Review of evidence considered for pregnancy Tdap recommendation

Summary from February & June 2011

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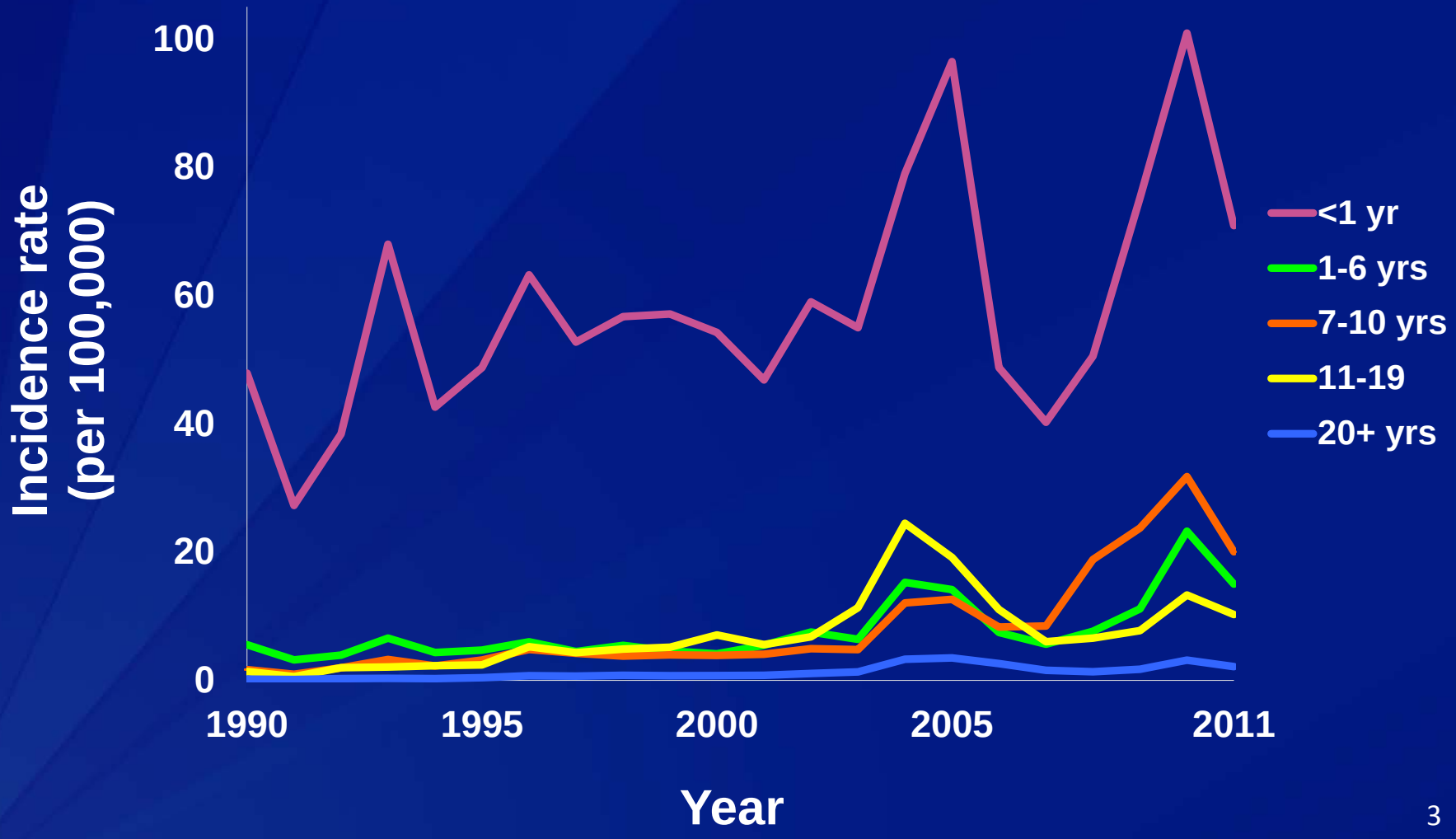
National Center for Immunization & Respiratory Diseases

