Importance of Timing of Maternal Combined Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Immunization and Protection of Young Infants

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(See the Editorial Commentary by Riley and Beigi on pages 545–7.)

Background. Pertussis booster vaccine (Tdap) recommendations assume that pertussis-specific antibodies in women immunized preconception, during, or after previous pregnancies persist at sufficient levels to protect newborn infants.

Methods. Pertussis-specific immunoglobulin G (IgG) was measured by IgG-specific enzyme-linked immunosorbent assay (ELISA) in maternal–umbilical cord serum pairs where mothers received Tdap during the prior 2 years. Geometric mean concentrations (GMCs) of pertussis antibodies and cord-maternal GMC ratios were calculated.

Results. One hundred five mothers (mean age, 25.3 years [range, 15.3–38.4 years]; mean gestation, 39 weeks [range, 37–43 weeks]) immunized with Tdap vaccine a mean of 13.7 months (range, 2.3–23.9 months) previously were included; 72 (69%) had received Tdap postpartum, 31 at a routine healthcare visit and 2 as contacts of another newborn. There was no difference in GMCs for pertussis-specific IgG in maternal delivery or infant cord sera for women immunized before (n = 86) or during (n = 19) early pregnancy. Placental transport of antibodies was 121%–186% from mothers immunized before and during pregnancy, respectively. Estimated GMC of IgG to pertussis toxin was <5 ELISA units (EU)/mL at infant age 2 months (start of infant immunization series). More infants of mothers immunized during pregnancy had pertussis toxin levels estimated to be higher than the lower limit of quantitation of the assay (4 EU/mL) through age 2 months (52% vs 38%; *P* = .34).

Conclusions. Infants of mothers immunized preconception or in early pregnancy have insufficient pertussis-specific antibodies to protect against infection. Maternal immunization during the third trimester, immunization of other infant contacts, and reimmunization during subsequent pregnancies may be necessary.

Keywords. Tdap; pertussis; maternal immunization; passive protection; infants.

Pertussis is the most poorly controlled vaccine-preventable disease in resource-rich countries. Waning pertussis immunity, either from natural infection or childhood immunization, is a factor because infected adolescents and adults are transmitters of pertussis, especially to very young infants [1–3]. Despite excellent infant pertussis immunization rates in the United States, pertussis-attributable morbidity and mortality in infants too young to have completed their primary immunization series with diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine at 2, 4, and 6 months of age remain unacceptably high [4–9]. For example, during the 2010 pertussis outbreak in California, the attack rate for pertussis among infants <6 months of age was 435 per 100 000 persons (19-fold higher than the rate in the general population) [9]. Ten

infants died; all but 1 was too young to have received the first pertussis immunization at age 2 months. This mirrors the experience in the rest of the United States; since the 1980s, pertussis-attributable deaths occur almost exclusively in infants <3 months of age [4–8].

Strategies to prevent pertussis in very young infants, such as adolescent and adult tetanus and diphtheria toxoids and acellular pertussis (Tdap) booster immunization and targeted immunization ("cocooning") of all infant caregivers, have been limited by low Tdap vaccine uptake and logistic and financial barriers [10–14]. An alternative approach would be to ensure that newborn infants are protected from birth through transplacental acquisition of "protective levels" of maternal pertussis-specific antibodies [12, 15–20]. This passive protection theoretically could protect infants until the first or second dose of the primary immunization series is completed. In 2011, the Advisory Committee on Immunization Practices (ACIP) to the Centers for Disease Control and Prevention (CDC) recommended Tdap vaccine for previously unimmunized pregnant women in the third trimester to achieve protection of young infants from pertussis [10]. However, because Tdap currently is recommended as a single lifetime dose, this strategy will not be effective unless maternal pertussis-specific antibodies persist long enough to protect infants at each pregnancy. This study sought to determine pertussis-specific immunoglobulin G (IgG) concentrations in delivery plasma from mothers who received Tdap vaccine within the prior 2 years. We assessed cord serum values from infants born to these women and estimated whether passively acquired maternal IgG levels could potentially protect infants through the first few months of life.

MATERIALS AND METHODS

Study Population

Since January 2008, previously Tdap-unimmunized postpartum women at Ben Taub General Hospital (BTGH), Houston, Texas, have been offered Tdap vaccine, as was recommended by the CDC, through a standing order protocol as part of a cocooning program [13, 21, 22]. BTGH is 1 of 2 tax-supported hospitals in the Harris Health System that provides care for a medically underserved, underinsured, predominantly Hispanic population. Mother-newborn pairs delivering at BTGH were eligible for inclusion in the current study if the delivery occurred at ≥37 weeks' gestation, the mother had documented receipt of Tdap vaccine within the previous 2 years, and plasma-serum pairs were available in sufficient quantity for testing. During June 2009 through May 2011, residual paired maternal delivery plasma–infant cord serum samples were collected prospectively from subjects meeting inclusion criteria. Mothers immunized 10 through 18 months, 21 months, and 24 months prior to the birth of the current infant (ie, preconception Tdap vaccine) were assessed for study inclusion. Paired samples were collected consecutively until the predefined monthly quota (n = 8) was completed. This study preceded the 2011 ACIP recommendation that Tdap vaccine be administered during late pregnancy; however, all women immunized during pregnancy, either through provider choice or because they were unaware they were pregnant at the time of immunization, who had available paired samples, also were included. Maternal demographics, date of prior Tdap administration, infant date of birth, and gestation were collected prospectively through the cocooning program database. The primary outcome was determination of pertussis-specific IgG in infants of mothers immunized within the prior 2 years. The secondary outcome was to determine if pertussis-specific IgG to pertussis toxin (PT; the only pertussis antigen for which decay of passively acquired maternal antibody has been directly measured [23]) would persist through the initiation of the infant primary immunization series. The study was approved by the Institutional Review Board of the Baylor College of Medicine.

Laboratory Methods

Paired maternal delivery–infant cord specimens were transported to the Baylor investigators' laboratory where they were processed to collect serum or plasma, aliquoted, and frozen at −80°C until testing. Aliquots (100 μL) of each sample were coded (each pair was assigned linked codes) and shipped to Sanofi Pasteur (Swiftwater, PA) where enzyme-linked immunosorbent assay (ELISA) testing for pertussis-specific IgG concentrations against PT, filamentous hemagglutinin (FHA), fimbrial proteins (FIM), and pertactin (PRN) was performed. Microtiter plates were coated with optimized concentrations of pertussis antigens diluted in a carbonate-bicarbonate (pH 9.6), plates were washed, and 1.0% buffered goat serum was added. Eight 2-fold serial dilutions of unknown sample were added, plates were incubated, and goat antihuman (IgG) horseradish peroxidase conjugate was added. After incubation, tetramethylbenzidine peroxidase substrate was added and the reaction was stopped with 2N sulfuric acid. Absorbance was measured at 450 nm. Parallel line analysis was used to determine sample concentrations by comparison to the reference standards. The lower limit of quantitation (LLOQ) for each assay was 4 ELISA units (EU)/mL for PT, FIM, and PRN, and 3 EU/mL for FHA. Values less than the LLOQ were considered to be half of the LLOQ for each assay.

Statistical Analysis

Statistics were performed using SPSS software version 20.0 (SPSS, Chicago, IL). Statistical significance for dichotomous outcomes was determined by χ^2 and Fisher exact tests.

Normally distributed demographic data were assessed by means. Where positive or negative skewing of data occurred, statistical significance was assessed by medians and the Mann-Whitney U test. Serum IgG values to PT, FHA, FIM, and PRN were reported as geometric mean concentrations (GMCs) with 95% confidence intervals. Subjects who met the diagnostic criteria for recent pertussis infection (maternal samples with serum IgG to PT >94 EU/mL [24]) were excluded from further analysis as predetermined by the study design. The efficiency of placental transfer of pertussis-specific antibodies was measured as the ratio of infant to maternal GMC. Differences between pertussis-specific IgG in women immunized preconception vs during pregnancy were assessed by Student t test of log-transformed serum IgG levels. Levels of PT-specific IgG present in infants at the time of initiation of the infant immunization series were calculated using the published half-life of passively acquired maternal pertussis-specific IgG to PT [23].

