endpoints and corresponds to the following; risk of gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage (vaginal or post-partum) in a cohort of women following vaccination with Boostrix as part of the maternal immunization program in Brazil (Exposed cohort) with a historical cohort of unvaccinated pregnant women before the implementation of this immunization program (Unexposed cohort).The risk of preterm birth and small for gestational age in neonates born to subjects in the exposed cohort and to subjects in the unexposed cohort will also be compared.

However, there are currently no available data regarding the immunogenicity of *Boostrix* in pregnant women, the effectiveness of IgG transplacental antibody transfer to neonates, and the subsequent safety and immunogenicity of the routine paediatric vaccination schedule in such infants.

Following the New Zealand Ministry of Health's recommendation to use Tdap during pregnancy an observational study was launched in February 2014, sponsored by the University of Auckland. This is a three-component observational PASS study that will collect data both retrospectively and prospectively. Data for all pregnant women and their infants in New Zealand between 2009 and 2013 will be obtained and pertussis vaccine exposure during pregnancy verified (part one). Two sub-studies will actively follow mothers who received Tdap during pregnancy with one also following their infants for one year after birth (Part two and three). Preliminary results were reported for study part 2 and study part 3 of the **EPI-PERTUSSIS-025 VS NZ SUPP (201024)**;

EPI-PERTUSSIS-025 VS NZ SUPP (201024) is an observational study to assess the safety of pertussis vaccine (Tdap) administered during pregnancy. As said previously, the New-Zealand study is made of 3 components: i) a retrospective analysis of national databases which will include all pregnant women and their infants over the period 2009-2013 (n=~325,000), and will provide background rates for non-vaccinated women and capture main events in the pregnancy outcomes depending on the vaccination status (safety outcomes measured will be adverse events in the pregnant women and adverse pregnancy outcomes), ii) a prospective study on adverse events in ~300 pregnant women in the first 4 weeks following Tdap vaccination (reactogenicity data, including local adverse events and general adverse events, will be analyzed descriptively), iii) a prospective study that will also collect some data on from ~450 infants born from vaccinated mothers (up to one year of age).The preliminary reports received for study parts 2 and 3 are as follows:

There were 101 (12.7%) events reported to the NZ Centre for Adverse Reaction Monitoring (CARM) and 21 (2.7%) Serious Adverse Events (SAE) reported. Of those, 2.1% were considered to be maternal, not foetal-related. These were predominantly complications related to the pregnancy such as bleeding and premature labour. Of the events deemed to be serious there were two perinatal deaths one of which was identified to be due to a congenital anomaly (Trisomy Chromosome 11q). The second perinatal death was a stillbirth with no specific cause identified. Seventeen (17) SAEs with maternal outcomes were reported. The investigator concluded that "*none of the SAEs were considered to be related to vaccination and rates were within what could be normally expected to occur in this sample of pregnant women. There was no pattern or consistent time to onset of these events. Tdap is well tolerated in pregnant women. Our findings are consistent with the data*

from studies involving non-pregnant women. We found no Serious Adverse Events in this study that were likely to have been caused by the vaccine". The reported SAEs are consistent with events anticipated to be reported by the pregnant population under study. No particular trend or safety concern was identified from the review of the SAEs from the PIPS study 2 and 3 Preliminary Maternal Outcomes reports.

4.5. Description of "exposure during breastfeeding" reports received worldwide from clinical, spontaneous and Post marketing sources:

Reports of exposure during breastfeeding received from spontaneous, clinical and postmarketing sources were also retrieved and reviewed. As of 02 August 2015, 10 cases of exposure to *Boostrix* vaccination during breastfeeding were reported worldwide (6 cases in United States, 1 case from Belgium and 2 cases from Germany). In none of those reports, adverse events linked to Boostrix exposure via breastfeeding were noted in the infants. Given the very limited information provided on those cases, there is currently insufficient information to conclude as regards the administration of Boostrix during breastfeeding, although none of those reports did highlight any particular safety issue or concern.

CONCLUSIONS

As of 02 August 2015, 908 US pregnancy reports (890 prospective and 18 retrospective) had been received in the Registry.

A cumulative overview of all pregnancy reports from the US Pregnancy Registry/PASS from 03May2005 to 02Aug2015 is presented in Table 1

Table1 Cummulative pregnancy reports from the US Pregnancy Registry/PASS (from 03May2005 to 02Aug2015)

US Pregnancy outcomes (Spontaneous and Post-Marketing cases)	Prospective Reports N = 890	Retrospective Reports N = 18
Lost to follow-up/unknown outcome	611	2
Ongoing	123	1
Live birth without birth defects	151	10
Live birth with birth defects	3	3
Spontaneous abortion without birth defects	2	0
Spontaneous abortion with birth defects	0	0
Stillbirth without birth defects	0	2
Stillbirth with birth defects	0	0
Elective termination without birth defects	0	0
Elective termination with birth defects	0	0

From the total number of the reports received in the Registry (N=890), 171 had a

known outcome. Of these, 94% reported a live birth with no congenital anomaly and there were 6 live born neonates presenting with birth defects (3.5%). Data from this Registry shows a very low rate of spontaneous abortion, possibly due to the fact that the vaccine is being administered in the postmarketing setting mainly during the third trimester of pregnancy. Two stillbirths were retrospectively reported with no congenital anomaly. In relation to reports of congenital anomalies, it is reassuring that the nature of the reported congenital anomalies does not appear to concentrate in a single organ disorder and no clustering was observed with respect to the timing of exposure and the sensitive period of organogenesis. In addition, all reported individual anomalies are relatively known and frequent in the general new-born population, and do not constitute a new syndrome.

The overall pregnancy data generated thus far from this Registry, including available data from clinical trials, post marketing (including the present Pregnancy Registry) and the spontaneous reports are reassuring and shows no evidence that vaccination with *Boostrix* increase the risk of abnormal outcomes including birth defects. Based on all data reviewed so far, the previously established favourable benefit-risk profile for *Boostrix* remains unchanged.

However, it's acknowledge that the number of pregnancies and outcomes accrued in this Registry since May 2005 represents a sample of insufficient size for reaching reliable and definitive conclusions about the risk, to pregnant females or their *in utero* offspring, of vaccination with *Boostrix* during pregnancy. In addition this Pregnancy Registry do not correspond to a "registry" from a pharmacoepidemiological viewpoint since they don't register all cases of pregnancy exposure to *Boostrix* given that they are based on voluntary reporting. Additional data from clinical trials are currently planned to specifically evaluate the use of *Boostrix* in pregnant women; this is due to the fact that multiple countries have recently instituted recommendations regarding the use of Tdap vaccine during pregnancy.

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before initiation of the study.

Currently, GSK plans to continue the Registry for an additional 4 years. Summary reports will be written annually and will be submitted with the Periodic Benefit-Risk Evaluation Report for *Boostrix* if applicable. A final report will be written and submitted after 5 years. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

Summary results of observational studies that are designed to inform the safety or effectiveness, including cost-effectiveness, of GSK vaccines/products as used in ordinary clinical practice are publicly registered within 8 months of completion of the analysis.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis.

REFERENCES

Anderson AN, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *British Medical Journal* 2000;320:1708-1712.

CDC, 2012: source Website:.cdc.gov/pertussis/clinical/treatment.html Accessed 20 September 2013.

CDC. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months --- Advisory Committee on Immunization Practices (ACIP), 2011. MMWR; 60(41);1424-1426.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for persons aged 0 through 18 years and adults aged 19 years and older--United States, 2013: MMWR Surveill Summ. 2013 Feb 1;62 Suppl 1:1.

Centers for Disease Control and Prevention (CDC). Birth Defects and Genetic Diseases Branch 6-digit code for reportable congenital anomalies. Revised 2008. Internet site: cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf.

Centers for Disease Control and Prevention (CDC). Birth defects. Internet site: cdc.gov/ncbddd/birthdefects/facts.html. Accessed: 27 November 2013(b).

Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization ractices (ACIP). MMWR Recomm Rep. 2011(d); 60(2): 1-64.

Centers for Disease Control and Prevention (CDC). Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months - Advisory Committee on Immunization Practices (ACIP), 2011. MMRW. 2011(a); 60(41): 1424-1426.

Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. MMWR. 2013(a); 62(7): 131-135.

Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations: Reports from the Collaborative Perinatal Project. Birth Defects Original Article Series 1975; Vol. 11, No. 10.

