Journée Européenne d'Information sur les Antibiotiques

Journée régionale sur le bon usage des antibiotiques
Jeudi 17 novembre 2020

Microbiote et impact en santé humaine

Pr. Vincent CATTOIR

Service de Bactériologie-Hygiène hospitalière, CHU de Rennes
CNR de la Résistance aux Antibiotiques (laboratoire associé « Entérocoques »)
Faculté de Médecine & Unité Inserm U1230, Université de Rennes 1
Section des Agents Anti-Infectieux et Comité de l'Antibiogramme de la SFM

CHU Rennes — CNR Résistance aux Antibiotiques — Université de Rennes 1 — Inserm La science pour la santé From science to health — FRM Fondation Recherche Médicale — Rennes Ville & Métropole — sfm Société Française de Microbiologie

Recherche en pleine explosion

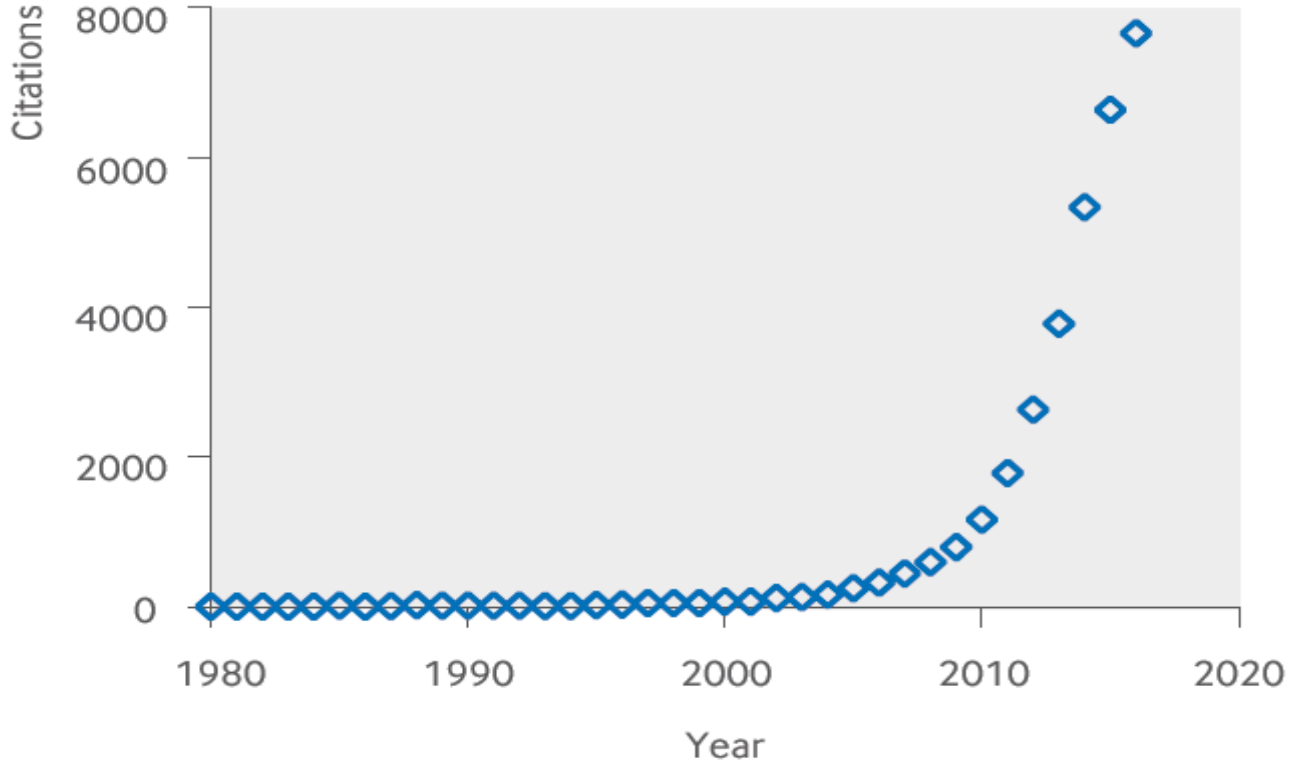
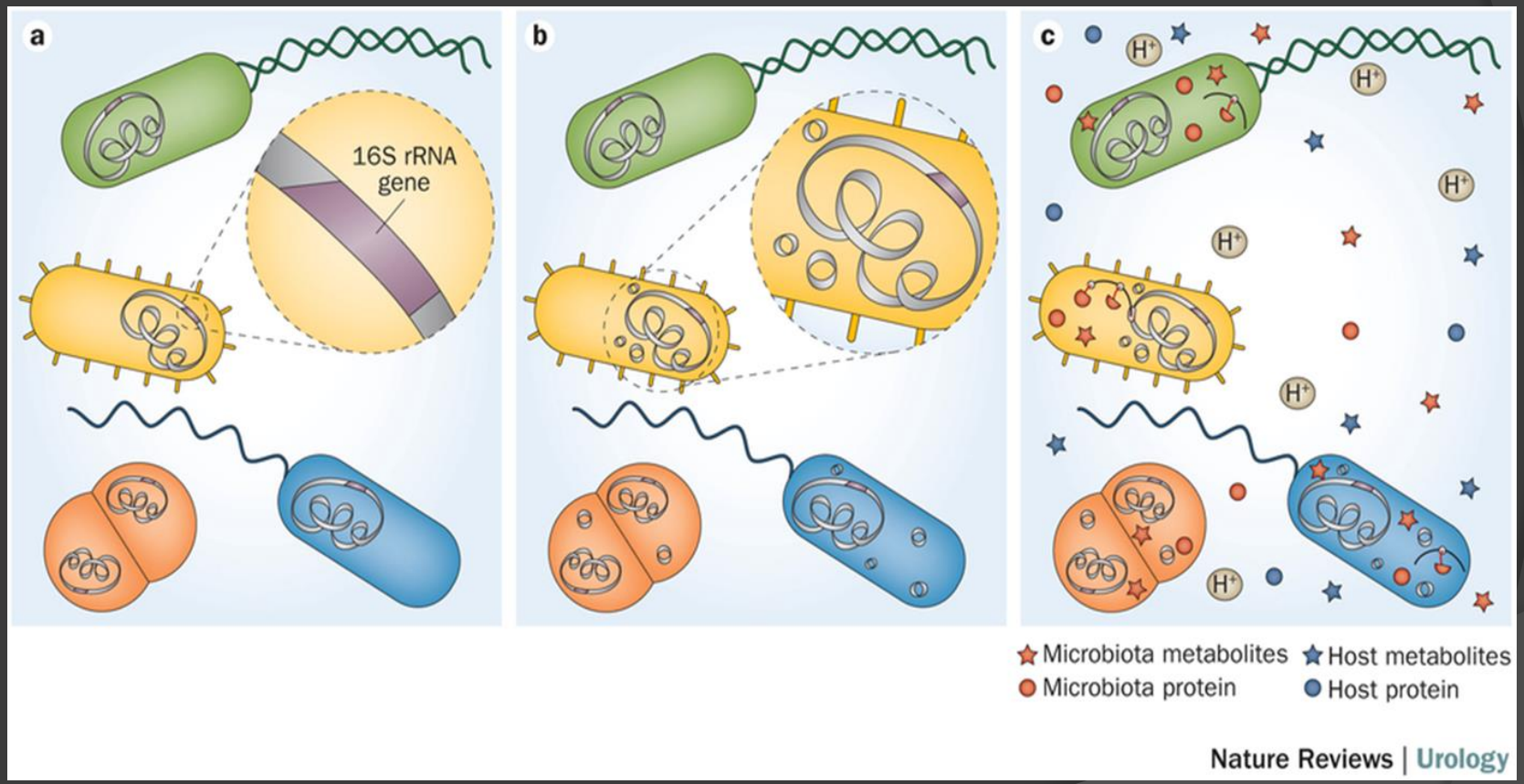


Fig 1| Increase in publications on the microbiome. When the search term "microbiome" was used to query PubMed from 1980 to 2016 an exponential increase in publications was seen in the past decade

Young VB, BMJ 2017

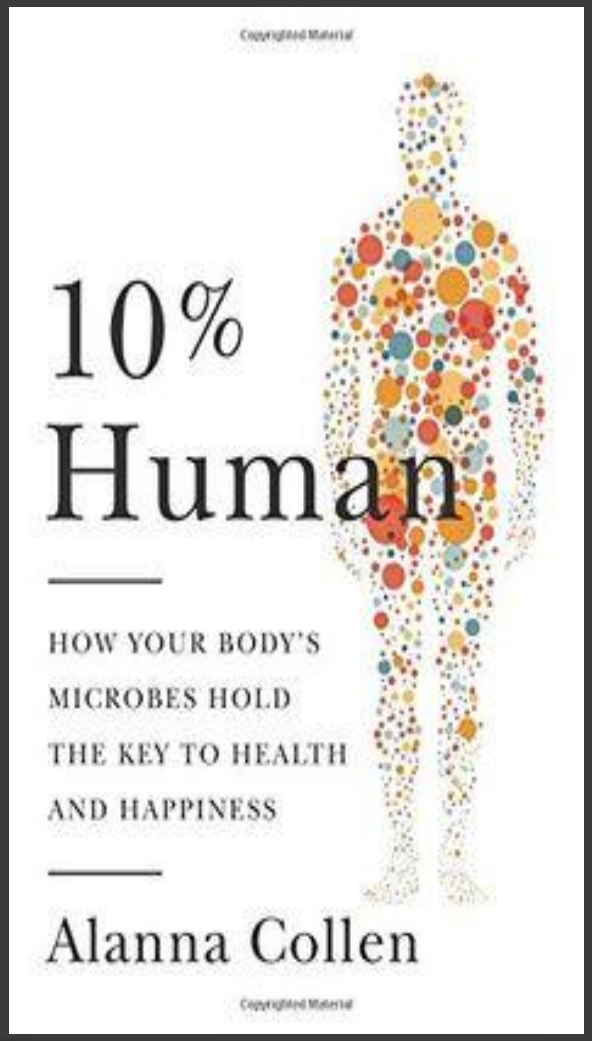
Microbiote & Microbiome

ARNr 16S | Microbiote | Microbiome



Whiteside et al., Nat Rev Urol 2015

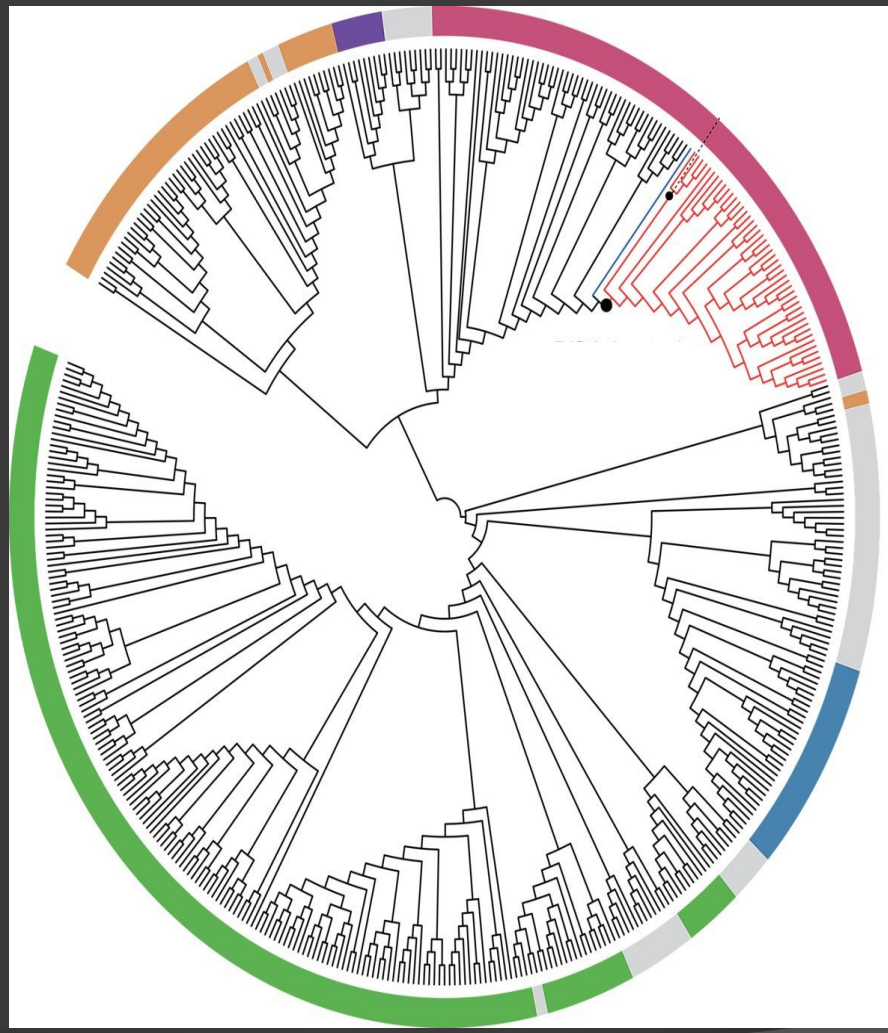
Microbiote humain



10^{14} bactéries, soit :

