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*

PASS information

Title	A post-marketing, observational, retrospective, cohort study to assess the safety of *Refortrix* (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Version identifier of the final study report	203153 (EPI-PERTUSSIS-037 VS BR)
Date of last version of the final study report	02 March 2018
EU PAS Register Number	EUPAS13406
Active substance	Diphtheria toxoid, Tetanus toxoid, Bordetella pertussis antigens (Pertussis toxoid, Filamentous Haemagglutinin and Pertactin)
Medicinal product	GlaxoSmithKline (GSK) Biologicals' combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine (*Refortrix*) (263855)
Product reference	DE/H/0210/001-002
Procedure number	NA
Marketing Authorization Holder (MAH)	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	To assess the risk of a series of pre-defined safety outcomes following routine vaccination with *Refortrix* in a cohort of pregnant women compared to a historical cohort of unvaccinated pregnant women in Brazil
Country of study	Brazil
Author	**Contributing authors:** • PPD Clinical and Epidemiology R&D Project Lead • PPD Project Statistician, Ningyang Group Co., for GSK Biologicals • PPD Lead Statistician • PPD Senior Manager, Regulatory Affairs

	• PPD Study Delivery Lead • PPD Expert Scientist SERM • PPD Senior Manager, SERM • PPD Regional Epidemiologist • PPD Medical Data Reviewer **Coordinating authors**: PPD Scientific Writer PPD Scientific Writer

Marketing authorization holder

MAH:	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
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1. ABSTRACT

Title

A post-marketing, observational, retrospective, cohort study to assess the safety of *Refortrix* (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.

Keywords

Post-marketing, cohort study, maternal immunization, Brazil

Rationale and background

Pertussis can cause serious and sometimes life-threatening complications in infants, especially within the first 6 months of life when it is too early to receive and complete their primary vaccination schedule against pertussis. In Brazil, between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age and the majority of cases occurred in infants [WHO, 2014]. The increased fatality rate in this age group led the country to introduce the acellular pertussis vaccination program in pregnant women. By the end of 2014, the National Immunization Program in Brazil (PNI) started the implementation of the maternal immunization program, administering one dose of combined reduced antigen content diphtheria-tetanus-acellular pertussis (Tdap) vaccine (*Refortrix*) during the last trimester of pregnancy (27 to 36 completed weeks of pregnancy or until 20 days before the delivery due date).

The effects of *Refortrix* vaccination in pregnant women were not evaluated in pre-licensure studies and most of the safety evaluations have been conducted using spontaneous reporting systems which have their own limitations like under reporting, reporting bias and quality issues. Therefore, studies using appropriate designs that focus on regions where the dTap maternal immunization programs are implemented to provide valuable information.

Research question and objectives

The aim of this retrospective study was to investigate the association between routine *Refortrix* vaccination during pregnancy and specific pregnancy-related adverse events (AEs) and AEs in neonates following the routine maternal *Refortrix* vaccination during pregnancy. The AEs identified for this study were those considered important in the context of maternal immunization and for which it was feasible to obtain the required data.

The diagnosis of pregnancy-related AEs followed the international case definitions and was obtained directly from the medical records. Since the vaccine was routinely administered in the third trimester of pregnancy, the events that were more commonly reported during this period were chosen as primary endpoints.

Co-primary objectives:

- To compare the risk of gestational diabetes, pregnancy-related hypertension and pregnancy hemorrhage (ante-partum [after 24 weeks of gestation], intra-partum or post-partum) in a cohort of women following vaccination with *Refortrix* 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).
- To compare 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.

Secondary objectives:

- To describe the risk of pregnancy-related AEs/neonate-related events of interest (premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth and neonatal hypoxic ischemic encephalopathy) in the Exposed and Unexposed cohorts.
- To describe the risk of congenital anomalies in neonates in the Exposed and Unexposed cohorts.
- To describe the risk of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

Study design:

- Type of design: An observational, retrospective, cohort, single-center study.
- This is a Targeted Safety Study (TSS) and a Post-Authorization Safety Study (PASS).
- Study population: The study population consisted of two cohorts:
  - Exposed cohort (cohort of pregnant women who received *Refortrix* as part of the maternal immunization program in Brazil)
  - Unexposed cohort (historical cohort of unvaccinated pregnant women before the implementation of the immunization program)
- Data collection: electronic Case Report Form (eCRF) based on medical chart data.
- Period of data collection: The minimum period of the data collection was expected to be 6 months assuming the availability of the subject medical files adequate to attain the sample size required for the analysis. The data of Unexposed subjects who delivered during the period from September 2012 to August 2014 was included. The maternal immunization program in Brazil was scheduled to start in September 2014. Therefore, the data of Exposed subjects was collected once the maternal immunization program was well implemented in Brazil and the inclusion of data started from May 2015 till the Exposed cohort was enrolled completely.
- Epoch 001: Retrospective data collection.

Setting

Subjects and study size, including dropouts:

The planned sample size of this study was 2400 subjects. Using a two-sided (alpha = 0.01) test assuming the ratio of subjects in the Exposed cohort to the Unexposed cohort was 1:1 and assuming a background proportion of events in the Unexposed cohort was 3%, a total of 2400 subjects [1200 subjects in each cohort], was needed to have more than 80% power to detect a relative risk of 2 or higher.

Follow-up period:

Exposed subjects were followed from immunization till delivery or end of pregnancy. The unexposed subjects were followed from pregnancy week 27 till delivery or end of pregnancy.

Variables:

Co-primary endpoints:

- Occurrence of any of the following pregnancy-related AEs in Exposed and Unexposed subjects.
  - Gestational diabetes.
  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome).
  - Pregnancy hemorrhage (ante-partum [after 24 weeks of gestation], intra-partum or post-partum).
- Occurrence of any of the following outcomes in neonates from Exposed and Unexposed subjects.
  - Preterm birth
  - Small for gestational age

Secondary endpoints:

- Occurrence of pregnancy-related AEs of interest/ neonate-related events up to delivery in Exposed and Unexposed subjects.
  - Premature rupture of membranes
  - Preterm premature rupture of membranes
  - Premature uterine contraction
  - Neonatal death
  - Maternal death
  - Still birth
  - Neonatal hypoxic ischemic encephalopathy
- Occurrence of congenital anomalies in the neonates of Exposed and Unexposed subjects.
- Occurrence of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

Data sources:

This retrospective study used the medical files and other hospital documents (admission list, images and other test results, etc.) for collecting demographic data, medical/gynecological history, pregnancy-related AEs of interest and AEs in neonates. No intervention or additional evaluation was done on the diagnosis or evaluation of these events and only the final diagnosis as described in the source document was included in the study.

To evaluate the vaccination exposure, the information in the anamnesis and pregnancy card archived in the medical files was used as the only source.

Results summary

- The demographic characteristics were balanced for both Exposed and Unexposed cohorts. The follow-up was on average shorter in the Exposed cohort than in the Unexposed cohort.
- Incidence proportions for primary pregnancy-related endpoints (gestational diabetes, pregnancy-related hypertension and pregnancy hemorrhage) were 8.34, 9.17 and 3.34 per 1000 for Exposed cohort and 17.47, 24.62,15.09 per 1000 for Unexposed cohort, respectively.
- Incidence proportions for primary birth outcome endpoints (Preterm birth and Small for gestational age) were 53.38 and 57.55 per 1000 for Exposed cohort and 96.11 and 49.25 for unexposed cohort, respectively.
- The unadjusted (exposed/unexposed) OR were lower than one for gestational diabetes (0.58 [95% CI: 0.36-0.94]), pregnancy hemorrhage (0.22 [95%CI: 0.07-0.64]) and preterm birth (0.52 [95%CI: 0.38-0.71]). Unadjusted OR for small for gestational age was more than one (1.16 [95%CI: 0.81-1.64]). The duration of FU period did not impact the incidence of small for gestational age.
- After adjustment for the follow-up period, the incidence rate ratio for gestational diabetes, pregnancy-related hypertension and pregnancy hemorrhage was 0.55 (95%CI:0.26-1.16), 0.43 (95% CI; 0.22-0.85), 0.25 (95%CI; 0.09-0.75), respectively.
- Incidence proportions for secondary endpoints ranged from 0.83 to 158.47 per 1000 in Exposed cohort, except for neonatal death, maternal death and neonatal hypoxic ischemic encephalopathy which did not have any event reported and ranged from 4.77 to 207.31 per 1000 in Unexposed cohort except for maternal death and neonatal hypoxic ischemic encephalopathy which did not have any event reported.
- Incidence proportions by study year in the Unexposed cohort were balanced for all endpoints except for pregnancy hemorrhage (26.02 [September 2012-August 2013] versus 4.74 [September 2013-August 2014] per 1000) and preterm birth (107.32 [September 2012-August 2013] versus 86.89 [September 2013-August 2014] per 1000). There were no cases of post-partum hemorrhage reported.

Conclusion:

- No increased risk of pregnancy related AEs and/or adverse birth outcomes following maternal vaccination with *Refortrix* during 3rd pregnancy trimester among pregnant women in Brazil was identified in the study.
- No association was found between vaccination with *Refortrix* and the pregnancy-related and neonatal adverse events evaluated in the study population.
- No safety concerns were identified in the study.
- The study results are in-line with the current knowledge on the safety profile of dTap vaccines when used during pregnancy.
- The study conclusions have to be interpreted with caution in the light of study limitations inherent to any retrospective observational study.

Marketing Authorization Holder (MAH):

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Names and affiliations of principal investigators:

Refer to Annex 4.

2. LIST OF ABBREVIATIONS

ACIP:	Advisory Committee on Immunization Practices
AE	Adverse Event
ATP Cohort	According-To-Protocol Cohort
CARS	Computer Aided Regulatory Submission
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CONEP	Comissão Nacional de Ética em Pesquisa
D-Rh	Rhesus factor
eCRF	electronic Case Report Form
EMA	European Medicines Agency
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practices
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorization Holder
MoH	Ministry of Health
OR	Odds Ratio
PAHO	Pan American Health Organization
PASS	Post-Authorization Safety Study
PII	Personally Identifiable Information

PNI	National Immunization Program (Brazil)
QC	Quality Control
SAE	Serious Adverse Event
SDD	Statistical Analysis System Drug Development
TC	Total Cohort
Tdap	Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine
TSS	Targeted Safety Study
UK	United Kingdom
USA	United States of America
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

3. ETHICS

3.1. Independent Ethics Committee (IEC)

The study protocol, the informed consent, and other information that required pre-approval were reviewed and approved by a national IEC.

3.2. Ethical conduct of the study

This study was conducted in accordance with "good pharmacovigilance practices (GPP)/ good clinical practice (GCP)" and all applicable regulatory requirements, including the Declaration of Helsinki.

3.3. Subject information and consent

A waiver for informed consent was obtained from the IEC and it was agreed that neither the CRA nor the sponsor representative will have access to medical chart or any other document that would identify the subject. Case report forms were provided for each subject's data to be recorded.

4. INVESTIGATORS

The detailed list of investigators and their affiliation centers is provided in Annex 4.

5. OTHER RESPONSIBLE PARTIES

Not applicable.

6. MILESTONES

Milestone	Planned date	Actual date
Start of data collection	Quarter 2 2016	14 July 2016
End of data collection	Quarter 4 2016	31 May 2017
Final report of study results	Quarter 2 2017	20 Mar 2018

7. RATIONALE AND BACKGROUND

7.1. Background

Pertussis can cause serious and sometimes life-threatening complications in infants, especially within the first 6 months of life when it is too early to receive and complete their primary vaccination schedule against pertussis. In Brazil, between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age and the majority

of cases occurred in infants [WHO, 2014]. The increased fatality rate in this group led the country to introduce the acellular pertussis vaccination program in pregnant women. By the end of 2014, the National Immunization Program in Brazil (PNI) started the implementation of the maternal immunization program [MoH, 2014], administering one dose of combined reduced antigen content diphtheria-tetanus-acellular pertussis (Tdap) vaccine (*Refortrix*) during the last trimester of pregnancy (27 to 36 completed weeks of pregnancy or until 20 days before the delivery due date).

Although the Tdap maternal immunization strategy has been implemented in the United Kingdom (UK), the United States of America (USA) and other countries, only limited data on the safety of *Refortrix* in pregnant women is available. The data from the Vaccine Adverse Event Reporting System (VAERS), pregnancy registries and case series have concluded that there is no indication of any safety concern about maternal, fetal and infant outcomes following vaccination during pregnancy with Tdap [Healy, 2006; Murphy, 2008; Gall, 2011; Zheteyeva, 2012; ACIP, 2013; CDC, 2015].

Immunization with inactivated vaccines during the last trimester of pregnancy can be beneficial because maternal antibodies can be transferred efficiently to the fetus across placenta, thus providing indirect protection to infants for the first months of life [Keller-Stanislawski, 2014]. Additionally, the risk of abnormal organogenesis is minimal at that gestational age.

7.2. Rationale

The effects of *Refortrix* vaccination in pregnant women were not evaluated in pre-licensure studies and most of the safety evaluations have been conducted using spontaneous reporting systems which have their own limitations like under reporting, reporting bias, estimation of population exposure and report quality issues. Therefore, observational studies using appropriate designs that focus on regions, like Brazil, where the maternal immunization program is starting can provide valuable information.

A retrospective cohort study in this country will present a unique opportunity to continue monitoring the safety of this vaccine in a large population of vaccinated pregnant women, especially in the immediate period after introduction at the end of 2014 of this maternal immunization program. This study will generate safety data that could be used to complement other data generated any other public health groups in Brazil. Together, these should provide a comprehensive evaluation of routine maternal Tdap vaccination in Brazilian pregnant women.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this retrospective study was to investigate the association between routine *Refortrix* vaccination during pregnancy and specific pregnancy-related adverse events (AEs) and AEs in neonates. The AEs identified for this study are those considered important in the context of maternal immunization [Zheteyeva, 2012; Kharbanda, 2014] and for which it would be feasible to obtain the required data.

The diagnosis of pregnancy-related AEs followed the international case definitions and was obtained directly from the medical records. The list of outcomes as potential pregnancy-related AEs of interest was derived from literature. Since the vaccine was routinely administered in the third trimester of pregnancy, the events that were more commonly reported during this period were chosen as primary endpoints.

8.1. Co-primary objectives

- To compare the risk of gestational diabetes, pregnancy-related hypertension and pregnancy hemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum) in a cohort of women following vaccination with *Refortrix* 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).
- To compare 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.

8.2. Secondary objectives

- To describe the risk of pregnancy-related AEs/neonate-related events of interest (premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth and neonatal hypoxic ischemic encephalopathy) in the Exposed and Unexposed cohorts.
- To describe the risk of congenital anomalies in neonates in the Exposed and Unexposed cohorts.
- To describe the risk of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

9. AMENDMENTS AND UPDATES

None

10. RESEARCH METHODS

10.1. Study design

- Type of design: An observational, retrospective, cohort, single-center study.
- This is a Targeted Safety Study (TSS) and a Post-Authorization Safety Study (PASS).
- Study population: The study population will consist of two cohorts:
  - Exposed cohort: cohort of pregnant women who received *Refortrix* as part of the maternal immunization program in Brazil.
  - Unexposed cohort: historical cohort of unvaccinated pregnant women before the implementation of the immunization program.

  Refer to Section 10.4.1 for definition of the study cohorts.
- Data collection: electronic Case Report Form (eCRF) based on medical chart review.
- Period of data collection: The minimum period of data collection is expected to be 6 months assuming the availability of the subject medical files adequate to attain the sample size required for the analysis. The data of Unexposed subjects who delivered during the period from September 2012 to August 2014 was to be included. The maternal immunization program in Brazil was scheduled to start in September 2014. Therefore, the data of Exposed subjects was collected once the maternal immunization program is well implemented in Brazil and the inclusion of data will start from May 2015 till the Exposed cohort is enrolled completely.
  - Epoch 001: Retrospective data collection.

The study cohorts and epoch foreseen in the study are presented in Table 1.

Table 1 Study cohorts and epoch foreseen in the study

Study Cohorts	Approximate number of subjects	Age (Min/Max)	Epochs
			Epoch 001
Exposed cohort	1200	18 years-45 years	x
Unexposed cohort	1200	18 years-45 years	x

Refer to Section 10.4.2 for definition of the endpoints.

10.1.1. Discussion of study design

Considering that *Refortrix* is routinely recommended for all pregnant women in Brazil through the maternal immunization program, randomized controlled trials are not considered ethical. Therefore, an observational cohort study provides the opportunity to evaluate the safety of this routinely used vaccine.

The feasibility assessment indicated that adequate and appropriate data exist and were available to allow a retrospective cohort design to be used, with the further advantage of being time efficient.

As maternal immunization with *Refortrix* is recommended by the Ministry of Health (MoH) and vaccine uptake was expected to be high with limited possibility to recruit contemporary unvaccinated pregnant women, the comparative cohort (Unexposed) comprised a historical cohort of pregnant women who delivered in the same hospital (study center) in the two years before implementation of the maternal immunization program with *Refortrix* (started in end of 2014) in Brazil.

Considering that up to 20% of the pregnant population in this area in Brazil were classified as high risk pregnancies, excluding this group from the study would represent an important selection bias and it would decrease the representativeness of the study population. In addition, high risk pregnancy is not an exclusion criterion to receive the Tdap vaccination according to the maternal immunization guidelines in Brazil [Mariane Raquel, 2013]. Therefore, the study included both low and high risk pregnancy women as determined and defined by local guidelines [MoH, 2010; MoH, 2012].

10.1.2. Feasibility assessment

A feasibility assessment was conducted in seven potential study centers from south-east Brazil during September 2014-November 2014.The objective was to assess the research capabilities and availability of data for the collection of pregnancy-related AEs and vaccination data, as well as to identify the most adequate study design for this setting. These sites were pre-selected based on their capacity to perform clinical research and with an available population of pregnant women that could be enrolled in the study. The results of this exercise demonstrated that at least three out of the seven centers evaluated have the potential to perform the study and have appropriate data available. The final decision to opt for a single center was due to its recruitment capacity, completeness of records of the pregnancy-related AEs/birth outcomes and transcript information from antenatal care visits on vaccination exposure for the Exposed cohort. Refer to Annex 6 for details on the feasibility assessment.

10.2. Setting

10.2.1. Number of subjects/centers

The study was conducted in a single center in south-east Brazil. The subjects who delivered in the study center from May 2015 were considered as potentially exposed and those who delivered before September 2014 were considered as potentially unexposed (the data of Unexposed subjects were included for the period of September 2012 – August 2014). The estimated number of subjects included in each cohort (Exposed and Unexposed) was 1200 (total 2400 subjects).

The study center was selected based on the accuracy and completeness observed in the medical records. The selected study center received approximately 300 pregnant women per month for delivery.

10.3. Subjects

10.3.1. Inclusion criteria

Deviations from inclusion criteria were not allowed because they could potentially jeopardize the scientific integrity of the study or regulatory acceptability. Therefore, adherence to the criteria as specified in the protocol was essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects between 18 and 45 years of age at the time of pregnancy under consideration for the study, who deliver in the study center.

  Note: Only the latest pregnancy in the specified period were included (to avoid multiple pregnancies from the same mother).

- Residents of the study area (city of PPD
- Subjects who were compliant with the routine antenatal care [Gestacao de Alto Risco, 2010; Cadernos de Attencao Basica, 2012], including at least one ultrasound assessment report early in the pregnancy.
- Subjects with the complete and relevant medical records available.

Inclusion criteria for the Exposed cohort:

- Subjects who received one dose of *Refortrix* vaccine in the recommended time period between 27 and 36 completed weeks of pregnancy (or as late as 20 days before delivery due date) as part of the maternal immunization program in Brazil, and according to the program recommendations from May 2015 onwards.
- Subjects with appropriate vaccination records.

Inclusion criteria for the Unexposed cohort:

- Subjects who had delivered in the same hospital (study center) before 01 September 2014 (September 2012-August 2014) and who did not receive Tdap vaccination during pregnancy to the best knowledge of the investigator.

10.3.2. Exclusion criteria

The following criterion were to be checked at the time of study entry. If the exclusion criterion applies, the subject was not to be included in the study:

- Subjects who have been transferred to other specialized centers, where their medical records would be inaccessible for the study (private clinics, psychiatric or prison hospitals, other state hospitals, etc).

10.4. Variables

10.4.1. Study cohort definitions

- Exposed cohort: Women, 18-45 years of age at the time of pregnancy, who delivered in the hospital (study center) from May 2015 and who received one dose of *Refortrix* during 27 to 36 weeks of pregnancy (or as late as 20 days before delivery due date) as part of the maternal immunization program in Brazil. The index date was considered as the date of *Refortrix* administration or where not specified, as 27 completed weeks of gestation.
- Unexposed cohort: Women, 18-45 years of age at the time of pregnancy, who delivered in the hospital (study center) before implementation of the maternal immunization program in Brazil in September 2014 and who did not receive Tdap vaccination during pregnancy as per information of the investigator. The Unexposed cohort included those subjects who had delivered in the period during September 2012-August 2014. This period was chosen because Tdap vaccine was not administered to pregnant women before the maternal immunization program was implemented in the country.

10.4.2. Endpoints

10.4.2.1. Co-primary endpoints

- Occurrence of any of the following pregnancy-related AEs in Exposed and Unexposed subjects
  - Gestational diabetes
  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome)
  - Pregnancy hemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum)
- Occurrence of any of the following outcomes in neonates from Exposed and Unexposed subjects
  - Preterm birth
  - Small for gestational age

10.4.2.2. Secondary endpoints

- Occurrence of pregnancy-related AEs of interest/neonate-related events up to delivery in Exposed and Unexposed subjects
  - Premature rupture of membranes
  - Preterm premature rupture of membranes
  - Premature uterine contraction
  - Neonatal death
  - Maternal death
  - Still birth
  - Neonatal hypoxic ischemic encephalopathy
- Occurrence of congenital anomalies in the neonates of Exposed and Unexposed subjects
- Occurrence of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort

10.4.3. Potential confounding factors

Age of the mother and high risk pregnancy were considered as important confounding factors for the occurrence of pregnancy-related AEs of interest, so they were to be controlled in the analysis.

Other potential important confounding factors associated with onset of the outcomes of interest were also collected: smoking, multiparity, multiple births, assisted fertilization, congenital anomalies (in parents or first degree relatives), alcohol consumption and recreational drug use. Antecedents of previous pregnancies were predictive factors for the development of a pregnancy-related AE and where available, they were described. These were: history of spontaneous abortion/ miscarriage, preterm delivery, preterm premature rupture of membranes (P-PROM), red blood cell isoimmunization [e.g., D-Rh (Rhesus factor) sensitized], pre-eclampsia, eclampsia and major congenital anomalies during previous pregnancies. Other conditions of interest to record were hypertension, diabetes and anemia.

Further, confounders included multi-fetal gestation, diagnosis of a fetus with aneuploidy or a major congenital anomaly, cervical insufficiency or incompetent cervix, premature contractions, bleeding throughout the gestation, gestational hypertension, maternal immunization with diphtheria, hepatitis B or other vaccines (Exposed cohort) and an active infection (treated or untreated).

The study started monitoring for pregnancy outcomes on the day of vaccine administration for the Exposed cohort and at 27 completed weeks of gestation for the Unexposed cohort, and end at the date of delivery. Only the outcomes of interest diagnosed and described in the medical files during the risk period included in the study.

The study outcomes were to be accounted in the same risk period for both the Exposed and Unexposed cohorts.

10.5. Data sources and measurement

This retrospective study used the medical files and other hospital documents (admission list, images and other test results, etc.) for collecting demographic data, medical/gynecological history, pregnancy-related AEs of interest and AEs in neonates. No intervention or additional evaluation was done on the diagnosis or evaluation of these events and only the final diagnosis as described in the source document included in the study.

To evaluate the vaccination, the information in the anamnesis and pregnancy card archived in the medical files were to be used as the only source.

10.6. Study size

The background proportions of different safety outcomes from publications [Munoz, 2005; Zheteyeva, 2012; Goldfarb, 2014; Assini, 2014] and as reported in the feasibility assessment from Brazil are summarized in Table 2 below.

Table 2 Background proportions of different safety outcomes

Safety Outcome	MUNOZ 2005 (Influenza Vaccination) - Proportion		GOLDFARB 2014*-Proportion		Feasibility assessment-Proportion (Brazil local data)
Exposure	VAC	UNVAC	VAC	UNVAC	UNVAC
Co-Primary endpoints					
Gestational Diabetes	2.2%	1.7%			2.95% (2.53-3.64)
Pre-eclampsia	4.8%	3.9%			1.6%
Vaginal or Intrauterine hemorrhage					16.4%
Preterm Delivery			7.8%	21.2%	Around 10%
Secondary endpoints					
Congenital Anomalies					0.79%
Transient Hypertension	6.7%	2.9%			14.3%
Eclampsia					1.6%
Premature Rupture of Membranes	2.6%	2.4%			3.53%
Still Birth					0.31%

VAC: Vaccinated group
UNVAC: Unvaccinated group
* Tdap vaccine coverage of 81.6%

Sample size:

The background proportions from the feasibility reports and literature for some of the co-primary endpoints ranged from 1.6% - 16.4%, from 0.79% - 10% for some of the secondary endpoints and unknown for the rest of the endpoints (refer to Table 2), besides

the power estimation for each endpoint were assessed in Table 3**.** Therefore, a conservative proportion of 3% was chosen for the sample size calculation.

Using a two-sided (alpha = 0.01) test, assuming the ratio of subjects in the Exposed cohort to the Unexposed cohort is 1:1 and assuming a background proportion of events in the Unexposed cohort to be 3%, a total of 2400 subjects [(1200 subjects in each cohort] was needed to have more than 80% power to detect a relative risk of 2 or higher.

The power estimation of each safety outcome with background proportions is presented in Table 3.

Table 3 Power estimation of each safety outcome with background proportions from the feasibility assessment without multiple adjustment and sample size of 1200 subjects in each cohort

Safety outcome	Assumed background proportion	Alpha level Two-sided	Ratio between vaccinated and control	Power for RR=2(%)*
Co-primary endpoints				
Gestational Diabetes	0.0295	0.05	1:1	94.0
Pre-eclampsia	0.016	0.05	1:1	72.6
Vaginal or intrauterine hemorrhage	0.164	0.05	1:1	>99.9
Preterm Delivery	0.1	0.05	1:1	>99.9
Secondary endpoints				
Congenital anomalies	0.0079	0.05	1:1	43.2
Transient Hypertension	0.143	0.05	1:1	>99.9
Premature Rupture of Membranes	0.0353	0.05	1:1	>99.9
Still birth	0.0031	0.05	1:1	20.0

Two independent proportions were used for the sample size calculation in PASS.
*RR: Relative risk

The sample size and power estimation is presented in Table 4.

Table 4 Sample size and power estimation without and with multiple adjustment for background proportions of 3% and 5% and relative risk of 2

Assumed background proportion	Multiple comparisons	Alpha level Two-sided	Number of vaccinated subjects	Ratio between vaccinated and control	Total Number of subjects needed	Power (%)
0.03	1	0.05	749	1:1	1498	80
0.05	1	0.05	435	1:1	870	80
0.03	5	0.01	1114	1:1	2228	80
0.05	5	0.01	647	1:1	1294	80

Two independent proportions were used for the sample size calculation in PASS.
Bonferroni adjustment was used for adjustment of alpha level.

10.7. Data transformation

A validated GSK defined electronic data collection tool was used as the method for data collection.

In all cases, Personally Identifiable Information (PII) was not collected nor transmitted to GSK (refer to Annex 2 for definition). Subject data necessary for analysis and reporting was entered into a validated database or data system. Clinical data management was performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs were reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review necessitated clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remained accountable for the study data. Refer to Annex 8 for details.

Once the database was archived and the study report is completed and approved by all parties, the participating investigator will be provided with a CD-ROM of the final version of the data generated from the investigational site.

10.8. Statistical methods

10.8.1. Analysis of demographics and baseline characteristics

The baseline and demographic characteristics of the Exposed and Unexposed cohorts was tabulated in a summary of statistics (mean, median, standard deviation and range) including age and gestational age.

10.8.2. Analysis of co-primary endpoints

The main analysis for co-primary objectives contained only the subjects with vaccination date in the Exposed cohort and subjects from the Unexposed cohort. If more than 10% of subjects had missing vaccination date in the Exposed cohort, a sensitivity analysis was to be performed using the imputed vaccination date to 27 completed weeks of gestational age to evaluate if this had any potential impact on the results.

The risk for each primary endpoint (gestational diabetes, pregnancy-related hypertension, pregnancy hemorrhage, preterm birth and small for gestational age) was calculated. For each specific endpoint, the number of subjects where the event occurred [between the index date (refer to Annex 2 for definition of index date) and the date of the delivery] was divided by the total number of subjects at risk for both the Exposed and Unexposed cohorts respectively, together with its exact 99% confidence interval (CI).The co-primary endpoints of pregnancy (gestational diabetes, pregnancy-related hypertension and pregnancy hemorrhage) was pooled together and of birth outcome (preterm birth and small for gestational age) was pooled together in addition. The analysis of the risk for the pooled endpoints was performed using the same method as for the separate co-primary endpoints.

The comparison of the relative risk with its two sided 95% CI of each primary endpoint between the Exposed cohort and the Unexposed cohort was obtained by means of logistic regression model, using the exposure status as a binary independent variable in the model. Absence of increased relative risk was concluded if the respective 95% CI contained 1.

Univariate analysis described the association between Tdap vaccination status, maternal age, parity and gestational age.

A multiple logistic regression model was fitted with a backward selection to identify the possible confounding factors for each of the primary safety event using an alpha level of 0.1. Potential confounders were parity, age of the mother at the start of the pregnancy and congenital anomalies (in parents or first degree relatives). Adjusted odds ratio (OR) and its 95% CI was derived from the final model.

10.8.3. Analysis of secondary endpoints

The relative risk for each secondary endpoint (pregnancy-related AEs and birth outcomes) was calculated by the number of subjects with at least one of each event occurring between the index date and the date of the delivery, corresponding to that endpoint divided by the total number of subjects at risk for both the Exposed and Unexposed cohort, together with its exact 95% CI. If more than 10% of subjects had missing vaccination date in the Exposed cohort, a sensitivity analysis was to be performed as for the co-primary endpoints.

In addition, the relative risk of all the co-primary and secondary endpoints was calculated by calendar year as well to evaluate the comparability among the Exposed and Unexposed cohorts.

10.8.4. Missing values

Missing or non-evaluable primary and secondary outcome measurements were not to be replaced. Therefore, the main analysis excluded subjects with missing or non-evaluable data.

A sensitivity analysis was also to be performed if more than 10% of the measurements are missing for each endpoint. In the first instance, missing outcomes was imputed with a value of ‘0’. In the second instance, all missing outcomes were imputed with a value of ‘1’. The risk for each endpoint was then analyzed using similar methods as mentioned in sections 10.8.2 and 10.8.3 for all the co-primary and secondary endpoints.

For subjects in the Exposed cohort whose date of the vaccination was not available, it was imputed to the completed 27th gestational week as the recommended start time for the vaccination for the sensitivity analysis.

10.8.5. Amendments to the statistical analysis

- As there were five co-primary endpoints in the primary analysis and the sample size was calculated based on an alpha level of 0.01, the main analysis of incidence proportion was calculated with a 99% CI instead of 95 % CI as planned in the protocol.

- Ante-partum data was not extracted in the final database. Hence, intra-partum and post-partum categories were included in the incidence rate analysis.

- Risk factors such as medical co-morbidities, non-pregnancy related hypertension, diabetes and sexually transmitted diseases were not included in the regression tables as they were entered as free-text in the eCRF.

10.9. Quality control

GSK monitored the study to verify that the data were authentic, accurate, and complete. Direct access to all study-site related data and indirect access to source data was mandatory for monitoring review.

While completed eCRFs were reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review necessitated clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remained accountable for the study data.

The final study dataset was archived and stored on a secured, access limited, computer platform SAS Drug Development (SDD) according to GSK Biological Standard Procedures. Specific statistical programs were written in SAS 9.2 (or higher) and validated according to the GSK standard procedures. The validation of the quality control (QC) of the statistical analysis was documented. All statistical programs, output files and QC documentation were saved as read-only files on SDD.

The final study protocol, the final statistical report and the QC document, and the final study report will be archived on a Document management system based on the Documentum platform: Computer Aided Regulatory Submission (CARS).

11. RESULTS

11.1. Participants

Table 5 presents the total number of subjects enrolled into the study (Total Enrolled cohort) as well as the number of subjects excluded from all analyses and from According to Protocol (ATP) analysis with reasons for exclusion. The main statistical analysis was performed on the Total Enrolled Cohort.

From a total of 2477 subjects enrolled into the study,

- 1203 subjects were in the Exposed cohort and 1259 subjects were in the Unexposed cohort,
- One subject was excluded from all statistical analysis with code 900 (due to missing information [i.e., no data reported but subject number allocated]),
- 29 subjects reported a protocol violation: 15 subjects (4 subjects from Exposed cohort and 11 subjects from Unexposed cohort) reported violation of study inclusion/exclusion criteria and 14 subjects had missing cohort information.
- Thus, 2447 subjects (98.8%) of the total enrolled subjects were included in the ATP cohort analysis (Table 5).
- Since, there was less than 5% of subjects eliminated from the Total enrolled cohort, no analysis was done on the ATP cohort.

Table 5 Number of subjects enrolled into the study as well as the number (without Subjects excluded from all stat analysis) excluded from ATP analyses with reasons for exclusion

	Total			Exposed Cohort		Unexposed Cohort		Missing	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total enrolled cohort	2477			1203		1259		15	
Subjects excluded from all stat analysis (code 900)	1	1		0	0	0	0	1	1
Protocol violation (inclusion/exclusion criteria) (code 2010)	29	29		4	4	11	11	14	14
ATP cohort	2447		98.8	1199		1248		0	

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total enrolled cohort

11.2. Descriptive data

Demographic characteristics

Table 6 presents the summary of demographic characteristics for the Total enrolled cohort.

- All subjects (100%) were residents of the study area (Table 6).
- Most of the subjects belonged to 20-24 years' age group (760 subjects [31.1%] [395 subjects in Exposed cohort and 365 subjects in Unexposed cohort]) (Table 6).
- The mean age at the beginning of pregnancy was 26.38 years (SD=6.20 years) and was balanced between Exposed and Unexposed cohorts (26.49 years [SD=6.15 years] vs. 26.28 years [SD=6.24 years]), respectively (Table 6)
- The demographic characteristics (study area, age at the beginning of pregnancy in years or in group) were balanced between Exposed and Unexposed cohort (Table 6).

Table 6 Summary of demographic characteristics (Total enrolled cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Resident of the study area	Yes	1199	100	1248	100	2447	100
	No	0	0.0	0	0.0	0	0.0
	Missing	4	-	11	-	15	-
Age group at the beginning of pregnancy in Years	18-19	147	12.3	198	15.9	345	14.1
	20-24	395	32.9	365	29.2	760	31.1
	25-29	301	25.1	311	24.9	612	25.0
	30-34	201	16.8	222	17.8	423	17.3
	35-39	124	10.3	120	9.6	244	10.0
	40 and above	31	2.6	32	2.6	63	2.6
	Missing	4	-	11	-	15	-
Age at the beginning of pregnancy in Years	Mean	26.49	-	26.28	-	26.38	-
	SD	6.15	-	6.24	-	6.20	-
	Median	25.00	-	25.00	-	25.00	-
	Minimum	18.00	-	18.00	-	18.00	-
	Maximum	44.00	-	45.00	-	45.00	-
	Missing	4	-	11	-	15	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
Note: Do not have available data for 14 subjects

Summary of general medical history is presented in Table 13 and Table 14.

Summary of characteristics, pregnancy related events/complications, new born safety events in previous pregnancy are presented in Table 15 to Table 18.

Summary of congenital anomalies at baseline for the Total cohort is presented in Table 19.

Summary of delivery details, ultrasound details, hospitalization details, hospitalization details by system organ class (SOC), habits, risk factors and additional information, chronic medications, medical indications for chronic medication by SOC, worst pregnancy related hypertension, pregnancy related hypertension during current pregnancy are presented Table 20 to Table 30.

Summary of vaccination history data and related information is presented in Table 31 to Table 33.

11.3. Primary objective results

11.3.1. Occurrence of pregnancy-related AEs

Table 7 presents the cumulative incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for Exposed cohort.

Table 8 presents the cumulative incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for Unexposed cohort

- In the Exposed cohort, the incidence proportion of,
  - Gestational diabetes was 8.34 per 1000 (99% CI; 3.10-17.85).
  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome) was 9.17 per 1000 (99% CI; 3.60-19.00).
  - Pregnancy (vaginal) hemorrhage (including ante-partum, intra-partum and post-partum hemorrhage) was 3.34 per 1000 (99% CI; 0.56-10.50; Table 7).
- In the Unexposed cohort, the incidence proportion of,
  - Gestational diabetes was 17.47 per 1000 (99% CI; 9.37-29.56).
  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome) was 24.62 per 1000 (99% CI; 14.72- 38.47).
  - Pregnancy (vaginal) hemorrhage (including ante-partum, intra-partum and post-partum hemorrhage) was 15.09 per 1000 (99% CI; 7.66-26.52). Refer to Table 8.

11.3.2. Occurrence of birth outcomes

- In the Exposed cohort, the incidence proportion of,
  - Preterm birth was 53.38 per 1000 (99% CI; 37.76-73.09).
  - Small for gestational age was 57.55 per 1000 (99% CI; 41.27-77.92; Table 7).
- In the Unexposed cohort, the incidence proportion of,
  - Preterm birth was 96.11 per 1000 person (99% CI; 75.10-120.99).
  - Small for gestational age was 49.25 per 1000 (99% CI; 34.63-67.77) Refer to Table 8.

Table 7 Cumulative incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for Exposed cohort - Main analysis

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	10	1199	8.34	3.10	17.85
Pregnancy-related hypertension@	11	1199	9.17	3.60	19.00
Pre-Eclampsia	10	1199	8.34	3.10	17.85
Eclampsia	2	1199	1.67	0.09	7.73
HELLP Syndrome	0	1199	0.00	0.00	4.42
Vaginal hemorrhage	4	1199	3.34	0.56	10.50
Preterm birth	64	1199	53.38	37.76	73.09
Small for gestational age	69	1199	57.55	41.27	77.92

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age)
Population at risk =Number of subjects with vaccination date in the Exposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage
@Note: In the total cohort, 146 pregnant women experienced gestational or pregnancy related hypertension independently of pre-eclampsia or eclampsia. For 93 subjects in the exposed cohort and 53 subjects in the unexposed cohort, pregnancy-related hypertension (after 20 weeks of gestation), gestational hypertension (after 20 weeks of gestation) or hypertensive disorders in pregnancy (HDP start date UNK) were recorded in the free text variable of the eCRF.

Table 8 Cumulative incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for Unexposed cohort - Main analysis

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	22	1259	17.47	9.37	29.56
Pregnancy-related hypertension@	31	1259	24.62	14.72	38.47
Pre-Eclampsia	30	1259	23.83	14.11	37.50
Eclampsia	0	1259	0.00	0.00	4.21
HELLP Syndrome	1	1259	0.79	0.00	5.90
Vaginal hemorrhage	19	1259	15.09	7.66	26.52
Preterm birth	121	1259	96.11	75.10	120.99
Small for gestational age	62	1259	49.25	34.63	67.77

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age)
Population at risk = Total number of subjects at risk in Unexposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage
@Note: In the total cohort, 146 pregnant women experienced gestational or pregnancy related hypertension independently of pre-eclampsia or eclampsia. For 93 subjects in the exposed cohort and 53 subjects in the unexposed cohort, pregnancy-related hypertension (after 20 weeks of gestation), gestational hypertension (after 20 weeks of gestation) or hypertensive disorders in pregnancy (HDP start date UNK) were recorded in the free text variable of the eCRF.

11.3.2.1. Comparison of incidence proportion of pregnancy related AEs and outcomes in Exposed and Unexposed cohort

- The unadjusted (exposed/unexposed) odds ratio (OR) was lower than one for gestational diabetes (0.58 [95% CI: 0.36-0.94]) (Table 64), pregnancy hemorrhage (0.22 [95%CI: 0.07-0.64]) (Table 70) and preterm birth (0.52 [95%CI: 0.38-0.71]) (Table 73).
- The unadjusted OR for small for gestational age was 1.16 (95% CI; 0.81-1.64) (Table 76).

Note: The above observed values should be interpreted with caution in the light of the relative shorter follow-up period in the Exposed cohort as compared to the Unexposed cohort.

Summary of birth outcome and Apgar score in subjects without still birth, in subjects without still birth and neonatal deaths and in subjects with neonatal deaths in current pregnancy are presented in Table 34 to Table 36.

11.3.3. Sensitivity analyses

- Due to the different length of the follow-up period between Exposed and Unexposed cohort, incidence rate (n/1000 person-weeks) was computed for the primary endpoint as a planned sensitivity analysis.
- These results showed lower incidence rate in the Exposed than in the Unexposed cohort for all primary endpoints except for small for gestational age as in the main analysis. However, adjustment for follow-up period reduced the magnitude of the difference (Table 37 to Table 39).
- The incidence rate ratio calculated using Poisson regression were 0.55 [95% CI; 0.26-1.16] for gestational diabetes, 0.43 [95% CI; 0.21-0.85] for pregnancy related hypertension, 0.25 [95% CI; 0.08-0.75] for vaginal hemorrhage, 0.64 [95% CI; 0.47-0.86] for pre-term birth and 1.34 [95% CI; 0.95-1.89] for small for gestational age between exposed and unexposed cohort (Table 40 to Table 44).

11.4. Secondary objective results

11.4.1. Pregnancy-related AEs and neonate-related events

Table 9 presents the cumulative incidence of pregnancy-related AEs and neonate-related events of interest in current pregnancy for Exposed cohort.

Table 10 presents the cumulative incidence of pregnancy-related AEs and neonate-related events of interest in current pregnancy for Unexposed cohort.

- In the Exposed cohort, the incidence proportion of,
  - Premature rupture of membranes was 158.47 per 1000 (95% CI; 136.73-182.67).
  - Preterm premature rupture of membranes was 14.18 per 1000 (95% CI; 8.26-22.70).
  - Premature uterine contraction was 26.69 per 1000 (95% CI; 18.26- 37.68).
  - Still birth was 0.83 per 1000 (95% CI; 0.02-4.65). Refer to Table 9.
- There were no events of neonatal death, maternal death and neonatal hypoxic ischemic encephalopathy reported in the Exposed cohort. Refer to Table 9.
- In the Unexposed cohort, the incidence proportion of,
  - Premature rupture of membranes was 207.31 per 1000 (95% CI; 182.92-234.04).
  - Preterm premature rupture of membranes was 28.59 per 1000 (95% CI; 20.03-39.59).
  - Premature uterine contraction was 42.89 per 1000 (95% CI; 32.22- 55.96).
  - Neonatal death was 6.35 per 1000 (95% CI; 2.74-12.52)
  - Still birth was 4.77 per 1000 (95% CI; 0.02-4.65). Refer to Table 10.

- There were no events of maternal death and neonatal hypoxic ischemic encephalopathy reported in the Unexposed cohort. Refer to Table 10.

11.4.2. Congenital anomalies

- The overall incidence of congenital anomalies (CA) was 2.50 per 1000 (95% CI; 0.52-7.31) in Exposed cohort and 17.47 per 1000 (95% CI; 10.95-26.46) in Unexposed cohort (Table 9 and Table 10).

Table 9 Cumulative incidence of pregnancy-related AEs and neonate-related events of interest in current pregnancy for Exposed cohort - Main analysis

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	190	1199	158.47	136.73	182.67
Preterm premature rupture of membranes	17	1199	14.18	8.26	22.70
Premature uterine contraction	32	1199	26.69	18.26	37.68
Neonatal death	0	1199	0.00	0.00	3.08
Maternal death	0	1199	0.00	0.00	3.08
Still birth	1	1199	0.83	0.02	4.65
Neonatal hypoxic ischemic encephalopathy	0	1199	0.00	0.00	3.08
Congenital anomalies	3**	1199	2.50	0.52	7.31

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for neonate-related events (Neonatal death, Still birth, Neonatal hypoxic ischemic encephalopathy and Congenital anomalies)
Population at risk =Number of subjects with vaccination date in the Exposed cohort
**_Microcephaly & Oculo-Auriculo-Vertebral Spectrum [PID_ PPD _Microcephaly [PID_ PPD and _Polydactyly [PID_ PPD were not included in the analysis of CA as these events were reported under “other events” or “birth complications events” in the eCRF and were not classified in the medical records as CA.

Table 10 Cumulative incidence of pregnancy-related AEs and neonate-related events of interest in current pregnancy for Unexposed cohort - Main analysis

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	261	1259	207.31	182.92	234.04
Preterm premature rupture of membranes	36	1259	28.59	20.03	39.59
Premature uterine contraction	54	1259	42.89	32.22	55.96
Neonatal death	8	1259	6.35	2.74	12.52
Maternal death	0	1259	0.00	0.00	2.93
Still birth	6	1259	4.77	1.75	10.37
Neonatal hypoxic ischemic encephalopathy	0	1259	0.00	0.00	2.93
Congenital anomalies	22	1259	17.47	10.95	26.46

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for neonate-related events (Neonatal death, Still birth, Neonatal hypoxic ischemic encephalopathy and Congenital anomalies)
Population at risk = Total number of subjects at risk in Unexposed cohort

11.4.3. Congenital anomalies narratives: Exposed cohort

The information encoded in the study database reflects the information available in the medical charts (source documents) and therefore the two sources of information are consistent. However, for three cases reported in the study data base in the Exposed Cohort, the CA classification was not available in the study database as this information was not available in the medical charts. A retrospective CA classification by the site was also not possible.

Overall, six cases reporting CA were identified in the Exposed Cohort: one case reported as CA in the study database was a reporting error (PID PPD additionally the CAs reported in two cases were classified as such in the study database (i.e. *Hypospadias* [PID PPD and *Bilateral Congenital Clubfoot* [PID PPD and the CAs reported in 3 cases were not classified as CA in the study database due to missing CA classification in the medical charts (i.e. *Microcephaly & Oculo-Auriculo-Vertebral Spectrum* [PID PPD *Microcephaly* [PID PPD and *Polydactyly* [PID PPD

- For the subject with PID number PPD the congenital anomaly reported (i.e., increased resistance of the uterine artery in the current gestation) was a reporting error.
- For the subject with PID number PPD the baby was diagnosed with Hypospadias at birth.
  - Hypospadias is an embryological congenital defect that occurs during urethral development, between 8 and 20 weeks' gestation. Often, this congenital anomaly is a result of a combination of environmental and genetic factors. Amongst the known environmental factors which might contribute to the

development of *Hypospadias* in offspring and the most frequently reported factors are the age of mother (> 35 years of age), weight of mother (overweight to obese) and the exposure to hormones.

  - The mother of this subject was 20 years of age at the beginning of the pregnancy and this was her first pregnancy. She had no reported and relevant pre-existing medical condition or congenital anomaly. She was a non-smoker and did not consume alcohol or illicit drug during the study. She had received H1N1 vaccine at 10 weeks of gestation and the Tdap vaccine during the 27 weeks of gestation. During pregnancy, she experienced as an Intra-uterine Growth Restriction as well and delivered at 37 gestational weeks by emergency cesarean. The baby was also reported *as Small for gestational age* (height 45 cm and weight 2.1 kg).
  - Given the etiology/pathophysiology of the conditions and the risk factors described above, it is reasonable to conclude that the reported congenital anomaly of *Hypospadias* is most likely not related to the administration of *Refortrix* to the mother during pregnancy.

