The development of immunity in early life

The National Congress on Perinatal Medicine
Oct. 15-17th 2020

Maria Vicario, PhD

The development of immunity in early life

1. The immune system
    - Protection during gestation
    - Switch in defensive mechanisms

2. The gut environment
    - Development of gut microbiota
    - The gut as a defensive organ
    - Development of gut immunity

3. Modulators of immunity
    - Maternal factors
    - Microbiota
    - Diet

4. Strategies to improve infant immunity

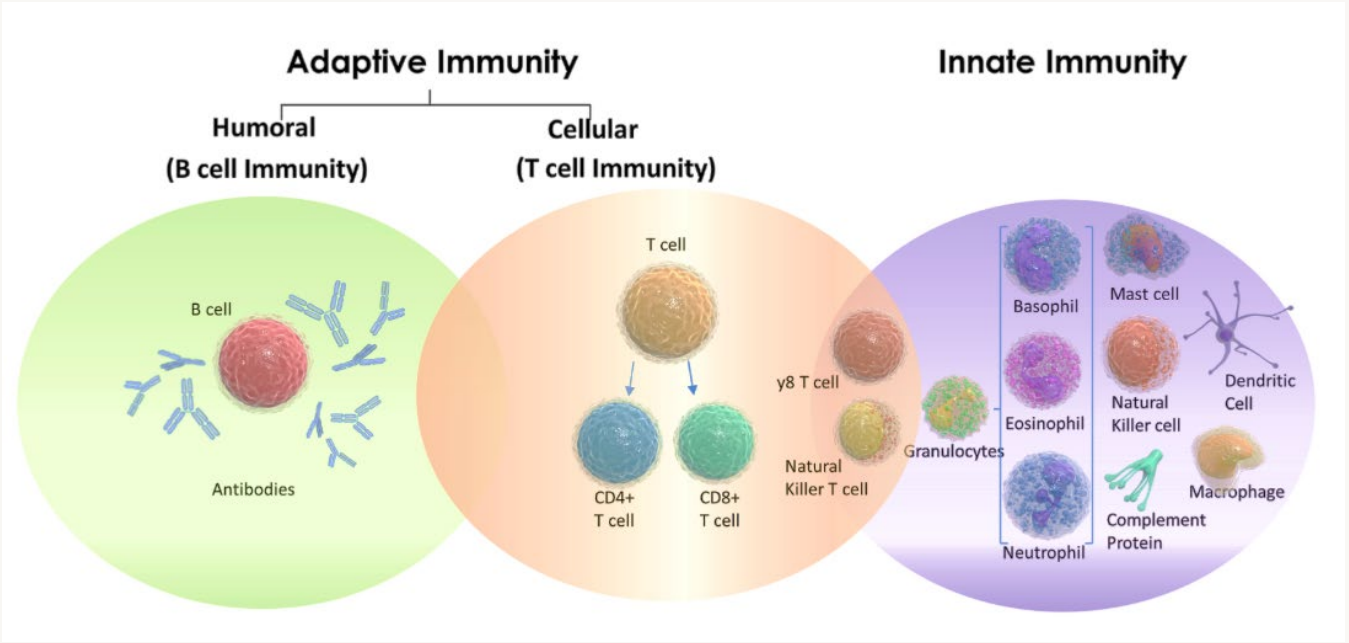
The immune system

Main function:

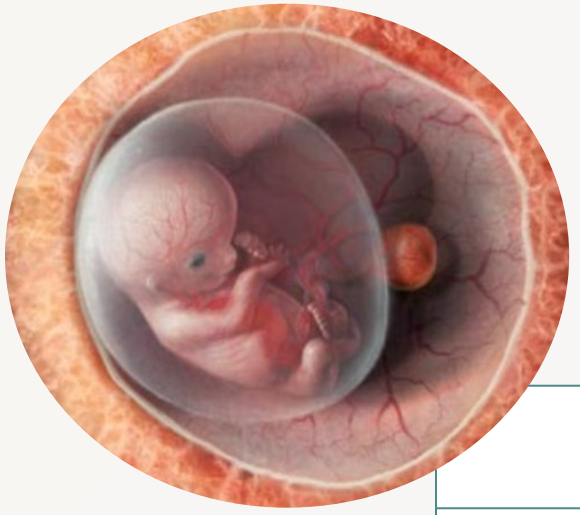
- Protection against infections
- Maintenance of homeostasis

Main characteristics:

- Organized in lymphoid structures and circulating cells
- Differentiates between self and foreign antigens
- Memory
- Develop different defensive mechanisms: innate and adaptive, by a great variety of immune cell types