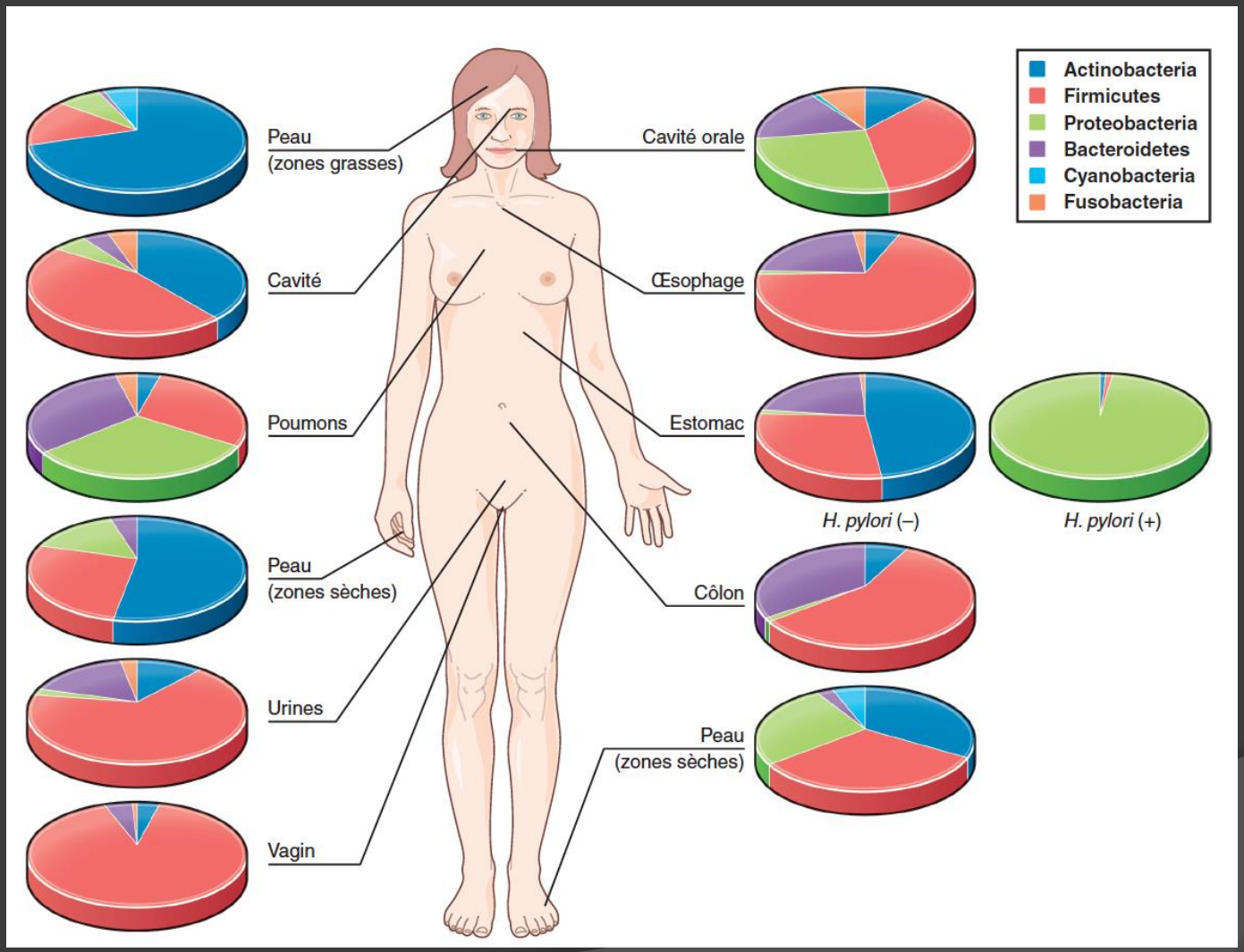
- 10 x plus que de cellules humaines
- 1-3 % du poids (1-2 kg)
- >1000 espèces différentes
- 100 x plus de gènes bactériens
- **1 microbiote unique / individu**

Phyla bactériens

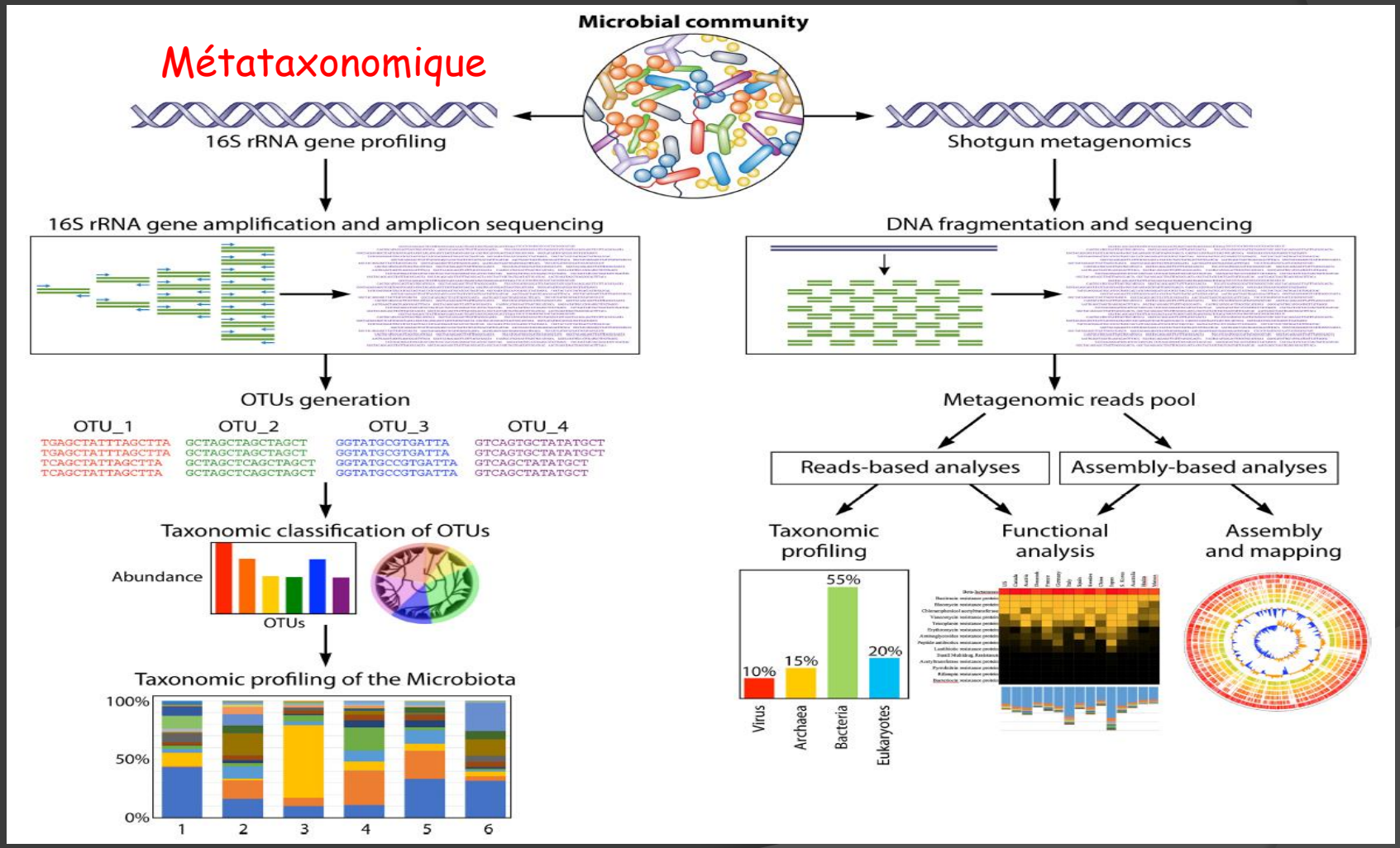


	Actinobacteria	*Actinomyces, Corynebactrium, Mycobacterium, Tropheryma, Propionibacterium, Bifidobacterium, Gardnerella, Atopobium*
	Bacteroidetes	*Bacteroides, Porphyromonas, Prevotella, Capnocytophaga*
	Cyanobacteria	
	Firmicutes	*Bacillus, Listeria, Staphylococcus, Enterococcus, Lactobacillus, Streptococcus, Clostridium, Eubacterium, Coprococcus, Roseburia, Faecalibacterium, Ruminococcus, Peptostreptococcus*
	Proteobacteria	(β) *Bordetella, Burkholderia, Neisseria* (ε) *Campylobacter, Helicobacter* (γ) *Aeromonas, Enterobacteriaceae, Legionella, Haemophilus, Acinetobacter, Pseudomonas, Vibrio*
AUTRES	Fusobacteria	*Fusobacterium*
	Spirochaetes	*Leptospira, Treponema*
	Tenericutes	*Mycoplasma, Ureaplasma*
	Verrumicrobia	*Akkermansia*

