Antibiotiques et impact sur le microbiote intestinal

Dr Claire ROUBAUD BAUDRON

MCU-PH, Pôle de Gérontologie Clinique

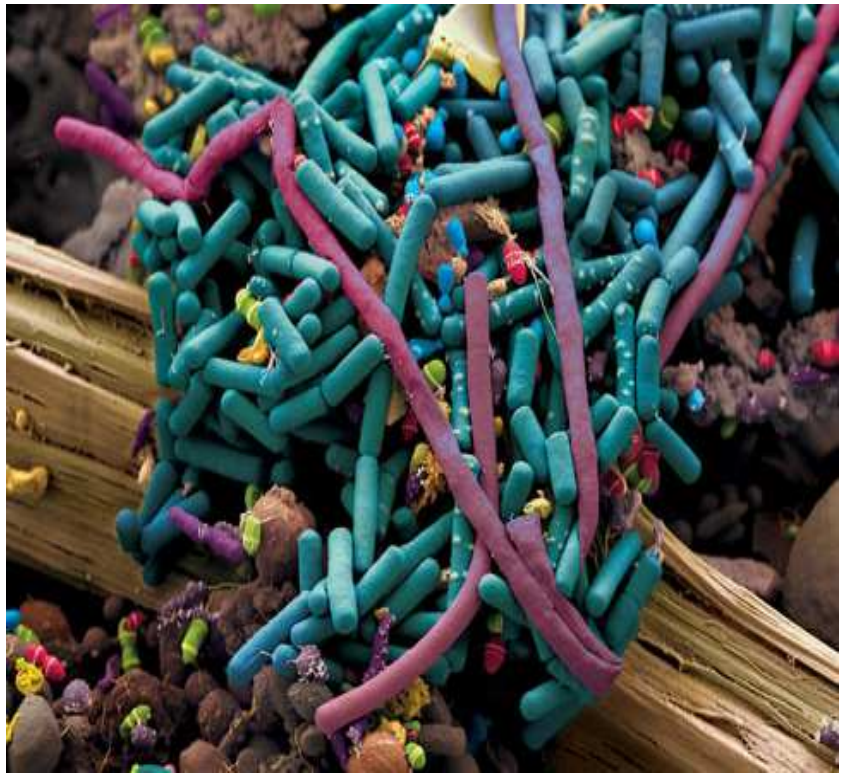
UMR BaRITOn INSERM U1053

Conflits d'intérêts

- Activité de conseil, conférences (Astellas)

Définition

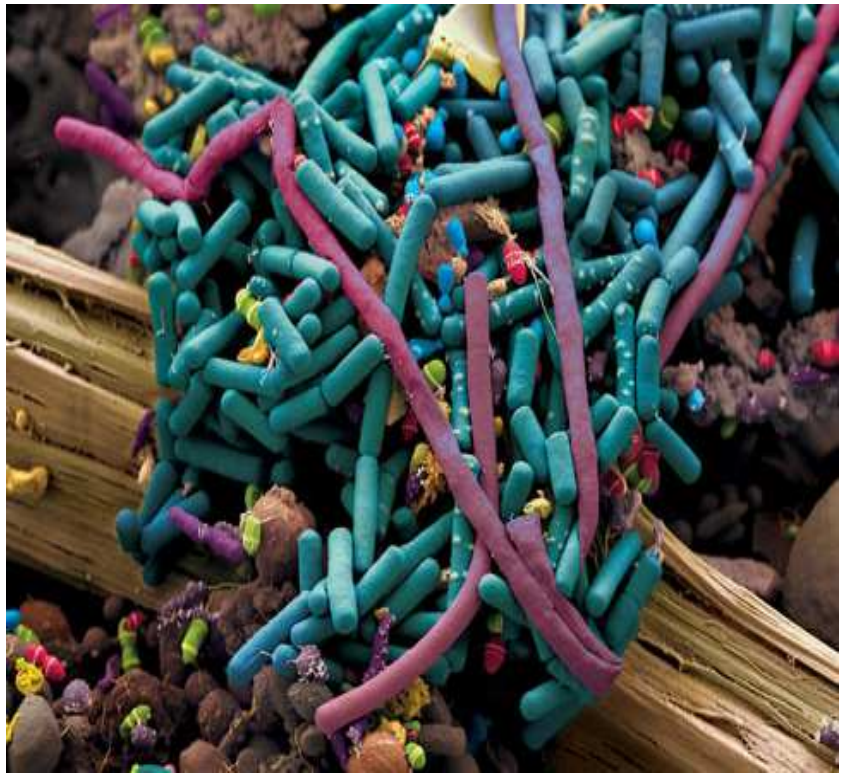
- **Microbiome**: ensemble des organismes et de leurs génomes qui colonisent différentes localisations anatomiques du corps humain

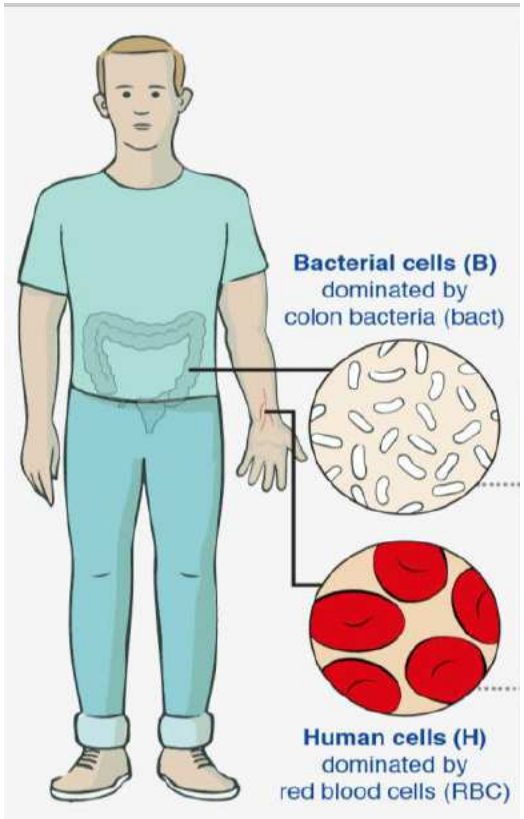


The Human Microbiome Project Consortium, 2012; Senders Cell 2016

Définition

- **Microbiome**: ensemble des organismes et de leurs génomes qui colonisent différentes localisations anatomiques du corps humain

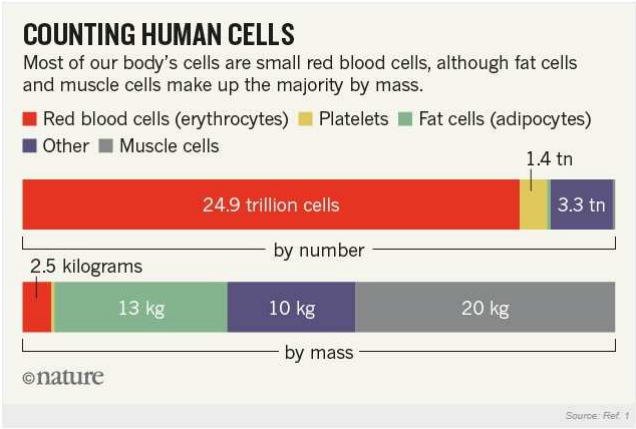




- Ratio ~ 1/1

$4x10^{13}$

$3x10^{13}$



The Human Microbiome Project Consortium, 2012; Senders Cell 2016

Composition du microbiote

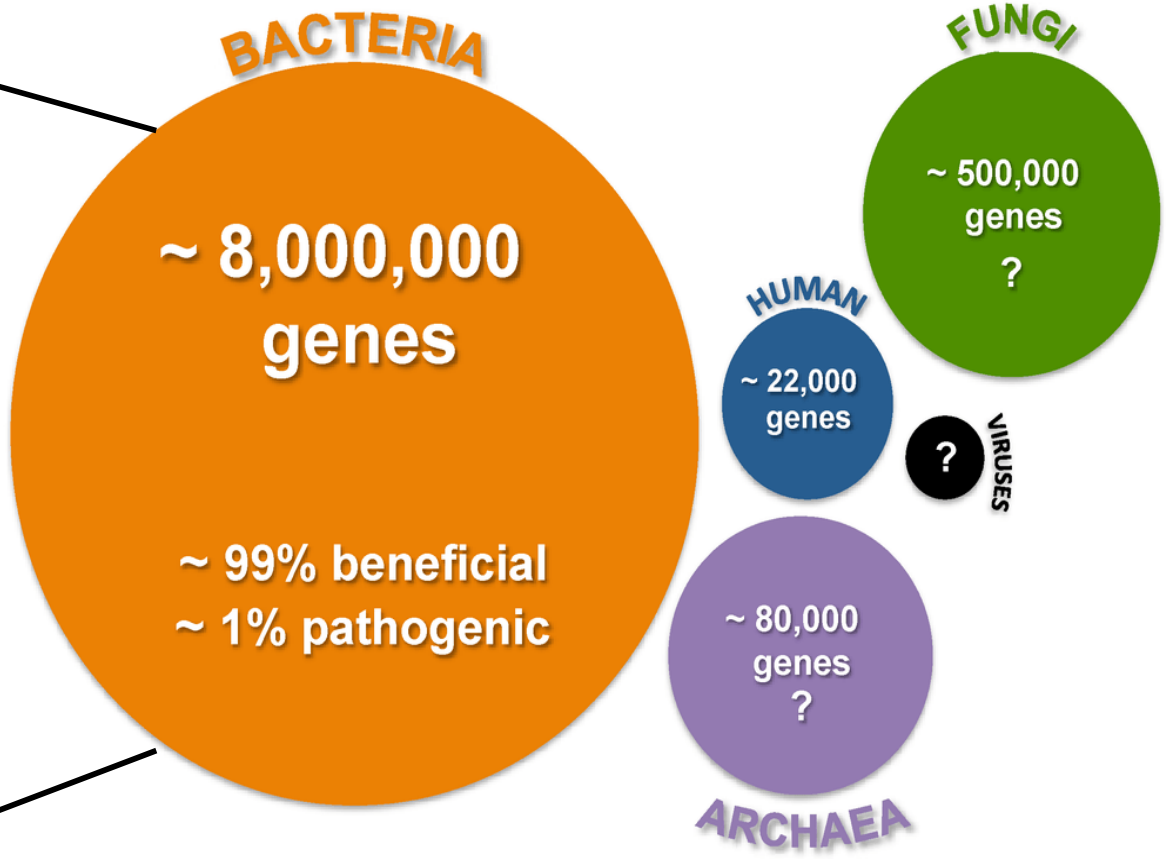
Dans le colon

90%

Firmicutes
Bacteroidetes

Actinobacteria
Protéobacteria

Autres



Cho and Blaser , 2014

Principaux phyla du microbiote intestinal

BACTEROIDETES

Gram -, Aérobie ou Anaérobie
+ Digestion ➔ **SCFA**
- ***Bacteroides fragilis,***
résistance

FIRMICUTES

Anaérobie (± falcutatif)
Gram +, Spores
+ Digestion ➔ **SCFA**
- *C. difficile*… **-** Enterococcus, streptococcus

ACTINOBACTERIA

Aérobie ou anaérobie
Bifidobacterium spp
++

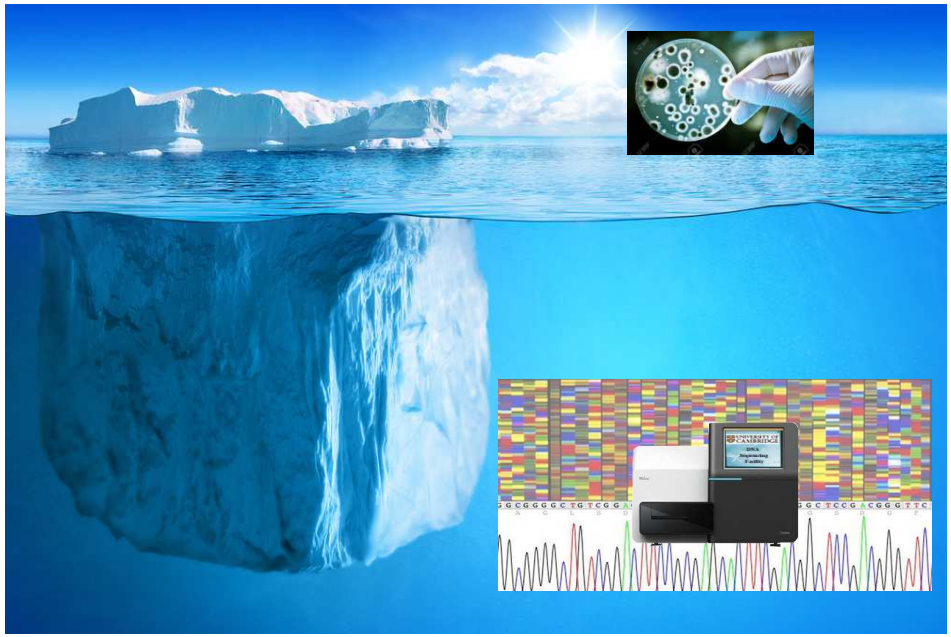
PROTEOBACTERIA

Gram -,
Anaérobie facultatifs
↗ = dysbiose
Entérobactéries

Kim *et al.* Immunol Rev 2017

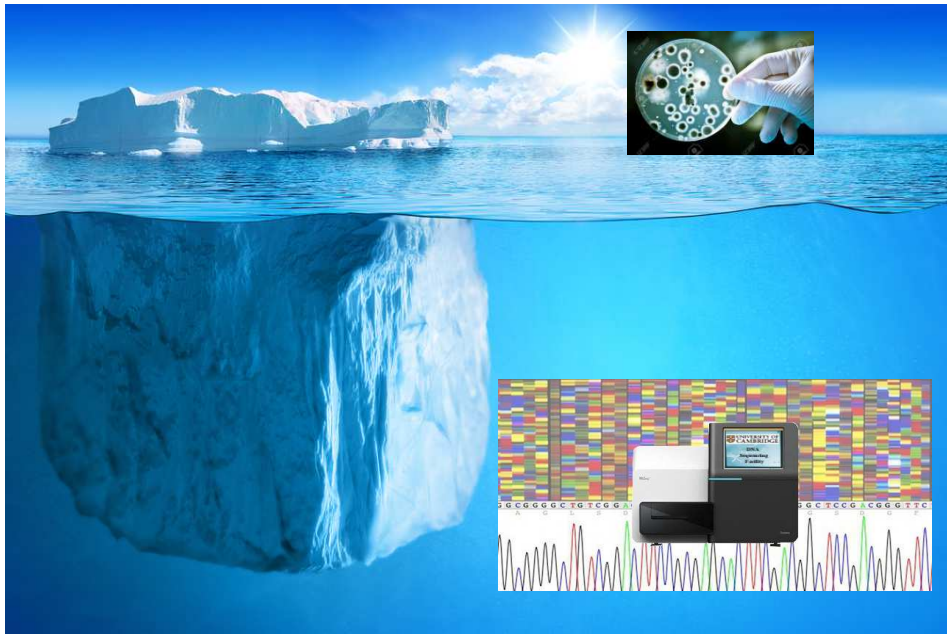
Étude du microbiote

80% des bactéries ne sont pas cultivables

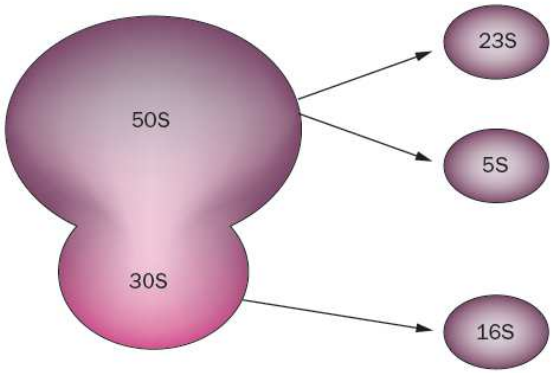


Étude du microbiote

80% des bactéries ne sont pas cultivables

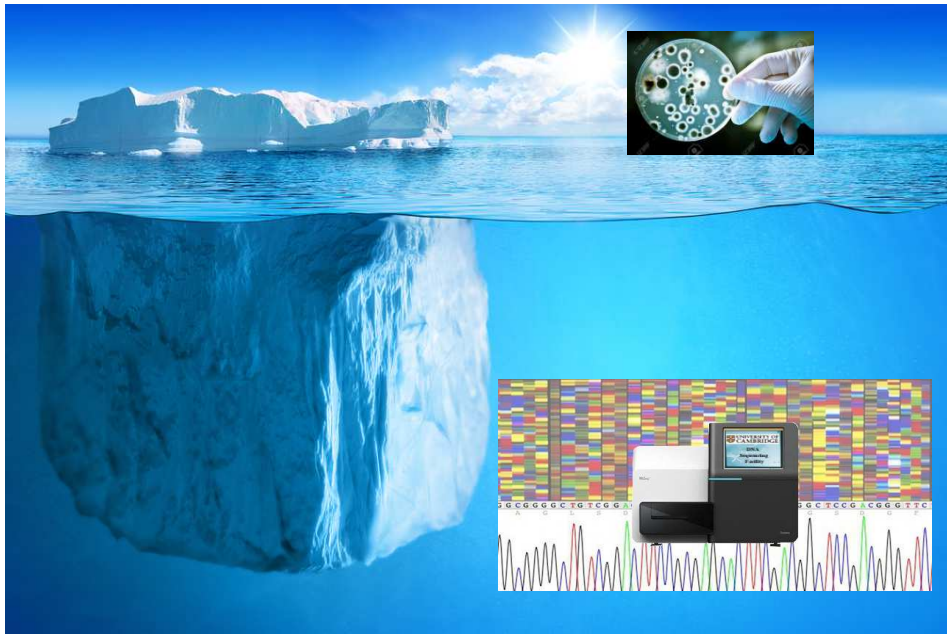


Ribosome, Unité 16S

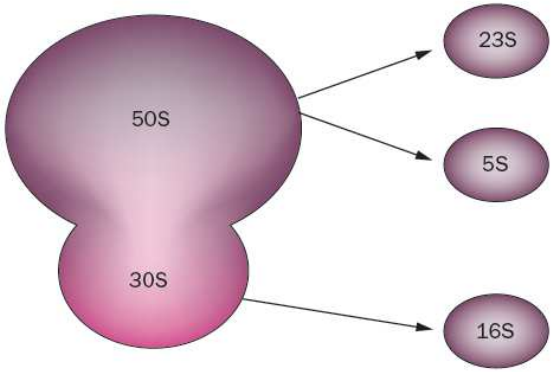


Étude du microbiote

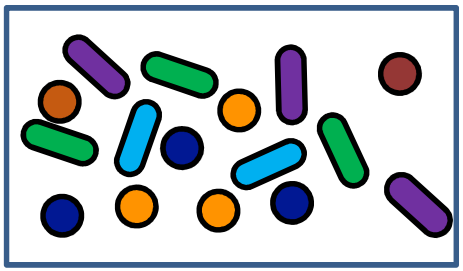
80% des bactéries ne sont pas cultivables



