



Neonatal pertussis vaccination

Can we do it?

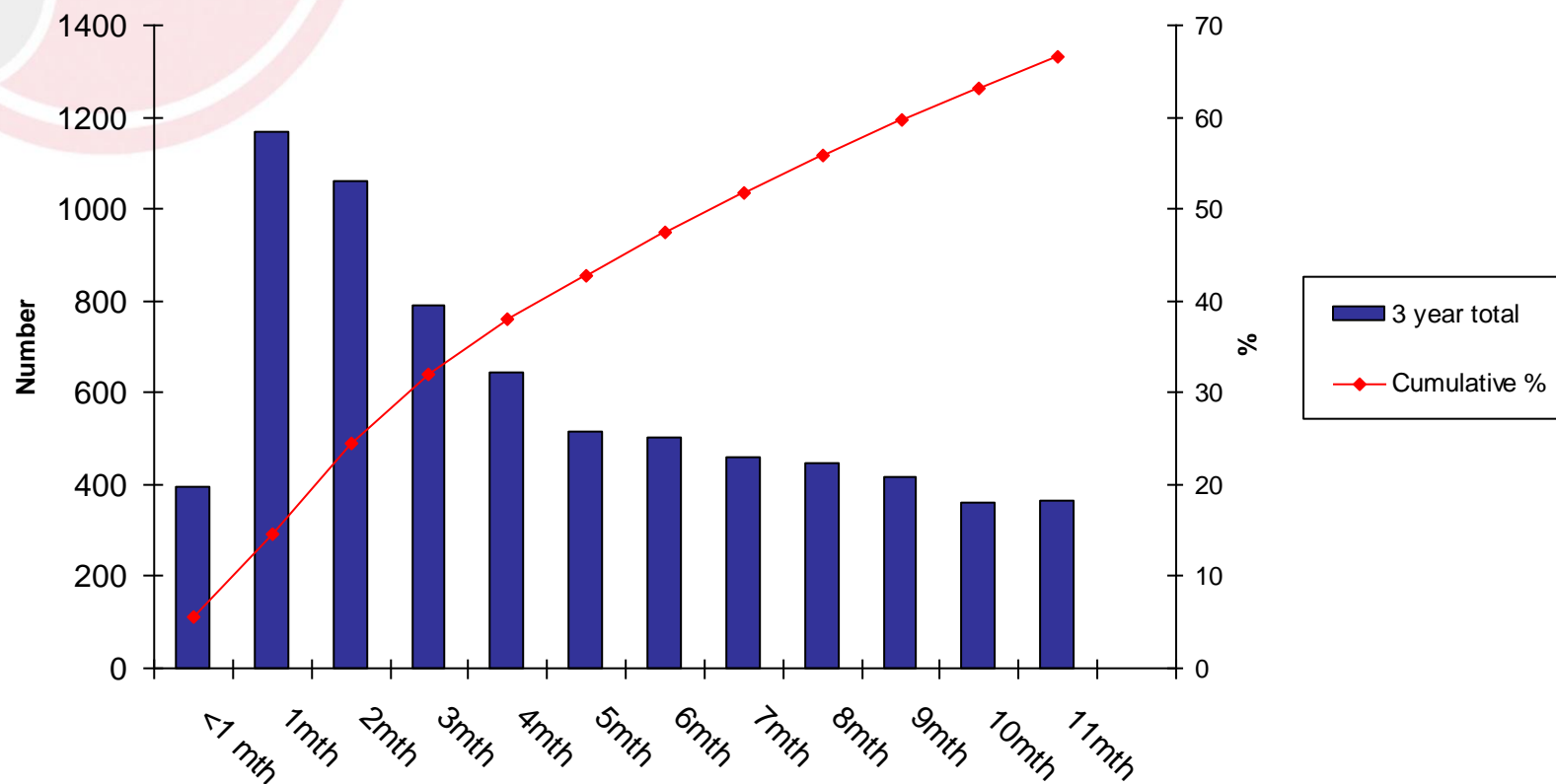
What can we expect?

Nick Wood

Outline

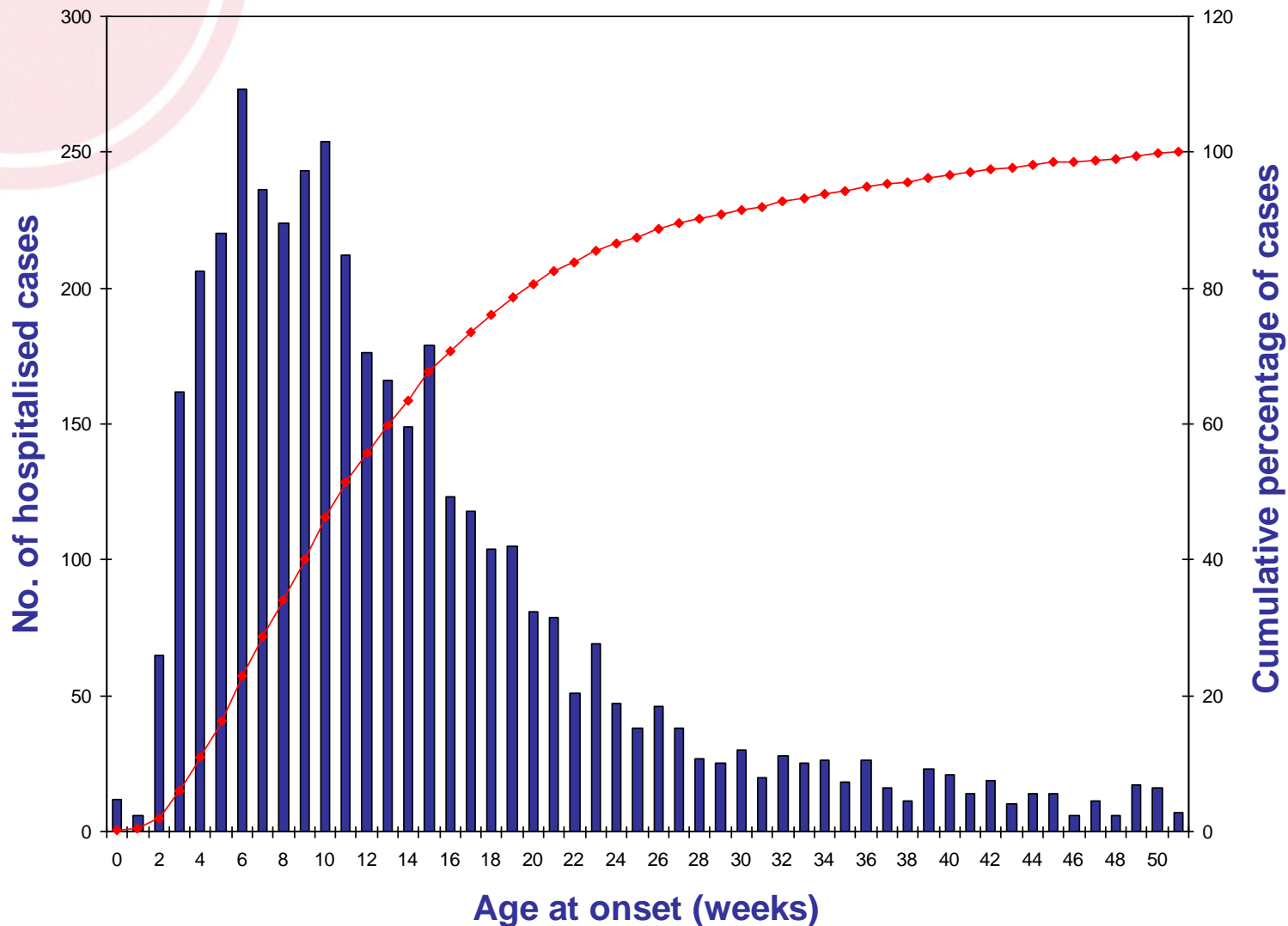
- History and epidemiology
- Newborn acellular pertussis vaccine trials
 - Immunological
 - Safety
- Specific areas of study
 - Maternal antibody influence
 - Vaccine interference
 - Cell mediated immunity
 - Immune longevity and booster response
- Expected impact

Pertussis deaths: US 1938-40 (N=10,730) ¹

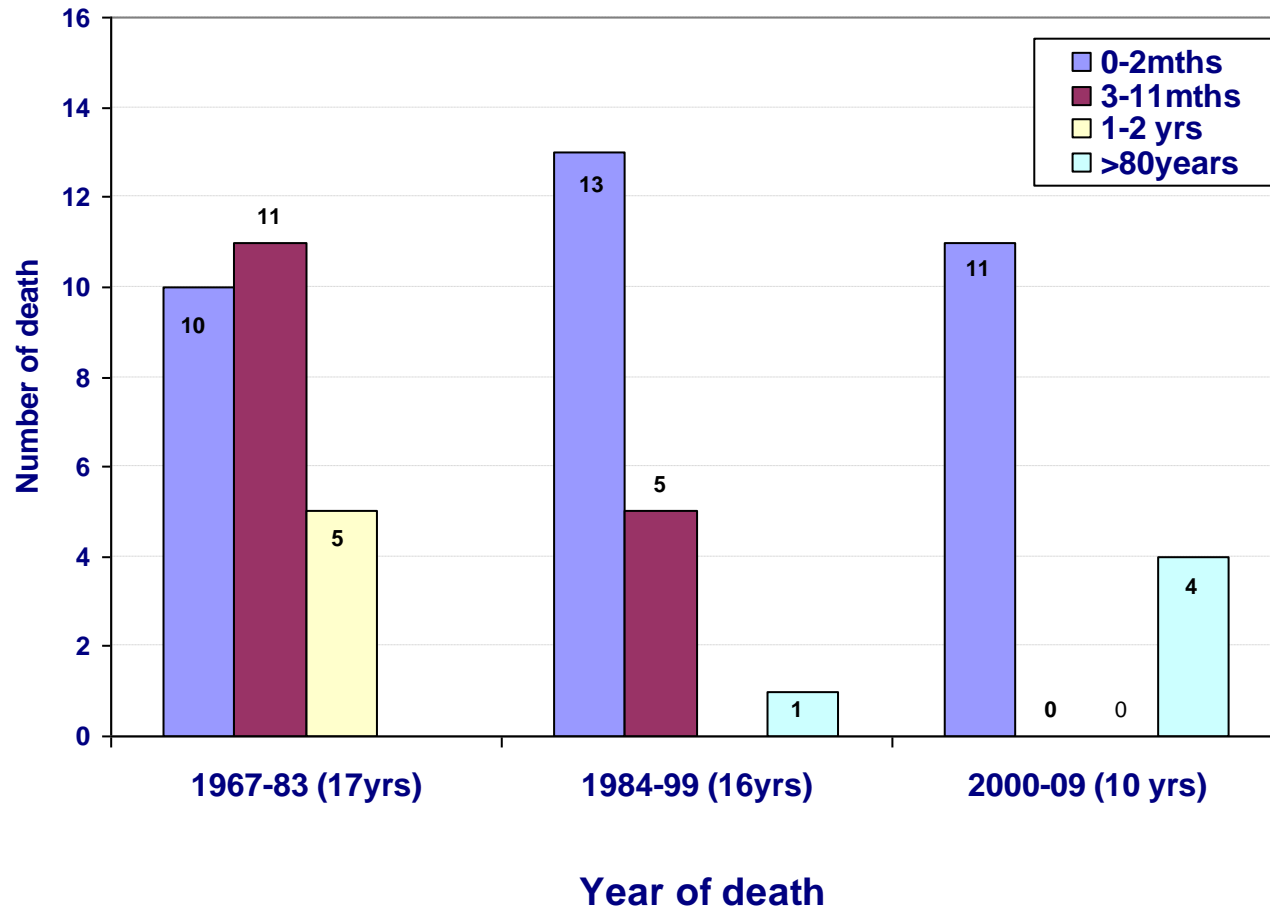


*1. Sako et al JAMA 1945; 127: 379 “ the exceptionally high mortality which pertussis causes in the first half year calls for thorough investigation of the possibility of increasing the resistance of young infants to the disease **by immunizing them shortly after birth...**”*