Microbiotes

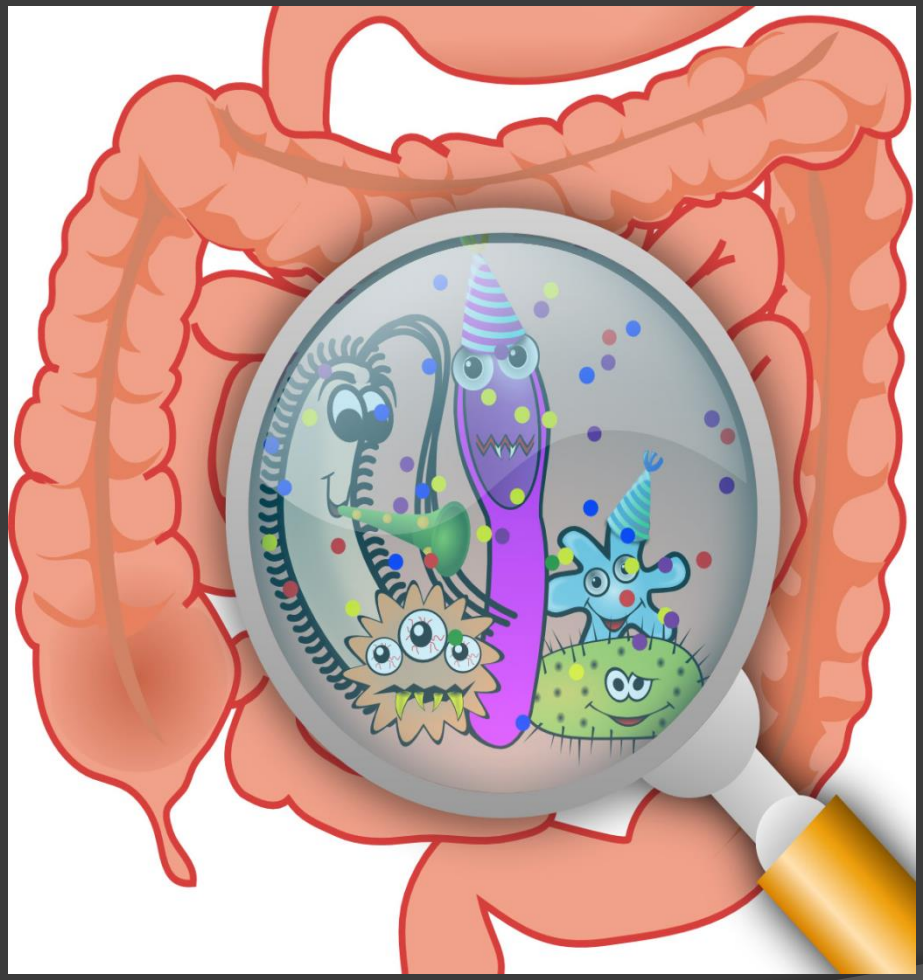


Métagénomique



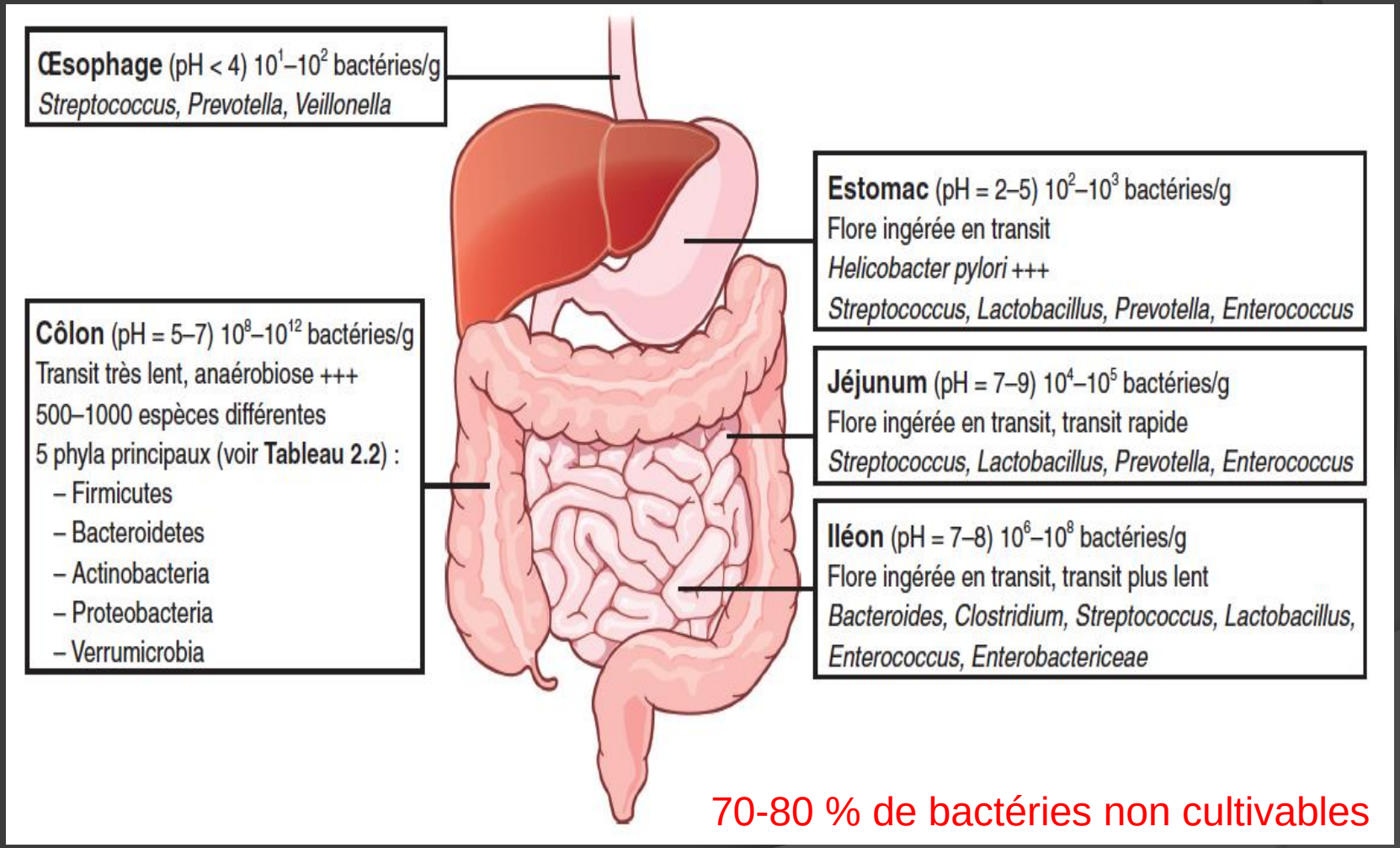
Milani et al., Microbiol Mol Biol Rev 2017

Tube digestif de l'homme



- 1er organe immunitaire (60-70 % des cellules de l'immunité)
- 2nd cerveau (100-200 millions de neurones)
- Surface énorme (400 m^2)

Microbiote intestinal

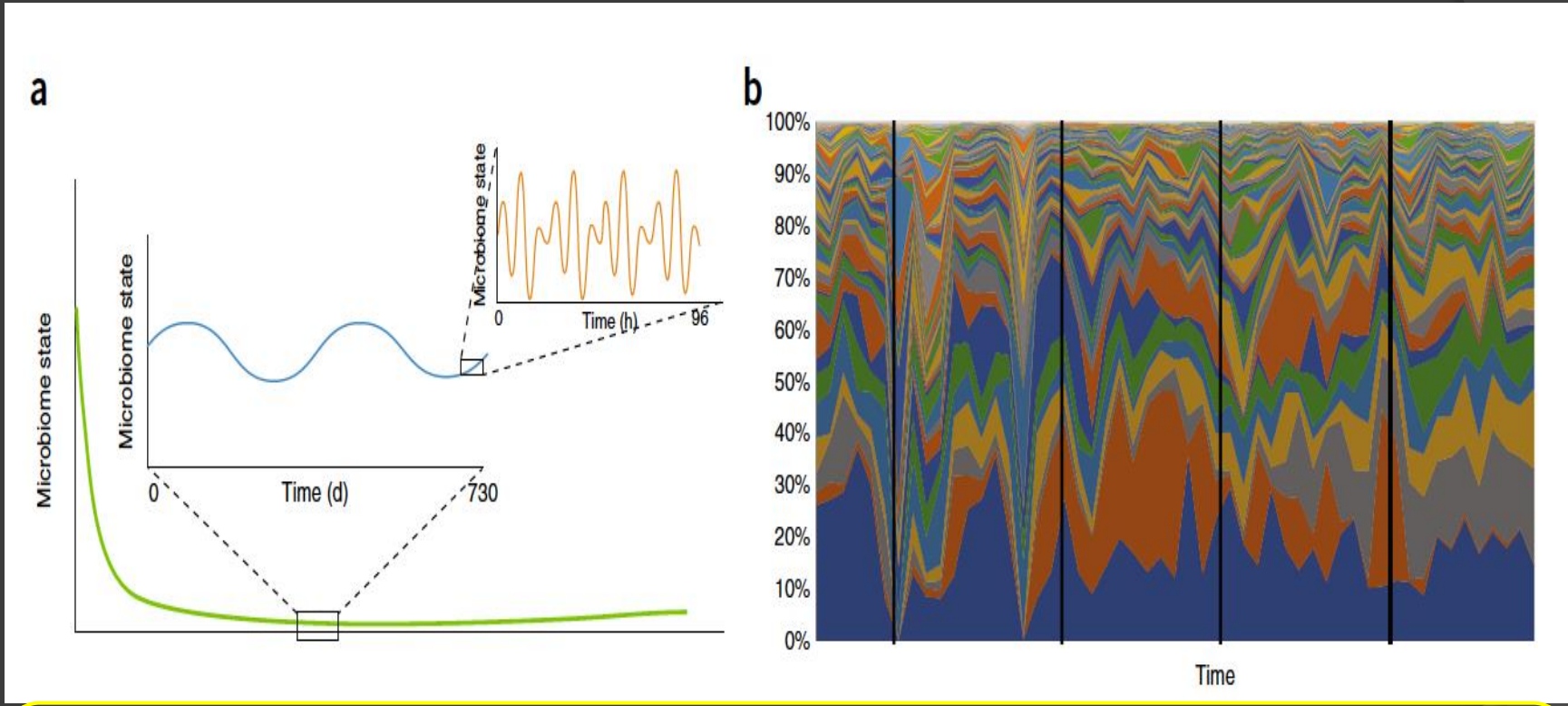


70-80 % de bactéries non cultivables

Espèces du microbiote intestinal

Phyla	Genres (espèces principales)
Firmicutes	*Ruminococcus* (*R. albus, R. flavefaciens, R. gnavus, R. torque*) *Coprococcus* (*C. eutactus*) *Anaerotruncus* (*A. colihominis*) *Clostridium* (*C. coccoides, C. hylemonae, C. methylpentosum*) *Eubacterium* (*E. rectale*) *Lactobacillus* *Butyrivibrio* (*B. crossotus*) *Faecalibacterium* (*F. prausnitzii*) *Roseburia* (*R. intestinalis*) *Veillonella* *Streptococcus* *Enterococcus*
Bacteroidetes	*Bacteroides* (*B. uniformis, B. thetaiotaomicron*) *Prevotella* (*P. copri*) *Xylanibacter*
Actinobacteria	*Collinsella* *Atopobium* *Bifidobacterium*
Proteobacteria	*Escherichia* (*E. coli*) *Desulfovibrio* *Helicobacter* (*H. pylori*)
Verrumicrobia	*Akkermansia*

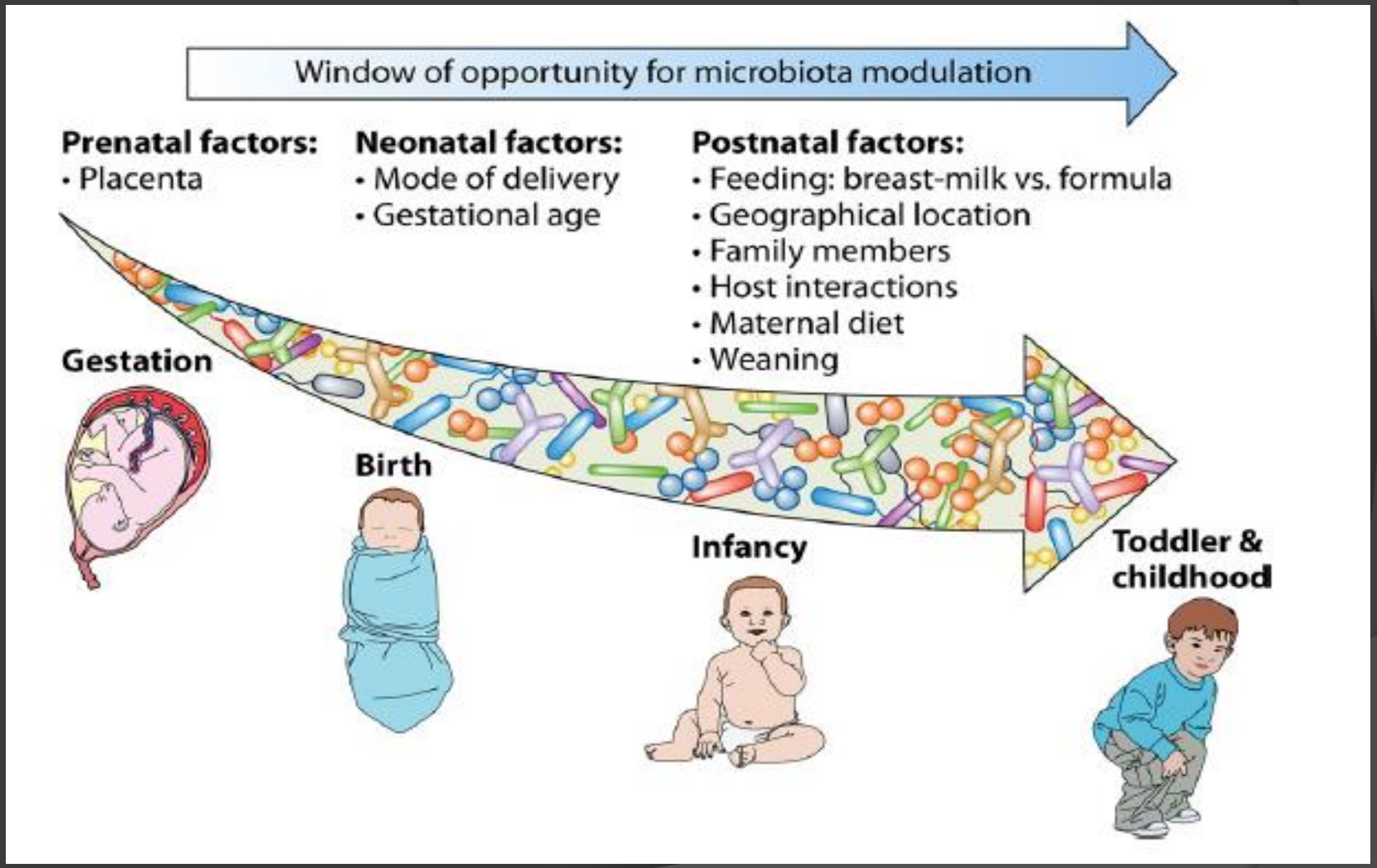
Dynamique du microbiote



Microbiote mâture vers l'âge de 3 ans
Microbiote stable chez l'adulte (sain) avec résilience
Microbiote qui se modifie chez les patients âgés

