Intestinal microbiota

The first 1000 days establish a symbiosis

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Intestinal microbiota

$10^{12\text{-}14}$ microorganisms, > 1500 different species

- Microorganisms : 10 x human body cells
- Total microbiota : Weight > of human brain
- Genetic potential : x 250 human genome

May be considered as an « organ » that can be even transplanted

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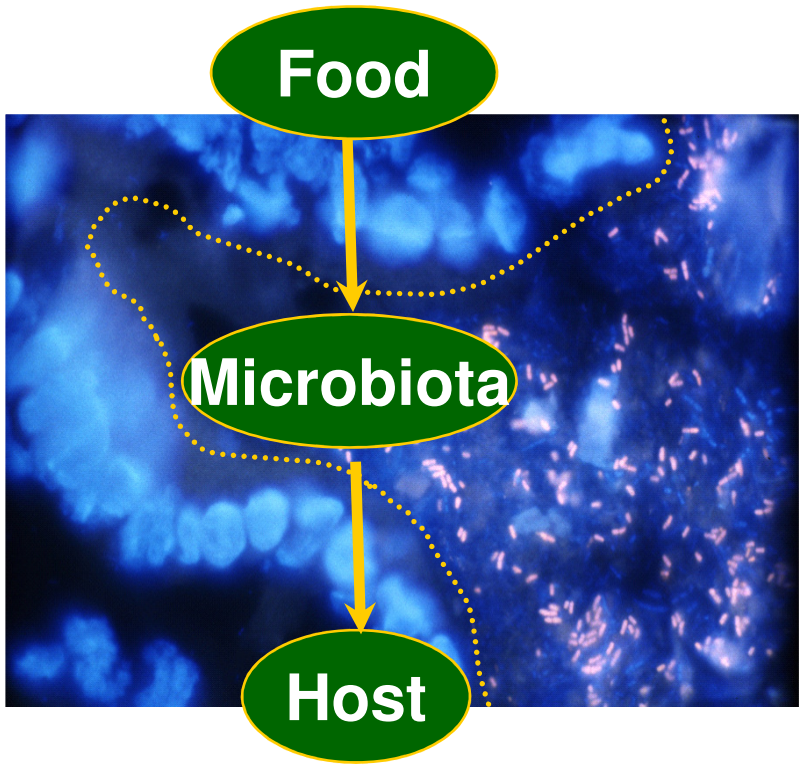
Human intestinal microbiota is a forgotten organ…

$10^{12\text{-}14}$ microorganisms, > 1500 different species



- ✓ **Interface between food and epithelium**
- ✓ **In touch with gut immune and neuro-enteric systems**
- ✓ **Major importance of gut microbiota diversity**
- ✓ **Concept of protective bacteria**

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Role of intestinal microbiota

- **Protects against enteric pathogens**
  - *Competes for nutrients*
  - *Degrades toxins*
  - *Impaires pathogen adherence & growth*
- **Secrete anti-bacterial substances**
  - *which protect against pathogens*
- **Produce AA, vitamins *(B12, K2....)***
- **Influence development of gut motility**
- **Intestinal immune system maturation**

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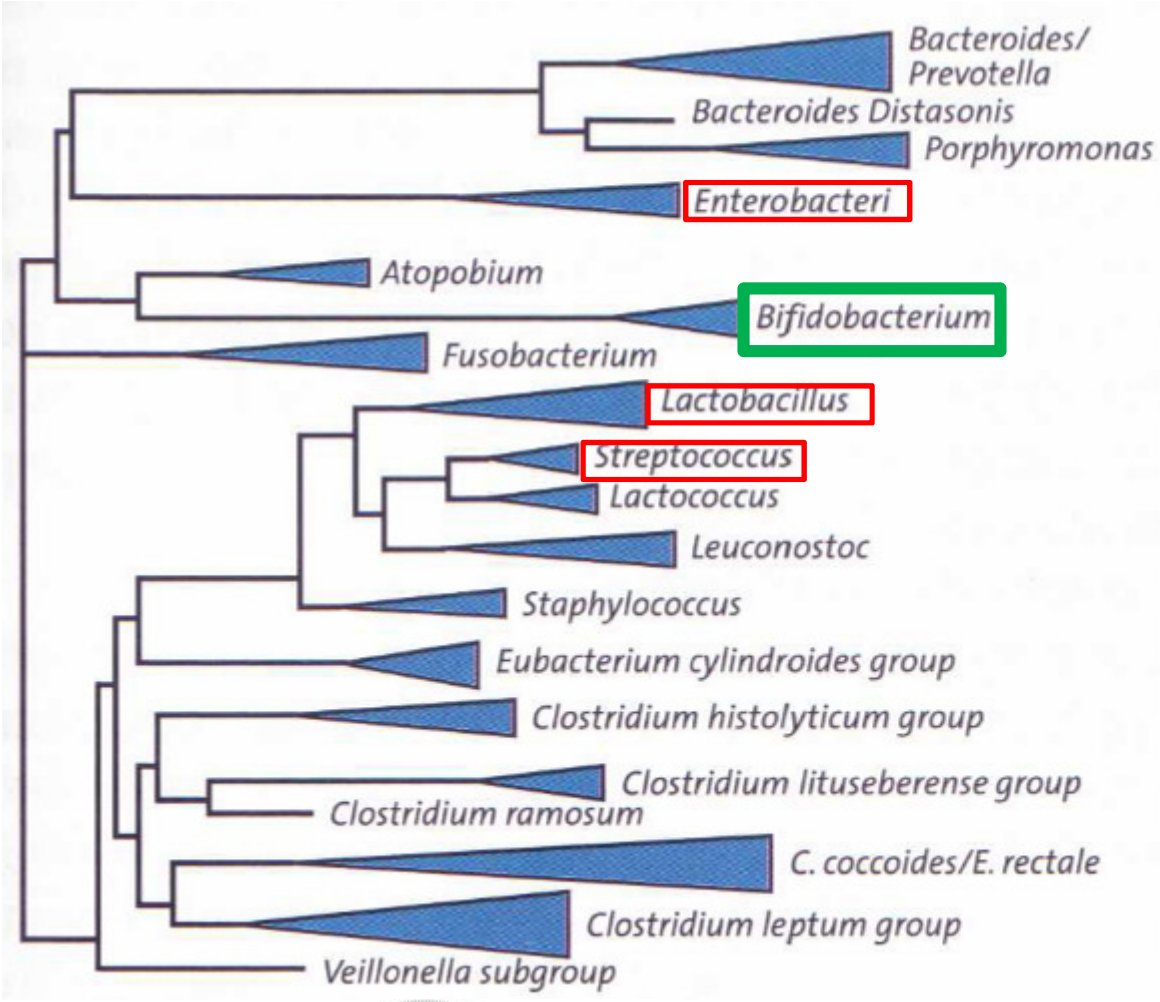
Intestinal microbiota

10^{12-14} microorganisms, > 1500 different species



Bacteroidetes 9-42%

Actinobacteria 1-10%

Firmicutes 14-31%

3 dominant phyla

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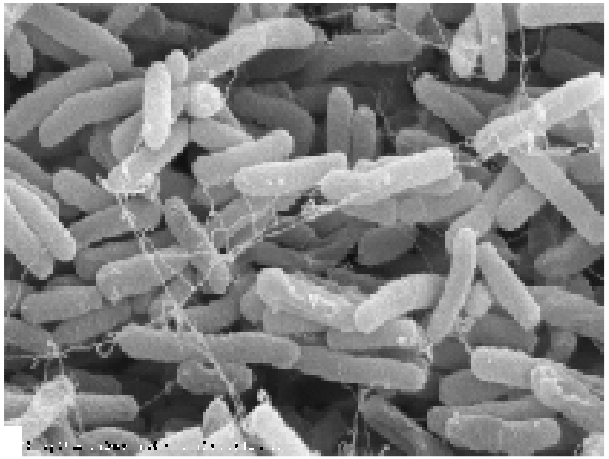
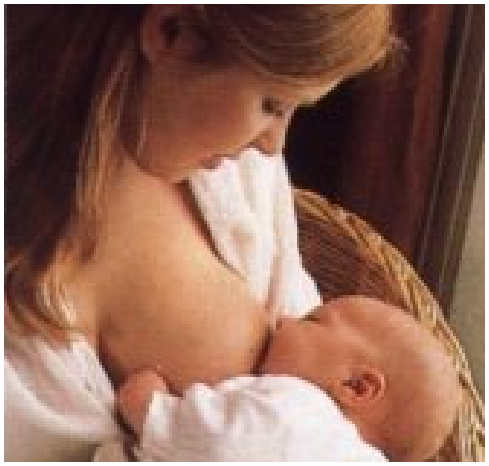
Content of the presentation

- **Factors of gut bacterial colonization**
- **Impact of microbiota on GI function**
- **Impact on health and diseases**
- **Modulation of intestinal microbiota**





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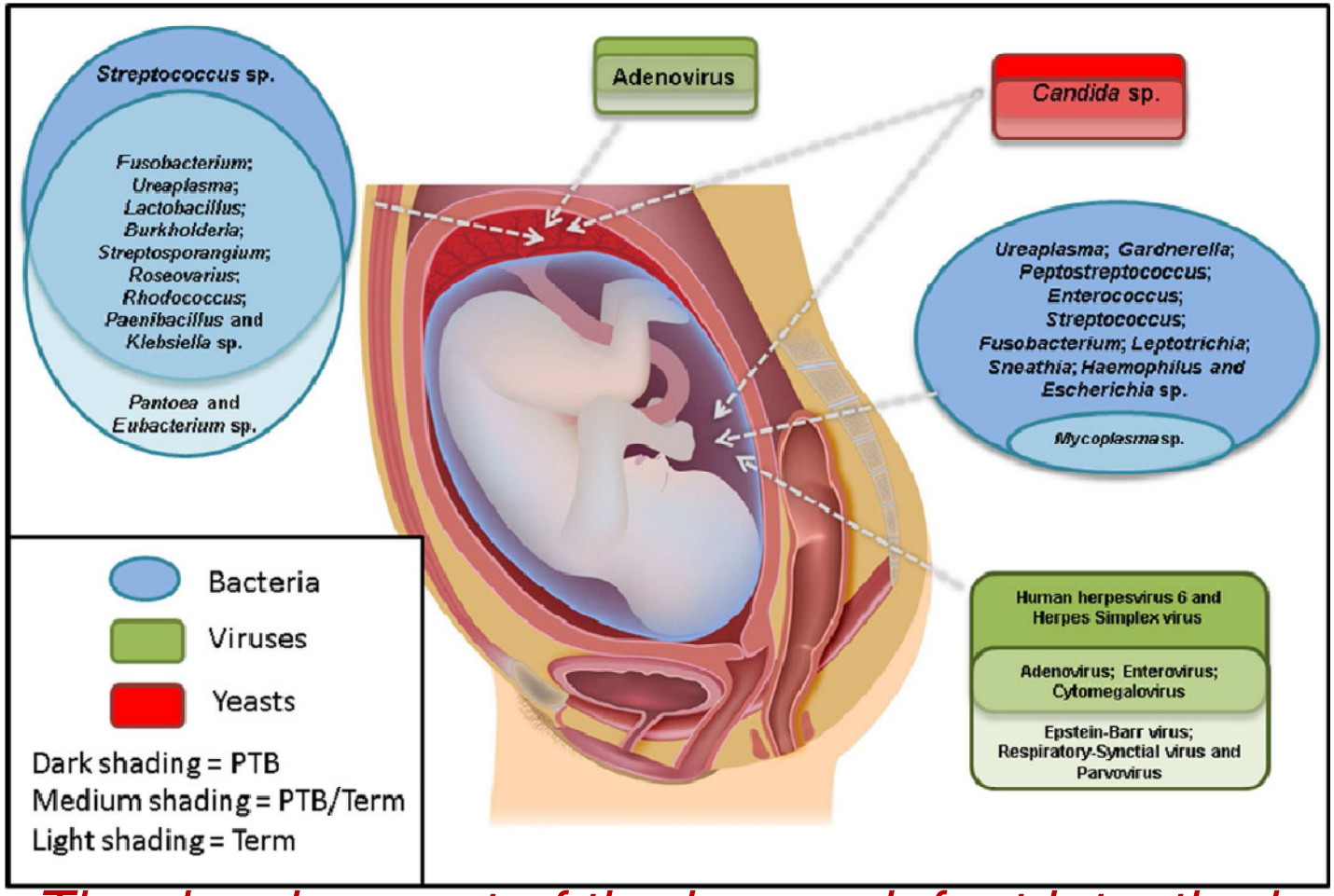
frontiers in IMMUNOLOGY

REVIEW ARTICLE
published: 27 November 2014
doi: 10.3389/fimmu.2014.00595

Exploring preterm birth as a polymicrobial disease: an overview of the uterine microbiome



The development of the human infant intestinal microbiota is a sequential process that begins in utero

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Fetal microbiota

Accumulating evidence contradicts the dogma that the fetus resides in a sterile environment

Placenta microbiome

Aagaard K et al, Sci Transl Med 2014

Bacteria in amniotic fluid and cord blood

Gimenez et al 2008; Collado et al 2016

Fetal membranes and colostrum microbiome

Martin et al 2003; Jones et al 2009; Cabrera-Rubio et al 2012;

Meconium harbors a bacterial community

Ardissone et al 2014; Collado et al 2016

Microbes in the nasopharynx of term newborns

Lohmann et al 2014; Galalger et al 2016

Role of intestinal microbiota in NEC

Bacteria are present in amniotic fluid and meconium

- Microbiota, chorio-amnionitis & term are related
- Temporal dynamics of gut dominant microbiota
- Timing & severity of NEC are microbiota related
- Poor microbiota diversity increases risks of NEC

1. Martinez et al Pediatr Res 2014
2. Ajoulat et al BMC Microbiology 2004
3. Zhou et al; PLOS one 2015
4. Mac Murtry et al. PLOS one 2015
5. Neu J et al.. Semin Perinatol. 2016
6. Elgin TG, et al Clin Ther. 2016.

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Bacterial colonization of the neonatal gut

More than 1500 bacterial anaeroby& aeroby progressively colonize the human gut

Colonization by bacteria occurs early and may be affected by several factors

- ***Term of pregnancy (prematurity)***
- ***Route of delivery (C-section, vaginal)***
- ***Hygiene of neonatal environment***
- ***Maternal bacterial gut microbiota***
- ***Diet of the infant (breast milk/formula)***
- ***Drugs (antibiotics, PPI….)***

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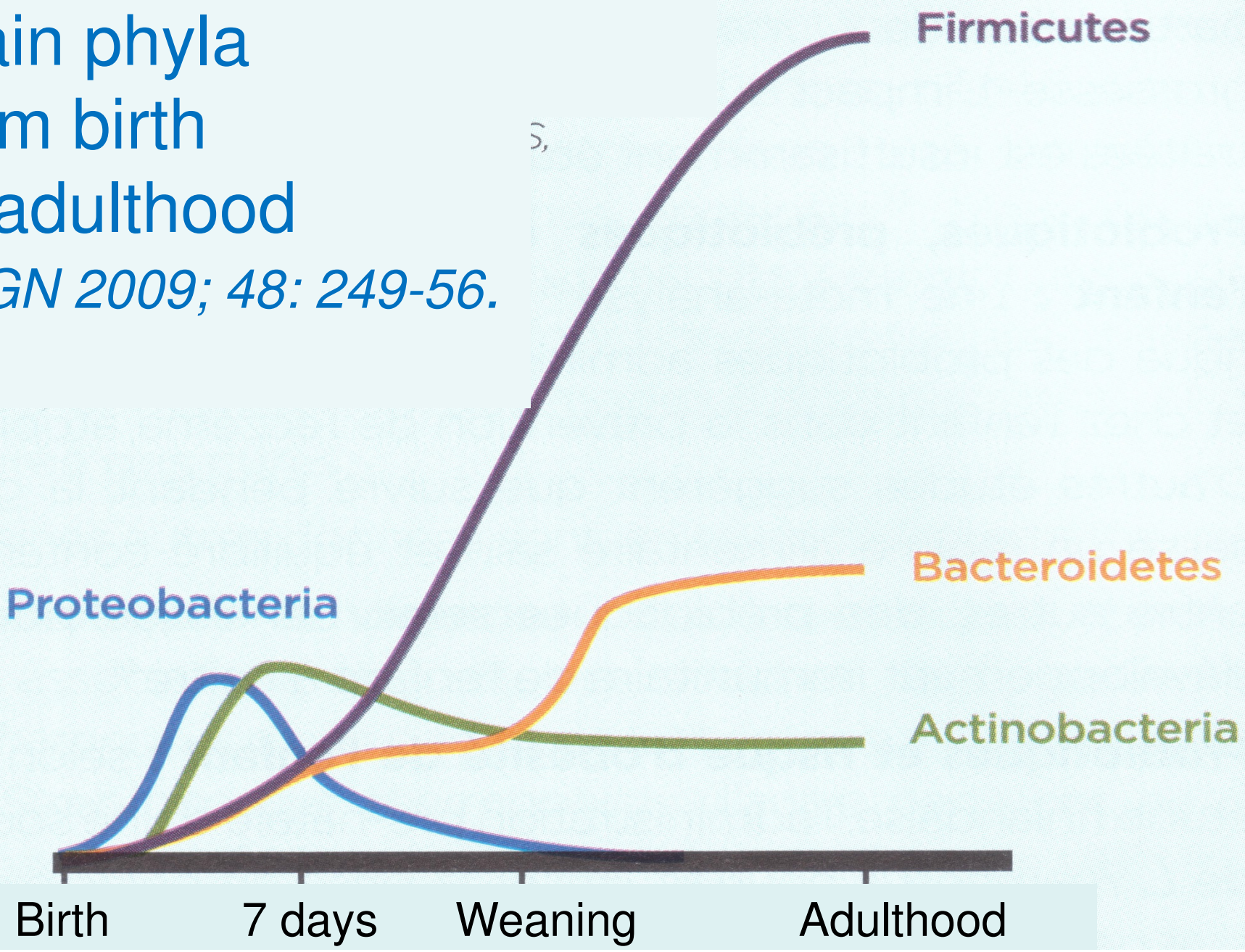
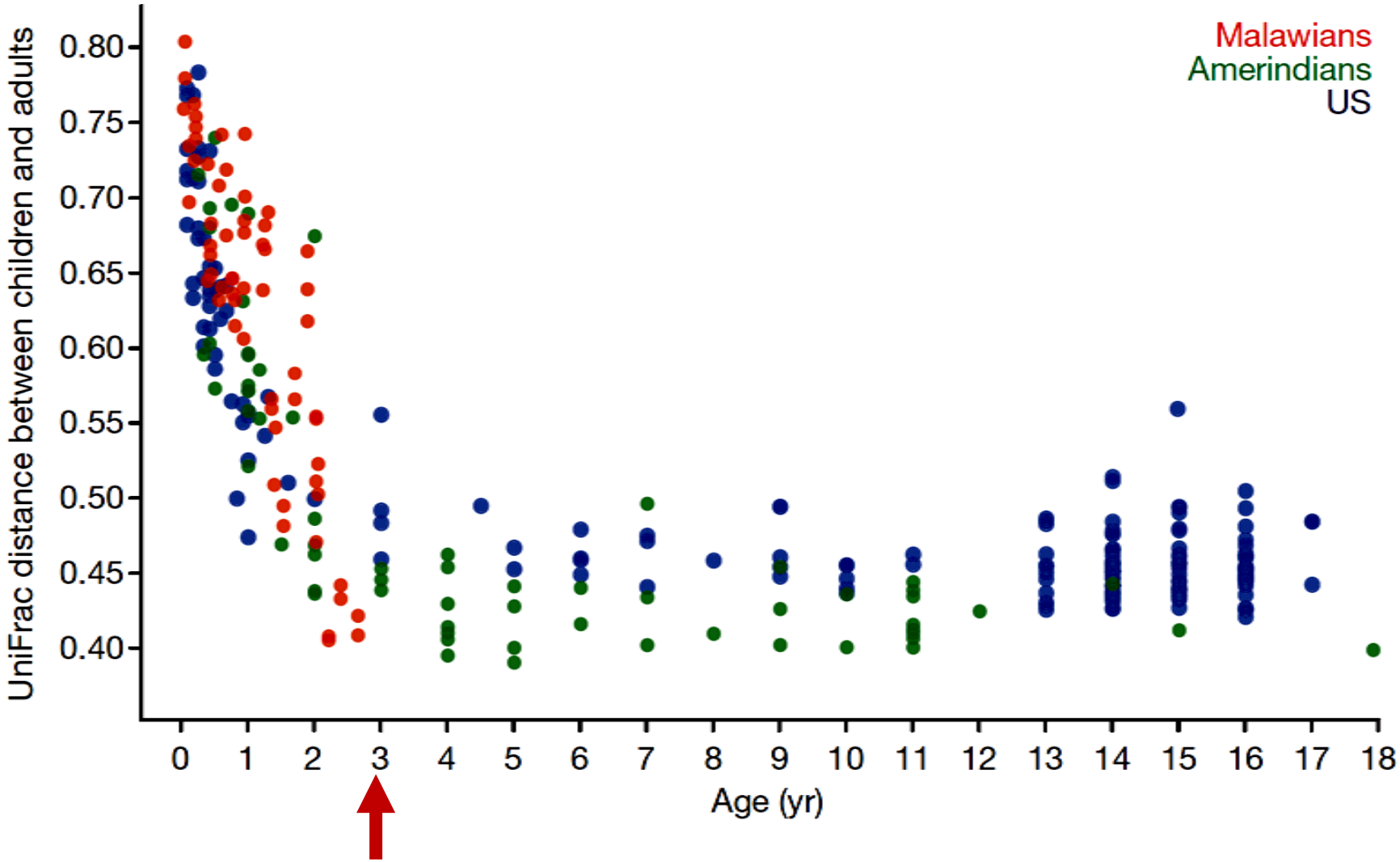
Course of the main phyla from birth to adulthood

JPGN 2009; 48: 249-56.



Human gut microbiome viewed across age and geography



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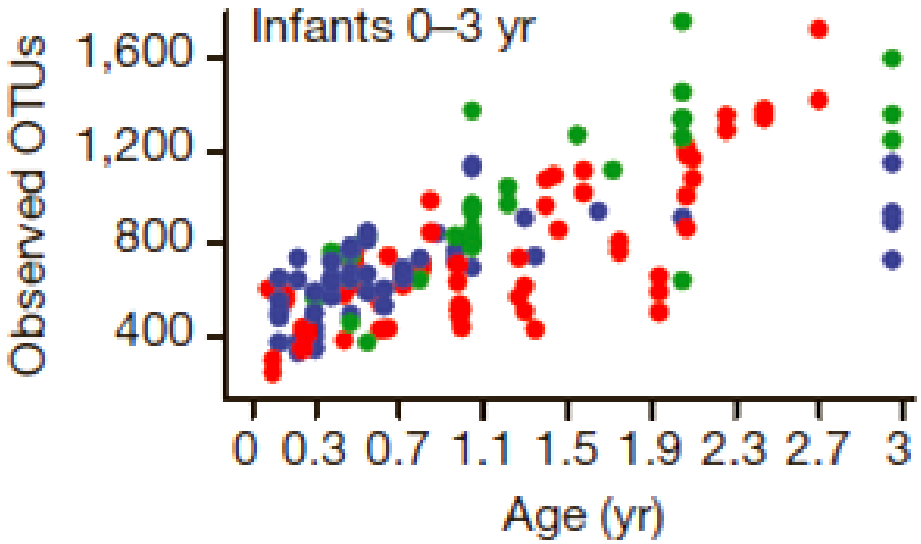
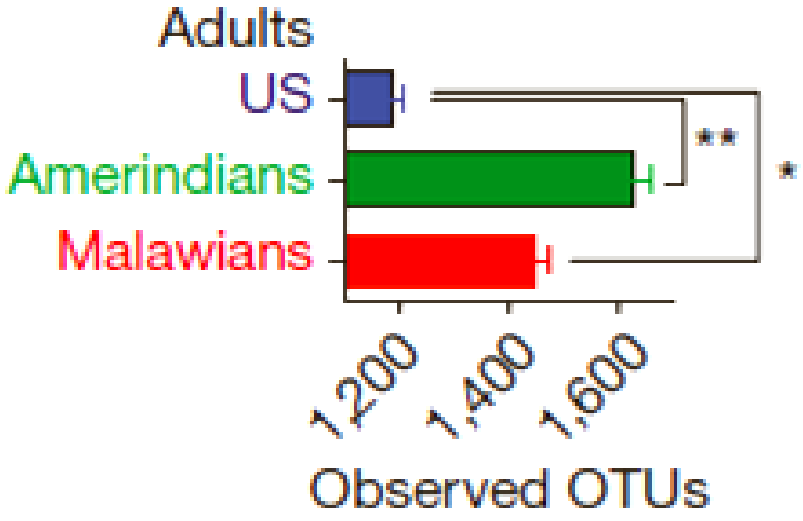
Yatsunenko T et al Nature 2012

Human gut microbiome viewed across age and geography

Bacterial diversity according to age and origin

Assessed by Operational, Taxonomic Units (OTUs)





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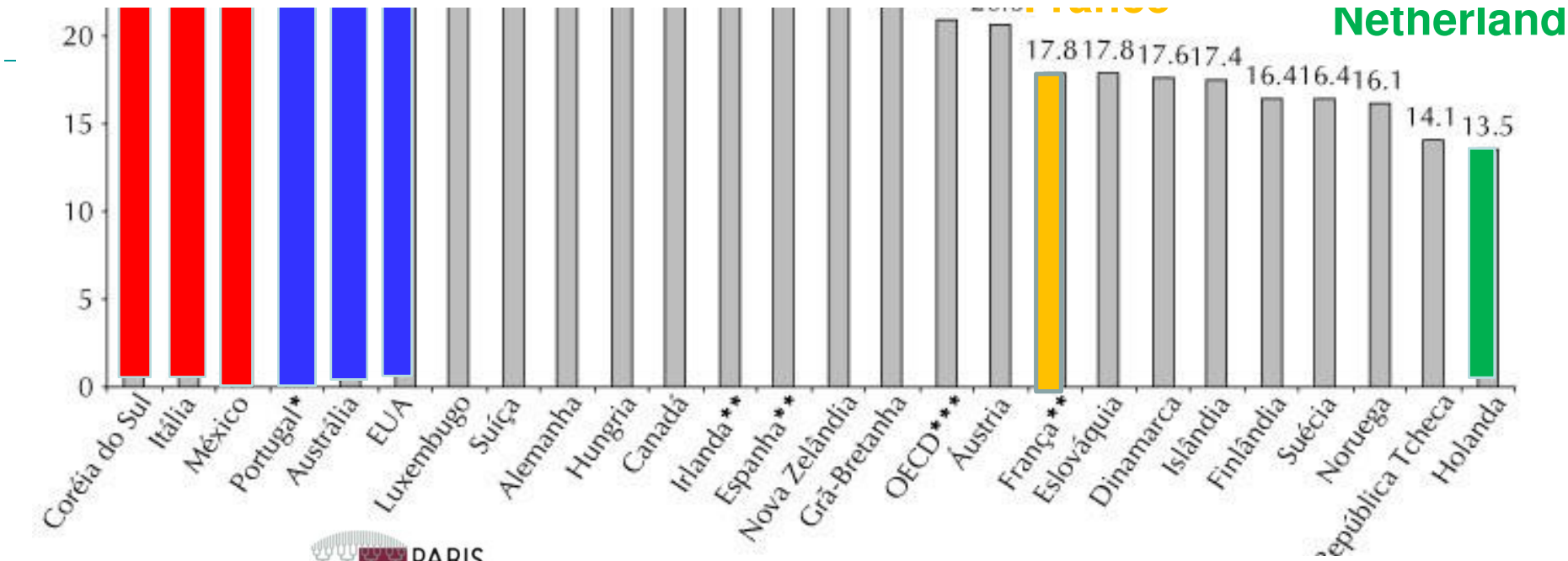

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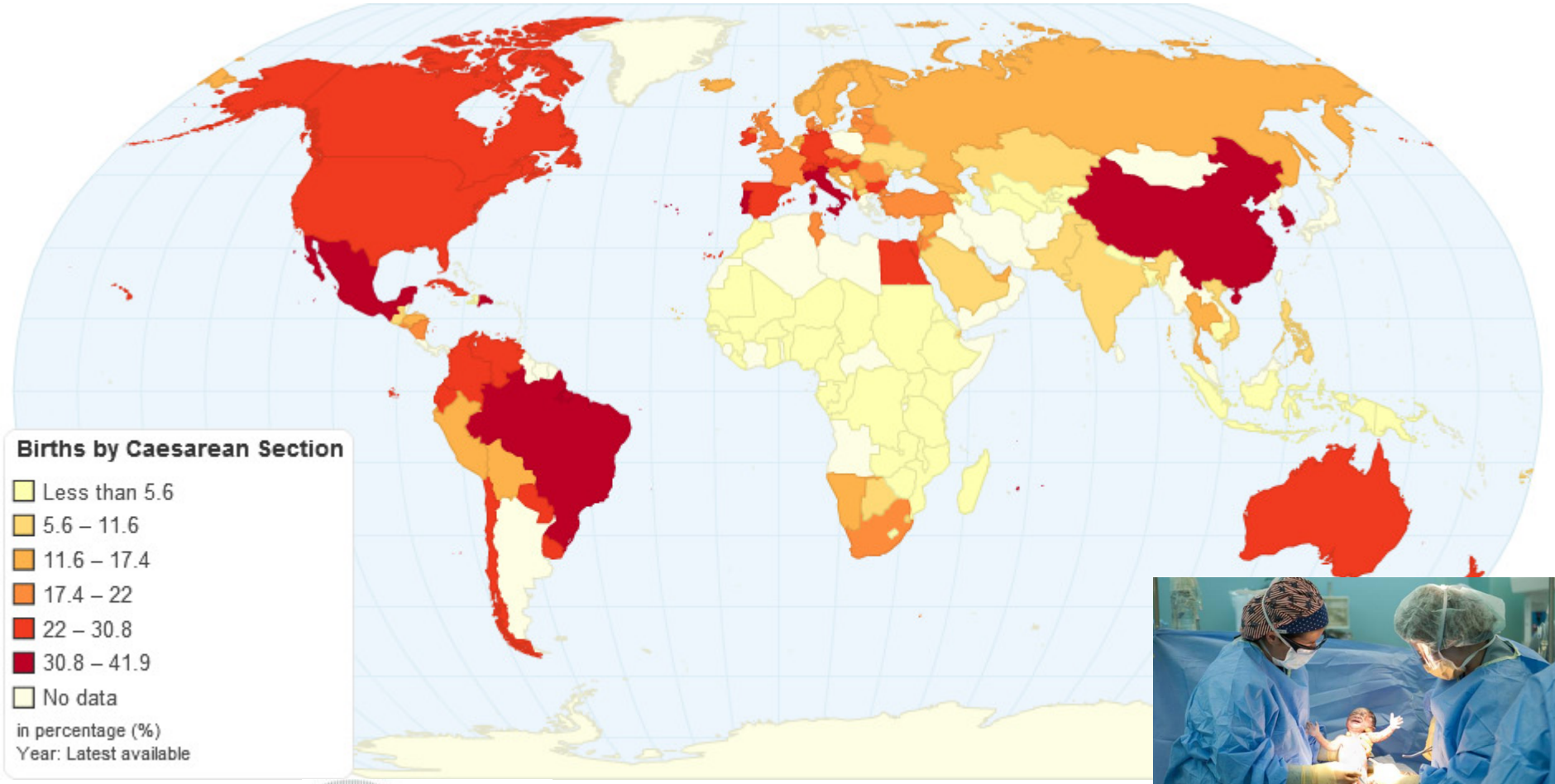
Brazil CS incidence 50.1% in 2009 Ministerio

Which Countries Conduct The Most Caesarean Sections?

