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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	GlaxoSmithKline Biologicals
Established Name	Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine, Adsorbed
Trade Name	Boostrix
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc	Tetanus toxoid, diphtheria toxoid, and pertussis antigens (inactivated pertussis toxin and formaldehyde-treated FHA and PRN) and aluminum hydroxide adjuvant

Dosage Form and Route of Administration	Single-dose vials and prefilled syringes containing a 0.5-mL suspension for intramuscular injection
Dosing Regimen	Single dose 5 or more years after the last DTaP series dose or after a Td dose. Additional doses may be administered 9 or more years after the initial Tdap dose or during the 3 rd trimester of pregnancy
Indication and Intended Population	Immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age

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GLOSSARY

BLA	biologics licensing application
CBER	Center for Biologics Evaluation and Research
CDC	U.S. Center for Disease Control and Prevention
CI	confidence interval
CrI	credible interval
IND	investigational new drug
IR	information request
MF	master file
Tdap	tetanus, diphtheria, and acellular pertussis
VEff	vaccine effectiveness

1. EXECUTIVE SUMMARY

In this submission, the applicant (GlaxoSmithKline Biologicals, or GSK) seeks approval for the indication, to provide protection against pertussis in infants younger than 2 months of age, for Boostrix when administered during the third trimester of pregnancy. The U.S. Center for Disease Control and Prevention's Advisory Committee on Immunization Practices currently recommends that all pregnant women receive a tetanus, diphtheria, and acellular pertussis (Tdap) vaccine dose during pregnancy to prevent pertussis in infants too young for routine immunization, preferably at 27–36 weeks of gestation. However, there are currently no vaccines licensed for this indication in the U.S.

In support of the proposed indication, GSK submitted the post-hoc re-analysis results of the Boostrix-specific data (referred to as EPI-PERTUSSIS-052) from a maternal Tdap immunization study published in Skoff et al. (2017). Skoff et al. (2017) was an observational, retrospective, matched, case-control study in infants two months of age or younger. Cases were identified through the CDC's Emerging Infection Program Network based on data collected between 1 January 2011 and 31 December 2014 at six sites. Control infants were identified through the birth hospitals of their matching cases, and in EPI-PERTUSSIS-052, cases and controls were also matched on age group (<2 weeks old, ≥2 weeks old). Mothers were classified as unvaccinated if they had no evidence of at least one Tdap vaccination given at least two weeks prior to their corresponding case infant's cough onset date. Otherwise, mothers were classified based on the timing of their most recent Tdap dose, relative to pregnancy (before, first or second trimester, third trimester, after).

The primary objective of EPI-PERTUSSIS-052 was to estimate the vaccine effectiveness (VEff) of maternal immunization during the third trimester against pertussis. To estimate the VEff in the third trimester, GSK first conducted a frequentist analysis, then updated those results with external data in a Bayesian analysis. In the frequentist analysis, GSK fit a conditional logistic regression model adjusted for age in weeks, maternal education, and household size that resulted in a preliminary vaccine effectiveness estimate of 78.0% (95% confidence interval: -38.0, 96.5). Sensitivity analyses accounting for the effects of excluding non-third trimester exposures, missing data, and ambiguous or multiply

exposed mothers produced similar results. For the Bayesian update, the prior was a weighted combination of an informative prior, which was derived from a Bayesian meta-analysis of four studies that estimated the VEff of the non-U.S. Boostrix formulation against pertussis when administered during pregnancy, and an uninformative, vague prior. From this Bayesian update, the VEff estimate was 83.4% (95% credible interval: 55.7, 92.5). Sensitivity analyses accounting for the relative weight given to the informative prior and the studies included in the informative prior produced similar point estimates and lower credible interval of greater than 0% in majority of the scenarios.

Overall, these results suggest that Boostrix is highly likely to have a vaccine effectiveness of at least 50% for the intended indication and most likely to have an effectiveness of approximately 80%. The results from sensitivity analyses addressing the effects of the analysis methods and missing data were similar. However, the effects of some aspects of the EPI-PERTUSSIS-052 study design cannot be addressed with sensitivity analyses, including: retrospective data collection, use of data from a study not intended for regulatory purposes, and re-analysis of a published study.

I defer to the clinical reviewer to assess the regulatory significance of the effectiveness results, given the lack of pre-specified acceptance criteria and the limitations in the study design noted. I also defer to the clinical reviewer on the safety and immunogenicity evaluations relevant to maternal immunization with Boostrix.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Please refer to the clinical review.

2.2 Currently Available, Pharmacologically Unrelated Treatments and Interventions for the Proposed Indication

There are no pertussis vaccines licensed in the U.S. for maternal immunization to prevent pertussis in infants. Boostrix is currently licensed in the U.S. for active booster immunization against tetanus, diphtheria, and pertussis in individuals 10 years of age and older. However, the U.S. Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) currently recommends that all pregnant women receive a tetanus, diphtheria, and acellular pertussis (Tdap) vaccine dose during pregnancy to prevent pertussis in infants too young for routine immunization, preferably at 27–36 weeks of gestation, as an off-label use. This recommendation was made for unvaccinated pregnant women in 2011 and for all women, regardless of vaccination status, in 2012.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

There are two alternative formulations of Boostrix licensed outside of the U.S. The non-U.S. formulation of Boostrix contains the same types and quantities of tetanus,

diphtheria, and pertussis antigens as the U.S. formulation of Boostrix, but has more aluminum. The non-U.S. formulation of Boostrix is licensed for maternal immunization during pregnancy against pertussis in Australia. Boostrix-IPV is a combination of non-U.S. Boostrix and an inactivated polio virus vaccine. Boostrix-IPV is currently licensed in the UK and Spain for maternal immunization against pertussis in the second or third trimester. These indications were granted based on the results of a randomized, cross-over, placebo-controlled immunogenicity trial examining the antibody titers of infants born to mothers vaccinated with the non-U.S. formulation of Boostrix, which demonstrated higher cord blood pertussis antigen titers in infants born to Boostrix vaccinated mothers relative to placebo vaccinated mothers.

Many countries recommend maternal immunization, as licensed or as off-label use, with guidelines similar to the ACIP's guidelines.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

CBER conducted extensive discussions with GSK about the studies needed to generate evidence in support of the proposed indication prior to submission of this BLA. Discussions originally focused on randomized clinical studies (see IND 8461/0.178, 182 and CBER responses dated 19 October 2014 and 24 June 2015), during which CBER stated that studies for licensure should be conducted with the U.S. Boostrix formulation. However, GSK determined that randomized clinical trials with the U.S. Boostrix formulation were infeasible, because of the ACIP or analogous recommendations, a low incidence of pertussis in young infants, and prevalent maternal vaccination in the U.S. and comparable countries.

GSK instead proposed EPI-PERTUSSIS-047 US DB, an observational cohort study of the safety of Boostrix when administered to pregnant women conducted at Kaiser Permanente Southern California, along with a clinical benefit study (EPI-PERTUSSIS-049) in the infants born to the mothers from EPI-PERTUSSIS-047 US DB (see IND 8461/0.199, 208; CBER responses sent 11 October 2016 and 6 June 2018; and CBER meeting summary sent 26 September 2018). CBER recommended that GSK consider additional supportive observational studies to supplement EPI-PERTUSSIS-047 US DB.

After GSK subsequently abandoned EPI-PERTUSSIS-049, they proposed a post-hoc re-analysis of the Boostrix-specific data from a CDC study of maternal Tdap immunization published in Skoff et al. (2017) (EPI-PERTUSSIS-052 VE DB US; see IND 8461/0.219, 221, 224, 225 and CBER response dated 10 July 2019). CBER disagreed that the results from this re-analysis would be sufficient to support the maternal immunization indication because the re-analysis would be subject to selection bias as a post-hoc analysis of published data and would be unlikely to have sufficient power. CBER expressed willingness to consider leveraging data from observational studies of non-US formulations of Boostrix into the analysis of the EPI-PERTUSSIS-052 data to support the maternal immunization indication, provided comparability of the pertussis antibody response between the US and non-US formulations of Boostrix was demonstrated.

GSK submitted the results from dTpa-029, and CBER agreed that this study was sufficient to address comparability of the pertussis immune response and that data from non-US Boostrix formulations could be used to support a maternal immunization indication (see IND 8461/0.229, 232). CBER suggested GSK consider a supportive analysis of the EPI-PERTUSSIS-052 data to characterize the vaccine effectiveness of Boostrix, such as a Bayesian analysis with a prior based on the non-US formulation data (see CBER response sent 24 January 2020). In response, GSK proposed a Bayesian analysis of the EPI-PERTUSSIS-052 data. GSK and CBER reached agreement on the details of this analysis prior to the BLA submission (see IND 8461/0.233, 234, 236, 240, 242, and 243; CBER responses sent 6 May 2020; 26 June 2020; 17 September 2020; 3 November 2020).

During CBER's review of the BLA, several statistical information requests (IRs) were sent to GSK, which are summarized in Table 1. The responses to all of these IRs were acceptable.

