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# Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women ☆

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## Abstract

**Objective:** Tetanus toxoid, reduced diphtheria toxoid, and acellular pertusiss (Tdap) vaccine is recommended during each pregnancy, regardless of prior receipt. Data on reactogenicity and immunogenicity, particularly after repeated Tdap, are limited. We compared local injection-site and systemic reactions and serologic response following Tdap in (1) pregnant and nonpregnant women and (2) pregnant women by self-reported prior Tdap receipt.

**Study design:** Pregnant women (gestational age 20–34 weeks) and nonpregnant women receiving Tdap were enrolled in this observational study. Injection-site and systemic reactions were assessed for one week post-vaccination. Pertussis toxin, filamentous hemagglutinin, pertactin, fimbriae, tetanus and diphtheria specific IgG antibody titers were determined by standardized enzyme-linked immunosorbent assay at baseline and 28 days post-vaccination. Reactogenicity and serologic responses were compared by pregnancy status, and within pregnant women by self-reported prior Tdap receipt.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Potential conflicts of interest

The other authors report no conflict of interest.

**Results:** 374 pregnant and 225 nonpregnant women were vaccinated. Severe local or systemic reactions or "any" fever were uncommon (≤3% for both groups). Moderate/severe injection-site pain was significantly higher in pregnant (17.9%) versus nonpregnant (11.1%) women, but did not prompt a healthcare visit. Proportions of other moderate/severe or any severe reactions were not significantly higher in pregnant compared to nonpregnant women. Moderate/severe (including pain) and severe reactions were not significantly higher in pregnant women receiving repeat versus first-time Tdap. Antibody titers increased from baseline to post-vaccination for all vaccine antigens in pregnant and nonpregnant women; postvaccination titers against pertussis toxin and filamentous hemagglutinin were significantly higher in nonpregnant versus pregnant women ($p < 0.01$).

**Conclusion:** Tdap was well-tolerated in pregnant and nonpregnant women. Pregnant women were more likely to report moderate/severe pain at the Tdap injection-site compared with nonpregnant women, but did not necessitate medical visits. Prior Tdap receipt did not increase occurrence of moderate/severe local or systemic reactions in pregnant women. Serologic responses to all vaccine antigens were robust.

## Abstract

Clinical Trial Registration@ClinicalTrials.gov.

### Keywords

Maternal vaccination; Tdap vaccine; Vaccine safety; Tdap reactogenicity; Tdap immunogenicity

## 1. Introduction

In 2012 the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommended that pregnant women receive adult tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) during each pregnancy to protect their infants against pertussis via transplacental antibody transfer [1]. Available Tdap safety data were reassuring, but Tdap had not been extensively studied in pregnant women pre-licensure. Monitoring Tdap safety during pregnancy is a public health priority, particularly following repeated Tdap doses [1,2]. To complement CDC's other maternal Tdap safety monitoring efforts, we conducted an observational study of pregnant women receiving Tdap vaccine.

Our primary objective was to compare local injection-site and systemic reactions following Tdap vaccination in pregnant women with nonpregnant women serving as controls [1,3,4]. Nonpregnant women served as the comparison group since there were prior data supporting the safety of Tdap in nonpregnant adults [1,3,4]. We hypothesized that the proportion of pregnant women with moderate/severe injection-site pain would not be higher than the proportion of nonpregnant women. A secondary objective was to compare reaction profiles between pregnant women receiving their first Tdap dose and those who reported prior Tdap receipt. We also explored cytokine levels in sera of women with and without severe reactions after Tdap. In addition, immune responses to all Tdap vaccine components at baseline and 28 days post-vaccination were compared in pregnant and nonpregnant women.

## 2. Materials and methods

### 2.1. Study design

This was a prospective, observational, cohort study conducted at two CDC-funded Clinical Immunization Safety Assessment (CISA) centers, Vanderbilt University Medical Center and Duke University Health System. The study protocol was approved by the institutional review boards at each study site and the CDC and registered at ClinicalTrials.gov (NCT02209623).

Pregnant women aged 18–45 years between 20 weeks 0 days and 33 weeks 6 days gestation, intending to receive 6 dap as part of standard ACIP guidelines, with a singleton pregnancy, English or Spanish literate, and with intention to be available throughout the study period were enrolled (see Supplemental Tables 1 and 2 for detailed eligibility criteria). In order to assess repeated Tdap exposure, women with prior Tdap vaccination were preferentially recruited.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.012 .

