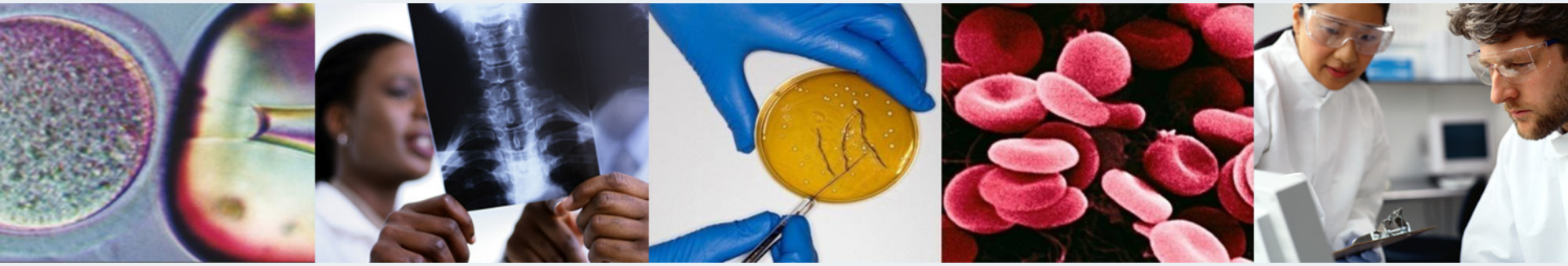


Immunity in Infants

IUIS-FAIS-ImmunoGambia 2016
West Africa Regional School on Immunology of Infectious Diseases

Mathieu Garand, Ph.D.
Senior Scientist Officer
MRC Unit The Gambia

Learning Objectives

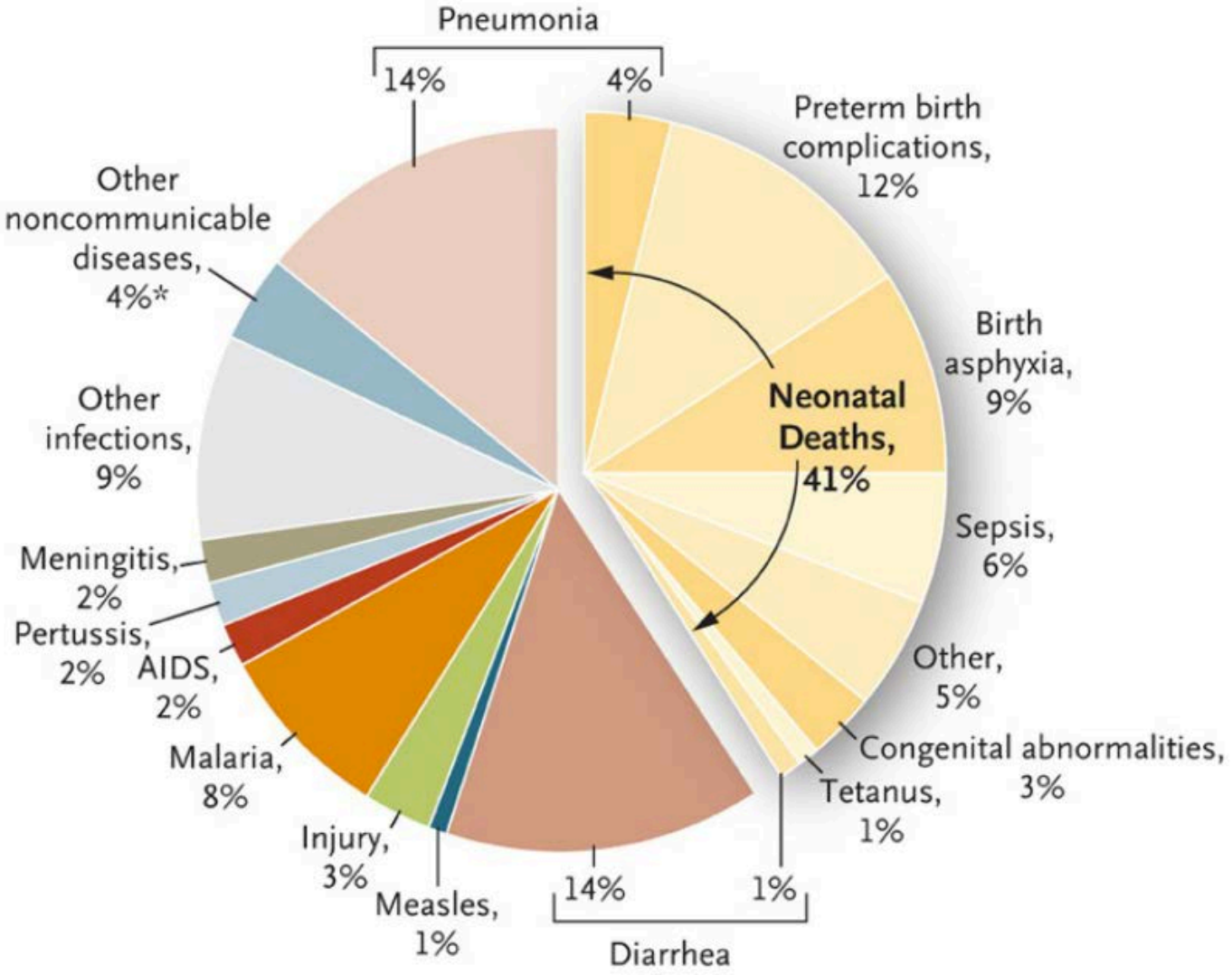
At the end of the lecture, you'll be able to:

1. **Summarize and explain the higher susceptibility to infection in infants.**
2. **Describe the origin of lymphocytes and lymphoid organ.**
3. **Differentiate active and passive immunity and illustrate immune memory.**
4. **Contrast the immune response of infants and adults in regards to cytokine production and effector function.**
5. **Discuss the effect of genetic, environment, and age on innate immune ontogeny.**
6. **Outline how neonatal and maternal vaccination can modulate the infant immune system.**
7. **Appreciate the importance of the microbiota.**

Infections as the Cause of Death

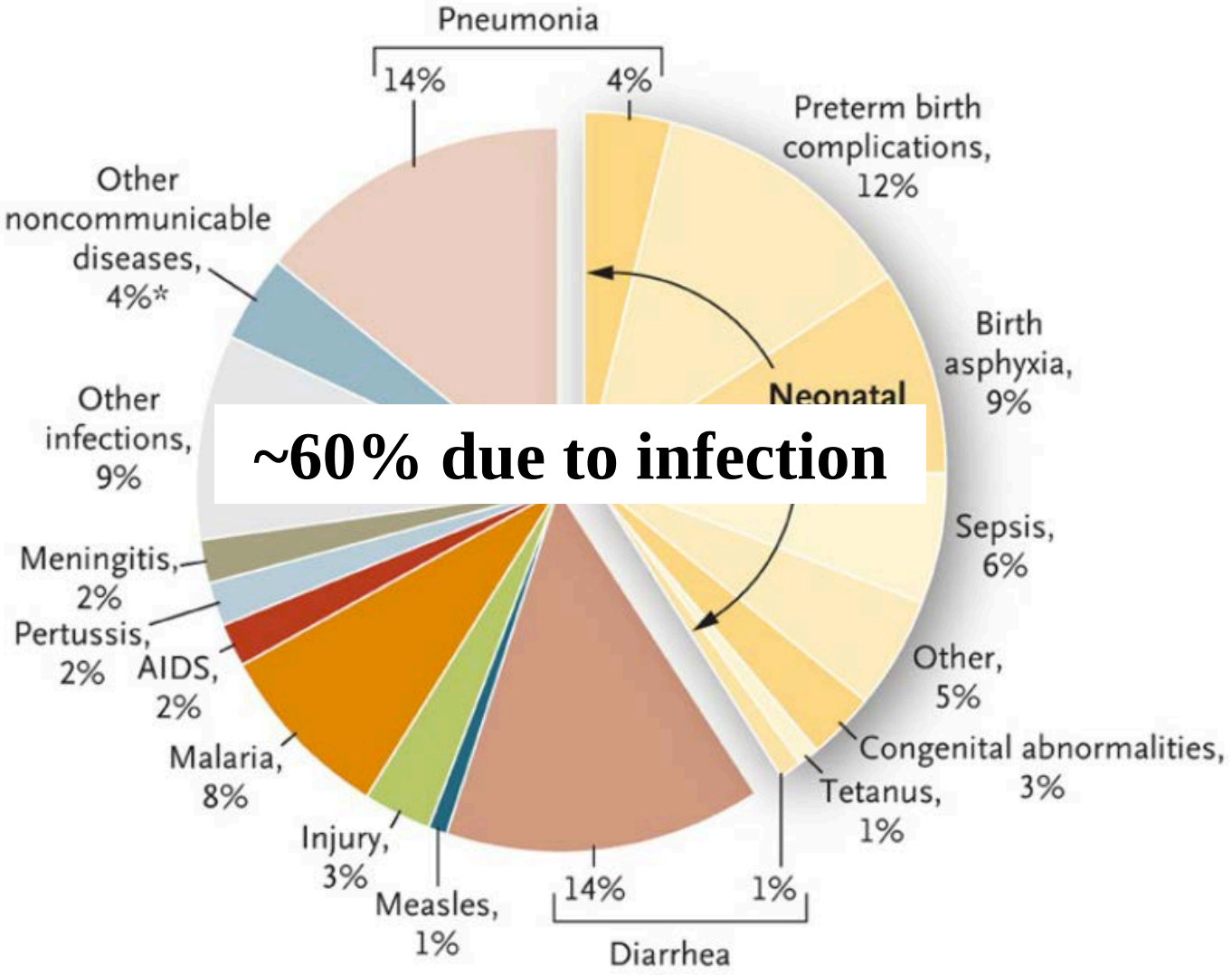
The magnitude may vary by global region, but the trend remains the same

Cause of Death for Children (< 5 yrs old)



N Engl J Med 2012;366:1328-34.

Cause of Death for Children (< 5 yrs old)



N Engl J Med 2012;366:1328-34.

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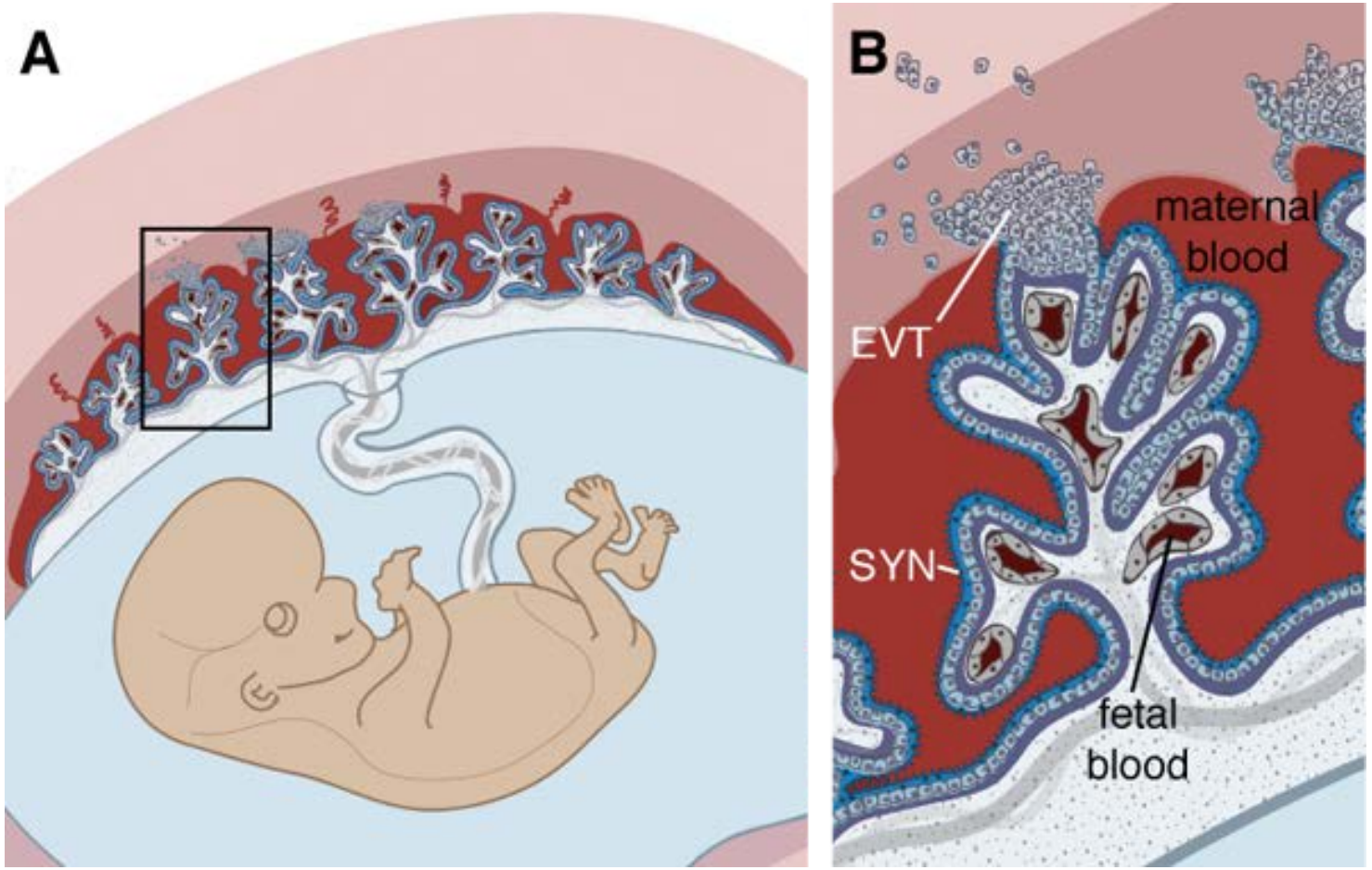
Immune System of Infants is Different

Fetal cells are in contact with the placenta and maternal blood; mechanisms are in place to prevent recognizing the surrounding as allo-antigen → immunosuppressive.



