



Maternal Immunization – can we do it, what can we expect?



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National Pertussis Workshop

**National Centre for Immunisation Research
and Surveillance**

Sydney, Australia

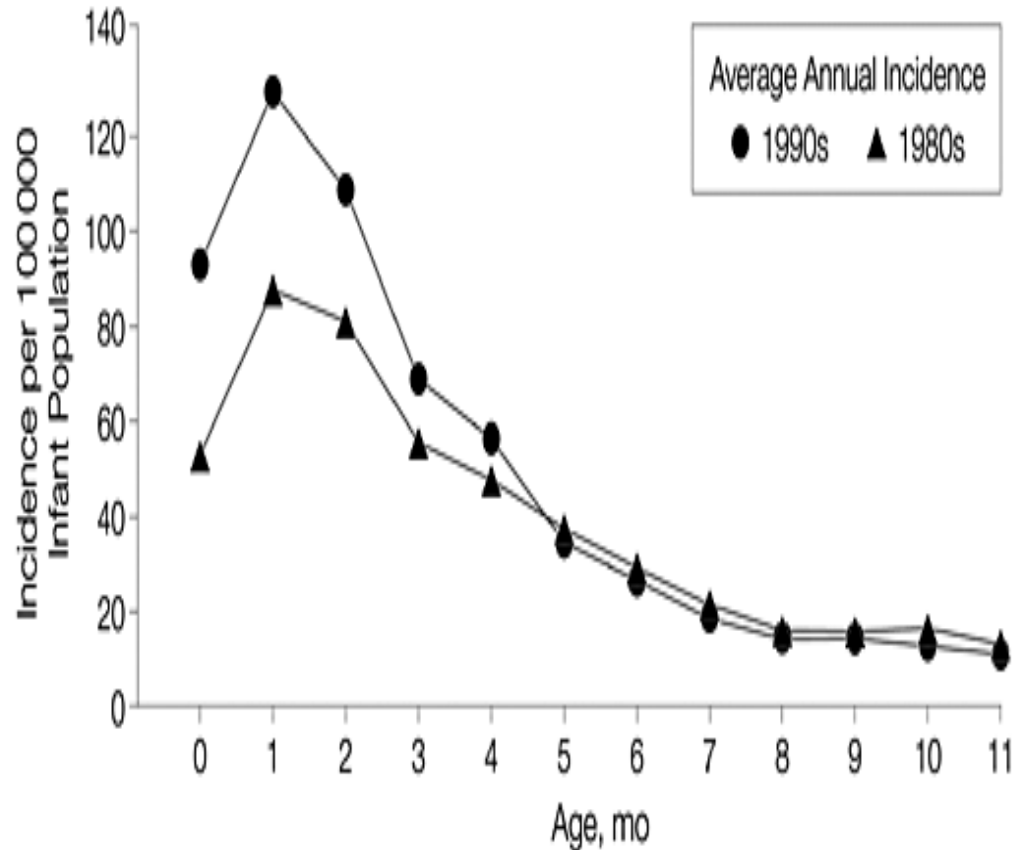
25-26 August 2011



Background

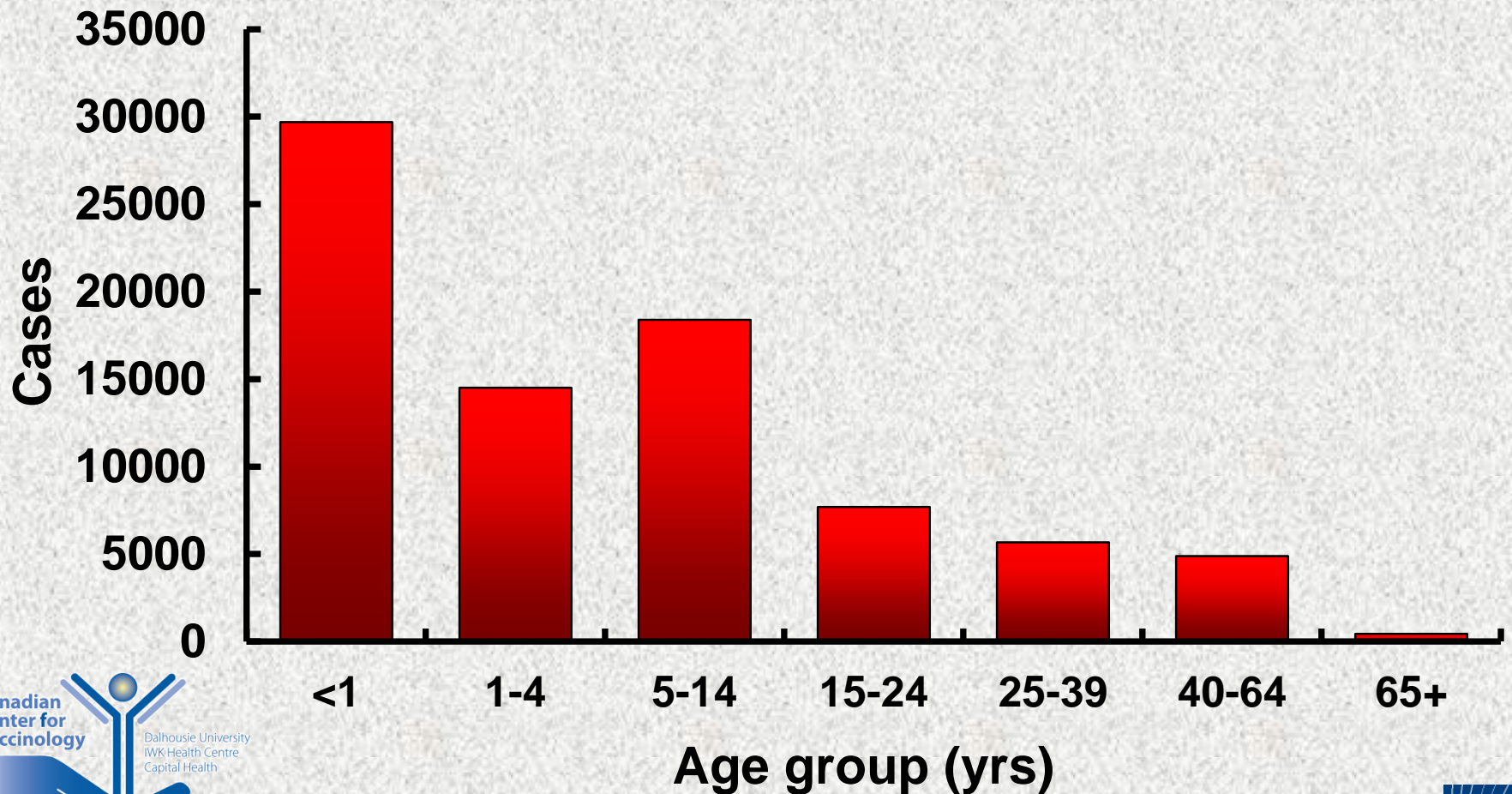
- Due to shifting epidemiology pertussis incidence continues to increase in infants <6 months of age who are too young to be vaccinated
- Active immunization has often not been successful in this age group because of the immaturity of the immune response
- Need for additional strategies beyond direct vaccine protection provided by routine primary series

