Microbiota and Microbiota Restoration for Recurrent C. diff Infections

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Helping people live better lives

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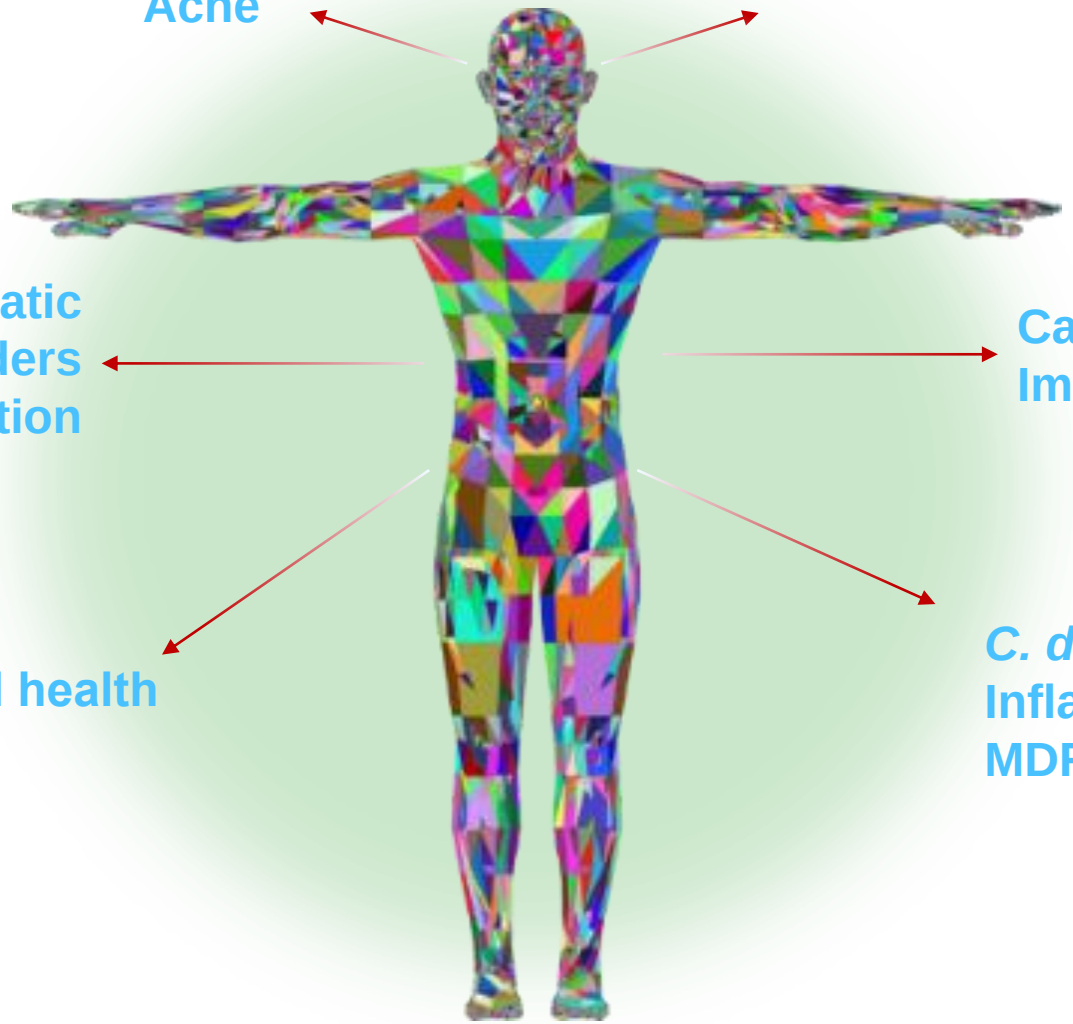
We All Have a Microbiome