http://bakardjievlab.org/research.html

The Acute Transition at Birth and the Neonatal Immune System

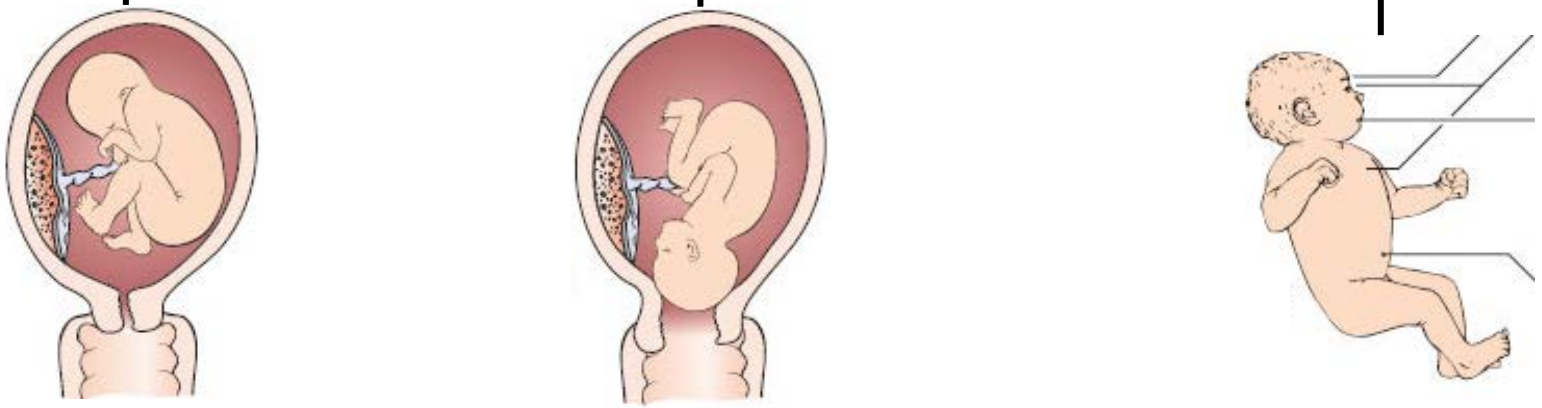
➢ **Due to limited antigen exposure *in utero*, newborns rely on their innate immune systems for protection**

Avoidance of alloimmune reaction between mother and fetus

Protection against perinatal pathogens

Transition from "sterile" intra-uterine environment to antigen-rich outside world

Degree of exposure to antigens

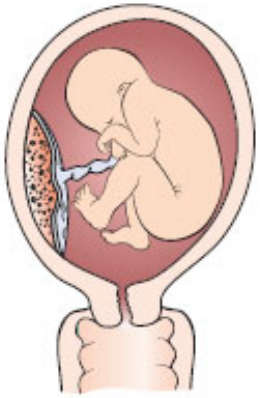


Importance of Protection from Infection

CONGENITAL INFECTION

Manifestations

- Growth retardation
- Congenital malformation
- Fetal loss



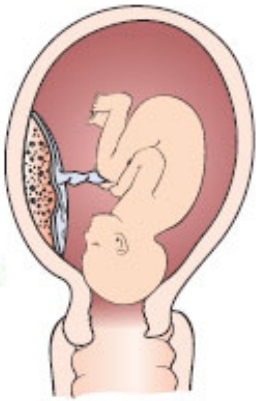
Rubella
CMV
HIV
Toxoplasma
T. pallidum
Parvovirus
VZV

PERINATAL INFECTION

Manifestations

- Meningitis
- Septicaemia
- Pneumonia
- Preterm labour

Gonococcus
Chlamydia
HSV
VZV
Group B strep
E. coli
Listeria



POSTNATAL INFECTION

Manifestations

- Meningitis
- Septicaemia
- Conjunctivitis
- Pneumonitis

N. gonorrhoeae
Chlamydia
Breast milk
HIV
CMV
Person-to-person
Group B strep
Listeria
E. coli
Umbilicus
Staphylococci
Tetanus

http://www.eplantscience.com/index/medicinal_microbiology/congenital_and_perinatal_infections.php

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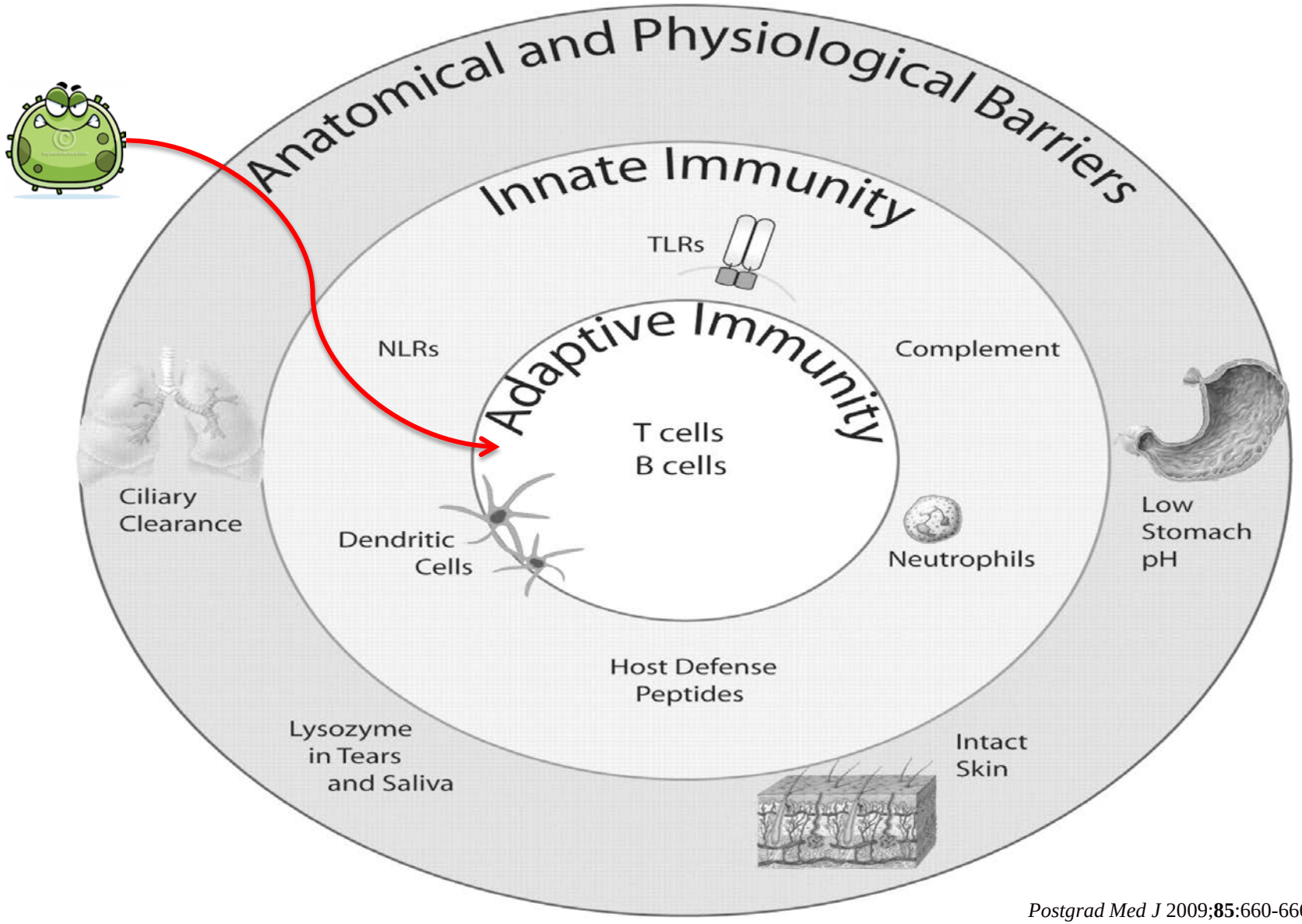
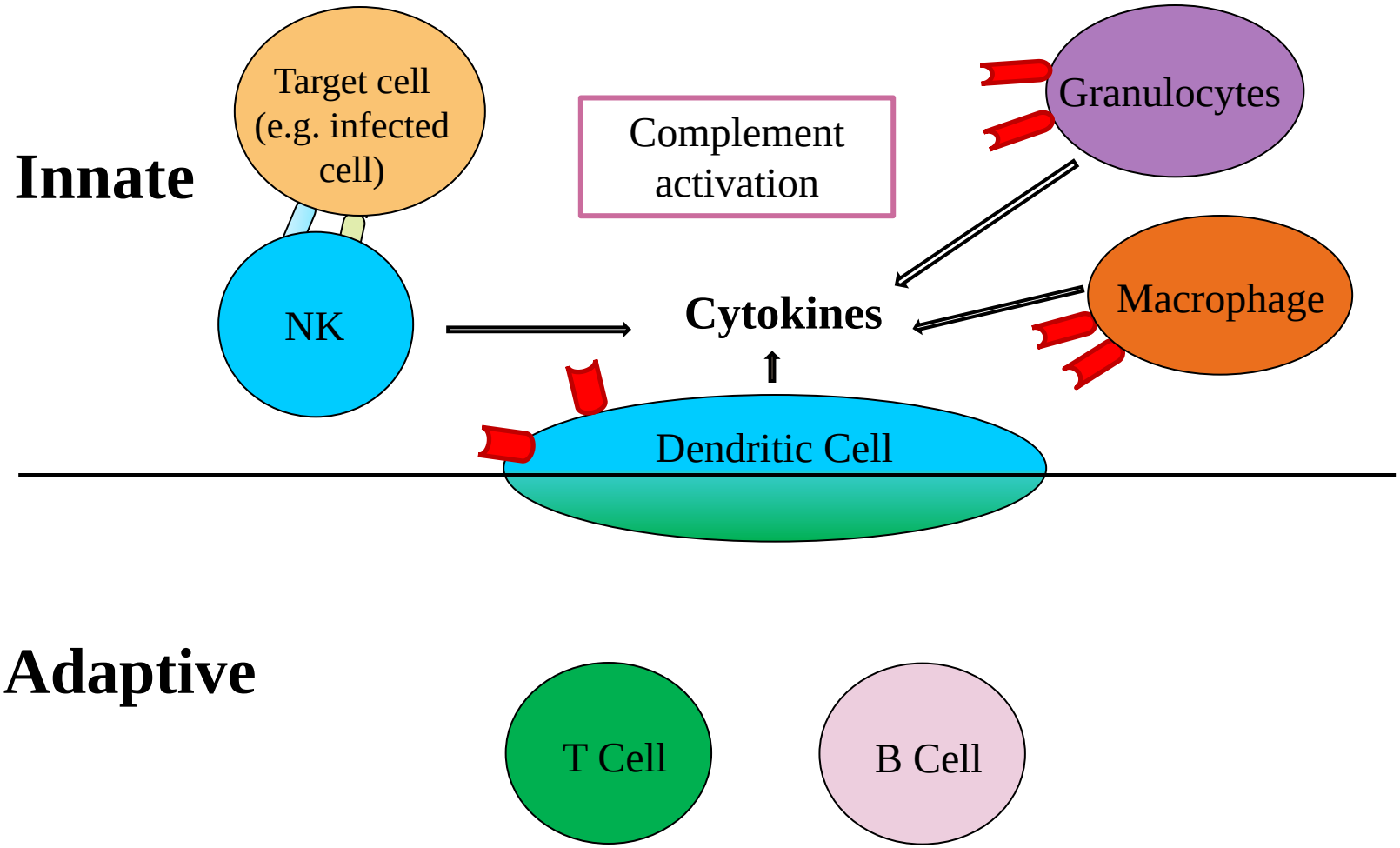
Barriers of the Immune System



Postgrad Med J 2009;**85**:660-666

Immune System Overview

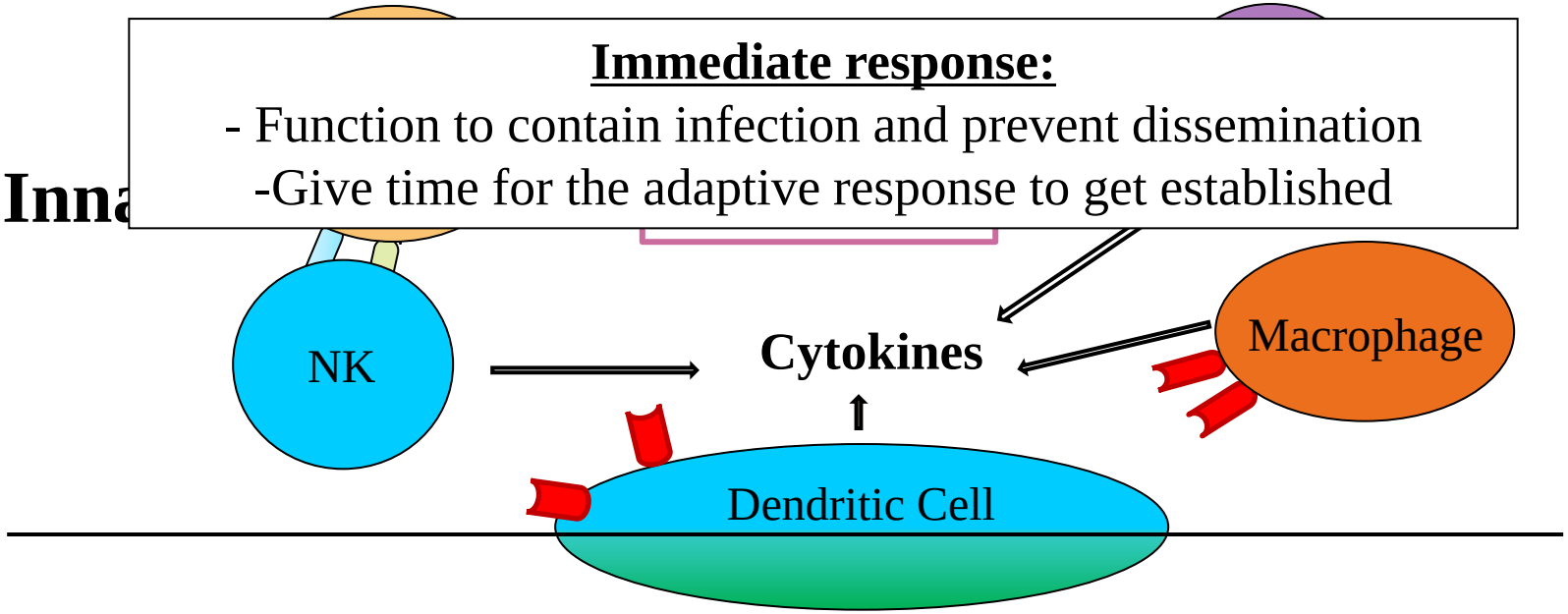


Immune System Overview

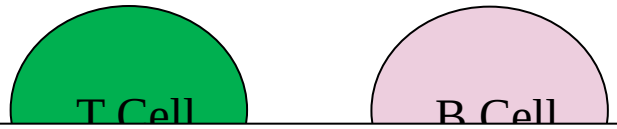
Inna

Immediate response:

- Function to contain infection and prevent dissemination
-Give time for the adaptive response to get established



Adaptive



Slower response (days):

