The safety of Boostrix following routine immunization of pregnant women

EPI-PERTUSSIS-047 VS US DB (207221)

Final Version of December 15, 2017

Sponsor: GlaxoSmithKline Biologicals

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Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	EPI-PERTUSSIS-047 VS US DB (207221)
Date of protocol	15DEC2017
Detailed Title	An observational, retrospective cohort database study to assess the safety of Boostrix (U.S. formulation), a reduced tetanus, diphtheria, acellular pertussis vaccine (Tdap), following routine immunization of pregnant women in the United States.
Sponsor signatory	Narcisa Mesaros, MD Clinical and Epidemiology R&D Project Leader (CEPL), DTP, Polio, Hib containing vaccines GSK Biologicals' R&D Center Belgium
Signature	_____
Date	_____

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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 mutually agreed upon study conduct procedures and/or study conduct documents provided by GlaxoSmithKline Biologicals (GSK Biologicals).
- To assume responsibility for the proper conduct of the study.
- That I am aware of, and will comply with applicable guidelines and all applicable regulatory requirements, such as the Declaration of Helsinki, International Ethical Guidelines for Epidemiological Studies (Council for International Organizations of Medical Sciences [CIOMS]), United States Food and Drug Administration (FDA) Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies using Electronic Healthcare Data, and International Society for Pharmacoepidemiology (ISPE) guidelines for Good Pharmacovigilance Practice (GPP).
- To ensure that all persons assisting me with the study are adequately informed about study-related duties and functions as described in the protocol.
- 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, within reason.

eTrack study number and Abbreviated Title	EPI-PERTUSSIS-047 VS US DB (207221)
Date of protocol	15DEC2017
Detailed Title	An observational, retrospective cohort database study to assess the safety of Boostrix (U.S. formulation), a reduced tetanus, diphtheria, acellular pertussis vaccine (Tdap), following routine immunization of pregnant women in the United States.
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SYNOPSIS

Detailed Title	An observational, retrospective cohort database study to assess the safety of Boostrix (U.S. formulation), a reduced tetanus, diphtheria, acellular pertussis vaccine (Tdap), following routine immunization of pregnant women in the United States.
Rationale for the study	To describe the safety of Boostrix administered during pregnancy by conducting a post-marketing study that will provide safety information to the public and healthcare providers. This will be one of the largest cohorts of pregnant women vaccinated with Boostrix in the U.S. Through partnership between Kaiser Permanente Southern California (KPSC) and the sponsor, GlaxoSmithKline (GSK), we will provide information about the safety of maternal vaccination with Boostrix and maternal and infant adverse events in a community setting.
Description of the database	Vaccination and medical event data will be extracted directly from the electronic health record (EHR, Health Connect), which is the legal record of all medical care received within the KPSC health care system. Records of vaccinations and medical events can only be entered by medical staff.
Objective	To compare the incidence of maternal and infant adverse events among women who were vaccinated with Boostrix on or after the 1st day of the 27th week of a low risk pregnancy to that among a historical comparison cohort of pregnant women (January 1, 2012 to December 31, 2013) who were unvaccinated with any Tdap vaccine throughout their low risk pregnancy.

Study design	• Type of study: Observational retrospective database study
	• Type of design: Matched cohort study
	• End of study: The date the database analysis is completed.
	• Primary completion date: The date of final collection of data for all primary outcomes
	• Study population: Low risk pregnant women 15 to 45 years old (inclusive) with prenatal care and continuous membership (allowing up to a 31-day gap) at KPSC between the 1st day of the 27th week of pregnancy and the index (vaccination) date.
	  o Exposed: Women who received the Tdap vaccine (Boostrix) on or after the 1st day of the 27th week of pregnancy; and who were not vaccinated with any other Tdap vaccine at any other time during the pregnancy in scope of this study.
	  o Unexposed: Women matched to the exposed

cohort, pregnant sometime during the approximate estimated period between 1/1/2012-12/31/2013 and did not receive any Tdap vaccine during the pregnancy in scope of this study.

- General study aspects: Subject-level data will be collected for pregnant women and their infants through the EHR. For each individual pregnant woman, follow up will begin on the date they received the Boostrix vaccine, or the index date for the unvaccinated cohort, and will end on the date of disenrollment or the end of pregnancy, whichever came first. Infants born in KPSC hospitals from unvaccinated and vaccinated mothers will be followed for 6 months.

Number of subjects

Approximately 15,000 pregnant women vaccinated with Boostrix over a period of approximately one year.

Unexposed pregnant women will be matched 1:1 to the exposed group and will be identified from a historical cohort. We aim to have a total sample size of approximately 30,000 pregnant women.

Endpoint(s)

Primary

The primary endpoints of interest are incident maternal and infant adverse events identified from KPSC's EHR system using the pregnancy episode flowsheet, diagnosis codes, and procedure codes after the index date for the exposed and unexposed groups. To avoid capture of preexisting conditions, diagnostic codes representing each condition should not appear prior to the index date within the pregnancy under study. Medical records of the potential events will then be reviewed by trained research associates to confirm the diagnosis and to ascertain that it is an incident event. Analyses will be done on chart confirmed incident events.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetrics and Gynecology
ADaM	Analysis Data Model
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIOMS	Council for International Organization of Medical Sciences
EDD	Estimated date of delivery
EHR	Electronic Health Records
FDA	United States Food and Drug Administration
GPP	Good Pharmacovigilance Practice
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act of 1996 (U.S.)
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KPSC	Kaiser Permanente Southern California
MRN	Medical Record Number
MACDP	Metropolitan Atlanta Congenital Defects Program
OB-GYN	Obstetrics and Gynecology
PHI	Protected Health Information
REDCap	Research Electronic Data Capture

Rh	Rhesus
RIPC	Regional Immunization Practices Committee
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Module
Tdap	Tetanus, diphtheria, acellular pertussis
U.S.	United States
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink

GLOSSARY OF TERMS

Adverse Events:	Pre-specified, pregnancy-related diagnoses or pregnancy outcomes to be compared between the exposed and unexposed cohorts.
Cohort study:	Epidemiology study where subjects in a study population are classified according to their exposure status and followed over time to ascertain the outcome(s).
Database study:	A study involving the use of pre-existing data maintained in an electronic format.
End of study:	For database studies, end of study is the date the database analysis is complete. For this study, that is the date the analysis of congenital anomaly (among KPSC-born infants through 6 months of age) is complete.
Exposed cohort:	Subjects classified as exposed to Tdap (Boostrix) on the 1st day of the 27th week of pregnancy or later.
eTrack:	GSK's tracking tool for clinical/epidemiology studies.
Health Connect:	Electronic health record system which is the legal record of all received medical care within the KPSC health care system.
Index date of the matched pair of exposed and unexposed pregnant women:	The unexposed cohort of pregnant women will be matched 1:1 to the exposed group of pregnant women for comparisons of maternal and infant adverse events between the two cohorts. The matched pair will have an index date, which is determined by the number of days from pregnancy start to Boostrix vaccination of the exposed woman. Every unexposed woman will be assigned an index date that is determined by the number of days from pregnancy start to the Boostrix vaccination date of her matched exposed woman. The same number of days calculated in the exposed woman will be added to the pregnancy start of the unexposed woman to identify her index date. Both groups will be followed from the index date to the events of interest and pregnancy outcomes.
"Low-risk" pregnant women:	Subjects without high-risk conditions defined by age <15 or >45, autoimmune disorder (systemic lupus erythematosus, mixed connective tissue disease), cervical incompetence, multiple gestation, rhesus (Rh)

	sensitization, and thyroiditis.
Pregnancy start:	Corresponds to a gestational age of 0 weeks based on the most reliable estimated date of delivery.
Primary completion date:	The date of final collection of data for all primary outcomes.
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 endpoints.
Subject:	Term used throughout the protocol to denote a person about whom some medical information has been recorded in a database.
Unexposed cohort:	Subjects classified as not exposed to any Tdap vaccine during the pregnancy under study

1. INTRODUCTION

1.1. Background

Whooping cough, also referred to as pertussis, is a highly contagious respiratory disease primarily caused by the bacterium *Bordetella pertussis*. The disease is most severe in unvaccinated or incompletely vaccinated infants, who may develop apnea, seizures secondary to hypoxia, pulmonary hypertension, pneumonia, otitis media, and death (1). Cyclical increases in pertussis incidence continue to be described every 3 to 5 years in most developed countries despite high vaccination coverage. This is explained largely by waning immunity both after vaccination and after natural infection (2-4).

Two tetanus-diphtheria-acellular pertussis (Tdap) vaccines (Adacel and Boostrix) were licensed for use in the United States (U.S.) in 2005 (5). These vaccines were recommended for routine use in non-pregnant adolescents and adults when introduced. In 2010, the California Department of Health began recommending Tdap vaccine to women at any stage of pregnancy in response to a pertussis outbreak and several infant deaths (6). One year later, the Advisory Committee on Immunization Practices (ACIP) advised Tdap to be administered during pregnancy, at 20 weeks gestation or later, to women who had not been previously vaccinated (7). In October 2012, ACIP expanded its recommendation of administering Tdap during pregnancy (8); in order to increase the protection of newborns, all pregnant women should be offered Tdap, regardless of whether they have received Tdap previously. While the ACIP recommends that optimal timing for Tdap administration is between 27 and 36 weeks gestation to optimize transfer of anti-pertussis antibodies, Tdap may be given at any time during pregnancy. Both Adacel and Boostrix can be used interchangeably.

Prelicensure clinical study data showed that the incidence of unsolicited adverse events reported in the 31 days after vaccination was comparable between recipients of Boostrix and Adacel (17.8% and 22.2% for Boostrix and Adacel, respectively). Serious adverse events during 0-6 months following vaccine were reported by 1.4% and 1.7% of subjects, respectively. During the 6-month extended safety evaluation period, no serious adverse events of a neuroinflammatory nature or with information suggesting an autoimmune etiology were reported in subjects who received Boostrix (9).

Safety events following Tdap immunization during pregnancy have been increasingly examined in recent years. A placebo-controlled clinical trial of Adacel administered to pregnant women (2008-2012) found no Tdap-associated serious adverse events (10). During a time when Tdap was not routinely recommended for pregnant women, spontaneous abortions were the most frequent pregnancy-specific adverse events (16.7%) identified through the Vaccine Adverse Event Reporting System (VAERS), a national database used for monitoring the safety of vaccines in the population (11). However, the number of pregnant women who received the vaccine was small (n=132) and likely a selective group since the vaccine was not in routine use. A small study observing a limited number of maternal and infant outcomes (chorioamnionitis, postpartum endometritis, premature rupture of membranes, 5-minute Apgar score, birth defects) also found no Tdap-associated adverse events (12). However, the authors found that Tdap was associated with women having decreased odds of cesarean delivery. In a study of 2010-

2012 live births in two California health care systems participating in the Vaccine Safety Datalink (VSD) project, no associations between Tdap and maternal hypertensive disorders were found, although a small but statistically significant increased risk of chorioamnionitis was observed (6.1% in vaccinated, 5.5% in unvaccinated) (13), a finding consistent with a larger subsequent study at seven U.S. health care system VSD sites (14). An increased risk of chorioamnionitis was also found in a different U.S.-based study of over one-million pregnant women (2010-2014), which also found an increased risk of postpartum hemorrhage, one case of post-immunization anaphylaxis, and 12 cases of post-delivery encephalopathy (15). However, this study did not find a significant association with preeclampsia/eclampsia or premature rupture of membranes. An evaluation of acute events post vaccination found no associations between Tdap immunization and a composite outcome of acute events, incident neurologic events or thrombotic events, or proteinuria in a large VSD cohort (16). Additionally, a study of infant outcomes found that Tdap was not significantly associated with increased risk for structural birth defects or microcephaly for vaccinations given during any week of pregnancy (17). Except for the aforementioned VSD studies in which Adacel comprised the majority of Tdap vaccines administered (13), the Tdap product in the other studies was not explicitly mentioned.

