JAMA | Preliminary Communication

Safety and Immunogenicity of Tetanus Diphtheria and Acellular Pertussis (Tdap) Immunization During Pregnancy in Mothers and Infants
A Randomized Clinical Trial

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IMPORTANCE Maternal immunization with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine could prevent infant pertussis.

OBJECTIVE To evaluate the safety and immunogenicity of Tdap immunization during pregnancy and its effect on infant responses to diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.

DESIGN, SETTING, AND PARTICIPANTS Phase 1-2, randomized, double-blind, placebo-controlled, clinical trial conducted from 2008 to 2012. Forty-eight pregnant women aged 18 to 45 years received Tdap (n = 33) or placebo (n = 15) at 30 to 32 weeks' gestation, with crossover immunization postpartum.

INTERVENTIONS Tdap vaccination at 30 to 32 weeks' gestation or postpartum.

MAIN OUTCOMES AND MEASURES Primary outcomes were maternal and infant adverse events, pertussis illness, and infant growth and development until age 13 months. Secondary outcomes were antibody concentrations in pregnant women before and 4 weeks after Tdap immunization or placebo, at delivery and 2 months' postpartum, and in infants at birth, at 2 months, and after the third and fourth doses of DTaP.

RESULTS No Tdap-associated serious adverse events occurred in women or infants. Injection site reactions after Tdap immunization were reported in 26 (78.8% [95% CI, 61.1%-91.0%]) and 12 (80% [95% CI, 51.9%-95.7%]) pregnant and postpartum women, respectively ($P > .99$). Systemic symptoms were reported in 12 (36.4% [95% CI, 20.4%-54.9%]) and 11 (73.3% [95% CI, 44.9%-92.2%]) pregnant and postpartum women, respectively ($P = .03$). Growth and development were similar in both infant groups. No cases of pertussis occurred. Significantly higher concentrations of pertussis antibodies were measured at delivery in women who received Tdap during pregnancy vs postpartum (eg, pertussis toxin antibodies: 51.0 EU/mL [95% CI, 37.1-70.1] and 9.1 EU/mL [95% CI, 4.6-17.8], respectively; $P < .001$) and in their infants at birth (68.8 EU/mL [95% CI, 52.1-90.8] and 14.0 EU/mL [95% CI, 7.3-26.9], respectively; $P < .001$) and at age 2 months (20.6 EU/mL [95% CI, 14.4-29.6] and 5.3 EU/mL [95% CI, 3.0-9.4], respectively; $P < .001$). Antibody responses in infants born to women receiving Tdap during pregnancy were not different following the fourth dose of DTaP.

CONCLUSIONS AND RELEVANCE This preliminary assessment did not find an increased risk of adverse events among women who received Tdap vaccine during pregnancy or their infants. For secondary outcomes, maternal immunization with Tdap resulted in high concentrations of pertussis antibodies in infants during the first 2 months of life and did not substantially alter infant responses to DTaP. Further research is needed to provide definitive evidence of the safety and efficacy of Tdap immunization during pregnancy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00707148

JAMA. 2014;311(17):1760-1769. doi:10.1001/jama.2014.3633
Corrected on January 24, 2017.

Editorial page 1736

Supplemental content at jama.com

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Pertussis is a highly contagious and potentially fatal vaccine-preventable disease that has reemerged in the United States despite high childhood immunization rates. Infants younger than 6 months are at greatest risk of disease, hospitalization, and death and account for more than 90% of all pertussis-associated deaths in the United States.[1] Infants too young to receive the primary diphtheria and tetanus toxoids and acellular pertussis (DTaP) immunization series as recommended at 2, 4, and 6 months of age depend on passive maternal antibodies for protection against pertussis. However, pregnant women have very low concentrations of pertussis antibodies to transfer to their newborn at the time of delivery.[2-4]

To protect young infants, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine was first recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention in 2008 for postpartum women and close contacts of infants,[5-7] then in 2011 for previously Tdap unimmunized pregnant women,[8] and in 2012 for all pregnant women during every pregnancy, regardless of prior Tdap immunization history.[9]

In this phase 1-2 study initiated prior to the ACIP recommendation to immunize pregnant women with Tdap, we evaluated the safety and immunogenicity of Tdap vaccine administered to women in the third trimester of pregnancy and measured placental transfer of maternal pertussis antibodies to the neonate, their persistence during the first 2 months of life, and their potential effect on infant immune responses to DTaP immunizations.

Methods

Study Design

This was a phase 1-2, randomized, double-blind, placebo-controlled clinical trial conducted in 3 National Institutes of Health Vaccine Treatment Evaluation Unit sites in the United States (Houston, Durham, Seattle) from October 2008 to May 2012. Healthy pregnant women aged 18 to 45 years and at low risk for obstetrical complications were recruited from academic and private obstetric office practices. Women with no underlying chronic medical conditions, a singleton pregnancy, and prenatal evaluation that predicted an uncomplicated pregnancy with normal first or second trimester screening test results and detailed anatomic fetal ultrasound at 18 to 22 weeks' gestation were invited to participate. Women who had previously received Tdap or any tetanus-containing vaccine within the prior 2 years were excluded (complete inclusion/exclusion criteria are reported in the eAppendix in Supplement). Race and ethnicity as defined by the participant were reported as required by the sponsor. After written informed consent was obtained, eligible pregnant women were randomized 2:1 to receive Tdap vaccine or a saline placebo injection at 30 through 32 weeks' gestation. Women who received saline during pregnancy were given Tdap vaccine postpartum prior to hospital discharge, and women who received Tdap during pregnancy were given saline postpartum (crossover vaccine administration to ensure blinding of investigators and participants).

Randomization was stratified by site with random block sizes. Each participant was assigned a unique treatment number that corresponded to her treatment allocation. Only the unblinded vaccine administrator had access to the treatment allocation. An age-matched comparison group of healthy nonpregnant women also received Tdap (open label). These nonpregnant women volunteers recruited from the community at each study site provided written informed consent prior to enrollment. Study visits for pregnant women occurred at the day of antepartum vaccination, 4 weeks after vaccination, at delivery, and at 2 and 4 months postpartum; for nonpregnant women, at enrollment, 4 weeks, and 6 months after Tdap immunization; and for infants, at birth and at ages 2 months, 7 months, and 13 months. The study protocol was approved by the institutional review board and ethics committee at each study site.

