The safety of Boostrix following routine immunization of pregnant women

EPI-PERTUSSIS-047 VS US DB (207221)

Final Version of December 15, 2017

Amendment 1 – November 13, 2018

Amendment 2 – November 12, 2019

Sponsor: GlaxoSmithKline Biologicals SA

Rue de l'Institut 89

1330 Rixensart, Belgium

Protocol Amendment 2 Sponsor Signatory Approval

eTrack study number and Abbreviated Title	207221 (EPI-PERTUSSIS-047 VS US DB)
Date of protocol	Final: 15 December 2017
Date of protocol amendment 1	Final: 13 November 2018
Date of protocol amendment 2	Final: 12 November 2019
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	**Nadia Meyer, MD** Clinical and Epidemiology R&D Project Leader (CEPL), DTP, Polio, Hib containing vaccines GSK Biologicals' R&D Center Belgium
Signature	_____
Date	_____

Protocol Amendment 1 Rationale

Amendment number: Amendment 1

Rationale/background for changes:

The protocol has been amended following the comments received from the Center for Biologics Evaluation and Research. The following changes were implemented:

- Objectives: The protocol has been modified to include pregnancies irrespective of low or high-risk status (to reflect the current use of the vaccine). A primary objective has been added to rule out a two-fold increase in the incidence of four pre-specified maternal and infant adverse events. A secondary objective has been added to explore differences in eight other pre-specified maternal and infant adverse events.
- Endpoints:
  - The list of endpoints has been reviewed in view of their medical and scientific significance. Prioritization of endpoints was also based on the 2014 collaboration between the Brighton Collaboration Foundation and the World Health Organization (WHO) to address gaps in the safety assessment of vaccines during pregnancy (1). The following endpoints were removed: Gestational diabetes, premature uterine contractions, macrosomia, fetal distress, placenta previa, and delivery methods. The following endpoints were added: Small for gestational age (SGA), preterm delivery, neonatal death, maternal death, and preterm pre-labor rupture of membranes (PPROM).
  - Spontaneous abortion with or without congenital anomaly (CA) and therapeutic abortion with or without CA occur, by definition, before 20 weeks of gestation (2). Therefore, these events will not be part of the main analysis on the safety of Boostrix administered after the 27th week of gestation. However, the incidence of these events will be collected for subjects who received Boostrix prior to the 27th week of gestation and described in the study report.
  - Endpoints have been classified as either primary or secondary.
- Risk factors: additional factors defining a pregnancy as “high-risk” have been added.
- Case definitions: Pre-specified maternal and infant adverse events reflect the data captured by ICD-9 and ICD-10 coding according to the clinical practice of obstetrics.
- Further details on the statistical methods have been added for each endpoint.

Protocol Amendment 2 Rationale

Amendment number: Amendment 2

Rationale/background for changes:

The protocol has been amended to modify the secondary endpoint of "post-partum hemorrhage (PPH)" to "transfusion during delivery hospitalization" as a proxy for severe PPH. We originally planned to identify PPH from automated diagnosis codes (ICD-9 and ICD-10) and then perform chart review to confirm the event. However, in October 2017 (ACOG Practice Bulletin PPH 2017), the threshold for estimated blood loss (EBL) for PPH diagnosis changed, affecting the comparison between the historical (~2012-2013) and the Boostrix exposed (2018-2019) cohorts. The potential for using EBL as an objective measure is limited by differential missingness of EBL data between these two cohorts as well as inconsistency in EBL measurements. We propose to use transfusion during delivery hospitalization as an indicator of severe blood loss and as a proxy for severe PPH. Transfusion can be captured by procedure codes, and transfusion data are stable across the study period. Transfusion is a relevant endpoint because hemorrhage that leads to blood transfusion is the leading cause of severe maternal morbidity in the United States (ACOG Practice Bulletin PPH 2017).

The following changes have been implemented.

- ***Secondary objectives; Data collection Figure 1; Statistical methods Tables 6 and 7 - "Post-partum hemorrhage" was changed to "Transfusion during delivery hospitalization."***
- ***Case definitions; Data collection and management - Transfusion during delivery hospitalization is captured by procedure codes and will not be chart reviewed.***
- ***Data collection Figure 1; Statistical methods Table 7 - Transfusion will be identified among pregnant women with delivery hospitalizations.***
- ***Analysis of primary and secondary objectives; Statistical methods Table 7 - The statistical method for analyzing transfusion will be an adjusted Poisson regression model. Robust variance estimation is not planned since the incidence is expected to be <2%.***

