Guidance on the use of Tdap during pregnancy

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on behalf of the Pertussis Vaccines Work Group

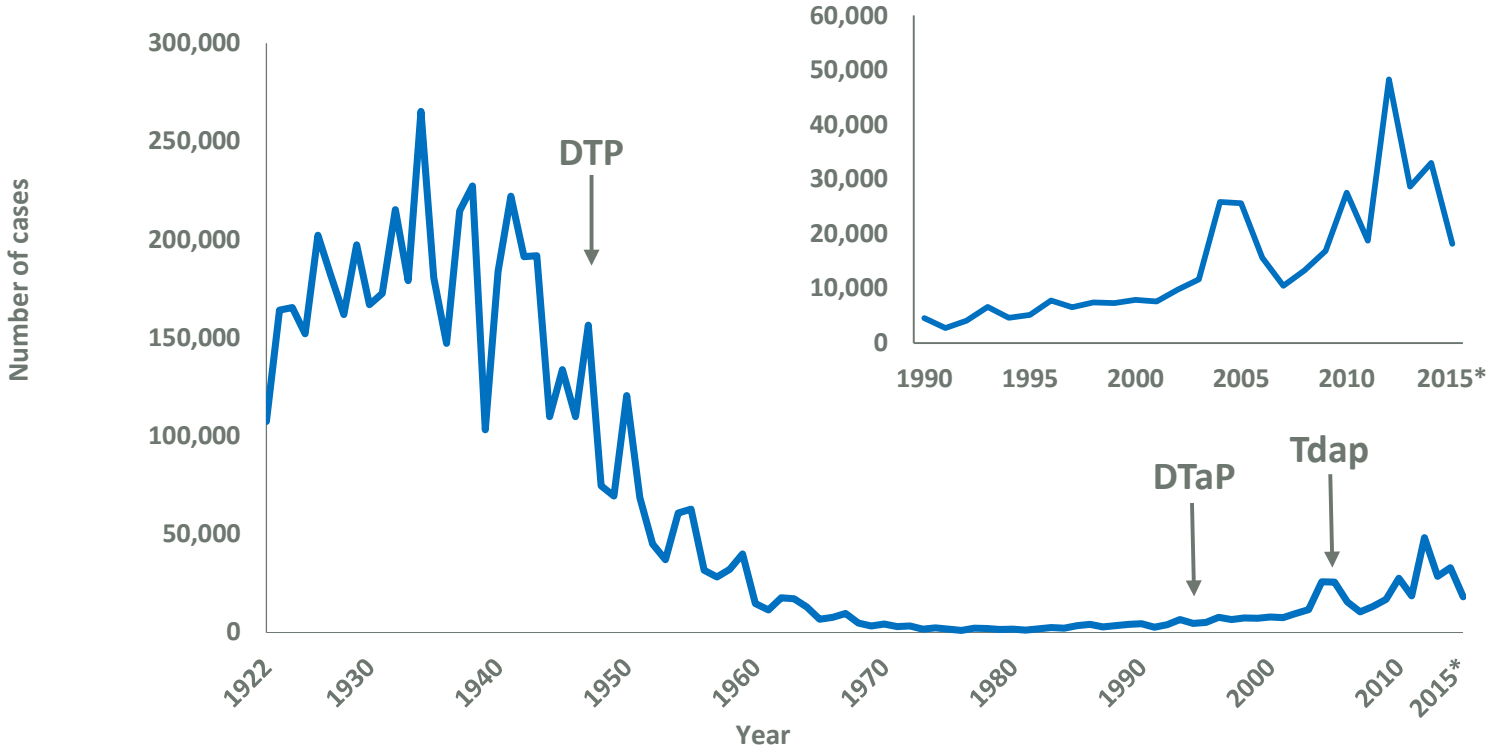
Advisory Committee on Immunization Practices

October 19, 2016

Overview

- Epidemiology of pertussis
- ACIP Tdap recommendation & guidance for use for pregnant women
- Tdap vaccines
- Safety to mother and infant
- Timing of Tdap administration during pregnancy
  - Immunogenicity
  - Effectiveness of preventing infant pertussis
  - Programmatic considerations
- WG conclusions
- Discussion