Ribosome, Unité 16S

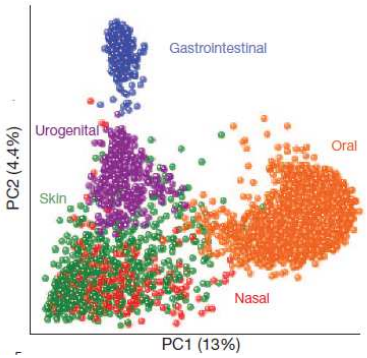


α-diversité

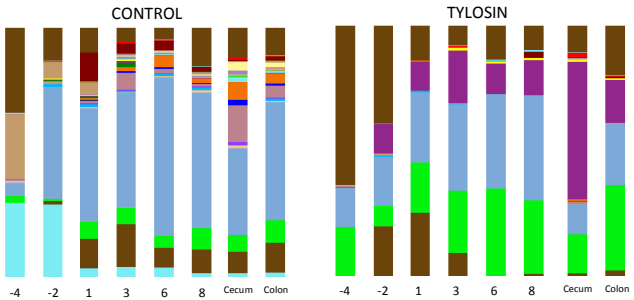


1 échantillon

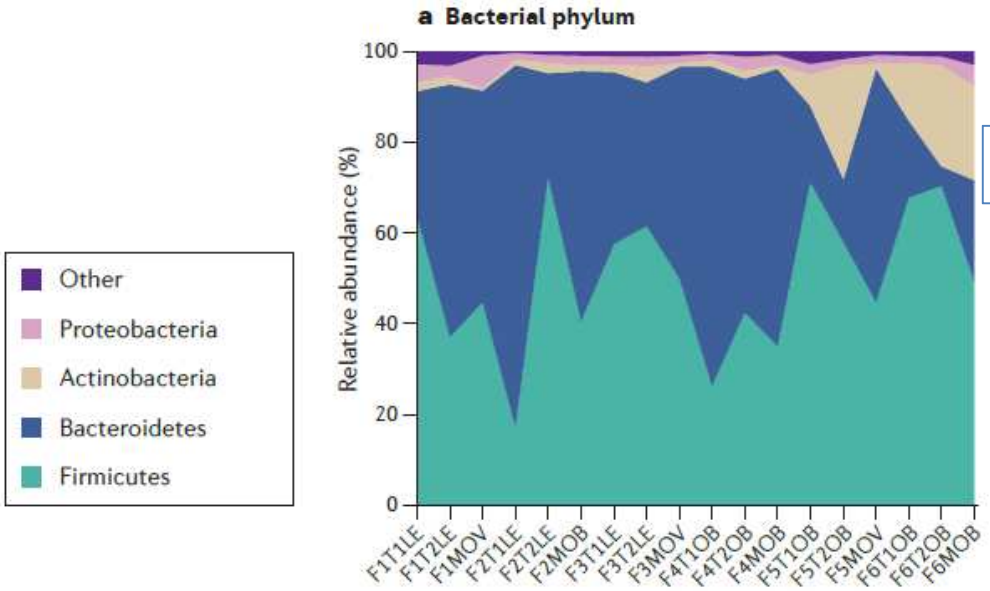
β-diversité



Composition taxonomique



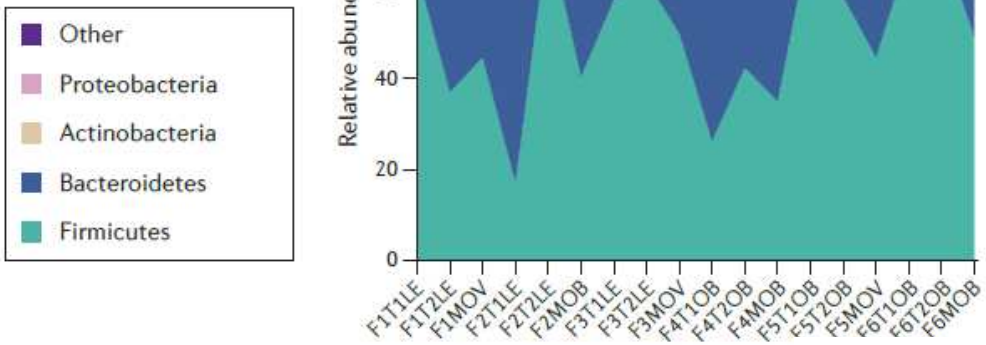
Microbiote et microbiome



Diversité taxonomique entre individus

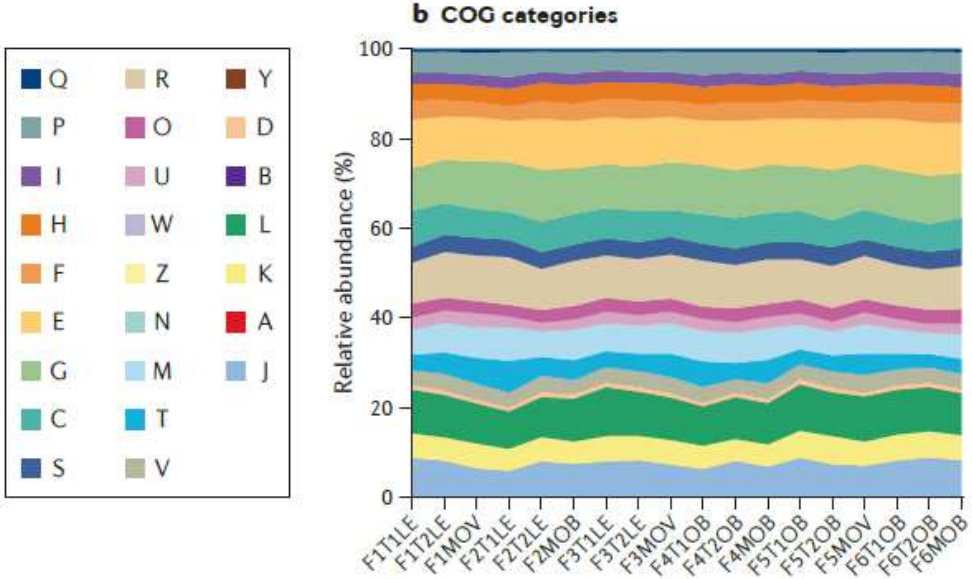
Cho & Blaser Nature Rev Genetics 2012

Microbiote et microbiome



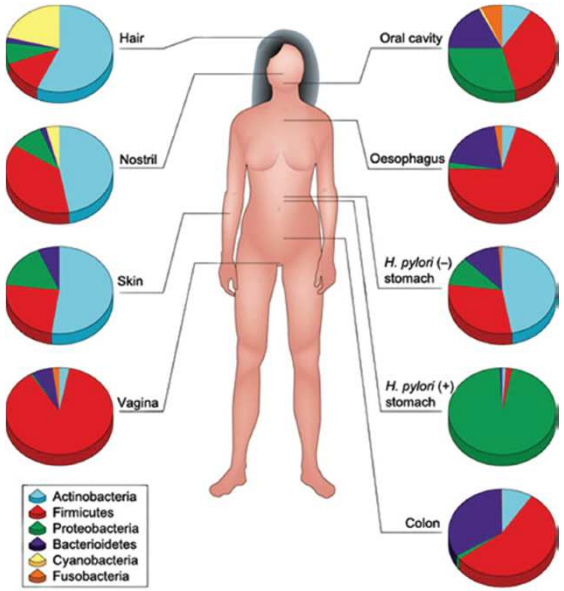
Diversité taxonomique entre individus

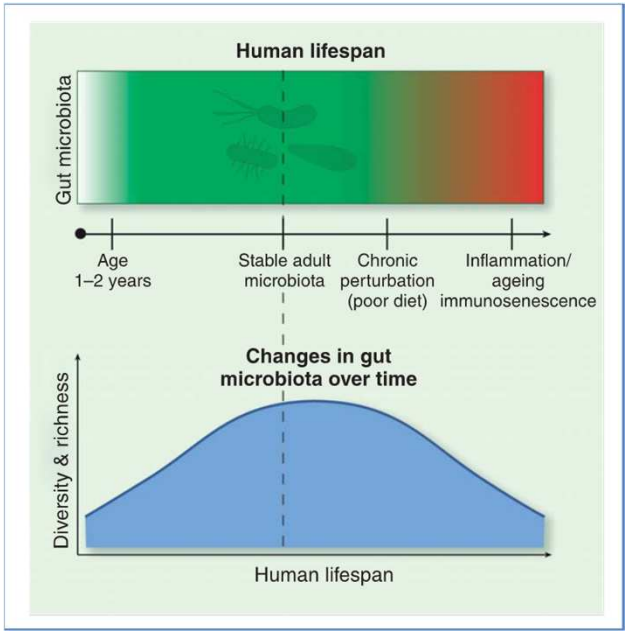
Stabilité des gènes et de leurs fonctions entre les individus

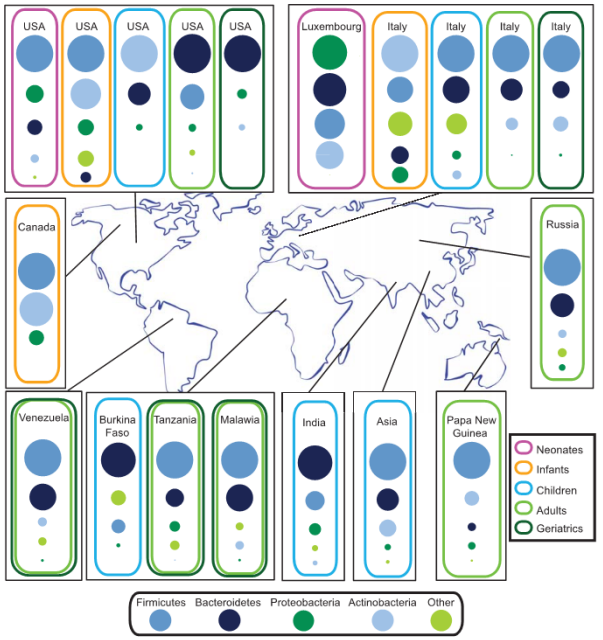


Cho & Blaser Nature Rev Genetics 2012

Variabilité du microbiote



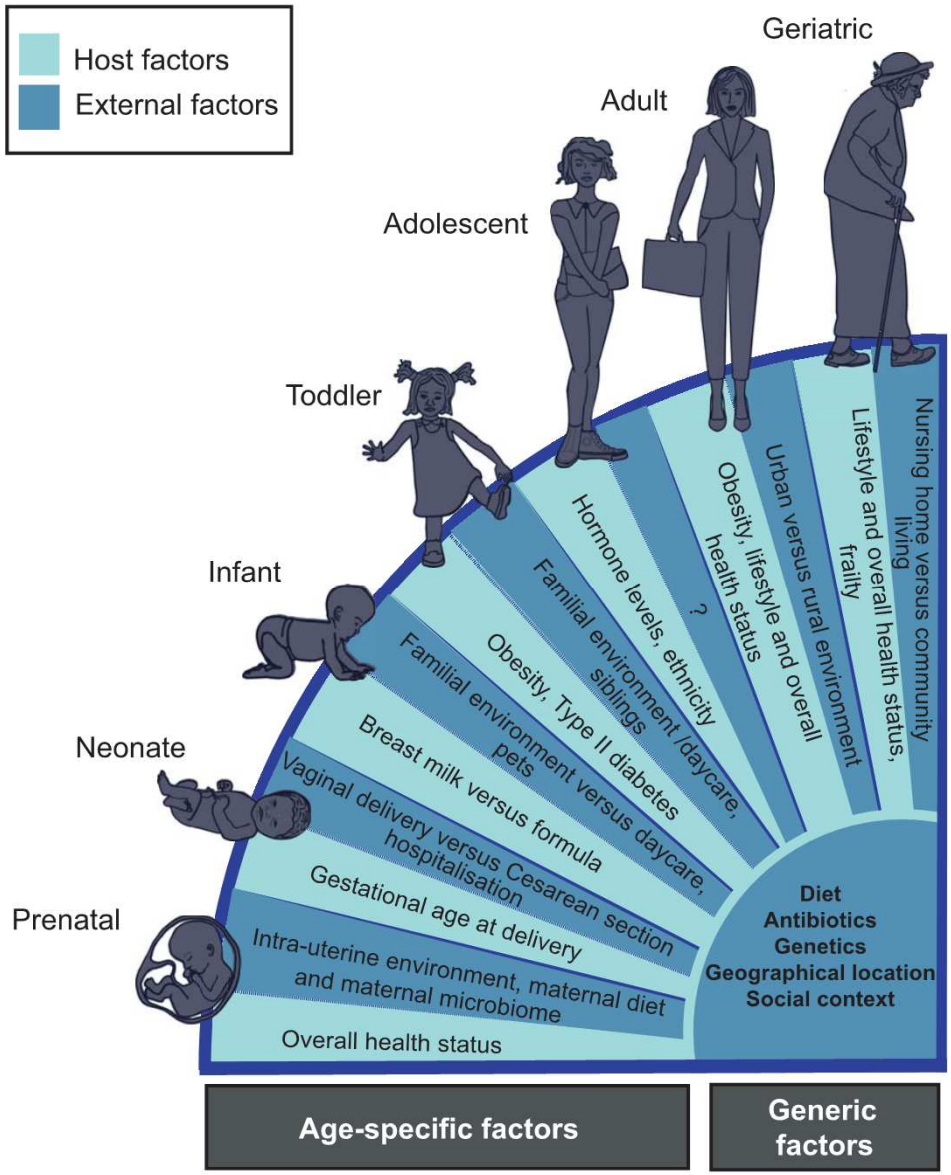




Site anatomique **Temps** **Site géographique**

Cho & Blaser Nature Rev Genetics 2012
Jernberg et al. Microbiology 2010
Greenhalgh *et al.* Environment Microbiol 2016
Peterson *et al.* Clin Exp Immunol 2014

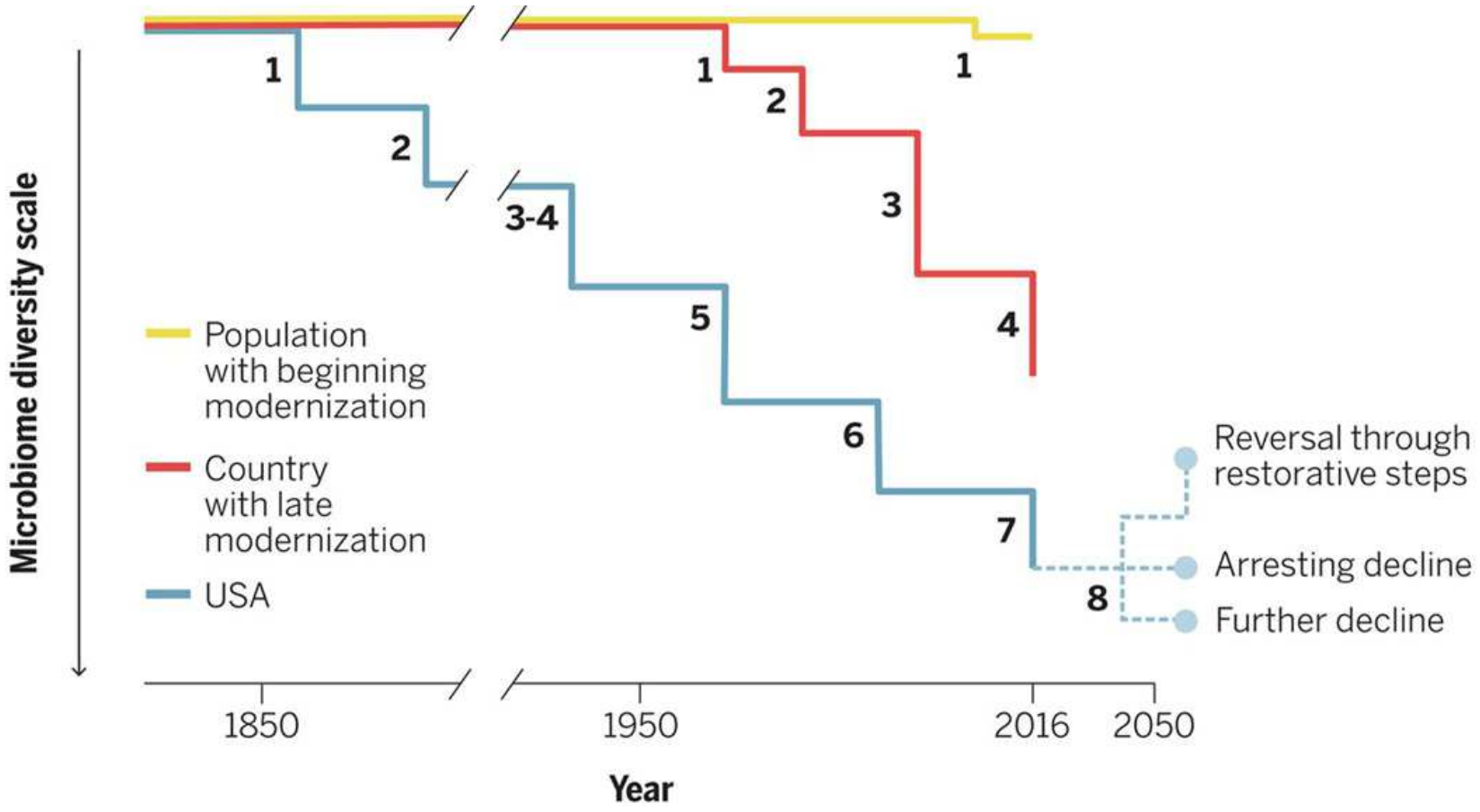
Les facteurs influençant le microbiote évoluent durant la vie



- Césarienne, allaitement
- Régime alimentaire
- Médicaments
  - **Antibiotiques**
  - IPP…
- Lieu de résidence
- …

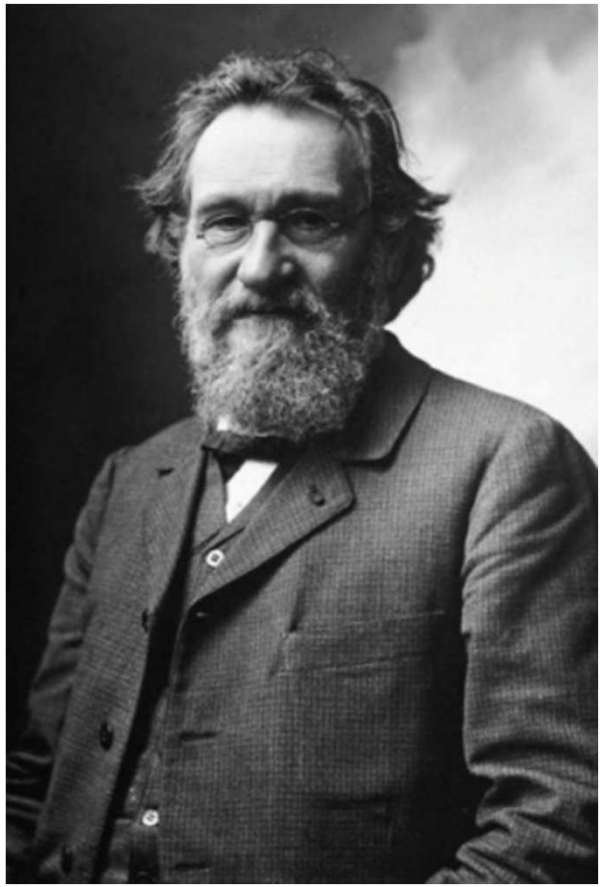
Greenhalgh *et al.* Environment Microbiol 2016

Diversité du microbiote au cours du temps

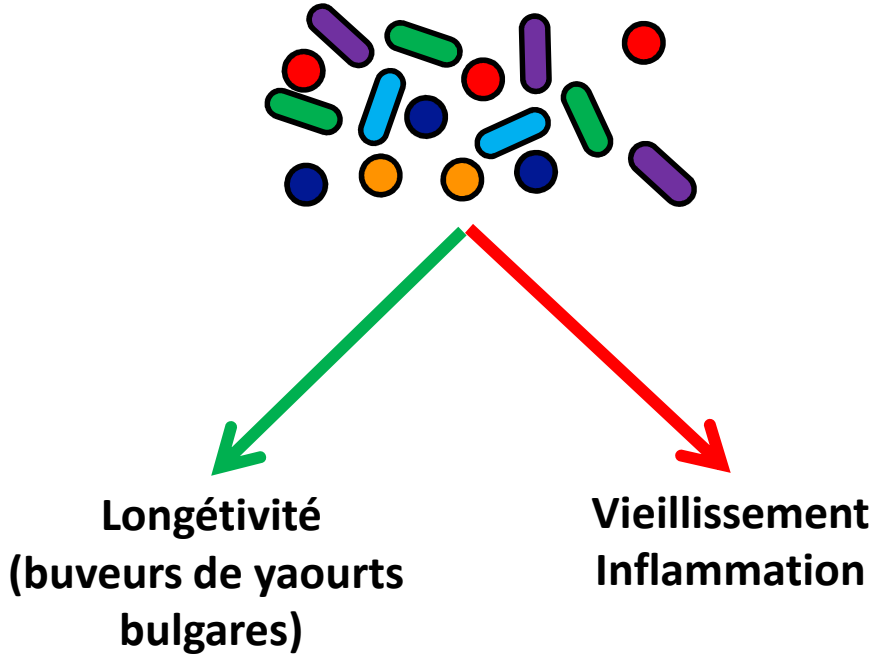


Blaser Science 2016

Influence du microbiote sur la santé

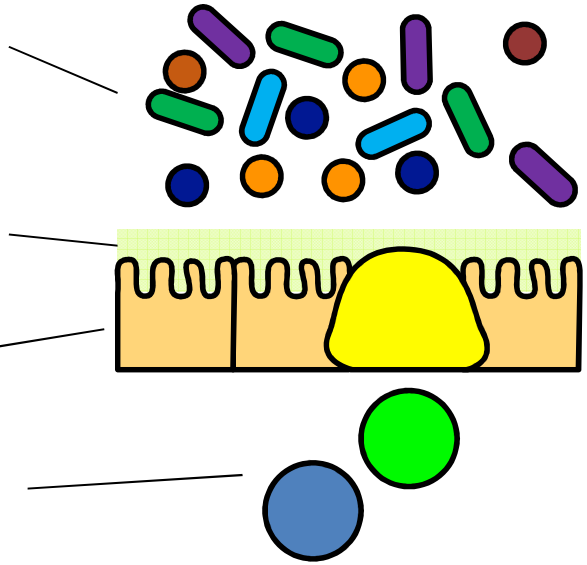


Metchnikoff 1907



Le microbiote influence notre santé

Microbiote



Mucus

Epithelium

Cellules immunitaires

⋮

Immunité systémique

…

Bevattini *et al.* Trends Mol Med 2016
Brown Immunology 2016

Le microbiote influence notre santé

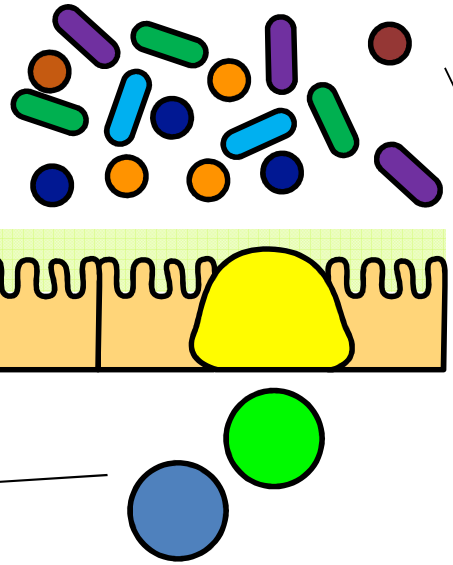
Microbiote

Mucus

Epithelium

Cellules immunitaires

Immunité systémique



Production de vitamines, digestion

Développement épithélial

Organes extra-digestifs

…

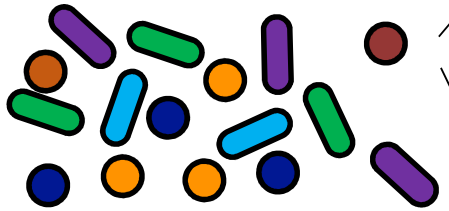
Bevattini *et al.* Trends Mol Med 2016
Brown Immunology 2016

