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Karolinska Institutet

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Effect of tebipenem on the normal gut microbiota of healthy adult population

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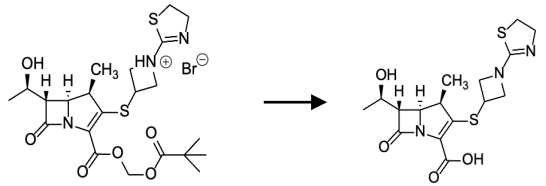
Transparency

- The study was funded by Spero Therapeutics
- Michael Nowak, David Melnick and Ian Critchley are all employees of Spero Therapeutics
- Paul Eckburg and Leanne Gasink are consultants of Spero Therapeutics

- Spero Therapeutics has not been involved directly or indirectly in activities related to investigation and analysis of the data.

Introduction

- Oral tebipenem pivoxil hydrobromide is an investigational carbapenem antibiotic currently in development for the treatment of cUTI, including acute pyelonephritis

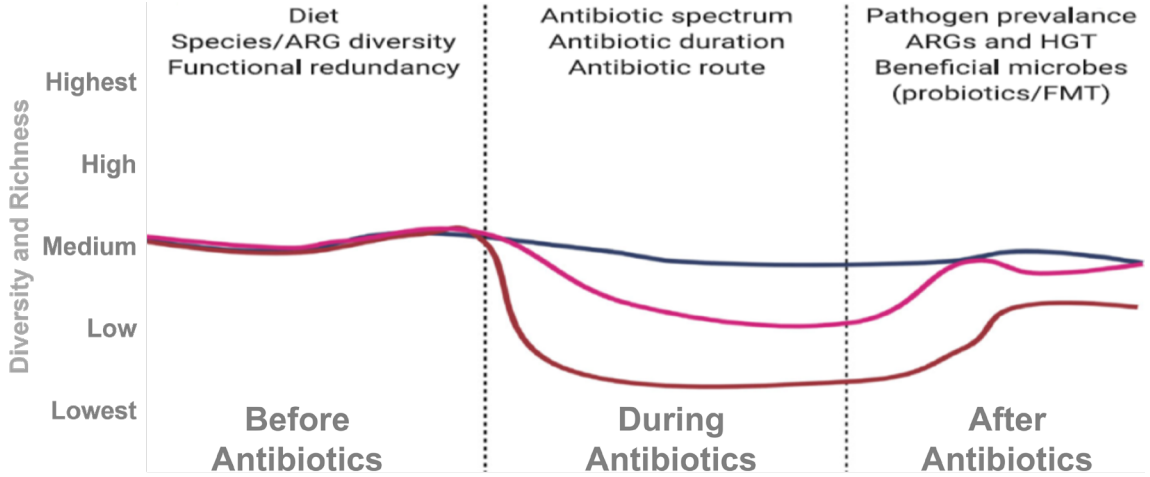


Tebipenem Pivoxil HBr
(orally bioavailable prodrug)

Tebipenem
(microbiologically active moiety)

- Broad-spectrum antimicrobials, including carbapenems, may impair the gut microbiota with alterations dependent not only on anti-anaerobic properties but also parameters with marked interindividual variability

- Perturbation of gut microbiome may be associated with several health complications and diminished colonization resistance
  - Compositions
  - Load of each taxa
  - Relative abundance
  - Selection of resistance



- Evaluation of collateral damage is important

Queen J, et al. *Gut Microbes*. 2020 Jul 3;11(4):1092-1103
Francino MP. *Front Microbiol*. 2016 Jan 12;6:1543
Woerther PL, et al. *Int J Antimicrob Agents*. 2018 Dec;52(6):762-770.

Introduction

- A greater understanding of how antibiotics alter the composition and function of the gut microbiome is of important clinical and societal utility
  - Extent of collateral damage on the gut microbiome
  - Rate of recovery to baseline microbiome composition after treatment

- We aimed to assess the potential ecological effects of oral tebipenem pivoxil hydrobromide on the gut microbiome of adult healthy population compared to amoxicillin-clavulanic acid (ClinicalTrials.gov Identifier: NCT04376554)

- Hypothesis:
  - The impact of oral tebipenem pivoxil hydrobromide on pertubations of the gut microbiome is comparable to that of amoxicillin-clavulanic acid.