Study Vaccines

Licensed Tdap vaccine (Adacel, Sanofi Pasteur) was administered as a 0.5-mL intramuscular injection containing 5 Lf tetanus toxoid, 2 Lf diphtheria toxoid, 2.5 µg detoxified pertussis toxin, 5 µg filamentous hemagglutinin, 3 µg pertactin, and 5 µg fimbriae types 2 and 3 in a sterile liquid suspension adsorbed onto aluminum phosphate in single-dose vials. The saline control (Hospira Inc) contained 2 mL of 0.9% sodium chloride for injection. Each vial was used for a single intramuscular dose of 0.5 mL. Infants received DTaP vaccine (Pentacel, Sanofi Pasteur) containing the same antigens as in Adacel (but in different quantities), plus inactivated poliovirus and *Haemophilus influenzae* type b conjugate (tetanus toxoid conjugate), administered by their pediatricians at 2, 4, 6, and 12 months of age.

Safety Assessments

Safety assessments were the primary outcomes. Injection site and systemic reactions were assessed in all women by 30-minute observation and completion of a 7-day symptom diary after each injection. Adverse events and serious adverse events were recorded at each study visit for pregnant women from the day of antepartum vaccination to 4 months postpartum, for nonpregnant women for 6 months after Tdap immunization, and for infants from birth to approximately 13 months of age. Whether an adverse event was attributable to vaccination was judged by the investigators considering temporality, biologic plausibility, and identification of alternative etiologies for each event. The outcomes of pregnancy were documented for mothers and infants at the time of delivery through review of delivery records. Infant growth (weight, length, and frontooccipital circumference) was assessed at each study visit at ages 2, 7, and 13 months, and development was assessed with the Bayley-III Scales of Infant and Toddler Development Third Edition Screening Test (PsychCorp) at the last study visit. Pertussis illness was evaluated in mothers and infants by documenting at each study visit any reported cough lasting more than 2 weeks.

Immunogenicity Assessments

Immunogenicity assessments were secondary outcomes. Blood samples were obtained from pregnant women prior to and 4 weeks after Tdap or placebo antepartum immunization, at de-

livery, and 2 months after the postpartum Tdap or placebo immunization; in infants at birth (cord blood), approximately age 2 months (prior to the first dose of DTaP), 7 months (4 weeks after the third dose of DTaP), and 13 months (4 weeks after the fourth dose of DTaP). Nonpregnant women had samples collected prior to and 4 weeks after Tdap immunization.

Antibody Assays

Serum antibody assays were performed by Sanofi Pasteur, Swiftwater, Pennsylvania, in a blinded manner. Pertussis IgG enzyme-linked immunosorbent assays (ELISAs) were used to quantify the concentration of antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3, expressed in ELISA Units per milliliter (EU/mL).[10] The lower limit of quantitation (LLOQ) was 3 EU/mL for filamentous hemagglutinin and 4 EU/mL for pertussis toxin, pertactin, and fimbriae types 2 and 3. Antitetanus toxoid antibodies were measured by IgG ELISA using the World Health Organization International Standard for Tetanus Immunoglobulin, Human, Lot TE3. The LLOQ of the assay was 0.01 International Units per milliliter (IU/mL). Antidiphtheria antibody responses were measured by the ability of the test sera to protect Vero cells from a diphtheria toxin challenge using World Health Organization reference serum. The lower limit of detection was 0.005 IU/mL.

Statistical Analysis

This phase 1-2 exploratory study was not powered to test any specific hypotheses. The primary outcome (safety) measures were the incidence of injection site and systemic reactions recorded 0 to 7 days after each injection, the frequency of vaccine-associated adverse events and serious adverse events, the incidence of pertussis illness captured by surveillance of reported cough lasting more than 2 weeks, infant growth measurements, and Bayley III developmental screening of infants. The secondary outcome (immunogenicity) measures were the concentration of IgG antibodies to the vaccine antigens (pertussis toxin, pertactin, filamentous hemagglutinin, fimbriae types 2 and 3, tetanus toxoid, and diphtheria toxoid).

Safety outcome measures were described using frequency, proportion, and 2-sided exact 95% CIs. All participants receiving at least 1 injection were included in the safety summaries. Pertussis antibody geometric mean concentration (GMC) and 95% CI were calculated for each time point and study group. Placental transfer of antibodies at delivery (ratio of cord blood GMC to maternal GMC) and antibody decay in infants (ratio of GMC at 2 months to cord blood GMC) were estimated. Spearman rank correlation was used to detect monotonically increasing or decreasing associations between concentrations and avoid influence of outlying observations. The GMC of pertussis antibodies after 3 doses of DTaP were correlated with cord blood levels in infants. Results less than the LLOQ were assigned one-half of the LLOQ for calculations of GMC and placental transmission. The proportion of participants with tetanus and diphtheria antibody concentrations of 0.1 IU/mL or greater and 1.0 IU/mL or greater and their 95% CIs were calculated.

The primary analysis of immunogenicity included participants who received 2 injections (1 vaccine and 1 saline placebo) and contributed both prevaccination and postvaccination blood samples for testing and for which valid results were reported. One mother and 4 infants were excluded from immunogenicity analyses because of errors in administration of immunizations to the infants (3 infants), a missing delivery blood sample (1 infant), and a mother receiving the postpartum injection more than 2 months late.

Frequencies were compared using a 2-sided Fisher exact test (2-way comparisons) and the Freeman-Halton extension (3-way comparisons). Two-sided *t* test was used to compare GMCs between groups. An individual α level of .05 was applied for assigning statistical significance. No imputation was carried out for missing data.

Analyses were performed using SAS version 9.3 (SAS Institute Inc) and R version 2.15.2 (2012-10-26) (R Project for Statistical Computing, http://www.r-project.org/).