Pertussis hospitalisation under 1 year olds 1994 - 2008



Age at death - pertussis Australia 1967 to 2009 (n=60)



Reviews Analyses

Bulletin of the World Health Organization, 63 (6) 1151–1169 (1985)

© World Health Organization 1985

The efficacy of DPT and oral poliomyelitis
immunization schedules initiated from birth
to 12 weeks of age

NEAL HALSEY¹ & ARTUR GALAZKA²

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Table 5. Serum agglutinin response following immunization with adsorbed pertussis vaccine schedules initiated from one day to three months of age

Investigator, year, and reference	Vaccine type	Potency in units per single dose	Amount of organisms $\times 10^9$ per single dose	No. of infants	Age at immunization (weeks or days, when specified)		Age at antibody testing (months)	Percentage with agglutinins	
					1st dose	2nd/3rd doses		$\geq 1:320$	GMT
Provenzano, 1965 (118)	DPT	7	10,10,10	8	1 day	1,2	3	25	48
Barrett, 1962 (11) ^{a,b,c}	DPT	NA		49	1-2 days	4-8,8-13	3-4		(50)
				33	4-8	8-13,13-16	4-5		(100)
Baraff, 1984 (8)	DPT	NA		10	3.5 days	8,18,26	9		105
				13	8	18,26	9		200
Pstragowska, 1966 (121)	DPT	NA		103	6 days	5,9	NA	23	62
Di Sant Agnese, 1949 (33) ^d	DPT		10,20,20	125	1	5,9	3.5	54	260
1950 (36)			10,20,20	108	1	5,9	6	33	126
			10,20,20	47	1	5,9	12	34	118
Gaisford, 1960 (51) ^e	DPT	NA		31	1	5,9	3.5	19	47
Butler, 1962 (20)	P		10,10,20	121	1	6,13	4		131
Miller, 1949 (95)	P		16,24,40	115	6	10,14	4.5	63	259
Waddell, 1946 (144) ^f	P		40,80,80	50	1	4,9	6	90	1432
			40,80,80	43	8	13,17	6	95	1740
Goerke, 1958 (56) ^g	DPT		30,30,30	80	<2	6,10	3.5	12	34
Adams, 1947 (2)	P		20,40,40	21	1	2,3	1	NA	160
				19	4	8,12	4-5	NA	80
Dupan, 1958 (38) ^d	DPT	NA			0-2	4-8,8-12	3		320
					4-8	8-12,12-17	4		450
Sako, 1947 (130) ^h	P	NA	8,12,20	1007	4-8	8-12,12-16	6-8	51	131
	DPT	NA	10,20,20	1294	4-8	8-12,12-16	6-8	28	71
Lippset, 1953 (87)	P		20,30,30	22	4	8,12	6	82	1280
Provenzano, 1959 (119) ^h	DPT	7	10,10,10	7	4	8,12	6		120
		7	10,10,10	25	4-12	8-16,12-20	6-8		92
Peterson, 1951 (112) ^{h,i}	DPT		20,40,40	289	6	12,18	7.5	71	642
Murphy, 1984 (100) ^j	DPT	8 5-11.5U		23	8-12	12-16,16-22	6-9		214
	DPT ^{ext} ^k	4-5.5 U		19	8-12	12-16,16-22	6-9		118
Weihl, 1963 (146) ^{l,m}	DPT	≥ 4 NIH		67	6-12	10-18,14-24	?	(85)	
	DPT ^{ext.}	≥ 4 NIH		31	6-12	10-18,14-24	?	(97)	
Swartz, 1984 (137) ⁿ	DPT	NA		14	8	14	4.5		363
	DPT	NA		44	8	12,26	7		258



The New England Journal of Medicine

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Volume 273

OCTOBER 28, 1965

Number 18

IMMUNIZATION AND ANTIBODY RESPONSE IN THE NEWBORN INFANT

I. Pertussis Inoculation within Twenty-four Hours of Birth

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CAMBRIDGE AND BRIGHTON, MASSACHUSETTS

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Provenzano RW, Wetterlow LH, Sullivan CL. *N Engl J Med* 1965; 273: 959-965.

- “Can the practitioner expect an **adequate** antibody response to inoculations given within 24 hours of birth?”
- “What **type of antigen** should be used – plain pertussis or combined diphtheria, tetanus and pertussis?”
- “Are the untoward **reactions** at this age such as to make the attempt unacceptable?”

Provenzano RW, Wetterlow LH, Sullivan CL. *N Engl J Med* 1965; 273: 959-965.

Pertussis-containing vaccine 6 to < 24 hours after birth

- **Group 1** P+P+P @ 3 week intervals *then* 2xDTP @ 4 week intervals
- **Group 2** 3xDTP @1 day, 1 month, 2 months
- Boosters with DTP @ 12 and 24 months
- N= 23

- “...the immune response continued to be suppressed in 75% up to 5 months of ageand in about 50% to the age of 15 months....these results suggest the possibility that “**immunologic paralysis**” had been induced by immunization on the first day of life.....”

Provenzano et al

- Small sample size
- Plain pertussis vaccine – 20 000 000 000 org/ml
 - Killed by thiomersol
- Measure pertussis agglutination titres
- No safety concerns

- Conclusion
 - “pertussis antigen, alone or combined, be used **cautiously** in neonates and that immunisation should probably not be attempted under 3 weeks of age”



ACELLULAR PERTUSSIS VACCINE TRIALS

40 YEARS LATER

Immunogenicity of a Three-Component Acellular Pertussis Vaccine Administered at Birth

Cesare Belloni, Annalisa De Silvestri, Carmine Tinelli, Maria A. Avanzini, Massimo Marconi, Fabio Strano, Giorgio Rondini and Gaetano Chirico
Pediatrics 2003;111;1042-1045
DOI: 10.1542/peds.111.5.1042

Pediatrics
2003

Neonatal Vaccination with an Acellular Pertussis Vaccine Accelerates the Acquisition of Pertussis Antibodies in Infants

MARKUS KNUF, MD,

N=317 infants

J. Pediatrics
2007

Poor Immune Responses to a Birth Dose of Diphtheria, Tetanus, and Acellular Pertussis Vaccine

NATASHA B. HALASA, MD, MPH, ALICE O'SHEA, RN, JIAN R. SHI, MD, BONNIE J. LAFLEUR, PhD, MPH, AND KATHRYN M. EDWARDS, MD

J. Pediatrics
2008

Acellular Pertussis Vaccine at Birth and One Month Induces Antibody Responses By Two Months of Age

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Helen Marshall, MBBS, DCH, MPH,§ and Don Robertson, MD, FRACP, FRCPA¶

PIDJ
2010

Background: Infants less than 3 months of age are at highest risk of hospitalization and death from pertussis. Several studies have examined antibody responses to pertussis vaccines at birth but no previous study has evaluated 2 doses of monovalent acellular pertussis vaccine (aPV) before 2 months of age.

Key Words: acellular pertussis vaccine, birth, immunogenicity

(*Pediatr Infect Dis J* 2010;29: 000–000)

Birth Pa vaccine study methods - vary


- Pa vaccine used
 - DTPa vs Pa
 - Different antigen amounts
 - Timing of dose
- Timing of serology
 - Laboratory
- Measurement of concomitant antigen responses
- Cell mediated immunity

Recent neonatal trials with acellular pertussis vaccines

	Belloni et al ITALY	Halasa et al USA	Knuf et al GERMANY	Wood et al AUSTRALIA
Vaccine	Pa Chiron	DTPa Sanofi	Pa GSK	Pa GSK
Pa antigen content	PT 5ug PRN 2.5ug FHA 2.5ug	PT 10ug PRN 3 ug FHA 3 ug Fim 5 ug	PT 25ug PRN 8ug FHA 25ug	PT 25ug PRN 8ug FHA 25ug
Combination vaccine	Acelluvax DTPa Polio Hib Hep B	IPV Daptacel ActHib Prevnar	Infanrix hexa	Infanrix hexa Prevenar
Serology	0,3,5,6,12 months	0,6,7,17,18 months	0,3,5,7 months	0,2,4,6,8 months
Site of ELISA	Not stated	Vanderbilt, US	GSK Belgium	GSK Belgium
Cellular immunity measured	No	No	No	Yes