Division of Bacterial Diseases

Overview

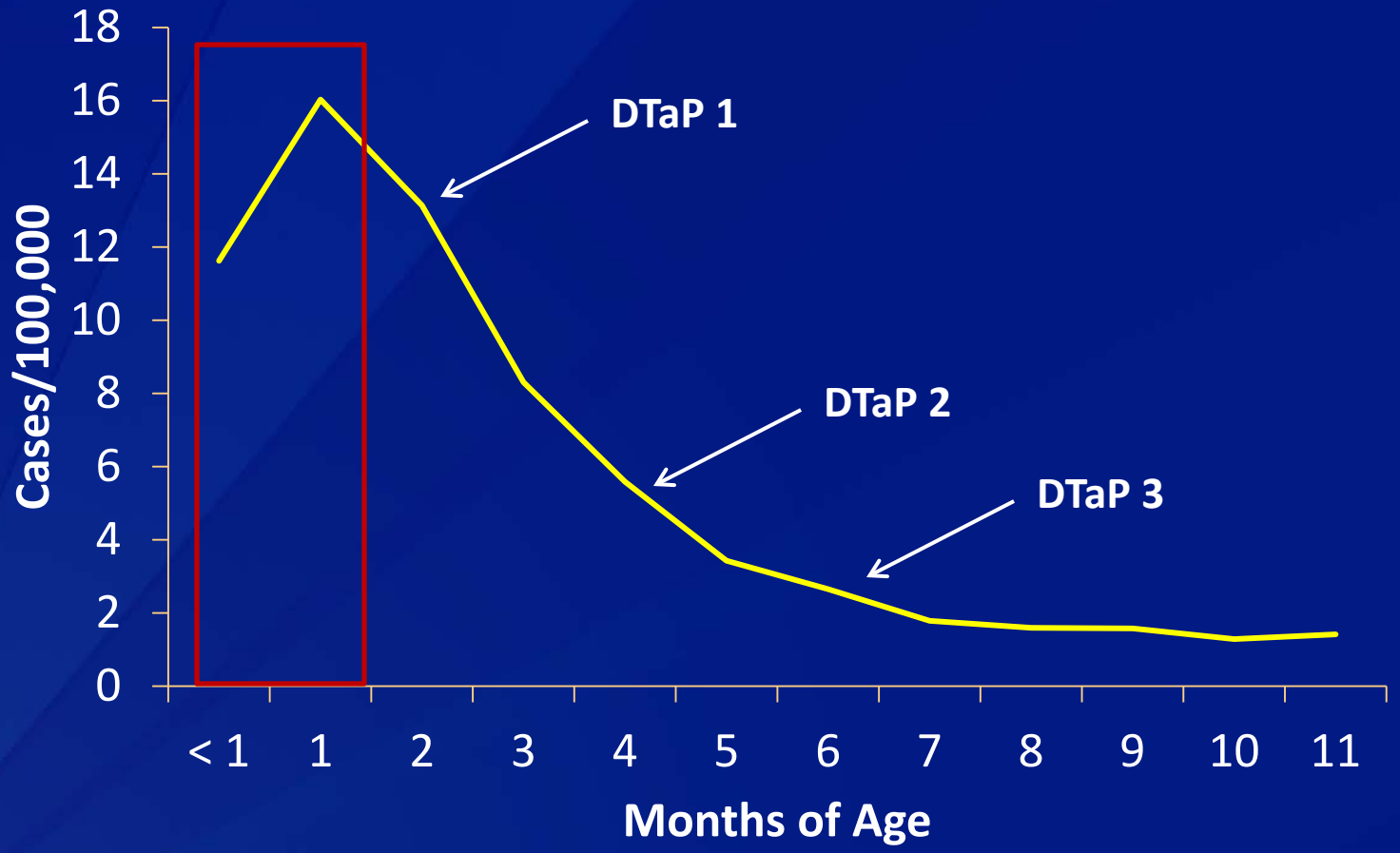
- **Epidemiology of infant pertussis**
- **Data considered and ACIP conclusions (February & June 2011)**
  - Vaccination strategies to protect infants
  - Safety to mother and fetus
  - Effectiveness of maternal antibodies
  - Interference to infant immune response to DTaP
  - Decision analysis