- Quantitative culture and 16S rDNA metagenomics were used

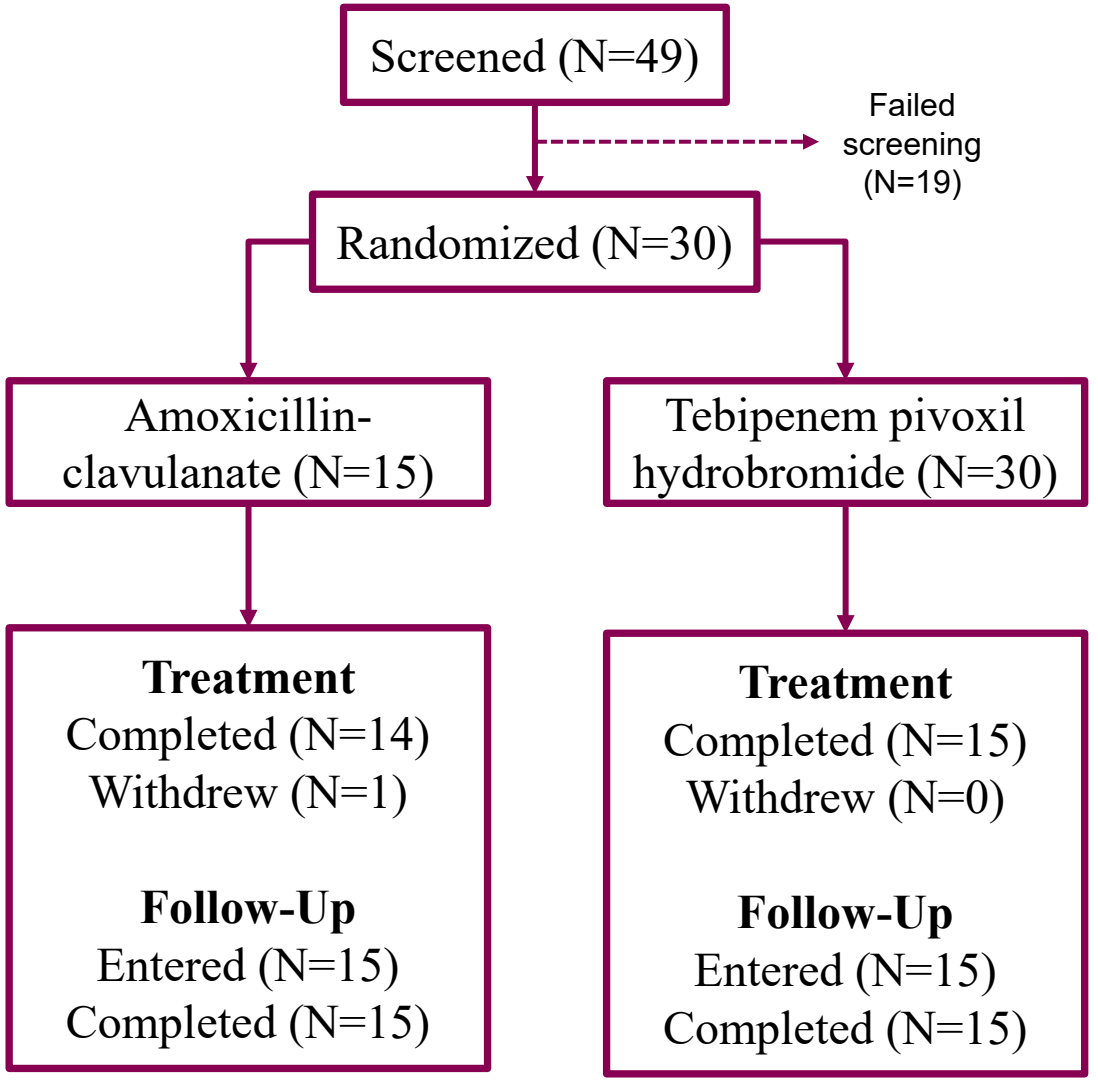
Methods

- Phase 1, single-center, open-label, randomized, parallel-group, active-control study

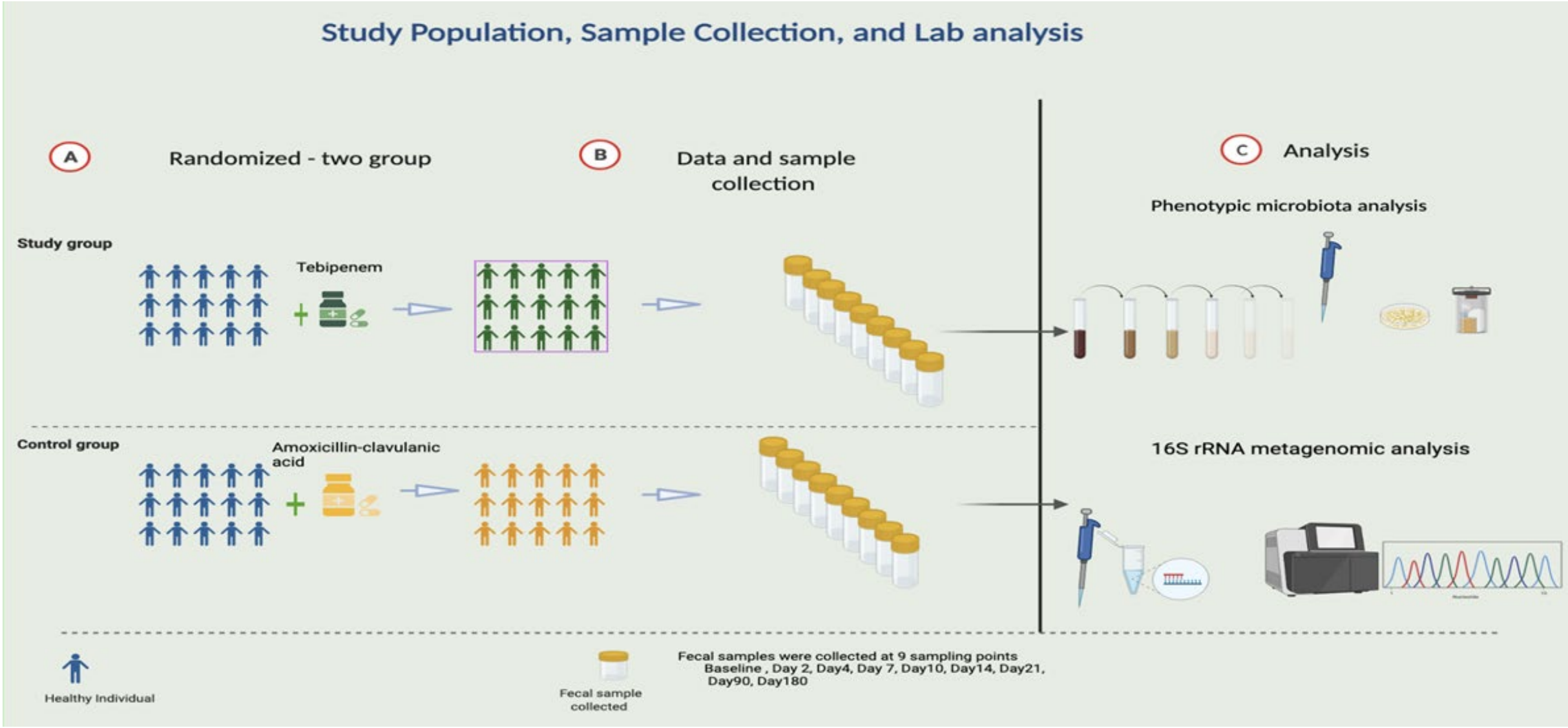
- Healthy study subjects were randomized (1:1) to a treatment arm:

- Oral tebipenem pivoxil hydrobromide 600mg q8h

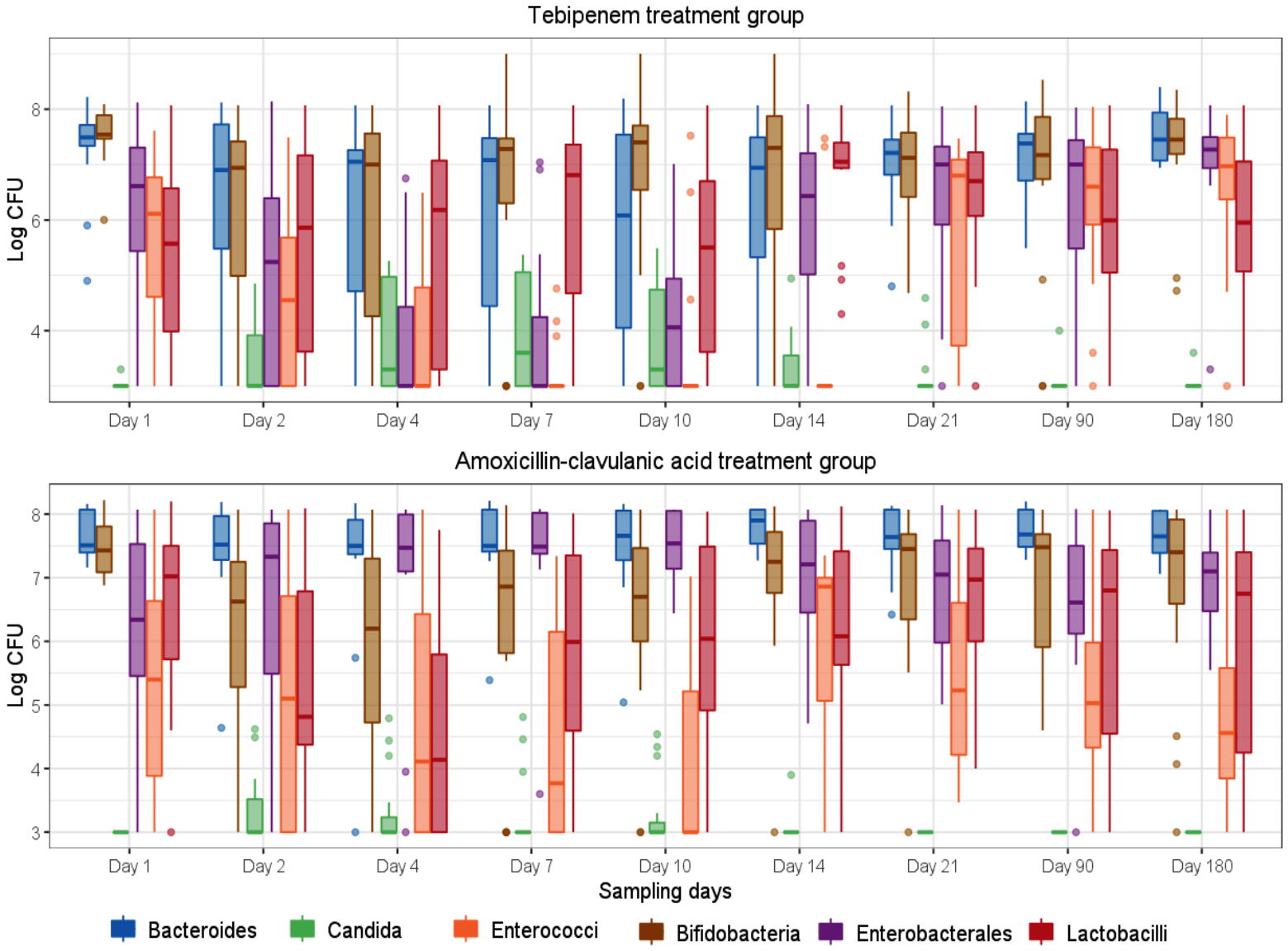
- Oral amoxicillin/clavulanate 500/125mg q8h



Methods


Study Population, Sample Collection, and Lab analysis
A
Randomized - two group
B
Data and sample collection
C
Analysis
Phenotypic microbiota analysis
Study group
Tebipenem
Control group
Amoxicillin-clavulanic acid
16S rRNA metagenomic analysis
Healthy Individual
Fecal sample collected
Fecal samples were collected at 9 sampling points
Baseline , Day 2, Day4, Day 7, Day10, Day14, Day21, Day90, Day180

Results



- More pronounced reductions in CFU observed in tebipenem group as compared to AMOX/CLAV for:
  - *Enterobacterales*
    - Day4 (TukeyHSD; p-value=0.000433),
    - Day7 (TukeyHSD; p-value=0.000509)
    - Day10 (TukeyHSD; p-value=0.00902)
  - *Enterococcus* spp.
    - Day4 (TukeyHSD; p-value=0.0247),
    - Day7 *(TukeyHSD; p-value=0.00027),*
    - Day10 (TukeyHSD; p-value=0.00436), and
    - Day14 (TukeyHSD; p-value=0.00305
- All measured genera showed recovery after 14 days in both groups (CFU counts reverted to baseline after treatment)
- Variable impact on *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* (not significant)

Phenotypic microbiome: clinically important taxa

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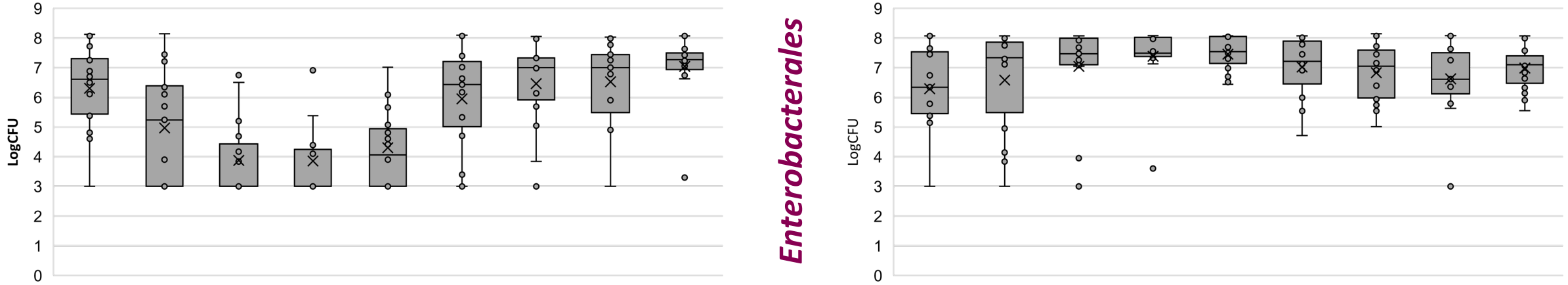
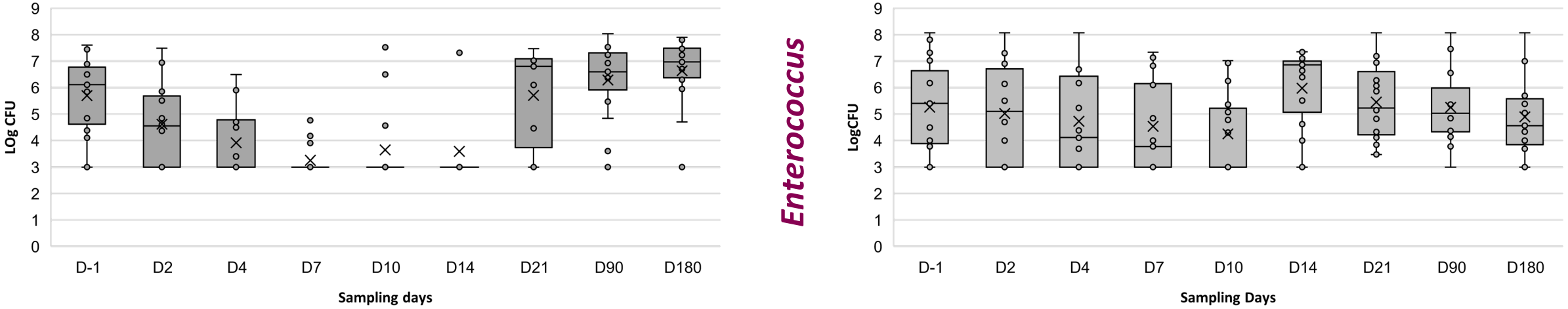
Tebipenem pivoxil hydrobromide group

