

The background of the slide is a microscopic image showing various cells. A large, semi-transparent white circle is positioned on the left side, partially overlapping the text. The cells are in various colors: purple, orange, and blue. Some cells have a textured, fuzzy surface, while others are smoother. There are also small, white, circular structures scattered throughout the image.

The development of immunity in early life

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

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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

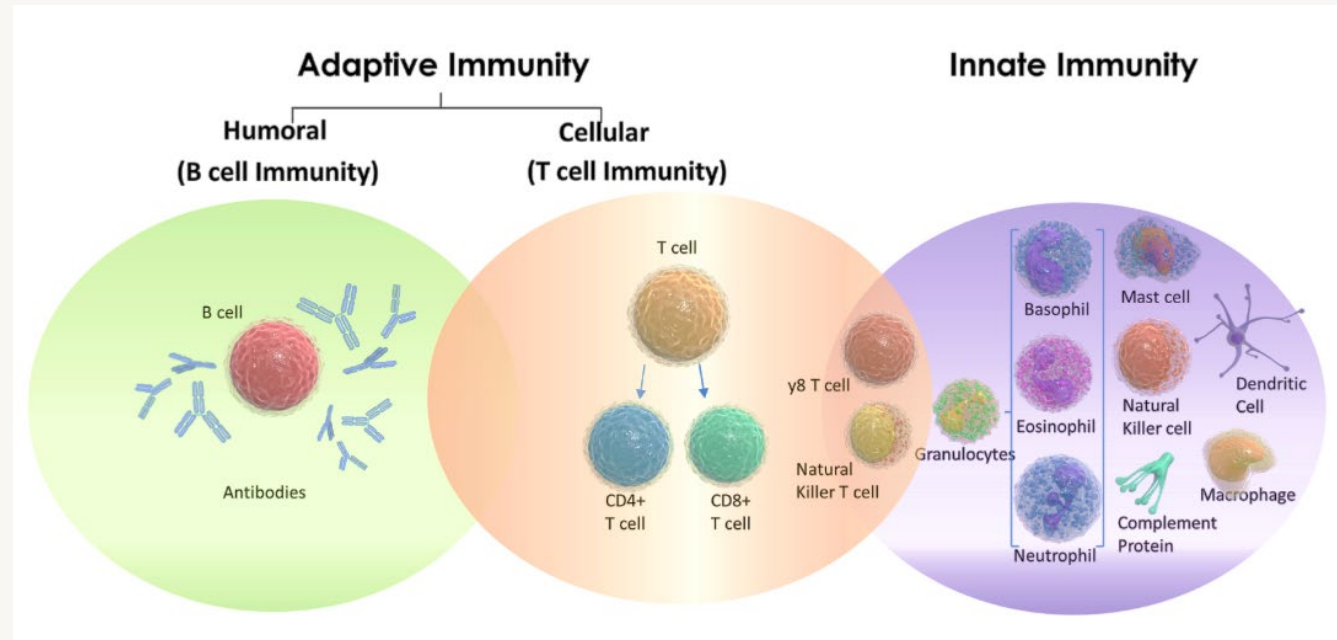
The immune system

Main function:

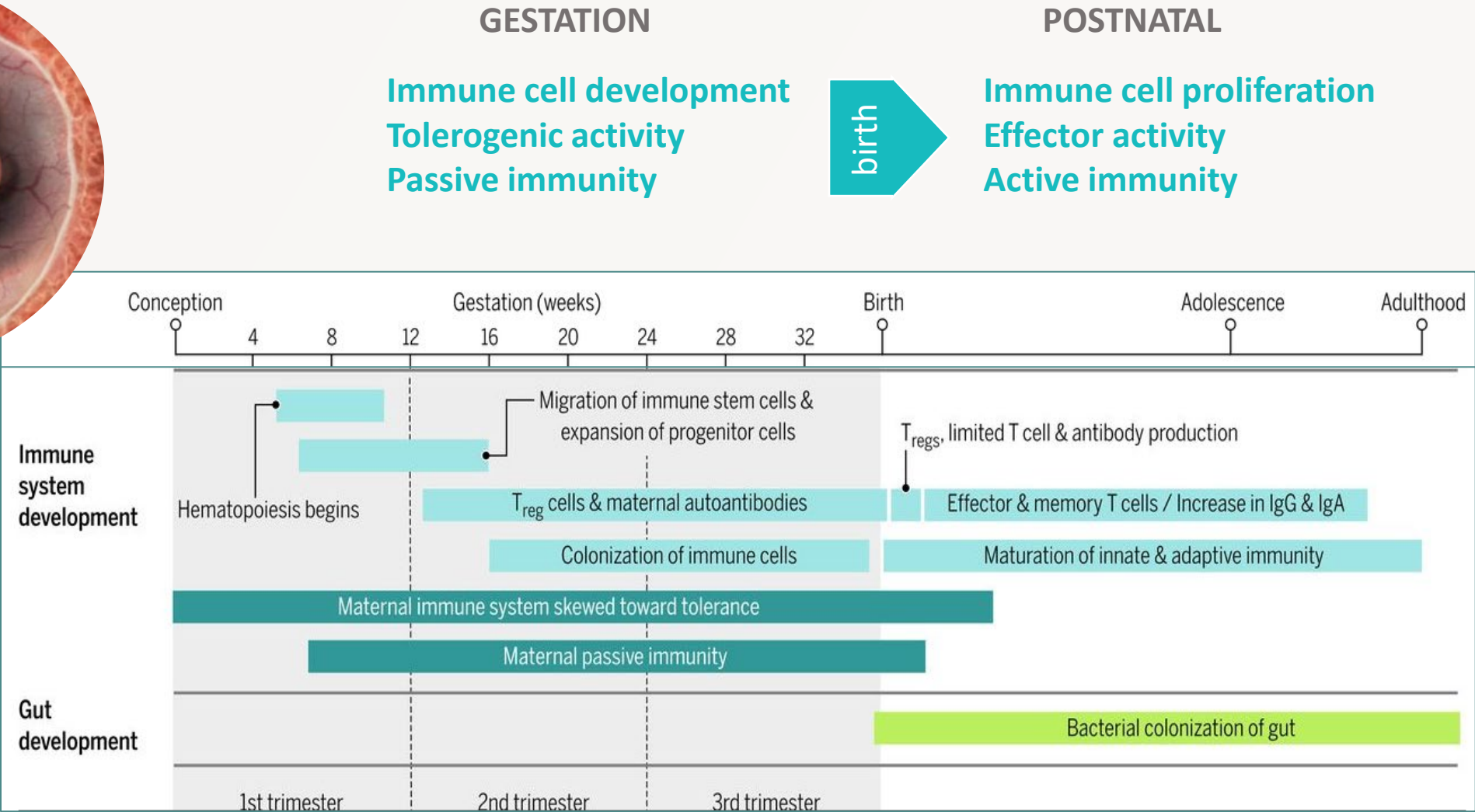
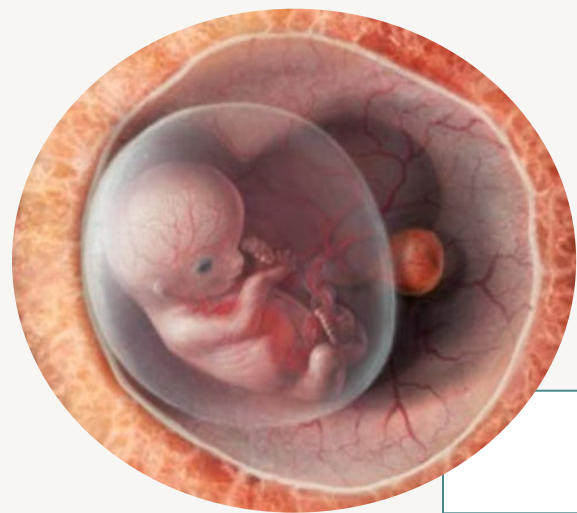
- Protection against infections
- Maintenance of homeostasis

Main characteristics:

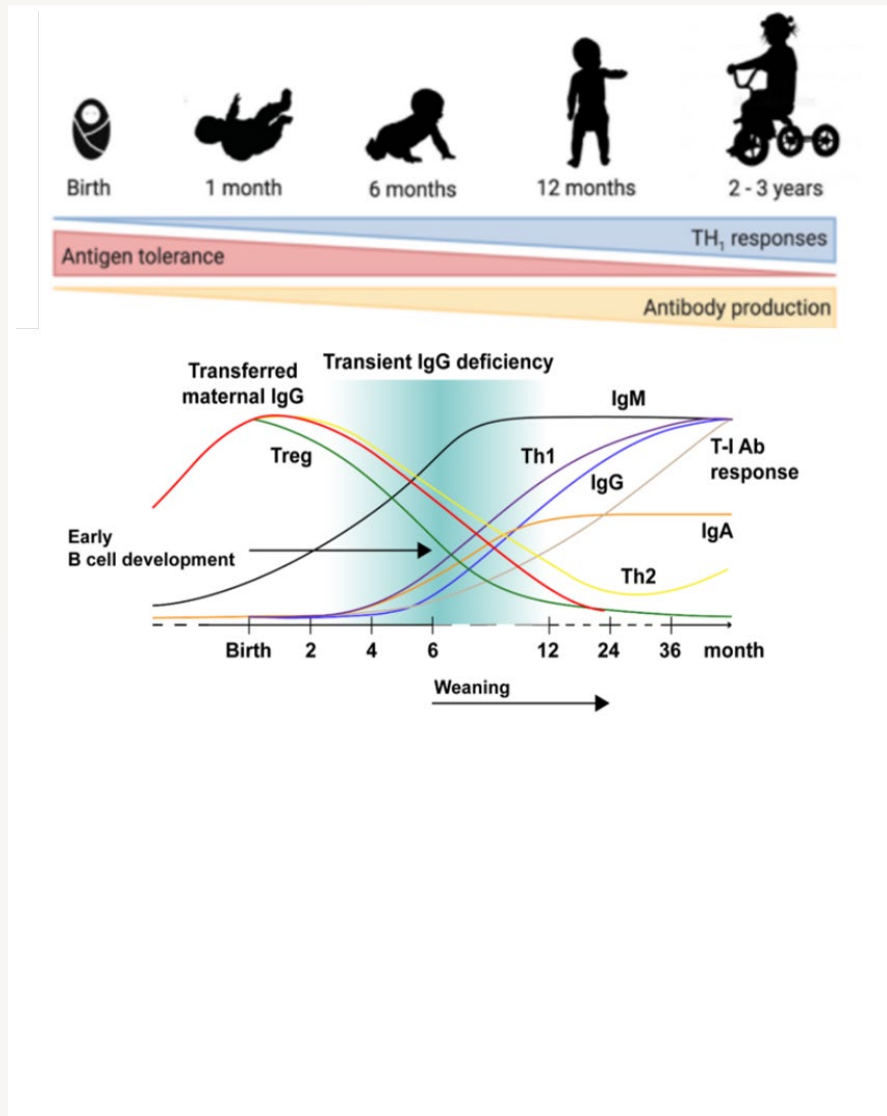
- Organized in lymphoid structures and circulating cells
- Differentiates between self and foreign antigens
- Memory
- Develop different defensive mechanisms: innate and adaptive, by a great variety of immune cell types



