# An Advisory Committee Review
# National Advisory Committee on Immunization (NACI)

## Literature Review on Immunization in Pregnancy with Tetanus Toxoid, Reduced Diphtheria Toxoid and Reduced Acellular Pertussis (Tdap) Vaccine: Safety, Immunogenicity and Effectiveness

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# PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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# EXECUTIVE SUMMARY

Pertussis is an endemic and cyclical disease in Canada that disproportionally affects infants less than 1 year of age. Lack of maternal immunity is assumed to increase an infant's susceptibility to infection, both by increasing the risk of disease in mothers (and subsequent transmission to the infant) and by not providing sufficient passive protection through antibody transfer (via the placenta or via breast milk).

Since the last National Advisory Committee on Immunization (NACI) recommendations were published in 2014, new evidence on the safety and effectiveness of Tdap administration in pregnancy has become available. To provide an update to NACI on the effects of immunization in pregnancy with Tdap, a search strategy was developed with a federal Reference Librarian (Health Library) and verified by the NACI Diphtheria/Tetanus/ Pertussis/Polio/Haemophilus Influenza B Working Group. The objective of the literature review was to provide further evidence for the development of guidance on maternal immunization in pregnancy as a strategy to reduce disease incidence and severe outcomes (defined as hospitalization or death) from pertussis infection in infants younger than 12 months of age.

A query of three databases (OvidMEDLINE, Embase, Cochrane Library) on November 28, 2016 (updated July 25, 2017) identified 59 relevant studies on immunogenicity, safety and effectiveness that were rated for quality and included for evidence synthesis. The type of evidence retrieved on this topic was diverse, including randomized controlled trials, cohort studies, and case-control studies, with the quality of evidence that ranged from good to poor. In the majority of reviewed studies, post immunization increases in antibody levels resulted in more than 90% of women achieving anti-PT levels ≥greater than or equal to10 IU/ml at one month following immunization. While no serologic correlate of clinical protection against pertussis currently exists, anti-PT levels greater than or equal to 10 IU/ml are considered to be protective against severe disease. In infants, maternal immunization was found to result in increased pertussis antibody concentrations, with avidity increasing linearly with time up to delivery. In the majority of studies, following the receipt of the fourth DTaP dose after 15 months of age, no statistically significant differences in antibody levels and avidity were observed between infants whose mothers received Tdap in pregnancy and those whose mothers did not receive Tdap in pregnancy. No major maternal or infant safety issues, including pregnancy outcomes, were reported in the reviewed literature.

Effectiveness of maternal Tdap immunization in pregnancy was estimated to be over 90% against pertussis in infants younger than 2 two months of age, with no deaths observed among infants whose mothers received Tdap prior to 36 weeks of pregnancy. Maternal immunization with Tdap in pregnancy likewise resulted in a reduction in infant disease severity and hospitalization. Vaccine effectiveness was also reported to persist after the receipt of the first three DTaP doses in infants, with immunization in pregnancy resulting in an additional reduction in riskof up to 70% in children whose mothers received Tdap in pregnancy. Many effectiveness studies did not specify which gestational week during pregnancy Tdap vaccine was provided, but the majority of studies included immunization during the late second and early third trimester.

Overall, the review of literature on Tdap administration in pregnancy provided good evidence that routine immunization programs are a safe and effective way to protect infants less than one year of age from severe outcomes of pertussis infection.

# I. INTRODUCTION

In 2013, following an approximately three fold increase in the number of nationally reported pertussis cases, NACI adopted several recommendations pertaining to the immunization of pregnant women with a tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine (Tdap). At the time, based on the reviewed evidence, NACI concluded that vaccination with Tdap vaccine in pregnancy was safe and immunogenic, and recommended that:

- depending on regional epidemiology, immunization with Tdap may be offered during pertussis outbreaks (as defined by a jurisdiction) to pregnant women who are 26 weeks gestation or greater irrespective of their immunization history, and
- pregnant women who have not been immunized with Tdap in adulthood should be offered a pertussis vaccine.

However, in view of the number of severe outcomes in newborns being observed in Canada, as well as the uncertainty about the potentially adverse effects of maternally derived antibodies on lowering the infant's response to immunization with Diphtheria and tetanus toxoids, acellular pertussis vaccine (DTaP) vaccine, routine immunization with Tdap vaccine in pregnancy was not recommended. Following the availability of new effectiveness data reported following the implementation of routine maternal immunization programs internationally, the NACI Diphtheria/Tetanus/Pertussis/Polio/Haemophilus Influenza B Working Group (PWG) was again tasked with reviewing the evidence on utilizing Tdap immunization in pregnancy as a strategy to reduce severe outcomes from pertussis infection (defined as hospitalization and death) in infants less than 12 months of age.

The specific topics for which a literature review was requested by the PWG included:

- the burden of pertussis in infants less than 12 months of age
- the safety of maternal immunization with Tdap vaccine
- the efficacy and effectiveness of maternal immunization with Tdap in preventing severe outcomes of pertussis infection in infants less than 12 months of age
- the effects of maternal Tdap immunization on an infant's immunological response to the primary vaccine schedule
- the impact of maternal Tdap immunization on long term protection against tetanus, diphtheria and pertussis in children.

# II. METHODS

The literature review of Tdap vaccine safety, immunogenicity and effectiveness was conducted in order to answer the research questions that were developed by the NACI PWG:

- Is there a significant difference in local or systemic adverse events (AE) for the mother following immunization with Tdap vaccine in pregnancy (all stages) compared to adult immunization outside pregnancy?
- Is there a significant difference in adverse fetal and neonatal health outcomes for the baby following immunization of their mother with Tdap vaccine in pregnancy?

- Is maternal immunization with Tdap significantly more efficacious or effective in preventing severe disease in infants under 12 months of age compared to no maternal immunization?
- Is the immunogenicity of DTaP vaccination in children born to mothers immunized with Tdap vaccine in pregnancy significantly different compared to infants born to mothers who were not immunized with Tdap vaccine in pregnancy?
- Does maternal immunization with Tdap significantly impact efficacy or effectiveness of DTaP vaccines in preventing related disease in children less than 4 to 6 years of age?

A literature search strategy employing broad search terms (Appendix A) was conducted through Embase, Medline and Cochrane Central libraries on November 28, 2016 (updated July 25, 2017). After removing duplicates, over 1,500 citations were screened by two reviewers for relevancy to the following research questions:

a. Safety of maternal immunization with Tdap (including safety of immunization repeated in every pregnancy):
   - Is there a significant difference in local and systemic AE following immunization with Tdap vaccine in pregnancy (all stages) compared to adult immunization outside pregnancy? (P = pregnant women; I = Tdap vaccination; C = adults (non-pregnant women) immunized with Tdap; O = AE (local and systemic)
   - Is there a significant difference in adverse fetal and neonatal health outcomes following immunization with Tdap vaccine in pregnancy? (P = pregnant women; I = Tdap vaccination; C = no maternal Tdap vaccination; O = fetal and neonatal health outcomes)

b. Vaccine immunogenicity following maternal immunization:
   - Is immunogenicity of DTaP vaccination in children born to mothers immunized with Tdap vaccine in pregnancy significantly different compared to infants born to mothers who were not immunized with Tdap vaccine in pregnancy? (P = infants under 24 months of age; I = maternal Tdap vaccination; C = infants born to mothers not vaccinated with Tdap in pregnancy; O = vaccine-contained antibody levels of tetanus, diphtheria and pertussis)
   - Is immunogenicity of DTaP vaccination in children born to mothers immunized with Tdap vaccine in the first or second trimester of pregnancy significantly different compared to infants born to mothers who immunized with Tdap vaccine in the third trimester of pregnancy? (P = infants under 24 months of age born to mothers vaccinated with Tdap prior to the third trimester of pregnancy; I = maternal Tdap vaccination; C = infants under 24 months of age born to mothers vaccinated with Tdap in the third trimester of pregnancy; O = vaccine-contained antibody levels (quantity and quality)of tetanus, diphtheria and pertussis

c. Vaccine efficacy and effectiveness following maternal immunization:
   - Is maternal immunization with Tdap significantly more efficacious or effective in preventing severe disease in infants under 12 months of age compared to no maternal immunization (P = infants under 12 months of age; I = maternal Tdap vaccination; C = no maternal Tdap vaccination; O = pertussis-related hospitalization or death)
   - Does maternal immunization with Tdap significantly affect efficacy or effectiveness of DTaP vaccines in preventing related disease in children less than 4 to 6 years of age (P = children 25 months to 6 years of age; I = maternal Tdap vaccination; C = no

maternal Tdap vaccination; O = tetanus, diphtheria and pertussis incidence, hospitalization and death)

Studies were screened for inclusion by one or two reviewers (OB, MT, or SDB) and inclusion of full-text studies was validated by a second reviewer (OB or MT). A standardized data screening and extraction form containing descriptive and quantitative data on study design, methods, interventions, population and outcomes was created using an online reference management software Distiller SR.

Inclusion criteria:

- Primary studies reporting outcomes (safety, immunogenicity, efficacy, effectiveness) in mother, fetus, or infant, following maternal immunization with pertussis vaccine
- Any publication status (e.g. peer-reviewed journals, grey literature abstracts and presentations)

Exclusion criteria:

- Not a primary research study (e.g. systematic review, economic study)
- Case reports
- Non-human study
- No maternal pertussis immunization intervention
- No relevant outcomes assessed (safety, efficacy, effectiveness, immunogenicity)
- Pertussis vaccine formulation not available in Canada
- Poster or abstract where full published results were already included in the review
- Duplicate

Quality appraisal of studies was performed by one reviewer (OB) and validated by a second reviewer (MT), according to NACI methodology outlined in Appendix C.

# III. RESULTS

## III.1 Immunogenicity

### III.1.1 Immunogenicity for the mother during pregnancy

Thirteen studies rated as good (3), fair (9), and poor (1), three of which were randomized controlled trials (RCTs), assessed immunogenicity of Tdap in pregnancy.

In a RCT rated as good, Perez et al.[(1)] evaluated the immunogenicity of Adacel one month following the vaccination of 90 women at 28 to 32 weeks gestation; 81 women who received 0.9% saline served as the control group. In women who received Tdap, anti-pertussis toxin (PT) levels increased 4-fold and anti-Pertactin (PRN) levels icreased 12-fold compared to those observed prior to vaccination ($p<0.001$). In another RCT by Munoz et al.[(2)]that was rated as good , 33 pregnant women were administered Adacel and 15 pregnant women received a 0.9% saline injection at 30 to 32 weeks gestation, followed by Tdap vaccine postpartum. A third group of 32 non-pregnant women also received Tdap. One month following Tdap administration in pregnancy, anti-PT levels increased 7-fold, anti-Pertussis flamentous hemagglutinin (FHA) 15-fold, anti-PRN 24-fold and anti-Fimbriae types 2 and 3 (FIM2/3) 60-fold compared to pre-immunization levels. There were no significant differences in antibody response to Tdap between the three groups. In the third RCT that was rated as fair, Hoang et al.[(3)]measured

immune responses following the administration of either Adacel (49 women) or tetanus-toxoid (47 women) at 25 weeks of pregnancy. One month after immunization, there was an approximate 4-fold increase in anti-PT, 16-fold increase in anti-FHA and a 32-fold increase in anti-PRN levels. Although concentrations of all measured antibodies remained higher at birth compared to pre-immunization levels, they were approximately half of those observed one month after immunization ($p < 0.001$).

In a study rated as fair, Maertens et al.[4] measured pertussis antibody levels in 57 women following immunization with Boostrix at mean 28.6 weeks gestation were compared to 41 women not immunized in pregnancy. At delivery, immunized women had approximately 5-fold higher anti-PT, 10-fold higher anti-FHA and 33-fold higher anti-PRN concentrations compared to women not immunized in pregnancy. From the same trial, in a study rated as good, Huygen et al.,[5]reported the results of humoral and cellular immune response measurements for a subset of 18 pregnant and 16 non-pregnant women. At twelve months following immunization, antibody levels in all women were approximately two-fold lower compared to those observed one month after immunization (significantly lower for anti-PT and anti-FHA), but remained significantly higher in both groups compared to pre-immunization levels. In contrast, cellular proliferative responses in non-pregnant women were 5 to 10 fold higher against PT and FHA, whereas in pregnant women they were only slightly increased one month following immunization. One year after vaccination, proliferative responses for all antigens returned to pre-immunization levels in both groups. Vaccine specific Interferon (IFN)-gamma levels in PT or FHA stimulated cultures were overall very low and not different from levels in non-stimulated cells. Similar increases in anti-PT Immunoglobulin G (IgG) levels were reported in a prospective study by Fallo et al[6] that was rated as fair. When compared to non-immunized women (n=99), anti-PT levels of women immunized with Tdap during pregnancy (n=105, mean 24.7 ± 4.8 weeks gestation), were approximately 4-fold higher at delivery. In a study rated as fair, Abu Raya et al.[7]measured antibody levels in 61 women who received Boostrix between 23 and 37 weeks of pregnancy and 20 pregnant women who did not receive the vaccine. At delivery, women vaccinated with Tdap had a 20-fold higher level of anti-PT and anti-PRN IgG, 15-fold higher anti-FHA IgG, and 3- to 8-fold higher serum anti-PT and anti-FHA Immunoglobulin A (IgA) levels than those in the control group. In a follow-up study rated as fair, Abu Raya et al.[8] also measured pertussis antibody concentrations in a subset of 38 immunized and 10 women not immunized in pregnancy 9 to 15 months after delivery. In immunized women, anti-PT and anti-PRN IgG declined to approximately half the levels observed at delivery; anti-FHA IgG concentrations were also lower, although not significantly. In the control group, IgG and IgA levels of all measured antibodies remained relatively unchanged for the duration of the study.

In a retrospective study rated as fair conducted by Healy et al.[9], antibody levels of 19 women immunized with Tdap in pregnancy (14 during the first trimester and 3 after 20 weeks gestation) were compared to those of 83 women immunized within 2 years of the study, but outside pregnancy. At delivery, there were no statistically significant differences between groups for any pertussis antigen (p ranged from 0.45 to 0.94). A small study rated as fair by Hardy-Fairbanks et al.[10] compared antibody levels between 5 women immunized with Adacel at any time in pregnancy and 53 unimmunized pregnant women. At delivery, antibody concentrations against PT, FHA, PRN and FIM2/3 were 2 to 20 fold higher in the vaccinated group. Vilaljeliu et al.[11] measured antibody levels in 132 women immunized in pregnancy with Adacel. Pre-vaccination, 37% of women had anti-PT levels ≥10 IU/ml, while one month post vaccination these levels were found in 90% of women, in a study rated as fair.

Two studies reported measurements of secretory IgA in colostrum and breast milk following Boostrix immunization in pregnancy. In a study rated as fair, Abu Raya et al.[12] compared anti-PT and anti-FHA IgA levels in 25 women immunized with Tdap and 12 women not immunized in pregnancy. At birth, secretory anti-FHA concentrations were approximately 4-fold higher in women vaccinated with Tdap, and remained 2-fold higher at 2, 4 and 8 weeks after delivery; anti-PT concentrations were similar between groups. At all time points, although relatively higher in the group of immunized women, anti-FHA and anti-PRN IgG were very low in both groups (anti-PT IgG was not detected). In another study rated as fair by De Schutter et al.[13], IgA concentrations were measured 2 months after delivery in women immunized in pregnancy (n=19), following delivery (n=34) and any time within (n=9) or beyond (n=12) five years preceding the study. No significant differences in the total secretory IgA levels were found between the 4 groups.

The effect of body mass index (BMI) on immune response was studied by Gandhi et al.[14] Following the immunization of 123 pregnant women with Boostrix, using a pertussis IgG antibody test kit that measured combined anti-PT and anti-FHA concentrations, study authors found no statistically significant antibody differences between women with a normal, overweight and obese BMI level, in a study rated as poor.

### III.1.2 Maternally derived antibody levels in infants prior to the receipt of DTaP

Four publications rated as good (2), fair (1), and poor (1) reported results from three RCTs. In a study rated as good by Perez et al.,[1] anti-PT and anti-PRN levels were compared in 90 infants born to mothers immunized with Adacel at 28-32 weeks gestation with those of 81 infants whose mothers received placebo. At delivery, infants born to immunized mothers had a mean cord blood anti-PT concentration of 28.25 EU/ml (95% confidence interval (CI): 21.06-37.90) and anti-PRN of 127.51 EU/ml (95%CI: 104.14-156.12). At two months of age, prior to the first dose of DTaP, anti-PT concentration declined to 10.95 EU/ml (95%CI: 8.71-13.77) and anti-PRN to 71.41 EU/ml (95%CI: 56.80-89.77). Despite the rapid degradation in children whose mothers received Tdap, both antibodies remained significantly higher compared to the control group. Similarly, Munoz et al.[2] assessed antibody levels of 33 infants born to mothers immunized with Adacel at 30 to 32 weeks of pregnancy and 15 infants whose mothers received Tdap postpartum, in a study rated as good. In cord blood, infants born to immunized mothers had an anti-PT concentration of 68.8 EU/ml (95%CI: 52.1-90.8), anti-FHA of 234.2 EU/ml (95%CI: 184.6-297.3), anti-PRN of 226.8 EU/ml (95%CI: 137.7-373.7) and anti-FIM2/3 of 1,867 EU/ml (95%CI: 1,211.7-2,876.8). In comparison to the infants in the control group, antibody concentrations were significantly (4 to 40-fold) higher in infants whose mothers received Tdap in pregnancy. At two months of age, a 2- to 4-fold decline was observed for all maternally derived antibodies in both groups. In infants whose mothers received Tdap in pregnancy, all antibody concentrations remained significantly higher than those observed in the control group infants (anti-PT 20.6 EU/ml [95% CI: 14.4-29.6] vs. 5.3 EU/ml [95% CI: 3-9.4]; anti-FHA 99.1 EU/ml [95% CI: 75.8-129.6] vs. 6.6 EU/ml [95% CI: 2.8-15.5], anti-PRN 75.7 EU/ml [95% CI: 43.9-130.6] vs. 5.2 EU/ml [95% CI: 2.4-11.5], and anti-FIM2/3 510.4 EU/ml [95% CI: 305.6-852.3] vs. 12 EU/ml [95% CI: 4.9-29.4]). In studies rated as fair, and poor respectively; Hoang et al.[3] and Maertens et al.[15]reported results from a trial that measured antibody levels in infants born to mothers immunized with Adacel (n=45) or tetanus toxoid-vaccine (n=47) between 18 and 36 weeks of pregnancy. At delivery, infants born to Tdap immunized mothers had significantly higher levels of anti-PT (21 IU/ml [95%CI: 16-28] vs. 7.2 IU/ml [95%CI: 5.6-9.4]), anti-FHA (93 IU/ml [95%CI: 65-133] vs. 27.6 IU/ml [95%CI: 20.9-36.7]) and anti-PRN (124 IU/ml [95%CI: 86-179] vs. 13.9 IU/ml [95%CI: 10.5-18.2]) than those in the Tetanus toxoid (TT) group. At two

months of age, prior to the first dose of DTaP, anti-PT, anti-FHA and anti-PRN blood levels remained significantly higher in infants born to Tdap immunized mothers (anti-PT 4.2 IU/ml [95%CI: 2.9-5.9] vs. 0.8 IU/ml [95%CI: 0.5-1.3]), anti-FHA 59 IU/ml [95%CI: 48-73] vs. 23.1 IU/ml [95%CI: 19.7-27]) and anti-PRN 46 IU/ml [95%CI: 32-66] vs. 7.8 IU/ml [95%CI: 6.6-9.4]).

In seven studies rated as fair, pertussis antibody levels were compared between term infants whose mothers received Tdap or no immunization in pregnancy, and four studies reported on antibody concentrations in relation to the timing of immunization. In the only study in which Adacel was used exclusively, which was rated as fair, Gall et al.[16] measured antibody levels in two groups of 52 infants whose mothers were vaccinated in the second trimester of pregnancy. Infants born to immunized mothers were found to have significantly higher titres for all pertussis antibodies at birth (mean anti-PT 28.2 vs. 11 EU/ml; anti FHA 104 vs. 26.8 EU/ml; anti-PRN 333 vs. 24.7 EU/ml; and anti-FIM2/3: 1199 vs. 82.8 EU/ml). Higher than 5 EU/ml anti-PT Geometric Mean Concentration (GMC) was found in 88% of infants whose mothers received Tdap (65%>10 EU/ml) and 40% of infants whose mothers were not immunized (12%>10EU/ml). In a study by Maertens et al.[17], rated as fair, antibody levels were compared in infants whose mothers received Boostrix at mean 28.5 weeks gestation (n=57) or no vaccination (n=41). In the Tdap group, levels of anti-FHA (140 IU/ml [95% CI: 109-180]), anti-PT (100.7 IU/ml [95% CI: 82-123]) and anti-PRN (697 IU/ml [95% CI: 573-848]) were 5-, 8- and 33-fold higher than in the control group, respectively. Despite a significant decrease in titers between birth and the age of 8 weeks, infants whose mothers were vaccinated maintained significantly higher antibody concentrations compared to those in the control group (anti-PT 15.5 IU/ml [95% CI: 12.1-20] vs. 1.1 IU/ml [95% CI: 0.7-1.6], anti-FHA 121 IU/ml [95% CI: 100-145] vs. 23 IU/ml [95% CI: 19-27] and anti-PRN 253 IU/ml [95% CI: 183-351] vs. 17 IU/ml [95% CI: 14.5-21]). Hardy-Fairbanks et al.[10]compared antibody levels of 11 infants whose mothers received Tdap in pregnancy to those of 53 infants whose mothers did not receive Tdap, in a study rated as fair. In the cord blood of 5 infants (3 mothers vaccinated during their first trimester and 2 during their second trimester) whose blood was available for analysis, antibody levels were over 3-fold higher compared to the control group. Statistically significant differences in antibody levels persisted up to the receipt of the primary series at two months of age (anti-PT 15.1 vs. 4.8 EI/ml, anti-FHA 41.6 vs. 5.6 EU/ml, anti-PRN 32.1 vs. 3.9 EU/ml, and anti-FIM2/3 296.4 vs. 13 EU/ml). In another smaller study rated as fair, Healy et al.[9] assessed antibody outcomes of 19 infants whose mothers were immunized with Tdap in pregnancy (76% received Tdap during the first trimester) and 83 infants whose mothers received Tdap within 2 years of the study, but outside pregnancy. After excluding infants with anti-PT greater than 94 EU/mL (infants of mothers who were presumed to have recently been exposed to natural pertussis) from the analysis, study authors did not find any statistically significant differences between any of the tested pertussis antigens. In a study reported through a conference abstract, Healy et al.[18] also measured anti-PT levels in 312 women immunized with Tdap at mean 31 weeks gestation and 314 women not immunized in pregnancy. Anti-PT concentrations were significantly higher in sera of infants whose mothers were immunized compared to the control group (47.3 IU/ml [95% CI: 42.1-53.15] vs. 12.93 IU/ml [95% CI: 11.8-14.7]). A study rated as fair conducted by Abu Raya et al.[7], compared cord blood antibody levels of infants born to mothers who received Boostrix (61) at mean 33 weeks of pregnancy or no vaccine (20) in pregnancy. At delivery, anti-PT 17.27 IU/ml (95%CI: 9.45-31.54), anti-FHA 196.74 IU/ml (95%CI: 163.42-236.86) and anti-PRN 161.51 IU/ml (95%CI: 114.68-227.46) were 10 to 15 fold higher in the Tdap group compared to the control group infants. Among infants whose mothers received Tdap, study authors also found significantly higher cord/maternal antibody ratios following immunization at 27 to 30 weeks gestation compared to 31 to 36 weeks gestation (anti PT 1.45 [95% CI: 1.26-1.64] vs. 1.04 [95% CI: 0.86,1.23]). In a subset of infants (52 infants born to immunized mothers and 8 infants born to mothers not immunized in pregnancy), Abu Raya et al.[19] also assessed antibody

avidity levels in a study rated as fair. Significantly higher anti-PT relative avidity index (RAI) was found in the Tdap compared to the control group of infants (73.77% [95% CI: 70.41–77.13] vs. 50.23% [95% CI: 32.41–68.06], $p < 0.001$). Higher anti-PT RAI ($p<0.03$) was also found in newborns whose mothers were immunized at 27 to 30 weeks gestation (n = 20) compared to those immunized at 31 to 36 weeks (n = 22) or more than 36 weeks (n = 7) gestation (79.53% [95% CI: 76.91–82.16], 71.56% [95% CI: 65.98–77.14] and 63.93% [95% CI: 47.31–80.56], respectively). Avidity maturation of umbilical cord anti-PT was found to increase linearly as a function of time between Tdap administration and delivery (Pearson $r = 0.346$, $p < 0.01$). In a prospective study with a control group that was rated as fair, Fallo et al[6], compared anti-PT IgG levels in infants born to mothers receiving (n=105) or not receiving (n=99) Tdap immunization in pregnancy. The study authors reported approximately 4.5 fold higher antibody levels in infants born to immunized mothers). In a subset of these infants (n=36) that were followed for two months, there was a noted rapid reduction in antibody concentrations prior to the receipt of first DTwP dose (GMC measured at delivery 48.4 EU/mL [95% CI: 28.4-62.2], at 1 month 17.7 EU/mL [95% CI: 11.5–25.1], and 2 months 11.6 EU/mL [95% CI: 8.1–20.1]). The study authors also assessed the efficiency of placental antibody transfer (measured as the ratio of the cord to maternal blood GMC), finding it to be higher in infants who were born to immunized mothers (1.46 vs. 1.18).

Antibody concentrations in relation to the timing of maternal immunization were also reported in two other studies. In a study rated as fair, Naidu et al.[20] measured cord antibody levels in infants whose mothers received Boostrix between 28 and 36 weeks gestation, and found anti-PRN and anti-PT levels to be significantly higher among infants whose mothers were immunized at 28 to 32 weeks (38 infants) compared to those immunized at 33 to 36 weeks (44 infants). In a different study rated as fair, Eberhardt et al.[21] compared cord antibody levels following maternal immunization with Boostrix at 13 to 25 weeks gestation (122 infants) and at more than 25 weeks gestation (213 infants) in a non-inferiority study of second versus third trimester immunization. Excluding infants whose mothers were immunized within 2 weeks of delivery, levels of anti-PT (57.1 EU/ml [95% CI: 47.8-68.2] vs. 44.4 [95% CI: 35.3-55.9]) or anti-FHA levels (284.4 EU/ml [95% CI: 241.3-335.2] vs. 237.6 [95% CI: 188-300.3]) of infants born to mothers immunized before 26 weeks gestation were non-inferior compared to immunization between 26 and 36 weeks of pregnancy. However, when adjusted for maternal age, gestational age, parity and SES score, anti-FHA GMC ratio was significantly higher (1.3; 95% CI: 1.04-1.7) in infants whose mothers were immunized prior to 26 weeks gestation. A significantly higher proportion of infants with anti-PT concentration above 20 EU/ml was also observed in the group whose mothers received immunization at less than 26 weeks gestation (80% vs. 64%. p= 0.006).

One study rated as poor by Gandhi et al.[14] also assessed antibody levels in infants of women immunized with Boostrix in relation to body weight. No statistically significant differences in neonatal antibody levels were found between infants born to mothers with normal, overweight or obese BMI. Another study rated as fair by Kent et al.[22] measured antibody levels in preterm infants (average gestational age at birth of 32 weeks and a median interval between maternal immunization with Tdap-Invasive Pneumococcal Vaccine (IPV) and delivery of 24 days). At two months of age, 30 infants born to immunized mothers had significantly higher antibody levels than 121 premature infants whose mothers were not immunized in pregnancy (anti-PT 3.53 IU/ml [95% CI: 2.18-5.71] vs. 1.49 IU/ml [95% CI: 1.28-1.74], anti-FHA 17.50 IU/ml (95% CI: 10.63-28.95) vs. 3.36 IU/ml [95% CI: 2.79-4.05] and anti-FIM2/3 33.58 IU/ml (95% CI: 17.04-66.17) vs. 4.13 IU/ml [95% CI: 3.15-5.41]). In another study that was conducted by Eberhardt et al[23] and rated as fair, the effects of maternal Tdap administration timing on infant anti-PT and anti-FHA were assessed in 85 preterm infants, of whom 37 of whom were born to mothers

immunized during the second trimester and 48 to mothers immunized during the third trimester. The study authors reported higher antibody GMC values after maternal Tdap immunization in second (mean interval to delivery 97 days) compared to third (mean interval to delivery 30 days) trimester (anti-PT 41.3 EU/mL [95% CI: 29.6-57.5] vs 22.1 EU/mL [95% CI: 14.3-34.2], and anti-FHA 201.1 EU/mL [95% CI: 149.7-270.1] vs 120.2 EU/mL [95% CI: 80.6-179.2]). In addition, all preterm infants whose mothers were immunized in the second trimester of pregnancy had anti-PT levels above 5 EU/mL, while these levels were observed in only 77% of infants whose mothers received Tdap in the third trimester of pregnancy. Time interval between vaccination and delivery required to maximize transplacental antibody transfer (at least a 4 fold increase in GMC) was estimated to be 15 days in the preterm population.

Infant antibody levels following maternal Tdap immunization were also measured in three observational studies. In a study rated as fair, Vilajeliu et al.[11] measured anti-PT levels in 132 infants following maternal immunization with Adacel between 20 and 26 weeks gestation, and found that 95% had an antibody concentration of ≥10 IU/ml (47% ≥40 IU/ml). In another fair quality study by Vilajeliu et al.[24] in which Adacel was provided to 37 mothers following 21 weeks gestation, mean cord blood anti-PT was 52.7 IU/ml (95%CI: 34.7-80.2). Highest anti-PT cord blood levels were found in infants whose mothers were immunized after 32 weeks of pregnancy (62.5 IU/ml [95%CI: 27.3-143.6]). In a cohort study rated as good of 129 infants born to mothers immunized with Tdap-IPV, Ladhani et al.[25] reported an anti-PT concentration of 11.2 IU/ml (95%CI: 9.6-13.1), anti-FH 46 IU/ml (95%CI: 39.8-53.1) and anti-FIM2/3 123 IU/ml (95%CI: 92.7-163.5) at two months of age.

In a small study that was rated as poor, Goldfarb et al[26]. reported on the effects of maternally derived antibodies on infant cellular immune responses against pertussis. On a sample of 19 mother-child blood pair samples at delivery, the study authors found increased levels of antibody-dependant neutrophil phagocytosis (anti-PT and anti-FIM, $p<0.001$) and natural killer (NK) cell degranulation (all four antigens, $p<0.01$) in the cord compared to maternal blood.

### III.1.3 Immunogenicity of DTaP in infants born to women immunized with Tdap in pregnancy

Results were available from three randomized control trials rated as good (1), fair (1); and poor (1), in which antibody was measured following DTaP administration. Munoz et al.[2] assessed antibody levels following the administration of four doses of DTaP at 2, 4, 6 and 12 months of age in 33 infants whose mothers received Adacel at 30-32 weeks gestation, and 15 infants whose mothers received placebo, in a study rated as good. At 7 months of age, infants born to immunized mothers had lower antibody concentrations to FHA (40.6 EU/ml [95% CI: 30.6-54] vs. 78.6 EU/ml [95%CI: 52.9-116.7]; $p<0.01$), anti-PT (64.9 EU/ml [95%CI: 53.8-78.3] vs. 96.6 EU/ml [95% CI: 56.7-164.6] and anti-FIM2/3 (113.9 EU/ml [95% CI 89.9-152.7] vs. 193.5 [95% CI: 105.5-354.7]) compared to the control group; anti-PRN levels were similar between groups. Infants whose mothers were not exposed to Tdap in pregnancy but had higher anti-FHA levels at birth, were also found to have lower antibody concentrations at 7 months of age (Spearman correlation 0.55, $p = 0.042$). One month following the administration of a booster dose, there were no statistically significant differences in antibody levels between groups. Similar results were reported in a study rated as fair conducted in Vietnam by Hoang et al.[3] and Maertens et al.[15] that measured antibody responses following the receipt of four doses of DTaP provided at 2, 3, 4 and 22 month of age. One month following the administration of the third dose of DTaP vaccine, there were no differences in anti-PT and anti-FHA concentrations in 45 infants whose mothers received Adacel and 37 infants whose mothers received TT vaccine. However,

significant higher anti-PRN levels were observed in infants whose mothers did not receive the pertussis vaccine in pregnancy (132.6 EI/ml [95%CI: 104-168] vs. 83 EI/ml [95%CI: 65-104]; p<0.006). At 22 months of age, one month after a DTaP booster dose, no significant differences were found between groups for any of the tested pertussis antibodies. Perez et al.[1] also measured immunological responses to PT and PRN antigens following two doses of DTaP in 90 infants born to mothers immunized with Adacel in pregnancy (28-32 weeks gestation) and 81 infants of mothers not immunized in pregnancy, in a study rated as good. Two months following the administration of the first DTaP dose, infants born to immunized mothers had statistically significant lower mean anti-PT (14.77 EU/ml [95%CI: 12.35-17.66 ] vs. 20.45 EU/ml [95%CI: 16.71-25.03]) and higher mean anti-PRN (35.35 EI/ml [95%CI: 27.59- 45.29] vs. 5.07 [95%CI: 4.15-6.19]) concentrations compared to infants in the control group. This was also observed at six months of age, prior to the administration of the third DTaP dose (anti-PT 49.09 EU/ml [95%CI: 40.86-58.99] vs. 69.13 EU/ml [95%CI: 59.10-80.87] and anti-PRN 16.75 EU/ml [95%CI: 12.94-21.68] vs. 4.51 EU/ml [95%CI: 3.80-5.35]). There was an observed increase in anti-PT and a decline in anti-PRN in both groups subsequent to DTaP administration.