Amoxicillin-clavulanate group

Enterobacterales

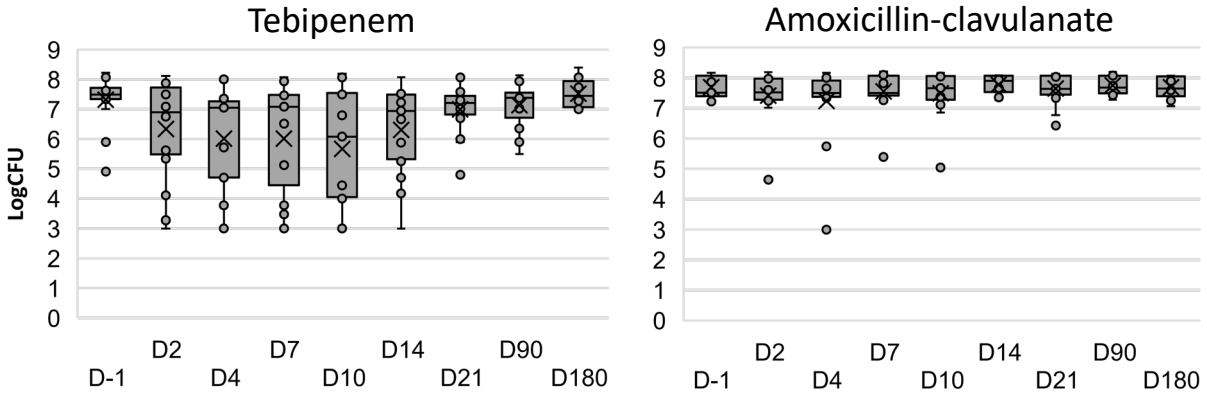


Enterococcus

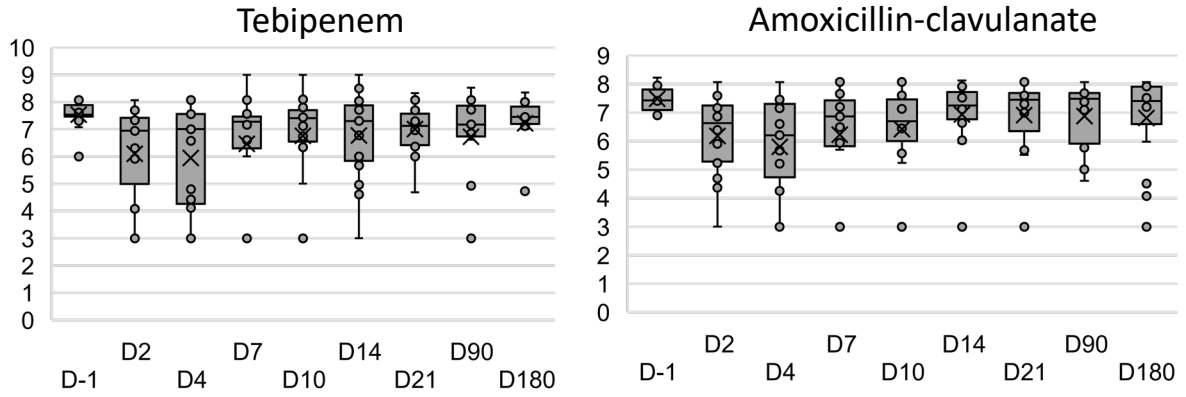


Phenotypic microbiome: clinically important taxa

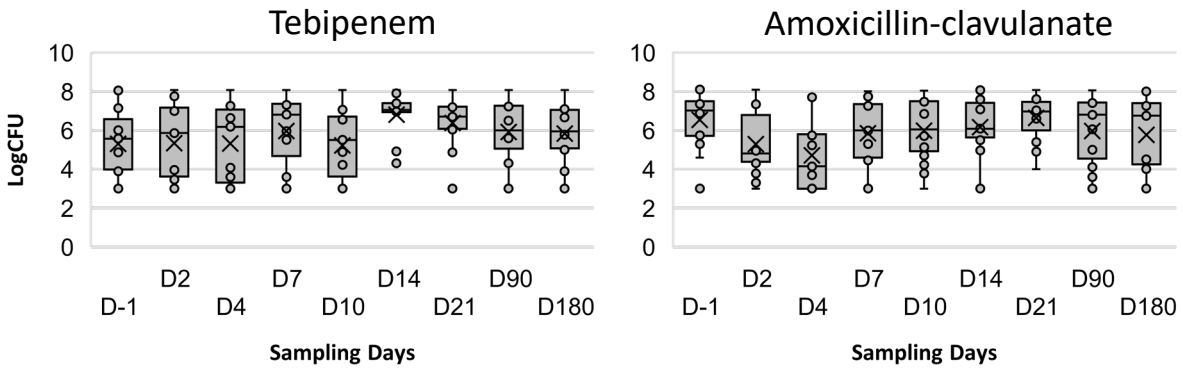
Bacteroides



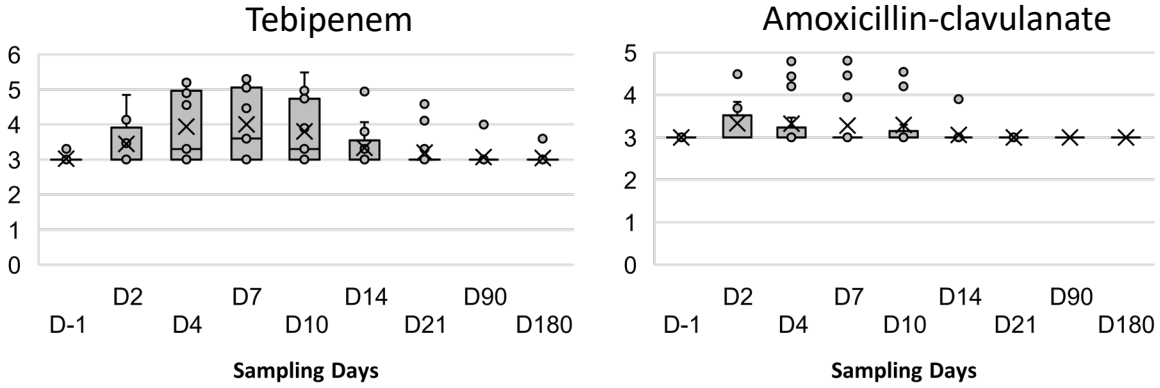
Bifidobacterium



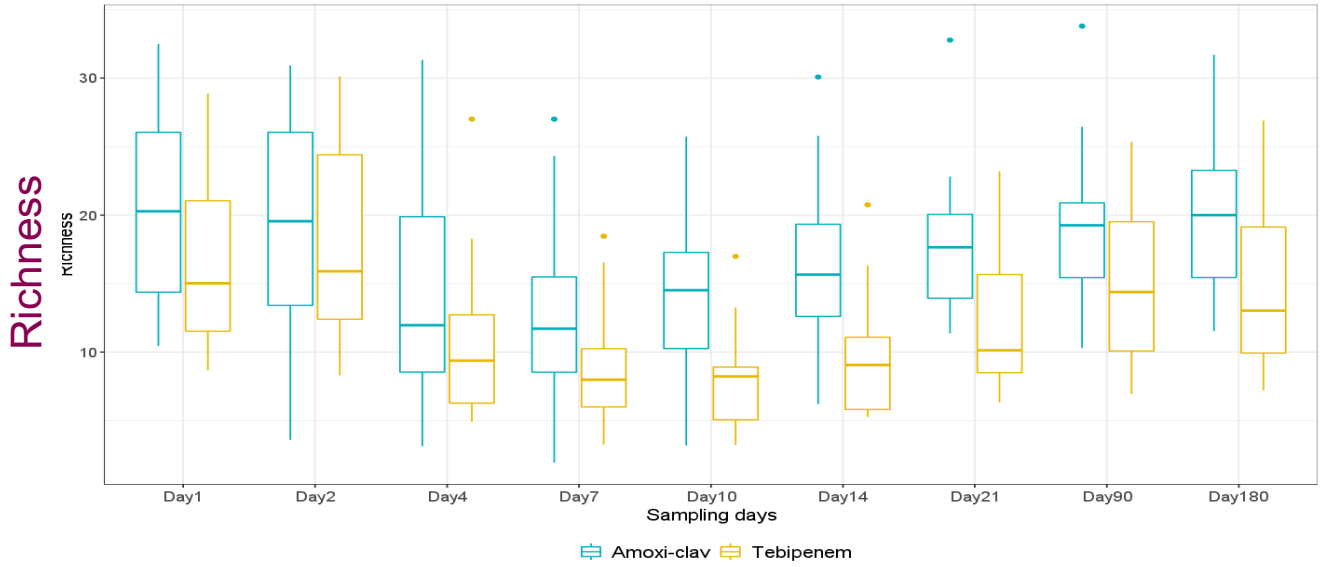
Lactobacillus



