Microbiota-mediated defense against intestinal infection.

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Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT)

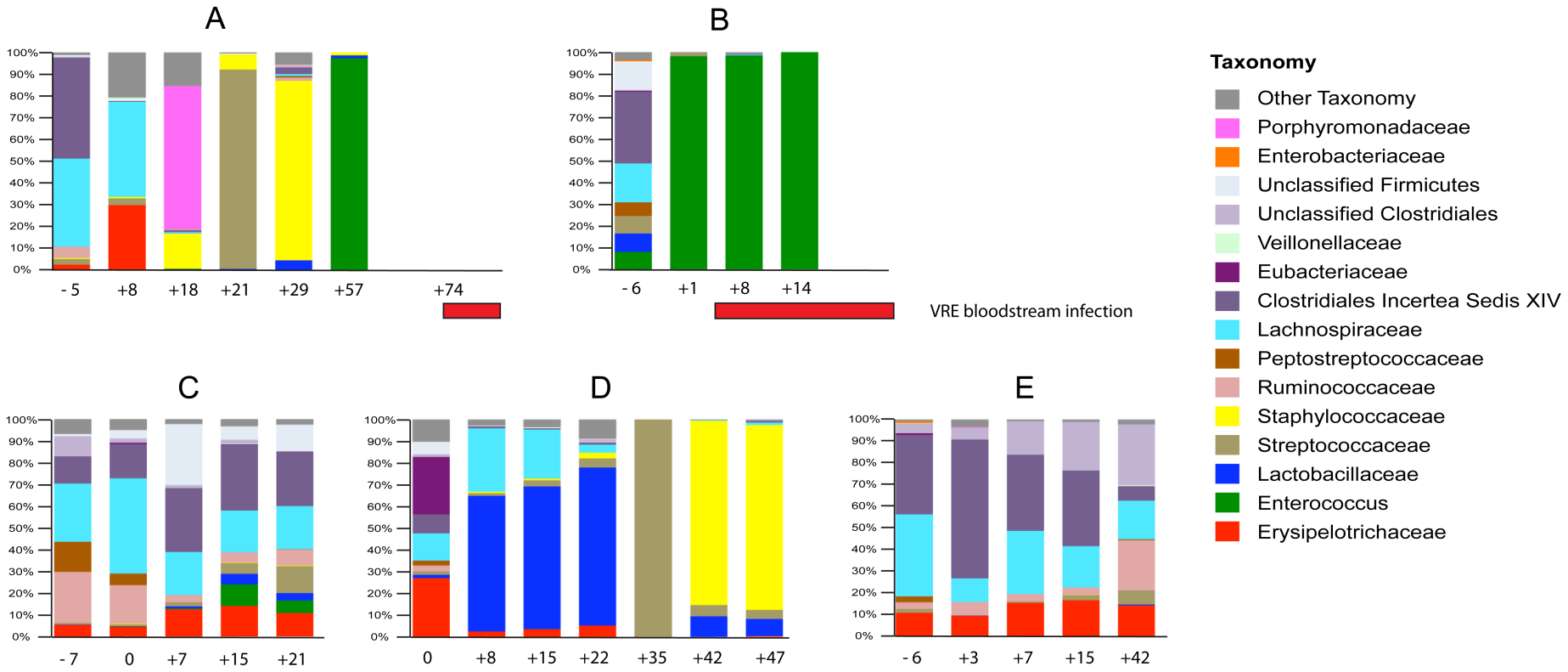
Pre-transplant conditioning:

- **Total body irradiation**
- **Cytotoxic chemotherapy**
- **Prophylactic antibiotic administration**

Mucositis – loss of epithelial integrity
Neutropenia
Monocytopenia
High risk of infection – frequent broad-spectrum antibiotic administration

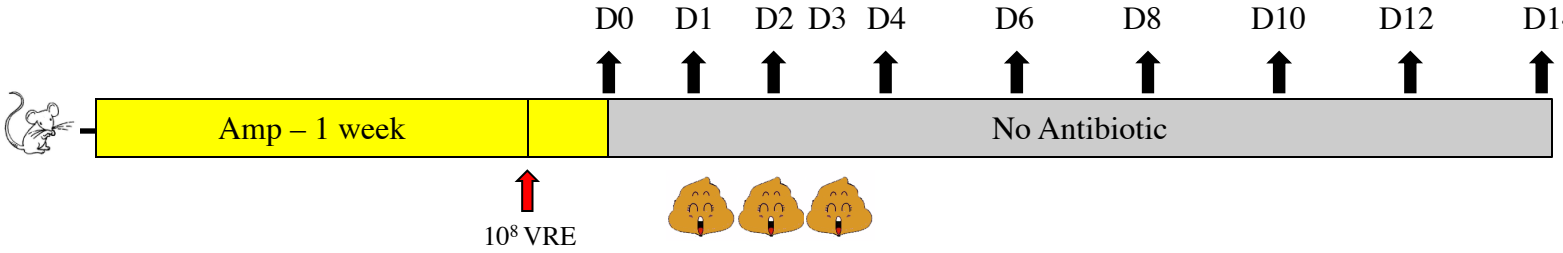
Graft versus host disease

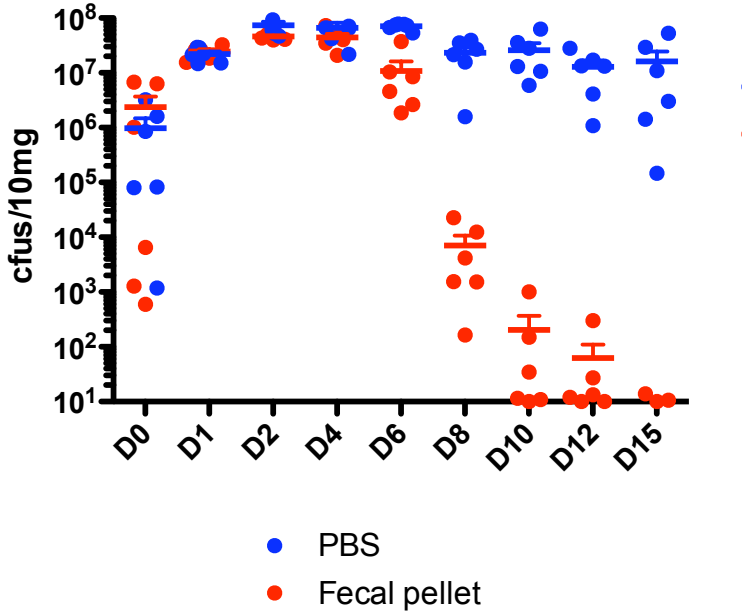
VRE Domination of the GI tract occurs in some patients following allogeneic hematopoietic stem cell transplantation and is associated with VRE bacteremia.

