Clinical Study of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) Safety in Pregnant Women

Kathryn Edwards, MD
Vanderbilt University School of Medicine
Monroe Carell, Jr. Children's Hospital at Vanderbilt

Geeta Swamy, MD
Duke University Dept of ObGyn
Division of Maternal-Fetal Medicine

Karen Broder, MD
Immunization Safety Office
Centers for Disease Control and Prevention

Disclaimer and Disclosures

- The findings and conclusions in this presentation are those of the presenters and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).
- Mention of a product or company name does not constitute endorsement by the CDC.
- The findings in this presentation are preliminary, data analysis is ongoing.

Outline

- To provide an overview of the clinical study of Tdap safety during pregnancy
- To provide preliminary results from the reactogenicity and immunogenicity analyses

Background

- The Advisory Committee on Immunization Practices (ACIP) has recommended that providers administer a dose of Tdap during each pregnancy (optimal timing 27-36 weeks gestation)*
- Available data support the safety of Tdap in pregnant women; but data on safety of repeat Tdap doses are limited
- As part of a comprehensive monitoring to evaluate the safety of Tdap in pregnant women, a clinical study was implemented in the CDC Clinical Immunization Safety Assessment (CISA) Project

*CDC MMWR Feb 2013

Aims: Primary

- To compare rates of injection-site and systemic reactions after Tdap in pregnant women versus non-pregnant women

Aims: Secondary

- To explore differences in injection-site and systemic reactions in pregnant women who received Tdap before the current pregnancy versus pregnant women who are receiving their first Tdap dose

Aims: Exploratory*

- To measure antibody levels to pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbria (FIM) and diphtheria and tetanus toxoids prior to and one month after administration of Tdap vaccine in both pregnant and non-pregnant women.

- To compare levels of cytokines in women (pregnant and non-pregnant) with severe local or systemic reactions after Tdap with those without reactions, using measurements of cytokines before, during, and after the reactions.

*Funded by a Bill and Melinda Gates Foundation grant to Vanderbilt

Studies in Progress

- *To assess rates of preterm and small for gestational age (SGA) births in women who received Tdap during pregnancy*
- *To assess rates of additional obstetrical and infant outcomes in pregnant women receiving Tdap (e.g., pregnancy related hypertension)*
- *To describe health outcomes and growth parameters through 6 months of life among infants born to women who received Tdap during pregnancy*

Methods

- Prospective observational study of women aged 18-45 years receiving Tdap as first or repeat doses at Vanderbilt and Duke University clinics
- Pregnant women at ≥20 and ≤34 weeks gestation receiving Tdap for routine care followed through delivery (Goal = 375)
- Non-pregnant women receiving Tdap for usual care or as a research procedure and followed through 1 month after vaccination (Goal =225)
- Prior Tdap/Td/TT history assessed by subject report and/or medical record/ registry

Methods - continued

- Rates of local and systemic reactions assessed during days 0-7* after Tdap using memory aid, with severity scales
- Blood collected at day 0 and 28 after Tdap
  - Pertussis Serology (ELISA) tests at Vanderbilt
  - Diphtheria/Tetanus toxoid serology tests at Duke
- Blood collected in women with severe local and systemic reactions and in controls without the reactions for cytokine analysis on Day 0, the day of the reaction, and Day 28
- Pregnancy outcomes assessed via chart review
- Infant outcomes assessed by phone interview and chart review at 3 and 6 months of life

*Day 0 is vaccination day

Noninferiority Analysis: Reactogenicity

- Comparisons of proportions with moderate/severe and severe reactions during 0-7 days post vaccination between pregnant women and non-pregnant women receiving Tdap and between pregnant women that received prior Tdap and those with no prior Tdap receipt
  - Primary hypothesis: Rates of moderate to severe reactions in pregnant women receiving Tdap will be non-inferior to non-pregnant women receiving Tdap
- One sided statistical tests, 95% confidence interval (CI), with noninferiority margin of 10% for moderate/severe and 5% for severe reactions

Summary of Pregnant Women by Site

	Vanderbilt N=250	Duke N=124
Non-White	70 (28%)	62 (50%)
Median Age (mean ± standard deviation (SD)	28.9 (28.9±5.6)	28.8 (29.7±5.6)
Median Gestation Age Weeks at Enrollment	30.1 (29.85±2.4)	28.4 (28.7±1.2)
Median Gestation Weeks at Delivery*	39.2 (39.1±1.6)	38.6 (38.2±2.0)
Prior Tdap Receipt	117 (47%)	81 (65%)
Prior Tdap/Td/ TT Receipt	200 (80%)	115 (93%)
Adacel-Sanofi Pasteur Receipt**	246 (99%)	118 (95%)
Influenza vaccine receipt past year	179 (72%)	91 (73%)

