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Application Type	Efficacy Supplement
STN	125111/904
CBER Received Date	December 10, 2021
PDUFA Goal Date	January 9, 2023 (initially October 10, 2022)
Division / Office	DVRPA/OVRR
Clinical Reviewer	Nadine Peart-Akindele, MD
Project Manager	Diana Oram, PhD Susan DeRocco-Keller, PhD Tatiana Claro da Silva, PhD
Priority Review	No
Reviewer Name	Rositsa B Dimova, PhD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Sang Ahnn, PhD Team Lead, VEB/DB/OBE
	Tsai-Lien Lin, PhD Branch Chief, VEB/DB/OBE
Applicant	Sanofi Pasteur
Established Name	Tetanus Toxoid, Reduced Diphtheria Toxoid and (5-component) Acellular Pertussis (Tdap5) Vaccine
Trade Name	Adacel®
Pharmacologic Class	Tdap Vaccine
Formulation(s), including Adjuvants, etc	Each 0.5 mL dose contains 5 Lf tetanus toxoid (T), 2 Lf diphtheria toxoid (d), and acellular pertussis antigens [2.5 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)]. Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, ≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde and 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative).
Dosage Form(s) and	0.5 mL, Intramuscular Injection

Route(s) of Administration	
Dosing Regimen	During the third trimester of pregnancy.
Indication(s) and Intended Population(s)	Immunization during the third trimester of pregnancy to prevent pertussis in infants younger than 2 months of age.

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GLOSSARY

ACIP	Advisory Committee on Immunization Practices
BLA	Biologics License Application
CBER	Center for Biologics Evaluation, Research and Review
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CSR	Clinical Study Report
DTaP	Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis
FDA	Food and Drug Administration

IR	Information Request
MF	Master File
OR	Odds Ratio
PI	Package Insert
RCT	Randomized Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SLR	Systematic Literature Review
Tdap	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis
Tdap5	Tetanus Toxoid, Reduced Diphtheria Toxoid and (5-component) Acellular Pertussis
UK	United Kingdom
US	United States
VE	Vaccine Effectiveness

1. Executive Summary

In this BLA efficacy supplement, Sanofi Pasteur applies for expansion of the indication for use of Adacel to include passive immunization against pertussis in infants of age of <2 months through vaccination of their mothers during the third trimester of pregnancy. This is a Real World Evidence (RWE) submission.

Adacel is a Tetanus Toxoid, Reduced Diphtheria Toxoid and (5-component) Acellular Pertussis (Tdap5) Vaccine and is delivered through an intramuscular injection. In the US, Adacel is indicated for active booster immunization against tetanus, diphtheria and pertussis. It is approved for use in persons 10 through 64 years of age.

Currently, the Centers for Disease Control and Prevention (CDC) recommends that all pregnant women receive a Tdap vaccine during the 27th through 36th week of each pregnancy, preferably during the earlier part of this time period, to prevent against pertussis in the newborns. Therefore, the conduct of a Randomized Controlled Trial (RCT) to evaluate Adacel may be infeasible for ethical reasons.

This BLA efficacy supplement contains the results of study Td500059, which would serve as the primary evidence of effectiveness. Study Td500059 represents a post-hoc analysis of data from a case-control study conducted by the CDC and published in Skoff et al. (2017).

Reference: Skoff TH, Blain AE, Watt J, Scherzinger K, McMahon M, Zansky SM, Kudish K, Cieslak PR, Lewis M, Shang N, Martin SW. 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. 2017, 65, 1977-1983.

Study Td512, a post-licensure safety surveillance study of Adacel in the United States, and the Adacel pregnancy registry are presented to serve as evidence of the safety of

Adacel in pregnant women and their infants. A systematic literature review (SLR) described by the applicant as assessing the effectiveness, immunogenicity, and safety of the use of Adacel or Adacel-Polio during pregnancy in women and their infants serve as supportive evidence.

This review focuses on the evaluation from the statistical perspective of the evidence of effectiveness of Adacel based on the results of study Td500059. For study Td512, please refer to the review by the pharmacovigilance reviewer, and for the SLR, please refer to the review by the RWE reviewer.

The original study (Skoff et al. 2017) was designed as an observational case-control study and enrolled infants with pertussis (cases) who were of age <2 months, with cough onset between 2011 and 2014 in the US. The controls were hospital-matched to the cases. The infants' mothers were considered vaccinated during pregnancy if Tdap was received ≥14 days before delivery. This study was not brand-specific with respect to the Tdap vaccination. As with other observational case-control studies, this study is subjected to bias arising from the selection of cases, selection of controls, ascertainment of exposure, and unmeasured confounding.

For this BLA submission, the applicant requested the data collected for Skoff et al. (2017) from the CDC and conducted their own analysis (study Td500059) of the Adacel-specific data. The primary objective of the study is to determine the effectiveness of Adacel against pertussis disease in infants < 2 months when administered during the third trimester of pregnancy and 14 days or more before delivery. As this study is a post-hoc analysis of a subset of the data collected in the Skoff et al. (2017) study, it is subjected to the same sources of bias as with the original study, as well as to inflated Type I and Type II errors. Therefore, the results of Study Td500059 need to be interpreted with caution and should be considered in relation to the severity of the disease and the totality of the evidence.

For their initial analysis, the applicant excluded from their respective dataset those infants whose age was <2 weeks due to an observed disproportionality in this subgroup between cases and controls. This was also the analysis approach used in the published Skoff et al. (2017) paper. However, the proposed indication in this application includes protection from pertussis for all infants of age <2 months. Per FDA's request this subgroup was included in the study dataset, and an additional matching based on infants' age (< 2 weeks of age, or ≥ 2 weeks of age) was applied. An additional sensitivity analysis using the original hospital-based matching only was also conducted. Of note, a similar approach was applied to the analyses conducted by GlaxoSmithKline Biologicals (GSK) for their BLA (STN 125106/1469) for Boostrix Tdap vaccine, which utilized the Boostrix-specific data subset of the Skoff et al. (2017) study.

The vaccine effectiveness (VE) of Adacel was defined based on the odds ratio for pertussis disease if the mother was vaccinated with Adacel compared to if not vaccinated. Conditional logistic regression model considering the individual matching, adjusted for covariates was used for the primary analysis with infant's age (in weeks) included in the model. The Primary Analysis Population (which is restricted to infants whose mothers

had been either unvaccinated or vaccinated with Adacel during the third trimester and at least 14 days before delivery) within the infant's age and hospital matched dataset for the Primary Objective, included 81 cases (5 [6.2%] of whom were vaccinated) and 116 controls (19 [16.4%] of whom were vaccinated). Based on a conditional logistic regression model adjusted for household size, the highest level of maternal education and infant's age, VE was estimated as 84.3% (95% CI: 24.8%; 96.7%). The respective Primary Analysis Population for the Primary Objective within the sensitivity analysis dataset, included 101 cases (5 [5.0%] of whom were vaccinated) and 171 controls (27 [15.8%] of whom were vaccinated). Based on a conditional logistic regression model adjusted for the highest level of maternal education and infant's age, VE was estimated as 88.0% (95% CI: 43.8%; 97.4%). Of note, the sensitivity analysis dataset was based on the originally planned hospital-based matching, and thus included a larger portion of the Skoff et al. (2017) collected data compared to the infant's age and hospital matched dataset. As a result, the sensitivity analysis led to a better precision of estimation of VE and represents a reasonable result in support of the primary objective. The statistical methodology applied for assessment of the study's primary objective in the context of an observational case-control study is adequate. The estimated vaccine effectiveness is consistent with VE estimates reported in other published observational studies (3 conducted in the UK, and 1 conducted in the US) identified by the applicant; however, most of these studies assessed VE of Adacel-Polio, the exposure period during pregnancy (for most studies) was wider than in the proposed timing, and implemented various estimands.

