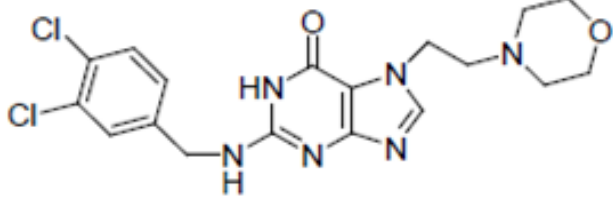


Microbiome Results from the phase 2, randomized, double-blind study of ibezapolstat compared with vancomycin for the treatment of *Clostridioides difficile* infection.

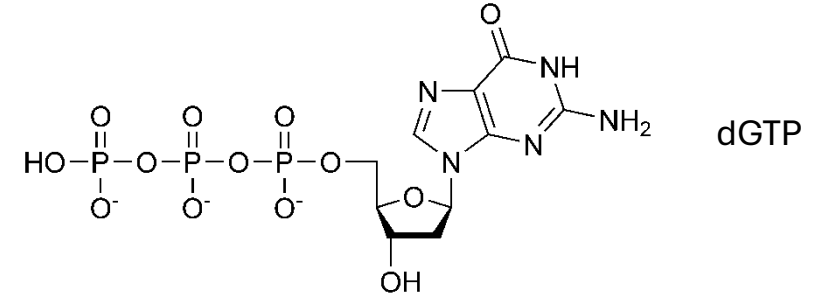
Kevin W. Garey, M Jahangir Alam, Khurshida Begum, Jacob McPherson, Taryn A. Eubank, Jinhee Jo, Michael H. Silverman for the Ibezapolstat Phase 2 Investigator Group

September 2024 ICDS, Bled Slovenia

Ibezapolstat (IBZ; ACX362E)

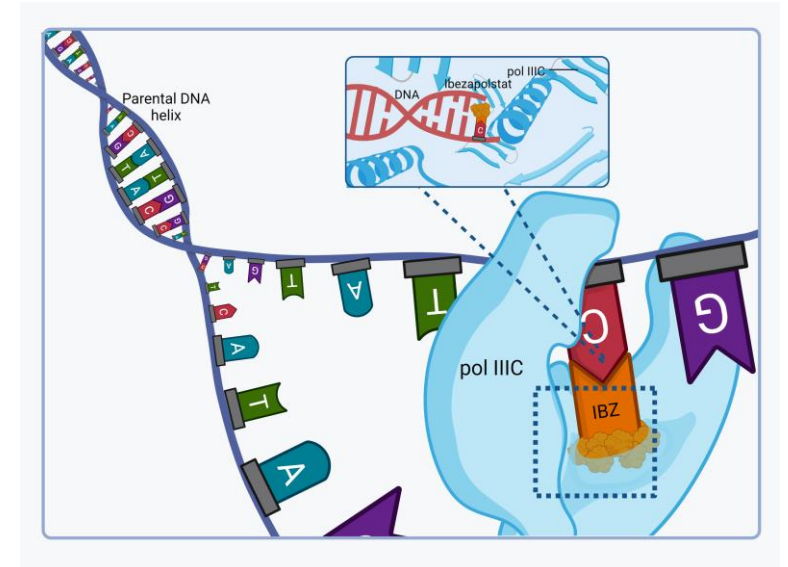


ACX-362



dGTP

- Ibezapolstat: small-molecule inhibitor of DNA pol III ϵ enzyme based upon competitive inhibition of dGTP (guanosine analog)
- DNA pol III ϵ : essential for 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
 - Other DNA pol III ϵ inhibitor compounds, in preclinical development for systemic treatment of resistant infections, show in vitro activity vs. the bioterrorism Category A pathogen *B. anthracis* (*Anthrax*), including a ciprofloxacin-resistant strain, with MICs of 0.5-2 μ g/mL. Selective microbiome effects will be tested in these compounds as well

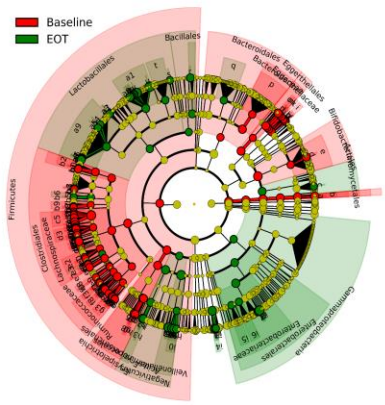


Xu et al. Bioorg Med Chem. 2019
<https://www.nature.com/articles/d43747-021-00149-0>

IBZ has been shown to have favorable effects on the microbiome

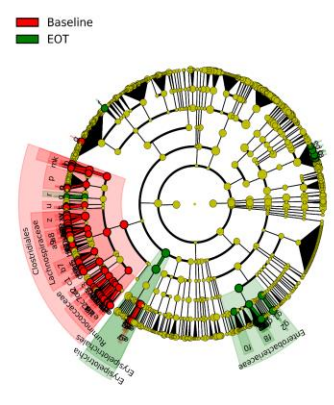
IBZ Phase 1 Healthy volunteer study in comparison with VAN

A. Vancomycin Changes in Phylogeny
by Linear discriminant analysis Effect Size (LEfSe)



- a: bacteriumF_3
- b: Actinomycesp_orataxon1
- c: Bifidobacteriumpseudocat
- d: Bifidobacterium
- e: Collinsellaefaciens
- f: Collinsellaefaciens
- g: Collinsella_4_B_47FAA
- h: Collinsellaefaciens
- i: Collinsella
- j: Senegalimassilaanaerobia
- k: Senegalimassila
- l: Adlercreutziaequifaciens
- m: Adlercreutzia
- n: Eggerthella
- o: Eggerthella
- p: Bacteroides
- q: Prevotella
- r: Gemmatimonadetes
- s: Granulicatellabadiacens
- t: Enterococcus
- u: Lactobacillusanimalis
- v: Lactobacillusmurinus
- w: Lactobacillusplantarum
- x: Lactobacillusrhamnosus
- y: Lactobacillusruminus_1
- z: Lactobacillusruminus_2
- a0: Lactobacillusruminus
- a1: Lactobacillus
- a2: Lactococcus
- a3: Lactococcuslactis_1
- a4: Streptococcusinfantis_1
- a5: Streptococcusmitis
- a6: Streptococcusthermophil
- a7: Streptococcusthermophil
- a8: Streptococcus
- a9: Streptococcus
- b0: Bacteroides_pectinophil

