Immunising the newborn baby and what it teaches about neonatal immunity

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Immunising the newborn

- What is “normal”
  - Pregnant woman
  - Fetus and newborn
- What happens when we immunise newborns
- What this teaches us
- What we should do

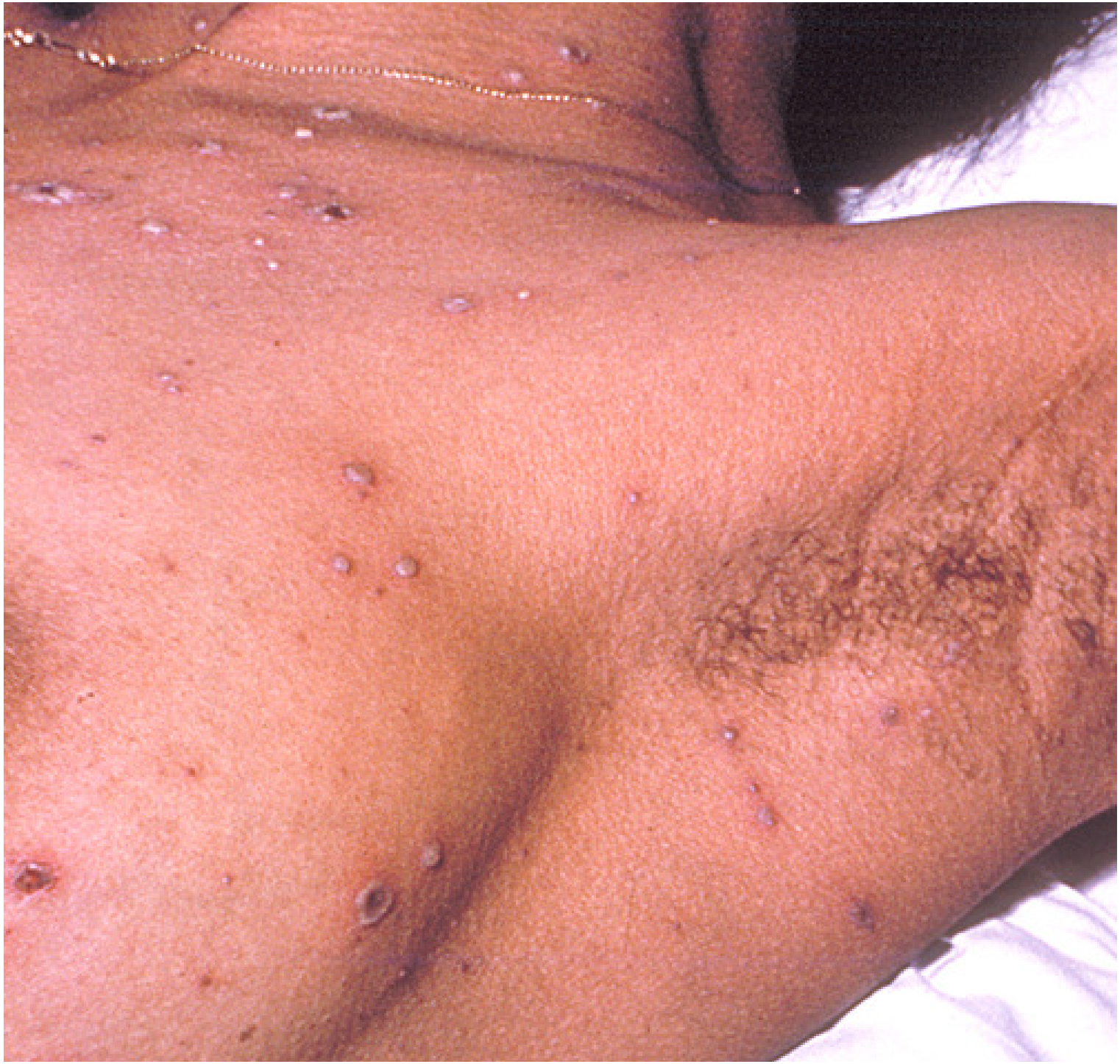
Caught on the horns of a dilemma

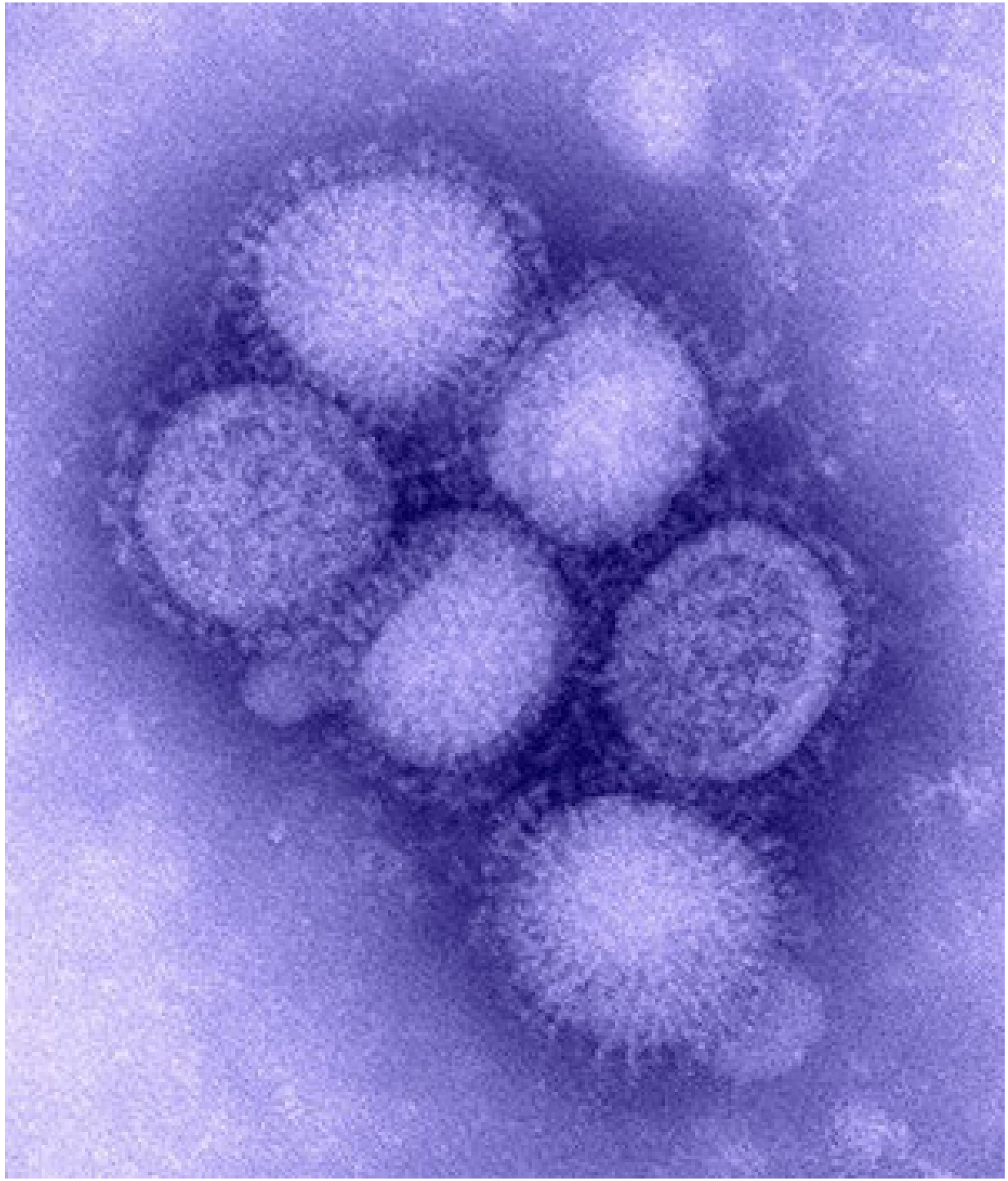
The horns of a dilemma

- Pregnant woman does not want to mount an immune response that will reject her baby
- Fetus does not want to produce cytokines that may trigger pre-term labour
- <u>But</u> mother and fetus need to fight off infections

Pregnant woman

- Impaired response to intracellular pathogens
- T_H1 usually required for Listeria, herpesvirus
- T-cell responses suppressed