2. Clinical and Regulatory Background

In this BLA efficacy supplement, Sanofi Pasteur applies for expansion of the indication of use for Adacel to include passive immunization against pertussis in early infancy through vaccination of women during pregnancy during the third trimester.

Adacel is a Tetanus Toxoid, Reduced Diphtheria Toxoid and (5-component) Acellular Pertussis (Tdap5) Vaccine and is delivered through an intramuscular injection. In the US, Adacel is indicated for active booster immunization against tetanus, diphtheria and pertussis. It is approved for use in persons 10 through 64 years of age.

In 2011, the US Advisory Committee on Immunization Practices (ACIP) recommended that unvaccinated pregnant women receive a dose of tetanus, diphtheria, and acellular pertussis (Tdap) vaccine to provide protection to infants from pertussis. This recommendation was later expanded in 2012 to include the use of Tdap during every pregnancy regardless of their previous Tdap vaccination history. Currently, the Centers for Disease Control and Prevention (CDC) recommends that all pregnant women receive a Tdap vaccine during the 27th through 36th week of each pregnancy, preferably during the earlier part of this time period.

Given the ACIP recommendations, a randomized controlled study (RCT), assessing the effectiveness of Adacel when administered during pregnancy to protect the infants against pertussis, appears to be infeasible for ethical and feasibility reasons. Therefore, the applicant sought to provide evidence of effectiveness using alternative data sources,

such as Real World Data (RWD). For this BLA efficacy supplement, the applicant submitted the results of the observational RWD study Td500059, which would serve as the primary evidence of effectiveness. Td500059 represents a post-hoc analysis of Adacel-related data, which was collected by the CDC for their case-control study published in Skoff et al. (2017).

Reference: Skoff TH, Blain AE, Watt J, Scherzinger K, McMahon M, Zansky SM, Kudish K, Cieslak PR, Lewis M, Shang N, Martin SW. 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. 2017, 65, 1977-1983.

The original submission (STN 125111/904/0) included the Study Protocol, Version 3, dated 17 June 2021 and the Statistical Analysis Plan (SAP), Version 1, dated July 7, 2021 for the post-hoc analysis study Td500059. Note that the protocol and the SAP had not been reviewed and agreed upon by the FDA prior to their implementation and submission to the BLA. Also, of note, study Td500059 does not include any safety objectives.

Td512, a post-licensure safety surveillance study of Adacel in the United States, and the Adacel pregnancy registry were referenced by the applicant as evidence of safety of Adacel in pregnant women and their infants. A systematic literature review (SLR), described by the applicant as assessing the effectiveness, immunogenicity, and safety of the use of Adacel or Adacel-Polio during pregnancy in women and their infants, was included in the submission as supportive evidence.

During the Filing Meeting, although the submission was determined fileable, deficiencies were identified, and were communicated to the applicant through an Information Request (IR) dated February 22, 2022. These included specifically a request for demonstration that the dataset is fit for purpose, clarification on the definitions of the variables in the submitted data, as well as a request for submission of additional data (such as vaccine type, manufacturer and brand of the vaccine, date for each vaccination, pregnancy date, estimated gestational age at birth, infant date of birth, date of cough onset, data from infants <2 weeks of age). This information and data elements were identified by the review team as necessary in order to assess the data integrity and quality of the study and to verify the presented analyses and evidence in support of the requested update on the product indication. Additional data, such as demographic characteristics of the infants and of their mothers, were requested as well, in order to describe the study population and to assess the generalizability of the study results. These data are also needed to assess comparability between the cases and controls, especially given that this is an observational study based on a subset of the original study population. Note that in the original study, cases and controls were matched only on being born in the same hospital.

On June 7, 2022, the applicant submitted an amendment (STN 125111/904/6) to the BLA supplement containing a Letter of Authorization to reference Type V Master File (MF) (b) (4) held by the CDC entitled "Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis (Tdap) vaccine for preventing pertussis in infants." Since the Master File contained a substantial amount of new data that had not been previously submitted to

or reviewed by the FDA, the amendment was designated as a Major Amendment on June 16, 2022, and a new goal date of January 10, 2023, was assigned. On June 27, 2022 (STN 125111/904/8), the applicant submitted the amended protocol for study Td500059 (version 4, dated June 17, 2022).

The data submitted by the applicant included only a part of the data variables collected by the CDC for their study (Skoff et al. 2017), and were thus lacking some demographic information and other data needed to verify their derived variables, as well as to assess the data quality and integrity. A Request for Information was submitted to the CDC, and respectively the requested data were provided to MF (b) (4) on August 19, 2022.

On November 3, an IR was sent to the applicant requesting data from infants <2 weeks of age, as well as updated study protocol, SAP and Clinical Study Report (CSR) for study Td500059 that include these data. The review team pointed out to the applicant that data from infants <2 weeks of age had not been included in the submitted data package and data analyses, although the proposed indication includes this age group. The applicant provided the requested data and the updated protocol and SAP, as well as the main updated results in STN 125111\904\14 on December 2, 2022. The final updated CSR was submitted to STN 125111\904\18 on December 23, 2022.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was assessed as fileable at the Filing Meeting, although deficiencies were identified and resolved through subsequent Information Requests. See section 2 above for details. As a result, the submission quality and completeness were determined as acceptable.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to the reviews of the corresponding discipline reviewers.

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

5.1 Review Strategy

This is a RWD submission. The primary evidence of effectiveness is provided by study Td500059. This statistical review is based on the CSR and submitted data from study Td500059. The data and the CSR were initially submitted by the applicant to STN 125111/904/0, however, updated information was submitted to subsequent amendments. Clarifying description of the submitted data variables was provided in STN 125111/904/3. The final study protocol, SAP, CSR ("supplemental") and data set used for this review were provided in STN 125111/904/14 and STN 125111/904/18. Additionally, for data verification purposes, the data collected by the CDC for the original study published in Skoff et al. (2017) were submitted by the CDC to their Master File MF (b) (4), Amendments 3 (infants aged <2 weeks) and 5 (infants aged ≥2 weeks).

Note that the data in this submission is not in a standardized data format (i.e., not in SDTM format) as it was collected by the CDC for other purposes.

The submission also includes a SLR, conducted by the applicant (protocol TD500065), as well as a post-licensure safety surveillance study Td512, both intended to serve as supportive evidence. Please refer to the reviews by the Real World Evidence (RWE) reviewer and Pharmacovigilance reviewer, respectively on these.

This review focuses on the evaluation of the evidence of effectiveness provided by study Td500059.

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

This review is primarily based on the information submitted in STN 125111/904/14 and STN 125111/904/18. As stated above, the initial submission for this application was submitted to STN 125111/904/0. Additionally, the data submitted by the CDC in their Master File MF (b) (4) was used for data verification purposes.

5.3 Table of Studies/Clinical Trials

Table 1. Summary of Study Td500059.