After written informed consent was obtained, data regarding race, ethnicity, medical history, obstetric history, and current pregnancy status were collected. Prior Tdap, tetanus and diphtheria toxoid (Td) or tetanus toxoid (TT) vaccination history was solicited by self-report and verified, to the extent possible, by confirmation within each health system's electronic medical record and/or state immunization information systems. Following baseline blood sampling, a single 0.5 mL intramuscular (IM) dose of either US-licensed Tdap (Adacel® or Boostrix® depending on clinical supply) was administered during routine prenatal care.

Nonpregnant women aged 18–45 years were recruited with similar eligibility criteria (Supplemental Tables 1 and 2). Prior receipt of Tdap was permitted in nonpregnant women as part of this research study. Vaccine manufacturer and lot number were recorded for all participants.

### 2.2. Vaccines

The Tdap Adacel® vaccine contained: 5 Limit of Flocculation units (Lf) tetanus toxoid, 2 Lf diphtheria toxoid, and acellular pertussis antigens [2.5 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)] [3]. The Tdap Boostrix® vaccine contained 5 Lf of tetanus toxoid, 2.5 Lf diphtheria toxoid, 8 mcg inactivated PT, 8 mcg FHA, and 2.5 mcg PRN [4].

### 2.3. Safety assessments

To monitor the safety profile after vaccination, all study participants were given a digital oral thermometer, ruler, and memory aid to record local and systemic reactions and other adverse events after vaccination. Subjects were observed in the clinic for 20 min post-vaccination. With Day 0 serving as the day of vaccination, participants were followed through Day 7 for symptoms of reactogenicity based on "worst" symptoms each day. Local reactions assessed included pain, tenderness, induration/swelling, and erythema [5–7]. Systemic reactions assessed included temperature (obtained around the same time each evening), malaise, body

aches (myalgia), headache, and feverishness [3–5,7]. Reactions were graded as mild, moderate, or severe (Supplemental Tables 3 and 4). Adverse events (AE) and serious adverse events (SAEs) were defined in accordance with the U.S. Food and Drug Administration [8]. Participants were contacted on study days 1–2 and 7–9 to review reactogenicity data and to assess for any AEs, SAEs, or concomitant medications. Any participant with severe local or systemic reactions within 7 days after vaccination was evaluated in the clinic within 72 h and an additional blood sample was obtained for cytokine assays ("supplemental visit"). A subject without any systemic reactions, or only mild injection-site reaction, within the same time frame, was recruited to serve as a control (Supplemental Tables 3 and 4).

### 2.4. Immunogenicity and cytokine assessments

Participants returned at approximately 28 days post-vaccination to obtain any new medical information and blood sample collection. For nonpregnant women, study participation ended with the day 28 visit. Data regarding birth outcomes and infant follow-up at 3 and 6 months of life were subsequently collected among pregnant subjects and their infants (data to be described in a separate report).

Pre- and post-Tdap vaccine immune responses were measured using an established enzyme-linked immunosorbent assay (ELISA) assay for serum Immunoglobulin G (IgG) to PT, FHA, PRN, and FIM [9]. Tetanus and diphtheria toxoid IgG levels were measured using a commercial standardized ELISA assay (Abcam; Cambridge, MA). Samples that had tetanus or diphtheria antibody levels above the upper limit of the assay were diluted until they were in range; each reported value for diphtheria and tetanus is the mean of ≥2 replicate assays.

For subjects with severe reactions and their controls, inflammatory cytokines were measured using the Mesoscale Discovery platform [10] with a dedicated SECTOR 2400 Imager. Cytokines studied included; Interleukin (lL)-5, 1L-6, 1L-8, 1L-10, and Tumor necrosis factor alpha (TNF-a). Cytokine levels, at the time of reaction, were compared in the same individual at the pre- and post-vaccination (28 days after vaccination) time periods and were compared with levels in controls by pregnancy status and study location.

