Impact de l'antibiothérapie prescrite au cours des ioa sur le microbiote intestinal

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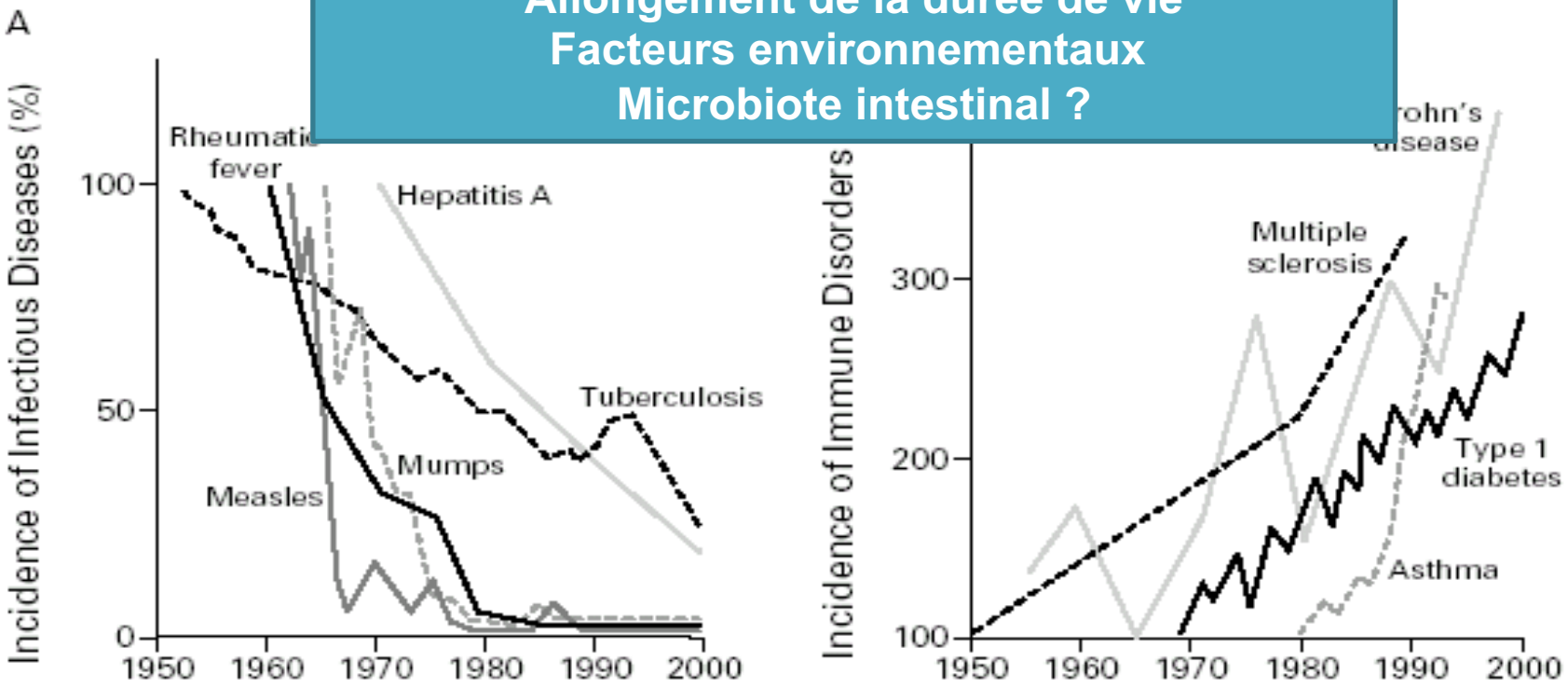
Centre Interrégional Rhône-Alpes Auvergne
de Référence des IOA complexes

DIU de diagnostic de précision et de médecine personalisée

Chronic diseases increased steadily worldwide

Diminution des décès pour infection bactérienne
Amélioration des conditions de vie
Allongement de la durée de vie
Facteurs environnementaux
Microbiote intestinal ?



Bach JF, N Eng J Med 2002

Courtesy J. Doré (INRA)

ARTICLE

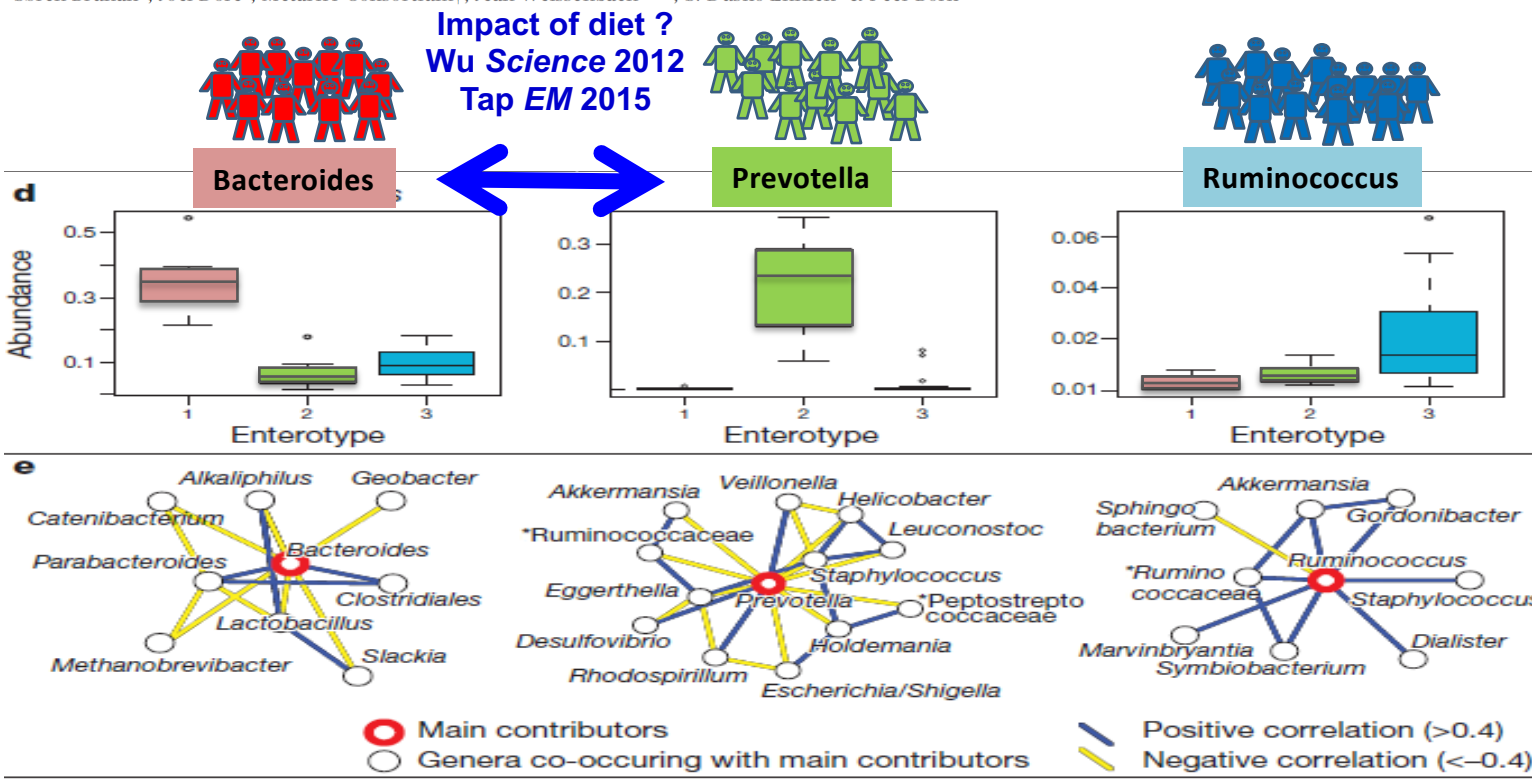
doi:10.1038/nature09944

Enterotypes of the human gut microbiome

Manimozhiyan Arumugam[1]*, Jeroen Raes[1,2]*, Eric Pelletier[3,4,5], Denis Le Paslier[3,4,5], Takuji Yamada[1], Daniel R. Mende[1], Gabriel R. Fernandes[1,6], Julien Tap[1,7], Thomas Bruls[3,4,5], Jean-Michel Batto[7], Marcelo Bertalan[8], Natalia Borruel[9], Francesc Casellas[9], Leyden Fernandez[10], Laurent Gautier[8], Torben Hansen[11,12], Masahira Hattori[13], Tetsuya Hayashi[14], Michiel Kleerebezem[15], Ken Kurokawa[16], Marion Leclerc[7], Florence Levenez[7], Chaysavanh Manichanh[9], H. Bjørn Nielsen[8], Trine Nielsen[11], Nicolas Pons[7], Julie Poulain[3], Junjie Qin[17], Thomas Sicheritz-Ponten[8,18], Sebastian Tims[15], David Torrents[10,19], Edgardo Ugarte[3], Erwin G. Zoetendal[15], Jun Wang[17,20], Francisco Guarner[9], Oluf Pedersen[11,21,22,23], Willem M. de Vos[15,24], Søren Brunak[8], Joel Doré[7], MetaHIT Consortium†, Jean Weissenbach[3,4,5], S. Dusko Ehrlich[7] & Peer Bork[1,25]

