Immune System Development in Pediatrics

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wellcome

10 Immune Characteristics of Early Life…

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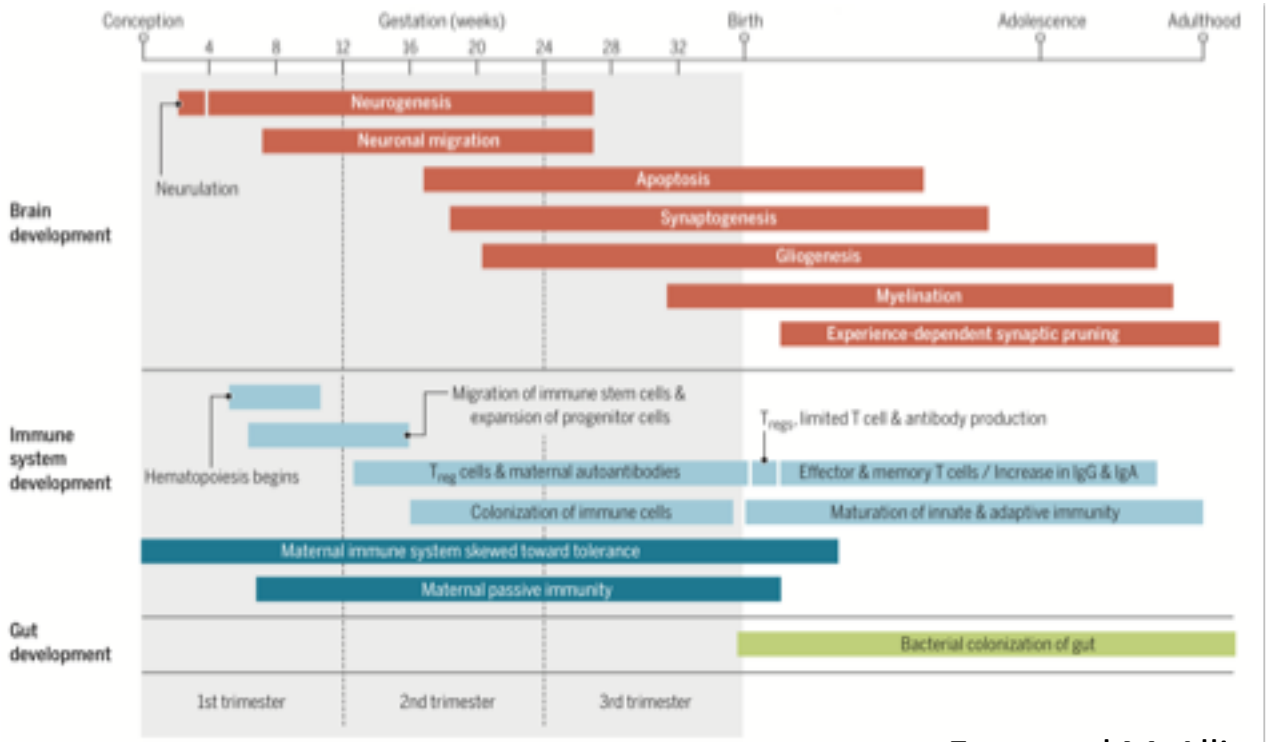
1. Early life is a developmentally sensitive period for immune ontogeny



Estes and McAllister, Science 2016

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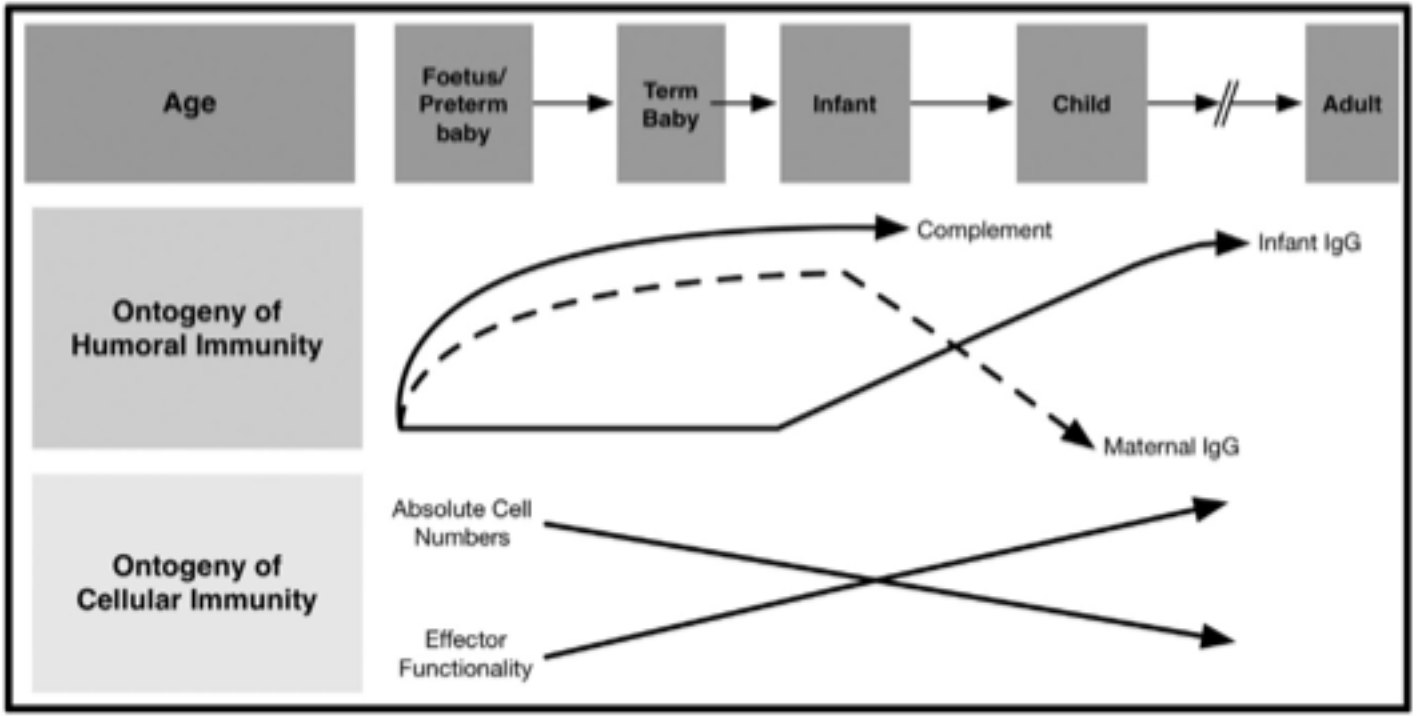
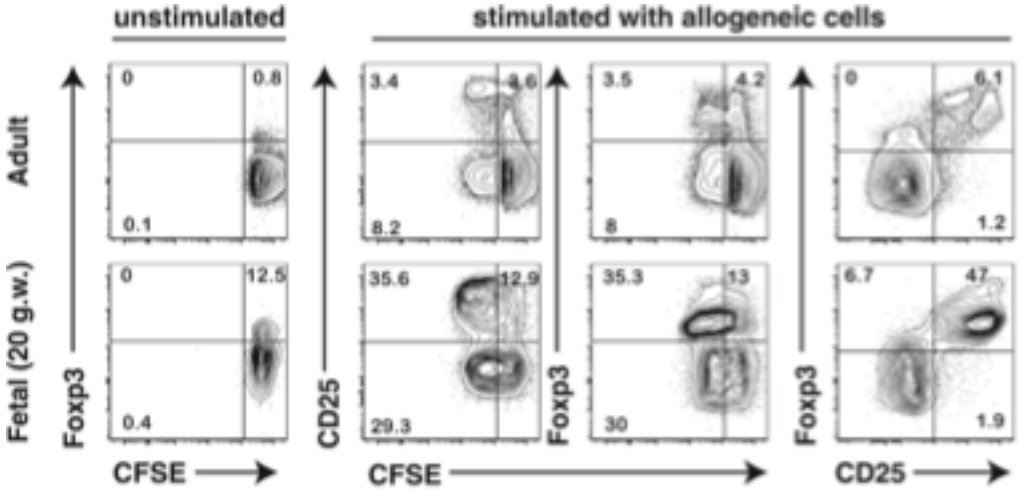