- Promote final clearance of infection
- Generate immune memory

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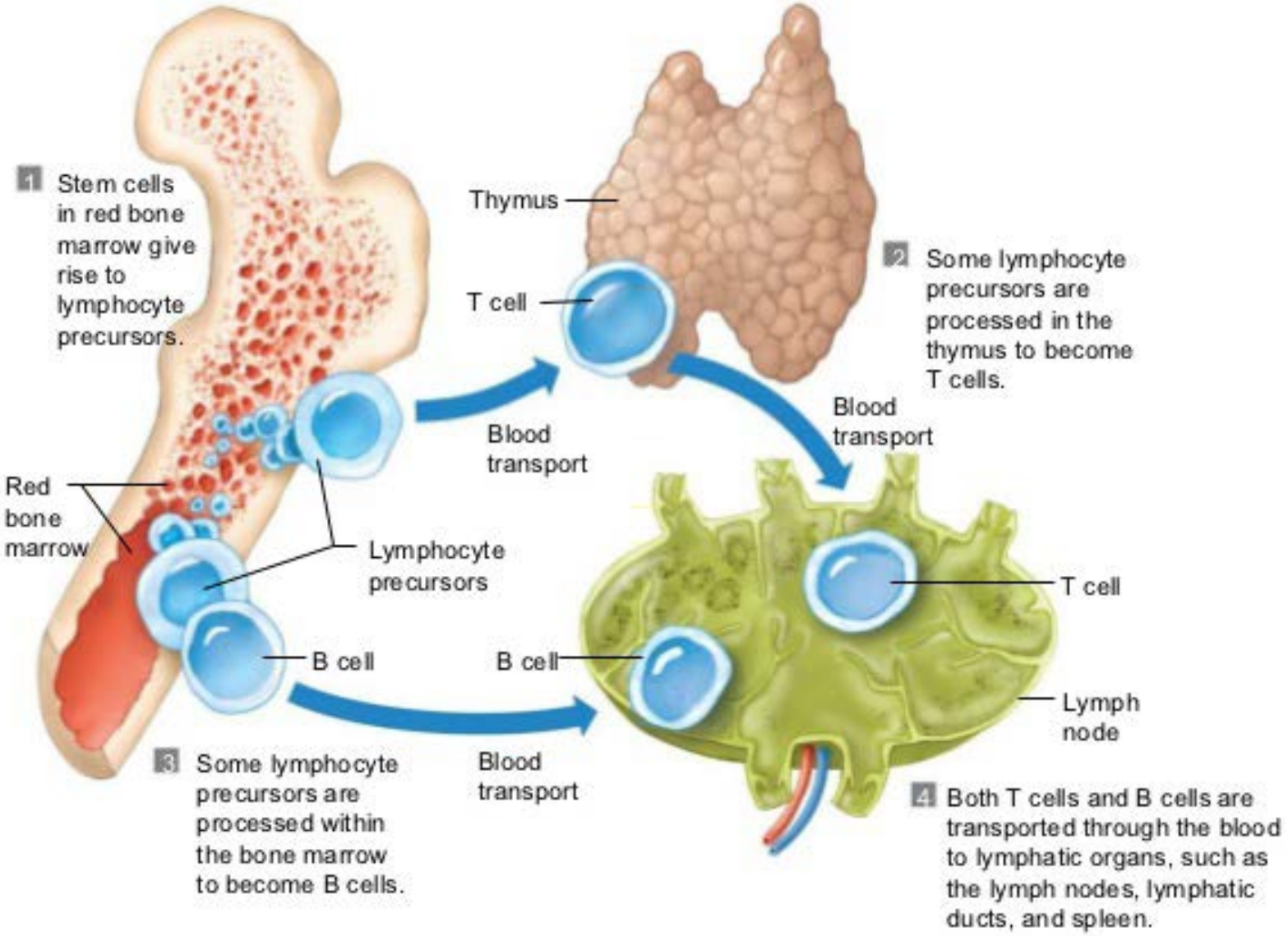
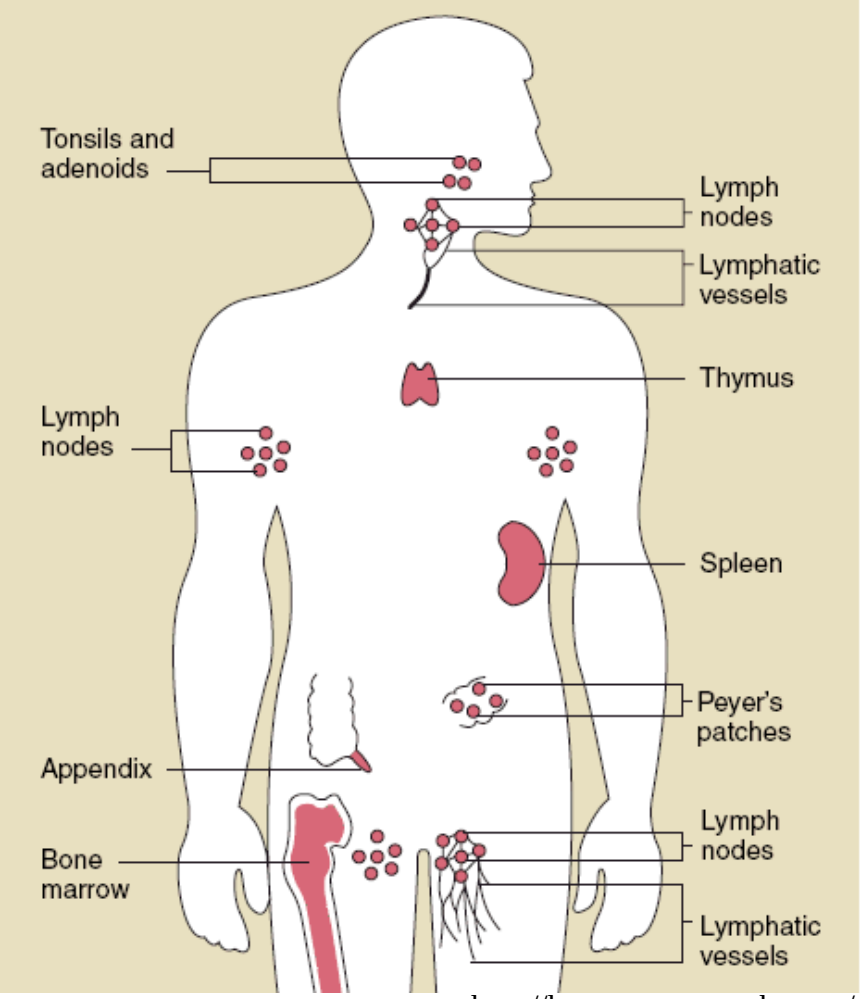
Origin of Lymphocytes



Tracking and Circulation of Lymphocytes

- Cells in constant movement.
- Some lymphocytes travel from primary to secondary lymphoid organ, others circulate between secondary organs.
- Travel in blood and lymphatic circulations.

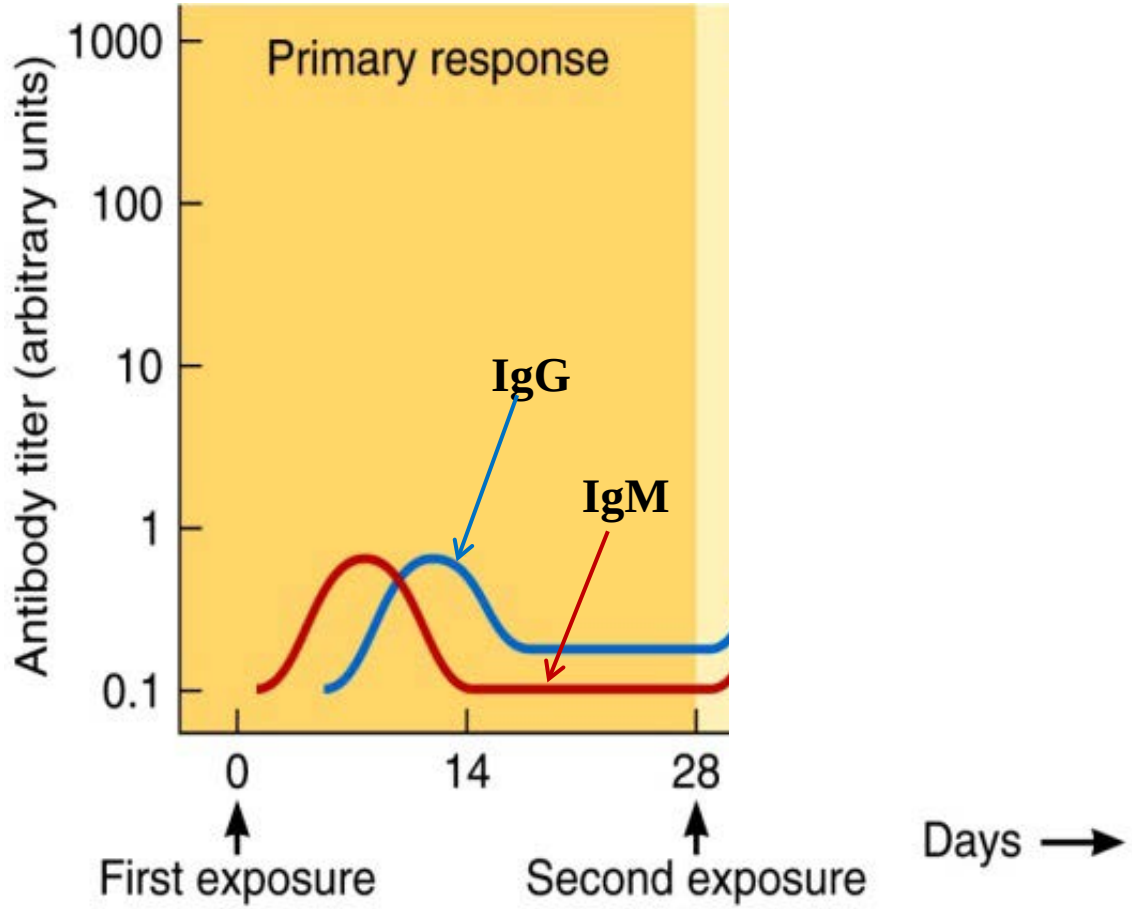
➢ The motility of lymphocytes increase the probability of cells encountering their specific antigens.



http://humananatomychart.us/

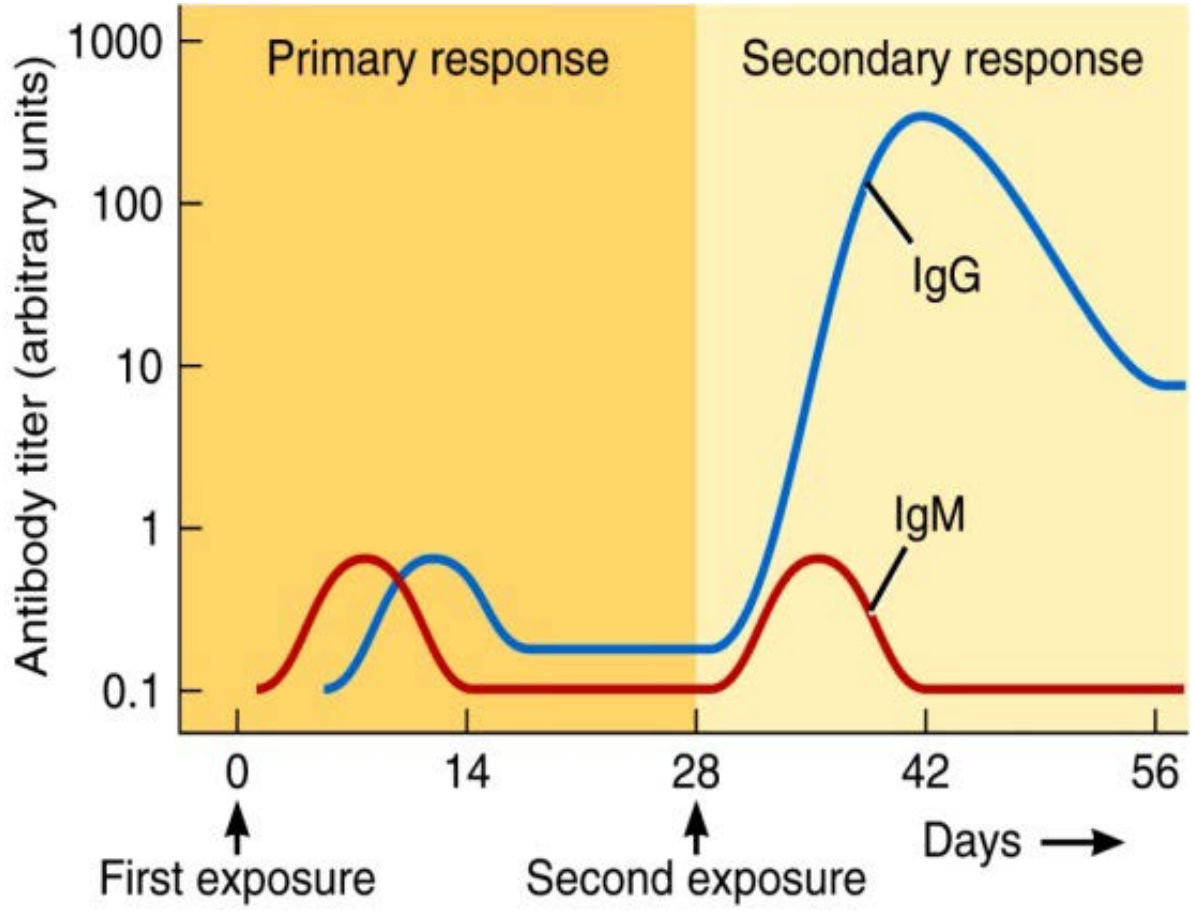
Immune Memory

❖ **Primary** immune response:
- Memory cells formed 3 to 6 days following exposure (slow).
- Produce effector B and T cells (and helper T cells) and memory cells.
- Antibodies titers fall, usually within 28 days.



Immune Memory

❖**Secondary** immune response:
- Stronger, quicker response; happens within hours.



http://classroom.sdmesa.edu/eschmid/Chapter17-Zoo145.htm

Types of Immunity

Active Immunity

- Resistance built up from contact with antigens.
- Increase in T and B cells leading to cell- and antibody-mediated responses.
- Production of memory cells.

Artificial Acquired Active Immunity

- Antigens introduced via a **vaccine** and stimulate cell- and antibody-mediated immune responses.
- Antigens are immunogenic, but not pathogenic .
- Production of memory cells.

Types of Immunity

Passive Immunity (Naturally Acquired Passive Immunity)

- Maternal transfer of antibodies to foetus across the placenta (IgG) and through breast milk (IgA, and potentially much more).
- Short term protection.
- No memory cells are produced.

Artificial Acquired Passive Immunity

- Injected antibodies to confer immediate protection.
- No memory cells are produced.
- Short term protection.