Protocol Amendment 2 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	207221 (EPI-PERTUSSIS-047 VS US DB)
Date of protocol	Final: 15 December 2017
Date of protocol amendment 1	Final: 13 November 2018
Date of protocol amendment 2	Final: 12 November 2019
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.
Principal Investigator name	**Hung Fu Tseng, PhD, MPH** Research Scientist III Kaiser Permanente Southern California Department of Research and Evaluation PPD Tel: PPD Fax: PPD Email: PPD
Signature	_____
Date	_____

- ----------Checksum----------!Ver.!Created On - -
05cc3b67a9ba431ae514559e26df5e5186fbe84a 2.0 11/18/2019 10:52:23 AM
- - ----------

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. Primary endpoints were differentiated from secondary endpoints to allow evaluating the safety of maternal vaccination with sufficient statistical power on the primary endpoints and to allow for hypothesis generation/signal detection on secondary endpoints. Primary endpoints were selected based on their medical relevance, also considering the background incidence or prevalence of these endpoints.
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.
Primary Objective	To rule out a two-fold increase (non-inferiority testing) in the incidence of each of the following maternal and infant adverse events: • Preeclampsia and/or eclampsia • Intra-uterine infections such as chorioamnionitis and endometritis • Small for gestational age (SGA) • Preterm delivery among women who were vaccinated with Boostrix on or after the 1st day of the 27th week of gestation as compared to the

	incidence in a historical cohort of pregnant women (approximately January 1, 2012 to December 31, 2013) who were unvaccinated with any Tdap vaccine throughout their pregnancy.
Secondary Objectives ***(amended 12 November 2019)***	1. To explore the difference (superiority testing) in the incidence rate of other maternal and infant adverse events, namely***:*** • ***Transfusion during delivery hospitalization (as a proxy for severe post-partum hemorrhage)*** • Poor fetal growth • Stillbirth/fetal death with or without congenital anomalies • Neonatal death (within 28 days of birth) • Maternal death (while pregnant or within 42 days of end of pregnancy) • Placental abruption • Preterm pre-labor rupture of membranes (PPROM) • Congenital anomalies (CA) at birth and through 6 months of age between women who were vaccinated with Boostrix on or after the 1st day of the 27th week of gestation and a historical cohort of pregnant women (approximately January 1, 2012 to December 31, 2013) who were unvaccinated with any Tdap vaccine throughout their pregnancy. 2. To describe the incidence of maternal and infant adverse events described above, as well as the incidence of spontaneous and therapeutic abortions with or without congenital anomalies, among pregnant women vaccinated with Boostrix before the 27th week of gestation.
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 outcomes • Study population: 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 (from the 27th week of gestation): 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.
- Unexposed: Women matched to the exposed cohort, pregnant sometime during the approximate estimated period between 1/1/2012-12/31/2013 who did not receive any Tdap vaccine during the pregnancy in scope of this study.

Of note, women vaccinated with Boostrix before the 27th week of gestation, with membership at the date of vaccination, and who were not vaccinated with any other Tdap vaccine at any other time during the pregnancy in scope of this study will be part of a descriptive analysis (secondary objective).

- 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) ***(amended 12 November 2019)***

Primary

Maternal and infant adverse events identified from KPSC's EHR system using the pregnancy episode flowsheet and diagnosis codes:

- Preeclampsia and eclampsia
- Intra-uterine infections such as chorioamnionitis and endometritis
- Small for gestational age (SGA)
- Preterm delivery

Secondary

Maternal and infant adverse events identified from KPSC's EHR system using the pregnancy episode flowsheet, diagnosis codes, procedure codes, or death records:

- ***Transfusion during delivery hospitalization***
- Poor fetal growth
- Stillbirth/fetal death with or without congenital anomalies
- Neonatal death (within 28 days of birth)
- Maternal death (while pregnant or within 42 days of end of pregnancy)
- Placental abruption
- Preterm pre-labor rupture of membranes (PPROM)
- Congenital anomalies (CA) at birth and through 6 months of age overall and by system organ class
- Spontaneous abortion (only for women exposed to Boostrix before the 27th week of gestation)
- Therapeutic abortion (only for women exposed to Boostrix before the 27th week of gestation)

To avoid capture of preexisting conditions, diagnostic codes representing each condition should not appear prior to the index date within the pregnancy under study. With the exception of SGA, preterm delivery, ***and transfusion***, 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
CA	Congenital anomaly / congenital anomalies
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.)
HIV	Human immunodeficiency virus
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
OB-GYN	Obstetrics and Gynecology
PHI	Protected health information

PPROM	Preterm pre-labor rupture of membranes
REDCap	Research Electronic Data Capture
RIPC	Regional Immunization Practices Committee
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Module
SGA	Small for gestational age
Tdap	Tetanus, diphtheria, acellular pertussis
U.S.	United States
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
WHO	World Health Organization

GLOSSARY OF TERMS

Adverse Events:	Pre-specified, pregnancy-related diagnoses or pregnancy outcomes or infant diagnosis 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 (from the 27th week of gestation):	Subjects classified as exposed to Tdap (Boostrix) on the 1st day of the 27th week of gestation 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.
Pregnancy start:	Corresponds to a gestational age of 0 weeks based on the most reliable estimated date of delivery.
Completion date:	The date of final collection of data for all 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 (3). 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 (4-6).