Goenka and Kollmann, J Infect 2015

2. Early life is tolerogenic…

- Increased frequency of Tregs
  - Functionally enhanced compared to adults
- CD71+ erythroid precursor cells
  - Deplete L-arginine, needed for T-cell function
- High circulating adenosine – anti-inflammatory
  - High CD73, alkaline phosphatase
  - Low adenosine deaminase

Naïve T-cells from 18-24 wk mesenteric lymph nodes, mixed lymphocyte reaction

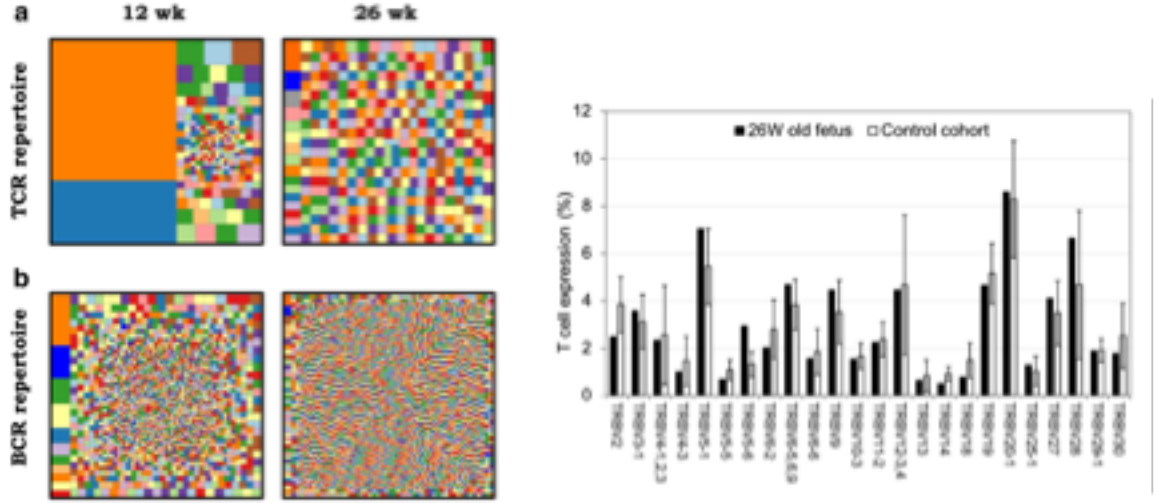


Different gene expression pattern
Arise from distinct HSC lineages

Mold JE *et al.*, Science 2010

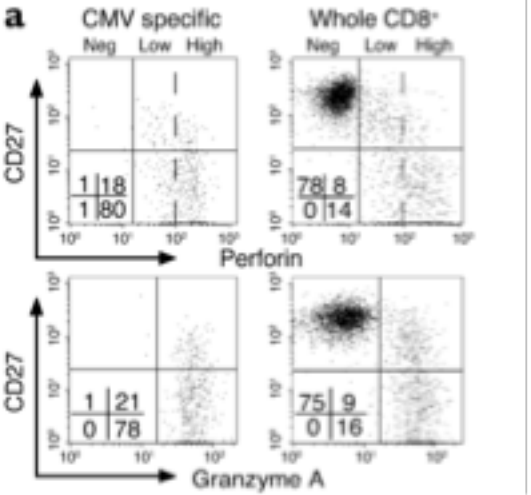
…but there is a robust and functional fetal immune repertoire

VDJ recombination from 8 weeks' gestation
Functional class switching and somatic hypermutation
By early T3, receptor diversity similar to healthy infants



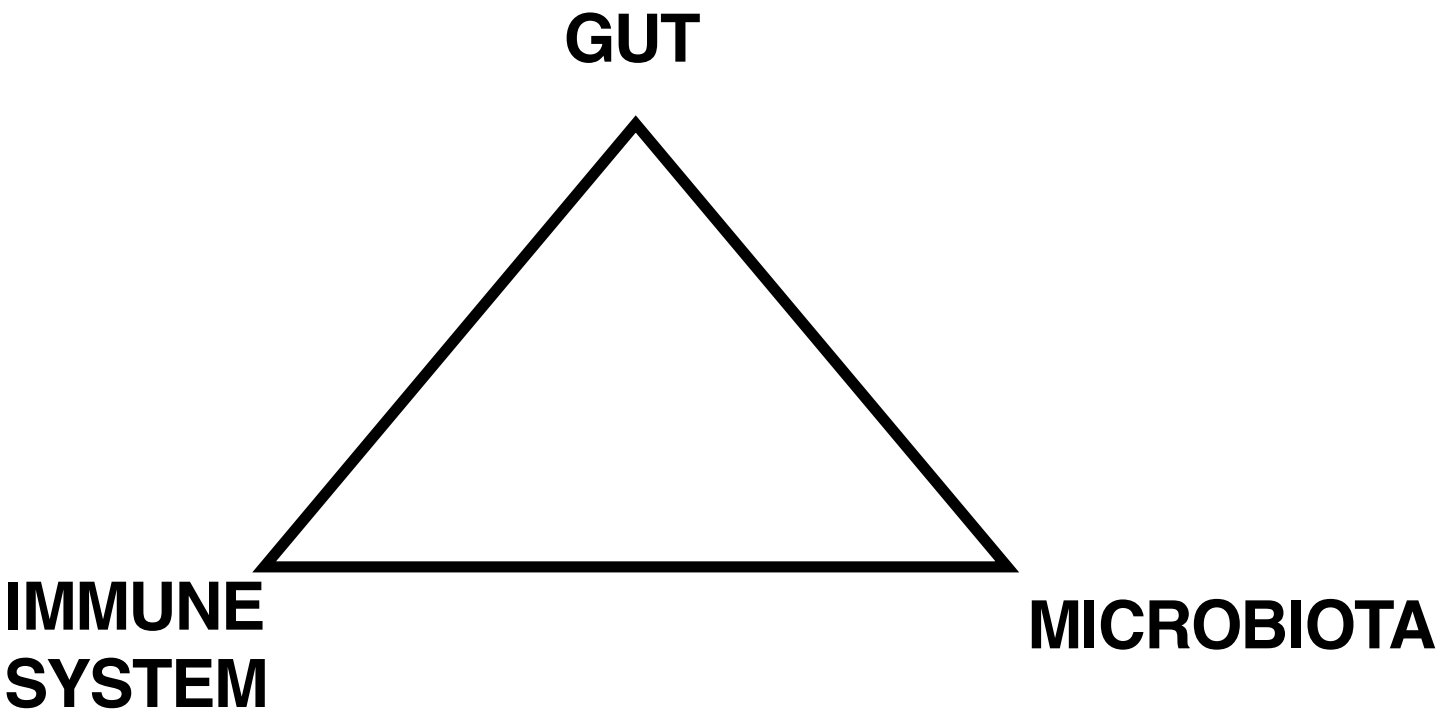
Rechavi and Somech, Semin Immunopathol 2017

cCMV infection: expansion and differentiation of mature CD8 T-cells, similar to adults