Duration **Geographic Location**	**Primary Objective of the Study**	**Study Design**	**Test Products; Dosage Regimen; Route of Administration**	**Included Subjects** **Number of Included Subjects**
2011 – 2014 (original study[1]) **USA** (California, Connecticut, Minnesota, New Mexico, New York, Oregon)	To determine the effectiveness of Adacel against pertussis disease in infants < 2 months when administered during the third trimester of pregnancy and 14 days or more before delivery.	Post-hoc subgroup analysis of Adacel-related data collected in the matched case-control (1:3) study by Skoff et al. (2017)[1, 2]	Adacel (Tdap5) 0.5 mL Intramuscular injection during pregnancy	Infants <2 months old with pertussis (cases) and their matched controls without pertussis **N Total:** 472[3] **N Cases:** 165[3] **N Controls:** 307[3]

[1] Skoff TH, Blain AE, Watt J, Scherzinger K, McMahon M, Zansky SM, Kudish K, Cieslak PR, Lewis M, Shang N, Martin SW. 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. 2017, 65, 1977-1983.
[2] Skoff et al. (2017) enrolled a total of N=933 infants, of whom 251 were cases and 682 were controls.
[3] A sensitivity analysis to the primary analysis for study Td500059 included a total of N=596 infants, of whom 179 were cases and 417 were controls.

5.5 Literature Reviewed

Skoff TH, Blain AE, Watt J, Scherzinger K, McMahon M, Zansky SM, Kudish K, Cieslak PR, Lewis M, Shang N, Martin SW. 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. 2017, 65, 1977-1983.

Please also refer to the review by the RWE reviewer regarding the SLR conducted by the applicant.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

This is an RWE submission. This review focuses on study Td500059, which serves as the primary evidence of effectiveness for this BLA submission.

6.1 Study Td500059

6.1.1 Objectives

Primary Objective: To determine the effectiveness of Adacel against pertussis disease in infants < 2 months when administered during the third trimester of pregnancy and 14 days or more before delivery.

Secondary Objectives:

1. To determine the effectiveness of Adacel against pertussis disease in infants < 2 months when administered to:
    - Pregnant women:
        - Following the current ACIP recommendations, i.e., from 27 through 36 weeks gestation, and 14 days or more before delivery
        - During the second and third trimesters and 14 days or more before delivery
        - During the first and second trimesters and 14 days or more before delivery
        - At any point during pregnancy and 14 days or more before delivery
    - Pre-pregnancy
    - Postpartum or less than 14 days before delivery
2. To determine the effectiveness of Adacel against hospitalization due to pertussis disease in infants < 2 months when administered to:
    - Pregnant women:
        - During the third trimester and 14 days or more before delivery
        - According to the ACIP recommendation of vaccination from 27 through 36 weeks gestation and 14 days or more before delivery
        - During the second and third trimesters and 14 days or more before delivery
        - During the first and second trimesters and 14 days or more before delivery
        - At any point during pregnancy and 14 days or more before delivery
    - Pre-pregnancy
    - Postpartum or less than 14 days before delivery

The applicant is applying for the indication of protection against pertussis in infants younger than 2 months of age when the vaccine is administered to their mothers during the third trimester of pregnancy.

Reviewer's comment: Of note, in the original submission, the primary objective was specified as "To determine the effectiveness of Adacel against pertussis disease in infants <2 months when administered during pregnancy following the current ACIP recommendations, i.e., from 27 to 36 weeks of gestation, and 14 days or more before delivery." However, based on discussions with the review team supporting the indication of immunization during the third trimester of pregnancy, in the updated protocol, SAP, and CSR, the originally stated primary objective was nominated as a secondary, and the respective primary objective was updated to reflect the proposed indication. Note also that the study did not specify Safety Objectives.

6.1.2 Design Overview

This study was a post-hoc analysis of data collected for the matched case-control study (Skoff et al., 2017), which was conducted by the CDC and was not Tdap vaccine brand-specific.

Skoff et al. (2017) Study

Briefly, the study enrolled infants with pertussis (cases) who were of age of <2 months, with cough onset between January 1, 2011 and December 31, 2014 from six US Emerging Infection Program Network states (statewide in California, Connecticut, Minnesota, and New Mexico, and in select counties of New York and Oregon). A case of pertussis was 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, or clinically compatible illness (cough ≥2 weeks with paroxysms, inspiratory whoop, or post-tussive vomiting). The controls were hospital-matched to the cases and were selected by birth certificate. For each enrolled case infant, the study authors enrolled up to 3 control infants. Enrolled infants were at least 2 days old, 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 not adopted or in foster care, and did not live in a residential care facility. The infants' mothers were interviewed to collect information on demographics, household characteristics, and healthcare providers. The study authors collected immunization history (date, brand, manufacturer, and lot number) on both the mothers and their infants. The infants' mothers were considered vaccinated during pregnancy if Tdap was received ≥14 days before delivery. The respective trimester of vaccination was calculated using the collected Tdap date, infant's date of birth, and gestational age. When more than 1 Tdap dose was received, the most recent dose was used for the analyses. The authors of the study stated that they excluded from the analyses infants who were <2 weeks old since there was a disproportionate proportion of enrolled controls compared to enrolled cases within this age group. The analyses were based on a conditional logistic regression model adjusted for covariates (household size, maternal education, household member with pertussis diagnosis, and infant age in weeks). Please refer to Skoff et al. (2017) for details.

Reviewer's comment: The Skoff et al. (2017) study was an observational, non-interventional RWD case-control study, and as such is subject to higher uncertainty and bias compared to RCTs. Note that in the study, cases and controls were matched to diminish the effect of confounding. However, only the hospital of birth was used as a matching variable. Although a conditional logistic regression model adjusting for covariates was used, unaccounted-for (unmeasured) confounding might have remained, and therefore the results of this study need to be interpreted with caution. I defer to the RWE reviewer regarding the quality of the data that was generated in the Skoff et al. (2017) study.

Study Td500059

The applicant requested the data collected for the Skoff et al. (2017) study from the CDC and used only the Adacel-related data. This is referred to as study Td500059. Of note, while the Skoff et al. (2017) study enrolled infants of age ≤2 months, they excluded from their analyses the subgroup of infants of age <2 weeks due to observed disproportionality between cases and controls in that age group. In the applicant's initial submission, the subgroup of infants of age <2 weeks were not included in the provided data set and all of their analyses. As mentioned above, the clinical review team recommended that this data need to be included in the analyses, since the indication includes this age group. The applicant subsequently obtained and provided these data for review and updated their analyses. Due to the observed disproportionality between cases and controls for infants < 2 weeks of age in the original study (see Table 2 below), in the updated analyses, in addition to hospital-based matching, the applicant also matched the cases to controls based on infants' age (< 2 weeks of age, or ≥ 2 weeks of age). The statistical reviewer also recommended that the applicant additionally conduct sensitivity analyses of the data set (that includes infants < 2 weeks of age) using the original hospital-based matching. Similar approach was also applied to the analyses conducted by GlaxoSmithKline Biologicals (GSK) for their BLA Supplement (STN 125106/1469) for Boostrix, which utilized the Boostrix-specific data subset of the Skoff et al. (2017) study.

Reviewer's comment: Study Td500059 represents a post-hoc analysis of data collected in the Skoff et al. (2017) study, and as such is subject to the uncertainties discussed above for the original study. It is also subject to bias due to the post-hoc nature of the analysis. Additionally, the study utilizes a subset of the data collected in the original study due to the exclusion of those infants whose mothers received Boostrix or an unknown vaccine, as well as those infants without a match due to these exclusions. Thus, this represents a subgroup analysis (not pre-specified in the original study), and as such is subject to lower power and inflated type I error (multiplicity). Therefore, the results of Study Td500059 need to be interpreted with caution and should be considered in relation to the totality of the evidence.

The applicant's rationale for not conducting a confirmatory RCT is for ethical reasons, since Adacel is already in use in the US for the sought indication as per the ACIP guidelines.