Considering that Boostrix is recommended to be used interchangeably with Adacel, and there are limited observational safety data on Boostrix during pregnancy, a post-marketing study describing the safety of Boostrix vaccine in pregnant women is particularly necessary and can provide timely safety information to the public and healthcare providers.

1.2. Rationale for the study

The rationale for the current study is to assess the safety of Boostrix administered on or after the 1st day of the 27th week of pregnancy by conducting a post-marketing study that will provide safety information to the public and healthcare providers. This will be one of the largest cohorts of pregnant women vaccinated with Boostrix in the U.S. Through partnership between Kaiser Permanente Southern California (KPSC) and the sponsor, GlaxoSmithKline (GSK), we will provide information about the safety of maternal vaccination with Boostrix and maternal and infant adverse events in a community setting.

The observational study design takes advantage of KPSC's electronic health record (EHR) system, Health Connect. We will capture adverse events following Boostrix vaccination in pregnant women and adverse events in an unexposed historical comparison cohort of pregnant women. Retrospective ascertainment of pregnant women through Health Connect is an efficient strategy in comparison to a recruitment study, which would be practically and financially infeasible because pregnant women are not likely to enroll in safety studies.

2. OBJECTIVE

2.1. Primary objective

The primary objective is to compare the incidence of maternal and infant adverse events among women who were vaccinated with Boostrix on or after the 1st day of the 27th week of a low risk pregnancy to that among a historical comparison cohort of pregnant women (approximate estimated period: January 1, 2012 to December 31, 2013) who were unvaccinated with any Tdap vaccine throughout their low risk pregnancy.

3. STUDY DESIGN

3.1. Study setting

KPSC is an integrated healthcare system that provides comprehensive prepaid health services for its 4.4 million members. There are 15 medical centers that include a total of 225 medical office buildings throughout Southern California. Members are racially diverse and include the entire socio-demographic spectrum, and over 99% are community-dwelling. The demographic makeup of the KPSC membership closely mirrors the Southern California population and the California census population (18). Compared to the racial/ethnic distribution of the U.S. population, the KPSC membership has twice as many individuals of Asian descent and three times as many Hispanics. Data regarding demographics, services, diagnoses, and procedures are tracked in the KPSC EHR (Health Connect) from the outpatient, emergency department, and hospital settings. Health Connect is the legal record of all medical care received within the KPSC system. Records of vaccinations and medical events can only be entered by medical staff. Pharmacy records and vaccinations are linked through patients' unique medical record numbers (MRNs). Vaccinations received outside of the health plan are recorded with appropriate documentation.

KPSC is a pre-paid health care system. Vaccines are typically provided to KPSC members at no charge, which is an incentive for members to receive immunizations within the system. Also, there is a very strong motivation for members to use services internally. For outside providers to be reimbursed by the health plan for covered emergent or contract care, claims must be submitted with documentation of the episode of care. Thus, the capture of care delivered to members by electronic administrative data is reasonably assumed to be very comprehensive. The KPSC Regional Immunization Practice Committee (RIPC) makes recommendations to ensure appropriate use of vaccination and implementation of new ACIP immunization recommendations within KPSC.

<u>Standard of care regarding use of Tdap in pregnant women</u>

On October 24, 2012, ACIP voted to recommend Tdap for pregnant women with every pregnancy irrespective of previous Tdap history. In December 2012, the KPSC RIPC followed ACIP guidance and recommended that providers of prenatal care implement a Tdap immunization program for all pregnant women. The guidance indicated that all health-care personnel should administer a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap. In order to maximize the

maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration was specified between 27 and 36 weeks gestation.

Prior to the conduct of this observational study of Boostrix in pregnancy, Adacel had been the only Tdap vaccine on the KPSC formulary.

Process for identifying pregnancy information

If a woman receives prenatal care at KPSC, her pregnancy is recorded in a pregnancy episode flowsheet. The flowsheet is contained in the woman's medical record and is created at the beginning of the pregnancy. It is appended with all pregnancy encounters including prenatal visits, the hospital admission for birth, as well as any post-partum visits. Pregnancy and birth information at KPSC including maternal age, pre-pregnancy height and weight, perinatal risk factors, prenatal visit information, complications of pregnancy and delivery, and procedures used during labor and delivery are available from the EHR and can be viewed in Health Connect.

Process for linking mothers and infants

As standard of care at KPSC, all infants born in KPSC hospitals are automatically assigned a MRN regardless of whether the mother is a current plan member. If the mother is a current member, the baby's MRN is automatically linked to her medical record in her pregnancy episode flowsheet.

3.2. Feasibility assessment

The following tables display data to describe Tdap vaccination among pregnant women at seven selected KPSC medical centers that will administer the Boostrix vaccine. Approximately 15,000 women vaccinated with Boostrix will be included in this study, over approximately a one-year period.

Pregnant women receiving the Tdap vaccine

The following table provides demographic information on pregnant women receiving the Tdap vaccine at seven selected medical centers at KPSC (Table 1). There were 19,804 pregnant women receiving the vaccine within these medical centers in 2016. Over half of them were of Hispanic race/ethnicity (57%). The age distribution shows that pregnant women aged 27-35 years old made up more than half (55%) of the Tdap-exposed pregnant women (Table 2).

Table 1. Race/ethnicity of women receiving the Tdap vaccine during pregnancy at seven selected medical centers at Kaiser Permanente Southern California, 2016

Mother's race/ethnicity	Frequency	Percent
Asian	2,494	12.6%
Black	1,643	8.3%
Hispanic	11,354	57.3%
Multiple	512	2.6%
Native American/ Alaskan	11	0.1%
Others	24	0.1%
Pacific Islander	23	0.1%
Unknown	33	0.2%
White (Non-Hispanic white)	3,710	18.7%
TOTAL	**19,804**	**100%**

Table 2. Age of women at Tdap vaccination during pregnancy at seven selected medical centers at Kaiser Permanente Southern California, 2016

Mother's age at vaccination (years)	Frequency	Percent
15-26	5,785	29.2%
27-35	10,858	54.8%
36-45	3,132	15.8%
>45	29	0.2%
TOTAL	**19,804**	**100%**

Membership among Tdap vaccinated pregnant women

At seven selected medical centers within KPSC, 18,875 (95.3%) pregnant women had continuous membership (allowing up to a 31-day gap) at least from the start of the 27th week of pregnancy (Table 3). There were 16,147 (82%) women who were members since the beginning of pregnancy.