Recent neonatal trials with acellular pertussis vaccines

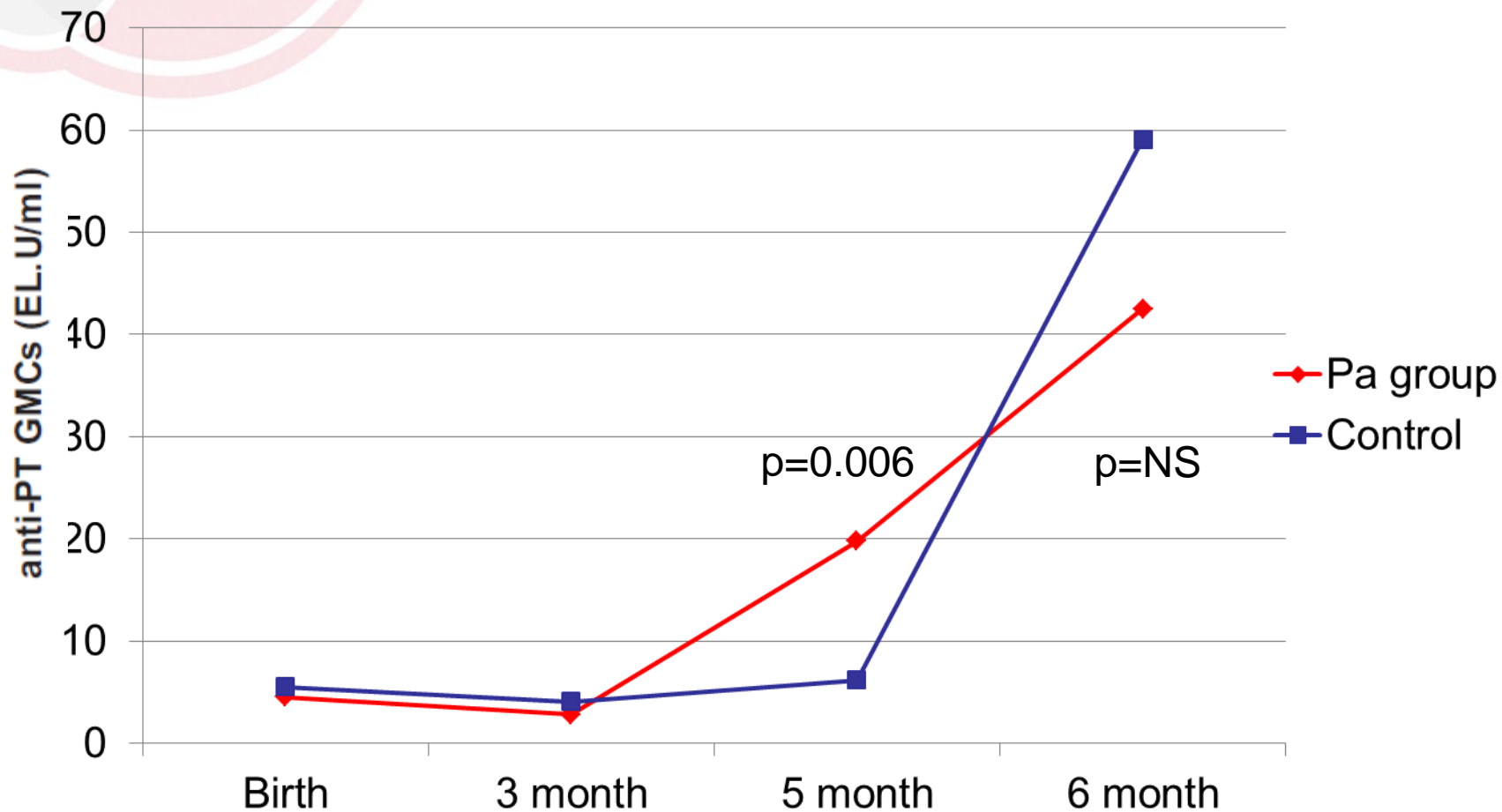
	Belloni et al ITALY	Halasa et al USA	Knuf et al GERMANY	Wood et al AUSTRALIA
Birth	Pa	DTPa	Pa	Pa
1 month				Pa
2 month		DTPa	DTPa	DTPa
3 month	DTPa			
4 month		DTPa	DTPa	DTPa
5 month	DTPa			
6 month		DTPa	DTPa	DTPa
7 month				
8 month				
11 month	DTPa			
Sample size	91	50	100	76

 = serology

Serology – primary response

- Pertussis antibodies
 - **PT**
 - **PRN**
 - **FHA**
 - Mother – at birth of infant
 - Infant at varying time points
- Hib, anti-HBs, dip, tetanus
 - Infant – 7 to 8 months old
 - 3 studies only (n= 257 infants)

Italy



Germany

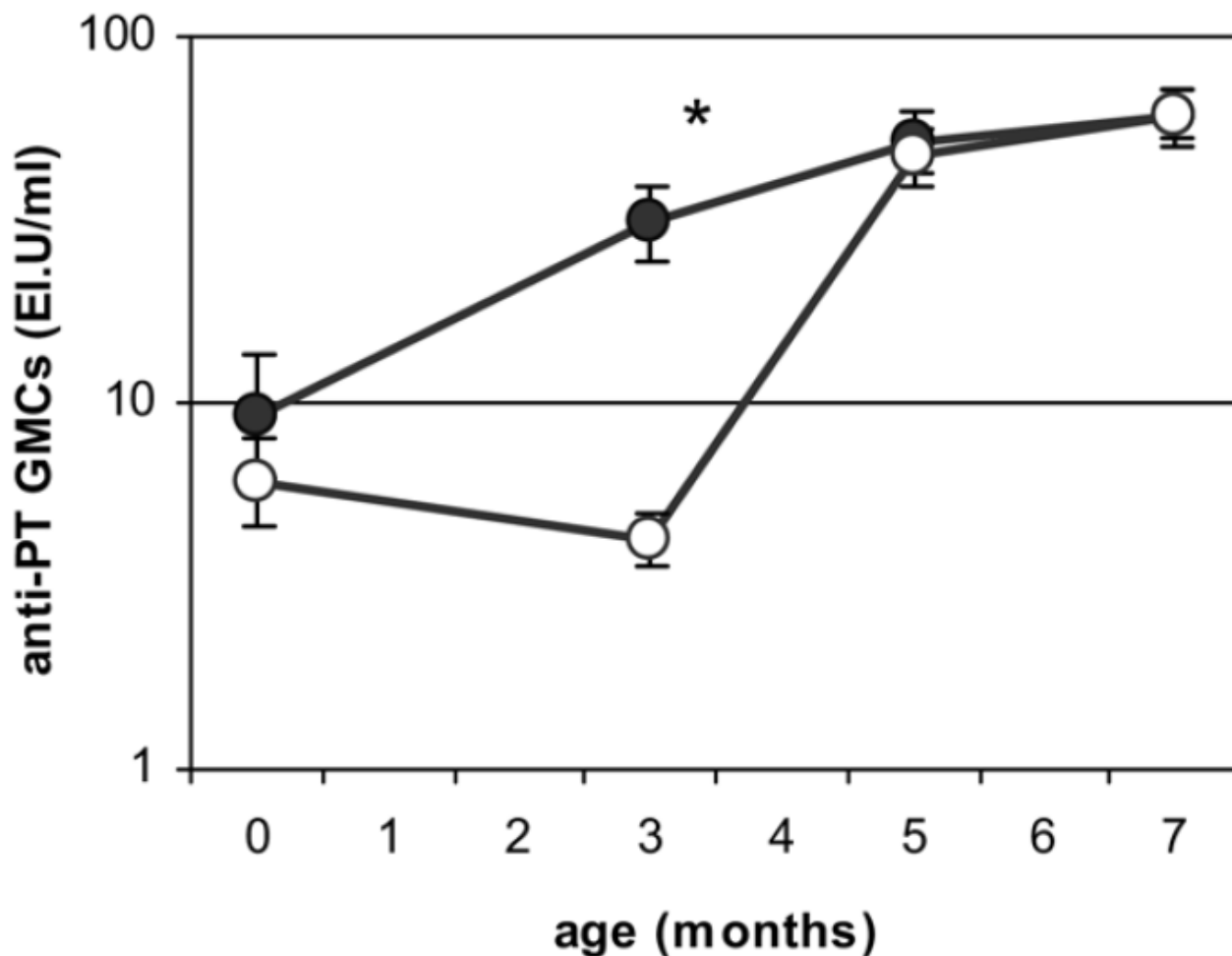
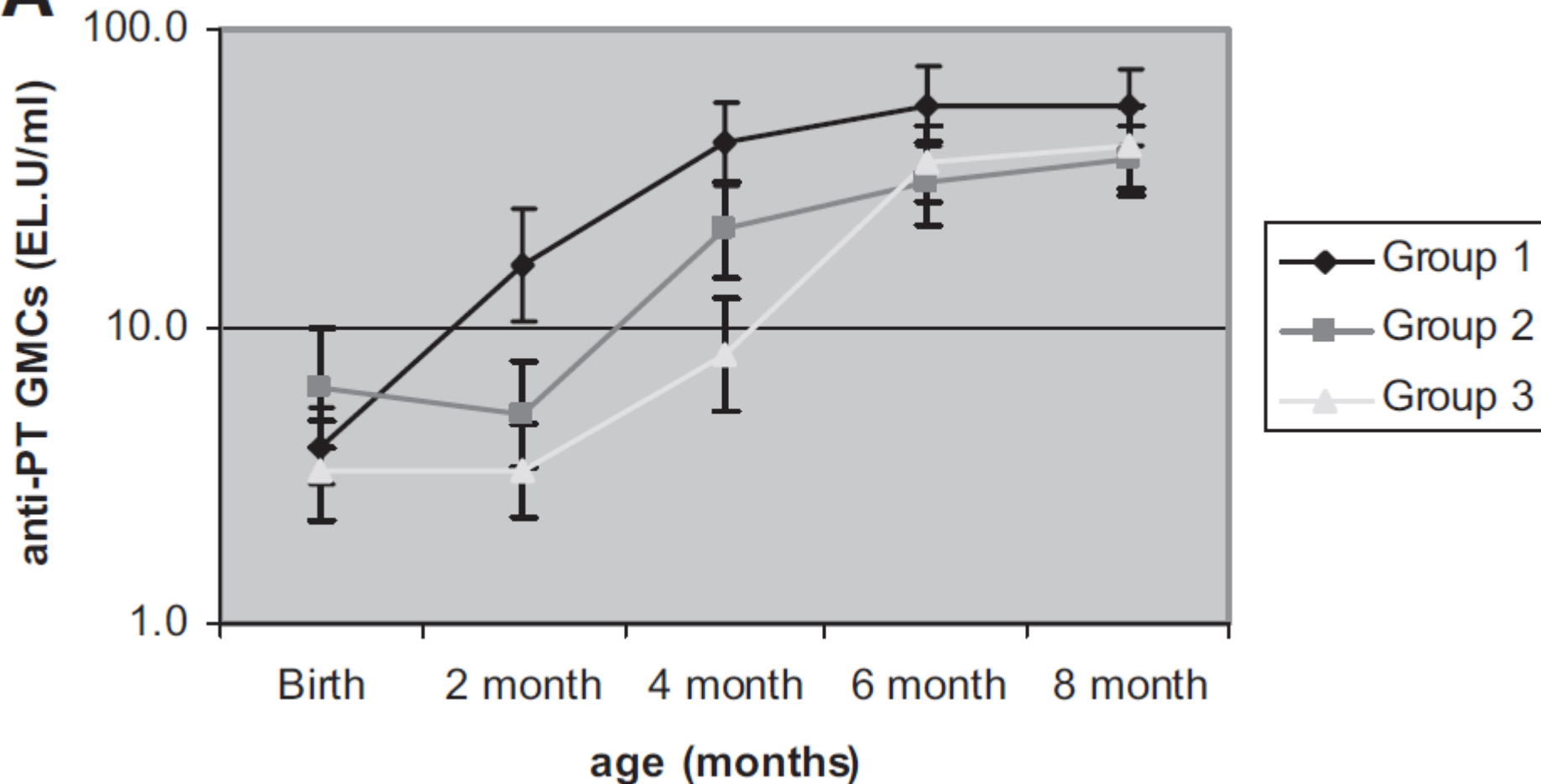
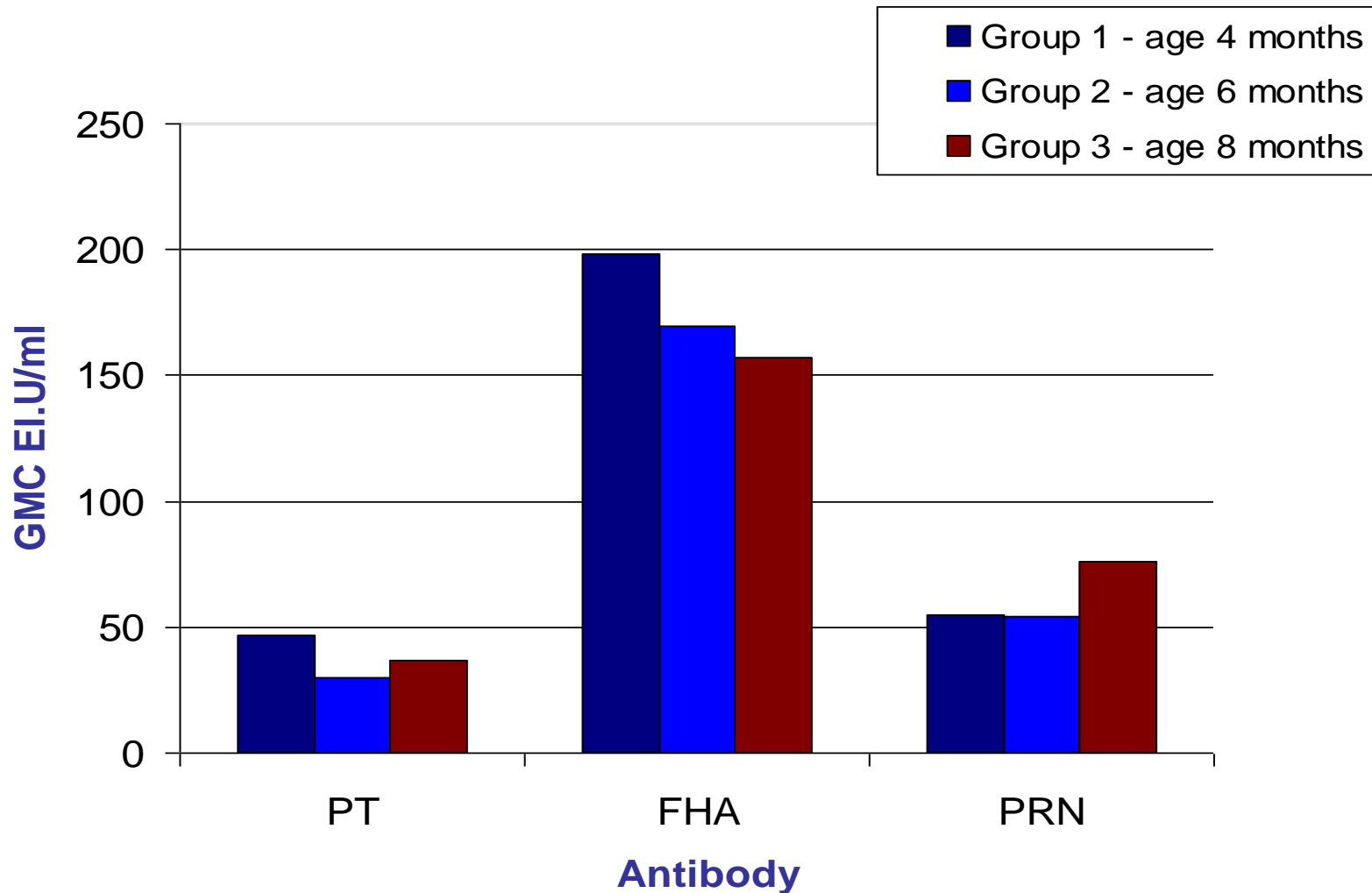