Conseil Supérieur de la Santé (CSS). Fiches de vaccination éditées par le CSS (CSS 9110). Vaccination anticoquelucheuse ; vaccination de l'adulte (2013) http://health.belgium.be/eportal/Aboutus/relatedinstitutions/SuperiorHealthCouncil/publications/factsheetsvaccination/13038500_FR?ie2Term=center&ie2section=9130&fodnlang=fr ; accessed on 25 November 2013

Correa-Villasenor A, Cragan J, Kucik J, O'Leary L, Siffel C, Williams L. The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the Centers for Disease Control and Prevention. Birth Defects Research (Part A) 2003;67:617-24.

Czeizel AE, Rockenbauer M. Tetanus toxoid and congenital abnormalities. Int J Gynecol Obstet. 1999; 64: 253-258.

Ellish NJ, Saboda K, O'Connor J, et al. A prospective study of early pregnancy loss. Hum. Reprod. 1996; 11: 406-12.

Fenster L, Hubbard AE, Windham GC, Waller KO, Swan SH. A prospective study of work-related physical exertion and abortion. *Epidemiology* 1997;8:66-74.

Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheriapertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol. 2011; 204: 334.e-5.

Joint Committee on Vaccination and Immunization (JCVI). JVCI meeting on pertussis immunization: August 2012. Draft minutes of discussions on the immunization of pregnant women against pertussis. Published 28 September 2012. http://transparency.dh.gov.uk/2012/09/28/jcvi-pertussis/ ; accessed on 08 August 2013.

Kennedy DL, Uhl K, Kweder SJ. Pregnancy exposure registries. Drug Safety. 2004; 27: 215-228.

Khattak S, K-Moghtader G, McMartin K, Barrera M, Kennedy D, Koren G. Pregnancy outcome following gestational exposure to organic solvents. *Journal of the American Medical Association* 1999;281:1106-1109.

Ministerio de Salud, Presidencia de la Nación, alert dated 25 January 2012. Whooping Cough: Increased cases and deaths. Internet site: msal.gov.ar/images/stories/alertas_epidemiologia/2012/alerta-1-tos-convulsa-2012.pdf; accessed on 28 August 2013.

Mitchell AA, Cottler LB, Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. *American Journal of Epidemiology* 1988;123:670-676.

New Zealand Pharmaceutical Management Agency (PHARMAC). Decision to amend the diphtheria, pertussis and tetanus vaccine (Boostrix) listing, 12 December 2012. Internet site: pharmac.govt.nz/2012/12/12/; accessed on 28 August 2013.

Osborn JF, Cattaruzza MS, Spinelli A. Risk of spontaneous abortion in Italy, 1978-1995, and the effect of maternal age, gravity, marital status, and education. *American Journal of Epidemiology* 2000;151:98-105.

Shakib JH, Korgenski K, Sheng X, Varner MW, Pavia AT, Byington CL. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: Pregnancy and infant health outcomes. J Pediatrics. 2013; 163: 5 (1422-1426.e4).

Silveria CM, Caceres VM, Dutra MG, Lopes-Camelo J, Castilla EE. Safety of tetanus toxoid in pregnant women: a hospital-based case-control study of congenital anomalies. Bull World Health Organ. 1995; 73: 605-608.

Talbot EA, Brown KH, Kirkland, KB, Baughman AL, Halperin SA, Broder KP. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine. 2010; 28: 8001-8007.

Technical Advisory Group (TAG) on Vaccine-preventable Diseases. Vaccination: a shared responsibility. Quito, Ecuador 3-5 July 2013.

Terranella A, Asay GR, Messonnier ML, Clark TA, Liang JL. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis. Pediatrics. 2013; 131(6): e1748-1756.

Wilcox AJ, Horney LF. Accuracy of spontaneous abortion recall. *American Journal of Epidemiology* 1984;120:727-733.

Wilcox AJ, Treloar AE, Sandler DP. Spontaneous abortion over time: comparing occurrence in two cohorts of women a generation apart. *American Journal of Epidemiology* 1981;114:548-553.

Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Sclatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early ls of pregnancy. *New England Journal of Medicine* 1988;319:189-194.

Wilcox AJ. Surveillance of pregnancy loss in human populations. *American Journal of Industrial Medicine* 1983;4:285-291.

Windham GC, Von Behren J, Fenster L, Schaefer C, Swan SH. Moderate maternal alcohol consumption and risk of spontaneous abortion. *Epidemiology* 1997;8:509-514.

Yenlik A. Zheteyeva Adverse event reports after tetanos toxoid, reduced diphteria toxoid, and acellular pertussis vaccines in pregnant woman. Am J Obstet Gynecol 2012;207:59.e1-7.

Study Protocol
Sponsor:
GlaxoSmithKline Biologicals
Rue de l'Institut 89
1330 Rixensart, Belgium

1. PASS INFORMATION

Title	Boostrix® Pregnancy Registry: a prospective, exploratory, cohort study to detect and describe any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Boostrix® during pregnancy or within 28 days preceding conception.
Protocol version identifier	201327 (EPI-PERTUSSIS-028 VS US PR)
Date of last version of the protocol	Final Version 1: 06 March 2014
EU PAS Register No	Not applicable
Active substance	J07AJ52, bacterial vaccine, pertussis vaccines
Medicinal product	Boostrix®, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed
Product reference	Not applicable
Procedure number	Not applicable
Marketing Authorization Holder	GlaxoSmithKline (GSK) Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	**Co-primary objectives** • To describe the characteristics of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes. • To assess the proportion of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days

	preceding conception) with any abnormal pregnancy outcomes.
Country of study	United States
Authors	Coordinating author: • [redacted] Scientific Writer, [redacted] contractor for GSK Biologicals GSK contributors: • [redacted] Senior Manager, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • [redacted] Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • [redacted] Director, Director, Head of Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance (Therapeutic) • [redacted] Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • [redacted] Director, Head of Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance (Prophylactic) • [redacted] Director, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance • [redacted] Senior Manager, Vaccine Value & Health Science Epidemiology • [redacted] Director, Global Regulatory Affairs

2. MARKETING AUTHORIZATION HOLDER

Marketing authorization holder	GlaxoSmithKline Biologicals Rue de l'Institut 89, 1330 Rixensart, Belgium

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
DTaP	Diphtheria and tetanus toxoids and acellular pertussis vaccine
DTP	Diphtheria and tetanus toxoids and whole cell pertussis vaccine
EDD	Estimated Date of Delivery
FDA	Food and Drug Administration
FHA	Filamentous Hemagglutinin
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HCP	Healthcare Professional
ICD-9 CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICH	International Conference on Harmonization
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post-Authorization Safety Study
PT	Pertussis Toxin
Td	Tetanus and diphtheria toxoid vaccine
Tdap	Combined reduced antigen content tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine
UK	United Kingdom
US	United States

3. RESPONSIBLE PARTIES

GlaxoSmithKline (GSK) Biologicals has the overall responsibility for the conduct of the study.

4. ABSTRACT

Title	Boostrix® Pregnancy Registry: a prospective, exploratory, cohort study to detect and describe any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Boostrix® during pregnancy or within 28 days preceding conception. 201327 (EPI-PERTUSSIS-028 VS US PR), Final Version 1: 06 March 2014
Main author	[redacted] Senior Manager, Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance, GSK Biologicals
Rationale and background	*Boostrix* is indicated for active booster immunization against tetanus, diphtheria, and pertussis as a single dose in individuals 10 years of age and older. The purpose of this Registry is to detect and describe any abnormal pregnancy outcomes, including teratogenicity, in females intentionally or unintentionally exposed to *Boostrix* during their pregnancies. The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the lack of data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing effort to assess the safety of *Boostrix*. The Registry was originally initiated on 03 May 2005, as part of a program of enhanced Pharmacovigilance. Following new European Union pharmacovigilance legislation, pregnancy registries are to be considered as post-authorization safety studies (PASS). The ongoing Registry will therefore be converted into a PASS. Timelines for collection of follow-up data will be adapted in order to correspond to the follow-up timelines of other GSK pregnancy registries. The intent of the Registry is to prospectively collect data describing exposure to *Boostrix* immediately before or during pregnancy, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy. Retrospective reports will be captured by the Registry but will not be included in the analyses of prospective reports.
Research question and objectives	**Co-primary objectives** • To describe the characteristics of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or

within 28 days preceding conception) with any abnormal pregnancy outcomes.

- To assess the proportion of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes.