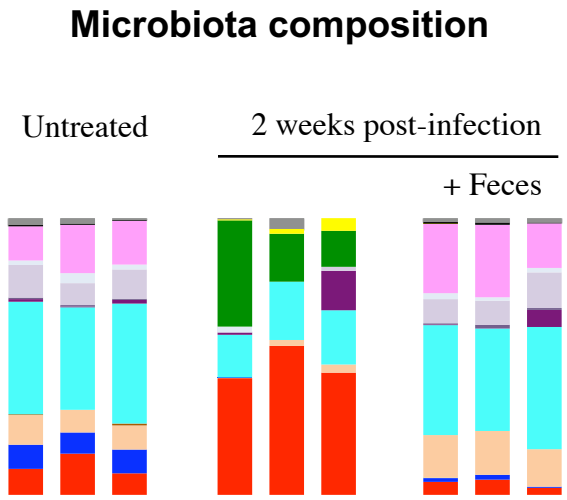


Ubeda et al. (2010) Journal of Clinical Investigation 120:4332.

"Normal" microbiota eliminates persistent VRE

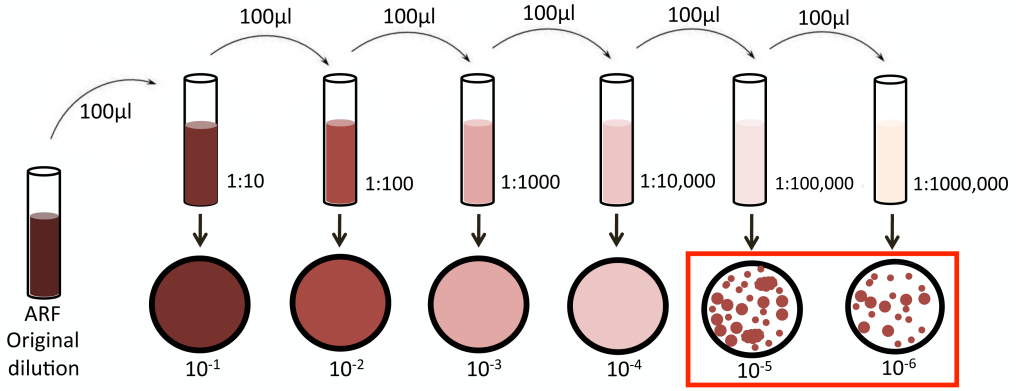


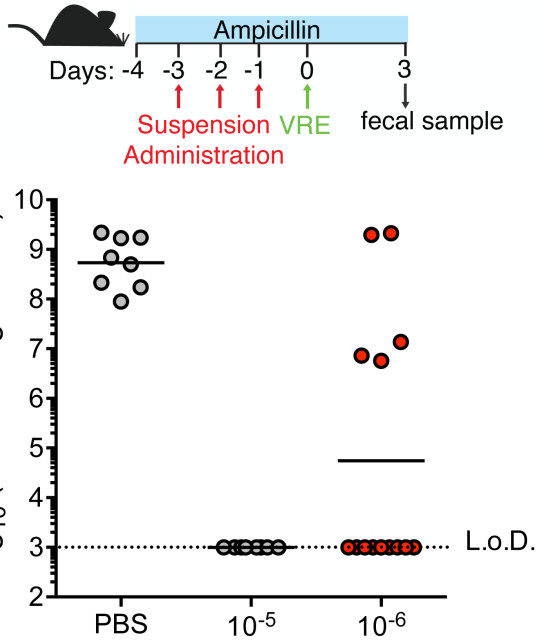


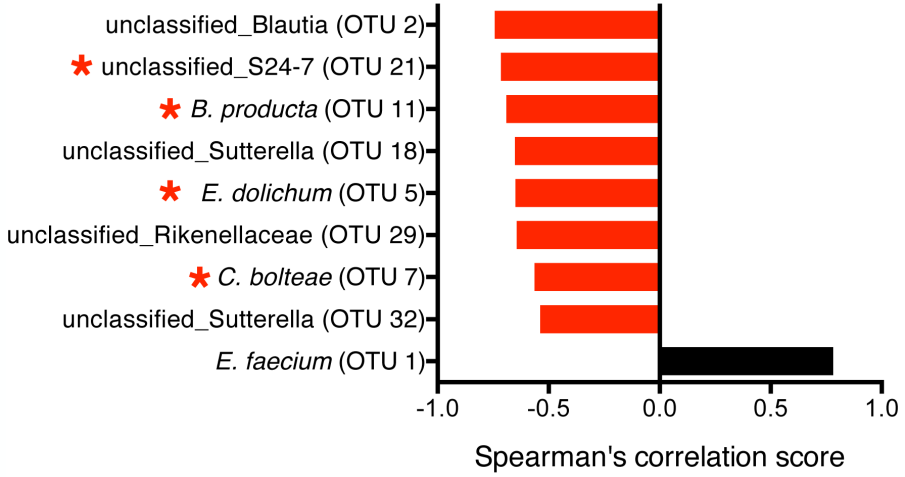


Ubeda et al. (2013) Infection and Immunity

Microbiota dilution facilitates identification of commensal taxa associated with colonization resistance.