Figure 1. Anti-pertussis antibody GMCs from birth until completion of primary vaccination (ATP cohort for immunogenicity). ●, Group aP; ○, group HBV. *95% CI on the GMC ratio between groups does not include “1.”

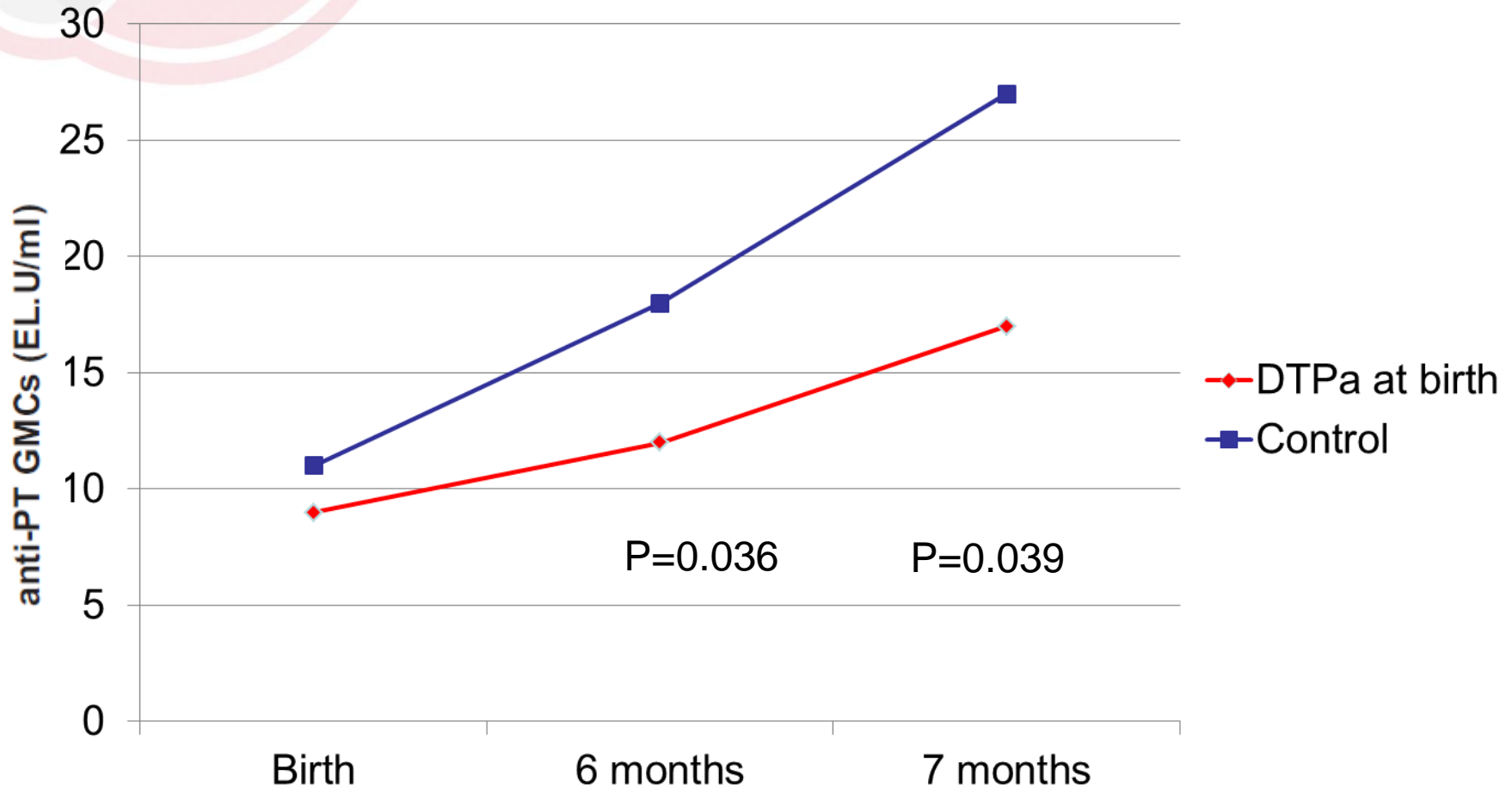
A



Antibody levels two months after 3rd dose of Pa



USA



Summary – primary pertussis response

- Waning of antibody from birth to 2-3 months old
- Earlier antibody responses in birth Pa group
 - 3 studies
 - PT, FHA, PRN significantly higher
- 1st dose primes and second dose increase
- Non significant difference at 7-8 months
 - 2 studies – Australia and Germany
- Contrary findings with DTPa at birth
 - ?vaccine interference



**Does pre-existing maternal antibody
influence pertussis antibody responses?**

Inhibition of infant responses (%)