Arumugam, Raes et al, Nature 2011

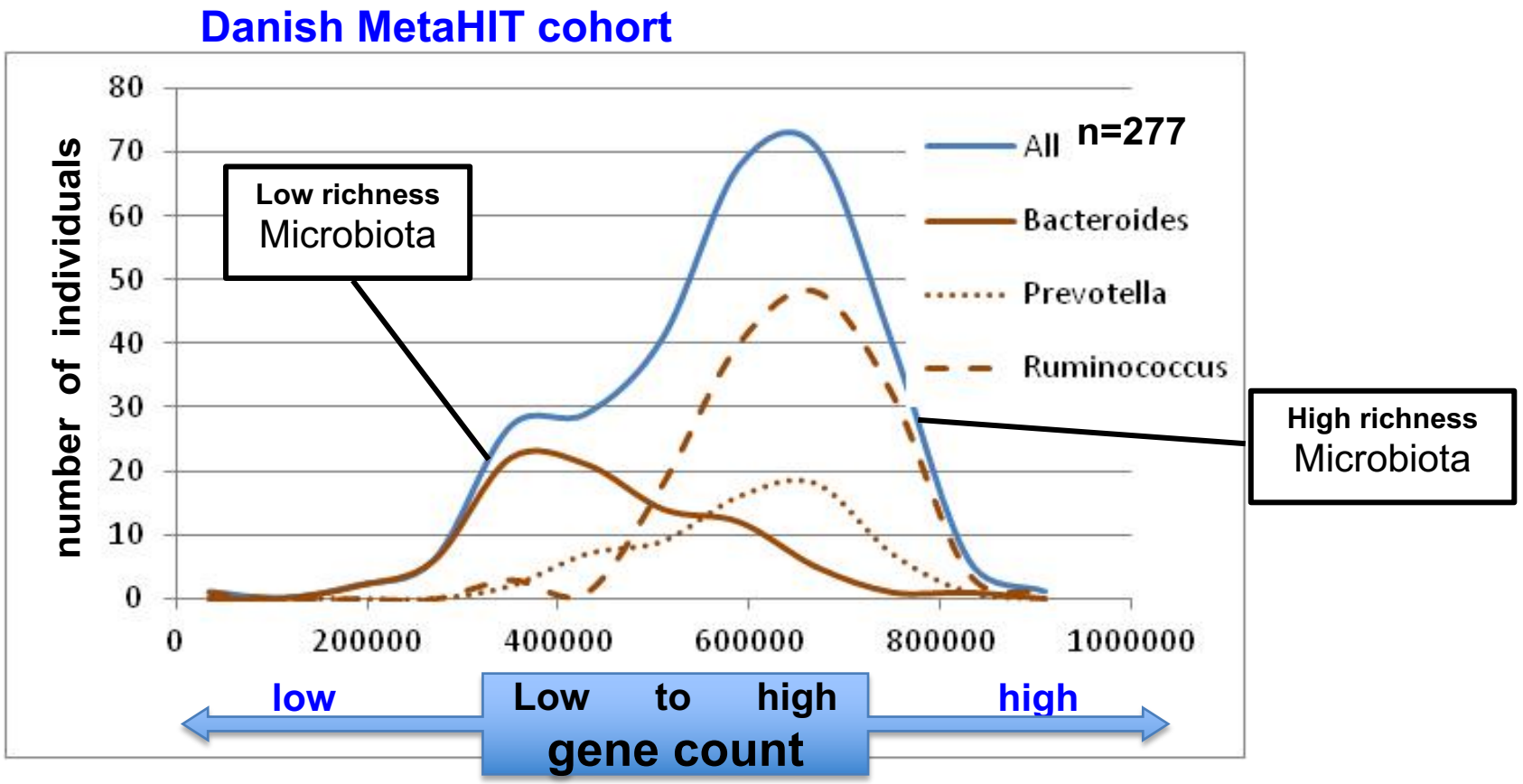
Impact of diet ?
Wu *Science* 2012
Tap *EM* 2015



Ecology underlying enterotypes should be better understood

Courtesy J. Doré (INRA)

Human microbiomes differ at the level of gene richness (diversity)



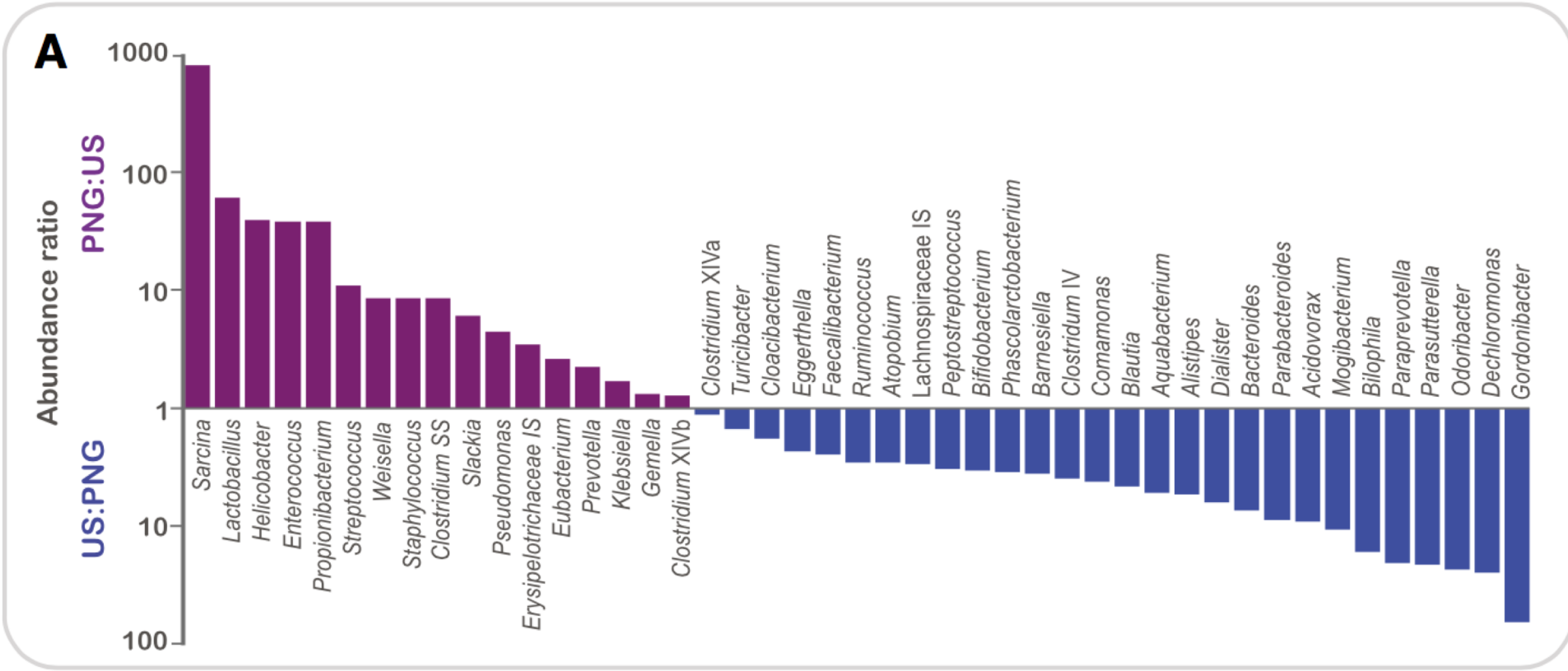
Wu et al, Science 2012

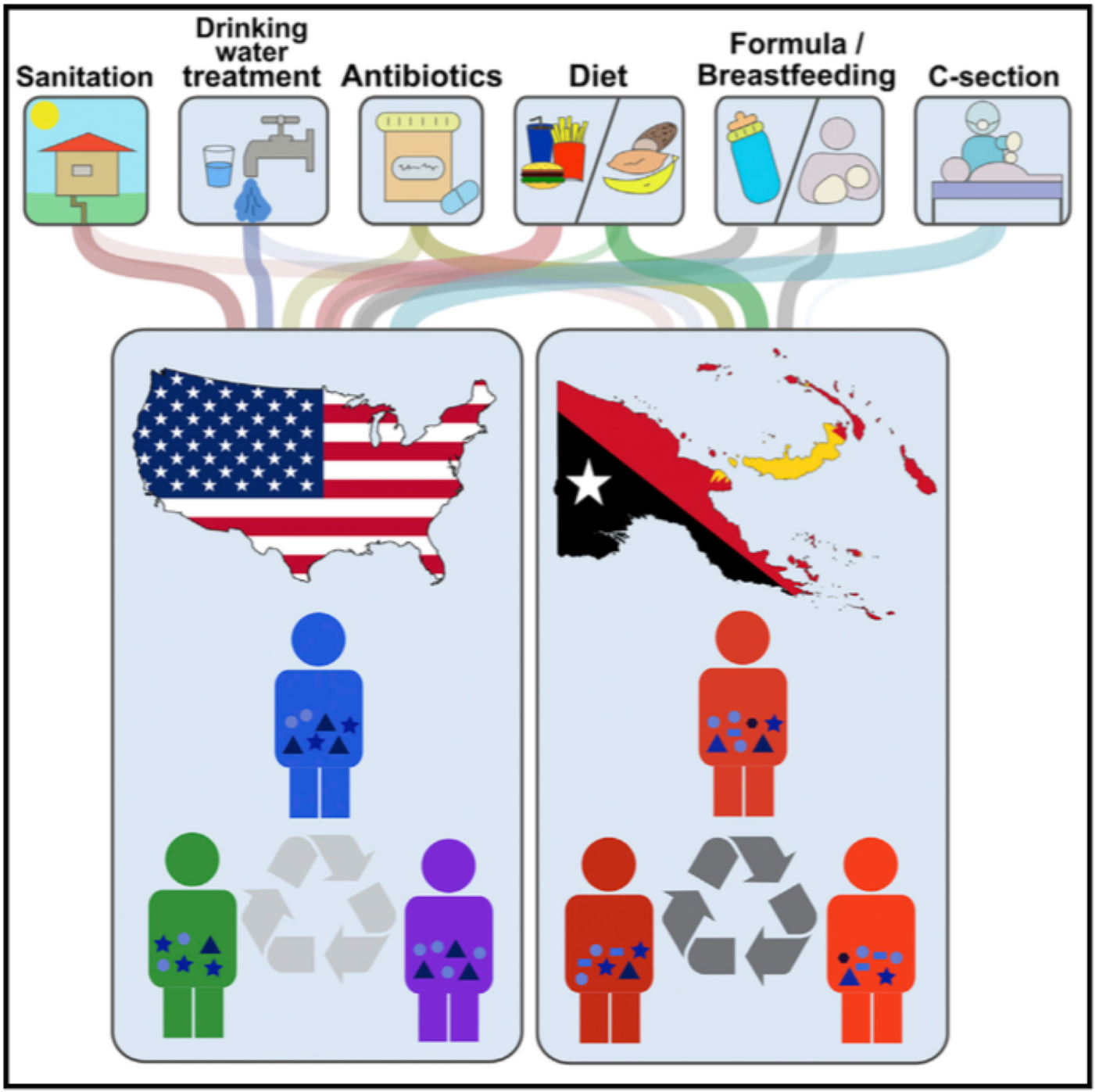
Nutrition may drive *Bacteroides* versus *Prevotella* enterotype…