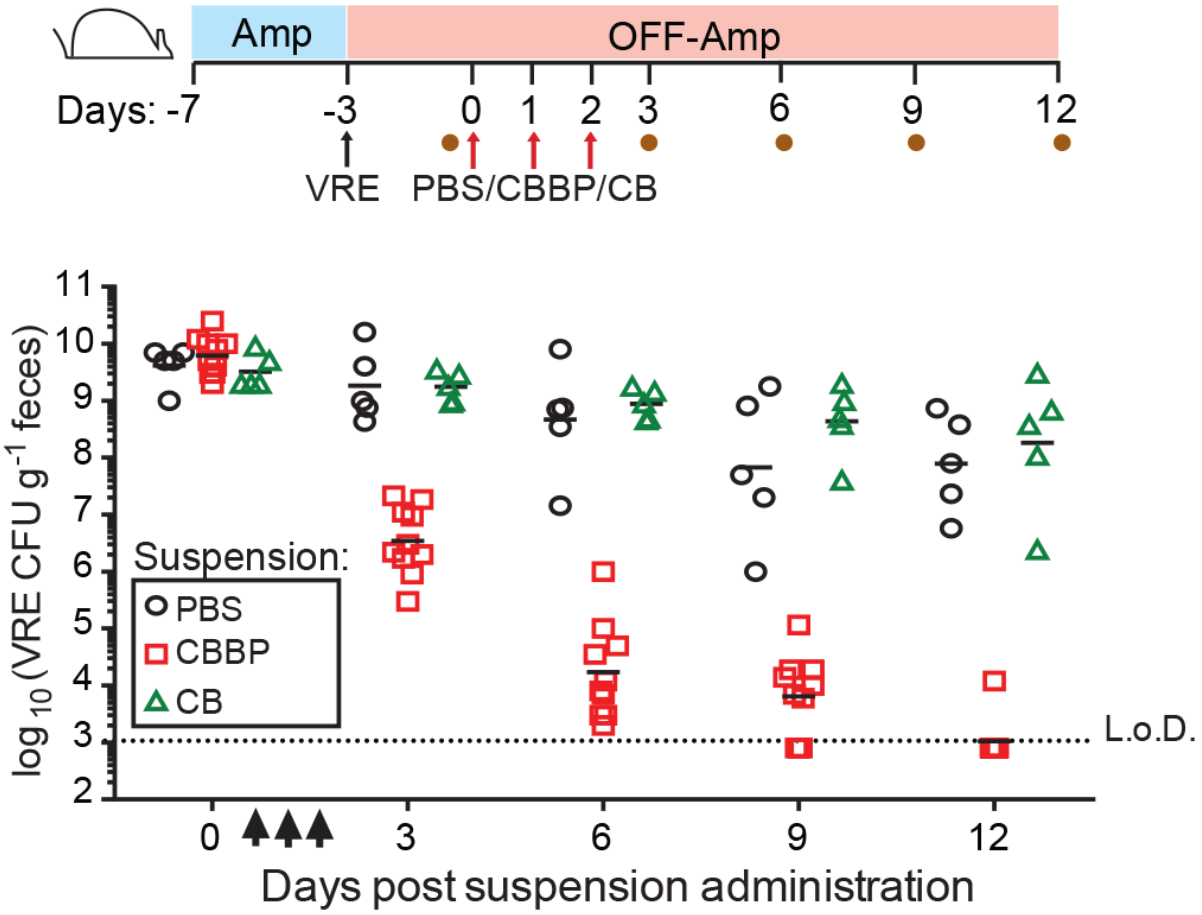






Caballero et al. 2017, Cell Host & Microbe 21(5):592-602

Four bacterial strains (CBBP) mediate colonization resistance against VRE.



CBBP

Clostridium bolteae

Bacteroides sartorii

Blautia producta

Parabacteroides distasonis

Caballero et al. 2017, Cell Host & Microbe 21(5):592-602

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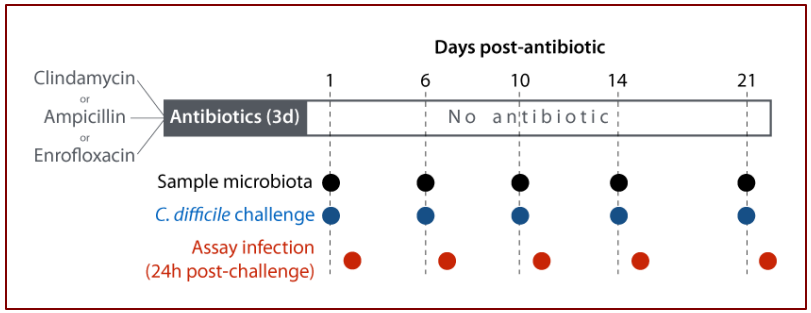
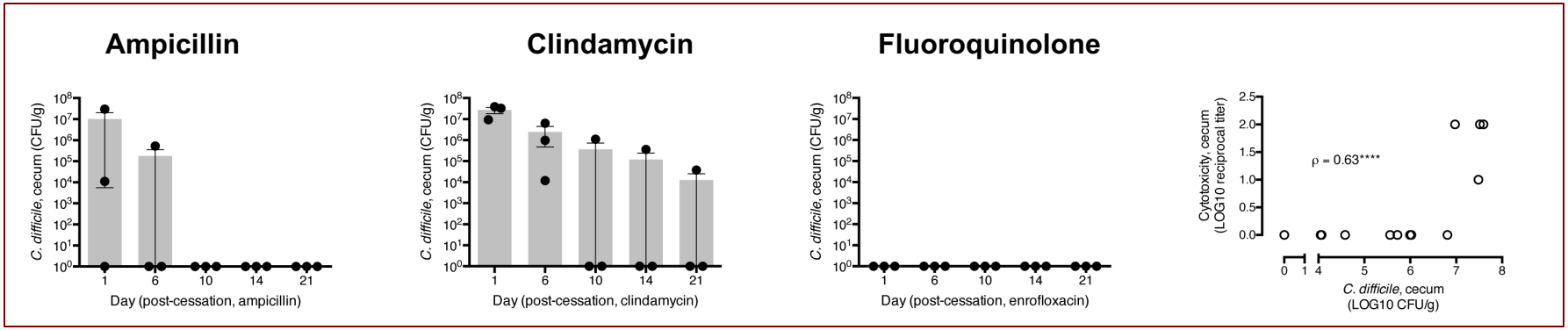
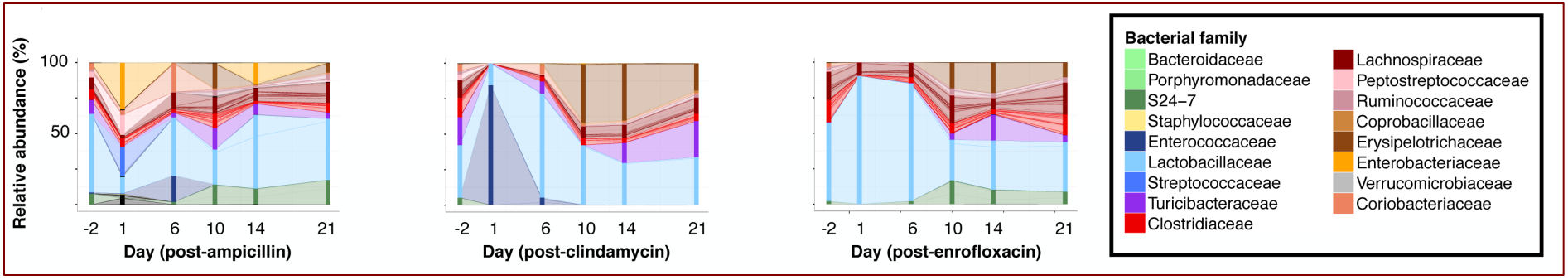
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

Different antibiotics: disparate duration of susceptibility to *Clostridium difficile* infection.