Table 1. BLA 125106/1469 IR Request Amendments

Amendment	Date IR Sent	Date Amendment Received	Summary
4	21 April 2021	05 May 2021	GSK's response to a request for a corrected systemic literature review figure, EPI-PERTUSSIS-052 dataset inconsistencies clarification
5	---	13 May 2021	CDC's responses to the 21 April 2021 IR added to GSK sub-amendment 4 responses
6	16 May 2021	01 June 2021	CDC's response to additional EPI-PERTUSSIS-052 dataset clarifications and GSK's sensitivity analysis results
7	29 June 2021	13 July 2021	GSK's response to additional EPI-PERTUSSIS-052 sensitivity analysis requests and dataset clarifications
10	24 May 2022	14 June 2022	GSK's response to request for revised EPI-PERTUSSIS-052 analyses using updated dataset
12	5 July 2022	19 July 2022	GSK's response to request for additional revised EPI-PERTUSSIS-052 analyses
16	17 August 2022	31 August 2022	GSK's response to package insert edits, including revisions to Section 14.3 description of the EPI-PERTUSSIS-052 analyses and results
17	9 September 2022	19 September 2022	GSK's response to package insert edits, including revisions to Section 14.3 description of the EPI-PERTUSSIS-052 analysis and results

Source: Created from the BLA 125106/1469 amendments

In addition, CBER held a teleconference with the CDC on 2 August 2021 about CBER's need for additional individual-level data from Skoff et al. (2017) that were not provided

to GSK. These data included the infants' birth dates, index (matched case cough onset) dates, and gestational age, which CBER would need to confirm the maternal exposure classification and relevant vaccination. The CDC was unwilling to share this data with GSK because of participant privacy but was willing to provide this data to CBER. The requested data were submitted in a separate dataset to MF5-27946. Table 2 lists the responses to IRs sent in response to this MF.

Table 2. MF5-27946 Information Request Amendments

Amendment	Date IR Sent	Date Amendment Received	Summary
2	13 December 2021	7 March 2022	CDC's response to a request for clarification about the Skoff et al. (2017) dataset
3	03 March 2022	28 March 2022	CDC's Skoff et al. (2017) dataset with participant identifier and a new dataset for infants < 2 weeks old

Source: Created from the MF5-27946 amendments

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Data Integrity

Because the EPI-PERTUSSIS-052 data were collected in a retrospective study sourced through medical records, the data are affected by typical limitations owing to the design, specifically, lack of data traceability, missing and ambiguous information, unavailability of information on confounders, inconsistent data collection process, and quality control across sites. These limitations may impact the reliability of the data or lead to biased results. Please refer to the clinical review for more details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Because the data used in EPI-PERTUSSIS-052 were originally collected by the CDC, I have referred not only to the EPI-PERTUSSIS-052 statistical analysis plan but also the CDC and Skoff et al. (2017) for information about data collection and selection.

For the studies used to generate the meta-analytic prior, I have referred to the published articles for details about their design, conduct, analysis, and results.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review refers to documents and datasets submitted to:

- Modules 1.11 and 5 of BLA 125106/1469 and its sub-amendments (Table 1)
- MF5-27946.0 and its amendments (Table 2)
- IND 8461.

5.5 Literature Reviewed

Amirthalingam, G, H Campbell, S Ribeiro, NK Fry, M Ramsay, E Miller, and N Andrews, 2016, Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction, *Clin Infect Dis*, 63(Suppl 4): S236–S243.

Andrews, A, H Campbell, S Ribeiro, N Fry, and G Amirthalingam, 2020, Boostrix-IPV® Report: Effectiveness of Maternal Pertussis Vaccination in Prevention of Confirmed Pertussis in Children in England Using the Screening Method Report to 30 September 2018, Public Health England (unpublished).

Bellido-Blasco, J, S Guiral-Rodrigo, A Míguez-Santiyán, A Salazar-Cifre, and F González-Morán, 2017, A Case–Control Study to Assess the Effectiveness of Pertussis Vaccination During Pregnancy on Newborns, Valencian Community, Spain, 1 March 2015 to 29 February 2016, *Euro Surveill*, 22(22): 30545.

Saul, N, K Wang, S Bag, H Baldwin, K Alexander, M Chandra, J Thomas, H Quinn, V Sheppeard, and S Conaty, 2018, Effectiveness of Maternal Pertussis Vaccination in Preventing Infection and Disease in Infants: The NSW Public Health Network Case-Control Study, *Vaccine*, 36(14): 1887–1892.

Schmidli, H, S Gsteiger, S Roychoudhury, A O'Hagan, D Spiegelhalter, and B Neuenschwander, 2014, Robust Meta-Analytic-Predictive Priors in Clinical Trials with Historical Control Information. *Biometrics*, 70(4): 1023–1032.

Skoff, TH, AE Blain, J Watt, K Scherzinger, M McMahon, SM Zansky, K Kudish, PR Cieslak, M Lewis, N Shang, and SW Martin, 2017, Impact of the US Maternal Tetanus, Diphtheria, and Acellular Pertussis Vaccination Program on Preventing Pertussis in Infants< 2 Months of Age: a Case-Control Evaluation, *Clin Infect Dis*, 65(12): 1977–1983.

Uriarte, PS, SSJ Rodríguez, IG Sancristobal, and NM Agirre, 2019, Effectiveness of dTpa Vaccination During Pregnancy in Preventing Whooping Cough in Infants Under 3 Months of Age. Bizkaia, Basque Country, Spain, *Heliyon*, 5(2): 01207.

6. DISCUSSION OF INDIVIDUAL STUDIES

6.1 EPI-PERTUSSIS-052

6.1.1 Objectives

The primary objective of EPI-PERTUSSIS-052 was to assess the effectiveness of Boostrix against pertussis in infants less than two months old when Boostrix is administered to mothers during the third trimester of pregnancy and at least 14 days before delivery.

The secondary objectives were to:

- Assess the effectiveness of vaccination with Boostrix against pertussis in infants less than two months old when administered to mothers before pregnancy, during the first or second trimester, and after pregnancy
- Assess the effectiveness of vaccination with Boostrix against pertussis in infants less than two months old when administered to mothers during pregnancy, at least 14 days before delivery
- Assess the effectiveness of vaccination with Boostrix against pertussis leading to hospitalization in infants less than two months old when administered to mothers before pregnancy, during the first or second trimester, during the third trimester, and after pregnancy

Reviewer's Comment: *GSK seeks the indication: protection against pertussis in infants younger than two months of age when administered during the third trimester of pregnancy. Therefore, I have focused on the primary objective which is most relevant to the desired indication.*

6.1.2 Study Design Overview

EPI-PERTUSSIS-052 was a re-analysis of data from an observational, retrospective, matched, case-control study conducted by the CDC. The original CDC results were published in Skoff et al. (2017) and included vaccine effectiveness (VEff) estimates for Tdap vaccination during pregnancy, regardless of brand. No brand-specific VEff estimates were given in Skoff et al. (2017), but a hypothesis test for the difference in brand-specific VEff was reported as not significant (p-value: 0.85).

6.1.2.1 Data Sources

In Skoff et al. (2017), cases were identified through the CDC's Emerging Infection Program Network (EIPN) based on data collected between 1 January 2011 and 31 December 2014 at six sites in the EIPN: California, Connecticut, Minnesota, New Mexico, and some counties in New York and Oregon.

Mothers were interviewed by telephone to collect demographic and medical care provider information. Medical care providers, including birth hospitals, surveillance case report forms, and birth certificate records were used to source data. Variables collected included: household size, maternal education, household member with a pertussis diagnosis, and infant's age in weeks.

Reviewer's Comment: *While the CDC states that the EPIN is nationally representative based on U.S. Census data, Skoff et al. (2017) only uses data from six of the 10 EIPN sites, and these sites are notably missing Southern states. Therefore, the EPI-PERTUSSIS-052 population may not be representative of the U.S. population.*

6.1.2.2 Infant Eligibility Criteria

Infants were broadly eligible if they were:

- At least two days old
- Born in a hospital in their state of residence
- At least 37 weeks gestational age at birth
- Not adopted or in foster care
- Not living in a residential care facility.

Mothers were only included once in the dataset and only a single infant was included per mother, so each mother-infant pair is unique.

6.1.2.3 Case Definition and Selection

A pertussis case was defined as cough illness and at least one of:

- Laboratory confirmation (PCR or culture)
- Epidemiological linkage to a laboratory-confirmed pertussis case
- Cough lasting two or more weeks with paroxysms, inspiratory whoop, or posttussive vomiting

Infants were included as cases if they met the infant eligibility criteria, were living in the catchment area on their cough onset (index) date, and met the pertussis case definition.

6.1.2.4 Control Selection and Matching

Potential control infants were identified based on birth certificates of infants born at the same hospital as the corresponding case infant, with the goal of collecting three controls per case. Infants were eligible as controls if they met the infant eligibility criteria, were born at the same hospital as a case infant, were less than two months old on their case infant's index date, and did not have a pertussis diagnosis prior to their case infant's index date. Control enrollment for each case ended when all potential control infants meeting the inclusion criteria were exhausted.