Reported pertussis incidence by age group: 1990-2011



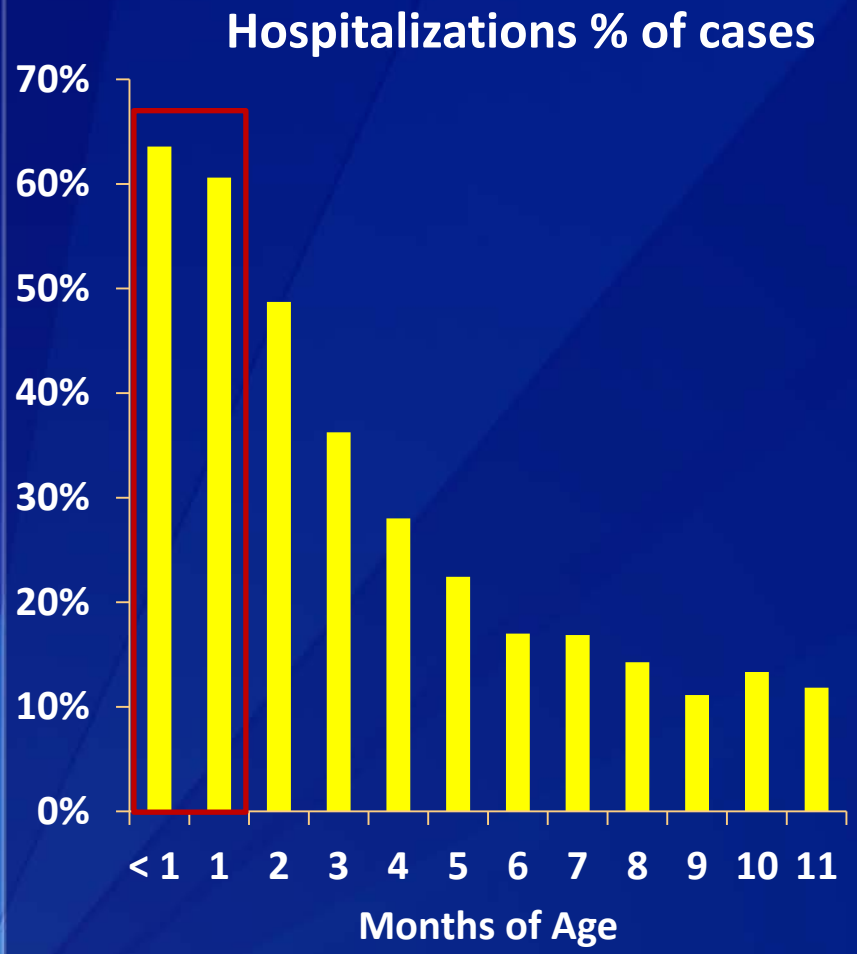
SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System

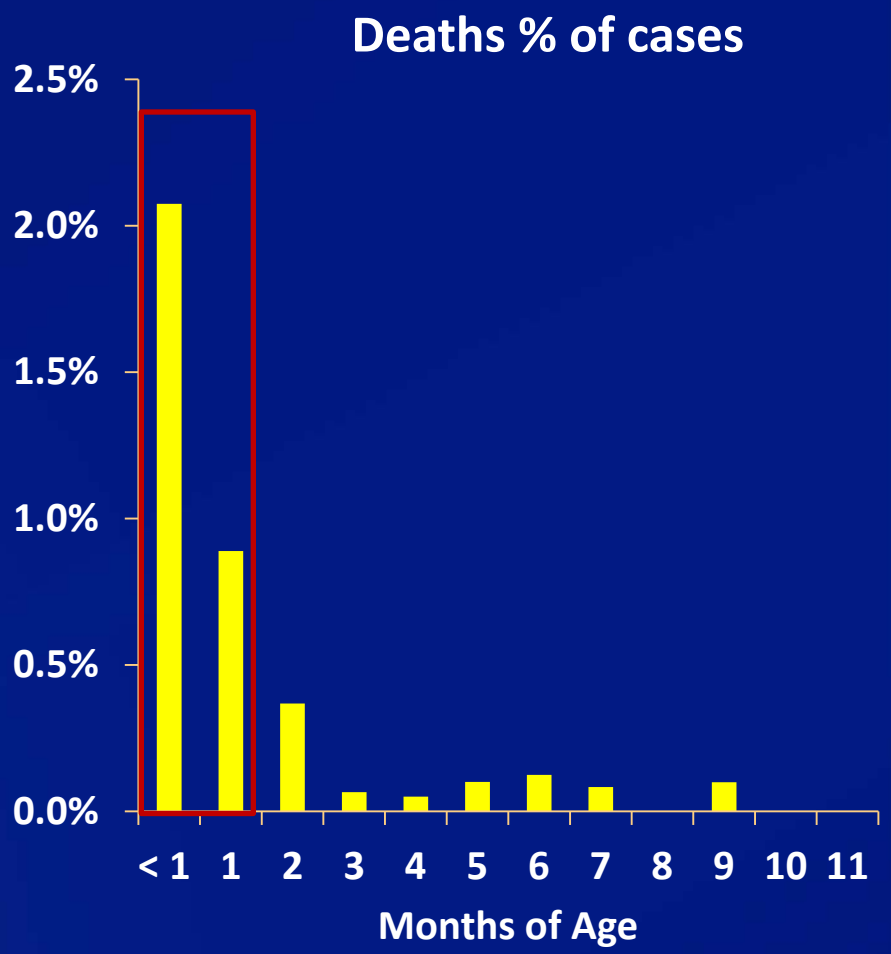
Pertussis incidence among infants, 2001-2011