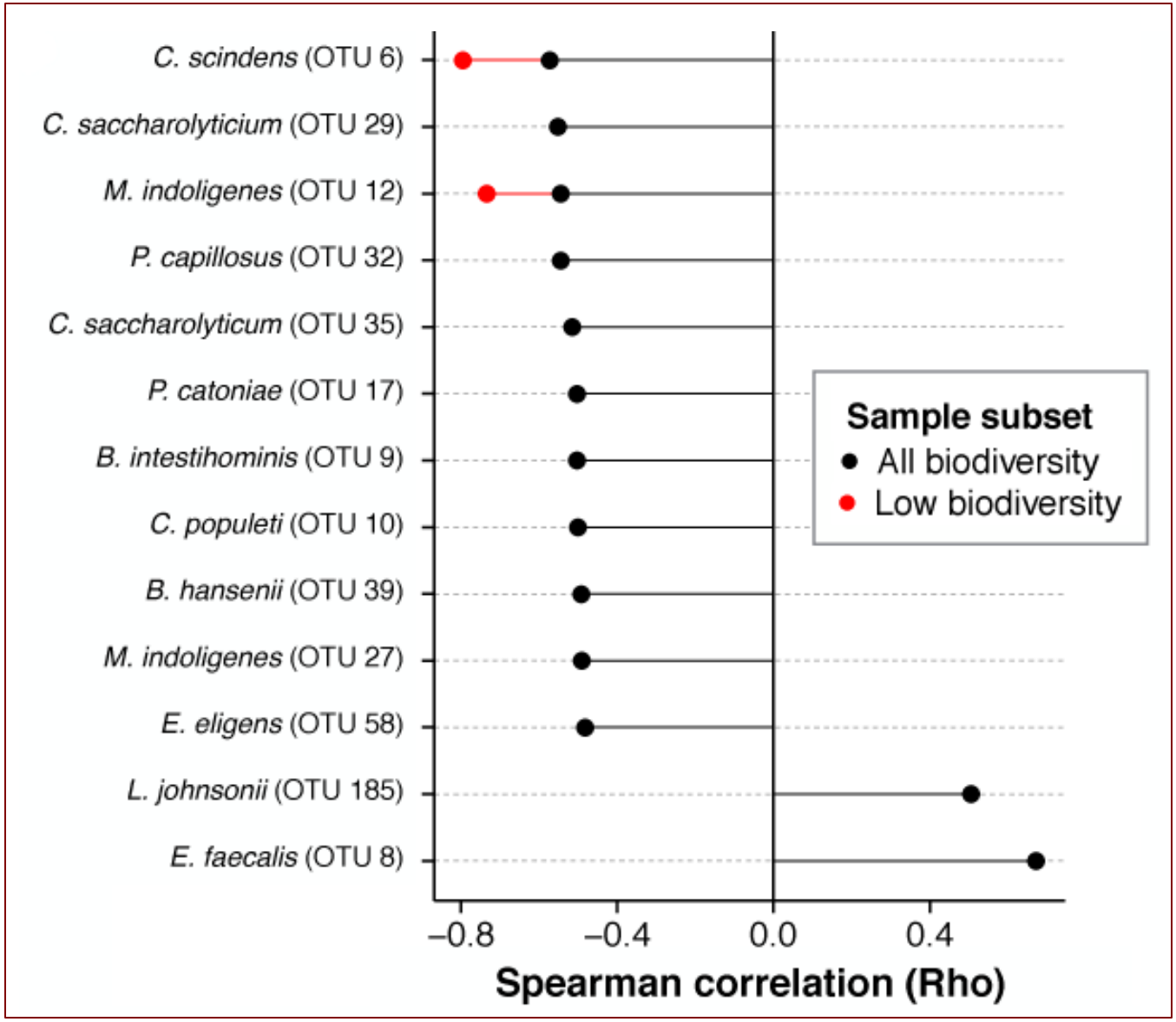






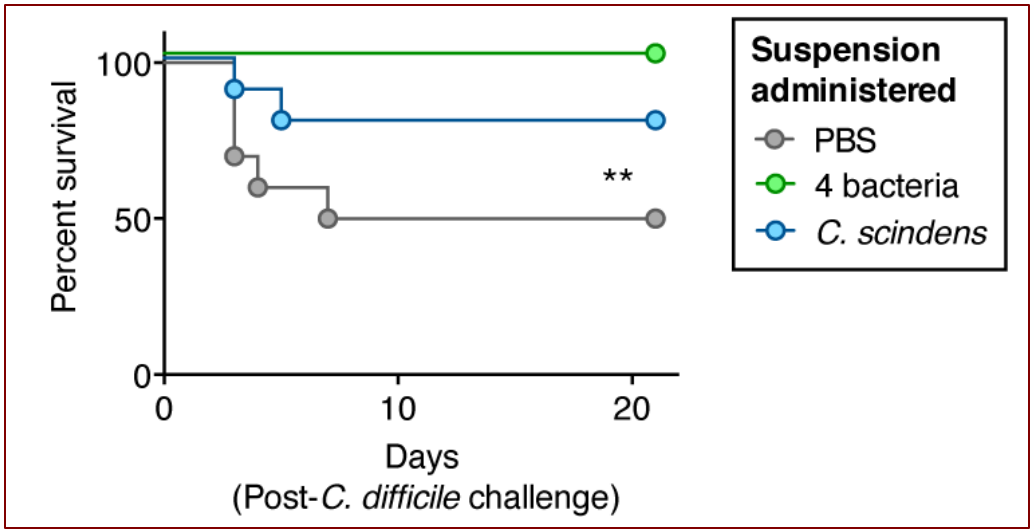
Buffie et al. (2015) Nature 517:205

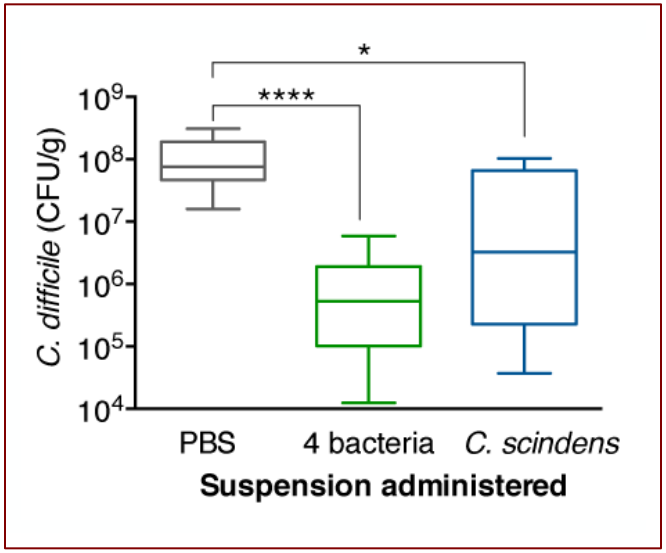
Correlating microbiota components & CDI resistance