Le microbiote influence notre santé

Pathogènes

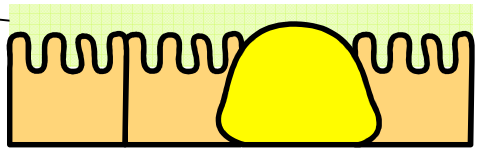
Résistance aux infections

Microbiote



Mucus

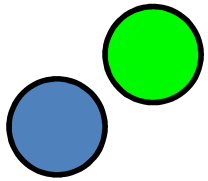
Epithelium



Production de vitamines, digestion

Développement épithélial

Cellules immunitaires



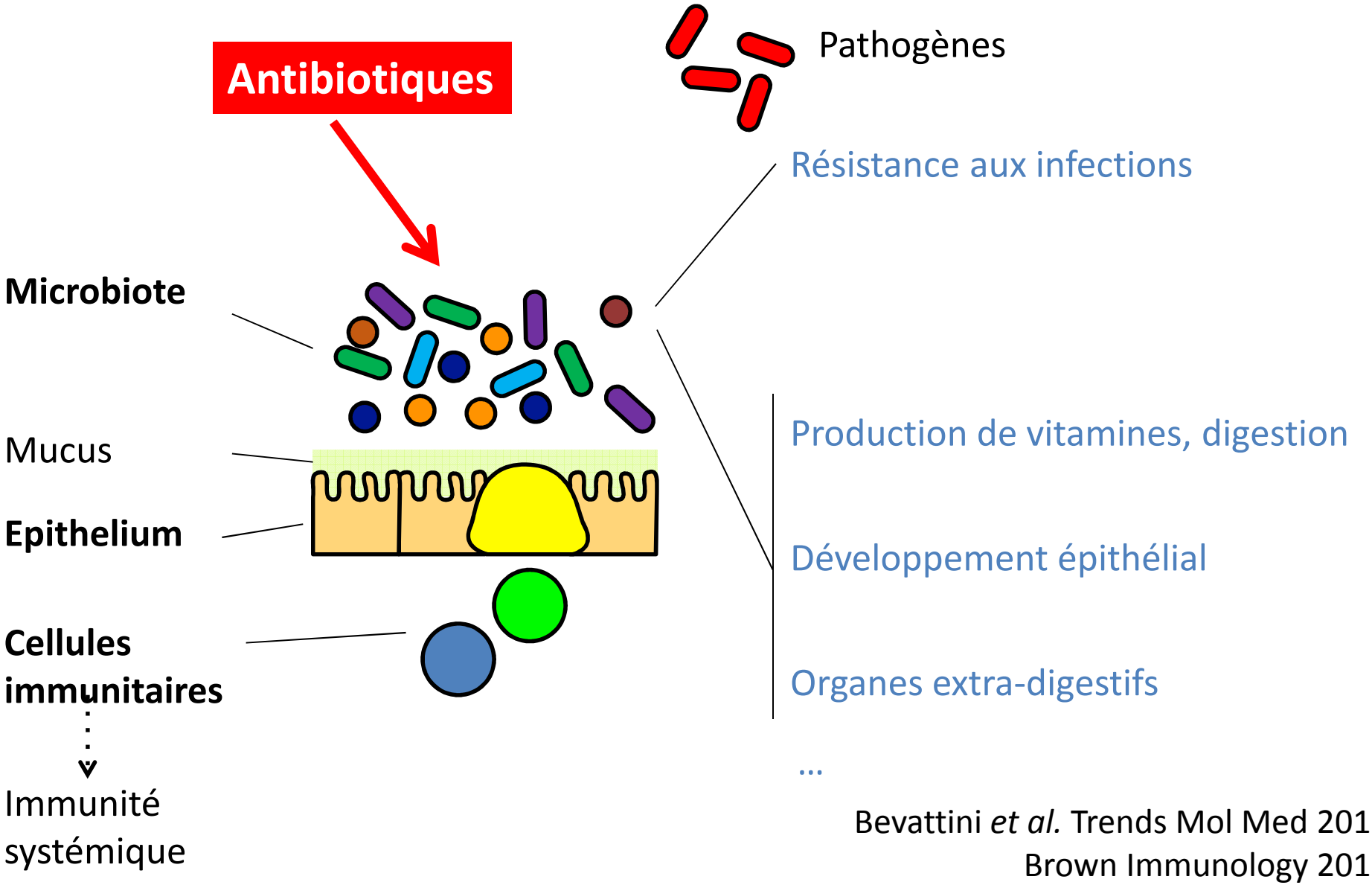
Organes extra-digestifs

…

Immunité systémique

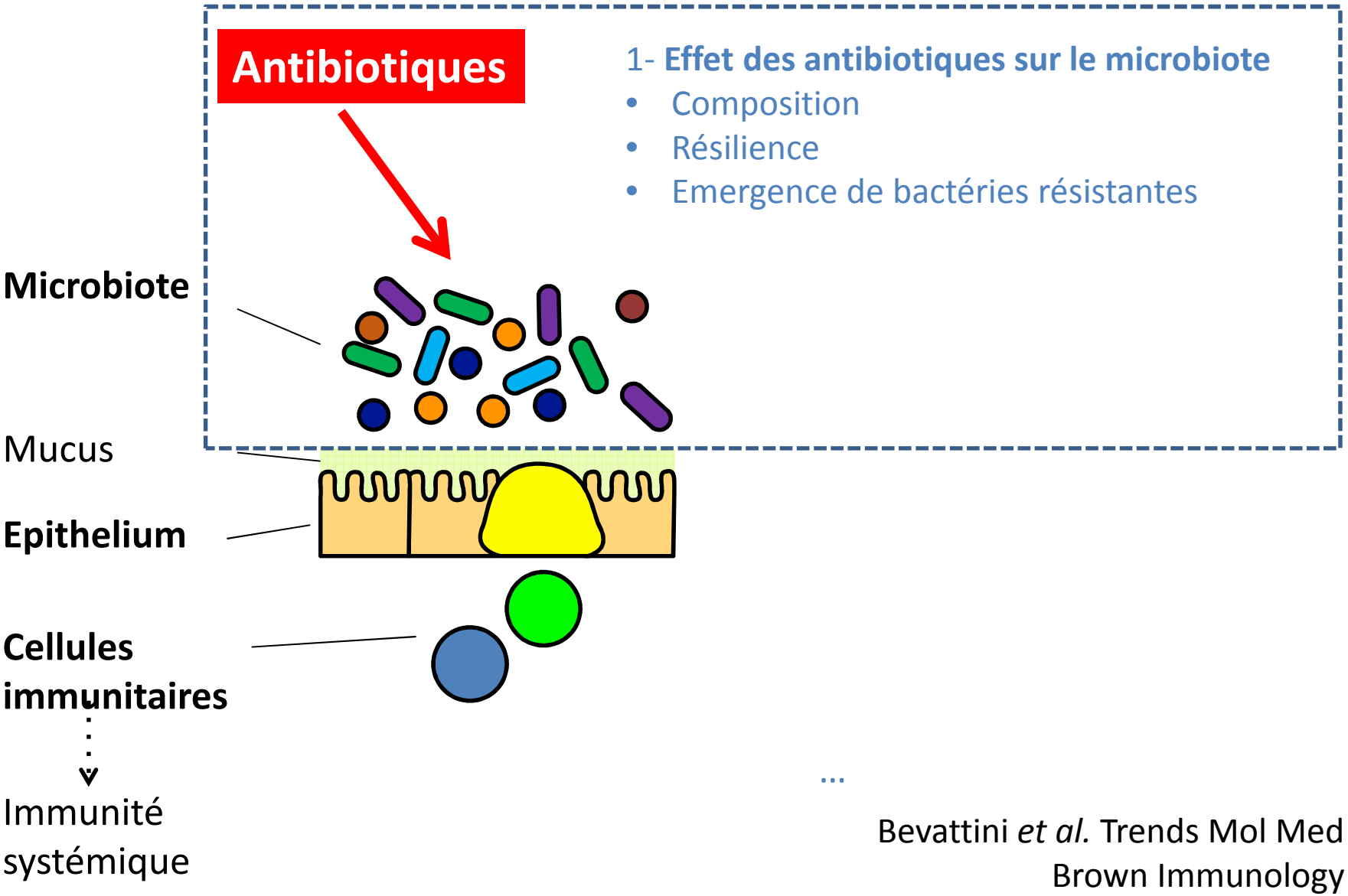
Bevattini *et al.* Trends Mol Med 2016
Brown Immunology 2016

Les antibiotiques perturbent le microbiote



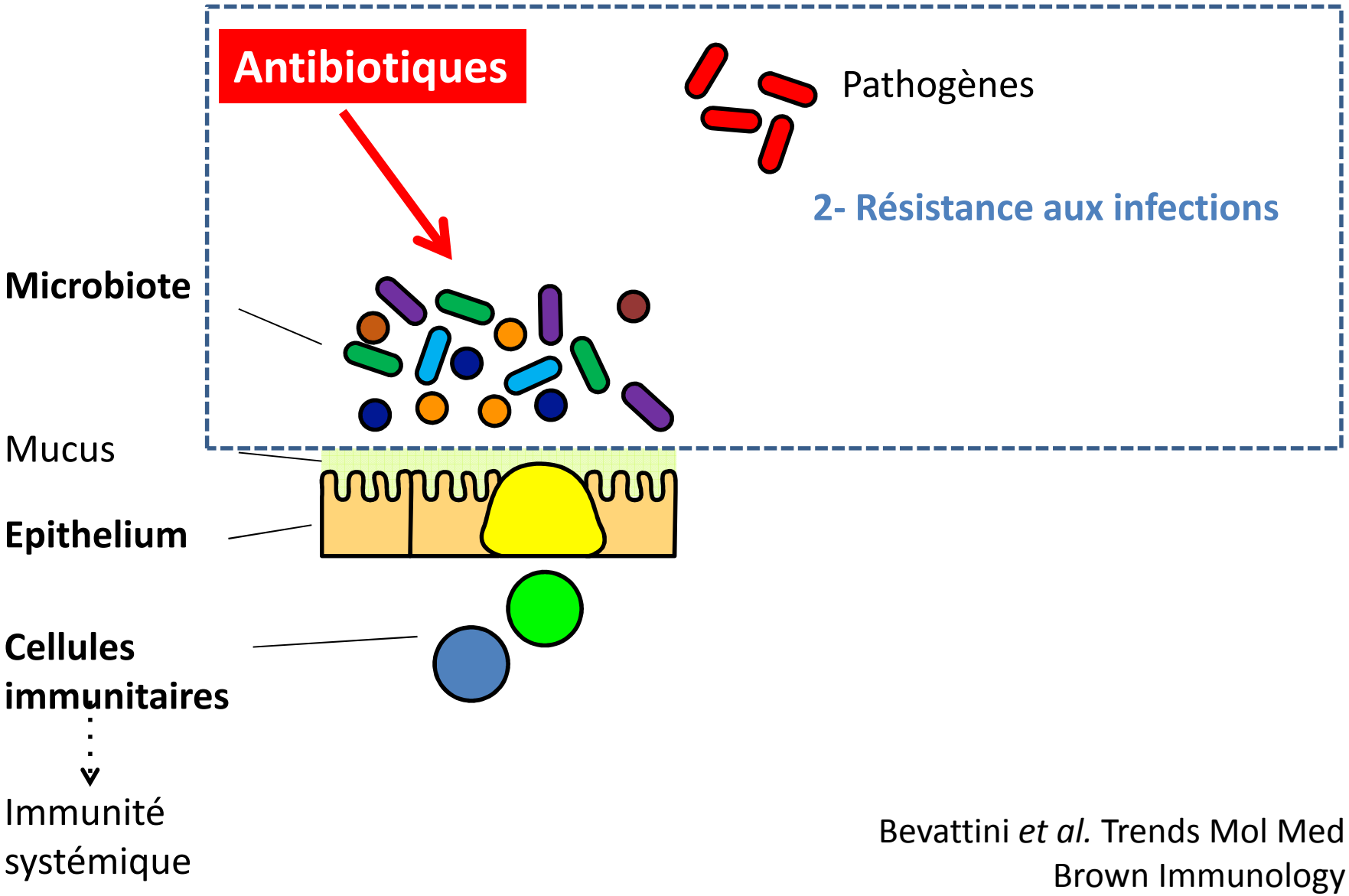
Bevattini *et al.* Trends Mol Med 2016
Brown Immunology 2016

Quels effets les antibiotiques ont-ils sur le microbiote ?



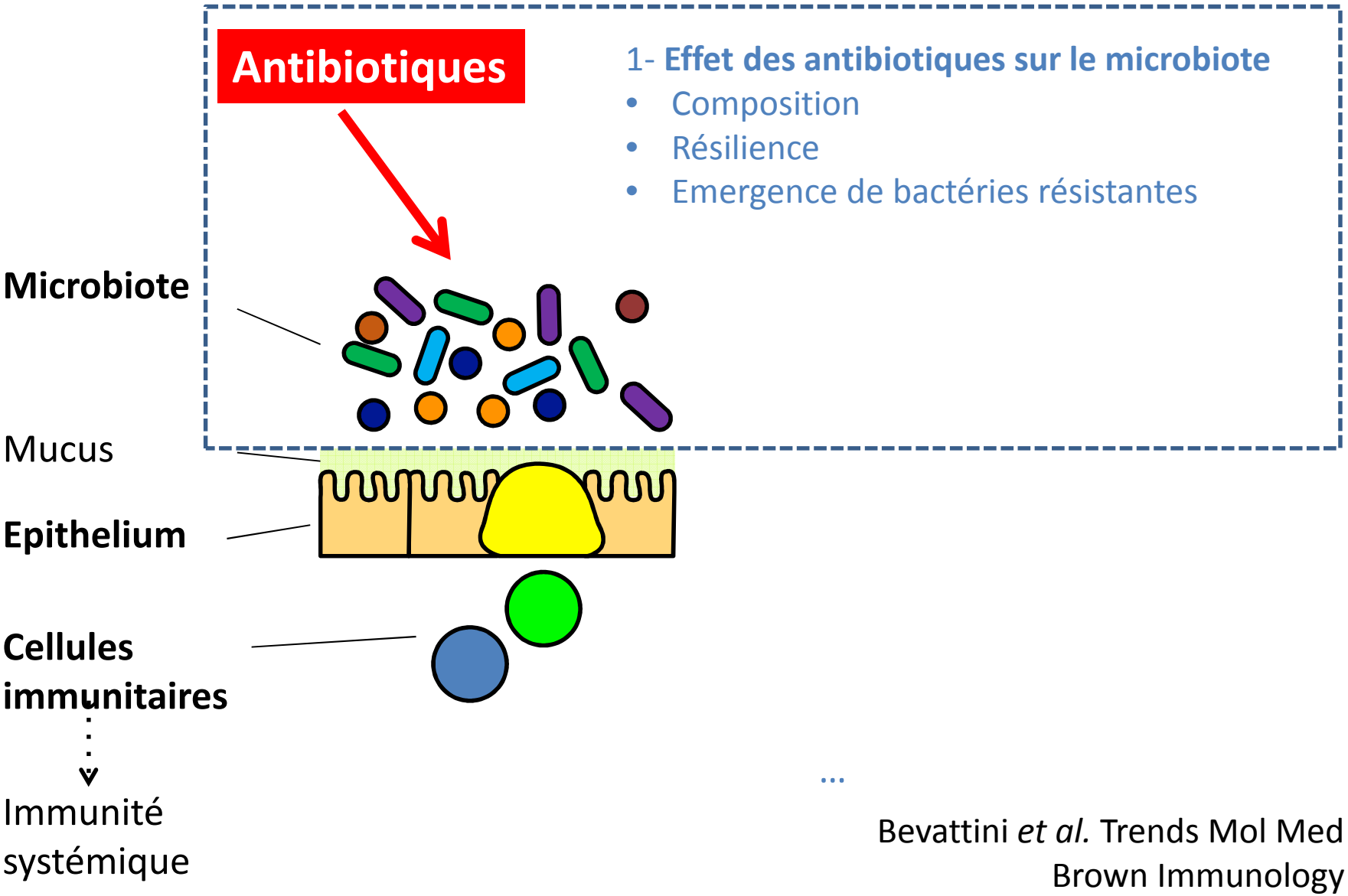
Bevattini *et al.* Trends Mol Med 2016
Brown Immunology 2016

Impact des antibiotiques sur la résistance aux infections



Bevattini *et al.* Trends Mol Med 2016
Brown Immunology 2016

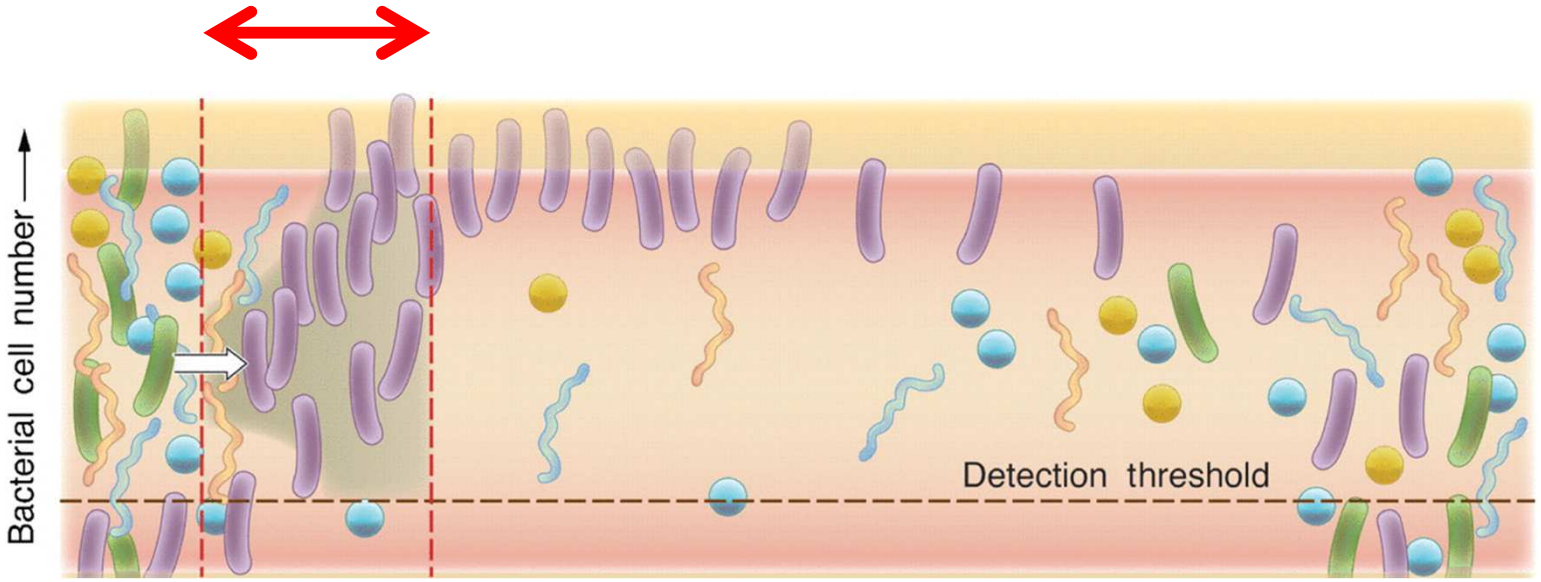
Quels effets les antibiotiques ont-ils sur le microbiote ?