Study design

- This study is a transition of an ongoing pregnancy registry (starting on 03 May 2005) into a PASS.
- This is a prospective*, observational, exploratory, cohort study. The *Boostrix* pregnancy registry study requires voluntary, prospective reporting of eligible pregnancies by patients and healthcare professionals (HCPs). Data such as vaccination with *Boostrix* during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy will be collected prospectively**.

  ** Exposed pregnancies reported to the Registry before the transition into a PASS (between 03 May 2005 and Q1 2014), from which data were collected and analyzed prospectively, will also be included in the analyses.*

  *** Some pregnancy exposures may be reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports.*
- Study population: pregnant women, residing in the United States (US), vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception volunteering to take part in the study.
- Type of study: self-contained.
- Data collection: initial and follow-up data will be collected using questionnaires. Follow-up of cases is performed within 3 months of the estimated date of delivery (EDD) to ascertain outcome and approximately 6 months and 12 months after the EDD (for all live births) to ascertain the presence of birth defects not diagnosed before.
- After transition of the ongoing pregnancy registry into a PASS, data will be collected for a minimum of 5 years, starting Q1 2014.

Population, including the setting and study population	In the US, *Boostrix* is indicated for active booster immunization against tetanus, diphtheria, and pertussis. Originally licensed for persons aged 10 through 18 years, the vaccine was approved by the Food and Drug Administration (FDA) for use in persons aged 19 through 64 years in 2008, and in persons aged 65 years and older in 2011. The study population includes women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception. ***Size of the potential "at-risk" population*** The US Census Bureau estimates that, as of 1 July 2012, the resident US female population was 62,744,930 between the ages of 15 and 44 years old [US Census Bureau, 2013]. The provisional fertility rate in the US in 2012 was 63.2 births per 1000 women aged 15-44 years and the provisional count of births was 3.96 millions [CDC, 2012]. ***Number of pregnant vaccinees*** *Boostrix* is classified as FDA Pregnancy Category B since September 2012. Since February 2013, *Boostrix* vaccination is recommended by the Advisory Committee on Immunization Practices (ACIP) in each pregnancy. More than 20 million doses of *Boostrix* were distributed in the US between May 2005 and July 2011. Experiences with the ongoing *Boostrix* pregnancy registry (391 exposed pregnancies reported prospectively and 5 exposed pregnancies reported retrospectively between 03 May 2005 and 02 August 2013) and other vaccine pregnancy registries indicate that it is likely that fewer than 100 pregnancies per year will be registered.
Variables	**Primary endpoint** Occurrence of any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception.
Data sources	Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Registration can be initiated from a HCP or from a consumer, in which case permission is requested to obtain confirmation and follow-up from their HCP. A toll-free telephone number for reporting adverse events (AEs) and vaccine-exposed pregnancies to the Registry will be listed in the product information leaflet and on the GSK Registry website. Retrospective post-marketing reports and relevant scientific publications are potential sources of supplementary

information.

Study size

No minimum sample size is required for this descriptive study.

Refer to Abstract Section "Study population" above for the size of the potential "at-risk" population and the number of pregnant vaccinees.

Data analysis

Pregnancy outcomes include spontaneous abortion (pregnancy loss before 20 weeks gestation), fetal deaths/stillbirths (loss at or after 20 weeks gestation), elective/therapeutic abortions and live births. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories.

Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration of vaccine during pregnancy. Reports of multiple exposures during a pregnancy are classified by the earliest trimester of exposure. The calculations of risk for birth defects are made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. An exact 95% confidence interval is calculated using standard statistical software. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation.

Spontaneous abortions without birth defects are excluded from the risk calculations.

All defects regardless of trimester of vaccine exposure will be included in the periodic summary reports of this Registry and stratified by trimester of exposure.

A section of each periodic summary report, separate from the analysis of prospective reports, will describe all abnormal outcomes of retrospectively reported cases.

Milestones

The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance, and will now be converted into a PASS. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014. Summary reports will be written annually. A final report will be written and submitted 18 months after the last annual report. After submission of the final report, GSK will continue the Registry pending Center for Biologics Evaluation and Research (CBER) review of the report and determination whether the Registry can be

discontinued.

References

Centers for Disease Control and Prevention (CDC). Recent Trends in Births and Fertility Rates Through December 2012. http://www.cdc.gov/nchs/data/hestat/births_fertility_december_2012/births_fertility_december_2012.htm. Accessed: 27 November 2013.

United States Census Bureau (US Census Bureau), Population Division. Annual Estimates of the Resident Population for Selected Age Groups by Sex: April 1, 2010 to July 1, 2012. Release date June 2013. http://www.census.gov/popest/data/national/asrh/2012/index.html. Accessed: 27 November 2013.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	Q1 2014[a]
End of data collection	Q4 2018[b]
Annual report 1	Q1 2015
Annual report 2	Q1 2016
Annual report 3	Q1 2017
Annual report 4	Q1 2018
Annual report 5	Q1 2019
Registration in the EU PAS register	Q1 2014
Final report	Q2 2020 (18 months after the last annual report)

[a] The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance. Following new European Union Pharmacovigilance legislation, pregnancy registries are to be considered as post-authorization safety studies (PASS). The ongoing Registry will therefore be converted into a PASS. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014.

[b] After submission of the final report, GSK will continue the Registry pending Center for Biologics Evaluation and Research (CBER) review of the report and determination whether the Registry can be discontinued.

7. RATIONALE AND BACKGROUND

7.1. Background

7.1.1. *Boostrix* vaccine

Boostrix is a vaccine indicated for active booster immunization against tetanus, diphtheria, and pertussis. It contains tetanus toxoid, diphtheria toxoid, and pertussis antigens (inactivated pertussis toxin [PT] and formaldehyde-treated filamentous hemagglutinin [FHA] and pertactin). Each 0.5-mL dose is formulated to contain 5 Lf of tetanus toxoid, 2.5 Lf of diphtheria toxoid, 8 μg of inactivated PT, 8 μg of FHA, and 2.5 μg of pertactin (69 kD outer membrane protein). Each antigen is individually adsorbed onto aluminium hydroxide.

7.1.2. Animal studies/human exposure

No published or unpublished clinical data on immunogenicity, efficacy, or effectiveness in pregnant women are available since pregnant women have been routinely excluded from clinical trials. However, there are no specific safety concerns or expectations of harm, and use in pregnancy is not contraindicated.

There are two non-clinical studies performed recently:

1. HLS HEY0017: A study of effects on fertility, embryo-fetal and prenatal and post-natal development in rats by intramuscular administration (including pre-mating

immunization phase) with *Boostrix*, *Boostrix* (United States [US] formulation), and *Boostrix IPV* (study report dated 2012, [GlaxoSmithKline Biologicals Clinical Study Report HLS HEY0017]).

2. HLS HEY0018: A study of effects on female fertility and embryo-fetal development in rabbits by intramuscular administration (including pre-mating immunization phase) with *Boostrix* and *Boostrix IPV* (study report dated 2013, [GlaxoSmithKline Biologicals Clinical Study Report HLS HEY0018]).

These studies have shown that there are no key safety findings after the use of *Boostrix* in rats and rabbits. The first study was mainly focused on the reproductive profile in rats and the other study explored the developmental toxicity in rabbits. In the reproductive toxicity study with rats, it was concluded that female rats did not develop important pre- and post-natal adverse effects and that *Boostrix* did not affect the growth or development of the offspring studied. In the developmental toxicity study with rabbits, it was concluded that female rabbits adequately tolerate *Boostrix* and that the vaccine did not adversely affect embryo-fetal development or survival.

In order to generate data on pregnancy outcomes, GSK closely monitored outcomes of unplanned pregnancies in clinical trials, and established a pregnancy exposure registry in the US on 03 May 2005.

Up to 02 August 2013, 10 pregnancy reports were received from clinical trials. Three pregnancies were exposed within 28 days prior to conception; these three pregnancies resulted in three infants without birth defects. Four pregnancies were exposed during the first trimester. Of these, three were lost to follow-up and one resulted in spontaneous abortion in a vaccinee with epilepsy, who was taking lamotrigine prior to and during the pregnancy. Two pregnancies were exposed during an unspecified trimester; both of which were lost to follow-up. The remaining one pregnancy involved exposure to *Boostrix* during an unspecified time prior to conception and no follow-up information has been received until now.