B. Ibezapolstat Changes in Phylogeny
by Linear discriminant analysis Effect Size (LEfSe)

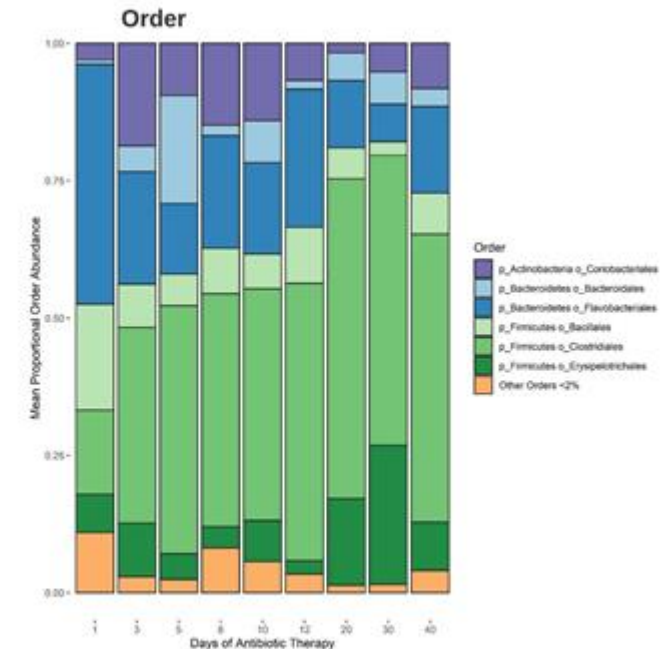


- a: Bifidobacteriumgallinarum
- b: Bifidobacteriumminimum
- c: Bifidobacteriummoukalabe
- d: Bifidobacteriumreuteri
- e: Bifidobacteriumstelenbos
- f: Lactococcuslactis_1
- g: Streptococcusalvarius
- h: ClostridialesbacteriumVE2
- i: Bacteroides_pectinophilus
- j: butyrate_producingbacteri
- k:
- l: Levylamassiliensis
- m: Levylia
- n: Clostridiumsp_L2_50
- o: Clostridiumsp_5Y8519
- p: Clostridium
- q: Eubacterium_sulci
- r:
- s: Eubacteriumventriosum
- t: Eubacterium_eligens
- u: Eubacterium
- v: Lachnospiraceabacterium
- w: Lachnospiraceabacterium
- x: Lachnospiraceabacterium
- y: Eubacterium_rectale
- z:
- a0: Anaerostipeshadrus
- a1: Blautiahanseii
- a2: Blautiahydrogenotrophic
- a3: Blautiaobum
- a4: Blautiaobum_1
- a5: Blautiaobum_2
- a6: Ruminococcus_gnavis
- a7: Ruminococcus_torques
- a8: Blautia
- a9: Butyrivibrio
- b0: Coprococcuscauli

IBZ:
More narrow spectrum
Increased proportion of Actinobacteriota

McPherson et al AAC 2022

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



IBZ:
Increased proportion of Actinobacteriota
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)

Microbiologic eradication (days 0-12)
anaerobic culture on CCFA

Microbiome changes (days 0-12)
qPCR and 16S rRNA

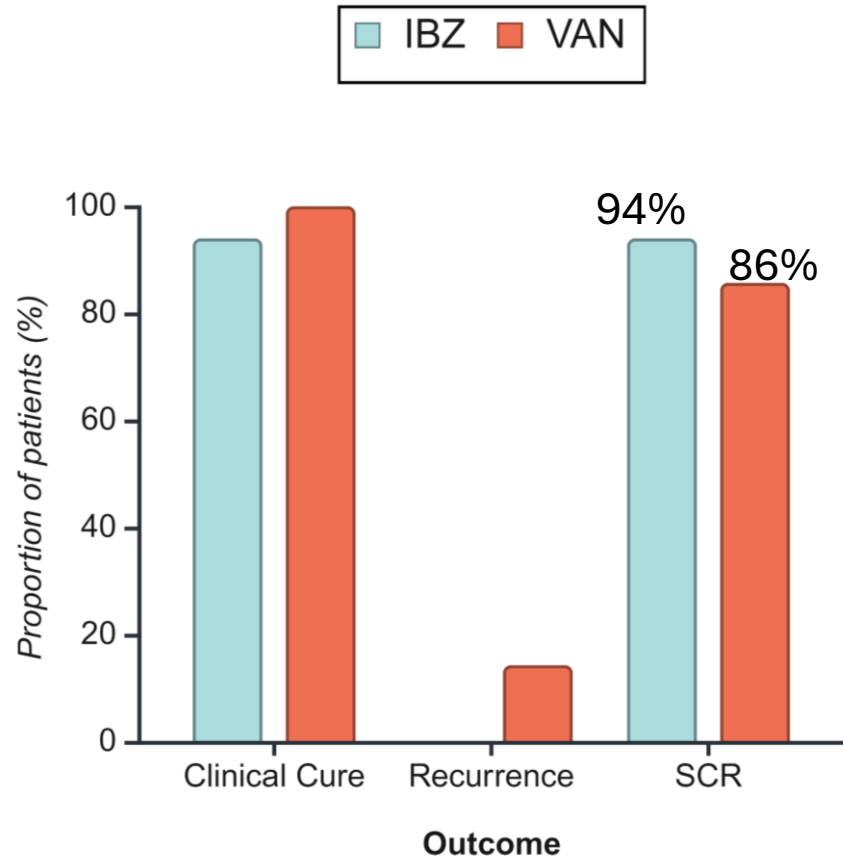
IBZ PH2b Microbiome Objectives

- Evaluate IBZ vs. vancomycin (VAN) in patients with CDI
 - Fecal microbiome effects
 - Pharmacokinetics
 - Microbiologic eradication
 - Metagenomic proportional change (16s rRNA)
 - Quantitative changes in relative taxa (qPCR)

RESULTS: Demographics and Baseline Information

	IBZ (n=16)	VAN (n=14)	P value
N	16	14	
Age, years ≥75 yo	64±13 5 (31.2%)	62±10 2 (14.3%)	0.57
Female	13 (81%)	11 (79%)	0.85
White	16 (100%)	13 (93%)	0.27
Hispanic or Latino	11 (69%)	11 (79%)	0.54
Charlson Comorbidity index	2.6±1.5	2.2±1.5	0.47
Number of UBMs at baseline Median (minimum, maximum)	6 (3-15)	6 (4-13)	
Baseline <i>C. difficile</i> ribotype strains			
F014-020	0	3	
F027	1	2	
F106	3	1	
F002	1	1	
F116	0	1	
Other	6	3	