6.1.3 Population

The eligibility criteria for the Skoff et al. (2017) study are described above (section 6.1.2). For Study Td500059, cases and controls were excluded if their mothers had received Boostrix or an unknown vaccine brand. Cases were also excluded if they did not have at least one matched control. Controls matched to a case which had been excluded, were excluded as well.

6.1.4 Study Treatments or Agents Mandated by the Protocol

As discussed above, Study Td500059 is a case-control study, and is of retrospective nature. The study assessed vaccine effectiveness (VE) of Adacel for prevention of pertussis in infants whose mothers had been vaccinated during pregnancy as compared to infants whose mothers had not been vaccinated. For the primary objective, the timing of vaccination was during the third trimester and 14 days before delivery, and for the secondary objectives other vaccination schedules were explored.

6.1.6 Sites and Centers

It is stated in Skoff et al. (2017) that the study was conducted statewide in California, Connecticut, Minnesota, and New Mexico, and in select counties of New York (Albany, Allegany, Cattaraugus, Chautauqua, Chemung, Clinton, Columbia, Delaware, Erie, Essex, Franklin, Fulton, Genesee, Greene, Hamilton, Livingstone, Montgomery, Monroe, Niagara, Ontario, Orleans, Otsego, Rensselaer, Saratoga, Schenectady, Schoharie, Schuyler, Seneca, Steuben, Warren, Washington, Wayne, Wyoming, and Yates) and Oregon (Clackamas, Multnomah, and Washington).

6.1.7 Surveillance/Monitoring

Please refer to the reviews by the clinical and pharmacovigilance reviewers.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint
Pertussis disease in infants younger than 2 months of age.

Secondary Endpoint
Pertussis disease requiring hospitalization in infants younger than 2 months of age.

Definitions
Case of pertussis: 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, or clinically compatible illness (cough ≥2 weeks with paroxysms, inspiratory whoop, or post-tussive vomiting).

Vaccination during pregnancy definitions: The following definitions were used. In the case of multiple Tdap vaccinations, the most recent one was considered.

- Pre-pregnancy: Vaccination before pregnancy is defined as the mother of the case or control having received the vaccine at any point before being pregnant.

- During pregnancy: Vaccination during pregnancy is considered valid if it was administered at any moment during pregnancy and at least 14 days prior to delivery.
- Post-partum: Vaccination after pregnancy was defined as getting the Tdap vaccine from 14 days before delivery to <2 months following delivery.

Pregnancy trimesters

- First trimester: 0 to ≤84 days (0 to 11 weeks and 6 days)
- Second trimester: ≥85 days and ≤188 days (12 weeks to 26 weeks and 6 days)
- Third trimester: ≥189 days (27 weeks or greater)

Criteria for success: The Td500059 study represents a post-hoc analysis of data collected in the Skoff et al. (2017) study. The Td500059's study protocol and SAP do not specify hypothesis tests or study success criteria. However, it is specified that 95% CIs for the respective odds ratios (OR), and for VE (defined as 1-OR) will be reported.

Reviewer's comment: Since the indication sought in this application is vaccine effectiveness for protection against pertussis in infants, whose mothers have been vaccinated with Adacel during the specified time frame (third trimester and 14 days before delivery) during pregnancy, the study success criterion may be considered as showing that the lower limit of the 95% CI for VE is greater than a clinically meaningful margin. I defer to the clinical reviewer on what criterion is clinically meaningful for the sought indication.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The data generated in the Skoff et al. (2017) study has previously been reviewed by the FDA as part of the data package for STN 125106/1469, submitted by GSK for Boostrix for a similar indication. The statistical reviewer for that file had identified some inconsistencies in the respective data, which were later clarified by the CDC. Most of these were related to the Boostrix-specific data. For the Adacel specific data, as a result of the discussion with the CDC, the vaccination status for one infant's mother was changed from unvaccinated to vaccinated before pregnancy.

For Study Td500059, in addition to the study protocol, the applicant submitted also an SAP.

Analysis Populations definitions:

- All included patients: Infants included in the original Skoff et al. study whose mothers are either unvaccinated or vaccinated with Adacel. Infants (cases and controls) whose mothers have received Boostrix or unknown Tdap vaccine, as well as controls who were matched to a case whose mother received Boostrix or unknown Tdap vaccine are excluded from the analysis set.
- Infants of unvaccinated mothers and mothers vaccinated with Adacel during the third trimester and 14 days or more before delivery: This is a subset of the "All included patients" set and includes the infants of unvaccinated mothers or mothers vaccinated with Adacel during the third trimester and 14 days or more before

delivery. Case infants who do not have at least one control, as well as controls who do not have a matching case are excluded.

- Infants of unvaccinated mothers and mothers vaccinated with Adacel following ACIP recommendations and 14 days or more before delivery: This is a subset of the "All included patients" set and includes the infants of unvaccinated mothers or mothers vaccinated with Adacel following ACIP recommendations (from 27 through 36 weeks gestation) and 14 days or more before delivery. Case infants who do not have at least one control, as well as controls who do not have a matching case are excluded.

The analysis populations for the rest of the secondary objectives were defined in a similar manner.

Analyses for the Primary Objective:

- **Primary Analysis**: It was conducted using the "Infants of unvaccinated mothers and mothers vaccinated with Adacel during the third trimester and 14 days or more before delivery" Analysis Population specified above.

  As discussed above, the updated primary analysis utilizes the data from the Skoff et al. (2017) study on infants of age ≤2 months, including those who were <2 weeks of age at enrollment. For the primary analyses, due to the observed disproportionality between cases and controls for infants < 2 weeks of age in the original study (see Table 2 below), in addition to hospital-based matching, the cases were also matched to controls based on infants' age (< 2 weeks of age, or ≥ 2 weeks of age).

  Statistical Method: The odds ratio for pertussis disease if vaccinated with Adacel compared to not vaccinated and 95% CI was estimated using a conditional logistic regression model (considering the individual matching). The primary analysis is based on a conditional logistic regression model adjusted for covariates. The regression model is built by first fitting a multivariable conditional regression with infant age at cough onset (as a quantitative covariate, even if not significant) and all covariates for which the p-value in a univariate conditional logistic regression is <0.20. The final model is built by backwards elimination, keeping those variables that have p-value <0.05 and infant age at cough onset (as a quantitative covariate; even if not significant). Infant's age was included in the model as it was considered a clinically relevant variable in the Skoff et al. (2017) study.

  Reviewer's comment: The applicant's approach appears acceptable.

  There was no imputation of missing data for this study. A sensitivity analysis using the conditional logistic regression model adjusted for the covariates used in Skoff et all. (2017), i.e., household size, maternal education, household member with pertussis diagnosis, and infant age, was planned as well.

The applicant also provided power calculations using the results from the Skoff et al. (2017) study, however these are post-hoc calculations and are of limited value, as the data had already been collected.

Analyses for the Secondary Objectives:
The same methods as for the primary objective were to be used for the secondary objectives. No adjustment of the type I error for multiplicity was planned.