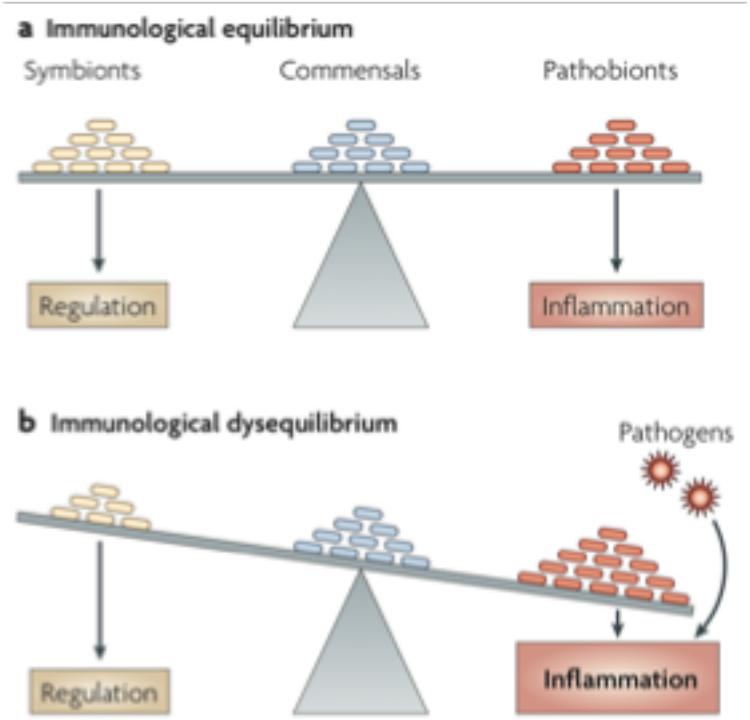


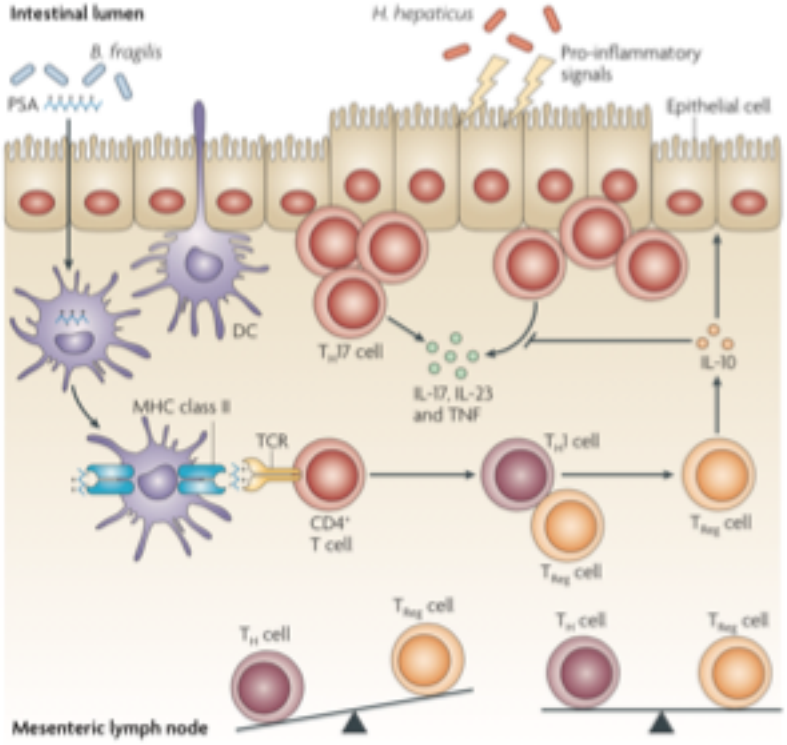
Marchant A *et al.*, J Clin Invest 2003

3. Immune, gut and microbiota development occur in tandem



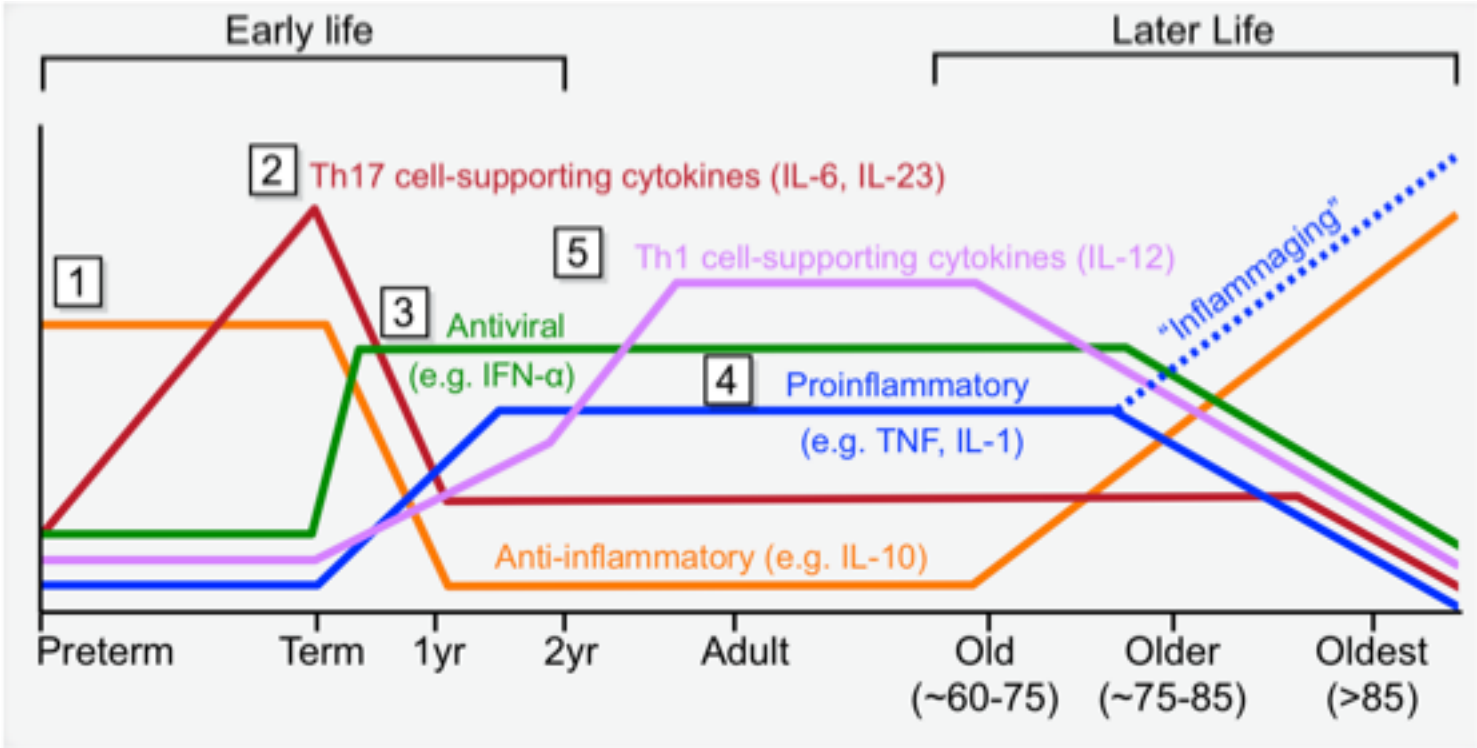
Bacterial colonization drives immune development and homeostasis