Pertussis trends 0-11 months of age

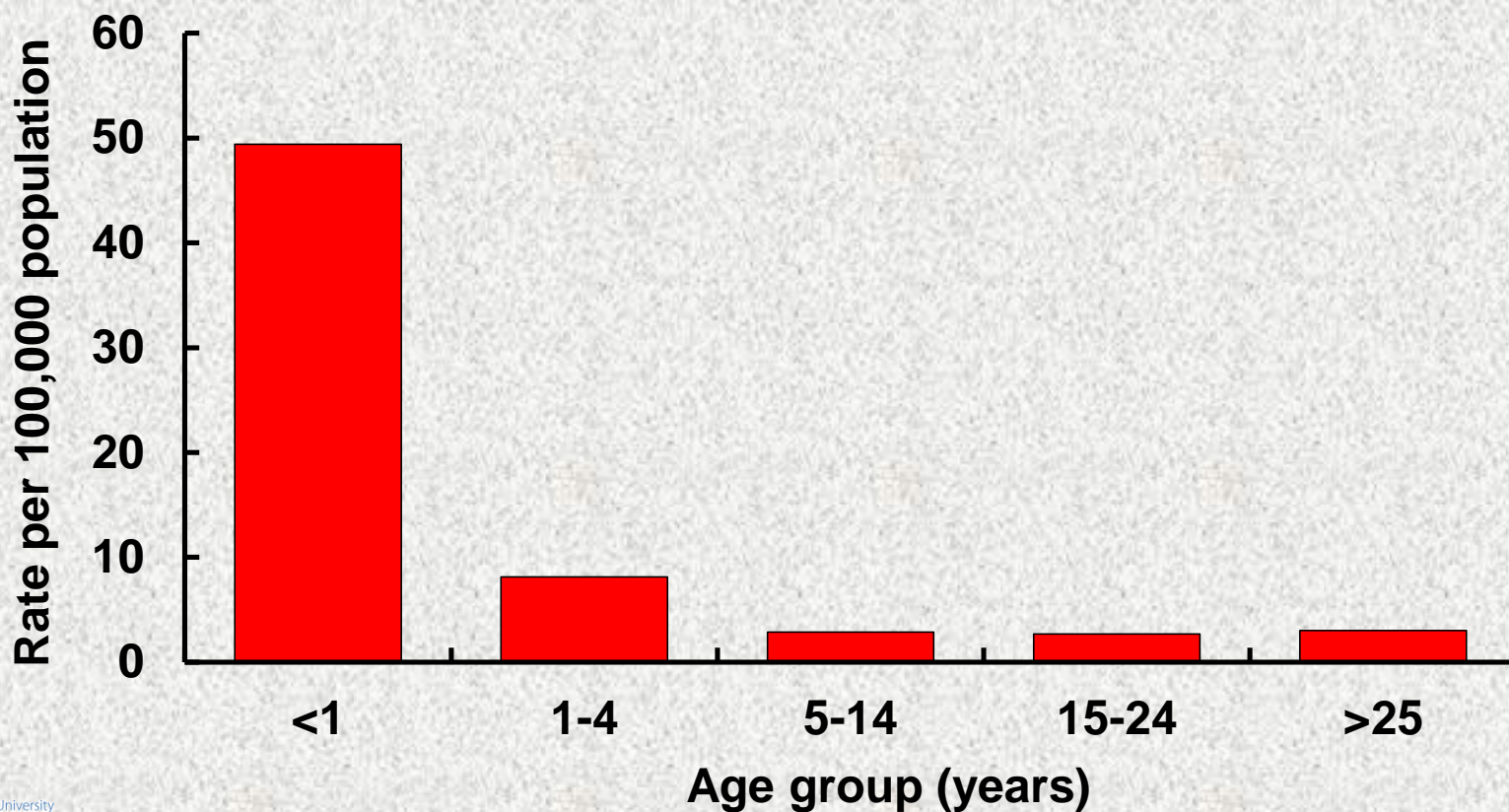


Pertussis – United States, 1985-2000

Age Distribution of Reported Cases



Pertussis Incidence, 2006

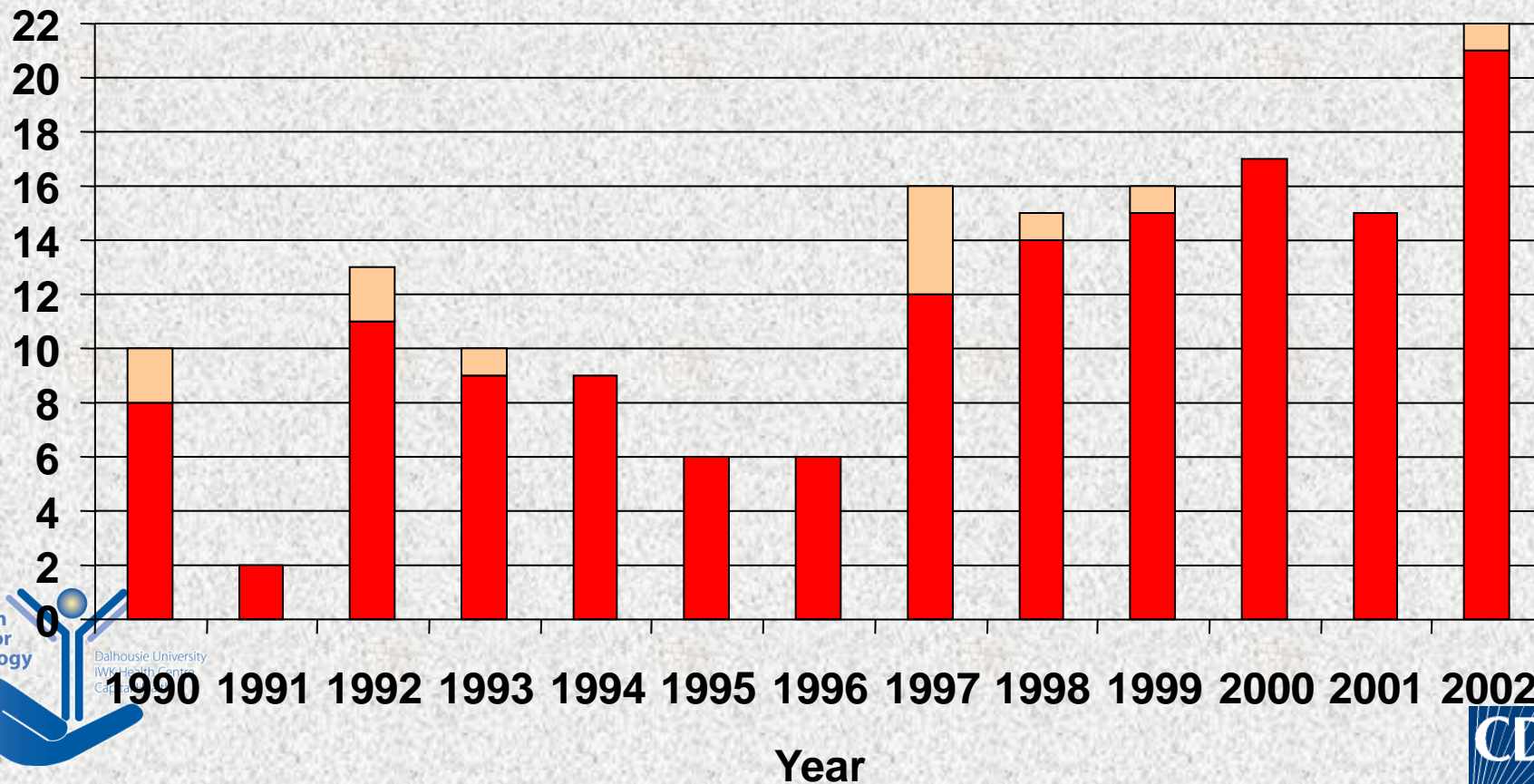


Reported Pertussis-associated Deaths* by Year, 1990-2002

Number of
deaths

*N=157

■ infant ■ other ages





Infant Pertussis

- In Canada, a case control study from 1991-2002
 - all 16 fatal cases of pertussis were infants 6 months of age or younger
 - 15 were 2 months of age or younger
 - mean age 6.5 weeks.
- Jan-Sept 2010: 4,017 cases, California
 - majority of infant cases <3 months of age