Caesarean rate per 100 live births in selected OECD countries*



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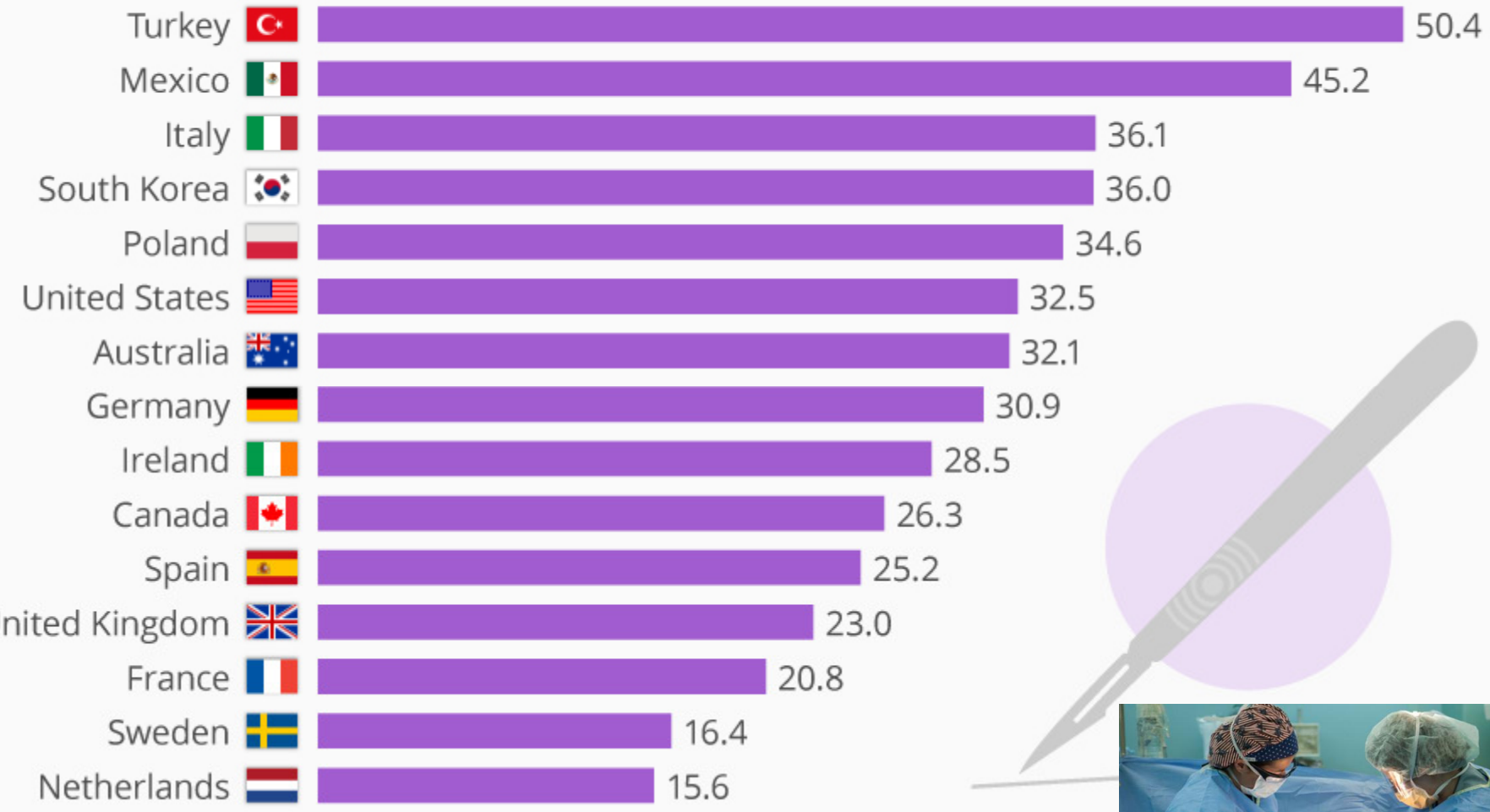

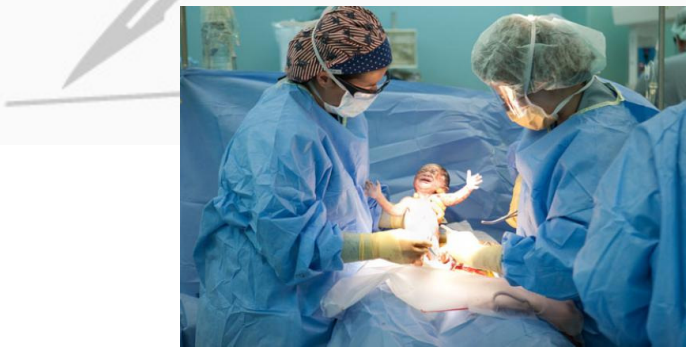

Source : OECD 2013

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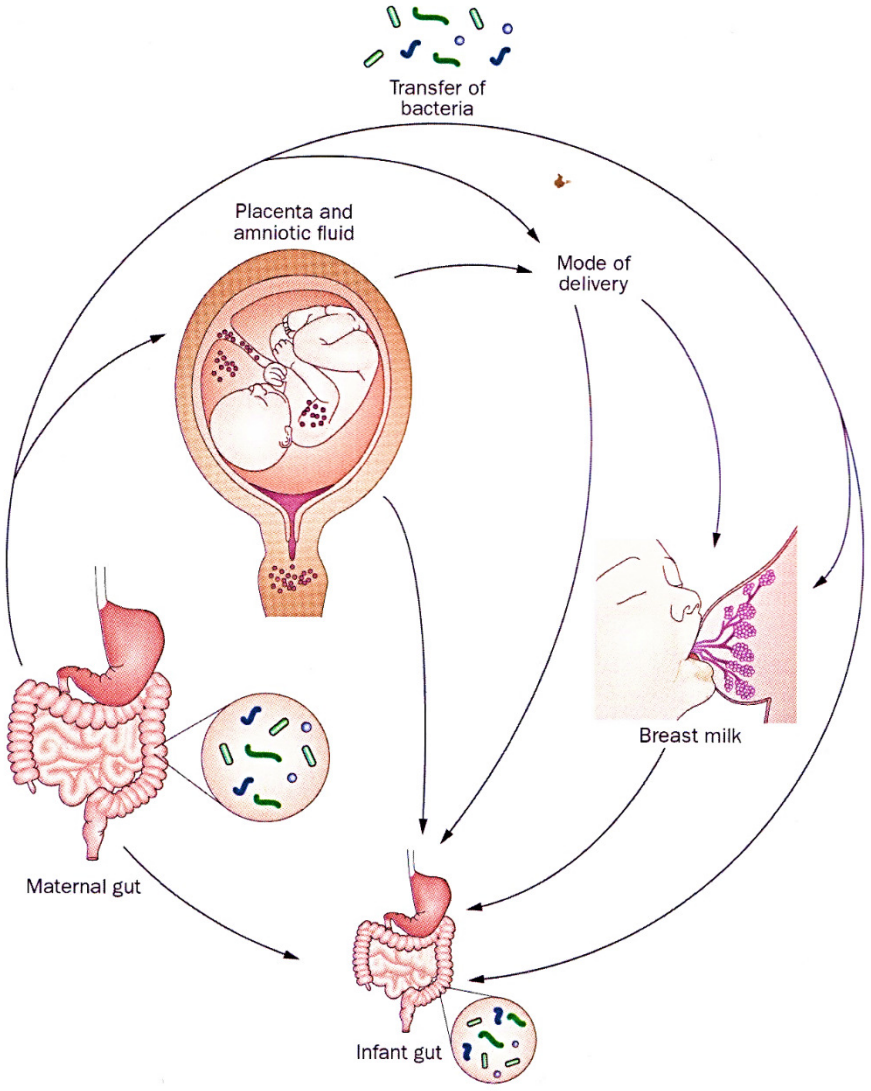

Complex relationships between fetal microbiota, maternal microbiota at birth and during breast feeding

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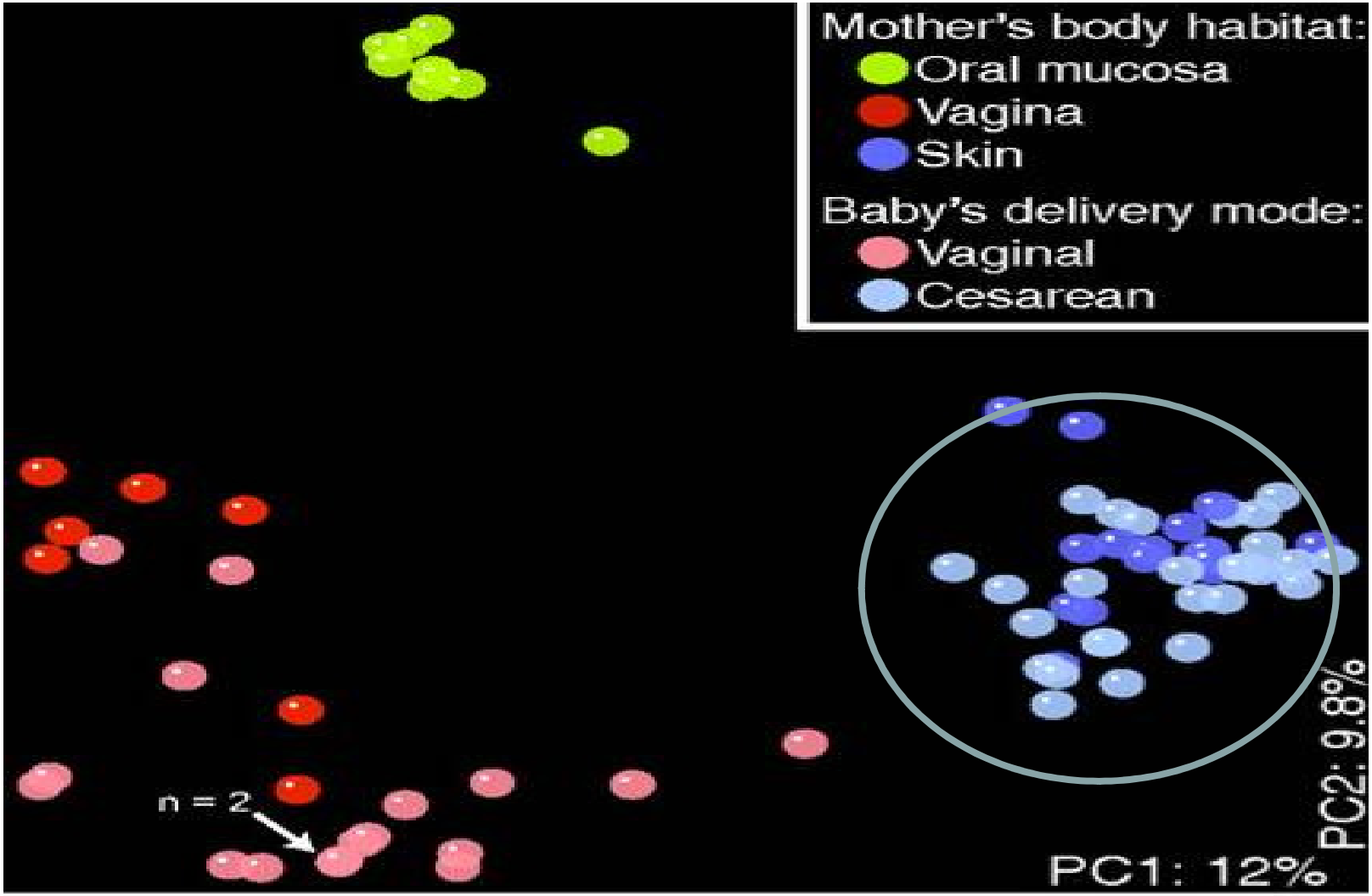
Nat Rev Gastroenterol Hepatol 2012; 9: 565-576

Bacterial colonization according to the mode of delivery



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Dominguez-Bello M G et al. PNAS 2010

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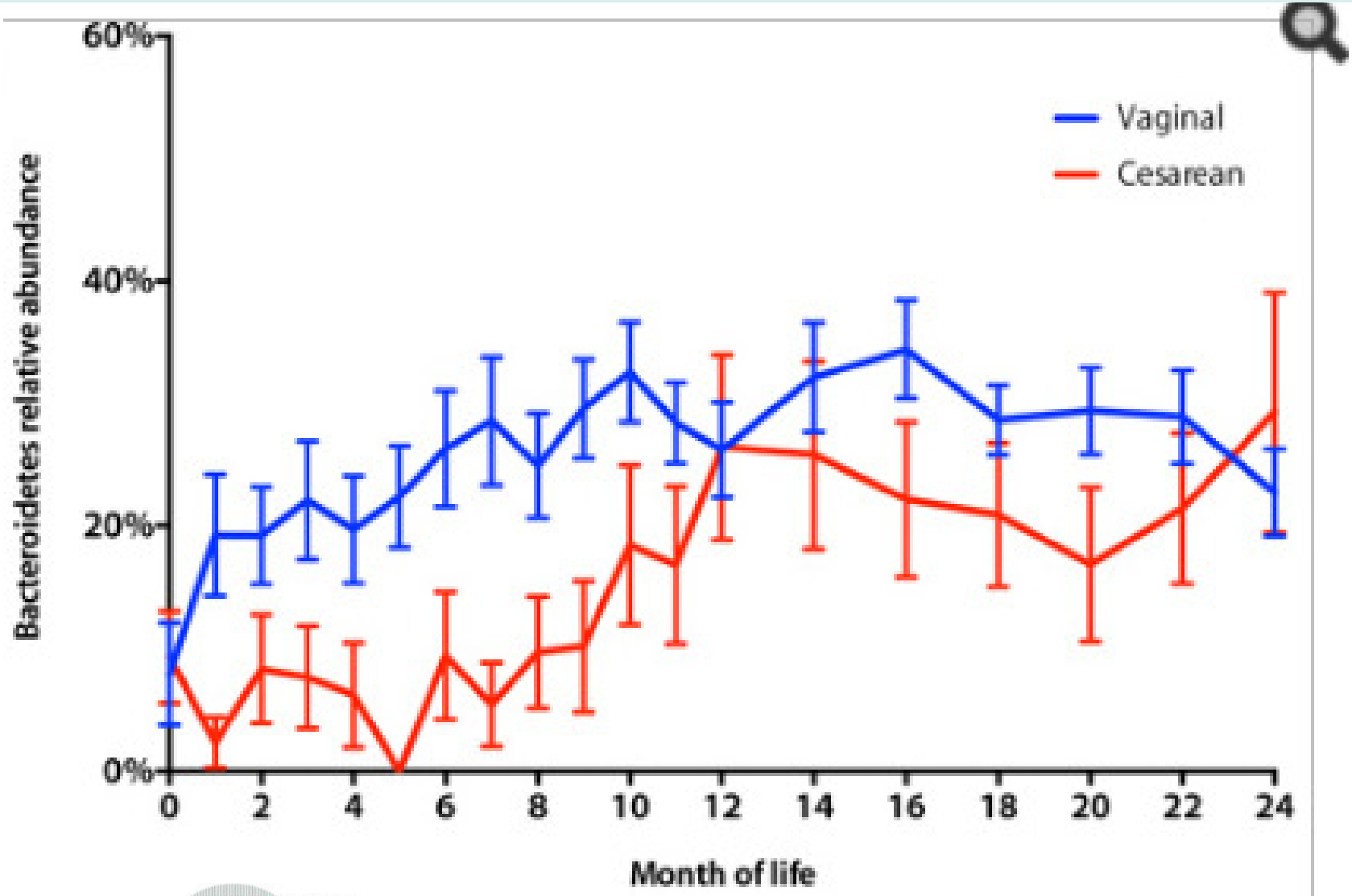

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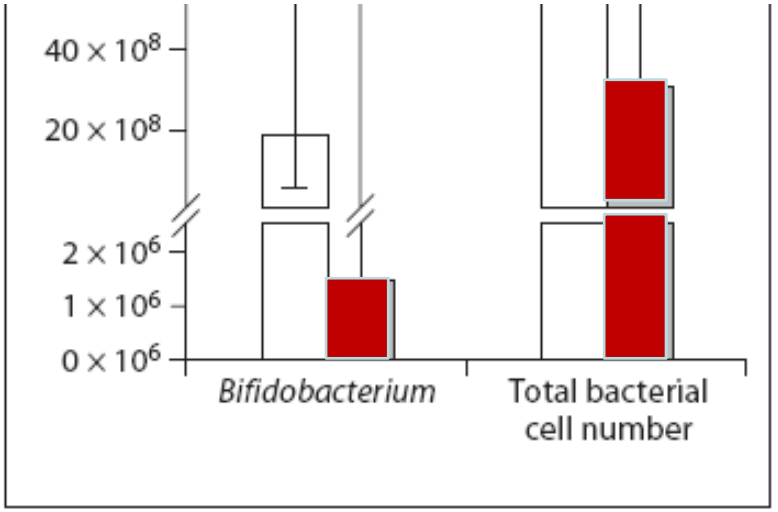
Bokulich NA et alSci Transl Med 2016; 8 (343)

At 6 months :

No significant difference…

But what happened before ?



Huurre, Neonatology, 2008

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Intestinal microbiota and type of feeding

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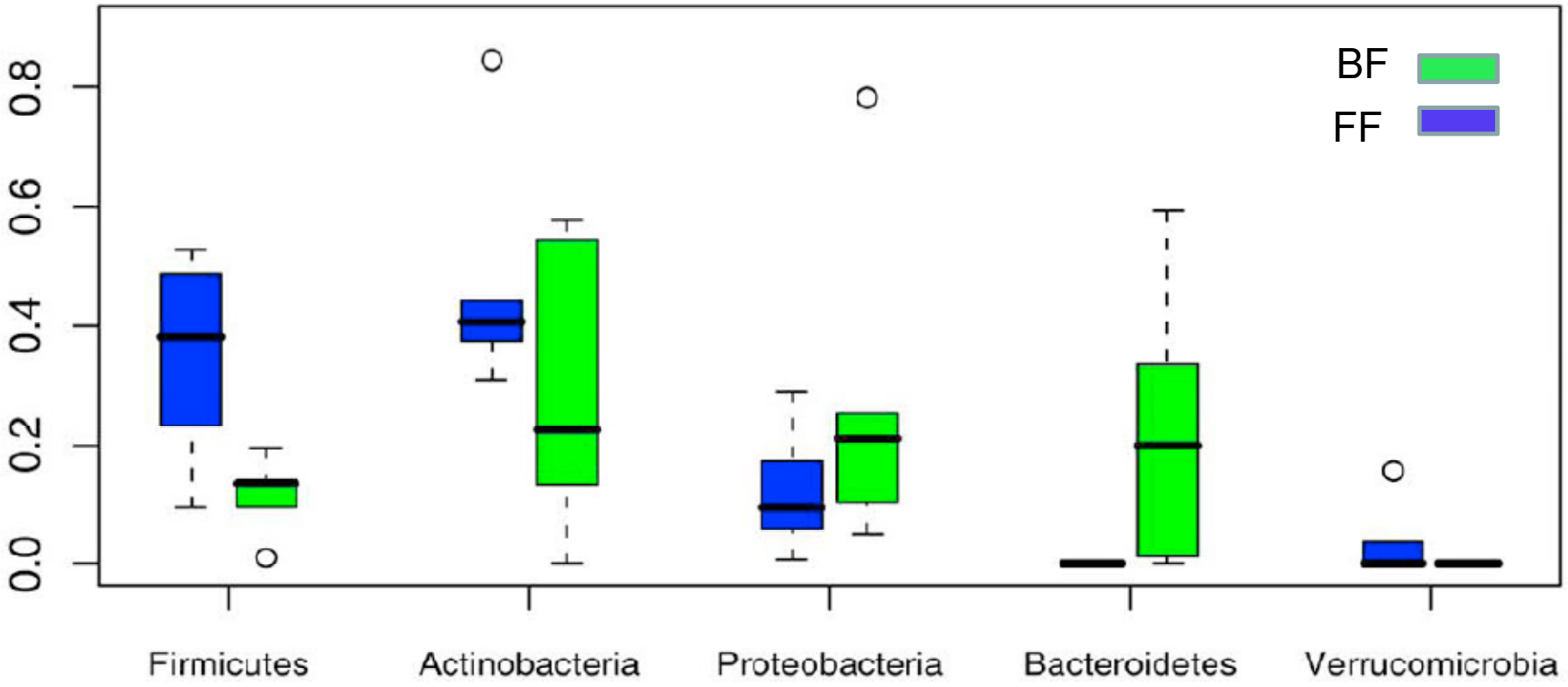
A metagenomic study of diet-dependent interaction between gut microbiota and host in infants reveals differences in immune response

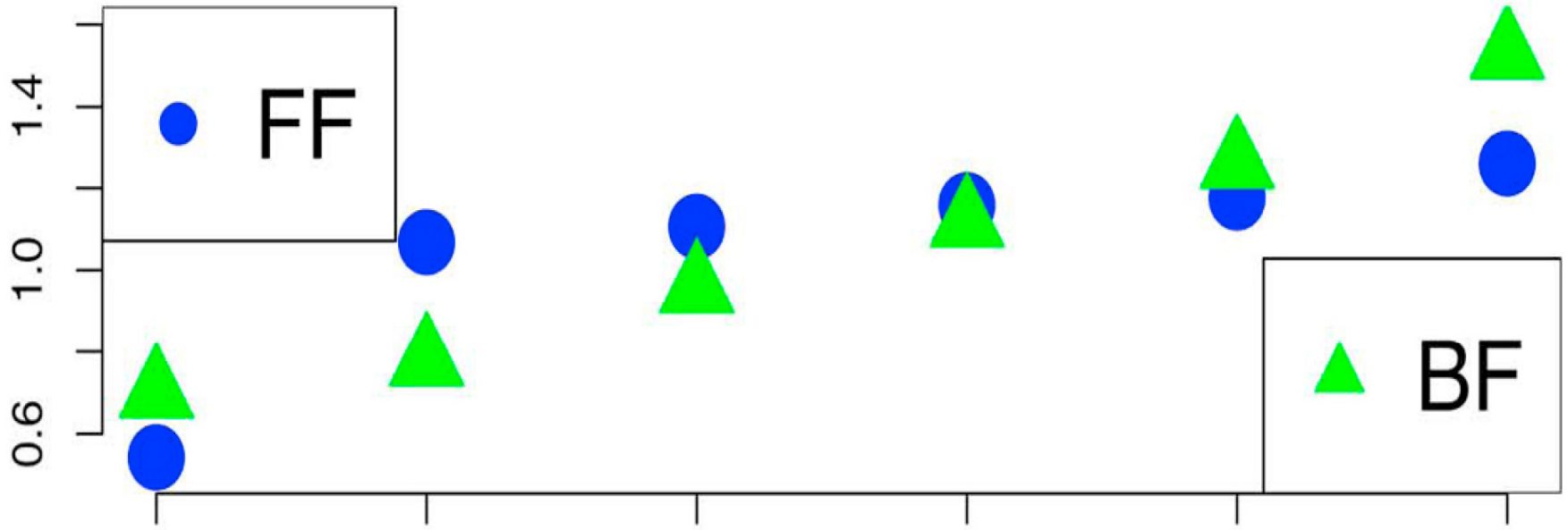
Phylogenetic distribution



Schwartz *et al. Genome Biology* 2012, **13**:r32

A metagenomic study of diet-dependent interaction between gut microbiota and host in infants reveals differences in immune response

Shannon index of bacterial diversity



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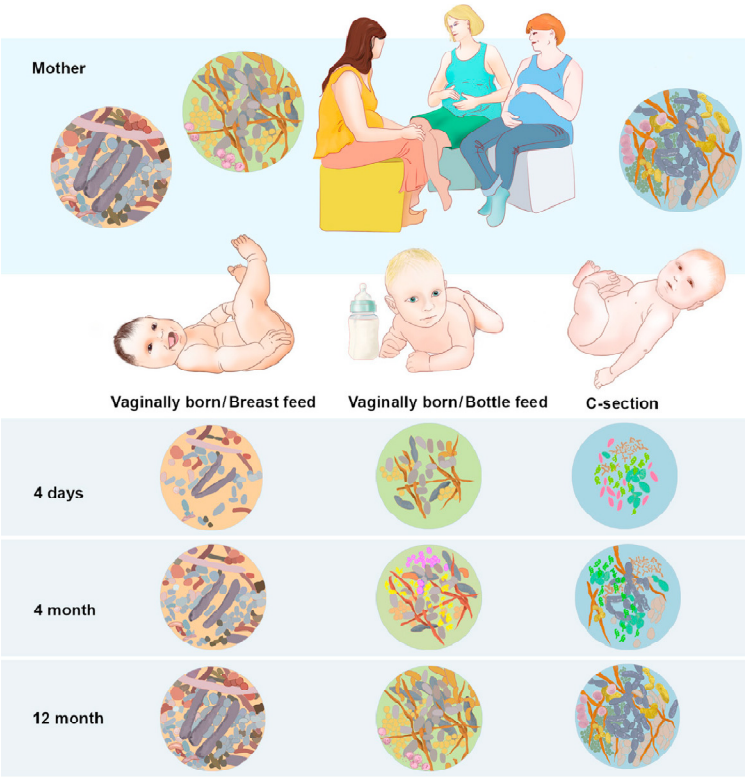
Schwartz *et al. Genome Biology* 2012, **13**:r32

Dynamics and Stabilization of the Human Gut Microbiome

Impact of mode of delivery and feeding



- Fecal metagenomic analysis from a cohort infants and their mothers during 1° year of life

- In contrast to vaginally delivered infants, the gut microbiota of infants delivered by C-section showed significantly less resemblance to their mothers.

- Major impact of nutrition on early microbiota composition and function, with cessation of breast-feeding, rather than introductionof solid food, being required for maturation into an adult-like microbiota.

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Bäckheld et al; Cell Host & Microbe 2015

Maternal microbiota / breastmilk

Breast milk is a source of microbes

Hunt et al 2011; Collado et al 2012

Milk and infant microbiota composition are influenced by

Maternal obesity

Collado et al 2012, Cabrera –Rubio et al AJCN 2012

Maternal allergy

Gronlund et al 2007; Bursch et al 2013

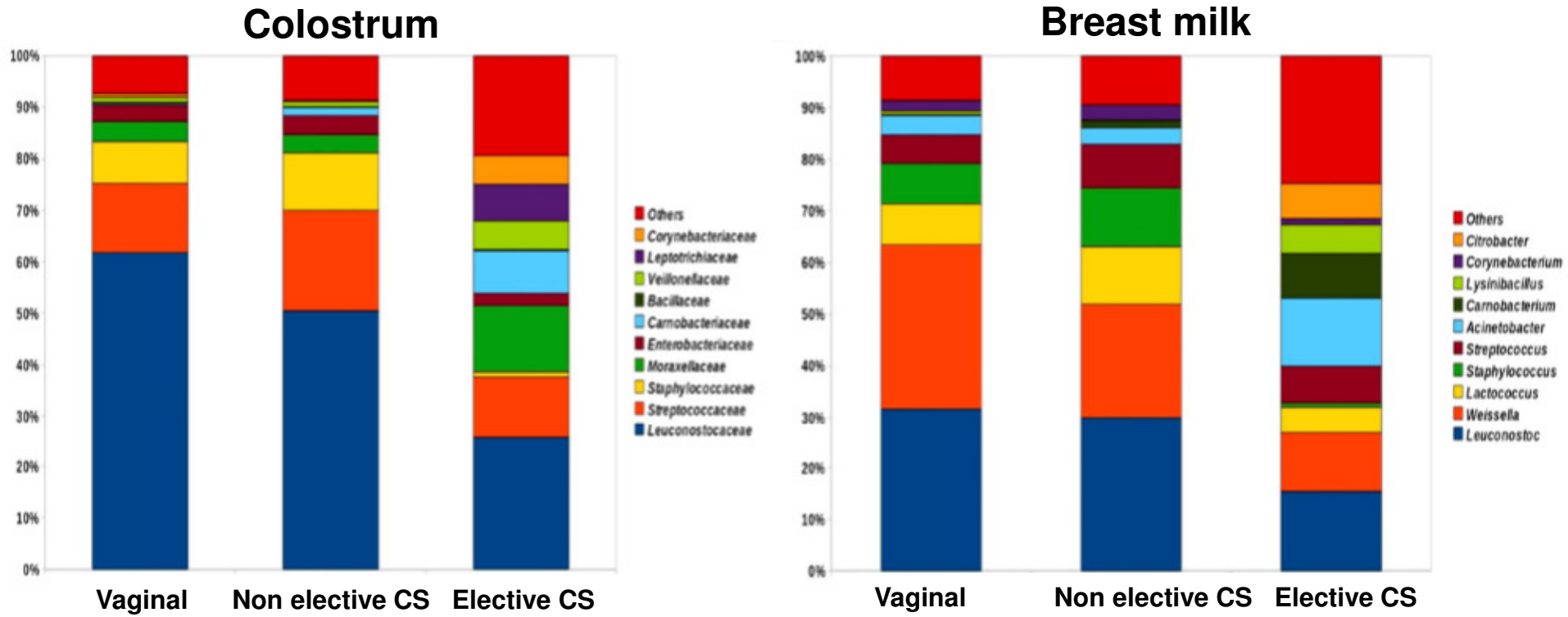
Mode of delivery

Cabreira-Rubio et al 2015

Geographical location or diet ?

Cabreira-Rubio et al 2012; Kumar H Front Microbiol 2016

Maternal weight / C-section / breastmilk



Am J Clin Nutr 2012;96:544–51.

- Bacteria are present in human milk and are not contaminants
- Breast milk are among the very first microbes entering the human body,
- The milk microbiome is influenced by factors including mode of delivery
- The milk microbiome could potentially play for human health.

Cabrera-Rubio et al J Dev Orig Health Dis. 2016; 7: 54-60.