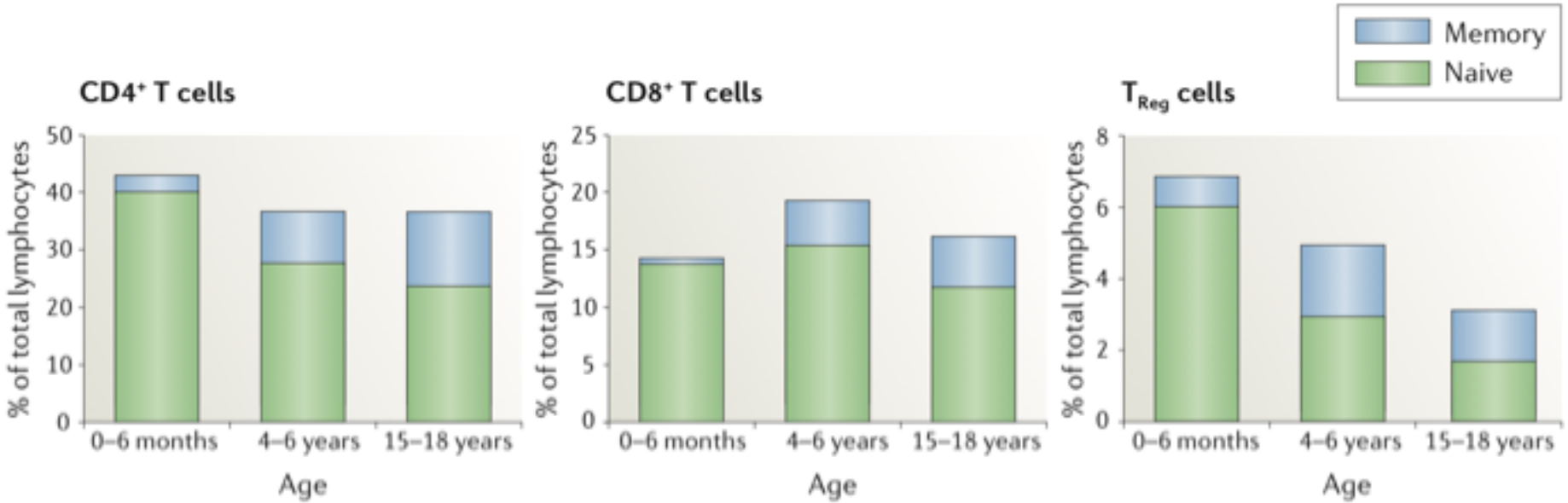
Round and Mazmanian, Nat Rev Immunol 2009

4. A programmed pattern of immune development occurs over time



Kollmann TR *et al.*, Immunity 2012

5. Adaptive immunity is naïve, leading to greater dependence on innate immunity



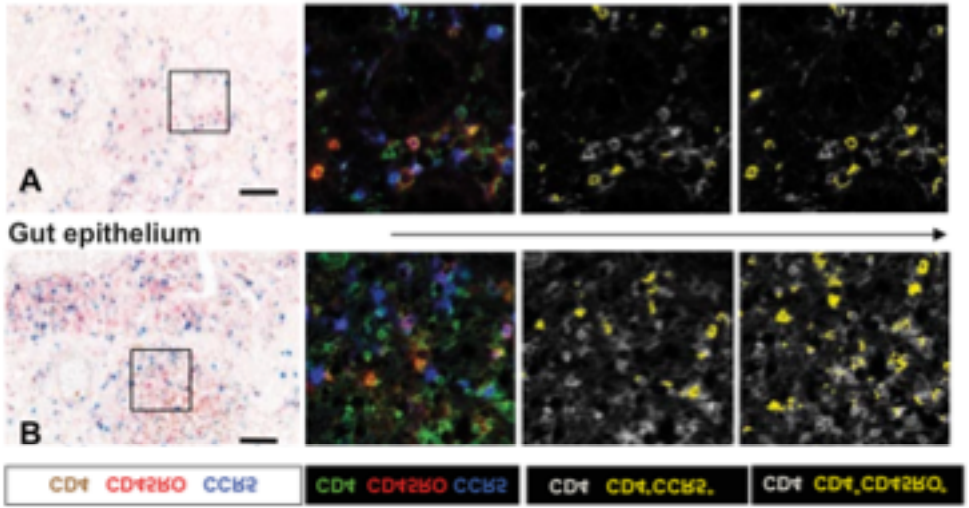
- Few effector memory T cells (and CD27+ B cells), different homing receptors, highly proliferative and apoptotic, reduced tissue-resident memory (TRM) cells

Dowling and Levy, Trends Immunol 2014

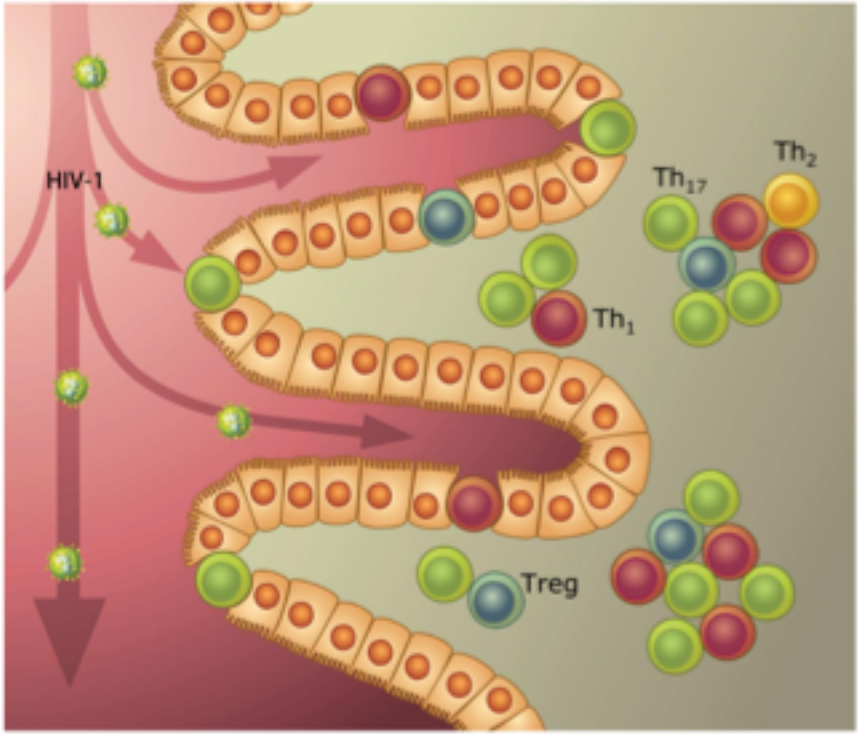
Prendergast AJ *et al.*, Nat Rev Immunol 2012

Infants have an abundance of target cells for HIV in the gut

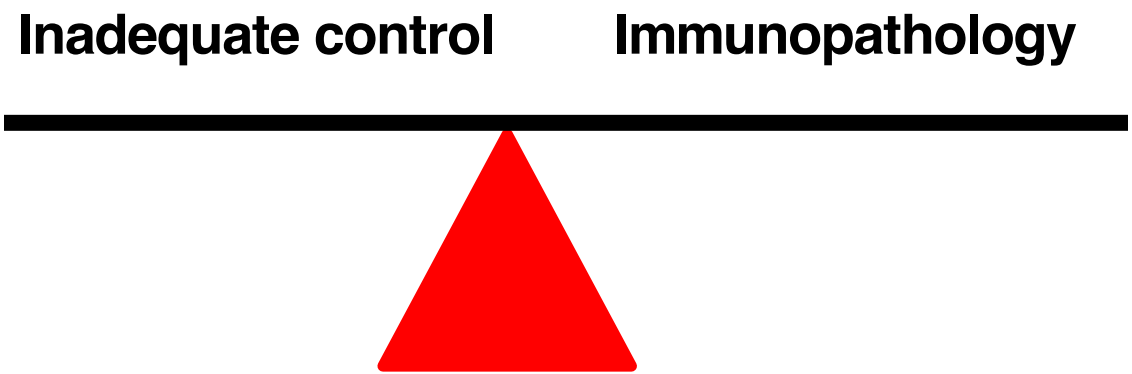
- Large pool of CD4+CCR5+ memory T-cells in infant gut mucosa, but not LN/cord blood
- Highly susceptible to HIV infection



