Role Of Gut Microbiota In The Development Of The Immune System and Allergy

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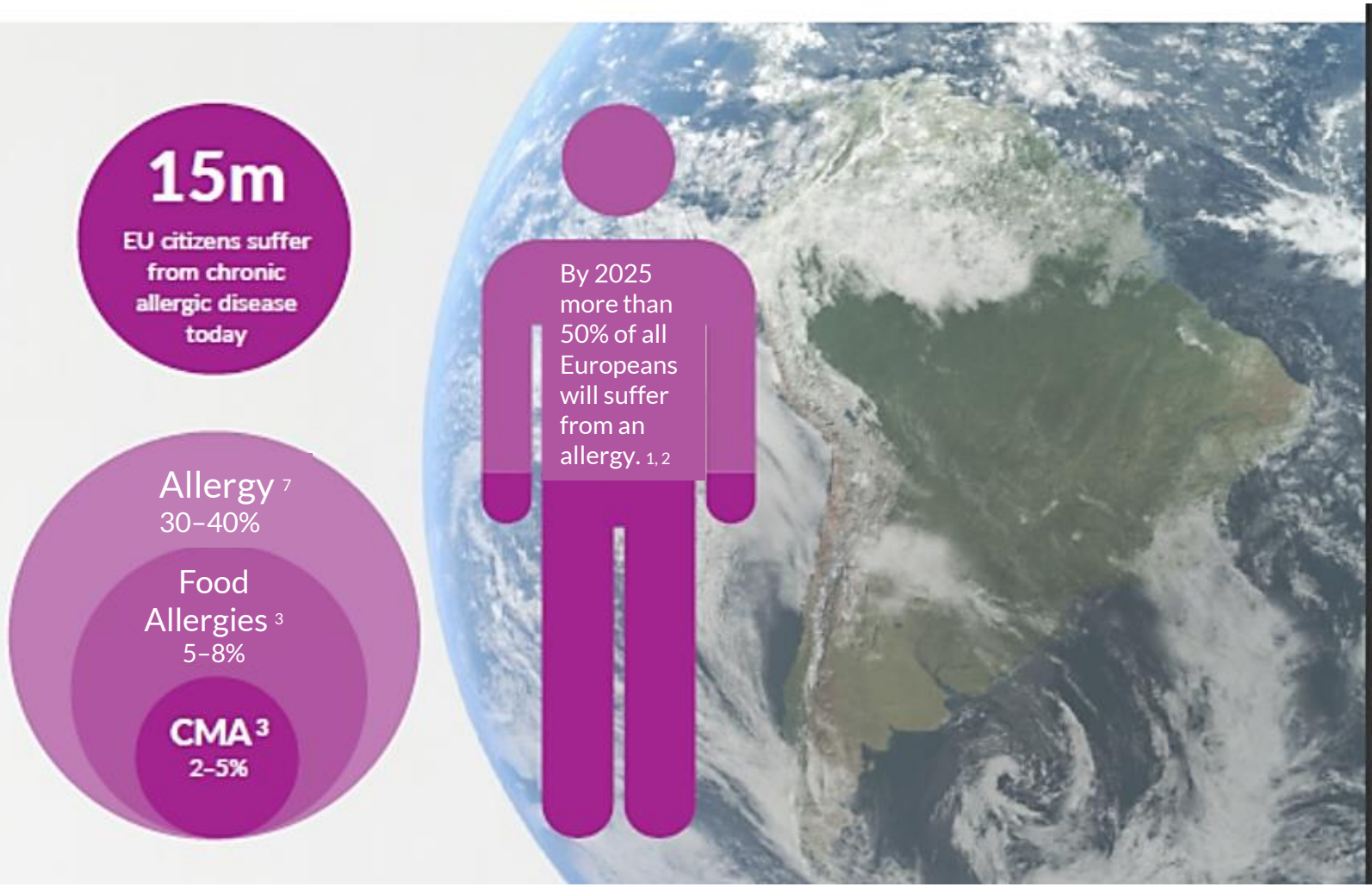
GLOBAL RISE IN ALLERGY

ALLERGIES ARE ON THE RISE: 30-40% OF THE WORLD POPULATION IS NOW ALLERGIC

- By the 2050s, allergies will affect up to 4 billion people globally[1,2]
- They are a rapidly increasing burden in developing countries
- Food allergies affect up to 8% of infants and young children globally,[3] with cow's milk being the leading cause[4-6]



THE PATTERN OF COW'S MILK ALLERGY IS BECOMING INCREASINGLY AGGRESSIVE

Prevalence is 2–5 % worldwide[1]

There has been a trend towards:

- Increasing **incidence** and **prevalence**[2]
- Increasing **persistence** into school age and beyond[3]
- Increasing **severity**[4]
- Increasing rate of hospitalisations[4]

Increasing trend of the number of hospital admissions for FIA among Italian children from 2006 to 2014[4]

ENVIRONMENTAL FACTORS MAY HAVE A ROLE
IN INCREASING THE RISK OF DEVELOPING ALLERGIES[1-3]

GENETIC FACTORS

Family history of allergy

20-40% higher allergy risk[4-6]

ENVIRONMENTAL FACTORS — NEW

C-section

Up to **30%** higher allergy risk[7]

Antibiotic use

X2 higher asthma risk[8]

Pollution

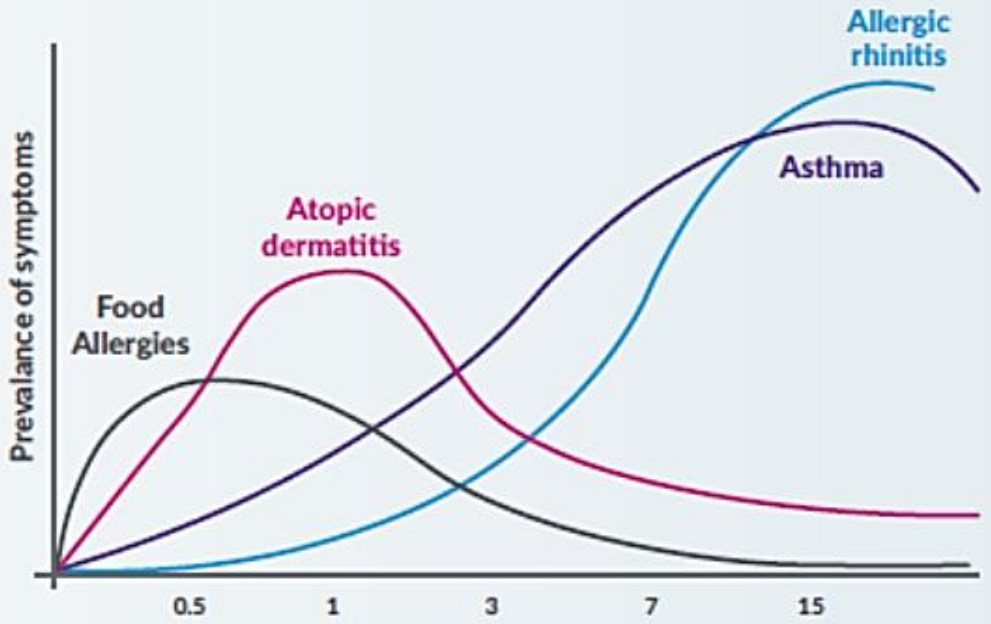
Up to **20%** higher wheezing risk[9,10]