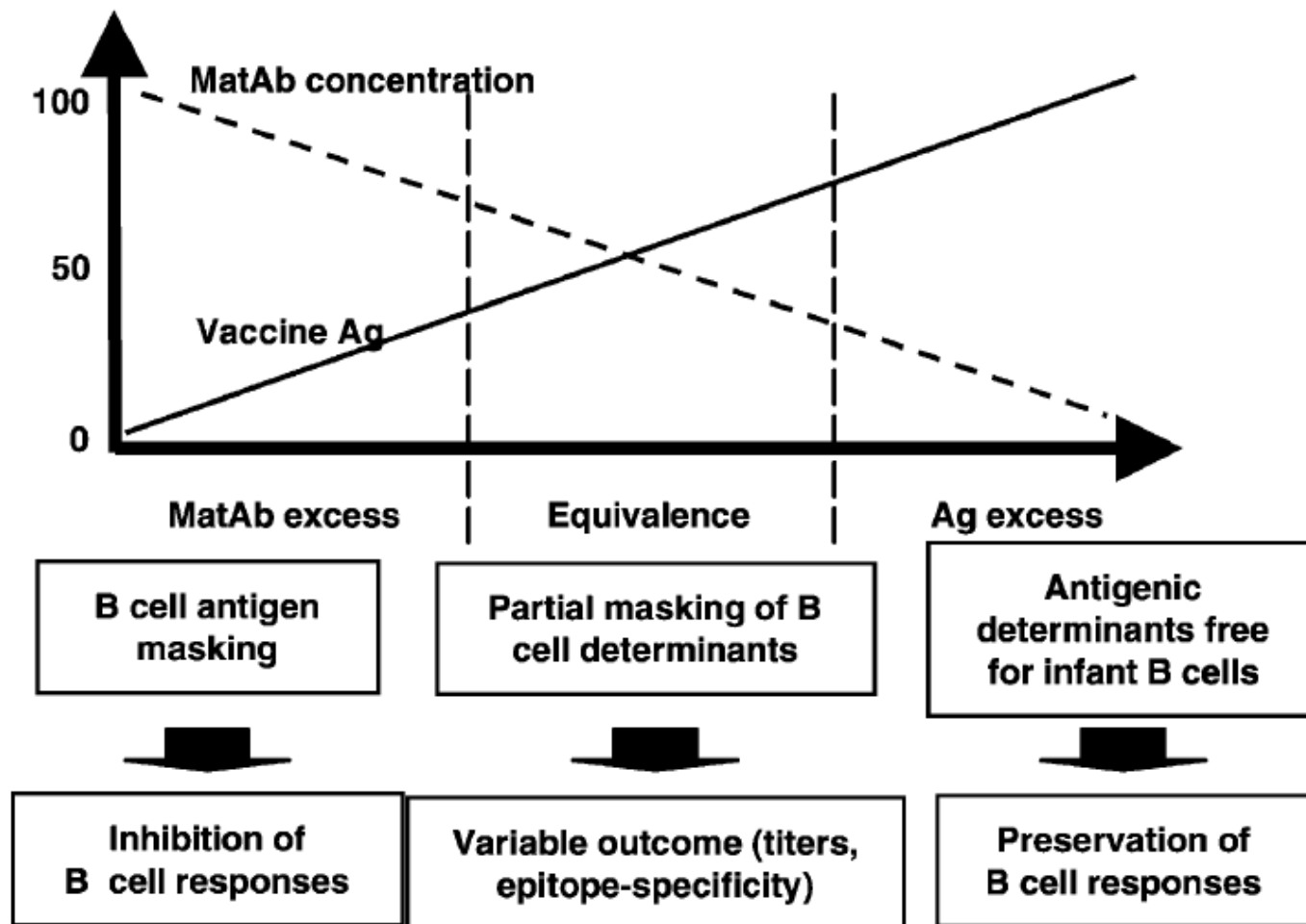
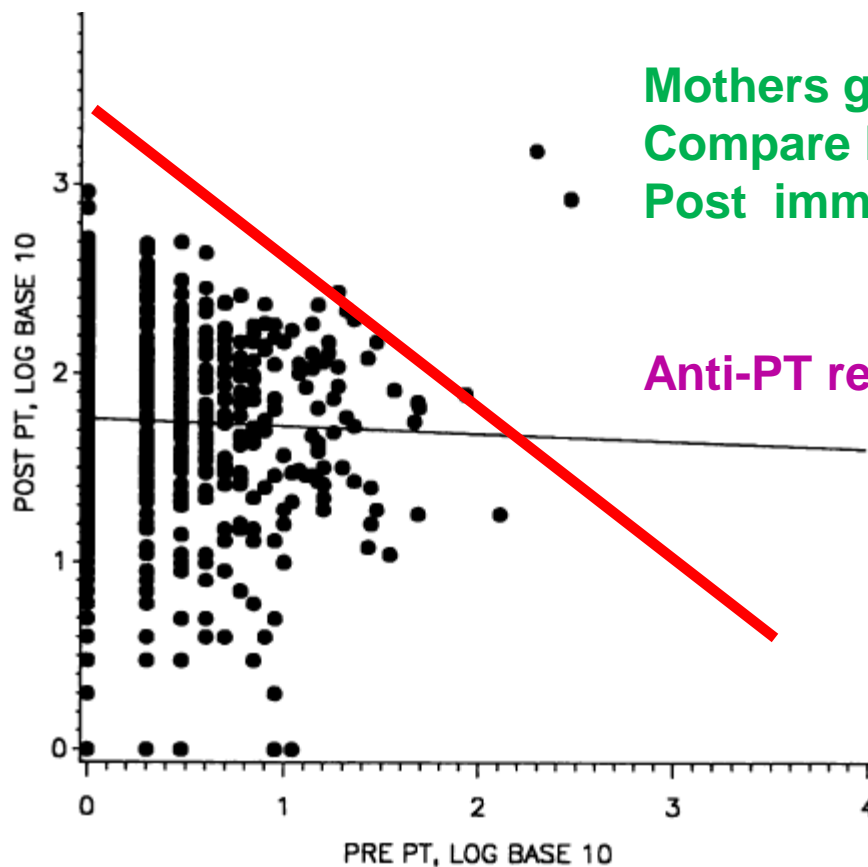


Fig. 3. Expected influence of maternal antibodies on infant antibody responses to subunit vaccines.

The Effect of Maternal Antibody on the Serologic Response and the Incidence of Adverse Reactions After Primary Immunization With Acellular and Whole-Cell Pertussis Vaccines Combined with Diphtheria and Tetanus Toxoids

Janet A. Englund, Edwin L. Anderson, George F. Reed, Michael D. Decker, Kathryn M. Edwards, Michael E. Pichichero, Mark C. Steinhoff, Margaret B. Rennels, Adamadia Deforest and Bruce D. Meade
Pediatrics 1995;96:580-584



Mothers given DTPw

- Compare levels at 2 months old with
- Post immunisation at 7 months old

Anti-PT response post DTPa = non sig

Figure. Relationship between preimmunization and postimmunization PT antibody levels after WCL (A) and DTaP (B). The slope of the linear regression for preimmunization versus postimmunization antibody is -0.04 for DTaP ($P = .26$), indicating no significant effect of preimmunization antibody on the postimmunization response. In contrast, the slope of the regression line is

Summary – Birth Pa trials

- Italy
 - No data
 - “no correlation was observed”
- USA
 - “no impact of maternally derived pre-existing antibodies on infant responses... although pre-existing pertussis antibody levels were low”
- Germany
 - No data
- Sydney
 - lower antibody levels when combined group data

How important is baseline maternal antibody level?

Birth Pa trials

Antibody GMC EL.U/ml	Belloni et al ITALY	Halasa et al USA	Wood et al AUSTRALIA
PT	4.5	9	5.1
PRN	4.6	27	5.5
FHA	16.6	11	13.6

Kirkland et al Clinical Infectious Disease 2009;49:584-7
Leuridan et al PIDJ 2011; 30: 608-9
Gall et al AJOG 2011;204:334.e1-5

Inhibition of infant responses (%)

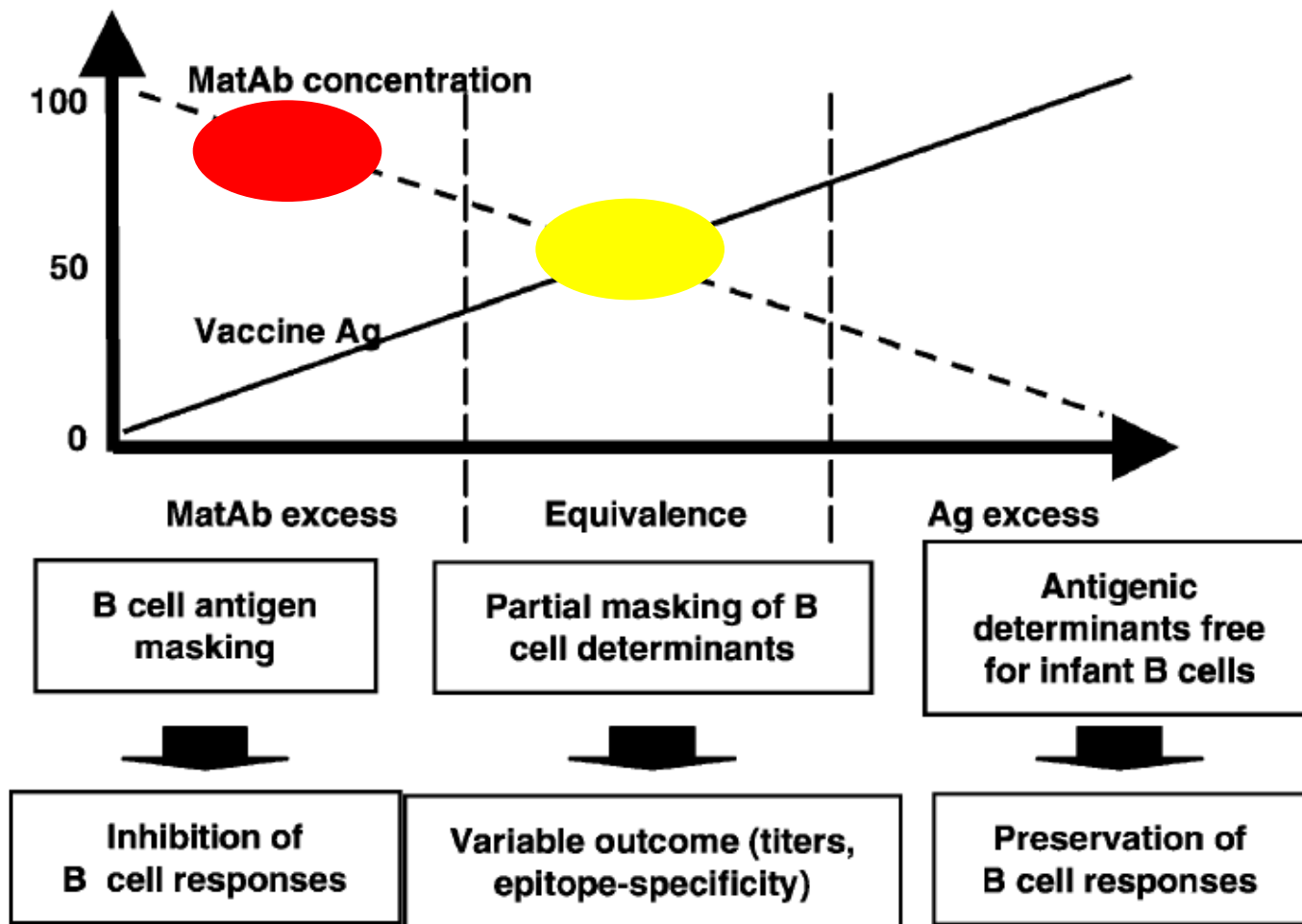


Fig. 3. Expected influence of maternal antibodies on infant antibody responses to subunit vaccines.



Does birth pertussis vaccine interfere
with **primary concomitant antigen**
responses?

