« Prévenir la dysbiose post-antibiotique»

Antoine Andremont

Professeur émérite UDP

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Lien d'intérêt : fondateur scientifique de DaVolterra

Pourquoi prévenir la dysbiose post antibiotiques ?

- Connaissance ancienne
  - Les résidus antibiotiques s'accumulent dans le colon durant les traitements (Oral & parenteral)
  - Ils induisent une profonde dysbiose
  - Ils sélectionnent les bactéries résistantes BGN, VRE, *C. difficile*) et les levures
- D'autres conséquences récemment mises à jour :
  - Métabolisme pédiatrique
  - Cancérologie +++.

Antibiotics in early life and obesity

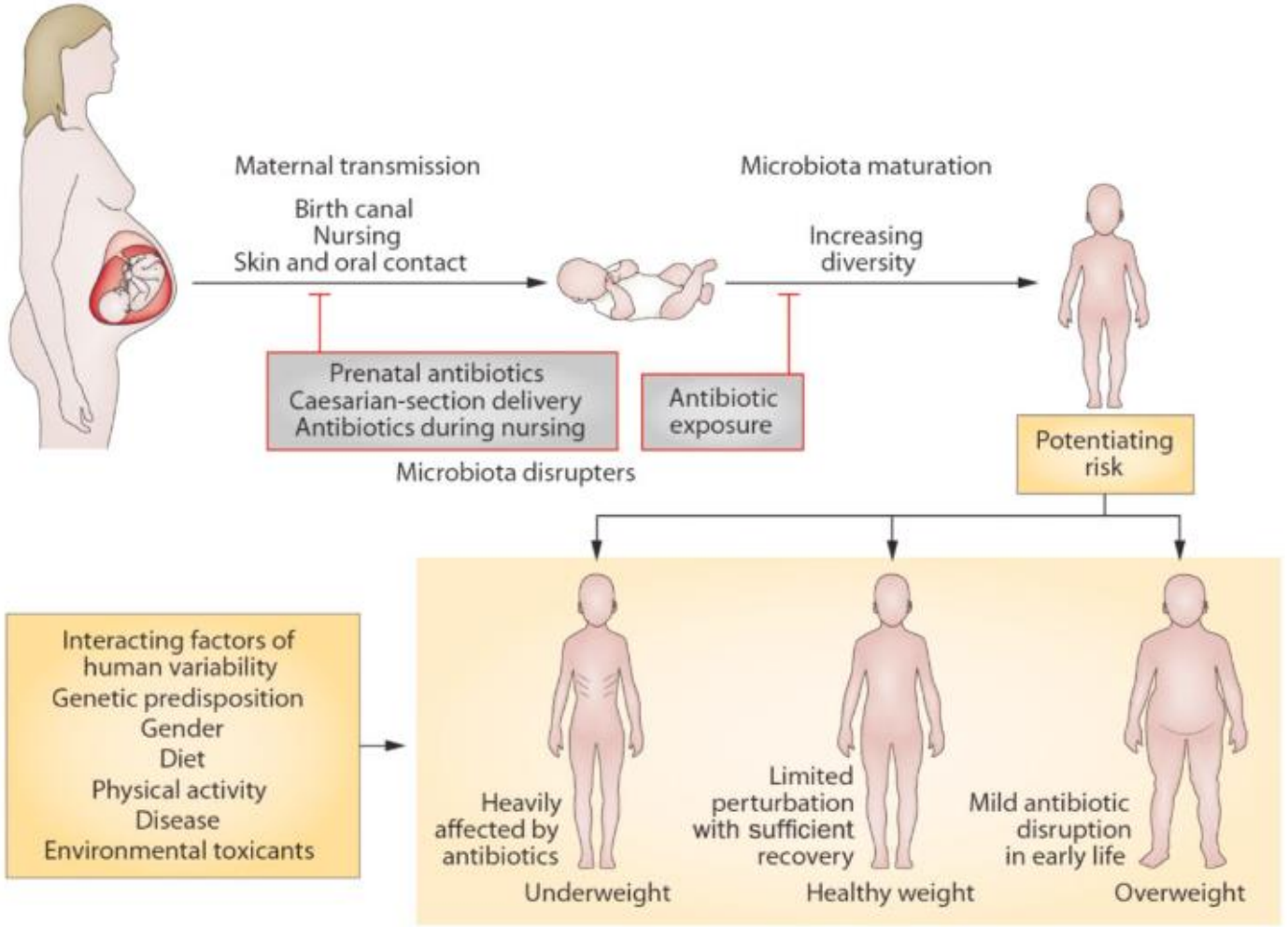
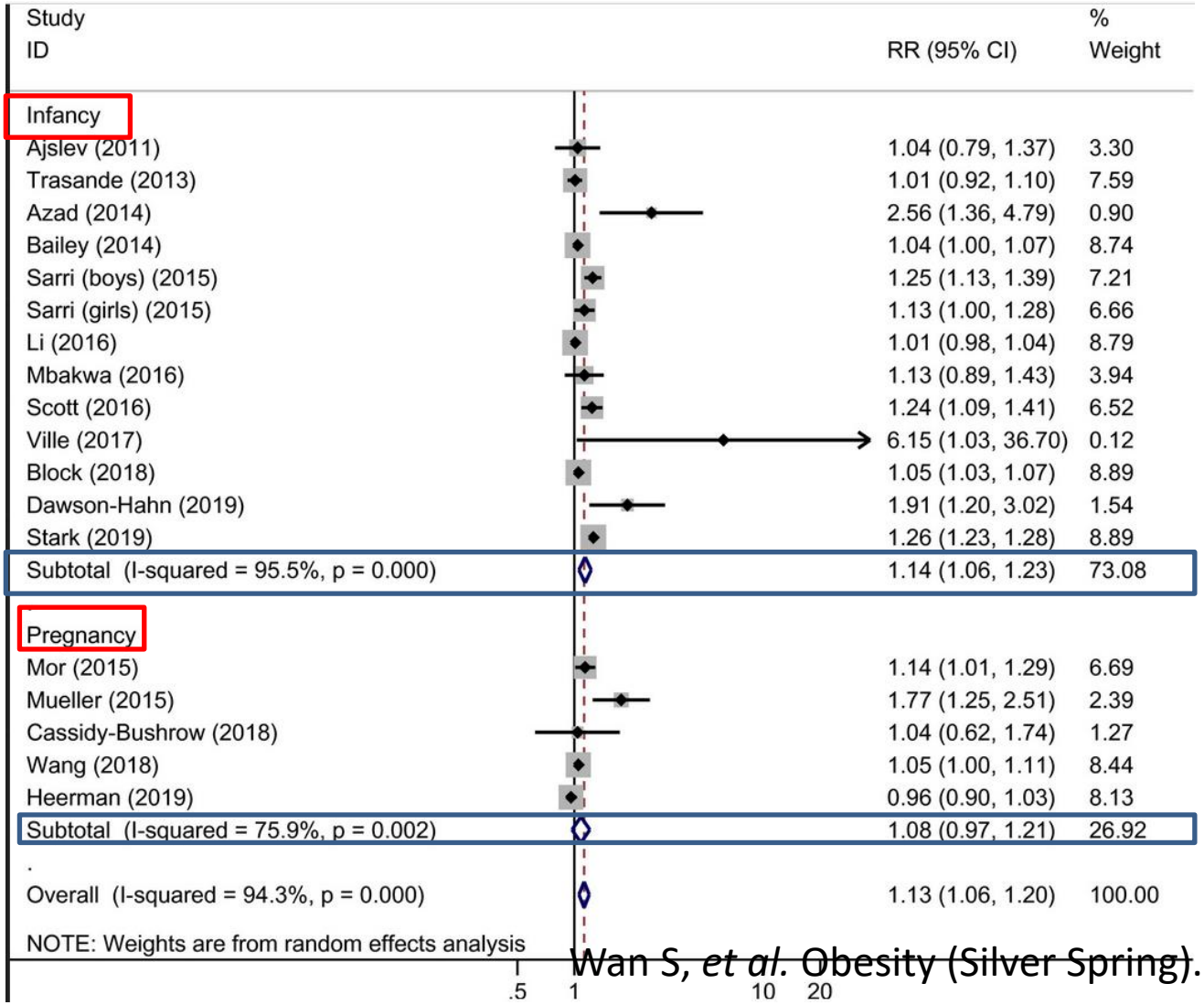


Figure 1. A model of microbiota transmission, maturation and perturbation in the first years of life and possible effects on weight

Cox L , et al. Nat. Rev. Endocr. 2015

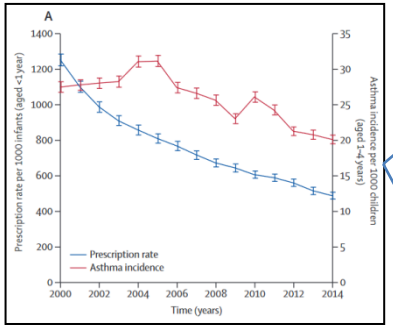
Exposure to antibiotics in infancy or pregnancy and the relative risk of childhood overweight or obesity.



Wan S, *et al.* Obesity (Silver Spring). 2020

Decreasing antibiotic use, the gut microbiota, and asthma incidence in children: evidence from population-based and prospective cohort studies

David M Patrick, Hind Sbihi*, Darlene L Y Dai*, Abdullah Al Mamun*, Drona Rasali, Caren Rose, Fawziah Marra, Rozlyn C T Boutin, Charisse Petersen, Leah T Stiemsma, Geoffrey L Winsor, Fiona S L Brinkman, Anita L Kozyrskyj, Meghan B Azad, Allan B Becker, Piush J Mandhane, Theo J Moraes, Malcolm R Sears, Padmaja Subbarao, B Brett Finlay, Stuart E Turvey*



Association of antibiotic use (<1 year) with the diagnosis of asthma (at age 5 years) in 2644 children

Faecal microbiology analysis of 917 children(≤1 year)

The reduction in the incidence of asthma might be an unexpected benefit of prudent antibiotic use during infancy, acting via preservation of the gut microbial community.