Four studies also reported on the findings from two non-randomized trials measuring post DTaP responses in children whose mothers received Tdap in pregnancy. Maertens et al.[17] measured immune responses following DTaP administration at 2, 3 and 4 months of age in 49 infants whose mothers received Boostrix at 29 weeks gestation and 21 infants born to mothers not immunized in pregnancy, in a study rated as fair. One month after the completion of the DTaP primary series, infants born to immunized mothers had significantly lower anti-PT concentrations compared to the control group (29 IU/ml [95% CI: 25–35] vs. 54 IU/ml [95% CI: 42–69]; p < 0.001), despite a rise in antibody levels observed pre-immunization. Contrary to this, infants born to mothers not immunized in pregnancy had lower anti-PRN and anti-FHA concentrations, although these differences were not significant (p=0.22 and p=0.20, respectively). In infants born to immunized mothers, there was a 2- to 4-fold decay in anti-PRN and anti-FHA levels from week 8 to month 5. In a follow-up study rated as fair, Maertens et al.[4] also reported the effects of a 15 month DTaP booster administration in 45 infants born to immunized mothers and 22 control group infants. Prior to the booster immunization, anti-PT (5.44 IU/ml [95% CI: 4.49-6.58] vs. 7.27 IU/ml (95% CI: 5.8-9.12]), anti-FHA (14.83 IU/ml [95% CI: 12.37-17.77] vs. 15.98 IU/ml [95%CI: 12.43-20.56]) and anti-PRN (4.44 IU [95% CI: 3.66-5.39] vs. 7.62 IU/ml [95% CI: 5.67-10.25]; p = 0.006) were lower in infants whose mothers received Tdap compared to infants in the control group. One month after booster dose administration, these infants continued to have lower concentrations of anti-PT (36.29 IU/ml [95% CI: 30.93-42.57] vs. 56.6 IU/ml [95% CI: 42.36-75.65]; p=0.006) and anti-FHA (100.86 IU/ml [95% CI: 84.93-119.77] vs. 139.42 IU/ml [95% CI: 112.68-172.51]; p=0.651), and a slightly higher level of anti-PRN (92.73 IU/ml [95% CI: 67.04-128.25] vs. 81.2 IU/ml [95% CI: 58.4-112.9]; p=0.272). In the same subsample of children (study rates as fair), Cabore et al[27]. also reported the results of antibody avidity measurements prior and one month following the receipt of the 4$^{th}$ DTaP dose. At 15 months of age, the mean antibody avidity in two groups was found to be similar, moderate for anti-PT, anti-FHA and anti-PRN. Following booster immunization, significant increases in antibody avidity were observed in both groups for all pertussis antibodies except anti-FHA in the intervention group. However, relative to controls, anti-PT RAI remained significantly lower in the intervention group (68.06% [95% CI: 63.98–72.41] vs. 78.65% [95% CI: 76.04–81.36]).

In a study rated as fair, Kent et al.[22] reported on post DTaP immunization outcomes of 30 premature infants (15 with results at 5 months of age) whose mothers received Tdap-IPV at 28 weeks gestation, and 121 premature infants (73 with results at 5 months of age) whose mothers were not immunized in pregnancy. Compared to 2 months of age, significantly higher (p<0.001) antibody concentrations were observed in both groups at 5 months, one month after the last

dose of DTaP provided at 2, 3 and 4 months of age. While no differences were observed one month following the completion of the primary DTaP series for anti-PT and anti-FIM2/3, lower anti-FHA levels were observed in infants whose mothers received Tdap in pregnancy (23.04 IU/ml [95% CI: 16.17-32.85] vs. 45.55 IIU/ml [95% CI: 37.64-55.12]; p=.003). At 12 months of age, there were no significant antibody differences between groups.

In addition, responses to DTaP immunization were reported in three observational studies. Ladhani et al.[25] assessed immune responses following the completion of a DTaP series provided at 2, 3 and 4 months of age in a study rated as good. One month following the third vaccine dose, antibody concentrations were lower in infants born to mothers immunized with Tdap-IPV in pregnancy compared to a historical cohort of children whose mothers were not immunized. These differences were statistically significant for anti-FHA (25.5 IU/ml [95%CI: 23-28.3] vs. 41.1 IU/ml [95%CI: 37.5-45.1]) and anti-PT (28.8 IU/ml [95%CI: 25.7-32.4] vs. 43.2 IU/ml [95%CI: 39.4-47.2]; p<0.001), but not for anti-FIM2/3 (113.9 IU/ml [95% CI: 99-131.1] vs. 224.9 IU/ml [95%CI: 196.1-258]; p=0.22). A significant inverse association was observed between antibody concentrations before and after primary immunization to PT (0.89-fold per 2-fold increase in pre-vaccination concentration; 95% CI: 0.81–0.98; p= 0.023) and FIM2/3 (0.92-fold; 95% CI: 0.86–0.98; p =0.011), whereas for FHA there was a positive association (1.20-fold; 95% CI, 1.11–1.31; p <0.001). The study authors also reported significantly lower serotype-specific GMCs for serotypes 1, 3, 4, 5, 6A, 7F and 9V compared to the historical cohort. Similar blunting effect of maternal Tdap immunization on pneumococcal vaccine immune response was also reported by Maertens et al.[28] In a study that was rated as good, the study authors found lower GMCs for antibodies to serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14 and 19A after two doses of Pneu-C-13 vaccine provided at 8 and 16 weeks of age in 54 children whose mothers were immunized with Tdap in pregnancy compared to those in the control group (n=25). After the receipt of dose 3 of Pneu-C-13 vaccine, lower antibody concentrations remained only for serotypes 1 and 4. Despite the observed lower GMCs in the group of infants whose mothers received Tdap in pregnancy, the proportion of children with antibody levels above 0.35 µg/mL were comparable between groups at all time points, with the exception of serotype 3 following primary vaccination. Lastly, in a small study rated as fair, Hardy-Fairbanks et al.[10] measured a post-booster DTaP response at 16 months of age in 14 infants whose mothers received Tdap in pregnancy (9 vaccinated in their third trimester). One month following the primary DTaP series provided at 2, 4 and 6 months of age, antibody concentrations were 0.7- to 0.8-fold lower among these infants compared to infants (n=32) whose mothers were not immunized in pregnancy. These differences disappeared at 15 and 19 months of age. Children in both groups showed increases in antibody concentration following a DTaP booster dose.

## III.2 Effectiveness

Three major studies rated as good (2), and fair (1); identified through the literature review, originated from the United Kingdom (UK), in which a national maternal immunization program has been implemented since October 2012. Dabrera et al.[29] published the results of an unmatched case-control study rated as fair in which 58 infants with disease onset (confirmed by polymerase chain reaction [PCR] or culture) at less than 8 weeks of age were compared to 55 infants who were known to not have a clinical or microbiological diagnosis of pertussis. Among infants with confirmed pertussis, 17% were born to mothers vaccinated during pregnancy as opposed to 71% in the control group. The unadjusted odds ratio (OR) for Tdap-IPV vaccination in pregnancy was 0.09 (95% CI: 0.03–0.23), giving an unadjusted vaccine effectiveness of 91% (95% CI: 77%–97%) prior to the receipt of DTaP. Similar vaccine effectiveness (93% [95% CI, 81%–97%]) was found after adjusting for sex, geographical area, and birth period. Data on

length of hospital stay were available for 47 cases. The median length of hospital stay was 4 days (range 0–6 days) for 8 cases of infants with pertussis whose mothers had been vaccinated in pregnancy, and 3.5 days (range 0–63 days) for 39 pertussis cases in the control group, whose mothers had not been vaccinated. There was no statistically significant difference between these 2 groups in terms of length of hospital stay, according to the rank-sum test (p=0.58).

Using the 2011-2013 data from the UK Clinical Practice Research Datalink (CPRD), in a study rated as good, Amirthalingam et al.[30] calculated Tdap-IPV vaccine effectiveness in infants less than 3 months of age for whom maternal immunization status was available (82 infants). In the year following the implementation of the same national maternal Tdap-IPV immunization program, vaccine effectiveness was estimated at 90% for infants less than 2 months of age and 91% [95% CI: 84-95] for infants less than 3 months of age. When estimates were adjusted for national coverage data seen outside of CPRD practices, vaccine effectiveness fell to 84% (95% CI: 71-93). In the year following program implementation, there were 3 deaths reported (from 14 in 2012), all in infants less than 9 weeks of age and born to mothers not immunized in pregnancy. In 2011, 2012 and 2013, there were 124, 282 and 86 hospitalizations (respectively) of infants less than 2 months of age. No fall in hospital admissions was reported for any of the age groups aged 3 months and older.

Using the same dataset (243 infants), Amirthalingam et al.[31] went on to report on vaccine effectiveness three years following the maternal Tdap-IPV program introduction in another study rated as good. Vaccine effectiveness against disease in infants aged less than 93 days was estimated to be 91% (95% CI: 88–94) and for infants less than 2 months of age it was 90% (95% CI: 86–93). Vaccine effectiveness against death was calculated at 95% (95% CI: 79–100). When a relative reduction of 20% in vaccine coverage was applied in a sensitivity analysis, vaccine effectiveness fell to 82% (95% CI: 74–88). Study authors also calculated the vaccine effectiveness of maternal immunization subsequent to the administration of first, second and third DTaP dose (2, 4 and 4 months of age). A total of 73 children born after October 2012 received a childhood vaccine; mothers of 26 of these children received Tdap. Of 73 children, 43 received 1 dose, 12 received 2 doses, and 18 received 3 doses of their primary pertussis vaccine series. Maternal vaccine effectiveness for infants who received 1 dose was 82% (95% CI: 65–91) and 69% (95% CI, 8%–90%) for infants who received 2 doses; for those with a completed schedule, the point estimate remained above 0%. With a relative 20% lower maternal vaccine coverage estimate, the effectiveness declined from 82% to 68% for infants who received 1 dose of DTaP.

Similar vaccine effectiveness estimates were also found in a US study rated as good that was conducted by Baxter et al.[32] In the study that followed health outcomes of approximately 150,000 infants, Tdap vaccine effectiveness for infants from birth through 7 days after the first DTaP dose was estimated at 87.9%. After controlling for the effects of DTaP vaccination, maternal immunization with Tdap was estimated to reduce pertussis risk in infants less than one year of age by 69%. In another US study by Winter et al.[33] that was rated as fair, infant outcomes were evaluated in a cohort of mothers with documented Tdap vaccination histories in the California Immunization Registry (CAIR). In the cohort, pertussis was reported in 25 infants ≤ 8 weeks of age and 35 infants ≤12 weeks of age. The overall vaccine effectiveness of maternal Tdap vaccination at 27–36 weeks gestation compared to cocooning was 85% (95% CI, 33%–98%) for preventing pertussis in infants ≤8 weeks of age and 72% (30%–89%) for preventing it in infants ≤12 weeks of age. Study authors found that infants whose mothers were vaccinated during the second trimester to be more likely to have pertussis at age ≤8 weeks (OR,

8.1; 95% CI, 1.3–49.0) or ≤12 weeks (4.6; 1.39–15.25) than infants whose mothers were immunized in the third trimester of pregnancy. Infants whose mothers received Tdap early in the third trimester (27–31 weeks gestation) had slightly lower odds of pertussis at ≤8 (0.43, 95% CI: 0.02-7.58) or ≤12 (0.62, 95% CI: 0.12-3.19) weeks of age than infants whose mothers received Tdap vaccine at 32–36 weeks gestation. Using the same database, in a study that was rated as fair, Winter et al.[34] also compared hospitalization outcomes of infants less than 63 days of age whose mothers received Tdap in pregnancy (n=49) to those born to mothers not immunized in pregnancy (n=371). Compared to the control group, infants whose mother were immunized with Tdap were older when they developed pertussis (p=0.03) and less likely to have the classic pertussis symptoms of paroxysmal cough (Relative Risk [RR], 0.41 [95% CI: 0.25–0.68]), apnea (0.66 [95% CI: 0.47–0.91]), cyanosis (0.53 [95%CI: 0.39–0.73]) or whoop (0.78 [95% CI: 0.62–0.99]). These infants were also found to have a significantly lower risk of hospitalization (RR, 0.5 [95% CI: 0.4–0.6]) or Intensive Care Unit (ICU) admission (0.8 [95% CI: 0.7–0.9), and if hospitalized, they had a shorter hospitalization stay (median 3 vs. 6 days; p=0.02). No infants in this group had seizures, required intubation, or died. The overall vaccine effectiveness of maternal immunization with Tdap for preventing hospitalization among infants with pertussis was 72% (95% CI, 49–85); 58% (15%–80%) after adjusting for infant's chronological and gestational age and receipt of DTaP vaccine. Similar results were also reported from Spain, where in a study rated as fair, Bellido-Blasco et al.[35] estimated the effects of a regional maternal pertussis vaccination program during the third trimester of pregnancy. A prospective matched case–control study found an adjusted VE of 90.9% (95% CI: 56.6-98.1) in infants less than 3 months of age.

In Argentina, in a study rated as poor, Vizotti et al.[36, 37] evaluated the effectiveness of a national maternal Tdap program that initiated in February 2012 using the national health surveillance system (SNVS).[65] A comparison was conducted of states in which maternal Tdap coverage was below (or equal to) and over 50%; cases identified between January 2010 and December 2013 were confirmed by PCR, culture or serology. In 2013, the number of cases was approximately 7 times lower in low coverage areas compared to those with more than 50% coverage. Nevertheless, at all times after 2012, there were fewer cases among 0-2 month infants in states with higher (>50%) compared to those with lower maternal coverage (≤50%).

## III.3 Adverse events

In total, 14 studies rated as good (2), fair (10), poor (1), and non-rated (1), reported on local and systemic AE following Tdap vaccination in pregnancy, including injection site reactions, fever, malaise and anaphylaxis; 23 studies included data on pregnancy complications or adverse fetal, neonatal or infant outcomes. In addition, the PWG was made aware of the US Vaccine Adverse Event Reporting System (VAERS) data that was presented to the Advisory Committee on Immunization Practices (ACIP) at its meeting in June 2016. Altogether, ten years of passively reported VAERS data and eight years of actively reported longitudinal US Vaccine Safety Datalink (VSD) data have been reported in peer-reviewed publications.

### IV.4.1 Maternal local and systemic adverse events

In a study rated as fair, Zhateyeva et al.[38] analyzed data for post-immunization AE in pregnancy that were reported to VAERS prior to the current ACIP recommendations. Between January 2005 and June 2010, 132 reports were submitted to VAERS. Of these, 14% (24/132) described local or systemic events. The most frequently reported AE during pregnancy were gestational diabetes (7 reports), injection site reactions (6 reports), anemia (5 reports) and

headache or fever with abdominal pain (3 reports). Reports submitted to VAERS following the ACIP recommendation were analyzed by Moro et al.[39] in a study rated as fair. Between November 2011 and June 2015, 392 pregnancy-related AE were reported. The largest number of reports pertained to injection site reactions (12%) or musculoskeletal, connective tissue or immune system disorders, including anaphylaxis (7%). Less than 5% of reports pertained to systemic reactions such as fever or chills. Complementary to these studies, a Centers for Disease Control (CDC) presentation to ACIP[40] provided additional data for the period from November 2011 to June 2016. From 464 cases associated with Tdap immunization in pregnancy that were reported to VAERS up to June 2016, 42% included reports with no description of an adverse event; 54% were submitted by the manufacturer. The most commonly reported AE were: injection site reactions or extremity myalgia (74 reports); systemic reactions such as fever, chills and headache (31 reports); gestational diabetes and hypertension (15 reports); musculoskeletal and connective tissue disorders (14 reports) and non-anaphylactic allergic reactions (12 reports). There were 5 reports each of Guillain-Barré syndrome and infections, and fewer than 5 reports for all other causes (n=31).

In addition to the US vaccine safety surveillance data, adverse outcomes following the administration of 1,258,723 doses of Tdap to pregnant women in Argentina were reported by Vizzotti et al.[36], in a study rated as poor. During the period from January 2012 to December 2014, a total of 7 local AE following immunization (rate of 1.59/100,000) were reported, including 2 episodes of rash and 5 episodes of vaccination site pain, redness or swelling. No serious or fatal events were reported by the study authors.

An analysis of VSD data from January 2007 and November 2015 was conducted by Kharbanda et al., in a study rated as fair.[41] Among 53,885 pregnant women with a singleton live birth who received Tdap, 43 required medical attention within 3 days following vaccination due to fever/malaise, seizure, altered mental status, allergic or other systemic or local reaction (rate of 8.1/10,000); the majority of events (15) were due to fever (rate of 2.8/10,000). When compared to the cohort of 109,253 pregnant women who did not receive Tdap (matched for age, study site and estimated pregnancy start date; assigned index date equivalent to the gestational age at vaccination for their match), the adjusted rate ratio for any 0 to 3 day event (post immunization/index date) was 1.19 (95% CI: 0.81–1.73). Except for the rate ratio for medically attended fever that was found to be significantly increased (5.4 [95% CI: 2.1–13.9]), no increased risk was found for neurologic events, incident gestational diabetes, thrombocytopenia, venous thromboembolism or cardiac events (myocarditis, pericarditis, cardiomyopathy, heart failure) in 42 days post vaccination. Analysis of medically attended acute events in women receiving concomitant and sequential Tdap and influenza vaccination using VSD data (period between January 2007 to November 2015) was conducted by Sukumaran et al., in a study rated as fair.[42] When adjusted for gestational age, study authors found no increased risk for any AE within 3 or 7 days following vaccine administration [1.13 (0.57 – 2.27); p=0.72 and 0.96 (0.58 – 1.61); p=0.88) between the groups. Similarly, the two groups did not differ in risk of fever within 3 or 7 days following concomitant vs. sequential vaccine administration [0.69 (95%CI: 0.15 – 3.23); p=0.64 and 1.60 (0.56 – 4.59); p=0.38). Using the VSD data for the same period, Sukumaran et al.[43] also compared the risk of AE in relation to the time of administration of a previous tetanus-containing vaccine in a study rated as fair. The authors did not find an increase in the frequency of fever (ARR (ARR): 0.66 [95% CI, 0.07-5.77; p=0.7]), allergic reaction (ARR: 1.55 [95% CI, 0. 13-18.45; p=0.73]) or local reactions (ARR: 0.49 [95% CI, 0.11-2.20; p=0.35]) up to 3 days post Tdap in women who received the vaccine at less than 2 years compared to those receiving the vaccine at more than 5 years following a tetanus containing vaccine. Similarly, no increase in the frequency of fever, allergic or local reactions was found between groups for the 7 day period following immunization.

AE following immunization with Tdap in pregnancy were reported in 3 RCTs. Munoz et al.[2] conducted a study rated as good in which 48 healthy women received either Tdap (n=33) or placebo (n=15) at 30-32 weeks of pregnancy or postpartum; a comparison group included 32 age-matched non pregnant women immunized with Tdap. There were no differences between groups in reporting any injection site reaction (p=1), pain at the injection site (p> 0.35) or headache, myalgia and malaise (p> 0.35) following Tdap administration. Local swelling and erythema were infrequent in all groups. The only difference reported by study authors was a lower occurrence of fever among women who received Tdap in pregnancy compared to those immunized postpartum (p=0.044). Perez et al.[1] conducted a similar study rated as good, in which 170 healthy women received either Tdap (n=90) or placebo (81) at 28 to 32 weeks gestation. Within 24 hours following immunization, non-serious local AE were reported by a third of study participants and 4% reported non-serious systemic AE. No statistically significant differences in reported AE were found between groups. No serious adverse events (SAE) were reported by the study authors. Hoang et al.[3] randomized 103 women to receive either Tdap (n=52) or tetanus-toxoid (n=51) vaccine between 19 and 35 weeks of pregnancy, in a study rated as fair. Approximately half of study participants in both groups reported at least 1 adverse event, with local pain and swelling being the most commonly reported. After Tdap vaccination, two individuals were hospitalized for fever and fatigue, which both resolved without complications. No significant differences were found in local or systemic events between the two groups.

In Australia, Regan et al.[44] in a study rated as fair followed up (survey and medical record review) on immunization outcomes in pregnancy after the receipt of Tdap alone (n=1,257), inactivated influenza alone (n=1,584) or Tdap and influenza vaccine concomitantly (n=1,506). Approximately 10% percent of women in all groups reported any adverse event following immunization. However, local reactions were more frequently reported in those receiving Tdap alone compared to influenza vaccine alone or together with Tdap (OR, 2.29 [95%CI: 1.61–3.26] and 1.73 [95% CI: 1.21–2.47]). A sub analysis of women who previously received Tdap in adulthood showed a more frequent reporting of AE compared to those who did not report receiving Tdap immunization (p = 0.04). These women had also greater odds of reporting pain or swelling at the injection site (OR, 2.00 [95% CI: 0.94–4.25]; p = 0.06).

Four prospective and two retrospective observational studies reported on maternal AE. In a study rated as fair, Petousis-Harris et al.[45] recruited 793 women from New Zealand for immunization with Tdap with or without influenza vaccine in the third trimester of pregnancy. Approximately one third of women also received inactivated influenza vaccine at the time of Tdap receipt. Although 79% of women reported experiencing pain at the injection site following Tdap, only 2.6% characterized pain as being severe. In addition, less than 0.5% women reported severe local swelling or erythema following Tdap immunization. The most frequently reported systemic AE following Tdap administration were fatigue (8.4%), headache/dizziness (3.9%), myalgia/arthralgia (3%), nausea/vomiting (2.8%) and fever (2.1%). In total, 3.9% of reported events were classified as serious, although a subsequent clinical review found none to be caused by Tdap vaccination. Maertens et al.[17] conducted a non-randomized control trial rated as fair, in Belgium, that compared the outcomes of Tdap immunization in 57 women during the third trimester of pregnancy with those of 42 women not immunized in pregnancy. Stiffness of the arm at the injection site was reported by 74% of study participants, and one individual reported fever. A total of 11 SAE were reported following Tdap and 3 occurred in the control group; none were considered by study authors to be related to vaccination. In a study rated as fair, Fortner et al.[46] compared the occurrence of AE in 361 pregnant women who received Tdap at 20-34 week of gestation and 161 non pregnant women immunized with Tdap. Rates of moderate to severe injection site pain and malaise within 7 days post immunization

were found to be higher in pregnancy ($p < 0.05$). Rates of fever, headaches, injection site swelling and redness were similar between groups. In a study by Perry et al.[47] that was rated as fair, over 700 pregnant women were assessed for local and systemic AE within 7 days of vaccine administration. In total, 67% of women reported to have at least 1 reaction to the vaccination and 25% had 2 reactions or more. Experienced by 65% of the study participants, pain or soreness at the injection site was the most common AE. Three percent of the individuals experienced fever of 38°C (two admitted to hospital) or more and 7% reported generalized body aches. Two individuals were treated in the emergency department regarding local reactions. In a study that was rated as fair, using insurance claims data, Layton et al.[48] reported on medically-attended AEs among over 200,000 women receiving Tdap during pregnancy or postpartum. In general, the study authors found AEs to be more frequently reported by women vaccinated postpartum that those who received Tdap after 27 weeks of pregnancy.

Two case reports, both rated as poor, were also identified through the literature search. Talbot et al.[49] reported on 16 unintentionally immunized pregnant health care workers who received Tdap during a hospital immunization campaign. Among these women, the study authors reported one case of severe swelling at the injection site and 2 cases of malaise in the 2 weeks after Tdap administration. Cabrera-Maqueda et al.[50] reported on two cases of optic neuritis diagnosed 2 and 3 weeks after Tdap immunization at 28 weeks gestation. In both cases, women did not have any underlying disease that would predispose them to optic neuritis, and both cases resolved without complications within three weeks of diagnosis.

### IV.4.2 Pregnancy complications and fetal/neonatal adverse events

In the analysis of data that was submitted to VAERS between January 1, 2005 and June 30, 2010, Zhateyeva et al.[38] identified 132 reports, in a study rated as fair. Spontaneous abortion with a median gestational age of 9 weeks and median onset interval from vaccination of 33 days was the most commonly reported adverse event (22 reports). In addition, study authors identified 2 cases of stillbirth (one due to placental abruption at 37 weeks gestation in which Tdap was administered several hours before and the second at 22 weeks gestation, 46 days after exposure to Tdap) and 6 reports of AE in infants: gastroschsis, laryngomalacia, patent foramen ovale, mild physiologic jaundice, transient tachypnea and bilateral hydroceles. In a study rated as fair, Moro et al.[39] published data from the analysis of VAERS reports submitted between November 1, 2011 and June 30, 2015. During this period, they identified 392 reports of which 3.8% (n=15) included still birth or spontaneous abortion, 2.8% (n=11) preterm birth and 3.1% (n=12) oligohydroamnios. Only 1% (n=4) included a major birth defect: ectopic kidney in a newborn, left heart syndrome, trisomy 12 and club foot. A CDC presentation to ACIP[40] provided additional data for the period from November 2011 to June 2016. During this time, 464 reports were submitted following Tdap immunization in pregnancy, with the majority (54%) originating from vaccine manufacturers; 42% did not contain information about an associated adverse event (primarily reported during the period when Tdap was not routinely recommended). Among AE identified in pregnancy, premature delivery at less than 37 weeks gestation (15 reports), stillbirth (13 reports) and oligohydroamnios (12 reports) were most commonly reported. Pregnancy-related AE also included: spontaneous abortion (n=4), failure to progress (n=4), polyhydroamnios (n=3), chorioamnionitis (n=3), breech presentation (n=2), preeclampsia (n=2), placenta previa (n=1), abruption placentae (n=1), premature rupture of membranes (n=1), preterm labor (n=1), contractions/sent to hospital (n=1), arrest of descent (n=1), prolonged labor (n=1) and induction of labor due to fetal tachycardia (n=1). From a total of 21 reported infant or fetal AE, most common were intrauterine growth restriction (n=8) and macrosomia (n=4). Other reports included a case of neonatal demise (cause of death: umbilical cord occlusion with fetal

vascular thrombus formation), polydactyly, neonatal respiratory disorder, lockjaw in infant, pneumonia in infant, large for gestational age, hypoglycemia in infant, fetal tachycardia and decreased fetal movement. Four major birth defects were noted: ectopic kidney (mother vaccinated at 17 weeks), hypoplastic left heart syndrome (mother vaccinated at 1.4 weeks), trisomy 12 (mother vaccinated at 28 weeks) and clubbed foot (time of maternal vaccination was not reported). The frequency of choriomanionitis reporting in VAERS was analyzed in a study rated as fair by Datwani et al.[51] Between July 1990 and February 2014, eight reports of choriomanionitis associated with Tdap immunization were identified, of which five (16.1% of total reports) in women only immunized with Tdap and three (9.6% from total reports) in women who received Tdap concomitantly with an inactivated influenza or Human papillomavirus 4-valent (HPV4) vaccine.

In addition, information from product-specific registries that are maintained by manufacturers was shared with the WG. Data from the Adacel registry collected between June 2005 and January 2011 was reported by Wang et al.[52] in a study rated as fair. During this time, there were 539 reports of Adacel administration to women already pregnant or who became pregnant less than 30 days post-vaccination: 49 from phase IV studies and 490 spontaneous reports. In 98 cases, women received one other vaccine or Tuberculin skin test. In phase IV studies, 10 serious and 5 non- SAE occurred, none of which were specified. Among spontaneous reports for which information was available, there were 10 preterm deliveries, 18 spontaneous abortions and one case of one sided hydronephrosis. There were also 29 serious and 41 non-serious unspecified AE. Information from the Boostrix registry (unpublished data) up to August, 2015 was provided to NACI by the manufacturer. In total, 908 pregnancy reports (890 prospective and 18 retrospective) have been submitted to the US registry and another 132 reports were further received in 20 other countries. The majority of these reports (n=669) were lost to follow-up or were with an unknown outcome, 150 were classified as ongoing and 202 reported live birth without a birth defect. There were 13 instances of live birth with a birth defect, 4 spontaneous abortions without a birth defect and 4 stillbirths without a birth defect.

Five studies rated as fair included an analysis of VSD data. Among those, DeSilva et al.[53] analyzed VSD data from January 1, 2007 to September 30, 2013 that included 324,463 singleton live births. Maternal Tdap was not found to be significantly associated with an increased risk for microcephaly in 3,321 women immunized at less than 14 weeks gestation (adjusted prevalence ratio [APR], 0.96 [95% CI, 0.36-2.58]), 20,568 women immunized between 27 and 36 weeks gestation (APR, 1.01 [95% CI, 0.63-1.61]), or during any week of pregnancy (n = 41,654; APR, 0.86 [95% CI, 0.60-1.24]). Sukumaran et al.[42] analyzed VSD data for the same period to determine immunization outcomes in pregnancy when Tdap was provided with and without the influenza vaccine. Among 4,554 women who received Tdap and influenza vaccines concomitantly, there were 7.3% (n=333) preterm deliveries. In addition, 5.8% (n=266) of infants were born with low birth weight and 9.6% were small for gestational age (SGA). When compared to infants whose mothers received Tdap and influenza vaccines sequentially, no differences in the occurrence of preterm delivery, low birth weight (less than 2500 grams) and SGA were found. There was also no increase in the relative risks for preterm delivery (0.95 [95% CI: 0.82 – 1.11]; p=0.52), low birth weight (0.92 [0.78 – 1.09]; p=0.34) or SGA (1.01 [98%CI: 0.88 – 1.15]; p=0.92). The study authors also did not find an association between adverse birth outcomes and gestational age at time of Tdap vaccination. In another analysis of VSD data from January 1, 2007 to November 15, 2013 that was conducted by Sukumaran et al.[43], adverse birth outcomes were analyzed in a birth cohort of 517,700 pregnancies according to the time since last tetanus-containing vaccine administration. In the cohort, 71.7% pregnancies ended in live birth, 14.8 % in spontaneous abortion, 13% in therapeutic abortion and 0.4% in stillbirth; Tdap was administered in 9.5% of pregnancies ending with live birth and

1.6% of pregnancies ending in spontaneous abortion, therapeutic abortion or stillbirth. Relative risk of adverse outcomes in 3,313 infants whose mothers received Tdap less than 2 years following TT vaccination and 7,226 infants whose mothers received Tdap 2 to 5 years following prior TT vaccination were compared to the control group of 10,633 infants whose mothers received Tdap more than 5 years after TT vaccination. No statistically significant differences in rates of adverse birth outcomes related to timing since prior TT vaccination were found. Among women immunized with Tdap at less than 2 years since TT vaccine, preterm delivery occurred in 6.6% of pregnancies (adjusted RR, 1.15 [95%CI, 0.98-1.34;p =0.08]), low-birth weight delivery occurred in 4.7% of pregnancies (adjusted RR, 1.10 [95%CI,0.92-1.32; p=0.31]) and SGA delivery occurred in 9.0% of pregnancies (adjusted RR, 0.99 [95% CI: 0.87-1.13; p=0.88]). Among women immunized with Tdap 2 to 5 years since the administration of a previous TT vaccine, preterm delivery occurred in 6.4% (adjusted RR, 1.06 [95%CI: 0.94-1.19; p=0.33]), low-birth weight delivery occurred in 4.7% (adjusted RR, 1.03 [95%CI: 0.89-1.18; p=0.72]) and SGA delivery occurred in 8.7% (adjusted RR, 0.96 [95% CI, 0.87-1.06; p=0.45]). An analysis of VSD data for infant outcomes (infants born between January 1, 2010 and November 15, 2012) from 2 California sites was also conducted by Kharbanda et al.[54], in a study rated as fair. Among 26,229 infants whose mother received Tdap in pregnancy, 8.4% were born SGA and 6.3% were preterm. When compared to infants of women who did not receive Tdap in pregnancy, the relative risk for SGA was 1.00 (95%CI, 0.96-1.06) and hazard ratio (HR) for preterm delivery was 1.03 (95%CI: 0.97-1.09). The preterm delivery rate of infants born to mothers vaccinated between 27 and 36 weeks gestation was slightly lower (5.3% vs 7.8%), but statistically significant (adjusted HR=0.88; 95% CI: 0.80-0.95) compared to infants of unvaccinated mothers. Study authors also found that among women immunized with Tdap, 6.1% were diagnosed with chorioamnionitis and 8.2% had a diagnosis of hypertensive disorder prior to 20 weeks of gestation. Compared to women who did not receive Tdap, those immunized with Tdap in pregnancy had a higher ARR for chorioamnionitis (1.19 [95%CI, 1.13-1.26]) and a marginally non-significant increase for a hypertensive disorder prior to 20 weeks of gestation (1.09 [95%CI, 0.99-1.20]). The median gestational week for women with chorioamnionitis was 28 weeks. Another analysis by DeSilva et al.[55] of data collected between January 2010 and November 2013 from seven VSD sites re-evaluated the association between chorioamnionitis and maternal immunization with Tdap during pregnancy. In an analysis of approximately 200,000 pregnancies, the study authors found a slightly increased risk for chorioamnionitis in women who received Tdap any time during pregnancy compared to unvaccinated women (adjusted rate ratio, ARR 1.23 [95% CI: 1.17-1.28]). However, the study authors did not find any increased risk for clinically significant infant outcomes associated with maternal chorioamnionitis including transient tachypnea of the newborn (ARR 1.04 [0.98, 1.11]), neonatal sepsis (ARR 1.06 [95% CI: 0.91-1.23]), neonatal pneumonia (ARR 0.94 [95% CI: 0.72-1.22]), respiratory distress syndrome (ARR 0.91 [95% CI: 0.66-1.26]), or newborn convulsions (ARR 1.16 [95% CI: 0.87-1.53]).

