gsk GlaxoSmithKline	**Statistical Analysis Plan**
Detailed Title:	Effectiveness of maternal immunization with *Boostrix*-at preventing pertussis among infants <2 Months old in the United States: analysis of a dataset from a case-control study conducted by the Centre for Disease Control.
eTrack study number and Abbreviated Title	210031 (EPI-PERTUSSIS-052 VE US DB)
Scope:	All data transferred by the US Centers for Disease Control and Prevention (CDC)
Date of Statistical Analysis Plan	Amendment 1 Final:08-March-2019
Co-ordinating author:	PPD (Lead Statistician)
Reviewed by:	PPD (Clinical and Epidemiology Project Lead)
	PPD (Lead epidemiologist)
	PPD (Lead statistical analyst)
	PPD (Scientific writer)
	PPD (Director US Health outcome)
	PPD (Manager US Health outcome)
	PPD (Global medical affairs lead)
	PPD (Regulatory Affair)
	PPD (Public disclosure representative)
Approved by:	PPD (Clinical and Epidemiology Project Lead)
	PPD (Lead epidemiologist)
	PPD (Lead statistician)
	PPD (Lead statistical analyst)
	PPD (Lead Scientific writer)

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LIST OF ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CIs	Confidence Intervals
CTRS	Clinical Trial Registry
EIP	Emerging Infection Program
GSK	GlaxoSmithKline
LL	Lower Limit of the confidence interval
N.A.	Not Applicable
OR	Odds Ratio
SAP	Statistical Analysis Plan
SE	Standard Error
SHS	Study Headline Summary
TFL	Tables Figures and Listings
TOC	Table of Content
UL	Upper Limit of the confidence interval
US	United States
VE	Vaccine Effectiveness

1. DOCUMENT HISTORY

Date	Description	Protocol Version
07-JAN-2019	First version	This is an analysis of the dataset of an epidemiological study performed by the US CDC assessing the effectiveness of maternal immunization with tetanus-diphtheria-acellular pertussis (Tdap) vaccines at preventing pertussis in infants. The objectives are the same as the original study, focussing at the effectiveness of Boostrix. Therefore, the analysis is solely described in a detailed SAP. A protocol has not been developed, as it did not have added value in these circumstances.
08-MAR-2019	Amendment 1 • Addition of a sensitivity analysis of the primary and secondary objectives • Clarification about the statistical model to assess the primary and secondary objectives	NA

2. STUDY DESIGN

2.1. Context of the SAP development

2.1.1. Background

Pertussis, also known as "whooping cough", is a highly contagious disease that is caused by the bacterium *Bordetella pertussis* and can cause prolonged periods of respiratory distress. In 2016, the Centers for Disease Control and Prevention (CDC) provisionally estimated that in 2016 there were approximately 16,000 cases of pertussis reported in the US with an incidence of 4.7 cases per 100,000. Pertussis incidence is reported to be high in the less than 6-month age group (incidence of 85.5 cases per 100,000 in 2016, corresponding to 1,253 cases) [Centers for Disease Control, 2016].

Young infants are most vulnerable to pertussis-related complications, particularly during the period preceding the initiation of 5-dose vaccination schedule with the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at 2 months of age [Centers for Disease Control, 2000]. Parents and siblings may play an important role in transmitting pertussis to vulnerable infants [Skoff, 2015].

Two tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines are licensed for use as a single booster dose among US adolescents and adults: *Boostrix* (GSK) and *Adacel* (Sanofi Pasteur). These vaccines have been licensed in the US since 2005 and can be used interchangeably [Kretsinger, 2006]. The primary goal of this vaccination is to protect the vaccine recipient. However, vaccination of close contacts can also indirectly protect infants. In 2011, The Advisory Committee on Immunization Practices (ACIP) recommended vaccination during pregnancy [Centers for Disease Control, 2011]. The recommendation was expanded in 2012 to include a dose of Tdap during every pregnancy [Centers for Disease Control, 2012]. This strategy not only helps protect the mother from pertussis infection and transmission of pertussis on to her infant,

but also provides passive immunity to the infant. Although the ACIP suggests that the preferred timing for Tdap administration is between 27 and 36 weeks gestation to optimize transplacental transfer of maternal anti-pertussis antibodies, Tdap may be given at any time during pregnancy.

The effectiveness of antenatal pertussis immunization has been evaluated in the UK [Amirthalingam, 2014; Dabrera, 2015; Amirthalingam, 2016], in Spain [Bellido-Blasco, 2016], in Australia [Saul, 2018] and in the US [Baxter, 2017; Skoff, 2017; Winter, 2017; Becker-Dreps, 2018]. In particular, a case-control study within 6 US Emerging Infection Program Network states evaluated the effectiveness of Tdap vaccination during pregnancy for preventing pertussis in infants < 2 months of age [Skoff, 2017]. This collaborative network includes the CDC and state and local health departments, academic institutions and laboratories. The multivariable Vaccine Effectiveness (VE) estimate for Tdap administered during the third trimester of pregnancy was 77.7% (95% confidence interval [CI], 48.3%–90.4%); VE increased to 90.5% (95% CI, 65.2%–97.4%) against hospitalized cases [Skoff, 2017]. The data collected in the study on the vaccination status of the subjects included brand, manufacturer and lot number, which were collected through medical providers or state immunization registries. Overall, 136 (56.7%) case mothers and 358 (66.9%) control mothers had at least 1 valid Tdap dose identified. A total of 43 of 136 (31.6%) vaccinated case mothers and 102 of 358 (28.5%) vaccinated control mothers received *Boostrix*, and 76 of 136 (55.9%) vaccinated case mothers and 207 of 358 (57.8%) vaccinated control mothers received *Adacel*; brand information was not available for the remaining 17 of 136 (12.5%) case mothers and 49 of 358 (13.7%) control mothers who had a record of Tdap receipt. The publication mentions that the point estimates of the effectiveness of either vaccine product at preventing infant disease when administered during the third trimester were not statistically different from one another (p = .85). There is no brand-specific vaccine effectiveness information available in the current publication [Skoff, 2017].

2.1.2.   Rationale for the study

All US studies have evaluated Tdap vaccines as a class of vaccines. GSK Biologicals is interested to describe the clinical benefit of maternal immunization with *Boostrix* in the prevention of infant pertussis in real-world setting.

In the US, *Boostrix* is currently indicated for active booster immunization against tetanus, diphtheria and pertussis and approved for use as a single dose in individuals greater than or equal to 10 years of age. Considering the current ACIP recommendation to administer a dose of Tdap during pregnancy to prevent pertussis in infants, GSK Biologicals intends to generate supporting data for maternal immunization indication and to update the *Boostrix* Product Information. Hence, effectiveness data to confirm the clinical benefit of maternal immunization with Boostrix to prevent pertussis in the infant is important.

Hence, GSK has requested the access to the data set of the case control study performed by Skoff *et al*. [Skoff, 2017]. This study estimates the vaccine effectiveness of any Tdap administered during pregnancy at preventing pertussis in infants < 2 months of age. The analysis of this study would be similar to the analysis performed by Skoff *et al*., focusing

on the estimation of the vaccine effectiveness of *Boostrix* administered during pregnancy in preventing pertussis in infants < 2 months.

2.1.3. Feasibility Assessment

A feasibility assessment was conducted after receiving the access to data. The objective was to assess the power for primary and secondary objectives. The power estimation was low for some of the secondary objectives (See section 13), and hence, the analysis should be interpreted with caution. Two analyses performed in the article which will not be feasible as the corresponding variables were not transferred to GSK (See section 13 point (5)). Therefore, these two analyses will not be performed in this study.

2.2. Study design

- **Study design:** An observational Matched Case-control study:
- **Outcome:**
  - Pertussis case group composed of infants who meet the pertussis diagnosis definition (see section 5)
  - Control group composed of infants who did not have a pertussis diagnosis prior to the cough onset date of the corresponding case infant

The reference period for a case infant and his or her matched controls was defined as the 30-day period prior to the case infant cough onset date.

