

Clostridium difficile Infection (CDI):

Discovering the need for new treatment
algorithms and care pathways

APRIL 4, 2013

CDI recurrence: The importance of intestinal microbiome

APRIL 4, 2013



FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

Microbiome as the flip side of *C. difficile* infection

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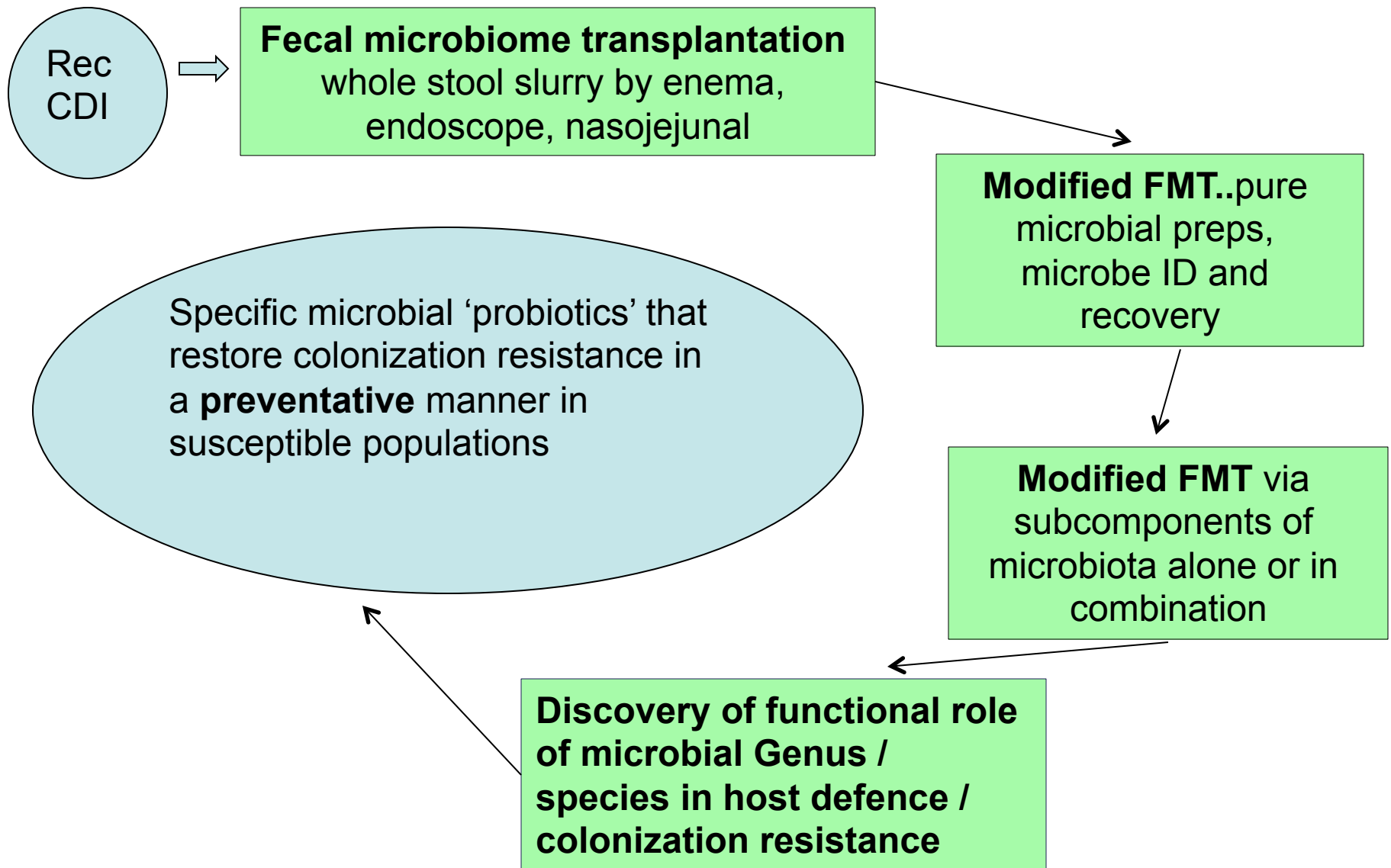
CONFLICT OF INTEREST DISCLOSURE SLIDE

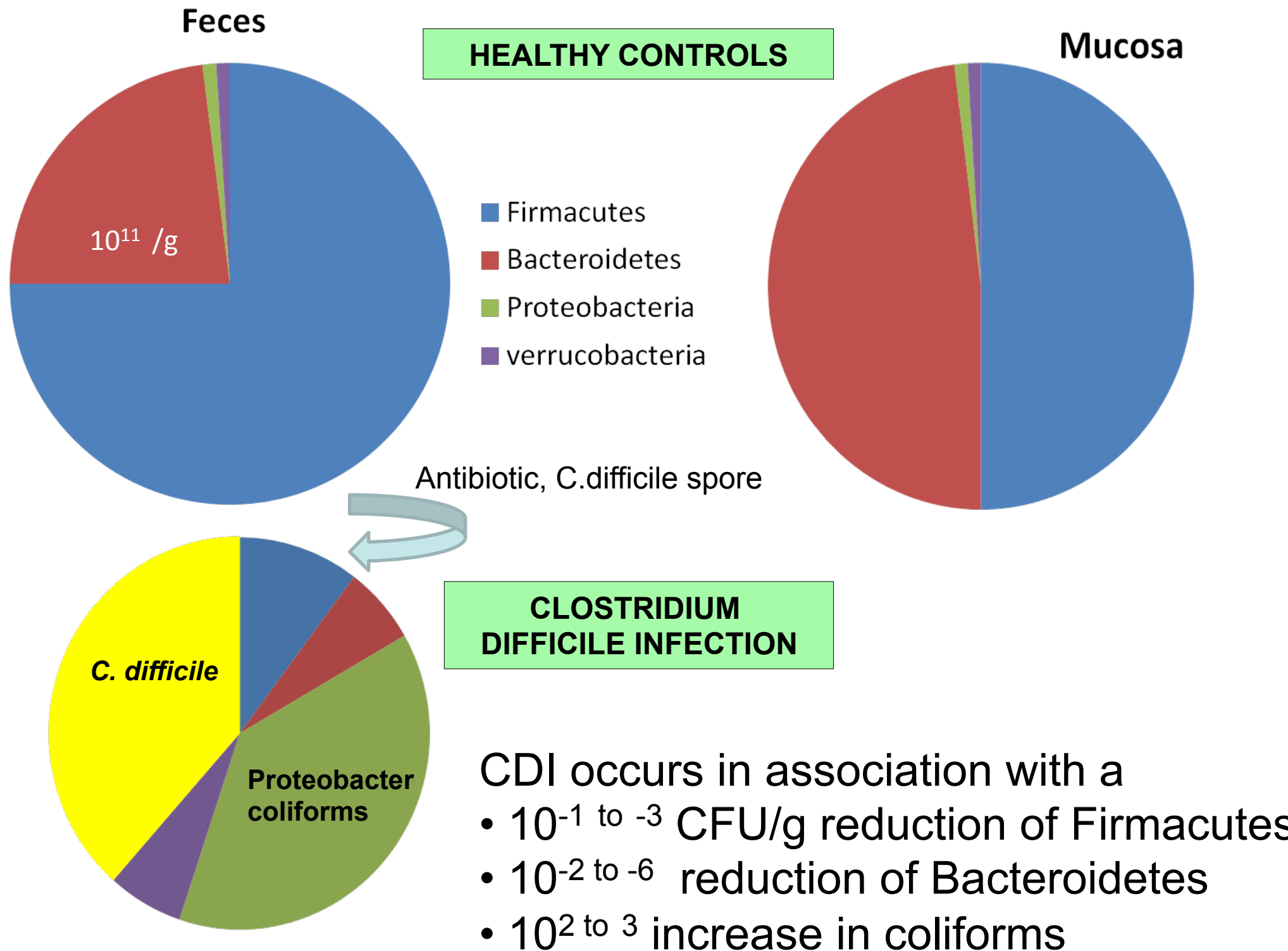
In the past 2 years I have been an employee of:	University of Calgary, Self Employed
In the past 2 years I have been a consultant of:	Clinical investigator for Cubist, Actelion, Optimer, Cempra. Advisory board for Pfizer , Merck
In the past 2 years I have held investments in the following pharmaceutical organizations, medical devices companies or communications firms:	NA
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In the past 2 years I have received honoraria from:	Cubist, Merck, Optimer, Pfizer
I agree to disclose approved and non-approved indications for medications in this presentation:	YES
I agree to use generic names of medications in this presentation:	YES

There are no relationships to disclose



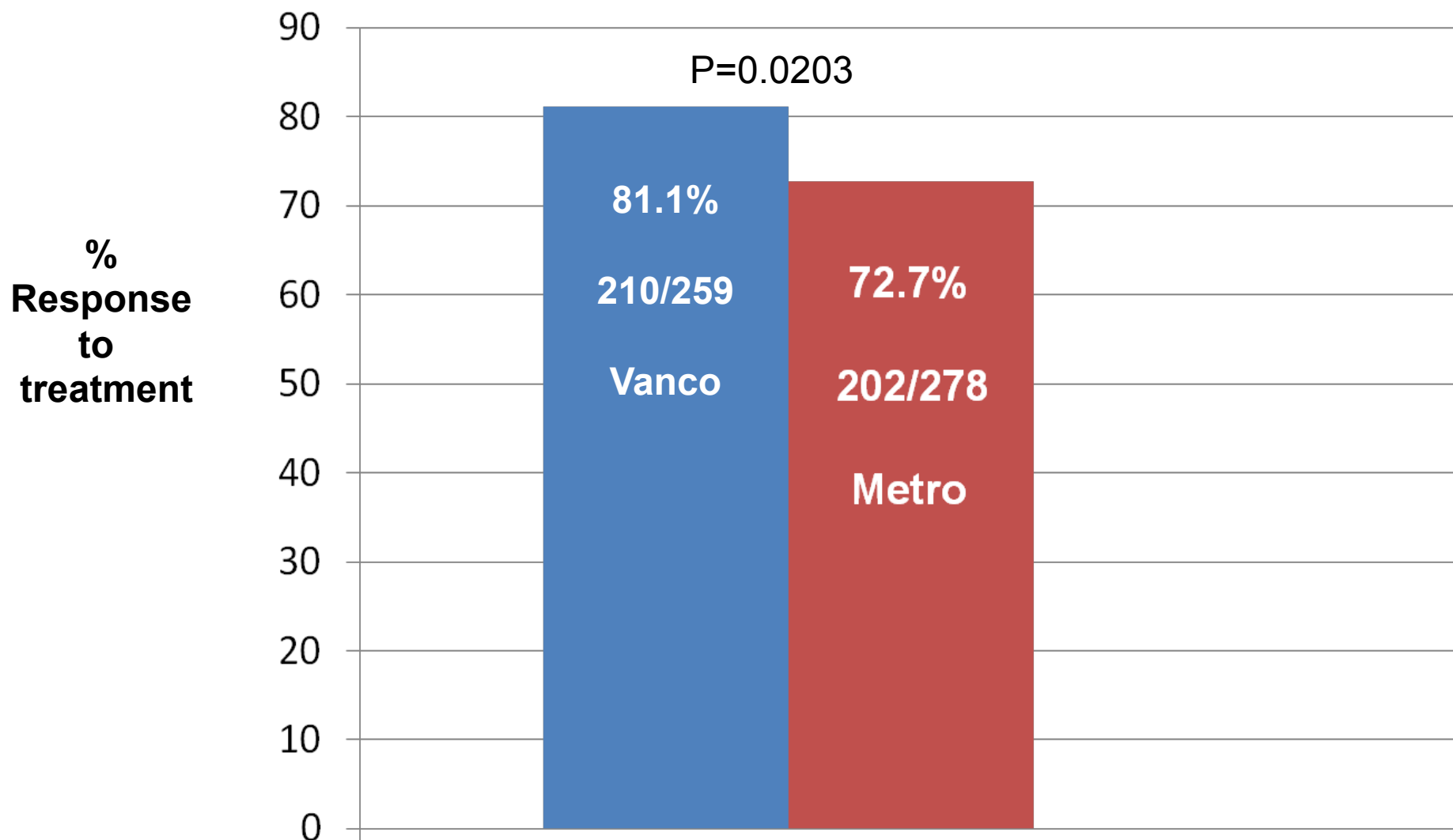
Establishing the role of components of the microbiome for the prevention and treatment of C. difficile infection.