Source: CDC, National Notifiable Diseases Surveillance System, 2011

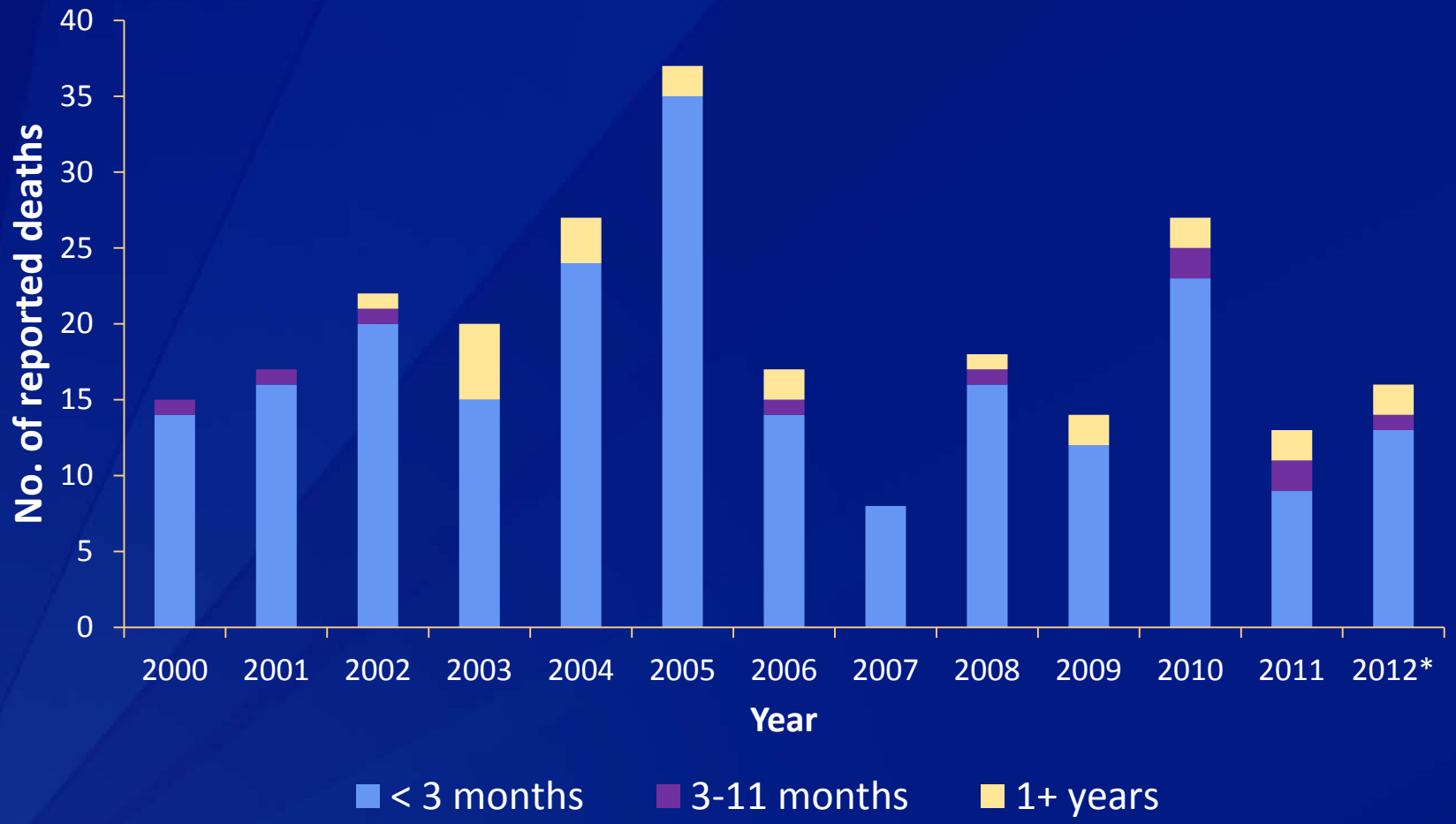
Hospitalizations and Deaths
% Total Infant Cases, 2001-2011





Source: CDC, National Notifiable Diseases Surveillance System, 2011

Pertussis deaths by age group, 2000-2012*



*2012 data are provisional and reflect deaths reported to NNDSS as of October 19, 2012.
Source: CDC. National Notifiable Diseases Surveillance System, 2012.