### 2.5. Statistical analysis

Descriptive analysis was performed. Symptoms of reactogenicity occurring from Days 0 to 7 were compared between pregnant and nonpregnant women. Moderate/severe injection-site pain was selected as primary outcome for the purpose of sample size and power calculation although all local and systemic reactions were analyzed. The primary null hypothesis was that the proportion of pregnant women with moderate/severe pain would be higher than nonpregnant women with 10% as the maximum clinically acceptable difference, assuming the proportion of moderate/ severe pain in nonpregnant women was less or equal to 25%. The sample size of 375 pregnant and 225 nonpregnant women, including a projected 5% drop-out, was designed to have at least 85% power to assert non-inferiority. For each reactogenicity outcome, the one-sided 95% confidence interval (CI) was calculated for the difference (delta) in the proportion in the pregnant women minus proportion in nonpregnant women. For the moderate/severe pain outcome, the one-sided 95%C1 of delta, adjusting for ethnicity and race, was also calculated using bootstrapping method [11]. The pre-specified

delta of 10% for moderate/severe or 5% for severe out-come was used to compare with each reaction's upper bound to decide whether a non-inferiority test was significant. 1f the upper limit was greater than the delta, the null hypothesis of inferiority could not be rejected at the 5% significance level [12]. Proportions of moderate/severe and severe reactions were also compared between pregnant women with and without previous Tdap receipt. We did not adjust for multiple comparisons in these analyses.

Geometric mean titers (GMTs) of antibody were calculated for all the pertussis, diphtheria, and tetanus antigens along with 95% C1s. Comparisons between pregnant and nonpregnant women and pregnant women with or without previous Tdap were performed by T-test. Paired T-tests were conducted for comparisons of pre- and post-vaccination titers, excluding F1M serology for those who received Boostrix® since this vaccine does not contain F1M [4].

Wilcoxon signed rank tests were conducted for pairwise comparisons among Day 0 visit, the supplemental visit, and the Day 28 visit for the cases with the severe reactions and between matched cases and controls for cytokine results at similar times due to the concern of the small sample size. 1f a cytokine value was below limit of detection (LOD), half of LOD was assigned as standard for the laboratory. All tests were two-sided except non-inferiority test and p value $<0.05$ was considered as statistical significance. All analyses were performed using R version 3.2.2.

## 3. Results

From July 2014 to July 2015, 374 pregnant women and 225 nonpregnant women were enrolled. Demographic and clinical characteristics of the study participants are described in Table 1. The median age at enrollment was similar between pregnant and nonpregnant women (28.9 years vs. 28.3 years). Among all pregnant women, median gestational age at enrollment was 29.2 weeks with 88.8% non-Hispanic ethnicity and 62.7% white and 32.2% black race. Among nonpregnant women, 95.1% reported non-Hispanic ethnicity and 78.5% white and 12.6% black race. Prior Tdap receipt was reported by over half of pregnant (52.9%) and nonpregnant (64.5%) women. Pregnant subjects primarily received Adacel® (Vanderbilt 98.4%; Duke 95.2%), while 100% of nonpregnant subjects at Vanderbilt and 77.3% at Duke received Adacel®. All remaining subjects received Boostrix® except four who did not have clear documentation of the specific product received.

### 3.1. Safety

Safety assessments comparing moderate, severe, and moderate/severe local and systemic reactions for pregnant and nonpregnant women are shown in Table 2. Compared with nonpregnant women, pregnant women were more likely to experience moderate/severe pain at the injection site (17.9% vs. 11.1% in pregnant and nonpregnant women, respectively), but the occurrence of other moderate/severe and all severe local and systemic reactions assessed were not different between pregnant and nonpregnant women. After adjusting for race and ethnicity in those reporting moderate/severe pain, the upper bound of 95% CI of the difference of proportion between pregnant and nonpregnant groups was 11.9%, indicating that the difference persisted. Severe local and systemic reactions or fever were uncommon

(≤3%) among all participants and no woman sought medical care for any reactions. Only two pregnant and five nonpregnant women reported fever (≥38 °C) after vaccination (Table 2). The most commonly occurring mild reactions among pregnant subjects were: injection-site tenderness (61.7%), pain (50.0%), and malaise (23.9%) and among nonpregnant subjects were: tenderness (73.5%), pain (66.4%) and headache (30.0%). When examining symptoms by post-vaccination day, the highest proportions of moderate/severe pain were reported on the first day after vaccination. There were no adverse events during the 20-minute post-vaccination observation period and no serious adverse events for 28 days post-vaccination.