- For the subject with PID number PPD the baby was diagnosed with Bilateral Congenital Clubfoot at birth.
  - Complete etiology of *Bilateral Congenital Clubfoot* is unknown and most infants have no identifiable genetic, syndromal or extrinsic cause [Parker, 2010]. Family history of Clubfoot, smoking and oligohydramnios are among the most common risk and factors associated with Congenital Clubfoot are the family history of Clubfoot, smoking and oligohydramnios.
  - The mother was 21 years old at the beginning of the pregnancy and this was her first pregnancy. She had no relevant pre-existing medical condition or congenital anomaly reported. She was a regular light-smoker and did not consume alcohol or illicit drug during the study. She had received the *Refortrix* vaccine during the 29th week of gestation and she delivered by vaginal route at 39 gestational weeks (height 47.5 cm and weight 2.6 kg).
  - Given the etiology /pathophysiology of the condition and the risk factors described above, it is reasonable to conclude that the reported *Bilateral Congenital Clubfoot* was not related to the administration of *Refortrix* to the mother during pregnancy.

- For the subject with PID number PPD the CA of *Microcephaly* (not due to Zika infection) & *Oculo- Auriculo-Vertebral Spectrum* (OAVS) were reported in the study database under "*other*" neonatal conditions.
  - *Microcephaly* is a rare neurological condition [Orioli, 2017] in which an infant's head is significantly smaller than the heads of other children of the same age and sex. *Microcephaly* can be caused by a variety of genetic and environmental factors. Factors other than genetic factors may include infections during pregnancy (such as rubella, toxoplasmosis or cytomegalovirus), severe malnutrition during the fetal life, craniosynostosis, a decreased oxygen to the fetal brain (cerebral anoxia) or exposure to harmful substances exposure during

pregnancy (such as illicit drugs, smoking, alcohol, heavy metals like arsenic and mercury or radiation) [Von der Hagen, 2014].

- *Oculo-Auriculo-Vertebral Spectrum* (OAVS) is a condition which may occur as a multiple congenital abnormality. Associated findings of this CA may include anomalies of the eye, brain, heart, kidneys and other organs and systems. OAVS involves primarily the derivatives of the first and second pharyngeal arches (which starts to develop in the 4th week of embryonic development) [Beleza-Meireles, 2014]. Most probably the mechanisms of OAVS are related to the development of these structures. Both genetic and environmental factors are thought to contribute to this craniofacial condition. However, the mechanisms are still poorly understood. Environmental factors such as maternal diabetes during pregnancy, thalidomide use during pregnancy, use of vasoactive drugs, smoking and multiple pregnancies might play a role in causation of this condition.
- The mother was 20 years old at the beginning of the pregnancy and this was her first pregnancy. She suffered from schizophrenia and was on treatment with Olanzapine as chronic medication. She was a regular smoker (moderate to heavy smoker ≥ 10 cigarettes/day) before the pregnancy. Her smoking status during pregnancy was unknown. The mother received the H1N1 vaccine during 7th week of gestation and the Tdap vaccine during the 35st week of gestation. She delivered by vaginal route at 38 gestational weeks (baby's height 44 cm and weight 2.7 kg with a head circumference of 30 cm). The site reported two complications at birth: *Microcephaly* (not due to Zika infection) and *Oculo-Auriculo-Vertebral Spectrum*.
- Given the conditions' etiology /pathophysiology and the risk factors described here above, it is reasonable to conclude that both conditions (*Microcephaly* [not due to Zika infection] and *OAVS*) were not related to the administration of *Refortrix* to the mother during pregnancy.

- For the subject with PID number PPD *Microcephaly* (not due to ZKV) was reported in the study database as birth complication.
  - Microcephaly is as described in the previous case.
  - The mother was 22 years old at the beginning of the pregnancy and this was her first pregnancy. She had no relevant pre-existing medical condition or congenital anomaly reported. She was a non-smoker and was not consuming alcohol or illicit drug during the study. The mother received the Tdap vaccine at 29th weeks of gestation and the H1N1 vaccine during the 30st week of gestation. She delivered by vaginal route at 37 gestational weeks (baby's height 48 cm and weight 3.1 kg with a head circumference of 30 cm). The site reported *Microcephaly (not due to ZKV)* as complication at birth in the study data base.
  - Given the condition's etiology /pathophysiology, it is reasonable to conclude that *Microcephaly (not due to ZKV)* was unlikely related to the administration of *Refortrix* to the mother during pregnancy.

- For the subject with PID number PPD *Polydactyly* was reported in the study database as birth complication.
  - During normal embryonic development, the baby's hand initially forms in the shape of a paddle, and at about the 6th or 7th week of gestation, it splits into separate fingers. Occurrences of *polydactyly* are sporadic, meaning that the condition occurs without an apparent cause, while some may be due to a genetic defect or underlying hereditary syndrome.
  - The mother was 24 years old at the beginning of the pregnancy and this was her second pregnancy. During her first pregnancy, she had a preterm premature rupture of membranes. She had no relevant pre-existing medical condition or congenital anomaly reported. She was a non-smoker and was not consuming alcohol or illicit drug during the study.
  - The mother received the DT and Hepatitis B vaccines during 13th week of gestation, Hepatitis B (2nd dose) and H1N1 vaccines during 23th week of gestation and Tdap vaccine during the 33st week of gestation. She delivered by emergency cesarean at 39 gestational weeks (baby's height 49 cm and weight 2.9 kg).
  - Given the condition's etiology /pathophysiology and the timing of the vaccination, it is reasonable to conclude that this polydactyly was not related to the administration of *Refortrix* to the mother during pregnancy.

11.4.4. Pregnancy-related AEs and birth outcomes per study year

Table 11 presents the cumulative incidence of pregnancy-related adverse events and birth outcomes by study year in current pregnancy for Unexposed cohort.

Table 12 presents the cumulative incidence of pregnancy-related AEs and neonate-related events of interest by study year in current pregnancy for Unexposed cohort.

- In the Unexposed cohort, between the period of September 2012 and August 2013 and the period of September 2013 and August 2014, the incidence proportion of
  - Gestational diabetes was 16.26 (95% CI; 7.80-29.90) and was 18.96 (95% CI; 9.80-33.11), respectively.
  - Pregnancy-related hypertension was 22.76 (95% CI; 12.45-38.19) and was 26.86 (95% CI; 15.64-43.00), respectively.
  - Pregnancy (vaginal) hemorrhage was 26.02 (95% CI; 14.87-42.25) and was 4.74 (95% CI; 0.98-13.85), respectively.
  - Preterm birth was 107.32 (95% CI; 83.00-136.53) and was 86.89 (95% CI; 65.46-113.10), respectively.
  - Small for gestational age was 22.76 (95% CI; 12.45-38.19) and was 26.86 (95% CI; 15.64-43.00), respectively. Refer to Table 11.
  - Premature rupture of membranes between was 204.88 (95% CI; 170.67-243.93) and between was 213.27 (95% CI; 178.81-252.43), respectively.

- Preterm premature rupture of membranes between was 34.15 (95% CI; 21.14-52.20) and was 23.70 (95% CI; 13.26-39.08), respectively.
- Premature uterine contraction was 40.65 (95% CI; 26.31-60.01) and was 45.81 (95% CI; 30.68-65.80), respectively.
- Neonatal death was 3.25 (95% CI; 0.39-11.75) and was 9.48 (95% CI; 3.48-20.63), respectively.
- Still birth was 34.15 (95% CI; 21.14-52.20) and was 23.70 (95% CI; 13.26-39.08), respectively.
- Congenital anomalies was 19.51 (95% CI; 10.08-34.08) and was 15.80 (95% CI; 7.58-29.05), respectively. Refer to Table 12.

Table 11 Cumulative incidence of pregnancy-related adverse events and birth outcomes by study year in current pregnancy for Unexposed cohort – Main analysis

					95% CI	
Adverse event Birth outcome	**Study year**	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	Sep2012-Aug2013	10	615	16.26	7.80	29.90
	Sep2013-Aug 2014	12	633	18.96	9.80	33.11
Pregnancy-related hypertension	Sep2012-Aug2013	14	615	22.76	12.45	38.19
	Sep2013-Aug 2014	17	633	26.86	15.64	43.00
Pre-Eclampsia	Sep2012-Aug2013	13	615	21.14	11.26	36.15
	Sep2013-Aug 2014	17	633	26.86	15.64	43.00
Eclampsia	Sep2012-Aug2013	0	615	0.00	0.00	6.00
	Sep2013-Aug 2014	0	633	0.00	0.00	5.83
HELLP Syndrome	Sep2012-Aug2013	1	615	1.63	0.04	9.06
	Sep2013-Aug 2014	0	633	0.00	0.00	5.83
Vaginal hemorrhage	Sep2012-Aug2013	16	615	26.02	14.87	42.25
	Sep2013-Aug 2014	3	633	4.74	0.98	13.85
Preterm birth	Sep2012-Aug2013	66	615	107.32	83.00	136.53
	Sep2013-Aug 2014	55	633	86.89	65.46	113.10
Small for gestational age	Sep2012-Aug2013	31	615	50.41	34.25	71.55
	Sep2013-Aug 2014	31	633	48.97	33.27	69.51

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age)
Population at risk = Number of subjects with delivery date in a given category of Unexposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post partum hemorrhage

Table 12 Cumulative incidence of pregnancy-related AEs and neonate-related events of interest by study year in current pregnancy for Unexposed cohort - Main analysis

					95% CI	
Adverse event Birth outcome	**Study year**	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	Sep2012-Aug2013	126	615	204.88	170.67	243.93
	Sep2013-Aug 2014	135	633	213.27	178.81	252.43
Preterm premature rupture of membranes	Sep2012-Aug2013	21	615	34.15	21.14	52.20
	Sep2013-Aug 2014	15	633	23.70	13.26	39.08
Premature uterine contraction	Sep2012-Aug2013	25	615	40.65	26.31	60.01
	Sep2013-Aug 2014	29	633	45.81	30.68	65.80
Neonatal death	Sep2012-Aug2013	2	615	3.25	0.39	11.75
	Sep2013-Aug 2014	6	633	9.48	3.48	20.63
Maternal death	Sep2012-Aug2013	0	615	0.00	0.00	6.00
	Sep2013-Aug 2014	0	633	0.00	0.00	5.83
Still birth	Sep2012-Aug2013	3	615	4.88	1.01	14.26
	Sep2013-Aug 2014	3	633	4.74	0.98	13.85
Neonatal hypoxic ischemic encephalopathy	Sep2012-Aug2013	0	615	0.00	0.00	6.00
	Sep2013-Aug 2014	0	633	0.00	0.00	5.83
Congenital anomalies	Sep2012-Aug2013	12	615	19.51	10.08	34.08
	Sep2013-Aug 2014	10	633	15.80	7.58	29.05

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for neonate-related events (Neonatal death, Still birth, Neonatal hypoxic ischemic encephalopathy and Congenital anomalies)
Population at risk = Number of subjects with delivery date in a given category of Unexposed cohort

Summary of all AEs/birth outcomes between previous and current pregnancy is presented in Table 45.

Cumulative incidence of pooled pregnancy related adverse events and pooled birth outcomes in current pregnancy for exposed cohort and unexposed cohort is presented in Table 46 and Table 47.

Cumulative incidence of pregnancy-related adverse events and birth outcomes, neonate-related events of interest by calendar year in current pregnancy for unexposed cohort is presented in Table 48 and Table 49.

Cumulative incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for exposed cohort (sensitivity analysis3) is presented in Table 50.

Cumulative incidence of pregnancy-related AEs and birth outcomes with and without any concomitant vaccination, with and without diphtheria-tetanus vaccination, with and without hepatitis B vaccination in current pregnancy for exposed cohort (sensitivity analysis5) are presented in Table 51 to Table 56.

Cumulative incidence of pregnancy-related AEs or neonate-related events of interest with and without any concomitant vaccination, with and without diphtheria-tetanus vaccination, with and without hepatitis B vaccination in current pregnancy for exposed cohort (sensitivity analysis5) are presented in Table 57 to Table 62.

Association between risk factors and gestational diabetes in current pregnancy for Total cohort is presented in Table 63.

Estimated unadjusted OR for exploring risk factors of gestational diabetes in current pregnancy for Total cohort is presented in Table 64.

Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of gestational diabetes in current pregnancy for Total cohort) is presented in Table 65.

Association between risk factors and pregnancy-related hypertension in current pregnancy for Total cohort is presented in Table 66.

Estimated unadjusted odds ratio for exploring the risk factors of pregnancy-related hypertension in current pregnancy for Total cohort) is presented in Table 67.

Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of pregnancy-related hypertension in current pregnancy for Total cohort is presented in Table 68.

Association between risk factors and vaginal hemorrhage in current pregnancy for Total cohort is presented in Table 69.

Estimated unadjusted odds ratio for exploring the risk factors of vaginal hemorrhage in current pregnancy for Total cohort is presented in Table 70.

Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of vaginal hemorrhage in current pregnancy for Total cohort) is presented in Table 71.

Association between risk factors and preterm birth in current pregnancy for Total cohort is presented in Table 72.

Estimated unadjusted odds ratio for exploring the risk factors of preterm birth in current pregnancy for Total cohort is presented in Table 73.

Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of preterm birth in current pregnancy for Total cohort is presented in Table 74.

Association between risk factors and small for gestational age in current pregnancy for Total cohort is presented in Table 75.

Estimated unadjusted odds ratio for exploring the risk factors of small for gestational age in current pregnancy for Total cohort is presented in Table 76.

Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of small for gestational age in current pregnancy for Total cohort is presented in Table 77.

11.5. Study limitations

11.5.1. Limitation of the research methods

The findings of this study should be interpreted with caution due to several factors that were not controlled in the study.

The follow up period was on average longer in the Unexposed cohort than in the Exposed cohort. For the Exposed cohort, the events after the date of *Refortrix* vaccination given as part of the maternal immunization program in Brazil were considered. For the Unexposed cohort, the events after the gestational age of 27 completed weeks were considered.

Another limitation inherent of observational epidemiological studies is a possible imbalance in the underlying risk profile because of different healthcare behavior and/or different propensity for vaccination, creating confounding by indication.

There is a reasonable possibility that timing of events with respect to the exposure might not have been always captured with appropriate accuracy, particularly with retrospective studies which make use of the existing data (which may be limited). However, considering that the antenatal care visits at regular intervals are standard of care in Brazil [MoH, 2010; MoH, 2012], the appropriate documentation of vaccination and pregnancy events for the Exposed cohort, and pregnancy events for the Unexposed cohort was expected. This allowed the determination of the timing of the events as compared to the moment of the exposure. The availability of these data was checked during the feasibility assessment (refer to Annex 6).

Incomplete and imprecise medical records could have led to bias and misclassification of the events. To minimize this, the feasibility assessment was performed in the study center selected to determine the quality and completeness of the medical records for both vaccination exposure and pregnancy outcomes. The pregnancy outcomes diagnosed at the study center during the pregnancy were recorded. However, for some of the outcomes this could be the earliest date of diagnosis at the site rather than the actual date of onset. Therefore, date of diagnosis was used based on the assumption that it was the date of

onset, although this might not be the case in some instances and was recognized as being a limitation of the study, inherent to any retrospective observational research.

The information on concomitant vaccinations administered during pregnancy was not available for the Unexposed cohort, but this information was retrieved for the Exposed cohort. This prevented formal quantitative comparison with the Unexposed cohort and is a limitation of the study.

Congenital anomalies diagnosed at birth were the only ones collected in the framework of the study as there was no post-delivery follow-up planned visit. Therefore, congenital anomalies which might be diagnosed at a later age were not captured. It should be noted that up to 30% of congenital anomalies are diagnosed up to 6 months of age [DeSilva, 2016]. Also, due to the difficulties in the data cleaning process, there were events which were not reported as congenital anomalies. However, the same follow-up period (i.e., up to delivery) was used for the two cohorts, minimizing therefore the impact on the overall conclusions of the study regarding the incidence of Congenital Anomalies.

Since the subjects were not contacted during the study, the assumption was therefore being made that the index date was 27 completed weeks of gestation, which was the earliest time point to receive the vaccination from the maternal immunization program in Brazil. The number of women without the date of *Refortrix* administration was therefore assessed following the data collection, if more than 10% of them were without the date of *Refortrix* administration, a sensitivity analysis was to be performed on top of the primary analysis (refer to section 10.8.2 for details) (as this could have created a potential selection bias in the Exposed cohort compared to the Unexposed cohort).

Another potential limitation was the possibility that the maternal Tdap vaccination program itself might have influenced the attitude of pregnant women towards attending antenatal care or medical consultation. This could have potentially led to an increased frequency of reporting of pregnancy-related AEs. However, the evaluation done during the feasibility assessment that was confirmed by other studies performed at the study center indicated a high acceptance of vaccination in the study population with no changes in the reporting or ascertainment of the expected pregnancy-related AEs. Therefore, the Exposed and Unexposed cohorts were assumed to be comparable.

When using a historical cohort as the unexposed comparison group, caution was required due to potential bias from changes over time and confounding factors including differences in standard of care and pregnancy management practices (from the perspective of both the pregnant woman and the health care professional). Using a comparative cohort collected over two calendar years provided some capacity to identify any such potential differences in relation to the Exposed cohort.

Considering that *Refortrix* was included in the national immunization program in Brazil, it was estimated that the vaccine would have high coverage rate among pregnant women and therefore complicating the enrolment of a contemporary Unexposed cohort. Hence, historical cohort was more deemed suitable for this study design over the contemporary cohort. However, in practice, this assumption was not met as the coverage rates post-introduction of maternal immunization remained low. The impact of this factor on the study results (if women with lower risk than the general pregnant population were more likely to get vaccinated) is not measurable but remains a possibility.

All primary and secondary endpoints showed a reduced OR, except for small for gestational age (SGA), in the exposed cohort compared to the unexposed cohort. The crude increased OR for SGA in the exposed cohort was not statistically significant due to the 95% CI crossing the unit. Additionally, it is important to note that the analysis was done as per the information encoded by the physicians in the eCRF. However, when the specific cases of SGA were reviewed, it was noted that among the 133 cases reported as SGA there were 31 cases where the newborns were born at term (>=37 gestational weeks) had a reported birth weight greater than or equal to 2.5 Kg (reference threshold at term as per Munoz, 2013) (refer to the individual listings appendix to this report). Also, among the 2317 cases reported as non-SGA, there were 24 cases for which the birth weight was smaller than 2.5 Kg (reference threshold at term as per Munoz, 2013) (refer to the individual listings appendix to the report). Since the gender of the newborns was not collected, this precluded the re-classification using more standardized tables such as WHO percentiles.

Moreover, in the study design the process of retrieving the data from secondary sources (medical records from physicians not involved in the study) has its own limitations namely the variability between physicians to identify, classify and report adverse pregnancy outcomes. The different time periods for the exposed and unexposed cohort could also have influenced this bias.

For secondary endpoints, confounding by contra-indication could have biased the OR between exposed and unexposed cohorts as it was less likely for pregnant women with high risk pregnancies to be vaccinated. This was especially important in the case of congenital anomalies, where a prenatal diagnosis of serious or life-incompatible anomalies likely restricted the pregnant woman for vaccination.

12. CONCLUSION

- No increased risk of pregnancy related AEs and/or adverse birth outcomes following maternal vaccination with *Refortrix* during 3rd pregnancy trimester among pregnant women in Brazil was identified in the study.
- No association was found between vaccination with *Refortrix* and the pregnancy-related and neonatal adverse events evaluated in the study population.
- No safety concerns were identified in the study.
- The study results are in-line with the current knowledge on the safety profile of dTap vaccines when used during pregnancy.
- The study conclusions have to be interpreted with caution in the light of study limitations inherent to any retrospective observational study.

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14. APPENDICES

14.1. Post text tables and figures

14.1.1. Descriptive data

Table 13 Summary of general medical history (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Subject known with any non-pregnancy related conditions/signs/symptoms/exanthematic diseases?	Yes	131	10.9	169	13.6	300	12.3
	No	1068	89.1	1078	86.4	2146	87.7
	Missing	4	-	12	-	16	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
Note: Do not have available data for 14 subjects

Table 14 Summary of general medical history by MedDRA system organ class (Total cohort)

			Exposed Cohort			Unexposed Cohort			Total		
Diagnosis before or during pregnancy	**MedDRA system organic class**	**Categories**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
6 months before beginning of pregnancy	Any event	Yes	1203	9	0.75	1259	26	2.07	2462	35	1.42
		Chronic Disease	1203	7	0.58	1259	21	1.67	2462	28	1.14
	Blood and lymphatic system	Yes	1203	0	0.00	1259	1	0.08	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Cardiac	Yes	1203	4	0.33	1259	12	0.95	2462	16	0.65
		Chronic Disease	1203	4	0.33	1259	12	0.95	2462	16	0.65
	Ear and labyrinth	Yes	1203	0	0.00	1259	1	0.08	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Endocrine	Yes	1203	1	0.08	1259	3	0.24	2462	4	0.16
		Chronic Disease	1203	1	0.08	1259	3	0.24	2462	4	0.16
	Hepatobiliary	Yes	1203	0	0.00	1259	1	0.08	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Metabolism and nutrition	Yes	1203	1	0.08	1259	2	0.16	2462	3	0.12
		Chronic Disease	1203	1	0.08	1259	2	0.16	2462	3	0.12
	Musculoskeletal and connective tissue	Yes	1203	0	0.00	1259	1	0.08	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Neoplasm benign, malignant and unspecified	Yes	1203	0	0.00	1259	1	0.08	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Nervous system	Yes	1203	0	0.00	1259	2	0.16	2462	2	0.08
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Renal and urinary	Yes	1203	1	0.08	1259	2	0.16	2462	3	0.12
		Chronic Disease	1203	1	0.08	1259	1	0.08	2462	2	0.08
	Respiratory, thoracic and mediastinal	Yes	1203	2	0.17	1259	1	0.08	2462	3	0.12
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Vascular	Yes	1203	0	0.00	1259	1	0.08	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00

			Exposed Cohort			Unexposed Cohort			Total		
Diagnosis before or during pregnancy	**MedDRA system organic class**	**Categories**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Beginning of pregnancy until vaccination date/27 completed weeks	Any event	Yes	1203	1	0.08	1259	0	0.00	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Renal and urinary	Yes	1203	1	0.08	1259	0	0.00	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
Vaccination date/27 completed weeks until delivery	Any event	Yes	1203	2	0.17	1259	0	0.00	2462	2	0.08
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Infections and infestations	Yes	1203	1	0.08	1259	0	0.00	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Respiratory, thoracic and mediastinal	Yes	1203	1	0.08	1259	0	0.00	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
During present pregnancy, but date unknown	Any event	Yes	1203	15	1.25	1259	3	0.24	2462	18	0.73
		Chronic Disease	1203	11	0.91	1259	2	0.16	2462	13	0.53
	Blood and lymphatic system	Yes	1203	1	0.08	1259	0	0.00	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Cardiac	Yes	1203	4	0.33	1259	1	0.08	2462	5	0.20
		Chronic Disease	1203	4	0.33	1259	1	0.08	2462	5	0.20
	Endocrine	Yes	1203	4	0.33	1259	0	0.00	2462	4	0.16
		Chronic Disease	1203	4	0.33	1259	0	0.00	2462	4	0.16
	Gastrointestinal	Yes	1203	1	0.08	1259	0	0.00	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Infections and infestations	Yes	1203	1	0.08	1259	1	0.08	2462	2	0.08
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Renal and urinary	Yes	1203	1	0.08	1259	0	0.00	2462	1	0.04
		Chronic Disease	1203	1	0.08	1259	0	0.00	2462	1	0.04
	Respiratory, thoracic and mediastinal	Yes	1203	3	0.25	1259	0	0.00	2462	3	0.12
		Chronic Disease	1203	2	0.17	1259	0	0.00	2462	2	0.08
	Skin and subcutaneous tissue	Yes	1203	0	0.00	1259	1	0.08	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00

			Exposed Cohort			Unexposed Cohort			Total		
Diagnosis before or during pregnancy	**MedDRA system organic class**	**Categories**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Unknown	Any event	Yes	1203	108	8.98	1259	142	11.28	2462	250	10.15
		Chronic Disease	1203	73	6.07	1259	92	7.31	2462	165	6.70
	Blood and lymphatic system	Yes	1203	10	0.83	1259	11	0.87	2462	21	0.85
		Chronic Disease	1203	5	0.42	1259	7	0.56	2462	12	0.49
	Cardiac	Yes	1203	31	2.58	1259	38	3.02	2462	69	2.80
		Chronic Disease	1203	28	2.33	1259	32	2.54	2462	60	2.44
	Endocrine	Yes	1203	19	1.58	1259	19	1.51	2462	38	1.54
		Chronic Disease	1203	16	1.33	1259	19	1.51	2462	35	1.42
	Gastrointestinal	Yes	1203	0	0.00	1259	2	0.16	2462	2	0.08
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Hepatobiliary	Yes	1203	2	0.17	1259	0	0.00	2462	2	0.08
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Infections and infestations	Yes	1203	5	0.42	1259	19	1.51	2462	24	0.97
		Chronic Disease	1203	0	0.00	1259	8	0.64	2462	8	0.32
	Metabolism and nutrition	Yes	1203	5	0.42	1259	10	0.79	2462	15	0.61
		Chronic Disease	1203	4	0.33	1259	8	0.64	2462	12	0.49
	Musculoskeletal and connective tissue	Yes	1203	2	0.17	1259	0	0.00	2462	2	0.08
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Neoplasm benign, malignant and unspecified	Yes	1203	0	0.00	1259	11	0.87	2462	11	0.45
		Chronic Disease	1203	0	0.00	1259	3	0.24	2462	3	0.12
	Nervous system	Yes	1203	8	0.67	1259	7	0.56	2462	15	0.61
		Chronic Disease	1203	7	0.58	1259	6	0.48	2462	13	0.53
	Psychiatric	Yes	1203	3	0.25	1259	2	0.16	2462	5	0.20
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Renal and urinary	Yes	1203	5	0.42	1259	2	0.16	2462	7	0.28
		Chronic Disease	1203	1	0.08	1259	2	0.16	2462	3	0.12
	Reproductive system and breast	Yes	1203	0	0.00	1259	4	0.32	2462	4	0.16
		Chronic Disease	1203	0	0.00	1259	2	0.16	2462	2	0.08
	Respiratory, thoracic and mediastinal	Yes	1203	21	1.75	1259	27	2.14	2462	48	1.95

			Exposed Cohort			Unexposed Cohort			Total		
Diagnosis before or during pregnancy	**MedDRA system organic class**	**Categories**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
		Chronic Disease	1203	10	0.83	1259	11	0.87	2462	21	0.85
	Skin and subcutaneous tissue	Yes	1203	2	0.17	1259	2	0.16	2462	4	0.16
		Chronic Disease	1203	1	0.08	1259	1	0.08	2462	2	0.08
	Vascular	Yes	1203	2	0.17	1259	1	0.08	2462	3	0.12
		Chronic Disease	1203	1	0.08	1259	1	0.08	2462	2	0.08
Overall	Any event	Yes	1203	131	10.89	1259	168	13.34	2462	299	12.14
		Chronic Disease	1203	89	7.40	1259	113	8.98	2462	202	8.20
	Blood and lymphatic system	Yes	1203	11	0.91	1259	12	0.95	2462	23	0.93
		Chronic Disease	1203	5	0.42	1259	7	0.56	2462	12	0.49
	Cardiac	Yes	1203	39	3.24	1259	51	4.05	2462	90	3.66
		Chronic Disease	1203	36	2.99	1259	45	3.57	2462	81	3.29
	Ear and labyrinth	Yes	1203	0	0.00	1259	1	0.08	2462	1	0.04
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Endocrine	Yes	1203	24	2.00	1259	22	1.75	2462	46	1.87
		Chronic Disease	1203	21	1.75	1259	22	1.75	2462	43	1.75
	Gastrointestinal	Yes	1203	1	0.08	1259	2	0.16	2462	3	0.12
		Chronic Disease	1203	0	0.00	1259	0	0.00	2462	0	0.00
	Hepatobiliary	Yes	1203	2	0.17	1259	1	0.08	2462	3	0.12
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Infections and infestations	Yes	1203	7	0.58	1259	20	1.59	2462	27	1.10
		Chronic Disease	1203	0	0.00	1259	9	0.71	2462	9	0.37
	Metabolism and nutrition	Yes	1203	6	0.50	1259	12	0.95	2462	18	0.73
		Chronic Disease	1203	5	0.42	1259	10	0.79	2462	15	0.61
	Musculoskeletal and connective tissue	Yes	1203	2	0.17	1259	1	0.08	2462	3	0.12
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Neoplasm benign, malignant and unspecified	Yes	1203	0	0.00	1259	12	0.95	2462	12	0.49
		Chronic Disease	1203	0	0.00	1259	4	0.32	2462	4	0.16
	Nervous system	Yes	1203	8	0.67	1259	9	0.71	2462	17	0.69
		Chronic Disease	1203	7	0.58	1259	7	0.56	2462	14	0.57
	Psychiatric	Yes	1203	3	0.25	1259	2	0.16	2462	5	0.20

			Exposed Cohort			Unexposed Cohort			Total		
Diagnosis before or during pregnancy	**MedDRA system organic class**	**Categories**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
		Chronic Disease	1203	0	0.00	1259	1	0.08	2462	1	0.04
	Renal and urinary	Yes	1203	8	0.67	1259	4	0.32	2462	12	0.49
		Chronic Disease	1203	3	0.25	1259	3	0.24	2462	6	0.24
	Reproductive system and breast	Yes	1203	0	0.00	1259	4	0.32	2462	4	0.16
		Chronic Disease	1203	0	0.00	1259	2	0.16	2462	2	0.08
	Respiratory, thoracic and mediastinal	Yes	1203	26	2.16	1259	28	2.22	2462	54	2.19
		Chronic Disease	1203	12	1.00	1259	11	0.87	2462	23	0.93
	Skin and subcutaneous tissue	Yes	1203	2	0.17	1259	3	0.24	2462	5	0.20
		Chronic Disease	1203	1	0.08	1259	1	0.08	2462	2	0.08
	Vascular	Yes	1203	2	0.17	1259	2	0.16	2462	4	0.16
		Chronic Disease	1203	1	0.08	1259	1	0.08	2462	2	0.08

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
Note: Do not have available data for 14 subjects

Table 15 Summary of characteristics of previous pregnancies (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Previous pregnancies	Yes	728	60.7	661	53.0	1389	56.8
	No	471	39.3	587	47.0	1058	43.2
	Missing	4	-	11	-	15	-
Gravidity	N	728	-	661	-	1389	-
	Mean	1.85	-	1.78	-	1.81	-
	SD	1.13	-	1.11	-	1.12	-
	Median	1.00	-	1.00	-	1.00	-
	Minimum	1.00	-	1.00	-	1.00	-
	Maximum	7.00	-	9.00	-	9.00	-
	Missing	475	-	598	-	1073	-
Parity category	0	68	9.3	72	10.9	140	10.1
	1	366	50.3	353	53.4	719	51.8
	2	189	26.0	173	26.2	362	26.1
	3-4	94	12.9	56	8.5	150	10.8
	5-HIGH	11	1.5	7	1.1	18	1.3
	Missing	0	0.0	0	0.0	0	0.0
	NA	475	-	598	-	1073	-
parity	N	728	-	661	-	1389	-
	Mean	1.52	-	1.39	-	1.46	-
	SD	1.02	-	0.95	-	0.99	-
	Median	1.00	-	1.00	-	1.00	-
	Minimum	0.00	-	0.00	-	0.00	-
	Maximum	7.00	-	9.00	-	9.00	-
	Missing	475	-	598	-	1073	-
Live births	Yes	655	90.1	583	89.0	1238	89.6
	No	72	9.9	72	11.0	144	10.4
	Missing	1	-	6	-	7	-
	NA	475	-	598	-	1073	-
Still births	Yes	19	2.6	9	1.4	28	2.0
	No	707	97.4	646	98.6	1353	98.0
	Missing	2	-	6	-	8	-
	NA	475	-	598	-	1073	-
Congenital anomalies	Yes	4	0.5	1	0.2	5	0.4
	No	724	99.5	653	99.8	1377	99.6
	Missing	0	0.0	7	-	7	-
	NA	475	-	598	-	1073	-
Ectopic pregnancies	Yes	7	1.0	8	1.2	15	1.1
	No	721	99.0	652	98.8	1373	98.9
	Missing	0	0.0	1	-	1	-
	NA	475	-	598	-	1073	-
Molar pregnancies	Yes	1	0.1	0	0.0	1	0.1
	No	727	99.9	661	100	1388	99.9
	Missing	0	0.0	0	0.0	0	0.0
	NA	475	-	598	-	1073	-
Miscarriages	Yes	195	26.8	192	29.0	387	27.9
	No	533	73.2	469	71.0	1002	72.1
	Missing	0	0.0	0	0.0	0	0.0
	NA	475	-	598	-	1073	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil

Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
Note: Do not have available data for 14 subjects

Table 16 Summary of pregnancy-related events/complications in previous pregnancies (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Any event	Yes	115	16.0	108	18.2	223	17.0
	No	605	84.0	487	81.8	1092	83.0
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Pre-eclampsia	Yes	28	3.9	20	3.4	48	3.7
	No	692	96.1	575	96.6	1267	96.3
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Eclampsia	Yes	2	0.3	4	0.7	6	0.5
	No	718	99.7	591	99.3	1309	99.5
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
HELLP syndrome	Yes	0	0.0	0	0.0	0	0.0
	No	720	100	595	100	1315	100
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Infection	Yes	7	1.0	4	0.7	11	0.8
	No	713	99.0	590	99.3	1303	99.2
	Missing	8	-	67	-	75	-
	NA	475	-	598	-	1073	-
Gestational diabetes	Yes	10	1.4	11	1.8	21	1.6
	No	710	98.6	584	98.2	1294	98.4
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Vaginal hemorrhage	Yes	3	0.4	9	1.5	12	0.9
	No	717	99.6	586	98.5	1303	99.1
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Premature rupture of membranes	Yes	6	0.8	4	0.7	10	0.8
	No	714	99.2	591	99.3	1305	99.2
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Preterm premature rupture of membranes	Yes	15	2.1	8	1.3	23	1.7
	No	705	97.9	587	98.7	1292	98.3
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Premature uterine contractions	Yes	26	3.6	24	4.0	50	3.8
	No	694	96.4	571	96.0	1265	96.2
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Pregnancy-related hypertension	Yes	28	3.9	35	5.9	63	4.8
	No	692	96.1	560	94.1	1252	95.2
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-
Neonatal death	Yes	6	0.8	9	1.5	15	1.1
	No	714	99.2	586	98.5	1300	98.9
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Neonatal hypoxic ischemic encephalopathy	Yes	1	0.1	1	0.2	2	0.2
	No	719	99.9	594	99.8	1313	99.8
	Missing	8	-	66	-	74	-
	NA	475	-	598	-	1073	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = Total number of subjects
n = Number of subjects in a given category
% = n / number of subjects with available results x 100
NA: Number of subjects who had their previous pregnancy values as No or Missing
Note: Do not have available data for 14 subjects

Table 17 Summary of new born safety events in previous pregnancies (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Any event	Yes	149	26.5	112	23.3	261	25.0
	No	414	73.5	369	76.7	783	75.0
	Missing	165	-	180	-	345	-
	NA	475	-	598	-	1073	-
Preterm babies - less than 37 weeks	Yes	79	13.2	69	13.5	148	13.4
	No	519	86.8	441	86.5	960	86.6
	Missing	130	-	151	-	281	-
	NA	475	-	598	-	1073	-
Post term babies - greater than 41 weeks	Yes	17	2.8	9	1.8	26	2.4
	No	580	97.2	499	98.2	1079	97.6
	Missing	131	-	153	-	284	-
	NA	475	-	598	-	1073	-
New born with low birth weight less than 2500 grams	Yes	72	12.8	58	11.5	130	12.2
	No	490	87.2	446	88.5	936	87.8
	Missing	166	-	157	-	323	-
	NA	475	-	598	-	1073	-
New born with birth weight greater than 4000 grams	Yes	29	5.1	16	3.2	45	4.2
	No	538	94.9	488	96.8	1026	95.8
	Missing	161	-	157	-	318	-
	NA	475	-	598	-	1073	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = Total number of subjects
n = Number of subjects in a given category
% = n / number of subjects with available results x 100
NA: Number of subjects who had their previous pregnancy values as No or Missing
Note1: Do not have available data for 14 subjects
Note2: One subject (among 14 subjects under missing category) had New born with low birth weight less than 2500 grams category this subject was not presented (as of other 13 subjects) as no other information was available for this subject

Table 18 Summary of new born safety events in subjects with at least one delivery in previous pregnancies

		Exposed Cohort N = 660		Unexposed Cohort N = 589		Total N = 1249	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Any event	Yes	149	27.1	112	23.6	261	25.5
	No	401	72.9	363	76.4	764	74.5
	Missing	110	-	114	-	224	-
Preterm babies - less than 37 weeks	Yes	79	13.5	69	13.7	148	13.6
	No	506	86.5	435	86.3	941	86.4
	Missing	75	-	85	-	160	-
Post term babies - greater than 41 weeks	Yes	17	2.9	9	1.8	26	2.4
	No	567	97.1	493	98.2	1060	97.6
	Missing	76	-	87	-	163	-
New born with low birth weight less than 2500 grams	Yes	72	13.1	58	11.6	130	12.4
	No	477	86.9	440	88.4	917	87.6
	Missing	111	-	91	-	202	-
New born with birth weight greater than 4000 grams	Yes	29	5.2	16	3.2	45	4.3
	No	525	94.8	482	96.8	1007	95.7
	Missing	106	-	91	-	197	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N =Number of subjects with at least one delivery in previous pregnancies
n = Number of subjects in a given category
% = n / number of subjects with available results x 100

Table 19 Summary of congenital anomalies at baseline (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Any congenital anomalies	Yes	5	0.4	2	0.2	7	0.3
	No	1194	99.6	1246	99.8	2440	99.7
	Missing	4	-	11	-	15	-
Congenital anomalies in the subject	Yes	1	25.0	2	100	3	50.0
	No	3	75.0	0	0.0	3	50.0
	Missing/NA	1199	-	1257	-	2456	-
Congenital anomalies for spouse	Yes	0	0.0	0	0.0	0	0.0
	No	4	100	1	100	5	100
	Missing/NA	1199	-	1258	-	2457	-
Congenital anomalies for first degree relatives	Yes	4	100	0	0.0	4	80.0
	No	0	0.0	1	100	1	20.0
	Missing/NA	1199	-	1258	-	2457	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
Note: Do not have available data for 14 subjects

Table 20 Summary of delivery details in current pregnancy (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Gestational age in weeks at the time of delivery	N	1199	-	1248	-	2447	-
	Mean	38.74	-	38.40	-	38.57	-
	SD	1.39	-	2.08	-	1.79	-
	Median	39.00	-	39.00	-	39.00	-
	Minimum	28.00	-	20.00	-	20.00	-
	Maximum	42.00	-	42.00	-	42.00	-
	Missing	4	-	11	-	15	-
Gestational age group in weeks at the time of delivery	<28 weeks [extreme preterm]	0	0.0	6	0.5	6	0.2
	28 to <32 weeks [very preterm]	3	0.3	11	0.9	14	0.6
	32 to <34 weeks [moderate preterm]	4	0.3	16	1.3	20	0.8
	34 to <37 weeks [late preterm]	57	4.8	95	7.6	152	6.2
	37 to <42 weeks [term]	1132	94.4	1109	88.9	2241	91.6
	42 and above [post-term]	3	0.3	11	0.9	14	0.6
	Missing	4	-	11	-	15	-
Assisted fertilization	Yes	4	0.3	1	0.1	5	0.2
	No	1194	99.7	1247	99.9	2441	99.8
	Missing	5	-	11	-	16	-
Multiparous women	Yes	728	60.7	661	53.0	1389	56.8
	Missing	4	-	11	-	15	-
Nulliparous pregnant of multiples during current pregnancy	Yes	1	0.1	6	0.5	7	0.3
	Missing	4	-	11	-	15	-
Nulliparous women with single fetuses	Yes	470	39.2	581	46.6	1051	43.0
	Missing	4	-	11	-	15	-
Total number of fetuses	1	672	99.3	587	98.2	1259	98.7
	2	5	0.7	11	1.8	16	1.3
	Missing	526	-	661	-	1187	-
Vaginal birth	Yes	686	62.1	633	96.1	1319	74.8
	No	418	37.9	26	3.9	444	25.2
	Missing	99	-	600	-	699	-
Type of vaginal birth	Normal	613	89.4	501	79.1	1114	84.5
	Forceps	73	10.6	132	20.9	205	15.5
	NA	517	-	626	-	1143	-
Caesarean birth	Yes	513	47.7	615	95.1	1128	65.5
	No	562	52.3	32	4.9	594	34.5
	Missing	128	-	612	-	740	-
Type of caesarean birth	Emergency	453	88.3	538	87.5	991	87.9
	Planned	60	11.7	77	12.5	137	12.1
	NA	690	-	644	-	1334	-
Still birth [intrauterine fetal death]	Yes	1	0.1	6	0.5	7	0.3
	No	1112	99.9	1143	99.5	2255	99.7
	Missing	90	-	110	-	200	-
Number of still births	1	1	100	6	100	7	100
	NA	1202	-	1253	-	2455	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100
SD = Standard deviation
Note: Do not have available data for 14 subjects

Table 21 Summary of ultrasound details in current pregnancy (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Ultra sound available?	Yes	1199	100	1248	100	2447	100
	No	0	0.0	0	0.0	0	0.0
	Missing	4	-	11	-	15	-
Gestational age during the earliest ultrasound done in weeks	N	1199	-	1248	-	2447	-
	Mean	10.56	-	10.53	-	10.55	-
	SD	2.93	-	2.92	-	2.92	-
	Median	11.00	-	10.00	-	11.00	-
	Minimum	1.00	-	3.00	-	1.00	-
	Maximum	16.00	-	17.00	-	17.00	-
	Missing	4	-	11	-	15	-
First trimester result*	Normal	1177	99.7	1231	99.7	2408	99.7
	Abnormal	3	0.3	4	0.3	7	0.3
	NA	23	-	24	-	47	-
second trimester result*	Normal	967	99.3	36	75.0	1003	98.1
	Abnormal	7	0.7	12	25.0	19	1.9
	NA	229	-	1211	-	1440	-
third trimester result*	Normal	725	94.4	147	50.9	872	82.5
	Abnormal	43	5.6	142	49.1	185	17.5
	NA	435	-	970	-	1405	-
First US done**	First	1180	98.9	1235	99.0	2415	98.9
	Second	13	1.1	13	1.0	26	1.1
	Third	0	0.0	0	0.0	0	0.0
	NA	10	-	11	-	21	-
First abnormal US seen***	First	3	6.1	4	2.6	7	3.4
	Second	6	12.2	12	7.7	18	8.8
	Third	40	81.6	139	89.7	179	87.7
	NA	1154	-	1104	-	2258	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
Note: * Worst outcome was used if subject reported more than one ultrasound
**No.of subjects who had their first ultrasound in first or second or third trimester with available results
***No.of subjects who had their first abnormal ultrasound seen in first or second or third trimester
N = Total number of subjects
n = Number of subjects in a given category
% = n / number of subjects with available results x 100
Note: Do not have available data for 14 subjects

Table 22 Summary of hospitalization details in current pregnancy (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Hospitalization	Yes	48	4.0	141	11.3	189	7.7
	No	1151	96.0	1107	88.7	2258	92.3
	Missing	4	-	11	-	15	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
Note: Do not have available data for 14 subjects

Table 23 Summary of hospitalization details in current pregnancy by system organ class (Total cohort)

	Exposed Cohort N= 1203		Unexposed Cohort N= 1259		Total N= 2462	
MedDRA System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**
Blood and lymphatic system disorders	1	0.08	4	0.32	5	0.20
Cardiac disorders	0	0.0	1	0.08	1	0.04
Gastrointestinal disorders	1	0.08	0	0.0	1	0.04
General disorders and administration site conditions	1	0.08	0	0.0	1	0.04
Hepatobiliary disorders	1	0.08	0	0.0	1	0.04
Infections and infestations	12	1.00	33	2.62	45	1.83
Injury, poisoning and procedural complications	1	0.08	0	0.0	1	0.04
Metabolism and nutrition disorders	1	0.08	9	0.71	10	0.41
Musculoskeletal and connective tissue disorders	1	0.08	1	0.08	2	0.08
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.08	1	0.08	2	0.08
Nervous system disorders	0	0.0	2	0.16	2	0.08
Pregnancy, puerperium and perinatal conditions	24	2.00	88	6.99	112	4.55
Psychiatric disorders	1	0.08	0	0.0	1	0.04
Renal and urinary disorders	3	0.25	2	0.16	5	0.20
Respiratory, thoracic and mediastinal disorders	1	0.08	1	0.08	2	0.08
Surgical and medical procedures	2	0.17	3	0.24	5	0.20
Vascular disorders	1	0.08	6	0.48	7	0.28

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = Total number of subjects
n = Number of subjects in a given category
% = n /N x 100
Note: Do not have available data for 14 subjects

Table 24 Summary of habits in current pregnancy (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Smoking - Before current pregnancy	Yes	97	8.1	144	11.6	241	9.9
	No	1099	91.9	1101	88.4	2200	90.1
	Missing	7	-	14	-	21	-
Type of smoker-Before	Occasional smoker	2	2.1	3	2.2	5	2.1
	Regular smoker	94	97.9	135	97.8	229	97.9
	Missing	1	-	6	-	7	-
	NA	1106	-	1115	-	2221	-
Type of regular smoker-Before	Light-smoker (1-9 cigarettes/day)	58	61.7	80	59.7	138	60.5
	Moderate to heavy smoker (≥ 10 cigarettes/day)	36	38.3	54	40.3	90	39.5
	Missing	0	-	1	-	1	-
	NA	1109	-	1124	-	2233	-
Smoking - During current pregnancy	Yes	93	7.8	132	10.6	225	9.2
	No	1101	92.2	1114	89.4	2215	90.8
	Missing	9	-	13	-	22	-
Type of smoker-During	Occasional smoker	2	2.2	2	1.6	4	1.8
	Regular smoker	90	97.8	124	98.4	214	98.2
	Missing	1	-	6	-	7	-
	NA	1110	-	1127	-	2237	-
Type of regular smoker - During	Light-smoker (1-9 cigarettes/day)	58	64.4	74	59.7	132	61.7
	Moderate to heavy smoker (≥ 10 cigarettes/day)	32	35.6	50	40.3	82	38.3
	NA	1113	-	1135	-	2248	-
Before current pregnancy-Alcohol	Yes	12	1.0	33	2.7	45	1.8
	No	1185	99.0	1207	97.3	2392	98.2
	Missing	6	-	19	-	25	-
Type of drinker-Before	Heavy drinker (≥ 8 drinks/week)	0	0.0	2	6.3	2	4.7
	Moderate drinker (up to 1 drink/day)	4	36.4	3	9.4	7	16.3
	Occasional drinker	7	63.6	27	84.4	34	79.1
	Missing	1	-	1	-	2	-
	NA	1191	-	1226	-	2417	-
During current pregnancy-Alcohol	Yes	12	1.0	31	2.5	43	1.8
	No	1183	99.0	1210	97.5	2393	98.2
	Missing	8	-	18	-	26	-
Type of drinker-During	Moderate drinker (up to 1 drink/day)	4	36.4	3	10.0	7	17.1
	Occasional drinker	7	63.6	27	90.0	34	82.9
	Missing	1	-	1	-	2	-
	NA	1191	-	1228	-	2419	-
Illicit drugs	Yes	7	0.6	16	1.3	23	0.9
	No	1192	99.4	1232	98.7	2424	99.1
	Missing	4	-	11	-	15	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects

n = number of subjects in a given category
% = n / Number of subjects with available results x 100
Note: Do not have available data for 14 subjects

Table 25 Summary of risk factors and additional information in current pregnancy (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Placenta abruption	Yes	1	0.1	11	0.9	12	0.5
	No	1198	99.9	1237	99.1	2435	99.5
	Missing	4	-	11	-	15	-
Placenta previa	Yes	4	0.3	3	0.2	7	0.3
	No	1195	99.7	1245	99.8	2440	99.7
	Missing	4	-	11	-	15	-
Infection	Yes	287	23.9	353	28.3	640	26.2
	No	912	76.1	895	71.7	1807	73.8
	Missing	4	-	11	-	15	-
Additional information on the subject	Yes	19	1.6	18	1.4	37	1.5
	No	1180	98.4	1230	98.6	2410	98.5
	Missing	4	-	11	-	15	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
Note: Do not have available data for 14 subjects

Table 26 Summary of chronic medications in current pregnancy (Total cohort)

		Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Characteristics	**Categories**	**n**	**%**	**n**	**%**	**n**	**%**
Chronic medications used during present pregnancy	Yes	144	12.0	170	13.6	314	12.8
	No	1055	88.0	1078	86.4	2133	87.2
	Missing	4	-	11	-	15	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
Note: Do not have available data for 14 subjects

Table 27 Summary of medical indications for chronic medication by system organ class in current pregnancy (Total cohort)

	Exposed Cohort N= 1203		Unexposed Cohort N= 1259		Total N= 2462	
MedDRA System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**
Blood and lymphatic system disorders	3	0.25	10	0.79	13	0.53
Cardiac disorders	2	0.17	1	0.08	3	0.12
Endocrine disorders	20	1.66	19	1.51	39	1.58
Infections and infestations	10	0.83	13	1.03	23	0.93
Metabolism and nutrition disorders	7	0.58	7	0.56	14	0.57
Musculoskeletal and connective tissue disorders	1	0.08	1	0.08	2	0.08
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0.0	1	0.08	1	0.04
Nervous system disorders	7	0.58	7	0.56	14	0.57
Pregnancy, puerperium and perinatal conditions	57	4.74	75	5.96	132	5.36
Psychiatric disorders	5	0.42	2	0.16	7	0.28
Renal and urinary disorders	0	0.0	1	0.08	1	0.04
Respiratory, thoracic and mediastinal disorders	5	0.42	2	0.16	7	0.28
Skin and subcutaneous tissue disorders	1	0.08	1	0.08	2	0.08
Vascular disorders	32	2.66	44	3.49	76	3.09

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
N = Total number of subjects
n = Number of subjects in a given category
% = n /N x 100
Note: Do not have available data for 14 subjects

Table 28 Summary of worst pregnancy related hypertension in current pregnancy (Total cohort)

	Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Categories	**n**	**%**	**n**	**%**	**n**	**%**
Eclampsia(After)	2	0.17	0	0.00	2	0.08
Eclampsia(Before)	1	0.08	0	0.00	1	0.04
HELLP Syndrome(After)	0	0.00	1	0.08	1	0.04
HELLP Syndrome(Before)	2	0.17	0	0.00	2	0.08
Pre-Eclampsia(After)	9	0.75	30	2.38	39	1.58
Pre-Eclampsia(Before)	8	0.67	6	0.48	14	0.57

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
n: Worst event among pre-eclampsia, eclampsia and HELLP will be counted per subject
N = Total number of subjects
% = n / N x 100
Note: Do not have available data for 14 subjects

Table 29 Summary of pregnancy related hypertension in current pregnancy (Total cohort)

	Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Categories	**n**	**%**	**n**	**%**	**n**	**%**
Eclampsia	1	0.08	0	0.00	1	0.04
HELLP Syndrome	2	0.17	1	0.08	3	0.12
Pre-Eclampsia	17	1.41	36	2.86	53	2.15
Pre-Eclampsia and Eclampsia*	2	0.17	0	0.00	2	0.08

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
n: One event during current pregnancy
*: Multiple events during current pregnancy
N = Total number of subjects
% = n / N x 100
Note: Do not have available data for 14 subjects
In the total cohort, 146 pregnant women experienced gestational or pregnancy related hypertension independently of pre-eclampsia or eclampsia. For 93 subjects in the exposed cohort and 53 subjects in the unexposed cohort, pregnancy-related hypertension (after 20 weeks of gestation), gestational hypertension (after 20 weeks of gestation) or hypertensive disorders in pregnancy (HDP start date UNK) were recorded in the free text variable of the eCRF.