Protection begins in the utero



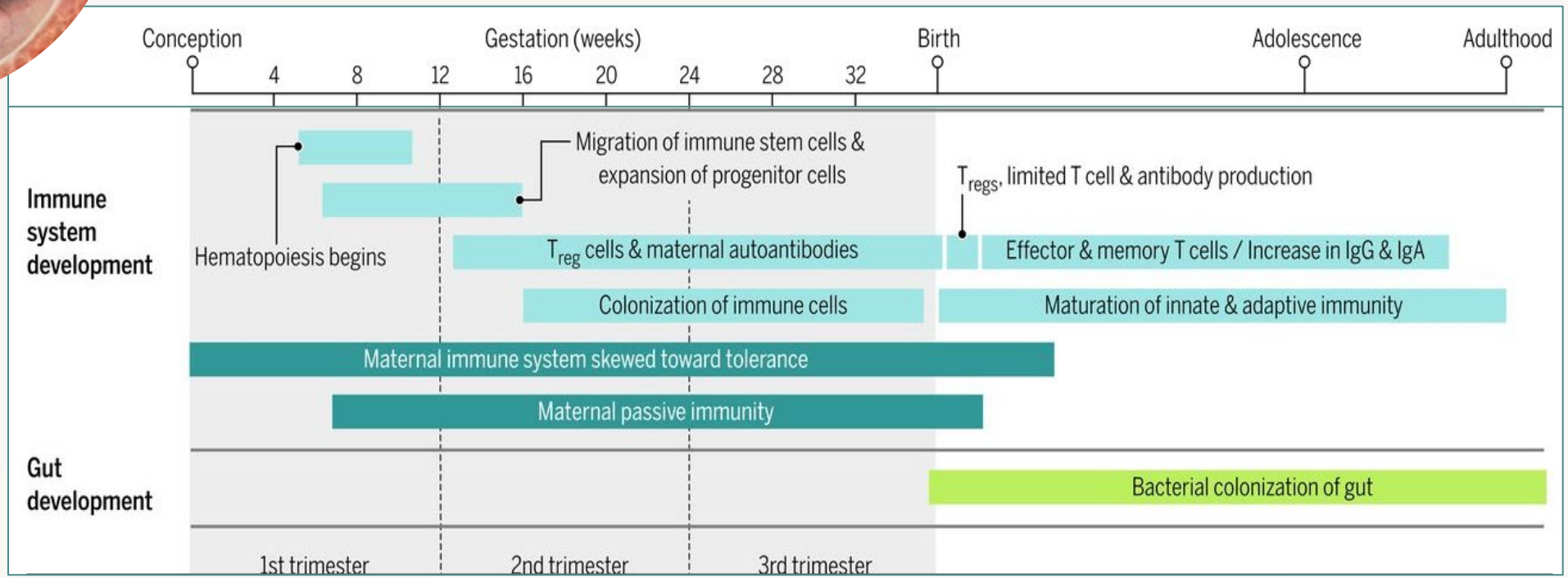
GESTATION

Immune cell development
Tolerogenic activity
Passive immunity

birth

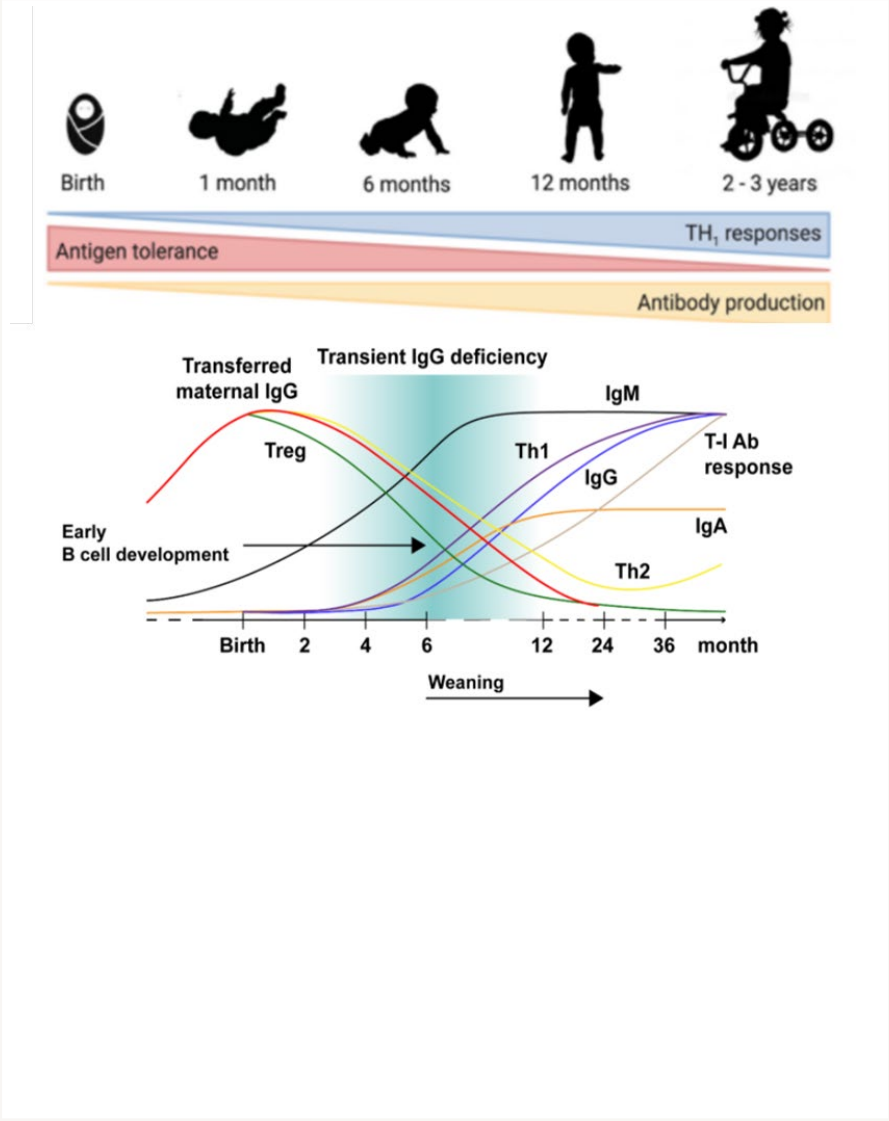
POSTNATAL

Immune cell proliferation
Effector activity
Active immunity



Estes & Mcallister, Science 2016

Protection mechanisms switch after birth

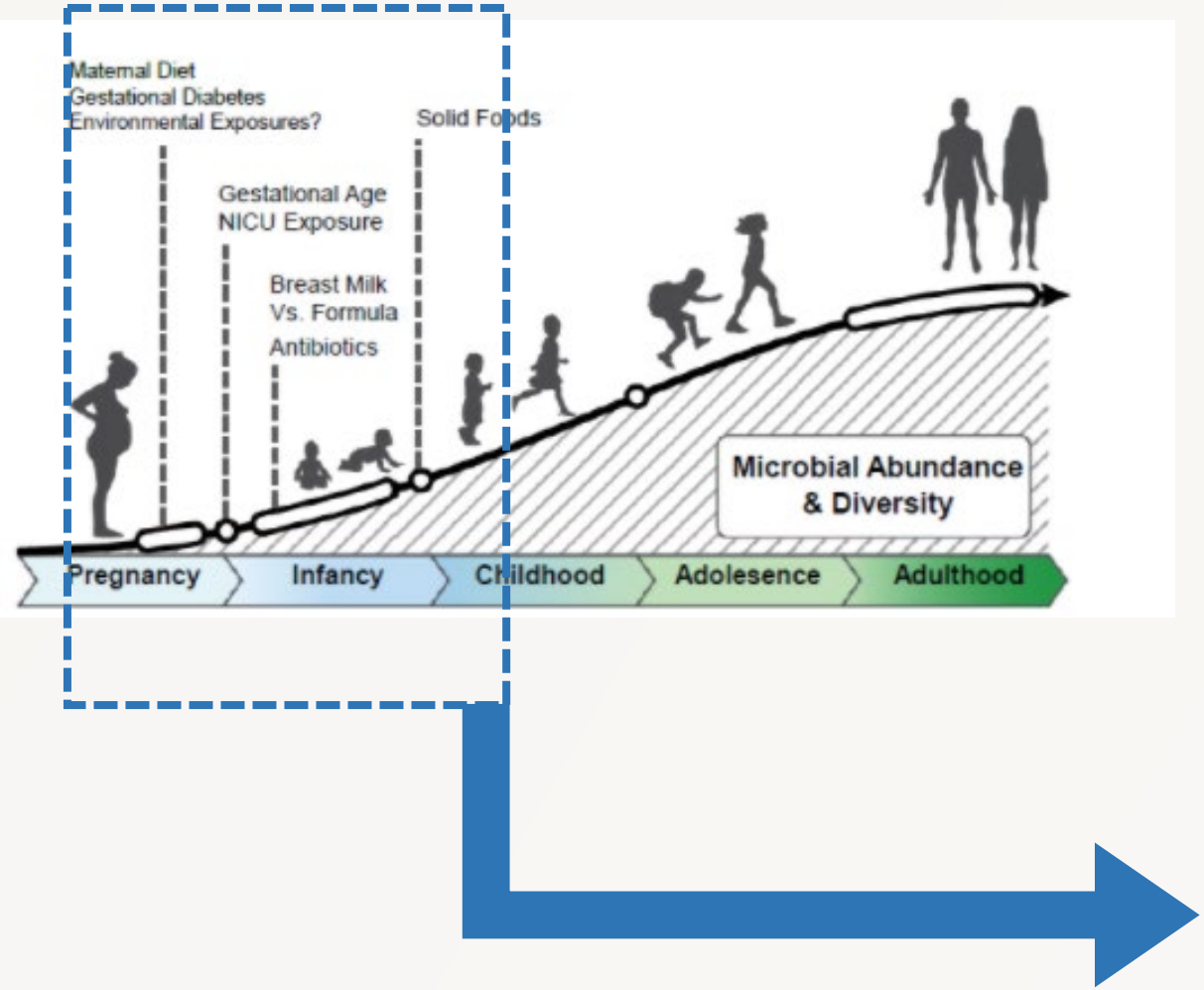


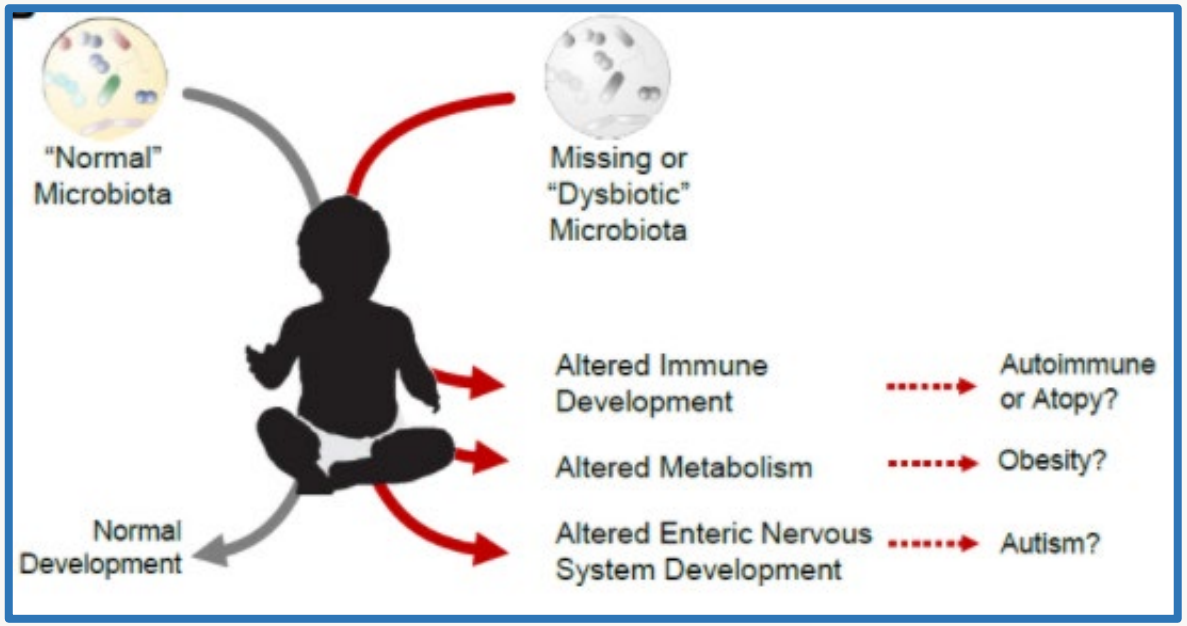
KEY FACTS

- Optimal development of immunity is essential to ensure protection later in life
- The first 6 months after birth are a “window of opportunity”, as contact with specific microbe-associated molecular patterns triggers a cascade of reactions crucial for infant gut maturation
