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REVIEW

Safety of Maternal Immunization Against Pertussis: A Systematic Review

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Abstract: The WHO recommends vaccination of all children against pertussis. However, newborn infants remain vulnerable to infection. Pertussis vaccination during pregnancy has been introduced in several countries to protect newborns via transplacental transfer of maternal pertussis antibodies to the infant. We reviewed the impact of maternal pertussis vaccination on the health of pregnant women, the developing fetus, and health of the newborn. We searched PubMed/MEDLINE, EMBASE, Scopus (Elsevier), Cochrane Database of Systematic Reviews, ProQuest, and Science Direct to identify studies that assessed the safety of maternal pertussis vaccination. Twenty-seven English language publications published between January 1995 and December 2018 were included in this review. Pregnant women receiving pertussis vaccines did not have increased rates of systemic or local reactions. There were no safety concerns with repeat vaccination with other tetanus-containing vaccines or their concomitant administration with influenza vaccines. Maternal pertussis vaccination did not adversely affect pregnancy, birth or neonatal outcomes. This review confirms the safety of maternal pertussis vaccination during pregnancy.
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PLAIN LANGUAGE SUMMARY

Newborn infants are particularly vulnerable to whooping cough in the first few months after birth. When women are vaccinated against whooping cough during pregnancy, their antibodies are transferred to the fetus, which protects the newborn infant from the disease. We summarized the published evidence of the safety of maternal immunization against whooping cough, both for the mother and infant. We found that vaccination against whooping cough was safe for both mothers and their newborn infants. Pregnant women were no more likely than non-pregnant women to experience injection site reactions or whole-body effects. There were no negative effects on the pregnancy, birth or the infant. Vaccination of pregnant women can be recommended for

protection of vulnerable infants during their first weeks of life.

INTRODUCTION

Pertussis affects individuals of all ages but is especially concerning in infants, who account for most of the hospitalizations and deaths associated with the disease [1]. A modeling study based on World Health Organization (WHO) data from 2014 estimated that 24.1 million cases and 160,700 deaths could be attributed to pertussis among children aged < 5 years. Of these, 5.1 million (21%) cases and 85,900 (53%) deaths occurred in infants aged < 1 year [2].

To reduce pertussis-related morbidity and mortality in infants and young children, the WHO recommends acellular pertussis (aP) or whole-cell pertussis (wP) vaccination for all infants, with the primary immunization series initiated at 6 weeks, and no later than 8 weeks of age [3]. However, infants are particularly susceptible to pertussis infection from multiple sources during the period between birth and start of their primary immunization series [4–7]. Studies have consistently documented high incidence rates and significant mortality in young infants [8–11]. For example, in the USA, the incidence of pertussis was 117.7/100,000 person-years in infants aged < 1 year between 2005 and 2010, with the highest rate in those aged 2 or 3 months (235.3/100,000 person-years or 247.7/100,000 person-years, respectively) [8]. Elsewhere, pertussis-related deaths were estimated to be 0.6 per 100,000 maternities for infants aged < 66 days in England during 2001 and 2011 [11]. The WHO does not currently recommend vaccination against pertussis before 6 weeks of age due to paucity of data on efficacy and safety, and lack of stand-alone aP vaccine [3, 12]. Risk-management through cocooning, where close contacts of the infants are vaccinated, has had limited success [3].

Maternal immunization during pregnancy, taking advantage of transplacental transfer of pertussis antibodies [1, 3, 12], was proposed to indirectly protect neonates against pertussis. This strategy achieves high pertussis antibody concentrations in infants [13], and is 64–93% effective in preventing disease among infants aged < 2 months [14–21]. Moreover, breakthrough disease among infants whose mothers were vaccinated during pregnancy was less severe than those born to unvaccinated mothers [22]. The WHO also suggests that vaccination of pregnant women is likely to be the most effective and cost-effective strategy for disease prevention in infants too young to be vaccinated [3].

Some patients and healthcare providers are hesitant to or do not vaccinate during pregnancy because of perceived (vaccine) safety [23–25]. Other barriers to vaccination during pregnancy from the patient and healthcare perspective include negative media, missed vaccination opportunity (immunization not offered or requested), lack of vaccine stock, inadequate reimbursement, and limited patient interest [26–31]. Evidence-based educational programs that emphasize vaccine safety during pregnancy and protection against disease in infancy help support vaccine confidence and recommendations. To capture supporting evidence, we conducted a systematic review of the safety of maternal pertussis vaccination (Tdap and Tdap-IPV vaccines) during pregnancy.

METHODS

Studies assessing pertussis vaccination during pregnancy were identified from a systematic search of PubMed/MEDLINE, EMBASE, Scopus (Elsevier), Cochrane Database of Systematic Reviews, ProQuest, and Science Direct. We also scanned the reference lists of identified publications and searched ProQuest thesis, Clinicaltrials.gov, relevant conference and congress abstracts, and the Trial Trove database. The protocol for this systematic review was registered on PROSPERO (PROSPERO 2016:CRD42016038317) [32].

Our initial search was restricted to English language publications between January 1995 and June 2016. Further searches were performed to capture relevant studies published between July 2016 and October 2018. We used a combination of keywords that included the

following: [1]: [(pertussis OR whooping cough) AND (vaccine OR Tdap OR immunization) AND (pregnancy OR pregnant OR pre-partum OR gestation OR maternal)], [2]: [1] AND (safety OR adverse event OR adverse reaction OR congenital abnormalities OR congenital disorder OR congenital malformation OR birth defects OR teratogens OR teratogenic agent OR teratogenicity OR pregnancy outcome OR pregnancy termination OR congenital anomaly OR developmental disorder OR adverse birth outcome).

PICOS (Patient Population or Problem, Intervention [treatment/test], Comparison [group or treatment], Outcomes, and Setting) criteria [33] were applied while considering interventional and observational studies in humans. Pregnant women and their offspring constituted the studied population. The intervention was pertussis immunization during pregnancy and the infant series of vaccination. Comparison groups were either no vaccination or standard of care vaccination, as well as pregnancy or no pregnancy. Outcomes reviewed were qualitative (nature, severity) and quantitative characterization of adverse events {number, frequencies, and relative measures [e.g. odds ratios (OR) and relative risk (RR)]} in pregnant women (including but not limited to local reactions and fever), in fetuses (including but not limited to spontaneous abortion, stillbirth, premature birth, birth weight, fetal growth, congenital malformation), and in infants prior to the first dose of primary immunization.

Reviews, meta-analyses, case reports, opinion pieces, letters to editors, and modeling studies were excluded. We also excluded studies on vaccination program improvement, vaccine uptake, vaccine acceptability and perception studies, and health economics studies.

A two-step process involving two independent reviewers at each step was employed to select studies for inclusion in the review. The first step included scanning titles and abstracts of retrieved references to select publications based on their relevance to our review. Publications of primary research studies reporting the safety of pre-partum pertussis vaccination were retained for full-text review. The second step consisted of a full-text review of the article to assess whether the report met the inclusion and exclusion criteria. Pre-structured MS Excel forms were used to extract relevant data from the included studies. Multiple factors including heterogeneity in study designs, vaccines used, outcomes measured, measurement/analysis methods, and the background pertussis incidence precluded a meta-analysis of the safety findings of the included studies.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

A total of 335 articles were identified from the comprehensive search criteria, of which 27 articles (summarized in Table 1) were included in this review (Fig. 1).

