TITLE PAGE

Division: Research and Development

Information Type: Non-Interventional PASS Protocol

Title:	An OTIS/MotherToBaby Pregnancy Registry-based observational cohort study to evaluate pregnancy and infant outcomes in individuals exposed to *Boostrix* as of the 1st day of the 27th week of gestation in the US (EPI-PERTUSSIS-075 VS US PR)
Compound Number:	776423
Development Phase	IV
Effective Date:	23 January 2023
Subject:	Safety in pregnancy
Author(s):	PPD, PhD, MPH

PASS INFORMATION

Title	An OTIS/MotherToBaby Pregnancy Registry-based observational cohort study to evaluate pregnancy and infant outcomes in individuals exposed to *Boostrix* as of the 1st day of the 27th week of gestation in the US
Protocol version identifier	219588 (EPI-PERTUSSIS-075 VS US PR)
Date of last version of protocol	Final: 23 January 2023
EU PAS (ENCEPP) register number	To be confirmed
Active substance	J07AJ52, pertussis, purified antigen, combinations with toxoids
Medicinal product	US *Boostrix* Vaccine
Product reference	Not applicable
Procedure number	Not applicable
Marketing authorisation holder(s)	GlaxoSmithKline (GSK) Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
Joint PASS	No
Research question and objectives	How do selected pregnancy and neonatal/early infant safety outcomes among pregnancies enrolled in the Organization of Teratology Information Specialists (OTIS) / MotherToBaby Pregnancy Registry who were vaccinated with the *Boostrix* Tdap vaccine on or after the 1st day of the 27th week of pregnancy compare to pregnancies unexposed to any Tdap vaccine during pregnancy? Study Objectives: • The **primary objectives** of the study are to evaluate if there is an increased risk for preterm birth, small for gestational age infants, or stillbirth in pregnancies exposed to *Boostrix* vaccination on or after the 1st day of the 27th week of gestation when compared to a cohort of individuals unexposed to any Tdap vaccine during their pregnancy.

	• The **secondary objectives** of the study are to evaluate if there is an increased risk of preeclampsia/eclampsia, premature rupture of the membranes, chorioamnionitis, neonatal sepsis, neonatal death, or neonatal intensive care admission for bronchopulmonary dysplasia in pregnancies exposed to *Boostrix* vaccination on or after the 1st day of the 27th week of gestation when compared to a cohort of individuals unexposed to any Tdap vaccine during their pregnancy.
Countries of study	United States
Author	PPD, PhD, MPH Professor of Pediatrics School of Medicine University of California San Diego 9500 Gilman Drive, MC 0828 La Jolla, CA 92093 Tel: PPD Email: PPD

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder(s)	GlaxoSmithKline (GSK) Biologicals Rue de l'Institut 89 1330 Rixensart, Belgium
MAH contact person	PPD PPD Vaccines Epidemiology, GSK GlaxoSmithKline Biologicals SA Rue de l'Institut 89 1330 Rixensart, Belgium

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
CA	California
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
EU	European Union
FDA	Food and Drug Administration
GA	Gestational Age
GSK	GlaxoSmithKline
HCP	Healthcare Provider
HR	Hazard Ratio
ICSR	Individual Case Safety Reports
IPW	Inverse Probability Weighting
IRB	Institutional Review Board
KPSC	Kaiser Permanente Southern California
LMP	Last Menstrual Period
MAH	Market Authorization Holder
NCHS	National Center for Health Statistics
NICU	Neonatal Intensive Care Unit
OTIS	Organization of Teratology Information Specialists
PASS	Post-Authorization Safety Studies
PROM	Premature Rupture of Membranes
PS	Propensity Score

PTB	Preterm Birth
RR	Relative Risk
SAP	Statistical Analysis Plan
SGA	Small for Gestational Age
SMD	Standardized Mean Differences
SOP	Standard Operating Procedure
US	United States
VAERS	Vaccine Adverse Event Reporting System

TRADEMARK INFORMATION

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1. RESPONSIBLE PARTIES

Sponsor

The Marketing Authorization Holder (MAH) will serve as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Primary contact:

PPD, PPD Vaccines Epidemiology, GSK

Email: PPD

Study Coordination.

The MAH has contracted with the University of California Research Center for the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Studies to provide scientific leadership and to conduct the study. The OTIS/MotherToBaby Research Center will conduct the study with review and input from the MAH.

The OTIS/MotherToBaby Research Center will use a combination of previously collected data as well as newly collected data using the same standard protocol. Participants are recruited from referrals into the OTIS/MotherToBaby Research Center, some of which come through the North American OTIS/MotherToBaby network of teratogen information counseling services. The North American OTIS/MotherToBaby network is a university and health department-based group of telephone information centers serving pregnant women and health care providers throughout the US and Canada. The OTIS/MotherToBaby network receives voluntary reports of pregnancy and exposures from women and health care providers.

Principal Investigator:

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Email: PPD

1.1. SPONSOR SIGNATORY

Title:	An OTIS/MotherToBaby Pregnancy Registry-based observational cohort study to evaluate pregnancy and infant outcomes in individuals exposed to *Boostrix* as of the 1st day of the 27th week of gestation in the US
Compound Number:	776423

Carol Koro, PhD
VP, Head of Vaccines Epidemiology

Date (DD Month YYYY)

Peggy Webster, MD
VP Head of Clinical Safety and Pharmocovigilance

Date (DD Month YYYY)

Note: Not applicable if an eSignature process is used to get the sponsor approval.

1.2. SPONSOR INFORMATION PAGE

Study ID: 219588 (EPI-PERTUSSIS-075 VS US PR)

Sponsor Legal Registered Address:

GlaxoSmithKline (GSK) Biologicals SA
Rue de l'Institut 89
1330 Rixensart, Belgium

Sponsor Contact Address

GlaxoSmithKline Biologicals SA
Avenue Fleming 20
1300 Wavre
Belgium
Tel: +32 10 85 51 11

Sponsor Medical Monitor Contact Information:

Refer to Safety Management Plan for details

Sponsor Serious Adverse Events (SAE) Contact Information:

Refer to Safety Management Plan for details

Regulatory Agency Identifying Number(s): Not applicable

1.3. INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

PPD

Investigator Signature	Date

1.4. STUDY ADVISORY COMMITTEE

The study *Boostrix* EPI-PERTUSSIS-075 VS US PR will use an independent existing external Scientific Advisory Board under the Vaccines and Medication in Pregnancy Surveillance System (VAMPSS) that provides oversight for the study and reviews study summary data on an annual basis. Members of the Board provide advice to the Registry investigators on interpretation of the data and provide advice on strategies for the dissemination of information regarding the study.

The VAMPSS Scientific Advisory Board is managed by the American Academy of Allergy, Asthma and Immunology. The Scientific Advisory Board is comprised of membership representing specialization in maternal fetal medicine, biostatistics, vaccine epidemiology, and representation from the Centers for Disease Control, National Institutes of Health/Child Health Institute, the American Academy of Pediatrics, and a consumer representative. The Board is chaired by a designated member, and each member has one vote. A dedicated charter describes roles and responsibilities of the Board members, and members complete conflict of interest disclosures on an annual basis.

2. ABSTRACT

Protocol Title: An OTIS/MotherToBaby Pregnancy Registry-based observational cohort study to evaluate pregnancy and infant outcomes in individuals exposed to *Boostrix* as of the 1st day of the 27th week of gestation in the US.

Rationale and Background

In June 2011, the U.S. Advisory Committee on Immunization Practices (ACIP) recommended immunization of pregnant women against pertussis (CDC, 2013). In 2012, the ACIP recommended that the Tdap vaccine be given to women during every pregnancy (preferably between 27-36 weeks' gestation). Since 2014 the maternal Tdap uptake measured by surveys conducted by the US Centers for Disease Control (CDC) has plateaued at 55% (Baïssas, 2021). Two Tdap vaccine brands are used for immunization during pregnancy in the US (CDC, 2017).

Based on current available evidence on the safety of *Boostrix* maternal immunization and the recommended gestational timing of administration of Tdap vaccine in pregnancy, there is specific interest in acquiring more safety data in a registry-type study regarding the risk of preterm birth (PTB), small for gestational age infants (SGA), stillbirth, preeclampsia/eclampsia, premature rupture of the membranes (PROM), chorioamnionitis, neonatal sepsis, neonatal death and neonatal intensive care unit (NICU) admission for bronchopulmonary dysplasia.

GSK proposes a registry study with PTB, SGA infants and stillbirth as the primary outcomes, and preeclampsia/eclampsia, PROM, chorioamnionitis, neonatal sepsis, neonatal death and NICU admission for bronchopulmonary dysplasia as the secondary outcomes. These outcomes were selected based on the current knowledge on the safety of Tdap vaccination during pregnancy, adverse events reported into the Vaccine Adverse Event Reporting System (VAERS) and the biological plausibility for the exposure timing of interest. This registry study EPI-PERTUSSIS-075 VS US PR will be established in collaboration with the OTIS/MotherToBaby Research Center, an organization with well-established measures proven to efficiently retain participants and provide more complete and meaningful data than the initial pregnancy registry established in 2005 (Kuznetsova, 2022).

Information regarding the safety of *Boostrix* in human pregnancy is essential from a public health perspective to help inform clinical practice.

Research question and Objectives

The overall aim of the study is to determine whether the risks of pregnancy and neonatal/ early infancy safety outcomes are increased among pregnant people in the Organization of Teratology Information Specialists (OTIS) / MotherToBaby Pregnancy Registry who were vaccinated with the *Boostrix* vaccine on or after the 1st day of the 27th week of pregnancy. The primary objectives of the study are to evaluate if there are increased risks for PTB, SGA infants, or stillbirth after *Boostrix* vaccination on or after the 1st day of the 27th week of pregnancy when compared to a cohort of pregnancies unexposed to any Tdap vaccine during pregnancy. The secondary objectives of the study are to evaluate the

risks of preeclampsia/eclampsia, PROM, chorioamnionitis, neonatal sepsis, neonatal death, or NICU admission for bronchopulmonary dysplasia following receipt of the *Boostrix* vaccine on or after the 1st day of the 27th week of pregnancy when compared to a cohort of pregnancies unexposed to any Tdap vaccine during pregnancy.

