Section 2.5 - Clinical Overview

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List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ATAGI	Australian Technical Advisory Group on Immunisation
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CTD	Common Technical Document
DTaP	Diphtheria, Tetanus, and acellular Pertussis
DTaP-HBV-IPV	Diphtheria and tetanus toxoids and acellular pertussis, hepatitis B virus, and inactivated poliovirus vaccine, Pediarix® from GlaxoSmithKline
DTaP-HBV-IPV/Hib	Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine, Infanrix® hexa from GlaxoSmithKline
DTaP-IPV-Hib	Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine and *Haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pediacel® from Sanofi Pasteur
DTaP-IPV/Hib	Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *Haemophilus* b conjugate (tetanus toxoid conjugate) vaccine Pentacel® from Sanofi Pasteur
DTaP-IPV//Hib	Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pentaxim® from Sanofi Pasteur
ELISA	enzyme-linked immunosorbent assay
EU	enzyme-linked immunosorbent assay unit
FHA	filamentous hemagglutinin
FIM	fimbriae types 2 and 3
GMC	geometric mean concentrations
HepB	hepatitis B
HPV4	quadrivalent human papillomavirus vaccine
HR	hazard ratio
IIV3 or TIV	trivalent inactivated influenza vaccine

IPV	inactivated poliomyelitis vaccine
IQR	interquartile range
IRR	incidence rate ratio
IRRS	Information Resources and Research Services
IU	International unit
JCVI	Joint Committee on Vaccination and Immunization
KPNC	Kaiser Permanente Northern California
LBS	literature based submission
LLOQ	lower limit of quantification
MCV4	quadrivalent meningococcal conjugate vaccine
MMR	measles, mumps, and rubella
NACI	National Advisory Committee on Immunization
NIAID	National Institute of Allergy and Infectious Diseases
NIP	National Immunisation Program
ONS	Office of National Statistics
OR	odds ratio
PBAC	Pharmaceutical Benefit Advisory Committee
PRN	pertactin
PT	pertussis toxoid
RR	relative risk/risk ratio
SAE	serious adverse event
SGA	small for gestational age
SmPC	Summary of Product Characteristics
Td	Tetanus diphtheria
Td Adsorbed	Tetanus and diphtheria toxoids adsorbed vaccine, Td Adsorbed® from Sanofi Pasteur
Tdap	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, brand unspecified
Tdap3	Tdap vaccine with 3 acellular pertussis components, Boostrix® from GlaxoSmithKline

Tdap5	Tdap vaccine with 5 acellular pertussis components, COVAXIS® from Sanofi Pasteur
Tdap3-IPV	Tdap3 vaccine with IPV, Boostrix-IPV® from GlaxoSmithKline
Tdap5-IPV	Tdap5 with IPV, REPEVAX® from Sanofi Pasteur
TGA	Therapeutic Goods Administration
US	United States
USPSTF	United States Preventive Services Task Force
VAERS	Vaccine Adverse Event Reporting System
VAR	Varicella
VE	vaccine effectiveness
VSD	Vaccine Safety Datalink

1 Product Development Rationale

1.1 Pharmacological Class and Target Indication

Pharmacological Class

COVAXIS® (Tdap5) belongs to the anti-infective for systemic use pharmacological class – Vaccines group ATC code J07AJ52.

REPEVAX® (Tdap5-IPV) belongs to the anti-infective for systemic use pharmacological class – Vaccines group ATC code J07CA02.

Current Indication

COVAXIS is a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine indicated for active booster immunization against tetanus, diphtheria, and pertussis.

Depending on the country, COVAXIS is approved for use in persons 4 years of age and older, 4 through 64 years of age, 10 years of age and older, 10 through 64 years of age, or 11 through 64 years of age.

In the European Union, COVAXIS is indicated for active immunization against tetanus, diphtheria, and pertussis in persons from 4 years of age as a booster following primary immunization.

REPEVAX has the same antigen content as COVAXIS with the addition of inactivated poliomyelitis vaccine (IPV). REPEVAX was co-developed with COVAXIS and is indicated for active booster immunization for the prevention of tetanus, diphtheria, pertussis, and poliomyelitis. Depending on the country, REPEVAX is approved for use in persons 3 or 4 years of age and above.

In the European Union, REPEVAX is indicated in persons from 3 years of age as a booster following primary immunization.

The composition of COVAXIS and REPEVAX is presented in Table 1.1.

Table 1.1: Antigen Composition of COVAXIS and REPEVAX

Active Ingredients (Per 0.5 mL Dose)	COVAXIS	REPEVAX
Tetanus Toxoid	Not less than 20 IU[a] (5 Lf)	Not less than 20 IU[a] (5 Lf)
Diphtheria Toxoid	Not less than 2 IU[a] (2 Lf)	Not less than 2 IU[a] (2Lf)
Pertussis Antigens		
Pertussis Toxoid (PT)	2.5 µg	2.5 µg
Filamentous Haemagglutinin (FHA)	5 µg	5 µg
Pertactin (PRN)	3 µg	3 µg
Fimbriae Types 2 and 3 (FIM)	5 µg	5 µg
Poliovirus (Inactivated)[b]		
Type 1 (Mahoney)	-	40 D-antigen units
Type 2 (MEF-1)	-	8 D-antigen units
Type 3 (Saukett)	-	32 D-antigen units

[a] As lower confidence limit (p = 0.95) of activity measured according to the assay described in the European Pharmacopoeia.

[b] Produced in Vero cells.

With this submission, Sanofi Pasteur seeks to obtain approval for the addition to the COVAXIS and REPEVAX Summary of Product Characteristics (SmPC) for an indication for the use of Tdap5 and Tdap5-IPVvaccines in pregnancy:

> "COVAXIS may be administered during pregnancy for prevention of pertussis in young infants."
>
> "REPEVAX may be administered during pregnancy for prevention of pertussis in young infants."

1.2 Scientific and Epidemiological Background

Epidemiology of Pertussis

Worldwide, in children younger than 5 years, there were an estimated 24.1 million cases of pertussis and an estimated 160,700 deaths from pertussis in 2014 according to a recent publication modeling these data (1). Of these, an estimated 5.1 million cases and an estimated 85,900 deaths occurred in infants younger than 1 year of age. The highest occurrence of pertussis and deaths due to pertussis are in the African and Southeast Asian regions. In the American region, in children younger than 1 year of age there were an estimated 400,000 cases of pertussis and an estimated 1,500 deaths from pertussis and in the Western Pacific region, an estimated 600,000 cases of pertussis and an estimated 1,000 deaths from pertussis. In the European region, in children younger than 1 year of age there were an estimated 300,000 cases of pertussis and an estimated 400 deaths from pertussis. Pertussis epidemics occur every 3–4 years.

In 2015, 40,195 (36,235 confirmed) cases of pertussis were reported to the European Surveillance System by 29 European Union/European Economic Area countries (2). The notification rate was 9.0 cases per 100,000 population. Infants were the most affected age group in the majority of Member States, particularly Spain and Portugal (349.2 and 205.4 cases per 100,000 population, respectively), followed by Denmark and Latvia. Age-specific rates were highest in children less than 1 year of age (73.1 cases per 100,000 population). Among infants with known months of age (84%), 85% were < 6 months of age and 57.5% were < 3 months of age.

In Canada, the highest mean incidence rates from 2005 to 2011 were among infants less than 1 year of age (72.2 cases per 100,000 population) (3). In 2012, there was a 7-fold increase in national incidence (13.40 per 100,000 population) due to outbreaks of pertussis in multiple jurisdictions across the country. In 2013 and 2014, national incidence decreased (3.63 and 4.29 per 100,000 population, respectively), followed by an increase to 9.79 per 100,000 in 2015 (3) due to outbreaks in multiple provinces (4). The rate of reported cases of pertussis was highest in children less than 1 year of age for each year from 2012 through 2015: 120.00, 44.15, 43.28, and 73.35 per 100,000 population in 2012, 2013, 2014, and 2015, respectively (3). One to 4 deaths related to pertussis occur each year in Canada, particularly in unimmunized or underimmunized infants less than 6 months of age (5).

In Australia, during a pertussis outbreak (2008–2012) the rate of pertussis peaked in the overall population in 2011 (173.5 cases per 100,000) with 333.8 cases per 100,000 in children less than 4 years of age (6). Between 2006 and 2012, infants aged < 6 months accounted for 42% (1,832 of 4,408) of pertussis-related hospitalizations. During this period there were 11 deaths attributed to pertussis; 10 of these deaths were in infants < 6 months of age (7). Rates of pertussis were lower overall in 2013 and 2014 (approximately 50 cases per 100,000) with 95.4 and 72.4 cases, respectively, per 100,000 in children less than 4 years of age (6). During 2014, there were 39 reported cases of pertussis in infants less than 6 weeks of age, and 98 reported cases in those 6 weeks to less than 4 months of age. One death, in a 7-month-old unvaccinated infant, was reported (8). In 2015 and 2016, the number of pertussis cases increased overall (94.5 and 83.1 cases per 100,000), mostly due to increased reporting in several states/territories, with 186.1 and 185.5 cases, respectively, in children less than 4 years of age (6).

Tdap Vaccination in Pregnancy

Part of protection against infectious diseases at birth is provided by maternal antibodies transported via the placenta during pregnancy (9). Severe pertussis disease, including hospitalization, intensive care unit admission and deaths, are most often seen in the first months of life prior to initiation of the primary vaccination series (10) (11) (12) (13).

Tetanus vaccination during pregnancy has been well established over several decades. Diphtheria was added when the Tetanus diphtheria (Td) product became more widely used. For adults, only combination vaccines are available against pertussis, containing also tetanus, diphtheria, and sometimes polio; depending on the manufacturer, composition differs in the number and amount of the inactivated pertussis components. Studies of pertussis vaccination during pregnancy began during the whole cell pertussis era, and continued with pediatric diphtheria, tetanus, and acellular pertussis (DTaP) combination vaccine (14) (15) (16) (17). Reactogenicity with these vaccines generally was thought to be unacceptably high. Beginning about 10 years ago, after lower-antigen, less-immunogenic Tdap vaccines became more widely available; interest in

pertussis maternal immunization grew and led to national recommendations following outbreaks in several countries.

Large database studies, several types of observational studies, as well as randomized controlled clinical trials have generated considerable safety, immunogenicity, and effectiveness data on the use of Tdap vaccine during pregnancy. Antibody responses to the antigens in Tdap vaccine in pregnant women have been shown not to differ from those in nonpregnant women and women immunized postpartum (18). The beneficial effect of maternal immunization with a pertussis-containing vaccine has been confirmed in several studies on the antibody titer in cord blood with higher concentrations of antibodies in infants until primary vaccination is started (18) (19).

There is no broad agreement regarding levels of protection for anti-pertussis antibodies (16) (18) (20) (21). Several studies have shown blunting of antibody responses, mostly for pertussis, in infants whose mothers were vaccinated during pregnancy (18) (19) (22) (23). The benefits of vaccinating during pregnancy and protecting a newborn outweigh the potential risk of blunting the infant's response to the primary series pertussis vaccine. Since infants are at greatest risk of severe disease and death from pertussis before 3 months of age – when their immune systems are least developed – any protection that can be provided is critical (24) (25).

Tdap vaccine is well tolerated in pregnant women. The incidence of solicited injection site and systemic reactions, unsolicited adverse events (AEs), and serious adverse events (SAEs) are generally similar between pregnant and nonpregnant women and consistent with reported rates for Tdap vaccine (18) (26). Studies have shown that there is no increase in risk of acute AEs or adverse birth outcomes in pregnant women who receive Tdap vaccine during pregnancy or a dose of Tdap vaccine during pregnancy after receiving a prior Tdap vaccine dose within the prior 5 years or more than 5 years prior (27) (28) (29). A slightly increased risk for chorioamnionitis has been reported in 3 large studies, although the absolute risk increases were very low (30) (31) (32).

Immunization Recommendations in Pregnancy

The United Kingdom Joint Committee on Vaccination and Immunization (JCVI) started an emergency program of vaccinating pregnant women with REPEVAX in 2012 in response to a current outbreak of pertussis. Initially REPEVAX was recommended to be used as it was the most suitable vaccine available for immediate use. The JCVI had no concerns about the safety of use of this vaccine at any stage in pregnancy. Recommendations from JCVI to maximize the protection to newborn infants was to offer immunization within the period from Week 28 to Week 38 of pregnancy and optimally from Week 28 to Week 32 (33).

In 2008, the Advisory Committee on Immunization Practices (ACIP) in the United States (US) initially recommended to replace the use of Td vaccine during pregnancy with a dose of Tdap vaccine in the immediate postpartum period and cocooning strategy for Tdap vaccination among adults and adolescents who anticipate contact with an infant aged < 12 months of age (34). Subsequently, in 2011, ACIP recommended the use of Tdap vaccine in pregnant women who previously had not received Tdap vaccine, preferably during the third or late second trimester (after 20 weeks of gestation); and if not administered during pregnancy, administered immediately postpartum (35). Further, cocooning recommendations were expanded upon for close contacts to include timing of the Tdap vaccine dose to be ideally at least 2 weeks before beginning close contact with the infant. Given the increased incidence of pertussis in the United States, the ACIP

recommendation was updated on 24 October 2012 and now recommends the use of Tdap vaccine during each pregnancy, preferably between 27 and 36 weeks of gestation, irrespective of prior vaccination history (36).

In Australia, the cocoon strategy has been recommended in the Australian Immunisation Handbook since 2003, when Tdap vaccine first became available for adolescents and adult vaccination, and has been provided and funded by state and territory governments as an outbreak response measure since 2008 to various populations at various times. In 2013, the Australian Immunisation Handbook pertussis vaccine recommendations were extended to include the option of vaccinating pregnant women in the third trimester of pregnancy, and in March 2015 this recommendation was updated to support a preference for pertussis vaccination during each pregnancy (optimally between 28 and 32 weeks), rather than postpartum (37).

In Canada, the National Advisory Committee on Immunization (NACI) updated recommendations for immunization in pregnancy with Tdap vaccine in February 2018 (38). NACI recommends that immunization with Tdap vaccine should be offered in every pregnancy, irrespective of previous Tdap immunization history. Further, NACI recommends that immunization with Tdap vaccine should ideally be provided between 27 and 32 weeks of gestation. Evidence also supports providing maternal Tdap vaccine over a wider range of gestational ages, and NACI recommends that it may be provided from 13 weeks up to the time of delivery in view of programmatic and unique patient considerations.

Additionally, the most recent World Health Organization (WHO) position paper on pertussis vaccines in September 2015 (39) includes the recommendation that national programs consider vaccination of pregnant women with 1 dose of Tdap vaccine in the second or third trimester and preferably at least 15 days before the end of the pregnancy. This maternal vaccination is an additional strategy to routine primary infant immunization in countries or settings where high or increasing infant morbidity/mortality from pertussis is present.

1.3 Overview of the Clinical Development Program

1.3.1 Rationale for Using Literature Based Submission

The sponsor opted for a literature based submission (LBS) using third party literature reviewed articles based on the following:

- The randomized clinical trials and cohort, case-coverage/-control, and observational studies currently published provide strong evidence for the safety, immunogenicity, and effectiveness of Tdap vaccination in pregnancy.
    - These studies are currently the basis for many of the country recommendations in use; JCVI, ACIP, Australian Immunisation Handbook, and NACI, as well as the most recent WHO position paper on pertussis vaccines from September 2015, are described in Section 1.2.
- Given both the existing national recommendations and the robust evidence of the effectiveness of Tdap vaccination in pregnancy, it would be unethical to perform a placebo-controlled randomized clinical trial.

- Conducting prospective placebo-controlled and/or randomized clinical trials to demonstrate a significant reduction in infant mortality and morbidity would require an extremely large sample size and would depend on pertussis epidemiology in the regions studied. Such studies would prove difficult and unwieldy, and were not undertaken by the Sponsor.

The overall objective of this Common Technical Document (CTD) is to provide data to demonstrate the safety, immunogenicity, and effectiveness of the use of Tdap vaccine during pregnancy in women and their infants, in order to add an indication and related information for Tdap5 and Tdap5-IPV vaccination during pregnancy in the European SmPC.

1.3.2 Literature Search Strategy

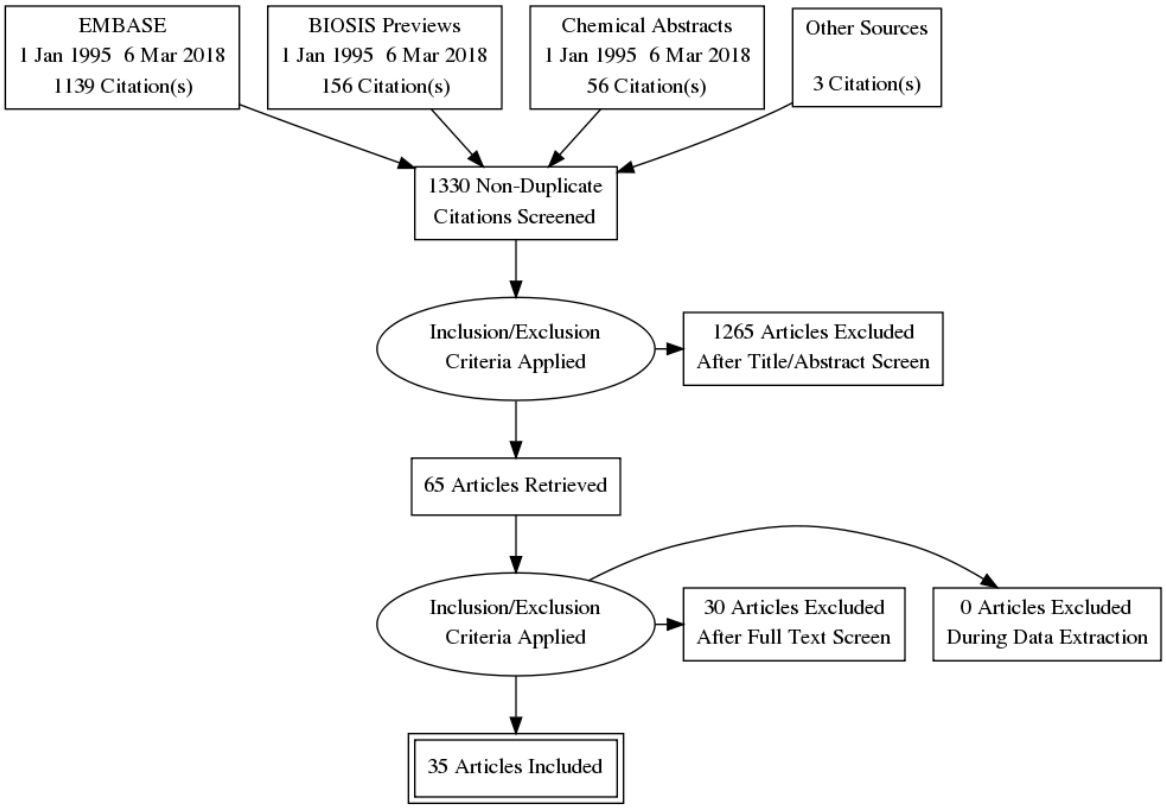
A formal literature review of pertussis vaccination during pregnancy was performed by the sponsor in January 2018. The search strategies were designed to comply with LBS guidelines and to search broadly enough to ensure that all relevant and up to date data were captured to update the prescribing information for COVAXIS and REPEVAX. Within the search and for this submission, COVAXIS and REPEVAX are to be considered equivalent vaccines for the protection against pertussis since their pertussis antigen components are identical.

The objectives of the structured literature review were to search the biomedical literature to determine: the effectiveness of COVAXIS/REPEVAX vaccination during pregnancy in the prevention of pertussis disease in young infants, the immune response to COVAXIS/REPEVAX vaccination during pregnancy in vaccinated pregnant women and their infants, and the safety of COVAXIS/REPEVAX vaccination during pregnancy in pregnant women and their infants.

The following databases were searched: EMBASE, BIOSIS Previews, and Chemical Abstracts. The majority of the articles were derived from the EMBASE database (includes MEDLINE). Given that Tdap vaccines were initially developed beginning in the mid-1990s, the search was restricted to literature published between 1 January 1995 and 6 March 2018. There were no language restrictions.

A PRISMA flow diagram of the database searches performed is provided in Figure 1. A summary of search methods are provided following the figure.

Figure 1: PRISMA Flow Diagram



Two search strategies were performed in EMBASE. The first was to search for articles related to safety/AEs related to Tdap vaccination during pregnancy. The second search was for articles related to immunogenicity/effectiveness of Tdap vaccination in pregnancy.

In the EMBASE search, 1102 publications were identified for safety/AEs and 378 for immunogenicity/effectiveness. After removing duplicates, 1088 and 376 publications, respectively were identified. The combined results were reviewed during the first stage review and a total of 15 additional duplicate publications were identified. Therefore, a total of 1139 publications were identified: 764 in the safety search, 54 in the immunogenicity/efficacy search, and 321 in both searches.

The BIOSIS search identified 156 publications, of which 20 were duplicates from the EMBASE search. A total of 136 new articles were added to the articles to be reviewed.

The Chemical Abstracts database search resulted in 56 publications. After duplicates from the EMBASE search were removed, 52 publications remained for review.

Two publications not found in the database searches above were identified via other sources such as the Canadian NACI literature review on immunization in pregnancy with Tdap vaccine (40). Additionally, 1 manuscript that is currently in press for publication was provided by the author and included.

These 1330 publications underwent 2 review processes. The first review excluded articles that were:

- Not relevant to the topic of Tdap vaccination in pregnancy
- Reviews, meta-analyses, case reports, immunization guidelines, opinion pieces, and letters to editors
- Studies on vaccination program improvement, vaccine uptake, vaccine acceptability and perception studies, and health economics studies

From this first review, 1265 articles were excluded and 65 articles were included for secondary review.

The secondary review was designed to assess more specific study criteria. First, it was determined whether the Tdap vaccine(s) used in the study were either COVAXIS or REPEVAX. The intent was to assure that studies specific to COVAXIS or REPEVAX were assessed and included in the submission. For the studies of immunogenicity and/or effectiveness, a threshold of 75% was set for the proportion of COVAXIS or REPEVAX used in the study. The 75% threshold was chosen to assure that the immunogenicity and effectiveness results were driven primarily by responses to COVAXIS or REPEVAX and not to other Tdap vaccines.

If the Tdap vaccine used was not specified in the paper, the sponsor contacted the corresponding author to get additional information about vaccine brand used if available.

For safety studies, however, a more conservative approach was used. Only studies that exclusively used Boostrix® (Tdap3) were excluded. However, safety studies where the Tdap vaccine used was unknown or was less than 75% COVAXIS or REPEVAX were included to assure that any relevant data were not omitted in the safety assessment.

After the secondary review of the 65 articles, another 30 articles were excluded for the reasons described previously and 35 articles remained for inclusion in the structured review: safety, 18 publications; safety and immunogenicity, 4 publications; immunogenicity, 9 publications; effectiveness, 4 publications

1.3.3 Assessment of Level of Evidence and Evidence Quality

Upon review of abstract or full published data, each article was assessed for its level and quality of evidence based on the criteria proposed by the United States Preventive Services Task Force (USPSTF) (41). The assessment for each article was validated by 2 expert opinions and was in line with the USPSTF standards. The levels of evidence allocated ranged from I to III with level I defined as evidence obtained from a randomized control trial and level III being based on clinical experience, a descriptive study, or case report or other type of review. Those that were considered level I carried greater weight of balanced data with fewer trial design limitations and less bias.

Level of evidence based on research design:

- I: Evidence obtained from at least one properly randomized controlled trial.
- II–1: Evidence obtained from well-designed controlled trials without randomization.

- II–2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II–3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III: Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

To assess the quality of the evidence, the USPSTF recommends a 3 category rating of the internal validity of each study: "good," "fair," and "poor" based on specific criteria for the type of study. To distinguish among *good*, *fair*, and *poor*, in general, a *good* study meets all criteria for that study design; a *fair* study does not meet all criteria but is judged to have no fatal flaw that invalidates its results; and a *poor* study contains a fatal flaw. In this LBS, evidence quality ranged from *good* to *poor*, with the majority being of *good* or *fair* quality.

The presentation of the studies in this document that were identified in the search output is ordered according to:

- the level of evidence and
- the quality of evidence

followed by the ascending date of publication.

1.4 Summary of Regulatory Interactions

Tdap5 vaccine (trade names: ADACEL®/Adacel®/COVAXIS®/Triaxis®/TRIAXIS®/ADACEL BOOST®) was first registered on 20 May 1999 in Canada, on 31 July 2001 in Germany, on 10 June 2005 in the United States, on 21 November 2005 in Australia, and is currently licensed in 67 countries, including 28 countries in the European Economic Area (EEA). In Europe, Canada, and many other countries, Tdap vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria, and pertussis in persons 4 years of age and above (10 through 64 years of age in the United States and 10 years of age and older in Australia) and is administered as a booster following primary immunization, determined on the basis of official recommendations.

Tdap5-IPV vaccine (trade names: REPEVAX®, ADACEL® POLIO, TRIAXIS® POLIO, ADACEL QUADRA) was first registered on 02 November 2001 in Germany, on 06 June 2006 in Australia, on 21 May 2010 in Canada, and is currently licensed in 42 countries, including 14 countries in the European Economic Area. Tdap-IPV vaccine is indicated for active booster immunization for the prevention of tetanus, diphtheria, pertussis and poliomyelitis in persons 3 years of age and above in European countries (4 years of age and above in Canada and international countries) and is administered as a booster following primary immunization, determined on the basis of official recommendations.