### 3.2. First Tdap exposure vs. repeat Tdap in pregnant women

In evaluating reactogenicity by prior Tdap receipt in pregnant women, 198 of 301 women self-reported prior Tdap receipt, while 74 pregnant women could not recall their Tdap history. Eight pregnant women in the study had more than one Tdap within the past 12 months and none experienced severe reactions or fever. Among those with documented prior Tdap receipt, 98 women had received prior Tdap in the past 1–5 years. Subjects (73) with unknown prior Tdap vaccination status were excluded from this portion of the analysis, but were notable for higher proportion of Hispanic ethnicity compared to women with known prior Tdap (22% vs. 6%). The proportions of pregnant women with moderate/severe reactions were not higher among pregnant women receiving a repeat Tdap dose versus those receiving their first, Fig. 1. Specifically, moderate/severe pain (17.0% vs. 18.7%) was not significantly higher and non-inferiority criteria were also met for all other moderate/severe and severe local and systematic reactions.

### 3.3. Immunogenicity

Compared to baseline, post-vaccination geometric mean antibody titers (GMT) to all vaccine antigens were significantly higher in both pregnant and nonpregnant women regardless of prior Tdap receipt (Table 3 and Supplemental Table 5). Compared to pregnant women, nonpregnant women had significantly higher post-vaccination GMTs for PT, FHA, tetanus, and diphtheria, but not for the FIM or PRN. Among pregnant women, those who were previously vaccinated with Tdap had significantly higher baseline GMTs than those without prior Tdap; however, post-vaccination GMTs to FIM, PRN, and tetanus were significantly higher in the pregnant women without prior Tdap receipt. All women in the study achieved titers of ≥0.1 International Units/ mL, the correlate of protection for tetanus and diphtheria toxoids after Tdap [3,4].

### 3.4. Cytokines

A total of six cases of severe local or systemic reactions were identified and seen by study staff and matched with six controls. Among cases, five women had severe local reactions (induration and/or swelling), a single subject had severe systemic reaction with fever (102.4 °F), and one had both local and systemic reactions (fever (101.2 °F),bodyaches(myalgias), 70 mm induration and 30 mmery- thema). Of the six women with severe reactions, three had no prior Tdap recorded. Cytokines were measured for all women with severe reactions and their controls. The majority of the results for IL-5, IL-6, IL-8, IL-10, and TNFα were all close to the lower limit of detection at all times measured (Table 4). The cytokine levels measured in cases with severe reactions did not

differ among pre and post-vaccination or supplemental visit samples, meaning, no statistically significant differences were noted in cytokine levels obtained at any of the Day 0, supplemental, or Day 28 visits.

## 4. Discussion

In our study, Tdap had a safety profile consistent with previous reports among nonpregnant [5,7,13] and pregnant persons [14–16]. Tdap was well-tolerated regardless of pregnancy status and prior Tdap receipt. Very few (≤3%) pregnant women who received a dose of Tdap vaccine reported severe reactions, and <1% of pregnant women reported any fever after vaccination. Contrary to our hypothesis, pregnant women were more likely to report moderate/severe pain at the Tdap injection-site compared with nonpregnant women; however, these symptoms did not necessitate medical visits. The frequency of pain reported among pregnant women was comparable to that previously reported in clinical trials for FDA licensure in nonpregnant persons [3]. Physical, hormonal, and psychological changes intrinsic to pregnancy may alter analgesic experience and perception [17]. One small study comparing pain between pregnant (n = 39) and nonpregnant (n = 22) women found increased, widespread, deep-tissue hypersensitivity during pregnancy [18]. In our study, similar proportions of other local reactions in pregnant versus nonpregnant women (including tenderness) were seen, suggesting non-biological factors may also account for the increased moderate/severe pain finding. Munoz reported similar proportions of injection-site pain (not graded) after Tdap in 26 pregnant and 12 nonpregnant women [13]. Fifty-one (of 370) Thai women receiving Tdap during pregnancy reported moderate or severe local reaction, which is a higher rate than we observed [19]. While not compared with nonpregnant women, New Zealand researchers utilized telephone interviews at 48 h and four weeks after Tdap and influenza vaccination in 793 pregnant women, and noted similar low rates of severe pain (2.6%), severe swelling and erythema (0.4%), and fever (2.1%) [14].