In another US study that was rated as fair, higher rates of chorioamnionitis were observed in an analysis of private insurance claims data. In a cohort of over 123,000 women receiving Tdap between 27 and 36 weeks gestation, Layton et al.[48] reported an increased relative risk of chorioamnionitis (adjusted HR 1.14 [95% CI: 1.10-1.18]) compared to women who did not receive Tdap during pregnancy. Higher risk (adjusted HR 1.23 [95% CI: 1.16-1.31]) of chorioamnionitis was also found in the cohort of 25,000 women who received Tdap prior to 37 weeks gestation. Among these women, compared to women immunized postpartum, the study authors also found an increased risk of post-partum hemorrhage (adjusted HR 1.34 [95% CI: 1.25-1.44]) and newborn seizures (adjusted HR 1.38 [95% CI: 1.08-1.76]). However, when study authors conducted a sensitivity analysis that included only women that received Tdap and

influenza vaccines concomitantly, no association was found between maternal Tdap immunization and chorioamnionitis or post-partum hemorrhage.

In a study rated as fair from the UK, Donegan et al.[56] analyzed Clinical Practice Research Datalink (CPRD) data from October 2012 to March 2013 that included 17,560 pregnant women immunized with Tdap-IPV of whom 6,184 had data on pregnancy outcomes. Each of the immunized women was matched to up to three historical unvaccinated controls. Among vaccinated women, within 2 weeks post vaccination, there were 7 reported stillbirths. The rate of observed stillbirths was similar to an overall estimated stillbirth rate based on national statistical data (incidence rate ratio (IRR), 0.97 [95% CI: 0.39-2.00]). In total, there were 12 recorded instances of stillbirth after vaccination with a calculated observed versus expected rate ratio of 0.85 (95% CI: 0.44 -1.61) and a conditional rate ratio (vaccinated versus unvaccinated women) of 0.85 (95% CI: 0.45-1.61). There were 2 cases of neonatal death within a week after delivery, in addition to the 12 cases of stillbirth; calculated observed versus expected rate ratio = 1.00 (95% CI: 0.20, 4.95). The study authors did not report any local or systematic AE within 2 weeks of the receipt of Tdap-IPV or cases of placental abruption, vasa praevia, fetal distress, or child renal failure after vaccination. Also, no significant differences between the vaccinated and unvaccinated cohort in the time to delivery (median gestation 40 weeks; HR 1.00, 95% CI: 0.97, 1.02) and median birth weight (p=0.81) were found.

Adverse outcomes in women who received Tdap in pregnancy were reported in 3 RCTs rated as good (2) and fair (1). Munoz et al.[2] conducted a study rated as good, in which 48 healthy women received either Tdap (n=33) or placebo (n=15) at 30-32 weeks of pregnancy or postpartum. A comparison group included 32 age-matched non-pregnant women immunized with Tdap. AE were reported by 84.8% of mothers in the Tdap group and 93.3% of mothers who received placebo; all resolved without sequelae. All infants were live born, mostly at term and by vaginal delivery. There were no significant differences in the infants' gestational age, birth weight, Apgar scores, neonatal examination or complications. There were no differences in the infants' growth and development up to 13 months of age. Perez et al.[1] conducted a similar study rated as good, in which 170 healthy women received either Tdap (n=90) or placebo (81) at 28-32 weeks gestation. No infant AE were reported by the study authors. In a study rated as fair, Hoang et al.[3] randomized 103 women to receive either Tdap (n=52) or TT (n=51) between 19 and 35 weeks of pregnancy. Approximately half of study participants in both groups reported at least 1 adverse event. One preterm delivery with stillbirth at seven months gestational age occurred at 5 weeks following vaccination with TT vaccine. Common symptoms of respiratory and gastrointestinal diseases were recorded, but none were classified as serious and did not require hospitalization; none were associated with maternal vaccination.

An assessment of pregnancy and neonatal outcomes using medical records was reported in 7 studies which were all rated as fair. Berenson et al.[57] conducted a review of 835 electronic medical charts of women immunized with Tdap in pregnancy: 65% of women also concomitantly received the influenza vaccine and 75.3% received Tdap vaccine between 27 and 36 weeks gestation. Chorioamnionitis was found in 3.5% (n=39), postpartum endometritis in 0.8% (n=9), preterm premature rupture of membranes in 3.2% (n=36) and preterm delivery in 5.2% (n=58) of immunized women. A higher proportion of infants born to mothers not immunized in pregnancy were born with low birth weight (9.1% vs. 5.5%) and very low birth weight (1.8% vs. 0.2%). Study authors did not find any significant differences in frequency of birth defects (AOR = 0.80 [95% CI; 0.38-1.67]), chorioamnionitis (AOR = 1.53 [95% CI; 0.80-2.90]) or combined infant outcomes (AOR = 0.80 [95% CI; 0.61-1.06]) by maternal vaccination status. Only statistical differences found by authors were in the lower rate of Neonatal Intensive Care Unit (NICU)

admission, particularly due to preterm birth and anemia, in infants born to immunized mothers ($p<0.05$). Morgan et al.[58] reported on outcomes of 7,152 infants born to women immunized at or after 32 weeks of pregnancy. A control group consisted of women not immunized in pregnancy. Stillbirth rate, frequency of major malformations, incidence of chorioamnionitis, 5-minute Apgar scores, and cord blood pH values were not significantly different between the two groups. Neonatal complications including ventilation requirement, sepsis, intraventricular hemorrhage, and neonatal death rates were also similar. Significant differences between the two groups were noted for preterm birth rate ($p<0.001$), SGA rate ($p=0.32$), and length of neonatal hospitalization ($p<0.001$), all found to be higher in the non-immunized cohort. Incidence of preterm birth after 32 weeks of gestation was found to be higher in women not immunized in pregnancy even after adjusting for prenatal care attendance, race, age, parity, BMI, and 17α-hydroxyprogesterone (OHP) (OR=1.88 [95% CI: 1.25–2.84]). A subgroup analysis of multiparous women who were administered at least two Tdap vaccines in the past 5 years (1,229) and those who received only a single dose (4,159) demonstrated comparable delivery and neonatal outcomes, including gestational age at delivery, stillbirth and major malformation rate, neonatal care admission, ventilation requirements, and incidence of neonatal death. A similar study of 138 women immunized with Tdap in pregnancy (552 controls) conducted by Shakib et al.[59] found no significant differences in preterm delivery, gestational age, or birth weight between groups. Congenital anomalies were 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 ($p=0.75$). In infants born to women receiving Tdap during pregnancy, 3.6% (95% CI: 0.8%-10.2%) had a diagnosis consistent with a complex chronic condition within 12 months compared with 10.4% (95% CI: 7.2-14.4%) of infants of controls ($p=0.054$). In a non-randomized control study conducted by Maertens et al.[17] in the Netherlands, infant outcomes from 55 pregnancies in which healthy women immunized with Tdap were compared to outcomes in 26 children whose mothers were not immunized. Eight reported SAE (6 in the Tdap and 2 in the control group) included: 1 premature delivery, 1 fever at birth, 1 hypoglycemia at birth, 1 pneumonia at birth, 2 infections requiring hospitalization at the age of 1 and 5 months, 1 episode of febrile seizures at the age of 2 months and 1 episode of extreme vomiting at the age of 5 months. No congenital disorders were detected among infants in either group. In a follow up study, Maertens et al.[4] followed up these infants up to 16 months of age, and found no difference in the proportion of infants who were hospitalized during the study period (10.9% vs. 12.5%; $p = 0.838$). Reasons for hospitalization were: pneumonia at birth (n=1), child suspected of meningitis infection (n=1), rotavirus infection (n=1), removal of birthmark by esthetic surgery (n=1), dehydration (n=1) and febrile seizures (n=1). In a large retrospective review of medical record data (proof of concept study), Zerbo et al.[60] assessed outcomes of 65,751 term infants who received their first dose of DTaP vaccine between 6 and 10 weeks of age and were born to women immunized with Tdap after 14 weeks of pregnancy. A control group consisted of 82,948 infants whose mothers were not immunized in pregnancy. After adjusting for child's age at vaccination, year of birth, maternal age, gestational diabetes, insurance, smoking status and ethnicity, maternal Tdap vaccination was not significantly associated with infant fever (adjusted OR = 0.92, 95% CI: 0.82–1.04) following DTaP administration. In a poster presented at the Annual Meeting of the Society for Maternal-Fetal Medicine, Judy et al.[61] presented the results of a retrospective study at the Stanford University medical center that assessed the outcomes of over 1,700 pregnancies in which a Tdap vaccine was received postpartum or antepartum. The study authors reported similar rates if major and minor congenital anomalies, neonatal sepsis, and maternal infectious outcomes between the two cohorts, with no cases of intrauterine fetal death reported in either group. After controlling for baseline characteristics, no increased risk was found in a multivariate model for major anomalies or the composite neonatal and obstetric outcomes.

An observational prospective study rated as poor by Walls et al.[62] in New Zealand followed 408 infants born to women who received Tdap between 28 and 38 weeks of pregnancy. Women whose fetus had congenital anomalies, severe structural and/or chromosomal abnormalities identified during prenatal screening were excluded from the study. In the study cohort, 94% of infants were delivered at term. Ten infants (2.5%) were identified as having medical events of significance or congenital anomalies and one infant was stillborn (0.2%) with no identified congenital anomalies. A total of 303 infants completed their 6-week check and 278 completed their 5-month check. In a similar study rated as fair conducted by Petousis-Harris et al.[45] in Australia, among 793 women who received Tdap between 28 and 38 weeks gestation, 8 reported SAE during labour and delivery. Two of these were perinatal deaths, one of which was due to a congenital abnormality and the other was unexplained. There was one cyanotic episode and five cases of a health service intervention. There were 9 pregnancies that ended preterm. Following a clinical review, none of the SAE were considered by study authors to be caused by Tdap vaccination.

Infant outcomes were also reported in three small observational studies. In a study by Klein et al[63], following an immunization of 13,427 adolescents, three pregnancies were reported in Tdap recipients: one miscarriage at 8 weeks gestation (considered not to be related to vaccination) and two pregnancies that resulted in normal healthy offspring. Similarly, following a hospital immunization campaign, Talbot et al.[49] identified 6 unintentionally immunized pregnant health care workers. No adverse outcomes in babies were reported by study authors. Acosta et al.[64] conducted a study rated as poor, which assessed birth outcomes for 9 cases of infants less than 3 months of age. Compared to non-vaccinated, infants born to vaccinated mothers did not show statistically significant differences ($p>0.05$) for duration of pregnancy (279 days vs. 278 days), weight at birth (3,290 grams vs. 3,220 grams), admission at NICU (1.58% vs. 1.87%) and Apgar test score<7 at 5 minutes (0.27% vs. 0%).

# IV. DISCUSSION/SUMMARY

Synthesis and analysis of the body of evidence is presented in the NACI Update on Tdap Immunization in Pregnancy

# VI. CONCLUSIONS

Synthesis and analysis of the evidence is presented in the NACI Update on Tdap Immunization in Pregnancy

# LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| AE | Adverse Event |
| AEFI | Adverse Event Following Immunization |
| aOR | adjusted Odds Ratio |
| AP | Antepartum |
| APR | Adjusted Prevalence Ratio |
| ARR | Adjusted Relative Risk |
| BMI | Body Mass Index |
| CDC | Centers for Disease Control |
| CI | Conference Interval |
| DTaP | Diphtheria and tetanus toxoids, acellular pertussis vaccine |
| DTwP | Diphtheria and tetanus toxoids, whole cell pertussis vaccine |
| EU | Endotoxin Unit |
| FHA | Pertussis flamentous hemagglutinin |
| FIM2/3 | Fimbriae types 2 and 3 |
| GBS | Guillain-Barré syndrome |
| GMC | Geometric Mean Concentration |
| GMT | Geometric Mean Titers |
| GW | Gestational Week |
| HBV | Hepatitis B Vaccine |
| HPV4 | Human papillomavirus 4-valent |
| HR | Hazard Ratio |
| ICU | Intensive Care Unit |
| IFN | Inferon |
| IgG | Immunoglobulin G |
| IgA | Immunoglobulin A |
| IPV | Invasive Pneumococcal Vaccine |
| IRR | Incidence Rate Ratio |
| IU | International Units |
| NACI | National Advisory Committee on Immunization |
| NICU | Neonatal Intensive Care Unit |
| NK | Natural Killer |
| OHP | Hydroxyprogesterone |
| PHAC | Public Health Agency of Canada |
| PCR | Polymerase Chain Reaction |
| PRN | Pertactin |
| PP | Postpartum |
| PT | Pertussis Toxin |
| PWG | NACI Diphtheria/Tetanus/ Pertussis/Polio/Haemophilus Influenza B Working Group |
| RAI | Relative Avidity Index |
| RCT | Randomized Controlled Trial |
| RDS | Respiratory distress syndrome |
| RR | Relative Risk |
| SAB | Spontaneous Abortion |
| SAE | Serious Adverse Event |
| SB | Stillbirth |

| | |
|---|---|
| SGA | Small for gestational age |
| sIgA | secretory Immunoglobulin A |
| TAB | Therapeutic Abortion |
| Tdap | Tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis vaccine |
| TIV | Trivalent inactivated influenza vaccine |
| TT | Tetanus Toxoid |
| UK | United Kingdom |
| VAERS | Vaccine Adverse Event Reporting (US) |
| WG | Working Group |

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# Appendix A: Search strategy and results

Embase and Medline searches were run Nov 28, 2016
Cochrane Central search was run Nov 29, 2016

Searches were updated July 25, 2017

Database(s): **Embase** 1974 to Present

Search Strategy:

| # | Searches | Results | Annotations |
|---|---|---|---|
| 1 | exp pertussis/ | 12374 | |
| 2 | (whoop* or pertuss*).tw,kf. | 28487 | |
| 3 | or/1-2 | 31782 | |
| 4 | exp Vaccine/ or exp Immunization/ | 413514 | |
| 5 | (vaccin* or immuniz* or immunis*).tw,nf. | 377836 | |
| 6 | or/4-5 | 500348 | |
| 7 | 3 and 6 | 13277 | |
| 8 | exp pertussis vaccine/ | 7737 | |
| 9 | (dtp or dtap or dtap?ipv or Adacel or Boostrix or Certiva or Daptacel or Hexavac or Hexaxim or Infanrix or Pentacel or Pentavac or Pediarix or Quadracel or Quintanrix or Refortix or Triavax or Tripacel or Tripedia or Tritanrix).mp. | 3625 | |
| 10 | or/8-9 | 10599 | |
| 11 | 7 or 10 | 16537 | |
| 12 | exp Pregnancy/ or Mother/ or Maternal exposure/ or Prenatal Care/ or Fetus/de, im | 795277 | |
| 13 | (pregnan* or matern* or mother* or antenat* or prenat* or f?etal or f?etus).ti,kf. | 469121 | |
| 14 | (matern* or antenat* or prenat* or f?etus or f?etal).tw. | 574956 | |
| 15 | (pregnan* or mother*).ab. /freq=2 | 340650 | |
| 16 | or/12-15 | 1153222 | |
| 17 | 11 and 16 | 1221 | |
| 18 | animal/ | 1741972 | |
| 19 | human/ | 18081030 | |
| 20 | 18 not (18 and 19) | 1324445 | |
| 21 | 17 not 20 | 1213 | |

| | | | |
|---|---|---|---|
| 22 | remove duplicates from 21 | 1146 | |

Database(s): **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

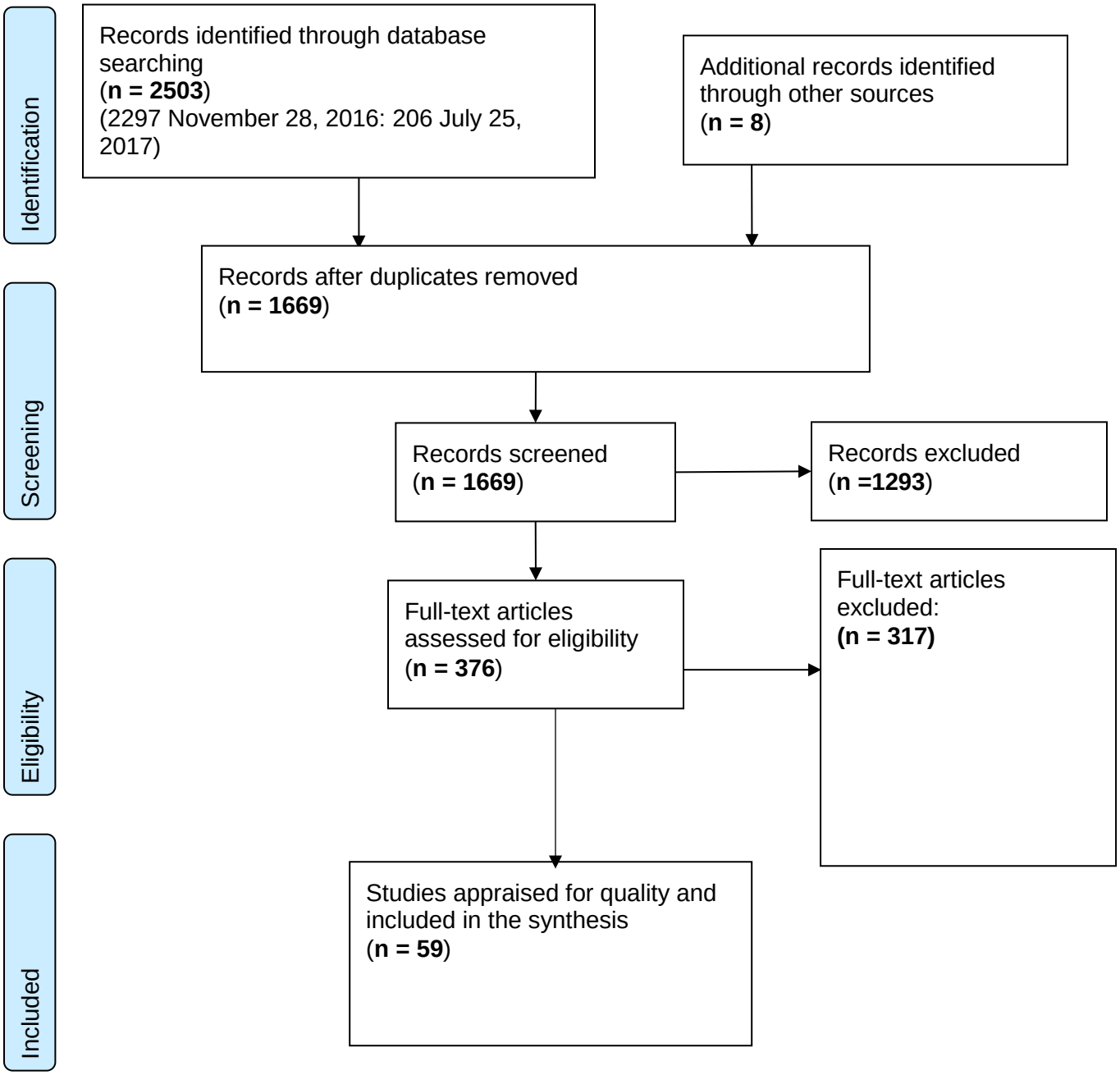
| # | Searches | Results | Annotations |
|---|---|---|---|
| 1 | Whooping cough/ or Bordetella pertussis/ | 11150 | |
| 2 | (whoop* or pertuss*).tw,kf. | 29624 | |
| 3 | or/1-2 | 30846 | |
| 4 | exp Vaccines/ or exp Immunization/ | 312920 | |
| 5 | (vaccin* or immuniz* or immunis*).tw,nf. | 364110 | |
| 6 | or/4-5 | 462851 | |
| 7 | 3 and 6 | 11021 | |
| 8 | exp Pertussis Vaccine/ | 7967 | |
| 9 | (dtp or dtap or dtap?ipv or Adacel or Boostrix or Certiva or Daptacel or Hexavac or Hexaxim or Infanrix or Pentacel or Pentavac or Pediarix or Quadracel or Quintanrix or Refortix or Triavax or Tripacel or Tripedia or Tritanrix).mp. | 2390 | |
| 10 | 8 or 9 | 9053 | |
| 11 | 7 or 10 | 13568 | |
| 12 | exp Pregnancy/ or Mothers/ or Maternal exposure/ or Prenatal Care/ or Fetus/de, im | 882305 | |
| 13 | (pregnan* or matern* or mother* or antenat* or prenat* or f?etal or f?etus).ti,kf. | 473376 | |
| 14 | (matern* or antenat* or prenat* or f?etus or f?etal).tw. | 510677 | |
| 15 | (pregnan* or mother*).ab. /freq=2 | 282029 | |
| 16 | or/12-15 | 1165907 | |
| 17 | 11 and 16 | 1029 | |
| 18 | animal/ | 6540188 | |
| 19 | human/ | 17431056 | |
| 20 | 18 not (18 and 19) | 4636432 | |
| 21 | 17 not 20 | 987 | |
| 22 | remove duplicates from 21 | 894 | |

Cochrane Central

ID Search
#1 MeSH descriptor: [Bordetella pertussis] this term only
#2 MeSH descriptor: [Whooping Cough] this term only
#3 whoop* or pertuss*:ti,ab,kw (Word variations have been searched)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Vaccines] explode all trees
#6 MeSH descriptor: [Immunization] explode all trees
#7 vaccin* or immuniz* or immunis*:ti,ab,kw (Word variations have been searched)
#8 #5 or #6 or #7
#9 #4 and #8
#10 MeSH descriptor: [Pertussis Vaccine] explode all trees
#11 dtap or dtap* or Adacel or Boostrix or Certiva or Daptacel or Hexavac or Hexaxim or Infanrix or Pentecel or Pentavac or Pediarix or Quadracel or Quintanrix or Refortix or Triavax or Tripacel or Tripedia or Tritanrix:ti,ab,kw (Word variations have been searched)
#12 #10 or #11
#13 #9 or #12
#14 MeSH descriptor: [Pregnancy] explode all trees
#15 MeSH descriptor: [Mothers] this term only
#16 MeSH descriptor: [Maternal Exposure] this term only
#17 MeSH descriptor: [Prenatal Care] this term only
#18 MeSH descriptor: [Fetus] this term only and with qualifier(s): [Drug effects - DE, Immunology - IM]
#19 pregnan* or matern* or mother* or antenat* or prenat* or fetal or foetal or fetus or foetus:ti,ab,kw (Word variations have been searched)
#20 #14 or #15 or #16 or #17 or #18 or #19
#21 #13 and #20

## Appendix B: Flow diagram of search strategy

Literature search strategy



## Appendix C: Level of evidence based on research design and quality (internal validity) rating of evidence

Table 1: Levels of Evidence Based on Research Design

| | |
|---|---|
| I | Evidence from randomized controlled trial(s). |
| II-1 | Evidence from controlled trial(s) without randomization. |
| II-2 | Evidence from cohort or case–control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy. |
| 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. |

Table 2: Definition of overall study quality

| | |
|---|---|
| **Good** | A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well. |
| **Fair** | A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion but has no known "fatal flaw". |
| **Poor** | A study (including meta-analyses or systematic reviews) that has at least one design-specific "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations. |
| *General design specific criteria are outlined in Harris et al., 2001[1]. | |

## Appendix D: Summary of evidence* related to maternal Tdap immunization in pregnancy

* In accordance with the system that has been recommended by the NACI Methods WG, studies in the tables 3 to 5 have been listed alphabetically in descending order according to evidence level and quality

**Table 3. Summary of evidence related to immunogenicity of Tdap acellular pertussis vaccination in pregnancy (mother)**

| STUDY DETAILS | | | | SUMMARY | | |
|---|---|---|---|---|---|---|
| **Study** | **Vaccine** | **Study Design** | **Participants** | **Summary of Key Findings Using Text or Data** | **Level of Evidence** | **Quality of Evidence** |
| **Flor M. Munoz, Nanette H. Bond, Maurizio Maccato, Phillip Pinell, Hunter A. Hammill, Geeta K. Swamy, Emmanuel B. Walter, Lisa A. Jackson, Janet A. Englund, Morven S. Edwards, C. Mary Healy, Carey R. Petrie, Jennifer Ferreira, Johannes B. Goll, Carol J. Baker**. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA.* 2014. 311:1760 | Adacel | Double masked, placebo-controlled RCT<br><br>USA | Group 1: 33 pregnant women who received Tdap at 30-32 weeks of gestation and saline postpartum<br><br>Group 2: 15 pregnant women who received saline at 30-32 weeks of gestation and Tdap postpartum<br><br>Group 3: 32 age-matched comparison group of healthy non-pregnant women immunized with Tdap<br><br>Inclusion criteria for Groups 1 and 2: healthy women 18 to 45 years-old with a singleton pregnancy and at low risk for obstetrical complications based on normal first or second trimester screening test | <u>Group 1:</u><br>• Anti-PT (EU/ml, 95% CI):<br>- Prior to Tdap: 7.9 (4.9-12.6)<br>- 4 weeks after Tdap: 56.5 (40.0-79.9)<br>- at delivery: 51.0 (37.1, 70.1)<br>- 2 months after delivery: 53.1 (39.4-71.7)<br>• Anti-FHA (EU/ml, 95%CI):<br>- Prior to Tdap: 15.1 (8.7-26.0)<br>- 4 weeks after Tdap: 234.4 (184.1-298.5)<br>- at delivery: 184.8 (142.8-239.1)<br>- 2 months after delivery: 199.8 (153.4-260.3)<br>• Anti-PRN (EU/ml, 95% CI):<br>- Prior to Tdap: 8.5 (5.5-12.9)<br>- 4 weeks after Tdap: 205.0 (117.1-359.1)<br>- at delivery: 192.2 (113.5-324.9)<br>- 2 months after delivery: 158.8 (93.5-269.8)<br>• Anti-FIM2/3 (EU/ml, 95% CI):<br>- Prior to Tdap: 27.2 (14.0-52.6)<br>- 4 weeks after Tdap: 1632.9 (954.5-2793.8)<br>- at delivery: 1601.3 (1073.4-2388.9)<br>- 2 months after delivery: 1354.8 (874.9-2097.9)<br><u>Group 2:</u><br>• Anti-PT (EU/ml, 95%CI): | I | Good, Small sample size |

| STUDY DETAILS | | | | | SUMMARY | |
|---|---|---|---|---|---|---|
| | | | results and detailed anatomic fetal ultrasound at 18–22 weeks' gestation. Women who in previous 2 years received any tetanus containing vaccine were excluded from the study. | - Prior to Tdap: 9.6 (5.2-17.6)<br>- 4 weeks after Tdap: 10.2 (5.6-18.7)<br>- at delivery: 9.1 (4.6-17.8)<br>- 2 months after delivery: 66.4 (42.2-104.8)<br>• Anti-FHA (EU/ml, 95%CI):<br>- Prior to Tdap: 23.2 (11.9-45.3)<br>- 4 weeks after Tdap: 23.6 (13.1-42.5)<br>- at delivery: 21.9 (10.9-44.1)<br>- 2 months after delivery: 270.9 (162.6-451.3)<br>• Anti-PRN (EU/ml, 95%CI):<br>- Prior to Tdap: 13.2 (5.8-30.1)<br>- 4 weeks after Tdap: 13.0 (5.7-29.6)<br>- at delivery: 12.2 (5.2-28.4)<br>- 2 months after delivery: 210.1 (80.3-549.6)<br>• Anti-FIM2/3 (EU/ml, 95%CI):<br>- Prior to Tdap: 36.4 (18.1-73.1)<br>- 4 weeks after Tdap: 38.2 (19.3-75.6)<br>- at delivery: 34.9 (16.3-74.8)<br>- 2 months after delivery: 2910.2 (1526.4-5548.5)<br><u>Group 3:</u><br>• Anti-PT (EU/ml, 95%CI):<br>- Prior to Tdap: 17.6 (12.5-24.7)<br>- 4 weeks after Tdap: 90.9 (69.1-119.7)<br>• Anti-FHA (EU/ml, 95%CI):<br>- Prior to Tdap: 30.1 (18.7-48.4)<br>- 4 weeks after Tdap: 285.6 (238.0-342.8)<br>• Anti-PRN (EU/ml, 95%CI):<br>- Prior to Tdap: 20.2 (14.5-28.1)<br>- 4 weeks after Tdap: 348.7 (209.1, 581.6)<br>• Anti-FIM2/3 (EU/ml, 95%CI):<br>- Prior to Tdap: 36.8 (21.2-63.9)<br>- 4 weeks after Tdap: 1785.1 (1222.5-2606.6)<br><br>No significant differences in antibody responses to Tdap vaccine between groups. Women in Group 1 had significantly higher concentrations of antibodies to all vaccine antigens at delivery than women in Group 2. | | |
| **Jesus Zacarias** | Adacel | RCT, double blind, | Group 1: 90 pregnant | <u>Group 1:</u> | I | Goo |

| STUDY DETAILS | | | | | SUMMARY | |
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| **Villarreal Perez, Jose Manuel Ramirez Aranda, Manuel de la O Cavazos, Michelle de J. Zamudio Osuna, Jose Perales Davila, Maria Romelia Ballesteros Elizondo, Marco Vinicio Gomez Meza, Francisco Javier Garcia Elizondo, Azucena M. Rodriguez Gonzalez**. Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. *Human vaccines & Immunotherapeutics.* 2017 Jan 2;13(1):128-135 | placebo: 0.9% saline solution | parallel group<br><br>Mexico | women 18 to 38 years of age immunized with Tdap at 30 to 32 weeks gestation<br><br>Group 2: 81 pregnant women 18 to 38 years of age immunized with saline at 30 to 32 weeks gestation<br><br>All women with low obstetric risk and normal anatomical ultrasound at 24-26 weeks gestation<br><br>Exclusion criteria: w/psychiatric disease (schizophrenia, psychosis, major depression), w/severe physical disease (diabetes mellitus, hypertension or degenerative diseases), consume drugs or tobacco, w/history of severe reactions to any vaccine immunized against tetanus and/or pertussis in the 2 years prior to the study. | • Anti-PT I (EU/mL, 95% CI):<br>- before immunization: 5.93 (4.55-7.74)<br>- after immunization: 24.04 (18.39-31.43)<br><br>• Anti-PRN (EU/mL, 95% CI):<br>- before immunization: 8.53 (6.71-10.85)<br>- after immunization: 112.08 (89.79-139.91)<br><br><u>Group 2:</u><br>• Anti-PT (EU/mL, 95% CI):<br>- before immunization: 7.90 (5.92-10.54)<br>- after immunization: 7.06 (5.24-9.50)<br><br>• Anti-PRN (EU/mL, 95% CI):<br>- before immunization: 8.08 (6.11-10.68)<br>- after immunization: 7.16 (5.38-9.53)<br><br>Difference in both antibody levels statistically significant after Tdap: (p-0.001) | | d |
| **Ha Thi Thu Hoang, Elke Leuridan, Kirsten Maertens, Trung Dac Nguyen, Niel Hens, Ngoc Ha Vu, Raissa Nadege Cabore, Hong Thi Duong, Kris Huygen, Pierre Van Damme,** | Adacel<br><br>TT | Randomized control study<br><br>Vietnam | Group 1: 49 women immunized with Tdap at 25 weeks of pregnancy<br><br>Group 2: 47 women immunized with TT at 25 weeks of pregnancy | <u>Group 1:</u><br>• Anti-PT (IU/ml, 95% CI):<br>- before immunization: 8.2 (6.4-10.6)<br>- one month after immunization: 33.1 (26-41.8)<br>- at delivery: 17.3 (13-22)<br>• Anti-FHA (IU/ml, 95% CI):<br>- before immunization: 16.7 (15.9-24.6)<br>- one month after immunization: 270 (211- | I | Fair, RCT study conducted in field cond |

| STUDY DETAILS | | | | SUMMARY | | |
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| **Anh Duc Dang.** Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during pregnancy. Vaccine. 2016. 34:151 | | | | 343)<br>- at delivery: 139 (1109-176)<br>• Anti-PRN (IU/ml, 95% CI):<br>- before immunization: 6.3 (4.6-8.6)<br>- one month after immunization: 229 (166-317)<br>- at delivery: 111 (76-163)<br><u>Group 2:</u><br>• Anti-PT (IU/ml, 95% CI):<br>- before immunization: 7.9 (4.9-10.4)<br>- one month after immunization: N/A<br>- At delivery: 5.7 (4.3-7.6)<br>• Anti-FHA (IU/ml, 95% CI):<br>- before immunization: 19.1 (15.1-24.1)<br>- one month after immunization: N/A<br>- at delivery: 17.3 (14-21.4)<br>• Anti-PRN (IU/ml, 95% CI):<br>- before immunization: 8.9 (6.6-12.1)<br>- one month after immunization: N/A<br>- at delivery: 9.4 (6.9-12.5)<br><br>After vaccination, all women responded to all pertussis antigens; women in Group 1 with significantly higher concentrations for all antibodies at birth ($p < 0.001$). | | itions |
| **Kris Huygen, Raissa Nadege Cabore, Kirsten Maertens, Pierre Van Damme, Elke Leuridan**. Humoral and cell mediated immune responses to a pertussis containing vaccine in pregnant and nonpregnant women. *Vaccine.* 2015. 33:4117 | Boostrix | Non randomized prospective matched control trial<br><br>Belgium | Group 1: 18 women immunized at 29 weeks gestation with Tdap<br><br>Group 2: 16 age matched non-pregnant women immunized with Tdap<br><br>For the 1 year follow-up, blood samples of 17/18 women in Group 1 and 11/16 women in Group 2 were available | <u>Group 1:</u><br>• Anti-PT (IU/mL, 95% CI):<br>- before immunization: 6.1 (3.9-9.5)<br>- one month after immunization: 52.7 (37.3-74.5)<br>- 12 months after immunization: 26 (18,37.6)<br><br>• Anti-FHA (IU/mL, 95% CI):<br>- before immunization: 32.1 (22.8-45.2)<br>- one month after immunization: 305 (238-390)<br>- 12 months after immunization: 148 (111-195)<br><br>• Anti-PRN GMC (IU/mL, 95% CI):<br>- before immunization: 59.2 (43.9-80) | II-2 | Good, Small sample |