Learning Objectives

1. ✓ **Summarize and explain the higher susceptibility to infection in infants.**
2. ✓ **Describe the origin of lymphocytes and lymphoid organ.**
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4. **Contrast the immune response of infants and adults in regards to cytokine production and effector function.**
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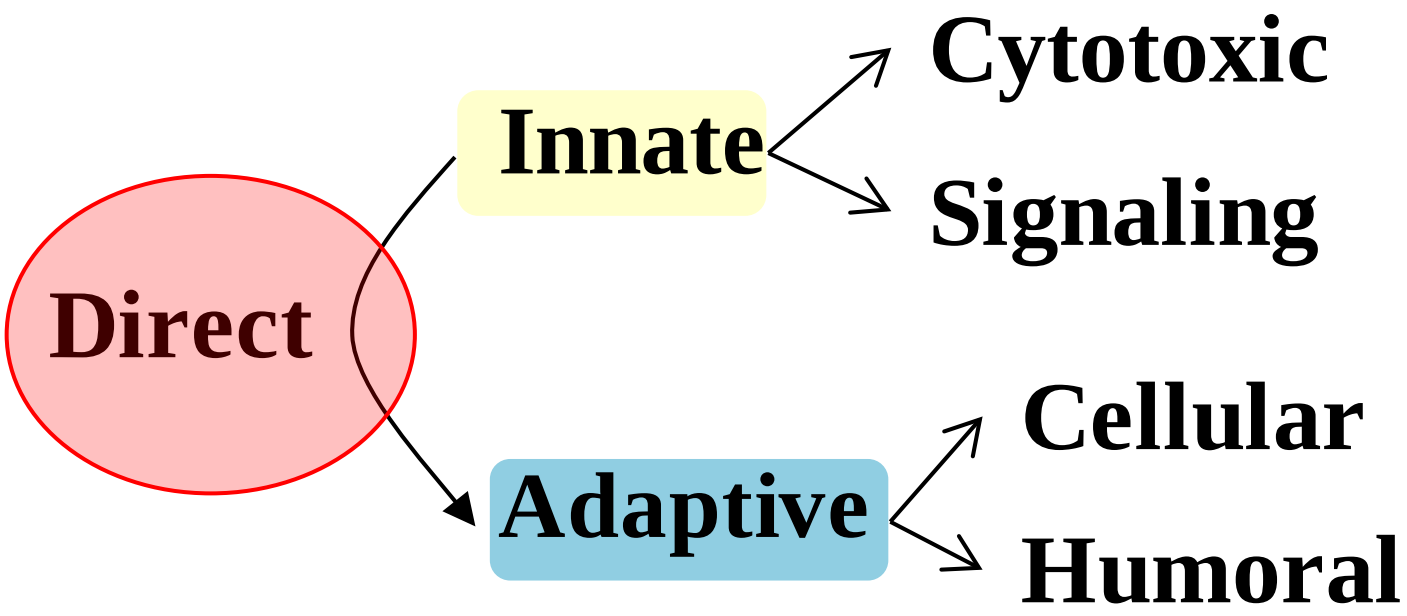
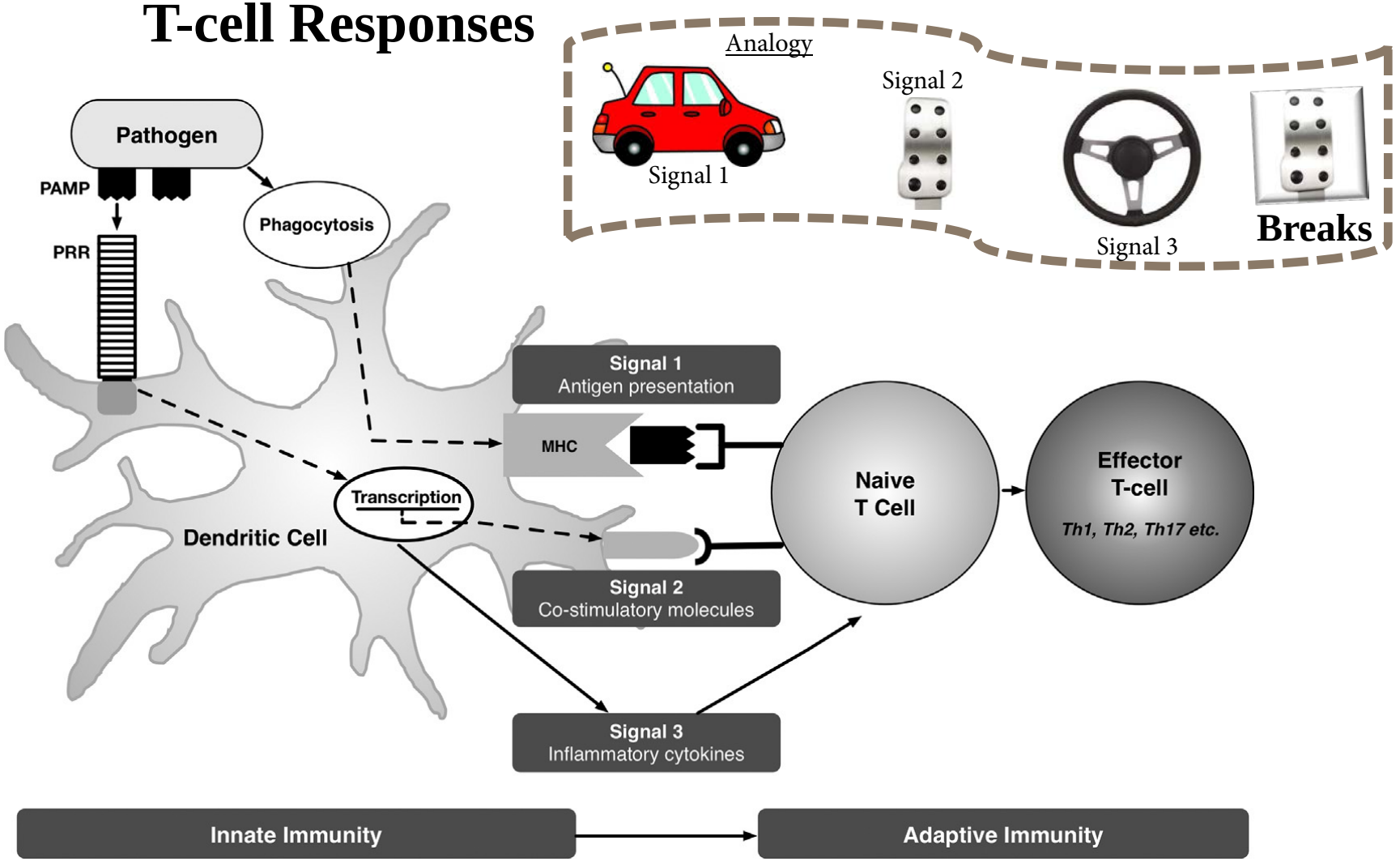
6. **Outline how neonatal and maternal vaccination can modulate the infant immune system.**
7. **Appreciate the importance of the microbiota.**

Components of the Immune System

➢ **We will use this simple diagram to guide us through the immune system and address the question: how different is the immune system of infants compared with adults?**

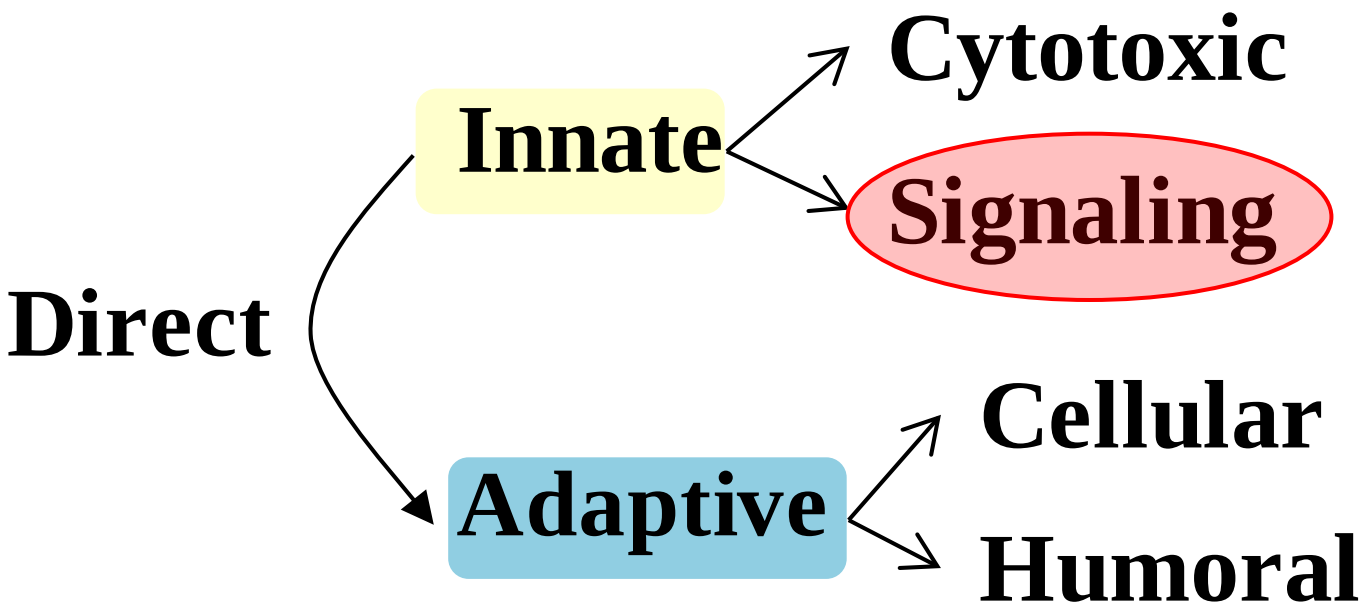


Signals from Innate Cells Control Antigen-Specific T-cell Responses



A Goenka and TR Kollmann 2015 *Journal of infection*

Components of the Immune System



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Changes in PRR-Induced Cytokine Secretion with Age

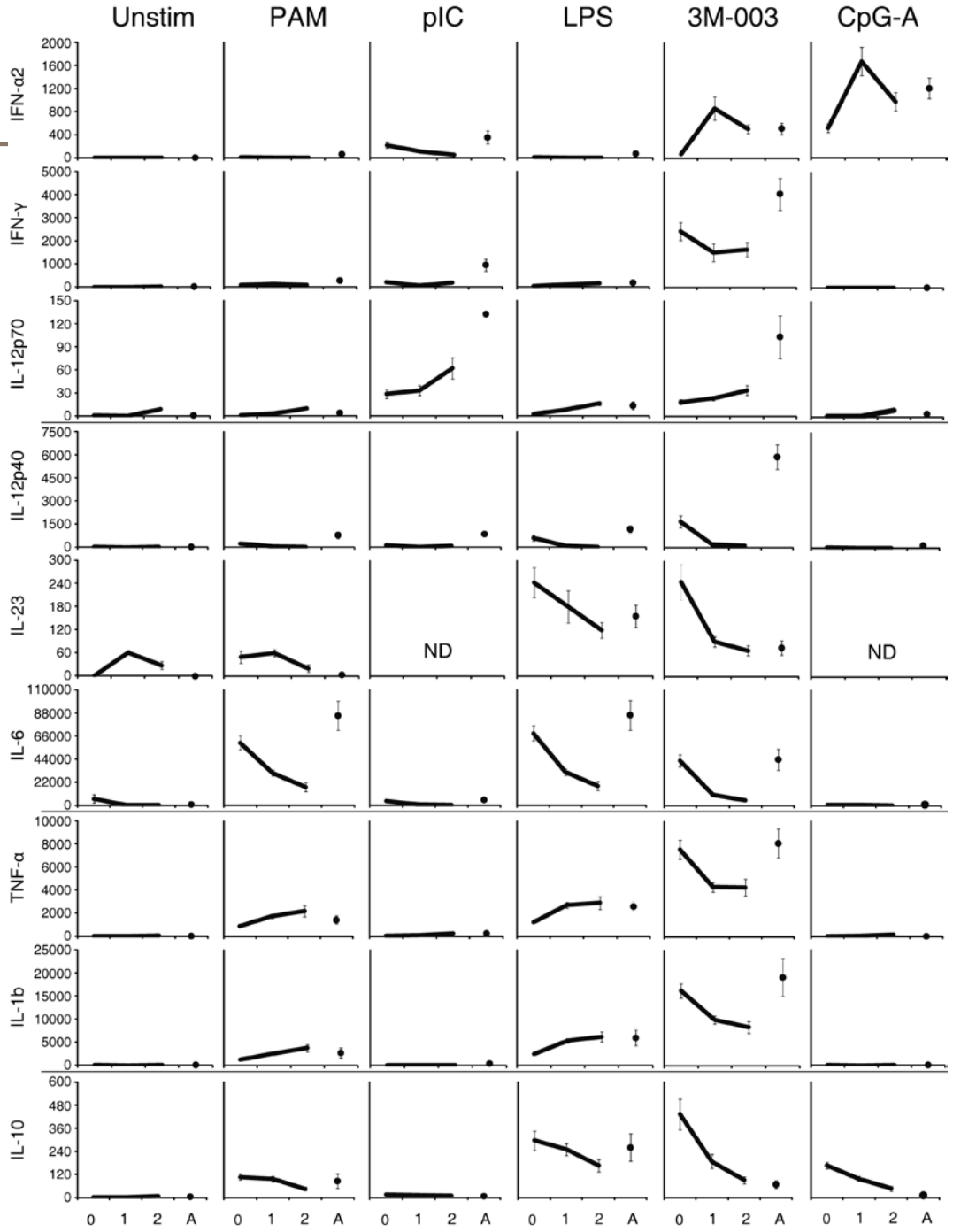

Figure from: NP Corbett *PlosONE* 2010 (5)
Additional supporting references:
TR Kollmann *Immunity* 2012 (37)
PM Lavoie *Journal of Infectious Diseases* 2010 (202)
TR Kollmann *J Immunology* 2009 (183)

MRC Unit The Gambia

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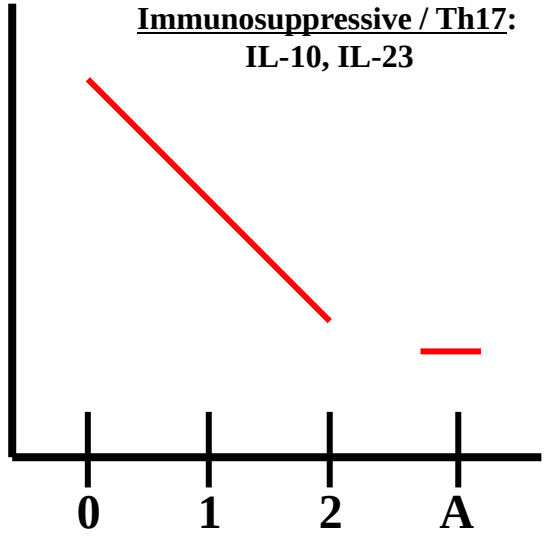