Lancet Respir Med 2020; 8: 1094-105

Impact of Gut Dysbiosis in Hemato-Oncology

DaVolterra

Patients with hematologic malignancies treated with intensive chemotherapy and/or irradiation

↓

Neutropenia

↓

Antibiotics

100% of patients with antibiotics

↓

HEALTHY MICROBIOME → DISRUPTED MICROBIOME

↓

- ***~ 11% of deaths in transplanted patients*** → **Infections (*C. diff*, resistant bacteria)**
- **Relapse**
- **Delayed Recovery**
- **Graft-versus-Host Disease** → ***~ 25% of deaths in transplanted patients***

↓

Reduced Overall Survival

Impact of Microbiome Dysbiosis: Reduced Overall Survival

Increased occurrence of **life-threatening complications** leading to non-relapse mortality

x2 Doubled mortality in patients with a low microbiome diversity

Sources: *Adapted from Shono & van den Brink, Nature Reviews Cancer 2018 ;* Gratwohl et al. Bone Marrow Transplant. 2005

Impact of Gut Dysbiosis in Immuno-Oncology

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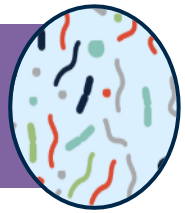
HEALTHY MICROBIOTA

Cancer patients treated with immune checkpoint inhibitors



Antibiotics

46% of patients with antibiotics

DISRUPTED MICROBIOTA

KEYTRUDA® (pembrolizumab) Injection 100 mg

OPDIVO® (nivolumab)

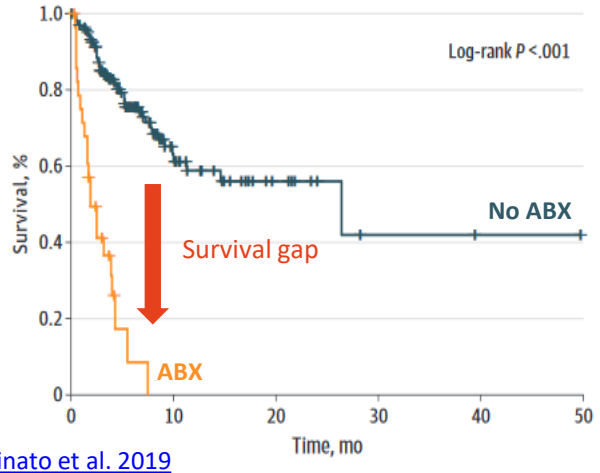
Impaired Immunity

Anti-tumor efficacy

Reduced Overall Survival

Reduced Overall Survival associated with Antibiotic Use

➔ **First prospective data in 2019**



Pinato et al. 2019

➔ **Multiple confirmations between 2018 and 2020**

50+ Publications and meta-analyses with concurring conclusions

-7mo **Overall Survival is reduced by 7 months** on average in patients receiving antibiotics and with a disrupted microbiome

Lurienne et al. 2020

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 160, NO. 2 • AUGUST 1989
 0022-1899/89/6002-0013$01.00

1985

Use of β-Lactamase-Producing Anaerobes to Prevent Ceftriaxone from Degrading Intestinal Resistance to Colonization

Florence Léonard, Antoine Andremont, Bernard Leclerq, Roger Labia, and Cyrille Tancrède

From the Laboratoire d'Ecologie Microbienne, Service de Réanimation Médico-Chirurgicale, Institut Gustave-Roussy, Villejuif, and Centre National de la Recherche Scientifique, Paris, France

- ✓A very surprising study in 6 human volunteers
- ✓We were expecting that the results would be highly homogeneous
- ✓Thus the small number of volunteers

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 160, NO. 2 • AUGUST 1989
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From the Laboratoire d'Ecologie Microbienne, Service de Réanimation Médico-Chirurgicale, Institut Gustave-Roussy,

Feces characteristics	Volunteers with Ceftriaxone IV 1G/dX5 days	
	n=4	n=2
Changes in counts : ✓ Anaerobes ✓ Fungi	 Stable Stable	 Decreased Increased
Antibiotic activity (mg/L)	<0.1	>1,500
B-lactamase activity (Bacteroides)	++++	0

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 160, NO. 2 • AUGUST 1989
 0022-1899/89/6002-0013$01.00

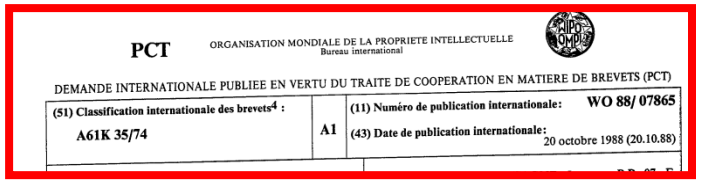
Use of β-Lactamase-Producing Anaerobes to Prevent Ceftriaxone from Degrading Intestinal Resistance to Colonization

Floren
Bernar

Results confirmed in human flora associated mice

*

1. Flora impacted by ceftriaxone
2. Protection afforded by administration of B-lactamase producing bacteroïdes
3. Protection impaired by co-administration of clavulanate



PCT ORGANISATION MONDIALE DE LA PROPRIETE INTELLECTUELLE
Bureau international

DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

(51) Classification internationale des brevets[4] :		(11) Numéro de publication internationale:	WO 88/ 07865
A61K 35/74	A1	(43) Date de publication internationale:	20 octobre 1988 (20.10.88)

First patent 1988

Administration of *Bacteroïdes* with B-lactams

- ✓Good results in mice **but,**
- ✓Impossible to produce industrially
- ✓No replacement possible because :
  1. GMO : risk of dissemination
  2. Proteins fragile and prod impossible then
  3. No trustable colonic delivery

Idea forgoten for ten years, revisited in the 90s :

1. Production of recombinant purified proteins
2. Development of new colonic vectors

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 75–79
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.1.75–79.2004

Vol. 48, No. 1

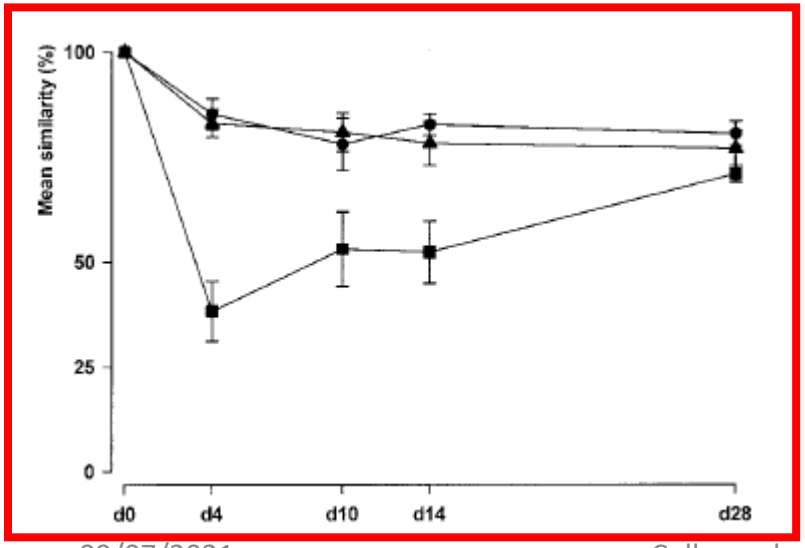
ipsat therapies

2004 in dogs

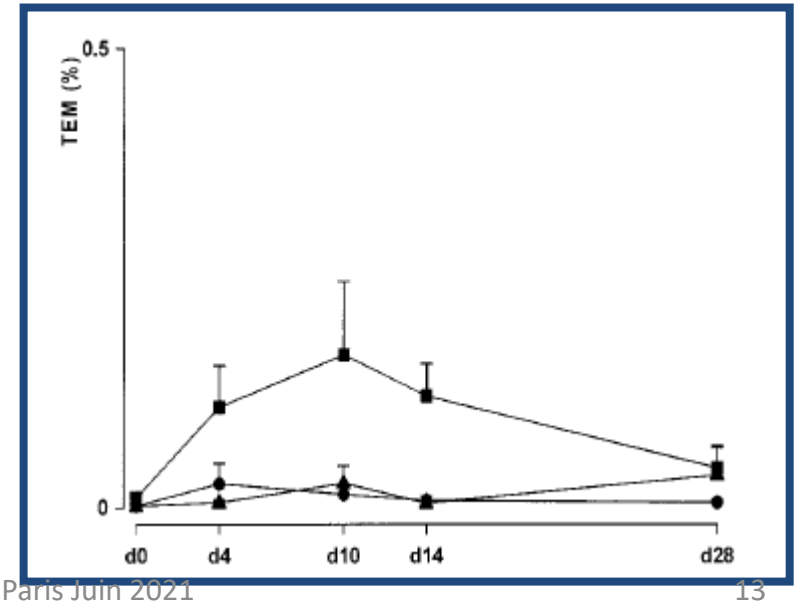
Orally Administered Targeted Recombinant Beta-Lactamase Prevents Ampicillin-Induced Selective Pressure on the Gut Microbiota: a Novel Approach to Reducing Antimicrobial Resistance

Jaana Harmoinen,[1]* Silja Mentula,[2] Matti Heikkilä,[1] Michel van der Rest,[3] Päivi J. Rajala-Schultz,[4] Curtis J. Donskey,[5] Rafael Frias,[1] Pertti Koski,[6] Nina Wickstrand,[6] Hannele Jousimies-Somer,[2]† Elias Westermarck,[1] and Kai Lindevall[7]

Similarity index DGGE



Counts of amp-R coliforms



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2009, p. 2455–2462
0066-4804/09/$08.00+0 doi:10.1128/AAC.00853-08