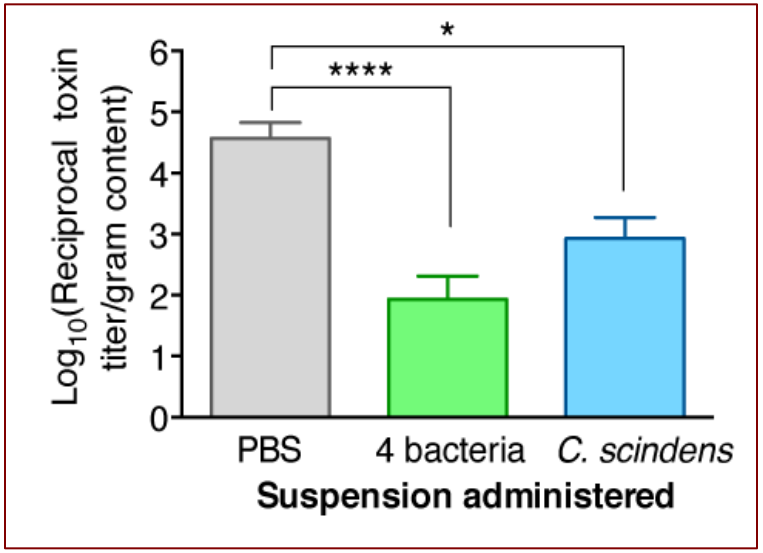


Buffie et al. (2015)

Protection against *C. difficile* mediated by four commensal bacterial species: *B. intestihominis*, *Blautia hansenii*, *Pseudoflavonifractor capillosus* and *C. scindens*