The Company Core Data Sheet for COVAXIS is version 17.0, dated 04 May 2018. This document was revised to add informational text about use of COVAXIS and REPEVAX during pregnancy.

The Company Core Data Sheet for REPEVAX is version 12.0, dated 04 May 2018. This document was revised to add informational text about use of COVAXIS and REPEVAX during pregnancy.

Throughout the remainder of this document, when a Sanofi Pasteur brand is specified, either COVAXIS or Adacel is used for Tdap5 vaccine depending on the brand administered in the reported studies; all studies reported with Tdap5-IPV vaccine used REPEVAX.

2 Overview of Biopharmaceutics

As COVAXIS and REPEVAX are inactivated, adjuvanted vaccine for intramuscular injection, no information relative to the bioavailability of the product components after administration was generated. 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, 5.3.1.1 Bioavailability Study Reports, 5.3.1.2 Comparative Bioavailability and Bioequivalence Study Report, and 5.3.1.3 In Vitro-In Vivo Correlation Study Reports, and 5.3.1 Reports of Biopharmaceutic Studies have therefore not been documented.

3 Overview of Clinical Pharmacology

No pharmacology studies have been conducted, as determination of pharmacological parameters (absorption, distribution, metabolism, and excretion) are not relevant with respect to clinical evidence and mechanism of action and do not provide useful information for determining dose recommendations.

The following serological assays, performed by Sanofi Pasteur's Global Clinical Immunology laboratory (GCI) in a blinded manner, were used to document the immune responses in the studies performed by Munoz et al (18), Halperin et al (19), Hardy-Fairbanks et al (22), and Healy et al (42).

- Response to the diphtheria vaccine antigen: neutralization test
- Response to the tetanus vaccine antigen: tetanus enzyme-linked immunosorbent assay (ELISA)
- Response to the acellular pertussis vaccine antigens:
  - Pertussis toxoid (PT) ELISA
  - Filamentous haemagglutinin (FHA) ELISA
  - Pertactin (PRN) ELISA
  - Fimbriae types 2 and 3 (FIM) ELISA
- Response to *Haemophilus influenzae* polyribosyl-ribitol- phosphate antigen: Farr-type radioimmunoassay

The remaining 9 studies used various different commercial or institutional laboratory methods to measure antibodies against the antigens in Tdap or Tdap-IPV vaccine. The methods are documented in each publication in Module 5.4.

4 Overview of Safety

The safety results from 21 publications and 1 article (Halperin et al (19)) in press identified in the literature search, the Sanofi Pasteur US Pregnancy Registry for Adacel and 1 Sanofi Pasteur-sponsored safety surveillance study that support Tdap vaccination during pregnancy are presented individually in this section.

Of the 21 publications and 1 in press article, 4 were reports of randomized clinical trials (Section 4.1), 12 were cohort or observational studies (Section 4.2), and 6 were cohort or observational studies where the Tdap vaccine brand was not specified (Section 4.3).

The Sanofi Pasteur US Pregnancy Registry for Adacel and the Sanofi Pasteur-sponsored safety surveillance study are summarized in Section 4.4.

4.1 Randomized Clinical Trials

A summary of the 4 randomized clinical trials that support the safety of Tdap vaccine in pregnant women and their infants is provided in Table 4.1.

Three publications are provided in Module 5.4 of this CTD and 1 article (Halperin et al (19)) is in press.

Safety objectives and methods are summarized for each study in [Section 2.1.1] of 2.7.4 Summary of Clinical Safety.

Ethical requirements of the studies were documented:

- All 4 randomized clinical trials were reviewed by an institutional review board and/or ethics committee and participants signed informed consent prior to participation.

Table 4.1: Randomized Clinical Trials Supporting Safety of Tdap Vaccine in Pregnant Women and Their Infants

Study Identifier	Study Design	Country/Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Munoz et al (2014) (18)	Phase I/II, randomized, double-blind, placebo-controlled, cross-over	United States Oct 2008–May 2012	Total pregnant women/infants: 48 Tdap vaccine: 33 Placebo: 15 Healthy nonpregnant women: 32	Pregnant women: Tdap5 or placebo Infants: DTaP5-IPV/Hib	I	Good
Villarreal Pérez et al (2017) (43)	Randomized, double-blind, parallel-group, placebo-controlled	Mexico Sep 2011–Aug 2014	Total pregnant women/infants: 171 Tdap vaccine: 90 Placebo: 81	Pregnant women: Tdap5 or placebo Infants: DTaP5-IPV//Hib	I	Good

Study Identifier	Study Design	Country/Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Halperin et al (2018) (19)	Randomized, controlled, observer-blinded, multicenter	Canada Nov 2007–Jun 2011 Mar 2012–Apr 2014	Pregnant women/infants: 273/272 Tdap vaccine: 135/134 Td Adsorbed vaccine: 138/138	Pregnant women: Tdap5 or Td Adsorbed Infants: DTaP5-IPV-Hib	I	Good
Hoang et al (2016) (44)	Randomized, controlled, multicenter	Vietnam Infants born: 22 Feb 2013–7 Oct 2013	Total pregnant women/infants: 103 Tdap vaccine: 52/51 Tetanus vaccine: 51/48	Pregnant women: Tdap5 or tetanus Infants: DTaP3-HBV-IPV/Hib	I	Fair

Note: The "3" or "5" designation following Tdap or DTaP is used to define the number of acellular pertussis components in the vaccine included in the study. In the individual summaries, to agree with the presentation in the publications, the numerical designation is not used unless needed for clarity (i.e., both Tdap3 and Tdap5 data presented within a study).

DTaP3-HBV-IPV/Hib: combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine, Infanrix® hexa; DTaP5-IPV//Hib: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pentaxim®; DTaP5-IPV-Hib: diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pediacel®; DTaP5-IPV/Hib: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pentacel®; Td Adsorbed: tetanus and diphtheria toxoids adsorbed vaccine; Tdap5: tetanus toxoid, reduced diphtheria toxoid, and (5-component) acellular pertussis vaccine, Adacel; USPSTF: United States Preventive Services Task Force

In 2014, Munoz et al (18) reported safety and immunogenicity results from a Phase I/II randomized, double-blind, placebo-controlled clinical trial of Tdap vaccine in pregnant women) and their infants that was conducted in the United States from October 2008 to May 2012 and was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Immunogenicity results are provided in Section 5.1.1.1 for women and in Section 5.1.2.1 for infants.

In this study, 48 healthy pregnant women and their infants and 32 healthy nonpregnant women (mean age [standard deviation (SD)], 28.9 [6.0] years) were enrolled. Thirty-three pregnant women received Tdap vaccine (mean age [SD], 28.1 [6.7] years) and 15 received placebo (27.8 [6.7] years) during pregnancy at 30 to 32 weeks of gestation. Pregnant women in the Tdap vaccine group received placebo postpartum and those in the placebo group received Tdap vaccine postpartum. The majority of pregnant women were White or Black/African American in the Tdap vaccine group (39.4% and 36.4%, respectively), the placebo group (46.7% in both groups), and in the control group (65.6% and 21.9%, respectively).

The proportion of women reporting any injection site reactions following Tdap immunization was not different between the groups (Tdap vaccine during pregnancy, Tdap vaccine postpartum, and nonpregnant women); pain was the most frequently reported across groups, and erythema and swelling were infrequent. Most symptoms were mild and resolved within 72 hours.

The proportion of women reporting any systemic symptom, and individual symptoms of headache, malaise, and myalgia were not significantly different among the 3 groups. The occurrence of fever after receipt of Tdap vaccine was significantly different between the 3 groups,

with pregnant women (3.0% [95% confidence interval (CI): 0.1%; 15.8%]) and nonpregnant women (9.4% [95% CI: 2.0%; 25.0%]) reporting it less frequently than postpartum women (26.7% [95% CI: 7.8%; 55.1%]; P = 0.044). However, the occurrence of fever in women receiving Tdap vaccine postpartum was not different from that of postpartum placebo recipients (P = 0.43). There was also no difference in the proportion of women with fever between recipients of Tdap vaccine during pregnancy and nonpregnant women (P = 0.36). Most systemic symptoms were mild and self-limited.

All infants were live born and mostly at term. There were no significant differences in the infants' gestational ages, birth weights, Apgar scores, neonatal examinations, or complications. There were no differences in the infants' growth and development, and no cases of pertussis illness occurred in mothers or infants.

There was no notable difference in the proportion of nonserious AEs in women who received Tdap vaccine during pregnancy and those who received it postpartum, or between their infants. The proportion of nonpregnant women reporting nonserious AEs was low. Serious AEs were reported by 10 women and 12 infants; none were attributed to vaccine by the investigator.

The authors concluded that this preliminary assessment did not find an increased risk of AEs among women who received Tdap vaccine during pregnancy or their infants. The authors noted that a limitation of this study was that the small number of participants potentially limited the ability to detect the occurrence of rare vaccine-related AEs, which may only be detected in large population-based studies. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2017, Villarreal Pérez et al (43) reported results of a randomized, double-blind, parallel group, placebo-controlled clinical trial that was conducted from September 2011–August 2014 in Mexico in women who received Tdap vaccine (n = 90) or placebo (n = 81) between 30 and 32 weeks of gestation. Immunogenicity results are provided in Section 5.1.1.1 for women and in Section 5.1.2.1 for infants.

The mean age (SD) was 24.2 (5.0) years in the Tdap vaccine group and 23.8 (5.0) years in the control group. Most of the women had received pertussis vaccines during childhood. There were no immediate events reported in either group. Mild local pain was the most commonly reported adverse reaction within 24 and 48 hours after vaccination in the Tdap vaccine group (22.2% and 7.8%, respectively) and in the placebo group (21.0% and 6.2%, respectively). No AEs were reported in the 30 days after vaccination in either group.

The authors concluded that the administration of Tdap vaccine in Mexican women was considered safe, with few adverse reactions occurring after vaccination; local reactions predominated. Limitations noted by the authors were related to immunogenicity and are provided in Section 5.1.1.1. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2018, Halperin et al (19) reported the results of a randomized, observer-blinded, controlled multi-center clinical trial of the safety and immunogenicity of women who received Tdap vaccine (n = 135) or tetanus and diphtheria toxoid adsorbed vaccine (Td Adsorbed®) vaccine (n = 138) during pregnancy (between 34 and 35 weeks of gestation) that was conducted from November

2007–April 2014 in Canada. Immunogenicity results are provided in Section 5.1.1.1 for women and in Section 5.1.2.1 for infants.

The mean (SD) age of women who received Td Adsorbed vaccine and Tdap vaccine was 31.4 (4.8) and 30.9 (5.3) years, respectively. Most women were White (87.0% and 79.3% in Td Adsorbed and Tdap vaccine groups, respectively).

Injection-site pain was reported by over 80% of both Td Adsorbed and Tdap vaccine recipients; most pain was described as mild or moderate and similar in both groups. Muscle aches, fatigue, and headache were reported by 16.9%–34.4% of participants. Mild fatigue was more common in Td Adsorbed than in Tdap vaccine recipients (23.4% vs. 13.3%; P = 0.041). Mild muscle ache was more common in Td Adsorbed vaccine recipients (20.4% vs. 4.4%; P < 0.001), while severe muscle aches were more common in Tdap vaccine recipients (4.4% vs. 0%; P = 0.014). Fever was not reported in any of the immunized participants.

There were 8 SAEs reported in Td Adsorbed vaccine recipients and 6 SAEs in Tdap vaccine recipients; none were assessed by the blinded local investigator to be vaccine related. There were no differences in rates of congenital abnormalities or neonatal complications between the 2 groups. There were 17 serious complications of pregnancy/labor, 9 in Td Adsorbed vaccine recipients and 8 in Tdap vaccine recipients; 4 of these events were assessed as possibly vaccine-related (1 Td Adsorbed vaccine recipient each with pre-eclampsia, premature delivery, and HELLP syndrome [hemolysis, elevated liver enzymes, low platelet count] and 1 Tdap vaccine recipient with gestational hypertension). There were 29 SAEs in infants of Td Adsorbed vaccine recipient mothers and 20 SAEs in infants of Tdap vaccine recipient mothers; none were assessed by the local investigator to be vaccine-related. No developmental differences were detected with the Bayley III assessment at 18 months of age (abnormal findings: infants of Td Adsorbed vaccine recipients: 3.2% [4/124]; infants of Tdap vaccine recipients: 3.3% [4/121]). There were no significant differences in infectious morbidity in the infants in either group; however, 5 infants of Td Adsorbed vaccine recipient mothers developed RSV and 1 infant of Tdap vaccine recipient mother developed RSV infection. No cases of pertussis were observed.

The authors concluded that this study demonstrated that Tdap vaccine is well tolerated during pregnancy. The authors noted several limitations of the study. The study was not powered to detect rare AEs following immunization or adverse pregnancy outcomes. Study sites were all in Canada and thus the results might not be generalizable to all populations. Additional limitations of this study are provided in Section 5.1.2.1. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2016, Hoang et al (44) reported results from a multicenter, randomized, controlled clinical trial of the safety and immunogenicity of women who received Tdap vaccine or tetanus vaccine between 18 and 36 weeks of gestation during pregnancy and their infants born from February 2013–October 2013 in Vietnam (44). Immunogenicity results are provided in Section 5.1.1.1 for women and in Section 5.1.2.1 for infants.

The mean (SD) age of women who received Tdap vaccine and tetanus only vaccine was 26.7 (5.3) and 26.5 (5.8) years, respectively. All women were Vietnamese. Of the 52 women in the Tdap vaccine group, 23 women experienced at least 1 solicited AE (mean duration of 1.3 days). Of the 51 women who received tetanus only vaccine, 22 women presented with at least 1 AE (mean duration of 1.2 days). The most common AEs were stiffness and swelling and itching

at the injection site. No unexpected AEs were observed following immunization in pregnant women in this study.

In total, 7 SAEs were reported in 6 women. After Tdap vaccination, fever was reported 1 day after vaccination (n = 1), and another woman complained of fatigue; both subjects were hospitalized for monitoring. Three episodes of premature contractions (all > 1 month after vaccination) were reported: 2 in the Tdap vaccine group and 1 in the tetanus only vaccine group. There was 1 preterm delivery with stillbirth at 7 months' gestational age in the tetanus only vaccine group (5 weeks following vaccination); no causal information was available.

Common symptoms of respiratory and gastrointestinal diseases were recorded in the infants; these events were not serious or related to vaccination. No congenital disorders were detected.

The authors concluded that this study adds to the scientific evidence that pertussis vaccination during pregnancy is safe and can be used as a means to close the susceptibility gap for pertussis among young infants. The authors noted that limitations of this study included drop-out rates due to people moving were unforeseen and could not be addressed; and recruiting and retaining both mothers and infants throughout the entire study protocol was not simple, but subject retention and follow-up was reasonable. Additional limitations are discussed in Section 5.1.2.1. **Overall, this study provides USPSTF evidence level I and evidence quality category of fair.**

4.2 Cohort and Observational Studies

A summary of 12 cohort and observational studies that support the safety of Tdap vaccine in pregnant women and/or their infants is provided in Table 4.2.

All publications are provided in Module 5.4 of this CTD.

Safety objectives and methods are summarized for each study in [Section 2.1.2] of 2.7.4 Summary of Clinical Safety.

Ethical requirements of the studies were documented:

- Zheteyeva et al (45) and Moro et al (46) noted that because the Vaccine Adverse Event Reporting System (VAERS) is a routine, government-sponsored surveillance system that does not meet the definition of research, their investigations were not subject to institutional review board review and informed consent requirements.
- Donegan et al (27) noted that the study protocol was approved by an Independent Scientific Advisory Committee and that no further ethical approval was required. Study uses the Clinical Practice Research Datalink (CPRD) database that includes anonymized patient information.
- Kharbanda et al (30) (47), DeSilva et al (48), and Sukumaran et al (28) noted that the studies were approved by institutional review boards and they received a waiver of informed consent.
- Morgan et al (29), Sukumaran et al (49), and Perry et al (50) noted institutional review board approval; no information on waiver of consent was noted.

- Regan et al (51) obtained consent from women for follow-up after Tdap vaccine administration from the routine vaccine safety monitoring program administered by the Western Australia Department of Health.
- Talbot et al (52) noted approval by a committee for protection of human subjects and exemption from review by the Centers for Disease Control and Prevention institutional review board.

Table 4.2: Cohort and Observational Studies Supporting Safety of Tdap Vaccine in Pregnant Women and/or Their Infants

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Zheteyeva et al (2012) (45)	Retrospective cohort (VAERS review)	United States 1 Jan 2005–30 Jun 2010	Pregnant women Tdap vaccine: 132 reports	Tdap5: 72% Tdap3: 15%: Unknown: 13%	II-2	Fair
Donegan et al (2014) (27)	Observational cohort	England Tdap-IPV during pregnancy 1 Oct 2012–31 Mar 2013 Matched historical unvaccinated pregnant women 1 Oct 2010–30 Sep 2012	Short-term risk (≥ 28 days data after vaccination): Tdap vaccine: 17,560 Overall risk (≥ 44 weeks data after estimated date of last menstrual period): Tdap vaccine: 6185 Matched historical unvaccinated: 18,523	Tdap5-IPV	II-2	Fair
Kharbanda et al (2014) (30)	Observational retrospective cohort	United States 1 Jan 2010–15 Nov 2012	Pregnant women: 123,494 Tdap vaccine: 26,229 Unvaccinated: 97,265	Tdap5 ≥ 80%[a]	II-2	Fair
Morgan et al (2015) (29)	Retrospective cohort	United States Jun 2013–Jul 2014	Pregnant women: 7378 Received Tdap vaccine: 7152 Declined Tdap vaccine: 226	Tdap5[b]	II-2	Fair

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Sukumaran et al (2015a) (49)	Retrospective cohort	United States 1 Jan 2007–15 Nov 2013	Total: Women: 36,844 Infants: 8994 Concomitant Tdap/influenza administration: Women: 8464 Infants: 4554 Sequential Tdap/influenza administration: Women: 28,380 Infants: 4440	Tdap5 > 80%[a]	II-2	Fair
Sukumaran et al (2015b) (28)	Retrospective cohort	United States 1 Jan 2007–15 Nov 2013	Pregnant women/infants Tdap vaccine: 29,155 Infants: 21,172	Tdap5 > 80%[a]	II-2	Fair
Regan et al (2016) (51)	Prospective cohort	Australia 13 Apr 2015–08 Jun 2015	Pregnant women Tdap vaccine: 1257 Tdap + Influenza vaccines: 1506 Influenza vaccine: 1584	Tdap5: 76.9% Tdap3: 23.0% Unknown: 0.1%	II-2	Fair
Moro et al (2016) (46)	VAERS review	United States 11 Oct 2011–30 Jun 2015	Pregnant women Tdap vaccine: 392 reports	Tdap5: 59.7% Tdap3: 33.2% Unknown: 7.1%	II-2	Fair
Kharbanda et al (2016) (47)	Observational retrospective cohort	United States 1 Jan 2007–15 Nov 2013	Vaccine coverage cohort: 438,487 Vaccine safety cohort: 427,097 Tdap vaccine exposed cohort: 53,855 Matched unexposed cohort: 109,253	Tdap5 ≥ 80%[a]	II-2	Fair
DeSilva et al (2017) (48)	Retrospective cohort	United States 1 Jan 2010–15 Nov 2013	Total pregnant women/infants: 197,564 Pregnant women/infants Tdap vaccine: 45,008	Tdap5 > 80%[c]	II-2	Fair
Perry et al (2017) (50)	Prospective observational	United States May 2014–Mar 2016	Pregnant women Tdap: 737 cases	Tdap5 74.1% Tdap3 25.9%[d]	II-2	Fair

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Talbot et al (2010) (52)	Observational safety	United States 1 Apr 2006–31 May 2006	Pregnant women Tdap vaccine: 16	Tdap5	III	Poor

Note: The "3" or "5" designation following Tdap is used to define the number of acellular pertussis components in the vaccine included in the study. In the individual summaries, to agree with the presentation in the publications, the numerical designation is not used unless needed for clarity (i.e., both Tdap3 and Tdap5 data presented within a study).

IPV: inactivated poliovirus vaccine; Tdap3, Tdap5: tetanus toxoid, reduced diphtheria toxoid, and (3- or 5-component) acellular pertussis vaccine, Adacel; Tdap5-IPV: REPEVAX; USPSTF: United States Preventive Services Task Force; VAERS: Vaccine Adverse Event Reporting System

[a] Elyse O. Kharbanda, MD, MPH, e-mail communication, January 16, 2018.

[b] Jamie L. Morgan, MD, e-mail communication, January 22, 2018.

[c] Malini DeSilva, MD, e-mail communication, January 16, 2018.

[d] Craig V. Towers, MD, FACOG, e-mail communication, February 9, 2018.

In 2012, Zheteyeva et al (45) reported results of a retrospective cohort study that characterized 132 reports identified in the VAERS in pregnant women who received Tdap vaccine during pregnancy from 1 January 2005–30 June 2010. A total of 95 (72%) reports indicated Adacel (Tdap5) was administered and there were 48 (36.4%) reports of Tdap vaccine administered alone. The trimester Tdap vaccine was administered was available for 110 (83.3%) reports, of which 85 (77.3%) reports indicated vaccination in first trimester. There were no AEs identified in 55 (41.7%) cases. There were no maternal or infant deaths.

The following pregnancy-specific AEs were identified: spontaneous abortion, 22 (16.7%); gestational diabetes, 7 (5.3%); oligohydramnios, 3 (2.3%); 2 (1.5%) each for induction of labor (1 chorioamnionitis reported as secondary to labor induction), stillbirth, ruptured ectopic pregnancy, preterm delivery; 1 (0.8%) each for subchronic hemorrhage by ultrasound, cesarean delivery, low-lying placenta on ultrasound, placental abruption and fetal intolerance, pre-eclampsia, prolonged labor, and toxemia.

The following non-pregnancy-specific AEs were identified: injection site reactions, 6 (4.5%); anemia, 5 (3.8%); headache or fever with abdominal pain, 3 (2.3%); 2 (1.5%) each for urinary tract infection, syncope, and upper respiratory infection; 1 (0.8%) each for influenza, nausea and vomiting, rash on arms/thigh, and superficial thrombophlebitis.

There was 1 report with a major congenital anomaly (gastroschisis).

The analysis did not reveal disproportionate reporting for spontaneous abortions in VAERS for Tdap vaccine compared with influenza vaccines. Disproportionality analysis for reports in pregnant women revealed that gestational diabetes, anemia, antepartum hemorrhage, oligohydramnios, and upper respiratory infection were reported to VAERS more frequently after Tdap vaccine than after inactivated influenza vaccines. However, further clinical review found that most of these conditions were minor, and there were no concerning patterns for these outcomes that required additional investigation.

The authors concluded that during a time when Tdap vaccine was not routinely recommended in pregnancy, review of reports to VAERS in pregnant women after Tdap vaccination did not identify any concerning patterns in maternal, infant, or fetal outcomes. The authors noted that VAERS has inherent limitations of all passive surveillance systems including underreporting, reporting biases, and inconsistency in quality of reports and that the regulatory definition of a serious report in VAERS may not reflect the true severity of an outcome. Since Tdap vaccine was not routinely recommended for use in pregnancy during the period of this review, no national survey was conducted to assessed Tdap vaccine coverage in pregnant women. Therefore, because there were no data on the number of Tdap vaccine doses administered to pregnant women, reporting rates cannot be calculated and findings are difficult to interpret. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2014, Donegan et al (27) reported results from an observational cohort study in pregnant women in the United Kingdom that examined stillbirths and other maternal and other neonatal outcomes of pertussis vaccination in pregnant women in the 6 months after initiation of the pertussis vaccine program from 1 October 2012–31 March 2013.

In total, 20,074 vaccinated pregnant women were identified in the CPRD database for the 6-month period of the study. Of these, 17,560 (87%) had ≥ 28 days of follow-up data after their vaccination record. The median age of pregnant women was 30 (26–34) years. Gestational age could be estimated for 13,371 (76%); median gestation age at vaccination was 31 (29–35) weeks.

For the primary objective, there were 5 recorded stillbirths within 2 weeks of vaccination. The expected number of stillbirths based on the Office of National Statistics (ONS) data was 7.2 stillbirths for the same period. Therefore, the observed vs. expected incidence rate ratio was 0.69 (95% CI: 0.23; 1.62), indicating no signal of a short-term increased risk of stillbirth after pertussis vaccination.

For pre-eclampsia, there was 1 event within 2 weeks after pertussis vaccination and 3 events at delivery (all live births) within 2 weeks after vaccination. There was 1 event of eclampsia after delivery. External estimates, as noted by the author, suggest a rate of 5 cases of severe pre-eclampsia per 1000 pregnancies (severity is not well recorded in the CPRD database so comparison is difficult) and 1 event of eclampsia per 2000 pregnancies.

In addition, there were 3 events of antepartum hemorrhage, 1 event of placenta previa, and 1 event of fetal distress within 14 days after vaccination. There were no events of uterine rupture, placental abruption, or vasa previa in the same timeframe.