Study Design

This is an observational cohort study of pregnancy and neonatal/early infancy outcomes in pregnancies with exposure to the *Boostrix* vaccine as well as pregnancies not exposed to a Tdap vaccine using data from the OTIS/MotherToBaby Pregnancy Registry. The incidence rates of maternal and infant outcomes for pregnancies exposed to the *Boostrix* vaccine on or after the 1st day of the 27th week of pregnancy until the end of pregnancy will be compared to those observed in a comparator cohort unexposed to any Tdap vaccine during pregnancy.

Population

The study population includes pregnant women participating in the OTIS/MotherToBaby Pregnancy Registry on or after 08 March 2004 (i.e., first date of enrollment into OTIS/MotherToBaby Pregnancy Studies) who meet study inclusion and exclusion criteria. The OTIS/MotherToBaby Pregnancy Registry includes women who reside in the US. The two cohorts of participants enrolled and followed for pregnancy and infant outcomes include: 1) pregnant individuals vaccinated with *Boostrix* on or after the 1st day of the 27th week of gestation, 2) pregnant individuals unexposed to any Tdap vaccine throughout their pregnancy.

Variables

Exposure will be defined as receipt of the *Boostrix* vaccine confirmed by maternal report and/or medical record, with information on the gestational timing of administration and date of vaccination captured. Pregnancy and infant outcomes of interest include PTB, stillbirth, SGA infants, preeclampsia/eclampsia, PROM, chorioamnionitis, neonatal sepsis, neonatal death and NICU admission for bronchopulmonary dysplasia.

Information on study outcomes will be obtained by maternal report and/or medical record review. Potential confounders or covariates to be collected include maternal age, race/ethnicity, pre-pregnancy body mass index, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, maternal exposures (including medication, vaccine,vitamin/mineral, and illnesses), and prenatal tests.

Data Sources

This study will use data collected as part of the OTIS/MotherToBaby Pregnancy Registry from maternal interviews, medical records (obstetric, delivery hospital, pediatric, and vaccine provider if applicable), and pregnancy exposure diary.

Study Size and Timing

The target sample size in each of the study cohorts are as follows: 1,500 pregnant individuals exposed to *Boostrix* on or after the 1st day of the 27th week of pregnancy and 1,500 pregnant individuals not exposed to any Tdap vaccine throughout their pregnancy. Each study cohort will consist of approximately 600 participants in each cohort that have previously been enrolled in the OTIS/MotherToBaby Pregnancy Registry before the end of pregnancy, have completed their pregnancies, have met the eligibility criteria, and have sufficient medical record and exposure data to meet the study objectives. An additional 900 participants per cohort will be enrolled over four years, with enrollment occurring before the end of pregnancy, have met the eligibility criteria, and have sufficient medical record and exposure data to meet study objectives.

Data Analysis

Demographic and other maternal characteristics will be compared between the two cohorts. The outcome analyses include:

1. comparison of proportion of PTBs among those enrolled prior to 37 weeks' gestation and resulting in a live born singleton infant between the *Boostrix*-exposed cohort and the comparison cohort by calculating hazard ratios and associated 95% confidence intervals.
2. comparison of proportion of stillbirths between the *Boostrix*-exposed cohort and the comparison cohort by calculating relative risks and associated 95% confidence intervals.
3. comparison of proportion of SGA infants ($\leq$10th centile for sex and gestational age) on birth weight, length, and head circumference among live born singletons between the *Boostrix*-exposed cohort and the comparison cohort by calculating relative risks and associated 95% confidence intervals.
4. comparison of proportion of preeclampsia/eclampsia diagnosed after the 1st day of the 27th week of gestation in pregnancies ending in livebirth or stillbirth between the *Boostrix*-exposed cohort and the comparison cohort by calculating relative risks and associated 95% confidence intervals.
5. comparison of proportion of cases of chorioamnionitis in pregnancies ending in livebirth or stillbirth between the *Boostrix*-exposed cohort and the comparison cohort by calculating relative risks and associated 95% confidence intervals.
6. comparison of proportion of PROM occurring after the 1st day of the 27th week of gestation in pregnancies ending in livebirth or stillbirth between the *Boostrix*-exposed cohort and the comparison cohort by calculating relative risks and associated 95% confidence intervals.
7. comparison of proportion of cases of neonatal sepsis occurring in pregnancies ending in live birth including twins or higher order multiples between the *Boostrix*-exposed cohort and the comparison cohort by calculating relative risks and associated 95% confidence intervals.

8. comparison of proportion of neonatal deaths occurring in pregnancies ending in live birth including twins or higher order multiples between the *Boostrix*-exposed cohort and the comparison cohort by calculating relative risks and associated 95% confidence intervals.
9. comparison of proportion of NICU admissions for bronchopulmonary dysplasia occurring in pregnancies ending in live birth including twins or higher order multiples between the *Boostrix*-exposed cohort and the comparison cohort by calculating relative risks and associated 95% confidence intervals.

Initial analysis will be unadjusted. Adjusted analyses will be conducted where numbers of events permit, multivariable analyses will be conducted to adjust for possible confounders.
For the *Boostrix*-exposed cohort, follow-up time with respect to the primary and secondary outcomes will start on the date of *Boostrix* vaccination, and for the comparator cohort, follow-up time will start on the 1st day of the 27th week of gestation.

Milestones

Planned dates of study milestones:

- Start date of data collection: 01 March 2023
- Last date of data collection: 31 December 2027
- Annual progress report submission: Annually beginning December 2023 through December 2027
- Final study report submission: 31 August 2028

3. AMENDMENTS AND UPDATES

Not applicable.

4. MILESTONES

Milestone	Planned date
Start of data collection	01 March 2023[1]
End of data collection	31 December 2027[2]
Study enrollment report	Monthly until end of recruitment
Annual status report of Postmarketing Requirements/Commitments due By:	06 December 2023 06 December 2024 06 December 2025 06 December 2026 06 December 2027
Registration in the European Union post-authorization studies (EU PAS) register	To be confirmed
Final study report submission	31 August 2028

[1] Pregnant women participating in the OTIS/MotherToBaby Pregnancy Registry on or after 08 March 2004 are eligible for study inclusion; however, selection of the 600 eligible pregnancies in each cohort from those enrolled prior to 01 March 2023 will be prioritized to include most recent years of enrollment. The start of data collection is defined as the planned date for starting data review for the first annual progress report.

[2] The end of data collection is defined as the planned date on which the analytic dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the study objectives.

5. RATIONALE AND BACKGROUND

5.1. Background

A US *Boostrix* pharmacovigilance pregnancy registry was initiated in 2005 (Kuznetsova, 2022) when *Boostrix* was licensed in the United States (US) for active booster immunization against diphtheria, tetanus, and pertussis (Tdap) in individuals aged 10 years and older. In June 2011, the US Advisory Committee on Immunization Practices (ACIP) recommended immunization of pregnant women against pertussis as a mean to protect their infants, who are vulnerable until they can receive their primary vaccination. (CDC, 2013). In October 2012, ACIP recommended that the Tdap vaccine be given to women during every pregnancy (preferably between 27–36 weeks gestation). Since 2014 the maternal Tdap uptake measured by surveys conducted by the US Centers for Disease Control (CDC) has plateaued at 55% (Baïssas, 2021). Two Tdap vaccine brands are used for immunization during pregnancy in the US (CDC, 2017).

The previous *Boostrix* US pregnancy registry EPI-PERTUSSIS-028 VS US PR (201327) was aimed at assessing the proportion with any abnormal pregnancy outcomes among registered pregnancies (women vaccinated with *Boostrix* during pregnancy or within 28 days preceding conception). From May 2005 to August 2019, 1,517 (1,455 prospective

and 62 retrospective) pregnancy reports were received from the pregnancy registry (Kuznetsova, 2022). Of the prospective reports, there were 1,188 lost to follow-up and 250 had known outcomes: 244 live infants with no apparent birth defects, 3 live infants with birth defects, and 3 spontaneous abortions with no apparent birth defects. Data from the *Boostrix* US pregnancy registry EPI-PERTUSSIS-028 VS US PR (201327) raised no safety concerns regarding *Boostrix* maternal immunization (Kuznetsova, 2022). However, the findings from the registry were limited by the modest number of follow-up reports (N=250) and the lack of representativeness of all pregnancies, the high proportion of loss to follow-up and the absence of a comparison cohort who were unexposed to Tdap vaccination during pregnancy.

On October 7 2022, the US Food and Drug Administration approved *Boostrix* for immunization during the third trimester of pregnancy to prevent pertussis in infants younger than two months of age (US FDA, 2022). This revised registry aims at monitoring the safety of *Boostrix* in this indication and is a postmarketing commitment.

To date, no specific safety concerns have been identified for Tdap maternal immunization (Vygen-Bonnet, 2020; Hall, 2020; Mohammed, 2021; Fakhraei, 2021), including *Boostrix*-specific studies (Perrett, 2020a; Perrett, 2020b; Petousis-Harris, 2019; Sancovski, 2019; Tseng, 2022).

The *Boostrix*-specific studies also include a large observational study (NCT03463577) conducted in the US by Kaiser Permanente Southern California (KPSC) in which the safety of *Boostrix* was assessed in 16,606 pregnant individuals who received *Boostrix* on or after the 27th week of pregnancy in 2018–19 compared with a historical cohort of individuals who were pregnant in 2012–14 and did not receive any Tdap vaccine during their pregnancy (Tseng, 2022). The study assessed a wide range of feto-maternal and neonatal outcomes. Overall, the study results support the safety of *Boostrix*.