Results

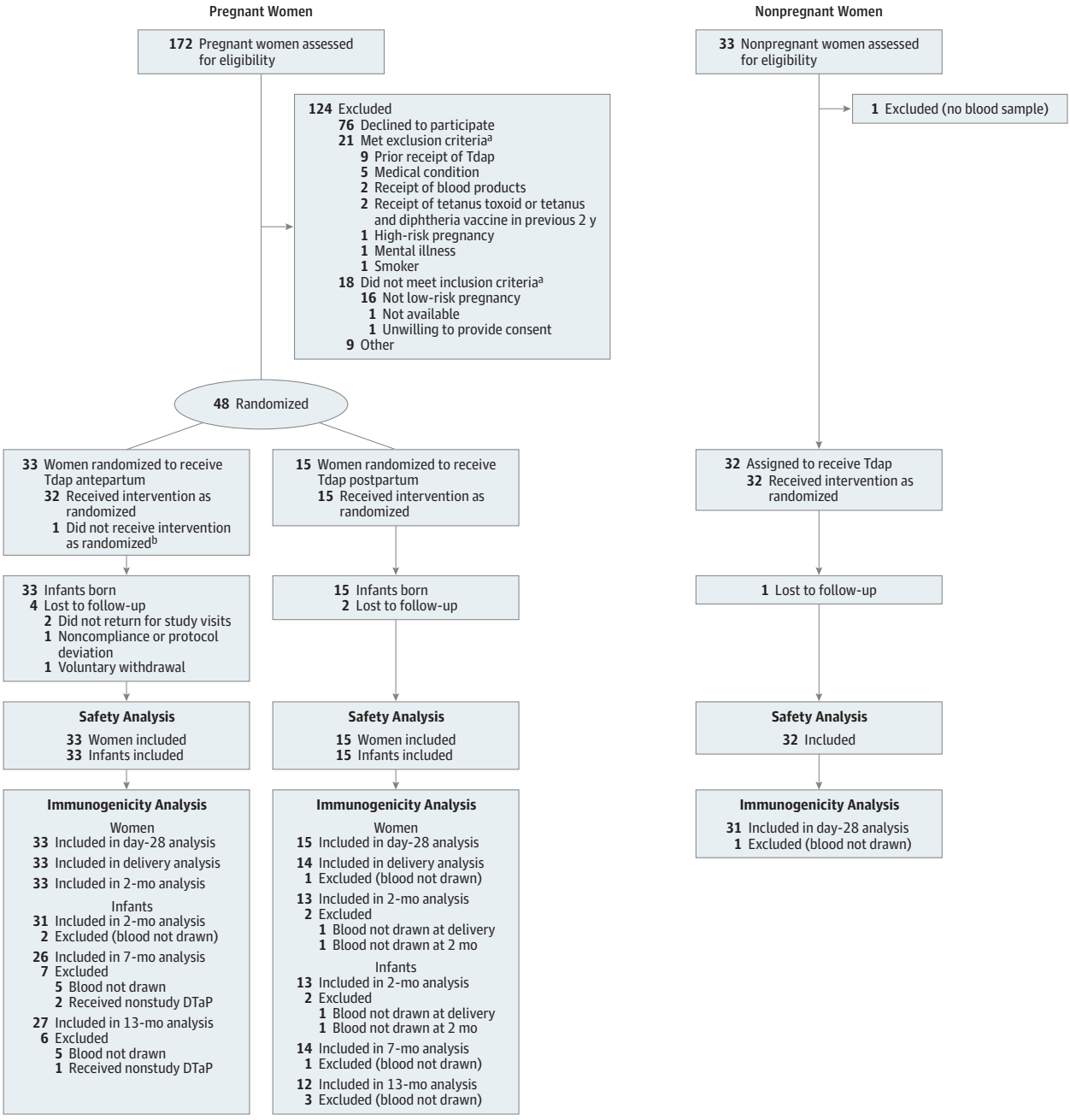
Forty-eight healthy pregnant women and their infants and 32 healthy nonpregnant women were enrolled. Thirty-three pregnant women received Tdap vaccine and 15 received placebo during pregnancy (**Figure**). The mean interval from Tdap immunization to delivery was 52.1 days (SD, 10.5 [95% CI, 48.4-55.8]) and the median interval was 54 days (range, 32-68). Demographic and clinical characteristics of study participants are described in **Table 1**.

Safety

The proportion of participants reporting any injection site reactions following Tdap immunization was not different between the groups: 78.8% (95% CI, 61.1%-91.0%) pregnant women, 80.0% (95% CI, 51.9%-95.7%) postpartum women, and 78.1% (95% CI, 60.0%-90.7%) nonpregnant women ($P > .99$) (**Table 2**). Following placebo administration, fewer pregnant women (20.0% [95% CI, 4.3%-48.1%]) and postpartum women (18.2% [95% CI, 7.0%-35.5%]) reported injection site reactions. Pain at the injection site was the most common symptom following Tdap immunization, reported in 75.8% (95% CI, 57.7%-88.9%) pregnant women, 73.3% (95% CI, 44.9%-92.2%) postpartum women, and 78.1% (95% CI, 60.0%-90.7%) nonpregnant women ($P \geq .35$); swelling and erythema were infrequent. Most symptoms were mild and resolved within 72 hours (eTable 1 in Supplement).

The proportion of participants with any systemic symptom was 36.4% (95% CI, 20.4%-54.9%) in women immunized during pregnancy, 73.3% (95% CI, 44.9%-92.2%) in women receiving Tdap postpartum, and 53.1% (95% CI, 34.7%-70.9%) in nonpregnant women ($P = .055$) (Table 2). The frequencies of headache, myalgia, and malaise were not significantly different among the 3 groups ($P \geq .35$), headache being more common than myalgia and malaise. The occurrence of fever after receipt of Tdap was significantly different between the 3 groups, with pregnant women (3.0% [95% CI, 0.1%-15.8%]) and nonpregnant women (9.4% [95% CI, 2.0%-25.0%]) reporting it less frequently than postpartum women (26.7% [95% CI, 7.8%-55.1%]) ($P = .04$). However, the occur-

Figure. Consort Flow Diagram



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

[a] Participants who did not meet more than 1 eligibility criterion are categorized by the first criterion met.