Concomitant antigen responses – birth group

	Belloni et al ITALY	Halasa et al USA	Knuf et al GERMANY	Wood et al AUSTRALIA
Concomitant antigen responses	Not measured			
Hib		same	Lower GMC and % > 0.15ug/ml	Lower Group 1 only
Hepatitis B		same	Lower Note: HBV was control	Lower Note: all given HBV
Diphtheria		lower	Same	same
Tetanus		same	same	same

Summary –potential vaccine interference

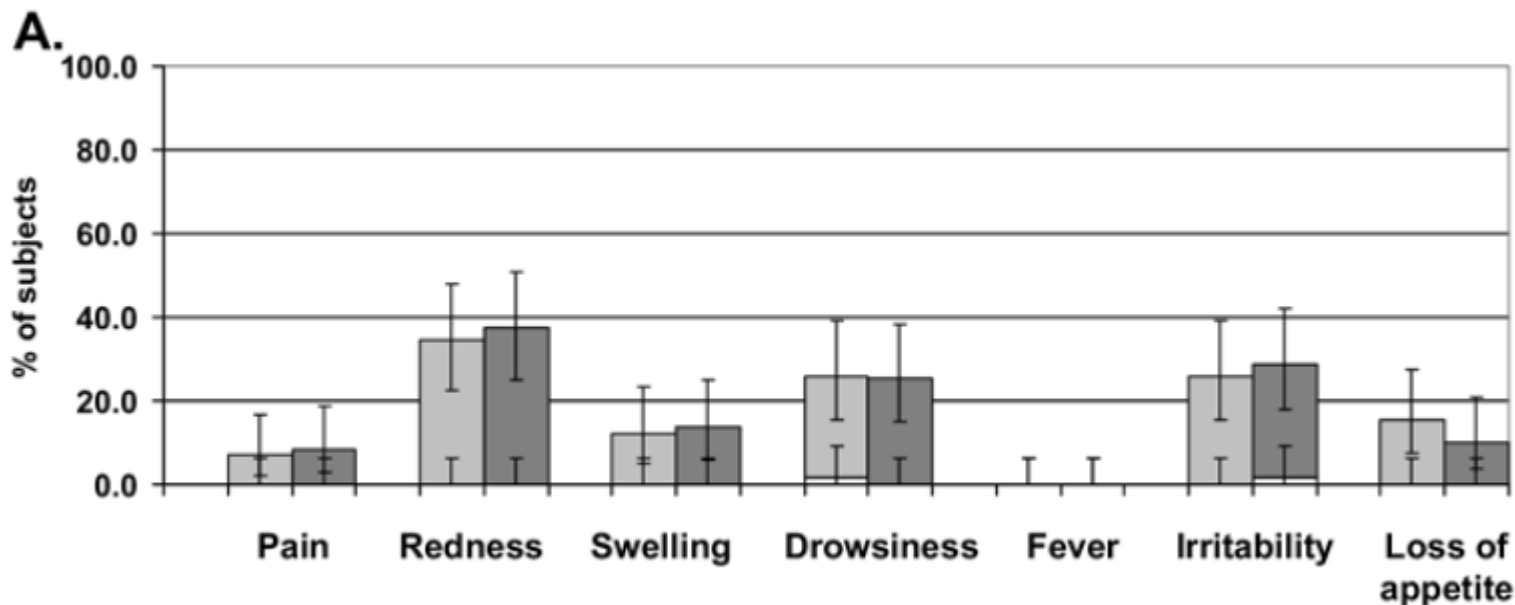
Hepatitis B surface antibody response at age 8 months - Australia

	anti-HBs GMC	10-100 %	101-1000 %	>1000 %
Group 1 and 2 n=39	409	12	62	26
Group 3 n=15	747.7	0	73	27



How safe is the birth dose of pertussis vaccine?

Reactogenicity - Germany

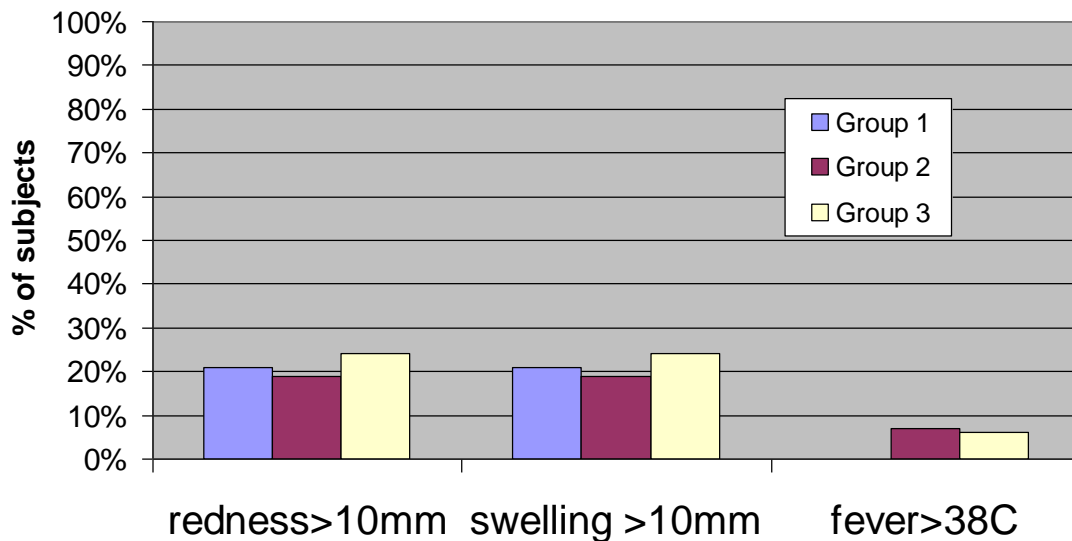


Reactogenicity - Australia

■ Birth dose

- Nil fever >38C
- Nil injection site reactions >10mm after birth Pa dose

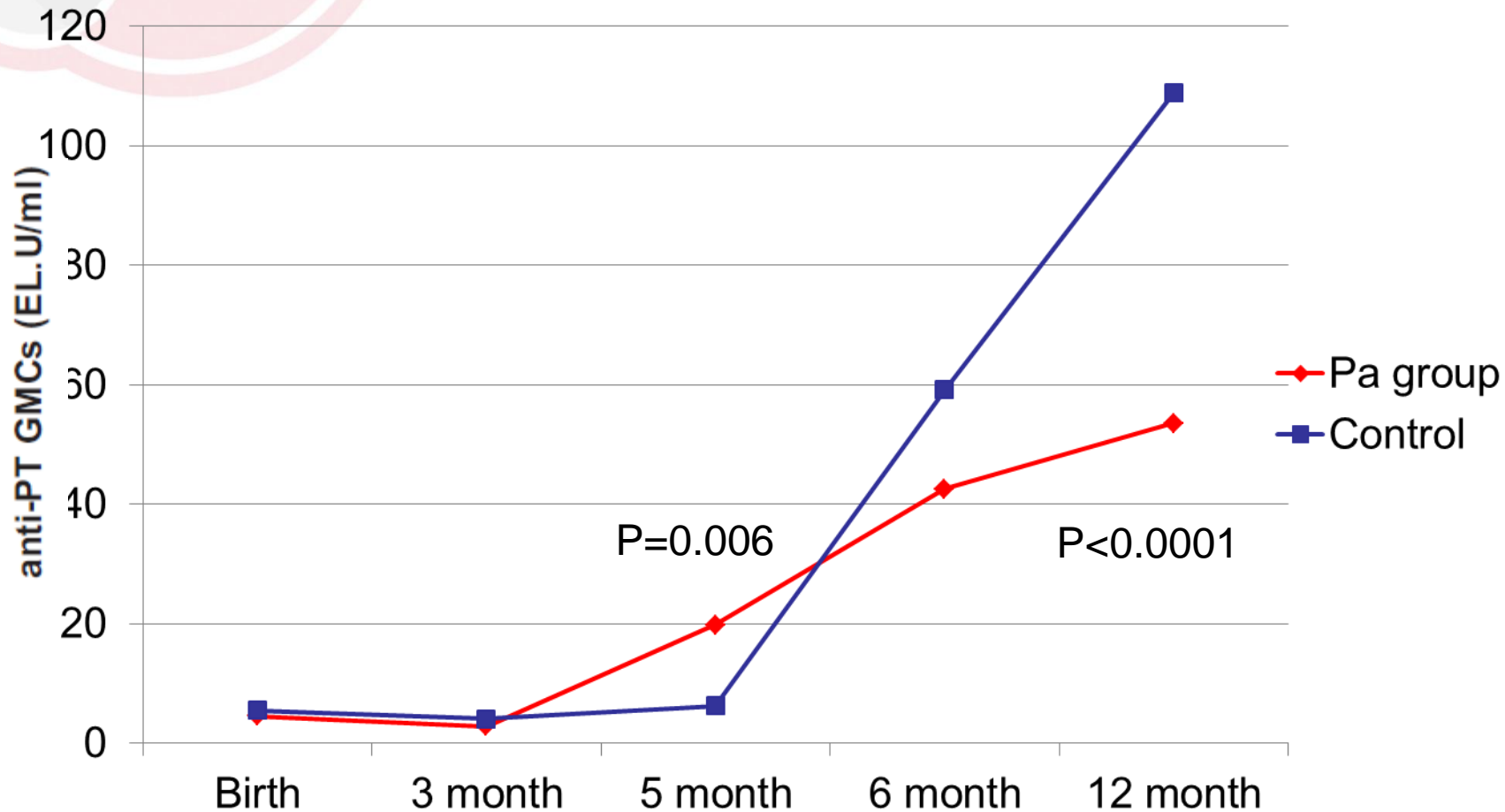
Reactogenicity at 6 months age by group





**Does birth pertussis vaccine influence
immune persistence and responses to
booster vaccines?**

Italy



Germany

- N=66
- Mean age 13.7 months and given Infanrix hexa

Table 1. Serological responses before and one month after the booster dose (ATP cohort for immunogenicity)