Candida



16S rDNA metagenomics



Tebipenem group

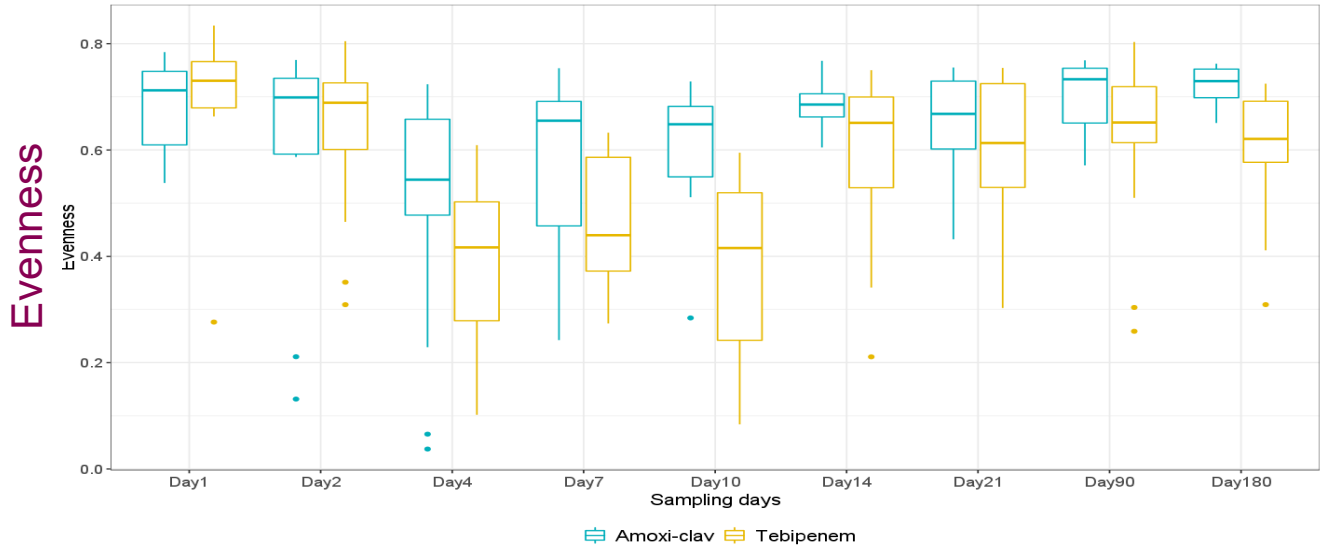
Between Day 1 and:

- Day 7 (TukeyHSD; p-value= 0.00489)
- Day 10 (TukeyHSD; p-value= 0.00123)
- Day 14 (TukeyHSD; p-value= 0.0205)

Amoxicillin-clavulanic acid group

Between Day 1 and:

- Day 7 (TukeyHSD; p-value=0.0522)



Tebipenem group

Between Day 1 and:

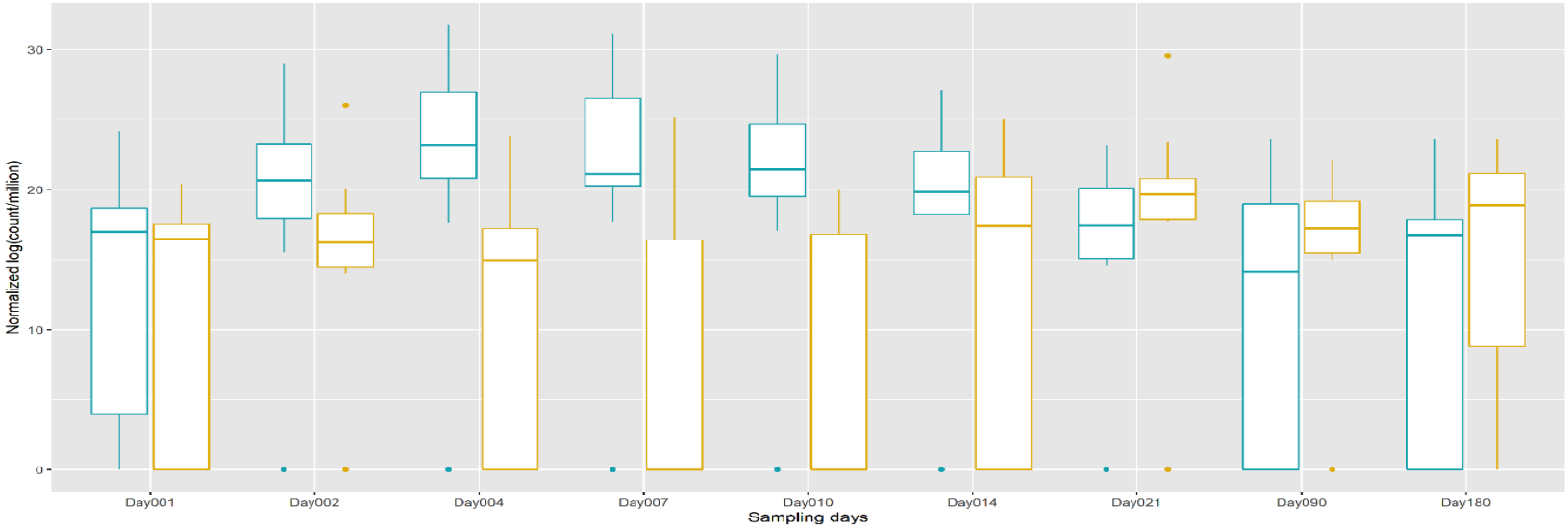
- Day4 (TukeyHSD; p-value=1.37E-6),
- Day7 (TukeyHSD; p-value=6.26E-4) and
- Day10 (TukeyHSD; p-value=3.83E-7).

Amoxicillin-clavulanic acid group

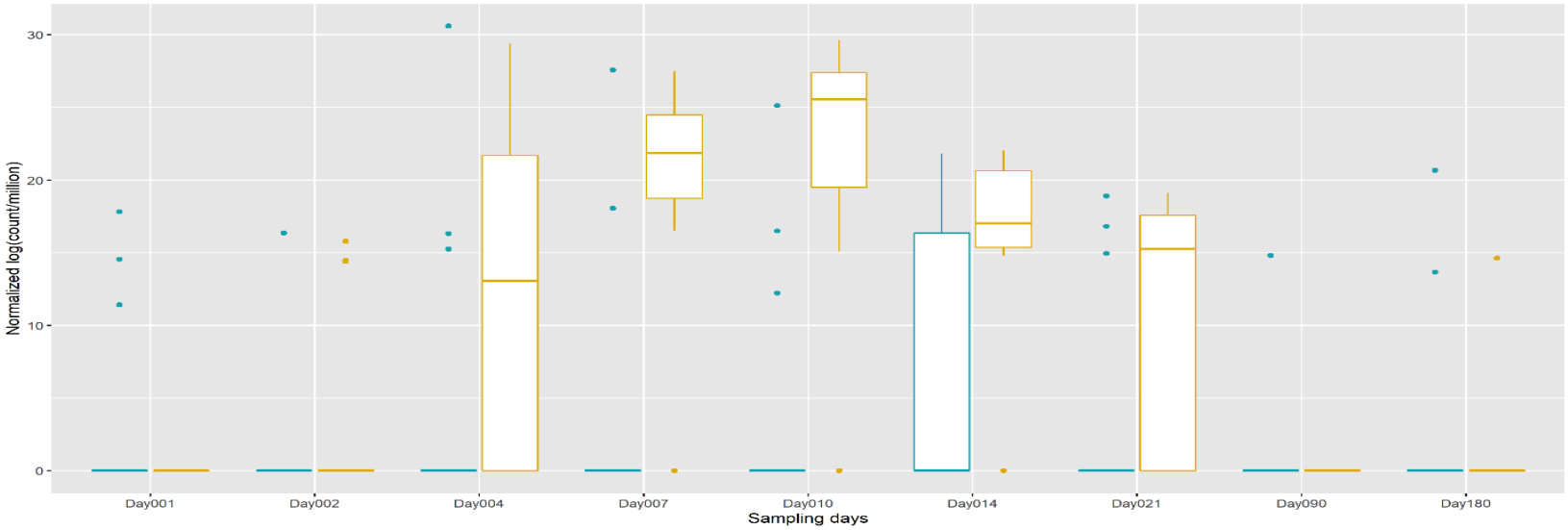
No significant difference

Differentially abundant taxa (16S rDNA)

Enterobacterales



Enterococcus



Amoxicillin-clavulanate

Tebipenem pivoxil hydrobromide

Differentially abundant taxa (16S rDNA)