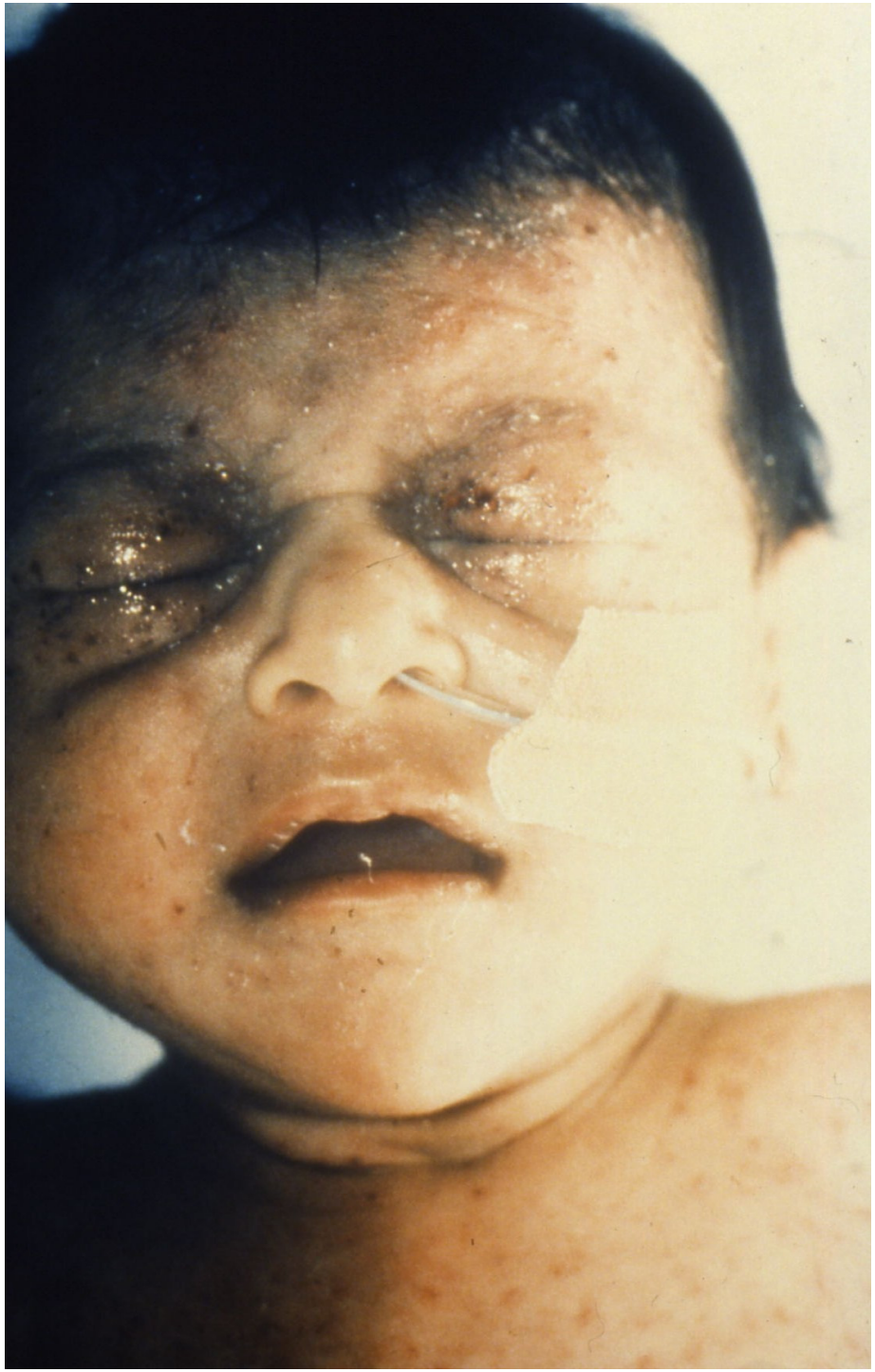


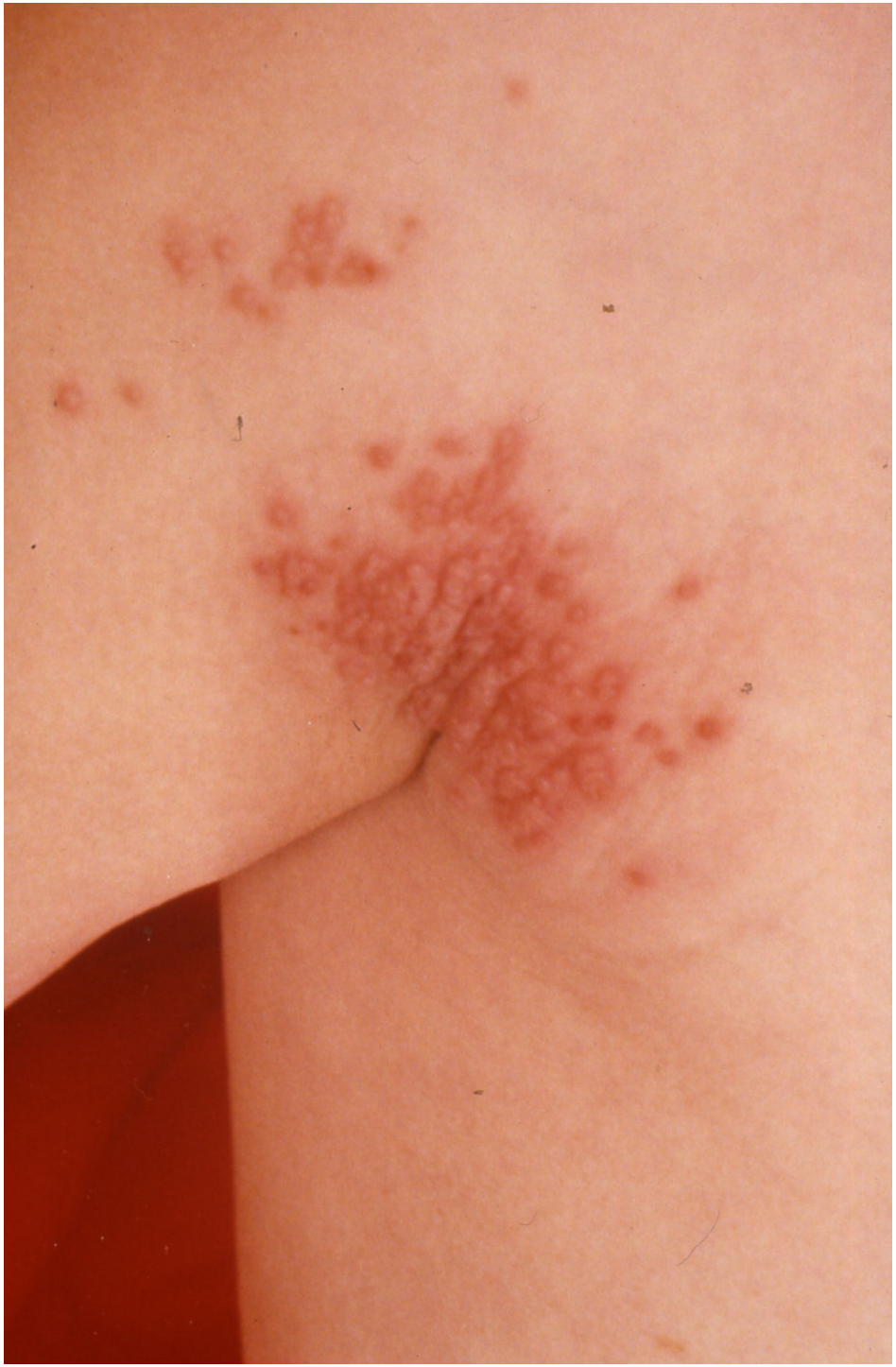


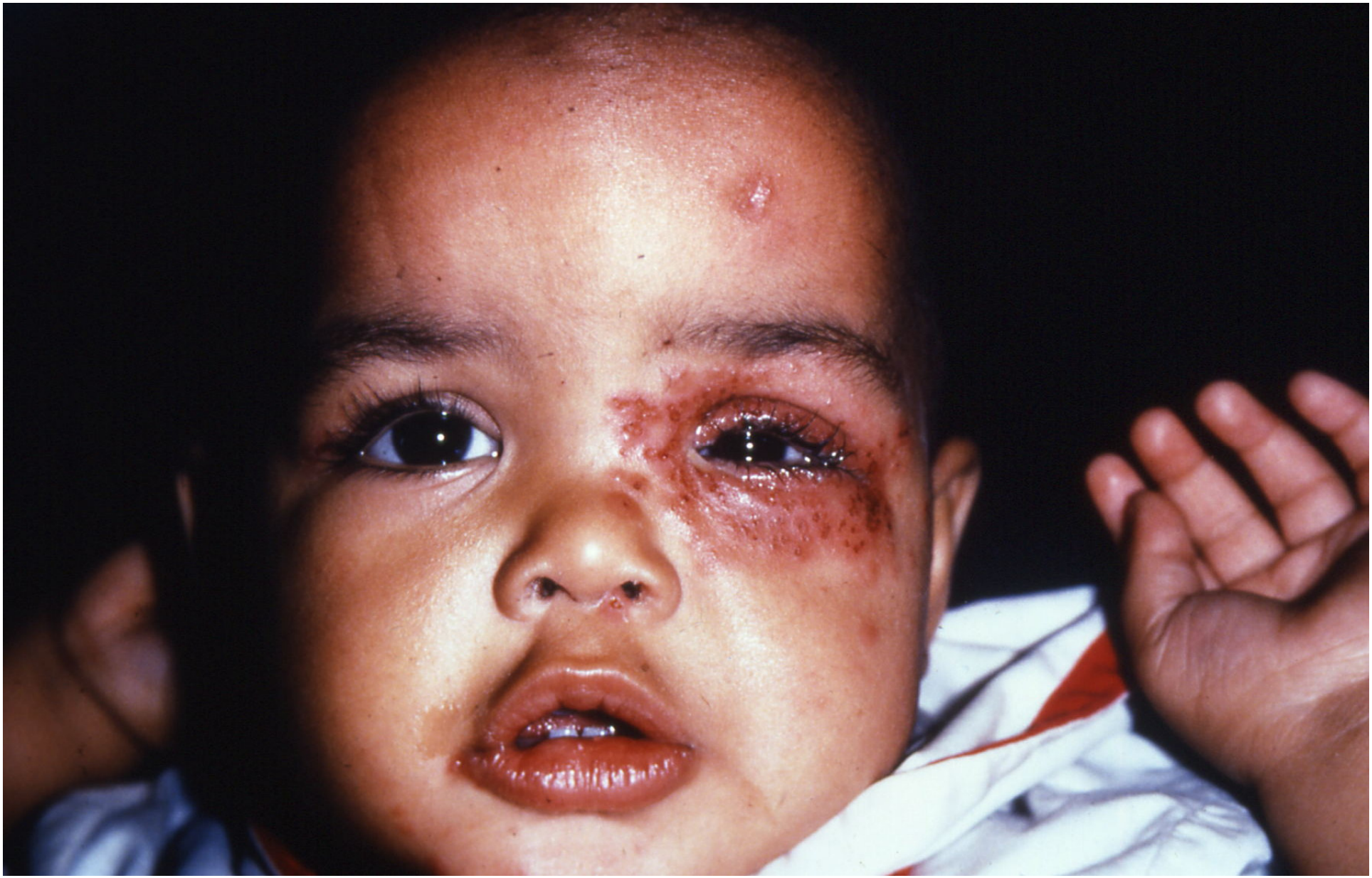

Truffles

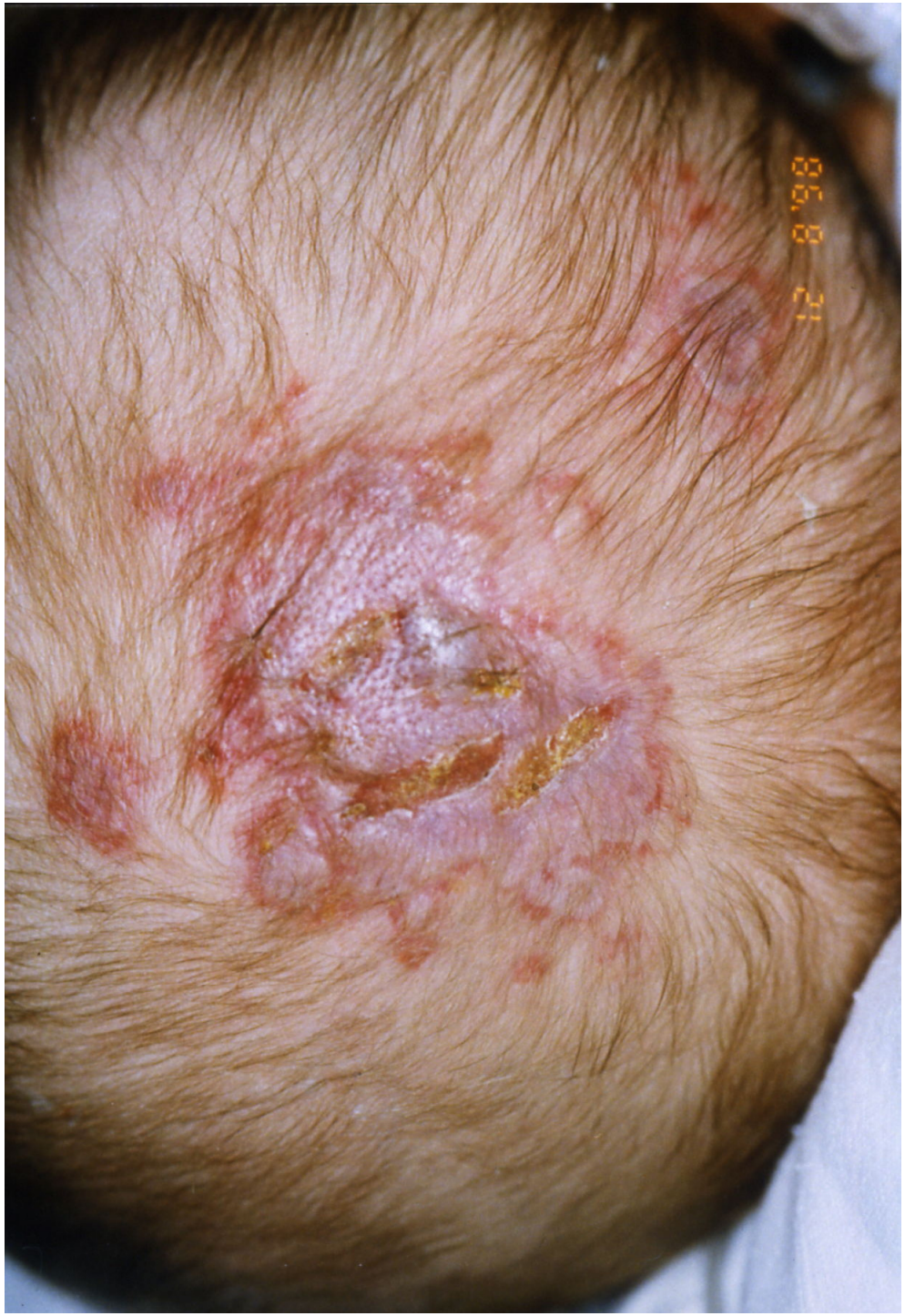
Fetus and newborn

- Pro-inflammatory cytokines dangerous
- Can induce rejection and pre-term labour
- Bias against T_H1 responses
- Low Toll-like receptor expression (innate immunity)
- More susceptible to microbial infection





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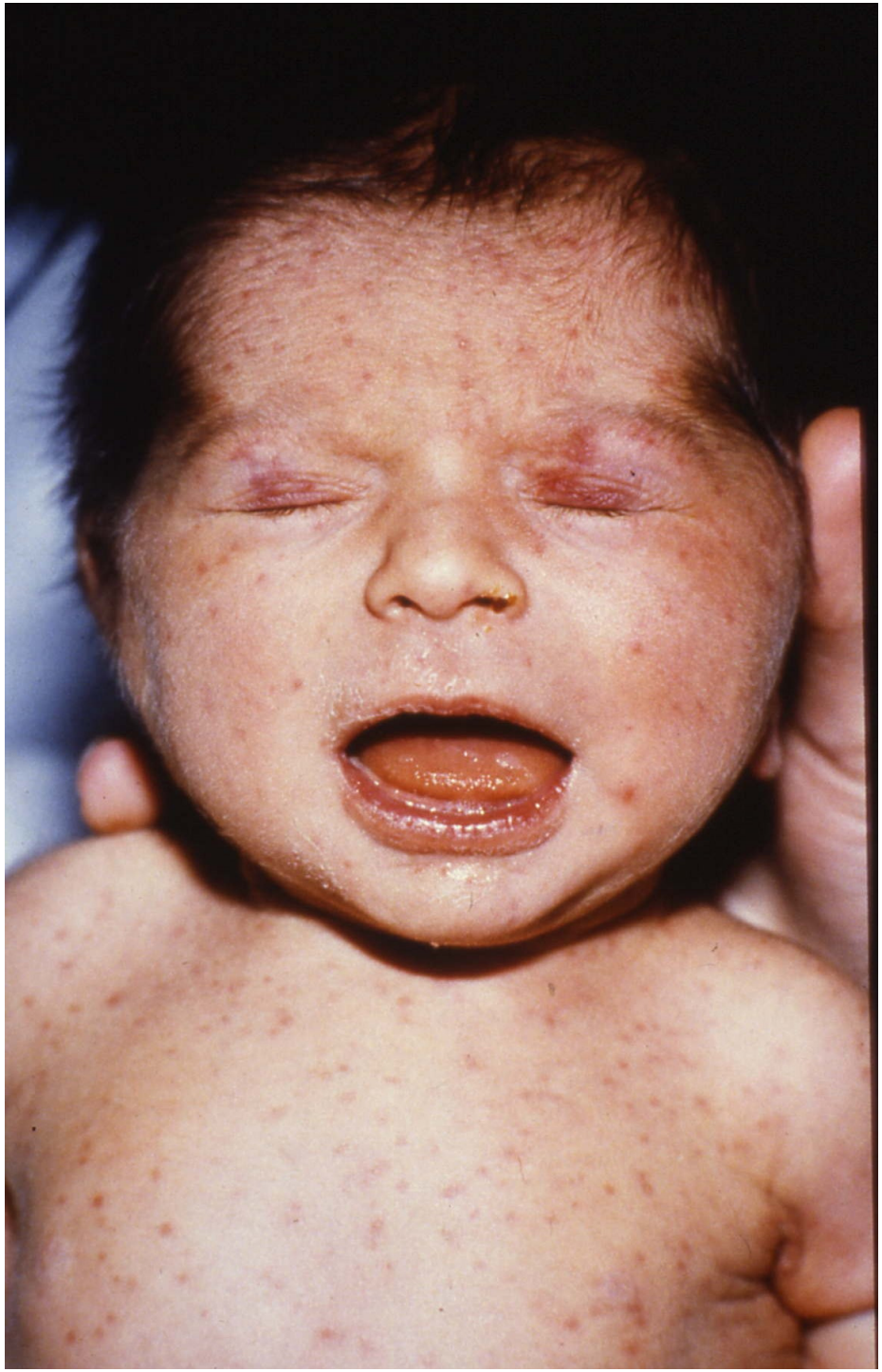