RESULTS

One hundred five maternal delivery–infant cord blood pairs where the mother had received Tdap vaccine 2–24 months before delivery were collected. The mean age of mothers was 25.3 years (range, 15.3–38.4 years); 95 mothers (91%) were Hispanic; the remainder were black (7%), and 1% each were white and Asian. The mean gestational age of newborn infants was 39.3 weeks (range, 37–43 weeks) and mean birth weight was 3361g (range, 2355–5115 g). Mothers had received Tdap vaccine a mean of 13.7 months (median 13.4 months [range, 2.3–23.9 months]) prior to delivery. Seventy-two women (69%) received Tdap vaccine following the birth of a prior infant at the study hospital; 31 were immunized as part of routine healthcare visits (29%) and 2 (1.9%) because they were contacts of another newborn infant. Nineteen of 105 women (18%) received Tdap vaccine during the current pregnancy. The mean gestation of these 19 at the time of Tdap immunization was 9.3 weeks (median, 6 weeks [range, 1–28 weeks]); 14 of these 19 (76%) received Tdap during the first trimester and 11 of the 14 (58%) before the sixth week of gestation. Only 3 women of the 19 (16%) received Tdap after 20 weeks' gestation, 1 each at 21, 27, and 29 weeks of gestation, respectively, as is now recommended by ACIP. Mothers immunized before or during pregnancy were similar by age, ethnicity, infant birth weight, and gestation at delivery.

The GMCs, 95% confidence intervals, and range for IgG concentration against each pertussis antigen for the 105 maternal–infant cord pairs are summarized in Table 1. Three mothers who had received Tdap vaccine 16–18 months previously most likely had recent pertussis exposure (IgG to PT of >94 EU/mL [24]), and serologic results from these women and their infants were excluded from further analysis. There was no difference in pertussis-specific IgG GMCs for any pertussis

Table 1. Geometric Mean Concentrations for Pertussis Antigen–Specific Immunoglobulin G Concentrations in Maternal Delivery and Infant Cord Sera

Antigen	Tdap During Pregnancy^a (n = 19)		Tdap Before Pregnancy (n = 86)		Tdap Before Pregnancy and No Evidence of Recent Infection^b (n = 83)	
	Maternal Delivery	Infant Cord	Maternal Delivery	Infant Cord	Maternal Delivery	Infant Cord
PT	10.5 (6.4–17.1) [2–29]	17.3 (11.1–26.8) [2–51]	14.0 (11.1–17.7) [2–282]	16.7 (13.2–21) [2–216]	12.8 (10.3–15.9) [2–71]	15.5 (12.4–19.4) [2–154]
FHA	49.3 (28.4–85.8) [4–556]	87.6 (56.3–136.4) [10–526]	50.9 (40.6–63.9) [4–1692]	73.0 (57.6–92.6) [3–1990]	50.4 (39.9–63.7) [4–1692]	72.9 (57.0–93.1) [3–1990]
FIM	103.1 (42.7–249) [5–1173]	191.8 (84.5–435.7) [14–2551]	138.2 (97.2–196.5) [2–1491]	182.6 (127.7–261.2) [2–3723]	132.1 (92.1–189.5) [2–1491]	173.1 (120.5–250.8) [2–3723]
PRN	40.4 (18.9–87.3) [2–1219]	70.0 (32.5–150.5) [10–1420]	39.5 (28.3–55.0) [2–3579]	58.4 (41.7–81.6) [2–3620]	38.8 (27.5–54.6) [2–3579]	57.6 (40.8–81.4) [2–3620]

Data are presented as GMC (95% confidence interval) [range] in ELISA units (EU) per milliliter.

Abbreviations: FHA, filamentous hemagglutinin; FIM, fimbrial proteins; PRN, pertactin; PT, pertussis toxin; Tdap, tetanus-diphtheria-acellular pertussis vaccine.

a Sixteen of 19 (84%) women were immunized before week 20 of gestation.

b Recent infection defined as maternal delivery sample with PT >94 EU/mL [24].

antigen comparing maternal delivery or placental cord specimens for women immunized before or during early pregnancy (P values ranged from .45–.94 and from .46–.82 for maternal delivery and cord specimens, respectively). 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.

The half-life of maternally acquired PT-specific IgG has been calculated by Van Savage et al to be approximately 36 days [23]. Applying this reported half-life and infant cord values from our study, we estimated the PT-specific IgG GMC in our study infants at 2 months of age, the age at which the first dose of DTaP vaccine is administered. The estimated PT-specific IgG was <5 EU/mL (Figure 1). Only 41 infants (40%) had a PT-specific IgG concentration at birth calculated to persist above the LLOQ of the assay at age 2 months. Slightly more infants of mothers who were immunized during pregnancy, and 2 of the 3 immunized after week 20, had PT levels at birth that would persist above the LLOQ (4 EU/mL) through 2 months of age (52% vs 38%; P = .34). As Van Savage et al [23] did not directly measure antibodies against FIM and PRN, and FHA is not specific for *Bordetella pertussis*, no attempt was made to calculate half-lives for these antibodies.
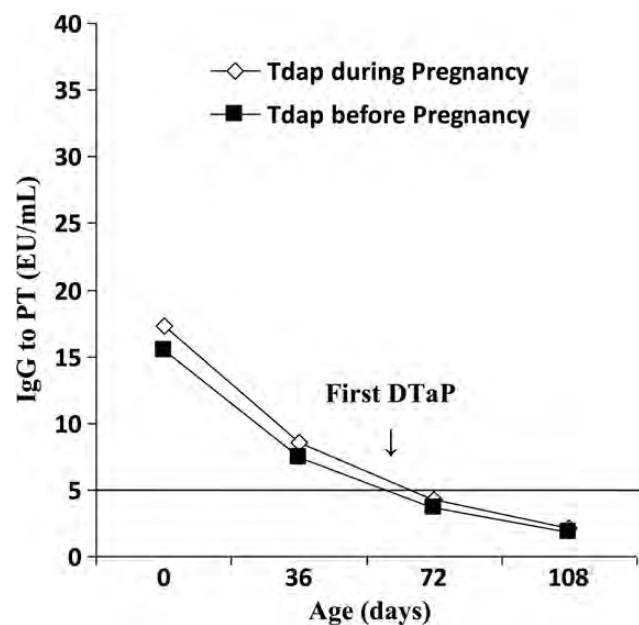

Figure 1. Geometric mean concentrations (GMCs) of pertussis toxin immunoglobulin G in infant cord sera and estimated infant concentrations through 3 months of age by maternal tetanus-diphtheria-acellular pertussis vaccine administration status. Confidence intervals for GMCs at birth are given in Table 1. Abbreviations: DTaP, diphtheria and tetanus toxoids and acellular pertussis; EU, ELISA unit; IgG, immunoglobulin G; PT, pertussis toxin; Tdap, tetanus-diphtheria-acellular pertussis vaccine.

DISCUSSION

This study is, to our knowledge, one of the first to critically evaluate currently recommended Tdap immunization strategies for women of childbearing age in the United States and to assess their likely impact on passive protection against pertussis in very young infants. Our findings indicate that although pertussis-specific IgG concentrations in plasma from delivering women were higher than those found in a similar cohort prior to Tdap booster vaccine recommendations for adolescents and adults [25], maternal antibodies waned quickly, even in women immunized during the first and second trimester, suggesting that Tdap may need to be administered during the late stages of each pregnancy. It is noteworthy that, although not reaching statistical significance, placental transport of pertussis antibodies was better in women immunized during pregnancy. Despite highly efficient placental transport of maternal antibodies in our cohort of women immunized within 2 years of delivery, pertussis antigen–specific IgG concentrations in their newborn infants were unlikely to be high enough to passively protect them through 2 or 3 months of age, the period of highest pertussis-related morbidity and mortality. Our findings have important public health implications because Tdap booster currently is recommended as a single lifetime dose [10, 26], although it is accepted that further booster doses may be necessary. Both single and multiple Tdap booster strategies assume protection of infants after each pregnancy. Our data indicate that, even if Tdap booster were given more frequently than the 10-year interval currently recommended for diphtheria and tetanus toxoids vaccine, this assumption may be erroneous.