Protection begins in the utero



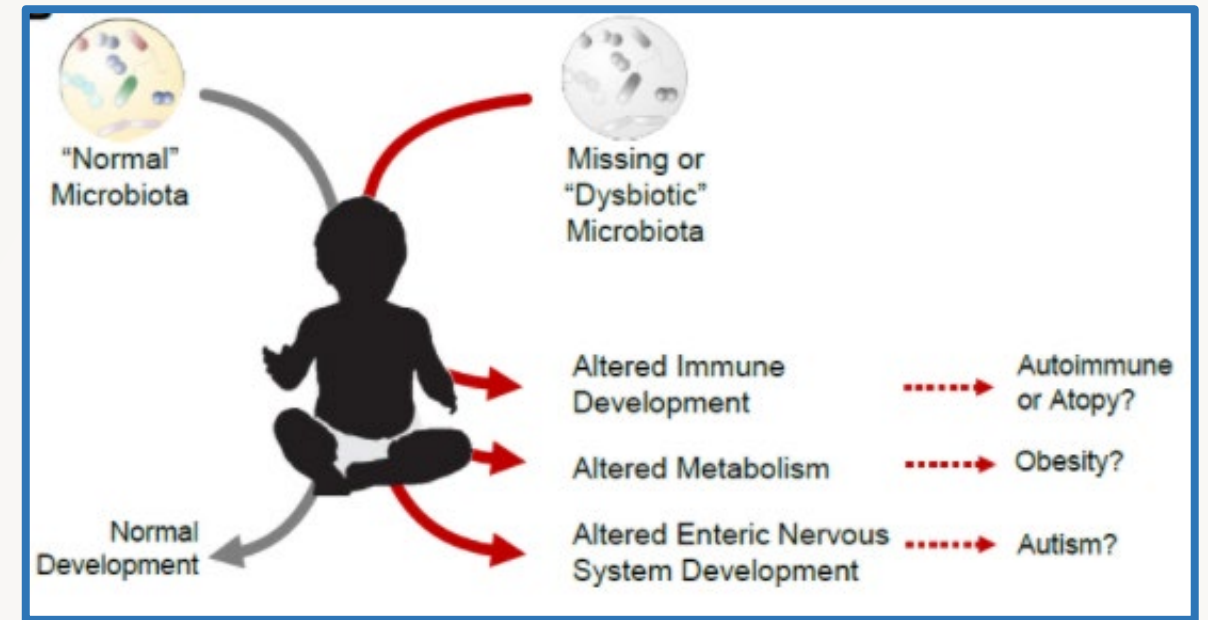
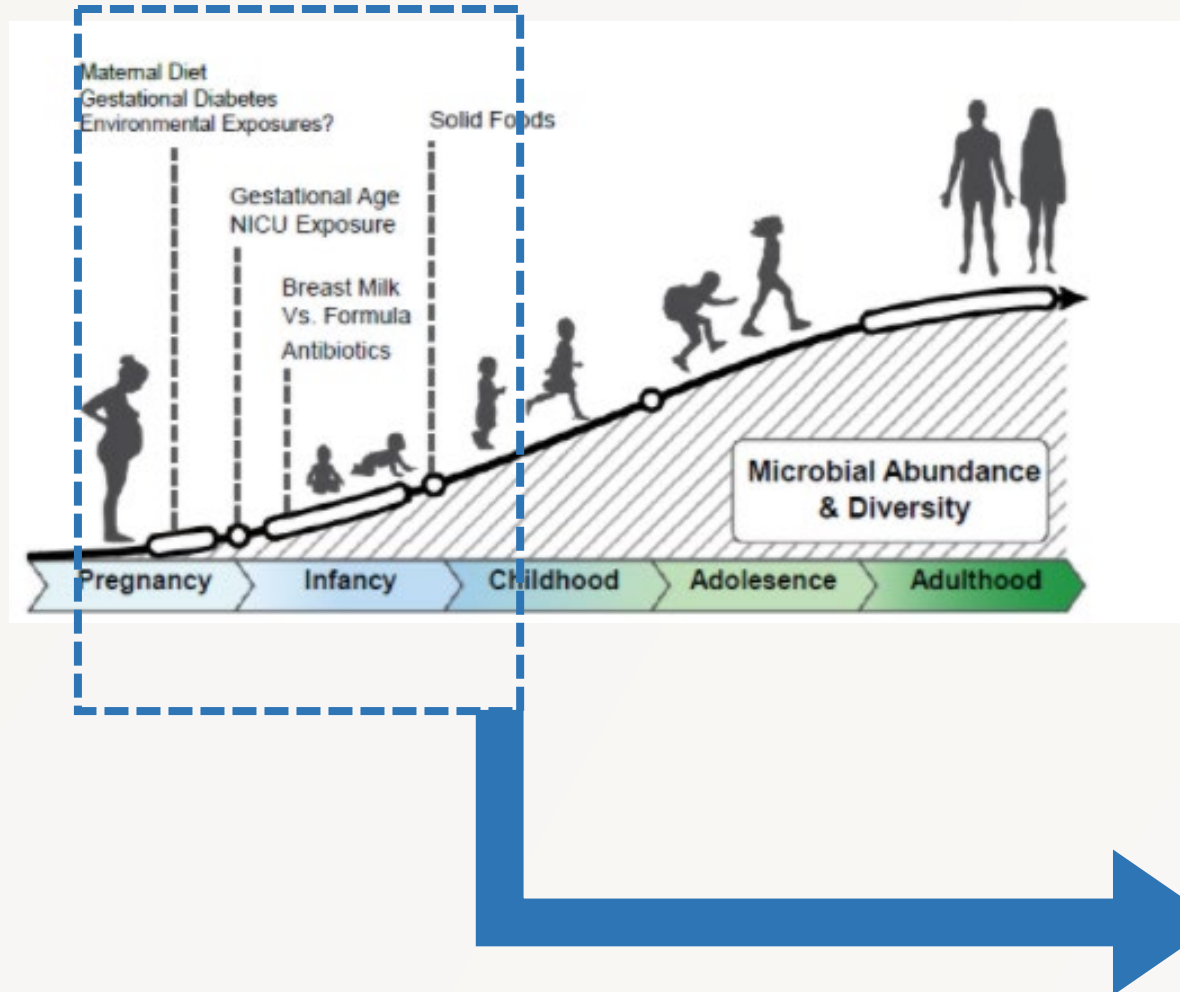
Protection mechanisms switch after birth