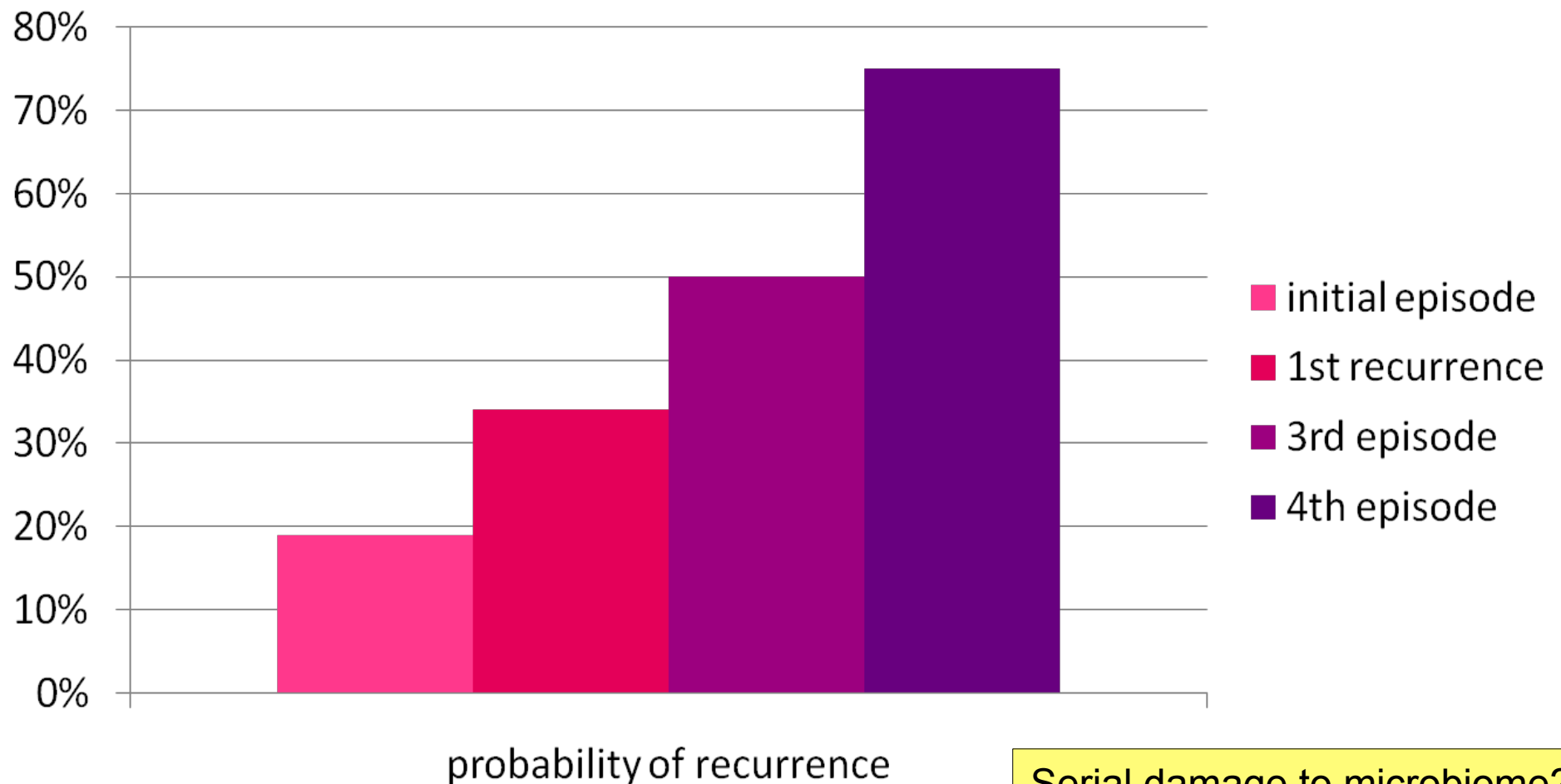


Comparison of metronidazole vs vancomycin in 2 trials

[Genzyme 301 and 302) S.Johnson et al, IDSA, San Diego, Oct 19, 2012



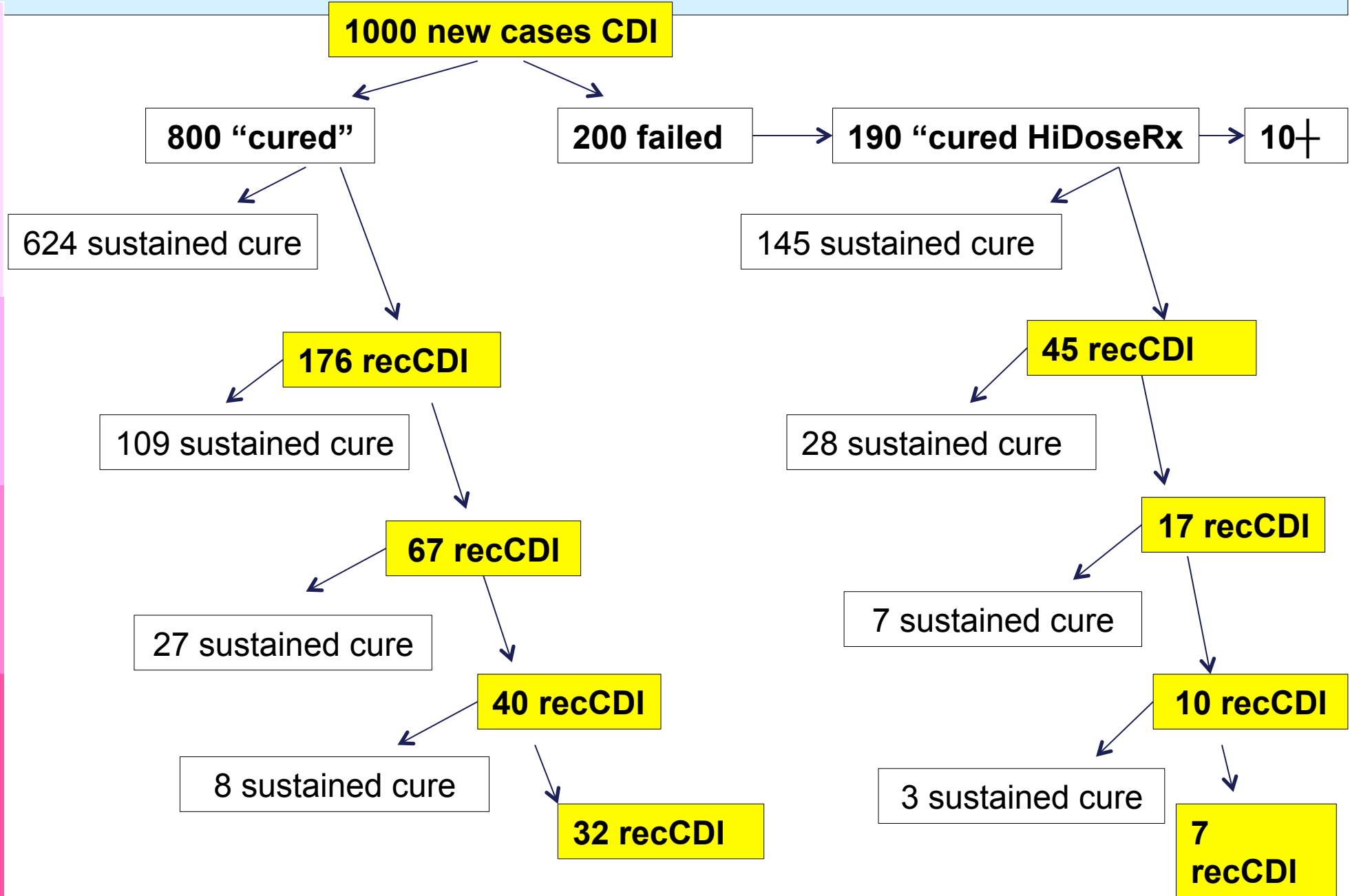
Increasing risk of recurrence of CDI after repeated recurrences; by-product is dependence on vancomycin



McFarland et al, ICHE 1999; 20: 43,
Gerding, Curr Top Microbiol Immunol 2000; 250: 127
Louie, 2011 NEJM
Van Nood, Kuijper and Keller, NEJM 2013

Serial damage to microbiome?
VS increased adherence/
persistence, biofilm, spore
density?

Treatment of 1000 cases of Clostridium difficile infection with metronidazole or vancomycin: effect of cumulative response patterns on total episodes of disease



Treatment of 1000 cases of Clostridium difficile infection with metronidazole or vancomycin: effect of cumulative response patterns on total episodes of disease

1000 new cases CDI

results in 1394 episodes of CDI

800 "cured"

200 failed

190 "cured HiDoseRx"