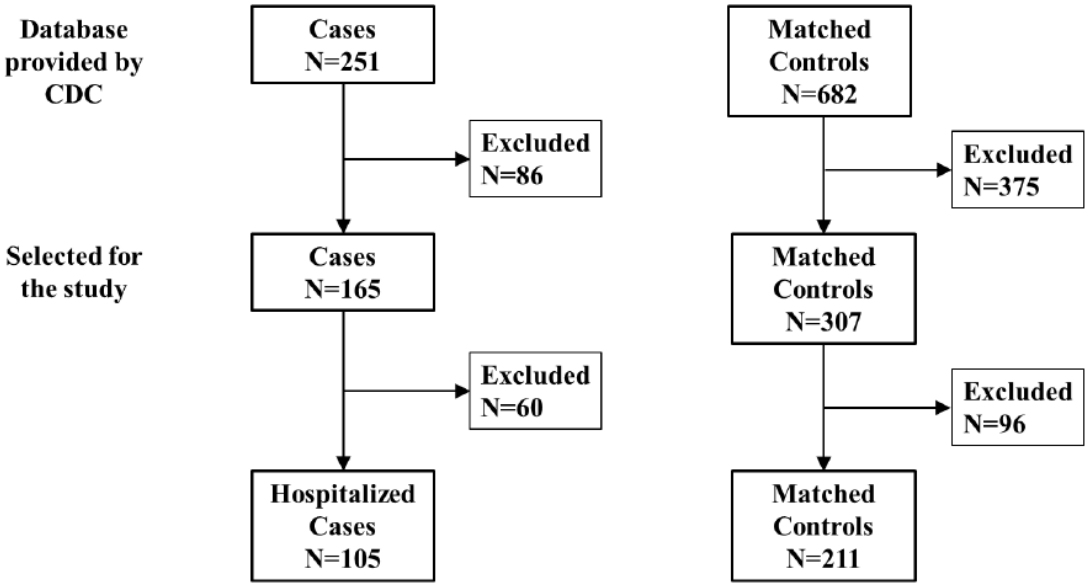
Reviewer's comment: This review focuses on the analyses associated with assessment of the primary objective which corresponds to the proposed indication.

Sensitivity Analyses
Sensitivity analyses were conducted using the data set that includes infants < 2 weeks of age using the original hospital-based matching.

6.1.10 Study Population and Disposition

The data set submitted by the applicant includes data on a total of 933 infants of age <2 months (251 cases and 682 controls). After exclusion of cases whose mothers have received Boostrix or unknown vaccine and their matched controls, as well as exclusion of controls whose mothers have received Boostrix or unknown vaccine and their respective cases, a total of 472 infants (165 cases and 307 matched controls) were included in the study (Figure 1 and Table 2).

Figure 1. Study Flow Chart



Source: Study Td500059 Final Supplemental Clinical Study Report, dated December 12, 2022, Version 1, Figure 1, p. 34.

6.1.10.1 Populations Enrolled/Analyzed

Study Td500059 included a total of 472 infants (165 cases and 307 controls).

6.1.10.1.1 Demographics

Table 2 shows the demographic characteristics of the included infants for the original Skoff et al. (2017) study, and for Study Td500059.

Reviewer's comment: Note that some of the demographic characteristics that were collected in the original study (shown in Table 2), were not requested by the applicant from the CDC, since they considered that this may potentially lead to identification of the participants. However, we had access to these data through the CDC's Master File (MF (b) (4).

Table 2. Demographic characteristics of included infants.

Characteristics[1]	**Skoff et al. 2017: Cases[2] n (%)**	**Skoff et al. 2017: Controls[2] n (%)**	**Td500059: Cases[3] n (%)**	**Td500059: Controls[3] n (%)**	**Td500059: Total[3] n (%)**
Total Number of Infants Enrolled	251	682	165	307	472
Infants State of Birth[1]:	-	-	-	-	-
California	172 (68.5)	-	-	-	-
Connecticut	14 (5.6)	-	-	-	-
Minnesota	19 (7.6)	-	-	-	-
New Mexico	22 (8.8)	-	-	-	-
New York	12 (4.8)	-	-	-	-
Oregon	12 (4.8)	-	-	-	-
Infants Age (in Weeks):	-	-	-	-	-
0 – 1	11 (4.4)	147 (21.6)	5 (3.0)	5 (1.6)	10 (2.1)
2 – 3	66 (26.3)	147 (21.6)	45 (27.3)	86 (28.0)	131 (27.8)
4 – 5	70 (27.9)	153 (22.4)	43 (26.1)	83 (27.0)	126 (26.7)
6 – 7	79 (31.5)	178 (26.1)	51 (30.9)	106 (34.5)	157 (33.3)
8	25 (10.0)	57 (8.4)	21 (12.7)	27 (8.8)	48 (10.2)
Infants Sex[1]:	-	-	-	-	-
Male	124 (49.4)	330 (48.4)	-	-	-
Female	127 (50.6)	352 (51.6)	-	-	-
Infants Race[1]:	-	-	-	-	-
White	199 (79.3)	543 (79.6)	-	-	-
Black	22 (8.8)	47 (6.9)	-	-	-
Other	25 (10.0)	73 (10.7)	-	-	-
Missing	5 (2.0)	19 (2.8)	-	-	-
Infants Ethnicity:	-	-	-	-	-
Hispanic	156 (62.2)	344 (50.4)	103 (62.4)	151 (49.2)	254 (53.8)
Not Hispanic	94 (37.5)	336 (49.3)	61 (37.0)	155 (50.5)	216 (45.8)

Characteristics[1]	**Skoff et al. 2017: Cases**[2] **n (%)**	**Skoff et al. 2017: Controls**[2] **n (%)**	**Td500059: Cases**[3] **n (%)**	**Td500059: Controls**[3] **n (%)**	**Td500059: Total**[3] **n (%)**
Missing	1 (0.4)	2 (0.3)	1 (0.6)	1 (0.3)	2 (0.4)
Mothers Education Status:	-	-	-	-	-
High school or less	147 (58.6)	236 (34.6)	98 (59.4)	101 (32.9)	199 (42.2)
More than high school	104 (41.4)	446 (65.4)	67 (40.6)	206 (67.1)	273 (57.8)
Household Size:	-	-	-	-	-
Two or fewer	25 (10.0)	179 (26.2)	17 (10.3)	79 (25.7)	96 (20.3)
More than two	226 (90.0)	503 (73.8)	148 (89.7)	228 (74.3)	376 (79.7)
Pertussis Diagnosis at Home:	-	-	-	-	-
Yes	21 (8.4)	4 (0.6)	16 (9.7)	0 (0.0)	16 (3.4)
No	230 (91.6)	678 (99.4)	149 (90.3)	307 (100.0)	456 (96.6)
Infants with a DTaP dose at least 14 days before enrollment date	2 (0.8)	3 (0.4)	2 (1.2)	2 (0.7)	4 (0.8)
Was the infant case hospitalized?:	-	-	-	-	-
Yes	157 (62.5)	-	105 (63.6)	-	105 (63.6)[4]
No	81 (32.3)	-	53 (32.1)	-	53 (32.1)[4]
Unknown	13 (5.2)	-	7 (4.2)	-	7 (4.2)[4]

[1] Some of the infants' characteristics, that were collected in the Skoff et al. (2017) study, were not included in the data set that the applicant obtained from the CDC. Although these were included in the CDC's MF (b) (4) for FDA's verification purposes, they are not shown here since the FDA was not authorized by the CDC to disclose these data.
[2] The Skoff et al. (2017) study enrolled infants who were of <2 weeks of age, however they were excluded from their primary analysis.
[3] Study Td500059 in addition to hospital of birth, matched cases to controls based on infants age (<2 weeks or ≥2 weeks).
[4] The % was calculated based on the total number of cases only.
Source: Created by the reviewer based on the data provided by the applicant and Skoff et al. (2017).

