Considerations for recommendation on Tdap for every pregnancy

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2012 case history: Fatal pertussis in infant born to mother who received Tdap 2 years prior

- **Infant (male, Hispanic)**
  - Illness at age 8 days, hospitalized at age 32 days
  - PCR (+) pertussis
  - Intubated, mechanical ventilation, ECMO*
  - Died at age 40 days
- **Mother**
  - 1 week prior to delivery developed cough illness
  - Received Tdap postpartum, 2 years prior
- **2 of 3 children ill**
- **Postpartum vaccine from previous pregnancy given, but did not protect infant**

*ECMO: extracorporeal membrane oxygenation

Information courtesy of Texas Department of State Health Services

Tdap for every pregnancy
Rationale

- **Continue efforts to remove barriers to improve Tdap uptake**
  - 78% - Adolescents (2011)
  - 8% - Adults (2010)
  - 2.6% - Women vaccinated during pregnancy (April 2012)
- **New data available on persistence of maternal antibodies**
- **Optimize strategies to prevent infant pertussis morbidity and mortality in light of record-setting increase in cases**

CDC. National and State Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2011. MMWR. 61(34);671-677

CDC. Adult Vaccination Coverage — United States, 2010. MMWR. 61(04);66-72

CDC. Tdap vaccination coverage among U.S. women who were pregnant any time during August 2011 - April 2012, Internet Panel Survey, April 2012. Unpublished

Background: Tdap vaccines

- FDA approved as single use only
- ACIP recommended as single lifetime dose
- 2011 - pregnancy recommendation only for those not previously immunized with Tdap

Data reviewed by WG

- Barriers to vaccinating pregnant women
- Antibody response and kinetics of Tdap during pregnancy
- Safety on multiple doses of Tdap
- Statistics on births in the United States

BARRIERS TO VACCINATING PREGNANT WOMEN WITH TDAP

Barriers to vaccinating pregnant women with Tdap

- **Undocumented Tdap vaccine history**
  - Provider hesitancy to vaccinate
- **Programs still focused on postpartum Tdap**
- **Getting the message out**
  - Several initiatives aimed at improving vaccination of pregnant women
- **Provider recommendation is the best predictor of vaccination (Tong 2008, Meharry 2012)**