Skin microbiome;
Acne

Gut-brain axis



Metabolic & hepatic
disorders
Insulin regulation

Cardiology
Immuno-oncology

Women's/maternal health

C. difficile infections
Inflammatory diseases
MDRO colonization

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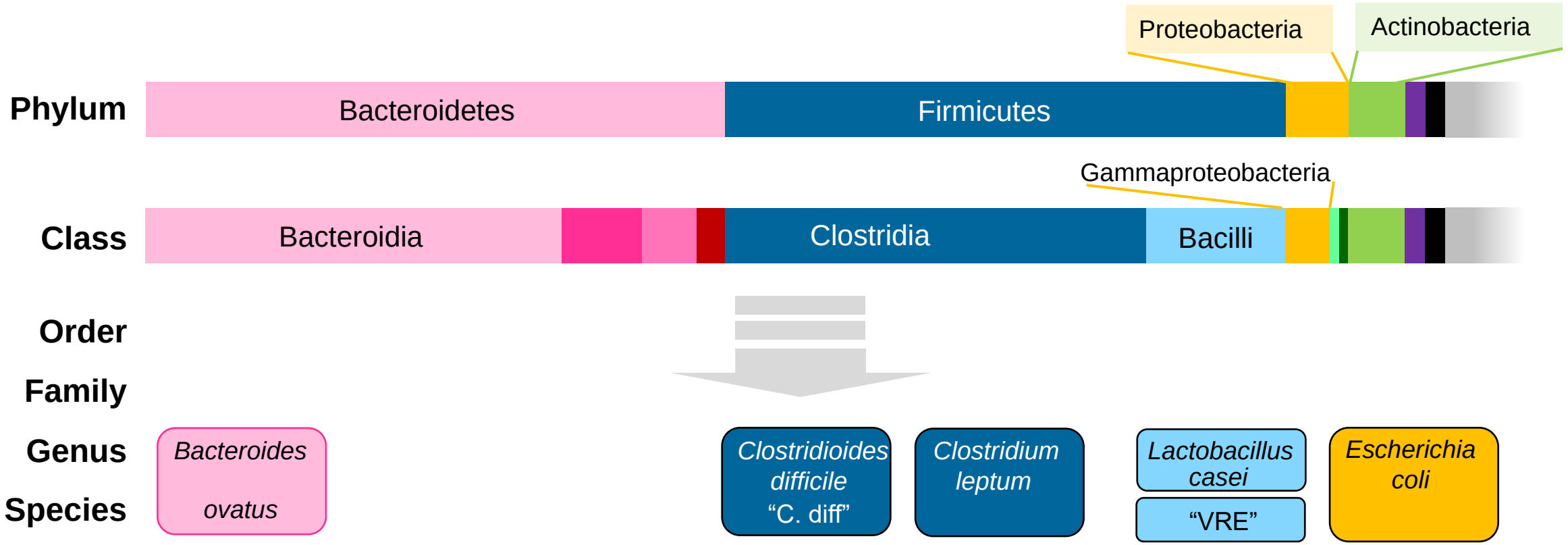
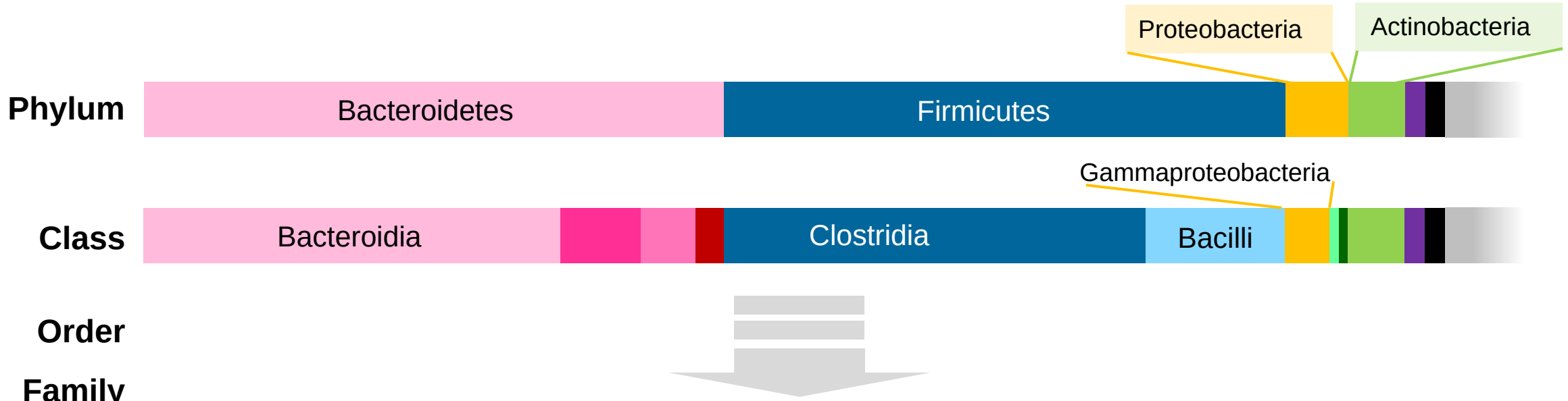
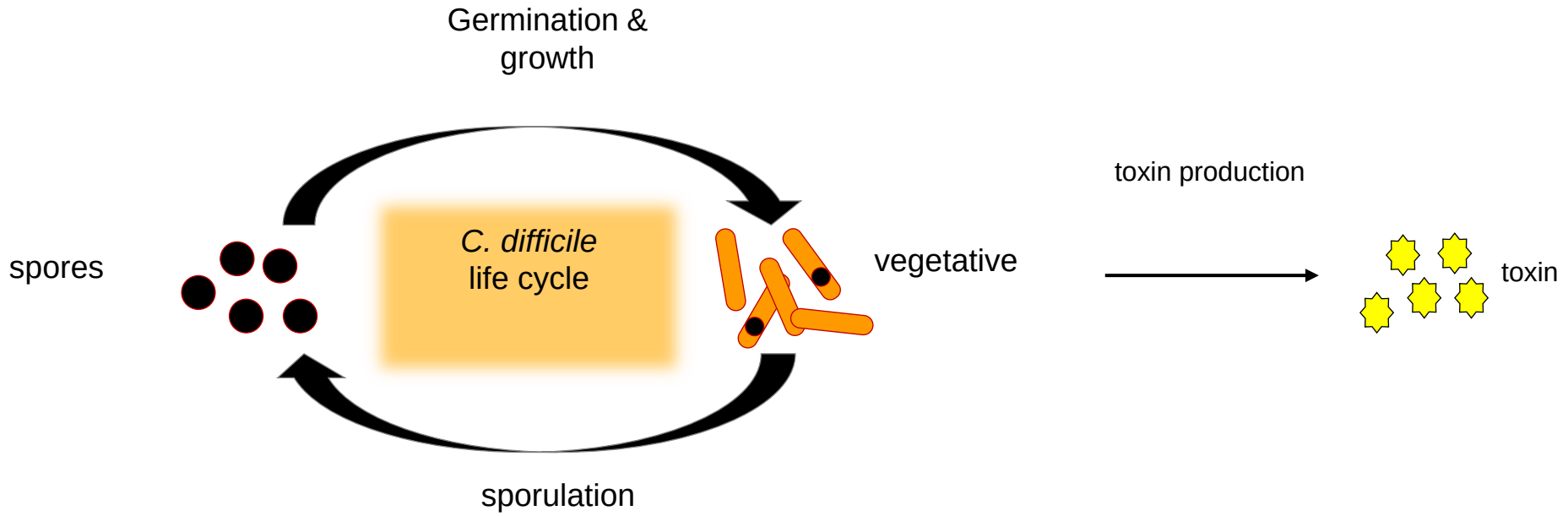
Microbiology 101: the Bacterial Kingdom