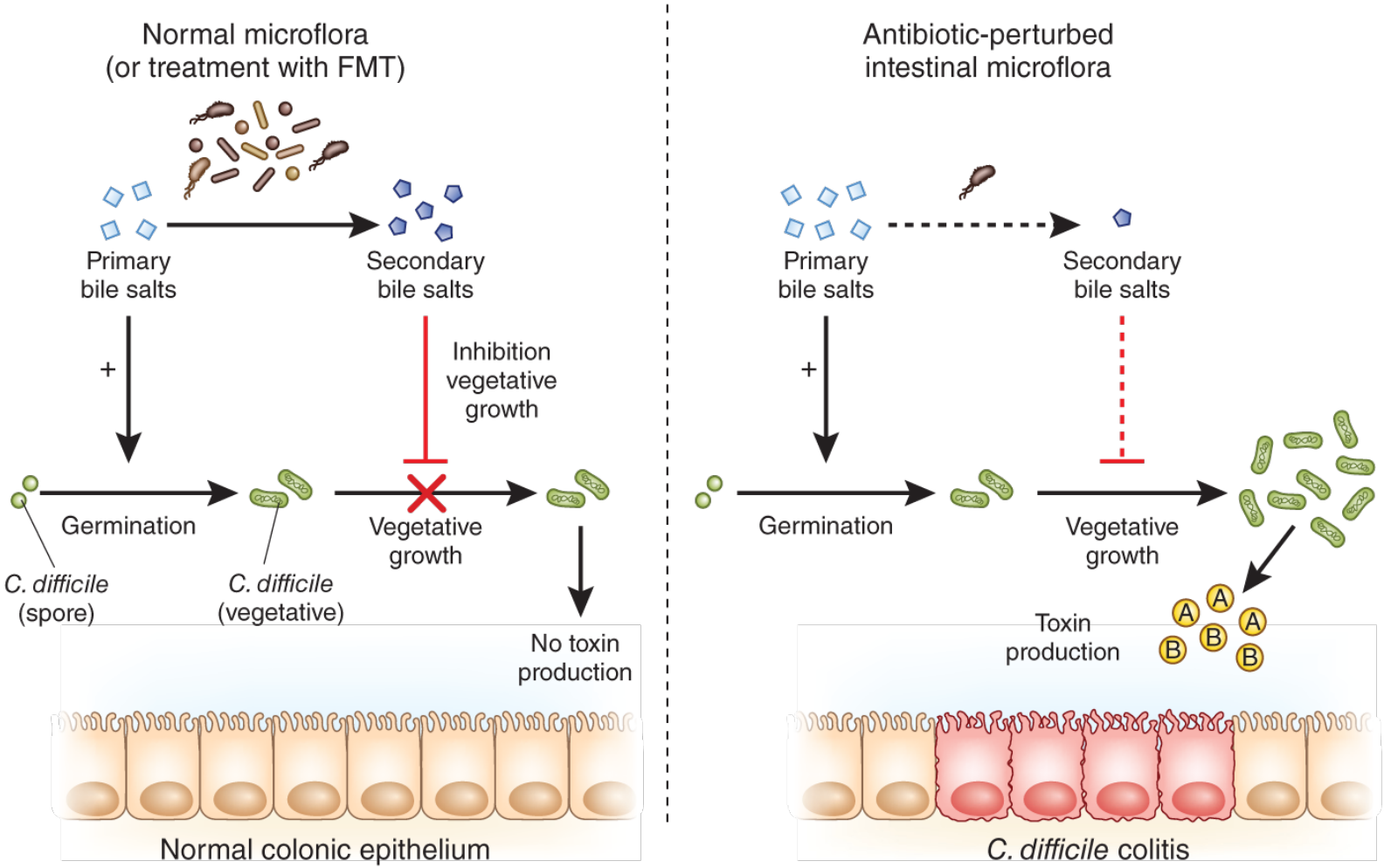






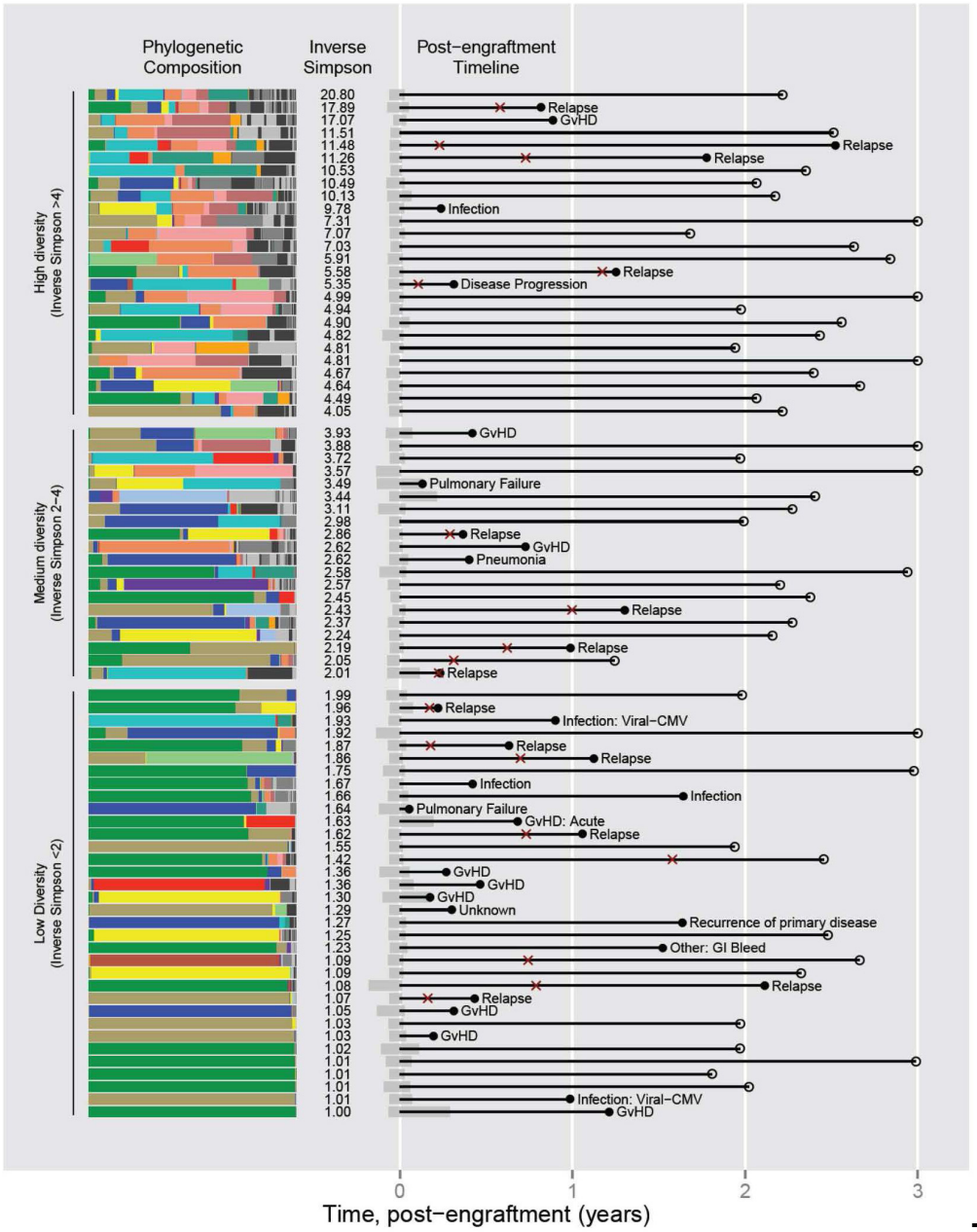
Buffie et al. (2015) Nature 517:205

Secondary bile salt-mediated inhibition of *Clostridium difficile* growth



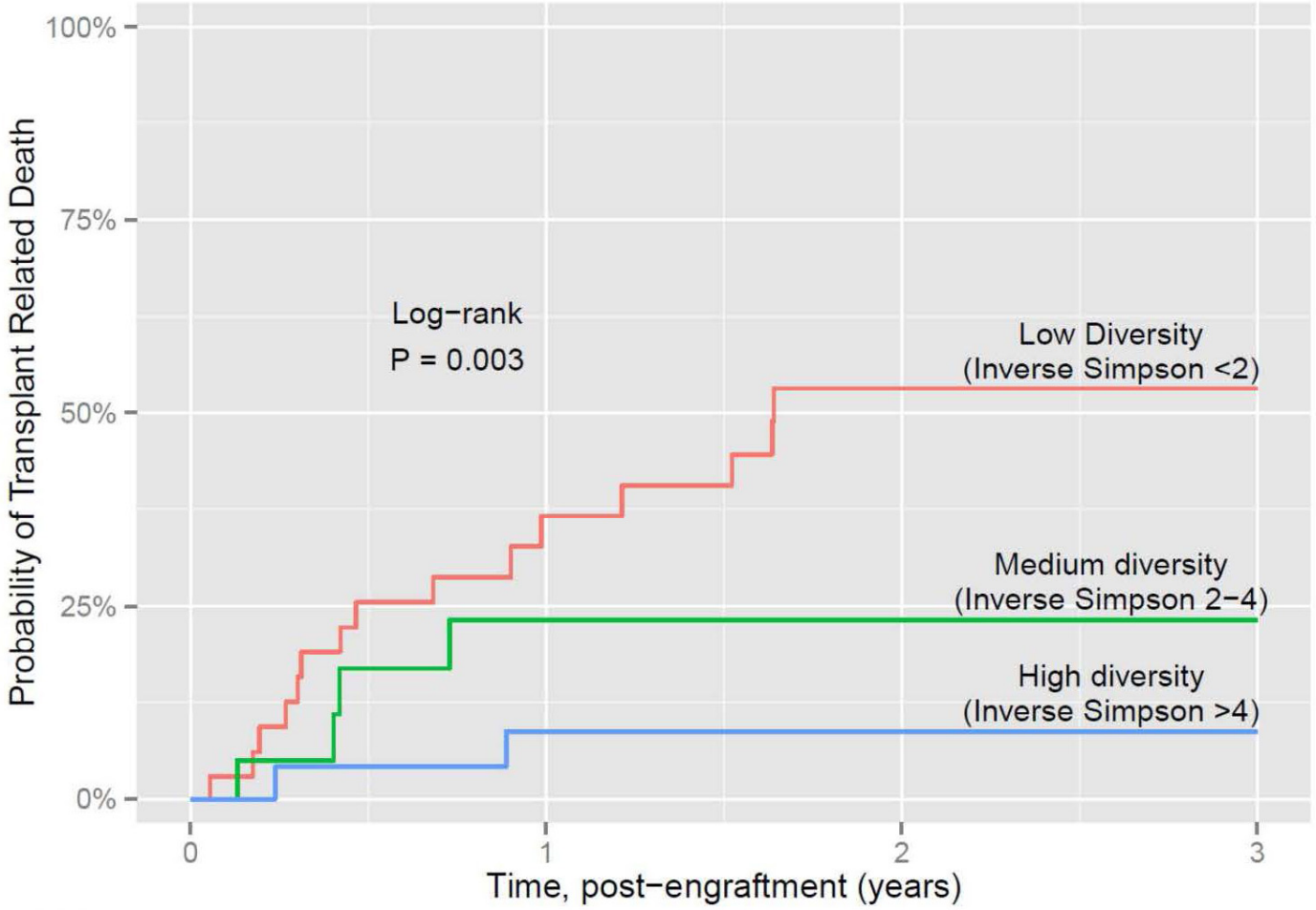
Taur & Pamer (2014) Nature Medicine

Allo-HSCT patients can be divided into low, intermediate and high microbiota diversity groups.