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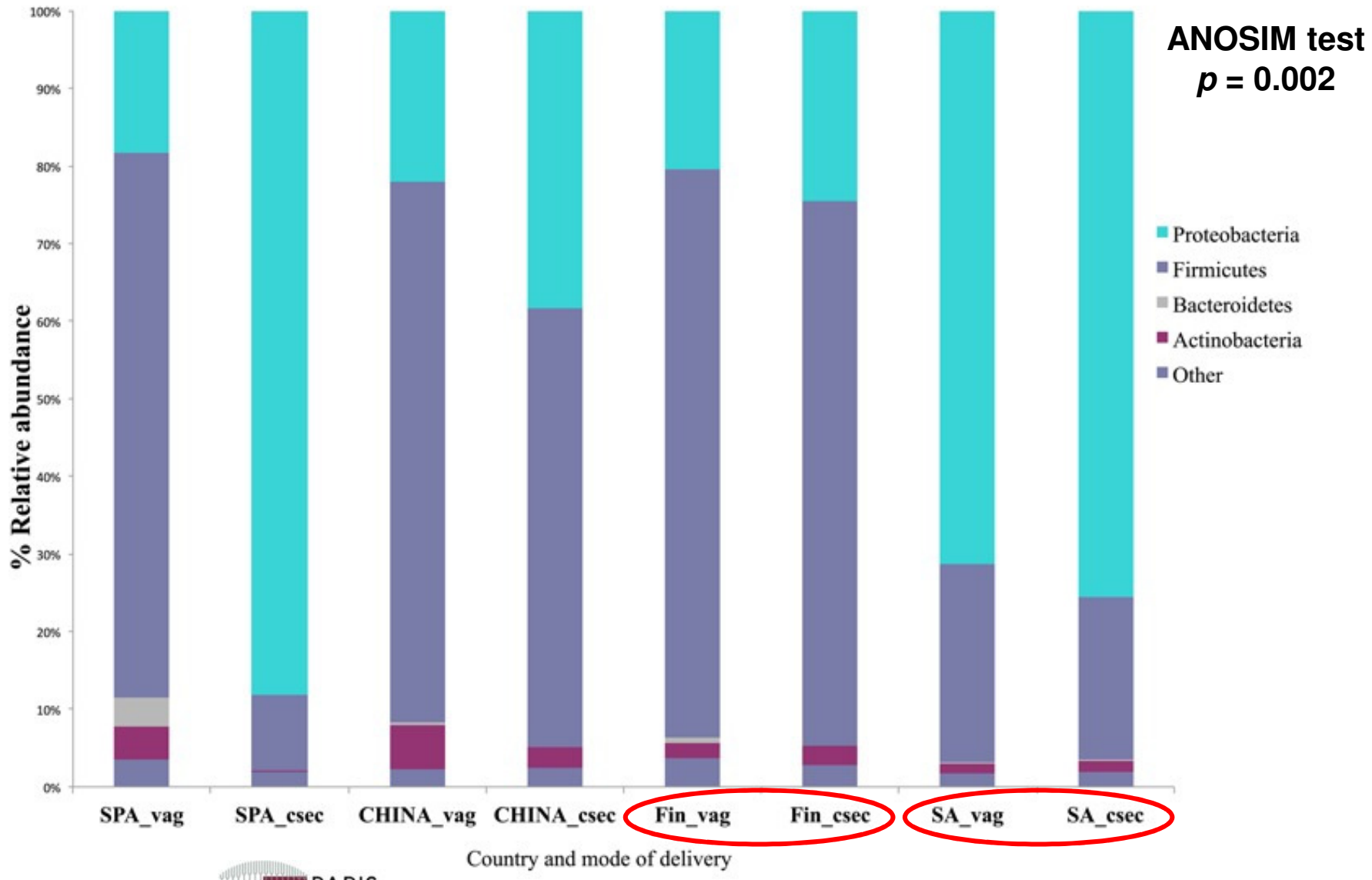
Mode of delivery/breastmilk/geography



ANOSIM test
***p* = 0.002**

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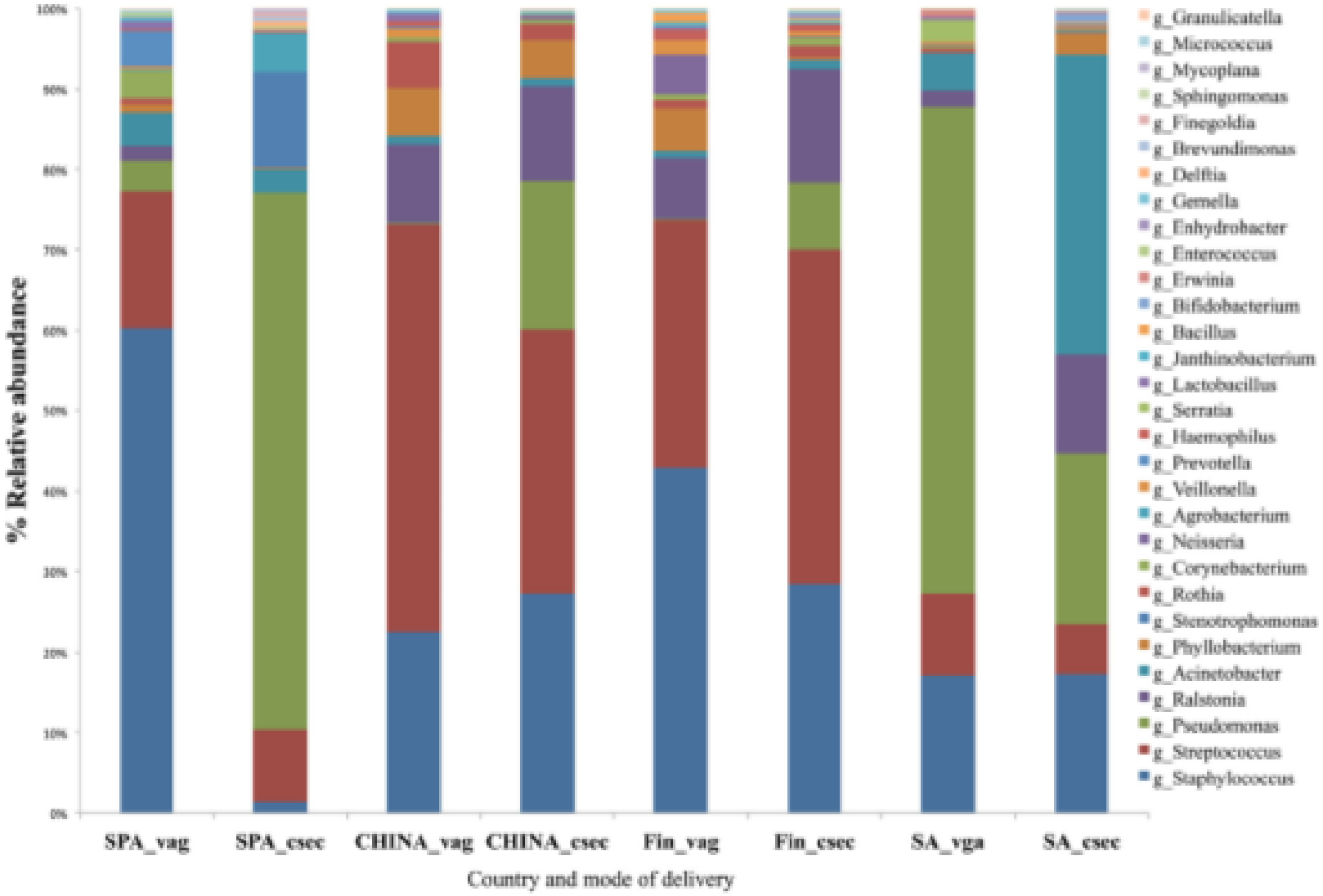
Kumar H et al. Front Microbiol 2016;7:1619.

Mode of delivery/breastmilk/geography



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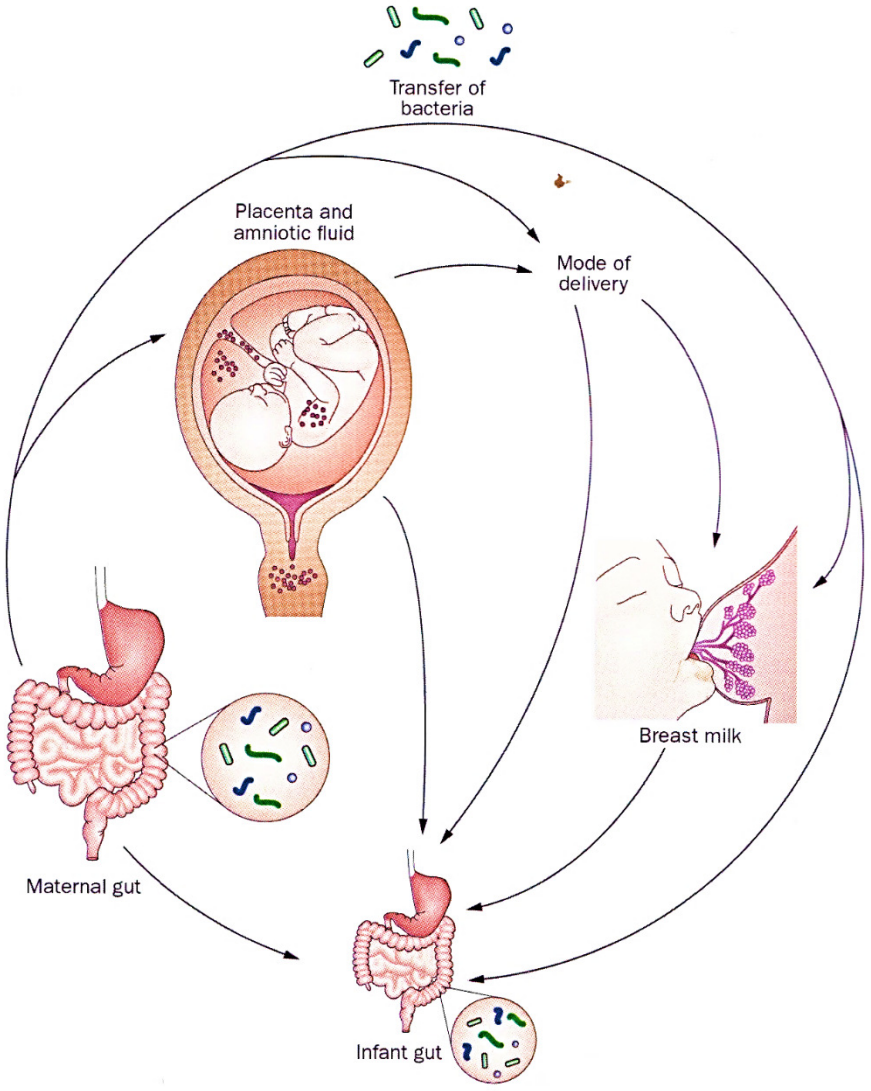
Kumar H et al. Front Microbiol 2016;7:1619.



The maternal microbial legacy is transmitted during pregnancy, at birth and during breast feeding for achieving symbiosis

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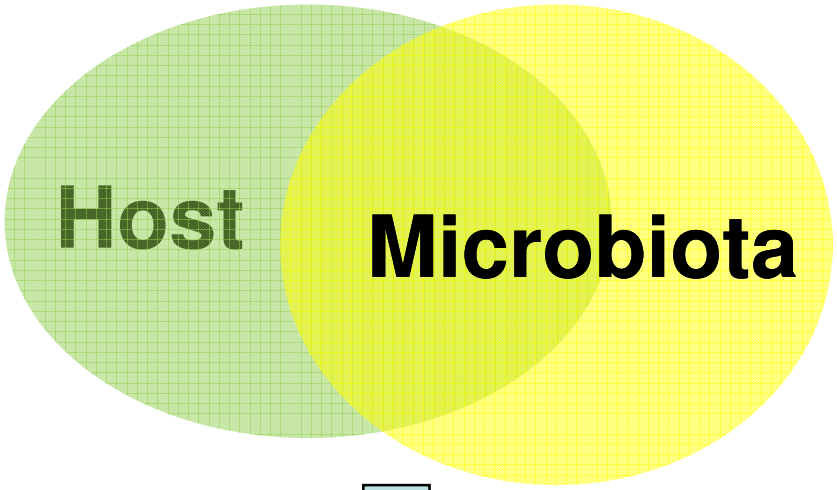
Nat Rev Gastroenterol Hepatol 2012; 9: 565-576

Symbiotic life : host and microbiota

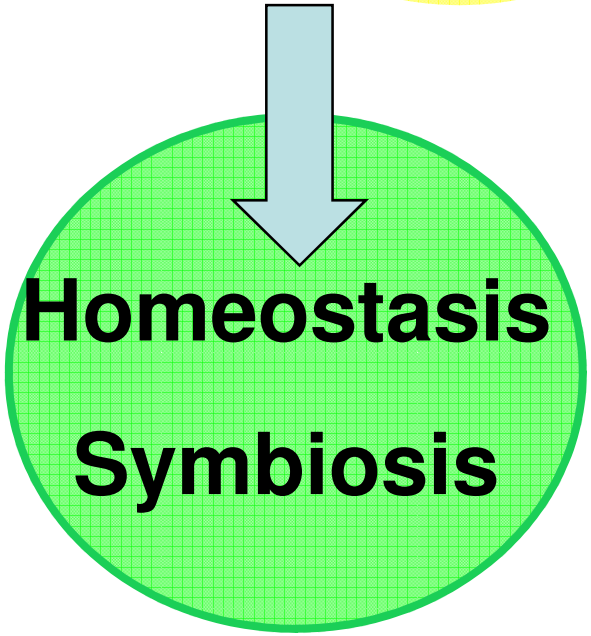
~ 10^{13} cells

~ 10^{6} genes



~ 10^{14} bacteria

~ 10^{8} genes



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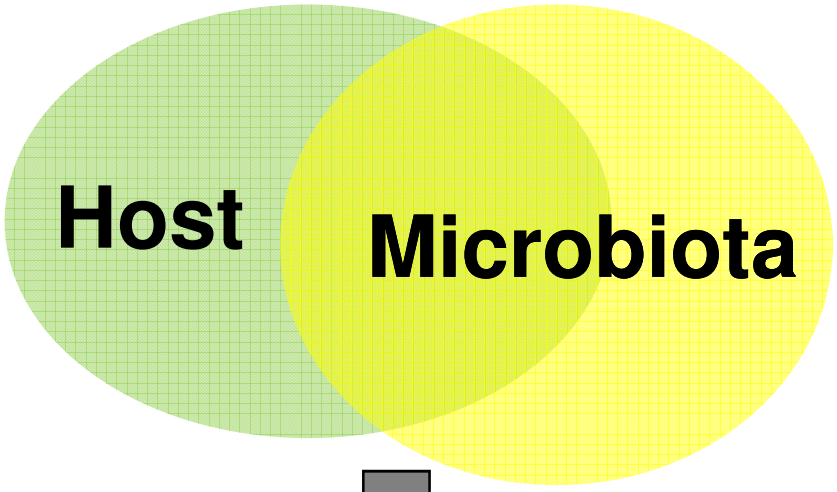

~ 10^{14} bacteria

~ 10^{8} genes

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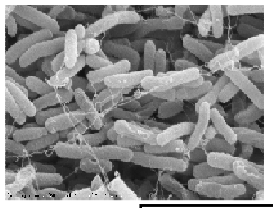
Intestinal microbiota

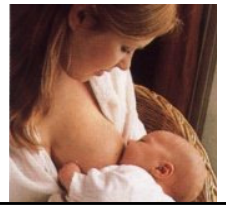
Neonatal bacterial colonization

Programming for life….?

Early programming

- Term of birth
- Mode of delivery
- Physical environment
- **Brest/formula feeding**
- Antibiotics use
- Proton pump inhibitors
- **Microbiota modulation**





Intestinal microbiota

Symbiosis

- **Immune tolerance**
- **Intestinal homeostasis**
- **Healthy metabolism**

Dysbiosis

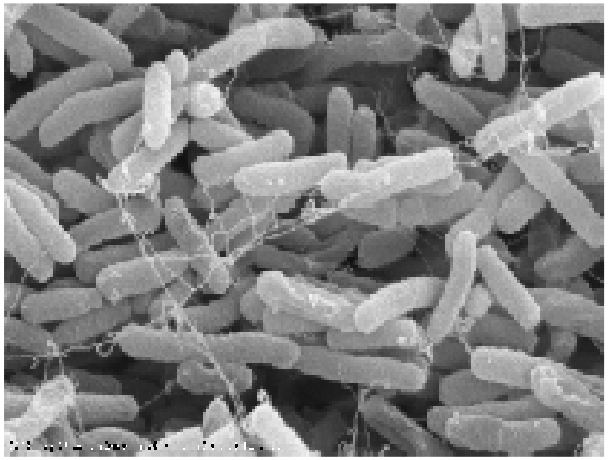
- **Immune disease** *(e.g. atopy, asthma, multiple sclerosis..)*
- **Intestinal diease** *(e.g. IBD, NEC, Cancer)*
- **Metabolic diease** *(e.g. Diabetes, Obesity…)*

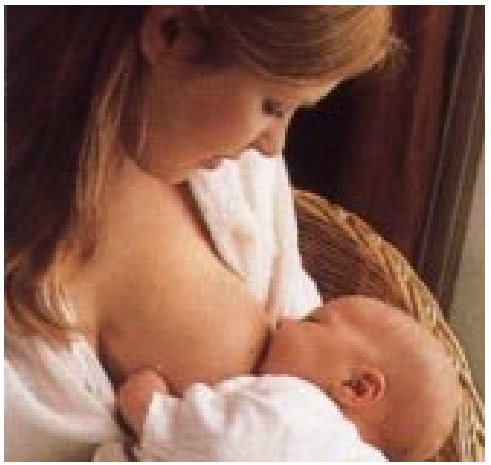
The concept of protective bacteria

O.Goulet Nutr Rev 2015

Content of the presentation

- Factors of gut bacterial colonization
- ***Impact of microbiota on GI function***
- **Impact on health and diseases**
- **Modulation of intestinal microbiota**





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Development of intestinal functions and intestinal microbiota

Expression of genes involved

in important intestinal function

- ***Angiogenesis***
- ***Nutrient absorption***
- ***Mucosal barrier fortification***
- ***Xenobiotic metabolism***
- ***Intestinal motility***
- ***Gut immune system***
- ***...../.....***

Postnatal intestinal maturation

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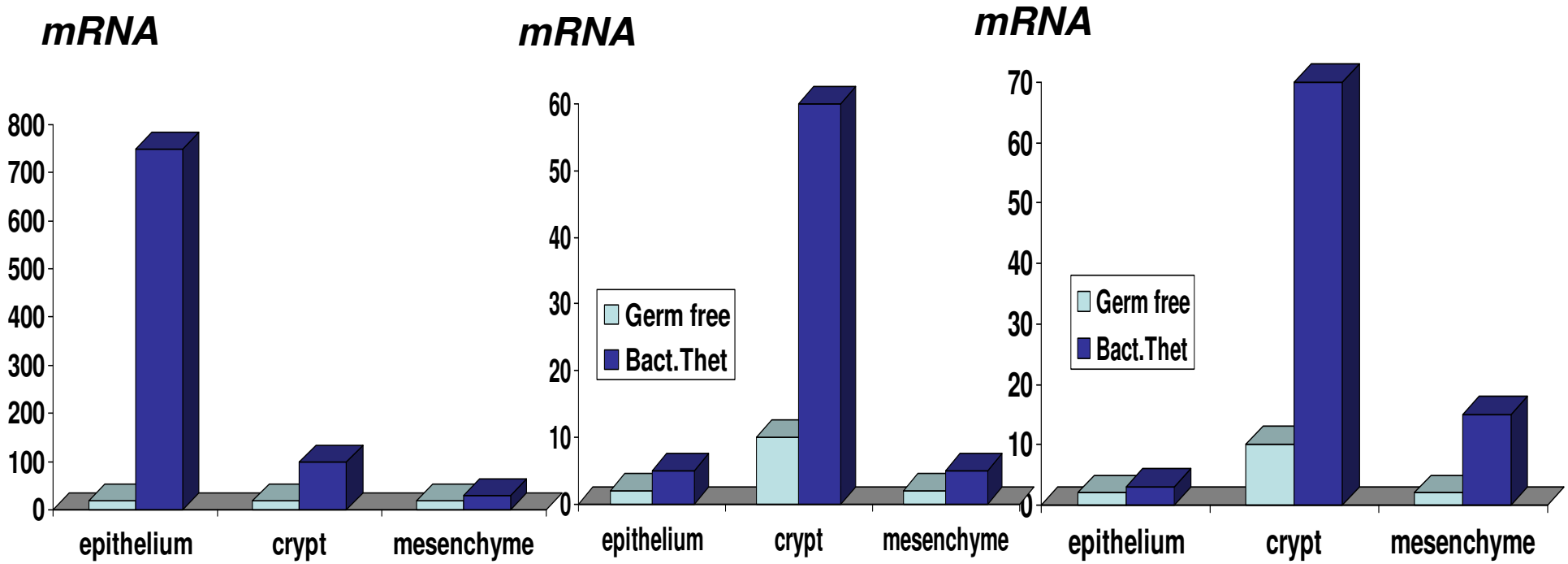
Development of intestinal functions and intestinal microbiota

Bacteroides thetaiotaomicron (B.theta)

component of the normal mouse and human intestinal microflora.



Small proline-rich protein-2 (Sprr2a)

Colipase

Angiogenin-3

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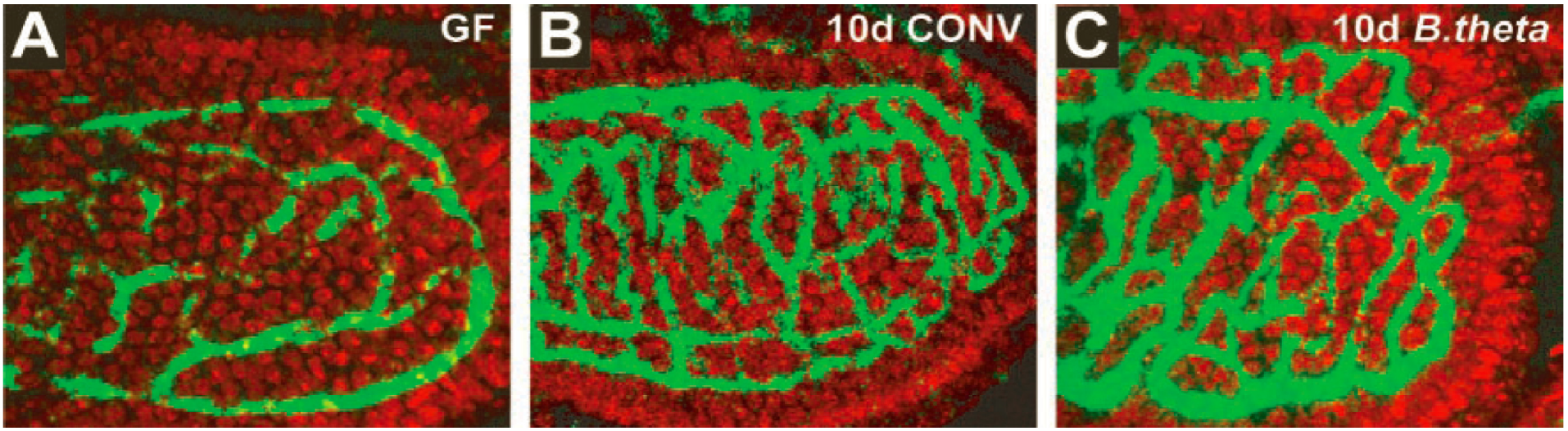
Hooper et al Science 2001; 291: 881-4

Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells

Thaddeus S. Stappenbeck, Lora V. Hooper, and Jeffrey I. Gordon*



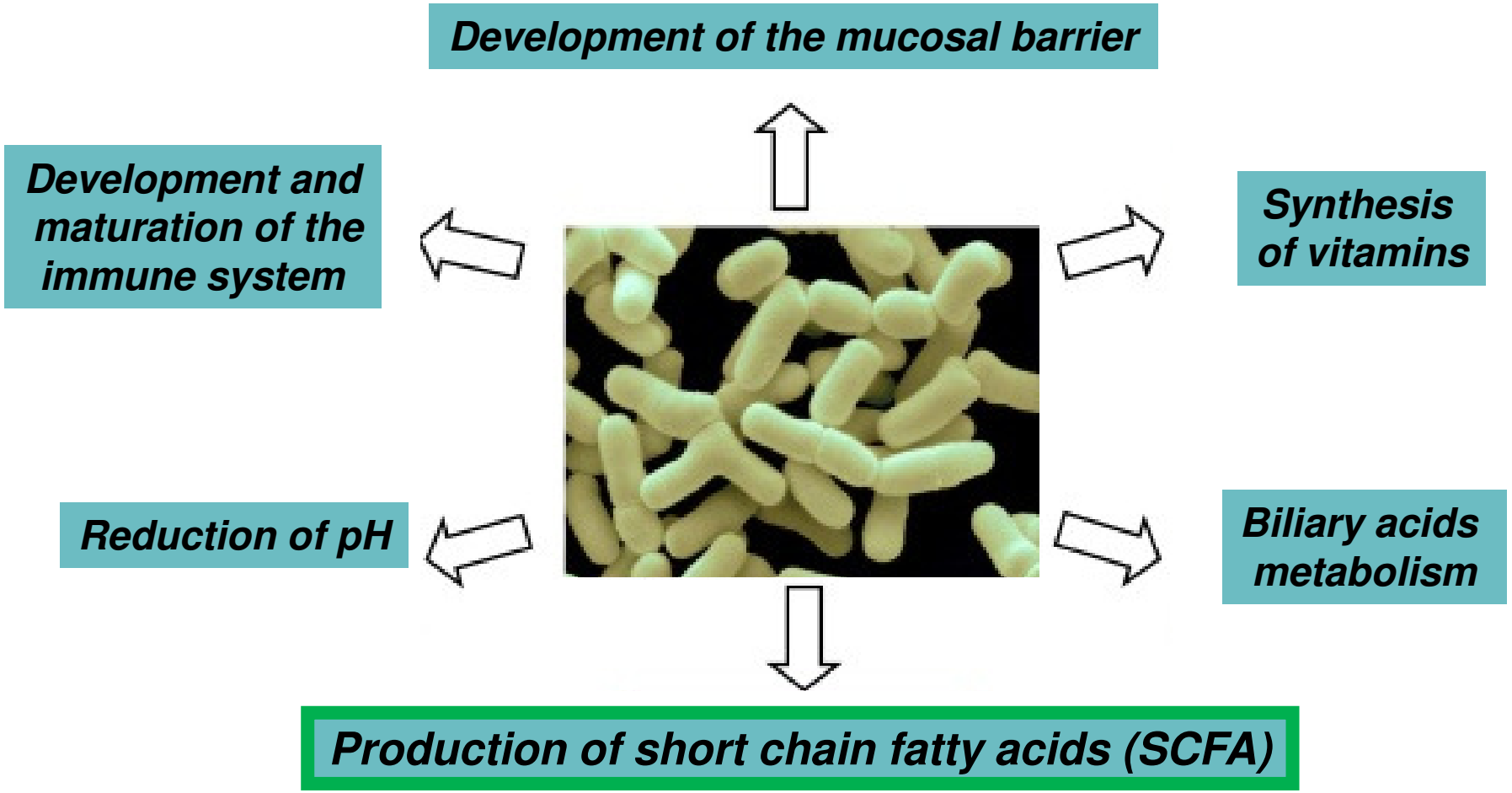
A: Germ free (GF) mouse

B: Age matched ex-germ-free conventionnalized (CONV) mouse killed 10 days after colonization

C: Ex-germ-free mouse 10 days after colonization with *B.thetaiotaomicron (B.theta)*

PARIS DESCARTES | November 26, 2002 | vol. 99 | no. 24 | 15451–15455

Metabolic effects of the colonic microbiota



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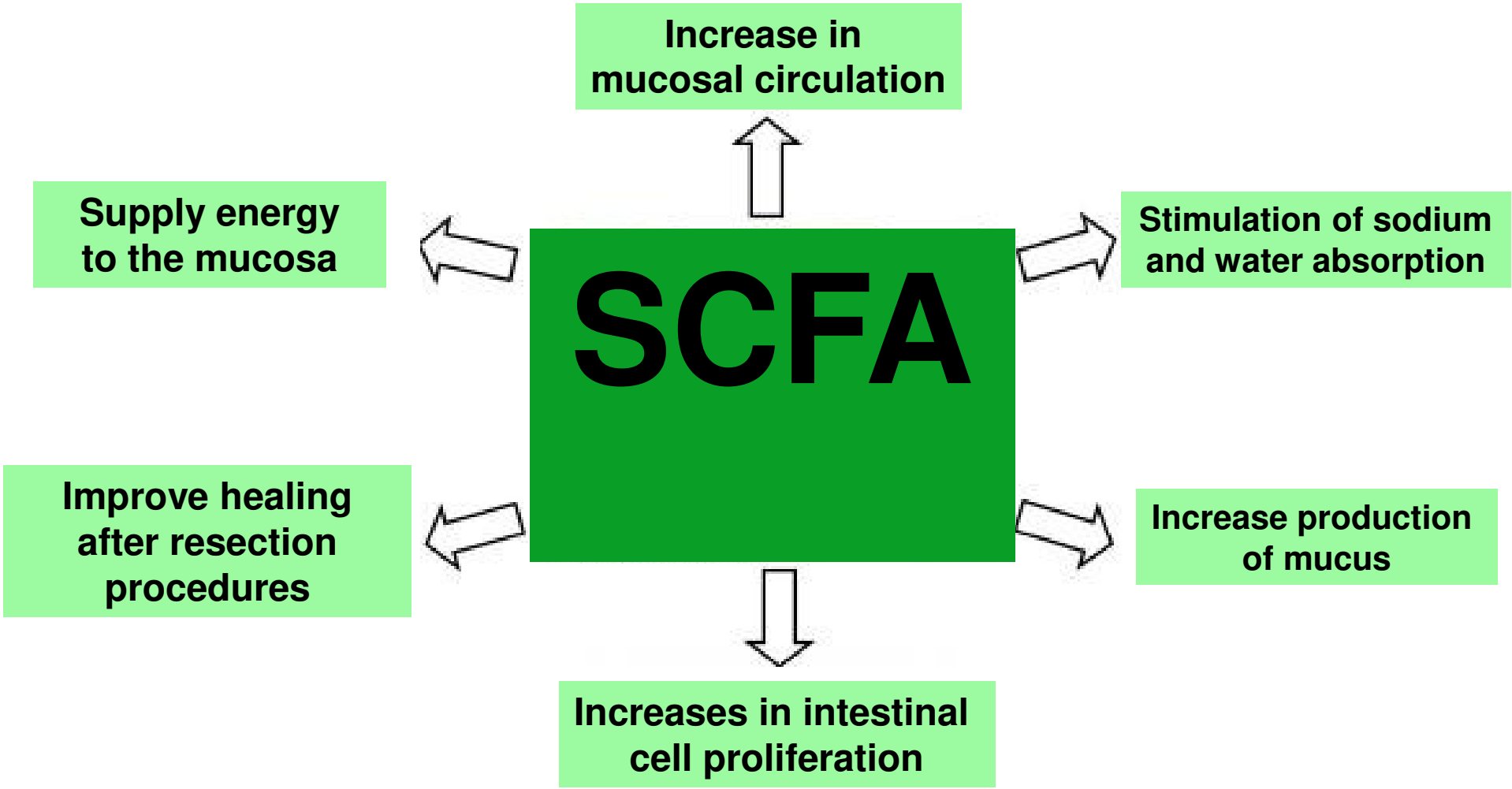
Goulet et al JPGN 2009

Effects of short chain fatty acids



Metabolic effect

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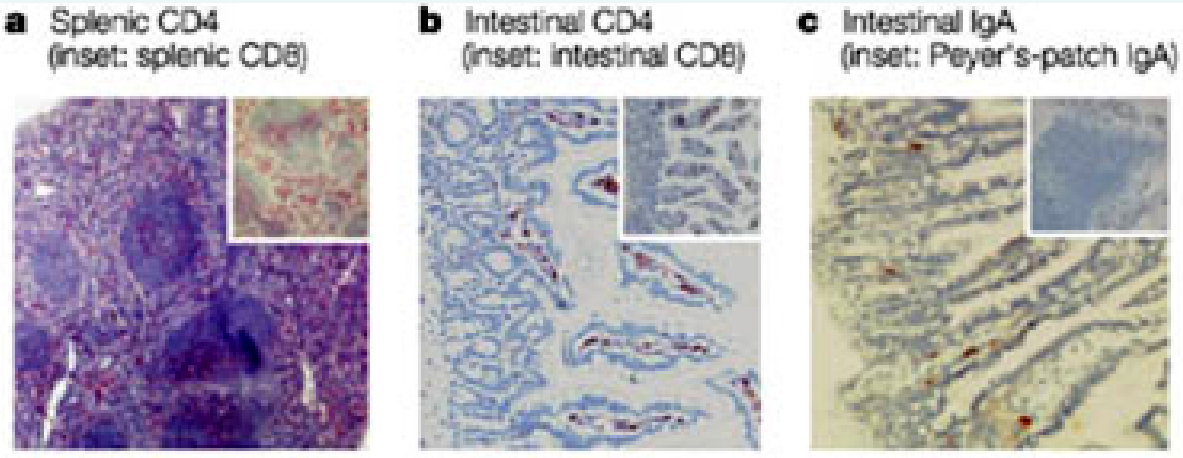
Bacterial colonization of the intestine induces the presence of T and B-lymphocytes and the capacity to produce IgAs