One of the difficulties in evaluating the likely impact of Tdap immunization on passive young infant protection from pertussis infection is that there is no generally accepted serologic correlate of pertussis immunity. Household contact studies in children and adults suggest that individuals with "high" levels of antibodies to PT, FIM, and PRN were less likely to develop clinical disease when exposed to pertussis [27]. A PT monovalent vaccine also was protective in a large clinical trial in Swedish infants [28]. IgG concentrations as low as 5 EU/mL for PT have been suggested as being protective in older children and adults [29]. Although these modest levels may be protective in these populations, which are already primed through their own immunizations or exposure to natural disease, these low levels are unlikely to protect very young infants who are dependent solely on antibody for protection and who lack the ability to mount a cell-mediated response for recovery. In our newborn cohort, 59% had inadequate PT-specific IgG concentrations at birth to sustain them above even that minimal level until after the second DTaP vaccine dose when some protection against life-threatening infection would be anticipated. Should the actual

"protective" level of PT IgG for newborn infants be higher, as is very likely, this implies that the majority of infants born to mothers immunized before the third trimester of pregnancy will have little or no protection against life-threatening pertussis.

In 2011, ACIP recommended that pregnant women receive Tdap in the third or late second trimester of pregnancy in preference to postpartum, which had been previously recommended [10, 30]. This change has been endorsed by the American College of Obstetrics and Gynecology [31]. One reason for this change in recommendation was the poor implementation of the 2006 recommendation for postpartum immunization and Tdap administration to every adolescent and adult with infant contact (cocooning). Our findings support the new recommendation but suggest that wherever possible, Tdap is optimally administered at weeks 30–32 of pregnancy so that maternal pertussis antigen–specific IgG levels are at their peak when placental transport is most efficient (ie, after 34 weeks' gestation) [32]. Deferring immunization until this time should not lead to worse maternal outcome because, although not well studied, increased maternal pertussis-associated morbidity and mortality is not reported during pregnancy [30]. Furthermore, although phase 1 studies of maternal immunization with Tdap are in progress, studies many decades ago with whole-cell pertussis vaccine administration late in pregnancy resulted in high levels of pertussis-specific antibodies in infants and no safety concerns [33]. High maternal pertussis antibodies did not result in blunting of infant immune response to their primary series of DTaP vaccines [15]. Although this remains a concern, further experience with Tdap coupled with continued pertussis-related morbidity and mortality in young infants prompted updated recommendations in 2011 in favor of immunization during pregnancy [10]. However, even if third-trimester immunization with Tdap vaccine was universally implemented, this strategy would benefit only the offspring from that pregnancy. Protection of future offspring would require repeated immunization with each subsequent pregnancy.

There are limitations to our study. First, the number of pregnant women studied, although comparable to other published reports [25, 34–37], is relatively small. Second, our cohort was predominantly Hispanic and may not reflect pertussis seroprevalence in other populations of pregnant women. We believe that this is unlikely because Hispanic infants are overrepresented in pertussis incidence and mortality, a fact believed to be in part because of increased circulation of pertussis in this population [7]. Thus, mothers of Hispanic ethnicity would be expected to have higher pertussis-specific IgG than women of other ethnicities as a consequence of natural boosting through exposure to natural infection, as was seen in earlier studies performed by our group prior to the licensure of Tdap [25]. Third, we did not obtain histories on pertussis-like illness in

the women, making it impossible to evaluate the possible effects of natural boosting on our observations. We used a validated serological correlate of definite recent infection [24], but because PT-specific IgG decreases rapidly, it is likely that natural boosting also occurred in women who did not meet this definition and thus we may have overestimated the amount available to infants as a consequence of maternal Tdap immunization alone. Finally, we calculated the rate of decay of maternally acquired pertussis antigen–specific IgG and, while this is defined for PT, that is not the case for antibodies to other antigens that possibly also play a role in protecting young infants. Better definition of the half-life of pertussis antigen–specific IgG in infants in the Tdap era is required to fully understand the implications of our study.

Preventing life-threatening pertussis in young infants in the 21st century is a challenging prospect that will require a multi-faceted approach because no single paradigm or vaccination strategy will be effective [12]. Our data demonstrate that the ability of maternally acquired pertussis antigen–specific IgG to persist and protect infants is short lived, making the issue of reimmunization an urgent consideration. Meanwhile, efforts to promote and effectively implement cocooning must continue [10, 12, 17, 38]. Further investigation of novel strategies to increase Tdap vaccine rates among adult populations also are urgently needed to achieve herd protection. Such investigation to reduce the burden of this poorly controlled vaccine-preventable disease will not be easy, but the risk of doing nothing will result in ongoing pertussis-related infant deaths as well as accompanying financial, emotional, and societal costs that are unacceptable.

Notes

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Use of Adult Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) in Pregnant Women, United States (US)

History of Recommendations for Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap)

- Adult Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) was licensed for single dose use in 2005.
- During 2006 a single dose of Tdap was recommended for adolescents age 11 through 18 years and adults age 19 through 64 years who had not previously received Tdap.
- In 2010 the recommendation was extended to include adults age 65 years and older if they have or anticipate having close contact with an infant aged <12 months and previously have not received Tdap.
- In 2010 it was also decided that Tdap can be administered regardless of interval since the last tetanus- or diphtheria-toxoid containing vaccine.

History of Maternal Tdap Vaccination

- Since 2006, Tdap has been recommended for use in postpartum mothers and other family members of newborn infants (who have never received Tdap) to protect infants from pertussis, a strategy referred to as cocooning.
- Cocooning programs have proven difficult to implement widely. Cocooning programs might achieve moderate vaccination coverage among postpartum mothers but have had limited success in vaccinating fathers or other family members.
- In 2011 Tdap was recommended for routine use in unvaccinated pregnant women: Health-care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester (after 20 weeks' gestation). If not administered during pregnancy, Tdap should be administered immediately postpartum.

Pertussis is a continuing health problem in the US

- The United States has experienced substantial increases in reported pertussis cases over the past several years. Provisional case counts for 2012 have surpassed the last peak year, 2010, with 41,880 pertussis cases and 14 deaths in infants aged <12 months.
- For infants, transplacentally transferred maternal antibodies might provide protection against pertussis in early life and before beginning the primary DTaP series. Several studies provide evidence supporting the existence of efficient transplacental transfer of pertussis antibodies. Active transport of maternal

Group work Decision introduction / Postintroduction licensure

immunoglobulin G does not substantially take place before 30 weeks of gestation The effectiveness of maternal antipertussis antibodies in preventing infant pertussis is not yet known, but pertussis-specific antibodies likely confer protection and modify the severity of pertussis illness. In addition, a woman vaccinated with Tdap during pregnancy likely will be protected at time of delivery, and therefore less likely to transmit pertussis to her infant.

- After receipt of Tdap, boosted pertussis-specific antibody levels peak after several weeks, followed by a decline over several months. One study of pregnant women who received Tdap within the prior 2 years noted that maternal antibodies waned quickly; even women immunized during the first or second trimester had low levels of antibodies at term

- Tetanus toxoid has been safely administered to millions of women worldwide; studies have shown no increase risk in birth defects following tetanus toxoid. Tdap safety in pregnant women was not studied in pre-clinical trials however post-licensure data suggests an acceptable safety profile.

- During a time when Tdap was not routinely recommended during pregnancy a review of adverse events following Tdap reported to the US spontaneous reporting system (VAERS) did not identify any concerning pattern in maternal, infant, or fetal outcomes.

- The main theoretical safety concern for administering repeat Tdap doses at short or frequent intervals is severe local reaction (e.g., arthus reactions)

- Observational studies in the US and Canada have evaluated safety of administering a single dose of Tdap after Td at intervals as short as ~2 years have not identified safety concerns.

- Since the 2011 ACIP vaccination recommendation, uptake of Tdap among pregnant women has been low; one survey of 1,231 women (August 2011 to April 2012) estimated that only 2.6% of women received Tdap during their recent pregnancy

- A model showed that Tdap during every pregnancy might prevent 906 infant pertussis cases, 462 pertussis-related hospitalizations and 9 deaths. Postpartum dose might prevent 549 infant cases, 219 pertussis hospitalizations and 3 deaths.

- Optimizing the current vaccination program and protecting infants who are at highest risk for death are immediate priorities. New data indicate that maternal antipertussis antibodies are short-lived; therefore, Tdap vaccination in one pregnancy will not provide high levels of antibodies to protect newborns during subsequent pregnancies

Task

To decide as a group whether to recommend routine immunization with Tetanus-diptheria-acellular pertussis vaccine to women during all pregnancies.

You need to describe to the Minister of Health in 5 minutes your rational for your decision.
Be sure to include whatever important studies or programmatic activities need to be implemented as a result of your decision.