In the original study, 479 (51.3%) of the included infants were female, 742 (79.5%) were White, 500 (53.6%) were of Hispanic ethnicity, and 775 (83.1%) were of age ≥2 weeks at enrollment. Among the case infants that were included, 172 (68.5%) were born in hospitals in California. The cases were more likely to be older, of Hispanic ethnicity, born to a mother with at most high school education, live in a larger household, and have a household member diagnosed with pertussis recently, compared to controls. As mentioned above, due to the observed disproportionality between cases and controls for infants < 2 weeks of age, for study Td500059, the controls were also matched to the cases based on infants' age (< 2 weeks of age, or ≥ 2 weeks of age). The additional matching based on infants' age (< 2 weeks of age, or ≥ 2 weeks of age) led to comparable age distribution between the cases and controls in the Td500059 study. For the rest of the

characteristics, the distribution was similar between the original study's population and the sub-population included in Study Td500059.

Reviewer's comment: While the additional matching based on infants' age (< 2 weeks of age, or ≥ 2 weeks of age) led to comparable age distribution between the cases and controls in the Td500059 study, it resulted in a smaller data subset than if matched based on hospital only. The hospital-only-based matching subset is instead used as a sensitivity analysis.

Table 3 below shows the distribution of the characteristics of the participants in the Analysis Population used for the Primary Objective, namely, infants of unvaccinated mothers and mothers vaccinated with Adacel during the third trimester and 14 days or more before delivery. In this subpopulation, the cases were more likely to be born to a mother with at most high school education, to live in a larger household, and have a household member diagnosed with pertussis recently, compared to controls. Ethnicity and age were comparable between cases and controls.

Table 3. Demographic characteristics of the Primary Analysis Population which includes infants of unvaccinated mothers and mothers vaccinated with Adacel during the third trimester and 14 days or more before delivery.

Characteristics	**Cases n (%)**	**Controls n (%)**	**Total n (%)**
Total Number of Included Infants	81	116	197
Infants Age (in Weeks):	-	-	-
0 – 1	5 (6.2)	5 (4.3)	10 (5.1)
2 – 3	21 (25.9)	34 (29.3)	55 (27.9)
4 – 5	20 (24.7)	33 (28.4)	53 (26.9)
6 – 7	25 (30.9)	33 (28.4)	58 (29.4)
8	10 (12.3)	11 (9.5)	21 (10.7)
Infants Ethnicity:	-	-	-
Hispanic	52 (64.2)	71 (61.2)	123 (62.4)
Not Hispanic	28 (34.6)	45 (38.8)	73 (37.1)
Missing	1 (1.2)	0 (0.0)	1 (0.5)
Mothers Education Status:[1]	-	-	-
High school or less	51 (63.0)	48(41.4)	99 (50.3)
More than high school	30 (37.0)	68 (58.6)	98 (49.7)
Household Size:[2]	-	-	-
Two or fewer	5 (6.2)	26 (22.4)	31 (15.7)
More than two	76 (93.8)	90 (77.6)	166 (84.3)
Pertussis Diagnosis at Home:	-	-	-
Yes	4 (4.9)	0 (0.0)	4 (2.0)
No	77 (95.1)	116 (100.0)	193 (98.0)
Was the infant case hospitalized?:	-	-	-
Yes	51 (63)	-	51 (63)[3]
No	23 (28.4)	-	23 (28.4)[3]
Unknown	2 (2.5)	-	2 (2.5)[3]

[1] p-value=0.002 (univariable conditional logistic regression).
[2] p-value=0.009 (univariable conditional logistic regression).
[3] The % was calculated based on the total number of cases only.
Source: Created by the reviewer using the data provided by the applicant.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The timing of vaccination of the mothers of the infants included in Study Td500059 is shown in Table 4 below.

Table 4. Timing of vaccination with Adacel of the mothers of the included infants in Study Td500059.

Timing of vaccination with Adacel of the infants' mothers	**Cases N=165 n (%)**	**Controls N=307 n (%)**	**Total N=472 n (%)**
Unvaccinated	96 (58.2)	141 (45.9)	237 (50.2)
Vaccinated before pregnancy	14 (8.5)	36 (11.7)	50 (10.6)
Vaccinated during the 1st trimester	0 (0)	3 (1.0)	3 (0.6)
Vaccinated during the 2nd trimester	2 (1.2)	5 (1.6)	7 (1.5)
Vaccinated during the 3rd trimester	7 (4.2)	33 (10.7)	40 (8.5)
Vaccinated after pregnancy	46 (27.9)	89 (29.0)	135 (28.6)
Vaccinated according to the ACIP recommendations, i.e., from 27 through 36 weeks gestation[1]	6 (3.6)	33 (10.7)	39 (8.3)

[1] This vaccination period is contained in the third trimester period.
Source: Created by the reviewer using the data provided by the applicant.

In the primary data set, of the women vaccinated during pregnancy, 80% (40/50) were vaccinated during the third trimester and at least 14 days before delivery.

6.1.10.1.3 Subjects Disposition

Table 5. Analysis Sets for pertussis disease in Study Td500059.

Analysis Sets	**Number of Cases**	**Number of Controls**	**Total**
All	165	307	472
During the third trimester and 14 days or more before delivery	81	116	197
Following ACIP recommendations (27-36 weeks of gestational age) and 14 days or more before delivery	80	115	195

Note: Analysis sets were defined based on the timings of vaccination and were not mutually exclusive.
Source: Created by the reviewer using the data provided by the applicant.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of the Primary Endpoint

The Analysis Population for the Primary Objective included 81 cases and 116 controls. Based on the conditional logistic regression model adjusted for household size, highest

level of maternal education and infant's age, VE was estimated as 84.3% (95% CI: 24.8%; 96.7%), Table 6.

Table 6. Vaccine effectiveness

Analysis	Number of Cases	Number Vaccinated Cases (%)	Number of Controls	Number Vaccinated Controls (%)	Odds Ratio (95% CI)	VE % (95% CI)
Primary (hospital and age [<2 or >=2 weeks] matching)	81	5 (6.2)	116	19 (16.4)	0.157 (0.033; 0.752)	84.3[1] (24.8; 96.7)
Sensitivity (hospital only matching)[2]	101	5 (5.0)	171	27 (15.8)	0.120 (0.026; 0.562)	88.0[3] (43.8; 97.4)

[1] From conditional logistic regression model adjusted for household size, highest level of maternal education and infant's age.
[2] See section Sensitivity Analyses below.
[3] From conditional logistic regression model adjusted for highest level of maternal education and infant's age.
Source: Created by the reviewer using the data provided by the applicant.

Reviewer's comment: I confirmed the applicant's results. The sensitivity analysis yielded a VE estimate with better precision because of the larger sample size.

6.1.11.2 Sensitivity Analyses

The applicant conducted a sensitivity analysis by using a conditional logistic model, adjusted for the variables used for the analysis in Skoff et al. (2017), namely using the variables of household size, highest level of maternal education, household member with pertussis diagnosis, and infant's age. The respective VE was estimated as 84.2% (95% CI: 24.5%; 96.7%).

As stated above, the applicant also conducted sensitivity analyses using the original hospital only based matching between cases and controls. This resulted in an inclusion of a total of 596 infants (179 cases and 417 controls), Table 7.

Table 7. Demographic characteristics of infants included in the Sensitivity Analysis Population (hospital only based matching between cases and controls).