Table 30 Summary of pregnancy related hypertension evolution during current pregnancy (Total cohort)

	Exposed Cohort N = 1203		Unexposed Cohort N = 1259		Total N = 2462	
Categories	**n**	**%**	**n**	**%**	**n**	**%**
Pre-Eclampsia (After), Eclampsia (After)	1	0.08	0	0.00	1	0.04
Pre-Eclampsia (Before), Eclampsia (Before)	1	0.08	0	0.00	1	0.04

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
n = Number of subjects in a given category
N = Total number of subjects
% = n / N x 100
Before: Event occurred before index date for unexposed cohort, vaccination date (for exposed cohort)
After: Event occurred after index date for unexposed cohort, vaccination date (for exposed cohort)
Note: Do not have available data for 14 subjects

Table 31 Tdap vaccination history data (Exposed cohort)

		Exposed cohort N = 1203	
Characteristics	**Categories**	**n**	**%**
Had the subject received any Tdap vaccination during pregnancy?	Yes	1199	100
	Missing	4	-
Dose number	1	1199	100
	Missing	4	-
Gestational age at the time of vaccination-in weeks	27	229	19.1
	28	245	20.5
	29	190	15.9
	30	155	12.9
	31	106	8.9
	32	77	6.4
	33	74	6.2
	34	58	4.8
	35	35	2.9
	36	26	2.2
	37	1	0.1
	39	1	0.1
	Missing	6	-

Exposed cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100

Table 32 Concomitant vaccination history data (Exposed cohort)

		Exposed cohort N = 1203	
Characteristics	**Categories**	**n**	**%**
Had the subject received other than Tdap vaccination during pregnancy?	Yes	1127	94.0
	No	72	6.0
	Missing/NA	4	-
HEPATITIS B vaccine taken in first trimester?	Yes	234	20.8
	No	893	79.2
	Missing/NA	76	-
HEPATITIS B [First trimester]	One dose	213	91.0
	Two doses	21	9.0
	Three doses	0	0.0
	Missing/NA	969	-
HEPATITIS B vaccine taken in second trimester?	Yes	323	28.7
	No	804	71.3
	Missing/NA	76	-
HEPATITIS B [Second trimester]	One dose	243	75.2
	Two doses	80	24.8
	Three doses	0	0.0
	Missing/NA	880	-
HEPATITIS B vaccine taken in third trimester?	Yes	244	21.7
	No	883	78.3
	Missing/NA	76	-
HEPATITIS B [Third trimester]	One dose	208	85.2
	Two doses	36	14.8
	Three doses	0	0.0
	Missing/NA	959	-
HEPATITIS B [overall]	One dose	121	26.1
	Two doses	211	45.5
	Three doses	132	28.4
	Missing/NA	739	-
HINI vaccine taken in first trimester?	Yes	456	40.5
	No	671	59.5
	Missing/NA	76	-
HINI [First trimester]	One dose	455	99.8
	Two doses	1	0.2
	Three doses	0	0.0
	Missing/NA	747	-
HINI vaccine taken in second trimester?	Yes	377	33.5
	No	750	66.5
	Missing/NA	76	-
HINI [Second trimester]	One dose	377	100
	Two doses	0	0.0
	Three doses	0	0.0
	Missing/NA	826	-
HINI vaccine taken in third trimester?	Yes	232	20.6
	No	895	79.4
	Missing/NA	76	-
HINI [Third trimester]	One dose	232	100
	Two doses	0	0.0
	Three doses	0	0.0
	Missing/NA	971	-

		Exposed cohort N = 1203	
Characteristics	**Categories**	**n**	**%**
HINI [overall]	One dose	1059	99.6
	Two doses	3	0.3
	Three doses	1	0.1
	Missing/NA	140	-
Diphteria/tetanus vaccine taken in first trimester?	Yes	248	22.0
	No	879	78.0
	Missing/NA	76	-
Diphtheria/tetanus [First trimester]	One dose	241	97.2
	Two doses	7	2.8
	Three doses	0	0.0
	Missing/NA	955	-
Diphtheria/tetanus vaccine taken in second trimester?	Yes	219	19.4
	No	908	80.6
	Missing/NA	76	-
Diphtheria/tetanus [Second trimester]	One dose	207	94.5
	Two doses	12	5.5
	Three doses	0	0.0
	Missing/NA	984	-
Diphtheria/tetanus vaccine taken in third trimester?	Yes	32	2.8
	No	1095	97.2
	Missing/NA	76	-
Diphtheria/tetanus [Third trimester]	One dose	31	96.9
	Two doses	1	3.1
	Three doses	0	0.0
	Missing/NA	1171	-
Diphtheria/tetanus [overall]	One dose	257	66.6
	Two doses	124	32.1
	Three doses	5	1.3
	Missing/NA	817	-
Concomitant vaccine taken in first trimester?	Yes	618	54.8
	No	509	45.2
	Missing/NA	76	-
Concomitant vaccine [First trimester]	One dose	378	61.2
	Two doses	144	23.3
	Three doses	85	13.8
	Four doses	9	1.5
	Five doses	2	0.3
	Six doses	0	0.0
	Seven doses	0	0.0
	Missing/NA	585	-
Concomitant vaccine taken in Second trimester?	Yes	618	54.8
	No	509	45.2
	Missing/NA	76	-
Concomitant vaccine [Second trimester]	One dose	339	54.9
	Two doses	185	29.9
	Three doses	74	12.0
	Four doses	19	3.1
	Five doses	1	0.2
	Six doses	0	0.0
	Seven doses	0	0.0
	Missing/NA	585	-

		Exposed cohort N = 1203	
Characteristics	**Categories**	**n**	**%**
Concomitant vaccine taken in third trimester?	Yes	432	38.3
	No	695	61.7
	Missing/NA	76	-
Concomitant vaccine [third trimester]	One dose	341	78.9
	Two doses	71	16.4
	Three doses	18	4.2
	Four doses	1	0.2
	Five doses	1	0.2
	Six doses	0	0.0
	Seven doses	0	0.0
	Missing/NA	771	-
Concomitant vaccine [overall]	One dose	568	50.4
	Two doses	170	15.1
	Three doses	142	12.6
	Four doses	103	9.1
	Five doses	84	7.5
	Six doses	57	5.1
	Seven doses	3	0.3
	Missing/NA	76	-

Exposed cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100

Table 33 Vaccination summary (Exposed cohort)

	Exposed cohort N = 1203	
Categories	**n**	**%**
Co-vaccinated cohort	1127	94.0
Tdap single vaccinated cohort	72	6.0

Exposed cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
N = Total number of subjects
n = Number of subjects in a given category
% = n / N x 100

14.1.2. Primary objective results

Table 34 Summary of birth outcome and Apgar score data in subjects without still births in current pregnancy

		Exposed Cohort N = 1202		Unexposed Cohort N = 1253		Total N = 2455	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Any birth outcome	Yes	110	9.2	158	12.8	268	11.0
	No	1088	90.8	1078	87.2	2166	89.0
	Missing	4	-	17	-	21	-
Small for gestational age[SGA]	Yes	68	5.7	62	5.0	130	5.3
	No	1130	94.3	1173	95.0	2303	94.7
	Missing	4	-	18	-	22	-
SGA - Height[cm]	N	62	-	58	-	120	-
	Mean	44.81	-	43.24	-	44.05	-
	SD	2.39	-	2.88	-	2.74	-
	Median	45.50	-	44.00	-	44.50	-
	Minimum	35.70	-	35.50	-	35.50	-
	Maximum	48.00	-	48.00	-	48.00	-
	Missing	1140	-	1195	-	2335	-
SGA - Weight[kg]	N	68	-	62	-	130	-
	Mean	2.28	-	2.00	-	2.15	-
	SD	0.37	-	0.50	-	0.46	-
	Median	2.40	-	2.20	-	2.30	-
	Minimum	1.00	-	0.50	-	0.50	-
	Maximum	3.00	-	2.70	-	3.00	-
	Missing	1134	-	1191	-	2325	-
SGA – BMI[kg/m**2]	N	62	-	58	-	120	-
	Mean	11.49	-	10.93	-	11.22	-
	SD	1.06	-	1.63	-	1.39	-
	Median	11.60	-	11.34	-	11.35	-
	Minimum	7.85	-	5.55	-	5.55	-
	Maximum	13.68	-	14.60	-	14.60	-
	Missing	1140	-	1195	-	2335	-
Preterm birth [<37 weeks]	Yes	63	5.3	120	9.7	183	7.5
	No	1135	94.7	1116	90.3	2251	92.5
	Missing	4	-	17	-	21	-
Preterm birth by gestational age category	<28 weeks	0	0.0	3	2.5	3	1.6
	28 to <32 weeks	3	4.8	8	6.7	11	6.0
	32 to <34 weeks	3	4.8	15	12.5	18	9.8
	34 to <37 weeks	57	90.5	94	78.3	151	82.5
	NA	1139	-	1133	-	2272	-
Gestation age [in weeks] for preterm birth babies	N	63	-	120	-	183	-
	Mean	35.10	-	34.38	-	34.63	-
	SD	1.51	-	2.39	-	2.15	-
	Median	36.00	-	35.00	-	35.00	-
	Minimum	28.00	-	24.00	-	24.00	-
	Maximum	36.00	-	36.00	-	36.00	-
	Missing	1139	-	1133	-	2272	-
Preterm birth - Height[cm]	N	55	-	113	-	168	-
	Mean	45.14	-	43.98	-	44.36	-
	SD	2.52	-	3.25	-	3.07	-
	Median	46.00	-	44.00	-	45.00	-
	Minimum	35.70	-	35.50	-	35.50	-

		Exposed Cohort N = 1202		Unexposed Cohort N = 1253		Total N = 2455	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
	Maximum	48.50	-	51.00	-	51.00	-
	Missing	1147	-	1140	-	2287	-
Preterm birth - Weight[kg]	N	63	-	120	-	183	-
	Mean	2.39	-	2.28	-	2.32	-
	SD	0.52	-	0.70	-	0.64	-
	Median	2.50	-	2.30	-	2.40	-
	Minimum	1.00	-	0.50	-	0.50	-
	Maximum	3.20	-	4.60	-	4.60	-
	Missing	1139	-	1133	-	2272	-
Preterm birth – BMI[kg/m**2]	N	55	-	113	-	168	-
	Mean	11.99	-	11.90	-	11.93	-
	SD	1.52	-	2.05	-	1.89	-
	Median	12.08	-	11.90	-	11.99	-
	Minimum	7.85	-	5.55	-	5.55	-
	Maximum	15.31	-	19.16	-	19.16	-
	Missing	1147	-	1140	-	2287	-
Overall - Height[cm]	N	1182	-	1226	-	2408	-
	Mean	48.29	-	47.57	-	47.92	-
	SD	2.13	-	2.52	-	2.36	-
	Median	48.25	-	48.00	-	48.00	-
	Minimum	33.00	-	35.50	-	33.00	-
	Maximum	53.50	-	57.00	-	57.00	-
	Missing	20	-	27	-	47	-
Overall - Weight[kg]	N	1198	-	1238	-	2436	-
	Mean	3.19	-	3.13	-	3.16	-
	SD	0.47	-	0.56	-	0.52	-
	Median	3.20	-	3.20	-	3.20	-
	Minimum	1.00	-	0.50	-	0.50	-
	Maximum	4.70	-	5.10	-	5.10	-
	Missing	4	-	15	-	19	-
Overall – BMI[kg/m**2]	N	1182	-	1226	-	2408	-
	Mean	13.68	-	13.80	-	13.74	-
	SD	1.46	-	1.56	-	1.51	-
	Median	13.60	-	13.86	-	13.74	-
	Minimum	7.85	-	5.55	-	5.55	-
	Maximum	28.47	-	22.50	-	28.47	-
	Missing	20	-	27	-	47	-
Head circumference[cm]	N	1197	-	1225	-	2422	-
	Mean	34.05	-	34.09	-	34.07	-
	SD	1.70	-	1.94	-	1.83	-
	Median	34.00	-	34.00	-	34.00	-
	Minimum	3.20	-	3.70	-	3.20	-
	Maximum	39.00	-	42.50	-	42.50	-
	Missing	5	-	28	-	33	-
Apgar score [Yes/No] at 1 min	Yes	1195	99.7	1237	100	2432	99.9
	No	3	0.3	0	0.0	3	0.1
	Missing	4	-	16	-	20	-
Apgar score category at 1 min	0-3	8	0.7	14	1.1	22	0.9
	4-6	62	5.2	72	5.8	134	5.5
	7-10	1125	94.1	1151	93.0	2276	93.6
	NA	7	-	16	-	23	-

		Exposed Cohort N = 1202		Unexposed Cohort N = 1253		Total N = 2455	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Apgar score at 1 min	N	1195	-	1237	-	2432	-
	Mean	8.32	-	8.41	-	8.37	-
	SD	1.11	-	1.18	-	1.15	-
	Median	9.00	-	9.00	-	9.00	-
	Minimum	0.00	-	1.00	-	0.00	-
	Maximum	10.00	-	10.00	-	10.00	-
	Missing	7	-	16	-	23	-
Apgar score[Yes/No] at 5 mins	Yes	1198	100	1237	100	2435	100
	No	0	0.0	0	0.0	0	0.0
	Missing	4	-	16	-	20	-
Apgar score category at 5 mins	0-3	0	0.0	2	0.2	2	0.1
	4-6	6	0.5	8	0.6	14	0.6
	7-10	1192	99.5	1227	99.2	2419	99.3
	NA	4	-	16	-	20	-
Apgar score at 5 mins	N	1198	-	1237	-	2435	-
	Mean	9.33	-	9.51	-	9.42	-
	SD	0.73	-	0.82	-	0.78	-
	Median	9.00	-	10.00	-	10.00	-
	Minimum	4.00	-	1.00	-	1.00	-
	Maximum	10.00	-	10.00	-	10.00	-
	Missing	4	-	16	-	20	-
Apgar score at 6-10 min[Yes/No]	Yes	10	0.8	16	1.3	26	1.1
	No	1188	99.2	1220	98.7	2408	98.9
	Missing	4	-	17	-	21	-
Apgar score category at [6-10 mins]	5	0	0.0	1	6.3	1	3.8
	6	0	0.0	3	18.8	3	11.5
	7	4	40.0	3	18.8	7	26.9
	8	3	30.0	3	18.8	6	23.1
	9	0	0.0	3	18.8	3	11.5
	10	3	30.0	3	18.8	6	23.1
	NA	1192	-	1237	-	2429	-
Apgar score at [6-10 mins]	N	10	-	16	-	26	-
	Mean	8.20	-	7.81	-	7.96	-
	SD	1.32	-	1.60	-	1.48	-
	Median	8.00	-	8.00	-	8.00	-
	Minimum	7.00	-	5.00	-	5.00	-
	Maximum	10.00	-	10.00	-	10.00	-
	Missing	1192	-	1237	-	2429	-
Birth complications	Yes	240	20.1	326	26.3	566	23.2
	No	957	79.9	912	73.7	1869	76.8
	Missing	5	-	15	-	20	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
Any birth outcome: Small for gestational age, Preterm birth
N = Number of subjects without still births
n = Number of subjects in a given category
Value = Value of the considered parameter
% = n / number of subjects with available results x 100
SD = Standard deviation
Note: one subject with Apgar score at 3 mins has been recorded in Apgar score at 6-10 min category

Table 35 Summary of birth outcome and Apgar score data in subjects without still births and neonatal deaths in current pregnancy

		Exposed Cohort N = 1202		Unexposed Cohort N = 1245		Total N = 2447	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Any birth outcome	Yes	110	9.2	155	12.6	265	10.9
	No	1088	90.8	1078	87.4	2166	89.1
	Missing	4	-	12	-	16	-
Small for gestational age[SGA]	Yes	68	5.7	60	4.9	128	5.3
	No	1130	94.3	1173	95.1	2303	94.7
	Missing	4	-	12	-	16	-
SGA - Height[cm]	N	62	-	58	-	120	-
	Mean	44.81	-	43.24	-	44.05	-
	SD	2.39	-	2.88	-	2.74	-
	Median	45.50	-	44.00	-	44.50	-
	Minimum	35.70	-	35.50	-	35.50	-
	Maximum	48.00	-	48.00	-	48.00	-
	Missing	1140	-	1187	-	2327	-
SGA - Weight[kg]	N	68	-	60	-	128	-
	Mean	2.28	-	2.05	-	2.17	-
	SD	0.37	-	0.45	-	0.42	-
	Median	2.40	-	2.20	-	2.30	-
	Minimum	1.00	-	0.70	-	0.70	-
	Maximum	3.00	-	2.70	-	3.00	-
	Missing	1134	-	1185	-	2319	-
SGA – BMI[kg/m**2]	N	62	-	58	-	120	-
	Mean	11.49	-	10.93	-	11.22	-
	SD	1.06	-	1.63	-	1.39	-
	Median	11.60	-	11.34	-	11.35	-
	Minimum	7.85	-	5.55	-	5.55	-
	Maximum	13.68	-	14.60	-	14.60	-
	Missing	1140	-	1187	-	2327	-
Preterm birth [<37 weeks]	Yes	63	5.3	117	9.5	180	7.4
	No	1135	94.7	1116	90.5	2251	92.6
	Missing	4	-	12	-	16	-
Preterm birth by gestational age category	<28 weeks	0	0.0	1	0.9	1	0.6
	28 to <32 weeks	3	4.8	7	6.0	10	5.6
	32 to <34 weeks	3	4.8	15	12.8	18	10.0
	34 to <37 weeks	57	90.5	94	80.3	151	83.9
	NA	1139	-	1128	-	2267	-
Gestation age [in weeks] for preterm birth babies	N	63	-	117	-	180	-
	Mean	35.10	-	34.60	-	34.77	-
	SD	1.51	-	1.94	-	1.81	-
	Median	36.00	-	35.00	-	35.00	-
	Minimum	28.00	-	26.00	-	26.00	-
	Maximum	36.00	-	36.00	-	36.00	-
	Missing	1139	-	1128	-	2267	-
Preterm birth - Height[cm]	N	55	-	113	-	168	-
	Mean	45.14	-	43.98	-	44.36	-
	SD	2.52	-	3.25	-	3.07	-
	Median	46.00	-	44.00	-	45.00	-
	Minimum	35.70	-	35.50	-	35.50	-
	Maximum	48.50	-	51.00	-	51.00	-
	Missing	1147	-	1132	-	2279	-

		Exposed Cohort N = 1202		Unexposed Cohort N = 1245		Total N = 2447	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Preterm birth - Weight[kg]	N	63	-	117	-	180	-
	Mean	2.39	-	2.32	-	2.35	-
	SD	0.52	-	0.65	-	0.61	-
	Median	2.50	-	2.30	-	2.40	-
	Minimum	1.00	-	0.70	-	0.70	-
	Maximum	3.20	-	4.60	-	4.60	-
	Missing	1139	-	1128	-	2267	-
Preterm birth – BMI[kg/m**2]	N	55	-	113	-	168	-
	Mean	11.99	-	11.90	-	11.93	-
	SD	1.52	-	2.05	-	1.89	-
	Median	12.08	-	11.90	-	11.99	-
	Minimum	7.85	-	5.55	-	5.55	-
	Maximum	15.31	-	19.16	-	19.16	-
	Missing	1147	-	1132	-	2279	-
Overall - Height[cm]	N	1182	-	1226	-	2408	-
	Mean	48.29	-	47.57	-	47.92	-
	SD	2.13	-	2.52	-	2.36	-
	Median	48.25	-	48.00	-	48.00	-
	Minimum	33.00	-	35.50	-	33.00	-
	Maximum	53.50	-	57.00	-	57.00	-
	Missing	20	-	19	-	39	-
Overall - Weight[kg]	N	1198	-	1232	-	2430	-
	Mean	3.19	-	3.14	-	3.16	-
	SD	0.47	-	0.54	-	0.51	-
	Median	3.20	-	3.20	-	3.20	-
	Minimum	1.00	-	0.70	-	0.70	-
	Maximum	4.70	-	5.10	-	5.10	-
	Missing	4	-	13	-	17	-
Overall – BMI[kg/m**2]	N	1182	-	1226	-	2408	-
	Mean	13.68	-	13.80	-	13.74	-
	SD	1.46	-	1.56	-	1.51	-
	Median	13.60	-	13.86	-	13.74	-
	Minimum	7.85	-	5.55	-	5.55	-
	Maximum	28.47	-	22.50	-	28.47	-
	Missing	20	-	19	-	39	-
Head circumference[cm]	N	1197	-	1225	-	2422	-
	Mean	34.05	-	34.09	-	34.07	-
	SD	1.70	-	1.94	-	1.83	-
	Median	34.00	-	34.00	-	34.00	-
	Minimum	3.20	-	3.70	-	3.20	-
	Maximum	39.00	-	42.50	-	42.50	-
	Missing	5	-	20	-	25	-
Apgar score [Yes/No] at 1 min	Yes	1195	99.7	1233	100	2428	99.9
	No	3	0.3	0	0.0	3	0.1
	Missing	4	-	12	-	16	-
Apgar score category at 1 min	0-3	8	0.7	11	0.9	19	0.8
	4-6	62	5.2	71	5.8	133	5.5
	7-10	1125	94.1	1151	93.3	2276	93.7
	NA	7	-	12	-	19	-

		Exposed Cohort N = 1202		Unexposed Cohort N = 1245		Total N = 2447	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Apgar score at 1 min	N	1195	-	1233	-	2428	-
	Mean	8.32	-	8.43	-	8.38	-
	SD	1.11	-	1.13	-	1.13	-
	Median	9.00	-	9.00	-	9.00	-
	Minimum	0.00	-	1.00	-	0.00	-
	Maximum	10.00	-	10.00	-	10.00	-
	Missing	7	-	12	-	19	-
Apgar score[Yes/No] at 5 mins	Yes	1198	100	1233	100	2431	100
	No	0	0.0	0	0.0	0	0.0
	Missing	4	-	12	-	16	-
Apgar score category at 5 mins	0-3	0	0.0	0	0.0	0	0.0
	4-6	6	0.5	6	0.5	12	0.5
	7-10	1192	99.5	1227	99.5	2419	99.5
	NA	4	-	12	-	16	-
Apgar score at 5 mins	N	1198	-	1233	-	2431	-
	Mean	9.33	-	9.52	-	9.43	-
	SD	0.73	-	0.74	-	0.74	-
	Median	9.00	-	10.00	-	10.00	-
	Minimum	4.00	-	4.00	-	4.00	-
	Maximum	10.00	-	10.00	-	10.00	-
	Missing	4	-	12	-	16	-
Apgar score at 6-10 min[Yes/No]	Yes	10	0.8	15	1.2	25	1.0
	No	1188	99.2	1218	98.8	2406	99.0
	Missing	4	-	12	-	16	-
Apgar score category at [6-10 mins]	5	0	0.0	1	6.7	1	4.0
	6	0	0.0	3	20.0	3	12.0
	7	4	40.0	2	13.3	6	24.0
	8	3	30.0	3	20.0	6	24.0
	9	0	0.0	3	20.0	3	12.0
	10	3	30.0	3	20.0	6	24.0
	NA	1192	-	1230	-	2422	-
Apgar score at [6-10 mins]	N	10	-	15	-	25	-
	Mean	8.20	-	7.87	-	8.00	-
	SD	1.32	-	1.64	-	1.50	-
	Median	8.00	-	8.00	-	8.00	-
	Minimum	7.00	-	5.00	-	5.00	-
	Maximum	10.00	-	10.00	-	10.00	-
	Missing	1192	-	1230	-	2422	-
Birth complications	Yes	240	20.1	322	26.1	562	23.1
	No	957	79.9	912	73.9	1869	76.9
	Missing	5	-	11	-	16	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
Any birth outcome: Small for gestational age, Preterm birth
N = Number of subjects without still births and neonatal deaths
n = Number of subjects in a given category
Value = Value of the considered parameter
% = n / number of subjects with available results x 100
SD = Standard deviation
Note: one subject with Apgar score at 3 mins has been recorded in Apgar score at 6-10 min category

Table 36 Summary of birth outcome and Apgar score data in subjects with neonatal deaths in current pregnancy

		Unexposed Cohort N = 8		Total N = 8	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Any birth outcome	Yes	3	100	3	100
	No	0	0.0	0	0.0
	Missing	5	-	5	-
Small for gestational age[SGA]	Yes	2	100	2	100
	No	0	0.0	0	0.0
	Missing	6	-	6	-
SGA - Height[cm]	N	0	-	0	-
	Mean	-	-	-	-
	SD	-	-	-	-
	Median	-	-	-	-
	Minimum	-	-	-	-
	Maximum	-	-	-	-
	Missing	8	-	8	-
SGA - Weight[kg]	N	2	-	2	-
	Mean	0.70	-	0.70	-
	SD	0.28	-	0.28	-
	Median	0.70	-	0.70	-
	Minimum	0.50	-	0.50	-
	Maximum	0.90	-	0.90	-
	Missing	6	-	6	-
SGA – BMI[kg/m**2]	N	0	-	0	-
	Mean	-	-	-	-
	SD	-	-	-	-
	Median	-	-	-	-
	Minimum	-	-	-	-
	Maximum	-	-	-	-
	Missing	8	-	8	-
Preterm birth [<37 weeks]	Yes	3	100	3	100
	No	0	0.0	0	0.0
	Missing	5	-	5	-
Preterm birth by gestational age category	<28 weeks	2	66.7	2	66.7
	28 to <32 weeks	1	33.3	1	33.3
	32 to <34 weeks	0	0.0	0	0.0
	34 to <37 weeks	0	0.0	0	0.0
	NA	5	-	5	-
Gestation age [in weeks] for preterm birth babies	N	3	-	3	-
	Mean	26.00	-	26.00	-
	SD	3.46	-	3.46	-
	Median	24.00	-	24.00	-
	Minimum	24.00	-	24.00	-
	Maximum	30.00	-	30.00	-
	Missing	5	-	5	-
Preterm birth - Height[cm]	N	0	-	0	-
	Mean	-	-	-	-
	SD	-	-	-	-
	Median	-	-	-	-
	Minimum	-	-	-	-
	Maximum	-	-	-	-
	Missing	8	-	8	-

		Unexposed Cohort N = 8		Total N = 8	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Preterm birth - Weight[kg]	N	3	-	3	-
	Mean	0.67	-	0.67	-
	SD	0.21	-	0.21	-
	Median	0.60	-	0.60	-
	Minimum	0.50	-	0.50	-
	Maximum	0.90	-	0.90	-
	Missing	5	-	5	-
Preterm birth – BMI[kg/m**2]	N	0	-	0	-
	Mean	-	-	-	-
	SD	-	-	-	-
	Median	-	-	-	-
	Minimum	-	-	-	-
	Maximum	-	-	-	-
	Missing	8	-	8	-
Overall - Height[cm]	N	0	-	0	-
	Mean	-	-	-	-
	SD	-	-	-	-
	Median	-	-	-	-
	Minimum	-	-	-	-
	Maximum	-	-	-	-
	Missing	8	-	8	-
Overall - Weight[kg]	N	6	-	6	-
	Mean	0.92	-	0.92	-
	SD	0.65	-	0.65	-
	Median	0.70	-	0.70	-
	Minimum	0.50	-	0.50	-
	Maximum	2.20	-	2.20	-
	Missing	2	-	2	-
Overall – BMI[kg/m**2]	N	0	-	0	-
	Mean	-	-	-	-
	SD	-	-	-	-
	Median	-	-	-	-
	Minimum	-	-	-	-
	Maximum	-	-	-	-
	Missing	8	-	8	-
Head circumference[cm]	N	0	-	0	-
	Mean	-	-	-	-
	SD	-	-	-	-
	Median	-	-	-	-
	Minimum	-	-	-	-
	Maximum	-	-	-	-
	Missing	8	-	8	-
Apgar score [Yes/No] at 1 min	Yes	4	100	4	100
	No	0	0.0	0	0.0
	Missing	4	-	4	-
Apgar score category at 1 min	0-3	3	75.0	3	75.0
	4-6	1	25.0	1	25.0
	7-10	0	0.0	0	0.0
	NA	4	-	4	-

		Unexposed Cohort N = 8		Total N = 8	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**
Apgar score at 1 min	N	4	-	4	-
	Mean	2.50	-	2.50	-
	SD	1.29	-	1.29	-
	Median	2.50	-	2.50	-
	Minimum	1.00	-	1.00	-
	Maximum	4.00	-	4.00	-
	Missing	4	-	4	-
Apgar score[Yes/No] at 5 mins	Yes	4	100	4	100
	No	0	0.0	0	0.0
	Missing	4	-	4	-
Apgar score category at 5 mins	0-3	2	50.0	2	50.0
	4-6	2	50.0	2	50.0
	7-10	0	0.0	0	0.0
	NA	4	-	4	-
Apgar score at 5 mins	N	4	-	4	-
	Mean	3.75	-	3.75	-
	SD	2.63	-	2.63	-
	Median	4.00	-	4.00	-
	Minimum	1.00	-	1.00	-
	Maximum	6.00	-	6.00	-
	Missing	4	-	4	-
Apgar score at 6-10 min[Yes/No]	Yes	1	33.3	1	33.3
	No	2	66.7	2	66.7
	Missing	5	-	5	-
Apgar score category at [6-10 mins]	5	0	0.0	0	0.0
	6	0	0.0	0	0.0
	7	1	100	1	100
	8	0	0.0	0	0.0
	9	0	0.0	0	0.0
	10	0	0.0	0	0.0
	NA	7	-	7	-
Apgar score at [6-10 mins]	N	1	-	1	-
	Mean	7.00	-	7.00	-
	SD	0.00	-	0.00	-
	Median	7.00	-	7.00	-
	Minimum	7.00	-	7.00	-
	Maximum	7.00	-	7.00	-
	Missing	7	-	7	-
Birth complications	Yes	4	100	4	100
	No	0	0.0	0	0.0
	Missing	4	-	4	-

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*
Any birth outcome: Small for gestational age, Preterm birth
N = Number of subjects with neonatal deaths
n = Number of subjects in a given category
Value = Value of the considered parameter
% = n / number of subjects with available results x 100
SD = Standard deviation

Table 37 Incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for exposed cohort - Sensitivity analysis 4

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Total number of person-weeks**	**Incidence rate (in 1000 person-weeks)**	**LL**	**UL**
Gestational diabetes	10	10770	0.93	0.35	1.99
Pregnancy-related hypertension	11	10770	1.02	0.40	2.12
Pre-Eclampsia	10	10770	0.93	0.35	1.99
Eclampsia	2	10770	0.19	0.01	0.86
HELLP Syndrome	0	10770	0.00	0.00	0.49
Vaginal hemorrhage	4	10770	0.37	0.06	1.17
Preterm birth	64	10770	5.94	4.20	8.14
Small for gestational age	69	10770	6.41	4.59	8.67

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and

Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age)

Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome

Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 38 Incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for unexposed cohort - Sensitivity analysis 4

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Total number of person-weeks**	**Incidence rate (in 1000 person-weeks)**	**LL**	**UL**
Gestational diabetes	22	12983	1.69	0.91	2.87
Pregnancy-related hypertension	31	12983	2.39	1.43	3.73
Pre-Eclampsia	30	12983	2.31	1.37	3.64
Eclampsia	0	12983	0.00	0.00	0.41
HELLP Syndrome	1	12983	0.08	0.00	0.57
Vaginal hemorrhage	19	12983	1.46	0.74	2.57
Preterm birth	121	12983	9.32	7.28	11.73
Small for gestational age	62	12983	4.78	3.36	6.57

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and

Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age)

Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome

Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 39 Incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for total cohort - Sensitivity analysis4

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Total number of person-weeks**	**Incidence rate (in 1000 person-weeks)**	**LL**	**UL**
Gestational diabetes	32	23753	1.35	0.81	2.09
Pregnancy-related hypertension	42	23753	1.77	1.14	2.60
Pre-Eclampsia	40	23753	1.68	1.08	2.50
Eclampsia	2	23753	0.08	0.00	0.39
HELLP Syndrome	1	23753	0.04	0.00	0.31
Vaginal hemorrhage	23	23753	0.97	0.53	1.62
Preterm birth	185	23753	7.79	6.39	9.39
Small for gestational age	131	23753	5.52	4.35	6.88

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and

Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age)

Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome

Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 40 Incidence rate ratio of Gestational diabetes between exposed and unexposed cohort via Poisson regression model (Total cohort)

		95% CI		
Independent variables (or) Characteristics	**Incidence rate ratio**	**LL**	**UL**	**p-value**
Exposed vs Unexposed	0.548	0.259	1.157	0.1147

95% CI =Wald confidence interval; LL=Lower limit; UL=Upper limit

Model is calculated by log (No. of Gestational diabetes cases) = log (offset variable) + intercept + (coeff × exposure status)

Table 41 Incidence rate ratio of Pregnancy-related hypertension between exposed and unexposed cohort via Poisson regression model (Total cohort)

		95% CI		
Independent variables (or) Characteristics	**Incidence rate ratio**	**LL**	**UL**	**p-value**
Exposed vs Unexposed	0.428	0.215	0.851	0.0155

95% CI =Wald confidence interval; LL=Lower limit; UL=Upper limit

Model is calculated by log (No. of Pregnancy-related hypertension cases) = log (offset variable) + intercept + (coeff × exposure status)

Table 42 Incidence rate ratio of Vaginal hemorrhage between exposed and unexposed cohort via Poisson regression model (Total cohort)

		95% CI		
Independent variables (or) Characteristics	**Incidence rate ratio**	**LL**	**UL**	**p-value**
Exposed vs Unexposed	0.254	0.086	0.746	0.0127

95% CI =Wald confidence interval; LL=Lower limit; UL=Upper limit

Model is calculated by log (No. of Vaginal hemorrhage cases) = log (offset variable) + intercept + (coeff × exposure status)

Table 43 Incidence rate ratio of Preterm birth between exposed and unexposed cohort via Poisson regression model (Total cohort)

		95% CI		
Independent variables (or) Characteristics	**Incidence rate ratio**	**LL**	**UL**	**p-value**
Exposed vs Unexposed	0.638	0.471	0.863	0.0036

95% CI =Wald confidence interval; LL=Lower limit; UL=Upper limit

Model is calculated by log (No. of Preterm birth cases) = log (offset variable) + intercept + (coeff × exposure status)

Table 44 Incidence rate ratio of Small for Gestational age between exposed and unexposed cohort via Poisson regression model (Total cohort)

		95% CI		
Independent variables (or) Characteristics	**Incidence rate ratio**	**LL**	**UL**	**p-value**
Exposed vs Unexposed	1.342	0.952	1.890	0.0931

95% CI =Wald confidence interval; LL=Lower limit; UL=Upper limit

Model is calculated by log (No. of Small for Gestational age cases) = log (offset variable) + intercept + (coeff × exposure status)

14.1.3. Secondary objective results

Table 45 Summary of all adverse events /birth outcomes between previous and current pregnancy (Total cohort)

		Exposed Cohort						Unexposed Cohort					
		Current pregnancy						Current pregnancy					
		Yes		No		Total		Yes		No		Total	
Adverse events or Birth outcomes	**Previous pregnancy**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Gestational diabetes	Yes	3	0.4	7	1.0	10	1.4	5	0.8	6	1.0	11	1.8
	No	18	2.5	692	96.1	710	98.6	21	3.5	563	94.6	584	98.2
	Total	21	2.9	699	97.1	720	100.0	26	4.4	569	95.6	595	100.0
Pregnancy-related hypertension	Yes	6	0.8	24	3.3	30	4.2	2	0.3	22	3.7	24	4.0
	No	10	1.4	680	94.4	690	95.8	12	2.0	559	93.9	571	96.0
	Total	16	2.2	704	97.8	720	100.0	14	2.4	581	97.6	595	100.0
Pre-eclampsia	Yes	6	0.8	22	3.1	28	3.9	2	0.3	18	3.0	20	3.4
	No	7	1.0	685	95.1	692	96.1	12	2.0	563	94.6	575	96.6
	Total	13	1.8	707	98.2	720	100.0	14	2.4	581	97.6	595	100.0
Eclampsia	Yes	0	0.0	2	0.3	2	0.3	0	0.0	4	0.7	4	0.7
	No	2	0.3	716	99.4	718	99.7	0	0.0	591	99.3	591	99.3
	Total	2	0.3	718	99.7	720	100.0	0	0.0	595	100.0	595	100.0
HELLP syndrome	No	2	0.3	718	99.7	720	100.0	0	0.0	595	100.0	595	100.0
	Total	2	0.3	718	99.7	720	100.0	0	0.0	595	100.0	595	100.0
Vaginal hemorrhage	Yes	0	0.0	3	0.4	3	0.4	0	0.0	9	1.5	9	1.5
	No	1	0.1	716	99.4	717	99.6	11	1.8	575	96.6	586	98.5
	Total	1	0.1	719	99.9	720	100.0	11	1.8	584	98.2	595	100.0
Preterm babies (<37 weeks)	Yes	11	1.8	68	11.4	79	13.2	14	2.8	51	10.1	65	12.9
	No	16	2.7	503	84.1	519	86.8	25	5.0	415	82.2	440	87.1
	Total	27	4.5	571	95.5	598	100.0	39	7.7	466	92.3	505	100.0
Premature rupture of membranes	Yes	2	0.3	4	0.6	6	0.8	0	0.0	4	0.7	4	0.7
	No	103	14.3	611	84.9	714	99.2	108	18.2	483	81.2	591	99.3
	Total	105	14.6	615	85.4	720	100.0	108	18.2	487	81.8	595	100.0
Preterm premature rupture of membranes	Yes	1	0.1	14	1.9	15	2.1	1	0.2	7	1.2	8	1.3
	No	6	0.8	699	97.1	705	97.9	14	2.4	573	96.3	587	98.7
	Total	7	1.0	713	99.0	720	100.0	15	2.5	580	97.5	595	100.0
Premature uterine contractions	Yes	1	0.1	25	3.5	26	3.6	3	0.5	21	3.5	24	4.0
	No	13	1.8	681	94.6	694	96.4	9	1.5	562	94.5	571	96.0
	Total	14	1.9	706	98.1	720	100.0	12	2.0	583	98.0	595	100.0
Neonatal death	Yes	0	0.0	6	0.8	6	0.8	1	0.2	8	1.3	9	1.5
	No	0	0.0	714	99.2	714	99.2	0	0.0	586	98.5	586	98.5
	Total	0	0.0	720	100.0	720	100.0	1	0.2	594	99.8	595	100.0
Still births (intrauterine fetal death)	Yes	0	0.0	19	2.8	19	2.8	1	0.2	8	1.3	9	1.5
	No	0	0.0	657	97.2	657	97.2	4	0.7	585	97.8	589	98.5
	Total	0	0.0	676	100.0	676	100.0	5	0.8	593	99.2	598	100.0
Neonatal hypoxic ischemic encephalopathy	Yes	0	0.0	1	0.1	1	0.1	0	0.0	1	0.2	1	0.2
	No	0	0.0	719	99.9	719	99.9	0	0.0	594	99.8	594	99.8
	Total	0	0.0	720	100.0	720	100.0	0	0.0	595	100.0	595	100.0
Congenital anomalies	Yes	1	0.1	3	0.4	4	0.5	0	0.0	1	0.2	1	0.2
	No	0	0.0	724	99.5	724	99.5	12	1.8	641	98.0	653	99.8
	Total	1	0.1	727	99.9	728	100.0	12	1.8	642	98.2	654	100.0

Exposed Cohort = Pregnant women who had received *Refortrix* as part of the maternal immunization program in Brazil
Unexposed Cohort = Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive *Refortrix*

n =Number of subjects with available results at previous pregnancy and current pregnancy
Note: Percentages are based on the number of subjects with available data at each event

Table 46 Cumulative incidence of pooled pregnancy related adverse events and pooled birth outcomes in current pregnancy for exposed cohort - Main analysis

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Pregnancy related adverse events	25	1199	20.85	13.49	30.78
Birth outcomes	111	1199	92.58	76.16	111.49

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
Pregnancy related adverse events: Gestational diabetes, Pre-eclampsia, Eclampsia, HELLP Syndrome, Vaginal hemorrhage (Ante partum, Intra partum and post-partum hemorrhage)
Birth outcomes: Preterm birth and Small for gestational age
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for birth outcomes
Population at risk =Number of subjects with vaccination date in the exposed cohort

Table 47 Cumulative incidence of pooled pregnancy related adverse events and pooled birth outcomes in current pregnancy for unexposed cohort - Main analysis

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Pregnancy related adverse events	70	1259	55.60	43.34	70.25
Birth outcomes	159	1259	126.29	107.42	147.52

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
Pregnancy related adverse events: Gestational diabetes, Pre-eclampsia, Eclampsia, HELLP Syndrome, Vaginal hemorrhage (Ante partum, Intra partum and post-partum hemorrhage)
Birth outcomes: Preterm birth and Small for gestational age
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for birth outcomes
Population at risk = Total number of subjects at risk in the unexposed cohort

Table 48 Cumulative incidence of pregnancy-related adverse events and birth outcomes by calendar year in current pregnancy for unexposed cohort – Main analysis

					95% CI	
Adverse event Birth outcome	**Calendar year**	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	2012(sep-dec)	4	212	18.87	5.14	48.31
	2013(jan-dec)	10	604	16.56	7.94	30.45
	2014(jan-aug)	8	432	18.52	7.99	36.49
Pregnancy-related hypertension	2012(sep-dec)	7	212	33.02	13.28	68.03
	2013(jan-dec)	10	604	16.56	7.94	30.45
	2014(jan-aug)	14	432	32.41	17.72	54.37
Pre-Eclampsia	2012(sep-dec)	7	212	33.02	13.28	68.03
	2013(jan-dec)	9	604	14.90	6.81	28.29
	2014(jan-aug)	14	432	32.41	17.72	54.37
Eclampsia	2012(sep-dec)	0	212	0.00	0.00	17.40
	2013(jan-dec)	0	604	0.00	0.00	6.11
	2014(jan-aug)	0	432	0.00	0.00	8.54
HELLP Syndrome	2012(sep-dec)	0	212	0.00	0.00	17.40
	2013(jan-dec)	1	604	1.66	0.04	9.22
	2014(jan-aug)	0	432	0.00	0.00	8.54
Vaginal hemorrhage	2012(sep-dec)	10	212	47.17	22.62	86.75
	2013(jan-dec)	7	604	11.59	4.66	23.88
	2014(jan-aug)	2	432	4.63	0.56	16.72
Preterm birth	2012(sep-dec)	20	212	94.34	57.63	145.70
	2013(jan-dec)	65	604	107.62	83.06	137.17
	2014(jan-aug)	36	432	83.33	58.37	115.37
Small for gestational age	2012(sep-dec)	13	212	61.32	32.65	104.86
	2013(jan-dec)	28	604	46.36	30.80	67.00
	2014(jan-aug)	21	432	48.61	30.09	74.31