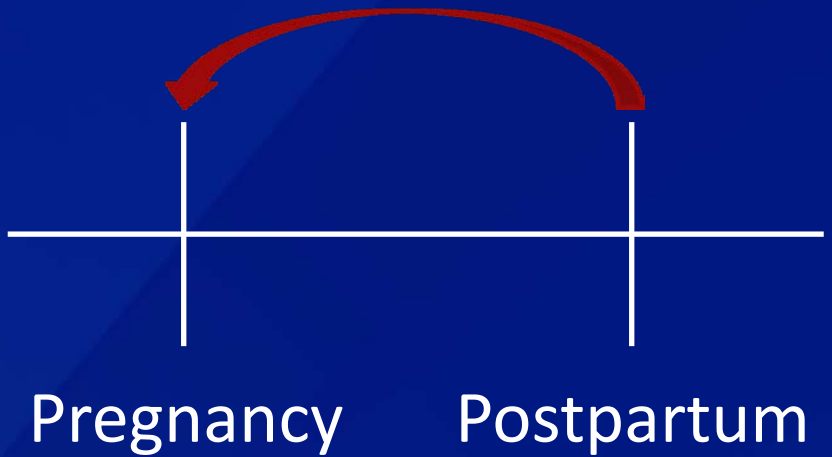
VACCINATION STRATEGIES TO PROTECT INFANTS

Protecting infants from pertussis "Cocooning"

- **Source of transmission to infants – majority not mother**
- **Tdap "cocooning" strategy**
  - All close contacts, mothers postpartum
  - Difficult to achieve coverage
  - Unknown effectiveness
  - Sub-optimal strategy

Wendelboe AM, et al. Transmission of Bordetella pertussis to Young Infants. Pediatr Infect Dis J 2007;26: 293–299
Bisgard KM, et al. Infant pertussis: who was the source? Pediatr Infect Dis J 2004; 23(11):985-989.
Healy CM, et al. Pertussis immunization in a high-risk postpartum population. Vaccine. 2009 Sep 18;27(41):5599-602.

Shifting the timing of mother's Tdap dose



- Provides earlier protection to mother and therefore indirect protection to infant
- High levels of transplacental maternal antibodies transferred to infants may provide direct protection

SAFETY TO MOTHER AND FETUS

Vaccines currently recommended during pregnancy - 2011

- **Inactivated viral vaccines, bacterial vaccines and toxoids are considered very safe during pregnancy**
- **Influenza vaccine**
  - Protects pregnant women and infants <6 months of age
  - ACIP recommends trivalent inactivated vaccine for all women who are or will be pregnant during the influenza season
- **Tetanus toxoid vaccine**
  - Protects infants born to women in developing countries from neonatal tetanus
  - WHO recommends 2 doses in first and 1 in each subsequent pregnancy
- **No evidence to demonstrate an increased risk to mother or fetus**

Presented to ACIP, June 2011

Tdap during pregnancy: Safety data reviewed by ACIP 2011

- **Vaccine Adverse Event Reporting System (VAERS)***
- **Pregnancy registry data (unpublished)**
  - Sanofi Pasteur
  - GlaxoSmithKline
- **Small studies (Gall 2011; Talbot 2010, unpublished)**

Gall SA,et al. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol 2011;204:334.e1–5.

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;28:8001–7.

Tdap during pregnancy: Safety data reviewed by ACIP

- **Vaccine Adverse Event Reporting System (VAERS)***
  - 132 of 106,573 VAERS reports after Tdap vaccines involved pregnant women (January 2005-June 2010)
    - 55 (42%) no AE reported
    - No maternal or infant deaths
    - Pregnancy specific AE: spontaneous abortion 22 (16.7%)
    - Non-pregnancy specific AE: injection site reaction 6 (4.5%)
    - One report major congenital anomaly (gastroschisis)
  - No unexpected patterns or unusual events

*Zheteyeva YA, et al. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol. 2012 Jul;207(1):59.e1-7.