[b] Received pharmacy stock vaccine, not study vaccine; included in analysis.

rence of fever in women receiving Tdap vaccine postpartum (26.7% [95% CI, 7.8%-55.1%]) was not different from that of postpartum placebo recipients (15.2% [95% CI, 5.1%-31.9%]) (P = .43). There was also no difference in the proportion of participants with fever between recipients of Tdap during pregnancy and nonpregnant women (P = .36). Most systemic symptoms were mild and self-limited (eTable 1 in Supplement).

Serious adverse events were reported by 22 participants, including 7 (21.2% [95% CI, 8.9%-38.9%]) women who received Tdap during pregnancy and 6 (18.1% [95% CI, 7.0%-35.5%]) of their infants; 2 (13.3% [95% CI, 1.7%-40.5%]) women given Tdap postpartum and 6 (40% [95% CI, 16.3%-67.7%]) of their infants; and 1 (3.1% [95% CI, <0.1%-16.2%]) nonpregnant woman (**Table 3**). None were judged to be attributable to

Table 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	Women		
	Pregnant		
	Tdap Antepartum/Placebo Postpartum (n = 33)	Placebo Antepartum/Tdap Postpartum (n = 15)	Nonpregnant Tdap (n = 32)
Ethnicity, No. (%)			
Nonhispanic	23 (69.7)	12 (80.0)	18 (56.3)
Hispanic	10 (30.3)	3 (20.0)	14 (43.8)
Race, No. (%)			
Asian	5 (15.2)	1 (6.7)	0
Black/African American	12 (36.4)	7 (46.7)	7 (21.9)
White	13 (39.4)	7 (46.7)	21 (65.6)
Multiracial	1 (3.0)	0	1 (3.1)
Other/unknown	2 (6.1)	0	3 (9.4)
Age, y			
Mean (SD)	28.1 (6.7)	27.8 (6.7)	28.9 (6.0)
Median (range)	30.5 (18-43)	27.0 (18-38)	28.5 (20-40)
Parity			
Mean (SD)	1.9 (1.1)	1.8 (0.8)	NA
Median (range)	2 (0-5)	2 (0-3)	
Mode of delivery, No. (%)			NA
Vaginal	24 (72.7)	6 (40)	
Cesarean	9 (27.3)	9 (60)	
Gestational age at delivery, wk, No. (%)			NA
≥37	30 (90.9)	14 (93.3)	
<37[a]	3 (9.1)	1 (6.7)	
Infant birth weight, kg			
Mean (SD)	3.2 (0.5)	3.5 (0.7)	NA
Median (range)	3.2 (2-4)	3.3 (2-4)	
Infant Apgar score at 1 and 5 min			
Mean (SD)	8 (1.4) and 8.9 (0.2)	7.9 (1.1) and 8.9 (0.4)	NA
Median (range)	8 (1-9) and 9 (8-9)	8 (5-9) and 9 (8-9)	
Infant initial examination, No. (%)			NA
Normal	30 (90.9)	12 (80)	
Abnormal	3 (9.1)[b]	3[11,c]	
Congenital anomalies, No. (%)	1[3,d]	2 (13.3)[e]	NA
Neonatal complications, No. (%)	4 (12.1)[f]	5 (33.3)[g]	NA

Abbreviations: NA, not applicable; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] All infants born at more than 35 weeks' gestation.

[b] Cephalohematoma (2) and hydrocele (1).

[c] Decreased breath sounds with increased anteroposterior diameter (1), laceration (1), large for gestational age and heart murmur (1).

[d] Bilateral renal pelviectasis.

[e] Asymptomatic atrial septal defect or ventricular septal defect (1) and cardiomyopathy (1).

[f] Tachypnea (1), jaundice (1), hypoglycemia (1).

[g] Hypoglycemia (1), hypoglycemia and tachypnea (2), tachypnea (1), bilateral pneumothorax (1).

Tdap vaccine. Nonserious adverse events occurred in 63.6% (95% CI, 45.1%-79.6%) of women given Tdap during pregnancy, 73.3% (95% CI, 45.0%-92.2%) of women given Tdap postpartum, and 28.1% (95% CI, 13.7%-46.7%) of nonpregnant women, as well as in 84.8% (95% CI, 68.1%-94.9%) of infants born to women vaccinated with Tdap antepartum and 93.3% (95% CI, 68.1%-99.8%) of infants born to women receiving Tdap postpartum. All resolved without sequelae.

All infants were live born, mostly at term and by vaginal delivery (Table 1). There were no significant differences in the infants' gestational ages, birth weights, Apgar scores, neonatal examinations, or complications. There were no differences in the infants' growth and development (eTable 2 and eTable 3 in Supplement), and no cases of pertussis illness occurred in mothers or infants.

Immunogenicity

At baseline, the antibody concentration to each of the vaccine antigens was low and comparable among the study groups. Antibody responses to Tdap vaccine in pregnant women were not different than those of nonpregnant women and women immunized postpartum (**Table 4**, eFigure 1 in Supplement). Women immunized with Tdap during pregnancy had significantly higher concentrations of antibodies to all vaccine antigens at delivery than women immunized postpartum (Table 4, eFigure 2 in Supplement). Infants born to mothers who received Tdap during pregnancy had significantly higher concentrations of pertussis antibodies at birth and at age 2 months (Table 4). The concentration of pertussis antibodies in cord blood was higher than in maternal serum at delivery, with linear correlation between maternal and infant concentrations (**Table 5**, eFigure 3 in Supplement). The ratio of the concentrations of antibodies to Tdap antigens remaining at 2 months in infants is shown in Table 5.