- Disrupting early gut community succession may lead to dysbiosis: the community loses key taxa, diversity, and/or metabolic capacity, and can impact health

Nguyen, PLOS Pathogens 2016

Microbiota development and impact on health



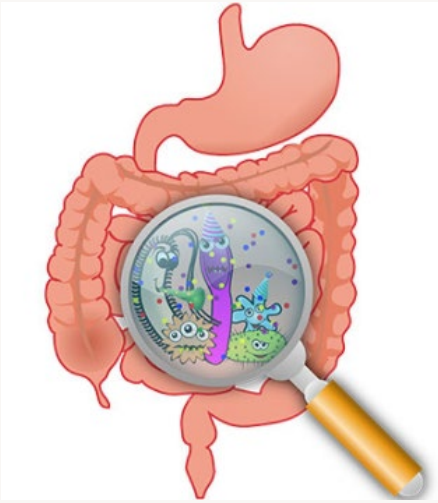


Acquisition of microbiota in early life is though to shape infant development

The gut as a defensive organ

Why a defensive role?

- The gastrointestinal tract is the largest surface of the body in contact with the external environment ($32m^2$)
- Hosts a unique microbiome (mutualism)
- Constantly exposed to luminal antigens: food, microbiota, potential pathogens



How an effective defense is mediated?