Microbiology 101: the Bacterial Kingdom

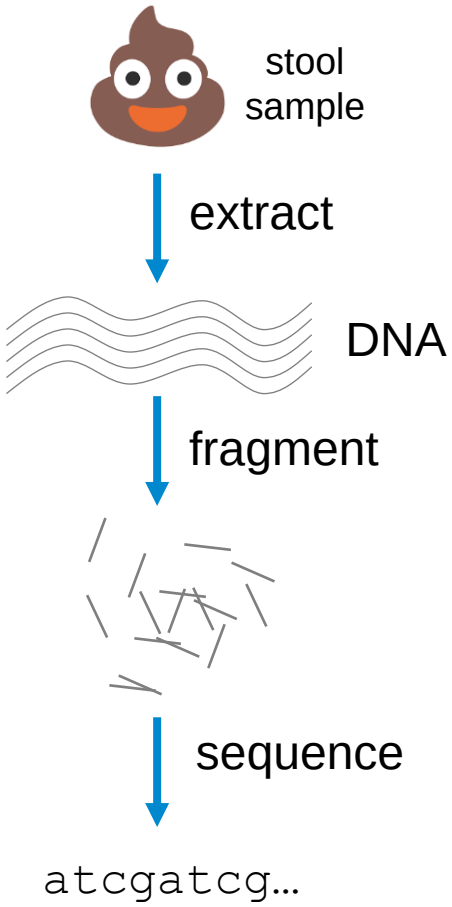


C. difficile: Biology of a Spore-Forming Pathogen



- *C. difficile*: rod-shaped bacteria
- Can form spores when conditions are unfavorable
- Spores are a dormant form of the bacteria, and are highly resistant to antibiotics and many cleaners
- Spores can germinate to the actively growing (vegetative form)
- Produces toxin proteins that are harmful to humans

How Scientists Identify the Bacteria in our Gut Microbiota



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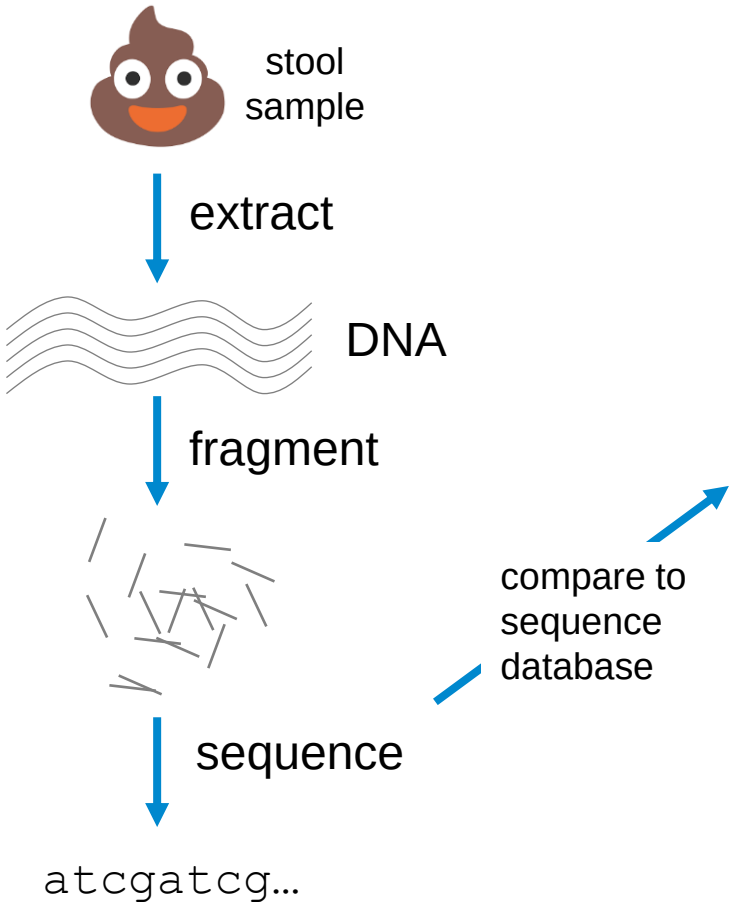
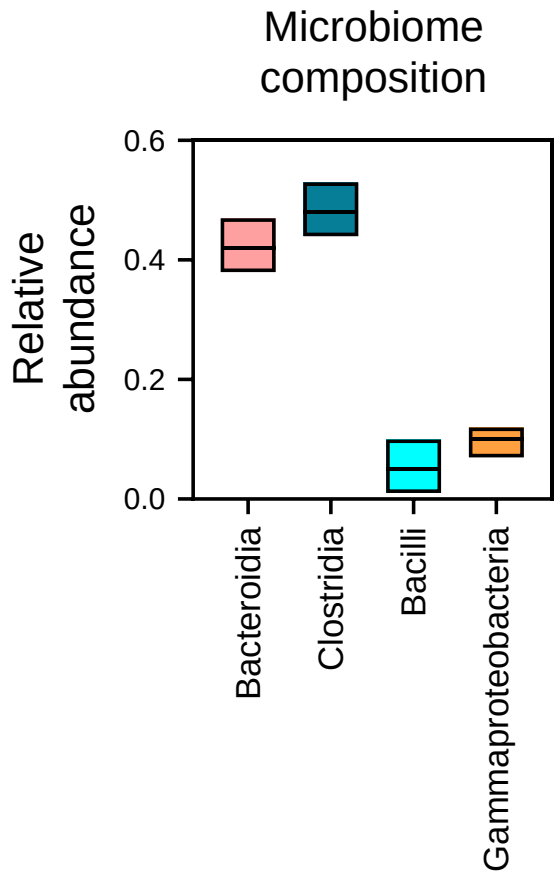
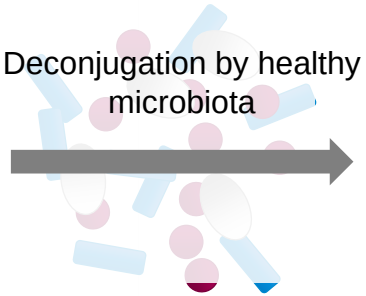
How Scientists Identify the Bacteria in our Gut Microbiota