GUT MICROBIOTA DYSBIOSIS
associated factor to the increase in allergy incidence[11,12]

DANONE EARLY LIFE NUTRITION

ALLERGY IN EARLY LIFE HAS REPERCUSSIONS FOR FUTURE HEALTH: THE ATOPIC MARCH

Allergies early in life predispose subjects for having other secondary allergies in later life, this is know as the concept of the Atopic March[1-3]



Preventation of the first allergies matters
The 'Atopic March'. Schematic representation of symptoms according to age. Once a child has developed atopic dermatitis or a food allergy in the first years of life, the child is more likely to develop other allergies, like allergic rhinitis or asthma later in life [1-4]

THE BURDEN OF ALLERGY GOES BEYOND SYMPTOMS…

PHYSICAL [1-4]

- Increased risk of future non-communicable diseases (NCDs) e.g. obesity, diabetes, heart disease, hypertension etc.

FINANCIAL [1,5,6]

€521M*

- Increased medication and health costs
- Increased indirect costs

(e.g. parental loss of income due to time off work)

PSYCHOLOGICAL [1,7]

- Distress for child and parents
- Impact on quality of life

SOCIAL [1,7]

- Social isolation
- Fear of future health problems

Strong rationale for developing effective strategies for infants at risk and with allergy.

EVOLUTION OF CARE
FROM AVOIDANCE TO ACTIVE TOLERANCE DEVELOPMENT

Oral Tolerance development is the ultimate allergy prevention

FROM: AVOIDANCE

- Avoid allergenic foods in hope of prevention
- Educate on management of allergic reactions'
- Wait and watch for the development of tolerance

TO: TOLERANCE DEVELOPMENT

- Early active introduction of potentially allergenic foods to support tolerance development before allergy develops and promoting acquisition of tolerance
- A balancing act between avoiding allergens and promoting acquisition of tolerance

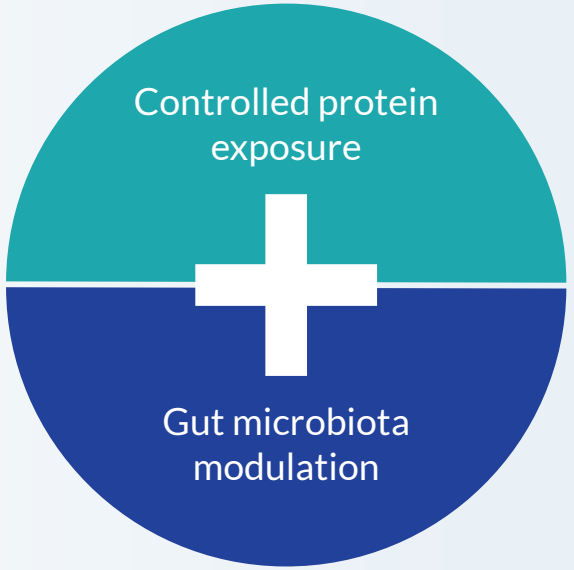
PRESENT: FROM AVOIDANCE TO ACTIVE TOLERANCE DEVELOPMENT

PARADIGM SHIFT

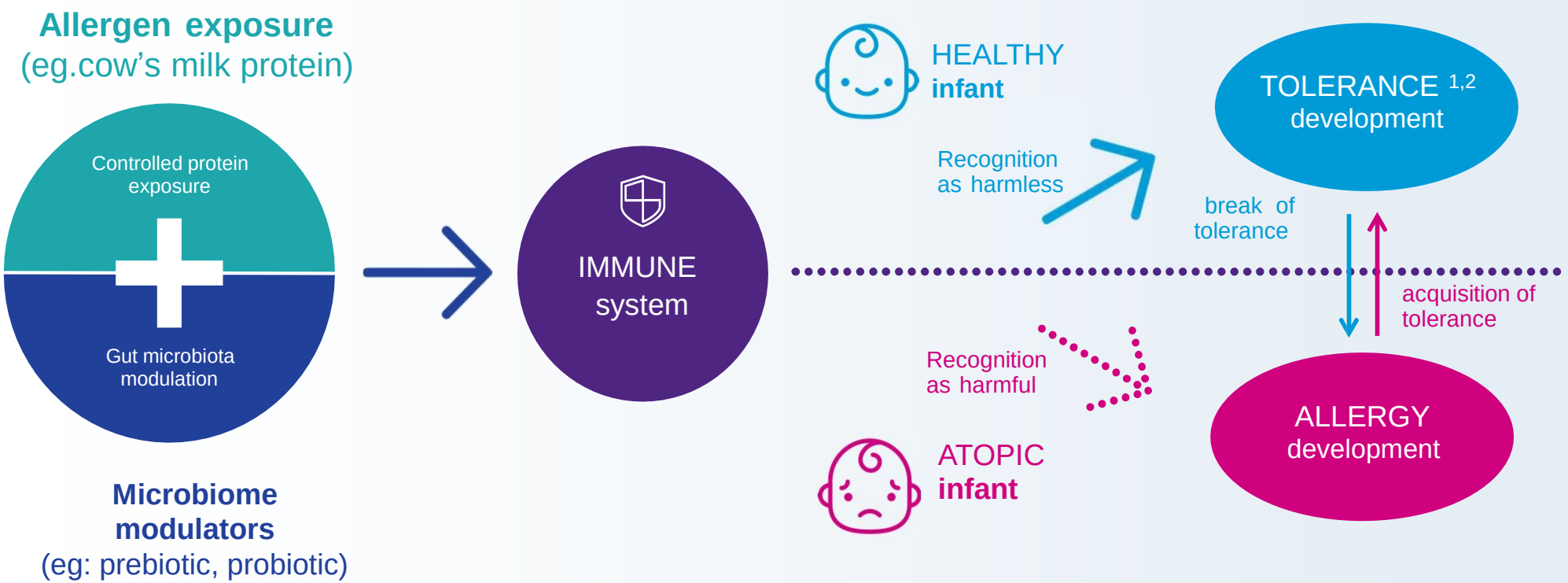
From
Allergen (protein) AVOIDANCE

To
Training immune system to build immune/oral TOLERANCE to reduce the risk and manage the disease (not only the symptoms)

