Emerging Therapies for *Clostridioides difficile* infection

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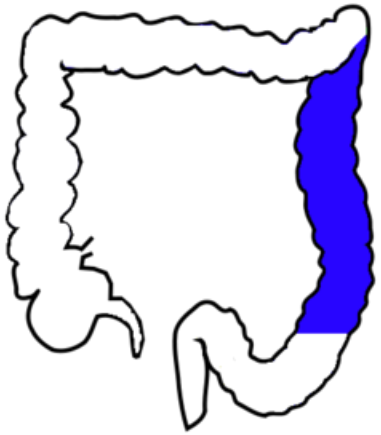
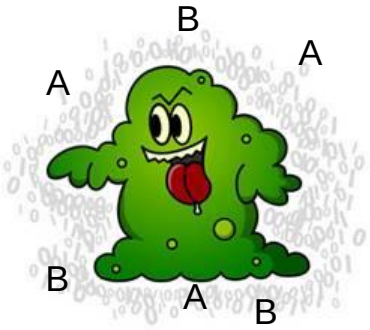
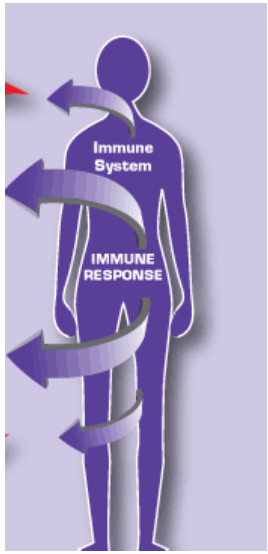
January 2025 AMR Stewardship Conference, Houston, Texas

UNIVERSITY of HOUSTON | COLLEGE OF PHARMACY

Therapeutic Goals for *C. difficile* Infection (CDI)



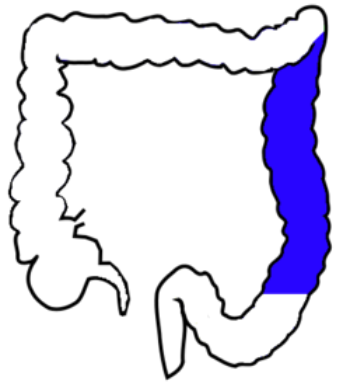


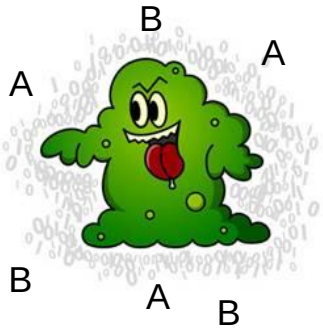


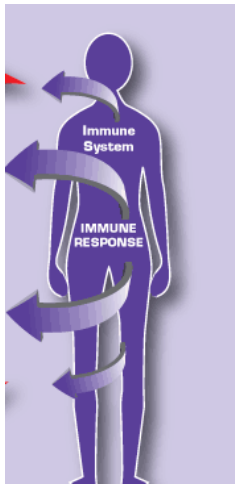
Essential:	Correct dysbiosis	Kill the organism	Adaptive immunity
Optional but nice:	Safe and convenient	Also affects toxins and spores	Short vs. long-term

Adamu BO, Lawley TD. *Curr Opin Microbiol.* 2013;16:596-601.

These therapeutic goals can then be translated to CDI Treatments (and today's objectives)







Current:	Probiotics/FMT Rebyota/Vowst Use narrow-spectrum antibiotics	~~Metronidazole~~ Vancomycin Fidaxomicin **Tetracyclines**	IVIG **Bezlotoxumab**
Future:	VE303	**Ibezapolstat**	**Toxoid vaccines (PF-06425090)**

Un-emerging therapy: Bezlotoxumab

LAST UPDATED: 6 January 2025

Bezlotoxumab: Global Deletion/Discontinuation

SUMMARY

Background[1]

- Like all companies, we review our product portfolio on an on-going basis – with careful consideration of the usage and relevance to physicians and patients.
- Based on a thoughtful and careful evaluation of guidelines for the clinical use of our medicine, bezlotoxumab, as well as the availability of other effective options to prevent recurrent C difficile infection (CDI), our company has made the difficult decision to voluntarily discontinue manufacturing and marketing of the product. There are no generics available.
- This decision is not related to any product safety or manufacturing issues with bezlotoxumab.

Timing and Supply

- We estimate our last supply of bezlotoxumab to the majority of the markets will be by the end of 2024.
    - In the U.S. we expect to supply bezlotoxumab into Q1 2025.
- Product discontinuation timing will vary by country depending on depletion of available supply.
- Bezlotoxumab will continue to be commercially available until the remaining inventory has been depleted, or the product reaches final expiry.
- We do not anticipate patient impact in markets since other effective options to prevent recurrent CDI are available.

PRODUCT LABELING

Please refer to the full product labeling for complete information that may be pertinent to your inquiry.

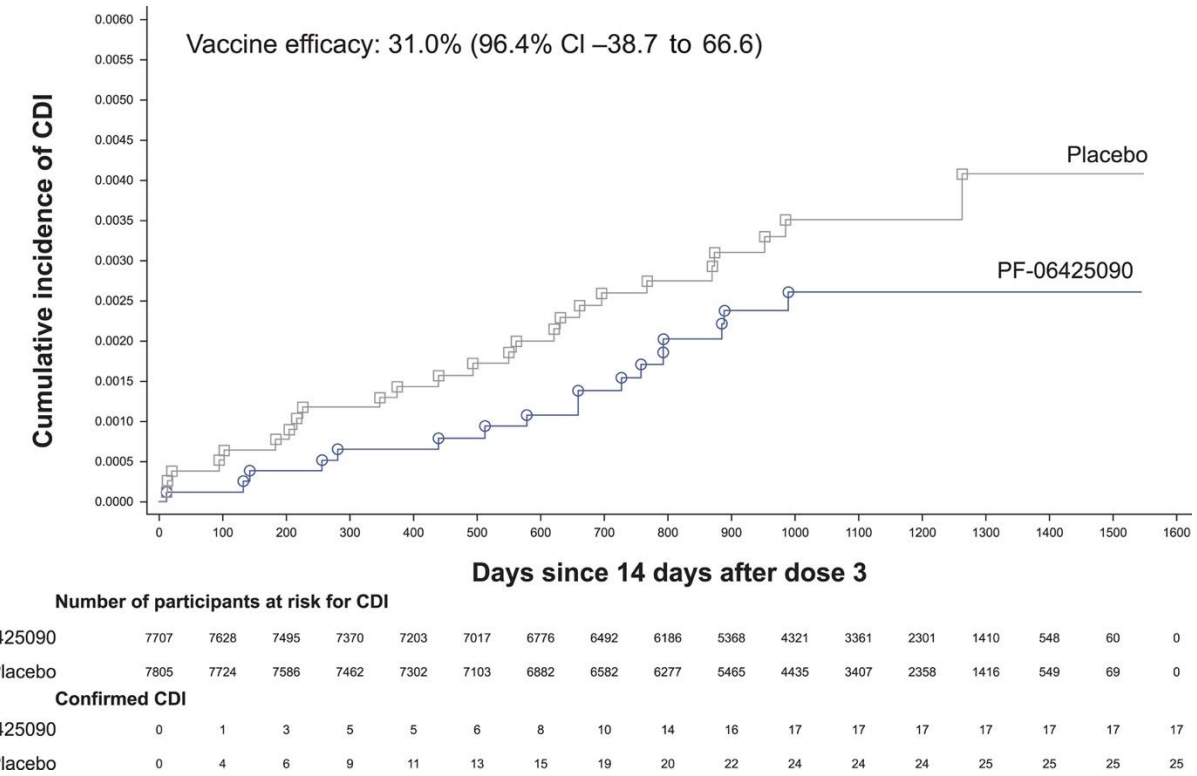
REFERENCES

1. Data on File.

Augment the Immune Response: *C. difficile* toxoid vaccines

Clover: CLOstridium difficile Vaccine Efficacy tRial: Phase III RCT detoxified toxin A/B vaccine in adults 50+ years

Primary endpoint not met



Enrolled: 17,535. Primary CDI cases: 42

Interesting Secondary endpoint findings

Treatment	PF-06425090	Placebo
CDI-related medical attention	0	11
Required antibiotic treatment	0	10
Mean duration of symptoms	3	16

"Company evaluating next steps for C. difficile vaccine program in coordination with regulatory agencies"

…and don’t say goodby to antibodies quite yet!

AstraZeneca

AstraZeneca Websites | Global site

What science can do | R&D | Our therapy areas | Our company | Careers | Investors | Media | Sustainability | Partnering

AstraZeneca advances science of infectious disease protection at IDWeek 2024

Data in RSV, combination vaccines, C. diff and influenza

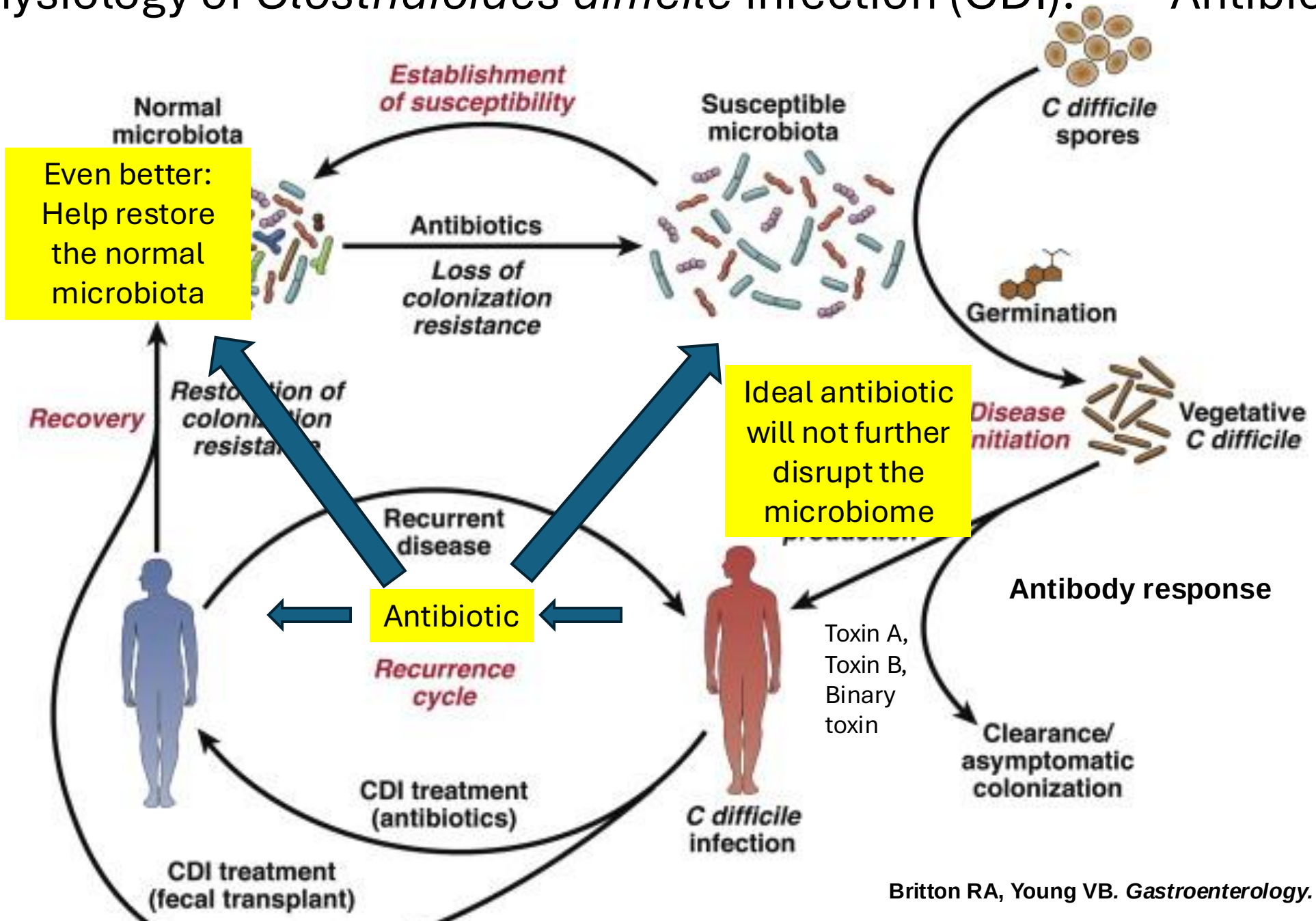
Data will be presented on *Beyfortus* (nirsevimab), AstraZeneca’s long-acting antibody for the prevention of RSV disease, showing that *Beyfortus* does not interfere with RSV detection by rapid antigen tests enabling accurate diagnosis to support clinical management.[10] Additional data, presented by our partner Sanofi, confirm the significant real-world effectiveness of *Beyfortus* in reducing RSV disease and hospitalisations in infants. These data build on recent evidence, including from the US Advisory Committee on Immunisation Practices, demonstrating *Beyfortus* was associated with a 90% reduction in RSV-associated hospitalisations in its first season.

Interim Phase II data on IVX-A12, an investigational combination virus-like particle vaccine, will be presented, demonstrating that IVX-A12 was well-tolerated and immunogenic against both RSV and hMPV in older adults 60 to 85 years of age.[6,7]

Pre-clinical data will be shared showing that AZD5148, an anti-toxin B neutralizing monoclonal antibody now in Phase I trials, may provide protection against *Clostridioides difficile (C. diff)* infection, a condition that can cause life-threatening diarrhea and intestinal inflammation.[9]

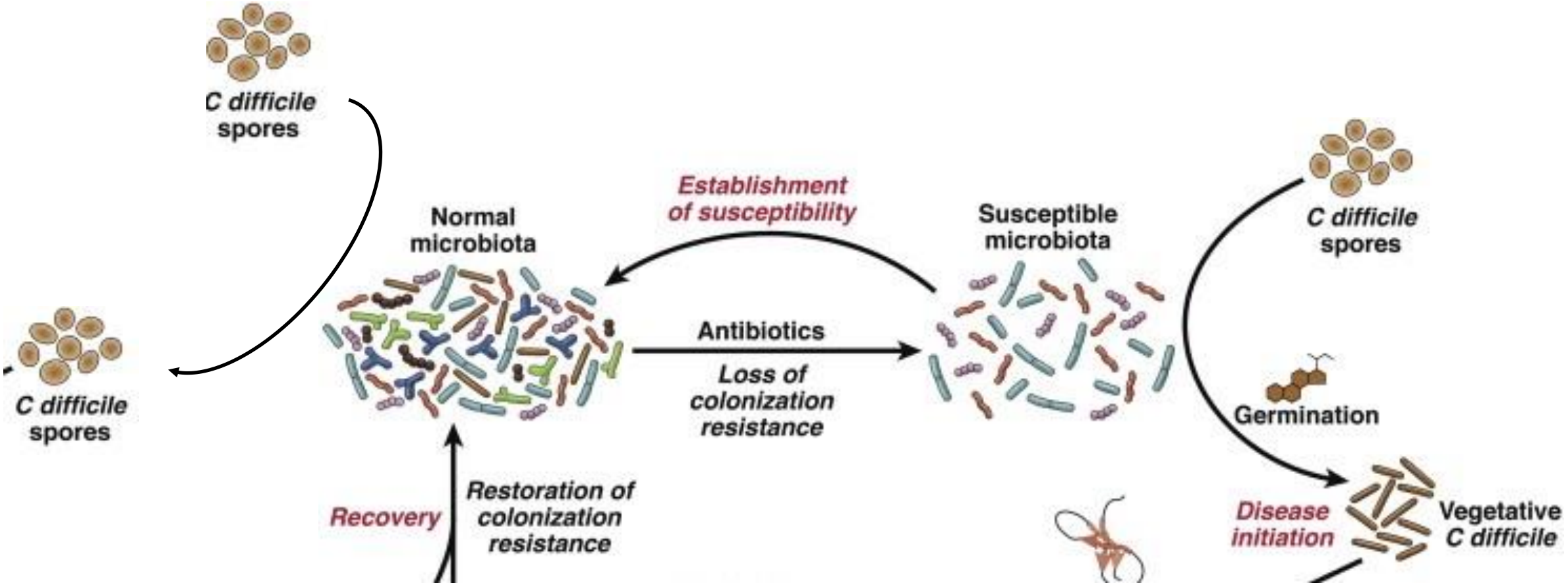
Additionally, AstraZeneca is presenting vaccine effectiveness data for *FluMist* (live attenuated influenza vaccine), recently approved in the US as the only vaccine for self- or caregiver administration for the prevention of influenza.[8]

Pathophysiology of *Clostridioides difficile* infection (CDI): Antibiotics!