Exposure (see definition of exposure in section 5.2):

- Infant's mother vaccinated with Boostrix
- Infant's mother unexposed to any Tdap vaccine
- **Study region:** 6 Emerging Infection Program Network sites (PPD PPD PPD PPD PPD in select counties of PPD , PPD) in the United States.
- **Study period:** from 1 January 2011 to 31 December 2014.
- **Study population:** All the eligible infant pertussis cases captured from EIP and corresponding matched controls.
- **Matching:** 1:3 matched cases and controls

For each enrolled case, the study site attempted to recruit 3 control infants using birth certificates of infants born at the same hospital for the case infants who were <2 months old and based on the case infant's cough onset date. Once all potential controls meeting these criteria were exhausted, control enrolment ended for that case infant.

2.3.   Data to be used for the analysis

2.3.1.   Description of data sources

Pertussis cases in infants have been identified through surveillance in 6 Emerging Infection Program (EIP) Network site in the United States. EIP is a collaborative pertussis surveillance network between CDC and state and local health department, academic institutions and laboratories that serves as a national resource for surveillance, prevention, and control of emerging infectious disease [1]. This case-control evaluation has been conducted statewide in PPD PPD PPD and PPD, and in select counties of PPD (PPD

and PPD and PPD (PPD, and PPD

2.3.2.   Inclusion criteria

2.3.2.1.   Inclusion criteria for case infants:

Case infants were eligible for the enrolment if they:

- were at least 2 days old and < 2 months old on the cough onset date
- resided in the catchment area on their cough onset date
- were born in a hospital in their state of residence
- were ≥37 weeks' gestational age at birth
- were neither adopted nor in foster care
- did not live in a residential care facility

2.3.2.2.   Inclusion criteria for control infants:

Control infants were eligible for the enrolment if they:

- were at least 2 days old and <2 months old on the case infant's cough onset date
- were born in a hospital in their state of residence
- were ≥37 weeks' gestational age at birth
- were neither adopted nor in foster care
- did not live in a residential care facility
- were born at the same hospital as the case infant
- did not have pertussis diagnosis prior to the cough onset date of the corresponding case infant

2.3.3. Exclusion criteria

The analysis set will include the subjects of the vaccinated/unvaccinated cases and controls matched to this case. Subjects with the following criteria will be excluded from the analysis:

- Infants (case and controls) whose mothers have received *Adacel* or mothers without brand information available, as well as controls who were matched to a case whose mother received *Adacel* or mothers without brand information available, will be excluded from the analysis of the effectiveness of vaccination with *Boostrix*.

3. OBJECTIVES

3.1. Primary objective

- To assess the effectiveness of vaccination with *Boostrix* at preventing pertussis in infants <2 months during the third trimester of pregnancy, at least 14 days before delivery.

3.2. Secondary objective

- To assess the effectiveness of vaccination with Boostrix at preventing pertussis in infants < 2 months when administered:
    - Before pregnancy
    - During the first or second trimester
    - After pregnancy

- To assess the effectiveness of vaccination with *Boostrix* at preventing pertussis in infants < 2 months when administered during pregnancy (first, second or third trimester, at least 14 days before delivery).

- To assess the effectiveness of vaccination with *Boostrix* at preventing pertussis leading to hospitalization in infants < 2 months when administered:
    - Before pregnancy
    - During the first or second trimester
    - During the third trimester of pregnancy
    - After pregnancy

NS: The hospitalization is evaluated during the course of the pertussis infection.

4.   ENDPOINTS

4.1.   Primary endpoint

- Occurrence of pertussis among infants <2 months old either born to women vaccinated with *Boostrix* during the third pregnancy trimester or not exposed to any Tdap vaccine during pregnancy):

4.2.   Secondary endpoints

- Occurrence of pertussis among infants <2 months old born to women either vaccinated with *Boostrix*:

    – Before pregnancy

    – During the first or second trimester

    – After pregnancy

  or not exposed to any Tdap vaccine during pregnancy

- Occurrence of pertussis among infants <2 months old born to women either vaccinated with *Boostrix* at any time during pregnancy or not exposed to any Tdap vaccine during pregnancy

- Occurrence of pertussis leading to hospitalization among infants <2 months old born to women either vaccinated with *Boostrix*:

    – Before pregnancy

    – During the first or second trimester

    – During the third trimester of pregnancy

    – After pregnancy

  or not exposed to any Tdap vaccine during pregnancy

5.   DEFINITIONS

5.1.   Definitions of cases and controls

- A pertussis case:

- A case of pertussis is defined as the onset of cough illness and at least 1 of the following:

    – laboratory confirmation (culture or polymerase chain reaction) of pertussis

    – epidemiological linkage to a laboratory-confirmed case

    – clinically compatible illness (cough ≥2 weeks with paroxysms, inspiratory whoop, or post-tussive vomiting)

  in an infant <2 months old between 1 January 2011 and 31 December 2014

- A matched control:

    - A matched control is defined as an infant who did not have a pertussis diagnosis prior to the cough onset date of the corresponding case infant and who fulfilled the eligibility criteria described in 2.3.2.1. For each enrolled case infant, the study team attempted to recruit 3 control infants from birth certificates of infants born at the same hospital as the case infant and who fulfilled the eligibility criteria described in 2.3.2.2

5.2. Definition of exposure

Mothers of case and control-infants were interviewed by telephone to collect information on demographics, mother and infant healthcare providers, and infant household contacts. Data of infants with pertussis were obtained from surveillance case report forms, maternal interviews, and birth certificate records; surveillance case report form data, which included hospitalization status, were collected via patient and physician interview. Pertussis vaccination status, including brand, manufacturer, and lot number, was collected through medical providers or state immunization registries for all enrolled case and control infants and their mothers. When complete vaccine history was unavailable in registries, all medical providers identified during the interview were contacted. Additionally, birth hospitals were contacted to obtain case and control maternal Tdap histories.

Maternal vaccine history was considered complete when follow-up was exhausted with all providers; if there was incomplete follow-up with providers but at least 1 valid Tdap dose was identified, these individuals were included in the analysis. Tdap doses were considered valid if received at least two weeks before the case-infant's cough onset date; for control-infants, the date of cough onset for the matched case-infant was used. Mothers were considered unvaccinated if all medical providers were contacted and did not provide documentation of Tdap vaccination and no Tdap records were identified in the immunization registry. When >1 Tdap dose was verified, the most recent valid dose was included in the analysis.

Mothers were classified as vaccinated before pregnancy if Tdap was received at any point prior to pregnancy with the case or control infant, vaccinated during pregnancy if they received Tdap ≥14 days before delivery, and vaccinated postpartum if Tdap was received <2 months following the case or control infant's birth or in the 14 days before delivery; the trimester during which Tdap was administered was calculated from the vaccination date, infant's date of birth, and infant's gestational age at birth. When available, lot numbers were verified with vaccine manufacturers to confirm vaccine type and brand. Mother were considered as vaccinated with *Boostrix* when the most recent Tdap valid dose was *Boostrix*.

6. STATISTICAL ANALYSES

6.1. Statistical considerations

6.1.1. General considerations

All analyses/summaries will be performed using either Statistical Analysis Software (SAS) version 9.2 or higher. Categorical variables will be summarized by the frequency and the percentage of each category. The following statistics will be presented for continuous variables: number of non-missing observations, mean, standard deviation, median and range (minimum and maximum).

Summary analysis will be performed to describe the number and percentage of each covariate in cases and controls. Percentage of missing data for each covariate will also be examined. If the percentage of missing data of one covariate is greater than 50%, this covariate would not be included in the final models.