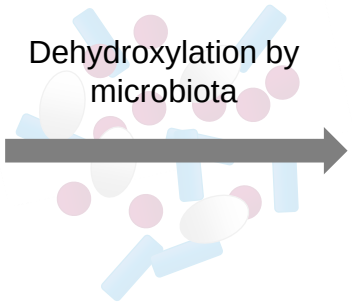


One Function of the Microbiota: Bile Acid Metabolism

Primary conjugated bile acids (BA)



Primary deconjugated bile acids (BA)



Secondary deconjugated bile acids (BA)

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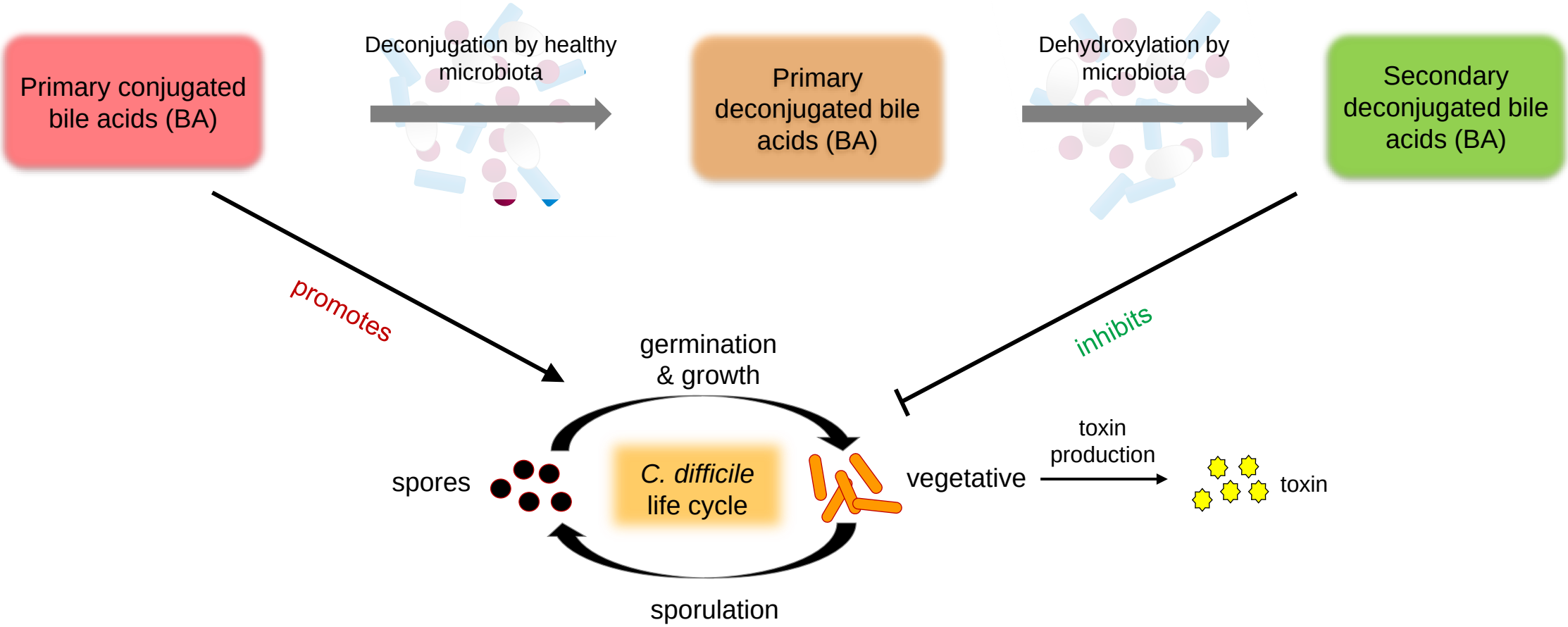
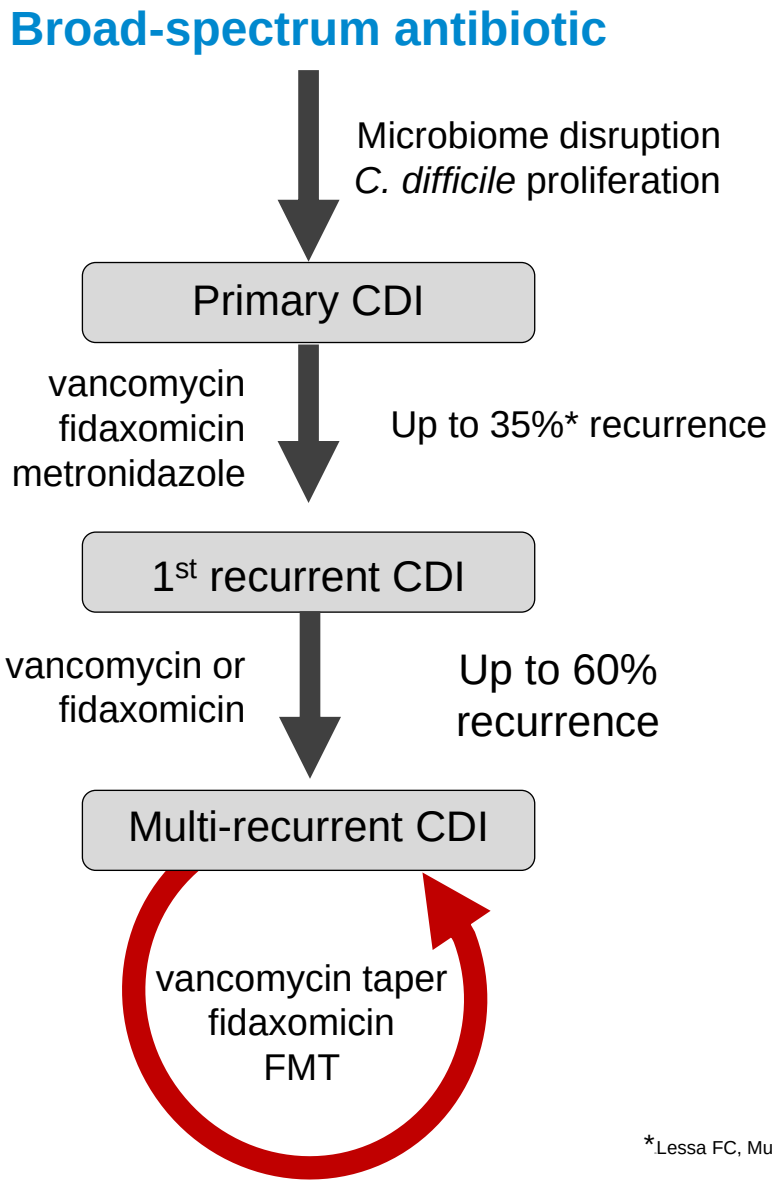
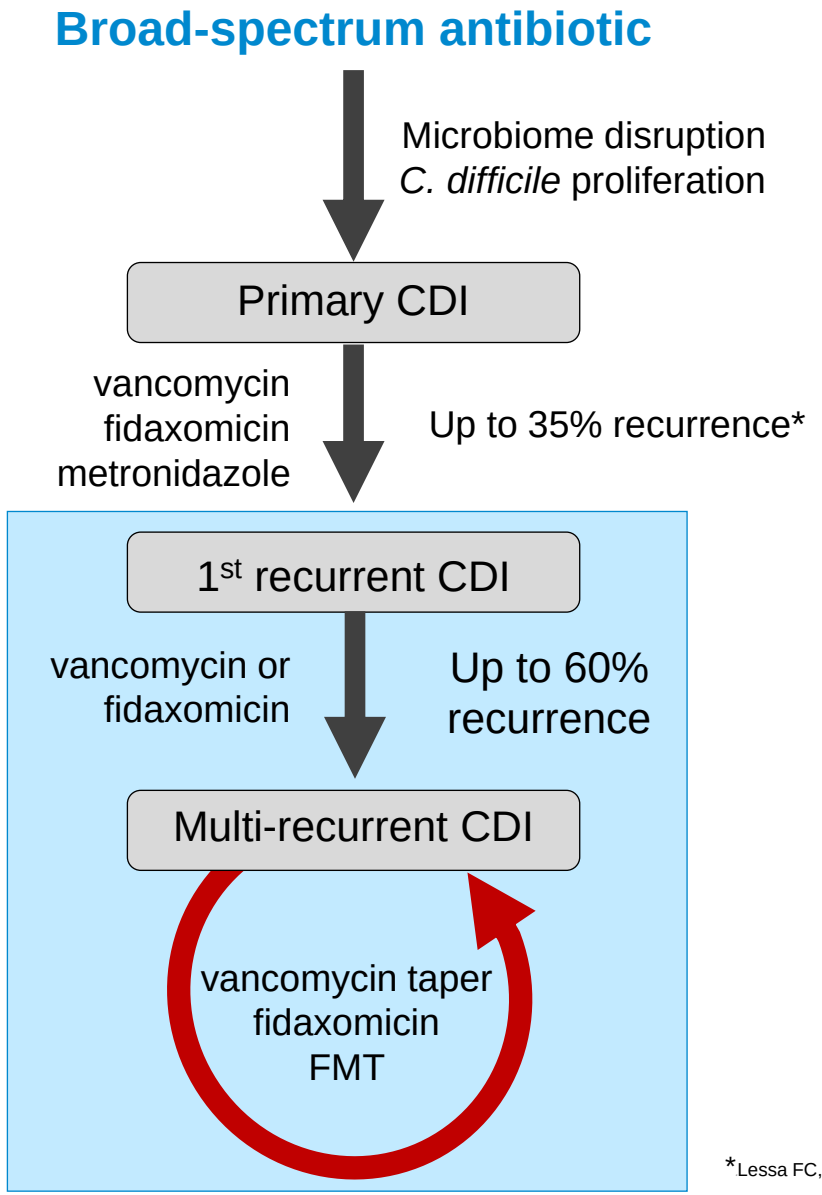