Bevattini *et al.* Trends Mol Med 2016
Brown Immunology 2016

Effets des antibiotiques sur la composition du microbiote

Antibiotiques



↘ Densité
↘ Diversité

Modification composition
↘ Anaréobie stricts
↗ Proteobactéria

Transferts horizontaux de résistance

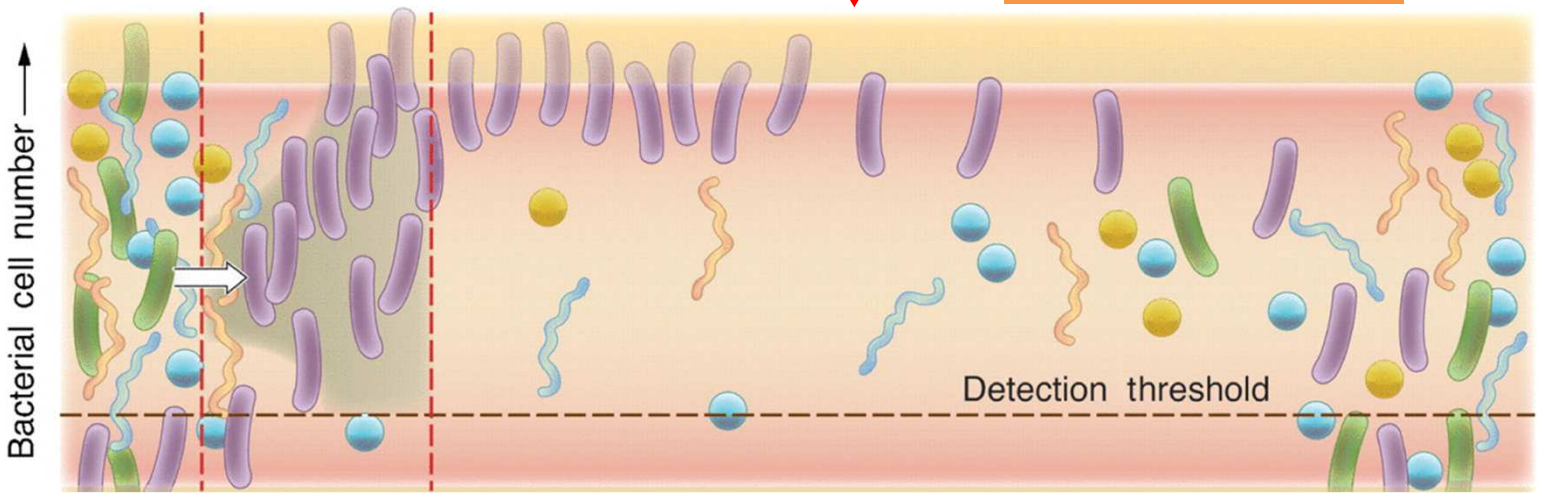
Jernberg ISME J 2007

Effets des antibiotiques sur la composition du microbiote

Antibiotiques

↗ Colonisation pathogènes

Favorise l'émergence de BMR



↘ Densité
↘ Diversité

Modification composition
↘ Anaréobie stricts
↗ Proteobactéria

Résilience ± complète
- **Type antibiotique**
- **Age**
- **…**

Jernberg ISME J 2007, **Dethlefsen** PNAS 2011

Facteurs influençant les effets des antibiotiques sur le microbiote

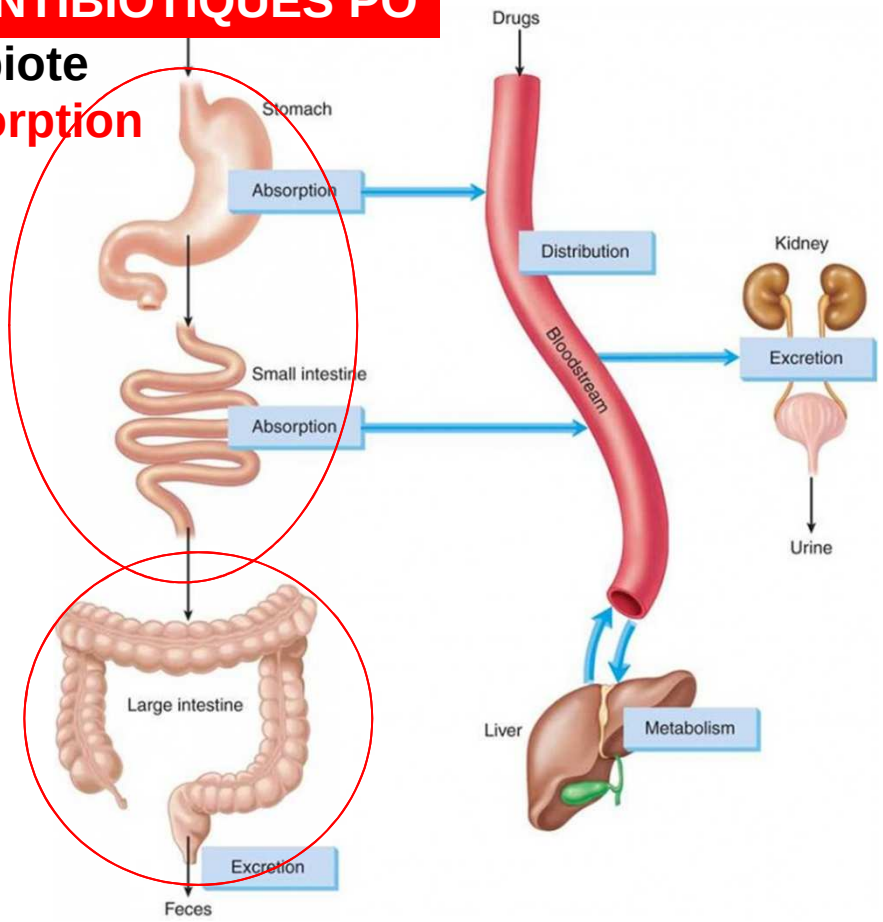
ANTIBIOTIQUES PO

SPECTRE D'ACTIVITE

Effet sur le microbiote en fonction de l'absorption

+

+++



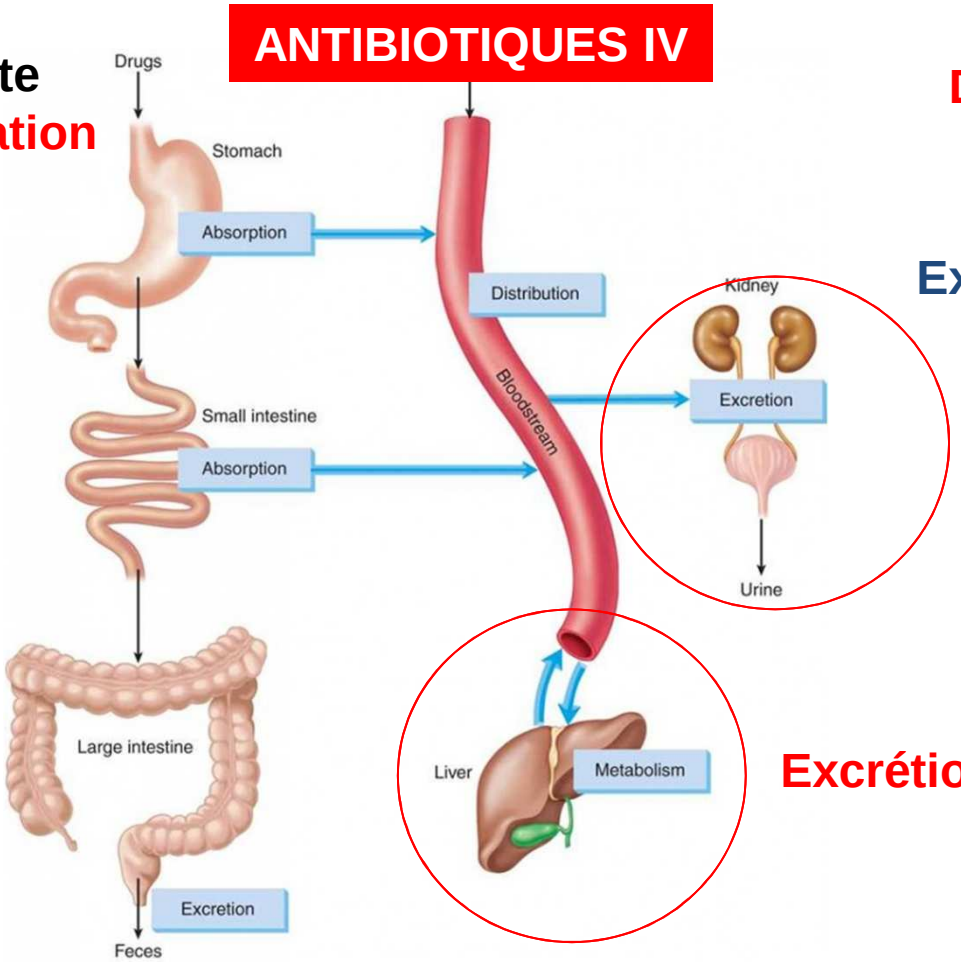
Levison Infect Dis Clin North Am 2009, **Zhang** *et al.* J Antimicrob Chemother 2013

Facteurs influençant les effets des antibiotiques sur le microbiote

Effet sur le microbiote en fonction de l'élimination

+

+++



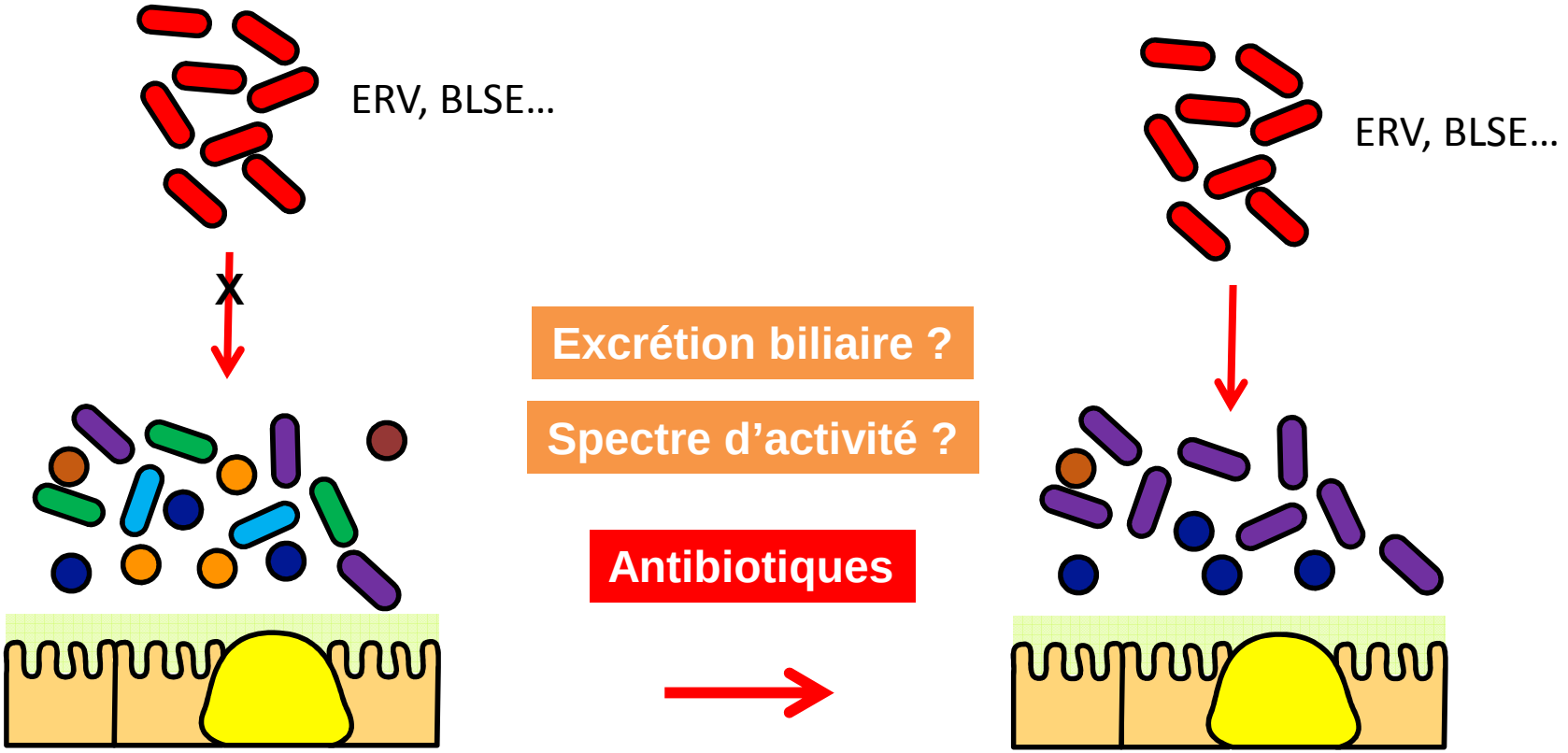
SPECTRE D'ACTIVITE

Excrétion rénale

Excrétion biliaire

Levison Infect Dis Clin North Am 2009, **Zhang** *et al.* J Antimicrob Chemother 2013

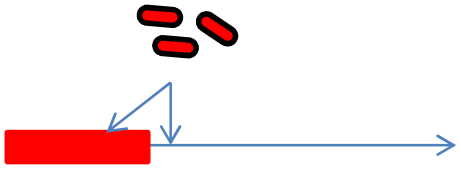
Effets des antibiotiques sur la colonisation des BMR



↘ **Bactéries anaérobie**
↗ **Enterocci**
↗ **γ-proteobactéries**

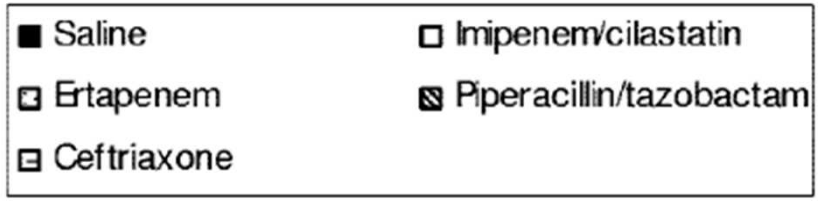
Stiefel AAC 2007

Effets des antibiotiques sur la flore intestinale

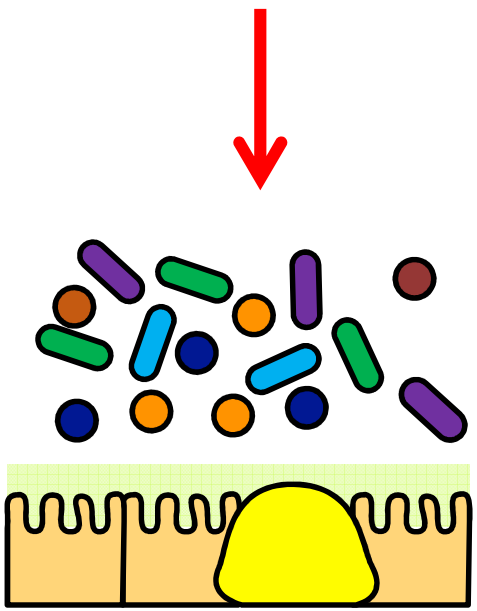


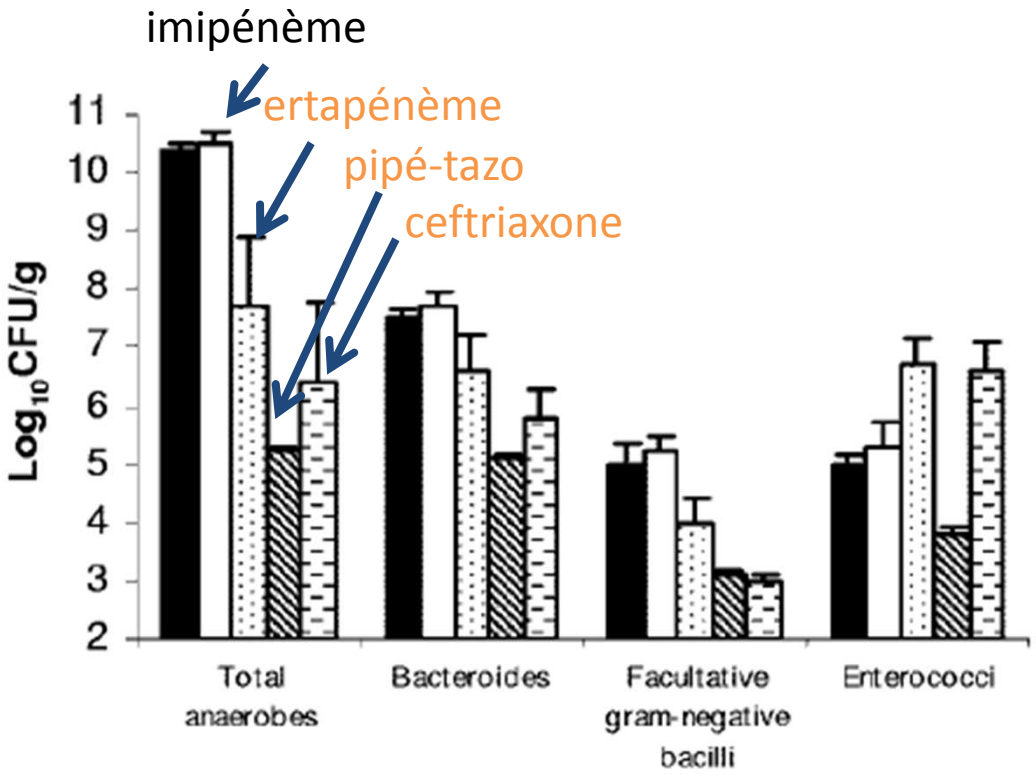
Excrétion biliaire ?

Spectre d'activité ?



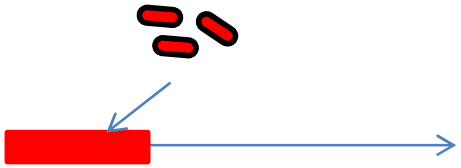
Antibiotiques





Stiefel AAC 2007

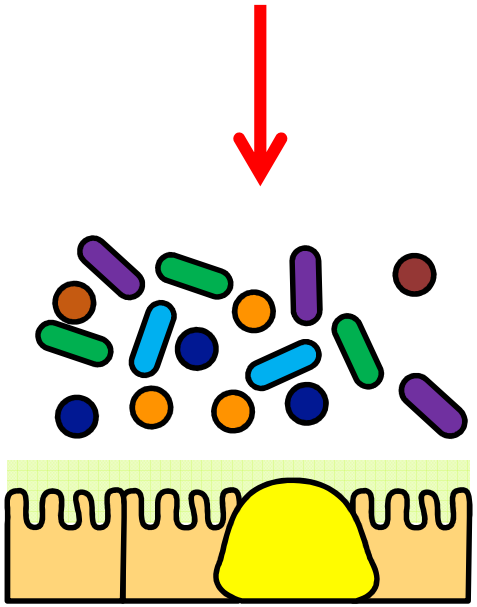
Effets des antibiotiques sur la colonisation des BMR



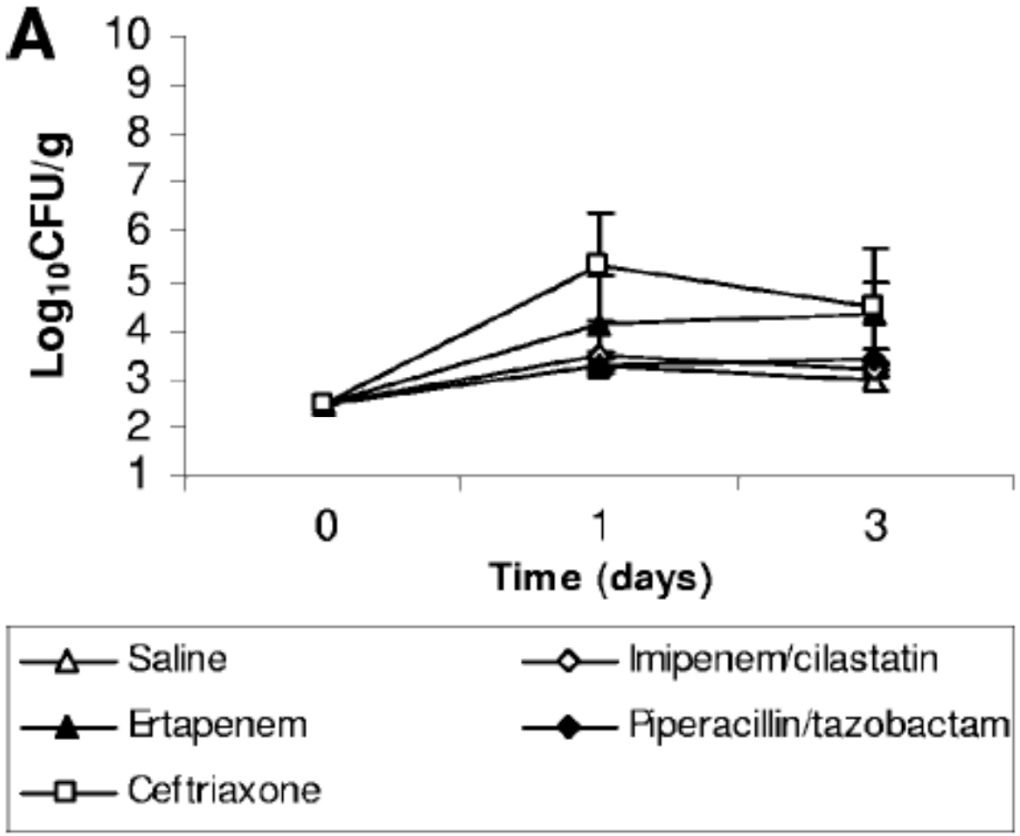
Excrétion biliaire ?