The *Boostrix* pregnancy registry was originally initiated as part of a program of enhanced pharmacovigilance. As of 02 August 2013, 391 pregnancies involving exposure to *Boostrix* in the US had been prospectively reported since the initiation of the pregnancy registry. Among these, 153 (39%) were lost to follow-up and 200 (51%) were ongoing at the time of last contact, including one report from a physician of an unspecified ‘congenital anomaly’ and one report from a healthcare provider regarding a defect noted from an abnormal prenatal screening test (left ventricular echogenic intracardiac focus) in a 22-year-old woman who was exposed to *Boostrix* during the third trimester. Outcomes were reported for 38 (10%) pregnancies, and consisted of 35 live infants born without birth defects, one spontaneous abortion at seven weeks gestation with exposure to *Boostrix* vaccine during the first trimester, and two live infants with birth defects exposed during the second trimester (plagiocephaly in a female diagnosed at two months of age, family history of occipital deformational plagiocephaly) and third trimester (mild left foot ligament laxity in a male diagnosed at birth). Five retrospective pregnancy reports were received up to 02 August 2013. Two pregnancies resulted in a live infant. The outcome of one pregnancy was unknown. The remaining two reports pertained to one spontaneous abortion at eight weeks of gestation with exposure during the first trimester and one

infant who was delivered at an unspecified gestational age and who was diagnosed at birth with pulmonary hypertension and arterial venous malformation (exposure during an unspecified trimester to both *Boostrix* and *Adacel,* on the same day). The infant died while hospitalized; the cause of death was not provided and it was unknown whether an autopsy was performed.

Since 2005, 60 prospective spontaneous reports and two retrospective spontaneous reports were received from outside the US. Among the pregnancies reported prospectively, 12 were reported to be ongoing, 28 were lost to follow-up and 19 had an outcome reported as normal delivery. One subject delivered a live infant with a congenital anomaly (trigonocephaly) approximately 5 days after vaccination. One out of the two pregnancies reported retrospectively resulted in the birth of a live infant without congenital anomaly, the other pregnancy with exposure during the third trimester resulted in the birth of a live infant with fetal pleural effusion and cardiomegaly. These events were considered as unlikely related to vaccination by the reporting physician.

In 2011, the Advisory Committee on Immunization Practices (ACIP) reviewed published and unpublished data from the Vaccine Adverse Event Reporting System, Sanofi Pasteur (*Adacel*) and GSK (*Boostrix*) pregnancy registries, and small studies [Talbot, 2010; Gall, 2011] investigating the administration of combined reduced antigen content tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnancy [Centers for Disease Control and Prevention (CDC), 2011a]. ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events (AEs) in pregnant women who received Tdap and that the few serious AEs reported were unlikely to have been caused by the vaccine. Both tetanus- and diphtheria-toxoid vaccines (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic [Silveria, 1995; Czeizel, 1999]. From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks gestation is preferred to minimize the risk for any low-frequency AEs and the possibility that any spurious association might appear causative [CDC, 2013a; Terranella, 2013].

Pregnancy and birth outcomes in infants born to women who did or did not receive Tdap vaccine during pregnancy were assessed in a retrospective cohort study [Shakib, 2013]. The study, ending in 2009, was performed before Tdap administration during pregnancy was recommended. From May 2005 through August 2009, 138 women 12-45 years of age with documented Tdap administration during pregnancy (cases) were identified at Intermountain Healthcare facilities; 552 pregnant women without documentation of Tdap immunization were randomly selected as controls. The mean age of pregnant women was 27 years for both cases (range: 14-40) and controls (range: 14-43) ($p = 0.735$). Of the immunized women, 63% received Tdap in the first trimester and 37% in the second or third trimester. The incidence of spontaneous or elective abortion was not higher in cases than in controls. There were no significant differences in pre-term delivery, gestational age, or birth weight between both groups. At least one congenital anomaly was identified in 3.7% infants in the exposed group and 4.4% infants in the control group ($p = 0.749$). In infants of exposed women, 3.6% had International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnoses consistent with complex chronic

conditions within 12 months compared with 10.4% of infants in the control group (p = 0.054). The authors concluded that there was no increase in adverse outcomes in infants born to women receiving Tdap compared to infants of women in the control group.

7.1.3. Medical conditions for use

Though the incidences of diphtheria, tetanus and pertussis during childhood have decreased with immunization programs, immunity to each of these diseases gradually decreases in the absence of administration of booster vaccine doses.

Pertussis is highly contagious (greater than 90% risks of infection have been reported among unvaccinated household contacts) and can cause severe disease, particularly among very young children. During the pre-vaccination era, pertussis was one of the most common childhood diseases and a major cause of infant mortality. Following the introduction of vaccines, the number of cases fell dramatically. In the US, the annual number of reported cases of pertussis decreased from an average of 175,000 per year between 1940 and 1945, to 2900 per year between 1980 and 1990 [CDC, 2012a]. Since the 1990s, the number of cases has been gradually increasing [WHO, 2012]. Despite high vaccination coverage, outbreaks have been reported in numerous countries including the US since 2004. In 2012, 48,277 cases of pertussis were reported in the US, but many more go undiagnosed and unreported. In recent years, adolescents and adults have accounted for a large proportion of cases of pertussis. In Europe, between 1998 and 2002, disease incidence remained steady among infants < 1 year of age; whereas the rate doubled in adolescents and adults, from 16% to 35% [Celentano, 2005]. Between 2008 and 2010, adolescents and adults accounted for more than 50% of all cases in Europe [EUVAC.NET, 2008; EUVAC.NET, 2009; EUVAC.NET, 2010]. A similar shift has been reported in the US [Murphy, 2008].

Pertussis can be severe in infants and children, but in adults the symptoms tend to be mild and indistinguishable from those of other respiratory infections [CDC, 2012a]. However, infected adults can still transmit the disease to susceptible individuals, including infants who have not completed the full vaccination course. It has been established that siblings and adolescent or adult family members with unrecognized pertussis represent the primary source of infection to infants [Bisgard, 2004; Jardine, 2009]. The majority of patients with pertussis will gradually recover; however, some develop potentially life-threatening complications, including pneumonia, neurological complications, otitis media, anorexia and dehydration. Young infants are most at risk of complications; CDC data from 1997 to 2000 found that pneumonia occurred in 5.2% of pertussis cases, but in infants younger than 6 months of age it occurred in 11.8% of cases [CDC, 2012a].

The occurrence of **diphtheria** is currently rare in the US primarily because of the high level of appropriate vaccination among children and because of an apparent reduction in the circulation of toxigenic strains of *Corynebacterium diphtheriae*. Between 2000 and 2012, 5 cases of diphtheria were reported in the US. The overall case fatality risk for diphtheria is 5-10% with higher risk in persons less than 5 years and older than 40 years of age (up to 20%), and has changed very little in the last 50 years [CDC, 2012b].

Tetanus is the only vaccine-preventable disease that is infectious, though not contagious. The incidence of tetanus increases with age due to inadequate booster vaccination in countries where immunization programs are implemented [CDC, 2011b]. In the US, tetanus has become a disease primarily affecting older adults. Vaccinated mothers confer protection to their infants through transplacental transfer of maternal antibody. Neonatal tetanus, which is fatal in 25% of affected neonates, occurs among infants born under unhygienic conditions to inadequately vaccinated mothers [Hackley, 1999]. In the US, 233 tetanus cases were reported between 2001 and 2008; among the 197 cases with known outcomes, the case-fatality rate was 13.2%. Among all persons with reported tetanus, the risk for fatal disease was greater among those aged ≥ 65 years than those aged < 65 years [CDC, 2011b].

Originally, *Boostrix* was licensed in 2005 for persons aged 10 through 18 years. In 2008, the US Food and Drug Administration (FDA) approved an expanded age indication for *Boostrix* to include persons aged 19 through 64 years. In 2011, the indicated age range was further expanded to include persons aged 65 years and older. *Boostrix* is now licensed in the US for use in persons aged 10 years and older as a single-dose booster vaccination. For prevention of tetanus, diphtheria, and pertussis, ACIP recommends that adolescents and adults receive a one-time booster dose of Tdap. Adolescents aged 11 through 18 years who have completed the recommended childhood diphtheria and tetanus toxoids and whole cell pertussis/ diphtheria and tetanus toxoids and acellular pertussis (DTP/ DTaP) vaccination series should receive a single dose of Tdap instead of Td vaccine, preferably at a preventive-care visit at the age of 11 or 12 years. For adults aged 19 through 64 years who previously have not received a dose of Tdap, a single dose of Tdap should replace a single decennial Td booster dose [CDC, 2011c]. Vaccination with Tdap is recommended for all adults aged 65 years and older [CDC, 2012c]. Tdap can be administered regardless of interval since the last tetanus- or diphtheria-toxoid containing vaccine. After receipt of Tdap, persons should continue to receive Td for routine booster vaccination against tetanus and diphtheria, in accordance with previously published guidelines [CDC, 2012c].