Taur et al. (2014) Blood 124:1174-82.

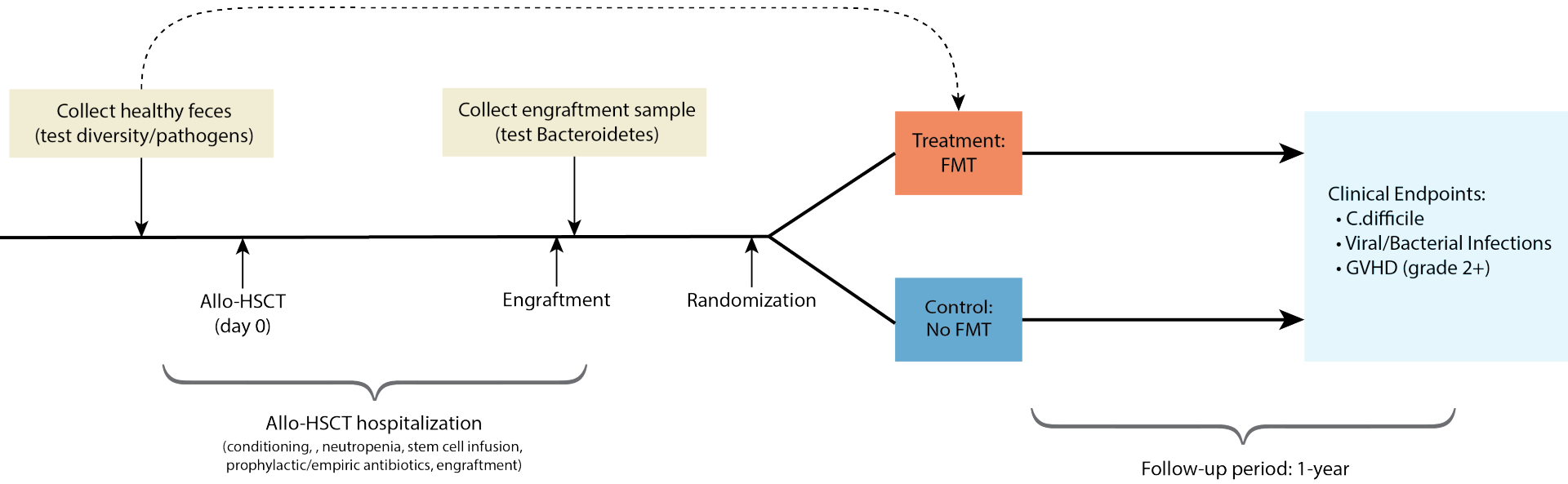
Transplant-related mortality is markedly reduced in patients with a diverse microbiota following engraftment



Number at Risk				
High diversity	26	21	17	4
Medium diversity	20	12	10	3
Low Diversity	34	17	7	2

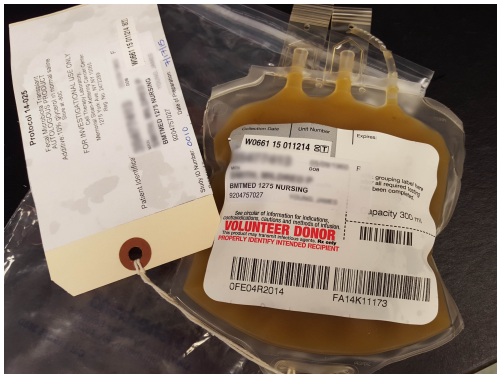
Taur et al. (2014) Blood 124:1174-82.