Britton RA, Young VB. *Gastroenterology.* 2014;146:1547-53.

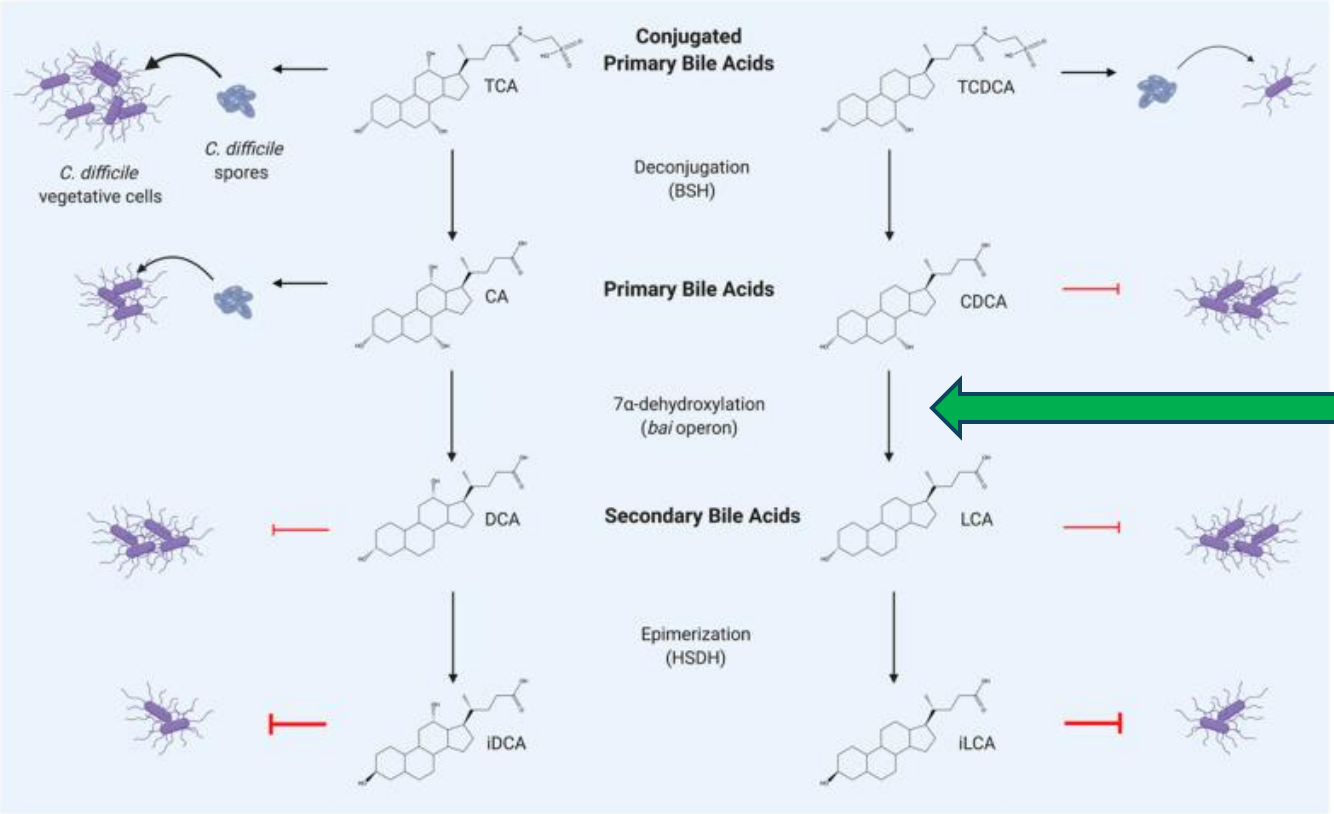
What is it about a normal microbiota that restores colonization resistance?



Britton RA, Young VB. *Gastroenterology.* 2014;146:1547-53.

Why does *C. difficile* require dysbiosis to cause infection?

Answer: These organisms maintain gut health. For example: Bile acids and CDI



Primary bile acids: BAD (promote C diff germination)

Healthy colon concentration: usually very low

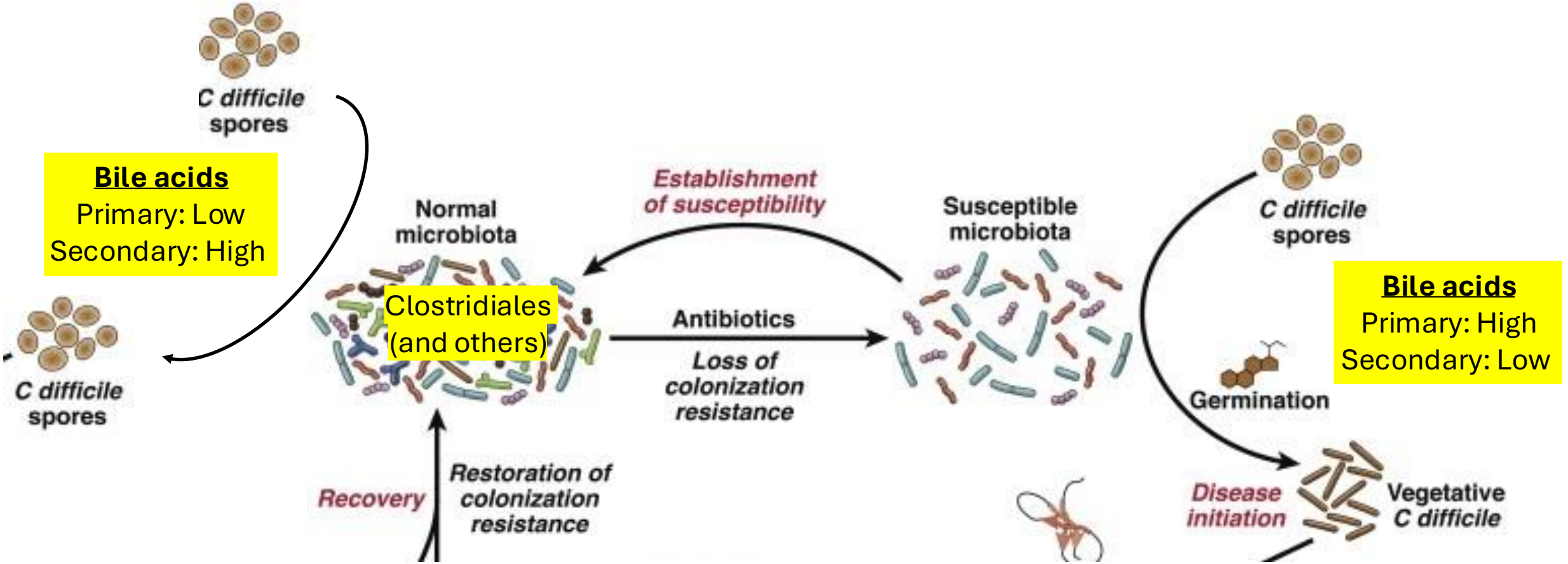
Bile acids are converted by specific gut microbiota

Secondary bile acids: Good (inhibit C diff growth)

Healthy colon concentrations: usually high

Most important taxa responsible for converting primary to secondary bile acids: Clostridiales

What is it about a normal microbiota that restores colonization resistance?

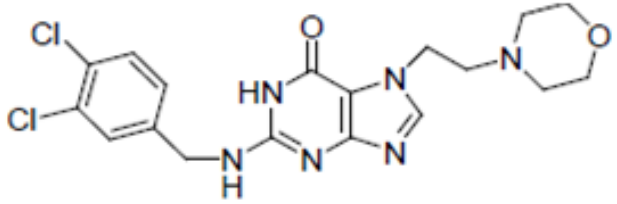


Britton RA, Young VB. *Gastroenterology.* 2014;146:1547-53.

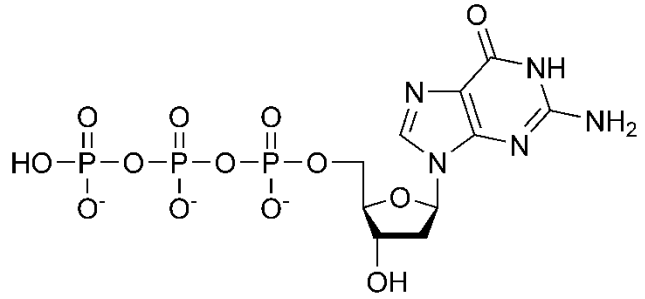
Antimicrobial pharmacobiome properties ideal for *C. difficile* drug development can be tested in early clinical trials

Property	Testable in Phase I Study	Testable in Phase 2 Study	NOTES
Pharmacokinetics	Yes	Yes	Concentrations should be above the organism MIC
Minimal collateral damage to gut microbiome?	Yes	Yes	Starting microbiome will be different between PH1 and PH2
Bile acid homeostasis (2:1 bile acid ratio)	Yes	Yes	Secondary bile acids should be depressed in PH2 study
C. difficile activity	No	Yes	*In vitro* activity of drug vs. C diff will be known before starting clinical trials

Ibezapolstat (IBZ; ACX362E)

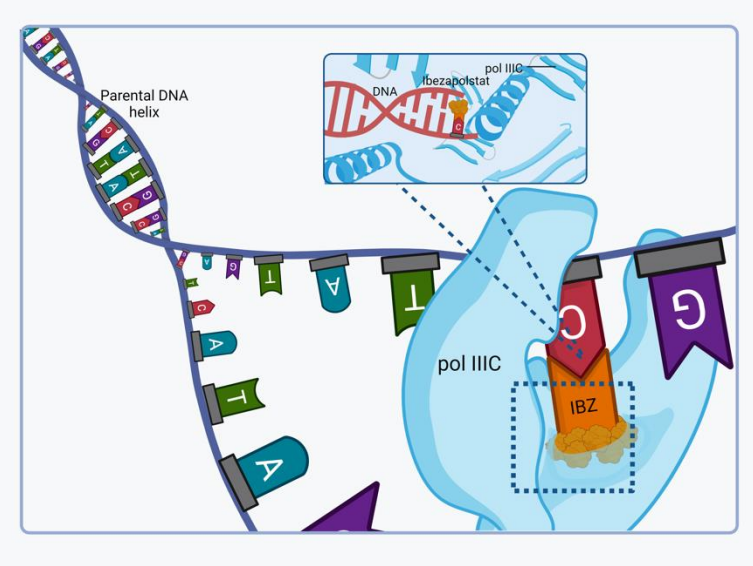


ACX-362



dGTP

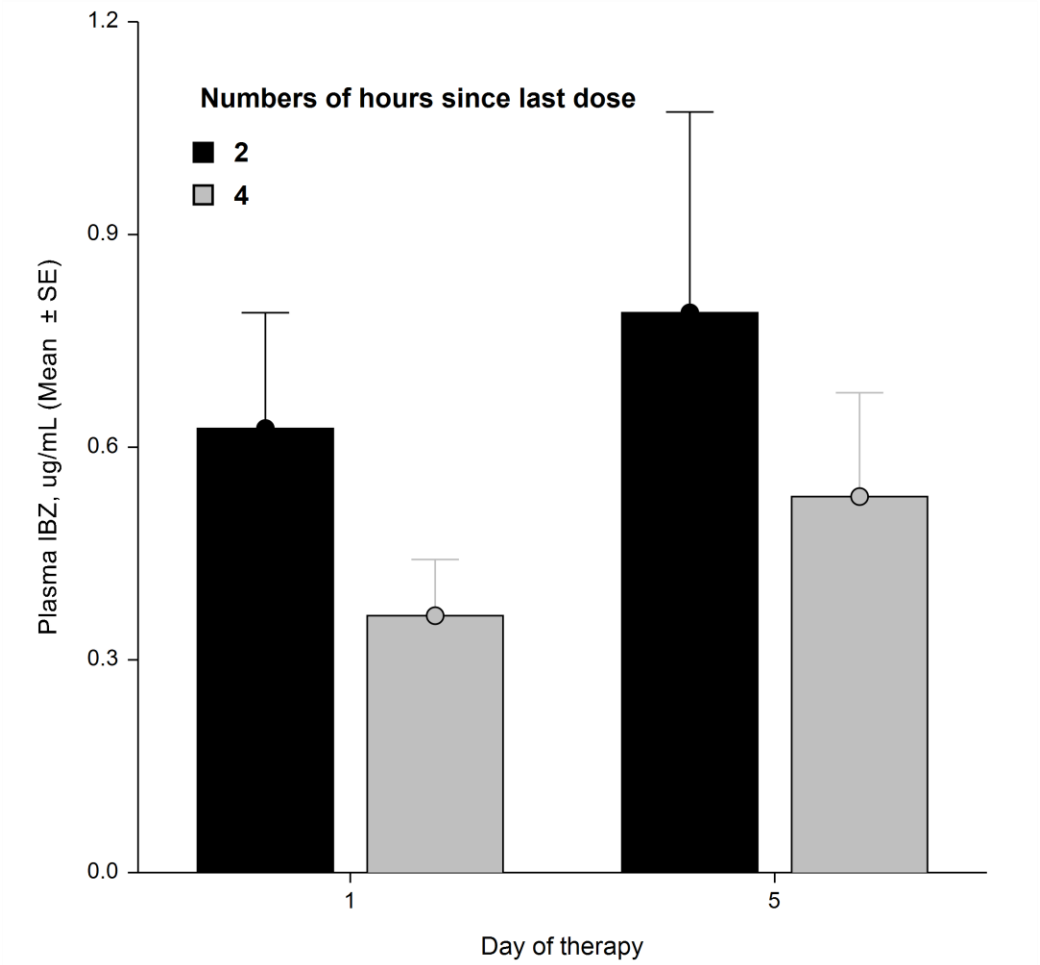
- Ibezapolstat: small-molecule inhibitor of DNA pol IIIC enzyme based upon competitive inhibition of dGTP (guanosine analog)
- DNA pol IIIC: essential for DNA replication of low G+C content Gram-positive bacteria (Bacillota / Firmicutes)
- Novel mechanism of action GPSS™ (**G**ram **P**ositive **S**elective **S**pectrum) including selective killing of certain Firmicutes but not others