At 7 months of age, after receipt of 3 doses of DTaP, infants of women who received Tdap during pregnancy achieved equivalent concentrations of antibodies to pertactin, pertussis toxin, and fimbriae types 2 and 3 and significantly lower

Table 2. Proportion of Participants With Injection Site and Systemic Reactions After Tdap or Saline Placebo Administration, by Study Group

Reaction	Women, No. (%) [95% CI]					
	Tdap Antepartum/Placebo Postpartum (n = 33)		Placebo Antepartum/Tdap Postpartum (n = 15)		Nonpregnant (Tdap) (n = 32)	*P* Value[a]
	Tdap	Placebo	Placebo	Tdap		
Injection site						
Pain	25 (75.8) [57.7-88.9]	5 (15.2) [5.1-31.9]	2 (13.3) [1.7-40.5]	11 (73.3) [44.9-92.2]	25 (78.1) [60.0-90.7]	.94
Erythema/redness	3 (9.1) [1.9-24.3]	1 (3.0) [0.1-15.8]	1 (6.7) [0.2-31.9]	0 [0.0-21.8]	2 (6.3) [0.8-20.8]	.84
Induration/swelling	3 (9.1) [1.9-24.3]	0 [0.0-10.6]	0 [0.0-21.8]	2 (13.3) [1.7-40.5]	1 (3.1) [0.1-16.2]	.36
Any injection site symptom	26 (78.8) [61.1-91.0]	6 (18.2) [7.0-35.5]	3 (20.0) [4.3-48.1]	12 (80.0) [51.9-95.7]	25 (78.1) [60.0-90.7]	>.99
Systemic						
Fever (oral temperature ≥38°C)[b]	1 (3.0) [0.1-15.8][c]	5 (15.2) [5.1-31.9][d]	0 [0.0-21.8]	4 (26.7) [7.8-55.1][d]	3 (9.4) [2.0-25.0][c]	.044
Headache	11 (33.3) [18.0-51.8]	5 (15.2) [5.1-31.9]	3 (20.0) [4.3-48.1]	7 (46.7) [21.3-73.4]	11(34.4) [18.6-53.2]	.65
Malaise	4 (12.1) [3.4-28.2]	3 (9.1) [1.9-24.3]	2 (13.3) [1.7-40.5]	3 (20.0) [4.3-48.1]	6 (18.8) [7.2-36.4]	.73
Myalgia	5 (15.2) [5.1-31.9]	3 (9.1) [1.9-24.3]	0 [0.0-21.8]	3 (20.0) [4.3-48.1]	6 (18.8) [7.2-36.4]	.86
Any systemic symptom	12 (36.4) [20.4-54.9]	9 (27.3) [13.3-45.5]	3 (20.0) [4.3-48.1]	11 (73.3) [44.9-92.2]	17 (53.1) [34.7-70.9]	.055
Any	26 (78.8) [61.1-91.0]	13 (39.4) [22.9-57.9]	5 (33.3) [11.8-61.6]	14 (93.3) [68.1-99.8]	27 (84.4) [67.2-94.7]	.53

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

[a] Fisher exact *P* values comparing individual symptom rates after Tdap doses among Tdap antepartum, Tdap postpartum, and nonpregnant women groups.

[b] The significant difference for fever is attributable to the increased rate in women who received Tdap postpartum (26.7%).

[c] *P* = .36 for rates of fever in women who received Tdap antepartum (3.0%) and nonpregnant women (9.4%).

[d] *P* = .43 for rates of fever in women who received placebo postpartum (15.2%) and women who received Tdap postpartum (26.7%).

concentrations of antibodies to filamentous hemagglutinin compared with infants whose mothers received placebo during pregnancy (40.6 EU/mL [95% CI, 30.6-54.0] vs 78.6 EU/mL [95% CI, 52.9-116.7], respectively; *P* < .01) (Table 4). However, at age 13 months, 1 month after the fourth dose of DTaP, the concentrations of pertussis antibodies were not statistically significantly different in the 2 infant groups (Table 4). Among infants born to women immunized with Tdap during pregnancy, no correlation was observed between cord antibody levels and antibody concentrations achieved after the third DTaP immunization. Among infants of women receiving Tdap postpartum, infants with higher filamentous hemagglutinin antibody levels at birth had lower concentrations at age 7 months (Spearman correlation, 0.55; *P* = .042) (Table 4). Tetanus and diphtheria antibody responses and protective levels achieved after the third and fourth DTaP doses were in general not statistically significantly different in the 2 infant groups (Table 4 and eTable 4 in Supplement).

Discussion

In 2012, the United States experienced the most severe pertussis epidemic in more than half a century, with nearly 42 000 reported cases.[12] The highest incidence of pertussis and its associated complications continue to occur among infants.[12,13] The majority of pertussis-related deaths occur in infants too young to be immunized (ages <2 months) or those incompletely immunized (ages <6 months).[1,12,13] In 2008, postpartum Tdap immunization of mothers and all contacts of infants (ages <12 months) was recommended to create a protective "cocoon" and prevent pertussis in this population.[7] However, this strategy proved to be challenging to implement, and maternal postpartum immunization alone was not effective in reducing the burden of infant disease.[14,15] Newborns are unlikely to have protective levels of pertussis antibodies at birth if their mothers have not received a recent dose of a pertussis-containing vaccine.[2-4] Evidence of rapid decline of pertussis antibody levels in adults and postpartum women immunized with Tdap, the ongoing burden of infant disease, and the increasing severity of pertussis outbreaks in the United States led to the 2012 ACIP recommendation to immunize all pregnant women with Tdap during every pregnancy.[9]

We report for the first time, to our knowledge, in a randomized controlled trial, that Tdap immunization of pregnant women in the third trimester was well tolerated and elicited immune responses similar to those elicited with immunization of nonpregnant women. Among primary outcomes, injection site and systemic reactogenicity rates in pregnant women were not significantly different than those observed among postpartum or nonpregnant women, and no Tdap vaccine–related adverse events or adverse pregnancy outcomes were observed. The safety of Tdap immunization in pregnancy also has been documented through passive surveillance by a Centers for Disease Control and Prevention Vac-

Table 3. Serious Adverse Events in Study Participants Receiving Tdap, by Study Group and Severity