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

Microbiota development and impact on health



Acquisition of microbiota in early life is thought 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 (32m²)
- 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

Gut defensive mechanisms

1. Non-specific

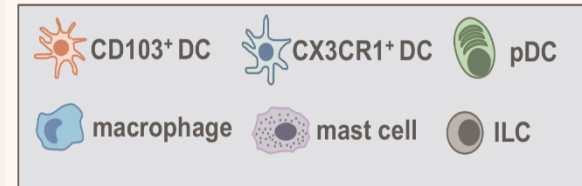
Luminal: microbiota, mucus layer, enzymes, pH

Functional: epithelial shedding, secretory activity, intestinal motility

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)

Innate immune cells

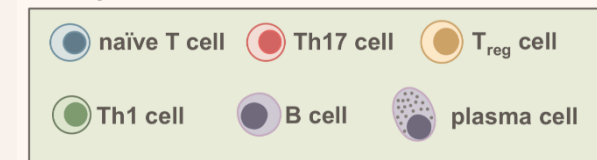


2. Specific

Adaptive immune system:

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

Adaptive immune cells



Gut-Associated Lymphoid Tissue (GALT)

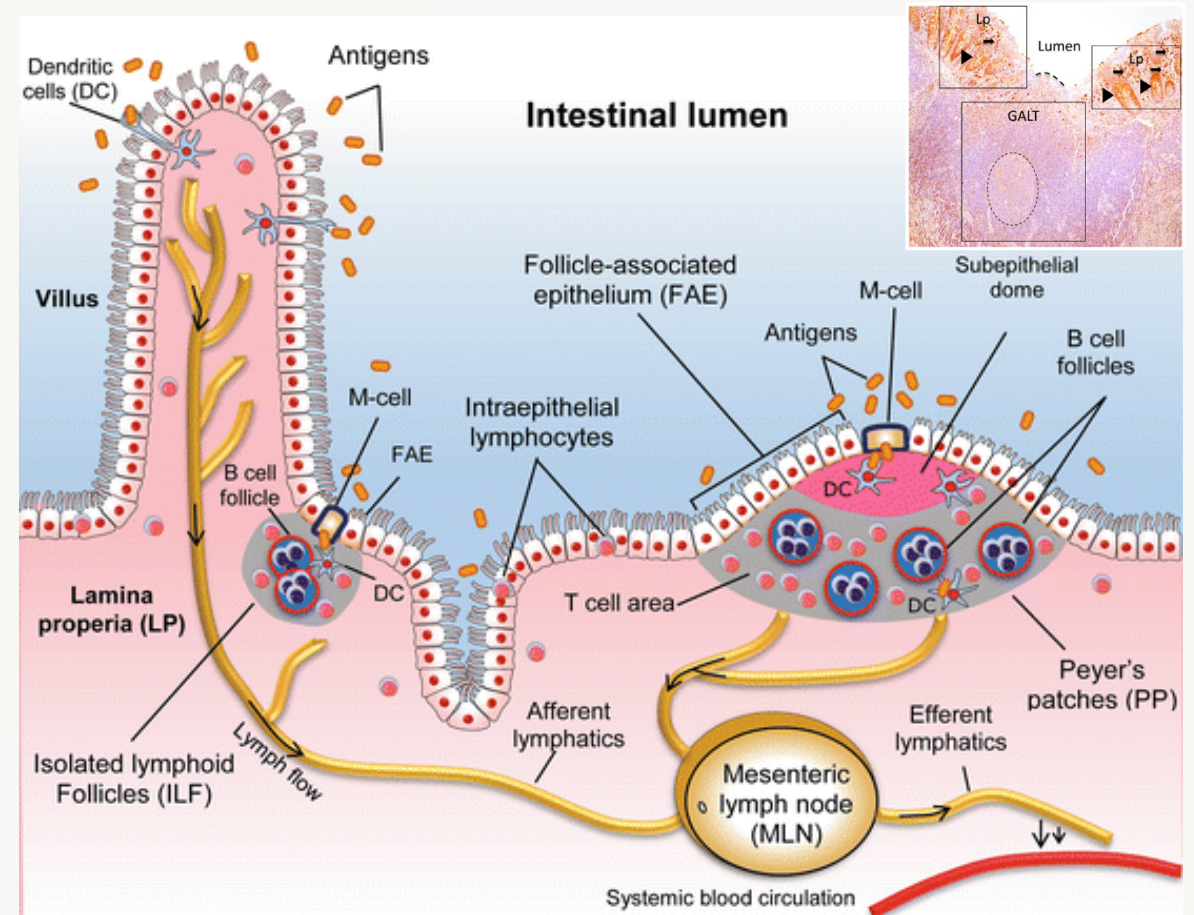
Structure of GALT

1. Organized GALT (Inductive GALT)

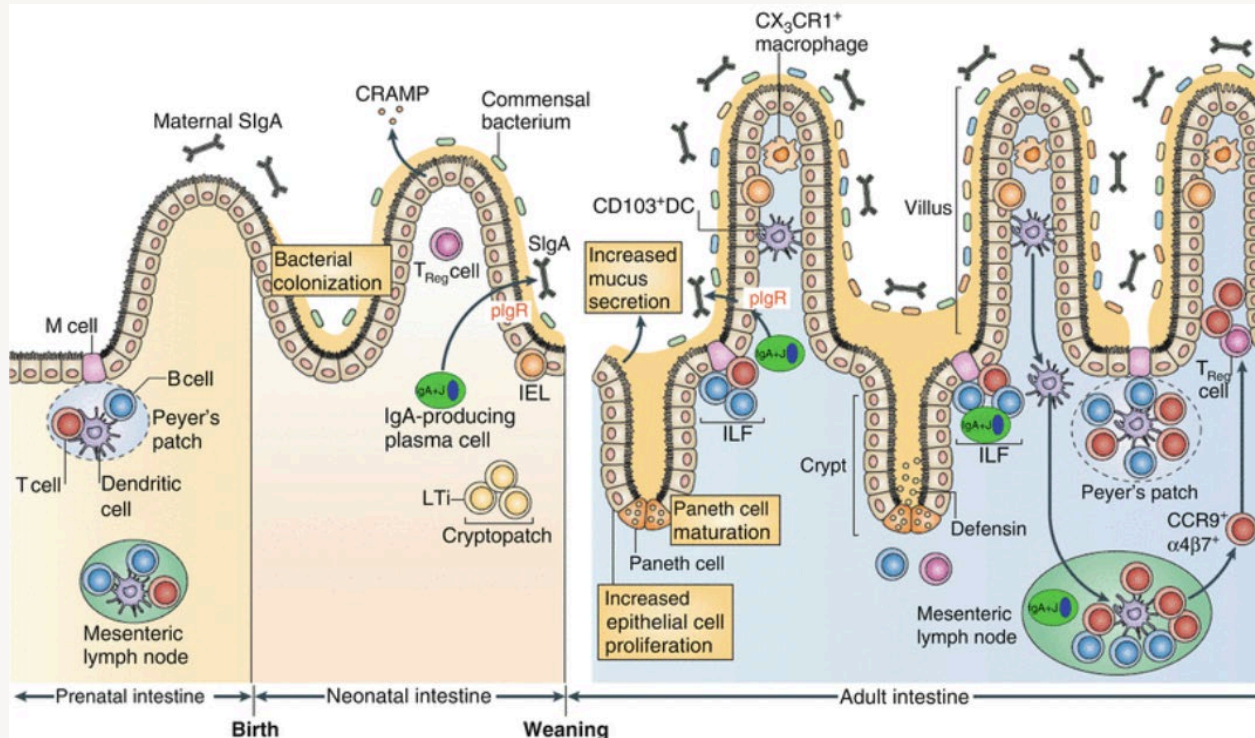
- Peyer's patches
- Lymphoid follicles and cryptopatches
- Mesenteric lymph nodes