Summary of Non-Pregnant Women by Site

	Vanderbilt N=150	Duke N=75
Non-White	26 (17%)	22 (29%)
Median Age (mean ± SD)	28.0 (29.8±6.1)	28.3 (30.0±6.0)
Prior Tdap Receipt	88 (59%)	59 (79%)
Prior Tdap/Td/TT Receipt	132 (88%)	71 (95%)
Adacel-Sanofi Pasteur Receipt	150 (100%)	58 (77%)
Influenza vaccine receipt past year	122 (81%)	65 (87%)

Local Reactions within 7 days after vaccination in Pregnant versus Non-pregnant women

LOCAL Symptoms	Pregnant N= 367*					Non-Pregnant N= 223*				
	None (%)	Mild (%)	Moderate (%)	Severe (%)	Moderate + Severe (%)	None (%)	Mild (%)	Moderate (%)	Severe (%)	Moderate + Severe (%)
Pain	116 (32%)	184 (50%)	65 (18%)	2 (1%)	67 (18%)	50 (22%)	148 (66%)	23 (10%)	2 (1%)	25 (11%)
Tenderness	69 (19%)	227 (62%)	69 (19%)	2 (1%)	71 (19%)	21 (9%)	164 (74%)	37 (17%)	1 (0%)	38 (17%)
Swelling	312 (85%)	34 (9%)	17 (5%)	4 (1%)	21 (6%)	184 (83%)	26 (12%)	9 (4%)	4 (2%)	13 (6%)
Redness	323 (88%)	24 (7%)	14 (4%)	7 (2%)	21 (6%)	186 (83%)	25 (11%)	5 (2%)	7 (3%)	12 (5%)

Definitions:

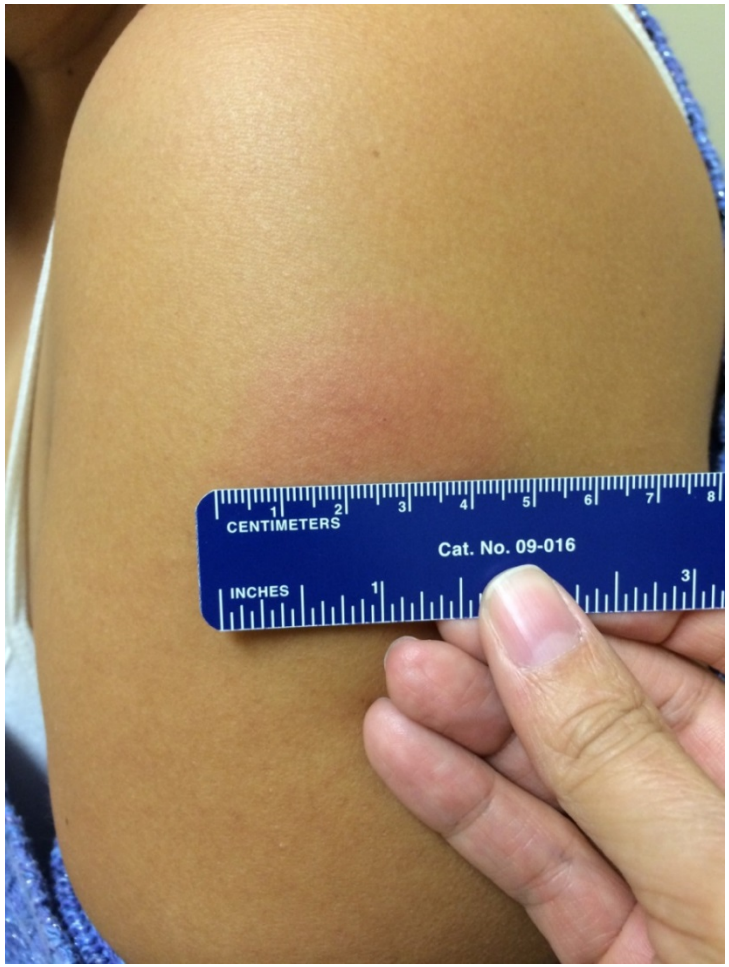
Moderate: Induration and erythema: 10-34 mm; Pain/tenderness: Interferes with activity but did not necessitate medical visit or absenteeism