 - 9 deaths, all in infants <2 months of age



Intervention Strategies

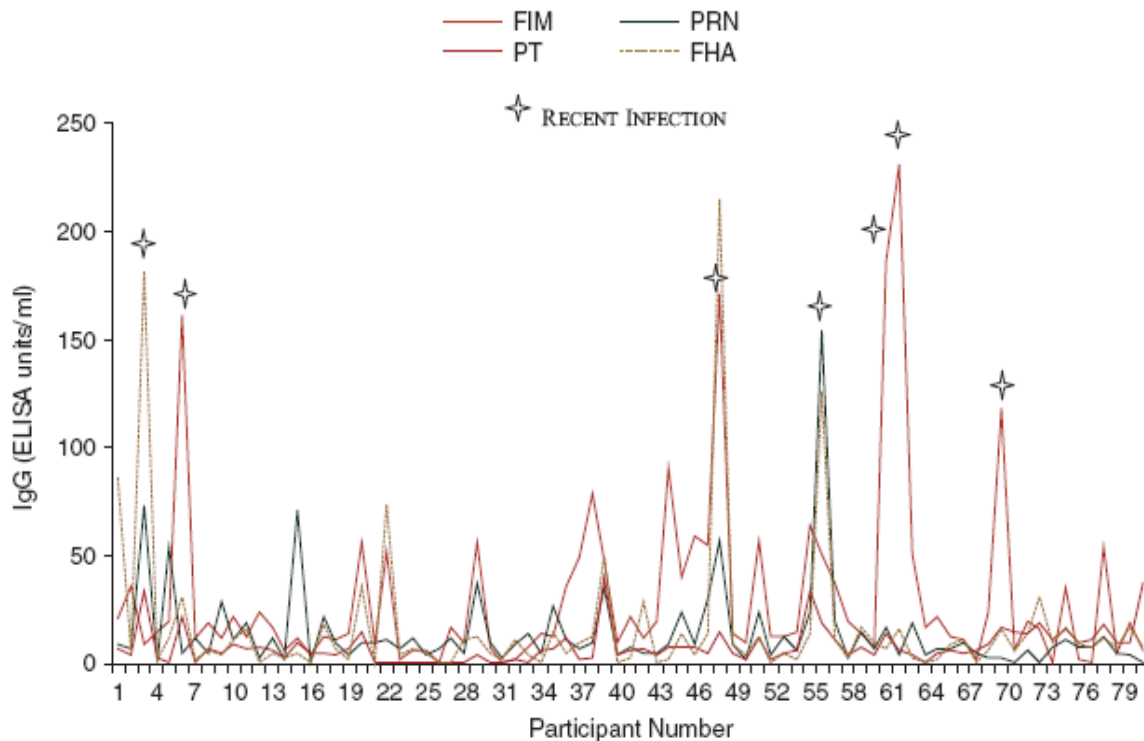
- Potential strategies being explored to improve protection of young infants include
 - Neonatal immunization
 - Pre-conceptual immunization of women
 - Targeted immunization of adults in close contact with newborns (cocoon strategy)
- However, these strategies may not protect in the vulnerable first weeks



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Maternal/Infant Antibody at Birth, US, 2006



- 21% of mothers and 26% of newborns had potentially “protective” antibody levels
 - 11% by 6 weeks