Vaccine Reactogenicity in Pregnant Women

Fifteen studies reported vaccine reactogenicity among pregnant women following immunization with Tdap or Tdap-IPV, among which nine were prospective clinical trials [13, 34–41] and six were database analyses [42–47] (Table 1). The most commonly reported reactions were injection site reactions, consistent with the Tdap label. While injection site reactions such as pain/tenderness, induration/swelling, itching, and erythema/redness were reported after Tdap/Tdap-IPV administration in most clinical studies, pregnancy was not considered to have increased the rates of these events [13, 34, 36–38, 40]. However, moderate-to-severe injection site pain was more frequent in pregnant women than nonpregnant women in one study [34]. Injection site reactions assessed over 7 days were more common after Tdap than placebo in one small clinical study [13] but occurred at similar rates over 48 h in another slightly larger study [40]. Systemic and local reactions occurred at similar frequencies in pregnant women receiving Tdap and those receiving tetanus vaccines in two clinical studies [35, 36].

Table 1 Characteristics and results of the reviewed studies

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Retrospective database reviews						
Berenson et al. [50]	Chart review [EMR of PW delivering at the University of Texas Medical Branch at Galveston, Galveston County, USA]	Nov 2012–Jun 2014	PW—singleton birth at ≥ 27 GW and adequate prenatal care	Tdap (n = 1109)[a] Tdap 27–36 GW (n = 835)[a] No Tdap (n = 650)[a]	Database analysis of PW	**Maternal adverse events and adverse fetal outcomes pre-delivery:** No significant differences in frequency of individual or combined maternal outcomes[b] for Tdap vs. no Tdap; including chorioamnionitis (aOR = 1.53 [95% CI 0.80–2.90]; p = 0.19) **Adverse birth and neonatal outcomes:** No significant differences in frequency of individual or combined neonatal outcomes[c] for Tdap vs. no Tdap Defects[c] were rare and frequency not significantly different for Tdap vs. no Tdap For infants admitted to NICU, number of days in the unit (p = 0.001) and frequency of admission for preterm birth (p = 0.03) or anemia (p = 0.03) lower for Tdap vs. no Tdap
Moro et al. [44]	Database review [VAERS database, USA vs. older published safety data]	Oct 2011–Jun 2015 (database) (vs. Jan 2005–Jun 2010 [published data])	Tdap PW with reported AEs following Tdap	Tdap at 0–13 GW (8.7%), 14–27 GW (12.0%) or ≥ 28 GW (79.2%); following ACIP recommendations for Tdap in PW (n = 392)[a] Tdap (Adacel, Sanofi Pasteur [59.7%], Boostrix, GSK [33.2%], unknown [7.1%]) (vs. Tdap in first [77%], second [19%] or third trimester [4%] before recommendations [n = 132][a])	Database analysis of PW reporting AEs (vs. published safety data)	**Reactogenicity:** Most frequently: ISRs (11.9%), systemic reactions (e.g., fever, chills; 4.3%), musculoskeletal and connective tissue disorders (3.6%), and immune system disorders (e.g., allergic reactions; 3.6%) **Maternal adverse events and adverse fetal outcomes pre-delivery:** Most frequently: oligohydramnios (3.1%), stillbirth (2.8%), and preterm delivery (2.8%), spontaneous abortion (1.0%) **Adverse birth and neonatal outcomes:** Death (n = 1), major birth defect (n = 4; 1.0%) **Other:** Proportion of stillbirths (2.8% vs. 1.5%) and ISRs (11.9% vs. 4.5%) increased and spontaneous abortions decreased (16.7% vs. 1.0%) after vs. before ACIP recommendations

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Kharbanda et al. [42]	Cohort database review [Claims, administrative and EHR data from 7 VSD sites in the USA[f] and EHR-linked vaccine registries]	Delivery Jan 2007–Nov 2013	PW with live birth (gestational trophoblastic disease, ectopic pregnancy, abortion, stillbirth, or unknown pregnancy outcome)	Tdap during pregnancy (any trimester) (n = 53,885) Tdap ≥ 20 GW (n = 44,063) No Tdap (n = 109,253)	Database analysis	**Reactogenicity:** Rate of any event[d] 0–3 days (ARR = 1.19 [95% CI 0.81–1.73]) or any neurological event[e] 0–42 days (ARR = 0.98 [95% CI 0.70–1.37]) similar after Tdap vs. no Tdap (all events rate < 0.1%) Rate of medical visits for fever within 3 days increased with Tdap vs. no Tdap (ARR = 5.4 [95% CI 2.1–13.9]) **Maternal adverse events:** Rate of proteinuria (ARR = 0.81 [95% CI 0.6–1.05]) or VTE (ARR = 0.65 [95% CI 0.40–1.05]) similar after Tdap vs. no Tdap (rate for both < 0.1%) Rate of gestational diabetes (ARR = 0.96 [95% CI 0.89–1.03]), thrombocytopenia (ARR = 0.85 [95% CI 0.73–0.98]), VTE (ARR = 0.58 [95% CI 0.35–0.97]), cardiac events (ARR = 0.90 [95% CI 0.70–1.15]) not increased by Tdap ≥ 20 GW vs. no Tdap
Sukumaran et al. [46]	Cohort database review [Claims, administrative and EHR data from 7 VSD sites in the USA[f] and EHR-linked vaccine registries]	Delivery Jan 2007–Nov 2013	Tdap PW, aged 14–49 y, with prior tetanus-containing vaccine data, singleton livebirth (live or non-Tdap tetanus-containing vaccine during pregnancy, trophoblastic disease, abortion, stillbirth, or ectopic pregnancy)	Tdap during pregnancy with < 2 y prior tetanus-containing vaccine (n = 4812) Tdap during pregnancy with 2–5 y prior tetanus-containing vaccine (n = 9999) Tdap during pregnancy with > 5 y prior tetanus-containing vaccine (n = 14,344)	Database analysis	**Reactogenicity:** Acute fever 0–3 days after Tdap: 0–3.5/10,000 PW in each group; 0–7 days after Tdap: 1.0–6.2/10,000 PW in each group Allergic reaction 0–3 days after Tdap: 1.0–2.1/10,000 PW; 0–7 days after Tdap: 3.5–4.2/10,000 PW Local reaction 0–3 days after Tdap: 4.2–11.2/10,000 PW; 0–7 days after Tdap: 12.5–17.0/10,000 PW Fever, allergic reactions, or local reactions not significantly different in PW who received tetanus-containing vaccine < 2 y vs. > 5 y or 2–5 y vs. > 5 y No reports of anaphylaxis, Arthus reactions, or Guillain–Barré syndrome **Maternal adverse events, adverse fetal outcomes pre-delivery, birth and neonatal outcomes:** Preterm delivery (≈ 6.5%), low birth weight (≈ 5%), SGA (≈ 9%) not significantly different in infants of PW who received tetanus-containing vaccine < 2 y vs. > 5 y or 2–5 y vs. > 5 y **Other:** Most PW who had received a tetanus-containing vaccine < 2 y (94%) or 2–5 y (85%) previously had received Tdap vs. only 17% of the > 5 y group