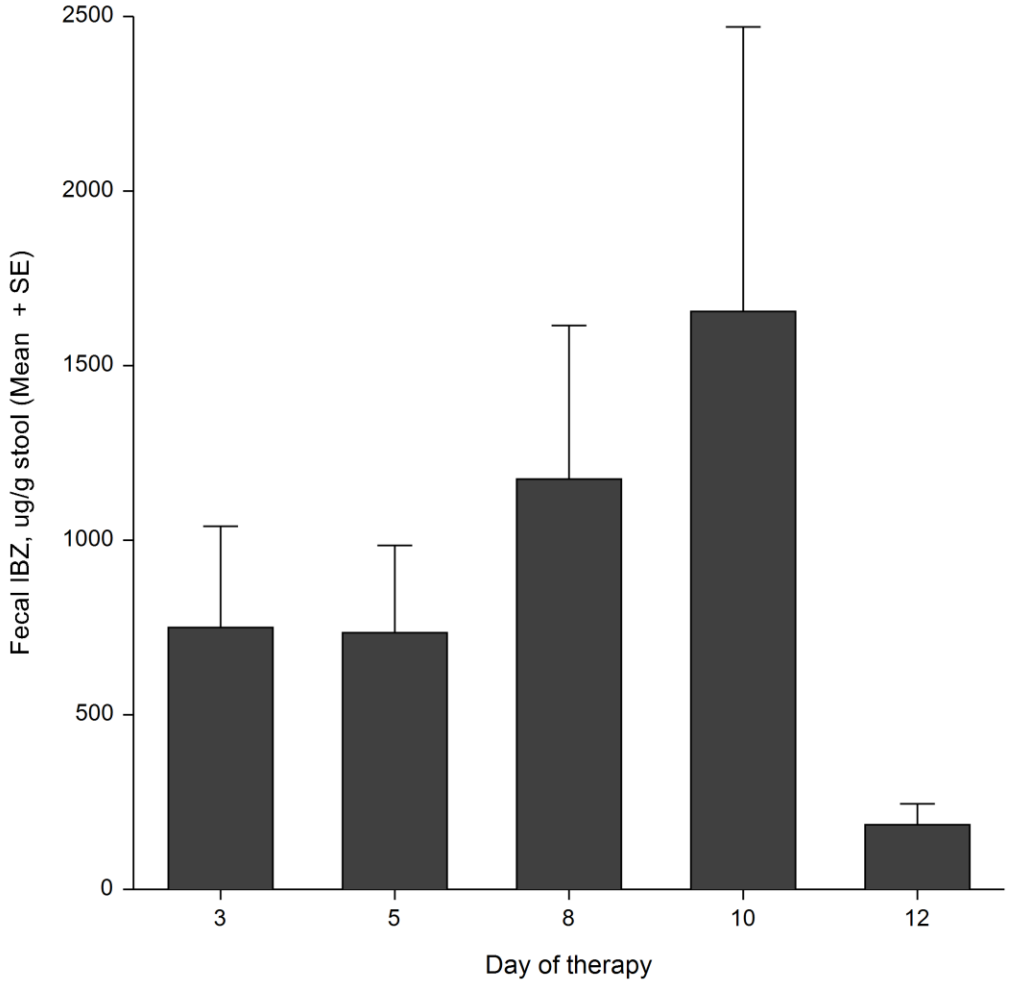
Xu et al. Bioorg Med Chem. 2019
https://www.nature.com/articles/d43747-021-00149-0

IBZ is non-absorbable:
Low Plasma and High Fecal Concentrations

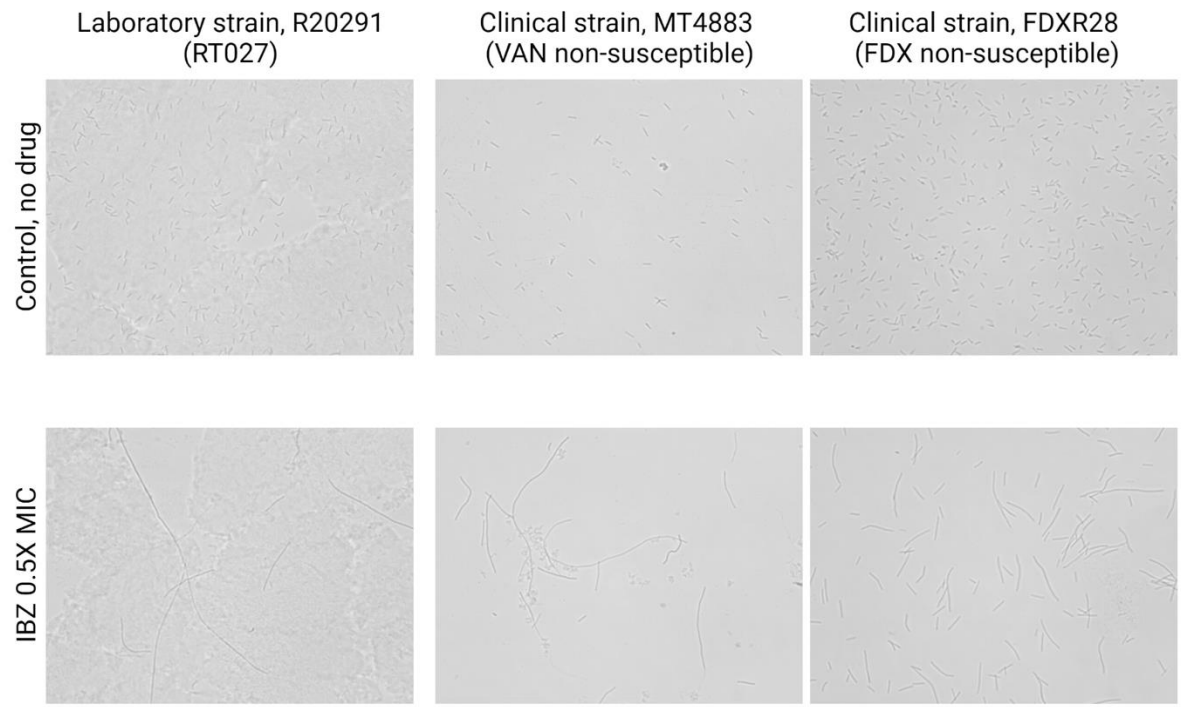
a. Plasma concentrations

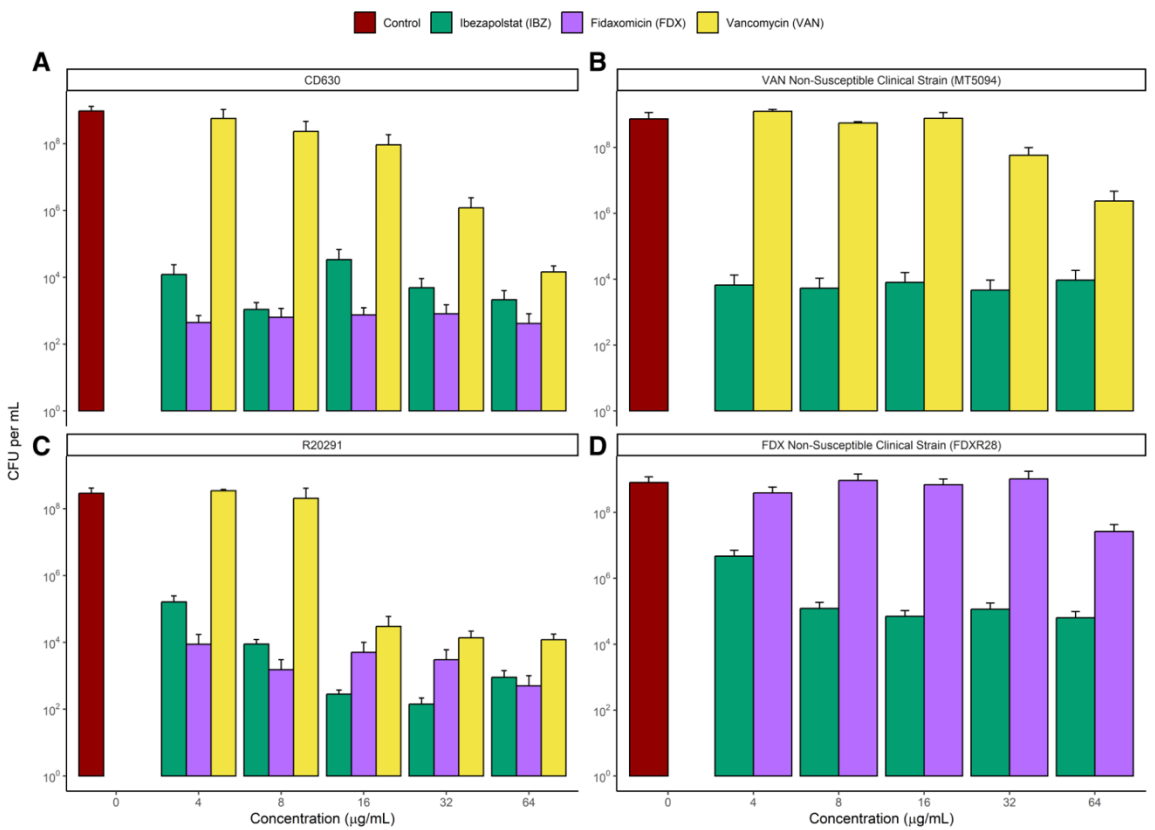


b. Fecal concentrations



IBZ is effective against VAN- and FDX-non-susceptible C. difficile strains

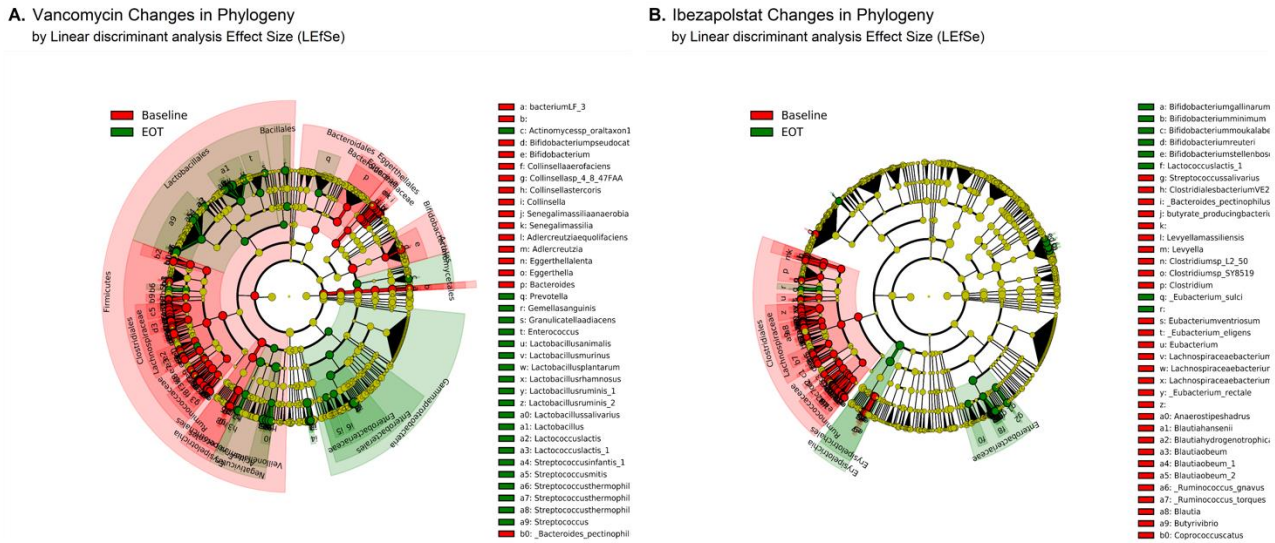




Basseres et al. Antimicrob Agents Chemother 2023

IBZ has been shown to have favorable effects on the microbiome

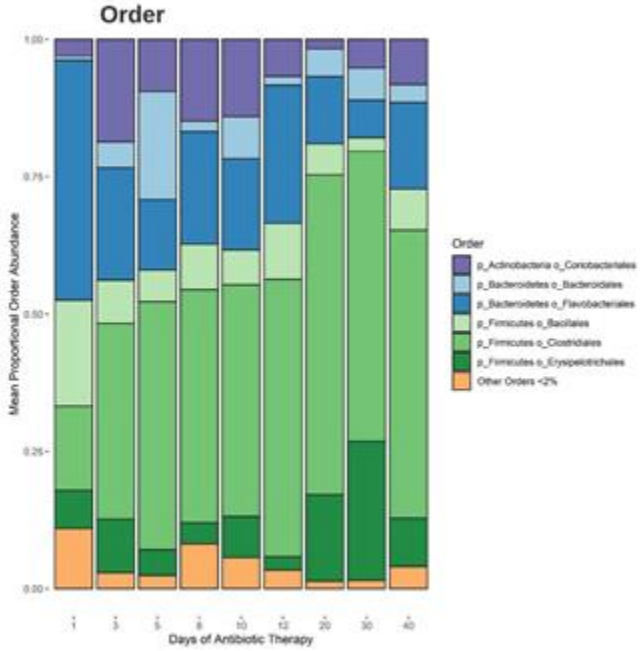
IBZ Phase 1 Healthy volunteer study in comparison with VAN



IBZ:
More narrow spectrum
Increased proportion of Actinobacteria

McPherson et al AAC 2022

IBZ Phase 2a. Single arm, no-comparator study of CDI patients (n=10)



IBZ:
Increased proportion of Actinobacteria
Increased proportion of Clostridiales

Garey et al CID 2022

Phase 2b Study design

Patients followed daily for 12 days + follow-up

Patients with mild/moderate CDI
diagnosed using an EIA free toxin kit

Ibezapolstat 450 mg BID X 10 days

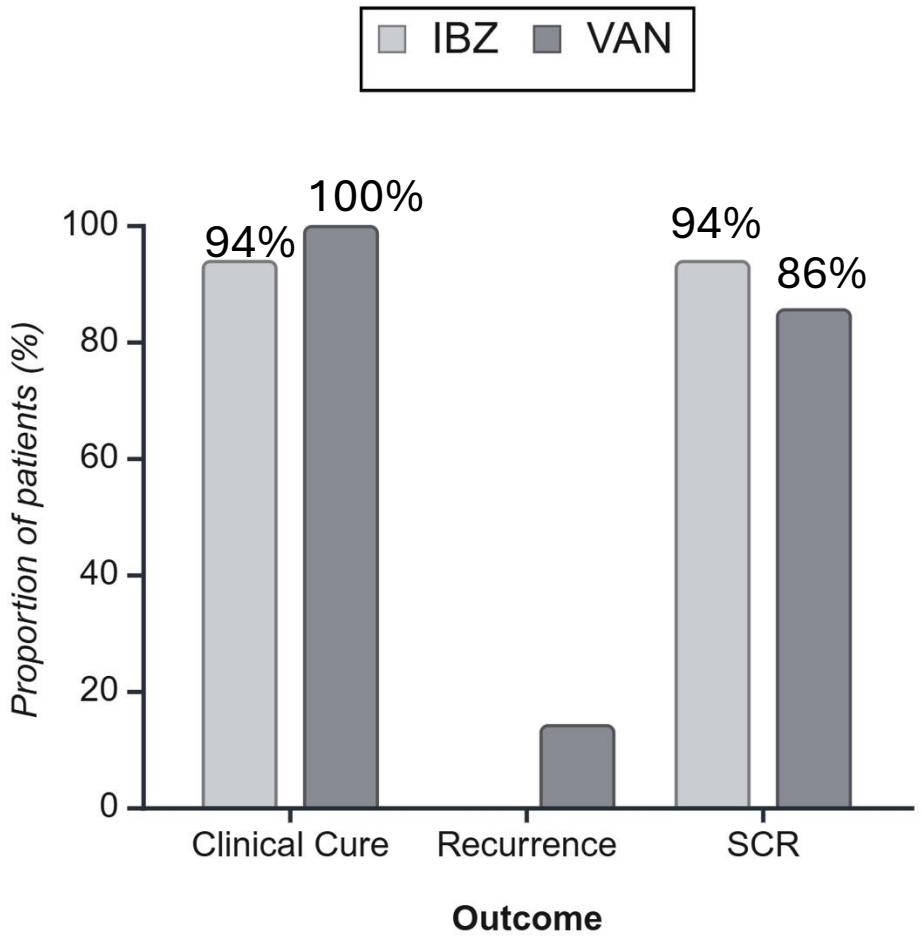
Vancomycin 125 mg QID X 10 days

Outcome Measures

- Initial clinical cure (day 12 evaluation)
- Sustained clinical cure (day 38)
- Extended clinical cure (3 months)
- Time to resolution of diarrhea (days 0-12)
- Safety (day 38)
- Pharmacokinetics (days 0-12)
- Microbiome changes (days 0-12)
  qPCR and 16S rRNA
- Bile acid changes (days 0-12)
  LC-MS/MS