	Antepartum		Postpartum		
	Pregnant Women (n = 33)	Infants of Pregnant Women (n = 33)	Pregnant Women (n = 15)	Infants of Pregnant Women (n = 15)	Nonpregnant Women (n = 32)
No. of participants with serious adverse events, No. (%) [95% CI]	7 (21.2) [8.9-38.9]	6 (18.2) [7.0-35.5]	2 (13.3) [1.7-40.5]	6 (40.0) [16.3-67.7]	1 (3.1) [<0.1-16.2]
No. of serious adverse events	7	7	2	10	1
No. with event by severity					
Mild	0	0	0	2	0
Moderate	3	2	1	5	0
Severe	3	5	1	0	1
Life-threatening	1	0	0	3	0
Event description by severity					
Mild				Atrial septum and ventricular septum defect Cardiomyopathy with biventricular hypertrophy[b]	
Moderate	Hypertension 48 d postvaccination Preterm contractions 33 d postvaccination Wound hematoma after cesarean delivery	Gastroenteritis requiring hospitalization Respiratory distress at birth	Vomiting requiring hospitalization 44 d after placebo injection	Bronchiolitis requiring hospitalization Respiratory distress/tachypnea[c] Anemia[c] Hypoglycemia[b] Poor feeding due to gastroesophageal reflux[b]	
Severe	Pregnancy-induced hypertension 30 d postvaccination Pancreatitis 3 mo after delivery Acute appendicitis 19 d after delivery	Choking with feeds requiring prolonged hospitalization Febrile seizures[a] Dehydration due to oral herpes simplex virus requiring hospitalization Bronchiolitis	Preterm labor requiring hospitalization 18 d after placebo injection		Pelvic fracture (motor vehicle crash)
Life-threatening	Fetal distress resulting in cesarean delivery 55 d postvaccination			Fetal distress resulting in cesarean delivery Fetal distress resulting in cesarean delivery[d] Bilateral pneumothoraces[d]	

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

[a] One infant with febrile seizures had 2 distinct seizure events, both of severe severity.

[b] The mild event of "cardiomyopathy with biventricular hypertrophy" and the 2 moderate events of "hypoglycemia" and "poor feeding" occurred in the same infant.

[c] The 2 moderate events "respiratory distress/tachypnea" and "anemia" occurred in the same infant.

[d] The 2 life-threatening events of "fetal distress" and "bilateral pneumothoraces" occurred in the same infant.

cine Adverse Event Report System review and in a 6-year report of the Adacel vaccine pregnancy registry.[16,17]

Secondary outcome assessments showed that Tdap administration at 30 through 32 weeks' gestation resulted in high pertussis antibody concentrations in maternal sera at delivery that persisted 2 months postpartum, potentially providing protection to the mother during pregnancy and in the postpartum period. Our findings suggest that third-trimester maternal immunization with Tdap results in efficient placental transfer of pertussis antibodies to the fetus and higher antibody concentrations in infants' cord blood than in maternal serum at delivery.[2-4,18]

An important finding from our study was that concentrations of vaccine-induced pertussis antibodies in sera from infants born to mothers immunized with Tdap during pregnancy were significantly higher at birth and at age 2 months than in infants whose mothers were immunized postpartum. This suggests that infant protection could occur during the period of highest risk of pertussis-associated mortality and morbidity. Although serum concentrations of pertussis antibodies that correlate with protection remain uncertain, high concentrations of antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3 are known to be protective.[19,20] Considering the accumulating evidence that the protective efficacy of Tdap immunization wanes rapidly, most women of childbearing age are likely to be similar to our study participants in their susceptibility to pertussis.[11,21]

Importantly, although infants born to mothers immunized with Tdap during pregnancy did manifest lower pertussis antibody concentrations to filamentous hemagglutinin following receipt of the third dose of DTaP vaccine, the reduction was modest (48.3%) and disappeared following receipt of the

fourth dose of DTaP, suggesting that priming and memory immune responses remained unaltered. Although the presence of maternal antibodies could result in a decreased response to active immunization in infants,[22] maternal pertussis antibodies have not been shown to interfere with immunization with acellular pertussis vaccines in young infants.[4,23] A recent observational study of 16 Tdap-immunized pregnant women also

Table 4. Geometric Mean Concentration of Antibodies to Tdap Vaccine Antigens in Sera From Mothers and Infants, and Nonpregnant Women, by Study Group and Time of Sample Collection

