



# Antibody responses to monovalent acellular pertussis vaccine at birth in relation to maternal dTpa pre-pregnancy

**Peter McIntyre**

On behalf of Nick Wood, Terry Nolan, Helen Marshall, Peter Richmond, Emma Gibbs

# Outline

- What was known prior to this study?
- Rationale and study design
- Results
- Implications



## What was known prior to study?

- 60% of deaths and 30% of hospitalisations  $\leq$  6 weeks
- $<$  10% in first 2 weeks after birth
- 4 small RCTs of neonatal acellular pertussis vaccine

# Studies of acellular pertussis vaccine in first week of life

**N=317** \* = significant (P<0.05)

	Belloni et al Chiron aP (N=91)	Halasa et al Sanofi DTaP (N=50)	Knuf et al GSK aP (N=100)	Wood et al GSK aP (N=76)
Pertussis Ab responses in birth aP group	Higher*	<u>Lower*</u> (post primary and booster)	Higher*	Higher*
Concomitant antigen responses		Lower dip, Hep B = Higher Hib and Polio*	Lower Hib and Hep B	Lower Hib and Hep B

**DTaP has “bystander effect” not seen with aP (Pediatrics 2008)**

# Rationale and Study design

## Study rationale – in 2009

- Neonatal vaccination immunogenicity data promising
  - aP not DTaP; small studies
- Hepatitis B recommended at birth in US, Australia and many LMIC countries with good coverage
- Poor coverage for influenza vaccine in pregnancy despite long-standing recommendations
  - Nervousness about interventions in pregnancy
- Cocooning recommended – impact on next pregnancy?

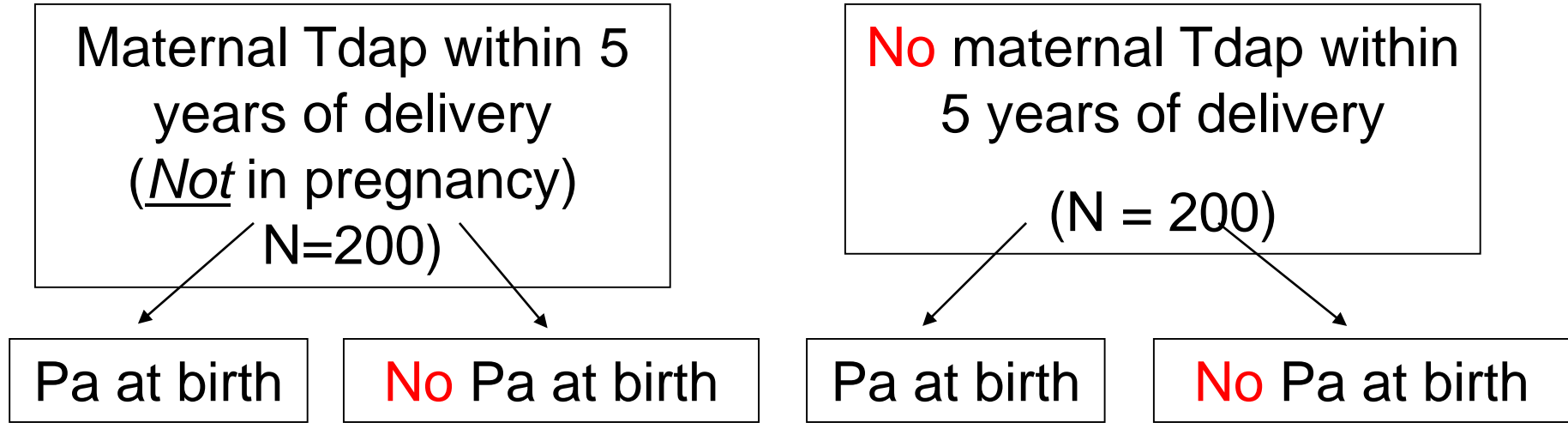


# Outcome measure – detectable antiPT and PRN Correlation with protection after household exposure <sup>1</sup>

- 209 RCT participants – Ab measured pre-exposure
- VE against severe (WHO) cough:
  - PT+PRN+FIM all detectable 85% (95% CI 65-93)
  - PT alone detectable 46% (95% CI 14-66)

1. Storsaeter et al Vaccine 16: 1907-16 1998

# Study Design








**Eligibility:** >36 weeks gestation, healthy, <120 hours after birth



## Aims and endpoints

- **AIM:** Immunogenicity and safety of Pa vaccine < 120 hours after birth vs first Pa-containing vaccine at 6 weeks
- **Primary endpoint:** Detectable (>5 EL.U/ml) IgG antibody to pertactin (PRN) and pertussis toxin (PT) at 10 weeks
  - Secondary endpoints:
    - Detectable PT and PRN at 6 weeks
    - Antibody responses in mothers with Tdap < 5 years

	aP* and Hep B n= 221	Hep B only n= 219	Serology
Birth (< 5days old)	<b>Monovalent aP*</b> Hepatitis B	Hepatitis B	Maternal 
6 weeks	DT <b>aP</b> -HepB-Hib-IPV Pneumococcal Rotavirus	DT <b>aP</b> -HepB-Hib-IPV Pneumococcal Rotavirus	
10 weeks			
4 months	DT <b>aP</b> -HepB-Hib-IPV Pneumococcal Rotavirus	DT <b>aP</b> -HepB-Hib-IPV Pneumococcal Rotavirus	
6 months	DT <b>aP</b> -HepB-Hib-IPV Pneumococcal	DT <b>aP</b> -HepB-Hib-IPV Pneumococcal	
8 months			