Spectre d'activité ?

Antibiotiques

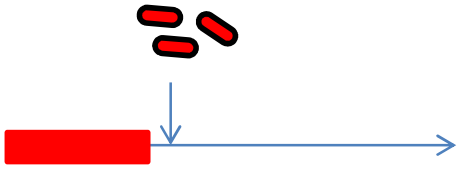


K. pneumoniae BLSE



Stiefel AAC 2007

Effets des antibiotiques sur la colonisation des BMR



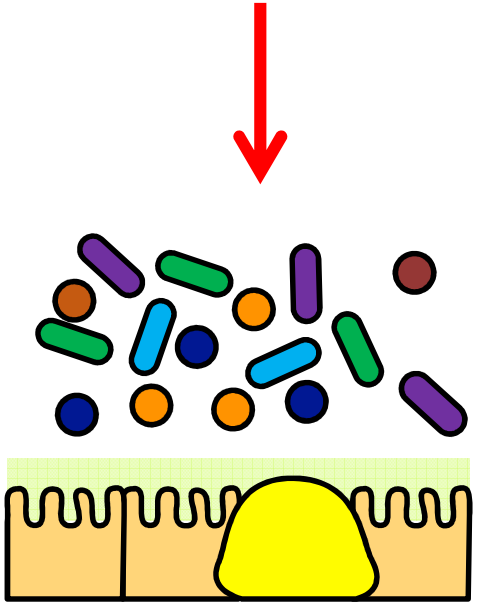
Excrétion biliaire ?

Effet sur les anaérobies ?

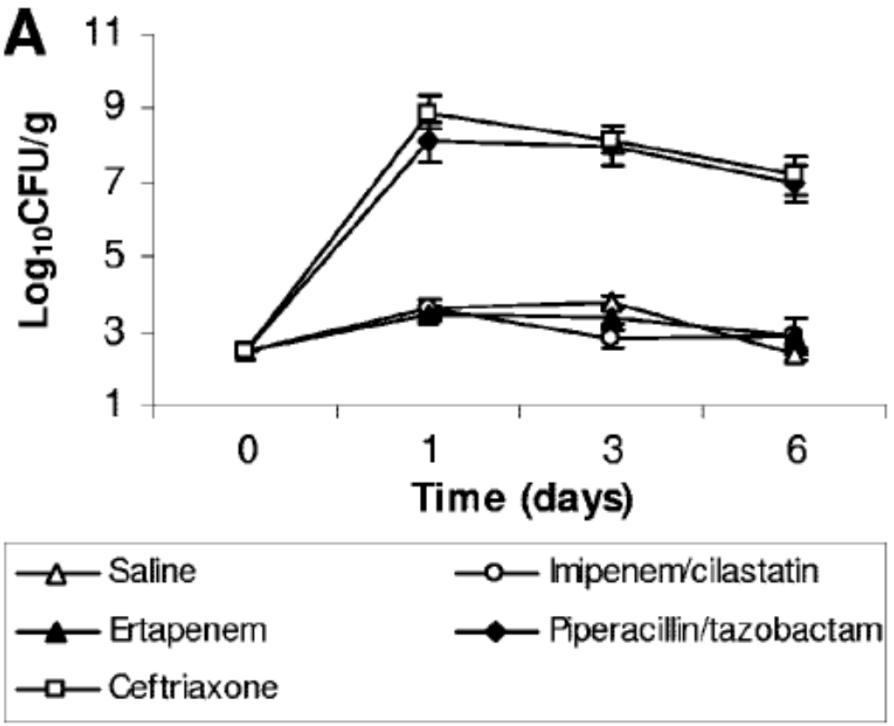
Spectre d'activité ?

Durée de l'effet ?

Antibiotiques

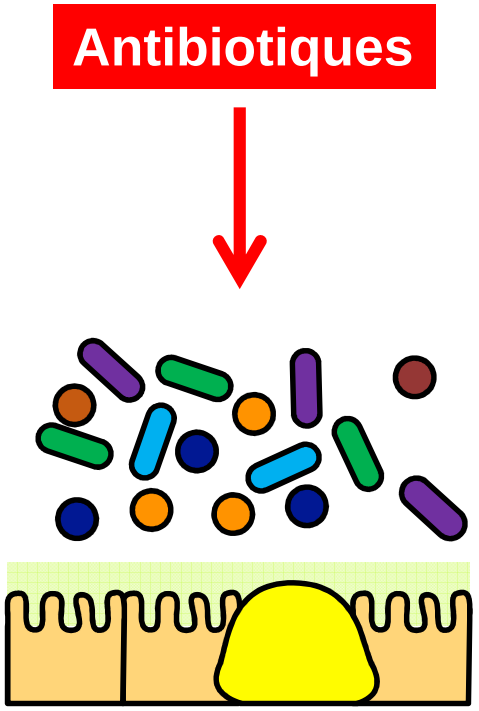


K. pneumoniae BLSE



Stiefel AAC 2007, **Wilcox** JAC 2017

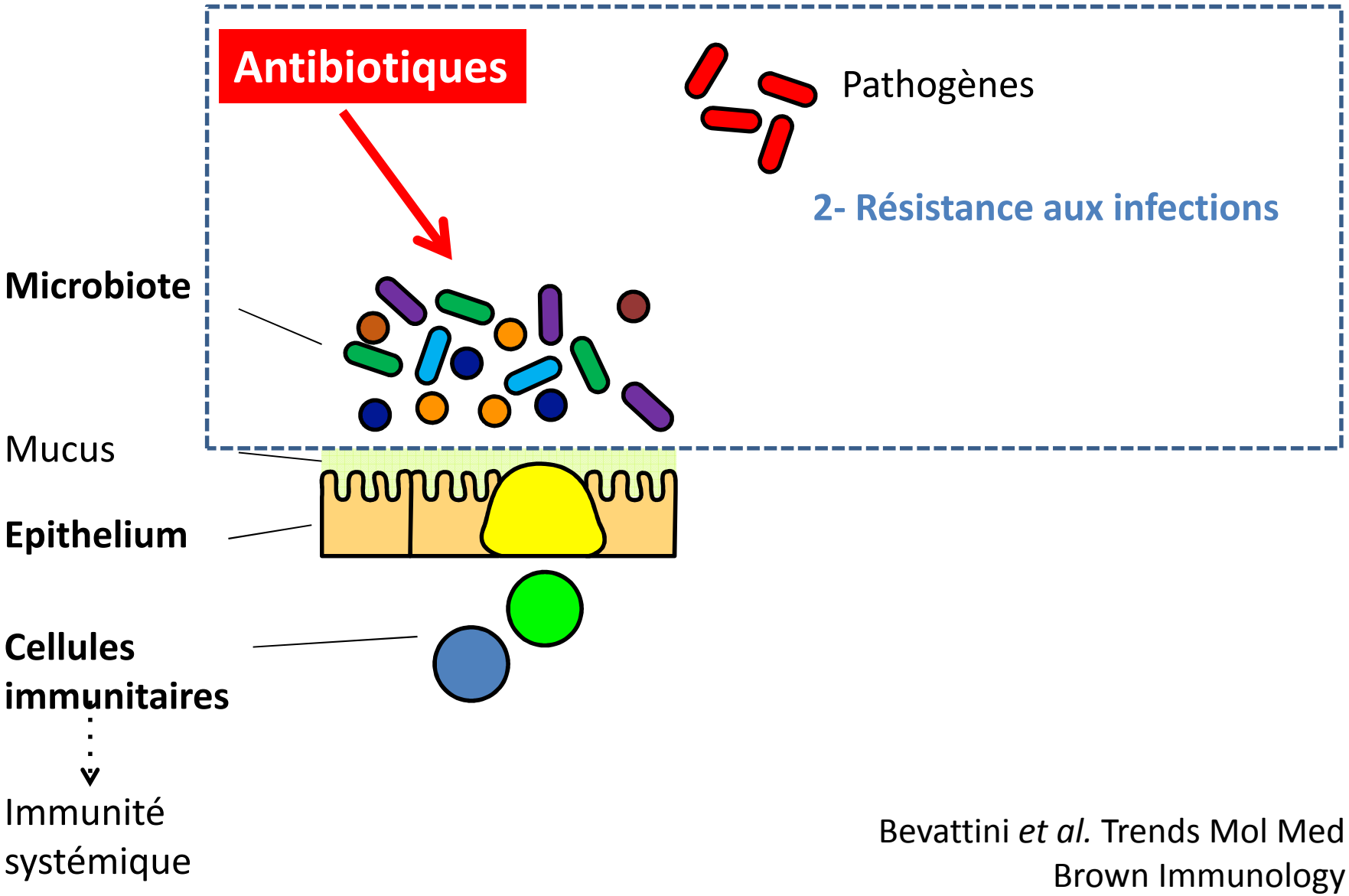
Excrétion biliaire ex Céphalosporines



Agent	Serum $t_{\frac{1}{2}}$, h	Protein binding, %	Urinary excretion, %	Biliary excretion, %
Cefadroxil	1.3–1.6	20	90	2
Cefalexin	0.8–1.0	10	90	0.5
Cefazolin	1.8	80	65	0.2
Cefaclor	0.6	25	50–60	0.05
Cefprozil	1.45	40	76	—
Cefuroxime axetil	1.3	33–50	90	—
Cefuroxime	1.3	35	95	0.5
Cefpodoxime proxetil	2.0–3.6	20	80	—
Cefixime	3.0–4.0	65	50	10
Ceftriaxone	8.5	83–96	65	30–40
Ceftazidime	1.8	17	80–90	3
Ceftobiprole	3–4	16	80–90	—
Ceftaroline	2.5	20	88	—

Wilcox JAC 2017

Impact des antibiotiques sur la résistance aux infections



Bevattini *et al.* Trends Mol Med 2016
Brown Immunology 2016

Massive Outbreak of Antimicrobial-Resistant Salmonellosis Traced to Pasteurized Milk

1985, Largest outbreak of salmonellosis ever recorded in US (n=250,000, even more)

1. **Prior antibiotic exposure increased the risk of developping the disease OR=5.5 (CI 1.2 – 24.8), p=0.033**

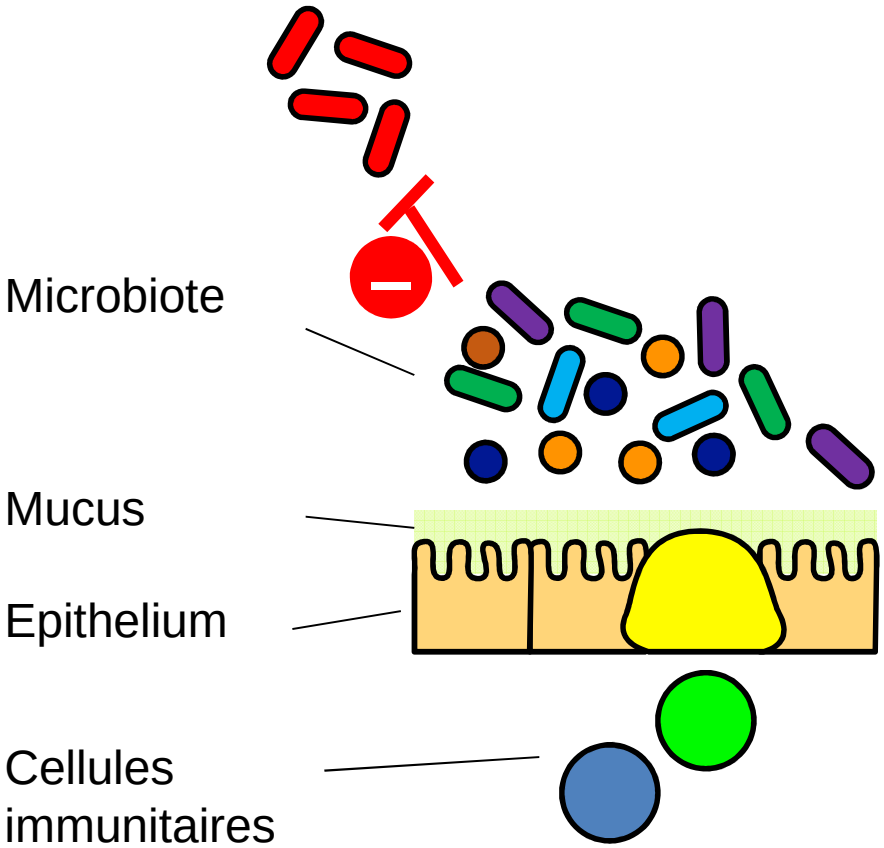
2. **The inoculum needed to cause disease was lower in persons with prior antibiotic exposure.**

Table 1.—Relationship Between Use of Antimicrobials in Month Before Illness and Average Daily Consumption of Implicated Brands of Milk*

	Took No Antibiotics		Took "Resistant"† Antibiotics		
	Cups	No.	Cups	No.	P‡
Ill	3.6	38	2.4	16	.010
Well	1.9	76	1.6	5	.184
P‡	.000039		.034		. . .

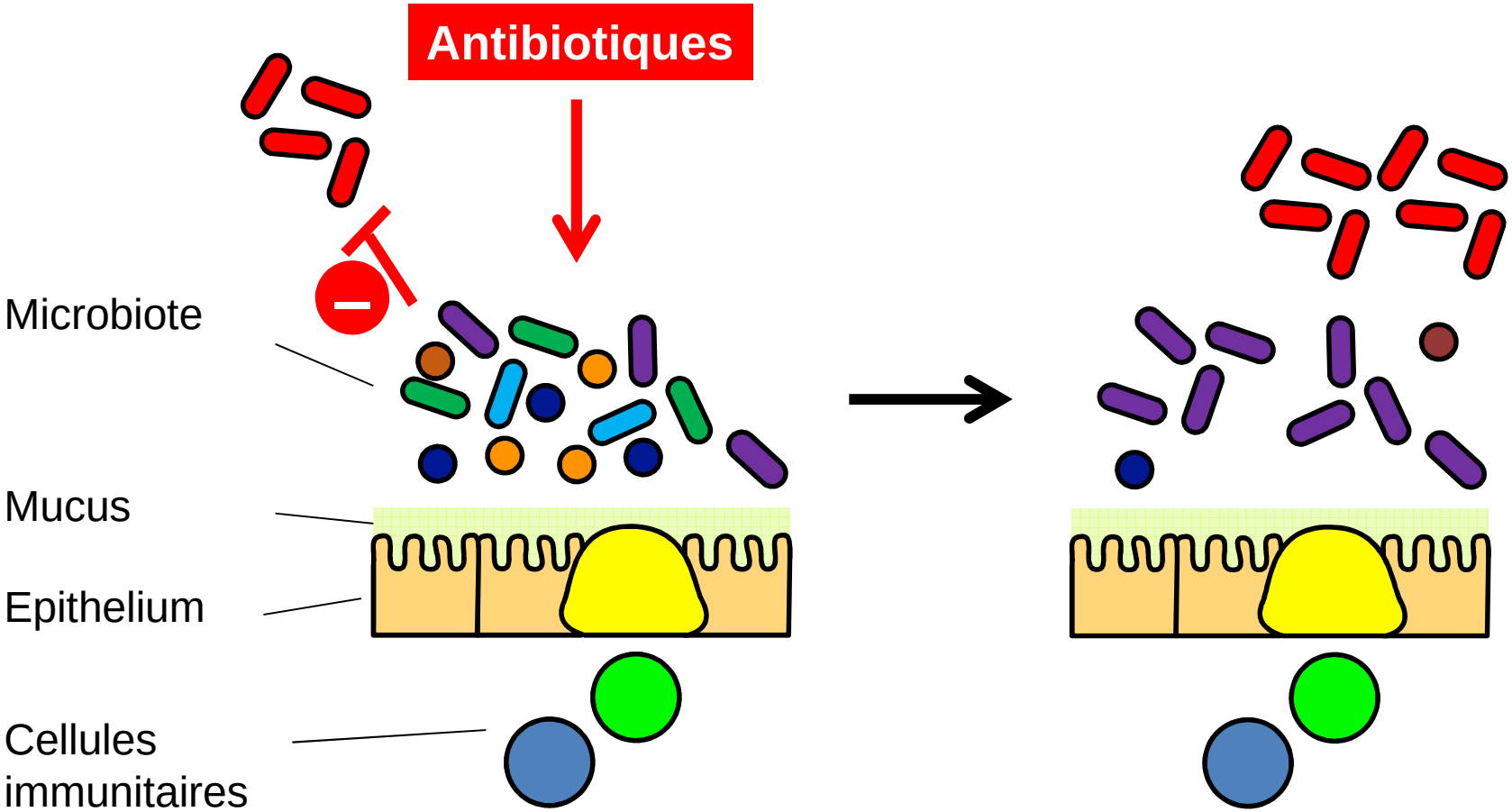
JAMA, Dec 11, 1987—Vol 258, No. 22

Principes de la résistance conférée par le microbiote



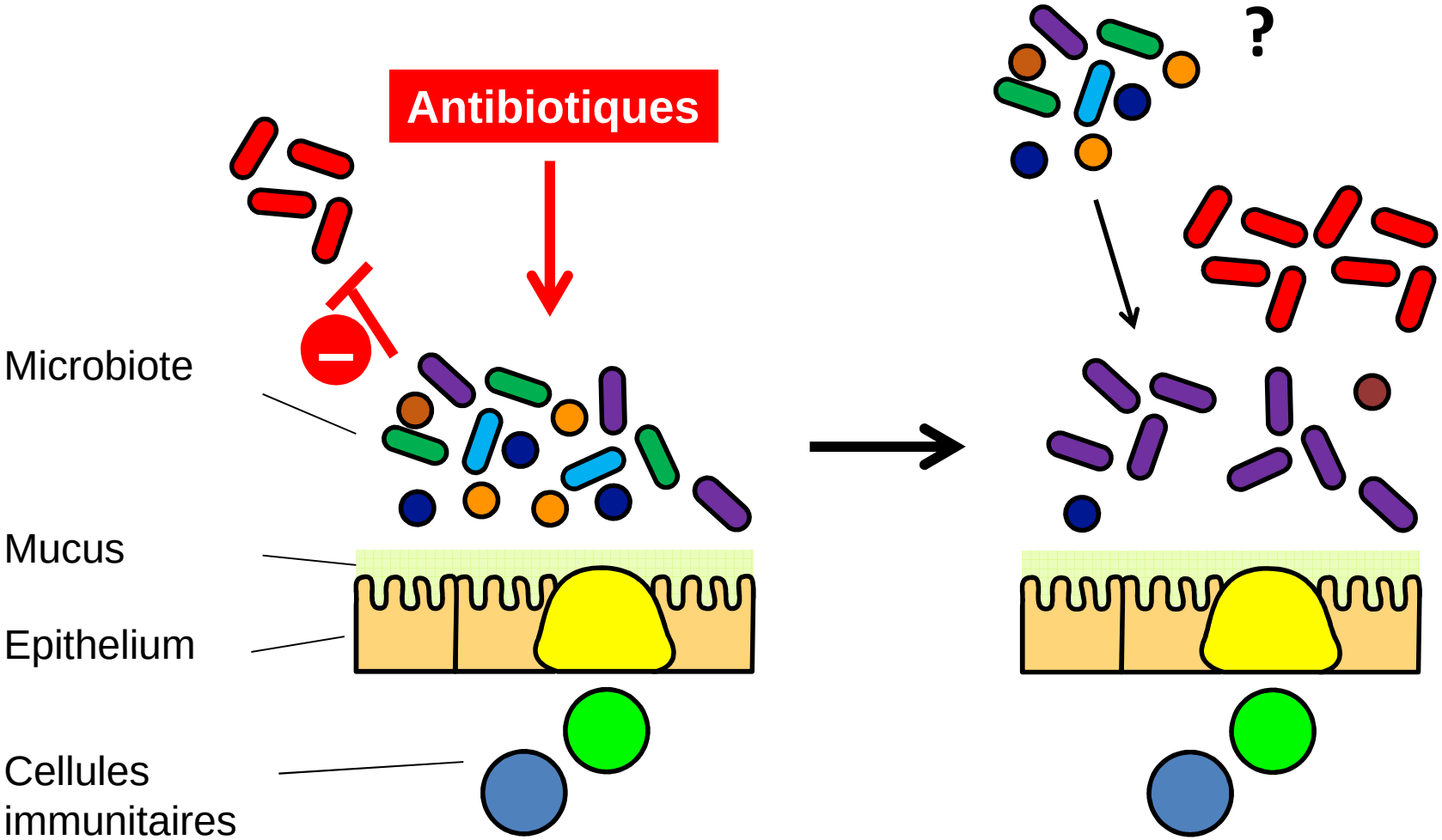
Becattini J Exp Med 2017, **Van Nood** NEJM 2013, **Caballero** Cell Host Microbes 2017