Characteristics	Cases n (%)	Controls n (%)	Total n (%)
Total Number of Included Infants	179	417	596
Infants Age (in Weeks):	-	-	-
0 – 1	10 (5.6)	100 (24.0)	110 (18.5)
2 – 3	48 (26.8)	91 (21.8)	139 (23.3)
4 – 5	46 (25.7)	87 (20.9)	133 (22.3)
6 – 7	54 (30.2)	110 (26.4)	164 (27.5)
8	21 (11.7)	29 (7.0)	50 (8.4)
Infants Ethnicity:	-	-	-
Hispanic	112 (62.6)	210 (50.4)	322 (54.0)

Characteristics	**Cases n (%)**	**Controls n (%)**	**Total n (%)**
Not Hispanic	66 (36.9)	205 (49.2)	271 (45.5)
Missing	1 (0.6)	2 (0.5)	3 (0.5)
Mothers Education Status:	-	-	-
High school or less	104 (58.1)	145(34.8)	249 (41.8)
More than high school	75 (41.9)	272 (65.2)	347 (58.2)
Household Size:	-	-	-
Two or fewer	20 (11.2)	105 (25.2)	125 (21.0)
More than two	159 (88.8)	312 (74.8)	471 (79.0)
Pertussis Diagnosis at Home:	-	-	-
Yes	17 (9.5)	1 (0.2)	18 (3.0)
No	162 (90.5)	416 (99.8)	578 (97.0)
Was the infant case hospitalized?:	-	-	-
Yes	114 (63.7)	-	114 (63.7)[1]
No	53 (29.6)	-	53 (29.6) [1]
Unknown	12 (6.7)	-	12 (6.7) [1]

[1] The % was calculated based on the total number of cases only.
Source: Created by the reviewer using the data provided by the applicant.

The demographic characteristics of infants included in the Primary Analysis Population (which includes infants of unvaccinated mothers and mothers vaccinated with Adacel during the third trimester and 14 days or more before delivery) within the Sensitivity Analysis Population are shown in Table 8.

Table 8. Demographic characteristics of infants included in the Analysis Population which includes infants of unvaccinated mothers and mothers vaccinated with Adacel during the third trimester and 14 days or more before delivery within the Sensitivity Analysis Population (hospital only based matching between cases and controls).

Characteristics	**Cases n (%)**	**Controls n (%)**	**Total n (%)**
Total Number of Included Infants	101	171	272
Infants Age (in Weeks):[1]	-	-	-
0 – 1	9 (8.9)	51 (29.8)	60 (22.1)
2 – 3	27 (26.7)	38 (22.2)	65 (23.9)
4 – 5	22 (21.8)	36 (21.1)	58 (21.3)
6 – 7	31 (30.7)	34 (19.9)	65 (23.9)
8	12 (11.9)	12 (7.0)	24 (8.8)
Infants Ethnicity:[2]	-	-	-
Hispanic	63 (62.4)	100 (58.5)	163 (59.9)
Not Hispanic	37 (36.6)	71 (41.5)	108 (39.7)
Missing	1 (1.0)	0 (0.0)	1 (0.4)
Mothers Education Status:[3]	-	-	-
High school or less	61 (60.4)	69 (40.4)	130 (47.8)
More than high school	40 (39.6)	102 (59.6)	142 (52.2)
Household Size:[4]	-	-	-

Characteristics	Cases n (%)	Controls n (%)	Total n (%)
Two or fewer	9 (8.9)	38 (22.2)	47 (17.3)
More than two	92 (91.1)	133 (77.8)	225 (82.7)
Pertussis Diagnosis at Home:	-	-	-
Yes	6 (5.9)	0 (0.0)	6 (2.2)
No	95 (94.1)	171 (100.0)	266 (97.8)
Was the infant case hospitalized?:	-	-	-
Yes	65 (64.4)	-	65 (64.4)[5]
No	25 (24.8)	-	25 (24.8)[5]
Unknown	11 (10.9)	-	11 (10.9)[5]

[1] p-value=0.0001 (univariable conditional logistic regression).
[2] p-value=0.1164 (univariable conditional logistic regression).
[3] p-value=0.0011 (univariable conditional logistic regression).
[4] p-value=0.0073 (univariable conditional logistic regression).
[5] The % was calculated based on the total number of cases only.
Source: Created by the reviewer using the data provided by the applicant.

It can be seen that in Table 8, that for the Primary Analysis Population within the Sensitivity Analysis Population, infant's age was significantly associated with case/control status, as was observed in the original Skoff et al. (2017) study, and in contrast to the Primary Analysis Population (Table 3) for the Primary Analysis, where infant's age was comparable between cases and controls due to the implemented additional age-based matching.

The respective VE was estimated as 88.0% (95% CI: 43.8; 97.4) using a conditional logistic regression model, adjusted for highest level of maternal education and infant's age. This sensitivity analysis yielded a VE estimate with better precision as a result of the larger sample size.

6.1.11.3 Subpopulation Analyses

The applicant also conducted Adacel-specific analyses that excluded all infants of age <2 weeks from the data set due to the observed disproportionality between cases and controls for that age group. Such approach was used in the Skoff et al. (2017) study. Accordingly, using this subpopulation, the applicant estimated VE of 92.5% (95% CI: 38.6; 99.1). However, as discussed above, infants of age <2 weeks are susceptible to pertussis, and as recommended by the clinical reviewer, need to be included in the study population for assessment of the proposed indication.

6.1.11.5 Systematic Literature Review

The applicant conducted an SLR of studies assessing the effectiveness, immunogenicity and safety of Adacel when administered during pregnancy. The SLR is referred to as Study TD500065 by the applicant. The SLR reported 4 published studies on VE (Table 9).

Table 9. Summary – Studies assessing VE of Adacel/Adacel-Polio for prevention of pertussis in infants when administered during pregnancy.

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	Reported VE (95% CI)
Amirthalingam et al (2014)	Case-coverage (also known as screening method)	England Infants born from 1 Oct 2012 with onset of disease by 30 Sep 2013 Maternal vaccine coverage: live births 1 Oct 2012–3 Sep 2013	Cases < 2 months of age: 71 Maternal coverage: 26,684 live births	Adacel-Polio (vaccination at least 7 days before delivery)	90% (82 to 95) Sensitivity Analysis: 82% (67 to 90)
Amirthalingam et al (2016)	Case-coverage (also known as screening method)	England Infants born from 1 Oct 2012 with onset of disease by 30 Sep 2014 Maternal vaccine coverage: live births 1 Oct 2012–31 Aug 2015	Cases < 3 months of age: 243 Maternal vaccine coverage: 72,781 live births	Adacel-Polio: 71% TdaP3-IPV: 29% (vaccination at least 7 days before delivery)	91% (88–94) Sensitivity Analysis: 85% (78–89)
Baxter et al (2017)	Retrospective cohort	United States Total infants born 2010–2015 Infants born whose mothers received Tdap vaccine 2010–2015	Total Infants: 148,981 Infants whose mothers received Tdap vaccine: 68,168 Cases: First 2 months of life: 17	Pregnant women: Adacel at least 99.5%) Infants: DTaP (no product specified) (vaccination at least 8 days before delivery)	91.4% (19.5 to 99.1)
Dabrera et al (2015)	Case-control	England and Wales Infants born 22 Oct 2012–11 Jul 2013 with disease onset at < 8 weeks of age	Cases: 58 Controls: 55	Adacel-Polio (Cases: median gestation at vaccination - 31.5 weeks [range 28–38 weeks]; Controls: 33 weeks [range 26–38 weeks]	93% (81%–97%)

Source: Adapted from Final Systematic Literature Review Report, dated June 6, 2022.

<u>Reviewer's comment:</u> Note that all the studies listed in Table 9 were observational and implemented various study designs. Of the 4 studies, only one was based on data from the US. Additionally, 3 of the studies assessed VE of the Adacel-Polio vaccine. The studies used various timings of vaccination during pregnancy and implemented different estimands. I defer to the RWE reviewer regarding the quality of the SLR.

For details on the quality of the cited studies and review of the SLR, please refer to the review by the RWE reviewer.

