# Probiotic Use in Preterm Infants and Children

## Differentiating Between Health and Disease


ANNENBERG CENTER FOR HEALTH SCIENCES
AT EISENHOWER
*Imparting knowledge. Improving patient care.*

*Presented by*
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**GI Care for Kids, LLC**
and
**Jonathan Malka, MD, FAAAAI**
**Pediatric Associates**



Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

This activity is supported by an educational grant from
**Mead Johnson Nutrition.**

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| *Advisor* | DiaSorin Molecular, Evolve Biosystems, Ironwood Pharmaceuticals, Janssen/Johnson & Johnson, |
| *Speaker* | Mead Johnson Nutrition, Nestlé USA, Nutricia/Dannonn |

**Jonathan Malka**, MD

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|---|---|
| *Advisor, Speakers Bureau* | Mead Johnson Nutrition |

For complete financial interest disclosures, see the course CE statement.

# Learning Objectives

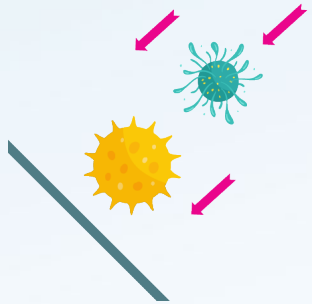
- Discuss immunity and its interaction with the microbiome in the developing child
- Evaluate the impact of dysbiosis in infancy and childhood on long-term health outcomes
- Review evidence for prebiotic and probiotic use in preterm and term infants

# Overview

- Discuss immunity in the developing child and interaction with the microbiome
  - Differentiate innate compared to adaptive immunity
- Provide an overview of the gut microbiome
  - Microbiota development and maturation
- Show impact of dysbiosis on long-term health
  - Factors that affect microbiome
  - Outcomes of dysbiosis; diarrhea, malnutrition, allergy, autoimmune disease
- Review and define *pre*-biotics and *pro*-biotics
- Provide evidence regarding prebiotic and probiotic use in preterm and term infants
  - Necrotizing enterocolitis
  - Allergy/atopy incidence reduction
  - Colic, antibiotic associated colitis, brain-gut function

# Immunity in the Developing Child and the Gut Microbiome

# Immune System



- The immune system is a network of cells, tissues, and organs that work together primarily to defend the body against attacks by “foreign” invaders.
- Designed to carry out rapid, specific, and protective responses against harmful pathogens or their biologic products.
- The mechanism of immunity function across a broad spectrum of clinical conditions spanning from resolution of infectious disease, recognition and rejection of tumors, tolerance or rejection of transplanted tissues or organs, autoimmunity, and allergy.

# Functions of the Immune System

| Function | Normal |
| --- | --- |
| **Defense** | Antimicrobial Activity |
| **Homeostasis** | Removal of damaged cells |
| **Surveillance** | Removal of mutant cells |

# Functions of the Immune System

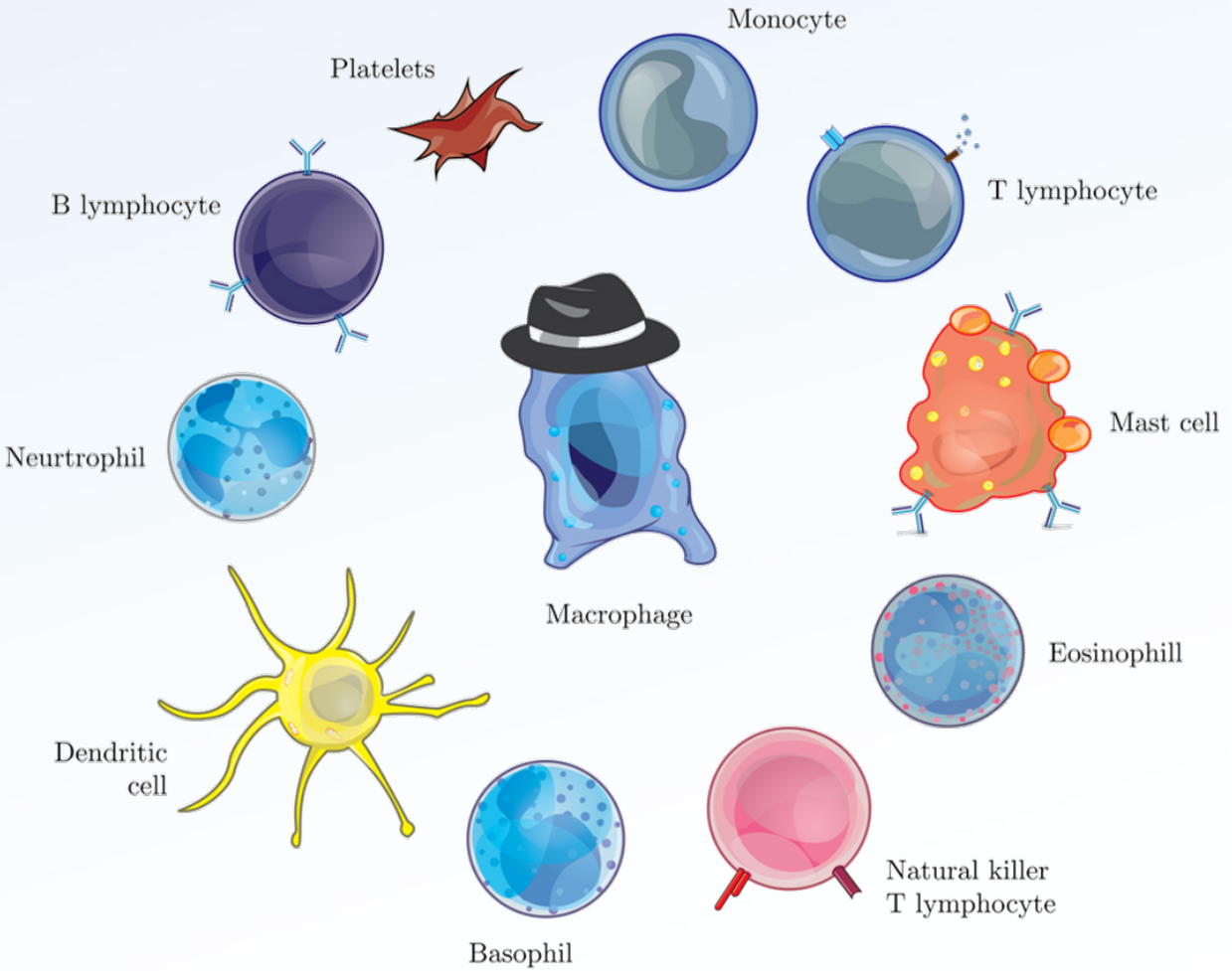
| Function | Normal | Hyperfunction |
|---|---|---|
| **Defense** | Antimicrobial Activity | Allergy |
| **Homeostasis** | Removal of damaged cells | Autoimmune Disease |
| **Surveillance** | Removal of mutant cells | None |

# Functions of the Immune System

| Function | Normal | Hyperfunction | Hypofunction |
|---|---|---|---|
| **Defense** | Antimicrobial Activity | Allergy | Immune Deficiency |
| **Homeostasis** | Removal of damaged cells | Autoimmune Disease | Malignancies |
| **Surveillance** | Removal of mutant cells | None | |

# Innate Immune System – Immunity You Are Born With

- Phagocytic cells
  (Macrophages, PMNs, Eos & DCs)
- Mediator cells
  (mast cells & basophils)
- Natural Killer cells (NK)
- Complement



# Innate Immune System – Immunity You Are Born With

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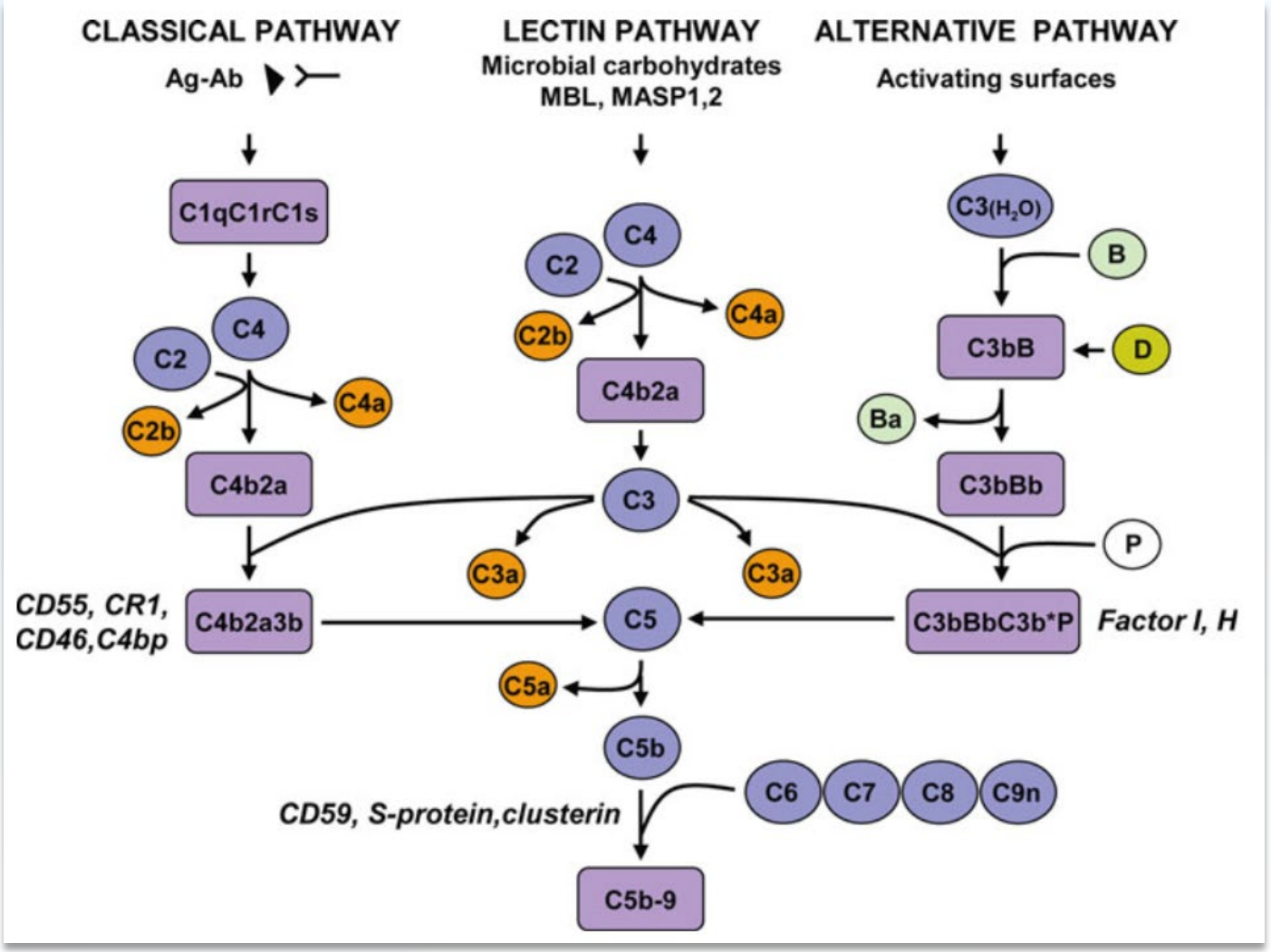



Tegla CA, et al. *Immunol Res.* 2011;51:45. Used by permission of *Springer Nature*.