Principes de la résistance conférée par le microbiote



Becattini J Exp Med 2017, **Van Nood** NEJM 2013, **Caballero** Cell Host Microbes 2017

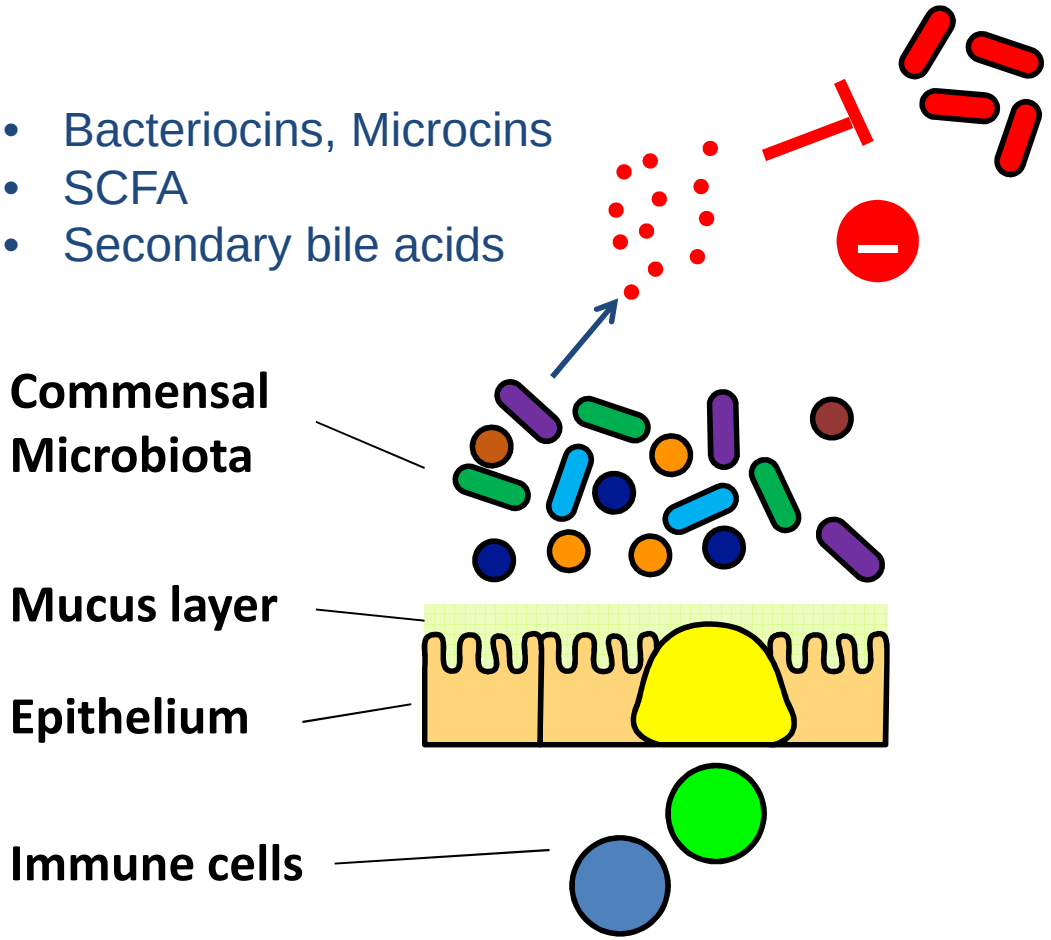
Principes de la résistance conférée par le microbiote



Becattini J Exp Med 2017, **Van Nood** NEJM 2013, **Caballero** Cell Host Microbes 2017

Le microbiote protège son hôte des pathogènes

- Bacteriocins, Microcins
- SCFA
- Secondary bile acids

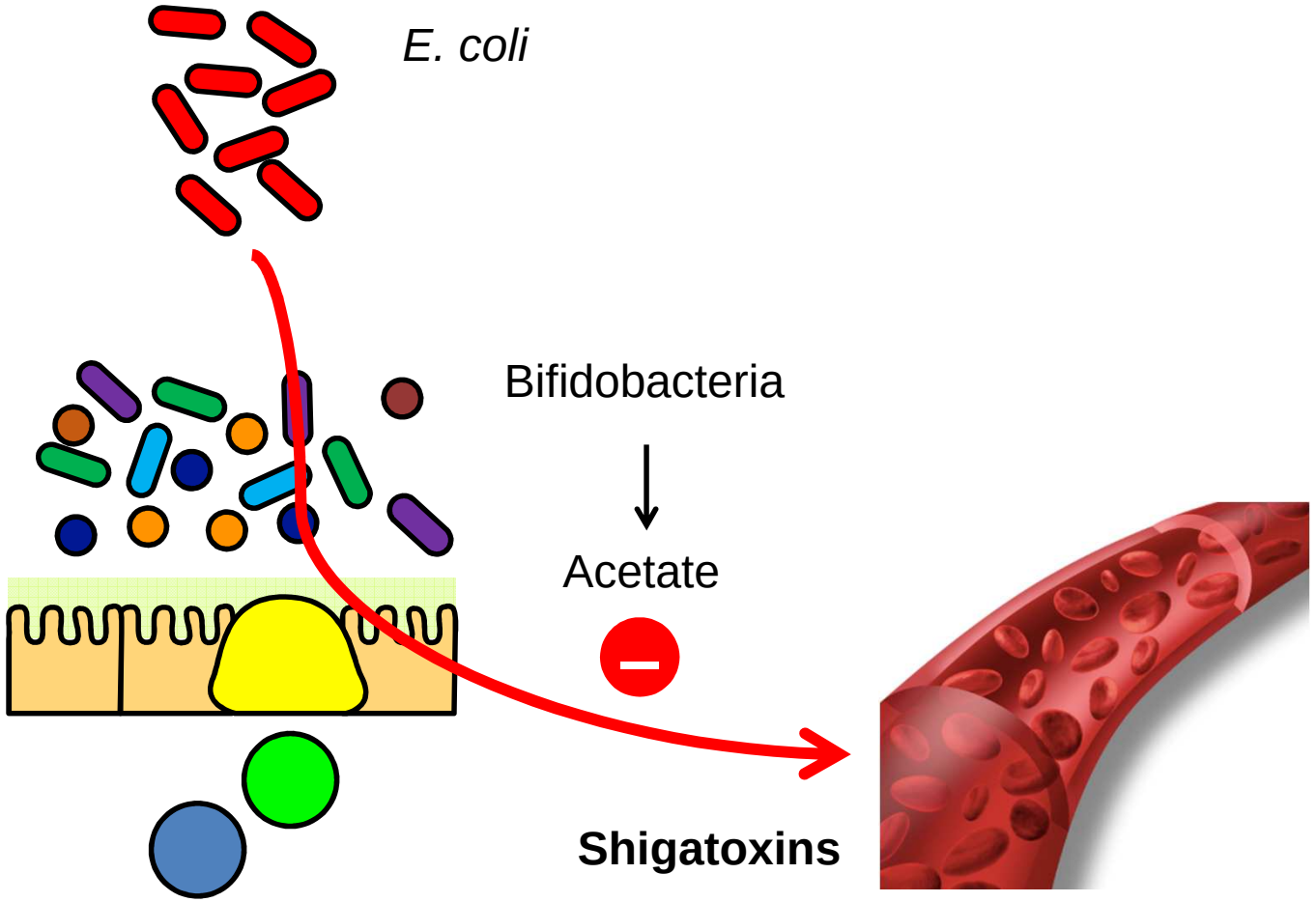


1- Inhibition directe

Production de molécules anti-bactériennes

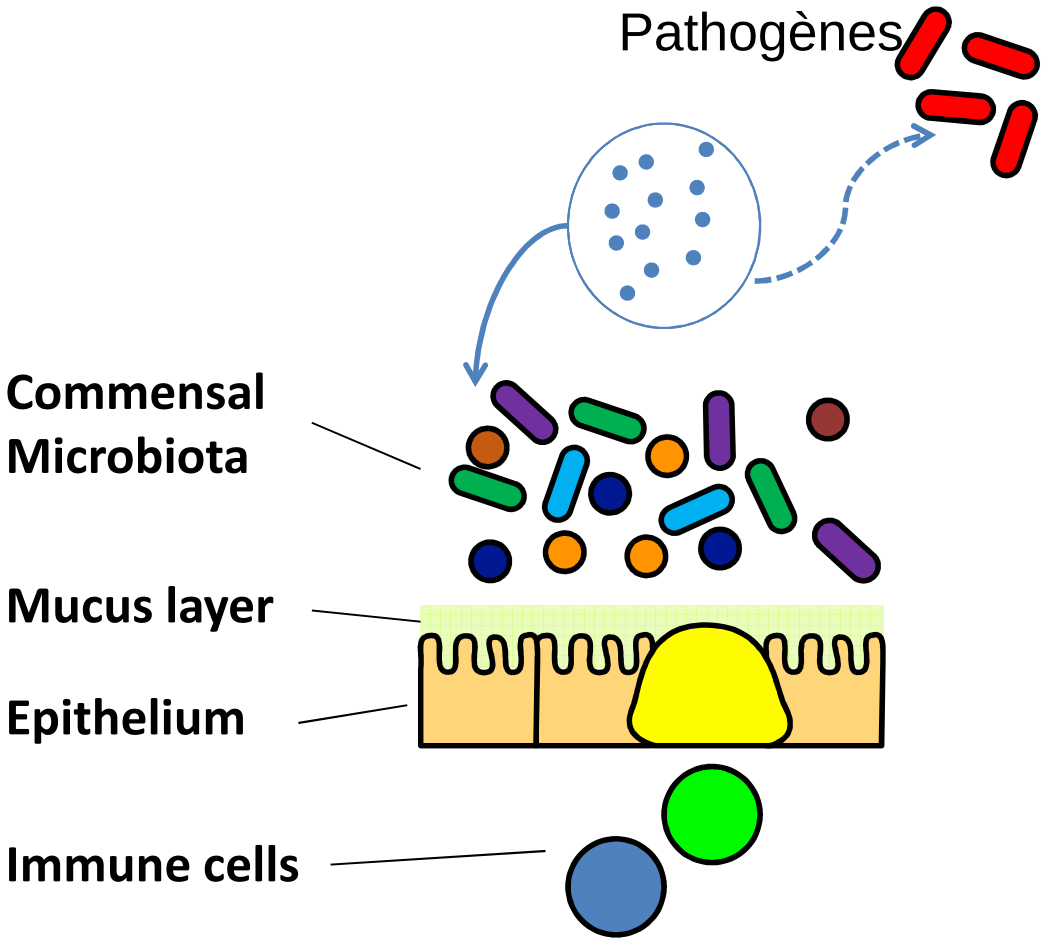
Ubeda Clin Translat Immunol 2017
Abt & Pamer Curr Opin Immunol 2014
Gauguet S *et al.* Infect Immun 2015
Clarke *et al.* Nat Med 2010

Le microbiote protège son hôte des pathogènes



Fukuda Nature 2011

Le microbiote protège son hôte des pathogènes



2- Compétition et privation de nourriture
(fer, carbohydrate…)

Exemple: acide sialique et
C. difficile
E. coli / EHEC

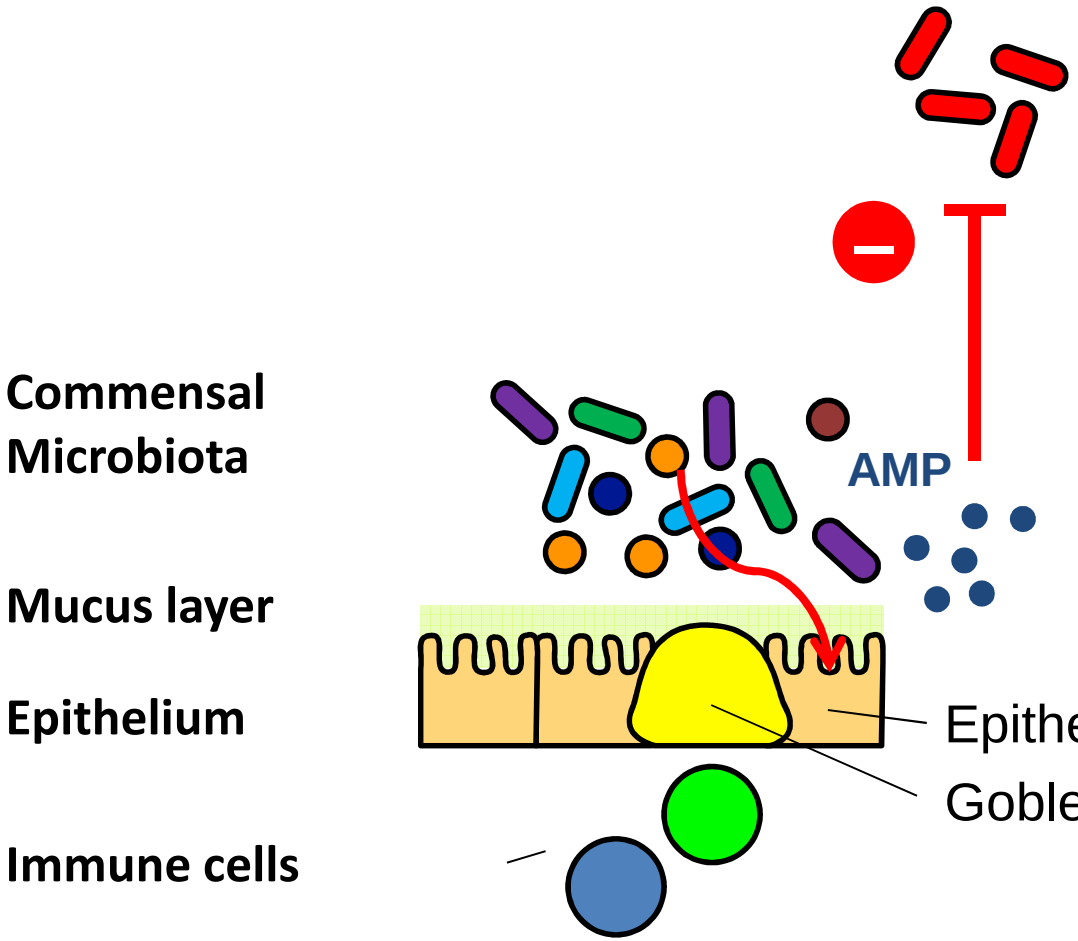
Ubeda Clin Translat Immunol 2017
Abt & Pamer Curr Opin Immunol 2014
Clarke *et al.* Nat Med 2010
Ng KM Nature 2013

Inhibition directe

Commensal	Pathogen	Mechanism
S. lugdunensis	*S. aureus*	Peptide antibiotic (bactericidal activity)
E. faecalis (pPD1 plasmid)	VRE	Plasmid-encoded bacteriocin (pathogen growth inhibition)
Bacillus thuringiensis	*C. difficile*	Bacteriocin
E. coli strain Nissle 1917	*S. typhimurium*	Microcins (antimicrobial activity), competition for iron
	E. coli O157:H7	Competition for carbohydrates
C. scidens	*C. difficile*	Bile acids conversion (inhibition of pathogen growth)
R. obeum	*V. cholerae*	interference with pathogen gene expression

Ubeda *et al.* Clin Translat Immunol 2017

Le microbiote influence le fonctionnement de l'épithélium

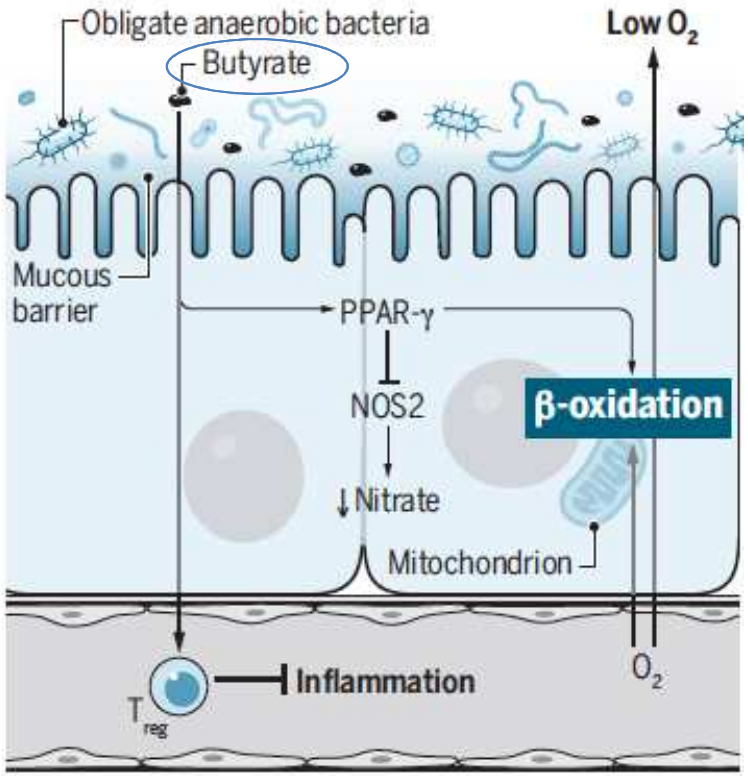


3- Action sur les cellules épithéliales

- Peptides anti-microbiens
- Production de mucus

Abt & Pamer Curr Opin Immunol 2014
Gauguet S *et al.* Infect Immun 2015
Clarke *et al.* Nat Med 2010

Exemple d'influence du microbiote sur le métabolisme épithélial

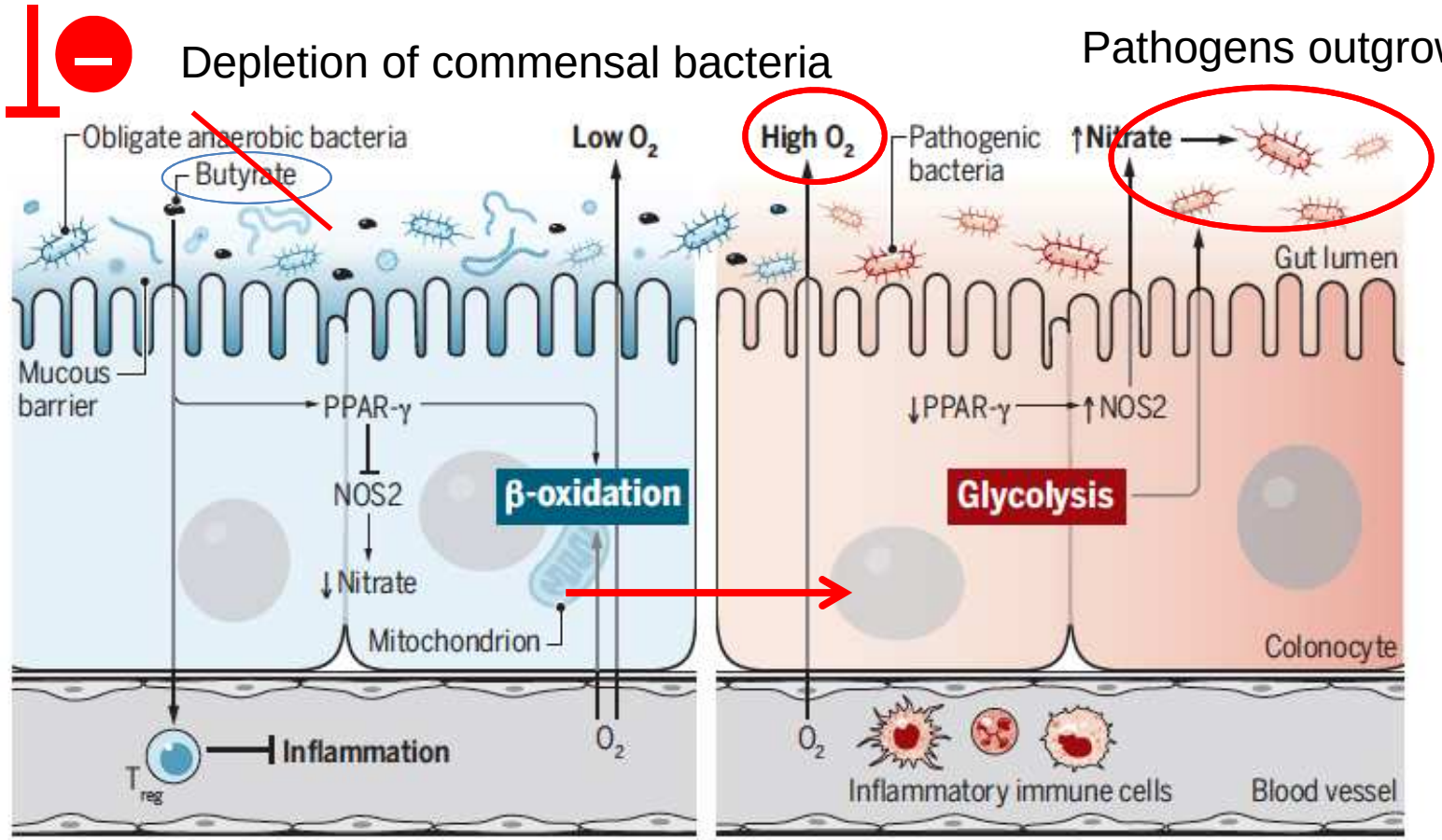


Symbiosis
In a normal, symbiotic situation, the gut is kept hypoxic by β-oxidation, and this maintains growth of obligate anaerobic bacteria.