\*GSK Pa vaccine = PT 25 mcg, FHA 25 mcg, PRN 8 mcg

# Serology

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- Pertussis antibodies (ELISA)
  - **PT**
  - **PRN**
  - **FHA**
- **Hib, anti-HepB, diphtheria, tetanus**
  - Infant – 8 months old
- Serology (ELISA) performed by GSK Vaccines, Belgium
  - Same laboratory as pilot study (Wood et al 2010)
- NHMRC clinical trial centre – statistical analysis

# Adverse events

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- Telephone contact 2 and 7 days post each vaccination
- Parental measurement of temperature and injection site reaction
  - Diary card
- Review at each visit
  - Hospitalisations
  - GP visits

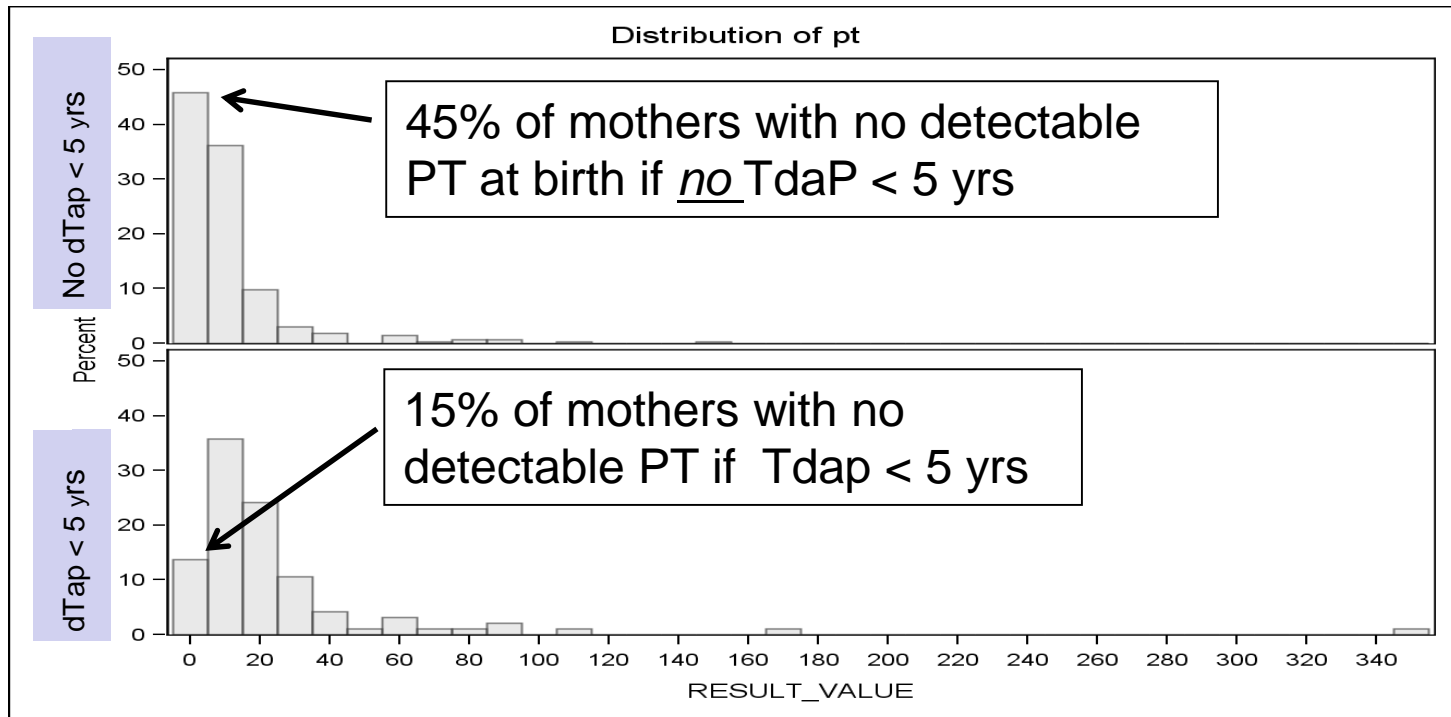
# Results

- **Demographics**
- **Maternal antibody by pre-pregnancy dTpa status**
- **Infant antibody endpoints**
  - Pertussis
  - Other antigens

## Participant demographics

	aP and Hep B at birth n=221	Hep B only n= 219
Mean birth weight (g) (range)	3479 (3417-3540)	3548 (3492-3605)
Mean gestation weeks	39.2 (>37)	39.2 (>37)
Male n (%)	117 (52.9%)	116 (52.9%)
Caucasian n (%)	189 (86%)	181 (83%)
Maternal age (mean years)	33.6	33.4
Maternal Tdap <5 years of pregnancy (n=96)	49 (22%)	47 (21%)
Mean months since maternal Tdap vaccine	21.4	21.2