	GMC (95% CI)							
	Pregnant and Nonpregnant Women				Infants			
						Months		
Antigen[a]/ Study Group	Prior to Immunization[b]	4 wk After Antepartum Tdap or Placebo[b]	At Delivery	2 Mo After Delivery	At Birth (Cord Blood)	2	7	13
Pertussis toxin, EU/mL								
Antepartum[c]	7.9 (4.9-12.6)	56.5 (40.0-79.9)	51.0 (37.1-70.1)[f]	53.1 (39.4-71.7)[f]	68.8 (52.1-90.8)[f]	20.6 (14.4-29.6)[f]	64.9 (53.8-78.3)	80.1 (57.3-112.1)
Postpartum[d]	9.6 (5.2-17.6)	10.2 (5.6-18.7)	9.1 (4.6-17.8)	66.4 (42.2-104.8)	14.0 (7.3-26.9)	5.3 (3.0-9.4)	96.6 (56.7-164.6)	83.9 (50.0-140.8)
Nonpregnant	17.6 (12.5-24.7)	90.9 (69.1-119.7)						
Filamentous hemagglutinin, EU/mL								
Antepartum[c]	15.1 (8.7-26.0)	234.4 (184.1-298.5)	184.8 (142.8-239.1)[f]	199.8 (153.4-260.3)	234.2 (184.6-297.3)[f]	99.1 (75.8-129.6)[f]	40.6 (30.6-54.0)[g]	69.9 (49.5-98.7)
Postpartum[d]	23.2 (11.9-45.3)	23.6 (13.1-42.5)	21.9 (10.9-44.1)	270.9 (162.6-451.3)	25.1 (10.5-60.3)	6.6 (2.8-15.5)	78.6 (52.9-116.7)[e]	108.9 (78.3-151.5)
Nonpregnant	30.1 (18.7-48.4)	285.6 (238.0-342.8)						
Pertactin, EU/mL								
Antepartum[c]	8.5 (5.5-12.9)	205.0 (117.1-359.1)	192.2 (113.5-324.9)[f]	158.8 (93.5-269.8)	226.8 (137.7-373.7)[f]	75.7 (43.9-130.6)[f]	72.3 (48.7-107.4)	203.3 (121.5-340.1)
Postpartum[d]	13.2 (5.8-30.1)	13.0 (5.7-29.6)	12.2 (5.2-28.4)	210.1 (80.3-549.6)	14.4 (5.4-38.4)	5.2 (2.4-11.5)	77.9 (38.9-152.6)	115.2 (54.8-242.1)
Nonpregnant	20.2 (14.5-28.1)	348.7 (209.1-581.6)						
Fimbriae 2 and 3, EU/mL								
Antepartum[c]	27.2 (14.0-52.6)	1632.9 (954.5-2793.8)	1601.3 (1073.4-2388.9)[f]	1354.8 (874.9-2097.9)	1867.0 (1211.7-2876.8)[f]	510.4 (305.6-852.3)[f]	113.9 (89.9-152.7)	231.9 (133.3-403.5)
Postpartum[d]	36.4 (18.1-73.1)	38.2 (19.3-75.6)	34.9 (16.3-74.8)	2910.2 (1526.4-5548.5)	48.5 (20.1-117.3)	12.0 (4.9-29.4)	193.5 (105.5-354.7)	358.8 (151.1-851.8)
Nonpregnant	36.8 (21.2-63.9)	1785.1 (1222.5-2606.6)						
Tetanus toxoid, IU/mL								
Antepartum[c]	2.0 (1.4-2.8)	15.3 (10.9-21.4)	12.2 (9.0-16.5)[f]	12.2 (9.4-15.9)	16.5 (12.6-21.7)[f]	4.5 (3.4-5.8)[f]	1.9 (1.4-2.5)	6.8 (4.7-9.9)[g]
Postpartum[d]	1.7 (1.2-2.3)	1.6 (1.2-2.2)	1.5 (1.1-2.1)	18.5 (11.7-29.4)	1.8 (1.3-2.6)	0.7 (0.4-1.1)	1.3 (0.7-2.2)	2.7 (1.5-4.8)
Nonpregnant	2.4 (1.8-3.3)	18.4 (13.0-26.2)						
Diphtheria toxoid, IU/mL								
Antepartum[c]	0.6 (0.3-1.1)	8.3 (5.0-13.8)	7.5 (4.6-12.2)[f]	6.5 (3.6-11.6)	9.4 (5.7-15.4)[f]	2.6 (1.6-4.3)[f]	0.6 (0.4-0.9)	5.3 (3.1-8.9)
Postpartum[d]	0.5 (0.2-1.0)	0.5 (0.2-1.0)	0.4 (0.2-0.9)	7.2 (4.1-12.7)	0.5 (0.2-1.2)	0.1 (0.1-0.3)	1.1 (0.6-2.0)	7.7 (3.0-19.4
Nonpregnant	0.7 (0.4-1.2)	4.6 (2.6-8.0)						

Abbreviations: EU, enzyme-linked immunosorbent assay units; GMC, geometric mean concentration; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

[a] Pertussis vaccine antigens: pertussis toxin, filamentous hemagglutinin, pertactin, fimbriae 2 and 3.

[b] At the prior to immunization time point and 4 weeks' postimmunization, n = 33 women immunized with Tdap antepartum, 15 postpartum, and 32 nonpregnant women.

[c] Mothers at delivery, n = 33 for all antigens; infants at birth, n = 31 for pertussis toxin and n = 33 for all other antibodies; infants at 2 months, n = 31; infants at 7 months, n = 26; and infants at 13 months, n = 27 for pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae types 2 and 3; n = 26 for tetanus, and n = 25 for diphtheria antibodies.

[d] Mothers at delivery, n = 14 for all antigens; infants at birth, n = 14, infants at 2 months, n = 13 for pertussis toxin, pertactin, fimbriae types 2 and 3, and n = 12 for filamentous hemagglutinin, tetanus, and diphtheria; infants at 7 months, n = 14, and infants at 13 months, n = 12.

[e] In this group, infants with higher filamentous hemagglutinin antibody levels at birth had lower concentrations at 7 months of age (Spearman correlation, 0.55; $P = .042$).

[f] $P < .001$ for Tdap antepartum vs Tdap postpartum groups.

[g] $P < .01$ for Tdap antepartum vs Tdap postpartum groups.

Table 5. Transplacental Transfer of Antibodies (Ratio of Infant Cord Blood Antibodies to Maternal Antibodies) and Antibody Concentrations in Infants at 2 Months of Age Compared With Concentrations at Birth (Ratio of Infant 2-Month Antibodies to Cord Blood Antibodies)

	Ratio (95% CI)			
	Tdap Antepartum/Placebo Postpartum (n = 31)		Placebo Antepartum/Tdap Postpartum (n = 14)	
Vaccine Antigen	Infant Cord Blood Antibodies to Maternal Antibodies at Delivery	Infant Antibodies at 2 Mo to Cord Blood Antibodies	Infant Cord Blood Antibodies to Maternal Antibodies at Delivery	Infant Antibodies at 2 Mo to Cord Blood Antibodies
Pertussis Toxin	1.23 (1.03 to −1.47)	0.34 (0.29 to 0.41)[a]	1.54 (1.15 to 2.05)	0.40 (0.29 to 0.56)[b]
Filamentous hemagglutinin	1.27 (1.13 to 1.42)	0.42 (0.36 to 0.49)	1.15 (0.74 to 1.76)	0.32 (0.19 to 0.53)[c]
Pertactin	1.19 (0.93 to 1.52)	0.31 (0.25 to 0.39)	1.19 (0.98 to 1.44)	0.42 (0.29 to 0.60)[b]
Fimbriae 2 and 3	1.26 (1.02 to 1.55)	0.26 (0.20 to 0.32)	1.49 (1.27 to 1.73)	0.25 (0.19 to 0.33)[b]
Tetanus	1.36 (1.14 to 1.62)	0.27 (0.22 to 0.31)[d]	1.19 (1.02 to 1.40)	0.38 (0.26 to 0.57)[c,d]
Diphtheria	1.26 (0.91 to 1.75)	0.28 (0.22 to 0.36)	1.28 (0.91 to 1.79)	0.28 (0.22 to 0.36)[c]

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

[a] n = 29.