Courtesy J. Doré (INRA)

Cell Reports

The Gut Microbiota of Rural Papua New Guineans: Composition, Diversity Patterns, and Ecological Processes

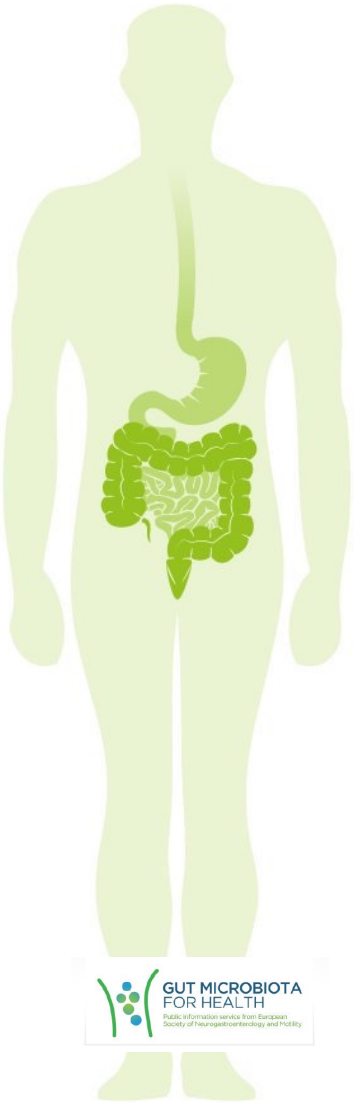



Sanitation
Drinking water treatment
Antibiotics
Diet
Formula / Breastfeeding
C-section

Although they are invisible, the bacteria in your gut are **essential to your health and wellbeing**. So what do these hundreds of trillions of microorganisms do for you?

MAKE
vitamins, including
B12, K AND FOLATE

DEFEND
against harmful
MICROORGANISMS



TEACH
THE IMMUNE SYSTEM
to tell friends from foes

INFLUENCE
the calories you harvest

PRODUCE
IMPORTANT MOLECULES
that travel around the body

GUT MICROBIOTA FOR HEALTH
Public information service from European Society of Neurogastroenterology and Motility

HELP
PRODUCE SEROTONIN,
important for optimal
GUT FUNCTION

Microbiote intestinal et maladies humaines

Dysbiose ou certains entérotypes associée à des maladies ou suspectées d'être associé

Pathologies inflammatoires du tube digestif

MICI
Crohn
RCUH

Pathologies inflammatoires systémiques

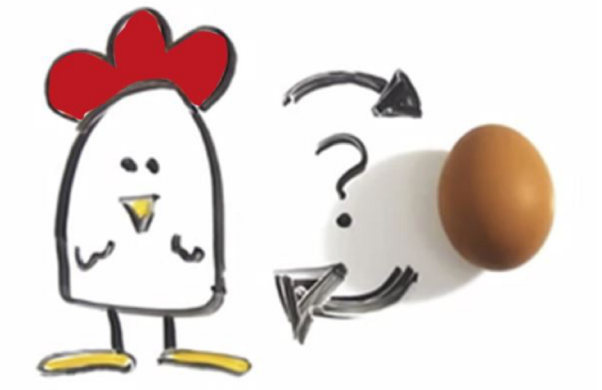
Lupus
Maladies auto-immunes

Pathologies du système nerveux central

Autisme
Parkinson
Démence

Pathologies métaboliques

Diabète
Obésité

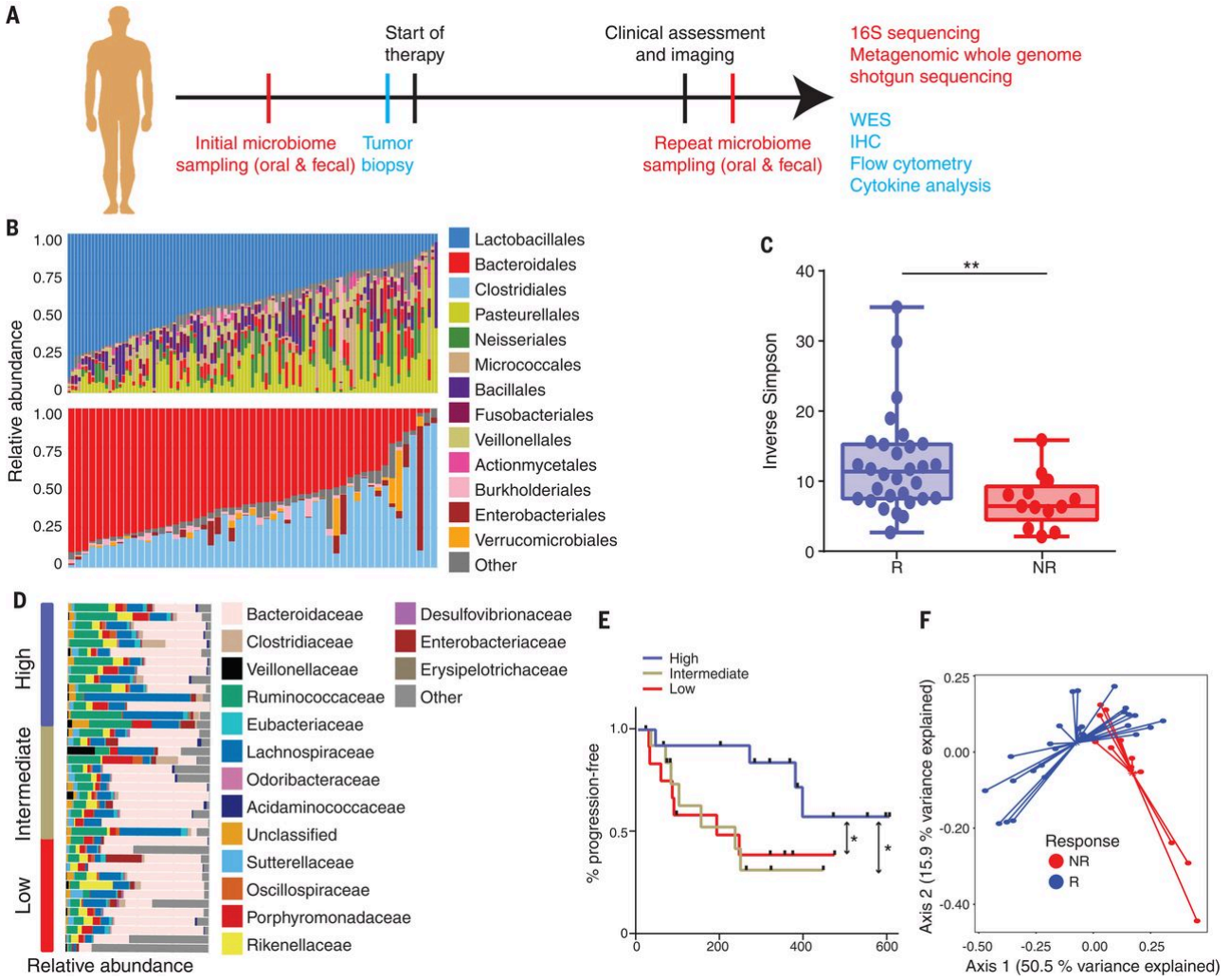


Cancer

Cancer du colon
Autres cancer

Vieillissement ?

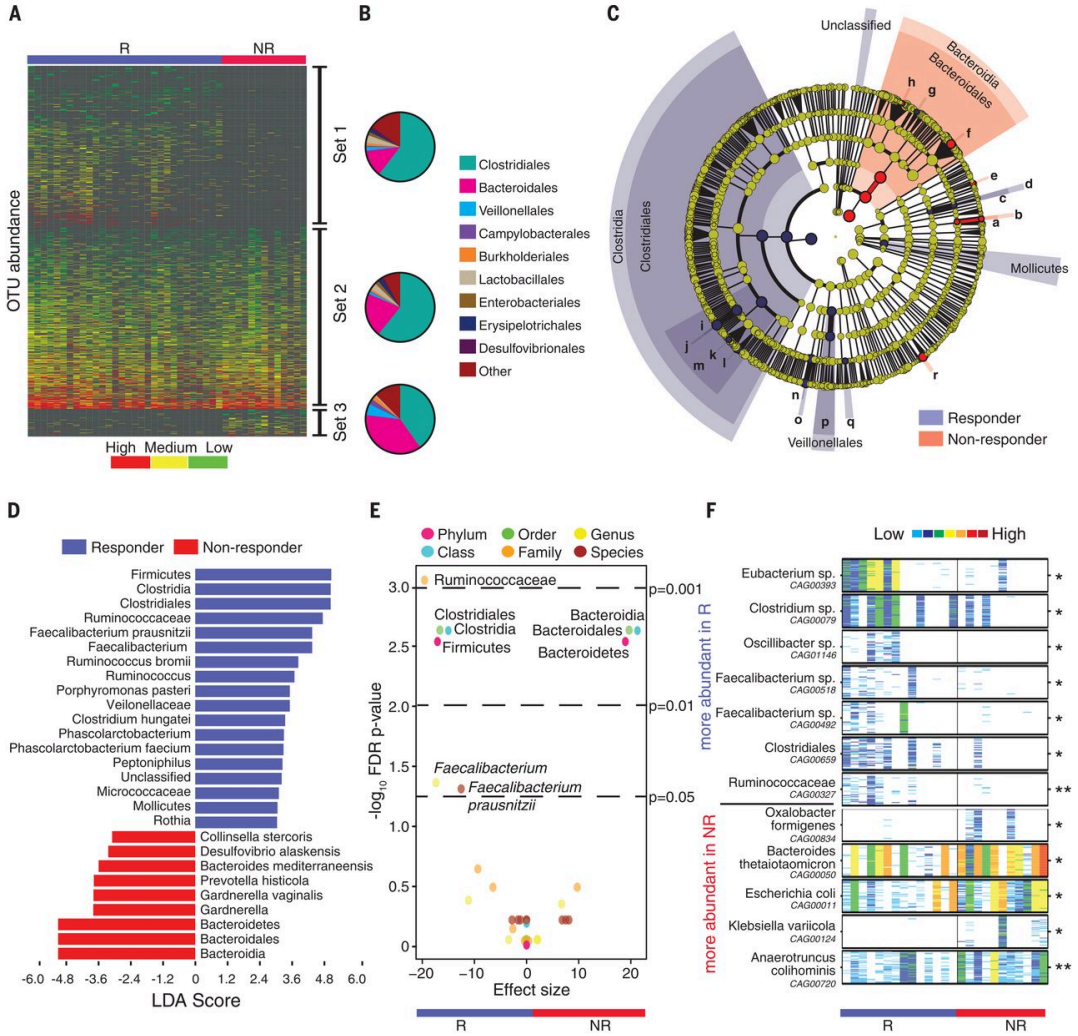
Higher gut microbiome diversity is associated with improved response to anti–PD-1 immunotherapy in patients with metastatic melanoma