Advice on the group work process
• Choose the chairman. Choose the Rapporteur (representing the Ministry of Health).
• Each member of the group will have a role of the different participants making this decision by assessing the evidence and considering the impact, safety, cost implications (cost savings?), potential acceptance and vaccine uptake.
• After the meeting the MOH has arranged for the chairman of the expert group to give a brief summary of their advice to the Minister of Health who is very concerned about the increasing threat of pertussis, particularly among young infants.

By the end of the session your group will have made a recommendation for or against administering Tdap during every pregnancy. **If recommended** a short list of priority studies/ assessments that will need to be conducted in the US to adequately evaluate the impact and safety of the recommendation need to be described. However, if the group **does not feel they are ready to make the recommendation**, a short list of studies/assessments will need to be described that are necessary before reconsidering the recommendation. The Composition of the National Committee on Immunization Practices Tdap Working Group is:
- Pediatrician(s) (infectious disease, social pediatrics, pediatric immunologist, pediatric pulmonologist)
- Epidemiologist
- An immunologist with expertise in maternal-infant immunity
- Post-licensure Vaccine Safety subject matter expert
- Representative from the National Regulatory Agency (FDA)
- National Immunization Program Manager
- Representative from the American College of Obstetrics and Gynecology
- Representative from the American College of Family Medicine
- Health economist
- Representative from the National Vaccine Program Office, Vaccine Injury Compensation Program, other stakeholders?

Group work Decision introduction / Postintroduction licensure
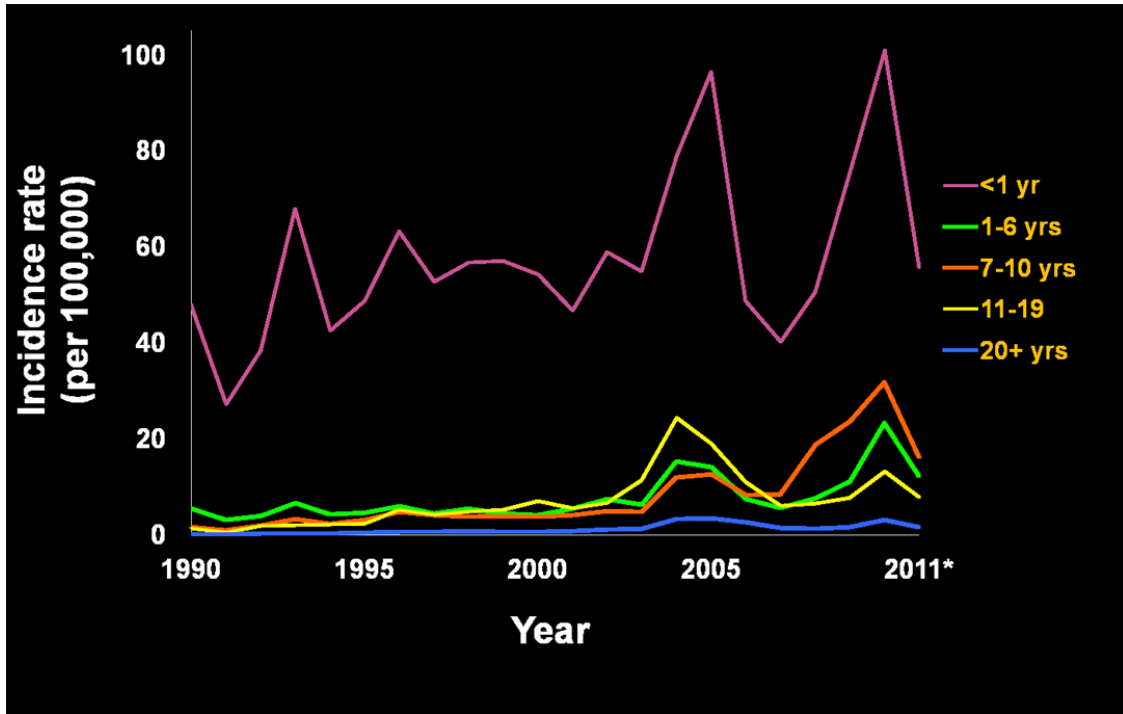
Reported pertussis-related deaths by age-group U.S., 1980-2009

Age-Group	1980-1989[1]	1990-1999[1]	2000-2009[2]
0-1 month	38	68	152
2-3 month	11	16	24
4-5 month	5	5	2
6-11 month	7	4	1
1-4 years	13	2	2
5-10 years	1	6	3
11-18 years	0	0	3
>18 years	1	2	8
Total	77*	103	194

Includes one case with unknown age
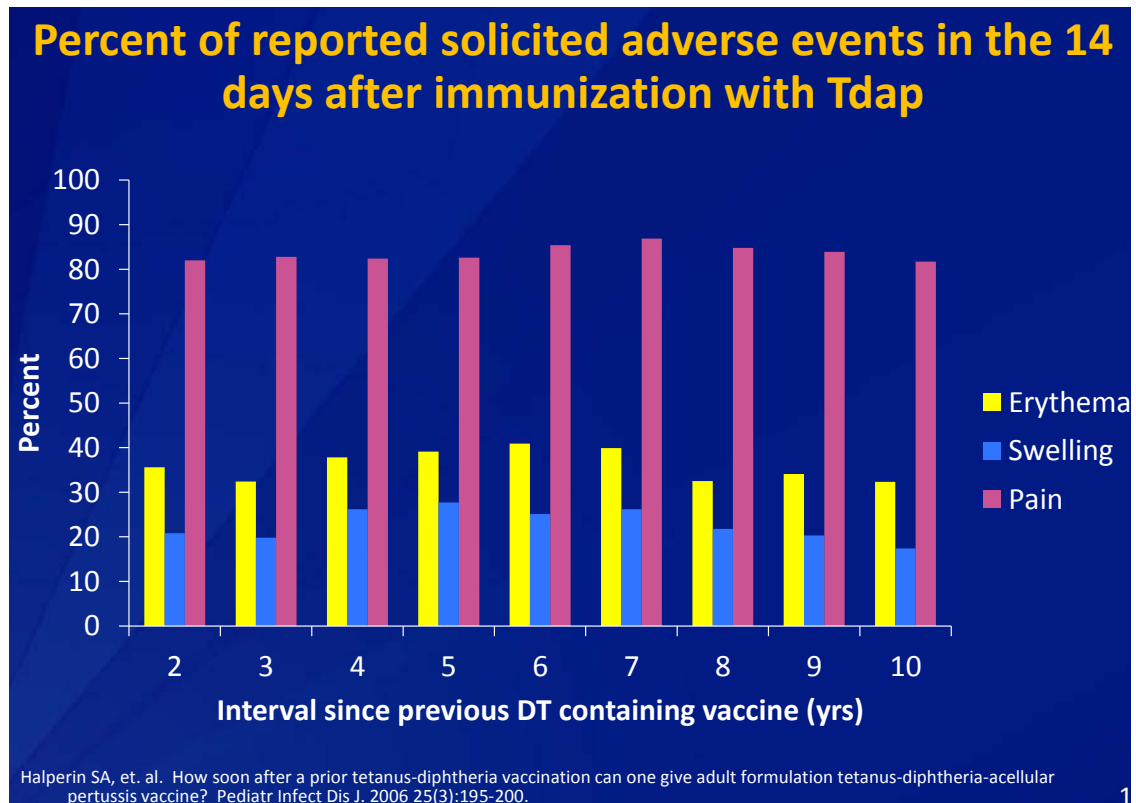[1] Vitek CR et al. Pediatr Infect Dis J 2003; 22(7):628-34.
[2] National Notifiable Diseases Surveillance System, CDC, 2009

- **Pertussis incidence has increased since 1980s**
- **Tdap has reduced the burden of pertussis in adolescents**
- **No evidence for "herd immunity" from Tdap**
- **Excellent initial DTaP vaccine effectiveness**
- **Moderate and immediate waning of DTaP immunity**

Shifting the timing of mother's Tdap dose

- "Cocooning" programs difficult to implement
- Provides earlier protection to mother and therefore indirect protection to infant
- High levels of transplacental maternal antibodies transferred to infants may provide direct protection

Percent of reported solicited adverse events in the 14 days after immunization with Tdap

Halperin SA, et. al. How soon after a prior tetanus-diphtheria vaccination can one give adult formulation tetanus-diphtheria-acellular pertussis vaccine? Pediatr Infect Dis J. 2006 25(3):195-200.