In GSK's re-analysis, infants were also matched on age group (< 2 weeks old, \geq 2 weeks old) within each stratum defined by birth hospital.

Reviewer's Comment: *In case-control studies, it is common practice to match on important confounders then more finely adjust for these confounders in the regression model to limit the effect of confounding without substantially reducing the sample size. I defer to the clinical and epidemiological reviewers to assess whether matching on birth hospital and age are an appropriate strategy for addressing important confounding factors in this study.*

For cases with more than three potential controls, it is unclear whether the CDC stopped attempting to recruit controls after three controls were enrolled or if they recruited as many controls as possible and chose three. If potential controls contacted earlier differ systematically from potential controls contacted later, recruiting until three controls are enrolled may introduce systematic bias.

6.1.2.5 Exposure Definition and Ascertainment

Maternal Tdap immunization information, including immunization date and vaccine type, manufacturer, brand, and lot, was collected from medical providers or state immunization registries for the mothers of all enrolled infants. The CDC attempted to verify the vaccine type, manufacturer, and brand based on the lot number. However, not all information could be verified, and some participants were missing some or all of this information. Maternal immunization records were considered complete after all information sources were contacted.

Reviewer's Comment: *Based on the data provided by GSK (referred to as the BLA dataset), the CDC appears to have collected no more than three immunization records per participant. It is unclear if the CDC did not identify any participants with more than three exposures or if the CDC limited their data collection to the three most recent exposures that could be identified.*

Mothers were classified as unvaccinated if they had no evidence of any Tdap vaccination given at least two weeks prior to their corresponding index date. If multiple Tdap doses were identified, the most recent was used to classify the mother's exposure relative to pregnancy.

Mothers were classified as:

- vaccinated before pregnancy if their most recent Tdap dose was given on or before their pregnancy start date
- vaccinated during the first or second trimester if their most recent Tdap dose was given after their pregnancy start date and < 189 days after their pregnancy start date
- vaccinated during the third trimester if their most recent Tdap dose was given at least 189 days after their pregnancy start date and at least 14 days before their infant's date of birth

- vaccinated after pregnancy if their most recent Tdap dose was given post-partum or no more than 14 days before their infant's date of birth and at least 14 days before their corresponding case infant's cough onset date.

Pregnancy start date was calculated from the infant's date of birth and gestational age.

Reviewer's Comment: *Because this study relies on retrospective exposure ascertainment, some mothers who received a Tdap vaccine may be misclassified as unvaccinated. If significant numbers of vaccinated mothers are misclassified as unexposed, the vaccine effectiveness estimate from this study may be lower than the true vaccine effectiveness. Similarly, mothers may be misclassified if a Tdap dose was not identified that was given after the most recent Tdap dose in the dataset. I defer to the clinical and epidemiological reviewers to assess the likelihood of exposure misclassification.*

6.1.3 Statistical Considerations and Analysis Plan

6.1.3.1 Analysis Set Definition

GSK's analysis included all infants born to mothers who were classified as unexposed or as exposed to Boostrix and whose matching stratum included at least one case and one control. Infants missing covariates were excluded from the analysis set.

6.1.3.2 Demographics

Frequencies and percentages of infants in the analysis set were to be presented. Participant characteristics for the analysis set were to be summarized using frequencies and percentages for categorical variables and means, standard deviations, minimums, maximums, and quartiles for continuous variables.

6.1.3.3 Primary Objective: Frequentist Analysis

VEff was to be estimated as $(1 - OR) \times 100\%$, where OR is the odds ratio for maternal Tdap exposure given infant pertussis case status. The OR was to be estimated using an adjusted conditional logistic regression (CLR) model with a categorial exposure variable: unvaccinated, vaccinated before pregnancy, vaccinated in the first or second trimester, vaccinated in the third trimester, and vaccinated after pregnancy. Covariates for the adjusted CLR model were to be selected if their p-value from a univariate CLR model of the odds of binary exposure (vaccinated or unvaccinated) was less than 0.2, as well as using clinical knowledge. Covariates with greater than 50% missing data were to be excluded from the analysis. The VEff estimate and 95% confidence interval, derived from the asymptotic normal 95% CI for the OR, were to be presented from the final adjusted model.

Two sensitivity analyses were to be conducted:

1. Estimating the VEff based on the same case definition and categorical exposure, but adjusting the CLR for all covariates included in the original Skoff 2017 publication
2. Estimating the VEff using only hospitalized cases and their corresponding controls with the same model as the primary analysis.

Reviewer's Comment: *GSK performed power calculations for the primary and secondary frequentist analyses, based on the observed numbers of cases and controls in the dataset. However, power calculations are of limited use when no additional data can be collected, such as when re-analyzing an existing dataset. The results of the study, including measures of uncertainty such as confidence or credible intervals, provide more direct evidence that the sample size was adequate to produce sufficiently precise estimates of the vaccine effectiveness.*

GSK's reanalysis is a post-hoc analysis of the data and is therefore subject to the limitations of a post-hoc analysis. To avoid data-drive analysis choices, GSK used the same models and methods as Skoff et al. (2017). However, because Skoff et al. (2017) had different objectives, these models and methods may not be the optimal ones to demonstrate effectiveness for GSK's proposed indication. Nevertheless, the methods are a reasonable choice.

6.1.3.4 Primary Objective: Bayesian Analysis

The overall approach for the Bayesian analysis was to conduct a systemic literature review to identify suitable studies of the vaccine effectiveness of Boostrix (US or non-US formulations), which would then be used to construct a robustified Bayesian meta-analytic-predictive prior. This prior would be combined with the Boostrix-specific results from Skoff et al. (2017) to estimate the vaccine effectiveness.

6.1.3.4.1 Systemic Literature Review

(b) (4) on GSK's behalf, performed a systemic literature review to identify epidemiological studies of the maternal immunization vaccine effectiveness of Tdap vaccines generally and effectiveness of Boostrix or Boostrix Polio against pertussis in infants two to three months of age. PubMed and EMBASE were searched for studies with relevant keywords between 1 January 2011 and 11 November 2020. Resulting studies were screened using a stepwise procedure, based on:

1. title and abstract
2. full text
3. data extraction,

where studies with the relevant information at each step were evaluated in the subsequent step. Studies published in any language were included if they assessed effectiveness of Tdap/Tdap-IPV when given during pregnancy against pertussis disease in infants

compared to no vaccination during pregnancy or assessed effectiveness in infants with any study design, including systematic reviews. Studies were excluded if:

- the effectiveness assessment was done after the infants' immunization series was finished
- there was incomplete information or missing information
- the study only examined safety or cost-effectiveness
- the study was not conducted in humans
- the study was published without peer-review.

All titles and abstracts were screened in duplicate by two independent researchers and discordant screening results were discussed. The first 10% of full texts were screened in duplicate by two independent researchers and any disagreements were adjudicated by a third researcher. If the two independent researchers disagreed on more than 5% of these first 10% of articles, the second 10% of articles were screened in duplicate as well. Any full text the first researcher was in doubt about was screened by a second researcher. Data extraction was performed by the junior researchers and reviewed by the senior researcher on the project.

From the results of this literature review, suitable studies of Boostrix/Boostrix Polio were selected for constructing the prior distribution. From each study, relevant estimates of vaccine effectiveness (expressed as the logarithmic-scale odds ratio) and corresponding confidence intervals were extracted. When multiple relevant estimates were available from a single study, the smallest estimate was chosen.

6.1.3.4.2 Robustified Bayesian Meta-Analytic-Predictive Prior

The prior is a robustified meta-analytic-predictive (MAP) prior, as described in Schmidli et al. (2014). The MAP prior is an informative prior derived from the posterior distribution from a Bayesian meta-analysis of the historical trial results. This informative MAP prior is a mixture of a fixed, pre-specified number of conjugate priors that approximates (minimizes the Kullback-Leibler divergence between) the meta-analysis posterior distribution. The robustified MAP prior is a weighted combination of the informative MAP prior and a vague prior.

The weights for the informative and vague priors, the vague prior distribution, and the hyperparameters distributions for Bayesian meta-analysis of the historical trial data must be pre-specified. GSK proposed the following to define a robustified MAP prior for the logarithm-scale odds (log odds) ratio:

- 90% weight for the informative prior, 10% weight for the vague prior
- A vague prior distribution of $Normal(0; \sigma)$, where σ is the observed standard error for the log odds ratio for an individual subject from EPI-PERTUSSIS-052
- Hyperparameter distributions for the expected log odds, μ , and the variance in the log odds between trials, τ :

$$\mu \sim Normal(0; 1,000,000)$$

$$\tau \sim \text{Half-Normal}(0; 0.5).$$

GSK chose the number of conjugate priors empirically, based on a heuristic assessment of the approximation (e.g. density plots and log-likelihoods).