Two tetanus-diphtheria-acellular pertussis (Tdap) vaccines (Adacel and Boostrix) were licensed for use in the United States (U.S.) in 2005 (7). 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 (8). 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 (9). In October 2012, ACIP expanded its recommendation of administering Tdap during pregnancy (10); 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 (11).

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 (12). 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 (13). 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 (14). 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) (15), a finding consistent with a larger subsequent study at seven U.S. health care system VSD sites (16). 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 (17). 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 (18). 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 (19). Except for the aforementioned VSD studies in which Adacel comprised the majority of Tdap vaccines administered (15), 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.

Primary endpoints were differentiated from secondary endpoints to allow evaluating the safety of maternal vaccination with sufficient power on the primary endpoints and to allow for hypothesis generation/signal detection on secondary endpoints.

Primary endpoints were selected based on their medical relevance, considering also the background incidence or prevalence of these endpoints.

2. OBJECTIVE

2.1. Primary objective

To rule out a two-fold increase (non-inferiority testing) in the incidence of each of the following maternal and infant adverse events:

- Preeclampsia and/or eclampsia
- Intra-uterine infections such as chorioamnionitis and endometritis
- Small for gestational age (SGA)
- Preterm delivery

among women who were vaccinated with Boostrix on or after the 1st day of the 27th week of gestation as compared to the incidence in a historical cohort of pregnant women (approximately January 1, 2012 to December 31, 2013) who were unvaccinated with any Tdap vaccine throughout their pregnancy.

2.2. Secondary objectives *(amended 12 November 2019)*

1. To explore differences (superiority testing) in the incidence rate of other maternal and infant adverse events, namely:

- ***Transfusion during delivery hospitalization (as a proxy for severe post-partum hemorrhage)***
- Poor fetal growth
- Stillbirth/fetal death with or without congenital anomalies
- Neonatal death (within 28 days of birth)
- Maternal death (while pregnant or within 42 days of end of pregnancy)
- Placental abruption
- Preterm pre-labor rupture of membranes (PPROM)
- Congenital anomalies (CA) at birth and through 6 months of age

  between women who were vaccinated with Boostrix on or after the 1st day of the 27th week of gestation and a historical cohort of pregnant women (approximately January 1, 2012 to December 31, 2013) who were unvaccinated with any Tdap vaccine throughout their pregnancy.

2. To describe the incidence of maternal and infant adverse events described above, as well as the incidence of spontaneous and therapeutic abortion with or without congenital anomalies, in pregnant women who were vaccinated with Boostrix before the 27th week of gestation.

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 (20). 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.

Standard of care regarding use of Tdap in pregnant women

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, will be included in the 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 pregnant women irrespective of their risk profile (low or high-risk) 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 pregnant women during the approximate estimated period from 1/1/2012 to 12/31/2013 who never received Tdap vaccine during pregnancy.

Of note, women vaccinated with Boostrix before the 27th week of gestation, with membership at the date of vaccination, and who were not vaccinated with any other Tdap vaccine at any other time during the pregnancy in scope of this study will be part of a descriptive analysis (secondary objective).

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. For the maternal death endpoint, pregnant women will be followed for 42 days after the end of pregnancy. Infants born in KPSC hospitals will be followed for 6 months.

4. STUDY POPULATION/CASE DEFINITION(S)

4.1. Study population

The exposed and unexposed cohorts will consist of pregnant women with evidence of prenatal care and continuous membership (allowing up to a 31-day gap) at KPSC between the 1st day of the 27th week of gestation 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 gestation at selected ob-gyn clinics at seven medical centers throughout KPSC (vaccination period planned to begin in January 2018). Unexposed pregnant women comprise women pregnant sometime during the approximate estimated period between 1/1/2012 and 12/31/2013 who 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 (21). Pregnancy start date will correspond to a gestational age of 0 weeks.

Matching process for pregnant women who were vaccinated with Boostrix after the 27th week of gestation

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.

Existing health conditions, age, lifestyle factors, and conditions of pregnancy can place a pregnancy at risk (22). Therefore, matching variables include maternal age at pregnancy start (± 1 year), race/ethnicity (White, Black, Hispanic, Asian, and Other) and multiple gestation. Other pregnancy high-risk conditions will be considered as potential covariates in the analysis (see Section 6.2.1 Covariates).