[b] n = 13.

[c] n = 12.

[d] P = .042 for Tdap antepartum vs Tdap postpartum groups. Otherwise, no statistically significant differences were observed when comparing ratio of infant cord blood antibodies to maternal antibodies at delivery or ratio of infant antibodies at 2 months to cord blood antibodies between the groups.

found only modest reductions in infant pertussis antibody levels following the third dose of DTaP vaccine.[24]

Our study has several potential limitations. First, the small number of participants potentially limited the ability to detect the occurrence of rare vaccine-related adverse events, which may only be detected in large population-based studies. Similarly, the small sample size limited the statistical power to detect differences in antibody responses in infants, particularly after administration of the third dose of DTaP vaccine. However, infant immune responses to the fourth dose of DTaP were robust and consistent with a good anamnestic response. Although a larger study might reveal a lower overall response to the primary series of DTaP in infants of women immunized during pregnancy, the biological significance would be uncertain and must be weighed against the potentially lifesaving protection provided by significantly higher concentrations of pertussis antibodies in the first 2 months of life. Second, we did not measure antibody concentrations in infants after the first dose of DTaP, but given the high concentrations present at birth and at 2 months, we would anticipate that high concentrations persisted beyond the second month of life. Last, this study was not designed to evaluate the efficacy of maternal immunization with Tdap to protect mothers or infants against pertussis disease, but our clinical surveillance did not identify any clinical cases of pertussis in study participants. Large prospective studies are needed to determine the effectiveness of Tdap vaccination during pregnancy in preventing pertussis illness among young infants. Until definitive evidence is obtained, our findings support current ACIP recommendations to immunize pregnant women with Tdap during pregnancy to protect infants against pertussis.

Conclusions

This preliminary evaluation did not find an increased risk of adverse events (primary outcome) among women who received Tdap vaccine at 30 through 32 weeks' gestation or their infants. Secondary outcomes assessments showed that maternal immunization with Tdap resulted in significantly higher concentrations of antibodies to all vaccine antigens in infants from birth until initiation of immunization with DTaP at age 2 months and did not substantially alter infant responses to DTaP. Further research is needed to provide definitive evidence of the safety and efficacy of Tdap immunization during pregnancy.

ARTICLE INFORMATION

Correction: This article was corrected online on January 24, 2017, for data errors in a table.

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Author Contributions: Drs Munoz and Baker had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Munoz, Ferreira, Goll, Baker.
Obtained funding: Munoz, Walter, Englund.
Administrative, technical, or material support: Munoz, Bond, Maccato, Pinell, Hammill, Walter, Jackson, Englund, Edwards, Petrie, Baker.
Study supervision: Munoz, Walter, Jackson, Englund, Baker.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Munoz reported serving as a speaker for Sanofi Pasteur; serving as a consultant for Novartis, GlaxoSmithKline, and Novavax; and conducting clinical trials sponsored by Hoffmann-LaRoche, GlaxoSmithKline Biologicals, and Gilead Sciences. Dr Swamy reported receiving consulting and lecturing fees, grant support for vaccine-related studies, and payment for advisory board service, lectures, and development of educational presentations from GlaxoSmithKline; and receiving grant funding from GlaxoSmithKline specific to influenza vaccine and human papillomavirus infection. Dr Walter reported serving as a consultant and advisor for Merck; serving as a speaker for Sanofi Pasteur; and conducting clinical

trials sponsored by GlaxoSmithKline, Merck, Novartis, and Pfizer. Dr Englund reported receiving research support from Novartis, Gilead, Chimerix, and Roche; serving as a consultant for GlaxoSmithKline in 2012-2013; serving on a GlaxoSmithKline data and safety monitoring board in 2012-13; and receiving travel expenses from Abbvie (part of Abbot) in 2013. Dr Edwards reported serving as consultant for and receiving grants from Novartis Vaccines. Dr Healy reported conducting trials with grants from Sanofi Pasteur and Novartis and serving as advisor for Novartis Vaccines. Dr Baker reported serving as consultant and advisory board member to Novartis Vaccines and as an advisory board member for Pfizer Inc. No other disclosures are reported.

Funding/Support: This study was supported by Division of Microbiology and Infectious Diseases Contracts N01AI80002C (Baylor College of Medicine, Houston, Texas), HHSN272200800004C (Group Health Research Institute, Seattle, Washington), and HHSN272200800057C (Duke University School of Medicine, Durham, North Carolina). Dr Englund was also supported in Seattle by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through grant UL1RR025014. Ms Petrie, Ms Ferreira, and Mr Goll performed this work supported by National Institute for Allergy and Infectious Diseases–Division of Microbiology and Infectious Diseases(DMID) contract (Clinical Research in Infectious Disease [CRID], HHSN272200800013C).

Role of the Sponsors: The National Institutes of Health and the DMID had a supervisory role in the design and conduct of the study but had no direct role in the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

Previous Presentation: Partial results of this study were presented by Dr Munoz at the Second International Neonatal and Maternal Immunization Meeting in Antalya, Turkey, March 3-5, 2013.

Additional Contributions: We gratefully acknowledge the women and infants who participated in this study, their obstetric and pediatric providers for contributing to the success of the trial, the physician assistants, nurses, coordinators, pharmacists, and administrative personnel at each of the participating Vaccine and Treatment Evaluation Units sites, the hospitals where study participants delivered, the members of the data and safety monitoring board and local safety monitors, and the team at National Institutes of Health/DMID and the EMMES Corporation (Gina Simone and Cyrille Amegashie) who supported this trial. We would also like to acknowledge W. Paul Glezen, MD, and Wendy A. Keitel, MD, from Baylor College of Medicine and Michael D. Decker, MD, MPH, David P. Greenberg, MD, and David R. Johnson, MD, MPH, from Sanofi Pasteur, for providing scientific guidance and expertise throughout the conduct of the study and manuscript preparation; Marcia A. Rench, BSN, Baylor College of Medicine, who assisted during the initial protocol design, and Susan Bobbitt, RN, study coordinator at the Baylor College of Medicine site. No compensation was received by any individual for assistance in the conduct of this study.

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