# Distribution of pertussis toxin antibody level according to maternal vaccine status



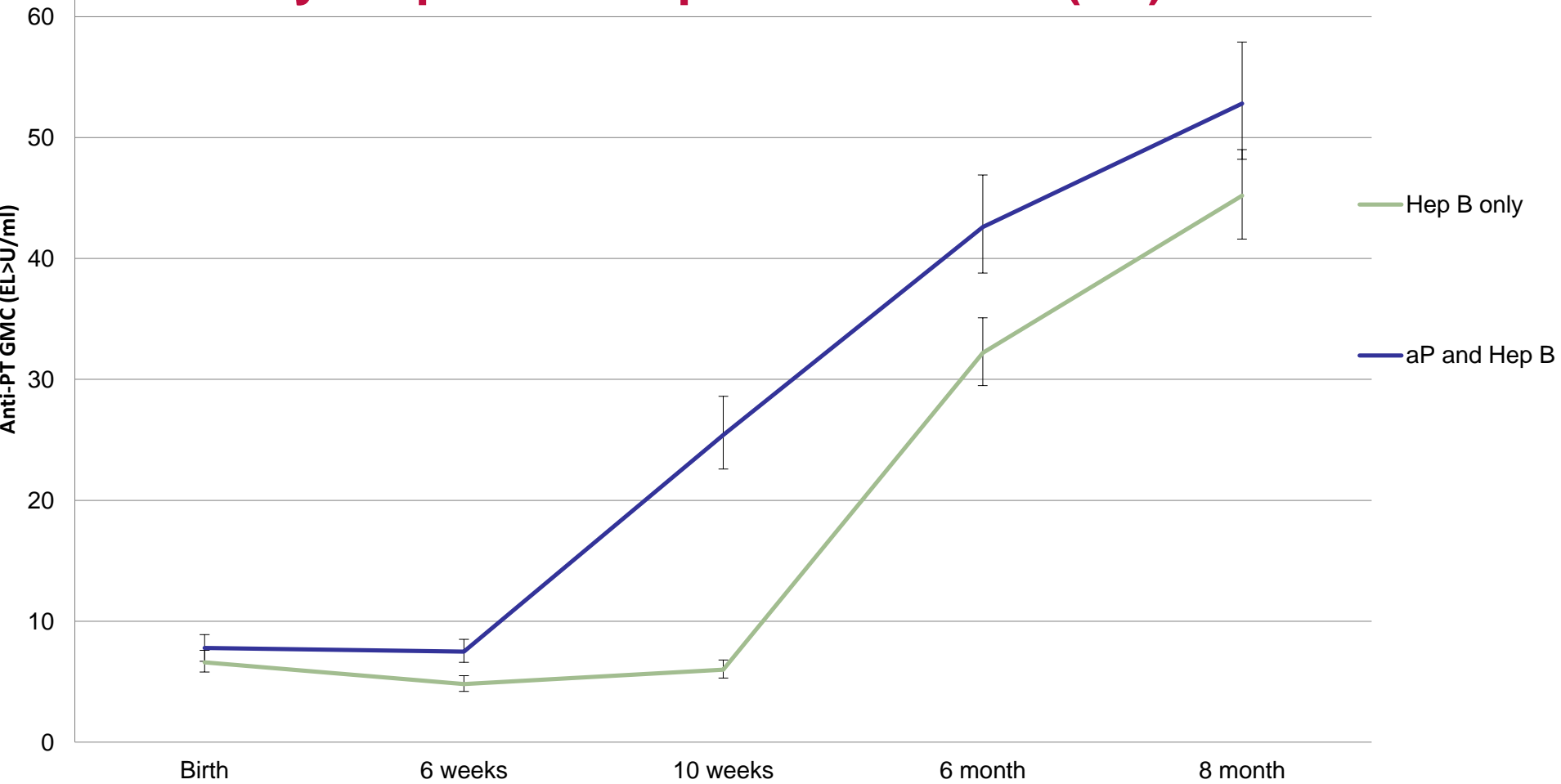
## Primary endpoint: @ Week 10 PT and PRN >5 EL.U/ml

	aP and Hep B n=221	Hep B only n= 219	Odds ratio* (95%CI)
All subjects n (%) (n=398)	192/206 <b>(93.2%)</b>	98/193 <b>(50.8%)</b>	13.3 (7.2-24.5) p <0.001
Maternal TdaP vaccine < 5 years (n=90)	43/47 <b>(91.5%)</b>	27/44 <b>(61.4%)</b>	13.1 (7.1-24.1) p<0.001
No maternal TdaP vaccine (n=308)	149/159 <b>(93.7%)</b>	71/149 <b>(47.7%)</b>	

\* Cochran-Mantel-Haensel chi square test



# Antibody responses to pertussis toxin (PT)



## PT and PRN antibody at 6 weeks

	PT antibody GMC (% above detectable)		PRN antibody GMC (% above detectable)	
	Pa at birth	Hep B	Pa at birth	Hep B
<b>All subjects</b> n (%) (n=410)	7.5 (64.8%)*	4.8 (37.4%)	10.9 (64.3%)*	7.4 (45%)
<b>Maternal dTaP &lt; 5 yrs</b> (n=91)	11.1 (82.2%)	8.6 (64.4%)	46.7 (95.6%)*	24.8 (78.3%)
<b>No maternal dTaP</b> (n=319)	6.7 (60%)*	4.0 (29.4%)	7.3 (55.8%)*	5.1 (35.1%)