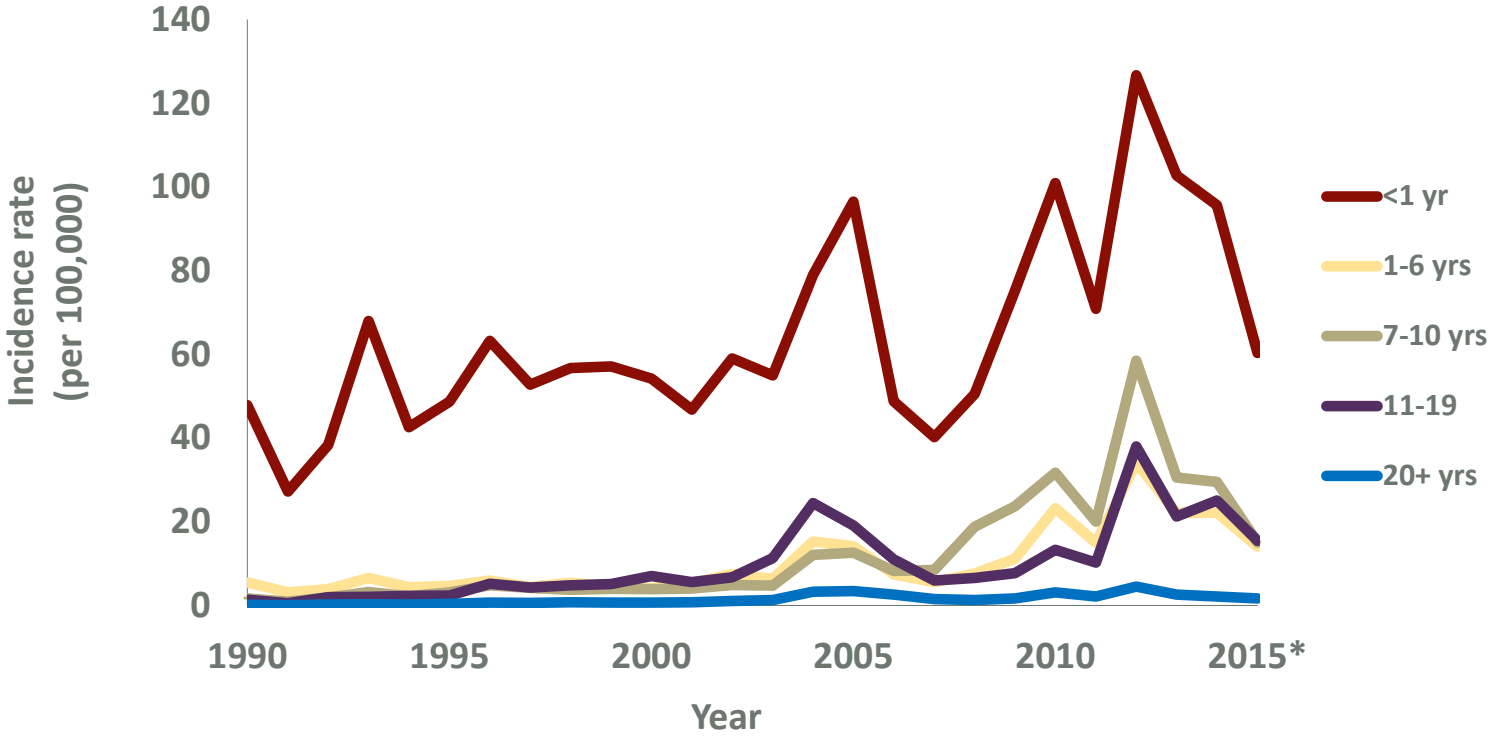
Reported NNDSS pertussis cases: 1922-2015*