Repeated doses of Td/TT were associated with increased moderate or severe reactions in older studies [7]. More recent studies assessing the safety of Tdap after Td/TT or repeat doses of Tdap, primarily in nonpregnant individuals, have not identified clinically important safety concerns. However, theoretical concerns exist that increased severe reactions could occur among pregnant women receiving repeated Tdap [1,7,20–22], especially among women with closely spaced pregnancies. We found no increase in moderate/severe or severe reactions in pregnant women who received prior Tdap, compared with those receiving Tdap for the first time. Our results are supported by a recent large retrospective cohort study, conducted through the Vaccine Safety Datalink (VSD), showing no difference in medically-attended acute adverse events in mothers or adverse birth outcomes among pregnant women related to timing of Tdap since the prior tetanus-containing vaccine [23]. Further consistent reports from a Thai study showed no increase in AEs among 98 women receiving at least one additional dose of tetanus-containing vaccine during pregnancy [19]. However, Perry et al reported 24 of 737 (3%) women would not accept Tdap in a subsequent pregnancy due to a reaction occurring in her current pregnancy [24]. In addition, a recent Australian cohort study, in pregnant women receiving Tdap, and/or influenza vaccine suggested that local reactions were more common after Tdap in pregnant women with a history of prior Tdap receipt versus those receiving their first Tdap dose [15]. As women continue to receive

additional doses of Tdap in subsequent pregnancies, it will be important to continue to monitor for adverse events.

In our study, post-vaccination titers showed statistically significant rises to all vaccine antigens in both pregnant and nonpregnant subjects. However, both pre- and post-vaccination antibody levels were lower among pregnant versus nonpregnant women. This finding has been inconsistently reported with other vaccine antigens, including Tdap and Influenza vaccines [13,25]. All women had seroprotective levels of antibody to diphtheria and tetanus toxoids after Tdap [3,4]. In the six women with severe reactions, systemic cytokines obtained immediately before and one month after vaccination were not statistically different from those obtained at the time of the severe adverse event and were not different than those seen in the control subjects.

Although we were able to prospectively follow 374 women receiving Tdap vaccination, our study has a few limitations, including differing racial and ethnic characteristics of women in the pregnant and nonpregnant groups. Yet, significant findings persisted after adjusting for race and ethnicity. If women with a previous Tdap had experienced a reaction after vaccination they may have been more reluctant to receive Tdap as part of their routine care, potentially biasing our results. We were also unable to confirm prior Tdap receipt for nearly 70 subjects.

## 5. Conclusion

Our study provides a population of prospectively enrolled pregnant and nonpregnant women in the United States who received Tdap with comprehensive local and systemic reaction assessments. Our findings provide reassurance of the safety of Tdap in both pregnant and nonpregnant women, and in those with prior Tdap receipt. In addition, robust serologic responses in both pregnant and nonpregnant women were seen after Tdap vaccination.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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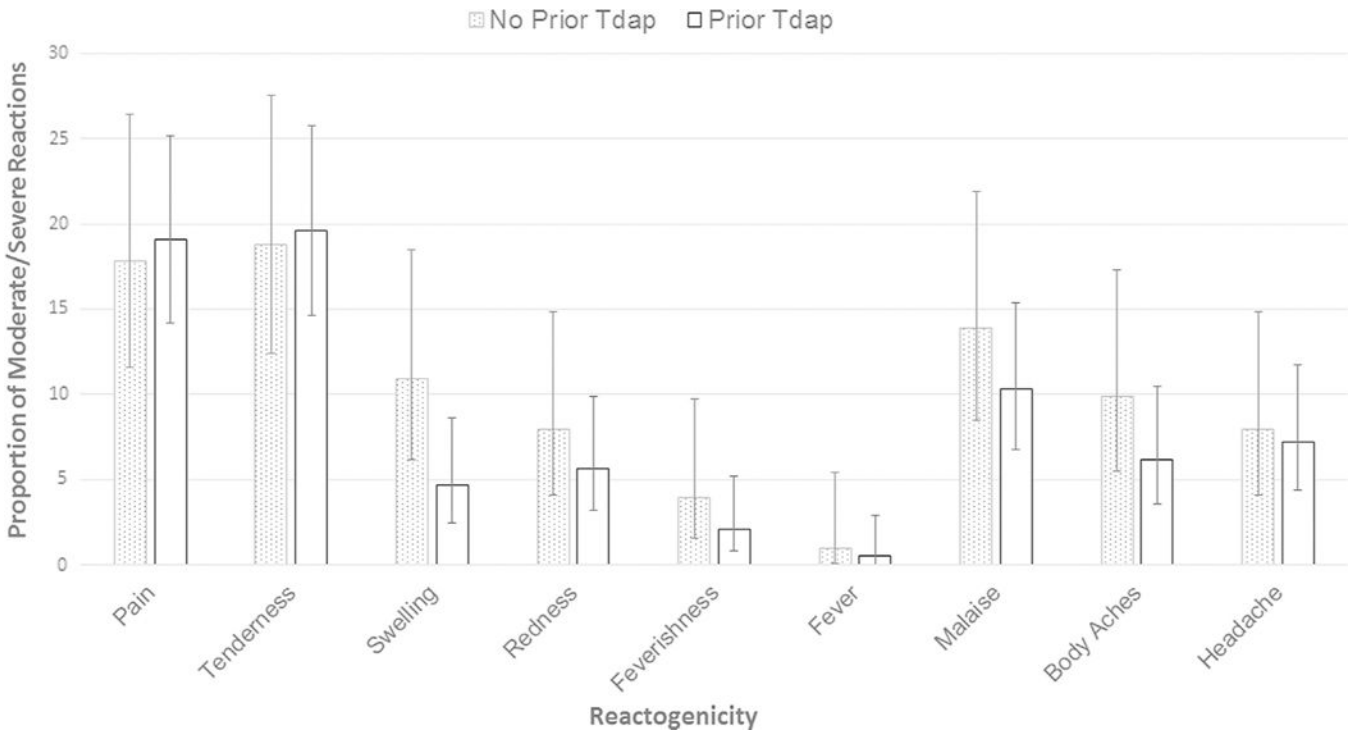