2. Diffuse GALT (Effector GALT):

- Intraepithelial lymphocytes
- Lamina propria lymphocytes



Development of the GALT



- 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

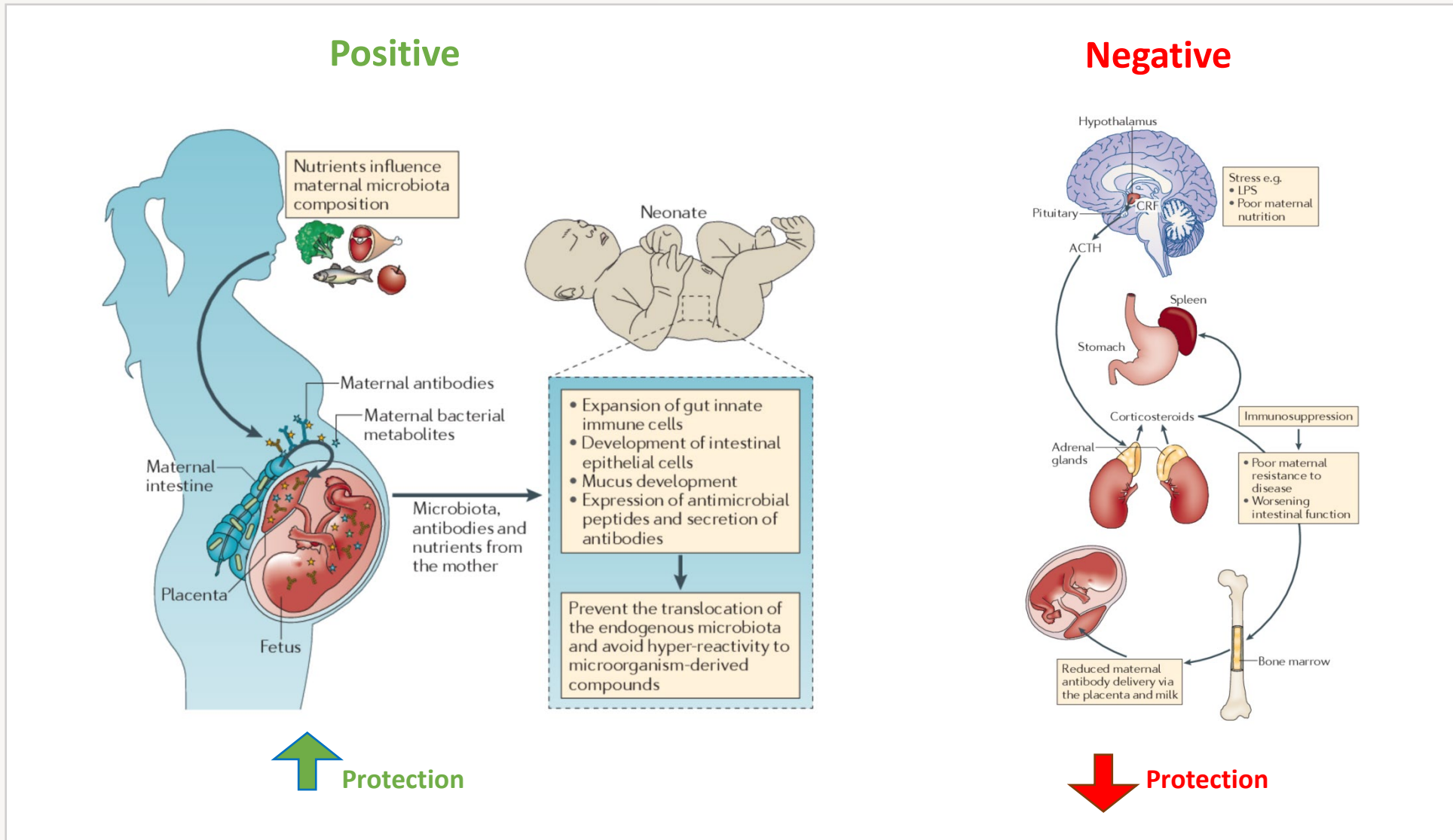
Intestinal structure

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

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



Microbiome impact on gut immune development

MICROBIOME DEVELOPMENT

UTERUS

Sparse colonization of placental tissue and amniotic fluid with the commensal bacteria from the mother.
Influence of maternal health conditions and immune status: obesity, gestational diabetes mellitus, atopic diseases.