Germ free mouse



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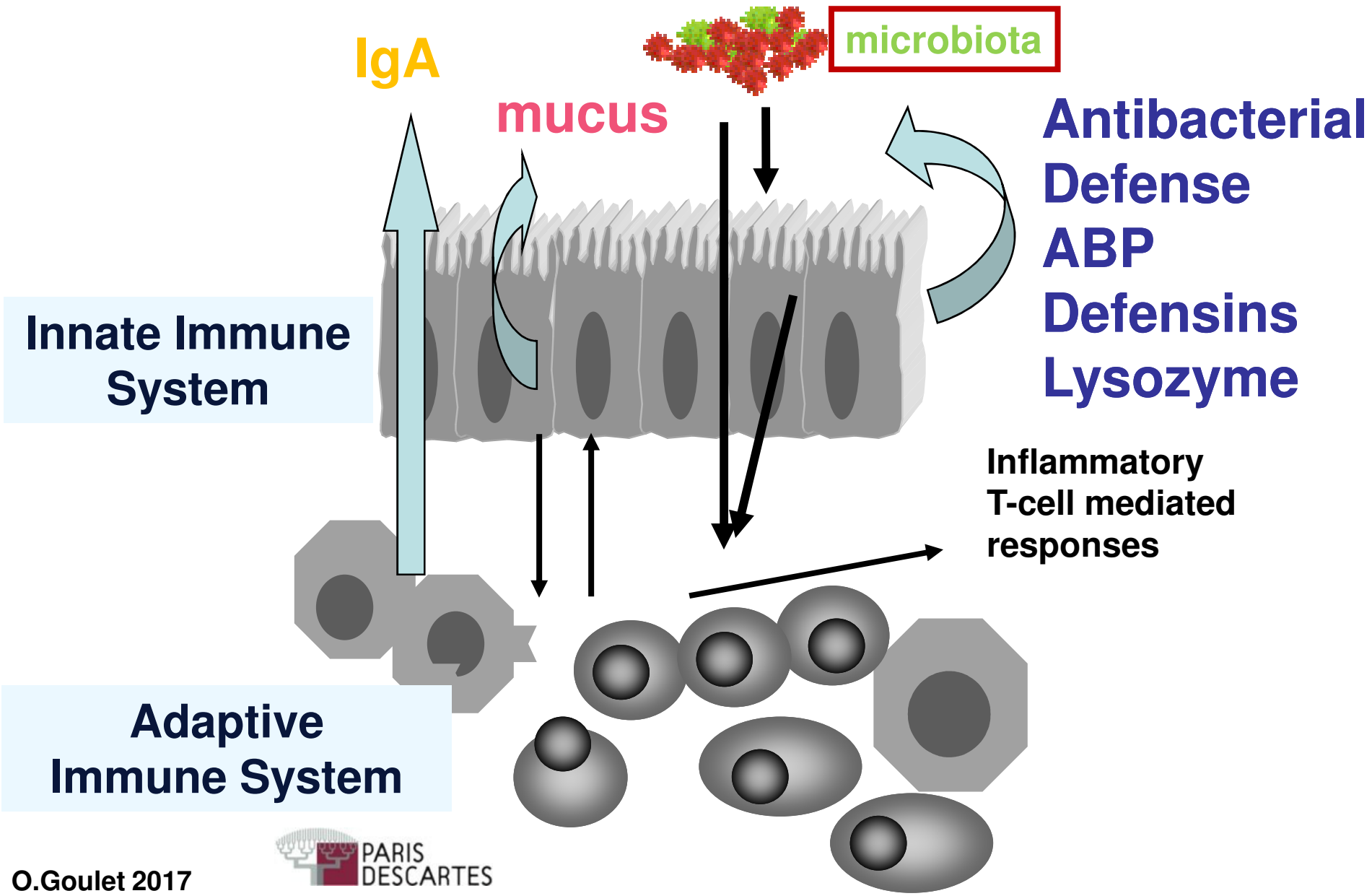
Nature review Immunology

Gut immune system



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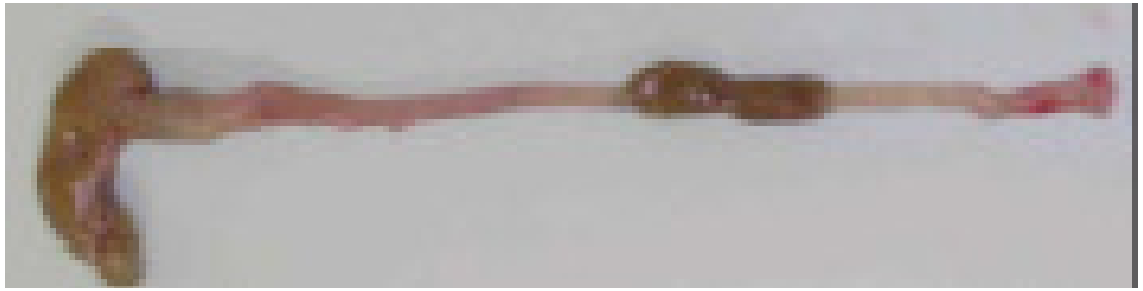
Intestinal microbiota and gut immunity

Lessons from the animal model

IL-10 KO

versus

Germ-free



Colonized

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Mueller et al. Cell 1990

Intestinal microbiota and gut immunity

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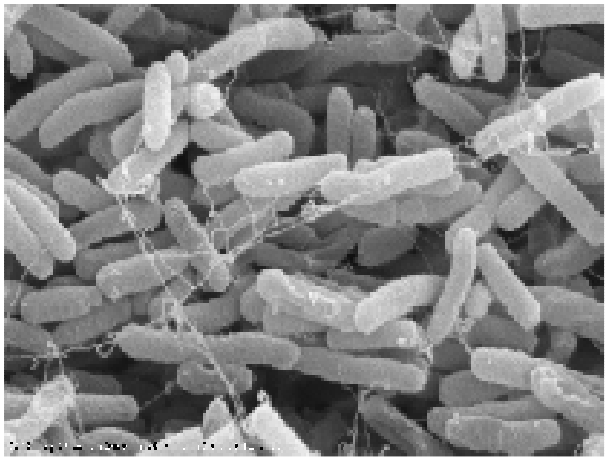
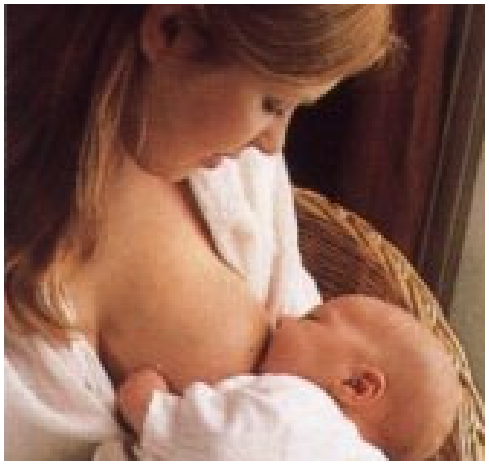
- Impact of microbiota on GI function
- **Impact on health and diseases**
- **Modulation of intestinal microbiota**





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Intestinal microbiota the first 1000 days

"All disease begins in the gut" (Hippocrates)

Symbiosis

- Balanced microbial composition
- **Immune regulation** allowing homeostasis

Dysbiosis

- Disruption or alteration of the microbiota diversity
- **Immune dysregulation** with inflammation,allergy

Microbiota related « programming »

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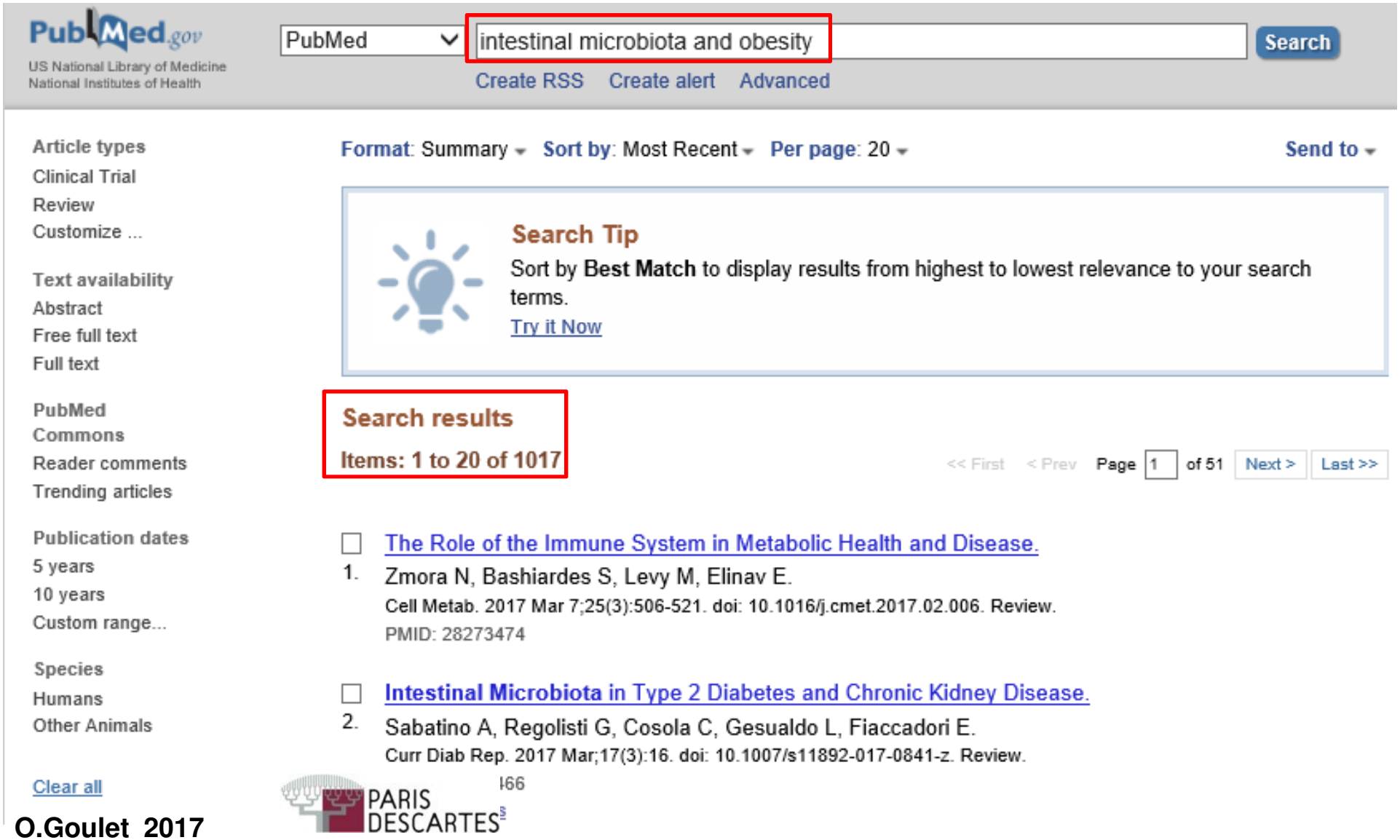
Intestinal microbiota and obesity



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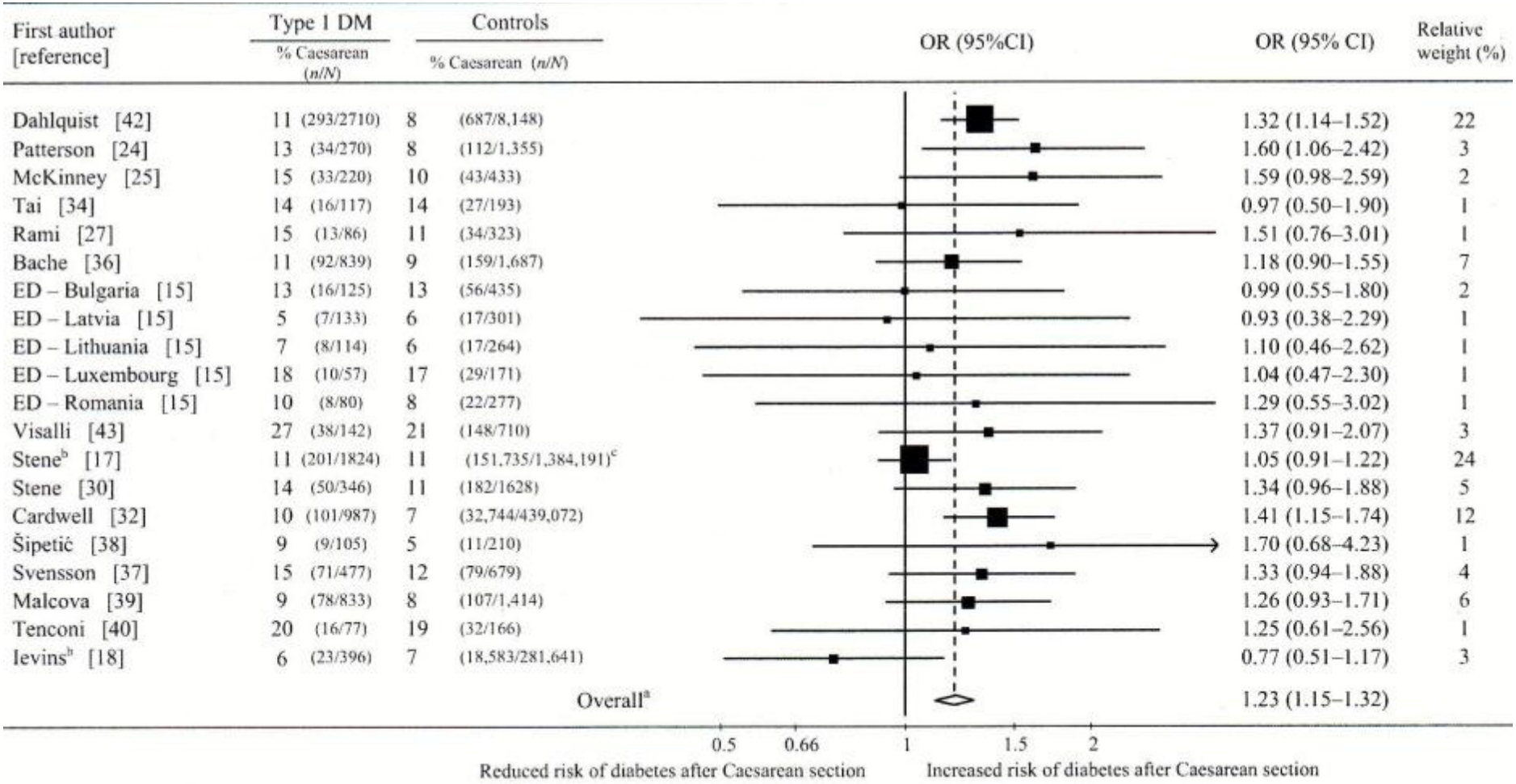
Meta-analysis C-delivery / Diabetes



First author [reference]	Type 1 DM % Caesarean (*n*/*N*)	Controls % Caesarean (*n*/*N*)	OR (95%CI)	OR (95% CI)	Relative weight (%)
Dahlquist [42]	11 (293/2710)	8 (687/8,148)		1.32 (1.14–1.52)	22
Patterson [24]	13 (34/270)	8 (112/1,355)		1.60 (1.06–2.42)	3
McKinney [25]	15 (33/220)	10 (43/433)		1.59 (0.98–2.59)	2
Tai [34]	14 (16/117)	14 (27/193)		0.97 (0.50–1.90)	1
Rami [27]	15 (13/86)	11 (34/323)		1.51 (0.76–3.01)	1
Bache [36]	11 (92/839)	9 (159/1,687)		1.18 (0.90–1.55)	7
ED – Bulgaria [15]	13 (16/125)	13 (56/435)		0.99 (0.55–1.80)	2
ED – Latvia [15]	5 (7/133)	6 (17/301)		0.93 (0.38–2.29)	1
ED – Lithuania [15]	7 (8/114)	6 (17/264)		1.10 (0.46–2.62)	1
ED – Luxembourg [15]	18 (10/57)	17 (29/171)		1.04 (0.47–2.30)	1
ED – Romania [15]	10 (8/80)	8 (22/277)		1.29 (0.55–3.02)	1
Visalli [43]	27 (38/142)	21 (148/710)		1.37 (0.91–2.07)	3
Stene[b] [17]	11 (201/1824)	11 (151,735/1,384,191)[c]		1.05 (0.91–1.22)	24
Stene [30]	14 (50/346)	11 (182/1628)		1.34 (0.96–1.88)	5
Cardwell [32]	10 (101/987)	7 (32,744/439,072)		1.41 (1.15–1.74)	12
Šipetić [38]	9 (9/105)	5 (11/210)		1.70 (0.68–4.23)	1
Svensson [37]	15 (71/477)	12 (79/679)		1.33 (0.94–1.88)	4
Malcova [39]	9 (78/833)	8 (107/1,414)		1.26 (0.93–1.71)	6
Tenconi [40]	20 (16/77)	19 (32/166)		1.25 (0.61–2.56)	1
Ievins[b] [18]	6 (23/396)	7 (18,583/281,641)		0.77 (0.51–1.17)	3
		Overall[a]		1.23 (1.15–1.32)	

Increased risk of type 1 Diabetes by 23%

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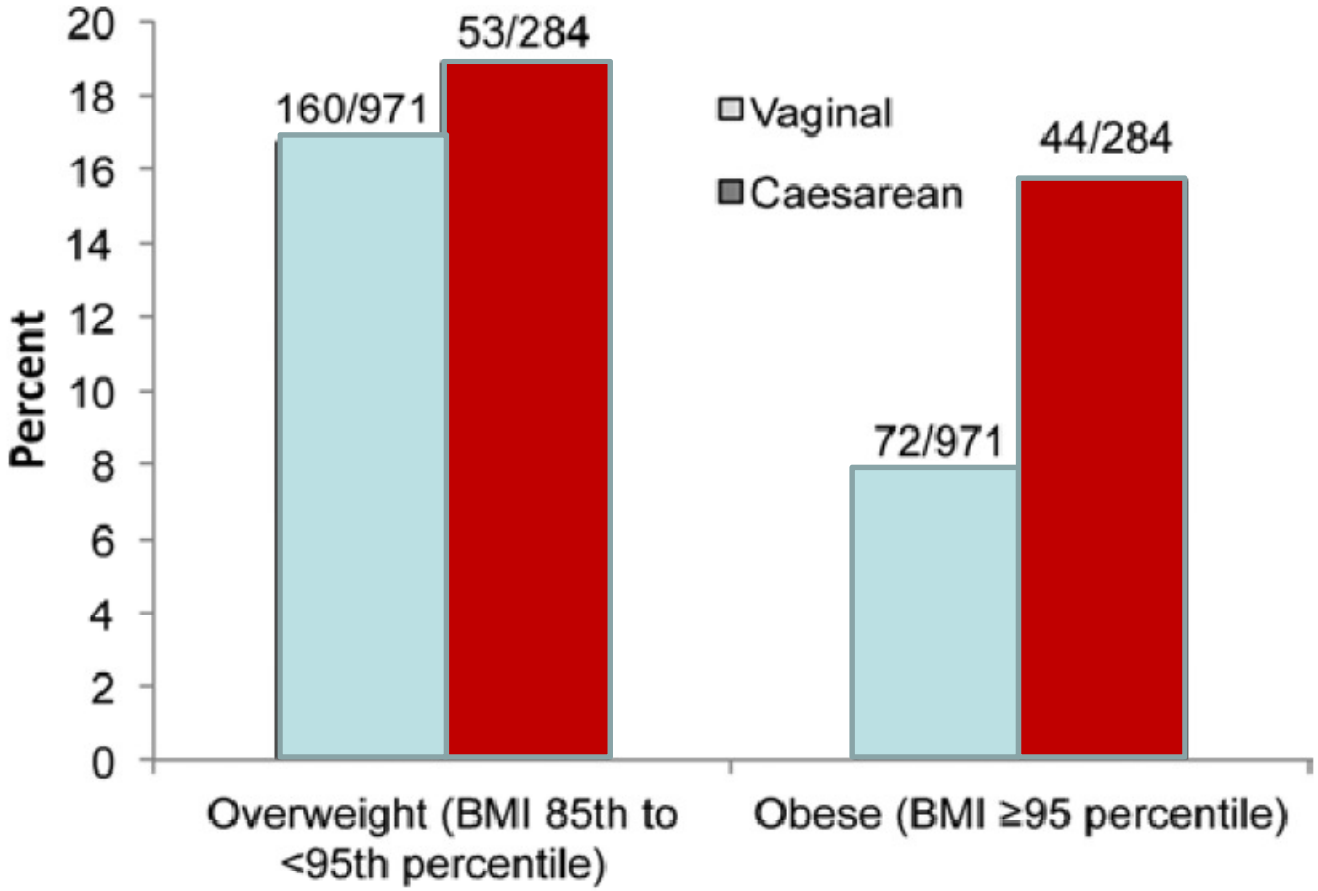
Cardwell, Diabetologia, 2008

Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study

Outcome at 3 years of age



Differences remain after adjusting according to mother BMI

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Arch Dis Child (2012).

Cesarean Section Is Associated with Increased Peripheral and Central Adiposity in Young Adulthood: Cohort Study

- Adults brazilian population
- Cross sectionnal study of 2063 (23-25 yrs)
- Anthropometric assessment of adiposity
- CS & adiposity indicators (Poisson model)

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Mesquita DN et al; Plos One 2013; 8(6) : e66827

Cesarean Section Is Associated with Increased Peripheral and Central Adiposity in Young Adulthood: Cohort Study

- Follow up rate : 31.8% and CS rate 32%
- CS associated with increased adiosity risk
  - *1.22 (95%CI 1.07;1.39) for waist circumference*
  - *1.25 (95%CI 1.10-1.42) for waist-height ratio*
  - *1.36 (95%CI 1.04-1.78) for triceps skinfold*
  - *1.43 (95%CI 1.08-1.91) for subscapular skinfold*
  - *1.45 (95%CI 1.18-1.79) for waist-hip-ratio*

After adjustement for a variety of early life confounders, subjects born by CS had higher risk for increased peripheral and central adiposity

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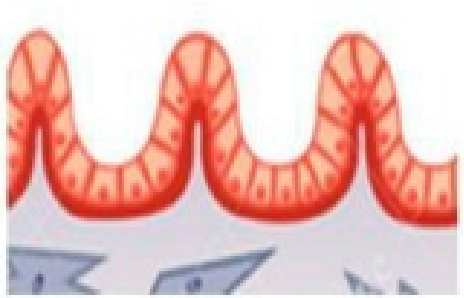
Mesquita DN et al; Plos One 2013; 8(6) : e66827

Intestinal microbiota and obesity



SCFA → ↑ Lipogenesis, ↑ Fat storage

FIAF → ↑ LPL, ↑ Fat storage

Gut permeability → ↑ LPS → ↑ Cytokines proinflammatory; ↑ LPS → ↑ eCB → ↑ adipogenesis

AMPK → Oxidation of fatty acids → ↑ adipogenesis

Fasting-induced adipose factor; involved in regulating glucose homeostasis, lipid metabolism, and insulin sensitivity

AMP-activated protein kinase; central regulator of energy homeostasis, which coordinates metabolic pathways and thus balances nutrient supply with energy demand.

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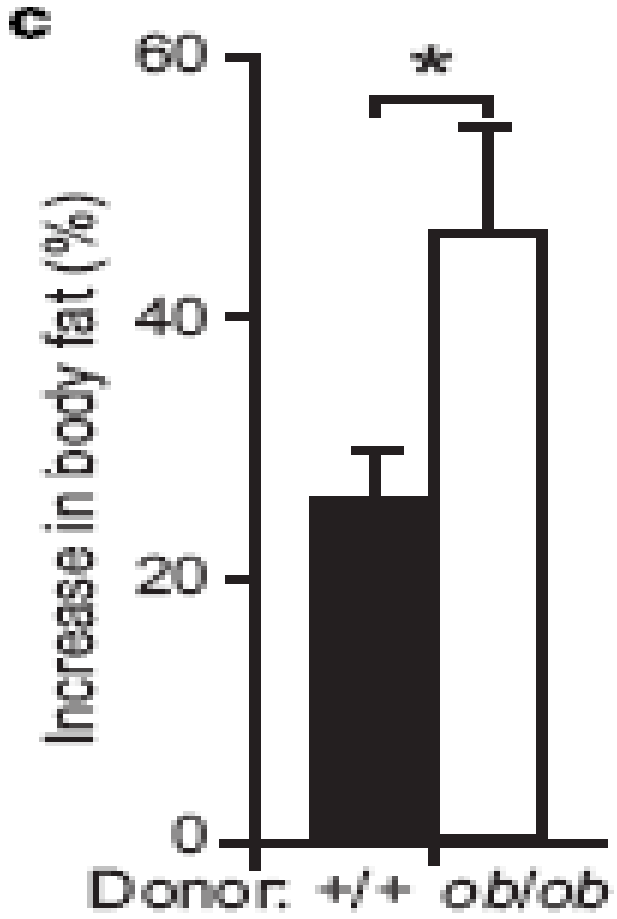
J Environ Res Public Helath 2015; 12: 162–175.

Intestinal microbiota and obesity

Obesity is a transmissible trait



- Fecal transplantation (FCT, with obese mice feces into lean germ free mice) renders 20% increase in visceral fat compared to FCT of lean mice
- Just after 14 days

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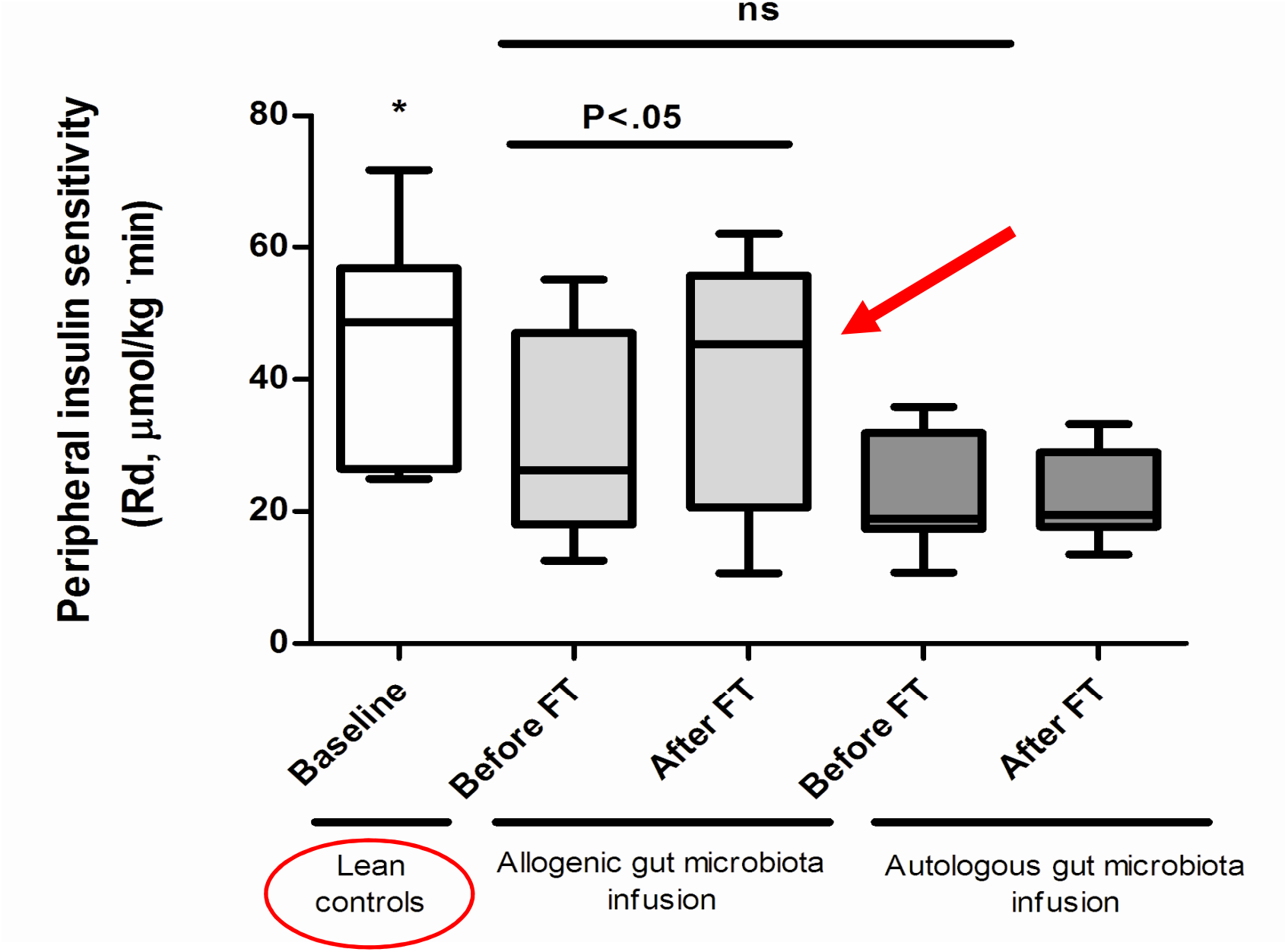
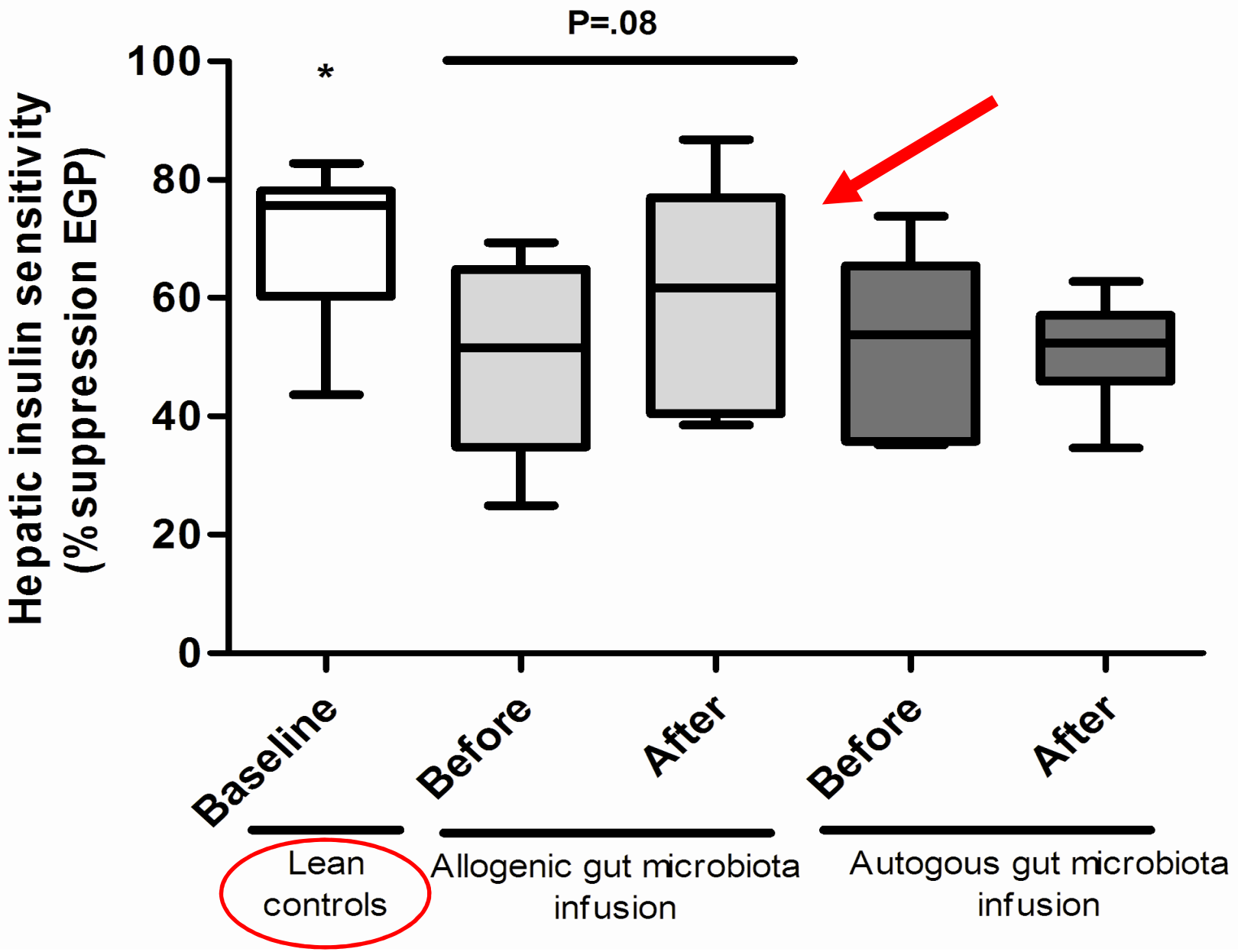
Turnbaugh, Nature 2006