**Fig. 1.**

Proportion of moderate/severe reactions among pregnant women with and without prior tdap receipt. Proportions of pregnant women with moderate/severe reactions among pregnant women receiving a repeat dose of Tdap versus those receiving their first dose. Error bars represent 95% confident intervals.

**Table 1**

Descriptive summary of participating women by site and pregnancy status.

| Characteristic | Vanderbilt | Duke | Both sites |
|---|---|---|---|
| Pregnant subjects | N = 250 | N = 124 | N = 374 |
| Nonwhite[1] | 28.0% (70) | 50.0% (62) | 35.4% (132) |
| Hispanic ethnicity | 14.4% (36) | 4.8% (6) | 11% (42) |
| Median age in years (mean ± 1 SD) | 28.9 (28.9 ±5.6) | 28.8 (29.7 ± 5.6) | 28.9 (29.2 ±5.6) |
| Median gestational age in weeks at enrollment (mean ± 1 SD) | 30.1 (29.9 ± 2.4) | 28.4 (28.7 ±1.2) | 29.2 (29.5 ±2.2) |
| Median gestational age in weeks at delivery (mean ± 1 SD) | 39.2 (39.1 ±1.6) | 38.6 (38.2 ± 2.0) | 39.1 (38.8 ±1.8) |
| Prior Tdap receipt | 46.7% (117) | 65.3% (81) | 52.9% (198) |
| Influenza vaccine receipt past year | 71.6% (179) | 73.4% (91) | 72.2% (2 7 0) |
| Nonpregnant subjects | N = 150 | N = 75 | N = 225 |
| Nonwhite[2] | 17.3% (26) | 29.3% (22) | 21.3% (48) |
| Hispanic ethnicity | 4.0% (6) | 6.7% (5) | 4.9% (11) |
| Median age in years (mean ± 1 SD) | 28.0 (29.8 ±6.1) | 28.3 (30.0 ± 6.0) | 28.3 (29.9 ±6.0) |
| Prior Tdap receipt | 58.7% (88) | 78.7% (59) | 65.3% (147) |
| 1nfluenza vaccine receipt past year | 81.3% (122) | 86.7% (65) | 83.1% (187) |

Numbers after percents are frequencies.

N is the number of non-missing values.

SD is standard deviation.

[1]Vanderbilt: 20% black, 2% other; Duke 47% black, 2% other.

[2]Vanderbilt: 10% black, 7% other; Duke 19% black, 8% other.