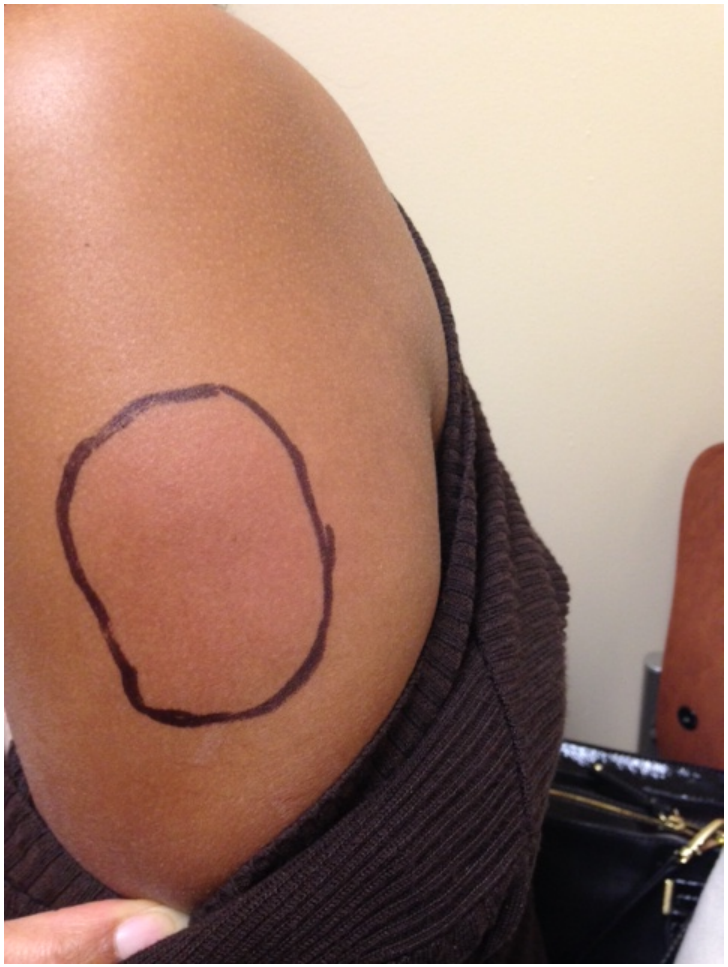
Severe: Induration and erythema: >=35 mm; Pain/tenderness: Prevents daily activity and resulted in medical visit or absenteeism

Non-inferiority criteria met for moderate/severe and severe local reactions in pregnant vs. non-pregnant women, except moderate/severe pain