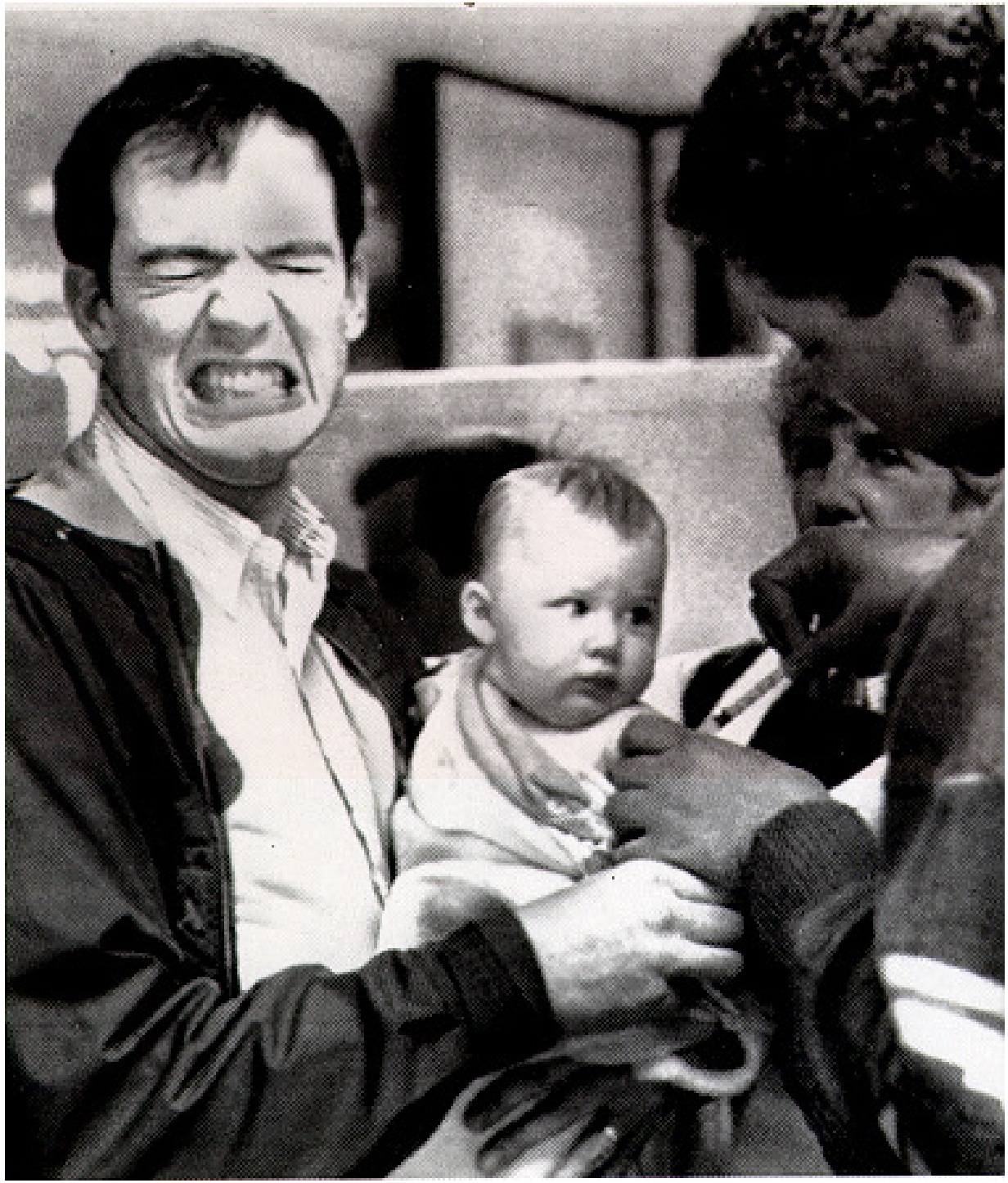




Newborn T-cell responses to vaccines

- Newborns respond well to BCG vaccine with mature T_H1 response
- Respond to OPV (and IPV): low T_H1, high Ab's
- Hepatitis B vaccine: low T_H1, high Ab's

B cells

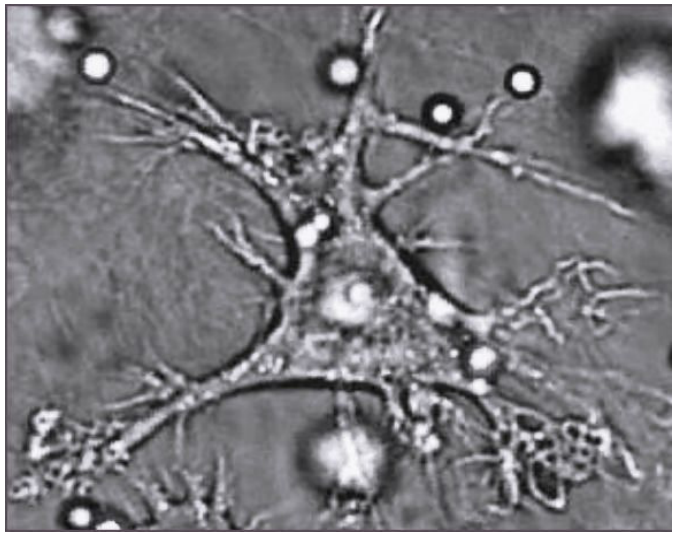
- Polio type 1 vaccine does not protect vs polio types 2 or 3
- Need all 3 polio strains in vaccine
- Antibody responses highly specific