\* P value <0.05 for GMC



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# PT and PRN antibody at 8 months

	PT antibody GMC (% above detectable)		PRN antibody GMC (% above detectable)	
	Pa at birth	Hep B	Pa at birth	Hep B
<b>All subjects</b> n (%) (n=366)	52.8 (100%)*	45.2 (100%)	88.6 (98.9%)	79.6 (98.9%)
<b>Maternal dTaP &lt; 5 yrs</b> (n=91)	44.2 (100%)	35.4 (100%)	52.1 (95.1%)	66.1 (97.2%)
<b>No maternal dTaP</b> (n=319)	47.9 (100%)*	55.6 (100%)	88.4 (100%)	96.6 (99.3%)

\* P value <0.05 for GMC



## Summary – pertussis antibody responses

- Significantly accelerated PT responses @ 6 and 10 weeks following aP within 5 days of birth
- Maternal dTap within 5 years pre-pregnancy significantly increases % detectable Ab and GMC @ 6 and 10 weeks
- But higher mat Ab  lower infant PT responses
- At 8 months, maternal status no longer significant
  - birth aP group still have significantly higher PT Ab



# Concomitant antigen responses at 8 months

## - no change in % reaching threshold but reduced GMC

		aP and Hepatitis B vaccine			Hepatitis B vaccine only			
Antibody	Threshold	N	% > threshold	GMC (95% CI)	N	% > threshold	GMC (95% CI)	P-value for GMC
<b>Hepatitis B</b>	>10 mIU/ml	150	99.3	1217.74 (984.5 - 1506.2)	145	100	2274.5 (1883.1 - 2747.2)	<.0001
<b>Hib</b>	>0.15 ug/ml	182	96.7	1.53 (1.3 -1.9)	183	96.7	2.12 (1.8- 2.6)	<b>0.02</b>
<b>Diphtheria</b>	>0.1 IU/ml	181	99.4	1.24 (1.1 -1.4)	183	100	1.78 (1.6 -2.0)	<b>0.0001</b>
<b>Tetanus</b>	>0.1 IU/ml	181	100	2.04 (1.8 -2.3)	183	100	2.69 (2.4 - 2.9)	<b>0.0002</b>

**Maternal dTpa status not significant except ? Hib**

## Safety measures following birth aP vaccine

	<b>aP and Hep B N (%)</b>	<b>Hep B only N (%)</b>
Fever >38C after birth dose	0 (0%)	1 (0.5%)
Any redness, swelling or hardness >10 mm after birth dose	12 (5%)	2 (1%)
Any medical advice sought Days 0 to 7 inclusive	6 (3%)	8 (4%)

## Implications of these results

- **Clinical protection?**
- **Relevant in the post-maternal dTpa era?**

# Severe infant pertussis: evidence of significant protection after 1 dose of pertussis-containing vaccine



## Maternal and Neonatal Vaccination Protects Newborn Baboons From Pertussis Infection

Jason M. Warfel,<sup>1</sup> James F. Papin,<sup>2</sup> Roman F. Wolf,<sup>2</sup> Lindsey I. Zimmeman,<sup>1</sup> and Tod J. Merkel<sup>1</sup>

<sup>1</sup>Division of Bacterial, Parasitic and Allergenic Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland; and <sup>2</sup>Oklahoma Baboon Research Resource, Comparative Medicine, University of Oklahoma Health Sciences Center, Oklahoma City

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1 dose DTPa @ 2 days = 2 doses = maternal DTPa  
in protecting against pertussis challenge




# SAGE statement – 2014

## Supplemental Strategies: Neonatal Immunization

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- Neonatal immunization not recommended at this time
  - Limited data on impact and safety
  - Lack of availability of an aP alone vaccine
  - Window period of susceptibility
- Continued evaluation recommended
  - Data from human and baboon infants receiving a single vaccine dose demonstrate protection against severe pertussis disease
  - – If data supporting immunogenicity, presumptive protection, and safety become available, it may have supplementary role along with maternal vaccination

## Next steps

- “Plugging pertussis immunity gap” is all about individual level protection of newborn infant
  - Limits on achievable maternal coverage
  - 17% breakthrough cases in UK case-control study<sup>1</sup>
  - ~ 10% of babies of immunised mothers no measureable PT @ delivery<sup>2</sup>
- Birth aP vaccine
  -  protection if mother has low antibody + prems
  - need aP vaccine

## Acknowledgements

- NHMRC Project grant funding (2009-2013)
  - NHMRC Clinical Trials Centre – statistical analysis
- GSK Vaccines for aP vaccine supply and serology
- Research nurses at each of the participating sites
- **Mothers and babies who participated in the study**