DELIVERY

Determines the composition of the pioneering microbes:

- Vaginal delivery:** *Lactobacillus*, *Prevotella*, *Enterobacteriaceae*. Resembles the vaginal microbiota
- C-section:** *Staphylococcus*, *Corynebacterium*, *Propionibacterium*. Resembles the skin microbiota and show delayed *Bacteroidetes* and *Bifidobacterium* colonization.

BREASTFEEDING ENVIRONMENT

Microbial transfer from BM: *Staphylococcus*, *Streptococcus*, *Propionibacterium*, etc.
Increases anaerobic organisms: *Bifidobacterium*, *Lactobacillus*, *Veillonella*, etc.
HMO support the growth of beneficial bacteria in the colon.

- Number of **siblings**
- Furred **pet** exposure
- Rural vs urban **living areas**
- Household **size**
- **Daycare** attendance

Antibiotics intake: microbial depletion and altered immune system development



Probiotics intake: selective bacterial enrichment

IMMUNE MATURATION

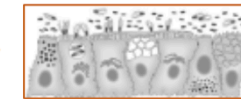
Molecular signals from the mother contribute to the expansion of intestinal innate immune populations and the secretion of antibodies into the intestinal lumen, as shown in mice models. The information about these mechanisms in human studies is still lacking.

C-section associated to immune system disorders in the child: atopic diseases, obesity, diabetes, etc.
Effect of the delivery mode on the immune system maturation is still not well described.

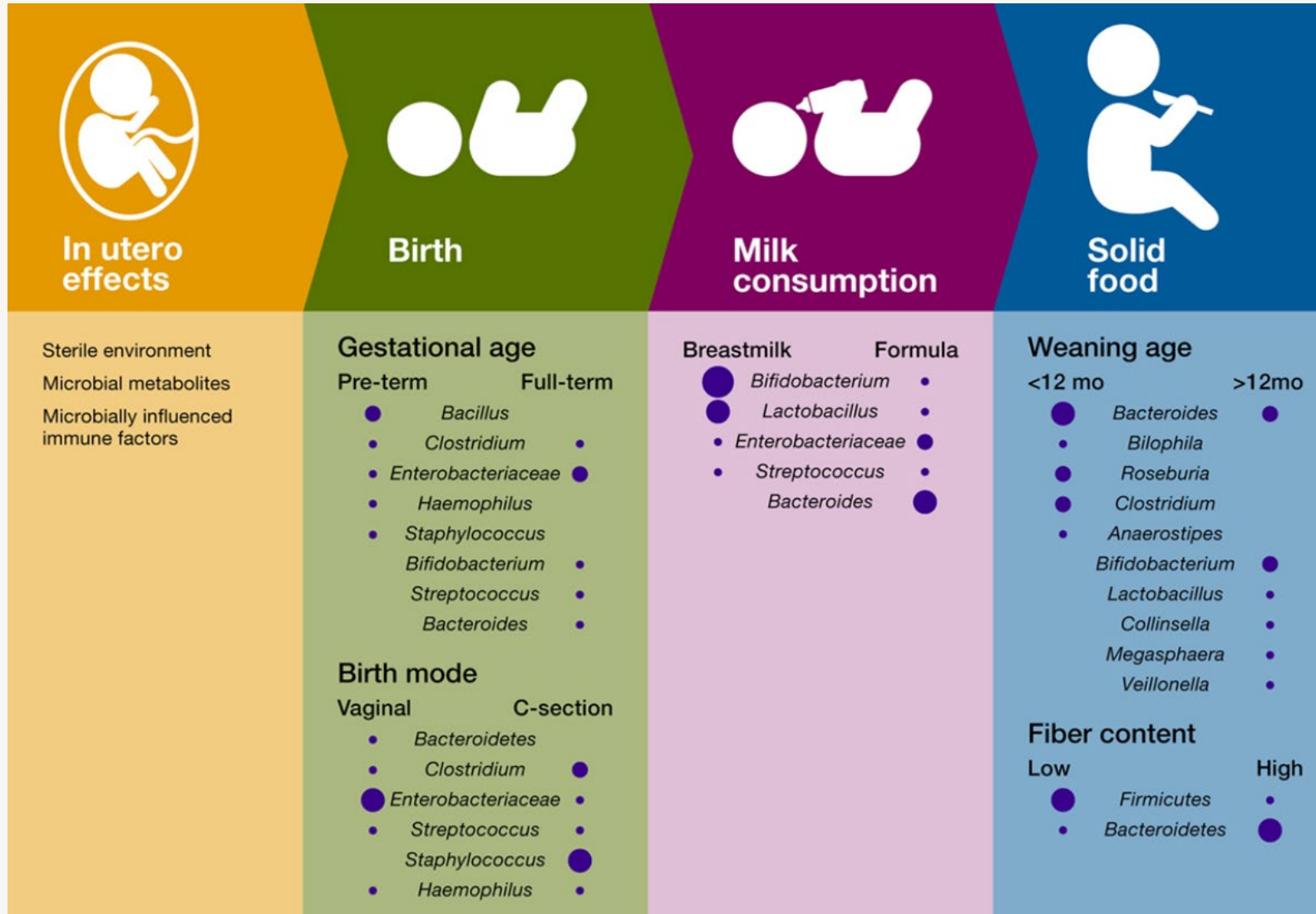
- **BM bacteria:** maintain colonization resistance against pathogens.
- **IgA, IgM and IgG:** protect the neonatal intestinal mucosal surface and limit inflammation.
- **Antimicrobial proteins:** lactalbumin, lysozyme, lactoferrin.
- **Cytokines** that modulate inflammatory responses.
- **HMOs** inhibit pathogen binding to gut mucosa
- Other **protective/immune modulating compounds:** leukocytes, glycosylated proteins, CD 14, etc.