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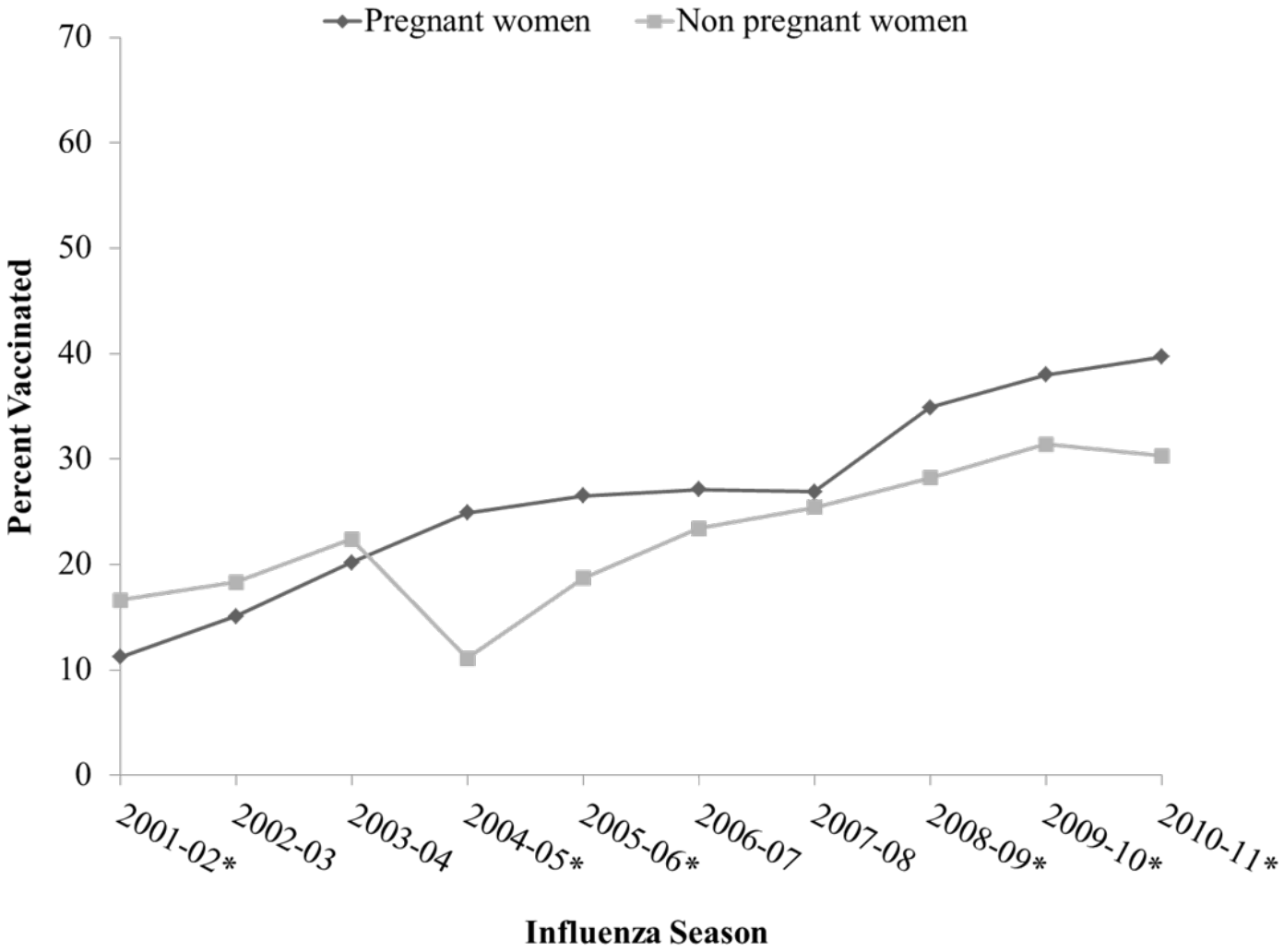
Tong A, et al. A cross-sectional study of maternity care providers' and women's knowledge, attitudes, and behaviours towards influenza vaccination during pregnancy. MJ Obstet Gynaecol Can. 2008 May;30(5):404-10.

Meharry et al. Reasons Why Women Accept or Reject the Trivalent Inactivated Influenza Vaccine (TIV) During PregnancyMatern Child Health J. 2012 Feb 25.

Influenza vaccination coverage in pregnant and nonpregnant women by influenza season