Reviewer's Comment: *Intuitively, the informative prior is the best guess at the distribution of the vaccine effectiveness (on the log-odds scale), based on the literature studies. Because finding this distribution is difficult, a combination of multiple distributions is used to approximate this informative prior. Based on the literature study results, this informative prior distribution is likely to put high probabilities on vaccine effectiveness values that suggest Boostrix is effective, and low probabilities on values that suggest no effect.*

Because the published studies may be subject to publication bias, are subject to study design limitations, and use non-U.S. Boostrix formulations, the prior should not rely too much on the literature studies' results. Therefore, the informative prior is combined with the vague prior, which will flatten the informative prior distribution and put lower probabilities on values that suggest Boostrix is effective.

6.1.3.4.3 Bayesian Vaccine Effectiveness Estimation

The posterior vaccine effectiveness and 95% credible interval were estimated from combining the robustified MAP prior with the log odds and associated variance from the frequentist analysis described in Section 6.1.3.3. Sensitivity analyses included:

- An assessment of the impact of the weights on the vaccine effectiveness and 95% credible interval estimates, which considers weights for the informative prior ranging between 0% and 100%
- An assessment of the impact of each study on the prior on the vaccine effectiveness and 95% credible interval estimates, which uses a leave-one-out analysis.

6.1.3.5 Secondary Objectives

These analyses were to use the same methods as the primary frequentist analysis (see Section 6.1.3.3), but the analysis sets were to include:

- infants born to mothers who were unexposed or received Boostrix before pregnancy or during the first or second trimester of pregnancy and their corresponding control infants,
- infants born to mothers who were unexposed during pregnancy or received Boostrix before pregnancy or during pregnancy and their corresponding control infants.

Reviewer's Comment: *Because the secondary objectives do not relate directly to the proposed indication, I did not review the corresponding analyses.*

6.1.4 Study Population

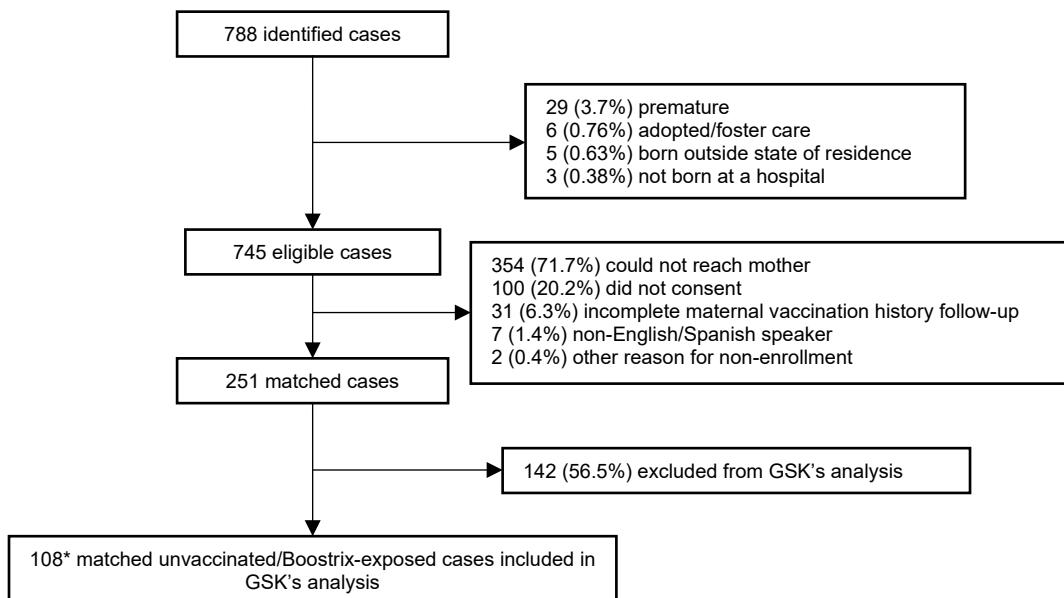
6.1.4.1 Study Population Disposition and Demographics

Figure 1 shows the disposition of cases and Figure 2 shows the disposition of controls enrolled in EPI-PERTUSSIS-052, starting from participants eligible for Skoff et al. (2017). Infants were excluded from Skoff et al (2017) primarily because their mothers could not be reached or did not consent to participate in the study.

Cases enrolled in Skoff et al. (2017) were generally similar to those who did not enroll, although enrolled cases were more likely to reside outside of California or New York, be a laboratory confirmed case, have private insurance, and be born to more educated mothers. Enrolled cases were less likely to have been hospitalized or have died.

Reviewer's Comment: *Non-participants may differ systematically from participants, which can impact the generalizability of the results. I defer to the clinical and epidemiological reviewers to assess the potential impacts of this on the generalizability of the study results.*

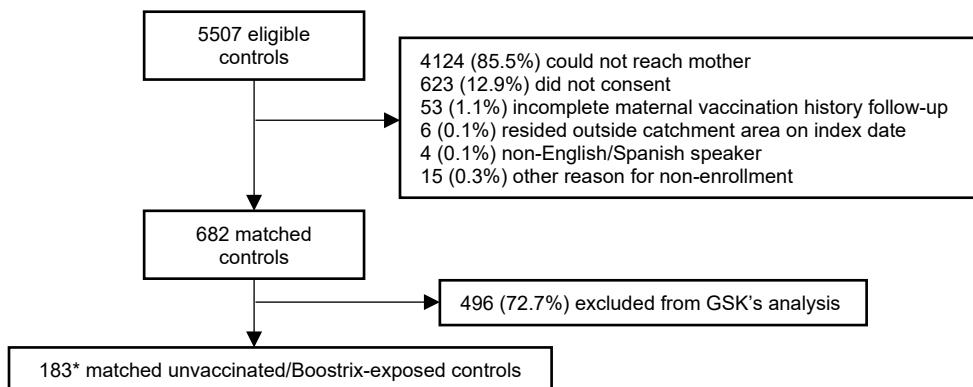
Figure 1. EPI-PERTUSSIS-052 Case Disposition Flowchart



*One case was excluded because of missing ethnicity

Source: Created from Skoff et al. (2017) and the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al.(2017) (MF5-27946/0.3) datasets

Figure 2. EPI-PERTUSSIS-052 Study Control Disposition Flowchart



*Three controls were excluded because their matching case was missing ethnicity

Source: Created from Skoff et al. (2017) and the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al.(2017) (MF5-27946/0.3) datasets

Table 3 shows the demographics of cases and controls enrolled in Skoff et al. (2017) and in EPI-PERTUSSIS-052. Skoff et al. (2017) case infants were more likely to be older, Hispanic, born to a mother with less education, live in a larger household, and have a household member diagnosed with pertussis recently, relative to controls. EPI-PERTUSSIS-052 case infants were also more likely to be Hispanic, born to a mother with less education, live in a larger household, and have a household member diagnosed with pertussis recently, relative to controls. Because of the matching, the age distributions are comparable for the EPI-PERTUSIS-052 case and control infants.

Table 3. Demographics of Cases and Controls

Demographic	Skoff: Cases	Skoff: Controls	EPI-052: Cases	EPI-052: Controls
Total Number of Infants	251	682	109	186
Infant's State of Birth	---	---	---	---
<i>California</i>	172 (68.5)	458 (67.2)	77 (70.6)	130 (69.9)
<i>Connecticut</i>	14 (5.6)	42 (6.2)	7 (6.4)	13 (7.0)
<i>Minnesota</i>	19 (7.6)	53 (7.8)	7 (6.4)	11 (5.9)
<i>New Mexico</i>	22 (8.8)	63 (9.2)	10 (9.2)	19 (10.2)
<i>New York</i>	12 (4.8)	30 (4.4)	5 (4.6)	7 (3.8)
<i>Oregon</i>	12 (4.8)	36 (5.3)	3 (2.8)	6 (3.2)
Infant's Age (in Weeks) Group	---	---	---	---
<i>0 – 1</i>	11 (4.4)	147 (21.6)	4 (3.7)	6 (3.2)
<i>2 – 3</i>	66 (26.3)	147 (21.6)	30 (27.5)	56 (30.1)
<i>4 – 5</i>	70 (27.9)	153 (22.4)	28 (25.7)	54 (29.0)
<i>6 – 7</i>	79 (31.5)	178 (26.1)	36 (33.0)	7 (3.8)
<i>8</i>	25 (10.0)	57 (8.4)	11 (10.1)	19 (10.2)
Infant's Sex	---	---	---	---
<i>Male</i>	124 (49.4)	330 (48.4)	59 (54.1)	92 (49.5)
<i>Female</i>	127 (50.6)	352 (51.6)	50 (45.9)	94 (50.5)
Infant's Race	---	---	---	---
<i>White</i>	199 (79.3)	543 (79.6)	89 (81.7)	144 (77.4)
<i>Black</i>	22 (8.8)	47 (6.9)	9 (8.3)	13 (7.0)
<i>Other</i>	25 (10.0)	73 (10.7)	10 (9.2)	22 (11.8)
<i>Missing</i>	5 (2.0)	19 (2.8)	1 (0.9)	7 (3.8)
Infant's Ethnicity	---	---	---	---
<i>Hispanic</i>	156 (62.2)	344 (50.4)	69 (63.3)	108 (58.1)
<i>Not Hispanic</i>	94 (37.5)	336 (49.3)	39 (35.8)	78 (41.9)
<i>Missing</i>	1 (0.4)	2 (0.3)	1 (0.9)	0
Infant's Pertussis Vaccination*	---	---	---	---
<i>Known Exposure</i>	2 (0.8)	3 (0.4)	2 (1.8)	0
<i>No Known Exposure</i>	249 (99.2)	676 (99.1)	107 (98.2)	184 (98.9)
Unknown Exposure Type	0	3 (0.4)	0	2 (1.1)
Mother's Education Status	---	---	---	---
<i>High school or less</i>	147 (58.6)	236 (34.6)	72 (66.1)	67 (36.0)
<i>More than high school</i>	104 (41.4)	446 (65.4)	37 (33.9)	119 (64.0)
Family Size	---	---	---	---
<i>Two or fewer</i>	25 (10.0)	179 (26.2)	6 (5.5)	49 (26.3)
<i>Three or more</i>	226 (90.0)	503 (73.8)	103 (94.5)	137 (73.7)
Pertussis Diagnosis at Home	---	---	---	---
<i>Yes</i>	21 (8.4)	4 (0.6)	6 (5.5)	0
<i>No</i>	230 (91.6)	678 (99.4)	103 (94.5)	185 (100)