V. Gopalakrishnan et al. Science 2018;359:97-103

Science
AAAS

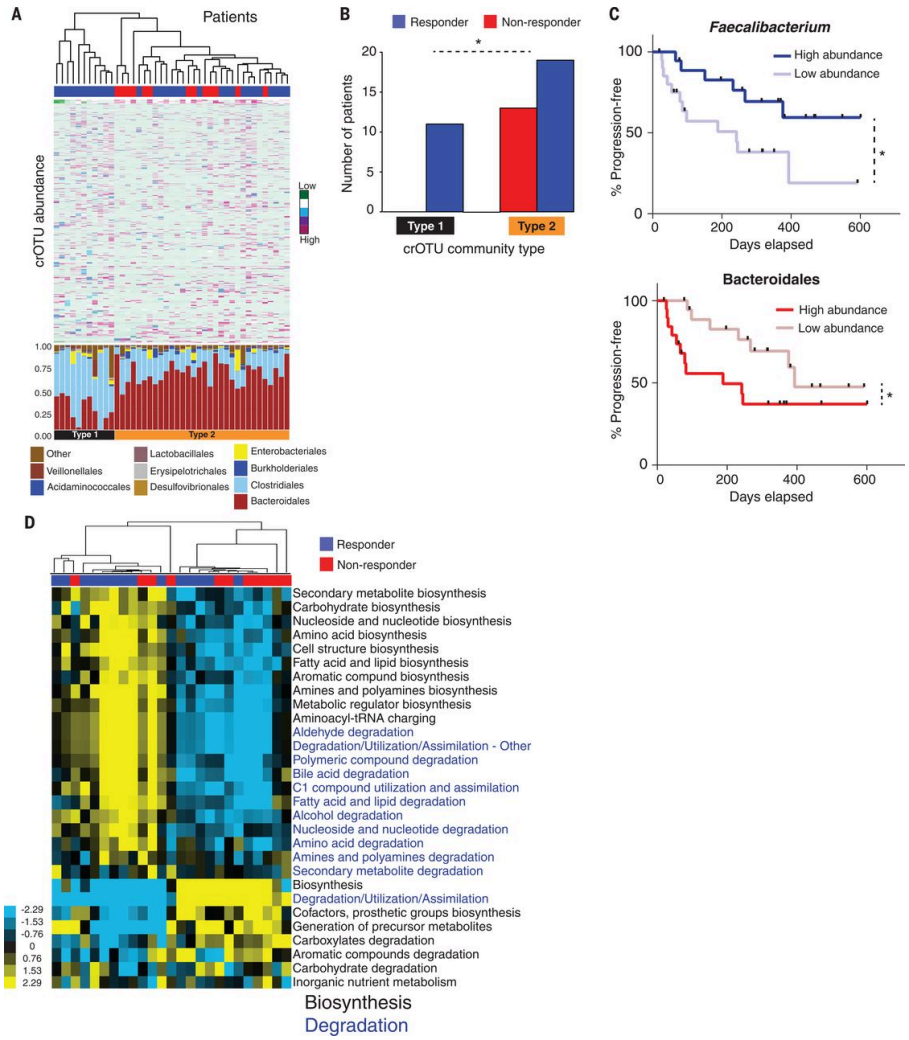
Compositional differences in the gut microbiome are associated with responses to anti–PD-1 immunotherapy.



V. Gopalakrishnan et al. Science 2018;359:97-103

Published by AAAS

Abundance of crOTUs within the gut microbiome is predictive of response to anti–PD-1 immunotherapy



V. Gopalakrishnan et al. Science 2018;359:97-103

Published by AAAS

Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study

Maris S Arcilla, Jarne M van Hattem*, Manon R Haverkate, Martin C J Bootsma, Perry J J van Genderen, Abraham Goorhuis, Martin P Grobusch, Astrid M Oude Lashof, Nicky Molhoek, Constance Schultsz, Ellen E Stobberingh, Henri A Verbrugh, Menno D de Jong, Damian C Melles, John Penders*

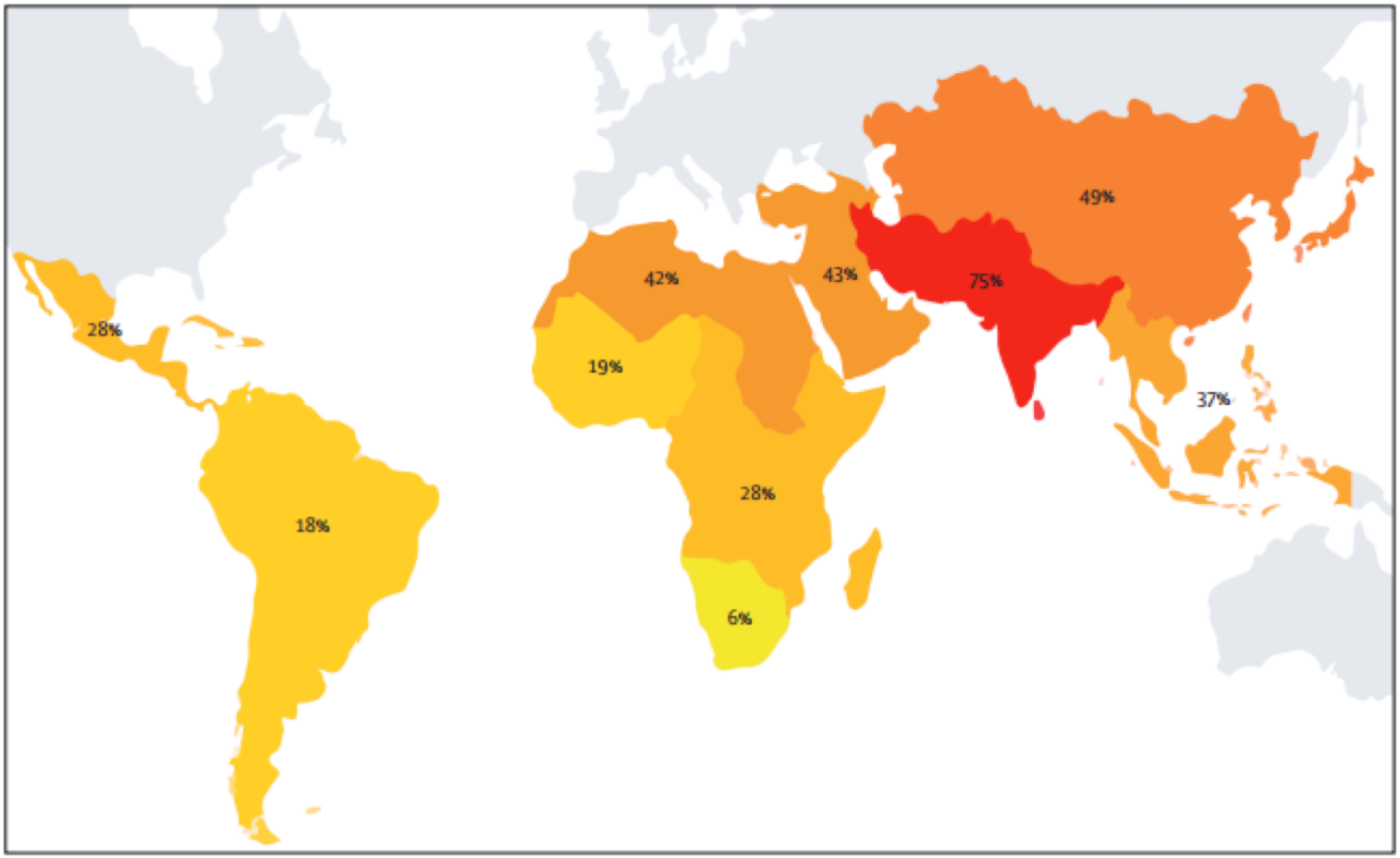
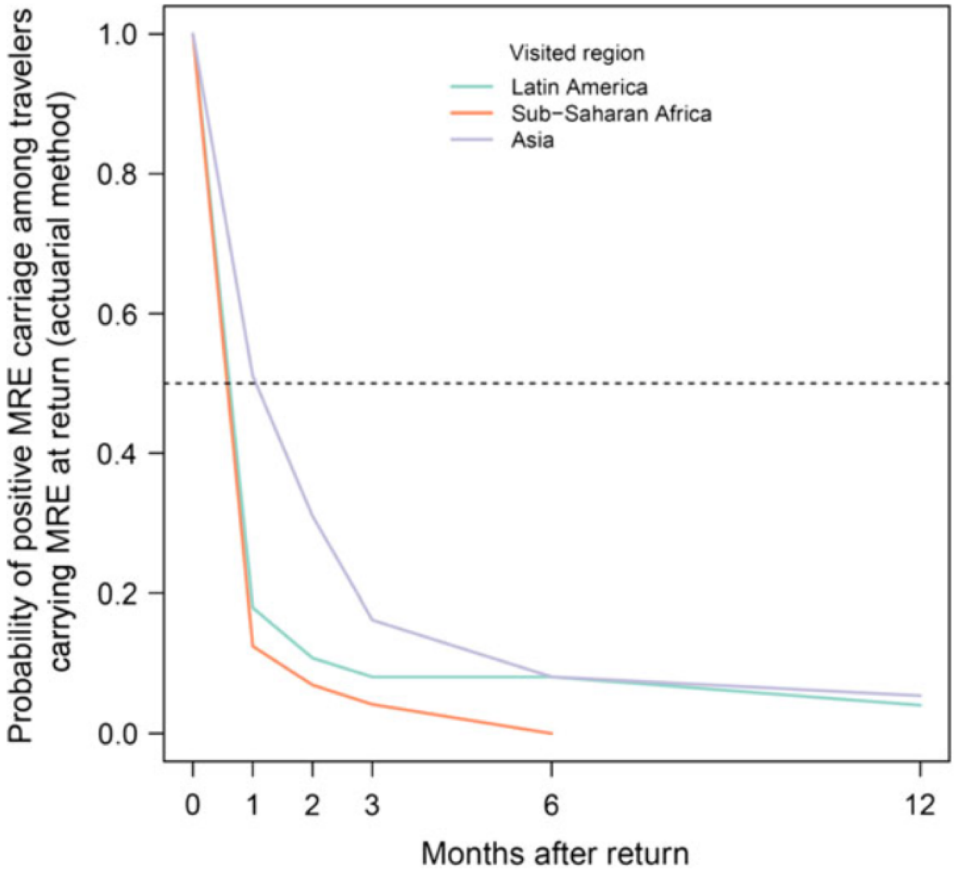