For *Boostrix* specifically, the study conducted at KPSC found an elevated adjusted relative risk (aRR) for intra-uterine infection (aRR = 1.28, 98.75% confidence interval [CI]: 1.12–1.47) within the pre-determined significance levels (the upper limit of the 98.75% CI for the aRR was below 2) and this increase was consistent with the background increasing trend of this diagnosis among all pregnant individuals at KPSC since 2011 (before the study vaccination period). This may reflect improved obstetric care. The other *Boostrix*-specific studies, including a clinical trial in pregnant subjects (Perrett, 2020a) and a population-based observational study in New Zealand (Griffin, 2018), did not find evidence of an increased risk.

The new registry study is intended to add to the existing safety data for *Boostrix* as compared to the US pregnancy registry EPI-PERTUSSIS-028 VS US PR (201327) and will be established in collaboration with the OTIS/MotherToBaby Research Center, an organization with well-established measures proven to efficiently retain participants and provide more complete and meaningful data.

5.2. Rationale

The purpose of this registry-based study is to monitor pregnancies exposed to *Boostrix* with exposure in the recommended window of administration and in line with its indication in the US (i.e., immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age). Endpoints were selected based on the current state of knowledge of the safety of *Boostrix* administered to individuals in their third pregnancy trimester and include potentially biologically plausible maternal and neonatal/ early infancy outcomes considering the timing of exposure.

6. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to examine how selected pregnancy and neonatal/early infant safety outcomes among pregnancies enrolled in the Organization of Teratology Information Specialists (OTIS) / MotherToBaby Pregnancy Registry who were vaccinated with the *Boostrix* Tdap vaccine on or after the 1st day of the 27th week of pregnancy compared to pregnancies unexposed to any Tdap vaccine during the same period, or earlier in pregnancy.

Study Objectives:

- The **primary objectives** of the study are to evaluate if there is an increased risk for preterm birth, small for gestational age infants, or stillbirth in pregnancies exposed to *Boostrix* vaccination on or after the 1st day of the 27th week of gestation when compared to a cohort of individuals unexposed to any Tdap vaccine during their pregnancy.
- The **secondary objectives** of the study are to evaluate if there is an increased risk of preeclampsia/eclampsia, premature rupture of the membranes, chorioamnionitis, neonatal sepsis, neonatal death, or neonatal intensive care admission for bronchopulmonary dysplasia in pregnancies exposed to *Boostrix* vaccination on or after the 1st day of the 27th week of gestation when compared to a cohort of individuals unexposed to any Tdap vaccine during their pregnancy.

These outcomes were selected based on the current knowledge on the safety of Tdap vaccination during pregnancy, adverse events reported into the Vaccine Adverse Event Reporting System (VAERS) and the biological plausibility for the exposure window of interest.

7. RESEARCH METHODS

7.1. Study Design

This study is an observational cohort study of pregnancy and neonatal/early infancy safety outcomes in pregnant women in the OTIS/MotherToBaby Pregnancy Registry who received the *Boostrix* vaccine any time on or after the 1st day of the 27th week of pregnancy. The comparator cohort includes pregnant women who received no Tdap vaccine from the first day of LMP to the end of pregnancy. The incidence rates of

maternal and infant outcomes for pregnancies exposed to the *Boostrix* vaccine on or after the 1st day of the 27th week of pregnancy until the end of pregnancy will be compared to those observed in a comparator cohort unexposed to any Tdap vaccine during pregnancy. The target sample size for the study by the end of a four-year recruitment period is 3,000 participants: 1,500 pregnant women in the *Boostrix* vaccine exposure cohort and 1,500 pregnant women in the Tdap vaccine-unexposed comparator cohort.

The study will be conducted by OTIS/MotherToBaby Research Center located at the University of California San Diego. The registry relies on voluntary reporting of pregnancy and exposures by women and health care providers who contact the North American OTIS/MotherToBaby Pregnancy Studies, or the MotherToBaby network.

The study design is appropriate for the study objectives in that mothers are enrolled in the OTIS/MotherToBaby Registry before the outcome of pregnancy is known, direct measures of relative and absolute risk can be computed, and a range of adverse pregnancy outcomes can be evaluated.

The study design includes the identification of women with *Boostrix* vaccine exposure on or after the 1st day of the 27th week of pregnancy, and a comparison group without exposure to a Tdap vaccine from the first day of LMP to the end of pregnancy.

Women who agree to enroll are consented verbally over the telephone and complete the initial telephone interview. Depending on the gestational timing of enrollment, several subsequent telephone interviews are conducted during pregnancy and after birth. Participants are also asked to maintain a pregnancy diary to supplement maternal interview data. Medical records for both the women and infant are obtained and abstracted for information to validate exposures and outcomes. Enrolled women are followed until the completion of pregnancy and follow-up for live born infants in this study will be up to 2 months after birth to determine infant outcomes.

7.2. Study Population and Setting

This study will use data that are collected as part of the existing OTIS/MotherToBaby Pregnancy Registry (described further in Section 7.4 Data Source) and housed in a structured database for analysis. The Registry includes pregnant women who reside in the US and allows for direct capture of information from participants through various health interviews as well as complementary information from a pregnancy diary. To obtain information provided by the treating physicians, data are also collected from medical records of pregnant women meeting the inclusion criteria and their infants.

When pregnant women are in contact with the OTIS/MotherToBaby Research Center, enrollment in the OTIS/MotherToBaby Pregnancy Registry is voluntary and requires informed consent of the pregnant woman.

The study population consists of two cohorts of pregnant women:

- **Cohort 1** – *Boostrix* vaccine exposed and

- **Cohort 2** – unexposed (no Tdap vaccine during pregnany) (See Section 7.5 for sample size).

Participants will be included into the two cohorts based on the following inclusion/exclusion criteria:

7.2.1. Inclusion/exclusion criteria

All participants must meet the following criteria to be eligible for inclusion in the study:

- Reside in the US at the time of enrollment
- Enrolled in the OTIS/MotherToBaby Pregnancy Registry and currently pregnant at the time of enrollment on or after 08 March 2004
- Pregnancy ending in either livebirth or stillbirth
- Availability of medical records for that pregnancy including from obstetric provider, hospital of delivery and pediatric provider

The study sample will consist of approximately 600 participants in each cohort that have previously been enrolled in the OTIS/MotherToBaby Pregnancy Registry before the end of pregnancy, have completed their pregnancies with either a livebirth or stillbirth outcome, and have sufficient medical record and exposure data to meet the study objectives. An additional 1,800 participants (900 in each cohort) will be enrolled over four years; these participants will enroll before the end of pregnancy, have completed their pregnancies with either a livebirth or stillbirth outcome, and have sufficient medical record and exposure data to meet the study objectives.

- Selection for consideration for inclusion of the 600 pregnancies in each cohort from those previously enrolled in the OTIS/MotherToBaby Pregnancy Registry will be made solely on the following criteria irrespective of pregnancy outcome
  - Pregnancy continuing as of the 1st day of the 27th week of gestation
  - Availability of data on Tdap vaccination status on or after the 1st day of the 27th week of gestation
  - If vaccinated, data available to document Tdap vaccination brand
  - Availability of the required medical records from obstetric, hospital and pediatric providers
  - Selection starting with most recent year of enrollment until sample size is met

Cohort 1: *Boostrix*-Exposed group

Inclusion Criteria

- Currently pregnant women at the time of enrollment who contacted the OTIS/MotherToBaby Research Center and who have documented exposure to *Boostrix* brand Tdap vaccination on or after the 1st day of the 27th week of pregnancy.

- Currently pregnant women at the time of enrollment who agreed to the conditions and requirements of the study including informed consent, the interview schedule and release of medical records.
- Availability of obstetric, delivery and pediatric medical records for the enrolled pregnancy

Exclusion Criteria

- Women who have previously been included in this study with a prior pregnancy.

Cohort 2: Tdap Vaccine-Unexposed Comparator Group

Inclusion Criteria

- Currently pregnant women at the time of enrollment who were not exposed to any Tdap vaccine from the first day of LMP to the end of pregnancy.
- Currently pregnant women at the time of enrollment who agree to the conditions and requirements of the study including informed consent, the interview schedule and release of medical records.
- Availability of obstetric, delivery and pediatric medical records for the enrollment pregnancy.

Exclusion Criteria

- Women who have received a Tdap vaccine anytime during pregnancy.
- Women who have previously been included in this study with a prior pregnancy.

7.2.2. Study conduct

The study will be conducted by investigators at the University of California OTIS/MotherToBaby Research Center. The OTIS/MotherToBaby organization is a network of university and health department based telephone information centers serving pregnant women and health care providers throughout the US (Leen-Mitchell, 2000). These services receive spontaneous telephone inquiries from women who are pregnant or considering pregnancy as well as from health care providers about the safety or risk associated with environmental exposures in pregnancy, including medications and vaccines. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and health care provider callers free of charge. These services also provide a basis for collaborative research such as this study. Thus, individual Teratogen Information Services located throughout the US serve as a primary source of referrals not only for *Boostrix*-exposed pregnancies but also for similarly ascertained pregnant women with no exposure to Tdap vaccination during pregnancy.

Other methods of raising awareness about the study are meeting exhibits at professional practice meetings nationally, regionally, and locally, direct mail to health care providers, media, social media, and website. Awareness activities will also be directed to maternal-fetal medicine specialists, obstetricians, primary care physicians (PCP), and other specialists caring for pregnant patients.

The GSK package labeling for *Boostrix* in the US contains information about the pregnancy exposure registry and encourages healthcare providers to register patients by calling the toll-free study number.

In addition, the American Academy of Allergy, Asthma, and Immunology as the study collaborator through the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS) will be asked to promote recruitment among colleagues. The existing toll-free number for North American callers currently being utilized by all OTIS/MotherToBaby Pregnancy Studies (877-311-8972) will be promoted.

The existing OTIS/MotherToBaby Pregnancy Registry contact and referral information is available on the study website and multiple methods are used to increase awareness through the website (https://mothertobaby.org/pregnancy-studies/), social media and print advertising. The US Food and Drug Administration (FDA) website (http://www.fda.gov/womens/registries/default.htm) lists the OTIS/MotherToBaby Pregnancy Studies and will have this Registry added to their listing. The study will also be listed on ClinicalTrials.gov.