| STUDY DETAILS | | | | SUMMARY | | |
|---|---|---|---|---|---|---|
| | | | | - one month after immunization: 667 (479-927)<br>- 12 months after immunization: 449 (275-733)<br><br><u>Group 2:</u><br>• Anti-PT levels (IU/mL, 95% CI):<br>- before immunization: 11.9 (6.2-22.9)<br>- one month after immunization: 79.5 (50.4-125.3)<br>- 12 months after immunization:28.3 (17.6-45.6)<br><br>• Anti-FHA levels (IU/mL, 95% CI):<br>- before immunization: 38.1 (26.7-54.4)<br>- one month after immunization: 319 (214-476)<br>- 12 months after immunization:129 (87-191)<br><br>• Anti-PRN levels (IU/mL, 95% CI):<br>- before immunization: 78.4 (56.6-108)<br>- one month after immunization: 574 (374-882)<br>- 12 months after immunization: 368 (186-730)<br><br>At month 1, antibody titres to all antigens increased significantly in both groups; there was no statistical difference in GMC either before or after immunization between two groups.<br><br>A month 12, mean GMC levels were approximately half the values observed at month 1 (significantly lower in both groups for PT and FHA but not for PRN). Compared to month 0, GMC values were significantly higher for all antigens in Groups 1 and 2 except for anti-PT in Group 2. However, when values for Group 2 women with high anti-PT values prior to vaccination were excluded, the mean for anti-PT GMC became significant ($p < 0.05$) when compared to month 0.<br><br>Cellular response:<br><br>At month 1 post immunization, Group 2 women showed 5 | | |

| STUDY DETAILS | | | | SUMMARY | | |
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| | | | | to 10 fold higher proliferative responses against PT and FHA. In contrast, only a slightly increased response was observed in Group 1. One year after vaccination, proliferative responses were back to baseline levels measured at month 0 for all antigens.<br><br>Vaccine specific IFN-gamma levels in PT or FHA stimulated cultures were overall very low and not different from levels in non-stimulated cells. IFN-gamma responses were higher in Group 2 than in Group 1. | | |
| **Bahaa Abu Raya, Isaac Srugo, Aharon Kessel, Michael Peterman, Avraham Vaknin, Ellen Bamberger**. The Decline of Pertussis-Specific Antibodies After Tetanus, Diphtheria, and Acellular Pertussis Immunization in Late Pregnancy. *Journal of Infectious Diseases.* 2015. 212:1869 | Boostrix | Prospective, non-randomized control study<br><br>Israel | Group 1: 38 Tdap-immunized women (mean age, 32.6 years; range, 20–47 years) vaccinated between 23.1 and 37.4 gestational weeks (mean, 50.6 days before delivery; range, 6–115 days).<br><br>Group 2: 10 women not immunized in pregnancy (mean age, 31.9 years; range, 26–40 years) | <u>Group 1:</u><br>• Anti-PT IgG (IU/mL, 95%CI):<br>- At delivery: 21.48 (12.51-36.89)<br>- 9 to 15 months after delivery: 11.72 (7.09-19.37)<br>• Anti-FHA IgG (IU/mL, 95%CI):<br>- At delivery: 185.95 (157.93-218.94)<br>- 9 to 15 months after delivery: 140.33 (113.46-173.57)<br>• Anti-PRN IgG (IU/mL, 95%CI):<br>- At delivery: 171.52 (120.73-243.67)<br>- 9 to 15 months after delivery: 83.74 (60.58-115.75)<br>• Anti-PT IgA (IU/mL, 95%CI):<br>- At delivery: 3.22 (2.39-4.34)<br>- 9 to 15 months after delivery: 2.61 (1.92-3.54)<br>• Anti-FHA IgA (IU/mL, 95%CI):<br>- At delivery: 30.16 (20.41-44.58)<br>- 9 to 15 months after delivery: 34.24 (25.03-46.85)<br><br><u>Group 2:</u><br>• Anti-PT IgG (IU/mL, 95%CI):<br>- At delivery: 0.77 (0.18-3.38)<br>- 9 to 15 months after delivery: 1.41 (0.32-6.14)<br>• Anti-FHA IgG (IU/mL, 95%CI): | II-2 | Fair, Single-center study |

| STUDY DETAILS | | | | SUMMARY | | |
|---|---|---|---|---|---|---|
| | | | | - At delivery: 12.02 (7.82-18.47)<br>- 9 to 15 months after delivery: 17.01 (9.31-31.05)<br>• Anti-PRN IgG (IU/mL, 95%CI):<br>- At delivery: 7.77 (1.94-31.07)<br>- 9 to 15 months after delivery: 5.98 (1.56-22.97)<br>• Anti-PT IgA (IU/mL, 95%CI):<br>- At delivery: 1.24 (0.63-2.47)<br>- 9 to 15 months after delivery: 0.82 (0.64-1.06)<br>• Anti-FHA IgA (IU/mL, 95%CI):<br>- At delivery: 2.42 (1.12-5.20)<br>- 9 to 15 months after delivery: 5.34 (3.56-8.02)<br><br>9–15 months after delivery pertussis-specific IgG levels had decreased significantly in Group 1 but remained higher than in Group 2. | | |
| **Bahaa Abu Raya, Isaac Srugo, Aharon Kessel, Michael Peterman, David Bader, Ron Gonen, Ellen Bamberger**. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels - a prospective study. *Vaccine.* 2014. 32:5787 | Boostrix | Prospective, non-randomized control study<br><br>Israel | Group 1: 61 Tdap-immunized women (mean age, 32.6 years; range, 20–47 years) vaccinated between 23.1 and 37.4 gestational weeks (mean, 50.6 days before delivery; range, 6–115 days).<br><br>Group 2: 20 women not immunized in pregnancy (mean age, 31.9 years; range, 26–40 years)<br><br>Serum collected at the time of delivery | <u>Group 1:</u><br>• Anti-PT IgG (IU/mL, 95%CI): 16.36 (9.57-27.98)<br>• Anti-FHA IgG (IU/mL, 95%CI): 192.04 (165.92-222.28)<br>• Anti-PRN IgG (IU/mL, 95%CI): 163.98 (119.51-225.06)<br>• Anti-PT IgA (IU/mL, 95%CI): 3.01 (2.36-3.83)<br>• Anti-FHA IgA (IU/mL, 95%CI): 32.67 (2.94-41.14)<br><br><u>Group 2:</u><br>• Anti-PT IgG (IU/mL, 95%CI): 0.74 (0.31-1.79)<br>• Anti-FHA IgG (IU/mL, 95%CI): 13.42 (8.90-20.26)<br>• Anti-PRN IgG (IU/mL, 95%CI): 8.46 (3.52-20.26)<br>• Anti-PT IgA (IU/mL, 95%CI): 1.19 (0.65-2.2)<br>• Anti-FHA IgA (IU/mL, 95%CI): 3.95 (2.8-5.58) | II-2 | Fair, single-center study |
| **Bahaa Abu Raya,** | Boostrix | Prospective | Group 1: 25 women with | <u>Group 1:</u> | II-2 | Fair, |

| STUDY DETAILS | | | | SUMMARY | | |
|---|---|---|---|---|---|---|
| **Isaac Srugo, Aharon Kessel, Michael Peterman, David Bader, Regina Peri, Nathanealla Ashtamker, Ron Gonen, Ellen Bamberger**. The induction of breast milk pertussis specific antibodies following gestational tetanus-diphtheria-acellular pertussis vaccination. *Vaccine.* 2014. 32:5632 | | observational study with a control group<br><br>Israel | singleton births, gestational age ≥36 weeks who received Tdap between 23.1 and 37.4 weeks gestation<br><br>Group 2: 12 women unvaccinated for pertussis during the current pregnancy<br><br>The mean time interval between vaccination and delivery was 51.7 days (median – 45 days; range – 15–115 days).<br><br>Breastmilk collected at delivery as well as 2, 4 and 8 weeks after delivery | • Anti-PT IgA (EU/ml, 95%CI):<br>- delivery (colostrum): 8.18 (4.44-15.07<br>- at 2 weeks: 1.01 (0.71-1.42)<br>- at 4 weeks: 0.9 (0.65-1.24)<br>- at 8 weeks: 1.01 (0.66-1.56)<br>• Anti-FHA IgA (EU/ml, 95%CI):<br>- delivery (colostrum): 24.12 (14.12-41.2)<br>- at 2 weeks: 3.64 (2.4-5.51)<br>- at 4 weeks: 2.7 (1.66-4.42)<br>- at 8 weeks: 2.22 (1.37-3.61)<br>• Anti-FHA IgG (EU/ml, 95%CI):<br>- delivery (colostrum): 2.19 (1.26-3.81)<br>- at 2 weeks: 1.44 (1.02-2.02)<br>- at 4 weeks: 01.44 (0.97-2.13)<br>- at 8 weeks: 1.4 (0.86-2.27)<br>• Anti-PRN IgG (EU/ml, 95%CI):<br>- delivery (colostrum): 2.46 (1.19-5.11)<br>- at 2 weeks: 1.03 (0.66-1.6)<br>- at 4 weeks: 0.72 (0.56-0.92)<br>- at 8 weeks: 0<br><u>Group 2:</u><br>• Anti-PT IgA (EU/ml, 95%CI):<br>- delivery (colostrum): 6.52 (2.19-19.41)<br>- 2 weeks: 1.37 (0.59-3.19)<br>- 4 weeks: 0.8 (0.65-0.99)<br>- 8 weeks: 1.11 (0.51-2.44)<br>• Anti-FHA IgA (EU/ml, 95%CI):<br>- delivery (colostrum): 6.52 (2.19-19.41)<br>- at 2 weeks: 1.37 (0.59-3.19)<br>- at 4 weeks: 1.54 (0.76-3.11)<br>- at 8 weeks: 0.94 (0.27-3.24)<br>• Anti-FHA IgG (EU/ml, 95%CI):<br>- delivery (colostrum): 1.42 (0.65-3.14)<br>- at 2 weeks: <1<br>- at 4 weeks: <1<br>- at 8 weeks: <1<br>• Anti-PRN IgG (EU/ml, 95%CI):<br>- delivery (colostrum): <0.6 | | Small sample size |

| STUDY DETAILS | | | | | SUMMARY | |
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| | | | | - at 2 weeks: <0.6<br>- at 4 weeks: <0.6<br>- at 8 weeks: 0<br>While differences in GMCs for anti-PT IgA, anti-FHA IgA and anti-PRN IgG, particularly at delivery vs. 2 weeks, were statistically significant at all time points, no differences were observed in anti-FHA IgG GMC over the study period.<br><br>Anti-PT IgG t was not detected in any of the samples.<br><br>In the colostrum, anti-FHA IgA was significantly higher than anti-PT IgA (24.12 EU/mL vs. 8.18 EU/mL, respectively, p < 0.004). | | |
| **Sara De Schutter, Kirsten Maertens, Lesley Baerts, Ingrid De Meester, Pierre Van Damme, Elke Leuridan**. Quantification of vaccine-induced anti-pertussis toxin secretory IgA antibodies in breast milk: comparison of different vaccination strategies in women. *Pediatric Infectious Disease Journal.* 2015. 34:e149 | Boostrix | Prospective observational study<br><br>Belgium | Group 1: 19 women vaccinated during pregnancy<br><br>Group 2: 34 women vaccinated shortly after or at delivery<br><br>Group 3: 9 women vaccinated less than 5 years before delivery<br><br>Group 4: 12 women who received no vaccination for at least 5 years before delivery<br><br>Samples were obtained at a median of 58 days after delivery (min–max: 44–91 days). | No significant difference was found for the total sIgA levels in the 4 groups.<br><br>Maternal vaccination during pregnancy or at birth significantly increased the anti-PT GMC compared to no immunization for at least 5 years (p = 0.012 and P = 0.001, respectively). | II-2 | Fair, Time of sample collection variable |
| **Fallo, Aurelia A., Neyro, Silvina E., Manonelles, Gabriela** | Tdap | Prospective observational study | Group 1: 105 women immunized with Tdap in pregnancy at 24.7 ± 4.8 | <u>Group 1:</u><br>• Anti-PT IgG (EU/ml, 95% CI): 35.1 (28.5-43.1) | II-2 | Fair |

| STUDY DETAILS | | | | SUMMARY | | |
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| **V., Lara, Claudia, Hozbor, Daniela, Zintgraff, Jonathan, Mazzeo, Silvina, Davison, Hector E., Gonzalez, Susana, Zapulla, Estella, Canle, Oscar, Huespe, Miguel, Galas, Marcelo, Lopez, Eduardo L.** Prevalence of Pertussis Antibodies in Maternal Blood, Cord Serum, and Infants From Mothers With and Those Without Tdap Booster Vaccination During Pregnancy in Argentina. Journal of the Pediatric Infectious Diseases Societ. 2016. | | Argentina | weeks gestation<br><br>Group 2: 99 women not immunized with Tdap in pregnancy<br><br>Serum collected at the time of delivery | <u>Group 2:</u><br>• Anti-PT IgG (EU/ml, 95% CI): 9.8 (8-12.1) | | |
| **Abbey J. Hardy-Fairbanks, Stephanie J. Pan, Michael D. Decker, David R. Johnson, David P. Greenberg, Kathryn B. Kirkland, Elizabeth A. Talbot, Henry H. Bernstein**. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. *Pediatric Infectious Disease Journal.* 2013. 32:1257 | Tdap | Observational, retrospective cohort study with a control group<br><br>USA | Group 1: 5 women who received Tdap (3 vaccinated during their first and 2 during their second trimester)<br><br>Group 2: 53 women not immunized with Tdap in pregnancy<br><br>Serum collected at the time of delivery | <u>Group 1 (EU/ml)</u><br>• Anti-PT: 14.3 (75% with more than 5 EU/ml)<br>• Anti-FHA: 32.5 (100% with more than 5 EU/ml)<br>• Anti-PRN: 24.4 (80% with more than 10 EU/ml)<br>• Anti-FIM2/3: 360.3 (100% with more than 10 EU/ml)<br><br><u>Group 2 (EU/ml)</u><br>• Anti-PT: 7.5 (55% with more than 5 EU/ml)<br>• Anti-FHA: 9.6 (66% with more than 5 EU/ml)<br>• Anti-PRN: 6.44 (36% with more than 10 EU/ml)<br>• Anti-FIM2/3: 17.7 (62% with more than 10 EU/ml)<br><br>At delivery, maternal GMCs were higher (1.9- to 20.4-fold) against PT, FHA, PRN and FIM in Group 1. A greater percentage of women in Group 1 had GMC against each | II-2 | Fair, Small sample size |

| STUDY DETAILS | | | | SUMMARY | | |
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| | | | | of the 4 pertussis antigens at or above levels considered to be protective by study authors. | | |
| **C. Mary Healy, Marcia A. Rench, Carol J. Baker.** Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. Clinical Infectious Diseases. 2013. 56:539 | Tdap | Retrospective cohort study<br><br>USA | Group 1: 19 women immunized with Tdap in pregnancy; 76% (14/19) received Tdap during the first trimester (only 3 with immunization after 20 weeks gestation).<br><br>Group 2: 83 women immunized with Tdap within 2 years of the study, but outside pregnancy | <u>Group 1:</u><br>• Anti-PT (IU/ml, 95% CI) : 10.5 (6.4–17.1)<br>• Anti FHA (IU/ml, 95% CI): 49.3 (28.4–85.8)<br>• Anti-PRN (IU/ml, 95% CI): 40.4 (18.9–87.30)<br>• Anti-FIM2/3 (IU/ml, 95% CI): 103.1 (42.7–249)<br><br><u>Group 2:</u><br>• Anti-PT (IU/ml, 95% CI): 12.8 (10.3–15.9)<br>• Anti FHA (IU/ml, 95% CI): 50.4 (39.9–63.7)<br>• Anti-PRN (IU/ml, 95% CI): 38.8 (27.5–54.6)<br>• Anti-FIM2/3 (IU/ml, 95% CI): 132.1 (92.1–189.5)<br><br>There was no difference in pertussis-specific IgG GMCs for any pertussis antigen for either group (p values ranged from 0.45–0.94). | II-2 | Fair, Small sample size |
| **Kirsten Maertens, Raissa Nadege Cabore, Kris Huygen, Niel Hens, Pierre Van Damme, Elke Leuridan**. Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. *Vaccine.* 2016. 34:142 | Boostrix | Non-randomized control trial<br><br>Belgium | Healthy pregnant women recruited from 5 hospitals in the province of Antwerp<br><br>Group 1: 57 women who received Tdap at mean 28.6 weeks of gestation<br><br>Group 2: 41 women who have not received any pertussis-containing vaccine for at least 10 years | <u>Group 1:</u><br>• Anti-PT GMC (IU/mL, 95%CI):<br>- before immunization: 4.5 (3.2-6.4)<br>- one month after immunization: 48 (39-59)<br>- at delivery: 31.4 (26-38)<br>• Anti-FHA GMC (IU/mL, 95%CI):<br>- before immunization: 21 (17-26)<br>- one month after immunization: 211 (170-263)<br>- at delivery: 107 (91-126)<br>• Anti-PRN GMC (IU/mL, 95%CI):<br>- before immunization: 24 (18-31)<br>- one month after immunization: 622 (511-756)<br>- at delivery: 602 (485.5-747)<br><u>Group 2 (n=41 samples available at delivery):</u><br>• Anti-PT GMC (IU/mL, 95%CI):<br>- baseline: 7.5 (5-11)<br>- at delivery: 6.4 (4.3-9.6)<br>• Anti-FHA GMC (IU/mL, 95%CI):<br>- baseline: 17.6 (13-24)<br>- at delivery: 21.4 (16.6-27.5) | II-2 | Fair, Representativeness of the control group |

| STUDY DETAILS | | | | SUMMARY | | |
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| | | | | • Anti-PRN GMC (IU/mL, 95%CI):<br>- baseline: 16.9 (11.6-24.6)<br>- at delivery: 18 (13-24)<br><br>Women in Group 1 had significantly higher GMCs to all antigens at delivery compared with women in Group 2. | | |
| **Alba Vilajeliu, Anna Gonce, Marta Lopez, Josep Costa, Laura Rocamora, Jose Rios, Irene Teixido, Jose M. Bayas, PERTU Working Group**. Combined tetanus-diphtheria and pertussis vaccine during pregnancy: transfer of maternal pertussis antibodies to the newborn. *Vaccine.* 2015. 33:1056 | Adacel, Sanofi | Prospective observational study<br><br>Spain | 132 women immunized in pregnancy for whom infant serology was available | Pre-vaccination, 37.1% (49/132) of baseline maternal sera had anti-PT levels ≥10 IU/ml. Post-vaccination, anti-PT titers met the definition of vaccine response in 53.8% (71/132) mothers, while another 48 had titers ≥10 IU/ml titers, although the increase was not sufficient to meet the definition of vaccine response. Levels of IgG against pertussis toxin ≥10 IU/ml were found in 90.2% (119/132) of maternal post-vaccination sera. | II-2 | Fair, Convenience sample of women with available blood results according to study design |
| **Manisha Gandhi, Sridevi Devaraj, Haleh Sangi-Haghpeykar, Joan Mastrobattista.** The effect of body mass index on post-vaccination maternal and neonatal pertussis | Boostrix | Nested cohort study<br><br>USA | Group 1: 29 women immunized in pregnancy and with BMI between 18 and 24.9 kg/m2 (normal weight)<br><br>Group 2: 54 women immunized in pregnancy and with BMI between 25 | Group 1 median antibody level: 172.6 IU/ml (range 6.4–514.4)<br><br>Group 2 median antibody level: 137.6 IU/ml (range 2.7–517.9)<br><br>Group 3 median antibody level: 147.2 IU/ml (range 14.4–439.6) | II-3 | Poor, Only women with adequate seru |

| STUDY DETAILS | | | | SUMMARY | | |
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| antibody levels. Journal of reproductive immunology. 2015. 112:34 | | | and 29.9 kg/m2 (overweight)<br><br>Group 3: 40 women immunized in pregnancy and with BMI over 30 kg/m2 (obese)<br><br>Maternal serum samples obtained at the time of delivery were evaluated for the level of pertussis IgG antibody using the GenWay Bordetella pertussis IgG antibody test kit that measures both anti-PT and anti-FHA GMCs. Serum pertussis IgG levels ≥30 IU/ml were considered protective. | No statistically significant differences in maternal antibody levels were found between groups. | | m sam ples inclu ded in anal ysis |

**Table 4. Summary of evidence related to passive immunogenicity for infant from acellular pertussis vaccination in pregnancy and immunogenicity of primary immunizations for baby**

| **Evidence related to passive immunogenicity for infant following acellular pertussis vaccination before DTaP vaccination** | | | | | | |
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| **STUDY DETAILS** | | | | | **SUMMARY** | |
| **Study** | **Vaccine** | **Study Design** | **Participants** | **Summary of Key Findings Using Text or Data** | **Level of Evidence** | **Quality of Evidence** |
| **Flor M. Munoz, Nanette H. Bond, Maurizio Maccato, Phillip Pinell, Hunter A. Hammill, Geeta K. Swamy, Emmanuel B. Walter, Lisa A. Jackson, Janet A. Englund, Morven S. Edwards, C. Mary Healy, Carey R. Petrie, Jennifer Ferreira, Johannes B. Goll, Carol J. Baker**. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA.* 2014. 311:1760 | Adacel<br><br>Placebo: 0.9% saline solution | RCT, double blind, placebo-controlled<br><br>USA | Group 1: 33 infants of women who received Tdap at 30 to 32 weeks of gestation<br><br>Group 2: 15 infants of women who received placebo at 30 to 32 weeks gestation | <u>Group 1:</u><br>• Anti-PT (EU/ml, 95% CI):<br>- cord blood: 68.8 (52.1-90.8)<br>- month 2 : 20.6 (14.4-29.6)<br>• Anti-FHA (EU/ml, 95% CI):<br>- cord blood: 234.2 (184.6-297.3)<br>- month 2 : 99.1 (75.8-129.6)<br><br>• Anti-PRN (EU/ml, 95% CI):<br>- cord blood: 226.8 (137.7-373.7)<br>- month 2 : 71.1 (42.4-119.1)<br>• Anti-FIM2/3:<br>- cord blood: 1,867.0 (1,211.7-2,876.8)<br>- month 2 : 510.4 (305.6-852.3)<br><br><u>Group 2:</u><br>• Anti-PT (EU/ml, 95% CI) :<br>- cord blood: 14.0 (7.3-26.9)<br>- month 2 : 5.3 (3.0-9.4)<br>• Anti-FHA (EU/ml, 95% CI):<br>- cord blood: 25.1 (10.5-60.3)<br>- month 2 : 6.6 (2.8-15.5)<br><br>• Anti-PRN (EU/ml, 95% CI):<br>- cord blood: 14.4 (5.4-38.4)<br>- month 2 : 5.2 (2.4-11.5)<br>• Anti-FIM2/3 (EU/ml, 95% CI):<br>- cord blood: 48.5 (20.1-117.3)<br>- month 2 : 12.0 (4.9-29.4) | I | Good, Small sample size |

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| | | | | Infants in Group 1 had significantly higher concentrations of pertussis antibodies at birth and at age 2 months. The concentration of pertussis antibodies in cord blood was higher than in maternal serum at delivery, with linear correlation between maternal and infant concentrations.<br><br>Infant cord blood GMCs were approximately 20% higher than in maternal sera. The pertussis antibody ratios of (infant cord blood)/(maternal antibody at delivery) and (infant 2 month/cord blood) were similar in Group 1 and 2. | | |
| **Jesus Zacarias Villarreal Perez, Jose Manuel Ramirez Aranda, Manuel de la O Cavazos, Michelle de J. Zamudio Osuna, Jose Perales Davila, Maria Romelia Ballesteros Elizondo, Marco Vinicio Gomez Meza, Francisco Javier Garcia Elizondo, Azucena M. Rodriguez Gonzalez**. Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. *Human vaccines & Immunotherapeutics.* 2016 | Adacel<br><br>placebo: 0.9% saline solution | RCT, double blind, placebo-controlled<br><br>Mexico | Group 1: 90 infants born to mothers immunized with Tdap at 30 to 32 weeks gestation; maternal mean age: 24 years<br><br>Group 2: 81 infants whose mothers received placebo at 30 to 32 weeks gestation; maternal mean age: 24 years | <u>Group 1:</u><br>• Anti-PT (EU/ml, 95%CI):<br>- cord blood: 28.25 (21.06-37.90)<br>- month 2 (prior to first DTaP dose) : 10.95 (8.71-13.77)<br>• Anti-PRN (EU/ml, 95%CI):<br>- cord blood: 127.51 (104.14-156.12)<br>- month 2 (prior to first DTaP dose) : 71.41 (56.80-89.77)<br><br><u>Group 2:</u><br>• Anti-PT (EU/ml, 95%CI):<br>- cord blood: 8.02 (5.84-11.00)<br>- month 2 (prior to first DTaP dose) : 6.20 (4.96-7.73)<br>• Anti-PRN (EU/ml, 95%CI):<br>- cord blood: 8.07 (5.84-11.14)<br>- month 2 (prior to first DTaP dose) : 6.93 (5.52-8.72)<br><br>Anti-PT and anti-PRN levels at 2 months in Group 1 similar to pre-vaccination levels in Group 2 | I | Good |
| **Kirsten Maertens, Thi Thu Ha Hoang, Trung Dac Nguyen, Raissa Nadege Cabore, Thi Hong Duong, Kris Huygen, Niel Hens,** | Adacel<br><br>TT | RCT<br><br>Vietnam | Group 1: 45 infants of women immunized with Tdap at mean 25 weeks of pregnancy<br><br>Group 2: 47 infants of | <u>Group 1:</u><br>• Anti-PT (IU/ml, 95% CI):<br>- cord blood: 21 (16,28)<br>- month 2 (prior to first DTaP dose) : 4.2 (2.9-5.9)<br>• Anti-FHA (IU/ml, 95% CI): | I | Poor, Randomization details not |

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| **Pierre Van Damme, Duc Anh Dang, Elke Leuridan**. The Effect of Maternal Pertussis Immunization on Infant Vaccine Responses to a Booster Pertussis-Containing Vaccine in Vietnam. *Clinical Infectious Diseases.* 2016. 63:S197<br><br>**Ha Thi Thu Hoang, Elke Leuridan, Kirsten Maertens, Trung Dac Nguyen, Niel Hens, Ngoc Ha Vu, Raissa Nadege Cabore, Hong Thi Duong, Kris Huygen, Pierre Van Damme, Anh Duc Dang**. Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during pregnancy. *Vaccine.* 2016. 34:151 | | | women immunized with TT at mean 25 weeks of pregnancy | - cord blood: 93 (65-133)<br>- month 2 (prior to first DTaP dose) : 59 (48-73)<br>• Anti-PRN (IU/ml, 95% CI):<br>- cord blood: 124 (86-179)<br>- month 2 (prior to first DTaP dose) : 46 (32-66)<br><br><u>Group 2:</u><br>• Anti-PT (IU/ml, 95% CI):<br>- cord blood: 7.2 (5.6-9.4)<br>- month 2 (prior to first DTaP dose) : 0.8 (0.5-1.3)<br>• Anti-FHA (IU/ml, 95% CI):<br>- cord blood: 27.6 (20.9-36.7)<br>- month 2 (prior to first DTaP dose) : 23.1 (19.7-27)<br>• Anti-PRN (IU/ml, 95% CI):<br>- cord blood: 13.9 (10.5-18.2)<br>- month 2 (prior to first DTaP dose) : 7.8 (6.6-9.4)<br><br>At all times for all antibody levels, the differences in GMC levels were statistically significant. | | provided |
| **Shamez N. Ladhani, Nick J. Andrews, Jo Southern, Christine E. Jones, Gayatri Amirthalingam, Pauline A. Waight, Anna England, Mary Matheson, Xilian Bai, Helen Findlow, Polly Burbidge, Vasili** | Repavax | Prospective observational study with a historical comparator<br><br>UK | 129 infants of mothers immunized during the third trimester of pregnancy<br><br>Serology collected at two months of age<br><br>The median interval (interquartile range [IQR]) | • Anti-PT (IU/ml, 95%CI): 11.2 (9.6-13.1)<br>• Anti-FHA (IU/ml, 95%CI): 46 (8-53.1)<br>• Anti-FIM2/3 (IU/ml, 95%CI): 123 (92.7-163.5) | II-2 | Good, No control group |

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| **Thalasselis, Bassam Hallis, David Goldblatt, Ray Borrow, Paul T. Heath, Elizabeth Miller**. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. *Clinical Infectious Diseases.* 2015. 61:1637 | | | between antenatal vaccination and infant birth was 9.9 weeks (IQR, 8.0–11.1). The infants' median (IQR) age at pre-immunization blood samples was 55 (52–58) days. | | | |
| **Bahaa Abu Raya, Ellen Bamberger, Meital Almog, Regina Peri, Isaac Srugo, Aharon Kessel**. Immunization of pregnant women against pertussis: the effect of timing on antibody avidity. *Vaccine.* 2015. 33:1948-52 | Boostrix | Non-randomized control study<br><br>Israel | Group 1: 52 infants born to Tdap-immunized women<br><br>Group 2: 8 infants born to women not immunized in pregnancy | Group 1 newborns had higher RAI of umbilical cord anti-PT than Group 2 infants: 73.77% ± 12.08 (95% CI, 70.41–77.13) vs. 50.23% ± 21.32 (95% CI, 32.41–68.06) (Mann–Whitney U test, $p < 0.001$)).<br><br>RAI of anti- PT was significantly higher for newborns of women immunized at 27 to 30 weeks gestation (n = 20) when compared with newborns of women immunized at 31 to 36 weeks (n = 22) and >36 weeks (n = 7), 79.53% ± 5.61(95% CI, 76.91–82.16) vs. 71.56% ± 12.58 (95% CI, 65.98–77.14) vs. 63.93% ± 17.98 (95% CI, 47.31–80.56), Kruskal–Wallis test, $p < 0.03$.<br><br>When analyzed as a function of the time elapsed between Tdap administration and delivery, anti-PT RAI increased linearly (Pearson $r = 0.346$, $p < 0.01$). | II-2 | Fair, Small sample size |
| **Bahaa Abu Raya, Isaac Srugo, Aharon Kessel, Michael Peterman, David Bader, Ron Gonen, Ellen Bamberger**. The | Boostrix | Non-randomized control study<br><br>Israel | Group 1: 61 infants born to Tdap-immunized women (mean age, 32.6 years; range, 20–47 years) vaccinated between 23.1 and 37.4 gestational weeks | <u>Group 1:</u><br>• Anti-PT (IU/ml, 95% CI): 17.27 (9.45-31.54)<br>- cord/maternal antibody ratio at 27 to 30 weeks: 1.45 (1.26-1.64)<br>- cord/maternal antibody ratio at 31 to 36 weeks: 1.04 (0.86-1.23) | II-2 | Fair, Single-center Stud |

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| effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels - a prospective study. *Vaccine.* 2014. 32:5787 | | | (mean, 50.6 days before delivery; range, 6–115 days)<br><br>Group 2: 20 infants born to women not immunized in pregnancy (mean age, 31.9 years; range, 26–40 years)<br><br>Cord blood IgG analyzed only | • Anti-FHA (IU/ml, 95% CI): 196.74 (163.42-236.86)<br>- cord/maternal antibody ratio at 27 to 30 weeks: 1.22 (1.11-1.34)<br>- cord/maternal antibody ratio at 31 to 36 weeks: 0.98 (0.86-1.76)<br>• Anti-PRN (IU/ml, 95% CI): 161.51 (114.68-227.46)<br>- cord/maternal antibody ratio at 27 to 30 weeks: 1.12 (1-1.25)<br>- cord/maternal antibody ratio at 31 to 36 weeks: 0.97 (0.94-1.16)<br><br><u>Group 2:</u><br>• Anti-PT (IU/ml, 95% CI): 1.12 (0.41-3.02)<br>• Anti-FHA (IU/ml, 95% CI) : 17.3 (10.23-28.68)<br>• Anti-PRN (IU/ml, 95% CI): 10.62 (4.46-25.32)<br><br>Anti-PT and anti-FHA GMCs were significantly higher in newborns of women immunized at 27 to 30 weeks as compared with 31 to 36 weeks. Ratios of all cord sera antibodies to maternal antibodies at delivery were significantly higher in infants whose mothers were vaccinated at 27 to 30 weeks gestation compared to those immunized at 31 to 36 weeks gestation. | | y |
| **Eberhardt, Christiane S., Blanchard-Rohner, Geraldine, Lemaitre, Barbara, Combescure, Christophe, Othenin-Girard, Veronique, Chilin, Antonina, Petre, Jean, Martinez de Tejada, Begona, Siegrist, Claire-Anne.** Pertussis Antibody Transfer to Preterm Neonates After Second- Versus Third-Trimester Maternal Immunization. Clinical Infectious | Tdap | Single-center prospective observational study<br><br>Switzerland | Group 1: 37 infants who were born to mothers immunized with Tdap during the second trimester of pregnancy (mean interval to delivery 97 days)<br><br>Group 2: 48 infants who were born to mothers immunized with Tdap during the third trimester of pregnancy (mean interval to delivery 30 days)<br><br>Of 85 preterm infants, 68 were born between GW 34- | <u>Group 1:</u><br>• Anti-PT (EU/mL, 95% CI): 41.3 (29.6-57.5)<br>• Anti-FHA (EU/mL, 95% CI) : 201.1 (149.7-270.1)<br><br><u>Group 2:</u><br>• Anti-PT (EU/mL, 95% CI): 22.1 (14.3-34.2)<br>• Anti-FHA (EU/mL, 95% CI): 120.2 (80.6-179.2)<br><br>The ratio of second- to third-trimester anti-PT cord blood antibodies were significantly higher (1.87 [95% CI, 1.06–3.29]; P = .032), even after adjustment for maternal age, gestational age at birth, parity, and socioeconomic status (2.04 [95% CI, 1.15–3.61]; P = .016). For anti-FHA antibodies, the GMC ratio was 1.67 (95% CI, 1.00–2.81; P = .051), with an adjusted ratio of 1.57 (95% CI, .93–2.67; | II-2 | Fair |