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and

Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age)

Population at risk = Number of subjects with delivery date in a given category of unexposed cohort

Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome

Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 49 Cumulative incidence of pregnancy-related AEs and neonate-related events of interest by calendar year in current pregnancy for unexposed cohort - Main analysis

					95% CI	
Adverse event Birth outcome	**Calendar year**	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	2012(sep-dec)	35	212	165.09	114.99	229.61
	2013(jan-dec)	145	604	240.07	202.58	282.47
	2014(jan-aug)	81	432	187.50	148.90	233.05
Preterm premature rupture of membranes	2012(sep-dec)	9	212	42.45	19.41	80.59
	2013(jan-dec)	19	604	31.46	18.94	49.12
	2014(jan-aug)	8	432	18.52	7.99	36.49
Premature uterine contraction	2012(sep-dec)	6	212	28.30	10.39	61.60
	2013(jan-dec)	32	604	52.98	36.24	74.79
	2014(jan-aug)	16	432	37.04	21.17	60.15
Neonatal death	2012(sep-dec)	0	212	0.00	0.00	17.40
	2013(jan-dec)	5	604	8.28	2.69	19.32
	2014(jan-aug)	3	432	6.94	1.43	20.29
Maternal death	2012(sep-dec)	0	212	0.00	0.00	17.40
	2013(jan-dec)	0	604	0.00	0.00	6.11
	2014(jan-aug)	0	432	0.00	0.00	8.54
Still birth	2012(sep-dec)	1	212	4.72	0.12	26.28
	2013(jan-dec)	2	604	3.31	0.40	11.96
	2014(jan-aug)	3	432	6.94	1.43	20.29
Neonatal hypoxic ischemic encephalopathy	2012(sep-dec)	0	212	0.00	0.00	17.40
	2013(jan-dec)	0	604	0.00	0.00	6.11
	2014(jan-aug)	0	432	0.00	0.00	8.54
Congenital anomalies	2012(sep-dec)	5	212	23.58	7.66	55.04
	2013(jan-dec)	12	604	19.87	10.27	34.70
	2014(jan-aug)	5	432	11.57	3.76	27.01

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and

Number of subjects where at least one event occurred after index date for neonate-related events (Neonatal death, Still birth, Neonatal hypoxic ischemic encephalopathy and Congenital anomalies)

Population at risk = Number of subjects with delivery date in a given category of unexposed cohort

Table 50 Cumulative incidence of pregnancy-related adverse events and birth outcomes in current pregnancy for exposed cohort - Sensitivity analysis3

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	8	970	8.25	2.65	19.15
Pregnancy-related hypertension	9	970	9.28	3.23	20.62
Pre-Eclampsia	8	970	8.25	2.65	19.15
Eclampsia	2	970	2.06	0.11	9.56
HELLP Syndrome	0	970	0.00	0.00	5.46
Vaginal hemorrhage	4	970	4.12	0.69	12.98
Preterm birth	51	970	52.58	35.55	74.69
Small for gestational age	53	970	54.64	37.24	77.11

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age)
Population at risk = Subjects who are not having vaccination at 27 gestational weeks in the exposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 51 Cumulative incidence of pregnancy-related adverse events and birth outcomes with any concomitant vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	8	1127	7.10	2.28	16.48
Pregnancy-related hypertension	10	1127	8.87	3.30	18.99
Pre-Eclampsia	10	1127	8.87	3.30	18.99
Eclampsia	1	1127	0.89	0.00	6.59
HELLP Syndrome	0	1127	0.00	0.00	4.70
Vaginal hemorrhage	3	1127	2.66	0.30	9.74
Preterm birth	55	1127	48.80	33.52	68.45
Small for gestational age	65	1127	57.68	40.92	78.79

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events with any concomitant vaccination and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age) with any concomitant vaccination
Population at risk = Total number of subjects at risk with any concomitant vaccination in the exposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 52 Cumulative incidence of pregnancy-related adverse events and birth outcomes without any concomitant vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	2	72	27.78	1.44	128.80
Pregnancy-related hypertension	1	72	13.89	0.07	103.20
Pre-Eclampsia	0	72	0.00	0.00	73.59
Eclampsia	1	72	13.89	0.07	103.20
HELLP Syndrome	0	72	0.00	0.00	73.59
Vaginal hemorrhage	1	72	13.89	0.07	103.20
Preterm birth	9	72	125.00	43.51	277.76
Small for gestational age	4	72	55.56	9.34	174.92

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events without any concomitant vaccination and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age) without any concomitant vaccination
Population at risk = Total number of subjects at risk without any concomitant vaccination in the exposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 53 Cumulative incidence of pregnancy-related adverse events and birth outcomes with diphtheria-tetanus vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	2	386	5.18	0.27	24.03
Pregnancy-related hypertension	2	386	5.18	0.27	24.03
Pre-Eclampsia	2	386	5.18	0.27	24.03
Eclampsia	0	386	0.00	0.00	13.73
HELLP Syndrome	0	386	0.00	0.00	13.73
Vaginal hemorrhage	3	386	7.77	0.88	28.44
Preterm birth	13	386	33.68	14.46	66.05
Small for gestational age	20	386	51.81	26.82	89.81

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events with diphtheria-tetanus vaccination and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age) with diphtheria-tetanus vaccination
Population at risk = Total number of subjects at risk with diphtheria-tetanus vaccination in the exposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 54 Cumulative incidence of pregnancy-related adverse events and birth outcomes without diphtheria-tetanus vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	8	813	9.84	3.16	22.85
Pregnancy-related hypertension	9	813	11.07	3.85	24.60
Pre-Eclampsia	8	813	9.84	3.16	22.85
Eclampsia	2	813	2.46	0.13	11.41
HELLP Syndrome	0	813	0.00	0.00	6.52
Vaginal hemorrhage	1	813	1.23	0.01	9.14
Preterm birth	51	813	62.73	42.41	89.11
Small for gestational age	49	813	60.27	40.40	86.21

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events without diphtheria-tetanus vaccination and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age) without diphtheria-tetanus vaccination
Population at risk = Total number of subjects at risk without diphtheria-tetanus vaccination in the exposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 55 Cumulative incidence of pregnancy-related adverse events and birth outcomes with hepatitis B vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	4	464	8.62	1.45	27.14
Pregnancy-related hypertension	5	464	10.78	2.32	30.50
Pre-Eclampsia	5	464	10.78	2.32	30.50
Eclampsia	0	464	0.00	0.00	11.42
HELLP Syndrome	0	464	0.00	0.00	11.42
Vaginal hemorrhage	2	464	4.31	0.22	19.99
Preterm birth	23	464	49.57	26.98	82.94
Small for gestational age	25	464	53.88	30.16	88.36

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events with hepatitis B vaccination and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age) with hepatitis B vaccination
Population at risk = Total number of subjects at risk with hepatitis B vaccination in the exposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 56 Cumulative incidence of pregnancy-related adverse events and birth outcomes without hepatitis B vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				99% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Gestational diabetes	6	735	8.16	2.09	21.31
Pregnancy-related hypertension	6	735	8.16	2.09	21.31
Pre-Eclampsia	5	735	6.80	1.47	19.25
Eclampsia	2	735	2.72	0.14	12.62
HELLP Syndrome	0	735	0.00	0.00	7.21
Vaginal hemorrhage	2	735	2.72	0.14	12.62
Preterm birth	41	735	55.78	35.90	82.40
Small for gestational age	44	735	59.86	39.17	87.28

99% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events without hepatitis B vaccination and
Number of subjects where at least one event occurred after index date for birth outcome events (preterm birth and small for gestational age) without hepatitis B vaccination
Population at risk = Total number of subjects at risk without hepatitis B vaccination in the exposed cohort
Pregnancy-related hypertension: Includes Pre-eclampsia, Eclampsia and HELLP Syndrome
Vaginal hemorrhage: Includes Ante partum, Intra partum and Post-partum hemorrhage

Table 57 Cumulative incidence of pregnancy-related AEs/neonate-related events of interest with any concomitant vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	178	1127	157.94	135.59	182.92
Preterm premature rupture of membranes	14	1127	12.42	6.79	20.84
Premature uterine contraction	27	1127	23.96	15.79	34.86
Neonatal death	0	1127	0.00	0.00	3.27
Maternal death	0	1127	0.00	0.00	3.27
Still birth	1	1127	0.89	0.02	4.94
Neonatal hypoxic ischemic encephalopathy	0	1127	0.00	0.00	3.27
Congenital anomalies	2	1127	1.77	0.21	6.41

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit
*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events with any concomitant vaccination and
Number of subjects where at least one event occurred after index date for neonate-related events with any concomitant vaccination
Population at risk = Total number of subjects at risk with any concomitant vaccination in the exposed cohort

Table 58 Cumulative incidence of pregnancy-related AEs/neonate-related events of interest without any concomitant vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	12	72	166.67	86.12	291.13
Preterm premature rupture of membranes	3	72	41.67	8.59	121.77
Premature uterine contraction	5	72	69.44	22.55	162.06
Neonatal death	0	72	0.00	0.00	51.23
Maternal death	0	72	0.00	0.00	51.23
Still birth	0	72	0.00	0.00	51.23
Neonatal hypoxic ischemic encephalopathy	0	72	0.00	0.00	51.23
Congenital anomalies	1	72	13.89	0.35	77.38

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events without any concomitant vaccination and

Number of subjects where at least one event occurred after index date for neonate-related events without any concomitant vaccination

Population at risk = Total number of subjects at risk without any concomitant vaccination in the exposed cohort

Table 59 Cumulative incidence of pregnancy-related AEs/neonate-related events of interest with diphtheria-tetanus vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	61	386	158.03	120.88	203.00
Preterm premature rupture of membranes	2	386	5.18	0.63	18.72
Premature uterine contraction	8	386	20.73	8.95	40.84
Neonatal death	0	386	0.00	0.00	9.56
Maternal death	0	386	0.00	0.00	9.56
Still birth	1	386	2.59	0.07	14.43
Neonatal hypoxic ischemic encephalopathy	0	386	0.00	0.00	9.56
Congenital anomalies	0	386	0.00	0.00	9.56

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events with diphtheria-tetanus vaccination and

Number of subjects where at least one event occurred after index date for neonate-related events with diphtheria-tetanus vaccination

Population at risk = Total number of subjects at risk with diphtheria-tetanus vaccination in the exposed cohort

Table 60 Cumulative incidence of pregnancy-related AEs/neonate-related events of interest without diphtheria-tetanus vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	129	813	158.67	132.47	188.53
Preterm premature rupture of membranes	15	813	18.45	10.33	30.43
Premature uterine contraction	24	813	29.52	18.91	43.92
Neonatal death	0	813	0.00	0.00	4.54
Maternal death	0	813	0.00	0.00	4.54
Still birth	0	813	0.00	0.00	4.54
Neonatal hypoxic ischemic encephalopathy	0	813	0.00	0.00	4.54
Congenital anomalies	3	813	3.69	0.76	10.78

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events without diphtheria-tetanus vaccination and

Number of subjects where at least one event occurred after index date for neonate-related events without diphtheria-tetanus vaccination

Population at risk = Total number of subjects at risk without diphtheria-tetanus vaccination in the exposed cohort

Table 61 Cumulative incidence of pregnancy-related AEs/neonate-related events of interest with hepatitis B vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	72	464	155.17	121.41	195.41
Preterm premature rupture of membranes	4	464	8.62	2.35	22.07
Premature uterine contraction	11	464	23.71	11.83	42.42
Neonatal death	0	464	0.00	0.00	7.95
Maternal death	0	464	0.00	0.00	7.95
Still birth	1	464	2.16	0.05	12.01
Neonatal hypoxic ischemic encephalopathy	0	464	0.00	0.00	7.95
Congenital anomalies	1	464	2.16	0.05	12.01

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events with hepatitis B vaccination and

Number of subjects where at least one event occurred after index date for neonate-related events with hepatitis B vaccination

Population at risk = Total number of subjects at risk with hepatitis B vaccination in the exposed cohort

Table 62 Cumulative incidence of pregnancy-related AEs/neonate-related events of interest without hepatitis B vaccination in current pregnancy for exposed cohort - Sensitivity analysis5

				95% CI	
Adverse event or Birth outcome	**No. of subjects***	**Population at risk**	**Incidence proportion (per 1000)**	**LL**	**UL**
Premature rupture of membranes	118	735	160.54	132.89	192.26
Preterm premature rupture of membranes	13	735	17.69	9.42	30.25
Premature uterine contraction	21	735	28.57	17.69	43.67
Neonatal death	0	735	0.00	0.00	5.02
Maternal death	0	735	0.00	0.00	5.02
Still birth	0	735	0.00	0.00	5.02
Neonatal hypoxic ischemic encephalopathy	0	735	0.00	0.00	5.02
Congenital anomalies	2	735	2.72	0.33	9.83

95% CI =Exact confidence interval; LL=Lower limit; UL=Upper limit

*Number of subjects where at least one event occurred between index date and date of delivery for pregnancy related adverse events without hepatitis B vaccination and

Number of subjects where at least one event occurred after index date for neonate-related events without hepatitis B vaccination

Population at risk = Total number of subjects at risk without hepatitis B vaccination in the exposed cohort

Table 63 Association between risk factors and gestational diabetes in current pregnancy (Total cohort)

		Gestational diabetes N = 72				No Gestational diabetes N = 2375				Missing Gestational diabetes N = 15				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Exposure status	Exposed	26	36.1	25.1	48.3	1173	49.4	47.4	51.4	4	26.7	7.8	55.1	0.0192
	Unexposed	46	63.9	51.7	74.9	1202	50.6	48.6	52.6	11	73.3	44.9	92.2	-
Maternal age in years at start of the pregnancy	18-19	2	2.8	0.3	9.7	343	14.4	13.1	15.9	0	0.0	0.0	-	<0.0001
	20-24	10	13.9	6.9	24.1	750	31.6	29.7	33.5	0	0.0	0.0	-	-
	25-29	11	15.3	7.9	25.7	601	25.3	23.6	27.1	0	0.0	0.0	-	-
	30-34	21	29.2	19.0	41.1	402	16.9	15.4	18.5	0	0.0	0.0	-	-
	35-39	20	27.8	17.9	39.6	224	9.4	8.3	10.7	0	0.0	0.0	-	-
	40 and above	8	11.1	4.9	20.7	55	2.3	1.7	3.0	0	0.0	0.0	-	-
Parity	Nulliparous	6	11.8	4.4	23.9	134	10.0	8.5	11.7	0	0.0	0.0	-	0.6837
	Multiparous	45	88.2	76.1	95.6	1204	90.0	88.3	91.5	0	0.0	0.0	-	-
Parity [Nulliparous + Multiparous]	0	6	11.8	4.4	23.9	134	10.0	8.5	11.7	0	0.0	0.0	-	0.5227
	1	23	45.1	31.1	59.7	696	52.0	49.3	54.7	0	0.0	0.0	-	-
	2	12	23.5	12.8	37.5	350	26.2	23.8	28.6	0	0.0	0.0	-	-
	3-4	9	17.6	8.4	30.9	141	10.5	8.9	12.3	0	0.0	0.0	-	-
	5-High	1	2.0	0.0	10.4	17	1.3	0.7	2.0	0	0.0	0.0	-	-
Infection during current pregnancy	Yes	14	19.4	11.1	30.5	626	26.4	24.6	28.2	0	0.0	0.0	-	0.1885
	No	58	80.6	69.5	88.9	1749	73.6	71.8	75.4	0	0.0	0.0	-	-
Placenta previa	Yes	0	0.0	0.0	5.0	7	0.3	0.1	0.6	0	0.0	0.0	-	0.6446
	No	72	100	95.0	100	2368	99.7	99.4	99.9	0	0.0	0.0	-	-
Placenta abruption	Yes	1	1.4	0.0	7.5	11	0.5	0.2	0.8	0	0.0	0.0	-	0.2679
	No	71	98.6	92.5	100	2364	99.5	99.2	99.8	0	0.0	0.0	-	-
Congenital anomalies in the subject	Yes	0	0.0	0.0	-	3	50.0	11.8	88.2	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	3	50.0	11.8	88.2	0	0.0	0.0	-	-
Congenital anomalies for spouse	Yes	0	0.0	0.0	-	0	0.0	0.0	52.2	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	5	100	47.8	100	0	0.0	0.0	-	-
Congenital anomalies for first degree relatives	Yes	0	0.0	0.0	-	4	80.0	28.4	99.5	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	1	20.0	0.5	71.6	0	0.0	0.0	-	-
Alcohol consumption before and/or during pregnancy	Yes	2	2.8	0.3	9.8	43	1.8	1.3	2.4	0	0.0	0.0	-	0.5384
	No	69	97.2	90.2	99.7	2321	98.2	97.6	98.7	0	0.0	0.0	-	-
Substance abuse before and/or during pregnancy	Yes	0	0.0	0.0	5.0	23	1.0	0.6	1.4	0	0.0	0.0	-	0.4015
	No	72	100	95.0	100	2352	99.0	98.6	99.4	0	0.0	0.0	-	-
Smoking before and/or during pregnancy	Yes	5	7.0	2.3	15.7	237	10.0	8.8	11.3	0	0.0	0.0	-	0.4118
	No	66	93.0	84.3	97.7	2134	90.0	88.7	91.2	0	0.0	0.0	-	-
Pregnancy-related hypertension in previous pregnancy	Yes	3	6.4	1.3	17.5	51	4.0	3.0	5.3	0	0.0	0.0	-	0.4232
	No	44	93.6	82.5	98.7	1217	96.0	94.7	97.0	0	0.0	0.0	-	-

		Gestational diabetes N = 72				No Gestational diabetes N = 2375				Missing Gestational diabetes N = 15				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Pre-eclampsia in previous pregnancy	Yes	3	6.4	1.3	17.5	45	3.5	2.6	4.7	0	0.0	0.0	-	0.3090
	No	44	93.6	82.5	98.7	1223	96.5	95.3	97.4	0	0.0	0.0	-	-
Eclampsia in previous pregnancy	Yes	0	0.0	0.0	7.5	6	0.5	0.2	1.0	0	0.0	0.0	-	0.6364
	No	47	100	92.5	100	1262	99.5	99.0	99.8	0	0.0	0.0	-	-
HELLP Syndrome in previous pregnancy	Yes	0	0.0	0.0	7.5	0	0.0	0.0	0.3	0	0.0	0.0	-	-
	No	47	100	92.5	100	1268	100	99.7	100	0	0.0	0.0	-	-
Infection in previous pregnancy	Yes	0	0.0	0.0	7.5	11	0.9	0.4	1.5	0	0.0	0.0	-	0.5212
	No	47	100	92.5	100	1256	99.1	98.5	99.6	0	0.0	0.0	-	-
Gestational diabetes in previous pregnancy	Yes	8	17.0	7.6	30.8	13	1.0	0.5	1.7	0	0.0	0.0	-	<0.0001
	No	39	83.0	69.2	92.4	1255	99.0	98.3	99.5	0	0.0	0.0	-	-
Vaginal hemorrhage in previous pregnancy	Yes	0	0.0	0.0	7.5	12	0.9	0.5	1.6	0	0.0	0.0	-	0.5029
	No	47	100	92.5	100	1256	99.1	98.4	99.5	0	0.0	0.0	-	-
Premature rupture of membranes in previous pregnancy	Yes	0	0.0	0.0	7.5	10	0.8	0.4	1.4	0	0.0	0.0	-	0.5411
	No	47	100	92.5	100	1258	99.2	98.6	99.6	0	0.0	0.0	-	-
Preterm premature rupture of membranes in previous pregnancy	Yes	0	0.0	0.0	7.5	23	1.8	1.2	2.7	0	0.0	0.0	-	0.3516
	No	47	100	92.5	100	1245	98.2	97.3	98.8	0	0.0	0.0	-	-
Premature uterine contraction in previous pregnancy	Yes	3	6.4	1.3	17.5	47	3.7	2.7	4.9	0	0.0	0.0	-	0.3462
	No	44	93.6	82.5	98.7	1221	96.3	95.1	97.3	0	0.0	0.0	-	-
Neonatal death in previous pregnancy	Yes	1	2.1	0.1	11.3	14	1.1	0.6	1.8	0	0.0	0.0	-	0.5164
	No	46	97.9	88.7	99.9	1254	98.9	98.2	99.4	0	0.0	0.0	-	-
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes	0	0.0	0.0	7.5	2	0.2	0.0	0.6	0	0.0	0.0	-	0.7853
	No	47	100	92.5	100	1266	99.8	99.4	100	0	0.0	0.0	-	-
New born with low birth weight [less than 2.5 kg] in previous pregnancy	Yes	6	16.2	6.2	32.0	124	12.1	10.1	14.2	0	0.0	0.0	-	0.4468
	No	31	83.8	68.0	93.8	905	87.9	85.8	89.9	0	0.0	0.0	-	-
Fetal macrosomia [newborn greater than 4 kg] in previous pregnancies	Yes	2	5.4	0.7	18.2	43	4.2	3.0	5.6	0	0.0	0.0	-	0.7103
	No	35	94.6	81.8	99.3	991	95.8	94.4	97.0	0	0.0	0.0	-	-
Pre-term baby [less than 37 weeks] in previous pregnancies	Yes	7	18.4	7.7	34.3	141	13.2	11.2	15.4	0	0.0	0.0	-	0.3505
	No	31	81.6	65.7	92.3	929	86.8	84.6	88.8	0	0.0	0.0	-	-

N = number of subjects
n = number of subjects in a given category

% = n / Number of subjects with available results x 100
P values: Chi-square test
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Note: Do not have available data for 14 subjects

Table 64 Estimated unadjusted odds ratio for exploring the risk factors of gestational diabetes in current pregnancy (Total cohort)

			95% CI		
Characteristic	**Compared levels**	**Unadjusted OR**	**LL**	**UL**	**p-value**
Exposure status	Exposed vs. Unexposed	0.579	0.356	0.943	0.0281
Maternal age at the start of the pregnancy (in years)	18-19Y vs. 20-24Y	0.437	0.095	2.007	0.2873
	25-29Y vs. 20-24Y	1.373	0.579	3.254	0.4719
	30-34Y vs. 20-24Y	3.918	1.827	8.400	0.0004
	35-39Y vs. 20-24Y	6.696	3.089	14.515	<.0001
	GE 40Y vs. 20-24Y	10.909	4.139	28.754	<.0001
Parity	Multiparous vs. Nulliparous	0.835	0.350	1.993	0.6840
Parity (Nulliparous + Multiparous)	1 vs. 0	0.738	0.295	1.847	0.5163
	2 vs. 0	0.766	0.282	2.081	0.6008
	3-4 vs. 0	1.426	0.494	4.114	0.5120
	≥5 vs. 0	1.314	0.149	11.579	0.8059
Infection during current pregnancy	Yes vs. NO	0.674	0.374	1.217	0.1912
Placenta previa	Yes vs. NO	<0.001	<0.001	>999.999	0.9893
Placenta abruption	Yes vs. NO	3.027	0.386	23.765	0.2921
Alcohol consumption before and/or during pregnancy	Yes vs. NO	1.565	0.371	6.589	0.5418
Substance abuse before and/or during pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9872
Smoking before and/or during pregnancy	Yes vs. NO	0.682	0.272	1.710	0.4146
Pregnancy-related hypertension in previous pregnancy	Yes vs. NO	1.627	0.489	5.416	0.4276
Pre-eclampsia in previous pregnancy	Yes vs. NO	1.853	0.554	6.194	0.3163
Eclampsia in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9891
HELLP in previous pregnancy	Not performed	.	.	.	.
Infection in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9903
Gestational diabetes in previous pregnancy	Yes vs. NO	19.806	7.763	50.529	<.0001
Vaginal hemorrhage in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9898
Premature rupture of membranes in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9907
Preterm premature rupture of membranes in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9859
Premature uterine contraction in previous pregnancy	Yes vs. NO	1.771	0.531	5.912	0.3525
Neonatal death in previous pregnancy	Yes vs. NO	1.948	0.251	15.126	0.5239
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9905
New born with low birth weight (<2.5 kg) in previous pregnancy	Yes vs. NO	1.413	0.578	3.454	0.4489
Fetal macrosomia (newborn > 4 kg) in previous pregnancies	Yes vs. NO	1.318	0.307	5.656	0.7106
Pre-term baby (<37 weeks) in previous pregnancies	Yes vs. NO	1.488	0.643	3.443	0.3534

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits

Table 65 Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of gestational diabetes in current pregnancy (Total cohort)

						95% CI	
Characteristic	**Compared levels**	**Coefficient**	**Standard error**	**P-value**	**Adjusted OR**	**LL**	**UL**
Independent factor	Continuous*	-4.2955	0.4581	<.0001	.	.	.
Maternal age at the start of the pregnancy (in years)	18-19Y vs. 20-24Y	-11.4565	340.0	0.9731	<0.001	<0.001	>999.999
	25-29Y vs. 20-24Y	-0.00114	0.6195	0.9985	0.999	0.297	3.364
	30-34Y vs. 20-24Y	1.2404	0.5292	0.0191	3.457	1.225	9.752
	35-39Y vs. 20-24Y	1.4614	0.5407	0.0069	4.312	1.494	12.442
	GE 40Y vs. 20-24Y	2.2337	0.6414	0.0005	9.334	2.655	32.814
Gestational diabetes in previous pregnancy	Yes vs. NO	2.8876	0.5180	<.0001	17.950	6.504	49.539

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits
* OR for continuous variables describes the effect of a difference of one unit

Table 66 Association between risk factors and pregnancy-related hypertension in current pregnancy (Total cohort)

		Pregnancy related hypertension N = 59				No pregnancy related hypertension N = 2388				Missing pregnancy related hypertension N = 15				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Exposure status	Exposed	22	37.3	25.0	50.9	1177	49.3	47.3	51.3	4	26.7	7.8	55.1	0.0430
	Unexposed	37	62.7	49.1	75.0	1211	50.7	48.7	52.7	11	73.3	44.9	92.2	-
Maternal age in years at start of the pregnancy	18-19	4	6.8	1.9	16.5	341	14.3	12.9	15.7	0	0.0	0.0	-	<0.0001
	20-24	13	22.0	12.3	34.7	747	31.3	29.4	33.2	0	0.0	0.0	-	-
	25-29	15	25.4	15.0	38.4	597	25.0	23.3	26.8	0	0.0	0.0	-	-
	30-34	12	20.3	11.0	32.8	411	17.2	15.7	18.8	0	0.0	0.0	-	-
	35-39	14	23.7	13.6	36.6	230	9.6	8.5	10.9	0	0.0	0.0	-	-
	40 and above	1	1.7	0.0	9.1	62	2.6	2.0	3.3	0	0.0	0.0	-	-
Parity	Nulliparous	3	9.4	2.0	25.0	137	10.1	8.5	11.8	0	0.0	0.0	-	0.8935
	Multiparous	29	90.6	75.0	98.0	1220	89.9	88.2	91.5	0	0.0	0.0	-	-
Parity [Nulliparous + Multiparous]	0	3	9.4	2.0	25.0	137	10.1	8.5	11.8	0	0.0	0.0	-	0.4602
	1	13	40.6	23.7	59.4	706	52.0	49.3	54.7	0	0.0	0.0	-	-
	2	9	28.1	13.7	46.7	353	26.0	23.7	28.4	0	0.0	0.0	-	-
	3-4	6	18.8	7.2	36.4	144	10.6	9.0	12.4	0	0.0	0.0	-	-
	5-High	1	3.1	0.1	16.2	17	1.3	0.7	2.0	0	0.0	0.0	-	-
Infection during current pregnancy	Yes	11	18.6	9.7	30.9	629	26.3	24.6	28.2	0	0.0	0.0	-	0.1839
	No	48	81.4	69.1	90.3	1759	73.7	71.8	75.4	0	0.0	0.0	-	-
Placenta previa	Yes	0	0.0	0.0	6.1	7	0.3	0.1	0.6	0	0.0	0.0	-	0.6771
	No	59	100	93.9	100	2381	99.7	99.4	99.9	0	0.0	0.0	-	-
Placenta abruption	Yes	1	1.7	0.0	9.1	11	0.5	0.2	0.8	0	0.0	0.0	-	0.1800
	No	58	98.3	90.9	100	2377	99.5	99.2	99.8	0	0.0	0.0	-	-
Congenital anomalies in the subject	Yes	0	0.0	0.0	97.5	3	60.0	14.7	94.7	0	0.0	0.0	-	0.2733
	No	1	100	2.5	100	2	40.0	5.3	85.3	0	0.0	0.0	-	-
Congenital anomalies for spouse	Yes	0	0.0	0.0	97.5	0	0.0	0.0	60.2	0	0.0	0.0	-	-
	No	1	100	2.5	100	4	100	39.8	100	0	0.0	0.0	-	-
Congenital anomalies for first degree relatives	Yes	1	100	2.5	100	3	75.0	19.4	99.4	0	0.0	0.0	-	0.5762
	No	0	0.0	0.0	97.5	1	25.0	0.6	80.6	0	0.0	0.0	-	-
Alcohol consumption before and/or during pregnancy	Yes	2	3.4	0.4	11.7	43	1.8	1.3	2.4	0	0.0	0.0	-	0.3734
	No	57	96.6	88.3	99.6	2333	98.2	97.6	98.7	0	0.0	0.0	-	-
Substance abuse before and/or during pregnancy	Yes	0	0.0	0.0	6.1	23	1.0	0.6	1.4	0	0.0	0.0	-	0.4488
	No	59	100	93.9	100	2365	99.0	98.6	99.4	0	0.0	0.0	-	-
Smoking before and/or during pregnancy	Yes	4	6.8	1.9	16.5	238	10.0	8.8	11.3	0	0.0	0.0	-	0.4153
	No	55	93.2	83.5	98.1	2145	90.0	88.7	91.2	0	0.0	0.0	-	-
Pregnancy-related hypertension in previous pregnancy	Yes	8	26.7	12.3	45.9	46	3.6	2.6	4.7	0	0.0	0.0	-	<0.0001
	No	22	73.3	54.1	87.7	1239	96.4	95.3	97.4	0	0.0	0.0	-	-
Pre-eclampsia in previous pregnancy	Yes	8	26.7	12.3	45.9	40	3.1	2.2	4.2	0	0.0	0.0	-	<0.0001
	No	22	73.3	54.1	87.7	1245	96.9	95.8	97.8	0	0.0	0.0	-	-

		Pregnancy related hypertension N = 59				No pregnancy related hypertension N = 2388				Missing pregnancy related hypertension N = 15				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Eclampsia in previous pregnancy	Yes	0	0.0	0.0	11.6	6	0.5	0.2	1.0	0	0.0	0.0	-	0.7076
	No	30	100	88.4	100	1279	99.5	99.0	99.8	0	0.0	0.0	-	-
HELLP Syndrome in previous pregnancy	Yes	0	0.0	0.0	11.6	0	0.0	0.0	0.3	0	0.0	0.0	-	-
	No	30	100	88.4	100	1285	100	99.7	100	0	0.0	0.0	-	-
Infection in previous pregnancy	Yes	0	0.0	0.0	11.6	11	0.9	0.4	1.5	0	0.0	0.0	-	0.6107
	No	30	100	88.4	100	1273	99.1	98.5	99.6	0	0.0	0.0	-	-
Gestational diabetes in previous pregnancy	Yes	2	6.7	0.8	22.1	19	1.5	0.9	2.3	0	0.0	0.0	-	0.0250
	No	28	93.3	77.9	99.2	1266	98.5	97.7	99.1	0	0.0	0.0	-	-
Vaginal hemorrhage in previous pregnancy	Yes	0	0.0	0.0	11.6	12	0.9	0.5	1.6	0	0.0	0.0	-	0.5949
	No	30	100	88.4	100	1273	99.1	98.4	99.5	0	0.0	0.0	-	-
Premature rupture of membranes in previous pregnancy	Yes	1	3.3	0.1	17.2	9	0.7	0.3	1.3	0	0.0	0.0	-	0.1008
	No	29	96.7	82.8	99.9	1276	99.3	98.7	99.7	0	0.0	0.0	-	-
Preterm premature rupture of membranes in previous pregnancy	Yes	0	0.0	0.0	11.6	23	1.8	1.1	2.7	0	0.0	0.0	-	0.4597
	No	30	100	88.4	100	1262	98.2	97.3	98.9	0	0.0	0.0	-	-
Premature uterine contraction in previous pregnancy	Yes	2	6.7	0.8	22.1	48	3.7	2.8	4.9	0	0.0	0.0	-	0.4066
	No	28	93.3	77.9	99.2	1237	96.3	95.1	97.2	0	0.0	0.0	-	-
Neonatal death in previous pregnancy	Yes	0	0.0	0.0	11.6	15	1.2	0.7	1.9	0	0.0	0.0	-	0.5517
	No	30	100	88.4	100	1270	98.8	98.1	99.3	0	0.0	0.0	-	-
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes	0	0.0	0.0	11.6	2	0.2	0.0	0.6	0	0.0	0.0	-	0.8288
	No	30	100	88.4	100	1283	99.8	99.4	100	0	0.0	0.0	-	-
New born with low birth weight [less than 2.5 kg] in previous pregnancy	Yes	7	26.9	11.6	47.8	123	11.8	9.9	13.9	0	0.0	0.0	-	0.0202
	No	19	73.1	52.2	88.4	917	88.2	86.1	90.1	0	0.0	0.0	-	-
Fetal macrosomia [newborn greater than 4 kg] in previous pregnancies	Yes	0	0.0	0.0	13.2	45	4.3	3.2	5.7	0	0.0	0.0	-	0.2797
	No	26	100	86.8	100	1000	95.7	94.3	96.8	0	0.0	0.0	-	-
Pre-term baby [less than 37 weeks] in previous pregnancies	Yes	4	14.8	4.2	33.7	144	13.3	11.4	15.5	0	0.0	0.0	-	0.8217
	No	23	85.2	66.3	95.8	937	86.7	84.5	88.6	0	0.0	0.0	-	-

N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
P values: Chi-square test
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Note: Do not have available data for 14 subjects

Table 67 Estimated unadjusted odds ratio for exploring the risk factors of pregnancy-related hypertension in current pregnancy (Total cohort)

			95% CI		
Characteristic	**Compared levels**	**Unadjusted OR**	**LL**	**UL**	**p-value**
Exposure status	Exposed vs. Unexposed	0.612	0.359	1.043	0.0712
Maternal age at the start of the pregnancy (in years)	18-19Y vs. 20-24Y	0.674	0.218	2.082	0.4931
	25-29Y vs. 20-24Y	1.444	0.682	3.058	0.3375
	30-34Y vs. 20-24Y	1.678	0.759	3.711	0.2014
	35-39Y vs. 20-24Y	3.498	1.621	7.548	0.0014
	GE 40Y vs. 20-24Y	0.927	0.119	7.202	0.9421
Parity	Multiparous vs. Nulliparous	1.086	0.326	3.610	0.8935
Parity (Nulliparous + Multiparous)	1 vs. 0	0.841	0.236	2.990	0.7889
	2 vs. 0	1.164	0.311	4.365	0.8215
	3-4 vs. 0	1.903	0.467	7.759	0.3697
	≥5 vs. 0	2.686	0.264	27.297	0.4035
Infection during current pregnancy	Yes vs. NO	0.641	0.331	1.242	0.1874
Placenta previa	Yes vs. NO	<0.001	<0.001	>999.999	0.9903
Placenta abruption	Yes vs. NO	3.726	0.473	29.338	0.2116
Alcohol consumption before and/or during pregnancy	Yes vs. NO	1.904	0.450	8.051	0.3813
Substance abuse before and/or during pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9884
Smoking before and/or during pregnancy	Yes vs. NO	0.655	0.235	1.825	0.4187
Pregnancy-related hypertension in previous pregnancy	Yes vs. NO	9.794	4.140	23.170	<.0001
Pre-eclampsia in previous pregnancy	Yes vs. NO	11.318	4.750	26.969	<.0001
Eclampsia in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9912
HELLP in previous pregnancy	Not performed	.	.	.	.
Infection in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9881
Gestational diabetes in previous pregnancy	Yes vs. NO	4.760	1.057	21.424	0.0421
Vaginal hemorrhage in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9876
Premature rupture of membranes in previous pregnancy	Yes vs. NO	4.889	0.600	39.865	0.1382
Preterm premature rupture of membranes in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9828
Premature uterine contraction in previous pregnancy	Yes vs. NO	1.841	0.426	7.952	0.4136
Neonatal death in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9862
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9924
New born with low birth weight (<2.5 kg) in previous pregnancy	Yes vs. NO	2.747	1.132	6.667	0.0255
Fetal macrosomia (newborn > 4 kg) in previous pregnancies	Yes vs. NO	<0.001	<0.001	>999.999	0.9752
Pre-term baby (<37 weeks) in previous pregnancies	Yes vs. NO	1.132	0.386	3.320	0.8218

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits

Table 68 Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of pregnancy-related hypertension in current pregnancy (Total cohort)

						95% CI	
Characteristic	**Compared levels**	**Coefficient**	**Standard error**	**P-value**	**Adjusted OR**	**LL**	**UL**
Independent factor	Continuous*	-3.9713	0.2316	<.0001	.	.	.
Pre-eclampsia in previous pregnancy	Yes vs. NO	2.4515	0.4772	<.0001	11.605	4.555	29.570

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits
* OR for continuous variables describes the effect of a difference of one unit

Table 69 Association between risk factors and vaginal hemorrhage in current pregnancy (Total cohort)

		Vaginal hemorrhage N = 23				No Vaginal hemorrhage N = 2424				Missing Vaginal hemorrhage N = 15				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Exposure status	Exposed	4	17.4	5.0	38.8	1195	49.3	47.3	51.3	4	26.7	7.8	55.1	0.0022
	Unexposed	19	82.6	61.2	95.0	1229	50.7	48.7	52.7	11	73.3	44.9	92.2	-
Maternal age in years at start of the pregnancy	18-19	4	17.4	5.0	38.8	341	14.1	12.7	15.5	0	0.0	0.0	-	<0.0001
	20-24	5	21.7	7.5	43.7	755	31.1	29.3	33.0	0	0.0	0.0	-	-
	25-29	6	26.1	10.2	48.4	606	25.0	23.3	26.8	0	0.0	0.0	-	-
	30-34	3	13.0	2.8	33.6	420	17.3	15.8	18.9	0	0.0	0.0	-	-
	35-39	4	17.4	5.0	38.8	240	9.9	8.7	11.2	0	0.0	0.0	-	-
	40 and above	1	4.3	0.1	21.9	62	2.6	2.0	3.3	0	0.0	0.0	-	-
Parity	Nulliparous	0	0.0	0.0	26.5	140	10.2	8.6	11.9	0	0.0	0.0	-	0.2441
	Multiparous	12	100	73.5	100	1237	89.8	88.1	91.4	0	0.0	0.0	-	-
Parity [Nulliparous + Multiparous]	0	0	0.0	0.0	26.5	140	10.2	8.6	11.9	0	0.0	0.0	-	0.0966
	1	11	91.7	61.5	99.8	708	51.4	48.7	54.1	0	0.0	0.0	-	-
	2	1	8.3	0.2	38.5	361	26.2	23.9	28.6	0	0.0	0.0	-	-
	3-4	0	0.0	0.0	26.5	150	10.9	9.3	12.7	0	0.0	0.0	-	-
	5-High	0	0.0	0.0	26.5	18	1.3	0.8	2.1	0	0.0	0.0	-	-
Infection during current pregnancy	Yes	5	21.7	7.5	43.7	635	26.2	24.5	28.0	0	0.0	0.0	-	0.6283
	No	18	78.3	56.3	92.5	1789	73.8	72.0	75.5	0	0.0	0.0	-	-
Placenta previa	Yes	1	4.3	0.1	21.9	6	0.2	0.1	0.5	0	0.0	0.0	-	0.0002
	No	22	95.7	78.1	99.9	2418	99.8	99.5	99.9	0	0.0	0.0	-	-
Placenta abruption	Yes	1	4.3	0.1	21.9	11	0.5	0.2	0.8	0	0.0	0.0	-	0.0078
	No	22	95.7	78.1	99.9	2413	99.5	99.2	99.8	0	0.0	0.0	-	-
Congenital anomalies in the subject	Yes	0	0.0	0.0	-	3	50.0	11.8	88.2	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	3	50.0	11.8	88.2	0	0.0	0.0	-	-
Congenital anomalies for spouse	Yes	0	0.0	0.0	-	0	0.0	0.0	52.2	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	5	100	47.8	100	0	0.0	0.0	-	-

		Vaginal hemorrhage N = 23				No Vaginal hemorrhage N = 2424				Missing Vaginal hemorrhage N = 15				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Congenital anomalies for first degree relatives	Yes	0	0.0	0.0	-	4	80.0	28.4	99.5	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	1	20.0	0.5	71.6	0	0.0	0.0	-	-
Alcohol consumption before and/or during pregnancy	Yes	0	0.0	0.0	14.8	45	1.9	1.4	2.5	0	0.0	0.0	-	0.5085
	No	23	100	85.2	100	2367	98.1	97.5	98.6	0	0.0	0.0	-	-
Substance abuse before and/or during pregnancy	Yes	0	0.0	0.0	14.8	23	0.9	0.6	1.4	0	0.0	0.0	-	0.6388
	No	23	100	85.2	100	2401	99.1	98.6	99.4	0	0.0	0.0	-	-
Smoking before and/or during pregnancy	Yes	1	4.3	0.1	21.9	241	10.0	8.8	11.2	0	0.0	0.0	-	0.3697
	No	22	95.7	78.1	99.9	2178	90.0	88.8	91.2	0	0.0	0.0	-	-
Pregnancy-related hypertension in previous pregnancy	Yes	1	8.3	0.2	38.5	53	4.1	3.1	5.3	0	0.0	0.0	-	0.4585
	No	11	91.7	61.5	99.8	1250	95.9	94.7	96.9	0	0.0	0.0	-	-
Pre-eclampsia in previous pregnancy	Yes	1	8.3	0.2	38.5	47	3.6	2.7	4.8	0	0.0	0.0	-	0.3848
	No	11	91.7	61.5	99.8	1256	96.4	95.2	97.3	0	0.0	0.0	-	-
Eclampsia in previous pregnancy	Yes	0	0.0	0.0	26.5	6	0.5	0.2	1.0	0	0.0	0.0	-	0.8137
	No	12	100	73.5	100	1297	99.5	99.0	99.8	0	0.0	0.0	-	-
HELLP Syndrome in previous pregnancy	Yes	0	0.0	0.0	26.5	0	0.0	0.0	0.3	0	0.0	0.0	-	-
	No	12	100	73.5	100	1303	100	99.7	100	0	0.0	0.0	-	-
Infection in previous pregnancy	Yes	0	0.0	0.0	26.5	11	0.8	0.4	1.5	0	0.0	0.0	-	0.7492
	No	12	100	73.5	100	1291	99.2	98.5	99.6	0	0.0	0.0	-	-
Gestational diabetes in previous pregnancy	Yes	0	0.0	0.0	26.5	21	1.6	1.0	2.5	0	0.0	0.0	-	0.6575
	No	12	100	73.5	100	1282	98.4	97.5	99.0	0	0.0	0.0	-	-
Vaginal hemorrhage in previous pregnancy	Yes	0	0.0	0.0	26.5	12	0.9	0.5	1.6	0	0.0	0.0	-	0.7384
	No	12	100	73.5	100	1291	99.1	98.4	99.5	0	0.0	0.0	-	-
Premature rupture of membranes in previous pregnancy	Yes	0	0.0	0.0	26.5	10	0.8	0.4	1.4	0	0.0	0.0	-	0.7606
	No	12	100	73.5	100	1293	99.2	98.6	99.6	0	0.0	0.0	-	-
Preterm premature rupture of membranes in previous pregnancy	Yes	1	8.3	0.2	38.5	22	1.7	1.1	2.5	0	0.0	0.0	-	0.0805
	No	11	91.7	61.5	99.8	1281	98.3	97.5	98.9	0	0.0	0.0	-	-
Premature uterine contraction in previous pregnancy	Yes	1	8.3	0.2	38.5	49	3.8	2.8	4.9	0	0.0	0.0	-	0.4097
	No	11	91.7	61.5	99.8	1254	96.2	95.1	97.2	0	0.0	0.0	-	-
Neonatal death in previous pregnancy	Yes	2	16.7	2.1	48.4	13	1.0	0.5	1.7	0	0.0	0.0	-	<0.0001
	No	10	83.3	51.6	97.9	1290	99.0	98.3	99.5	0	0.0	0.0	-	-
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes	0	0.0	0.0	26.5	2	0.2	0.0	0.6	0	0.0	0.0	-	0.8920
	No	12	100	73.5	100	1301	99.8	99.4	100	0	0.0	0.0	-	-

		Vaginal hemorrhage N = 23				No Vaginal hemorrhage N = 2424				Missing Vaginal hemorrhage N = 15				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
New born with low birth weight [less than 2.5 kg] in previous pregnancy	Yes	1	8.3	0.2	38.5	129	12.2	10.3	14.4	0	0.0	0.0	-	0.6810
	No	11	91.7	61.5	99.8	925	87.8	85.6	89.7	0	0.0	0.0	-	-
Fetal macrosomia [newborn greater than 4 kg] in previous pregnancies	Yes	0	0.0	0.0	26.5	45	4.2	3.1	5.6	0	0.0	0.0	-	0.4656
	No	12	100	73.5	100	1014	95.8	94.4	96.9	0	0.0	0.0	-	-
Pre-term baby [less than 37 weeks] in previous pregnancies	Yes	1	10.0	0.3	44.5	147	13.4	11.4	15.5	0	0.0	0.0	-	0.7539
	No	9	90.0	55.5	99.7	951	86.6	84.5	88.6	0	0.0	0.0	-	-

N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
P values: Chi-square test
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Note: Do not have available data for 14 subjects

Table 70 Estimated unadjusted odds ratio for exploring the risk factors of vaginal hemorrhage in current pregnancy (Total cohort)

			95% CI		
Characteristic	**Compared levels**	**Unadjusted OR**	**LL**	**UL**	**p-value**
Exposure status	Exposed vs. Unexposed	0.217	0.073	0.638	0.0055
Maternal age at the start of the pregnancy (in years)	18-19Y vs. 20-24Y	1.771	0.473	6.637	0.3963
	25-29Y vs. 20-24Y	1.495	0.454	4.922	0.5083
	30-34Y vs. 20-24Y	1.079	0.256	4.536	0.9178
	35-39Y vs. 20-24Y	2.517	0.671	9.448	0.1714
	GE 40Y vs. 20-24Y	2.436	0.280	21.173	0.4198
Parity	Multiparous vs. Nulliparous	>999.999	<0.001	>999.999	0.9737
Parity (Nulliparous + Multiparous)	1 vs. 0	>999.999	<0.001	>999.999	0.9586
	2 vs. 0	>999.999	<0.001	>999.999	0.9647
	3-4 vs. 0	1.000	<0.001	>999.999	1.0000
	≥5 vs. 0	1.000	<0.001	>999.999	1.0000
Infection during current pregnancy	Yes vs. NO	0.783	0.289	2.117	0.6293
Placenta previa	Yes vs. NO	18.318	2.116	158.557	0.0083
Placenta abruption	Yes vs. NO	9.972	1.234	80.593	0.0310
Alcohol consumption before and/or during pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9845
Substance abuse before and/or during pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9890
Smoking before and/or during pregnancy	Yes vs. NO	0.411	0.055	3.061	0.3854
Pregnancy-related hypertension in previous pregnancy	Yes vs. NO	2.144	0.272	16.915	0.4692
Pre-eclampsia in previous pregnancy	Yes vs. NO	2.429	0.307	19.209	0.4001
Eclampsia in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9945
HELLP in previous pregnancy	Not performed	.	.	.	.
Infection in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9925
Gestational diabetes in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9896
Vaginal hemorrhage in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9922
Premature rupture of membranes in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9928
Preterm premature rupture of membranes in previous pregnancy	Yes vs. NO	5.293	0.655	42.799	0.1181
Premature uterine contraction in previous pregnancy	Yes vs. NO	2.327	0.294	18.381	0.4233
Neonatal death in previous pregnancy	Yes vs. NO	19.846	3.953	99.634	0.0003
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9952
New born with low birth weight (<2.5 kg) in previous pregnancy	Yes vs. NO	0.652	0.083	5.091	0.6832
Fetal macrosomia (newborn > 4 kg) in previous pregnancies	Yes vs. NO	<0.001	<0.001	>999.999	0.9831
Pre-term baby (<37 weeks) in previous pregnancies	Yes vs. NO	0.719	0.091	5.716	0.7554