Recurrent C. diff Infections: a Microbiota Disruption Problem



*Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med*. 2015;372(9):825-834.

Recurrent C. diff Infections: a Microbiota Disruption Problem

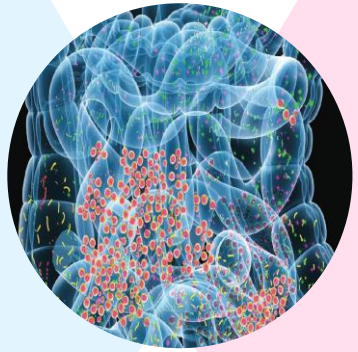


*Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med*. 2015;372(9):825-834.

* Powerofmicrobiome.com

Rebiotix Inc., a Ferring Company: Investigational Microbiota-Based Live Biotherapeutics to Treat rCDI

Healthy Gut Microbiota	Dysbiotic Microbiota
High **diversity** and high microbial **population**	Decreased **diversity** and microbial **population**
Dominated by **spore & non-spore forming** microbes, predominantly Clostridia and Bacteroidia	**Spore-forming** phyla reduced; dominated by different bacterial classes, possibly including opportunistic pathogens
Key non-spore-forming class **Bacteroidia** constitutes ~30% of bacteria in healthy gut	Key non-spore-forming class **Bacteroidia** highly depleted by antibiotics
Opportunistic anaerobes in low abundance (Gammaproteobacteria…)	Frequent overgrowth by Gammaproteobacteria like *E. coli* and *Klebsiella*
Bacteria, their metabolites, and their signals to host help **resist pathogen colonization**	Altered metabolism, altered signaling, **lower pathogen resistance**



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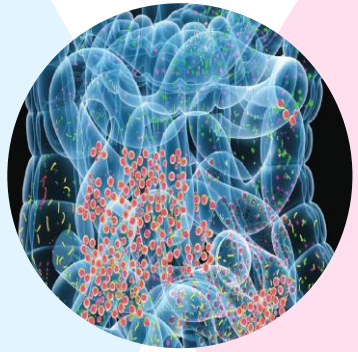
Rebiotix Inc., a Ferring Company: Investigational Microbiota-Based Live Biotherapeutics to Treat rCDI