*N is the number of non-missing values

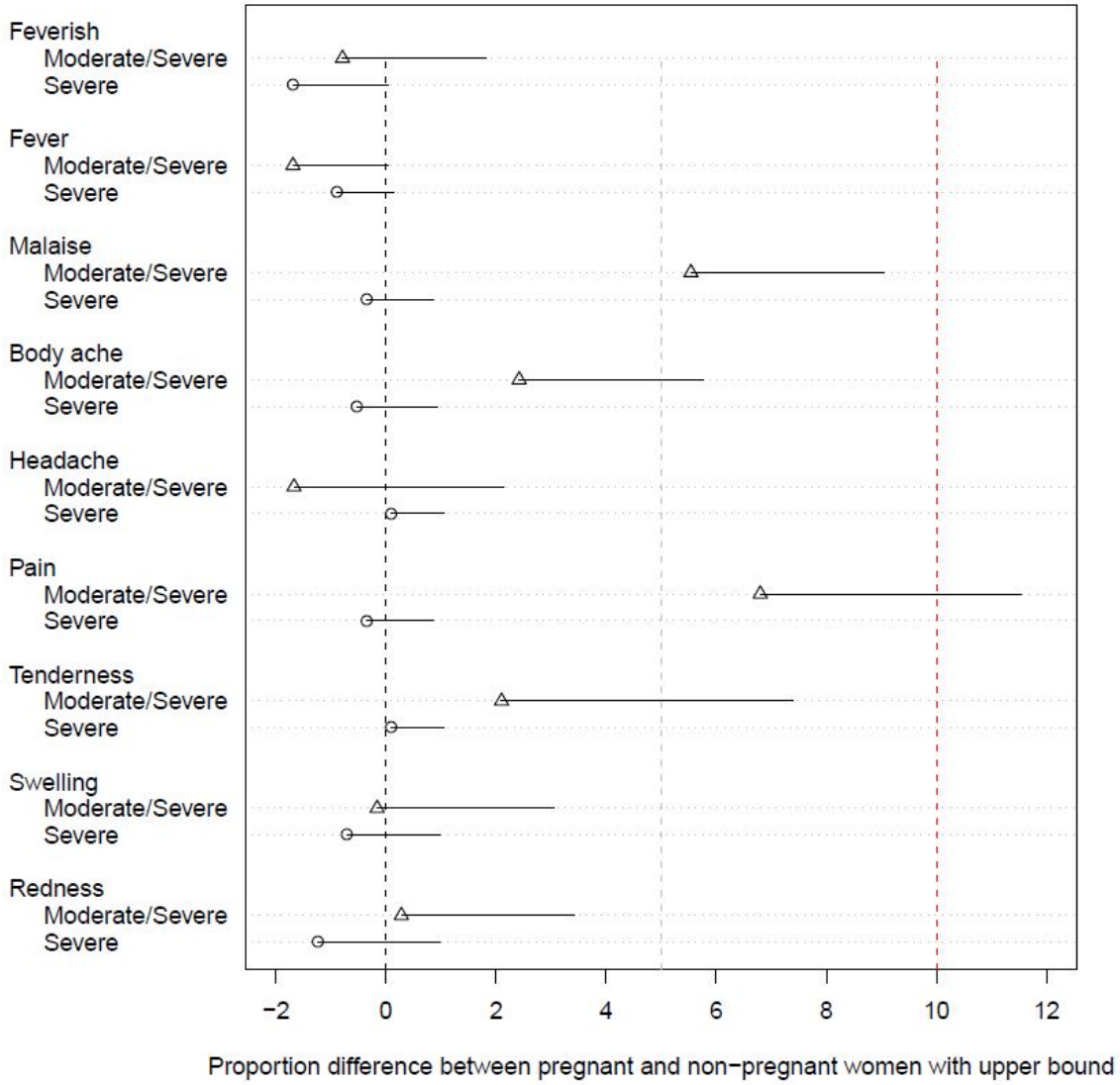
Severe Local Reactions: Pregnant Women





Patient consent provided

Proportion Difference Between Pregnant and Non-Pregnant Women with 95% Confidence Interval Upper Bound



Systemic Symptoms within 7 days after vaccination Pregnant versus Non-pregnant women

SYSTEMIC Symptoms	Pregnant N= 367*					Non-Pregnant N= 223*				
	None (%)	Mild (%)	Moderate (%)	Severe (%)	Moderate + Severe (%)	None (%)	Mild (%)	Moderate (%)	Severe (%)	Moderate + Severe (%)
Fever**	363 (99%)	1 (0%)	2 (1%)	0 (0%)	2 (1%)	213 (96%)	5 (2%)	3 (1%)	2 (1%)	5 (2%)
Feverishness	339 (92%)	16 (4%)	10 (3%)	2 (1%)	12 (3%)	195 (87%)	19 (9%)	4 (2%)	5 (2%)	9 (4%)
Malaise	240 (65%)	88 (24%)	37 (10%)	2 (1%)	39 (11%)	155 (70%)	57 (26%)	9 (4%)	2 (1%)	11 (5%)
Body aches	283 (77%)	55 (15%)	26 (7%)	3 (1%)	29 (8%)	178 (80%)	33 (15%)	9 (4%)	3 (1%)	12 (5%)
Headaches	257 (70%)	83 (23%)	25 (7%)	2 (1%)	27 (7%)	136 (61%)	67 (30%)	19 (9%)	1 (0%)	20 (9%)

Definitions:

Moderate: fever ≥ 100.4 - < 102.2° F; Other symptoms: Interferes with activity but did not necessitate medical visit or absenteeism