ACIP conclusions: Tdap during pregnancy is acceptably safe to woman and fetus

- Td and TT used extensively in pregnant women
- Data support safety of Tdap in mother and newborn
- Data not sufficient to exclude occurrence of a rare adverse event
- Current data suggest that potential risks (if any) are likely to be small

BENEFIT OF MATERNAL ANTIBODIES

Geometric mean concentrations (GMCs) and percentage of placental transfer of antibodies to PT, FHA, and PRN in maternal and cord serum samples

Antigen (EU/ml)	Number of samples tested		GMC (95% CI) [range]		Placental transfer (%)
	Maternal serum	Cord serum	Maternal serum	Cord serum	
PT	196	196	9.9 (8.6-11.3) [1-233]	16.2 (14.2) [1-348]	164
FHA	195	192	21.5 (18.6-24.8) [2-731]	34.8 (30.1-40.14) [1-850]	162
PRN	196	195	13.5 (11.7-15.6) [2-292]	17.1 (15.2-20.5) [2-272]	131

PT = pertussis toxin; FHA=filamentous hemagglutinin; PRN=pertactin; EU, enzyme-linked immunoassay unit

de Voer RM, et al. Seroprevalence and placental transportation of maternal antibodies specific for Neisseria meningitidis serogroup C, Haemophilus influenzae type B, diphtheria, tetanus, and pertussis. Clin Infect Dis. 2009 Jul 1;49(1):58-64.

Tdap vaccination leads to higher antibody levels in infants

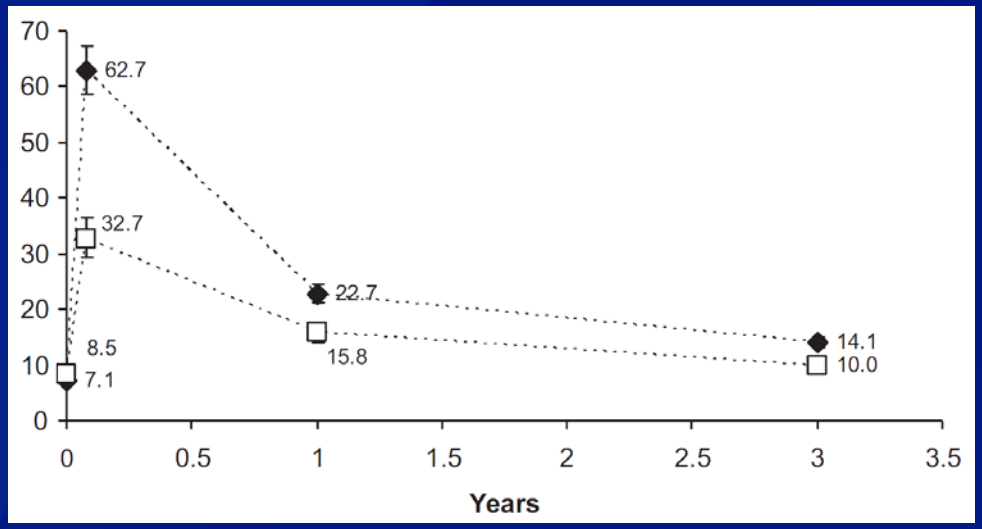
Outcome Antibodies	Mother did not receive Tdap, mean (SEM) n=52	Mother received Tdap, mean (SEM) n=52	P value[a]	Pearson correlation coefficient (P value[a])
PT	11.010 (1.796)	28.220 (2.768)	< .001	0.158 (.055)
FHA	26.830 (4.022)	104.15 (21.664)	.002	0.165 (.045)
PRN	24.700 (5.765)	333.01 (56.435)	< .001	0.965 (< .001)
FIM 2/3	82.83 (14.585)	1198.99 (189.937)	< .001	0.293 (< .001)

FHA, filamentous hemagglutinin; FIM, fimbriae; PRN, pertactin; PT, pertussis toxin;
[a] Significant at .05 level.

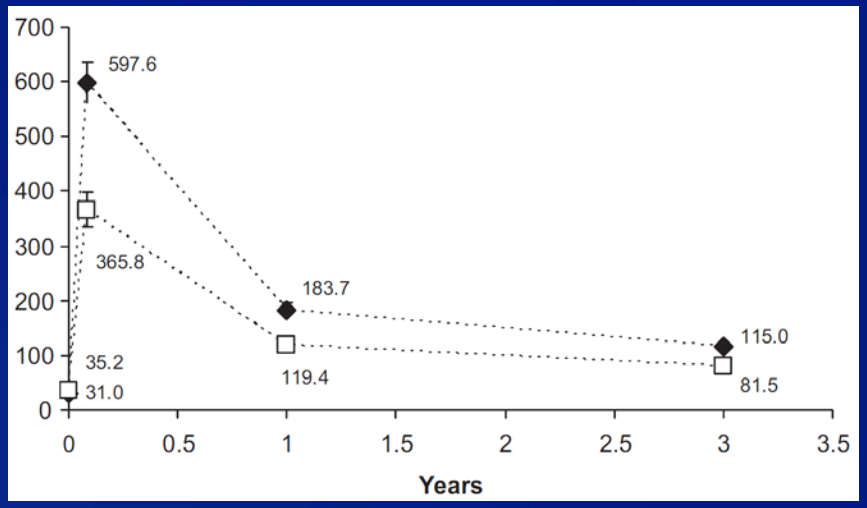
Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. Am J Obstet Gynecol 2011;204:x.ex-x.ex.