Figure 1: Percentages of travellers that acquired β-lactamase-producing Enterobacteriaceae per subregion, according to the United Nations geoscheme

High Rate of Acquisition but Short Duration of Carriage of Multidrug-Resistant Enterobacteriaceae After Travel to the Tropics

Etienne Ruppé,[1,2,3] Laurence Armand-Lefèvre,[1,2,3] Candice Estellat,[4,5,6,a] Paul-Henri Consigny,[7,a] Assiya El Mniai,[1]



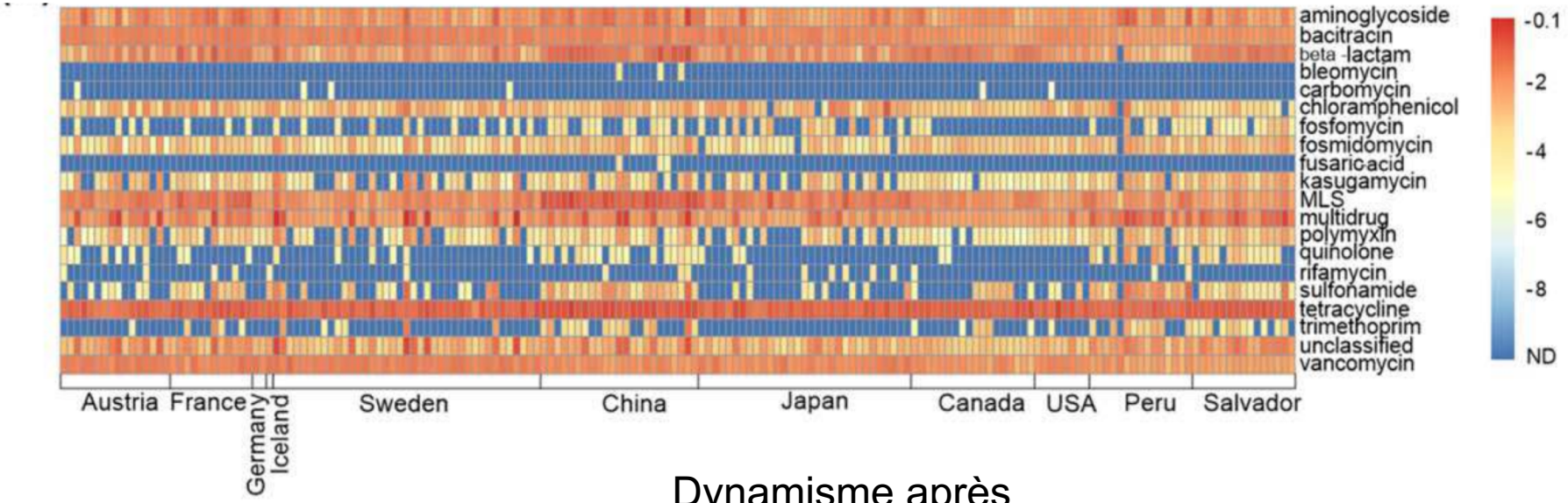
Risk of MRE acquisition in multivariate analysis

- Region visited (P < .001)
- β-lactam use during travel
  (OR, 4.08; 95% CI, 1.39–11.97; P = .011)
- Diarrhea during travel
  (OR, 1.90; 95% CI, 1.31–2.75; P < .001)
- Type of travel
  (all-inclusive resorts vs others; P = .033)

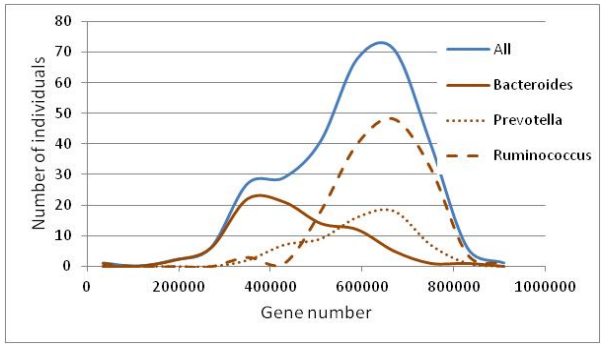
Clinical Infectious Diseases 2015;61(4):593–600

Microbiote et résistome

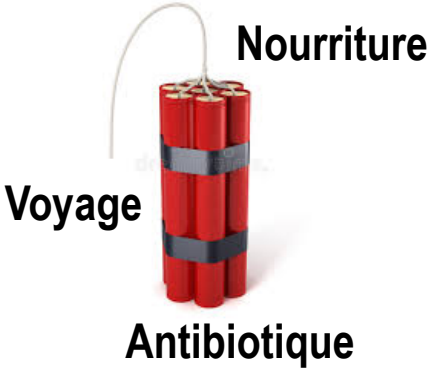
Antimicrobial Resistance Genes (ARG)



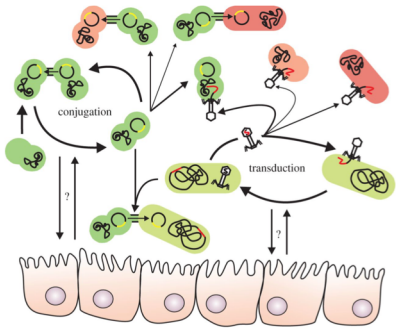
Rôle des différents Entérotypes/communautés ?