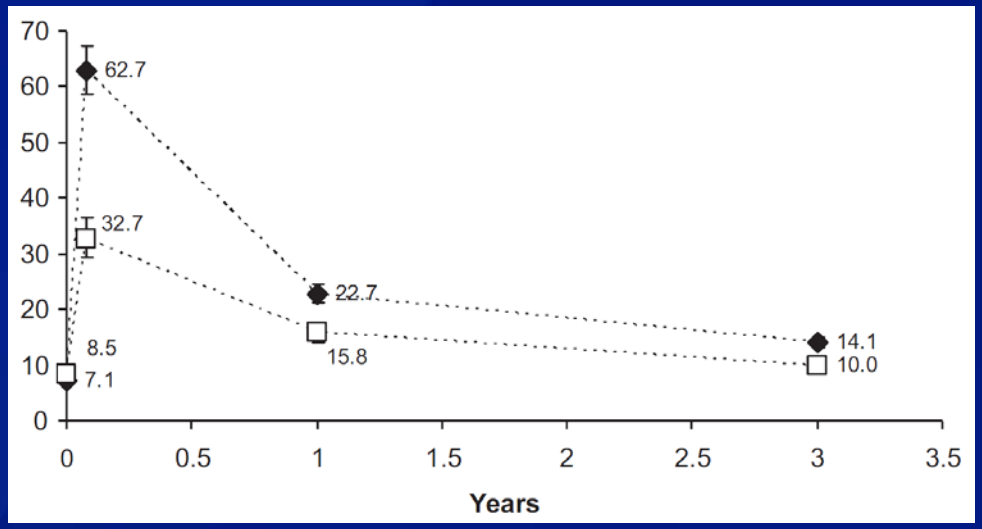


Kennedy ED, Ahluwalia IB, Ding H, Lu PJ, Singleton JA, Bridges CB. Monitoring seasonal influenza vaccination coverage among pregnant women in the United States. Am J Obstet Gynecol. 2012 Sep;207(3 Suppl):S9-S16. Epub 2012 Jul 9.

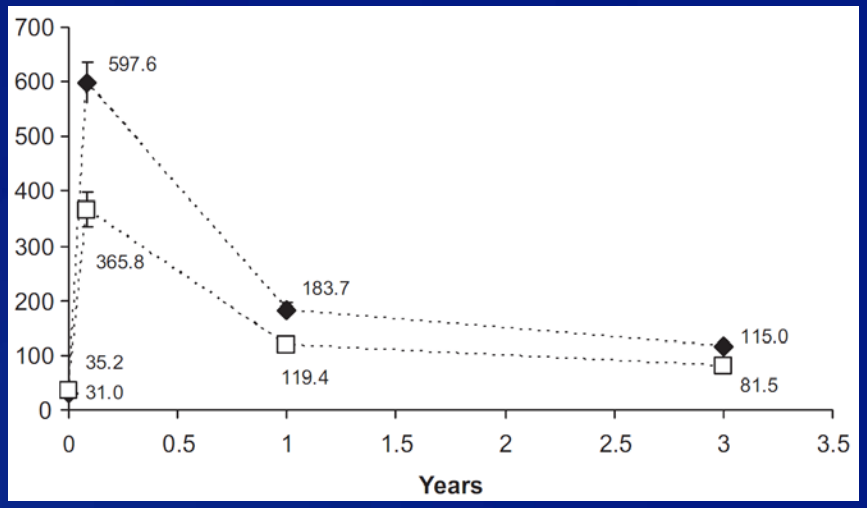
TDAP PROTECTION FOR SUBSEQUENT PREGNANCIES

Persistence of pertussis antibodies 3 years after Tdap vaccination of adults

Anti-PT antibody GMCs (EU.L/mL)



Anti-FHA antibody GMCs (EU.L/mL)