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)



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.

Evidence of interference "Blunting"

- **Whole cell pertussis (wP):**
  - Immune response to wP vaccine was lower in infants with high circulating maternal antibodies in cord blood than in infants with a low cord blood levels (van Savage 1990; Adams 1947; Sako 1945; Baraff 1958; Burstyn 1983, Englund 1995)

- **Acellular pertussis (aP):**
  - Response to aP vaccine lower, but not similarly inhibited by circulating maternal antibody (van Savage 1990; Englund1995; Roduit 2002; Henninger 1994; Halperin unpublished)
  - Blunting largely resolve by completion of 3rd DTaP dose (Halperin, personal communication)

ACIP Conclusions: Tdap during pregnancy may prevent infant pertussis (during the same pregnancy)

- Efficient maternal-infant antibody transfer after Tdap
- Infant – maternal antibodies likely confer protection and modify the severity of pertussis illness
- Optimize concentration of maternal antibodies to fetus, unvaccinated women get Tdap during pregnancy

Comparing Tdap during pregnancy to postpartum Tdap

DECISION ANALYSIS

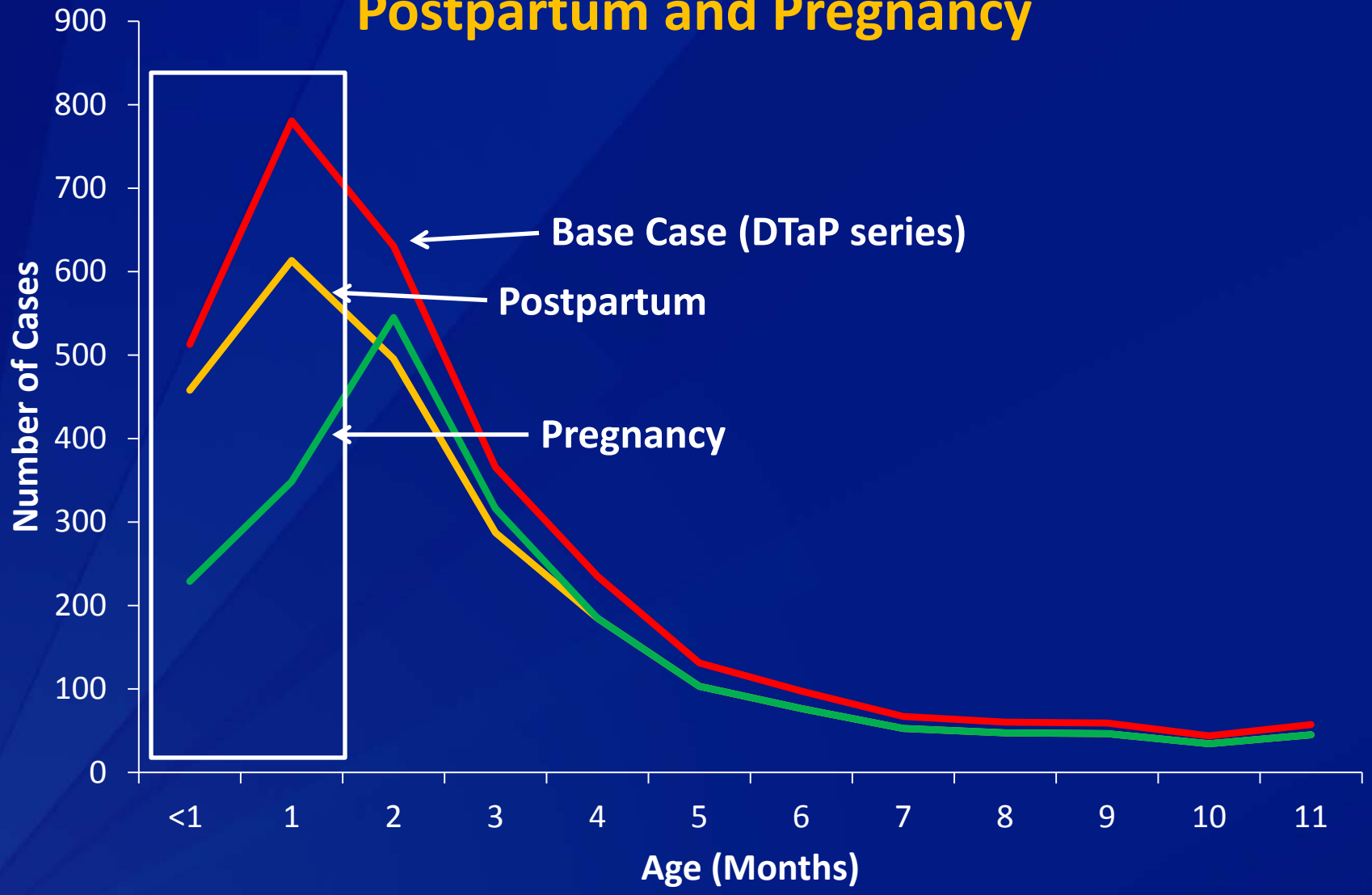
Decision Analysis: Objectives

- **Analyze the impact of two alternative Tdap interventions in preventing infant pertussis**
  - Pregnancy dose
  - Postpartum dose
- **Quantify theoretical risk of infant pertussis due to blunting**

Decision Analysis: Model

- **Simulated birth cohort model**
  - 2009 US birth cohort – 4.1 million infants
- **Analytic horizon**
  - Direct cost of infant disease only over the first year of life
  - Life years lost based on life expectancy of 77.9 years
- **Assumptions**
  - Pregnancy dose
    - 3rd trimester vaccination
    - Increased risk of disease in 3rd and 4th months of life (blunting)
  - Postpartum dose
    - Immediately postpartum, in hospital
    - 2 week delay in vaccine effectiveness (Halperin 2011)