T cells

- Neonatal BCG vaccine protects against TB
- Also against atypical mycobacteria + leprosy
- T cell responses less specific

Dendritic cells

- Important antigen-presenting cells
- BCG vaccine intradermal
- Improved T_H1 response



Toll-like receptors (TLR)

- Receptors for microbial molecules
- Innate immune response
- TLR stimulators (agonists) as adjuvants
  - Monophosphoryl lipid A and HPV vaccine

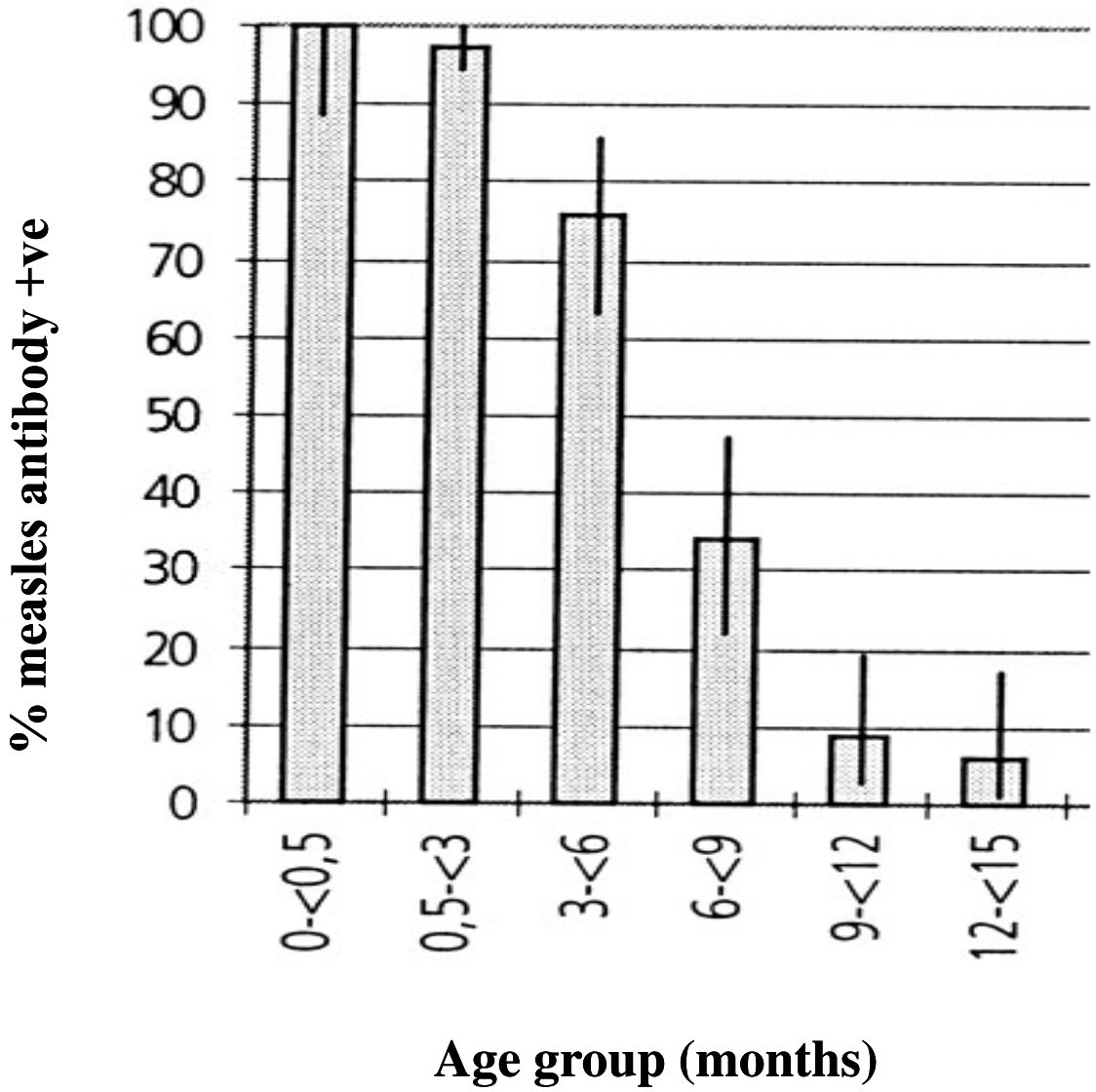
Post-natal immune response

- Initial T_H2 polarisation
- Increasing T_H1 response with age
- Hygiene hypothesis

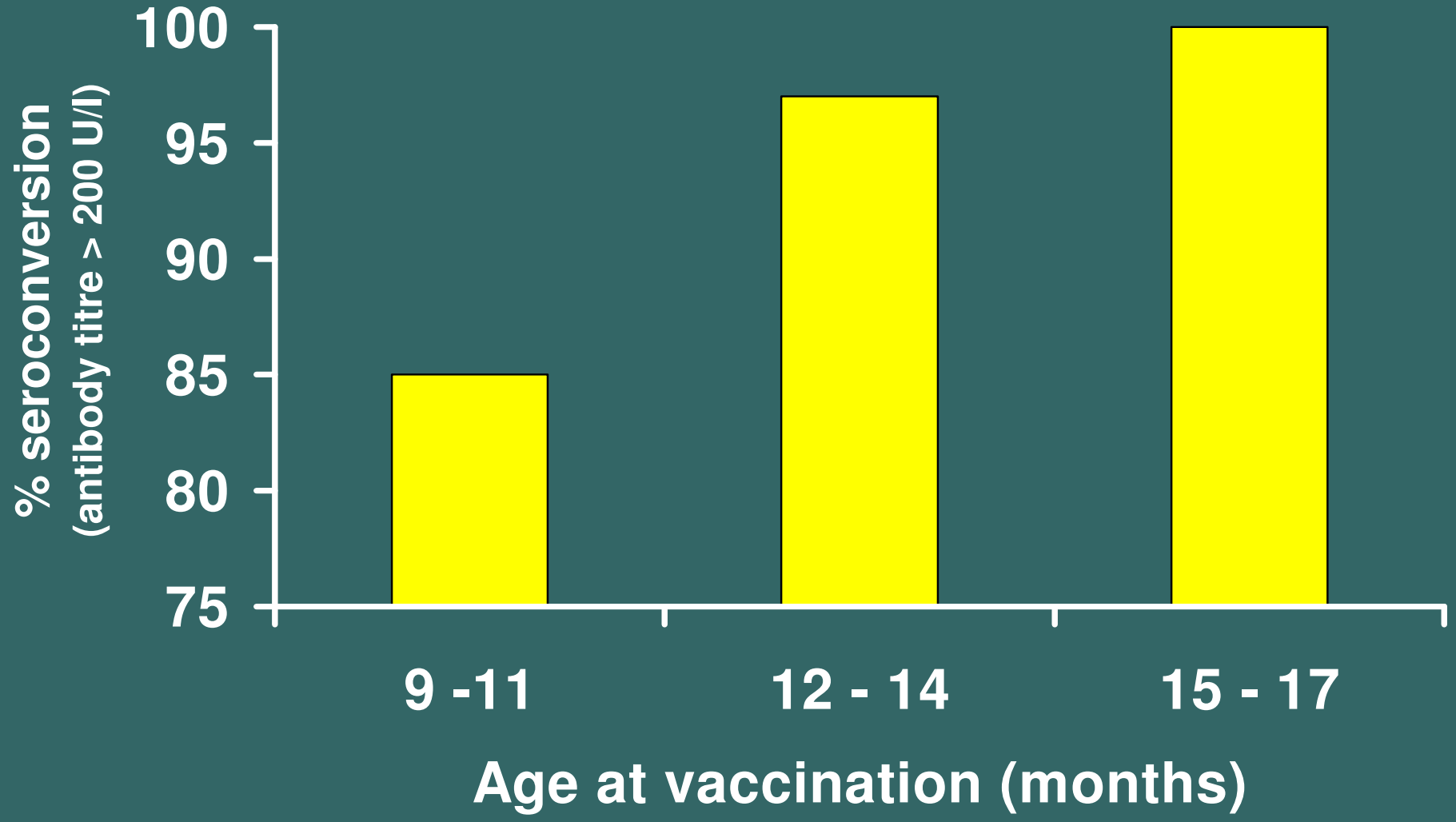
Maternal IgG antibody

- Protects against infection
- Active transport across placenta
- May interfere with immunisation