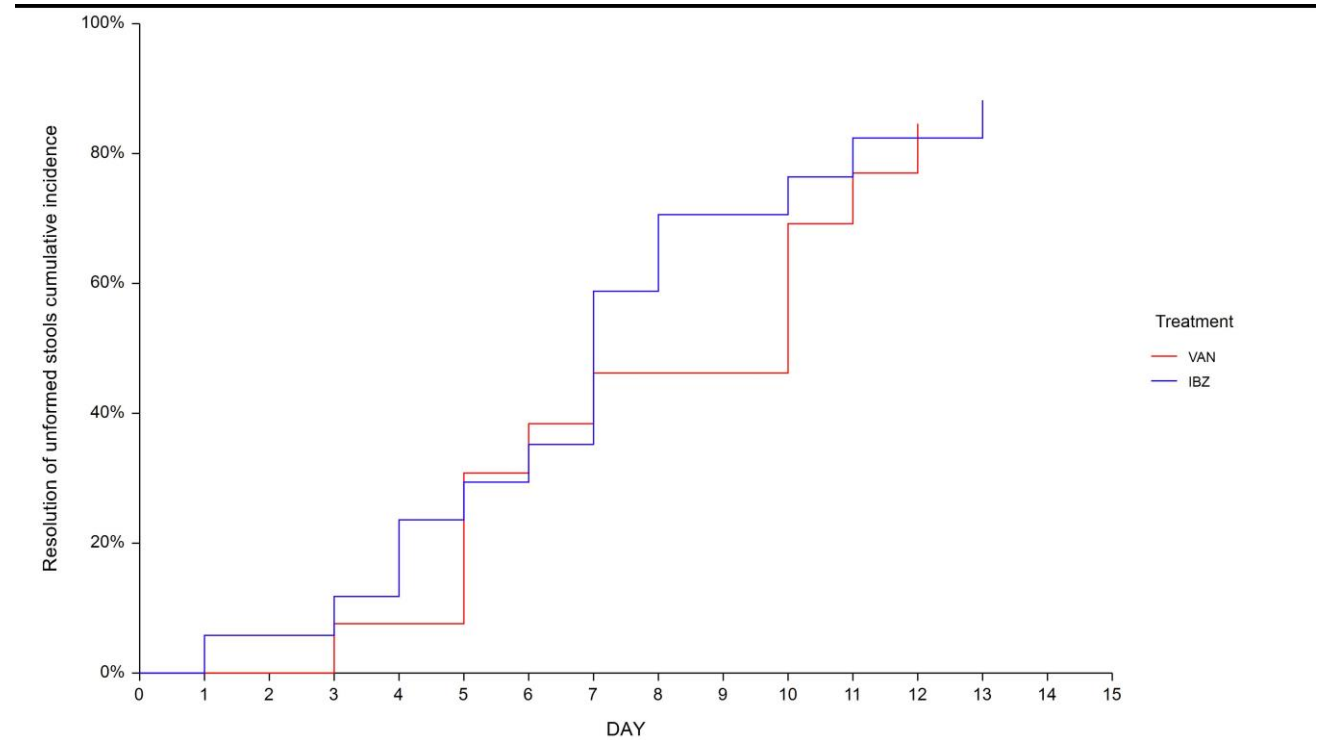
Figure 2a. Efficacy analysis



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

Figure 2b. Time to resolution of diarrhea

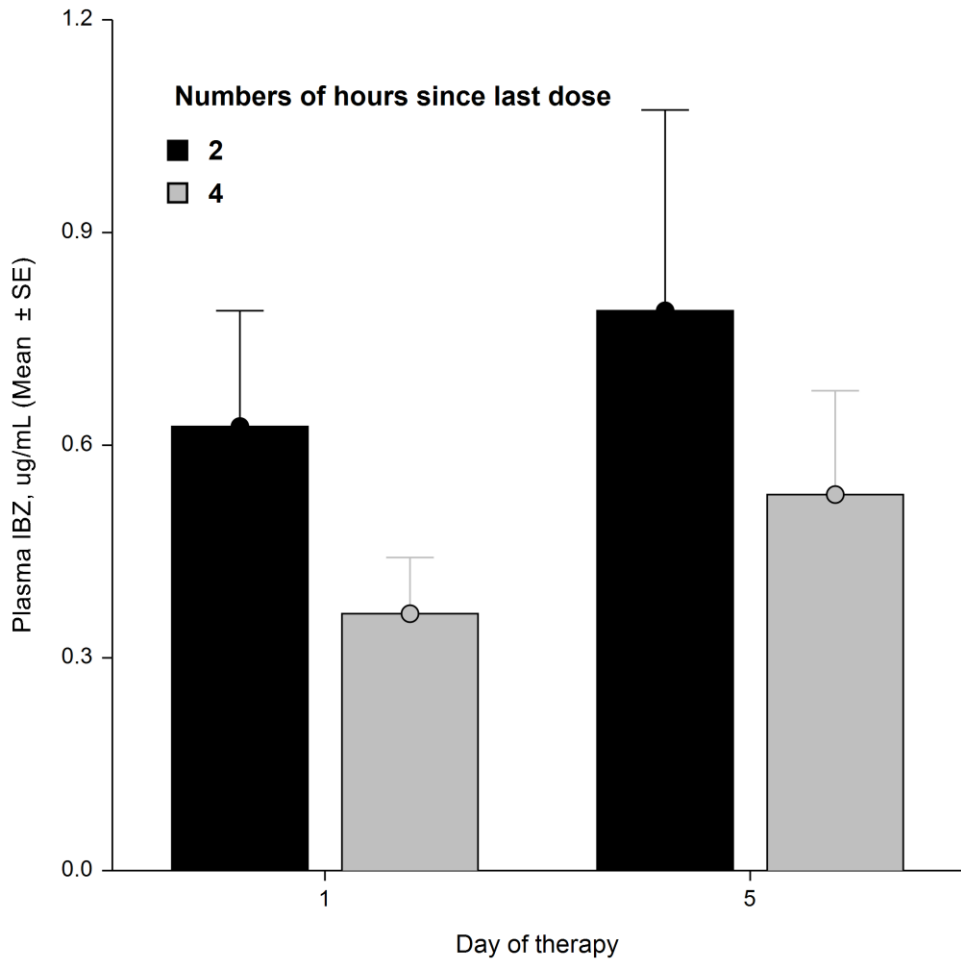
Cumulative incidence of UBM resolution



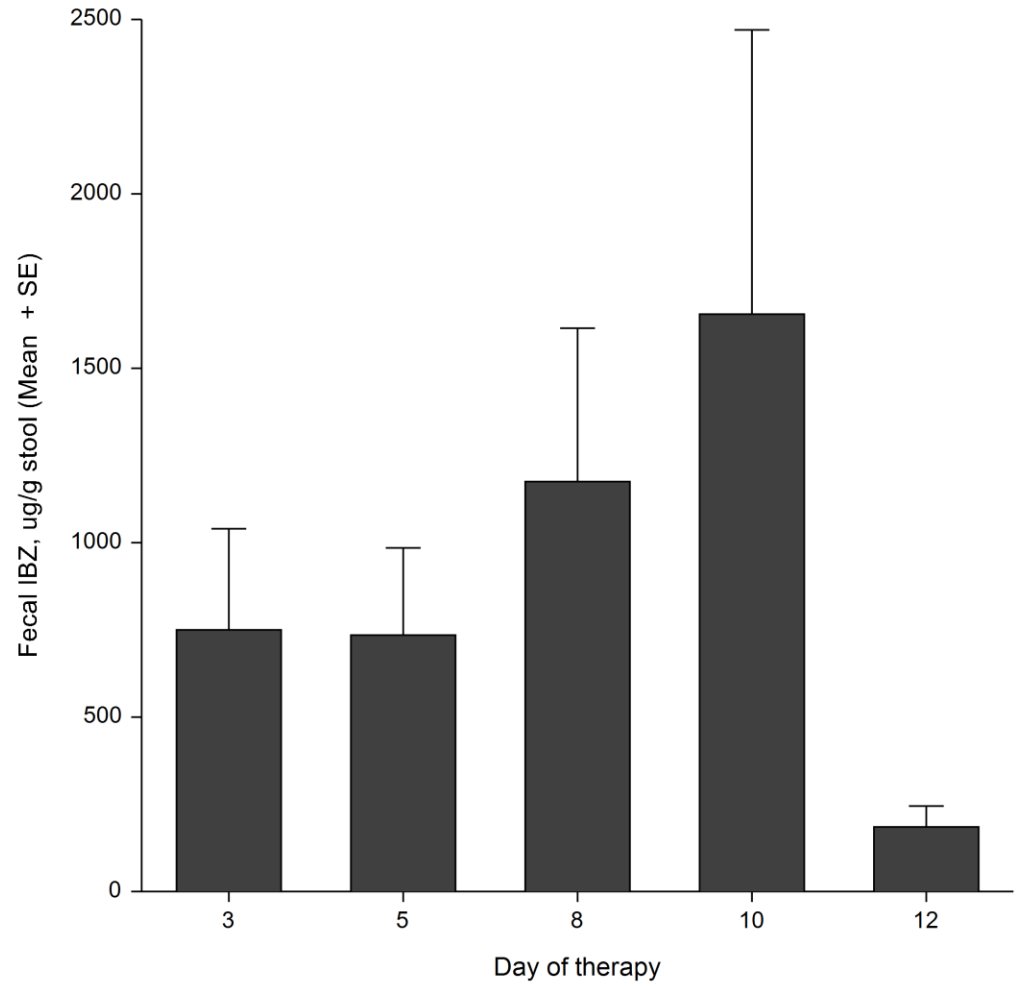
SCR: sustained clinical response; UBM: unformed bowel movement