- **Favors bacterial diversity** → appropriate immune maturation
- **Innate immune responsiveness**
- Specific allergen **sensitization/tolerance**

GUT IMMUNITY MATURATION



Factors influencing bacteria taxa



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: Bifidobacteria and Lactobacilli

- **Formula**

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

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

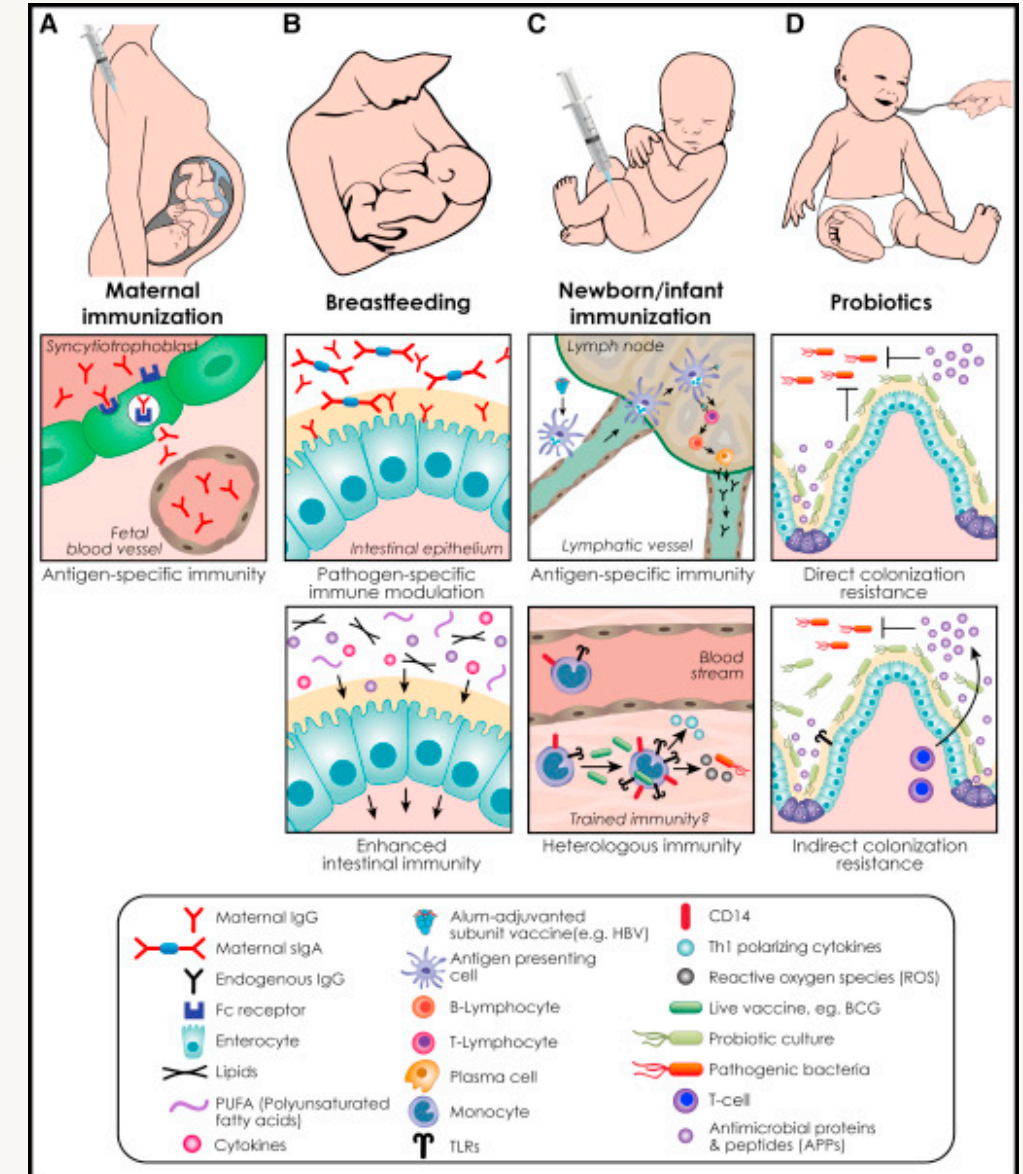
- sIgA, IgG
- Bioactive compounds, immune cells

C. Early life immunization

- Specifically targeted pathogens
- Attenuated vaccines

D. Probiotics

- Avoid colonization
- Bacteriocin production
- Enhance innate immunity and epithelial defence



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 parallels 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