Vol. 53, No. 6

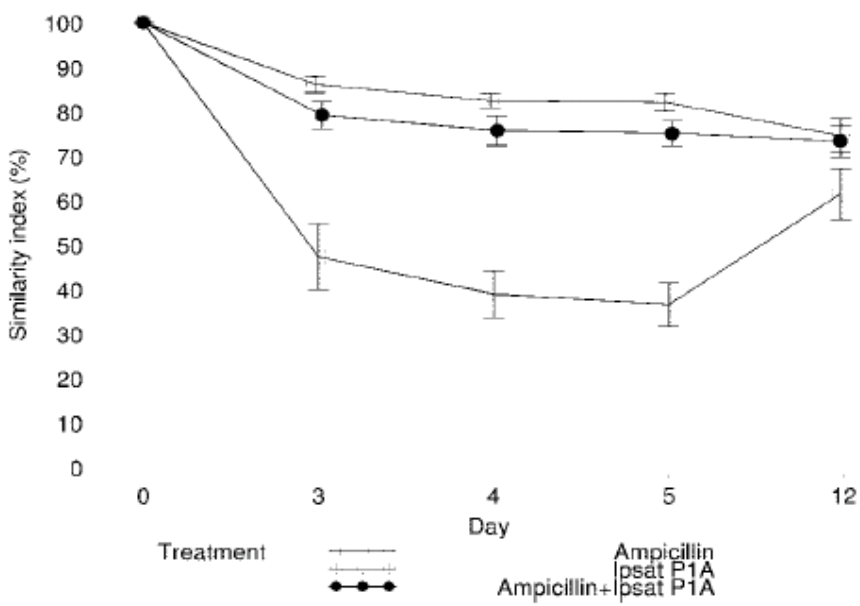
ipsat therapies

2009 in humans

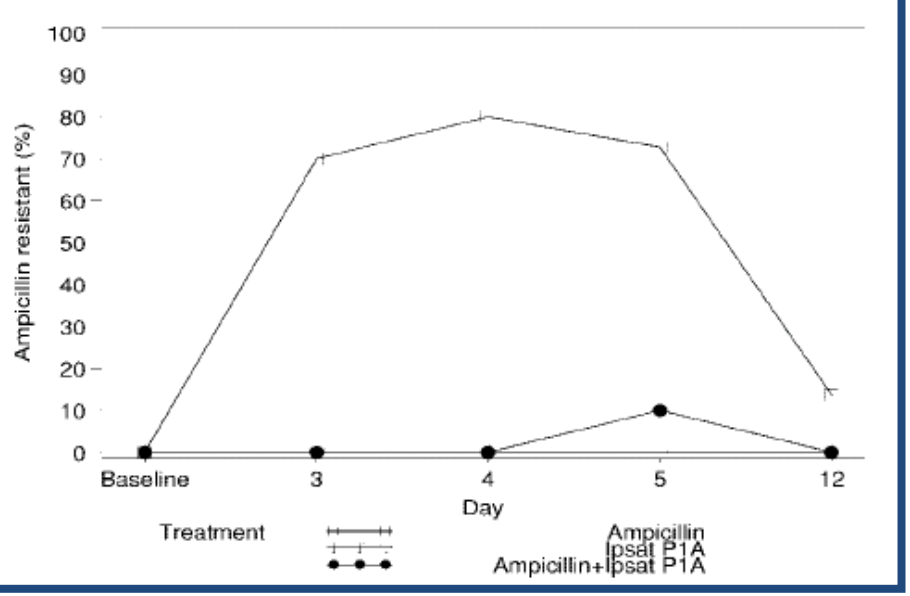
P1A Recombinant β-Lactamase Prevents Emergence of Antimicrobial Resistance in Gut Microflora of Healthy Subjects during Intravenous Administration of Ampicillin[▽]

Ann-Mari Tarkkanen,[1] Tuula Heinonen,[1]† Rain Jõgi,[2] Silja Mentula,[3] Michel E. van der Rest,[4] Curtis J. Donskey,[5] Tuomas Kemppainen,[6] Konstantin Gurbanov,[1]* and Carl Erik Nord[7]

Similarity index DGGE



Counts of amp-R coliforms



Major obstacles on the road to success for ipsat therapies

- ✓Limited spectrum of their enzyme
- ✓No direct benefit
- ✓High costs of goods
- ✓No more funding
- ✓**End of story…?**

The revival development of the beta-lactamase approach

Fichier Édition Affichage Historique Marque-pages Outils ?

SYN-004 :: Synthetic Biolog...

www.syntheticbiologics.com/product-pipeline/microbiome-focused-pipeline/syn-004

synthetic biologics

Synthetic BIOLOGICS

about product pipeline news & media investors contact

Overview

C. difficile is the leading type of hospital acquired infection and is frequently associated with intravenous (IV) beta-lactam antibiotic treatment. Beta-lactam antibiotics are often the treatment of choice for hospitalized patients with infections; they include commonly used penicillin and cephalosporin antibiotics, such as ceftriaxone. However, antibiotics have the potential to cause harmful effects within the gastrointestinal (GI) tract including disruption of the natural balance of the gut microbiome, leading to 453,000 *C. difficile* infections (CDI) and > 29,000 *C. difficile*-related deaths in the United States each year.

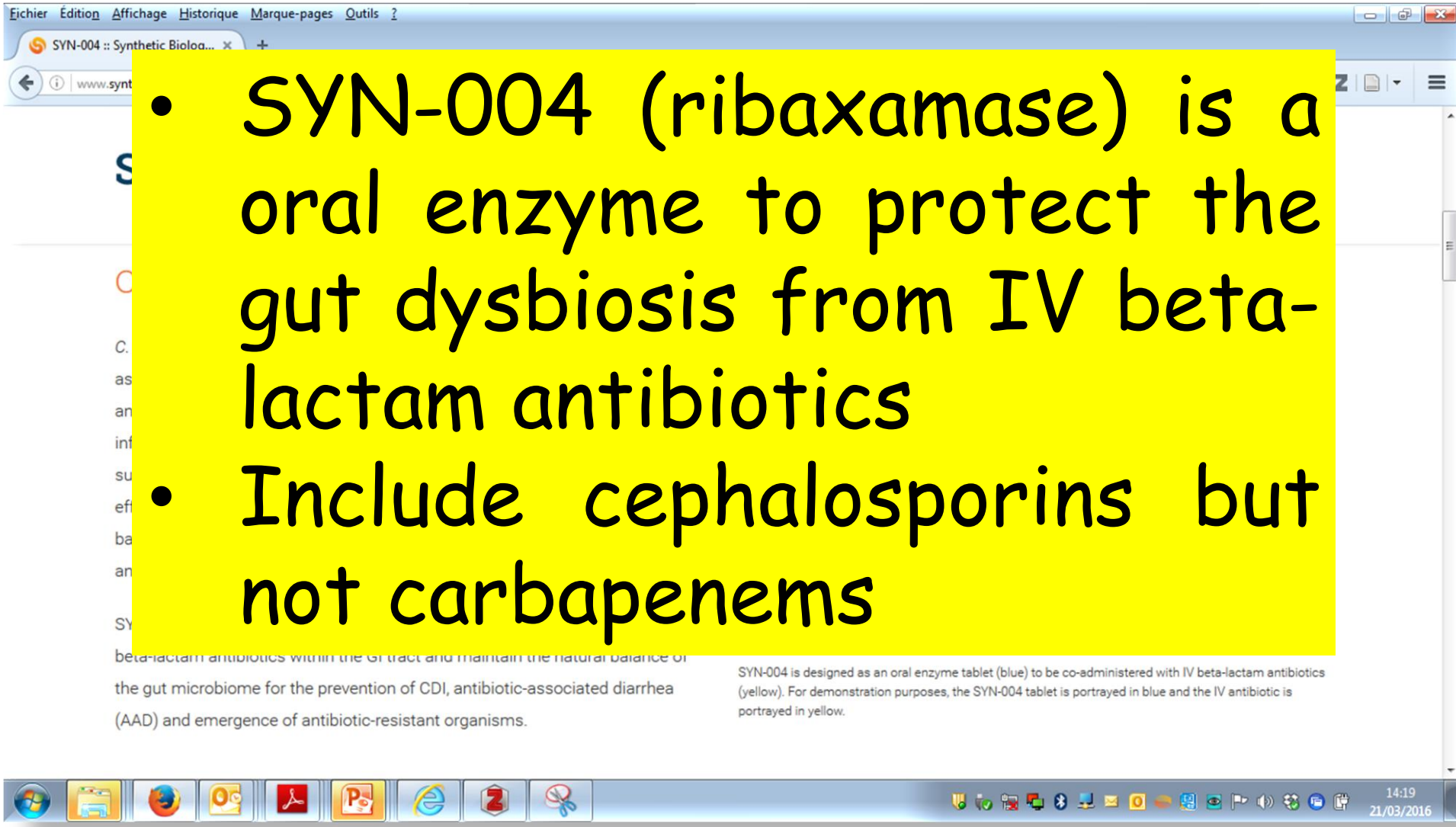
SYN-004 is an oral prophylactic therapy designed to degrade certain IV beta-lactam antibiotics within the GI tract and maintain the natural balance of the gut microbiome for the prevention of CDI, antibiotic-associated diarrhea (AAD) and emergence of antibiotic-resistant organisms.

SYN-004 is designed as an oral enzyme tablet (blue) to be co-administered with IV beta-lactam antibiotics (yellow). For demonstration purposes, the SYN-004 tablet is portrayed in blue and the IV antibiotic is portrayed in yellow.