Byndloss Science 2017, **Cani** Science 2017

Exemple d'influence du microbiote sur le métabolisme épithélial

Antibiotics

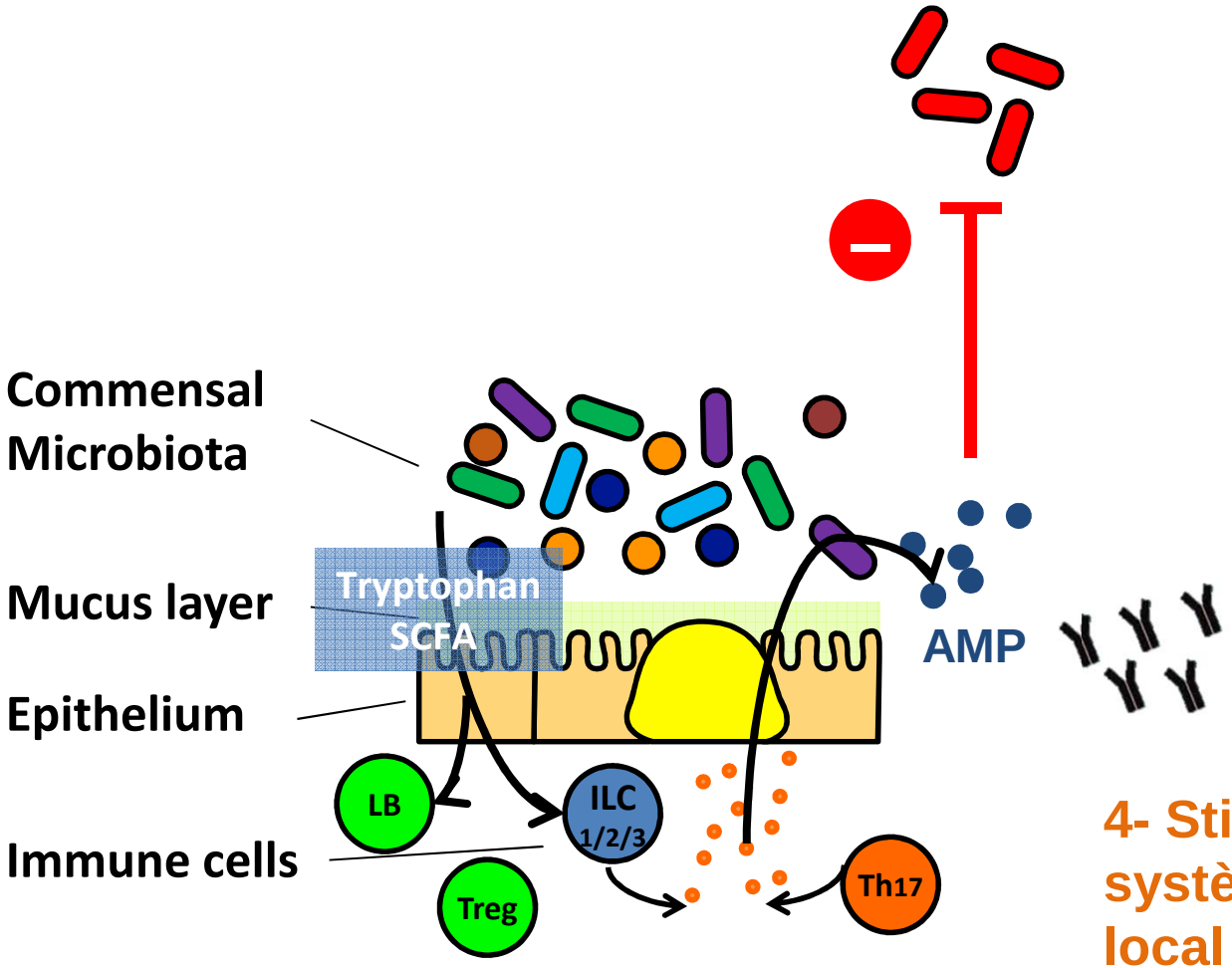


Symbiosis
In a normal, symbiotic situation, the gut is kept hypoxic by β-oxidation, and this maintains growth of obligate anaerobic bacteria.

Dysbiosis
After treatment with antibiotics, colonocyte metabolism changes to glycolysis, which allows the outgrowth of pathogenic bacteria.

Byndloss Science 2017, **Cani** Science 2017

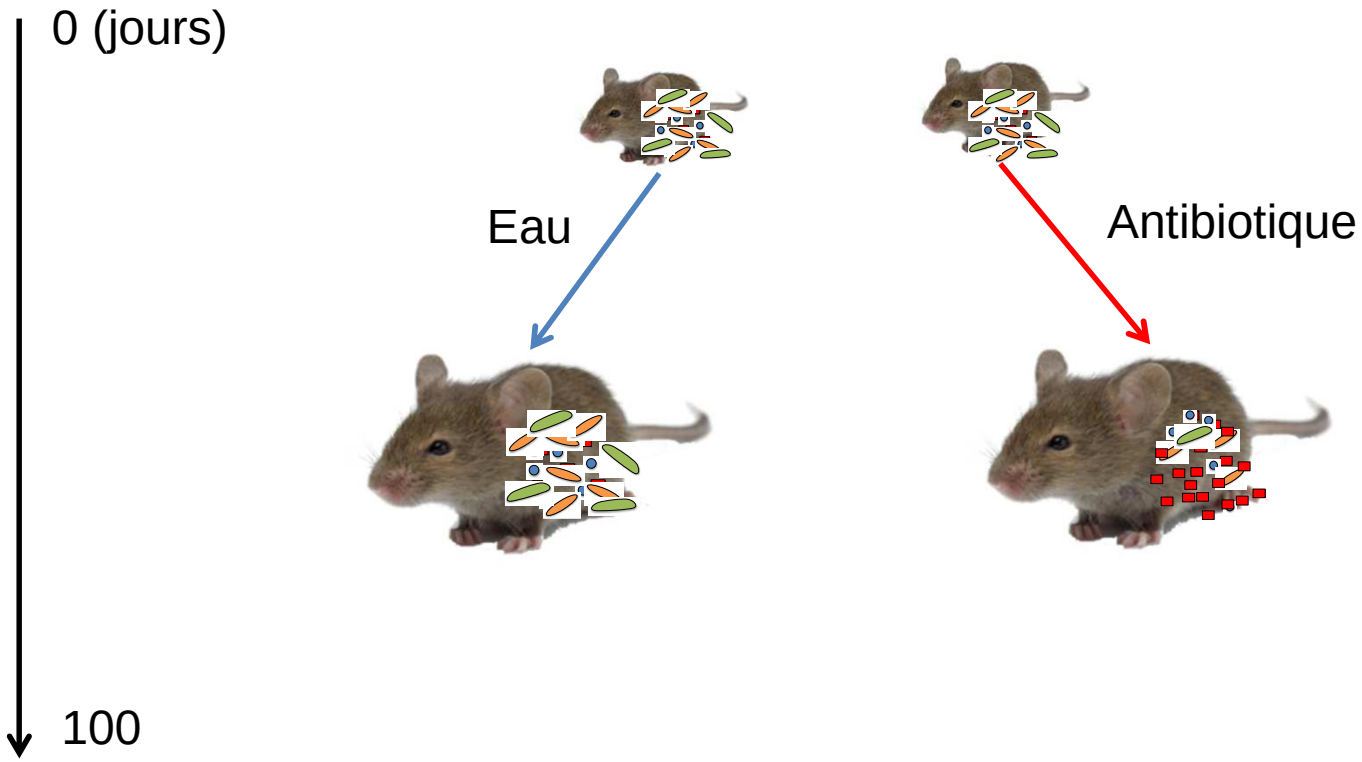
Le microbiote influence l'immunité locale et systémique



4- Stimulation du système immunitaire local et systémique

Ivanov et al. Cell 2009
Honda & Littman Nature 2016
Gauguet S *et al.* Infect Immun 2015
Clarke *et al.* Nat Med 2010

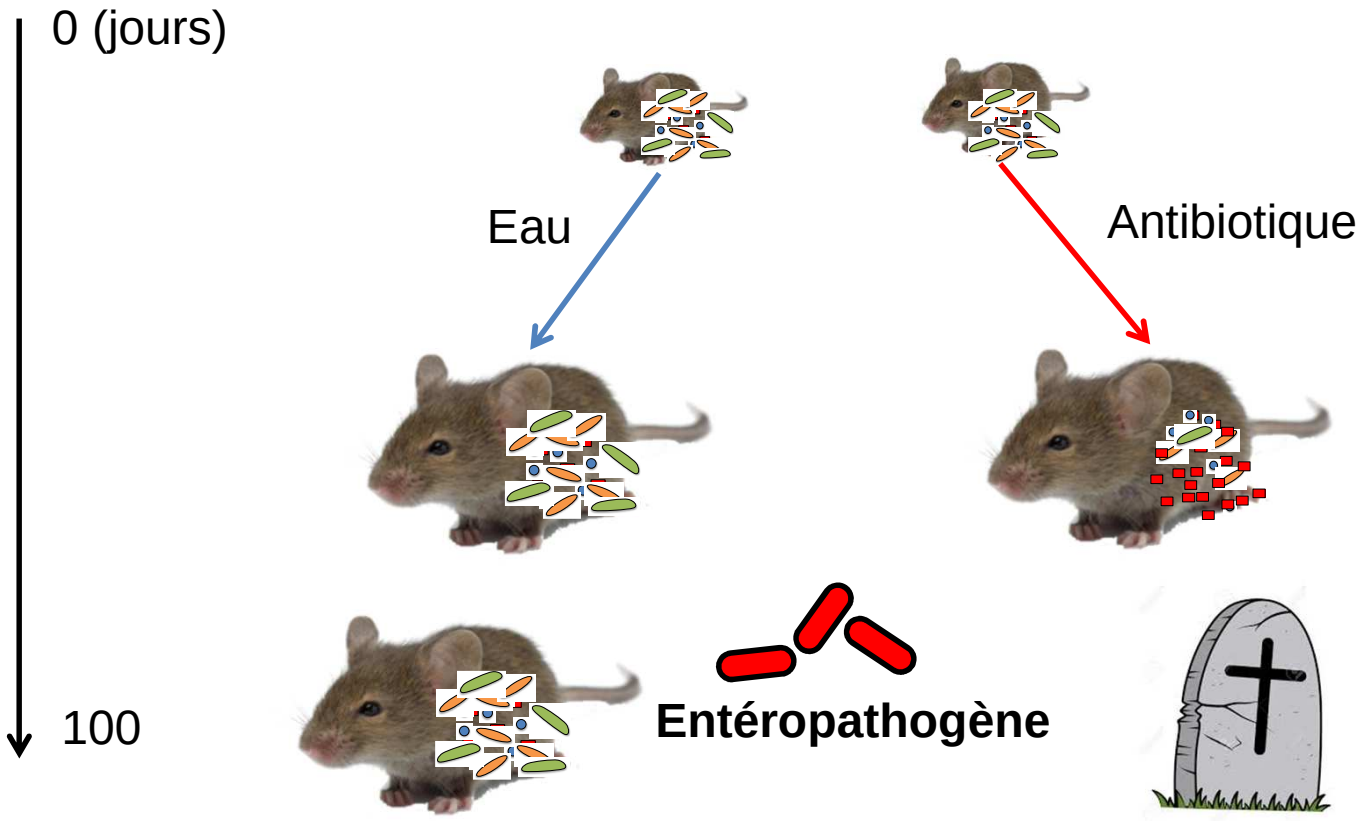
Antibiotique, microbiote et résistance aux infections



NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Roubaud Baudron *et al.* manuscrit en préparation

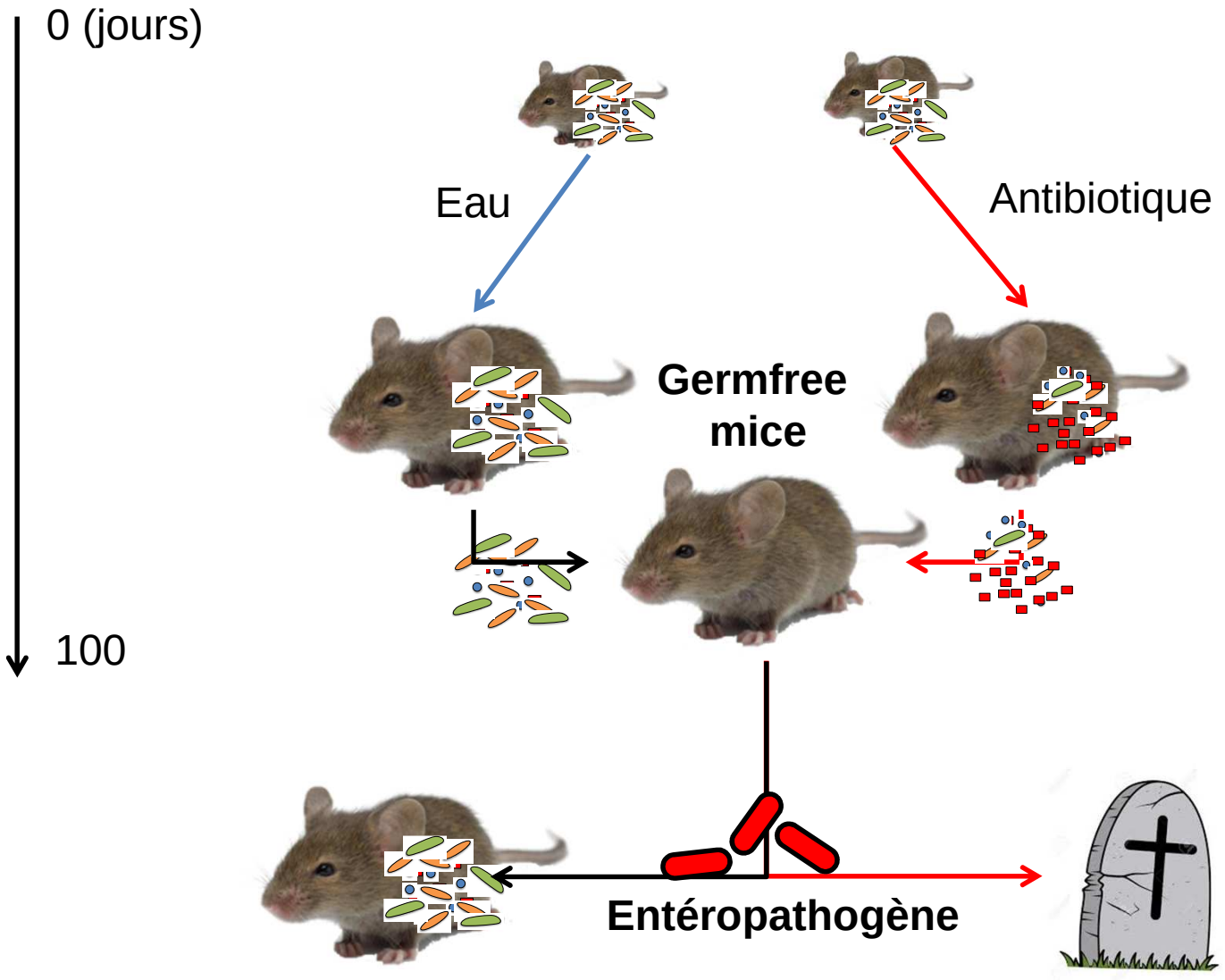
Antibiotique, microbiote et résistance aux infections



NYU School of Medicine
NYU LANGONE MEDICAL CENTER

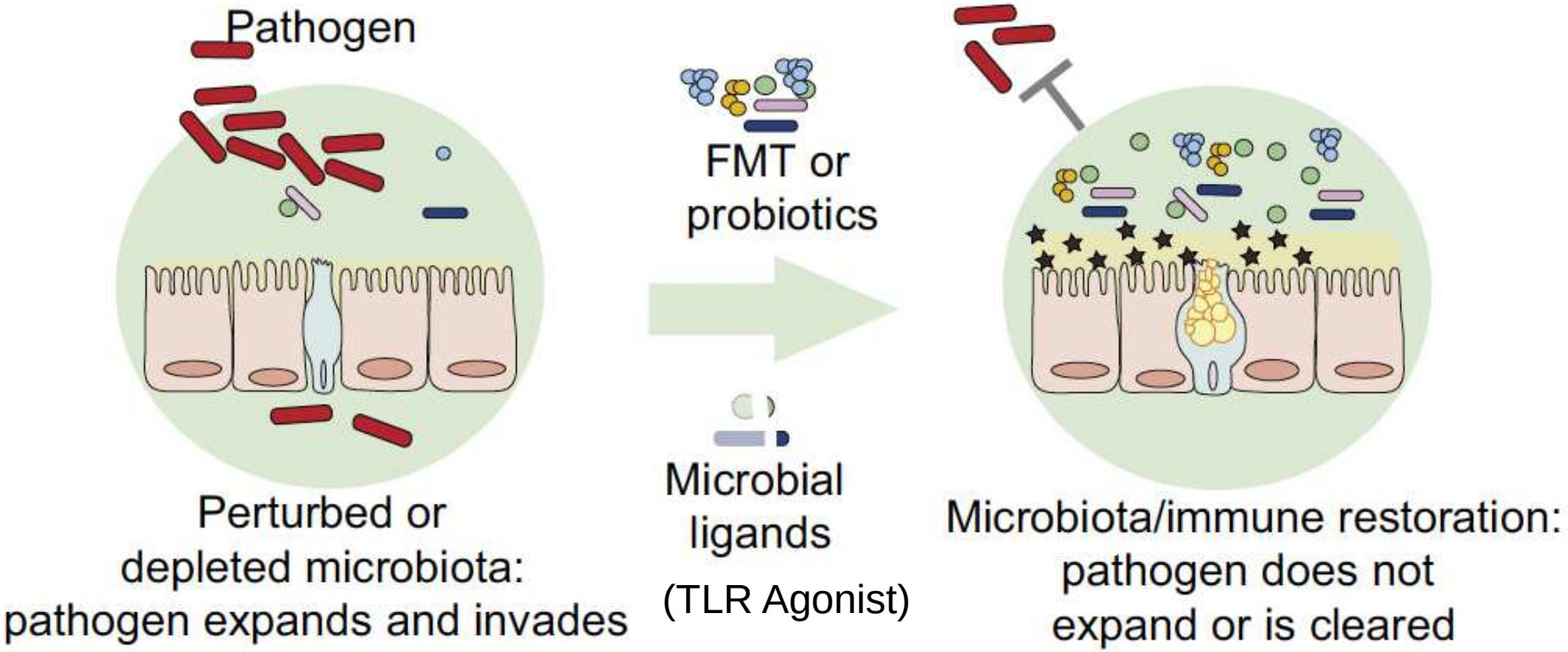
Roubaud Baudron *et al.* manuscrit en préparation