For time to delivery, a total of 6185 vaccinated women were identified who had adequate follow-up (≥ 44 weeks after estimated date of last menstrual period) and data on pregnancy outcome and gestational age. The median age was 30 (26–34) years and they were vaccinated at a median gestational age of 33 weeks (30–36). There was no significant difference in the time to delivery in the vaccinated and matched unvaccinated cohorts (median gestation 40 weeks; HR 1.00, 95% CI: 0.97; 1.02).

For overall risk of AEs of interest, there were 12 (0.19%) events of stillbirth after vaccination (about 1 per 500 deliveries). The expected number of stillbirths based on distribution of gestational age and the ONS background data, under the assumption of no increased risk, was 15.8 stillbirths. The observed vs. expected rate ratio was 0.85 (95% CI: 0.44; 1.61). The

vaccinated women were further matched to 18,523 unvaccinated historical controls and the resulting conditional rate ratio for the overall risk of stillbirth in vaccinated vs. unvaccinated women was 0.85 (95% CI: 0.45; 1.61).

There were no significant differences in the rates of any of the pre-specified events; no safety signals were identified. There were no records of maternal death, antepartum hemorrhage, uterine rupture, placental abruption, vasa previa, fetal distress, or child renal failure after vaccination. There were no significant increases in the risk of any of the pre-defined AEs in the analysis that included all women with a pregnancy in the 6 months after vaccine program initiation regardless of vaccination status. Single events of antepartum hemorrhage and placental abruption were identified in women eligible for vaccination; there were no events of maternal death, uterine rupture, vasa previa, fetal distress, or child renal failure.

The authors concluded that in women given pertussis vaccination in the third trimester, there is no evidence of an increased risk of any of an extensive predefined list of AEs related to pregnancy. In particular, there was no evidence of an increased risk of stillbirth. Given the recent increases in the rate of pertussis infection and morbidity and mortality in neonates, these early data provide initial evidence for evaluating the safety of the vaccine in pregnancy for health professionals and the public and can help to inform vaccination policy making. The authors noted several limitations of the study. There were no a priori calculations on the power of the study. The analysis presented, in general, can exclude 2-fold risks; however, it cannot rule out smaller increases in risk, and the short study period limits the possibility of examining longer term AEs. Potential confounders that are known to be associated with the risk of AEs in pregnancy were not adjusted for in this study. However, 2 of the potentially most important confounders (maternal and gestational age) were accounted for in the analysis. It is possible that women choosing not to be vaccinated have inherently different risks because of unmeasured confounders. There is the possibility of missing event data in the CPRD database, which may have led to an underestimation of the rate of AEs. The sensitivity and specificity of the mother-child link is unknown. Given that the recommendation was for vaccination in the third trimester of pregnancy, the risk of congenital malformations was not prespecified as an AE of interest. However, this is continuously monitored through routine pharmacovigilance, and no signal of an increased risk has been raised. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2014, Kharbanda et al (30) reported results from an observational retrospective cohort study using data from 2 Vaccine Safety Datalink (VSD) sites in California to evaluate risks of selected adverse obstetric events or birth outcomes following maternal Tdap vaccination in pregnancies ending in a live birth between 1 January 2010 and 15 November 2012. A total of 123,494 eligible pregnant women were identified in the period under study. Of these, 26,229 (21.2%) received Tdap vaccine during pregnancy and 92% had the vaccine administered during the second and third trimester. The total of unexposed pregnant women was 97,265. Adacel (Tdap5) was received by ≥ 80% of pregnant women (Elyse O. Kharbanda, MD, MPH, e-mail communication, January 16, 2018).

Among women who received Tdap vaccine at any time during pregnancy, 6.1% were diagnosed with chorioamnionitis compared with 5.5% of unexposed women (adjusted relative risk [RR] = 1.19 [95% CI: 1.13; 1.26). In the subset of women vaccinated between 27 and 36 weeks of gestation, this risk was still increased but less so (adjusted RR = 1.11 [95% CI: 1.03; 1.21]). Among preterm births (< 37 weeks of gestation), there was not an elevated risk of

chorioamnionitis (adjusted RR = 0.87 [95% CI: 0.64; 1.16]). Among women with chorioamnionitis and without it, the median gestational week of vaccination was 28 weeks. In women receiving Tdap vaccine before 20 weeks of gestation, 8.2% developed a hypertensive disorder of pregnancy vs. 8.0% of unexposed women (adjusted RR = 1.09 [95% CI: 0.99; 1.20]).

Receipt of Tdap vaccine during pregnancy was not associated with increased risk of preterm or SGA births. Among all pregnancies, 8.4% of those who received Tdap vaccine during pregnancy and 8.3% who were unexposed to the vaccine had an SGA birth (adjusted RR = 1.00 [95% CI: 0.96; 1.06]). The rate of preterm delivery among women receiving Tdap vaccine during pregnancy at 36 weeks of gestation or earlier was 6.3%, whereas the rate for unexposed women was 7.8% (adjusted hazard ratio [HR] = 1.03 [95% CI: 0.97; 1.09]).The findings for SGA were similar in the subset of women vaccinated between 27 and 36 weeks of gestation. The preterm delivery rate of 5.3% among women vaccinated between 27 and 36 weeks of gestation was slightly lower than the rate of 7.8% among the unvaccinated cohort. These differences were statistically significant (adjusted HR = 0.88 [95% CI: 0.80; 0.95]).

The authors concluded that receipt of Tdap vaccine during pregnancy was not associated with increased risk of preterm delivery or SGA birth or with hypertensive disorders of pregnancy, although a small but statistically significant increased risk of being diagnosed with chorioamnionitis was observed. The authors noted several limitations in this study. The population only included pregnancies ending in a live birth. The study was limited to women from a single state with continuous insurance coverage, complete birth data available, and at least 1 medical visit during pregnancy resulting in underrepresentation of the highest-risk pregnancies, occurring in women with intermittent insurance coverage. More than 10% of women were excluded because their complete birth data were not available. Data presented reflect outcomes associated with a single Tdap vaccine dose administered during pregnancy. Because current recommendations from the ACIP are to administer Tdap vaccine in every pregnancy, continued monitoring of the safety of repeated Tdap vaccine doses in a geographically diverse population will be important. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2015, Morgan et al (29) reported the results of a retrospective cohort study of pregnancy outcomes that was conducted from June 2013–July 2014 at a hospital and its affiliated prenatal clinics in Texas. This study included a total of 7378 pregnant women and compared women who accepted Tdap vaccination (7152 [97%]) after 32 weeks of gestation (in accordance with the 2012 ACIP guidelines) with those who declined Tdap vaccination (226 [3%]) during pregnancy.

There was no difference in stillbirths, major malformations, chorioamnionitis, 5-minute Apgar score, or cord blood pH between the 2 groups. Neonatal complications including ventilation requirement, sepsis, intraventricular hemorrhage, and neonatal death were also similar. However, preterm birth rates at 36 weeks of gestation or less (6% vs. 12%, $P < 0.001$), incidence of SGA (10% vs. 15%, $P = 0.03$), and length of neonatal hospitalization (3.9 vs. 4.7 days, $P < 0.001$) were all significantly increased in the unvaccinated cohort. No difference in neonatal outcomes was noted between women who were administered at least 2 Tdap vaccines in the past 5 years (n = 1229) and those who received only a single dose (n = 4159).

The authors concluded that no adverse pregnancy outcomes were identified in association with antepartum Tdap vaccination. This remained true in women receiving more than 1 Tdap vaccine

in a 5-year timeframe. The authors noted that limitations of the study included fixed sample size, rarity of many study outcomes, and the possibility of type II error inherent to the fixed sample size, especially with regard to rare study outcomes such as stillbirth, major malformations, and neonatal death. There is also potential for unmeasured cofounders. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2015, Sukumaran et al (49) reported the results of a retrospective cohort study using data from 7 VSD sites (Washington, Oregon/Washington, Northern California, Southern California, Minnesota, Wisconsin, and Colorado) that was conducted from 1 January 2007–15 November 2013 to evaluate the safety of co-administering Tdap and influenza vaccines during pregnancy by comparing AEs after concomitant and sequential vaccination.

A total of 36,844 pregnancies were identified in which Tdap and influenza vaccines were administered: concomitantly in 8,464 (23%) pregnancies and sequentially in 28,380 (77%) pregnancies. The study cohort size for birth outcomes was 4,554 (51%) pregnancies with concomitant Tdap and influenza vaccine administration and 4,440 (49%) with sequential Tdap and influenza vaccine administration. Tdap vaccine was most often administered later in pregnancy (37% in the second trimester, 56% in the third trimester), whereas influenza vaccine was administered relatively evenly throughout pregnancy (34% given in the first trimester, 34% in the second trimester, 32% in the third trimester). Adacel (Tdap5) was received by ≥ 80% of pregnant women (Elyse O. Kharbanda, MD, MPH, e-mail communication, January 16, 2018).

Acute AEs after vaccination were rare. No statistically significant increased risk of fever or any medically attended acute AE in pregnant women vaccinated concomitantly compared with sequentially was found. When analyzing women at 20 weeks of gestation or greater during periods of influenza vaccine administration, there were no differences in preterm delivery, low-birth-weight, or SGA neonates between women vaccinated concomitantly compared with sequentially in pregnancy.

The authors concluded that concomitant administration of Tdap and influenza vaccines during pregnancy was not associated with a higher risk of medically attended adverse acute outcomes or birth outcomes compared with sequential vaccination. The authors noted several limitations of the study. The study analyzed only acute events in women who sought medical care. Chart review was not used to determine if an adverse outcome was related to vaccination. The study relied on birth weight and gestational age data from the electronic medical record and birth certificates. In the analysis, adjustment for all potential confounders, including race and ethnicity, smoking status, and prior preterm delivery were unable to be done. Finally, there was no long-term follow-up of the infants to monitor for any AEs. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2015, Sukumaran et al (28) reported the results of a retrospective cohort study that assessed whether receipt of Tdap vaccine during pregnancy administered in close intervals from prior tetanus-containing vaccinations is associated with acute maternal AEs and adverse birth outcomes using data from 7 VSD sites (Northern California, Southern California, Colorado, Minnesota, Oregon, Washington, and Wisconsin) from 1 January 2007–15 November 2013.

Women who received Tdap vaccine in pregnancy following a prior tetanus-containing vaccine less than 2 years before, 2 to 5 years before, and more than 5 years before were included. Women

who were vaccinated with Tdap vaccine in pregnancy and had a prior tetanus-containing vaccine more than 5 years before served as controls.

A total of 29,155 pregnancies were identified; the majority of Tdap vaccinations were administered from 2010 through 2013 (98.1%), and most were administered in 2013 (54.0%). In the overall cohort, Tdap vaccine was most often administered in the third trimester (67.4%). Maternal age, length of enrollment, and gestational age at Tdap vaccination were significantly different in the 3 study groups ($P < 0.001$). Most pregnant women who received a prior tetanus-containing vaccine less than 2 years before (94%) and 2 to 5 years before (85%) their current Tdap vaccine had previously received Tdap vaccine (as opposed to a non-Tdap tetanus-containing vaccine) vs. only 17% of controls ($P < 0.001$). Adacel (Tdap5) was received by ≥ 80% of pregnant women (Elyse O. Kharbanda, MD, MPH, e-mail communication, January 16, 2018).

There were no statistically significant differences in rates of medically attended acute AEs (fever, local reactions [limb pain, limb swelling, cellulitis, lymphadenitis, and Arthus reaction], and allergic reactions [allergy, urticaria, and anaphylaxis]) or adverse birth outcomes (preterm delivery, low birth weight, and SGA) related to timing since prior tetanus-containing vaccination.

The authors concluded that among women who received Tdap vaccination during pregnancy, there was no increased risk of acute AEs or adverse birth outcomes for those who had been previously vaccinated less than 2 years before or 2 to 5 years before compared with those who had been vaccinated more than 5 years before. These findings suggest that relatively recent receipt of a prior tetanus-containing vaccination does not increase risk after Tdap vaccination in pregnancy. The authors noted several limitations of the study. There was limited power for the acute AEs analysis. Women with no prior documented tetanus-containing vaccination were excluded, which comprised 52% of the Tdap-vaccinated cohort, to reduce misclassification. There is the potential for some confounding due to differences in the type of vaccine received because the majority of the women in the study who were vaccinated with tetanus-containing vaccines less than 2 years before received Tdap vaccine and those vaccinated more than 5 years before had previously received Td vaccine. Additionally, medical charts were not reviewed to validate the AEs, which would correct for any potential overestimation of the rates of acute reactions following Tdap vaccination in pregnancy. Finally, the VSD population is an insured population, and these findings may not be generalizable to the entire US population. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2016, Regan et al (51) reported results from a prospective cohort study conducted in Western Australia using the routine vaccine safety monitoring program that assessed the reactogenicity of pertussis and influenza vaccines administered during pregnancy. Complete AE information following immunization was obtained from 1584 (84.4%) women who received trivalent influenza vaccine (TIV), 1257 (88.1%) who received Tdap vaccine exclusively, and 1506 (81.4%) who received TIV and Tdap vaccines concomitantly. There was no difference in demographic characteristics of women by vaccine type. The majority (97.3%) of women who received a Tdap vaccine during pregnancy were in the third trimester; whereas, the majority of women who received TIV (exclusively) during pregnancy were in the second trimester of pregnancy (55.0%; $P < 0.001$). One-half of women who were immunized with TIV received Vaxigrip® (54.1%), 40.4% received Fluvax®, 4.7% received Fluarix®, and 0.8% received another brand of TIV. The majority of women who were immunized with Tdap vaccine received Adacel

(Tdap5) (76.9%); 23.0% received Boostrix (Tdap3), and 0.1% received an unknown brand of Tdap vaccine.

Follow-up took place between 13 April 2015 and 08 June 2015. A total of 468 (10.8%) women reported an AE following immunization. There was no difference in the proportion of women who reported an AE following immunization by vaccine group; 10.3% of women who received TIV reported experiencing an AE following immunization within 7 days of vaccination. Similarly, 11.4% of women who received Tdap vaccine and 10.7% of women who received TIV and Tdap vaccines concomitantly reported experiencing an AE following immunization (P = 0.39 and P = 0.77, respectively). A total of 2.4% of women reported a fever following vaccination; there was no difference in the proportion of women who reported a fever by vaccine type (P ≥ 0.44).

Overall, 5.1% of women reported a local reaction, or pain or swelling at the injection site. Local reactions were more commonly reported in women who received Tdap vaccine or Tdap and TIV vaccines concomitantly as compared to women who received TIV. There was no significant difference in the proportion of women who reported an AE or local reaction following immunization, by Tdap vaccine brand or by TIV brand. A similar trend in AEs was observed when restricting the analysis to vaccinations administered in third trimester. Women who received pertussis vaccine in third trimester were more than twice as likely to report a local reaction as compared to women who received influenza vaccine in the third trimester (odds ratio [OR]: 2.50; 95% CI: 1.32; 4.74), but were just as likely to report a rash (OR: 3.31; 95% CI: 0.43; 25.76). For medically attended events, there was no difference in the proportion of women who received TIV (2.0%), Tdap vaccine (1.6%) or TIV and Tdap vaccines (1.5%) concomitantly.

A record of pertussis vaccination in 2012 was located for 70 (2.5%) of the women who received a Tdap vaccine in 2015. Women who received a Tdap vaccine dose in 2011/2012 and 2015 more frequently reported experiencing any AE following immunization compared to women who had no dose recorded in 2011/2012 (P = 0.04) and had significantly greater odds of visiting a general practitioner for treatment of an AE following immunization (P = 0.03). There was evidence suggesting women who received a Tdap vaccine dose in 2011/2012 and 2015 were at greater odds of reporting pain or swelling at the injection site compared to women who did not receive a dose in 2011/2012 (OR: 2.00; 95% CI: 0.94; 4.25), although this difference was not statistically significant (P = 0.06).

The authors concluded that the results support the safety of TIV and Tdap vaccines administered exclusively or in combination during pregnancy, with a slight increase in mild, expected AEs following Tdap vaccine. Given the low incidence of febrile and other systemic reactions reported by recently immunized pregnant women, these results support the safety of antenatal influenza and pertussis vaccination. The authors noted several limitations of the study. Events reported by women in this study were not medically verified, indicating the results are subject to some reporting bias. This study was designed to monitor women prospectively 7 days post-vaccination; events occurring after this period would not be captured. However, no events were reported to the state's passive AE monitoring program in pregnant women outside of this study. The use of short message service may have somehow influenced the measurement of AEs following immunization; however, because the same method was used to collect information for TIV and Tdap vaccines, this would not have impacted the comparisons. Additionally, this study was underpowered to examine rare medically attended events (e.g., anaphylaxis). Future research may

wish to address these types of events specifically. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2016, Moro et al (46) reported results of a VAERS review of pregnant women who received Tdap vaccine that characterized reports to VAERS in pregnant women who received Tdap vaccine after the updated recommendation in 2011 from ACIP for all pregnant women to routinely receive a dose of Tdap vaccine (2011–2015) and compared the pattern of AEs with the period before the updated recommendation (2005–2010).

There were 132 reports of Tdap vaccination identified in VAERS before the recommendation, as reported by Zheteyeva et al (45). After the recommendation, there were a total of 392 reports of Tdap vaccination. In 329 (83.9%) reports, Tdap was the only vaccine received, including 234 (59.7%) reports where Adacel (Tdap5) was received. The trimester Tdap vaccine was administered was available for 333 (84.9%) reports, of which 264 (79.2%) reports indicated vaccination in third trimester compared to 4% before the recommendation.

After the recommendation there was 1 neonatal death and no maternal deaths; none were reported before the recommendation. The most frequent pregnancy-specific outcome was oligohydramnios (12 [3.1%] reports) followed by stillbirth and preterm delivery (11 [2.8%] reports each). The most frequent non-pregnancy-specific outcomes were injection site reactions (47 [11.9%] reports) and systemic reactions (e.g., fever, chills; 17 [4.3%]) reports). There was an increase in proportion of reports observed for stillbirths (from 1.5% to 2.8%) and injection site reactions/arm pain (from 4.5% to 11.9%) compared to the period before the recommendation. There was a decrease in reports of spontaneous abortion noted (from 16.7% to 1%) compared to the period before the recommendation.

A total of 26 reports of repeat Tdap vaccine were received in VAERS; 13 reports included AEs: 4 reports of injection site pain or arm pain; 2 reports each of oligohydramnios, intrauterine growth restriction/poor fetal growth, and elevated blood pressure/abdominal pain; and 1 report each of stillbirth with trisomy 12, maternal urinary tract infection, and maternal systemic reactions (e.g., fever, chills).

The authors concluded that no new or unexpected vaccine AEs were noted among pregnant women who received Tdap vaccine after routine recommendations for maternal Tdap vaccination. Changes in reporting patterns would be expected, given the broader use of Tdap vaccine in pregnant women in the third trimester. The authors noted that VAERS has inherent limitations of all passive surveillance systems including under reporting, reporting biases, and inconsistency in quality of reports. Some of these limitations were noted in this review as it was observed that almost a third of reports originated from 1 facility which accounted for half of all pregnancy-specific conditions. Events occurring temporally closer to the time of vaccination are more likely to be reported to VAERS. Therefore, VAERS data must be interpreted with caution and cannot generally be used to assess causality. The regulatory definition of a serious report in VAERS can have limitations as it may not reflect the true severity of an outcome. An important limitation of VAERS is its inability to calculate the incidence or prevalence of AEs because data on the number of pregnant women vaccinated are not collected. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2016, Kharbanda et al (47) reported results from an observational retrospective matched cohort study using data from 7 VSD sites in 6 states (California, Colorado, Minnesota, Oregon,

Washington, and Wisconsin) to describe selected safety outcomes (i.e., medically attended acute events, neurologic events, proteinuria, and venous thromboembolism) following maternal Tdap vaccination in women with a live birth from 1 January 2007–15 November 2013.

The vaccine coverage cohort consisted of 438,487 pregnancies. During the study period, receipt of Tdap vaccine during pregnancy was 14%. The first increase in Tdap vaccinations in pregnant women occurred in 2010. By 2013, 41.7% of women with live births received Tdap vaccine during pregnancy with most vaccinations (75%) occurring in the third trimester (≥ 28 weeks of gestation). Adacel (Tdap5) was received by ≥ 80% of pregnant women (Elyse O. Kharbanda, MD, MPH, e-mail communication, January 16, 2018).

The vaccine safety cohort consisted of 427,097 pregnancies, with 59,878 (14%) of these pregnant women receiving Tdap vaccine during pregnancy. The final matched cohort contained 53,885 women exposed to Tdap vaccine during pregnancy and 109,253 women who were not exposed to Tdap vaccine during pregnancy. Most women were between 20 and 34 years of age (73%) and > 95% received medical care in their first trimester. As compared to the unvaccinated, women receiving Tdap vaccine during pregnancy were slightly less likely to be hospitalized before the vaccine/index date (8.3% vs. 9.1%) and they were more likely to have adequate/plus prenatal care (78.8% vs. 74.6%).

There were 43 (8.1 per 10,000) medically attended events (i.e., allergic reaction, fever and malaise, seizure, altered mental status, or local or other reaction) reported in the 0–3 days following receipt of Tdap vaccine at any time during pregnancy compared with 74 events (6.8 per 10,000) in unvaccinated women within 3 days of their matched index date (adjusted incidence rate ratio [IRR] = 1.19 [95% CI: 0.81; 1.73]). Of the 0–3 day outcomes, there was an increased rate of fever following Tdap vaccination compared with the matched 3-day window in the unvaccinated cohort (2.8 vs. < 1 per 10,000; adjusted IRR = 5.4 [95% CI: 2.1; 13.9]). Neurologic events, proteinuria, and venous thromboembolism did not differ significantly within 42 days between the vaccinated and unvaccinated cohorts.

In the subset of women receiving Tdap vaccine at ≥ 20 weeks of gestation, as compared to their unvaccinated matches, there was no increased risk for incident gestational diabetes, thrombocytopenia, venous thromboembolism, or predefined cardiac events within 42 days of vaccination.

The authors concluded that in this study, in the year following ACIP recommendations to administer Tdap vaccine in every pregnancy, 41.7% of women with live births across multiple health systems were vaccinated. There were no observed increased risks for any pre-specified maternal safety outcomes within 42 days of vaccination. Continued efforts to promote Tdap vaccination during pregnancy are needed. Several limitations were noted by the authors. First, in the assessment of Tdap vaccine coverage, the cohort only includes women with live births and continuous health insurance and from specific geographical regions. Tdap vaccine coverage during pregnancy may be lower in women with interrupted insurance coverage and in women from other regions of the United States. The data is limited to pregnancies for the period 2007–2013. This may have led to missing more recent increases in Tdap vaccine coverage. Second, for the evaluation of Tdap vaccine safety, analyses were limited to specific pre-specified maternal events. These outcomes do not represent all relevant outcomes for assessment of maternal vaccine safety and thus the findings should be considered in conjunction with other large post-marketing

studies of maternal Tdap vaccine safety. Finally, as an observational study, unmeasured or residual confounding is possible. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

An increased risk of diagnosed chorioamnionitis in women vaccinated with Tdap vaccine during pregnancy was previously detected at 2 VSD sites in a study reported by Kharbanda et al (30) in 2014 as presented above.

In 2017, DeSilva et al (48) reported the results of a retrospective cohort study using data from 7 VSD sites (Northern California, Southern California, Colorado, Minnesota, Oregon, Washington, and Wisconsin) that re-evaluated the association of chorioamnionitis and other risks after maternal Tdap vaccination for pregnancies ending in a live birth between 1 January 2010 and 15 November 2013. The analyses included 197,564 pregnancies ending in a live birth identified among women 14–44 years of age: 152,556 (77.2%) unexposed; 45,008 (22.8%) Tdap-exposed, with 22,772 vaccinations between 27–36 weeks of gestation during 2010–2013 in California and 2012–2013 for the other sites. Adacel (Tdap5) was received by ≥ 80% of pregnant women (Malini DeSilva, MD, e-mail communication, January 16, 2018).

Chorioamnionitis was recorded in 6.4% of women who received Tdap vaccination any time during pregnancy and 5.2% of women who did not (adjusted RR [95% CI]: 1.23 [1.17; 1.28]). This association was not found in women delivering at < 34 weeks gestational age (adjusted RR [95% CI]: 0.87 [0.59; 1.30]). Compared with unvaccinated women, there were no significant increased risks (adjusted RR [95% CI]) for transient tachypnea of the newborn (1.03 [0.96; 1.11]), neonatal sepsis (1.06 [0.91; 1.23]), neonatal pneumonia (0.94 [0.72; 1.22]), respiratory distress syndrome (0.91 [0.66; 1.26]), newborn convulsions (1.16 [0.87; 1.53]), or the composite outcome including any of these outcomes (1.04 [0.98; 1.11]) in infants born to Tdap-vaccinated women. Results were similar when evaluating vaccinations given during the recommended time period and when stratifying the results by gestational age at birth.