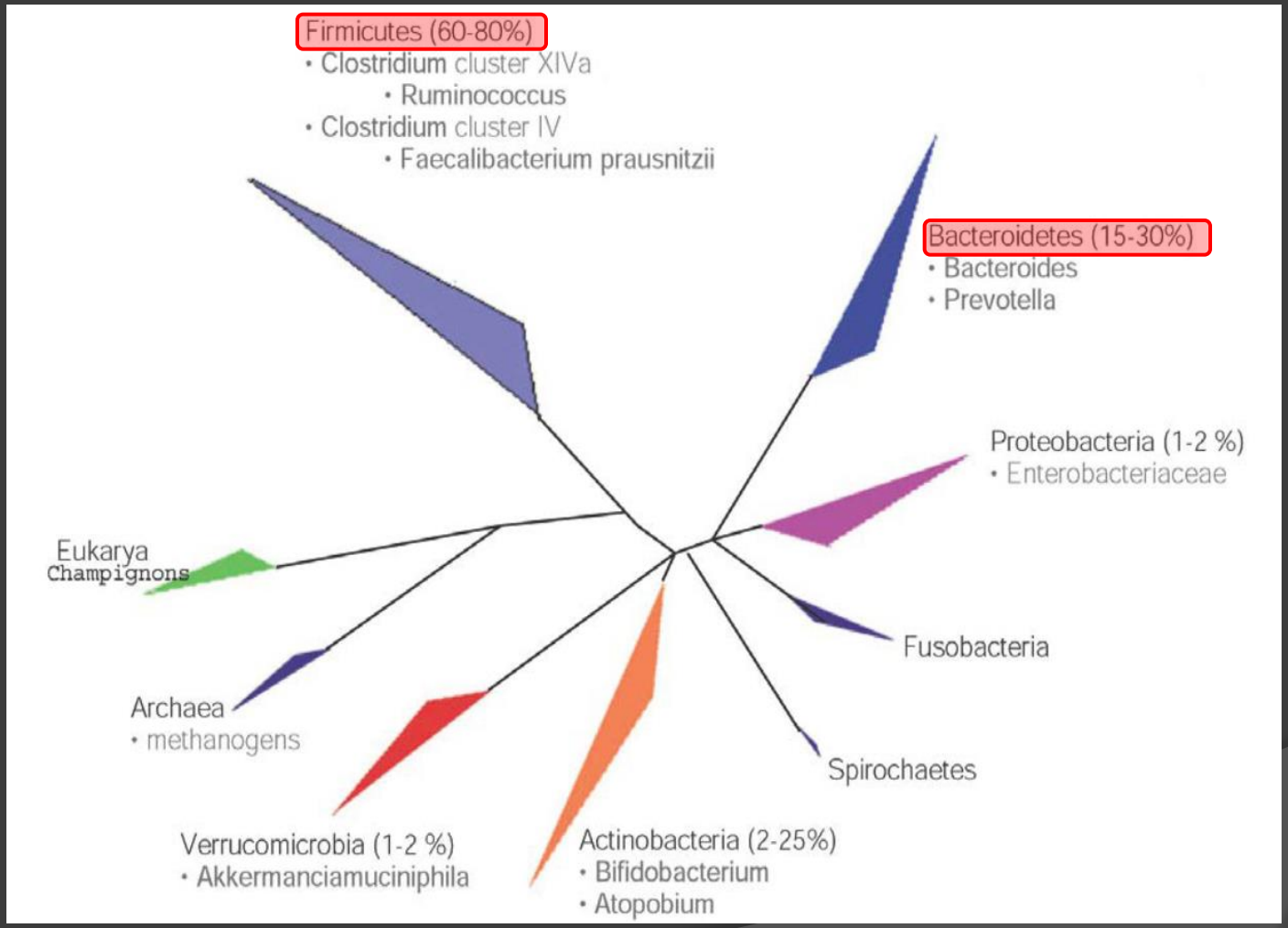
Gilbert et al., Nat Med 2018

Maturation du microbiote



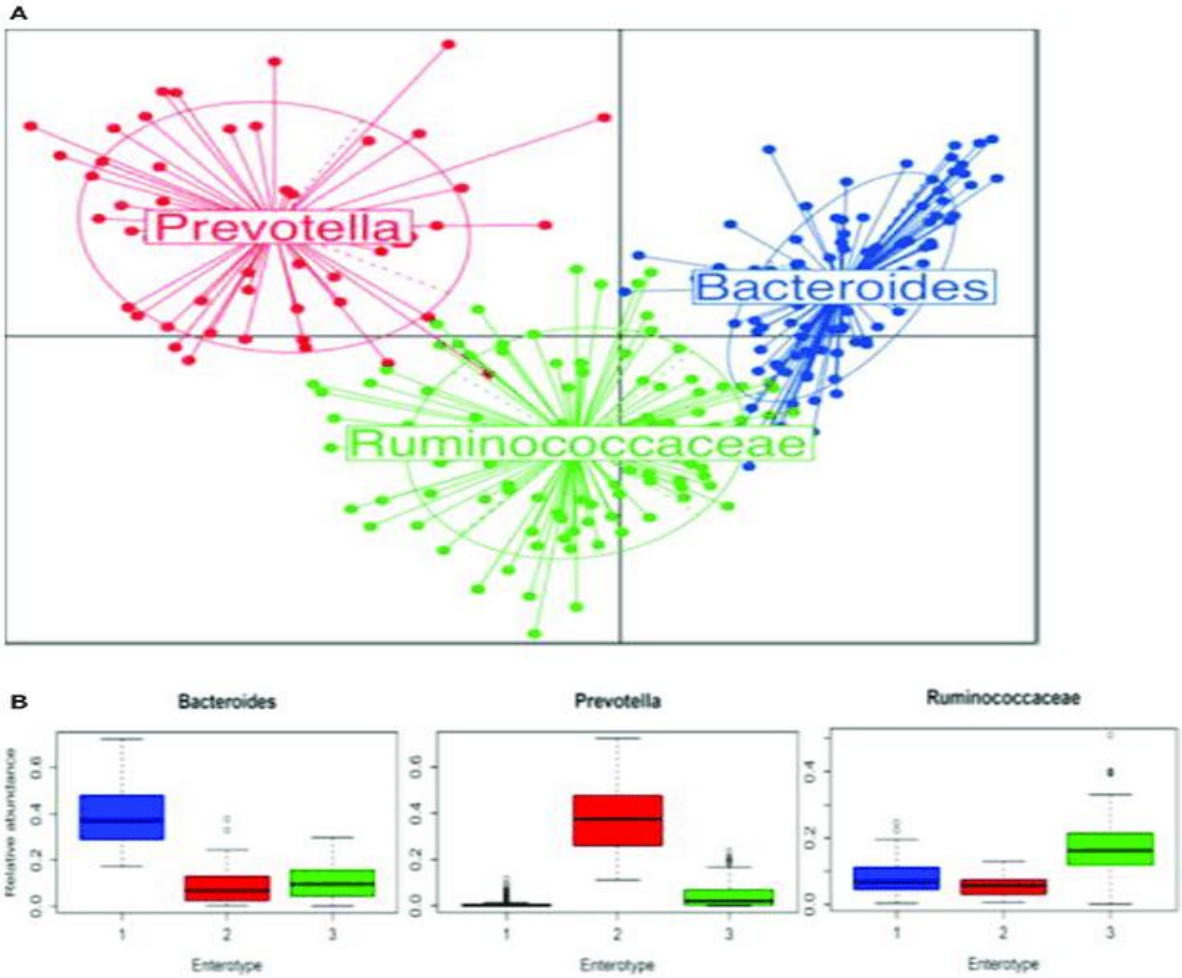
Milani et al., Microbiol Mol Biol Rev 2017

Microbiote adulte 'normal'