14:19
21/03/2016

The current development of the beta-lactamase approach : IV treatments only

- SYN-004 (ribaxamase) is a oral enzyme to protect the gut dysbiosis from IV beta-lactam antibiotics
- Include cephalosporins but not carbapenems



Use of ribaxamase (SYN-004), a β-lactamase, to prevent *Clostridium difficile* infection in β-lactam-treated patients: a double-blind, phase 2b, randomised placebo-controlled trial

John F Kokai-Kun, Tracey Roberts, Olivia Coughlin, Chenxiong Le, Heidi Whalen, Ralph Stevenson, Vincent J Wacher, Joseph Sliman

	Placebo (N=206)	Ribaxamase (N=206)
Local laboratory-confirmed *C difficile* infections		
Number of patients (%)	7 (3·4%)	2 (1·0%)
Risk reduction (95% CI)	..	2·4% (−0·6 to 5·9)*
One-sided p value†	..	0·045
Central laboratory-confirmed *C difficile* infections		
Number of patients (%)	8 (3·9%)	2 (1·0%)
Risk reduction (95% CI)	..	2·9% (−0·2 to 6·6)
p value	..	0·027
Patients receiving treatment for *C difficile* infections‡		
Number of patients (%)	6 (2·9%)	1 (0·5%)
Risk reduction (95% CI)	..	2·4% (−0·3 to 5·8)
p value	..	0·028

	Placebo	Ribaxamase	p value
Clostridium difficile			
Screening	5 (2%)	3 (1%)	0·239
End of treatment period 2	14 (8%)	7 (4%)	0·059
4-week follow-up visit	18 (9%)	11 (6%)	0·088
Vancomycin-resistant enterococci			
Screening	8 (4%)	5 (2%)	0·198
End of treatment period 2	69 (37%)	36 (19%)	0·0001
4-week follow-up visit	71 (36%)	40 (20%)	0·0002
Extended-spectrum, β-lactamase-producing Gram-negative bacilli			
Screening	46 (22%)	37 (18%)	0·134
End of treatment period 2	30 (16%)	31 (17%)	0·565
4-week follow-up visit	44 (22%)	49 (25%)	0·714

Risk reduction in *C. difficile* desease

Risk reduction in resistant bacetria colonisation

Lancet Infect Dis 2019; 19: 487–96

May 11, 2017

SYN-004 (Ribaxamase) Receives Breakthrough Therapy Designation from U.S. Food and Drug Administration for Prevention of Clostridium difficile Infection

Synthetic Biologics Announces Positive Outcome of End-of-Phase 2 Meeting with FDA on SYN-004 (ribaxamase) Development

-- Single Phase 3 Clinical Trial May be Sufficient for Approval for Prevention of Antibiotic-Mediated Clostridium difficile Infection (CDI) --

-- SYN-004 (ribaxamase) is in Development as Potentially the First Intervention Designed to Specifically Prevent Antibiotic Damage to the Microbiome --

NEWS PROVIDED BY
Synthetic Biologics, Inc. →
Nov 21, 2018, 07:00 ET

SHARE THIS ARTICLE

R on

May 11, 2017

SYN-004 (Ribaxamase) Receives Breakthrough Therapy Designation from U.S. Food and Drug Adı

Mais :

- Spectre toujours limité n'incluant pas les carbapénèmes
- Ni les produits avec des inhibiteurs récents de beta-lactamases
- Ni les autres antibiotiques
- Et peut-être une question de safety…

Intervention Designed to Specifically Prevent Antibiotic Damage to the Microbiome --

NEWS PROVIDED BY
Synthetic Biologics, Inc. →
Nov 21, 2018, 07:00 ET

SHARE THIS ARTICLE

En dépit de ces résultats très encourageants :

- Un cours de bourse catastrophique
- Une réorientation vers la cancérologie

Synthetic BIOLOGICS

SYN-004 Safety and Tolerability in Allo-HCT Subjects

ClinicalTrials.gov Identifier: NCT04692181

Recruitment Status : Recruiting
First Posted : December 31, 2020
Last Update Posted : March 2, 2021

See **Contacts and Locations**

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Colonic targeting of non-specific adsorbants: A possible alternative?

DaVolterra

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(19) World Intellectual Property Organization
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(43) International Publication Date
23 November 2006 (23.11.2006)

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A61K47/36 (2006.01)

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(25) Filing Language: English

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60/682,074 18 May 2005 (18.05.2005) US

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(74) Agents: PORTAL, Gerard et al.; Cabinet Beau de Lomenie, 158, rue de l'Universite, F-75007 Paris (FR).

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Published:
with international search report
before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

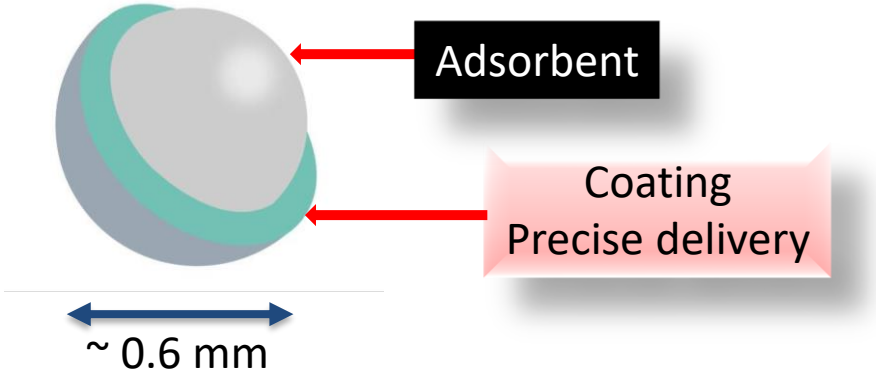
2006
CNRS/DaVolterra/UP7/UP11

- ✓No adsorption in the upper intestine
- ✓Delivery in the late ileum
- ✓Adsorption of ATBs in ceacum and colon
- ✓Will it work in practice ?

Strategies to protect microbiome against antibiotics

Adsorbent strategy– Da Volterra– general principle

DAV132

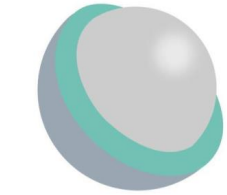


- Broad spectrum powerful adsorbent
- Adsorbs antibiotics from all classes under human gut like conditions
- Targeted ileo-caecum delivery
- Oral AND IV treatments

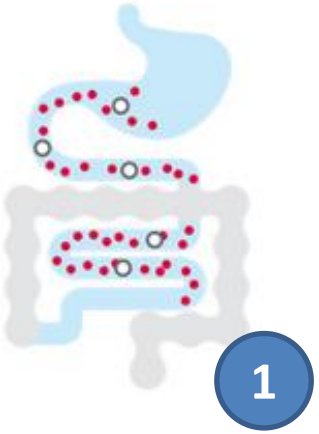
de Gunzburg et al. (2015) J. Clin. Pharmacol. 55, 10-6

The concept behind DAV132

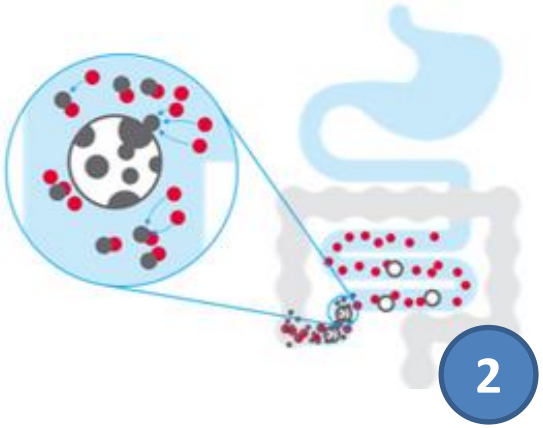
DAV132



- *DAV132*
- *Antibiotics*



DAV132 is orally administered together with the antibiotic. Antibiotics are absorbed in the upper gastro-intestinal tract without interference while the coating of DAV132 is intact.

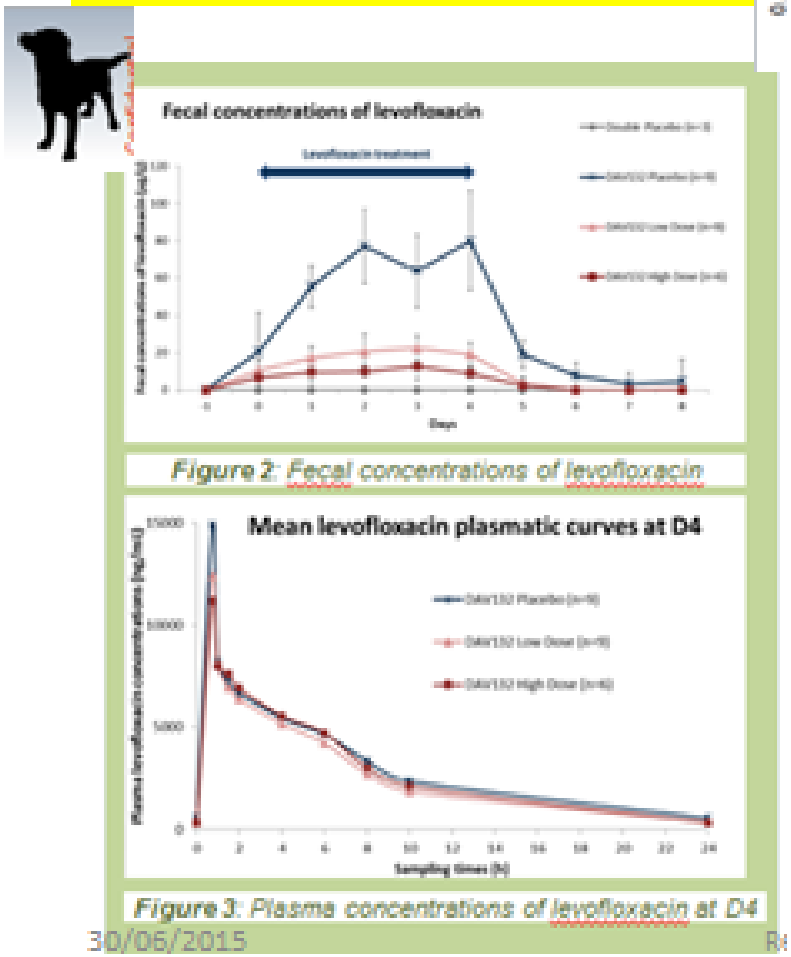


DAV132 coating opens in the colon and the adsorbent irreversibly captures the antibiotics.