For example, suppose there is a 28-year-old (at pregnancy start) Hispanic pregnant woman expecting twins 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 Hispanic woman pregnant sometime between 1/1/2012 and 12/31/2013, who was 27-29 years of age at pregnancy start and had a multiple gestation pregnancy, 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. 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.

4.2. Case definitions *(amended 12 November 2019)*

Endpoints of interest will be extracted from the EHR using the pregnancy episode flowsheet, diagnosis codes (ICD-9 and ICD-10 codes), procedure codes, or death records. 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 (23-31).

With the exception of SGA, preterm delivery, ***and transfusion,*** chart review will be performed for the pre-specified maternal and infant adverse events to confirm the events and that the events are incident after the index date.

4.3. 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.

4.4. 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 gestation and the index (vaccination) date.
- **Exposed cohort** (from the 27th week of gestation): Pregnant women vaccinated with Boostrix on or after the 1st day of the 27th week of gestation; 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

Note: Pregnant women vaccinated with Boostrix during pregnancy before the 27th week of gestation, with membership at the date of vaccination, and who were not vaccinated with any other Tdap vaccine at any other time during the pregnancy in scope of this study will be part of a descriptive analysis (secondary objective).

5. DATA COLLECTION AND MANAGEMENT *(amended 12 November 2019)*

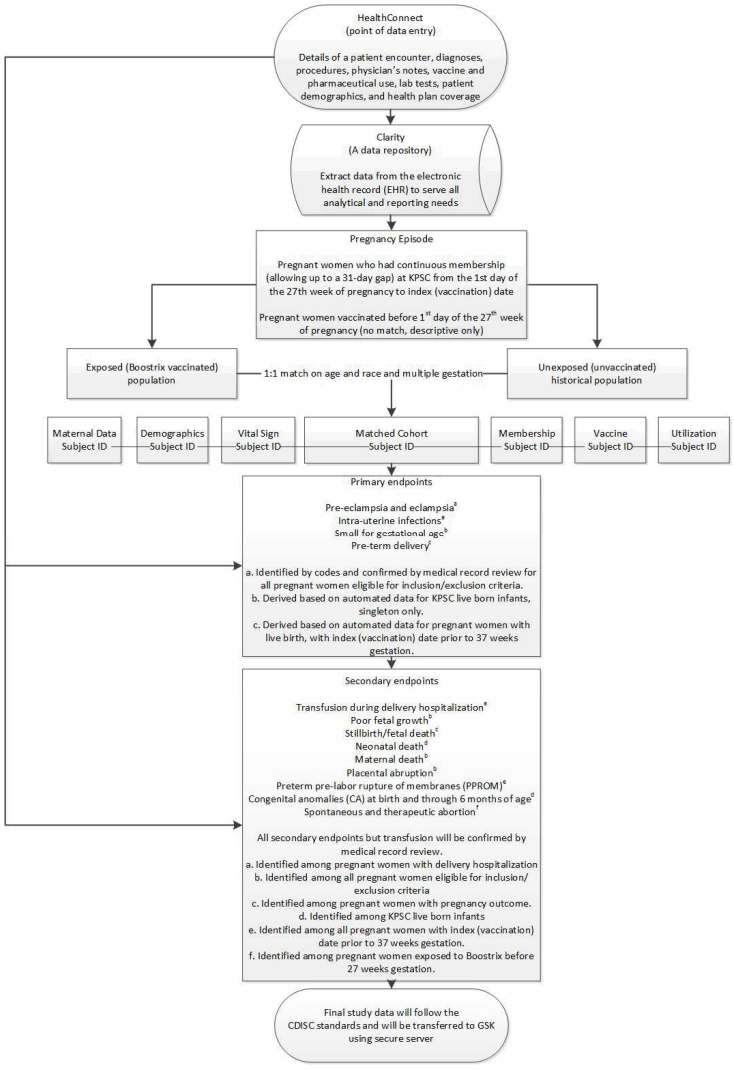
Vaccination and medical event data will be extracted directly from the EHR (Health Connect), which is the legal record of all medical care received within the KPSC system. Figure 1 provides an overview of the data flow for this study. All details of a patient encounter, including diagnoses, procedures, 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), procedure codes, or death records.

We will rely on automated data from the EHR to ascertain SGA, preterm delivery, ***and transfusion***. For other endpoints, 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 when applicable (i.e., events diagnosed during pregnancy that may have onset prior to index date). Events will be reviewed in the chart in which the incident diagnosis code is identified (i.e., mother's chart or infant's chart). Unknown pregnancy outcomes and KPSC live born singleton infants with unknown birthweight will also be chart reviewed. 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 (32). 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 questions in the abstraction form, and explanations 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., Pinnacle 21); and produce submission documentation including DEFINE.XML and Study Data Reviewers Guide for SDTM and ADaM.