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits

Table 71 Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of vaginal hemorrhage in current pregnancy (Total cohort)

						95% CI	
Characteristic	**Compared levels**	**Coefficient**	**Standard error**	**P-value**	**Adjusted OR**	**LL**	**UL**
Independent factor	Continuous*	-4.2397	0.3464	<.0001	.	.	.
Exposure status	Exposed vs. Unexposed	-2.7016	1.1088	0.0148	0.067	0.008	0.590
Placenta previa	Yes vs. NO	5.5905	1.8417	0.0024	267.870	7.249	>999.999
Neonatal death in previous pregnancy	Yes vs. NO	2.9178	0.8591	0.0007	18.501	3.435	99.646

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits
* OR for continuous variables describes the effect of a difference of one unit

Table 72 Association between risk factors and preterm birth in current pregnancy (Total cohort)

		Preterm birth N = 185				No Preterm birth N = 2251				Missing Preterm birth N = 26				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Exposure status	Exposed	64	34.6	27.8	41.9	1135	50.4	48.3	52.5	4	15.4	4.4	34.9	<0.0001
	Unexposed	121	65.4	58.1	72.2	1116	49.6	47.5	51.7	22	84.6	65.1	95.6	-
Maternal age in years at start of the pregnancy	18-19	27	14.6	9.8	20.5	315	14.0	12.6	15.5	3	11.5	6.0	61.0	<0.0001
	20-24	46	24.9	18.8	31.7	711	31.6	29.7	33.6	3	11.5	6.0	61.0	-
	25-29	46	24.9	18.8	31.7	564	25.1	23.3	26.9	2	7.7	2.3	51.8	-
	30-34	36	19.5	14.0	25.9	387	17.2	15.7	18.8	0	0.0	0.0	28.5	-
	35-39	24	13.0	8.5	18.7	217	9.6	8.5	10.9	3	11.5	6.0	61.0	-
	40 and above	6	3.2	1.2	6.9	57	2.5	1.9	3.3	0	0.0	0.0	28.5	-
Parity	Nulliparous	20	22.5	14.3	32.6	120	9.3	7.7	11.0	0	0.0	0.0	52.2	0.0003
	Multiparous	69	77.5	67.4	85.7	1175	90.7	89.0	92.3	5	100	47.8	100	-
Parity [Nulliparous + Multiparous]	0	20	22.5	14.3	32.6	120	9.3	7.7	11.0	0	0.0	0.0	52.2	0.0072
	1	47	52.8	41.9	63.5	668	51.6	48.8	54.3	4	80.0	28.4	99.5	-
	2	15	16.9	9.8	26.3	346	26.7	24.3	29.2	1	20.0	0.5	71.6	-
	3-4	6	6.7	2.5	14.1	144	11.1	9.5	13.0	0	0.0	0.0	52.2	-
	5-High	1	1.1	0.0	6.1	17	1.3	0.8	2.1	0	0.0	0.0	52.2	-
Infection during current pregnancy	Yes	41	22.2	16.4	28.8	599	26.6	24.8	28.5	0	0.0	0.0	28.5	0.0589
	No	144	77.8	71.2	83.6	1652	73.4	71.5	75.2	11	100	71.5	100	-
Placenta previa	Yes	0	0.0	0.0	2.0	7	0.3	0.1	0.6	0	0.0	0.0	28.5	0.7367
	No	185	100	98.0	100	2244	99.7	99.4	99.9	11	100	71.5	100	-
Placenta abruption	Yes	3	1.6	0.3	4.7	7	0.3	0.1	0.6	2	18.2	2.3	51.8	<0.0001
	No	182	98.4	95.3	99.7	2244	99.7	99.4	99.9	9	81.8	48.2	97.7	-
Congenital anomalies in the subject	Yes	0	0.0	0.0	-	3	50.0	11.8	88.2	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	3	50.0	11.8	88.2	0	0.0	0.0	-	-
Congenital anomalies for spouse	Yes	0	0.0	0.0	-	0	0.0	0.0	52.2	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	5	100	47.8	100	0	0.0	0.0	-	-
Congenital anomalies for first degree relatives	Yes	0	0.0	0.0	-	4	80.0	28.4	99.5	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	1	20.0	0.5	71.6	0	0.0	0.0	-	-
Alcohol consumption before and/or during pregnancy	Yes	5	2.7	0.9	6.2	40	1.8	1.3	2.4	0	0.0	0.0	30.8	0.6122
	No	180	97.3	93.8	99.1	2200	98.2	97.6	98.7	10	100	69.2	100	-
Substance abuse before and/or during pregnancy	Yes	4	2.2	0.6	5.4	19	0.8	0.5	1.3	0	0.0	0.0	28.5	0.1926
	No	181	97.8	94.6	99.4	2232	99.2	98.7	99.5	11	100	71.5	100	-
Smoking before and/or during pregnancy	Yes	17	9.2	5.4	14.3	224	10.0	8.8	11.3	1	9.1	0.2	41.3	0.9389
	No	168	90.8	85.7	94.6	2022	90.0	88.7	91.2	10	90.9	58.7	99.8	-
Pregnancy-related hypertension in previous pregnancy	Yes	4	5.3	1.5	13.1	50	4.0	3.0	5.3	0	0.0	0.0	52.2	0.7744
	No	71	94.7	86.9	98.5	1185	96.0	94.7	97.0	5	100	47.8	100	-
Pre-eclampsia in previous pregnancy	Yes	4	5.3	1.5	13.1	44	3.6	2.6	4.8	0	0.0	0.0	52.2	0.6635
	No	71	94.7	86.9	98.5	1191	96.4	95.2	97.4	5	100	47.8	100	-

		Preterm birth N = 185				No Preterm birth N = 2251				Missing Preterm birth N = 26				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Eclampsia in previous pregnancy	Yes	0	0.0	0.0	4.8	6	0.5	0.2	1.1	0	0.0	0.0	52.2	0.8227
	No	75	100	95.2	100	1229	99.5	98.9	99.8	5	100	47.8	100	-
HELLP Syndrome in previous pregnancy	Yes	0	0.0	0.0	4.8	0	0.0	0.0	0.3	0	0.0	0.0	52.2	-
	No	75	100	95.2	100	1235	100	99.7	100	5	100	47.8	100	-
Infection in previous pregnancy	Yes	2	2.7	0.3	9.3	9	0.7	0.3	1.4	0	0.0	0.0	52.2	0.1980
	No	73	97.3	90.7	99.7	1225	99.3	98.6	99.7	5	100	47.8	100	-
Gestational diabetes in previous pregnancy	Yes	3	4.0	0.8	11.2	18	1.5	0.9	2.3	0	0.0	0.0	52.2	0.2242
	No	72	96.0	88.8	99.2	1217	98.5	97.7	99.1	5	100	47.8	100	-
Vaginal hemorrhage in previous pregnancy	Yes	1	1.3	0.0	7.2	11	0.9	0.4	1.6	0	0.0	0.0	52.2	0.9051
	No	74	98.7	92.8	100	1224	99.1	98.4	99.6	5	100	47.8	100	-
Premature rupture of membranes in previous pregnancy	Yes	0	0.0	0.0	4.8	10	0.8	0.4	1.5	0	0.0	0.0	52.2	0.7215
	No	75	100	95.2	100	1225	99.2	98.5	99.6	5	100	47.8	100	-
Preterm premature rupture of membranes in previous pregnancy	Yes	6	8.0	3.0	16.6	17	1.4	0.8	2.2	0	0.0	0.0	52.2	0.0001
	No	69	92.0	83.4	97.0	1218	98.6	97.8	99.2	5	100	47.8	100	-
Premature uterine contraction in previous pregnancy	Yes	7	9.3	3.8	18.3	40	3.2	2.3	4.4	3	60.0	14.7	94.7	<0.0001
	No	68	90.7	81.7	96.2	1195	96.8	95.6	97.7	2	40.0	5.3	85.3	-
Neonatal death in previous pregnancy	Yes	1	1.3	0.0	7.2	13	1.1	0.6	1.8	1	20.0	0.5	71.6	0.0004
	No	74	98.7	92.8	100	1222	98.9	98.2	99.4	4	80.0	28.4	99.5	-
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes	0	0.0	0.0	4.8	2	0.2	0.0	0.6	0	0.0	0.0	52.2	0.9372
	No	75	100	95.2	100	1233	99.8	99.4	100	5	100	47.8	100	-
New born with low birth weight [less than 2.5 kg] in previous pregnancy	Yes	14	23.0	13.2	35.5	113	11.3	9.4	13.4	3	60.0	14.7	94.7	0.0001
	No	47	77.0	64.5	86.8	887	88.7	86.6	90.6	2	40.0	5.3	85.3	-
Fetal macrosomia [newborn greater than 4 kg] in previous pregnancies	Yes	3	4.9	1.0	13.7	42	4.2	3.0	5.6	0	0.0	0.0	52.2	0.8614
	No	58	95.1	86.3	99.0	963	95.8	94.4	97.0	5	100	47.8	100	-
Pre-term baby [less than 37 weeks] in previous pregnancies	Yes	25	37.9	26.2	50.7	119	11.5	9.6	13.6	4	80.0	28.4	99.5	<0.0001
	No	41	62.1	49.3	73.8	918	88.5	86.4	90.4	1	20.0	0.5	71.6	-

N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
P values: Chi-square test
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Note: Do not have available data for 14 subjects

Table 73 Estimated unadjusted odds ratio for exploring the risk factors of preterm birth in current pregnancy (Total cohort)

			95% CI		
Characteristic	**Compared levels**	**Unadjusted OR**	**LL**	**UL**	**p-value**
Exposure status	Exposed vs. Unexposed	0.520	0.380	0.712	<.0001
Maternal age at the start of the pregnancy(in years)	18-19Y vs. 20-24Y	1.325	0.809	2.170	0.2638
	25-29Y vs. 20-24Y	1.261	0.826	1.925	0.2836
	30-34Y vs. 20-24Y	1.438	0.914	2.263	0.1165
	35-39Y vs. 20-24Y	1.709	1.020	2.865	0.0418
	GE 40Y vs. 20-24Y	1.627	0.666	3.972	0.2851
Parity	Multiparous vs. Nulliparous	0.352	0.207	0.600	0.0001
Parity (Nulliparous + Multiparous)	1 vs. 0	0.422	0.242	0.738	0.0025
	2 vs. 0	0.260	0.129	0.524	0.0002
	3-4 vs. 0	0.250	0.097	0.643	0.0040
	≥5 vs. 0	0.353	0.044	2.801	0.3245
Infection during current pregnancy	Yes vs. NO	0.785	0.548	1.125	0.1874
Placenta previa	Yes vs. NO	<0.001	<0.001	>999.999	0.9829
Placenta abruption	Yes vs. NO	5.284	1.355	20.607	0.0165
Alcohol consumption before and/or during pregnancy	Yes vs. NO	1.528	0.596	3.919	0.3779
Substance abuse before and/or during pregnancy	Yes vs. NO	2.598	0.875	7.717	0.0855
Smoking before and/or during pregnancy	Yes vs. NO	0.913	0.544	1.533	0.7317
Pregnancy-related hypertension in previous pregnancy	Yes vs. NO	1.336	0.469	3.802	0.5873
Pre-eclampsia in previous pregnancy	Yes vs. NO	1.525	0.533	4.363	0.4314
Eclampsia in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9862
HELLP in previous pregnancy	Not performed	.	.	.	.
Infection in previous pregnancy	Yes vs. NO	3.729	0.791	17.574	0.0961
Gestational diabetes in previous pregnancy	Yes vs. NO	2.817	0.811	9.785	0.1030
Vaginal hemorrhage in previous pregnancy	Yes vs. NO	1.504	0.192	11.804	0.6980
Premature rupture of membranes in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9883
Preterm premature rupture of membranes in previous pregnancy	Yes vs. NO	6.230	2.381	16.300	0.0002
Premature uterine contraction in previous pregnancy	Yes vs. NO	3.075	1.329	7.119	0.0087
Neonatal death in previous pregnancy	Yes vs. NO	1.271	0.164	9.842	0.8186
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9880
New born with low birth weight (<2.5 kg) in previous pregnancy	Yes vs. NO	2.339	1.248	4.382	0.0080
Fetal macrosomia (newborn > 4 kg) in previous pregnancies	Yes vs. NO	1.186	0.357	3.941	0.7807
Pre-term baby (<37 weeks) in previous pregnancies	Yes vs. NO	4.704	2.761	8.014	<.0001

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits

Table 74 Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of preterm birth in current pregnancy (Total cohort)

						95% CI	
Characteristic	**Compared levels**	**Coefficient**	**Standard error**	**P-value**	**Adjusted OR**	**LL**	**UL**
Independent factor	Continuous*	-3.2547	0.3566	<.0001	.	.	.
Exposure status	Exposed vs. Unexposed	-0.5061	0.2756	0.0663	0.603	0.351	1.035
Maternal age at the start of the pregnancy (in years)	18-19Y vs. 20-24Y	0.5188	0.6883	0.4510	1.680	0.436	6.474
	25-29Y vs. 20-24Y	-0.1343	0.4530	0.7670	0.874	0.360	2.125
	30-34Y vs. 20-24Y	0.6583	0.4114	0.1095	1.931	0.862	4.325
	35-39Y vs. 20-24Y	1.0124	0.4300	0.0186	2.752	1.185	6.393
	GE 40Y vs. 20-24Y	1.0044	0.7086	0.1564	2.730	0.681	10.949
Pre-term baby (<37 weeks) in previous pregnancies	Yes vs. NO	1.5389	0.2964	<.0001	4.659	2.606	8.330

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits
* OR for continuous variables describes the effect of a difference of one unit

Table 75 Association between risk factors and small for gestational age in current pregnancy (Total cohort)

		Small for Gestational age N = 131				No small for Gestational age N = 2303				Missing small for Gestational age N = 28				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Exposure status	Exposed	69	52.7	43.8	61.5	1130	49.1	47.0	51.1	4	14.3	4.0	32.7	0.0008
	Unexposed	62	47.3	38.5	56.2	1173	50.9	48.9	53.0	24	85.7	67.3	96.0	-
Maternal age in years at start of the pregnancy	18-19	22	16.8	10.8	24.3	320	13.9	12.5	15.4	3	10.7	5.0	53.8	<0.0001
	20-24	39	29.8	22.1	38.4	718	31.2	29.3	33.1	3	10.7	5.0	53.8	-
	25-29	36	27.5	20.0	36.0	574	24.9	23.2	26.7	2	7.1	1.9	45.4	-
	30-34	18	13.7	8.4	20.8	403	17.5	16.0	19.1	2	7.1	1.9	45.4	-
	35-39	13	9.9	5.4	16.4	228	9.9	8.7	11.2	3	10.7	5.0	53.8	-
	40 and above	3	2.3	0.5	6.5	60	2.6	2.0	3.3	0	0.0	0.0	24.7	-
Parity	Nulliparous	8	13.3	5.9	24.6	131	9.9	8.4	11.6	1	14.3	0.4	57.9	0.6441
	Multiparous	52	86.7	75.4	94.1	1191	90.1	88.4	91.6	6	85.7	42.1	99.6	-
Parity [Nulliparous + Multiparous]	0	8	13.3	5.9	24.6	131	9.9	8.4	11.6	1	14.3	0.4	57.9	0.5131
	1	36	60.0	46.5	72.4	678	51.3	48.6	54.0	5	71.4	29.0	96.3	-
	2	9	15.0	7.1	26.6	352	26.6	24.3	29.1	1	14.3	0.4	57.9	-
	3-4	7	11.7	4.8	22.6	143	10.8	9.2	12.6	0	0.0	0.0	41.0	-
	5-High	0	0.0	0.0	6.0	18	1.4	0.8	2.1	0	0.0	0.0	41.0	-
Infection during current pregnancy	Yes	23	17.6	11.5	25.2	617	26.8	25.0	28.7	0	0.0	0.0	24.7	0.0064
	No	108	82.4	74.8	88.5	1686	73.2	71.3	75.0	13	100	75.3	100	-
Placenta previa	Yes	0	0.0	0.0	2.8	7	0.3	0.1	0.6	0	0.0	0.0	24.7	0.8029
	No	131	100	97.2	100	2296	99.7	99.4	99.9	13	100	75.3	100	-
Placenta abruption	Yes	1	0.8	0.0	4.2	9	0.4	0.2	0.7	2	15.4	1.9	45.4	<0.0001
	No	130	99.2	95.8	100	2294	99.6	99.3	99.8	11	84.6	54.6	98.1	-
Congenital anomalies in the subject	Yes	0	0.0	0.0	-	3	50.0	11.8	88.2	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	3	50.0	11.8	88.2	0	0.0	0.0	-	-
Congenital anomalies for spouse	Yes	0	0.0	0.0	-	0	0.0	0.0	52.2	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	5	100	47.8	100	0	0.0	0.0	-	-
Congenital anomalies for first degree relatives	Yes	0	0.0	0.0	-	4	80.0	28.4	99.5	0	0.0	0.0	-	-
	No	0	0.0	0.0	-	1	20.0	0.5	71.6	0	0.0	0.0	-	-
Alcohol consumption before and/or during pregnancy	Yes	4	3.1	0.8	7.6	41	1.8	1.3	2.4	0	0.0	0.0	26.5	0.5170
	No	127	96.9	92.4	99.2	2251	98.2	97.6	98.7	12	100	73.5	100	-
Substance abuse before and/or during pregnancy	Yes	3	2.3	0.5	6.5	20	0.9	0.5	1.3	0	0.0	0.0	24.7	0.2448
	No	128	97.7	93.5	99.5	2283	99.1	98.7	99.5	13	100	75.3	100	-
Smoking before and/or during pregnancy	Yes	23	17.6	11.5	25.2	218	9.5	8.3	10.8	1	7.7	0.2	36.0	0.0105
	No	108	82.4	74.8	88.5	2080	90.5	89.2	91.7	12	92.3	64.0	99.8	-
Pregnancy-related hypertension in previous pregnancy	Yes	2	3.4	0.4	11.9	52	4.2	3.1	5.4	0	0.0	0.0	45.9	0.8484
	No	56	96.6	88.1	99.6	1199	95.8	94.6	96.9	6	100	54.1	100	-
Pre-eclampsia in previous pregnancy	Yes	2	3.4	0.4	11.9	46	3.7	2.7	4.9	0	0.0	0.0	45.9	0.8884
	No	56	96.6	88.1	99.6	1205	96.3	95.1	97.3	6	100	54.1	100	-

		Small for Gestational age N = 131				No small for Gestational age N = 2303				Missing small for Gestational age N = 28				
				95% CI				95% CI				95% CI		
Characteristics	**Categories**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**P-values**
Eclampsia in previous pregnancy	Yes	0	0.0	0.0	6.2	6	0.5	0.2	1.0	0	0.0	0.0	45.9	0.8571
	No	58	100	93.8	100	1245	99.5	99.0	99.8	6	100	54.1	100	-
HELLP Syndrome in previous pregnancy	Yes	0	0.0	0.0	6.2	0	0.0	0.0	0.3	0	0.0	0.0	45.9	-
	No	58	100	93.8	100	1251	100	99.7	100	6	100	54.1	100	-
Infection in previous pregnancy	Yes	0	0.0	0.0	6.2	11	0.9	0.4	1.6	0	0.0	0.0	45.9	0.7528
	No	58	100	93.8	100	1239	99.1	98.4	99.6	6	100	54.1	100	-
Gestational diabetes in previous pregnancy	Yes	3	5.2	1.1	14.4	18	1.4	0.9	2.3	0	0.0	0.0	45.9	0.0815
	No	55	94.8	85.6	98.9	1233	98.6	97.7	99.1	6	100	54.1	100	-
Vaginal hemorrhage in previous pregnancy	Yes	0	0.0	0.0	6.2	12	1.0	0.5	1.7	0	0.0	0.0	45.9	0.7336
	No	58	100	93.8	100	1239	99.0	98.3	99.5	6	100	54.1	100	-
Premature rupture of membranes in previous pregnancy	Yes	2	3.4	0.4	11.9	8	0.6	0.3	1.3	0	0.0	0.0	45.9	0.0539
	No	56	96.6	88.1	99.6	1243	99.4	98.7	99.7	6	100	54.1	100	-
Preterm premature rupture of membranes in previous pregnancy	Yes	2	3.4	0.4	11.9	21	1.7	1.0	2.6	0	0.0	0.0	45.9	0.5720
	No	56	96.6	88.1	99.6	1230	98.3	97.4	99.0	6	100	54.1	100	-
Premature uterine contraction in previous pregnancy	Yes	1	1.7	0.0	9.2	46	3.7	2.7	4.9	3	50.0	11.8	88.2	<0.0001
	No	57	98.3	90.8	100	1205	96.3	95.1	97.3	3	50.0	11.8	88.2	-
Neonatal death in previous pregnancy	Yes	0	0.0	0.0	6.2	14	1.1	0.6	1.9	1	16.7	0.4	64.1	0.0012
	No	58	100	93.8	100	1237	98.9	98.1	99.4	5	83.3	35.9	99.6	-
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes	1	1.7	0.0	9.2	1	0.1	0.0	0.4	0	0.0	0.0	45.9	0.0072
	No	57	98.3	90.8	100	1250	99.9	99.6	100	6	100	54.1	100	-
New born with low birth weight [less than 2.5 kg] in previous pregnancy	Yes	8	17.0	7.6	30.8	119	11.7	9.8	13.9	3	60.0	14.7	94.7	0.0026
	No	39	83.0	69.2	92.4	895	88.3	86.1	90.2	2	40.0	5.3	85.3	-
Fetal macrosomia [newborn greater than 4 kg] in previous pregnancies	Yes	0	0.0	0.0	7.5	45	4.4	3.2	5.9	0	0.0	0.0	52.2	0.3016
	No	47	100	92.5	100	974	95.6	94.1	96.8	5	100	47.8	100	-
Pre-term baby [less than 37 weeks] in previous pregnancies	Yes	9	19.6	9.4	33.9	135	12.8	10.8	14.9	4	80.0	28.4	99.5	<0.0001
	No	37	80.4	66.1	90.6	922	87.2	85.1	89.2	1	20.0	0.5	71.6	-

N = number of subjects
n = number of subjects in a given category
% = n / Number of subjects with available results x 100
P values: Chi-square test
LL, UL for percentage = Exact 95% Lower and Upper confidence limits
Note: Do not have available data for 14 subjects

Table 76 Estimated unadjusted odds ratio for exploring the risk factors of small for gestational age in current pregnancy (Total cohort)

			95% CI		
Characteristic	**Compared levels**	**Unadjusted OR**	**LL**	**UL**	**p-value**
Exposure status	Exposed vs. Unexposed	1.155	0.812	1.644	0.4224
Maternal age at the start of the pregnancy (in years)	18-19Y vs. 20-24Y	1.266	0.738	2.170	0.3912
	25-29Y vs. 20-24Y	1.155	0.724	1.840	0.5454
	30-34Y vs. 20-24Y	0.823	0.464	1.457	0.5029
	35-39Y vs. 20-24Y	1.050	0.551	2.001	0.8828
	GE 40Y vs. 20-24Y	0.921	0.276	3.067	0.8927
Parity	Multiparous vs. Nulliparous	0.715	0.332	1.538	0.3905
Parity (Nulliparous + Multiparous)	1 vs. 0	0.869	0.395	1.913	0.7281
	2 vs. 0	0.419	0.158	1.108	0.0795
	3-4 vs. 0	0.802	0.283	2.272	0.6773
	≥5 vs. 0	<0.001	<0.001	>999.999	0.9860
Infection during current pregnancy	Yes vs. NO	0.582	0.368	0.921	0.0209
Placenta previa	Yes vs. NO	<0.001	<0.001	>999.999	0.9856
Placenta abruption	Yes vs. NO	1.961	0.247	15.593	0.5244
Alcohol consumption before and/or during pregnancy	Yes vs. NO	1.729	0.610	4.903	0.3030
Substance abuse before and/or during pregnancy	Yes vs. NO	2.675	0.785	9.121	0.1158
Smoking before and/or during pregnancy	Yes vs. NO	2.032	1.269	3.255	0.0032
Pregnancy-related hypertension in previous pregnancy	Yes vs. NO	0.824	0.196	3.467	0.7913
Pre-eclampsia in previous pregnancy	Yes vs. NO	0.936	0.221	3.952	0.9278
Eclampsia in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9878
HELLP in previous pregnancy	Not performed	.	.	.	.
Infection in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9892
Gestational diabetes in previous pregnancy	Yes vs. NO	3.737	1.069	13.064	0.0390
Vaginal hemorrhage in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9887
Premature rupture of membranes in previous pregnancy	Yes vs. NO	5.549	1.152	26.738	0.0327
Preterm premature rupture of membranes in previous pregnancy	Yes vs. NO	2.093	0.479	9.144	0.3264
Premature uterine contraction in previous pregnancy	Yes vs. NO	0.460	0.062	3.392	0.4459
Neonatal death in previous pregnancy	Yes vs. NO	<0.001	<0.001	>999.999	0.9878
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes vs. NO	21.951	1.356	355.415	0.0297
New born with low birth weight (<2.5 kg) in previous pregnancy	Yes vs. NO	1.543	0.704	3.380	0.2786
Fetal macrosomia (newborn > 4 kg) in previous pregnancies	Yes vs. NO	<0.001	<0.001	>999.999	0.9781
Pre-term baby (<37 weeks) in previous pregnancies	Yes vs. NO	1.661	0.784	3.519	0.1850

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits

Table 77 Estimated coefficients for the adjusted logistic regression model for exploring the risk factors of small for gestational age in current pregnancy (Total cohort)

						95% CI	
Characteristic	**Compared levels**	**Coefficient**	**Standard error**	**P-value**	**Adjusted OR**	**LL**	**UL**
Independent factor	Continuous*	-3.3069	0.1811	<.0001	.	.	.
Smoking before and/or during pregnancy	Yes vs. NO	0.8812	0.3773	0.0195	2.414	1.152	5.056
Premature rupture of membranes in previous pregnancy	Yes vs. NO	2.0789	0.8407	0.0134	7.996	1.539	41.539
Neonatal hypoxic ischemic encephalopathy in previous pregnancy	Yes vs. NO	3.3069	1.4258	0.0204	27.299	1.669	446.436

OR: odds ratio
95% CI: 95% confidence interval
LL, UL: lower and upper confidence limits
* OR for continuous variables describes the effect of a difference of one unit

15. ANNEXES

Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	203153	27 Nov 2017	List of stand-alone documents
2	203153	27 Nov 2017	Glossary of terms
3	203153	27 Nov 2017	Trademarks
4	203153	27 Nov 2017	List of principal and coordinating investigators
5	203153	27 Nov 2017	Sponsor Information
6	203153	27 Nov 2017	Feasibility assessment
7	203153	27 Nov 2017	Definitions and evaluations of selected terms and adverse events of interest in pregnant women participating in clinical trials (adapted from [Munoz, 2013])
8	203153	27 Nov 2017	Planned variables to be collected in electronic Case Report Form (eCRF)
9	203153	27 Nov 2017	Recommendations for *Refortrix* vaccine in Brazil
10	203153	27 Nov 2017	Report sign-off

Annex 2 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.
Anonymized data:	Information about an individual that GSK or a third party cannot reasonably attribute to the individual, or could only attribute to the individual by expending a disproportionate amount of time, effort or expense (e.g. de-identified or aggregated information). For the purpose of this policy, Key-Coded personally identifiable information shall not be considered Anonymized Information
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).
Congenital anomalies:	The collection of congenital anomalies is based on the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [CDC, 2015] and include morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the fetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception. Live-born neonates with transient (postural) defects, infectious conditions or biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognized congenital birth defect.

Eclampsia:	Features of pre-eclampsia are accompanied by new onset generalized seizures. See more at Pregnancy-related hypertension.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all subjects at all time points within that epoch allows to draw a complete conclusion. Typical examples of epochs are retrospective data collection and prospective data collection, etc.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.
Gestational Age:	Gestational age is based on first day of the last menstrual period (LMP) OR the first trimester ultrasound, if no known date of LMP OR known date of fertilization; with the second trimester beginning at week 14 0/7, and the third trimester beginning at week 28 0/7.
Gestational diabetes:	Onset or first recognition of abnormal glucose tolerance during pregnancy (the diagnosis is based on administration of glucose challenge test at 24-28 weeks of gestation). Includes Class A1: Euglycaemia achieved with diet and/or exercise and Class A2: Euglycaemia achieved with medication. Refer to Annex 7 for details on diagnosis.
HELLP syndrome:	Form of severe pre-eclampsia with associated laboratory abnormalities including hemolysis (H), elevated liver (EL) function tests and low platelets (LP) with or without proteinuria. Refer Pregnancy-related or gestational hypertension for more details. Patients are classified as having partial HELLP syndrome when one or two laboratory abnormalities of HELLP occur.

High-risk pregnancy:	Pregnancy that threatens the health or life of the mother or her fetus. Risk factors for a high-risk pregnancy can include existing health conditions such as high blood pressure, diabetes, being Human Immunodeficiency Virus (HIV)-positive, overweight, obesity, multiple births and young or old maternal age.
Index date:	For the Exposed cohort, the index date was the date of *Refortrix* vaccination given as part of the maternal immunization program in Brazil. For the Unexposed cohort, the gestational age of 27 completed weeks was considered as the index date. Only the events for each endpoint occurring after the index date for both groups were considered.
Key coded information:	Refers to encoded or otherwise pseudo-anonymized Personally Identifiable Information (PII) from which direct identifiers have been removed and replaced by a unique identifier or random code. Key coded PII shall not be considered anonymized information.
Last Menstrual period (LMP):	Considered as the first day of the LMP before conception (fertilization) onset. The first day of LMP is equal to first day of gestation. The estimated day of conception (fertilization) is calculated as the first day of LMP plus 14 days.
Live birth:	Delivery of a live infant, regardless of maturity or birth weight, as determined by the presence of spontaneous respirations, a heartbeat, and spontaneous movement.
Maternal death:	Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.
Neonatal death:	Death of neonate at any time from birth to 28 days of life, regardless of gestational age.
Neonatal hypoxic ischemic encephalopathy:	A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty in initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or due to another cause.

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.
Personally Identifiable Information (PII):	Information which directly (e.g. by name) or indirectly (e.g. by one or more identifiers such as height, weight, date of birth, initials etc) is considered, either individually or in combination, to have the potential to allow identification of named individuals. Different jurisdictions apply varying criteria to define 'personally identifiable data'. In the case of data collected during GlaxoSmithKline (GSK) sponsored clinical trials and processed via Biometrics and Data Sciences (BDS), the true identity of the data of the subject is substituted by a code and the "key" linking the code with the true identity is held by a third party outside GSK (the investigator). These data are generally considered not to be personally identifiable.
Placental abruption:	Partial or total placental detachment prior to delivery of fetus.
Placenta previa:	Presence of placental tissue overlying or proximate to the internal cervical os with or without bleeding, which ranges from spotting to hemorrhagic shock.
Post-Authorization Safety Study:	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.).

Post-partum hemorrhage:	Excessive blood loss after delivery i.e. estimated blood loss in excess of 500 ml after vaginal delivery and estimated blood loss in excess of 1000 ml after Caesarean delivery. The other symptoms are ≥10% drop in hematocrit, need for blood transfusion, symptomatic hypotension, dizziness, pallor and oliguria.
Pre-eclampsia:	An acute pregnancy related hypertensive condition characterized by hypertension (>140 and/or >90 mmHg) and/or proteinuria (>300 mg in a 24-hour urine specimen) occurring after the 20th week of gestation and resumes after delivery
Pregnancy/gestational duration:	Pregnancy duration was classified using the gestational age according to the duration of pregnancy in number of completed weeks: • Preterm was defined as birth before 37 weeks of gestation. • Full term was defined as birth between 37 and 41 weeks of gestation. • Post-term was defined as birth after 41 weeks of gestation.
Pregnancy-related hypertension:	Blood pressure systolic >140 and/or diastolic >90 mmHg, documented in at least two separate measurements after 20 weeks of gestation, without proteinuria or other stigmata of pre-eclampsia, and returning to normal post-partum. Hypertension usually resolves by 12 weeks' post-partum. For this study, this will include pre-eclampsia, eclampsia and HELLP Syndrome.
Premature rupture of membranes (PROM):	Spontaneous rupture of fetal membranes that occurs before the onset of labor.
Premature uterine contraction:	Uterine contractions without cervical change.
Preterm birth:	Birth before 37 weeks of gestation.
Preterm Premature rupture of membranes (P-PROM):	Spontaneous rupture of fetal membranes that occurs before the onset of labor before 37 weeks of gestation.
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.

Serious Adverse Event (SAE): A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalization or prolongation of existing hospitalization,

Note: In general, hospitalization signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalization are also considered AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent

everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

Site Monitor: An individual assigned by the sponsor who is responsible for assuring the proper conduct of epidemiological studies at one or more investigational sites.

Small for gestational age (SGA): Birth weight less than 10% for infants of same gestational age and gender in same population.

Still birth: Death of the fetus(es) at ≥22 weeks of gestation, occurring antepartum or intrapartum.

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.

Subject number: A unique number identifying a subject, assigned to each subject consenting to participate in the study.

Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.
Vaginal or intrauterine hemorrhage:	Vaginal or intrauterine hemorrhage which may be caused due to partial or total detachment of placenta or due to presence of placental tissue overlying or proximate to the internal cervical os with or without bleeding, which ranges from spotting to hemorrhagic shock. This includes the following diagnosis- placental abruption and placenta previa.

Annex 3 Trademarks

The following trademarks are used in the present report.

Note: In the body of the report (including the synopsis), the names of the vaccine will be written without the superscript symbol ™ or ® and in *italics*.

Trademark of the GSK group of companies	Generic description
Refortrix	Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine

Annex 4 List of principal and coordinating investigators

Investigator's name	Sub-investigators	Center number*	Investigational site (institution /hospital)	Location (complete address)	Phone number Fax number
PPD	PPD	PPD	PPD	PPD PPD Brazil	Phone: PPD Fax: PPD

* GSK Biologicals' assigned center number

Annex 5 Sponsor Information

1. Sponsor:

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

2. Sponsor Study Monitor:

Refer to the local study contact information document.

Annex 6 Feasibility assessment

The details on feasibility assessment are available upon request.

Annex 7 Definitions and evaluations of selected terms and adverse events of interest in pregnant women participating in clinical trials (adapted from Munoz, 2013)

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
PREGNANCY RELATED TERMS				
GESTATIONAL AGE ESTIMATES: Dating of Pregnancy	Dating from: -first day of last menstrual period (LMP), OR -1st trimester ultrasound if no known LMP or the ultrasound is not consistent with LMP, OR -known date of fertilization (e.g. by Assisted Reproductive Technology or Intrauterine Insemination). [ACOG, 2014]		Test for urine or serum β-HCG -urine test: positive about 10-12 days after conception. -serum test: positive about 5-7 days after conception. The estimated date of conception or pregnancy onset is calculated as the last menstrual period plus 14 days. Ultrasound (US): Gestational age is assessed in the 1st trimester (< 14 weeks) by measurement of crown-rump length. In the second trimester (14 to 20 weeks), the biparietal diameter is used (accuracy is within +/- 10 days up to 34 weeks, then +/- 3 weeks). At term, abdominal circumference and femoral length are used. US limited by: insufficient standardization, operator variability and expertise, lack of large population based reference, assumption that all fetuses with the same measurements have the same gestational age without accounting for true differences in fetal growth in early gestation or genetic and other familiar factors.	-The Committee on Obstetric Practice, American Institute of Ultrasound in Medicine and Society for Maternal-Fetal. Committee Opinions: Method for estimating Due Date. Number 611, October 2014 (accessed on-line on 13/Oct/2014 at: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Method-for-Estimating-Due-Date).

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
TRIMESTER OF GESTATION	Pregnancy is divided in three trimesters: -First trimester: up to and including 13 6/7 weeks of gestation. -Second trimester: 14 0/7 weeks to 27 6/7 weeks of gestation. -Third trimester: 28 0/7 weeks of gestation and beyond.			
LENGTH OF PREGNANCY	Preterm: up to and including 36 6/7 weeks of gestation. Term: 37 0/7 weeks through 41 6/7 weeks of gestation [ACOG, 2013]. Early term: Birth at 37 0/7 to <39 weeks of gestation. Post-term (S: post-mature): 42 0/7 weeks of gestation and beyond.		Estimated Date of Delivery (EDD)= 40 0/7 weeks (280 days) from the first day of the last menstrual period or by Ultrasound examination.	The American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Committee Opinions: Definition of Term Pregnancy. Number 579, November 2013 (accessed on-line on 13/Oct/2014 at: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Definition-of-Term-Pregnancy)
PREGNANCY OUTCOMES				
LIVE BIRTH S: Live born	Delivery of a live infant, regardless of maturity or birth weight, as determined by the presence of spontaneous respirations, a heartbeat, and spontaneous movement			

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
SPONTANEOUS ABORTION S: miscarriage, pregnancy loss	Pregnancy ending spontaneously before 22 weeks of gestation (i.e. up to and including 21 6/7 weeks of gestation) [EMEA, 2005]. Includes death of embryo/ fetus in utero (missed abortion), or blighted ovum /anembryonic pregnancy (i.e. fertilized ovum whose development has ceased at an early stage). Subgroups: -Early miscarriage if it occurs during the first trimester. -Late miscarriage when it occurs during the second trimester.	Overall rates: The prevalence of spontaneous abortion reported by several authors among clinical pregnancies (i.e. recognized pregnancies following a missed menstrual period) for all age groups combined is about 12-18% of all pregnancies in first or second trimester. -Early miscarriage: Up to 20%of pregnancies. -Late miscarriage: Up to 2% of pregnancies. Risk factors: Studies have shown that approximately 50% of spontaneous abortions are associated with fetal chromosome abnormalities [Brown 2008]. Many studies have shown that maternal age is one of the strongest and most consistent risk factor.	Note: case definitions vary between countries, as definition of viability is varied between resource settings (e.g. 20-24 weeks versus 28 weeks and corresponding fetal weight of 500 mgr. vs. 1000 mgr). Document circumstances of fetal loss, physical exam/estimated gestational age of the product if feasible and/or collect results of available studies including pathology report of fetus and placenta to establish a possible etiology, association/causality. Genetic testing if available; a karyotype may or may not be performed as part of routine clinical care. Of note, it may not be possible to perform evaluation if the subject does not seek medical attention.	- European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorization Data. London, UK: EMEA; 2005. - Brown S. Miscarriage and its associations. Seminars in Reproductive Medicine 2008; 26(5): 391-400. - Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. New England Journal of Medicine1988;319: 189–94. - Harlap S, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. Lancet 1980; 2:173–6.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
STILLBIRTH S: Stillborn, Fetal Demise/Death, Deadborn	Delivery of a death fetus after 22 0/7 weeks of gestation [EMEA, 2005]. Categories: - During pregnancy or antepartum. - Intrapartum. Subgroups: -Early Stillbirth: Delivery 22 0/7 – <28 weeks and/or ≥500 -1000 grams. -Late Stillbirth: Delivery ≥ 28 0/7 weeks and/or >1,000 grams	Overall rates [ACOG, 2009]: 6.2/1,000 births or 1 in 160 deliveries. -Early stillbirth: 3.2/1,000 births. -Late stillbirth: 3.1/1,000 births. Risk factors: Non-Hispanic black race, nulliparity, maternal age >35 years, hypertension, diabetes, obesity BMI >30, multiple gestations, smoking, drug and alcohol use, infections, growth restriction, and placental anomalies.	Includes macroscopic examination for fetal anomalies, and if available, autopsy and karyotype; cord and placental examination and pathology. Document antepartum events: maternal factors, fetal factors (e.g., IUGR), external factors (e.g., trauma), and peripartum events such as preterm premature rupture of membranes (PPROM), infection, abruption, cord events.	- European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-authorization Data. London, UK: EMEA; 2005. - American College of Obstetricians and Gynecologists. Management of stillbirth. ACOG Practice Bulletin Number 102. Obstetrics and Gynecology2009; 113: 748–61. (accessed on-line on 13/Oct/2014 at: https://stillbirthmatters.files.wordpress.com/2014/05/acog-management-of-stillbirth1.pdf)
CONGENITAL ANOMALIES S: Birth defects, Malformations	The collection of congenital anomalies is based on the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [CDC,2007] and include morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the fetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception.	Minor anomaly: Rates vary widely depending on study. Minor malformations and developmental variants occur in 14 - 40% of otherwise normal newborns [Leppig, 1987]. Major anomaly: Apparent at birth in approximately 3% of population [CDC, 2013].	An exact cause or mechanism for a major defect can be determined in less than 50% of the cases. Some agents cause major defects if exposure occurs during a specific critical period of gestation, but not at other times. After organogenesis has been completed (about 8 weeks after conception or 10 weeks after last menstrual period), the observable effect may be limited to fetal growth restriction or functional rather than gross structural defects [Sadler,2009]. The primary outcomes relative to stage of exposure are as follows: Pre-implantation: embryonic lethality	Centers for Disease Control. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; 2007. (accessed on-line on 13/Oct/2014 at: http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf) - Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, MooreCA. Guidelines for case classification for the National Birth Defects Preven-tion Study. Birth Defects Research Part A: Clinical and Molecular Teratology2003; 67:193–201.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	Live-born neonates with transient (postural) defects, infectious conditions or certain biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognized congenital birth defect. Morphological anomalies: Abnormalities of body structure or function that are present at birth and are of prenatal origin. Categories: Minor anomaly: Anatomic variant or defect that do not have serious medical, functional or cosmetic consequences for the child. Includes those found in association with major anomalies. Major anomaly: Structural or functional defect that require surgical/medical treatment, have serious adverse effects on health or development (functional), or have significant cosmetic impact. [Rasmussen, 2003].		Implantation to time of organogenesis: morphological defects. Fetal → neonatal stage: functional disorders, growth retardation, Carcinogenesis. A certain pattern of minor malformations may have important predictive value in identifying more serious associated problems, some of which may be unrecognizable at an early age. Specific patterns of multiple minor malformations may be presenting signs of a genetic condition or malformation syndrome.	- Leppig KA, Werler MM, Cann CI, Cook CA, Holmes LB. Predictive value of minor anomalies. Association with major malformations. Journal of Pediatrics1987; 110: 530–7. -Sadler TW. Langman's medical embryology. 11th ed. Lippincott Williams and Q4Wilkins; 2009. - Centers for Disease Control and Prevention. Update on overall prevalence of major birth defects-Atlanta, Georgia, 1978–2005. MMWR; 2013. (accessed on-line on 13/Oct/2014 at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm)
ELECTIVE OR THERAPEUTIC TERMINATION OF PREGNANCY S: Induced abortion	Expulsion of products of conception with medical or surgical assistance. The termination of the pregnancy can be elective or therapeutic. -Elective: performed for personal choice/socio-economic reasons, excluding maternal or fetal health reasons.			