*2015 data are provisional

SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service

Reported pertussis incidence by age group: 1990-2015*



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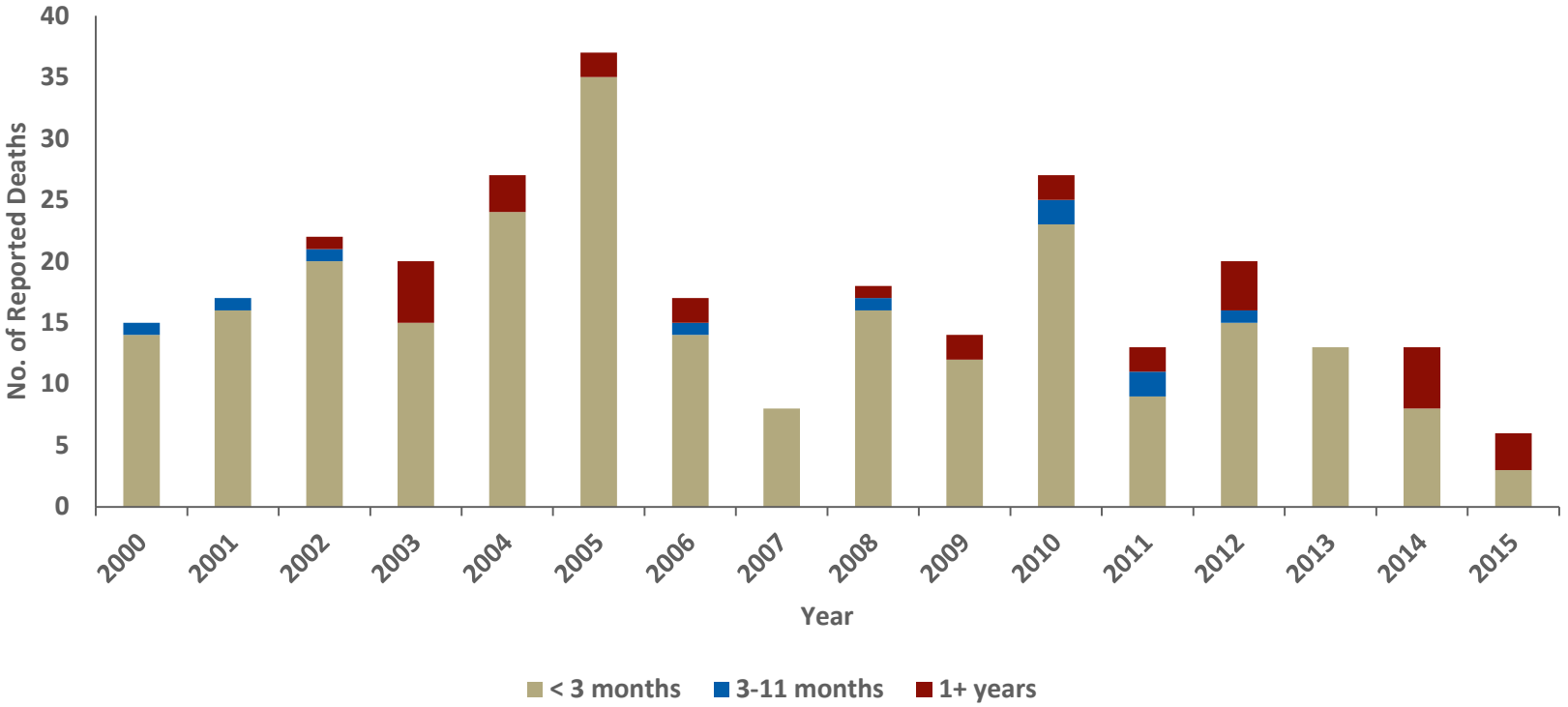
SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System