6.2. Demography

6.2.1. Subject characteristics

The number and percentage of subjects included in the analysis set will be tabulated.

Subject characteristics (infant's sex, infant's race, infant's ethnicity, gestational age at the time of delivery for the mother, infant's age at the index date (cough onset date) (weeks), infant's state of residence, household size, household members with pertussis diagnosis) will be described for the analysis set.

6.3. Analysis for primary objective – VE with Boostrix at preventing pertussis in infants<2 months during the third trimester of pregnancy, at least 14 days before delivery

6.3.1. Study population

This analysis will include cases from mothers either whose *Boostrix* administration was recorded during the third trimester or unexposed to any Tdap vaccine during the pregnancy and matched controls.

6.3.2. Statistical method

A summary of cases and controls together with its corresponding percentages for mothers either whose *Boostrix* administration was recorded during third trimester or unexposed to any Tdap vaccine during the pregnancy vaccination will be presented.

The maternal vaccination status will be categorized as "unvaccinated with any Tdap vaccine", and vaccinated with "*Boostrix* during the third pregnancy trimester". Case's and control's mothers classified as unvaccinated will be used as the reference group. The association between maternal *Boostrix* vaccination and pertussis in infants will be analysed using conditional logistic regression.

A conditional logistic regression with single exposure variable for the univariate analysis will be performed to examine the unadjusted association between maternal *Boostrix* vaccination and pertussis, as well as the association between other covariates (infant's sex, infant's race, infant's ethnicity, household size, maternal education, infant age (weeks), and household member with pertussis diagnosis) and outcome, respectively.

Covariates that will be statistically significant at 20% (i.e. p-value < 0.2) will be included in the multivariable conditional logistic regression model. Covariates that might not statistically significant in the univariate analysis, but considered as a clinical significant determinant based on previous clinical experience will also be included in the multivariable conditional logistic regression model (such as infant age (weeks)).

A backward selection will be performed among all selected covariates from univariate analysis for the final model using an alpha level of 0.2. The final conditional logistic regression model will be performed to estimate the adjusted odds ratios and corresponding 95%CIs.

Vaccine effectiveness will be estimated as (1-odds ratio) × 100%. Confidence intervals are calculated based on the conditional binomial distribution of cases in the exposed group and the total number of cases (see section 10.1.3).

If needed, as a sensitivity analysis, a multivariate conditional logistic regression model including all the covariates included in the original publication [Skoff, 2017] will be performed. This model will include the following covariates: household size >2 persons, maternal education, household member with pertussis diagnosis, and infant age (weeks).

6.4. Analysis for secondary objectives

6.4.1. Analysis for secondary objective –VE with Boostrix at preventing pertussis in infants <2 months old, when administered before pregnancy, during first or second trimester, after pregnancy Study population

This analysis will include cases from mothers either whose *Boostrix* administration was recorded before pregnancy or during the first or second trimester or after pregnancy or unexposed to any Tdap vaccine during the pregnancy and matched controls.

6.4.1.1.   Statistical method

A summary of cases and controls together with its corresponding percentages for mothers either whose *Boostrix* administration was recorded at different time points (before pregnancy, during pregnancy, and after pregnancy) or unexposed to any Tdap vaccine during the pregnancy vaccination will be presented.

Maternal *Boostrix* vaccination status will be categorized as unvaccinated with Tdap vaccine, vaccinated with *Boostrix* before pregnancy, during the first or second trimester and after pregnancy.

The univariate and multivariable conditional logistic regression model will be analysed using the same method as the primary objective (see section 6.3.2).

Note: in order to use a similar statistical model as in the original publication [Skoff, 2017], the VE of Boostrix for four vaccination periods (before pregnancy, during first or second trimester, during the third trimester (1ary objective), and after pregnancy) will be assessed in a single model including 5 categories for maternal vaccination status, the above-listed 4 vaccination periods and the non-vaccination as the reference.

6.4.2.   Analysis of VE with Boostrix at preventing pertussis in infants <2 months when administered during pregnancy (first, second or third trimester, at least 14 days before delivery)

6.4.2.1.   Study population

This analysis will include cases from mothers either whose *Boostrix* administration was recorded during pregnancy (first, second and third trimester) or unexposed to any Tdap vaccine during the pregnancy and matched controls.

6.4.2.2.   Statistical method

The analysis of VE of *Boostrix* administration at preventing pertussis among infants <2 months old for vaccination occurring during pregnancy will be analysed using the same method as the primary objective (see section 6.3.2).

6.4.3.   Analysis of VE with *Boostrix at* preventing pertussis leading to hospitalization before pregnancy, during first or second trimester, during third trimester, after pregnancy

6.4.3.1.   Study population

This analysis will include hospitalized cases from mothers either whose *Boostrix* administration was recorded before pregnancy, during pregnancy (first, second and third trimester), after pregnancy or unexposed to any Tdap vaccine during the pregnancy and matched hospitalized controls.

6.4.3.2. Statistical method

The analysis of VE of *Boostrix* administration in preventing pertussis hospitalization among infants <2 months old for vaccination occurring before pregnancy, during first or second trimester, during third trimester, after pregnancy will be analysed using the same method as the primary objective (see section 6.3.2).

7. ANALYSIS INTERPRETATION

Except for analysis on objectives with predefined success criterion and an appropriate type I error control, comparative analyses are descriptive with the aim to characterize the difference between groups. The use of these descriptive analyses should be limited to supportive analysis of confirmatory analyses or hypothesis generation.

8. CONDUCT OF ANALYSES

8.1. Sequence of analyses

Description	Analysis ID	Disclosure Purpose (CTRS=public posting, SR=study report, internal)	Dry run review needed (Y/N)	*Study Headline Summary (SHS)*requiring expedited communication to upper management (Yes/No)	Reference for TFL
Final analysis	ANALYSIS_E1_01	CTRS, SR	N	Yes	All tables from TFL in this Annex 3 see Section 12

9. LIST OF FINAL REPORT TABLES, LISTINGS AND FIGURES

The TFL TOC provides the list of tables/listings and figures needed for the study report. It also identifies the tables eligible for each analyses and their role (synopsis, in-text, post-text, SHS, CTRS,…). The post-text material contains all source material for the study report and accordingly a post-text table may be redundant with an in-text table.

10.   ANNEX 1 STANDARD DATA DERIVATION RULE AND STATISTICAL METHODS

10.1.   Statistical Method References

10.1.1.   Clopper-Pearson exact CI

The exact two-sided 95% CIs for a proportion within a group will be the Clopper-Pearson exact CI [Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. *Biometrika*. 1934;26:404-413].

10.1.2.   Conditional logistic regression

The odds ratio (OR) is the ratio of the odds of an event occurring in one group to the odds of it occurring in another group. Due to the nature of binary outcome and matched case-control study design, the following conditional logistic regression model will be fitted for deriving the corresponding ORs:

$$\ln(\frac{P}{1-P}) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k + \varepsilon$$

where $\ln(\frac{P}{1-P})$ is the log an odds of probability of event occurs in one group given a set of independent variables, β_0 is the intercept, β_1 is the coefficient of X_1 (exposure) and so on. ε is the error term of the equation.

The odds ratio for example for exposure and its corresponding 95% CI will be estimated by e^{β_1} and $e^{\beta_1 \pm (Z_{1-0.025} \times SE(\beta_1))}$, where $Z_{1-0.025}$ is the 97.5 percentiles of the standard normal distribution, and SE is the standard error of the estimated nature log of β_1.

10.1.3.   Vaccine effectiveness

The Vaccine Effectiveness (VE) is estimated as 1 – the odds ratio. The same transformation is used to derive the CIs from those obtained for the odds ratio.

10.1.4.   Handling of missing data

Missing data will not be imputed in this analysis.

Covariates with a percentage of missing data greater than 50% will be excluded from analysis.