- Intestinal **barrier** (anatomical and functional barrier)
- Contains the largest **immune cell population** in the body
- **Oral tolerance** to food-derived and comensal microbiota

Helander, Scand J Gastroenterol 2014

Gut defensive mechanisms

1. **Non-specific**

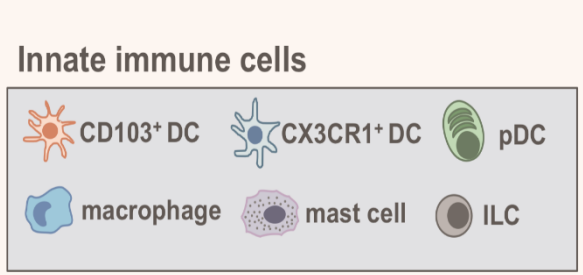
   Luminal: microbiota, mucus layer, enzymes, pH

   Functional: epithelial shedding, secretory activity, intestinal motility

2. **Specific**

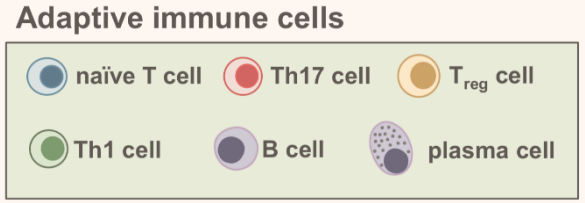
Innate immune system:

- antimicrobial peptides
- epithelial cells (MHC-I, cytokines)
- fagocytes and antigen-presenting cells
- complement proteins, cytokines
- pathogen-recognition receptors (NK, NKT, B1, mast cells)



Adaptive immune system:

- lymphocytes (T and B), plasma cells
- mucosal immunoglobulins (sIgA, IgM, IgG)
- cytokines, chemokines



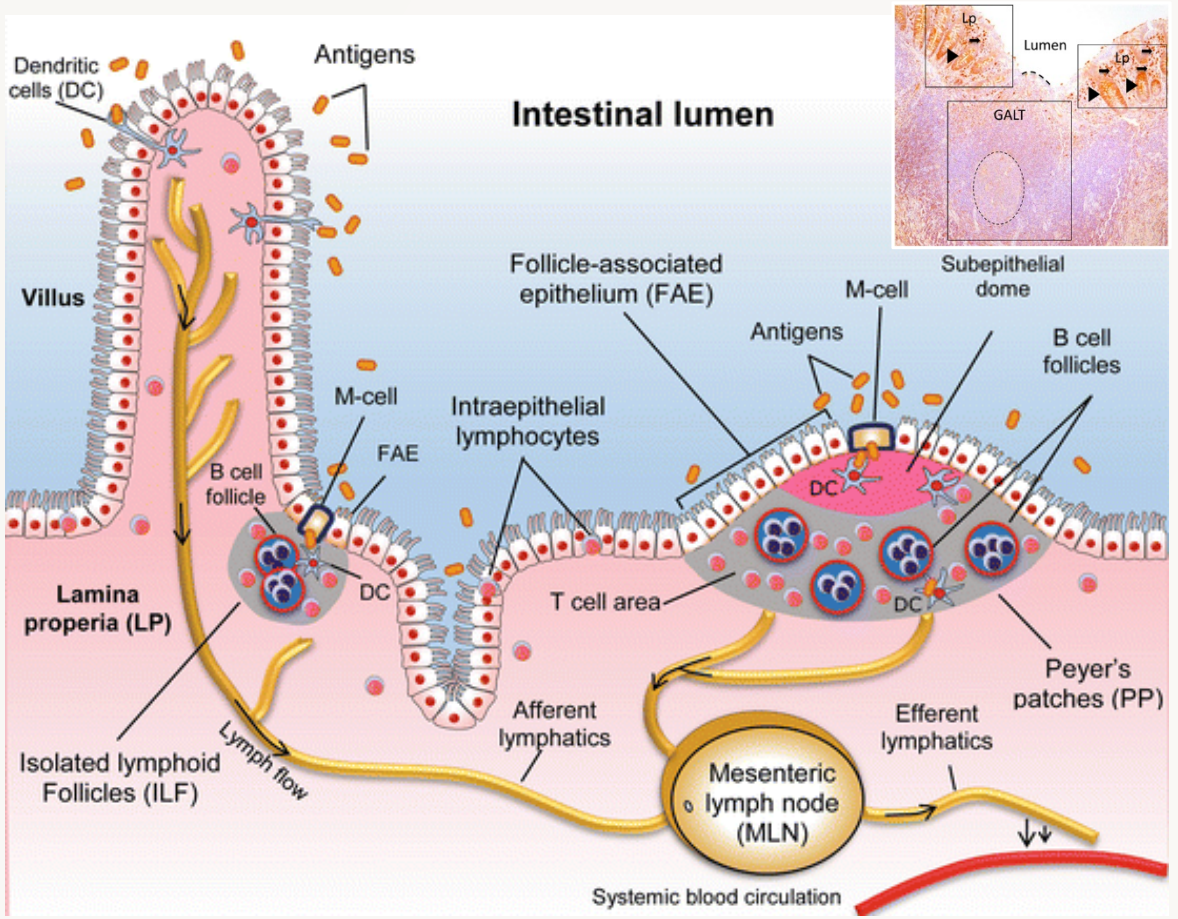
Gut-Associated Lymphoid Tissue (GALT)

Okumura, Proc Jpn Acad Ser B Phys Biol Sci 2016

Structure of GALT

1. **Organized GALT** (Inductive GALT)
   - Peyer's patches
   - Lymphoid folicles and cryptopatches
   - Mesenteric lymph nodes