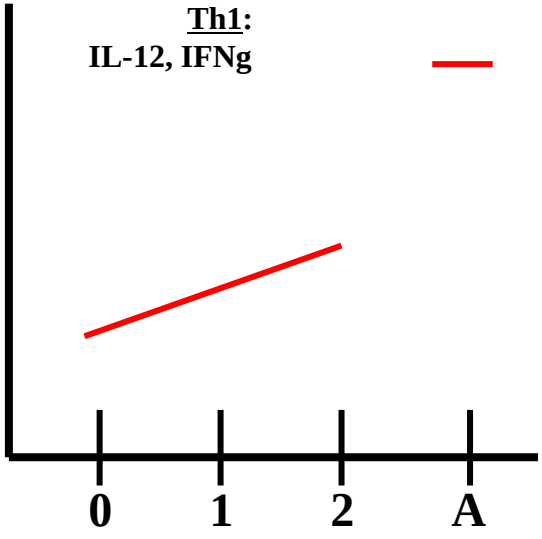

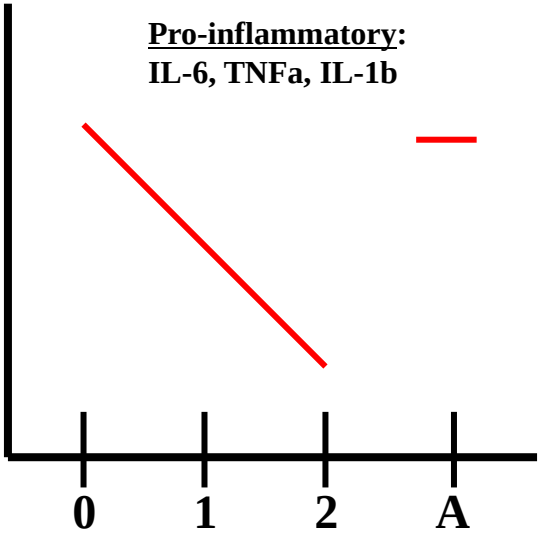

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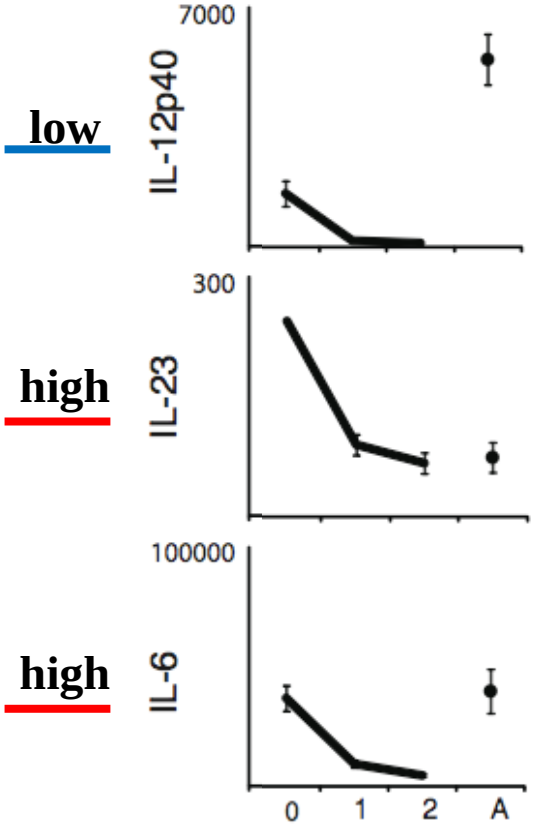
PRR-Induced Th17-Supporting Cytokine Secretion Decreases with Age

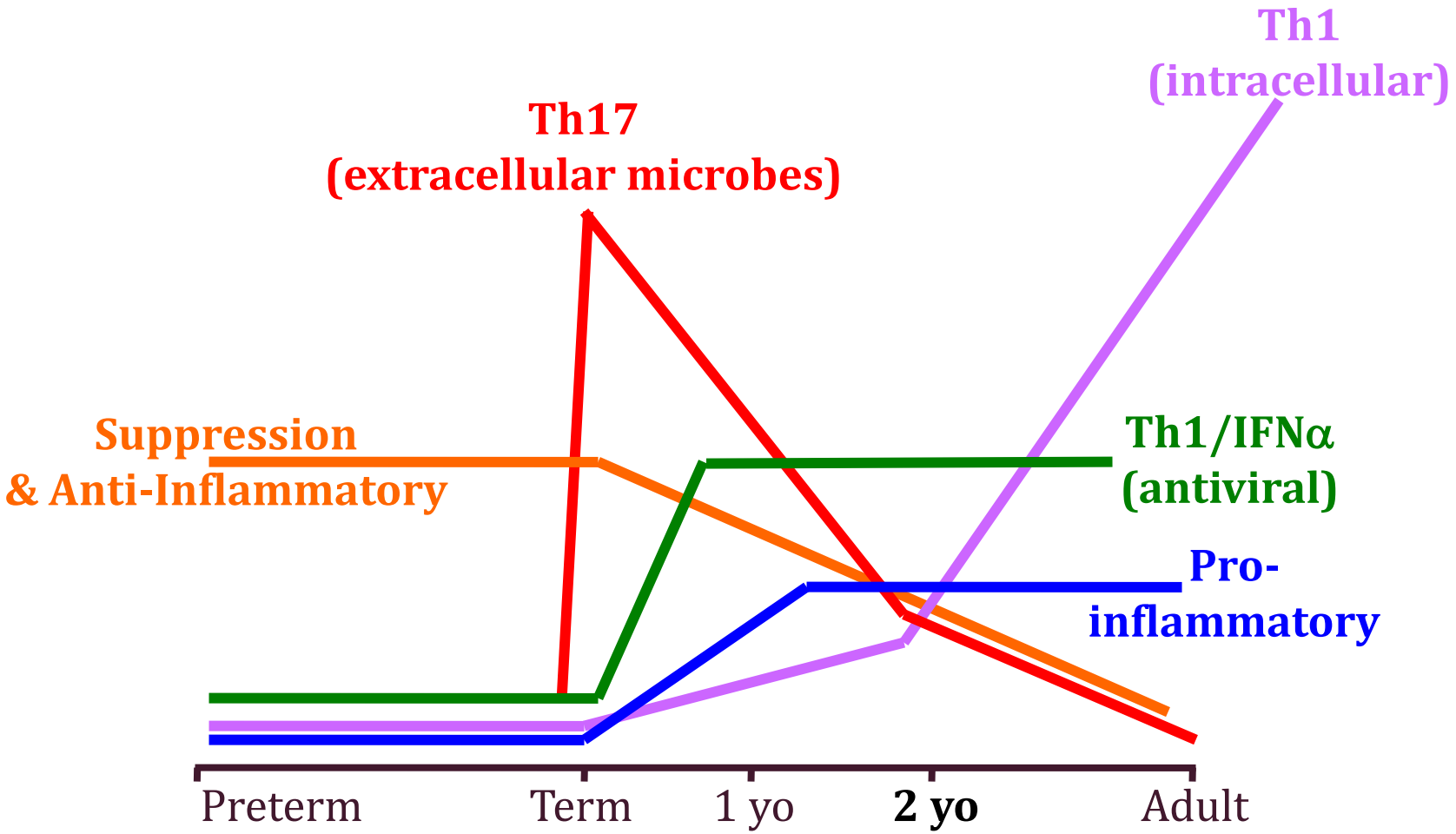
TLR7/8 stimulation



NP Corbett *PlosONE* 2010 (5)

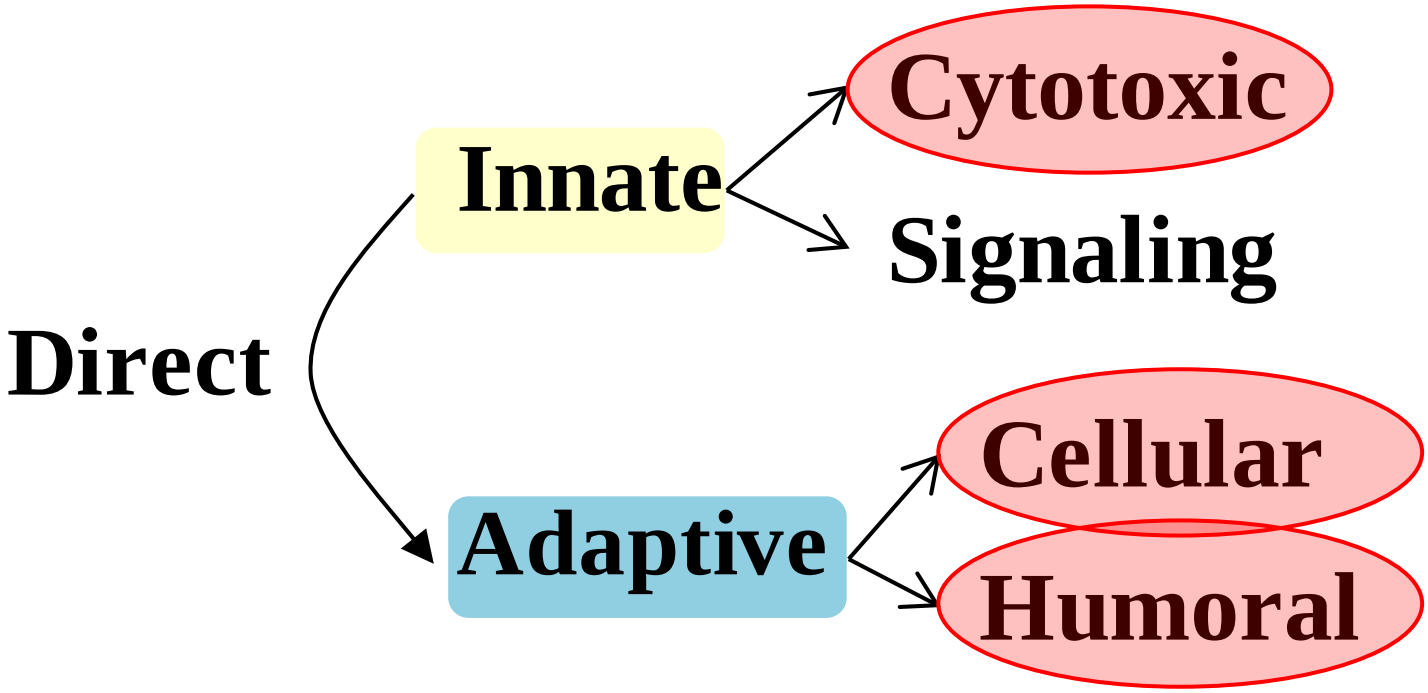
Response to PRR Stimulation Changes with Age

- **Pattern corresponds with function:**



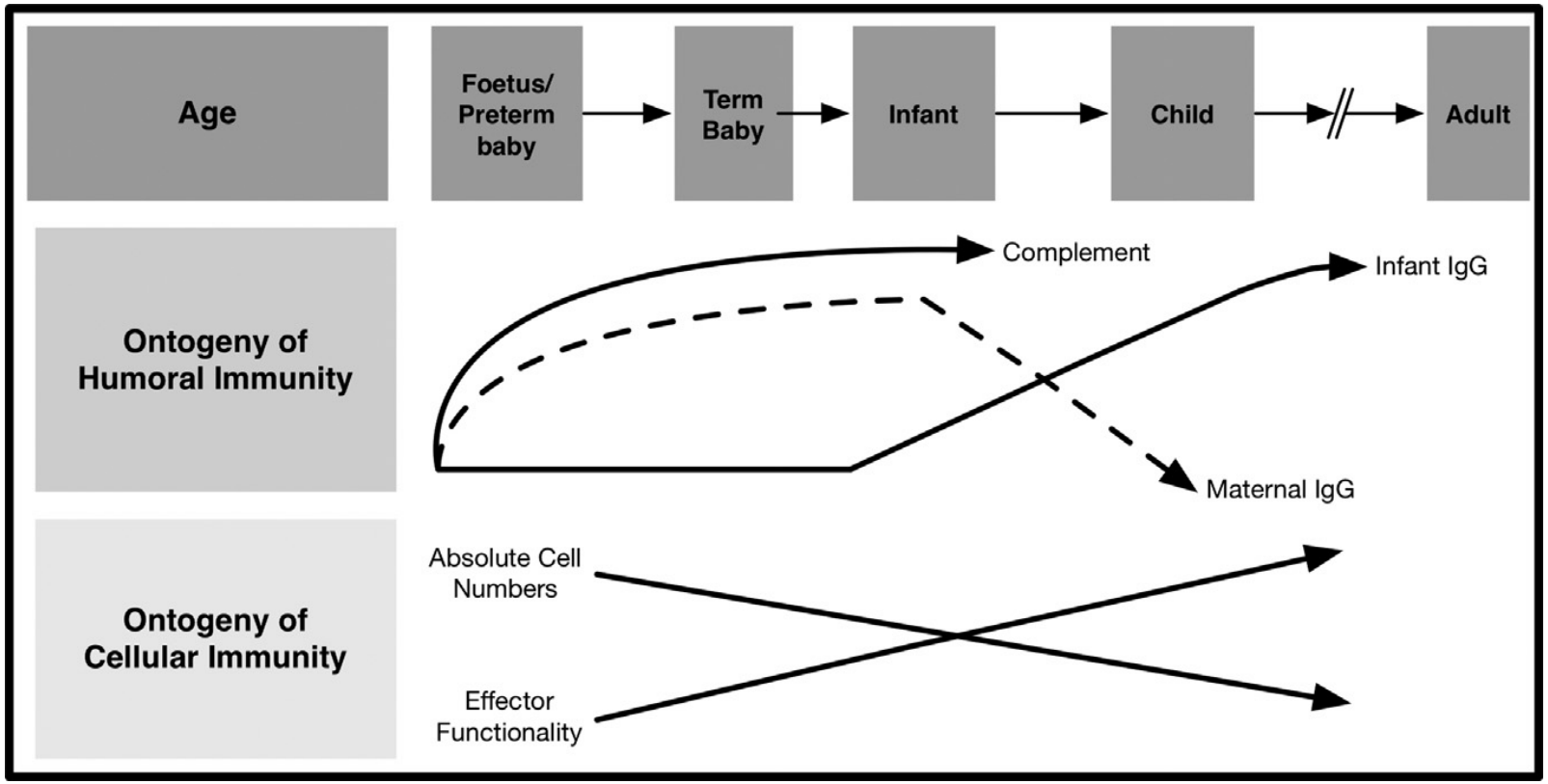
Adapted from TR Kollmann *Immunity* 2012