11.   ANNEX 2 REFERENCES

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12. ANNEX 3: STUDY SPECIFIC MOCK TFL

The following drafted study specific mocks will be used.

The data display, title and footnote is for illustration purpose and will be adapted to the study specificity as indicated in the TFL TOC. Note that there may be few changes between the study specific SAP mock TFL and the final TFLs as editorial/minor changes do not require a SAP amendment

Note that the mock numbered x, y, z is newly designed mock for which there is no standard template available. Unnecessary columns may be deleted and inapplicable TFL can be removed.

13. ANNEX 4: FEASIBILITY ASSESSMENT REPORT FOR EPI-PERTUSSIS-052 (210031)

The number of cases and controls for vaccinated with Boostrix together with unvaccinated was checked after receiving the data in house. The following power estimation was based on the total number of cases and controls from Table 1

Table 1 **Number of cases versus controls for different groups infants < 2 months**

Boostrix vaccination status	Cases, No (%)	Controls, No (%)
Total	147	279
Unvaccinated	104 (71%)	177 (63%)
Vaccinated Before pregnancy	2 (1%)	8 (3%)
Vaccinated at any time during pregnancy	9 (6%)	39 (14%)
First or second trimester	1 (1%)	8 (3%)
Third trimester	8 (5%)	31 (11%)
Vaccinated After pregnancy	32 (22%)	55 (20%)

1. Power estimation for primary objective

The current primary objective proposed

- To assess the effectiveness of vaccination with *Boostrix* at preventing pertussis in infants <2 months during the third trimester of pregnancy, at least 14 days before delivery.

Table 2 **Number of cases versus controls for infants < 2 months vaccinated during the third trimester of pregnancy versus unvaccinated**

Boostrix vaccination status	Cases, No (%)	Controls, No (%)
Total	112	208

Coverage rate assumed to use 0.1, 0.15 and 0.2 for power calculation for the primary objective;

Ncases = 112;

Ratio of case/control=1:2;

Correlation between case/control of 0.2;

Table 3   Power estimation for primary objective

VE	Coverage rate	Power
50%	0.1	26.91%
	0.15	38.87%
	0.2	49.15%
60%	0.1	40.62%
	0.15	58.17%
	0.2	71.09%
70%	0.1	59.08%
	0.15	79.44%
	0.2	90.17%

If a true VE of 70% with 0.15 coverage rate, it is almost 80% power to proceed with this study. The VE provided by CDC previously was even more than 80% (82.75%). With that amount of VE, we could have enough power for this primary objective.

2. Power estimation for secondary objective – Before pregnancy

Table 4   Number of cases versus controls for infants < 2 months vaccinated before pregnancy versus unvaccinated

Boostrix vaccination status	Cases, No (%)	Controls, No (%)
Total	106	185

Coverage rate assumed to use 0.05 and 0.1 for power calculation for the secondary objective;

Ncases = 106;

Ratio of case/control=1:1.7;

Correlation between case/control of 0.2;

Table 5   Power estimation for secondary objective – vaccinated before pregnancy versus unvaccinated

VE	Coverage rate	Power
50%	0.05	10.80%
	0.1	19.38%
60%	0.05	14.47%
	0.1	28.87%
70%	0.05	19.72%
	0.1	43.01%

The estimated power is quite low for this objective, the analysis will be performed, however interpretation needs more caution.

3. Power estimation for secondary objective – During 1st and 2nd trimester pregnancy

Table 6 **Number of cases versus controls for infants < 2 months vaccinated during the first or second trimester of pregnancy versus unvaccinated**

Boostrix vaccination status	Cases, No (%)	Controls, No (%)
Total	105	185

Number of cases is quite close to Table 4 – previous objective. With the same coverage rate assumed and case/control ratio, the power will be similar as in Table 5, therefore, the power for this objective was not calculated. Similar conclusion that the estimated power is quite low for this objective, the analysis will be performed, however interpretation needs more caution.

4. Power estimation for secondary objective – after pregnancy

Table 7 **Number of cases versus controls for infants < 2 months vaccinated after pregnancy versus unvaccinated**

Boostrix vaccination status	Cases, No (%)	Controls, No (%)
Total	136	232

Coverage rate assumed to use 0.1, 0.15 and 0.2 for power calculation for the secondary objective;

Ncases = 136;

Ratio of case/control=1:2;

Correlation between case/control of 0.2;

Table 8 **Power estimation for secondary objective – vaccinated after pregnancy versus unvaccinated**

VE	Coverage rate	Power
5%	0.1	5.08%
	0.15	5.18%
	0.2	5.27%

* VE value was from the paper [Skoff, 2015]

The estimated power is quite low for this objective, the analysis will be performed, however interpretation needs more caution.

5. The two proposed secondary objectives

- To assess the effectiveness of *Boostrix* when administered to women before pregnancy at preventing pertussis disease among infants <2 months old for the following timing of administration:

  – >2 years before pregnancy

  – <=2 years before pregnancy

- To assess the effectiveness of *Boostrix* at preventing pertussis disease among infants <2 months old for maternal immunization occurring during the third trimester of pregnancy, 30 days or more before delivery.

These two objectives cannot be assessed, as there is no info for pregnancy date to derive 2 years before pregnancy or not; and there is no info for delivery date to derive 30 days of more before delivery. The two objectives will be skipped from the SAP. And the rational of not putting those two objectives will be added in the SAP.

6. Secondary objective – during pregnancy

- To assess the effectiveness of vaccination with Boostrix at preventing pertussis in infants < 2 months when administered during pregnancy (first, second or third trimester, at least 14 days before delivery).

This is a sum of first, second and third trimester during pregnancy which should provide enough power, given considering only the third trimester during pregnancy will have sufficient power for the analysis.

- To assess the effectiveness of vaccination with *Boostrix* at preventing pertussis leading to hospitalization in infants < 2 months when administered:

    –   Before pregnancy

    –   During the first or second trimester

    –   During the third trimester of pregnancy

    –   After pregnancy

Table 9   Number of cases versus controls for different groups in hospitalized infants < 2 months

Boostrix vaccination status	Cases, No (%)	Controls, No (%)
Total	102	171
Unvaccinated	76 (75%)	109 (64%)
Vaccinated Before pregnancy	2 (2%)	4 (2%)
Vaccinated at any time during pregnancy	4 (4%)	21 (12%)
First or second trimester	0 (0%)	7 (4%)
Third trimester	4 (4%)	14 (8%)
Vaccinated After pregnancy	20 (20%)	37 (22%)

Similar analyses will be performed in hospitalized infants < 2 months, the count was summarized in Table 9.

![gsk GlaxoSmithKline logo]	**Ad Hoc Statistical Analysis Plan**
Detailed Title:	Effectiveness of maternal immunization with *Boostrix*-at preventing pertussis among infants <2 Months old in the United States: analysis of a dataset from a case-control study conducted by the Centre for Disease Control.
eTrack study number and Abbreviated Title	210031 (EPI-PERTUSSIS-052 VE US DB)
Scope:	Bayesian leveraging of historical effectiveness data for the study analysis
Date of Statistical Analysis Plan	Final: 31 March 2020

APP 9000058193 Statistical Analysis Plan Template V4 (Effective date: 3June2019)

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LIST OF ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
CIs	Confidence Intervals
GSK	GlaxoSmithKline
SAP	Statistical Analysis Plan
VE	Vaccine Effectiveness

1   DOCUMENT HISTORY

Date	Description	Protocol Version
31-MAR-2020	First version	This is an analysis of the dataset of an epidemiological study performed by the US CDC assessing the effectiveness of maternal immunization with tetanus-diphtheria-acellular pertussis (Tdap) vaccines at preventing pertussis in infants. The objectives are the same as the original study, focussing at the effectiveness of *Boostrix*. Therefore, the analysis is solely described in a detailed SAP. A protocol has not been developed, as it did not have added value in these circumstances.