**Table 2**

Local and systemic reactions following Tdap vaccination among pregnant and nonpregnant women on vaccination day and the following 7 days.*

| | Pregnant N = 374 | | | Nonpregnant N= 225 | | |
|---|---|---|---|---|---|---|
| | Moderate[1] | Severe[2] | Moderate/Severe | Moderate[1] | Severe[2] | Moderate/Severe |
| *Local symptoms* | | | | | | |
| Pain | 65 (17.4%) | 2 (0.5%) | 67 (17.9%) | 23 (10.2%) | 2 (0.9%) | 25 (11.1%) |
| Tenderness | 69 (18.4% | 2 (0.5%) | 71 (19.0%) | 37 (16.4%) | 1 (0.4%) | 38 (16.9%) |
| Swelling/induration | 17 (4.6%) | 4(1.1%) | 21 (5.6%) | 9 (4.0%) | 4 (1.8%) | 13 (5.8%) |
| Erythema | 14 (3.7%) | 7 (1.9%) | 21 (5.6%) | 5 (2.2%) | 7 (3.1%) | 12 (5.3%) |
| *Systemic symptoms* | | | | | | |
| Fever | 2 (0.5%) | 0 (0.0%) | 2 (0.5%) | 3 (1.3%) | 2 (0.9%) | 5 (2.2%) |
| Feverishness | 10 (2.7%) | 2 (0.5%) | 12 (3.2%) | 4(1.8%) | 5 (2.2%) | 9 (4.0%) |
| Malaise | 37 (9.9%) | 2 (0.5%) | 39 (10.4%) | 9 (4.0%) | 2 (0.9%) | 11 (4.9%) |
| Body aches (myalgias) | 26 (7.0%) | 3 (0.8%) | 29 (7.8%) | 9 (4.0%) | 3 (1.3%) | 12 (5.3%) |
| Headaches | 25 (6.7%) | 2 (0.5%) | 27 (7.2%) | 19 (8.4%) | 1 (0.4%) | 20 (8.9%) |

*Tdap in pregnant women did not meet the non-inferiority criterion for rates of Moderate/severe pain (the primary safety outcome for sample size calculation); difference pregnant women - minus nonpregnant women 6.8% (one sided 95% confidence interval upper bound 11.5%); no woman sought medical care for injection-site pain.

[1]Moderate: Induration and erythema: 10–34 mm; fever ≥38 - <39 °C; Other symptoms: Interferes with activity but did not necessitate medical visit or absenteeism.

[2]Severe: Induration and erythema: ≥35 mm; fever ≥39 °C; Other symptoms: Prevents daily activity and resulted in medical visit or absenteeism.

**Table 3**

Geometric mean titers for Tdap antigens between pregnant and nonpregnant women.

| | Pregnant | | | Nonpregnant | | | Nonpregnant/Pregnant | | P Value |
|---|---|---|---|---|---|---|---|---|---|
| | N | GMT | 95%CI (lower, upper) | N | GMT | 95%CI (lower, upper) | GMT ratio | 95%CI (lower, upper) | T test |
| PT at Day 0 | 365 | 8.7 | 8.0, 9.4 | 222 | 9.6 | 8.6, 10.8 | 1.1 | 1.0, 1.3 | 0.14 |
| PT at Day 28 | 365 | 43.1 | 38.8, 47.9 | 222 | 61.8 | 53.7, 71.2 | 1.4 | 1.2, 1.7 | <0.01* |
| FHA at Day 0 | 365 | 23.9 | 21.2, 26.8 | 222 | 29.6 | 25.8, 33.9 | 1.2 | 1.0, 1.5 | 0.02* |
| FHA at Day 28 | 365 | 114.8 | 104.7, 125.9 | 222 | 145.0 | 130.3, 161.4 | 1.37 | 1.1, 1.5 | <0.01* |
| FIM at Day 0^ | 359 | 61.4 | 51.3, 73.4 | 205 | 98.2 | 77.4, 124.5 | 1.60 | 1.2, 2.1 | <0.01* |
| FIM at Day 28^ | 359 | 807.7 | 718.4, 908.0 | 205 | 800.3 | 695.8, 920.5 | 1.0 | 0.8, 1.2 | 0.92 |
| PRN at Day 0 | 365 | 27.5 | 23.9, 31.7 | 222 | 47.9 | 39.9, 57.6 | 1.7 | 1.4, 2.2 | <0.01* |
| PRN at Day 28 | 365 | 261.3 | 233.1, 292.9 | 222 | 264.4 | 232.2, 301.1 | 1.0 | 0.9, 1.2 | 0.89 |
| Tetanus at Day 0 | 365 | 1.3 | 1.1, 1.4 | 222 | 1.7 | 1.5, 1.9 | 1.3 | 1.1, 1.6 | <0.01* |
| Tetanus at Day 28 | 365 | 9.6 | 8.8, 10.4 | 222 | 9.8 | 8.9, 10.8 | 1.03 | 0.9, 1.2 | 0.7 |
| Diphtheria at Day 0 | 365 | 0.3 | 0.2, 0.3 | 222 | 0.4 | 0.3, 0.5 | 1.6 | 1.3, 2.0 | <0.01* |
| Diphtheria at Day 28 | 365 | 1.8 | 1.6, 2.0 | 222 | 2.0 | 1.8, 2.3 | 1.1 | 0.9, 1.3 | 0.2 |