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Sukumaran et al. [45]	Cohort database review [Claims, administrative and EHR data from 7 VSD sites in the USA[f] and EHR-linked vaccine registries]	Jan 2007–Nov 2013	PW aged 14–49 y, singleton livebirth, Tdap and influenza vaccine during pregnancy (any live vaccines in pregnancy, multiple gestations, trophoblastic disease, abortion, stillbirth, or ectopic pregnancy, > 1 tetanus vaccine or similar influenza vaccine in pregnancy)	Tdap 20–37 GW + influenza vaccine concomitantly during pregnancy (any trimester) (n = 8464) Tdap 20–37 GW + influenza vaccine sequentially during pregnancy (any trimester) (n = 28,380)	Database analysis	**Reactogenicity:** Frequency of medically attended fever (< 4.5/10,000) and any acute reaction (< 25.5/10,000) (0–3 days and 0 –7 days) did not differ between PW receiving Tdap and influenza vaccines concomitantly vs. sequentially ($p > 0.3$) There were no cases of Arthus reaction or Guillain–Barré Syndrome There was no interaction between acute AEs and GW at Tdap vaccination **Maternal adverse events, adverse fetal outcomes pre-delivery, birth and neonatal outcomes (N = 4554 vs. 4440):** Preterm delivery (≈ 7%), low birth weight (≈ 6%), SGA (≈ 10%) not significantly different in infants of PW who received Tdap and influenza vaccine concomitantly vs. sequentially ($p > 0.3$) There was no interaction between adverse birth outcomes and GW at Tdap vaccination
Datwani et al. [51]	Database review [VAERS database, USA]	Jul 1990–Feb 2014	PW with chorioamnionitis	Any vaccine during pregnancy (including Tdap) (n = 31)	Database analysis	**Maternal adverse events and adverse fetal outcomes pre-delivery:** *Chorioamnionitis*: Vaccines most frequently documented in reports of chorioamnionitis were inactivated vaccines (90%), most commonly 2009 H1N1 inactivated influenza (32%), quadrivalent human papillomavirus (29%), and Tdap (26%) In 58% of reports, PW had ≥ 1 risk factor for chorioamnionitis Additional adverse outcomes specified but association with specific vaccine not reported **Adverse birth and neonatal outcomes:** Adverse outcomes specified but association with specific vaccine not reported

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Wang et al. [57]	Registry review [Sanofi Pasteur Adacel Pregnancy Registry]	Jun 2005–Jan 2011	PW receiving Adacel during or < 30 days before pregnancy	Tdap (Adacel, Sanofi Pasteur) (n = 539)[a]: Phase IV studies (n = 49) Prospective reports (n = 480) Retrospective reports (n = 10)	Database analysis	**Maternal events:** Phase IV studies: 10% non-serious AEs, 20% SAEs, 69% no AEs Prospective reports: 7% non-serious AEs, 6% SAEs, 55% no AEs, 33% NR Retrospective reports: 20% SAEs, 80% no AEs **Maternal adverse events, adverse fetal outcomes pre-delivery, birth and neonatal outcomes:** Phase IV studies: 86% term delivery, 4% preterm delivery, 4% elective abortion, 2% spontaneous abortion, and 4% lost to follow-up 43 infants with no congenital anomaly, 1 with right-side hydronephrosis Prospective reports: 19% term delivery, 2% preterm delivery, < 1% very preterm delivery with no congenital abnormality, < 1% elective abortion, 3% spontaneous abortion, 26% lost to follow-up, 50% awaiting pregnancy outcome Retrospective reports: 80% term delivery, 20% spontaneous abortion 7 infants no congenital abnormality, 1 infant with patent foramen ovale and peripheral pulmonic stenosis **Other:** Data raise no concerns for maternal or infant health following Tdap during pregnancy

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Morgan et al. [55]	Cohort database review [EPIC electronic medical charting system at Parkland hospital and affiliated clinics, Texas, USA]	Jun 2013–Jul 2014	PW	Tdap ≥ 32 GW (n = 7152) No Tdap (n = 226) Prior Tdap (< 5 y) + Tdap ≥ 32 GW (n = 1229) Tdap ≥ 32 GW (single dose) (n = 4159)	Database analysis	**Maternal adverse events and adverse fetal outcomes pre-delivery:** Frequency of stillbirths and *chorioamnionitis* for Tdap vs. no Tdap not significantly different Preterm birth rates increased with no Tdap vs. Tdap (AOR = 1.88 [95% CI 1.25–2.84]) **Adverse birth and neonatal outcomes:** Frequency of major malformations, 5-min Apgar score < 4, cord blood pH ≤ 7, and neonatal requirement for ventilation, intraventricular hemorrhage, sepsis, and death for Tdap vs. no Tdap not significantly different Frequency of SGA (10% vs. 15%, p = 0.03) and length of neonatal hospitalization (3.9 says vs. 4.7 days, p < 0.001) lower for Tdap vs. no Tdap Delivery and neonatal outcomes[g] not significant different between women who received multiple doses of Tdap vs. those who received a single dose
Donegan et al. [53]	Cohort database review [Clinical Practice Research Datalink data from > 650 primary care practices in the UK]	Oct 2012–Mar 2013	PW	Any pertussis-containing vaccine 30–36 GW (n = 6185) No vaccine (HC) (n = 18,523)	Database analysis + comparison with published national data	**Maternal adverse events and adverse fetal outcomes pre-delivery:** Frequency of stillbirth, preeclampsia, eclampsia, placenta previa, cesarean section, premature labor (without delivery), postpartum hemorrhage not significantly different between Tdap and no Tdap Observed stillbirth rate in 17,560 vaccinated PW vs. expected stillbirth rate in published national statistics data ratio: 0.69 (95% CI 0.23–1.62) **Adverse birth and neonatal outcomes:** Intrauterine growth retardation/low birth weight/weight < 2500 g and neonatal death (within 7 days) not significantly different between Tdap and no Tdap

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Kharbanda et al. [54]	Cohort database review [Administrative and EHR data from 2 Kaiser Permanente VSD sites (Northern and Southern California), USA]	Delivery Jan 2010–Nov 2012	PW aged 14–49 y, singleton livebirth (≥ 1 live vaccine during pregnancy; Tdap, ≤ 7 days after estimated pregnancy start or ≤ 7 days before delivery)	Tdap (Adacel in majority) during pregnancy (n = 26,229)[a] Second + third trimester (92%) No Tdap (n = 97,265)[a] Tdap before pregnancy (46%)	Database analysis	**Maternal adverse events and adverse fetal outcomes pre-delivery:** *Chorioamnionitis:* 6.1% vs. 5.5% for Tdap vs. no Tdap; ARR = 1.19 (95% CI 1.13–1.26; $p < 0.001$) Tdap at 27–36 GW vs. no Tdap ARR = 1.11 (95% CI 1.03–1.21; $p = 0.009$) *Hypertensive disorder of pregnancy:* 8.2% vs. 8.0% for Tdap < 20 GW vs. no Tdap; ARR = 1.09 (95% CI 0.99–1.20) *Preterm delivery (< 37 GW):* Tdap at any time during pregnancy not associated with increased risk of preterm delivery (ARR = 1.03 [95% CI 0.97–1.09) Tdap at 27–36 GW vs. no Tdap ARR = 0.88 (95% CI 0.80–0.95; $p = 0.002$) **Adverse birth and neonatal outcomes:** Tdap at any time during pregnancy not associated with increased risk of SGA (ARR = 1.00 [95% CI 0.96–1.06) Tdap at 27–36 GW vs. no Tdap ARR = 1.03 (95% CI 0.96–1.10)
Shakib et al. [56]	Cohort database review [EHR of Intermountain Healthcare Enterprise Data Warehouse, USA]	May 2005–Aug 2009	PW	Tdap during pregnancy (n = 138) First trimester (63%), second trimester (17%), third trimester (20%) No Tdap (n = 552)	Database analysis	**Maternal adverse events and adverse fetal outcomes pre-delivery:** Spontaneous or elective abortion: 2.9% vs. 8.9% for Tdap vs. no Tdap Stillbirth: 0 vs. 0.9% for Tdap vs. no Tdap Preterm live birth (< 37 GW): 6.0% vs. 7.5% for Tdap vs. no Tdap No significant differences between Tdap and no Tdap **Adverse birth and neonatal outcomes:** No increased risk of congenital abnormalities or additional health problems in the first year of life for infants of Tdap PW vs. no Tdap PW