Antibody Levels after a Dose of Tdap

Time	Geometric Mean Antibody Titers			
	PT	FHA	PRN	FIM
Pre-boost	11.6	34.1	8.9	49.4
1 month	149.4	443.1	276.8	1065.5
1 year	48.5	104.4	75.2	314.2
3 years	33.3	78.5	51.4	177.2
5 years	28.2	64.5	45.0	151.7

Geometric mean titers (GMT) in children at different time points for 3 pertussis antibodies (anti-PT, anti-FHA, anti-PRN)

GMT	Anti-PT (95% CI) (Npos/N) (%)*	Anti-FHA (95% CI) (Npos/N) (%)*	Anti-PRN (95% CI) (Npos/N) (%)*
Cord blood			
Group A [‡]	6.1 (3.5–10.6) (12/22) (54%)	22.2 (12.9–38) (19/22) (86%)	20.3 (11.8–35) (19/22) (86%)
Group B [‡]	19.0 (11.7–30.7) (21/22) (95%)	247.0 (161–379) (22/22) (100%)	278.0 (154–502) (22/22) (100%)
Infant month 1			
Group A [‡]	3.1 (1.6–6.0) (5/14) (35%)	10.6 (5–22) (10/14) (71%)	9.8 (5.2–18) (8/14) (57%)
Group B [‡]	10.3 (6.3–16.8) (18/22) (81%)	152.1 (104–220) (22/22) (100%)	167.4 (102–274) (22/22) (100%)

*Npos/N =number of positive samples/total number of available samples; % positive samples.

[‡]Group A: first born children, before the maternal booster dose; group B: second cohort of children, born after the maternal booster dose.

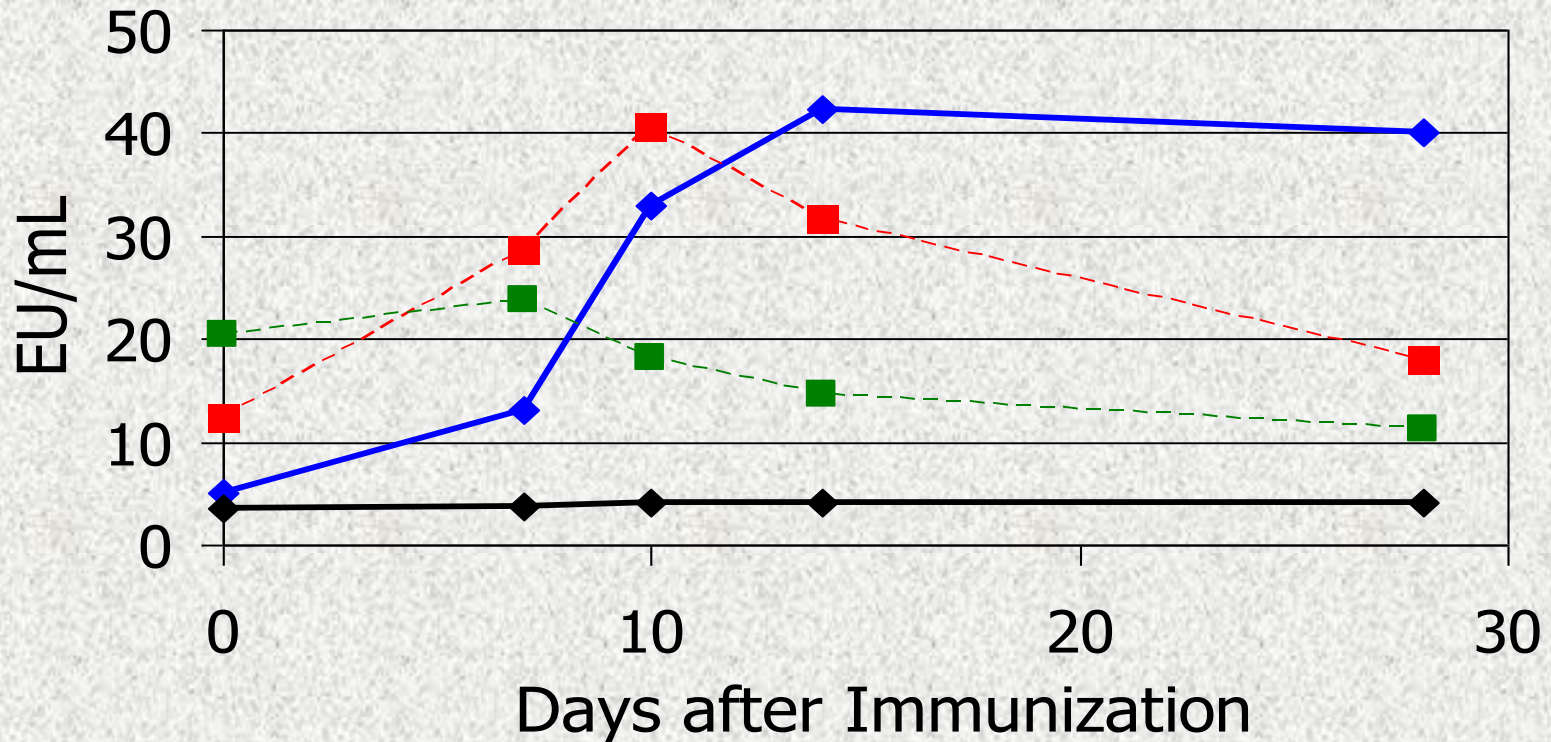
PT =pertussis toxin; FHA=filamentous hemagglutinin; PRN=pertactin; CI=confidence interval.