Antibiotique, microbiote et résistance aux infections



Roubaud Baudron *et al.* manuscrit en préparation

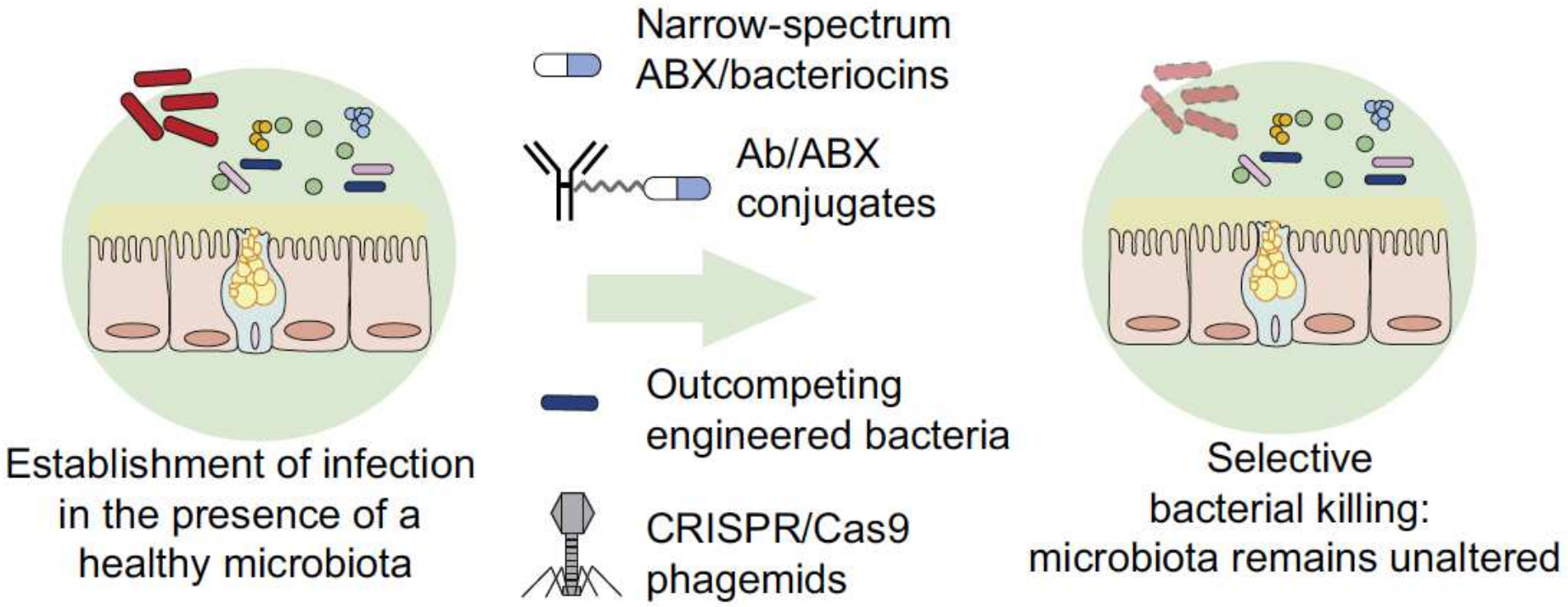
Quelles solutions ? Restaurer le microbiote lésé



Becattini Trends Mol Med 2016

Quelles solutions ? utiliser des traitements plus sélectifs préservant le microbiote

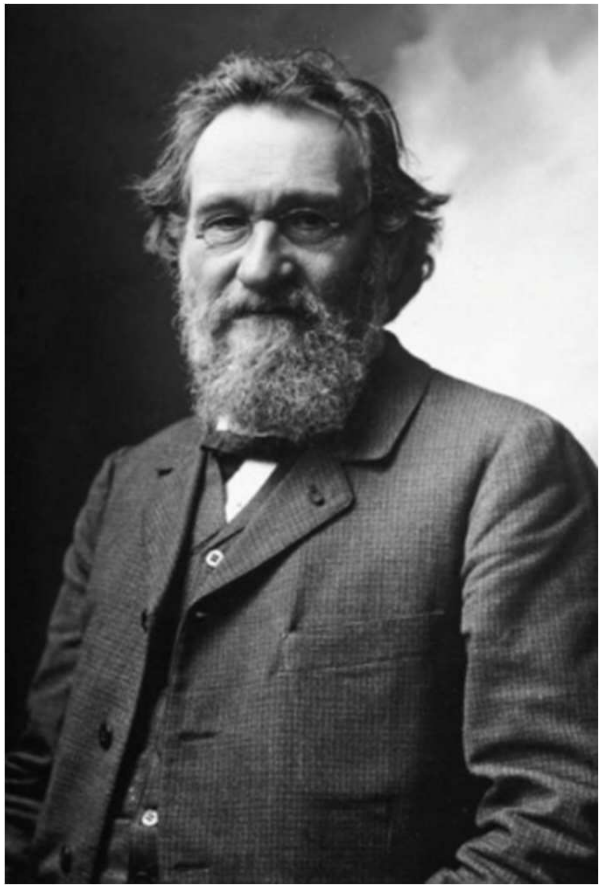
Diminuer la prescription antibiotique



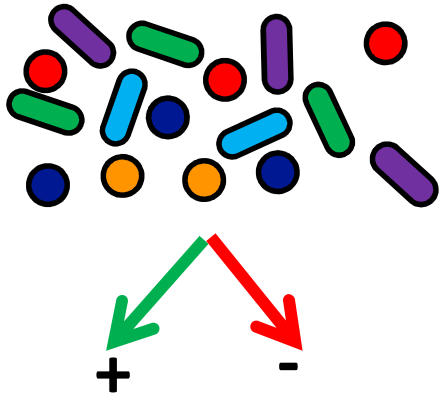
Cleave specific DNA sequence

Becattini Trends Mol Med 2016

100 ans plus tard



Metchnikoff 1907



- Le microbiote confère une résistance aux infections
- Quelles bactéries sont protectrices ?
- Les antibiotiques provoquent une dysbiose
  ⇒ colonisation et développement des pathogènes
- Caractéristiques des antibiotiques
- Avenir ?
  ⇒ Utilisation de probiotiques ?
  ⇒ Antibiothérapie plus ciblée ?

Merci

Martin J Blaser

Guillermo I Perez Perez

Victoria E Ruiz

Alexander Swan

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Bruce A Vallance, University of British Columbia, Vancouver, Canada

CHU Hôpitaux de Bordeaux

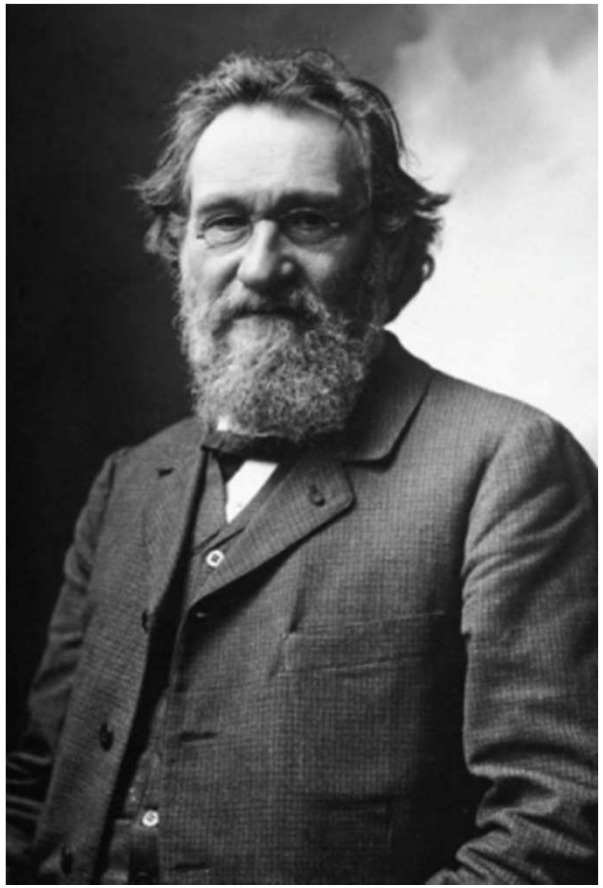
SGBSO
SOCIÉTÉ DE GÉRONTOLOGIE DE BORDEAUX ET DU SUD-OUEST

Groupe Pasteur Mutualité

Philippe Foundation

Merci pour votre attention

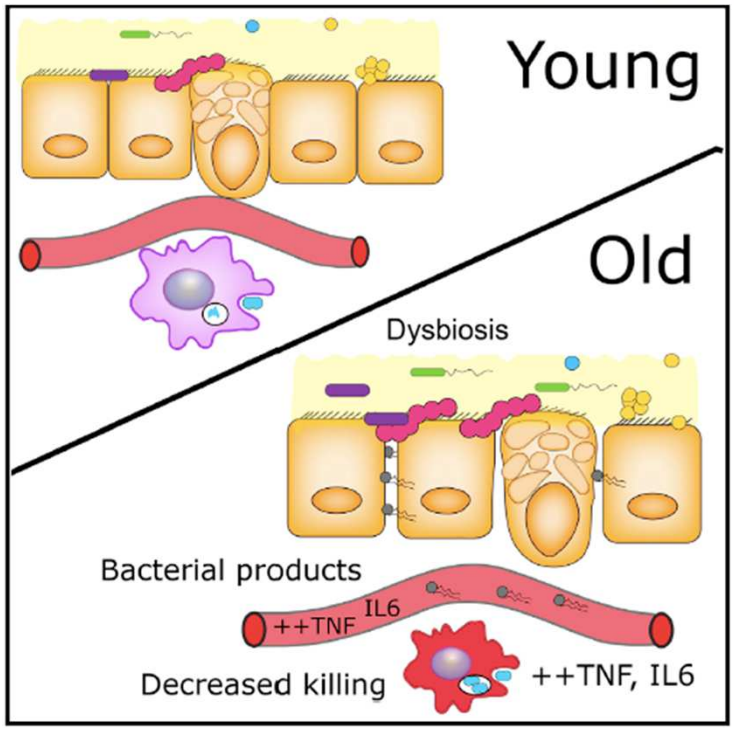
Influence du microbiote sur la santé ?



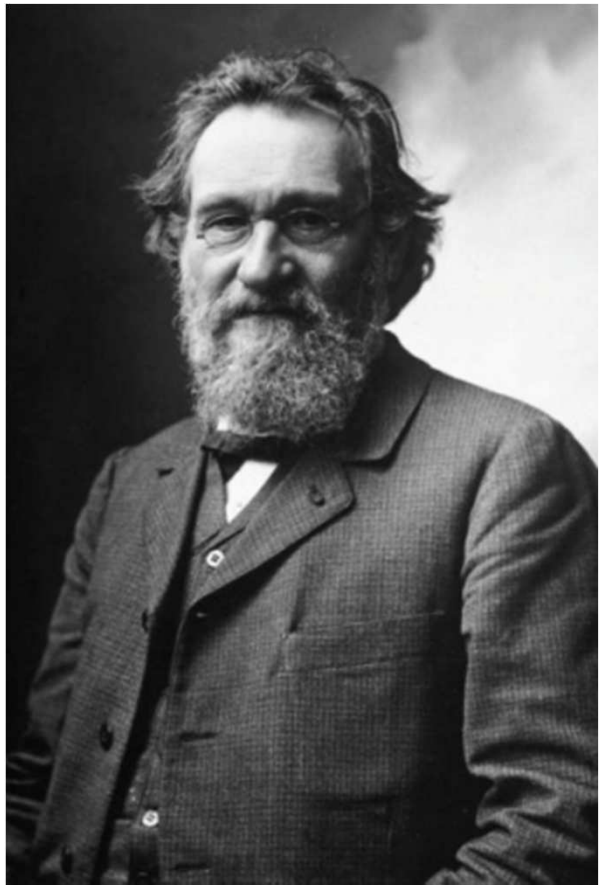
Metchnikoff

Cell Host & Microbe

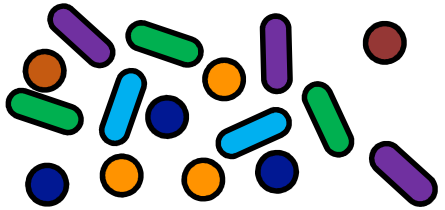
Age-Associated Microbial Dysbiosis Promotes Intestinal Permeability, Systemic Inflammation, and Macrophage Dysfunction Netusha Thevaranjan,



Influence du microbiote sur la santé



Metchnikoff 1907



Longétivité Vieillissement
(buveurs de yaourts bulgares)

Effect of streptomycin on experimental *Salmonella* infections in mice

Number of *S. enteritidis* inoculated*	Percent infected	
	Streptomycin-treated mice †	Untreated control mice ‡
10^{8-9}		100
10^{7-8}		82.7
10^{6-7}		61.1
10^{5-6}		42.1
10^{4-5}		29.5
10^{3-4}		18.8
10^{2-3}	100	9.5
10-100	85	2.4
1-10	63	0

Dose: 50mg

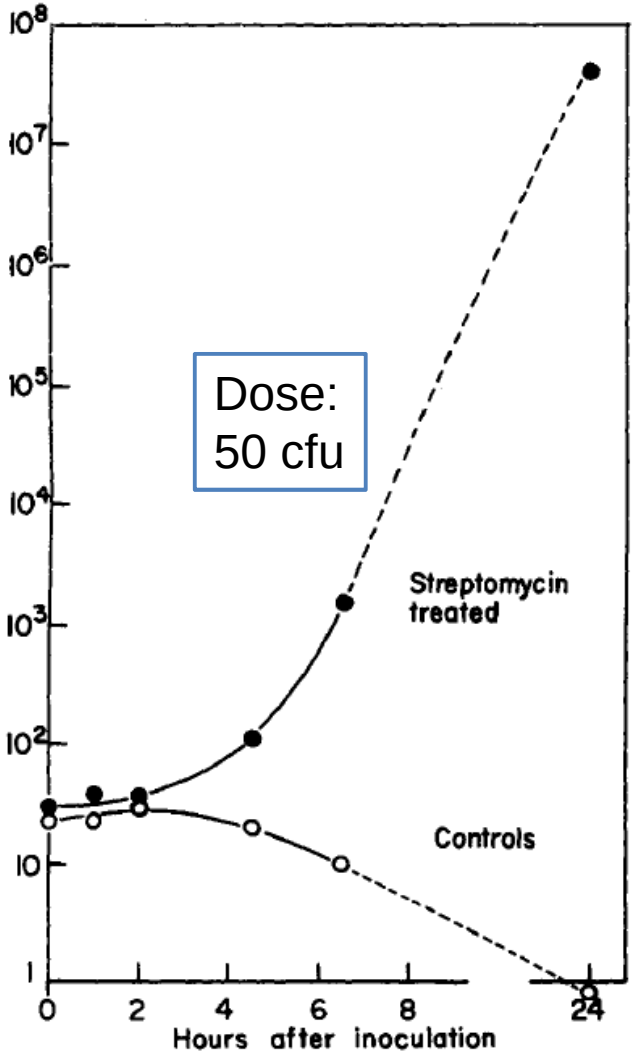
* Inoculated 1 day after streptomycin treatment.

† Infection determined by necropsy cultures of spleen

‡ Infection determined by necropsy cultures of spleen or by fecal culture on 6th day

M Bonhoff and CP Miller. J Infect Dis 1962; 117-27.

Effect of streptomycin pre-treatment on *Salmonella* infection in mice

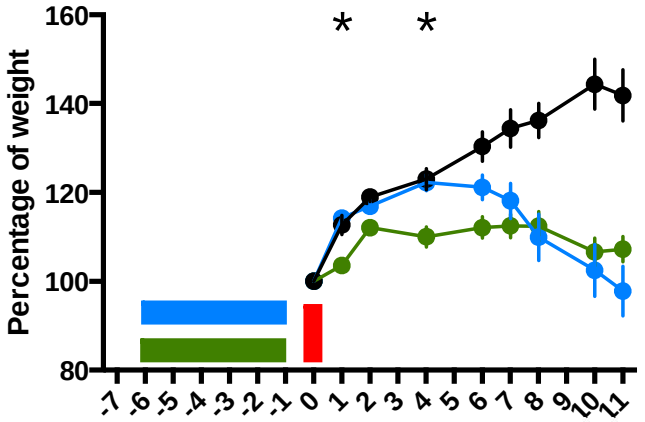


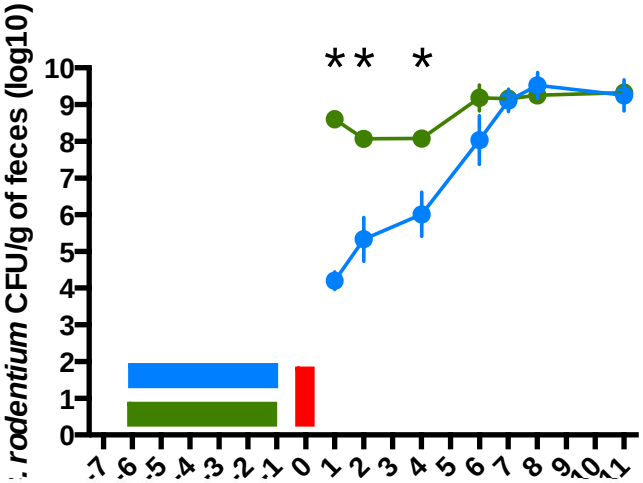
M Bonhoff and CP Miller. J Infect Dis 1962; 117-27.

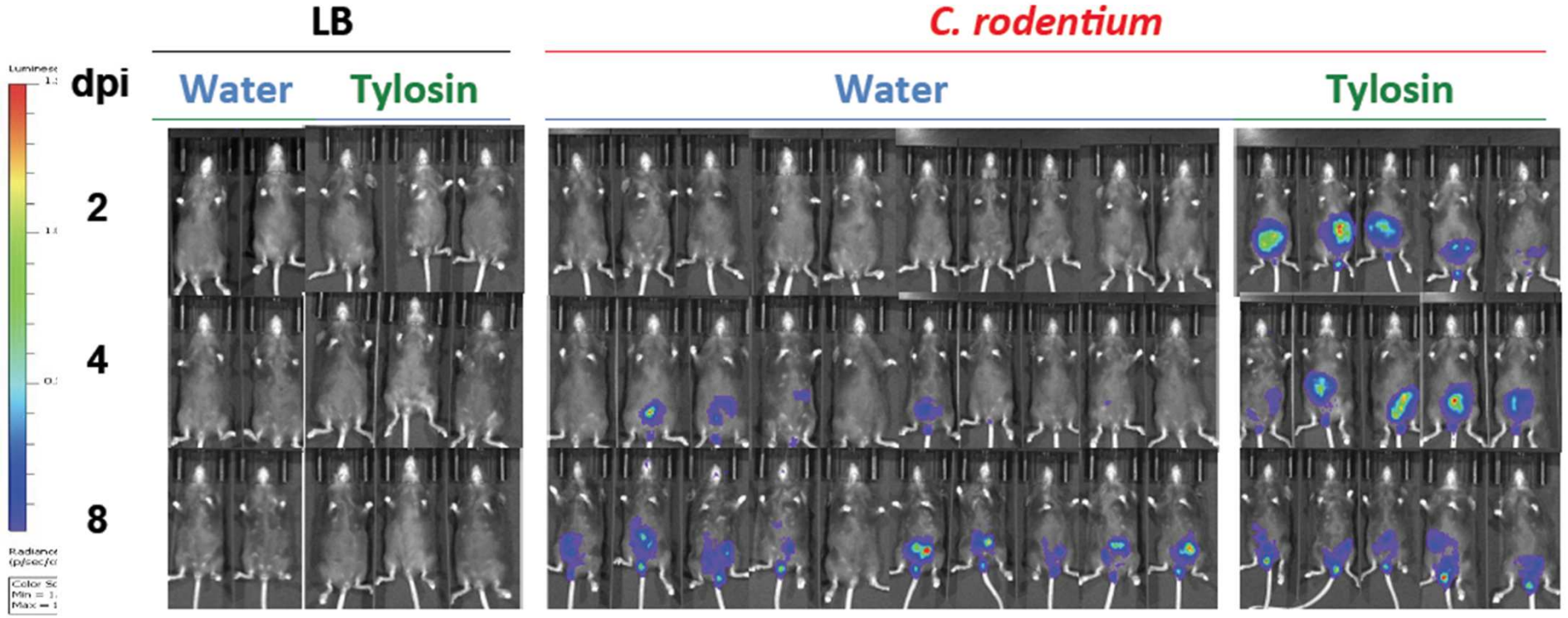
Les antibiotiques diminuent la résistance aux infections

Effect of antibiotic exposure on clinical characteristics with challenge 1 day later

Controls LB
Water + *C. rodentium*
Tylosin + *C. rodentium*
C. rodentium infection $2.5x10^8$ CFU
Water
Tylosin
* $p<0.05$ Tylosin versus water







Variabilités le long du tube digestif