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Zheteyeva et al. [47]	Database review [VAERS database, USA]	Jan 2005–Jun 2010	PW who received Tdap during pregnancy with or without adverse events	Tdap (Adacel, Sanofi Pasteur [72%], Boostrix, GSK [15.2%], unknown [12.9%]) during pregnancy (any trimester)[a] (n = 132) First trimester (77%)	Database analysis	**Reactogenicity:** ISRs in 4.5% of reports **Maternal adverse events and adverse fetal outcomes pre-delivery:** Most frequently reported: spontaneous abortion (16.7%) at 5–16 GW, 9–61 days after Tdap Stillbirth in 2 reports and preterm delivery in 3 reports **Adverse birth and neonatal outcomes:** Isolated adverse infant outcomes in 4.5% of reports; major birth defect reported in 1 infant (gastroschisis) **Other:** No unusual pattern of adverse maternal, birth or neonatal outcomes reported
Layton et al. [43]	Database review [Truven MarketScan® Commercial Claims and Encounters insurance claims database]	2010–2014	PW with singleton livebirth or stillbirth born > 26 GW + infants	Tdap ≥ 27 GW (n = 123,780)[a] Tdap < 27GW (n = 25,037)[a] Tdap ≤ 7 days postpartum (n = 59,040)[a] No Tdap (n = 871,117)[a] Matched newborns (n = 677,075)[a]	Database analysis	**Reactogenicity:** Uncommon; most frequently local pain (24.22 per 10,000 PW); appeared least common with Tdap ≥ 27 GW Fever reported in 6.2 per 10,000 PW **Maternal adverse events and adverse fetal outcomes pre-delivery:** Placental abruption, premature rupture of membranes, caesarian section, preeclampsia/eclampsia generally similar between Tdap ≥ 27 GW vs. no Tdap in PW *Chorioamnionitis:* IPTW-weighted risks: 2.8%–3.6% Tdap ≥ 27 GW vs. no Tdap: RR = 1.11 (95% CI 1.07–1.15) Tdap < 27 GW vs. no Tdap: RR = 1.19 (95% CI 1.11–1.28) *Postpartum hemorrhage:* IPTW-weighted risks: 2.3%–3.1% Tdap ≥ 27 GW vs. no Tdap: RR = 1.23 (95% CI 1.18–1.28) Tdap < 27 GW vs. no Tdap: RR = 1.34 (95% CI 1.25–1.44) **Adverse birth and neonatal outcomes:** No increased risk of adverse neonatal outcomes with Tdap at ≥ 27 GW or < 27 GW vs. no Tdap

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
De Silva et al. [52]	Database review [Administrative and EHR data from 7 VSD sites in California, Colorado, Minnesota, Oregon, Washington and Wisconsin, USA]	Jan 2010–Sep 2013	PW with singleton livebirth, ≥ 1 outpatient visit during pregnancy, (Tdap < 8 days after pregnancy start or < 8 days before delivery, live vaccine)	Tdap during pregnancy (n = 45,008)[a] Tdap 27–36 GW (n = 22,772)[a] No Tdap (n = 152,556)[a]	Database analysis	**Maternal adverse events and adverse fetal outcomes pre-delivery:** *Chorioamnionitis*: Tdap vs. no Tdap in PW: 6.4% vs. 5.2%; ARR = 1.23 (95% CI 1.17–1.28) Tdap 27–36 GW vs. no Tdap in PW: 6.3% vs. 5.3%; ARR = 1.20 (95% CI 1.14–1.28) **Adverse birth and neonatal outcomes:** Transient tachypnea of newborn, neonatal sepsis, neonatal pneumonia, respiratory distress syndrome, newborn convulsions, or the composite of any of these outcomes similar between Tdap vs. no Tdap in PW and Tdap 27–36 GW vs. no Tdap in PW
Becerra-Culqui et al. [59]	Cohort database review [Kaiser Permanente Southern California hospitals, USA]	Delivery Jan 2011–Dec 2014	PW with natural conception and singleton livebirth at 22–45 GW	Tdap (Adacel, Sanofi Pasteur) during pregnancy (interquartile range 26–33 GW) (n = 39,077) No Tdap (n = 42,916)	Database analysis with 1.2–6.5 y of follow-up data	**Adverse birth and neonatal outcomes:** Autism spectrum disorder: incidence rate of 3.78/1000 person-y in children of vaccinated PW vs. 4.05/1000 person-y in children of unvaccinated PW; aHR 0.85 (95% CI: 0.77–0.95)

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Griffin et al. [48]	Cohort database review [National Health Index (NHI) Database including all pregnant women in New Zealand]	2013	PW with live or stillbirth ≥ 20 GW in 2013 (birthweight < 400 g, missing maternal or gestational age, live births < 28 GW, not eligible for Tdap at 28–38 GW in 2013)	Tdap 28–38 GW (Boostrix, GSK) (n = 8178)[a] No Tdap (n = 60,372)[a]	Database analysis	**Maternal adverse events and adverse fetal outcomes pre-delivery:** Gestational hypertension, preeclampsia, intrauterine growth retardation, postpartum hemorrhage, gestational diabetes mellitus, chorioamnionitis, placental abruption, premature rupture of membranes, fetal distress, maternal fever before or after labor, anemia during pregnancy and purpura, maternal neurologic disorders similar between Tdap vs. no Tdap (aHR = 0.85–1.10 across outcomes) Tdap associated with reduced risk of pre-eclampsia with severe features (aHR = 0.61; 95% CI 0.39–0.94), preterm labor (0.32; 0.17–0.62) and delivery (0.72; 0.63–0.83), antenatal bleeding (0.61; 0.49–0.78) Tdap associated with increased risk of hospitalization for lactation disorders (1.63, 1.15–2.33) *Chorioamnionitis:* Tdap vs. no Tdap: aHR = 1.10 (95% CI 0.70–1.75) *Postpartum hemorrhage:* Tdap vs. no Tdap: aHR = 1.05 (95% CI 0.96–1.15) One maternal death (no Tdap group); insufficient cases of eclampsia and stillbirth in Tdap group for analysis
Sukumaran et al. [60]	Case–control database review [VSD data from Kaiser Permanente Northern California, Southern California, Colorado and Northwest, and Marshfield Clinic Research Foundation hospitals, USA]	Delivery Jan 2004–June 2014	PW enrolled at a VSD site with ≥ 1 prenatal care visit; their infants enrolled until age 6 mo or death (live vaccine during pregnancy, multiple gestation, birth at < 34 GW, infant with major birth defects or death during delivery) Matched controls for outcomes of interest	25,222 cases of hospitalized infants, 25,222 matched controls; 157 infants died, 157 matched controls Tdap and/or influenza vaccine No Tdap and/or influenza vaccine	Conditional logistic regression analysis to estimate odds of maternal vaccination in matched cases and controls	**Risk of hospitalization:** aOR for Tdap: 0.94 (95% CI 0.88–1.01; p = 0.09) aOR for Tdap or influenza vaccine: 0.97 (95% CI 0.90–1.05; p = 0.44) **Risk of death:** aOR for Tdap: 0.44 (95% CI 0.17–1.13; p = 0.09) aOR for Tdap or influenza vaccine: 0.32 (95% CI 0.08–1.24; p = 0.10)
Prospective studies						