*Infants exposed to pertussis antigen containing vaccines at least 14 days before their index date.

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al. (2017) (MF5-27946/0.3) datasets

6.1.4.2 Maternal Pertussis Vaccine Exposure

6.1.4.2.1 Maternal Exposure Timing

Table 4 shows the classification of mothers by immunization timing for all infants enrolled in Skoff et al. (2017) and in EPI-PERTUSSIS-052. In both, mothers were mostly likely to be unexposed or exposed after pregnancy.

Table 4. Maternal Pertussis Vaccination Timing

Maternal Vaccination Timing	Skoff: Cases	Skoff: Controls	EPI-052: Cases	EPI-052: Controls
Unvaccinated	111 (44.2)	276 (40.5)	76 (69.7)	116 (62.4)
Before pregnancy	25 (10.0)	88 (12.9)	1 (0.9)	5 (2.7)
First or second trimester	7 (2.8)	33 (4.8)	1 (0.9)	6 (3.2)
Third trimester	18 (7.2)	109 (16.0)	4 (3.7)	18 (9.7)
After pregnancy	90 (35.9)	176 (25.8)	27 (24.8)	41 (22.0)

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff 2017 (MF5-27946/0.3) datasets

Reviewer's Comment: *The CDC provided corrections to several mothers' exposure timing classifications, based on additional information gathered after the publication of Skoff et al. (2017):*

- (b) (6) : should be classified as vaccinated before pregnancy
- (b) (6) : should be classified as vaccinated before pregnancy
- (b) (6) : should be classified as vaccinated after pregnancy.

GSK incorporated these corrections into a revised dataset provided in BLA 125106/1469.10, and this corrected dataset was used for all results in this review.

A total of 73 mothers in Skoff et al. (2017) were exposed more than once to Tdap vaccines. Of these 73 mothers, 33 were only exposed to Sanofi's vaccines and were not considered further. The remaining 40 mothers were exposed at least once to a Tdap with GSK/Boostrix or missing manufacturer and brand. Among these 40 multiply exposed mothers, the majority (32) had exposures separated by one or more years and were exposed before and during or after pregnancy. However, the remaining eight mothers had at least two exposures within one year or less or were exposed multiple times during their pregnancy (Table 5). The effect of the maternal exposure classification for these eight women with multiple exposures in a short period of time is considered in a sensitivity analysis (see Section 6.1.5.1).

Table 5. EPI-PERTUSSIS-052 Mothers with Multiple Proximate Tdap Exposures*

Participant	Exposure Timing in Main Analysis	1 st Tdap: Expo	1 st Tdap: Manu Brand	2 nd Tdap: Expo	2 nd Tdap: Manu Brand	3 rd Tdap: Expo	3 rd Tdap: Manu Brand
(b) (6)	Before	Before	Unk/Unk	Before	Sanofi/Ada	---	---
	Before	Before	Sanofi/Ada	Before	GSK/Boost	---	---
	1T/2T	1T/2T	Unk/Unk	1T/2T	Sanofi/Ada	---	---
	3T	1T/2T	GSK/Boost	3T	GSK/Boost	---	---
	After	3T	Unk/Unk	After	GSK/Boost	---	---
	After	After	GSK/Boost	After	GSK/Boost	---	---
	After	Before	Unk/Unk	3T	GSK/Boost	After	GSK/Boost
	After	Before	Unk/Unk	3T	GSK/Boost	After	Unk/Unk

*Ada: Adacel, Boost: Boostrix; Unk: Unknown

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al. (2017) (MF5-27946/0.3) datasets

6.1.4.2.2 Maternal Exposure Manufacturer and Brand

Table 6 shows the number of exposed mothers by infant cases status and relevant exposure manufacturer and brand for the Skoff et al. (2017) study. Among exposed mothers, approximately 10% had no known manufacturer or brand for both cases and controls. The majority of exposed mothers with non-missing manufacturer and brand received Sanofi/Adacel. A small proportion of mothers had inconsistent (e.g. GSK/Adacel) or partially missing (e.g. GSK/Unknown) manufacturer and brand information. The effects of ambiguous or missing manufacturer and brand are considered in a sensitivity analysis (see Section 6.1.5.1).

Table 6. Skoff et al. (2017) Study Maternal Exposure by Manufacturer and Brand for Exposed Mothers

Manufacturer	Brand	Case	Control
GSK	Boostrix	43 (30.7)	112 (27.6)
GSK	Unknown	1 (0.7)	1 (0.2)
Unknown	Boostrix	1 (0.7)	1 (0.2)
Sanofi	Adacel	77 (55.0)	236 (58.1)
Sanofi	Unknown	---	4 (1.0)
Unknown	Adacel	2 (1.4)	2 (0.5)
Sanofi	Boostrix	---	1 (0.2)
Other	Unknown	---	2 (0.5)
Unknown	Unknown	16 (11.4)	47 (11.6)

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al. (2017) (MF5-27946/0.3) datasets

Reviewer's Comment: The CDC confirmed that inconsistent or unknown manufacturer and brand were recorded as given by health care providers. Where possible, the CDC attempted to resolve these issues using vaccine lot numbers. While this rate of missingness or inconsistency for an important variable is higher than usually seen in

clinical trials for regulatory purposes, it is fairly typical of retrospective, observational studies. This is a significant limitation of retrospective studies.

Among the 387 unexposed Skoff et al. (2017) mothers, 281 had a missing or unknown manufacturer and brand. All of these mothers either had no exposure records or only had exposure records for Td vaccines. Another 103 unexposed mothers from Skoff et al. (2017) had a manufacturer or brand listed, but no immunization records. The remaining three unexposed Skoff et al. (2017) mothers had a single vaccination record, which did not necessarily correspond to their relevant manufacturer and brand (Table 7).

Table 7. Skoff et al. (2017) Study Unexposed Mothers with Vaccination Records

Participant	Manufacturer/ Brand*	Vaccination Date	Vaccine Type	Vaccine Manufacturer	Vaccine Brand
(b) (6)	GSK/Boost	(b) (6)	Td	Unknown	Unknown
	GSK/Boost		TT	Sanofi	Adacel
	Sanofi/Unk		Tdap	Sanofi	Decavac

*Ada: Adacel; Boost: Boostrix; Unk: Unknown

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al (2017) (MF5-27946/0.3) datasets

Reviewer's Comment: *The CDC confirmed that unknown and missing brand information for unexposed subjects meant no known information. The CDC also clarified that the 103 unexposed mothers who had a relevant brand and manufacturer but no immunization records were mothers who were only exposed after their infants' index dates. The manufacturer and brand were from the exposures after the index dates and should have been removed.*

For the remaining three unexposed participants:

- (b) (6) : The CDC stated that the GSK/Boostrix information are from an exposure after the index date.
- (b) (6) : The CDC could not confirm that the TT/Sanofi/Adacel exposure was a Sanofi/Adacel vaccine based on the lot number, so they assumed the vaccination was a TT vaccine and classified this mother as unexposed. The GSK/Boostrix information is from an exposure after the index date.
- (b) (6) : Because the CDC could not confirm that the exposure was a Tdap based on the lot number, the CDC classified this mother as unexposed.

The CDC also clarified that according to the contacted health care providers, the mother of participant (b) (6) was exposed before pregnancy to a Tdap/Unknown/Unknown vaccine and again before pregnancy to a Td/Sanofi/Decavac. Based on the lot number for the second vaccination, the CDC determined that the second vaccine was in fact a Tdap/Sanofi. Therefore, this mother was classified as exposed before pregnancy to a Tdap/Sanofi/Unknown vaccine.