10+

624 sustained cure

145 sustained cure

176 recCDI

45 recCDI

109 sustained cure

28 sustained cure

67 recCDI

17 recCDI

27 sustained cure

7 sustained cure

40 recCDI

10 recCDI

8 sustained cure

3 sustained cure

32 recCDI

7
recCDI

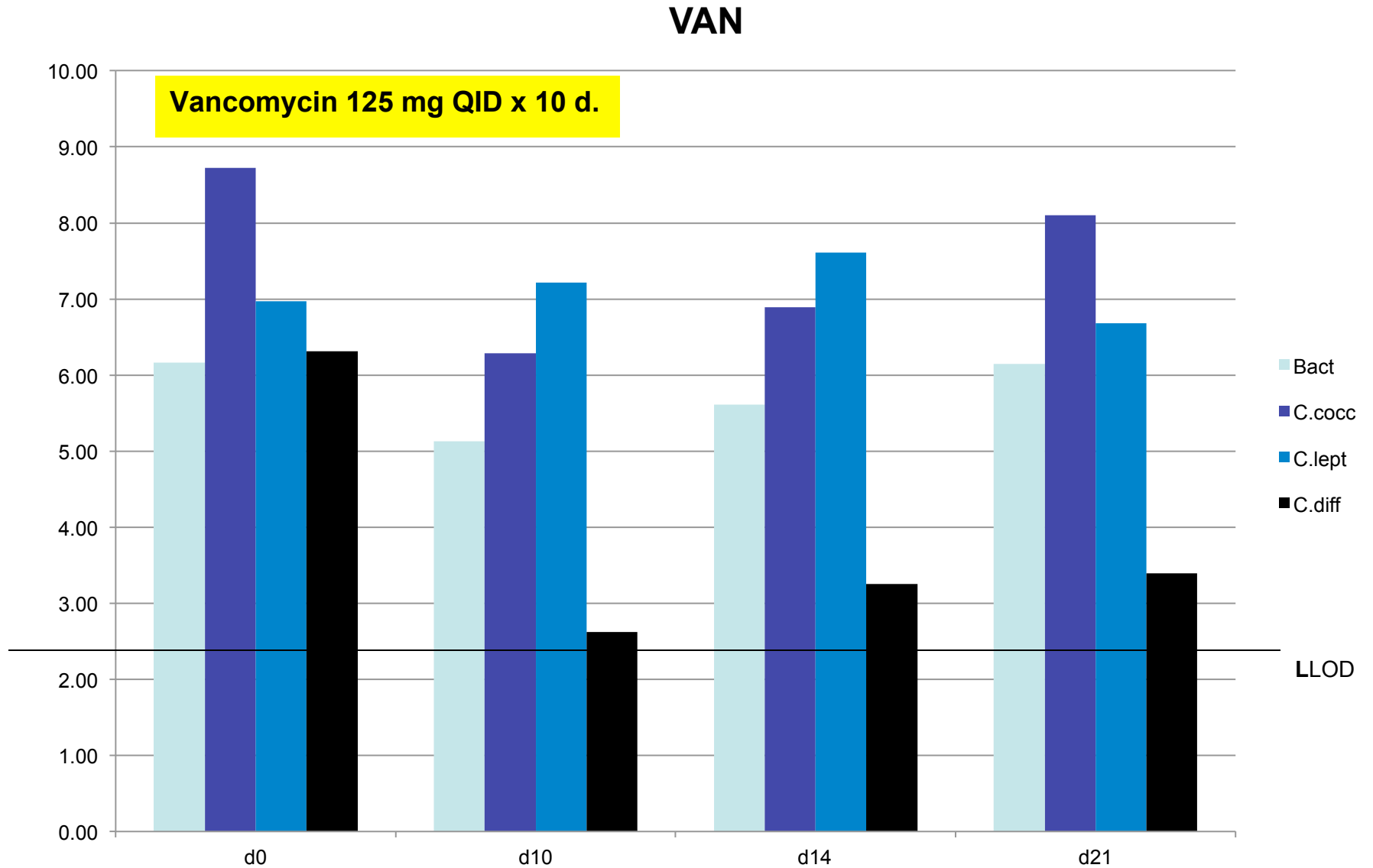
PRIMARY

1ST REC

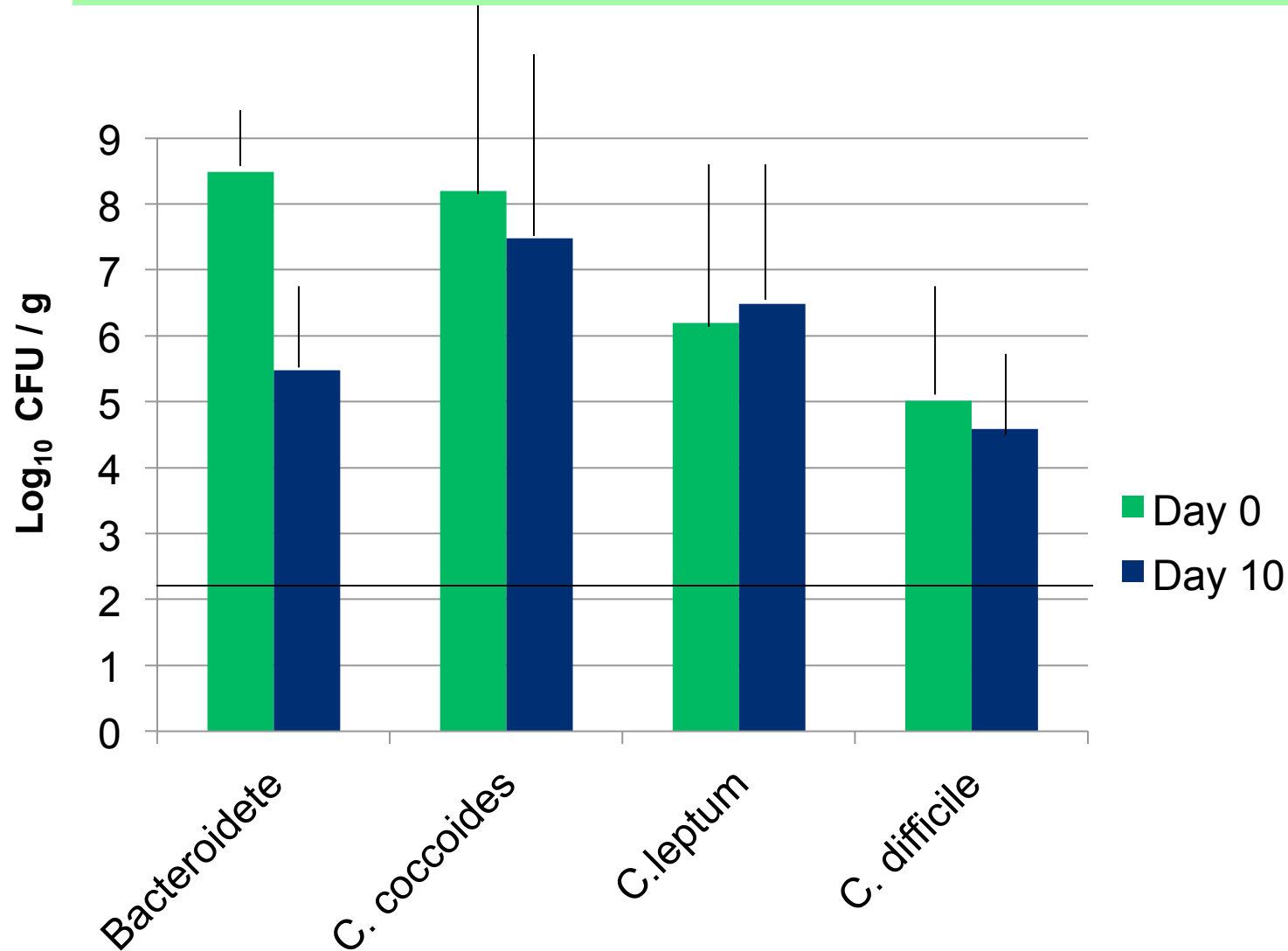
2ND rec

3 & 4th REC

Effect of Vancomycin on Bacteroidetes, C. coccoides [XIV], C.leptum and C difficile counts during and after treatment of CDI in Genzyme 301 patients

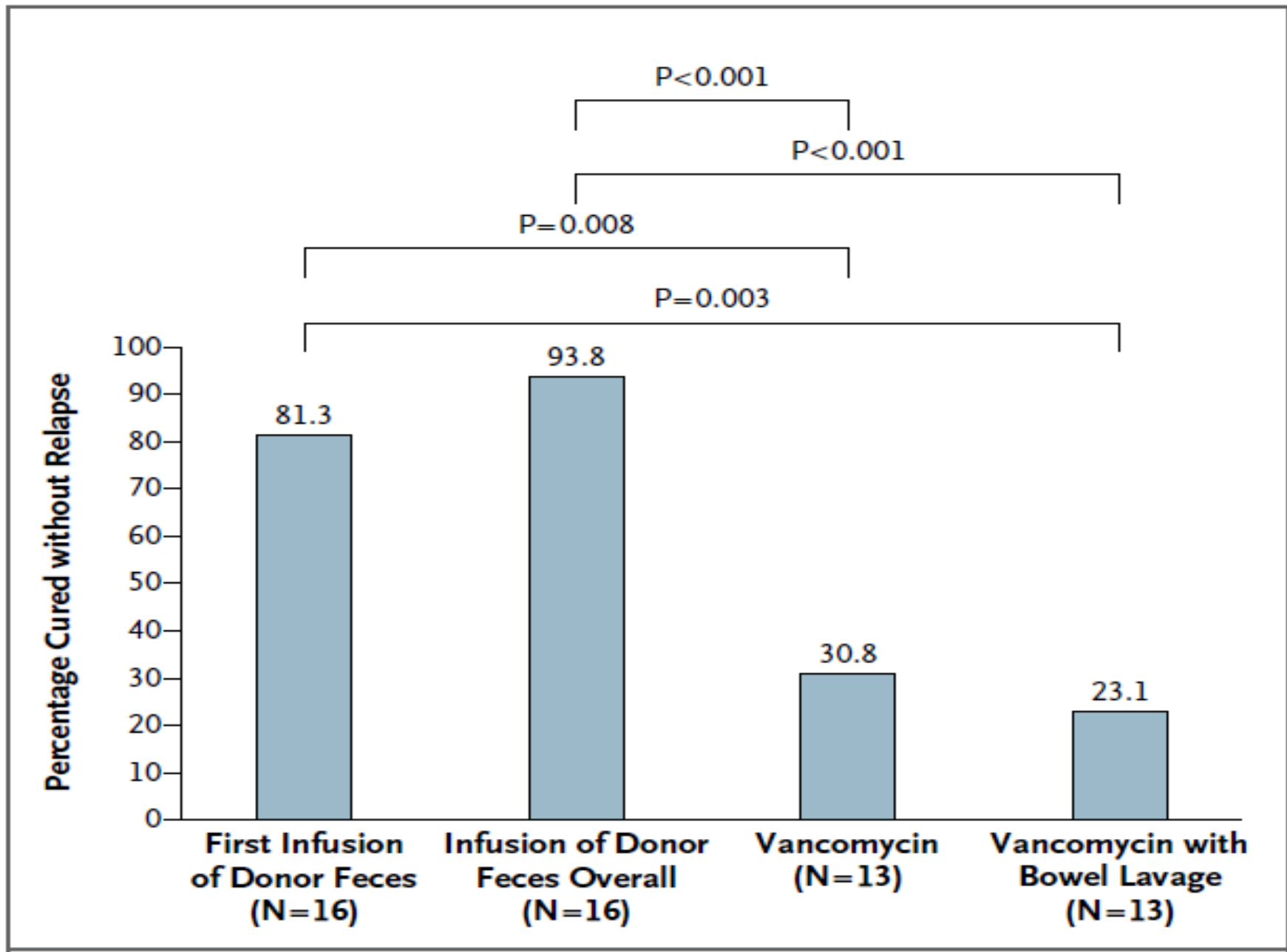


METRONIDAZOLE EFFECT ON COMPONENTS OF MICROBIOME, Genzyme 301 + met controls



Changes in 3 main component normal microbiota in patients randomized to metronidazole 375 mg QID as treatment of CDI in the Genzyme 301 study