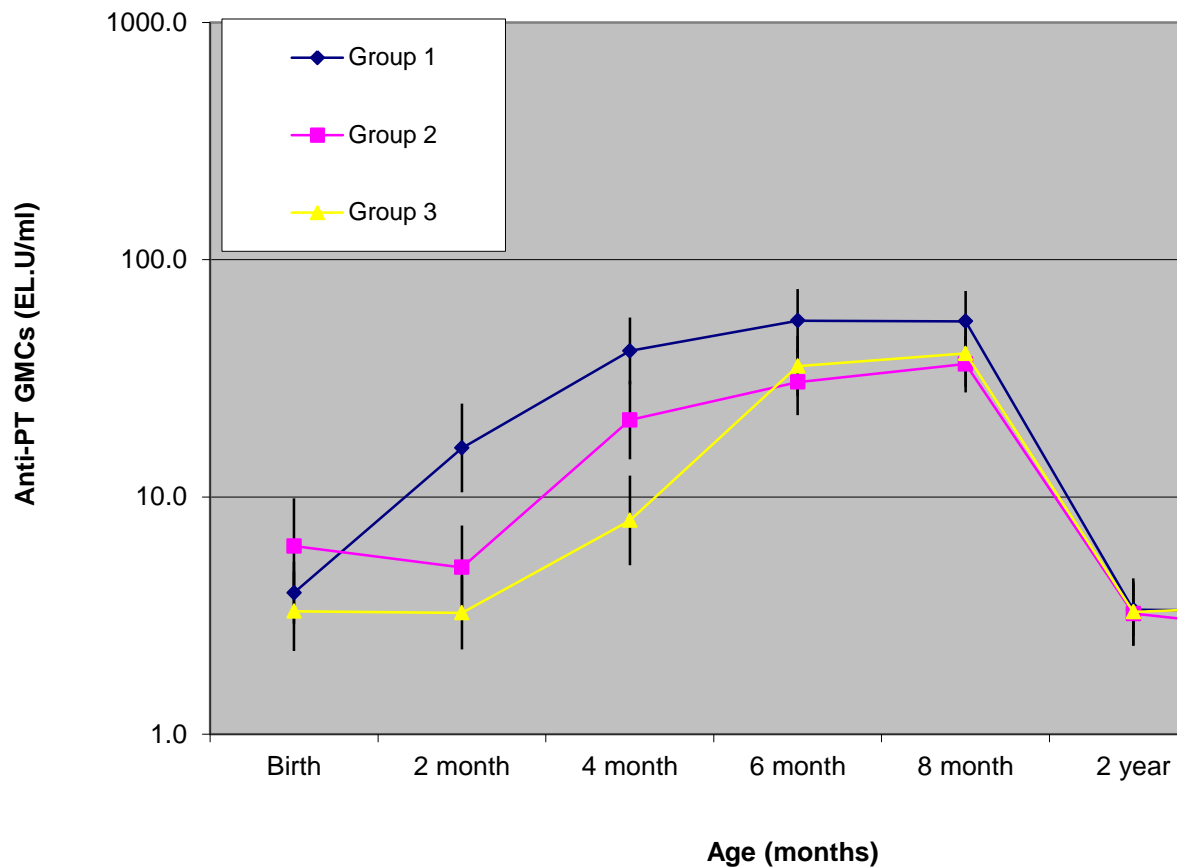
Antibody	Time point	Group aP			Group HBV		
		N	% (95% CI)	GMC/GMT (95% CI)	N	% (95% CI)	GMC/GMT (95% CI)
PT	Pre	29	86.2 (68.3; 96.1)	12.7 (8.8; 18.2)	33	75.8 (57.7; 88.9)	9.2 (6.7; 12.6)
≥5 EI.U/ml	Post	29	100 (88.1; 100)	60.1 (45.5; 79.4)	33	100 (89.4; 100)	73.2 (59.8; 89.5)
FHA	Pre	29	100 (88.1; 100)	104.5 (67.5; 161.7)*	33	100 (89.4; 100)	63.3 (46.5; 86.3)*
≥5 EI.U/ml	Post	29	100 (88.1; 100)	601.0 (451.1; 800.7)	33	100 (89.4; 100)	438.0 (339.0; 565.8)
PRN	Pre	29	96.6 (82.2; 99.9)	26.2 (17.6; 38.8)	33	93.9 (79.8; 99.3)	24.2(17.6; 33.3)
≥5 EI.U/ml	Post	29	100 (88.1; 100)	409.1 (312.3; 535.8)	33	100 (89.4; 100)	397.1 (289.1; 545.4)

Nil significant difference in pertussis booster response between groups

Lower response to Hib in birth group

Knuf et al J Pediatr. 2010 Apr;156(4):675-8.

Australia





What about cell mediated immunity?

T cell immunity is important for pertussis protection

- Mouse models – Mills et al
- Pertussis – survive intracellularly
- Pa vaccines infancy = Th1 predominance > Th2

INFECTION AND IMMUNITY, Oct. 1996, p. 4078–4084
0019-9567/96/\$04.00+0
Copyright © 1996, American Society for Microbiology

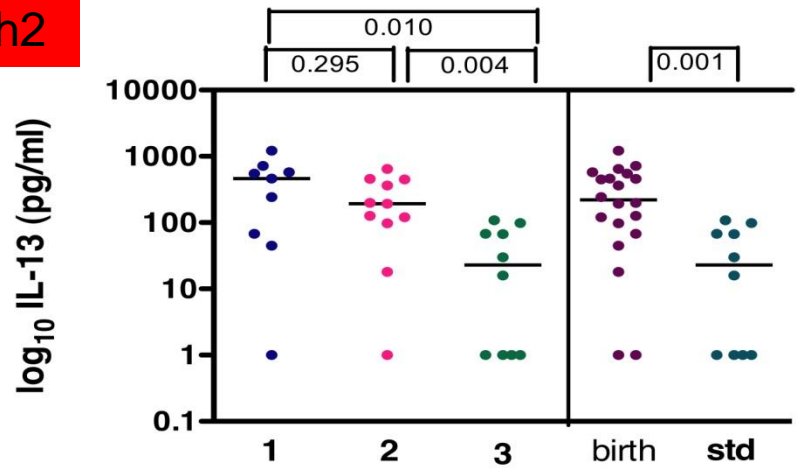
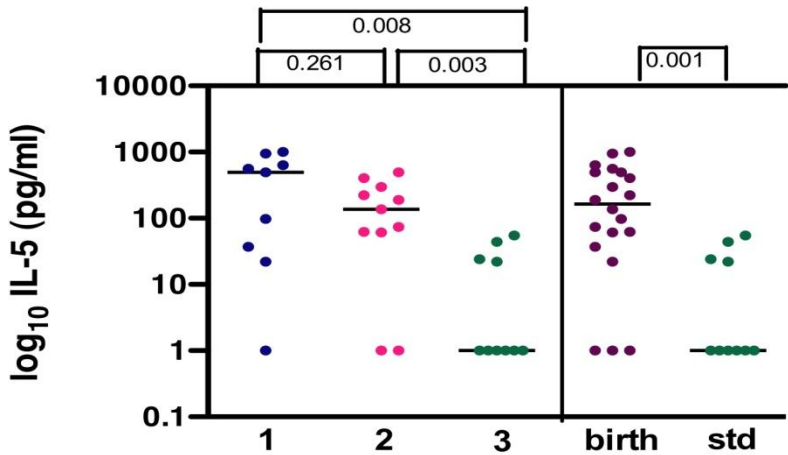
Vol. 64, No. 10

Pertussis-Specific Cell-Mediated Immunity in Infants after Vaccination with a Tricomponent Acellular Pertussis Vaccine

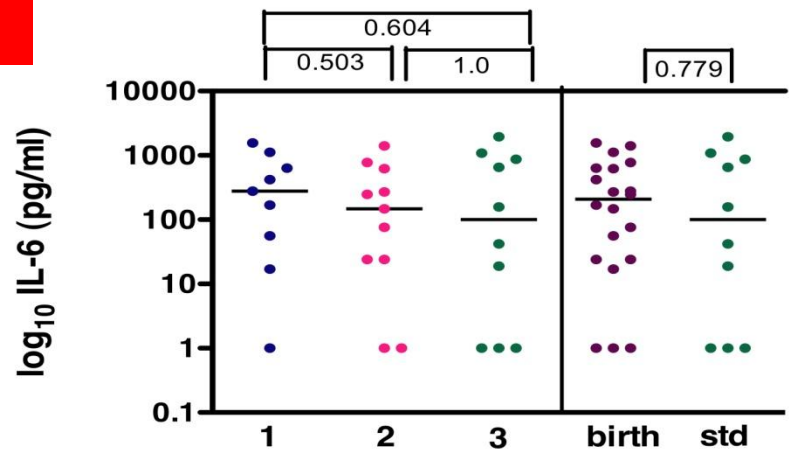
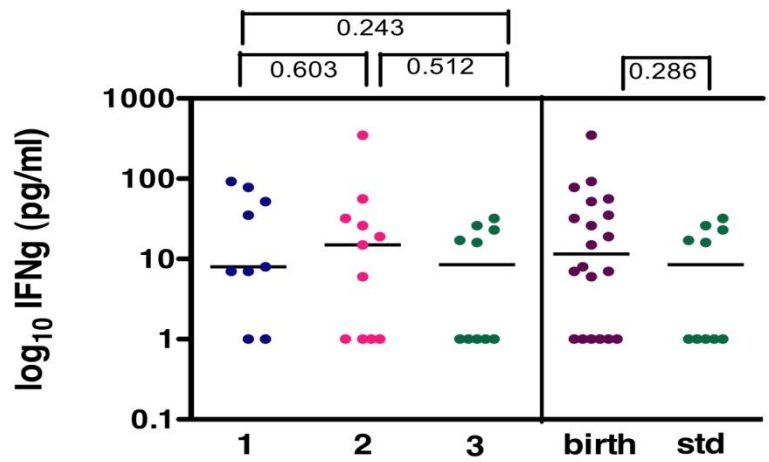
F. ZEPP,^{1*} M. KNUF,¹ P. HABERMEHL,¹ H. J. SCHMITT,² C. REBSCH,¹ P. SCHMIDTKE,¹
R. CLEMENS,³ AND M. SLAOU³

Cytokine response to pertussis antigens

Th2



Th1



Neonatal vaccination drives Th2 polarised memory development

Questions arising from these findings

- will Th-memory responses remain sufficiently Th2-polarised to influence injection-site responses at subsequent booster?
- will strongly Th2-polarised memory against pertussis antigens influence host responses to pathogens at infection sites?
- are the group potentially “at risk” of atopy?



Can we do it?

**What can we expect from birth
pertussis vaccination?**

Study of the risk factors for severe childhood pertussis based on hospital surveillance data

Valérie Briand*, Isabelle Bonmarin, Daniel Lévy-Bruhl

*National Institute for Public Health Surveillance, Department of Infectious Diseases,
12 rue du Val d'Osne, 94415 Saint-Maurice Cedex, France*

Received 11 August 2006; received in revised form 6 July 2007; accepted 15 July 2007