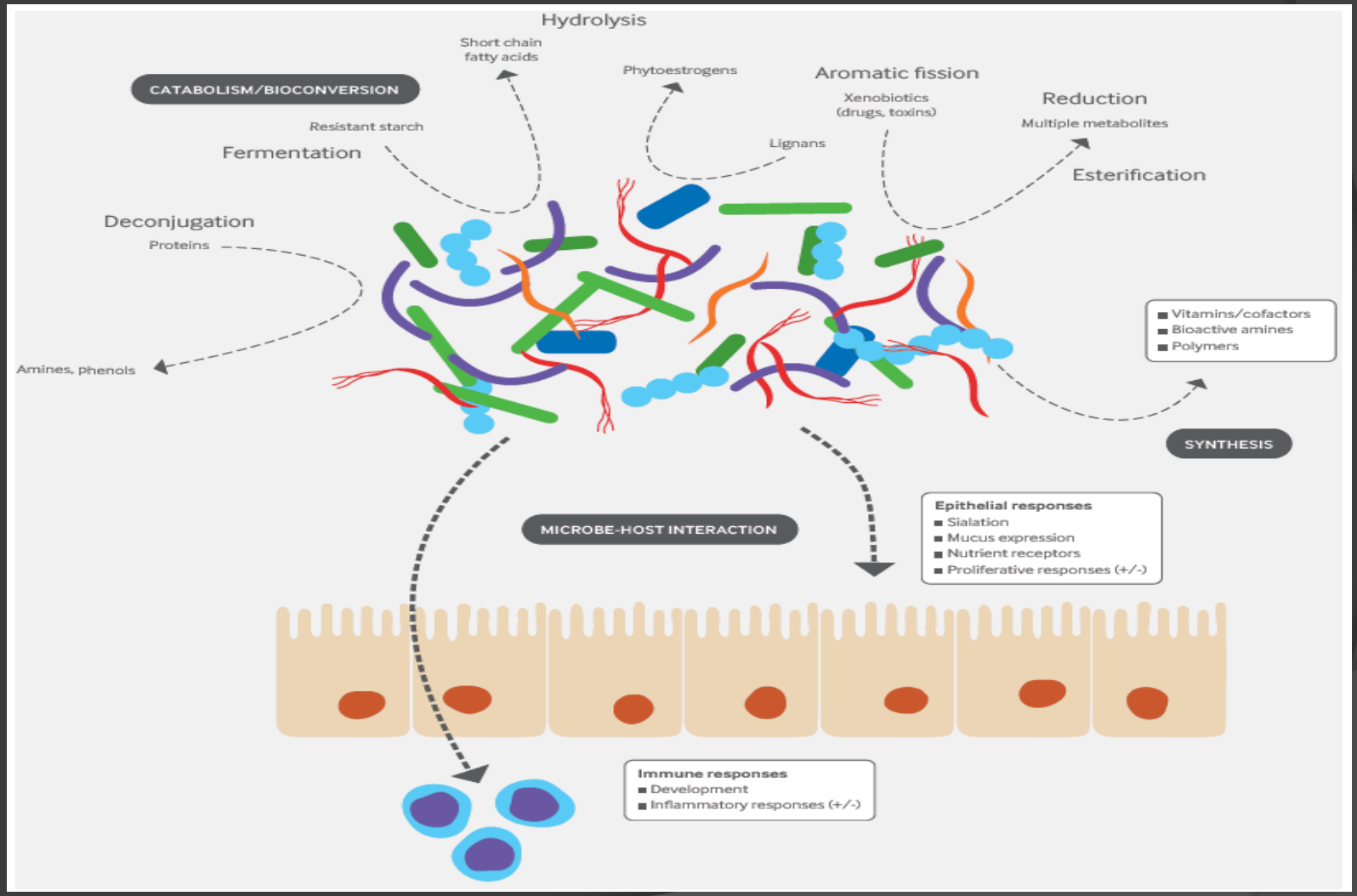
Cherbuy et al., Innov Agron 2013

Entérotypes



Arumugam et al., Nature 2011

Rôles du microbiote intestinal



Young VB, BMJ 2017

Facteurs influençant le microbiote

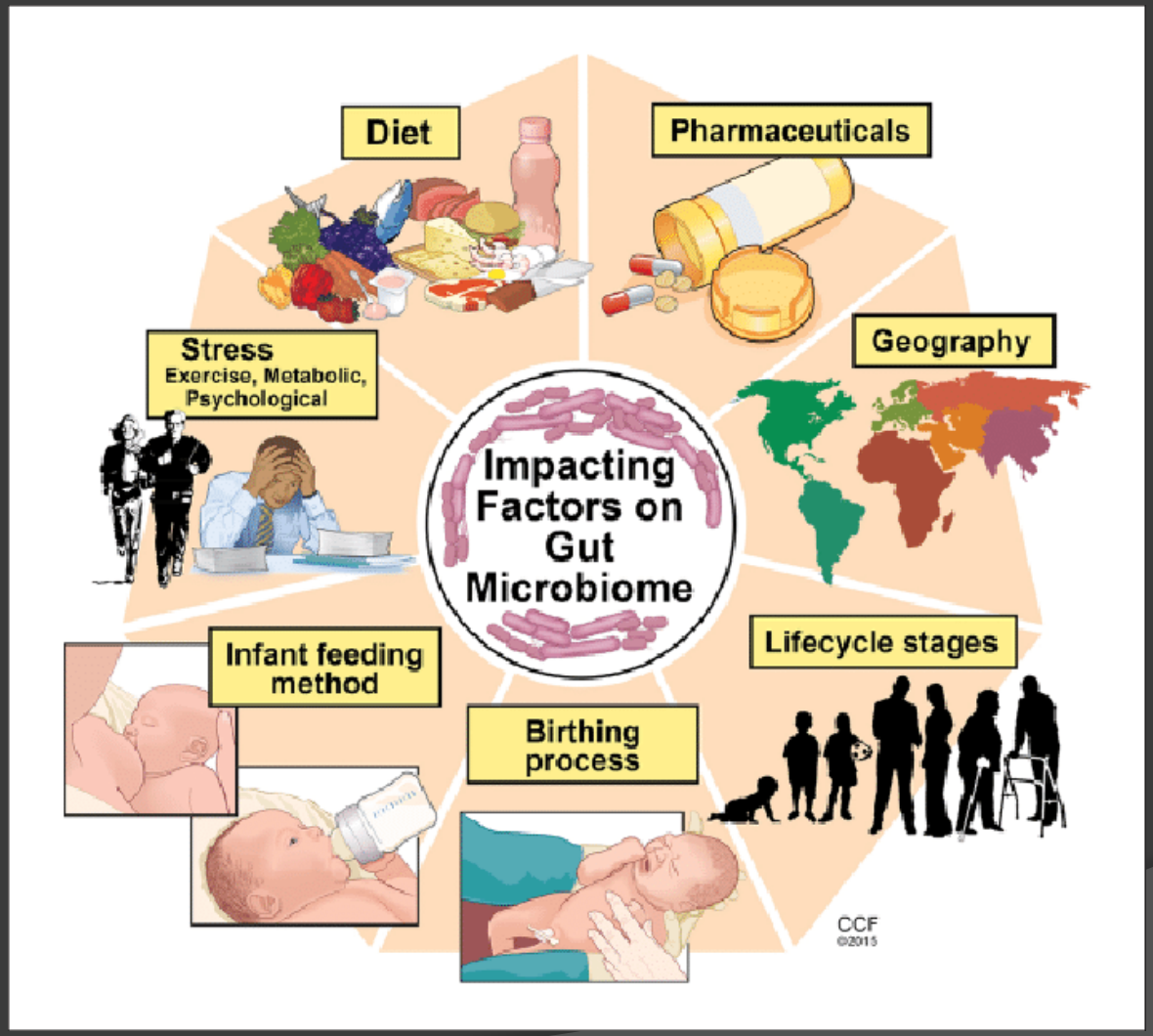
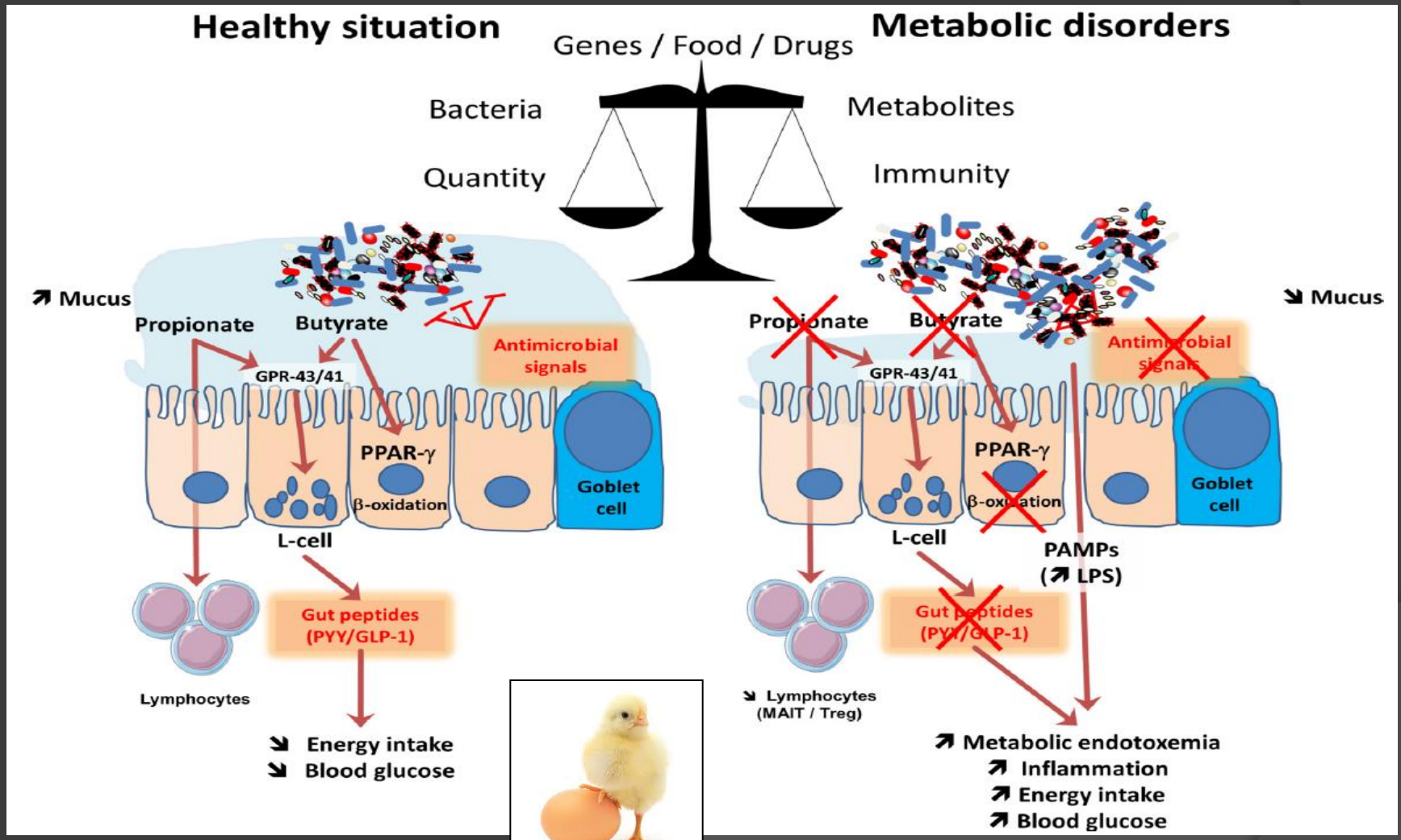


Illustration by David Schumick, BS, CMI

Dysbiose



Cani PD, Gut 2018

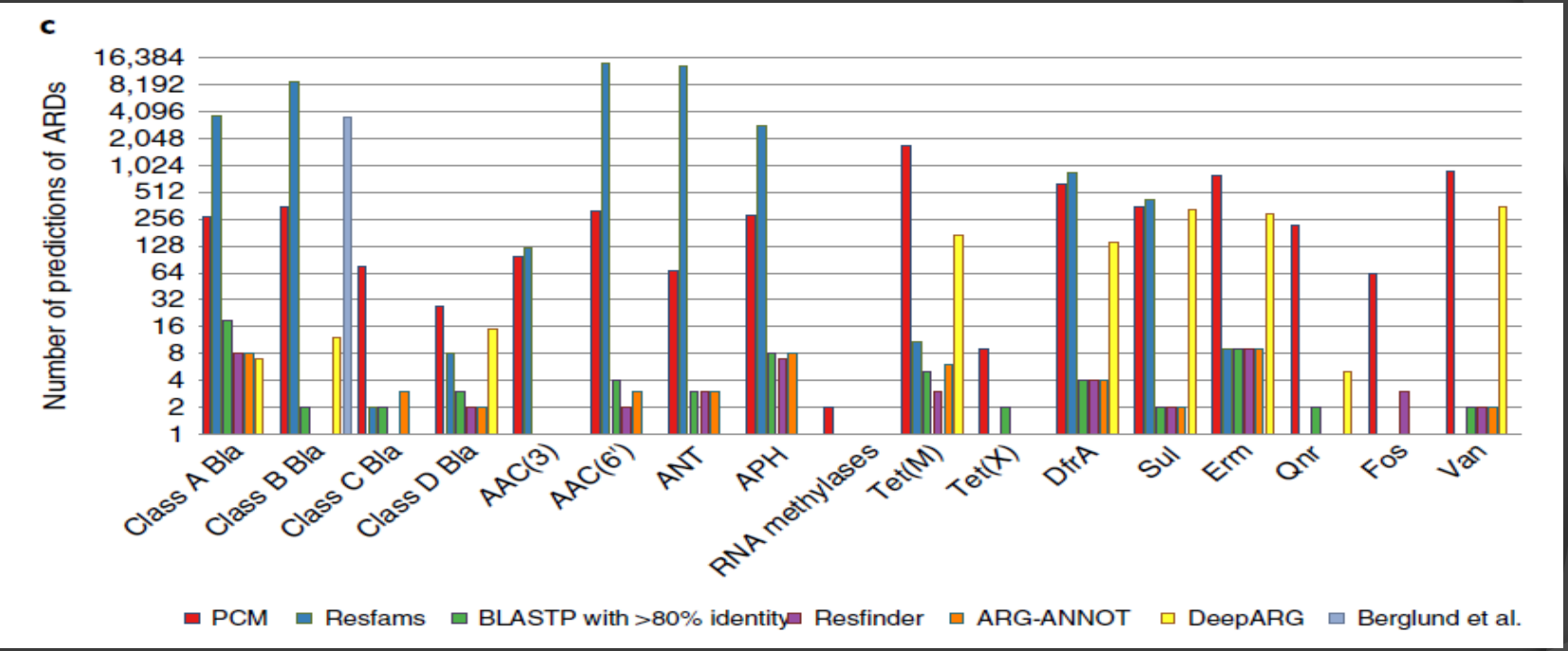
Relations pathologies-dysbioses

Pathologies	Observations les plus pertinentes et corrélations potentielles
Maladie de Crohn	Diminution de la diversité du microbiote Réduction de *F. prausnitzii*
Rectocolite hémorragique	Diminution de la diversité du microbiote Réduction de *A. muciniphila*
Syndrome de l'intestin irritable	Augmentation de *Dorea* et de *Ruminococcus*
Infection à *Clostridium difficile*	Forte diminution de la diversité du microbiote Présence de *C. difficile*
Cancer colorectal	Variation des *Bacteroides* Augmentation des Fusobacteria
Allergie / Atopie	Diversité altérée Signatures microbiennes spécifiques
Maladie cœliaque	Composition altérée particulièrement dans l'intestin grêle
Diabète de type 1	Signature microbienne particulière
Diabète de type 2	Signature microbienne particulière
Obésité	Rapport *Bacteroidetes*/*Firmicutes* spécifique (1:100)