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	-Therapeutic: performed to preserve the health or save the life of a pregnant woman.			
ECTOPIC PREGNANCY S: Extra-uterine pregnancy	Condition in which a fertilized ovum implants outside the uterine cavity, most often in the fallopian tube (97%).	Affects 1.5% to 2% of all pregnancies and poses a significant threat to women of reproductive age. It is the leading cause of maternal death during the first trimester of pregnancy. Risk factors: tubal surgery, genital tract infections leading to pelvic inflammatory disease, previous ectopic pregnancy, and in utero exposure to diethylstilbestrol [ACOG, 2008].	Diagnosis is generally based on: clinical symptoms/signs, diagnostic transvaginal ultrasonography, abnormal serum progesterone level of less than 5 ng/mL and/or an inappropriate increase in hCG.	- Kurt T. Barnhart. Ectopic pregnancy. N Engl J Med 2009; 361:379-87. - American College of Obstetricians and Gynecologists. Medical Management of Ectopic Pregnancy. ACOG Practice Bulletin Number 94. Obstetrics and Gynecology Jun 2008; 111(6): 1479–85.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
MOLAR PREGNANCY S: gestational trophoblastic neoplasia, gestational trophoblastic tumor	Pregnancy marked by a neoplasm within the uterus, whereby part or all of the chorionic villi are converted into a mass of clear vesicles. Histologically distinct disease entities encompassed by this general terminology include: complete and partial hydatidiform moles, invasive moles, gestational choriocarcinomas, and placental site trophoblastic tumors.	The incidence is estimated at 1-3 per 1000 pregnancies for partial or complete hydatidiform moles. The malignant invasive moles (choriocarcinoma and placental site trophoblastic tumor/epithelioid trophoblastic tumor) are very rare, 0.2% of the gestational trophoblastic disease cases [ESMO, 2013; ACOG, 2004]. Risk factors: extremes of maternal age and prior molar pregnancy. The risk of repeat molar pregnancy after 1 mole is about 1%, or about 10-20 times the risk for the general population.	The disease is most frequently diagnosed on the basis of increasing or plateauing hCG values. Patients should be monitored with serial determinations of quantitative hCG values. A baseline post-evacuation chest X-ray should be considered.	- American College of Obstetricians and Gynecologists. Diagnosis and Treatment of Gestational Trophoblastic Disease. ACOG Practice Bulletin Number 53. Obstetrics and Gynecology June 2004; 103 (6):1365-77. - M. J. Seckl, N. J. Sebire, R. A. Fisher, F. Golfier, L. Massuger & C. Sessa, on behalf of the ESMO Guidelines Working Group. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2013; 24 (Supplement 6): vi39–vi50.
PREGNANCY RELATED ADVERSE EVENTS OF INTEREST				
VAGINAL OR INTRAUTERINE HEMORRHAGE S: Obstetric Hemorrhage, Major obstetric hemorrhage	Vaginal or intrauterine hemorrhage that encompasses antepartum (i.e. bleeding from the genital tract after 24 weeks of gestation), intrapartum, and postpartum bleeding (i.e. within 24 hours post-delivery). A major obstetric hemorrhage is defined as blood loss from uterus or genital tract >1500 mL or a decrease	Antepartum hemorrhage: has an incidence of 2–5% of all pregnancies beyond 24 weeks [Walfish, 2009]. Infrequent (14% of cases occur before 32 weeks' gestation) and up to 60% between 32-37 weeks' gestation [Munoz, 2013]. Risk factors for placenta previa:	Given the wide range of definitions applied to maternal hemorrhage, it is important to combine the clinical presentation and objective data, while keeping in mind the probability of concealed bleeding within the uterus, peritoneal cavity, and retroperitoneal space, and the relative masking of haemodynamic signs of hemorrhagic	- American College of Obstetricians and Gynecologists. Cervical insufficiency. ACOG Practice Bulletin No. 76, Postpartum Hemorrhage International Journal of Gynecology and Obstetrics Oct 2006: 108 (4): 1034-47 (accessed on-line on 13/Oct/2014 at: https://www.acog.org/~/media/Distri

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	in hemoglobin of >4 gr/dl or acute loss requiring transfusion of >4 units of blood, or signs or symptoms of hypovolemia. Common causes of blood loss: - Antepartum hemorrhage: placenta previa (presence of placental tissue overlying or proximate to the internal cervical os), placental abruption (partial or total placental detachment prior to delivery of fetus), uterine rupture, bleeding from vaginal or cervical lesions, etc. - Postpartum Hemorrhage: uterine atony, retained products of conception, abnormal placentation (abnormal attachment of the placenta to the uterine wall and includes accreta, increta, and percreta, depending on the extent of uterine invasion), genital tract trauma, uterine inversion, puerperal sepsis, uterine pathology such as fibroids, etc.	prior uterine trauma, multiparity, advanced maternal age, previous C-section or other uterine surgery, and prior placenta previa. Risk factors for placental abruption: hypertension, pre-eclampsia, advanced maternal age, multiparity, maternal/paternal tobacco use, cocaine use, trauma, premature rupture of membranes, chorioamnionitis, and prior abruption. Risk factors for uterine rupture: prior uterine surgery, trauma, uterine anomalies, dystocia, use of uterotonic drugs, and abnormal placentation. Post-partum hemorrhage: Primary postpartum hemorrhage, which occurs in 4–6% of pregnancies, is caused by uterine atony in 80% or more of cases [ACOG,2006]. Risk factors for Postpartum Hemorrhage: Prolonged labor, Augmented labor, Rapid labor, History of postpartum hemorrhage, Episiotomy, especially mediolateral, Preeclampsia, Overdistended uterus (macrosomia, twins, hydramnios), Operative delivery, Asian or Hispanic ethnicity, Chorioamnionitis. Risk factors for abnormal	shock due to the physiological adaptations of pregnancy. Diagnosis is based on clinical presentation; ultrasound and placental pathology if available.	cts/District%20II/PDFs/Final_Hemorrhage_Web.pdf - Walfish M et al. Maternal hemorrhage. Br. J. Anaesth. (2009) 103 (suppl 1): i47-i56. -Munoz et al. Research on vaccines during pregnancy: Protocol design and assessment of safety, Vaccine, (2013): 31 (40): 4274-4279, Appendixes

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
		placentation: placenta previa with or without previous uterine surgery, prior myomectomy, prior cesarean delivery, Asherman's syndrome, submucous leiomyomata, and maternal age older than 35 years.		
PREMATURE RUPTURE OF MEMBRANES (PROM) AND PRETERM PREMATURE RUPTURE OF MEMBRANES (P-PROM)	PROM: Spontaneous rupture of fetal membranes that occurs before the onset of labor. Preterm PROM (P-PROM): Spontaneous rupture of fetal membranes that occurs before the onset of labor before 37 weeks' gestation.	Term PROM may occur in 8% of pregnancies, P-PROM in approximately one-third of all preterm births or 4% of all births [ACOG, 2007]. Risk factors: Numerous maternal and fetal factors involved, particularly infection, obstetric factors including abruption placenta, as well as previous P-PROM or premature delivery. Recurrence for P-PROM is 16-32%.	Assessment of gestational age and assessment of maternal and fetal risks, including intrauterine infection, labor, fetal compromise.	-American College of Obstetricians and Gynecologists. Premature rupture of membranes. ACOG Practice Bulletin Number 80. Obstetrics and Gynecology2007; 109:1007–20.
PREMATURE UTERINE CONTRACTIONS AND PREMATURE LABOR	Premature uterine contractions: Uterine contractions without cervical change. Premature labor: Cervical change in the presence of regular uterine contractions that occur before 37 weeks of gestation.	Refer to incidence of preterm delivery: 12% of all live births [ACOG, 2012].	Collect any clinical and laboratory information that is available. Standard work-up may include: vaginal examination, uterine monitoring, and fetal monitoring. Work-up to determine etiology or association to study product may include: evaluation for infections (urine culture, Group B streptococcus, Chlamydia, gonococcus, *Trichomonas vaginalis*, bacterial vaginosis), drug screen, and ultrasound to rule out abruption, cord prolapse, oligo/polyhydramnios.	- American College of Obstetricians and Gynecologists. Management of preterm labor. ACOG Practice Bulletin Number 127. International Journal of Gynecology and Obstetrics 2012 Jun; 19(6):1308-17.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
INTRAUTERINE GROWTH RESTRICTION / POOR FETAL GROWTH S: IUGR S: Fetal growth retardation	Estimated or actual birth weight below the 10th percentile for gestational age.	10% of live births [ACOG, 2013]. Risk factors: Numerous, classified as maternal, placental, fetal.	May include ultrasound (specific biometric parameters and estimated fetal weight), umbilical artery Doppler velocimetry, amniocentesis, chromosomes, and assessment of maternal risk factors (infection, hypertension, etc.). NOTE: curves used to determine %iles should account for gender and race/ethnicity	- American College of Obstetricians and Gynecologists. Fetal Growth Restriction. ACOG Committee Opinion Number 134. Obstetrics and Gynecology May 2013;121: 1122–33.
GESTATIONAL HYPERTENTION, PREECLAMPSIA AND ECLAMPSIA S: Pregnancy Related Hypertension, Pregnancy Induced Hypertension (PIH), Toxemia	Gestational hypertension: Blood pressure systolic >140 and/or diastolic >90 mmHg, documented in at least 2 separate measurements after 20 weeks of gestation, without proteinuria or other stigmata of preeclampsia, and returning to normal post-partum. Hypertension usually resolves by 12 weeks postpartum Pre-eclampsia: Hypertension (>140 and/or >90 mmHg) occurring after the 20th week of gestation, and up to 6 weeks postpartum, combined with other abnormalities such as proteinuria (>300 mg in a 24 hr urine specimen). HELLP syndrome: Form of severe pre-eclampsia with associated laboratory abnormalities including hemolysis (H), elevated liver (EL) function tests, and low platelets (LP), with or without proteinuria.	Hypertensive disease occurs in 12-22% of pregnancies [ACOG, 2001; ACOG, 2002]. As many as 25% of women with gestational hypertension will develop preeclampsia. The reported incidence of preeclampsia is 5-8% of pregnancies, usually first pregnancies. Risk factors: First pregnancy, multiple gestation, preeclampsia in previous pregnancy, chronic hypertension, pre-gestational diabetes, vascular and connective tissue disorders, nephropathy, antiphospholipid antibody syndrome, obesity, age >35 years, non-Hispanic black race.	Blood pressure elevation should be sustained and documented in two independent measurements. Additional assessments include a random or 24-hour urine protein determination of 300 mg/dL, other laboratory testing to establish severity and collection of available data on fetal well-being.	- American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin Number 33. Obstetrics and Gynecology 2002; 99:159–67. - American College of Obstetricians and Gynecologists. Chronic hypertension in pregnancy. ACOG Practice Bulletin Number 29. Obstetrics and Gynecology2001; 98:177–85.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	Eclampsia: If the features of pre-eclampsia are accompanied by new onset generalized seizures. Chronic Hypertension with superimposed preeclampsia: Chronic hypertension definition PLUS preeclampsia definition			
GESTATIONAL DIABETES MELLITUS S: Diabetes of pregnancy	Onset or first recognition of abnormal glucose tolerance during pregnancy (old definition still used by ACOG). Diagnosis based on administration of glucose challenge test at 24-28 weeks' gestation	1% to 14%, with 2-5% being the most common figure [ACOG, 2001].	Includes urine glucose measurement during routine prenatal care visits; a fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], or A1C ≥6.5 percent using a standardized assay, or a random plasma glucose ≥200 mg/dL [11.1 mmol/L] that is subsequently confirmed by elevated fasting plasma glucose or A1C, as noted above. Glucose tolerance screening is universal at 24-28 weeks of gestation.	- American College of Obstetricians and Gynecologists. Gestational diabetes. ACOG Practice Bulletin Number 30. Obstetrics and Gynecology2001;98: 525–38.
MATERNAL DEATH	Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. Direct obstetric death: death of the mother resulting from conditions or complications which are unique to pregnancy and occur during the antepartum, intrapartum, or postpartum period. Indirect obstetric death: A maternal death that is not directly due to	The global maternal mortality rate is estimated to be about 210 maternal deaths per 100,000 live births [WHO,2013]. Indirect causes and obstetric hemorrhage are the largest causes of maternal death worldwide. Of the direct causes of death, hemorrhage is the leading cause of maternal death, followed by hypertensive disorders and sepsis. Regional estimates varied substantially [Say, 2014].		- Trends in Maternal Mortality: 1990 to 2013. Estimates by WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division. (accessed on-line on 13/Oct/2014 at: http://apps.who.int/iris/bitstream/10665/112682/2/9789241507226_eng.pdf?ua=1) -Lale Say et al, Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2: e323–33

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	obstetric cause (such as from previously existing disease, or disease developing during pregnancy, labor, or the puerperium but that was not unique to pregnancy.) Late Maternal Death: Death of woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy.			
NEONATAL RELATED EVENTS				
BIRTH WEIGHT (BW)	Small for gestational age (SGA): Birth weight < 10% for newborns of same gestational age and gender in same population (<2500g at term). Low birth weight: BW <2500 g (5.5 lb). Very low birth weight: BW <1500 g (3.3 lb) Extremely low birth weight: BW <1000 g (2.2 lb). Large for gestational age (LGA): Birth weight > 90% for newborns of same gestational age in same population (>4000g at term). High Birth Weight (Macrosomia): BW >4000 g (8.13 lb).	SGA newborns are predisposed to complications, including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis, respiratory distress syndrome, and neonatal death. One of the primary risk factors of LGA is poorly-controlled maternal diabetes (pre-existing diabetes mellitus/gestational). Other risk factors in decreasing order of importance, are as follows: a history of macrosomia, maternal weight before pregnancy, weight gain during pregnancy, multiparity, male fetus, gestational age more than 40 weeks, ethnicity, maternal birth weight, maternal height, maternal age younger than 17 years and a positive 50g glucose	Birth weight: Objective is measurement of weight on the day of delivery (OR first weight obtained). Varies with singleton vs. multiple gestation, gestational age, gender, race, ethnicity, maternal nutritional status (BMI), and maternal health status. Birth weight is one of the most sensitive – and also one of the most important – measures of the well-being of children. Weight at birth is directly influenced by the general level of health status of the mother. Assessment of Birth Weight is in relation to Gestational Age (BW/GA): -Gestational age should be based on best obstetric estimate, usually prenatal ultrasound or first day of last menstrual period if ultrasound not available; or neonatal physical exam. -Weight should be based on objective measurement on the day of birth.	

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
		screen with a negative result on the three-hour glucose tolerance test.	-Estimate of BW/GA should be based on population specific curves	
PRETERM BIRTH	Birth before 37 weeks of gestation. Late Preterm: 34 to <37 weeks Moderate Preterm: 32 to <34 weeks Very Preterm: 28 to < 32 weeks Extreme Preterm: < 28 weeks	10-15% of all pregnancies, with most recent National Vital Statistics Report showing a decline to 11.72% in recent years. Extreme preterm birth occurs in less than 1% of live births [ACOG, 2003].	Includes physical examination and determination of gestational age, and evaluation for maternal or infant causes of premature delivery. Assessment requires gestational age assessment by best available obstetric estimate, usually prenatal ultrasound or first day of the last menstrual period if ultrasound not available. Also, assessed by pediatric estimate through physical and neurological examination of newborn at birth. This is less desirable as this assessment is affected by abnormal fetal growth, placental anatomic and functional anomalies, maternal nutrition, racial and ethnic background, population and genetic factors, and birth weight for GA.	-American College of Obstetricians and Gynecologists. Management of preterm labor. ACOG Practice Bulletin Number 43. International Journal of Gynecology and Obstetrics 2003;82: 127–35.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
NEONATAL DEATH	Death of newborn at any time from birth to 28 days of life, regardless of gestational age. Subgroups: Very early neonatal death: < 24hrs Early neonatal death: from birth to < 7 days Late neonatal death: 7 to < 28 days Intrapartum-related neonatal death (previously called: asphyxia deaths): neonatal death of term babies with neonatal encephalopathy or who cannot be resuscitated (or for whom resuscitation is not available). Also, includes babies who die from birth injury without hypoxic brain injury)	The early neonatal death rate is estimated to be 8.4 per 1000 liveborn; 67.1% occur by day 3 of life [Vogel, 2014]. Prematurity is the main cause of early neonatal deaths (~62%).	Causes of death and rates may vary according to whether the birth setting was in a hospital or in the community	- Vogel JP et al, on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121 (Suppl. 1): 76–88.
NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) S: HIE, Birth Asphyxia, Perinatal Asphyxia, Neonatal encephalopathy	A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or be due to another cause.	Rates may vary widely. The incidence of HIE in developed countries is estimated to be 1.5 per 1,000 live births [Kurinczuk, 2010]. Estimates in developing countries range from 2.3–26.5 per 1,000 live births [Horn,2013].	Assessed by clinical and laboratory findings: 5 minute Apgar score of 0-3, Respiratory distress and Acidosis (pH < 7.0), altered tone, depressed level of consciousness, seizures, multiorgan involvement. Diagnostic tests: - MRI is preferred imaging study. - CT can identify focal lesions, hemorrhage, diffuse cortical injury - EKG (ECG) and continuous EKG (ECG) May result in neonatal death or permanent damage to the brain and other organs. May be associated with perinatal events, rarely to prenatal events.	- Kurinczuk JJ, White-Koning M, Badawi N: Epidemiology of neonatal encephalopathy and hypoxic–ischemic encephalopathy. Early Hum Dev 2010, 86(6):329-338. - Horn AR, Swingler GH, Myer L, Harrison MC, Linley LL, Nelson C, Tooke L, Rhoda NR, Robertson NJ: Defining hypoxic ischemic encephalopathy in newborn infants: benchmarking in a South African population. J Perinat Med 2013, 41(2):211-217.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
FAILURE TO THRIVE OR GROWTH DEFICIENCY	Inability to maintain expected growth rate over time, evaluated by plotting individual weight gain and growth on standard growth charts for the population.	Failure to thrive (FTT) is a common problem, however precise epidemiological data is lacking. The population prevalence of FTT has been found to range anywhere between 1.3% and 20.9% depending on the definition of FTT that is used. FTT accounts for 1–5% of pediatric hospital admissions under 2 year of age [Sullivan, 2004]	Normal newborn weight gain includes weight loss of up to 10% of birth weight in the first 1-2 weeks of life, with steady, predictable weight gain thereafter. Progress varies by gestational and post-natal age, genetic and environmental factors. Definitions vary. Fall of weight below 5th percentile for age often used. Olsen et al have described multiple different anthropometric criteria for failure to thrive. These criteria include signs of failure to gain weight (weight < 75% of median weight for chronological age, weight for chronological age < 5th percentile, weight deceleration crossing > 2 major percentile lines, etc), failure to grow (length for chronological age < 5th percentile), and failure to grow and gain weight (weight < 80% of median weight for length, body mass index < 5th percentile) [Olsen, 2007]	- Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. Arch Dis Child. February2007; 92(2):109-114. - Peter B Sullivan. Commentary: The epidemiology of failure-to-thrive in infants. Int. J. Epidemiol. (2004) 33 (4): 847-848.

Annex 8 Planned variables to be collected in electronic Case Report Form (eCRF)

Demographic data:

Age (in years)

Resident

Medical antecedents:

Chronic hypertension

Diabetes mellitus

Anemia

Nutritional disorders: Malnutrition, overweight, obesity

Infectious diseases (e.g.: Chagas disease, Malaria, HIV, Hepatitis, Tuberculosis)

Other Chronic Diseases: Heart disease, rheumatic disease, epilepsy, renal disease, thyroid and other endocrine diseases

Blood transfusion

Accidents

Major surgeries

Neurologic diseases

Gynecological history

Menstrual cycles: Duration in days, interval in days and regular

Prior use of contraceptive methods

Sexually transmitted diseases

Gynecological surgeries (at what age, diagnosis)

Breast problems

Obstetric Antecedents:

Number of pregnancies: including miscarriage, ectopic pregnancy

Number of deliveries

Type of deliveries: forceps, Caesarean, spontaneous, vaginal

Number of miscarriages including spontaneous, induced, therapeutic

Number of live births

Interval between pregnancies

Number of newborns: Preterm (before 37 weeks), Post term (> 42 weeks)

Rh isoimmunization

Number of newborns of low birth weight (less than 2,500 gm) and more than 4000 gm

Early neonatal deaths (if during hospitalization): Up to seven days of life

Late neonatal deaths (if during hospitalization): Between 7 and 28 days

Stillbirth (intrauterine fetal death) and gestational age at which the event occurred

Newborns with jaundice, transfusion, hypoglycemia

Events or complications in previous pregnancies: Hemorrhage, pre-eclampsia, other

Complications in puerperium: Hemorrhage, infections, other

Current Pregnancy History:

Date (first day/month/year) of the last menstrual period

Weight

Ultrasound scan result

Lab tests: Blood group, Rh, hemoglobin, glycaemia, other

Vaccination(s)

Concomitant medications reported at the time of delivery

Hospitalization during this pregnancy

Habits: Smoking, alcohol and illicit drugs

Pregnancy events

Gestational diabetes

Pre-eclampsia

Eclampsia

HELLP Syndrome

Placenta abruption

Placenta previa

Vaginal hemorrhage

- Ante-partum
- Intra-partum
- Post-partum

Birth Outcomes

Pre-term birth (weeks of gestation)

Small for gestational age (birth weight in grams)

Apgar score

Other events

Premature rupture of membranes

Preterm premature rupture of membranes

Premature uterine contraction

Premature labor

Neonatal death

Maternal death

Still birth

Neonatal hypoxic ischemic encephalopathy

Congenital anomalies

Annex 9 Recommendations for *Refortrix* vaccine in Brazil

The recommendation for *Refortrix* vaccine in Brazil is available upon request.

Annex 10 Report sign-off

Investigator Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: A post-marketing, observational, retrospective, cohort study to assess the safety of *Refortrix* (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.

Study: 203153 (EPI-PERTUSSIS-037 VS BR) Development Phase: IV

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator:	Mauro Sancovski
Affiliation /investigational center:	Professor Titular da Disciplina de Obstetrícia da Faculdade de Medicina do ABC
Signature of Investigator:	
Date:	

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Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: A post-marketing, observational, retrospective, cohort study to assess the safety of *Refortrix* (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.

Study: 203153 (EPI-PERTUSSIS-037 VS BR) Development Phase: IV

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory:	Narcisa Mesaros
Title of Sponsor Signatory:	Clinical and Epidemiology R&D Project Lead, DTP, Polio and Hib containing vaccines - R&D Centre Belgium, GlaxoSmithKline Biologicals, SA
Signature:	_____
Date:	_____

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PASS INFORMATION

Title:	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Protocol version identifier:	203153 (EPI-PERTUSSIS-037 VS BR)
Date of last version of the protocol:	Final Version 1: 11 September 2015
EU PAS Register No:	To be determined.
Active substance:	Diphtheria toxoid, Tetanus toxoid, *Bordetella pertussis* antigens (Pertussis toxoid, Filamentous Haemagglutinin and Pertactin)
Medicinal product:	GlaxoSmithKline (GSK) Biologicals' combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine (Refortrix™) (263855)
Product reference:	DE/H/0210/001-002
Procedure number:	To be allocated.
Marketing Authorisation Holder (MAH):	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Joint PASS:	No
Research question and objectives:	To assess the risk of a series of pre-defined safety outcomes following routine vaccination with *Refortrix* in a cohort of pregnant women compared to a historical cohort of unvaccinated pregnant women in Brazil
Country of study:	Brazil
Authors:	**Contributing authors:** • PPD, Director, Epidemiology • PPD, Director, Epidemiology • PPD, Epidemiologist • PPD, Epidemiology Scientist • PPD, Epidemiology Analyst • PPD, Regional Epidemiology Director, LATAM • PPD, Senior Epidemiologist, LATAM • PPD Project Statistician, Ningyang Group Co., for GSK Biologicals • PPD, Lead Statistician • PPD, Study Delivery Lead • PPD, Local Delivery Lead, Quintiles, for GSK Biologicals • PPD, Clinical Safety

	Representative • PPD, Safety Scientist • PPD, Study Data Manager, Tata Consultancy Services, for GSK Biologicals • PPD, Global Patent representative • PPD, Manager, Global Regulatory Affairs **Coordinating author:** • PPD, Scientific Writer

MARKETING AUTHORISATION HOLDER

MAH:	GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
MAH contact person:	PPD, Director, Epidemiology, GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium

GSK Biologicals' protocol for post-authorisation safety studies INS-BIO-PASS-1000 v14.1.1

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2. LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
ATP Cohort	According-To-Protocol Cohort
CARS	Computer Aided Regulatory Submission
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CONEP	Comissão Nacional de Ética em Pesquisa
D-Rh	Rhesus factor
eCRF	electronic Case Report Form
EMA	European Medicines Agency
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GVP	Good Pharmacovigilance Practices
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing Authorisation Holder
MoH	Ministry of Health
OR	Odds Ratio
PAHO	Pan American Health Organization
PASS	Post-Authorisation Safety Study
PII	Personally Identifiable Information

PNI	National Immunization Program (Brazil)
QC	Quality Control
SAE	Serious Adverse Event
SDD	Statistical Analysis System Drug Development
TC	Total Cohort
Tdap	Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine
TSS	Targeted Safety Study
UK	United Kingdom
USA	United States of America
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

3. RESPONSIBLE PARTIES

GSK Biologicals has the overall responsibility for the conduct of the study.

PPD (Director, Epidemiology) is the GSK Biologicals designated contact person for this study.

Refer to Annex 4 for the list of principal and coordinating investigators.

4. ABSTRACT

Title	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Version and date of the protocol	Final Version 1: 11 September 2015
Main author	PPD, GlaxoSmithKline Biologicals
Rationale and background	Pertussis can cause serious and sometimes life-threatening complications in infants, especially within the first 6 months of life when it is too early to receive and complete their primary vaccination schedule against pertussis. In Brazil, between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age and the majority of cases occurred in infants. The increased fatality rate in this group led the country to introduce the acellular pertussis vaccination program in pregnant women. By the end of 2014, the National Immunization Program in Brazil (PNI) started implementation of the maternal immunization program, administering one dose of combined reduced antigen content diphtheria-tetanus-acellular pertussis (Tdap) vaccine (*Refortrix*) during the last trimester of pregnancy (27 to 36 completed weeks of pregnancy or until 20 days before the delivery due date). The effects of *Refortrix* vaccination in pregnant women were not evaluated in pre-licensure studies and most of the safety evaluations have been conducted using spontaneous reporting systems which have their own limitations like under/over reporting, reporting bias and quality issues. Therefore, studies using appropriate designs that focus on regions where the maternal immunization program is starting can provide valuable information.
Research question and objectives	The aim of this retrospective study is to investigate the association between routine *Refortrix* vaccination during pregnancy and specific pregnancy-related adverse events (AEs) and AEs in neonates following the routine maternal *Refortrix* vaccination during pregnancy. The AEs identified for this study are those considered important in the context of maternal immunization [Zheteyeva, 2012; Kharbanda, 2014] and for which it would be feasible to obtain the required data (refer to section 10.1.2). The diagnosis of pregnancy-related AEs will follow the international case definitions (refer to Annex 7) and will be

obtained directly from the medical records. Since the vaccine is routinely administered in the third trimester of pregnancy, the events that are more commonly reported during this period have been chosen as primary endpoints.

Co-primary objectives:

- To compare the risk of gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum) in a cohort of women following vaccination with *Refortrix* 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).
- To compare 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.

Secondary objectives:

- To describe the risk of pregnancy-related AEs/neonate-related events of interest (premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth and neonatal hypoxic ischaemic encephalopathy) in the Exposed and Unexposed cohorts.
- To describe the risk of congenital anomalies in neonates in the Exposed and Unexposed cohorts.
- To describe the risk of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

Study design

- Type of design: An observational, retrospective, cohort, single-centre study.
- This is a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).
- Study population: The study population will consist of two cohorts:
  - Exposed Cohort (cohort of pregnant women who received *Refortrix* as part of the maternal immunization program in Brazil)
  - Unexposed Cohort (historical cohort of unvaccinated pregnant women before the implementation of the immunization program)
- Data collection: electronic Case Report Form (eCRF) based on medical chart data.
- Period of data collection: The minimum period of the data collection is expected to be 6 months assuming the availability of the subject medical files adequate to attain the sample size required for the analysis. The data of Unexposed subjects who delivered during the period from September 2012 to August 2014 will be included. The maternal immunization program in Brazil was scheduled to start in September 2014. Therefore, the data of Exposed subjects will be collected once the maternal immunization program is well implemented in Brazil and the inclusion of data will start from May 2015 till the Exposed cohort is enrolled completely.
  - Epoch 001: Retrospective data collection.

Population

The study population will consist of pregnant women aged between 18 and 45 years, who are residing in the study area (city of São Bernardo do Campo) and delivered in the 2 years before or during the period following the implementation of the PNI. The subjects who delivered in the study centre from May 2015 will be considered as potentially exposed subjects who had opportunity to receive vaccine and those who delivered before implementation of the PNI (September 2014) will be considered as potentially unexposed subjects. Subjects meeting all the inclusion/exclusion criteria will be eligible for enrolment in the study.

Variables

Co-primary endpoints:

- Occurrence of any of the following pregnancy-related AEs in Exposed and Unexposed subjects.
  - Gestational diabetes.

  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome).
  - Pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum).

- Occurrence of any of the following outcomes in neonates from Exposed and Unexposed subjects.
  - Preterm birth
  - Small for gestational age

Secondary endpoints:

- Occurrence of pregnancy-related AEs of interest/ neonate-related events up to delivery in Exposed and Unexposed subjects.
  - Premature rupture of membranes.
  - Preterm premature rupture of membranes.
  - Premature uterine contraction.
  - Neonatal death.
  - Maternal death.
  - Still birth.
  - Neonatal hypoxic ischaemic encephalopathy.
- Occurrence of congenital anomalies in the neonates of Exposed and Unexposed subjects.
- Occurrence of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

Data sources

This retrospective study will use the medical files and other hospital documents (admission list, images and other test results, etc.) for collecting demographic data, medical/gynaecological history, pregnancy-related AEs of interest and AEs in neonates. No intervention or additional evaluation will be done on the diagnosis or evaluation of these events and only the final diagnosis as described in the source document will be included in the study.

To evaluate the vaccination exposure, the information in the anamnesis and pregnancy card archived in the medical files will be used as the only source.

Study size

The planned sample size of this study is 2400 subjects. Using a two-sided (alpha = 0.01) test assuming the ratio of subjects in the Exposed cohort to the Unexposed cohort is 1:1 and assuming a background proportion of events in the Unexposed cohort to be 3%, a total of 2400 subjects [1200 subjects in each cohort], will be needed to have more than 80% power to

detect a relative risk of 2 or higher.

Data analysis

The main analysis for co-primary objectives will contain only the subjects with vaccination date in the Exposed cohort and subjects from the Unexposed cohort. If more than 10% of subjects have missing vaccination date in the Exposed cohort, a sensitivity analysis will be performed with the imputed vaccination date to 27 completed weeks of gestational age.

The risk for each primary endpoint (gestational diabetes, pregnancy-related hypertension, pregnancy haemorrhage, preterm birth and small for gestational age) will be calculated. For each specific endpoint, the number of subjects where the event occurred (between the index date and the date of the delivery) will be divided by the total number of subjects at risk for both the Exposed and Unexposed cohorts respectively, together with its exact 95% confidence interval (CI).

The co-primary endpoints of pregnancy (gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage) will be pooled together as well as the birth outcomes (preterm birth and small for gestational age). The analysis of the risk for the pooled endpoints will be performed using the same method as for the separate co-primary endpoints.

The comparison of the risk with its two sided 95% CI of each primary endpoint between the Exposed cohort and the Unexposed cohort will be obtained by means of logistic regression. Univariate analysis will describe the association between Tdap vaccination status, maternal age, parity and gestational age.

A multiple logistic regression model will be fitted with a backward selection to identify the possible confounding factors for each of the primary outcomes using an alpha level of 0.1. Potential confounders will be parity, age of the mother at the start of the pregnancy and congenital anomalies (in parents or first degree relatives). Adjusted odds ratio (OR) and its 95% CI will be derived from the final model.

Milestones

Data collection is planned to start in Quarter 2-2016 and end in Quarter 4-2016. The final report of study results is planned in Quarter 2-2017.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	Quarter 2 2016
End of data collection	Quarter 4 2016
Final report of study results	Quarter 2 2017

7. RATIONALE AND BACKGROUND

7.1. Background

Pertussis can cause serious and sometimes life-threatening complications in infants, especially within the first 6 months of life when it is too early to receive and complete their primary vaccination schedule against pertussis. In Brazil, between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age and the majority of cases occurred in infants [WHO, 2014]. The increased fatality rate in this group led the country to introduce the acellular pertussis vaccination program in pregnant women. By the end of 2014, the National Immunization Program in Brazil (PNI) started implementation of the maternal immunization program [MoH, 2014], administering one dose of combined reduced antigen content diphtheria-tetanus-acellular pertussis (Tdap) vaccine (*Refortrix*) during the last trimester of pregnancy (27 to 36 completed weeks of pregnancy or until 20 days before the delivery due date).

Although the Tdap maternal immunization strategy has been implemented in the United Kingdom (UK), the United States of America (USA) and other countries, only limited data on the safety of *Refortrix* in pregnant women is available. The data from the Vaccine Adverse Event Reporting System (VAERS), pregnancy registries and case series have concluded that there is no indication of any safety concern about maternal, foetal and infant outcomes following vaccination during pregnancy with Tdap [Healy, 2006; Murphy, 2008; Gall, 2011; Zheteyeva, 2012; ACIP, 2013; CDC, 2015].

Immunization with inactivated vaccines during the last trimester of pregnancy can be beneficial because maternal antibodies can be transferred efficiently to the foetus across placenta, thus providing indirect protection to infants for the first months of life [Keller-Stanislawski, 2014]. Additionally, the risk of abnormal organogenesis is minimal at that gestational age.

7.2. Rationale

The effects of *Refortrix* vaccination in pregnant women were not evaluated in pre-licensure studies and most of the safety evaluations have been conducted using spontaneous reporting systems which have their own limitations like under/over reporting, reporting bias and quality issues. Therefore, observational studies using appropriate designs that focus on regions where the maternal immunization program is starting can provide valuable information.

A retrospective cohort study in this country will present a unique opportunity to continue monitoring the safety of this vaccine in a large population of vaccinated pregnant women, especially in the immediate period after introduction at the end of 2014 of this maternal immunization program. This study will generate safety data that could be used to complement other data generated by the Ministry of Health (MoH) in Brazil. Together, these should provide a comprehensive evaluation of routine maternal Tdap vaccination in Brazilian women.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this retrospective study is to investigate the association between routine *Refortrix* vaccination during pregnancy and specific pregnancy-related adverse events (AEs) and AEs in neonates. The AEs identified for this study are those considered important in the context of maternal immunization [Zheteyeva, 2012; Kharbanda, 2014] and for which it would be feasible to obtain the required data (refer to section 9.1.2).

The diagnosis of pregnancy-related AEs will follow the international case definitions (refer to Annex 7) and will be obtained directly from the medical records. The list of outcomes as potential pregnancy-related AEs of interest is derived from literature. Since the vaccine is routinely administered in the third trimester of pregnancy, the events that are more commonly reported during this period have been chosen as primary endpoints. Refer to Annex 2 for the definition of each of these events.

8.1. Co-primary objectives

- To compare the risk of gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum) in a cohort of women following vaccination with *Refortrix* 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).
- To compare 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.

8.2. Secondary objectives

- To describe the risk of pregnancy-related AEs/neonate-related events of interest (premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth and neonatal hypoxic ischaemic encephalopathy) in the Exposed and Unexposed cohorts.

- To describe the risk of congenital anomalies in neonates in the Exposed and Unexposed cohorts.

- To describe the risk of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

9. RESEARCH METHODS

9.1. Study design

- Type of design: An observational, retrospective, cohort, single-centre study.
- This is a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).
- Study population: The study population will consist of two cohorts:
  - Exposed Cohort (cohort of pregnant women who received *Refortrix* as part of the maternal immunization program in Brazil)
  - Unexposed Cohort historical cohort of unvaccinated pregnant women before the implementation of the immunization program)

  Refer to Section 9.3.1 for definition of the study cohorts.
- Data collection: electronic Case Report Form (eCRF) based on medical chart review.
- Period of data collection: The minimum period of data collection is expected to be 6 months assuming the availability of the subject medical files adequate to attain the sample size required for the analysis. The data of Unexposed subjects who delivered during the period from September 2012 to August 2014 will be included. The maternal immunization program in Brazil was scheduled to start in September 2014. Therefore, the data of Exposed subjects will be collected once the maternal immunization program is well implemented in Brazil and the inclusion of data will start from May 2015 till the Exposed cohort is enrolled completely.
  - Epoch 001: Retrospective data collection.

The study cohorts and epoch foreseen in the study are presented in Table 1.

Table 1 Study cohorts and epoch foreseen in the study

Study Cohorts	Approximate number of subjects	Age (Min/Max)	Epochs
			Epoch 001
Exposed cohort	1200	18 years-45 years	x
Unexposed cohort	1200	18 years-45 years	x

Refer to Section 9.3.2 for definition of the endpoints.

9.1.1. Discussion of study design

Considering that *Refortrix* is now routinely recommended for all pregnant women in Brazil through the maternal immunization program, randomised controlled trials are not considered ethical. Therefore, an observational cohort study provides the opportunity to evaluate the safety of this routinely used vaccine.

The feasibility assessment (refer to section 9.1.2 for details) indicated that adequate and appropriate data exist and are available to allow a retrospective cohort design to be used, with the further advantage of being time efficient.

As maternal immunization with *Refortrix* is recommended by the Ministry of Health (MoH) and vaccine uptake is expected to be high with limited possibility to recruit contemporary unvaccinated pregnant women, the comparative cohort (Unexposed) will comprise a historical cohort of pregnant women who delivered in the same hospital (study centre) in the two years before implementation of the maternal immunization program with *Refortrix* (started in end of 2014) in Brazil.

Considering that more than 20% of the pregnant population in this area in Brazil are classified as high risk pregnancies (refer to Annex 6), excluding this group from the study would represent an important selection bias and it would decrease the representativeness of the study population. In addition, high risk pregnancy is not an exclusion criterion to receive the Tdap vaccination according to the maternal immunization guidelines in Brazil [ESC, 2014]. Therefore the study will include both low and high risk pregnancy women as determined and defined by local guidelines [MoH, 2010; MoH, 2012].

9.1.2. Feasibility assessment

A feasibility assessment was conducted in seven potential study centres from south-east Brazil during September 2014-November 2014.The objective was to assess the research capabilities and availability of data for the collection of pregnancy-related AEs and vaccination data, as well as to identify the most adequate study design for this setting. These sites were pre-selected based on their capacity to perform clinical research and with an available population of pregnant women that could be enrolled in the study. The results of this exercise demonstrated that at least three out of the seven centres evaluated have the potential to perform the study and have appropriate data available. The final decision to opt for a single centre was due to its recruitment capacity, completeness of records of the pregnancy-related AEs/birth outcomes and transcript information from antenatal care visits on vaccination exposure for the Exposed cohort. Refer to Annex 6 for details on the feasibility assessment.

9.2. Setting

9.2.1. Number of subjects/centres

The study will be conducted in a single centre in south-east Brazil. The subjects who delivered in the study centre from May 2015 will be considered as potentially exposed and those who delivered before September 2014 will be considered as potentially unexposed (the data of Unexposed subjects will be included for the period of September 2012 – August 2014). The estimated number of subjects to be included in each cohort (Exposed and Unexposed) is 1200 (total 2400 subjects). Refer to Section 9.5 for a detailed description of the criteria used in the estimation of sample size.

The study centre was selected based on the accuracy and completeness observed in the medical records. The selected study centre receives approximately 300 pregnant women per month for delivery. Refer to Section 9.2.5.1 for details on screening of the subjects.

9.2.2. Inclusion criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study or regulatory acceptability. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects between 18 and 45 years of age at the time of pregnancy under consideration for the study, who deliver in the study centre.

  Note: Only the latest pregnancy in the specified period will be included (to avoid multiple pregnancies from the same mother).

- Residents of the study area (city of São Bernardo do Campo).
- Subjects who were compliant with the routine antenatal care [Gestacao de Alto Risco, 2010; Cadernos de Attencao Basica, 2012], including at least one ultrasound assessment report early in the pregnancy.
- Subjects with the complete and relevant medical records available.

Inclusion criteria for the Exposed cohort:

- Subjects who received one dose of *Refortrix* vaccine in the recommended time period between 27 and 36 completed weeks of pregnancy (or as late as 20 days before delivery due date) as part of the maternal immunization program in Brazil, and according to the program recommendations from May 2015 onwards.
- Subjects with appropriate vaccination records.

Inclusion criteria for the Unexposed cohort:

- Subjects who had delivered in the same hospital (study centre) before 01 September 2014 (September 2012-August 2014) and who did not receive Tdap vaccination during pregnancy to the best knowledge of the investigator.

9.2.3. Exclusion criteria

The following criterion should be checked at the time of study entry. If the exclusion criterion applies, the subject must not be included in the study:

- Subjects who have been transferred to other specialised centres, where their medical records would be inaccessible for the study (private clinics, psychiatric or prison hospitals, other state hospitals, etc).

9.2.4. Outline of the study procedures

The study procedures consist only of the collection of retrospective data from the source documents (refer to section 9.4 for data sources) available at the study centre.

Table 2 represents the list of procedures in the study.

Table 2 List of study procedures

Epoch 001: Retrospective data collection from medical files	
Screening	○
Check inclusion/exclusion criteria	●
Allocate subject number	●
Obtain demographic data	●
Obtain medical history and gynaecological history	●
Obtain data on vaccination during the pregnancy (Exposed cohort)	●
Record any risk factor of interest *	●
Record clinical data on pregnancy relevant to the specified study period**	●
Record data from physical examination of the neonate	●
Record adverse pregnancy outcome and follow-up	●
Record intercurrent medical conditions and/or medications***	●
Study conclusion	●

● is used to indicate a study procedure that requires documentation in the individual eCRF. Details of the data to be collected in eCRF are presented in Annex 8.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.
*Risk factors of interest: Refer to Section 9.3.3 for details.
**In case of multiple pregnancies, details of the latest pregnancy in the specified period will be included.
***The intercurrent medical conditions and/or medications reported at the time of delivery will be recorded.

The events of interest to be collected from the medical files are presented in Table 3.

Table 3 Events of interest to be collected from the medical files

Events*	Time point
Gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum)	After week 27
Preterm birth	After week 27 up to week 37
Small for gestational age	After week 27
Premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth, neonatal hypoxic ischaemic encephalopathy	After week 27
Congenital anomalies	After week 27 up to birth.

*For definitions, refer to Annex 2.

9.2.5. Detailed description of study procedures

9.2.5.1. Screening

Potential subjects in the age range for the study will be identified using the electronic admission listings at the centre. This will provide a list of total candidate subjects eligible for the study. For the Unexposed cohort, to reach an equal number of subjects who delivered in each of the two years, a random sample of subjects will be selected each month (using Microsoft Excel or equivalent application). This will enable identification of 50 eligible subjects per month to reach the required number of 600 subjects per year. In contrast, for the Exposed cohort, all subjects who delivered from May 2015 onwards will be considered sequentially for enrolment until the total number of 1200 is reached. This will facilitate investigating any trends over time in AE reporting.

Only the medical files from those candidate subjects will be evaluated to determine if they qualify for the study.

9.2.5.2. Check inclusion and exclusion criteria

Check all applicable inclusion and exclusion criteria as described in Sections 9.2.2 and 9.2.3 before enrolment.

9.2.5.3. Allocate subject number

Subject numbers will be allocated sequentially to the medical file of each subject who has been included in the study.

9.2.5.4. Obtain demographic data, medical and gynaecological antecedents

Age of the subject in years and area of residence will be obtained from the medical file. Medical history including diabetes, hypertension and haemorrhage in previous pregnancies will be obtained. The gynaecological history including parity, type of

delivery, pre-vaccination ultrasound report and delivery month/year will be obtained if applicable.

9.2.5.5. Obtain concomitant vaccination history (Exposed cohort)

The information on *Refortrix* vaccination during pregnancy including gestational age when the vaccination was administered and date of administration will be obtained from the vaccination section in the medical file. Also, the information on any concomitant vaccination administered during the pregnancy will be obtained.

9.2.5.6. Record risk factors

All the available data on risk factors will be obtained from medical file (refer to Annex 8).

9.2.5.7. Record clinical data of pregnancy

All the events of interest (refer to Table 3) diagnosed and recorded in the medical file in the period after 27 completed weeks of the pregnancy will be included. Other pregnancy events will not be evaluated.

9.2.5.8. Record data from physical examination of neonate

Height, weight, head circumference, Apgar scores and birth complications will be obtained from medical file of the mother.

9.2.5.9. Record adverse pregnancy outcome

Adverse pregnancy outcomes and pregnancy-related or neonate-related events of interest will be recorded.

9.2.5.10. Record intercurrent medical conditions/medications

Intercurrent medical conditions and medications reported at the time of delivery, if any, will be recorded.

9.2.5.11. Study conclusion

The investigator will:

- review all the data collected to ensure accuracy and completeness
- complete the Study Conclusion screen in the eCRF.

The information on pregnancy-related AEs/outcomes and birth outcomes will be obtained from medical file according to the details on final visit available in the medical file.

9.3. Variables

9.3.1. Study cohort definitions

- Exposed cohort: Women, 18-45 years of age at the time of pregnancy, who delivered in the hospital (study centre) from May 2015 and who received one dose of *Refortrix* during 27 to 36 weeks of pregnancy (or as late as 20 days before delivery due date) as part of the maternal immunization program in Brazil. The index date will be considered as the date of *Refortrix* administration or where not specified, as 27 completed weeks of gestation.
- Unexposed cohort: Women, 18-45 years of age at the time of pregnancy, who delivered in the hospital (study centre) before implementation of the maternal immunization program in Brazil in September 2014 and who did not receive Tdap vaccination during pregnancy as per information of the investigator. The Unexposed cohort will include those subjects who had delivered in the period during September 2012-August 2014. This period was chosen because Tdap vaccine was not administered to pregnant women before the maternal immunization program was implemented in the country.

9.3.2. Endpoints

9.3.2.1. Co-primary endpoints

- Occurrence of any of the following pregnancy-related AEs in Exposed and Unexposed subjects.
  - Gestational diabetes.
  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome).
  - Pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum).
- Occurrence of any of the following outcomes in neonates from Exposed and Unexposed subjects.
  - Preterm birth.
  - Small for gestational age.

9.3.2.2. Secondary endpoints

- Occurrence of pregnancy-related AEs of interest/neonate-related events up to delivery in Exposed and Unexposed subjects.
  - Premature rupture of membranes.
  - Preterm premature rupture of membranes.
  - Premature uterine contraction.

  - Neonatal death.
  - Maternal death.
  - Still birth.
  - Neonatal hypoxic ischaemic encephalopathy.

- Occurrence of congenital anomalies in the neonates of Exposed and Unexposed subjects.
- Occurrence of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

9.3.3. Potential confounding factors

Age of the mother and high risk pregnancy are considered as important confounding factors for the occurrence of pregnancy-related AEs of interest, so they will be controlled in the analysis.

Other potential important confounding factors associated with onset of the outcomes of interest will also be collected: smoking, multiparity, multiple births, assisted fertilisation, congenital anomalies (in parents or first degree relatives), alcohol consumption and recreational drug use. Antecedents of previous pregnancies would be predictive factors for the development of a pregnancy-related AE and where available, they will be described. These are: history of spontaneous abortion/ miscarriage, preterm delivery, preterm premature rupture of membranes (P-PROM), red blood cell isoimmunisation [e.g., D-Rh (Rhesus factor) sensitised], pre-eclampsia, eclampsia and major congenital anomalies during previous pregnancies. Other conditions of interest to record are hypertension, diabetes and anaemia.

Further, confounders may include multi-foetal gestation, diagnosis of a foetus with aneuploidy or a major congenital anomaly, cervical insufficiency or incompetent cervix, premature contractions, bleeding throughout the gestation, gestational hypertension, maternal immunization with diphtheria, hepatitis B or other vaccines [Exposed cohort (refer to section 9.2.5.5)] and an active infection (treated or untreated).

The study will start monitoring for pregnancy outcomes on the day of vaccine administration for the Exposed cohort and at 27 completed weeks of gestation for the Unexposed cohort, and end at the date of delivery. Only the outcomes of interest diagnosed and described in the medical files during the risk period will be included in the study. For details, refer to Table 3. The study outcomes would be accounted in the same risk period for both the Exposed and Unexposed cohorts.

9.4. Data sources

This retrospective study will use the medical files and other hospital documents (admission list, images and other test results, etc.) for collecting demographic data, medical/gynaecological history, pregnancy-related AEs of interest and AEs in neonates. No intervention or additional evaluation will be done on the diagnosis or evaluation of

these events and only the final diagnosis as described in the source document will be included in the study.

To evaluate the vaccination, the information in the anamnesis and pregnancy card archived in the medical files will be used as the only source.

9.5. Study size

The background proportions of different safety outcomes from publications [Munoz, 2005; Zheteyeva, 2012; Goldfarb, 2014; Passini, 2014] and as reported in the feasibility assessment from Brazil are summarised in Table 4 below.

Table 4 Background proportions of different safety outcomes

Safety Outcome	MUNOZ 2005 (Influenza Vaccination) - Proportion		GOLDFARB 2014*-Proportion		Feasibility assessment-Proportion (Brazil local data)
Exposure	VAC	UNVAC	VAC	UNVAC	UNVAC
Co-Primary endpoints					
Gestational Diabetes	2.2%	1.7%			2.95% (2.53-3.64)
Pre-eclampsia	4.8%	3.9%			1.6%
Vaginal or Intrauterine haemorrhage					16.4%
Preterm Delivery			7.8%	21.2%	Around 10%
Secondary endpoints					
Congenital Anomalies					0.79%
Transient Hypertension	6.7%	2.9%			14.3%
Eclampsia					1.6%
Premature Rupture of Membranes	2.6%	2.4%			3.53%
Still Birth					0.31%

VAC: Vaccinated group
UNVAC: Unvaccinated group
* Tdap vaccine coverage of 81.6%

Sample size:

The background proportions from the feasibility reports and literature for some of the co-primary endpoints ranged from 1.6% - 16.4%, from 0.79% - 10% for some of the secondary endpoints and unknown for the rest of the endpoints (refer to Table 4), besides the power estimation for each endpoint were assessed in Table 5**.** Therefore, a conservative proportion of 3% was chosen for the sample size calculation.

Using a two-sided (alpha = 0.01) test, assuming the ratio of subjects in the Exposed cohort to the Unexposed cohort is 1:1 and assuming a background proportion of events in the Unexposed cohort to be 3%, a total of 2400 subjects [(1200 subjects in each cohort] will be needed to have more than 80% power to detect a relative risk of 2 or higher.

The power estimation of each safety outcome with background proportions is presented in Table 5.