GMC = gemetric mean concentration

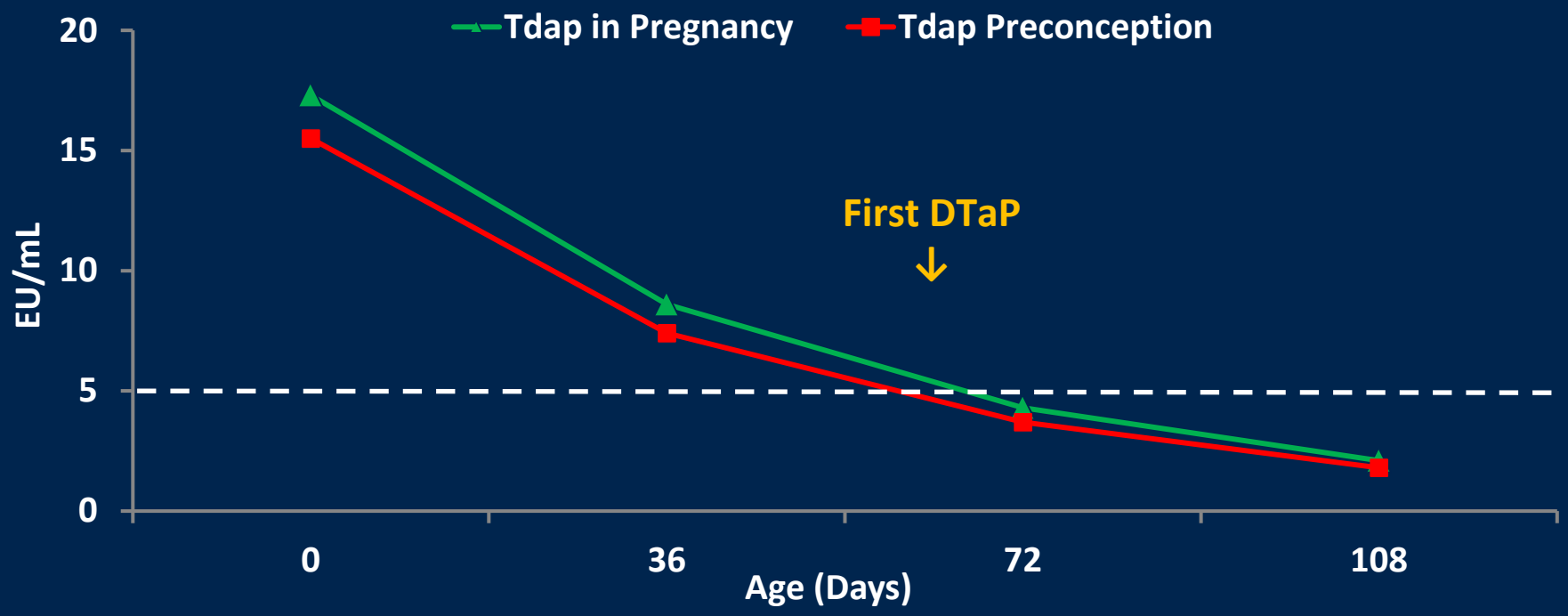
Weston W, et. al. Persistence of antibodies 3 years after booster vaccination of adults with combined acellular pertussis, diphtheria and tetanus toxoids vaccine. Vaccine. 2011 Nov 3;29(47):8483-6.

Decline of maternal antibody concentrations after receipt of Tdap

- **105 maternal delivery: placental cord pairs**
  - Mean time from Tdap vaccine: 13.7mths (2.3-23.9)
    - ~70% Tdap postpartum after prior baby
    - 19 immunized during pregnancy
      - Median gestation: 6 weeks (1 – 28 weeks)
- **Methods**
  - IgG Geometric mean concentrations (GMCs) measured
  - Cord: maternal GMC ratios were calculated.
  - Pertussis toxin (PT)-specific IgG present in infants at age 2 mths estimated using the accepted half-life of maternal pertussis-specific IgG to PT (36 days).

Healy C. IDSA 2012, in press.

PT-specific IgG (GMC) in Cord Sera and Estimated Decay with Age*



At age 2 months (time of first DTaP):

- Estimated GMC of PT-specific IgG is < 5 EU/ml
- 60% of infants have PT-specific IgG concentration < 4 EU/ml (LLOQ)
- More of pre-conception group are < LLOQ (62% vs. 48%; P=0.34)

* Assuming $t_{1/2}$ of 36.3 days (*J Infect Dis* 1990 ;161:487-92)

Healy C. IDSA 2012, in press

Texas Children's Hospital

BCM Baylor College of Medicine

Study: Summary from results

- Efficient placental transport of pertussis-specific antibodies
- Little difference in pertussis-specific IgG in neonates of women vaccinated before or early in pregnancy
- At time of first DTaP (2 mths), estimated concentration of PT-specific IgG in infants fell to levels likely too low to ensure protection in mothers immunized preconception.