ClinicalTrials.gov ID NCT04247542

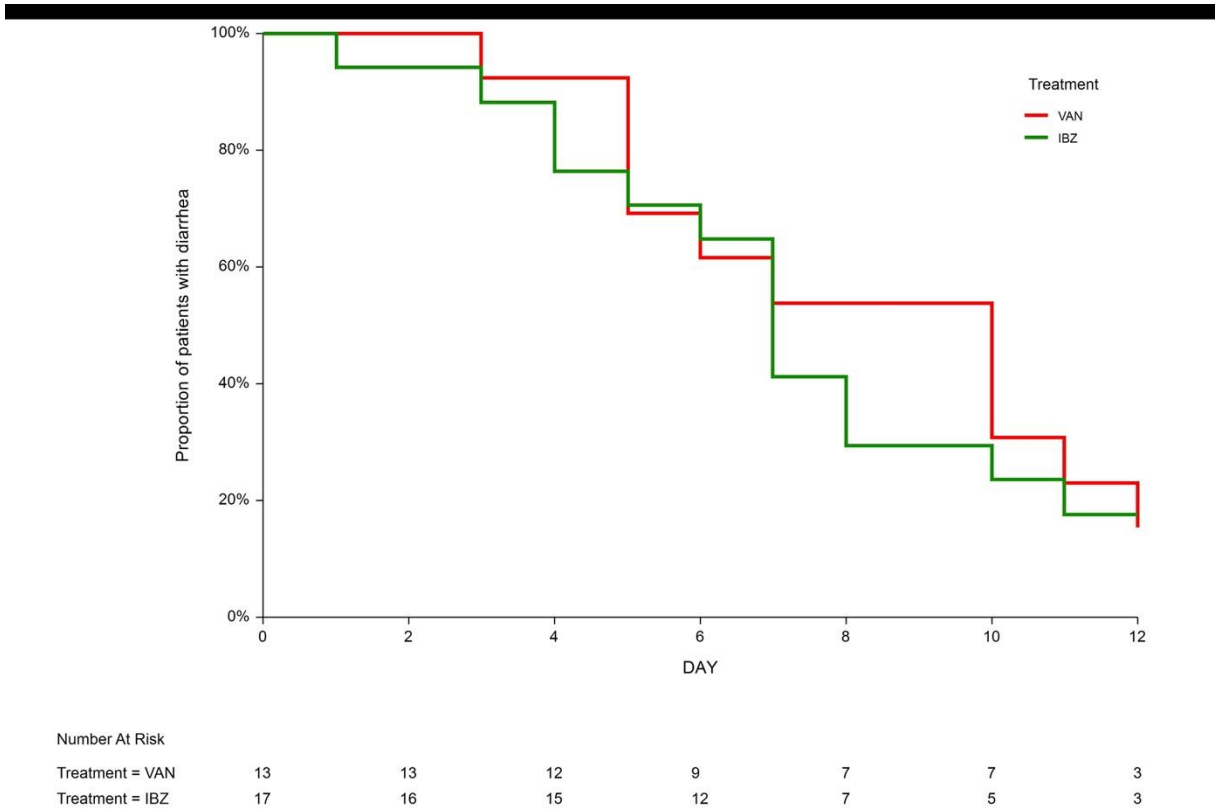
Efficacy analysis



Number of events	15	14	0	2	15	12
Number of patients	16	14	16	14	16	14

Time to resolution of diarrhea

Cumulative incidence of UBM resolution

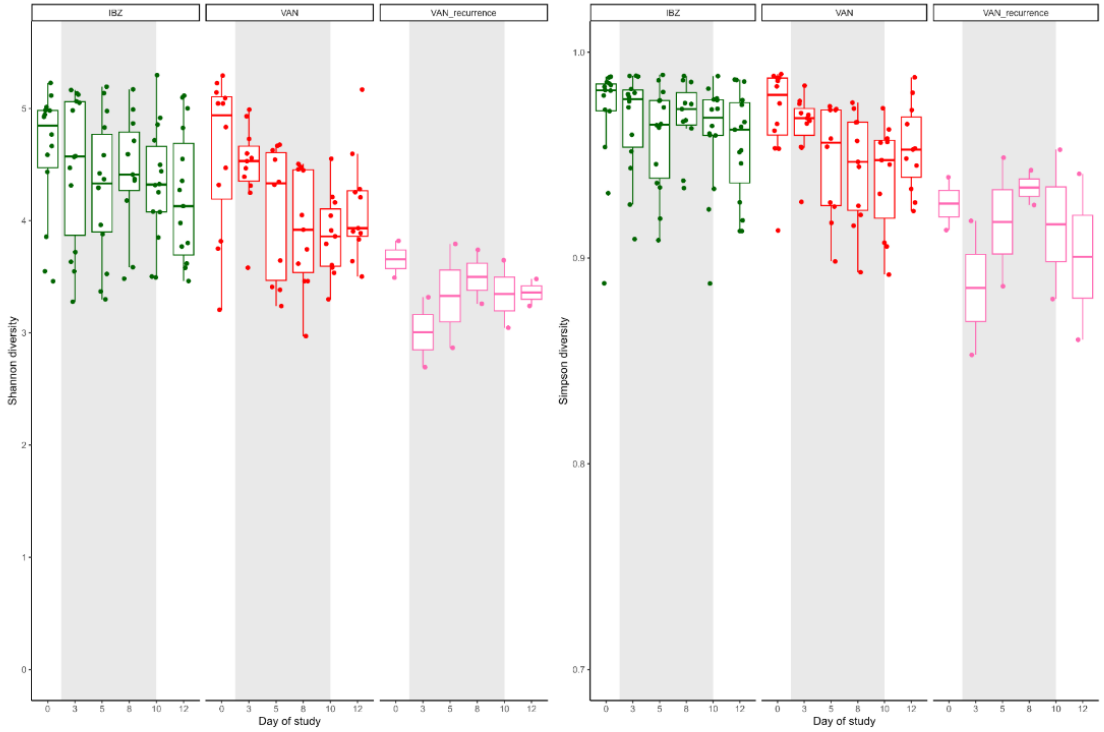


Number At Risk							
Treatment = VAN	13	13	12	9	7	7	3
Treatment = IBZ	17	16	15	12	7	5	3

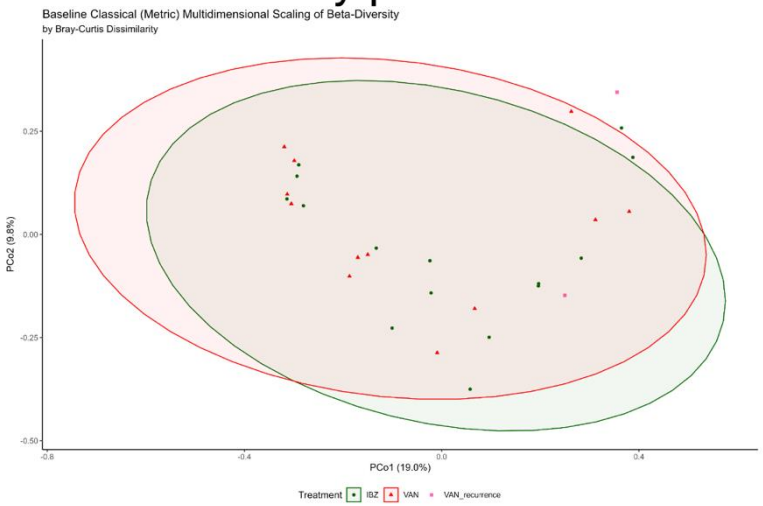
SCR: sustained clinical response; UBM: unformed bowel movement

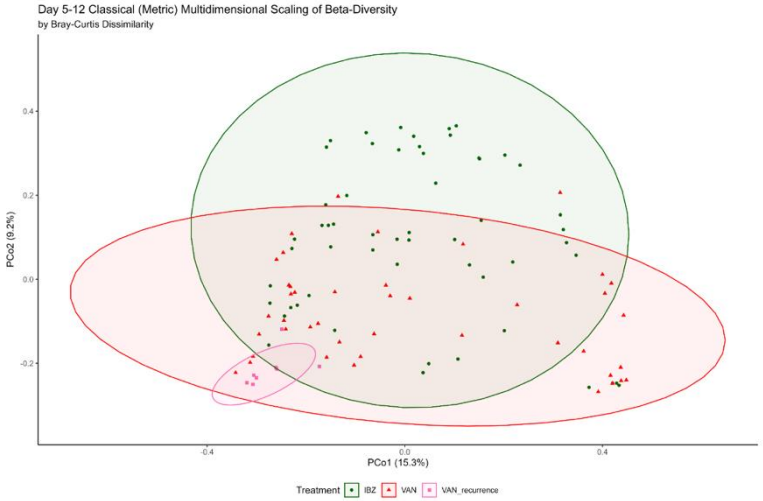
Focus on CDI Recurrence. Alpha and Beta Diversity