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**Questions?**

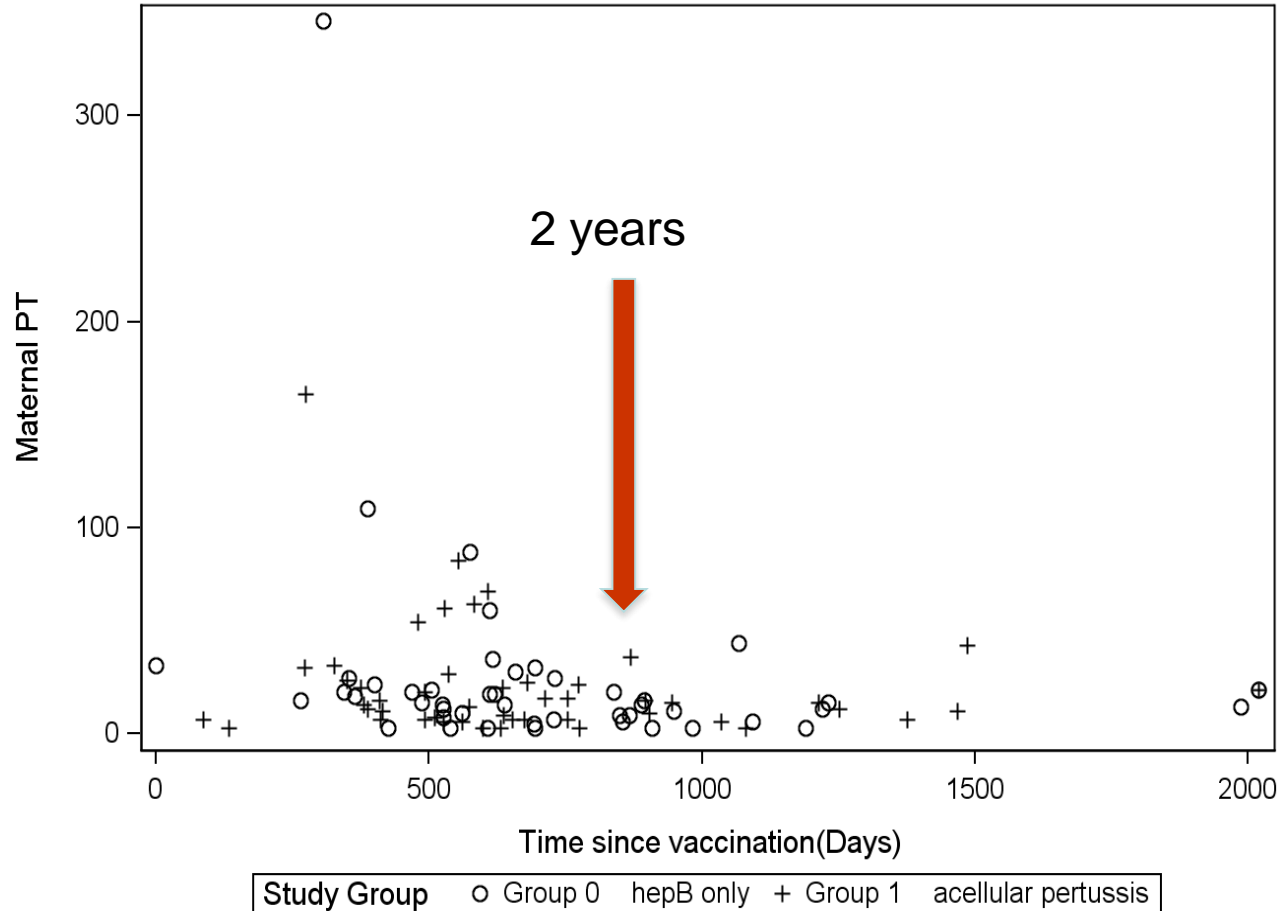
# Supplementary slides



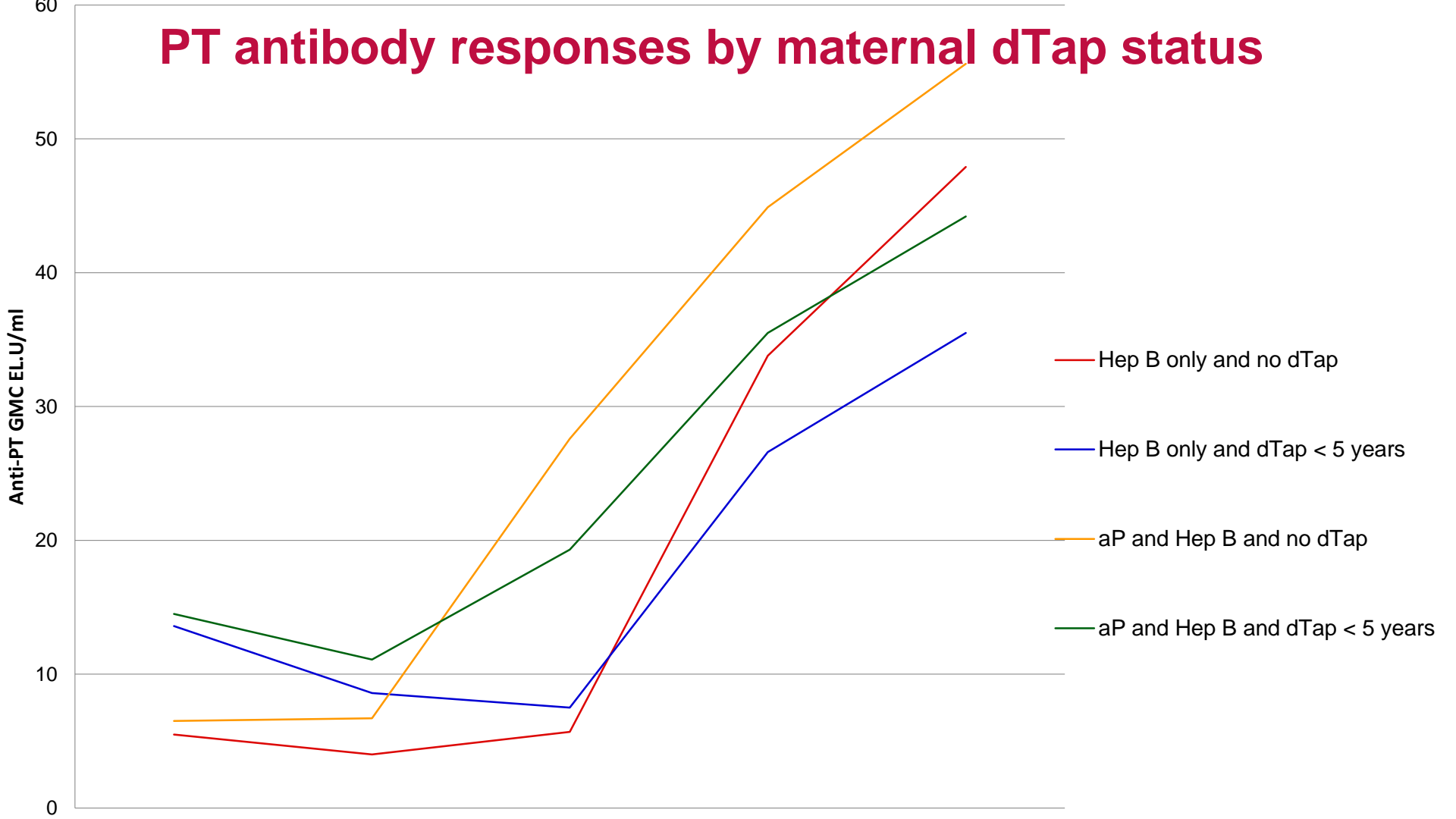