# Innate Immunity – Mechanism of Action

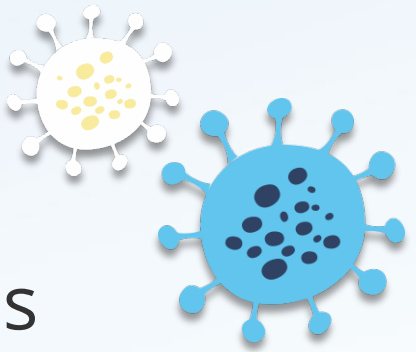
Two basic strategies of immune recognition:

Recognition of **microbial non-self.**

Recognition of **missing self.**

# What Is the Adaptive Immune System?

# Adaptive Immune System

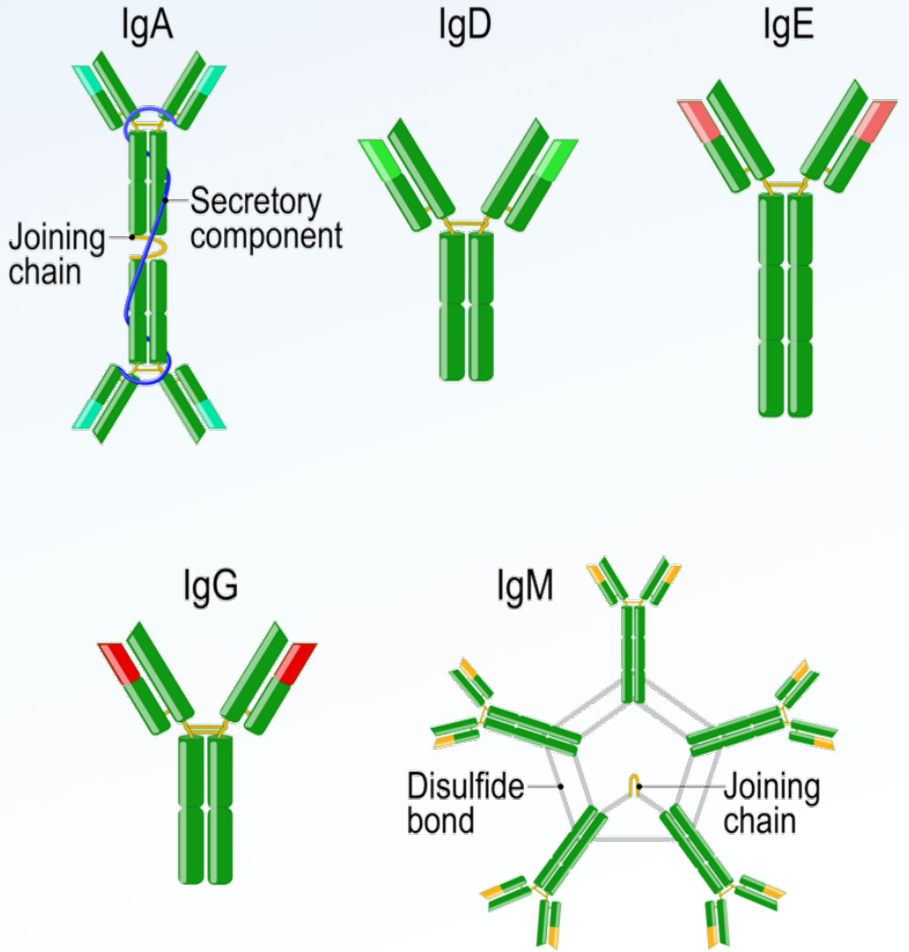


- Adaptive immune cells originating from lymphocytes differentiate to recognize specific antigens.

- As rearrangements within the genes in the immune cells occur during this developmental process:
  - Antigens present in the host (self-antigens) interact with the emerging cell population to eliminate those adaptive immune cells that would attack the host
  - Retain only those cells that will target any non–self-antigens.

# Adaptive Immune System Components

- T-cells (Th1, Th2, Th17 and Treg)
- B-cells
- Th2 → B-Cells IgG, A, M and E
- IgG (IgG1, IgG2, IgG3 and IgG4)




Bellanti JA. *Immunology IV.* Springer Nature, 2012.

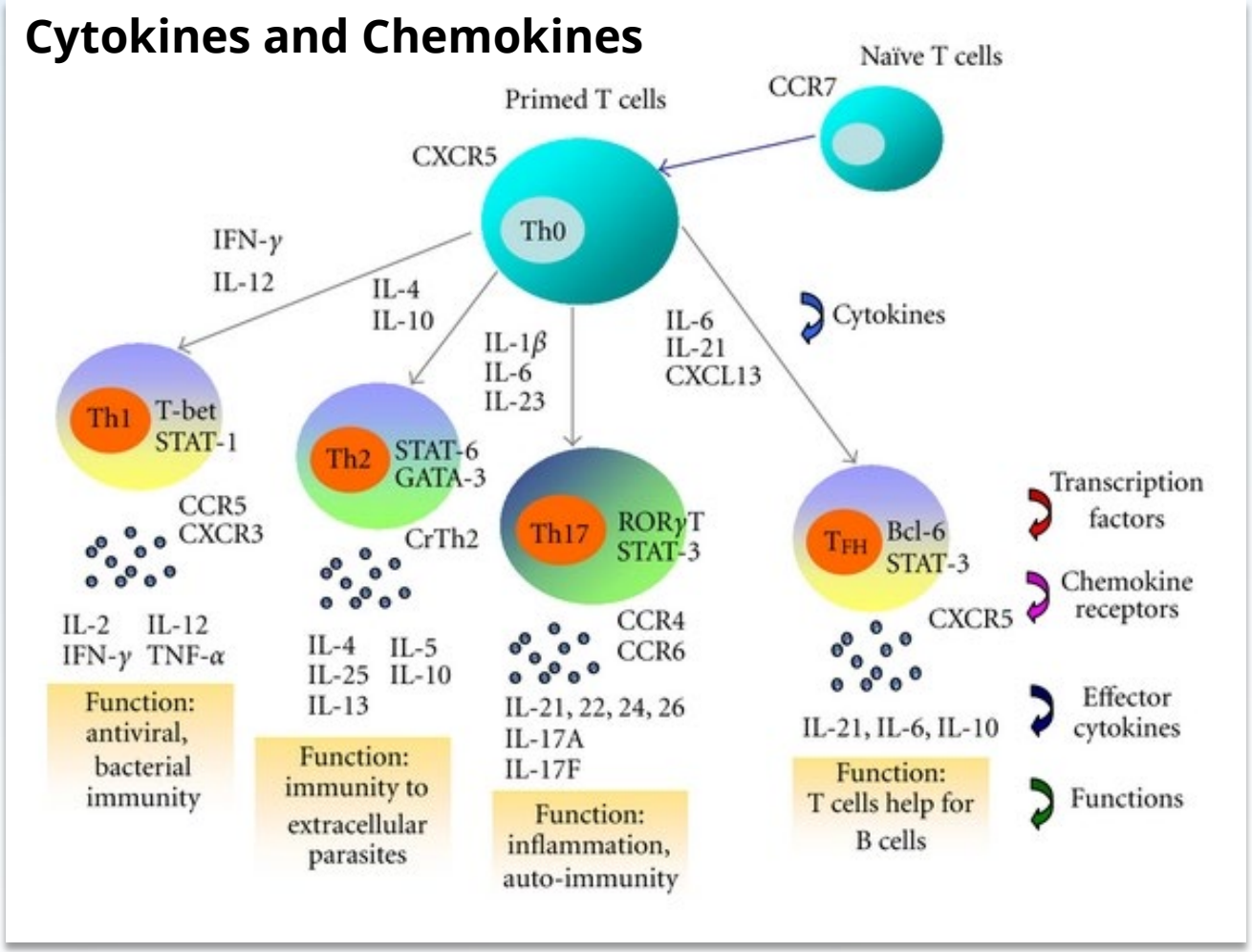
# Adaptive Immune System – Cytokines and Chemokines

- Cytokines are a group of protein and peptide that comprise the intercellular communication network of every cell system of the body, including the immune system.

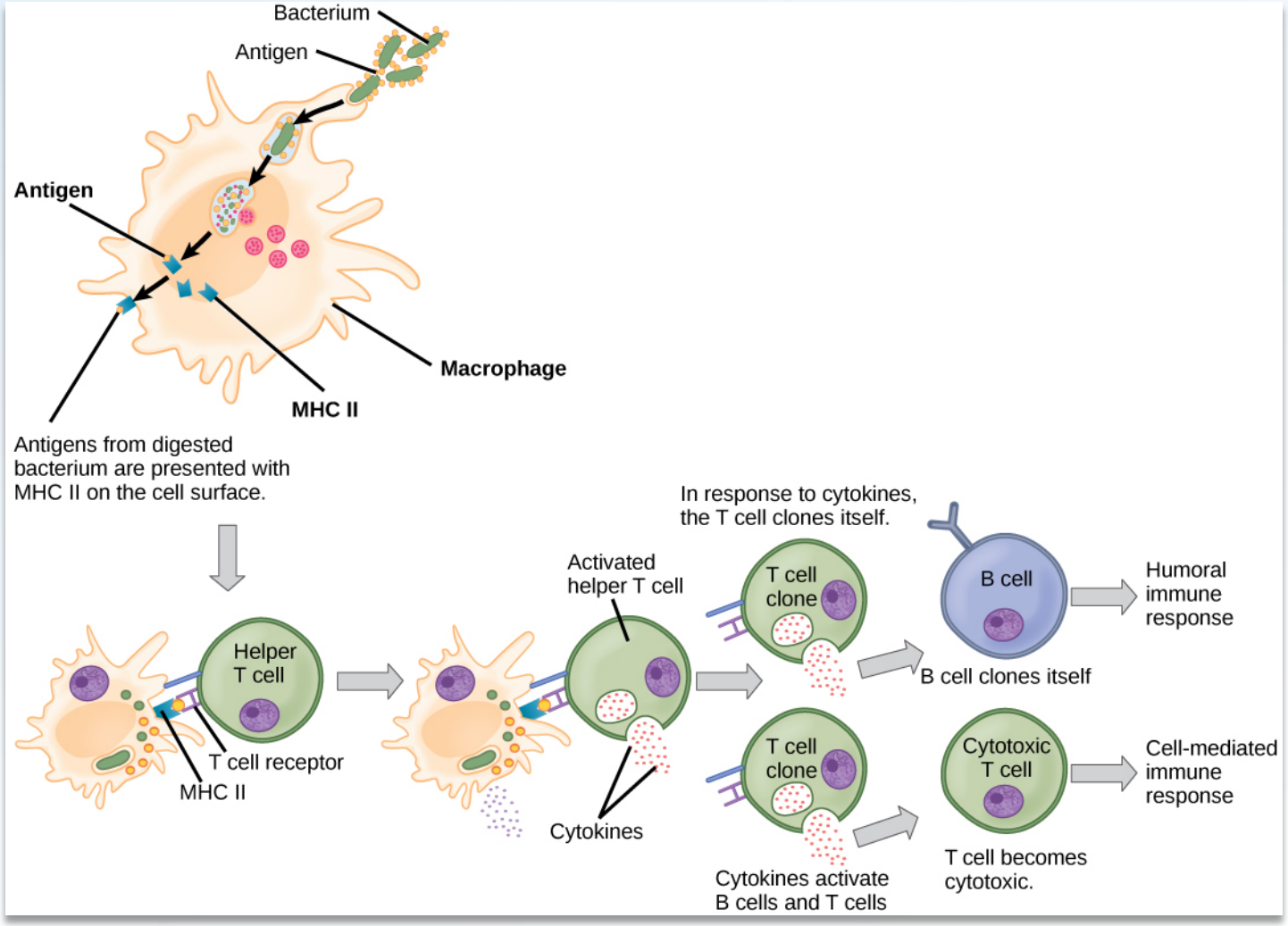
  They function as signaling molecules to regulate the growth, differentiation, activation, and inhibition of all cellular aspects of both the innate and adaptive immune responses.