Healthy Gut Microbiota	Microbiota-Based Therapeutics
High **diversity** and high microbial **population**	High **diversity** and high microbial **population** per dose
Dominated by **spore & non-spore forming** microbes, predominantly Clostridia and Bacteroidia	Drug processing preserves microbial communities, including **spore- & non–spore-forming** microbes
Key non-spore-forming class **Bacteroidia** constitutes ~30% of bacteria in healthy gut	Consistent **Bacteroidia** per dose
Opportunistic anaerobes in low abundance (Gammaproteobacteria…)	Shifts in microbiome composition and diversity associated post-treatment, including **Bacteroidia**
Bacteria, their metabolites, and their signals to host help **resist pathogen colonization**	



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Two Formulations in Clinical Development

- ✓ Liquid suspension of a broad consortium of live spore-forming and non-spore-forming microbes
- ✓ Biologically sourced with rigorous safety screening program
- ✓ Rectally administered in a health-care setting
- ✓ Completed five controlled clinical trials, including pivotal Phase 3

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Robust RBX2660 Clinical Program in rCDI – Designed to Yield Consistent and Reliable Evidence

Study Design Criteria	PUNCH™ CD[1]	PUNCH™ CD2[2,3]	PUNCH™ CD Open Label[4,5]	PUNCH™ CD3[6,7]	PUNCH™ CD3-OLS*[8,9]
Phase	2	2b	2	3	3
Consistent Patient Population: Recurrent CDI	✓	✓	✓	✓	✓+
Consistent Efficacy Endpoint: Reducing Recurrent CDI	✓	✓	✓	✓	✓
Consistent Product: Same Manufacturing Process	✓	✓	✓	✓	✓
Placebo-Controlled Study	Open-label	Yes	Open-label	Yes	Open-label
Total Subjects Enrolled (Active + Control)	40	150	272	320	293*
Primary Efficacy Population	32	133	142	262	154*
Follow-up Duration	6 months	24 months	24 months	6 months	6 months

*Expanded rCDI patient population (eg, IBD, IBS, and immunocompromised). Ad hoc data; enrollment is ongoing.

1. Orenstein R, et al. Clin Infect Dis. 2016;62(5):596-602; 2. Dubberke ER, et al. Clin Infect Dis. 2018;67(8):1198-1204; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02299570?term=NCT02299570&draw=2&rank=1. Accessed September 20, 2021; 4. Mische S. Presented at 2018 Digestive Disease Week; Washington, DC; June 2-5, 2018; 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02589847?term=NCT02589847&draw=2&rank=1. Accessed September 20, 2021; 6. Lee C. Presented at 2021 Digestive Disease Week Online; May 21-23, 2021; 7. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03244644?term=rbx2660&draw=2&rank=4. Accessed September 20, 2021; 8. Kraft C. Presented at 2021 Digestive Disease Week Online; May 21-23, 2021; 9. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03931941?term=rbx2660&draw=2&rank=1. Accessed September 20, 2021.

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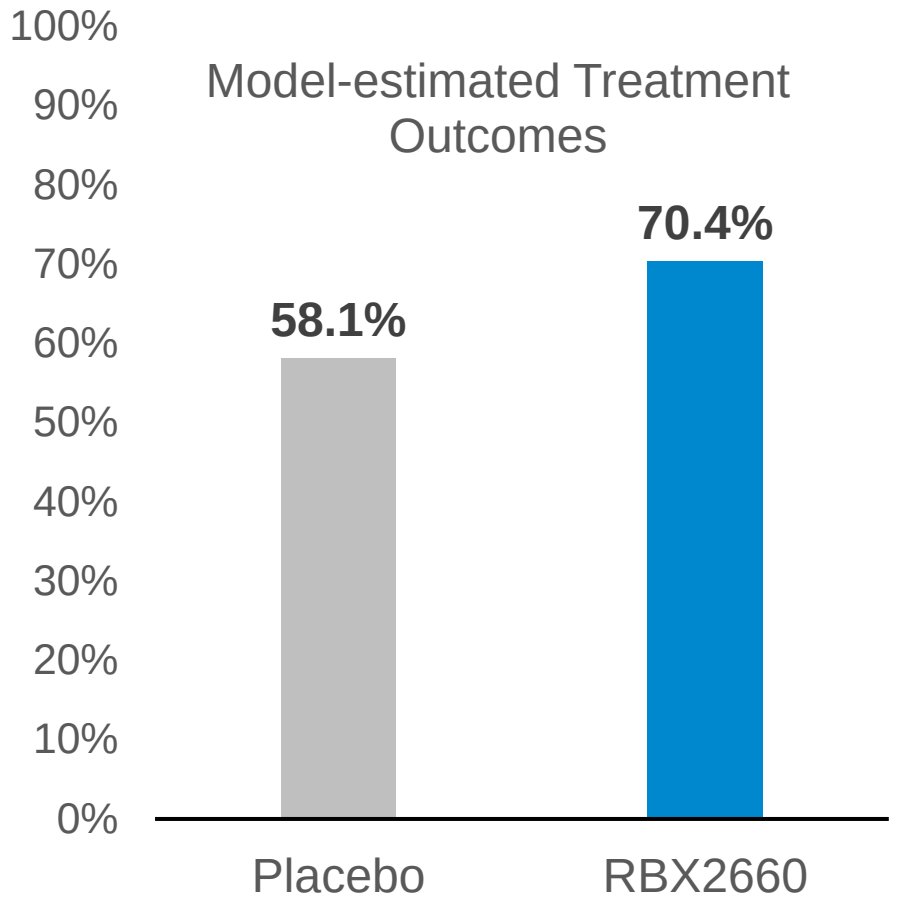
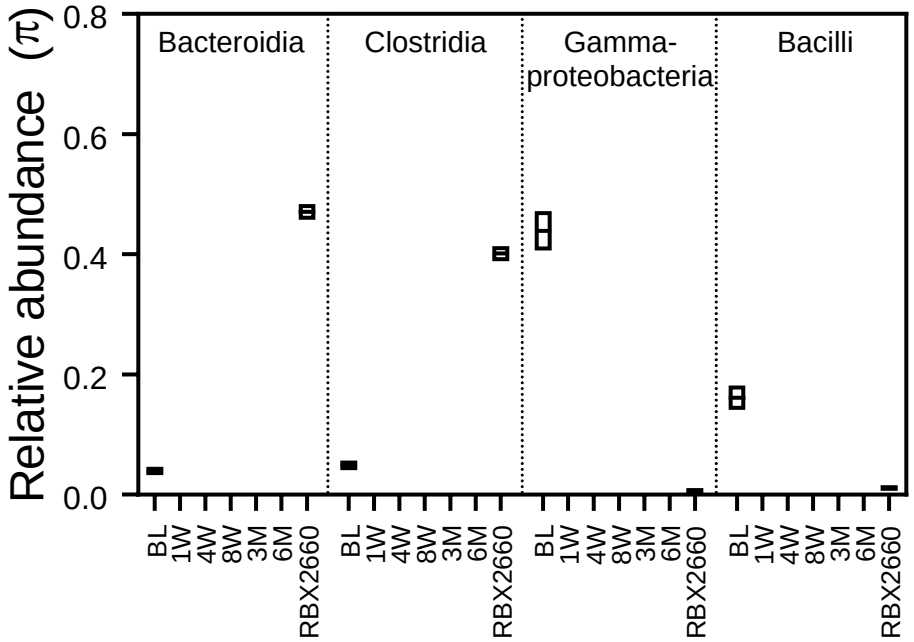
PUNCH™ CD3: Investigational RBX2660 was superior to placebo