Healy C. IDSA 2012, in press

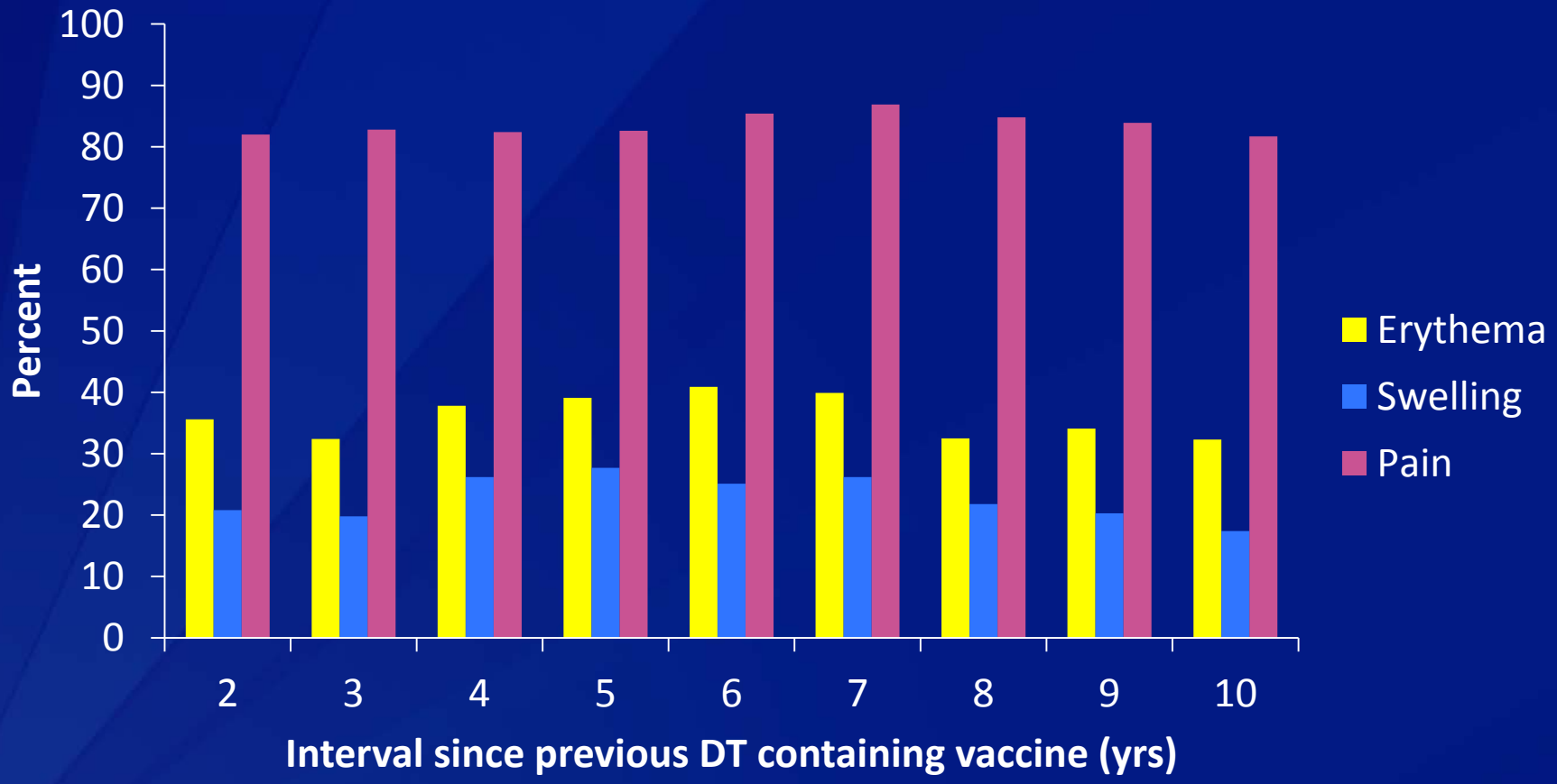
Tdap protection for subsequent pregnancies: WG conclusions

- A single dose of Tdap at one pregnancy is insufficient to provide protection for subsequent pregnancies.