Table 5 Power estimation of each safety outcome with background proportions from the feasibility assessment without multiple adjustment and sample size of 1200 subjects in each cohort

Safety outcome	Assumed background proportion	Alpha level Two-sided	Ratio between vaccinated and control	Power for RR=2(%)*
Co-primary endpoints				
Gestational Diabetes	0.0295	0.05	1:1	94.0
Pre-eclampsia	0.016	0.05	1:1	72.6
Vaginal or intrauterine haemorrhage	0.164	0.05	1:1	>99.9
Preterm Delivery	0.1	0.05	1:1	>99.9
Secondary endpoints				
Congenital anomalies	0.0079	0.05	1:1	43.2
Transient Hypertension	0.143	0.05	1:1	>99.9
Premature Rupture of Membranes	0.0353	0.05	1:1	>99.9
Still birth	0.0031	0.05	1:1	20.0

Two independent proportions were used for the sample size calculation in PASS.
*RR: Relative risk

The sample size and power estimation is presented in Table 6.

Table 6 Sample size and power estimation without and with multiple adjustment for background proportions of 3% and 5% and relative risk of 2

Assumed background proportion	Multiple comparisons	Alpha level Two-sided	Number of vaccinated subjects	Ratio between vaccinated and control	Total Number of subjects needed	Power (%)
0.03	1	0.05	749	1:1	1498	80
0.05	1	0.05	435	1:1	870	80
0.03	5	0.01	1114	1:1	2228	80
0.05	5	0.01	647	1:1	1294	80

Two independent proportions were used for the sample size calculation in PASS.
Bonferroni adjustment was used for adjustment of alpha level.

9.6. Data management

A validated GSK defined electronic data collection tool will be used as the method for data collection.

In all cases, Personally Identifiable Information (PII) will not be collected nor transmitted to GSK (refer to Annex 2 for definition). Subject data necessary for analysis and reporting will be entered into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate

clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data. Refer to Annex 8 for details.

Once the database is archived and the study report is complete and approved by all parties, the participating investigator will be provided with a CD-ROM of the final version of the data generated from the investigational site.

9.7. Data analysis

All the statistical calculations will be done in SAS 9.2 or higher.

In case of multiple pregnancies, only the latest pregnancy in the specified period will be included in the study to avoid correlation of the safety endpoints from different pregnancies for one subject. The latest pregnancy will be considered in the study and the analysis.

9.7.1. Cohorts for analyses

9.7.1.1. Total Cohort (TC)

The TC will include all subjects enrolled in the study. All the information for these subjects will be entered in the eCRF.

9.7.1.2. According-To-Protocol (ATP) Cohort

The ATP cohort will include all the evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol).

9.7.2. Analysis of demographics and baseline characteristics

The baseline and demographic characteristics of the Exposed and Unexposed cohorts will be tabulated in a summary of statistics (mean, median, standard deviation and range) including age and gestational age.

9.7.3. Analysis of co-primary endpoints

The main analysis for co-primary objectives will contain only the subjects with vaccination date in the Exposed cohort and subjects from the Unexposed cohort. If more than 10% of subjects have missing vaccination date in the Exposed cohort, a sensitivity analysis will be performed using the imputed vaccination date to 27 completed weeks of gestational age to evaluate if this has any potential impact on the results.

The risk for each primary endpoint (gestational diabetes, pregnancy-related hypertension, pregnancy haemorrhage, preterm birth and small for gestational age) will be calculated. For each specific endpoint, the number of subjects where the event occurred [between the index date (refer to Annex 2 for definition of index date) and the date of the delivery] will be divided by the total number of subjects at risk for both the Exposed and Unexposed

cohorts respectively, together with its exact 95% confidence interval (CI).The co-primary endpoints of pregnancy (gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage) will be pooled together and of birth outcome (preterm birth and small for gestational age) will be pooled together in addition. The analysis of the risk for the pooled endpoints will be performed using the same method as for the separate co-primary endpoints.

The comparison of the risk with its two sided 95% CI of each primary endpoint between the Exposed cohort and the Unexposed cohort will be obtained by means of logistic regression model, using the exposure status as a binary independent variable in the model. Absence of increased risk will be concluded if this CI contains 1.

Univariate analysis will describe the association between Tdap vaccination status, maternal age, parity and gestational age.

A multiple logistic regression model will be fitted with a backward selection to identify the possible confounding factors for each of the primary safety event using an alpha level of 0.1. Potential confounders will be parity, age of the mother at the start of the pregnancy and congenital anomalies (in parents or first degree relatives). Adjusted odds ratio (OR) and its 95% CI will be derived from the final model.

9.7.4. Analysis of secondary endpoints

The risk for each secondary endpoint (pregnancy-related AEs and birth outcomes) will be calculated by the number of subjects with at least one of the each event occurring between the index date (refer to Annex 2 for definition of index date) and the date of the delivery, corresponding to that endpoint divided by the total number of subjects at risk for both the Exposed and Unexposed cohort, together with its exact 95% CI. If more than 10% of subjects have missing vaccination date in the exposed cohort, a sensitivity analysis will be performed as for the co-primary endpoints.

In addition, the risk of all the co-primary and secondary endpoints will be calculated by calendar year as well to evaluate the comparability among the Exposed and Unexposed cohorts.

9.7.5. Handling of missing data

Missing or non-evaluable primary and secondary outcome measurements will not be replaced. Therefore, the main analysis will exclude subjects with missing or non-evaluable data.

A sensitivity analysis will also be performed if more than 10% of the measurements are missing for each endpoint. In the first instance, missing outcomes will be imputed with a value of ‘0’. In the second instance, all missing outcomes will be imputed with a value of ‘1’. The risk for each endpoint will then be analysed using similar methods as mentioned in sections 9.7.3 and 9.7.4 for all the co-primary and secondary endpoints.

For subjects in the Exposed cohort whose date of the vaccination is not available, it will be imputed to the completed 27th gestational week as the recommended start time for the vaccination for the sensitivity analysis.

9.7.6. Conduct of analysis

9.7.6.1. Sequence of analyses

The statistical analyses will be performed when all data are available. All analyses will be performed on final and clean data.

9.7.6.2. Statistical considerations for interim analyses

No interim analyses are planned for this study.

9.8. Quality control

GSK will monitor the study to verify that the data are authentic, accurate, and complete. Direct access to all study-site related and indirect access to source data is mandatory for the purpose of monitoring review.

While completed eCRFs are reviewed by a GSK Biologicals' Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

To ensure compliance with Good Clinical Practice (GCP) and all applicable 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. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The final study dataset will be archived and stored on a secured, access limited, computer platform SAS Drug Development (SDD) according to GSK Biological Standard Procedures. Specific statistical programs will be written in SAS 9.2 (or higher) and validated according to the GSK standard procedures. The validation of the quality control (QC) of the statistical analysis will be documented. All statistical programs, output files and QC documentation will be saved as read-only files on SDD.

The final study protocol and possible amendments, the final statistical report and the QC document, and the final study report(s) will be archived on a Document management system based on the Documentum platform: Computer Aided Regulatory Submission (CARS).

9.9. Limitations of the research methods

There is a possibility that timing of events with respect to the exposure may not always be captured with appropriate accuracy, particularly with retrospective studies which make use of the existing data (which may be limited). However, considering that the antenatal

care visits at regular intervals are standard of care in Brazil [MoH, 2010; MoH, 2012], the e appropriate documentation of vaccination and pregnancy events for the Exposed cohort, and pregnancy events for the Unexposed cohort is expected. This will allow the determination of the timing of the events as compared to the moment of the exposure. The availability of these data was checked during the feasibility assessment (refer to Annex 6).

Incomplete and imprecise medical records could lead to bias and misclassification of the events. To minimise this, the feasibility assessment was performed in the study centre selected to determine the quality and completeness of the medical records for both vaccination exposure and pregnancy outcomes. The pregnancy outcomes diagnosed at the study centre during the pregnancy are recorded. However, for some of the outcomes this may be the earliest date of diagnosis at the site rather than the actual date of onset. Therefore, date of diagnosis will be used based on the assumption that it is the date of onset, although this may not be the case in some instances and is recognised as being a limitation of the study.

The information on concomitant vaccinations administered during pregnancy will not be available for the Unexposed cohort, but this information can be retrieved for the Exposed cohort. This will prevent formal quantitative comparison with the Unexposed cohort and is a limitation of the study. However, the availability of information on other vaccines given to pregnant women who received Tdap will enable some insight and comment on whether any increased safety signal observed may be solely attributed to *Refortrix*.

Congenital anomalies diagnosed at birth will be used as there will be no post-delivery follow-up visit. Therefore, anomalies which may manifest at a later stage will not be captured.

For vaccinated subjects, whilst the date of *Refortrix* vaccination is being systematically collected, there is a possibility that it may not always be available with the appropriate level of accuracy needed. For example, index date (refer to Annex 2 for definition) may not always be available from the medical files with no feasible means of subsequently obtaining this information. The potential lack of the date of *Refortrix* vaccination for every subject in the Exposed cohort is therefore considered as a study limitation. Since the subjects will not be contacted during the study, the assumption will therefore be made that the index date is 27 completed weeks of gestation, which is the earliest time point to receive the vaccination from the maternal immunization program in Brazil. The number of women without the date of *Refortrix* administration will therefore be assessed following the data collection, if more than 10% of them are without the date of *Refortrix* administration, a sensitivity analysis will be performed on top of the primary analysis (refer to section 9.7.3 for details) (as this could create a potential selection bias in the Exposed cohort compared to the Unexposed cohort).

Another potential limitation is the possibility that the maternal Tdap vaccination program itself may have influenced the attitude of pregnant women towards attending antenatal care or medical consultation. This could potentially lead to an increased frequency of reporting of pregnancy-related AEs. However, the evaluation done during the feasibility assessment that was confirmed by other studies performed at the study centre indicated a high acceptance of vaccination in the study population with no changes in the reporting or ascertainment of the expected pregnancy-related AEs. Therefore, the Exposed and Unexposed cohorts are assumed to be comparable.

When using a historical cohort as the unexposed comparison group, caution is required due to potential bias from changes over time and confounding factors including differences in standard of care and pregnancy management practices (from the perspective of both the pregnant woman and the health care professional). Using a comparative cohort collected over two calendar years will provide some capacity to identify any such potential differences in relation to the Exposed cohort.

9.10. Other aspects

Not Applicable.

10. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), applicable local guidelines in Brazil, all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

GSK will obtain favourable opinion/approval to conduct the study prior to a site initiating the study in that country or will document that neither a favourable opinion nor an approval to conduct the study is needed.

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

- Independent Ethics Committee (IEC)/ Comissão Nacional de Ética em Pesquisa (CONEP) review and favourable opinion/approval of study protocol and any subsequent amendments.

As this study will be based on a retrospective analysis from medical records, informed consent will not be requested from the subjects in this study [PAHO, 2005] and a waiver from this process will be requested by the investigator from the IEC and CONEP.

No contact will be established with the subjects to obtain, clarify or record information and anonymisation of source data will be guaranteed.

10.1. Data Privacy

Data privacy will be protected by using anonymised individual data (refer to Annex 2 for definition of anonymised data). No Personally Identifiable Information (PII) will be collected in the study, including date of birth. No GSK Biologicals personnel or delegates will have the ability to link data to an identifiable individual.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the 06 June 2013 European Medicines Agency (EMA) - EMA/873138/2011 Guideline on Good Pharmacovigilance Practices (GVP) [EMA, 2013], the sponsors of

non-interventional studies based on secondary data sources are not required to report suspected adverse events or adverse reactions as Individual Case Safety Reports (VI.C.1.2.1).

Only the pregnancy and birth outcomes related to primary and secondary objectives (refer to section 8) will be recorded and collected retrospectively from the subjects participating in the study. Other post-vaccination AEs or Serious Adverse Events (SAEs) have been collected and reported to the national pharmacovigilance system Notivisa, [Notivisa, 2015] as per the country regulations.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Posting of information on publicly available registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers following finalisation of the protocol and, whenever possible, before initiation of the data extraction/ analysis.

Summary results of observational studies that are designed to inform the safety, effectiveness, including cost-effectiveness, of GSK vaccines/products (and other informative studies) 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. At the time of publication, this protocol will be fully disclosed.

12.2. Provision of study results to investigators

Where required by applicable regulatory requirements, the investigator signatory will be requested for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreed location.

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Annex 1 List of stand-alone documents

No.	Document Reference No	Date	Title
1	203153	21 Jul 2015	List of stand-alone documents
2	203153	21 Jul 2015	Glossary of terms
3	203153	21 Jul 2015	Trademarks
4	203153	21 Jul 2015	List of principal and coordinating investigators
5	203153	21 Jul 2015	Sponsor Information
6	203153	19 Jan 2015	Feasibility assessment
7	203153	21 Jul 2015	Definitions and evaluations of selected terms and adverse events of interest in pregnant women participating in clinical trials (adapted from [Munoz, 2013])
8	203153	21 Jul 2015	Planned variables to be collected in electronic Case Report Form (eCRF)
9	203153	21 Jul 2015	Recommendations for *Refortrix* vaccine in Brazil
10	203153	21 Jul 2015	Protocol Sponsor Signatory Approval
11	203153	21 Jul 2015	Protocol Investigator Agreement
12	203153	21 Jul 2015	ENCePP checklist for study protocols

Annex 2 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 unfavourable 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.

Anonymised data:

Information about an individual that GSK or a third party cannot reasonably attribute to the individual, or could only attribute to the individual by expending a disproportionate amount of time, effort or expense (e.g. de-identified or aggregated information). For the purpose of this policy, Key-Coded personally identifiable information shall not be considered Anonymised Information

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).

Congenital anomalies:

The collection of congenital anomalies is based on the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [CDC, 2015] and include morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the foetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception.

Live-born neonates with transient (postural) defects, infectious conditions or biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognised congenital birth defect.

Eclampsia:	Features of pre-eclampsia are accompanied by new onset generalized seizures. See more at Pregnancy-related hypertension.
Eligible:	Qualified for enrolment into the study based upon strict adherence to inclusion/exclusion criteria.
Epidemiological study:	An observational or interventional study without administration of medicinal product(s) as described in a research protocol.
Epoch:	An epoch is a self-contained set of consecutive time points or a single time point from a single protocol. Self-contained means that data collected for all subjects at all time points within that epoch allows to draw a complete conclusion. Typical examples of epochs are retrospective data collection and prospective data collection, etc.
eTrack:	GSK Biologicals' tracking tool for clinical/ epidemiological trials.
Evaluable:	Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis (see Section 9.7.1.2 for details on criteria for evaluability).
Gestational Age:	Gestational age is based on first day of the last menstrual period (LMP) OR the first trimester ultrasound, if no known date of LMP OR known date of fertilisation; with the second trimester beginning at week 14 0/7, and the third trimester beginning at week 28 0/7.
Gestational diabetes:	Onset or first recognition of abnormal glucose tolerance during pregnancy (the diagnosis is based on administration of glucose challenge test at 24-28 weeks of gestation). Includes Class A1: Euglycaemia achieved with diet and/or exercise and Class A2: Euglycaemia achieved with medication. Refer to Annex 7 for details on diagnosis.
HELLP syndrome:	Form of severe pre-eclampsia with associated laboratory abnormalities including haemolysis (H), elevated liver (EL) function tests and low platelets (LP) with or without proteinuria. Refer Pregnancy-related or gestational hypertension for more details. Patients are classified as having partial HELLP syndrome when one or two laboratory abnormalities of HELLP occur.

High-risk pregnancy:	Pregnancy that threatens the health or life of the mother or her fetus. Risk factors for a high-risk pregnancy can include existing health conditions such as high blood pressure, diabetes, being Human Immunodeficiency Virus (HIV)-positive, overweight, obesity, multiple births and young or old maternal age.
Index date:	For the Exposed cohort, the index date will be the date of *Refortrix* vaccination given as part of the maternal immunization program in Brazil. For the Unexposed cohort, the gestational age of 27 completed weeks will be considered as the index date. Only the events for each endpoint occurring after the index date for both groups will be considered.
Key coded information:	Refers to encoded or otherwise pseudo-anonymised Personally Identifiable Information (PII) from which direct identifiers have been removed and replaced by a unique identifier or random code. Key coded PII shall not be considered anonymised information.
Last Menstrual period (LMP):	Considered as the first day of the LMP before conception (fertilisation) onset. The first day of LMP is equal to first day of gestation. The estimated day of conception (fertilisation) is calculated as the first day of LMP plus 14 days.
Live birth:	Delivery of a live infant, regardless of maturity or birth weight, as determined by the presence of spontaneous respirations, a heartbeat, and spontaneous movement.
Maternal death:	Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.
Neonatal death:	Death of neonate at any time from birth to 28 days of life, regardless of gestational age.
Neonatal hypoxic ischaemic encephalopathy:	A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty in initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or due to another cause.

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.
Personally Identifiable Information (PII):	Information which directly (e.g. by name) or indirectly (e.g. by one or more identifiers such as height, weight, date of birth, initials etc) is considered, either individually or in combination, to have the potential to allow identification of named individuals. Different jurisdictions apply varying criteria to define 'personally identifiable data'. In the case of data collected during GlaxoSmithKline (GSK) sponsored clinical trials and processed via Biometrics and Data Sciences (BDS), the true identity of the data of the subject is substituted by a code and the "key" linking the code with the true identity is held by a third party outside GSK (the investigator). These data are generally considered not to be personally identifiable.
Placental abruption:	Partial or total placental detachment prior to delivery of foetus.
Placenta previa:	Presence of placental tissue overlying or proximate to the internal cervical os with or without bleeding, which ranges from spotting to haemorrhagic shock.
Post-Authorisation Safety Study:	A pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised 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 authorisation and where the investigation of safety is the specific stated objective. Note: The phrase ‘In accordance with the terms of the European marketing authorisation’ means that the product is used according to the European label (e.g., within the recommended dose range, the approved formulation, indication etc.).

Post-partum haemorrhage:	Excessive blood loss after delivery i.e. estimated blood loss in excess of 500 ml after vaginal delivery and estimated blood loss in excess of 1000 ml after Caesarean delivery. The other symptoms are ≥10% drop in haematocrit, need for blood transfusion, symptomatic hypotension, dizziness, pallor and oliguria.
Pre-eclampsia:	An acute pregnancy related hypertensive condition characterised by hypertension (>140 and/or >90 mmHg) and/or proteinuria (>300 mg in a 24 hour urine specimen) occurring after the 20th week of gestation and resumes after delivery
Pregnancy/gestational duration:	Pregnancy duration will be classified using the gestational age according to the duration of pregnancy in number of completed weeks: • Preterm will be defined as birth before 37 weeks of gestation. • Full term will be defined as birth between 37 and 41 weeks of gestation. • Post-term will be defined as birth after 41 weeks of gestation.
Pregnancy-related hypertension:	Blood pressure systolic >140 and/or diastolic >90 mmHg, documented in at least two separate measurements after 20 weeks of gestation, without proteinuria or other stigmata of pre-eclampsia, and returning to normal post-partum. Hypertension usually resolves by 12 weeks post-partum. For this study, this will include pre-eclampsia, eclampsia and HELLP Syndrome.
Premature rupture of membranes (PROM):	Spontaneous rupture of foetal membranes that occurs before the onset of labour.
Premature uterine contraction:	Uterine contractions without cervical change.
Preterm birth:	Birth before 37 weeks of gestation.
Preterm Premature rupture of membranes (P-PROM):	Spontaneous rupture of foetal membranes that occurs before the onset of labour before 37 weeks of gestation.
Research protocol:	A document that describes the objective(s), design, methodology, statistical considerations, and organisation 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.

Serious Adverse Event (SAE): A SAE is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

   Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity, OR

   Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or

prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect in the offspring of a study subject.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.

Site Monitor: An individual assigned by the sponsor who is responsible for assuring the proper conduct of epidemiological studies at one or more investigational sites.

Small for gestational age (SGA): Birth weight less than 10% for infants of same gestational age and gender in same population.

Still birth: Death of the foetus(es) at ≥22 weeks of gestation, occurring antepartum or intrapartum.

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.

Subject number: A unique number identifying a subject, assigned to each subject consenting to participate in the study.

Targeted Safety Study:	Studies specifically planned or conducted to examine an actual or hypothetical safety concern in a product marketed anywhere in the world. This includes any GSK sponsored pharmaco-epidemiological study or clinical trial conducted anywhere in the world with the aim of identifying or quantifying a safety hazard. Although all clinical trials collect safety information as a matter of routine, only those initiated to examine a specific safety concern are considered a targeted safety study.
Vaginal or intrauterine haemorrhage:	Vaginal or intrauterine haemorrhage which may be caused due to partial or total detachment of placenta or due to presence of placental tissue overlying or proximate to the internal cervical os with or without bleeding, which ranges from spotting to haemorrhagic shock. This includes the following diagnosis- placental abruption and placenta previa.

Annex 3 Trademarks

The following trademark is used in the present protocol.

Note: In the body of the protocol (including the abstract), the name of the vaccine will be written without the superscript symbol ™ and in *italics*.

Trademark of the GlaxoSmithKline group of companies	Generic description
Refortrix™	Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine

Annex 4 List of principal and coordinating investigators

The contact details and list of all investigators are available upon request.

Annex 5 Sponsor Information

Sponsor:

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

Sponsor Study Monitor:

Refer to the local study contact information document.

Annex 6 Feasibility assessment

The details on feasibility assessment are available upon request.

Annex 7 Definitions and evaluations of selected terms and adverse events of interest in pregnant women participating in clinical trials (adapted from Munoz, 2013)

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
PREGNANCY RELATED TERMS				
GESTATIONAL AGE ESTIMATES: Dating of Pregnancy	Dating from: -first day of last menstrual period (LMP), OR -1st trimester ultrasound if no known LMP or the ultrasound is not consistent with LMP, OR -known date of fertilization (e.g. by Assisted Reproductive Technology or Intrauterine Insemination). [ACOG, 2014]		Test for urine or serum β-HCG -urine test: positive about 10-12 days after conception. -serum test: positive about 5-7 days after conception. The estimated date of conception or pregnancy onset is calculated as the last menstrual period plus 14 days. Ultrasound (US): Gestational age is assessed in the 1st trimester (< 14 weeks) by measurement of crown-rump length. In the second trimester (14 to 20 weeks), the biparietal diameter is used (accuracy is within +/- 10 days up to 34 weeks, then +/- 3 weeks). At term, abdominal circumference and femoral length are used. US limited by: insufficient standardization, operator variability and expertise, lack of large population based reference, assumption that all fetuses with the same measurements have the same gestational age without accounting for true differences in fetal growth in early gestation or genetic and other familiar factors.	-The Committee on Obstetric Practice, American Institute of Ultrasound in Medicine and Society for Maternal-Fetal. Committee Opinions: Method for estimating Due Date. Number 611, October 2014 (accessed on-line on 13/Oct/2014 at: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Method-for-Estimating-Due-Date).

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
TRIMESTER OF GESTATION	Pregnancy is divided in three trimesters: -First trimester: up to and including 13 6/7 weeks of gestation. -Second trimester: 14 0/7 weeks to 27 6/7 weeks of gestation. -Third trimester: 28 0/7 weeks of gestation and beyond.			
LENGTH OF PREGNANCY	Preterm: up to and including 36 6/7 weeks of gestation. Term: 37 0/7 weeks through 41 6/7 weeks of gestation [ACOG, 2013]. Early term: Birth at 37 0/7 to <39 weeks of gestation. Post-term (S: post-mature): 42 0/7 weeks of gestation and beyond.		Estimated Date of Delivery (EDD)= 40 0/7 weeks (280 days) from the first day of the last menstrual period or by Ultrasound examination.	The American College of Obstetricians and Gynecologists Committee on Obstetric Practice Society for Maternal-Fetal Medicine. Committee Opinions: Definition of Term Pregnancy. Number 579, November 2013 (accessed on-line on 13/Oct/2014 at: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Definition-of-Term-Pregnancy)
PREGNANCY OUTCOMES				
LIVE BIRTH S: Live born	Delivery of a live infant, regardless of maturity or birth weight, as determined by the presence of spontaneous respirations, a heartbeat, and spontaneous movement			

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
SPONTANEOUS ABORTION S: miscarriage, pregnancy loss	Pregnancy ending spontaneously before 22 weeks of gestation (i.e. up to and including 21 6/7 weeks of gestation) [EMEA, 2005]. Includes death of embryo/ fetus in utero (missed abortion), or blighted ovum /anembryonic pregnancy (i.e. fertilized ovum whose development has ceased at an early stage). Subgroups: -Early miscarriage if it occurs during the first trimester. -Late miscarriage when it occurs during the second trimester.	Overall rates: The prevalence of spontaneous abortion reported by several authors among clinical pregnancies (i.e. recognized pregnancies following a missed menstrual period) for all age groups combined is about 12-18% of all pregnancies in first or second trimester. -Early miscarriage: Up to 20%of pregnancies. -Late miscarriage: Up to 2% of pregnancies. Risk factors: Studies have shown that approximately 50% of spontaneous abortions are associated with fetal chromosome abnormalities [Brown 2008]. Many studies have shown that maternal age is one of the strongest and most consistent risk factor.	Note: case definitions vary between countries, as definition of viability is varied between resource settings (e.g. 20-24 weeks versus 28 weeks and corresponding fetal weight of 500 mgr. vs. 1000 mgr). Document circumstances of fetal loss, physical exam/estimated gestational age of the product if feasible and/or collect results of available studies including pathology report of fetus and placenta to establish a possible etiology, association/causality. Genetic testing if available; a karyotype may or may not be performed as part of routine clinical care. Of note, it may not be possible to perform evaluation if the subject does not seek medical attention.	- European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-authorization Data. London, UK: EMEA; 2005. - Brown S. Miscarriage and its associations. Seminars in Reproductive Medicine 2008; 26(5): 391-400. - Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE,et al. Incidence of early loss of pregnancy. New England Journal of Medicine1988;319: 189–94. - Harlap S, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. Lancet 1980; 2:173–6.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
STILLBIRTH S: Stillborn, Fetal Demise/Death, Deadborn	Delivery of a death fetus after 22 0/7 weeks of gestation [EMEA, 2005]. Categories: - During pregnancy or antepartum. - Intrapartum. Subgroups: -Early Stillbirth: Delivery 22 0/7 – <28 weeks and/or ≥500 -1000 grams. -Late Stillbirth: Delivery ≥ 28 0/7 weeks and/or >1,000 grams	Overall rates [ACOG, 2009]: 6.2/1,000 births or 1 in 160 deliveries. -Early stillbirth: 3.2/1,000 births. -Late stillbirth: 3.1/1,000 births. Risk factors: Non-Hispanic black race, nulliparity, maternal age >35 years, hypertension, diabetes, obesity BMI >30, multiple gestations, smoking, drug and alcohol use, infections, growth restriction, and placental anomalies.	Includes macroscopic examination for fetal anomalies, and if available, autopsy and karyotype; cord and placental examination and pathology. Document antepartum events: maternal factors, fetal factors (e.g., IUGR), external factors (e.g., trauma), and peripartum events such as preterm premature rupture of membranes (PPROM), infection, abruption, cord events.	- European Medicines Agency (Committee for Medicinal Products for Human Use). Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-authorization Data. London, UK: EMEA; 2005. - American College of Obstetricians and Gynecologists. Management of stillbirth. ACOG Practice Bulletin Number 102. Obstetrics and Gynecology2009; 113: 748–61. (accessed on-line on 13/Oct/2014 at: https://stillbirthmatters.files.wordpress.com/2014/05/acog-management-of-stillbirth1.pdf)
CONGENITAL ANOMALIES S: Birth defects, Malformations	The collection of congenital anomalies is based on the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) guidelines [CDC,2007] and include morphological, functional, chromosomal or genetic anomalies, regardless of whether detected at birth or not, the fetus is delivered dead or alive, or defects are identified by prenatal ultrasound, amniocentesis or examination of the products of conception. Live-born neonates with transient (postural) defects, infectious	Minor anomaly: Rates vary widely depending on study. Minor malformations and developmental variants occur in 14 - 40% of otherwise normal newborns [Leppig, 1987]. Major anomaly: Apparent at birth in approximately 3% of population [CDC, 2013].	An exact cause or mechanism for a major defect can be determined in less than 50% of the cases. Some agents cause major defects if exposure occurs during a specific critical period of gestation, but not at other times. After organogenesis has been completed (about 8 weeks after conception or 10 weeks after last menstrual period), the observable effect may be limited to fetal growth restriction or functional rather than gross structural defects [Sadler,2009]. The primary outcomes relative to stage of exposure are as follows: Pre-implantation: embryonic lethality	Centers for Disease Control. Birth defects and genetic diseases branch 6-digit code for reportable congenital anomalies; 2007.(accessed on-line on 13/Oct/2014 at: http://www.cdc.gov/ncbddd/birthdefects/documents/macdpcode0807.pdf) - Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, MooreCA. Guidelines for case classification for the National Birth Defects Preven-tion Study. Birth Defects Research Part A: Clinical and Molecular Teratology2003;

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	conditions or certain biochemical disorders are classified as being without congenital anomalies unless there is a reasonable possibility that the condition reflects an unrecognized congenital birth defect. Morphological anomalies: Abnormalities of body structure or function that are present at birth and are of prenatal origin. Categories: Minor anomaly: Anatomic variant or defect that do not have serious medical, functional or cosmetic consequences for the child. Includes those found in association with major anomalies. Major anomaly: Structural or functional defect that require surgical/medical treatment, have serious adverse effects on health or development (functional), or have significant cosmetic impact. [Rasmussen, 2003].		Implantation to time of organogenesis: morphological defects. Fetal → neonatal stage: functional disorders, growth retardation, Carcinogenesis. A certain pattern of minor malformations may have important predictive value in identifying more serious associated problems, some of which may be unrecognizable at an early age. Specific patterns of multiple minor malformations may be presenting signs of a genetic condition or malformation syndrome.	67:193–201. - Leppig KA, Werler MM, Cann CI, Cook CA, Holmes LB. Predictive value of minor anomalies. Association with major malformations. Journal of Pediatrics1987; 110: 530–7. -Sadler TW. Langman's medical embryology. 11th ed. Lippincott Williams and Q4Wilkins; 2009. - Centers for Disease Control and Prevention. Update on overall prevalence of major birth defects-Atlanta, Georgia, 1978–2005. MMWR; 2013. (accessed on-line on 13/Oct/2014 at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm)
ELECTIVE OR THERAPEUTIC TERMINATION OF PREGNANCY S: Induced abortion	Expulsion of products of conception with medical or surgical assistance. The termination of the pregnancy can be elective or therapeutic. -Elective: performed for personal choice/socio-economic reasons, excluding maternal or fetal health reasons. -Therapeutic: performed to preserve the health or save the life of a			

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	pregnant woman.			
ECTOPIC PREGNANCY S: Extra-uterine pregnancy	Condition in which a fertilized ovum implants outside the uterine cavity, most often in the fallopian tube (97%).	Affects 1.5% to 2% of all pregnancies and poses a significant threat to women of reproductive age. It is the leading cause of maternal death during the first trimester of pregnancy. Risk factors: tubal surgery, genital tract infections leading to pelvic inflammatory disease, previous ectopic pregnancy, and in utero exposure to diethylstilbestrol [ACOG, 2008].	Diagnosis is generally based on: clinical symptoms/signs, diagnostic transvaginal ultrasonography, abnormal serum progesterone level of less than 5 ng/mL and/or an inappropriate increase in hCG.	- Kurt T. Barnhart. Ectopic pregnancy. N Engl J Med 2009; 361:379-87. - American College of Obstetricians and Gynecologists. Medical Management of Ectopic Pregnancy. ACOG Practice Bulletin Number 94. Obstetrics and Gynecology Jun 2008; 111(6): 1479–85.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
MOLAR PREGNANCY S: gestational trophoblastic neoplasia, gestational trophoblastic tumor	Pregnancy marked by a neoplasm within the uterus, whereby part or all of the chorionic villi are converted into a mass of clear vesicles. Histologically distinct disease entities encompassed by this general terminology include: complete and partial hydatidiform moles, invasive moles, gestational choriocarcinomas, and placental site trophoblastic tumors.	The incidence is estimated at 1-3 per 1000 pregnancies for partial or complete hydatidiform moles. The malignant invasive moles (choriocarcinoma and placental site trophoblastic tumour/epithelioid trophoblastic tumour) are very rare, 0.2% of the gestational trophoblastic disease cases [ESMO, 2013; ACOG, 2004]. Risk factors: extremes of maternal age and prior molar pregnancy. The risk of repeat molar pregnancy after 1 mole is about 1%, or about 10-20 times the risk for the general population.	The disease is most frequently diagnosed on the basis of increasing or plateauing hCG values. Patients should be monitored with serial determinations of quantitative hCG values. A baseline post-evacuation chest X-ray should be considered.	- American College of Obstetricians and Gynecologists. Diagnosis and Treatment of Gestational Trophoblastic Disease. ACOG Practice Bulletin Number 53. Obstetrics and Gynecology June 2004; 103 (6):1365-77. - M. J. Seckl, N. J. Sebire, R. A. Fisher, F. Golfier, L. Massuger & C. Sessa, on behalf of the ESMO Guidelines Working Group. Gestational trophoblastic disease: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2013; 24 (Supplement 6): vi39–vi50.
PREGNANCY RELATED ADVERSE EVENTS OF INTEREST				
VAGINAL OR INTRAUTERINE HEMORRHAGE S: Obstetric Hemorrhage, Major obstetric hemorrhage	Vaginal or intrauterine hemorrhage that encompasses antepartum (i.e. bleeding from the genital tract after 24 weeks of gestation), intrapartum, and postpartum bleeding (i.e. within 24 hours post-delivery). A major obstetric hemorrhage is defined as blood loss from uterus or genital tract >1500 mL or a decrease	Antepartum hemorrhage: has an incidence of 2–5% of all pregnancies beyond 24 weeks [Walfish, 2009]. Infrequent (14% of cases occur before 32 weeks gestation) and up to 60% between 32-37 weeks gestation [Munoz, 2013]. Risk factors for placenta previa:	Given the wide range of definitions applied to maternal hemorrhage, it is important to combine the clinical presentation and objective data, while keeping in mind the probability of concealed bleeding within the uterus, peritoneal cavity, and retroperitoneal space, and the relative masking of haemodynamic signs of haemorrhagic	- American College of Obstetricians and Gynecologists. Cervical insufficiency. ACOG Practice Bulletin No. 76, Postpartum Haemorrhage International Journal of Gynecology and Obstetrics Oct 2006: 108 (4): 1034-47 (accessed on-line on 13/Oct/2014 at:

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	in hemoglobin of >4 gr/dl or acute loss requiring transfusion of >4 units of blood, or signs or symptoms of hypovolemia. Common causes of blood loss: - Antepartum hemorrhage: placenta previa (presence of placental tissue overlying or proximate to the internal cervical os), placental abruption (partial or total placental detachment prior to delivery of fetus), uterine rupture, bleeding from vaginal or cervical lesions, etc. - Postpartum Hemorrhage: uterine atony, retained products of conception, abnormal placentation (abnormal attachment of the placenta to the uterine wall and includes accreta, increta, and percreta, depending on the extent of uterine invasion), genital tract trauma, uterine inversion, puerperal sepsis, uterine pathology such as fibroids, etc.	prior uterine trauma, multiparity, advanced maternal age, previous C-section or other uterine surgery, and prior placenta previa. Risk factors for placental abruption: hypertension, pre-eclampsia, advanced maternal age, multiparity, maternal/paternal tobacco use, cocaine use, trauma, premature rupture of membranes, chorioamnionitis, and prior abruption. Risk factors for uterine rupture: prior uterine surgery, trauma, uterine anomalies, dystocia, use of uterotonic drugs, and abnormal placentation. Post-partum hemorrhage: Primary postpartum hemorrhage, which occurs in 4–6% of pregnancies, is caused by uterine atony in 80% or more of cases [ACOG,2006]. Risk factors for Postpartum Hemorrhage: Prolonged labor, Augmented labor, Rapid labor, History of postpartum hemorrhage, Episiotomy, especially mediolateral, Preeclampsia, Overdistended uterus (macrosomia, twins, hydramnios), Operative delivery, Asian or Hispanic ethnicity, Chorioamnionitis. Risk factors for abnormal	shock due to the physiological adaptations of pregnancy. Diagnosis is based on clinical presentation; ultrasound and placental pathology if available.	https://www.acog.org/~/media/Districts/District%20II/PDFs/Final_Hemorrhage_Web.pdf - Walfish M et al. Maternal haemorrhage. Br. J. Anaesth. (2009) 103 (suppl 1): i47-i56. -Munoz et al. Research on vaccines during pregnancy: Protocol design and assessment of safety, Vaccine, (2013): 31 (40): 4274-4279, Appendixes

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
		placentation: placenta previa with or without previous uterine surgery, prior myomectomy, prior cesarean delivery, Asherman's syndrome, submucous leiomyomata, and maternal age older than 35 years.		
PREMATURE RUPTURE OF MEMBRANES (PROM) AND PRETERM PREMATURE RUPTURE OF MEMBRANES (P-PROM)	PROM: Spontaneous rupture of fetal membranes that occurs before the onset of labor. Preterm PROM (P-PROM): Spontaneous rupture of fetal membranes that occurs before the onset of labor before 37 weeks gestation.	Term PROM may occur in 8% of pregnancies, P-PROM in approximately one-third of all preterm births or 4% of all births [ACOG, 2007]. Risk factors: Numerous maternal and fetal factors involved, particularly infection, obstetric factors including abruption placenta, as well as previous P-PROM or premature delivery. Recurrence for P-PROM is 16-32%.	Assessment of gestational age and assessment of maternal and fetal risks, including intrauterine infection, labor, fetal compromise.	-American College of Obstetricians and Gynecologists. Premature rupture of membranes. ACOG Practice Bulletin Number 80. Obstetrics and Gynecology2007;109:1007–20.
PREMATURE UTERINE CONTRACTIONS AND PREMATURE LABOR	Premature uterine contractions: Uterine contractions without cervical change. Premature labor: Cervical change in the presence of regular uterine contractions that occur before 37 weeks of gestation.	Refer to incidence of preterm delivery: 12% of all live births [ACOG, 2012].	Collect any clinical and laboratory information that is available. Standard work-up may include: vaginal examination, uterine monitoring, and fetal monitoring. Work-up to determine etiology or association to study product may include: evaluation for infections (urine culture, Group B streptococcus, Chlamydia, gonococcus, *Trichomonas vaginalis*, bacterial vaginosis), drug screen, and ultrasound to rule out abruption, cord prolapse, oligo/polyhydramnios.	- American College of Obstetricians and Gynecologists. Management of preterm labor. ACOG Practice Bulletin Number 127. International Journal of Gynecology and Obstetrics 2012 Jun; 19(6):1308-17.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
INTRAUTERINE GROWTH RESTRICTION / POOR FETAL GROWTH S: IUGR S: Fetal growth retardation	Estimated or actual birth weight below the 10th percentile for gestational age.	10% of live births [ACOG, 2013]. Risk factors: Numerous, classified as maternal, placental, fetal.	May include ultrasound (specific biometric parameters and estimated fetal weight), umbilical artery Doppler velocimetry, amniocentesis, chromosomes, and assessment of maternal risk factors (infection, hypertension, etc.). NOTE: curves used to determine %iles should account for gender and race/ethnicity	- American College of Obstetricians and Gynecologists. Fetal Growth Restriction. ACOG Committee Opinion Number 134. Obstetrics and Gynecology May 2013;121: 1122–33.
GESTATIONAL HYPERTENTION, PREECLAMPSIA AND ECLAMPSIA S: Pregnancy Related Hypertension, Pregnancy Induced Hypertension (PIH), Toxemia	Gestational hypertension: Blood pressure systolic >140 and/or diastolic >90 mmHg, documented in at least 2 separate measurements after 20 weeks of gestation, without proteinuria or other stigmata of preeclampsia, and returning to normal post-partum. Hypertension usually resolves by 12 weeks postpartum Pre-eclampsia: Hypertension (>140 and/or >90 mmHg) occurring after the 20th week of gestation, and up to 6 weeks postpartum, combined with other abnormalities such as proteinuria (>300 mg in a 24 hr urine specimen). HELLP syndrome: Form of severe pre-eclampsia with associated laboratory abnormalities including hemolysis (H), elevated liver (EL) function tests, and low platelets (LP), with or without proteinuria. Eclampsia: If the features of pre-	Hypertensive disease occurs in 12-22% of pregnancies [ACOG, 2001; ACOG, 2002]. As many as 25% of women with gestational hypertension will develop preeclampsia. The reported incidence of preeclampsia is 5-8% of pregnancies, usually first pregnancies. Risk factors: First pregnancy, multiple gestation, preeclampsia in previous pregnancy, chronic hypertension, pre-gestational diabetes, vascular and connective tissue disorders, nephropathy, antiphospholipid antibody syndrome, obesity, age >35 years, non-Hispanic black race.	Blood pressure elevation should be sustained and documented in two independent measurements. Additional assessments include a random or 24-hour urine protein determination of 300 mg/dL, other laboratory testing to establish severity and collection of available data on fetal well-being.	- American College of Obstetricians and Gynecologists. Diagnosis and management of preeclampsia and eclampsia. ACOG Practice Bulletin Number 33.Obstetrics and Gynecology 2002; 99:159–67. - American College of Obstetricians and Gynecologists. Chronic hypertension in pregnancy. ACOG Practice Bulletin Number 29. Obstetrics and Gynecology2001; 98:177–85.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	eclampsia are accompanied by new onset generalized seizures. Chronic Hypertension with superimposed preeclampsia: Chronic hypertension definition PLUS preeclampsia definition			
GESTATIONAL DIABETES MELLITUS S: Diabetes of pregnancy	Onset or first recognition of abnormal glucose tolerance during pregnancy (old definition still used by ACOG). Diagnosis based on administration of glucose challenge test at 24-28 weeks gestation	1% to 14%, with 2-5% being the most common figure [ACOG, 2001].	Includes urine glucose measurement during routine prenatal care visits; a fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], or A1C ≥6.5 percent using a standardized assay, or a random plasma glucose ≥200 mg/dL [11.1 mmol/L] that is subsequently confirmed by elevated fasting plasma glucose or A1C, as noted above. Glucose tolerance screening is universal at 24-28 weeks of gestation.	- American College of Obstetricians and Gynecologists. Gestational diabetes. ACOG Practice Bulletin Number 30. Obstetrics and Gynecology2001;98: 525–38.
MATERNAL DEATH	Death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. Direct obstetric death: death of the mother resulting from conditions or complications which are unique to pregnancy and occur during the antepartum, intrapartum, or postpartum period. Indirect obstetric death: A maternal death that is not directly due to obstetric cause (such as from	The global maternal mortality rate is estimated to be about 210 maternal deaths per 100,000 live births [WHO,2013]. Indirect causes and obstetric hemorrhage are the largest causes of maternal death worldwide. Of the direct causes of death, hemorrhage is the leading cause of maternal death, followed by hypertensive disorders and sepsis. Regional estimates varied substantially [Say, 2014].		- Trends in Maternal Mortality: 1990 to 2013. Estimates by WHO, UNICEF, UNFPA, The World Bank and the United Nations Population Division. (accessed on-line on 13/Oct/2014 at: http://apps.who.int/iris/bitstream/10665/112682/2/9789241507226_eng.pdf?ua=1) -Lale Say et al, Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2: e323–33

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	previously existing disease, or disease developing during pregnancy, labor, or the puerperium but that was not unique to pregnancy.) Late Maternal Death: Death of woman from direct or indirect causes more than 42 days but less than one year after termination of pregnancy.			
NEONATAL RELATED EVENTS				
BIRTH WEIGHT (BW)	Small for gestational age (SGA): Birth weight < 10% for newborns of same gestational age and gender in same population (<2500g at term). Low birth weight: BW <2500 g (5.5 lb). Very low birth weight : BW <1500 g (3.3 lb) Extremely low birth weight: BW <1000 g (2.2 lb). Large for gestational age (LGA): Birth weight > 90% for newborns of same gestational age in same population (>4000g at term). High Birth Weight (Macrosomia): BW >4000 g (8.13 lb).	SGA newborns are predisposed to complications, including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis, respiratory distress syndrome, and neonatal death. One of the primary risk factors of LGA is poorly-controlled maternal diabetes (pre-existing diabetes mellitus/gestational). Other risk factors in decreasing order of importance, are as follows: a history of macrosomia, maternal weight before pregnancy, weight gain during pregnancy, multiparity, male fetus, gestational age more than 40 weeks, ethnicity, maternal birth weight, maternal height, maternal age younger than 17 years and a positive 50g glucose screen with a negative result on	Birth weight: Objective is measurement of weight on the day of delivery (OR first weight obtained). Varies with singleton vs. multiple gestation, gestational age, gender, race, ethnicity, maternal nutritional status (BMI), and maternal health status. Birth weight is one of the most sensitive – and also one of the most important – measures of the well-being of children. Weight at birth is directly influenced by the general level of health status of the mother. Assessment of Birth Weight is in relation to Gestational Age (BW/GA): -Gestational age should be based on best obstetric estimate, usually prenatal ultrasound or first day of last menstrual period if ultrasound not available; or neonatal physical exam. -Weight should be based on objective measurement on the day of birth. -Estimate of BW/GA should be based on population specific curves	

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
		the three-hour glucose tolerance test.		
PRETERM BIRTH	Birth before 37 weeks of gestation. Late Preterm: 34 to <37 weeks Moderate Preterm: 32 to <34 weeks Very Preterm: 28 to < 32 weeks Extreme Preterm: < 28 weeks	10-15% of all pregnancies, with most recent National Vital Statistics Report showing a decline to 11.72% in recent years. Extreme preterm birth occurs in less than 1% of live births [ACOG, 2003].	Includes physical examination and determination of gestational age, and evaluation for maternal or infant causes of premature delivery. Assessment requires gestational age assessment by best available obstetric estimate, usually prenatal ultrasound or first day of the last menstrual period if ultrasound not available. Also assessed by pediatric estimate through physical and neurological examination of newborn at birth. This is less desirable as this assessment is affected by abnormal fetal growth, placental anatomic and functional anomalies, maternal nutrition, racial and ethnic background, population and genetic factors, and birth weight for GA.	-American College of Obstetricians and Gynecologists. Management of preterm labor. ACOG Practice Bulletin Number 43. International Journal of Gynaecology and Obstetrics 2003;82: 127–35.
NEONATAL DEATH	Death of newborn at any time from birth to 28 days of life, regardless of gestational age. Subgroups: Very early neonatal death: < 24hrs Early neonatal death: from birth to < 7 days Late neonatal death: 7 to < 28 days Intrapartum-related neonatal death (previously called: asphyxia deaths): neonatal death of term babies with	The early neonatal death rate is estimated to be 8.4 per 1000 liveborns; 67.1% occur by day 3 of life [Vogel, 2014]. Prematurity is the main cause of early neonatal deaths (~62%).	Causes of death and rates may vary according to whether the birth setting was in a hospital or in the community	- Vogel JP et al, on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network. Maternal complications and perinatal mortality: findings of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121 (Suppl. 1): 76–88.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
	neonatal encephalopathy or who cannot be resuscitated (or for whom resuscitation is not available). Also includes babies who die from birth injury without hypoxic brain injury)			
NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) S: HIE, Birth Asphyxia, Perinatal Asphyxia, Neonatal encephalopathy	A disturbance of neurological function in the earliest days of life in the term infant manifested by difficulty initiation and maintaining respiration, depression of tone and reflexes, abnormal level of consciousness and often seizures, which may follow an intrapartum hypoxic insult or be due to another cause.	Rates may vary widely. The incidence of HIE in developed countries is estimated to be 1.5 per 1,000 live births [Kurinczuk, 2010]. Estimates in developing countries range from 2.3–26.5 per 1,000 live births [Horn,2013].	Assessed by clinical and laboratory findings: 5 minute Apgar score of 0-3, Respiratory distress and Acidosis (pH < 7.0), altered tone, depressed level of consciousness, seizures, multiorgan involvement. Diagnostic tests: - MRI is preferred imaging study. - CT can identify focal lesions, hemorrhage, diffuse cortical injury - EKG (ECG) and continuous EKG (ECG) May result in neonatal death or permanent damage to the brain and other organs. May be associated with perinatal events, rarely to prenatal events.	- Kurinczuk JJ, White-Koning M, Badawi N: Epidemiology of neonatal encephalopathy and hypoxic–ischaemic encephalopathy. Early Hum Dev 2010, 86(6):329-338. - Horn AR, Swingler GH, Myer L, Harrison MC, Linley LL, Nelson C, Tooke L, Rhoda NR, Robertson NJ: Defining hypoxic ischemic encephalopathy in newborn infants: benchmarking in a South African population. J Perinat Med 2013, 41(2):211-217.
FAILURE TO THRIVE OR GROWTH DEFICIENCY	Inability to maintain expected growth rate over time, evaluated by plotting individual weight gain and growth on standard growth charts for the population.	Failure to thrive (FTT) is a common problem, however precise epidemiological data is lacking. The population prevalence of FTT has been found to range anywhere between 1.3% and 20.9% depending on the definition of FTT that is used. FTT accounts for 1–5% of paediatric hospital admissions under 2 year of age [Sullivan, 2004]	Normal newborn weight gain includes weight loss of up to 10% of birth weight in the first 1-2 weeks of life, with steady, predictable weight gain thereafter. Progress varies by gestational and post-natal age, genetic and environmental factors. Definitions vary. Fall of weight below 5th percentile for age often used. Olsen et al have described multiple different anthropometric criteria for failure to thrive. These criteria include signs of	- Olsen EM, Petersen J, Skovgaard AM, Weile B, Jorgensen T, Wright CM. Failure to thrive: the prevalence and concurrence of anthropometric criteria in a general infant population. Arch Dis Child. February2007; 92(2):109-114. - Peter B Sullivan. Commentary: The epidemiology of failure-to-thrive in infants. Int. J. Epidemiol. (2004) 33 (4): 847-848.