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Munoz et al. [13]	Randomized, double-blind, placebo-controlled [NIH VTEU sites in the USA (n = 3: Houston, Durham, Seattle)]	Oct 2008–May 2012	PW aged 18–45 y Non-PW age-matched to PW (previous Tdap or any tetanus-containing vaccine within the prior 2 y, high risk for obstetric complications)	PW: Tdap (Adacel, Sanofi Pasteur) at 30–32 GW Infants: DTaP-IPV-Hib (Pentacel) at 2, 4, 6, 12 mo (33 PW and infants) PW: Placebo (Tdap [Adacel] postpartum) Infants: DTaP-IPV-Hib (Pentacel) at 2, 4, 6, 12 mo (15 PW and infants) Non-PW: Tdap (Adacel) (n = 32)	AE monitoring in clinical trial (infants for up to 13 mo)	**Reactogenicity:** Frequency of any ISR after Tdap was not different for PW (78.8% [95% CI 61.1–91.0]), postpartum women (80.0% [95% CI 51.9–95.7]) and nonpregnant women (78.1% [95% CI 60.0–90.7]) ($p > 0.99$) but was lower after placebo (PW: 20.0% [95% CI 4.3–48.1]; postpartum women: 18.2% [95% CI 7.0–35.5]); usually mild and resolved within 72 h Most frequently: local pain (> 70% per group; $p = 0.94$); swelling and erythema infrequent (< 13% per group; $p > 0.3$) Frequency of any systemic symptom after Tdap was not significantly different for PW (36.4% [95% CI 20.4–54.9]), postpartum women (73.3% [95% CI 44.9–92.2]) or in nonpregnant women (53.1% (95% CI 34.7–70.9%]) ($p = 0.055$); usually mild and self-limiting Frequency of fever after Tdap was higher in postpartum women (26.7% [95% CI 7.8–55.1]) than PW (3.0% [95% CI 0.1–15.8]) or nonpregnant women (9.4% [95% CI 2.0–25.0]) ($p = 0.04$) but was similar in postpartum women receiving Tdap vs. placebo (15.2% [95% CI 5.1–31.9]; $p = 0.43$) and in Tdap PW and Tdap nonpregnant women ($p = 0.36$) Frequencies of headache, myalgia, and malaise not significantly different between groups ($p \geq 0.35$); headache was most frequent (33.3% and 46.7% for PW and postpartum women, respectively) **Maternal adverse events and adverse fetal outcomes pre-delivery:** None attributed to Tdap **Birth and neonatal outcomes:** All live born, mostly at term and by vaginal delivery No significant differences in gestational ages, birth weights, Apgar scores, neonatal examinations, complications, growth or development

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Regan et al. [39]	Cohort [Telephone survey of PW receiving Tdap and/or TIV in Western Australia, Australia]	Apr 2015–Jun 2015	PW	Tdap (Adacel, Sanofi Pasteur [76.9%], Boostrix, GSK [23%], unknown [0.1%]) second/third trimester (n = 1257) TIV any trimester (no Tdap) (n = 1584) Tdap third trimester + TIV any trimester (n = 1506)	Telephone survey of PW receiving Tdap and/or TIV	**Reactogenicity:** Frequency of any reaction, fever, rigors, fatigue, vomiting, malaise, myalgia, or medically attended events similar in PW receiving Tdap, TIV, or Tdap + TIV ($p > 0.1$) Frequency of ISRs (Tdap: 7.1%, TIV: 3.2%, Tdap + TIV: 5.4%; $p < 0.001$ for Tdap vs. TIV, $p = 0.002$ for Tdap + TIV vs. TIV), rash (0.9%, 0.3%, 0.3%; $p = 0.03$, 1.00), headache (2.8%, 4.3%, 3.9%; $p = 0.03$, 0.58), and congestion (2.9%, 4.3%, 3.1%, $p = 0.04$, 0.07) significantly different for Tdap vs. TIV Any maternal AE after Tdap in 2015 more frequent in PW who had also received Tdap in 2011–2012 (13/70; 18.6%) than those who had not (291/2693; 10.8%; $p = 0.04$; OR = 1.88 [95% CI 1.02–3.48])[h] **Adverse birth and neonatal outcomes:** All women who had delivered at follow-up had a healthy infant
Hoang et al. [36]	Randomized, controlled [Ha Nam province (3 villages), Northern Vietnam]	Delivery Feb 2013–Oct 2013	PW	PW: Tdap (Adacel, Sanofi Pasteur, Canada) 18–36 GW (n = 52) Infants: DTaP-IPV-Hib-HepB (Infanrix hexa, GSK) at age 2, 3, 4 mo Tetanus vaccine (IVAC, Vietnam) (n = 51) Infants: DTaP-IPV-Hib-HepB (Infanrix hexa, GSK) at age 2, 3, 4 mo	AE monitoring in clinical trial	**Reactogenicity:** 23 PW experienced ≥ 1 solicited AE after Tdap (mean duration, 1.3 days) and 22 PW experienced ≥ 1 solicited AE after tetanus vaccine (mean duration, 1.2 days) Most common adverse events were stiffness, swelling and injection site itching Serious AEs reported with Tdap: fever (n = 1) and fatigue (n = 1) **Maternal adverse events and adverse fetal outcomes pre-delivery:** Premature contractions > 1 mo after Tdap (n = 2) or tetanus vaccine (n = 1) **Adverse birth and neonatal outcomes:** No AEs related to vaccination reported

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Maertens et al. [37]	Controlled cohort [Five hospitals in Antwerp, Belgium]	Feb 2012–Sep 2014	PW with healthy livebirths, no pertussis-containing vaccine for ≥ 10 y	Tdap (Boostrix, GSK) mean 28.6 GW (PW: 57, infants (Infanrix hexa, GSK): 55) No Tdap (PW: 42, infants: 26)	AE monitoring in clinical trial	**Reactogenicity:** Adverse events, mostly mild and self-limiting, reported by 46 PW after Tdap Most frequent AEs were injection site stiffness (N = 42) and minor injection site swelling; fever reported in 1 PW after Tdap (1.75%) **Maternal adverse events and adverse fetal outcomes pre-delivery:** Of the 11 serious AEs[i] in PW receiving Tdap, none related to Tdap Three SAE reported in PW not receiving Tdap **Adverse birth and neonatal outcomes:** Serious AEs requiring infant hospitalization reported after Tdap (n = 7) and no Tdap (n = 1)[j] No congenital disorders detected
Petousis-Harris et al. [38]	Observational, cohort [Primary care and antenatal centers in North Island (3 District Health Boards) or South Island (Canterbury) of New Zealand]	North Island: Jan 2014–Jun 2014 South Island: Sep 2012–Jun 2014	PW with ≥ 1 ultrasound during pregnancy, adequate prenatal care, ± TIV	Tdap (Boostrix, GSK) at 28–38 GW (n = 793)[k]	Active AE monitoring for up to 4 weeks after vaccination	**Reactogenicity:** Most frequent ISR was pain (mild-moderate: 78.9%, severe: 2.6%); swelling (7.6%) and erythema (5.8%) uncommon and resolved in < 48 h in ≈ 50% of cases Systemic events were fever (2.1%), headache/dizziness (3.9%), nausea/vomiting (2.8%), fatigue (8.4%) and myalgia/arthralgia (3.0%) **Maternal adverse events and adverse fetal outcomes pre-delivery:** SAEs in 31 PW (3.9%), 23 resulting in hospitalization (obstetric bleeding [4], hypertension [2], infection [4], tachycardia [1], preterm labor [9], exacerbation of pre-existing condition [2], preeclampsia [1]) **Adverse birth and neonatal outcomes:** Two perinatal deaths (congenital abnormality [1], unexplained [1])
Walls et al. [58]	Observational, cohort [Canterbury region of New Zealand]	Sep 2012–Nov 2014	PW with ≥ 1 ultrasound during early pregnancy, adequate prenatal care, ± TIV (fetus with congenital/severe structural/chromosomal abnormalities during prenatal screening)	Tdap (Boostrix, GSK) 28–38 GW (403 PW + 408 infants: 345 followed for 12 mo, 63 followed for 6–12 mo)[a]	Maternal reports and healthcare provider information prospectively collected	**Birth and neonatal outcomes:** 94% delivered at term; 6% delivered pre-term (< 37 GW) Isolated medically significant events in 10 infants (2.5%); 1 stillborn (reason unknown despite postmortem) No evidence of increase in any adverse neonatal/infant outcome vs. baseline population rates