Effect donor faeces on peripheral insulin sensitivity



A.Vrieze, Gastroenterology 2012

Effect donor faeces on hepatic insulin sensitivity

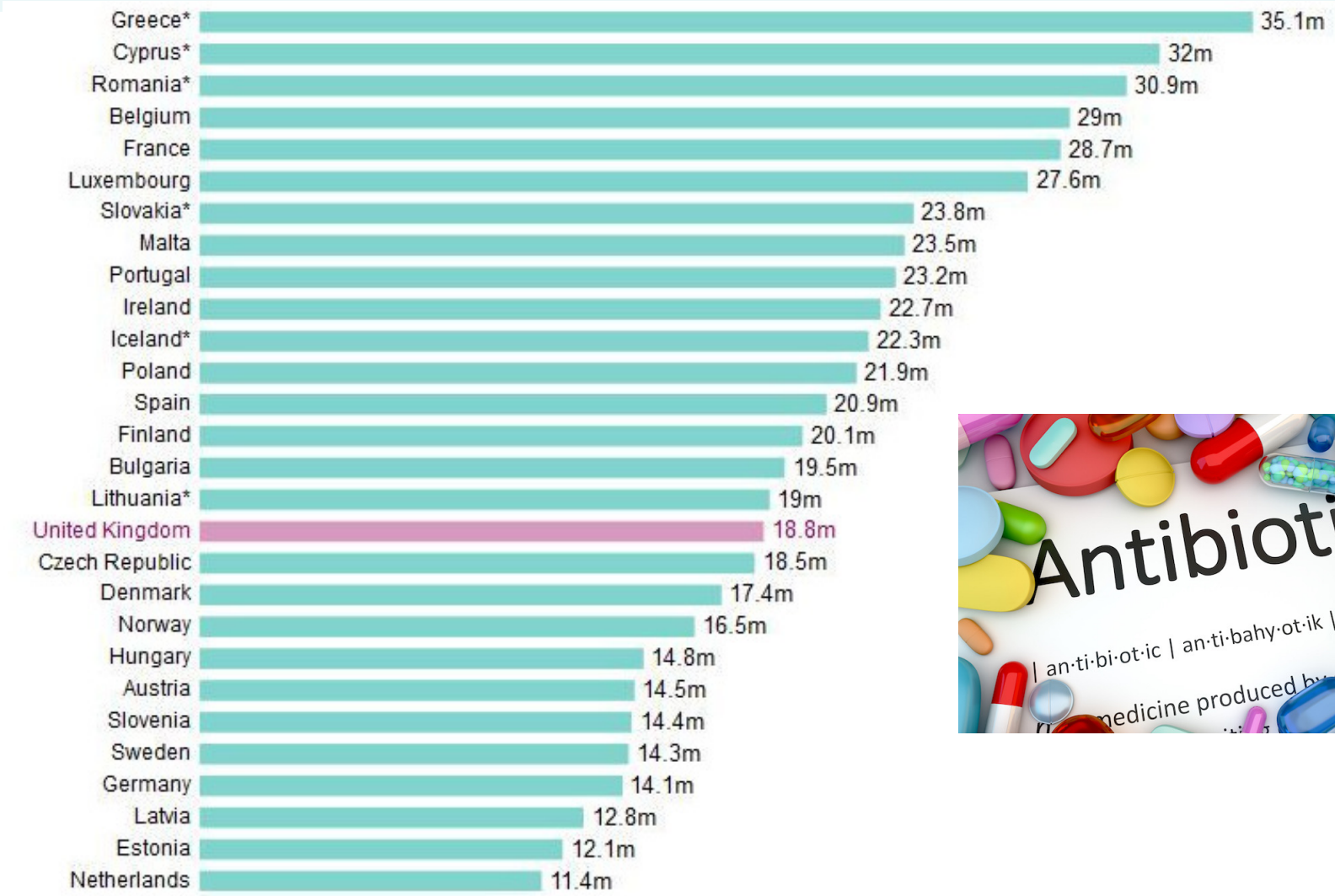


A. Vrieze, Gastroenterology 2012


Antibiotics
| an·ti·bi·ot·ic | an·ti·bahy·ot·ik | an·
medicine produced by or der
harmfu

Antibiotic consumption in Europe

Defined as daily dose per 1,000 inhabitants per day

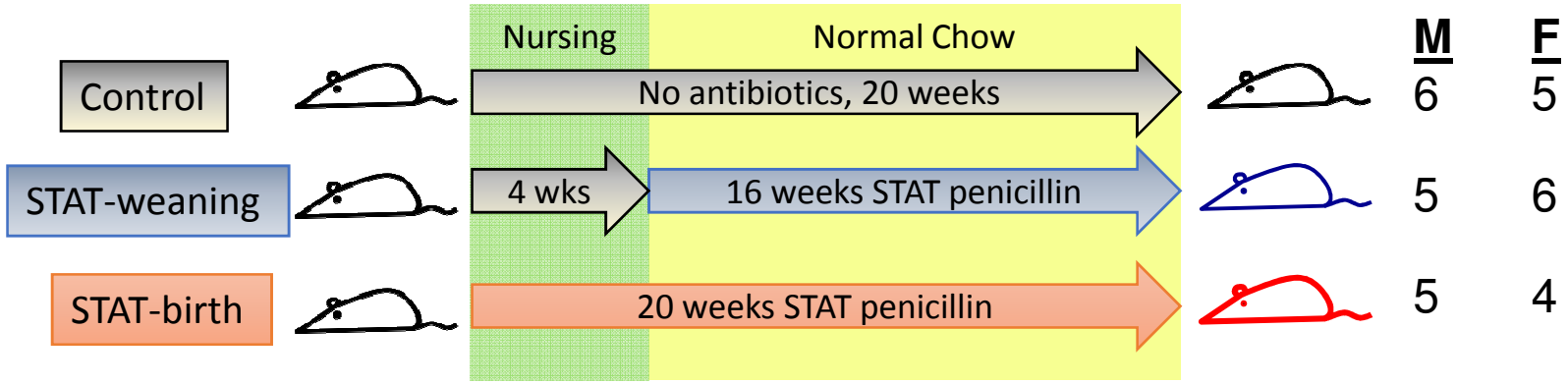


Data applies to prescriptions outside of hospitals *Country provided only total care data, which applies to community sector and hospital use

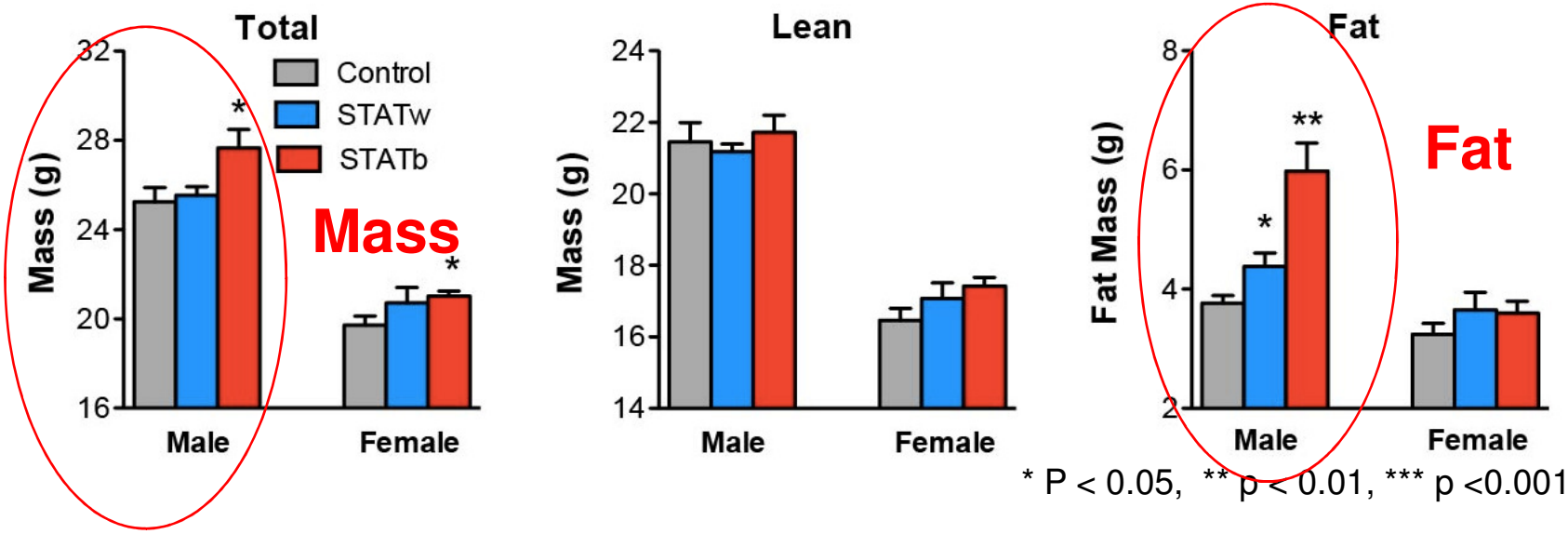
Source: ECDC

O.Goulet 2017

The effect of pre- or post-weaning antibiotic exposure



Body Composition at 20 weeks by DEXA scanning



* P < 0.05, ** p < 0.01, *** p <0.001

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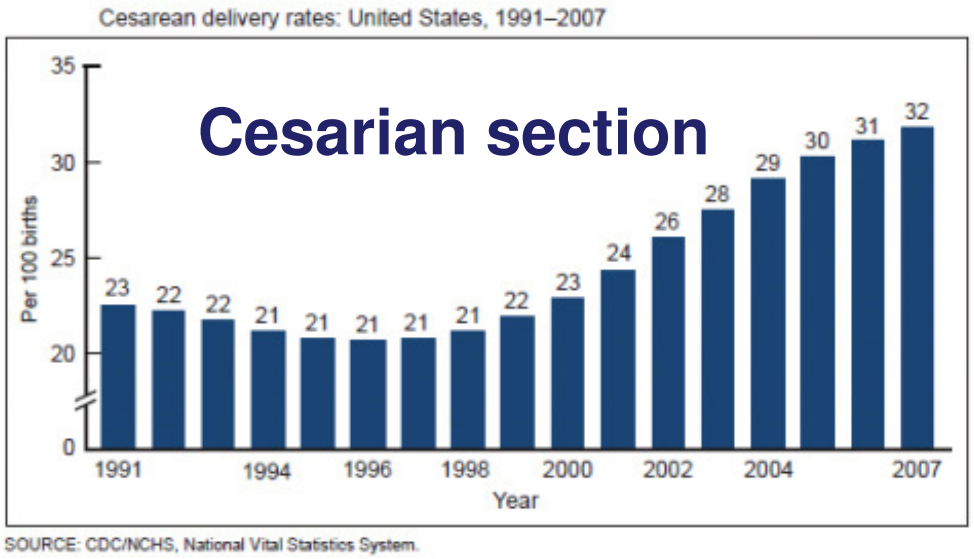
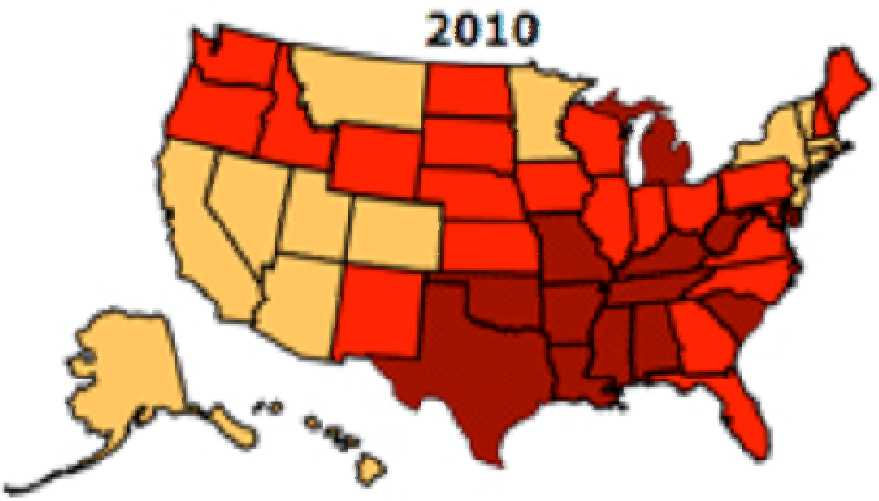
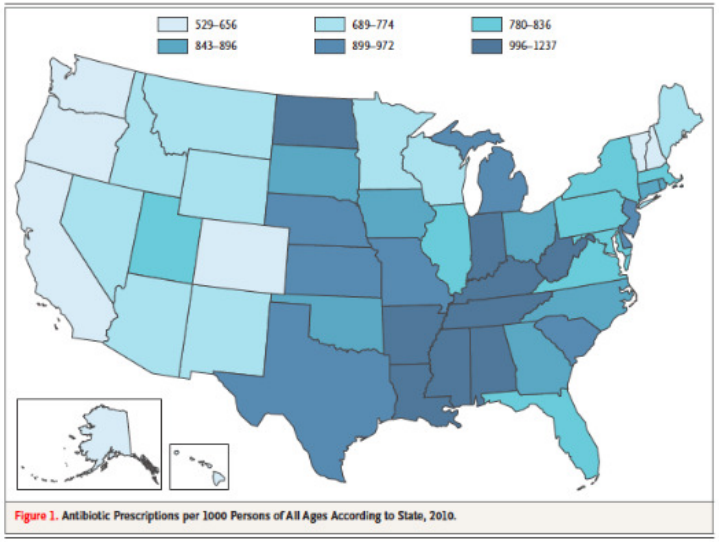
From Laura Cox 2014



- Epidemiological data should be used carefully because of bias, confounding factors…
- However they open new fields of investigation and science



Obesity



Antibiotic use

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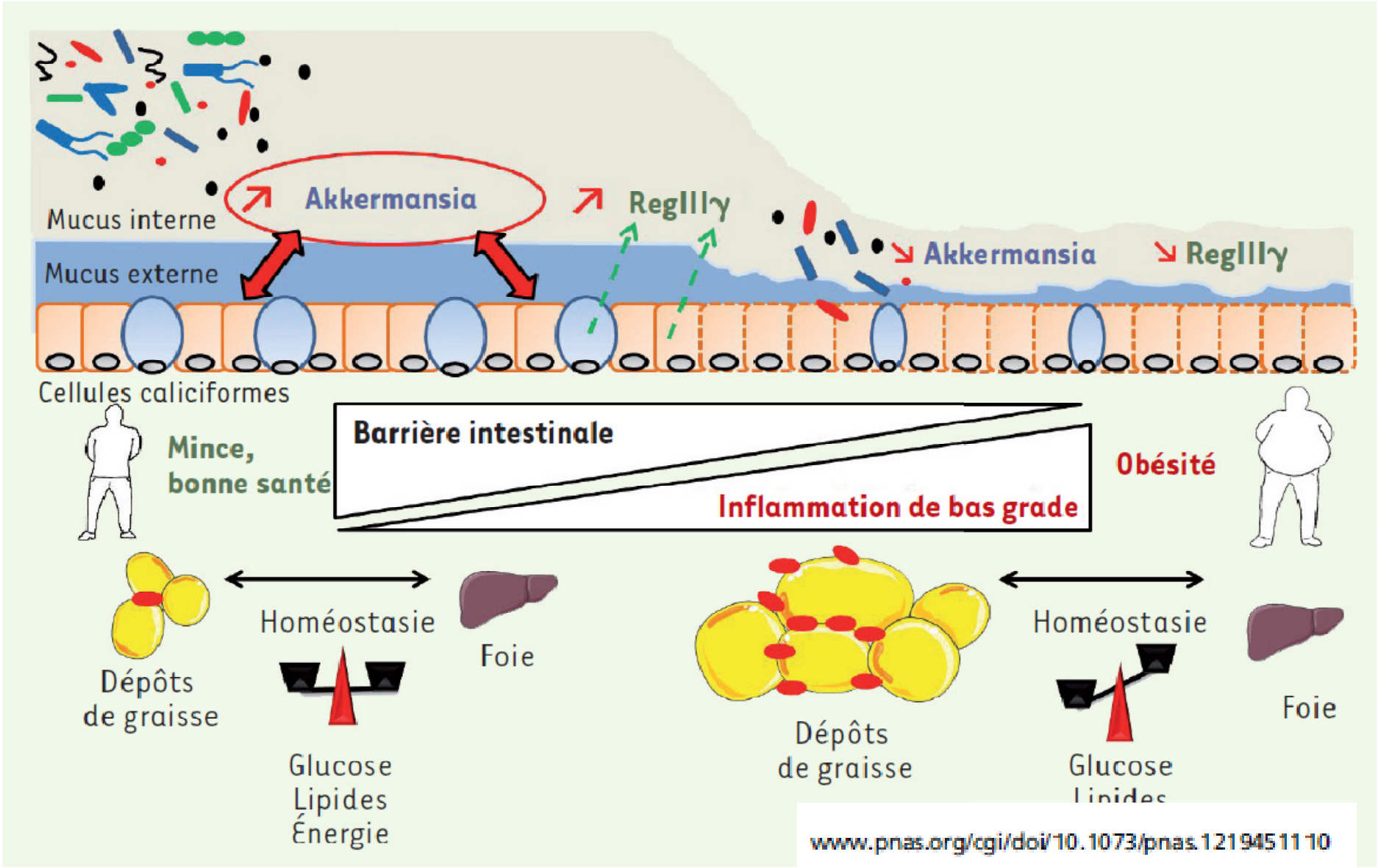
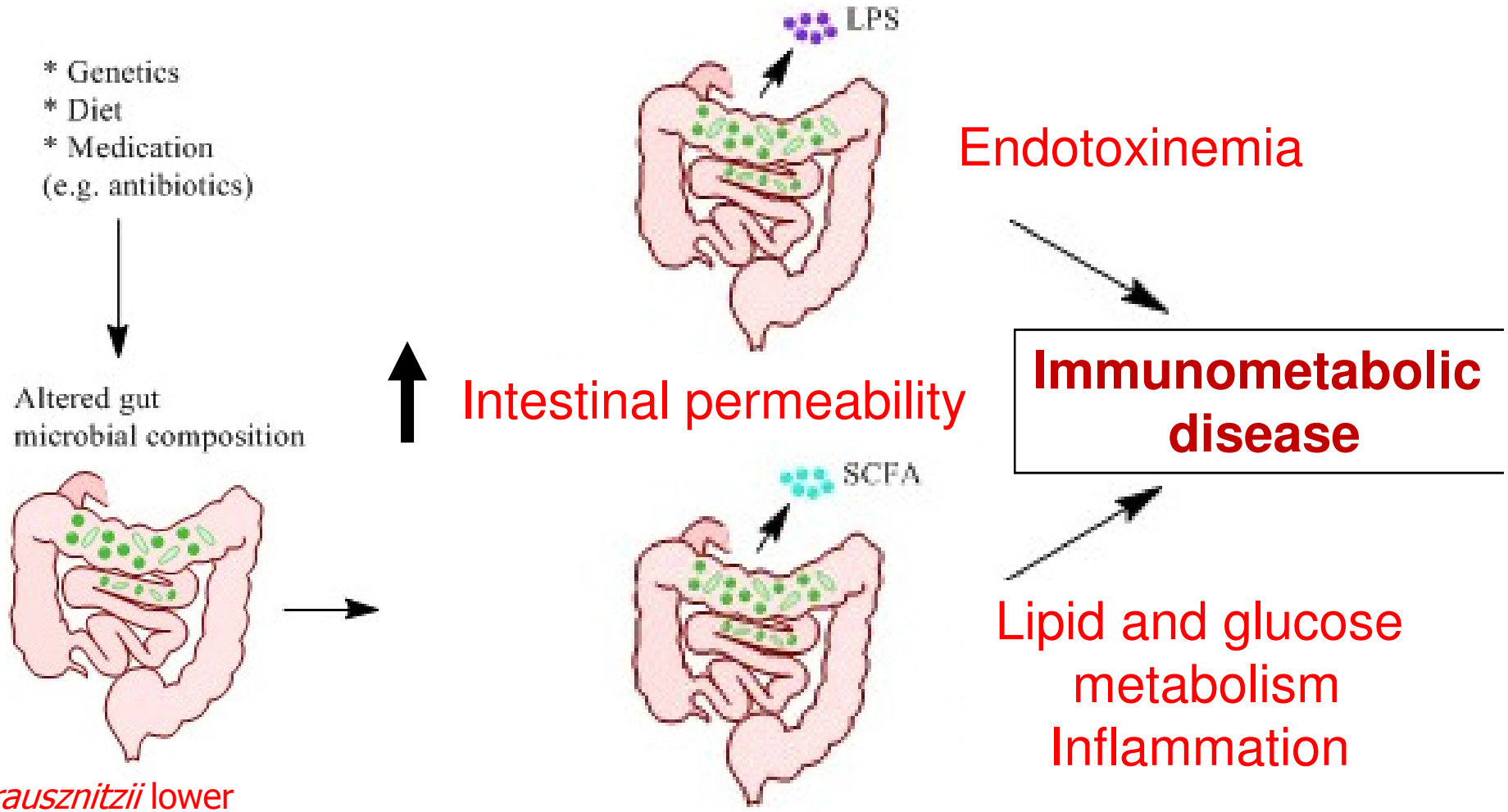
«protective effects» *Akermansia muciniphila*



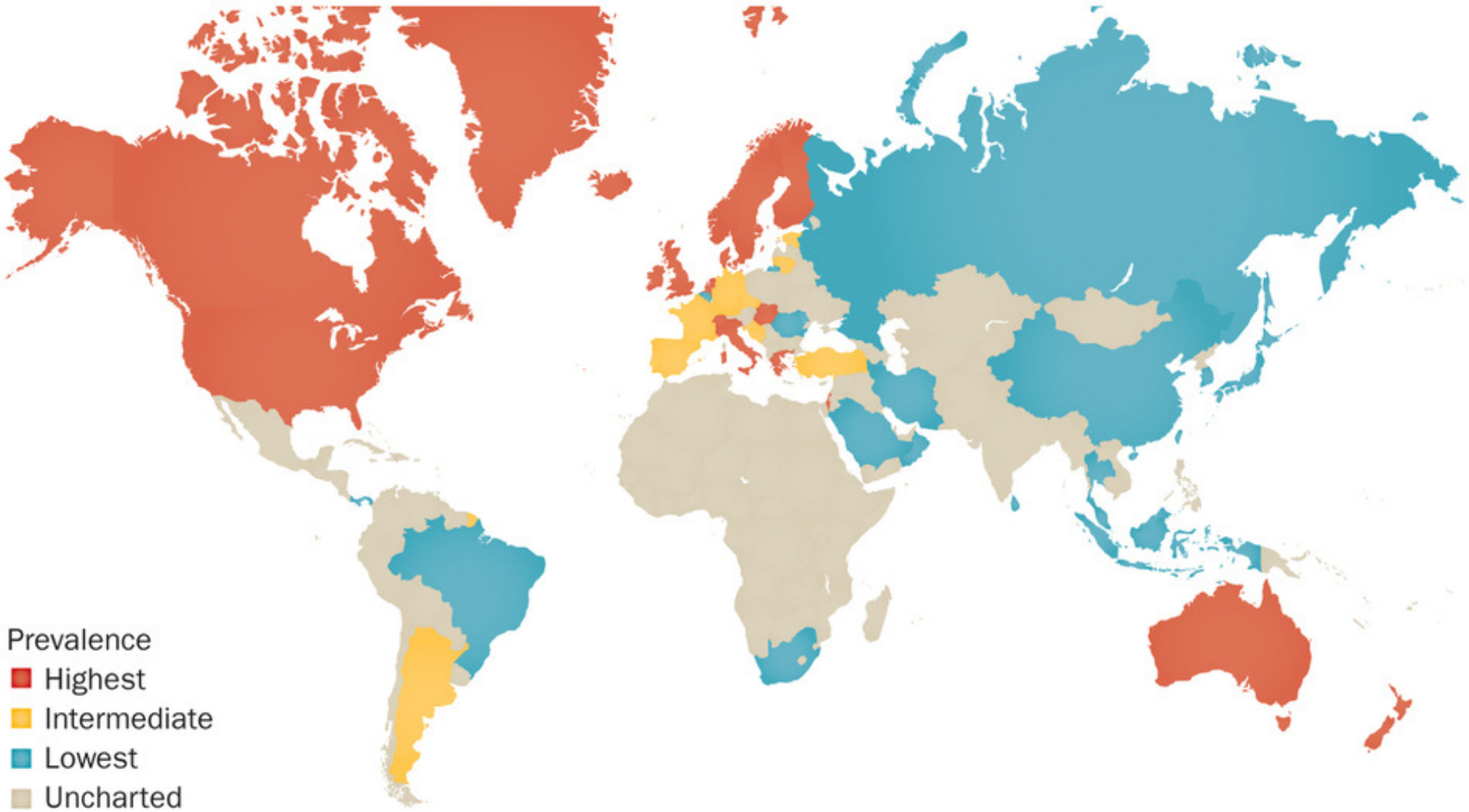
www.pnas.org/cgi/doi/10.1073/pnas.1219451110

Overview of the relationships between gut microbiota and immuno-metabolic disease



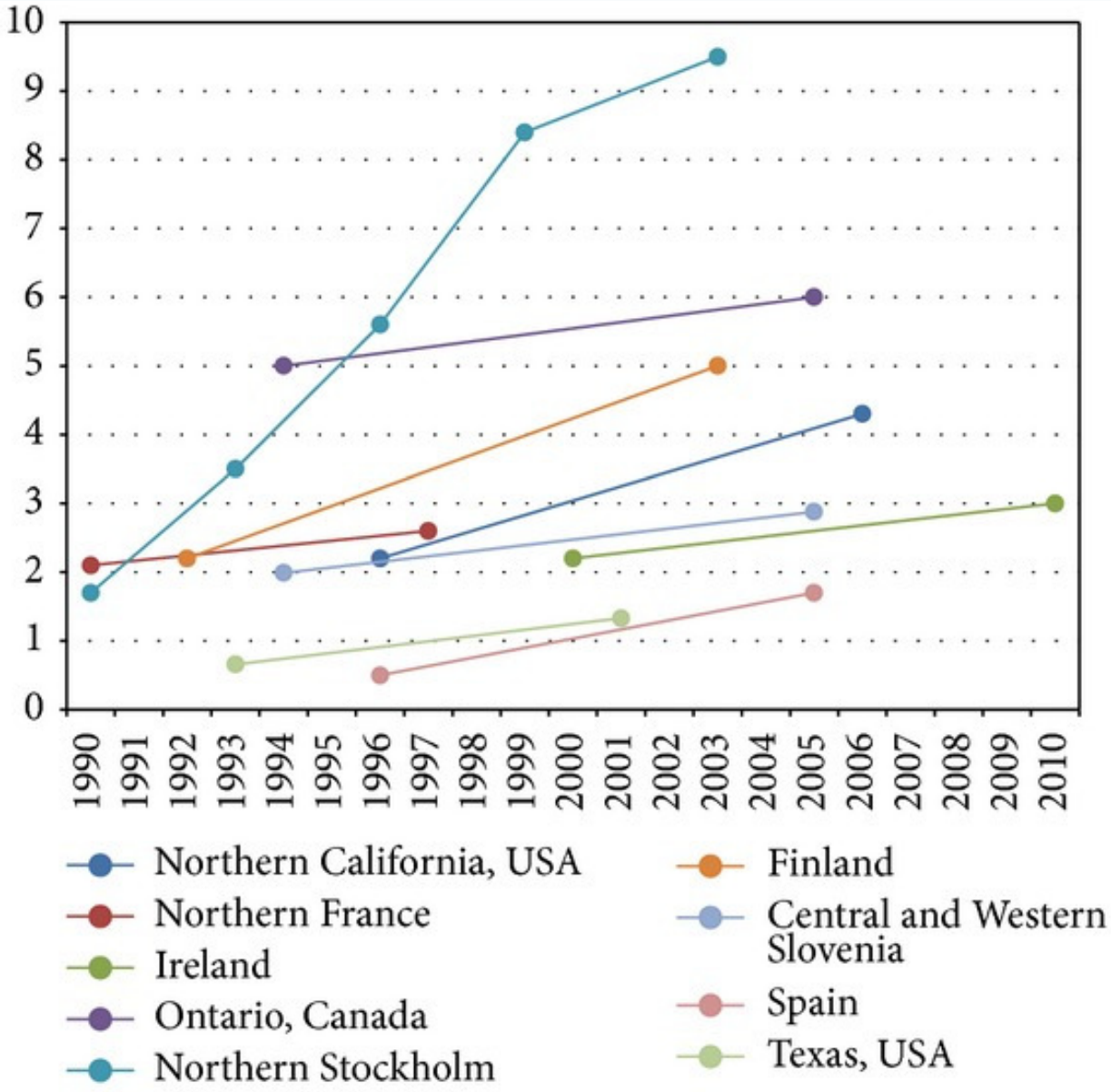
Smits/Nieuwdorp, Gastroenterology 2013

The global burden of IBD : from 2015 to 2025



Nature Reviews | Gastroenterology & Hepatology 2015

Increasing incidence of Crohn's disease



O.Goulet 2017

Zhai *et al. BMC Gastroenterology* (2016) 16:2
DOI 10.1186/s12876-015-0405-0

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Increasing rate of inflammatory bowel disease: a 12-year retrospective study in NingXia, China

Huihong Zhai[1†], Aiqin Liu[2], Wenyu Huang[2], Xin Liu[2], Shanshan Feng[1], Jing Wu[2], Yuping Yao[2], Chao Wang[2], Qianqian Li[2], Qian Hao[2], Jianguo Hu[2] and Shutian Zhang[3,4,5*]