Information on the Registry will also be made available 1) in GSK product literature and promotional materials, and 2) via a link from the GSK website. Additional venues for publicizing the Registry include: 1) linking the Registry website to other specialty provider and maternal health interest websites, 2) posting notices in appropriate journals, and 3) later, presenting Registry data at obstetrics-related scientific and clinical meetings. The Sponsor will also provide information about the Registry at appropriate professional meetings. The Sponsor may facilitate awareness among prescribers through Medical Science Liaisons. The Sponsor will encourage exposed women or their Healthcare Providers to contact the Registry directly.

Pregnant women are entered in a cohort at the time of enrollment into the OTIS/MotherToBaby Pregnancy Registry. Information is collected on their pregnancy to date, and they are then followed for the duration of their pregnancy. In addition, infants will be followed for the specified safety events up to 2 months of age.

Depending on the gestational timing of enrollment, subsequent telephone interviews will be conducted according to the Schedule shown in Table 3 Section 7.4. Follow up interviews will be conducted by telephone, and medical records for both the women and infant will be obtained and abstracted for information to validate exposures and outcomes.

The participants may reside anywhere in the US, and may be of any age. Those who are under 18 years of age at the time of enrollment may enroll with parent/guardian consent.

Upon study initiation, eligible participants from existing OTIS/MotherToBaby Registry data will be identified, and recruitment of newly enrolled participants is expected to continue for 4 years, or until the target of 1,500 women exposed to *Boostrix* is reached, whichever comes first. After recruitment of the last participant, infant follow-up will continue for 2 months after the last live birth. Given the prevalence of *Boostrix* vaccination in pregnancy, and annual rates of enrollment of between 1,500 and 2,000 pregnant women overall in all MotherToBaby Pregnancy Studies, the planned four-year

recruitment period for this study is reasonable. However, should recruitment numbers fail to meet targets, specific additional awareness and marketing efforts will be initiated by the MotherToBaby research team.

7.3. Variables

Variables for the exposures, outcomes, demographics, and clinical characteristics of interest are included below (Table 1 and Table 2). Data on these variables will be collected via maternal interview and medical record review per standard processes described in the OTIS/MotherToBaby Pregnancy Registry standard operating procedures. Detailed operational definitions will be provided in the Statistical Analysis Plan (SAP).

7.3.1. Identification of Exposure and Comparator

Exposure is defined as any dose of US *Boostrix* on or after the 1st day of the 27th week of pregnancy, as reported by the mother or medical record. Detailed information regarding vaccine exposure status of participants is obtained through the maternal interviews and at the pregnancy outcome interview (0 to 6 weeks after the expected due date or end of pregnancy). Participants are directly queried about the specific vaccines they received, including information on the gestational timing, dates of exposure, and brand. Vaccine exposures are coded using the Slone Drug Dictionary. Maternal report that a Tdap vaccine was received is complemented by requesting medical records from the obstetric provider. Additionally, hospital of delivery, and pediatric medical records are requested for all participants.

A participant is classified as unexposed if she reports that she did not receive any Tdap vaccine, and her medical record shows no indication that she received any Tdap vaccine. A participant is classified as exposed if she reports in maternal interview that she received the *Boostrix* vaccine or if there is supporting documentation in the medical record for receipt of the *Boostrix* vaccine. If maternal report indicates no receipt of a *Boostrix* vaccine but the medical record indicates that the *Boostrix* vaccine was administered, the medical record will supersede maternal report and the participant would be classified as *Boostrix* vaccine-exposed. Moreover, where maternal report indicates that the *Boostrix* vaccine was received but documentation in the medical record is discordant (i.e., no indication in medical record that *Boostrix* vaccine was administered), the maternal report would supersede medical record for classification as exposed.

The estimated gestational weeks to qualify participants for the study for exposure and to classify outcomes is based on weeks from the first day of LMP which is counted as day 0. In circumstances where the date of LMP is not available or uncertain, or when a prenatal ultrasound estimates a gestational week that is discrepant according to obstetric guidelines, gestational week of pregnancy will be assigned based on the earliest available ultrasound (ACOG, 2017).

7.3.2. Classification of Exposure, Pregnancy, and Infant Outcomes

Exposure, pregnancy, and infant outcome variables (Table 1) are obtained by maternal report and/or medical record review as part of existing procedures for the OTIS/MotherToBaby Pregnancy Registry.

Table 1 Exposure, Comparator and Outcome Variables

Variable	Role	Data Source(s)	Operational Definition
Exposure to the *Boostrix* vaccine	Exposure	Maternal report, Vaccine record (e.g., yellow card), Medical record	Maternal report or medical record documentation of exposure to the *Boostrix* vaccine on or after the 1st day of the 27th week of pregnancy
Gestational timing of the *Boostrix* vaccine	Exposure	Maternal report Vaccine record (e.g., yellow card) Medical record	Maternal report or medical record documentation of the dates of the *Boostrix* vaccine administration on or after the 1st day of the 27th week of pregnancy
No Tdap vaccine exposure during pregnancy	Comparator	Maternal report Medical record	Maternal report of no exposure to any Tdap vaccine at any time from the first day of the LMP to the end of pregnancy; no documentation of Tdap vaccine in medical record
Preterm delivery	Primary Outcome	Maternal report Medical record	Maternal report and medical record documentation of a spontaneous or induced delivery after the 1st day of the 27th week of gestation or date of *Boostrix* vaccination, (whichever comes later) and <37 gestational weeks (as counted from the first day of LMP) (See Section 7.3.1 for operational definition of LMP) (CDC, 2021)
Stillbirth	Primary Outcome	Maternal report Medical record	Maternal report and medical record documentation of a non-deliberate fetal death that occurs after the 1st day of the 27th week of gestation or date of *Boostrix* vaccination, (whichever comes later), but prior to delivery (Prager, 2021)
Small for gestational age infant	Primary Outcome	Maternal report Medical record	Maternal report and medical record documentation of birth size for liveborn infants born after the 1st day of the 27th week of gestation or date of *Boostrix* vaccine, whichever comes later) (weight, length, or head circumference) ≤10th percentile for sex and gestational age using NCHS pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants are used for preterm infants (Olsen, 2010; Schlaudecker, 2017)
Preeclampsia / eclampsia	Secondary Outcome	Maternal report Medical record	Maternal report and medical record documentation of preeclampsia. Preeclampsia is defined as hypertension in conjunction with at least one of the following: proteinuria; thrombocytopenia; impaired liver function; renal insufficiency; pulmonary edema; or visual or cerebral disturbances. The disorder usually occurs after 20 weeks of pregnancy and worsens over time.

Variable	Role	Data Source(s)	Operational Definition
			Eclampsia is a life-threatening condition that is considered a complication of severe preeclampsia and characterized by coma and/or seizures that are unrelated to a preexisting brain condition. Onset of preeclampsia/eclampsia as an outcome for this study is defined as onset after the 1st day of the 27th week of gestation or *Boostrix* vaccination date (whichever comes later).
Premature rupture of the membranes (PROM)	Secondary Outcome	Maternal report Medical record	Maternal report and medical record documentation of premature rupture of the membranes (amniotic sac). Premature rupture of the membranes is before labor begins on or after the 1st day of the 27th week of gestation or date of *Boostrix* vaccination (whichever comes later) and prior to 37 weeks' gestation.
Chorioamnionitis	Secondary Outcome	Maternal report Medical record	Maternal report and medical record documentation of chorioamnionitis. Chorioamnionitis classified using Brighton collaboration definition (Kachikis, 2019) Please refer to details in Appendix 1
Neonatal sepsis of early onset	Secondary Outcome	Maternal report Medical record	Maternal report and medical record documentation of neonatal sepsis. Sepsis defined as isolation of pathogenic species from blood or cerebrospinal fluid culture within 72 hours of birth and antibiotic treatment for at least 5 days or until death (provisional definition pending confirmation of the ability to implement extraction in medical records)
Neonatal intensive care (NICU) for bronchopul-monary dysplasia	Secondary Outcome	Maternal report Medical record	Maternal report and medical record documentation of NICU care for bronchopulmonary dysplasia. Admission to the NICU defined as admission for any number of days for diagnosis of bronchopulmonary dysplasia
Neonatal death	Secondary Outcome	Maternal report Medical record	Maternal report and medical record documentation of neonatal death. Neonatal death defined as death of a live born infant within 28 days of birth

Abbreviations: CDC, Centers for Disease Control and Prevention; LMP, last menstrual period; NCHS, National Center for Health Statistics

7.3.3. Demographics and Clinical Characteristics

Potential confounders and other covariates to be collected include maternal age, race/ethnicity, pre-pregnancy body mass index, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, and prenatal tests. Table 2 provides a description of corresponding variables to be included in this study. The SAP will provide greater detail on covariable definitions.