The authors concluded that despite an observed association between maternal Tdap vaccination and maternal chorioamnionitis, no increased risk for clinically significant infant outcomes associated with maternal chorioamnionitis were identified. This study supports the safety of maternal Tdap vaccination for infant outcomes. The authors noted several limitations of the study. One limitation of this study was the small number of infants born < 34 weeks gestation, as much of the literature related to chorioamnionitis and neonatal outcomes has focused on early premature infants. Although the majority of infants in the study were born >34 weeks gestational age, the lack of an association between maternal Tdap vaccination and infant infections, respiratory problems, and convulsions is important. The results for infants born at gestational age < 34 weeks were consistent with results for the entire cohort, but the CIs were larger. A second limitation of this study was reliance on electronic health record data, specifically diagnostic codes; chart reviews to validate the infant outcomes were not performed. Differences between countries and over time make it difficult to compare the background rates in this study with published rates. Selection bias may have occurred due to the inclusion criteria requiring continuous insurance enrollment and a prenatal clinic visit, thus excluding many high risk pregnancies where adverse neonatal outcomes may be more common. However, the inclusion criteria also allowed for the exposure of interest to occur; maternal Tdap vaccination would be unlikely to occur if a patient does not present for prenatal care. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2017, Perry et al (50) reported results from a prospective observational study conducted in the United States from May 2014–March 2016 that evaluated solicited reactions and vaccination experience following Tdap vaccination during pregnancy. A total of 737 patients were evaluated. The mean age was 28.6 years (range, 16–44 years). The mean gestational age at the time of vaccination was 30.1 weeks (± 2.9 weeks), 86% of the population was white (non-Hispanic). Of the patients that participated, 496 (67%, 95% CI: 64%; 71%) had at least 1 reaction to the vaccination, and 187 (25%, 95% CI: 22%; 29%) had 2 reactions or more. The most common reaction was pain/soreness at the injection site, 476 (65%, 95% CI: 61%; 68%). Of the 737 cases, 546 (74.1%) were administered Adacel (Tdap5) (362 [66%] had at least 1 reaction) and 191 (25.9%) were administered Boostrix (Tdap3) (134 [70%] had at least 1 reaction); there was no difference between these results (P = 0.37) (Craig V. Towers, MD, FACOG, e-mail communication, February 9, 2018).

Of 33 patients co-vaccinated with Tdap and influenza vaccines, 24 had a Tdap vaccine reaction and 9 did not have a reaction (P = 0.62). Of 25 patients co-administered Tdap vaccine and Rh hyperimmune globulin, 20 had a Tdap vaccine reaction and 5 did not have a reaction (P = 0.19). Therefore, co-administration of Tdap and influenza vaccines or Tdap vaccine and Rh hyperimmune globulin did not appear to increase the development of a Tdap vaccine reaction.

The presence of common medical disorders (diabetes, hypertension, and other chronic illnesses) did not increase the risk for developing a Tdap vaccine reaction. The only other identified reactions were 12 (1.6%) cases of itching, 7 (0.9%) with severe fatigue, and 3 (0.4%) with a severe headache.

Overall, the majority of patients stated that the vaccination was tolerated; 24 patients (3%, 95% CI: 2%; 5%) stated that they would not accept receipt of Tdap vaccine in a subsequent pregnancy because of the response that occurred in the current pregnancy.

The authors concluded that these data demonstrate that maternal reactions following receipt of Tdap vaccine are common (two-thirds of the study population). A potential concern is the finding that some patients might refuse a repeat vaccination in a subsequent pregnancy due to these reactions. The authors noted that limitations of the study included whether patients had received Tdap vaccine in a prior pregnancy or whether they had received the vaccination for other reasons within 2–5 years of the study administration was not assessed. Additionally, the patient population was 86% white (non-Hispanic) and may not be fully extrapolated to a generalized pregnant population. Another limitation is that even though the study did not show a higher Tdap vaccine reaction rate in patients that were co-administered Tdap and influenza vaccines or Tdap vaccine and Rh hyperimmune globulin; this could represent a type 2 error. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2010, Talbot et al (52) reported the results of a observational study to describe reactogenicity of Tdap vaccine in a subset of pregnant women who received the vaccine during pregnancy at a medical center in New England as part of a vaccination campaign during a respiratory illness outbreak in 2006. A total of 16 pregnant women received Tdap vaccine in this study; 4, 8, and 4 in the first, second, and third trimesters, respectively. The most commonly reported solicited AE was injection site pain (80.0% and 78.6% of 2-week survey respondents and daily survey respondents, respectively), followed by injection site redness (30.0% and 30.8%, respectively), injection site swelling (10.0% and 30.8%, respectively), and subjective fever (20.0% and 7.1%, respectively).

Medical visits were reported by 42.9% of daily survey respondents. One pregnant woman reported severe swelling at the injection site; all other reported solicited events were moderate in intensity. No unsolicited AEs or SAEs were reported. All 16 women reported giving birth to full-term infants who had normal newborn evaluations.

The authors concluded that the results of this study (for the overall population) add to the body of evidence that a short interval between tetanus-containing vaccine and a single dose of Tdap vaccine is safe. The authors noted that limitations of the study included that the study may have overestimated rates of AEs because health care personnel who experienced more severe reactions may have been more likely to respond to the survey. This study also relied on self-reported Td/tetanus toxoid vaccine history, taken as long as a week after vaccination for the daily survey, and a month for the 2-week survey. To demonstrate that these self-reports were accurate, in a subset of these survey respondents, self-reports of whether previous Td/tetanus toxoid was $< \text{or} \geq 2$ years ago were compared against the medical record and it was found that 93% of reports were accurate. **Overall, this study provides USPSTF evidence level III and evidence quality category of poor.**

4.3 Publications With Unspecified Tdap Vaccine

Table 4.3 summarizes 6 cohort and observational studies that report safety outcomes in women who received Tdap vaccine during pregnancy and/or their infants. In these studies, the brand of Tdap vaccine was not specified.

All publications are provided in Module 5.4 of this CTD.

Safety objectives and methods are summarized for each study in [Section 2.1.3] of 2.7.4 Summary of Clinical Safety.

Ethical requirements of the studies were documented:

- Shakib et al (53), Berenson et al (32), Zerbo et al (54), and Layton et al (31) had their studies reviewed and approved by an institutional review board(s). Shakib et al noted that a waiver of informed consent was granted by the institutional review boards and Layton et al used de-identified insurance claims data and no informed consent is required. Informed consent was not mentioned in other publications; Berenson et al extracted data from electronic medical records and Zerbo et al used data from the Kaiser Permanente Northern California (KPNC) pregnancy database.
- Datwani et al (55) and Moro et al (56) reported results from reviews that used the VAERS database. Because VAERS is a routine, government-sponsored surveillance system that does not meet the definition of research, these 2 studies were not subject to institutional review board review and informed consent requirements.

Table 4.3: Cohort and Observational Studies in Pregnant Women and/or Their Infants With Brand of Tdap Vaccine Not Specified

Study Identifier	Study Design	Country /Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Shakib et al (2013) (53)	Retrospective cohort	United States May 2005–Aug 2009	Pregnant women: Tdap: 138 Unvaccinated: 552	Tdap	II-2	Fair
Datwani et al (2015) (55)	VAERS review	United States 1 Jul 1990–2 Feb 2014	3389 pregnancy reports	Tdap	II-2	Fair
Berenson et al (2016) (32)	Retrospective review	United States 1 Nov 2012–30 Jun 2014	Pregnant women Tdap: 1109 Unvaccinated: 650	Tdap	II-2	Fair
Zerbo et al (2016) (54)	Retrospective cohort	United States 1 Jan 2009–1 Oct 2015	Infants of mothers who received Tdap: 148,699	Tdap DTaP-HBV-IPV	II-2	Fair
Layton et al (2017) (31)	Cohort study	United States 2010–2014	1,079,034 deliveries Tdap Optimal prenatal (27+ weeks): 123,780 Early prenatal (< 27 weeks): 25,037 Postpartum: 59,040 Unvaccinated: 871,177	Tdap	II-2	Fair
Moro et al (2017) (56)	VAERS review	United States 1 Jan 1990 – 31 Dec 2014	Reports of major birth defects following vaccination during pregnancy: Total: 50 Tdap: 9	Tdap	II-2	Fair

DTaP-HBV-IPV: diphtheria and tetanus toxoids and acellular pertussis, hepatitis B virus, and inactivated poliovirus vaccine, Pediarix®; Tdap: tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine; USPSTF: United States Preventive Services Task Force; VAERS: Vaccine Adverse Event Reporting System

In 2013, Shakib et al (53) reported the results of a retrospective cohort study of pregnancy and birth outcomes in infants born to women who did (n = 138) or did not (n = 552) receive Tdap vaccine during pregnancy at Intermountain Healthcare in Utah from May 2005–August 2009. The mean age of pregnant women was 27 years for both cases (range = 14–40) and controls (range = 14–43) (P = 0.735). Of the 138 immunized women, 87 (63%) received Tdap vaccine in the first trimester, 24 (17%) in the second, and 27 (20%) in the third. During this time, Tdap vaccine was given most commonly as wound prophylaxis. The incidence of spontaneous or elective abortion was no greater in Tdap vaccine cases than in controls. Of the 138 women who

received Tdap vaccine during a pregnancy, 4/138 (2.9%; 95% CI: 0.9%; 7.7%) had spontaneous or elective abortions compared with 49/552 (8.9%; 95% CI: 6.7%; 11.6%) of controls (P = 0.019). No pregnancy in Tdap vaccine cases resulted in stillbirth, 5 (0.9%) control pregnancies resulted in a stillborn infant. There were no significant differences in preterm delivery, gestational age, or birth weight between groups. One or more congenital anomaly was identified in 3.7% (95% CI: 1.2%; 8.5%) of case infants and 4.4% (95% CI: 2.7%; 6.5%) of control infants (P = 0.749). In infants born to women receiving Tdap vaccine during pregnancy, 3.6% (0.8%; 10.2%) had International Classification of Diseases, Ninth Revision–Clinical Modification (ICD-9-CM) diagnoses consistent with complex chronic conditions within 12 months compared with 10.4% (95% CI: 7.2%; 14.4%) of infants of controls (P = 0.054).

The authors concluded that documented Tdap vaccine administration during pregnancy was uncommon and occurred most often in the first trimester as prophylaxis following trauma. No increase in adverse outcomes was identified in infants born to women receiving Tdap vaccine compared with infants of controls. The authors noted several limitations: Tdap vaccine administration was uncommon and the cohort was small; it is possible that miscoding in pregnancy and birth outcomes may have occurred, and other factors such as parity, previous pregnancy loss, and family history of congenital conditions could have affected the study findings; and data were observational and collected retrospectively. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2015, Datwani et al (55) reported the results from a review of 3389 pregnancy reports in the VAERS database from 1 July 1990–2 February 2014. There were a total of 31 chorioamnionitits reports, of which of 18 met criteria for clinical chorioamnionitis, 9 for histological, 3 for both, and 1 undetermined. Of these reports, 8 (26%) were associated with Tdap vaccine: 5 (16.1%) Tdap vaccine only, 2 (6.4%) trivalent inactivated influenza vaccine (IIV3) and Tdap vaccine, and 1 (3.2%) quadrivalent human papillomavirus vaccine (HPV4) and Tdap vaccines. Other reports were associated with: 8 (25.8%) HPV4 vaccine, 7 (22.6%) 2009 inactivated H1N1 vaccine, 3 (9.7%) 2009 inactivated H1N1 and IIV3 vaccines, 2 (6.4%) IIV3, and 1 (3.2%) each for hepatitis B (HepB) + varicella (VAR) + Td vaccines, measles, mumps, and rubella (MMR) + VAR vaccines, and VAR vaccine. Adverse pregnancy and neonatal outcomes among chorioamnionitis reports included the following: 9 (29%) reports of fetal death (3 spontaneous abortions and 6 stillbirths); 22 live births (71%) which included 6 (19%) reports of preterm birth and 16 (52%) reports of term birth; 2 (6%) reports of postpartum hemorrhage and 1 (3%) report of maternal admission to the intensive care unit.

The authors concluded that this review of VAERS database over a period of 24 years found few cases of chorioamnionitis following receipt of any vaccine reported to VAERS, which does not suggest a safety concern. The authors noted several limitations. VAERS is a passive surveillance system that may be prone to biased reporting (over- or underreporting) and inconsistency in the completeness and quality of reports. Because VAERS accepts reports from any reporter, the information provided by individuals with little or no medical training, may adversely affect the quality of the report. Events that occur close to the time of vaccination are more likely to be reported. VAERS also generally cannot determine whether a vaccine caused an AE. Stimulated reporting can occur after publicity around a potential AE. VAERS does not collect data on the number of individuals vaccinated; therefore, it is not possible to calculate the incidence or

prevalence of AEs. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2016, Berenson et al (32) reported the results of a retrospective review of medical charts at a southeast Texas public hospital to compare maternal and infant outcomes from pregnant women who delivered a singleton infant between 1 November 2012 and 30 June 2014 and received (n = 1109) or did not receive (n = 650) Tdap vaccine during pregnancy. The mean gestational age at vaccination was 30.3 ± 4.6 weeks (median 29.8 weeks, range: 1 week–40 weeks), with 75.3% of women (835/1109) receiving the vaccine within the recommended interval of 27–36 weeks gestation. Most women were Hispanic (50.0% and 38.9%, respectively, of women who received or did not receive Tdap vaccine during pregnancy) or White (29.8% and 33.8%, respectively). Maternal Tdap vaccination was associated with decreased odds of cesarean delivery (vaginal, 405 [62.3%] and 759 [68.4%]; cesarean, 245 [37.7%] and 350 [31.6%; vaginal compared to cesarean, adjusted OR = 0.78 [95% CI: 0.63; 0.98], P = 0.03). There were no associations observed between maternal Tdap vaccination and the other pre-specified maternal outcomes (i.e., chorioamnionitis, postpartum endometritis, preterm delivery, preterm premature rupture of membranes, induced labor) or infant outcomes (low birth weight, very low birth weight, SGA, 5-minute Apgar score, birth defects, and neonatal intensive care unit admission).

The authors concluded that Tdap vaccination during pregnancy does not increase the risk of adverse outcomes. The authors noted several limitations for the study. The relatively small sample size led to low power to detect significant differences for individual outcomes with low frequencies. The analysis included only conditions that providers noted on their patients' medical charts, and considered the outcome absent if not noted. The study included all women who were vaccinated regardless of whether they received the vaccine during the recommended window (27–36 weeks gestation). The retrospective study design may have resulted in residual confounding by including categories that were too broad or other unaccounted for factors. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2016, Zerbo et al (54) reported the results of a retrospective cohort study, using the database established by linking KPNC live births and their mothers, that evaluated the association between receipt of Tdap vaccine during pregnancy and fever 0–3 days after the first dose of a DTaP-containing vaccine in 148,699 infants who were born from 1 January 2009–1 October 2015 at gestational age ≥ 37 weeks and received their first dose of DTaP combination vaccine between 6 and 10 weeks of age. Among these infants, 2005 (1.4%) had a fever 0–3 days post-immunization. Tdap vaccination during pregnancy was not associated with infant fever 0–3 days after first dose of DTaP (adjusted OR = 0.92, 95% CI: 0.82; 1.04). Risk of fever did not vary by Tdap vaccine receipt during either the second or third trimester.

The authors concluded that no association between maternal Tdap vaccination and infant fever during 0–3 days after a first dose of DTaP vaccine was found. The authors noted several limitations. Infant fever was limited to those who came to medical attention. Medical records were not reviewed to determine the exact cause of fever. Post-vaccination fever with regard to vaccines administered concomitantly with DTaP was not analyzed. The effect of breastfeeding was not taken into account. The use of last menstrual period to determine gestational age in certain women may have affected the accuracy of the trimester specific results. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2017, Layton et al (31) reported the results of an administrative US insurance claims-based cohort study of adverse birth outcomes and timing of Tdap vaccine administration that compared women (N = 1,079,034) with optimal prenatal (27+ weeks; n = 123,780) or early prenatal (< 27 weeks; n = 25,037) Tdap immunization during pregnancy with those not immunized in pregnancy (871,177) during 2010–2014. Women who received Tdap vaccine postpartum (n = 59,040) were also included. A total of 677,075 linked newborns were identified; 11.5% were immunized optimally and 2.3% immunized early. In all women who received Tdap vaccine, the most common medically-attended adverse reactions experienced were pain in limb or fever. There was 1 case of anaphylaxis in a women who received Tdap vaccine postpartum, 12 cases of maternal encephalopathy occurred in women who received Tdap vaccine in the optimal or postpartum periods (all post-delivery), and no cases of GBS. Optimally-timed Tdap immunization was associated with small increased RRs of: chorioamnionitis (RR = 1.11, [95% CI: 1.07; 1.15], overall risk = 2.8%), and postpartum hemorrhage (RR = 1.23 [95% CI: 1.18; 1.28], overall risk = 2.4%) as compared to women who did not receive Tdap vaccine during pregnancy; however, these relative increases corresponded to low absolute risk increases. Early Tdap vaccine receipt was also associated with chorioamnionitis (RR = 1.19 [95% CI: 1.11; 1.28]), postpartum hemorrhage (RR = 1.34 [95% CI: 1.25; 1.44]), and premature rupture of membranes (RR = 1.08 [95% CI: 1.02; 1.15]). Neonatal intensive care unit admission, respiratory distress, and neonatal jaundice were common; all had incidence > 6%. Optimally-timed or early prenatal Tdap immunizations were not associated with increased risks for any of these outcomes compared to non-Tdap vaccine receivers.

The authors concluded that Tdap vaccine was not associated with increased risk of any adverse newborn outcome. Overall, prenatal Tdap immunization was not associated with newborn AEs, but potential associations with chorioamnionitis consistent with 1 previous study and postpartum hemorrhage require further investigation. The authors noted limitations of the study including potential for unmeasured confounding as women receiving guideline-concordant immunizations may also be receiving more thorough surveillance, detailed diagnoses, and comprehensive care compared to women not receiving recommended Tdap vaccine; the use of diagnosis coding for outcomes may result in misclassification; women in this study have employer-sponsored commercial insurance, and thus the results may not be generalizable to publically-insured or uninsured women; and gestational age is not available in insurance claims data and there may be residual inaccuracies in the gestational age estimation. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2017, Moro et al (56) reported results from a review of the VAERS database for birth defects in pregnant women who received a vaccine during pregnancy from 1 January 1990–31 December 2014. Birth defects after human papillomavirus vaccine (HPV), VAR, MMR, and anthrax vaccination were excluded as they have been studied in pregnancy registries or other epidemiological studies. A total of 50 reports of major birth defects were identified; in 28 reports, the vaccine was given during the first trimester and 25 were reports with single vaccines administered. A total of 9 reports with Tdap vaccine, alone or in combination were identified: Tdap vaccine only was noted in 5 reports, Tdap and IIV3 vaccines in 2 reports, and 1 report each for HPV4 and Tdap vaccines and quadrivalent meningococcal conjugate vaccine (MCV4) and Tdap vaccines. Other reports were associated with: IIV3 (12), HepB (4), MCV4 (2), 2009 monovalent H1N1 (4), and other combinations (14). Birth defects accounted for 0.03% of all reports received by VAERS during the study period and 3.2% of pregnancy reports. Reported

defects affected predominately the musculoskeletal (N = 10) or nervous (N = 10) systems. No unusual clusters or specific birth defects were identified.

The authors concluded that this review of the VAERS database found that major birth defects were infrequently reported, with no particular condition reported disproportionally. The author noted that with birth defects, a limitation is that there may be significant underreporting not only because of the spontaneous nature of VAERS, but also due to the period of time between vaccination and delivery, and the fact that many defects are not necessarily obvious or symptomatic immediately after birth. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

4.4 Sanofi Pasteur US Pregnancy Registry for Adacel and Post-Licensure Safety Surveillance Study

Sanofi Pasteur has not conducted prospective clinical studies in pregnant or lactating women. The US Adacel Pregnancy Registry was initiated in June 2005 to capture Tdap vaccine exposure during pregnancy at the request of the US Food and Drug Administration.

Study Td512 was performed by Sanofi Pasteur as part of a post-licensure safety surveillance study of Tdap vaccine in the United States and included an analysis of maternal and fetal outcomes in women exposed to Adacel during pregnancy.

The Adacel Pregnancy Registry and Study Td512 are summarized in Table 4.4. Additional information is provided in [Section 6] of 2.7.4 Summary of Clinical Safety.

Table 4.4: Adacel Pregnancy Registry and Sanofi Pasteur Post-Licensure Safety Surveillance Study

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine
US Adacel Pregnancy Registry	Pregnancy registry	United States Jun 2005–16 Mar 2017 (ongoing)	Pregnant women: 1,518	Tdap5
Td512	Post-licensure, epidemiological surveillance study	United States 02 Sep 2005–16 Oct 2006	Pregnant women: Tdap vaccine: 225 Matched controls: 675	Tdap5

Tdap5: tetanus toxoid, reduced diphtheria toxoid, and (5-component) acellular pertussis vaccine, Adacel; US: United States

Since the establishment of the US Adacel Pregnancy Registry in June 2005 through 16 March 2017, a total of 1518 cases of Tdap vaccine exposure in women within either 30 days before their last menstrual period or during pregnancy, were reported to Sanofi Pasteur. Of these, 317 cases were reported in clinical trials/ Phase IV studies, including 72 cases reported from studies not sponsored by Sanofi Pasteur.

Approximately 93.3% of the pregnancy cases originated from the United States. The remaining cases were from Argentina, Australia, Brazil, Canada, Colombia, Germany, Israel, Mexico, Peru, Venezuela, and Vietnam.

The reporting of pregnancy cases increased significantly in 2010, was stable for several years, but then has decreased from 2013 on, even accounting for reporting lag time. Noteworthy, in 2010 there was an important pertussis outbreak in California, which most likely explains the increased reporting of pregnancy exposure (57), and a number of other outbreaks have since been reported throughout the United States (58).

Outcomes

Among these 1518 cases of pregnancy exposure, the outcomes were obtained in 567 cases (37.3%), and are as follows:

- Delivery of a child in 471 cases:
  - Normal babies: 455 (96.6% of cases with reported outcome) neonates
  - Babies with a congenital anomaly: 16 neonates including 1 who died within a few days of birth
- Interruption of the pregnancy occurred in 95 cases (percentage is reported as percent of cases where pregnancy interruption was recorded):
  - Ectopic pregnancies: 3 (3.1%) cases
  - Voluntary termination of pregnancy: 41 (43.1%) cases
  - Spontaneous abortions (< 20 weeks): 43 (45.3%) cases including 1 missed abortion that needed curettage.
    In 1 case the nature of pregnancy termination has not been defined (1%) and 1 case of missed abortion (1%) after embryonic demise (approximately 8 weeks).
  - Late fetal death (≥ 20 weeks): 6 (6.3%) cases

The outcome has not been reported in 951 of all cases (62.6%). This latter count includes ongoing pregnancies.

Congenital anomalies, fetal deaths, and spontaneous abortions are discussed in more detail in [Section 6] of 2.7.4 Summary of Clinical Safety.

In summary, few cases of congenital anomalies were reported, the period of embryogenesis being not compatible with a role of the vaccine in all but one case. For the latter, the role of the vaccine appears to be unlikely. Overall, no pattern of anomaly was observed. No safety signal was raised from the review of pregnancy exposure to Tdap vaccine.

Based upon available data, no specific risks have been identified in conjunction with Tdap vaccine exposure during pregnancy.

In Study Td512, a large retrospective observational database study, the safety of Adacel health outcomes were reviewed in a cohort of over 120,000 persons who received Adacel in a course of routine health care. Among them, 225 women were identified as being vaccinated with Adacel during pregnancy or within 28 days prior to becoming pregnant. The ages ranged from 14 to 51 years at time of vaccination. Thirty-nine of them received the vaccine within 2 weeks prior to the date of their last menstrual period, 110 were vaccinated during the first trimester (defined as 80 day period following the date of last menstrual period), and 47 received the vaccine during the second or third trimester). For 29 women, the trimester of pregnancy at vaccination could not be

determined. The outcomes of the pregnancies were 165 live births, 21 spontaneous abortions, 1 late fetal death, 33 elective abortions, 1 ectopic pregnancy, and 4 lost to follow-up.

To help interpret incidence rates of pregnancy outcomes in Adacel-exposed women, 3 controls were randomly chosen from among non-Adacel-exposed women in the Kaiser Permanente databases, matched by age and the date of first positive pregnancy test. Although these control women did not receive Adacel, they may or may not have received another vaccine. For 5 out of 7 types of pregnancy outcomes (i.e., early fetal death [< 20 weeks of gestation], late fetal death [at least 28 weeks of gestation], elective abortion, ectopic pregnancy, and lost to follow-up) the rates in Adacel-exposed women were similar to those among controls. The rate of live births was slightly higher among Adacel-exposed women (IRR = 1.120; 95% CI: 1.017; 1.233; P = 0.033), and the rate of spontaneous abortions (< 20 weeks of gestation) was slightly lower in Adacel-exposed cases (IRR = 0.618; 95% CI: 0.396; 0.964; P = 0.033). Because the CI limits for both IRRs were extremely close to 1 and given the possibility of residual biases, no meaningful interpretation of these statistically significant findings could be made.

The rates and IRRs of 42 unique fetal outcomes were analyzed in Adacel recipients and none were more significantly frequent among infants born to Adacel-exposed mothers compared to control infants.

Three cases of SAEs with fatal outcomes were detected in the study and were reported to regulatory authorities. One case involved a pregnant woman who received a dose of Adacel at 2.5 weeks of gestation. Complete atrioventricular canal defect was detected in the fetus via ultrasound at 23 weeks of gestation. Fetal demise occurred at 33 weeks of gestation (200 days post-vaccination). Several dysmorphic features were suggestive of Downs Syndrome, which was confirmed by karyotyping. This event was not considered related to study vaccine. In each of the 2 other cases, on further follow up it was determined that the mothers were administered Adacel more than 30 days before the date of conception. Therefore the fetus was not considered to be exposed to the vaccine.