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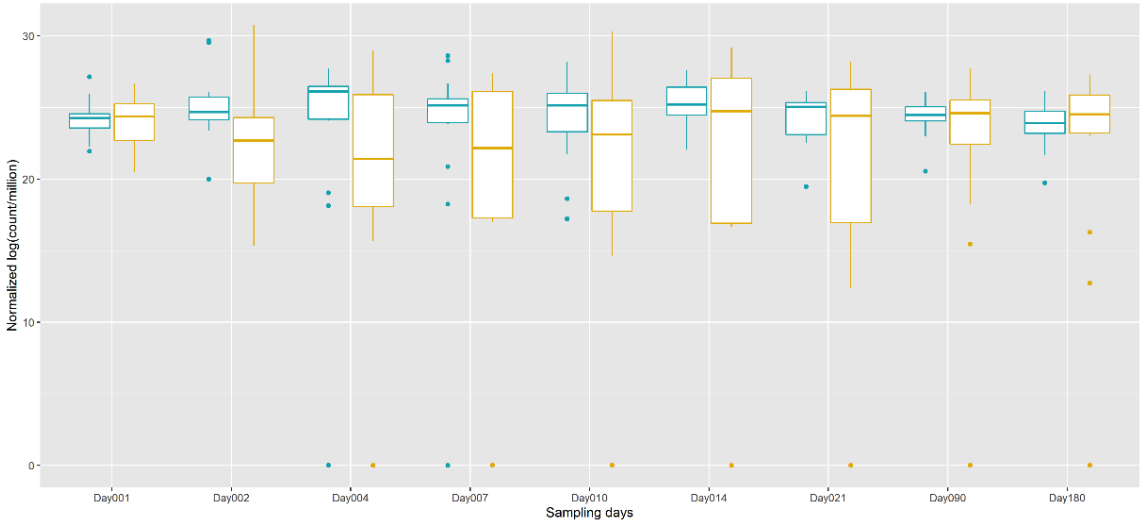
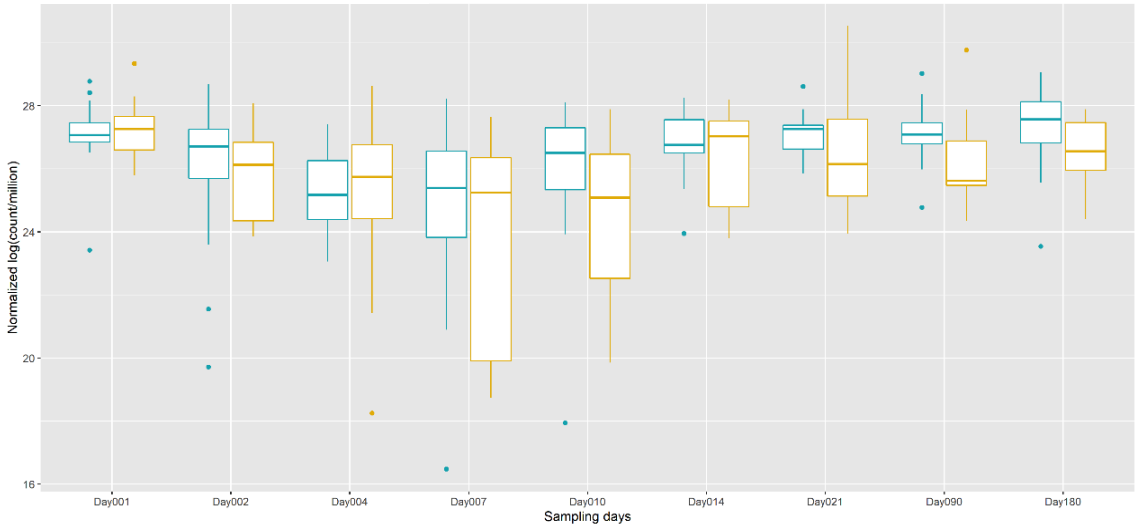
Bacteroides