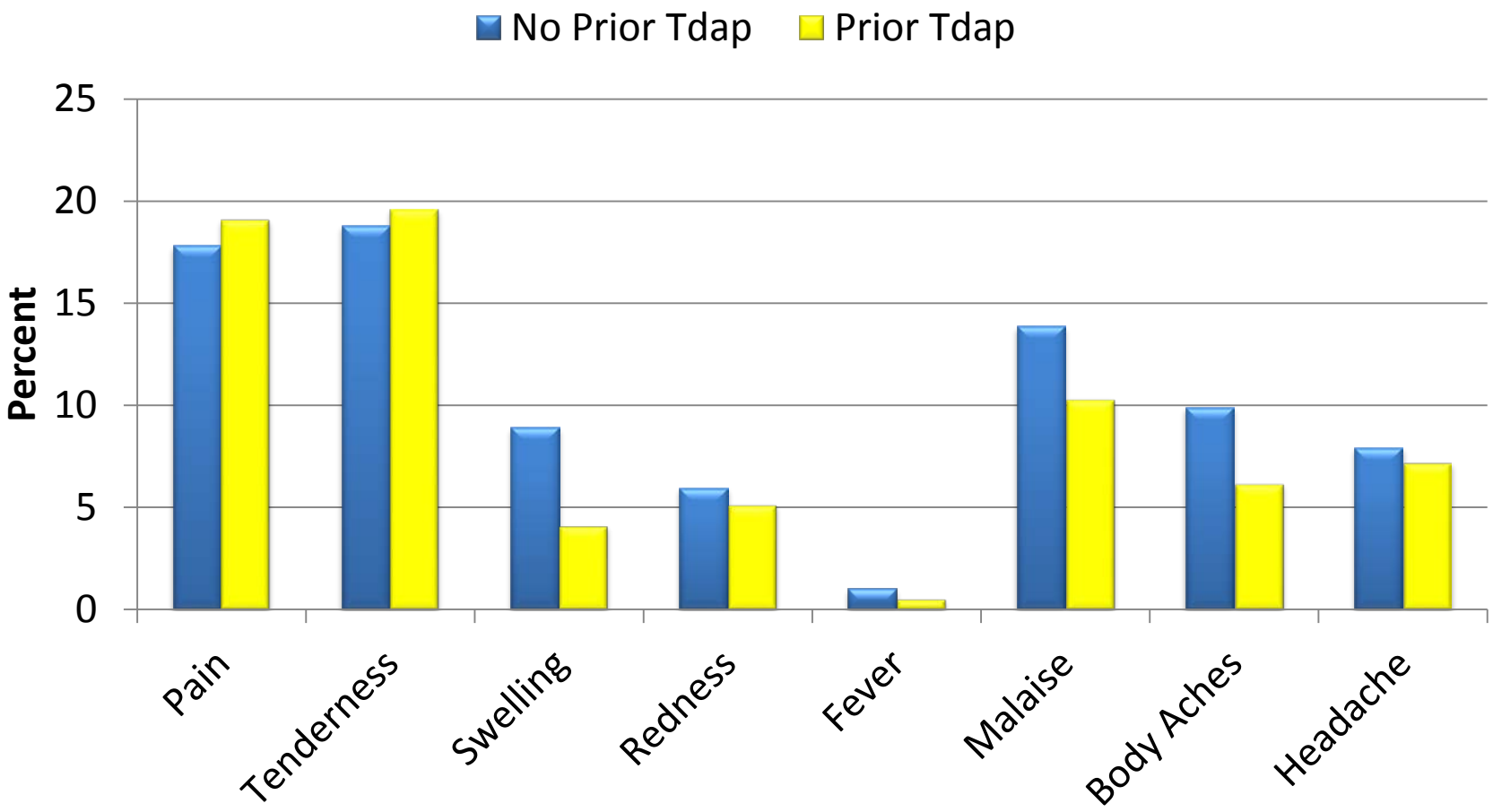
Severe: fever ≥ 102.2° F; Other symptoms: Prevents daily activity and resulted in medical visit or absenteeism

Non-inferiority criteria met for all moderate/severe and severe systemic reactions in pregnant vs. non-pregnant women