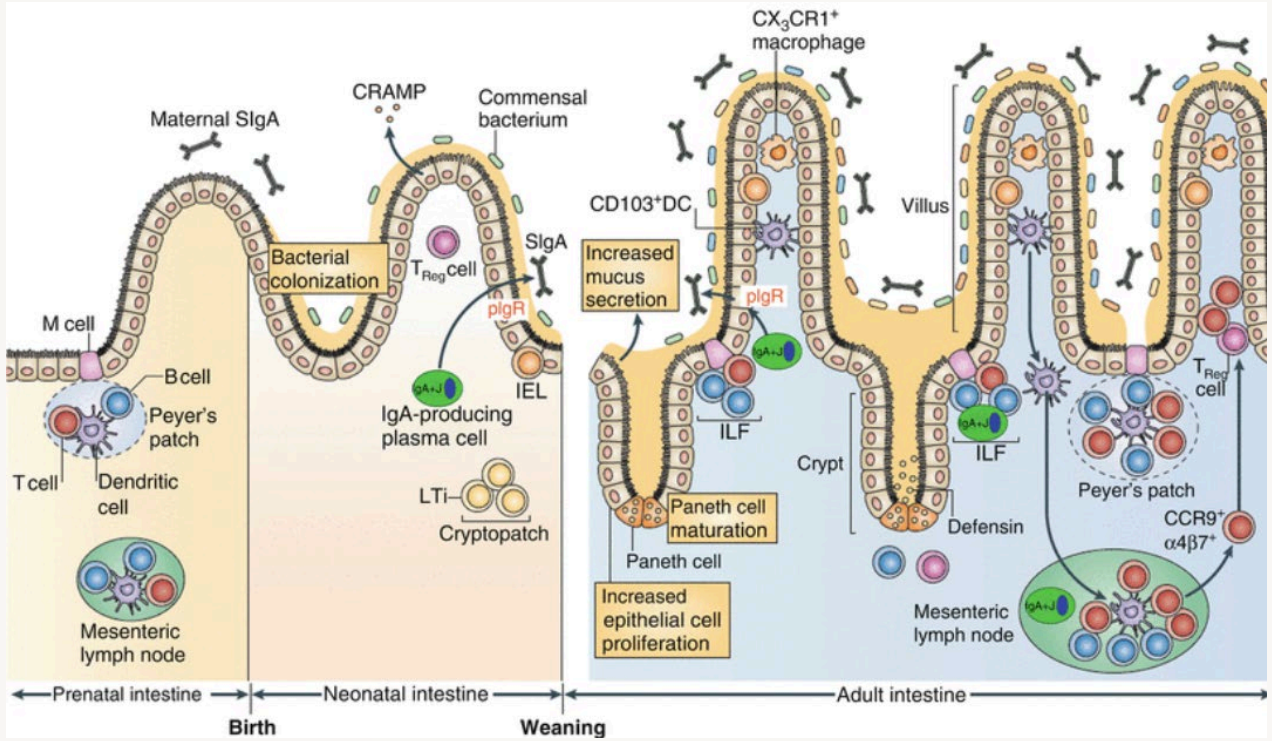
2. **Diffuse GALT** (Effector GALT):
   - Intraepithelial lymphocytes
   - Lamina propia lymphocytes



Spencer, Front Immunol 2012; Zgair, Neuro-Immuno-Gastroenterology, Springer 2016

Development of the GALT

Exposure to environmental antigens



- Lack of sIgA, effector lymphocytes
- Absence of crypts and Paneth cells
- Low epithelial proliferation
- Small lymphoid aggregates

Innate
- Mucous layer thickness, composition
- Antimicrobial peptides
- Innate lymphocytes

Adaptive
- Ig-producing cells, Igs
- T & B lymphocytes
- Expansion of lymphoid structures

Intestinal structure
- Villus/Crypt ratio
- Epithelial proliferation & differentiation
- Functional activity (digestion, secretion)

Renz, Nat Rev Immunol 2011

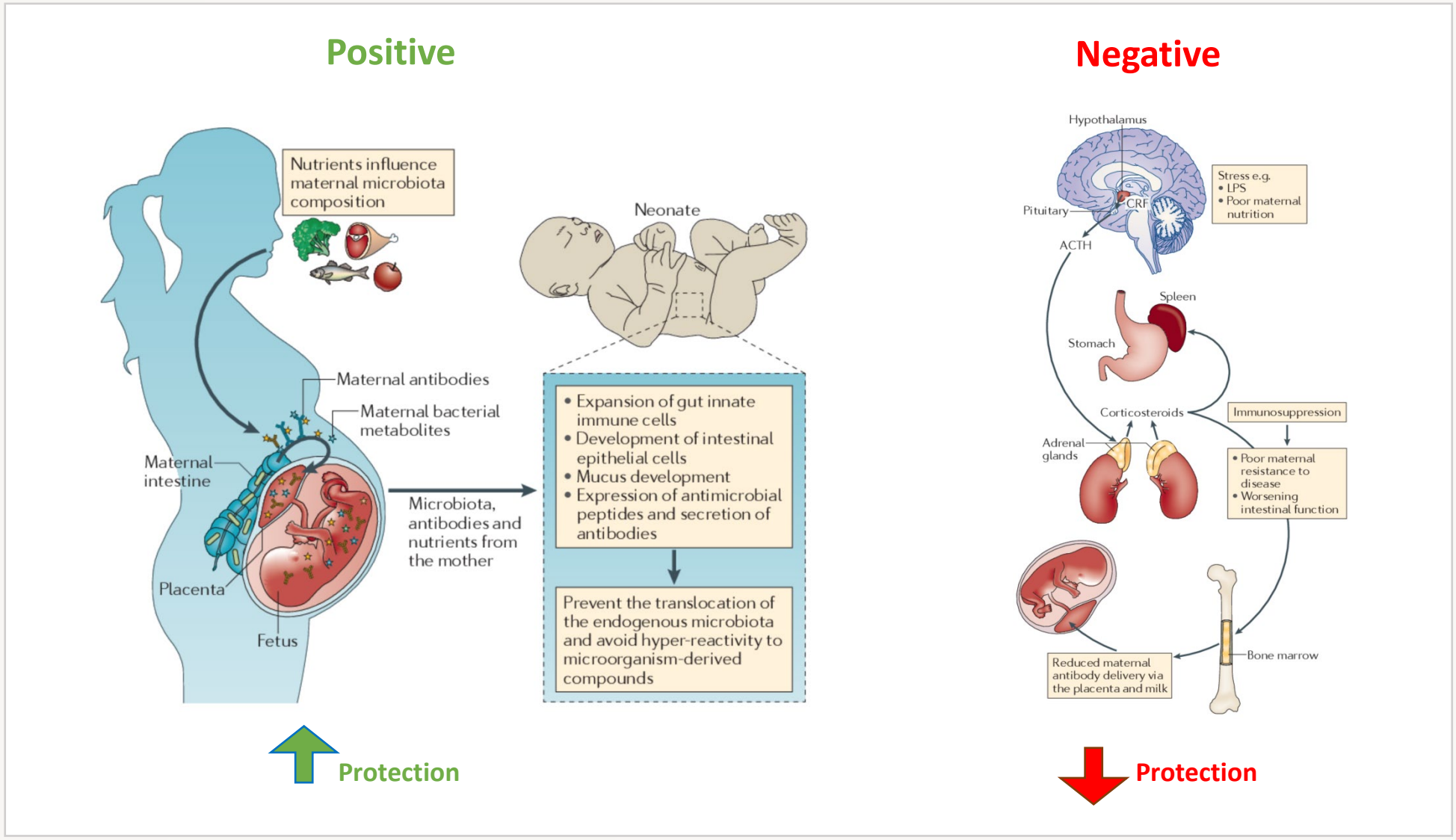
Factors influencing the immune development of the neonate