Components of the Immune System



Early Life Ontogeny of Humoral and Cellular Immune Components

- **T cell-dependent Ab response is achieved by 1yo, T cell-independent by 2yo.**
- **By 6mo, it's mostly infant Ab.**



A Goenka and TR Kollmann *Journal of infection* 2015

- **↑ Neutrophile and NK, but less functional**
- **B cells mostly naive**
- **T cells naive and ↑ Treg**

➔ **delayed response**

Learning Objectives

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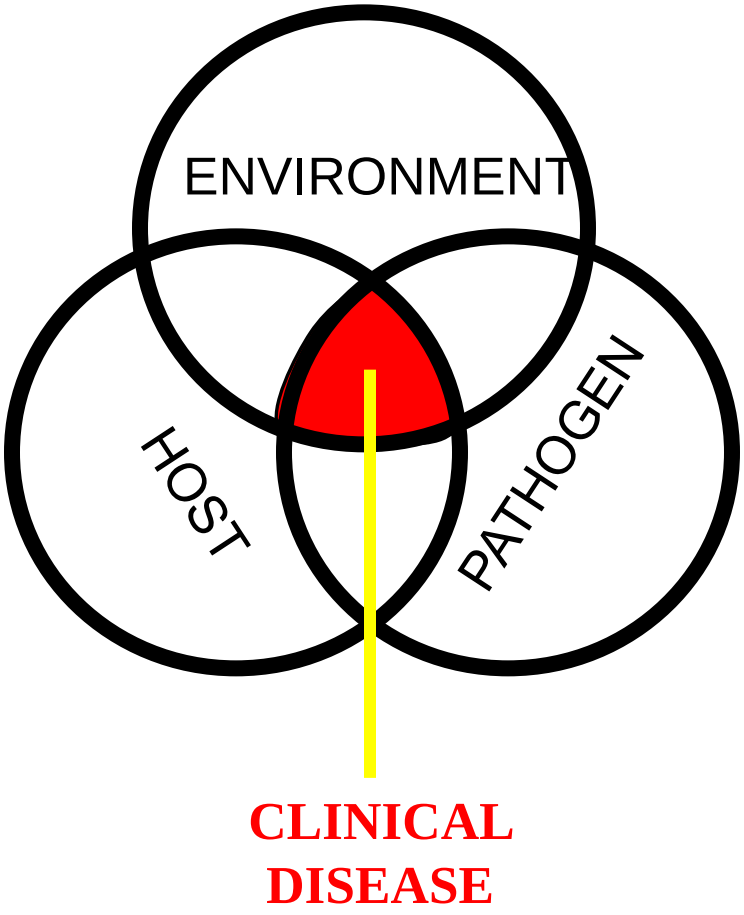
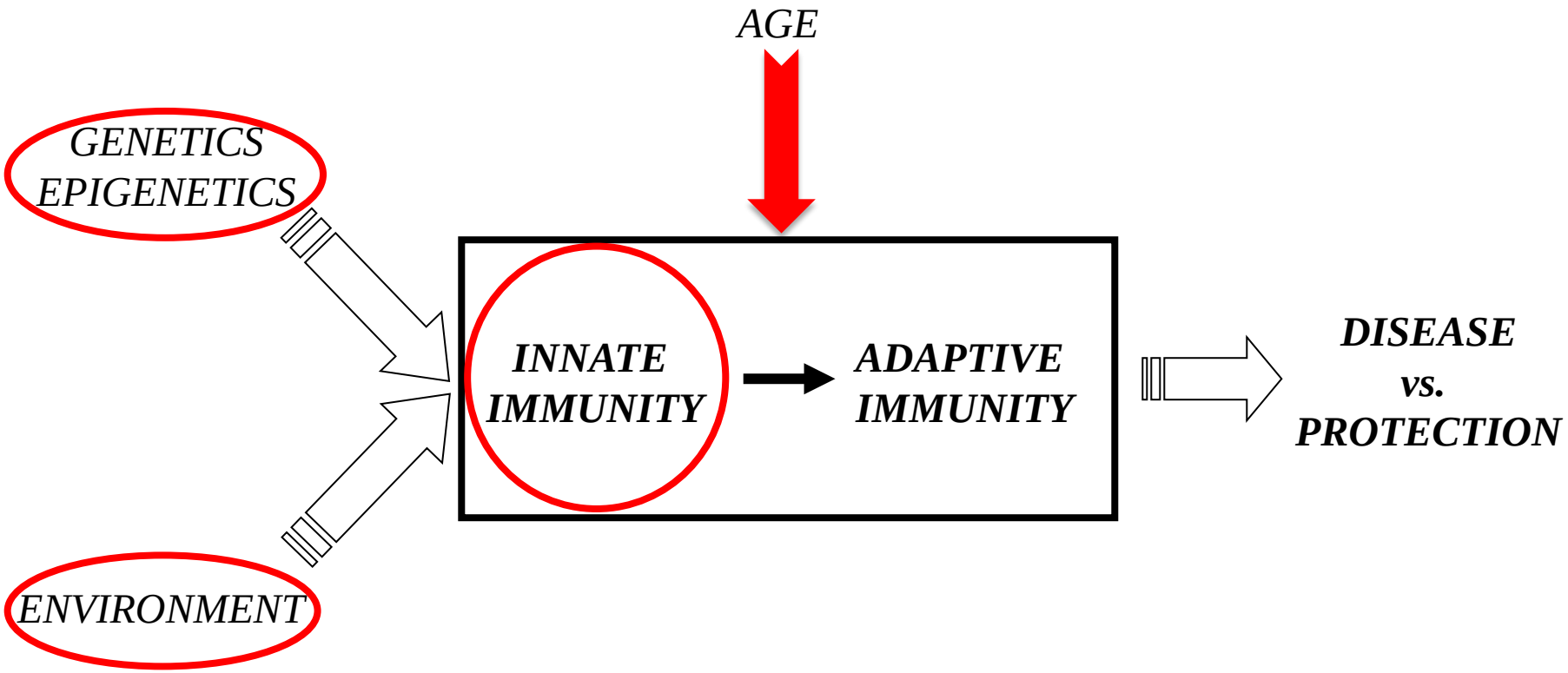
Determinants of Clinical Disease

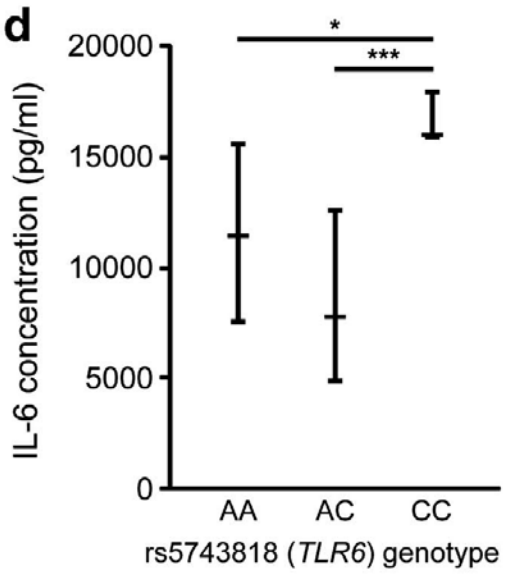


Host and Environmental Factors Affect Innate Immunity



- ✓ MJ Newport *Frontier In Immunology* 2014; LK Beura *Nature* 2016; EJ Carr *Nature Immunol* 2016; P Brodin *Cell* 2015; A Panda *J Immunol* 2010; M Garand *Innate Immunity* 2016; P Cho *Genes and Immunity* 2013

SNPs are Associated with Cytokine Production in Response to TLR7/8 Stimulation



P Cho *Genes and Immunity* 2013

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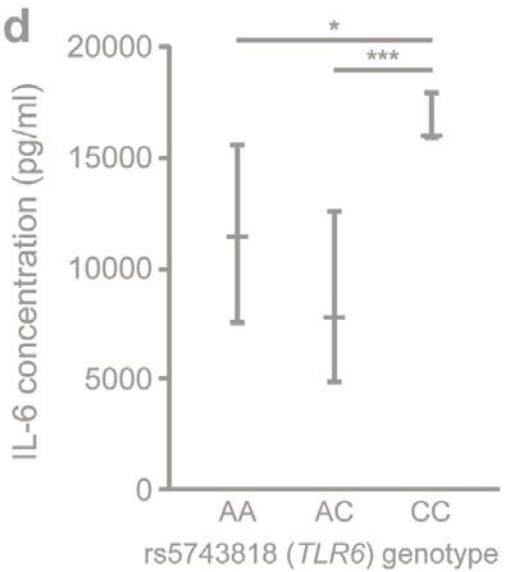
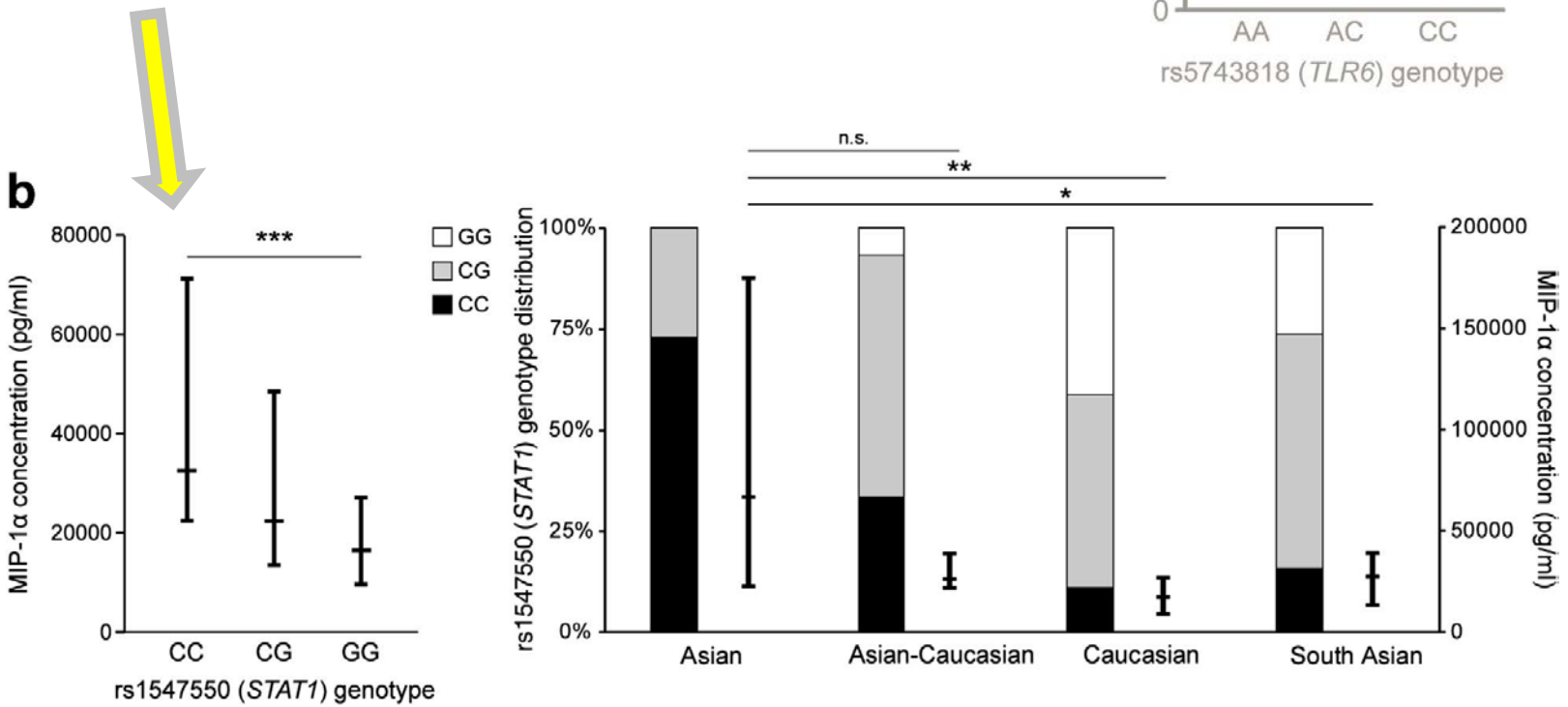
Race Influenced Cytokine Production in Response to TLR7/8 Stimulation via Differential Genotype Distributions





P Cho *Genes and Immunity* 2013

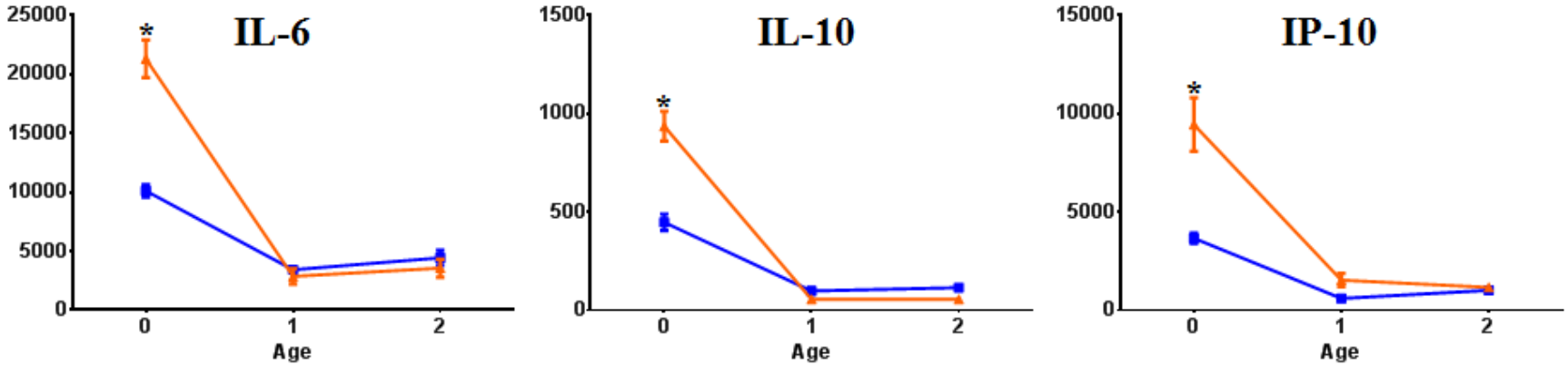
Environment Impacts Innate Immune Ontogeny