- Chemokines are a specialized subset of cytokines that function to induce directed cell movement, ie, chemotaxis, in nearby responsive cells; they are chemotactic cytokines, hence the name “chemokines.”

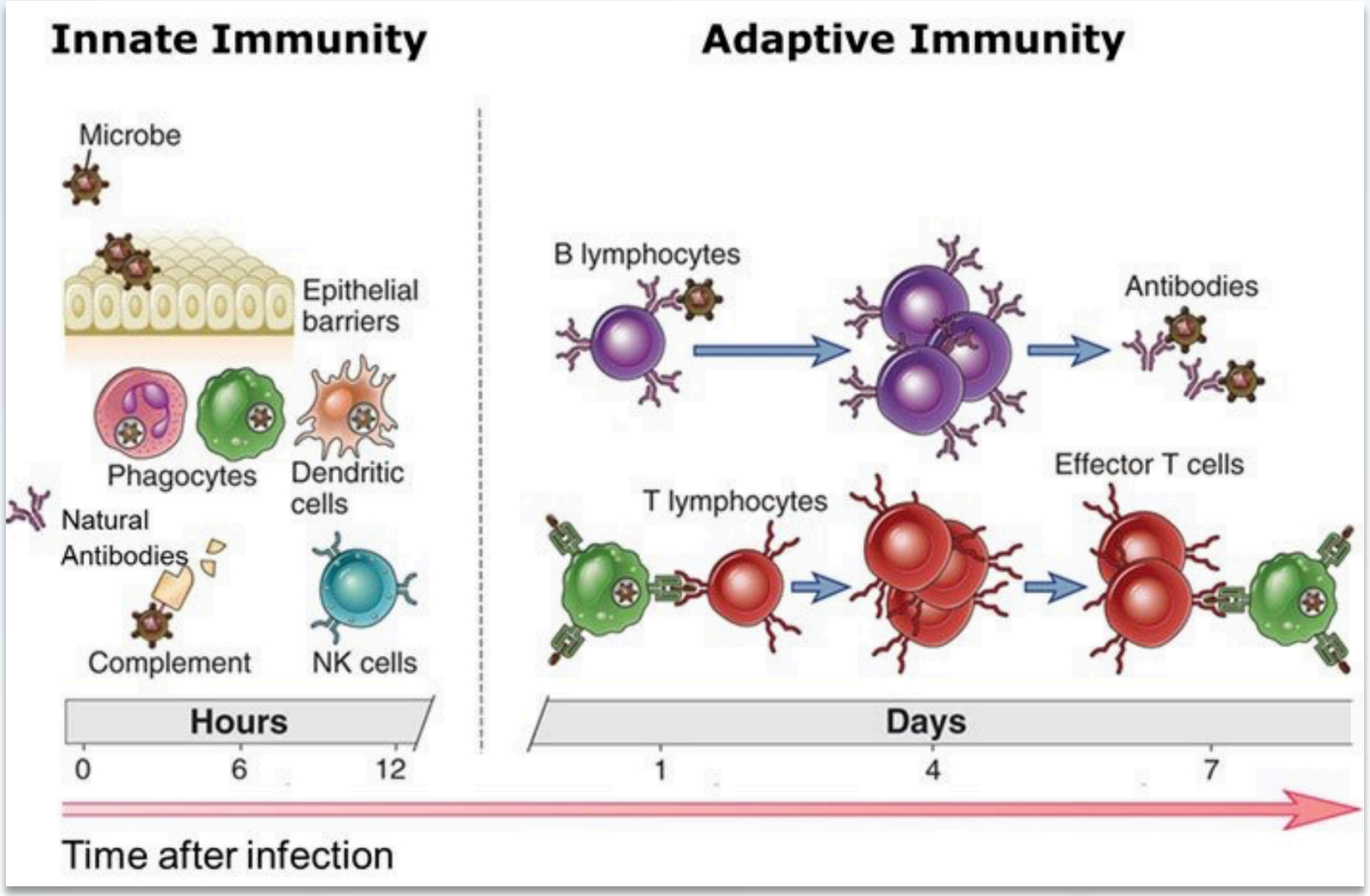
# Adaptive Immune System – Cytokines and Chemokines



# Adaptive Immune System



# Innate and Adaptive Immunity

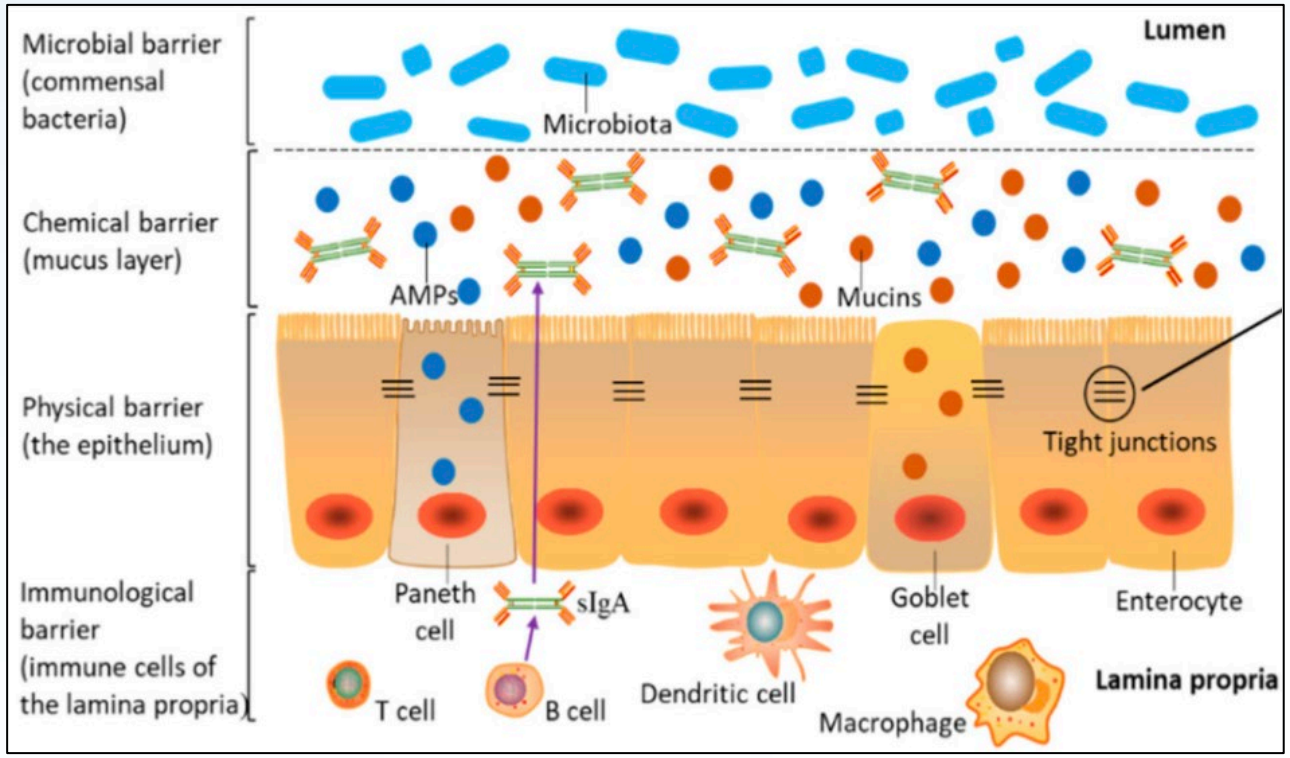



Adapted from Abbas AK, et al. *Cellular & Molecular Immunology (8th Edition).* Elsevier, 2014.

# Microbiota, Microbiome and Normal Development vs Dysbiosis

# Role of GI Barrier – Provides First Line of Defense

- Chemical barrier: Layer of mucus, barrier to pathogens, accommodates commensal bacteria
- Physical barrier: Column of epithelial cells with junctions between the cells, controls permeability
- Immunological barrier:
  - Contains gut-associated lymphoid tissue (GALT)
  - Builds tolerance to antigens and defends against pathogens
  - Produces secretory immunoglobulin A (sIgA): prevents pathogens from adhering to and penetrating the epithelium





1. Gao Y et al. *Toxins (Basel)*. 2020;12(10):619. Used under terms of a Creative Commons License CC BY 4.0.
2. Brucklacher-Waldert V et al. *Front Immunol*. 2014;5:488.