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| Diseases. 2017. 64:1129 | | | 37 and 17 between GW 30-34).<br><br>Only cord blood was analyzed. | P = .092).<br><br>All preterm infants whose mothers were immunized in the second trimester of pregnancy had anti-PT level above 5 EU/mL, while these levels were observed in only 77% of infants whose mothers received Tdap in the third trimester of pregnancy.<br><br>Time interval between vaccination and delivery required to maximize transplacental antibody transfer (defined as at least a 4-fold increase in GMC) was estimated to be 15 days in the preterm population. | | |
| **Christiane S. Eberhardt, Geraldine Blanchard-Rohner, Barbara Lemaitre, Meriem Boukrid, Christophe Combescure, Veronique Othenin-Girard, Antonina Chilin, Jean Petre, Begona Martinez de Tejada, Claire-Anne Siegrist**. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. *Clinical Infectious Diseases.* 2016. 62:829 | Boostrix | Non-inferiority non-randomized control study<br><br>Switzerland | Group 1: 122 infants born to mothers immunized at 13-25 weeks gestation<br><br>Group 2: 213 infants born to mothers immunized at ≥26 weeks gestation (57% immunized at less than 30 days prior to delivery and 32% at less than 15 days)<br><br>Antibody levels measured in cord blood only<br><br>Cord blood samples of 90 neonates of nonvaccinated mothers recruited in a previously conducted similar study (prior to maternal Tdap recommendation), used as negative controls | <u>Group 1:</u><br>• Anti-PT (EU/ml, 95% CI): 57.1 (47.8-68.2)<br>• Anti-FHA: 284.4 (95% CI : 241.3-335.2)<br>• 98% of infants with anti-PT ≥5 EU/ml; 80% with anti-PT ≥20 EU/ml<br><u>Group 2:</u><br>• Anti-PT (EU/ml, 95% CI):<br>o ≥26 weeks gestation: 31.1 (25.7-37.7)<br>o 26 to 36 weeks gestation: 44.4 (1.26-1.64)<br>o 37 to 38 weeks gestation: 25.1 (17.9–35.3)<br>o 39 to 41 weeks gestation: 9.0 (5.0–16.2)<br>• Anti-FHA (EU/ml, 95% CI)<br>o ≥26 weeks gestation: 140.2 (115.3-170.3)<br>o 26 to 36 weeks gestation: 237.6 (188-300.3)<br>o 37 to 38 weeks gestation: 92.7 (69.0–124.7)<br>o 39 to 41 weeks gestation: 31.0 (16.9–56.6)<br><br>GMC levels similar in infants whose mothers were immunized <2 weeks prior to delivery and not immunized (anti-PT 9.9; 95% CI: 7.2,13.6 vs 11.1; 95% CI: 8.3,15.0 and anti-FHA 33.3; 95% CI: 24.7,45.1 vs 23.4; 95% CI: 16.3,33.4)<br><br>GMC ratios adjusted for maternal age, gestational age, parity and SES score were significantly higher (p<0.001) for Group 1: anti-PT 1.9 (95% CI: 1.4,2.5) and anti-FHA 2.2 (95% CI: 1.7,3.0); when restricting the analysis only to | II-2 | Fair, Antibody persistence in infants was not measured but calculated |

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| | | | | Group 2 infants whose mothers were vaccinated at 26 to 36 weeks gestation, only anti-FHA GMC ratios remained statistically significant (1.3; 95% CI: 1.04,1.7).<br><br>25% difference in seroprotection (anti-PT ≥20 EU/ml) rates between Groups 1 and 2 demonstrated superiority of earlier over later immunization (p<0.001); restricting the third trimester to immunization at 26 to 36 weeks gestation did not have an effect on the statistical significance (80% vs. 64%. p= 0.006).<br><br>Optimal interval of immunization determined by study authors estimated to be between 30 and 120 days prior to delivery, i.e. immunization between 13 and 33 weeks of gestation conferred seropositivity (anti-PT >5 EU/mL) to all infants up to 3 months of age. | | |
| **Fallo, Aurelia A., Neyro, Silvina E., Manonelles, Gabriela V., Lara, Claudia, Hozbor, Daniela, Zintgraff, Jonathan, Mazzeo, Silvina, Davison, Hector E., Gonzalez, Susana, Zapulla, Estella, Canle, Oscar, Huespe, Miguel, Galas, Marcelo, Lopez, Eduardo L.** Prevalence of Pertussis Antibodies in Maternal Blood, Cord Serum, and Infants From Mothers With and Those Without Tdap Booster Vaccination During Pregnancy in Argentina. Journal of the Pediatric Infectious Diseases Societ. 2016. | Tdap | Prospective observational study<br><br>Argentina | Group 1: 105 infants whose mothers were immunized with Tdap in pregnancy at 24.7 ± 4.8 weeks gestation<br><br>Group 2: 99 infants whose mothers were not immunized with Tdap in pregnancy<br><br>Only cord blood was analyzed for the complete cohort | <u>Group 1:</u><br>• Anti-PT (EU/mL, 95% CI): 51.3 (41.3-63.8)<br><br><u>Group 2:</u><br>• Anti-PT (EU/mL, 95% CI): 11.6 (9.7-14)<br><br>In subset (n=36) of Group 1 infants:<br>• Anti-PT (EU/mL, 95% CI), cord blood : 48.4 (28.4-62.2)<br>• Anti-PT (EU/mL, 95% CI), 1 month of age : 17.7 (11.5-25.1)<br>• Anti-PT (EU/mL, 95% CI), 2 months of age : 11.6 (8.1-20.1)<br><br>Efficiency of placental antibody transfer measured as the ratio of the cord to maternal blood GMC was estimated to be 1.46 in Group 1 and 1.18 in Group 2 infants. | II-2 | Fair |

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| **Stanley A. Gall, John Myers, Michael Pichichero**. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. American Journal of Obstetrics & Gynecology. 2011. 204:334.e1 | Adacel | Cohort study with a control group<br><br>USA | Group 1: 52 women who received Tdap during pregnancy<br><br>Group 2: 52 women who did not receive Tdap during pregnancy<br><br>Cord blood analyzed only<br><br>All Group 1 mothers encouraged to get immunized at 2nd trimester of pregnancy; exact timing of vaccination is unknown | <u>Group 1:</u><br>• Anti-PT (EU/ml): 28.2 (65%>10 EU/ml; 12%<5 EU/ml)<br>• Anti FHA (EU/ml): 104 (94%>10 EU/ml; 4%<3 EU/ml)<br>• Anti-PRN (EU/ml): 333 (90%>10 EU/ml; 4%<5 EU/ml)<br>• Anti-FIM2/3 (EU/ml): 1199 (92%>10 EU/ml; 2%<5 EU/ml)<br><br><u>Group 2:</u><br>• Anti-PT (EU/ml): 11 (12%>10 EU/ml; 60%<5 EU/ml)<br>• Anti FHA (EU/ml): 26.8 (64%>10 EU/ml; 6%<3 EU/ml)<br>• Anti-PRN (EU/ml): 24.7 (54%>10 EU/ml; 14%<5 EU/ml)<br>• Anti-FIM2/3 (EU/ml): 82.8 (74%>10 EU/ml; 15%<5 EU/ml)<br><br>Group 1 had significantly higher cord blood GMCs for all pertussis antibodies. | II-2 | Fair, No information provided about the cohort, the study just measured and compared antibody level in discarded blood samples |
| **Abbey J. Hardy-Fairbanks, Stephanie J. Pan, Michael D. Decker, David R. Johnson, David P. Greenberg, Kathryn B. Kirkland, Elizabeth A. Talbot, Henry H. Bernstein**. Immune responses in infants whose mothers received Tdap vaccine | Tdap | Observational, retrospective cohort study with a control group<br><br>USA | Group 1: 11 infants (n=5 for cord blood samples) whose mothers received Tdap in pregnancy (3 vaccinated during their first and 2 during their second trimester)<br><br>Group 2: 53 infants whose mothers were not immunized with Tdap in pregnancy | <u>Group 1:</u><br>• Anti-PT (EU/ml):<br>- cord blood: 33.5 (100% above 5 EU/ml)<br>- month 2 (prior to first DTaP dose) : 15.1 (83% above 5 EU/ml)<br>• Anti-FHA (EU/ml):<br>- cord blood: 66.1 (100% above 5 EU/ml)<br>- month 2 (prior to first DTaP dose) : 41.6 (89% above 5 EU/ml)<br>• Anti-PRN (EU/ml):<br>- cord blood: 48.5 (80% above 10 EU/ml)<br>- month 2 (prior to first DTaP dose) : 32.1 | II-2 | Fair, Small sample size |

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| during pregnancy. *Pediatric Infectious Disease Journal.* 2013. 32:1257 | | | | (78% above 10 EU/ml)<br>• Anti-FIM2/3 (EU/ml):<br>- cord blood: 9,129 (100% above 10 EU/ml)<br>- month 2 (prior to first DTaP dose) : 296.4 (100% above 10 EU/ml)<br><br><u>Group 2:</u><br>• Anti-PT (EU/ml):<br>- cord blood: 12.6 (71% above 5 EU/ml)<br>- month 2 (prior to first DTaP dose) : 4.8 (31% above 5 EU/ml)<br>• Anti-FHA (EU/ml):<br>- cord blood: 15.9 (81% above 5 EU/ml)<br>- month 2 (prior to first DTaP dose) : 5.6 (53% above 5 EU/ml)<br>• Anti-PRN (EU/ml):<br>- cord blood: 8.9 (40% above 10 EU/ml)<br>- month 2 (prior to first DTaP dose) : 3.9 (18% above 10 EU/ml)<br>• Anti-FIM2/3 (EU/ml):<br>- cord blood: 25.7 (70% above 10 EU/ml)<br>- month 2 (prior to first DTaP dose) : 13 (59% above 10 EU/ml)<br><br>At delivery, Group 1 infants had 2.0- to 2.5-fold higher antibody concentrations to pertussis antigens than those of their mothers.<br><br>At 2 months of age, pertussis antibody GMCs in Group 1 remained 3.2- to 22.8-fold higher than those in Group 2. | | |
| **C. Mary Healy, Marcia A. Rench, Carol J. Baker**. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. *Clinical* | Tdap | Retrospective cohort study<br><br>USA | Group 1: 19 infants whose mothers were immunized with Tdap in pregnancy; 76% (14/19) received Tdap during the first trimester (only 3 with immunization after 20 weeks gestation).<br><br>Group 2: 83 infants whose mothers were immunized | <u>Group 1:</u><br>• Anti-PT (EU/ml, 95% CI): 17.3 (11.1–26.8)<br>• Anti FHA (EU/ml, 95% CI): 87.6 (56.3–136.4)<br>• Anti-PRN (EU/ml, 95% CI): 70.0 (32.5–150.5)<br>• Anti-FIM2/3 (EU/ml, 95% CI): 191.8 (84.5–435.7)<br><br><u>Group 2:</u><br>• Anti-PT (EU/ml, 95% CI): 15.5 (12.4–19.4)<br>• Anti FHA (EU/ml, 95% CI): 72.9 (57.0–93.1) | II-2 | Fair, Small sample size |

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| *Infectious Diseases.* 2013. 56:539 | | | with Tdap within 2 years of the study, but outside pregnancy.<br><br>Cord blood analyzed only<br><br>Infants of mothers presumed to have had a recent infection (defined as maternal delivery sample with PT >94 EU/mL) were excluded. | • Anti-PRN (EU/ml, 95% CI): 57.6 (40.8–81.4)<br>• Anti-FIM2/3 (EU/ml, 95% CI): 173.1 (120.5–250.8)<br><br>There was no difference in pertussis-specific IgG GMCs for any pertussis antigen (p values ranged between 0.46 and 0.82).<br><br>Placental transport of maternal pertussis-specific IgG 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.<br><br>40% of infants were estimated to retain anti-PT levels above 4 EU/ml through 2 months of age; slightly more (52% vs 38%; P = .34) in Group 1, including 2 of the 3 infants born to mothers who received Tdap after 20 weeks gestation. | | |
| **Alison Kent, Shamez N. Ladhani, Nick J. Andrews, Mary Matheson, Anna England, Elizabeth Miller, Paul T. Heath,PUNS study group**. Pertussis Antibody Concentrations in Infants Born Prematurely to Mothers Vaccinated in Pregnancy. *Pediatrics.* 2016;138(1). | Repavax | Retrospective analysis of data collected through a larger RCT<br><br>UK | Group 1: 30 premature infants of mothers immunized with Tdap at 28 weeks of gestation<br><br>Group 1: 121 premature infants of mothers not immunized in pregnancy<br><br>All serology collected at 2 months of age<br><br>Median interval between immunization and delivery was 24 days. Average gestational age at birth was 32 weeks. | <u>Group 1:</u><br>• Anti-PT (µg/mL, 95% CI): 3.53 (2.1-5.71)<br>• Anti-FHA (µg/mL, 95% CI): 17.50 (10.63-28.95)<br>• Anti-FIM2/3 (µg/mL, 95% CI): 33.58 (17.04-66.17)<br><u>Group 2 (GMC µg/mL, 95% CI):</u><br>• Anti-PT (µg/mL, 95% CI): 1.49 (1.28-1.74)<br>• Anti-FHA (µg/mL, 95% CI): 3.36 (2.79-4.05)<br>• Anti-FIM2/3 (µg/mL, 95% CI): 4.13 (3.15-5.41)<br><br>Significantly higher antibody concentrations observed at 2 months for all antigens in Group 1 (P < .001) | II-2 | Fair, Post-hoc analysis of clinical trial data |
| **Kirsten Maertens, Raissa Nadege Cabore, Kris Huygen, Niel Hens, Pierre Van Damme, Elke** | Boostrix | Non-randomized control trial<br><br>Belgium | Infants born to healthy pregnant women recruited from 5 hospitals in the province of Antwerp | <u>Group 1:</u><br>• Anti-PT (IU/ml, 95% CI):<br>- cord blood: 100.7 (82-123)<br>- month 2 (prior to first DTaP dose) : 15.5 (12.1-20) | II-2 | Fair, Representativeness |

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| **Leuridan**. Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. *Vaccine.* 2016. 34:142 | | | Group 1: 57 infants of women who received Tdap at mean 28.6 weeks of gestation<br><br>Group 2: 41 infants of age matched women who have not received any pertussis-containing vaccine in 10 years preceding the study (26 samples available at month 2)<br><br>The mean interval between the Tdap immunization and delivery was 77.1 days (39–117 days). | • Anti-FHA (IU/ml, 95% CI):<br>- cord blood: 140 (109-180)<br>- month 2 (prior to first DTaP dose) : 121 (100-145)<br>• Anti-PRN (IU/ml, 95% CI):<br>- cord blood: 697 (573-848)<br>- month 2 (prior to first DTaP dose) : 253 (183,351)<br><br><u>Group 2:</u><br>• Anti-PT (IU/ml, 95% CI):<br>- cord blood: 12.4 (8-19)<br>- month 2 (prior to first DTaP dose) 1.1 (0.7-1.6)<br>• Anti-FHA (IU/ml, 95% CI):<br>- cord blood: 27.5 (21.5-35)<br>- month 2 (prior to first DTaP dose) : 23 (19-27)<br>• Anti-PRN (IU/ml, 95% CI):<br>- cord blood: 21 (15.5-28)<br>- month 2 (prior to first DTaP dose) : 17 (14.5-21)<br><br>Despite a significant decrease in antibody titers between birth and the age of 8 weeks, GMCs to all antigens remained significantly higher in Group 1 infants. | | of the control group |
| **Madison A. Naidu, Ruth Muljadi, Miranda L. Davies-Tuck, Euan M. Wallace, Michelle L. Giles**. The optimal gestation for pertussis vaccination during pregnancy: a prospective cohort study. *American Journal of Obstetrics & Gynecology.* 2016. 215:237.e1 | Boostrix | Cohort study with a control group<br><br>Australia | Group 1: 38 singleton infants of healthy women immunized at 28 to 32 weeks of pregnancy<br><br>Group 2: 44 singleton infants of healthy women immunized at 33 to 36 weeks of pregnancy<br><br>Group 3: 27 singleton infants of non-immunized healthy women | <u>Group 1 (IU/ml):</u><br>• Anti-PT: 4.18<br>• Anti-FHA: 5.56<br>• Anti-PRN: 5.83<br><br><u>Group 2 (IU/ml):</u><br>• Anti-PT: 3.5<br>• Anti-FHA: 5.03<br>• Anti-PRN: 5.31<br><br><u>Group 3 (IU/ml):</u><br>• Anti-PT: 2.8<br>• Anti-FHA: 4.21 | II-2 | Fair, One study site |

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| | | | Antibody levels measured in cord blood only | • Anti-PRN: 4.9<br><br>When pre-vaccination maternal antibody levels were taken into account, PT antibody levels approached significance in Group 1 vs Group 2 (P =.06), while PRN antibody levels were significantly higher in Group 1 vs. Group 2 (P =.03); no significant difference was found for FHA. | | |
| **Alba Vilajeliu, Laia Ferrer, Jordina Munros, Anna Gonce, Marta Lopez, Josep Costa, Jose M. Bayas, PERTU Working Group**. Pertussis vaccination during pregnancy: Antibody persistence in infants. *Vaccine.* 2016. 34:3719 | Adacel | Prospective observational study | 37 infants whose mothers were immunized between 21 and 38 weeks of gestation<br><br>The median week of gestation at birth was 40, and the median time at blood draw was 45 days. | Anti-PT cord blood levels (IU/ml, 95% CI):<br>• 3 infants of mothers immunized at 20 to 26 weeks gestation: 29.9 (11.2, 79.5)<br>• 17 infants of mothers immunized at 27 to 31 weeks gestation: 52.5 (29.4,93.8)<br>• 13 infants of mothers immunized at 32 to 36 weeks gestation: 62.5 (27.3,143.6)<br>• 2 infants of mothers immunized at ≥37 weeks gestation: 83.7<br>Anti-PT level prior to primary immunization (IU/ml, 95% CI):<br>• 3 infants of mothers immunized at 20 to 26 weeks gestation: 2.5<br>• 17 infants of mothers immunized at 27 to 31 weeks gestation: 6.8 (2.9,15.6)<br>• 13 infants of mothers immunized at 32 to 36 weeks gestation: 8.7 (4.0,19.0)<br>• 2 infants of mothers immunized at ≥37 weeks gestation: 31.1<br>Mean cord blood GMC was 52.7 IU/ml (95%CI: 34.7,80.2) vs pre-immunization of 7.5 IU/ml (95%CIL 4.2,13.3). Study authors estimated that at two months of age, 51% of infants would have detectable titers; 30% would have a titer of ≥10 IU/ml.<br><br>Women vaccinated with Tdap after 27 weeks of gestation were expected by study authors to sustain the highest anti-PT levels over time, although the finding was not significant (p = 0.0842). | II-2 | Fair, Antibody level in infants not measured, but estimated |
| **Alba Vilajeliu, Anna Gonce, Marta Lopez,** | Adacel | Prospective observational study | 132 infants born to women immunized in pregnancy | Ant-PT IgG ≥10 IU/ml was found in 94.7% (125/132) and Ant-PT IgG ≥40 IU/ml was found in of 47% of neonates. | II-2 | Fair, Conv |

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| **Josep Costa, Laura Rocamora, Jose Rios, Irene Teixido, Jose M. Bayas, PERTU Working Group**. Combined tetanus-diphtheria and pertussis vaccine during pregnancy: transfer of maternal pertussis antibodies to the newborn. *Vaccine.* 2015. 33:1056 | | Spain | | The ratio of transplacental transfer of IgG anti-PT was 146.6%.<br><br>Lin's concordance index rate between post-vaccination maternal and newborn levels was 0.8 (95% CI 0.8,0.9).<br><br>Anti-PT GMT in the first months of life was estimated according to the 43 day half-life of maternal antibodies. Based on this premise, 66% of infants would have had a level of ≥10 IU/ml and 89% ≥5 IU/ml at two months of age. | | enience sample of women with available blood result according to study design |
| **Manisha Gandhi, Sridevi Devaraj, Haleh Sangi-Haghpeykar, Joan Mastrobattista**. The effect of body mass index on post-vaccination maternal and neonatal pertussis antibody levels. *Journal of reproductive immunology.* 2015. 112:34 | Boostrix | Nested cohort study<br><br>USA | Group 1: 29 women immunized in pregnancy and with BMI between 18 and 24.9 kg/m2 (normal weight)<br><br>Group 2: 54 women immunized in pregnancy and with BMI between 25 and 29.9 kg/m2 (overweight)<br><br>Group 3: 40 women immunized in pregnancy and with BMI over 30 kg/m2 (obese)<br><br>Cord blood samples obtained at the time of delivery were evaluated for the level of pertussis IgG antibody using the GenWay Bordetella pertussis IgG | Group 1 median antibody level: 202 IU/ml (range 8–531); 89.7% with adequate seroprotective level<br><br>Group 2 median antibody level: 140.5 IU/ml (range 8–531); 87% with adequate seroprotective level<br><br>Group 3 median antibody level: 195.7 IU/ml (range 23.7-537); 97.5% with adequate seroprotective level<br><br>No statistically significant differences in neonatal antibody levels were found between groups. | II-3 | Poor, Only women with adequate serum samples included in analysis |

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| | | | antibody test kit that measures both anti-PT and anti-FHA GMCs. Serum pertussis IgG levels ≥30 U/ml were considered protective. | | | |
| **Goldfarb I.T.,** Maternal Tdap: How do antibodies protect newborns against pertussis? *American Journal of Obstetrics & Gynecology* (2017) S205 | Tdap | Prospective cohort study<br><br>USA | Maternal serum and cord blood samples collected from 19 mother-child pairs at delivery<br><br>Phagocytosis was assessed using flow cytometry by measuring the uptake of fluorescent antigen-coated beads, pre-incubated with patient antibodies by monocytes and neutrophils.<br><br>NK cell activation was assessed using flow cytometry by incubating NK cells on antibodycoated ELISA plates and measuring CD107a, MIP1b, IFNg, standard degranulation markers.<br><br>Placental transfer efficiency was analyzed by calculating the percent of the response of antigen-specific antibody in cord blood as a percentage of the response in maternal blood. | Antibody-dependant neutrophil phagocytosis (ADNP) was more activated in cord compared to maternal blood for FIM and PTX (p-value 0.0007 and 0.0001).<br><br>Antibody dependant cellular phagocytosis (ADCP) decreased functionality of the FHA antigen in cord compared to maternal blood (p-value 0.0002).<br><br>All 4 antigens stimulated significantly more NK cell degranulation in the cord compared to maternal blood (p-value < 0.01 for all comparisons). The antibodies that generated highest levels of NK cell activation were also found to have highest placental transfer efficiency (137-942%). | Conference poster | N/A |
| **Healy C.M, Swaim L, Rench M, Harrison M, Baker C.J,** Third- | Tdap | Study method not described | Group 1: 312 infants of women who received Tdap at mean 31.2 weeks of | <u>Group 1:</u><br>Anti PT (IU/mL, 95% CI): 47.3 (42.10-53.15); 86%> 15 IU/ml | Conference | N/A |

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| Trimester Tdap Immunization Elicits Substantial Pertussis Toxin Immunoglobulin G in Neonates, Open Forum Infectious Diseases, Volume 2, Issue suppl_1, 1 December 2015, 1877, https://doi.org/10.1093/ofid/ofv133.1426 | | USA | gestation (mean 57 days prior to delivery)<br><br>Group 2:314 infants of women who did not receive Tdap in pregnancy<br><br>Cord blood analyzed only | <u>Group 2:</u><br>Anti PT (IU/mL, 95% CI) : 12.93 (11.8-14.17); 14%> 15 IU/ml<br><br>45% of infants born to immunized mothers estimated to maintain anti-PT> 20 IU/mL through 2 months of age. | poster | |

**Evidence related to infant immunogenicity following DTaP vaccination**

| **STUDY DETAILS** | | | | | **SUMMARY** | |
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| **Study** | **Vaccine** | **Study Design** | **Participants** | **Summary of Key Findings Using Text or Data** | **Level of Evidence** | **Quality of Evidence** |
| **Flor M. Munoz, Nanette H. Bond, Maurizio Maccato, Phillip Pinell, Hunter A. Hammill, Geeta K. Swamy, Emmanuel B. Walter, Lisa A. Jackson, Janet A. Englund, Morven S. Edwards, C. Mary Healy, Carey R. Petrie, Jennifer Ferreira, Johannes B. Goll, Carol J. Baker**. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical | Maternal: Adacel<br><br>Infant: Pentacel | RCT, double blind, placebo-controlled<br><br>USA | Group 1: 33 infants of women who received Tdap at 30-32 weeks of gestation<br><br>Group 2: 15 infants of women who received Tdap postpartum<br><br>DTaP provided at 2-4-6-12 months of age | <u>Group 1 (EU/ml, 95% CI):</u><br>• Anti-PT:<br>- At 7 months: 64.9 (53.8-78.3)<br>- At 13 months: 80.1 (57.3-112.1)<br>• Anti-FHA:<br>- At 7 months: 40.6 (30.6-54.0)<br>- At 13 months: 69.9 (49.5-98.7)<br>• Anti-PRN:<br>- At 7 months: 72.3 (48.7-107.4)<br>- At 13 months: 203.3 (121.5-340.1)<br>• Anti-FIM2/3:<br>- At 7 months: 113.9 (89.9-152.7)<br>- At 13 months: 231.9 (133.3-403.5)<br><br><u>Group 2 (EU/ml, 95% CI):</u><br>• Anti-PT:<br>- At 7 months: 96.6 (56.7-164.6)<br>- At 13 months: 83.9 (50.0-140.8)<br>• Anti-FHA:<br>- At 7 months: 78.6 (52.9-116.7)<br>- At 13 months: 108.9 (78.3-151.5)<br>• Anti-PRN: | I | Good, Small sample size |

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| trial. *JAMA.* 2014. 311:1760 | | | | - At 7 months: 77.9 (38.9-152.6)<br>- At 13 months: 115.2 (54.8-242.1)<br>• Anti-FIM2/3:<br>- At 7 months: 193.5 (105.5-354.7)<br>- At 13 months: 358.8 (151.1-851.8)<br><br>At 7 months of age, infants in Group 1 had equivalent concentrations of antibodies to PRN and FIM2/3, and significantly lower ($p<0.01$) concentrations to FHA compared to Group 2 infants. However, at 13 months of age, antibodies were comparable in the 2 infant groups.<br><br>Among Group 2 infants, those with higher FHA antibody levels at birth had lower concentrations at 7 months of age (Spearman correlation 0.55, $p = 0.042$). | | |
| **Jesus Zacarias Villarreal Perez, Jose Manuel Ramirez Aranda, Manuel de la O Cavazos, Michelle de J. Zamudio Osuna, Jose Perales Davila, Maria Romelia Ballesteros Elizondo, Marco Vinicio Gomez Meza, Francisco Javier Garcia Elizondo, Azucena M. Rodriguez Gonzalez**. Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. *Human vaccines & Immunotherapeutics.* 2016. | Maternal: Adacel or placebo (0.9% saline solution)<br><br>Infant: Pentavalent DTaP | RCT, double blind, parallel group<br><br>Mexico | Group 1: 90 infants of women immunized with Tdap at 30 to 32 weeks gestation<br><br>Group 2: 81 infants of women immunized with placebo<br><br>DTaP provided at 2-4-6 months of age | • Anti-PT:<br>- month 4 (prior to second DTaP dose): 14.77 (12.35-17.66)<br>- month 6 (prior to third DTaP dose): 49.09 (40.86-58.99)<br>• Anti-PRN:<br>- month 4 (prior to second DTaP dose): 35.35 (27.59-45.29)<br>- month 6 (prior to third DTaP dose): 16.75 (12.94-21.68)<br><br><u>Group 2 (EU/ml, 95% CI):</u><br>• Anti-PT:<br>- month 4 (prior to second DTaP dose): 20.45 (16.71-25.03)<br>- month 6 (prior to third DTaP dose): 69.13 (59.10-80.87)<br>• Anti-PRN:<br>- month 4 (prior to second DTaP dose): 5.07 (4.15-6.19)<br>- month 6 (prior to third DTaP dose): 4.51 (3.80-5.35)<br><br>In Group 1, anti-PRN levels declined up to the 6 month follow-up period with a poor response to the first two | I | Good |

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| | | | | doses of DTaP vaccine; difference between groups for both anti-PT and anti-PRN was statistically significant at 4 and 6 months of age (p=0.008 and p=0.007, respectively). | | |
| **Kirsten Maertens, Thi Thu Ha Hoang, Trung Dac Nguyen, Raissa Nadege Cabore, Thi Hong Duong, Kris Huygen, Niel Hens, Pierre Van Damme, Duc Anh Dang, Elke Leuridan**. The Effect of Maternal Pertussis Immunization on Infant Vaccine Responses to a Booster Pertussis-Containing Vaccine in Vietnam. *Clinical Infectious Diseases.* 2016. 63:S197<br><br>**Ha Thi Thu Hoang, Elke Leuridan, Kirsten Maertens, Trung Dac Nguyen, Niel Hens, Ngoc Ha Vu, Raissa Nadege Cabore, Hong Thi Duong, Kris Huygen, Pierre Van Damme, Anh Duc Dang**. Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during | Maternal: Adacel or TT vaccine<br><br>Infant: Infanrix-hexa or wP containing vaccine | Randomized control study<br><br>Vietnam | Group 1: 30 infants whose mothers were immunized with Tdap at 25 weeks of pregnancy and who received 4 doses of Infanrix-hexa (35 infants with 3 doses of Infanrix-hexa)<br><br>Group 2: 37 infants whose mothers were immunized with TT at 25 weeks of pregnancy and received 4 doses of Infanrix-hexa<br><br>DTaP provided at 2-3-4-22 months of age | <u>Group 1 (IU/ml, 95% CI):</u><br>• Anti-PT:<br>- one month after dose 3 (month 5): 70 (58-84)<br>- one month after dose 4 (month 23): 129 (97.5-170.7)<br>• Anti-FHA:<br>- one month after dose 3 (month 5): 77 (66-90)<br>- one month after dose 4 (month 23): 161.3 (134.1-193.9)<br>• Anti-PRN:<br>- one month after dose 3 (month 5): 83 (65-104)<br>- one month after dose 4 (month 23): 159 (141.2-179)<br><br><u>Group 2 (IU/ml, 95% CI):</u><br>• Anti-PT:<br>- one month after dose 3 (month 5): 67 (53-84)<br>- one month after dose 4 (month 23): 133.7 (106.6-167.6)<br>• Anti-FHA:<br>- one month after dose 3 (month 5): 66.6 (56-78)<br>- one month after dose 4 (month 23): 181.7 (160.0-206)<br>• Anti-PRN:<br>- one month after dose 3 (month 5): 132.6 (104-168)<br>- one month after dose 4 (month 23): 187.1 (163.8-213.6) | I | Poor, Randomization details not provided |

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| pregnancy. *Vaccine.* 2016. 34:151 | | | | At month 5, differences in GMCs similar for anti-PT and anti-FHA, and significantly different for anti-PRN (p=0.006)<br><br>No significant difference in antibody levels between Group 1 and 2 found after the administration of the fourth DTaP dose | | |
| **Shamez N. Ladhani, Nick J. Andrews, Jo Southern, Christine E. Jones, Gayatri Amirthalingam, Pauline A. Waight, Anna England, Mary Matheson, Xilian Bai, Helen Findlow, Polly Burbidge, Vasili Thalasselis, Bassam Hallis, David Goldblatt, Ray Borrow, Paul T. Heath, Elizabeth Miller**. Antibody responses after primary immunization in infants born to women receiving a pertussis-containing vaccine during pregnancy: single arm observational study with a historical comparator. *Clinical Infectious Diseases.* 2015. 61:1637 | Maternal: Repavax<br><br>Infant: Pediacel<br><br>Prevnar 13 | Prospective observational study with a historical comparator<br><br>UK | Group 1: 129 infants of mothers immunized during the third trimester of pregnancy<br><br>Group 2: 197 infants of non-immunized mothers<br><br>The median interval (interquartile range [IQR]) between antenatal vaccination and infant birth was 9.9 weeks (IQR, 8.0–11.1). The infants' median (IQR) age at post-immunization blood samples was 151 days (144–161).<br><br>DTaP provided at 2-3-4 months<br><br>Pneu-C-13 provided at 2 and 4 months | <u>Group 1 (IU/ml, 95% CI):</u><br>• Anti-PT at 5 months: 28.8 (25.7,32.4)<br>• Anti-FHA at 5 months: 25.5 (23,28.3)<br>• Anti-FIM2/3 at 5 months: 113.9 (99,131.1)<br>• pre vs. post immunization ratios:<br>  • Anti-PT: 2.64 (95%CI: 2.12-3.3)<br>  • Anti-FHA: 0.56 (95%CI: 0.48-0.65)<br>  • Anti-FIM2/3: 0.82 (95%CI: 0.59-1.13)<br><br><u>Group 2 (IU/ml, 95% CI):</u><br>• Anti-PT at 5 months: 43.2 (39.4-47.2)<br>• Anti-FHA at 5 months: 41.1 (37.5-45.1)<br>• Anti-FIM2/3 at 5 months: 224.9 (196.1-258)<br><br>Group 1 vs. Group 2 post immunization ratios:<br>• Anti-PT: 0.67 (95%CI: 0.58-0.77)<br>• Anti-FHA: 0.62 (95%CI: 0.54-0.71)<br>• Anti-FIM2/3: 0.51 (95%CI: 0.42-0.62)<br><br>All antibody concentrations were significantly lower post immunization in Group 1 when compared to pre-immunization concentrations and Group 2 (p<0.001), with the exception of anti-FIM2/3 where the p value did not reach statistical significance (p=0.22).<br><br>A significant inverse association within individuals was observed between antibody concentrations before and after primary immunization to PT (0.89-fold per 2-fold increase in pre-vaccination concentration; 95% CI, .81–.98; P = .023) and FIMs (0.92-fold; 95% CI, .86–.98; P = .011), while for FHA there was a positive association | II-2 | Good, No control group |