Table 3. Membership among women receiving the Tdap vaccine during pregnancy at seven selected medical centers at Kaiser Permanente Southern California, 2016

Membership during pregnancy*	Frequency	Percent
Gestation: 0 to 26 weeks only	260	1.3%
Gestation: 27 weeks to delivery only	2,728	13.8%
Gestation: 0 weeks to delivery	16,147	81.5%
Partial membership**	669	3.4%
TOTAL	**19,804**	**100%**

* Represents women with membership (allowing up to a 31-day gap) during the entire indicated period.
** 447 had membership during the post-vaccine pregnancy period

Gestational age at Tdap vaccination

There were 19,554 (98.7%) pregnant women who received Tdap vaccination at or after 27 weeks of pregnancy (Table 4). There were 18,611 (94.0%) women who were vaccinated between 27 and 36 weeks gestation.

Table 4. Gestational age of women at Tdap vaccination during pregnancy at seven selected medical centers at Kaiser Permanente Southern California, 2016

Gestational age at vaccination	Frequency	Percent
<27 weeks	250	1.3%
27 weeks to 32 weeks	15,111	76.3%
33 weeks to 36 weeks	3,500	17.7%
>36 weeks	943	4.8%
TOTAL	**19,804**	**100%**

Note: Only those women meeting eligibility criteria, including membership and low risk status, will be included in the primary analysis.

Rationale for historical comparison cohort

The estimated period of 1/1/2012-12/31/2013 was chosen for the unvaccinated comparison group because Tdap uptake ranged between 27% and 38% during this time (Table 5). The aim is to restrict the unvaccinated population to approximately 2012-2013 to minimize the concerns of confounding by indication. Given that Tdap uptake exceeded 65% starting in 2014, a concurrent unvaccinated cohort will yield a small and selective sample, and is not representative of an unvaccinated group.

Table 5. Tdap vaccine receipt during pregnancy at Kaiser Permanente Southern California, 2011-2016

	Tdap during pregnancy		No Tdap during pregnancy	
Year	**Frequency**	**Percent**	**Frequency**	**Percent**
2011	18325	40.0%	27471	60.0%
2012	13128	27.6%	34486	72.4%
2013	18309	38.3%	29519	61.7%
2014	32660	65.3%	17366	34.7%
2015	35754	68.4%	16513	31.6%
2016	38475	69.3%	17058	30.7%

3.3. Study design overview

The study design is an observational retrospective matched cohort study. This proposed research will be conducted among pregnant women who are members of KPSC.

The exposed cohort will consist of "low risk" pregnant women who received the Tdap vaccine (Boostrix) on or after the 1st day of the 27th week of pregnancy during the vaccination period at ob-gyn clinics of seven selected medical centers. Approximately 15,000 women vaccinated with Boostrix will be included in this study over approximately a one year period. The unexposed cohort will consist of "low risk" pregnant women during the approximate estimated period from 1/1/2012 to 12/31/2013 who never received Tdap vaccine during pregnancy. "Low risk" refers to pregnant

women without the following conditions: Age <15 or >45, autoimmune disorder (systemic lupus erythematosus, mixed connective tissue disease), cervical incompetence, multiple gestation, rhesus (Rh) sensitization, and thyroiditis. Existing health conditions, age, lifestyle factors, and conditions of pregnancy can place a pregnancy at risk (19). A subset of these conditions is considered in the exclusion criteria. Other high-risk conditions will be considered as potential covariates.

Subject-level data will be collected for pregnant women and their infants through the EHR. For each individual pregnant woman, analytical follow up will begin on the date they receive the Boostrix vaccine, or the index date for the unvaccinated cohort, and will end on the date of disenrollment or the end of pregnancy, whichever came first. Infants born in KPSC hospitals will be followed for 6 months.

4. STUDY POPULATION/CASE DEFINITION(S)

The exposed and unexposed cohorts will consist of low risk pregnant women 15 to 45 years of age. "Low risk" refers to pregnant women with no high-risk conditions: autoimmune disorder (systemic lupus erythematosus, mixed connective tissue disease), cervical incompetence, multiple gestation, Rh sensitization, and thyroiditis. The pregnant women must have prenatal care and continuous membership (allowing up to a 31-day gap) at KPSC between the 1st day of the 27th week of pregnancy and the index (vaccination) date.

Women will be considered exposed if they received Boostrix on or after the 1st day of the 27th week of pregnancy at selected ob-gyn clinics at seven medical centers throughout KPSC (vaccination period planned to begin in January 2018). Unexposed pregnant women comprise those who were pregnant sometime during the approximate estimated period between 1/1/2012 and 12/31/2013 and did not receive any Tdap vaccine during pregnancy. If needed, we will consider adding additional years to increase the eligible number of unexposed pregnant women. Gestational age will be estimated from the most reliable estimated date of delivery (EDD) which is based on the last menstrual period, the first accurate ultrasound examination, or both. Obstetric providers are recommended to reference guidelines from the American College of Obstetrics and Gynecology (ACOG) to calculate EDD (20). Pregnancy start date will correspond to a gestational age of 0 weeks.

Matching process

The unexposed cohort will be matched 1:1 to the exposed group for comparisons of maternal and infant adverse events between the two cohorts. Every unexposed woman will be assigned an index date that is determined by the number of days from pregnancy start to the Boostrix vaccination date of her matched exposed woman. The same number of days calculated in the exposed woman will be added to the pregnancy start of the unexposed woman to identify her index date. Matching variables include maternal age at pregnancy start (± 1 year), and race/ethnicity (White, Black, Hispanic, Asian, and Other).

For example, suppose there is a low risk 28-year-old (at pregnancy start) Hispanic pregnant woman with a pregnancy start date of 2/18/2018 receiving Boostrix on 8/30/2018 on the 194th day of her pregnancy (from pregnancy start date to vaccination).