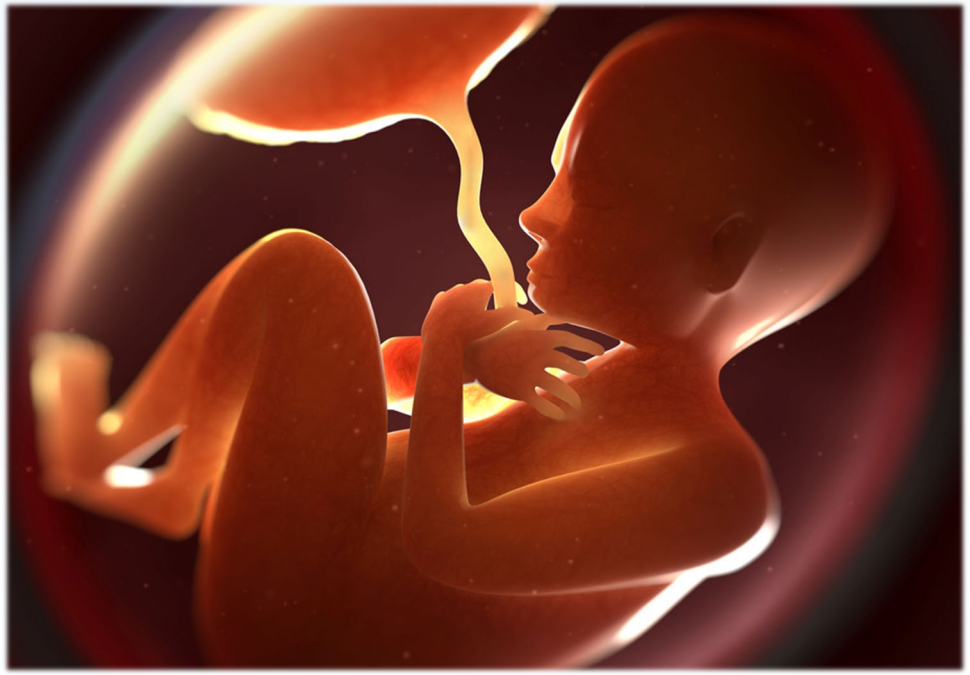
GUT MICROBIOTA FOR HEALTH by ESNM

# Analysis of the fetal intestine suggests limited bacterial colonization with potential immunological functions

ESNM
European Society of Neurogastroenterology & Motility

Andreu Prados • 27 April 2020

Whether bacterial colonization starts in utero is still a matter for scientific debate. The study of the fetal intestinal content collected from terminated pregnancies reveals some evidence for early bacterial colonization linked to distinct immune imprinting.



Rackaityte E, et al. *Nat Med*. 2020; 26(4):599-607. doi: 10.1038/s41591-020-0761-3.
Collado MC, Segata N. *Nat Med*. 2020; 26(4):469-70. doi: 10.1038/s41591-020-0836-1.
Image credit: Henrik5000/Getty Images

# The Significance of the Gut to the Immune System

- Bacteria-like structures in pockets of human fetal meconium at mid-gestation; electron microscopy, 16S ribosomal ribonucleic acid sequencing
  - 3 bacterial profiles identified in the fetal intestinal content samples
  - Associated with distinct gene expression, distinct patterns of T-cell composition
- Fetal *M. luteus* isolates promoted immune regulation by
  - Inducing tolerogenic antigen presenting cells in the lamina propria
  - Reducing the pro-inflammatory interferon-gamma production by fetal memory T-cells

Rackaityte E, et al. *Nat Med*. 2020; 26(4):599-607. doi: 10.1038/s41591-020-0761-3.
Collado MC, Segata N. *Nat Med*. 2020; 26(4):469-70. doi: 10.1038/s41591-020-0836-1.

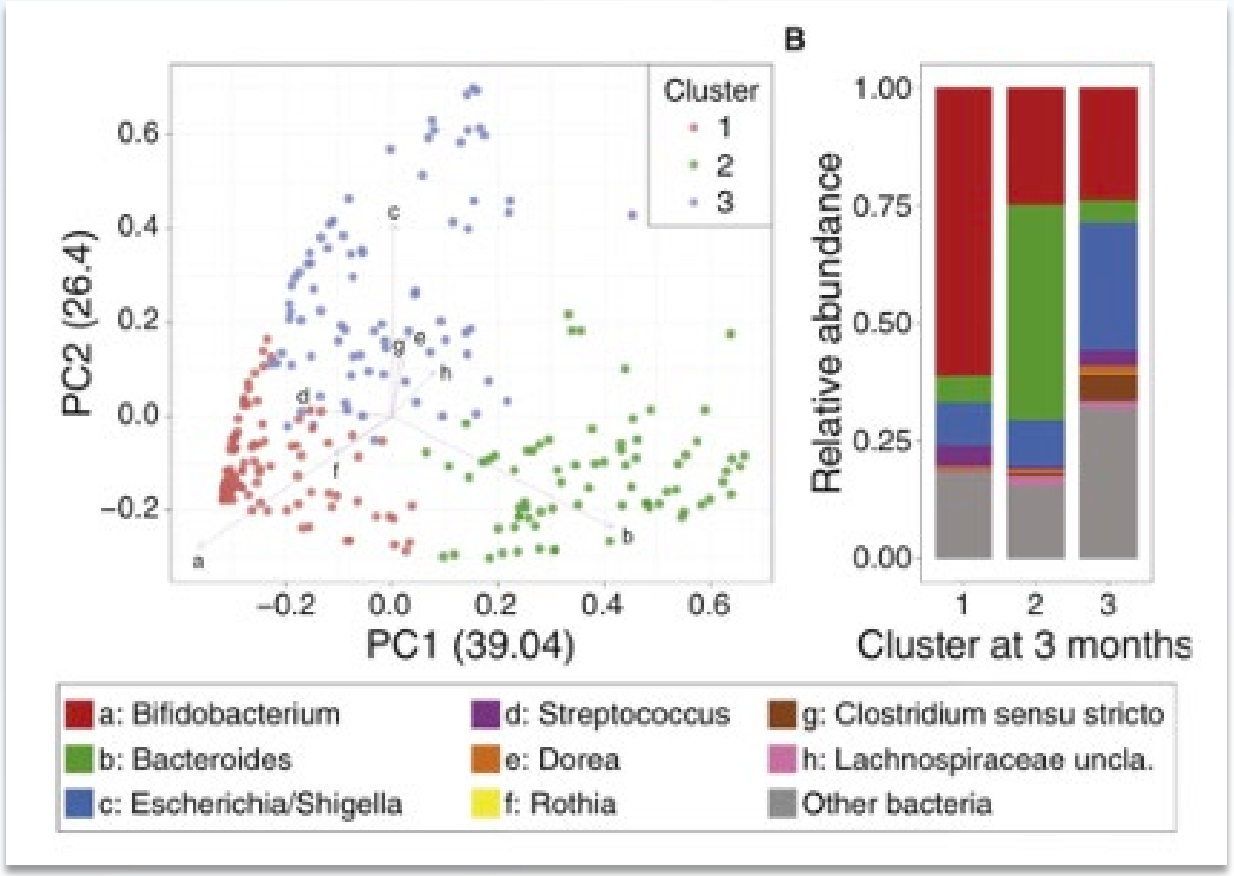
# Diet a Key Influencer of Infant GI Microbiome

- Human milk directly contributes to the establishment of the microbiome
- Gut microbiota composition differs between breastfed and formula-fed infants
- Breastfed infants: Characterized by higher abundance of bifidobacteria and lactobacilli
- Formula-fed infants: Increased amounts of bacteroides, clostridia, and Enterobacteriaceae, including opportunistic pathogens such as *Clostridium difficile* and *Escherichia coli*

Cacho NT, Lawrence RM. *Front Immunol.* 2017;8:584. Lee SA, et al. *Nutr Res Pract.* 2015:9(3):242-8. Gritz EC, Bhandari V. *Front Pediatr.* 2015;3:17. Bäckhed F, et al. *Cell Host Microbe.* 2015;17(5):690-703.
Image credit: top, Iurii Krasilnikov/bigstock; bottom, Science Photo Library

# Diet Contributes to Evolution of the Infant Gut Microbiota

Authors from the EAT study investigated a nested cohort of infants undergoing randomized introduction of allergenic solids as part of a randomized controlled trial to prevent food allergy.

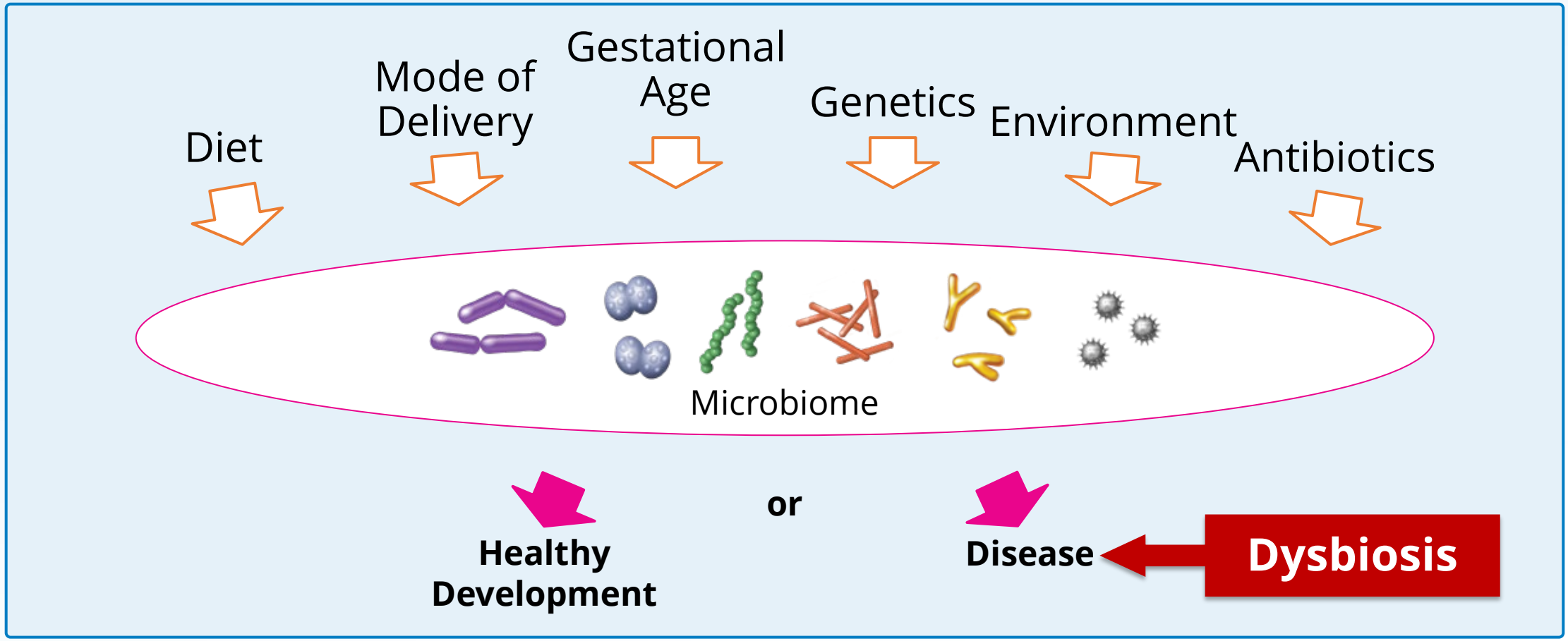


# Diet Contributes to Evolution of the Infant Gut Microbiota

- In the EAT study, early peanut and egg introduction, if consumed in sufficient quantity, was shown to protect against the development of peanut and egg allergies between age 1 and 3 years
- It has been demonstrated that the early introduction of allergenic foods alongside ongoing breastfeeding between age 3 and 6 months led to an increase in overall gut microbiota, in particular promoting an influx of various microbes including *Prevotellaceae and Escherichia/Shigella*
- Interestingly, the presence of *Prevotella* has been shown to be associated with high-fiber diet, including in remote villages with less frequent chronic inflammatory disorders

# Each Person Develops a Unique GI Microbiome

## *Influenced by:*




Martin R, et al. *Benef Microbes.* 2010;1(4):367-82. Stiemsma LT, Michels KB. *Pediatrics.* 2018;141(4):e20172437. Yang I, et al. *Nurs Res.* 2016;65(1):76

# Functions of the Intestinal Microbiota

| Functions | Mechanisms/Effects |
|---|---|
| **Digestive and metabolic functions** | • Vitamin production<br>• Fermentation of nondigestible CHO → SCFA<br>• Dietary carcinogens metabolism |
| **Neuronal development** | • Modulation of brain gut axis during neuronal development<br>• Motor control and anxiety behavior |
| **Protective functions against pathogenic bacteria** | • Pathogen displacement<br>• Nutrient competition<br>• Production of antimicrobial factors<br>• Activation of local immune response<br>• Contribute to the intestinal barrier function |
| **Immune development** | • IgA production<br>• Control of local and general inflammation<br>• Tightening of junctions<br>• Induction of tolerance to foods |

CHO, carbohydrates; SCFA, short-chain fatty acids; IgA, immunoglobulin A.