Rates of cure of recurrent CDI. Van Nood, JJ Keller, NEJM Jan 2013



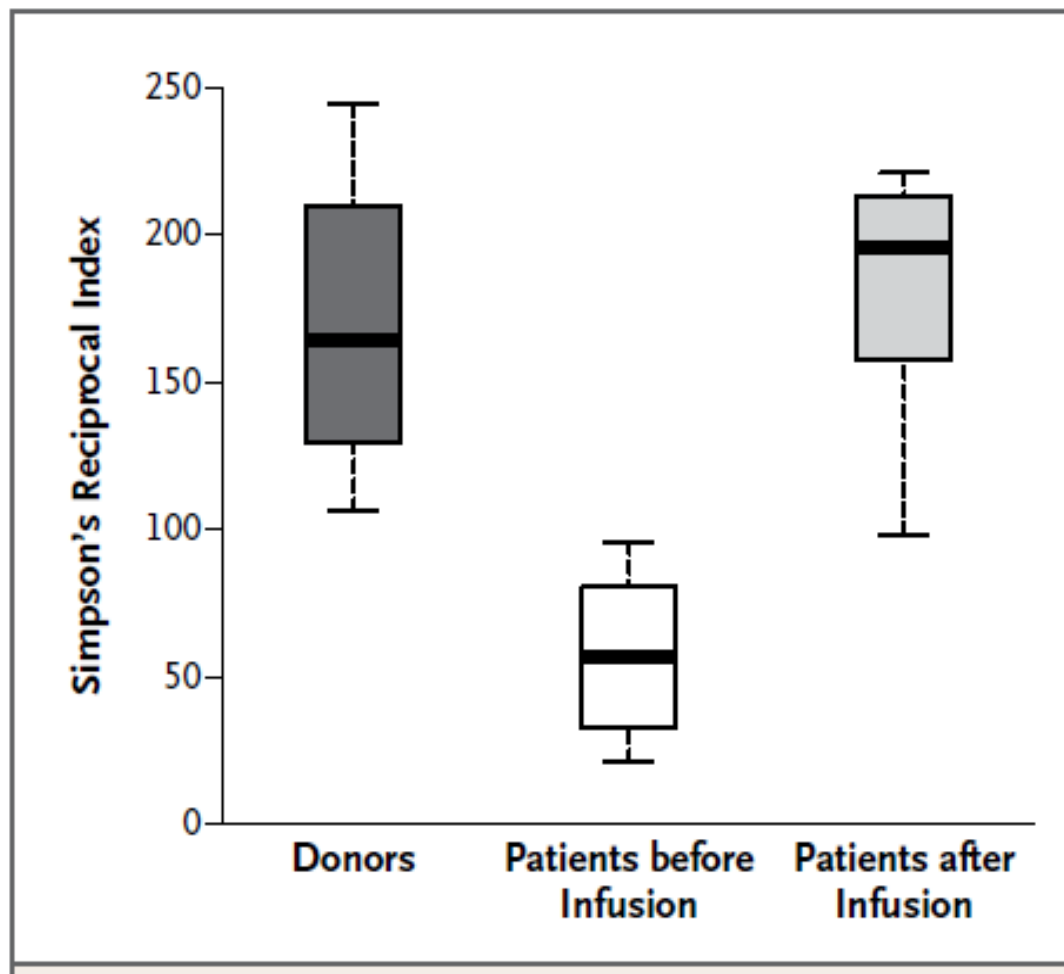
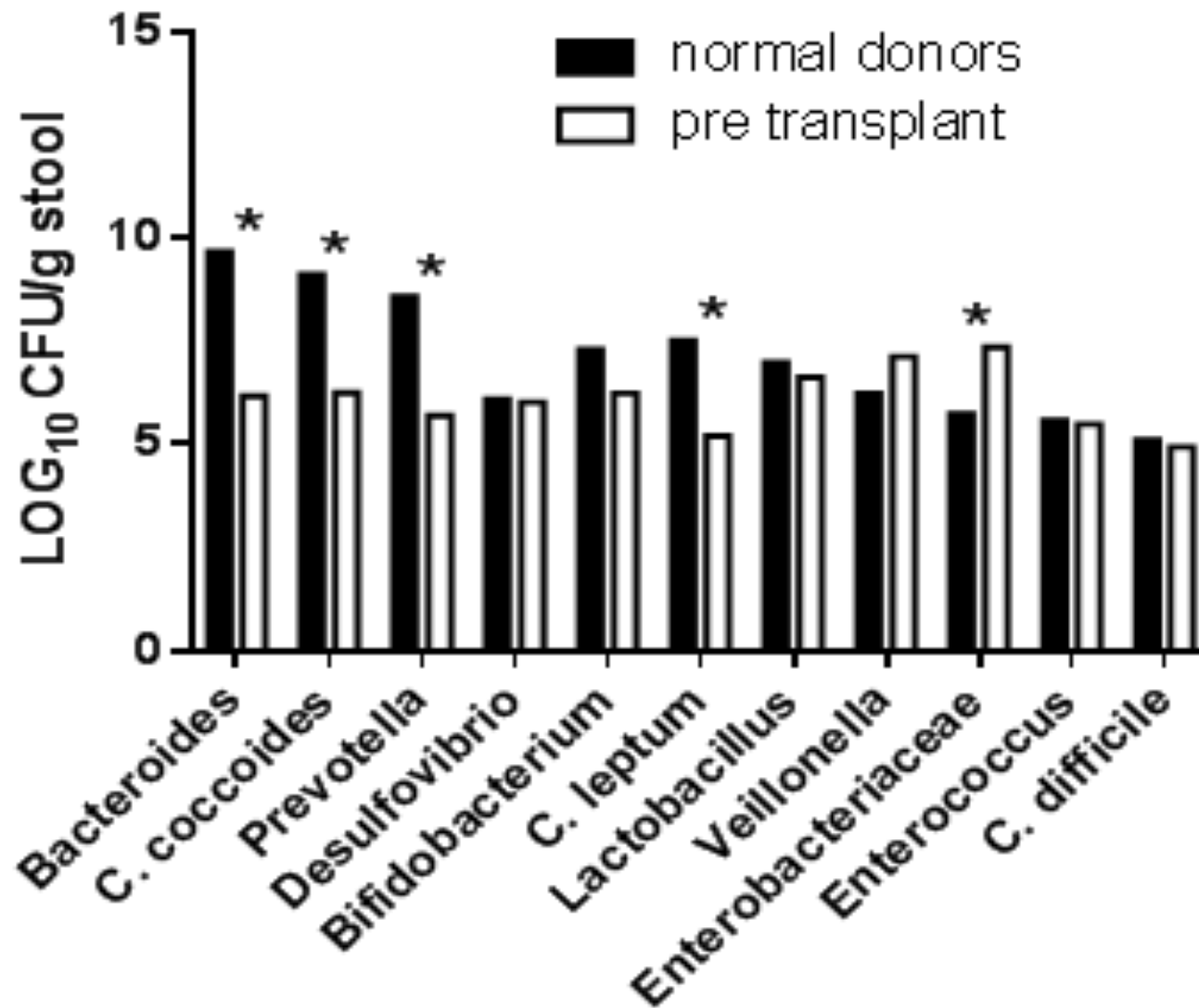


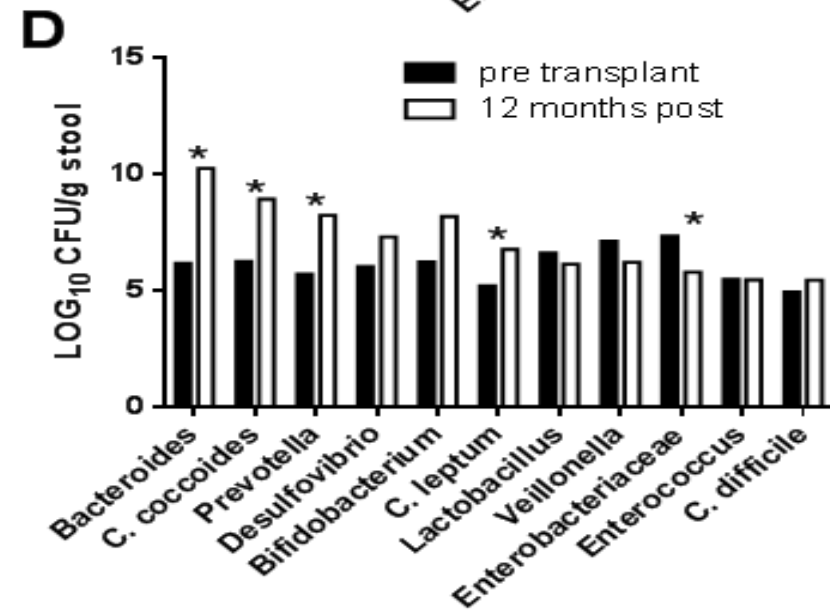
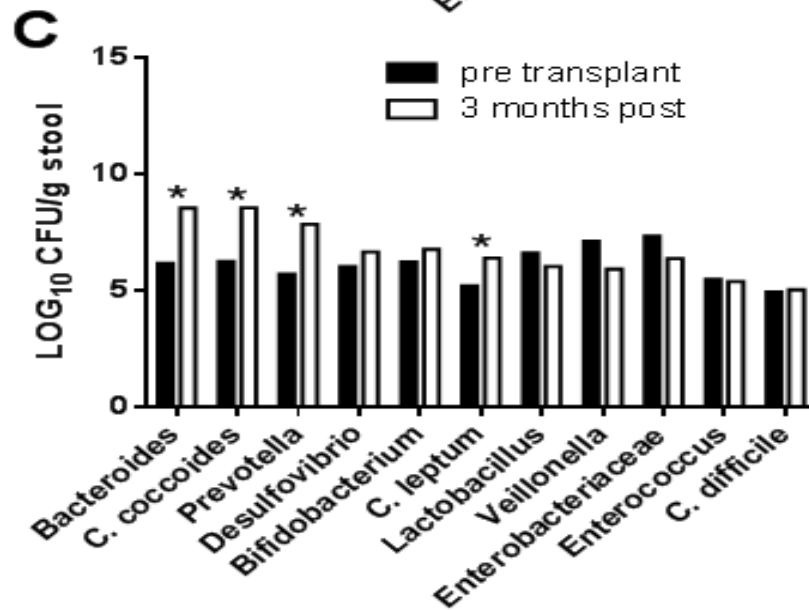
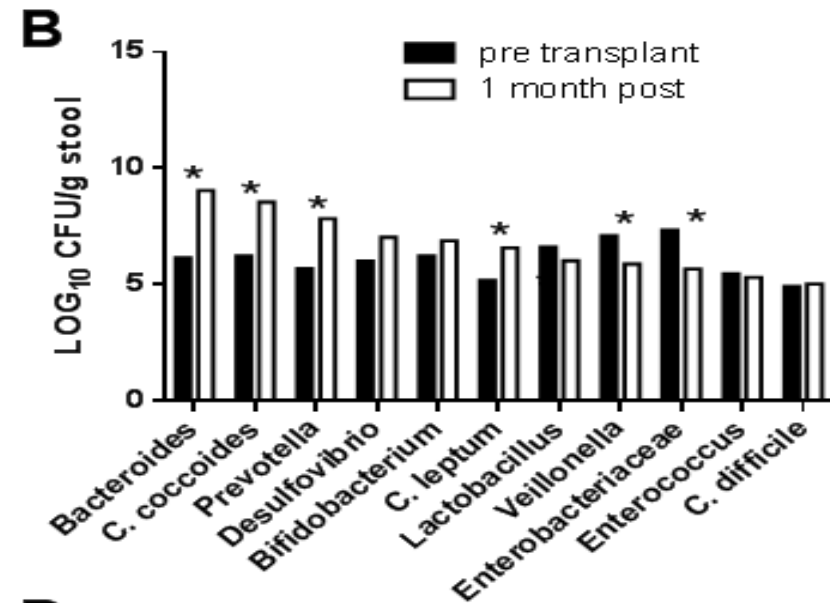
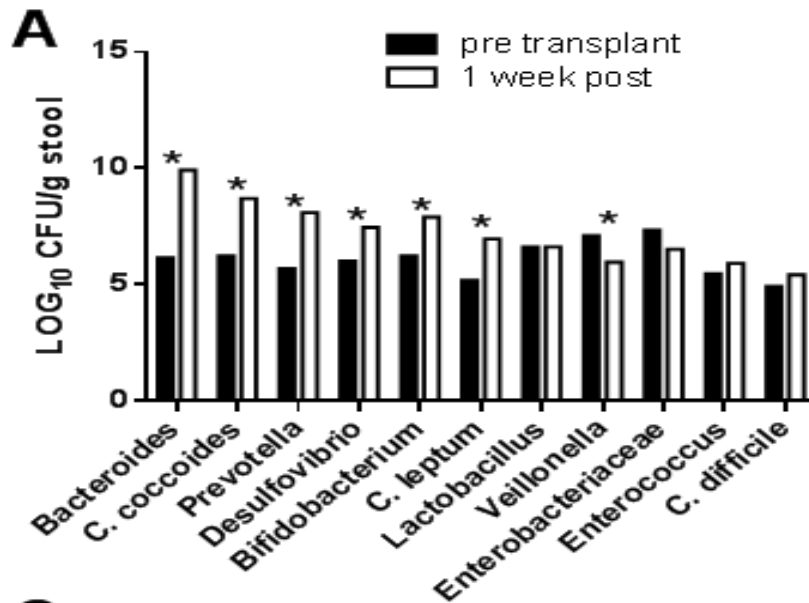
Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