- Treatment success: absence of CDI recurrence at 8 weeks after a single dose of blinded investigational treatment
- Novel *a priori* Bayesian analysis leveraged outcome data from the prior Phase 2B trial; success defined as meeting a minimum threshold of 0.975 posterior probability of superiority (RBX2660 versus placebo)
- **RBX2660 met the pre-specified threshold of success over placebo**



PUNCH CD3: Shifts in Microbiome Composition after RBX2660

- At baseline (BL), responder's microbiomes differed from healthy (RBX2660)
  - Key differences: depleted Clostridia, Bacteroidia increased Gammaproteobacteria, Bacilli



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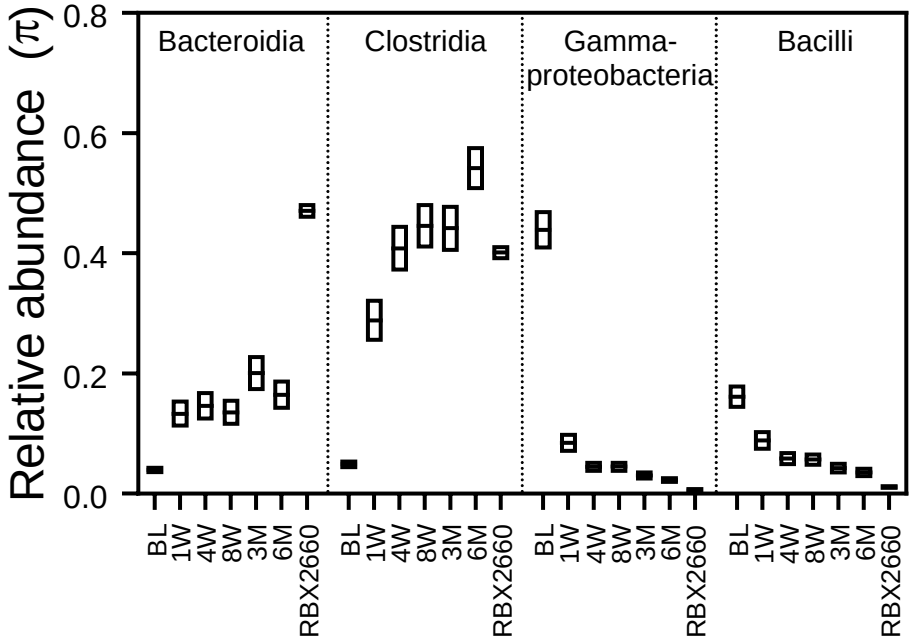
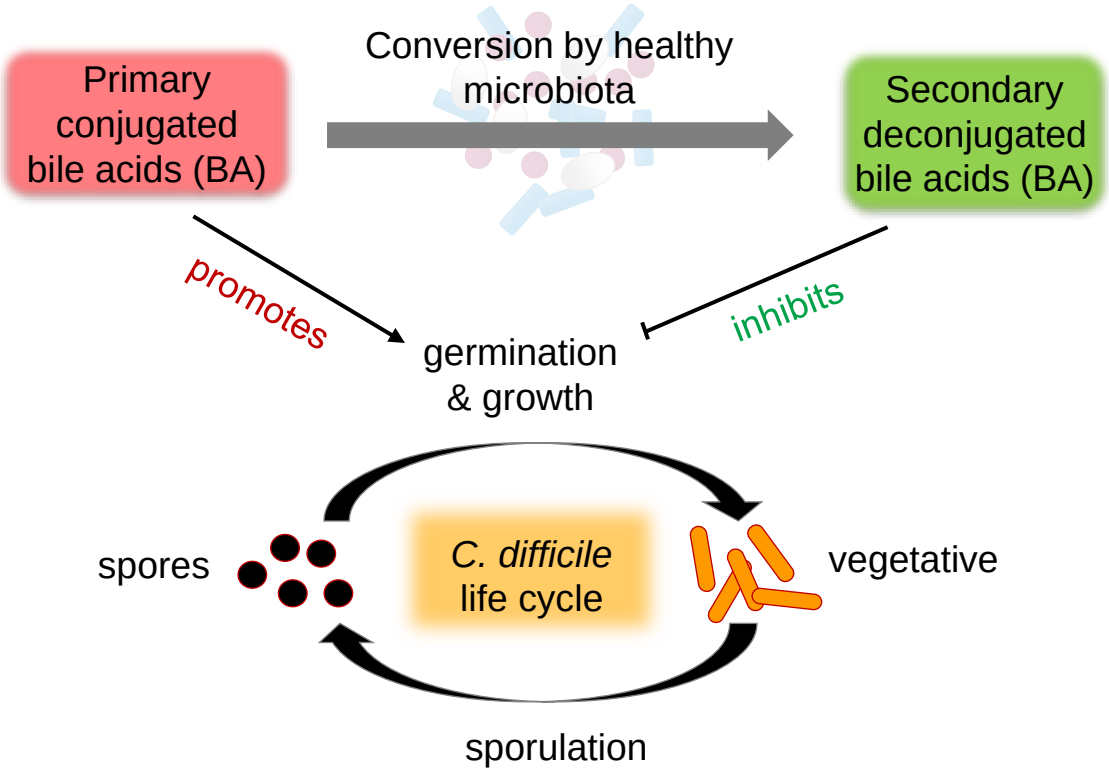
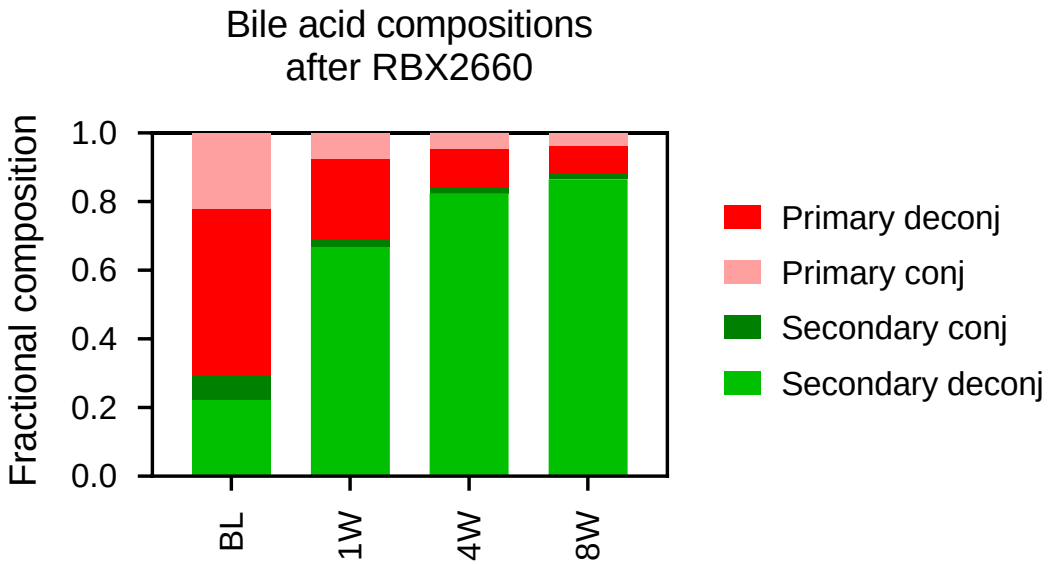
- At baseline (BL), responder's microbiomes differed from healthy (RBX2660)
  - Key differences: depleted Clostridia, Bacteroidia increased Gammaproteobacteria, Bacilli
- Treatment responders were restored toward RBX2660 as early as 1 week after RBX2660 treatment
- Microbiome shifts continued to at least 6 months after treatment