Bunders M *et al.*, Blood 2012



6. Outcomes of infections are highly age-dependent



Prendergast AJ *et al.*, Nat Rev Immunol 2012

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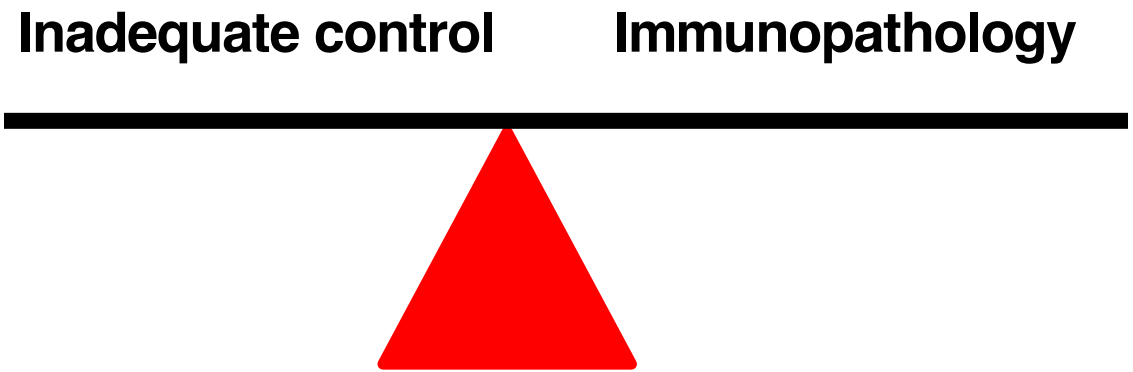
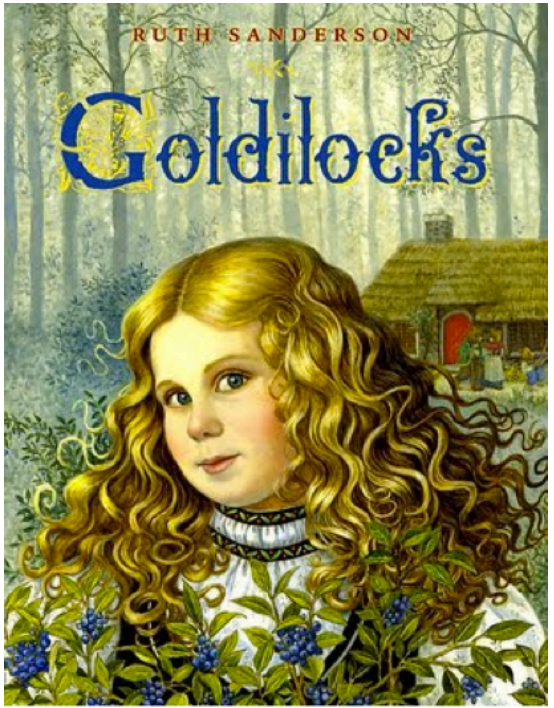
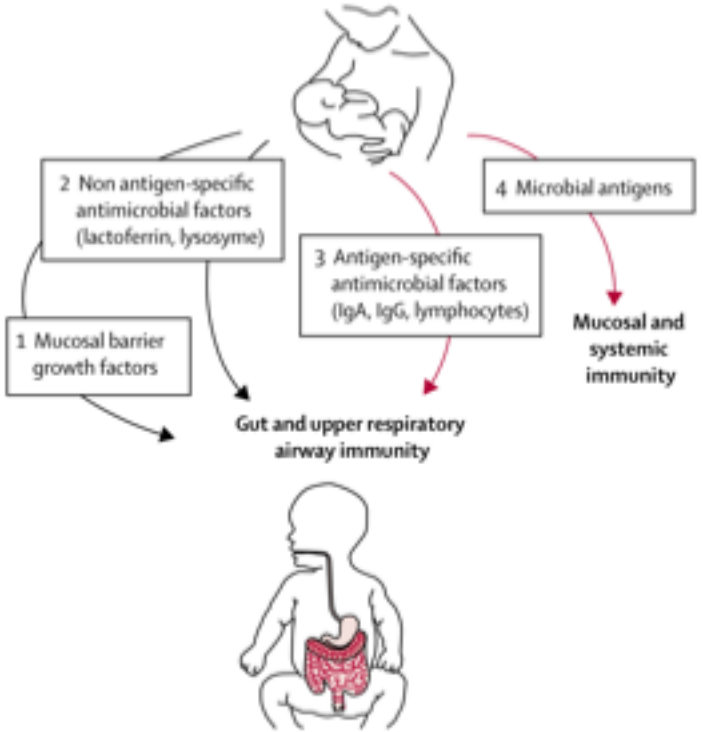