2   BACKGROUND

2.1   Rational for the adhoc analysis plan

Pertussis, also known as "whooping cough", is a highly contagious disease that is caused by the bacterium *Bordetella pertussis* and can cause prolonged periods of respiratory distress. In 2016, the Centers for Disease Control and Prevention (CDC) provisionally estimated that in 2016 there were approximately 16,000 cases of pertussis reported in the US with an incidence of 4.7 cases per 100,000. Pertussis incidence is reported to be high in the less than 6-month age group (incidence of 85.5 cases per 100,000 in 2016, corresponding to 1,253 cases) [CDC, 2016].

Young infants are most vulnerable to pertussis-related complications, particularly during the period preceding the initiation of 5-dose vaccination schedule with the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at 2 months of age [CDC, 2000]. Parents and siblings may play an important role in transmitting pertussis to vulnerable infants [Skoff, 2015].

Two tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines are licensed for use as a single booster dose among US adolescents and adults: *Boostrix* (GSK) and *Adacel* (Sanofi Pasteur). These vaccines have been licensed in the US since 2005 and can be used interchangeably [Kretsinger, 2006]. The primary goal of this vaccination is to protect the vaccine recipient. However, vaccination of close contacts can also indirectly protect infants. In 2011, The Advisory Committee on Immunization Practices (ACIP) recommended vaccination during pregnancy [CDC, 2011]. The recommendation was expanded in 2012 to include a dose of Tdap during every pregnancy [CDC, 2013]. This strategy not only helps protect the mother from pertussis infection and transmission of pertussis on to her infant, but also provides passive immunity to the infant. Although the ACIP suggests that the preferred timing for Tdap administration is between 27 and 36 weeks gestation to optimize transplacental transfer of maternal anti-pertussis antibodies, Tdap may be given at any time during pregnancy.

The effectiveness of antenatal pertussis immunization has been evaluated in the UK [Amirthalingam, 2014; Dabrera, 2015; Amirthalingam, 2016], in Spain [Uriarte, 2019; Bellido-Blasco, 2017], in Australia [Saul, 2018], in the US [Baxter, 2017; Skoff, 2017; Winter, 2017a; Winter, 2017b; Becker-Dreps, 2018], in Argentina [Romanin, 2019] and in Brazil [Fernandes, 2019]. In particular, a case-control study within 6 US

EIP network sites evaluated the effectiveness of Tdap vaccination during pregnancy for preventing pertussis in infants <2 months of age [Skoff, 2017]. This collaborative network includes the CDC and state and local health departments, academic institutions and laboratories. The multivariable vaccine effectiveness (VE) estimate for Tdap administered during the third trimester of pregnancy was 77.7% (95% confidence interval [CI]: 48.3, 90.4); VE increased to 90.5% (95% CI: 65.2, 97.4) against hospitalized cases [Skoff, 2017]. The data collected in the study on the vaccination status of the subjects included vaccine brand name, vaccine manufacturer's name and vaccine lot number, which were collected through medical providers or state immunization registries. Overall, 136 (56.7%) case mothers and 358 (66.9%) control mothers had at least 1 valid Tdap dose identified. A total of 43 of 136 (31.6%) vaccinated case mothers and 102 of 358 (28.5%) vaccinated control mothers received *Boostrix*, and 76 of 136 (55.9%) vaccinated case mothers and 207 of 358 (57.8%) vaccinated control mothers received *Adacel*; brand information was not available for the remaining 17 of 136 (12.5%) case mothers and 49 of 358 (13.7%) control mothers who had a record of Tdap receipt. The publication mentions that the point estimates of the effectiveness of either vaccine product at preventing infant disease when administered during the third trimester were not statistically different from one another (p = .85). There is no brand-specific vaccine effectiveness information available in the current publication [Skoff, 2017].

GSK established a data use agreement with the CDC to access the dataset of the Skoff [Skoff, 2017]. study in order to assess specifically the effectiveness of *Boostrix* maternal immunization against pertussis disease in infants (study EPI-PERTUSSIS-052 VE DB US). The dataset has been received from the CDC in the SAS format.

After exclusion of controls matched to cases born to mothers vaccinated with *Adacel* or vaccinated with Tdap without vaccine brand specification, cases with no matched controls and controls not matched to any remaining case, the study population included 107 cases and 183 matched controls. Adjusting for infant's age, maternal education and household size, the effectiveness of *Boostrix* maternal vaccination when administered during third trimester of pregnancy was 65.3% (95% CI [-64.9, 92.7]).

While the point estimate is consistent with the non-brand specific analysis, supporting the benefit of maternal immunization with *Boostrix*, the large confidence interval did not allow to formally demonstrate the effectiveness of *Boostrix* maternal immunization.

Following GSK questions on GSK's data generation plan for the clinical benefit of maternal immunization with *Boostrix* submitted to the IND in the October 16, 2019 and December 19, 2019, amendments, CBER suggested performing additional supportive analyses to characterize *Boostrix* effectiveness leveraging non-US formulation data in a Bayesian framework.

The analysis plan describes the proposed Bayesian analysis.

2.2 EPI-PERTUSSIS-052 Study design

- **Study design:** An observational matched case-control study.

  - Outcome:

    Pertussis case group: composed of infants who met the pertussis diagnosis definition.

    Control group: composed of infants who did not have a pertussis diagnosis prior to the cough onset date of the corresponding case infant.

  - Exposure**:**

    Infant's mother vaccinated with Tdap vaccine.

    Infant's mother unexposed to any Tdap vaccine.

- **Study region:** 6 EIP network sites (state-wide in California, Connecticut, Minnesota, New Mexico and in select counties of New York and Oregon) in the US.

- **Study period:** 1 January 2011 to 31 December 2014 for identification of cases and controls.

- **Study population:** All eligible infant pertussis cases captured from EIP and corresponding matched controls.

- **Matching:** 1:3 matched cases and controls

  - For each enrolled case, the study site attempted to recruit 3 control infants using birth certificates of infants born at the same hospital for the case infants who were <2 months old on the case infant's cough onset date. Once all potential controls meeting these criteria were exhausted, the control enrolment ended for that case infant.

Description of data sources: Pertussis cases in infants were identified through disease surveillance in the 6 EIP Network sites in the US. EIP is a collaborative pertussis surveillance network between the CDC and the state and local health departments, academic institutions and laboratories that serves as a national resource for surveillance, prevention, and control of emerging infectious diseases.

2.3 Historical data used for the analysis

A systematic literature review was performed to identify epidemiological studies published in peer-reviewed journals that evaluated the effectiveness of maternal immunization with Tdap (Tetanus, Diphtheria, and Pertussis) vaccines and more specifically with *Boostrix/Boostrix Polio* at preventing pertussis disease in the young vulnerable infants (under 2-3 months of age) who are not yet protected against pertussis by the first pediatric vaccination immunization series. Details on the research strategy has been submitted to the Boostrix IND.

Out of 13 studies on the effectiveness of maternal immunization with Tdap vaccine (Table 1), 4 studies provided estimates of the effectiveness of *Boostrix/Boostrix-Polio* (Table 2). The use of *Boostrix/Boostrix Polio* is explicitly mentioned in three publications

[Amirthalingam, 2016; Saul, 2018; Uriarte, 2019]. One publication does not mention t
he vaccine brand, but the study investigator confirmed in a communication with GSK the
use of *Boostrix* [Bellido-Blasco, 2017].

In addition to these published studies, GSK entered an agreement with Public Health
England (PHE) for the provision of a report of a recent analysis performed by PHE on the
effectiveness of maternal immunization with Boostrix Polio. This analysis is not yet
published in peer-reviewed journals. The study report prepared by PHE used the
screening method to measure VE, as in the study published by Amirthalingam
[Amirthalingam, 2016], but covered a longer period of time (i.e. 4 years from 1
 September 2014 to 30 September 2018 for the report, vs. 1 year and 3 months from 1
July 2014 to 30 September 2015 for the 2016 publication).