    - Cocooning doses given to father and grandparent before birth

Decision Analysis: Number of Infant Cases - Postpartum and Pregnancy



Mean Reduction in Infant Pertussis Morbidity and Mortality Relative to Base Case*

		Cocooning		
	Pregnancy	Postpartum	+ Father	+ Grandparent
Cases	33%	20%	29%	32%
Hospitalizations	38%	18%	28%	32%
Deaths	49%	16%	25%	29%
Program cost (72% coverage)	$171 million	$171 million	$342 million	$513 million

* Base case = DTaP series only

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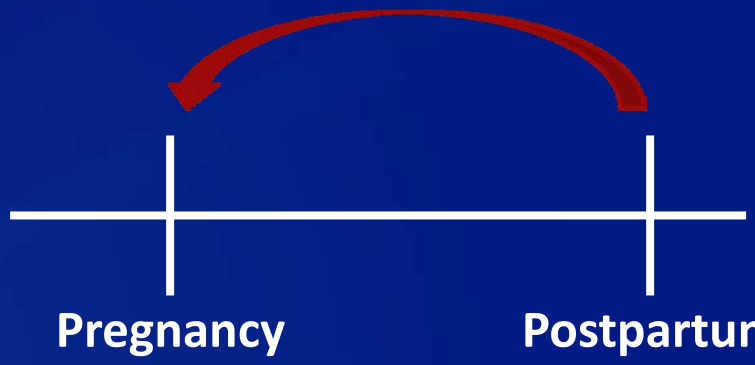
Decision Analysis: Conclusions

- Every scenario, the impact of vaccinating during pregnancy is favorable
- Tdap during pregnancy prevents more infant cases, hospitalizations and deaths
- Vaccination during pregnancy could avert more cases and deaths at no additional cost than postpartum vaccination with or without additional cocooning doses



ACIP Conclusions
June 2011

- Postpartum vaccination is a suboptimal national strategy to prevent infant pertussis morbidity and mortality.
- Vaccinating pregnant women during the late second or third trimester is acceptably safe for both mother and fetus.
- Programmatic cost of vaccinating with Tdap during pregnancy or postpartum is the same.
- Theoretical risk of blunting outweighed by benefits
- Late second or third trimester maternal vaccination may prevent infant pertussis (during the same pregnancy).

2011 ACIP Tdap recommendation for pregnant women

ACIP recommends that women's health-care personnel implement a Tdap vaccination program for pregnant women who previously have not received Tdap. Health-care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester (after 20 weeks' gestation). If not administered during pregnancy, Tdap should be administered immediately postpartum.

CDC. Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months --- Advisory Committee on Immunization Practices (ACIP), 2011. MMWR; 60(41);1424-1426

QUESTIONS?