a. Alpha diversity plots



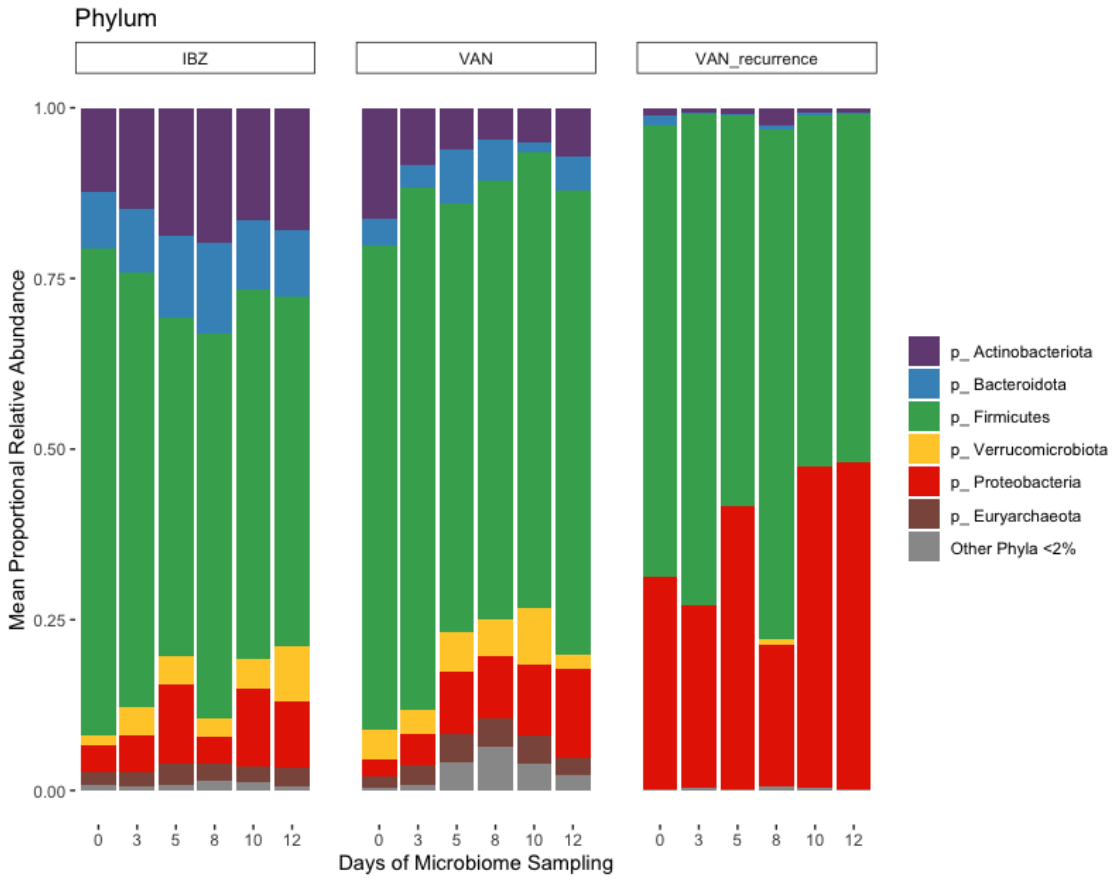
b. Beta diversity plots

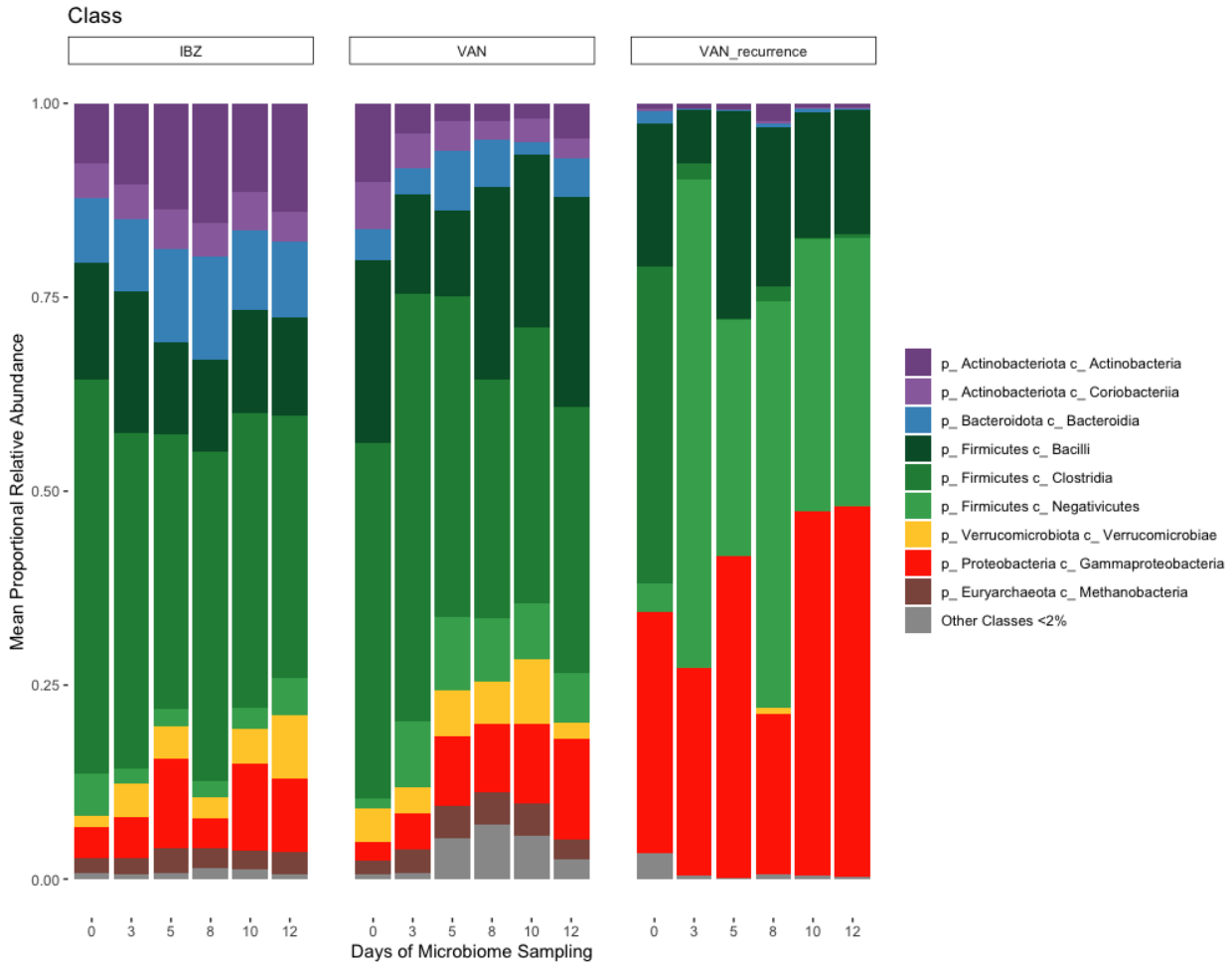




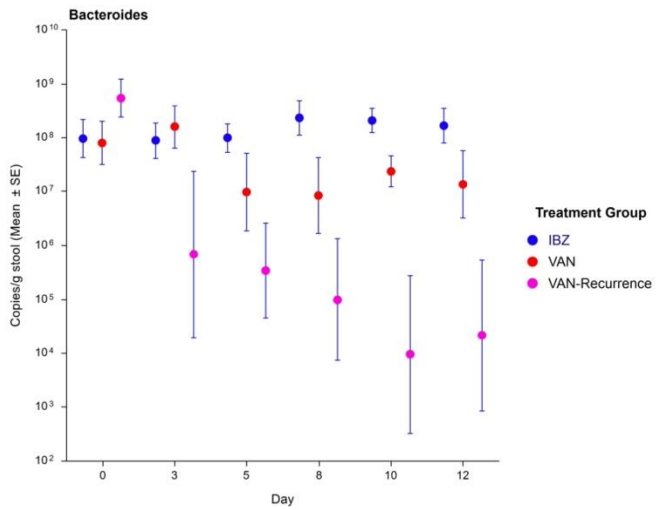
IBZ: n=16; VAN (no recurrence): n=12; VAN (recurrence: n=2)

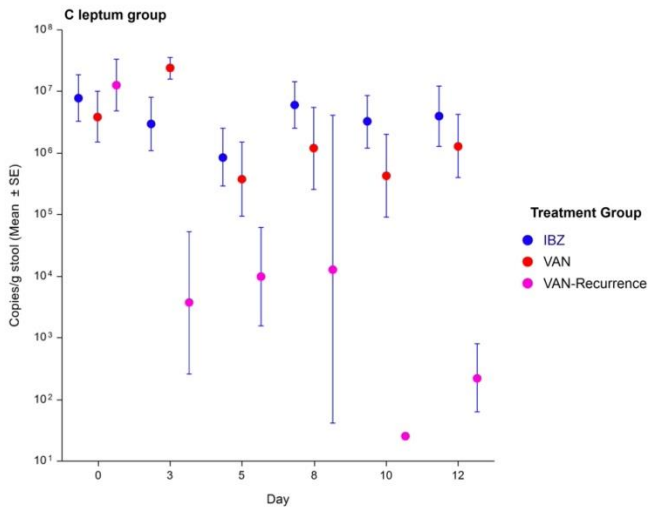
CDI recurrence associated with marked microbiome disruption

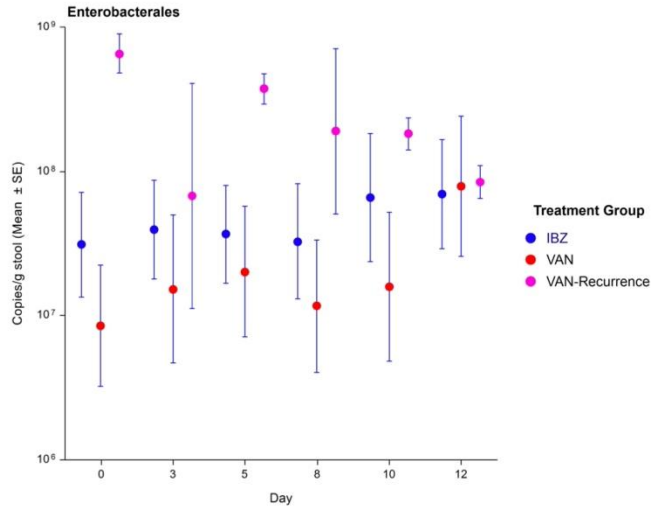


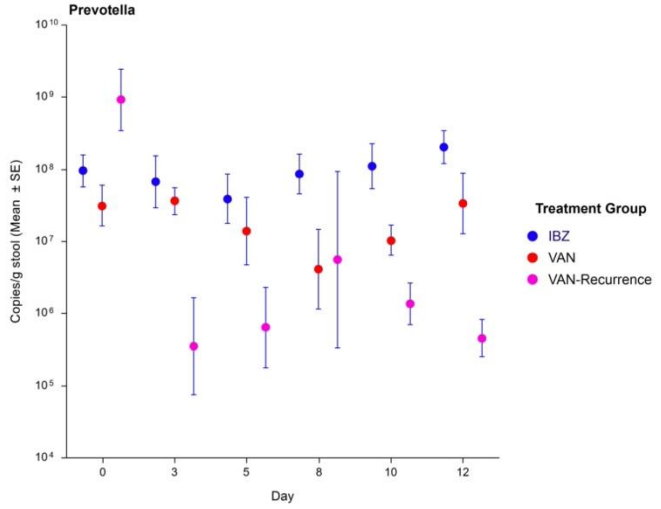


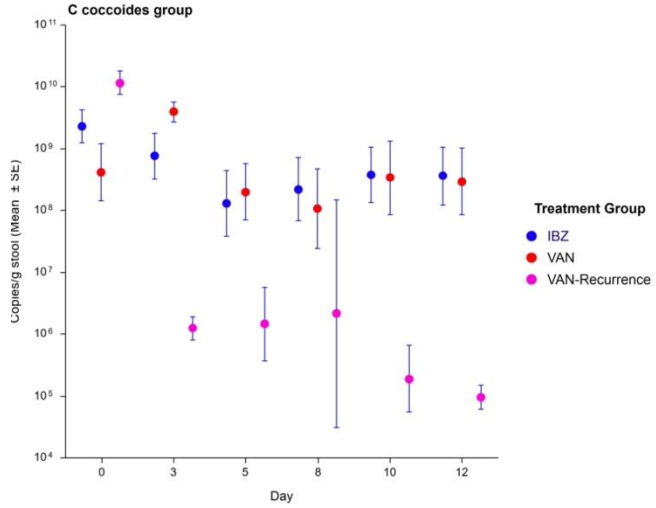
CDI recurrence associated with marked microbiome disruption

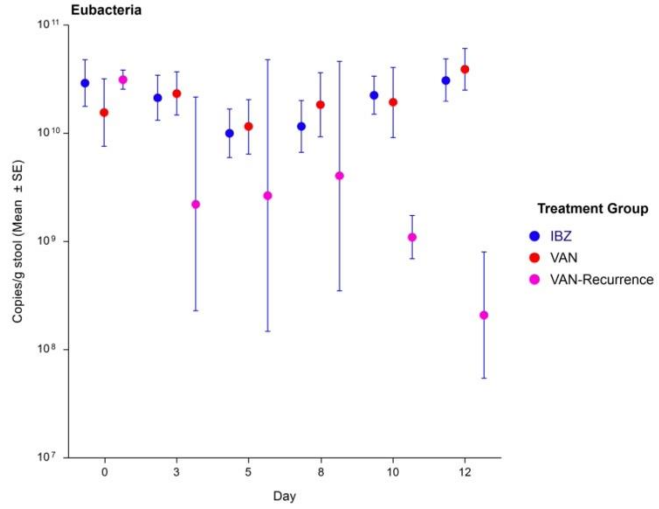






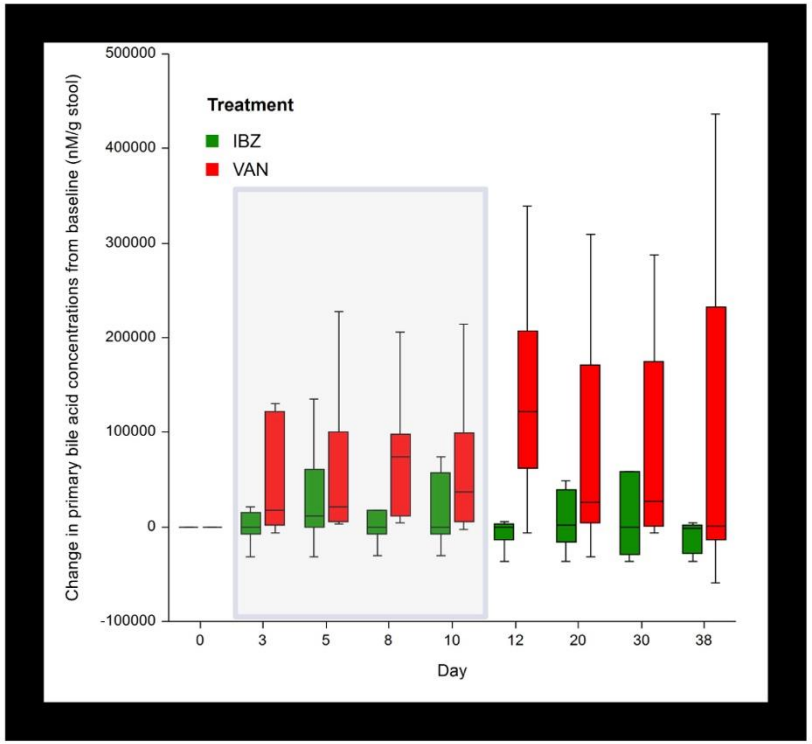




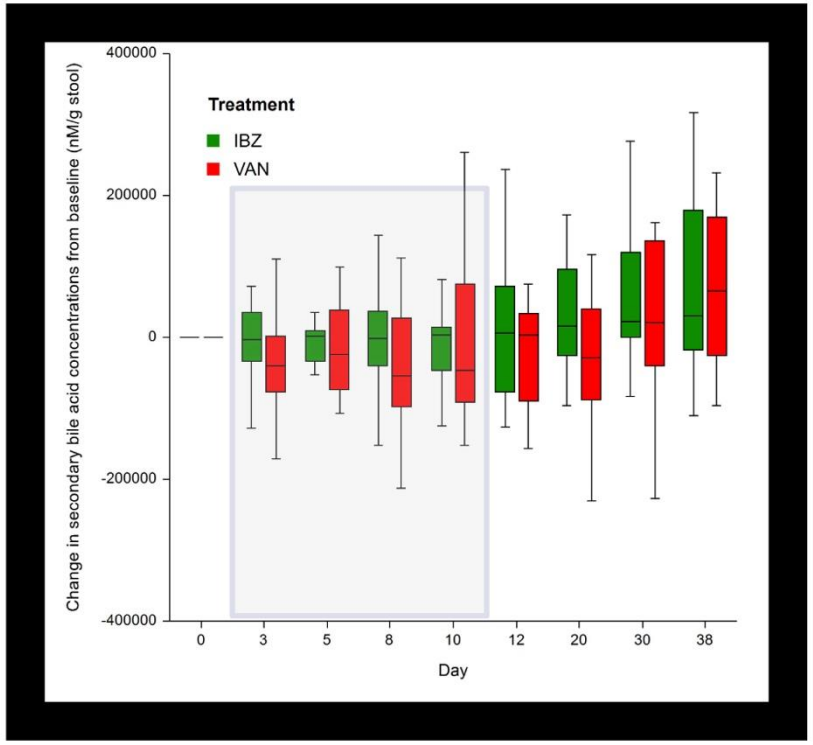


Change in bile acid homeostasis in CDI patients given ibezapolstat (IBZ) vs. vancomycin (VAN)

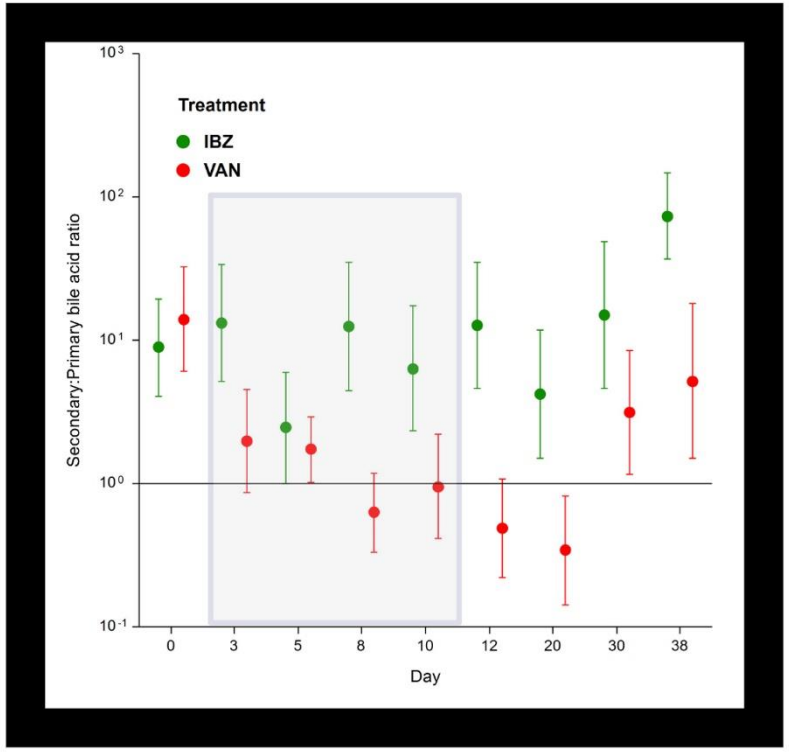
a. Change in primary bile acids



b. Change in secondary bile acids



c. Secondary to primary bile ratio



IBZ

- FDA (and EU) approved plans for go-ahead to phase III
- Expected start of recruitment: 2025 (hopefully)

Could we use the same ‘pharmacobiome’ principles to repurpose current antimicrobials?