Table 1 Overview of Tdap effectiveness studies (by country alphabetical order)

Reference	Design	Setting and study population	Study period	Size	Vaccines used	Results
Romanin et al., 2019	Matched case-control	**Argentina**, six hospitals. Case: infant <2 months of age, laboratory confirmed by conventional or real-time PCR. Five controls per case, matched on mother's residential health district and receipt of healthcare at a participating hospital within the same province as the hospital at which the case-patient was identified.	September 24, 2012-March 31, 2014 and December 1, 2014-March 31, 2016	71 cases and 300 controls	Not mentioned in publication Note: information received from investigator: vaccine providers varied by study year	Adjusted VE of Tdap during pregnancy in the prevention of pertussis among infants <2 months of age: 80.7% (95% Confidence Intervalle [CI]: 52.1, 92.2%). Adjusted VE 77.6% (95% CI: 39.1, 91.8%) for Tdap given during the second trimester and 82.7% (95% CI: 46.4%, 94.4%) for Tdap given in the third trimester
Saul et al, 2018	Matched Case-control	**Australia, state of New South Wales (NSW)** Case: infant <6 months at symptom onset, with laboratory definitive evidence of pertussis – in the absence of recent vaccination For each case a control born in a public hospital (in the same local health district where the case was resident) was randomly selected from a list with the births in the period up to 3 days before or after the cases' birthdate. If the control refused participation, further controls were selected in the same manner.	16 August 2015 to 17 August 2016	Infants < 6 months: 117 cases and 117 controls Infants < 3 months: 48 cases and 48 controls	*Boostrix*	- VE against pertussis disease in infants < 6 months: 39% (95% CI: -12, 66%) 2 sub-analyses - VE against pertussis disease in infants < 3 months 69% (95% CI: 13, 89%) - VE against hospitalization for pertussis 94% (95% CI: 59, 99%) in infants < 6 months
Fernandes et al, 2019	Unmatched case-control	**Brazil, São Paulo State** Case of pertussis: clinically compatible cough illness in an infant aged <8 weeks at disease onset, with laboratory confirmation (culture or real-time polymerase chain reaction) For each enrolled infant case, 4 to 6 control infants recruited from birth certificates of infants resident in the same city as the case (born within one month before or after the reference case).	February 2015-July 2016	42 cases 249 controls	Not mentioned in the publication	After adjustment for maternal age and household income, VE 80.7% (95% CI, 55.9, 91.6%)
Amirthalingam et al, 2014	Screening method	**England** Cases: Laboratory confirmed pertussis cases (<3 months) born after October 1st, 2012 and with a specimen or onset set-up up to 30 Sept 2013 Maternal vaccine coverage estimated from English practices in the CPRD based on 26 684 women with a livebirth from Oct 1, 2012 (week 40, 2012) until Sept 3,	Effectiveness was assessed just in infants born after October 1st, 2012 and with a specimen or	82 cases	Tdap-IPV (*Repevax*)	VE based on 82 confirmed cases in infants aged < 3 months: 91% (95% CI: 84, 95) VE 90% (95% CI: 82, 95%) when restricted to cases in infants aged < 2 months

Reference	Design	Setting and study population	Study period	Size	Vaccines used	Results
		2013 (week 36, 2013). This figure represents about 4% of all livebirths in England in 2012 (694 241).	onset set-up up to 30 Sept 2013			
Dabrera et al, 2015	Case-control	**England and Wales** Case: infant aged <8 weeks at pertussis onset, confirmed by real-time polymerase chain reaction or culture. Controls were selected by family doctors (healthy infants born consecutively after the case in each practice)	Between October 2012 and July 2013	58 cases and 55 controls	Not mentioned in the publication but it is mentioned in other publications (Amirthalingam et al., 2014) that during this period Tap-IPV (*Repevax*) was used in the UK	Adjusted VE for sex, geographical area and birth period 93% (95% CI: 81, 97%)
Amirthalingam et al, 2016	Screening method	**England** Coverage derived from 2 primary care data sets: 1) routine collection (Immform), 2) sentinel primary care data source, the Clinical Practice Research Datalink (CPRD) Cases: reported cases with laboratory confirmation either at the local hospital microbiology laboratory (culture); through the regional PHE laboratory network (PCR available through the regional network since July 2014 for all age groups, previously only offered for hospitalized infants by the national reference laboratory); or at the national reference laboratory (serological testing available since 2001 for all age groups and, since January 2013, oral fluid testing for suspected cases initially aged 8–16 years and extended to those aged 5–16 years from July 2013).	Oct 2012 - Sep 2015	Overall analysis: 243 cases, of whom 35 had been born to vaccinated mothers There were 71 cases during the period of dT3aP-IPV use.	*Boostrix-IPV*	Overall effectiveness of 91% (95% CI: 88–94%) for infants <3 months of age and 90% (95% CI: 86, 93%) for infants <2 months of age. VE against death: 95% (95% CI: 79, 100%). The maternal VE of dT5aP-IPV and dT3aP-IPV did not significantly differ and was calculated at 93% (95% CI: 89, 95%) and 88% (95% CI: 79, 93%), respectively.
PHE, 2020	Screening method	**England** Coverage derived from 2 primary care data sets: 1) routine collection (Immform), 2) sentinel primary care data source, the Clinical Practice Research Datalink (CPRD) Pertussis disease cases were identified as part of the enhanced pertussis surveillance program.	01 Sept 2014 – 30 Sep 2018	403 cases < 93 days of age without childhood vaccination excluding cases whose mother was vaccinated within 7 days of delivery, of which 309 were below 2 month of age	*Boostrix-IPV*	VE 87% (95% CI: 84, 90%) VE for infants < 2 M 87% (95% CI: 84%, 90%)

Reference	Design	Setting and study population	Study period	Size	Vaccines used	Results
Bellido-Blasco *et al.*, 2017	Case-control	**Spain, Valencia Region** Cases: infants less than 3 months of age with pertussis infection confirmed by PCR, having not yet received primary vaccination. For every case, 3 controls paired by age who were unvaccinated and for whom the absence of whooping cough (by checking clinical records or phone interviews with parents and paediatrician/family doctor) and absence of any episodes of cough and bronchiolitis were confirmed, were included.	1 March 2015 to 29 February 2016	22 cases and 66 controls	*Boostrix* (confirmed by investigator)	VE 90.9% (95% CI: 56.6, 98.1%)
Uriarte *et al.*, 2019	Screening method	**Spain, Basque country** Cases of pertussis in infants identified in: - National registry of notifiable diseases - The minimum data set of admissions to hospitals in the province - The Basque Microbiological Information System (SIMCAPV) Tdap coverage in pregnant women: for the numerator, basic patient data on women born before 31 December 1996 (women over 18 years of age) who had been vaccinated with Tdap were obtained. For the denominator, a registry of metabolic diseases that lists all the newborn infants in the Basque Country was used. The newborn infants of mothers who were resident in Bizkaia in the study period were selected.	A February 2015-31 January 2016	19 pertussis cases in infants under 3 months of age were reported to the notifiable disease surveillance system	*Boostrix*	VE 89% (95% CI: 72, 96%)
Baxter *et al*, 2017	Retrospective cohort study	**United States** Kaiser Permanente of Northern California (KPNC) Hospitals, California, USA Infants born full-term (>37 weeks' gestation) in KPNC Hospitals and enrolled in Kaiser health plan by 4 months of age with mothers who were continuously enrolled in Kaiser during pregnancy. Mothers born pre-1996 to ensure they had received whole cell pertussis vaccine priming	2010 to 2015	n=148,981 Mothers vaccinated during pregnancy at least 8 days before birth=68,168 (45.8%) and not vaccinated=79,292 (53.2%).	"the pertussis vaccines purchased by Kaiser Permanente Northern California, which are the focus of this study, were manufactured by GlaxoSmithKline and Sanofi Pasteur"	Maternal Tdap VE 91.4% (95% CI: 19.5, 99.1%) in infants <2 months of age. Tdap VE for infants who had 0 DTaP doses (from birth through 7 days after the first dose): 87.9%; Tdap VE for infants who had protection from 1 DTaP dose (ie, from day 8 after dose 1 through day 7 of dose 2) :81.4%; Tdap VE for infants who had protection from 2 DTaP doses, but