Cherbuy et al., Innov Agron 2013

Résistome intestinal

= Ensemble des gènes de résistance à un ou plusieurs antibiotiques

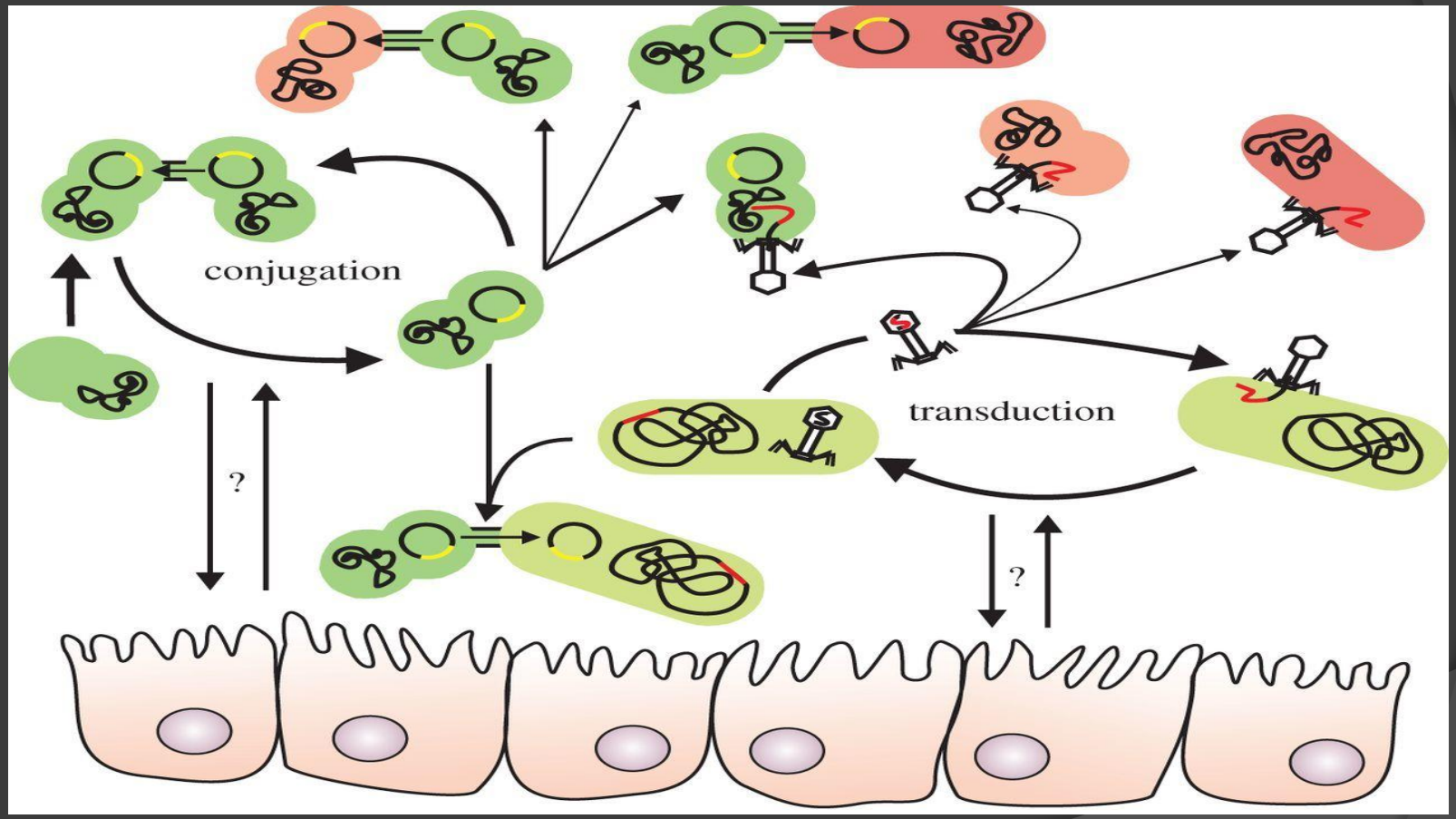


>6000 gènes de résistance prédits (sur 3,9 millions de protéines)

➔ Microbiote intestinal = réservoir majeur de gènes de résistance

Ruppé et al., Nat Microbiol 2018

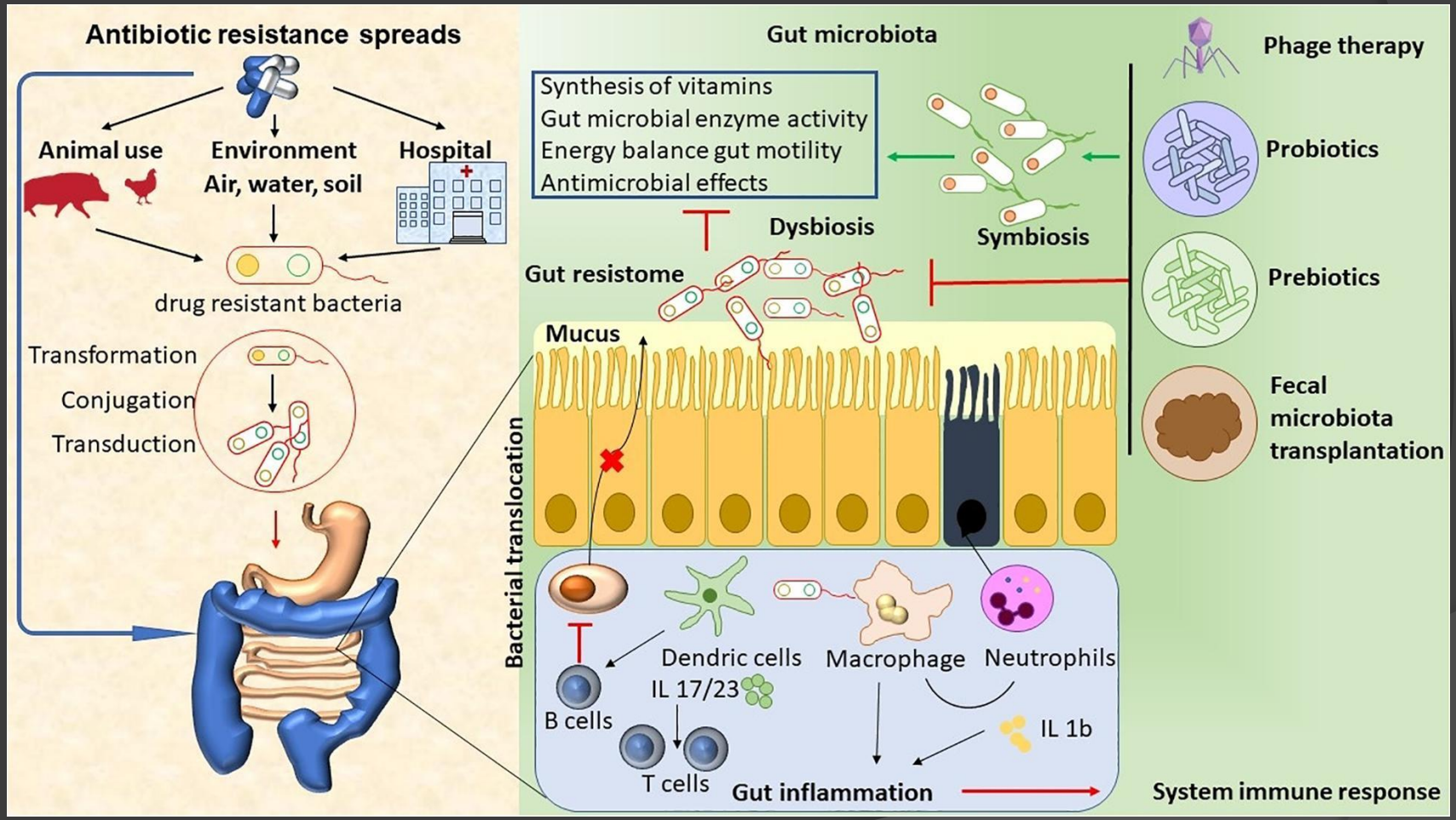
Transferts de la résistance



Bactéries anaérobies commensales en vert, bactéries pathogènes en rouge.

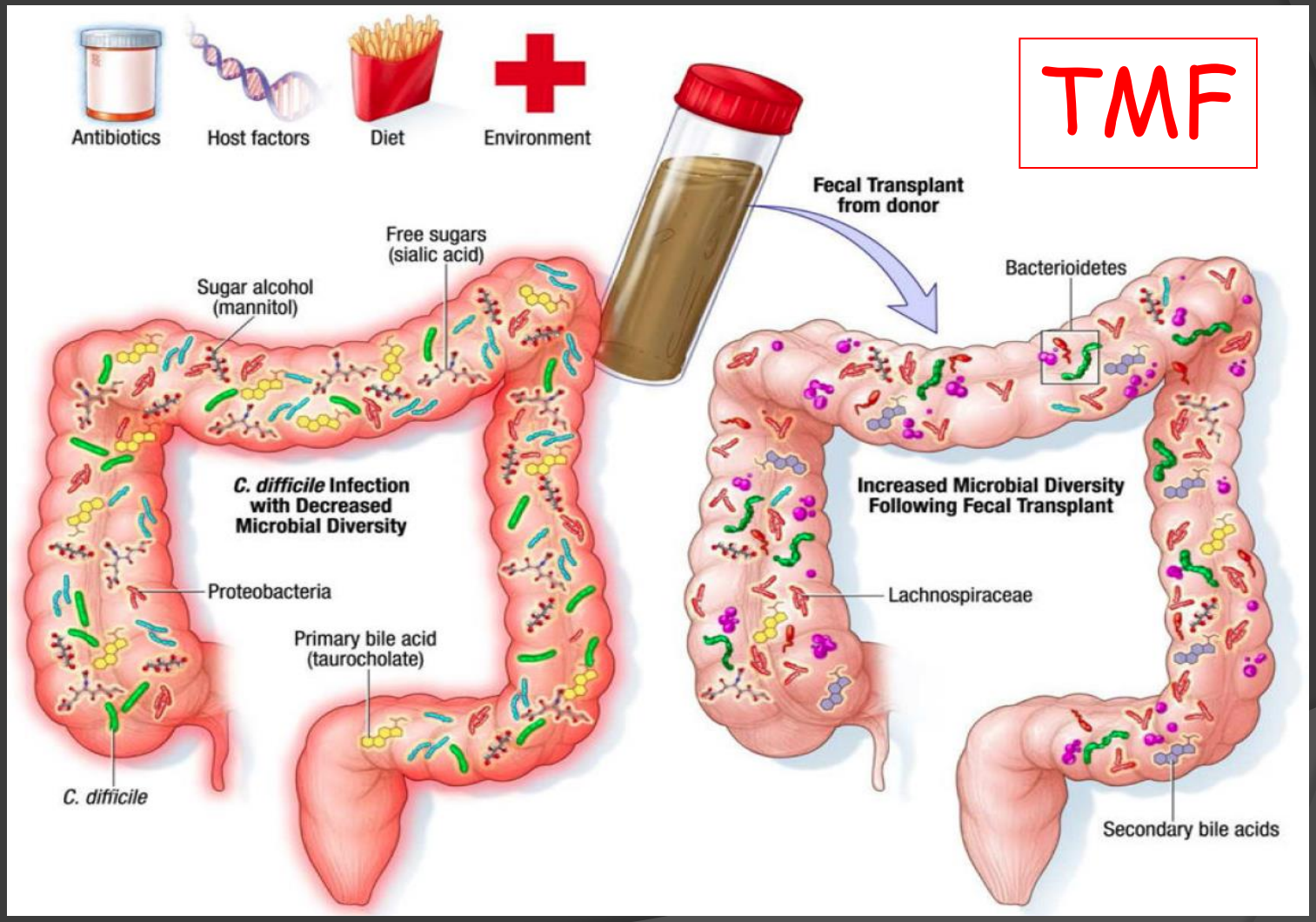
van Schaik et al., Philos Trans R Soc Lond B Biol Sci 2015

Manipulations du microbiote



Tsigalou et al., Front Microbiol 2020

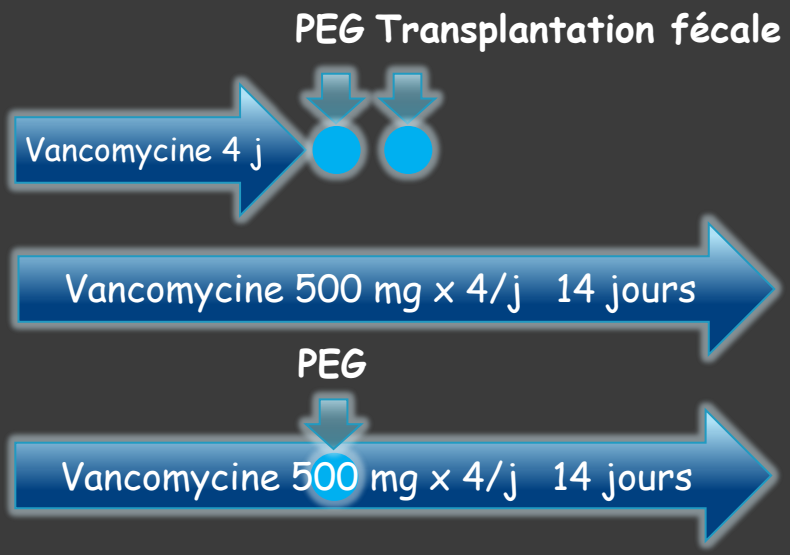
Transplantion de microbiote fécal



Kelly et al., Gastroenterol 2015

1er essai clinique de TMF dans l'ICD

- Principal critère : résolution de la diarrhée sans récidive après 10 sem.
- 3 bras randomisés:



- Etude arrêtée après analyse intermédiaire
- Excellent profil de tolérance
- **Effets secondaires mineurs :**
  - Diarrhée transitoire
  - Douleurs abdominales modérées