Figure 1. Illustration of data flow *(amended 12 November 2019)*



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 and secondary pre-specified events of interest *(amended 12 November 2019)*

The pre-specified events of interest are maternal and infant outcomes identified from KPSC's EHR system using the pregnancy episode flowsheet, diagnosis codes, procedure codes, or death records 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 (23-31). In addition, we will use a commonly accepted definition to identify congenital anomalies, such as that used by the National Birth Defects Prevention Network (33). Additional birth outcomes will be captured for descriptive purposes, but not considered adverse events: 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. All pre-specified events of interest will be collected through the completion date. Analyses will be done on chart confirmed incident events when applicable.

Table 6 List of primary and secondary endpoints *(amended 12 November 2019)*

Primary endpoints	Preeclampsia and/or eclampsia
	Intra-uterine infections such as chorioamnionitis and endometritis
	Small for gestational age (SGA)
	Preterm delivery
Secondary endpoints	***Transfusion during delivery hospitalization***
	Poor fetal growth
	Stillbirth/fetal death with or without congenital anomalies
	Neonatal death (within 28 days of birth)
	Maternal death (while pregnant or within 42 days of end of pregnancy)
	Placental abruption
	Preterm pre-labor rupture of membranes (PPROM)
	Congenital anomalies at birth and through 6 months of age
	Spontaneous abortion with or without congenital anomalies (only for women exposed to Boostrix before the 27th week of gestation)
	Therapeutic abortion with or without congenital anomalies (only for women exposed to Boostrix before the 27th week of gestation)

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 (22).

Medical conditions indicative of a high-risk pregnancy to be considered as covariates include:

- thyroiditis,
- diabetes,
- other autoimmune diseases (mixed connective tissue disease such as systemic lupus erythematosus),
- renal and cardiac chronic diseases,
- obesity (pre-pregnancy BMI>40),
- pre-existing hypertension,
- Rhesus sensitization,
- HIV infection,
- syphilis infection,
- cervical incompetence.

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

- smoking status
- 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
- Medicaid insurance (public health insurance: Indication of low income status)

6.2.2. Analysis of primary and secondary objectives *(amended 12 November 2019)*

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.

For events identified at delivery such as SGA, preterm delivery, ***and transfusion during delivery hospitalization,*** 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 number of women for whom the condition can be assessed in the denominator. The adjusted relative risk with CI will be estimated by a Poisson regression model with adjustment for potential confounders. If the outcome is common (i.e., incidence>2%), a Poisson regression model with robust variance estimation will be used to estimate the relative risk (34). For primary endpoints, a two-sided 98.75% CI will be used for the relative risk with multiple comparison adjustment, while for secondary endpoints a two-sided 95% CI will be used.

For events identified any time after the index date such as intra-uterine infection, we will calculate crude incidence and 95% 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. The person-year for a pregnant woman will be the time from the index date to the date of each adverse event, end of the pregnancy, or disenrollment, whichever comes first. The adjusted relative risk with CI will be estimated by a Poisson regression model accounting for the follow-up time with adjustment for potential confounders. If the outcome is common (i.e., incidence>2%), a Poisson regression model with robust variance estimation will be used to estimate the relative risk. For primary endpoints, a two-sided 98.75% CI will be used for the relative risk with multiple comparison adjustment, while for secondary endpoints a two-sided 95% CI will be used.

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 (35). 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 live born infants. The adjusted relative risk with 95% CI will be estimated by a Poisson regression model with adjustment for potential confounders. If the outcome is common (i.e., incidence >***2***%), a Poisson regression model with robust variance estimation will be used to estimate the relative risk.

The following table outlines the planned method of analysis by endpoint.

Table 7 Analytic population and statistical methods by endpoint (*amended 12 November 2019*)

Primary endpoints	**Analytic population**	**Statistical Methods**
Preeclampsia and eclampsia	All pregnant women eligible for inclusion/exclusion criteria	Adjusted Poisson regression model accounting for follow up time, with robust variance estimate
Intra-uterine infections such as chorioamnionitis and endometritis	All pregnant women eligible for inclusion/exclusion criteria	Adjusted Poisson regression model accounting for follow up time, with robust variance estimate
Small for gestational age (SGA)	KPSC live born infant, singleton only**	Adjusted Poisson regression model, with robust variance estimate
Preterm delivery	Pregnant women with live birth, with index (vaccination) date prior to 37 weeks gestation	Adjusted Poisson regression model, with robust variance estimate
Secondary endpoints	**Analytic population**	**Statistical Methods**
Transfusion during delivery hospitalization	Pregnant women with ***delivery hospitalization***	Adjusted Poisson regression model
Poor fetal growth	All pregnant women eligible for inclusion/exclusion criteria	Adjusted Poisson regression model accounting for follow up time, with robust variance estimate
Stillbirth/fetal death*	Pregnant women with pregnancy outcome	Adjusted Poisson regression model
Neonatal death (within 28 days of birth)	KPSC live born infants	Adjusted Poisson regression model
Maternal death (while pregnant or within 42 days of end of pregnancy)	All pregnant women eligible for inclusion/exclusion criteria	Adjusted Poisson regression model accounting for follow up time
Placental abruption	All pregnant women eligible for inclusion/exclusion criteria	Adjusted Poisson regression model accounting for follow up time
Preterm pre-labor rupture of membranes (PPROM)	All pregnant women, with index (vaccination) date prior to 37 weeks gestation	Adjusted Poisson regression model accounting for follow up time
Congenital anomalies (CA) at birth and through 6 months of age	KPSC live born infants	Adjusted Poisson regression model, with robust variance estimate if outcome is common
Spontaneous abortion	Pregnant women exposed to Boostrix before the 27th week of gestation	Descriptive analysis (proportion)
Therapeutic abortion	Pregnant women exposed to Boostrix before the 27th week of gestation	Descriptive analysis (proportion)