Buccigrossi et al. *Curr Opin Gastroenterol.* 2013. 29:31-38.

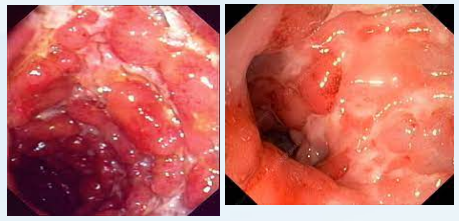
# Dysbiosis

Dysbiosis is any perturbation of the normal microbiome content that could disrupt the symbiotic relationship between the host and associated microbes, a disruption that can result in diseases, such as inflammatory bowel disease and other gastrointestinal (GI) disorders, including gastritis, peptic ulcer disease, irritable bowel syndrome, and even gastric and colon cancer.

- Perturbation of normal microbiota
- Disrupts symbiosis
- Associated with short- and long-term health implications, including inflammatory and autoimmune diseases

Floch MH, et al. The Microbiota in Gastrointestinal Pathophysiology. Elsevier. 2017.

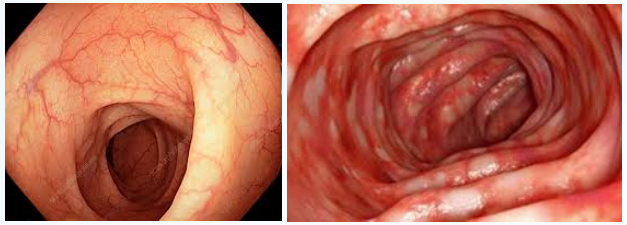
# Where Are the Microbes Causing GI Disease With Dysbiosis?

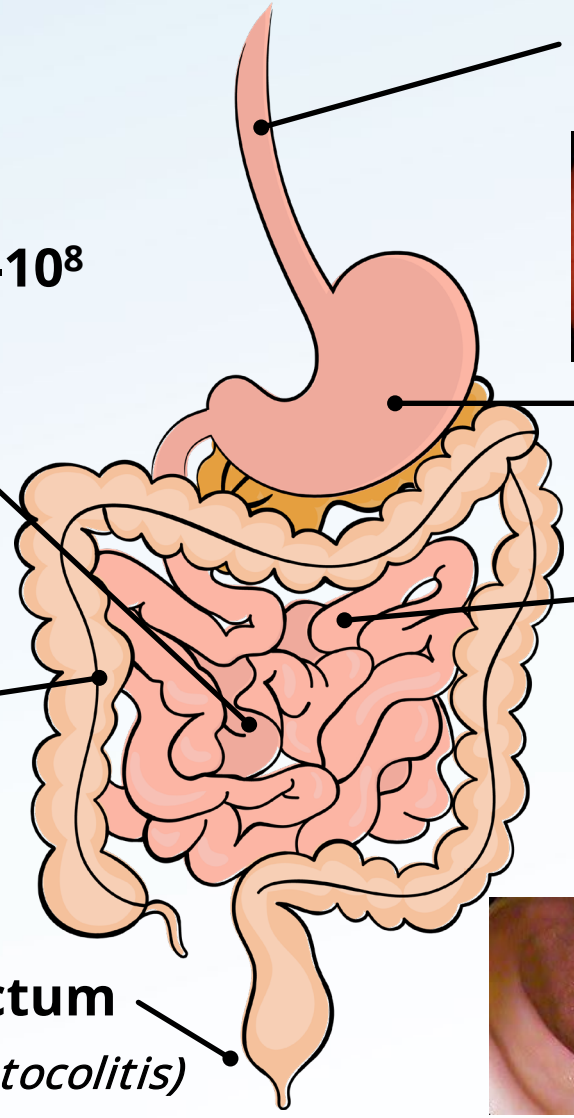


Distal Ileum $10^7$-$10^8$

*(NEC, IBD)*

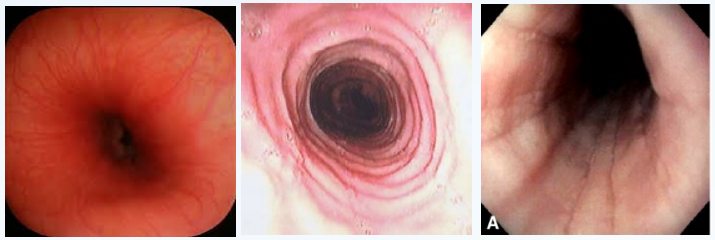
Colon $10^{11}$





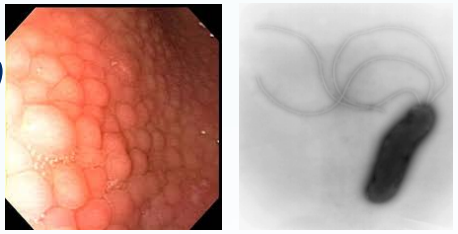
Esophagus 0-$10^2$

*(Eosinophilic Esophagitis)*



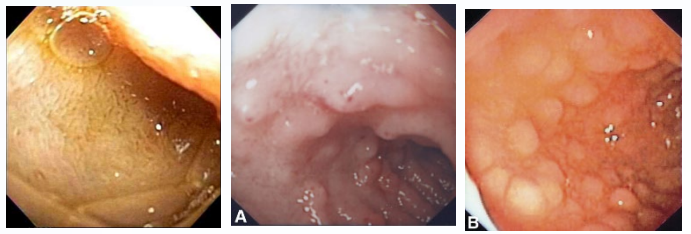
Stomach 0-$10^2$

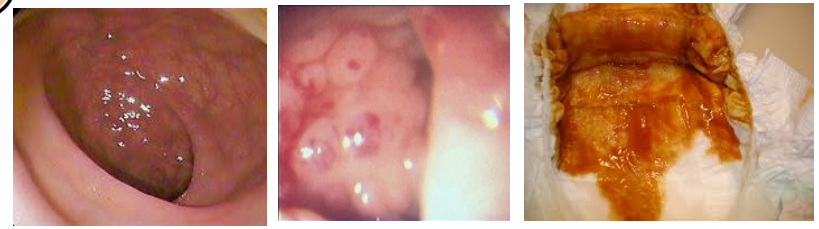
*(H. pylori Infection)*



Jejunum $10^2$

*(Celiac Disease)*



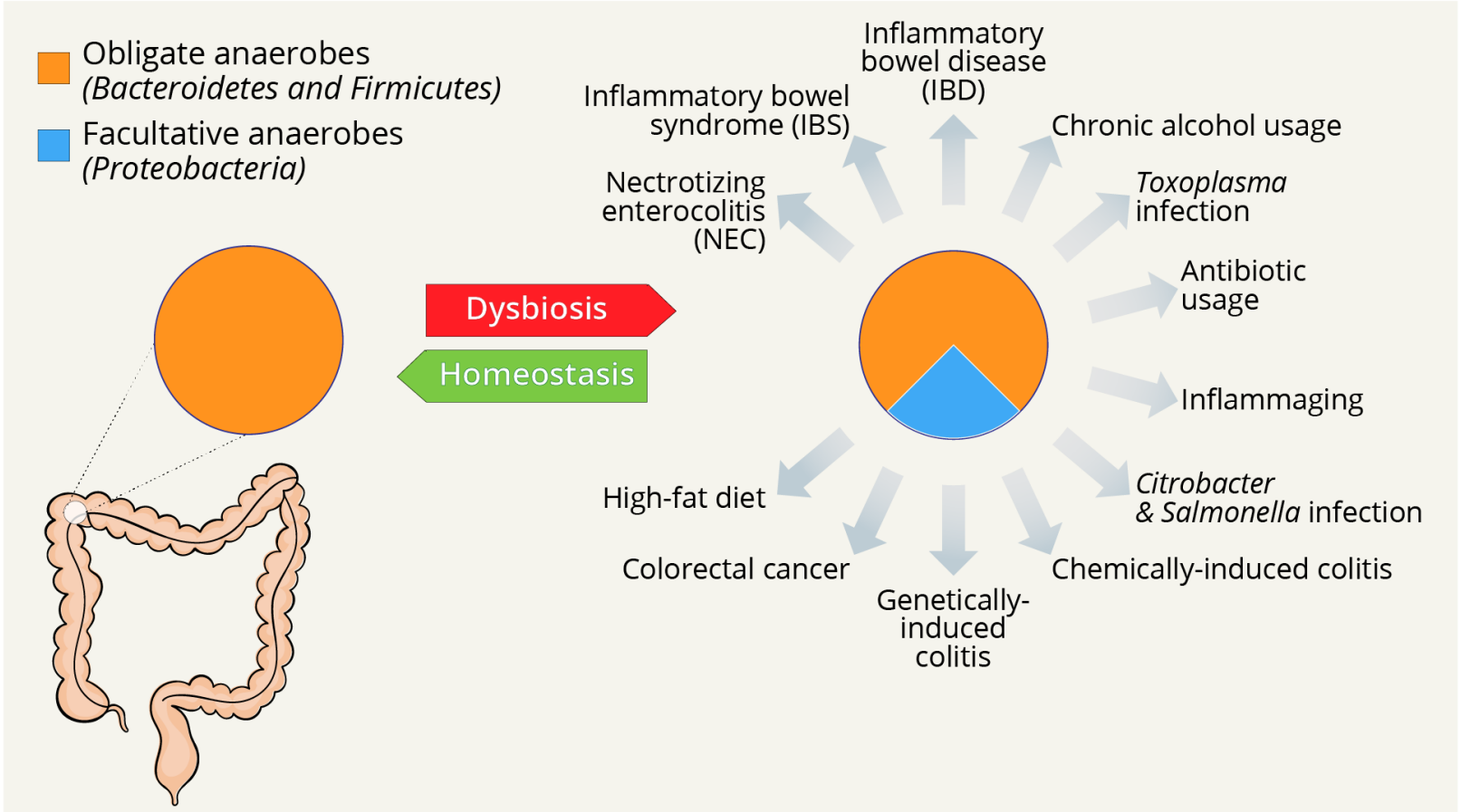


Rectum

*(Allergic protocolitis)*

# Where Are the Microbes Causing GI Disease With Dysbiosis?

Figure. **Dysbiosis: From Fiction to Function**




Adapted from Tiffany CR and Bäumer AJ. *Am J Physiol Gastrointest Liver Physiol.* 2019;317:G602-G608.