Pertussis deaths by age group, 2000-2015*



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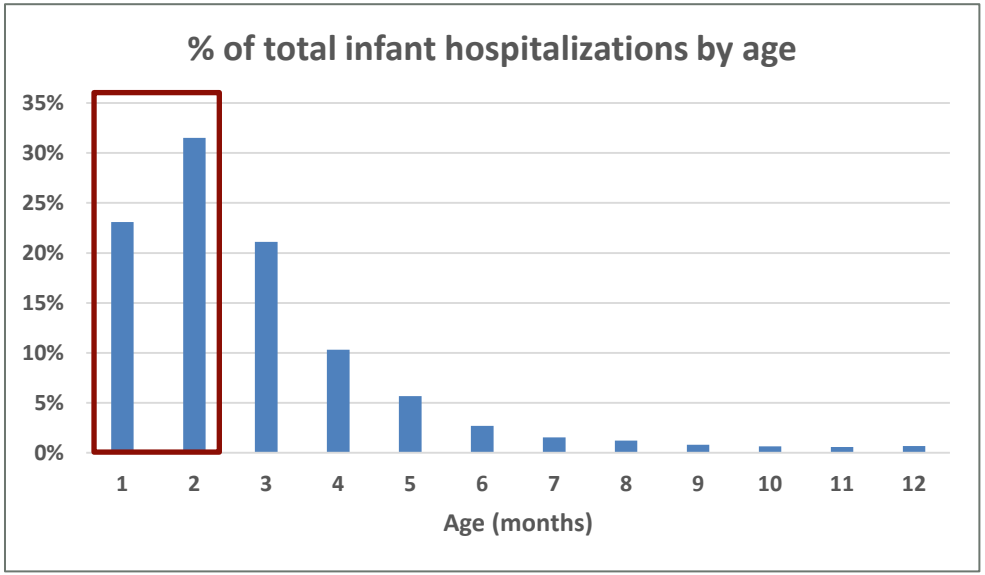
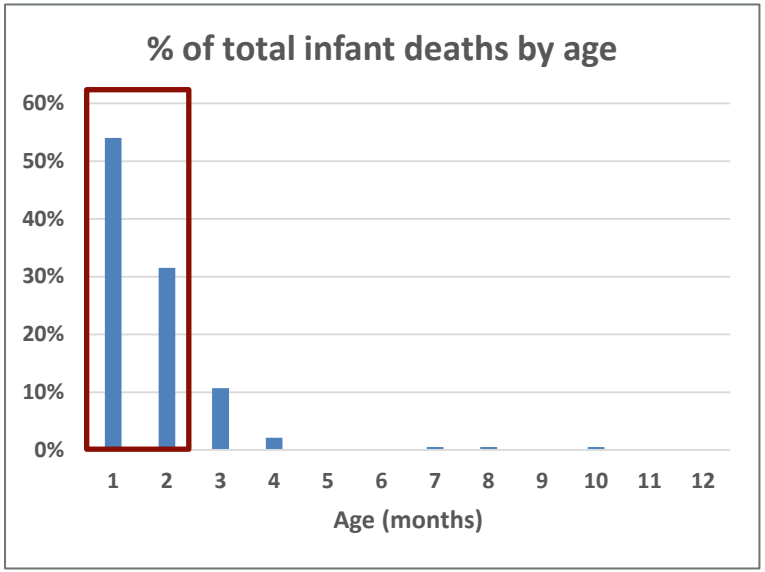
SOURCE: CDC. National Notifiable Diseases Surveillance System, 2015

Hospitalizations and deaths in infants <12 months of age, % of total pertussis cases, 2004-2015*





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SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System

ACIP Tdap recommendation for pregnant women*

2011

- ACIP recommended a single dose of Tdap for pregnant women

2012

- ACIP expanded the recommendation to a dose of Tdap during *every* pregnancy

*Use of Tdap in pregnant women is an off-label recommendation.

ACIP Tdap recommendation for pregnant women*

- *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.*

Guidance for Use

- *To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks gestation although Tdap may be given at any time during pregnancy. For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum.*

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Composition of currently available Tdap vaccines*

Trade name	Manufacturer	Pertussis antigens (µg)				Diphtheria toxoids (Lf)	Tetanus toxoids (Lf)	Age for licensed use
		PT	FHA	PRN	FIM			
Adacel	Sanofi Pasteur	2.5	5	3	5	2	5	10—64 yrs
Boostrix	GSK	8	8	2.5	-	2.5	5	≥10 yrs

Abbreviations: Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; PT = pertussis toxin; FHA = filamentous hemagglutinin; PRN = pertactin; FIM = fimbriae

* Vaccine dosage and administration: 0.5mL intramuscular injection

Safety to mother and infant

Tdap vaccination of pregnant women

CDC Immunization Safety Office:
Postlicensure vaccine safety monitoring infrastructures

System	Collaboration	Description
Vaccine Adverse Event Reporting System (VAERS)	CDC and FDA	• US frontline spontaneous reporting system to detect potential vaccine safety problems
Vaccine Safety Datalink (VSD)	CDC and Healthcare Plans	• Large linked database system used for active surveillance and research
Clinical Immunization Safety Assessment (CISA) Project	CDC and Academic Centers	• Expert collaboration which conducts individual clinical vaccine safety assessments and clinical research

Courtesy of the CDC Immunization Safety Office

CDC monitoring activities for maternal Tdap safety

- **Vaccine Adverse Event Reporting System (VAERS)**
  - Ongoing monitoring
- **Vaccine Safety Datalink (VSD)**
  - Surveillance and research outcomes include
    - Preterm delivery and small for gestational age (SGA); acute vaccine-related adverse events; obstetric events; birth defects
  - Access to EMR and medical records to validate cases and denominator(s) for rates
- **Clinical Immunization Safety Assessment (CISA) Project***
  - Tdap safety in pregnant women (NCT02209623)¶
  - Safety of simultaneous Tdap and Inactivated Influenza Vaccine (IIV) in pregnant women (NCT02783170)