* Stillbirth/fetal death will be described with or without congenital anomalies separately, but will be analyzed as one outcome.
** There are no well accepted SGA metrics for infants born to pregnant women with multiple gestation.

6.2.3. Analyses interpretation

Analysis of primary endpoints will be used to evaluate the safety of maternal vaccination and concluded to be non-inferior if the upper limit of the 98.75% CI for the adjusted relative risk is below 2.

While the analysis of primary endpoints will be used to evaluate the safety of maternal vaccination with sufficient statistical power, the analysis of secondary endpoints will be used for hypothesis generation/signal detection.

6.3. Sample size considerations

The power computation for the primary objective was performed using PASS non-inferiority of two independent proportions using Miettinen and Nurminen method. Although the power is not based on the Poisson regression model, it is expected to reflect the power on the planned analysis since inference on proportion and incidence rate provide similar results when incidence rates are low.

The following table (Table 8) shows the power to rule out a two-fold increase considering an assumed possible design bias leading to a 1.25 relative risk increase.

To be able to make independent conclusions for each of the four primary endpoints while controlling the type I error below 2.5%, a Bonferroni adjustment will be used, i.e., each primary endpoint will be evaluated using a one-sided 0.625% (2.5% type I error / 4 primary endpoints) nominal type I error. More specifically, the upper limit of the two-sided 98.75% CI will be used to make conclusions.

Considering that the four primary endpoints are expected to have an incidence rate above 1%, the power to conclude that maternal immunization is non-inferior for any primary endpoint is at least 95% and the power to conclude that maternal immunization is non-inferior for all 4 primary endpoints is at least 80% (100% - 4*beta).

Table 8 Power to rule out a two-fold increase with 15,000 pregnant women in each cohort

Incidence rate in unvaccinated cohort	One-sided type I nominal error	True relative risk	Power	Beta
1%	0.625%	1.25	95.7%	4.3%

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 anomalies among the exposed and unexposed cohorts, we note that the most plausible time period for development of congenital anomalies is during early pregnancy (35). Cautious interpretation of maternal Boostrix immunization and congenital anomalies 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 risk of bias if the prevalence of adverse events is higher or lower in either exposed or unexposed cohorts due to coding variation or secular trends. 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 (36, 37). 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.

If a safety signal is identified, further exploration of the data will be completed to investigate alternative potential sources for the Boostrix-outcome 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 pregnant women vaccinated on or after the 1st day of the 27th week of 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).

9. REFERENCES

1. Munoz FM, Eckert LO, Katz MA, Lambach P, Ortiz JR, Bauwens J, et al. Key terms for the assessment of the safety of vaccines in pregnancy: Results of a global consultative process to initiate harmonization of adverse event definitions. Vaccine. 2015;33(47):6441-52.

2. Centers for Disease Control and Prevention (CDC) 2018; Accessed https://www.cdc.gov/features/pregnancy-infant-loss-day/index.html on November 2, 2018.

3. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev. 2005;18(2):326-82.

4. Koepke R, Eickhoff JC, Ayele RA, Petit AB, Schauer SL, Hopfensperger DJ, et al. Estimating the effectiveness of tetanus-diphtheria-acellular pertussis vaccine (Tdap) for preventing pertussis: evidence of rapidly waning immunity and difference in effectiveness by Tdap brand. J Infect Dis. 2014;210(6):942-53.

5. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap Effectiveness in Adolescents. Pediatrics. 2016;137(3):e20153326.

6. Tartof SY, Lewis M, Kenyon C, White K, Osborn A, Liko J, et al. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics. 2013;131(4):e1047-52.

7. Broder KR, Cortese MM, Iskander JK, Kretsinger K, Slade BA, Brown KH, et al. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-3):1-34.