Table 2 Demographic and Clinical Variables, Maternal and Paternal age

Variable	Role	Data Source(s)	Operational Definition
Maternal Age (years)	Confounder	Maternal report	Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Paternal Age (years)	Confounder	Maternal report	Paternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Maternal Race	Confounder	Maternal report	Maternal (Caucasian/White, Black, Asian/Pacific Islander, Native American, Other).
Maternal Ethnicity	Confounder	Maternal report	Maternal (Hispanic, Non-Hispanic).
Maternal Education	Confounder	Maternal report	Maternal Educational Category (years of completed education <12, 12-15, >15).
Socioeconomic Category	Confounder	Maternal report	Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (1-5).
Maternal Height	Confounder	Maternal report	Maternal height (cm)
Maternal Pre-pregnancy body weight	Confounder	Maternal report	Maternal pre-pregnancy body weight (kg)
Maternal Pre-pregnancy body mass index	Confounder	Maternal report	Maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25-29.9, >=30)
Number of times pregnant	Confounder	Maternal report Medical record	Number of times ever pregnant (1, 2-3, 4-5, >=6) (confirm with medical record)
Previous live birth or stillbirth deliveries	Confounder	Maternal report Medical record	Number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, >=5) (confirm with medical record)
Previous pregnancies ending in spontaneous abortion	Confounder	Maternal report Medical record	Number of previous pregnancies ending in spontaneous abortion (0, 1, 2, >=3) (confirm with medical record)
Previous pregnancies ending in elective termination	Confounder	Maternal report Medical record	Number of previous pregnancies ending in elective termination (0, 1, 2, >=3) (confirm with medical record)
Previous pregnancies ending in preterm birth	Confounder	Maternal report Medical record	Number of previous pregnancies ending in preterm birth (confirm with medical record if available)
Previous pregnancies ending in growth restricted infant	Confounder	Maternal report Medical record	Number of previous pregnancies ending in infant with intrauterine growth restriction (confirm with medical record if available)
Gestational age at study enrollment	Confounder	Maternal report	Weeks of pregnancy at time of enrollment, continuous and categorical (≤13, 13.1-19.9, ≥20): gestational age is calculated from the first date of LMP
Referral source	Confounder	Maternal report	Source options: Sponsor, OTIS service, health care provider, Internet, Other.
Prenatal, Multivitamin, or Folic acid	Confounder	Maternal report	Prenatal, Multivitamin or Folic Acid supplement use by timing (began prior to conception, post-conception only, not taken at all)
Alcohol use in pregnancy	Confounder	Maternal report	Yes/No. Dose and frequency are captured

Variable	Role	Data Source(s)	Operational Definition
Tobacco use in pregnancy	Confounder	Maternal report	Yes/No. Dose and frequency are captured
Medication and vaccine use in pregnancy	Confounder	Maternal report	Prescription and over-the-counter medications, vaccines are captured for the period from the first day of LMP through the end of pregnancy; dose, frequency, duration, and indication including stop and start dates are collected
Maternal pregnancy exposure to a known human teratogen	Confounder	Maternal report	Maternal pregnancy exposure to a known human teratogen
Comorbid maternal medical history	Confounder	Maternal report Medical record	Comorbid maternal medical history (e.g., chronic hypertension, asthma)
Current pregnancy ending in a major birth defect	Confounder	Maternal report Medical record	A major structural or chromosomal defect that has either cosmetic or functional significance to the child (e.g., a cleft lip) classified using CDC coding criteria

Methods for identifying and controlling for these confounders and/or effect modifiers are described in Section 7.7.1. The SAP will provide greater detail on the definitions of, the identification of and the controlling for confounders and/or effect modifiers.

7.4. Data sources

Teratogen Information Services (MotherToBaby sites) provide referrals from pregnant women who call and who are interested in participating in the OTIS/MotherToBaby Pregnancy Registry. Healthcare providers are also informed that patients with Tdap exposure can be referred to the OTIS /MotherToBaby Pregnancy Registry. Active recruitment strategies are also used, e.g., direct mailings to healthcare providers, website, and professional meetings.

Enrollment in the OTIS/MotherToBaby Pregnancy Registry is voluntary and requires informed consent by the pregnant woman. The OTIS/MotherToBaby Research Center is responsible for verifying the participant selection criteria, enrolling each participant, and securing informed consent, providing all pregnancy and post-partum follow-up interviews and medical record review, recording and storage of all data, and subsequent data analysis and interpretation.

As part of the OTIS/MotherToBaby Pregnancy Registry protocol, data are collected using maternal interview(s), medical record review (obstetric, delivery hospital, pediatric, and vaccine provider, if applicable), and the pregnancy exposure diary (Table 3). The exposure diary is used as a supplemental source of information about medications, vaccines taken or received in pregnancy.

Table 3 Timing of Cohort Enrollment, Interviews, Examinations, and Medical Records

	Any Time In Pregnancy	20-22 Weeks' Gestation[2]	32-34 Weeks' Gestation[3]	0-6 Weeks Post-Delivery	0-2 Months Post-Delivery
Referral[1]	√				
Enrollment and Consent[1]	√				
Enrollment Interview[1]	√				
Interim Interview I		√			
Interim Interview II			√		
Pregnancy Outcome Interview and Request for Medical Records				√	
Medical Record Acquisition and Review					√

[1] Participants may enroll in the study any time during pregnancy.
[2] If participant is enrolled and Intake Interview is conducted after 18 weeks' gestation, only one interim interview is conducted during pregnancy at 32-34 weeks gestation.
[3] If participant is enrolled and Intake Interview is conducted at 30 weeks' gestation or after, no Interim Interview is collected.

Medication or vaccine exposures entered into the database are coded using the Slone Drug Dictionary. Data are recorded on hard copies of forms and these records are retained by OTIS/MotherToBaby at the Research Center. These forms are considered the primary data sources for studies and can be adapted to add new data elements. Data from these forms are extracted and entered into a customized OTIS/MotherToBaby study database located in the Research Center.

7.4.1. Maternal Interviews

Below is a detailed description of each interview as conducted under the OTIS/MotherToBaby Pregnancy Registry protocol:

- **Intake/Enrollment Interview**: A structured maternal intake telephone interview is conducted at enrollment by a trained Research Associate from the OTIS/MotherToBaby Research Center. This interview includes questions on the following: pregnancy history, including major congenital malformations, genetic disorders, number of live births, and multiple gestations; current health history; pre-pregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education and ethnicity; income category; current medication use, both prescription and over the counter; other environmental or occupational exposures, alcohol, tobacco, caffeine and illicit drug

use, vaccine exposure prior to and during pregnancy; current pregnancy complications including illnesses; family history of adverse pregnancy outcomes, including major congenital malformations and genetic disorders; names and addresses of health care providers; and vaccine use during pregnancy. To supplement future interviews and improve recall, participants are given a pregnancy exposure diary to record any additional exposures (medications, vaccinations, vitamins, etc.) or events as the pregnancy progresses. Each woman is also sent the informed consent document and the US Health Insurance Portability and Accountability Act (HIPAA) Authorization Addendum (when applicable) via electronic signature or paper, and a research HIPAA compliant obstetric medical record release form.

- **Interim Interviews I and II**: Telephone interviews are conducted at 20-22- and 32-34-weeks' gestation (if enrolled before the interview interval) by a trained Research Associate from the OTIS Research Center. Women who have enrolled prior to 18 weeks post-LMP will be interviewed by telephone at 20-22 weeks post-LMP, 32-34 weeks post-LMP and within 2 to 6 weeks after the expected due date. Women who have enrolled between 19 and 20 weeks post-LMP will be interviewed at 32-34 weeks post-LMP (See Table 3). These interviews are intended to update records of pregnancy exposures (medications, vaccinations, vitamins, etc.), results of prenatal tests, events of interest since last interview (including if the pregnancy has ended prior to the expected due date), and contact information.
- **Pregnancy Outcome Interview**: A structured telephone interview is conducted by a trained Research Associate from the OTIS Research Center at 0 to 6 weeks after the expected due date, or at an interim interview point or earliest convenient time for the participant if pregnancy has ended. This interview elicits information based on type of birth:
  - For women with live born infants: date of delivery, hospital location and mode of delivery; sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including preeclampsia/eclampsia, premature rupture of the membranes, malformations; type and length of hospital stay for pregnant women and their infants; survival of the infant to 28 days of life; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures, results of prenatal tests occurring since the previous interview, and additional study-related outcomes for mothers and infants including neonatal sepsis and bronchopulmonary dysplasia.
  - For women with stillborn infants: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview, sex of the infant, delivery or birth complications including preeclampsia/eclampsia and premature rupture of the membranes, malformations, birth size and autopsy results if available.

7.4.2. Medical Records and General Pediatric Evaluation

Upon completion of the outcome interview, each woman is sent a packet electronically or by hard copy mail containing research HIPAA compliant medical records release forms for the delivery hospital, obstetrician, pediatrician, and vaccine provider if applicable. For women whose pregnancies have ended in stillbirth, records release forms are mailed for prenatal diagnosis (if applicable), pathology or autopsy reports if available. Each eligible woman is asked to sign (electronically or by wet signature) the medical records release forms, as well as UCSD HIPAA Authorization Addendum (if they or their infant receives medical care at UCSD/Rady Children's hospital) and to return them along with the pregnancy exposure diary form.

Upon receipt of the signed medical records release forms, a standard physical evaluation form is mailed to each pediatrician or other physician responsible for the care of each live born infant through 2 months of age.

Medical records are reviewed by trained abstractors to supplement information self-reported by the participant related to vaccine exposure, outcomes, prenatal tests, and medical history.

7.4.3. Scientific Advisory Board

An existing external Scientific Advisory Board under the Vaccines and Medication in Pregnancy Surveillance System (VAMPSS) provides oversight for the study and reviews study summary data on an annual basis. Members of the Board provide advice to the Registry investigators on interpretation of the data and provide advice on strategies for the dissemination of information regarding the study.

The VAMPSS Scientific Advisory Board is managed by the American Academy of Allergy, Asthma and Immunology. The Scientific Advisory Board is comprised of membership representing specialization in maternal fetal medicine, biostatistics, vaccine epidemiology, and representation from the Centers for Disease Control, National Institutes of Health/Child Health Institute, the American Academy of Pediatrics, and a consumer representative. The Board is chaired by a designated member, and each member has one vote. A dedicated charter describes roles and responsibilities of the Board members, and members complete conflict of interest disclosures on an annual basis.