# Vaginal delivery – a major source of bacteria for the infant

# C-Section Rates by Gestational Age in the US

National Vital Statistics Reports

Volume 66, Number 1 January 5, 2017

## Births: Final Data for 2015

by Joyce A. Martin, M.P.H.; Brady E. Hamilton, Ph.D.; Michelle J.K. Osterman, M.H.S.; Anne K. Driscoll, Ph.D.; and T.J. Mathews, M.S., Division of Vital Statistics

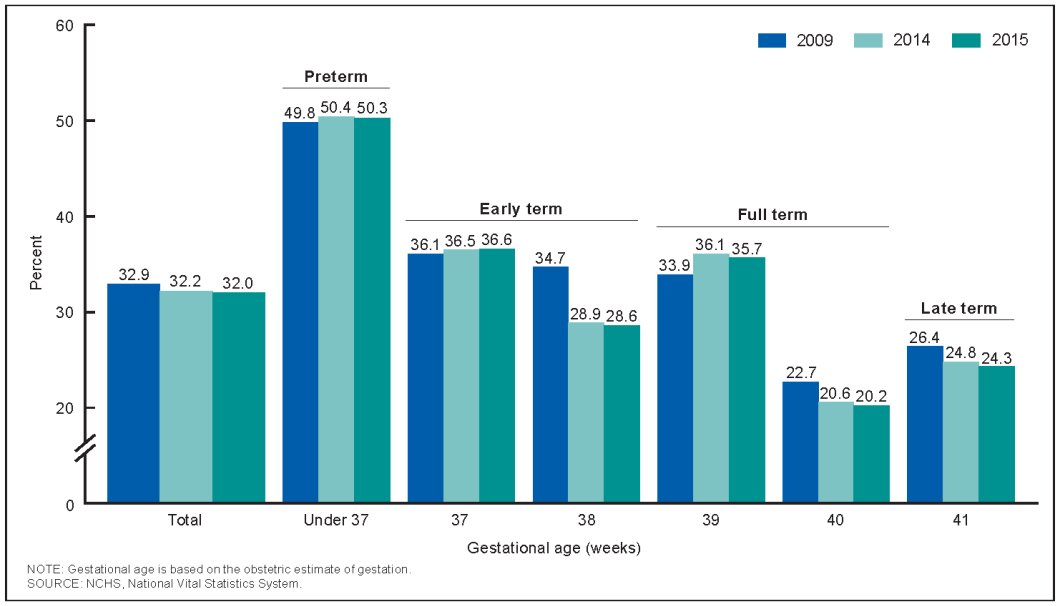
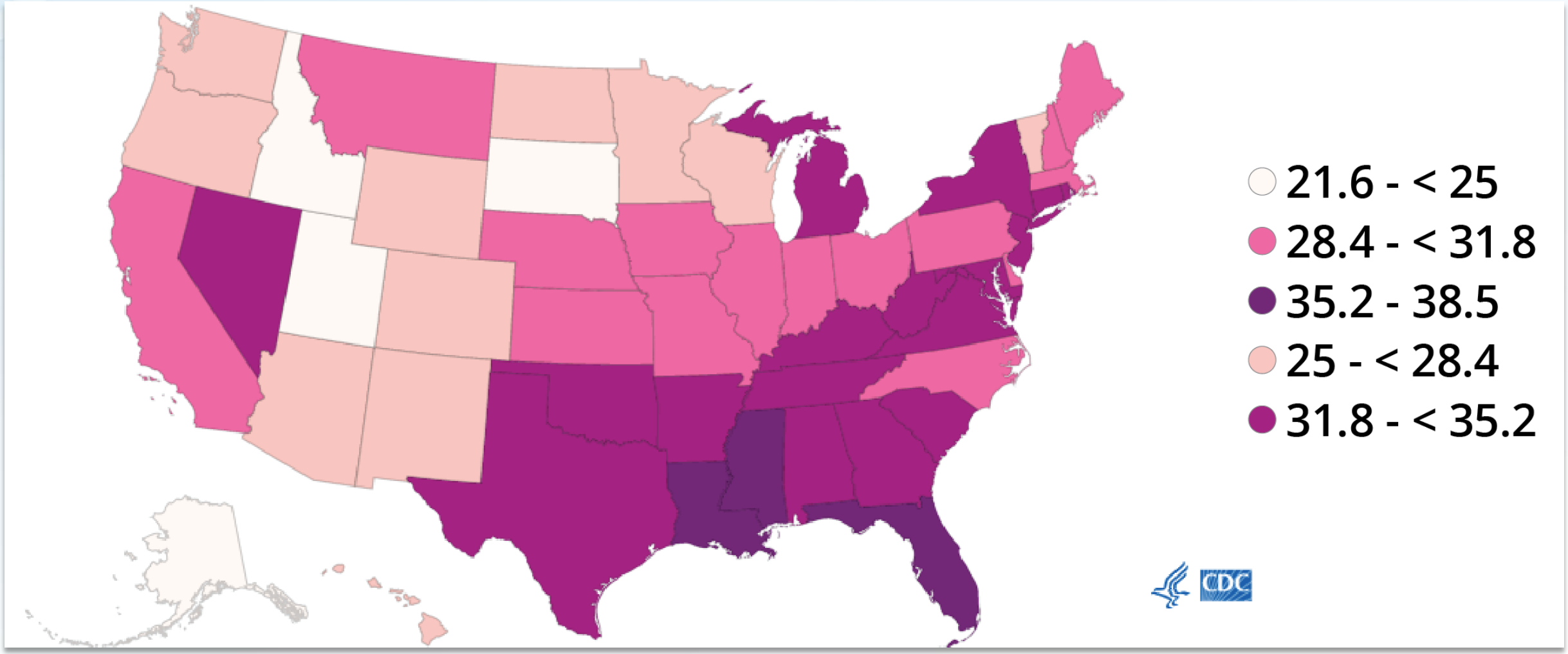



**Figure 1. Cesarean delivery, by gestational age: 2009, 2014, and 2015**

Martin JA, et al. *Natl Vital Stat Rep*. 2017;66(1):1.

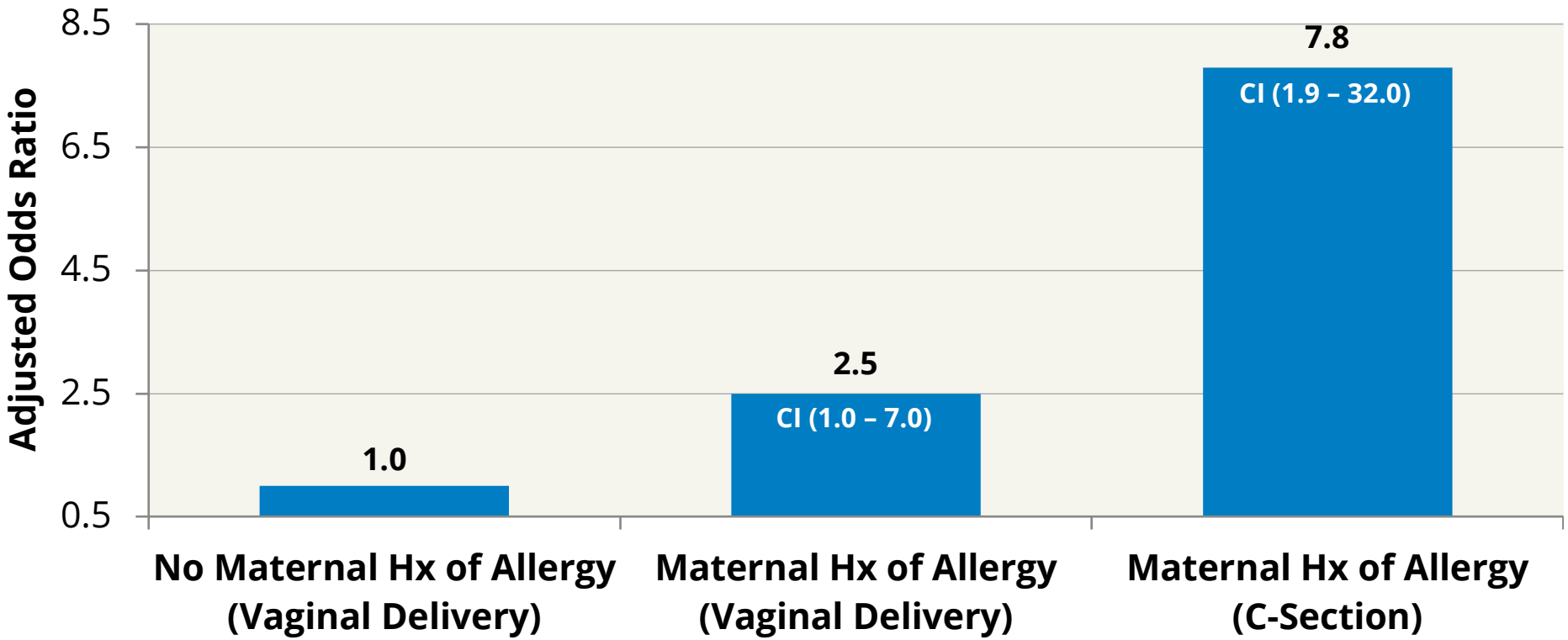
# C-Section Rates in the US by State




Centers for Disease Control and Prevention. Accessed April 26, 2021. https://www.cdc.gov/nchs/pressroom/sosmap/cesarean_births/cesareans.htm.

# Influence of Cesarean Delivery on Relative Risk of Childhood Food Allergy

Table. **Food Allergy and Mode of Delivery**




Food allergy to egg confirmed by testing at age 1–2 year. *p<0.01; adjusted for covariates

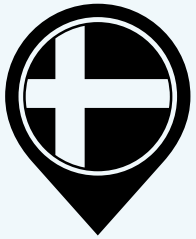
Eggesbo M, et al. *J Allergy Clin Immunol.* 2003;112:420-426.

# Influence of Cesarean Delivery on Relative Risk of Childhood Food Allergy

Medical Xpress | IMMUNOLOGY

**C-section children run increased risk of deeloping food allergies – as opposed to very preterm children**

Örebro Universitet • 10 September 2018



1.09 million newborns
2001-2012
Sweden

**Percent diagnosed with food allergy**

| **2.4%** | **2.9%** | **1.9%** |
|---|---|---|
| Baseline risk | 21% higher risk | 26% lower risk |
| Vaginal/full-term delivery | Cesarean delivery | Very preterm birth |
| **n = 901,262** | **n = 185,117** | **n = 7741** |

# Influence of Cesarean Delivery on Relative Risk of Childhood Food Allergy

Medical Xpress | IMMUNOLOGY

NewScientist | Health

## Boost C-section babies by giving them vaginal bacteria

Jessica Hamzelou • 1 February 2016

nature medicine

## Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

Maria G. Dominguez-Bello, Kassandra M. De Jesus-Laboy, Nan Shen, Laura M. Cox, Amnon Amir, Antonio Gonzalez, Nicholas A. Bokulich, Se Jin Song, Marina Hoashi, Juana I Rivera-Vinas, Keimari Mendez, Rob Knight & Jose C Clemente • 1 February 2016

Mitselou N, et al. *J Allergy Clin Immunol.* 2018;142(5):1510-1514.e2.