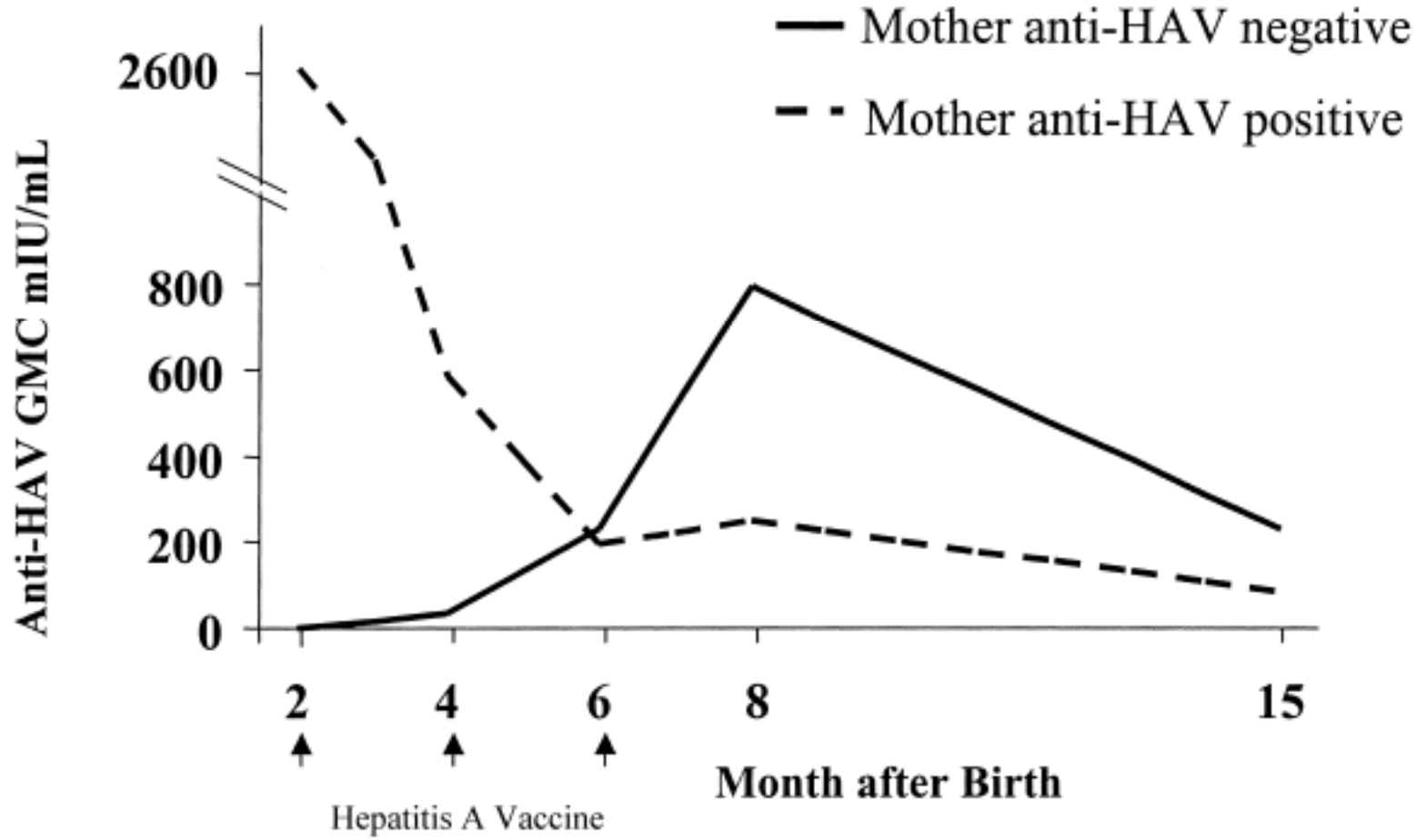
Maternal measles antibody



Measles vaccination and age



Maternal hepatitis A antibody and infant response to vaccination



Exceptions

- **Maternal antibody not completely protective:**
  - **RSV**
  - **Pertussis**

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IMMUNIZATION AND ANTIBODY RESPONSE IN THE NEWBORN INFANT

I. Pertussis Inoculation within Twenty-four Hours of Birth

R. William Provenzano, M.D., † Leslie H. Wetterlow, B.S.,‡ and Charles L. Sullivan, M.D.§
CAMBRIDGE AND BRIGHTON, MASSACHUSETTS

Pertussis-containing vaccine 6 to < 24 hours after birth

(Provenzano et al 1965)

- **Group 1** **P+P+P @ 3 week intervals**

  ***then* 2 x DTPw @ 4 week intervals, 1 month post**

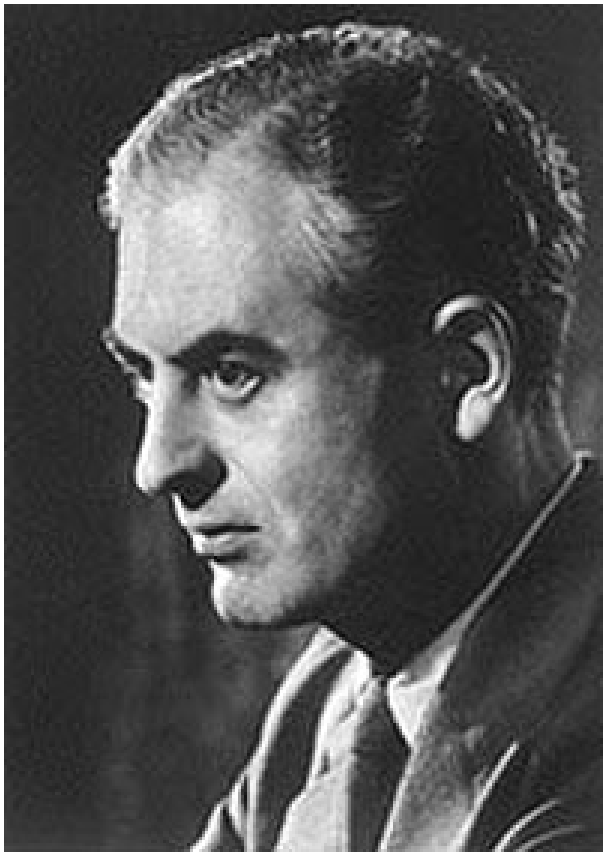
- **Group 2** **3 x DTPw @ 1 day, 1 month, 2 months**

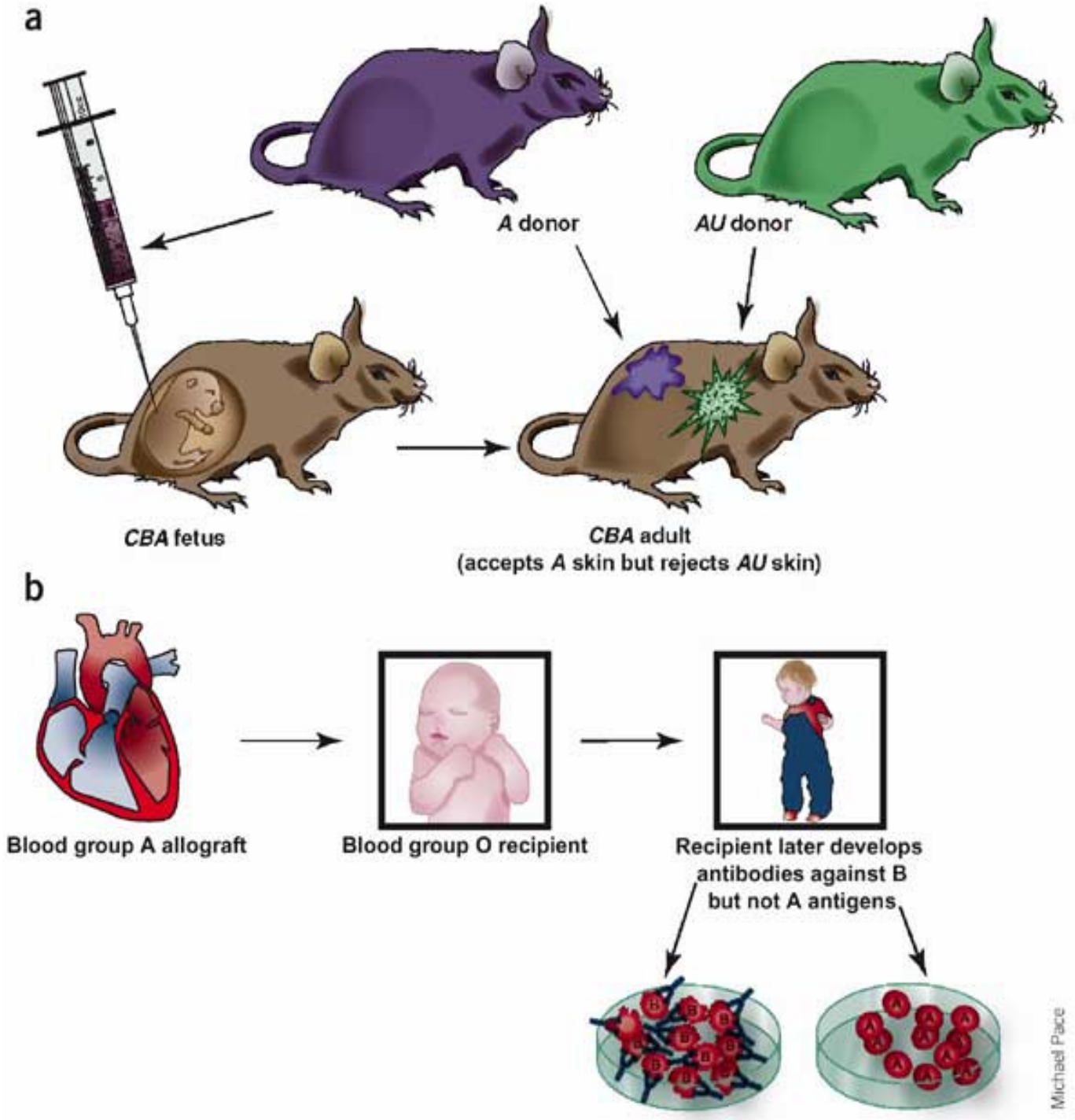
- **Boosters with DTPw @ 12 and 24 months**
- **N= 23**

Immunological paralysis

- Immune response to pertussis suppressed in 75% of infants up to 5 months of age
- in about 50% to age 15 months
- Suggests “immunologic paralysis”
- Induced by early immunisation

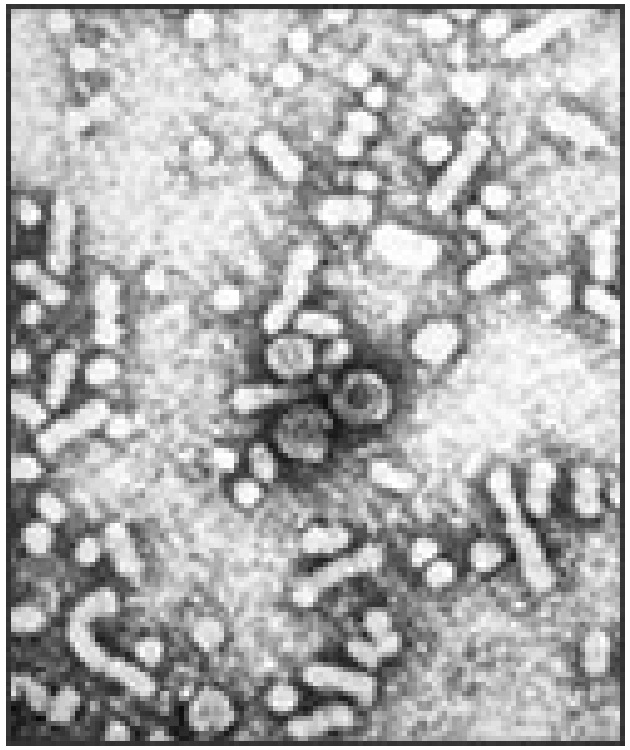
Tolerance: Burnet & Medawar




a
A donor
AU donor
CBA fetus
CBA adult
(accepts A skin but rejects AU skin)
b
Blood group A allograft
Blood group O recipient
Recipient later develops
antibodies against B
but not A antigens
Michael Pace

Hepatitis B

- Mother chronic carrier (HBeAg positive)
- Risk to baby: 85-90%
- HBs antigen, no Ab
- Tolerance
- Immune paresis



Neonatal hepatitis B immunisation

- Hepatitis B vaccine prevents 72% (60-80%)
- Vaccine + HB-Ig prevents 86 - 92% of cases
- Overcome tolerance, although vaccine just surface antigen
- Adjuvant