*Registered at ClinicalTrials.gov

¶ Presented to ACIP in June 2015

Courtesy of the CDC Immunization Safety Office

Maternal pertussis vaccination -- safety data collected in the United States continue to be reassuring

- Pattern of adverse events observed in VAERS in pregnant women receiving Tdap and their infants is consistent with expectations

- Studies of >50,000 women receiving Tdap during pregnancy in the VSD show no increased risk for adverse maternal or infant health outcomes*

- Clinical study in the CISA Project shows Tdap was well tolerated in both pregnant and non-pregnant women, including pregnant women receiving a repeated Tdap dose

*Kharbanda EO et al. JAMA. 2014;312(18):1897-904.; Sukumaran L, et al. JAMA. 2015 314(15):1581-7, Sukumaran L, et al. ObGyn. 2015;126(5): 1069–1074; Kharbanda EO et al. Vaccine 2016; 34: 968-73.

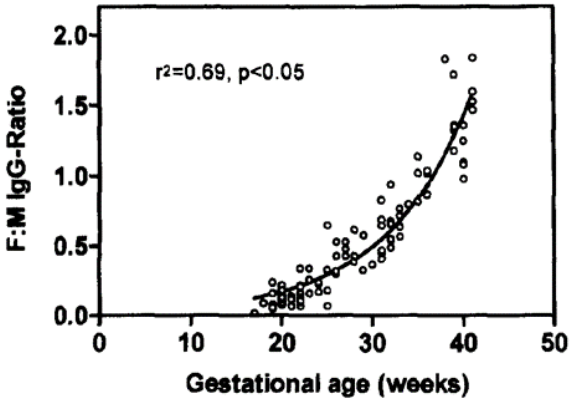
Courtesy of the CDC Immunization Safety Office

Immunogenicity and effectiveness

Tdap vaccination of pregnant women

Baseline information: Pertussis

- No well-defined serologic correlates of protection for pertussis
  - Pertussis toxin (PT) important virulence factor
- After receipt of Tdap, minimum of 2 wks for antibody development
- During pregnancy, active IgG transport begins ~17 wks gestation, increasing with gestation
  - Accelerated uptake ~34 wks gestation
- Immune response to Tdap similar in pregnant and non-pregnant women
  - Efficient placental transfer of vaccine-induced pertussis antibodies
    - Higher antibody concentration in cord blood vs. maternal serum



Fetal:maternal ratio of IgG level related to gestational age

Malek A, et al. 1996 AJRI

Timing of Tdap vaccination and cord blood antibody levels

ACIP Guidance: 27—36 wks

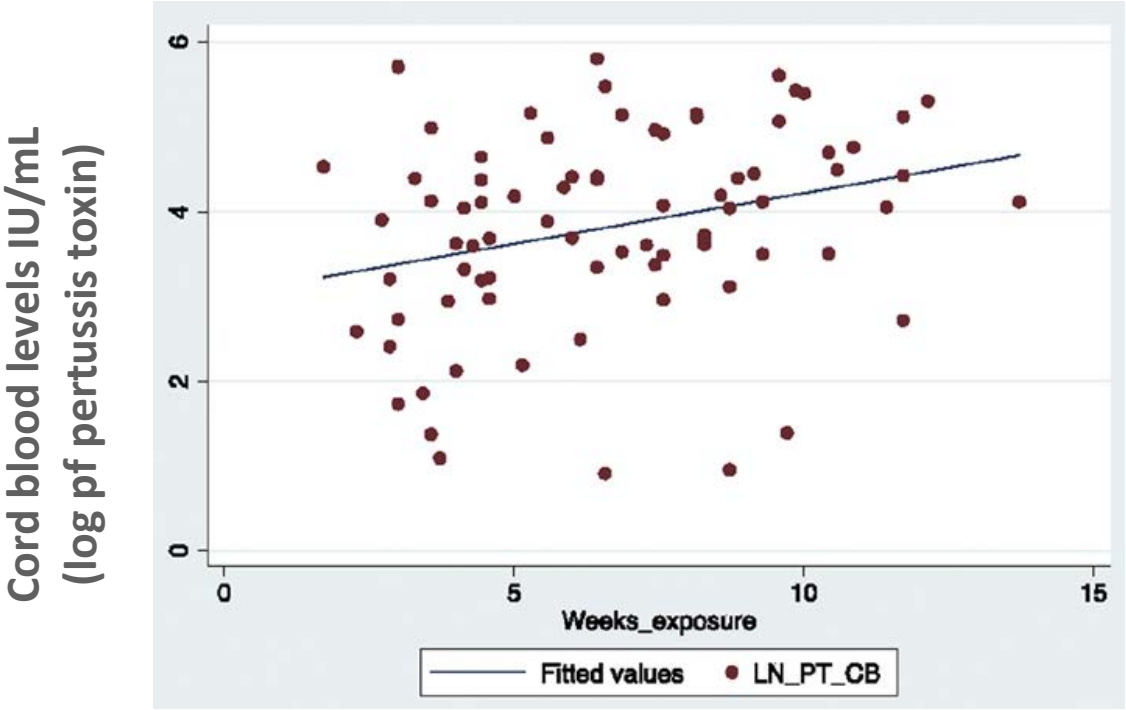
	Cord blood antibody levels (standard deviation)		
	lnPT	**lnFHA**	**lnPRN**
No Tdap (n=27)	2.80 (1.20)	4.21 (1.06)	4.90 (1.04)
Tdap at 28-32 wks (n=38)	4.18 (1.01)	5.56 (0.99)	5.83 (0.93)
Tdap at 33-36 wks (n=44)	3.50 (1.25)	5.03 (1.19)	5.31 (1.17)
p-value[a]	<0.001	<0.001	0.001