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PARIS DESCARTES

Early-life exposures associated with 

use and risk of subsequent Crohn's disease

Scandinavian Journal of Gastroenterology, 2008; 43: 961–966

HANS HILDEBRAND[1], PETTER MALMBORG[1], JOHAN ASKLING[2], ANDERS EKBOM[2] & SCOTT M. MONTGOMERY[2–4]

Association Between the Use of 

in the First Year of Life and Pediatric Inflammatory Bowel Disease

Am J Gastroenterol 2010; 105:2687–2692;

Souradet Y. Shaw, MSc[1,2], James F. Blanchard, MD, PhD[1,2] and Charles N. Bernstein, MD[1,3]

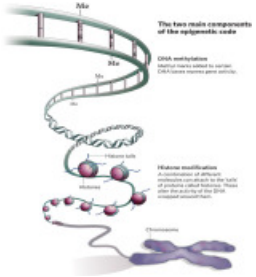
use and inflammatory bowel diseases in childhood

Anders Hviid, Henrik Svanström and Morten Frisch

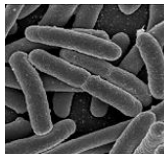
Gut 2011 60: 49-54 originally published online October 21, 2010

Crohn's disease pathophysiology

Endogeneous genetic factors



Exogeneous factors
Environment
Microbiota



immune responses intestinal mucosa

down-regulation

homeostasy

Intestinal inflammation

no down-regulation

IBD

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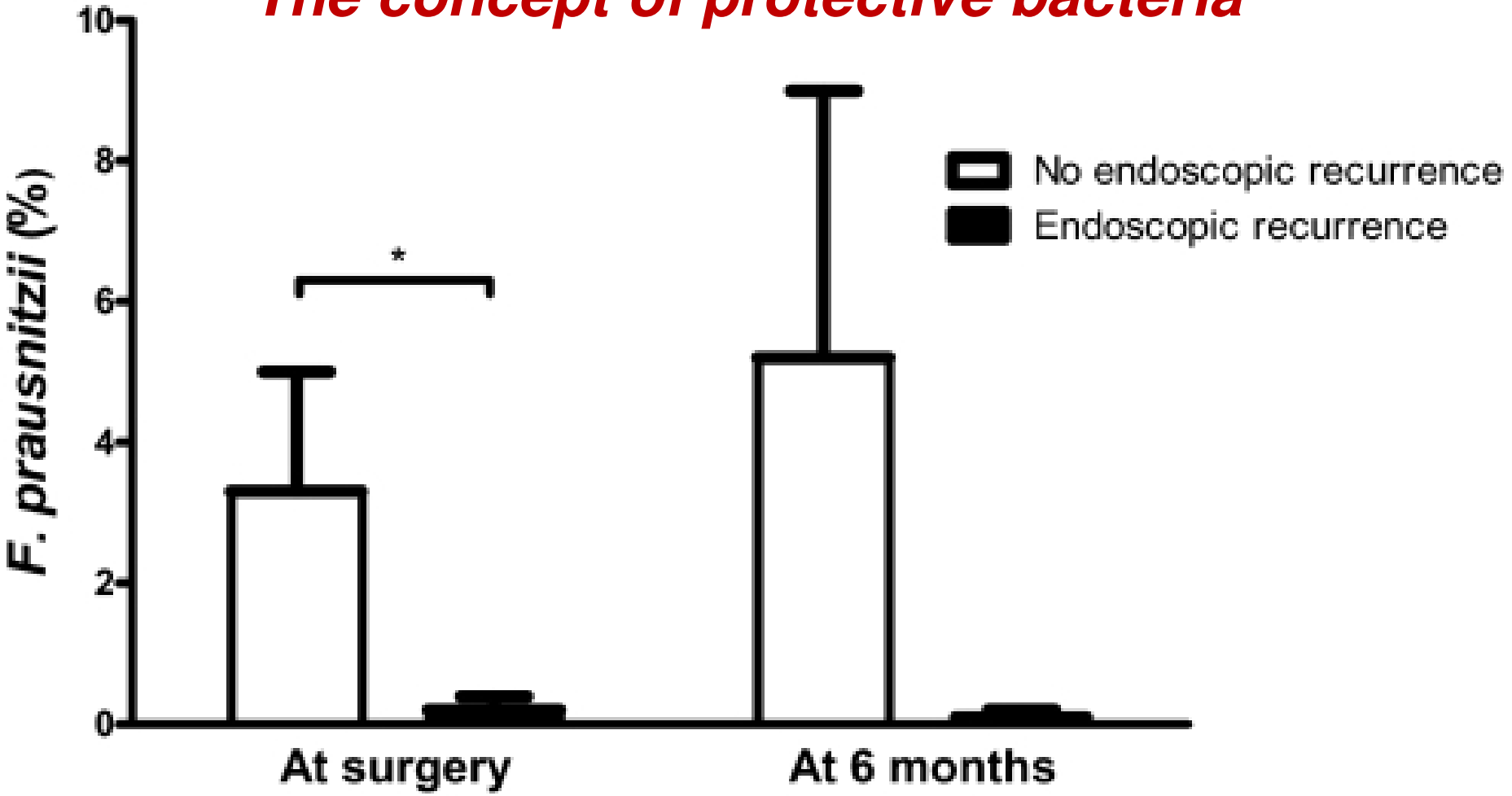
Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of CD patients

The concept of protective bacteria



Sokol et al Proc Natl Acad Sci 2008; 105: 16731–16736.

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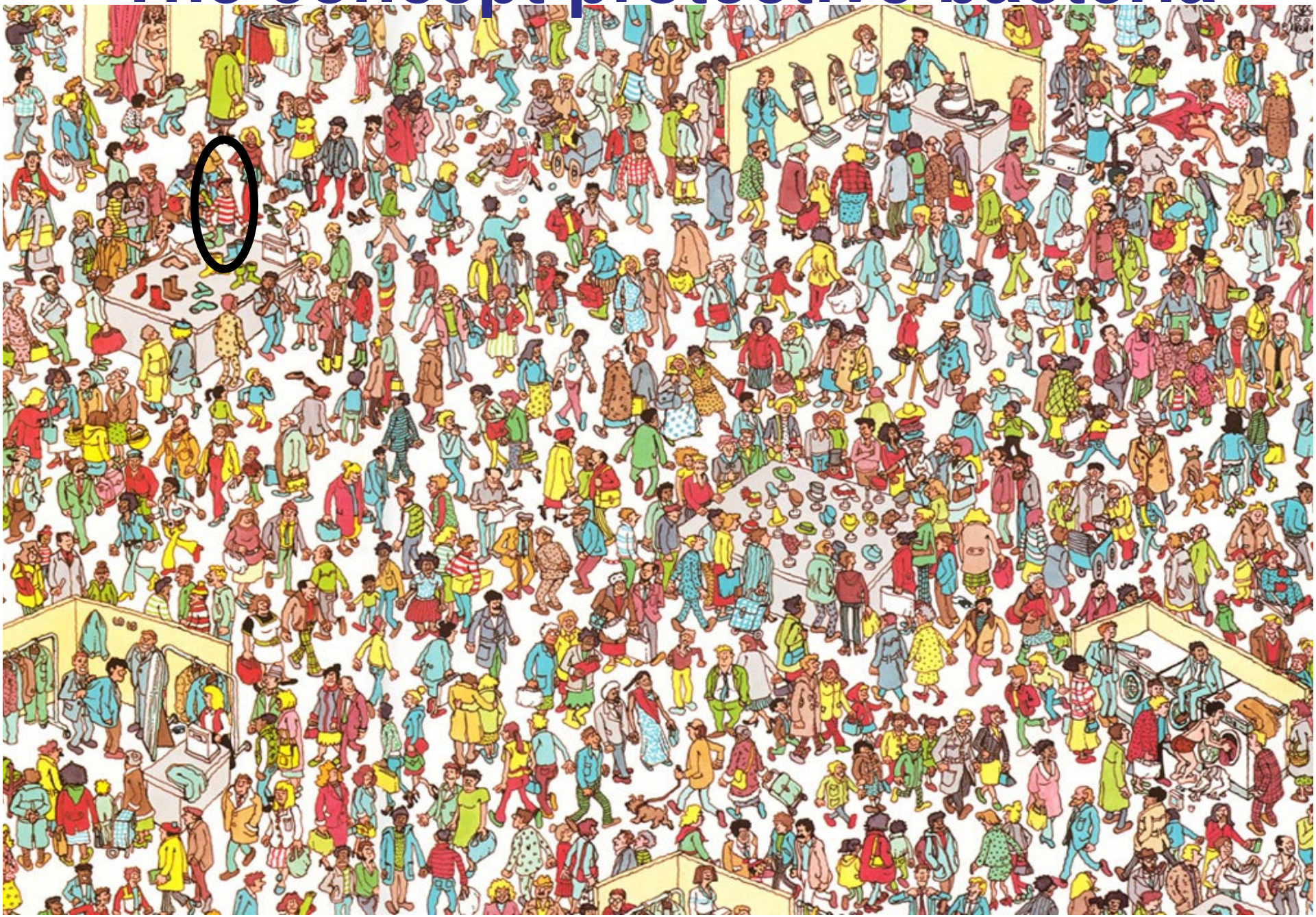
The concept protective bacteria



Perturbations of intestinal microbiota with antibiotics or PPI

- **Fallani M, Amarri S, Uusijarvi A, et al.** Determinants of the human infant intestinal microbiota after introduction of first complementary foods in five European centres. Microbiology. 2011 Feb 17. [Epub ahead of print]
- **Hildebrand H, Malmborg P, Askling J, Ekbom A, Montgomery SM.** Early-life exposures associated with antibiotic use and risk of subsequent Crohn's disease. Scand J Gastroenterol. 2008; 13: 1-6.
- **Penders J, Kummeling I, Thijs C.** Infant antibiotic use and wheeze and asthma risk - a systematic review and meta-analysis. Eur Respir J. 2011 Jan 13. [Epub ahead of print]
- **Penders J, Thijs C, Mommers M et al.** Intestinal lactobacilli and the DC-SIGN gene for their recognition by dendritic cells play a role in the aetiology of allergic manifestations. Microbiology. 2010;156:3298-305.
- **Ajslev TA, Andersen CS, Gamborg M, Sørensen TI, Jess T.** Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. Int J Obes .2011 Mar 8. [Epub ahead of print]
- **Canani RB, Cirillo P, Roggero P, et al and the Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP).** Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006; 117: e817-20.
- **Alm B, Erdes L, Möllborg P, Pettersson R, Norvenius SG, Aberg N, Wennergren G.** Neonatal antibiotic treatment is a risk factor for early wheezing. Pediatrics. 2008; 121: 697-702
- **Shaw SY**, **Blanchard JF**, **Bernstein CN**. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. Am J Gastroenterol. 2010;105:2687-92.
- Virta L, Auvinen A, Helenius H, Huovinen P, Kolho KL. Association of repeated exposure to antibiotics with the development of pediatric Crohn's disease--a nationwide, register-based finnish case-control study. Am J Epidemiol. 2012 Apr 15;175(8):775-84

PPI: diarrhea and pneumonia

Characteristics	Controls ($n = 95$)	GA Inhibitors ($n = 91$)
Age, median, mo (IQR)	10 (8–15)	10 (8–16)
Male, *n* (%)	50 (53)	48 (53)
Weight, median, kg (IQR)	9.3 (8–10)	9.1 (8–15)
Length, median, cm (IQR)	74 (70–78)	74 (70–80)
Patients presenting with		
Acute gastroenteritis in the previous 4 mo, *n* (%)	17 (18)	18 (20)
Acute gastroenteritis in the follow-up period, *n* (%)	19 (20)	43 (47)[a,b]
Pneumonia in the previous 4 mo, *n* (%)	1 (1)	3 (3)
Pneumonia in the follow-up period, *n* (%)	2 (2)	11 (12)[a,b]

[a] $P < .05$, GA inhibitor users versus control children.

[b] $P < .05$, 4 months before versus 4 months after the enrollment.

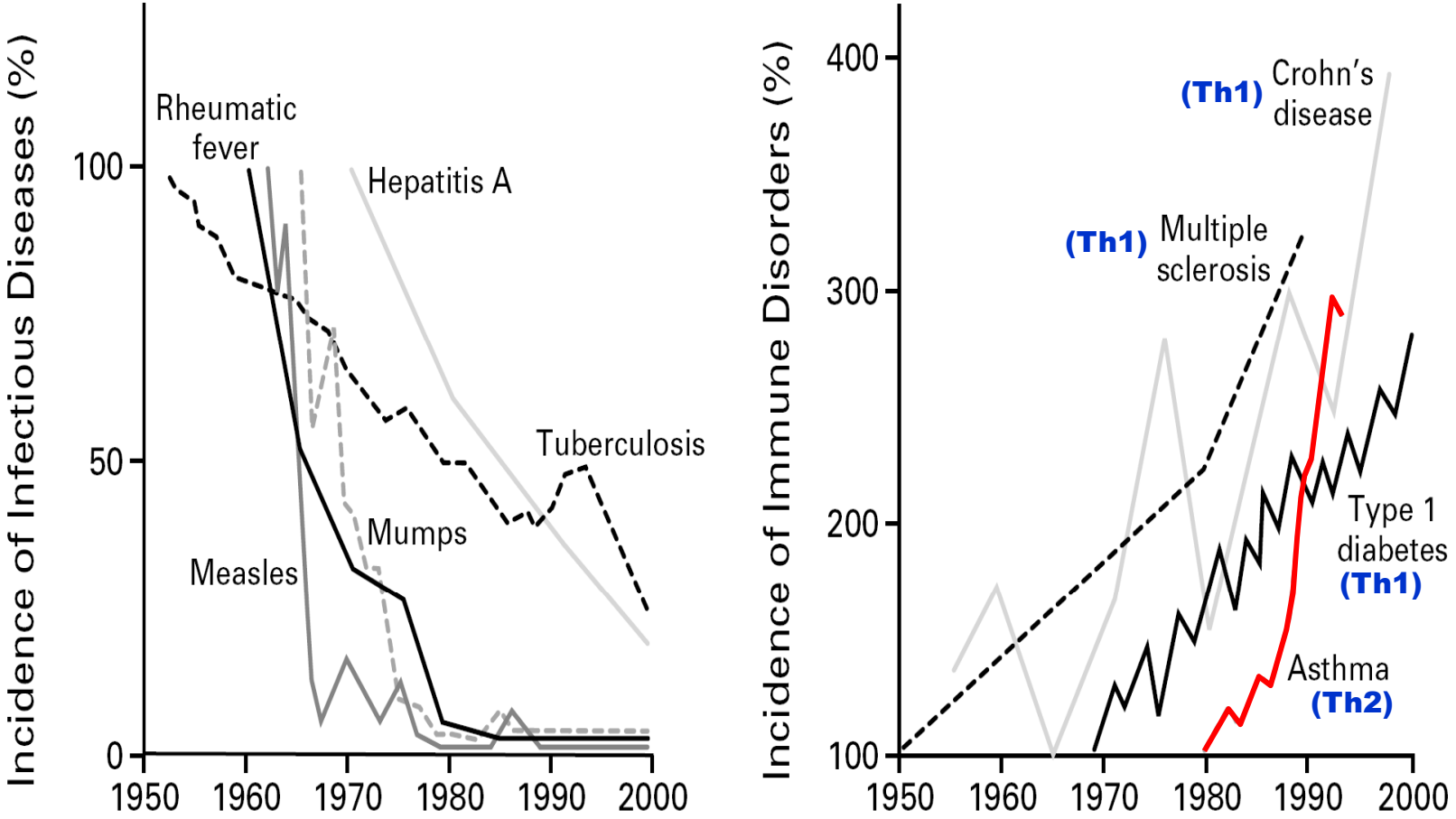
IQR indicates interquartile range.

Therapy With Gastric Acidity Inhibitors Increases the Risk of Acute Gastroenteritis and Community-Acquired Pneumonia in Children
Roberto Berni Canani, Pia Cirillo, Paola Roggero, Claudio Romano, Basilio Malamisura, Gianluca Terrin, Annalisa Passariello, Francesco Manguso, Lorenzo Morelli and Alfredo Guarino
Pediatrics 2006;117;e817

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Chronic diseases prevalence in the last 50 years

Decrease in infections is associated with increase immune disorders



Bach JF. N Engl J Med. 2002;347:911-920,

The NEW ENGLAND JOURNAL of MEDICINE

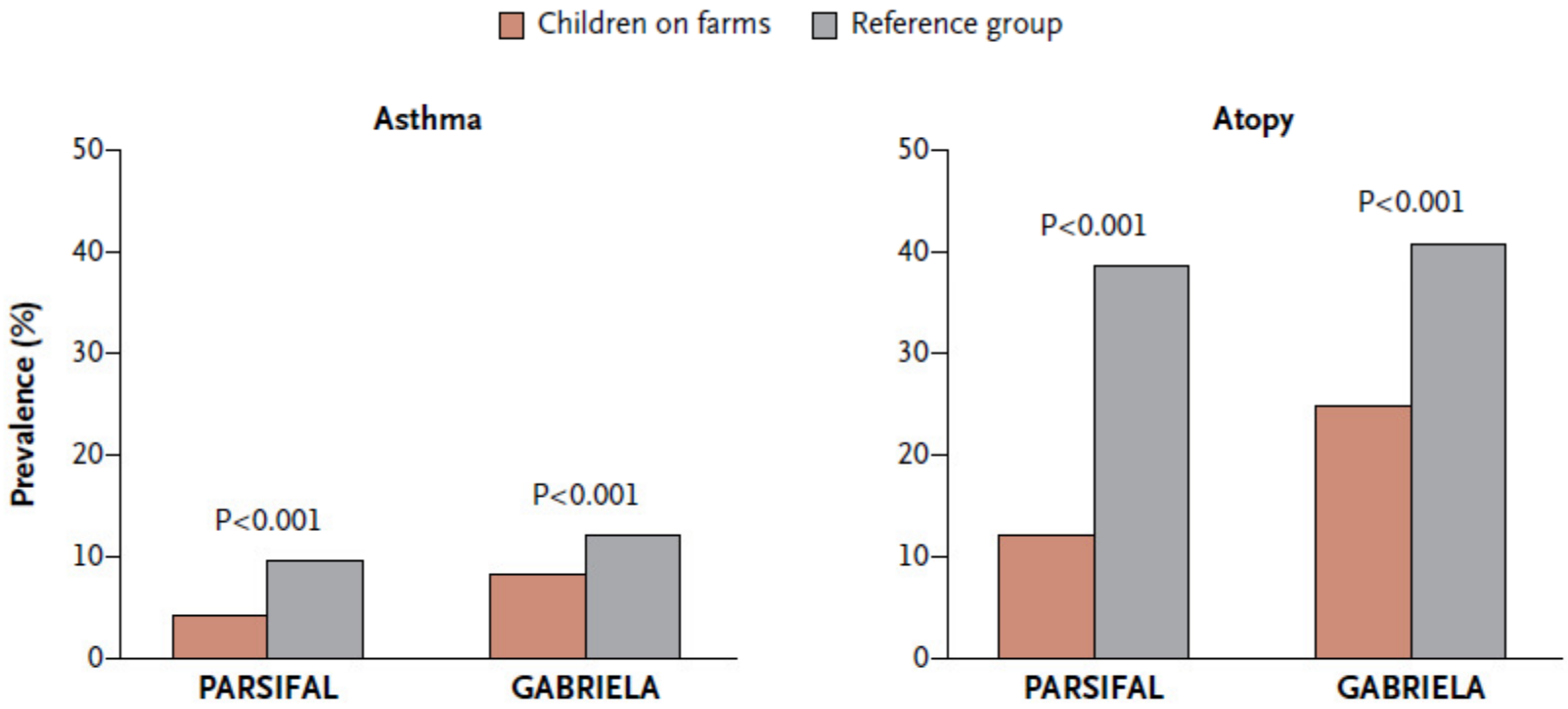
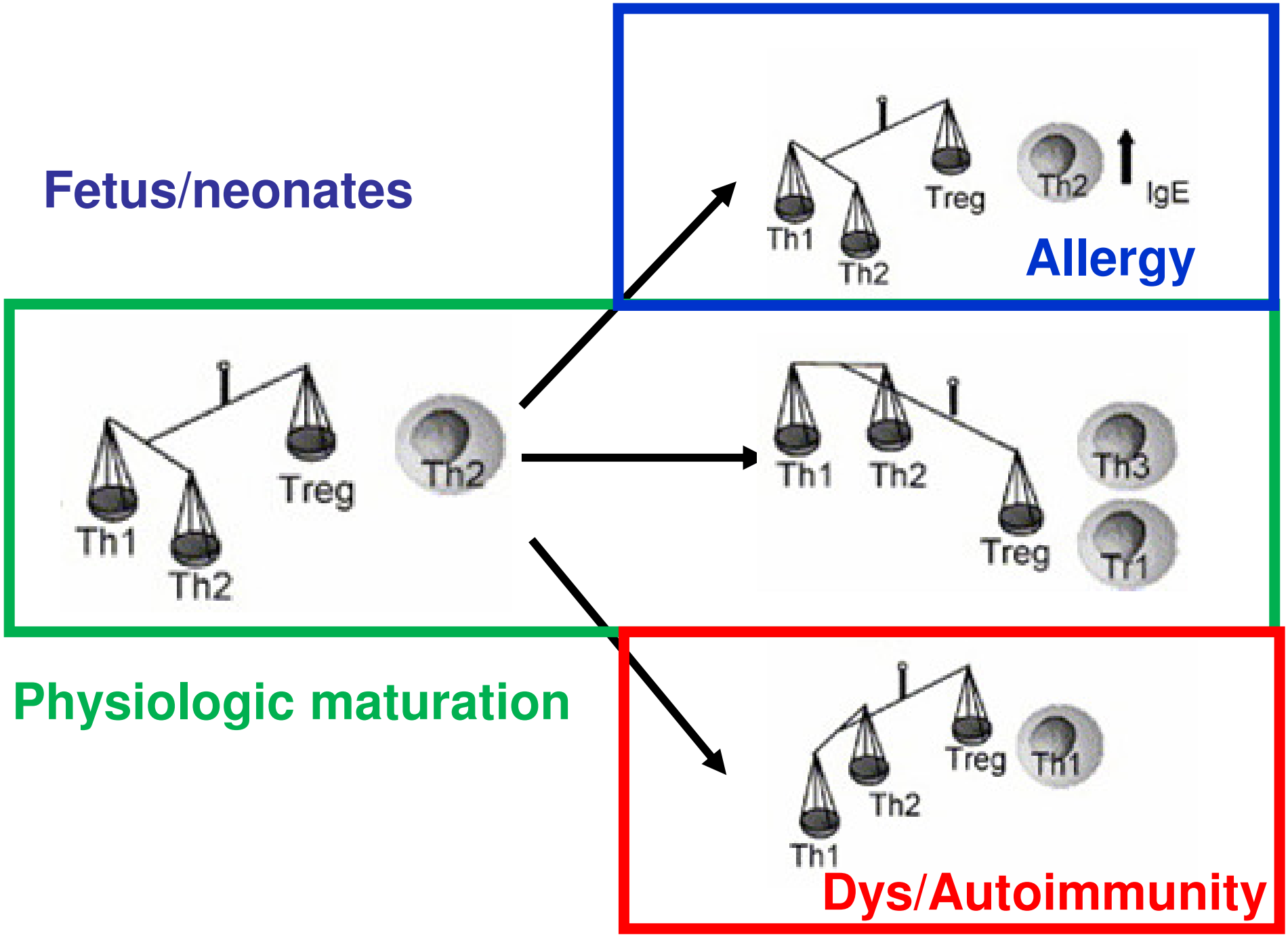


Figure 1. Prevalence of Asthma and Atopy among Children Living on Farms as Compared with Reference Groups.

The PARSIFAL study population included 6843 school-age children 6 to 13 years of age, and the GABRIELA study population included 9668 children between 6 and 12 years of age. Calculations of prevalence in GABRIELA were weighted on the basis of the total number of children who were eligible for inclusion in the study (34,491 children).


Fetus/neonates
Th1
Th2
Treg
Th2
IgE
Allergy
Th1
Th2
Treg
Physiologic maturation
Th1
Th2
Treg
Th2
Th1
Th2
Treg
Th3
Tr1
Th1
Th2
Treg
Th1
Dys/Autoimmunity

Bacterial colonization and host defense

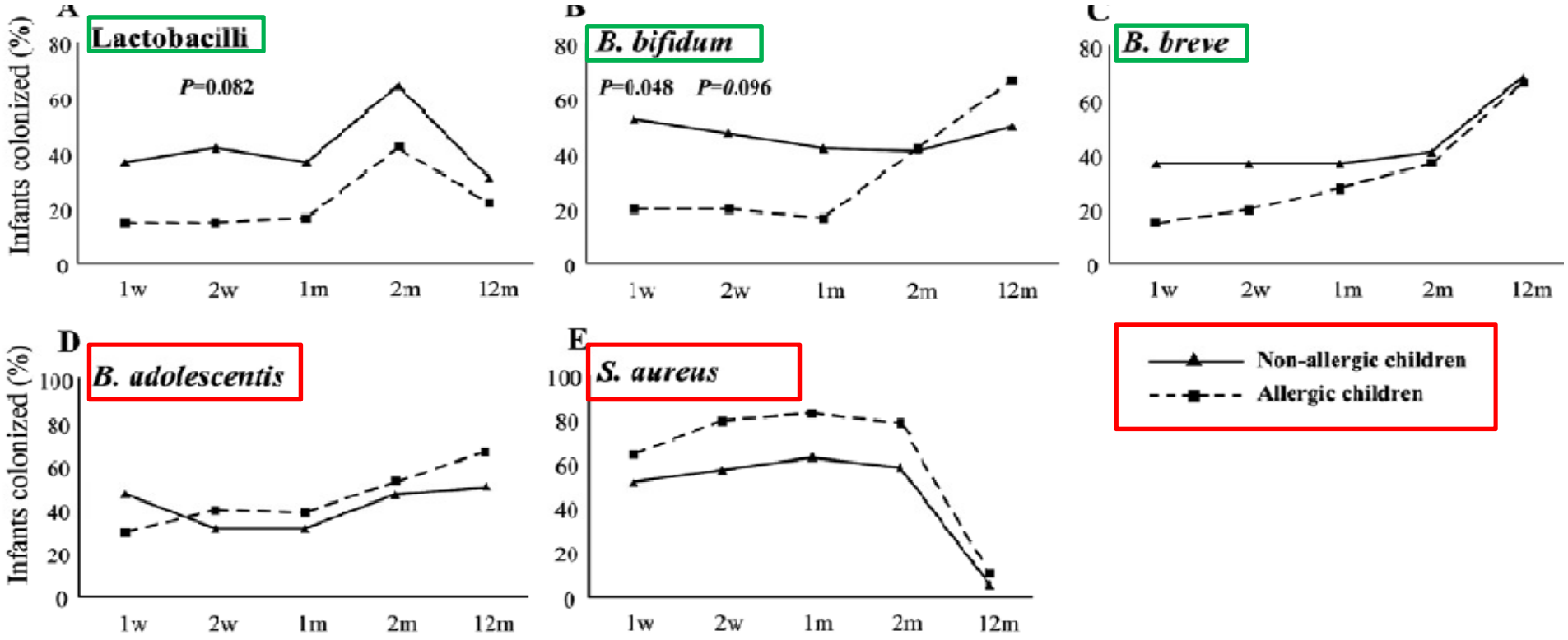
"The hygiene hypothesis"

Due to a decreased exposure to microorganisms **during infancy**, the mucosal immune system fails to develop properly resulting in aberrant responses to allergens and autoantigens leading to an increase disease burden.

Bach JF. N Engl J Med. 2002;347:911-920.