Multiple doses of Tdap

SAFETY TO MOTHER AND FETUS

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



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

Presented to ACIP, October 2010

Reported adverse events
Receipt of Tdap or Tdap-IPV <2 yrs after Td

- **Most commonly reported at injection site (3 to 14 days)**
  - Pain (67.9% – 82.6%)
  - Redness (20.2% – 25.2%)
  - Swelling (19.4% – 37.8%)
- **Systemic adverse events:**
  - Headache (20.2%)
  - Fever (1.7%-9.6%)
  - Myalgia (15.3%)
- **Serious adverse events related to the receipt of Tdap or Tdap-IPV - not reported or observed**

Beytout J, et. al. Safety of Tdap-IPV given 1 month after Td-IPV booster in healthy young adults: a placebo controlled trial. Hum Vaccin 2009;5(5).

Talbot EA, et. al. The safety of immunizing with tetanus-diphtheria-acellular pertussis vaccine (Tdap) less than 2 years following previous tetanus vaccination: Experience during a mass vaccination campaign of healthcare personnel during a respiratory illness outbreak. Vaccine (2010).

Reported adverse events after 2nd Tdap dose at 5 or 10 years after 1st Tdap dose

- **Well tolerated**
  - Most common: injection site pain
  - Frequency of reported adverse events was similar to receipt after 1st Tdap and to a naïve group
- **Of few serious adverse events reported, none attributed to receipt of vaccine**

Knuf M, et al. Repeated administration of a reduced-antigen-content diphtheria-tetanus-acellular pertussis and poliomyelitis vaccine (dTpa-IPV; Boostrix™ IPV). Hum Vaccin. 2010 Jul;6(7):554-61

Booy R, et al. A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix™) is immunogenic and well tolerated in adults. Vaccine. 2010 Dec 10;29(1):45-50.

Halperin SA, et al. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. Vaccine. 2011 Oct 26;29(46):8459-65.

Halperin SA, et al. Immune responses in adults to revaccination with a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine 10 years after a previous dose. Vaccine. 2012 Jan 20;30(5):974-82.

Concerns about severe hypersensitivity reactions with multiple doses of Tdap for pregnant women

- **Arthus reaction**
  - Immune complex–mediated (type III) hypersensitivity
  - Localized area of tissue necrosis from acute immune complex vasculitis
  - Develops 4–12 hours after vaccination
  - Usually resolve without sequelae

- **Extensive limb swelling**
  - Not disabling
  - Not often brought to medical attention
  - Resolves without complication within 4–7 days

Historical data: Tetanus and diphtheria toxoids

- **Hypersensitivity associated with higher levels of pre-existing antibody**
  - Antigen content (D vs. d)
  - Product formulation (alum adjuvant results in better duration at lower concentration)
  - Short interval
  - Number of doses
- **Post 2nd Tdap tetanus GMCs did not differ from post 1st dose with 5-year interval (Halperin 2011)**
- **Excess risk of serious hypersensitivity unlikely**

Halperin SA, et al. Tolerability and antibody response in adolescents and adults revaccinated with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed (Tdap) 4-5 years after a previous dose. Vaccine. 2011 Oct 26;29(46):8459-65.

Historical data: Tetanus toxoid during pregnancy

- WHO recommends 2 or more doses of tetanus toxoid during pregnancy (to complete primary series) to prevent neonatal tetanus
- Data on number of doses administered and adverse events not systematically collected
- Major studies have not reported clinically significant severe adverse events beyond local redness, swelling, pain and tenderness, and systemic events like fever, body-ache, or lethargy.

Schofield FD, et al., Neonatal tetanus in New Guinea. Effect of active immunization in pregnancy. Br Med J, 1961. 2(5255): p. 785-9.

Newell, K.W., et al., The use of toxoid for the prevention of tetanus neonatorum. Final report of a double-blind controlled field trial. Bull World Health Organ, 1966. 35(6): p. 863-71.