In response to pertussis epidemics, several Health Authorities from different countries (US, United Kingdom [UK], New Zealand, Argentina, etc.) recommended Tdap vaccination in pregnancy in order to indirectly protect newborns that are more at risk of acquiring pertussis, before they begin the primary vaccination series. In the US, ACIP voted on 24 October 2012 to recommend Tdap vaccination in each pregnancy. Maternal vaccination programs with Tdap vaccines have also been recommended by Public Health Authorities in a number of other countries (Switzerland, Mexico, Brazil, Argentina, Ireland, UK, and Pan American Health Organization) [CDC, 2013a; HPA, 2013a]. The UK Health Protection Agency is currently evaluating the effectiveness of maternal immunization. A pertussis vaccination program for pregnant women was introduced on 01 October 2012 and pregnant women were offered a 5-component acellular pertussis containing vaccine (diphtheria-tetanus-acellular pertussis-inactivated polio) between 28 and 38 weeks of gestation. Between October 2012 and June 2013, the uptake of pertussis vaccine in pregnant women in the UK was approximately 50%; there has been a slight decline in uptake during 2013 [HPA, 2013b]. Surveillance data captured until end of July 2013, 9 months after initiation of the vaccination program, were presented recently. These data show that the target population of women is strongly supportive of

immunization against pertussis in pregnancy. Since October 2012 pertussis activity has fallen, especially in infants aged less than 3 months of age. Early calculations of programme effectiveness are high and safety data are reassuring [Campbell, 2013].

7.1.4. Characteristics of exposure

Women can be intentionally or unintentionally exposed to vaccines during pregnancy. In general, the women are closely monitored throughout the remainder of the pregnancy.

Refer to Section 9.2.1.2 for potential annual exposure in pregnant women.

7.1.5. Potential benefits of product

No clinical data on the safety or immunogenicity of the use of *Boostrix* during pregnancy or lactation have been generated. It is generally accepted that inactivated vaccines pose no risk to the pregnant or lactating woman [CDC, 2011d]. In the absence of supporting data, *Boostrix* should only be administered to pregnant women when clearly needed, and when the possible benefit outweighs the possible risks to the fetus. In the US, Tdap vaccination is recommended by ACIP in each pregnancy ([CDC, 2013a], see Section 7.1.3).

7.2. Rationale

The purpose of this Registry is to detect and describe any abnormal pregnancy outcomes, including teratogenicity, in females intentionally or unintentionally exposed to *Boostrix* during their pregnancies The combination of the large number of women who are of reproductive capacity and may be exposed to tetanus, diphtheria, and pertussis; and the lack of data concerning exposure to *Boostrix* during pregnancy makes such a Registry an important component of the ongoing effort to assess the safety of *Boostrix*. The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance. Following new European Union Pharmacovigilance legislation, pregnancy registries are to be considered as PASS. The ongoing Registry will therefore be converted into a PASS. Timelines for collection of follow-up data will be adapted in order to correspond to the follow-up timelines of other GSK pregnancy registries. The *Boostrix* pregnancy registry was and will be maintained by Vaccine Clinical Safety and Pharmacovigilance.

The Registry requires voluntary, prospective reporting of eligible pregnancies by patients and HCPs. Patient confidentiality is strictly maintained. The intent of the Registry is to prospectively collect data describing exposure to *Boostrix* immediately before or during pregnancy, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Co-primary objectives

- To describe the characteristics of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes.
- To assess the proportion of registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception) with any abnormal pregnancy outcomes.

Refer to Section 9.3.1 for the definition of the primary endpoint.

9. RESEARCH METHODS

9.1. Study design

9.1.1. Overview

- This study is a transition of an ongoing pregnancy registry (starting on 03 May 2005) into a PASS.
- This is a prospective*, observational, exploratory, cohort study. The *Boostrix* pregnancy registry study requires voluntary, prospective reporting of eligible pregnancies by patients and HCPs. Data such as vaccination with *Boostrix* during pregnancy or within 28 days preceding conception, potential confounding factors (such as exposure to other medications) and information related to the outcome of the pregnancy will be collected prospectively**.

  ** Exposed pregnancies reported to the Registry before the transition into a PASS (between 03 May 2005 and Q1 2014), from which data were collected and analyzed prospectively, will also be included in the analyses.*
- *** Some pregnancy exposures may be reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports.*
- Study population: pregnant women, vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception, volunteering to take part in the study.
- Type of study: self-contained.
- Data collection: initial and follow-up data will be collected using questionnaires. Follow-up of cases is performed within 3 months of the estimated date of delivery (EDD) to ascertain outcome and approximately 6 months and 12 months after the EDD (for all live births) to ascertain the presence of birth defects not diagnosed before.
- After transition of the ongoing pregnancy registry into a PASS, data will be collected for a minimum of 5 years, starting Q1 2014.

9.1.2. Rationale for study design

This prospective cohort study is designed as a Registry. After market authorization, AEs that occur after administration of the vaccine can and should always be reported. In that case, however, there is no clear group in which the events occur and so a proper rate of occurrence cannot be estimated. In this pregnancy registry, participants are recruited between administration of the vaccine and the potential occurrence of an AE (i.e., a teratogenic effect in the offspring). This allows for a more proper estimation of the rate of occurrence of these events. Nevertheless, the results of this study still need to be regarded with caution as the exact number of women exposed during pregnancy is unknown. Incidences of events can therefore not be calculated from the study data.

Furthermore, it is likely that pregnant women who accept vaccination may differ from those who refuse vaccination in underlying health status, propensity to seek medical care, propensity to report AEs and differences in access to medical care in general. The differential response/participation by vaccinated versus unvaccinated pregnant women in a pregnancy registry could significantly bias risk estimates and possibly in unpredictable ways, because of the inability to collect adequate data to characterize the non-responders. Therefore, the risks of any identified birth defects will be compared to those in the general population, such as that defined by the Metropolitan Atlanta Congenital Defects Program (MACDP).

9.2. Setting

9.2.1. Study population

9.2.1.1. Patient population

In the US, *Boostrix* is indicated for active booster immunization against tetanus, diphtheria, and pertussis. Originally licensed for persons aged 10 through 18 years, the vaccine was approved by the FDA for use in persons aged 19 through 64 years in 2008, and in persons aged 65 years and older in 2011.

The study population includes women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception.

9.2.1.2. Potential annual exposure

Size of the potential "at-risk" population

The US Census Bureau estimates that, as of 1 July 2012, the resident US female population was 62,744,930 between the ages of 15 and 44 years old [US Census Bureau, 2013]. The provisional fertility rate in the US in 2012 was 63.2 births per 1000 women aged 15-44 years and the provisional count of births was 3.96 millions [CDC, 2012d].

Number of pregnant vaccinees

Boostrix was originally classified as FDA Pregnancy Category C, which was changed to Category B in September 2012, as a study of developmental toxicity in female rats showed no key safety concerns. Pregnancy Category B means that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Since February 2013, *Boostrix* vaccination is recommended by the ACIP in each pregnancy.

More than 20 million doses of *Boostrix* were distributed in the US between May 2005 and July 2011. Experiences with the ongoing *Boostrix* pregnancy registry (391 exposed pregnancies reported prospectively and five exposed pregnancies reported retrospectively between 03 May 2005 and 02 August 2013) and other vaccine pregnancy registries (e.g., smallpox vaccine [CDC, 2003], varicella vaccine [Shields, 2001], and *Twinrix*) indicate that it is likely that fewer than 100 pregnancies per year will be registered.

9.2.2. Patient recruitment

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Since the initiation of the Registry in 2005, GSK has taken several measures to increase the rate of pregnancy registration (accrual). A GSK Registry web page has been created with instructions for enrolling patients in the Registry and GSK has requested that the FDA post a link to this web page on their Pregnancy Registry Website. In response to a 2008 request from the FDA to facilitate enrollment, GSK initiated a dedicated toll-free telephone number [redacted] at which US-based callers can receive assistance in the registration of pregnancies. Notice of this new toll-free number was posted on the GSK web page in January 2009; the new toll-free number was added to the US Prescribing Information in early 2009. The Prescribing Information and GSK Registry website each give a brief summary of the purpose and intent of the Registry, along with telephone and fax contact information.