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Villarreal Pérez et al. [40]	Randomized, double-blind, parallel group, placebo-controlled [12 outpatient health centers of the Nuevo Leon Health Services, Mexico]	Sep 2011–Aug 2014	PW aged 18–38 y, low obstetric risk, normal anatomical ultrasound in second trimester(psychiatric or severe physical disease, drug or tobacco use, history of severe reactions to any vaccine or febrile illness in the 72 h prior to vaccination, immunization against tetanus and/or pertussis < 2 y previously)	Tdap at 30–32 GW (90 PW + infants) Placebo (81 PW + infants)	AE monitoring in clinical trial	**Reactogenicity:** Uncommon, AEs reported in 41% of PW with Tdap and 31% with placebo in first 24 h; most frequently local reactions that had resolved by 48 h Most common within 24 h: mild local pain; similar with Tdap vs. placebo (22% vs. 21%)
Fortner et al. [34]	Observational, cohort [Two CDC-funded CISA centers (Vanderbilt University Medical Center, Duke University Health System), USA]	Jul 2014–Jul 2015	PW aged 18–45 y with singleton pregnancy and Tdap vaccination at 20–33 GW Controls: non-PW aged 18–45 y	Tdap (Adacel or Boostrix) 20–33 GW (374 PW) Tdap (Adacel or Boostrix) (225 non-PW)	Active AE monitoring for up to 4 weeks after vaccination	**Reactogenicity:** Local symptoms in PW vs. non-PW: moderate/severe pain (17.9% vs. 11.1%), tenderness (19.0% vs. 16.9%), swelling/induration (5.6% vs. 5.8%), erythema (5.6% vs. 5.3%); each event severe in < 2% of PW and < 3.5% of non-PW Moderate/severe pain was more common in PW than non-PW Systemic symptoms in PW vs. non-PW: moderate/severe fever (0.5% vs. 2.2%), feverishness (3.2% vs. 4.0%), malaise (10.4% vs. 4.9%), body aches/myalgias (7.8% vs. 5.3%), headaches (7.2% vs. 8.9%); each event severe in < 1% of PW and < 2.5% of non-PW No woman required medical care for any reaction Moderate/severe and severe local and systemic reactions not affected by previous Tdap vaccination

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Halperin et al. [35]	Randomized, single-blind, parallel group, Td-controlled [Centers in Canada (Halifax, Montreal, Ottawa, Calgary, Edmonton, Vancouver)]	Nov 2007–Jun 2011 and Mar 2012–Apr 2014	Healthy PW aged 18–45 y at ≥ 30 GW, with low risk for complications (history of significant medical disorder, receipt of high-dose systemic corticosteroids or, in previous 5 y, pertussis or previous Td/Tdap or, within 3 mo, blood products or immunoglobulin, except rhesus immunoglobulin or, within 2 weeks, any vaccine, except influenza, or sensitivity to any component of Td or Tdap)	Tdap (Adacel, Sanofi Pasteur) ≥ 30 GW (n = 135) Td ≥ 30 GW (n = 138)	AE monitoring for 8 days after vaccination; infant developmental testing (Bayley-III Scales of Infant and Toddler Development) at age 18 mo	**Reactogenicity:** Injection site pain in > 80% of both groups; predominantly mild Erythema, swelling in about 10%–20% of both groups; predominantly mild Muscle aches, fatigue, headache in 16.9%–34.4% of both groups; predominantly mild Events less common with Tdap vs. Td: mild fatigue (13.3% vs. 23.4%; p = 0.041), mild muscle aches (4.4% vs. 20.4%; $p < 0.001$) Events more common with Tdap vs. Td: severe muscle aches (4.4% vs. 0%; p = 0.014) **Maternal adverse events and adverse fetal outcomes pre-delivery:** No serious AEs in PW considered related to Tdap or Td except: gestational hypertension (n = 1 Tdap) and hemolysis, elevated liver enzymes, low platelet count syndrome + preeclampsia + premature delivery (n = 1 Td)—possibly related **Adverse birth and neonatal outcomes:** No differences in rates of congenital abnormalities or neonatal complications between infants of Tdap and Td PW No serious AEs in infants considered related to Tdap or Td No developmental differences between infants of Tdap and Td PW (3% abnormal findings in each group)

Table 1 continued

Author, year [references]	Study design [setting/data source]	Recruitment/ study dates	Inclusion (exclusion) criteria	Interventions (number of participants)	Methods	Results
Wanlapakorn et al. [41]	Randomized, controlled [King Chulalongkorn Memorial Hospital, Bangkok, Thailand]	Apr 2015–Sep 2016	Healthy PW aged 18–45 y, with low risk for complications; infants born after 36 GW and weighing 2500 g	PW: Tdap (Boostrix, GSK) 26–36 GW (n = 370)	Active AE monitoring for 7 days after vaccination; passive AE monitoring thereafter	**Reactogenicity:** No AEs reported in the first 30 min after vaccination Most frequently local pain (76.2%; mild: 62.4%, moderate: 13.8%) then low-grade fever (5.1%), swelling (4.1%; mild: 4.1%), erythema (1.4%, mild: 1.4%) Not affected by receipt of previous tetanus-containing vaccine **Maternal adverse events and adverse fetal outcomes pre-delivery:** No serious AEs in PW considered related to Tdap Gestational diabetes (2.7%) or hypertension (1.4%), premature delivery (6.7%) and other serious AEs not more frequent than reported among all deliveries in hospital (N = 4636) Not affected by receipt of previous tetanus-containing vaccine *Chorioamnionitis: 0.5%* **Adverse birth and neonatal outcomes:** No serious AEs (including deaths, congenital defects and birth asphyxia) in infants considered related to Tdap Not affected by maternal receipt of previous tetanus-containing vaccine

ACIP Advisory Committee on Immunization Practices, *AE* adverse event, *ARR* adjusted rate ratio/relative risk, *aHR* adjusted hazard ratio, *aOR* adjusted odds ratio, *CI* confidence interval, *CDC* Centers for Disease Control and Prevention, *CISA* Clinical Immunization Safety Assessment, *CNS* central nervous system, *EHR* electronic health record, *EMR* electronic medical records, *GW* gestational weeks, *HC* historical control, *IPTW* inverse-probability of treatment weights, *ISR* injection site reaction, *mo* month(s), *NICU* neonatal intensive care unit, *NIH VTEU* National Institute of Health Vaccine Treatment Evaluation Unit, *NR* not reported, *OR* odds ratio, *PW* pregnant women, *RR* relative risk, *SAE* serious adverse events, *SGA* small for gestational age, *TIV* trivalent influenza vaccine, *VSD* Vaccine Safety Datalink, *VAERS* Vaccine Adverse Event Reporting System, *WA* Western Australia, *y* year(s)

[a] PW could have also received other vaccines, including any of influenza, hepatitis A, hepatitis B, meningococcal, and pneumococcal vaccine

[b] Maternal outcomes included chorioamnionitis, postpartum endometritis, preterm premature rupture of membranes, preterm delivery (delivery < 37 GW), and a composite endpoint including these outcomes. Mode of delivery and need for induction were also considered

[c] Neonatal outcomes included low birth weight, very low birth weight, small for gestational age, Apgar score < 8 at 5 min of life, admission to NICU, and birth defects. Birth defects included spina bifida, transposition of great arteries, atrioventricular septal defect, cleft palate, cleft lip, and diaphragmatic hemia (all 0–2% frequency per group); Tetralogy of Fallot, rectal and large intestinal atresia/stenosis, reduction deformity of upper limbs, and gastroschisis not observed

[d] Any event included allergic reaction, fever, malaise, seizure, altered mental status, or local or other reaction

[e] Any neurological event included autonomic disorders, cranial nerve disorders, CNS degeneration/demyelinating conditions, peripheral neuropathy, Guillain–Barré syndrome, meningoencephalitides, movement disorders, paralytic syndromes, and spinocerebellar disease