7.5. Study size

The target sample sizes in each of the study cohorts are as follows:

- 1,500 women exposed to *Boostrix* on or after the 1st day of the 27th week of gestation through the end of pregnancy
- 1,500 women unexposed to any Tdap vaccine throughout their pregnancy

Including an estimated 600 eligible participants per cohort already enrolled in the OTIS/MotherToBaby Pregnancy Registry, enrollment of 1,500 participants in each of the cohort groups is planned for completion within 4 years. Participants are eligible to enroll at any time in pregnancy including prior to the gestational timing of the recommended Tdap vaccine. (Examples of gestational timing of enrollment, exposure, and outcome are shown in Figure 1 and Figure 2). Thus, some initially enrolled pregnancies will no longer be eligible for analysis due to pregnancy losses (spontaneous abortion, elective termination, stillbirth prior to the 27th week of gestation, or lost-to-follow-up). Additionally, some pregnancies will not be eligible for inclusion due to failure to release medical records. The final sample size of 1,500 per cohort will represent all pregnancies that met full inclusion/exclusion criteria. From this sample of livebirths and stillbirths, we conservatively estimate that at least 1,425 in each cohort will represent pregnancies ending in liveborn singleton infants.

Figure 1 Example of Participant Qualified for Boostrix-exposed

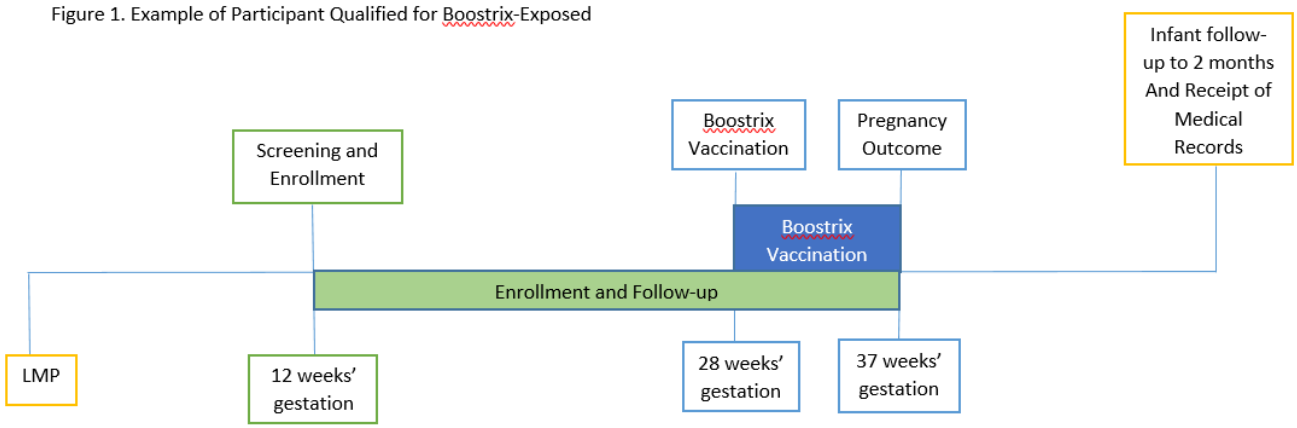

Figure 2 Example of Participant Qualified for Tdap unexposed

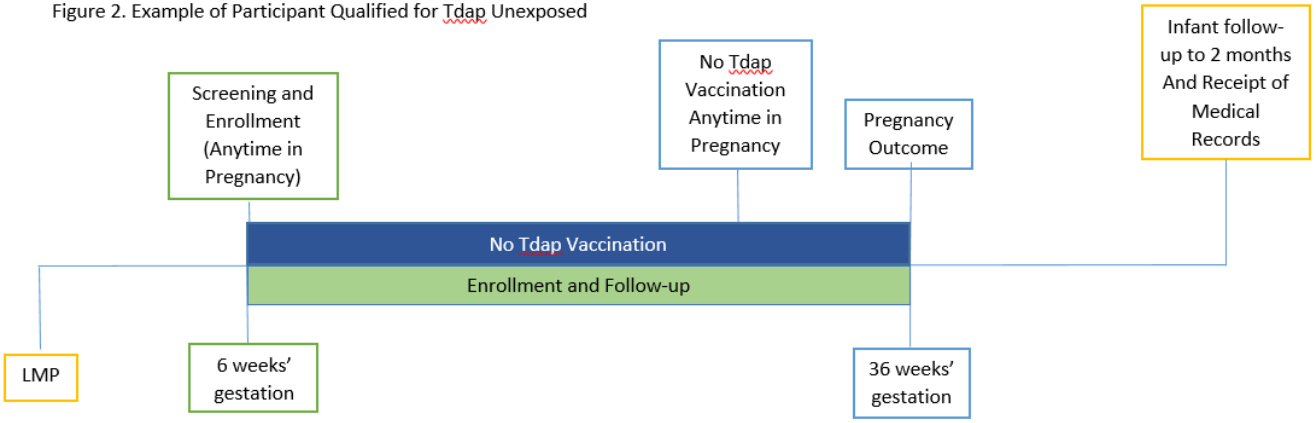

Table 4 gives the minimum detectable effect size with 80% power for 2 of the primary endpoints and for 1 of the secondary endpoints. Other secondary endpoints are expected to be less frequent than 1-2% in the comparator group. Therefore, statistical power will be limited and only high relative risks will be detectable for these secondary endpoints. This also applies to the primary outcome of stillbirth.

Table 4 Sample Size and Detectable Effect Size with 80% Power for Comparison of *Boostrix*-Exposed to Comparison

Endpoint	N in Each Group	Rate in Comparison Group	Relative Risk	Power[1]
Preterm delivery	1425	10%[2]	1.4	80%
SGA	1425	10%[3]	1.4	80%
Chorioamnionitis	1469	3%	1.7	80%

[1] All tests are two-sided with alpha = 0.05, based on Fisher's exact test. Calculations conducted using R.
[2] (Ferré, 2016)
[3] (CDC, 2017; Nellhaus, 1968; Olsen, 2010)

7.6. Data management

As per the OTIS/MotherToBaby Pregnancy Registry protocol, data are collected using maternal interview, medical record, and the pregnancy diary. Maternal interview data are recorded on hard copies of forms, and these forms will be retained by OTIS/MotherToBaby. These forms are considered the primary data sources for the registry. The interviews are semi-structured and follow interview data collection forms to ensure that all study questions are addressed. Data from each interview form is entered into the study database at the end of the interview by the same person who conducted the interview. Medical records are requested from the hospital of delivery (maternal and neonatal information), obstetric provider (maternal information), and pediatrician (neonatal/infant). When records are received and catalogued, data is abstracted by trained personnel from each record using a standard abstraction form and entered into the study database. Medical records and medical record abstraction forms are hard copies or electronic copies and are retained on a secure server or in locked files. Data from maternal interview and medical record abstraction forms are entered into a customized OTIS/MotherToBaby Pregnancy Registry database located in the Research Center and developed specifically for the OTIS/MotherToBaby Pregnancy Research Studies.

The database itself has built in range limits for key variables that prevent certain data entry errors. In addition, all data entry is validated for a series of predefined critical variables and a random subset are validated for non-critical variables. The registry statistician also conducts reviews of the cumulative data in the database for distributions and values that are illogical.

Access to the database is controlled by password, with different access privileges assigned. An audit log is built into the database to archive all such entry edits.

Hard copies of participant files and participant signed consent forms are kept in locked cabinets in locked file rooms, or electronically secured files, under the supervision of the study investigators.

7.6.1. Data handling conventions

All prenatal exposures to medications and vaccines are coded using the Slone Drug Dictionary (http://sites.bu.edu/slone-drug-dictionary/).

Twins and higher order multiples are excluded from analyses of preterm birth and SGA infants due to inherent risk of that outcome.

Loss-to-follow-up status is designated if a participant withdraws from the study, or if the study staff are unable to contact the study participant within 12 months of the estimated end of pregnancy in order to obtain outcome information. Pregnancies that are lost-to-follow-up will not be included in the analysis for the primary and secondary outcomes.

Coding of outcomes is performed by the study staff using the definitions provided in the protocol. Sources of information on exposure and outcome are the participant and medical records.

Missing values for the critical data for OTIS/MotherToBaby studies are typically very few and nearly always less than 10%. Complete case analysis is planned and there is generally no need to include imputation strategies; however, depending on the prevalence of missingness, sensitivity analyses will be conducted. These will be documented in the SAP.

7.6.2. Resourcing needs

Not applicable.

7.7. Data analysis

7.7.1. Essential analysis

A stepwise approach will be used for the analysis. The initial analysis will be descriptive and unadjusted. Where numbers permit, multivariable analyses will be conducted for the analyses to adjust for possible confounders.

Statistical methods:

A detailed SAP will be prepared and finalized prior to the conduct of any study analysis. Maternal characteristics will be summarized within each cohort for the annual progress and final reports.

Table 5 Summary of Exposure Window for Selected Primary and Secondary Outcomes

Outcome	Exposure Window
Preterm Delivery	1st day of the 27th week of gestation to the 5th day of the 37th week of pregnancy
SGA	1st day of the 27th week of gestation to the end of the pregnancy
Chorioamnionitis	1st day of the 27th week of gestation to the end of the pregnancy

For the binary endpoints of **SGA and Chorioamnionitis,** the comparison will be on the proportion of events occurring after the 1st day of the 27th week of gestation or the date of *Boostrix* vaccination (whichever comes later) between the *Boostrix*-exposed cohort and the comparison cohort. A point estimate of the crude (i.e., unadjusted) relative risk (RR) of the *Boostrix*-exposed cohort versus the comparison cohort, as well as its 95% confidence interval (CI) will be computed.

Due to the observational nature of the study, the above crude estimate of RR will be further adjusted for potential confounders using a propensity score (PS) approach, if there are a sufficient number of events (to be detailed in Statistical Analysis Plan). A complete list of potential confounders will be provided in a separate table for each outcome prior to the final analysis, based on scientific knowledge including literature review. In addition, all of the following three criteria will be applied in accordance with the definition of confounders (Greenland, 1999; Xu, 2018), to identify confounders to be included in the PS model: 1) by assessing each considered variable in a logistic regression model containing exposure and the outcome to determine if inclusion of that single covariate changes the estimate of the odds ratio for exposure by 10% or more; 2) standardized mean differences (SMD) greater than 0.1; 3) association with the outcome with p-value <0.2 in the unexposed group. Care will be taken not to include those variables that are strongly associated with the exposure but only weakly associated with the outcome (Brookhart, 2006).