Intervention Strategies

- Potential strategies being explored to improve protection of young infants include
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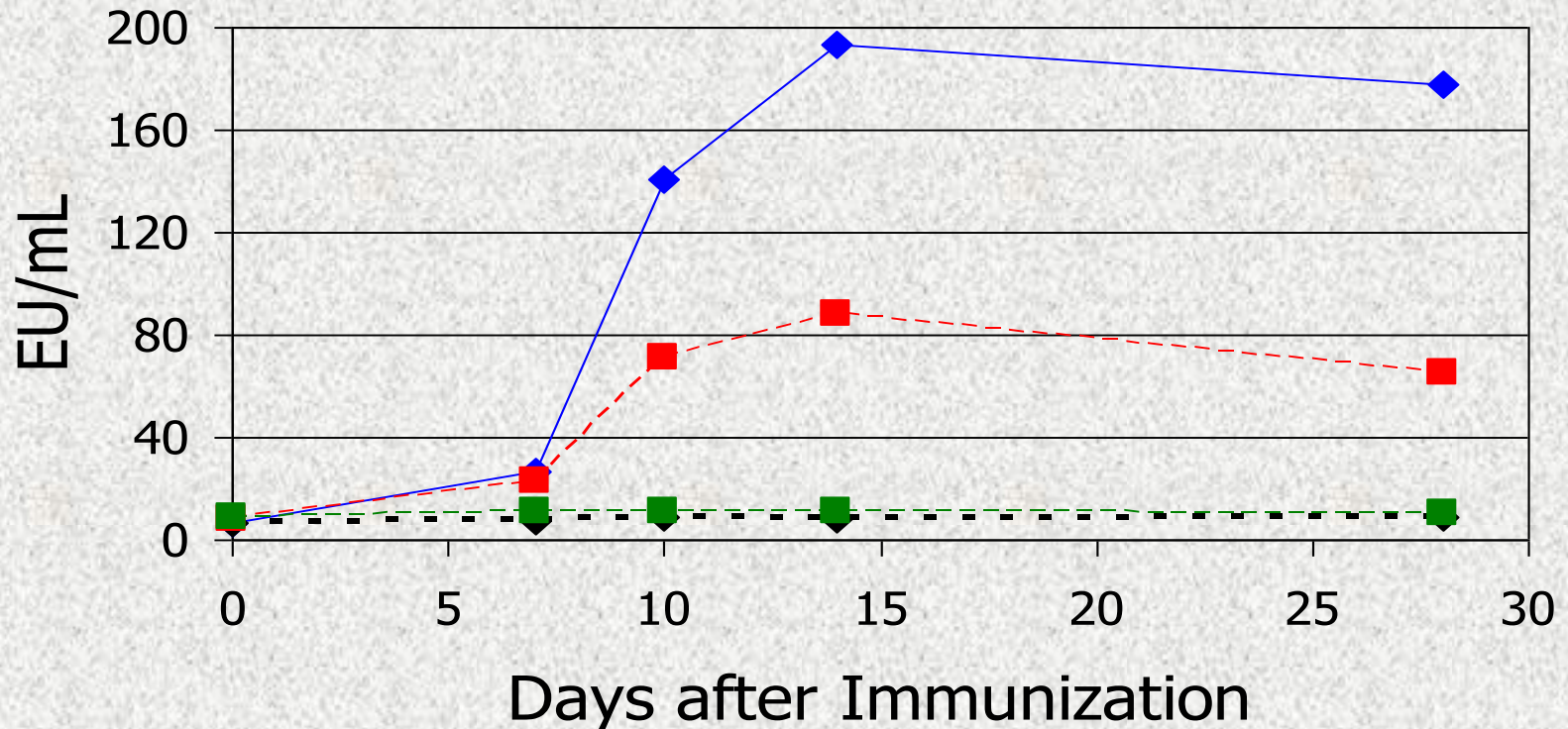
Serum PT Antibody Response