We will match her with a low risk Hispanic woman pregnant sometime between 1/1/2012 and 12/31/2013, who was 27-29 years of age at pregnancy start, with an index date assigned to be the 194th day of pregnancy, and who never received Tdap vaccine during pregnancy. If a match is not feasible within the proposed two-year period, the pool of unexposed women can be expanded to include unexposed pregnant women from additional years. The matched pair will have an index date, which is determined by the number of days from pregnancy start to Boostrix vaccination of the exposed woman. Both groups will be followed for events of interest from the index date. In this example, both women will be followed from the 194th day of their pregnancy.

4.1. Number of subjects

Approximately 15,000 pregnant women vaccinated with Boostrix over a period of approximately one year. Unexposed pregnant women, matched 1:1 to the exposed group, will be identified from a historical cohort. Therefore, we aim to have a total sample size of approximately 30,000 pregnant women.

4.2. Inclusion criteria

- Pregnant women with prenatal care and continuous membership (allowing up to a 31-day gap) at KPSC between the 1st day of the 27th week of pregnancy and the index (vaccination) date.
- **Exposed cohort:** Pregnant women vaccinated with Boostrix on or after the 1st day of the 27th week of pregnancy; who were not vaccinated with any other Tdap vaccine at any other time during the pregnancy in scope of this study.
- **Unexposed cohort:** Women matched to the exposed cohort and pregnant sometime during the approximate estimated period between 1/1/2012-12/31/2013 and did not receive any Tdap vaccine during the pregnancy in scope of this study.

For the analysis of congenital anomalies among live births, at birth and through six months of age, the following additional inclusion criteria for infants will be applied:

- Live born
- Born in KPSC hospitals

4.3. Exclusion criteria

Pregnant women will be analytically excluded from the primary analysis if they are “high risk.” High-risk conditions include the following:

- Age at pregnancy start <15 or >45 years
- Autoimmune disorder (systemic lupus erythematosus, mixed connective tissue disease)
- Cervical incompetence
- Multiple gestation
- Rh sensitization

- Thyroiditis

5. DATA COLLECTION AND MANAGEMENT

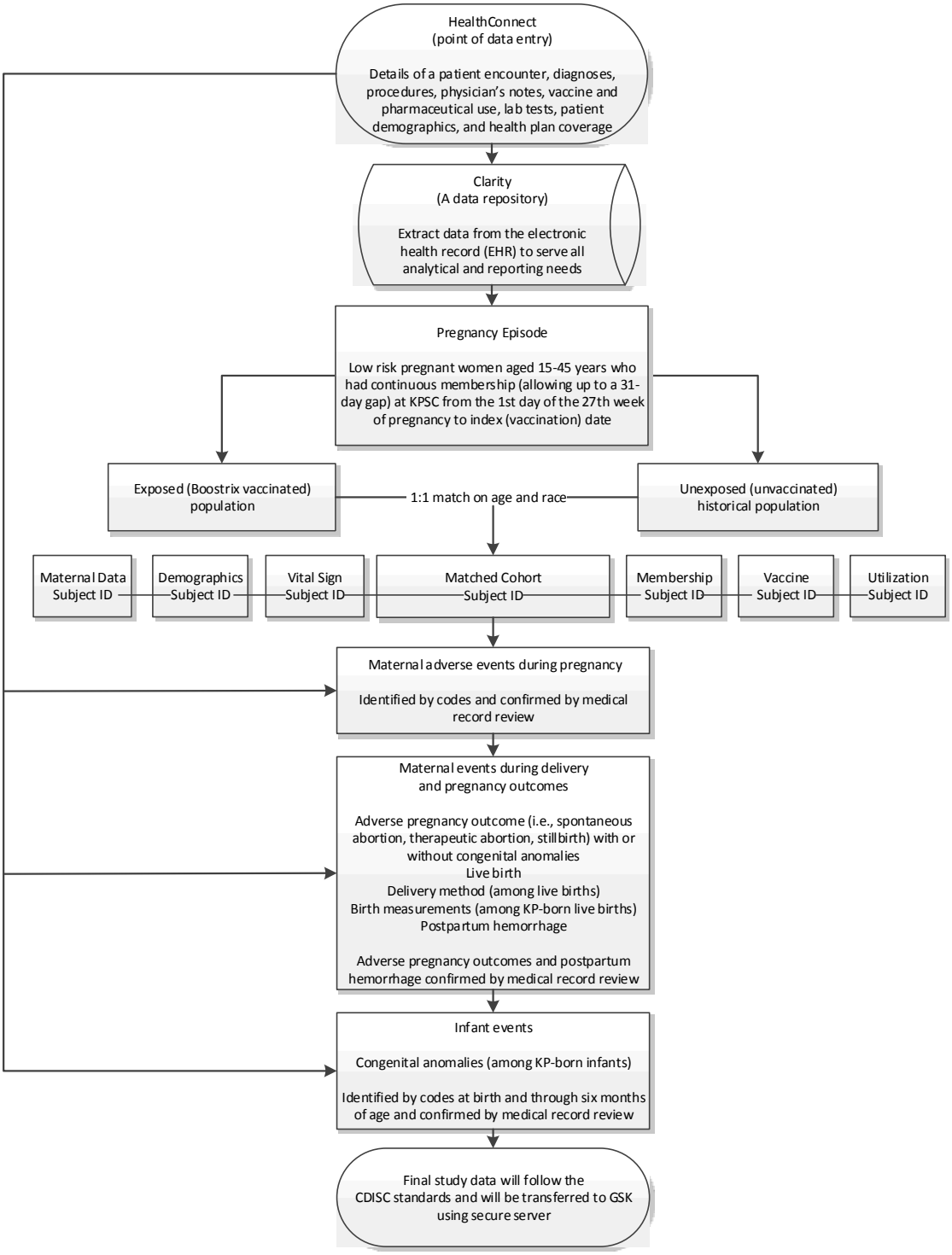
Vaccination and medical event data will be extracted directly from the EHR (Health Connect), which is the legal record of all medical care received within the KPSC system. Figure 1 provides an overview of the data flow for this study. All details of a patient encounter, including diagnoses, procedures, and physician's notes, are entered into the EHR at the point of care. All vaccinations are entered into the EHR when they are given, with vaccine, dose, manufacturer, and lot number entered at the time of vaccination. Vaccinations received outside of the health plan are recorded with appropriate documentation. Records of vaccinations and medical events can only be entered by medical staff. Endpoints of interest will be extracted from the EHR using the pregnancy episode flowsheet, diagnosis codes (ICD-9 and ICD-10 codes), and procedure codes.