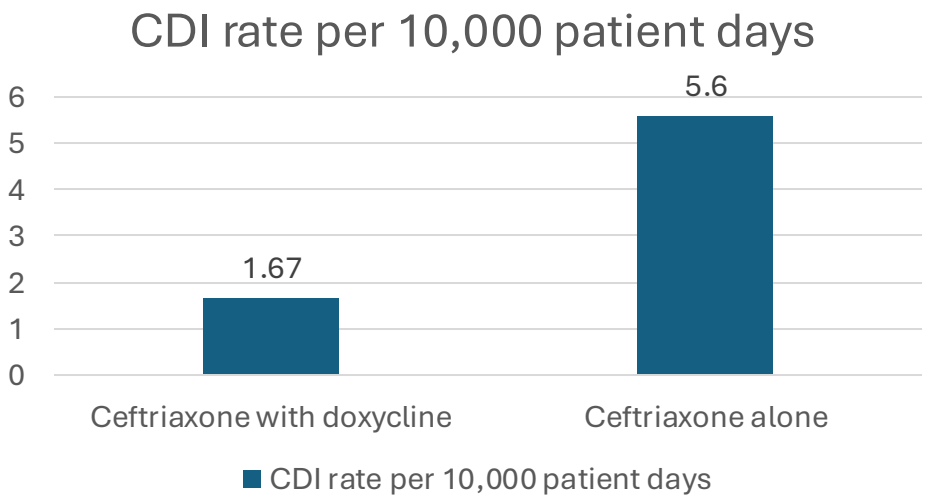
Should Tetracyclines be considered CDI-treatment antibiotics? Why?

Does Doxycycline Protect Against Development of *Clostridium difficile* Infection?

Sarah B. Doernberg,[1] Lisa G. Winston,[1] Daniel H. Deck,[2] and Henry F. Chambers[1]

[1]Department of Internal Medicine, Division of Infectious Diseases, University of California, San Francisco, and [2]Department of Pharmaceutical Sciences, San Francisco General Hospital, California

2,734 hospitalizations, patients followed for 30-days for new onset CDI



CID 2012;615-20

REVIEW

Check for updates

Tigecycline for the treatment of patients with *Clostridium difficile* infection: an update of the clinical evidence

Konstantinos S. Kechagias[1] · Stamatia Chorepsima[1] · Nikolaos A. Triarides[1,2] · Matthew E. Falagas[1,2,3]

IV Tigecycline use in CDI

- Broad Spectrum Antibiotic, but does not induce proliferation or production of toxin. (*Baines et al. JAC 2006*)
- MIC_{50}= 0.125 mcg/ml
  MIC_{90}= 0.25 mcg/ml
  (*Hecht et al. AAC 2007*)
- Successful treatment of 4 patients refractory to standard therapy (*Herpers et al. CID 2009*)

Eur J Clin Microbiol Infect Dis 2020:1053-8

Omadacycline (OMC): Potent *in vitro* activity against *C. difficile* and no CDI cases observed in phase 2-3 clinical trials

In vitro activity against *C. difficile*

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

EPIDEMIOLOGY AND SURVEILLANCE
August 2020 Volume 64 Issue 8 10.1128/aac.00522-20
https://doi.org/10.1128/aac.00522-20

In Vitro* Activity of Omadacycline, a New Tetracycline Analog, and Comparators against *Clostridioides difficile

Khurshida Begum[a], Eugénie Bassères[a], Julie Miranda[a], Chris Lancaster[a], Anne J. Gonzales-Luna[a], Travis J. Carlson[b], Tasnuva Rashid[a], David W. Eyre[c,d], Mark H. Wilcox[e,f], M. Jahangir Alam[a], Kevin W. Garey[a]

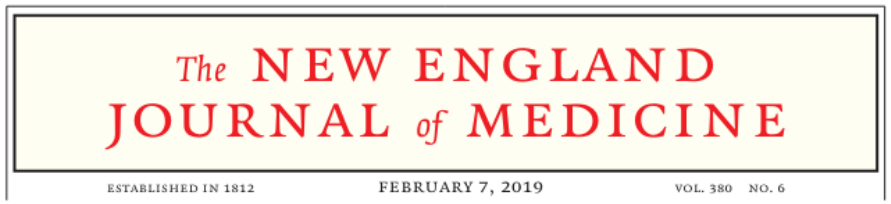
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

CLINICAL THERAPEUTICS
February 2019 Volume 63 Issue 2 10.1128/aac.01581-18
https://doi.org/10.1128/aac.01581-18

Omadacycline Gut Microbiome Exposure Does Not Induce *Clostridium difficile* Proliferation or Toxin Production in a Model That Simulates the Proximal, Medial, and Distal Human Colon

Ines B. Moura[a], Anthony M. Buckley[a], Duncan Ewin[a], Sharie Shearman[a], Emma Clark[a], Mark H. Wilcox[a,b], Caroline H. Chilton[a]

Low propensity to cause *C. difficile* infection



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 7, 2019 VOL. 380 NO. 6

Omadacycline for Community-Acquired Bacterial Pneumonia

Roman Stets, M.D., Ph.D., Monica Popescu, M.D., Joven R. Gonong, M.D., Ismail Mitha, M.D., William Nseir, M.D., Andrzej Madej, M.D., Ph.D., Courtney Kirsch, B.S., Anita F. Das, Ph.D., Lynne Garrity-Ryan, Ph.D., Judith N. Steenbergen, Ph.D., Amy Manley, B.S., Paul B. Eckburg, M.D., Evan Tzanis, B.S., Paul C. McGovern, M.D., and Evan Loh, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Omadacycline for Acute Bacterial Skin and Skin-Structure Infections

William O'Riordan, M.D., Sinikka Green, M.D., J. Scott Overcash, M.D., Ivan Puljiz, M.D., Ph.D., Symeon Metallidis, M.D., J. Gardovskis, M.D., Lynne Garrity-Ryan, Ph.D., Anita F. Das, Ph.D., Evan Tzanis, B.S., Paul B. Eckburg, M.D., Amy Manley, B.S., Stephen A. Villano, M.D., Judith N. Steenbergen, Ph.D., and Evan Loh, M.D.

Once-daily oral omadacycline versus twice-daily oral linezolid for acute bacterial skin and skin structure infections (OASIS-2): a phase 3, double-blind, multicentre, randomised, controlled, non-inferiority trial

*William O'Riordan, Carrie Cardenas, Elliot Shin, Alissa Sirbu, Lynne Garrity-Ryan, Anita F Das, Paul B Eckburg, Amy Manley, Judith N Steenbergen, Evan Tzanis, Paul C McGovern, Evan Loh, on behalf of the OASIS-2 Investigators**

Begum K, et al. Antimicrob Agents Chemother. 2020; Moura IB, et al. Antimicrob Agents Chemother 2019
Stets R, et al. N Engl J Med. 2019; O'Riordan W, et al. N Engl J Med 2019; O'Riordan W, et al. Lancet Infect Dis. 2019

Objectives

- Could we apply the same principles we used to help develop ibezapolstat to better understand why tetracyclines have such a low propensity to cause CDI
  - ….and maybe help develop them as CDI-directed antibiotics!

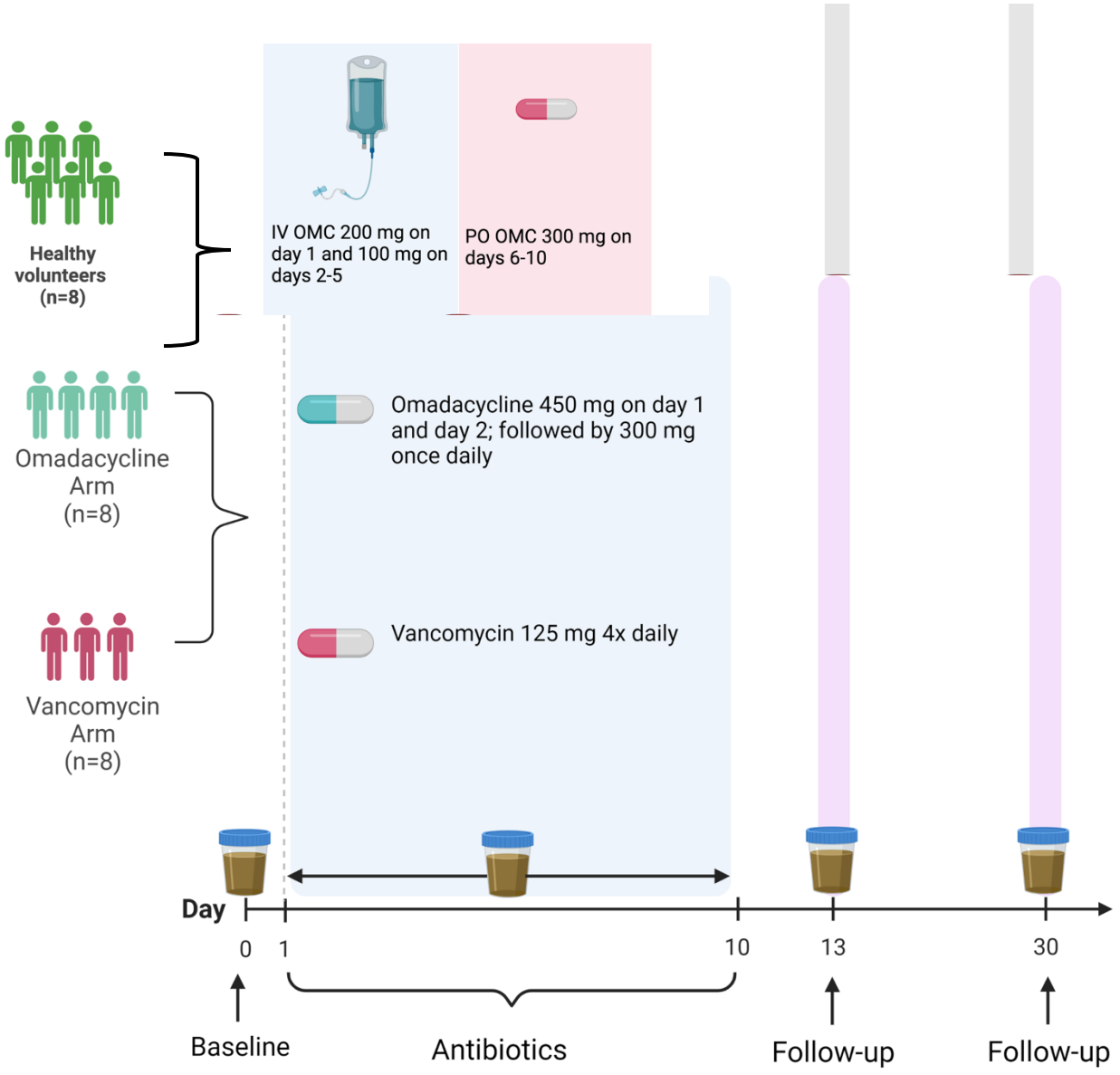
- In healthy volunteers given intravenous (IV) or oral omadacycline (OMC) to investigate changes during therapy in:
  - Fecal pharmacokinetics
  - Gut microbiome changes
  - Targeted metabolomics (bile acids)