Via

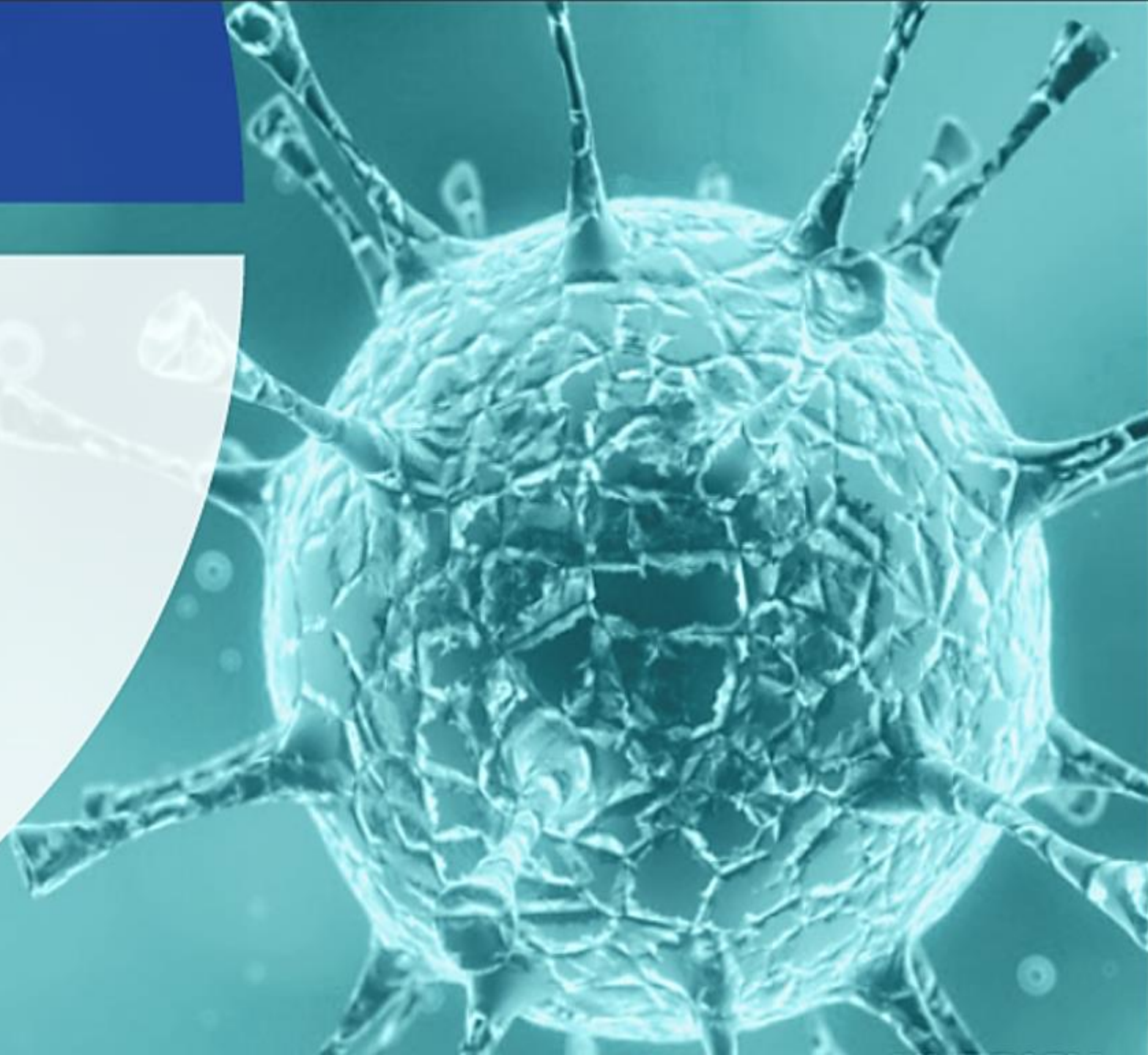


PRESENT: FROM AVOIDANCE TO ACTIVE TOLERANCE DEVELOPMENT - EXPOSURE NEEDED TO TRAIN THE IMMUNE SYSTEM



TRAINING THE IMMUNE SYSTEM:

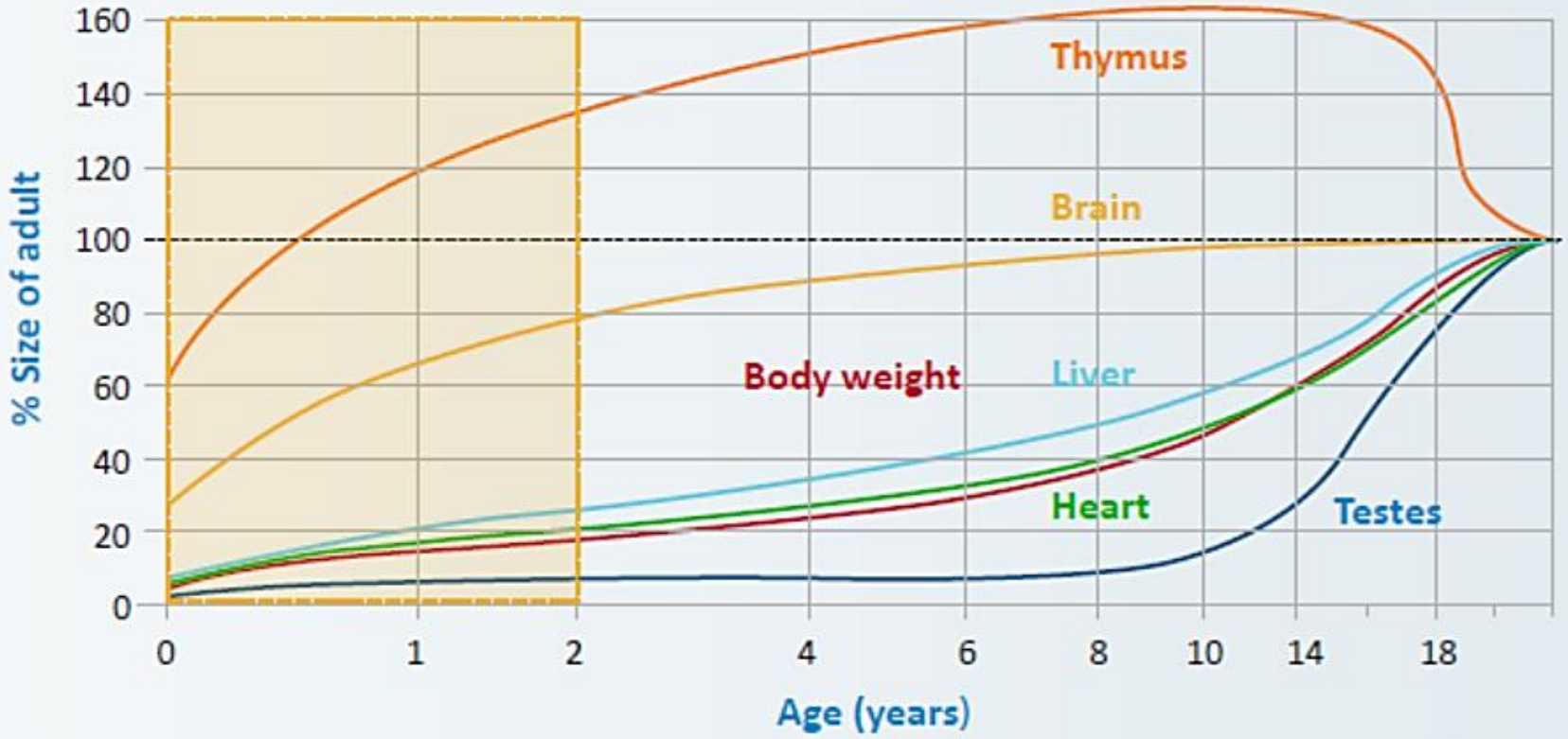
INTERPLAY WITH THE GUT MICROBIOTA



KEY DEVELOPMENT STAGES OF THE IMMUNE SYSTEM OCCURS IN THE FIRST 1000 DAYS (1)

- The immune system is not fully developed at birth, but matures over the first few years of life.
- Newborns have a limited capacity to initiate immune responses.

Different components of the immune system develop at different times.1



Reference 2

BEYOND DIGESTIVE FUNCTION THE GUT IS OUR LARGEST IMMUNE ORGAN

- Early life is a critical period, as the infant's immune system is still maturing and is influenced by the gut microbiota.

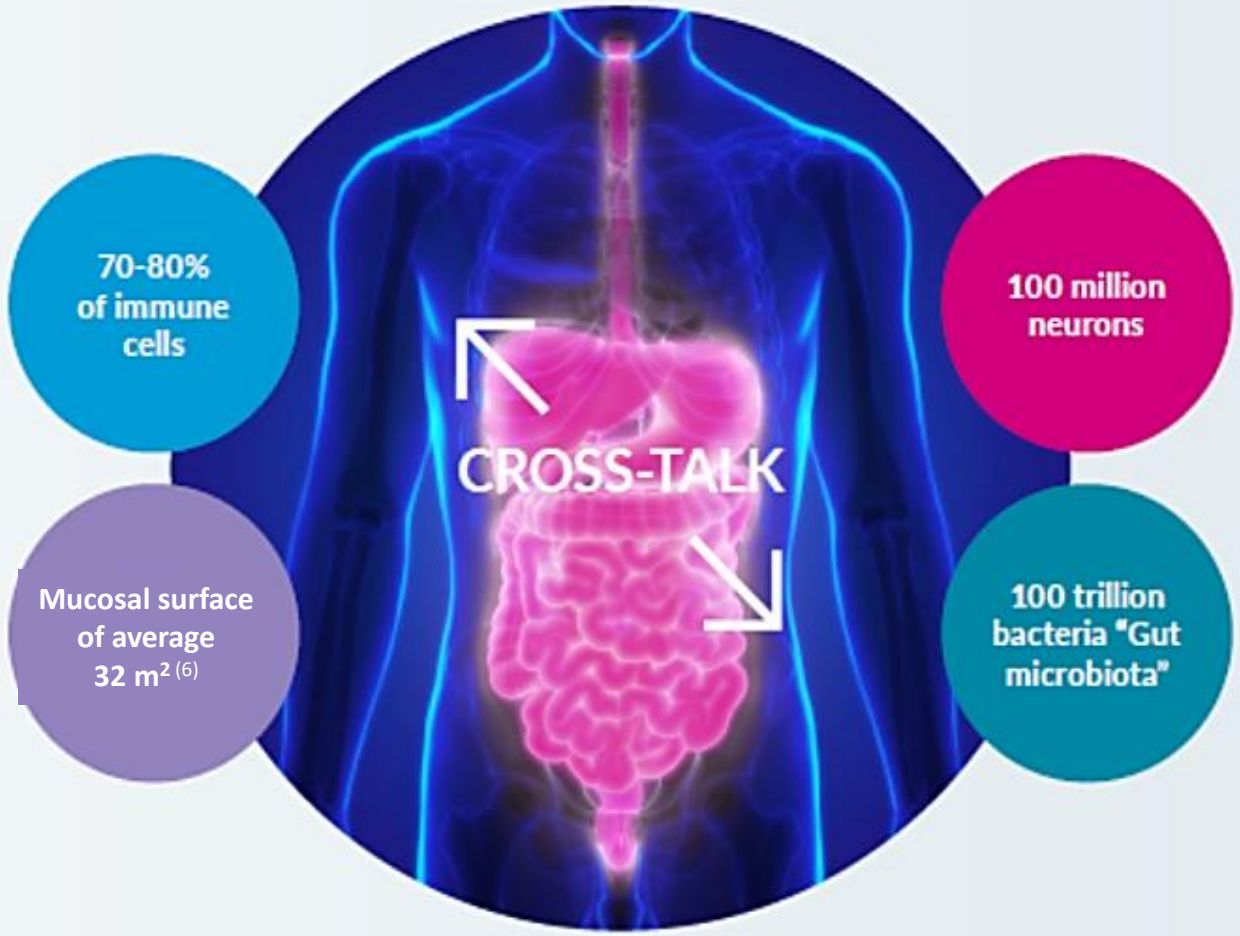
- There is high potential for crosstalk between the gut microbiota[1] and the immune system as 70-80% of immune cells reside in the gut microbiota.[2]