It was concluded that the comparison of outcomes in Adacel-exposed pregnancies and non-Adacel-exposed pregnancies did not identify any significant safety issues.

4.5 Summary of Safety in the Literature

In the majority of studies, Tdap vaccine was administered to pregnant women in the second or third trimester of pregnancy.

The most common reactions following Tdap vaccine administration were injection site reactions. Munoz et al (18) reported that approximately 80% of women who received Tdap vaccine while they were pregnant or immediately postpartum, and nonpregnant women reported injection site reactions (pain, erythema/redness, or induration/swelling). Injection site pain was reported in the Halperin et al (19) study by over 80% of pregnant women who received Tdap or Td Adsorbed vaccine during pregnancy. Additionally, in a small observational study reported by Talbot et al (52), injection site pain was reported by approximately 80% of women who received Tdap vaccine during pregnancy. In a study reported by Villarreal Pérez et al (43), the percentage of pregnant women reporting mild local pain within 24 and 48 hours after vaccination with Tdap

vaccine during pregnancy (22.2% and 7.8%, respectively) was similar in women who received a placebo injection during pregnancy (21.0% and 6.2%, respectively).

Systemic symptoms (headache, malaise, and myalgia) were reported in the Munoz et al (18) study by 36.4%, 73.3%, and 53.1% of women who received Tdap vaccine while they were pregnant, immediately postpartum, and in nonpregnant women, respectively (P = 0.055). The occurrence of fever in women receiving Tdap vaccine postpartum (26.7%) was not different from that of postpartum placebo recipients (15.2%; P = 0.43). There was also no difference in the proportion of participants with fever between recipients of Tdap vaccine during pregnancy (3.0%) and nonpregnant women (9.4%; P = 0.36).

Muscle aches, fatigue, and headache were reported by 16.9%–34.4% of participants in the Halperin et al study (19); severe muscle aches were more common in Tdap vaccine recipients than in Td Adsorbed recipients (4.4% vs. 0%; P = 0.014). No fever was reported. The most commonly reported solicited systemic AE reported in the Talbot et al (52) study was subjective fever (7.1%–20%).

Hoang et al (44) reported that at least 1 solicited AE was experienced by 44% and 43% of women who received Tdap vaccine during pregnancy and who received tetanus only vaccine during pregnancy, respectively; the most common AEs were stiffness and swelling and itching at the injection site. In women who received Tdap vaccine during pregnancy in a study reported by Perry et al (50), 67% had at least 1 solicited reaction to the vaccination, and 25% had 2 solicited reactions or more; the most common reaction was pain/soreness at the injection site (65%).

In randomized clinical trials reported by Munoz et al (18) and Halperin et al (19), none of the SAEs reported in women or infants were attributed to Tdap vaccine by the investigators. No causal information was available for the SAEs (fever, n = 1; fatigue, n = 1; and premature contractions, n = 2) reported by Hoang et al.

In the Halperin et al study (19), there were no differences in rates of congenital abnormalities or neonatal complications between women who received Tdap vaccine during pregnancy and those who received Td Adsorbed vaccine during pregnancy. There were 17 serious complications of pregnancy/labor, 9 in Td Adsorbed vaccine recipients and 8 in Tdap vaccine recipients; 4 of these events were assessed as possibly vaccine-related (1 Td Adsorbed vaccine recipient each with pre-eclampsia, premature delivery, and HELLP syndrome [hemolysis, elevated liver enzymes, low platelet count] and 1 Tdap vaccine recipient with gestational hypertension).

The majority of cohort and observational studies assessed pre-defined maternal and infant outcomes for pregnant women who received Tdap (or Tdap-IPV) vaccine during pregnancy and showed that there was no difference in these outcomes compared with pregnant women who did not receive Tdap vaccine during pregnancy.

- Kharbanda et al (30) reported no increased risk of preterm delivery or SGA birth or with hypertensive disorders of pregnancy.
- Kharbanda et al (47) reported that increased risk was not observed for the composite of medically attended events (i.e., allergic reaction, fever and malaise, seizure, altered mental status, or local or other reaction) in the 0–3 days following vaccination (adjusted IRR = 1.19 [95% CI: 0.81; 1.73]) or in maternal safety outcomes (i.e., neurologic events, proteinuria, and venous thromboembolism in vaccinated cohort compared to unvaccinated cohort) within

42 days after vaccination. Additionally, there was no increased risk for incident gestational diabetes, thrombocytopenia, venous thromboembolism, or predefined cardiac events within 42 days of vaccination in the subset of women receiving Tdap vaccine at ≥ 20 weeks of gestation (consistent with the 2011 ACIP recommendations).

  - However, 1 component of the composite of medically attended events, fever within 3 days, was more common in the vaccinated cohort than in the unvaccinated cohort (2.8 vs. < 1 per 10,000; adjusted IRR = 5.4 [95% CI: 2.1; 13.9]).

- Morgan et al (29) reported that there was no difference in stillbirths, major malformations, chorioamnionitis, 5-minute Apgar score, cord blood pH, or in neonatal complications including ventilation requirement, sepsis, intraventricular hemorrhage, and neonatal death.
  - However, in women who did not receive Tdap vaccine during pregnancy, there were significantly increased preterm birth rates at 36 weeks of gestation or less (6% vs. 12%, P < 0.001), incidence of SGA (10% vs. 15%, P = 0.03), and length of neonatal hospitalization (3.9 vs. 4.7 days, P < 0.001).
- Donegan et al (27) reported that there was no increased risk of stillbirth, maternal or neonatal death, pre-eclampsia, eclampsia, antepartum or postpartum hemorrhage, fetal distress, uterine rupture, placenta previa, vasa previa, cesarean delivery, low birth weight, or neonatal renal failure.

Kharbanda et al (30) reported a small but statistically significant increased risk of being diagnosed with chorioamnionitis among women who received Tdap vaccine at any time during pregnancy (6.1% of Tdap-exposed women compared with 5.5% of unexposed women; adjusted RR = 1.19 [95% CI: 1.13; 1.26) and in women vaccinated between 27 and 36 weeks of gestation (adjusted RR = 1.11 [95% CI: 1.03; 1.21]). Based on this observed association, DeSilva et al (48) conducted a study to re-evaluate this risk. In the study reported by DeSilva et al, chorioamnionitis was recorded in 6.4% of women who received Tdap vaccination any time during pregnancy and 5.2% of women who did not (adjusted RR [95% CI]: 1.23 [1.17; 1.28]). This association was not found in women delivering at < 34 weeks gestational age (adjusted RR [95% CI]: 0.87 [0.59; 1.30]). Compared with unvaccinated women, there were no significant increased risks for transient tachypnea of the newborn, neonatal sepsis, neonatal pneumonia, respiratory distress syndrome, or newborn convulsions in infants born to Tdap-vaccinated women. The results of this re-evaluation showed that there was no increased risk for clinically significant infant outcomes associated with maternal chorioamnionitis.

Adverse events following administration of Tdap vaccine in pregnancy that were reported to the VAERS system before the recommendation for Tdap vaccine during pregnancy (1 January 2005–30 June 2010) were reported by Zheteyeva et al (45) and after the recommendation (11 October 2011–30 June 2015) by Moro et al (46). A total of 132 reports of Tdap vaccine administered to pregnant women were identified in VAERS prior to the recommendation and 392 reports after the recommendation. Prior to the recommendation, Tdap vaccine was administered to most pregnant women during the first trimester, and after the recommendation, during the third trimester. Before the recommendation, there were no maternal or infant deaths reported. The AEs reported did not identify any concerning patterns in maternal, infant, or fetal outcomes. After the recommendation there was 1 neonatal death and no maternal deaths. The most frequent pregnancy-specific outcome was oligohydramnios (12 [3.1%] reports) followed by stillbirth and preterm delivery

(11 [2.8%] reports each). The authors concluded that no new or unexpected vaccine AEs were noted among pregnant women who received Tdap vaccine after routine recommendations for maternal Tdap vaccination.

Concomitant administration of Tdap and influenza vaccines during pregnancy, reported by Sukumaran et al (49), was not associated with a higher risk of medically attended adverse acute outcomes (i.e., fever or acute reactions [limb pain, limb swelling, cellulitis, lymphadenitis, Arthus reaction, allergy, urticaria, and anaphylaxis]) or birth outcomes (i.e., preterm delivery, low birth weight, and SGA) compared with sequential vaccination. The safety of concomitant or sequential administration of Tdap and influenza vaccines was also reported by Regan et al (51). In this study, there was a slight increase in mild, expected AEs (i.e., local reactions and rash) following Tdap vaccine, and a low incidence of febrile and other systemic reactions, as well as medically attended events, reported by recently immunized pregnant women following Tdap or influenza vaccines administered exclusively or in combination. Zheteyeva et al (45) also compared AE reporting rates following Tdap vaccination with those after influenza vaccine. The analysis did not reveal disproportionate reporting for spontaneous abortions in VAERS for Tdap vaccine compared with influenza vaccines. Although gestational diabetes, anemia, antepartum hemorrhage, oligohydramnios, and upper respiratory infection were reported to VAERS more frequently after Tdap vaccine than after inactivated influenza vaccines, after further clinical review, it was found that most of these conditions were minor, and there were no concerning patterns for these outcomes that required additional investigation. Perry et al (50) analyzed 33 women who received concomitant Tdap and influenza vaccines and 25 women who had concomitant Tdap vaccine and Rh hyperimmune globulin, no increase in reactions were found ($P = 0.62$ and $P = 0.19$, respectively).

Sukumaran et al (28) found that among women who received Tdap vaccination during pregnancy, there was no increased risk of acute AEs (fever, local reactions [limb pain, limb swelling, cellulitis, lymphadenitis, and Arthus reaction], and allergic reactions [allergy, urticaria, and anaphylaxis]) or adverse birth outcomes (preterm delivery, low birth weight, and SGA) for those women who had been previously vaccinated less than 2 years before or 2 to 5 years before compared with those who had been vaccinated more than 5 years before. These findings suggest that relatively recent receipt of a prior tetanus-containing vaccine does not increase risk after Tdap vaccination in pregnancy. Morgan et al (29) also compared pregnancy outcomes in women who were administered Tdap vaccine in consecutive pregnancies within a 5-year timespan. No difference in neonatal outcomes was noted between women who were administered at least 2 Tdap vaccines in the past 5 years and those who received only a single dose.

In publications where the brand of Tdap vaccine was unspecified, safety outcomes were similar to those presented for the studies with Adacel (i.e., COVAXIS).

5 Overview of Efficacy

5.1 Immunogenicity

The immunogenicity results from 12 publications and 1 article (Halperin et al (19)) in press identified in the literature search that support Tdap vaccination during pregnancy are presented individually by results in women and in infants in this section.

5.1.1 Antibody Responses to Tdap Vaccine in Pregnant Women and Their Infants at Birth

5.1.1.1 Randomized Clinical Trials

A summary of the 4 randomized clinical trials that support the immunogenicity of Tdap vaccine in pregnant women and their infants is provided in Table 5.1.

Three publications are provided in Module 5.4 of this CTD and 1 article (Halperin et al (19)) is in press.

Immunogenicity objectives and methods are summarized for each study in [Section 2.1.1] of 2.7.3 Summary of Clinical Efficacy.

Ethical requirements of the studies were documented:

- All 4 randomized clinical trials were reviewed by an institutional review board and/or ethics committee and participants signed informed consent prior to participation.

Table 5.1: Randomized Clinical Trials Supporting Immunogenicity of Tdap Vaccine in Pregnant Women and Their Infants at Birth

Study Identifier	Study Design	Country/Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Munoz et al (2014) (18)	Phase I/II, randomized, double-blind, placebo-controlled, cross-over	United States Oct 2008–May 2012	Total pregnant women/infants: 48 Tdap vaccine: 33 Placebo: 15 Healthy nonpregnant women: 32	Pregnant women: Tdap5 or placebo Infants: DTaP5-IPV/Hib	I	Good
Villarreal Pérez et al (2017) (43)	Randomized, double-blind, parallel-group, placebo-controlled	Mexico Sep 2011–Aug 2014	Total pregnant women/infants: 171 Tdap vaccine: 90 Placebo: 81	Pregnant women: Tdap5 or placebo Infants: DTaP5-IPV//Hib	I	Good

Study Identifier	Study Design	Country/Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Halperin et al (2018) (19)	Randomized, controlled, observer-blinded, multicenter	Canada Nov 2007–Jun 2011 Mar 2012–Apr 2014	Pregnant women/infants: 273/272 Tdap vaccine: 135/134 Td Adsorbed vaccine: 138/138	Pregnant women: Tdap5 or Td Adsorbed Infants: DTaP5-IPV-Hib	I	Good
Hoang et al (2016) (44)	Randomized, controlled, multicenter	Vietnam Infants born: 22 Feb 2013–7 Oct 2013	Total pregnant women/infants: 103 Tdap vaccine: 52/51 Tetanus vaccine: 51/48	Pregnant women: Tdap5 or tetanus Infants: DTaP3-HBV-IPV/Hib	I	Fair

Note: The "3" or "5" designation following Tdap or DTaP is used to define the number of acellular pertussis components in the vaccine included in the study. In the individual summaries, to agree with the presentation in the publications, the numerical designation is not used unless needed for clarity (i.e., both Tdap3 and Tdap5 data presented within a study).

DTaP3-HBV-IPV/Hib: combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine, Infanrix hexa; DTaP5-IPV//Hib: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pentaxim; DTaP5-IPV-Hib: diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pediacel; DTaP5-IPV/Hib: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pentacel; Td Adsorbed: tetanus and diphtheria toxoids adsorbed vaccine; Tdap5: tetanus toxoid, reduced diphtheria toxoid, and (5-component) acellular pertussis vaccine, Adacel; USPSTF: United States Preventive Services Task Force

In 2014, Munoz et al (18) reported safety and immunogenicity results from a Phase I/II, randomized, double-blind, placebo-controlled clinical trial that was conducted from October 2008–May 2012 and was sponsored by the NIAID. The trial enrolled 48 healthy pregnant women and their infants and 32 healthy nonpregnant women. Safety results are provided in Section 4.1.

Antibody responses to each pertussis antigen in Tdap vaccine at 4 weeks after vaccination in pregnant women were not different than those in non-pregnant women (geometric mean concentrations [GMCs]: PT, 56.5 EU/mL vs. 90.9 EU/mL; FHA, 234.4 EU/mL vs. 285.6 EU/mL; PRN, 205.0 EU/mL vs. 348.7 EU/mL; FIM, 1632.9 EU/mL vs. 1785.1 EU/mL). At delivery (median interval from Tdap immunization to delivery was 54 days [range, 32–68 days]), all antibody responses to each pertussis antigen in women who received Tdap vaccine during pregnancy were statistically significantly higher than those in women who received placebo during pregnancy ($P < 0.001$) (GMCs: PT, 51.0 EU/mL vs. 9.1 EU/mL; FHA, 184.8 EU/mL vs. 21.9 EU/mL; PRN, 192.2 EU/mL vs. 12.2 EU/mL; FIM, 1601.3 EU/mL vs. 34.9 EU/mL). Two months after delivery, women vaccinated postpartum (placebo group) had statistically higher GMCs for antibodies to anti-PT than women who received Tdap vaccine during pregnancy (66.4 EU/mL [95% CI: 42.2; 104.8] vs. 53.1 EU/mL [95% CI: 39.4; 71.7]; $P < 0.001$, 2-sided t-test).

The concentration of pertussis antibodies in cord blood was higher than in maternal serum at delivery, with linear correlation between maternal and infant concentrations. The ratio of the concentrations of antibodies to Tdap vaccine antigens at delivery and remaining at 2 months in infants whose mothers received Tdap vaccine or placebo during pregnancy (i.e., comparing ratio of infant cord blood antibodies to maternal antibodies at delivery or ratio of infant antibodies at 2 months to cord blood antibodies) ranged from 1.15 to 1.54 and 0.25 to 0.42, respectively. There were no statistically significant differences for any comparisons of the ratios for the pertussis antigens.

The authors concluded that overall, antibody responses to Tdap vaccine in pregnant women were not different than those in nonpregnant women and women immunized postpartum. Limitations of this study were related to the infant series and are provided in Section 5.1.2.1. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2017, Villarreal Pérez et al (43) reported results of a randomized, double-blind, parallel group, placebo-controlled clinical trial conducted from September 2011–August 2014 that included 171 pregnant Mexican women who received Tdap vaccine (n = 90) or placebo (n = 81) between 30 and 32 weeks of gestation. Safety results are provided in Section 4.1.

The pre-vaccination GMCs of anti-PT and anti-PRN antibodies were similar in the 2 groups. Post-vaccination, GMCs of anti-PT (24.04 EU/mL [95% CI: 18.39; 31.43] vs. 7.06 EU/mL [95% CI: 5.24; 9.50]) and anti-PRN (112.08 EU/mL [95% CI: 89.79; 139.91] vs. 7.16 EU/mL [95% CI: 5.38; 9.53]) antibodies in the Tdap vaccine group were statistically significantly higher than in the control group (Mann-Whitney test, P = 0.001).

The cord:2-month old child serum ratio for PRN was 1.78 and for PT was 2.5.

The authors concluded that women who received Tdap vaccine in the third trimester of pregnancy achieved high antibody levels against 2 pertussis antigens (PT and PRN). The authors noted that a limitation in this study was that only 2 out of 3 recommended antibodies against *B. pertussis*—PRN and PT—were measured to determine immunogenicity because of technical accessibility problems which prevented measuring the other antigen as was originally planned. However, anti-PT is considered representative of the vaccine's immunogenicity. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2018, Halperin et al (19) reported results from an observer-blinded, multicenter, randomized clinical trial of the safety and immunogenicity of Tdap immunization during pregnancy in Canada that was conducted from November 2007–April 2014 and enrolled a total of 273 women (Tdap vaccine, n = 135; Td Adsorbed vaccine, n = 138). Safety results are provided in Section 4.1.

In pregnant women who received Tdap vaccine during the third trimester, antibodies against PT, FHA, PRN, and FIM reached peak levels by delivery (44.8, 162.9, 282.4, and 881.3 EU/mL, respectively) or by 2 months postpartum (45.7, 168.7, 314.2, and 826.1 EU/mL, respectively), and were significantly higher than those of Td Adsorbed vaccine recipients at all post-vaccination time points (delivery: 5.8, 12.7, 8.1, and 21.0 EU/mL, respectively; 2 months after delivery: 8.1, 19.0, 11.0, 28.3, respectively). In pregnant women who received Tdap vaccine, antibody levels against all pertussis antigens decreased in a somewhat linear manner for the 12 months postpartum, with levels declining by just more than 50% for the pertussis antigens (PT, 21.5 EU/mL; FHA, 76.7 EU/mL; PRN, 134.8 EU/mL; FIM, 336.7 EU/mL); however, all

remained significantly higher than pre-vaccination levels. Antibody levels against all pertussis antigens at 12 months after delivery in the Td Adsorbed group were similar to the levels at 2 months after delivery.

Fetal to maternal antibody ratios were > 1 for PT, FHA, PRN, and FIM suggesting active transport of antibody across the placenta.

The authors concluded that this study demonstrated that Tdap vaccine during pregnancy results in levels of antibodies at birth that may provide protection during the highest risk of severe pertussis in the first few months of life. Limitations noted by the authors for this study were related to the infant series and are provided in Section 5.1.2.1. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2016, Hoang et al (44) reported results from a multicenter, randomized, controlled clinical trial of the safety and immunogenicity of Tdap immunization during pregnancy that was conducted in Vietnam from February 2013–October 2013 in 52 pregnant women who were vaccinated with Tdap vaccine and 51 pregnant women who were vaccinated with tetanus only vaccine. Safety results are provided in Section 4.1.

The mean gestational age at vaccination was 25.8 weeks for the Tdap vaccine group and 24.9 weeks for the tetanus only vaccine group (P = 0.155). Prior to vaccination, both groups had similar GMCs for antibodies to pertussis antigens that were analyzed (PT, FHA, and PRN). At delivery, women in the Tdap vaccine group had significantly higher GMCs for antibodies to these pertussis antigens (P < 0.001) compared with the tetanus only vaccine group: PT, 17.3 IU/mL (95% CI: 13; 22) vs. 5.7 IU/mL (95% CI: 4.3; 7.6); FHA, 139 IU/mL (95% CI: 109; 176) vs. 17.3 IU/mL (95% CI: 14; 21.4); PRN, 111 IU/mL (95% CI: 76; 163) vs. 9.4 IU/mL (95% CI: 6.9; 12.5).

Significantly higher concentrations were observed for all antigens in the cord blood samples in the Tdap vaccine group. A statistically significant difference was observed for the transplacental transport rate (cord/maternal titer at delivery) between the groups for FHA antibodies (Tdap vaccine group, 1.04 (0.96); tetanus only vaccine, 1.83 (0.89); P < 0.001). There were no differences in this rate for the other antigens in Tdap vaccine.

The authors concluded that maternal antibodies induced by vaccination during pregnancy close the susceptibility gap for pertussis in young infants. Limitations noted by the authors for this study were related to the infant series and are provided in Section 5.1.2.1. **Overall, this study provides USPSTF evidence level I and evidence quality category of fair.**

5.1.1.2 Cohort and Observational Studies

A summary of 5 cohort and observational studies that support the immunogenicity of Tdap vaccine in pregnant women is provided in Table 5.2.

All publications are provided in Module 5.4 of this CTD.

Immunogenicity objectives and methods are summarized for each study in [Section 2.1.2] of 2.7.3 Summary of Clinical Efficacy.

Ethical requirements of the studies were documented:

- Gall et al (59) noted that the study had institutional approval; no information on informed consent was noted.
- Hardy-Fairbanks et al (22), Vilajeliu et al (60), and Fallo et al (61) noted that the studies were approved by institutional review boards or ethics committees and informed consent was obtained.
- Healy et al (42) noted that the study was approved by the institutional review board; no information on informed consent was noted.

Table 5.2: Cohort and Observational Studies Supporting Immunogenicity of Tdap Vaccine in Pregnant Women and Their Infants at Birth

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Gall et al (2011) (59)	Retrospective cohort	United States Oct 2008–Dec 2009	Paired maternal/umbilical cord blood samples Tdap vaccine during pregnancy: 52 Unvaccinated during pregnancy: 52	Tdap5	II-2	Fair
Hardy-Fairbanks et al (2013) (22)	Prospective cohort	United States Tdap vaccine during pregnancy: 2006 pseudo-outbreak Unvaccinated during pregnancy: Mar 2008–Feb 2009	Pregnant women/infants Tdap vaccine: 16 Unvaccinated: 54	Pregnant women: Tdap5 Infants: DTaP (multiple products)	II-2	Fair
Healy et al (2013) (42)	Prospective cohort	United States Jun 2009–May 2011	Paired maternal delivery plasma/infant cord samples Tdap vaccine: 105	Tdap5	II-2	Fair
Vilajeliu et al (2015) (60)	Prospective, observational	Spain May 2012–Aug 2013	Pregnant women/infants Tdap vaccine: 132	Tdap5	II-2	Fair

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Fallo et al (2016) (61)	Prospective observational	Argentina Period 1: 2011–2012 Period 2: 2013–2014	Period 1 Unvaccinated pregnant women/infants: 100 Non-pregnant non-immunized women: 69 Period 2 Tdap vaccine during pregnancy Women: 105 Infants: Cord blood/1 month: 36 2 months: 32	Tdap5	II-2	Fair

Note: The "5" designation following Tdap is used to define the number of acellular pertussis components in the vaccine included in the study. In the individual summaries, to agree with the presentation in the publications, the numerical designation is not used.

DTaP: diphtheria, tetanus, and acellular Pertussis; Tdap5: tetanus toxoid, reduced diphtheria toxoid, and (5-component) acellular pertussis, Adacel; USPSTF: United States Preventive Services Task Force

In 2011, Gall et al (59) reported results of a retrospective cohort study conducted from October 2008–December 2009 in the United States that compared antibodies in 104 paired maternal and umbilical cord blood samples from women who received Tdap vaccine during pregnancy (n = 52) and did not receive Tdap vaccine in pregnancy (n = 52).

Newborns born from mothers who received Tdap vaccine during pregnancy had significantly higher concentrations of pertussis antibodies in cord blood to each pertussis antigen (PT, FHA, PRN, and FIM) when compared with newborns from mothers who did not receive Tdap vaccine.

There was a significant increase in the odds that newborns from mothers who received Tdap vaccine during pregnancy were protected against pertussis based on anti-PT (88.5% vs. 40.4%; OR, 11.32; 95% CI: 4.10; 31.24: $P < 0.0001$) and anti-FIM (98.1% vs. 84.6%; OR, 9.27; 95% CI: 1.12; 77.07: $P = 0.0146$) antibody concentrations compared with newborns from mothers who did not receive Tdap vaccine during pregnancy. There was no significant difference in protection for FHA and PRN between the 2 groups.

The authors concluded that administering Tdap vaccine during pregnancy increases antibody levels against pertussis antigens. Maternal Tdap vaccination may prevent neonatal pertussis infection. No limitations were noted by the authors. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2013, Hardy-Fairbanks et al (22) reported results from a prospective cohort study of pregnant women who received Tdap vaccine during pregnancy in the United States that enrolled 16 pregnant women (mean age 31 years) vaccinated prenatally with Tdap vaccine during the 2006 pseudo-outbreak (4 during the first trimester, 8 in the second, and 4 in the third) and 54 pregnant women (control group) who delivered between March 2008 and February 2009. Maternal and cord serum samples were collected from 5 women and their infants in the Tdap vaccine group and 53 women and their infants in the control group.