The effects of the ambiguous exposures for participants (b) (6) are considered in a sensitivity analysis (see Section 6.1.5.1)

6.1.5 Effectiveness Analyses Results

6.1.5.1 Primary Objective: Frequentist Analysis of Pertussis Cases

The analysis set for the frequentist analysis of pertussis cases included 108 cases and 183 controls, of which four cases and 18 controls were exposed in the third trimester. The vaccine effectiveness when administered in the third trimester was estimated from a model adjusted for infant age, maternal education, and household size, resulting in a vaccine effectiveness estimate of 78.0% (95% CI: -38.0, 96.5).

Reviewer's Comment: *I have mostly confirmed GSK's covariate selection for the adjusted model using a likelihood ratio test, although I found a significant p-value (< 0.2) for household pertussis diagnosis. Nevertheless, given that no controls had household pertussis diagnoses, it is reasonable to exclude this variable from the model as including this variable would adversely impact model fit.*

I have confirmed the adjusted model results, although these results may have residual confounding either from covariates that were not included in the model or covariates in the model that are insufficiently adjusted for.

The results from the adjusted model are suggestive, but the extremely wide confidence intervals reflect the lack of sufficient power for the third trimester vaccination caused by the small number of third trimester cases. Therefore, the results are inconclusive.

GSK conducted several sensitivity analyses, using conditional logistic regression models with the same covariates as the primary frequentist analysis, but varying the EPI-PERTUSSIS-052 analysis dataset:

1. Unexposed/Third Trimester Only: Only data from infants whose mothers were unexposed or exposed to Boostrix in the third trimester were included.
2. Ambiguously/Multiply Exposed Mothers: Exposures of mothers with ambiguous or multiple exposures were adjudicated as given in Table 8. All other mothers referenced in Table 5 and Table 7 were classified as in the main analysis.
3. Inclusion of (b) (6) stratum: Stratum (b) (6) was removed from the primary analysis because of missing ethnicity for the case infant. This stratum was included in this reanalysis.
4. Missing data: Missing manufacturer and brand were imputed as GSK and Boostrix for mothers exposed to GSK/Missing, Missing/Boostrix, and Missing/Missing Tdap vaccinations.

Table 8. Adjudication of Ambiguous and Multiply Exposed Mothers' Exposures

Participant	Original Timing	Original Manu/Brand*	Sensitivity Timing*	Sensitivity Manu/Brand*
(b) (6)	Unexposed	Sanofi/Unk	Excluded	Excluded
	After	GSK/Boostrix	3T	Unk/Unk
	After	GSK/Boostrix	3T	GSK/Boostrix
	After	Unk/Unk	3T	GSK/Boostrix
	Before	Sanofi/Unk	Before	Unk/Unk

*Manu: Manufacturer; Unk: Unknown; 3T: Third trimester

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al. (2017) (MF5-27946/0.3) datasets and CBER's IR sent on 24 May 2022 and GSK's response.

Table 9 shows the results of the sensitivity analyses, which were generally consistent with the primary analysis results.

Table 9. EPI-PERTUSSIS-052 Primary Frequentist Analysis Sensitivity Results

Sensitivity Analysis	Cases: Total	Cases: 3 rd Trimester	Controls: Total	Controls: 3 rd Trimester	VEff (95% Confidence Interval)
1	73	3	107	15	100 (-Infinity, 100)
2	107	5	180	18	59.8 (-91.1, 91.5)
3	109	4	186	18	77.7 (-39.4, 96.4)
4	128	7	236	23	52.5 (-50.1, 85.0)

Source: Created from BLA 125106/1469.10 information amendment Tables 3-6 (pp. 6-9)

Reviewer's Comment: Because there were only three third trimester-exposed cases included in Sensitivity Analysis 1, the results of this analysis are not reliable as there are too few cases to reliably estimate the vaccine effectiveness.

The results from Sensitivity Analysis 2 suggest that the results are not substantially impacted by the ambiguous or multiply exposed mothers.

The results from Sensitivity Analysis 3 are very similar to the results from the primary analysis, suggesting that inclusion of the (b) (6) stratum does not substantially impact the study results.

Sensitivity Analysis 4 is unlikely to represent a realistic scenario, as the majority of mothers with non-missing manufacturer and brand received non-Boostrix vaccines, so the majority of mothers with missing manufacturer and brand are unlikely to be Boostrix exposed.

6.1.5.2 Primary Objective: Bayesian Analysis Results

6.1.5.2.1 Systemic Review Results

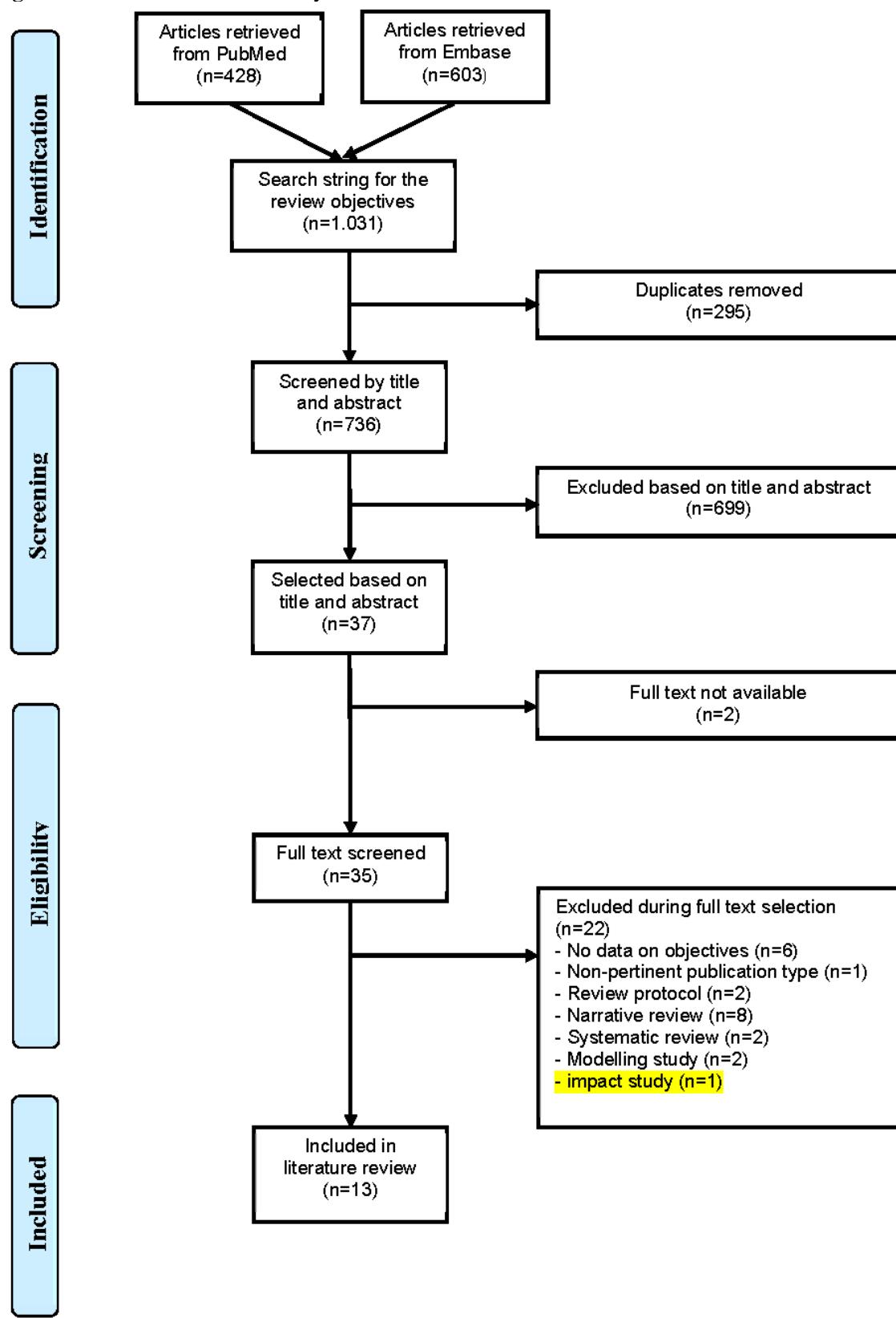
Figure 3 shows the results of the systemic literature review. A total of 736 articles were identified in PubMed and Embase, based on their title and abstract. Of these 736 articles, the majority were excluded based on their title or abstract, leaving 35 articles for the full

text screening. Of these 35 articles, most were excluded because they were not a relevant study (e.g. narrative review, systemic review, modeling study, review protocol, etc.) leaving 13 studies included in the literature review. Of these 13 studies, four provided Boostrix-specific VEff estimates, and these four studies were selected for the Bayesian meta-analytic prior. One of the studies, Amirthalingam et al. (2016), was replaced by an unpublished report from Public Health England (Andrews et al. 2020) that uses the same analysis methods as Amirthalingam et al. (2016) but comprises a longer period of follow-up. All four studies were conducted before Boostrix was licensed for maternal immunization in their respective countries.