NAPA
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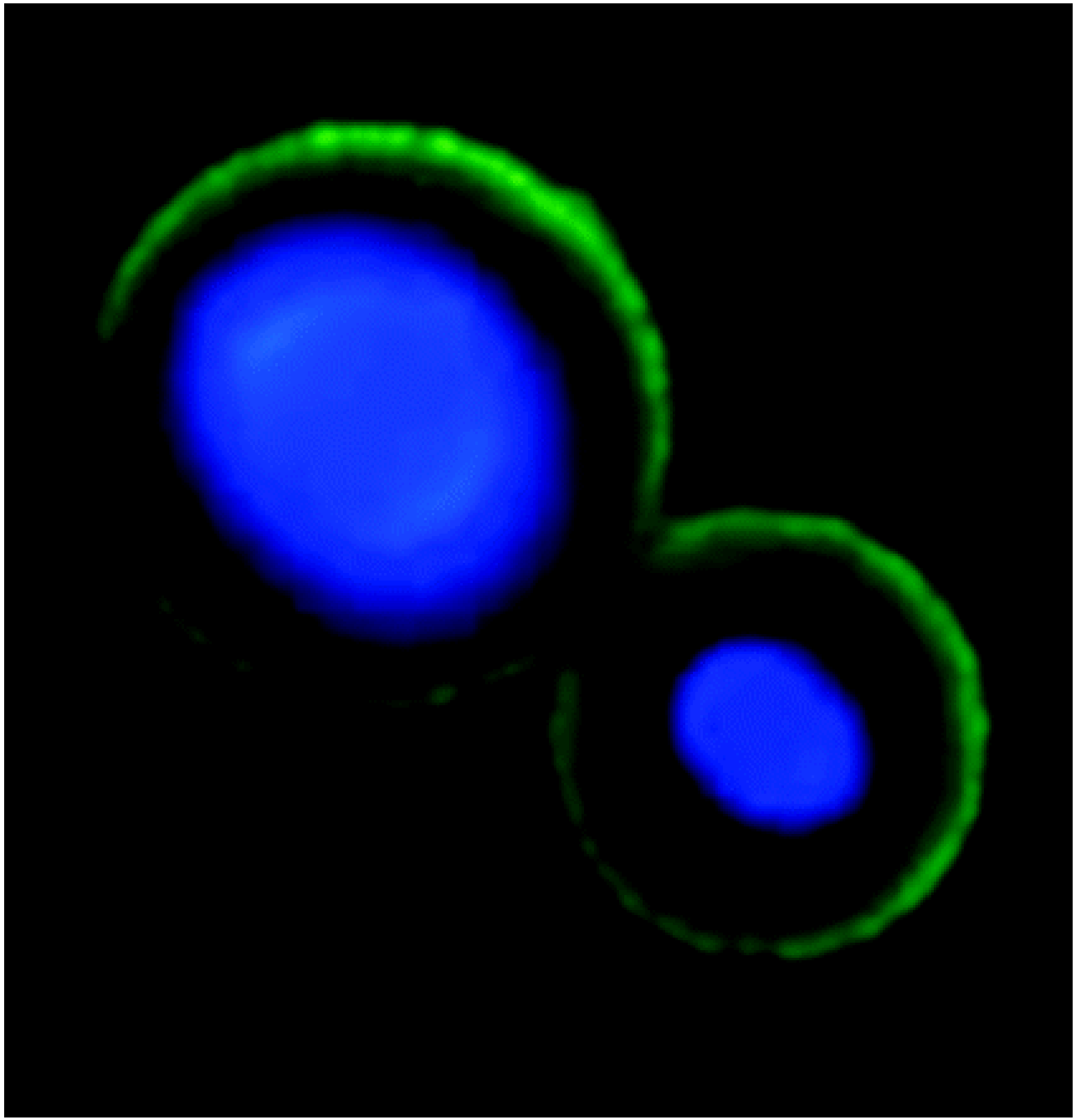


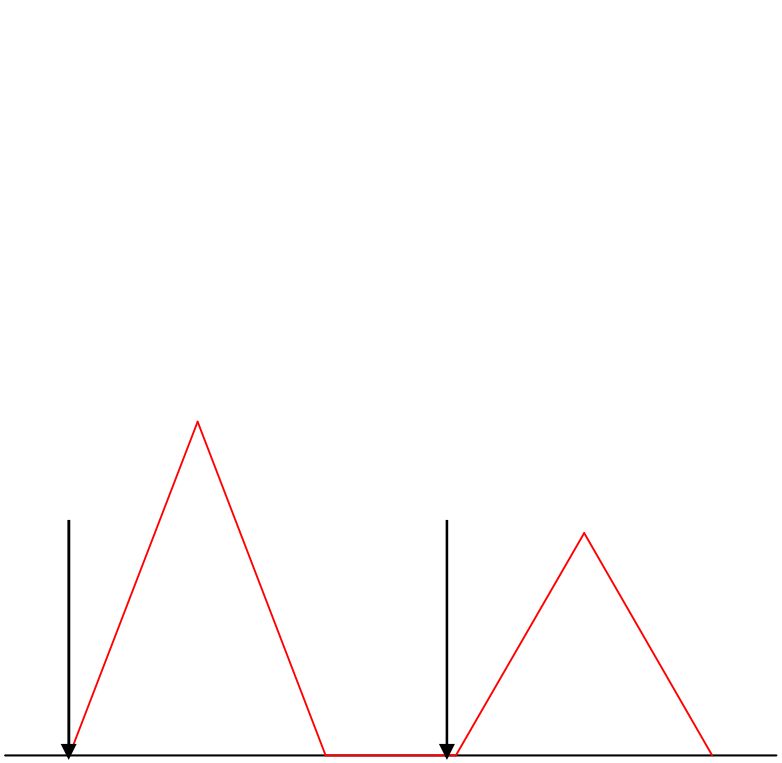
Polysaccharide

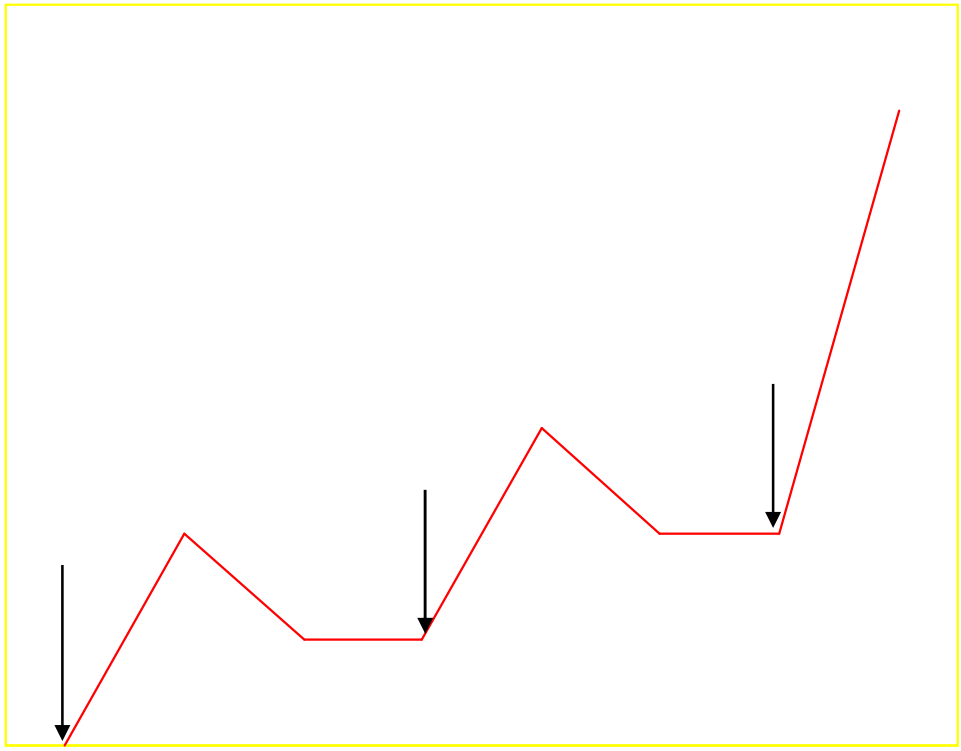
- Outer capsule: sugar
- GBS, *E.coli* K1
- Hib, pneumococcus, meningococcus
- No or very poor antibody response to polysaccharide as vaccine until >18 months

Conjugate vaccines

- Hapten principle
- Conjugate polysaccharide to protein
- Use immunogenic protein (diph, tet)