IBZ Plasma and Fecal Concentrations

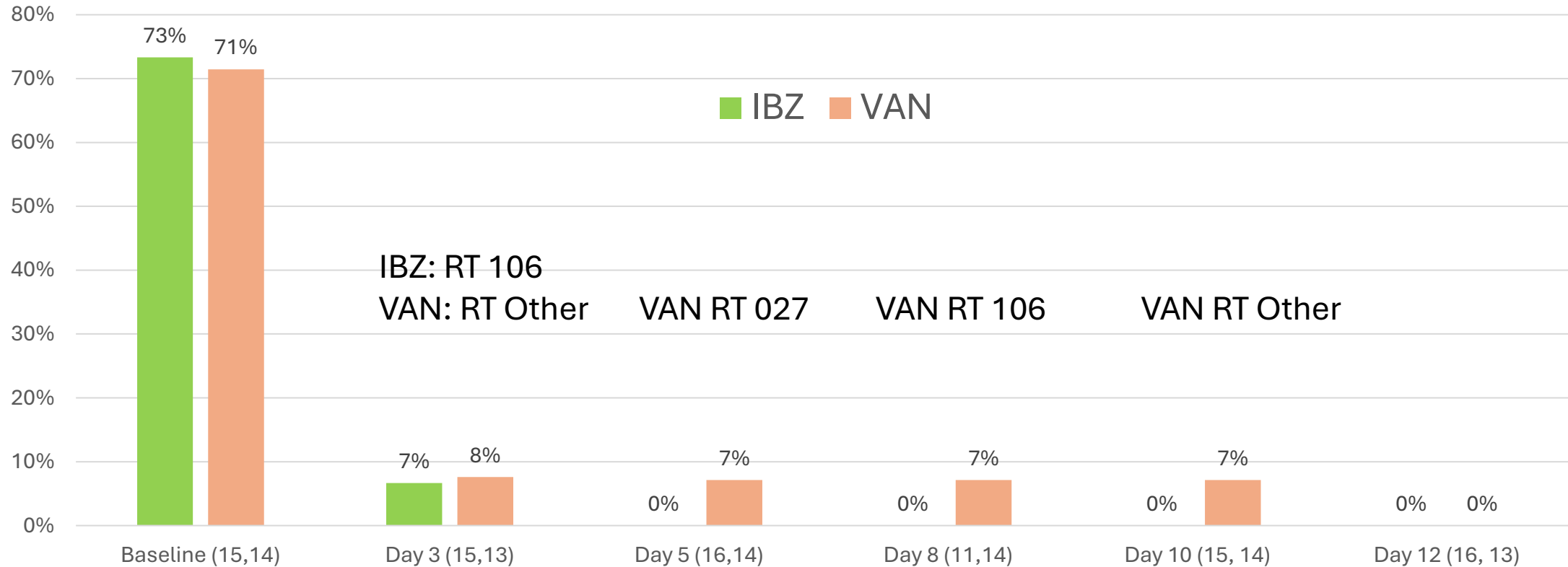
a. Plasma concentrations



b. Fecal concentrations



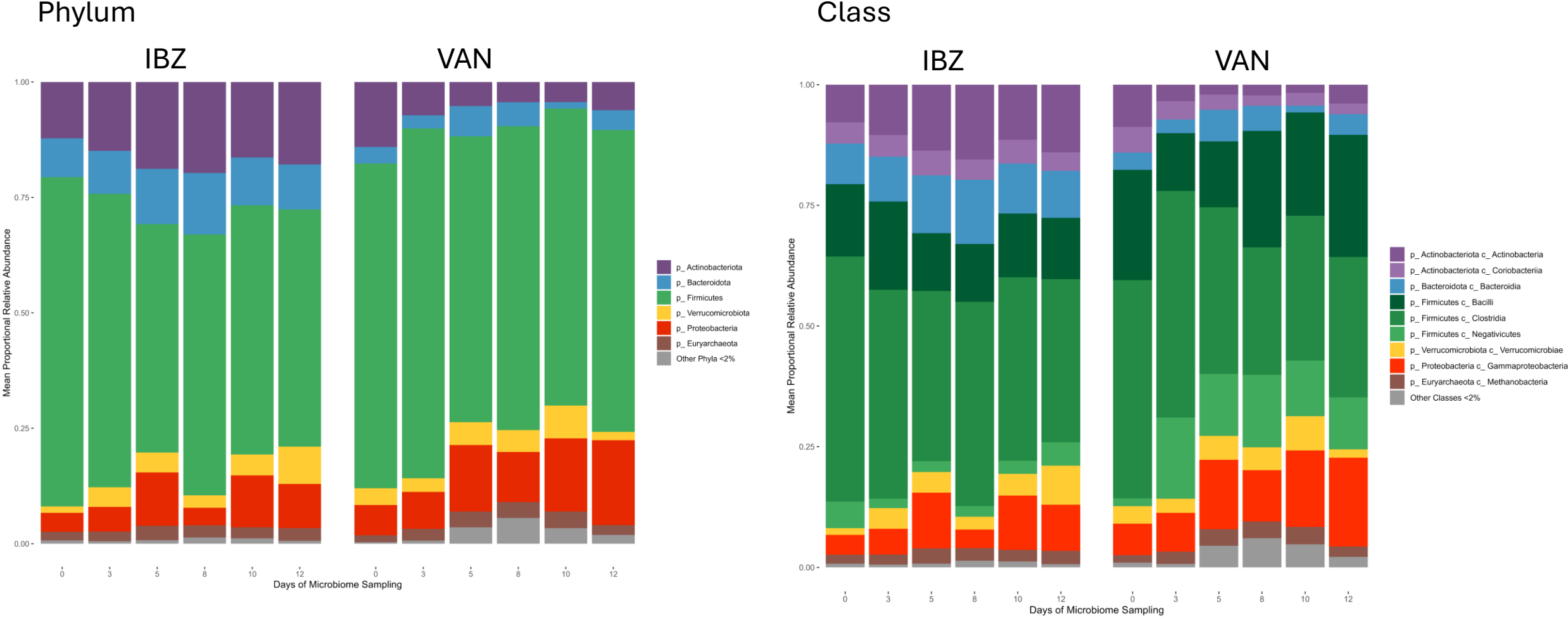
Microbiologic Eradication



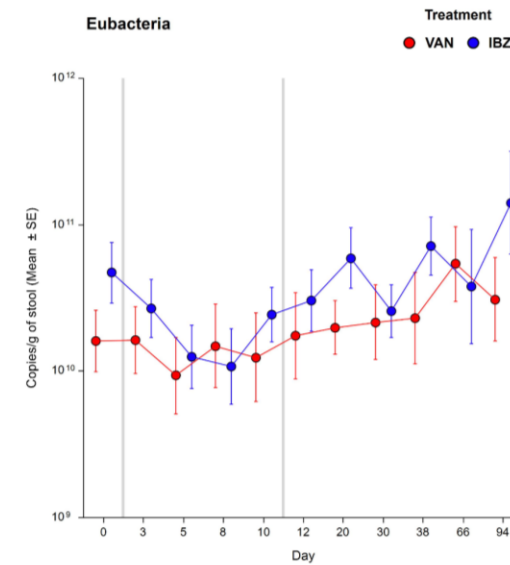