Two different study designs are used: case-control and case-coverage. Table 10 summarizes the design features and relevant results from the two case-control studies: Bellido-Blasco et al. (2017) and Saul et al (2018). Bellido-Blasco et al. (2017) was conducted in the Valencia region of Spain, starting several months after a maternal immunization recommendation was made and only included infants who were unexposed to a pertussis antigen containing vaccine. While the original publication does not describe the vaccine brand, GSK confirmed with the authors that Boostrix was the only Tdap vaccine used in Valencia during the study period.

Saul et al. (2018) was conducted in New South Wales, Australia several months after a maternal vaccination campaign began and included infants who were exposed to pertussis antigen containing vaccines, which begins at six weeks of age in Australia.

Figure 3. EPI-PERTUSSIS-052 Systematic Literature Flowchart



Source: Adapted from 22 April 2022 IR Response (BLA 125106/1469.4), Figure 1

Table 10. EPI-PERTUSSIS-052 Summary of Case-Control Literature Studies

Study Design & Results	Bellido-Blasco et al. (2017)	Saul et al. (2018)
Country (Region)	Spain (Valencia)	Australia (NSW)
Maternal Vaccination Advice: Type, Start Date	Recommended, January 2015	Campaign, April 2015
Study Dates	March 2015–February 2016	August 2015–August 2016
Maternal Vaccines	Boostrix (note from author)	Boostrix
Prospective Exposure Collection	Probably (registry)	No
Maternal Vaccination Timing	1 st –3 rd Trimester	3 rd Trimester
Case Ascertainment	Required Reporting	Required Reporting
Prospective Case Collection	Yes	Yes
Eligible Case Infants: Age, Tdap vaccination	< 3months, unvaccinated	< 3months, not specified
Control to Case Matching	3:1 on age ± 15 days	1:1 on birthdate ± 3 days
Control Ascertainment	2 from same medical practice 1 from same maternity clinic	1 born in public hospital from same local health district
Cases	5/22	19/48
Controls	41/66	33/48
VE (95% CI)	87.3% (34.2%, 97.5%)	64% (18%, 84%)

Source: Adapted from Bellido-Blasco et al. (2017), Saul et al. (2018), and the BLA 125106/1469.0 EPI-PERTUSSIS-052 Statistical Analysis Plan 31 March 2020 version, Table 3 (pp. 43-44)

Table 11 summarizes the design features and relevant results from the two case-coverage studies: Andrews et al. (2020) and Uriarte et al. (2019). Case-coverage studies estimate the odds of pertussis cases being vaccinated, accounting for the population-level vaccination rate, and estimate VE_{eff} as one minus the odds of vaccination.

Andrews et al. (2020) was an analysis of Public Health England data. Pertussis has been a reportable disease since at least 2011, and the UK's maternal immunization program began central provision of Boostrix-IPV in July 2014. The immunization program originally recommended vaccination between 28 and 32 weeks, but since April 2016 has recommended vaccination between 16 and 32 weeks. British infants are vaccinated against pertussis at 8, 12, and 16 weeks of age. Andrews et al. (2020) uses data from Public Health England on laboratory-confirmed cases of pertussis, and Clinical Practice Research Datalink (CPRD) data on vaccine coverage. CPRD is a real-world data provider sponsored by the UK Medicines & Healthcare products Regulatory Agency and UK National Institute for Health Research. CPRD collects electronic health record data from patient primary care practices, including immunization records, across the UK and links them to other health-related data, such as hospital records and mother-baby linkage. Andrews et al. (2020) estimated the vaccination rate for each mother based on her age group and infant's birth week using data from English women who gave birth between September 2014 and December 2018.

Uriarte et al. (2019) used cases and immunization data from Basque Country, Spain. Case data were available from the national registry of notifiable diseases, hospital admissions data, and the Basque Microbiological Information System, a laboratory surveillance system that includes public and private laboratories. Vaccine coverage was estimated by the ratio of the number of women aged 18 to 45 and pregnant women aged 45 to 50 who

were vaccinated with Boostrix relative to the total number of pregnancies in Basque Country reported to a metabolic disease registry. VEff was estimated $1 - \text{odds}(\text{vaccinated case})/\text{odds}(\text{vaccination})$.

Table 11. EPI-PERTUSSIS-052 Summary of Case-Coverage Literature Studies

Study Design & Results	Andrews et al. (2020)	Uriarte et al. (2019)
Country (Region)	United Kingdom (England)	Spain (Basque Country)
Maternal Vaccination Advice: Type, Start Date	Campaign, October 2012	Recommendation, Feb 2015
Study Dates	Sept 2014–Sept 2018	Feb 2015–Jan 2016
Maternal Vaccines	Boostrix IPV	Boostrix (0.5)
Maternal Vaccination Timing	~ 2 nd –3 rd Trimester	~3 rd Trimester
Case Ascertainment	Required Reporting	Required Reporting
Eligible Case Infants: Age	< 3 months	< 3 months
Coverage Data Source	Clinical Practice Research Datalink	Immunization data for women aged 18–< 50 & newborn registry
Coverage Estimates	~60%–80% stratified by mother's age in years (<28, 28–32, ≥33)	93.7%
Cases	106/403	12/19
VE (95% CI)	87% (84%, 90%)	89% (72%, 96%)

Source: Adapted from Andrews et al. (2020), Uriarte et al. (2019), and the BLA 125106/1469.0 EPI-PERTUSSIS-052 Statistical Analysis Plan 31 March 2020 version, Table 3 (pp. 43-44)

Reviewer's Comment: *The prior distribution reflects a range of plausible values for the vaccine effectiveness, given the current scientific understanding. For a meta-analytic prior, the studies included will ideally be as similar as possible in their population, design, and analysis to the study that generates the data used to calculate the posterior. However, it is not necessary that the studies be identical in their population, design, and analyses to be informative for the prior. Including a wider range of plausible values in the prior, even if from less similar studies, makes the prior vaguer and increases the strength of evidence needed from the data to demonstrate effectiveness.*

The strength of evidence from case-coverage studies depends on how accurately the background vaccine exposure rate has been estimated for each participant. More accurate estimates of the background exposure rate will yield stronger evidence. The Uriarte 2019 study uses a single estimate of the background exposure rate which is unlikely to reflect the background exposure rate of all the participants.

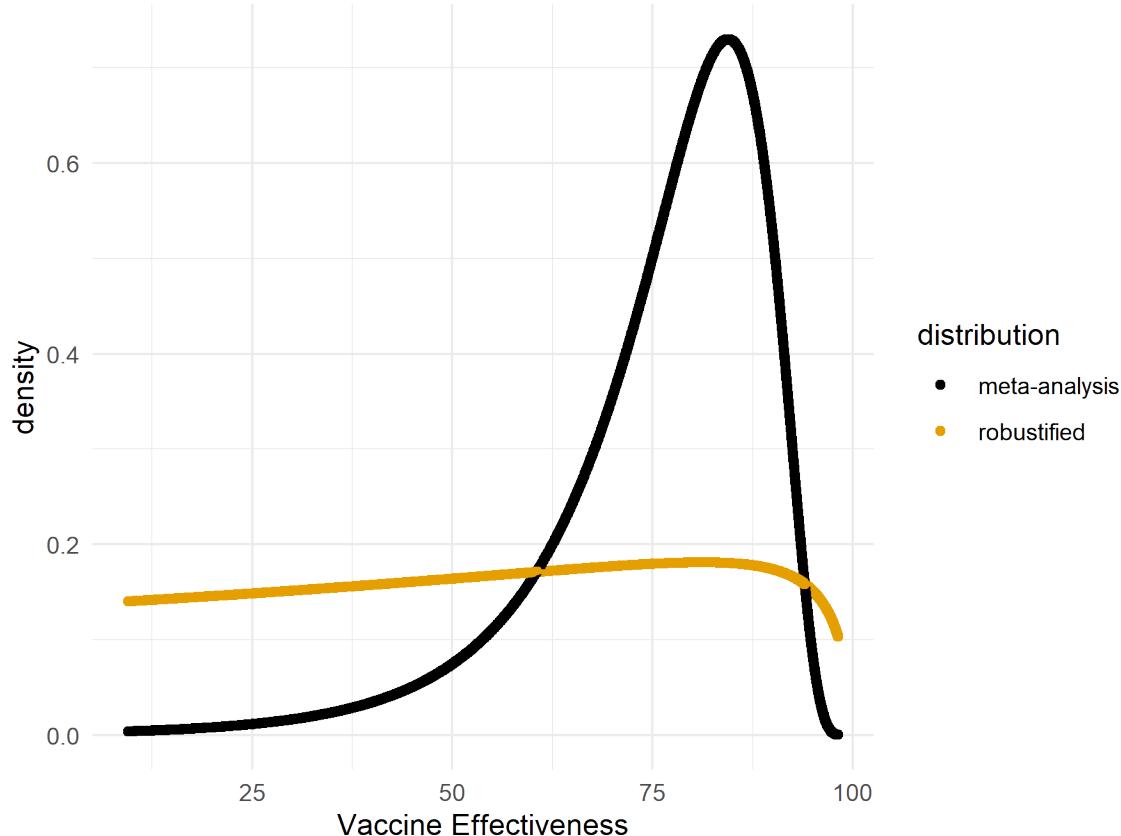
6.1.5.2.2 Bayesian Meta-Analytic-Predictive Prior

To form the Bayesian meta-analytic-predictive prior, GSK chose VEff estimates from cases in infants < 3 months old and excluding immunized infants, if possible. When multiple estimates were available, GSK chose the lowest estimate. The VEff estimates used in the prior are given in Table 10 and Table 11.