Antibiotic residues are bound to DAV132 and eliminated with feces

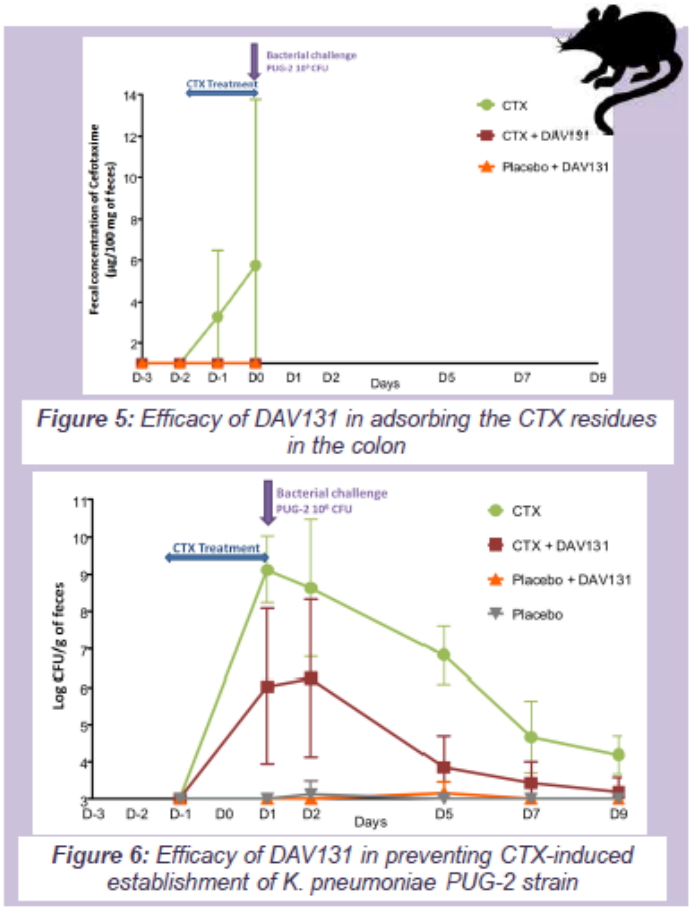
Pre-clinical efficacy of DAV 131

In dogs treated by levofloxacin IV



ICAAC 2012

In mice treated by cefotaxime IP

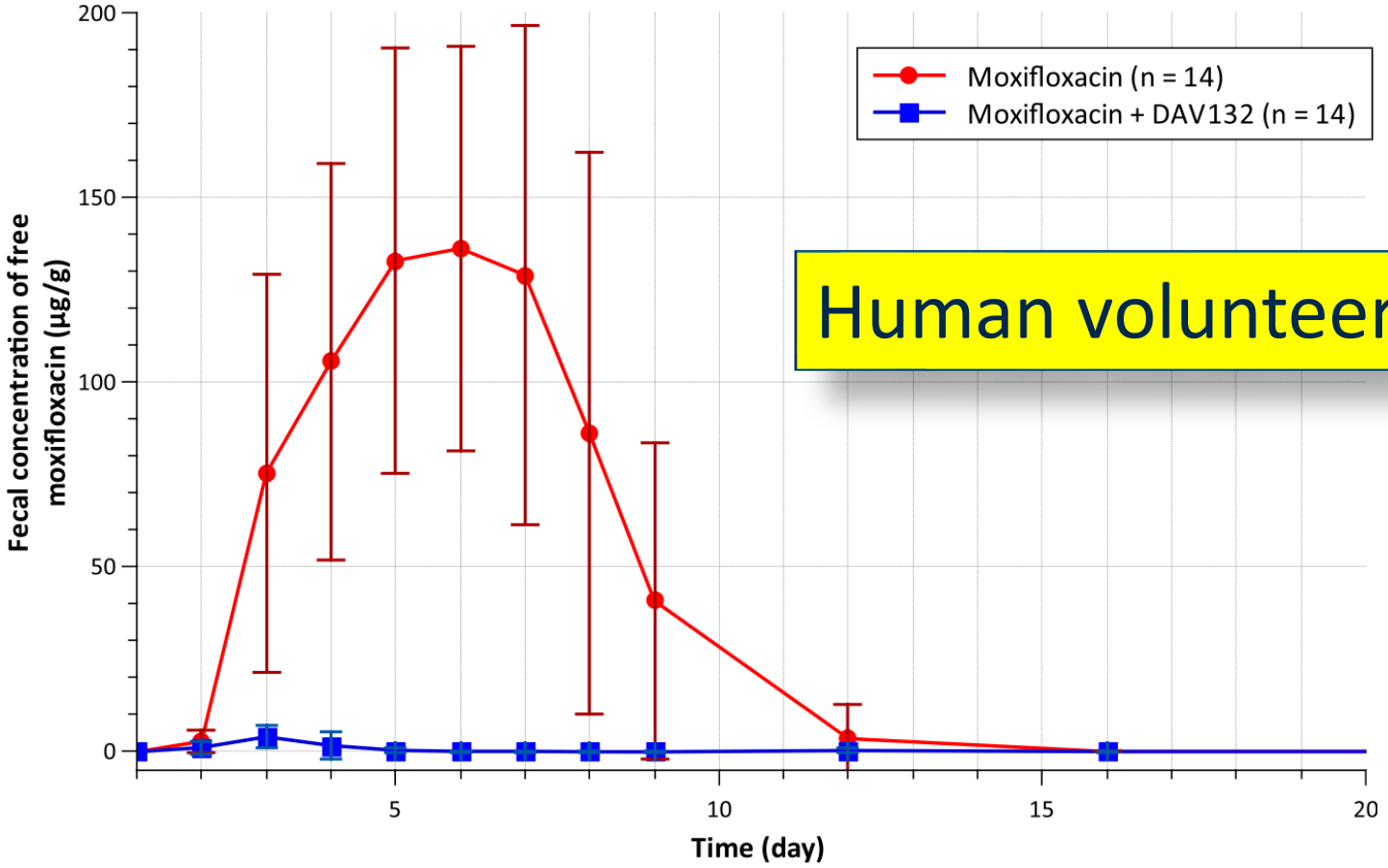


Grall N. *et al.* AAC 2013

2nd Clinical Study: DAV132-CL-1002

Results - Moxifloxacin Pharmacokinetics in the Feces (1/2)

- Free moxifloxacin fecal concentrations (mean ± SD, µg/g of feces) over time (days) in healthy volunteers



Human volunteers

Gunzburg et al. JID 2017

LOQ: 40 ng/g of feces

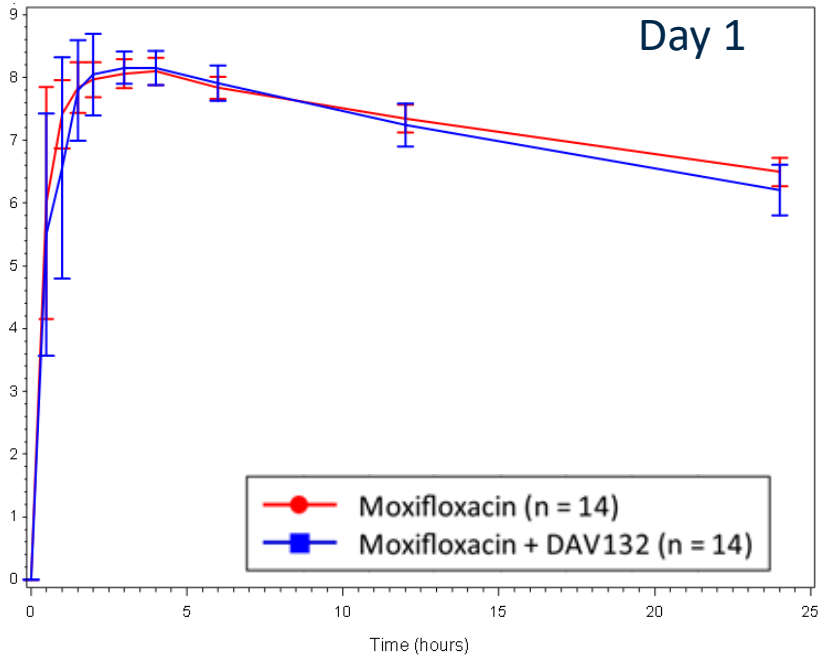
DaVolterra

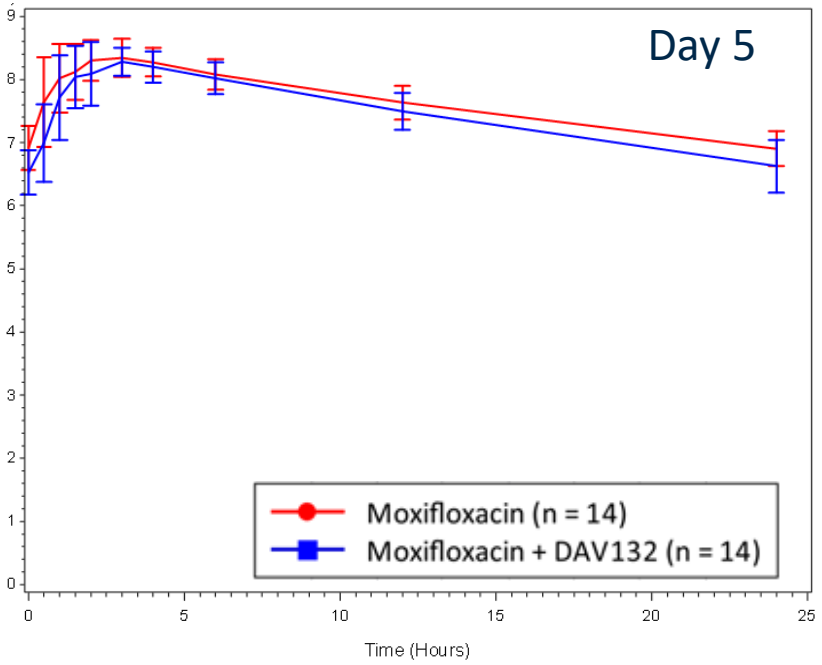
2nd Clinical Study: DAV132-CL-1002

Results - Moxifloxacin Plasma Pharmacokinetics

Human volunteers

- Moxifloxacin plasma concentrations (mean Log ± SD, µg/mL) on Day 1 and Day 5 over time (hours) in healthy volunteers