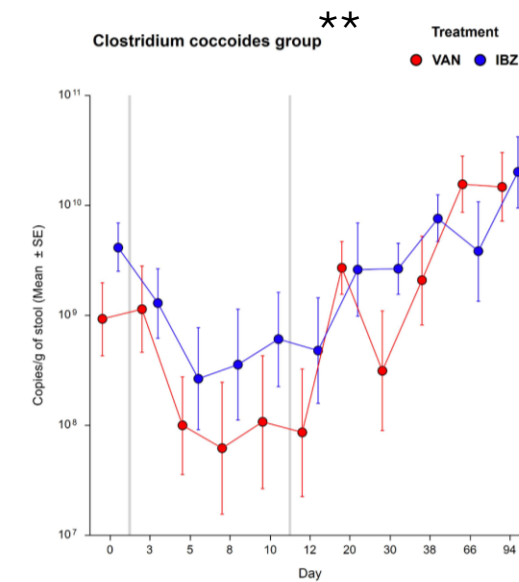
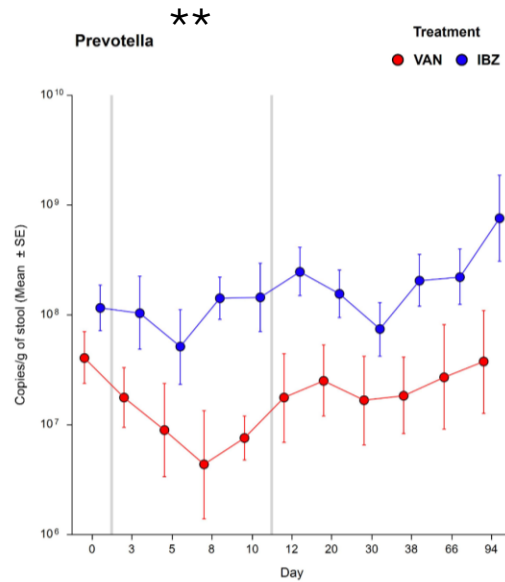
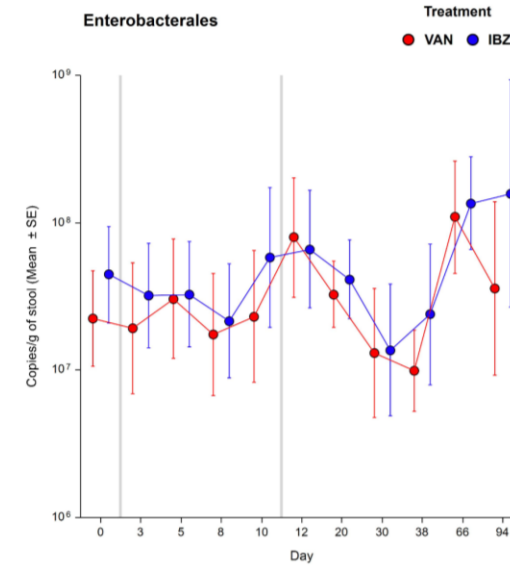
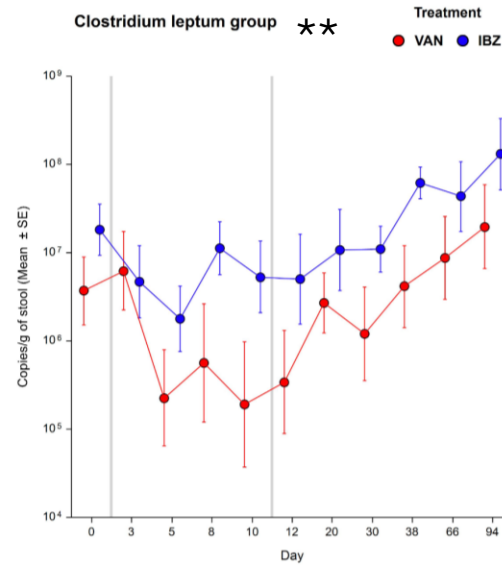
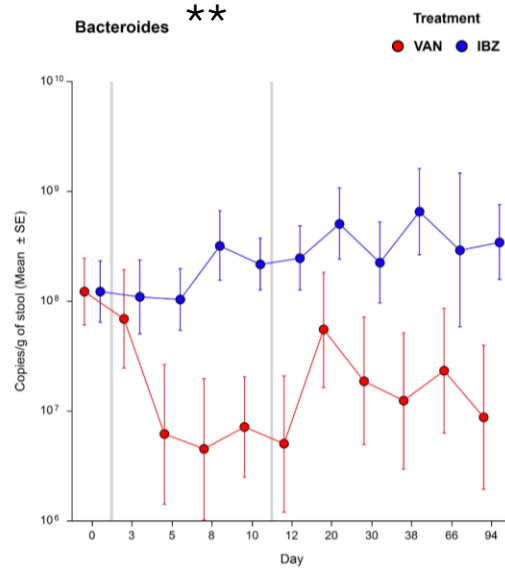
IBZ: One patient with positive *C. difficile* growth past baseline