General statistics on births in the US, 2009

❑ **Number of births: 4,130,665[1]**

❑ **Percent born preterm: 12.2%[1]**

❑ **Mean age at first birth: 25.2 yrs[1]**

❑ **2.06 children born/woman (est. 2011)[2]**

Group work Decision introduction / Postintroduction licensure

Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months — Advisory Committee on Immunization Practices (ACIP), 2011

Compared with older children and adults, infants aged <12 months have substantially higher rates of pertussis and the largest burden of pertussis-related deaths. Since 2004, a mean of 3,055 infant pertussis cases with more than 19 deaths has been reported each year through the National Notifiable Diseases Surveillance System (CDC, unpublished data, 2011). The majority of pertussis cases, hospitalizations, and deaths occur in infants aged ≤2 months, who are too young to be vaccinated; therefore, other strategies are required for prevention of pertussis in this age group. Since 2005, the Advisory Committee on Immunization Practices (ACIP) has recommended tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) booster vaccines to unvaccinated postpartum mothers and other family members of newborn infants to protect infants from pertussis, a strategy referred to as cocooning (1). Over the past 5 years, cocooning programs have proven difficult to implement widely (2,3). Cocooning programs might achieve moderate vaccination coverage among postpartum mothers but have had limited success in vaccinating fathers or other family members. On June 22, 2011, ACIP made recommendations for use of Tdap in unvaccinated pregnant women and updated recommendations on cocooning and special situations. This report summarizes data considered and conclusions made by ACIP and provides guidance for implementing its recommendations.

ACIP recommends a single Tdap dose for persons aged 11 through 18 years who have completed the recommended childhood diphtheria and tetanus toxoids and pertussis/diphtheria and tetanus toxoids and acellular pertussis (DTP/DTaP) vaccination series and for adults aged 19 through 64 years who have not previously received Tdap (1,4). ACIP also recommends that adults aged 65 years and older receive a single dose of Tdap if they have or anticipate having close contact with an infant aged <12 months and previously have not received Tdap (5). Two Tdap vaccines are available in the United States. Adacel (Sanofi Pasteur) is licensed for use in persons aged 11 through 64 years. Boostrix (GlaxoSmithKline Biologicals) is licensed for use in persons aged ≥10 years (6).

The ACIP Pertussis Vaccines Work Group reviewed unpublished Tdap safety data from pregnancy registries and the Vaccine Adverse Event Reporting System (VAERS) and published studies on use of Tdap in pregnant women. The Work Group also considered the epidemiology of pertussis in infants and provider and program feedback, and then presented policy options for consideration to ACIP. These updated recommendations on use of Tdap in pregnant women are consistent with the goal of reducing the burden of pertussis in infants.

Safety of Tdap in Pregnant Women

In prelicensure evaluations, the safety of administering a booster dose of Tdap to pregnant women was not studied. Because information on use of Tdap in pregnant women was lacking, both manufacturers of Tdap established pregnancy registries to collect information and pregnancy outcomes from pregnant women vaccinated with Tdap. Data on the safety of administering Tdap to pregnant women are now available. ACIP reviewed published and unpublished data from VAERS, Sanofi Pasteur (Adacel) and GlaxoSmithKline (Boostrix) pregnancy registries, and small studies (7,8). ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine. Both tetanus and diphtheria toxoids (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria-toxoid containing vaccines administered during pregnancy have not been shown to be teratogenic (9,10). From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks' gestation is preferred to minimize the risk for any low-frequency adverse event and the possibility that any spurious association might appear causative.

Transplacental Maternal Antibodies

For infants, transplacentally transferred maternal antibodies might provide protection against pertussis in early life and before beginning the primary DTaP series. Several studies provide evidence supporting the existence of efficient transplacental transfer of pertussis antibodies (7,11,12). Cord blood from newborn infants whose mothers received Tdap during pregnancy or before pregnancy had higher concentrations of pertussis antibodies when compared with cord blood from newborn infants of unvaccinated mothers (7,11). The half-life of transferred maternal pertussis antibodies is approximately 6 weeks (12). The effectiveness of maternal antipertussis antibodies in preventing infant pertussis is not yet known, but pertussis-specific antibodies likely confer protection and modify the severity of pertussis illness (13,14). In addition,

a woman vaccinated with Tdap during pregnancy likely will be protected at time of delivery, and therefore less likely to transmit pertussis to her infant. After receipt of Tdap, boosted pertussis-specific antibody levels peak after several weeks, followed by a decline over several months (15,16). To optimize the concentration of maternal antibodies transferred to the fetus, ACIP concluded that unvaccinated pregnant women should receive Tdap, preferably in the third or late second (after 20 weeks gestation) trimester.

Interference with Infant Immune Response to Primary DTaP Vaccination

Several studies have suggested that maternal pertussis antibodies can inhibit active pertussis-specific antibody production after administration of DTaP vaccine to infants of mothers vaccinated with Tdap during pregnancy, referred to as blunting (12,17). Because correlates of protection are not fully understood, the clinical importance of blunting of an infant's immune response is not clear. Evidence suggests that any blunting would be short-lived because circulating maternal antibodies decline rapidly (12,18). Circulating maternal pertussis antibodies might reduce an infant's risk for pertussis in the first few months of life but slightly increase risk for disease because of a blunted immune response after receipt of primary DTaP doses. The benefit would be to reduce the risk for disease and death in infants aged <3 months, but the trade-off might be to increase the occurrence of pertussis in older infants; however, this group experiences a substantially lower burden of hospitalizations and mortality (National Notifiable Diseases Surveillance System, CDC, unpublished data, 2011).

Currently, two clinical trials are being conducted to measure the immune response of infants receiving DTaP immunization at ages 2, 4, and 6 months whose mothers received Tdap during the third trimester of pregnancy (19,20). These trials also are designed to evaluate safety and immunogenicity of Tdap during pregnancy, but are not sufficiently powered to assess disease endpoints. Analysis of interim data from one trial (19, unpublished data) measured infant antibody to pertussis antigens in a blinded fashion for two groups: infants whose mothers received Tdap and infants whose mothers received Td. The first group had elevated antipertussis antibody levels compared with the second at birth and before dose 1, which might be the result of passive antibody transfer, but had lower antipertussis antibody levels after dose 3. In both groups, antipertussis antibody levels were comparable before doses 2 and 3. Although the first group had lower antipertussis antibody levels after dose 3, the evidence of sufficient immune response to DTaP doses compared with the second group was reassuring. ACIP concluded that the interim data are consistent with previously published literature suggesting a short duration of blunting of the infant response, and that the potential benefit of protection from maternal antibodies in newborn infants outweighs the potential risk for shifting disease burden to later in infancy.

Cocooning

Cocooning is defined as the strategy of vaccinating pregnant women immediately postpartum and all other close contacts of infants aged <12 months with Tdap to reduce the risk for transmission of pertussis to infants. Cocooning has been recommended by ACIP since 2005. Cocooning programs have achieved moderate postpartum coverage among mothers but have had limited success in vaccinating fathers or other family members (3) (CDC, unpublished data, 2011). Programmatic challenges make implementation of cocooning programs complex and also impede program expansion and sustainability (2). The effectiveness of vaccinating postpartum mothers and close contacts to protect infants from pertussis is not yet known, but the delay in antibody response among those vaccinated with Tdap after an infant's birth might result in insufficient protection to infants during the first weeks of life (21). ACIP concluded that cocooning alone is an insufficient strategy to prevent pertussis morbidity and mortality in newborn infants. Regardless, ACIP concluded that cocooning likely provides indirect protection to infants and firmly supports vaccination with Tdap for unvaccinated persons who anticipate close contact with an infant.

Decision and Cost Effectiveness Analysis

A decision analysis and cost effectiveness model was developed to assess the impact and cost effectiveness of maternal Tdap vaccination during pregnancy compared with immediately postpartum. The model showed that Tdap vaccination during pregnancy would prevent more infant cases, hospitalizations, and deaths compared with the postpartum dose for two reasons: 1) vaccination during pregnancy benefits the mother and infant by providing earlier protection to the mother, thereby protecting the infant at birth; and 2) vaccination during late pregnancy maximizes transfer of maternal antibodies to the infant, likely providing direct protection to the infant for a period after birth. Model results were most sensitive to efficacy of maternal antibodies and risk for disease as a result of blunting; however, a sensitivity analysis in which infants were assumed to have as little as 20% efficacy of maternal antibodies and a 60% increase in risk for disease as a result of blunting found that maternal vaccination during pregnancy was more cost effective and prevented a greater proportion of infant cases and deaths than postpartum maternal vaccination (22).