- No significant difference between groups for AUC_{0-24} on Day 1 (p=0.806) and Day 5 (p=0.139)

⇨ Maintenance of moxifloxacin plasma concentrations when DAV132 is associated with moxifloxacin vs. moxifloxacin alone

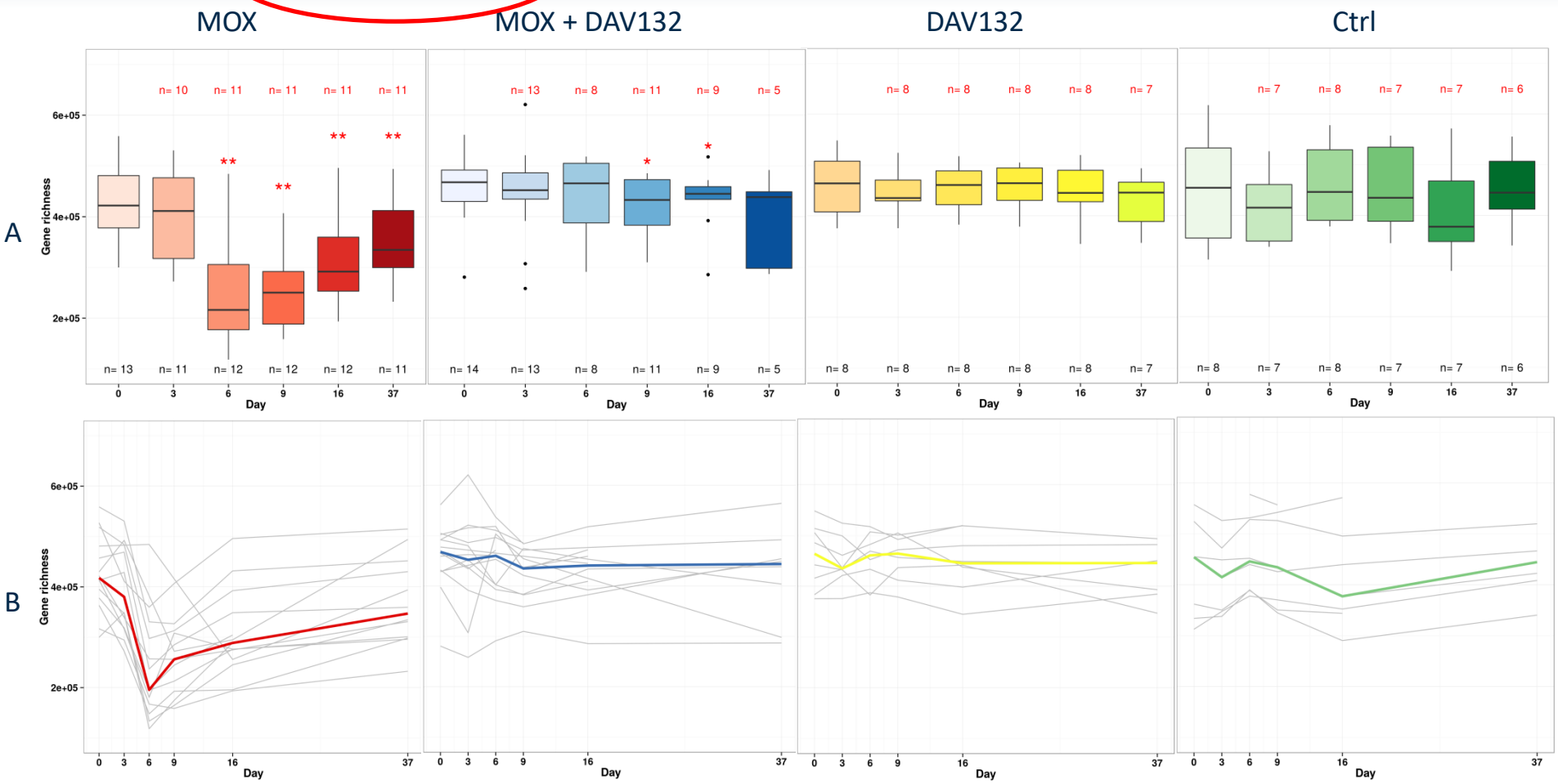
LOQ: 10 ng/mL of plasma

Gunzburg et al. JID 2017

DaVolterra

DAV132-CL-1002. Metagenomics

Results - gene richness



Gene richness profiles per day (A), per day and per individual (grey lines) and observed medians (B). Black numbers (n) correspond to the number of individuals in the boxplot; red numbers (n) correspond to the number of individuals considered for the paired test.

⇨ Moxifloxacin causes a 50% drop in gene richness at D6 which is abrogated by DAV132

Gunzburg et al. JID 2017

DaVolterra

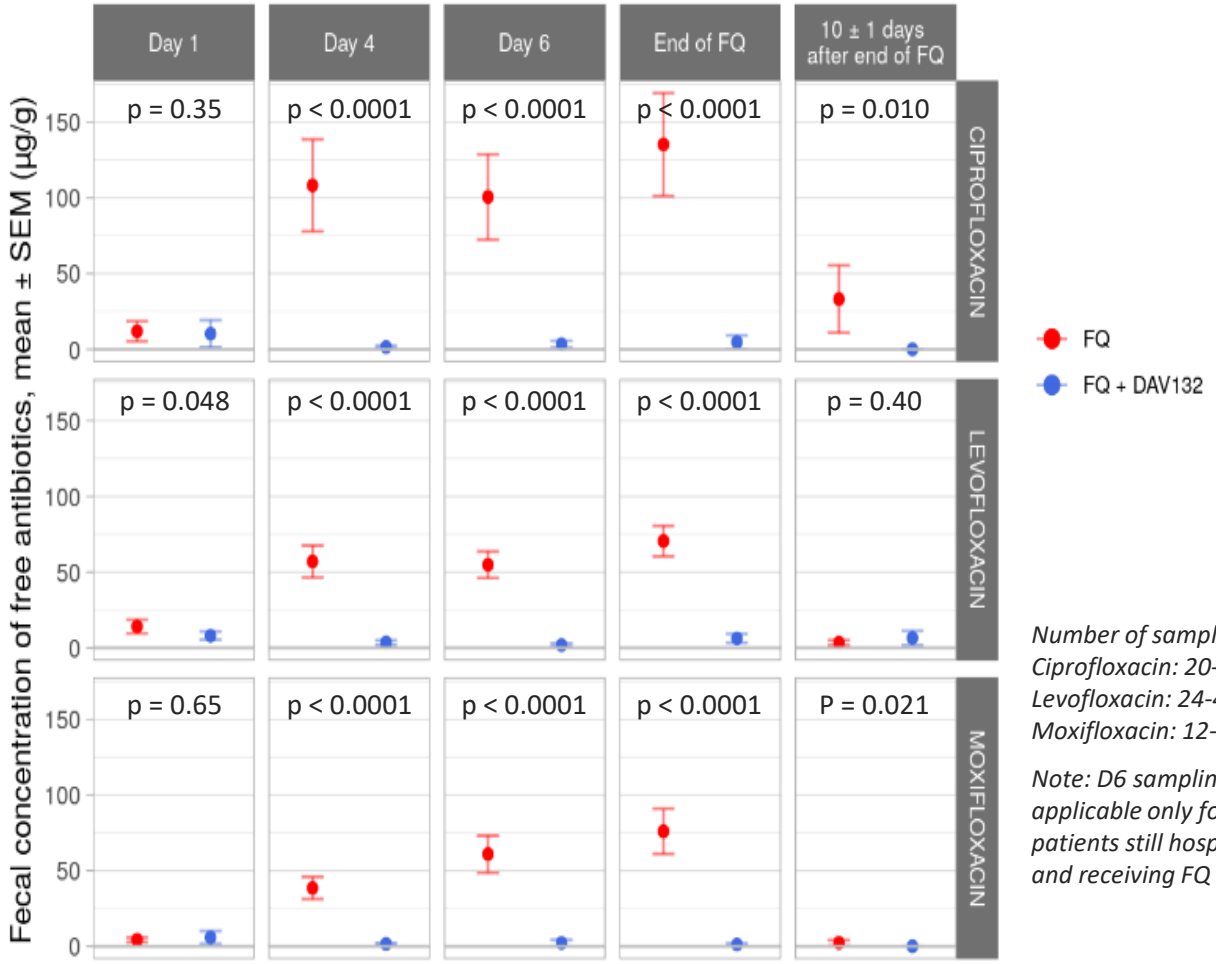
Phase 2 study in 242 hospitalized patients with co-morbidities treated by various fluoroquinolones without or with DAV132
The SHIELD Study

30th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Paris, France
18–21 April 2020

DAV132 Reduces fecal Fluoroquinolone Concentrations

During treatment, fecal FQ levels were lowered by >97% with DAV132 vs. No DAV132



Number of samples/group:
Ciprofloxacin: 20-36
Levofloxacin: 24-42
Moxifloxacin: 12-20

Note: D6 sampling applicable only for patients still hospitalized and receiving FQ at D6