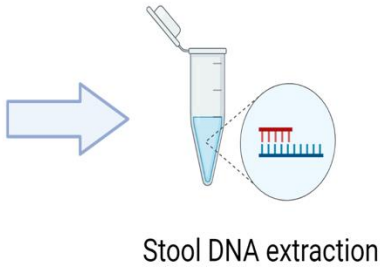
Phase 1, healthy volunteer study

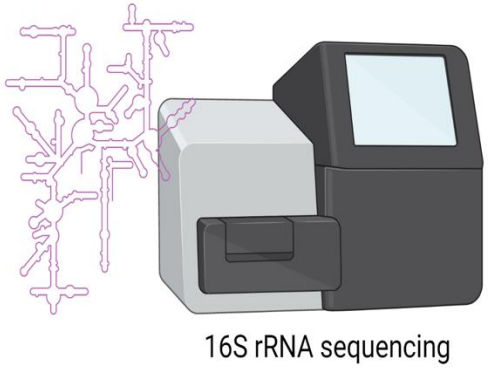
Intravenous omadacycline

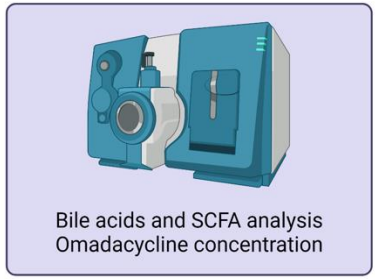
Oral omadacycline

Oral vancomycin



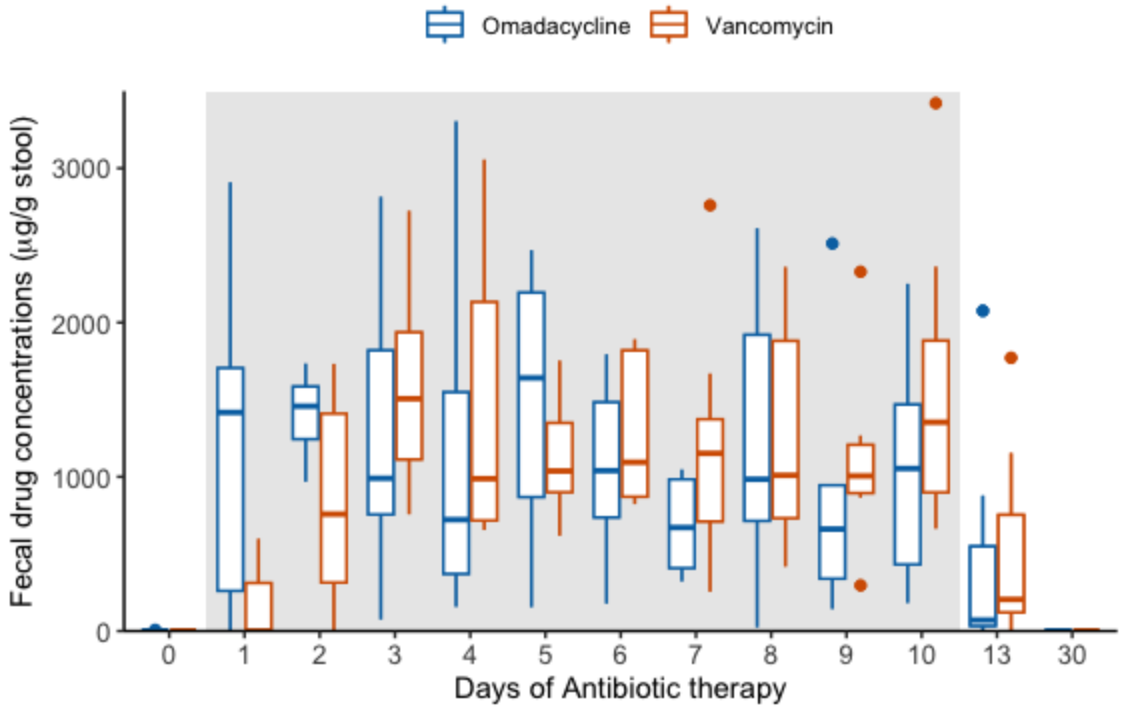




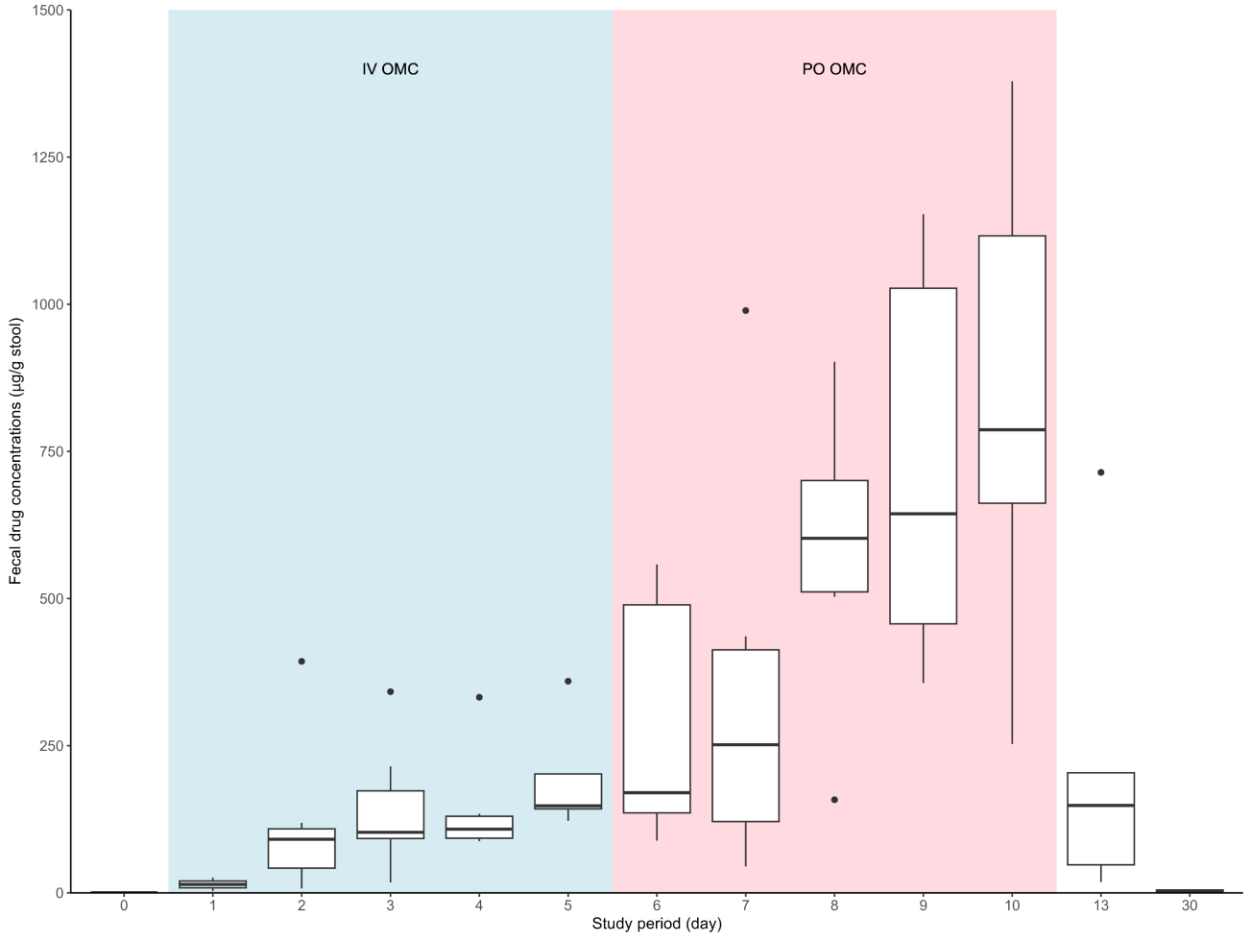


Omadacycline Fecal Pharmacokinetics

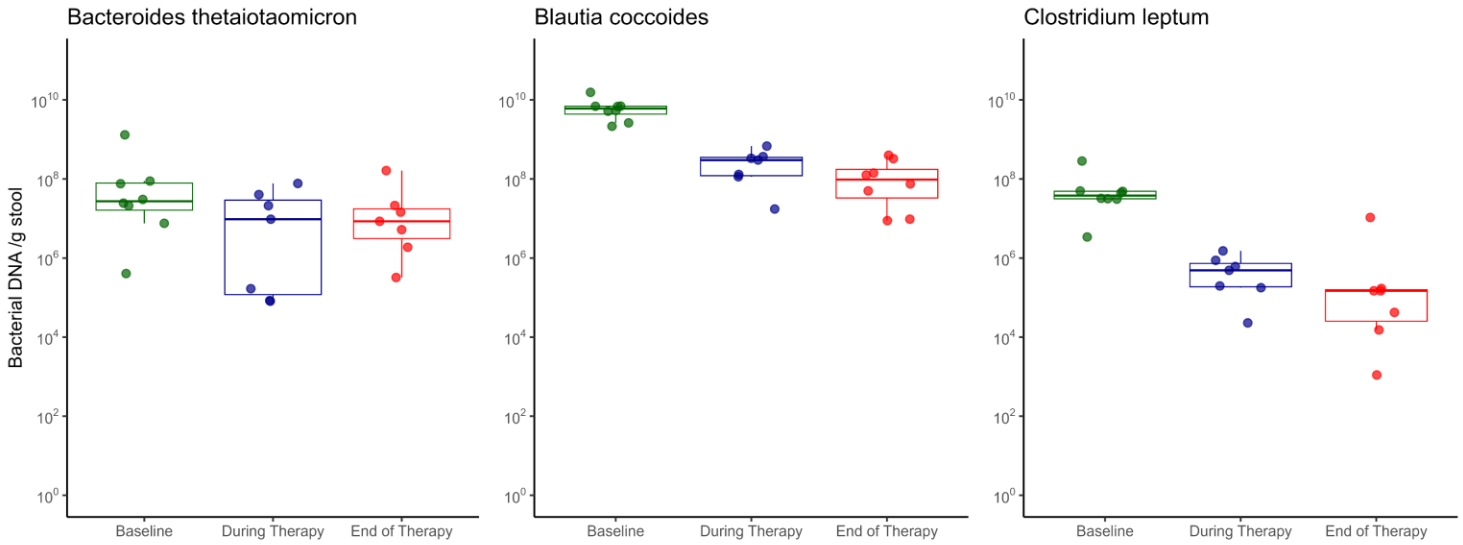
PK: oral omadacycline vs. oral vancomycin

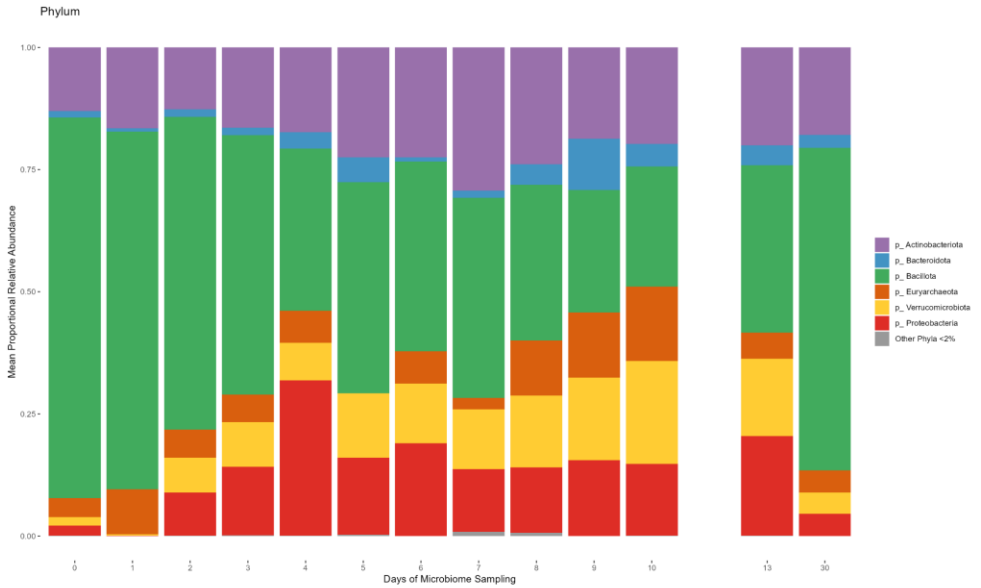


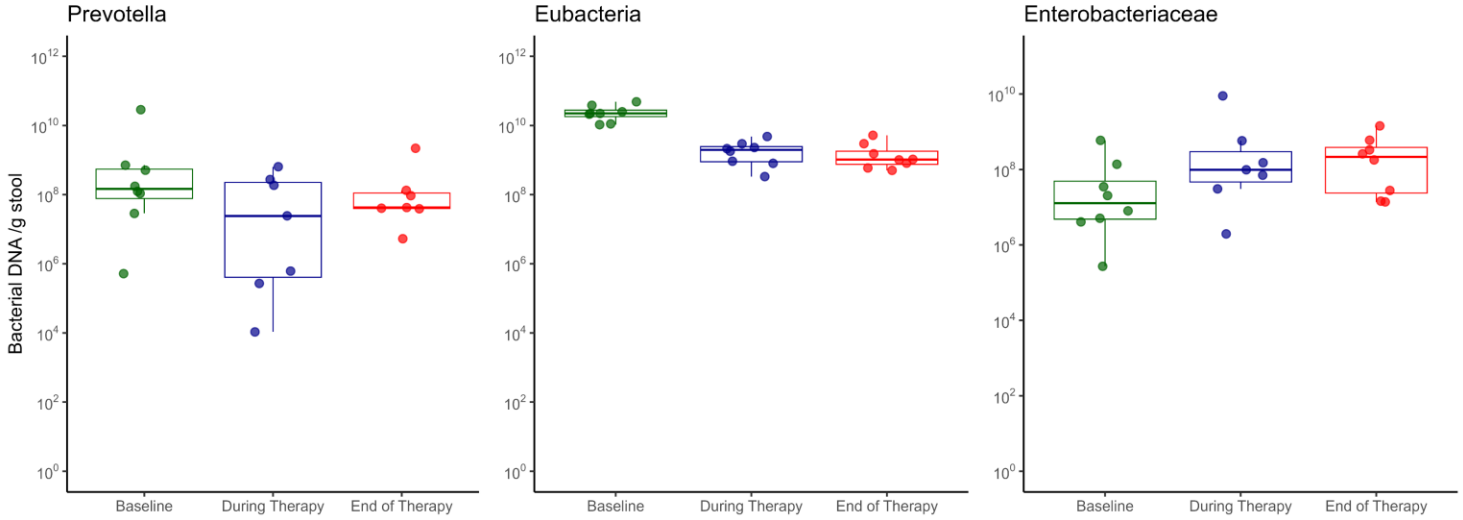
PK: IV omadacycline vs. oral omadacycline

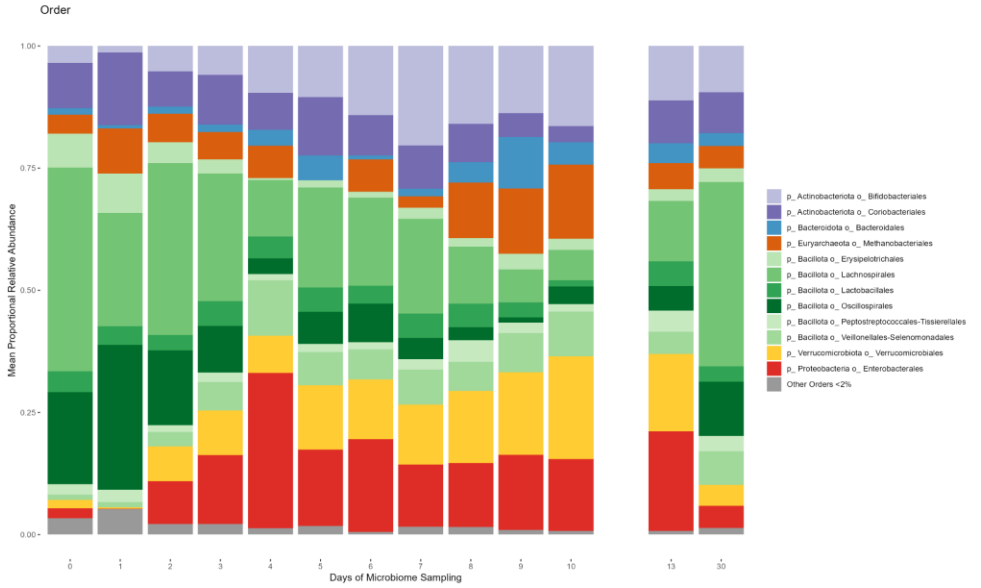


OMC preserved key microbiome taxa including Actinobacteriota (SCFA metabolism) and Lachnospirales (bile acid metabolism)