Early Colonization with a Group of Lactobacilli Decreases the Risk for Allergy at Five Years of Age Despite Allergic Heredity

Maria A. Johansson[1]*, Ylva M. Sjögren[1], Jan-Olov Persson[2], Caroline Nilsson[3], Eva Sverremark-Ekström[1]*

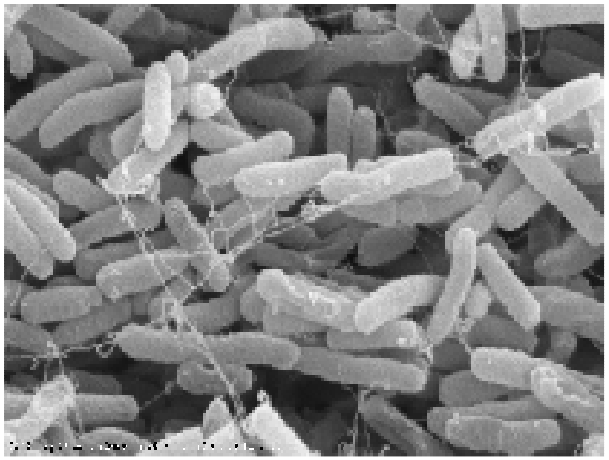


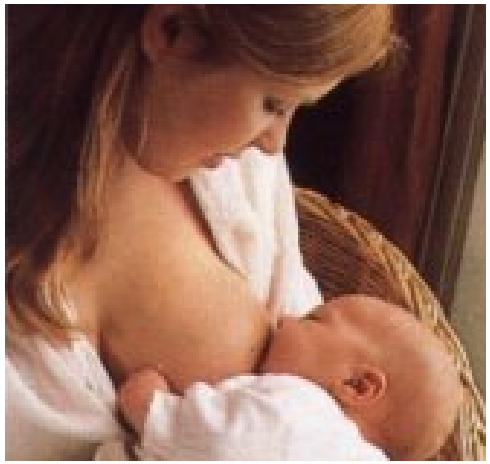
Early life gut microbiota composition associates with allergic disease at age five

PLoS One. 2011;6(8):e23031

Content of the presentation

- Factors of gut bacterial colonization
- Impact of microbiota on GI function
- Impact on health and diseases
- ***Modulation of intestinal microbiota***





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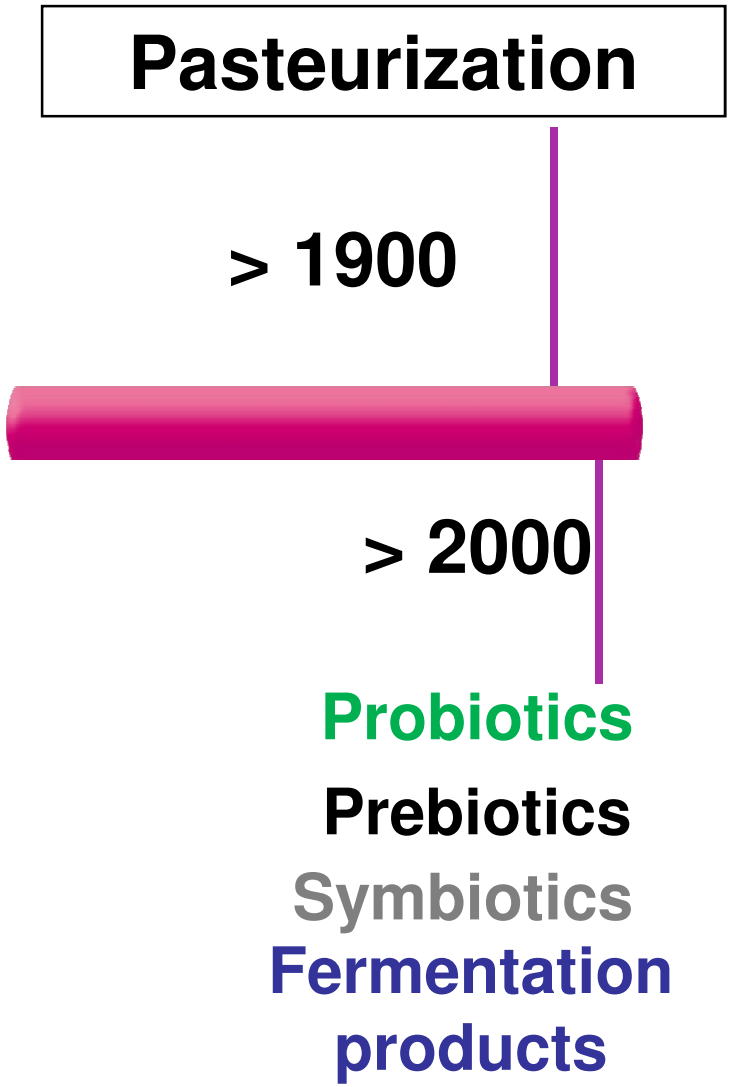
The concept of modulating intestinal microbiota

Probiotics

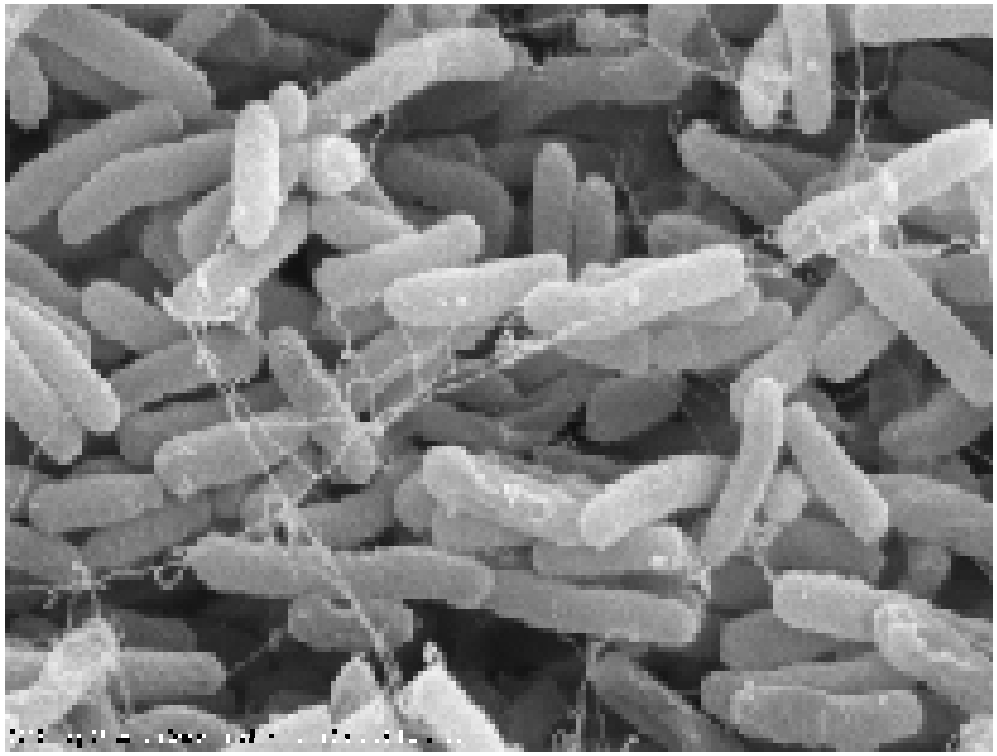
Prebiotics

Symbiotics

Postbiotics
(Fermentation Products)



Modulation of intestinal microbiota

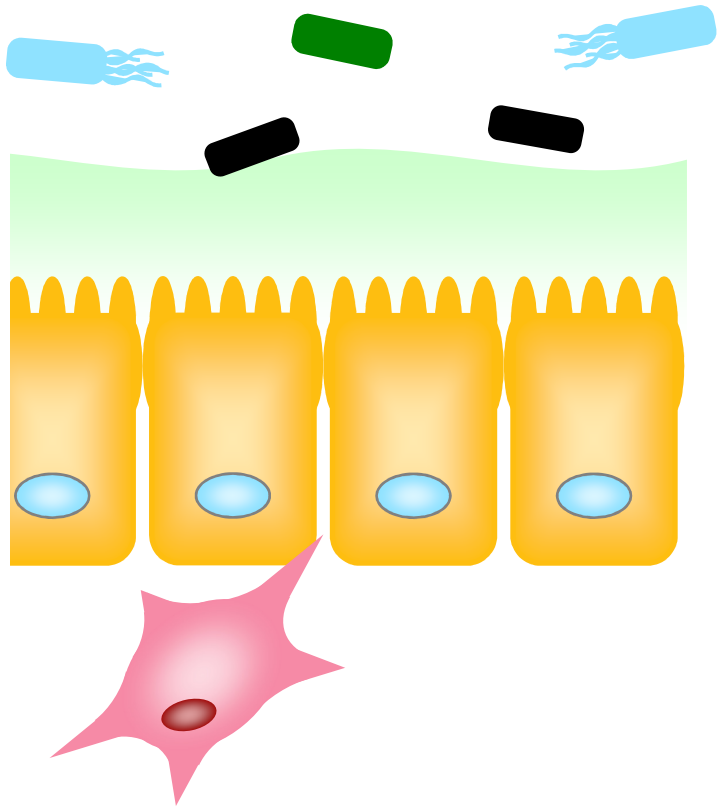


Mimicking intestinal microbiota of normal brest fed infants looks logical

Probiotic organisms

Probiotics : "live microorganisms which when administered in adequate amounts confer a health benefit on the host"

- Various mechanisms of action have been postulated :
  - Competition with pathogen bacteria[2]
  - Acidification of the colon environment[2,3]
  - Production of bioactive molecules[2,3]
  - Immunomodulation[2,3]



1. FAO/WHO. Health and nutritional properties of probiotics in food 2001
2. Chermesh I *et al. World J Gastroenterol* 2006;**12**:853-7
3. Mach T. *J Physiol Pharmacol* 2006;**57**:S23-33

Probiotic organisms

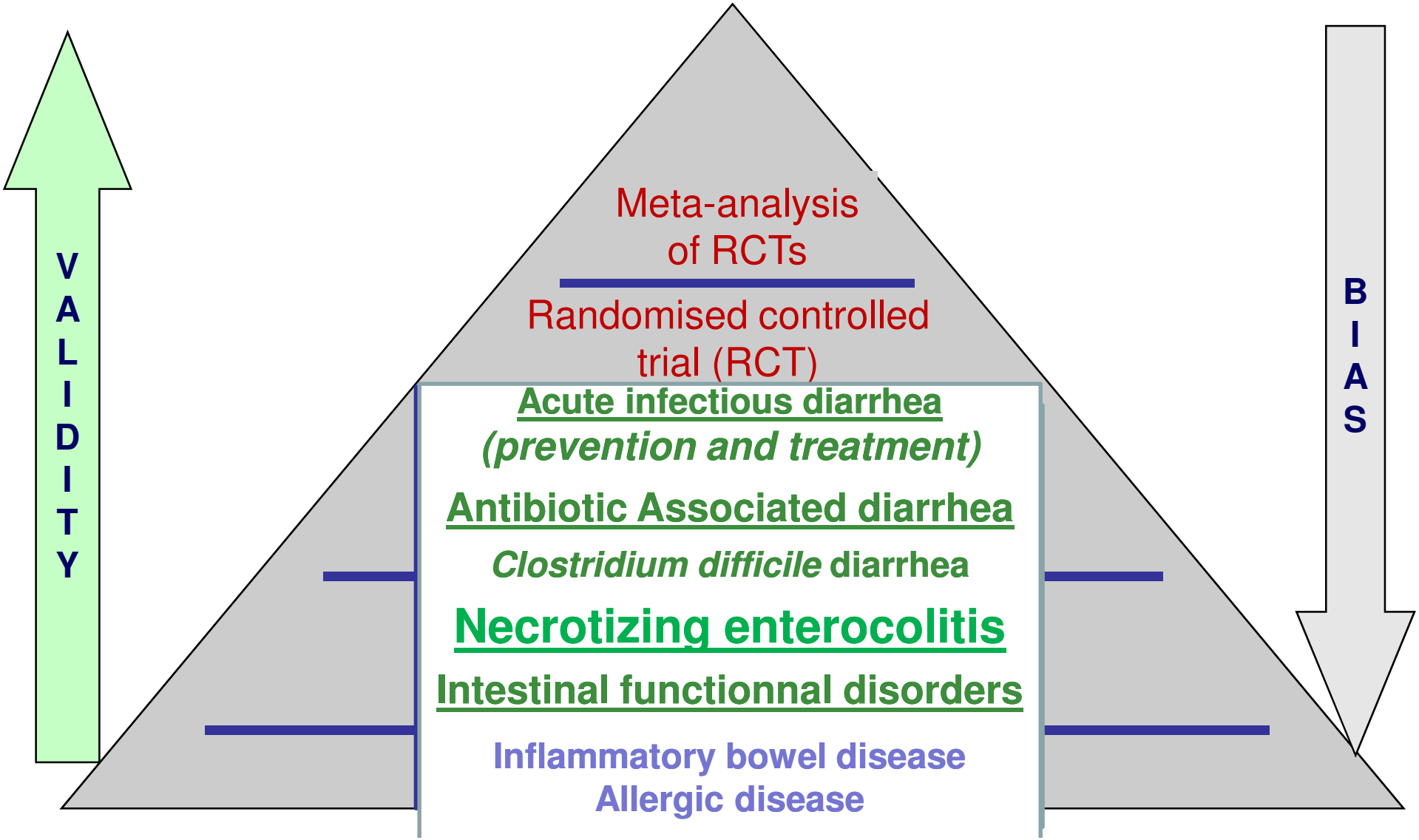
Live microorganisms, which when consumed in adequate amounts, confer a health benefit on the host

Lactobacillus sp
Bifidobacterium sp

Streptococcus salivarius
Streptococcus thermophilus
Enterococcus faecium
E coli
Clostridium butyricum
Saccharomyces boulardii

Probiotic in clinical practice

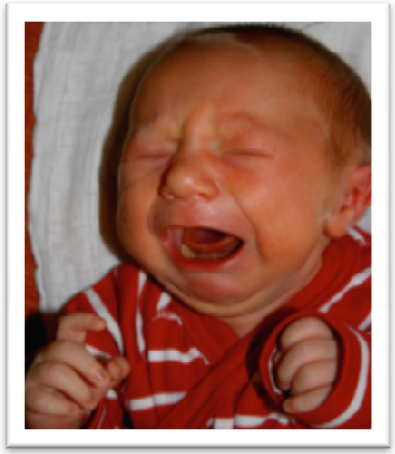
Evidence based efficacy in the following settings



Gut microbiota of colic infant

Slower Colonization
(De Weerth 2013)

↓ Diversity and Stability
(Rhoads 2009, de Weerth 2013, Roos 2013)



↑ Clostridia
(Lehtonen 1994, Pärtty 2013)

↑ Proteobacteria
(Savino 2004, 2009, Rhoads 2009, De Weerth 2013)

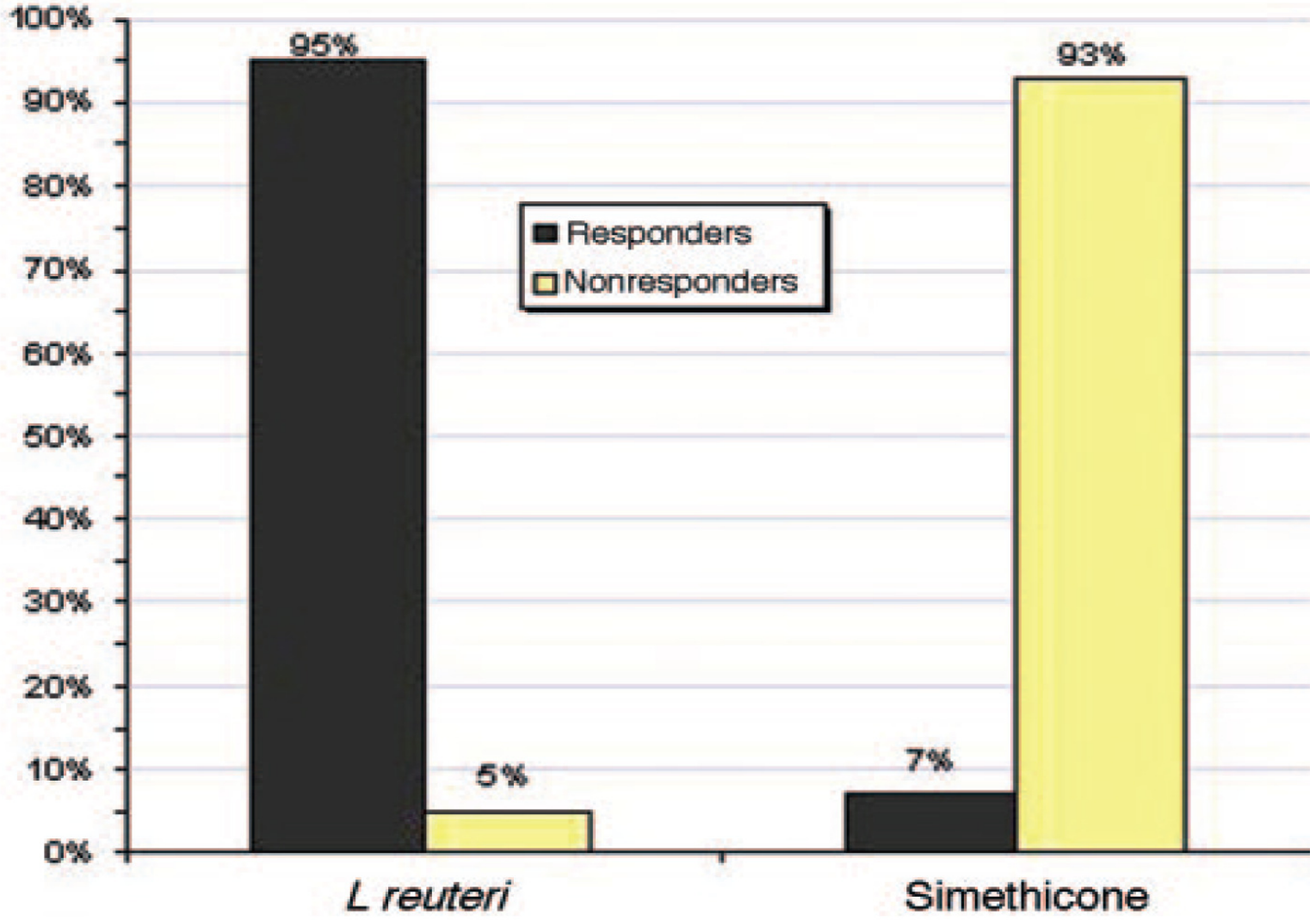
↓ Lactobacilli
(Pärtty 2012, De Weerth 2013)

↓ Bifidobacteria
(Pärtty 2012 , De Weerth 2013)

Lactobacillus reuteri (American Type Culture Collection Strain 55730) Versus Simethicone in the Treatment of Infantile Colic: A Prospective Randomized Study

Francesco Savino, Emanuela Pelle, Elisabetta Palumeri, Roberto Oggero and Roberto Miniero

Pediatrics 2007;119:e124-e130

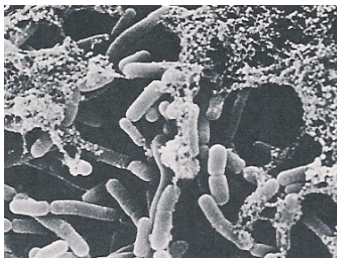


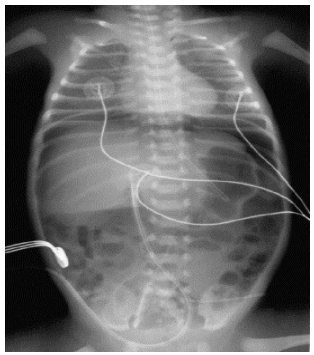
Necrotizing enterocolitis (NEC)

- NEC is an acute inflammatory intestinal disease that remains a significant health problem for premature infants

- It is one of the leading cause of morbidity (SBS) and mortality among these infants worldwide

- NEC occurs in 1 to 5% of all neonatal ICU admissions and in 5-15% of all very low birth weight (<1500g) infants

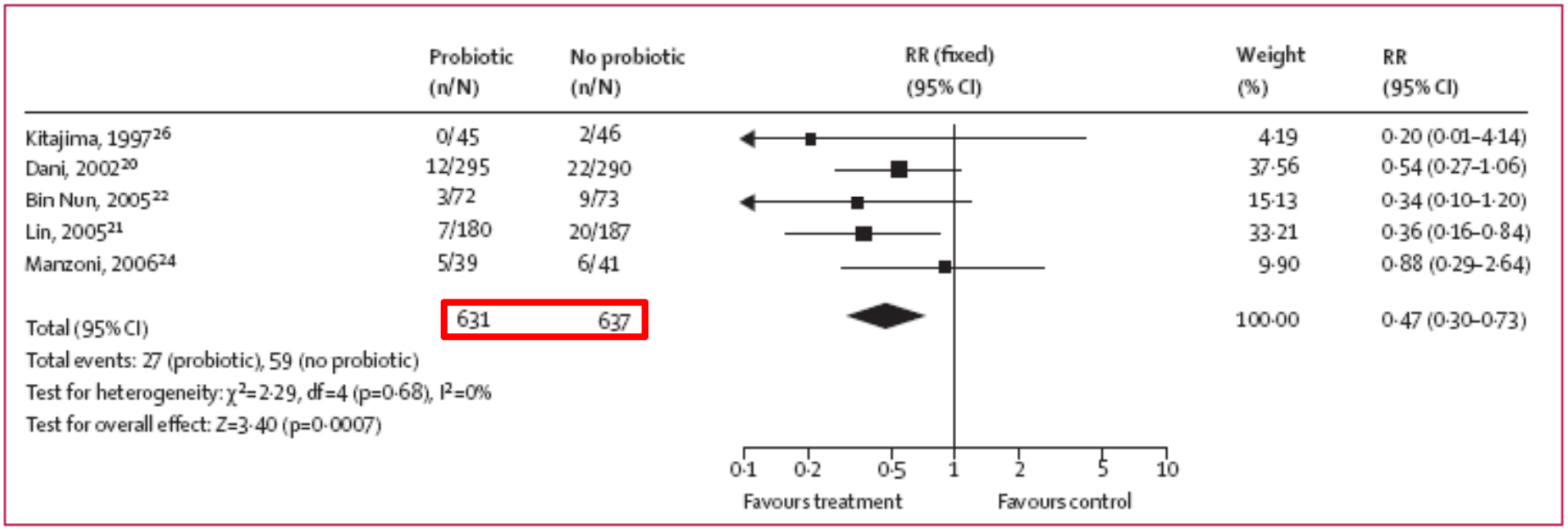




Neu J.
Curr Opin Clin Nutr Metab Care.
2015 May;18(3):285-8.

Probiotics for the prevention of NEC

Reduce incidence and mortality

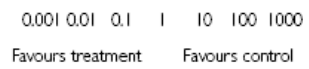


Deshpande G and Rao S, Lancet 2007

Probiotics for the prevention of NEC

Reduce incidence and mortality

Study	Probiotics n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 All cause neonatal mortality					
Bin-Nun 2005	3/72	8/73		20.4	0.38 [0.11, 1.38]
Dani 2002	0/295	2/290		6.5	0.20 [0.01, 4.08]
Lin 2005	7/180	20/187		50.4	0.36 [0.16, 0.84]
Manzoni 2006	5/39	6/41		15.0	0.88 [0.29, 2.64]
Reuman 1986	1/15	3/15		7.7	0.33 [0.04, 2.85]
Subtotal (95% CI)	**601**	**606**		**100.0**	**0.43 [0.25, 0.75]**
Total events: 16 (Probiotics), 39 (Control)					
Test for heterogeneity chi-square=2.10 df=4 p=0.72 I^2 =0.0%					
Test for overall effect z=2.99 p=0.003					
02 NEC realted mortality					
Bin-Nun 2005	0/72	3/73		58.0	0.14 [0.01, 2.75]
Dani 2002	0/295	2/290		42.0	0.20 [0.01, 4.08]
Subtotal (95% CI)	**367**	**363**		**100.0**	**0.17 [0.02, 1.37]**
Total events: 0 (Probiotics), 5 (Control)					
Test for heterogeneity chi-square=0.02 df=1 p=0.89 I^2 =0.0%					
Test for overall effect z=1.66 p=0.1					



BAlFaleh K, Bassler D; Cochrane Analysis 2008

Probiotics for the prevention of NEC

Conclusions of the Cochrane review

- Enteral supplementation of probiotics reduced the risk of severe NEC and mortality in preterm infants.

- This analysis supports a change in practice in premature infants > 1000 g at birth.

- Data regarding outcome of ELBW infants could not be extracted from the available studies; therefore, a reliable estimate of the safety and efficacy of administration of probiotic supplements cannot be made in this high risk group.

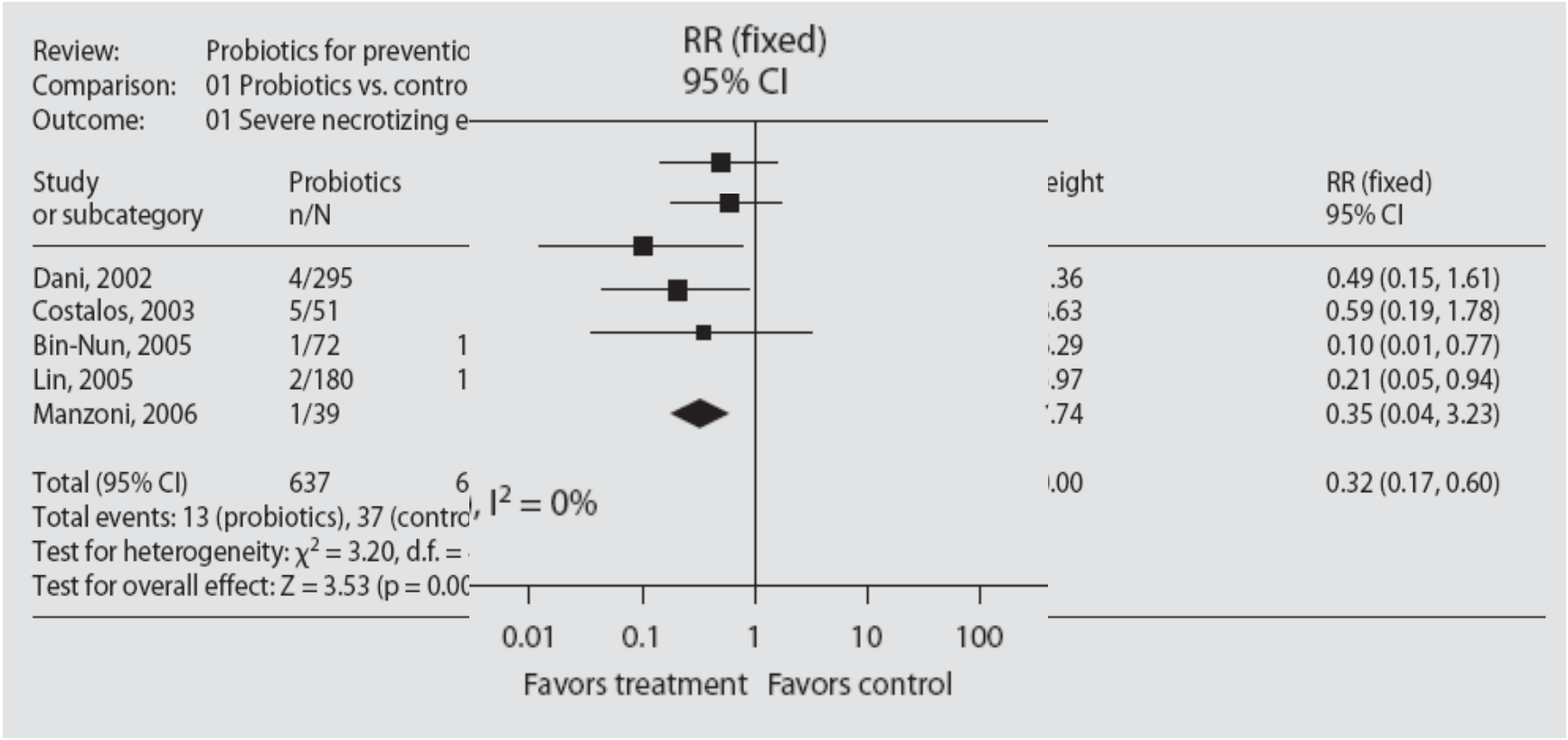
- A large randomized controlled trial is required to investigate the potential benefits and safety profile of probiotics spplementation in ELBW infants

BAlFaleh K, Bassler D; Cochrane Analysis 2008

Probiotics Reduce the Risk of Necrotizing Enterocolitis in Preterm Infants: A Meta-Analysis

Neonatology 2010;97:93–99

Reduce incidence and mortality



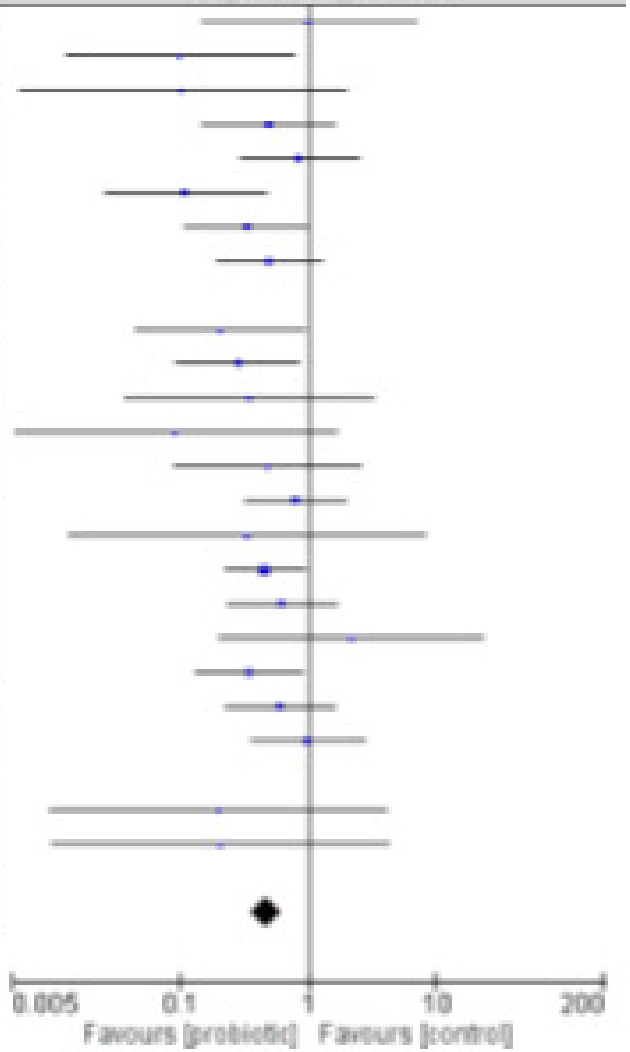
Prevention of necrotizing enterocolitis with probiotics: a systematic review and meta-analysis

PeerJ 2016

Sonja C. Sawh[1], Santosh Deshpande[1,*], Sandy Jansen[1,*], Christopher J. Reynaert[1,*] and Philip M. Jones[2,*]

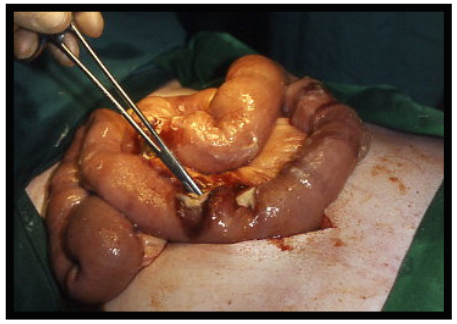
Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Hosni 2012	2	50	2	51	1.9%	1.02 [0.15, 6.96]
Bin-Nun 2005	1	72	10	73	1.7%	0.10 [0.01, 0.77]
Braga 2011	0	119	4	112	0.8%	0.10 [0.01, 1.92]
Dani 2002	4	295	8	290	4.9%	0.49 [0.15, 1.61]
Demirel 2013	6	135	7	136	6.1%	0.86 [0.30, 2.50]
Dilli 2015a	2	100	18	100	3.4%	0.11 [0.03, 0.47]
Dilli 2015b	4	100	12	100	5.7%	0.33 [0.11, 1.00]
Fernandez-Carrocera 2013	6	75	12	75	8.0%	0.50 [0.20, 1.26]
Kitajima 1997	0	45	0	46		Not estimable
Lin 2005	2	180	10	187	3.1%	0.21 [0.05, 0.94]
Lin 2008	4	217	14	217	5.8%	0.29 [0.10, 0.85]
Manzoni 2006	1	39	3	41	1.4%	0.35 [0.04, 3.23]
Manzoni 2014	0	238	5	247	0.8%	0.09 [0.01, 1.70]
Mihatsch 2010	2	91	4	89	2.5%	0.49 [0.09, 2.60]
Oncel 2014	8	200	10	200	8.4%	0.80 [0.32, 1.99]
Patole 2014	0	79	1	80	0.7%	0.34 [0.01, 8.16]
ProPrems 2013	11	548	24	551	13.9%	0.46 [0.23, 0.93]
Rojas 2012	6	176	10	184	7.0%	0.63 [0.23, 1.69]
Rouge 2009	2	45	1	49	1.2%	2.18 [0.20, 23.21]
Samanta 2009	5	91	15	95	7.3%	0.35 [0.13, 0.92]
Sari 2011	6	110	10	111	7.2%	0.61 [0.23, 1.61]
Serce 2013	7	122	7	122	6.7%	1.00 [0.36, 2.77]
Tewari 2015	0	61	0	59		Not estimable
Van Niekerk 2014a (HIV-exposed)	0	37	2	37	0.8%	0.20 [0.01, 4.03]
Van Niekerk 2014b (HIV-unexposed)	0	54	2	56	0.8%	0.21 [0.01, 4.22]
Total (95% CI)		**3279**		**3308**	**100.0%**	**0.47 [0.36, 0.61]**
Total events	79		191			

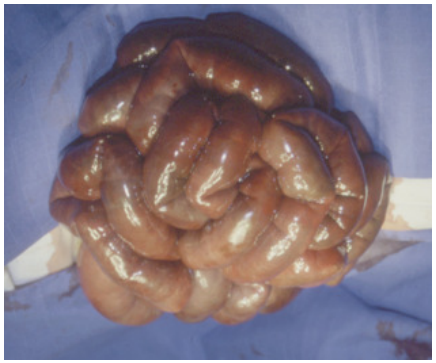
Heterogeneity: Tau² = 0.00; Chi² = 19.69, df = 22 (P = 0.60); I² = 0%
Test for overall effect: Z = 5.67 (P < 0.00001)



How live bacteria could prevent NEC

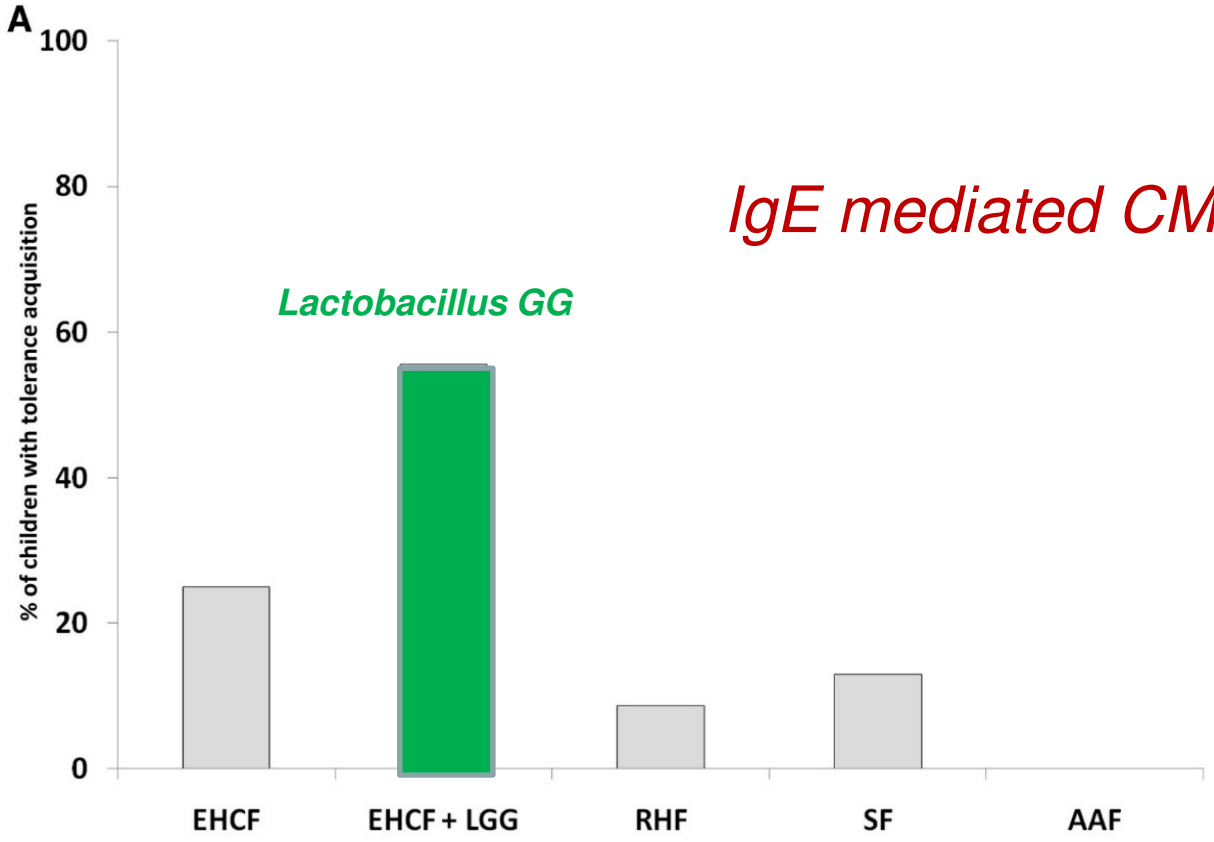
- Reduced colonization by pathogens (barrier effect)
- Increased intestinal barrier (permeability) to translocation of bacteria into the bloodstream
- Modification of the host response to microbial products (sensitization/immunization)
- Increased bacterial diversity of the microbiota
- Antiinflammatory effects of live bacteria (probiotics)





Formula Selection for Management of Children with Cow's Milk Allergy Influences the Rate of Acquisition of Tolerance: A Prospective Multicenter Study

Rate of patients acquiring tolerance after 12 months of exclusion diet with different formulas



Berni Canani R et al. J Pediatr 2013; 163: 771-7.