9.2.3. Selection of a comparison group

This registry study is a prospective cohort study. Active enrollment of a valid internal comparison group is not feasible. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation. Background risks from existing, external systems (e.g., the National Birth Defects Prevention Network and the National Center for Health Statistics) will be used.

9.2.4. Study period

The Registry was originally initiated on 03 May 2005, as part of a program of enhanced pharmacovigilance, and will now be converted into a PASS. GSK plans to continue the Registry for a minimum of 5 years, starting Q1 2014. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

9.2.5. Inclusion criteria

A subject will be included in the Registry if all of the following criteria are met:

- Exposure to vaccine occurs during pregnancy or within 28 days preceding conception.
- Subject is a US resident.
- A HCP is identified (name, address and phone number).
- Subject can be identified (by GSK or HCP).

Data from registered subjects will be included in the analyses if the following criterion is met:

- Pregnancy is ongoing and the outcome is unknown.

9.2.6. Exclusion criterion

Data from registered subjects will not be included in the analyses if the following criterion is met:

- Outcome of pregnancy is known at the time of initial report. Types of known outcomes include prenatal testing reports in which the results are abnormal or outside the reference range, indicating possible abnormality in the fetus. Pregnancies in which prenatal testing indicates a normal pregnancy would also be excluded because inclusion of such pregnancies could potentially bias results toward a lower overall estimate of risk for defects [Honein, 1999]. Typically pregnancies > 16 weeks gestation will have undergone prenatal testing that can identify whether a child has congenital abnormalities.

9.3. Variables

9.3.1. Primary endpoint

- Occurrence of any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception.

9.3.2. Data to be collected

Initial and follow-up data will be collected using questionnaires. The following data will be collected:

- Patient identifier.
- Maternal data, including date of birth, date of last menstrual period (LMP), EDD.
- Maternal relevant medical/family history.

- Paternal relevant medical/family history.
- Type of conception.
- Prenatal testing.
- Maternal prenatal drug/vaccine exposure, including drug/vaccine name, date of administration, route of administration, dose, lot number, indication.
- Pregnancy outcome.
- Method of delivery.
- Infant/fetal information, including gestational weeks at birth/miscarriage/ termination, gender, length, weight, Apgar score.
- Description of birth defects, if applicable.
- AEs experienced by the fetus/infant or the mother.
- Reporter information.
- Any additional data that seems relevant for this study.

9.4. Data sources

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. Registration can be initiated from a HCP or from a consumer, in which case permission is requested to obtain confirmation and follow-up from their HCP. A toll-free telephone number for reporting AEs and vaccine-exposed pregnancies to the Registry is listed in the product information leaflet and on the GSK Registry website. Retrospective post-marketing reports and relevant scientific publications are potential sources of supplementary information.

9.5. Study size

No minimum sample size is required for this descriptive study.

Refer to Section 9.2.1.2 for the size of the potential "at-risk" population and the number of pregnant vaccinees.

9.6. Data management

9.6.1. Data collection

Initial and follow-up data will be collected using questionnaires. Initial data will be collected before the outcome is known. Follow-up of cases will be performed at the following timepoints:

- Within 3 months of the EDD, to ascertain outcome. At least three attempts to obtain outcome information will be made before any case is considered lost to follow-up.

- An additional follow-up will be done for all live births approximately 6 months and 12 months after the EDD to ascertain the presence of birth defects not diagnosed at the time of the initial follow-up.

9.6.2. Processing of reports

Initial reports are entered into the GSK safety database by Client Response Center staff using existing mechanisms and practices. Medical Dictionary for Regulatory Activities (MedDRA) is used in the database to code AEs.

Follow-up is conducted by the Case Management Group. The HCP is contacted if she/he requests or if initial information is insufficient or needs clarification. The HCP is encouraged to keep a copy of the initial completed form in the patient's chart.

9.6.2.1. Solicitation of outcome

Within three months after the EDD and if the HCP has not already provided the outcome, she/he is sent an outcome form (questionnaire), along with a copy of the initial completed pregnancy form. The mode of communication is the one through which the initial information was received (telephone, fax, or postal mail).

At least three attempts are made to secure the outcome information from the HCP. The second and third attempts utilize all modes of contact available (mail, fax, telephone). If outcome is not received from the HCP and contact information is available for the patient, she is then contacted by mail or fax.

In the event of an abnormal outcome and with the mother's permission, attempts are made to solicit information from the pediatrician and/or other specialists who have provided healthcare/consultation to the child.

9.6.2.2. Classification of outcomes

This Registry uses the term 'birth defects' for outcomes sometimes referred to as 'congenital anomalies'. For purposes of analysis, pregnancy outcomes are dichotomized according to the presence or absence of birth defects. The latter group is further categorized as: 1) live births, 2) spontaneous abortions (i.e., pregnancy losses) and 3) induced abortions.

This Registry adopts a definition of a child with a birth defect as any live or stillborn neonate with a structural or chromosomal abnormality diagnosed before 6 years of age. The Registry employs a conservative approach of including all morphologic anomalies, including minor ones, as birth defects.

To provide consistency in the definitions of major defects in this Registry, CDC MACDP criteria are used for the classification of defects [CDC, 2008; Correa-Villasenor, 2003]. Some of the conditions excluded from the MACDP criteria for major structural defects may actually have major clinical, functional, or genetic significance. Therefore, minor malformations not appearing in the CDC inclusion list may be classified as birth

defects in this Registry. In addition, CDC guidelines disqualify as defects those findings that are present in infants delivered at less than 36 weeks of gestation and are attributable to prematurity itself, such as a patent ductus arteriosus or inguinal hernias. Infants with infectious conditions (e.g., neonatal sepsis) or isolated biochemical abnormalities (e.g., hyperbilirubinemia) are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized congenital abnormality. All other congenital abnormalities are included in the 'birth defects' category, regardless of whether the neonate is delivered alive, including structural defects in neonates delivered prior to 20 weeks of gestation or weighing less than 500 g.

9.7. Data analysis

Pregnancy outcomes include spontaneous abortion (pregnancy loss before 20 weeks gestation), fetal deaths/stillbirths (loss at or after 20 weeks gestation), elective/therapeutic abortions and live births. Gestational weeks are counted from the date of the LMP. The second trimester is considered to begin at week 14 and the third trimester begins at week 28. The presence or absence of birth defects or other abnormalities is evaluated within each of the preceding outcome categories.

Pregnancy outcomes are stratified by the trimester of exposure, with an additional stratum for preconception exposure with no subsequent administration of vaccine during pregnancy. Reports of multiple exposures during a pregnancy (i.e., multiple administrations of *Boostrix*) are classified by the earliest trimester of exposure. When exposure occurs before and after conception, the exposure is classified by the dose administered after conception. The calculations of risk for birth defects are made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. An exact 95% confidence interval is calculated using standard statistical software. The outcomes of the study will be assessed against known rates from an external reference group for the likelihood of a safety signal warranting further investigation.

The majority of spontaneous abortions occur early in pregnancy [Wilcox, 1981; Wilcox, 1983; Ellish, 1996]. If spontaneous abortions were to be evaluated as an outcome of interest, it would be essential to enroll pregnancies as soon as possible after vaccination with *Boostrix*. Because enrollment and recognition of pregnancy would occur at various times, it would be virtually impossible to meaningfully evaluate the effects of *Boostrix* on pregnancy loss [Kennedy, 2004]. Therefore, spontaneous abortions without birth defects are excluded from the risk calculations.

The risk in the general population of all birth defects meeting CDC criteria is approximately 3% (1 of 33) of live births [CDC, 2013b]. The estimated risk cited in the medical literature varies because of differences in case definitions, populations sampled and ascertainment methods. The Collaborative Perinatal Project, using a broader case definition and prospective ascertainment, reports a frequency of 5% to 7% [Chung, 1975]. Most major structural defects originate during the first trimester of pregnancy, which is the critical time for organogenesis [CDC, 2013b]. For such defects, exposures occurring in the second or third trimester are not likely to be causally associated. However, for the sake of completeness and to enable the assessment of possible increases

in the frequency of birth defects, all defects will be included in the periodic summary reports of this Registry.