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| | | | | (1.20-fold; 95% CI, 1.11–1.31; P < .001).<br><br>Infants in Group 1 had lower antibody concentrations than in Group 2 after primary immunization for all 3 pertussis antigens.<br><br>*For pneumococcal vaccine antigens at 5 months:*<br><br><u>Group 1 (IU/ml, 95% CI):</u><br>• Serotype 1 1.35 (1.18–1.54)<br>• Serotype 3 0.56 (.51–.63)<br>• Serotype 4 1.08 (.96–1.22)<br>• Serotype 5 0.57 (.50–.65)<br>• Serotype 6A 0.90 (.75–1.07)<br>• Serotype 6B 0.36 (.31–.42)<br>• Serotype 7F 2.04 (1.80–2.32)<br>• Serotype 9V 0.72 (.61–.85)<br>• Serotype 14 4.76 (3.94–5.76)<br>• Serotype 18C 1.08 (.92–1.26)<br>• Serotype 19A 1.27 (1.06–1.51)<br>• Serotype 19F 4.01 (3.48–4.64)<br>• Serotype 23F 0.64 (.54–.78)<br><br><u>Group 2 (IU/ml, 95% CI):</u><br>• Serotype 1 1.84 (1.63–2.07)<br>• Serotype 3 1.65 (1.49–1.82)<br>• Serotype 4 1.55 (1.41–1.70)<br>• Serotype 5 0.96 (.87–1.08)<br>• Serotype 6A 1.56 (1.35–1.80)<br>• Serotype 6B 0.32 (.29–.36) 38.7<br>• Serotype 7F 2.63 (2.37–2.93)<br>• Serotype 9V 0.93 (.83–1.04)<br>• Serotype 14 5.28 (4.54–6.13)<br>• Serotype 18C 1.19 (1.06–1.34)<br>• Serotype 19A 1.56 (1.38–1.77)<br>• Serotype 19F 4.57 (4.04–5.16)<br>• Serotype 23F 0.69 (.60–.79) | | |

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| **Maertens K, Burbidge P, Van Damme P, Goldblatt D, Leuridan E.** Pneumococcal Immune Response in Infants Whose Mothers Received Tdap Vaccination During Pregnancy. Pediatr Infect Dis J. 2017 Apr 10. doi: 10.1097/INF.0000000000001601 | Maternal : Boostrix<br><br>Infants : Prevnar 13 | Prospective cohort study with a control group<br><br>Belgium | Group 1: 49 children whose mothers were immunized with Tdap in pregnancy<br><br>Group 2: 24 children whose mothers were not immunized with Tdap in pregnancy<br><br>Children immunized with Pneu-C-13 at 8 and 16 weeks of age, with booster dose provided at 12 months of age<br><br>*Data provided only for pneumococcal vaccine antigens* | <u>Group 1 (µg/ml, 95% CI):</u><br>- Month 5 :<br>• Serotype 1 1.00 (0.79-1.28)<br>• Serotype 3 0.53 (0.39-0.71)<br>• Serotype 4 0.97 (0.80-1.17)<br>• Serotype 5 0.48 (0.37-0.61)<br>• Serotype 6A 0.80 (0.59-1.10)<br>• Serotype 6B 0.24 (0.17-0.34)<br>• Serotype 7F 1.67 (1.37-2.04)<br>• Serotype 9V 0.54 (0.42-0.70)<br>• Serotype 14 3.41 (2.47-4.70)<br>• Serotype 18C 0.86 (0.68-1.08)<br>• Serotype 19A 1.17 (0.92-1.50)<br>• Serotype 19F 3.31 (2.51-4.36)<br>• Serotype 23F 0.41 (0.30-0.56)<br>- Month 15 :<br>• Serotype 1 1.15 (0.92-1.44)<br>• Serotype 3 0.71 (0.60-0.85)<br>• Serotype 4 0.84 (0.69-1.02)<br>• Serotype 5 0.93 (0.77-1.13)<br>• Serotype 6A 5.32 (4.26-6.65)<br>• Serotype 6B 2.57 (1.95-3.39)<br>• Serotype 7F 1.85 (1.54-2.22)<br>• Serotype 9V 0.78 (0.65-0.93)<br>• Serotype 14 5.11 (3.96-6.59)<br>• Serotype 18C 0.62 (0.52-0.75)<br>• Serotype 19A 3.61 (2.85-4.58)<br>• Serotype 19F 3.80 (3.09-4.67)<br>• Serotype 23F 1.09 (0.84-1.41)<br><br><u>Group 2 (µg/ml, 95% CI):</u><br>- Month 5 :<br>• Serotype 1 1.99 (1.31-3.02)<br>• Serotype 3 0.86 (0.64-1.14)<br>• Serotype 4 1.53 (1.03-2.25)<br>• Serotype 5 0.93 (0.66-1.31)<br>• Serotype 6A 1.49 (0.98-2.25)<br>• Serotype 6B 0.29 (0.19-0.45) | II-2 | Good |

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| | | | | • Serotype 7F 2.71 (1.75-4.20)<br>• Serotype 9V 1.18 (0.79-1.77)<br>• Serotype 14 7.41 (4.44-12.35)<br>• Serotype 18C 1.10 (0.72-1.68)<br>• Serotype 19A 2.21(1.55-3.14)<br>• Serotype 19F 4.88 (3.08-7.73)<br>• Serotype 23F 0.59 (0.35-0.99)<br>- Month 15 :<br>• Serotype 1 1.88 (1.29-2.75)<br>• Serotype 3 0.70 (0.51-0.95)<br>• Serotype 4 1.40 (1.02-1.91)<br>• Serotype 5 1.01 (0.78-1.30)<br>• Serotype 6A 7.68 (5.38-10.96)<br>• Serotype 6B 3.87 (2.70-5.63)<br>• Serotype 7F 2.55 (1.93-3.38)<br>• Serotype 9V 0.99 (0.69-1.41)<br>• Serotype 14 7.65 (4.87-12.01)<br>• Serotype 18C 0.81 (0.53-1.24)<br>• Serotype 19A 3.60 (2.39-5.41)<br>• Serotype 19F 3.77 (2.68-5.31)<br>• Serotype 23F 1.65 (1.16-2.35)<br><br>The proportion of children with antibody levels above 0.35 µg/mL were comparable between groups at all time points, with the exception of serotype 3 following primary vaccination. | | |
| **Cabore, Raissa Nadege, Maertens, Kirsten, Dobly, Alexandre, Leuridan, Elke, Van Damme, Pierre, Huygen, Kris.** Influence of maternal vaccination against diphtheria, tetanus, and pertussis on the avidity of infant antibody responses to a pertussis containing vaccine in | Maternal: Boostrix<br><br>Infants: Infanrix-hexa | Non-randomized control trial<br><br>Belgium | Group 1: 46 infants born from mothers who have been vaccinated with Tdap between 22 and 33 gestational weeks<br><br>Group 2 : 24 infants born from mothers who have not received Tdap during pregnancy<br><br>Infants were vaccinated according to the national 8, | <u>Group 1 (Geometric Mean of Relative Avidity Index [RAI] as %, 95% CI)</u>:<br>• Anti-PT:<br>- At 15 months: 55.40 (51.14-60.01)<br>- At 16 months: 68.06 (63.98-72.41)<br>• Anti-FHA:<br>- At 15 months: 47.82 (43.04-53.13)<br>- At 16 months: 50.51 (44.32-57.57)<br>• Anti-PRN:<br>- At 15 months: 44.13 (39.94-48.76)<br>- At 16 months: 59.05 (52.56-66.34) | II-2 | Fair |

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| Belgium. Virulence. 2017. 1-10 | | | 12, 16 weeks priming schedule, with the fourth dose provided at 15 months. | Group 2 (Geometric Mean of RAI as %, 95% CI):<br>• Anti-PT:<br>- At 15 months: 59.64 (53.48-66.52<br>- At 16 months: 78.65 (76.04-81.36)<br>• Anti-FHA:<br>- At 15 months: 50.13 (46.05-54.57)<br>- At 16 months: 58.94 (50.06-69.39)<br>• Anti-PRN:<br>- At 15 months: 46.89 (42.68-51.52)<br>- At 16 months: 64.82 (57.18-73.49)<br><br>Differences between groups were not statistically different except for RAI of anti-PT antibodies after the fourth vaccine dose ($p< 0.003$).<br><br>Regression analysis found avidity of infant anti-PRN (both groups) and anti-FHA at month 16 to be significantly influenced (increased) by the age of the mother | | |
| **Abbey J. Hardy-Fairbanks, Stephanie J. Pan, Michael D. Decker, David R. Johnson, David P. Greenberg, Kathryn B. Kirkland, Elizabeth A. Talbot, Henry H. Bernstein**. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. *Pediatric Infectious Disease Journal.* 2013. 32:1257 | Maternal: Tdap<br><br>Infant: Pediarix or Infanrix-hexa | Observational, retrospective cohort study with a control group<br><br>USA | Group 1: 14 infants whose mothers received Tdap in pregnancy (3 vaccinated during their first and 2 during their second trimester); n=9 for month 15 blood samples<br><br>Group 2: 32 infants whose mothers were not immunized with Tdap in pregnancy; n=24 for month 15 and n=26 for month 19 blood samples<br><br>DTaP at 2-4-6-15 months | Group 1 (EU/ml):<br>• Anti-PT:<br>- at month 7 (post primary series): 56.8 (100% above 5 EU/ml)<br>- at month 15 (pre-booster): 17.6 (88% above 5 EU/ml)<br>- at month 19 (post-booster): 64 (92% above 5 EU/ml)<br>• Anti-FHA:<br>- at month 7 (post primary series): 61.4 (100% above 5 EU/ml)<br>- at month 15 (pre-booster): 24.5 (100% above 5 EU/ml)<br>- at month 19 (post-booster) : 86.9 (100% above 5 EU/ml)<br>• Anti-PRN:<br>- at month 7 (post primary series): 34.1 (93% above 10 EU/ml)<br>- at month 15 (pre booster) : 11.4 (63% above 10 EU/ml)<br>- at month 19 (post-booster): 100.2 (92% | II-2 | Fair, Small sample size |

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| | | | | above 10 EU/ml)<br>• Anti-FIM2/3:<br>- at month 7 (post primary series): 15 (67% above 10 EU/ml)<br>- at month 15 (pre-booster) : 2 (none above 10 EU/ml)<br>- at month 19 (post-booster): 2 (none above 10 EU/ml)<br><br><u>Group 2 (EU/ml):</u><br>• Anti-PT:<br>- at month 7 (post primary series): 75.2 (100% above 5 EU/ml)<br>- at month 15 (pre-booster): 14.2 (85% above 5 EU/ml)<br>- at month 19 (post-booster): 75.1 (100% above 5 EU/ml)<br>• Anti-FHA:<br>- at month 7 (post primary series): 83.6 (100% above 5 EU/ml)<br>- at month 15 (pre-booster): 22.7 (85% above 5 EU/ml)<br>- at month 19 (post-booster): 93.2 (100% above 5 EU/ml)<br>• Anti-PRN:<br>- at month 7 (post primary series): 50.7 (94% above 10 EU/ml)<br>- at month 15 (pre-booster): 11.7 (48% above 10 EU/ml)<br>- at month 19 (post-booster): 105.2 (92% above 10 EU/ml)<br>• Anti-FIM2/3:<br>- at month 7 (post primary series): 10 (40% above 10 EU/ml)<br>- at month 15 (pre booster) : 8.3 (37% above 10 EU/ml)<br>- at month 19 (post-booster): 34.2 (65% above 10 EU/ml) | | |

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| | | | | Following the primary series, GMCs were 0.7- to 0.8-fold lower in Group 1, except for FIM (1.5-fold greater).<br><br>Because some children received products which did not contain FIM2/3, results were not relevant.<br><br>At every time point, % of infants considered having protective antibody levels were higher in Group 1 until 7 months of life.<br><br>In response to the booster dose, children in both groups showed increases in antibody concentration. | | |
| **Alison Kent, Shamez N. Ladhani, Nick J. Andrews, Mary Matheson, Anna England, Elizabeth Miller, Paul T. Heath, PUNS study group**. Pertussis Antibody Concentrations in Infants Born Prematurely to Mothers Vaccinated in Pregnancy. *Pediatrics.* 2016. 138 | Maternal: Repavax<br><br>Infant: Pediacel, Menjugate and, Prevnar 13 | Retrospective analysis of data collected through a larger RCT<br><br>UK | Group 1: 30 premature infants of mothers immunized with Tdap at 28 weeks of gestation (15 with results at 5 months of age)<br><br>Group 1: 121 premature infants of mothers not immunized in pregnancy (73 with results at 5 months of age)<br><br>Median interval between immunization and delivery was 24 days. Average gestational age at birth was 32 weeks.<br><br>DTaP provided at 2-3-4 months | <u>Group 1 (µg/mL, 95% CI):</u><br>• Anti-PT:<br>- At 5 months: 37.15 (26.08-52.93)<br>- At 12 months: 8.49 (5.92-12.17)<br>• Anti-FHA:<br>- At 5 months: 23.04 (16.17-32.85)<br>- At 12 months: 16.44 (12.29-21.99)<br>• Anti-FIM2/3:<br>- At 5 months: 119.55 (66.90-213.63)<br>- At 12 months: 25.78 (16.90-39.36)<br><br><u>Group 2 (µg/mL, 95% CI):</u><br>• Anti-PT:<br>- At 5 months: 44.07 (37.89-51.26)<br>- At 12 months: 10.75 (9.37-12.34)<br>• Anti-FHA:<br>- At 5 months: 45.55 (37.64-55.12)<br>- At 12 months: 19.07 (16.33-22.27)<br>• Anti-FIM2/3:<br>- At 5 months: 135.14 (100.86-181.08) | II-2 | Fair, Post-hoc analysis of clinical trial data |

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| | | | | - At 12 months: 37.24 (30-46.23)<br><br>Compared to antibody levels at 2 months of age, significantly higher GMCs (all antigens) observed in both groups one month after 3rd dose of DTaP (P < .001); only anti-FHA levels lower in Group 1 vs 2 (p=.003)<br><br>At 12 months of age, there were no significant antibody differences between groups. | | |
| **Kirsten Maertens, Raissa Nadege Cabore, Kris Huygen, Niel Hens, Pierre Van Damme, Elke Leuridan**. Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. *Vaccine.* 2016. 34:142 | Maternal: Boostrix<br><br>Infant: Infanrix-hexa | Non-randomized control trial<br><br>Belgium | Group 1: 49 infants of women who received Tdap at mean 28.6 weeks of gestation<br><br>Group 2: 21 infants of age matched women who have not received any pertussis-containing vaccine in 10 years preceding the study<br><br>DTaP provided at 2-3-4 months | <u>Group 1 (IU/ml, 95% CI):</u><br>• Anti-PT at 5 months: 29 (25–35)<br>• Anti-FHA at 5 months: 65 (56–75)<br>• Anti-PRN at 5 months: 68 (56–84)<br><br><u>Group 2 (IU/ml, 95% CI):</u><br>• Anti-PT at 5 months: 54 (42–69)<br>• Anti-FHA at 5 months: 54 (41–70)<br>• Anti-PRN at 5 months: 87 (62–121)<br><br>At 1 month after the third hexavalent vaccine dose, GMCs to PT were significantly lower in Group 1 infants (p < 0.001). However, anti-PT GMCs had risen from week 8 to month 5. For anti-PRN (p = 0.220) and anti-FHA (p = 0.198), the difference in GMC was not significant. In Group 1 infants, there was decay in titers from week 8 to month 5 for these two antibodies. | II-2 | Fair, Representativeness of the control group |
| **Kirsten Maertens, Raissa Nadege Cabore, Kris Huygen, Sandra Vermeiren, Niel Hens, Pierre Van Damme, Elke Leuridan**. Pertussis | Maternal: Boostrix<br><br>Infant: Infanrix-hexa | Non-randomized control trial<br><br>Belgium | Group 1: 45 infants 16 months of age born to mothers immunized with Tdap at mean 28.6 weeks of pregnancy<br><br>Group 2: 22 infants 16 | <u>Group 1 (IU/ml, 95% CI):</u><br>• Anti-PT:<br>- One month after primary immunization (8, 12, 16 weeks of age): 29.31 (24.6,34.93)<br>- Before fourth (booster) Tdap dose: 5.44 (4.49,6.58)<br>- One month after 4th Tdap dose: 36.29 | II-2 | Fair, High observed drop-out rates |

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| vaccination during pregnancy in Belgium: Follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age. *Vaccine.* 2016. 34:3613 | | | months of age who received booster born to mothers without Tdap in the 10 years preceding the study<br><br>DTaP provided at 2-3-4-15 months | (30.93,42.57)<br>• Anti-FHA:<br>- One month after primary immunization (8, 12, 16 weeks of age): 64.9 (53.8, 78.3)<br>- Before fourth (booster) Tdap dose: 14.83 (12.37,17.77)<br>- One month after 4th Tdap dose: 100.86 (84.93,119.77)<br>• Anti-PRN:<br>- One month after primary immunization (8, 12, 16 weeks of age): 68.44 (55.85,83.89)<br>- Before fourth (booster) Tdap dose: 4.44 (3.66,5.39)<br>- One month after 4th Tdap dose: 92.73 (67.04,128.25)<br><br><u>Group 2 (IU/ml, 95% CI):</u><br>• Anti-PT:<br>- One month after primary immunization (8, 12, 16 weeks of age): 54.10 (42.36,69.09)<br>- Before fourth (booster) Tdap dose: 7.27 (5.8,9.12)<br>- One month after 4th Tdap dose: 56.6 (42.36,75.65)<br>• Anti-FHA:<br>- One month after primary immunization (8, 12, 16 weeks of age): 53.73 (41.10,70.23)<br>- Before fourth (booster) Tdap dose: 15.98 (12.43-20.56)<br>- One month after 4th Tdap dose: 139.42 (112.68-172.51)<br>• Anti-PRN:<br>- One month after primary immunization (8, 12, 16 weeks of age): 87.05 (62.17-121.89)<br>- Before fourth (booster) Tdap dose: 7.62 (5.67-10.25)<br>- One month after 4th Tdap dose: 81.2 (58.4-112.9) | | |

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| | | | | One month after 3 DTaP doses, anti-PT GMC was significantly lower ($p < 0.001$) and anti-Prn GMS non-significantly lower in Group 1. Group 2 had non-significantly lower anti-FHA.<br><br>Before the administration of DTaP booster dose, anti-Prn GMC was significantly lower ($p = 0.003$) in Group 1; anti-PT and anti-FHA were non-significantly lower.<br><br>One month after booster dose, anti-PT GMC significantly lower ($p = 0.006$) and anti-FHA, non-significantly lower in Group 1; anti-Prn, non-significantly lower in Group 2<br><br>After the booster dose, a rise in concentrations was observed for all antibodies, with no significant differences in rate increases between groups except for anti-Prn for which the increase rate was significantly higher in Group 1 ($p = 0.001$).<br><br>Antibody decay was most pronounced for anti-PT. | | |

**Table 5: Summary of evidence related to the safety of acellular pertussis vaccine in pregnancy (mother)**

| **Evidence related to safety of Tdap acellular pertussis vaccine in pregnancy (mother)** | | | | | | |
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| **STUDY DETAILS** | | | | | **SUMMARY** | |
| **Study** | **Vaccine** | **Study Design** | **Participants** | **Summary of Key Findings Using Text or Data** | **Level of Evidence** | **Quality of Evidence** |
| **Flor M. Munoz, Nanette H. Bond, Maurizio Maccato, Phillip Pinell, Hunter A. Hammill, Geeta K. Swamy, Emmanuel B. Walter, Lisa A. Jackson, Janet A. Englund, Morven S. Edwards, C. Mary Healy, Carey R. Petrie, Jennifer Ferreira, Johannes B. Goll, Carol J. Baker.** Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA.* 2014. 311:1760 | Adacel<br><br>Placebo: 0.9% saline solution | RCT, double masked, placebo-controlled<br><br>USA | Inclusion criteria (Groups 1 and 2): healthy women 18 to 45 years-old with a singleton pregnancy and at low risk for obstetrical complications based on normal first or second trimester screening test results and detailed anatomic fetal ultrasound at 18–22 weeks' gestation. Women who in previous 2 years received any tetanus containing vaccine were excluded from the study.<br><br>Group 1: 33 pregnant women who received Tdap at 30-32 weeks of gestation and saline postpartum<br><br>Group 2: 15 pregnant women who received saline at 30-32 weeks of gestation and Tdap postpartum<br><br>Group 3: 32 age-matched comparison group of healthy non-pregnant women immunized with Tdap. | <u>Group 1:</u><br>• 78.8% reported any injection site reaction following Tdap<br>• 20% reported any injection site reaction following placebo<br>• 75.8% reported pain at the injection site following Tdap<br>• 36.4% reported any systemic symptom following Tdap<br>• 21.2% reported a SAE<br><br><u>Group 2:</u><br>• 80.0% reported any injection site reaction following Tdap<br>• 18.2% reported any injection site reaction following placebo<br>• 73.3% reported pain at the injection site following Tdap<br>• 73.3% reported any systemic symptom following Tdap<br>• 13.3% reported a SAE<br><br><u>Group 3:</u><br>• 78.1% reported any injection site reaction<br>• 75.8% reported pain at the injection site<br>• 53.1% reported any systemic symptom following Tdap<br>• 3.1% reported a SAE<br><br>Between groups, there were no differences in reporting any injection site reactions following Tdap immunization (p=1.0) or pain at the injection site (p= > 0.35); swelling and erythema were infrequent. Most symptoms were mild, | I | Good, Small sample size |

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| | | | | and resolved within 72 hours.<br><br>The occurrence of fever after receipt of Tdap was significantly different between the groups, with Group 1 (3.0%) and Group 3 (9.4%) reporting it less frequently than Group 2 (26.7%) (p=0.044). However, the occurrence of fever postpartum in Group 2 (26.7%) was not different from that of Group 1 (15.2%) (p=0.43). There was no difference in the proportion of participants with fever between Group 1 and Group 3 (p=0.36).<br><br>The frequencies of headache, myalgia and malaise were not significantly different among the three groups (p= > 0.35).<br><br>No SAEs were judged to be attributable to Tdap vaccine. | | |
| **Jesus Zacarias Villarreal Perez, Jose Manuel Ramirez Aranda, Manuel de la O Cavazos, Michelle de J. Zamudio Osuna, Jose Perales Davila, Maria Romelia Ballesteros Elizondo, Marco Vinicio Gomez Meza, Francisco Javier Garcia Elizondo, Azucena M. Rodriguez Gonzalez.** Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. *Human vaccines & Immunotherapeutics.* 2016. | Adacel<br><br>Placebo: 0.9% saline solution | RCT, double blind, parallel group<br><br>Mexico | Pregnant women 18 to 38 years of age with low obstetric risk and normal anatomical ultrasound at 24-26 weeks gestation and their infants; immunization at 30 to 32 weeks gestation<br><br>Exclusion criteria: w/psychiatric disease (schizophrenia, psychosis, major depression), w/severe physical disease (diabetes mellitus, hypertension or degenerative diseases), consume drugs or tobacco, w/history of severe reactions to any vaccine immunized against tetanus and/or pertussis in the 2 years prior to the study<br><br>Group 1 (Tdap): n=90 | AEs assessed at 30 minutes, 24 and 48 hours, and one month after vaccination<br><br>Approximately 35% of study participants reporting non-serious local AEs and 4% non-serious systemic AEs<br><br>No statistically significant differences between groups were found; SAEs were not reported by the study authors. | I | Good |

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| | | | Group 2 (control): n=81 | | | |
| **Ha Thi Thu Hoang, Elke Leuridan, Kirsten Maertens, Trung Dac Nguyen, Niel Hens, Ngoc Ha Vu, Raissa Nadege Cabore, Hong Thi Duong, Kris Huygen, Pierre Van Damme, Anh Duc Dang.** Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during pregnancy. *Vaccine.* 2016. 34:151 | Adacel<br><br>TT | RCT<br><br>Vietnam | Group 1: 52 pregnant women immunized with Tdap<br><br>Group 2: 51 pregnant women immunized with TT | <u>Group 1:</u><br>- 23 women with at least 1 AE<br>- 45% experienced injection site pain and swelling<br>- 4 SAEs: fever (1) and fatigue (1) requiring hospitalization, and premature contractions (2)<br><br><u>Group 2:</u><br>- 22 women with at least 1 AE<br>- 2 SAE: premature contractions (1) and preterm delivery (1)<br><br>The most common AE in both groups were stiffness, swelling and itching at the injection site.<br><br>All premature contractions occurred more than1 month after vaccination. Preterm delivery occurred 5 weeks after vaccination.<br><br>No significant differences were found between groups. | I | Fair, RCT study conducted in field conditions |
| **Katherine Donegan, Bridget King, Phil Bryan.** Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ.* 2014. 349:g4219 | Repavax, Sanofi | Observational, retrospective analysis of the Clinical Practice Research Datalink (CPRD) database.<br><br>UK | Analysis included data from October 2012 to March 2013.<br><br>17,560 pregnant women with more than 28 days of follow-up data after vaccination | Within 2 weeks post vaccination, there were:<br>- 3 reported cases of antepartum haemorrhage<br>- 1 reported case of placenta praevia<br>- 1 reported case of fetal distress, and<br>- no recorded cases of maternal death, uterine rupture, placental abruption, or vasa praevia. | II-2 | Fair, No adjustment for smoking, alcohol and drug use, parity, socioeconomic status and |

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| **Fortner K.B., Edwards K.M., Broder K.R., Jimenez N., Zhu Y., Walter E.B., Heine R.P., Moro P., Liang J.L., G. K. Swamy.** Reactogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women. *American Journal of Obstetrics and Gynecology. Conference: 36th Annual Meeting of the Society for Maternal-Fetal Medicine: The Pregnancy Meeting. Atlanta, GA United States. Conference. Publication:* 2016. 214:S193 | Tdap | Observational, prospective cohort study with comparison group | Group 1: 361 pregnant women who received Tdap at 20-34 week of gestation<br><br>Group 2: 161 non pregnant women immunized with Tdap<br><br>AEs recorded up to 7 days post immunization | Group 1:<br>- 53% with prior Tdap<br>- 68.8% reported pain at the injection site (17% moderate and 0.6% severe)<br>- Swelling or redness reported by approximately 15% of individuals<br>- 1% reported fever<br>- ≤1% reported severe malaise, headaches or body aches<br>Group 2:<br>- 69% with prior Tdap<br>- 77.6% reported pain at the injection site (8.7% moderate and none severe)<br>- Swelling or redness reported by approximately 15% of individuals<br>- 5.7% reported fever<br>- ≤1% reported severe malaise, headaches or body aches<br>Rates of moderate to severe injection site pain and malaise were in Group 1 ($p < 0.05$); all events resolved without medical intervention. Rates of fever, headaches, injection site swelling and redness were similar between the two groups.<br><br>Rates of other AEs were similar between groups. | II-2 | Fair, Poster Abstract |
| **Elyse Olshen Kharbanda, Gabriela Vazquez-Benitez, Heather S. Lipkind, Nicola P. Klein, T. Craig Cheetham, Allison L. Naleway, Grace M. Lee, Simon Hambidge, Michael L. Jackson, Saad B.** | Adacel<br><br>Boostrix | Observational, retrospective analysis of data (matched cohort design) from January 1, 2007 to November 15, 2013 of the Vaccine Safety Datalink (VSD) from 7 sites | Group 1: 53,885 pregnant women with singleton live births immunized with Tdap<br><br>Group 2: 109,253 pregnant women matched for maternal age, study site and estimated pregnancy start date who were not immunized with Tdap in | <u>Group 1:</u><br>• 43 medically attended event (allergic reaction, fever, and malaise, seizure, altered mental status, or local or other reaction) within 3 days following vaccination; rate= 8.1/10,000<br>• Rate of medical visits for fever within 3 days following Tdap = 2.8/10,000<br><br><u>Group 2:</u><br>• 74 medically attended events within 3 days of | II-2 | Fair, VSD cohort only includes women with |

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| **Omer, Natalie McCarthy, James D. Nordin.** Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007-2013. *Vaccine.* 2016. 34:968 | | USA | pregnancy | matched index date; rate: 6.8/10,000<br>• Rate of medical visits for fever within 3 days of matched index case <1/10,000<br><br>Adjusted Rate Ratio for any 0-3 day event between groups = 1.19 (95% CI: 0.81–1.73)<br><br>Adjusted Rate Ratio for any 0-42 day neurologic event between groups = 0.98 (95% CI: 0.70–1.37)<br><br>Adjusted Rate Ratio for medically attended fever within 3 days following vaccination = 5.4 (95% CI: 2.1–13.9)<br><br>Neurologic events within 42 days following maternal Tdap occurred at the same rate (9.6/10,000); rates for proteinuria and venous thromboembolism did not differ significantly between groups.<br><br>Risk for incident gestational diabetes, thrombocytopenia, venous thromboembolism or cardiac events (myocarditis, pericarditis, cardiomyopathy, or heart failure) within 42 days of vaccination were non-statistically different between groups. | | live births and continuous health insurance |
| **Layton, J. Bradley, Butler, Anne M., Li, Dongmei, Boggess, Kim A., Weber, David J., McGrath, Leah J., Becker-Dreps, Sylvia.** Prenatal Tdap immunization and risk of maternal and newborn adverse events. Vaccine. 2017. 35:4072 | Tdap | Administrative insurance claims (MarketScan Commercial) insurance claims databases for the years 2010–2014 | Group 1: 123,780 women immunized at 27 or more weeks gestation<br><br>Group 2: 25,037 women immunized at <27 weeks gestation<br><br>Group 3: 59,040 immunized postpartum (control)<br><br>Only women with singleton pregnancies included | <u>Group 1 (per 10,000):</u><br>• Anaphylaxis: 0<br>• Fever: 3.80<br>• Cellulitis: 2.18<br>• Pain in limb: 17.58<br>• Encephalopathy: 0.57<br>• GBS: 0<br><br><u>Group 2 (per 10,000):</u><br>• Anaphylaxis: 0<br>• Fever: 5.19<br>• Cellulitis: 17.18<br>• Pain in limb: 36.80<br>• Encephalopathy: 0<br>• GBS: 0 | II-2 | Fair |

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| | | | | Group 3 (per 10,000):<br>• Anaphylaxis: 0.17<br>• Fever: 11.69<br>• Cellulitis: 8.81<br>• Pain in limb: 32.88<br>• Encephalopathy: 0.85<br>• GBS: 0<br><br>Occurrence of anaphylaxis and fever were assessed for 3 days following immunization, cellulitis and pain in limb were assessed for 7 days, while encephalopathy and GBS were assessed for 42 days. | | |
| **Kirsten Maertens, Raissa Nadege Cabore, Kris Huygen, Niel Hens, Pierre Van Damme, Elke Leuridan.** Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. *Vaccine.* 2016. 34:142 | Boostrix | Non-randomized control trial<br><br>Belgium | Healthy pregnant women from 5 hospitals in the province of Antwerp<br><br>Group 1: 57 women who received Tdap at mean 28.6 weeks of gestation<br><br>Group 2: 42 women who have not received any pertussis-containing vaccine for at least 10 years | Group 1:<br><br>50 AEs were reported in 46 women. Most symptoms were mild and self-limited and were resolved within 72 hours after vaccination.<br><br>Stiffness of the arm at the injection site reported by 74% (42) of women; fever reported by 1 individual<br><br>5 AEs (vaginal thrush, reflux, fever <38.5◦C, extensive limb swelling and rashes on the abdomen and arms) required the use of medication.<br><br>A total of 11 SAEs were reported, none considered to be related to vaccination.<br><br>Group 2:<br><br>3 SAEs were reported. | II-2 | Fair, Representativeness of the control group |
| **Pedro L. Moro, Janet Cragan, Naomi Tepper, Yenlik Zheteyeva, Oidda Museru, Paige Lewis, Karen Broder.** Enhanced surveillance of tetanus toxoid, reduced diphtheria | Adacel<br><br>Boostrix | Observational, retrospective analysis of data reported to VAERS between November 1, 2011 and June 30, 2015<br><br>USA | 392 reports identified in which Tdap was provided in pregnancy with or without other vaccines | • 11.9% (47) pertained to injection site reactions and 4.3% (17) to systemic reactions (e.g., fever, chills).<br>• 7.2% (28) pertained to musculoskeletal, connective tissue or immune system disorders, including allergic reactions (4 reported on anaphylaxis). | II-2 | Fair, Passive reporting system (potential |