- **Maternal**:
  - Nutrition
  - Immune status
  - Infections
  - Stress

- **Microbial**:
  - Delivery mode
  - Antibiotic consumption
  - Environmental: infections, pets, hygiene

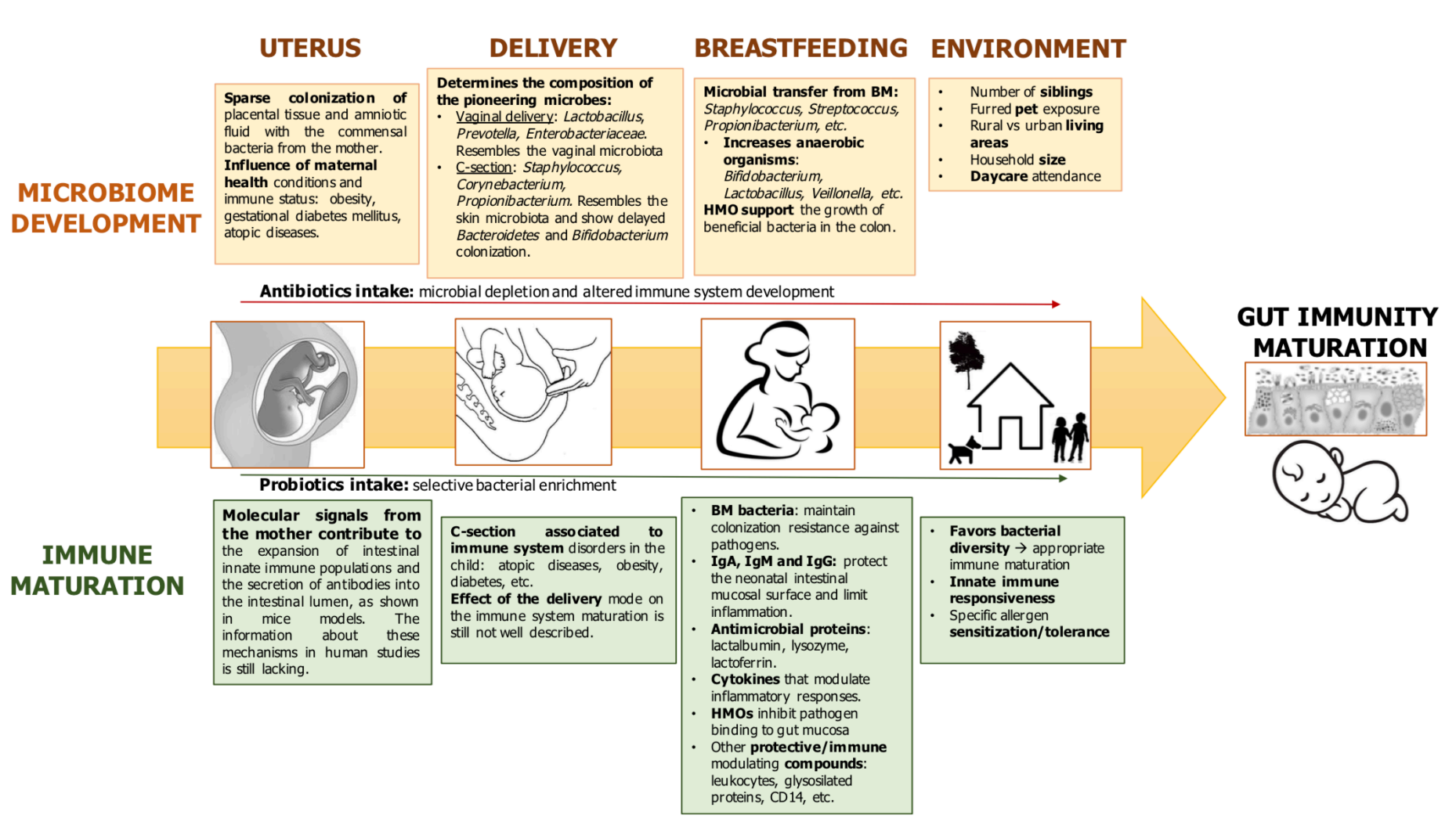
- **Dietary**:
  - Breast milk (bioactive compounds)
  - Formula