Guidance for Use

Maternal vaccination. ACIP recommends that women's health-care personnel implement a Tdap vaccination program for pregnant women who previously have not received Tdap. Health-care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester (after 20 weeks' gestation). If not administered during pregnancy, Tdap should be administered immediately postpartum.

Cocooning. ACIP recommends that adolescents and adults (e.g., parents, siblings, grandparents, child-care providers, and health-care personnel) who have or anticipate having close contact with an infant aged <12 months should receive a single dose of Tdap to protect against pertussis if they have not previously received Tdap. Ideally, these adolescents and adults should receive Tdap at least 2 weeks before beginning close contact with the infant.

Special Situations

Pregnant women due for tetanus booster. If a tetanus and diphtheria booster vaccination is indicated during pregnancy for a woman who has previously not received Tdap (i.e., more than 10 years since previous Td), then Tdap should be administered during pregnancy, preferably during the third or late second trimester (after 20 weeks' gestation).

Wound management for pregnant women. As part of standard wound management care to prevent tetanus, a tetanus toxoid–containing vaccine might be recommended for wound management in a pregnant woman if 5 years or more have elapsed since last receiving Td. If a tetanus booster is indicated for a pregnant woman who previously has not received Tdap, Tdap should be administered.

Pregnant women with unknown or incomplete tetanus vaccination. To ensure protection against maternal and neonatal tetanus, pregnant women who have never been vaccinated against tetanus should receive three vaccinations containing tetanus and reduced diphtheria toxoids. The recommended schedule is 0, 4 weeks, and 6 to 12 months. Tdap should replace 1 dose of Td, preferably during the third or late second trimester (after 20 weeks' gestation) of pregnancy.

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OBSTETRICS

Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women

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OBJECTIVE: We sought to characterize reports to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women who received tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap).

STUDY DESIGN: We searched VAERS for reports of pregnant women who received Tdap from Jan. 1, 2005, through June 30, 2010. We conducted a clinical review of reports and available medical records.

RESULTS: We identified 132 reports of Tdap administered to pregnant women; 55 (42%) described no adverse event (AE). No maternal or infant deaths were reported. The most frequent pregnancy-specific AE was spontaneous abortion in 22 (16.7%) reports. Injection site reac-

tions were the most frequent non-pregnancy–specific AE found in 6 (4.5%) reports. One report with a major congenital anomaly (gastroschisis) was identified.

CONCLUSION: During a time when Tdap was not routinely recommended in pregnancy, review of reports to VAERS in pregnant women after Tdap did not identify any concerning patterns in maternal, infant, or fetal outcomes.

Key words: acellular pertussis vaccine, adverse events, epidemiology, pregnancy, reduced diphtheria toxoid, surveillance, tetanus toxoid, vaccine safety

Administration of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) to a pregnant woman induces formation of maternal antibodies against pertussis that are transferred to the fetus across the placenta.[1] Transplacentally transferred antibodies might provide protection

★ **EDITORS' CHOICE** ★

against pertussis infection in young infants.[1,2] In addition, Tdap vaccination of pregnant women and other family members directly prevents pertussis in these individuals and may indirectly protect infants by reducing the risk for pertussis

transmission, a strategy known as cocooning.[3] Infants <3 months of age are too young to receive the primary pertussis vaccination series and have the highest risk for death from pertussis. Therefore, strategies to prevent pertussis in these infants are essential.[4]

Tdap was licensed by the Food and Drug Administration (FDA) in 2005 for booster immunization against tetanus, diphtheria, and pertussis for individuals 10-64 years of age, and is available in the United States from 2 manufacturers: Adacel (Sanofi Pasteur, Swiftwater, PA)[5] and Boostrix (GlaxoSmithKline Biologicals, Rixensart, Belgium).[6] Since 2008 the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended using Tdap in the immediate postpartum period in women who did not previously receive Tdap to protect both mothers and infants from pertussis.[7] ACIP did not routinely recommend use of Tdap in pregnant women, but recommended that providers consider use in certain situations that included instances when a pregnant woman has insufficient tetanus or diphtheria protection until delivery, or is at

✎ For Editors' Commentary, see Contents

increased risk for pertussis (eg, adolescents aged 11-18 years, health care personnel, and women employed in institutions or living in a community in which a pertussis outbreak is occurring).[7] In 2011 ACIP assessed that the strategy focusing on cocooning had not achieved the intended goal of reducing the burden of pertussis in infants. In October 2011, CDC published an updated ACIP recommendation that health care providers administer Tdap during the third or late second trimester (>20 weeks' gestation) to women who have not previously received Tdap.[8]

To provide safety evidence to help inform the ACIP deliberations for Tdap use in pregnant women, we conducted a review of reports to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women given Tdap from 2005 through 2010.

MATERIALS AND METHODS
Data sources
VAERS is a spontaneous reporting system coadministered by CDC and FDA.[9] Established in 1990, VAERS monitors vaccine safety and accepts adverse event (AE) reports following receipt of any US-licensed vaccine.[10] VAERS is not designed to assess causal associations between vaccines and AEs; its primary purpose is to detect potential vaccine safety concerns that may be further investigated in defined populations.[11] The VAERS report form collects demographic and health information, including information about the vaccination and AE experience.[12] It does not specifically collect information on pregnancy status. AE signs and symptoms recorded in each VAERS report are coded by trained staff using an internationally standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA).[13] Each report can be coded with ≥1 MedDRA term. Reports are also classified as "serious" based on the Code of Federal Regulations[14] if they contain information that the AE resulted in death, hospitalization, prolongation of hospitalization, life-threatening illness, persistent or significant disability, or congenital anomalies. For this study,

the definition of "serious" was slightly modified and did not include reports on hospitalizations for delivery unless they required prolonged stay in a hospital due to delivery complications or postpartum conditions. Medical records are routinely requested for nonmanufacturer serious VAERS reports.

We searched the VAERS database for reports of pregnant women vaccinated in the United States with Tdap, with or without other vaccines, from Jan. 1, 2005, through June 30, 2010. We conducted an automated search using the following criteria: MedDRA terms in 2 System Organ Classes "Pregnancy, Puerperium, and Perinatal Conditions" and "Congenital, Familial, and Genetic Disorders"; MedDRA term "Drug Exposure During Pregnancy"; and a text string search for the term "preg" in the report. Reports that had at least one of these criteria were included in the data set for further evaluation.

Clinical reviews
CDC and FDA medical officers reviewed all US reports identified in the VAERS database using the automated search to confirm pregnancy status at time of vaccination, calculate gestational age, and characterize AEs. We included reports on infants born to women vaccinated with Tdap during pregnancy. For each report we assigned a primary diagnosis. If >1 AE was reported for the same individual, we assigned the diagnosis based on what we believed was the primary clinical event of concern and assumed the primary event was the pregnancy-specific event unless information suggested otherwise. Complex reports were reviewed by physicians on the study team with expertise in obstetrics and neonatology. If a VAERS report described AEs in >1 person, we treated each person as a separate report. Reports that indicated the reported subject was not pregnant or that Tdap was administered prior to the last menstrual period were excluded.

Gestational age at the time of vaccination and at the time of the AE was calculated based on: (1) clinical determination of health care provider, (2) earliest ultrasound assessment (if the former was

not available), or (3) last menstrual period, estimated delivery date, or estimated date of conception (if the first 2 options were not available) found in VAERS report and/or medical records. We used the following definition for trimesters: first (0-13 weeks), second (14-27 weeks), and third (≥28 weeks).[15] Spontaneous abortion (SAB) was defined as fetal demise <20 weeks' gestation, stillbirth was defined as fetal demise ≥20 weeks' gestation, and preterm delivery was defined as a live birth <37 weeks' gestation. Causality between reported AEs and Tdap was not assessed.

