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

**C. Mary Healy,[1,2,3] Marcia A. Rench,[1,3] and Carol J. Baker[1,2,3,4]**

[1]Center for Vaccine Awareness and Research, Texas Children's Hospital, [2]Ben Taub General Hospital, [3]Department of Pediatrics, and [4]Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas

**(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

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Correspondence: C. Mary Healy, MD, 1102 Bates St, Suite 1120, Houston, TX 77030 (chealy@bcm.edu).

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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 $\chi^2$ 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**

| | Tdap During Pregnancy[a] (n = 19) | | Tdap Before Pregnancy (n = 86) | | Tdap Before Pregnancy and No Evidence of Recent Infection[b] (n = 83) | |
|---|---|---|---|---|---|---|
| Antigen | 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 (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.

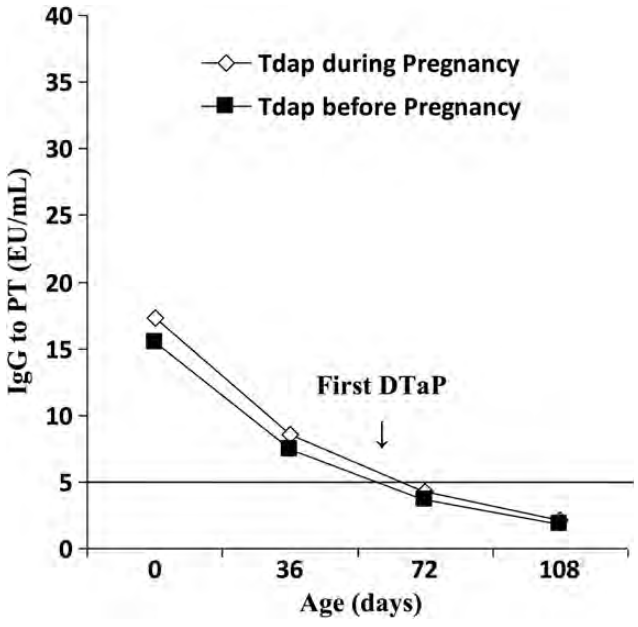


**Figure 1.** Geometric mean concentrations (GMCs) of pertussis toxin immunoglobulin G in infant cord sera and estimated infant concentrations through 3 months of age by maternal tetanus-diphtheria-acellular pertussis vaccine administration status. Confidence intervals for GMCs at birth are given in 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 multifaceted 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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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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