- Consists of several types of lymphoid tissue, e.g. Peyer's patches, known as the gut-associated lymphoid tissue (GALT).[3,4]

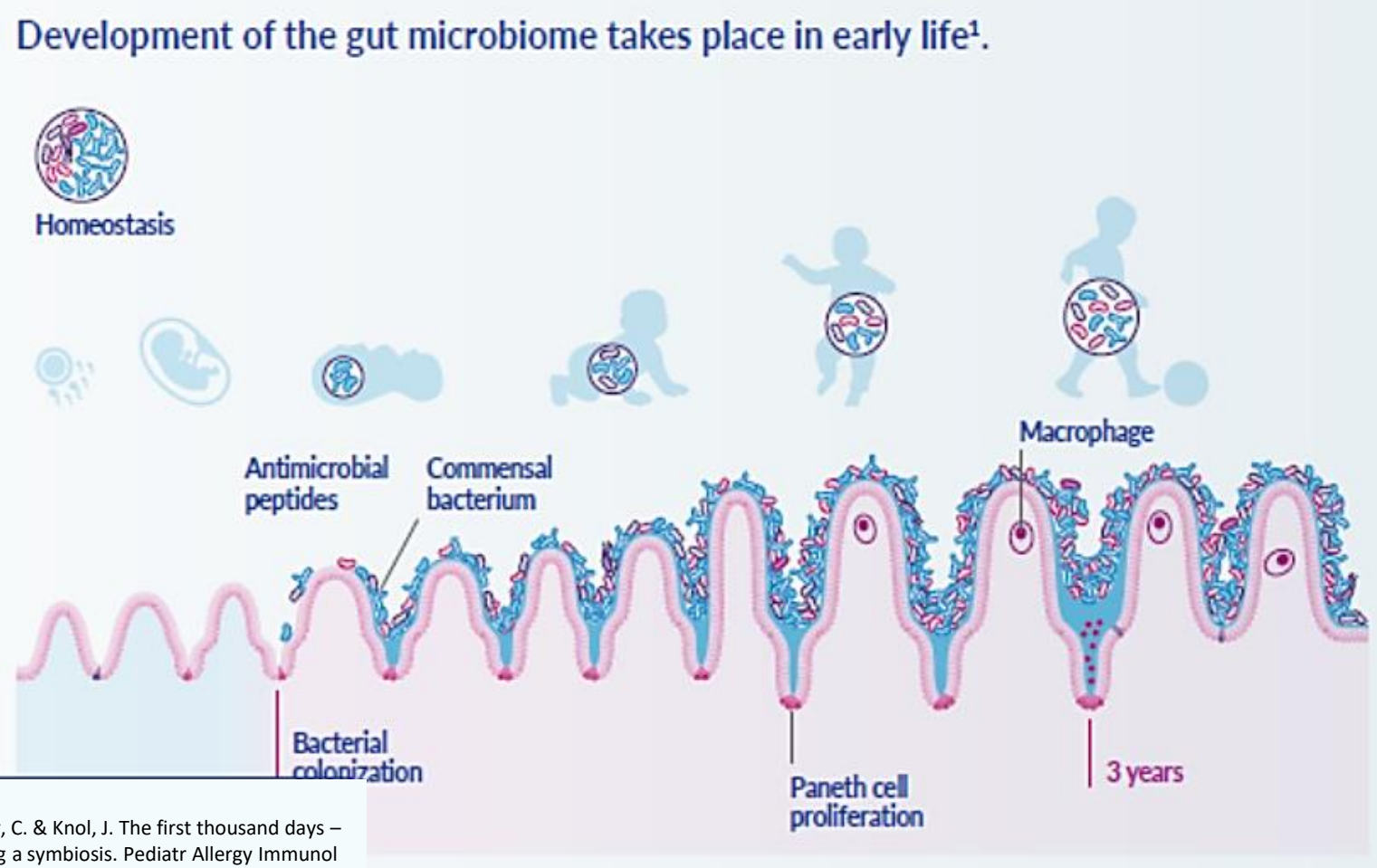
- The GALT is important both for defense and **tolerance**.[3,4]

- The gut plays a critical role in developing and sustaining immune balance.[2,5]

- Microbial interactions are important drivers in the maturation of the immune system.[5]