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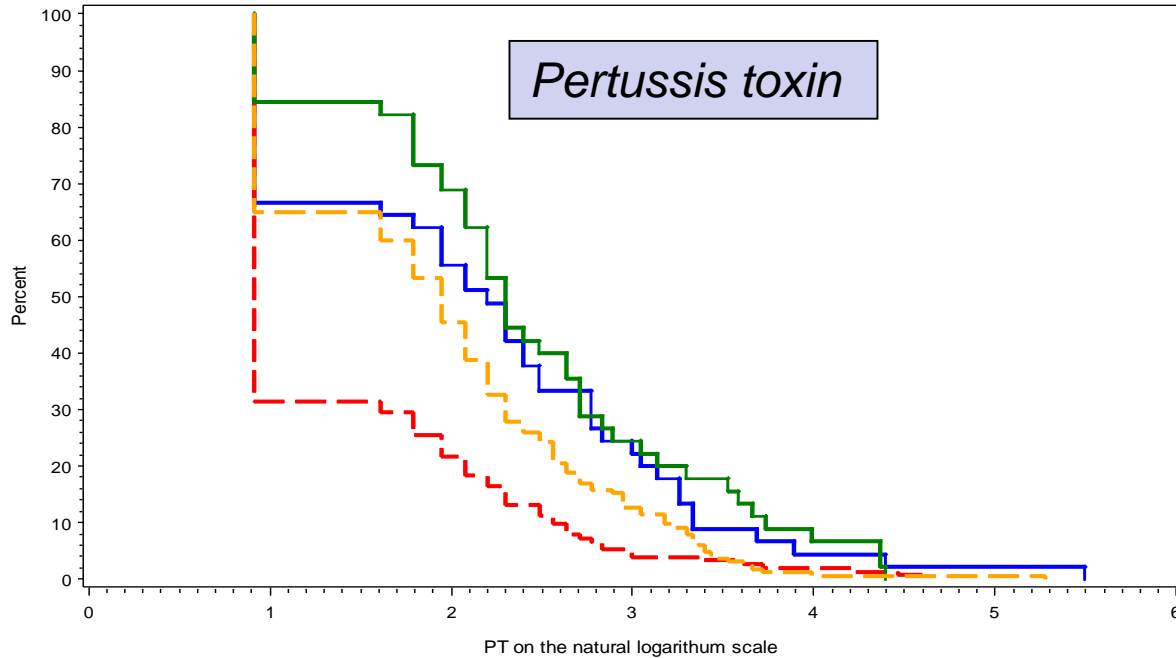
# Scatter plot of maternal PT in mothers with dTap < 5 yrs