Chart abstraction will be performed for the pre-specified maternal and infant adverse events to confirm the event and that they are incident after the index date. Medical record review will also be conducted to confirm adverse pregnancy outcomes (i.e., spontaneous abortion, therapeutic abortion, stillbirth), unknown pregnancy outcome, and unknown delivery method. Chart abstractors will not be masked to the exposure status as they will have access to the entire medical record within Health Connect, including vaccination status. Data will be abstracted directly from Health Connect. For the chart abstracted data, the study team will develop a chart abstraction form in the Research Electronic Data Capture system (REDCap) and a chart abstraction manual (21). The chart abstraction manual will be developed for the purposes of ensuring standardization and uniformity of data collection among the chart abstractors. The chart abstraction manual may include guidance on how to navigate through the EHR to search for pertinent information (including screenshots of the EHR for reference), directives for how to address each question in the abstraction form, and an explanation of clinical terms and other variable definitions. A sample of abstraction forms will be quality checked by a second person. Logic and data range checks will be performed on the abstracted data collected electronically in REDCap.

Electronic data and chart reviewed data will be combined into a Statistical Analysis Software (SAS) dataset for analysis. Double programming will be performed to check the total number of eligible subjects included in the analysis. All other programming will be reviewed by a second person. The results of the original and validation programming will be compared, any discrepancies will be investigated, and action will be taken to resolve discrepancies.

The study datasets will be formatted according to Clinical Data Interchange Standards Consortium (CDISC). We will develop specifications to include information about the number of domains, mapping rules, and will output the dataset according to the SAS study dataset, required analysis report and CDISC implementation guide; map the original SAS data to the domains according to the specification to create Study Data Tabulation Module (SDTM) and Analysis Data Model (ADaM) datasets; validate the SDTM and ADaM datasets using an open source CDISC validation program (e.g., OpenCDISC); and produce submission documentation including DEFINE.XML and Study Data Reviewers Guide.

Figure 1. Illustration of data flow



6. STATISTICAL METHODS

This study will involve both descriptive and multivariable analyses, and all analyses will be conducted using the SAS statistical software package (version 9.3 or later).

6.1. Primary pre-specified events of interest

The pre-specified events of interest are maternal and infant outcomes (Table 6) identified from KPSC's EHR system using the pregnancy episode flowsheet, diagnosis codes, and procedure codes for the exposed and unexposed groups. While these events are recorded as part of routine care, in general, ACOG recommended guidelines are used by KPSC providers to diagnose and manage these conditions (22-35). In addition, we will use a commonly accepted definition to identify congenital anomalies, such as that used by the Metropolitan Atlanta Congenital Defects Program (MACDP) (36, 37). Additional birth outcomes will be captured for descriptive purposes, but not considered adverse events: gestational age at birth, birth weight, birth length, head circumference, and Apgar scores. To avoid capture of preexisting conditions, diagnostic codes representing each condition should not appear prior to the index date within the pregnancy under study. Medical records of the potential pregnancy and postpartum maternal events, and congenital anomalies diagnosed before and after birth will be reviewed by trained research associates to confirm the event and to ascertain that it is incident (i.e., onset is indeed after the index date). Medical record review will also be conducted on adverse pregnancy outcomes (i.e., spontaneous abortion, therapeutic abortion, stillbirth), unknown pregnancy outcome, and unknown delivery method. All pre-specified events of interest will be collected through the primary completion date. Analyses will be done on chart confirmed incident events.

Table 6. List of maternal and infant outcomes

Description
Maternal events during pregnancy
Placenta abruption/placenta previa
Pre-eclampsia and eclampsia
Fetal distress
Gestational diabetes
Intra-uterine infections (e.g., chorioamnionitis, endometritis)
Pre-mature uterine contractions
Poor fetal growth (e.g., intrauterine growth restriction)
Macrosomia
Maternal events during delivery and pregnancy outcomes
Spontaneous abortion with or without congenital anomalies
Therapeutic abortion with or without congenital anomalies
Stillbirth with or without congenital anomalies
Live birth
Delivery method (i.e., vaginal, cesarean)
Maternal postpartum events
Postpartum hemorrhage
Infant events (among KPSC-born live births)
Presence or absence of congenital anomalies at birth and through 6 months of age

6.2. Statistical methods

6.2.1. Covariates

Baseline characteristics of pregnant women and information on other relevant covariates will be extracted through automated data. Data will be in the form of International Classification of Diseases, 9th or 10th Revision (ICD-9 or ICD-10) codes or structured data fields. While data on these characteristics will be collected, only the potential confounders associated with the exposure or outcome will be considered in adjusted analyses and will be a subset of the covariates of interest. Identification of the potential confounders will be determined through bivariate analyses and by prior knowledge based on the literature (19).

Some of the covariates of interest to be collected and explored (if data are available) include:

- smoking status
- pre-pregnancy body mass index
- alcohol use
- length of membership prior to 27 weeks gestation (but after pregnancy start)
- health care utilization (receipt of medical care) prior to the index date (but after pregnancy start)
- number of previous pregnancies

- history of pregnancy loss
- receipt of other vaccines during pregnancy, e.g., influenza vaccine
- receipt of vaccines containing diphtheria, tetanus toxoid or pertussis containing antigens within one year before pregnancy
- season of pregnancy start
- medical history/underlying conditions recorded during pregnancy
- Medicaid insurance (public health insurance: Indication of low income status)

6.2.2. Analysis of primary objective

Demographics and pregnancy information will be compared between the exposed and unexposed cohorts. Bivariate analyses will be conducted for all covariates of interest. Continuous variables will be summarized by means, medians, ranges, and standard deviations and compared using t-tests; categorical variables will be summarized by frequency distributions and compared using chi-square tests for the exposed and unexposed groups. Potential confounders will be determined based on bivariate analyses and scientific relevance.