Reference	Design	Setting and study population	Study period	Size	Vaccines used	Results
						not yet 3 doses: 6.4%; and Tdap VE for infants who had 3 DTaP doses: 65.9%
Winter *et al*, **2017a**	Retrospective cohort	**United States** Retrospective cohort study of infants <63 days of age born during study period. Data sources: CDPH pertussis surveillance reports, CDPH Centre for Health Statistics (birth certificate records) and California Immunization Registry (Tdap immunization records of mothers)	January 2011 to December 2015	Pertussis cases n=752; known maternal vaccination status=420 (prenatal Tdap vaccination [n=49], no prenatal Tdap [n=371])	Tdap acellular vaccines available in the USA (*Boostrix* and *Adacel*)	Infected infants with vaccinated mothers were significantly less likely to be hospitalized Odds Ratio OR=0.42 (95% CI: 0.20, 0.85), VE 58% (95% CI: 14.9, 79.6%) after adjustment. Hospitalized infants with vaccinated mothers had shorter periods of admission and none required intubation or died.
Winter *et al*, **2017b**	Retrospective cohort	**United States** Infants younger than 8 weeks in California born from mothers that received Tdap vaccination between 27-36 weeks of gestation compared to those that received vaccination postpartum Vaccination took place either between 27-36 weeks of gestation or 0-14 days postpartum	2013 and 2014	74 504 mothers, among which 42 941 (58%) were vaccinated during pregnancy and 31 563 (42%) post partum. 321 cases in infants younger than 8 weeks and 1562 in infants <12 months	Tdap acellular vaccines available in the USA	Tdap vaccination received at 27-36 weeks' gestation was 85% (95% CI: 33, 98%) more effective than postpartum vaccination at preventing pertussis in infants <8 weeks. Vaccination at 27-36 weeks' gestation was more effective at preventing pertussis in infants compared to vaccination in the second trimester
Skoff *et al.*, **2017**	Case-control	**United States** Pertussis cases <2 months old from 6 US Emerging Infection Program Network states. Controls were hospital-matched and selected by birth certificate	1 January 2011 and 31 December 2014	240 cases and 535 controls	*Boostrix* and *Adacel*	VE Tdap administered during the third trimester of pregnancy: 77.7% (95% CI: 48.3, 90.4%); VE 90.5% (95% CI, 65.2, 97.4%) against hospitalized cases VE Tdap administered first or second trimester: 64.3% (95% CI: –13.8, 88.8) VE Tdap administered before pregnancy: 50.8% (95% CI: 2.1, 75.2) The effectiveness point estimates of either vaccine product (*Boostrix* or *Adacel*) at preventing infant disease

Reference	Design	Setting and study population	Study period	Size	Vaccines used	Results
						when administered during the third trimester, were not statistically different from one another (P = .85).
Becker-Dreps *et al*, **2018**	Retrospective cohort	**United States** Truven Health Analytics Market - Scans Commercial Claims and Encounters Databases Cohort of pregnant women and their infants (≤18 months) delivered during study period Pertussis: either an inpatient pertussis diagnosis alone or an outpatient pertussis diagnosis plus antibiotic treatment with azithromycin, clarithromycin, erythromycin, or trimethoprim/sulfamethoxazole within 7 days. Possible pertussis included both definitions above, and also in outpatient visits with a diagnosis of cough, plus a claim for a pertussis laboratory test, and antibiotic treatment with a macrolide or trimethoprim/sulfamethoxazole within 7 days.	between June 2010 and December 2014	675,167 mother–infant pairs	Current Procedural Terminology codes used to determine the maternal immunization status do not allow to identify brands	Among infants whose mothers received prenatal Tdap, the rate of diagnosed pertussis was 43% lower (Hazard Ratio HR 0.57, 95% CI: 0.35, 0.92), and the rate of inpatient-only diagnosed pertussis was 68% lower (HR 0.32, 95% CI: 0.11, 0.91) than infants whose mothers did not receive prenatal or postpartum Tdap Between 6 and 18 months of life, there were no differences in pertussis rates by receipt of prenatal Tdap after adjustment for the infant's DTaP receipt (HR 0.69, 95% CI: 0.26, 1.86 for pertussis and HR 2.60, 95% CI: 0.15, 46.2 for inpatient-only pertussis).

Table 2 **Key features of the observational effectiveness studies with Boostrix/Boostrix Polio vaccination during pregnancy**

Study ID	Study countries	Study Design Objectives	Study period	Vaccine (time of vaccination during pregnancy)	Age of infants
Amirthalingam *et al.,* 2016	UK (England)	Retrospective observational study (screening method to evaluate the effectiveness and ecological design to describe the impact) • Maternal VE against laboratory-confirmed pertussis disease and death in infants • Maternal VE by timing of vaccination • Maternal VE of *Repevax* and Maternal VE of *Boostrix Polio* • Maternal VE for infants commencing primary infant series • Impact of maternal immunization on the disease epidemiology	Oct 2012 - Sep 2015 01 Oct 2012 – 30 Jun 2014 01 Jul 2014 – 30 Sep 2015	Repevax (3rd trimester) *Boostrix Polio* (3rd trimester)	Below 3 months of age Older infants (up to 23 months of age) with primary DTP dose
PHE, 2020	UK (England)	Retrospective observational study (screening method) • VE against laboratory-confirmed pertussis disease in unvaccinated infants below 3 months and infants below 2 months • VE against pertussis hospitalization and death in unvaccinated infants below 3 months • VE by timing of vaccination • VE in infants who have received primary DTP doses	01 Sept 2014 – 30 Sep 2018	*Boostrix Polio* (initially 28-32 weeks gestation, from 1st April 2016, 16-32 weeks)	Below 2 and3 months Older infants with primary DTP dose
Bellido-Blasco *et al.,* 2017	Spain (Valencian Community)	Prospective observational study (1:3 matched case-control) • Maternal VE against laboratory-confirmed pertussis disease in infants	01 Mar 2015 – 29 Feb 2016	*Boostrix* (3rd trimester)	Below 3 months of age
Saul *et al.,* 2018	Australia	Prospective observational study (1:1 matched case-control)	17 Aug 2015 -16 Aug 2016	*Boostrix* (3rd trimester)	Below 6 months of age

Study ID	Study countries	Study Design Objectives	Study period	Vaccine (time of vaccination during pregnancy)	Age of infants
	(New South Wales state)	• Maternal VE against laboratory-confirmed pertussis disease in infants			(Sub-group "below 3 months of age" and sub-group ""hospitalized")
Uriarte *et al.*, 2019	Spain (Basque country)	Retrospective observational study (screening method to evaluate the effectiveness) • Maternal VE against pertussis disease in infants under 3 months of age (notified cases)	1 February 2015 -31 January 2016	*Boostrix* (3rd trimester)	Below 3 months of age

3 OBJECTIVES

This adhoc analysis plan is focussing on the primary study objective, namely:

To assess the effectiveness of vaccination with *Boostrix* at preventing pertussis in infants <2 months during the third trimester of pregnancy, at least 14 days before delivery.

4 STATISTICAL ANALYSES

4.1 Establishing prior based on non-US effectiveness study

In line with the study objective only estimates of VE before 3 months of age and when most infants have not yet started DTP infant immunization will be used to establish a prior.