Microbiota diversity is expressed as Simpson's Reciprocal Index of diversity in fecal samples obtained from nine patients before and 14 days after the first infusion of donor feces, as compared with their donors. The index ranges from 1 to 250, with higher values indicating more diversity. The box-and-whisker plots indicate interquartile ranges (boxes), medians (dark horizontal lines in the boxes), and highest and lowest values (whiskers above and below the boxes).

qPCR analysis of the gut microflora in normal donors and *C. difficile* infected patients. CFU, colony forming units,* $p < 0.05$, LLOD 10^{3-4}

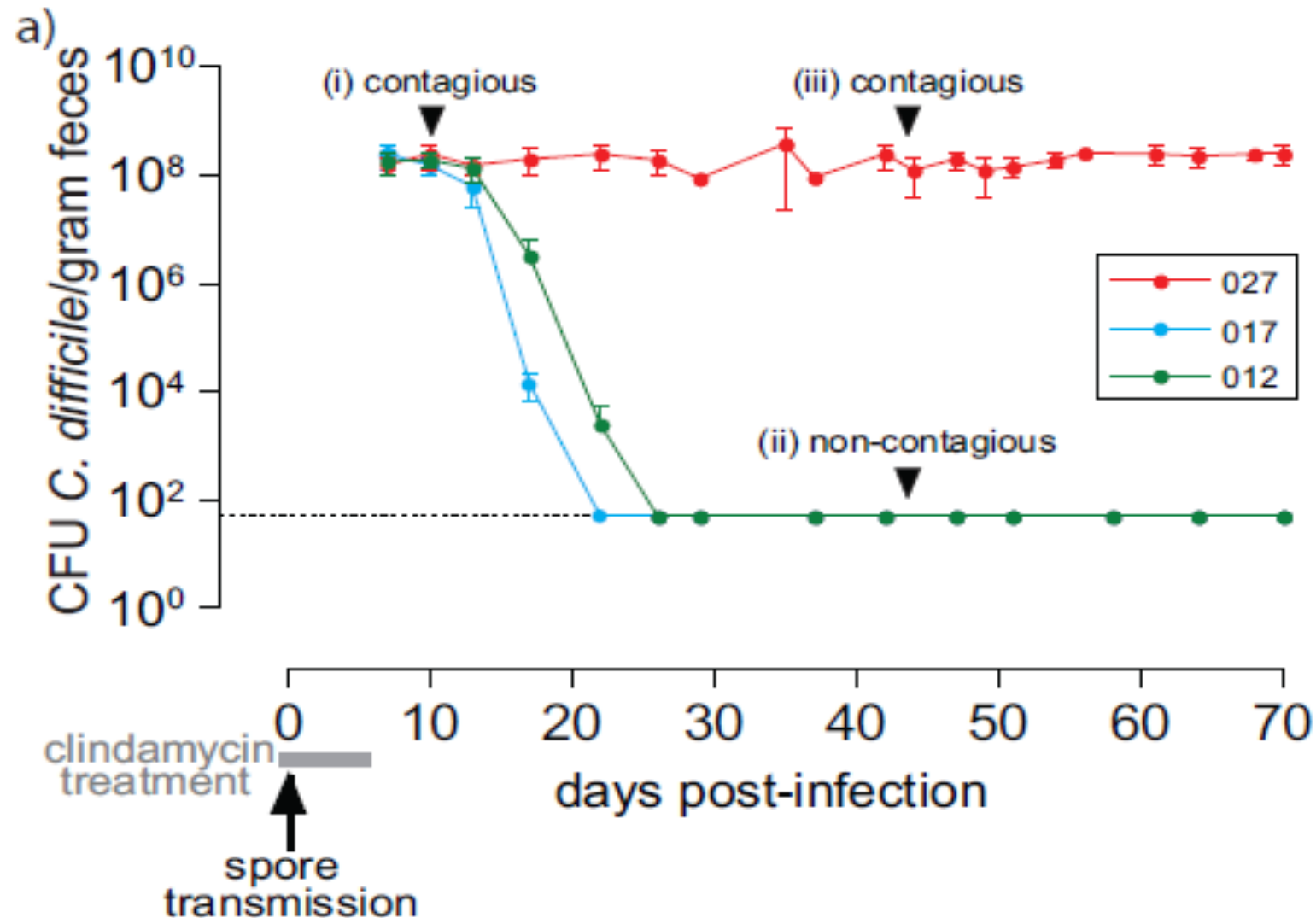


qPCR analysis of the gut microflora in *C. difficile* infected patients pre and over time post bacteriotherapy. Pre therapy microflora levels are compared to (A) 1 week, (B) 1 month, (C) 3 months and (D) up to 1 year post bacteriotherapy. CFU, colony forming units,* $p < 0.05$.

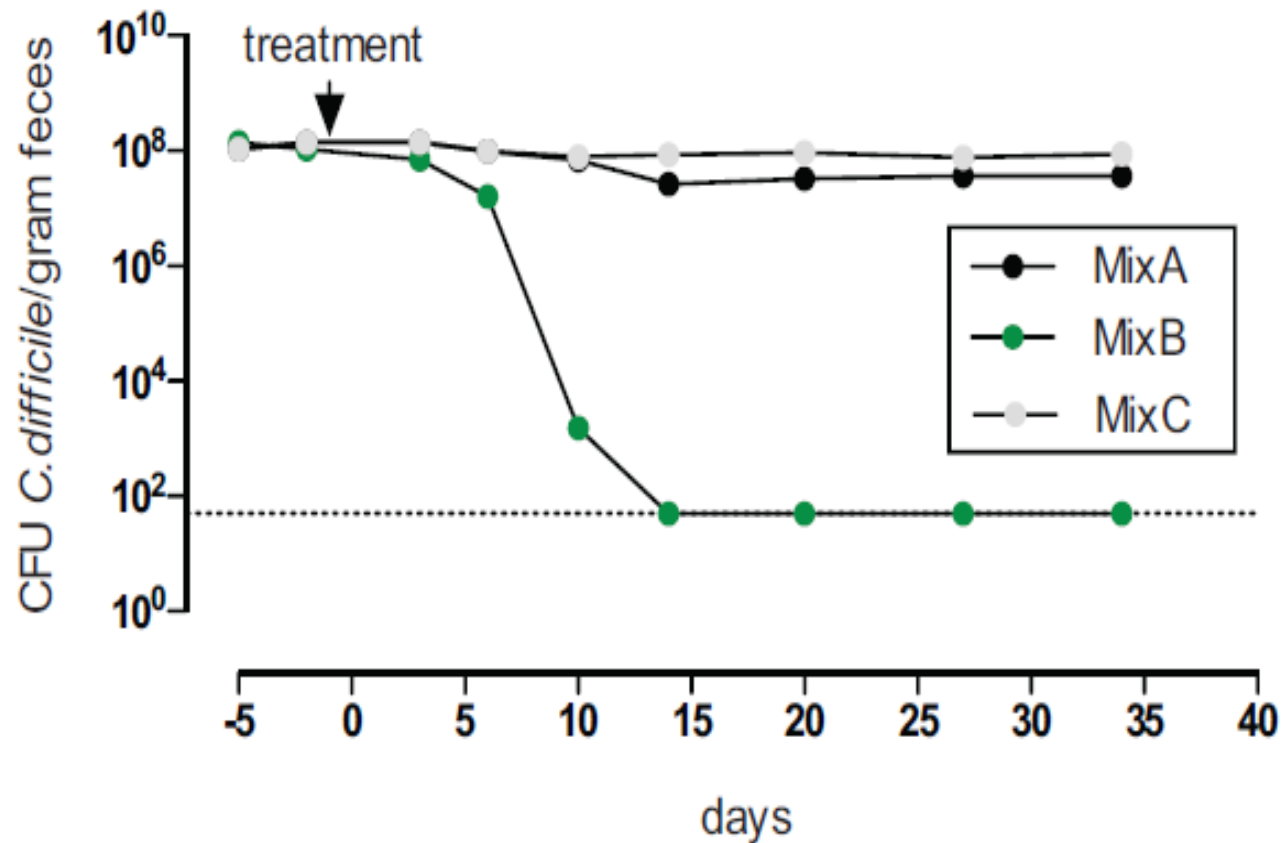


N=28; 800 ml fecal slurry x 1, or 12-17 ml of pelleted and resuspended fecal microbes orally x1.

Lawley et al, Plos Pathogens, October 2012. Ribotype 027 persists post infection in C57BL mice, whereas ribotype 012 [630], and 017 [toxAneg] clear spontaneously. 027 is a special strain type. All strains were clindamycin R/ermB pos.



Mix B [*Bacteroides* sp nov, *Enterorhabdus* sp, *E. Hirae*, *Lactobac. Reuteri*, *S. Warneri*, *Anaerostipes* sp.nov] clears supershedder state in C57BL/6 mice post *Cdiff* infection by 027 spores/clindamycin. Mix A and C are dual organism combinations. Lawley et al, Plos Pathogens Oct 2012.