We will calculate crude incidence and 95% confidence intervals (CI) for each adverse event for the exposed and unexposed groups. The incidence of each maternal adverse event during pregnancy will be calculated separately and will consist of the total number of women with the condition in the numerator and the total person time in the denominator. For the analysis of each adverse event, each individual pregnant woman will be followed from the date she received the Boostrix vaccine, or the assigned index date, to the date of each adverse event, end of the pregnancy, or disenrollment, whichever comes first.

The incidence of each pregnancy outcome (i.e., spontaneous abortion with or without congenital anomalies, therapeutic abortion with or without congenital anomalies, stillbirth with or without congenital anomalies, live birth) will be calculated separately and will consist of the total number of women with each pregnancy outcome in the numerator and the total number of women with pregnancy outcomes in the denominator. The incidence of each delivery method (i.e., vaginal, cesarean) will be calculated as the total number of women with vaginal live birth or cesarean live birth, respectively, in the numerator and the total number of women with live birth in the denominator.

Postpartum hemorrhage will be ascertained through the end of the delivery hospitalization. The incidence of postpartum hemorrhage will be calculated as the total number of women with postpartum hemorrhage in the numerator and the total number of women with either live birth or stillbirth in the denominator.

Congenital anomalies will be identified at birth and through 6 months of age among infants born in KPSC hospitals. Most congenital anomalies are diagnosed by 6 months of age (38). The prevalence of congenital anomalies (overall, by type, at birth, and through 6 months of age) will be calculated as the number of infants with a congenital anomaly in the numerator and the total number of infants born in KPSC hospitals in the denominator.

The proportion of live births without congenital anomalies will be calculated as 1 minus the proportion of live births with congenital anomalies among all KPSC born live births.

The unadjusted and adjusted hazard ratio with 95% CI for each maternal adverse event during pregnancy comparing the Boostrix exposed cohort and the matched unexposed cohort will be estimated by stratified proportional hazards model with and without adjustment for potential confounders. The adjusted analysis is the main analysis of interest. Separate proportional hazards regression analysis for each adverse event will be conducted.

The proportional hazards model accounts for the possible different lengths of membership between exposed and unexposed cohorts. If the follow-up times are similar between cohorts, we may use a Poisson model to estimate the incidence rate ratio.

The adjusted and unadjusted relative risk with 95% CI for maternal events during delivery and pregnancy outcomes, postpartum hemorrhage, and congenital anomalies among KPSC-born infants identified at birth and identified at 6 months of age comparing the Boostrix exposed cohort and the matched unexposed cohort will be estimated by a Poisson regression model with and without adjustment for potential confounders. If the outcome is common (i.e., incidence>5%), a Poisson regression model with robust variance estimation will be used to estimate the relative risk (39). The adjusted analysis is the main analysis of interest. Separate Poisson regression analysis for each adverse event will be conducted. All analyses will be completed by the end of study.

No formal adjustment for multiple comparisons will be performed. Since this is a safety study, to avoid missing a potential safety signal, a conservative approach will be taken without adjusting for multiple comparisons (e.g., Bonferroni adjustment).

6.2.3. Sensitivity Analysis

A sensitivity analysis for all maternal and infant adverse events will be conducted by additionally including low risk women vaccinated before 27 weeks and all high-risk pregnancies, previously excluded from the primary analysis. The incidence of adverse events in women vaccinated with Boostrix at any time during pregnancy, regardless of risk level and exposure time period, will be compared to that in a matched historical comparison cohort of unvaccinated pregnant women. Women with high-risk pregnancies vaccinated with Boostrix at any time during pregnancy will be additionally matched to a historical group of unvaccinated women by high-risk condition (autoimmune condition, cervical incompetence, Rh sensitization, multiple gestation, thyroiditis). If a match is not feasible, a woman will be matched to the most appropriate unvaccinated high-risk woman, based on condition of high risk. Otherwise, women will be matched to unvaccinated high-risk women in aggregate, regardless of their high-risk condition. Women excluded from the primary analysis due to not meeting the membership criteria (continuous membership between the 1st day of the 27th week of pregnancy and the index [vaccination] date) will also be included in the sensitivity analysis. For those without membership on the vaccination date, we will only report vaccination without outcomes.

The adjusted and unadjusted hazard ratio or relative risk with 95% CI for each maternal and infant adverse event comparing the Boostrix exposed cohort and the matched

unexposed cohort will be estimated by stratified proportional hazards model or Poisson regression model with and without adjustment for potential confounders.

6.3. Sample size considerations

The sample size estimation was performed using SAS software package (version 9.3) PROC POWER procedure for testing two proportions. It was based on a 1:1 matched cohort study design, given power=0.8, alpha=0.05 and detectable relative risk=1.2, 1.5, 1.8 or 2. Because pre-eclampsia and placental abruption have the lowest incidence, we selected these 2 conditions for the sample size estimation. If the desired sample size can be reached, we are confident that we can achieve sufficient power for other more common conditions such as gestational diabetes. The incidence of pre-eclampsia and placental abruption at KPSC was obtained from a study by Getahun, et al. (40). The estimated background incidence of pre-eclampsia and placental abruption during the entire pregnancy was 5.6% and 1.16%, respectively. We assumed that all events occurred after 20 weeks of pregnancy, and that vaccination could occur at any time after the 27th week of pregnancy (from the population of Tdap-vaccinated women described in Table 4, 49% received Tdap between weeks 27-29, and 28% received Tdap between weeks 30-32). We used half of 5.6% and 1.16% as the background incidence for the unexposed (unvaccinated) group. This was done because if the index date (i.e., the vaccination date of the exposed group) occurred around week 30, only half of the events would occur after the index date. This is a conservative estimate (low incidence estimate) for determining the required sample size since the true incidence would likely be higher if the majority of the events occurred near the time of delivery and vaccination preceded most of the events.