PT: pertussis toxin; FHA: filamentous hemagglutinin; FIM: fimbriae types 2 and 3; PRN: pertactin. GMT refers to geometric mean titer of antibody to respective antigens.

Day 0 represents serology drawn before vaccination. Day 28 is 28 days after vaccination.

^Analyzed subjects receiving Adacel® only.

*Statistically significant ($p < 0.05$).

## Table 4

Summary of Cytokine Results between Cases with Severe Reaction and Controls.

| Cytokine | Cases, N = 6 Median (mean ± STD) Pg/mL | Controls, N = 6 Median (mean ± STD) Pg/mL | P value |
|---|---|---|---|
| IL-6 Day 0 | 0.8 (0.9 ± 0.7) | 0.9 (0.9 ± 0.6) | 1.00 |
| IL-6 Supplemental Visit | 0.8 (1.1 ±0.8) | 0.8 (1.0 ±0.8) | 0.53 |
| IL-6 Day 28 | 1.1 (1.0 ±0.5) | 0.5 (0.7 ± 0.4) * | 0.59 |
| IL-8 Day 0 | 8.8 (14.1 ±13.1) | 6.0 (6.8 ± 2.5) | 0.06 |
| IL-8 Supplemental Visit | 9.6 (21.5 ±24.1) | 7.0 (7.5 ±2.1) | 0.40 |
| IL-8 Day 28 | 11.1 (22.6 ±30.0) | 5.0 (6.4 ± 2.6) * | 0.06 |
| IL-10 Day 0 | 0.4 (0.4 ±0.1) | 0.4 (0.4 ± 0.2) | 0.83 |
| IL-10 Supplemental Visit | 0.3 (0.7 ± 0.9) | 0.3 (0.3 ±0.1) | 0.42 |
| IL-10-Day 28 | 0.3 (0.4 ±0.1) | 0.4 (0.5 ± 0.3) * | 0.59 |
| TNF-α Day 0 | 0.4 (0.6 ± 0.4) | 0.4 (0.5 ± 0.2) | 0.37 |
| TNF-α Supplemental Visit | 0.8 (0.9 ± 0.5) | 0.4 (0.5 ± 0.2) | 0.20 |
| TNF-α Day 28 | 0.8 (0.9 ± 0.4) | 0.4 (0.5 ± 0.4) * | 0.20 |
| IL- 5 Day 0 | 0.3 (0.4 ± 0.2) | 0.3 (0.3 ±0.1) | 0.86 |
| IL- 5 Supplemental Visit | 0.5 (0.7 ± 0.6) | 0.3 (0.3 ± 0.0) | 0.18 |
| IL- 5 Day 28 | 0.3 (0.3 ± 0.2) | 0.3 (0.6 ± 0.7) * | 1.00 |

IL: Interleukin. TNF: Tumor Necrosis Factor. Pg: picograms.

Day 0 represents serology drawn before vaccination. Supplemental Visit refers to the additional visit after vaccination with report of severe local or systemic reaction (or controls). Day 28 is 28 days after vaccination.

Information based on 1 Duke case (nonpregnant) and 5 Vanderbilt cases (3 nonpregnant and 2 pregnant).

One control subject did not have results for cytokines at Day 28;

* “”values are based on 5 control samples instead of 6 controls.