Criteria for review of a specific individual report include:

- Is the timing of the vaccination with *Boostrix* commensurate with the ontogenetic development of the organ(s) affected by the abnormalities?
- Is there another known or likely cause (e.g., pre-existing genetic or chromosomal defect or exposure to a known teratogen)?
- Is the congenital abnormality not previously described (i.e., is it new to medical science)?
- Is there a unique constellation of defects (i.e., is there a new syndrome)?

Criteria for review of aggregate data include:

- Is there a deviation from the expected frequency of all defects indicating an increase in the overall risk of defects?
- Is there a deviation from the expected frequencies of individual defects?
- Is there uniqueness (e.g., a pattern) of the abnormalities that is suggestive of a common etiology?

Studies have shown that the risk of spontaneous abortion is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 10% to 22% [Wilcox, 1981; Wilcox, 1983; Wilcox, 1988; Fenster, 1997; Windham, 1997; Khattak, 1999; Anderson, 2000; Osborn, 2000].

While the Registry is to be limited to prospective reports, some pregnancy exposures are reported after pregnancy outcome has been identified (retrospective reports). The Registry will capture retrospective reports, but these reports will not be included in the analyses of prospective reports. In general, retrospective notification of outcomes following exposure to drugs or vaccines is biased toward reporting the severe and unusual cases and is not reflective of the general experience with the drug. Information about the total number of exposed pregnancies, i.e., the pool of exposures from which the retrospective reports arise, is unknown; therefore, incidences of outcomes cannot be calculated from these data. A series of reported birth defects, however, can be analyzed to detect patterns of specific congenital abnormalities and can identify early signals of new vaccine-associated risks. A section of each periodic summary report, separate from the analysis of prospective reports, will describe all abnormal outcomes of retrospectively reported cases.

Exposed pregnancies reported to the Registry before the transition into a PASS (between 03 May 2005 and Q1 2014), from which data were collected and analyzed prospectively, will also be included in the analyses.

9.8. Quality control

Data will be recorded using questionnaires. Subject data necessary for analysis, follow-up and reporting will be entered/transmitted into a validated database or data system. Data management will be performed in accordance with applicable GSK standards.

To ensure compliance with Good Clinical Practice (GCP) and all other applicable guidelines and regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study.

9.9. Limitations of the research methods

This Registry is a prospective cohort study. Active enrollment of a valid internal comparison group is not feasible. Therefore, background risks from existing, external systems (e.g., the National Birth Defects Prevention Network and the National Center for Health Statistics) are used. The potential limitations of comparisons between Registry and background data depend upon the event(s) being compared and will be discussed on an *ad hoc* basis in the relevant periodic Registry reports.

Potential sources of biases are described below:

- As reporting of pregnancies is voluntary, it is possible that even among prospectively reported pregnancies there could be bias in type of pregnancies which are reported. For example, high-risk pregnancies may be more likely to be reported.
- The calculation of risk, which does not include spontaneous abortions or voluntary terminations for which no defects have been reported, may introduce bias. It is unknown what proportions of these pregnancies consist of potentially normal outcomes versus congenital abnormalities. GSK attempts to obtain information on anomalies detected at the time of the outcome, but this may not be known to the reporting physician.
- Those pregnancies that have reached EDD 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.

Refer to Section 9.1.2 for other potential limitations of the study.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with the International Conference on Harmonization (ICH) Guideline for GCP or other applicable guidelines, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonized Tripartite Guideline for clinical investigation of medicinal products in the pediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favorable opinion/approval to conduct the study prior to study start or will document that neither a favorable opinion nor an approval to conduct the study is needed.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board review and favorable opinion/approval of study protocol and any subsequent amendments;

- Institutional Review Board review and favorable opinion/approval of waiver for documentation of informed consent.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Reporting of vaccine-exposed pregnancies to the Registry is voluntary. All reports received by the Registry will be entered into the GSK safety database and reported to regulatory authorities according to applicable regulations.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study information from this protocol will be posted on publicly available clinical trial registers following finalization of the protocol and, whenever possible, before initiation of the study.

GSK plans to continue the Registry for 5 years. Summary reports will be written annually and will be submitted with the Periodic Benefit-Risk Evaluation Report for *Boostrix*. A final report will be written and submitted after 5 years. After submission of the final report, GSK will continue the Registry pending CBER review of the report and determination whether the Registry can be discontinued.

Summary results of observational studies that are designed to inform the safety or effectiveness, including cost-effectiveness, of GSK vaccines/products as used in ordinary clinical practice are publicly registered within 8 months of completion of the analysis. GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature; manuscripts are submitted within 18 months of the completion of the analysis.

13. REFERENCES

Anderson AN, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ*. 2000; 320: 1708-1712.

Bisgard KM, Pascual FB, Ehresmann KR, et al. Infant pertussis: who was the source? *Pediatr Infect Dis J*. 2004; 23(11): 985-989.

Campbell, H. Pertussis vaccination during pregnancy in England. In: Fifth Eurovaccine Conference; 2013 Nov 06; Stockholm, Sweden. Abstract. http://www.ecdc.europa.eu/en/eurovaccine/Documents/Forms/AllItems.aspx?RootFolder=%2Fen%2Feurovaccine%2FDocuments%2FEurovaccine%202013. Accessed: 09 December 2013.

Celentano LP, Massari M, Paramatti D, et al. Resurgence of pertussis in Europe. *Pediatr Infect Dis J*. 2005; 24 (9): 761-765.

Centers for Disease Control and Prevention (CDC). Women with smallpox vaccine exposure during pregnancy reported to the National Smallpox Vaccine Pregnancy Registry - United States, 2003. *MMWR*. 2003; 52: 386-388.

Centers for Disease Control and Prevention (CDC). Birth Defects and Genetic Diseases Branch 6-digit code for reportable congenital anomalies. Revised 2008. http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf

Centers for Disease Control and Prevention (CDC). Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months - Advisory Committee on Immunization Practices (ACIP), 2011. *MMRW*. 2011(a); 60(41): 1424-1426.

Centers for Disease Control and Prevention (CDC). Tetanus Surveillance - United States, 2001- 2008. *MMWR*. 2011(b); 60(12): 365-369.

Centers for Disease Control and Prevention (CDC). FDA Approval of Expanded Age Indication for a Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine. *MMWR*. 2011(c); 60(37): 1279-1280.

Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011(d); 60(2): 1-64.

Centers for Disease Control and Prevention (CDC). Chapter 15: Pertussis. In: Atkinson W, Wolfe S, Hamborsky J, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases [Pink Book]. 12th edn. Washington, DC: Public Health Foundation; 2012(a): 215–232. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/pert.pdf.

Centers for Disease Control and Prevention (CDC). Chapter 6: Diphtheria. In: Atkinson W, Wolfe S, Hamborsky J, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases [Pink Book]. 12th edn. Washington, DC: Public Health Foundation; 2012(b):75–86. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/dip.pdf.

Centers for Disease Control and Prevention (CDC). Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) Vaccine

in Adults Aged 65 Years and Older - Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR*. 2012(c); 61(25): 468-470.

Centers for Disease Control and Prevention (CDC). Recent Trends in Births and Fertility Rates Through December 2012(d). http://www.cdc.gov/nchs/data/hestat/births_fertility_december_2012/births_fertility_december_2012.htm. Accessed: 27 November 2013.

Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women--Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR*. 2013(a); 62(7): 131-135.

Centers for Disease Control and Prevention (CDC). Birth defects. http://www.cdc.gov/ncbddd/birthdefects/facts.html. Accessed: 27 November 2013(b).

Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations: Reports from the Collaborative Perinatal Project. *Birth Defects Original Article Series.* 1975; 11 (10).

Correa-Villasenor A, Cragan J, Kucik J, O'Leary L, Siffel C, Williams L. The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the Centers for Disease Control and Prevention. *Birth Defects Research (Part A).* 2003; 67: 617-24.

Czeizel AE, Rockenbauer M. Tetanus toxoid and congenital abnormalities. *Int J Gynecol Obstet.* 1999; 64: 253-258.

Ellish NJ, Saboda K, O'Connor J, et al. A prospective study of early pregnancy loss. *Hum Reprod.* 1996; 11: 406-12.

European surveillance network for vaccine-preventable diseases (EUVAC.NET). Pertussis surveillance report 2008. http://www.euvac.net/graphics/euvac/pdf/pertussis_2008.pdf.

