**Summary of vaccine safety studies of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and their infants**

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| **Study design** | **Study period\*** | **Vaccine** | **Population** | **Findings/Conclusions** |
| **Vaccine Adverse Events Reporting System** | | | | |
| Spontaneous system | 2005–2010 | Tdap | 132 pregnant women or their infants | No unusual or unexpected pattern of maternal, infant or fetal adverse events. (*1*) |
| Spontaneous system | 2011–2015 | Tdap | 392 pregnant women or their infants | No new unexpected vaccine safety concerns noted among pregnant women who received Tdap. (*2*) |
| Spontaneous system | 1990–2014 | Tdap, Td, 4vHPV,  Influenza,  HepB, MMR, VAR | 3389 pregnancy reports | 31 reports of chorioamnionitis following receipt of any vaccines, representing 1% of pregnancy reports to VAERS;  26% reported Tdap vaccine administered;  Majority of reports had at least one risk factor for chorioamnionitis. (*3*) |
| **Vaccine Safety Datalink** | | | | |
| Retrospective cohort; 7 sites | 2007–2013 | Tdap | 29,155 pregnant women | No increased risk of medically attended acute adverse events (fever, allergy, and local reactions) or adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight) related to timing since prior tetanus-containing vaccination (i.e., less than 2 years before, 2 to 5 years before, and more than 5 years before). (*4*) |
| Retrospective cohort; 7 sites | 2007–2013 | Tdap, Influenza | Pregnant women:  8,464 concomitantly  28,380 sequentially | No statistically significant increased risk of fever or any medically attended acute adverse event in pregnant women concomitantly administered vaccine compared with sequentially administered vaccine;  No differences in both groups in pregnancy outcomes (e.g., small for gestational age, low birth weight, preterm delivery). (*5*) |
| Retrospective cohort; 7 sites | 2007–2013 | Tdap | Pregnant women:  41,654 vaccinated;  282,809 unvaccinated | Tdap vaccination during pregnancy was not associated with increased risk for birth defects, including microcephaly, among live birth offspring. (*6*) |
| Retrospective cohort; 7 sites | 2007–2013 | Tdap | Pregnant women:  53,885 vaccinated;  109,253 matched unvaccinated | No increased risks for acute neurologic events, proteinuria, thrombocytopenia or venous thromboembolism following maternal vaccination;  No increased risk for fever, malaise, allergic, local and other reactions. (*7*) |
| Retrospective cohort; 2 sites | 2010–2012 | Tdap | Pregnant women:  26,229 vaccinated;  97,265 unvaccinated | Receipt of Tdap during pregnancy was not associated with increased risk of hypertensive disorders of pregnancy or preterm or SGA birth;  Small but statistically significant increased risk of chorioamnionitis diagnosis observed; but did not observe increased risk of preterm birth, a major sequela of chorioamnionitis. (*8*) |
| **Other Studies** | | | | |
| Tdap/Td exposure during phase 3 randomized controlled trial | 2001–2002 | Tdap, Td | Pregnant women:  23 received Tdap;  7 received Td | During trial participation, 30 women became pregnant 1 or more times;  Tdap group: 5 spontaneous abortion and 2 preterm births;  Td group: 1 therapeutic abortion and 2 preterm births;  For Tdap and Td groups, 23 newborns (including 4 preterm births) reported normal. (*9*) |
| Tdap exposure during mass vaccination campaign | 2006 | Tdap | 16 pregnant women | All gave birth to full-term infants who had normal newborn evaluations. (*10*) |
| Retrospective cohort | 2005–2009 | Tdap | From 162,448 pregnancies:  138 vaccinated;  552 unvaccinated (randomly selected controls) | Tdap administration occurred most often in the first trimester as prophylaxis following trauma;  Incidence of spontaneous or elective abortions no greater in vaccinated than unvaccinated;  No significant differences in preterm delivery, small for gestational age, or birth weight between groups;  No increase in adverse outcomes noted among infants from vaccinated group compared with unvaccinated group. (*11*) |
| Sanofi Pasteur Vaccine Pregnancy Registry;  prospective reports | 2005–2011 | Tdap | 480 pregnant women | Data from registry do not raise concern for maternal or infant health  Adverse event: 27 (6%) serious adverse events, 33 (7%) non-serious adverse events, 262 (55%) no adverse events, and 158 (33%) did not report an adverse event;  Birth outcome: 93 (19%) term deliveries, 7 (2%) preterm deliveries, 1 (<1%) very preterm delivery with no congenital anomaly, 2 (<1%) elective abortions, 16 (3%) spontaneous abortions, 123 (26%) lost to follow-up and 238 (50%) awaiting pregnancy outcome. (*12*) |