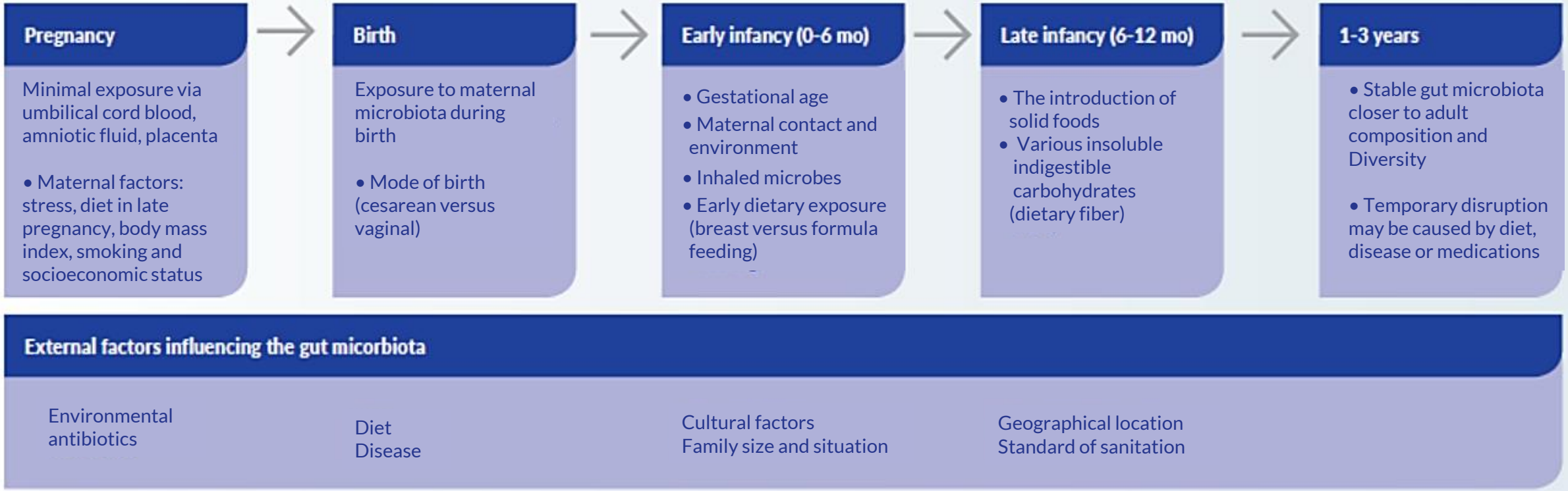


DEVELOPMENT OF THE GUT MICROBIOTA AND IMMUNE SYSTEM TAKES PLACE OVER TIME



References
1. Wopereis, H., Oozeer, R., Knipping, K., Belzer, C. & Knol, J. The first thousand days – intestinal microbiology of early life: establishing a symbiosis. Pediatr Allergy Immunol 25, 428-438, doi:10.1111/pai.12232 (2014).

GUT MICROBIOTA COLONIZATION IS A PROCESS OVER TIME AND IS AFFECTED BY MANY FACTORS



EARLY LIFE DISRUPTIONS IN MICROBIOTA ARE ASSOCIATED WITH ALLERGY DEVELOPMENT

Babies delivered by Caesarean section at higher risk of asthma and allergies

http://www.dailymail.co.uk/home/index.html

Asthma at 8 years of age in children born by caesarean section

C. Roduit et al., 2009, Thorax, 64(2):107-13

Br J Dermatol. 2013 Nov;169(5):983-91. doi: 10.1111/bjd.12476.

Full Text Online WILEY ONLINE LIBRARY

Does early life exposure to antibiotics increase the risk of eczema? A systematic review.

Tsakok T[1], McKeever TM, Yeo L, Flohr C.

Curr Opin Pulm Med. 2017 Jan;23(1):41-47.

Role of microbiome in the pathophysiology and disease course of asthma.

Singanayagam A[1], Ritchie AI, Johnston SL.

Does Antibiotic Exposure During Infancy Lead to Development of Asthma?* Marra et al., 2006, Chest, 129(3):610-8

Cesarean delivery showed link with gut microbiota, atopic dermatitis

http://www.healio.com/dermatology/dermatitis/news/

ORIGINAL PAPER

Shifts in *Lachnospira* and *Clostridium sp.* in the 3-month stool microbiome are associated with preschool age asthma

Leah T. Stiemsma, Marie-Claire Arrieta, Pedro A. Dimitriu, Jasmine Cheng, Lisa Thorson, Diana L. Lefebvre, Meghan B. Azad, Padmaja Subbarao, Piush Mandhane, Allan Becker, Malcolm R. Sears, Tobias R. Kollmann, , William W. Mohn, B. Brett Finlay, Stuart E. Turvey

Clinical Science
Oct 26, 2016.

INTESTINAL FLORA

- Intestinal flora composition plays an important role in the development of allergic diseases and airway inflammation because of its potential effects on TH1-type immunity, generation of TGF, and IgA production.

NUTRICIA

INTESTINAL FLORA TIC

- There has been speculation that exposure to these microbial agents in early life, when immune maturation is critical, could play an important role in maturation of type 1 T helper cell (TH1) immune responses and could inhibit the development of allergic type 2 T helper cell (TH2) responses and IgE antibody production .

NUTRICIA

PROBIOTICS

- Probiotics are a class of active microorganisms that are beneficial to the host by colonization in the human body and altering the composition of the flora at a certain part of the host.
- Prebiotics are non digestible food ingredients that have a beneficial effect on the host by selectively stimulating the growth and activity of probiotics to improve host health.
- Symbiotic are a combination of probiotics and prebiotics .

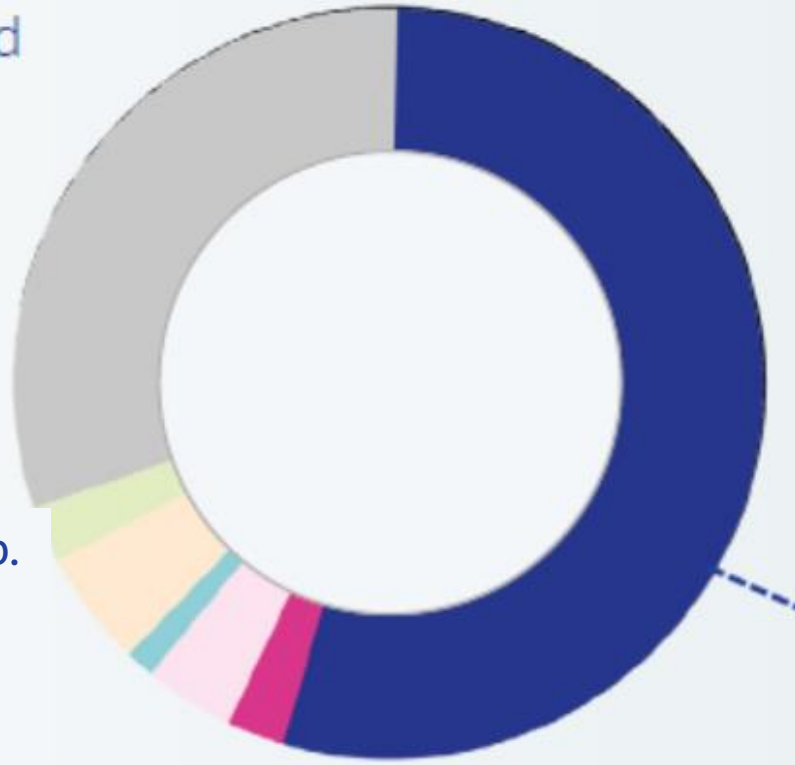
NUTRICIA

SYMBIOTIC

- Probiotics, prebiotics, and symbiotic can ameliorate the host immune system via gut ecosystem and may be beneficial for the treatment of allergic diseases such as asthma.
- Some animal experiments have shown that probiotics can effectively inhibit IgE production and the accumulation of eosinophils.
- Probiotics also show effects in the prevention and treatment of allergic diseases.