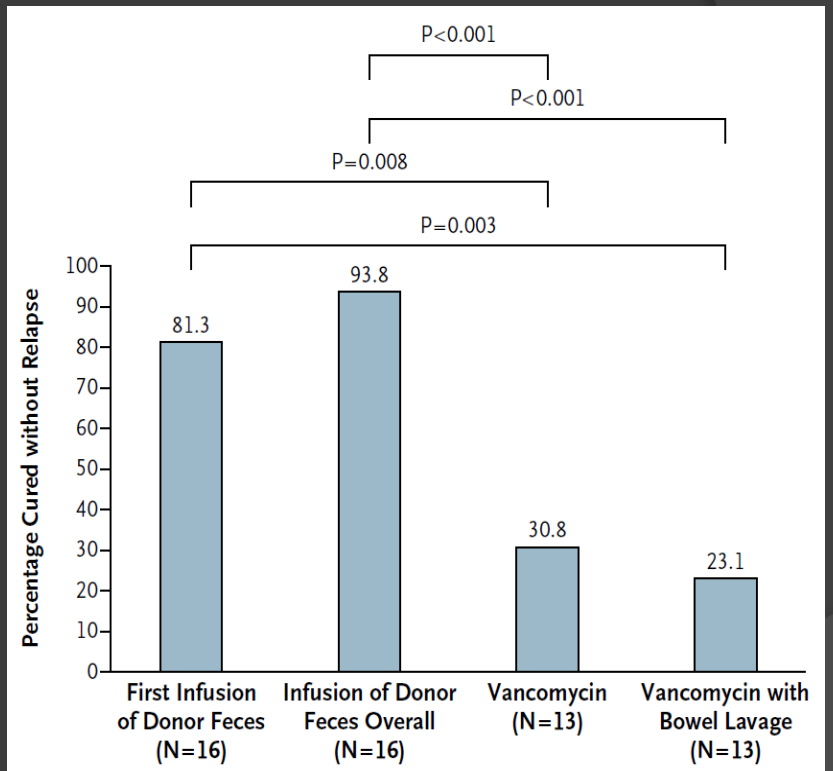


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

PEG : polyéthylèneglycol. Utilisé pour le lavage intestinal

Van Nood et al., New Engl J Med 2013

Restauration de la diversité

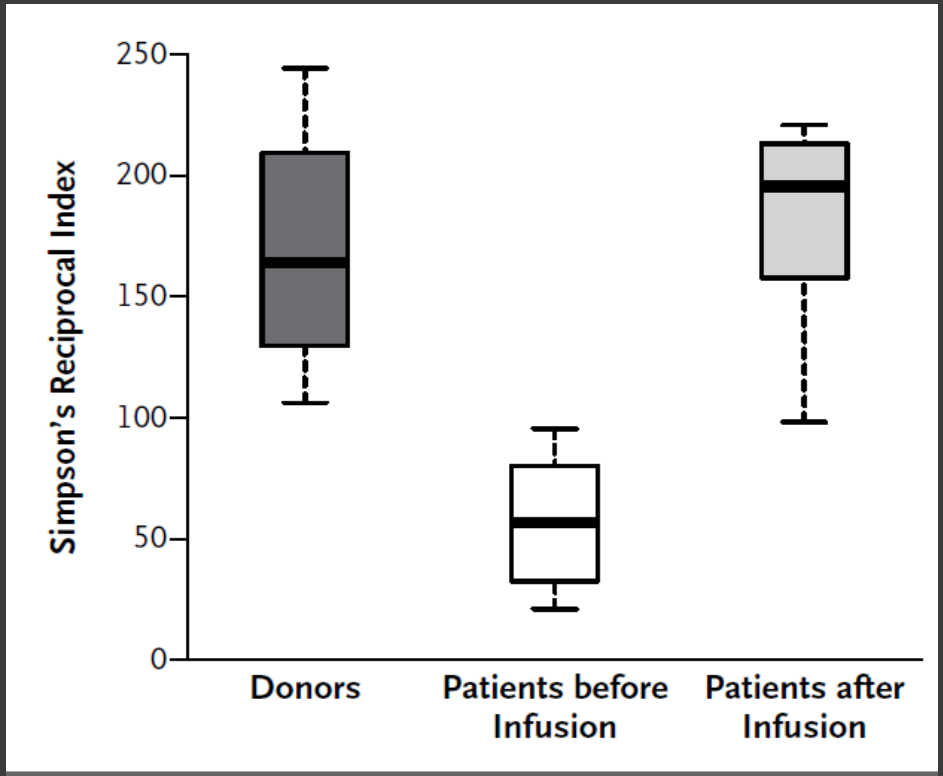
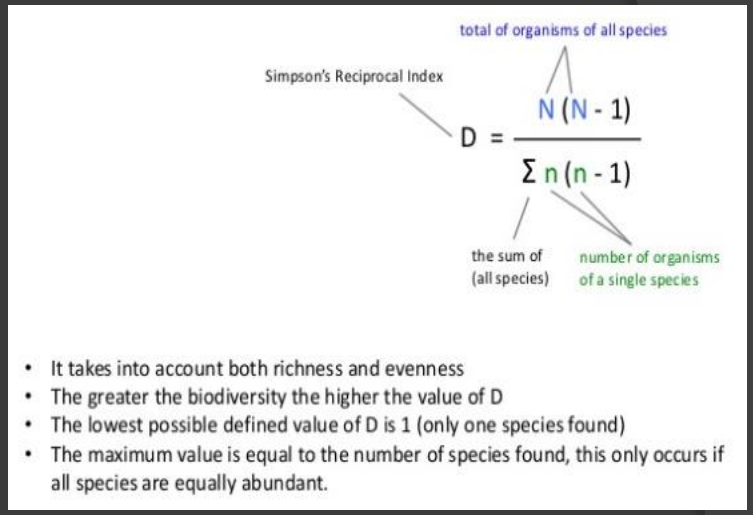


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.



Mean D for patients before FMT = **57 +/- 26**
Mean D for patients 2 weeks after FMT = **179 +/- 42 (P<0.001)**
Mean D for donors = **172 +/- 54**

Van Nood et al., New Engl J Med 2013

TMF pour la décolonisation BMR

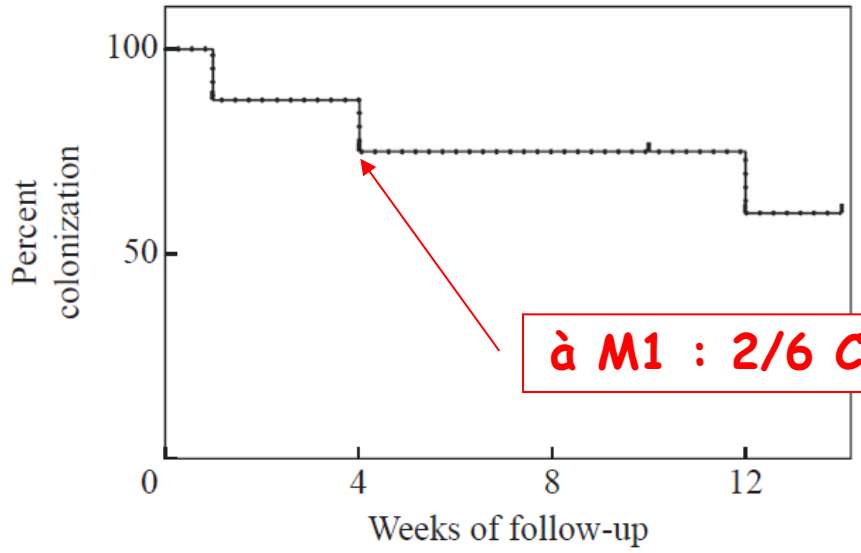


Figure 1. Clearance of carbapenem-resistant Enterobacteriaceae (CRE) and vancomycin-resistant enterococci (VRE) carriage among eight patients according to rectal swabs: Kaplan–Meier analysis of the percentage of colonization, documented by polymerase chain reaction (PCR) or agar culture. Day 0 is defined as the day the patient received the faecal microbiota transplantation. There was no statistical difference between PCR and culture.

Seulement 8 patients

(6 colonisés par EPC et 2 par ERV)

à M1 : 2/6 CPE- et 1/2 ERV-

Essais cliniques randomisés pour confirmation

Davido et al., J Hosp Infect 2017

Pro-/Pré-/Symbiotiques

Concept	Definition
Probiotics	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host
Prebiotic	A selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health
Synbiotics	Products that contain both probiotics and prebiotics, with conferred health benefits

WGO Guidelines 2017

Probiotiques

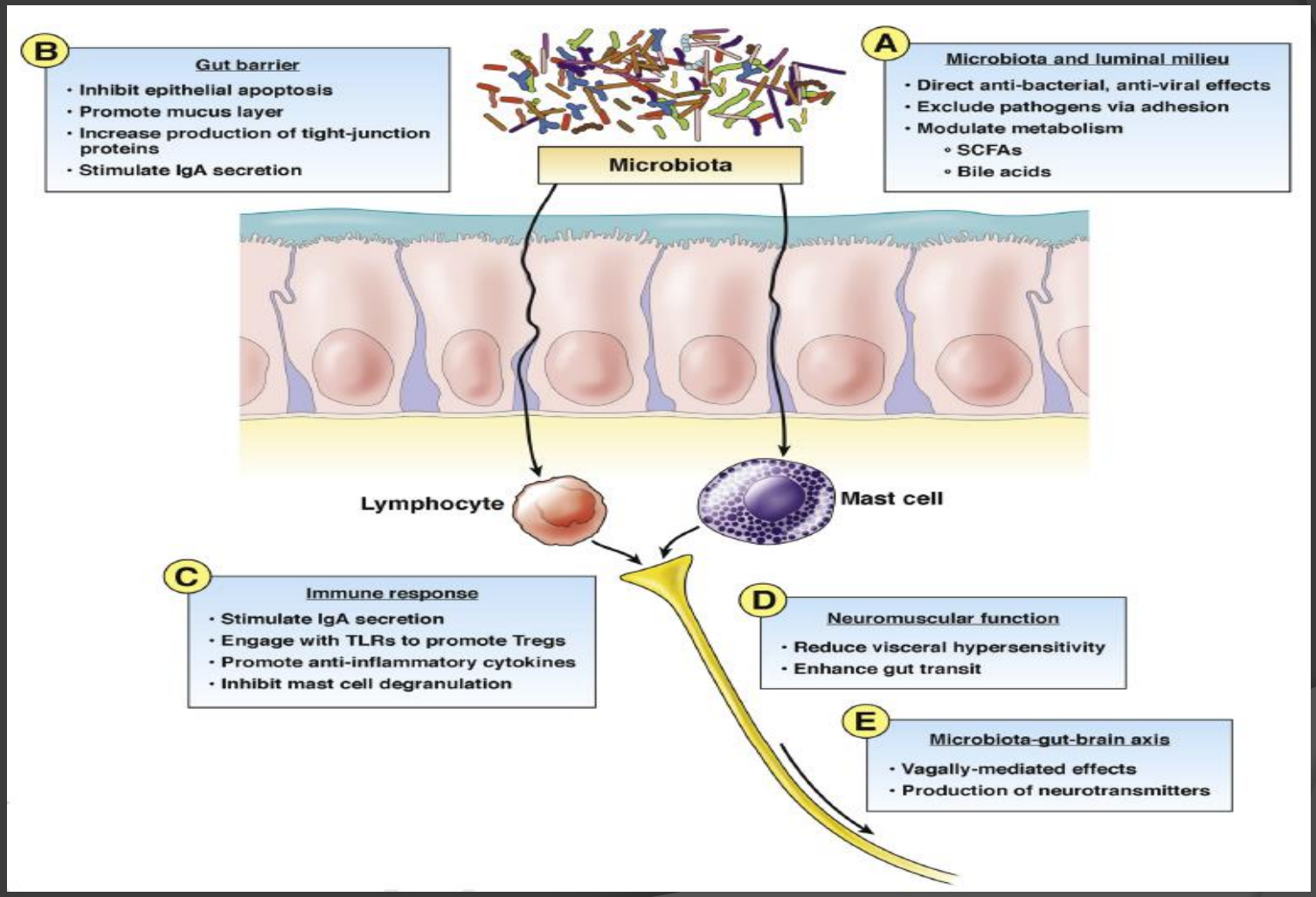
Le plus souvent des bactéries lactiques

Type *Lactobacillus*	Type *Bifidobacterium*	Other Lactic Acid Bacteria	Other Microorganisms
L. acidophilus [(a),*]	*B. adolescentis* [(a)]	*Enterococcus faecium* [(a)]	*Bacillus clausii* [(a),*]
L. amylovorus [(b),*]	*B. animalis* [(a),*]	*Lactococcus lactis* [(b),*]	*Escherichia coli Nissle 1917* [(a)]
L. casei [(a),(b),*]	*B. bifidum* [(a)]	*Streptococcus thermophilus* [(a),*]	*Saccharomyces cerevisiae (boulardi)* [(a),*]
L. gasseri [(a),*]	*B. breve* [(b)]		
L. helveticus [(a),*]	*B. infantis* [(a)]		
L. johnsonii [(b),*]	*B. longum* [(a),*]		
L. pentosus [(b),*]			
L. plantarum [(b),*]			
L. reuteri [(a),*]			
L. rhamnosus [(a),(b),*]			

[(a)] Mostly as pharmaceutical products; [(b)] mostly as food additives; * QPS (Qualified Presumption of Safety) microorganisms.