InPT = log transformed pertussis toxin; InFHA = log transformed filamentous hemagglutinin; InPRN = log transformed pertactin; SD = standard deviation.

[a] Analysis of variance for differences across 3 groups

Table 2 from Naidu et al. Pertussis vaccination during pregnancy. Am J Obstet Gynecol 2016. (Australia)

Positive correlation between number of weeks exposed to Tdap and infant cord blood levels to IgG anti-PT levels



r=0.31, p=0.004

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Geometric mean concentration of anti-PT IgG in Tdap-immunized and unimmunized women and newborns

	Geometric mean concentration PT IU/mL (95% CI)		
Immunization status	**Maternal sera**	**Cord sera**	**Cord:Maternal Ratio[1] (95% CI)**
No Tdap (n=61)	0.74 (0.31–1.79)	1.12 (0.41–3.02)	2 (1.04–2.95)
Tdap at 27–30 wks (n=21)	33.39 (18.10–61.59)[2]	46.04 (24.29–87.30)[2]	1.45 (1.26–1.64)[3]
Tdap at 31–36 wks (n=30)	9.94 (4.54–21.73)[4]	8.69 (3.66–20.63)[5]	1.04 (0.86–1.23)
Tdap at >36 wks (n= 7)	28.09 (12.45–63.43)[3]	21.12 (7.93–56.22)[6]	0.97 (0.27–1.67)[6]

[1] Ratio presented as mean (95% CI)
[2] P < .001, compared with corresponding measurements for unimmunized women (maternal sera, newborn cord sera and cord to maternal sera ratio)
[3] P = .004, compared with the ratio of cord to maternal sera IgG to PT for women immunized at 31–36 weeks
[4] P = .002, compared with the maternal sera IgG to PT for unimmunized women
[5] P < .004, compared with the cord sera IgG to PT for unimmunized women
[6] P < .004, compared with the cord sera IgG to PRN for unimmunized women

Table 2 from: Abu Raya et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – A prospective study. Vaccine 2014. (Israel)

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Infant Cord Blood Geometric Mean Concentrations (GMC) by Gestational Age at Maternal Tdap

Gestational wk Tdap received	No.	Anti-PT GMC* (95% CI)	Anti-FHA GMC* (95% CI)
13-16	26	44.2 (32.2–60.7)	297.9 (206.7–429.4)
17-21	42	53.1 (37.2–75.7)	267.3 (205.4–347.9)
22-25	54	68.3 (52.8–88.3)	291.8 (222.8–382.2)
26-29	30	70.3 (49.0–100.8)	376.8 (257.0–552.7)
30-33	16	74.9 (38.3–146.4)	417.3 (232.7–748.4)
34-36	72	32.7 (24.1–44.3)	173.0 (126.5–236.6)
37-38	74	25.1 (17.9–35.3)	92.7 (69.0–124.7)
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* Enzyme-linked immunosorbent assay units (EU)/mL

Table 3 from Eberhardt et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. CID 2016. (Switzerland)

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Distribution of anti-PT infant cord blood concentrations according to time between maternal Tdap and delivery