# Association Between Mode of Delivery and Microbiotic Characteristics[a]

- Gut microbiota formed 3 clusters, with mode of delivery as the major discriminating factor:
  - Bifidobacterium-rich
  - Bacteroides-rich
  - Escherichia/Shigella-rich
- Higher *Clostridium sensu stricto* abundance at 3 months increased the risk of atopic dermatitis at months 3 and 12
- Introduction of allergenic foods increased Shannon diversity and *Prevotellaceae* and *Proteobacteria* abundance compared with exclusively breastfed infants

a. In a study of 1303 exclusively breastfed infants, fecal samples were collected at baseline and through 12 months.

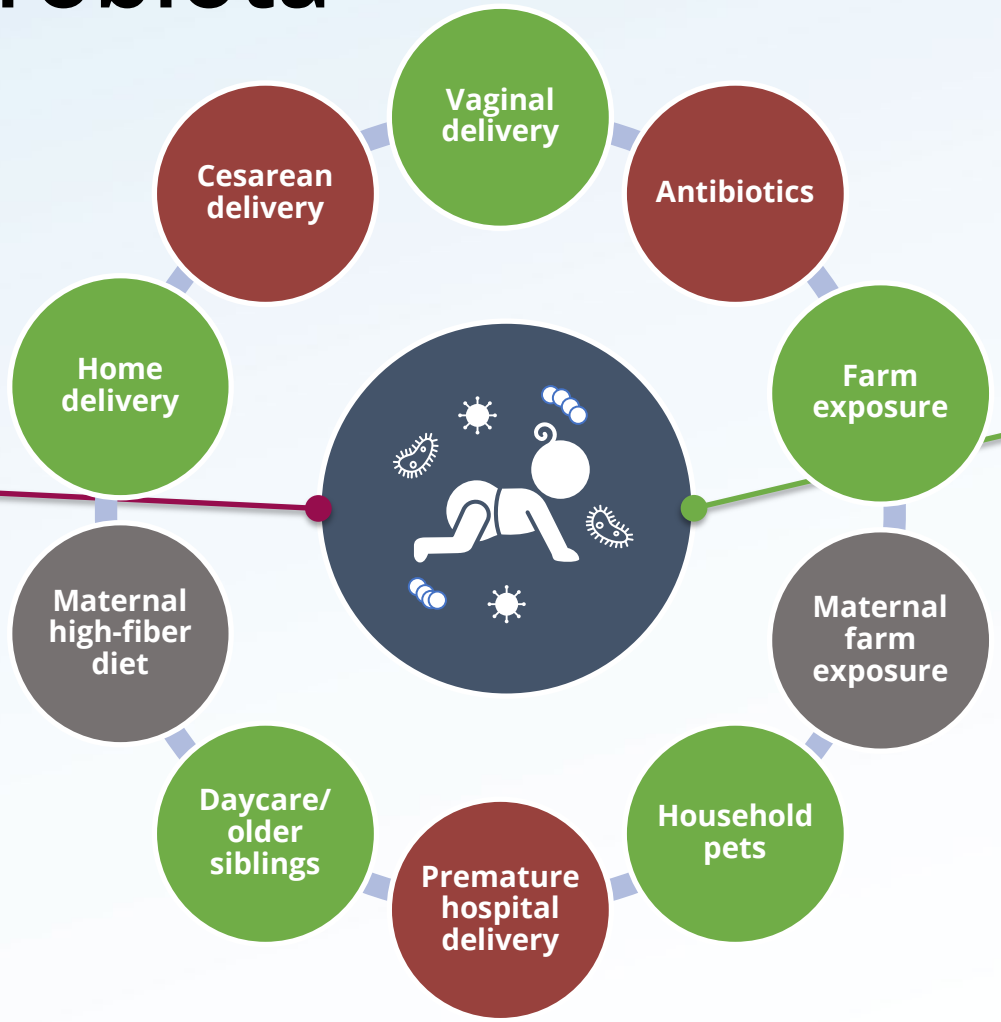
**When the Newborn Microbiome is Changed…**

**Increase in Autoimmune, Allergic, and Inflammatory Diseases**

# Infant Exposures Help Define Their Intestinal Microbiota

**Increase in relative abundance**
- *C difficile*
- *Veillonella*

**Overall bacterial community**
- Reduced diversity




**Increase in relative abundance**
- *Facalibacterium*
- *Lachnospira*
- *Veillonella*
- *Rothia*
- *Roseburia*
- *Alistipes*
- *Lachnospiraceae*
- *Ruminococcus*
- *Dialister*
- *Acinetobacter Iwoffi* F78
- *Lactobacillus*
- *Bifidobacterium*
- *Akkermansia*

**Bacterial components**
- Lipopolysaccharide
- Polysaccharide A

**Bacterial metabolites**
- Acetate

**Overall bacterial community**
- Increased diversity

Adapted from Sbihi H, et al. *Allergy.* 2019;74:2103–2115.

# Prebiotics, Probiotics, and Neonatal Care

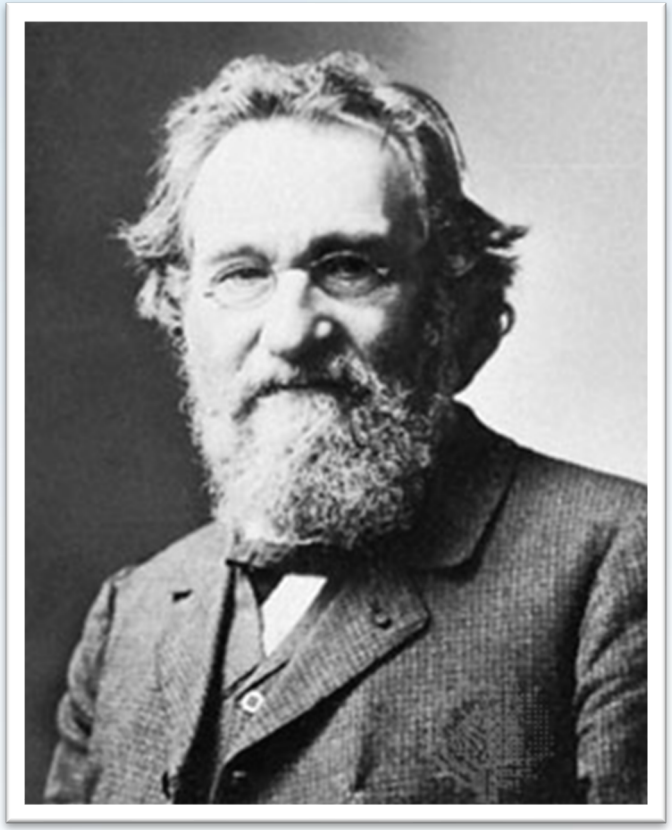
# ISAPP Definitions for Terminology

- **Probiotic:** “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” [1]
- **Prebiotic:** ”a substrate that is selectively utilized by host microorganisms conferring a health benefit” [2]
- **Synbiotic:** ”a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host” [3]

ISAPP, International Scientific Association for Probiotics and Prebiotics.


1. Hill C, et al. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506-514.
2. Gibson GR, et al. *Nat Rev Gastroenterol Hepatol*. 2017;14(8):491-502.
3. Swanson KS, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17(11):687-701.

# Ingestion of Bacteria Proposed as Beneficial



**Elie Metchnikoff (1845-1916)**

- Suggested that ingested bacteria could have positive influence on microflora in the intestinal tract
- Hypothesized that lactobacilli were important for human health and longevity
- Promoted yogurt and fermented foods as healthy

# Ingestion of Bacteria Proposed as Beneficial

**Lactobacillus sp[1,2]**

*L acidophilus*
*L brevis*
*L delbrueckii*
*L fermentum*
*L gasseri*
*L johnsonii*
*L paracasei*
*L plantarum*
*L reuteri*
*L rhamnosus GG (LGG)*
*L salivarius*

**Bifidobacterium sp[1,2]**

*B bifidum*
*B breve*
*B infantis*
*B longum*
*B adolescentis*
*B lactis (Bb12)*

**Other microbes[2]**

*Escherichia coli Nissle 1917*
*Saccharmyces boulardii*
*Saccharomyces cerevisiae*
*Enterococcus sp*

# Probiotics

- Nonpathogenic, live microorganisms in the food supply that, when **consumed or ingested** in adequate amounts, are capable of conferring a health benefit to the host

- Main genera used in commercial probiotics:
  - *Bifidobacteria*
  - *Lactobacilli*
  - Yeasts (*S boulardii*)

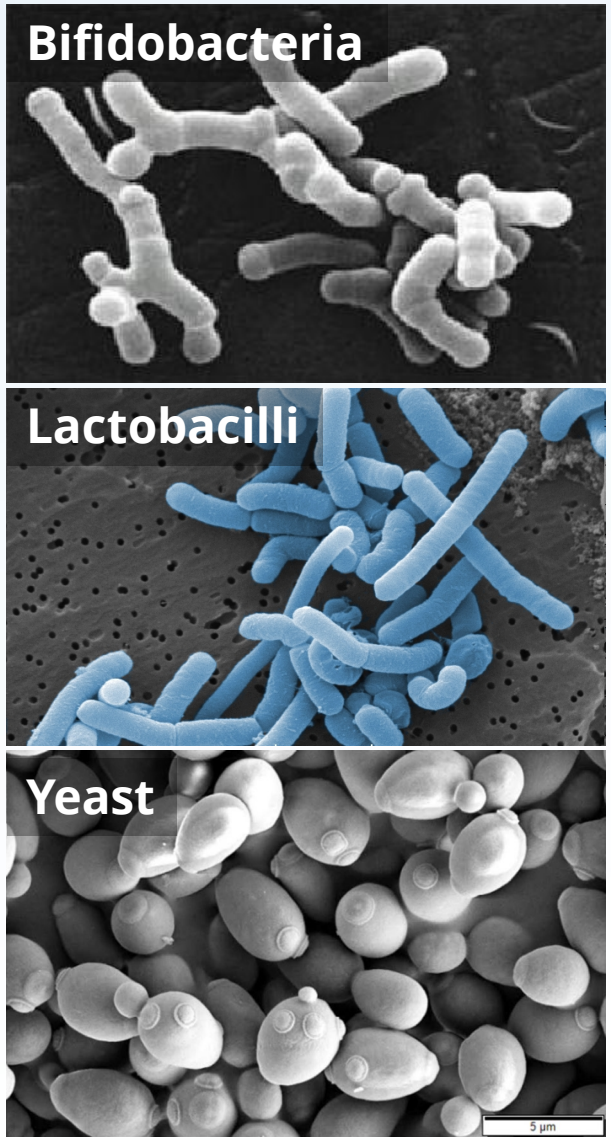



Image of bifidobacteria from https://commons.wikimedia.org/wiki/File:Bifidobacterium_longum_en_microscopie_%C3%A9lectronique.jpg. Image of lactobacilli from https://commons.wikimedia.org/wiki/File:Lactobacillus_paracasei.jpg. Image of yeast from https://commons.wikimedia.org/wiki/File:Saccharomyces_cerevisiae_SEM.jpg.