HUMAN MILK INFLUENCES THE DEVELOPMENT OF THE GUT MICROBIOTA

Healthy vaginally born breastfed infants have *Bifidobacteria* dominated gut bacteria[1]

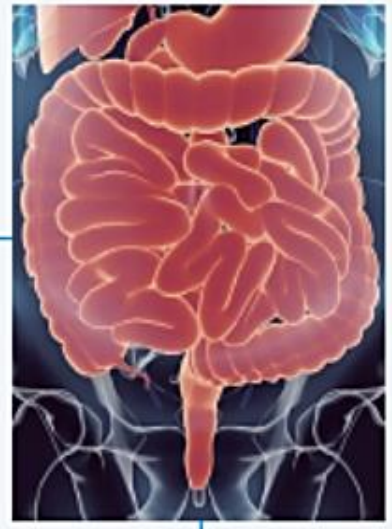


Gut microbiota of healthy, breast-fed infants

FACTORS CAN IMPACT GUT MICROBIOTA

- **Developmental origins or maternal microbiota**
- **Mode of delivery**
  (vaginal vs. caesarean section)
- **Duration of gestation**
  (term vs. preterm)
- **Early dietary feeding**
  (breast vs. formula complementary feeding)
- **Use of antibiotics, and/or probiotics**
- **External environmental factors**
  (geographical environment, family size, exposure to pets)

Gut microbiota



Healthy status

- **Immune tolerance**
- **Gastrointestinal homoeostasis**
- **Healthy metabolism**

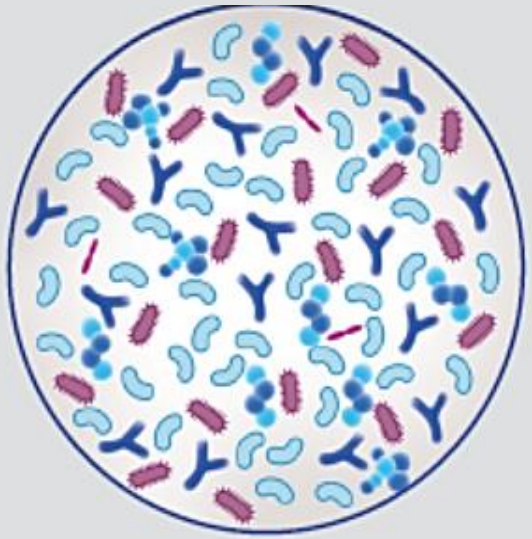
Dysbiosis

- **Immune disease**
  (allergy, asthma)
- **Gastrointestinal disease**
  (IBD)
- **Metabolic disease**
  (obesity, diabetes)

GUT MICROBIOTA DYSBIOSIS

HEALTHY

Gut microbiota composition of healthy, vaginally delivered breast-fed infants



Higher levels of beneficial bacterial species

Bacteroides fragilis
Bifidobacterium
Lactobacillus
Bacteroides
Enterococcus

DYSBIOSIS

Gut microbiota composition of C-section delivered infants

- Higher levels of potentially harmful bacteria
- Reduced levels of beneficial bacterial species

Clostridium difficile
Staphylococcus aureus
Escherichia coli
Enterobacteriaceae

Figure 1. Hypothetical image to illustrate the concept of dysbiosis.

GUT MICROBIOTA IN INFANCY

Gut microbiota dysbiosis in early life may delay oral tolerance, which can play an important role in the development of immunerelated diseases such as food allergy and atopic dermatitis

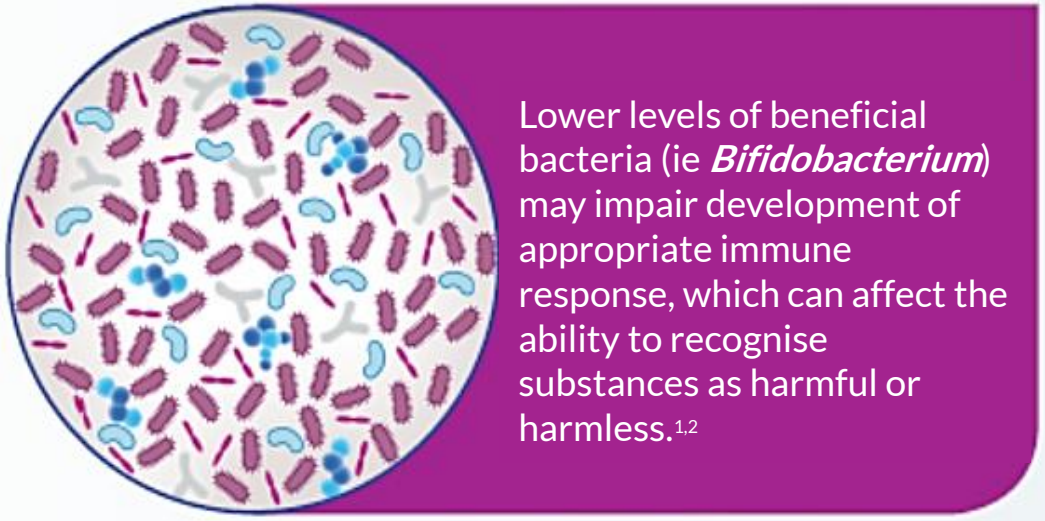
Gut microbiota dysbiosis in allergic infants in early life

Acquisition of oral tolerance may be Delayed [1-3]

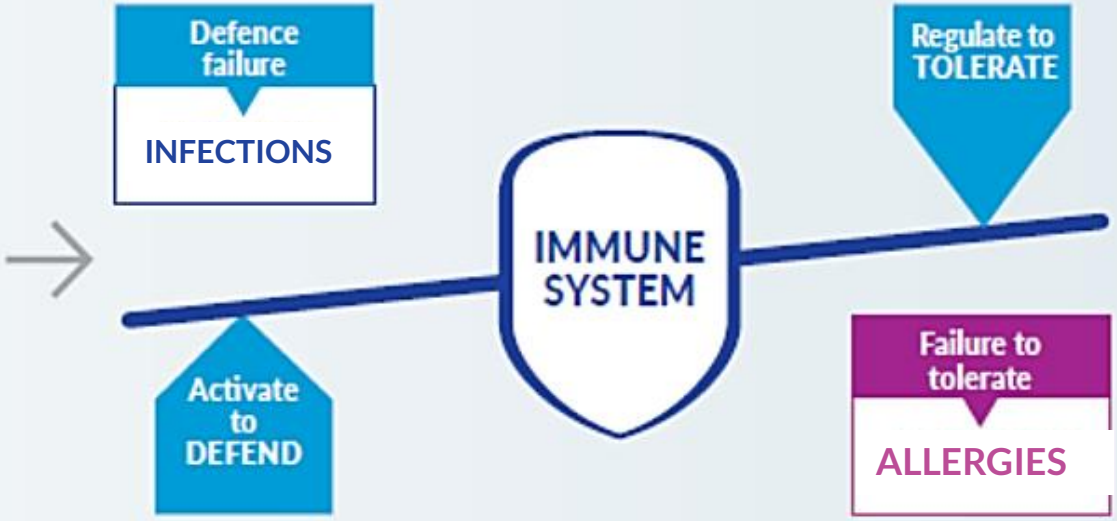
Immune related diseases may develop[1-3]