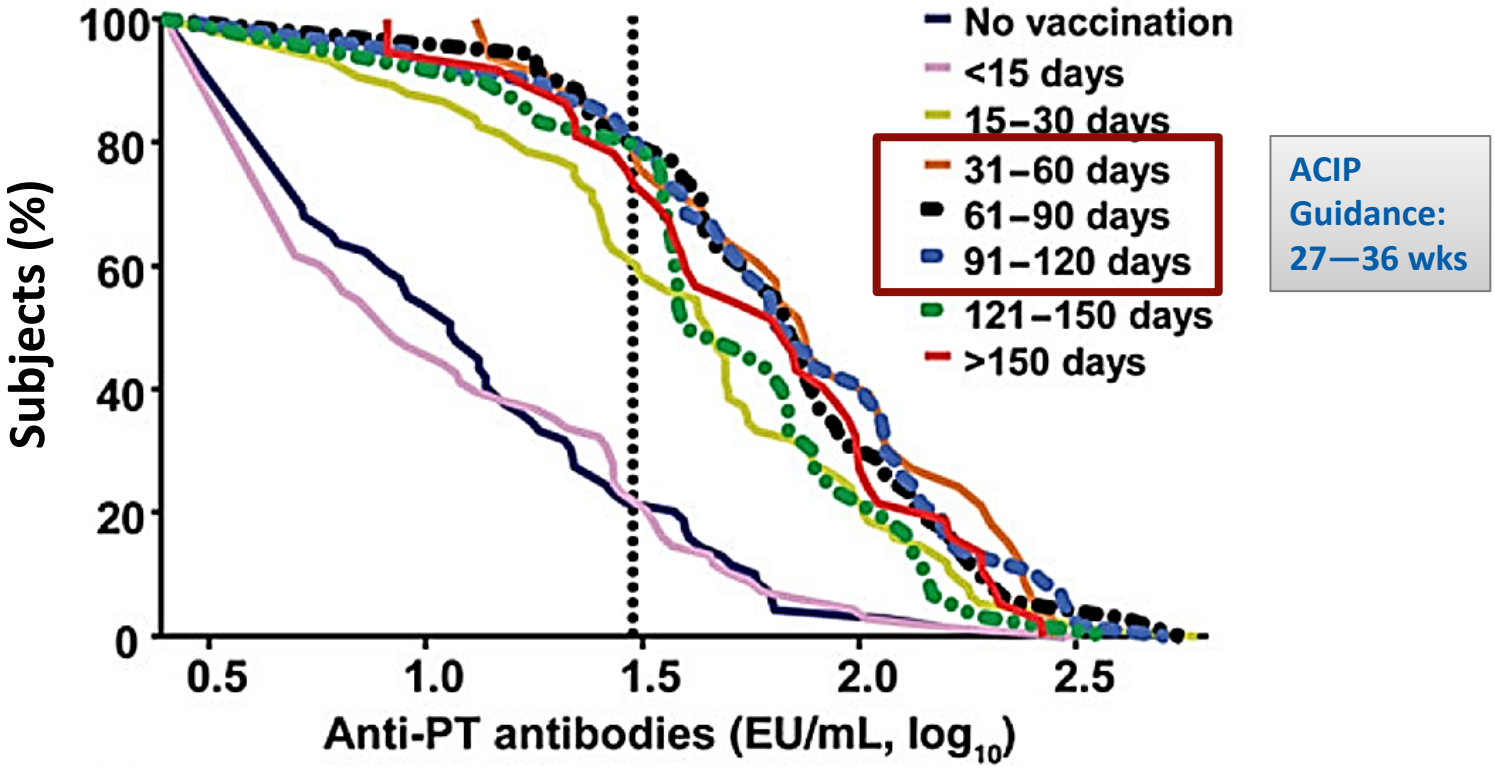

Figure 2 from Eberhardt et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. CID 2016. (Switzerland)

Summary of immunogenicity studies

- Infants of Tdap vaccinated mothers were born with significantly higher anti-pertussis antibodies compared to infants of unvaccinated mothers

- Within the 27– 36 weeks administration “window”
  - Concentration of anti-pertussis antibodies in infant cord blood were higher when mothers were vaccinated earlier
  - Longer exposure to vaccine allows for higher vaccine induced antibody levels produced by mother and transferred to infant

- Infant cord blood concentration of anti-pertussis antibodies similarly high when maternal Tdap administered before 27 weeks

Studies show agreement that maternal Tdap vaccination very effective at preventing infant pertussis infection