# PT antibody responses by maternal dTap status



# Reverse cumulative distribution curves at week 6



Hep B only and no dTap

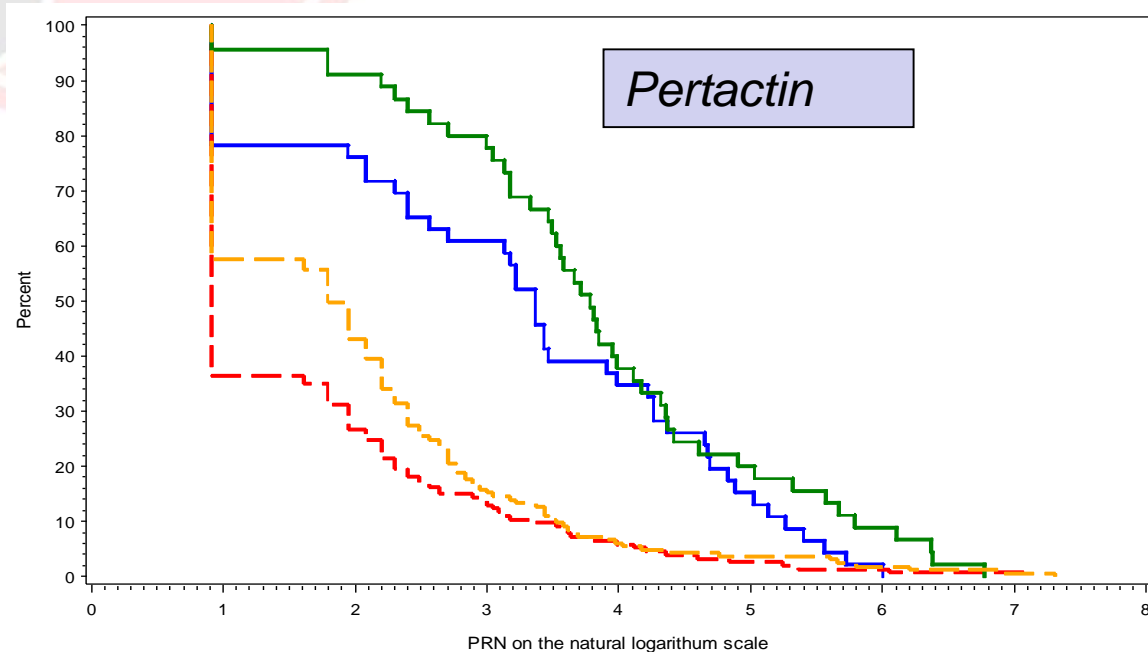
aP and Hep B and no dTap

Hep B only and dTap < 5 yrs

aP and Hep B and dTap < 5 yrs



# Reverse cumulative distribution curves at week 6



Hep B only and no dTap

aP and Hep B and no dTap

Hep B only and dTap < 5yrs

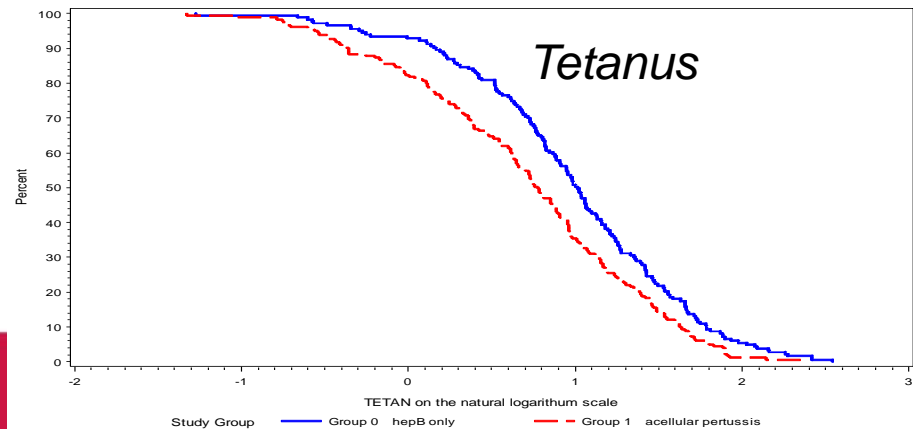
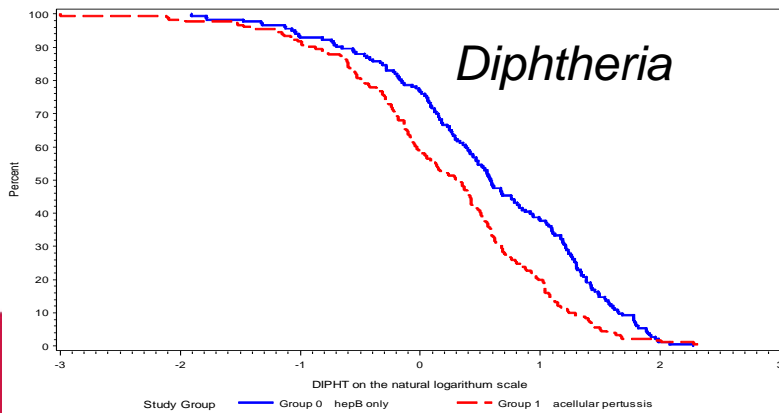
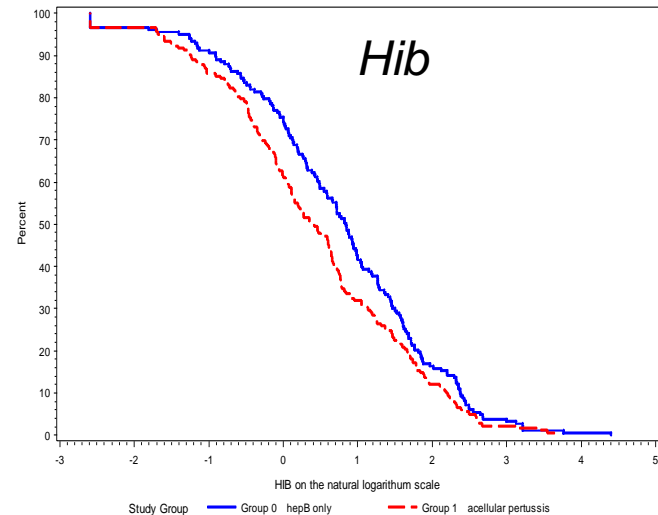
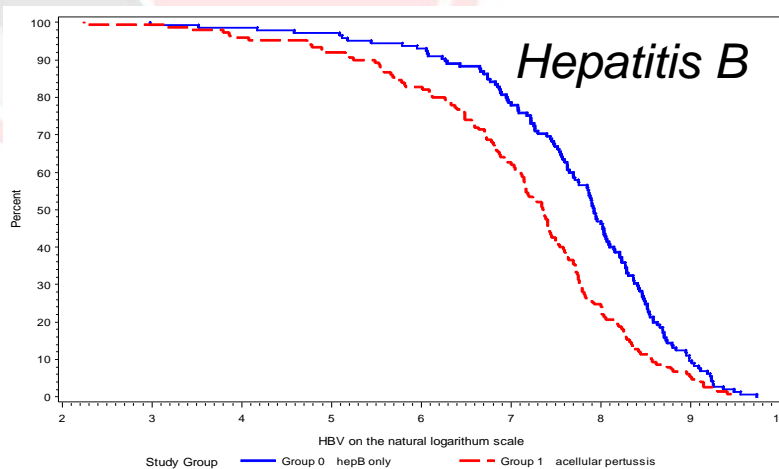
aP and Hep B and dTap < 5yrs