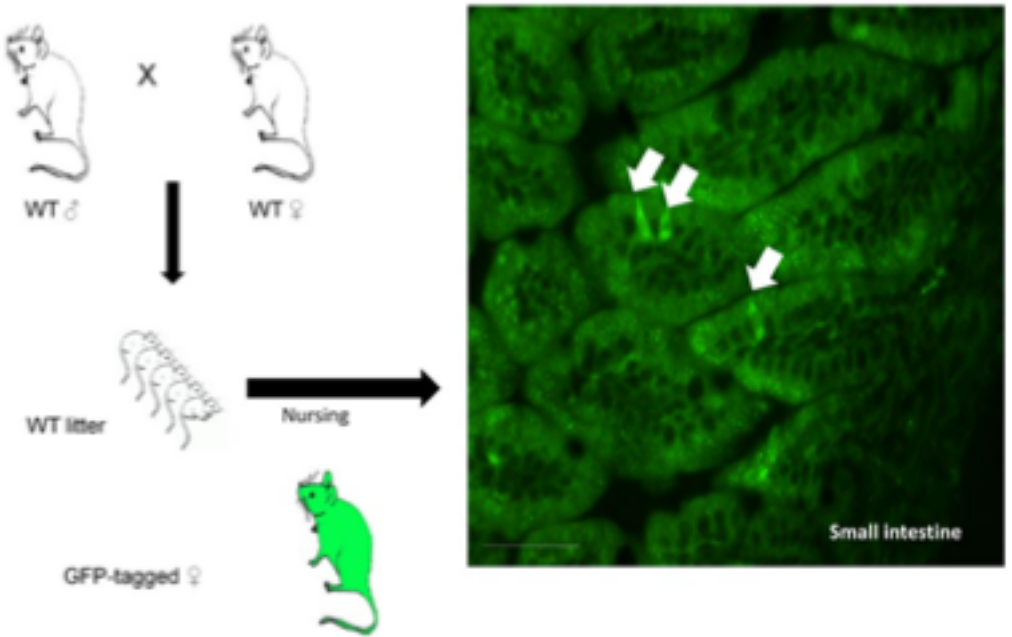


Prendergast AJ *et al*., Nat Rev Immunol 2012

7. Infant immunity is shaped by and shared with the mother

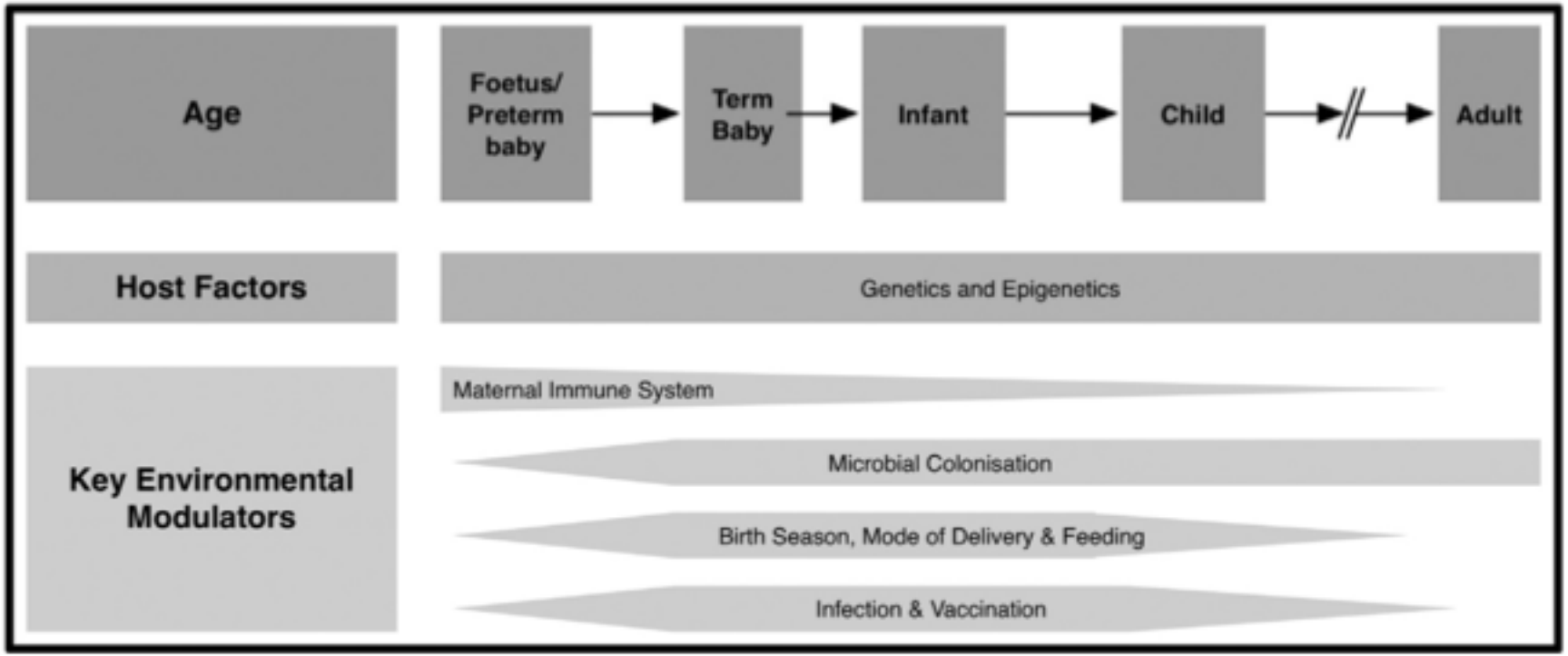


"Common maternal and infant mucosal immune system"



Moles J-P *et al.*, Pediatr Allergy Immunol 2017

8. Environmental exposures shape immune development



Goenka and Kollmann, J Infect 2015

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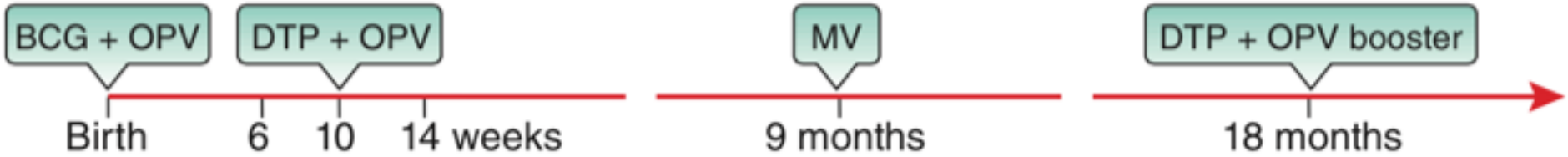

Aaby P *et al*., Nat Immunol 2014

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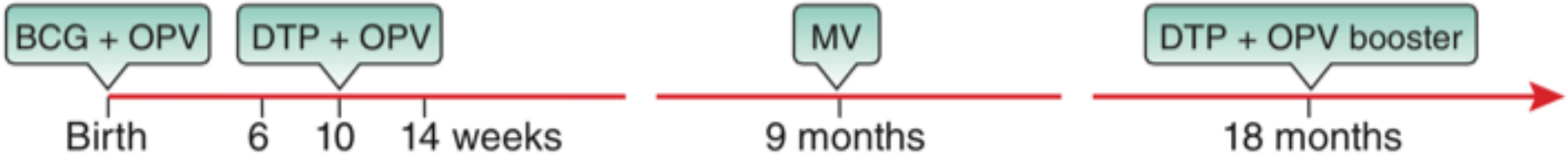

Table 2 Mortality after immunization with the BCG vaccine

Follow-up period	MRR Small RCT	MRR Large RCT	Combined MRR
3 days	0.17 (0.02–1.35)	0.49 (0.21–1.15)	0.42 (0.19–0.92)
4 weeks	0.18 (0.06–1.37)	0.55 (0.34–0.89)	0.52 (0.33–0.82)
12 months	0.41 (0.14–1.18)	0.83 (0.63–1.08)	0.79 (0.61–1.02)

Aaby P *et al.,* Nat Immunol 2014

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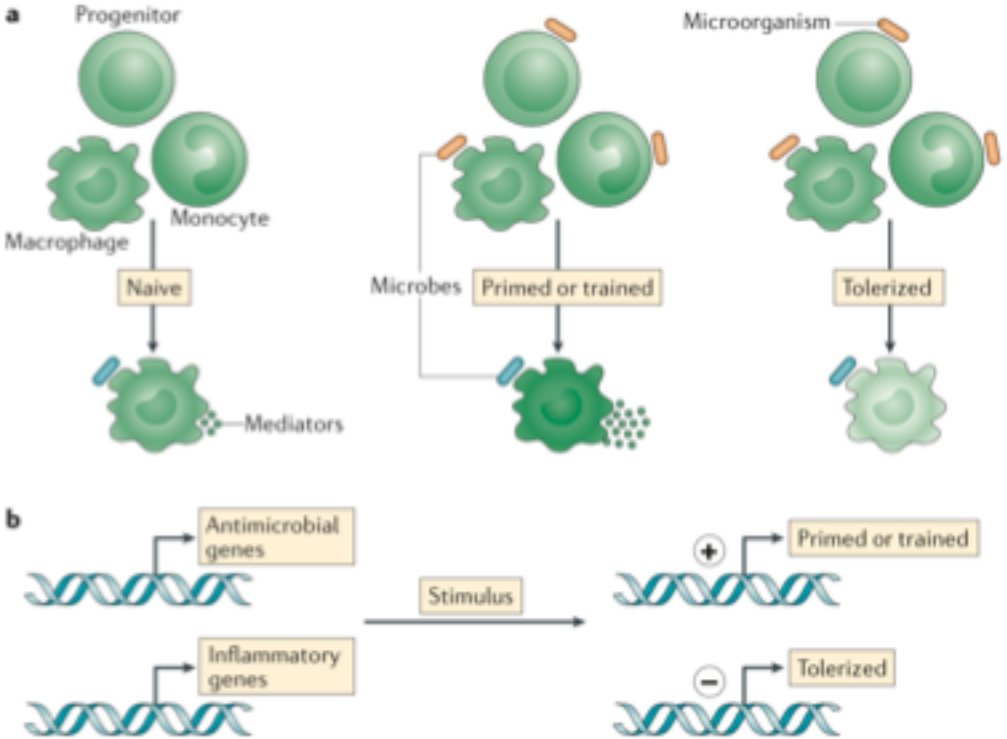
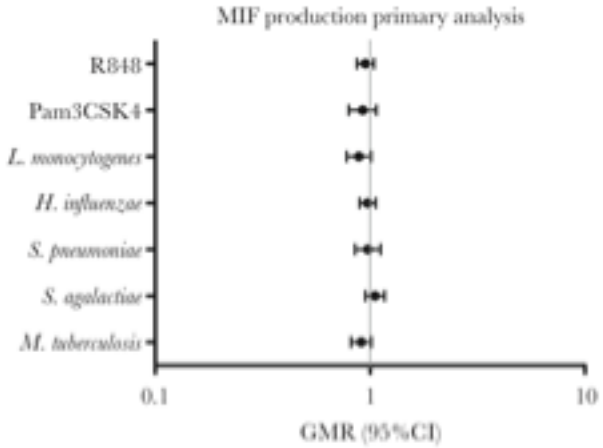