Proportional reporting ratios
To assess for disproportionately higher reporting of AEs after Tdap administered to pregnant women, we calculated proportional reporting ratios (PRRs)[16,17] compared to inactivated influenza vaccines, which have been determined to have an acceptable safety profile in pregnancy.[18,19] We compared proportions of MedDRA terms after Tdap with proportions of the same MedDRA terms after trivalent inactivated influenza vaccines (TIV) and influenza A (H1N1) 2009 monovalent vaccine (used during the 2009 through 2010 pandemic) administered without Tdap to pregnant women. For TIV and monovalent vaccine administered in pregnancy, we used VAERS reports identified for previously conducted and published studies.[18,19] We excluded reports from analysis if no AE was reported or if live vaccines (contraindicated during pregnancy[20]) or anthrax vaccine (not recommended during pregnancy[21]) were administered concomitantly. We identified MedDRA terms with disproportionately higher reporting after Tdap by applying criteria of Evans et al[16] (PRR ≥2.0, Yates χ^2 ≥4.0, and number of reports ≥3 in the Tdap group). Clinical reviews were conducted for all MedDRA terms with a PRR ≥2.0.

Because VAERS is a routine, government-sponsored surveillance system that does not meet the definition of research, this investigation was not subject to institutional review board review and informed consent requirements.

RESULTS

During Jan. 1, 2005, through June 30, 2010, VAERS received a total of 106,573 US reports after Tdap; 163 reports met criteria of pregnancy reports using the automated search. Of these reports, 33 were excluded: 28 reports indicated that the subject was not pregnant, 2 reports indicated that Tdap was received postpartum, 2 reports indicated vaccination in children, and 1 report was a duplicate. Two reports described AEs in infant and mother; each of these reports was treated as 2 separate reports (1 for infant and 1 for mother). After the clinical review, 132 reports were identified as true pregnancy reports and were used for further analysis. Six (4.5%) reports were classified as serious and included 2 reports of ruptured ectopic pregnancies that required laparotomy; and 1 report each of stillbirth at 37 weeks' gestation due to placental abruption, influenza, gastroschisis in a newborn, and laryngotracheomalacia in a 3-month-old infant. In all these reports, the serious classification was based on the person requiring hospitalization. No maternal or infant deaths were reported.

Characteristics of VAERS reports are presented in Table 1. A majority of the reports (69, 52.3%) were received from manufacturers. In 48 (36.4%) reports Tdap was the only vaccine received. The median maternal age was 22 years. Information to determine the trimester of Tdap exposure was available for 110 (83.3%) reports. In most of the reports where trimester at time of vaccination was known, 85 (77.3%), indicated that Tdap was administered during the first trimester of pregnancy. A total of 95 (72.0%) reports indicated administration of Adacel.

In all, 55 (41.7%) reports did not describe any AE; these reports were submitted because vaccine had been administered during pregnancy at a time period when Tdap in pregnancy was not routinely recommended (Table 2). The most frequent pregnancy-specific outcome was SAB in 22 (16.7%) reports. The median gestational age at the time of SAB was 9 weeks (range, 5–16 weeks). The median onset interval between vaccination and SAB was 33 days (range,

9–61 days). We did not observe any temporal clustering of SAB reports. Two stillbirth cases were reported. One case occurred in a 20-year-old woman at 37 weeks of gestation and was reported to be due to placental abruption; Tdap was administered several hours before the outcome. The other case was in a 27-year-old woman at 22 weeks of gestation (46 days after exposure to Tdap) with no other pregnancy complications reported before fetal demise.

There were 3 infants born preterm: (1) the first to a 22-year-old woman with a cesarean section at 36 weeks of gestation, described as being indicated because of a history of having a cesarean section delivery; the woman delivered a normal infant; (2) the second case was in a 40-year-old woman with multiple previous pregnancies who also had preeclampsia; she delivered a normal infant at 35 weeks of gestation; and (3) the third case was in an 18-year-old woman who delivered a normal infant at 35 weeks of gestation.

The most frequent non-pregnancy-specific outcomes were injection site reactions, in 6 (4.5%) reports (Table 2).

Six (4.5%) reports indicated adverse infant outcomes, including 1 report each of gastroschisis, patent foramen ovale and peripheral pulmonic stenosis, physiologic neonatal jaundice, transient tachypnea and infiltrates in the lower lobes, bilateral hydrocele, and laryngotracheomalacia (Table 2). Only 1 of these infants had a major birth defect (gastroschisis). This infant was born to a 15-year-old mother who received Tdap and quadrivalent human papillomavirus vaccines concomitantly at approximately 8 weeks' gestation; additional information regarding the maternal history was not available.

In all, 24 (18.2%) pregnancies resulted in vaginal deliveries (including 2 preterm). Eight (6.1%) pregnancies resulted in cesarean deliveries, which included 1 preterm delivery in a 22-year-old woman (described above). Reasons for cesarean deliveries were described in 5 of 8 reports and included 2 reports of severe fetal bradycardia and placental abruption; and 1 report each of macrosomia, arrest of descent, and prolonged labor. Four elective abortions were reported. These reports did not describe any AEs

and reasons for elective termination of pregnancy were not indicated.

Proportional reporting ratios

The PRR screening criteria were met for higher proportional reporting after Tdap in pregnancy for the following MedDRA terms: anemia, antepartum hemorrhage, gestational diabetes, oligohydramnios, and upper respiratory tract infection

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TABLE 1

US VAERS reports following Tdap in pregnant women (n = 132)

Characteristic	Value
Serious reports, n (%)	6 (4.5)
Tdap administered alone,[a] n (%)	48 (36.4)
Median maternal age, y (range)[b]	22 (13–42)
Median interval from vaccination to adverse event, d (range)[c]	7 (0–268)
Median gestational age at time of vaccination, wk (range)[d]	6 (1–37)
Trimester of pregnancy at time of vaccination (n = 110),[e] n (%)	
First (0–13 wk)	85 (77.3)
Second (14–27 wk)	21 (19.1)
Third (≥28 wk)	4 (3.6)
Brand name of Tdap, n (%)	
Adacel[f]	95 (72.0)
Boostrix[g]	20 (15.2)
Unknown	17 (12.9)
Type of reporter, n (%)	
Manufacturer	69 (52.3)
Provider	42 (31.8)
Other	20 (15.2)
Patient/parent	1 (0.8)

Characteristics of Vaccine Adverse Event Reporting System (VAERS) reports received following Tdap vaccine in pregnant women, United States, Jan. 1, 2005, through June 30, 2010 (n = 132).

Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] Other vaccines given with Tdap included meningococcal conjugate (7; 5.4%); human papillomavirus (7; 5.4%); measles, mumps, and rubella (4; 3.1%); and influenza (3; 2.3%); [b] Missing for 1 pregnant woman; [c] Unknown for 61 reports; [d] Unknown for 43 reports; [e] Unknown for 22 reports; [f] Sanofi Pasteur, Swiftwater, PA; [g] GlaxoSmithKline Biologicals, Rixensart, Belgium.

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TABLE 2
Adverse events[a] in pregnant women following Tdap vaccine, VAERS

Adverse events	n	%
Pregnancy-specific adverse events		
Spontaneous abortion[b]	22	16.7
Gestational diabetes	7	5.3
Oligohydramnios[c]	3	2.3
Induction of labor[d]	2	1.5
Stillbirth	2	1.5
Ruptured ectopic pregnancy	2	1.5
Preterm delivery	2	1.5
Subchorionic hemorrhage by ultrasound	1	0.8
Cesarean delivery	1	0.8
Low-lying placenta on ultrasound	1	0.8
Placental abruption and fetal intolerance	1	0.8
Preeclampsia[e]	1	0.8
Prolonged labor	1	0.8
Toxemia[f]	1	0.8
Total	47	35.6
Non-pregnancy–specific outcomes		
Injection site reactions	6	4.5
Anemia	5	3.8
Headache or fever with abdominal pain	3	2.3
Urinary tract infection	2	1.5
Syncope	2	1.5
Upper respiratory infection	2	1.5
Influenza	1	0.8
Nausea and vomiting	1	0.8
Rash on arms/thigh	1	0.8
Superficial thrombophlebitis	1	0.8
Total	24	18.2
Infant outcomes		
Gastroschisis	1	0.8
Laryngotracheomalacia (diagnosed at age 3 mo)[e]	1	0.8
Patent foramen ovale and peripheral pulmonic stenosis	1	0.8
Mild physiologic jaundice	1	0.8
Transient tachypnea and infiltrates in lower lobes	1	0.8
Bilateral hydrocele	1	0.8
Total	6	4.5
No adverse events	55	41.7

Reported adverse events[a] in pregnant women following receipt of Tdap vaccine, Vaccine Adverse Event Reporting System (VAERS), Jan. 1, 2005, through June 30, 2010 (n = 132).

Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] Based on primary reported diagnosis identified during clinical review–1 diagnosis assigned to 1 report; [b] Pregnancy outcomes were not reported in 65 (42%) reports–other pregnancy outcomes included 4 (3.0%) elective termination of pregnancy, 24 (18.2%) vaginal deliveries, and 8 (6.1%) cesarean deliveries; [c] 2 cases with oligohydramnios had induction of labor as secondary diagnosis and 1 case had threatened abortion in early pregnancy as secondary diagnosis; [d] Chorioamnionitis was reported as secondary to labor induction; [e] Preterm delivery reported as secondary diagnosis for this case; [f] Threatened abortion in early pregnancy is reported for this case as secondary diagnosis.

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(Table 3). No disproportionality was found in reporting SAB, stillbirth, or preterm deliveries.

The 3 reports with the MedDRA code for anemia were nonserious reports. The lowest hemoglobin values listed in 3 reports ranged from 9.3–10 g/dL. All anemia cases were treated with iron supplements and prenatal vitamins.

The 3 antepartum hemorrhage reports were nonserious: 1 case of vaginal bleeding/threatened abortion in early pregnancy that subsequently resolved (pregnancy resulted in full-term delivery without complications), 1 subchorionic hemorrhage detected by ultrasound at 12 weeks' gestation that occurred before Tdap, and 1 subchorionic hemorrhage detected by ultrasound at 6 weeks' gestation that was described as "small."

Seven reports were coded as gestational diabetes, all of which were nonserious. Among these cases, the median age of the women was 31 years (range, 25–38 years). Four of the 7 reports described at least 1 risk factor for gestational diabetes that included a body mass index reported as "high" in 3 reports, and history of gestational diabetes in a previous pregnancy in 1 report. One report coded as gestational diabetes described history of type 2 diabetes mellitus and did not refer to the current pregnancy.

Three mothers had oligohydramnios occurring at 33, 40, and 36 weeks of gestation. However, 2 reports did not appear to meet clinical criteria for oligohydramnios (amniotic fluid index <5 cm)[22] as these patients had an amniotic fluid index >5 cm. All 3 women delivered term normal infants with normal birth weight. In one case, a nuchal cord had to be reduced and brief intubation of the newborn was performed.

+Three women developed upper respiratory infection at 3, 23, and 20 weeks of gestation. The first 2 pregnancies resulted in SAB at 9 weeks and term vaginal delivery, respectively, and the outcome of the third pregnancy was not reported.

COMMENT
During 2005 through 2010 when Tdap was not routinely recommended for use

in pregnant women, we found 132 reports submitted to VAERS after receipt of Tdap in pregnant women, accounting for approximately 0.1% of all US reports after Tdap during this period. Our review did not find any unusual or unexpected pattern of maternal, infant, or fetal AEs. A sizable minority of reports (42%) did not describe an AE other than the exposure to Tdap during pregnancy. About 5% of reports met the definition of serious, which is lower than observed in the pregnancy registry of one of the Tdap manufacturers.[23]

SAB was the most frequent pregnancy-specific outcome, reported in 16.7% of reports. SAB is a relatively common event that occurs in about 15-20% of all pregnancies.[24] SAB was also the most frequent pregnancy-specific AE reported in studies of influenza vaccine safety.[18,19] Our analysis did not reveal disproportionate reporting for SAB in VAERS for Tdap compared with influenza vaccines. We identified only 1 infant with a major birth defect in our review: an infant with gastroschisis born to a 15-year-old mother who concomitantly received Tdap with human papillomavirus vaccine. The prevalence of gastroschisis in the United States is 3.73 cases per 10,000 live births[25] and the risk factor most consistently identified for gastroschisis is younger maternal age.[26] Because the total number of pregnant women vaccinated with Tdap is not known, it is difficult to interpret the VAERS findings. No other infants with major birth defects were reported.

As expected, the most frequent non-pregnancy-specific outcome was injection site reaction found in 4.5% of reports; injection site reactions have been identified as a common AE in prelicensure trials in non-pregnant persons.[5,6]

Disproportionality analysis for reports in pregnant women revealed that gestational diabetes, anemia, antepartum hemorrhage, oligohydramnios, and upper respiratory infection were reported to VAERS more frequently after Tdap than after inactivated influenza vaccines. However, further clinical review found that most of these conditions were minor, and there were no concerning patterns for these outcomes that required

TABLE 3
MedDRA terms among pregnant women after Tdap vaccines compared to inactivated influenza vaccines

MedDRA term	Tdap reports, no. (%) (n = 71)	MIV + TIV, no. (%) (n = 467)	PRR (95% CI)
Anemia	3 (4.2)	1 (0.2)	19.73 (2.1–187.1)
Antepartum hemorrhage	3 (4.2)	1 (0.2)	19.73 (2.1–187.1)
Gestational diabetes	7 (9.9)	3 (0.6)	15.35 (4.1–58.0)
Oligohydramnios	3 (4.2)	3 (0.6)	6.58 (1.4–32.0)
Upper respiratory tract infection	3 (4.2)	3 (0.6)	6.58 (1.4–32.0)

CI, confidence interval; *MedDRA*, Medical Dictionary for Regulatory Activities; *MIV*, monovalent inactivated vaccine (H1N1); *PRR*, proportional reporting ratio; *Tdap*, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; *TIV*, trivalent inactivated influenza vaccine.

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additional investigation. Because most VAERS reports were from women vaccinated during the first trimester, we were not able to separately evaluate VAERS reports of vaccinations in second and third trimesters of pregnancy. As a national surveillance system, VAERS may be used to detect signals of potential vaccine safety concerns, which can be further explored in carefully designed epidemiological studies. For example, during the 2010-2011 influenza season, a vaccine safety signal for febrile seizures after TIV in young children was identified in VAERS[27] and subsequently confirmed in the Vaccine Safety Datalink,[28] an active surveillance system used to monitor the safety of vaccines in the United States. VAERS has inherent limitations of all passive surveillance systems including underreporting, reporting biases, and inconsistency in quality of reports. Events occurring temporally closer to the time of vaccination are more likely to be reported to VAERS[9]; birth defects diagnosed months after the vaccination may be underreported. Therefore, VAERS data must be interpreted with caution and cannot generally be used to assess causality.[9] The regulatory definition of a serious report in VAERS can have limitations as it may not reflect the true severity of an outcome. For example, in our review 1 stillbirth report at 37 weeks was coded as serious because the patient was hospitalized, whereas a second stillbirth report at 22 weeks was coded as nonse-

rious because the report did not indicate the patient had been hospitalized.

Since Tdap was not routinely recommended for use in pregnancy during the period of this review, no national survey was conducted to assessed Tdap coverage in pregnant women. Therefore, because there were no data on the number of Tdap doses administered to pregnant women, reporting rates cannot be calculated and findings are difficult to interpret.

Prelicensure trials of Tdap did not include pregnant women, and the package inserts for Tdap state that the products should only be used in pregnancy if they are clearly needed.[5,6] ACIP may sometimes make recommendations for off-label use of vaccines after thorough review of risks and benefits.[29]

Our findings are consistent with those of previous observations. Case-control studies of tetanus toxoid have found no association between vaccination with tetanus toxoid during pregnancy and congenital anomalies.[30,31] Few studies have been conducted on the safety of Tdap in pregnant women. A recent review from 2005 through 2011 of the Adacel Vaccine Pregnancy Registry reported 539 pregnant women who received Tdap during pregnancy. Among the 480 spontaneous prospective reports in this series, 27 (5.6%) were classified as serious AEs using a similar definition as our review and there were 16 (3.3%) SAB and 8 (1.7%) preterm deliveries.[23] In another study of 4524 health care workers who were vaccinated with Tdap during a mass

vaccination campaign, 16 women received Tdap during pregnancy, all of whom gave birth to full-term infants who had normal newborn evaluations.[32]

In June 2011, ACIP recommended that health care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester (>20 weeks' gestation).[8] Although we anticipate that Tdap will continue to have a good safety profile, it is important to continue safety monitoring as more pregnant women are vaccinated.

CONCLUSION

In this comprehensive review encompassing >5 years of reports to VAERS in pregnant women who received Tdap during a time when Tdap was not routinely recommended for pregnant women, we identified no safety concerns. Although our review was subject to limitations of a spontaneous reporting system, our data provide useful baseline information as the new ACIP recommendation for routine use of Tdap in pregnant women is implemented.[8] ■

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