The following table (Table 7) shows that to detect a 20% increased risk of preeclampsia with 80% power, we will need about 15,000 vaccinated women to be included in the analysis. This number will allow us to detect a 50% increased risk of placental abruption with more than 80% power. The sample size estimation would be similar with similar sized detectable hazard ratios.

Table 7. Sample size required to detect various relative risks of pre-eclampsia and placental abruption

Outcome	Reference Proportion (incidence rate of unexposed group)	Relative Risk	Sample size of exposed group	Total sample size
Pre-eclampsia	0.028	1.2	14,942	29,884
		1.5	2,704	5,408
		1.8	1,178	2,356
		2	805	1,610
Placental abruption	0.0058	1.2	73,953	147,906
		1.5	13,434	26,868
		1.8	5,872	11,744
		2	4,024	8,048

7. STUDY CONSIDERATIONS

Most of the Boostrix exposures during pregnancy will occur at 27 weeks gestation or later. As such, we expect pregnancy outcomes that occur earlier in pregnancy such as spontaneous abortion and therapeutic abortion to be rare in our study. Furthermore, while we will describe the frequency of congenital anomaly among the exposed and unexposed cohorts, we note that the most plausible time period for development of congenital anomalies is early in pregnancy (38). Cautious interpretation of maternal Boostrix immunization and congenital anomaly is warranted.

One potential limitation is that the exposed (Boostrix vaccinated) cohort and the unexposed cohort come from different time periods. With the exposed cohort from the ICD-10 era and the unexposed cohort from the ICD-9 era there is a potential concern that adverse event differences between the cohorts may be due to coding variation. There is a potential risk of bias if the prevalence of adverse events is higher or lower in either exposed or unexposed cohorts due to coding variation. This issue is not specific to KPSC but rather affects all health care organizations and similar research conducted in the U.S. However, this is not a major concern at KPSC as there is specific mapping (crosswalk) between ICD-9 and ICD-10 for all of the outcomes (41, 42). Most importantly, no matter which system is used, a comprehensive list of codes will be used to identify all potential events of interest. In addition, a review of medical records will be conducted to determine whether the events are truly incident events with onset after the index date (vaccination date for the exposed). Similarly, by using a historical cohort to identify the unexposed group to compare to a current exposed cohort, there is a concern that the baseline incidence of the selected safety endpoints will vary significantly between the Tdap (*Boostrix)* vaccination period and the historical comparison period. However, the advantage of comparing to a historical population of pregnant women during approximately 2012-2013 is that we are identifying an unvaccinated group during a period when prenatal Tdap vaccine uptake was low, making these pregnant women more representative of an unvaccinated cohort. A current unvaccinated cohort would yield a small and selective sample (given over 70% Tdap uptake) that is not representative of an unvaccinated group and would be affected by confounding by indication.

The proportional hazards analyses proposed to evaluate associations between Tdap exposure and adverse events consider the potential for women in the exposed and unexposed groups to have different follow-up times. However, due to the inclusion of women later in pregnancy (27 weeks gestation), we expect minimal difference in loss to follow-up, and therefore may consider a Poisson approach instead. No formal adjustment for multiple comparisons will be performed. Since this is a safety study, to avoid missing a potential safety signal, a conservative approach will be taken without adjusting for multiple comparisons (e.g., Bonferroni adjustment).

If a safety signal is identified, further exploration of the outcome data will be completed to investigate potential sources for the association, including but not limited to changing secular trends or coding practices.

8. CONDUCT OF THE STUDY

GlaxoSmithKline (GSK) will engage KPSC to provide activities including conducting the study on behalf of GSK. The study will be conducted by the Investigator at KPSC's premises under the oversight of the sponsor, GSK. Through this partnership, we will provide critical information about the safety of maternal vaccination with Boostrix in a community setting.

8.1. Regulatory and ethical considerations

The study will be conducted in accordance with all applicable regulatory requirements, including all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki, International Ethical Guidelines for Epidemiological Studies (CIOMS), FDA Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies using Electronic Healthcare Data, and ISPE guidelines for Good Pharmacovigilance Practice (GPP).

The KPSC team will obtain approval of the final protocol from the Institutional Review Board (IRB) at KPSC prior to study start.

8.2. Informed consent and data privacy

Subjects included in this study will be identified among KPSC health plan members. Informed consent is not required because Boostrix is a licensed vaccine given to eligible KPSC members as part of routine clinical care. KPSC will obtain IRB approval for the use of patient data and to ensure protection of data privacy. Individual written Health Insurance Portability and Accountability Act (HIPAA) authorizations prior to initiating data collection will not be required.

8.3. Additional data

Additional summary level data will be provided from KPSC to GSK throughout the course of the study. This will include aggregated data from automated data sources, and will include the following:

- Monthly vaccine uptake report including uptake among pregnant women and non-pregnant individuals. Uptake among pregnant women will be broken down by women vaccinated at 27 weeks and above versus women vaccinated before 27 weeks.
- Quarterly cohort identification report, i.e., exposure data: This report will provide the uptake among low-risk pregnant women vaccinated at week 27 and beyond gestation, with additional inclusion/exclusion criteria applied as indicated in the study protocol.
- Quarterly identification of pre-specified adverse events and pregnancy outcomes.
- Quarterly report demonstrating the progress of chart review for the pre-specified adverse events (e.g. number of events identified, number in progress of being reviewed, number completed).

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Protocol Sponsor Signatory Approval

eTrack study number and Abbreviated Title	EPI-PERTUSSIS-047 VS US DB (207221)
Date of protocol	15DEC2017
Detailed Title	An observational, retrospective cohort database study to assess the safety of Boostrix (U.S. formulation), a reduced tetanus, diphtheria, acellular pertussis vaccine (Tdap), following routine immunization of pregnant women in the United States.
Sponsor signatory	Narcisa Mesaros, MD Clinical and Epidemiology R&D Project Leader (CEPL), DTP, Polio, Hib containing vaccines GSK Biologicals' R&D Center Belgium
Signature	PPD
Date	19-DEC-2017

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