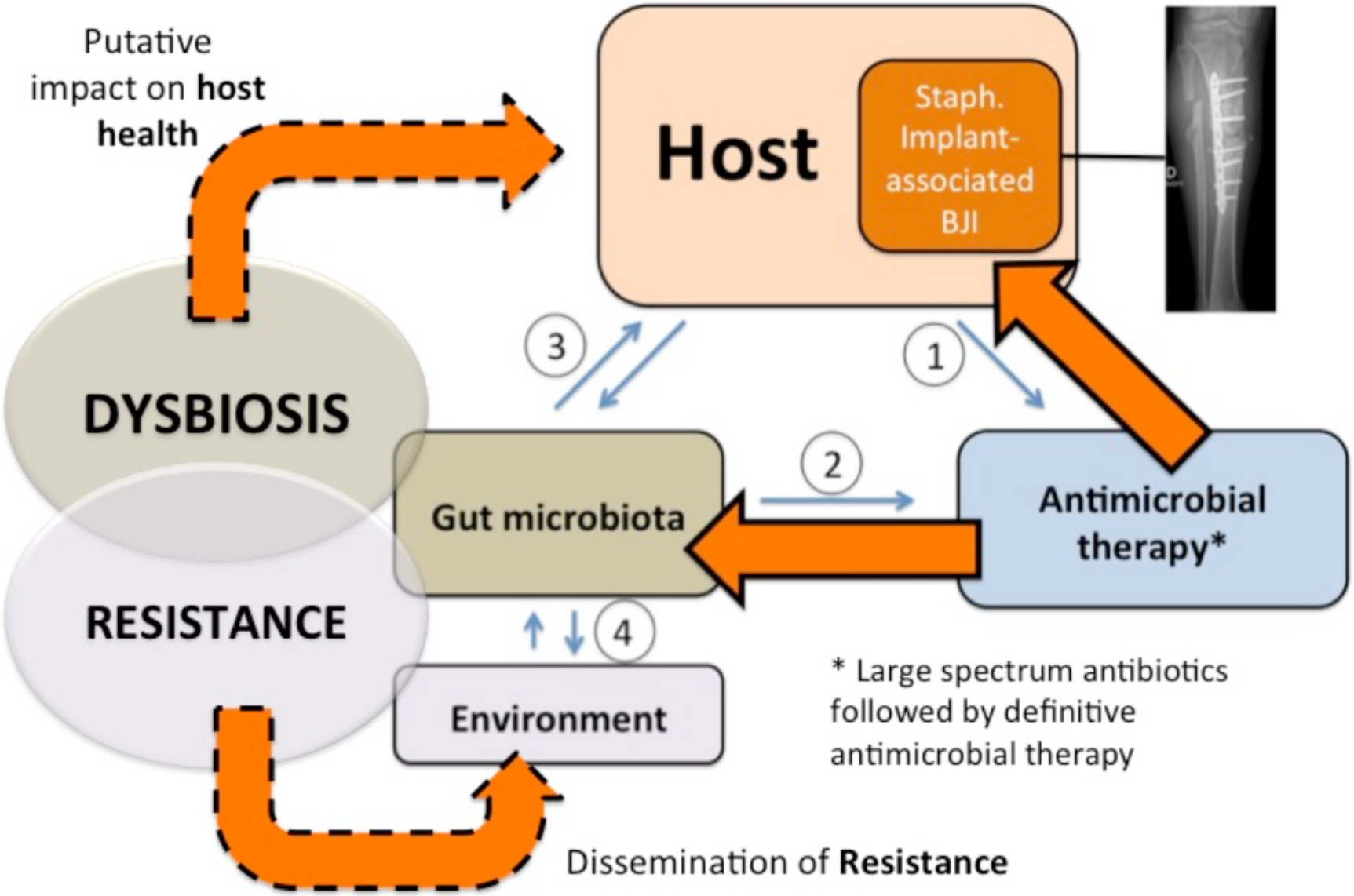


Dynamisme après exposition



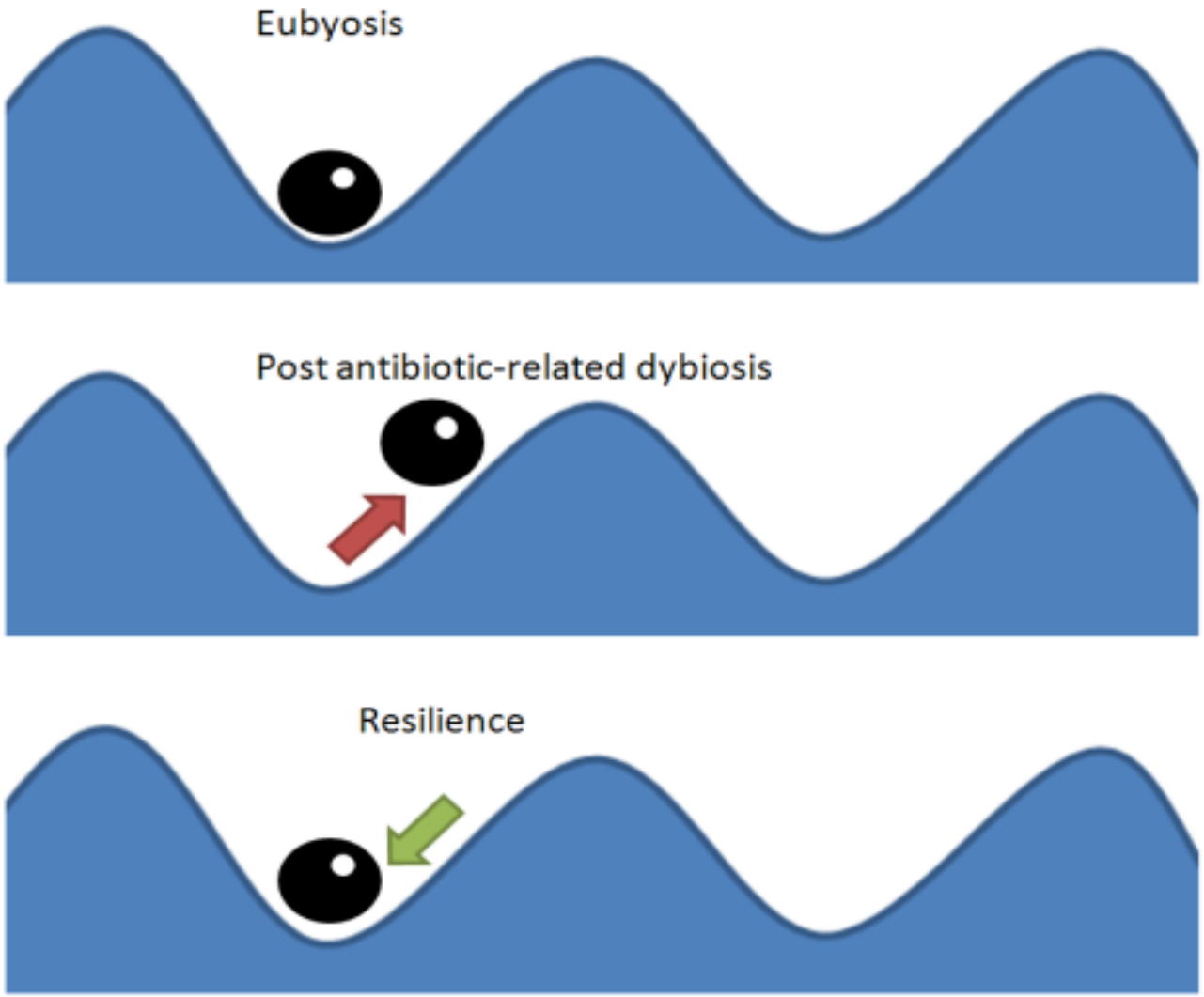
Diffusion de la résistance




Putative impact on **host health**
Host
Staph. Implant-associated BJI
DYSBIOSIS
RESISTANCE
Gut microbiota
Antimicrobial therapy*
Environment
1
2
3
4
* Large spectrum antibiotics followed by definitive antimicrobial therapy
Dissemination of **Resistance**

T. Ferry

Dysbiosis



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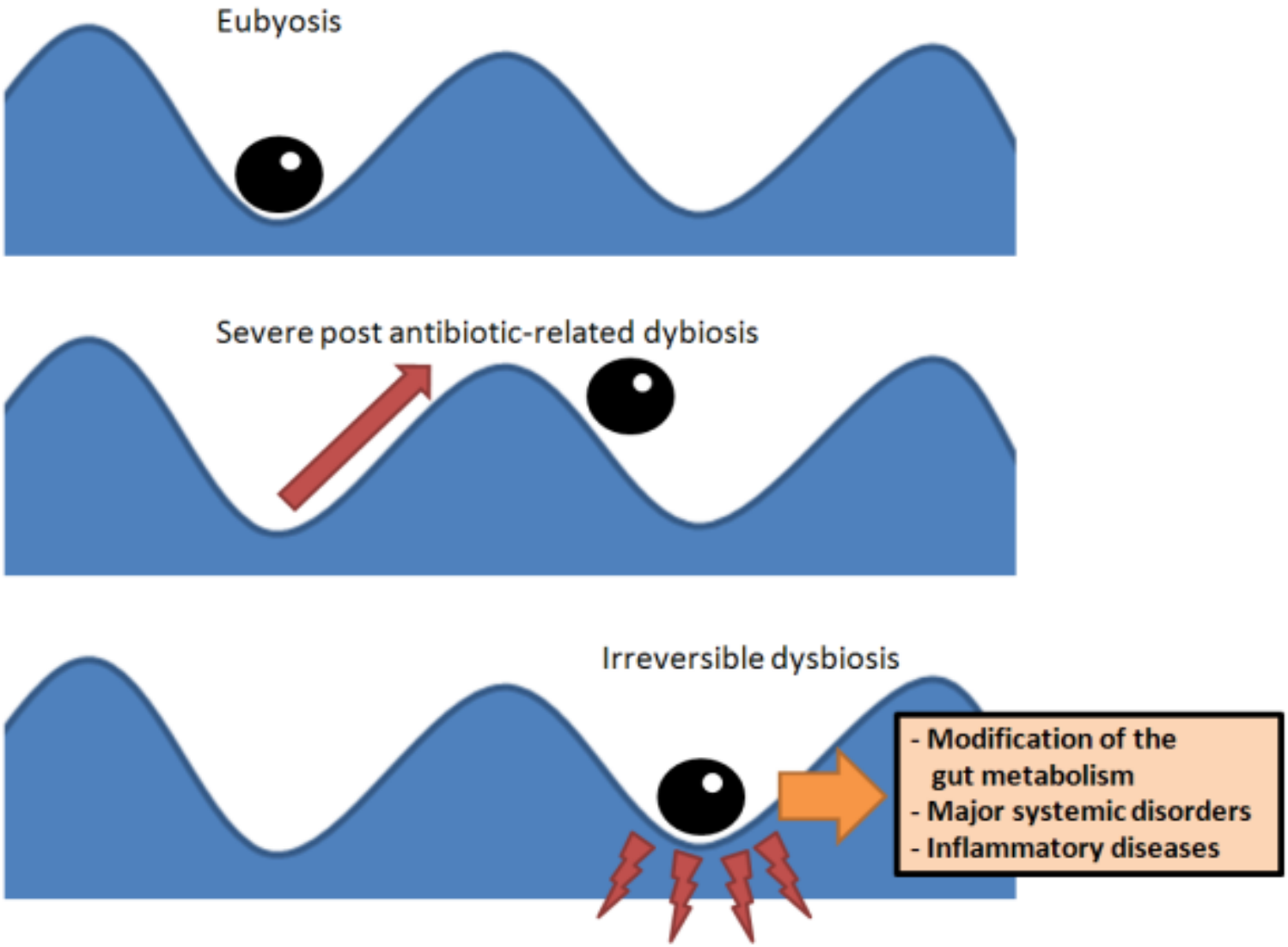
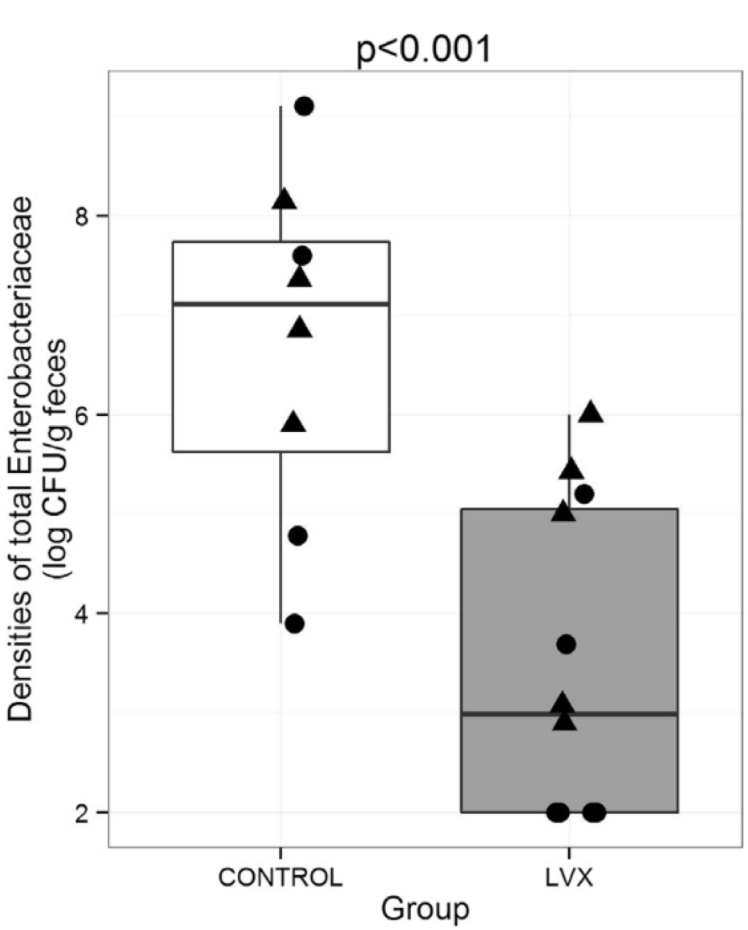
Severe Post-Antibiotic Dysbiosis (SPAD)