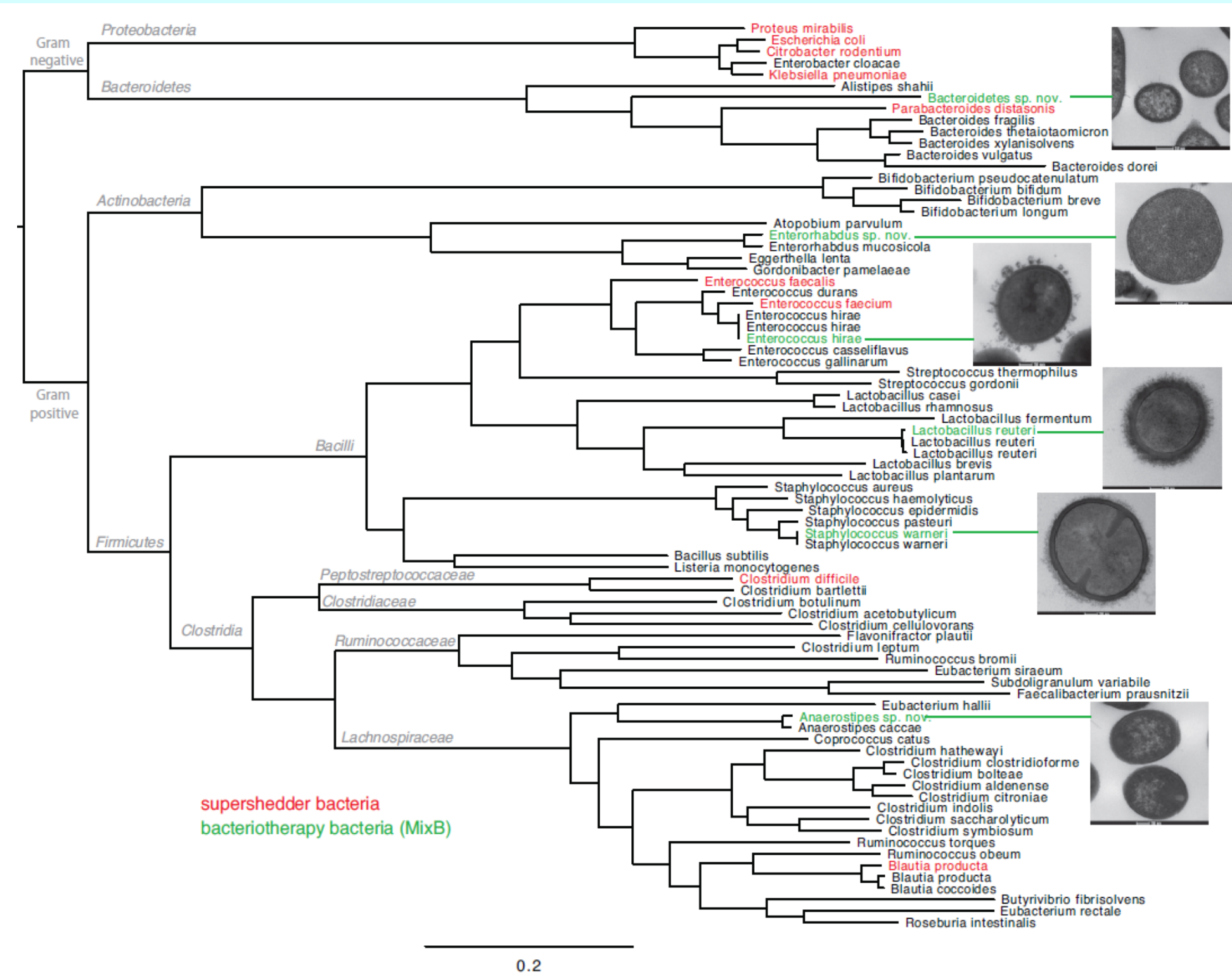


Table 3. Antagonism of *Clostridium difficile* in gnotobiotic mice inoculated with various indigenous bacteria

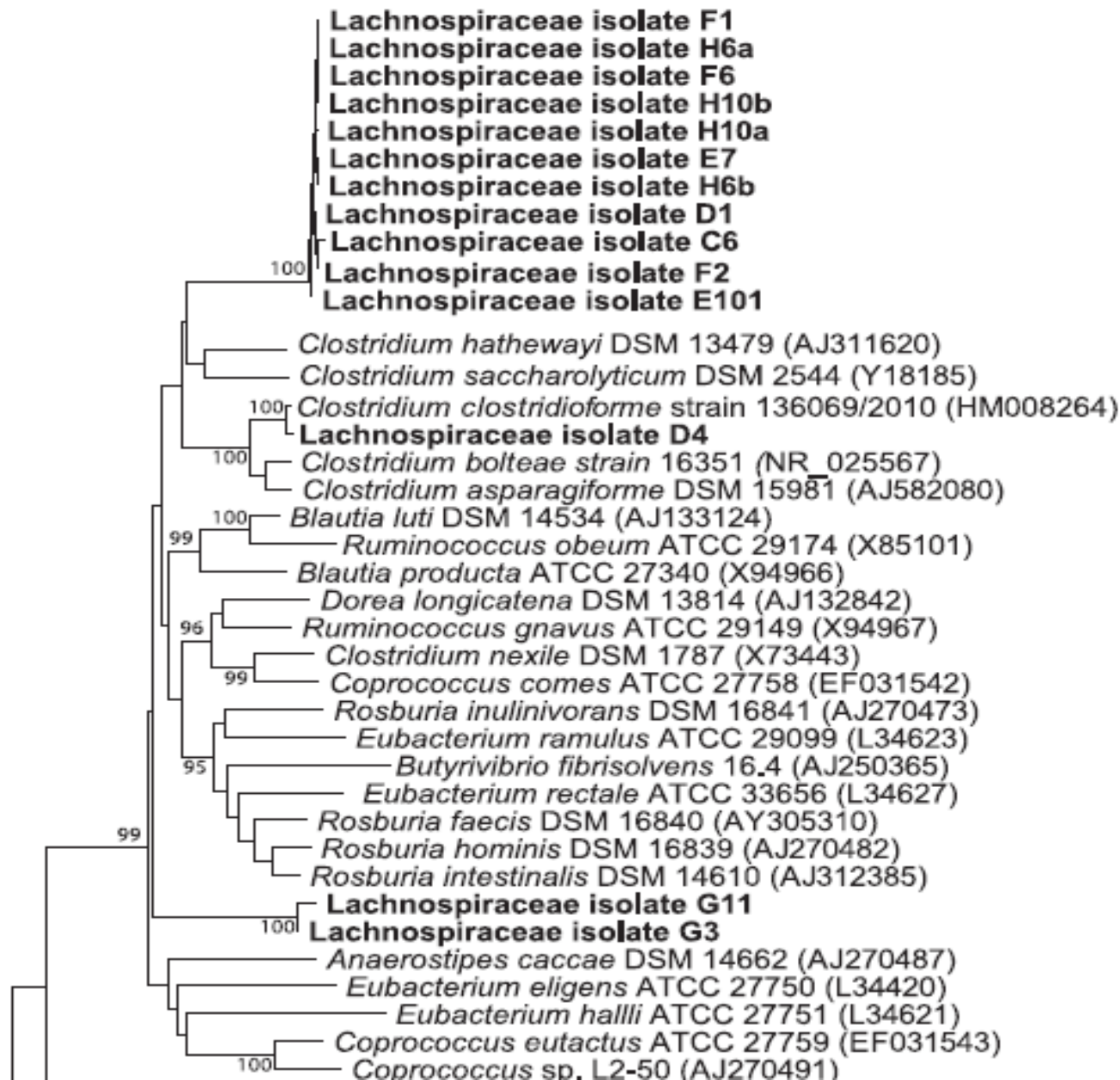
<i>Flora of gnotobiotic mice</i>	<i>Days after inoculation with C. difficile</i>	
	3 (N = 5)	7 (N = 7)
<i>E. coli</i> + faeces of CV mice	< 3.0 (0)	< 3.0 (0)
<i>E. coli</i> + CHF faeces of CV mice	< 3.0 (0)	< 3.0 (0)
<i>E. coli</i> + faeces of LF mice	< 3.0 (0)	< 3.0 (0)
<i>E. coli</i> + clostridia (F strains)	7.1 ± 0.32 (5) ^a	7.2 ± 0.27 (7)
<i>E. coli</i> + lactobacilli (L strains)	7.7 ± 0.11 (5)	8.1 ± 0.17 (7)
<i>E. coli</i> + bacteroides (B strains)	7.5 ± 0.32 (5)	8.0 ± 0.44 (7)
(<i>C. difficile</i> monoassociation)	8.4 ± 0.16 (5)	8.8 ± 0.05 (7)

^aMean count (log₁₀) ± SD of *C. difficile* per gram of faeces when present; values in parentheses refer to the number of mice yielding the organisms.

Itoh, Lee, Kawamura. Lab. Animals 1987; 21:20-25

DATA FAVORS CLOSTRIDIAL ORGANISMS

Lachnospiraceae spp limits severity of disease in CD challenged mice



Clostridial
cluster XIV
represent by
C.coccoides
probe.

XIVa

Table 1 Composition of stool substitute (RePOOPulate)

Closest species match, inferred by alignment
of 16S rRNA sequence to GreenGenes database^a

Acidaminococcus intestinalis

Bacteroides ovatus

Bifidobacterium adolescentis (two different strains)

Bifidobacterium longum (two different strains)

Blautia producta

Clostridium cocleatum

Collinsella aerofaciens

Dorea longicatena (two different strains)

Escherichia coli

Eubacterium desmolans

Eubacterium eligens

Eubacterium limosum

Eubacterium rectale (four different strains)

Repopulate : Emma Allen-Vercoe
and Elaine Petrof, U Guelph and
Queens U, respectively. Microbiome
2013.

Eubacterium ventriosum

Faecalibacterium prausnitzii

Lachnospira pectinoshiza

Lactobacillus casei/paracasei

Lactobacillus casei

Parabacteroides distasonis

Raoultella sp.