[f] Kaiser Permanente Northern California, Southern California, Colorado and Northwest (Oregon and Washington), Marshfield Clinic (Wisconsin), Group Health Cooperative (Washington), and HealthPartners (Minnesota)

[g] Delivery and neonatal outcomes included gestational age at delivery, stillbirth and major malformation rate, neonatal care admission, ventilation requirements, and incidence of neonatal death

[h] Women were considered to have received a previous dose of Tdap only if record of a vaccination during the area's 2011–2012 parental pertussis vaccination program could be located on the program database

[i] SAEs included preeclampsia, premature contractions, hypertension, oligohydramnios, and placenta previa

[j] The 8 SAE requiring infant hospitalization for at least 1 h were premature delivery, fever at birth, hypoglycemia at birth, pneumonia at birth, infection at the age of 1 months, infection at the age of 5 months, febrile seizures at the age of 2 months, and extreme vomiting at the age of 5 months (n = 1 for all)

[k] TIV administered with Tdap in 27.5%

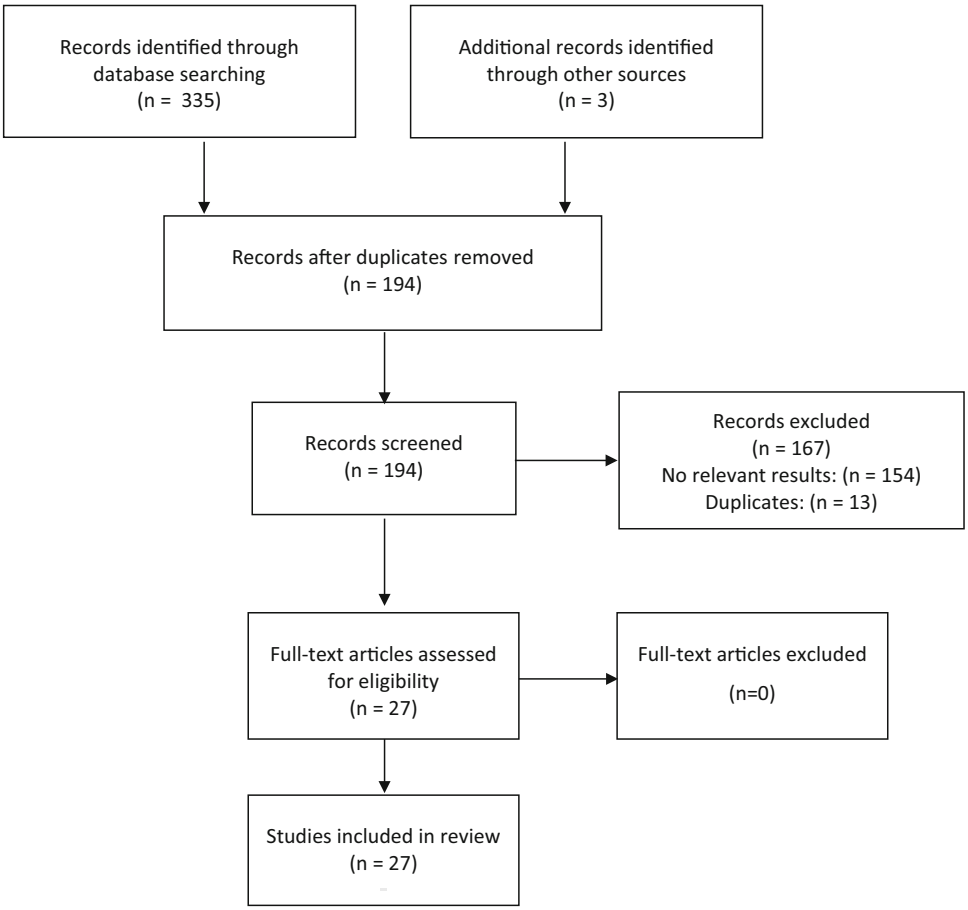

Fig. 1 PRISMA diagram of results of search strategy

Most studies, irrespective of whether database analyses [42–46, 48] or clinical studies [13, 34, 36–39, 41] reported fever in women who received pertussis vaccination during pregnancy; the incidence ranged from 0% to 5.1% in Tdap vaccinated pregnant women (Table 1). Kharbanda et al. [42] found that Tdap-vaccinated pregnant women were 5.4-times more likely to experience medically attended (i.e. requiring a visit to a health care professional) fever in the 3 days post-vaccination than unvaccinated pregnant women in a large database analysis (adjusted incident rate ratio [AIRR] = 5.4 [95% CI 2.1–13.9]). In contrast, a small clinical study by Munoz et al. [13] showed that the frequency of fever in Tdap-vaccinated pregnant women was comparable with that following placebo, and to that among Tdap-vaccinated non-pregnant women, but lower than that in women vaccinated postpartum. A factor potentially contributing to differences in the reported rate of fever was the timing of vaccination. The rate of fever appears lower in women vaccinated $\geq$ 27 weeks' gestation than in those vaccinated earlier (< 27 weeks' gestation) or within 7 days postpartum (3.80 per 10,000 pregnant women vs. 5.19 per 10,000 and 11.69 per 10,000 women, respectively) [43]. Database analyses and clinical studies that reported other systemic adverse events following Tdap vaccination during pregnancy, such as headache, nausea/vomiting, malaise, myalgia and fatigue, found that pregnancy did not increase the reported rate of these adverse events [13, 34, 36–38, 40, 42].

The reactogenicity events reported were predominantly mild and self-limiting. Two clinical studies reported that either no [41] or < 2% [34] of pregnant women experienced serious injection site reactions after Tdap

and < 1% experienced serious systemic symptoms [34]. Across individual reactogenicity symptoms, < 20% of pregnant women experienced moderate-to-severe events, commonly injection site pain or tenderness [34, 41].

Concerns about the safety of repeat vaccination with Tdap (or in women who had previously received a tetanus-containing vaccine) at sometimes short intervals between successive pregnancies persist [49]. Regan et al. [39] reported a trend towards increased odds of several adverse event in women with a history of Tdap vaccination 3 years before the current Tdap vaccination during pregnancy (in 2011–2012 vs. current year 2015), but myalgia was the only specific event reported with significantly increased odds [odd ration; 4.92 (1.11–21.83)]. The frequency of systemic and local reactions, including fever, among Tdap-vaccinated pregnant women who had received a dose of tetanus-containing vaccine within 1–-5 years previously was similar to that in those who had no such vaccinations in two clinical studies [34, 41]. In addition, the rate of acute adverse events reported in a database analysis, among pregnant women who received a tetanus-containing vaccine < 2 years and 2–5 years was similar to that reported in those vaccinated > 5 years previously [45].

The safety of concomitant maternal vaccination with Tdap and influenza vaccines during pregnancy was assessed in two studies [39, 45]. Regan et al. [39] found no evidence of enhanced safety risks with concomitant Tdap and trivalent influenza vaccination compared with Tdap vaccination, as reported by pregnant women using a variety of reactogenicity measures (Table 1). A large US database review found no differences in the frequency of medically attended fever or any acute reaction between pregnant women who received Tdap and influenza vaccines concomitantly compared with sequentially [45].