*N is the number of non-missing values

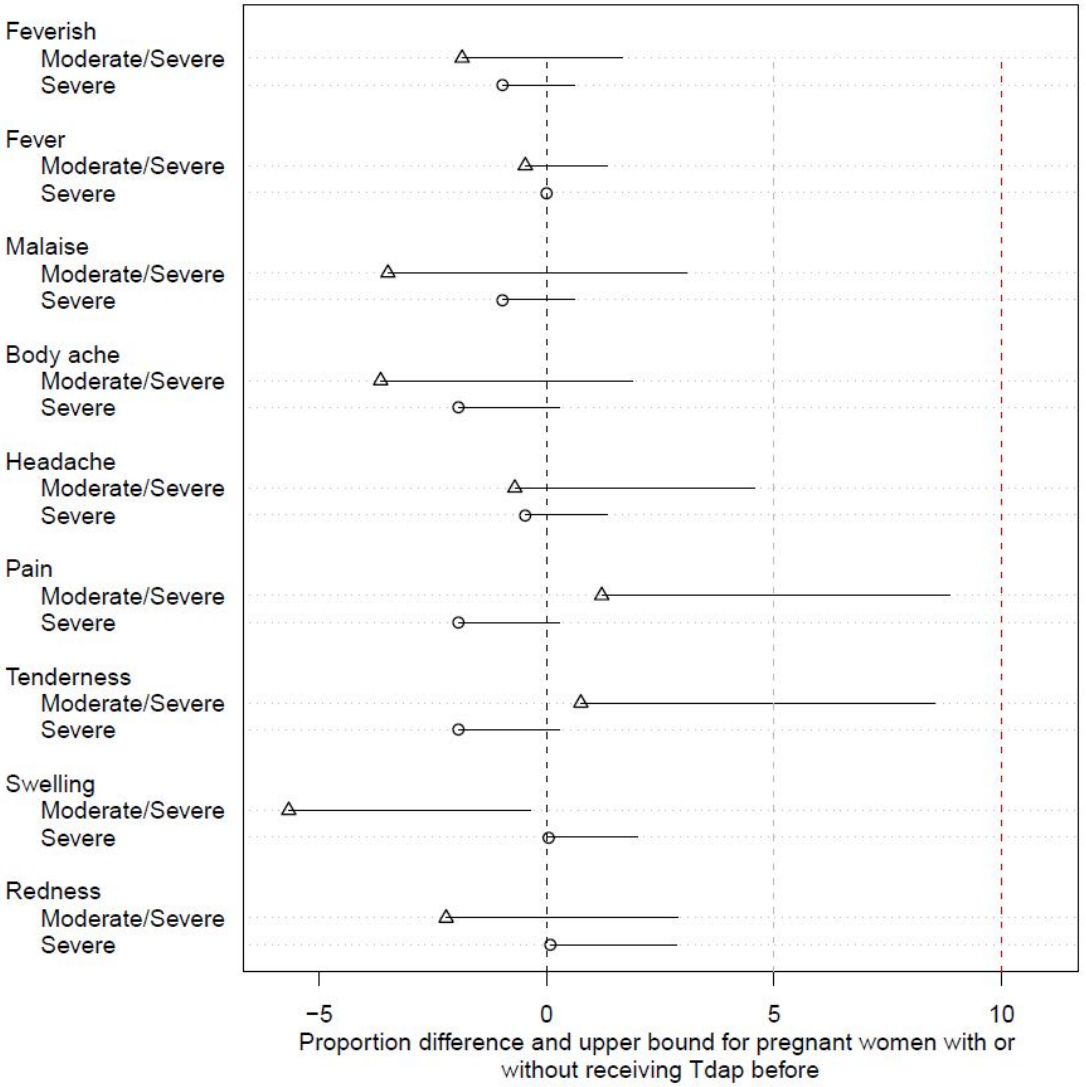
**N=589; pregnant N=366 and non-pregnant N=223

Rates of Moderate+Severe Reactions Among Pregnant Women With and Without Prior Tdap Receipt within 7 days after vaccination



All comparisons for moderate/severe or severe reactions met non-inferiority criteria

Proportion Difference and Upper Bound for Pregnant Women With or Without Receiving Tdap Before with 95% Confidence Interval Upper Bound



Clinical Outcomes During 0-7 Days After Vaccination

- No women sought medical care for a vaccine reaction
- No serious adverse events reported

Geometric Mean Titers for Tdap Pertussis Antigens Between Pregnant and Non-Pregnant Women Among All Subjects

Antigen	Pregnant			Non-Pregnant		
	N	GMT	95%CI (Lower, Upper)	N	GMT	95%CI (Lower, Upper)
PT at Day 0	365	8.6	8, 9.4	222	9.6	8.6, 11
PT at Day 28	365	43.1	39, 47.9	222	61.8	53.6, 71
FHA at Day 0	365	23.9	21, 26.8	222	29.6	25.8, 34
FHA at Day 28	365	114.8	105, 125.9	222	145.0	130.3, 161
FIM at Day 0	365	61.1	51, 73.0	222	92.4	73.4, 116
FIM at Day 28	365	770.9	682, 871.0	222	641.2	537.0, 766
PRN at Day 0	365	27.5	24, 31.7	222	47.9	39.9, 58
PRN at Day 28	365	261.3	233, 292.9	222	264.4	232.2, 301

100% of subjects achieved seroprotection levels for Diphtheria and Tetanus
Diphtheria 0.1 IU/ml is the protective level of serum antibody
Tetanus 0.1 IU/ml by ELISA is the protective level of antibody

Geometric Mean Titers for Tdap Pertussis Antigens Between Pregnant and Non-Pregnant Women Among All Subjects

Antigen	Non-Pregnant/ Pregnant		P value
	GMT ratio	95%CI (Lower, Upper)	T test
PT at Day 0	1.1	1.0, 1.3	0.14
PT at Day 28	1.4	1.2, 1.7	<0.01*
FHA at Day 0	1.2	1.0, 1.5	0.02*
FHA at Day 28	1.3	1.1, 1.5	<0.01*
FIM at Day 0	1.5	1.1, 2.0	<0.01*
FIM at Day 28	0.8	0.7, 1.0	0.09
PRN at Day 0	1.7	1.4, 2.2	<0.01*
PRN at Day 28	1.0	0.9, 1.2	0.89