Roseburia faecalis

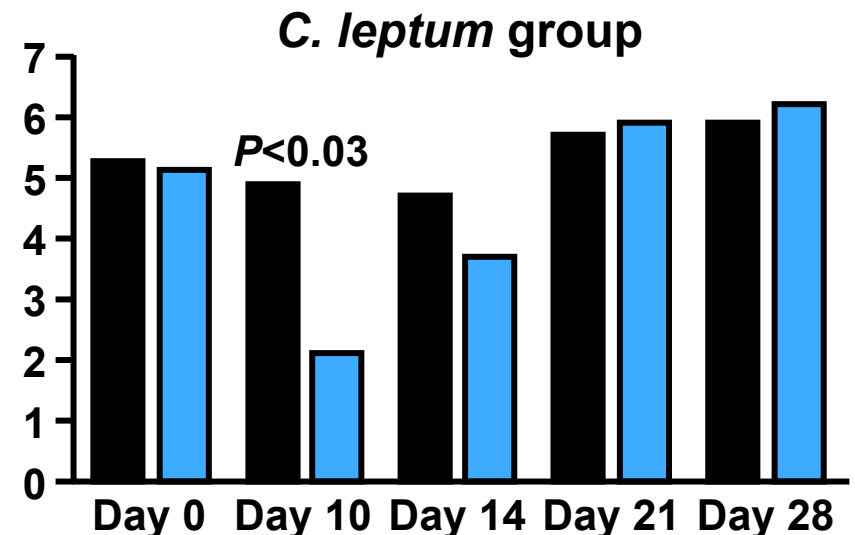
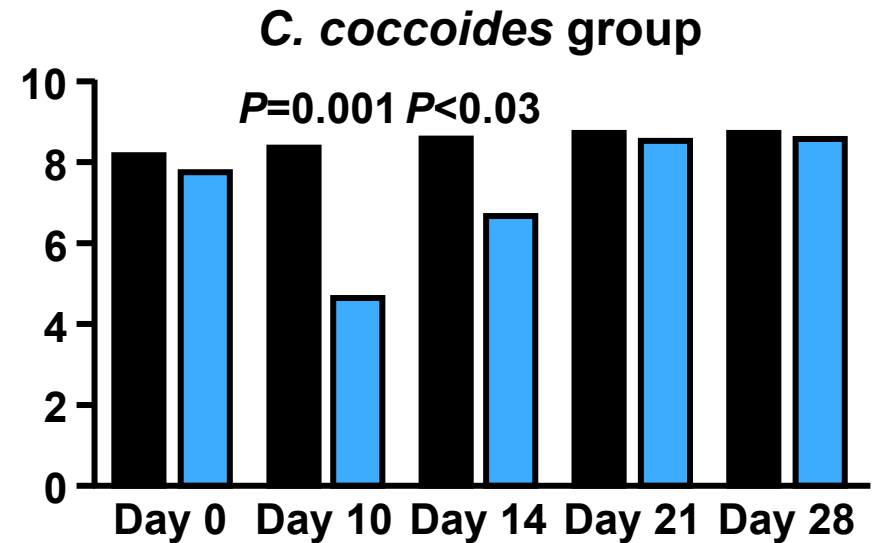
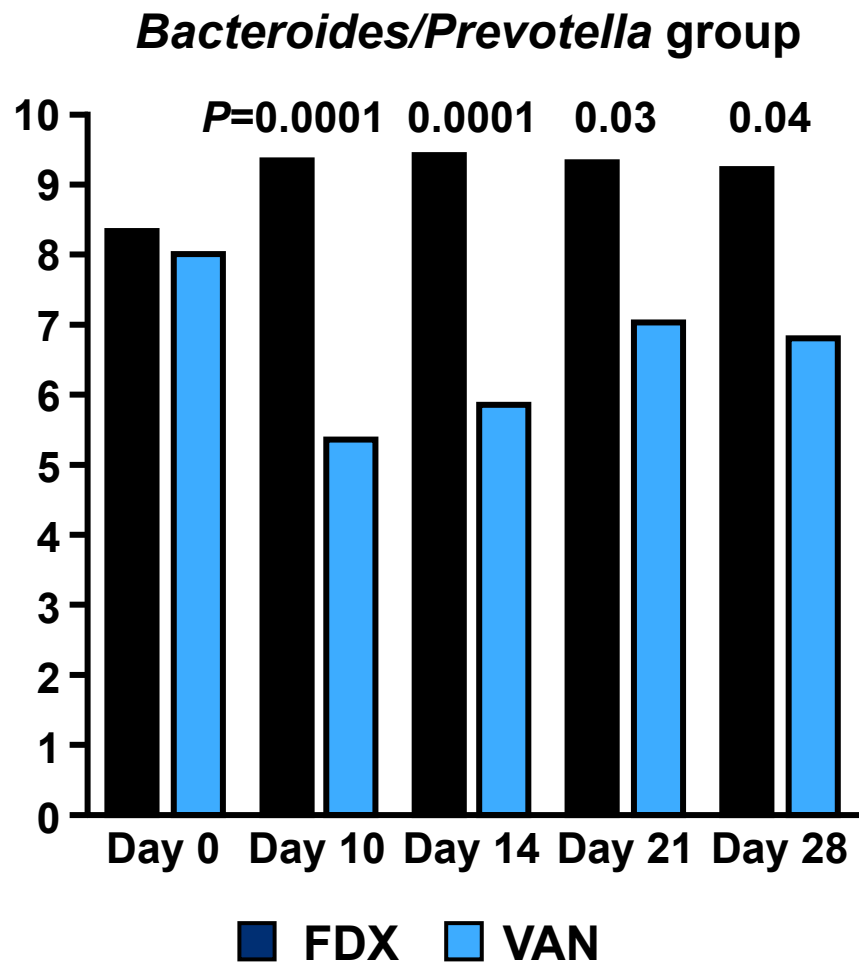
Roseburia intestinalis

Ruminococcus torques (two different strains)

Ruminococcus obeum (two different strains)

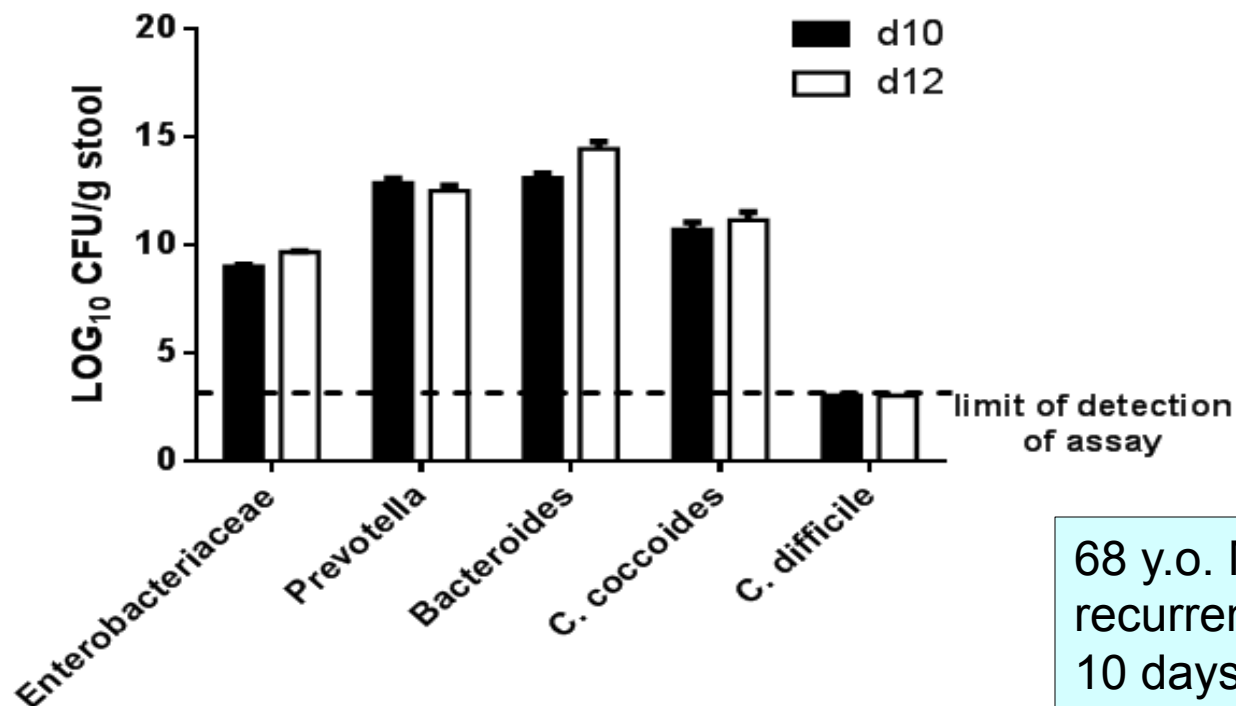
Streptococcus mitis^b

Log₁₀ CFU/gm Feces of Major Cultivable and Noncultivable Genera of the Normal Fecal Microbiota; n=20 (Fidaxomicin phase 3 [003] protocol)



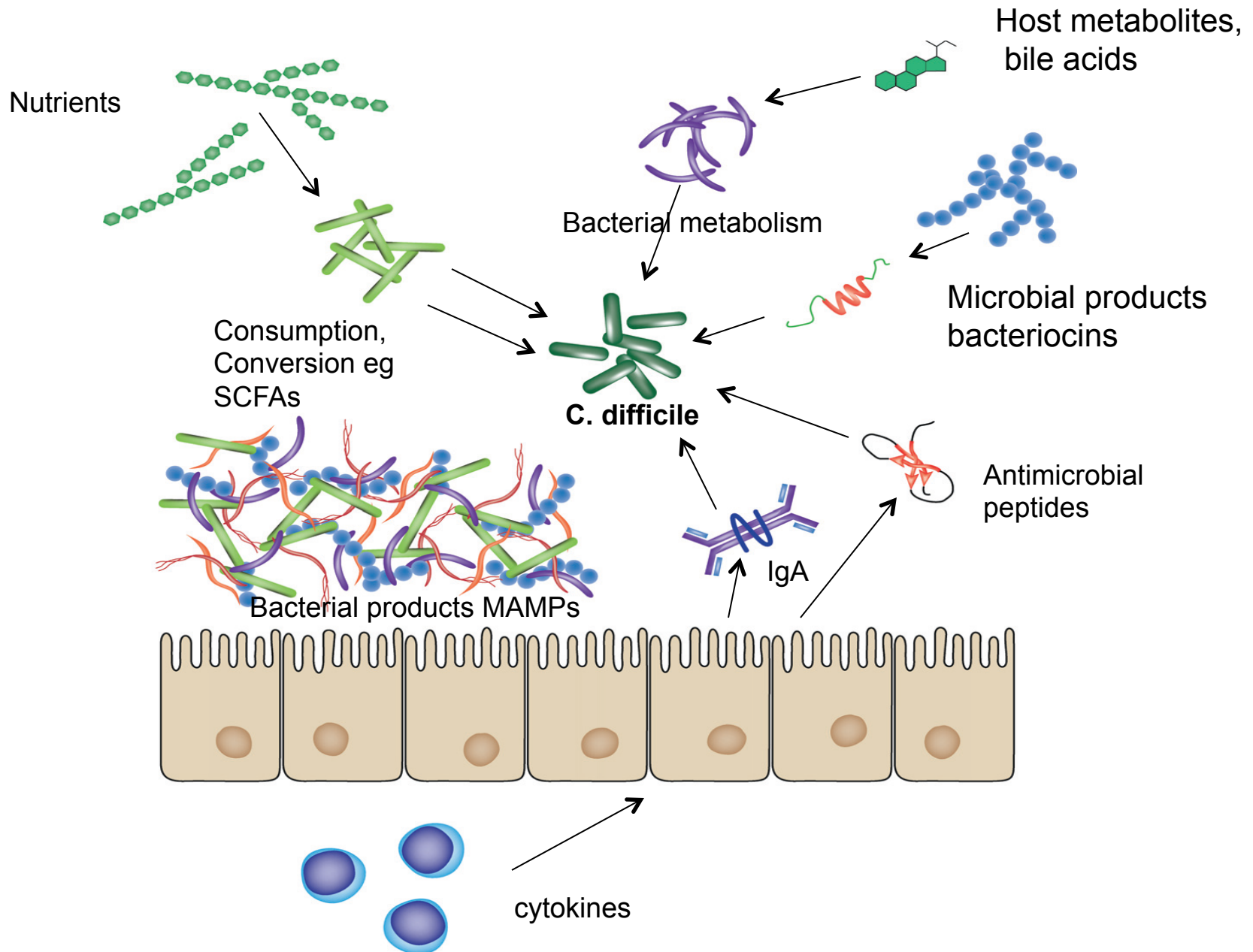
Off label use of fidaxomicin

- Use as a fidaxomicin 'chaser', following vancomycin [Johnson & Gerding, CID jan. 2013]
- Treatment of multiple recurrent CDI. Will 10 days BID work? Longer? Taper dose?