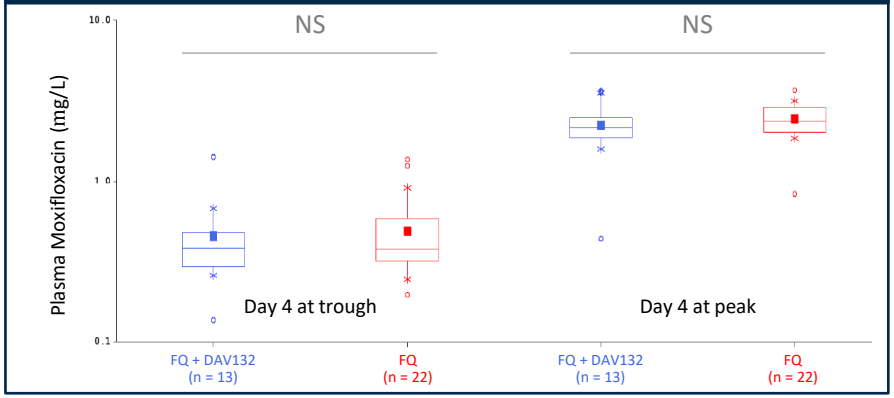
Sources: internal data, manuscript in preparation

Analyses performed on the PPS

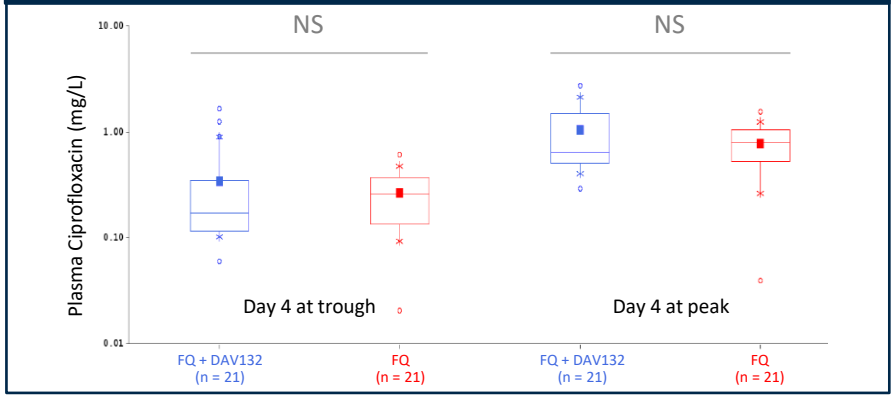
SHIELD Safety Results Display Favorable Safety Profile (2/2)

No Impact of DAV132 on the Plasma Concentration of Fluoroquinolones

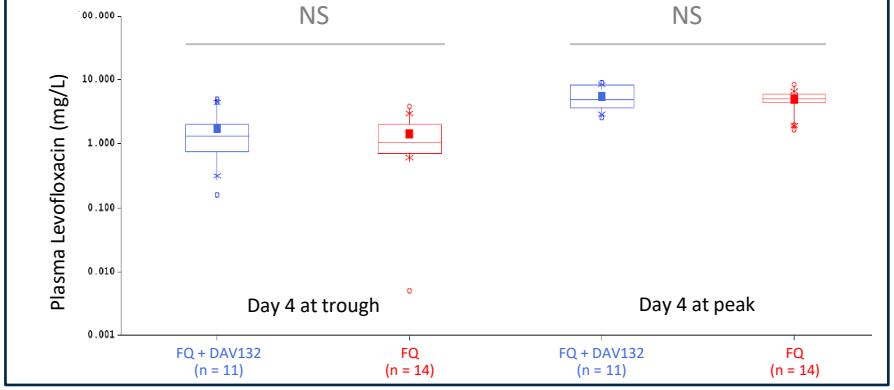
No significant impact of DAV132 on the plasma concentration of moxifloxacin i.v. (400 mg, once-a-day)



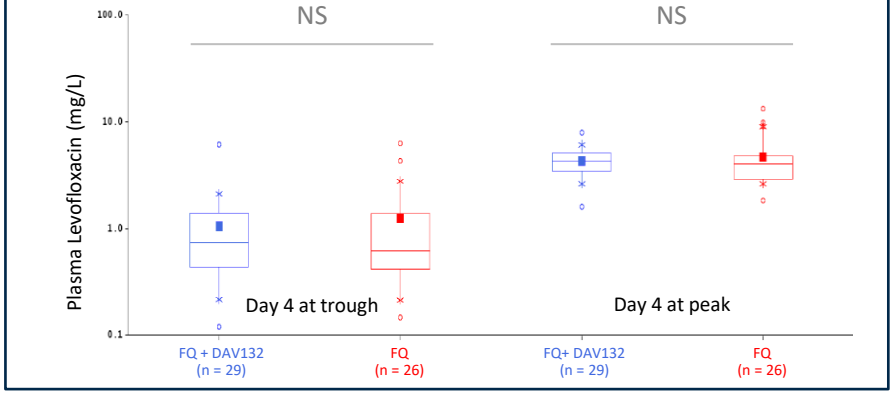
No significant impact of DAV132 on the plasma concentration of ciprofloxacin i.v. (200 mg twice-a-day)



No significant impact of DAV132 on the plasma concentration of levofloxacin **oral** (500 mg, once-a-day)



No significant impact of DAV132 on the plasma concentration of levofloxacin i.v. (500 mg, once-a-day)



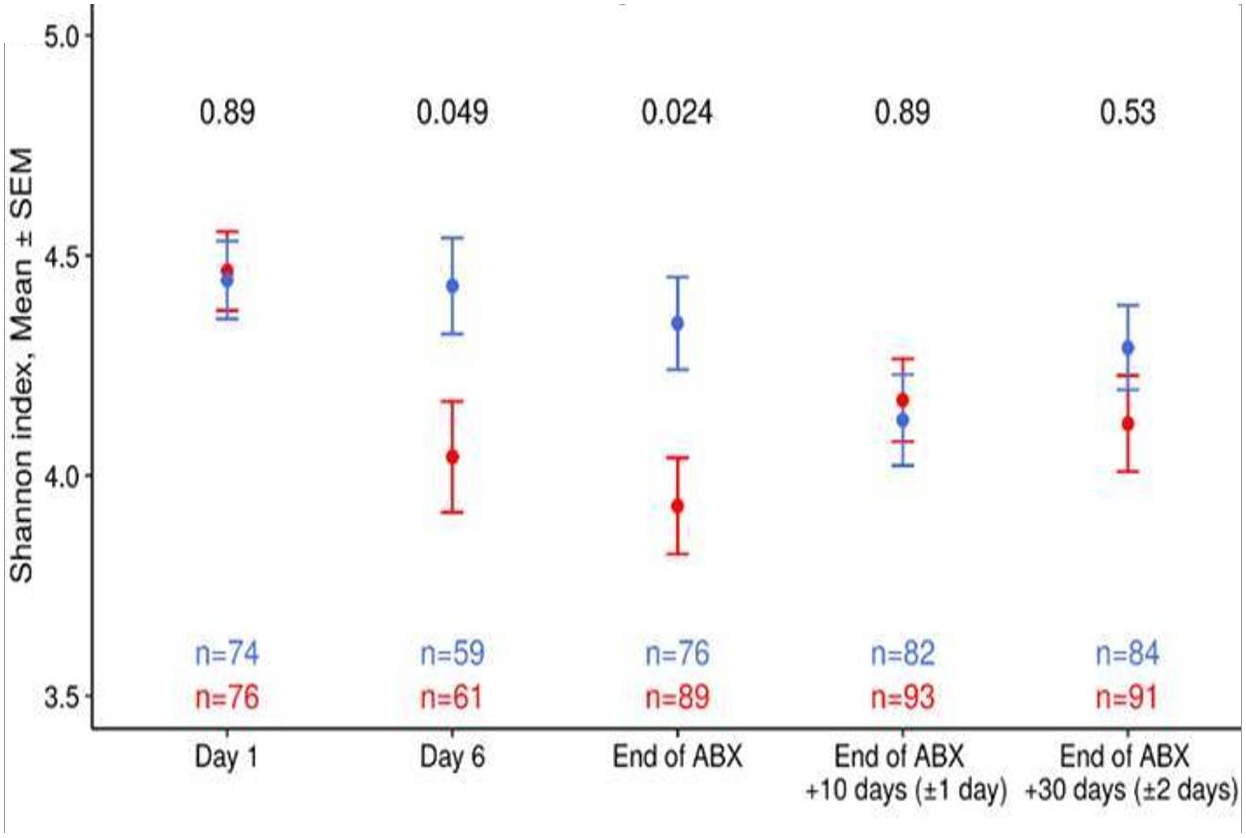
FQ
FQ + DAV132

Sources: Unpublished data

Analyses performed on the PPS

DAV132 Preserves the Gut Microbiota of Patients from Fluoroquinolone-Induced Disruption

Intestinal microbiota diversity is significantly protected with DAV132



Stool samples. Wilcoxon test with Benjamini-Hochberg correction.