—◆— PT IgG Tdap
- -■- - PT IgA Tdap

—◆— PT IgG Control
- -■- - PT IgA Control

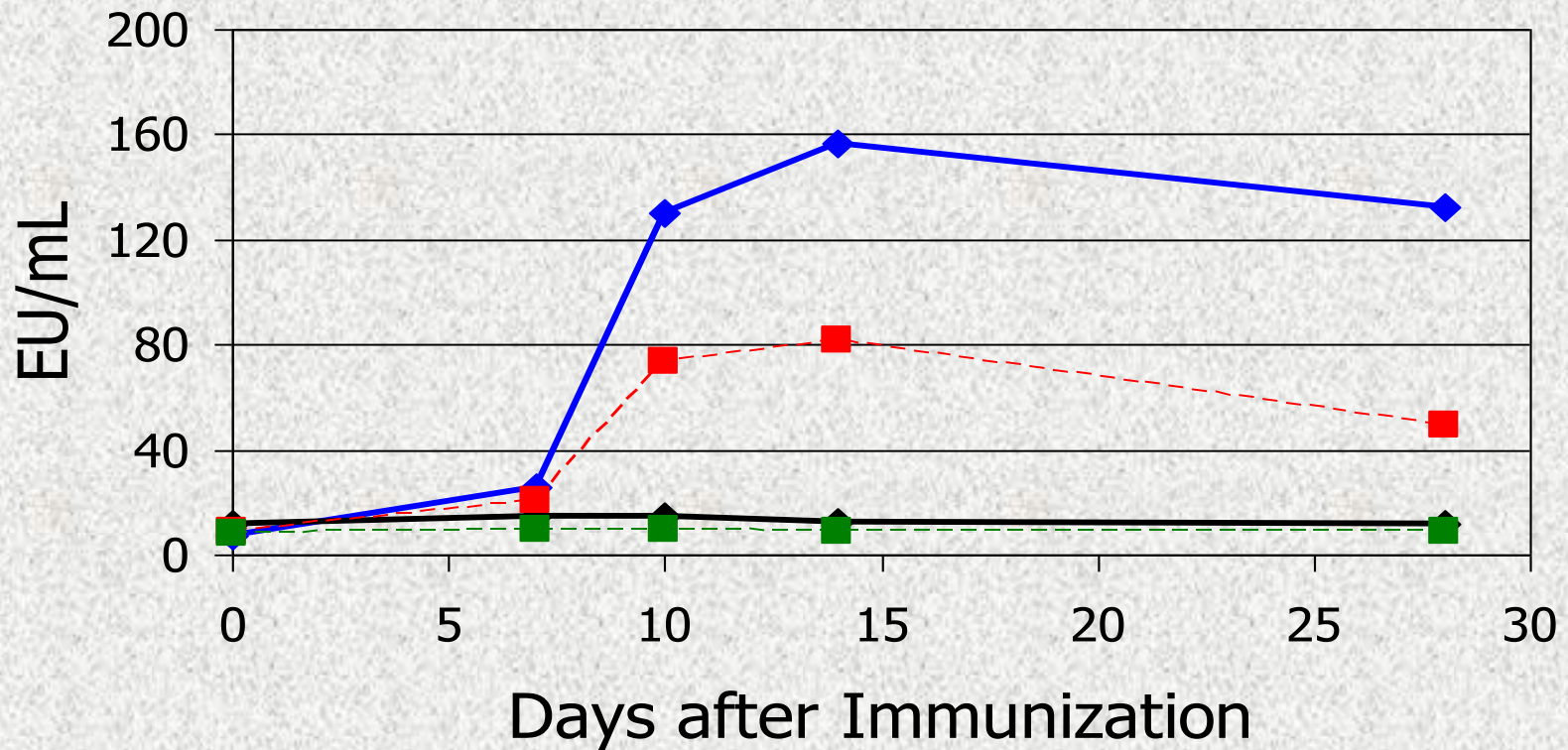
Serum PRN Antibody Response



—◆— PRN IgG Tdap
- -■- - PRN IgA Tdap

- ◆ - PRN IgG Control
- ■ - PRN IgA Control

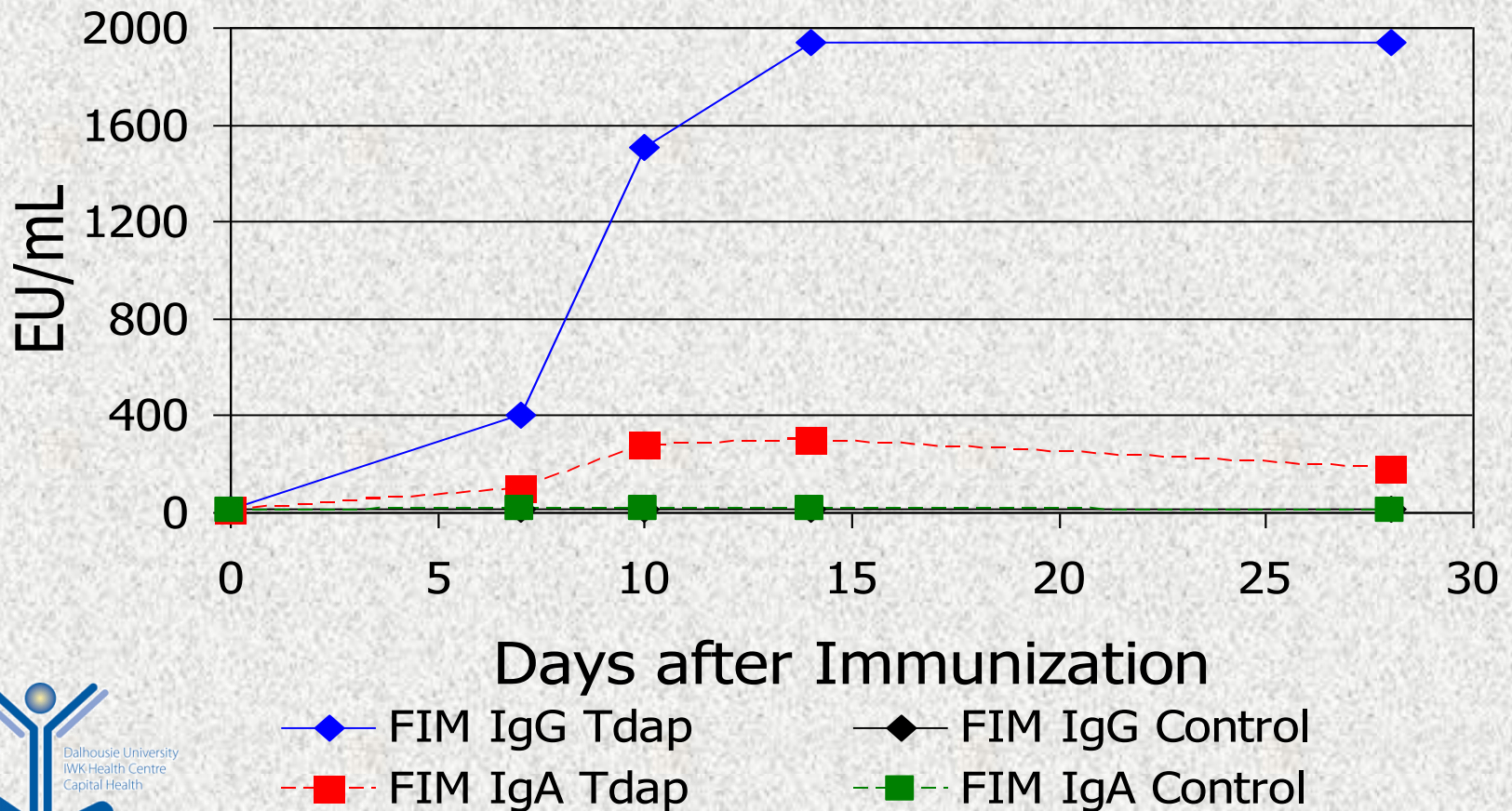
Serum FHA Antibody Response



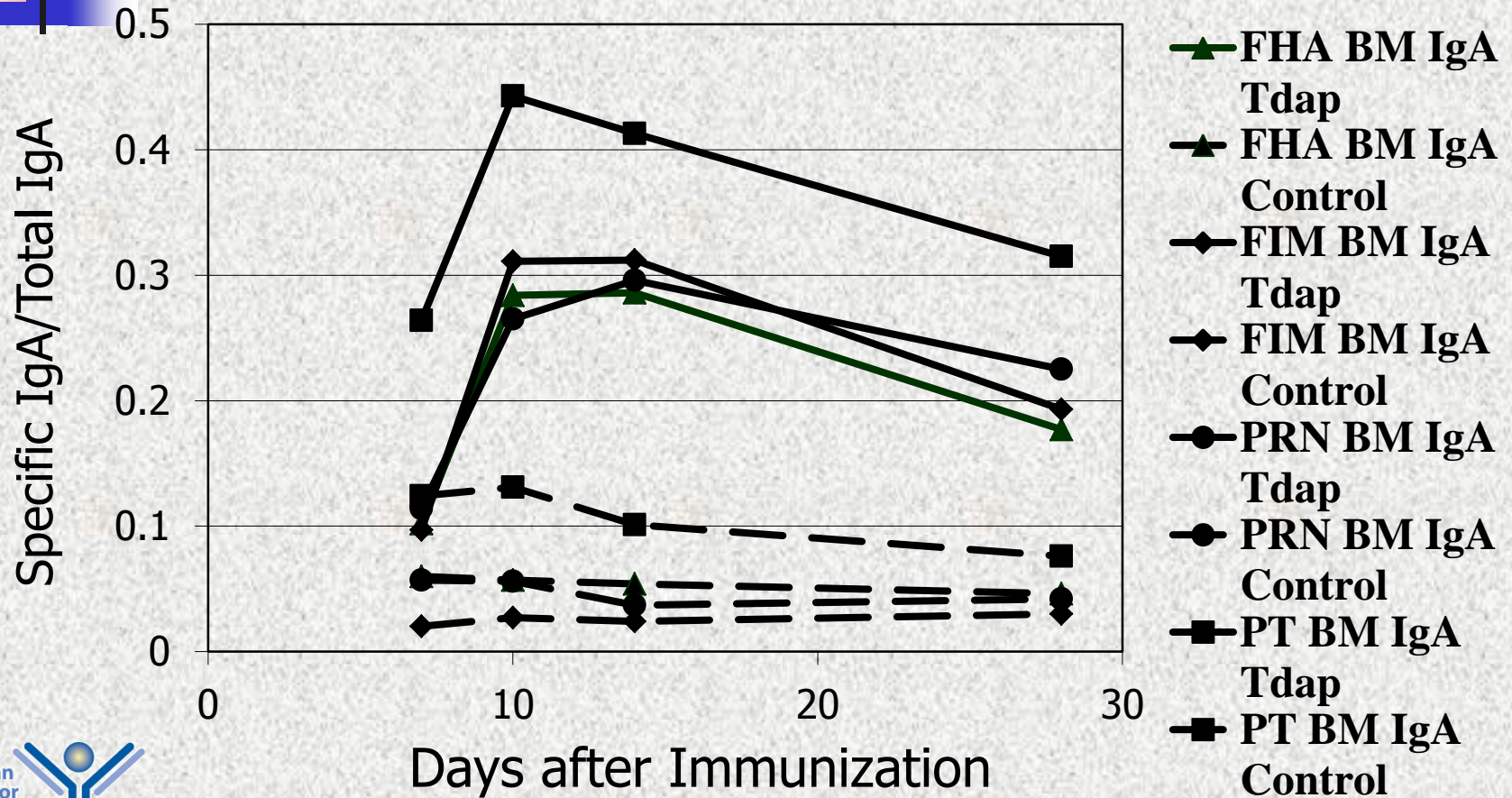
—◆— FHA IgG Tdap
- -■- - FHA IgA Tdap

—◆— FHA IgG Control
- -■- - FHA IgA Control

Serum FIM Antibody Response



Breast Milk Antibody Response





Rationale for Maternal Immunization

- This absence of protection leaves open a window of susceptibility in the newborn
- Vaccinating women during the third trimester of pregnancy offers the possibility of protecting infants from birth until immunity is induced by active vaccination





FDA Pregnancy-Use Ratings

Category	Description
A	Controlled studies show no risk -Adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester of pregnancy.
B	No evidence of risk in humans -Adequate, well controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals; OR, In the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.
C	Risk can not be ruled out -Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. <i>There is a chance of fetal harm if the drug is administered during pregnancy; but the potential benefits may outweigh the potential risk.</i>
X	Contraindicated in Pregnancy -Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient.

“Historical” Data on Maternal Immunization

Study	Year	No	Vaccine /Doses	Safety	Effectiveness
Lichty	1938	42	3 wP	Arm pain	Not reported
Cohen/ Mishulow	1941- 1946	~170	6 wP	Arm pain, lump, no adverse pregnancy outcomes	0/8 immunized and 3/6 unimmunized exposed infants developed pertussis
Kendrick	1945	57	3 wP	Not reported	Not reported
Adams	1947	16	3 wP	Not reported	Not reported
Cohen	1951	106	3 wP	Mild injection site; no adverse pregnancy outcomes	0/2 exposed infants of immunized women developed pertussis