PUNCH CD3: Shifts in Bile Acid Compositions after RBX2660

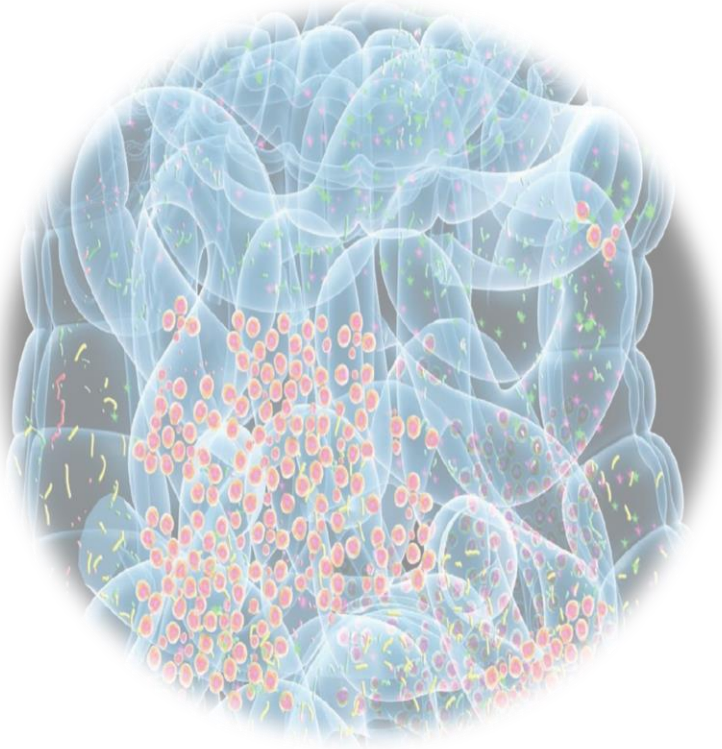
- Prior to treatment (BL), primary bile acids were predominant
- As early as seven days after RBX2660 treatment, secondary bile acids were predominant, continuing to at least 6 months





Summary

- Every person carries an extensive and diverse community of microbes that influence daily health
- The community of healthy human bacterial microbiota can be disrupted by antibiotics, leading to C. diff infections and recurrent C. diff infections
- Investigational live biotherapeutics aim to reduce recurrent C. diff infections
- In multiple clinical trials RBX2660 clinically reduced recurrent C. diff infections and treatment was associated with a shift in microbiome and metabolite compositions, demonstrating the potential of microbiota-based live therapies to address disease



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