*Statistically significant ($P < 0.05$)

100% of subjects achieved protective levels for Diphtheria and Tetanus
Diphtheria 0.1 IU/ml is the protective level of serum antibody
Tetanus 0.1 IU/ml by ELISA is the protective level of antibody

Geometric Mean Titers for Tdap Pertussis Antigens Between Pregnant Women Who Received Previously Received Tdap or Not

Antigen	Tdap before			No Tdap before		
	N	GMT	95%CI (Lower, Upper)	N	GMT	95%CI (Lower, Upper)
PT at Day 0	194	9.9	8.8, 11	100	7.4	6.4, 8.4
PT at Day 28	194	46.2	39.9, 53	100	38.4	31.6, 46.7
FHA at Day 0	194	30.8	26.3, 36	100	20.1	16.1, 25.1
FHA at Day 28	194	103.7	91.6, 117	100	119.9	102.5, 140.3
FIM at Day 0	194	98.0	78.3, 123	100	43.3	30.5, 61.5
FIM at Day 28	194	655.0	562.1, 763	100	931.7	725.1, 1197.2
PRN at Day 0	194	40.5	33.8, 49	100	21.7	16.5, 28.5
PRN at Day 28	194	228.1	199.4, 261	100	306.1	239.7, 390.8

100% of subjects achieved seroprotection levels for Diphtheria and Tetanus
Diphtheria 0.1 IU/ml is the protective level of serum antibody
Tetanus 0.1 IU/ml by ELISA is the protective level of antibody

Geometric Mean Titers for Tdap Pertussis Antigens Between Pregnant Women Who Received Previously Received Tdap or Not

Antigen	No Tdap before / Tdap before		P value
	GMT ratio	95%CI (Lower, Upper)	T test
PT at Day 0	0.7	0.6, 0.9	<0.01*
PT at Day 28	0.8	0.7, 1.1	0.14
FHA at Day 0	0.7	0.5, 0.9	<0.01*
FHA at Day 28	1.2	0.9, 1.4	0.15
FIM at Day 0	0.4	0.3, 0.7	<0.01*
FIM at Day 28	1.4	1.1, 1.9	0.02*
PRN at Day 0	0.5	0.4, 0.7	<0.01*
PRN at Day 28	1.3	1.0, 1.7	0.04*

*Statistically significant ($P < 0.05$)

100% of subjects achieved seroprotection levels for Diphtheria and Tetanus
Diphtheria 0.1 IU/ml is the protective level of serum antibody
Tetanus 0.1 IU/ml by ELISA is the protective level of antibody

Summary of Subjects tested for Cytokine

- There were 6 subjects with severe reactions and 6 matched controls who didn't have severe reactions.
- They were matched by pregnancy status.

Subject	Vanderbilt N=10		Duke N=2	
	Pregnant	Non-Pregnant	Pregnant	Non-pregnant
Case	2	3	0	1
Control	2	3	0	1

Summary of Cytokine Results between Cases and Controls: IL-6, IL-8, and IL-10

Cytokine	N	Cases N=6 Median (mean ± STD) pg/ml	Controls N=6 Median (mean ± STD) pg/ml	P value
IL-6 Day 0	12	0.8 (0.9±0.7)	0.9 (0.9±0.6)	1.00
IL-6 Supplemental Visit	12	0.8 (1.1±0.8)	0.8 (1.0±0.8)	0.53
IL-6 Day 28	11	1.1 (1.0±0.5)	0.6 (0.7±0.4)	0.59
IL-8 Day 0	12	8.8 (14.1±13.1)	6.0 (6.8±2.5)	0.06
IL-8 Supplemental Visit	12	9.6 (21.5±24.1)	7.0 (7.5±2.1)	0.40
IL-8 Day 28	11	11.1 (22.6±30.0)	5.0 (6.4±2.6)	0.06
IL-10 Day 0	12	0.4 (0.4±0.1)	0.4 (0.4±0.2)	0.83
IL-10 Supplemental Visit	12	0.3 (0.7±0.9)	0.3 (0.3±0.1)	0.42
IL-10 Day 28	11	0.3 (0.4±0.1)	0.4 (0.5±0.3)	0.59

Information based on 1 Duke case (non-pregnant) and 5 Vanderbilt cases (3 non-pregnant and 2 pregnant)