8. California Department of Public Health 2010; Accessed http://www.eziz.org/PDF/CDPH%20Pertussis%20Immunization%20Policy%20July%202010.pdf on October 31, 2017.

9. CDC. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis (Tdap) Vaccine from the Advisory Committee on Immunization Practices, 2010. Morb Mortal Wkly Rep;60 (01):13-5.

10. CDC Advisory Committee for Immunization Practices Recommends Tdap Immunization for Pregnant Women 2012; Accessed http://www.cdc.gov/media/releases/2012/a1024_Tdap_immunization.html on November 8, 2017.

11. GlaxoSmithKline Biologicals; Accessed at Food and Drug Administration at http://www.fda.gov/downloads/BiologicsBloodVaccines/UCM152842.pdf on September, 22, 2017.

12. Munoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA. 2014;311(17):1760-9.

13. Zheteyeva YA, Moro PL, Tepper NK, Rasmussen SA, Barash FE, Revzina NV, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol. 2012;207(1):59.e1-7.

14. Berenson AB, Hirth JM, Rahman M, Laz TH, Rupp RE, Sarpong KO. Maternal and infant outcomes among women vaccinated against pertussis during pregnancy. Hum Vaccin Immunother. 2016;12(8):1965-71.

15. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway A, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA. 2014;312(18):1897-904.

16. DeSilva M, Vazquez-Benitez G, Nordin JD, Lipkind HS, Klein NP, Cheetham TC, et al. Maternal Tdap vaccination and risk of infant morbidity. Vaccine. 2017;35(29):3655-60.

17. Layton JB, Butler AM, Li D, Boggess KA, Weber DJ, McGrath LJ, et al. Prenatal Tdap immunization and risk of maternal and newborn adverse events. Vaccine. 2017;35(33):4072-8.

18. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Klein NP, Cheetham TC, Naleway AL, et al. Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007-2013. Vaccine. 2016;34(7):968-73.

19. DeSilva M, Vazquez-Benitez G, Nordin JD, Lipkind HS, Romitti PA, DeStefano F, et al. Tdap Vaccination During Pregnancy and Microcephaly and Other Structural Birth Defects in Offspring. Jama. 2016;316(17):1823-5.

20. Koebnick C, Langer-Gould AM, Gould MK, Chao CR, Iyer RL, Smith N, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. Perm J. 2012;16(3):37-41.

21. American College of Obstetricians and Gynecologists. Methods for estimating the due date. Committee Opinion No. 700. Obstet Gynecol. 2017;129:e150-4.

22. Eunice Kennedy Shriver National Institute of Child Health and Human Development 2017; Accessed https://www.nichd.nih.gov/health/topics/high-risk/conditioninfo/pages/factors.aspx on October 30, 2017.

23. American College of Obstetricians and Gynecologists. Premature rupture of membranes. Practice Bulletin No. 172. Obstet Gynecol. 2016;128(4):e165-77.

24. American College of Obstetricians and Gynecologists. Executive summary: hypertension in pregnancy. Obstet Gynecol. 2013;122:1122-31.

25. American College of Obstetricians and Gynecologists. Intrapartum management of intraamniotic infection. Committee Opinion No. 712. Obstet Gynecol. 2017;130:e95-101.

26. American College of Obstetricians and Gynecologists. Management of preterm labor. Practice Bulletin No. 171. Obstet Gynecol. 2016;128:e155-64.

27. American College of Obstetricians and Gynecologists. Fetal growth restriction. Practice Bulletin No. 134. Obstet Gynecol. 2013;121:1122-33.

28. American College of Obstetricians and Gynecologists. Practice Bulletin No. 183: Postpartum Hemorrhage. Obstet Gynecol. 2017;130(4):e168-e86.

29. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 102: management of stillbirth. Obstet Gynecol. 2009;113(3):748-61.

30. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 135: Second-trimester abortion. Obstet Gynecol. 2013;121(6):1394-406.

31. American College of Obstetricians and Gynecologists. The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. Obstet Gynecol. 2015;125(5):1258-67.

32. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.

33. National Birth Defects Prevention Network 2018; Accessed https://www.nbdpn.org/icd10.php on November 1, 2018.

34. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6.

35. DeSilva M, Munoz FM, McMillan M, Kawai AT, Marshall H, Macartney KK, et al. Congenital anomalies: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2016;34(49):6015-26.

36. ICD10Data.com 2017; Accessed http://www.icd10data.com/.

37. Centers for Medicare & Medicaid Services 2017; Accessed https://www.cms.gov/Medicare/Coding/ICD10/2017-ICD-10-CM-and-GEMs.html on October 30, 2017.