Maternal factors influence immune system of the neonate



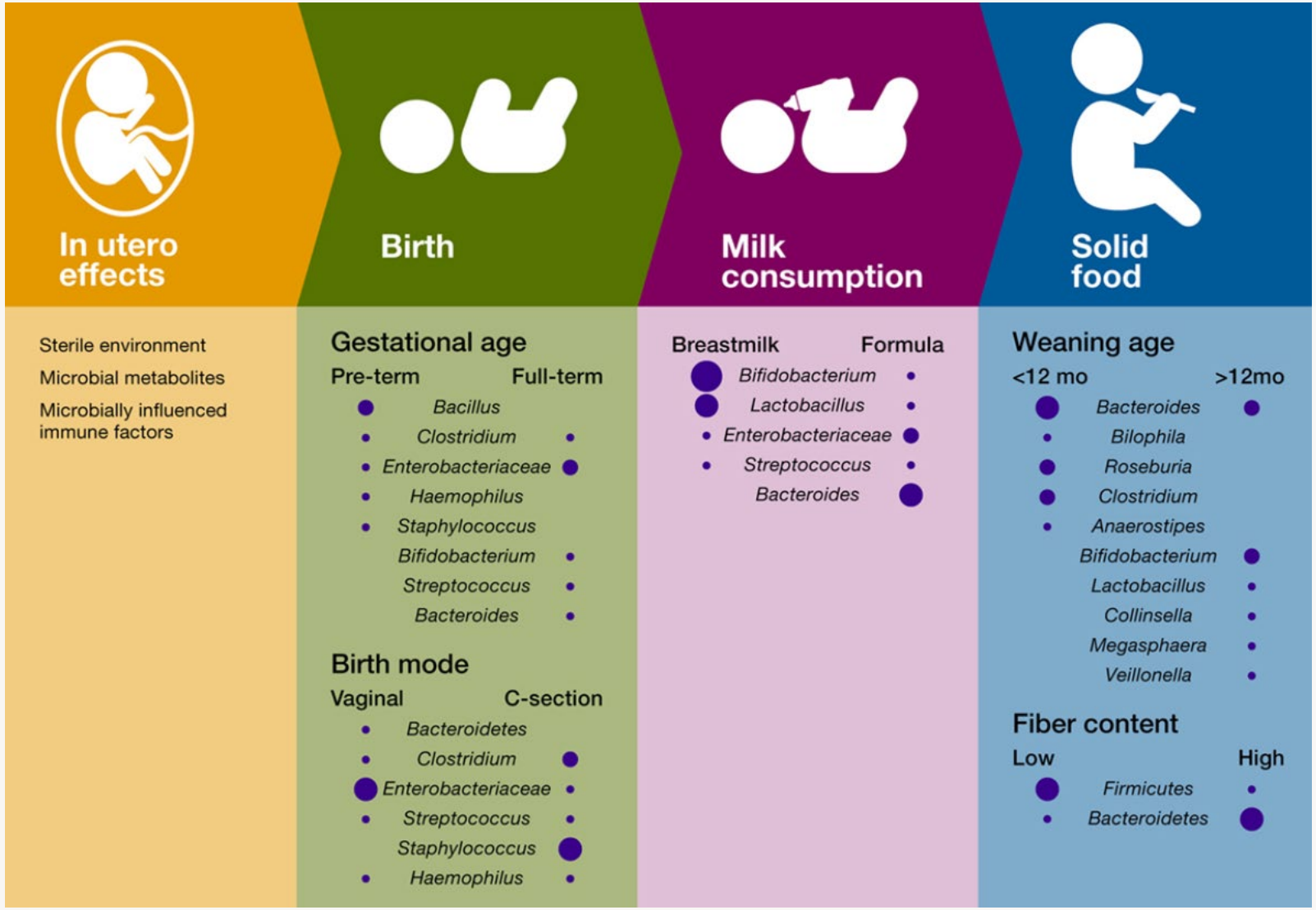
MacPherson, Nat Rev Immunol 2017

Microbiome impact on gut immune development



Dzidic, Med Sci 2018

Factors influencing bacteria taxa



Laforest-Lapointe, Front Immunol, 2016

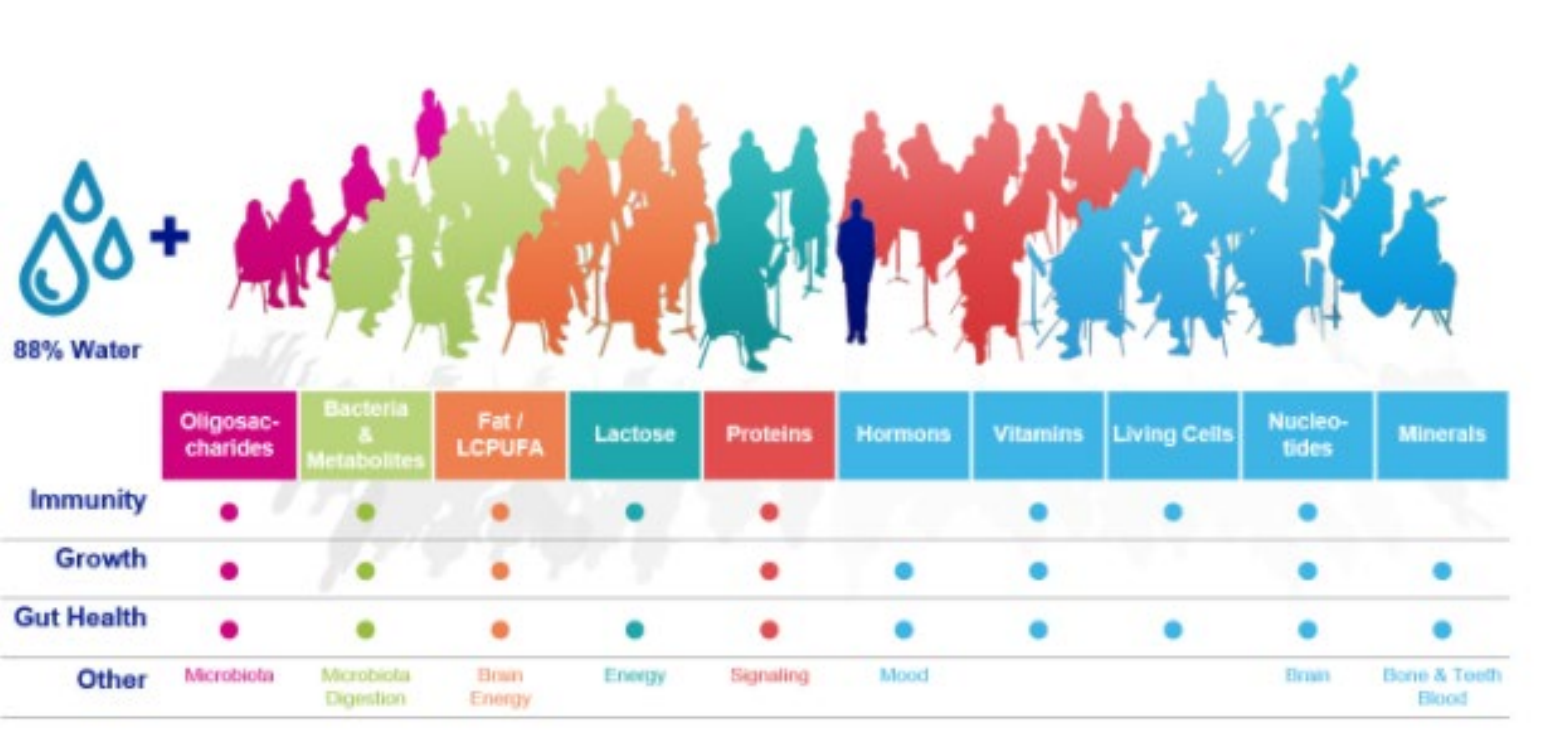
Diet influences immune development of the neonate