In case different estimates are available in the paper it is proposed to take the most conservative estimate ie the estimate with the lowest point estimate of vaccine effectiveness.

Table 3 provides the different estimated VE available in the articles/reports. The ones proposed for establishing the prior are shown in red font.

A Bayesian random effect model on the log odds ratio (= log(1-VE)) is proposed to estimate the prior for VEs. The Bayesian method is recommended when the number of studies is limited as the frequentist approach tends to under estimate the variability of estimates. Non informative prior will be used for the μ (the expected log odds ratio) and τ (the variance between studies) will be considered. Namely the prior for μ will be a normal distribution for 0 mean and 1000000 variance while the prior for τ will be a half normal distribution with parameters 0 and 0.5.

The log odds ratio for each study is presented in Figure 1. It shows that the CIs around the log odds ratio are symmetrically distributed and therefore a meta-analysis considering normal distribution is adequate.

Table 3   Summary of the effectiveness of maternal immunization with *Boostrix* (non US-licensed formulation)/*Boostrix Polio* at preventing pertussis in young infants

| Country	Design	Confounding control	Method	Vaccine and recommended administration timing in mother	Endpoint	Effectiveness of maternal immunization with *Boostrix/Boostrix Polio* at preventing infant pertussis	Reliability weight
UK*	Screening method	week of birth & mother age as per 3 groups	logistic regression	*Boostrix Polio* (initially 28-32 weeks gestation, from 1st April 2016, 16-32 weeks)	Pertussis disease in infant below 3 months of age, before primary immunization	87% (95% CI: 84, 90%)	good because - robust data sources (information on 403 cases collected through enhanced surveillance during 4 years and coverage estimates from a representative network of GPs). - limitation of the screening method mitigated through a sensitivity analysis by varying vaccine coverage - moderate risk of bias due to confounding
					Pertussis disease in in infant below 2 months of age	87% (95% CI: 84, 90%)	
Spain	Case-control	age+/-15 days, same practice, the study was conducted in a single year.	conditional logistic regression adjusted for household size, breastfeeding status and weeks of gestational age	*Boostrix* (27-36 weeks gestation)	Pertussis disease in infant below 3 months of age	90.9% (95% CI: 56.6, 98.1%) – asymptotic, adjusted for breastfeeding only 90.4% (95% CI: 52.7,99%) exact method, adjusted for breastfeeding only 87.3% (95% CI: 34.2, 97.5%) asymptotic, adjusted for all 3 confounders	Fair because - robust design (prospective matched case-control study, with two sources of controls and PCR confirmation of pertussis) - study conducted in a single region over a short time period, with limited number of cases (N=22). -there was no matching by mother's age.

Country	Design	Confounding control	Method	Vaccine and recommended administration timing in mother	Endpoint	Effectiveness of maternal immunization with *Boostrix/Boostrix Polio* at preventing infant pertussis	Reliability weight
							- there is a moderate risk of bias due to confounding
Australia	Case-control	birth date+/-3 days & area	conditional logistic regression adjusted for infant vaccination, breastfeeding status, gender, household size	Boostrix (3rd trimester)	Pertussis disease in infants below 3 months of age	69% (95% CI: 13, 89%) adjusted 64% (95% CI: 18, 84%) unadjusted	Good because - robust prospective matched case-control design, enrolling 69% of pertussis cases in the most populated region of Australia (hospitalized and non hospitalized), with laboratory confirmation of pertussis diagnosis. The number of cases less than 3 months of age was 48. - moderate risk of confounding and participation bias
Spain	Screening method	the study was conducted in one year upon maternal immunization recommendation. There was no matching.	Farrington CI	*Boostrix* (27-36 weeks gestation)	Pertussis disease in infant below 3 months of age	89% (95% CI: 72, 96%)	Poor because - the screening design is highly sensitive to the accuracy of vaccine coverage and the study may entail inaccuracies in the calculation of the numerator and denominator - the method does not allow adjustment for potential confounders - the limited number of subjects (short time period, single region) which is associated to larger risk of publication bias

* data from the 2020 PHE report as this covers a larger time span than the 2016 Amirthalingam study

Figure 1 Observed log odds ratio for historical studies
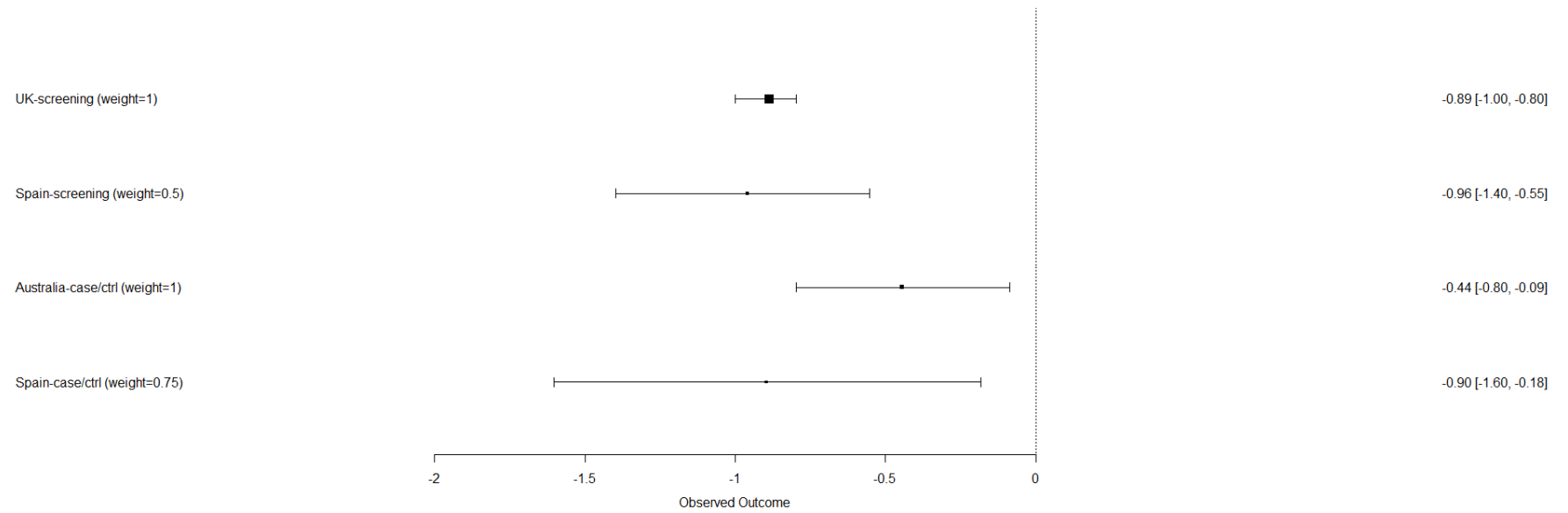
4.2 Bayesian analysis of EPI-PERTUSSIS-052

The gMAP function in R RBest package will be used to build a Meta-Analytic-Predictive (MAP) Prior as described in the paper by Schmidli [Schmidli, 2014]. The prior will be robustified with a mix of a non-informative prior with the MAP prior from the meta-analysis. This mixed prior will be used for estimating VE using the data from EPI-PERTUSSIS-052.

The weight used for mixing the non informative component should be set up according to how reliable/representative the historical data is. GSK considers that the non-US data are reliably representing the US VE because the 2 formulations induce similar immunogenicity. However, considering a potential publication bias, a weight of 90% is proposed for the non-US data versus a weight of 10% for non-informative prior without effect of *Boostrix* vaccination.

The mixed prior will be used to obtain a posterior distribution with 95% credibility interval.

The generation of mixed prior and posterior credibility interval will be obtained from robustify and postmix functions in R RBest package.

To assess the impact of the weight in the mix prior, 95% credibility interval will be generated according to the weight ranging from 0% to 100%.

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