- **TLR stimulation at birth, 1, and 2 year of age: assay multiple cytokines**

Asian

Caucasian

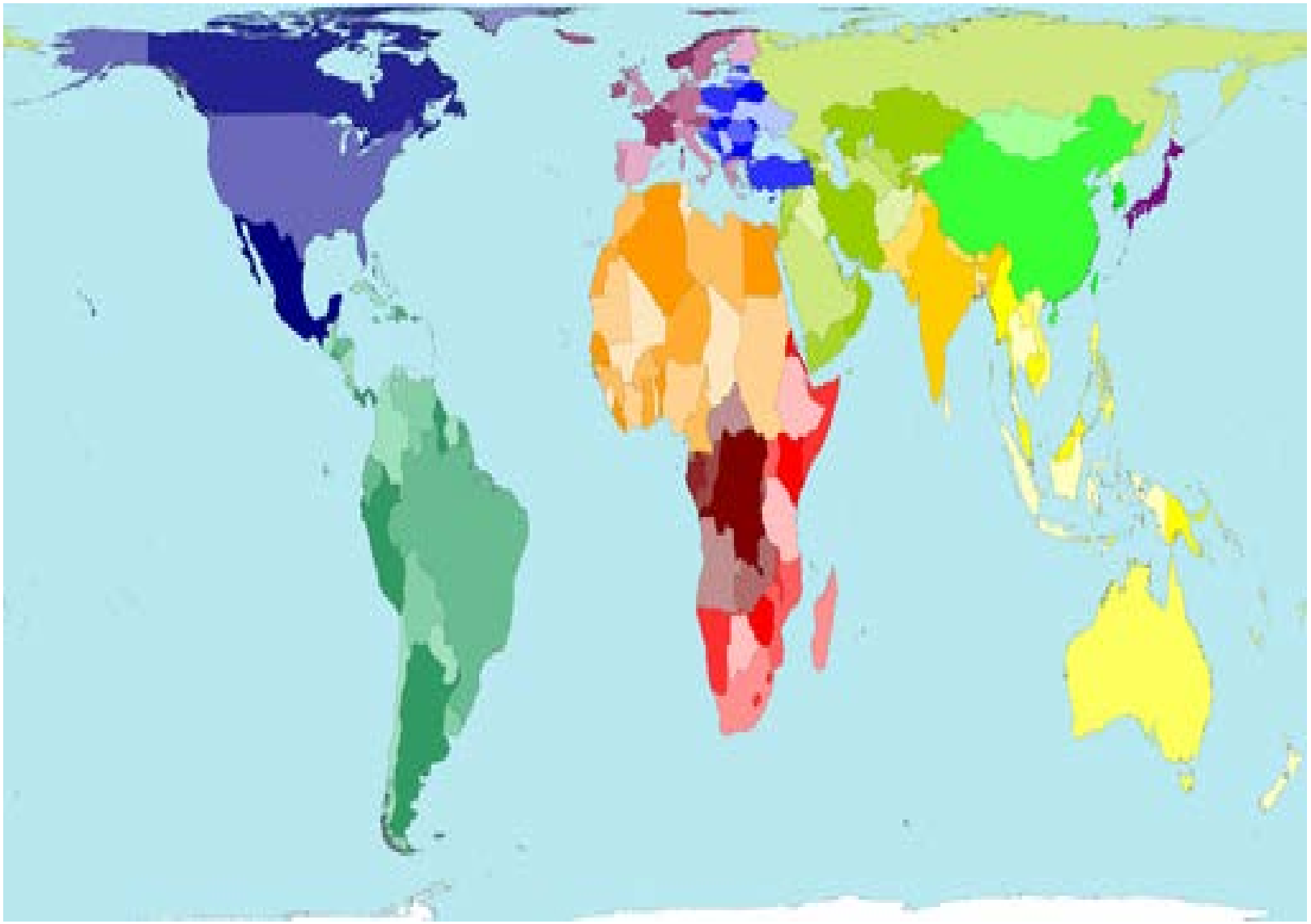
Same city, same hospital



M Garand *Innate Immunity* 2016

MRC Unit The Gambia

World Map



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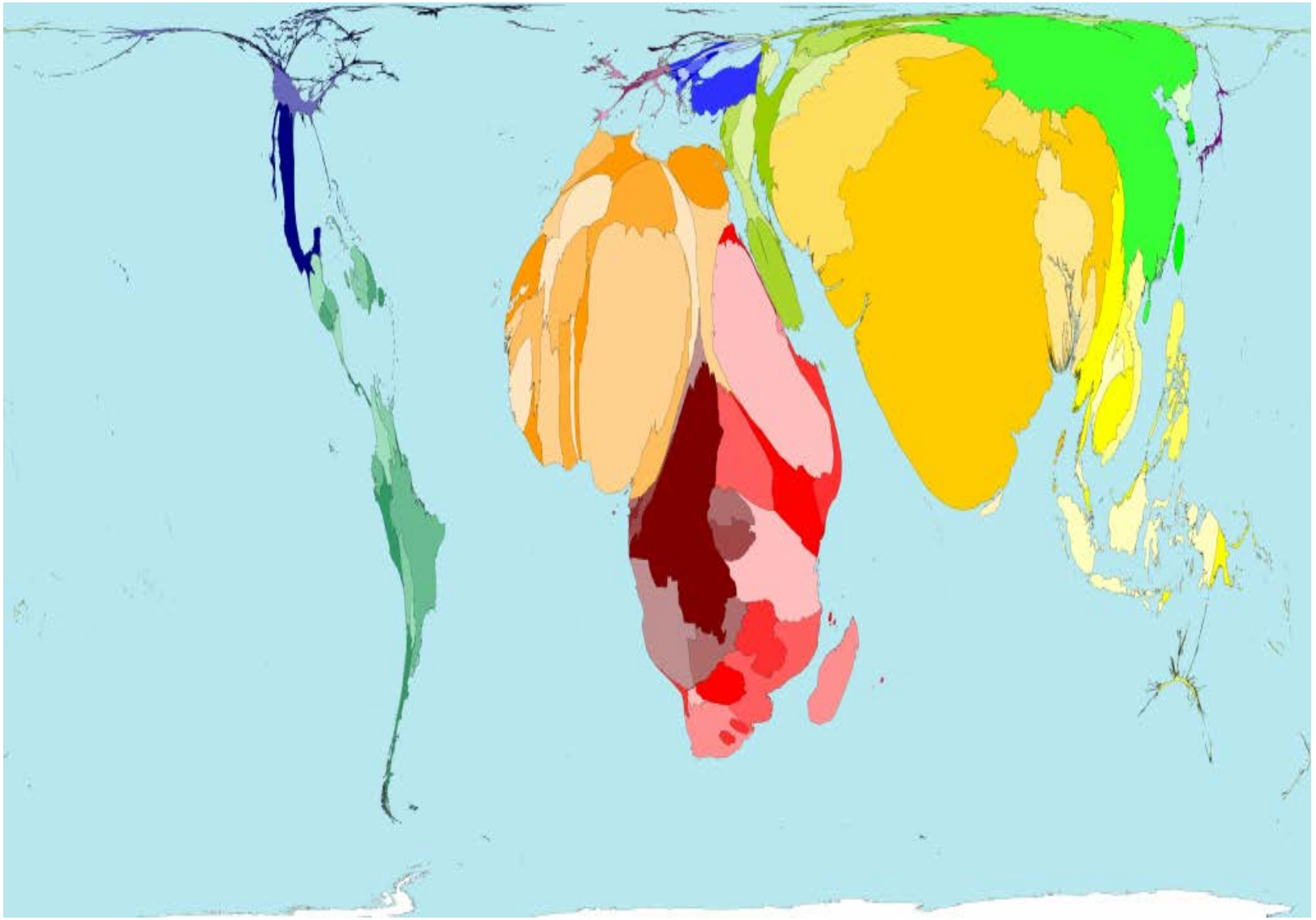
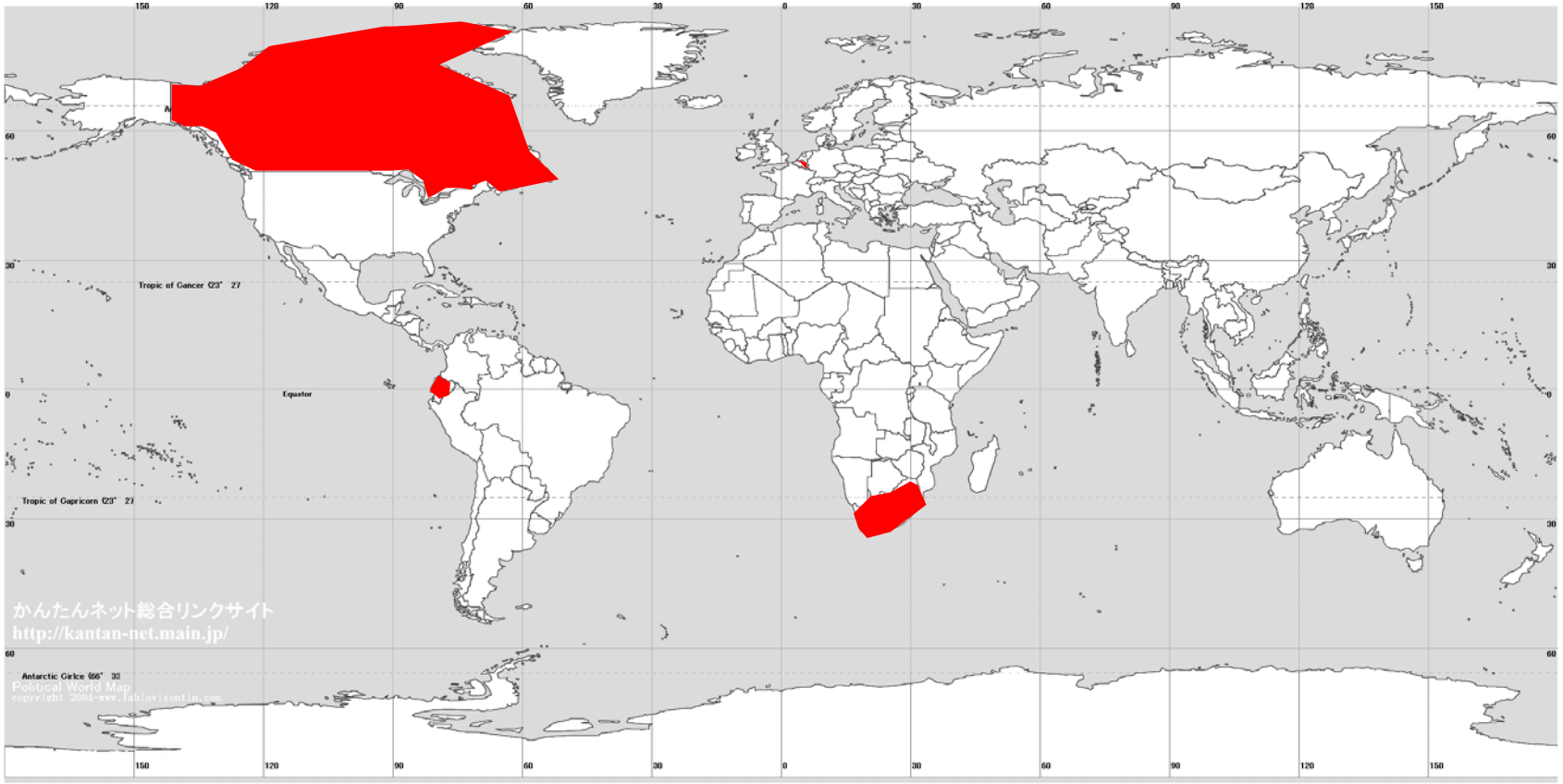
Infant Death from Infection



worldmapper.org

PRR-Mediated Cytokine Response in 2yo Infants Across 4 Continents

➢ Contrasting innate immune responses between country with different **social economical status**, **BCG vaccination**, and **prevalence of helminth infection**.

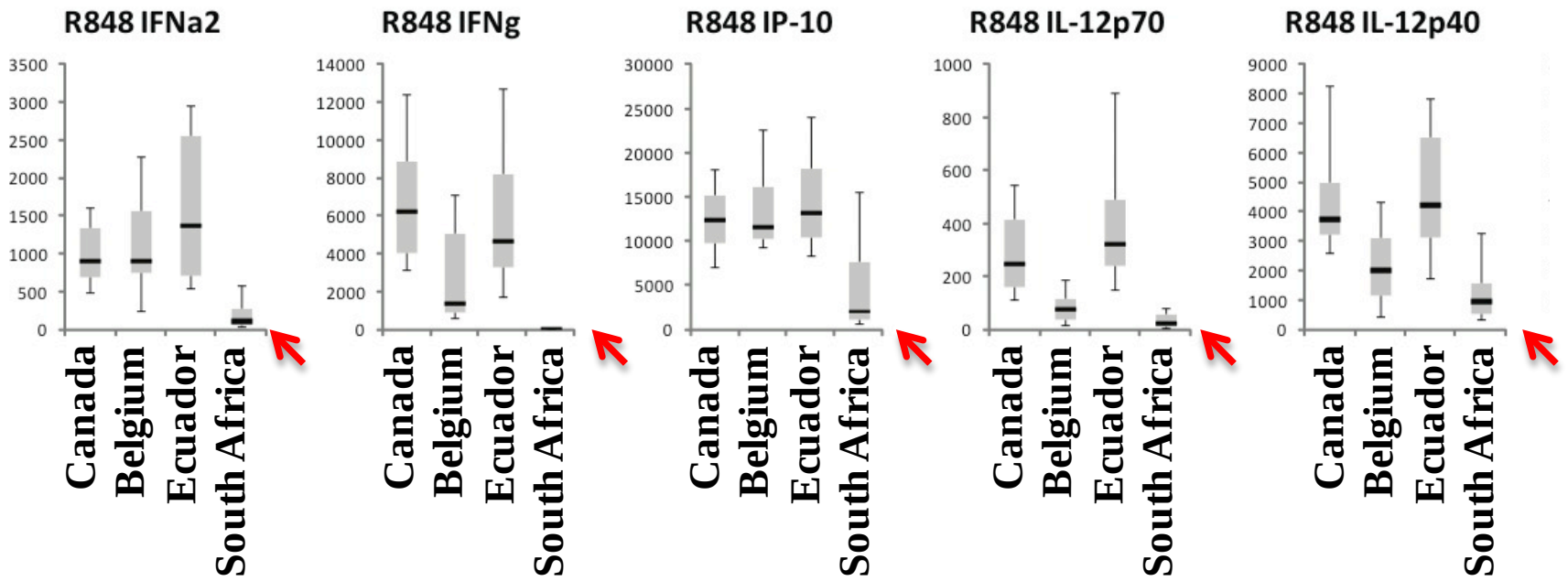


KK Smolen et al *JACI* 2014

PRR-Mediated Cytokine Response in 2yo Infants Across 4 Continents

- Most notable differences in infants from South Africa.