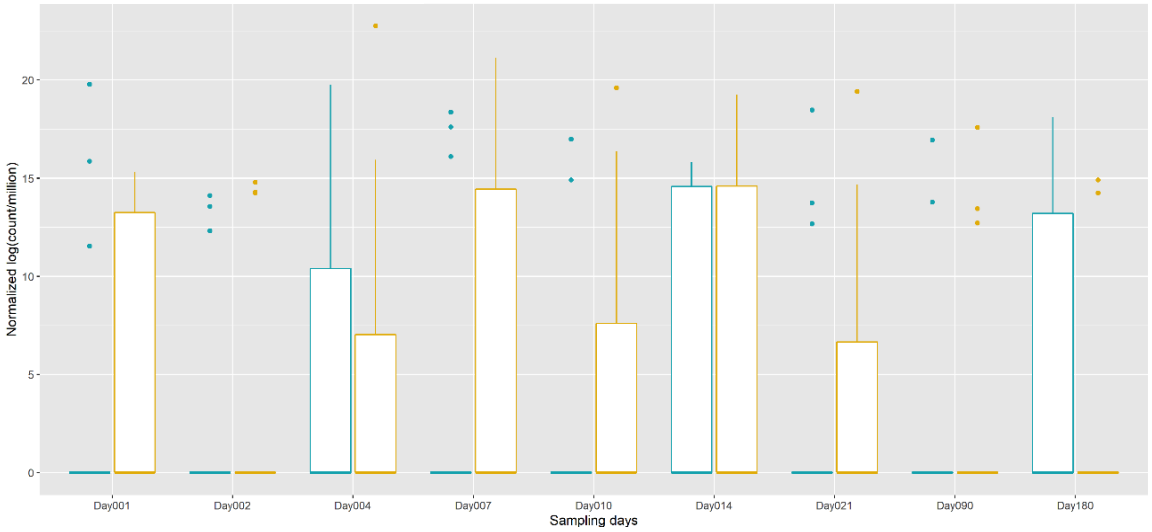


Clostridiales

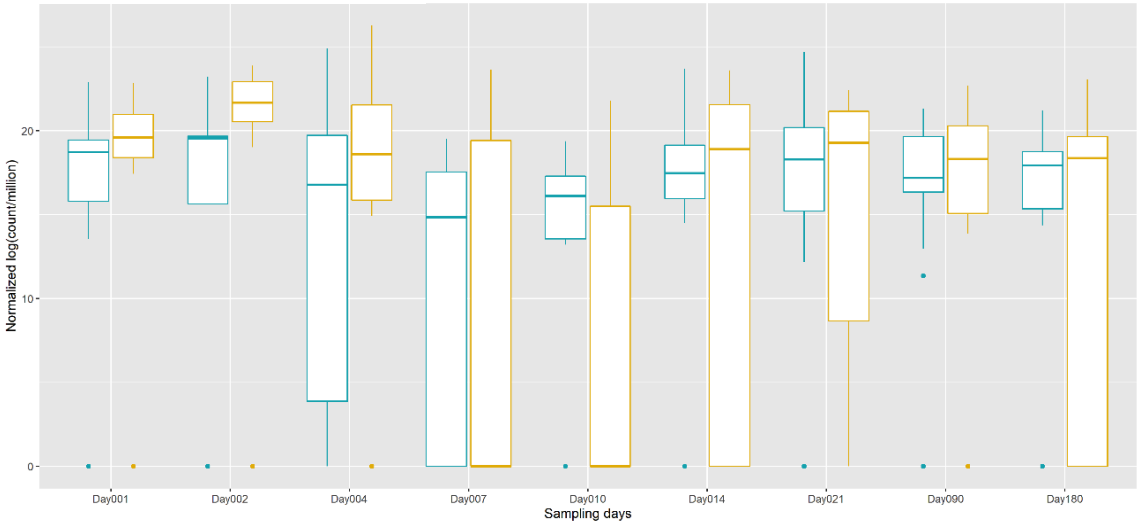


Amoxicillin-clavulanate

Lactobacillus

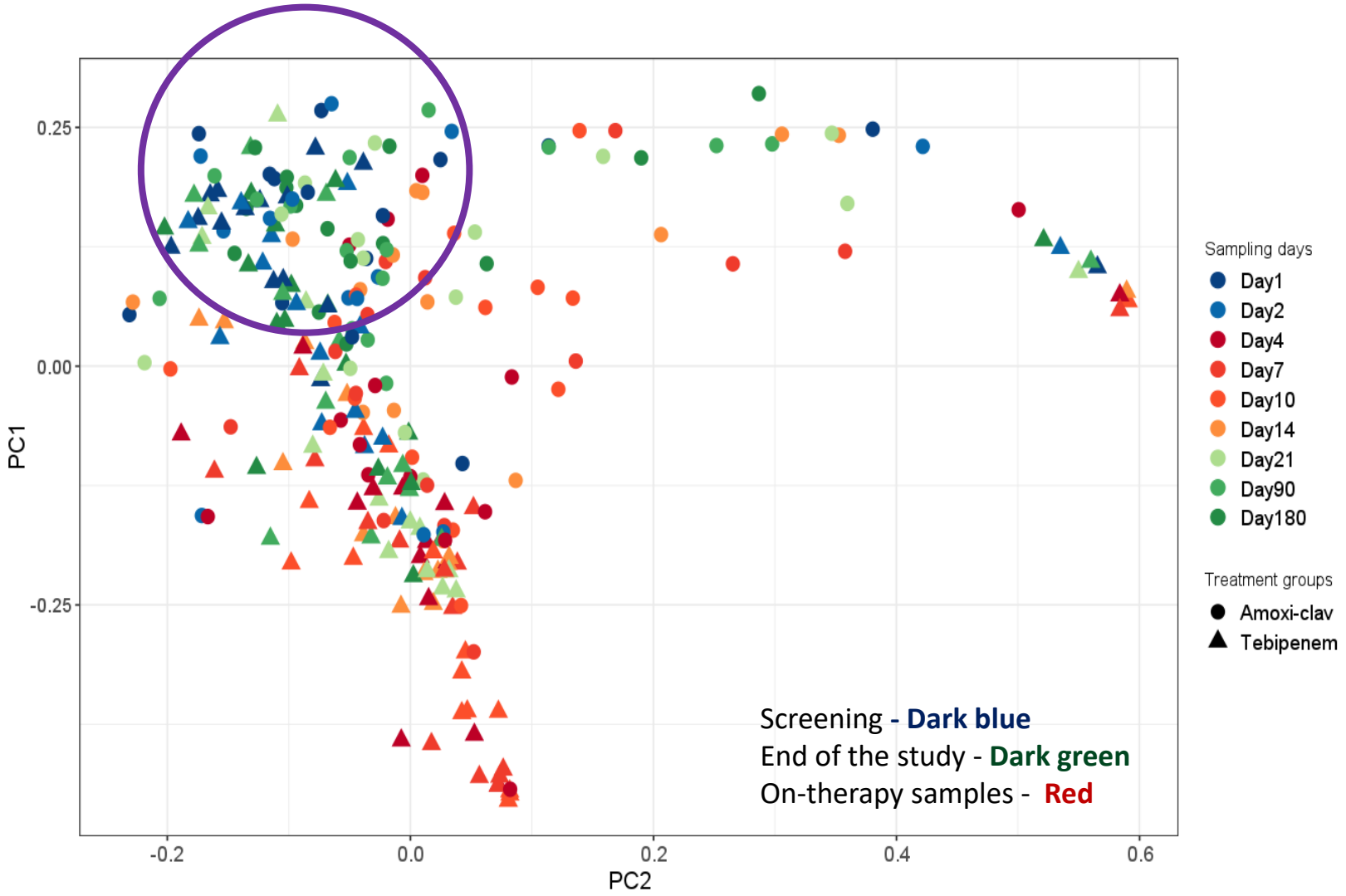


Bifidobacterium



Tebipenem pivoxil hydrobromide

Recovery of the microbiome



- Beta-diversity analysis shows microbiome significantly impacted in both treatment groups with most subjects undergoing recovery after treatment
- OTU composition of of many samples belonging to the beginning of treatment were similar to follow-up samples (i.e., Day 21, Day 90, Day 180)

Principal coordinate analysis (PCoA) plot based on Bray-Curtis measure where each point represents a sample

Selection or emergence of resistance

- Selection of *Candida spp.* relatively higher in tebipenem group
  - 40.0% in the tebipenem group vs. 11.8% in the amoxicillin-clavulanic acid group

- Selection of *Clostridioides difficile* was low
  - 2.2% in the tebipenem group vs. 0% in the amoxicillin-clavulanic acid group

- Selection of resistant strains of *Enterobacterales* was low in both treatment groups:
  - Cefotaxime resistance - 3.7% for tebipenem group vs. 17.0% for amoxicillin-clavulanate group
  - Meropenem resistance - 5.4% for tebipenem group vs. 1.48% for amoxicillin-clavulanate group
  - Tebipenem resistance - 4.4% for tebipenem group vs. 12.5% for amoxicillin-clavulanate group
  - Very low emergence of decreased susceptibility to tebipenem observed in tebipenem group (*E. coli*, n=1 and *Enterobacter bugandensis*, n=1)

Conclusion

- Effects of tebipenem were more pronounced against *Enterobacterales* and *Enterococcus* spp. compared to amoxicillin/clavulanate but reverted to baseline after 14-21 days
  - Quantitative culture showed more clear recovery compared to the 16S rDNA method

- No apparent impact on *Bifidobacterium* spp. or *Lactobacillus* spp. between treatment groups with minimal difference observed in *Bacteroides* spp.
  - Microbiome balance either unchanged or recovered

- Emergence of resistance low
  - Colonization with MDR pathogens during treatment period (diminished colonization resistance) less likely with intended outpatient use
  - 16S rDNA method provide no information regarding emergence of resistance

Acknowledgements

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- Study participants for their willingness to participate in the study and adherence to the protocol
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