Markowiak & Slizewska, Nutrients 2017

Mécanismes d'action des probiotiques



Quigley EM, Clin Gastroenterol Hepatol 2018

Prébiotiques et symbiotiques

Table 4. Examples of prebiotics and synbiotics used in human nutrition [134,145,146].

Human Nutrition	
Prebiotics	**Synbiotics**
FOS	
GOS	
Inulin	*Lactobacillus* genus bacteria + inulin
XOS	*Lactobacillus*, *Streptococcus* and *Bifidobacterium* genus bacteria + FOS
Lactitol	*Lactobacillus*, *Bifidobacterium*, *Enterococcus* genus bacteria + FOS
Lactosucrose	*Lactobacillus* and *Bifidobacterium* genus bacteria + oligofructose
Lactulose	*Lactobacillus* and *Bifidobacterium* genus bacteria + inulin
Soy oligosaccharides	
TOS	

Abbreviations: FOS—fructooligosaccharides; GOS—galactooligosaccharides; TOS—transgalactooligosaccharides; XOS—xylooligosaccharides.

Markowiak & Slizewska, Nutrients 2017

Evidence clinique

>3500 publications sur l'utilisation des probiotiques
>1000 publications sur l'utilisation des prébiotiques

Table 7 Oxford Centre for Evidence-Based Medicine levels of evidence for treatment benefits relative to the question "Does this intervention help?"

Evidence level	Study type
1*	Systematic review of randomized trials or *n*-of-1 trials
2*	Randomized trial or observational study with dramatic effect
3*	Nonrandomized controlled cohort / follow-up study †
4*	Case-series, case-control studies, or historically controlled studies †
5	Mechanism-based reasoning

Source: "2011 Levels of Evidence," Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653).

* The level may be downgraded on the basis of study quality, imprecision, indirectness—the study's population, intervention, comparison, and outcome (PICO) criteria do not match the question's PICO; because of inconsistency between studies; or because the absolute effect size is very small. The level may be upgraded if there is a large or very large effect size.

† As always, a systematic review is generally better than an individual study.

Du 'nutribiotique' au 'pharmabiotique'

WGO Guidelines 2017

Utilité clinique chez l'adulte

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Diarrhea					
Antibiotic-associated diarrhea	Yogurt with *Lactobacillus casei* DN114, *L. bulgaricus,* and *Streptococcus thermophilus*	≥ 10^{10} CFU daily	1	[11]	Prevention of AAD in various clinical settings (in-patients and outpatients)
	Lactobacillus acidophilus CL1285 and *L. casei* (Bio-K+ CL1285)	≥ 10^{10} CFU daily	1	[11]	
	Lactobacillus rhamnosus GG	10^{10} CFU/capsule twice daily	1	[11]	
	Saccharomyces boulardii CNCM I-745	5x10^{9} CFU/capsule or 250 mg twice daily	1	[11,12]	
***Helicobacter pylori* (HP)**					
Coadjuvant therapy for HP eradication	*Saccharomyces boulardii* CNCM I-745	5x10^{9} CFU/capsule or 250 mg twice daily	1	[7]	Reduction in therapy-related side effects
Liver disease					
Hepatic encephalopathy	Nonabsorbable disaccharides (lactulose)	45–90 g/daily	1	[29]	–
Postoperative sepsis in elective gastrointestinal surgery patients					
	Lactobacillus acidophilus, L. plantarum, and *Bifidobacterium longum* 88	2.6 × 10^{14} CFU daily	1	[63]	–
IBD—pouchitis					
Maintenance of clinical remission	Mixture containing strains of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve* and *Streptococcus salivarius subsp. thermophilus*.	1800 billion bacteria daily	1	[66]	–
Lactose maldigestion—reducing associated symptoms					
	Yogurt with live cultures of *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*	At least 10^{8} CFU of each strain per gram of product	1	[70]	–

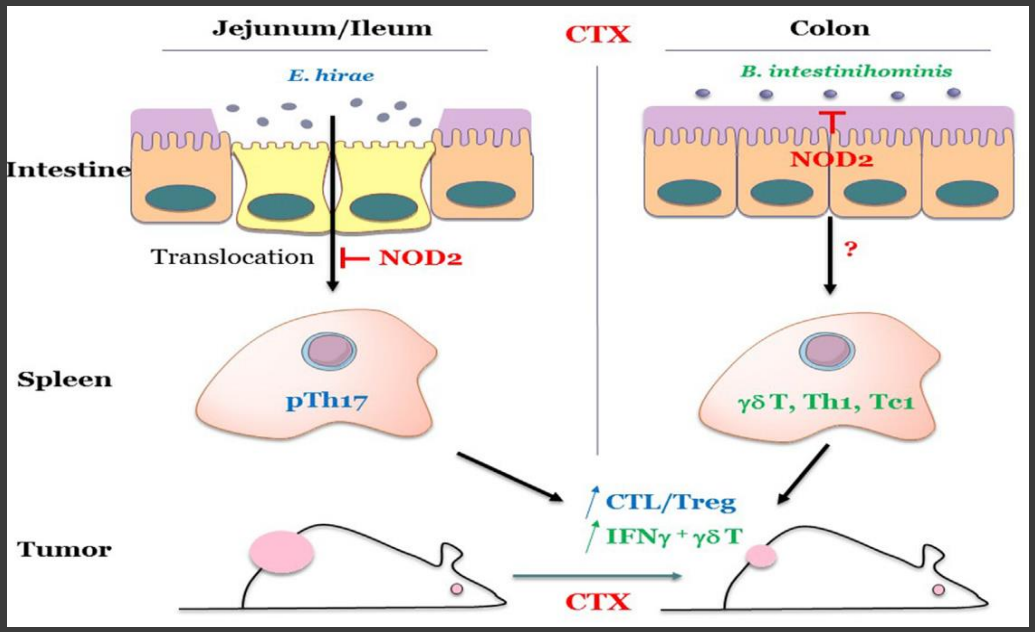
Utilité clinique chez l'enfant

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Treatment of acute gastroenteritis	LGG	≥ 10^{10} CFU/day (typically 5–7 days)	1	[72,73]	ESPGHAN/ESPID recommendations 2014; ESPGHAN Working Group on Probiotics. Meta-analysis of RCTs
	Saccharomyces boulardii CNCM I-745	250–750 mg/day (typically 5–7 days)	1	[72,74]	
Prevention of antibiotic-associated diarrhea	LGG	1–2 × 10^{10} CFU	1	[86,87]	ESPGHAN Working Group on Probiotics
	Saccharomyces boulardii	250–500 mg	1	[12]	
Prevention of nosocomial diarrhea	LGG	10^{10}–10^{11} CFU, twice daily	1	[12]	Meta-analysis of RCT
Infections in children attending day-care centers	LGG		1	[89–91]	Prevention of AAD in hospitalized patients
Infantile colic—management	*Lactobacillus reuteri* DSM 17938	10^{8} CFU, once daily, for 21 days	1	[105–110]	Reduced crying time (documented mainly in breastfed infants). Meta-analysis of RCTs
Infantile colic—prevention	*Lactobacillus reuteri* DSM 17938	10^{8} CFU, once daily, up to 3 months of age	1	[111]	–
	LGG	10^{10}–10^{11} CFU, twice daily	1	[112]	Meta-analysis of RCTs
Abdominal pain–related functional gastrointestinal disorders	*Lactobacillus reuteri* DSM 17938	10^{8} CFU/d for 4 weeks	1	[114,115]	–

LGG, *Lactobacillus rhamnosus* GG

'Oncobiotiques'

Enterococcus hirae and *Barnesiella intestinihominis* Facilitate Cyclophosphamide-Induced Therapeutic Immunomodulatory Effects

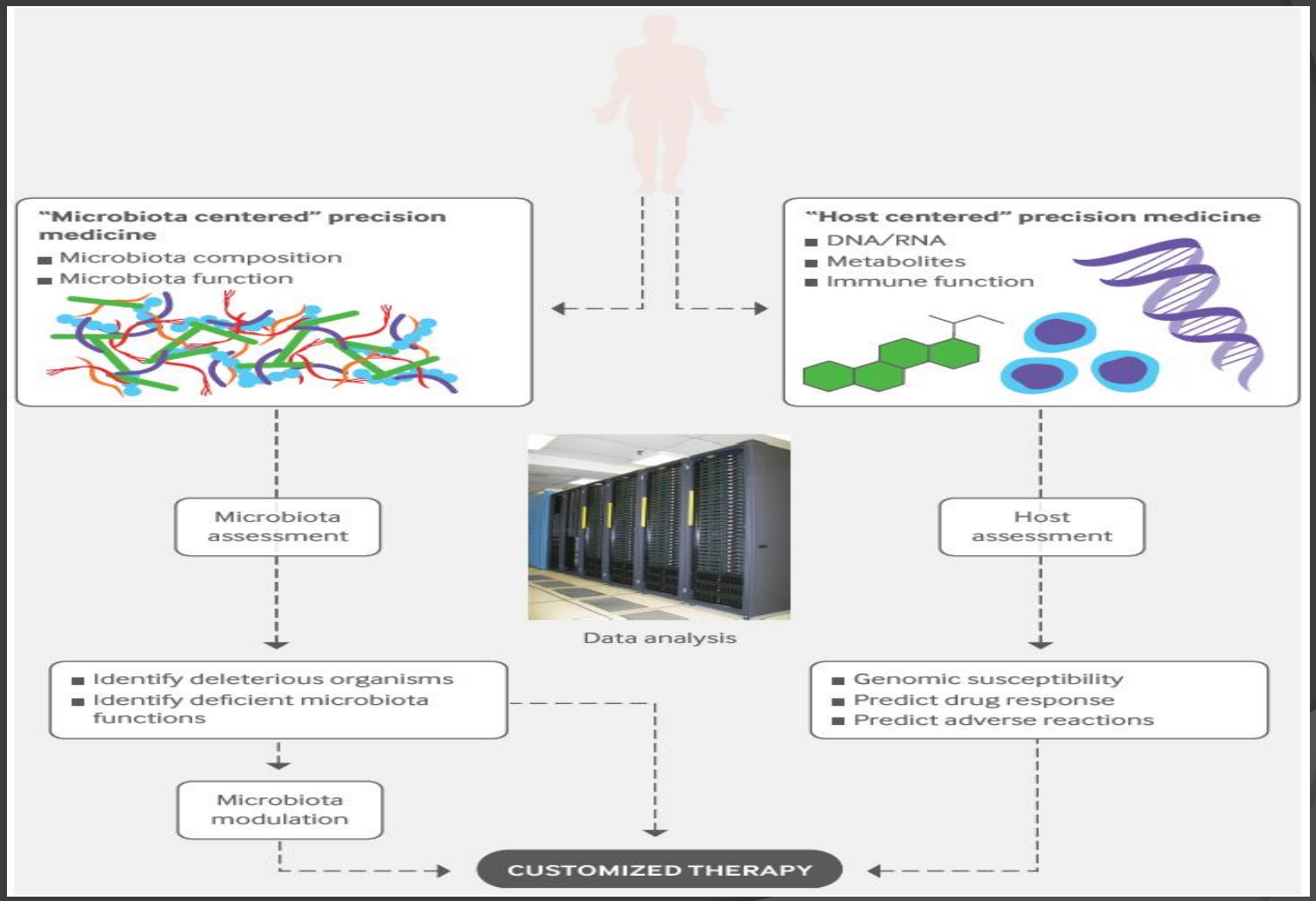


Highlights

- *E. hirae* restored the efficacy of CTX in antibiotics-treated mice
- *E. hirae* and *B. intestinihominis* enhanced cognate anticancer immune responses
- NOD2 receptors limit the bioactivity of *E. hirae* and *B. intestinihominis*
- $CD4^+$ T cell responses against *E. hirae* are associated with survival in cancer patients

Daillère et al., Immunity 2016

Médecine personnalisée



Young VB, BMJ 2017

Merci pour votre attention