Day RL et al. *Future Sci OA*. 2019;5(4):FSO391.
Douglas LC, Sanders ME. *J Am Diet Assoc*. 2008;108(3):510-521.

# Prebiotics

- Food ingredients that benefit the host by stimulating the growth or activity of components of the gut microbiota
- Typically nondigestible oligosaccharides that are fermented by colonic bacteria
- Certain bacteria generate energy from these fermentation products

Oozeer R et al. *Am J Clin Nutr*. 2013;98(2):561S-71S.

# Breastmilk HMOs Can Help Balance the Microbiota and Support the Developing Immune System (Prebiotic Effect)

- Balance the microbiota
  - Enhance growth of bifidobacteria
  - Inhibits adhesion of pathogens

- Support the infant's developing immune system
  - Circulate in the bloodstream
  - HMOs influence lymphocyte maturation and promote a shift in T-cell response

# Premature Infants: Set-up for an Altered Microbiota and its Potential Consequences

- C-section birth
- Less chances of being breast fed
- NICU microbes
- Antibiotics

**Delayed establishment of microbiota**

**Aberrant composition of microbiota**

**Inadequate GALT development and maturation**

**Decreased gut barrier (mucin, permeability)**

**Poor humoral and cellular immune response**

Kim J, et al. Up To Date. 2018.
Thomas JP, et al. *Acta Paediatr.* 2017; 106:1729.

# Contributors to and Consequences of Gut Dysbiosis

## Contributors

- Hospital environment
- Maternal microbiota
- Mode of delivery
- Feeding type
- Home environment
- Antibiotics
- Feeding tube biofilms (preterm)

## Dysbiosis-associated diseases

**Preterm infants:**

- Necrotizing enterocolitis (NEC)
- Late-onset sepsis

**All infants:**

- Neurodevelopmental impairment
- Colic
- Atopic and autoimmune diseases
- Type 1 diabetes
- Metabolic disorders and obesity

Underwood MA, et al. *J Perinatol*. 2020;40(11):1597-1608.

# Premature Infants: Set-up for an Altered Microbiota and its Potential Consequences

- Early recognition and aggressive treatment of necrotizing enterocolitis (NEC) has improved clinical outcomes
- NEC accounts for substantial long-term morbidity in survivors of neonatal intensive care
- NEC is particularly significant in preterm very low birth weight (VLBW) infants (BW <1500 g)

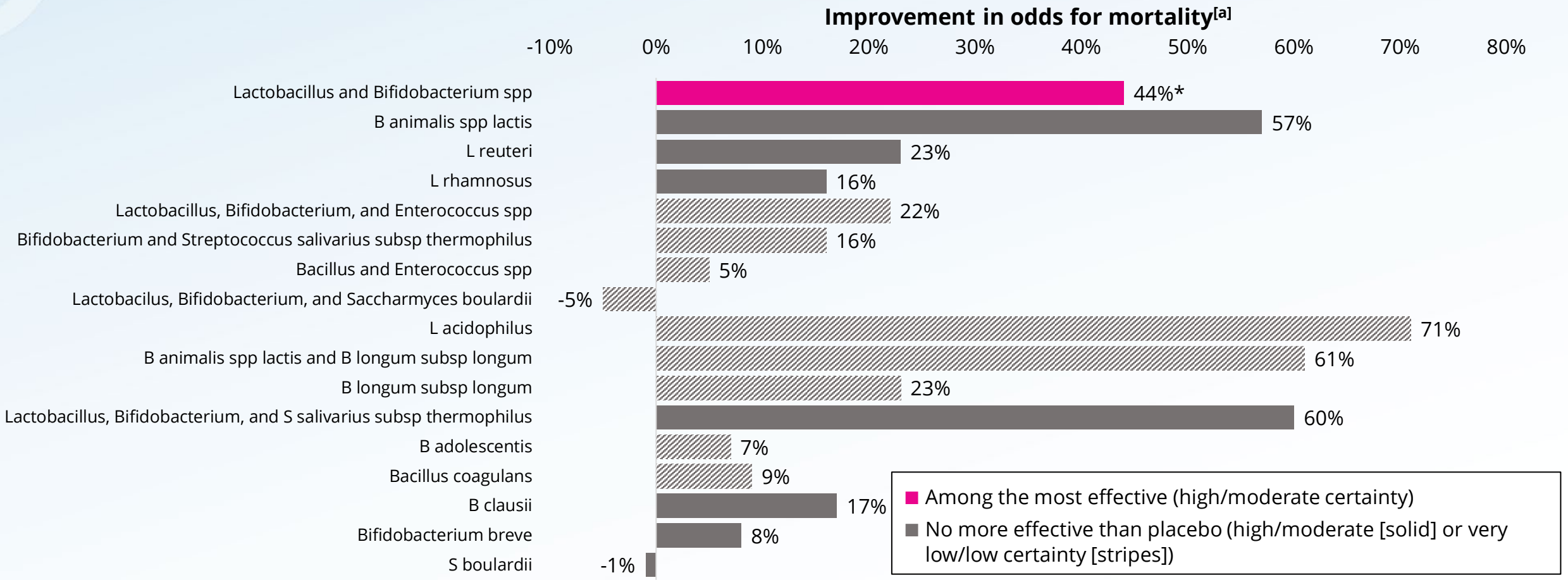
Kim J, et al. *UpToDate.* 2018.
Thomas JP, et al. *Acta Paediatr.* 2017;106:1729

# Probiotics for Prevention of Necrotizing Enterocolitis in Preterm Infants (Update)

- Meta-analysis of 24 trials
- Probiotic supplementation was shown to:
  - Reduce severe NEC (typical relative risk [RR], 0.43; 95% CI, 0.33-0.56)
  - Reduce mortality (typical RR, 0.65; 95% CI, 0.52-0.81)
- Probiotics had no effect on:
  - Nosocomial sepsis (typical RR, 0.91; 95% CI, 0.80-1.03)
- Probiotics containing either lactobacillus alone or in combination with bifidobacterium were effective
- Head-to-head studies are needed "to assess the most effective preparations, timing, and length of therapy"

AlFaleh K, Anabrees J. *Cochrane Database Syst Rev*. 2014;(4):CD005496.
Kim J, et al. *Up To Date.* 2018

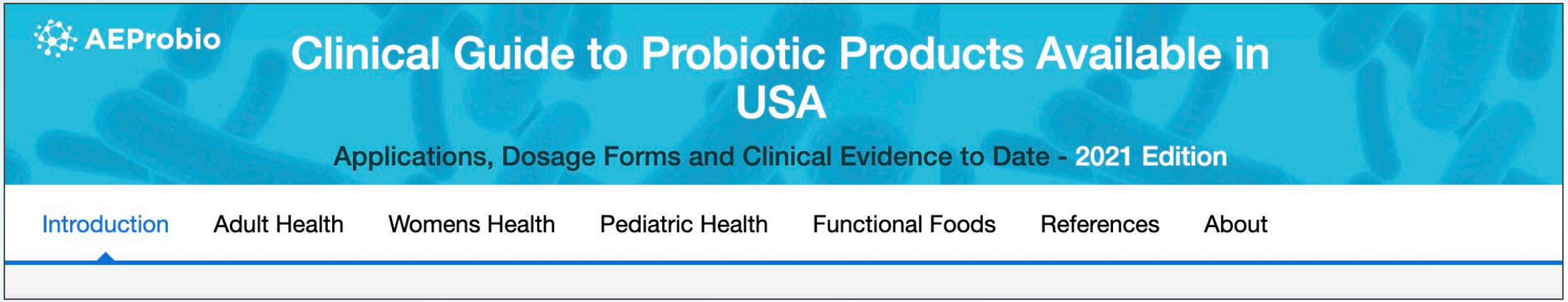
# Probiotic Effect on Mortality in Preterm Infants




a. In a meta-analysis of 63 trials of preterm infants (n = 15,712) comparing probiotics with placebo
*Statistically significant

Morgan RL, et al. *Gastroenterology*. 2020;159(2):467-480.

# Clinical Guide to Probiotic Products Available in the US




For more information, visit **http://www.usprobioticguide.com/**

Skokovic-Sunjic D. AEProbio. January 2021. Accessed April 12, 2021. http://www.usprobioticguide.com/PBCIntroduction.html?utm_source=intro_pg&utm_medium=civ&utm_campaign=USA_CHART.

# Summary

- Provided an overview of how the infant's immune system develops and the interaction with the gastrointestinal microflora
- Described the growing problem and epidemiology (ie, prevalence) of pediatric allergy worldwide
- Noted the importance of the gastrointestinal microbiome in health and disease
- Reviewed how prebiotics and probiotics can alter intestinal microflora and potentially change health outcomes

# ADDITIONAL RESOURCES

# Clinical Practice Guidelines

AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders [1]

**Key guideline recommendations:**

- For preterm (born before 37 weeks), low birthweight (<2500 g) infants, specific probiotics can prevent mortality and necrotizing enterocolitis, reduce the number of days required to reach full feeds, and decrease the duration of hospitalization.
- Certain probiotics should be considered for the prevention of C. *difficile* infection in adults and children who take antibiotics and for the management of pouchitis, a complication of ulcerative colitis that has been treated surgically.

Su GL, et al. *Gastroenterology*. 2020;159:697-705.

# Clinical Practice Guidelines

AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders [1]

**Key guideline recommendations:**

- Probiotics do not appear to be beneficial for children in North America who have acute gastroenteritis — they should not be given routinely to children who present to the emergency room due to diarrhea.
- There was insufficient evidence for AGA to make recommendations regarding the use of probiotics to treat C. *difficile* infection, Crohn's disease, ulcerative colitis or IBS. For these conditions, AGA suggests that patients consider stopping probiotics, as there are associated costs and not enough evidence to suggest lack of harm.

Su GL, et al. *Gastroenterology*. 2020;159:697-705.

# Key Concepts

**Where are the microbiota?**

- Found throughout the GI tract
- Organized into specific compartments on the mucosal surface and within the gut lumen

**Who are they?**

- The microbiota of early childhood is very unstable and highly susceptible to environmental influences
- In adults, *Firmicutes* and *Bacteroidetes* are the 2 predominant phyla
- Great deal of diversity at the species level that defines a unique microbial signature for each of us

**What are they doing?**

- Nutrition and metabolism
- Regulation of the immune system
- Maintenance of gut structure

**How can they be manipulated?**

- Prebiotics/diet
- Probiotics/fecal transplantation
- Synbiotics (combination of pre- and probiotics)