Pregnancy Registries

Total 539 reports in Adacel Registry (Sanofi Pasteur)

- 49 study reports
 - 34 (69%) with no AEs, 10 (20%) SAEs, 5 (10%) non-serious AEs
 - 47 (96%) with known pregnancy outcome, 44 live births with 1 unrelated congenital anomaly (dx pre-vaccination)
- 490 spontaneous reports, 480 from prospective reports and 10 from retrospective reports
 - 267 (54%) with no AEs, 29 (6%) SAEs, 34 (7%) non-serious AEs, and 158 (34%) with AE status not reported
 - 480 prospective spontaneous reports:
 - 119 (25%) with known pregnancy outcome, 101 live births with no congenital anomaly
 - 10 retrospective spontaneous reports:
 - 10 (100%) with known pregnancy outcome, 8 live births with 1 congenital anomaly (multiple medications and vaccines)



VAERS

- Jan 1 2005-Jun 30, 2010
 - 129 (1.2%) of 10,350 reports after Tdap involved administration during pregnancy
 - 4 (3.1%) classified as serious
 - No deaths
 - 20 (15.5%) spontaneous abortion
 - 6 (4.7%) gestational diabetes
 - 3 (2.3%) oligohydramnios
 - 3 (2.3%) toxemia of pregnancy
 - 2 (1.6%) congenital abnormality (gastroschisis, PDA)
 - 2 (1.6%) stillbirth
 - No unexpected pattern or unusual events



Recent Observational Study

TABLE 1
Newborn antibody levels stratified whether mothers Tdap

Outcome Antibodies	Mother did not receive Tdap, mean (SEM) n = 52	Mother received Tdap, mean (SEM) n = 52	P value^a
Diphtheria	0.571 (0.157)	1.970 (0.291)	< .001
Tetanus	4.237 (1.381)	9.015 (0.981)	.004
PT	11.010 (1.796)	28.220 (2.768)	< .001
FHA	26.830 (4.022)	104.15 (21.664)	.002
PRN	24.700 (5.765)	333.01 (56.435)	< .001
FIM 2/3	82.83 (14.585)	1198.99 (189.937)	< .001

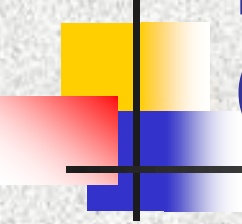
FHA, filamentous hemagglutinin; FIM, fimbriae; PRN, pertactin; PT, pertussis toxin; Tdap, tetanus, reduced diphtheria, and acellular pertussis antigens vaccine.