Maternal Adverse Events and Adverse Fetal Outcomes Pre-delivery

Twenty-one publications were identified that assessed maternal adverse events in women who received Tdap during pregnancy and pregnancy outcomes (Table 1). Of these, 15 were database analyses [42–48, 50–57]. Chorioamnionitis was identified as slightly increased in pregnant women who received Tdap (relative risk 1.19; 95% confidence interval [CI] 1.13–1.26) in a 2010–2012 retrospective, observational, cohort study using data from two Vaccine Safety Datalink sites [54]. Chorioamnionitis increased by a marginally lesser extent in women vaccinated between 27 and 36 gestational weeks (1.11; 95% CI 1.03–1.21). However, pre-term birth (a major chorioamnionitis sequela) was not increased. Subsequently, similar results were reported from database analyses by Layton et al. [43] and DeSilva et al. [52]; both analyses found small but significant increases in chorioamnionitis in women vaccinated with Tdap during pregnancy compared with unvaccinated pregnant women [43, 52]. In contrast, other database analyses found no significant difference in chorioamnionitis between women who did and did not receive the Tdap vaccine during pregnancy [48, 50, 55], including those who received ≥ 2 Tdap doses in the past 5 years [55]. An analysis of 31 chorioamnionitis cases among 3389 pregnancy reports in the Vaccine Adverse Event Reporting System (VAERS) database (between 1990 and 2014) identified that 58% of cases were in women with pre-existing risk factors [51]. Tdap (26%), H1N1 inactivated influenza vaccine (32%) and the quadrivalent human papillomavirus vaccine (29%) accounted for the majority of chorioamnionitis cases reported to the VAERS.

Other pregnancy outcomes, including pre-eclampsia/eclampsia, intrauterine growth retardation, premature labor/contraction, postpartum hemorrhage, placenta previa, elective and spontaneous abortions, oligohydramnios, proteinuria, venous thromboembolism, cardiac events, and gestational hypertensive disorder have also been evaluated. These adverse events were not significantly increased among Tdap-vaccinated vs. non-vaccinated pregnant women across multiple database analyses [42, 43, 47, 48, 50, 53–56] and clinical studies [13, 41, 58], even when consecutive doses of Tdap vaccine were repeated at intervals of < 5 years [55]. Although Layton et al. [43]

found a small increase in postpartum hemorrhage in Tdap vaccinated compared with unvaccinated pregnant women (RR = 1.23; 95% CI 1.18–1.28) [43], the database analyses of Donegan et al. [53] and Griffin et al. [48] found no such increase with vaccination. "Serious" adverse pregnancy outcomes occurred at similar rates in Tdap- and Td-vaccinated pregnant women in a randomized prospective trial [35], and in Tdap plus influenza sequentially- or concomitantly-vaccinated pregnant women identified in an other database analysis [45].

There was no causal association between the Tdap vaccine and adverse outcomes reported in several clinical studies [13, 37, 38, 41].

Adverse Birth and Neonatal Outcomes/ Complications

Concerns regarding potential adverse birth and neonatal outcomes can influence decisions and recommendations about Tdap vaccination during pregnancy. Outcomes assessed included preterm birth, stillbirth, development-related parameters such as low/very low birth weight or small size for gestational age, neonatal death, birth defects (including atrioventricular septal defect, spina bifida, cleft palate, cleft lip and diaphragmatic hernia), major malformations, congenital anomalies, neonatal complications, respiratory disorders, APGAR score, and cord blood pH values (Table 1). No significant increase in any of these outcomes were identified among infants of Tdap-vaccinated compared to non-vaccinated pregnant women, or from expected norms, regardless of design (database analysis vs. clinical trial), population, or setting [13, 41, 43, 50, 52–56, 58]. In addition, no differences in the rates of serious adverse outcomes were observed in infants of Tdap- and Td-vaccinated pregnant women, and none of the serious adverse outcomes reported were considered related to vaccination [35]. Hoang et al. [36] reported that infants of Tdap-vaccinated women presented common symptoms of respiratory and gastrointestinal diseases, although no events were serious or considered related to vaccination. Furthermore, Tdap vaccination during pregnancy does not appear to be associated with an increase in the diagnosis of autism spectrum disorder [59].

There was no increase in acute adverse events or adverse birth outcomes in infants of women who received Tdap vaccination during pregnancy following previous vaccination with a tetanus-containing vaccine < 2 years or 2–5 years before compared with those whose mothers had been vaccinated > 5 years [45]. Nor between infants of women who had received single vs. multiple (< 5 years) doses of Tdap [55]. The timing of Tdap relative to influenza vaccine in had no influence on the frequency of preterm delivery, low birth weight and small for gestational age in infants of women who received sequential or concomitant immunization with these vaccines during pregnancy [46].

Infants of women who received Tdap during pregnancy did not need more or more intense healthcare support than those from women who did not receive the vaccine, with no increases recorded in the days of neonatal hospitalization or neonatal intensive care unit (NICU) admission [50, 55], or in the number of health encounters with complex chronic conditions by age 12 months [56]. In addition, there was no significant association between infant hospitalization or death in the first 6 months of life and receipt of maternal Tdap or Tdap plus influenza vaccine [60].

DISCUSSION

Concerns about maternal pertussis vaccination, at a time when the mother is cautious about their own health and that of their unborn child, may adversely influence acceptance and uptake of the vaccine. This review confirms the safety of maternal pertussis vaccination during pregnancy, and provides evidence to support decision-making and counseling on this intervention. Although local and systemic reactions were reported among vaccinated pregnant women in clinical studies and database analyses, these were usually mild and self-limiting and generally well tolerated. Such reactions were not influenced by repeat exposure to Tdap, vaccines containing tetanus

toxoid or by concomitant vaccination with influenza vaccines (Table 1).

This review provides reassurance that vaccination against pertussis during pregnancy does not adversely affect maternal, fetal or neonatal health (Table 1). Although the studies reviewed used different methodologies and reporting measures, they were generally in agreement. However, in the future, it may be possible to better synthesize the available data if initiatives, such as that of the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project, coordinated by the Brighton Collaboration Foundation [61], are adopted. The GAIA project was initiated to provide guidance for harmonizing the data collected in case report forms used for safety monitoring, with the aim of improving data collection and understanding of vaccine-related outcomes in pregnancy.

The potential impact of Tdap vaccination during pregnancy on chorioamnionitis varies, with some studies suggesting an increased rate of the condition [43, 52, 54] and others no such increase [48, 50, 55]. Nonetheless, chorioamnionitis is uncommonly reported (1% of pregnancy reports to VAERS databases), and usually observed in pregnant women with known risk factors for the condition [51].

There is currently no definitive reactogenicity data by trimester, or on pregnancy, birth and neonatal outcomes. In Ireland, the National Immunization Advisory Committee (NIAC) recommended (in 2016) that pregnant women should be given the vaccine as early as 16 weeks' gestational [62]. This advice was based on a study [63] which found that the immune response was robust when the vaccine was given early in second trimester. The extended eligibility criteria for the vaccine in the UK made the vaccine available to women beginning in the sixteenth week of pregnancy since April 2016 (previously available from 28 weeks), and may have contributed to the increase in the coverage during pregnancy [64]. Examination of the impact of the earlier vaccination during pregnancy will be informative.

In recent years, many countries including the UK, USA, Australia, New Zealand, and several others in Europe and Latin America have introduced pertussis vaccination during pregnancy. Of note, this review included data from most of these countries and regions. There were no apparent geographic differences in the safety profile of maternal pertussis immunization during pregnancy and on infant outcomes.

Our systematic review has a number of limitations that need to be considered. Despite a rigorous systematic search to identify all available articles published between 1995 and 2018, we cannot exclude the possibility of missing some studies and nor did we assess publication bias. Our broad inclusion criteria resulted in a diverse range of included studies which complicates the overall interpretation of results as there was no standardized reporting of adverse events/complications. In addition, a large proportion of the articles reviewed were from the USA. The strength of our review lies in our general adherence to established methods for conducting systematic reviews, including an extensive search across multiple databases, and a wide inclusive publication date range.

CONCLUSION

In conclusion, our review consolidates knowledge on the safety profile of maternal pertussis immunization during pregnancy and on the infant. Maternal immunization does not adversely affect pregnancy, birth or neonatal outcomes. Evidence presented confirms the safety of maternal pertussis immunization, and supports recommendations for pertussis vaccination during pregnancy.

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