Common terms or Adverse Events	Definition	Background rates and risk factors, if appropriate	Comments	References
			failure to gain weight (weight < 75% of median weight for chronological age, weight for chronological age < 5th percentile, weight deceleration crossing > 2 major percentile lines, etc), failure to grow (length for chronological age < 5th percentile), and failure to grow and gain weight (weight < 80% of median weight for length, body mass index < 5th percentile) [Olsen, 2007]	

Annex 8 Planned variables to be collected in electronic Case Report Form (eCRF)

Demographic data:

Age (in years)

Resident

Medical antecedents:

Chronic hypertension

Diabetes mellitus

Anaemia

Nutritional disorders: Malnutrition , overweight, obesity

Infectious diseases (e.g.: Chagas disease, Malaria, HIV, Hepatitis, Tuberculosis)

Other Chronic Diseases: Heart disease, rheumatic disease, epilepsy, renal disease, thyroid and other endocrine diseases

Blood transfusion

Accidents

Major surgeries

Neurologic diseases

Gynaecological history

Menstrual cycles: Duration in days, interval in days and regular

Prior use of contraceptive methods

Sexually transmitted diseases

Gynaecological surgeries (at what age, diagnosis)

Breast problems

Obstetric Antecedents:

Number of pregnancies :including miscarriage, ectopic pregnancy

Number of deliveries

Type of deliveries: forceps, Caesarean, spontaneous, vaginal

Number of miscarriages including spontaneous, induced, therapeutic

Number of live births

Interval between pregnancies

Number of newborns: Preterm (before 37 weeks), Post tem (> 42 weeks)

Rh isoimmunization

Number of newborns of low birth weight (less than 2,500 gm) and more than 4000 gm

Early neonatal deaths (if during hospitalisation): Up to seven days of life

Late neonatal deaths (if during hospitalisation): Between 7 and 28 days

Stillbirth (intrauterine foetal death) and gestational age at which the event occurred

Newborns with jaundice, transfusion, hypoglycaemia

Events or complications in previous pregnancies : Haemorrhage, pre-eclampsia, other

Complications in puerperium: Haemorrhage, infections, other

Current Pregnancy History:

Date (first day/month/year) of the last menstrual period

Weight

Ultrasound scan result

Lab tests: Blood group, Rh, haemoglobin, glycaemia, other

Vaccination(s)

Concomitant medications reported at the time of delivery

Hospitalisation during this pregnancy

Habits: Smoking, alcohol and illicit drugs

Pregnancy events

Gestational diabetes

Pre-eclampsia

Eclampsia

HELLP Syndrome

Placenta abruption

Placenta previa

Vaginal haemorrhage

- Ante-partum
- Intra-partum
- Post-partum

Birth Outcomes

Pre term birth (weeks of gestation)

Small for gestational age (birth weight in grams)

Apgar score

Other events

Premature rupture of membranes

Preterm premature rupture of membranes

Premature uterine contraction

Premature labour

Neonatal death

Maternal death

Still birth

Neonatal hypoxic ischaemic encephalopathy

Congenital anomalies

Annex 9 Recommendations for *Refortrix* vaccine in Brazil

The recommendation for *Refortrix* vaccine in Brazil is available upon request.

Annex 10 Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	203153 (EPI-PERTUSSIS-037 VS BR)
Date of protocol	Final Version 1: 11 September 2015
Detailed Title	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Sponsor signatory	Laurence Baril, Director, Epidemiology, GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Signature	_____
Date	_____

For internal use only

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Annex 10 Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	203153 (EPI-PERTUSSIS-037 VS BR)
Date of protocol	Final Version 1: 11 September 2015
Detailed Title	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Sponsor signatory	Laurence Baril, Director, Epidemiology, GlaxoSmithKline Biologicals Rue de l'Institut, 89 1330 Rixensart, Belgium
Signature	PPD
Date	21 Sept. 2015

For internal use only

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Annex 11 Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any mutually agreed future protocol amendments or protocol administrative changes, with the terms of the study agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP), other applicable guidelines and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the sponsor, and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.

eTrack study number and Abbreviated Title	203153 (EPI-PERTUSSIS-037 VS BR)
Date of protocol	Final Version 1: 11 September 2015
Detailed Title	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Investigator name	_____
Signature	_____
Date	_____

For internal use only

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Annex 12 ENCePP Checklist for study protocols

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	17
1.1.2 End of data collection[2]	☒	☐	☐	17
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	15

Comments:

The EU PASS registration will be updated in the final version.

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16 16-17
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15-17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	27
2.1.5 If applicable, that there is no a priori				

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16-18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	24-25
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	23-24

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	17
4.2.4 Disease/indication?				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.5 Co-morbidity?	☒	☐	☐	17
4.2.6 Seasonality?	☐	☐	☒	
	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19-20

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	19-24
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	29
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	19
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	23 and 24
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	29

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	24
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	24
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	24
8.1.3 Covariates?	☒	☐	☐	24
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	24
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	24
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	24
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	25-26

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	27-28
10.2 Is the choice of statistical techniques described?	☒	☐	☐	27-28
10.3 Are descriptive analyses included?	☒	☐	☐	27-28
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	28
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	28
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29
11.3 Are methods of quality assurance described?	☒	☐	☐	29
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	29
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	29
12.1.2 Information biases?	☒	☐	☐	29
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	18
12.3 Does the protocol address other limitations?	☒	☐	☐	30

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	31

Comments:

The study still has to be submitted to EC/IRB.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☒	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	32

Comments:

Name of the main author of the protocol: PPD Director, Epidemiology, GlaxoSmithKline Biologicals

Date: / /

Signature: _____

Instructions for Local ICF development

The LOC should ensure that all local legal regulatory requirements are satisfied before finalizing the Local ICF. It is strongly recommended to align the content of the Local ICF with the content of the Model ICF and this template.

When developing a Local ICF, all changes to the content that affect the meaning of the Model ICF should be justified and documented locally. Any **black bold** text in the final Model ICF is GSK Vaccines' **mandatory** wording and should be retained, any alterations or additions to this text must be communicated to the central team prior to the finalization of the local ICF.

Refer to Appendix A Best Practices document for the development of the Local ICF.

Significant changes in the local ICF compared to the Model ICF related to the processing and use of human biological samples and data need to be tracked in the Informed Consent Significant Changes Tracking Form. For example, changes in the sample use and/or future research; sample retention period; what happens to samples or data if a subject withdraws consent; any restriction in sharing samples or data with other researchers; any changes to what data can be collected. These changes are tracked to ensure that GSK and other third parties collecting and using samples and data from GSK clinical trials are informed of and can comply with what was agreed to by the subject in the informed consent he/she signed.

Note: In the final Local ICF all text should be in the same format i.e. any bold text must be in normal font and red instruction text must not be retained.

Note: In some exceptional cases, a space for subject/patient initials and date may be required by the IRB / IEC on each page; if so, a space can be included. However, this must be implemented only if specifically requested and not as a general practice.

Refer to SOP-GSKF-407, GUI_51905 and GUI-BIO-CLIN-0014 for more information.

(Delete the instructions above from the Final Local ICF).

INFORMED CONSENT FORM

Study identification	203153 (EPI-PERTUSSIS-037 VS BR)
Study title	A post-marketing, observational, retrospective, cohort study to assess the safety of Refortrix™ (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
Model ICF version number and date	**Version 1, 11 September 2015** **Replace with version and date of local ICF.**
Company Name	**GlaxoSmithKline (GSK) Biologicals S.A.**
Subject/Patient identification	**Insert subject/patient ID here**

INTRODUCTION

You are asked to take part in an epidemiological research study. You can decide if you want to take part in this study or not. Your choice will not change the quality of care that you will receive outside of this study. Please take time to read the following information about the study. Feel free to ask any questions that you may have.

What is informed consent?

Informed consent means agreeing to take part in an epidemiological study, but only when you fully understand the implications for yourself. You sign this informed consent form only if you agree to take part in a study. Signing the form shows that you have understood all implications and you want to take part. Before you decide to join a study, you can discuss everything you heard from your doctor or nurse with your family, elders, friends and other people you trust.

What is an epidemiological study?

Epidemiological studies are set up to help learn more about diseases and medical conditions that are public health concerns. This involves understanding the patterns, causes and effects of the disease in specific populations so that it can be controlled or prevented.

What is this study trying to find out?

GSK Biologicals' reduced-antigen-content dTpa vaccine, *Refortrix*, is a combination booster vaccine (a vaccine against more than one disease combined into one shot) indicated for individuals from the age of four years onwards against diphtheria, tetanus and pertussis diseases. It was first licensed for use in Germany in 1999. A number of

studies have shown that *Refortrix* is safe and effective. However, the effect of *Refortrix* has not been studied during pregnancy.

Vaccinating women during pregnancy may help in protecting the newborn against pertussis disease which can be very serious or even fatal in babies before they start their primary vaccination series against pertussis. This is because the antibodies (proteins produced in response to an antigen) produced by the mother are passed to the baby through the placenta (a temporary organ that joins the mother and baby and feeds the baby in the womb). Around 18 countries including the United States of America, New Zealand and the United Kingdom recommend routine Tdap vaccination for pregnant women.

This study will find out more information on the safety of this vaccine in pregnant women. About 2400 women will take part in the study. Among these, the data regarding pregnancy-related adverse events/birth outcomes from 1200 pregnant women in whom the vaccine was not administered will be compared to the same outcomes in 1200 pregnant woman in whom the vaccine was administered routinely.

Who is GSK?

GSK is a group of companies that makes and sells vaccines, medicines and other health products. The Belgian company GlaxoSmithKline Biologicals SA, which is part of GSK group, planned this study and pays for the study to happen. However, GlaxoSmithKline Biologicals SA may transfer specific rights and obligations resulting from this study to any company of the GSK group, including the right of access to and use of the data collected (through the data collection tool) from this study as stated below.

IF YOU DECIDE TO JOIN THIS STUDY

What do you need to do?

This is an observational, retrospective (collection of information recorded in the past) study involving the use of the relevant medical data from your medical records. This study does not involve any other procedures or tests. If you agree to participate you will need to sign this form on the last page. You will receive a copy of it.

What benefits can you expect?

There will be no direct benefit for you in taking part in this study.

This study will help us to learn more about the safety of this vaccine which is now routinely used in pregnant women in Brazil.

What side effects or risks can you expect?

This is a retrospective observational study which does not involve any medical procedures, administration of medication or collection of samples. Therefore, there are no foreseen risks involved in taking part in this study.

What about your personal and medical information?

If changes are made to this text it needs to be checked with the local Legal team that this is aligned with local rules and regulations. These changes must be discussed with the central study team and GSK Vaccines' ICF taskforce for alignment prior to the finalization of the local ICF, so that the impact for data sharing can be taken into account. Significant changes to this section must be documented in the Tracking Form.

It is very important that your personal and medical information stay confidential and secure. Your personal and medical information will be protected in accordance with current law.

When you sign this consent form you agree that your personal and medical information can be used as described here.

- Your personal and medical information may be checked by GSK and others (like agencies that approve and monitor studies). This is to make sure that the study is being run properly.
- Besides that, only the researchers at this study site can use information that identifies you (such as name and address) and only for the purpose of the study.
- Your information collected during the study will be labelled with a code number (for example, PPD It will not include your name or address. The study doctor will have the link between your name and the code number.
- The link between your name and the code number will not be shared. Only the code number and coded information will be sent to GSK.
- GSK will use your coded information for research only, including research looking at improving the quality and efficiency in conducting clinical research trials in general.
- GSK may:
  - keep it electronically, and analyse it by computer to find out what the study is telling us. This may be done by GSK or a third party, in which case GSK will ensure that the third party is required to keep your data secure.
  - share it with regulatory agencies that approve new vaccines and medicines,
  - share it with people who check that the study is done properly (like the independent ethics committee or review boards),
  - combine it with results from other studies to learn more about the vaccine and

related conditions. This may help us to assess the risks and benefits of GSK (or other) vaccines or medicines, or to improve disease understanding,

- publish study results in medical journals, for meetings and on the internet for other researchers to use. Your name will not appear in any publication.
- share coded information with other companies, organisations or universities to carry out research, including research looking at improving the quality and efficiency in conducting clinical research trials in general.

Personal and medical data collected during the epidemiological study may be moved to, stored and used in the country where you live or another country where GSK or those working with GSK work.

Use of this information may take place in countries with lower data protection rules than the country where you live. GSK will make sure that if your data are moved to another country, it will still be treated as stated in this Informed Consent Form.

A description of this epidemiological study will be available on the GSK Clinical Study Register http://www.gsk-clinicalstudyregister.com/ and may also appear in clinical trial registries in countries in which the epidemiological study is conducted.

A description of this epidemiological study will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

If you withdraw your consent for us to use your personal information you will no longer be able to continue in the study.

At any time, you may ask to see your personal information and correct it if necessary.

In some circumstances you may not be able to access your study information while the study is ongoing. However the study doctor will share any important medical information if it is relevant to your health during the course of the study.

LEGAL AND FINANCIAL MATTERS

Will you be paid for being in the study?

This section should be completed locally. State clearly what you will be providing to subjects as a result of their participation - Reimbursements for expenses incurred as a result of participation in the study for example, travel costs and money for wages lost due to visits to health facilities. The amount should be determined in agreement with the local legal team.

Can you share this information?

The information we give you belongs to GSK. We ask that you keep it private. But you can share it in confidence with your doctor, family or friends when you discuss about taking part in the study and your healthcare.

Who should you contact if you have questions?

Identify who the subject/ legally acceptable representative should contact for information about the study, the subject's rights or study-related injuries. This section may be completed at Country Level.

Person to contact for any questions: **Include name, address, telephone number.**

Person to contact about your rights: **Include name, address, telephone number.**

Consent statement

The study has been explained to me. I have read the information (or have had the information read to me). I have been given enough time to make a decision. I have had the chance to ask questions and I am satisfied with the answers. I am aware that I can change my mind at any time and stop taking part in the study without giving a reason. By signing this form I agree

- to take part in the study
- that my information is used as described in the form

Participant

Signature Date:

Thumb print (if participant cannot read or write):

Name:

I confirm that I have conducted the consent process according to applicable regulations.

Person conducting consent

Signature Date:

Name:

I confirm that I am independent of the study, that I attended the consent process and that I have read the information for the study.

Witness

Signature Date:

Name:

Delete the following Appendix in the Final local ICF.

Appendix A GlaxoSmithKline Vaccines Best Practices Document for the Development of the Local ICF

Introduction

The local informed consent form (ICF) is created based on the GSK Vaccines internally approved model ICF and is adapted according to country or local requirements.

The model ICF is the recommended content and structure which contains all ICH and GSK required elements and is aligned with the study protocol.

The content of the local ICF should be aligned with the Model ICF and any local specifications and regulations included.

The local GSK approved version should be submitted for ethical/regulatory approval and should be presented to the subject/patient and/or their legally acceptable representative.

It is essential that the version of the local ICF is accurately tracked, with a unique version number, date and reference to the model ICF on which it is based, to ensure that the correct version of the ICF is used and can be identified if needed.

It is strongly recommended to have a final local ICF, back-translated in English, available in the Investigator's study file to ensure site readiness in case of audits and/or inspections.

Objective

These best practices are intended to give adequate support and to ensure consistency while developing the local ICF from the model ICF.

It is a tool to know what changes are not permitted and what changes can be justified and/or are required per local regulations and site specific information.

The development of the accurate and complete local ICF is a local responsibility and alignment with the model ICF is essential to study conduct.

Any changes made to the local ICF from the model ICF must be documented at local level.

Human Sample Management

The collection of human tissue samples, the intended use, and secondary use, if retained, and how the subject's confidentiality would be maintained for the retained samples, must be reported in the ICF.

To avoid ethical and legal implications and invalidating the study data, any changes made to this section must be discussed with the central study team for alignment prior to the finalization of the local ICF.

Significant changes to this section must be documented in the Tracking Form.

Subject/patient data after withdrawal

The retention of samples collected and data recorded before withdrawal and the continued collection of safety information after withdrawal must be reported in the ICF. Check local regulations and seek local legal advice for the use of data after subject/patient withdrawal. If any changes are made to this section in response to a request from any source, these changes must be discussed with the central study team for alignment prior to the finalization of the local ICF, so that the impact for database collection and sample destruction can be taken into account.

Significant changes to this section must be documented in the Tracking Form.

What about your personal and medical information?

The content of this section is required by ICH-GCP and must be included in the ICF so that the subject is well informed before consenting to participation. Omitting this information would be violating the confidentiality and the data privacy of the subject/patient and could have legal implications. If any changes are made to this section in response to a request from any source, these changes must be discussed with the central study team for alignment prior to the finalization of the local ICF, so that the impact for data sharing can be taken into account.

Significant changes to this section must be documented in the Tracking Form.

Type of changes

Changes to the local ICF can be classified into 3 categories:

'Not permitted' changes

BOLD BLACK mandatory text in the model ICF should not be changed.

'Required' changes

Required changes must be made in the local ICF to add country-specific or center-specific information. (Indicated as **BOLD RED** text in the model ICF e.g. investigator details).

'Justified' changes

Justified changes may be necessary in some countries to comply with local requirements / regulations or to comply with a specific template e.g. country specific compensation guidance text.

In addition, some text can be clarified / simplified, provided the meaning remains the same as in the model ICF and does not contradict or change the intended meaning of the model ICF.

Changes that require a specific rationale or justification, that may be necessary in specific situations e.g. storage duration of samples, or changes required by the relevant Ethics Committees, can also be justified.

Best Practices per ICF Section

This table describes the type of changes (not permitted, required or justified) for each ICF section of the local ICF compared to the model ICF.

ICF section	Type of changes	Rationale/Impact
Study Identification		
Check if study identification is identical to Model ICF.	Not permitted	The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.
Study Title		
Check if study title is identical to Model ICF.	Not permitted	The study title allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.

ICF section	Type of changes	Rationale/Impact
Model ICF Version Number and Date		
Update with version and date of Local ICF and check if reference to the Model ICF version and date is included. Specify country and subset if applicable.	Required	It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.
Company Name		
Check if company name is GlaxoSmithKline (GSK) Biologicals S.A. or the local GSK affiliate if this is required by local regulations.	Justified	A change to this section is permitted if it is justified by local regulations. For some countries, the local GSK affiliate should be indicated as Company Name.
Subject/Patient Identification		
Check whether there is space foreseen to insert the subject ID.	Required	The subject/patient ID should be mentioned on the ICF to be able to link the subject/patient ID with the corresponding source documents and RDE entries.
Header		
Check if study identification in header is identical to Model ICF.	Not permitted	The study identification and study number allows us to link the document to the study protocol, the corresponding IRB/IEC approvals, all relevant study documentation and ensures that the subject/patient is linked to the correct study.

ICF section	Type of changes	Rationale/Impact
If applicable, insert specifics in case of multiple model ICFs	Justified	The document specifics (e.g. for a certain sub-cohort) are to be indicated in the header to ensure that the subject/patient is linked to the correct study specificity.
Footer		
Indicate version of Local ICF and check if reference to the Model ICF version is included. Specify country and subset if applicable.	Required	It is mandatory to include an ICF version number, the date of the final version, the page number and the total number of pages (for the Local and Model ICF). Each ICF type has to be uniquely identified and must include a reference to the source. The version of the local ICF allows us to link the ICF to the corresponding approval documents. If the version is omitted in the local ICF, the subject/patient may not receive the most up to date ICF and thus may not receive the complete information required to make an informed consent.
INTRODUCTION		
Explain the consent process and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	Freely given and written informed consent must be obtained from each subject/patient/LAR prior to study participation. Informed consent involves an education and information exchange that takes place between the researcher and the potential subject/patient. How the process of consenting looks like, needs to be explained in the ICF. The text can be simplified, if necessary.

ICF section	Type of changes	Rationale/Impact
Explain that the study involves research. Explain the purpose of the study. Explain the approximate number of subjects involved in the study. Explain the expected duration of the subject's participation in the study	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent.
What is this study trying to find out?		
Describe the study aim and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	Text can be simplified if necessary.
Who is GSK?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The role of the sponsor should be explained in this section. The text can be simplified if necessary.
IF YOU DECIDE TO JOIN THE STUDY		
Which vaccine/therapy will you be given?		
Explain the study treatment, the probability for random assignment to the treatments and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary
What do you need to do?		
Explain the study procedures to be followed including all invasive procedures. Explain the subject's responsibilities. Explain those aspects of the study that are experimental.	Justified	The content of this section is required by ICH-GCP. If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary

ICF section	Type of changes	Rationale/Impact
What benefits can you expect in the study?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. The reasonably expected benefits or indirect benefits or if there is no direct clinical benefit for the subjects/patients must be included in the local ICF. Text can be simplified if necessary
What side effects or risks can you expect?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. The reasonably foreseeable risks or inconveniences to the subject should be mentioned in the ICF. If any of this information is omitted in the local ICF, the subject may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
Check if the text on autoimmune diseases (applicable if product/vaccine contains an adjuvant) is identical to the Model ICF.	Not permitted	The text on autoimmune diseases has been approved by GSK upper management following feedback from Authorities. The pIMDwording should remain consistent in all projects and countries. There is a reputational risk associated to the fact that GSK might seem to be sharing different information with Subjects/Patients/Externally on AID.
Check if the text on *Rotarix*, if applicable, is identical to the Model ICF.	Not permitted	This text has been approved by GSK upper management following feedback from Authorities.

ICF section	Type of changes	Rationale/Impact
What about pregnancy and breastfeeding?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	If any of this information is omitted in the local ICF, the subject/patient may not receive the complete information required to make an informed consent. Text can be simplified if necessary.
Are there other vaccines/products or treatment?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	It is an ICH-GCP requirement to provide to the subject information on alternative procedures or treatment that may be available and their important potential benefits and risks. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.
Add currently available local alternatives, if applicable.	Required	This information must be added locally to the ICF using the most current information regarding the treatments that are available in the country.
Do you have to stay in the study?		
Explain voluntary participation and check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The content of this section is required by ICH-GCP. Omitting any of this information would be violating the rights of the subject/patient to freely participate to the study and would be putting the company reputation at risk. Text can be simplified if necessary.

ICF section	Type of changes	Rationale/Impact
Can you be asked to leave the study?		
Explain the foreseeable circumstances under which the subject's participation in the study may be terminated.	Justified	The content of this section is required by ICH-GCP. Text can be simplified if necessary.
What happens if you leave the study?		
Check if the text on the use of data after subject/patient withdrawal is identical to the Model ICF. [Check local regulations and seek local legal advice] [If the text needs to be changed it should be discussed with the central project team for alignment prior to the finalization of the local ICF].	Justified	The bold text in this section has been approved by Medical Governance. Changes to this section in response to a request from any source, can have an impact for database collection and sample handling and should therefore be discussed with the central teams for alignment. Also refer to the Clarification Paper on the Handling of Data after Subject Withdrawal. Significant changes to this section must be documented in the Tracking Form.
Who will be looking at the information from this study?		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary). [If the text needs to be changed, it should be reviewed by the local legal team]. [If the text needs to be changed it should be discussed with the central study team for alignment prior to the finalization of the local ICF].	Justified	The content of this section is required by ICH-GCP and must be included in the ICF so that the subject is well informed before consenting to participation. Omitting this information would be violating the confidentiality and the data privacy of the subject/patient and could have legal implications. Text can be simplified if necessary. Significant changes to this section must be documented in the Tracking Form.

ICF section	Type of changes	Rationale/Impact
What will happen with your blood and <other> samples?		
Check if all mandatory wording from the Model ICF is present in the Local ICF.	Not permitted	If this text is changed, there is a risk to use human samples outside the subject's/patient's consent. This has major ethical implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc. Significant changes to this section must be documented in the Tracking Form
Check if the QA (Quality Assurance), test improvement and new test method development in the scope of the study protocol is reported in the Local ICF.	Not permitted	This testing will be done at <u>all times</u>, assuming it is allowed as per individual subject's/patient's consent. If this testing is not mentioned in the ICF, there is a risk that GSK will be unable to perform the protocol tests and therefore this type of testing cannot be omitted. Also refer to the Clarification Paper on the future use of biospecimens.

ICF section	Type of changes	Rationale/Impact
Check Local regulations regarding storage duration. Check if the wording "for a maximum of 20 years" is not changed into "for 20 years". [If there are concerns regarding this text then this should be discussed with the central project team for alignment prior to the finalization of the local ICF]	Justified	It is necessary to put a defined storage period in the ICF. As a standard, GSK proposes to store samples for "for a maximum of "20 years. Attention should be paid to the used wording "**for a maximum of**" 20 years. This wording allows GSK to cover different situations (e.g. to keep samples for maximum 20 years, to destroy samples when GSK no longer wants to store them or no longer is interested in testing, when physical integrity of some type of samples does not permit such long storage, etc). Any changes to this section should be captured in the Sample Retention Period Form. This will allow the laboratory to take the appropriate measures for sample storage, "for a maximum of 20" years or as defined in the ICF and documented in the section called "other". Significant changes to this section must be documented in the Tracking Form

ICF section	Type of changes	Rationale/Impact
Check local regulations regarding future research. [If there are concerns regarding this text then this should be discussed with the central study team for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. However, the wording of the text itself should not be changed and nothing should be added! We capture this info in the CRF/eCRF, which contains standard wording so if the wording in the ICF is changed, this will not be matching. This form allows the central study team to track the actual testing at GSK (or laboratories used for GSK-sponsored studies) with the individual subject's/patient's consent and local regulations. If this text is changed, there is a risk to use human samples outside the subject's consent. This has major ethical and legal implications and can lead to a loss of company reputation, lack of confidence, invalid study data, etc. Also refer to the Clarification Paper on the future use of biospecimens.
LEGAL AND FINANCIAL MATTERS		
What happens if you get injured while taking part in this study?		
- For UK, US and countries without special local regulations, check if compensation section is not changed compared to the section in the Model ICF. [If changes are made, the CMD (Country Medical Department) should ensure that all local legal regulatory requirements are satisfied.]	Justified	The content of this section is required by ICH-GCP. In the UK and in countries where there is no local scheme, GSK will apply the Clinical Trial Compensation guidelines set down by the UK Association of British Pharmaceutical Industry (ABPI) to compensate subjects/patients for GSK sponsored clinical study related injury

ICF section	Type of changes	Rationale/Impact
- For other countries where there is compensation for injury, the CMD (Country Medical Department) should ensure that the rules and conventions required locally are applied.	Justified	The content of this section is required by ICH-GCP and must be completed so that the subject/patient is well informed before consenting to participation.
Will you be paid for being in the study?		
Information related to this section is added at a regional or country level.	Required	The content of this section is required by ICH-GCP and must be included in the ICF so that the subject/patient is well informed before consenting to participation. The anticipated prorated payment or other financial benefit, if any, to the subject for participating in the study should be mentioned in the ICF. Explain if expenses incurred by subjects for clinical visits made because of their participation in the study will be reimbursed or not.
Do you have to pay anything to be in the study?		
This section is optional. Information related to this section is added at a regional or country level when it is appropriate for a study and/or is required by local practice.	Justified	If appropriate for a study, include here information on cost/expenses that subject/patient will have to bear for taking part in the study i.e., whether the subject/patient or the subject's/patient's insurance will be charged for any study item or procedure. According to ICH-GCP, the anticipated expenses, if any, to the subject/patient for participating in the study should be mentioned.

ICF section	Type of changes	Rationale/Impact
Can you share this information?		
Explain that the subject is allowed to share information with his/her family, friends, doctor and/or healthcare.	Justified	If an IEC/IRB objects to the inclusion of the preferred text regarding GSK's intellectual property rights, the author informs the Global Patent representative in the project team and he/she or their manager may agree with the amendments or suggest an alternate wording within the designated period.
Who should you contact if you have questions?		
Add local contact details.	Required	The content of this section is required by ICH-GCP. The subject/patient must have a contact person for further information regarding the study, his rights and who to contact in the event of trial-related injury.
Consent statement		
Check if the meaning of the text is not changed compared to the Model ICF (Text can be simplified if necessary).	Justified	The consent statement should be aligned with ICH-GCP requirements. Omitting any of the information can have legal implications
Check local regulations regarding future research (type 4 testing). Check if the wording is identical to the wording in the body of the ICF. [If there are concerns regarding this text then this should be discussed with the central project team and GSK Vaccines' central ICF taskforce for alignment prior to the finalization of the local ICF]	Justified	A change to this section is justified, since depending on local regulations, this type of testing is allowed or not. This type of testing is optional for the subject/patient, meaning that if this testing is mentioned in the body of the ICF, a tick box should be available in the consent statement. The wording of the text itself, should not be changed and nothing should be added! We capture this info in the CRF/eCRF, which contains standard wording so if the wording in the ICF is changed, this will not be matching with the CRF/eCRF.

ICF section	Type of changes	Rationale/Impact
Check local regulations for the legal of age of consent, the use of LARs, witnesses and any documentation requirements.	Justified	An additional line can be added if two LARs or two witnesses are needed as per local law. Refer to SOP_54823 and local regulations.

MODULAR APPENDICES

List of modular appendices available for the study report and ICH-specific appendices - Study Information equivalent numbering

Modular appendices	ICH numbering
Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement	16.1.5
Individual listings	16.2

Statistical Analysis Plan

Study alias & e-track number(s): EPI-PERTUSSIS-037 VS BR (203153)

Detailed Title:	A post-marketing, observational, retrospective, cohort study to assess the safety of RefortrixTM (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.
SAP version	Final
SAP date	01-APR-2017
Scope:	All data pertaining to the above study.
Co-ordinating author:	<PPD (Biostatistician)>
Other author(s):	
Adhoc reviewers:	<PPD (Safety physician)>
Approved by:	<PPD (Epidemiologist)> <PPD (Lead statistician)>

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The complete statistical analysis plan and results presentation is divided into 2 parts: the first part detailing the analyses to be performed (known as SAP, current document) and a second part, annex (-es) (called TFL) describing the flow and format of tables, figures and listings to be annexed to the SR.

LIST OF ABBREVIATIONS

AE	Adverse event
ATP	According-To-Protocol
CI	Confidence Interval
CRF	Case Report Form
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
N.A.	Not Applicable
OR	Odds Ratio
PASS	Post-Authorisation Safety Study
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SR	Study Report
TC	Total Cohort
Tdap	Combined reduced-antigen-content diphtheria, tetanus and acellular pertussis (Tdap) vaccine
TSS	Targeted Safety Study
TFL	Tables Figures and Listing template annexed to SAP
UL	Upper Limit of the confidence interval

1. DOCUMENT HISTORY

Date	Description	Protocol Version
22-MAR-2017	Version 1	Final Version 1 11 September 2015

2. STUDY DESIGN

- Type of design: An observational, retrospective, cohort, single-centre study.
- This is a Targeted Safety Study (TSS) and a Post-Authorisation Safety Study (PASS).
- Study size: The planned sample size of this study is 2400 subjects. Using a two-sided (alpha = 0.01) test assuming the ratio of subjects in the Exposed cohort to the Unexposed cohort is 1:1 and assuming a background proportion of events in the Unexposed cohort to be 3%, a total of 2400 subjects [1200 subjects in each cohort], will be needed to have more than 80% power to detect a relative risk of 2 or higher.

The following group names will be used for the statistical analyses:

Group order in tables	Group label in tables	Group definition for footnote
1	Exposed Cohort	Pregnant women who had received Refortrix as part of the maternal immunization program in Brazil
2	Unexposed Cohort	Women pregnant before implementation of the maternal immunization program in Brazil who didn't receive Refortrix

The exposed cohort will be divided into co-vaccinated cohort and single-vaccinated cohort. The single-vaccinated cohort includes subjects who had received only Refortrix; and the co-vaccinated cohort includes subjects who had received Refortrix and other vaccination(s). This analysis will be performed depending on the number of subjects in each subgroup.

Group order in tables	Group label in tables	Group definition for footnote
1	Co-vaccinated exposed Cohort	Pregnant women who had received Refortrix and other vaccination(s) as part of the maternal immunization program in Brazil
2	Single-vaccinated exposed Cohort	Pregnant women who had received only Refortrix as part of the maternal immunization program in Brazil

3. OBJECTIVES

3.1. Co-primary objectives

- To compare the risk of gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum) in a cohort of women following vaccination with *Refortrix* 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).
- To compare 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.

3.2. Secondary objectives

- To describe the risk of pregnancy-related AEs/neonate-related events of interest (premature rupture of membranes, preterm premature rupture of membranes, premature uterine contraction, neonatal death, maternal death, still birth and neonatal hypoxic ischaemic encephalopathy) in the Exposed and Unexposed cohorts.
- To describe the risk of congenital anomalies in neonates in the Exposed and Unexposed cohorts.
- To describe the risk of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

4. ENDPOINTS

4.1. Co-primary endpoints

- Occurrence of any of the following pregnancy-related AEs in Exposed and Unexposed subjects.
  - Gestational diabetes.
  - Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome).
  - Pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum).
- Occurrence of any of the following outcomes in neonates from Exposed and Unexposed subjects.

- Preterm birth.
- Small for gestational age.

4.2. Secondary endpoints

- Occurrence of pregnancy-related AEs of interest/neonate-related events up to delivery in Exposed and Unexposed subjects.
  - Premature rupture of membranes.
  - Preterm premature rupture of membranes.
  - Premature uterine contraction.
  - Neonatal death.
  - Maternal death.
  - Still birth.
  - Neonatal hypoxic ischaemic encephalopathy.
- Occurrence of congenital anomalies in the neonates of Exposed and Unexposed subjects.
- Occurrence of pregnancy-related AEs and birth outcomes per calendar year in the Unexposed cohort.

5. STUDY POPULATION

5.1. Total Cohort (TC)

The TC will include all subjects enrolled in the study. All the information for these subjects will be entered in the eCRF.

5.2. According-To-Protocol (ATP) Cohort

The ATP cohort will include all the evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol).

The list of applicable elimination codes for each cohort can be found in the study specific form FORM-BIO-CLIN-9004-05 Criteria for eliminating subjects from the analyses.

Cohort	Elimination codes	Eli Type
ATP cohort for analysis	900, 2010	MA

6. STATISTICAL METHODS

All the statistical calculations will be done in SAS 9.2 or higher.

The primary analysis will be based on the Total cohort. Should the percentage of subjects excluded from the ATP cohort for analysis of safety be greater than 5%, a second analysis will be performed on the ATP cohort to complement the analysis of the Total cohort.

6.1. Analysis of demographics/baseline characteristics

The baseline and demographic characteristics of the Exposed and Unexposed cohorts will be tabulated in a summary of statistics.

- Frequency tables will be generated for categorical variables such as resident of the study area and previous pregnancies etc.

- Mean, median, standard deviation and range will be provided for continuous data such as maternal age and gestational age.

6.1.1. Demographic characteristics

The number of enrolled subjects as well as the number excluded from ATP analyses will be presented.

Demographic characteristics (age and resident of the study area) will be summarised using descriptive statistics (for all non-missing observations) overall and by group.

6.1.2. Clinical characteristics

The following tables will be generated for the following characteristics:

- General medical history

The percentage of subjects reporting any of the non-pregnancy related conditions, signs or symptoms or exanthematic diseases in the general medical history will be tabulated overall and by group. The diagnosis entry for before or during the pregnancy and the diagnosis entry details will be summarized overall and by group.

- Congenital anomalies

The percentage of subjects reporting any congenital anomalies (total, in the subjects, and/or for spouse, and/or for first degree relatives) will be described in a frequency table overall and by group.

- Obstetric history

The percentage of subjects who had previous pregnancies will be tabulated overall and by group. Among those who had previous pregnancies, the gravidity and parity number will be summarized and the percentage of subjects who had congenital anomalies, ectopic pregnancies, molar pregnancies, miscarriages will be tabulated.

The percentage of subjects who had events/complications (pre eclampsia, eclampsia, HELLP syndrome, infection, gestational diabetes, vaginal haemorrhage, premature rupture of membranes, preterm premature rupture of membranes, premature uterine contractions, pregnancy-related hypertension, neonatal death, neonatal hypoxic ischaemic encephalopathy) in previous pregnancies will also be tabulated overall and by group.

The percentage of subjects who had new born safety events (preterm babies, post term babies, new born with low birth weight, new born with birth weight > 4000 grams) will be summarized overall and by group in this section as well.

- Current pregnancy

The characteristics for current pregnancy will be described overall and by group. The characteristic include gestational age in weeks at the time of the present delivery, assisted fertilization, multiparity ultrasound, hospitalization, type of delivery, risk factors, habits, the use of illicit drugs, the use of chronic medications, etc.

- DTAP vaccination history and concomitant vaccination history

The percentage of subjects who had DTAP vaccination history, including the number of doses and gestational age at the time of vaccination will be summarized. Similar analysis will be performed for concomitant vaccination history. The percentage for co-vaccinated exposed cohort and single exposed cohort will also be tabulated.

6.2. Analysis of co-primary endpoints

The main analysis for co-primary objectives will contain only the subjects with vaccination date in the Exposed cohort and subjects from the Unexposed cohort. If more than 10% of subjects have missing vaccination date in the Exposed cohort, a sensitivity analysis will be performed using the imputed vaccination date to 27 completed weeks of gestational age to evaluate if this has any potential impact on the results.

The risk for each primary endpoint (gestational diabetes, pregnancy-related hypertension, pregnancy haemorrhage, preterm birth and small for gestational age) will be calculated for both exposed and unexposed cohorts. Similar analyses will be performed for co-vaccinated exposed cohort, single-vaccinated exposed cohort and unexposed cohort.

For each specific endpoint, the number of subjects where the event occurred [between the index date (refer to Annex 2 in protocol for definition of index date) and the date of the delivery] will be divided by the total number of subjects at risk for both the Exposed and Unexposed cohorts respectively, together with its exact 99% confidence interval (CI).

The co-primary endpoints of pregnancy (gestational diabetes, pregnancy-related hypertension and pregnancy haemorrhage) will be pooled together and of birth outcome (preterm birth and small for gestational age) will be pooled together in addition. The analysis of the risk for the pooled endpoints together with its exact 95% CI will be performed using the same method as for the separate co-primary endpoints.

The comparison of the risk with its two sided 99% CI of each primary endpoint between the Exposed cohort and the Unexposed cohort will be obtained by means of logistic regression model, using the exposure status as a binary independent variable in the model.

Univariate analyses will describe the association between the each primary endpoint and all potential risk factors such as: Tdap vaccination status, maternal age at the start of the pregnancy, parity and gestational age, congenital anomalies (in parents or first degree relatives), maternal comorbidities and complications during previous pregnancies, etc. In addition, potential interaction terms will be added if deemed necessary after exploring the data.

Afterwards, a multiple logistic regression model will be fitted with a backward selection to identify the possible confounding factors which were detected from the univariate analysis using an alpha level of 0.1. Adjusted odds ratio (OR) and its 95% CI will be derived from the final model.

6.3. Analysis of secondary endpoints

The risk for each secondary endpoint (pregnancy-related AEs and birth outcomes) will be calculated by the number of subjects with at least one of the events occurring between the index date (refer to Annex 2 in protocol for definition of index date) and the date of the delivery, corresponding to that endpoint divided by the total number of subjects at risk for both the Exposed and Unexposed cohort, together with its exact 95% CI. If more than 10% of subjects have missing vaccination date in the exposed cohort, a sensitivity analysis will be performed as for the co-primary endpoints.

In addition, the risk of all the co-primary and secondary endpoints will be calculated by calendar year as well to evaluate the stability among the Exposed (total, co-vaccinated and single-vaccinated) and Unexposed cohorts.

6.4. Sensitivity analysis

A sensitivity analysis will also be performed if more than 10% of the measurements are missing for each endpoint. In the first instance, missing outcomes will be imputed with a value of '0'. In the second instance, all missing outcomes will be imputed with a value of '1'. The risk for each endpoint will then be analysed using similar methods as mentioned in sections 6.2 and 6.3 for all the co-primary and secondary endpoints.

6.5. Additional analysis not in the protocol

- The index date was defined as 27 weeks completed (28 weeks) gestational age in the unexposed cohort. However, in the exposed cohort, some of the subjects had the vaccination dates at 27 gestational weeks. Therefore, a sensitivity analysis for the primary analysis will be performed by excluding these subjects who had vaccination date at 27 gestational weeks.

- The index date for exposed cohort will be the real vaccination date which is around 27-36 gestation weeks; however, the index date for unexposed cohort will be imputed to 27 completed gestation weeks; it means that the unexposed cohort will have longer mean follow up period .Therefore, there is a risk of higher number of observed events in the unexposed vs. the exposed cohorts which could underestimate the risk ratio estimate. Therefore, a sensitivity analysis will be added as to summarize the total Follow-up period between two cohorts and to calculate the total IR = total number of events/ total person-years.

- Summary table for the cross-tabulation of each endpoint (primary and secondary) between previous pregnancies and current pregnancy will be presented.

- Incidence tables will be presented for pregnancy-related adverse events and birth outcomes with/without concomitant vaccination overall and separately, diphtheria-tetanus vaccination, hepatitis B vaccination in the exposed cohort.

7. STATISTICAL CALCULATIONS

7.1. Methodology for computing CI

All CI will be two sided 99% CI for co-primary objectives analysis and 95% CI for the other analyses.

7.1.1. Confidence interval for risk

The analysis of the risk for each specific endpoint will be performed using exact 99% confidence interval (CI).

If *n* is the number of subjects where the event occurred among the total number of subjects *N*, the risk can be estimated by *n/N*. Its exact *(1-α)%* confidence interval is obtained from:

*CINV(α /2,2*n)/2/N* as the lower boundary

and

CINV((1-α /2),2(n+1))/2/N* as the upper boundary.

where *CINV(probability, degrees of freedom)* returns the inverse of the chi-squared probability distribution and α is the type I error rate.

The comparison of the risk with its two sided 99% CI of each specific endpoint between the Exposed cohort and the Unexposed cohort will be obtained by means of logistic regression model, using the exposure status as a binary independent variable in the model.

Logit P=a+bx, *x* is exposure status

Where regression coefficient b is a log OR (it means that *exp(b)* is OR), 99%CI of OR will be exp(b ± 2.58*se(b)).

7.2. Number of decimals

The following decimal description will be used for the analyses.

Parameters	Number of decimal digits
% of count, including LL & UL of CI	2
p-value	3
Minimum, maximum, range	Number of decimals in the raw data
Mean, median	Number of decimals in the raw data +1
SD	Number of decimals in the raw data +2

LL = Lower Limit UL = Upper Limit CI = Confidence Interval
SD = Standard deviation

7.3. Handling of missing data

Missing or non-evaluable primary and secondary outcome measurements will not be replaced. Therefore, the main analysis will exclude subjects with missing or non-evaluable data.

For subjects in the Exposed cohort whose date of the vaccination is not available, it will be imputed to the 27th completed gestational week as the recommended start time for the vaccination for the sensitivity analysis.

7.4. Derived and transformed data

- Index date: For the Exposed cohort, the index date will be the date of Refortrix vaccination given as part of the maternal immunization program in Brazil. For the Unexposed cohort, the gestational age of 27 completed weeks will be considered as the index date.

- For Primary pregnancy-related AEs endpoints: Gestational diabetes, Pregnancy-related hypertension (including pre-eclampsia, eclampsia and HELLP syndrome), and Pregnancy haemorrhage (ante-partum (after 24 weeks of gestation), intra-partum or post-partum), only the events after the index date will be selected for the analysis for this co-primary objective.

- Subjects had at least one pre-eclampsia and/or eclampsia and/or HELLP syndrome will be counted once for the analysis for pregnancy-related hypertension endpoint. The worst event among pre-eclampsia, eclampsia and HELLP will be counted for summary of the event. For example, if a subject had one episode of pre-eclampsia and one episode of eclampsia, this subject will be summarized to have the episode of eclampsia as this is the worst event during the study period.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

The statistical analyses will be performed when all data are available. All analyses will be performed on final and clean data.

Description	Analysis ID	Disclosure Purpose	Reference for TFL
Final Analysis	E1_01	Statistical analysis report	All tables from TFL dated xxxxxx

8.2. Statistical considerations for interim analyses

No interim analyses are planned for this study.

Annex 10 Report sign-off

Investigator Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: A post-marketing, observational, retrospective, cohort study to assess the safety of *Refortrix* (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.

Study: 203153 (EPI-PERTUSSIS-037 VS BR) Development Phase: IV

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Investigator:	Mauro Sancovski
Affiliation /investigational center:	Professor Titular da Disciplina de Obstetrícia da Faculdade de Medicina do ABC
Signature of Investigator:	PPD
Date:	13/Mar/2018

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Sponsor Signatory Approval Page

Please note that by signing this page, you take responsibility for the content of the Study Report, including appendices

STUDY TITLE: A post-marketing, observational, retrospective, cohort study to assess the safety of *Refortrix* (Tdap) when administered during pregnancy in a maternal immunization program in Brazil.

Study: 203153 (EPI-PERTUSSIS-037 VS BR) Development Phase: IV

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name of Sponsor Signatory: Narcisa Mesaros

Title of Sponsor Signatory: Clinical and Epidemiology R&D Project Lead, DTP, Polio and Hib containing vaccines - R&D Centre Belgium,

PPD SmithKline Biologicals, SA
PPD

Signature:

Date: 12-MAR-2018

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