The confounders identified above may be used to build the PS for exposure (Rosenbaum, 2002). R package 'twang' or similar R package available at the time of analysis will be used for this purpose, following which SMD will be used to check the balance of the covariates between the cohorts.

The primary analyses will be performed to estimate the causal relative risk using the method of inverse probability weighting (IPW) based on the PS. In the IPW approach, we will use stabilized weights that are further trimmed to be between 0.1 and 10 if necessary (Austin, 2015). The 95% CIs will be obtained using the bootstrap estimated variance and asymptotic normality, with 200 bootstrap samples.

A secondary analysis will be conducted using outcome regression, i.e., a logistic regression model will be fitted with the binary outcome (Y), and exposure (A) and propensity score (L) as regressors. Standardization will be performed to obtain the

estimated causal risk ratio (Hernán, 2019), which has the interpretation as the marginal or population averaged risk ratio. The CIs are obtained by bootstraps.

For the endpoint of **preterm delivery**, only pregnancies ending in delivery after the 1st day of the 27th week of gestation or the date of *Boostrix* vaccination (whichever comes later), enrolled prior to 37 weeks' gestation, and whose pregnancies result in a live-born singleton will be included in the analysis. Further, in the *Boostrix*-exposed group, exposure to vaccine must take place between the 1st day of the 27th week of gestation and before 36 weeks' and 5 days (allowing at least one day after vaccination for preterm delivery). Because women can meet criteria for eligibility for the study at arbitrary times following the 1st day of the 27th week of gestation, they may not be followed from the beginning of the relevant gestational age window. Those who experience the event prior to enrollment will never enter the study, leading to left truncation of the time to event. This can produce selection bias. In addition, vaccine exposure can occur on or any time after the 1st day of the 27th week of gestation in pregnancy, so exposure status is time-dependent. To address these issues, survival analysis methods will be used. Fleming-Harrington estimate at 37.0 weeks' gestation will be used to estimate the preterm delivery rate and 95% CI in each of the cohorts (Fleming, 1984; Pan, 1998). The Cox proportional hazards marginal structural model (MSM) incorporating time-dependent vaccine exposure and relevant covariates will be used to estimate the causal hazard ratio (HR) and 95% CI (Hernán, 2001).

There may be potential biases in individuals who do or do not meet the requirement of releasing medical records in order to be eligible for inclusion in the study. Comparisons on key baseline covariates for those who were excluded from eligibility solely on the basis of medical records availability will be compared to those included in the study.

There may be potential biases involved in changing definitions of selected study outcomes over time. For example, criteria for preeclampsia/eclampsia have been modified in recent years. A sensitivity analysis (below) is planned to address this issue.

There can also be a "healthy vaccinator" bias which is a potential confounder that may be difficult to control for. In other words, women who elect to receive the *Boostrix* vaccine may have other lifestyle characteristics that are unmeasured or poorly measured that are associated with the pregnancy and infant outcomes of interest. A sensitivity analysis (below) to address this issue.

7.7.2. Sensitivity analyses

To address changes over time in diagnostic criteria for preeclampsia/eclampsia, year of enrollment will be considered as a potential confounder in analyses. However, an additional sensitivity analysis will be conducted by stratifying the analysis on data collection prior to and after the year the diagnostic criteria modifications were implemented.

In addition, if major discrepancies are identified by descriptive analysis of baseline characteristics and outcomes for the participants previously enrolled in the OTIS/MotherToBaby Pregnancy Registry and the participants newly enrolled over 4

years, further exploratory stratified analyses could be conducted, provided the sample size allows for it.

To address potential unmeasured confounding associated with being a "healthy vaccinator", a second sensitivity analysis will be conducted restricting the sample in each cohort to those who received the recommended influenza vaccination in pregnancy. This ensures that both the exposed and comparator groups were at least compliant with one vaccine recommendation in pregnancy.

Although major birth defects are not expected to be causally related to Tdap vaccination exposure that takes place long after completion of embryogenesis when most major birth defects occur, major birth defects will be considered as a potential confounder in analyses. For example, prenatal diagnosis of a major birth defect could influence willingness to receive a Tdap vaccination later in pregnancy. In turn the major birth defect could independently influence risk of stillbirth, PTB or SGA. To further address this issues, a third sensitivity analysis will be conducted excluding infants in both cohorts with documented major birth defects.

7.7.3 General considerations for data analyses

A detailed SAP will be prepared and finalized prior to the conduct of any study analysis or reporting.

Analyses of data at the completion of the study will be performed according to the methods as described in Sections 7.7.1 to 7.7.2

Since each outcome and each comparison has its unique potential confounder list and set of subjects, propensity scores are generated for each analysis endpoint separately.

7.8. Quality control and quality assurance

As noted in Section 7.7, quality control measures are in place throughout the entire period of data collection and data entry. Training and retraining of study staff is monitored per study SOP, and validation of data entry for critical study variables is conducted. Data exported for interim and final analyses for this study will be checked for logical errors, and range checks are performed.

The method and duration of storage of data is addressed in the informed consent. All records are maintained for a minimum of 15 years following study completion.

Data will be reviewed on an annual basis by the VAMPSS external advisory board which meets annually and reviews all annual progress and final study reports as well as manuscripts that are produced from the study results. The committee comments on the study progress and poses questions that arise which are addressed by the investigators.

Final data sets are cleaned and utilized for preparation of the analyses and study reports. All analyses (coding and output) are reviewed by the lead study statistician and at least one other staff statistician. Study reports are reviewed by the OTIS/MotherToBaby

Pregnancy Registry Research Manager and the Investigators. All data sets and analytic files are archived indefinitely at the OTIS/MotherToBaby Research Center, and analyses can be replicated as necessary.

7.9. Limitations of the research methods

This study will use data from the well-established OTIS/MotherToBaby Pregnancy Registry which collects detailed data on prenatal/birth exposures (including timing of exposures during pregnancy) and outcomes. The primary limitation of this cohort study utilizing volunteer participants is potential selection bias in that women who agree to enroll in the study may represent particularly high- or low-risk pregnancies (Johnson, 2001). For example, women who receive the vaccine and have a history of preterm delivery (high baseline risk) may be more likely to preferentially enroll than women who did not receive the vaccine and who did not have a history of prior preterm delivery because of concerns about their pregnancy. In addition, the study results will be strictly generalizable to women fitting the profile of the sample of women who enroll.

There could be differences between the vaccinated and unvaccinated cohorts that may not be able to be adjusted or accounted for due to the nature and collection of the data. The planned sensitivity analysis restricting the sample to those in both cohorts who received the recommended influenza vaccine in pregnancy may address this to some extent. It is possible that demographic variables will be associated with vaccination (MMWR, 2021). As such, in reviewing annual reports, if clear differences in demographic factors (i.e., age, race/ethnicity, socioeconomic status, education) are noted, enhancement of recruitment efforts to increase diversity will be taken into consideration. Finally, as noted in the analysis plan, those who are otherwise eligible for the study but do not return medical records will be compared on key demographic and selected outcome characteristics to pregnancies that are included in the study analyses.

Although extensive efforts will be made to retain newly recruited participants into the Registry, some participants will be lost during follow up. It could be possible that participants lost during follow up and with missing data on outcomes may be different compared to those with complete follow up data. In previous OTIS/MotherToBaby studies, loss-to-follow-up rates have been low, typically <5% (Chambers, 2016). However, the characteristics of women lost to follow up will be compared to those who are retained to understand the direction and magnitude of the bias due to loss to follow up.

The study design has relative strengths with respect to the control of many potential confounders. Information will be collected on a variety of factors which may be related to exposure and to pregnancy outcome. Misclassification bias due to poor recall is thought to be reduced in study designs such as this where participants are enrolled before the outcome of pregnancy is known. Misclassification bias is further reduced by having medical records as a source of data. Another strength of the study design is the anticipated minimal loss-to-follow-up rate. Based on previous experience of the investigators in the OTIS Pregnancy Studies and other similar studies, and the frequent participant contact, loss-to-follow-up is expected to be less than 5%, and therefore not expected to pose a threat to the validity of study results.

7.9.1. Study closure/uninterpretability of results

In consultation with the Scientific Advisory Board, discontinuation of the study will be considered at such time as:

- Sufficient information has accumulated to meet the scientific objectives of the study
- Other methods of gathering appropriate information become achievable or are deemed preferable
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow up. Upon initiation of the study, recruitment is expected to continue for 4 years or until the target of 1,500 women exposed to *Boostrix* is reached, whichever comes first. Regular review of enrollment numbers will be performed. If target enrollment numbers are not being met, additional efforts will be implemented in marketing and awareness activities to achieve the targeted sample size.

7.10. Other aspects

None

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

The study is approved through the University of California San Diego Human Research Protections Program (Institutional Review Board or IRB). All OTIS/MotherToBaby Research Study participants must agree to the IRB-approved oral consent form at the time of enrollment and before completing the intake interview. Each participant is asked to sign the IRB-approved informed consent document electronically or on hard copy form, but written consent is not required for participation in the study. Each participant is also asked to sign for release of medical information to allow the OTIS/MotherToBaby Research Center to obtain information on the pregnancy and the pregnancy outcome from the participant's obstetrician, the hospital of delivery, and from the infant's pediatrician.

The original oral and signed informed consent documents, and copies of the medical records release forms will be maintained at the OTIS/MotherToBaby Research Center.

Pregnant women under the age of 18 who are eligible for the study and who wish to participate will require written consent of their parent or guardian prior to the initial intake interview and written assent from themselves. Consent/assent forms and study participation materials are available in English or Spanish.

8.2. Subject confidentiality

The OTIS/MotherToBaby Research Center makes every effort to assure participant confidentiality. Personally identifiable information is maintained in secure files with restricted access limited to only authorized personnel.