European surveillance network for vaccine-preventable diseases (EUVAC.NET). Pertussis surveillance annual report 2009. http://www.euvac.net/graphics/euvac/pdf/pertussis_2009.pdf.

European surveillance network for vaccine-preventable diseases (EUVAC.NET). Pertussis surveillance report 2010. http://www.euvac.net/graphics/euvac/pdf/pertussis_2010.pdf.

Fenster L, Hubbard AE, Windham GC, Waller KO, Swan SH. A prospective study of work-related physical exertion and abortion. *Epidemiology.* 1997; 8: 66-74.

Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. *Am J Obstet Gynecol.* 2011; 204: 334.e-5.

GlaxoSmithKline Biologicals Clinical Study Report HLS HEY0017. Boostrix, Boostrix-IPV and Boostrix US Vaccines: Study for Effects on Fertility, Embryo-fetal and Pre- and Postnatal Development in the CD Rat by Intramuscular Administration (including Pre-mating Immunisation phase).

GlaxoSmithKline Biologicals Clinical Study Report HLS HEY0018. Boostrix Vaccines: Study for Effects on Female Fertility and Embryo-Fetal Development in the New Zealand White Rabbit by Intramuscular Administration (Including Pre-Mating Immunisation Phase).

Hackley BK. Immunizations in Pregnancy: A Public Health Perspective. *Journal of Nurse-Midwifery.* 1999; 44(2): 106-117.

Health Protection Agency (HPA). Questions and answers - Pertussis vaccination programme for pregnant women. Updated 11 February 2013(a). http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/WhoopingCough/ImmunisationForPregnantWomen/whooqandaPertussisVaccinationProgrammeforPregnantWom/ Accessed: 27 November 2013.

Health Protection Agency (HPA). Pertussis Vaccination Programme for Pregnant Women: vaccine coverage estimates in England, October 2012 to June 2013. Health Protection Report. 2013(b); 7(40). http://www.hpa.org.uk/hpr/archives/2013/hpr4013.pdf.

Honein MA, Paulozzi LJ, Cragan JD, Correa A. Evaluation of selected characteristics of pregnancy drug registries. *Teratology.* 1999; 60(6): 356-364.

Jardine A, Conaty SJ, Lowbridge C, et al. Who gives pertussis to infants? Source of infection for laboratory confirmed cases less than 12 months of age during an epidemic, Sydney, 2009. *Commun Dis Intell.* 2010; 34(2): 116-121. http://www.health.gov.au/internet/main/publishing.nsf/Content/cdi3402-1. Accessed: 09 December 2013.

Kennedy DL, Uhl K, Kweder SJ. Pregnancy exposure registries. *Drug Safety.* 2004; 27: 215-228.

Khattak S, K-Moghtader G, McMartin K, Barrera M, Kennedy D, Koren G. Pregnancy outcome following gestational exposure to organic solvents. *JAMA.* 1999; 281: 1106-1109.

Murphy TV, Slade BA, Broder KR, et al. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008; 57(RR-4): 1-51.

Osborn JF, Cattaruzza MS, Spinelli A. Risk of spontaneous abortion in Italy, 1978-1995, and the effect of maternal age, gravity, marital status and education. *Am J Epidemiol.* 2000; 151: 98-105.

Shakib JH, Korgenski K, Sheng X, Varner MW, Pavia AT, Byington CL. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: Pregnancy and infant health outcomes. *J Pediatrics.* 2013; 163: 5 (1422-1426.e4).

Shields KE, Galil K, Seward J, Sharrar RG, Cordero JF, Slater E. Varicella vaccine exposure during pregnancy: Data from the first 5 years of the Pregnancy Registry. *Obstet Gynecol.* 2001; 98: 14-19.

Silveria CM, Caceres VM, Dutra MG, Lopes-Camelo J, Castilla EE. Safety of tetanus toxoid in pregnant women: a hospital-based case-control study of congenital anomalies. *Bull World Health Organ.* 1995; 73: 605-608.

Talbot EA, Brown KH, Kirkland, KB, Baughman AL, Halperin SA, Broder KP. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. *Vaccine*. 2010; 28: 8001-8007.

Terranella A, Asay GR, Messonnier ML, Clark TA, Liang JL. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis. *Pediatrics.* 2013; 131(6): e1748-1756.

United States Census Bureau (US Census Bureau), Population Division. Annual Estimates of the Resident Population for Selected Age Groups by Sex: April 1, 2010 to July 1, 2012. Release date June 2013. http://www.census.gov/popest/data/national/asrh/2012/index.html. Accessed: 27 November 2013.

Wilcox AJ, Treloar AE, Sandler DP. Spontaneous abortion over time: comparing occurrence in two cohorts of women a generation apart. *Am J Epidemiol.* 1981; 114: 548-553.

Wilcox AJ. Surveillance of pregnancy loss in human populations. *Amer J Industr Med.* 1983; 4: 285-291.

Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. *New Engl J Med.* 1988; 319: 189-194.

Windham GC, Von Behren J, Fenster L, Schaefer C, Swan SH. Moderate maternal alcohol consumption and risk of spontaneous abortion. *Epidemiology.* 1997; 8: 509-514.

World Health Organization (WHO). WHO vaccine-preventable diseases: monitoring system - 2012 global summary. Disease incidence. 2012. http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tsincidenceper.htm. Accessed: 28 November 2013.

Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	List of stand-alone documents
2	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	ENCePP Checklist for study protocols
3	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	Glossary of terms
4	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	Trademarks
5	201327 (EPI-PERTUSSIS-028 VS US PR)	06-MAR-2014	Protocol Sponsor Signatory Approval

Annex 2 ENCePP Checklist for study protocols

Annex 3 Glossary of terms

Adverse event:	Any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, or temporally associated with a study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.
Cohort study:	A form of epidemiological study where subjects in a study population are classified according to their exposure status/disease and followed over time (prospective/ retrospective) to ascertain the outcome(s).
Eligible:	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Non-interventional (observational) Human Subject Research:	Studies where medicinal products, should they be administered, are prescribed in normal (routine) medical practice. No medical care or medical/scientific procedures as required in a research protocol are administered to participants except as part of routine medical care.
Post-Authorization Safety Study (PASS):	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product. This includes all GSK sponsored non-interventional studies and clinical trials conducted anywhere in the world that are in accordance with the terms of the European marketing authorization and where the investigation of safety is the specific stated objective. Note: The phrase 'In accordance with the terms of the European marketing authorization' means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).

Prospective study:	A study in which the subjects/cases are identified and then followed forward in time in order to address one or more study objectives.
Protocol amendment:	The International Conference on Harmonization (ICH) defines a protocol amendment as: 'A written description of a change(s) to or formal clarification of a protocol.' GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations and organization of a study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.
Retrospective study:	A study that looks backward in time (e.g., at events that occurred in the past; outcomes and exposure can no longer be influenced), usually using medical records, databases or interviews in order to address one or more study objectives.
Self-contained study:	Study with objectives not linked to the data of another study.
Study population:	Sample of population of interest.
Subject:	Term used throughout the protocol to denote an individual who has been contacted in order to participate or participates in the epidemiological study or a person about whom some medical information has been recorded in a database.

Annex 4 Trademarks

The following trademarks are used in the present study outline. Note: In the remainder of the document, the names of the vaccines will be written without the superscript symbol ™ or ®.

Trademarks of the GlaxoSmithKline group of companies	Generic description
Boostrix®	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed
Boostrix® IPV	combined diphtheria, tetanus, acellular pertussis (adsorbed) and inactivated poliomyelitis vaccine
Twinrix®	hepatitis A inactivated & hepatitis B (recombinant) vaccine

Trademarks not owned by the GlaxoSmithKline group of companies	Generic description
Adacel® (Sanofi Pasteur)	tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed

Annex 5 Protocol sponsor signatory approval

eTrack study number and Abbreviated Title	201327 (EPI-PERTUSSIS-028 VS US PR)
Date of protocol	Final Version 1: 06 March 2014
Detailed Title	Boostrix® Quadrivalent Pregnancy Registry: a prospective, exploratory, cohort study to detect and describe any abnormal pregnancy outcomes in women intentionally or unintentionally vaccinated with Boostrix® Quadrivalent during pregnancy or within 28 days preceding conception.
Sponsor signatory	[redacted] Director, Head of Safety Evaluation & Risk Management, Vaccine Clinical Safety and Pharmacovigilance
Signature	_____
Date	_____