VAN: Four patients with positive *C. difficile* growth past baseline

Microbiome. Favorable microbiome results were observed with IBZ



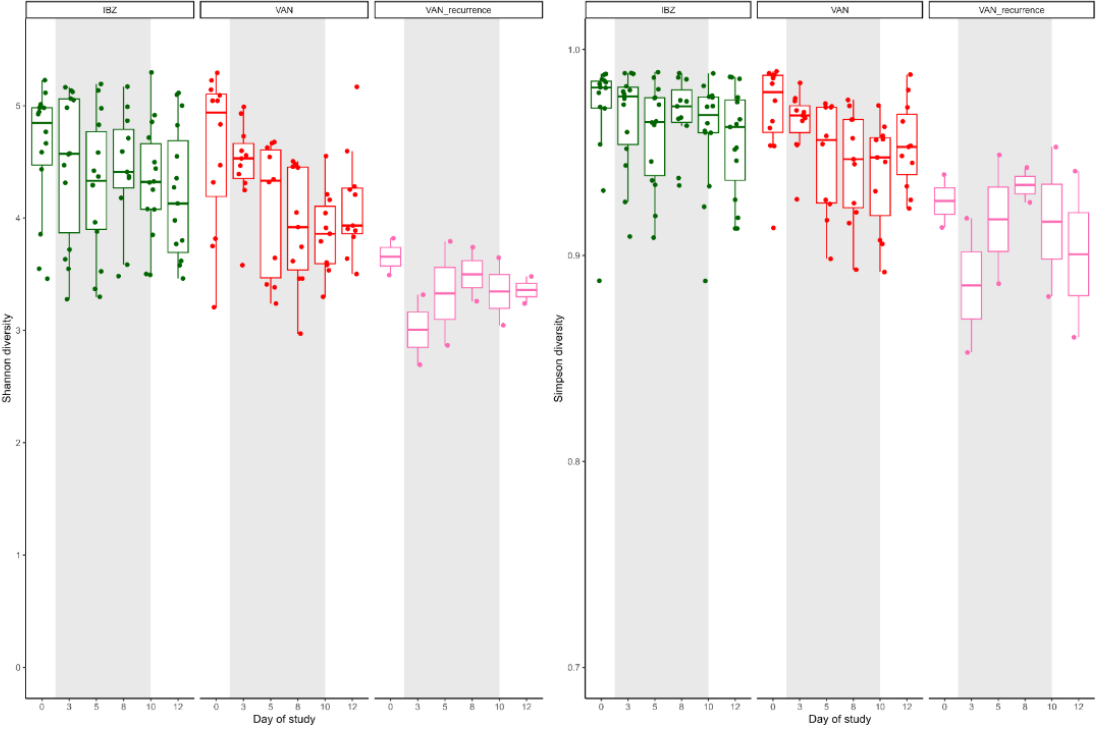
IBZ qPCR microbiome analysis



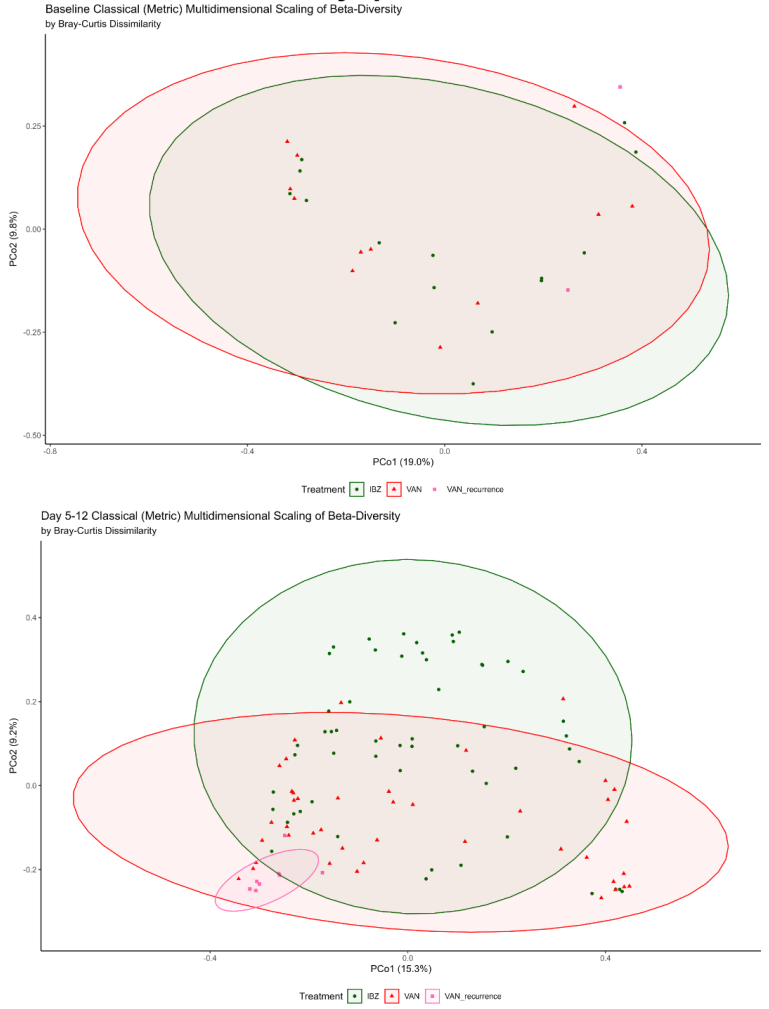
**p<0.01

Focus on CDI Recurrence. Alpha and Beta Diversity

a. Alpha diversity plots

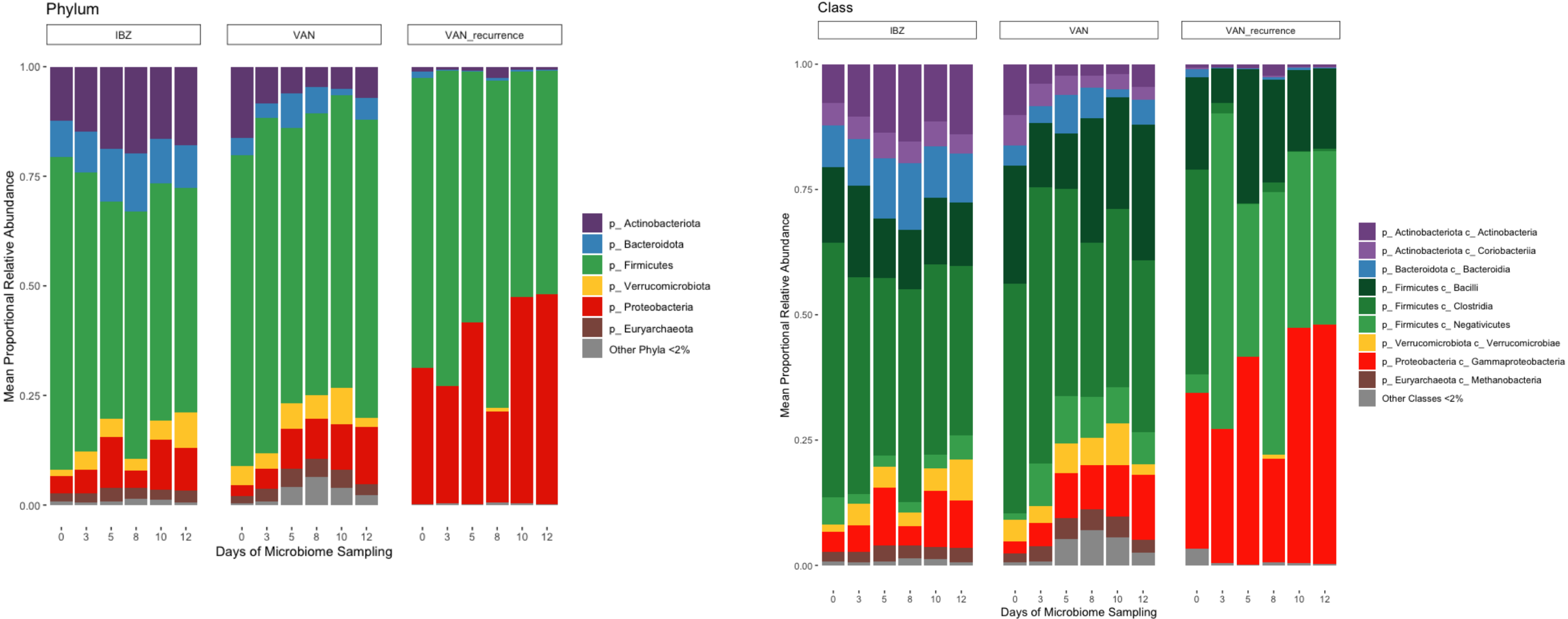


b. Beta diversity plots

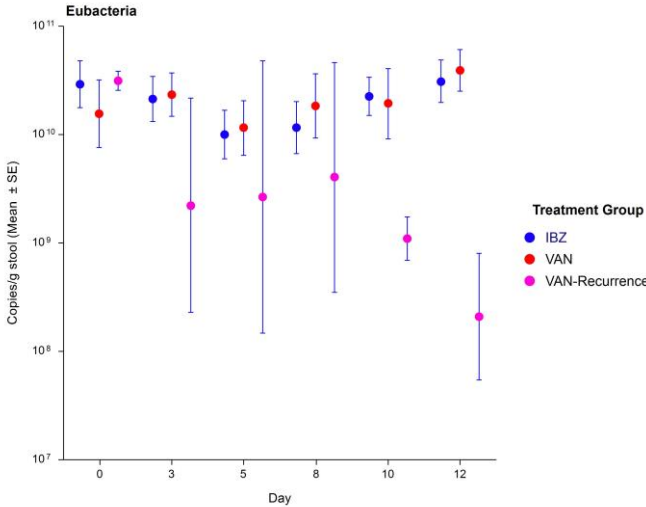