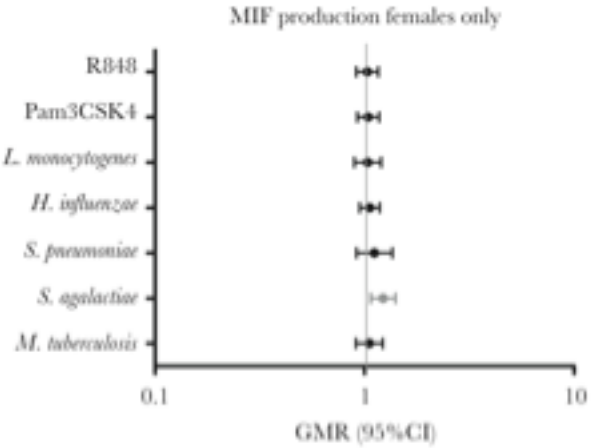
Goodridge HS *et al.*, Nat Rev Immunol 2016

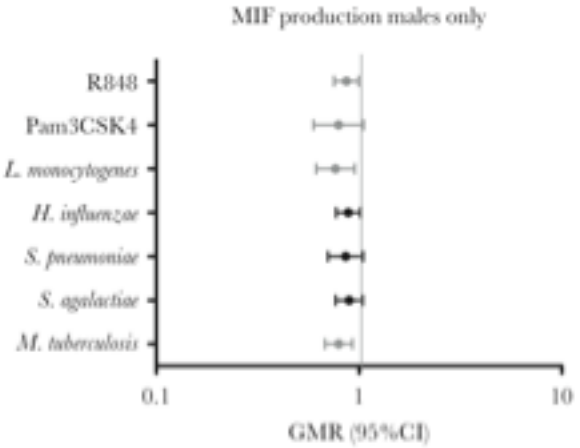
9. Boys and girls are not the same immunologically

Infants randomized to BCG or no BCG
Production of macrophage migration inhibitory factor (MIF) differed by sex

BCG vaccination →

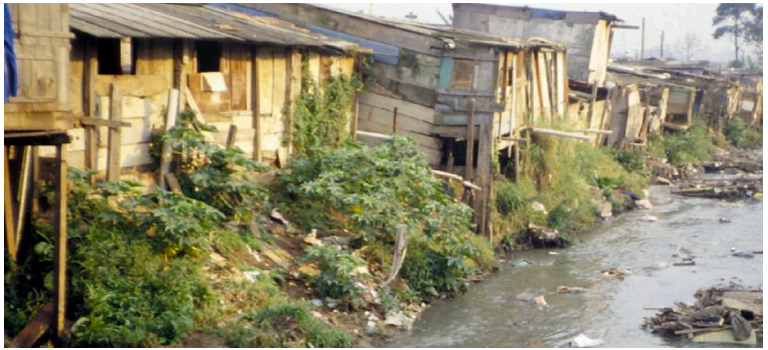






Freyne B *et al*., J Infect Dis 2018

10. The immunological battleground in developing countries is different



- Higher prevalence of preterm and LBW
- Co-infections
- Environmental exposures including toxins
- Seasonality

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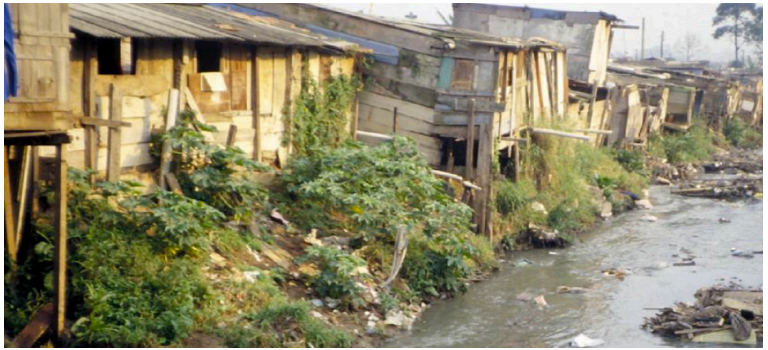

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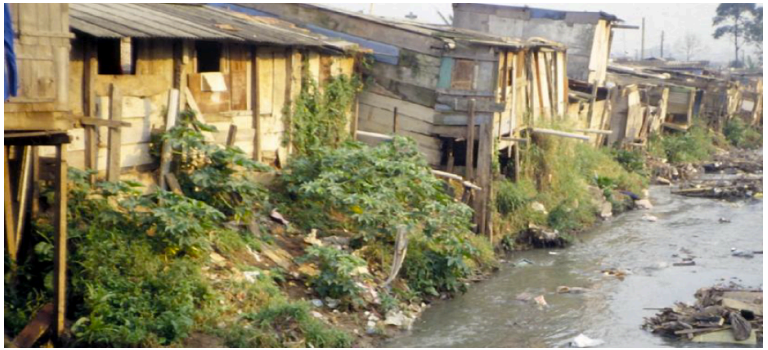
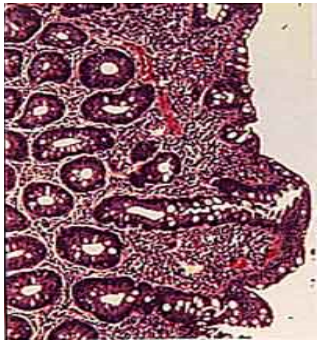
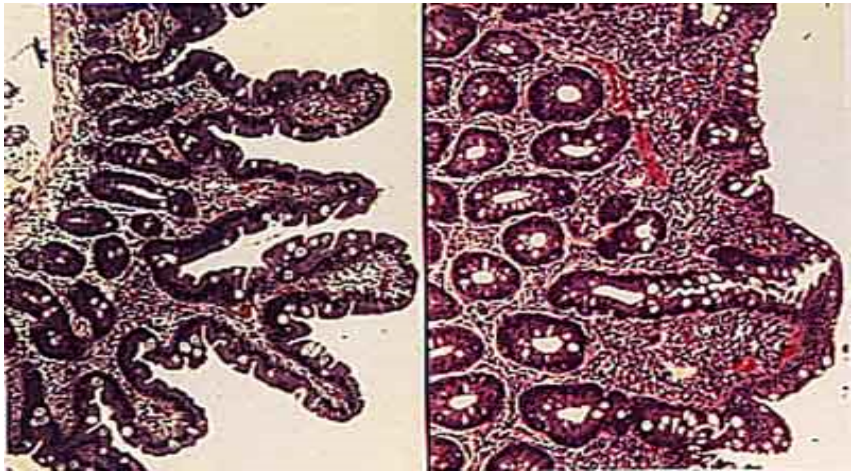