OTIS/MotherToBaby Research Center Investigators, data collection and management staff reside at the at the University of California, San Diego. These personnel, under the supervision of the Investigators, have access to the physical files and electronic data, have documented completion of human subjects research training, and are listed individually as authorized to have access to the study data on the study IRB-approved research plan.

Sponsor representatives and the Scientific Advisory Committee have access to de-identified summary data as part of the periodic annual review and the final study report. Final study data files for analysis are stripped of identifiers and archived without personal identifiers.

Care will be taken to ensure that no individual participant is identifiable in the data tables published in the Annual Reports, or other presentations or publications.

9. LEGAL BASIS FOR PROCESSING INDIVIDUAL HUMAN DATA

The authors confirm that study data is Individual Human Data (IHD) owned by GSK and OTIS and that:

- The proposed use of the IHD is **Study Use*** as outlined in the patient consent.

  *Study Use means - the use of IHD is as stated in the original study protocol and/or aligned with the informed consent form to answer the study objectives and satisfy regulatory requirements and learn more about the product studied and the disease/ condition studied. This includes bringing the product to market or maintaining market access which includes working with government agencies, insurers or health care payers and aiding GSK's understanding of clinical efficacy, safety, or effectiveness of the product.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The purpose of the study is to monitor pregnant individuals exposed to *Boostrix* and to evaluate selected pregnancy and infant outcomes in study participants exposed to *Boostrix*. A Safety Management Plan (SMP) has been developed for the study to provide detailed information on the study specific pharmacovigilance processes and procedures.

This study adopts the following ICH definitions:

Adverse event: *Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment*.

- 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 including those used in combination with a medical device. For a marketed Medicinal Product, this can also include failure to produce expected benefits (i.e. lack of efficacy, with or without an adverse event), and adverse events associated with circumstances of Overdose whether accidental or intentional, Medication Errors, Abuse or effects of drug withdrawal, or Misuse or those related to a deficiency occurring with a medical device.

Serious adverse event: *any untoward medical occurrence that at any dose that 1) results in death, 2) is life threatening, 3) requires inpatient hospitalization or prolongs existing hospitalization, 4) results in persistent or significant disability/incapacity or 5) is a congenital anomaly.*

a. Safety management and reporting for the cohort that have previously been enrolled in the OTIS/MotherToBaby Pregnancy Registry

This study involves data that exist as structured data by the time of study start. In this structured pregnancy database, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

Only the safety events specified in the study objectives, including non-serious events, will be solicited and systematically collected and tabulated. A descriptive summary of safety data will be provided in the annual progress report.

a. Safety management and reporting for the cohort that will be enrolled in the study as of study start date (anticipated March 01, 2023).

For *Boostrix*-exposed study participants, pre-defined specific outcomes that are classified as serious adverse events (SAEs) will be identified and reported. These pre-defined SAEs include stillbirth, neonatal death, neonatal sepsis, and neonatal intensive care admission for bronchopulmonary dysplasia. These SAEs will be reported to the GSK Safety Department within 24 hours after all criteria for study inclusion have been met including availability of medical records after the end of pregnancy and the two month follow-up period. The OTIS Research Center Investigators will report to GSK these predefined events as soon as they become aware of the SAEs (study inclusion criteria met, and identification of the event through data abstraction). These will be classified as solicited individual case safety reports (ICSRs), and reported using MedWatch. SAE identified in the context of the study (outside the pre-defined events listed in Table 1) should be managed, classified and submitted as spontaneous reports to GSK in line with the appropriate time frames.

Other safety pre-defined events (Table 1), including non-serious events, will be systematically collected and summarized in table form in annual progress reports and final study report. Descriptive summary of safety data will be provided in the annual progress reports.

There will be no causality assessments performed during this study as this is observational and there is no intervention.

Please note as this is a pregnancy safety study, pregnancy exposures do not need to be reported to the Safety Department as the pregnancy exposure denominator is provided to Safety via study reports. Pregnancy outcomes will be reported as solicited events as described above.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target audience

Healthcare providers treating pregnant patients, women of reproductive age and pregnant persons, and regulatory authorities are the target audiences.

11.2. Study reporting and publications

Key design elements of this study will be posted in publicly accessible databases such as Clinicaltrials.gov. Furthermore, key results of this study will be posted in publicly accessible databases within the required timeframe from completion of the data collection where applicable.

Progress reports will be prepared annually by study investigators and reviewed by GSK. Additionally, the standing Scientific Advisory Board meets annually and reviews all interim data, and annual progress reports. Annual progress reports will include descriptive analyses with study tables (e.g., recruitment, enrollment, demographic and baseline characteristics, primary, secondary pregnancy and infant outcomes, and preliminary conclusions of the Advisory Board.

Upon closure of the study, a final report will be generated by the study investigators, reviewed by the standing advisory committee and GSK, and then submitted by GSK to the relevant regulatory authorities.

The data will also be considered for reporting at scientific conferences or for publication in scientific journals. Preparation of such manuscripts will be prepared independently by study investigators and in accordance with the current guidelines for Strengthening the Reporting of Observational studies in Epidemiology (von Elm, 2008). Study investigators will follow the international committee of medical journal editors (ICMJE) recommendations for authorship and acknowledgements. GlaxoSmithKline will be entitled to review the results and interpretations included in the manuscript prior to submission for publication.

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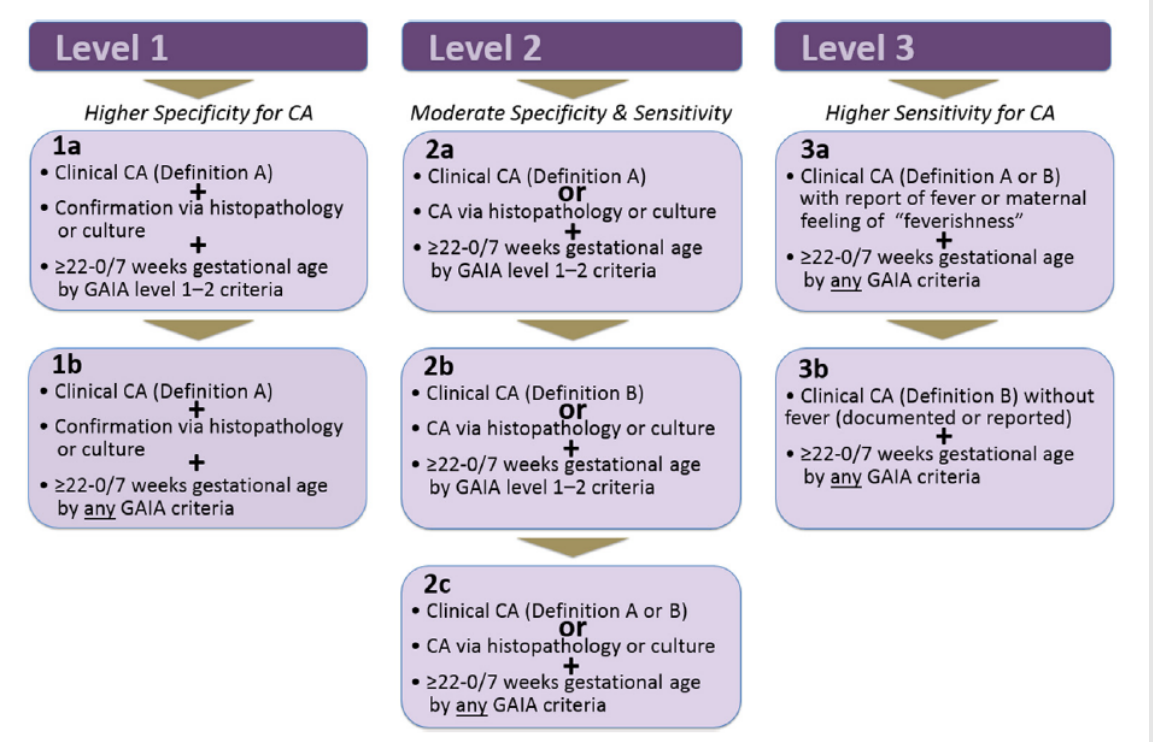
13. APPENDICES

Core table shells and figures will be included in the Statistical Analysis Plan

Appendix 1 Brighton Collaboration Case Definition for Chorioamnionitis with Levels 1-3 of Certainty (Kachikis, 2019)



Clinical Definition A:

Maternal fever ≥38 degrees Celsius on one occasion.

Plus one or more:

- Baseline fetal tachycardia (fetal heart rate [FHR] >160 beats per minute [bpm] for 10 minutes or longer, excluding accelerations, decelerations, and periods of marked variability or, where continuous monitoring is not available, an FHR exceeding 160 bpm during and after at least 3 consecutive contractions).
- Maternal white blood cell (WBC) count ≥15 000 per mm^3 in the absence of corticosteroids.
- Definite purulent fluid from the cervical ostium (os).

Clinical Definition B

Maternal fever ≥38 degrees Celsius on one occasion.

Plus two of the following:

- Maternal tachycardia (heart rate [HR] >100 bpm)
- Baseline fetal tachycardia (FHR >160 bpm for 10 minutes or longer, excluding accelerations, decelerations, and periods of marked variability or, where continuous monitoring is not available, an FHR exceeding 160 bpm during and after at least 3 consecutive contractions)
- Purulent fluid from the cervical os.
- Uterine tenderness.
- Maternal WBC ≥15 000 per mm^3 in the absence of corticosteroids.

Histologic diagnosis:

- Positive finding of invasion of maternal polymorphonuclear leukocytes into the placental plate, the chorion and/or amnion which meets criteria based on a widely accepted histopathologic staging and grading system [such as Redline, Salafia, or Blanc criteria]

Culture criteria:

- Positive culture of amniotic fluid (via amniocentesis)

  And/or

- Positive culture of placental membranes (between chorion/amnion)

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Approval	PPD g this document for the reasons specifically noted on the approval page of the document. 23-Jan-2023 12:15:36 GMT+0000

Approval	PPD the content of this document and authorize its issuance. 23-Jan-2023 12:36:45 GMT+0000

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