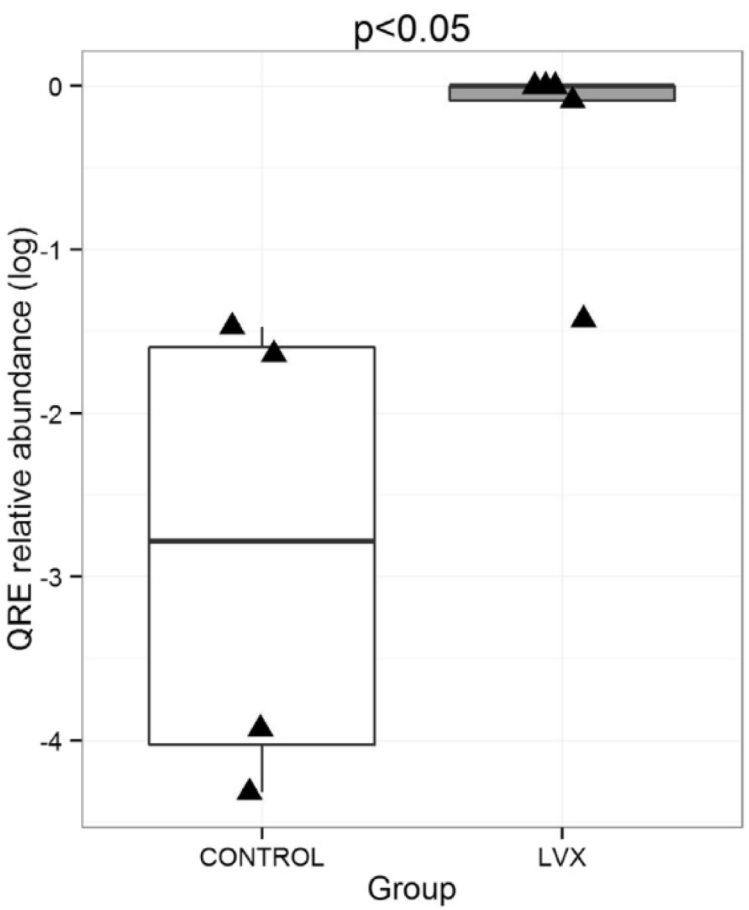
T. Ferry

Impact of a short exposure to levofloxacin on faecal densities and relative abundance of total and quinolone-resistant *Enterobacteriaceae*

J. Bernard [1], L. Armand-Lefèvre [2, 3, 4], E. Luce [2], A. El Mniai [2], F. Chau [3, 4], E. Casalino [1], A. Andremont [2, 3, 4], E. Ruppé [2, 3, 4, *]



Quinolone-resistant *Enterobacteriaceae*

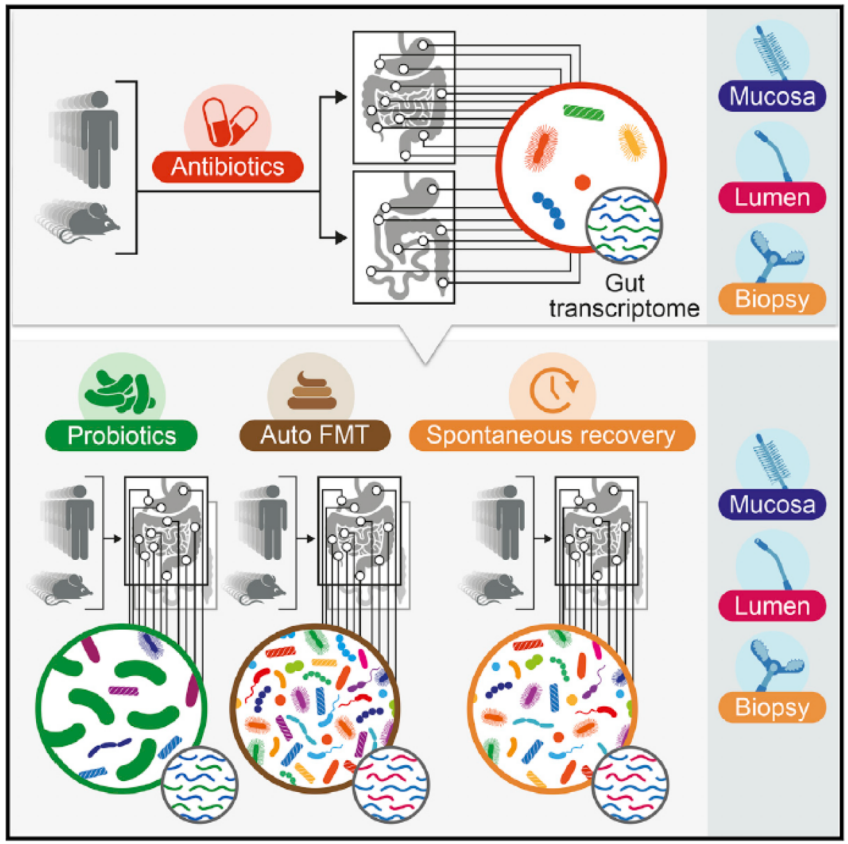


Clinical Microbiology and Infection 22 (2016) 646.e1e646.e4

Suez et al., 2018, Cell 174, 1406–1423

Cell

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

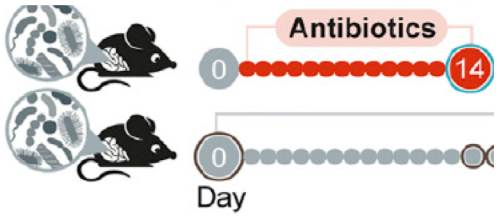


Suez et al., 2018, Cell 174, 1406–1423

Cell

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

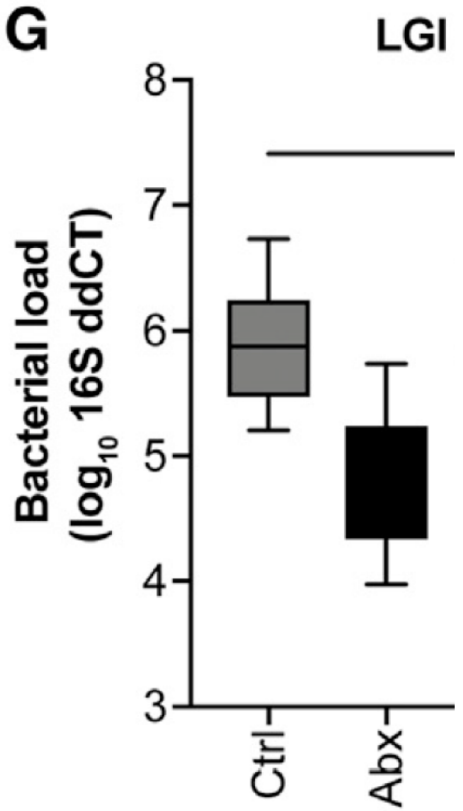
Ciprofloxacine + métronidazole



Cell

Suez et al., 2018, Cell 174, 1406–1423

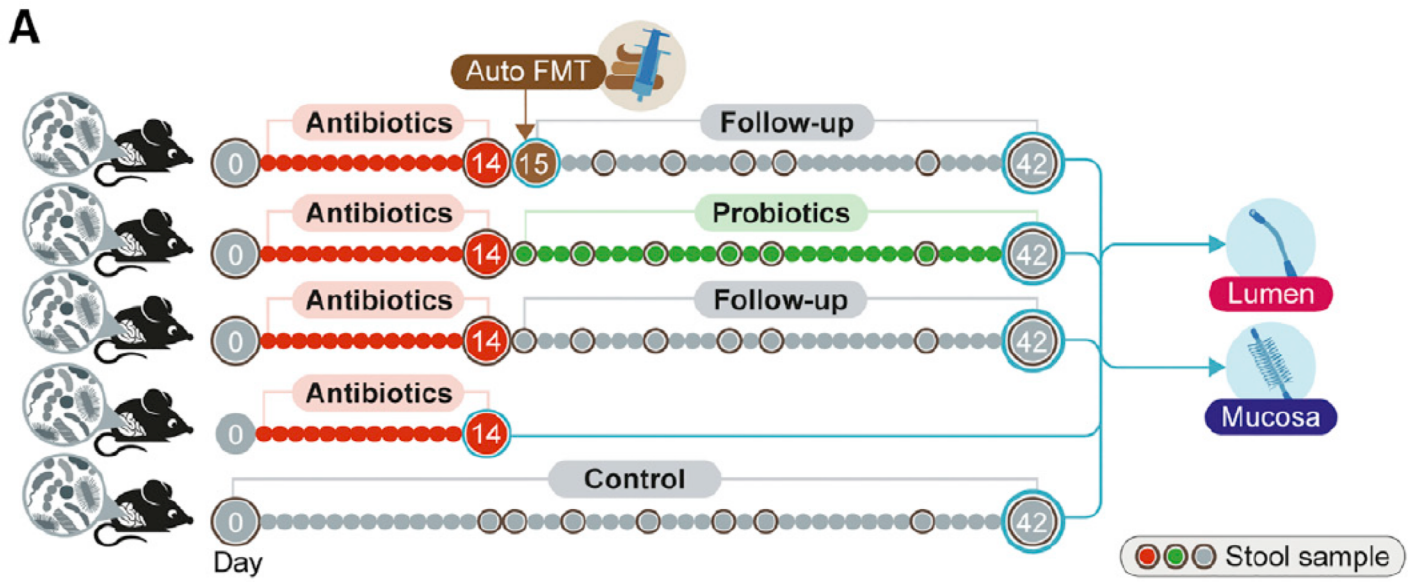
Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT



Suez et al., 2018, Cell 174, 1406–1423

Cell

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

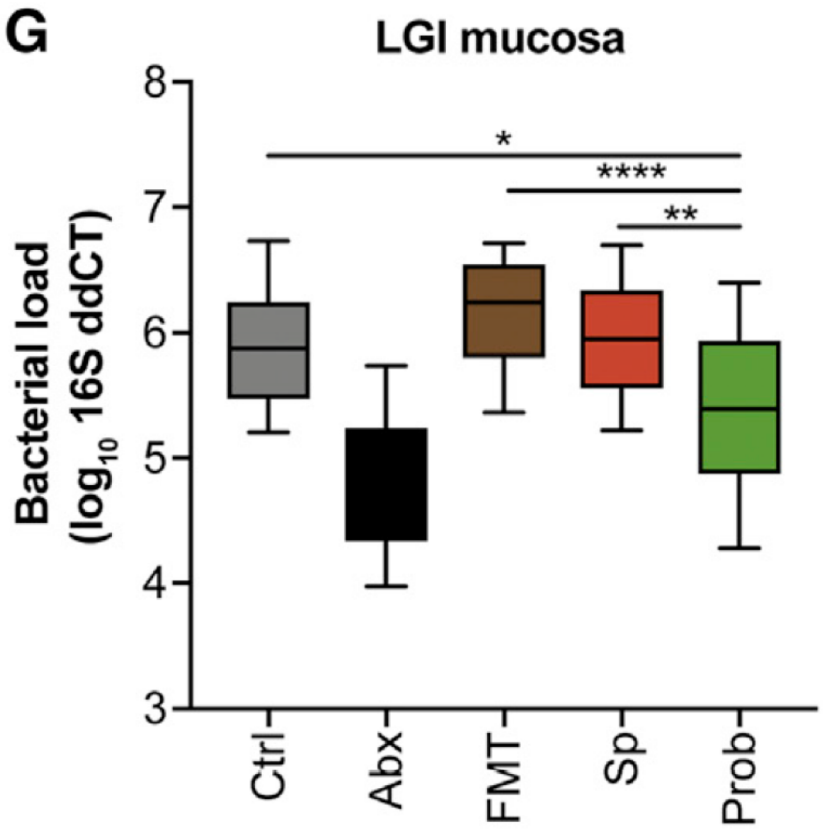


Probitics: Supherb Bio-25 bi-daily, which is described by the manufacturer to contain at least 25 billion active bacteria of the following species: *B. bifidum, L. rhamnosus, L. lactis, L. casei subsp. casei, B. breve, S. thermophilus, B. longum subsp. longum, L. casei subsp. paracasei, L. plantarum and B. longum subsp. infantis.*

Cell

Suez et al., 2018, Cell 174, 1406–1423

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT



Interventional Study of Bone and Joint Infections related gut Dysbiosis (OSIRIS study): first results of a prospective multicenter trial

JOSSE Jérôme[1,7] ; MONTEIX Alice[1,7] ; BOUTOILLE David[2] ; DAUCHY Frédéric-Antoine[3] ; ZELLER Valérie[4] ; SENNEVILLE Eric[5] ; Le CAMUS Corentin[6] ; LEVAST Benoît[6] ; LAURENT Frédéric[1,7] and FERRY Tristan[7,8]

[1] Hôpital de la Croix-Rousse, HCL – Service de Bactériologie – Lyon – France; [2] CHU Nantes, Hôtel-Dieu – Service de Maladies Infectieuses et Tropicales – Nantes – France; [3] CHU Bordeaux – Service de Maladies Infectieuses et Tropicales – Bordeaux – France; [4] GH Diaconesses-Croix Saint-Simon – Service de Médecine Interne et Rhumatologie – Paris – France; [5] CH Tourcoing, CHRU Lille – Service Universitaire des Maladies Infectieuses et du Voyageur – Tourcoing – France; [6] MaaT Pharma – Lyon – France; [7] International Centre for Infectiology Research (CIRI) – Lyon – France; [8] Hôpital de la Croix-Rousse, HCL – Service Maladie Infectieuses et Tropicales – Lyon – France

Hospices Civils de Lyon

28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

INTRODUCTION

Bone and joint infections (BJI) often require a prolonged antimicrobial therapy that can affect the gut microbiota. Few days of treatment are sufficient to induce dysbiosis, an intestinal disorder characterized by accumulation of microbiota imbalance, host-microbiota crosstalk dysfunction and inflammation. Dysbiosis and antibacterial pressure can favor the selection of Multi Drug Resistant Bacteria (MDRB) and some bacterial pathogens like *Clostridium difficile*.

The OSIRIS project is a multicenter interventional study investigating the impact of antibiotics on clinical condition and gut microbiota in patients with BJI treatment. The aim is to analyze relationships between antibiotics and dysbiosis in order to evaluate the potential of Fecal Microbiota Transfer (FMT) as a strategy to restore the gut ecosystem. Here, in a first step of the global study, we investigated the emergence of MDRB and *C. difficile* in gut microbiota of BJI patients with a prolonged antimicrobial therapy.

Overall, the objective will be to restore the patient's gut microbiota using an autologous FMT strategy named **MaaT031**.

STUDY OBJECTIVES

- **Primary**:

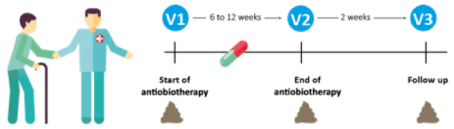
→ Evaluate the impact of antibiotic treatment on diarrhea in patients with BJI and its correlation to gut microbiota alteration

- **Secondary**:

- Characterize of the gut dysbiosis and its prevalence in patients with BJI and under antibiotic treatment
- Quantify the proportion of extended-spectrum beta-lactamase (ESBL) producing bacteria after and before treatment
- Evaluate fecal MDRB carriage incidence
- Evaluate health economy parameters
- Identify the targeted population with suspicion of infections, experiencing diarrhea events and eligible for MaaT031 microbiotherapy

STUDY FLOW CHART - METHODS - POPULATION

- Fecal samples from patients treated for BJI were collected along 3 visits:



- Screening of ESBL/Carbapenemase-producing enterobacteriaceae (CPE)/Vancomycin Resistant Enterococci (VRE)/MRSA carriage : stools plating on selective chromogenic media (bioMérieux)
- Species identification : Vitek MS (bioMérieux)
- Antimicrobial phenotypes confirmation : disk-diffusion method
- *Clostridium difficile* presence : tested by quick test (*C. diff* quick check complete, Alere) and confirmed by PCR (Xpert *C. difficile*, Cepheid)

French participative hospitals:
- Bordeaux, Pellegrin Hospital
- Lyon, Croix-Rousse Hospital
- Nantes, Hôtel-Dieu
- Paris, Groupe hospitalier Diaconesses Croix Saint-Simon
- Centre Hospitalier de Tourcoing, CHRU de Lille

Studied population and clinical data

- 62 patients included, 54 evaluable
- 40 males / 22 females
- Prosthetic-joint infection: 21
- Osteosynthesis: 14
- Native BJI: 27
- Average age: around 60 years
- Body Mass Index mean: 27.4
- Episodes of cumulative diarrhea (defined as a minimum of 3 liquid stools per day during 3 days):
  - V1: 1 episode
  - V2: 11 episodes
  - V3: 6 episodes
- Average term of antimicrobial therapy : 65.5 days

RESULTS

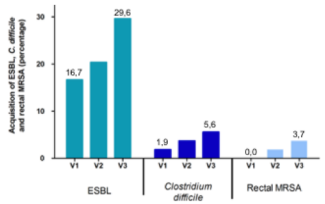


Fig 1: Proportion of fecal carriage of ESBL, *Clostridium difficile* and fecal MRSA during the treatment of evaluable patients (n = 54)

→ The data show a **raise** of MDRB fecal carriage between V1 and V3:
- ESBL: 16.7% – 29.6%
- *C. difficile:* 1.9% – 5.6%
- Fecal MRSA: 0% – 3.7%

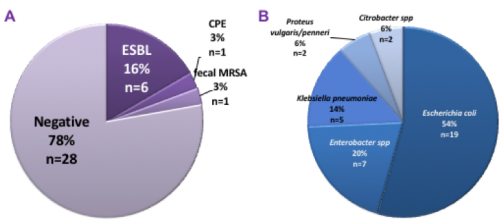


Fig 2: A) Acquisition of MDRB among the patients without MDRB at baseline and for who V2 and V3 data were available. B) Proportion of species detected among the ESBL isolated at V1, V2 and V3 (n=35)

→ Among MDRB that patients acquire during the antibiotic therapy, the most detected are **ESBL** (75%, 6/8)
→ The predominant species of ESBL is ***Escherichia coli*** (54%), followed by *Enterobacter spp* (20%)

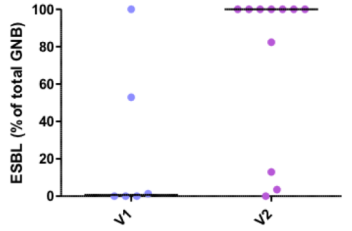


Fig 3: Quantification of ESBL among gram negative bacteria (GNB, relative abundance in %) in the intestinal microbiota of 13 patients at V1 and/or V2

→ The quantification data reveal a trend to a higher proportion of ESBL at V2:
- V1 median at 0,71% of GNB
- V2 median at 100% of GNB

CONCLUSIONS

Our microbiology results indicate a significant acquisition of MDRB after BJI treatment. Qualitative analysis confirm the expected predominance of ESBL bacteria, quantitative analysis indicate an increase of the MDRB portage in the positive samples between V1 and V2.

- **Clinical data** are under investigation, first reports show an increased prevalence of diarrhea episodes over the antibiotherapy course.
- **Fecal biomarkers** and **fecal microbiota** analysis by Next Generation Sequencing are under investigation

In conclusion, preliminary results of the OSIRIS study clearly indicate the impact of antibiotics treatments on the fecal microbiota ecology. Resistant bacteria may be eradicated or reduced in the colon of the patient using the MaaT031 product to restore the original microbiota. This microbiotherapy strategy would thus help on the limitation of the dissemination of bacteria such as ESBL positive germs, *C. difficile*, MRSA or CPE that represent a threat for nosocomial infections as well as healthcare global management and cost.

Overall, data on bacteria resistances with **NGS** and **biomarkers** supports will drive the next development steps of an **autologous microbiotherapy strategy** to treat patients under long-term antimicrobial therapy and eradicate MDRB carriage and dissemination in hospitals and within the community.

MaâT

ECCMID 2018

Conclusion

- **Le microbiote intestinal est associé**
  - à un (bonne) santé
  - à (la survenue de ?) certaines pathologies
  - à une meilleure réponse à des traitements curatifs
- **Le microbiote est impacté au cours d'une antibiothérapie**
- **Les antibiotiques utilisés au cours des IOA ont sans doute un impact majeur**
  - Antibiothérapie probabiliste
  - Fluoroquinolones
  - Combinaisons
  - Durée prolongée
- **Nécessité de mieux comprendre l'impact des antibiotiques au cours des IOA**
- **Traitement préventif ou curatif de la dysbiose au cours des IOA**