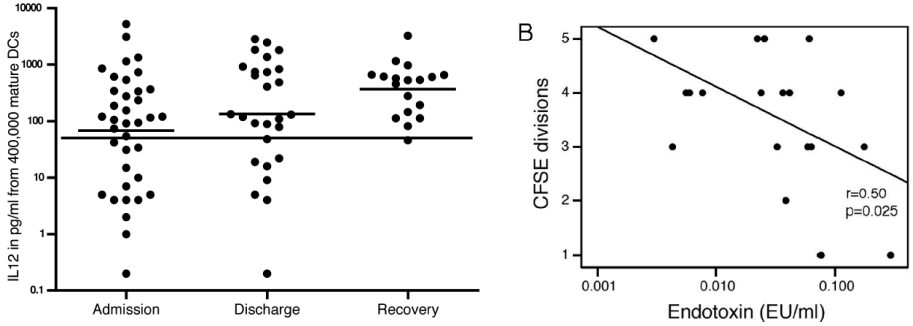
Environmental enteropathy is almost universal in developing countries

Chronic intestinal inflammation
Impaired barrier function
Microbial translocation



Dendritic Cell Anergy Results from Endotoxemia in Severe Malnutrition[1]

Stephen Miles Hughes,[2]*†‡§ Beatrice Amadi,‡ Mwiya Mwiya,‡ Hope Nkamba,§ Andrew Tomkins,† and David Goldblatt*



Hughes SM *et al.*, J Immunol 2009

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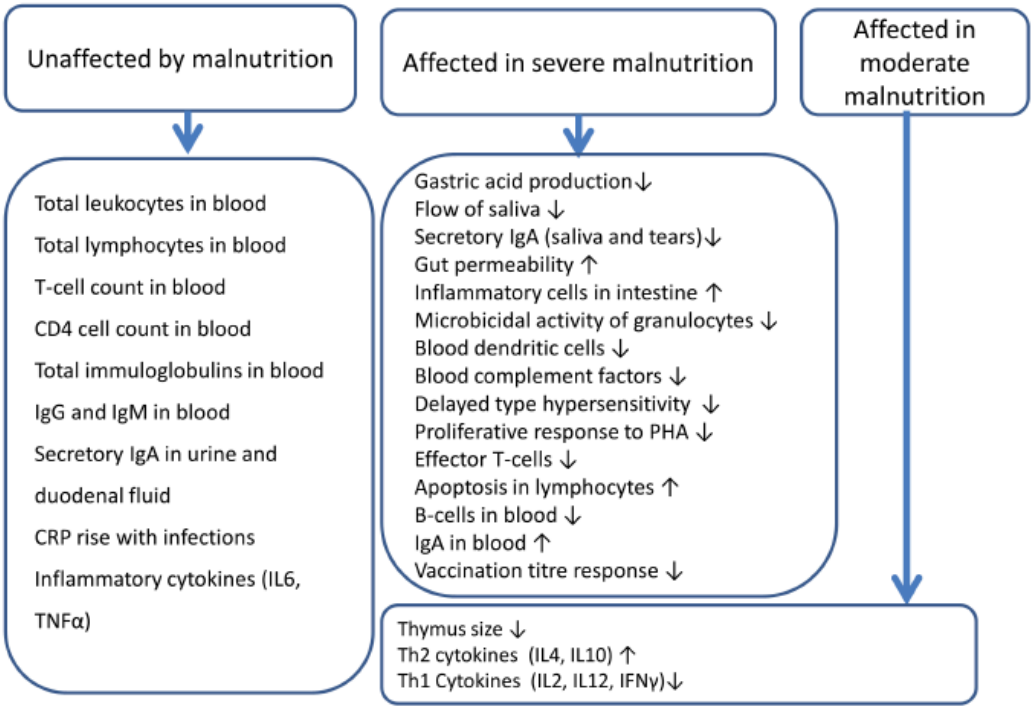
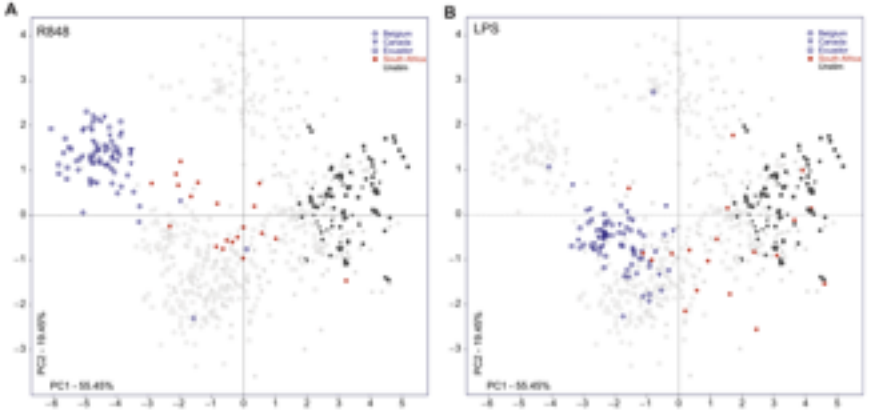


- Generally good rates of protection from protein and polysaccharide vaccines
  - Titres may be lower in malnutrition
- Responses to T-cell dependent (live) vaccines may be suboptimal

Rytter M *et al.,* PLOS One 2014

10. The immunological battleground in developing countries is different

	Belgium	Canada	Ecuador	South Africa
N	14	20	43	20
Infant characteristics				
Mean age (mo), mean ± SD	24.7 ± 4.3	19.1 ± 0.8	26.7 ± 1.28	24.7 ± 0.6
Birth weight (g), mean ± SD	2996.2 ± 796.3	3339.6 ± 448.2	3475.1 ± 988.3	3018.4 ± 383.6
Birth mode (vaginal/c-section)	13/1	11/13	34/9	20/0
Gestational age, mean ± SD	38.4 ± 3.4	39.2 ± 1.5	38.9 ± 1.1	37.8 ± 2.4
Premature < 37 wk (% of total)	2 (14%)	1 (4.5%)	0 (0%)	3 (15%)
Weight (g), mean ± SD	13364.3 ± 1786.1	11190.9 ± 1392.5	11501.16 ± 1010.7	11205.0 ± 1300.7
Height (cm), mean ± SD	92.2 ± 4.6	82.2 ± 3.0	84.3 ± 2.5	84.4 ± 0.91
WAZ, mean ± SD	0.69 ± 1.2	−0.05 ± 0.9	−0.32 ± 0.93	−0.58 ± 0.95
LAZ, mean ± SD	1.56 ± 0.8	−0.30 ± 0.9	−0.78 ± 1.49	−1.07 ± 1.20
WLZ, mean ± SD	−0.18 ± 1.4	0.17 ± 1.0	0.16 ± 0.79	−0.03 ± 0.87



Smolen KK *et al.*, J Allergy Clin Immunol 2014

Summary

- Dynamic, adaptive programmed assembly throughout childhood
  - “Layered” immune development, specific functions at different ages
  - Tolerogenic early life, reduced Th1 responses, naïve cell predominance
  - Increase in Th1 and pro-inflammatory responses during infancy
- Age-dependent outcome of infections
- Interlinked maternal and infant immunity, breast milk highly adaptive, long-term immune seeding
- Early life is a developmentally sensitive period
  - Influence of infant sex
  - Impact of environment, geography, infections, vaccines, nutrition