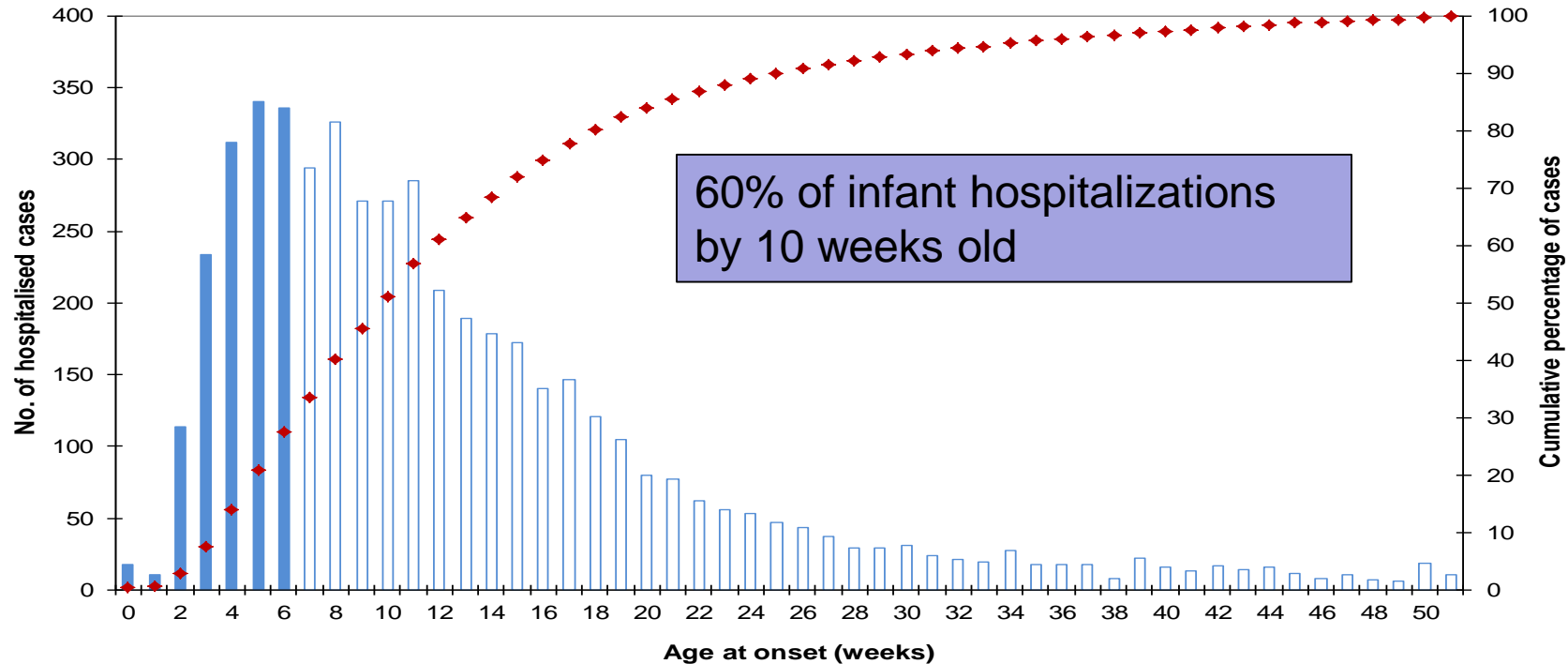
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# Concomitant antigen responses



# Pertussis hospitalisations in infants aged <12 months, Australia, July 1998 - June 2012



Source: AIHW National Hospital Morbidity Database

# Infant pertussis deaths – Australia 1999-2013 N=20