At delivery, maternal and cord antibody concentrations to pertussis antigens (PT, FHA, PRN, and FIM) were higher among the Tdap vaccine group (maternal: 14.3, 32.5, 24.4, and 360.3 EU/mL, respectively; cord: 33.5, 66.1, 48.5, and 912.9 EU/mL, respectively); compared with the control group (maternal: 7.5, 9.6, 6.4, and 17.7 EU/mL, respectively; cord: 12.6, 15.9, 8.9, and 25.7 EU/mL, respectively); maternal: 1.9- to 20.4-fold greater; cord: 2.7- to 35.5-fold greater.

Tdap vaccine group infants had higher antibody concentrations to pertussis antigens than those of their mothers (2.0- to 2.5-fold greater) at delivery. Similarly, among mother–infant pairs in the control group, infants at delivery had higher antibody concentrations to pertussis antigens than those of their mothers (1.4- to 1.7-fold greater). A greater percentage of women who received the Tdap vaccine during pregnancy (75.0%–100%) and their infants cord blood (80.0%–100%) had antibody concentrations to each of the 4 pertussis antigens that were at or above the defined benchmark protective concentrations (defined as > 5 EU/mL for PT and FHA and > 10 EU/mL for PRN and FIM) as compared with the control group (35.8%–66.0% and 39.6%–81.1%, respectively).

The authors concluded that women who received Tdap vaccine during pregnancy and their infants had higher antibody concentrations to all of the antigens in the vaccine at birth than women who did not receive Tdap vaccine during pregnancy. The authors noted several important limitations. Sample size was dependent on access to a small group of already vaccinated pregnant women, many of whom did not have cord blood collected at delivery due to delayed institutional review board approval. The study may also not be representative of other geographical areas, particularly with respect to ethnicity, race, and age. Not all participants provided complete sets of specimens. Additionally, the Tdap vaccine and control groups were not followed over the same time period. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2013, Healy et al (42) reported the results of a prospective cohort study conducted from June 2009–May 2011 that compared antibodies in paired maternal and umbilical cord blood samples from women at a single hospital in Texas who received Tdap vaccine 2 to 24 months before delivery.

A total of 105 mothers (mean age of mothers, 25.3 years [range, 15.3–38.4 years]; mean gestational age of newborns, 39 weeks [range, 37–43 weeks]) immunized with Tdap vaccine a mean of 13.7 months (range, 2.3–23.9 months) previously were included (maternal delivery–infant cord blood pairs). The majority of mothers were Hispanic (91%). Of these 105 women, 19 (18%) received Tdap vaccine during the current pregnancy; most were immunized in the first trimester before the sixth week of gestation and only 3 women received Tdap vaccine after 20 weeks of gestation.

There was no difference in GMCs of antibodies to pertussis antigens in maternal delivery or infant cord sera for women immunized before (n = 86) or during early (n = 19) pregnancy. Placental transport of maternal pertussis-specific antibodies was efficient, ranging from 121% to 165% for PT, 145% to 178% for FHA, 131% to 186% for FIM, and 148% to 173% for PRN, for mothers immunized before and during pregnancy, respectively.

Estimated GMC of antibody to PT was < 5 EU/mL at infant age 2 months (start of infant immunization series). Only 41 infants (40%) had a PT-specific antibody concentration at birth calculated to persist above the lower limit of quantification (LLOQ) (4 EU/mL) of the assay at age 2 months. Slightly more infants of mothers who were immunized during pregnancy, and 2 of the 3 immunized after Week 20, had PT levels at birth that would persist above the LLOQ through 2 months of age (52% vs. 38%; P = 0.34).

The authors concluded that infants of mothers' immunized preconception or in early pregnancy have insufficient pertussis-specific antibodies to protect against infection. Maternal immunization during the third trimester, immunization of other infant contacts, and re-immunization during subsequent pregnancies may be necessary. The authors noted limitations of the study. The number of pregnant women studied is relatively small. The cohort was predominantly Hispanic and may not reflect pertussis seroprevalence in other populations of pregnant women. Histories on pertussis-like illness in the women were not obtained, making it impossible to evaluate the possible effects of natural boosting on observations. The rate of decay of maternally acquired pertussis antigen–specific IgG was calculated and, while this is defined for PT, that is not the case for antibodies to other antigens that possibly also play a role in protecting young infants. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2015, Vilajeliu et al (60) reported the results of a prospective observational study conducted from May 2012–August 2013 in Spain to compare anti-PT levels in pregnant women who received Tdap vaccine during pregnancy and their infants. A total of 132 cases had samples (pre-, post-, and newborn) available and were included in the study analysis. The mean (SD) age of pregnant women was 34.2 (4.3) years. The median (Q1–Q3) weeks of gestation at Tdap vaccination was 27.2 (21.7–30.8) weeks. The majority of cases were from Spain (77.3%) and America (15.9%). Pre-vaccination, 37.1% (49) of baseline maternal sera had anti-PT levels ≥ 10 EU/mL. Post-vaccination, anti-PT levels met the definition of vaccine response in 53.8% (71) mothers, while another 48 had levels ≥ 10 EU/mL. Anti-PT levels ≥ 10 EU/mL were found in 90.2% (119) of maternal post-vaccination sera, and 94.7% (125) of neonates. All newborn samples had detectable concentrations, with 47.0% having levels ≥ 40 EU/mL.

The GMC of antibodies to anti-PT was 7.9 EU/mL (95% CI: 6.8; 9.2) in maternal pre-vaccination sera, 31.1 EU/mL (95% CI: 26.6; 36.3) in maternal post-vaccination sera, and 37.8 EU/mL (95% CI: 32.3; 44.1) in newborns (P < 0.001). The ratio of transplacental transfer of antibodies to anti-PT was 146.6%. There was a concordance between determinations > 10 EU/mL in maternal and newborn sera of 88.6% (117). Lin's concordance index rate between post-vaccination maternal and newborn levels was 0.8 (95% CI: 0.8; 0.9). No significant differences between maternal age group, history of immune system disorders, twin pregnancy, weeks of vaccine administration, weeks between vaccination and delivery, newborn sex were found. Estimations of GMCs of antibodies to anti-PT based on the half-life of maternal antibodies indicated that at 2 months of age before the first primary series dose, 66% of infants would have levels ≥ 10 EU/mL and 89% would have detectable levels (≥ 5 EU/mL).

The authors concluded that there was a high correlation between antibody levels in maternal blood and in newborns from mothers vaccinated during pregnancy with Tdap vaccine, with higher levels in newborns, which should be sufficient to provide protection against pertussis during the first months of life. Vaccination of pregnant women seems to be an immunogenic strategy to protect newborns. The authors noted several limitation of this study. Information on previous doses of pertussis vaccination and the personal histories of pertussis disease were not collected. A higher sample size would be desired. Likewise, other pertussis antigens potentially involved in protection against pertussis infection were not determined and data of clinical protection against pertussis was not available. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2016, Fallo et al (61) reported the results of a prospective observational study of paired maternal blood and umbilical cord blood samples in pregnant women who did (2013–2014) or did not (2011–2012) receive maternal Tdap vaccination in Argentina. This study included serologic data from 205 healthy pregnant women (105 with Tdap vaccination and 100 without) and 69 healthy nonpregnant women. The mean (SD) age of mothers was 26.5 (6.3) years in women who received Tdap vaccine, 26.7 (6.5) years in women who did not receive Tdap vaccine, and 28 (6) years in the control group. Mothers received their Tdap vaccine at a mean (SD) of 24.7 (4.8) weeks of gestation (range, 13.2–36.6 weeks).

The GMCs of antibodies to anti-PT in women and in cord samples at delivery were statistically significantly higher in women who received Tdap vaccine during pregnancy compared with those without Tdap immunization ($P < 0.0001$ and $P < 0.0003$). The anti-PT level was < 5 EU/mL in 3 (2.9%) of the 105 mothers who received Tdap vaccine during pregnancy and 16 (16.1%) of the 99 mothers not immunized during pregnancy ($P < 0.001$).

In both groups (immunized and non-immunized), the cord blood concentrations of anti-PT were higher than the anti-PT concentrations in maternal serum at delivery. These concentrations were linearly correlated. The placental antibody transference efficiencies (measured as the ratio of the cord blood GMC to the maternal GMC) were 1.46 for women who received Tdap vaccine during pregnancy and 1.18 for mothers not immunized during pregnancy.

Antibody levels of anti-PT following birth were evaluated in 36 infants in the first month of life and 32 of these 36 infants in the second month of life. The antibody concentrations to anti-PT in cord blood (48.4 EU/mL) decreased through the first (17.7 EU/mL) and second month of life (11.6 EU/mL).

A tendency toward lower antibody levels at delivery in mothers vaccinated before 20 weeks of gestation was observed, but there were no significant differences between maternal or cord serum levels and weeks of gestation at Tdap vaccination.

The authors concluded that women who received Tdap vaccine during pregnancy had significantly higher serum/cord GMCs to antibodies for anti-PT at birth than mothers who did not receive a Tdap vaccine. Timing of the immunization was not correlated with antibody concentrations. Infants born to mothers who received Tdap vaccine during pregnancy had significantly higher levels of anti-PT antibodies during their first 2 months of life. The authors noted that this study has some potential limitations. First, only PT antibodies were measured, because other pertussis antigens were not available in Argentina when the study was done. Second, this study was prospective and observational rather than randomized, and Tdap-

immunized pregnant women and nonimmunized women were not enrolled concurrently. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

5.1.2 Antibody Responses to DTaP-containing Vaccine in Infants of Women Who Received Tdap Vaccine During Pregnancy

5.1.2.1 Randomized Clinical Trials

A summary of the 5 randomized clinical trials that support the immunogenicity of Tdap vaccine in infants whose mothers received Tdap vaccine during pregnancy is provided in Table 5.3.

Four publications are provided in Module 5.4 of this CTD and 1 article (Halperin et al (19)) is in press.

Immunogenicity objectives and methods are summarized for each study in [Section 2.2.1] of 2.7.3 Summary of Clinical Efficacy.

Ethical requirements of the studies were documented:

- All 5 randomized clinical trials were reviewed by an institutional review board and/or ethics committee and participants signed informed consent prior to participation.

Table 5.3: Randomized Clinical Trials Supporting Immunogenicity Through the Booster Dose in Infants of Women Who Received Tdap Vaccine During Pregnancy

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Munoz et al (2014) (18)	Phase I/II, randomized, double-blind, placebo-controlled, cross-over	United States Oct 2008–May 2012	Total pregnant women/infants: 48 Tdap vaccine: 33 Placebo: 15 Healthy nonpregnant women: 32	Pregnant women: Tdap5 or placebo Infants: DTaP5-IPV/Hib	I	Good
Villarreal Pérez et al (2017) (43)	Randomized, double-blind, parallel-group, placebo-controlled	Mexico Sep 2011–Aug 2014	Total pregnant women/infants: 171 Tdap vaccine: 90 Placebo: 81	Pregnant women: Tdap5 or placebo Infants: DTaP5-IPV//Hib	I	Good
Halperin et al (2018) (19)	Randomized, controlled, observer-blinded, multicenter	Canada Nov 2007–Jun 2011 Mar 2012–Apr 2014	Pregnant women/infants: 273/272 Tdap vaccine: 135/134 Td Adsorbed vaccine: 138/138	Pregnant women: Tdap5 or Td Adsorbed Infants: DTaP5-IPV-Hib	I	Good

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Hoang et al (2016) (44)	Randomized, controlled, multicenter	Vietnam Infants born: 22 Feb 2013– 7 Oct 2013	Total pregnant women/infants: 103 Tdap vaccine: 52/51 Tetanus vaccine: 51/48	Pregnant women: Tdap5 or tetanus Infants: DTaP3-HBV-IPV/Hib	I	Fair
Maertens et al (2016) (23)	Randomized, controlled, multicenter (Booster dose, infants from Hoang et al)	Vietnam 4 Apr 2015– 10 Jun 2015	Infants of women: Tdap vaccine during pregnancy: 30 Tetanus only vaccine during pregnancy: 37	Pregnant women: Tdap5 or tetanus Infants: DTaP3-HBV-IPV/Hib	I	Poor

Note: The "3" or "5" designation following Tdap or DTaP is used to define the number of acellular pertussis components in the vaccine included in the study. In the individual summaries, to agree with the presentation in the publications, the numerical designation is not used unless needed for clarity (i.e., both Tdap3 and Tdap5 data presented within a study).

DTaP3-HBV-IPV/Hib: combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine, Infanrix hexa; DTaP5-IPV//Hib: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pentaxim; DTaP5-IPV-Hib: diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pediacel; DTaP5-IPV/Hib: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pentacel; Td Adsorbed: tetanus and diphtheria toxoids adsorbed vaccine; Tdap5: tetanus toxoid, reduced diphtheria toxoid, and (5-component) acellular pertussis vaccine, Adacel; USPSTF: United States Preventive Services Task Force

In 2014, Munoz et al (18) reported safety and immunogenicity results from a Phase I/II, randomized, double-blind, placebo-controlled clinical trial of Tdap vaccine in pregnant women and their infants that was conducted in the United States from October 2008–May 2012 and was sponsored by the NIAID. The study assessed the potential effect on infant immune responses to diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *Haemophilus* b conjugate (tetanus toxoid conjugate) vaccine (DTaP-IPV/Hib) immunizations through the booster dose. Safety results are provided in Section 4.1 and immunogenicity results for pregnant women are provided in Section 5.1.1.1.

Pertussis antibodies in infants born to mothers immunized during pregnancy were significantly higher at birth and 2 months than in infants whose mothers were immunized postpartum ($P < 0.001$ for Tdap vaccine antepartum vs. Tdap vaccine postpartum groups).

At 7 months of age, after receipt of 3 doses of DTaP-IPV/Hib vaccine, infants of women who received Tdap vaccine during pregnancy achieved equivalent concentrations of antibodies to PRN, PT, and FIM and significantly lower concentrations of antibodies to FHA compared with infants whose mothers received placebo during pregnancy (40.6 EU/mL [95% CI: 30.6; 54.0] vs. 78.6 EU/mL [95% CI: 52.9; 116.7], respectively; $P < 0.01$). However, at 13 months of age,

1 month after the fourth dose of DTaP-IPV/Hib vaccine, GMCs of pertussis antibodies were not statistically different in the 2 infant groups.

The authors concluded that maternal immunization with Tdap vaccine resulted in significantly higher concentrations of antibodies to all vaccine antigens in infants from birth until initiation of immunization with DTaP-IPV/Hib at age 2 months and did not substantially alter infant responses to DTaP-IPV/Hib. The authors noted several limitations. The small sample size limited the statistical power to detect differences in antibody responses in infants, particularly after administration of the third dose of DTaP vaccine. Second, antibody concentrations in infants after the first dose of DTaP were not measured. Last, this study was not designed to evaluate the efficacy of maternal immunization with Tdap vaccine to protect mothers or infants against pertussis disease. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2017, Villarreal Pérez et al (43) reported results of a randomized, double-blind, parallel group, placebo-controlled clinical trial conducted from September 2011–August 2014 in infants whose mothers received Tdap vaccine or placebo between 30 and 32 weeks of gestation in Mexico. The study assessed the interference of maternal antibodies from administration of Tdap vaccine during pregnancy in infants through the primary series of diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *haemophilus* b conjugate (tetanus toxoid conjugate) vaccine (DTaP-IPV//Hib). Immunogenicity results for pregnant women are provided in Section 5.1.1.1.

At 2 months, prior to the first dose of DTaP-IPV//Hib vaccine, infants of mothers who received Tdap vaccine during pregnancy had statistically significant higher GMCs of anti-PRN (71.41 EU/mL [95% CI: 56.80; 89.77]; P = 0.001) and anti-PT (95% CI: 10.95 EU/mL [95% CI: 8.71; 13.77]; P = 0.001) antibodies than infants of mothers who received placebo during pregnancy (6.93 EU/mL [95% CI: 5.52; 8.72]) and (6.20 EU/mL [95% CI: 4.96; 7.73]). Prior to the DTaP-IPV//Hib vaccine doses at 4 and 6 months, infants of mothers who received Tdap vaccine during pregnancy had statistically significant higher GMCs of anti-PRN antibodies (35.35 EU/mL [95% CI: 27.59; 45.29] and 16.75 EU/mL [95% CI: 12.94; 21.68], respectively; P = 0.001) than infants of mothers who received placebo during pregnancy (5.07 EU/mL [95% CI: 4.15; 6.19] and 4.51 EU/mL [95% CI: 3.80; 5.35], respectively); however the GMCs of anti-PRN antibodies decreased through 6 months in both groups. At these same 2 time points, the infants of mothers who received placebo during pregnancy had statistically higher GMCs of anti-PT antibodies (20.45 EU/mL [95% CI: 16.71; 25.03] and 69.13 EU/mL [95% CI: 59.10; 80.87], respectively) than infants of mothers who received Tdap vaccine during pregnancy (14.77 EU/mL [95% CI: 12.35; 17.66] and 49.09 EU/mL [95% CI: 40.86; 58.99], respectively); the GMCs of anti-PT antibodies increased through 6 months in both groups.

The authors concluded that the children of mothers who were vaccinated with Tdap vaccine experience delayed production of anti-pertussis antibodies for up to 6 months. The vaccination of pregnant women with Tdap vaccine generates antibodies in the mother that can be lost within 2 months; however, Tdap vaccination appears to be a feasible and safe strategy for providing their children with antibodies against pertussis. In addition to the limitation noted in Section 5.1.1.1, other limitations included that children were not followed up to determine whether they later contracted whooping cough, which would be demonstration of the vaccine's immunogenicity. Also, antibodies against PRN decreased rapidly during the child's second month of life; however,

it is unknown whether these levels remained protective against the disease. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2018, Halperin et al (19) reported results from an observer-blinded, multicenter, randomized clinical trial of the safety and immunogenicity of Tdap immunization during pregnancy in Canada that was conducted from November 2007–April 2014. Safety results are provided in Section 4.1 and immunogenicity results for pregnant women are provided in Section 5.1.1.1. A total 273 women were randomized and immunized with Td Adsorbed vaccine (n = 138) or Tdap vaccine (n = 135). Of the 272 infants born, 126 (91.3%) of 138 infants of mothers who received Td Adsorbed vaccine and 121 (90.3%) of 134 infants of mothers who received Tdap vaccine completed the study.

The primary outcome measure was met for all 4 pertussis antibodies; antibody levels at birth in the infants of Tdap-immunized women were non-inferior to the antibody levels at 6 months (post-infant primary series Dose 2) in infants of Td Adsorbed-immunized women.

While pertussis antibody levels at birth and at 2 months of age (prior to the first diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine and *Haemophilus* b conjugate [tetanus toxoid conjugate] vaccine [DTaP-IPV-Hib] primary series dose) were significantly higher in infants of Tdap-immunized women compared with infants of Td Adsorbed-immunized women ($P < 0.001$ for all comparisons), these higher levels diminished over time. At 4 months of age (post-primary series Dose 1 and pre-Dose 2), antibody levels were higher in infants of Tdap-immunized women for FHA, PRN, and FIM ($P < 0.001$ for all comparisons) and equal for PT. By 6 months of age (post-primary series Dose 2 and pre-Dose 3), antibody levels against PT and FHA were lower in infants of Tdap-immunized women compared to infants of Td Adsorbed-immunized women; PRN and FIM were similar between the 2 groups. By 7 months of age (post-primary series Dose 3), antibody levels were lower for all pertussis antigens in infants of Tdap-immunized women ($P = 0.002$ for PT and $P < 0.001$ for FHA, PRN, and FIM). These significantly lower levels persisted for all antigens at 12 months of age and for PT, FHA, and FIM post-booster.

The authors concluded that this study demonstrated that Tdap vaccine during pregnancy results in higher levels of antibodies early in infancy but lower levels after the primary vaccine series. The higher levels at birth may provide protection during the highest risk of severe pertussis in the first few months of life, but this may be at the expense of increased susceptibility during the second half of the first year of life. The authors noted that a limitation of the study was that all infants in the study were immunized with acellular pertussis vaccine and the effects of maternal immunization with Tdap vaccine on an infant series with whole cell pertussis-containing vaccines which are used in many parts of the world may differ. **Overall, this study provides USPSTF evidence level I and evidence quality category of good.**

In 2016, Hoang et al (44) reported the immunogenicity results of a randomized, controlled trial conducted in Vietnam of maternal Tdap or tetanus only immunization through the primary series in 51 infants of women who received Tdap vaccine during pregnancy and 48 infants of women who received tetanus only vaccine during pregnancy. Pregnant women received Tdap vaccine or tetanus only vaccine between 18 and 35 weeks of gestation during pregnancy and their infants were born from February 2013–October 2013. Safety results are provided in Section 4.1 and

immunogenicity results for pregnant women are provided in Section 5.1.1.1. The immunogenicity results following the booster dose were reported by Maertens et al (23) and are presented below.

The mean gestational age at delivery was 39.5 weeks in both study groups. Significantly higher concentrations were observed for all antigens in the cord blood samples in the Tdap vaccine group. At Month 2, GMCs of antibodies to all pertussis antigens were still significantly higher in the Tdap vaccine group. At Month 5, the antibody concentration for PRN was significantly lower in the Tdap vaccine group (132.6 EU/mL [95% CI: 104; 168] vs. 83 EU/mL [95% CI: 65; 104], P = 0.006); however, the GMCs of anti-PT (P = 0.753) and anti-FHA (P = 0.198) antibodies did not differ significantly between the 2 groups.

The authors concluded that there was a minimal blunting effect for anti-PRN antibodies. Further research is needed to assess the effects of high maternal antibody titers on the immune responses of infants to whole cell pertussis vaccines used in low- and middle-income countries. A comparative study on different brands of pertussis vaccines in pregnancy could shed light on the induction of qualitative and quantitative differences between the induced maternal antibodies. The authors noted limitations of the study included a change in the planned infant series vaccine due to a national change from whole cell to acellular pertussis vaccine for safety reasons unrelated to this study and hence a delayed start of the first vaccine dose in infants. Also, the intention was to analyze the children's samples in Vietnam to avoid transport to Belgium where the women and the umbilical cords samples were tested. However, cross-validation of a subset of the children's samples revealed major differences in the results. Therefore, all samples were transported to and tested in Belgium. Leftover samples were used, resulting in a limited amount of missing data (16.1%). Cross-validation in a Canadian laboratory indicated good correlation of the data.
Overall, this study provides USPSTF evidence level I and evidence quality category of fair.

In 2016, Maertens et al (23) reported the post-booster responses in 30 infants included in the Tdap vaccine group and 37 infants included in the tetanus only vaccine group in the Hoang et al (44) study described above. The study was conducted from 4 April 2015–10 June 2015. Infants were vaccinated with a fourth dose of combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine (DTaP-HBV-IPV/Hib) at a mean age of 22.18 months (range, 18.5–24.7 months).

One month after administration of the booster dose, the GMCs of pertussis antibodies were comparable but lower in infants whose mothers received Tdap vaccine during pregnancy than in infants whose mothers received tetanus only vaccine during pregnancy: anti-PT (129.0 [95% CI: 97.5; 170.7] vs. 133.7 [95% CI: 106.6; 167.6], anti-FHA (161.3 [95% CI: 134.1; 193.9] vs. 181.7 [95% CI: 160.3; 206.0], and anti-PRN (159.0 [95% CI: 141.2; 179.0] vs. 187.1 [95% CI: 163.8; 213.6]).

The authors concluded that the blunting of infant pertussis responses induced by maternal immunization, measured after a primary series of acellular pertussis vaccine, was resolved with the booster acellular pertussis vaccine dose. These results add to the evidence for national and international decision makers on maternal immunization as a vaccination strategy for protection of young infants against infectious diseases. The authors noted a number of limitations. First, no blood samples were taken before the administration of the fourth vaccine dose. Second, due to a delay in ethical approval, not all children were vaccinated with the same vaccine as a fourth vaccine dose. During the follow-up of the study, there was a dropout rate due to moving of

participants to other provinces. **Overall, this study provides USPSTF evidence level I and evidence quality category of poor.**

5.1.2.2 Cohort and Observational Studies

A summary of 4 cohort and observational studies supporting the immunogenicity of Tdap vaccine in infants of pregnant women who received Tdap vaccine during pregnancy is provided in Table 5.4.

All publications are provided in Module 5.4 of this CTD.

Immunogenicity objectives and methods are summarized for each study in [Section 2.2.2] of 2.7.3 Summary of Clinical Efficacy.

Ethical requirements of the studies were documented:

- Ladhani et al (62) noted that the Public Health England (PHE) Research Sponsorship Review Group considered that the evaluation was designed and conducted solely to judge an intervention already in clinical use and thus met the National Research Ethics Service criteria for a service evaluation and did not require formal ethics review. Written informed consent for participation was obtained from parents/guardians.
- Hardy-Fairbanks et al (22), Vilajeliu et al (63), and Kent et al (64) noted that the studies were approved by institutional review boards or ethics committees and informed consent was obtained.