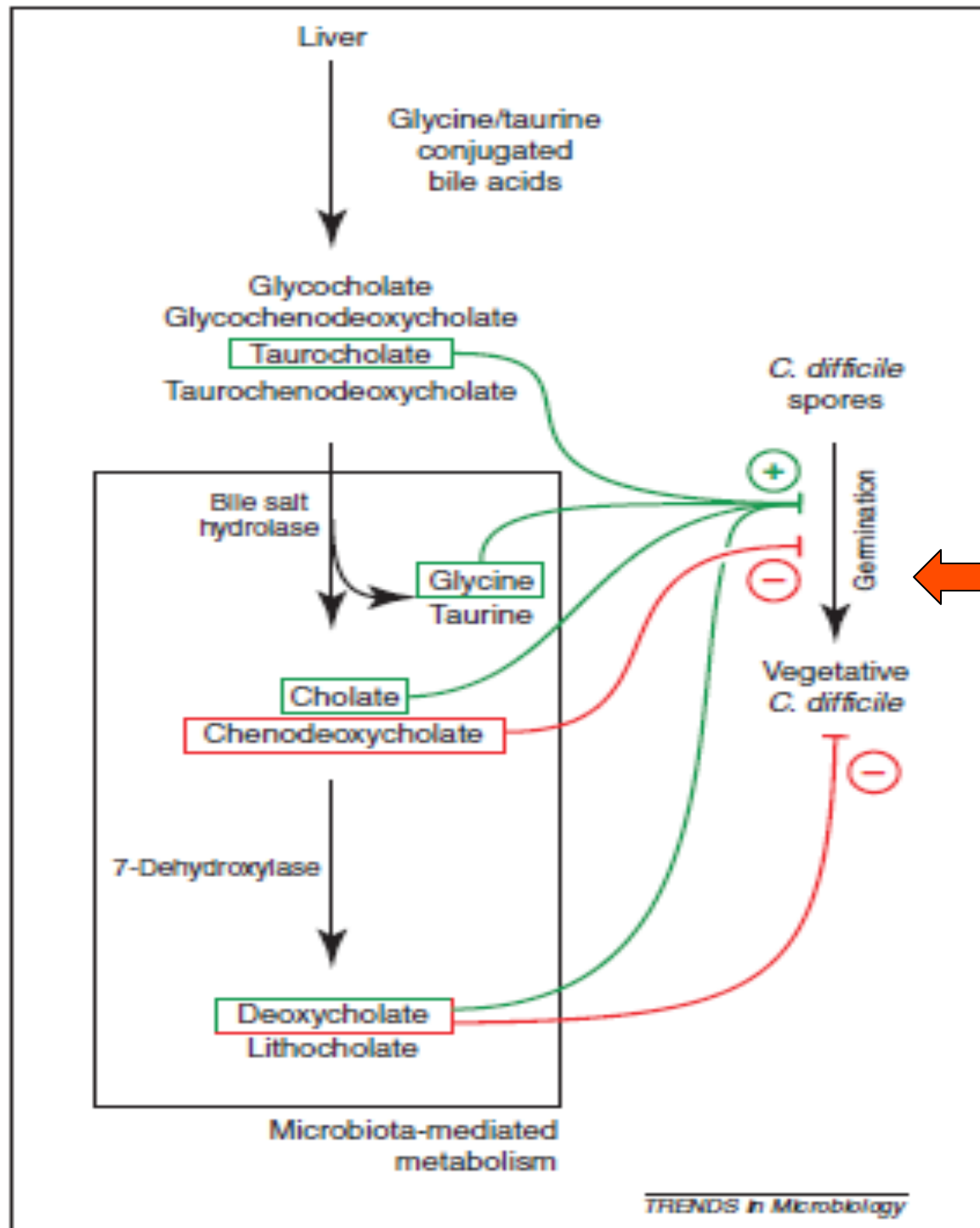


68 y.o. M with 5 recurrence, treated with 10 days of FDX.

Strategies to maintain colonization resistance against *C. difficile*.



Bile Acid metabolism and control of CD sporulation



CamSA, a cholate-meta-benzene sulfonic derivative blocks taurocholate stimulation of germination. Infected mice are prevented from illness. JID 2013 E. Abel – Santos, UNLV

Establishing the role of components of the microbiome for the prevention and treatment of C. difficile infection.

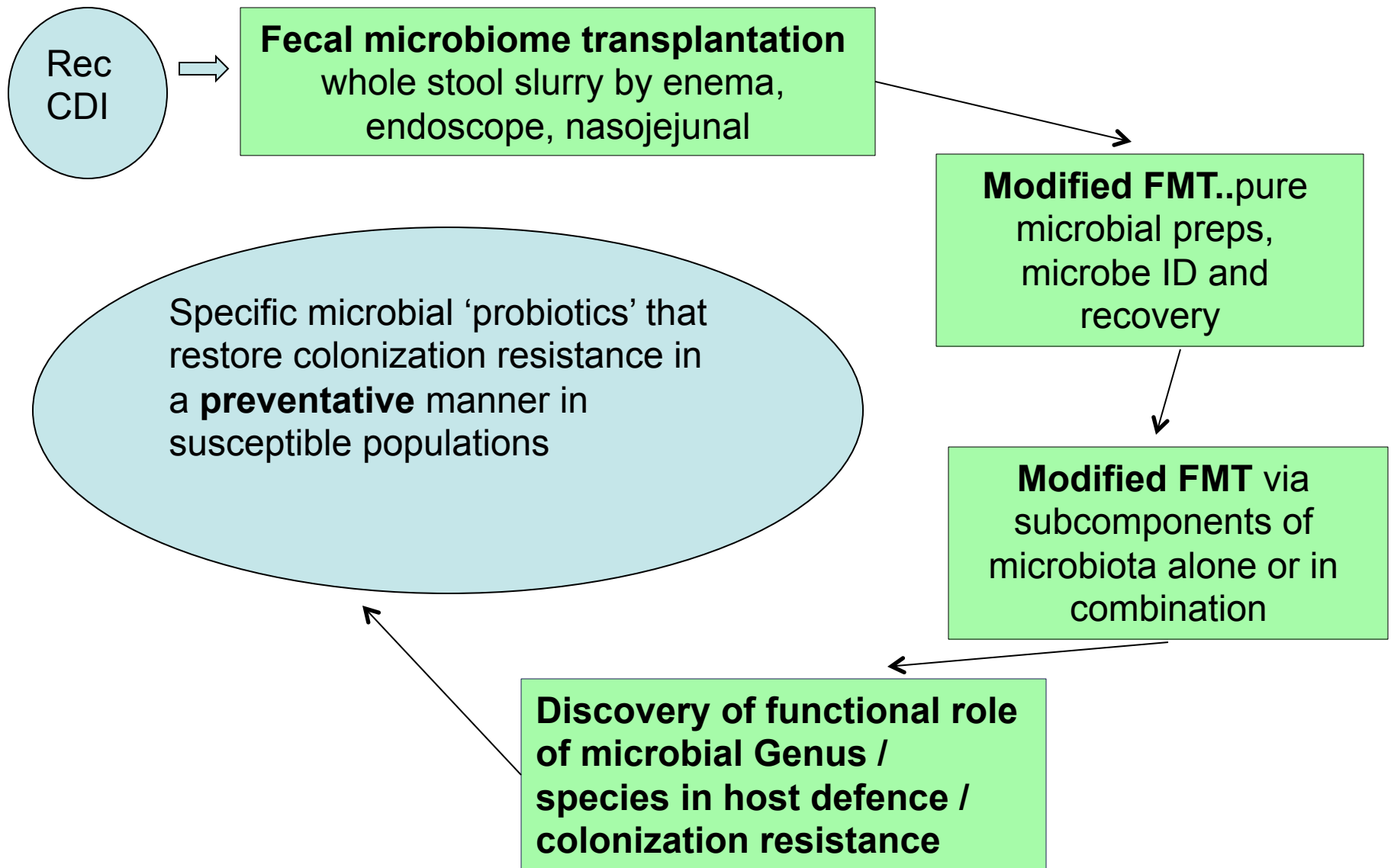
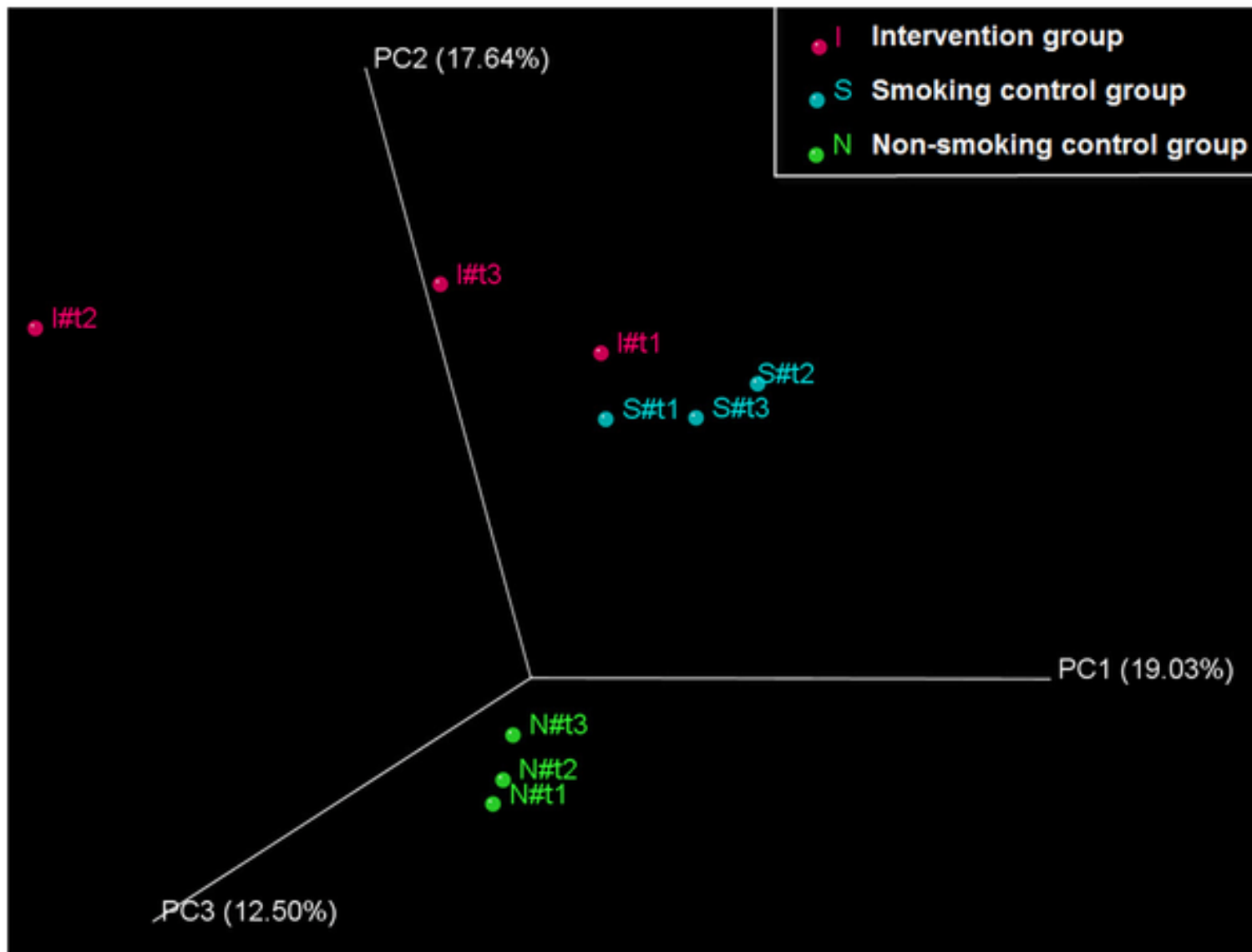


Figure 2. Phylogeny-based Principal Component Analysis.



Biedermann L, Zeitz J, Mwinyi J, Sutter-Minder E, et al. (2013) Smoking Cessation Induces Profound Changes in the Composition of the Intestinal Microbiota in Humans. PLoS ONE 8(3): e59260. doi:10.1371/journal.pone.0059260
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0059260>