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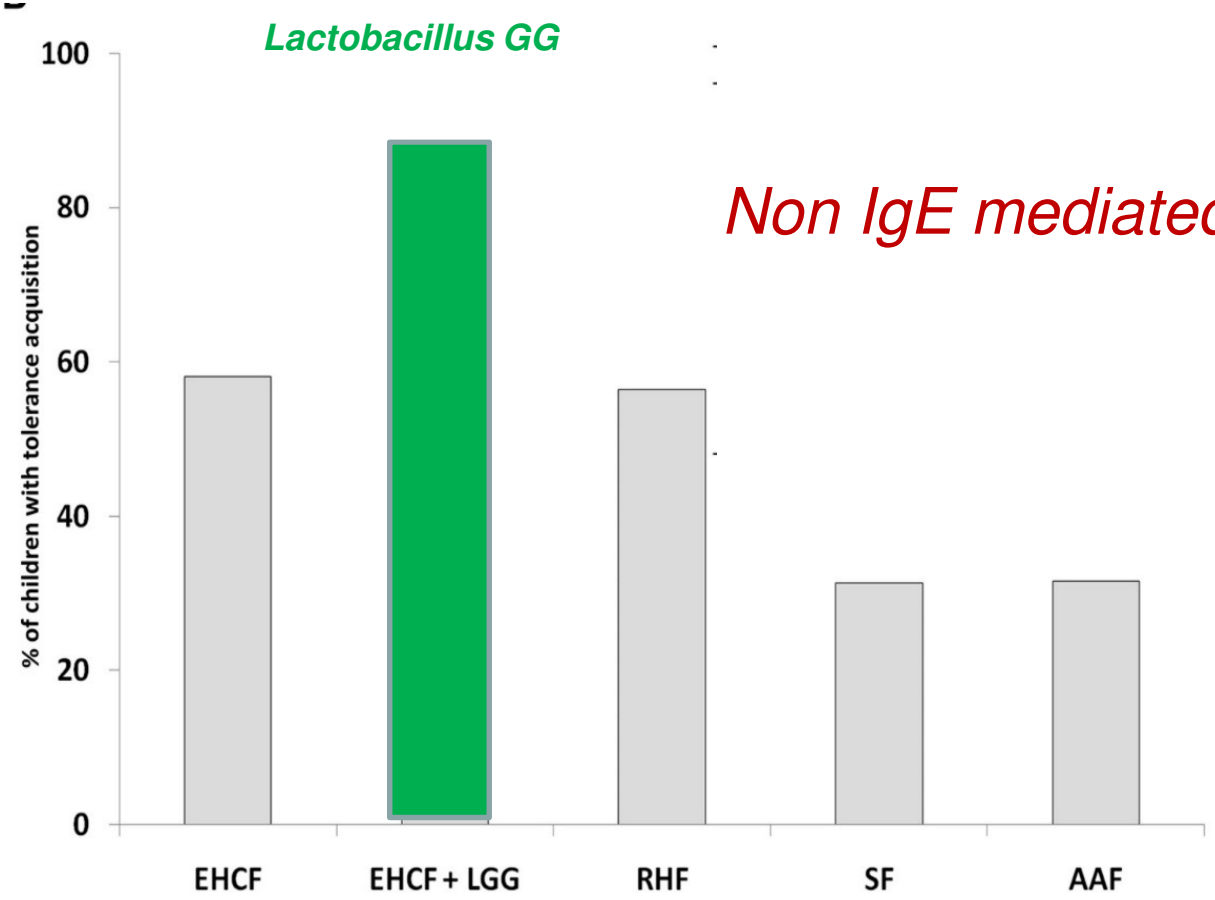
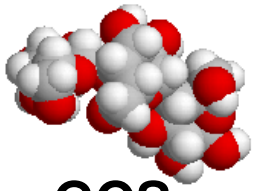


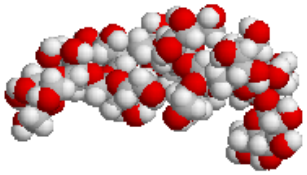
Non IgE mediated

Berni Canani R et al. J Pediatr 2013; 163: 771-7.

Prebiotics



GOS



FOS

Definition

Non assimilable food ingredient that has a beneficial effect in humans or animals by stimulating selectively one or more bacterial species of the intestinal microbiota

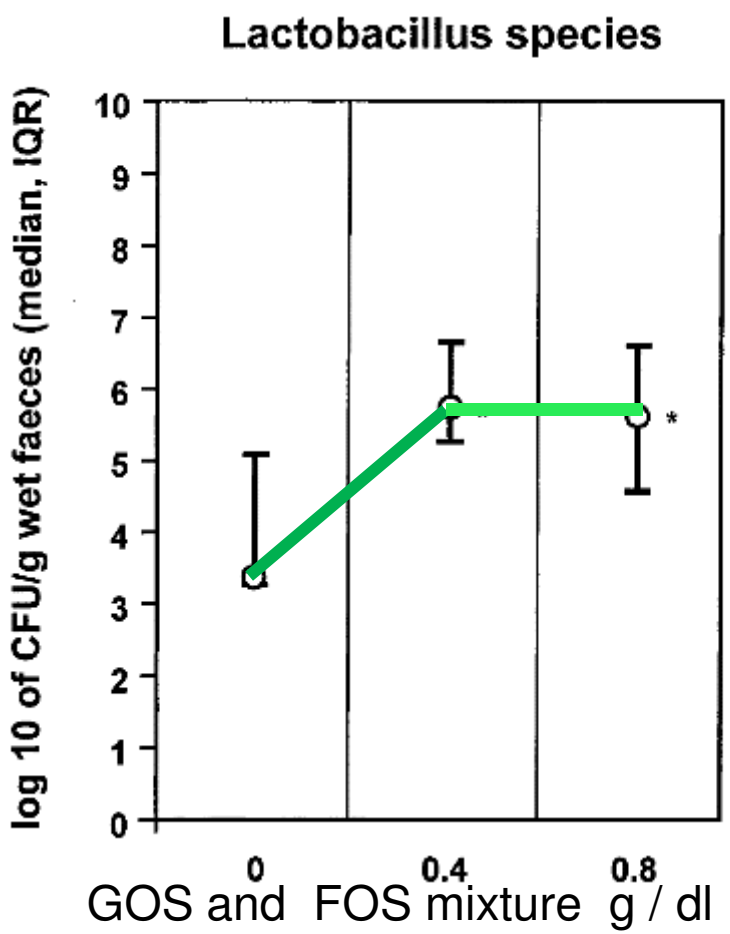
Gibson et Roberfroid 1995

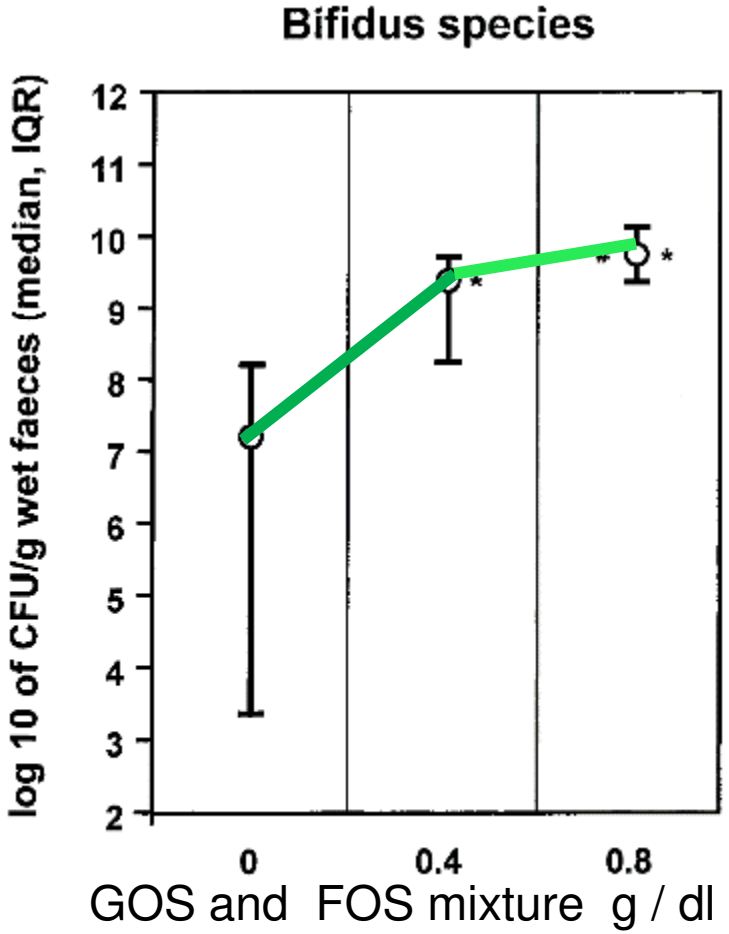
Results of metanalysis

Journal	Pre/Pro/Syn	Studies	RR	CI 95%	Target
Cochrane DBSR 2007	Prebiotic Full term	7 studies 2 studies Allergy	0.42 1.62	**0.21 – 0.84** 0.62 – 4.26	**Positive Eczema** NS
Arch Pediatr Adol Med 2009	**Prebiotic Full term**	**24 studies N= 1459**	**0.65**	**-0.76 - -0.54**	**Increased Bifidobacteria & Lactobacilli**
Nur J 2012	Pre-Pro-Syn	12 Pre studies N=1563	NS	NS	Stool frequency
Cochrane DBSR 2013	**Prebiotics**	**4 studies**	**0.68**	**0.48 _ 0.97**	**Allergy/eczema**
Clin Nutr 2013	Prebiotics Preterm < 37s	5 studies N = 345	1.24	0.56 – 2.72	Prevention of NEC & sepsis
J Int Med Res 2013	**Pre-Pro-Syn**	**3 studies Prebiotics**	**0.80**	**0.54 – 1.18**	**Eczema**

Dosage-Related Bifidogenic Effects of Galacto- and Fructooligosaccharides in Formula-Fed Term Infants

*G. Moro, *I. Minoli, †M. Mosca, ‡S. Fanaro, §J. Jelinek, §B. Stahl, and §G. Boehm





O.Goulet 2016

Journal of Pediatric Gastroenterology and Nutrition
34:291–295 © March 2002 Lippincott Williams & Wilkins, Inc., Philadelphia

Prebiotics (*GOS/FOS*) in infancy

Formula-fed infants with GOS/FOS mixture

- *Increase Bifidobacteria*
- *Decrease of pathogens*
- *Decrease stool pH*
- *Increase secretory IgA*
- *Reduce atopic disease*
- *Reduce rate of infection*
- *Improve stool consistency*

reproducing an intestinal situation very similar to breast fed infants

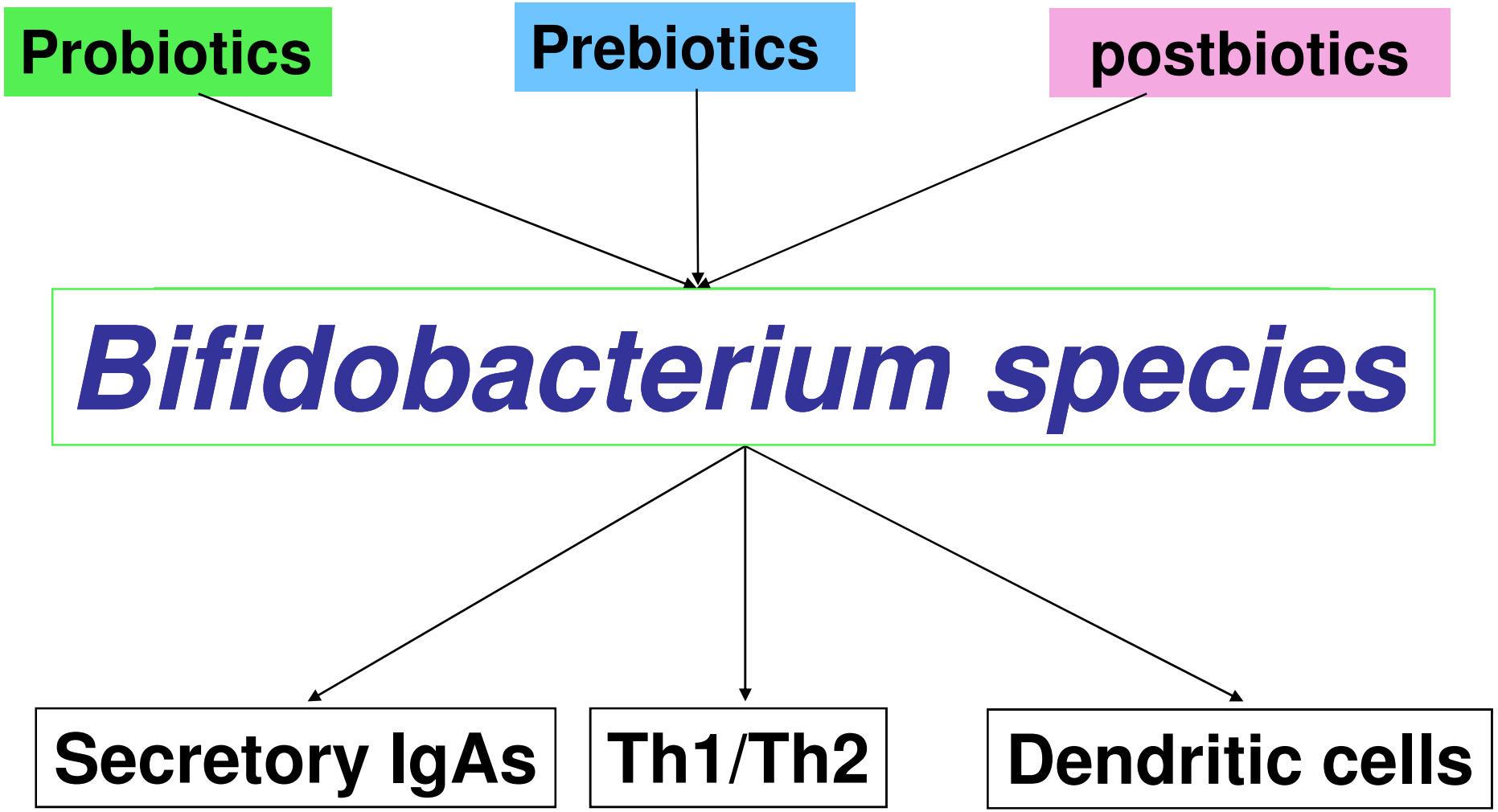
Fermentation products / postbiotics

Bifidobacterium breve C50* and *Streptococcus thermophilus

- **Immune properties**

- **Reviewed** *in Granier et al Pediatr Res 2013;74: 238*
- **Clinical benefits**
  - **IgA response to polio vaccin** (Mullie et al Ped Res 2004)
  - **Pevention of gastroenteritis** (Thibault et al JPGN 2004)
  - **Enhance thymus size** (Indrio et al Pediatr Res 2007)
  - **Reduce inflammation** (Campeotto et al Br J Nutr 2011)
  - **Prevention of allergy** (Morisset et al Eur J Clin Nutr 2011)
  - **GI symptoms in infants** (van de Heijning et al, Nutients 2014

Microbiota modulation in infants formula feeding



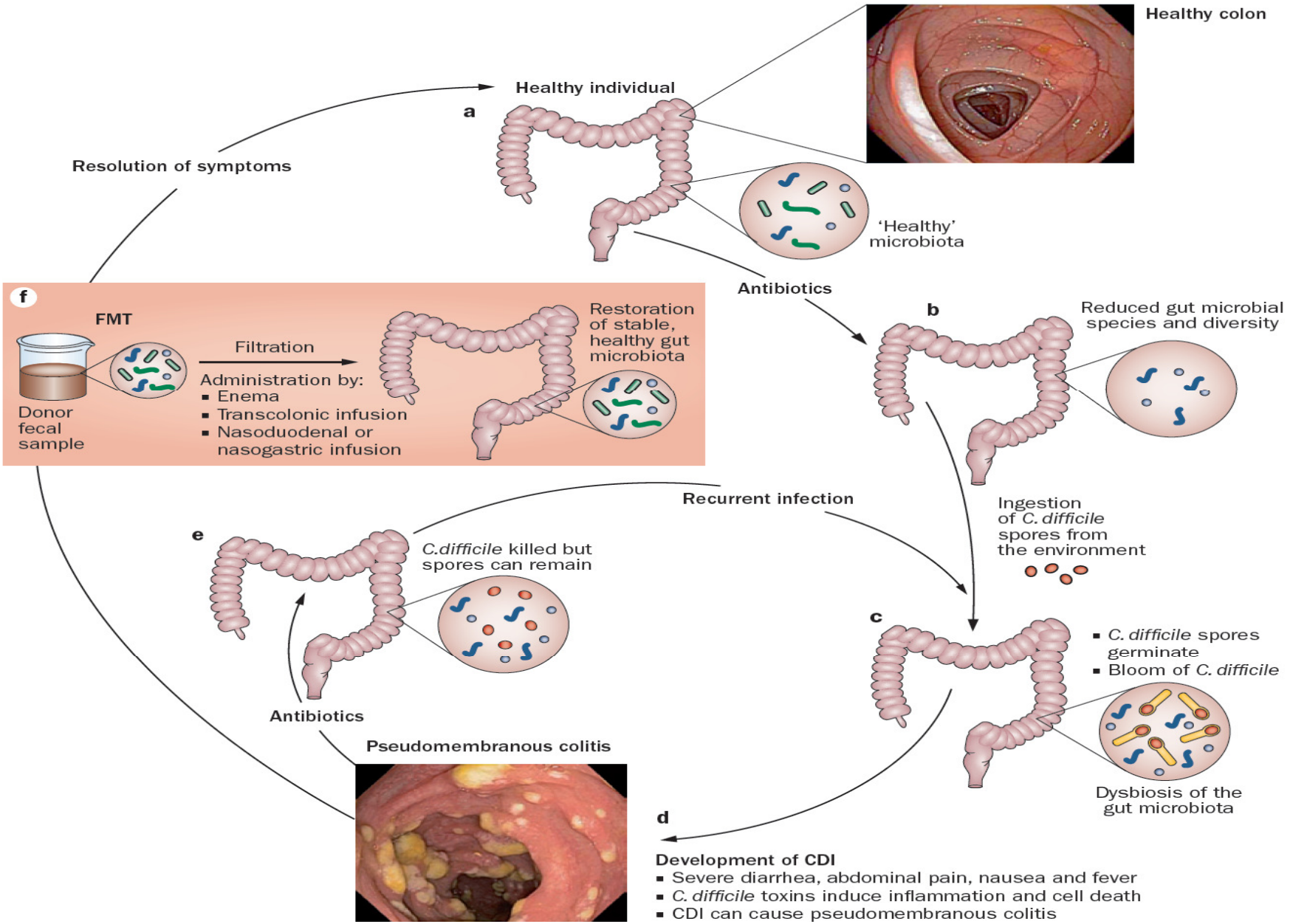
Fecal microbiota transplantation: current status and future directions

Expert Rev. Gastroenterol. Hepatol. 5(6), 653–655 (2011)

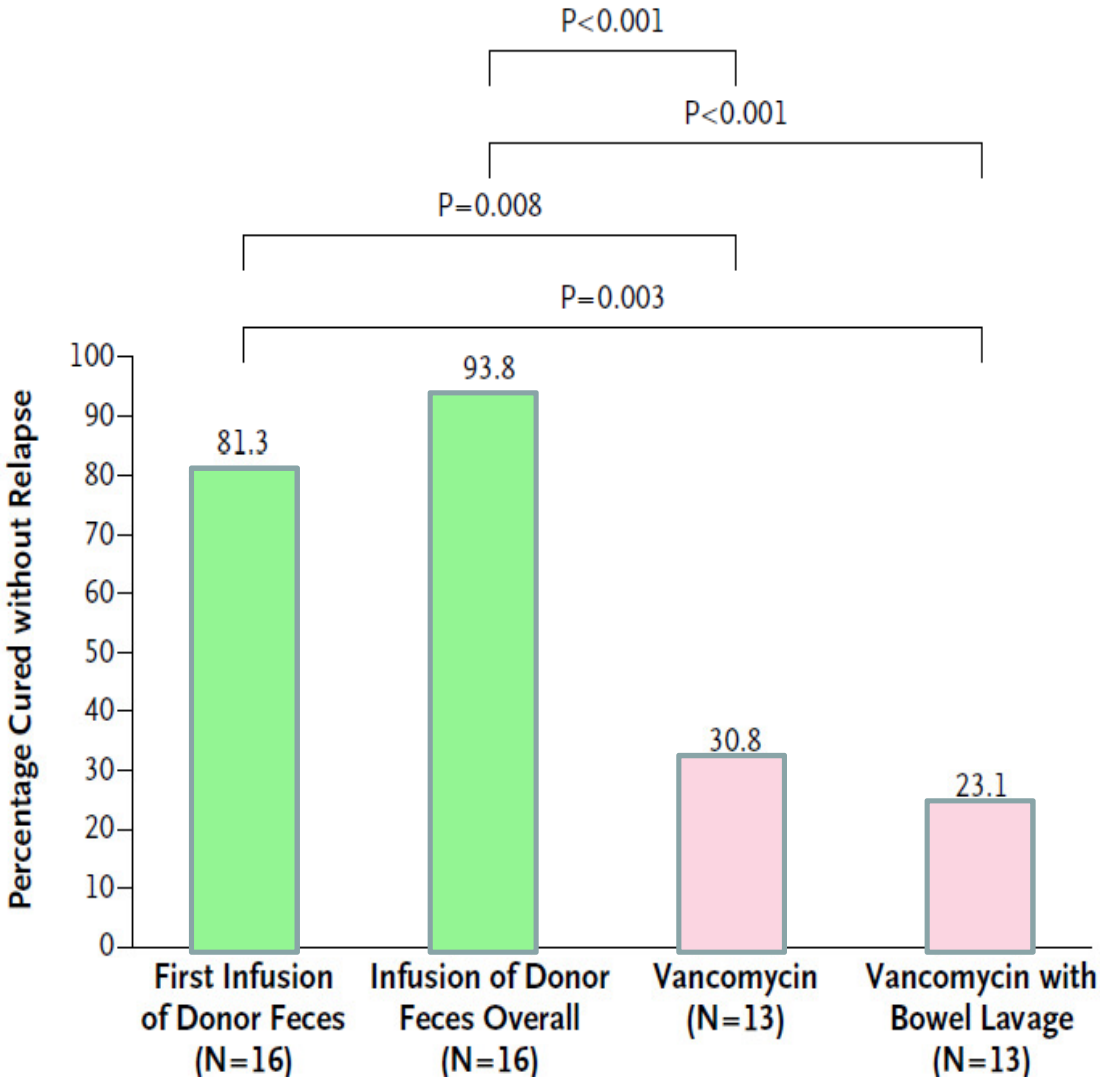
"Fecal microbiota transplantation is likely to feature prominently in the treatment of both relapsing and severe *Clostridium difficile* colitis."

"The challenge now is to capitalize on these early observations and determine whether fecal microbiota transplantation can be positioned as an adjunct therapy in ulcerative colitis to further improve our patients' quality of life."

Intestinal microbiota is a new and fascinating organ that can be transplanted both in animals and humans



Fecal transplantation for resistant CD infection
FT *vs* oral Vancomicine



Van Nood N et. al. NEJM 2013

Intestinal microbiota the first 1000 days

Messages

- The development of the human infant intestinal microbiota is a sequential process that begins *in utero* and continues during the first 2 to 3 years of life.
- Microbial *composition* and *diversity* are shaped by host genetics and multiple environmental factors, of which diet is an important contributor

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Intestinal microbiota the first 1000 days

Messages

- Microbiota implementation is a crucial process, as an early « programming »
- Development and maturation of the GI tract are influenced by gut microbiota
- In turn, early feeding, by influencing microbiota ***(Bifidobacteria)*** is a key issue

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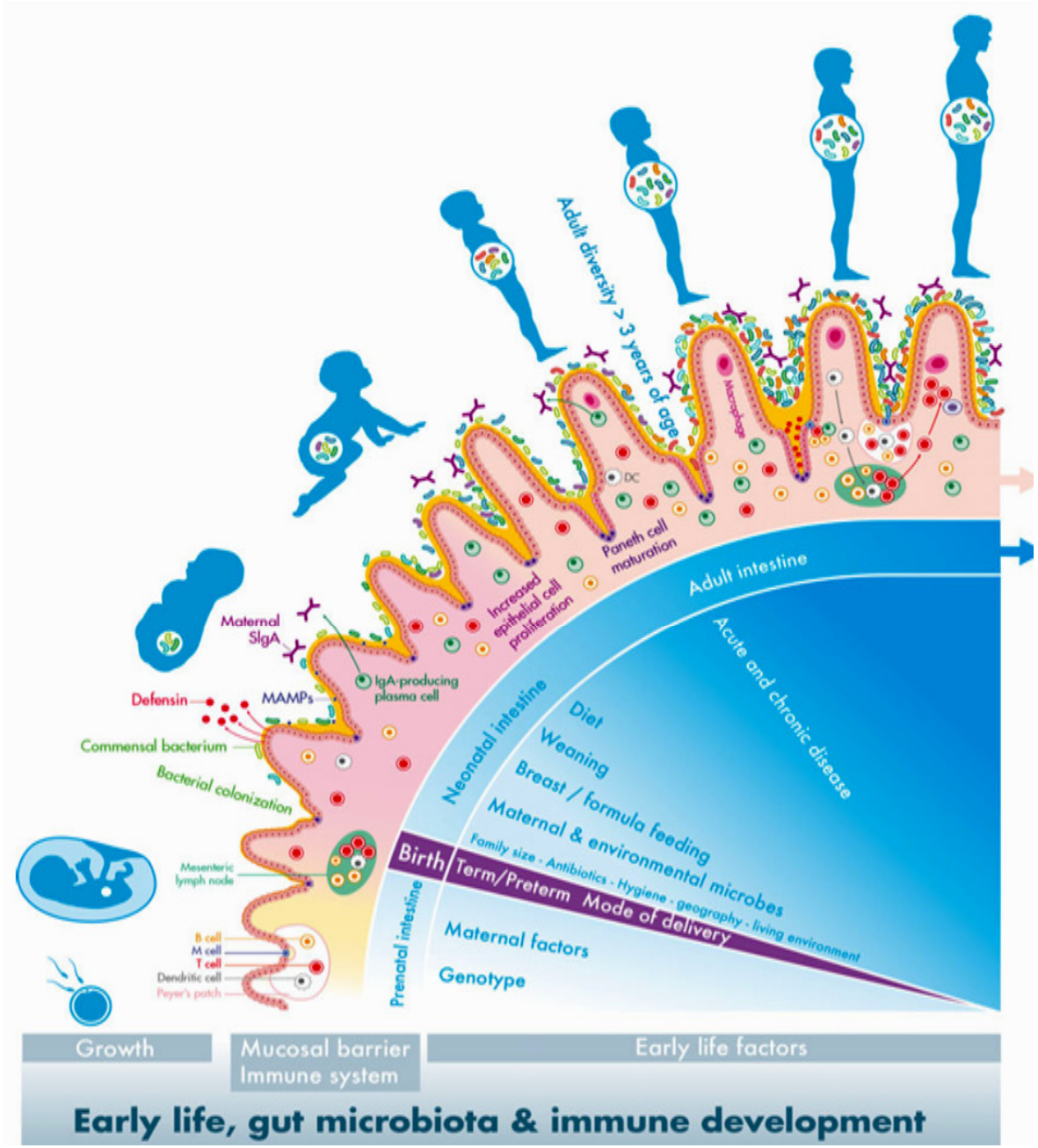
Intestinal microbiota the first 1000 days

- Gut bacteria are known to regulate the gut and systemic immune system via a variety of molecular mechanisms
- Disturbances and imbalances in the microbiota may be a contributory factor to immune-mediated disease such as IBD or allergy
- Modulation of microbiota is a promising strategy for treating dysbiosis

Wallace TC et al. Human gut microbiota and its relationship to health and disease. Nutr Rev. 2011;69(7):392-403.
Mondot S, et al The human gut microbiome and its dysfunctions. Dig Dis. 2013;31(3-4):278-285.
Weng M, Walker WA. The role of gut microbiota in programming the immune phenotype. J Dev Orig Health Dis. 2013;4(3):203-214.
Arrieta MC et al. The intestinal microbiome in early life: health and disease. Front Immunol. 2014; 5: 427-45



The first 1000 days establish a symbiosis

Wopereis H et al.
Pediatr Allergy Imunnol 2014

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Muchas gracias

Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

Centre des Mardi.org
Le portail des maladies rares digestives

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

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