Polysaccharide vs conjugate vaccines





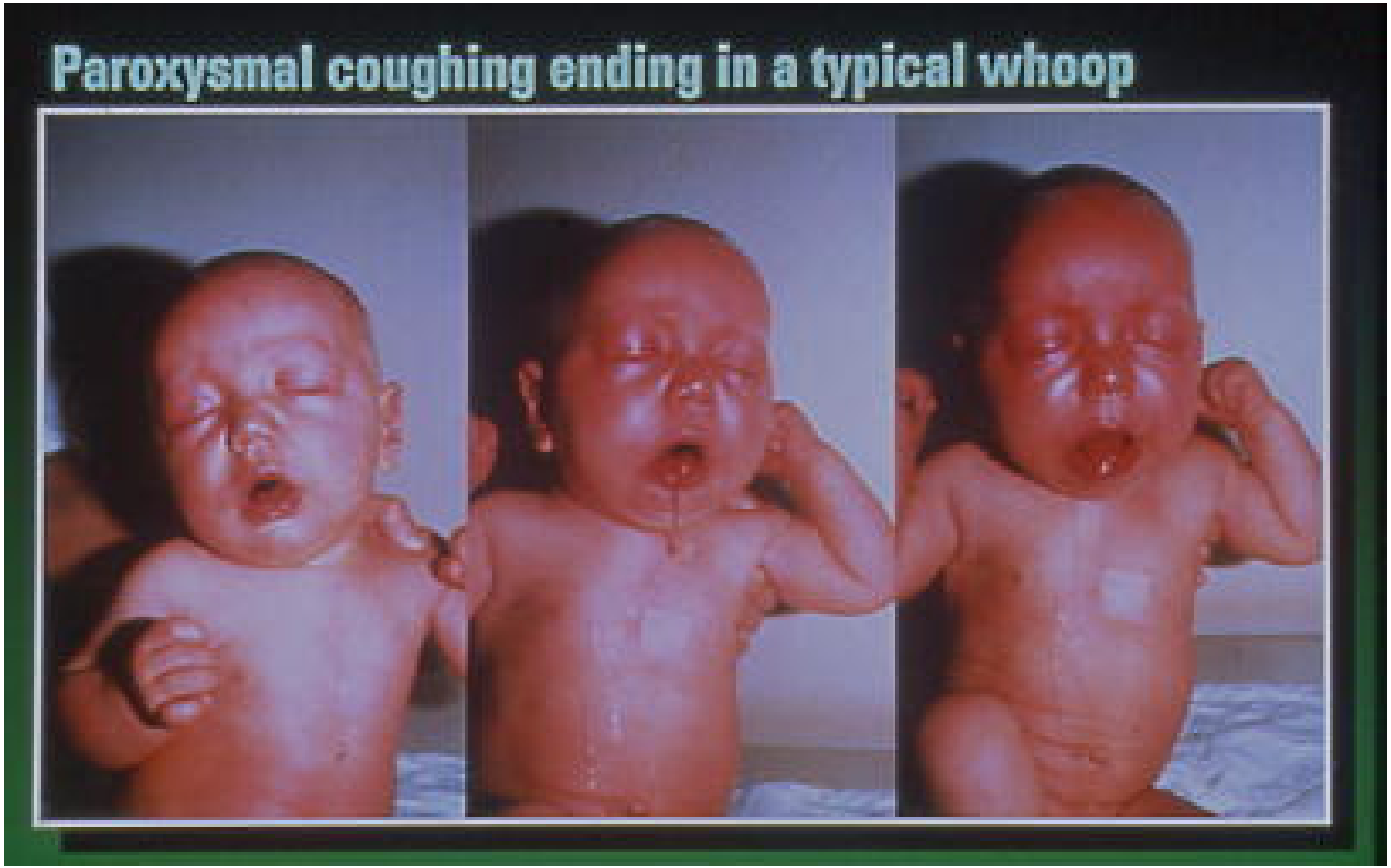
Polysaccharide

- T cell independent
- Hyporesponsiveness
- Transient immunity

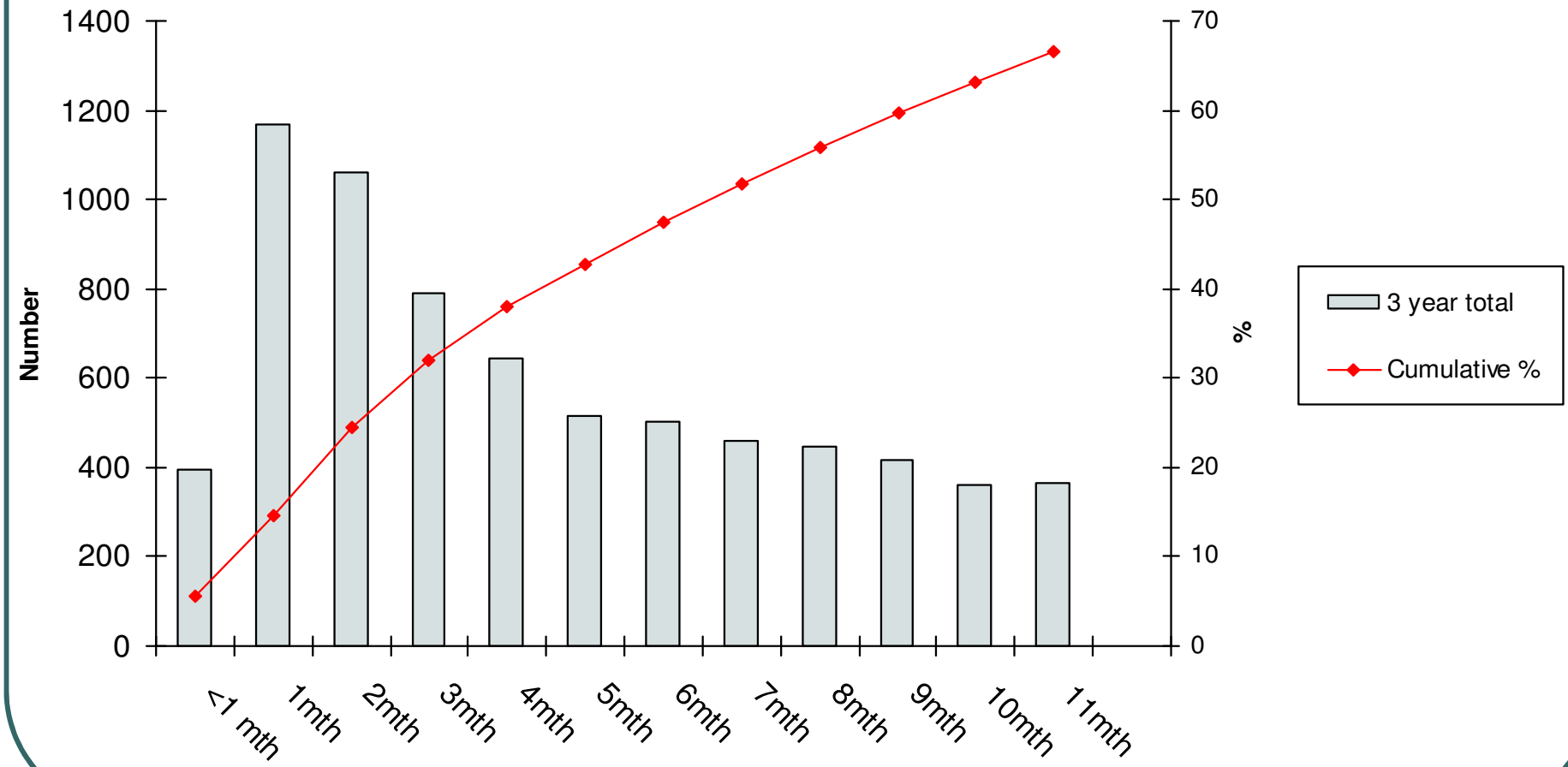
Conjugate

- T cell dependent
- Memory cells
- Lasting immunity

Pertussis – affects newborns



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



Sako et al JAMA 1945; 127: 379

Can a birth dose protect against pertussis?

Pertussis birth dose study

- Nick Wood
- Peter McIntyre

- NCIRS

Study design

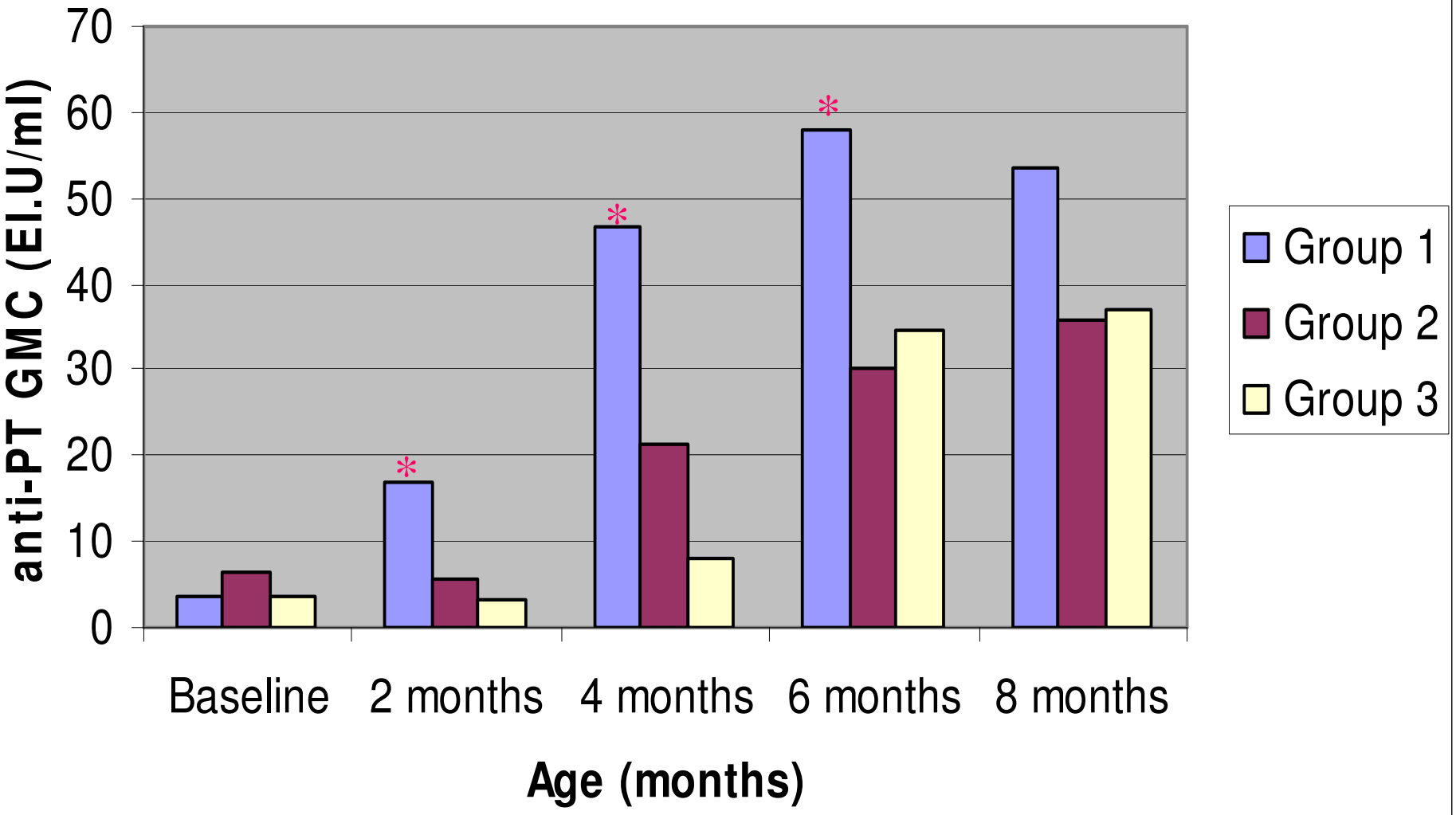
	Group 1 N= 27 (5 doses)	Group 2 N= 23 (4 doses)	Group 3 N=26 (3 doses)
Birth **(< 5 days old)**	**Pa*** Hepatitis B	**Pa*** Hepatitis B	Hepatitis B
1 month	**Pa***		
2 months	Infanrix Hexa Prevenar	Infanrix Hexa Prevenar	Infanrix Hexa Prevenar
4 months	Infanrix Hexa Prevenar	Infanrix Hexa Prevenar	Infanrix Hexa Prevenar
6 months	Infanrix Hexa Prevenar	Infanrix Hexa Prevenar	Infanrix Hexa Prevenar
8 months			