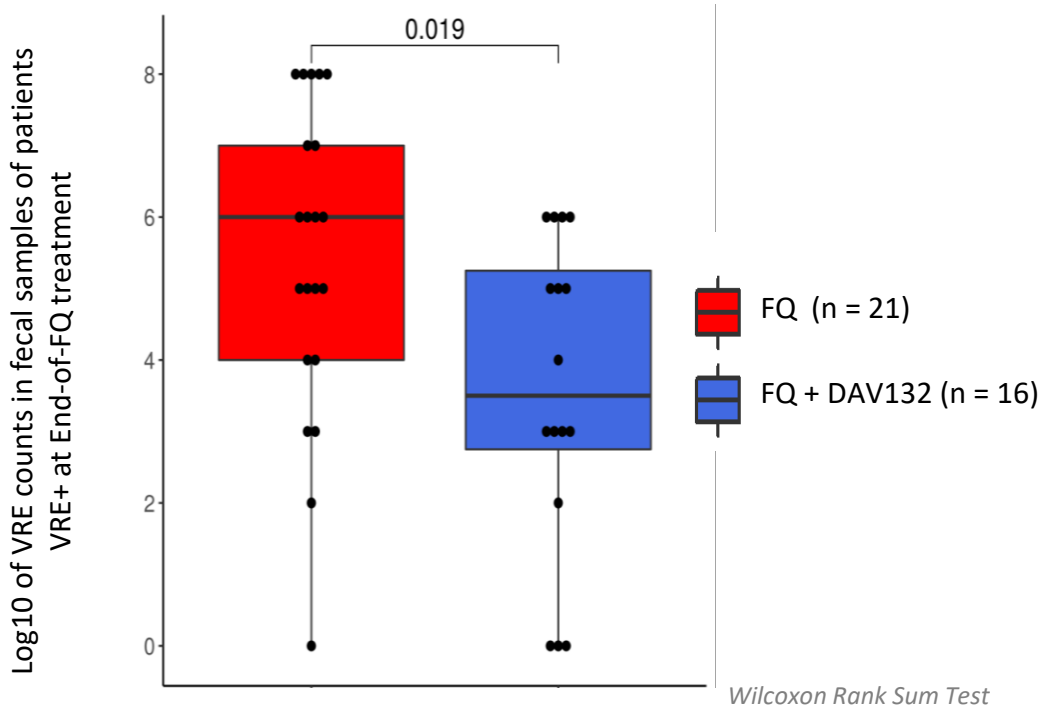
Note: D6 sampling applicable only for patients still hospitalized and receiving FQ at D6

Sources: internal data, manuscript in preparation

Analyses performed on the PPS

Significant Reduction in the Counts of (VRE) at End-of-FQ Treatment in Patients Treated with DAV132

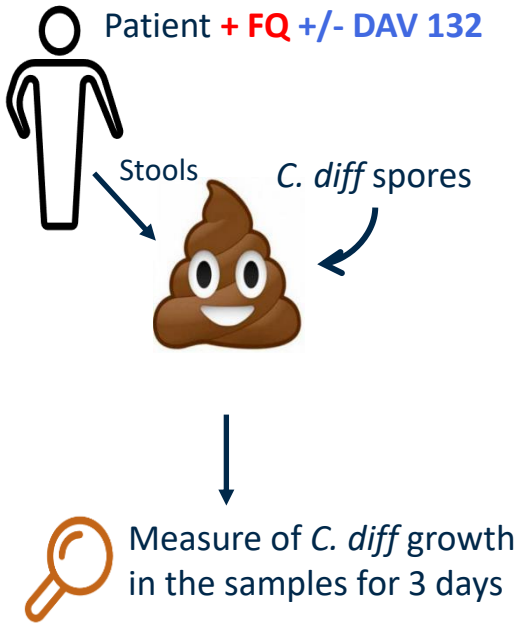
VRE counts at End-of-FQ treatment are reduced in the feces of patients treated with DAV132 (not carriers at Day 1)



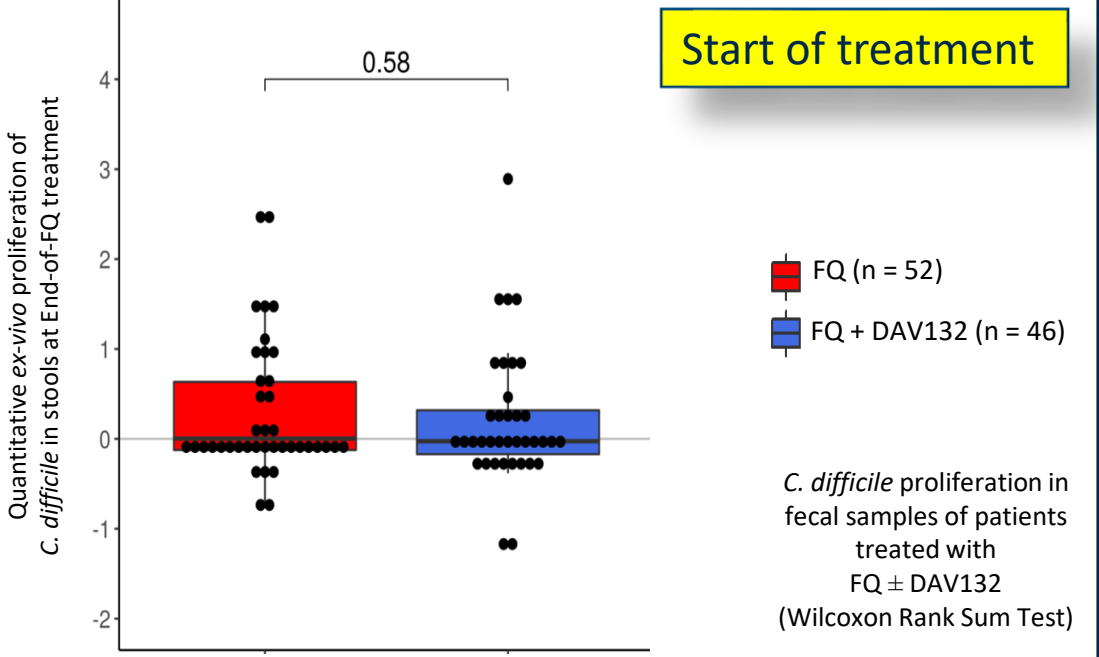
Sources: internal data, manuscript in preparation

Analyses performed on the Safety Set

Resistance to Colonization of Feces by *C. diff* is preserved with DAV132



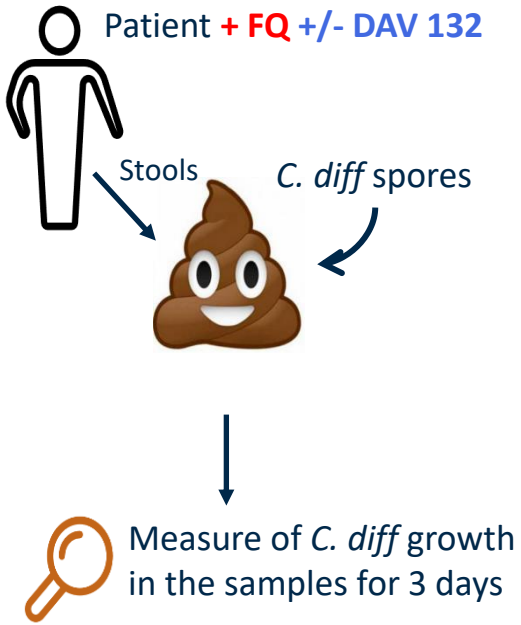
Resistance to colonization by *C. difficile* in the feces of patients is similar at baseline in patients who will receive or not DAV132



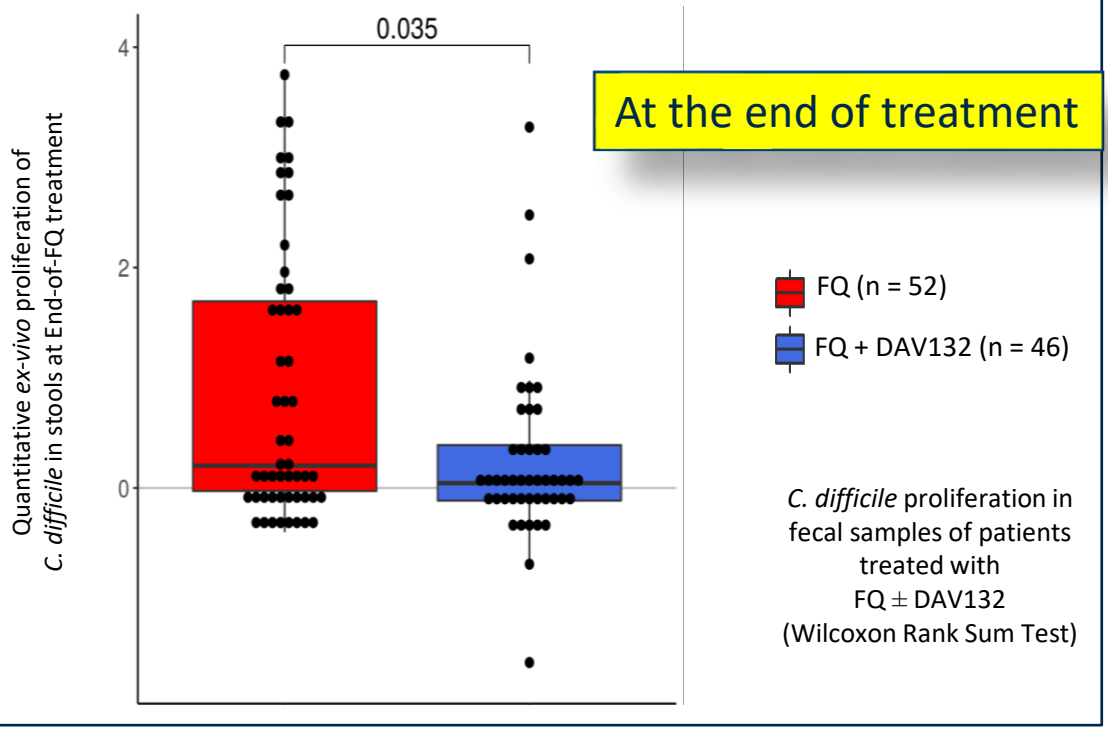
Sources: Borriello et al. J Med Microbiol. 1986 ; Harris et al., Antimicrob. Agents Chemother. 2020

Colonization Resistance Assay for *C. diff* in Stool (CRACS)

Resistance to Colonization of Feces by *C. diff* is preserved with DAV132



Resistance to colonization by *C. difficile* in the feces of patients is maintained in patients who receive DAV132 + FQ antibiotics



Sources: Borriello et al. J Med Microbiol. 1986 ; Harris et al., Antimicrob. Agents Chemother. 2020

Au total

- Au moins deux approches sont possibles pour protéger le microbiote durant l'antibiothérapie :
  - Hydrolyze enzymatique
  - Inactivation par adsorbtion
- Dans les deux cas :
  - Orientation des développements vers les marchés de cancérologie à haute valeur ajoutée
  - En raison des couts de développements
  - De la non reconnaissance de l'end-point « microbiote sain » ou « colonisation à bactéries résistantes » par les agences de régulation

Merci beaucoup pour votre attention !