Addressing the underlying dysbiosis is critical and nutrition can play a role in modulating the gut microbiota[4]

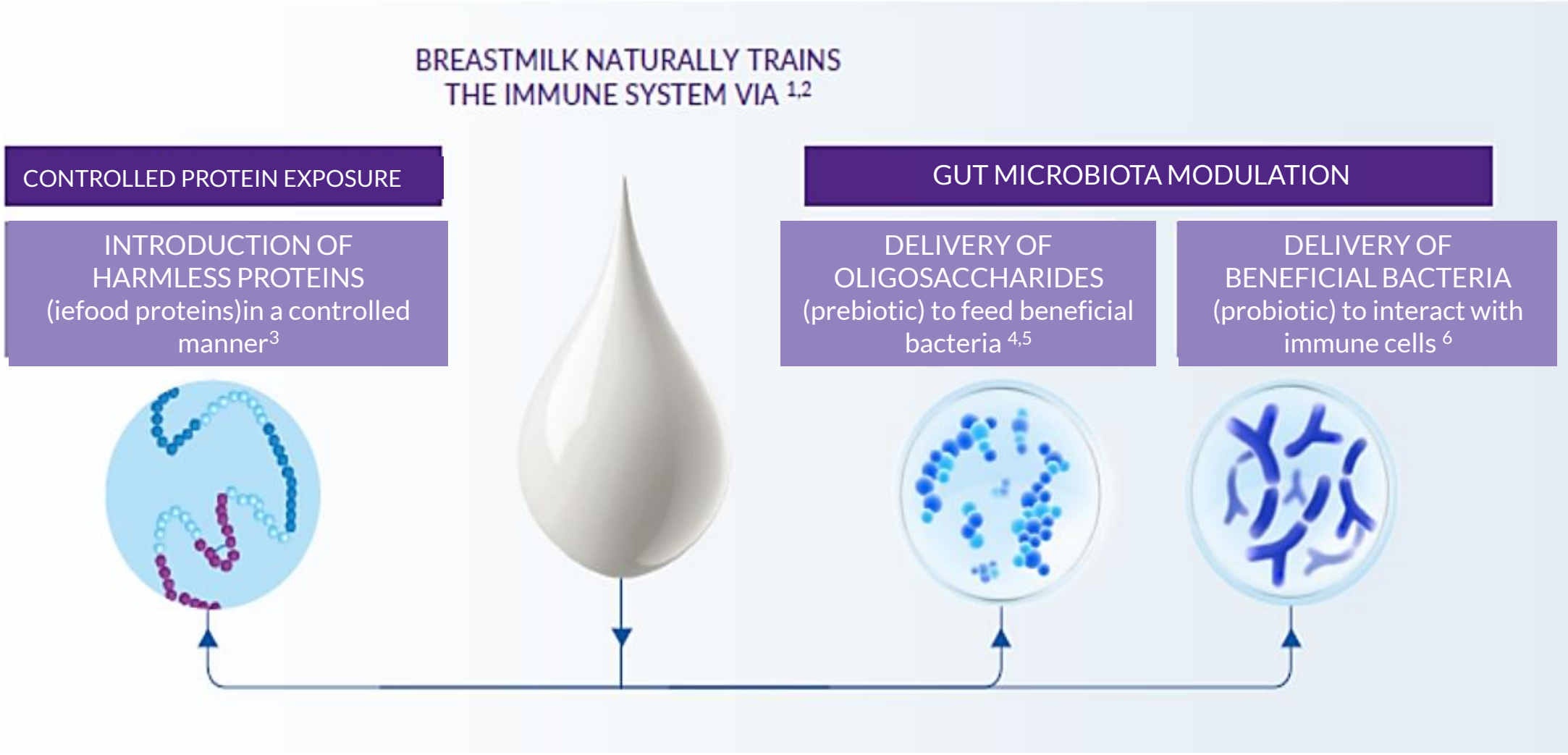
GUT MICROBIOTA DYSBIOSIS



Lower levels of beneficial bacteria (ie ***Bifidobacterium***) may impair development of appropriate immune response, which can affect the ability to recognise substances as harmful or harmless.[1,2]



BREAST MILK IS ONE OF THE KEY INFLUENCERS OF GUT MICROBIOTA TO SUPPORT DEVELOPMENT OF HEALTHY IMMUNE RESPONSE



BREASTFEEDING IS RECOMMENDED FOR PREVENTION OF FOOD ALLERGY

Breast milk is the gold standard to train the immune system[1]

The World Health Organization recommends exclusive breast-feeding for the first six months of life[2]

- International guidelines for allergy prevention universally recommend breastfeeding for at least 4-6 months with parallel introduction of complementary feeding from 4-6 months including potentially allergenic foods.
- If breastfeeding is insufficient or not possible, infants at high-risk based on atopic heredity can be recommended a hypoallergenic formula to reduce the risk of allergy development.[2, 3]
- International guidelines also recommend the use of 'prebiotic supplementation in not-exclusively breastfed infants' for the prevention of allergy [4], and the additional positive recommendation on the use of probiotics in not-exclusively breastfed infants at high risk of developing allergies.[5]

OUTLOOK

- The pattern of CMPA are becoming increasingly aggressive
- Prevention of first allergies matter to stop the Allergic March
- Active management of Allergy : from Avoidance to Tolerance Induction
- Gut microbiota plays a critical role in infant's "Immune Development and Allergy"
- Healthy breastfed infant's gut is dominated by Bifidobacteriaum species.
- Gut DYSBIOSIS may delay oral tolerance which contribute to the development of immune related diseases as Allergy.
- Human milk naturally trains the immune system and prevents and manage CMPA via :

  - Controlled protein exposure,
  - HMOS(prebiotic effect))to feed healthy bacteria,
  - Beneficial bacteria like Bifidobacterum Breve (probiotic effect)

Thank You