MacLennan, R., et al., Immunization against neonatal tetanus in New Guinea. Antitoxin response of pregnant women to adjuvant and plain toxoids. Bull World Health Organ, 1965. 32(5): p. 683-97.

Hardegree, M.C., et al., Immunization against neonatal tetanus in New Guinea: 2. Duration of primary antitoxin responses to adjuvant tetanus toxoids and comparison of booster responses to adjuvant and plain toxoids. Bulletin of the World Health Organization, 1970. 43(3): p. 439-51.

Safety of multiple doses of Tdap: WG conclusions

- Challenges reviewing historical data
- Available data and experience with tetanus toxoid vaccines suggests no increased risk of adverse events
- Safety monitoring plan important

STATISTICS ON BIRTHS IN THE US

General statistics on births in the US, 2009

- Number of births: 4,130,665[1]
- Percent born preterm: 12.2%[1]
- Mean age at first birth: 25.2 yrs[1]
- 2.06 children born/woman (est. 2011)[2]

1 http://www.cdc.gov/nchs/fastats/births.htm;
2 https://www.cia.gov/library/publications/the-world-factbook/geos/us.html

Number of months from 1st to 2nd birth for women aged 15–44 yrs who had at least one birth: United States, 2006–2010

	#	No 2nd birth	Interval between 1st and 2nd birth (months)[1]				
			12 or less	13-24	25-36	37-48	49+
		Percent distribution (standard error)					
Total	**34,353**	**30.0 (1.0)**	**2.5 (0.3)**	**17.5 (0.7)**	**17.2 (0.7)**	**12.3 (0.7)**	**20.6 (0.8)**
Race and ethnicity							
Non-Hispanic (single race)							
White	19565	31.1 (1.3)	1.7 (0.3)	1.7 (0.3)	17.0 (1.0)	18.4 (1.0)	13.0 (1.0)
Black	5216	32.2 (1.6)	3.5 (0.7)	3.5 (0.7)	16.4 (1.3)	12.7 (1.1)	11.0 (1.4)
Asian	1208	33.9 (5.3)	0.6 (0.3)	0.6 (0.3)	15.0 (4.3)	14.7 (3.2)	7.6 (2.9)
Hispanic	6760	25.1 (1.9)	3.0 (0.8)	20.2 (1.3)	16.4 (1.5)	12.3 (2.0)	23.0 (1.4)

[1]Refers to intervals between deliveries, not intervals between first and second babies born as a multiple birth. Pregnancies resulting in multiple births (e.g., twins) are considered one delivery.

Gladys Martinez G, Daniels K, Chandra A. Fertility of Men and Women Aged 15–44 Years in the United States: National Survey of Family Growth, 2006–2010. National Health Statistics Reports. No. 51, 2012. http://www.cdc.gov/nchs/data/nhsr/nhsr051.pdf

Interpregnancy interval, Pregnancy Surveillance System, 2010*

Interpregnancy interval† (all races) (n=554,361)	National prevalence	
	Number	%
< 6 months	64,860	11.7
6 - <18 months	143,579	25.9
≥18 months	345,921	62.4

* The Pregnancy Surveillance System (PNSS) is part of a program-based surveillance system that monitors the nutritional status of low-income infants, children, and women in federally funded maternal and child health programs.

† Interpregnancy Interval is the amount of time between pregnancies and calculated as the number of months between the date the last pregnancy ended and the date of the last menstrual period.