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

Serology

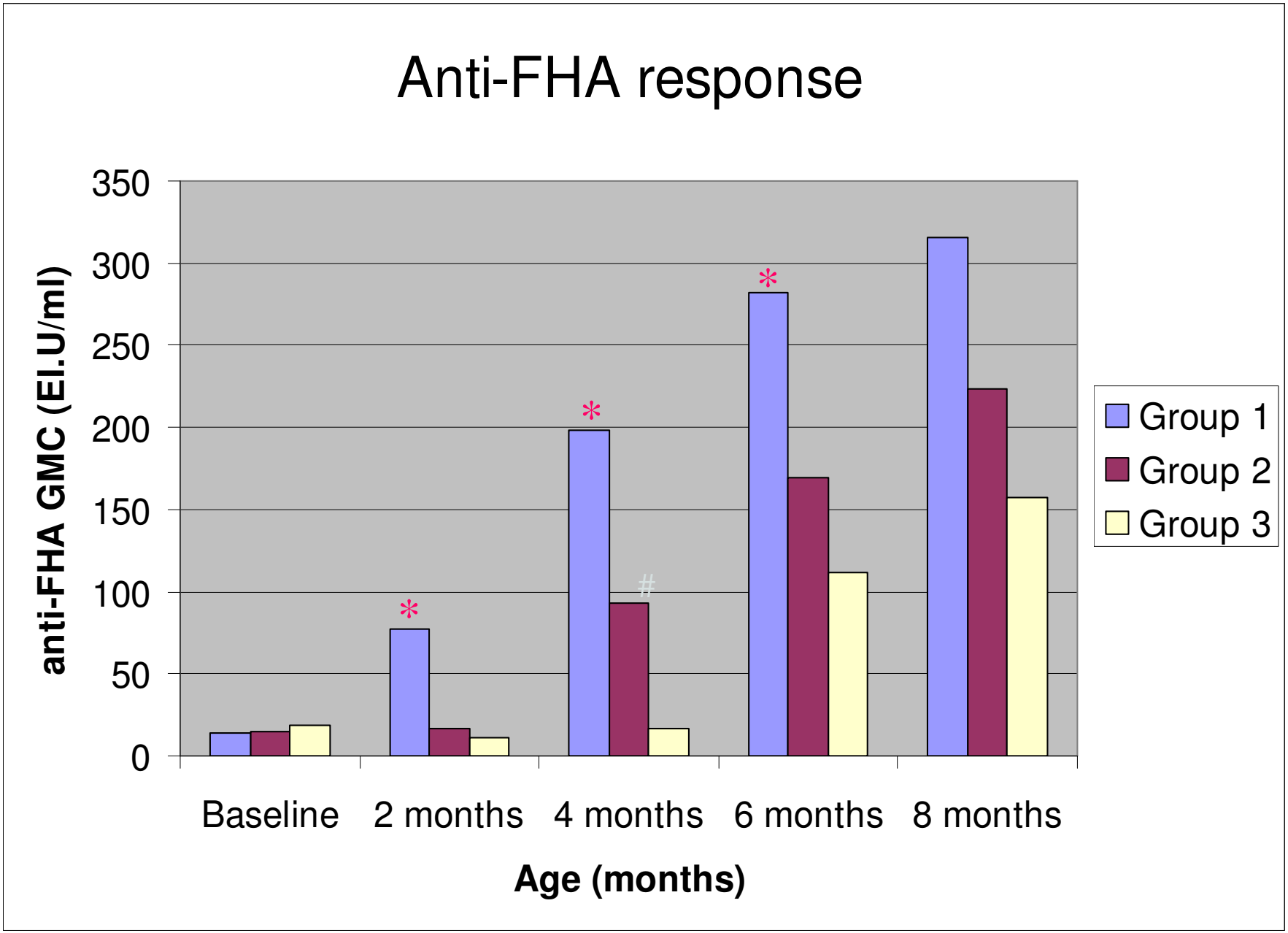
- Pertussis antibodies
  - PT
  - PRN
  - FHA
  - Mother – at birth of infant
  - Infant at 2, 4, 6 and 8 months old
- Hib, anti-HBs, diphtheria, tetanus
  - Infant – 8 months old

Anti-PT response



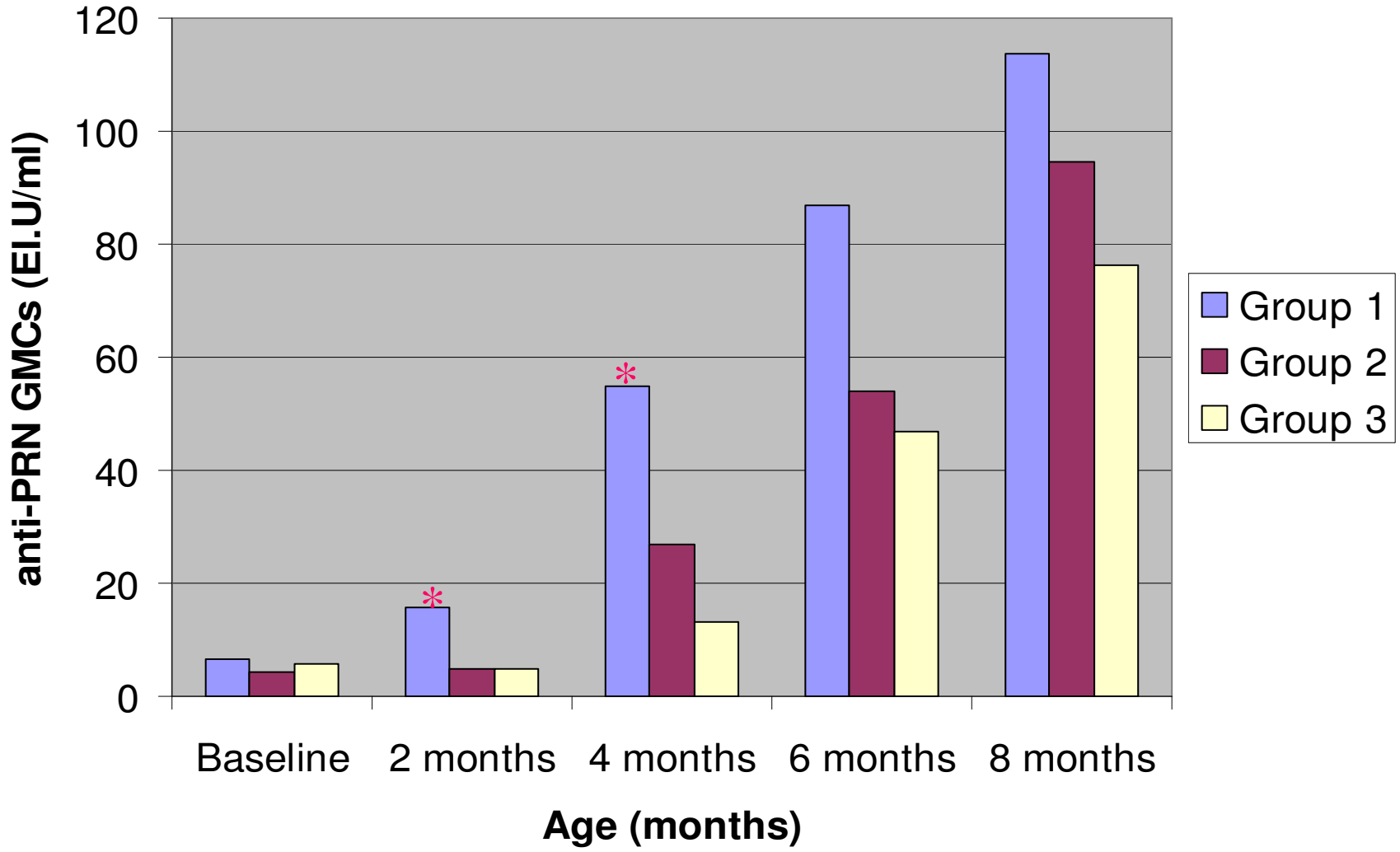
*Gp 1 vs Gp 2 and 3: P<0.05

(Group 1 = Pa at birth + 1m)



***Gp 1 vs Gp 2 and 3: P<0.05**

Anti-PRN response



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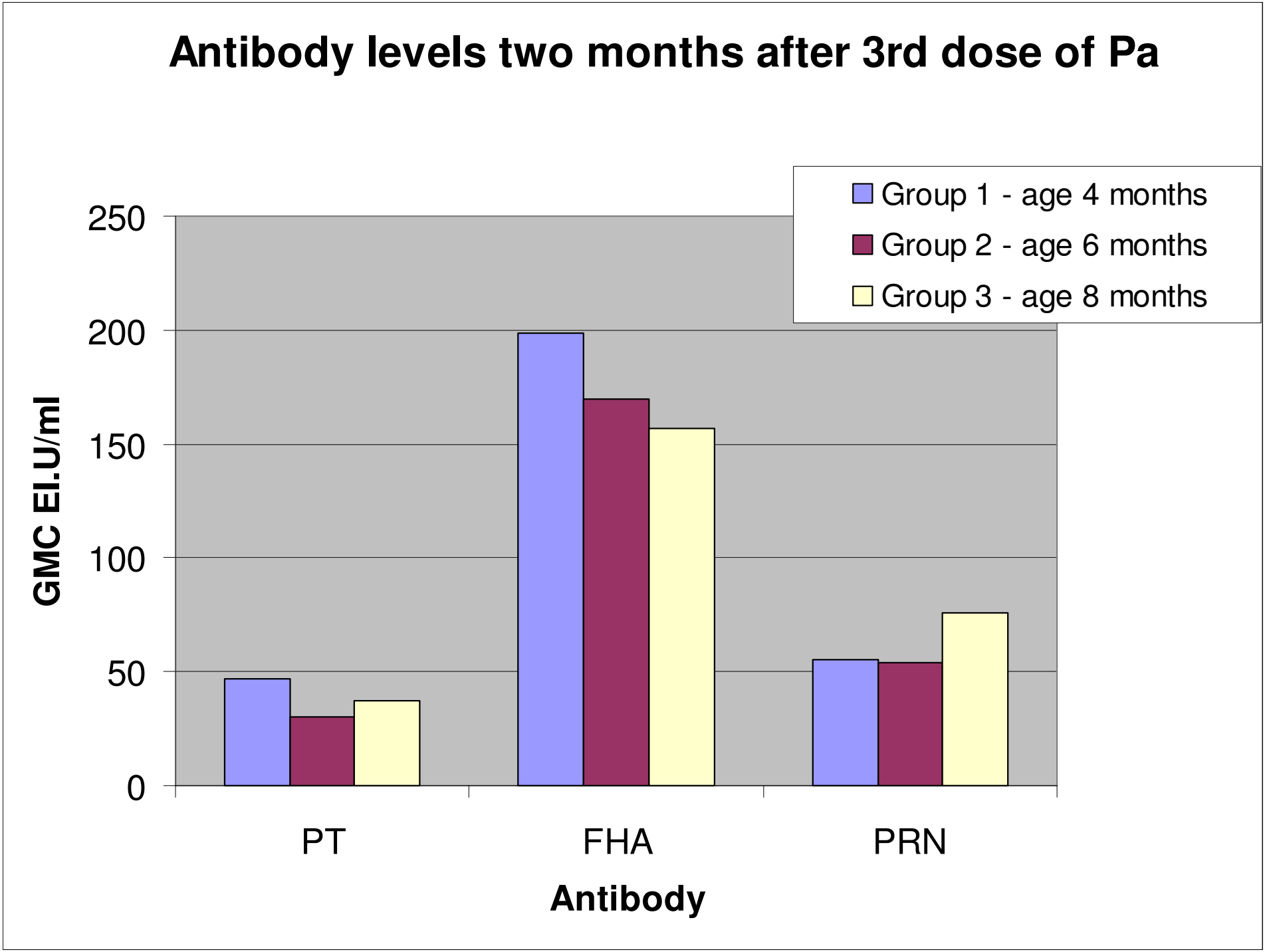
Antibody levels two months after 3rd dose of Pa
Group 1 - age 4 months
Group 2 - age 6 months
Group 3 - age 8 months
250
200
150
100
50
0
GMC EI.U/ml
PT
FHA
PRN
Antibody

What this study adds

- **Two doses Pa (birth and one month) is immunogenic by 2 months**
- **No hyporesponsiveness**
- **Could protect infants earlier**

Other studies of birth dose of Pa

- Possibility of reduced response later
- Need large randomised controlled trial
- NHMRC funded, recruiting

Conclusions: neonatal vaccines

- Newborn T_H1 cell response reduced
- Maternal antibodies can interfere
- Tolerance
- Dendritic cells and Toll-like receptors
- Adjuvants
- Birth dose pertussis vaccine

The future

- Further studies of neonatal vaccines
- Ways of improving the neonatal immune response: e.g. new adjuvants, new routes
- Dendritic cells and Toll-like receptors
- New vaccines: RSV, HIV

Acknowledgements

- Nick Wood
- Claire –Anne Siegrist
- Melanie Wong