APPENDIX A AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

GlaxoSmithKline Biologicals SA Vaccines R & D Protocol Amendment 2	
eTrack study number and Abbreviated Title	207221 (EPI-PERTUSSIS-047 VS US DB)
Amendment number:	Amendment 2
Amendment date:	Final: 12 November 2019
Rationale/background for changes:	

The protocol has been amended to modify the secondary endpoint of "post-partum hemorrhage (PPH)" to "transfusion during delivery hospitalization" as a proxy for severe PPH. We originally planned to identify PPH from automated diagnosis codes (ICD-9 and ICD-10) and then perform chart review to confirm the event. However, in October 2017 (ACOG Practice Bulletin PPH 2017), the threshold for estimated blood loss (EBL) for PPH diagnosis changed, affecting the comparison between the historical (~2012-2013) and the Boostrix exposed (2018-2019) cohorts. The potential for using EBL as an objective measure is limited by differential missingness of EBL data between these two cohorts as well as inconsistency in EBL measurements. We propose to use transfusion during delivery hospitalization as an indicator of severe blood loss and as a proxy for severe PPH. Transfusion can be captured by procedure codes, and transfusion data are stable across the study period. Transfusion is a relevant endpoint because hemorrhage that leads to blood transfusion is the leading cause of severe maternal morbidity in the United States (ACOG Practice Bulletin PPH 2017).

The following changes have been implemented.

- ***Secondary objectives; Data collection Figure 1; Statistical methods Tables 6 and 7 - "Post-partum hemorrhage" was changed to "Transfusion during delivery hospitalization."***
- ***Case definitions; Data collection and management - Transfusion during delivery hospitalization is captured by procedure codes and will not be chart reviewed.***
- ***Data collection Figure 1; Statistical methods Table 7 - Transfusion will be identified among pregnant women with delivery hospitalizations.***
- ***Analysis of primary and secondary objectives; Statistical methods Table 7 - The statistical method for analyzing transfusion will be an adjusted Poisson***

regression model. Robust variance estimation is not planned since the incidence is expected to be <2%.

Amended text has been included in *bold italics* and deleted text in ~~strikethrough~~ in the following sections:

Synopsis:

Secondary Objectives	• ~~Post-partum hemorrhage~~ ***Transfusion during delivery hospitalization (as a proxy for severe post-partum hemorrhage)***
Endpoint(s)	**Secondary** • ~~Post-partum hemorrhage~~ ***Transfusion during delivery hospitalization*** With the exception of SGA, ~~and~~ preterm delivery, ***and transfusion***, 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.

Section 2.2 Secondary objectives

- ~~Post-partum hemorrhage~~ ***Transfusion during delivery hospitalization (as a proxy for severe post-partum hemorrhage)***

Section 4.2 Case definitions

With the exception of SGA, ~~and~~ preterm delivery, ***and transfusion,*** chart review will be performed for the pre-specified maternal and infant adverse events to confirm the events and that the events are incident after the index date.

Section 5 Data collection and management

We will rely on automated data from the EHR to ascertain SGA, ~~and~~ preterm delivery, ***and transfusion***.

Figure 1. Illustration of data flow was updated and changes include:

- Post-partum hemorrhage secondary endpoint was changed to "Transfusion during delivery hospitalization"
- Modified sentence "All secondary endpoints ***but transfusion*** will be confirmed by medical record review"
- Secondary endpoints, footnote a, modified to say "Identified among pregnant women with ~~KPSC delivery~~ ***delivery hospitalization***"

Section 6.1 Primary and secondary pre-specified events of interest

Table 6 List of primary and secondary endpoints

Secondary endpoints	~~Post-partum hemorrhage~~ ***Transfusion during delivery hospitalization***
	Poor fetal growth
	Stillbirth/fetal death with or without congenital anomalies
	Neonatal death (within 28 days of birth)
	Maternal death (while pregnant or within 42 days of end of pregnancy)
	Placental abruption
	Preterm pre-labor rupture of membranes (PPROM)
	Congenital anomalies at birth and through 6 months of age
	Spontaneous abortion with or without congenital anomalies (only for women exposed to Boostrix before the 27th week of gestation)
	Therapeutic abortion with or without congenital anomalies (only for women exposed to Boostrix before the 27th week of gestation)

Section 6.2.2 Analysis of primary and secondary objectives

For events identified at delivery such as SGA, ~~and~~ preterm delivery, ***and transfusion during delivery hospitalization,*** we will calculate crude incidence and 95% confidence intervals (CI) for each adverse event for the exposed and unexposed groups.

Table 7 Analytic population and statistical methods by endpoint

Secondary endpoints	Analytic population	Statistical Methods
~~Post-partum hemorrhage~~ ***Transfusion during delivery hospitalization***	Pregnant women with ~~KPSC delivery~~ ***delivery hospitalization***	Adjusted Poisson regression model~~, with robust variance estimate~~