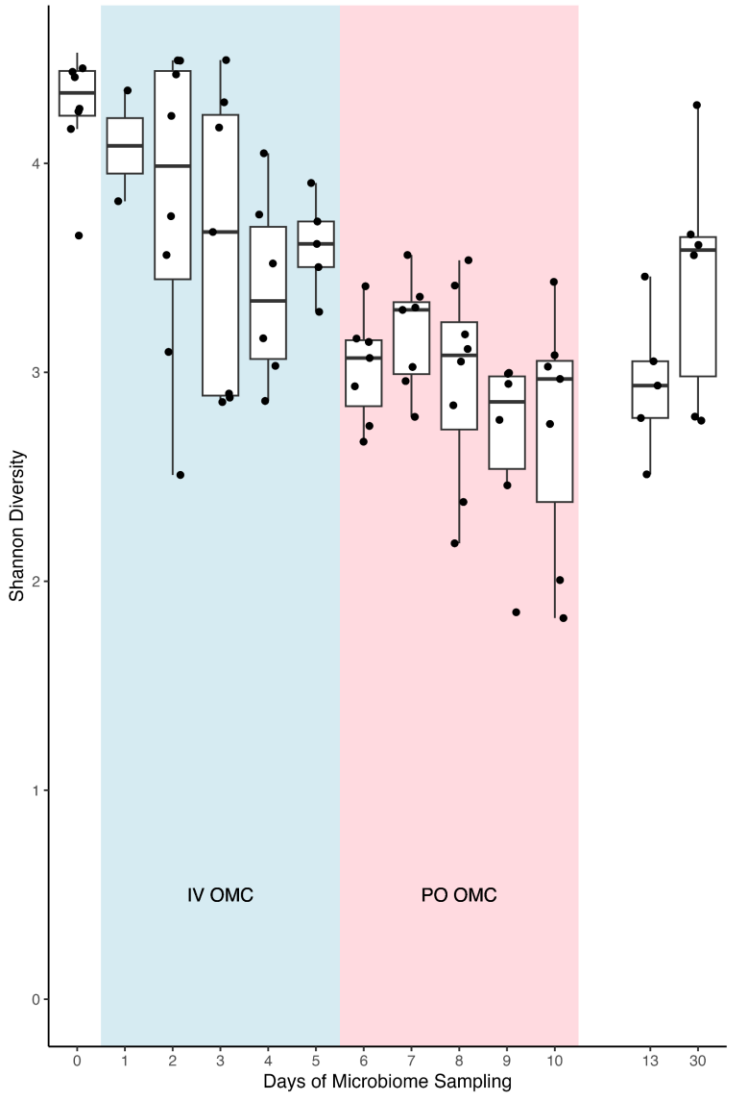


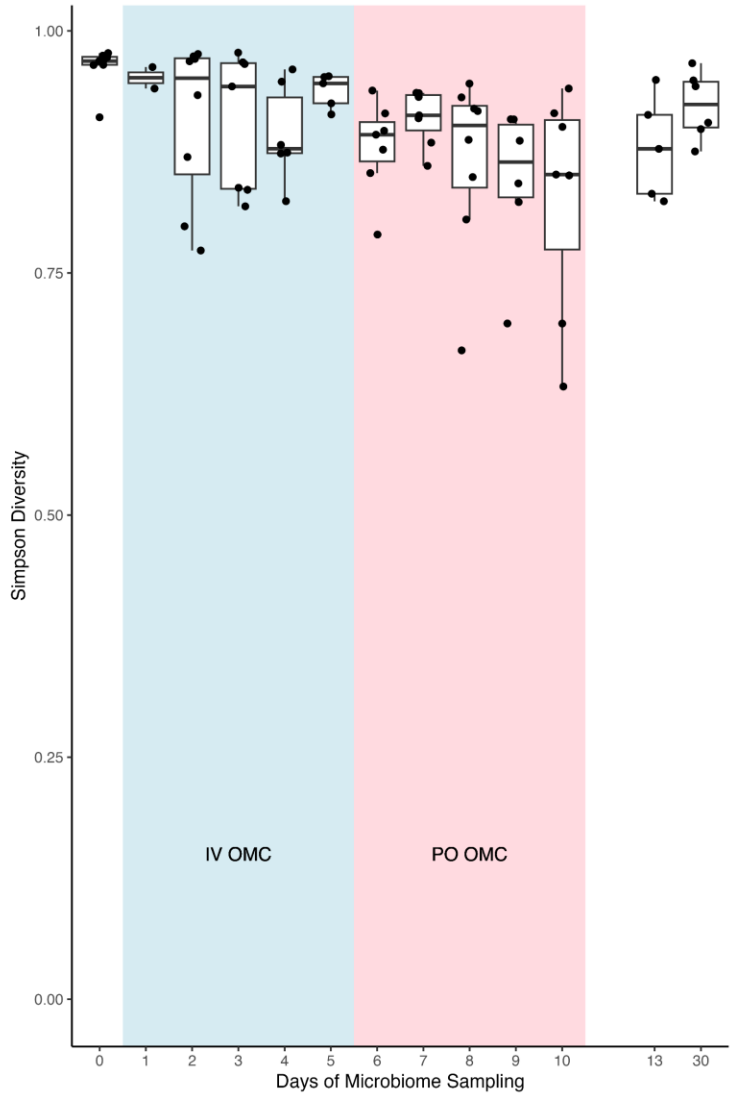




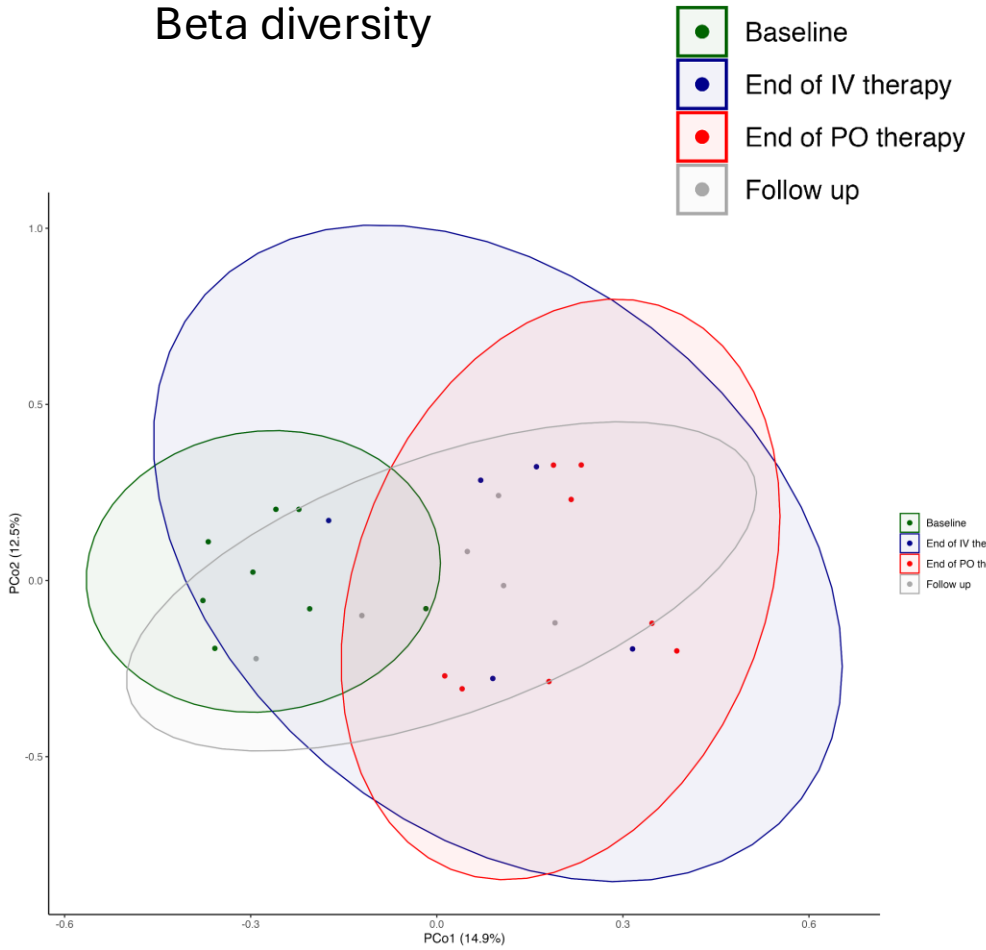
Omadacycline effect on the gut microbiome

Alpha Diversity

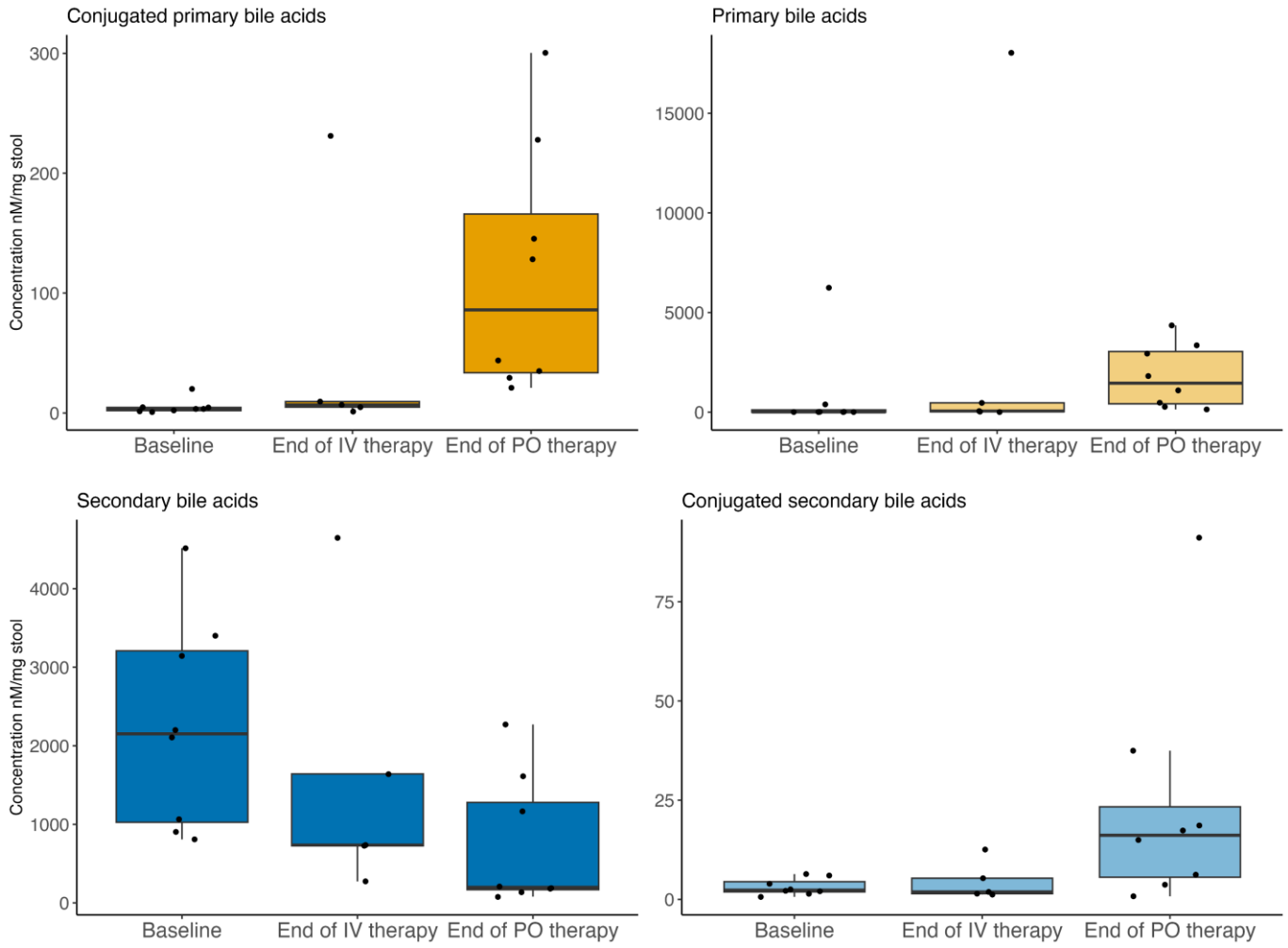




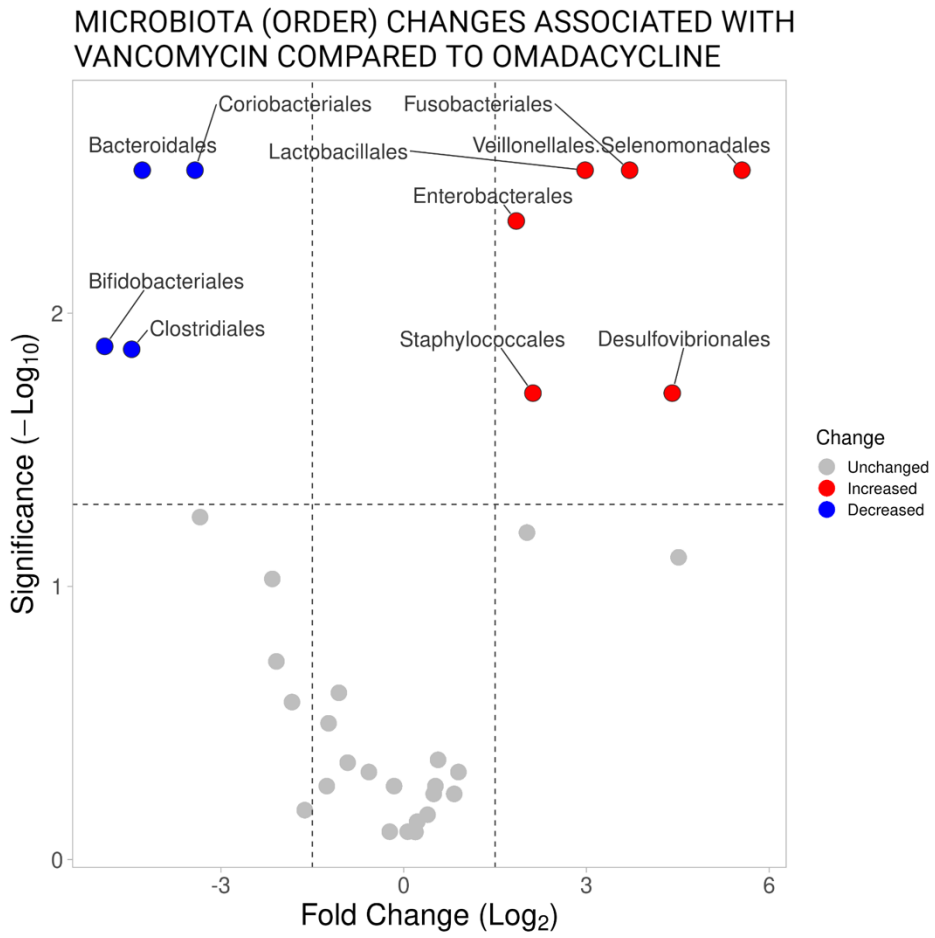
Beta diversity



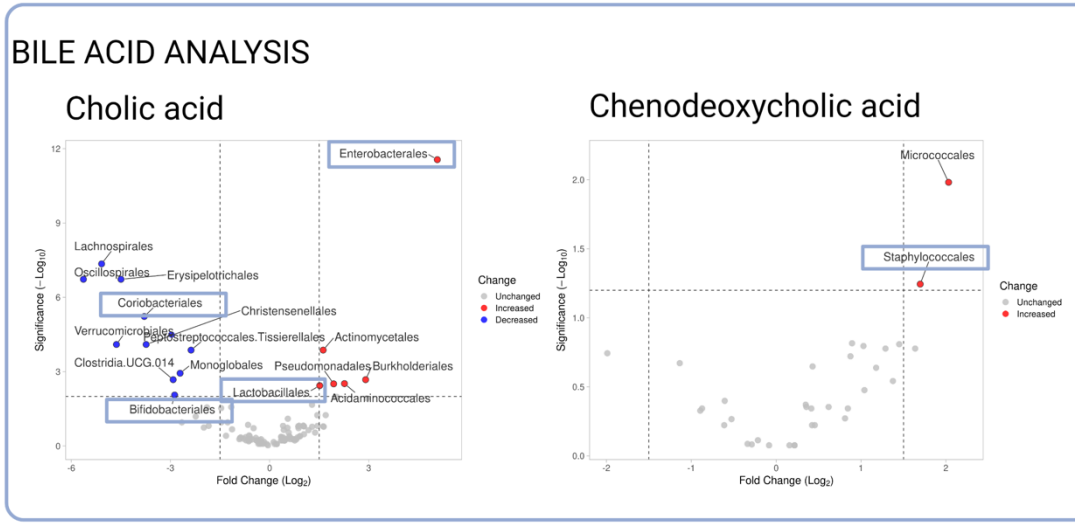
OMC IV preserved secondary bile acids



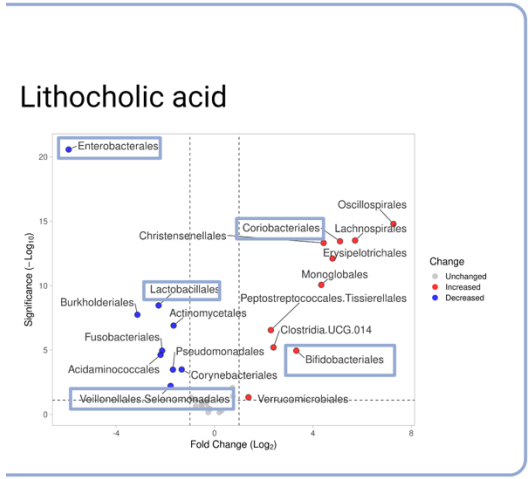
Changes in bacterial taxa were same taxa responsible for changes in bile acid homeostasis



Primary Bile Acids:



Secondary Bile Acids:



Conclusions

- CDI has always led the way to push science and infectious disease
  - Poster child for a microbiome disease
- Pathophysiology of CDI and knowledge of the microbiome has revolutionized new antimicrobial drug discovery and development
  - Targeted-therapy antibiotics = kill the pathogen, spare the microbiome
- This knowledge can also be used to explain low-risk antibiotics
  - ….and maybe discover new CDI-directed antibiotics

Acknowledgements

UH Center for Infectious Diseases and Microbiome Research

Faculty
Kevin W Garey
Chenlin Hu
Jinhee Jo (omada)
Taryn A. Eubank
M Jahangir Alam
Eugenie Basseres
Khurshida Begum
Onye Ononogbu
Abe Shremo
Elizabeth Wang

PhD students
Thanh Le
Md. Ekramul Karim
Jacob McPherson
Josef Fowler

Lab Manager
Holly Bootle

GareyLab Funding
NIAID R01AI139261
NIAID T32AI141349
NIAID PO1AI152999
Merck Pharmaceuticals
Paratek Pharmaceuticals
Seres Health

Acurx Pharmaceuticals

Acknowledgements
Figures by BioRender