6.1.12 Safety Analyses

There were no Safety Analyses conducted in Study Td500059. Please refer to the reviews by the clinical and pharmacovigilance reviewers regarding the safety assessments in this submission.

7. INTEGRATED OVERVIEW OF EFFICACY

There were no integrated analyses of efficacy conducted in this BLA supplement submission.

8. INTEGRATED OVERVIEW OF SAFETY

There were no integrated analyses of safety conducted in this BLA supplement submission.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

In this BLA efficacy supplement, Sanofi Pasteur applies for expansion of the indication of use for Adacel (Tetanus Toxoid, Reduced Diphtheria Toxoid and [5-component] Acellular Pertussis [Tdap5]) to include passive immunization against pertussis in infants of age of <2 months through vaccination of women during the third trimester of pregnancy.

In 2011, the US ACIP recommended that unvaccinated pregnant women receive a dose of tetanus, diphtheria, and acellular pertussis (Tdap) vaccine to provide protection to infants from pertussis. This recommendation was expanded in 2012 to include the use of Tdap during every pregnancy regardless of their previous Tdap vaccination history. Currently, the CDC recommends that all pregnant women receive a Tdap vaccine during the 27th through 36th week of each pregnancy, preferably during the earlier part of this time period.

Due to the ACIP/CDC recommendations, it is considered unethical to conduct an RCT for assessing the effectiveness of Adacel when administered during pregnancy to protect the infants against pertussis. Therefore, the applicant sought to provide evidence of effectiveness using alternative data sources, such as RWD. For this BLA efficacy supplement, the applicant submitted the results of an observational RWD study Td500059, which would serve as the primary evidence of effectiveness. Td500059 is a post-hoc analysis of the Adacel-related data generated in the case-control study published in Skoff et al. (2017), which was conducted by the CDC.

Study Td500059 assesses only the effectiveness of Adacel, and does not assess its safety. In their application package, to address assessment of safety, the applicant referenced study Td512, a post-licensure safety surveillance study of Adacel in the United States, and the Adacel pregnancy registry as evidence of safety of Adacel in pregnant women and their infants. An SLR (referred to as Study TD500065), described by the applicant as assessing the effectiveness, immunogenicity, and safety of the use of Adacel or Adacel-

Polio during pregnancy in women and their infants, was included in the submission as supportive evidence. Please refer to the reviews by the pharmacovigilance reviewer and by the RWE reviewer regarding evaluation of study Td512 and the SLR. This review focuses on the evaluation of the statistical methodology of study Td500059.

The primary objective of Study Td500059 was to determine the effectiveness of Adacel against pertussis disease in infants < 2 months when administered during the third trimester of pregnancy and 14 days or more before delivery. The study also had secondary objectives assessing VE of Adacel when administered according to other schedules, as well as for prevention of hospitalization due to pertussis disease. However, there was no adjustment of the Type I error for multiplicity.

I verified the key results of Study Td500059. The key findings are the following.

- The Skoff et al. (2017) study was an observational, retrospective, case-control study, and as such is subjected to higher uncertainty and bias compared to an RCT. The study implemented matching between cases and controls using the hospital of birth as a matching variable. As with other observational case-control studies, it is subjected to bias arising from the selection of cases, selection of controls, ascertainment of exposure, and unmeasured confounding.
- Study Td500059 represents a post-hoc analysis of a subset of the data collected in the Skoff et al. (2017) study, specifically of the Adacel-related data. Thus, it may be subjected to an inflated Type I error (false positive rate). Additionally, the study utilizes a subset of the data collected in the original study and thus represents a subgroup analysis (not pre-specified in the original study), and as such is also subjected to a lower power. Therefore, the results of Study Td500059 need to be interpreted with caution and should be considered in relation to the totality of the evidence.
- In the Skoff et al. (2017) study, due to the observed disproportionality between cases and controls for infants < 2 weeks of age, infants of age < 2 weeks were excluded from their analyses. As this subpopulation is included in the proposed indication for Adacel, upon FDA's request, for study Td500059, in addition to hospital of birth, the controls were also matched to the cases based on infants' age (< 2 weeks of age, or ≥ 2 weeks of age). A sensitivity analysis was conducted using the original hospital-only based matching.
- The vaccine effectiveness of Adacel was defined based on the odds ratio for pertussis disease if vaccinated with Adacel compared to not vaccinated. Conditional logistic regression model considering the individual matching, adjusted for covariates, was used for the primary analysis with infant's age (in weeks) included in the model (as it was considered a clinically relevant variable in the Skoff et al. 2017 study).
- The primary dataset in Study Td500059 included a total of 472 infants (165 cases and 307 controls), while the sensitivity analysis dataset included a total of 596 infants (179 cases and 417 controls).

- The Primary Analysis Population for the Primary Objective, which is restricted to infants whose mothers had been either unvaccinated or vaccinated with Adacel during the third trimester and at least 14 days before delivery, included 81 cases (5 [6.2%] of whom were vaccinated) and 116 controls (19 [16.4%] of whom were vaccinated). Based on the conditional logistic regression model adjusted for household size, highest level of maternal education and infant's age, VE was estimated as 84.3% (95% CI: 24.8%; 96.7%).

- The Primary Analysis Population for the Primary Objective within the Sensitivity Analysis dataset, which is restricted to infants whose mothers had been either unvaccinated or vaccinated with Adacel during the third trimester and at least 14 days before delivery, included 101 cases (5 [5.0%] of whom were vaccinated) and 171 controls (27 [15.8%] of whom were vaccinated). Based on the conditional logistic regression model adjusted for highest level of maternal education and infant's age, VE was estimated as 88.0% (95% CI: 43.8%; 97.4%). The VE estimate using the Sensitivity Analysis Population has better precision.
- As the Sensitivity Analysis dataset led to a better estimation precision for VE, as it discarded a smaller portion of the originally collected data and used the original matching, this estimate represents a reasonable result in support of the primary objective.
- The statistical methodology applied for assessment of the study's primary objective in the context of an observational case-control study is adequate.
- The estimated vaccine effectiveness is consistent with VE estimates reported in other observational studies in the literature identified by the applicant. However, these studies implemented various study designs, and of the 4 reported studies, only one was based on data from the US. Additionally, 3 of the studies assessed VE of the Adacel-Polio vaccine. The studies also used various timings of vaccination during pregnancy and implemented different estimands. I defer to the RWE reviewer regarding the quality of the SLR.

10.2 Conclusions and Recommendations

In conclusion, due to the ACIP/CDC recommendations, it is considered unethical to conduct an RCT for assessing the effectiveness of Adacel when administered during pregnancy to protect the infants against pertussis. Study Td500059 was conducted as a post-hoc analysis of a subset of the data collected in the Skoff et al. (2017) study, and as such may be subjected to bias and to inflated Type I and Type II errors. Therefore, the results of Study Td500059 need to be interpreted with caution and should be considered in relation to the totality of the evidence.

Using Adacel-specific data from the Skoff et al, (2017) study, based on a conditional logistic regression model adjusted for covariates, Adacel's vaccine effectiveness for prevention of pertussis in infants up to 2 months of age, when administered during the third trimester in pregnancy and at least 14 days before delivery, was estimated as 88.0% (95% CI: 43.8%; 97.4%) in support to the primary objective. The statistical methodology in the context of an observational case-control study was adequate. The estimated vaccine

effectiveness is consistent with the VE estimates reported in other four observational studies in the literature identified by the applicant; however, most of these studies assessed VE of Adacel-Polio, the exposure period during pregnancy for most studies was wider than in the proposed timing, and various estimands were implemented.