CDC. Summary of Health Indicators, 2010 Pregnancy Nutrition Surveillance, Pregnancy Nutrition Surveillance System. http://www.cdc.gov/pednss/pnss_tables/pdf/national_table2.pdf

Women by number of children ever born*, June 2010

Age (yrs)	Total women	Total women	Number of children ever born (%)						
			None	One	Two	Three	Four	Five and six	Seven or more
15 to 44	**61,481**	**100.0**	**47.1**	**16.9**	**20.4**	**10.4**	**3.4**	**1.5**	**0.3**
15 to 19	10,273	100.0	94.6	4.4	0.6	0.3	-	-	-
20 to 24	10,493	100.0	70.5	18.1	9.0	2.0	0.3	0.1	-
25 to 29	10,501	100.0	47.6	22.7	18.7	7.8	2.3	0.8	0.1
30 to 34	9,923	100.0	29.7	19.2	29.2	14.3	5.2	2.1	0.4
35 to 39	9,917	100.0	19.7	18.5	32.6	19.7	5.9	3.1	0.4
40 to 44	10,374	100.0	18.8	18.5	33.3	19.1	6.8	2.7	0.8

*Question asked: How many children have you ever had?“ and does not distinguish between number of children and number of births.

Fertility of American Women: 2010; June Supplement to the Current Population Survey.
http://www.census.gov/hhes/fertility/data/cps/2010.html

Statistics on births: WG conclusions

- Tdap maternal pertussis antibodies would wane greatly between subsequent pregnancies
- Very small proportion would receive 4 or more doses of Tdap

WG conclusions

Tdap FOR EVERY PREGNANCY

ACIP WG conclusions: Tdap for every pregnancy Safety

- **Data reassuring on 2 doses of Tdap**
- **Data and experience with tetanus toxoid vaccine suggests no excess risk of adverse events**
  - ~5% of women would receive 4 or more doses
- **Supported ongoing safety monitoring and requested that CDC commit to safety studies to address concerns about the potential increase in severe adverse events after Tdap is given during subsequent pregnancies**

Plans for safety monitoring in pregnant women vaccinated with Tdap

- **Vaccine Adverse Event Reporting System (VAERS)**
  - Enhanced monitoring for adverse events in pregnant women following Tdap
  - Inherent limitations of passive surveillance, including biased reporting
- **Vaccine Safety Datalink (VSD)**
  - Implementing studies assessing acute adverse events, adverse pregnancy outcomes affecting the mother and birth outcomes (excluding congenital anomalies) following receipt of Tdap (and other vaccines) during pregnancy.
    - Study power for Tdap depends on uptake and may take a few years

ACIP WG conclusions: Tdap for every pregnancy

- A single dose of Tdap at one pregnancy was insufficient to provide protection for subsequent pregnancies.

- Benefits of vaccination outweigh the theoretical risks of severe adverse events

ACIP WG conclusions: Tdap for every pregnancy

- With poor Tdap uptake (2.6%), the WG is continuing efforts to remove barriers to improve vaccine uptake and optimize strategies to prevent infant pertussis morbidity and mortality.

- More universal recommendation for pregnant women would remove real and/or perceived barriers to vaccination

Actions to improve Tdap uptake in pregnant women

- **Removing barriers**
  - National Vaccine Advisory Committee
  - National Foundation for Infectious Diseases
- **Communication/Education**
  - CDC Communications
  - ACOG
  - Text4Baby
- **Monitoring coverage in pregnant women**
  - Pregnancy risk assessment monitoring system (PRAMS)
  - CDC Internet panel survey of pregnant women

Proposed changes to 2011 recommendation for pregnant women

- Dose of Tdap irrespective of previous Tdap history
- Tdap for every pregnancy
- Simplify recommendation by moving language on timing of dose to guidance section

Proposed recommendation
October 2012

ACIP recommends that providers of prenatal care implement a Tdap immunization program for all pregnant women. Health-care personnel should administer a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap. If not administered during pregnancy, Tdap should be administered immediately postpartum.

Guidance for use
October 2012

- Optimal timing for Tdap administration is between 27 and 36 weeks gestation to maximize the maternal antibody response and passive antibody transfer to the infant.

- Tdap is very safe in all trimesters and can be given at any time during pregnancy

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DISCUSSION AND VOTE