	Vaccine effectiveness (95% confidence intervals)	Definitions	
		Infant age at pertussis onset	Mother gestational age received Tdap
United Kingdom			
Observational[1], screening method	91% (83%-95%)	<3 mths	at least 28 days before birth*
Case-Control[2], retrospective	91% (77%-97%), unadjusted 93% (81%-97%), adjusted¶	<2 mths	cases: 31.5 wks (range, 28–38) controls: 33 wks (range, 26–38)
United States			
Cohort[3], retrospective	85% (33%-98%)	<2 mths	27-36 wks vs. postpartum Tdap
Case-Control[4], retrospective	78% (44%-91%)	<2 mths	27-36 wks

*2012 UK recommendation: Tdap between 28 and 38 weeks

¶ Adjusted for sex, geographical area, and birth period

[1]Amirthalingam G, et al. 2014; [2]Dabrera G, et al. 2015; [3]Winter K, et al. 2016; [4]CDC, unpublished

Effectiveness of maternal Tdap on pertussis severity in infants

Infants born to vaccinated mothers

- Older when developed pertussis
  - Median: 45 days vs. 35 days; p=0.03
- Less likely have classic pertussis symptoms
- Significantly lower risk of hospitalization and ICU admission
  - Hospitalization: RR 0.5; p<0.001
  - ICU: RR 0.8; p=0.012
- No deaths due to pertussis

Winter K, et al. Effectiveness of prenatal Tdap vaccination on pertussis severity in infants. Clin Infect Dis. 2016 Sep 13. [Epub ahead of print]

Bridging immunogenicity and effectiveness data

- Minimal concentration of antibodies to confer protection from pertussis disease in infants unknown

- Important to ensure enough time between mother's receipt of Tdap and infant's birth to allow for maximizing the concentration of maternal antibodies
  - May be better achieved by vaccinating at an earlier gestational age
  - However, vaccination too early during pregnancy may not allow for sustained antibodies through the infant's first DTaP dose at age 2 months

Options to modify current window (27 through 36 weeks)

1. Expanding window to include earlier Tdap administration (e.g., as early as 22 wks)

2. Narrowing window (27-32 wks)

3. No change to current window (27-36), but emphasize earlier administration within window

Programmatic considerations

- Tdap uptake in pregnant women steadily increasing

- Vaccinating earlier could increase opportunity to educate and vaccinate pregnant women and increase protection among preterm infants
  - Percent born preterm (<37 completed wks gestation): 9.6%
    - Early (<34 completed wks): 2.8%
    - Late (34-36 completed wks): 6.8%

- Narrowing window could potentially decrease opportunity to vaccinate

HHS. Births: Final data for 2014. National Vital Statistics Report. 2015. Vol 64. No. 12. www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_12.pdf

WG conclusions

- Maternal Tdap vaccination is effective at preventing infant pertussis
- Vaccinating earlier may be beneficial at optimizing production and transfer of maternal antibodies to infants
- Concerns how changing the “window” impact maternal Tdap program and effectiveness of preventing pertussis in infants
  - Not equate higher concentration from earlier vaccination to better effectiveness without knowing whether durability and concentration of maternal antibodies would be maintained until infant is old enough to receive DTaP
- Without effectiveness data specific to vaccinating women earlier during pregnancy, WG cautious to “over-interpret” results from studies

WG deliberations:
Options to modify current window (27 through 36 weeks)

1. Expanding window to include earlier Tdap administration (e.g., as early as 22 wks)
   - No support
2. Narrowing window (27-32 wks)
   - Minority
3. No change to current window (27-36), but emphasize earlier administration within window
   - Majority

ACIP Tdap recommendation for pregnant women*

- *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.*

Guidance for Use (***CURRENT***)

- ***To maximize the maternal antibody response and passive antibody transfer to the infant, optimal timing for Tdap administration is between 27 and 36 weeks gestation although Tdap may be given at any time during pregnancy.*** *For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum.*

*Use of Tdap in pregnant women is an off-label recommendation.

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Guidance for Use (***DRAFTED CHANGE***)

- ***Tdap should be administered between 27 and 36 weeks gestation, although it may be given at any time during pregnancy. Currently available data suggest that vaccinating earlier in the 27 through 36 week window will maximize passive antibody transfer to the infant.*** *For women not previously vaccinated with Tdap, if it is not administered during pregnancy, Tdap should be administered immediately postpartum.*

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