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| toxoid, and acellular pertussis (Tdap) vaccines in pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 2011-2015. *Vaccine.* 2016. 34:2349 | | | | | | issues with underreporting, reporting bias, and inconsistency in report quality) |
| **Perry, Jamie,Towers, Craig V., Weitz, Beth, Wolfe, Lynlee.** Patient reaction to Tdap vaccination in pregnancy. Vaccine. 2017. 35:3064 | Tdap | Prospective observational study | 737 pregnant women recruited at the time of Tdap administration<br><br>Local and systemic AEs were assessed 1-7 days post vaccination including: pain, soreness, swelling or redness at the injection site, as well as temperature or generalized body aches | 496 women found to have at least 1 reaction to the vaccination and 187 had 2 more reactions; 24 women stated that they would not accept receipt of Tdap in a subsequent pregnancy because of the reported AE.<br><br>No stillbirths or neonatal deaths were reported to occur in the cohort. | II-2 | Fair |
| **Helen Petousis-Harris, Tony Walls, Donna Watson, Janine Paynter, Patricia Graham, Nikki Turner.** Safety of Tdap vaccine in pregnant women: an observational study. *BMJ Open.* 2016. 6:e010911 | Boostrix | Observational, prospective study<br><br>New Zealand | 793 women with at least one ultrasound early in pregnancy who received Tdap between 28 and 38 weeks gestation | Approximately 1/3 of individuals reporting systemic AEs also received influenza vaccine.<br><br>Local AEs:<br>• 79.0% reported mild or moderate pain (2.6% severe)<br>• 7.6% reported swelling (0.4% severe)<br>• 5.8% reported erythema (0.4% severe)<br>Systemic AEs:<br>• 2.1 % fever<br>• 3.9% headache/dizziness | II-2 | Fair, Recall bias due to lack of diary in one |

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| | | | | • 3% myalgia/arthralgia<br>• 2.8% nausea/vomiting<br>• 8.4% fatigue<br>Of 31 (3.9%) serious AEs occurring during pregnancy, there were 23 hospitalisations: obstetric bleeding (4), hypertension (2), infection (4), tachycardia (1), preterm labour (9), exacerbation of pre-existing condition (2) and pre-eclampsia (1). All had variable onset time from vaccination.<br><br>No SAEs considered by clinical review to be caused by Tdap vaccination | | group of participants |
| **Annette K. Regan, Lauren E. Tracey, Christopher C. Blyth, Peter C. Richmond, Paul V. Effler.** A prospective cohort study assessing the reactogenicity of pertussis and influenza vaccines administered during pregnancy. *Vaccine.* 2016. 34:2299 | Adacel<br><br>Boostrix<br><br>Trivalent inactivated influenza vaccine (TIV) (Vaxigrip and Fluvax) | Observational, retrospective analysis of ante-natal immunization database (WA Health)<br><br>Australia | Group 1: 1,584 women who received TIV exclusively<br><br>Group 2: 1,257 who received Tdap exclusively<br><br>Group 3: 1,506 who received TIV and Tdap concomitantly | Group 1:<br>• 10.3% reported AEFI (any)<br>• 3.2% reported local AE<br>Group 2:<br>• 11.4% reported AEFI (any)<br>• 7.1% reported local AE<br><br>Group 3:<br>• 10.7% reported AEFI (any)<br>• 5.4% reported local AE<br>There was no difference in the proportion of women who reported an AEFI (any) or fever by vaccine group.<br><br>Local reactions were more commonly reported in Group 2 than in Group 1 (OR: 2.29; 95%CI: 1.61–3.26) and Group 3 than in group 1 (OR: 1.73; 95% CI: 1.21–2.47).<br><br>1.7% of women reported seeking any type of medical care for AEFI; 11 women presented to a hospital emergency department: four in Group 1, one in Group 2 and six in Group 3.<br><br>In all cases, AEFI symptoms resolved and ended in healthy infant delivery.<br><br>A sub-analysis of women who previously received Tdap in adulthood showed a more frequent reporting of AEFI compared to women who did not report Tdap | II-2 | Fair, Events reported were not medically verified |

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| | | | | immunization (p = 0.04). These women had also greater odds of reporting pain or swelling at the injection site OR: 2.00; 95% CI: 0.94–4.25; p = 0.06). | | |
| **Lakshmi Sukumaran, Natalie L. McCarthy, Elyse O. Kharbanda, Eric S. Weintraub, Gabriela Vazquez-Benitez, Michael M. McNeil, Rongxia Li, Nicola P. Klein, Simon J. Hambidge, Allison L. Naleway, Marlene M. Lugg, Michael L. Jackson, Jennifer P. King, Frank DeStefano, Saad B. Omer, Walter A. Orenstein.** Safety of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis and Influenza Vaccinations in Pregnancy. *Obstetrics & Gynecology.* 2015. 126:1069 | Tdap<br><br>Influenza | Observational, retrospective analysis of data (matched cohort design) from January 1, 2007 to November 15, 2013 of the Vaccine Safety Datalink (VSD) from 7 sites<br><br>USA | Group 1: 8,464 pregnant women who received Tdap and inactivated influenza vaccine concomitantly<br><br>Group 2: 28,380 pregnant women who received Tdap and influenza vaccine sequentially | <u>Group 1, rate/10,000:</u><br>• Any acute reaction within 3 days post immunization: 13 (n=11)<br>• Any acute reaction within 7 days post immunization: 22.4 (n=19)<br>• Fever within 3 days post immunization: 2.4 (n=2)<br>• Fever within 7 days post immunization: 3.5 (n=3)<br><u>Group 2, rate/10,000:</u><br>• Any acute reaction within 3 days post immunization: 11.3 (n=32)<br>• Any acute reaction within 7 days post immunization: 25.4 (n=72)<br>• Fever within 3 days post immunization: 3.2 (n=9)<br>• Fever within 7 days post immunization: 4.2 (n=12)<br>RRs (95% CI, p) after adjusting for gestational age:<br>• Any acute reaction within 3 days post immunization: 1.13 (0.57 – 2.27; p=0.72<br>• Any acute reaction within 7 days post immunization: 0.96 (0.58 – 1.61; p=0.88)<br>• Fever within 3 days post immunization: 0.69 (0.15 – 3.23; p=0.64)<br>• Fever within 7 days post immunization: 1.60 (0.56 – 4.59; p=0.38<br>There was no association between acute AE and gestational age at Tdap vaccination. | II-2 | Fair, Only acute events in women who sought medical care were analyzed |
| **Lakshmi Sukumaran, Natalie L. McCarthy, Elyse O. Kharbanda, Michael M. McNeil, Allison L. Naleway, Nicola P. Klein, Michael L. Jackson, Simon J. Hambidge, Marlene M. Lugg, Rongxia Li, Eric S. Weintraub, Robert A.** | Tdap | Observational, retrospective analysis of data (matched cohort design) from January 1, 2007 to November 15, 2013 of the Vaccine Safety Datalink (VSD) from 7 sites | Group 1: 4,812 women immunized with Tdap in pregnancy less than 2 years following the receipt of a tetanus containing vaccine<br><br>Group 2: 9,999 women immunized with Tdap in pregnancy 2 to 5 years following the receipt of a | <u>Group 1:</u><br>• Fever beginning up to 3 days post Tdap: 2.1/10,000; Adjusted RR, 0.66 (95% CI, 0.07-5.77; P = .70)<br>• Allergic reactions up to 3 days post Tdap: 2.1/10,000; Adjusted RR, 1.55 (95% CI, 0. 13-18.45; P = .73)<br>• Local reactions up to 3 days post Tdap: 4.2/10,000; Adjusted RR, 0.49 (95% CI, 0.11-2.20; P = .35)<br><u>Group 2:</u><br>• Fever beginning up to 3 days post Tdap: <1/10,000<br>• Allergic reactions up to 3 days post Tdap: 1/10,000; ARR, 0.71 (95% CI, 0.06-8.13; P = .78) | II-2 | Fair, Medical charts review to validate AEs was |

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| **Bednarczyk, Jennifer P. King, Frank DeStefano, Walter A. Orenstein, Saad B. Omer.** Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes Among Pregnant Women With Prior Tetanus-Containing Immunizations. *JAMA.* 2015. 314:1581 | | USA | tetanus containing vaccine<br><br>Group 3 (control): 14,344 women immunized with Tdap in pregnancy more than 5 years following the receipt of a tetanus containing vaccine | • Local reactions up to 3 days post Tdap: 7/10,000; ARR, 0.77 (95% CI, 0.31-1.95; P = .78)<br><br><u>Group 3:</u><br>• Fever beginning up to 3 days post Tdap: 3.5/10,000<br>• Allergic reactions up to 3 days post Tdap: 1.4/10,000<br>• Local reactions up to 3 days post Tdap: 11.2/10,000<br>There were no identified cases of anaphylaxis, Arthus reaction, or Guillain-Barré syndrome following vaccination. | | not conducted |
| **Yenlik A. Zheteyeva, Pedro L. Moro, Naomi K. Tepper, Sonja A. Rasmussen, Faith E. Barash, Natalia V. Revzina, Dmitry Kissin, Paige W. Lewis, Xin Yue, Penina Haber, Jerome I. Tokars, Claudia Vellozzi, Karen R. Broder.** Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. American Journal of Obstetrics & Gynecology. 2012. 207:59.e1 | Adacel<br><br>Boostrix | Observational, retrospective analysis of data reported to VAERS between January 1, 2005 and June 30, 2010<br><br>USA | 132 reports identified in which Tdap was provided in pregnancy | 41.7% (55) did not describe any AE and were submitted because Tdap was administered at a time period when it was not routinely recommended<br><br>In total, there were 24 reports with non-pregnancy specific outcomes. The most frequent were:<br>• injection site reactions in 4.5% (6) reports<br>• anemia in 3.8% (5) reports, and<br>• headache or fever with abdominal pain in 2.3% (3) reports | II-2 | Fair |
| **Carla Vizzotti, Maria V. Juarez, Eduardo Bergel, Viviana Romanin, Gloria Califano, Sandra** | Tdap | Observational, retrospective analysis of national AEFI data from January 2012 to | 1,258,723 doses administered to pregnant women | A total of 20 AEFI reported (1.59 per 100,000 administered doses):<br>• 7 AEs were mild and related to the vaccine (2 episodes of rash after vaccination and 5 local reactions with local pain, redness and swelling). | II-3 | Poor, Individual data on |

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| **Sagradini, Carolina Rancano, Analia Aquino, Romina Libster, Fernando P. Polack, Juan Manzur.** Impact of a maternal immunization program against pertussis in a developing country. Vaccine. 2016. | | December 2014 | | • 12 AEs corresponded to program errors, i.e. the vaccine was administered before the recommended age of 20 weeks gestation or pregnant women were revaccinated with Tdap at subsequent pregnancy<br>No serious or fatal events were reported. | | vaccination status not available (impossible to estimate VE) |
| **Talbot EA, Brown KH, Kirkland KB, Baughman AL, Halperin SA, Broder KR.** The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine. 2010 Nov 23;28(50):8001-7. doi: 10.1016/j.vaccine.2010.09.034. | Adacel | Observational Study<br><br>USA | 16 unintentionally immunized pregnant health care workers | 1 reported severe swelling at the injection site and 2 reported feeling feverish (without documented fever) in the 2 weeks after Tdap; all recovered without treatment | III | fair |
| **Cabrera-Maqueda J.M., Ester B.G.A., Clares R.H., Luna F.R., Ana** | Tdap | Case report | Two cases of optic neuritis in pregnant women following Tdap vaccination; | <u>Case 1:</u><br>Age: 38<br>Tdap administration: 28 WG | III | Poor |

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| **M.O., Lallana J.M., Fernandez, J. M.** Optic neuritis during pregnancy following TDPA vaccination: Report of two cases. 2017. | | | previous medical history unremarkable | Diagnostic at: 31 WG<br>Therapy: high-dose IV methylprednisone<br><br><u>Case 2:</u><br>Age: 38<br>Tdap administration: 28 WG<br>Diagnostic at: 30 WG<br>Th: none<br><br>Complete clinical remission and resolution of optic nerve swelling achieved in both cases two months after diagnosis | | |

**Table 6: Summary of evidence related to the safety of acellular pertussis vaccine in pregnancy (baby)**

| **Evidence related to safety of Tdap acellular pertussis vaccine in pregnancy (infant)** | | | | | | |
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| **STUDY DETAILS** | | | | | **SUMMARY** | |
| **Study** | **Vaccine** | **Study Design** | **Participants** | **Summary of Key Findings Using Text or Data** | **Level of evidence** | **Quality of Evidence** |
| **Flor M. Munoz, Nanette H. Bond, Maurizio Maccato, Phillip Pinell, Hunter A. Hammill, Geeta K. Swamy, Emmanuel B. Walter, Lisa A. Jackson, Janet A. Englund, Morven S. Edwards, C. Mary Healy, Carey R. Petrie, Jennifer Ferreira, Johannes B. Goll, Carol J. Baker.** Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA.* 2014. 311:1760 | Adacel<br><br>Placebo: 0.9% saline solution | RCT, double masked, placebo-controlled<br><br>USA | Inclusion criteria: healthy women 18 to 45 years-old with a singleton pregnancy and at low risk for obstetrical complications based on normal first or second trimester screening test results and detailed anatomic fetal ultrasound at 18–22 weeks' gestation. Women who in previous 2 years received any tetanus containing vaccine were excluded from the study.<br><br>Group 1: 33 infants of pregnant women who received Tdap at 30-32 weeks of gestation and saline postpartum<br><br>Group 2: 15 infants of pregnant women who received saline at 30-32 weeks of gestation and Tdap postpartum | All infants were live born, mostly at term and by vaginal delivery. There were no significant differences in the infants' gestational age, birth weight, Apgar scores, neonatal examination or complications. There were no differences in the infants' growth and development up to 13 months of age.<br><br>AEs were reported by 84.8% of mothers in Group 1 and 93.3% of mothers in Group 2. All resolved without sequelae.<br><br>SAEs were reported by 18.1% of mothers in Group 1 and 3.1% of mothers in Group 2. None were judged to be attributable to Tdap vaccine. | I | Good, Small sample size |
| **Jesus Zacarias Villarreal Perez, Jose Manuel Ramirez Aranda, Manuel de la** | Adacel<br><br>Placebo: 0.9% | RCT, double blind, parallel group<br><br>Mexico | Pregnant women 18 to 38 years of age with low obstetric risk and normal anatomical ultrasound at | No data reported on adverse infant outcomes | I | Good |

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| **O Cavazos, Michelle de J. Zamudio Osuna, Jose Perales Davila, Maria Romelia Ballesteros Elizondo, Marco Vinicio Gomez Meza, Francisco Javier Garcia Elizondo, Azucena M. Rodriguez Gonzalez**. Randomized clinical trial of the safety and immunogenicity of the Tdap vaccine in pregnant Mexican women. *Human vaccines & Immunotherapeutics.* 2016. | saline solution | | 24-26 weeks gestation and their infants; immunization at 30 to 32 weeks gestation<br><br>Exclusion criteria: w/psychiatric disease (schizophrenia, psychosis, major depression), w/severe physical disease (diabetes mellitus, hypertension or degenerative diseases), consume drugs or tobacco, w/history of severe reactions to any vaccine immunized against tetanus and/or pertussis in the 2 years prior to the study<br><br>Group 1 (Tdap): n=90<br><br>Group 2 (control): n=81 | | | |
| **Ha Thi Thu Hoang, Elke Leuridan, Kirsten Maertens, Trung Dac Nguyen, Niel Hens, Ngoc Ha Vu, Raissa Nadege Cabore, Hong Thi Duong, Kris Huygen, Pierre Van Damme, Anh Duc Dang**. Pertussis vaccination during pregnancy in Vietnam: Results of a randomized controlled trial Pertussis vaccination during pregnancy. *Vaccine.* 2016. 34:151 | Adacel<br><br>TT<br><br>Infanrix hexa | RCT<br><br>Vietnam | Group 1: 51 infants whose mothers were immunized with Tdap<br><br>Group 2: 48 infants whose mothers were immunized with TT | In Group 2, one preterm delivery with stillbirth at seven months gestational age occurred 5 weeks following vaccination.<br><br>Common symptoms of respiratory and gastrointestinal diseases were recorded, but were not classified as serious (did not require hospitalization) and not associated with maternal vaccination. | I | Fair, RCT study conducted in field conditions |

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| **Abbey B. Berenson, Jacqueline M. Hirth, Mahbubur Rahman, Tabassum H. Laz, Richard E. Rupp, Kwabena O. Sarpong**. Maternal and infant outcomes among women vaccinated against pertussis during pregnancy. *Human vaccines & Immunotherapeutics.* 2016. 12:1965 | Adacel<br><br>Boostrix | Observational, retrospective review of patient medical charts (EMR data)<br><br>USA | Women with a singleton delivery and their infants born in the University of Texas Medical Branch at Galveston; only charts of women with 4 or more prenatal care visits and delivery at >27 weeks of age included in the review.<br><br>75.3% of women (835/1109) received Tdap vaccine between 27 and 36 weeks gestation; 65% of Group 1 also received influenza vaccine.<br><br>Group 1 (Tdap): n=1109<br><br>Group 2 (non-Tdap): n=650 | <u>Group 1:</u><br>• Chorioamnionitis: 3.5% (39)<br>• Postpartum endometritis: 0.8% (9)<br>• Preterm premature rupture of membranes: 3.2% (36)<br>• Preterm delivery: 5.2% (58)<br>• Low birth weight (<2500g): 5.5% (61)<br>• Very low birth weight (<1500g): 0.2% (2)<br>• SGA (<10th percentile): 4.2% (46)<br><br>• Apgar score at 5 min of life <8: 1.3% (14)<br>• Birth defects: 1.6% (18)<br>• NICU admission: 9.3% (103)<br>• Days in NICU: 11.5±12.6<br>• Admission to NICU as a result of preterm birth: 48.5% (50)<br>• Admission to NICU as a result of anemia: 9.7% (10)<br>• Any infant outcome: 14.3% (159)<br><br><u>Group 2:</u><br>• Chorioamnionitis: 2.2% (14)<br>• Postpartum endometritis: 0.8% (5)<br>• Preterm premature rupture of membranes: 2.9% (19)<br>• Preterm delivery: 9.1% (59)<br>• Low birth weight (<2500g): 9.1% (59)<br>• Very low birth weight (<1500g): 1.8% (12)<br>• SGA (<10th percentile): 4.8% (31)<br>• Apgar score at 5 min of life <8: 1.5% (10)<br>• Birth defect: 2.3% (15)<br>• NICU admission: 13.2% (86)<br>• Days in NICU: 23.9±31.1<br>• Admission to NICU as a result of preterm birth: 64% (55)<br>• Admission to NICU as a result of anemia: 20.9% (18)<br>• Any infant outcome: 18.9% (123)<br><br>Authors did not find any significant differences in frequency of birth defects, chorioamnionitis or combined infant outcomes by maternal vaccination status. Only statistical differences found by authors were in the lower rate of NICU admission, particularly due to preterm birth | II-2 | Fair, Study included women with adequate prenatal care. |

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| | | | | and anemia, in Group 1 (p<0.05). | | |
| **Hema Datwani, Pedro L. Moro, Theresa Harrington, Karen R. Broder.** Chorioamnionitis following vaccination in the Vaccine Adverse Event Reporting System. *Vaccine.* 2015. 33:3110 | Adacel<br><br>Boostrix | Observational, retrospective analysis of the VAERS data from July 1990 to February 2014<br><br>USA | Pregnant women who received Tdap with or without other vaccines | In total, 8 reports of choriomanionitis were identified of which 5 (16.1%) for Tdap only and 3 (9.6%) for Tdap provided concomitantly with TIV or HPV4 vaccines | II-2 | Fair, VAERS: -a |
| **DeSilva M., Vazquez Benitez G., Nordin J.D., Lipkind H.S., Klein N.P., Cheetham T.C., Naleway A.L., Hambidge S.J., Lee G.M., Jackson M.L., McCarthy N.L., Kharbanda, E. O..** Maternal Tdap vaccination and risk of infant morbidity. Vaccine. 2017. 35:3655 | Tdap | Retrospective observation study of VSD data reported from January 1, 2010 to November 15, 2013 (7 sites); analysis specific for determining the risk of chorioamnionitis and associated complications post Tdap immunization<br><br>USA | Analysis of 197,564 singleton live births<br><br>Group 1: Received Tdap in pregnancy (n=45,008)<br><br>Group 2: Did not receive Tdap in pregnancy (n=152,556)<br><br>Analysis included women who were continuously insured from 6 months prior to their last menstrual period through 6 weeks postpartum, with 1 outpatient visit during pregnancy. | Maternal Tdap administrated **at any time during pregnancy** (Group 1, n=45,008 vs Group 2, n=152,556):<br>Chorioamnionitis:<br>• Incidence rate (IR) (%): 6.41 (grp 1); 5.22 (Grp 2)<br>• Rate difference (RD) (/100 live births): 1.16 (0.9-1.42)<br>• Rate ratio: 1.23 (1.17-1.28)<br>Composite outcome:<br>• IR (%): 2.86 (Grp 1); 3.16 (Grp 2)<br>• RD (/100 live births): 0.11(-0.07-0.29)<br>• Rate ratio: 1.04 (0.98-1.11)<br>TTN:<br>• IR (%): 2.16 (Grp 1); 2.31 (Grp 2)<br>• RD (/100 live births): 0.07(-0.09-0.22)<br>• Rate ratio: 1.03 (0.96-1.11)<br>Neonatal sepsis:<br>• IR (%): 0.51 (Grp 1); 0.62 (Grp 2)<br>• RD (/100 live births): 0.03(-0.05-0.10)<br>• Rate ratio: 1.06 (0.91-1.23)<br>Pneumonia:<br>• IR (%): 0.16 (Grp 1); 0.24 (Grp 2)<br>• RD (/100 live births): 0.00(-0.04-0.04)<br>• Rate ratio: 0.94 (0.72-1.22)<br>Respiratory distress syndrome (RDS):<br>• IR (%): 0.11 (Grp 1); 0.14 (Grp 2)<br>• RD (/100 live births): -0.01(-0.05-0.03)<br>• Rate ratio: 0.91 (0.66-1.26)<br>Convulsions in newborn: | II-2 | Fair |

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| | | | | • IR (%): 0.15 (Grp 1); 0.17 (Grp 2)<br>• RD (/100 live births): 0.02(-0.02-0.06)<br>• Rate ratio: 1.16 (0.87-1.53)<br><br>Maternal Tdap administrated **during recommended time period of pregnancy, 27-36 weeks** (Group 1, n=22,772 vs Group 2, n=133,882):<br>Chorioamnionitis:<br>• IR (%): 6.28 (Grp 1); 5.31 (Grp 2)<br>• RD (/100 live births): 0.98 (0.65-1.32)<br>• Rate ratio: 1.20 (1.14-1.28)<br>Composite outcome:<br>• IR (%): 2.87 (Grp 1); 3.10 (Grp 2)<br>• RD (/100 live births): 0.13(-0.11-0.37)<br>• Rate ratio: 1.02 (0.94-1.12)<br>TTN:<br>• IR (%): 2.28 (Grp 1); 2029 (Grp 2)<br>• RD (/100 live births): 0.20(-0.02-0.41)<br>• Rate ratio: 1.08 (0.98-1.19)<br>Neonatal sepsis:<br>• IR (%): 0.44 (Grp 1); 0.59 (Grp 2)<br>• RD (/100 live births): -0.01(-0.11-0.08)<br>• Rate ratio: 0.90 (0.73-1.11)<br>Pneumonia:<br>• IR (%): 0.15 (Grp 1); 0.13 (Grp 2)<br>• RD (/100 live births):-0.01(-0.06-0.05)<br>• Rate ratio: 0.82 (0.57-1.17)<br>RDS:<br>• IR (%): 0.09 (Grp 1); 0.13 (Grp 2)<br>• RD (/100 live births):-0.02(-0.06-0.03)<br>• Rate ratio: 0.79 (0.50-1.26)<br>Convulsions in newborn:<br>• IR (%): 0.12 (Grp 1); 0.17 (Grp 2)<br>• RD (/100 live births):-0.01(-0.06-0.04)<br>• Rate ratio: 0.88 (0.58-1.31)<br><br>Maternal Tdap administrated **at any time during pregnancy, infants born <34 GWs** (Maternally vaccinated (Group 1, n=426 vs Group 2, n=2711): | | |

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| | | | | Chorioamnionitis:<br>• IR (%): 6.57 (Grp 1); 8.15 (Grp 2)<br>• RD (/100 live births):-1.02(-3.51-1.47)<br>• Rate ratio: 0.87 (0.59-1.30)<br>Composite outcome:<br>• IR (%): 24.41 (Grp 1); 25.64 (Grp 2)<br>• RD (/100 live births):0.18 (-4.20-4.57)<br>• Rate ratio: 1.02 (0.83-1.26)<br>TTN:<br>• IR (%): 11.97 (Grp 1); 10.73 (Grp 2)<br>• RD (/100 live births):0.84 (-2.48-4.15)<br>• Rate ratio: 1.07 (0.79-1.45)<br>Neonatal sepsis:<br>• IR (%): 11.27 (Grp 1); 11.73 (Grp 2)<br>• RD (/100 live births):0.85 (-2.22-3.93)<br>• Rate ratio: 1.11 (0.81-1.51)<br>Pneumonia:<br>• IR (%): 2.11 (Grp 1); 4.46 (Grp 2)<br>• RD (/100 live births):-0.95(-2.76-0.86)<br>• Rate ratio: 0.60 (0.30-1.19)<br>RDS:<br>• IR (%): 1.17 (Grp 1); 1.70 (Grp 2)<br>• RD (/100 live births):-0.26(-1.59-1.07)<br>• Rate ratio: 0.84 (0.33-2.14)<br>Convulsions in newborn:<br>• IR (%): 1.17 (Grp 1); 1.48 (Grp 2)<br>• RD (/100 live births):-0.12(-1.49-1.24)<br>• Rate ratio: 0.98 (0.38-2.50) | | |
| **Malini DeSilva, Gabriela Vazquez-Benitez, James D. Nordin, Heather S. Lipkind, Paul A. Romitti, Frank DeStefano, Elyse O. Kharbanda.** Tdap Vaccination During Pregnancy and | Adacel<br><br>Boostrix | Retrospective observation study of VSD data reported from January 1, 2007 through September 30, 2013 (7 sites); analysis specific for risk of microcephaly post Tdap | Analyses included 324,463 singleton live births.<br><br>Included infants with birth weight and gestational age data and to be enrolled in health insurance for 4 months or more during the first year of life, with 1 or more outpatient visit(s); | Maternal Tdap was not found to be significantly associated with increased risk for microcephaly for vaccinations occurring at less than 14 weeks' gestation (n = 3,321; APR, 0.96 [95% CI, 0.36-2.58]), between 27 and 36 weeks' gestation (n = 20,568; APR, 1.01 [95% CI, 0.63-1.61]), or during any week of pregnancy (n = 41,654; APR, 0.86 [95% CI, 0.60-1.24]). | II-2 | Fair, Potential limitations with the VSD surveillanc |

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| Microcephaly and Other Structural Birth Defects in Offspring. *JAMA.* 2016. 316:1823 | | immunization<br><br>USA | their mothers were required to be continuously insured from 6 months prior to their last menstrual period through 6 weeks postpartum, with 1 or more outpatient visit(s) during pregnancy. | | | e system include incomplete data on Tdap vaccinations, diagnosed structural birth defects and important covariates (including maternal alcohol use) as well non-inclusion of birth |

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| | | | | | | defects in loss or elective termination of pregnancy |
| **Katherine Donegan, Bridget King, Phil Bryan.** Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ.* 2014. 349:g4219 | Repavax, Sanofi | Observational, retrospective analysis of the Clinical Practice Research Datalink (CPRD) data reported between October 2012 and March 2013<br><br>UK | 17,560 pregnant women for whom at least 28 days of follow-up data after vaccination was available.<br><br>6,184 immunized women with data on pregnancy outcomes and gestational age; each matched (age and gestational month) to up to three historical unvaccinated controls | Within 2 weeks post vaccination, there were 7 reported stillbirths; the rate was similar (7.2) to the overall estimated (based on national statistical data) rate of stillbirths with an observed versus expected IRR of 0.97 (95% CI: 0.39-2.00).<br><br>In total, there were 12 recorded instances of stillbirth after vaccination; the calculated observed versus expected rate ratio was 0.85 (95% CI: 0.44, 1.61) and the conditional rate ratio (vaccinated versus unvaccinated women) was 0.85 (95% CI: 0.45-1.61).<br><br>There were 2 cases of neonatal death within a week after delivery, in addition to the 12 cases of stillbirth; the calculated observed versus expected rate ratio was 1.00 (95% CI: 0.20, 4.95).<br><br>No significant differences were found in the time to delivery in the vaccinated and unvaccinated cohorts (median gestation 40 weeks; HR 1.00, 95% CI: 0.97, 1.02).<br><br>There were no differences in median birth weight between the vaccinated and the matched unvaccinated cohort (P=0.81).<br><br>There were no records of placental abruption, vasa praevia, fetal distress, or child renal failure after | II-2 | Fair, No adjustment for smoking, alcohol and drug use, parity, socioeconomic status and use of medication |

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| | | | | vaccination. | | |
| **Elyse O. Kharbanda, Gabriela Vazquez-Benitez, Heather S. Lipkind, Nicola P. Klein, T. Craig Cheetham, Allison Naleway, Saad B. Omer, Simon J. Hambidge, Grace M. Lee, Michael L. Jackson, Natalie L. McCarthy, Frank DeStefano, James D. Nordin.** Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA. 2014. 312:1897 | Tdap | Observational, retrospective analysis of VSD data reported from January 2010 to November 2012 (2 California sites)<br><br>USA | Group 1: 26,229 women who received Tdap in pregnancy<br><br>Group 2: 97,265 women who did not receive Tdap in pregnancy<br><br>2,014 (7.7%) received Tdap during the first trimester, 10,935 (41.7%) received Tdap during the second trimester, and 13,280 (50.6%) received Tdap during the third trimester. | <u>Group 1:</u><br>• 6.1% diagnosed with chorioamnionitis<br>• 8.2% diagnosed with a hypertensive disorder prior to 20 weeks of gestation (immunization with Tdap prior to 20 weeks of gestation )<br>• 8.4% with SGA<br>• 6.3% preterm<br><br><u>Group 2:</u><br>• 5.5% diagnosed with chorioamnionitis<br>• 8% diagnosed with a hypertensive disorder prior to 20 weeks of gestation<br>• 8.3% with SGA<br>• 7.8% preterm<br><br>When adjusting for site, receipt of 1 or more other vaccines in pregnancy and the propensity score, the ARR for chorioamnionitis was 1.19 (95% CI, 1.13-1.26) and for hypertensive disorder prior to 20 weeks of gestation was 1.09 (95% CI, 0.99-1.20).<br><br>Median gestational week for women with and without chorioamnionitis was 28 weeks.<br><br>When adjusting for site, receipt of influenza vaccines and the propensity score, the RR for SGA (SGA,<10$^{th}$ percentile) birth was 1.00 (95% CI, 0.96-1.06) and HR for preterm delivery was 1.03 (95% CI, 0.97-1.09)<br><br>Compared to Group 2 women, the preterm delivery rate in Group 1 women vaccinated between 27 and 36 weeks' gestation was slightly lower (5.3% vs 7.8%), but statistically significant (adjusted HR=0.88; 95% CI, 0.80-0.95). | II-2 | Fair, Analysis limited only for those with continuing insurance coverage |
| **Layton, J. Bradley, Butler, Anne M., Li, Dongmei, Boggess, Kim A., Weber, David J., McGrath, Leah J.,** | Tdap | Administrative insurance claims (MarketScan Commercial) insurance claims | Group 1: 123,780 women immunized at 27 or more weeks gestation<br><br>Group 2: 25,037 women | Group 1 (95% CI):<br>• Preeclampsia/Eclampsia: 0.90 (0.87, 0.93)<br>• Premature rupture of membranes: 1.08 (1.05, 1.11)<br>• Chorioamnionitis: 1.14 (1.10, 1.18) | II-2 | Fair |

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| **Becker-Dreps, Sylvia.** Prenatal Tdap immunization and risk of maternal and newborn adverse events. Vaccine. 2017. 35:4072 | | databases for the years 2010–2014 | immunized at <27 weeks gestation<br><br>Group 3: 59,040 immunized postpartum (control)<br><br>Only women with singleton pregnancies included<br><br>Birth outcomes adjusted HR for Groups 1 and 2 was calculated relative to Group 3. | • Cesarean section: 0.93 (0.92, 0.94)<br>• Placental abruption: 0.82 (0.76, 0.89)<br>• Post-partum hemorrhage: 1.21 (1.17, 1.26)<br>• Neonatal jaundice 1.06 (1.04, 1.08)<br><br>Group 2 (95% CI):<br>• Preeclampsia/Eclampsia: 0.99 (0.93, 1.05)<br>• Premature rupture of membranes: 1.04 (0.99, 1.10)<br>• Chorioamnionitis: 1.23 (1.16, 1.31)<br>• Cesarean section: 0.97 (0.95, 0.98)<br>• Placental abruption: 0.93 (0.80, 1.07)<br>• Post-partum hemorrhage: 1.34 (1.25, 1.44)<br>• Seizures: 1.38 (1.08, 1.76)<br><br>No statistically significant increase in risk was found in Group 1 or Group 2 infants for: NICU admission, respiratory distress, pulmonary hypertension, encephalopathy or neonatal sepsis.<br><br>In a sensitivity analysis that included only women who received Tdap and influenza vaccines concomitantly, no association was found between maternal Tdap immunization and chorioamnionitis or post-partum hemorrhage. | | |
| **Kirsten Maertens, Raissa Nadege Cabore, Kris Huygen, Sandra Vermeiren, Niel Hens, Pierre Van Damme, Elke Leuridan.** Pertussis vaccination during pregnancy in Belgium: Follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age. | Boostrix<br><br>Infanrix-hexa | Non-randomized control trial<br><br>Belgium | Infants of healthy pregnant women from 5 hospitals in the province of Antwerp<br><br>Group 1: infants of 55 women who received Tdap at mean 28.6 weeks of gestation<br><br>Group 2: infants of 26 women who have not received any pertussis-containing vaccine for at least 10 years | The proportion of infants hospitalized until 16 months of age did not differ between both study groups (10.9% in Group 1 and 12.5% in Group 2; p = 0.838).<br><br>Reasons for hospitalization were: pneumonia at birth (1), child suspected of meningitis infection (1), rotavirus infection (1), removal of birthmark by esthetic surgery (1), dehydration (1) and febrile seizures (1). | II-2 | Fair, High observed drop-out rates |