TLR7/8 stimulation in 2yo infants:



KK Smolen et al *JACI* 2014

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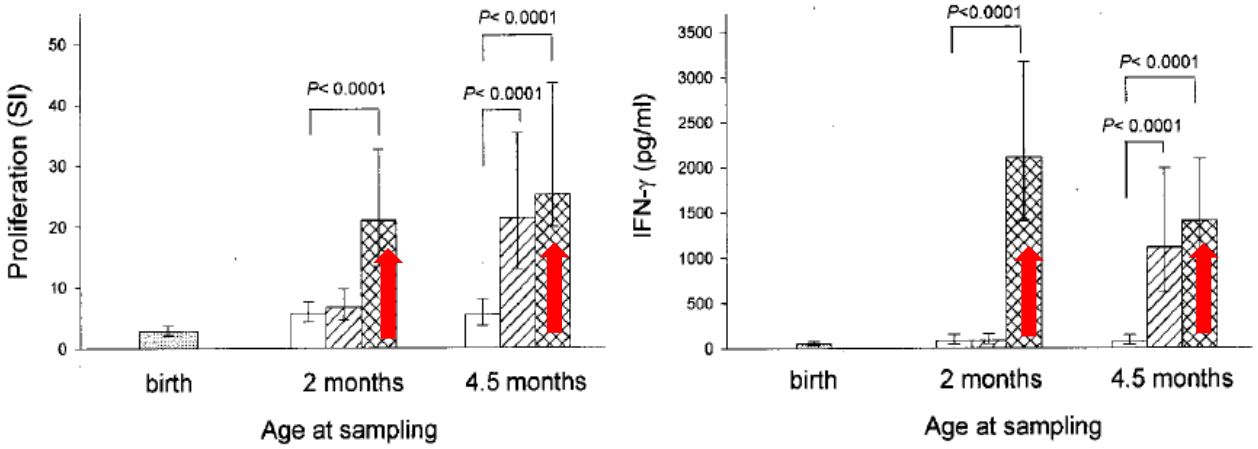
Bacille Calmette-Guerin (BCG) Vaccine and Non-Specific Effects

BCG: Induce strong Th1 response in newborns when given at birth (works better in low-resource settings)



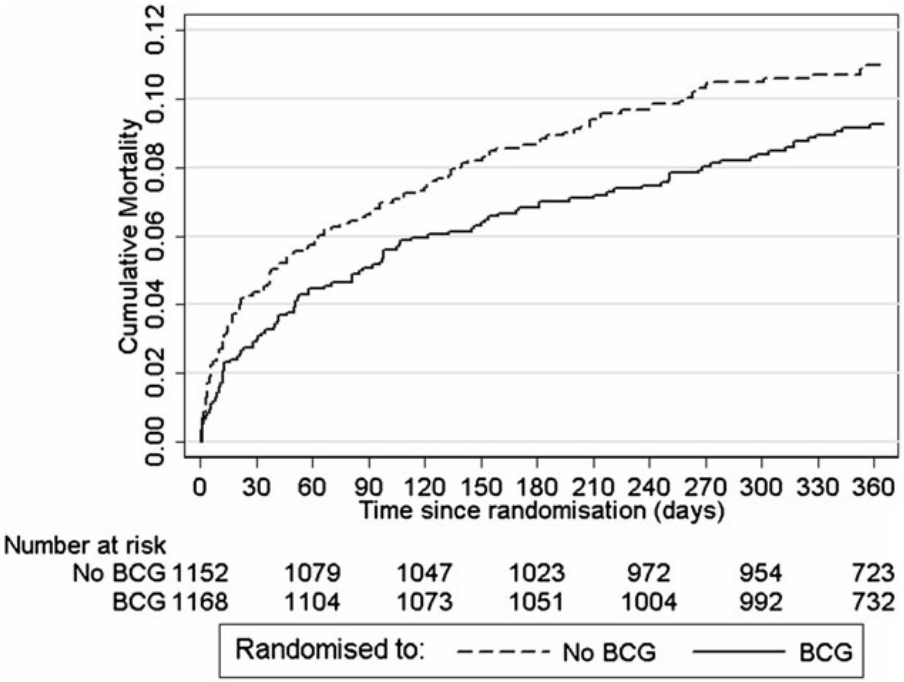
MOC Ota J Immunol 2002

Beneficial non-specific effects:

- **Great potential to decrease all-cause infant mortality, but:**
  - **It is a complex field, further studies are a must.**
  - **Not limited to BCG, also reported for other vaccines (measles, DTP).**

P Aaby *J Infect Dis* 2011
S Biering-Sorensen *PID* 2012
KJ Jensen *J Infect Dis* 2015

Beneficial Non-Specific Effects of BCG

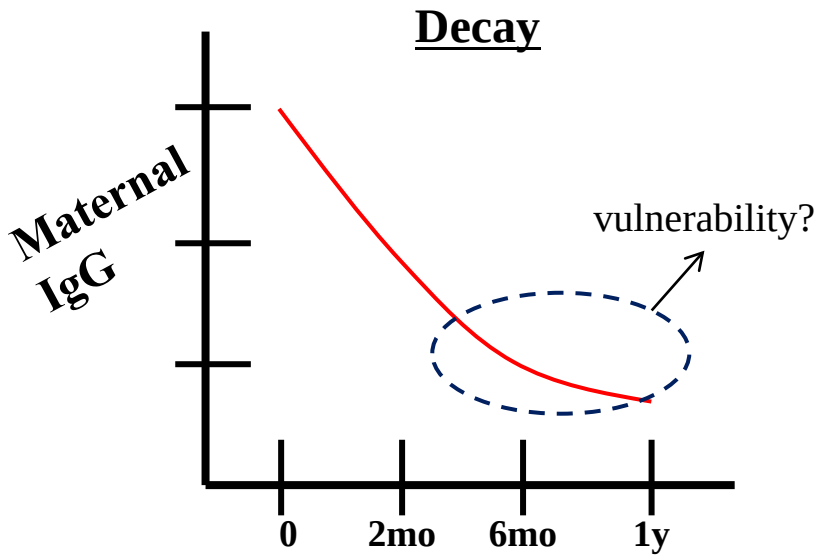


17% reduction in mortality with BCG given at birth (in low-birth-weight newborns).

P Aaby *J Infect Dis* 2011

- **More about this subject by Dr. Aaby**

Immune Protection Early in Life: Maternal Antibodies

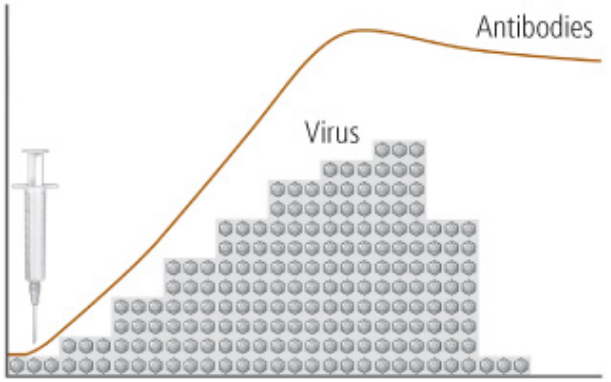


Maternal antibodies:

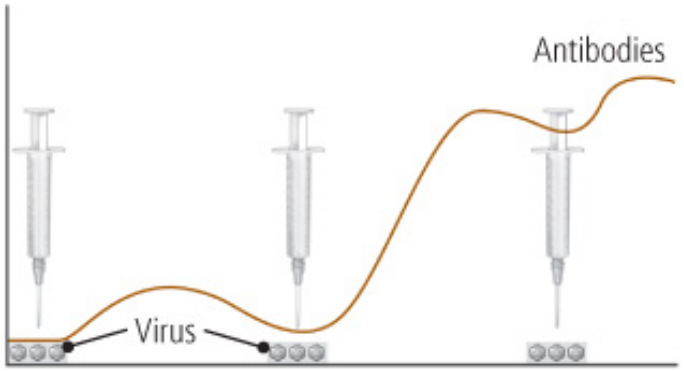
- **Affect efficacy of vaccination**
- **Decay depends on concentration and type**
- **However, T cell response not affected by maternal antibody**

Type of Vaccinations

- Live, attenuated vaccines:
  - Less virulent form of pathogen (usually viruses).
  - Elicit strong immune responses (T and B cell).
  - **Remote** chance of mutation to virulent form
  - Contraindicated for immunosuppressed individuals and pregnant women.



- Inactivated vaccines:
  - Completely dead microbe.
  - Elicit weaker response (B-cell only), more doses often required.
  - More stable and "safer" than live vaccines.



http://www.health.harvard.edu/flu-resource-center/vaccines-and-your-health.htm

Maternal Immunization

- **Immunization in neonates isn't simple.**
- **Results of immunization for certain infection, e.g. RSV, are elusive.**

Alternative → Maternal vaccination

However, for efficient vaccination, we need to fill certain gaps:

- ❑ **What is a good correlate of protection?**
- ❑ **When and how often to immunize?**
- ❑ **What type of IgG are generated?**
- ❑ **What is the effect of IgG concentration in the mother at vaccination?**
- ❑ **What is the effect of nutrition and breastfeeding on the protection provided by maternal antibodies?**

A Marchant/M Sadarangani/**M Garand** *The Lancet Infectious Disease* 2016, In Press

Learning Objectives

1. ✓ **Summarize and explain the higher susceptibility to infection in infants.**
2. ✓ **Describe the origin of lymphocytes and lymphoid organ.**
3. ✓ **Differentiate active and passive immunity and illustrate immune memory.**
4. ✓ **Contrast the immune response of infants and adults in regards to cytokine production and effector function.**
5. ✓ **Discuss the effect of genetic, environment, and age on innate immune ontogeny.**
6. ✓ **Outline how neonatal and maternal vaccination can modulate the infant immune system.**
7. **Appreciate the importance of the microbiota.**

Microbiota

100 TRILLION

The human microbiome is made up of more than 100 trillion bacteria, fungi, protozoa, and viruses that live on and inside the body.

10X

We have 10 times more microbial cells in our body than human cells and the majority live in our guts—especially the large intestine, or colon.

The bacteria in our microbiomes are essential to human health and aid in biological processes such as:

- $E=mc^2$ — Extracting energy from food
- RETINOL, FOLATE, RIBOFLAVIN, BIOTIN, NIACIN — Producing essential vitamins
- Regulating our immune system
- Regulating our glucose levels and metabolism
- Protecting us against disease-causing microbes

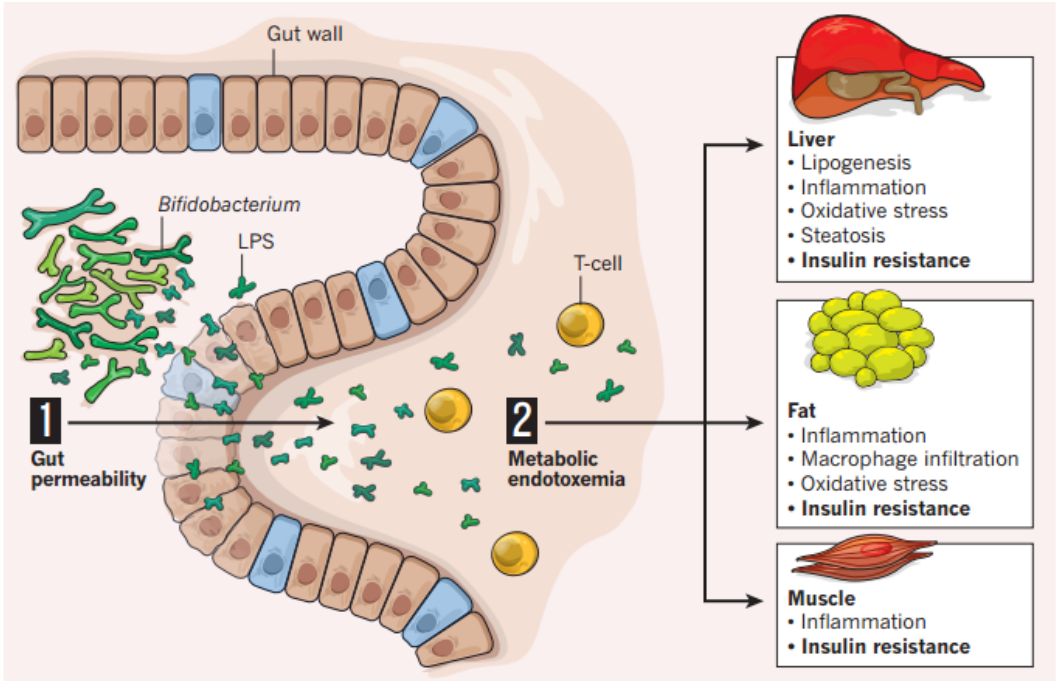
SYMBIOTIC

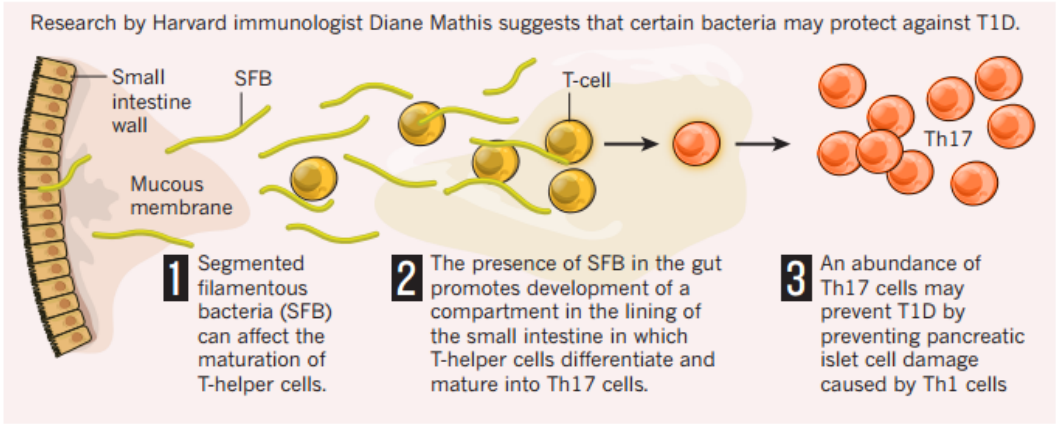
The beneficial and symbiotic relationship between humans and our microbiomes has likely evolved and changed throughout human development.

Personal microbial communities shift throughout a person's life and are influenced by diet, exercise, medications such as antibiotics, pathogens, and other environmental factors.

http://www.serestherapeutics.com/our-science/microbiome-overview

Microbiota: Lots of Research Effort





http://www.gutmicrobiotaforhealth.com/

L Gravitz *Nature* 2012

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Thank You

Questions

To Help You to Think About Your Questions...