^a Significant at .05 level.

Gall. *Effect of maternal immunization with Tdap. Am J Obstet Gynecol* 2011.

Do High Levels of Passive Antibody at Birth Interfere with the Active Immune Response?

- Anti-PT antibody levels after 2, 4, 6 month immunization series
 - 28%-56% reductions in infants of mothers with high compared to low antibody levels at delivery after DTP
 - 3% reduction for DTaP
- Anti-FHA, anti-FIM
 - 16%, 18% reduction after DTP
 - 8%, 17% reduction after DTaP



Dartmouth/Hitchcock Med Center (New Hampshire), 2006

- Immunization of HCWs in response to outbreak
 - 16 pregnant HCP received Tdap
 - 54 controls –recruited at time of delivery
- Infants (n=5)
 - Antibody levels remained persistently higher up to first DTaP
 - Following 3rd DTaP, pertussis antibody levels slightly lower
 - Before and after 4th DTaP, pertussis antibody levels similar



Randomized Controlled Trials

- Baker et al. Safety and immunogenicity of Tdap
 - NIAID sponsored
 - Efficiency of placental transfer of antibodies
 - Persistence of antibodies in infants
 - Effect of maternal antibodies on active immunization
 - 48 pregnant women, 32 non-pregnant
 - Tdap or placebo
 - Enrollment started Jan 2009
 - Complete enrollment in March 2011?
 - Final infant visit April 2012
- Halperin et al.
 - Dalhousie (CCfV) sponsored
 - Grant from Sanofi Pasteur



CCfV Study: Methods

- Study Design
 - Double-blind randomized clinical trial using Tdap and Td vaccine. Participants randomized in a 1:1 ratio
- Study Subjects
 - 440 healthy women 18-45 years of age in late third trimester of pregnancy (≥ 34 - <35 weeks) recruited for first phase
 - Safety pause after the first 50 women/infants with interim analysis by Data Monitoring and Safety Board (17 June 2011)

Interim Safety: Local Adverse Events

Adverse Event	Percent Reporting (95% confidence interval)		
	Severity	Group A	Group B
Total Local	Any	75.0 (53.3, 90.2)	80.8 (60.6, 93.4)
	Severe	0.0 (0.0, 14.2)	7.7 (0.9, 25.1)
Pain	Any	66.7 (44.7, 84.4)	80.8 (60.6, 93.4)
	Severe	0.0 (0.0, 14.2)	7.7 (0.9, 25.1)
Erythema	Any ^a	8.3 (1.0, 27.0)	15.4 (4.4, 34.9)
	Severe ^b	0.0 (0.0, 14.2)	0.0 (0.0, 13.2)
Swelling	Any ^a	4.2 (0.1, 21.1)	7.7 (0.9, 25.1)
	Severe ^b	0.0 (0.0, 14.2)	0.0 (0.0, 13.2)

a: $\geq 1\text{mm}$

b: $\geq 50\text{mm}$

Interim Safety: Systemic Adverse Events

Adverse Event	Percent Reporting (95% confidence interval)		
	Severity	Group A	Group B
Total Systemic	Any	33.3 (15.6, 55.3)	42.3 (23.4, 63.1)
	Severe	12.5 (2.7, 32.4)	7.7 (0.9, 25.1)
Fever	Any ^a	0.0 (0.0, 14.2)	0.0 (0.0, 13.2)
	Severe ^b	0.0 (0.0, 14.2)	0.0 (0.0, 13.2)
Muscle Ache	Any	16.7 (4.7, 37.4)	26.9 (11.6, 47.8)
	Severe	8.3 (1.0, 27.0)	0.0 (0.0, 13.2)
Headache	Any	16.7 (4.7, 37.4)	23.1 (9.0, 43.6)
	Severe	0.0 (0.0, 14.2)	3.8 (0.1, 19.6)
Fatigue	Any	16.7 (4.7, 37.4)	30.8 (14.3, 51.8)
	Severe	4.2 (0.1, 21.1)	3.8 (0.1, 19.6)

a: $\geq 38^{\circ}\text{C}$

b: $> 40^{\circ}\text{C}$



Interim Safety: Serious Adverse Events (Women)

- No SAEs were reported in either group of women (Td or Tdap)

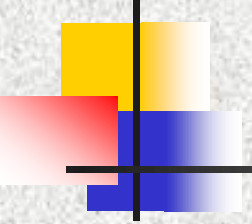
Interim Safety: Serious Adverse Events (Infants)

Adverse Event	Description	Infant Group C	Infant Group D	Vaccine Related
Prolongation of hospitalization post-delivery	ventricular septal defect	1		No
	hyperbilirubinemia		2	No
	cord around neck	1		No
	respiratory distress	2	1	No
Hospitalization	RSV	2		No
	variant of normal sleep activity	1		No
	fever	2		No
	viral meningitis		1	No



Interim Safety: Infant Serology

- For one group, evidence of lower geometric mean antibody levels 1 month after 3rd DTaP
- Analyzed antibody levels at 0, 2, 4, 6 months
 - Elevated titers in same group at birth and 2 months
 - For both groups, comparable antibody levels at 4 or 6 months
 - For both groups, increase in antibody from 6 to 7 months
- Recommended continuation of study (Stage 2)



US Advisory Committee on Immunization Practice (ACIP) 22 June 2011

- “Women’s health care providers should implement a maternal Tdap vaccination program for women who have not previously received Tdap. Health care providers should administer Tdap preferably during the third or late second trimester*. Alternatively, administer Tdap immediately postpartum.”
- *After 20 weeks gestation



Summary

- Interim safety analysis of the first 50 women of our RCT indicates that vaccination of women with Tdap or Td during pregnancy is not associated with significant adverse maternal, fetal, or infant outcomes.
- Interim immunogenicity analysis of the first 48 infants demonstrates significant differences in antibody levels at 7 months of age; however, substantial increases in antibody levels at 0 and 2 months
- DMSB recommended continuation of study



Conclusion

- Vaccinating women during the third trimester of pregnancy might protect the infant against pertussis through placental transfer of maternal antibodies, resulting in high antibody levels in the infant at the time of birth as well as early appearance of mucosal antibodies in breast milk.
- This offers the possibility of protecting the infant against pertussis from birth until immunity is achieved by active vaccination.



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Questions?