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| *Vaccine.* 2016. 34:3613 | | | | | | |
| **Kirsten Maertens, Raissa Nadege Cabore, Kris Huygen, Niel Hens, Pierre Van Damme, Elke Leuridan**. Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study. *Vaccine.* 2016. 34:142 | Boostrix | Non-randomized control trial<br><br>Belgium | Infants of healthy pregnant women from 5 hospitals in the province of Antwerp<br><br>Group 1: infants of 55 women who received Tdap at mean 28.6 weeks of gestation<br><br>Group 2: infants of 26 women who have not received any pertussis-containing vaccine for at least 10 years | 8 SAEs requiring hospitalization for at least 1 hour were reported: seven in Group 1 and one in Group 2.<br><br>Reported SAEs included: 1 premature delivery, 1 fever at birth,1 hypoglycemia at birth, 1 pneumonia at birth, 2 infections requiring hospitalization at the age of 1 and 5 months, 1 episode of febrile seizures at the age of 2 months and 1 episode of extreme vomiting at the age of 5 months.<br><br>No congenital disorders were detected among the infants in the study. | II-2 | Fair, Representativeness of the control group |
| **Jamie L. Morgan, Sangameshwar R. Baggari, Donald D. McIntire, Jeanne S. Sheffield**. Pregnancy outcomes after antepartum tetanus, diphtheria, and acellular pertussis vaccination. *Obstetrics & Gynecology.* 2015. 125:1433 | Tdap | Observational, review of pregnancy outcomes using the Parkland Hospital database of pregnancy, delivery, and neonatal records<br><br>USA | Analysis included infants born to pregnant women who were offered Tdap immunization between June 2013 and July 2014.<br>Group 1: 7,152 infants of women who received Tdap at or after 32 weeks gestation.<br><br>Group 2: 226 infants of women who declined Tdap at or after 32 weeks gestation | <u>Group 1:</u><br>- Birth weight: 3,370+/-513g<br>- 6% preterm (≤36 weeks gestation)<br>- 10% SGA<br>- length of neonatal hospitalization: 3.9 +/-3<br><u>Group 2:</u><br>- Birth weight: 3,232+/-592g<br>- 12% preterm (≤36 weeks gestation)<br>- 15% SGA<br>- length of neonatal hospitalization: 4.7+/-6.2<br>Stillbirth rate, frequency of major malformations, incidence of chorioamnionitis, 5-minute Apgar scores, and cord blood pH values were not significantly different between the two groups.<br><br>Neonatal complications including ventilation requirement, sepsis, intraventricular hemorrhage, and neonatal death rates were also similar.<br><br>Significant difference between groups noted for preterm birth rate (p<0.001), SGA (SGA, <10th percentile) rate (p=0.32), and length of neonatal hospitalization (p<0.001)<br><br>Incidence of preterm birth after 32 weeks of gestation | II-2 | Fair, Analysis based only on data analysis in hospital EMRs |

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| | | | | remained significantly higher in Group 2 after adjusting for prenatal care attendance, race, age, parity, BMI, and 17α-OHP: OR=1.88 (95% CI 1.25–2.84).<br><br>A subgroup analysis of multiparous women who were administered at least two Tdap vaccines in the past 5 years (1,229) and those who received only a single dose (4,159) demonstrated comparable delivery and neonatal outcomes, including gestational age at delivery, stillbirth and major malformation rate, neonatal care admission, ventilation requirements, and incidence of neonatal death. | | |
| **Pedro L. Moro, Janet Cragan, Naomi Tepper, Yenlik Zheteyeva, Oidda Museru, Paige Lewis, Karen Broder.** Enhanced surveillance of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines in pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 2011-2015. *Vaccine.* 2016. 34:2349 | Adacel<br><br>Boostrix | Observational, retrospective analysis of data reported to VAERS between November 1, 2011 and June 30, 2015<br><br>USA | 392 reports identified in which Tdap was provided in pregnancy with or without other vaccines | 3.8% (15) reported on still birth or spontaneous abortion.<br><br>1% (4) on major birth defects (ectopic kidney in a newborn whose mother received Tdap at 17 weeks of gestation; left heart syndrome in an infant whose mother received Tdap early during the first trimester; trisomy 12 identified; and club foot)<br><br>2.8% (11) identified preterm birth and 3.1% (12) described oligohydroamnios | II-2 | Fair, Passive reporting system (potential issues with underreporting, reporting bias, and inconsistency in report quality) |
| **Helen Petousis-** | Boostrix | Observational, | 793 women with at least | Of 8 reported SAEs during labour and delivery: two were | II-2 | Fair, |

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| **Harris, Tony Walls, Donna Watson, Janine Paynter, Patricia Graham, Nikki Turner.** Safety of Tdap vaccine in pregnant women: an observational study. BMJ Open. 2016. 6:e010911 | | prospective study<br><br>New Zealand | one ultrasound early in pregnancy who received Tdap between 28 and 38 weeks gestation | perinatal deaths, one of which was due to a congenital abnormality, the other unexplained. There was one cyanotic episode and five cases where concern for fetal well-being resulted in health service intervention.<br><br>There were 9 pregnancies that ended preterm.<br><br>No SAEs considered by clinical review to be caused by Tdap vaccination | | Recall bias due to lack of diary in one group of participants |
| **Julie H. Shakib, Kent Korgenski, Xiaoming Sheng, Michael W. Varner, Andrew T. Pavia, Carrie L. Byington.** Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: pregnancy and infant health outcomes. *Journal of Pediatrics.* 2013. 163:1422 | Tdap | Observational, retrospective analysis of the Intermountain EMR database<br><br>USA | Analysis included data from May 2005 to August 2009.<br><br>Group 1: 138 women with documented Tdap during pregnancy<br><br>Group 2: 552 pregnant women with no documentation of Tdap vaccination | Majority of women (63%) received Tdap in the first trimester, 24 (17%) in the second and 27 (20%) in the third.<br><br><u>Group 1:</u><br>• 4 cases (2.9%; 95% CI 0.9-7.7%) with spontaneous or elective abortions<br>• No cases of stillbirth<br>• 8 cases (6.0%; 95% CI 2.8-11.8%) of preterm delivery (<37 weeks)<br>• 5 cases (3.7%; 95% CI 1.2%-8.5%) of congenital anomalies<br>• 62% (83/134) of infants with one health care encounter by 12 months of age; 3.6% (3/83) with complex chronic condition<br><br><u>Group 2:</u><br>• 49 (8.9%; 95% CI 6.7-11.6%) with spontaneous or elective abortions<br>• 5 cases of stillbirth<br>• 38 cases (7.5%; 95% CI 5.4-10.3%) of preterm delivery (<37 weeks)<br>• 22 cases (4.4%; 95% CI 2.7%-6.5%) of congenital anomalies | II-2 | Fair, Retrospective analysis of EMR data |

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| | | | | • 61% (307/505) of infants with one health care encounter by 12 months of age; 10% (32/307) with complex chronic condition<br><br>The incidence of spontaneous or elective abortion was no greater in Tdap cases than in controls. There were no significant differences in preterm delivery, gestational age, or birth weight between groups. | | |
| **Lakshmi Sukumaran, Natalie L. McCarthy, Elyse O. Kharbanda, Eric S. Weintraub, Gabriela Vazquez-Benitez, Michael M. McNeil, Rongxia Li, Nicola P. Klein, Simon J. Hambidge, Allison L. Naleway, Marlene M. Lugg, Michael L. Jackson, Jennifer P. King, Frank DeStefano, Saad B. Omer, Walter A. Orenstein.** Safety of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis and Influenza Vaccinations in Pregnancy. *Obstetrics & Gynecology.* 2015. 126:1069 | Adacel<br><br>Boostrix<br><br>Influenza | Observational, retrospective analysis (matched cohort design) of VSD data reported from January 1, 2007, through September 30, 2013 (7 sites)<br><br>USA | Group 1: 4,554 singleton infants of women who received Tdap and Influenza vaccine concomitantly<br><br>Group 2: 4,400 singleton infants of women who received Tdap and influenza vaccine sequentially | <u>Group 1:</u><br>• Preterm delivery: 7.3% (333)<br>• Low birth weight: 5.8% (266)<br>• SGA: 9.6% (439)<br><br><u>Group 2:</u><br>• Preterm delivery: 6.6% (295)<br>• Low birth weight: 5.7% (252)<br>• SGA: 9.7% (432)<br><br>There were no differences in the occurrence preterm delivery (defined as gestational age <37 weeks), low birth weight (LBW, birth weight <2500 grams), and SGA (SGA, <10th percentile for gestational age and sex) infants between groups.<br><br>When adjusted for gestational age at Tdap vaccination in weeks, VSD site, length of enrollment (months), prenatal care utilization index, maternal comorbidity, pregnancy complication, maternal age, seasonality of preterm delivery, Relative Risks (95% CI) and P-values were:<br>• Preterm delivery: 0.95(0.82 – 1.11); P=0.52<br>• Low birth weight: 0.92(0.78 – 1.09); P=0.34<br>• SGA: 1.01(0.88 – 1.15); P=0.92<br>No interaction between adverse birth outcomes and gestational age at time of Tdap vaccination was found. | II-2 | Fair, Only acute events in women who sought medical care were analyzed |
| **Lakshmi Sukumaran, Natalie L. McCarthy, Elyse O. Kharbanda, Michael M. McNeil, Allison L. Naleway,** | Adacel<br><br>Boostrix | Observational, retrospective analysis (matched cohort design) of VSD data reported | Analysis included infants born<br><br>Group 1: 3,313 singleton infants of women who | <u>Group 1:</u><br>• Preterm delivery occurred in 6.6% of women; Adjusted RR, 1.15 (95%CI, 0.98-1.34; P = .08)<br>• Low-birth weight delivery occurred in 4.7% of women; Adjusted RR, 1.10 (95%CI,0.92-1.32; P = .31) | II-2 | Fair, Medical charts |

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| **Nicola P. Klein, Michael L. Jackson, Simon J. Hambidge, Marlene M. Lugg, Rongxia Li, Eric S. Weintraub, Robert A. Bednarczyk, Jennifer P. King, Frank DeStefano, Walter A. Orenstein, Saad B.** Omer. Association of Tdap Vaccination With Acute Events and Adverse Birth Outcomes Among Pregnant Women With Prior Tetanus-Containing Immunizations. *JAMA.* 2015. 314:1581 | | from January 2007 to November 2013 (7 sites).<br><br>USA | received Tdap <2 years following prior tetanus containing vaccine<br><br>Group 2: 7,226 singleton infants of women who received Tdap 2 to 5 years following prior tetanus containing vaccine<br><br>Group 3 (control): 10,633 singleton infants of women who received Tdap >5 years following prior tetanus containing vaccine<br><br>The pregnancy outcomes of the final study cohort of 517,700 pregnancies were: live birth (71.7%), spontaneous abortion (14.8%), therapeutic abortion (13%) and stillbirth (0.4%).<br><br>Tdap was administered in 9.5% of pregnancies ending with live birth and 1.6% of spontaneous abortion (SAB), stillbirth (SB) or therapeutic abortion (TAB) pregnancies. | • SGA delivery occurred in 9.0% of women; Adjusted RR, 0.99 (95% CI, 0.87-1.13; P = .88)<br><br><u>Group 2:</u><br>• Preterm delivery occurred in 6.4% of women; Adjusted RR, 1.06 (95%CI, 0.94-1.19; P = .33)<br>• Low-birth weight delivery occurred in 4.7% of women; Adjusted RR, 1.03 (95%CI,0.89-1.18; P = .72)<br>• SGA delivery occurred in 8.7% of women; Adjusted RR, 0.96 (95% CI, 0.87-1.06; P = .45)<br><br><u>Group 3:</u><br>• Preterm delivery occurred in 6.8% of women<br>• Low-birth weight delivery occurred in 5.1 % of women<br>• SGA delivery occurred in 9.1% of women | | review to validate AEs was not conducted |
| **Wang M., Khromava A., Mahmood A., N. Dickson.** Pregnant women receiving tetanus-diphtheria-acellular pertussis (Tdap) vaccine: 6 Years of adacel vaccine | Adacel® (Sanofi) | Observational, retrospective analysis of the Sanofi Pasteur Adacel registry data reported between June 2005 and January 2011 | 539 reports of Adacel administration to women already pregnant or who became pregnant <30 days post-vaccination were identified. | 49 cases from phase IV studies and 490 spontaneous reports. In 98 cases, women received one other vaccine or Tuberculin skin test.<br><br>In phase IV studies, there were 20% (10) SAEs and 10% (5) AEs; among spontaneous reports, there were 29 SAEs and 41AEs – all unspecified. | II-2 | Fair, Poster abstract |

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| pregnancy registry data. Pharmacoepidemiology and drug safety. 2011. 20:S60 | | | | From reports for which information was available, in total there were 10 preterm deliveries, 18 spontaneous abortions and one case of one-sided hydronephrosis. | | |
| **Ousseny Zerbo, Berwick Chan, Kristin Goddard, Ned Lewis, Karin Bok, Nicola P. Klein, Roger Baxter**. Kaiser Permanente Northern California pregnancy database: Description and proof of concept study. *Vaccine.* 2016. 34:5519 | Tdap<br><br>DTaP-HBV-IPV, Pediatrix, GSK | Observational, retrospective review of EMR data<br><br>Proof of concept study - use of Kaiser Permanente Northern California (KPNC) database to evaluate AE outcomes (fever after receipt of the first dose of DTaP vaccine) in infants born to mothers immunized with Tdap in pregnancy<br><br>USA | 148,699 singleton infants of women ≥18 years of age born at ≥37 weeks of age who received their first dose of DTaP vaccine between 6 and 10 weeks of age<br><br>Tdap received any time from the 14th week of pregnancy<br><br>First dose of DTaP received at 6 to 10 weeks of age<br><br>Group 1 (Tdap): n=65,751<br><br>Group 2 (non-Tdap): n=82,948 | <u>Group 1:</u><br>Frequency of fever 0-3 days post DTaP: 1.2% (816)<br><br><u>Group 2:</u><br>Frequency of fever 0-3 days post DTaP: 1.4% (1189)<br><br>After adjusting for child's age at vaccination, year of birth, maternal age at child's birth, gestational diabetes, type of insurance, smoking status during pregnancy and race, maternal Tdap vaccination was not significantly associated with infant fever (aOR = 0.92, 95% CI 0.82–1.04). | II-2 | Fair, limited to only infant fever that were reported, reasons for fevers not defined. |
| **Yenlik A. Zheteyeva, Pedro L. Moro, Naomi K. Tepper, Sonja A. Rasmussen, Faith E. Barash, Natalia V. Revzina, Dmitry Kissin, Paige W. Lewis, Xin Yue, Penina Haber, Jerome I. Tokars, Claudia Vellozzi, Karen R. Broder.** Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis | Adacel<br><br>Boostrix | Observational, retrospective analysis of data reported to VAERS between January 1, 2005 and June 30, 2010<br><br>USA | 132 reports identified in which Tdap was provided in pregnancy | 41.7% (55) did not describe any AE and were submitted because Tdap was administered at a time period when it was not routinely recommended.<br><br>With 22 reports, spontaneous abortion was the most commonly reported AE (median gestational age was 9 weeks and the median onset interval from vaccination was 33 days) followed by 7 reports of gestational diabetes.<br><br>2 stillbirth cases were reported: one due to placental abruption at 37 weeks gestation in which Tdap was administered several hours before and the second at 22 weeks gestation, 46 days after exposure to Tdap.<br><br>6 AEs were reported in infants, including gastroschsis, laryngomalacia, patent foramen ovale, mild physiologic | II-2 | Fair, Data obtained through a passive AE reporting system |

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| vaccines in pregnant women. American Journal of Obstetrics & Gynecology. 2012. 207:59.e1 | | | | jaundice, transient tachypnea and bilateral hydroceles.<br><br>3 normal preterm pregnancies were reported. | | |
| **Klein NP, Hansen J, Lewis E, Lyon L, Nguyen B, Black S, Weston WM, Wu S, Li P, Howe B, Friedland LR.** Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a United States health maintenance organization. Pediatr Infect Dis J. 2010 Jul;29(7):613-7. doi: 10.1097/INF.0b013e3181d581f9 | Boostrix | Open, prospective, observational study<br><br>USA | N= 13,427 10 to 18-year-old adolescents enrolled in the Northern California Kaiser Permanente Health Care Plan and receiving Tdap | Three pregnancies reported in Tdap recipients:<br>-One miscarriage at 8 weeks gestation. The miscarriage was not considered to be related to vaccination.<br>-Other 2 pregnancies resulted in normal healthy offspring. | II-2 | Poor |
| **Tony Walls, Patricia Graham, Helen Petousis-Harris, Linda Hill, Nicola Austin**. Infant outcomes after exposure to Tdap vaccine in pregnancy: an observational study. *BMJ Open.* 2016. 6:e009536 | Boostrix | Observational, prospective study<br><br>New Zealand | Infants of 403 women (408 infants) with at least one ultrasound early in pregnancy who received Tdap between 28 and 38 weeks gestation<br><br>Women whose fetus had congenital anomalies, severe structural and/or chromosomal abnormalities identified during prenatal screening were excluded from the study. | 385 infants followed up delivered at term (94%); 23 (6%) infants were born at less than 37 weeks gestation. One infant weighing <1500 g and eight infants between 1500 and 2500 g.<br><br>10 infants (2.5%) identified as having medical events of significance or congenital anomalies. One infant was stillborn (0.2%) with no congenital abnormalities identified.<br><br>A total of 303 infants completed their 6-week check and 278 completed their 5-month check. All Z-scores for weight were all normally distributed. | II-2 | Poor, Inability to detect less common AE |

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| **Acosta J., Benages C., Diaz M.A., Xiberta M., F. Muniz**. Preventing pertussis in the early infant: Development and results of a prenatal vaccination program. *Acta Medica International.* 2016. 3:78 | Tdap | Observational, review of Hospital General de Catalonia chart data from 2011 to 2015 | Group 1: 9 infants less than 3 months of age with confirmed B. pertussis infection<br><br>Group 2: 54 individuals with confirmed B. pertussis infection | All cases in Group 1 required hospitalization and had a longer duration of hospitalization compared to Group 2 (10.2 days vs. 0.36 days; p<0,05).<br><br>Comparison of birth outcomes of infants born to vaccinated vs. non vaccinated mothers did not show statistically significant differences for: duration of pregnancy (279 days vs. 278 days; p>0,05), weight at birth (3290 vs. 3220; p>0,05), admission at NICU (1,58% vs. 1,87%; p>0,05) and Apgar test score<7 at 5 minutes (0,27% vs. 0%; p>0,05). | III | Poor |
| **Talbot EA, Brown KH, Kirkland KB, Baughman AL, Halperin SA, Broder KR.** The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine. 2010 Nov 23;28(50):8001-7. doi: 10.1016/j.vaccine.2010.09.034. | Adacel | Observational Study<br><br>USA | 16 unintentionally immunized pregnant health care workers | No adverse outcomes in babies | III | Poor |
| **Judy Amy, Anuja Singh, Henry Lee, Shabnam Gaskari, Laura Brodzinsky, Jamie Vik, Maurice Druzin, Yasser El-** | Tdap | Retrospective, observational study<br><br>USA | Group 1: 877 women who received Tdap antepartum<br><br>Group 2: 837 women who received Tdap postpartum | Demographic characteristics such as race, maternal age, primary payor, and gestational diabetes differed between the AP and PP TDaP cohorts (p < 0.0001).<br><br>The rate of preterm delivery <32 weeks of gestation was higher in Group 2 (4.0% vs. 2.0%, p=0.02). | Poster | N/A |

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| **Sayed, Natali Aziz,** TDaP vaccination safety in pregnancy: a comparison of neonatal and obstetric outcomes among women receiving antepartum and postpartum vaccination[61] | | | Neonatal Composite: Apgar < 7 at 5 minutes, neonatal sepsis, very low birth weight, NICU admission, prolonged length of stay<br><br>Obstetric Composite: Preterm premature rupture of membranes, preterm labor, chorioamnionitis, endometritis, gestational age < 37weeks | Rates of major and minor congenital anomalies, neonatal sepsis, and maternal infectious outcomes similar between cohorts; no cases of intrauterine fetal demise<br><br>After controlling for any baseline characteristics with bivariate analysis, women in Group 1 did not demonstrate increased risk ($p < 0.1$) of major anomalies, neonatal composite outcome, or obstetric composite outcome in the multivariate model.<br><br>There were 12 cases (1.4%) of endometritis in Group 1 vs 4 cases (0.5%) in Group 2; $p=0.055$. | | |

**Table 7: Summary of evidence related to the effectiveness of maternal Tdap against infant pertussis**

| **Evidence related to effectiveness of Tdap acellular pertussis vaccine in pregnancy to protect infants** | | | | | | |
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| **STUDY DETAILS** | | | | | **SUMMARY** | |
| **Study** | **Vaccine** | **Study Design** | **Participants** | **Summary of Key Findings Using Text or Data** | **Level of Evidence** | **Quality of Evidence** |
| **Gayatri Amirthalingam, Helen Campbell, Sonia Ribeiro, Norman K. Fry, Mary Ramsay, Elizabeth Miller, Nick Andrews**. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. *Clinical Infectious Diseases.* 2016. 63:S236 | Repavax | Effectiveness was calculated using the data from the Clinical Practice Research Datalink (CPRD)<br><br>UK | 243 infants aged <93 days for whom maternal immunization data was available | <u>Infants prior to primary DTaP series:</u><br><br>• VE of 91% (95% confidence interval [CI], 88%–94%) was calculated for infants <3 months of age. VE for infants <2 months of age (with an average matched coverage of 64.3%) was 90% (95% CI, 86%–93%); recalculation of VE assuming a relative reduction of 20% in vaccine coverage provided a VE of 82% (95% CI, 74%–88%).<br>• VE against death was calculated at 95% (95% CI, 79%–100%), consistent with the overall VE against disease of 91%.<br><br><u>Infants subsequent to primary DTaP series:</u><br><br>• A total of 73 children born after week 40 of 2012 received a childhood vaccine. The mothers of 26 children received Tdap. Of the 73 children, 43 received 1 dose, 12 had received 2 doses, and 18 had received 3 doses of their primary pertussis vaccines.<br>• VE for infants who received 1 dose: 82% [95% CI, 65%–91%]; for infants who received 2 doses: 69% (95% CI, 8%–90%); for infants following the completion of the primary infant schedule point estimate remained above 0%.<br>• With lower VE estimates, the effect of a 20% relative risk reduction was greater, declining from 69% to 43% for infants who received 2 doses of DTaP. | II-2 | Good |
| **Gayatri Amirthalingam, Nick** | Repavax | Effectiveness was calculated using the | 82 cases for which maternal immunization | Total number of cases:<br>Infants less than 1 month of age: | II-2 | Good |

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| **Andrews, Helen Campbell, Sonia Ribeiro, Edna Kara, Katherine Donegan, Norman K. Fry, Elizabeth Miller, Mary Ramsay**. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet.* 2014. 384:1521 | | data from the Clinical Practice Research Datalink (CPRD)<br><br>UK | status was available, Tdap | 2011: 16<br>2012: 43<br>2013: 10<br>Infants 1 month of age:<br>2011: 57<br>2012: 161<br>2013: 37<br>In infants 2 month of age:<br>2011: 25<br>2012: 73<br>2013: 18<br><br>VE in infants younger than 3 months was estimated at 91% (95% CI: 84-95). Vaccine effectiveness was similar (90%) when the analysis was restricted to infants younger than 2 months. -When coverage data using the levels seen nationally outside CPRD practices (49% vs. 62%) was calculated, VE fell to 84% (95% CI: 71-93).<br><br>Total number of hospitalizations:<br>Infants less than 1 month of age:<br>2011: 25<br>2012: 73<br>2013: 18<br>Infants 1 month of age:<br>2011: 99<br>2012: 209<br>2013: 68<br>Infants 2 month of age:<br>2011: 59<br>2012: 158<br>2013: 54<br><br>No fall in hospital admissions was reported in any age groups aged 3 months or older in 2013 compared with 2011.<br><br>In 2012, there were 14 deaths in infants with confirmed pertussis, all of whom were born before the maternal program was introduced. In 2013, there were three | | |

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| | | | | pertussis-related deaths in infants whose mothers were not vaccinated in pregnancy. All fatalities in 2012 and 2013 were in infants too young to be protected by vaccine (age 2–9 weeks at disease onset or sample date). | | |
| **Baxter, Roger, Bartlett, Joan, Fireman, Bruce, Lewis, Edwin,Klein, Nicola P.** Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis. Pediatrics. 2017. 139(5) doi: 10.1542/peds.2016-4091 | Tdap | Retrospective cohort study of infants born at Kaiser Permanente Northern California(KPNC) from 2010 to 2015 | 148, 981 infants born in KPNC hospitals from 2010 to 2015<br><br>All mothers received whole cell vaccine for their primary series. | • VE (first 2 months): 91.4% (95% [CI], 19.5 to 99.1).<br>• VE (entire 1st year): 69.0% (95% CI, 43.6 to 82.9)<br>• VE (before any infant dose): 87.9% (95% CI, 41.4 to 97.5)<br>• VE (between doses 1 and 2): 81.4% (95% CI, 42.5 to 94.0)<br>• VE (between doses 2 and 3): 6.4% (95% CI, −165.1 to 66.9)<br>• VE (after dose 3): 65.9% (95% CI, 4.5 to 87.8) | II-2 | Good |
| **Winter K, Nickell S, Powell M, Harriman K**. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. Clin Infect Dis. 2017 Jan 1;64(1):3-8. PubMed PMID: 27624955 | Tdap | Observational, retrospective analysis of California Department of Public Health (CDPH) and California Immunization Registry (CAIR) data<br><br>US | 74 504 mothers (7.5%) of California birth 2013-14 cohort: 42 941 (58%) were vaccinated during pregnancy and 31 563 (42%) post-partum.<br><br>Among Tdap vaccinated women, 77% received Tdap at 27–36 weeks gestation, 14% vaccinated prior to 27 weeks gestation and 9% vaccinated after 36 weeks gestation | In the cohort, pertussis was reported in 25 infants ≤ 8 weeks of age and 35 infants ≤12 weeks of age.<br><br>The overall VE of Tdap vaccination at 27–36 weeks gestation was 85% (95% CI, 33%–98%) for preventing pertussis in infants <8 weeks of age and 72% (30%–89%) for preventing it in infants ≤12 weeks of age.<br><br>VE of Tdap at any point during the pregnancy was 64% (95% CI, 11%–85%) for preventing pertussis in infants <8 weeks of age and 53% (8%–76%) for preventing it in infants ≤12 weeks of age.<br><br>Among 15 case patients ≤12 weeks of age whose mothers were vaccinated during pregnancy, only 6 (40%) were vaccinated at 27–36 weeks gestation. Infants whose mothers were vaccinated during the second trimester were significantly more likely to have pertussis at age <8 weeks (OR, 8.1; 95% CI, 1.3–49.0) or ≤12 weeks (4.6; 1.39–15.25), when controlling for the age of the mother, number of prior births, and preterm birth.<br><br>Infants whose mothers received Tdap early in the third trimester (27–31 weeks gestation) had lower odds of pertussis at <8 (0.96, 95% CI: 0.74-1.25) or ≤12 (0.92, | II-2 | Good |

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| | | | | 95% CI: 0.79-1.07) weeks of age than infants whose mothers received Tdap vaccine at 32–36 weeks gestation. | | |
| **Kathleen Winter, James D. Cherry, Kathleen Harriman**. Effectiveness of Prenatal Tetanus, Diphtheria, and Acellular Pertussis Vaccination on Pertussis Severity in Infants. *Clinical Infectious Diseases.* 2016 | Tdap | Observational, retrospective analysis of California Department of Public Health (CDPH) and California Immunization Registry (CAIR) data<br><br>US | Maternal immunization status and outcomes were evaluated in infants with pertussis onset occurring at <63 days of age and born from 1 January 2011 through 31 December 2015.<br><br>Group 1: 49 infants whose mothers received Tdap in pregnancy<br><br>Group 2: 371 infants whose mothers did not receive Tdap in pregnancy | 76% (37) of mothers in Group 1 received Tdap during their third trimester of pregnancy.<br><br>Infants in Group 1 were older when they developed pertussis<br>(P = .03) and less likely to have the classic pertussis symptoms of paroxysmal cough (RR, 0.41; 95% CI, .25–.68), apnea (0.66; .47–.91), cyanosis (0.53; .39–.73), or whoop (0.78; .62–.99); frequency of posttussive vomiting was similar between groups.<br><br>Infants in Group 1 had significantly lower risk of hospitalization (RR, 0.5; 95% CI, .4–.6) or ICU admission (0.8; .7–.9). Among hospitalized infants, those in Group 1 had shorter hospitalization stays (median 3 vs 6 days; P = .02). No infants in Group 1 had seizures, required intubation, or died.<br><br>After adjustment for infant's chronological and gestational age, infants in Group 1 remained to have significantly lower risk for hospitalization (OR, 0.4; 95% CI, .2–.9) or ICU admission (OR, 0.5; 95% CI, .2–1.2).<br><br>The overall VE for preventing hospitalization among infants with pertussis was 72% (95% CI, 49%–85%); after adjustment for the infant's chronological and gestational age and receipt of DTaP vaccine, it was 58% (15%–80%). | II-2 | Good, Complete maternal Tdap immunization |
| **Gavin Dabrera, Gayatri Amirthalingam, Nick Andrews, Helen Campbell, Sonia Ribeiro, Edna Kara, Norman K. Fry, Mary Ramsay**. A case-control study to estimate the effectiveness of | Repavax | Unmatched case-control study<br><br>UK | Group 1: 58 infants aged <8 weeks at disease onset, who were positive by PCR at the national reference laboratory or culture confirmed<br><br>Group 2: 55 infants <8 weeks of age known not to have a clinical or microbiological diagnosis of | In Group 1, mothers of 10 infants (17%) had been vaccinated during pregnancy. In Group 2, 39 mothers of 55 controls (71%) had been vaccinated during pregnancy.<br><br>The unadjusted OR for vaccination in pregnancy was 0.09 (95% CI, .03–.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%).<br><br>Data on length of hospital stay were available for 47 | II-2 | Fair |

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| maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. *Clinical Infectious Diseases.* 2015. 60:333 | | | pertussis | cases. The median length of hospital stay was 4 days (range, 0–6 days) for 8 cases in Group 1 and 3.5 days (range, 0–63 days) for 39 cases in Group 2. There was no statistically significant difference between these 2 groups in terms of length of hospital stay, according to the rank-sum test (P = .58). | | |
| **Bellido-Blasco, Juan, Guiral-Rodrigo, Silvia, Miguez-Santiyan, Ana, Salazar-Cifre, Antonio, Gonzalez-Moran, Francisco.** A case-control study to assess the effectiveness of pertussis vaccination during pregnancy on newborns, Valencian community, Spain, 1 March 2015 to 29 February 2016. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin. 2017. | Tdap | A prospective matched case–control study; data collected for Spain | Data collected one year after the implementation of a regional (Valencian Community of approximately 5 million inhabitants) maternal Tdap immunization program<br><br>VE calculation was based on 22 cases (real-time PCR confirmed) and 66 controls; 18 of 22 cases were hospitalized.<br><br>Mothers of five cases (23%) and of 41 controls (62%) were vaccinated during pregnancy. | Adjusted VE of maternal Tdap vaccination in preventing pertussis in infants less than 3 months of age was estimated to be 90.9% (95% CI: 56.6, 98.1). | II-2 | Poor |
| **Carla Vizzotti, Maria V. Juarez, Eduardo Bergel, Viviana Romanin, Gloria Califano, Sandra Sagradini, Carolina Rancano, Analia Aquino, Romina Libster, Fernando P. Polack, Juan Manzur**. Impact of a maternal immunization program | Tdap | Program effectiveness was estimated through a retrospective national health surveillance system (SNVS) analysis (clinical and laboratory modules). Analysis was performed in cases | Population based<br><br>Maternal program started in February of 2012, reaching 51% coverage in the first year and 63% coverage in the second year (2013); wP vaccine used for primary immunization. | - Cases and incidence in infants less than 12 months of age (/100,000):<br>2010: 854; 112.9<br>2011: 2,355; 311.4<br>2012: 1,510; 199.7<br>2013: 895; 118.4<br><br>- Number of deaths (national), infants less than 12 months of age:<br>2010: 16<br>2011: 76<br>2012: 32 | II-3 | Poor, Individual data on vaccination status not available |

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| against pertussis in a developing country. *Vaccine.* 2016.<br><br>**Vizzotti C, Neyro S, Katz N, Juárez MV, Perez Carrega ME, Aquino A, Kaski Fullone F.** Maternal immunization in Argentina: A storyline from the prospective of a middle income country. Vaccine. 2015 Nov 25;33(47):6413-9. doi: 10.1016/j.vaccine.2015.07.109. Review. PubMed PMID: 26277071 | | (patients with suspected illness and B. pertussis isolation in culture and/or amplification of B. pertussis-specific DNA by PCR and/or serology by antipertussis toxin IgG, or in patients with symptoms and epidemiologically linked to a laboratory-confirmed case) that were identified between January 2010 and December 2013.<br><br>Argentina | | 2013: 10<br><br><u>All cases</u>: In areas with maternal Tdap coverage was <50%, a second disease peak was observed in 2012 (twice the incidence rate compared to areas with >50% coverage); however, in 2013, the number of cases was approximately 7 times lower in these areas compared to areas with >50% coverage.<br><br><u>Infants 0-2 months of age</u>: At all times after 2012, there were fewer cases in states with higher (>50%) vs. lower (<50%) coverage. | | (not possible to estimate VE) |