Table 5.4: Cohort or Observational Studies Supporting Immunogenicity Through the Booster Dose in Infants of Women Who Received Tdap Vaccine During Pregnancy

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Ladhani et al (2015) (62)	Observational	United Kingdom Dec 2012–Jul 2014 Historical cohort: 2011–2012	Infants of women who received Tdap-IPV vaccine during pregnancy: 141 Historical cohort infants of unvaccinated pregnant women: 246	Pregnant women: Tdap5-IPV Infants: DTaP5-IPV-Hib	II-2	Good
Hardy-Fairbanks et al (2013) (22)	Prospective cohort	United States Tdap vaccine during pregnancy: 2006 pseudo-outbreak Unvaccinated during pregnancy: Mar 2008–Feb 2009	Pregnant women/infants Tdap vaccine: 16 Unvaccinated: 54	Pregnant women: Tdap5 Infants: DTaP (multiple products)	II-2	Fair

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Vilajeliu et al (2016) (63)	Prospective, observational	Spain Nov 2014	Infants of women who received Tdap vaccine during pregnancy: 37	Tdap5	II-2	Fair
Kent et al (2016) (64)	Observational	England May 2012–May 2014	Premature infants Mothers received Tdap-IPV vaccine during pregnancy: 31 Mothers unvaccinated during pregnancy: 129	Pregnant women: Tdap5-IPV Infants: DTaP5-IPV-Hib	II-2	Fair

Note: The "5" designation following Tdap or DTaP is used to define the number of acellular pertussis components in the vaccine included in the study. In the individual summaries, to agree with the presentation in the publications, the numerical designation is not used.

DTaP: diphtheria, tetanus, and acellular pertussis; DTaP5-IPV-Hib: Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed combined with inactivated poliomyelitis vaccine and *Haemophilus* b conjugate (tetanus toxoid conjugate) vaccine, Pediacel; IPV: inactivated poliovirus vaccine; Tdap5: tetanus toxoid, reduced diphtheria toxoid, and (5-component) acellular pertussis vaccine, Adacel/COVAXIS; Tdap5-IPV: REPEVAX; USPSTF: United States Preventive Services Task Force

In 2015, Ladhani et al (62) reported the results of an open, non-randomized, observational study conducted from December 2012–July 2014 in the United Kingdom that compared antibody levels after the primary series in 141 infants of mothers who received Tdap-IPV during the third trimester with a historical cohort (2011–2012) of 246 infants of unvaccinated mothers.

In infants born to women who received Tdap-IPV during pregnancy, the median interval (interquartile range [IQR]) between antenatal vaccination and infant birth was 9.9 (IQR, 8.0–11.1) weeks. The infants' median (IQR) ages at pre- and post-immunization blood samples were 55 (52–58) and 151 (144–161) days, respectively, and ages at each vaccination visit were 59 (57–61), 89 (86–95), and 119 (115–128) days.

Infants had high pertussis antibody concentrations pre-immunization but only PT antibodies increased post-primary series immunization (fold-change, 2.64; 95% CI: 2.12; 3.30; $P < 0.001$), whereas FHA antibodies fell (fold-change, 0.56; 95% CI: 0.48; 0.65; $P < 0.001$). Compared with infants of unvaccinated mothers, PT, FHA, and FIM antibodies were lower post-primary series vaccination, with fold-differences of 0.67 (95% CI: 0.58; 0.77; $P < 0.001$), 0.62 (95% CI: 0.54; 0.71; $P < 0.001$) and 0.51 (95% CI: 0.42; 0.62; $P < 0.001$), respectively.

The authors concluded that antenatal pertussis immunization results in high infant pre-immunization antibody concentrations, but blunts subsequent responses to pertussis vaccine antigens. In countries with no pertussis booster until school age, continued monitoring of protection against pertussis is essential. The authors noted that historical controls have limitations. Lack of randomization may result in bias due to differences in characteristics of participating subjects and non-contemporary comparisons may be affected by temporal changes that could

influence antibody responses. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of good.**

In 2013, Hardy-Fairbanks et al (22) reported results of prospective cohort study conducted from March 2008–February 2009 in the United States that included infants who had their primary series (2, 4, and 6 months) and booster dose (12–18 months) of DTaP vaccine and whose mothers received or did not receive Tdap vaccine during pregnancy.

At 2 months of age (before the first infant vaccination), pertussis antibody GMCs in infants of mothers vaccinated with Tdap vaccine during pregnancy remained higher than those of control infants (3.2- to 22.8-fold greater). Following the primary series, antibody concentrations to pertussis antigens were modestly lower in the Tdap vaccine group (0.7- to 0.8-fold lower), except for FIM (1.5-fold greater). Antibody concentrations before and after the booster dose of DTaP at 12–18 months of life showed no notable differences between groups. The differences in FIM values before and after the booster dose are difficult to interpret, due to the differences in FIM content of the different DTaP vaccine preparations.

At every time point, the percentages of infants who achieved benchmark concentrations of antibody were higher in the Tdap vaccine group until 7 months of life. At this point, the concentration of FIM antibody decreased, likely due to the absence of FIM in most of the DTaP vaccine products administered to the Tdap vaccine group.

During the period between birth and the first dose of DTaP, the antibody concentrations to pertussis antigens of infants in the Tdap vaccine group remained in the presumed protective range and were higher than those of control infants. At 7 months, the GMCs of antibodies in the Tdap vaccine group and the control group, respectively, were 56.8 and 75.2 EU/mL for PT, 61.4 and 83.6 EU/mL for FHA, 34.1 and 50.7 for PRN, and 15.0 and 10.0 EU/mL for FIM. The GMCs of all antibodies decreased prior to the booster dose (ranged from 2.0 EU/mL for FIM to 24.5 EU/mL for FHA in the Tdap vaccine group and from 8.3 EU/mL for FIM to 22.7 EU/mL for FHA in the control group). In response to the booster dose given at 12 to 18 months of age, with the exception of FIM, both the Tdap vaccine and control groups showed increases in GMCs of antibodies to PT (64.0 and 75.1 EU/mL, respectively), FHA (86.9 and 93.2 EU/mL, respectively), PRN (100.2 and 105.2 EU/mL, respectively), and FIM (2.0 and 34.2 EU/mL, respectively).

The authors concluded that maternal Tdap immunization resulted in higher pertussis antibody concentrations during the period between birth and the first primary series vaccine dose. Although slightly decreased immune responses following the primary series were seen compared with controls, differences did not persist following the booster dose. In addition to the limitations noted in Section 5.1.1.2, control group infants received different formulations of DTaP vaccine, containing different antigen concentrations. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2016, Vilajeliu et al (63) reported the results of a prospective observational study conducted in November 2014 in Spain that compared anti-PT levels in 37 infants whose mothers received Tdap vaccine during pregnancy. The mothers received Tdap vaccine between 21 and 38 weeks of gestation, with the majority between 27 and 36 weeks. The majority of cases were from Spain (75.7%) and America (10.8%). A total of 48.7% of infants were male. The Tdap vaccine was administered between 1 and 19 weeks before delivery (median: 9.1 weeks). No infant was born

before 37 weeks of gestation. The median days between delivery and collection of the infant blood sample (follow-up) was 45 days (Q1–Q3: 42–48).

Infants of Tdap-vaccinated women showed a decline in the GMC of antibodies to anti-PT between peripartum and follow-up levels of 52.7 IU/mL (95% CI: 34.7; 80.2) in umbilical cord blood and an estimated 7.5 IU/mL (95% CI: 4.2; 13.3) at 2 months of age (Wilcoxon test paired samples, $P < 0.001$). There was no significant differences in anti-PT antibody concentrations according to the time elapsed between Tdap vaccine administration and the gestational age at delivery (Mann–Whitney, $P = 0.1964$). It was estimated that, at 2 months of age, 51.4% of infants would have detectable concentrations and 29.7% a high cut-off (≥ 10 IU/mL). Newborns of women vaccinated with Tdap vaccine during the third trimester (≥ 27 weeks of gestation) were expected to sustain the highest GMCs of antibodies to anti-PT over time, although the finding was not significant (Mann–Whitney, $P = 0.0842$).

The authors concluded that more than half the infants of mothers immunized during late pregnancy presented pertussis antibodies (anti-PT) before the start of primary infant vaccination. The authors noted that the study has some limitations. Information on previous doses of pertussis vaccination and the personal histories of pertussis disease were not collected. A higher sample size including premature infants would have been desirable. Other pertussis antigens potentially involved in protection against pertussis infection were not determined. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

In 2016, Kent et al (64) reported the results of a post hoc observational substudy of a multicenter, randomized, controlled vaccination trial in premature infants conducted from May 2012–May 2014 at neonatal units in England that compared pertussis antibody concentrations before and after primary immunization in premature infants whose mothers received Tdap-IPV in pregnancy with those born to unvaccinated mothers.

Mothers of 31 (19%) of 160 premature infants born at 28 to 35 weeks of gestation had received Tdap-IPV vaccine during pregnancy. The median gestation at maternal Tdap-IPV vaccine administration was 28.5 weeks (IQR: 28.0–29.6) and the median interval between vaccination and delivery was 24 days (IQR: 9–35). The median birth gestation was slightly older in infants of vaccinated mothers compared with unvaccinated mothers (32.6 vs. 31.0 weeks), although this difference was not statistically significant ($P = 0.057$).

Compared with infants of unvaccinated mothers, those born to Tdap-IPV vaccinated mothers had significantly higher antibody concentrations for pertussis (PT, FHA, and FIM) antigens at 2 months ($P < 0.001$. After primary immunization, infants of Tdap-IPV vaccinated mothers had significantly lower antibody concentrations for FHA (23.04 µg/mL [95% CI: 16.17; 32.85] vs. 45.55 µg/mL [95% CI: 37.64; 55.12]; $P = 0.003$), compared with infants of unvaccinated mothers; there were no other significant differences for the other pertussis antibody concentrations (PT and FIM) between the groups. At 12 months of age, no significant differences for the pertussis antibody concentrations between groups were found.

The authors concluded that maternal vaccination with Tdap-IPV vaccine administered early in the third trimester may provide protection for infants born prematurely. The authors noted that there are some limitations with these data. As an observational substudy of a larger clinical trial, the trial design did not permit measurement of antibody concentrations (either maternal or infant) at birth. There was limited information on maternal vaccination history outside of pregnancy.

Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.

5.1.3 Summary of Immunogenicity in the Literature

Antibody Responses to Tdap Vaccine in Pregnant Women and Their Infants at Birth

One study, reported by Munoz et al (18), compared antibody responses to each antigen in Tdap vaccine in women who received Tdap vaccine during the third trimester of pregnancy and nonpregnant women. At 4 weeks after vaccination, there were no differences in antibody responses to the pertussis antigens in Tdap vaccine between these groups. At 2 months after delivery, Munoz et al (18) reported that women vaccinated postpartum with Tdap vaccine had statistically higher GMCs for antibodies to anti-PT than women who received Tdap vaccine during pregnancy; however, the GMCs for antibodies to anti-FHA, anti-PRN, anti-FIM were similar between the groups.

In the randomized clinical trials of women who received Tdap vaccine during pregnancy reported by Munoz et al (18), Villarreal Pérez et al (43), Halperin et al (19), and Hoang et al (44), the pre-vaccination GMCs for antibodies to each pertussis antigen were similar in each group within a study. At delivery, women who received Tdap vaccine during pregnancy had significantly higher antibody responses to each pertussis antigen compared with women who received placebo (18) (43), Td adsorbed vaccine (19), or tetanus only vaccine (44) during pregnancy.

Halperin et al (19) assessed the GMCs of antibodies to pertussis antigens through 12 months postpartum in women who received Tdap or Td Adsorbed vaccine during the third trimester of pregnancy. Antibody levels against all pertussis antigens decreased in a somewhat linear manner for the 12 months postpartum in women who received Tdap vaccine during pregnancy, with levels declining by just more than 50%; however, all remained significantly higher than pre-vaccination levels. Antibody levels against all pertussis antigens at 12 months after delivery in the Td Adsorbed group were similar to the levels at 2 months after delivery.

Munoz et al (18), Halperin et al (19), and Hoang et al (44) reported transplacental transfer of pertussis antibodies. At delivery, the ratios of infant cord blood pertussis antibodies to maternal pertussis antibodies were > 1 suggesting active transport of antibody across the placenta. Villarreal Pérez et al (43) reported that the cord:2-month old child serum ratio for PRN was 1.78 and for PT was 2.5.

Hardy-Fairbanks et al (22) and Gall et al (59) both reported that maternal and cord antibody concentrations to pertussis antigens (PT, FHA, PRN, and FIM) were higher among women who received Tdap vaccine during pregnancy compared with women who did not receive Tdap vaccine during pregnancy. A greater percentage of women who received the Tdap vaccine during pregnancy (75.0%–100%) and their infants cord blood (80.0%–100%) had antibody concentrations to each of the 4 pertussis antigens that were at or above defined benchmark protective concentrations at birth (defined as > 5 EU/mL for PT and FHA and > 10 EU/mL for PRN and FIM) as compared with the control group of unvaccinated women and their infants (35.8%–66.0% and 39.6%–81.1%, respectively) (22). Additionally, there was a significant increase in the odds that newborns from mothers who received Tdap vaccine during pregnancy were protected against pertussis based on anti-PT (88.5% vs. 40.4%; OR, 11.32; 95% CI: 4.10; 31.24: P < 0.0001), and anti-FIM (98.1% vs. 84.6%; OR, 9.27; 95% CI: 1.12; 77.07: P = 0.0146)

antibody concentrations, but not on FHA and PRN, compared to newborns from mothers who did not receive Tdap vaccine during pregnancy (59).

The importance of timing of maternal Tdap immunization was studied by Healy et al (42). There was no difference in GMCs of antibodies to pertussis antigens in maternal delivery or infant cord sera for women immunized before or during early pregnancy in the United States. Placental transport of maternal pertussis-specific antibodies was efficient, ranging from 121% to 165% for PT, 145% to 178% for FHA, 131% to 186% for FIM, and 148% to 173% for PRN, for mothers immunized before and during pregnancy, respectively. Estimated GMC of antibody to PT was < 5 EU/mL at infant age 2 months (start of infant immunization series). Only 41 infants (40%) had a PT-specific antibody concentration at birth calculated to persist above the LLOQ (4 EU/mL) of the assay at age 2 months. Slightly more infants of mothers who were immunized during pregnancy, and 2 of the 3 immunized after Week 20, had PT levels at birth that would persist above the LLOQ through 2 months of age (52% vs. 38%; P = 0.34).

Vilajeliu et al (60) compared anti-PT levels in women during pregnancy (pre- and post-vaccination) with respect to levels in the newborn at delivery. Anti-PT levels ≥ 10 IU/mL were found in 90.2% of maternal post-vaccination sera, and 94.7% of neonates. All newborn samples had detectable concentrations, with 47.0% having levels ≥ 40 IU/mL. The ratio of transplacental transfer of antibodies to anti-PT was 146.6%. There was a concordance between determinations > 10 IU/mL in maternal and newborn sera of 88.6%. Lin's concordance index rate between post-vaccination maternal and newborn levels was 0.8 (95% CI: 0.8; 0.9).

Fallo et al (61) reported that newborns born from mothers (n = 105) who received Tdap vaccine during pregnancy had significantly higher concentrations of antibodies in cord blood to anti-PT when compared to newborns from mothers who did not receive Tdap vaccine (n = 100). The placental antibody transference efficiencies for PT were 1.46 for women who received Tdap vaccine during pregnancy and 1.18 for mothers not immunized during pregnancy. The antibody concentrations to anti-PT in cord blood (48.4 EU/mL) decreased through the first (17.7 EU/mL) and second month of life (11.6 EU/mL).

Timing of gestational Tdap vaccine administration was assessed by Fallo et al (61) and a tendency toward lower antibody levels at delivery in mothers vaccinated before 20 weeks of gestation was observed; but, there were no significant differences between maternal or cord serum levels and weeks of gestation at Tdap vaccination.

Antibody Responses to DTaP-containing Vaccines in Infants of Women who Received Tdap Vaccine During Pregnancy

Antibody responses to pertussis antigens through the infant series or booster dose of DTaP vaccines in infants whose mothers received Tdap vaccine during the infant series or received placebo or a tetanus-containing vaccine during pregnancy were reported by Munoz et al (18), Villarreal Pérez et al (43), Halperin et al (19), Hoang et al (44), and Hardy-Fairbanks (22).

In these 4 randomized clinical trials and in 1 prospective cohort study, at 2 months of age prior to the first primary series dose of DTaP vaccine, antibody concentrations to all pertussis antigens were statistically significantly higher in infants whose mothers received Tdap vaccine during pregnancy compared with infants whose mothers received placebo (or no Tdap vaccine during pregnancy in the Hardy-Fairbanks et al study) or tetanus-containing vaccines during pregnancy.

At 6 months of age (pre-Dose 3), Villarreal Pérez et al (43) reported that infants of mothers who received Tdap vaccine during pregnancy had significantly higher GMCs of anti-PRN antibodies than infants of mothers who received placebo during pregnancy and infants of mothers who received placebo during pregnancy had significantly higher GMCs of anti-PT antibodies (69.13 EU/mL) than infants of mothers who received Tdap vaccine (49.09 EU/mL). Additionally, at this same time point Halperin et al reported antibody levels against PT and FHA were lower in infants of Tdap-immunized women compared to infants of Td Adsorbed-immunized women; PRN and FIM were similar between the 2 groups.

In general, it should be noted that antibody levels after the primary series and booster dose of DTaP are lower (*blunted*) in infants of mothers immunized with Tdap vaccine during pregnancy. Munoz et al found that at 7 months of age, after receipt of 3 doses of DTaP-IPV/Hib (2, 4, 6, month schedule), infants of women who received Tdap vaccine during pregnancy achieved equivalent concentrations of antibodies to PRN, PT, and FIM, and significantly lower concentrations of antibodies to FHA compared with infants whose mothers received placebo during pregnancy (40.6 EU/mL vs. 78.6 EU/mL, respectively; $P < 0.01$). However, at this same time point, Halperin et al reported antibody levels that were significantly lower for all pertussis antigens in infants of Tdap-immunized women ($P = 0.002$ for PT and $P < 0.001$ for FHA, PRN, and FIM).

In a small prospective cohort study of 16 pregnant women who received Tdap vaccine during pregnancy and 54 pregnant women who did not, reported by Hardy-Fairbanks et al (22), antibody concentrations to pertussis antigens after the primary series at 7 months of age, after receipt of 3 doses of DTaP-containing vaccine (2, 4, 6, month schedule), were modestly lower in the Tdap vaccine group (0.7- to 0.8-fold lower), except for FIM (1.5-fold greater).

Hoang et al (44) found that at 5 months of age, after receipt of 3 doses of DTaP-HBV-IPV-Hib (2, 3, 4 month schedule), infants whose mothers received Tdap vaccine during pregnancy achieved equivalent concentrations of antibodies to PT and FHA, and had significantly lower concentrations to PRN compared with infants whose mothers received tetanus only vaccine during pregnancy (132.6 EU/mL vs. 83 EU/mL, $P = 0.006$).

In the study reported by Halperin et al (19), significantly lower GMCs persisted pre-booster at 12 months for all the pertussis antibodies and post-booster for PT, FHA, and FIM in women who received Tdap vaccine during pregnancy. In smaller studies, Munoz et al (18) and Maertens et al (23) reported that GMCs of pertussis antibodies were not statistically different 1 month after the booster dose in infants of women who received Tdap vaccine during pregnancy compared with placebo in the Munoz et al study and with tetanus only vaccine in Maertens et al study. Hardy-Fairbanks reported that antibody concentrations (anti-PT, anti-FHA, and anti-PRN) before and after the booster dose of DTaP at 12–18 months of age showed no notable differences between groups.

Another study reported by Vilajeliu et al (63) included 37 infants whose mothers received Tdap vaccine during pregnancy in Spain. Infants of Tdap-vaccinated women showed a decline in the GMC of antibodies to anti-PT between peripartum and follow-up levels of 52.7 IU/mL (95% CI: 34.7; 80.2) in umbilical cord blood and an estimated 7.5 IU/mL (95% CI: 4.2; 13.3) at 2 months of age (Wilcoxon test paired samples, $P < 0.001$). There was no significant differences in anti-PT antibody concentrations according to the time elapsed between Tdap vaccine administration and

the gestational age at delivery (P = 0.1964). It was estimated that, at 2 months of age, 51.4% of infants would have detectable titers and 29.7% a high cut-off (≥ 10 IU/mL). Newborns of women vaccinated with Tdap vaccine during the third trimester (≥ 27 weeks of gestation) were expected to sustain the highest GMCs of antibodies to anti-PT over time, although the finding was not significant (Mann–Whitney, P = 0.0842).

Ladhani et al (62) reported the results from an observational study of 141 infants born to women who received Tdap-IPV in pregnancy that compared the antibody responses following the primary series with a historical cohort of 246 infants of unvaccinated mothers. Infants had high pertussis antibody concentrations pre-immunization but only PT antibodies increased post-primary series immunization (fold-change, 2.64; 95% CI: 2.12; 3.30; P < 0.001), whereas FHA antibodies fell (fold-change, 0.56; 95% CI: 0.48; 0.65; P < 0.001). Compared with infants of unvaccinated mothers, PT, FHA, and FIM antibodies were lower post-primary series vaccination, with fold-differences of 0.67 (95% CI: 0.58; 0.77; P < 0.001), 0.62 (95% CI: 0.54; 0.71; P < 0.001) and 0.51 (95% CI: 0.42; 0.62; P < 0.001), respectively.

Kent et al (64) compared pertussis antibody concentrations before and after primary immunization in premature infants whose mothers received Tdap-IPV in pregnancy (n = 31) with those born to unvaccinated mothers (n = 129). Compared with infants of unvaccinated mothers, those born to Tdap-IPV vaccinated mothers had significantly higher antibody concentrations for pertussis (PT, FHA, and FIM) antigens at 2 months (P < 0.001). After primary immunization, infants of Tdap-IPV vaccinated mothers had significantly lower antibody concentrations for FHA (23.04 µg/mL vs. 45.55 µg/mL; P = 0.003) compared with infants of unvaccinated mothers; there were no other significant differences between the groups. At 12 months of age; there were no significant differences between groups in the pertussis antibody concentrations.

5.2 Vaccine Effectiveness

5.2.1 Case-Coverage, Case-Control, and Cohort Studies

A summary of 4 vaccine effectiveness (VE) case-coverage/-control and cohort studies that support the use of Tdap vaccine during pregnancy is provided in Table 5.5.

All publications are provided in Module 5.4 of this CTD.

Vaccine effectiveness objectives and methods are summarized for each study in [Section 2.3] of 2.7.3 Summary of Clinical Efficacy.

Ethical requirements of the studies were documented:

- The 2 publications by Amirthalingam et al (24) (65) had no mention of review by an ethical committee; both studies used the CPRD database, a primary care dataset containing anonymized information for patients.
- Baxter et al (66) noted that the study was approved by an institutional review board. The study used unique medical record numbers in the KPNC database to link mothers and infants.

- Dabrera et al (67) noted that the study was undertaken as part of a national outbreak response, ethical approval was not required and data collation was covered by existing information governance approvals.

Table 5.5: Case-Coverage, Case-Control, and Cohort Studies Supporting Vaccine Effectiveness of Tdap Vaccine During Pregnancy to Protect Young Infants From Pertussis Disease

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Amirthalingam et al (2014) (65)	Case-coverage	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: 82 Maternal coverage: 26,684 live births	Tdap5-IPV	II-2	Good
Amirthalingam et al (2016) (24)	Case-coverage	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: 243 Maternal vaccine coverage: 72,781 live births	Tdap5-IPV 71% TdaP3-IPV 29%	II-2	Good
Baxter et al (2017) (66)	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 First year of life: 103	Pregnant women: Tdap5 (almost 80%)[a] Infants: DTaP (no product specified)	II-2	Good

Study Identifier	Study Design	Country/ Study Period	Number of Subjects	Study Vaccine	USPSTF Evidence Level	USPSTF Evidence Quality
Dabrera et al (2015) (67)	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	Tdap5-IPV	II-2	Fair

Note: The "3" or "5" designation following Tdap is used to define the number of acellular pertussis components in the vaccine included in the study. In the individual summaries, to agree with the presentation in the publications, the numerical designation is not used unless needed for clarity (i.e., both Tdap3 and Tdap5 data presented within a study).

DTaP: diphtheria, tetanus, and acellular pertussis; IPV: inactivated poliovirus vaccine; Tdap3, Tdap5: tetanus toxoid, reduced diphtheria toxoid, and (3-component or 5-component) acellular pertussis vaccine, Adacel; Tdap5-IPV: REPEVAX; USPSTF: United States Preventive Services Task Force

[a] Nicola P. Klein, MD, oral communication, October 8, 2017.

In 2014, Amirthalingam et al (65) reported results from a case-coverage study to estimate the effectiveness of maternal pertussis vaccination following initiation of a vaccination program in England offering 5-component acellular pertussis Tdap-IPV vaccine to all pregnant women between 28 and 38 weeks of gestation. Maternal vaccine coverage was estimated for 26,684 women in the CPRD database with a live birth from 1 October 2012–3 September 2013. Based on data from the CPRD database, maternal vaccine coverage by week peaked in January 2013 (78%) and then fell gradually through end of August 2013 (60%). Based on national data, coverage peaked in February 2013 (60%) and then fell to a reported coverage of 56% in September 2013.