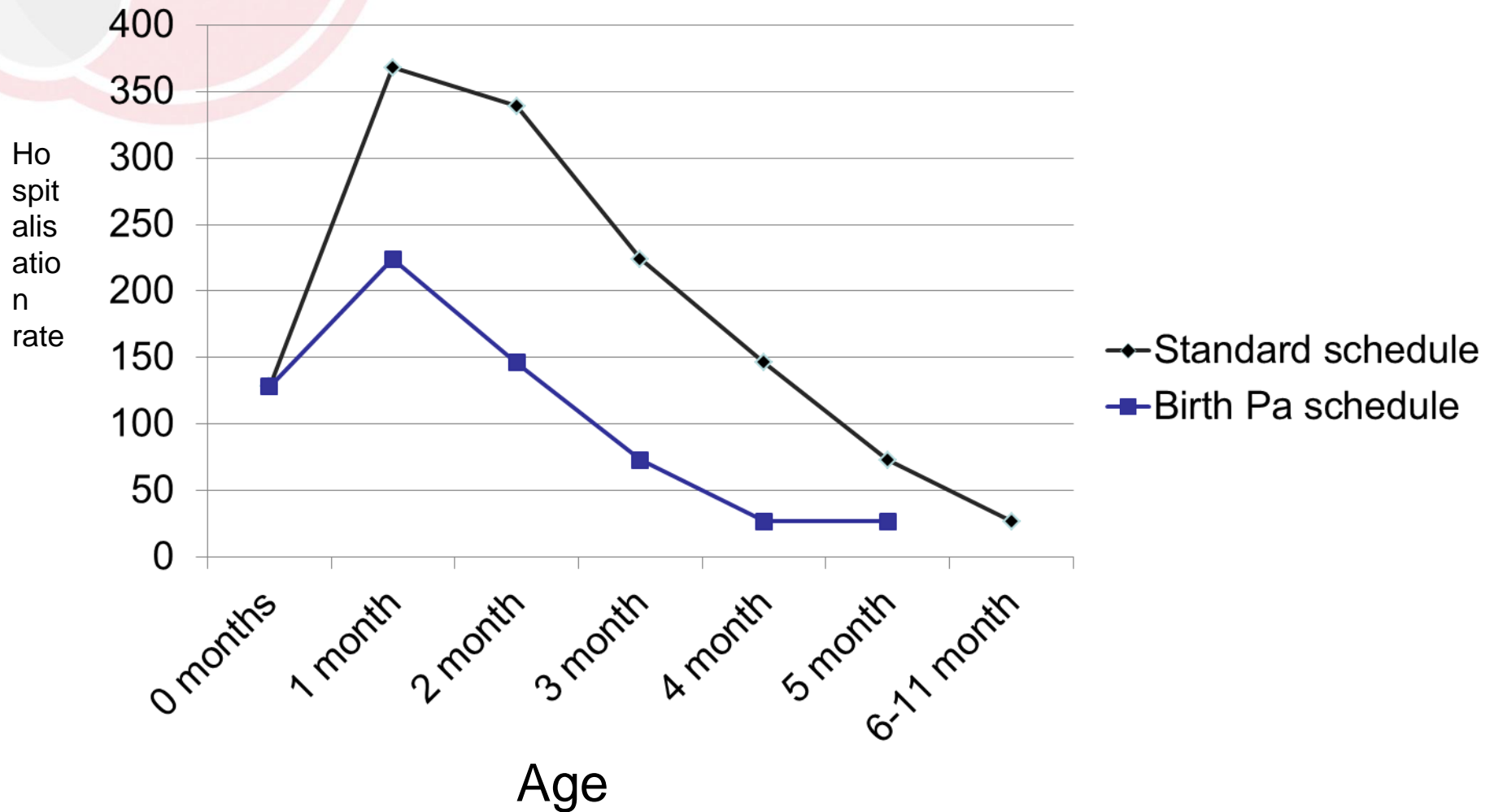
Available online 2 August 2007

Table 2
Factors associated with severe pertussis in children aged 2–11 months

	Univariate analysis		Multivariate analysis ^a	
	OR ^b	CI ^b	OR ^b	CI ^b
Age at onset of symptoms (months)				
2–3	1	–	1	–
4–5	0.50	0.26–0.98	0.70	0.30–1.64
6–11	0.38	0.16–0.91	0.37	0.12–1.11
Number of doses of vaccine				
0	1	–	1	–
1	0.45	0.23–0.85	0.42	0.19–0.91
2 or 3	0.08	0.01–0.59	0.13	0.02–0.98

Some evidence that 1 dose may be protective

What can we expect? – Australian hospitalisation rates



Equivalent anti-PT levels 2 months earlier with Pa at birth
Possible shift rates by 2 months

Provenzano RW, Wetterlow LH, Sullivan CL. *N Engl J Med* 1965; 273: 959-965.

More data needed

ven

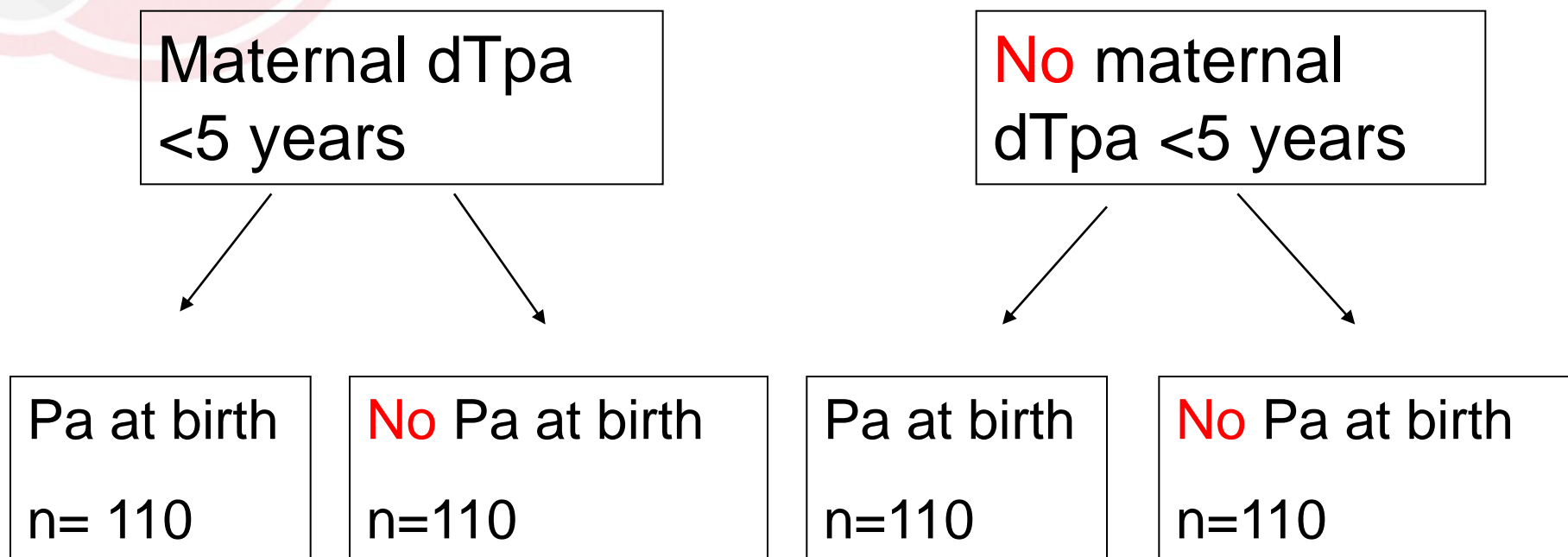
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Current NHMRC funded multicentre trial - underway

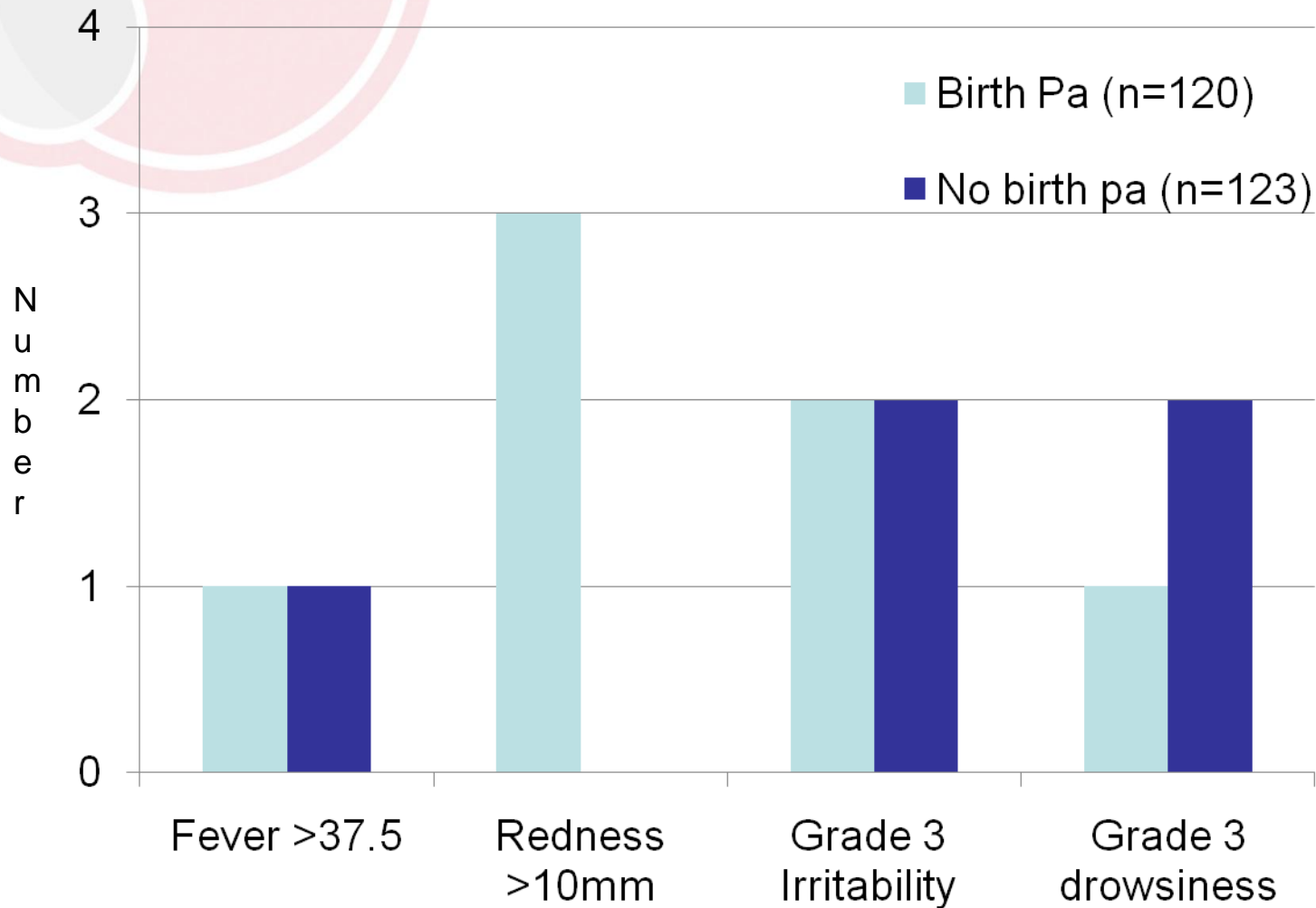


SEROLOGY – birth, 6 weeks, 10 weeks, 6 and 8 months

CMI – 10 weeks and 8 months

N=349 to date

Safety data so far.....



Solicited adverse events days 0-2

Birth vaccination is well established

- WHO EPI schedule – OPV, BCG, Hep B
- Healthcare contact at birth
- Immunologically
 - ACTIVE antibody and CMI production
 - vs passive antibody
 - Neonatal tetanus = maternal immunisation
- ? Combination **HepB-Pa** vaccine – potential
- ? 5 vs 3 component Pa vaccine
- ? cost effectiveness
- ?parental and physician attitudes

Summary

- Monovalent Pa studies to date (n=317)
 - Earlier pertussis antibody
 - Concomitant antigen responses – reduced but ?significance
 - Th2 polarised responses early
 - Safe
 - No hyporesponsiveness
- Key Questions
 - Influence of maternal antibody
 - Vaccine interference and hyporesponsiveness
 - How effective?

Acknowledgements

- Peter McIntyre and NCIRS
- Foundation for Children
- GSK – Pa supply and serology testing
- NHMRC Birth Pa vaccine trial staff
 - **Sydney** - Rose Joyce, Carol Sheinberg, Jane Ho
 - **Melbourne** – Terry Nolan, Jodie McVernon, Marita Kefford
 - **Adelaide** – Helen Marshall, Susan Lee
 - **Perth** – Peter Richmond, Jenny Kent