- **Breast milk**
  - sIgA, sIgM, IgG in colostrum and mature milk
  - Immune cells: macrophages, neutrophils, T lymphocytes (γ/δ)
  - Cytokines: TNF-α, TGF-β, IL-6, IL-10, IL-7
  - Soluble Fas (CD95) favors tolerance; sCD14, binds LPS
  - Innate defence factors: lactoferrin, lysozyme, α-lactalbumin, lactoperoxidase
  - Prebiotics: HMO to promote acid lactic-producing bacteria
  - Probiotics: Bifidobaceria and Lactobacilli

- **Formula**
  - Approximate nutrient composition of breast milk
  - Supplements added (vitamins, HMO, lipids)
  - **Lack of immune** factors and **growth factors**

Brandtzaeg, Human Health Handbook 2013

Human milk promotes immune and gut development of the neonate



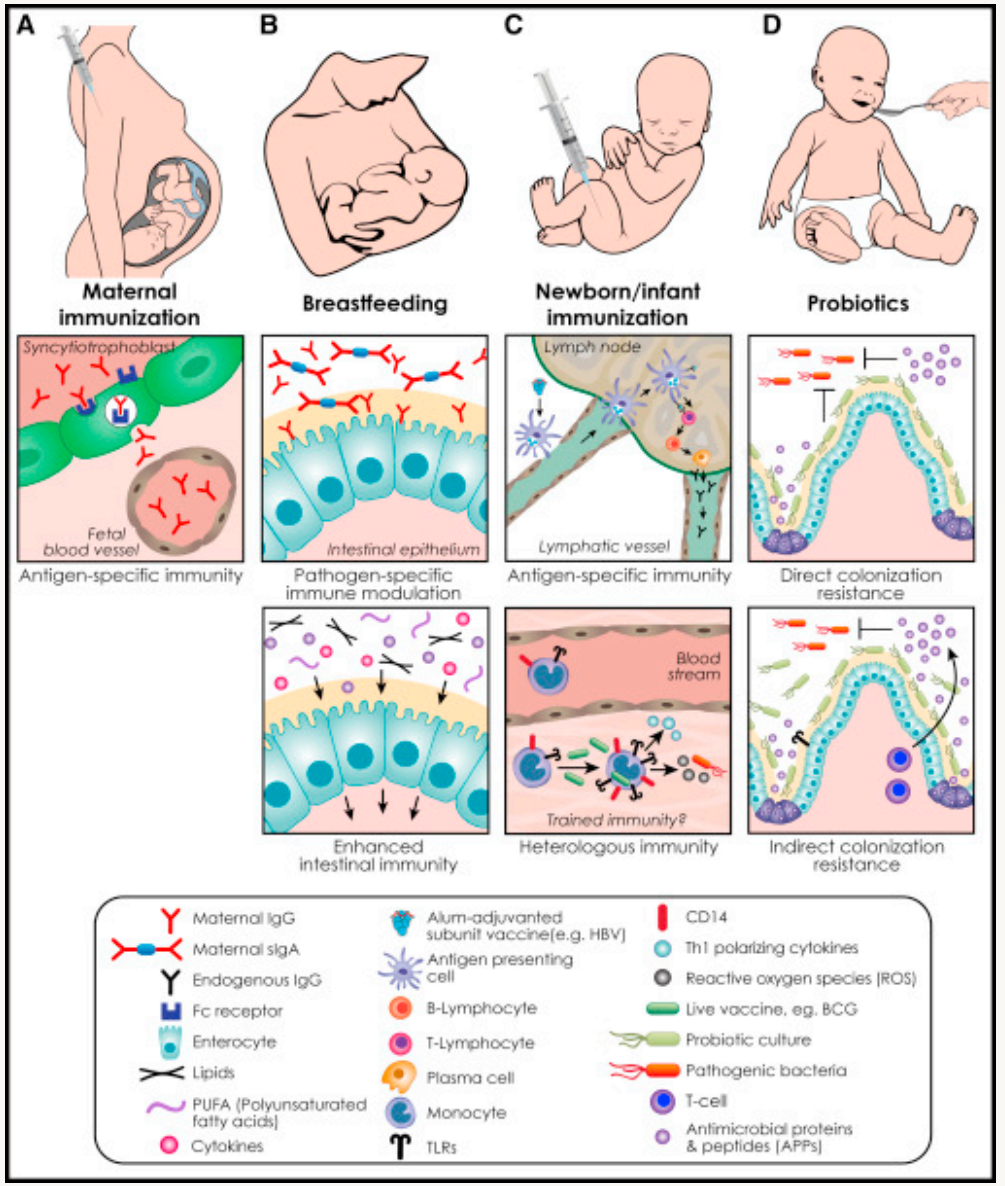
Opportunities to enhance infant immunity

A. **Maternal immunization**
- Passive transfer of IgG (fetus and newborn)

B. **Breastfeeding**
- sIgA, IgG
- Bioactive compounds, immune cells

C. **Early life immunization**
- Specifically targeted pathogens
- Attenuated vaccines

D. **Probiotics**
- Avoid colonization
- Bacteriocin production
- Enhance innate immunity and epithelial defence



Kollmann, Immunity 2017

Take-home messages

- Immune **protection** of the infant begins early in **gestation**
- At birth, defensive mechanisms switch from **tolerogenic** to **effector** activity
- The decrease in **passive** protection from mother's immunity after birth paralels the increase in **activation** of infant immune system
- Exposure to environmental antigens promotes **gut maturation** and **immune development** in the intestinal mucosa
- The infant **gut microbiome** pattern is driven by birth, weaning, and introduction of solid foods, and is influenced by changes in **host immune function**
- Strategies to **enhance infant immune** system can be applied from gestation to the first years of life

Thank you for your attention