| Phase 1-2 clinical trial | 2008–2012 | Tdap, Placebo (saline) | Pregnant women:  33 received Tdap;  15 received placebo | No increased risk of adverse events was observed among women who received Tdap or their infants;  Growth and development were similar in both infant groups. (*13*) |
| Retrospective cohort; public hospital | 2012–2014 | Tdap | Pregnant women:  1,109 vaccinated;  650 unvaccinated | No increased risk associated with Tdap administration during pregnancy for maternal outcomes (i.e., chorioamnionitis, postpartum endometritis, preterm delivery, preterm premature rupture of membranes and induced labor) or infant outcomes (i.e., low birth weight, very low birth weight, small for gestational age, 5-minute Apgar score, birth defects, and neonatal intensive care unit admission). (*14*) |
| Retrospective cohort | 2013–2014 | Tdap | Pregnant women:  7,152 vaccinated;  226 unvaccinated | No difference in stillbirths, major malformations, chorioamnionitis, 5-minute Apgar score, cord blood pH, or rates of neonatal complications;  No increased risk for preterm birth, small for gestational age, and length of neonatal hospitalization;  No difference in neonatal outcomes between women given at least two doses of Tdap in past 5 years and those who received a single dose. (*15*) |
| **Studies from Other Countries** | | | | |
| Clinical trial  Mexico | 2011–2014 | Tdap,  Placebo (saline) | Pregnant women:  90 received Tdap  81 received placebo | Most common reaction among Tdap and placebo groups was mild local pain in 22% and 21%, respectively. (*16*) |
| Retrospective cohort  United Kingdom | 2012–2013 | Tdap | 20,074 pregnant women who received Tdap compared to matched historical unvaccinated control group | No evidence of increased risk of stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa previa, caesarean delivery, low birth weight, or neonatal renal failure;  No evidence vaccination accelerated time to delivery compared with historical controls. (*17*) |
| Prospective cohort  Belgium | 2012–2014 | Tdap | Pregnant women:  57 vaccinated;  42 unvaccinated | Reported adverse events within this study (73.7% showed mild to moderate injection site pain and swelling) did not differ from the expected side effects described in vaccine package insert;  Among infants, no unexpected risk pattern or congenital disorders detected. (*18*) |
| Prospective observational  New Zealand | 2012–2014 | Tdap | 793 pregnant women | Injection site reactions common, minor and self-limiting; systemic reactions uncommon;  Vaccination with Tdap well tolerated; no severe adverse events likely caused by vaccine. (*19*) |
| Summary of maternal vaccination program  Argentina | 2012–2014 | Tdap | 20 pregnancy reports | 7 reports of mild reaction following receipt of Tdap;  12 reports due to program errors (i.e., Tdap administered before recommended gestational age or revaccinated with Tdap);  No reported serious or fatal events. (*20*) |
| Prospective observational  New Zealand | 2012–2014 | Tdap | 408 infants whose mothers received Tdap during pregnancy | No significant differences in birth weight, gestational age at birth, congenital anomalies or infant growth as compared with baseline population data. (*21*) |
| Randomized control  Vietnam | 2013 | Tdap, TT | Pregnant women:  52 received Tdap;  51 received TT | No unexpected adverse events observed following either Tdap or TT other than the expected side effects described in vaccine package insert.  No significant differences in safety issues between the Tdap and TT groups.  Among infants, no unexpected risk pattern or congenital disorders detected. (*22*) |
| Prospective cohort  Australia | 2015 | Tdap, TIV | Pregnant women:  1,257 received only Tdap;  1,584 received only TIV;  1,506 received Tdap and TIV concomitantly | One in 10 women who received Tdap, TIV or Tdap and TIV concomitantly experienced any reaction during the week following vaccination;  No difference in proportion who reported any reaction, however a significantly higher proportion who received Tdap reported experiencing swelling or pain at injection site; increase more pronounced in women who received a recent dose of Tdap. (*23*) |

**Abbreviations**: HepB = hepatitis B vaccine; 4vHPV = human papillomavirus vaccine (quadrivalent); MMR = measles, mumps, and rubella vaccine; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td = tetanus and diphtheria toxoids; TIV= trivalent inactivated influenza vaccine; TT= tetanus toxoid; VAR = varicella vaccine.

**\*** Tdap was not recommended for pregnant women until 2012.

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