Summary of Cytokine Results between Cases and Controls: TNF-α and IL5

Cytokine	N	Cases N=6 Median (mean ± STD) pg/ml	Controls N=6 Median (mean ± STD) pg/ml	P value
TNF-α Day 0	12	0.4 (0.6±0.4)	0.4 (0.5±0.2)	0.37
TNF-α Supplemental Visit	12	0.8 (0.9±0.5)	0.4 (0.5±0.2)	0.20
TNF-α Day 28	11	0.8 (0.9±0.4)	0.4 (0.5±0.4)	0.20
IL-5 Day 0	12	0.3 (0.4±0.2)	0.3 (0.3±0.1)	0.86
IL-5 Supplemental Visit	12	0.5 (0.7±0.6)	0.3 (0.3±0.0)	0.18
IL-5 Day 28	11	0.3 (0.3±0.2)	0.3 (0.6±0.7)	1.00

Information based on 1 Duke case (non-pregnant) and 5 Vanderbilt cases (3 non-pregnant and 2 pregnant)

Conclusions

- Tdap was well tolerated in both pregnant and non-pregnant women
- Moderate/severe injection-site pain occurred more frequently among pregnant women, but rates were consistent with clinically reported rates for the Tdap vaccine (16% per Adacel® package insert) and did not lead to medical visits
- 53% of the pregnant women received prior Tdap and rates of moderate/severe reactions were similar in pregnant women receiving the first or repeat Tdap
- Both pregnant and non-pregnant women had significantly higher antibody titers to all antigens after vaccination
- Obstetric and fetal outcome data are being collected

CISA Maternal Tdap Study Team

- **CISA lead site: Vanderbilt University**
  - Principal Investigators: Kathryn Edwards, Kimberly Fortner
- **CISA contributing site: Duke University**
  - Principal Investigators : Geeta Swamy, Chip Walter
- **CDC**
  - Principal Investigators : Karen Broder, Pedro Moro, Immunization Safety Office, National Center for Emerging and Zoonotic Infectious Diseases
  - Investigator: Jennifer Liang, Division of Bacterial Disease, National Center for Immunization and Respiratory Diseases
  - Investigator: Naomi Tepper, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion
- **National Vaccine Program Office (NVPO)**
  - Karin Bok

Study registered in www.clinicaltrials.gov (NCT02209623)

Study funded by CDC and the National Vaccine Program Office; additional funding for laboratory components provided to Vanderbilt by the Bill and Melinda Gates Foundation

ADDITIONAL SLIDES

Severe Reactions among Cases: Local Symptoms within 7 days after vaccination Pregnant versus Non-pregnant women

LOCAL Symptoms	Case: Pregnant N=2				Case: Non-Pregnant N=4			
	None (%)	Mild (%)	Moderate (%)	Severe (%)	None (%)	Mild (%)	Moderate (%)	Severe (%)
Pain	1 (50%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	2 (50%)	1 (25%)	1 (25%)
Tenderness	1 (50%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	2 (50%)	1 (25%)	1 (25%)
Swelling	0 (0%)	0 (0%)	1 (50%)	1 (50%)	1 (25%)	0 (0%)	2 (50%)	1 (25%)
Redness	0 (0%)	0 (0%)	0 (0%)	2 (100%)	2 (50%)	0 (0%)	0 (0%)	2 (50%)

Definitions:

Moderate: Induration and erythema: 10-34 mm; Pain/tenderness: Interferes with activity but did not necessitate medical visit or absenteeism

Severe: Induration and erythema: >=35 mm; Pain/tenderness: Prevents daily activity and resulted in medical visit or absenteeism

Non-inferiority criteria met for moderate/severe and severe local reactions in pregnant vs. non-pregnant women, except moderate/severe pain

Severe Reactions among Cases: Systemic Symptoms within 7 days after vaccination Pregnant versus Non-pregnant women

SYTEMIC Symptoms	Case: Pregnant N=2				Case: Non-Pregnant N=4			
	None (%)	Mild (%)	Moderate (%)	Severe (%)	None (%)	Mild (%)	Moderate (%)	Severe (%)
Fever	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)	1 (25%)	1 (25%)
Feverishness	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)	0 (0%)	2 (50%)
Malaise	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)	1 (25%)	1 (25%)
Body aches	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	0 (0%)	1 (25%)	1 (25%)
Headaches	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	1 (25%)	0 (0%)	1 (25%)

Definitions:

Moderate: fever ≥ 100.4 - < 102.2° F; Other symptoms: Interferes with activity but did not necessitate medical visit or absenteeism

Severe: fever ≥ 102.2° F; Other symptoms: Prevents daily activity and resulted in medical visit or absenteeism

Non-inferiority criteria met for all moderate/severe and severe systemic reactions in pregnant vs. non-pregnant women