GSK used a mixture of three normal distributions to approximate the meta-analysis distribution. Figure 4 shows this mixture distribution (referred to as the meta-analysis distribution in the figure), and the weighted combination of this mixture distribution and

an uninformative vague prior when the informative prior has 90% weight (referred to as the robustified distribution in the figure).

Figure 4. EPI-PERTUSSIS-052 Bayesian Meta-Analytic-Predictive Prior and Robustified Bayesian Meta-Analytic-Predictive Prior



Source: Created from the BLA 125106/1469.0 EPI-PERTUSSIS-052 Statistical Analysis Plan 31 March 2020 version, Table 3 (p. 43-44)

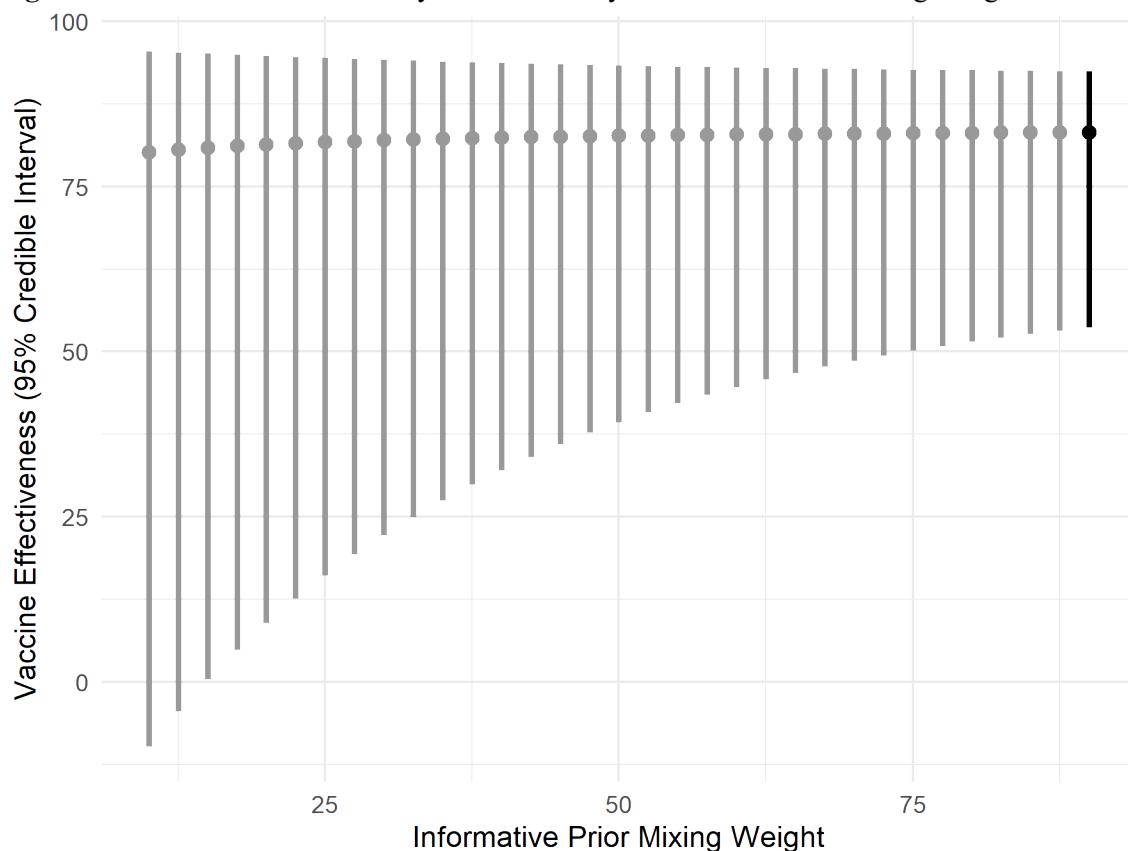
Reviewer's Comment: *The MAP prior distribution indicates that vaccine effectiveness values greater than 50% are highly likely and that values around 80% are most likely, while values less than 50% are highly unlikely, as are values near 100%. This is consistent with the results of the literature studies.*

The robustified MAP prior distribution is much flatter, indicating that the probability of vaccine effectiveness values less than and greater than 50% are fairly similar. Under this prior distribution, vaccine effectiveness values greater than 50% are only slightly more likely than those less than 50%. This is consistent with a relatively conservative prior for the Boostrix vaccine effectiveness.

6.1.5.2.3 Bayesian Analysis Results

Figure 5 shows the results of the Bayesian analysis with informative prior weights ranging from 10% to 90%. At the pre-specified 90%, the VEff was 83.4% (95% Credible Interval: 55.7, 92.5).

Figure 5. EPI-PERTUSSIS-052 Bayesian Results by Informative Prior Mixing Weight*



*Black point and line indicate the pre-specified 90% mixing weight

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al. (2017) (MF5-27946/0.3) datasets

Reviewer's Comment: Given the prior and the EPI-PERTUSSIS-052 data, there is a 95% probability that the true VEff falls within the 95% credible interval. That is, while the point estimate is the most likely VEff, the credible interval gives the range of VEffs that are highly likely, given the prior and the data.

The 95% credible interval lower bound was greater than 0% for informative prior weights of 20% and greater.

The sensitivity analysis results were generally consistent with the results from the primary analysis (Table 12).

Table 12. EPI-PERTUSSIS-052 Bayesian Sensitivity Analysis Results

Sensitivity Analysis	VEff (95% Credible Interval)
1	87.2 (39.5, 96.0)
2	79.7 (81.4, 90.5)
3	83.3 (54.5, 92.4)
4	73.7 (22.5, 88.1)

Source: Created from BLA 125106/1469.12 information amendment Table 1 (p. 3)

Reviewer's Comment: I also performed a sensitivity analysis for the prior, using a leave-one-out approach. The prior was constructed from three of the four studies, leaving each one out in turn, and the primary analysis was repeated with each of these leave-one-out priors. Table 13 shows the results of this analysis, which are generally consistent with the results from the primary analysis.

Table 13. EPI-PERTUSSIS-052 Leave-One-Out Prior Sensitivity Analyses Results

Omitted Study	VEff (95% Credible Interval)
Andrews	79.8 (46.5, 92.4)
Uriarte	81.9 (46.5, 92.5)
Bellido-Blasco	82.8 (49.8, 92.7)
Saul	86.2 (66.3, 93.4)

Source: Created from the EPI-PERTUSSIS-052 (BLA 125106/1469.10) and Skoff et al. (2017) (MF5-27946/0.3) datasets

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

EPI-PERTUSSIS-052 was a Bayesian re-analysis of a CDC study of maternal immunization against pertussis in infants (Skoff et al. 2017) that focused on the Boostrix-relevant data. Skoff et al. (2017) was a retrospective case-control study using cases reported to the CDC's disease surveillance network and controls recruited from the same birth hospitals as cases.

EPI-PERTUSSIS-052 demonstrated that when Boostrix is administered to pregnant women in the third trimester, the vaccine effectiveness against pertussis in infants aged two months old and less is most likely to be 83.4% and highly likely to be at least 55.7%. Across a wide range of sensitivity analyses, the estimated vaccine effectiveness was approximately 80% and highly likely to be greater than 40%. Overall, these results suggest that Boostrix is highly likely to have a vaccine effectiveness of at least 50% for the intended indication and most likely to have an effectiveness of approximately 80%. The results from sensitivity analyses addressing the effects of the analysis methods and missing data were similar. However, the effects of some aspects of the EPI-PERTUSSIS-052 study design cannot be addressed with sensitivity analyses, including retrospective data collection, use of data from a study not intended for regulatory purposes, and re-analysis of a published study.

10.2 Conclusions and Recommendations

In general, EPI-PERTUSSIS-052 demonstrated that Boostrix is likely to have vaccine effectiveness against pertussis in infants less than two months old when administered to their mothers during the third trimester of pregnancy. I defer to the clinical reviewer to assess the regulatory significance of the effectiveness results, given the lack of pre-specified acceptance criteria and the limitations in the study design noted. I also defer to the clinical reviewer on the safety and immunogenicity evaluations relevant to maternal immunization with Boostrix.