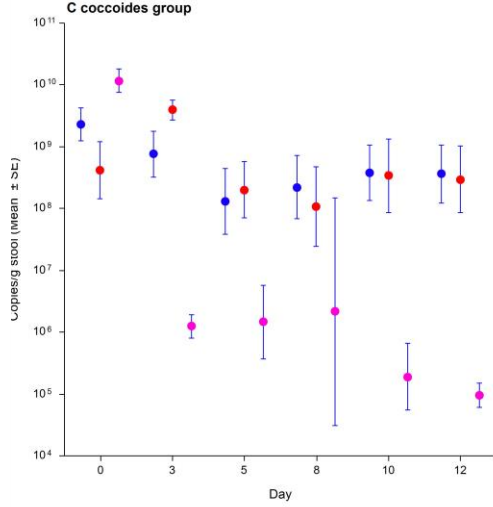
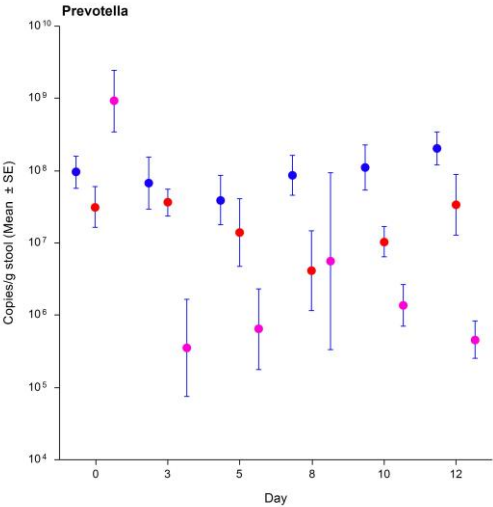
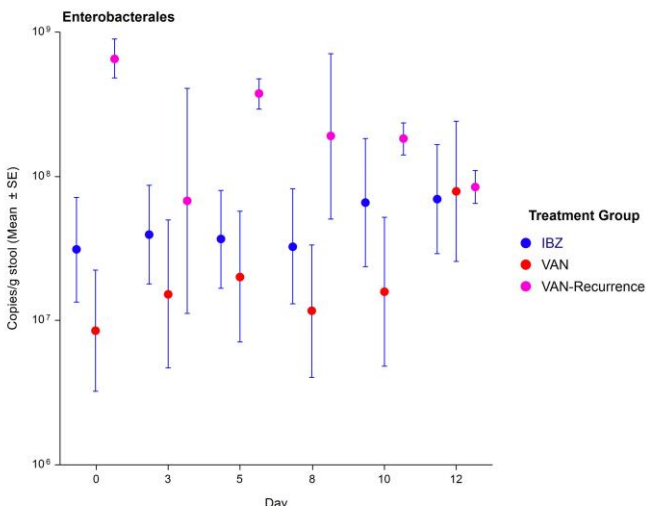
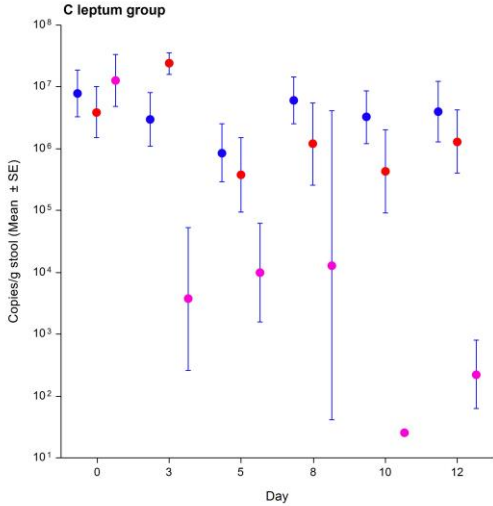
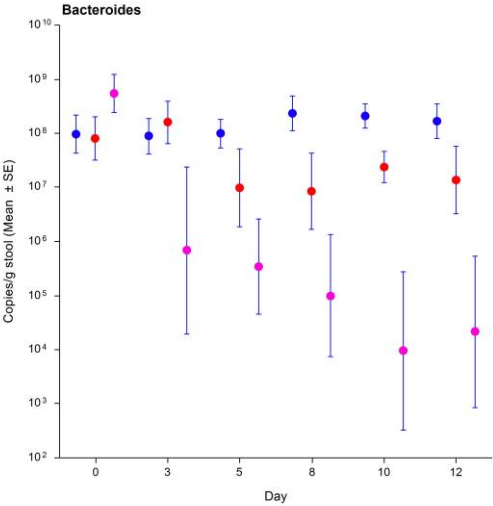


IBZ: n=16; VAN (no recurrence): n=12; VAN (recurrence: n=2)

CDI recurrence associated with marked microbiome disruption



CDI recurrence associated with marked microbiome disruption

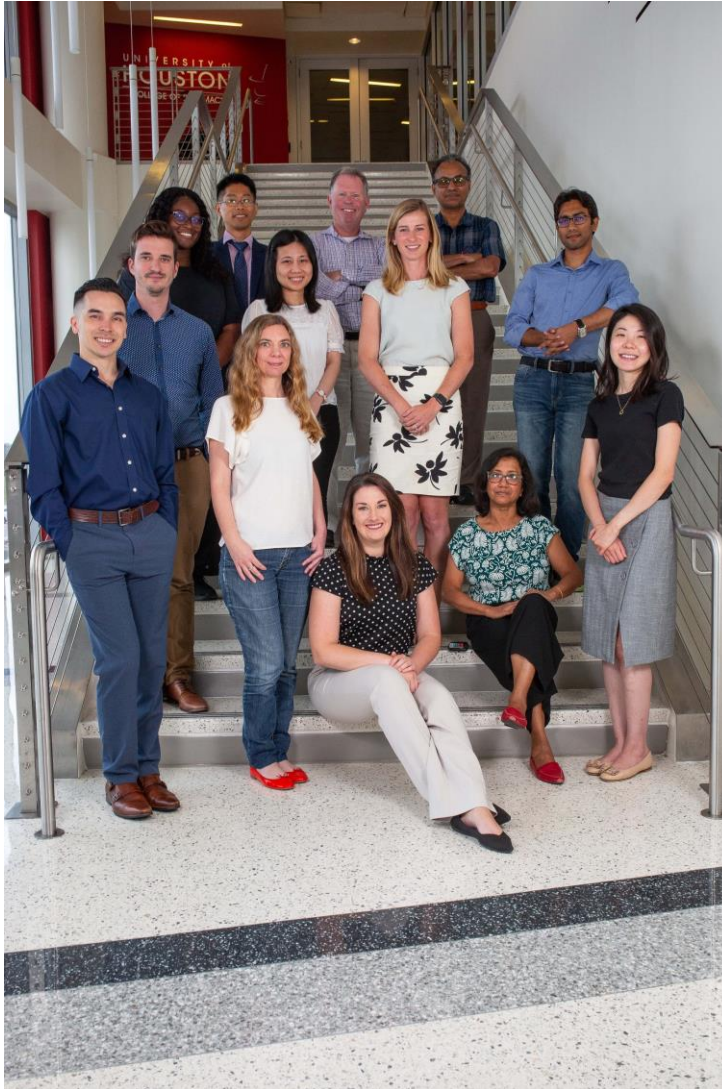


Conclusions

- IBZ had a clinically comparable cure rates and safety profile to VAN
 - No CDI recurrence vs. 2 VAN-treated patients
- IBZ had favorable PK and microbiome results to VAN
 - Higher colonic / low systemic concentrations
 - Fewer cases of persistently positive *C. difficile*
 - Increased proportion of Actinobacteriota
 - Increased quantity of beneficial Bacillota (Firmicutes)
- These results warrant further development in phase 3 trials.

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