Cases of laboratory-confirmed pertussis peaked in October 2012 then subsequently fell across all age groups; but was consistently higher in infants less than 3 months of age. In the first 9 months of 2013 compared with the same period in 2012, infants less than 3 months of age had the highest incidence of laboratory-confirmed pertussis but also the greatest fall after initiation of the vaccine program (328 cases in 2012 vs. 72 cases in 2013, -78% [95% CI: -72%; -83%). For the same period, a similar proportionate fall in hospital admissions for infants younger than 3 months was also observed (440 admissions in 2012 vs. 140 admissions in 2013, -68% [95% CI: -61%; -74%]).

In 2012, there were 14 deaths in infants with confirmed pertussis, all of whom were born before the vaccination program was introduced. In 2013, there were 3 pertussis-related deaths in infants whose mothers were not vaccinated in pregnancy. These fatalities were all in infants too young to be protected by vaccine (age 2–9 weeks at disease onset or sample date). There was a 79% fall in infant deaths from 2.02 per 100,000 live births in 2012 to 0.43 per 100,000 live births in 2013.

A total of 90 laboratory-confirmed cases of pertussis were included from infants born from 1 October 2013 with onset of disease by 30 September 2013. In these cases, 14 mothers (16%) were vaccinated during pregnancy (12 at least 7 days before birth, 1 within 7 days of birth, and 1 after birth). Age at onset of pertussis in infants was less than 2 months in 79 cases (88%), of which 66 cases (73%) were in infants of mothers who were not vaccinated during pregnancy. For

the analysis of VE, 82 cases were included after exclusion of ineligible cases (1 case in which the mother was vaccinated within 7 days of birth, and cases matched to zero coverage).

The primary analysis for maternal vaccination at least 7 days before birth in infants younger than 3 months gave a VE of 91% (95% CI: 84%; 95%). Vaccine effectiveness was the same for vaccination at least 28 days before birth and 7–27 days before birth (91%). An analysis for vaccination at least 7 days before birth in infants younger than 2 months gave a VE of 90% (95% CI: 82%; 95%). When coverage was reduced to a level that would more closely match routine coverage data (national data), VE was reduced slightly in infants younger than 3 months (84%) and younger than 2 months (82%).

Of the 6 confirmed cases in infants old enough to have completed their primary schedule (age ≥ 120 days) and born to mothers eligible for the program, only 2 had completed their primary course before disease onset; neither of their mothers received a pertussis vaccine during pregnancy.

The authors concluded that the vaccination program showed high VE against pertussis infection in infants, and that the program was well accepted, with routine coverage peaking at 60%. The assessment of the program of pertussis vaccination in pregnancy in England is consistent with high VE. This effectiveness probably results from protection of infants by both passive antibodies and reduced maternal exposure, and will provide valuable information to international policy makers. The authors noted the following limitation. Coverage varied by maternal age, which was a potential confounder because it will also be correlated to parity and other factors that could be associated with her likelihood of developing or acquiring pertussis and information on such additional factors (e.g., parity, ethnic group, and socioeconomic factors) was not sufficiently complete to be controlled for in the analysis. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of good.**

In 2016, Amirthalingam et al (24) provided an update to estimates of VE of the maternal vaccination program in England for the period from 1 October 2012–31 August 2015. In July 2014, the vaccine distributed for the national program in the United Kingdom was changed from a 5-component pertussis vaccine (Tdap5-IPV) to a 3-component pertussis vaccine (Tdap3-IPV).

From the CPRD database, there were a total of 72,781 live births from 1 October 2012 until 31 August 2015. The coverage of the maternal program in England achieved in the first year of the program was sustained over the subsequent 2 years. Monthly coverage from the national Immform data indicated that coverage was sustained between 50% and 62% from January 2013 to December 2015, with coverage increasing during the winter months and lower in the summer months, which may be attributed to the seasonal influenza program in England. In the CPRD dataset, vaccination coverage reached a peak of 78% in mothers giving birth in the first week of January 2013, but showed seasonal fluctuations (60% in summer months to 70% in winter months) similar to those observed with the Immform data; coverage in 2015 (70%) remained stable to the end of August 2015. Following introduction of the vaccine program, the majority (more than two-thirds) of women vaccinated received vaccine at least 8 weeks prior to delivery.

The primary analysis of vaccination at least 7 days prior to birth included 243 laboratory-confirmed cases of pertussis from infants born in the period from 1 October 2012 with onset by 30 September 2014. Of these cases, 35 had been born to vaccinated mothers, giving an overall VE

of 91% (95% CI: 88%; 94%) for infants < 3 months of age and 90% (95% CI: 86%; 93%) for infants < 2 months of age. There was no difference in VE for infants whose mothers received vaccine at least 4 weeks prior to delivery or 1 to 3 weeks prior to delivery (91% [95% CI: 88%; 94%] and 91% [95% CI: 80%; 96%], respectively). For infants whose mothers received vaccine up to 1 week before delivery and within 1 to 2 weeks following delivery (n = 3), VE was 43% (95% CI: −35%; 76%).

The maternal VE of the 5-component acellular pertussis vaccine and the 3-component acellular pertussis vaccine did not significantly differ (93% [95% CI: 89%; 95%] and 88% [95% CI: 79%; 93%], respectively).

From the 243 cases, there were a total of 11 deaths in infants, of whom 1 infant had a mother who had been vaccinated at least 1 week before delivery, but < 10 days. Vaccine effectiveness against death was calculated at 95% (95% CI: 79%; 100%).

A total of 73 children had received a childhood vaccine and were born after 1 October 2012. Of these children, the mothers of 26 had been vaccinated (number of cases from mothers vaccinated/total cases for dose: 11/43 children received 1 dose, 5/12 children received 2 doses, and 10/18 received 3 doses of their primary pertussis vaccines. Estimated VE indicates that maternal vaccination continues to offer protection to children who have received a first primary dose (82%), after which protection conferred through maternal immunization declines for infants who have received 2 doses (69%) and after completion of the primary infant schedule (29%), which is based on small numbers, declines further, although the point estimate remains above 0%.

The authors concluded that VE was > 90% for infants whose mothers received vaccine at least 1 week prior to delivery. Vaccine effectiveness was 95% against infant deaths. High levels of protection are conferred to infants who have received their first dose of the primary series and benefit is still above 0% after the third dose. In the United Kingdom, the pertussis vaccine program for pregnant women has been recommended as an outbreak response measure. Joint Committee on Vaccination and Immunization recommendation: women are recommended to receive pertussis vaccine from 20 weeks during pregnancy. No specific limitations were noted by the authors. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of good.**

In 2017, Baxter et al (66) reported the results of a retrospective cohort study of mothers who received Tdap vaccine during pregnancy and their infants at KPNC from 2010–2015. Among infants born during the study period, the percentage whose mothers received Tdap vaccine during pregnancy increased after the ACIP recommendations (< 1% in 2006–2008, 11.9% in 2010 to 87.4% by 2015). The majority of pregnant women vaccinated in KPNC from 2010–2015 received the Tdap vaccine at ≥ 20 weeks of gestation (75.1% for infants born between 2010 and 2012 and 98.4% for infants born between 2013 and 2015); by 2013, most pregnant women were vaccinated between 27 and 36 weeks of gestation (44.8% for infants born between 2010 and 2012 and 91.7% for infants born between 2013 and 2015). The percentage of mothers who received the Tdap vaccine during postpartum Days 0 to 14 peaked at 31.7% for infants born in 2010 and declined thereafter to 1.8% for infants born in 2015.

The study population consisted of 148,981 infants born from 2010–2015. The mothers of 68,168 infants, 45.8% of the study population, received the Tdap vaccine during pregnancy at least 8 days before birth. Seventeen infants (11.4 per 100,000 infants) in the study population

tested positive for pertussis by 2 months of age, and 110 (73.8 per 100,000 infants) tested positive by 1 year of age. Of the 110 pertussis cases in the first year of life, 103 were included in the analyses after censoring criteria for disenrollment were applied.

The VE of Tdap vaccine during pregnancy (≥ 8 days before birth) was 91.4% during the first 2 months of life and 69.0% during the first year of life. According to the investigator (Nicola P. Klein, MD, oral communication, October 8, 2017), about 80% of the pregnant women received Adacel (Tdap5). The VE of Tdap vaccine during pregnancy at preventing pertussis in infants by number of DTaP vaccine doses received by infants was 87.9% for 0 doses, 81.4% for 1 dose, 6.4% for 2 doses, and 65.9% for 3 doses. Within 30 days before or after the polymerase chain reaction test, 10 of the 17 infants were hospitalized for pertussis; no deaths occurred.

The authors concluded maternal Tdap vaccination during pregnancy was highly effective at protecting infants against pertussis before their first dose of the DTaP vaccine, and protection continued after the first DTaP dose through the first year of life. There was no evidence supporting the effectiveness of maternal postpartum cocooning with the Tdap vaccine. The study validates the current US recommendation to vaccinate with Tdap during pregnancy, and suggests that widespread use of Tdap vaccination in pregnancy can result in significant decreases in pertussis, particularly in young infants before their first DTaP vaccine dose or who are protected by only 1 dose of DTaP. The authors noted several limitations of the study. In some analyses, the number of pertussis cases was low. Because a large majority of mothers were vaccinated between 27 and 36 weeks of gestation, the study did not have power to assess the optimal timing of Tdap vaccination during pregnancy. The study was restricted to mothers who had received whole cell pertussis vaccines in infancy, so the results may not be generalizable to the coming generation of mothers vaccinated entirely with DTaP in childhood. The decision of whether to test an infant was clinical, and there may not have been complete case ascertainment if physicians did not test for pertussis or parents did not seek care. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of good.**

In 2015, Dabrera et al (67) reported results from a case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales. This study included infants born between 22 October 2012 and 11 July 2013 who had pertussis disease onset at < 8 weeks of age. Sufficient information was obtained from general practitioners (30 cases) or through routine telephone follow-up (28 cases) for a total of 58 cases and 55 controls included in the analysis. Of the 58 cases, 10 mothers (17%) had been vaccinated during pregnancy, compared with 39 of 55 (71%) mothers of controls. The median gestations at vaccination were 31.5 weeks (range, 28–38 weeks) for cases and 33 weeks (range, 26–38 weeks) for controls. The unadjusted OR for vaccination in pregnancy was 0.09 (95% CI: 0.03; 0.23), giving an unadjusted VE of 91% (95% CI: 77%; 97%). After adjustment for sex, geographical area, and birth period, the VE was similar at 93% (95% CI: 81%; 97%). When the analysis was restricted to the 30 cases and 55 controls from the general practitioner's responses, the estimates were similar for the unadjusted VE (88% [95% CI: 62%; 96%]) and the adjusted VE (90% [95% CI: 68%; 97%]).

The authors concluded that maternal pertussis vaccination is effective in preventing pertussis infection in infants aged < 8 weeks and may be considered in other countries experiencing high levels of pertussis notifications. The authors noted several limitations. An unmatched analysis was performed since there were insufficient matched pairs with complete information. Data on case vaccination status were obtained by both postal and telephone follow-up, whereas data on controls

were obtained by questionnaire only. Information on breastfeeding status was not collected. Other potential confounders may include number of children in households, childcare attendance, smoking, and maternal education. **Overall, this study provides USPSTF evidence level II-2 and evidence quality category of fair.**

5.2.2 Summary of Vaccine Effectiveness in the Literature

The studies presented demonstrate that Tdap vaccination of the pregnant woman results in protection in the newborn from pertussis disease. Amirthalingam et al (24) (65), Baxter et al (66), and Dabrera et al (67) found VE rates of 91% to 93% for prevention of pertussis disease in infants up to 3 months of age.

High levels of VE of maternal pertussis vaccination was seen when Tdap-IPV (or Tdap) was given at least 7 days before birth, 7–27 days before birth, and at least 28 days before birth in infants less than 3 months of age (91% to 93%) and in infants less than 2 months of age, at least 7 days before birth (90%), 8 days or more before birth (91%), and more than 7 weeks before birth (93%) (24) (65) (66) (67).

The protection from maternal antibodies has been shown to be effective throughout the first year of life beyond the protection afforded by the primary series of DTaP. Amirthalingam et al (24) evaluated maternal vaccination VE in infants of mothers vaccinated during pregnancy with Tdap-IPV vaccine. They found that infants whose mothers received the vaccine during pregnancy were more protected at each of the first 3 doses of the DTaP vaccine. Vaccine effectiveness after the first 3 DTaP vaccine doses was high after the first and second doses but was lower after the third dose (82%, 69%, and 29%). Baxter et al (66) also looked at VE in the infant after maternal Tdap vaccination after each of the first 3 doses of DTaP vaccine and found that it was high after the first and third doses (81.4% and 65.9%). After the second dose of DTaP and before the third dose, the point estimate of VE fell to 6.4%, with a wide CI, due to few pertussis cases and the modest difference in incidence rates during the brief follow-up time between the second and third doses. Overall, they found that maternal Tdap vaccination confers a significant amount of protection against pertussis over the entire first year of life (69%), even after infants are immunized with DTaP.

6 Limitations of Structured Literature Review

There are a few limitations of the structured literature review. First, there is the potential for publication bias. The limitation of the review to only published studies can bias the results toward the positive. Also, in the 35 studies found, there was variability of methodology, study populations, datasets, laboratory methods, and antibodies tested between studies. Thus, it was not possible to conduct inter-study comparisons. The 35 studies also had differences in evidence level and quality in review. Lastly, the findings of individual studies may not be generalizable to all populations.

7 Benefits and Risks Conclusions

There are now extensive data available to support the use of Tdap and Tdap-IPV vaccination in pregnant women to provide protection for infants too young to be vaccinated. These data came from numerous clinical studies conducted in the United States, Canada, Australia, and the United Kingdom; all of these countries have recommendations for the vaccination of pregnant women with Tdap vaccine. Studies were conducted using primarily either COVAXIS or REPEVAX.

The studies presented demonstrate that Tdap vaccination of the pregnant woman results in protection in the newborn from pertussis disease. Amirthalingam et al (24) (65), Baxter et al (66), and Dabrera et al (67) found VE rates of 91%–93% for prevention of pertussis disease in infants up to 3 months of age.

Women vaccinated with Tdap vaccine during pregnancy mount a robust immune response and pass those antibodies onto their infants (59).The magnitude and persistence of the response offer protection of the mother against pertussis during pregnancy and after delivery. Munoz et al (18) studied the antibody responses of women vaccinated with Tdap vaccine during pregnancy, postpartum, and in nonpregnant women. Antibody responses to PT, FHA, PRN, and FIM were similar in women vaccinated antepartum and in nonpregnant women (GMCs: PT, 57 EU/mL vs. 91 EU/mL; FHA, 234 EU/mL vs. 286 EU/mL; PRN, 205 EU/mL vs. 349 EU/mL; FIM, 1633 EU/mL vs. 1785 EU/mL). Antibody concentrations to PT, FHA, PRN, and FIM were higher at delivery in those vaccinated antepartum than in those vaccinated postpartum (GMCs: PT, 51 EU/mL vs. 9 EU/mL; FHA, 185 EU/mL vs. 22 EU/mL; PRN, 192 EU/mL vs. 12 EU/mL; FIM, 1601 EU/mL vs. 35 EU/mL). In addition, the infants of the women vaccinated antepartum had higher antibody concentrations at 2 months of age when compared to those infants of mothers who were vaccinated postpartum (GMCs: PT, 21 EU/mL vs. 5 EU/mL; FHA, 99 EU/mL vs. 7 EU/mL; PRN, 76 EU/mL vs. 5 EU/mL; FIM, 510 EU/mL vs. 12 EU/mL).

High levels of VE of maternal pertussis vaccination were seen when Tdap-IPV (or Tdap) was given at least 7 days before birth, 7–27 days before birth, and at least 28 days before birth in infants less than 3 months of age (91%) and in infants less than 2 months of age, at least 7 days before birth (90%) and more than 7 weeks before birth (93%) (65) (67).

The protection from maternal antibodies has been shown to be effective throughout the first year of life beyond the protection afforded by the primary series of DTaP. Amirthalingam et al (24) evaluated maternal vaccination VE in infants of mothers vaccinated antenatally with Tdap-IPV vaccine. They found that infants whose mothers received the vaccine during pregnancy were more protected at each of the first 3 doses of the DTaP vaccine. Vaccine effectiveness after the first 3 DTaP vaccine doses was high after the first and second doses but was lower after the third dose (82%, 69%, and 29%). Baxter et al (66) also looked at VE in the infant after maternal Tdap vaccination and found that maternal Tdap vaccination confers a significant amount of protection against pertussis over the entire first year of life (69%), even after infants are immunized with DTaP.

In general, it should be noted that antibody levels after the primary series and booster dose of DTaP are lower (*blunted*) in infants of mothers immunized with Tdap vaccine during pregnancy. Munoz et al (18) found that at 7 months of age, after receipt of 3 doses of DTaP-IPV/Hib, infants of women who received Tdap vaccine during pregnancy achieved equivalent concentrations of

antibodies to PRN, PT, and FIM, and significantly lower concentrations of antibodies to FHA compared with infants whose mothers received placebo during pregnancy (40.6 EU/mL vs. 78.6 EU/mL, respectively; $P < 0.01$). However at 13 months, 1 month after the fourth dose of DTaP-IPV/Hib, the concentration of pertussis antibodies were not statistically significantly different in the 2 infant groups.

Halperin et al (19) studied a considerably larger number of infants of mothers vaccinated with Tdap vaccine during pregnancy and saw that the antibody levels achieved at birth for PT, FHA, PRN, and FIM were higher compared to infants of mothers vaccinated with Td Adsorbed vaccine during pregnancy. However, they had significantly lower antibody levels for all pertussis antibodies at 7 months of age. These differences persisted pre-booster at 12 months for all the pertussis antibodies and post-booster for PT, FHA, and FIM.

It is important to note that the clinical significance of this blunting is not known. To date, there is no evidence that blunting leads to greater risk of pertussis disease during infancy. It would be expected that if there were an impact of blunting on the risk of pertussis during infancy, there would be evidence of lower DTaP VE estimates for infants of mothers who had received Tdap vaccine during pregnancy.

Baxter et al (66) found no evidence of this in their study. Protection from pertussis after maternal Tdap vaccination was high (> 80%) both before and after the first infant dose of DTaP. The Tdap VE estimate was 65.9% after the third DTaP dose. While these results should be interpreted with caution because of the wide CIs of VE after the second DTaP dose (VE 6.4% CI: −165.1%; 66.9%), it is reassuring that at every level of DTaP vaccine exposure, children whose mothers received the Tdap vaccine are better protected than those whose mothers did not receive the vaccine. The Baxter results are similar to those from Amirthalingam et al (24), who found high VE after the first and second DTaP doses (82% and 69%, respectively) and lower VE after the third dose (29%). As the authors discuss, these numbers would have been negative if the antibody blunting were clinically impactful.

In England, antenatal pertussis immunization using Tdap-IPV vaccine was introduced in October 2012. Antenatal pertussis immunization results in high infant pre-immunization antibody concentrations. Maternal vaccination during the third trimester is effective in affording higher levels of pertussis antibody protection to the newborn infant. Vaccination early in the third trimester was more effective than later in pregnancy (68).

Vaccinating parents with Tdap during the 4 weeks following delivery did not reduce pertussis diagnoses in infants. Western Australia now provides Tdap vaccine to pregnant women during the third trimester (69).

Recent studies have sought to determine the optimal timing for Tdap vaccination during pregnancy. Abu Raya et al (70) in Israel reported that Tdap vaccination of pregnant women between 27–30 weeks was associated with highest umbilical cord GMCs of anti-PT and anti-FHA antibodies compared with vaccination beyond 31 weeks of gestation. A recent study of second versus third trimester vaccination in pregnant women showed higher umbilical cord GMCs of anti-PT and anti-FHA antibodies in the second trimester as compared to vaccination in the third trimester (71). The United Kingdom has changed its recommendations to favor starting vaccination during the second rather than third trimester of pregnancy (72).

Munoz et al (18) also assessed the safety of Tdap vaccination during pregnancy. No Tdap-associated SAEs occurred in women or infants. Injection-site reactions after Tdap vaccination were reported in 26 (78.8%), 12 (80%), and 25 (78.1%) pregnant, postpartum, and nonpregnant women, respectively (P > 0.99). Systemic symptoms were reported in 12 (36.4%), 11 (73.3%), and 17 (53.1%) pregnant, postpartum, and nonpregnant women, respectively (P = 0.055). Growth and development were similar in both infant groups. No cases of pertussis occurred.

Zheteyeva et al (45) and Moro et al (46) reported data on AEs reported to the VAERS system during 2 time intervals: 1 January 2005–30 June 2010 and 11 October 2011–30 June 2015, respectively. Zheteyeva assessed VAERS reports during a time when pregnant women were not being vaccinated routinely. A total of 132 reports of Tdap vaccine administered to pregnant women were identified in VAERS during the early time period. The trimester Tdap vaccine was administered was available for 110 (83.3%) reports, of which 85 (77.3%) reports indicated vaccination in first trimester. There were no maternal or infant deaths reported. The AEs reported did not identify any concerning patterns in maternal, infant, or fetal outcomes.

Moro et al found that after the recommendation for vaccination during pregnancy, there were a total of 392 reports of Tdap vaccination. The trimester Tdap vaccine was administered was available for 333 (84.9%) reports, of which 264 (79.2%) reports indicated vaccination in third trimester compared to 4% before the recommendation.

After the recommendation there was 1 neonatal death and no maternal deaths. The most frequent pregnancy-specific outcome was oligohydramnios (12 [3.1%] reports) followed by stillbirth and preterm delivery (11 [2.8%] reports each). The authors concluded that no new or unexpected vaccine AEs were noted among pregnant women who received Tdap vaccine after routine recommendations for maternal Tdap vaccination.

Donegan et al (27) evaluated the safety of Tdap vaccine use in pregnancy in the United Kingdom after recommendations for vaccination in pregnancy began in 2012. Pregnant women who received pertussis vaccination in their third trimester did not have increased risk of stillbirth, or in pregnant women or their infants increased risk of maternal or neonatal death, pre-eclampsia, eclampsia, antepartum or postpartum hemorrhage, fetal distress, uterine rupture, placenta previa, vasa previa, cesarean delivery, low birth weight, or neonatal renal failure.

Kharbanda et al (30) studied safety of Tdap vaccination in 2 VSD sites in California. Receipt of Tdap vaccine during pregnancy was also not associated with increased risk of preterm delivery or SGA birth or with hypertensive disorders of pregnancy, although a small but statistically significant increased risk of being diagnosed with chorioamnionitis was observed.

Chorioamnionitis data were therefore further investigated in the VAERS database (Vaccine Adverse Event Reporting System, US Center for Disease Control and Prevention) and the relationship with Tdap vaccine administration during pregnancy could not be confirmed (55). Since this review there have been 2 further large studies (one that is an extension of the study above) that purport to show a slightly increased risk of chorioamnionitis in mothers vaccinated with Tdap vaccine during pregnancy, though the absolute risk increases were very low (48) (31). These studies report no clinically significant infant outcomes related to the maternal chorioamnionitis. The authors conclude that despite an observed association between maternal Tdap vaccination and maternal chorioamnionitis, the studies support the safety of maternal Tdap vaccination for infant outcomes.

It is unclear whether these findings of chorioamnionitis are confounded by another unmeasured variable such as race/ethnicity, since Asian followed by Hispanic women are at higher risk of chorioamnionitis than are White and African-American women (73). These results for chorioamnionitis have not been reported in safety studies outside the United States.

Kharbanda et al (47) assessed acute safety outcomes for maternal Tdap vaccination from 7 VSD sites. There was no increased risk for pre-specified maternal safety outcomes of acute AEs (i.e., medically attended neurologic events [autonomic disorders, cranial nerve disorders, CNS degeneration/ demyelinating conditions, peripheral neuropathy, Guillain-Barré syndrome, meningoencephalitides, movement disorders, paralytic syndromes, and spinocerebellar disease], proteinuria, and venous thromboembolism) observed within 42 days after vaccination.

Study Td512 was designed to identify any signals of potentially vaccine-related AEs not detected during pre-licensure studies. Database review for maternal and fetal outcomes in women exposed to Tdap vaccine during pregnancy was performed as part of this study. The comparisons of maternal outcomes (i.e., live births, spontaneous abortions, early or late fetal death, elective abortions, and ectopic pregnancies) and fetal outcomes (i.e., congenital anomalies) in Tdap-exposed pregnancies and non-Tdap-exposed pregnancies did not identify any significant safety issues.

In the Adacel Pregnancy Registry, few cases of congenital anomalies were reported. In all but 1 case, vaccination occurred after embryogenesis. For this 1 case, the role of the vaccine in the development of congenital anomalies appears to be unlikely.

Based upon available data, no specific risks have been identified in conjunction with COVAXIS or REPEVAX exposure during pregnancy.

While continued monitoring for predominant sources of infection for infants may help to improve pertussis prevention strategies, recommendations for vaccination during pregnancy should directly increase protection of infants, regardless of the source of infection (12).

In summary, vaccination with COVAXIS or REPEVAX in pregnant women has been shown to protect infants from pertussis disease during the first year of life. This vaccination is generally well tolerated by pregnant women and no safety issues have been identified in infants after vaccination. Thus the benefits of this vaccination of pregnant women with COVAXIS or REPEVAX are considerable and outweigh the potential risks.

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