14-025: Randomized Trial of Auto-FMT in Allo-HSCT

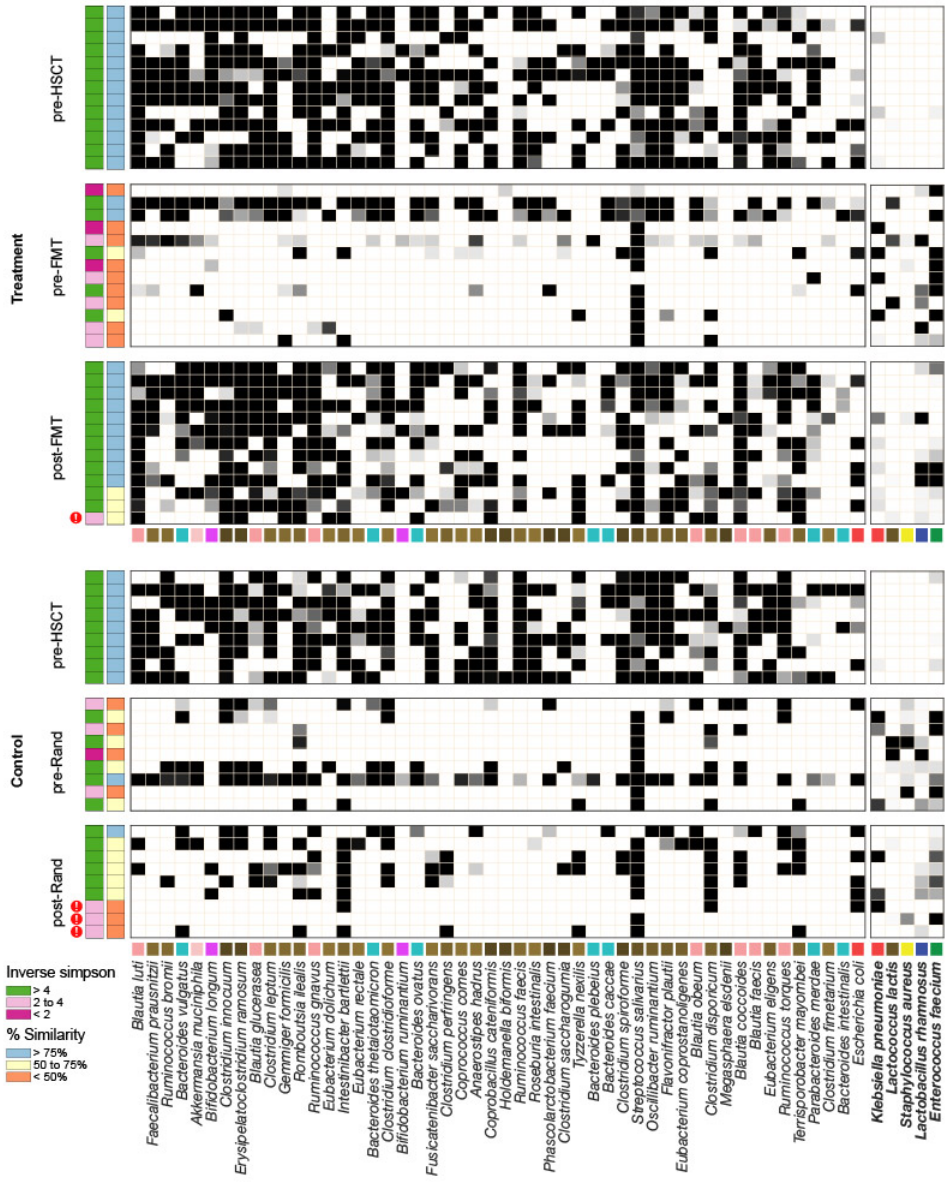


- **215 allo-HSCT patients enrolled (since Jan 2015)**
  - **31 patients currently**
  - **55 excluded, detectable Bacteroidetes at engraftment**
  - **61 excluded, other reasons (initial sample failed pathogen screen)**
  - **20 withdrew from study**

- **59 Randomized**
  - **29Treatment (FMT)**
  - **30 Control**

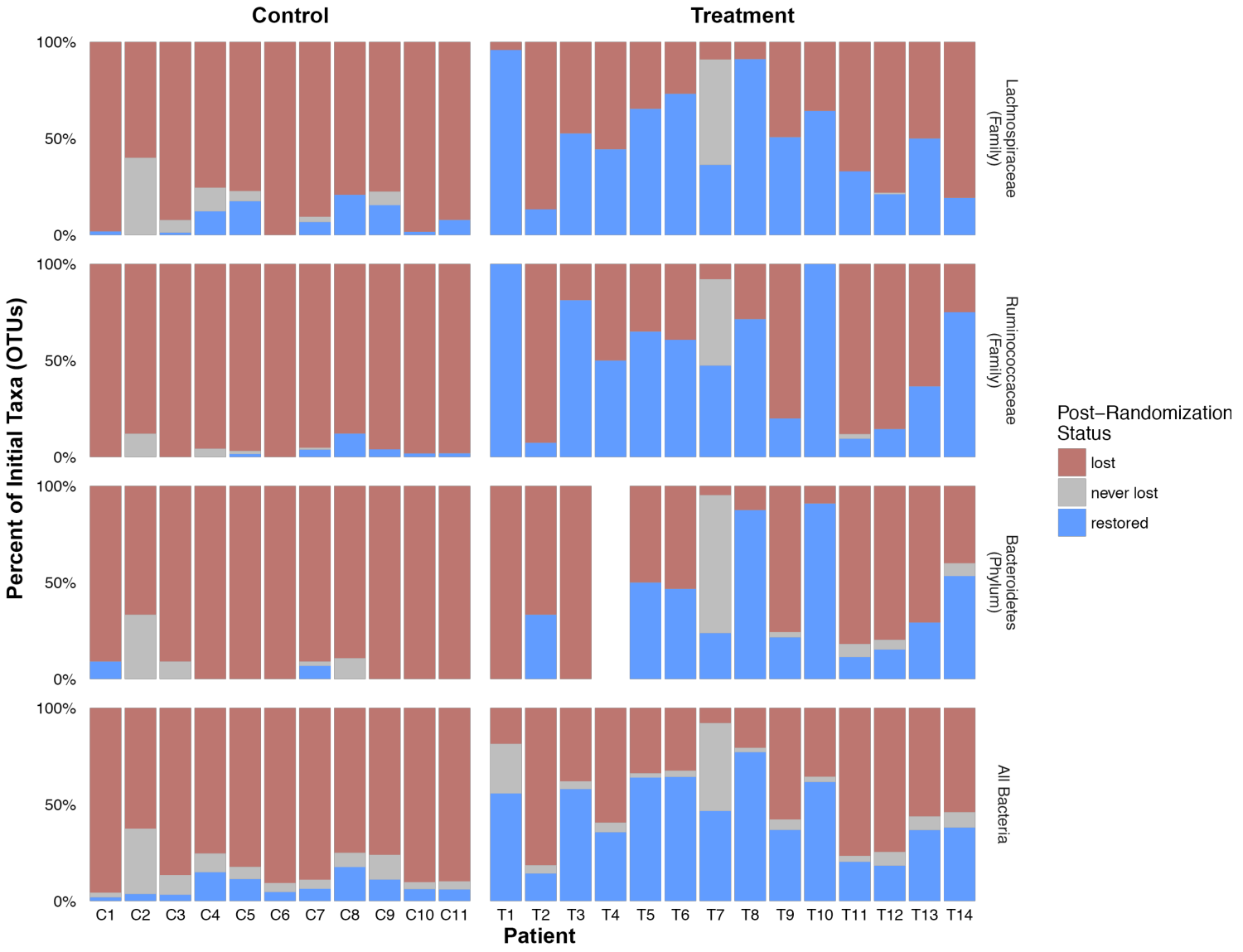


Auto-FMT re-establishes pre-HCT microbiota.



Taur et al., 2018 Science Translational Medicine, In Press

Auto-FMT re-establishes pre-HCT commensal bacterial families.



Taur et al., 2018 Science Translational Medicine, In Press

Microbiota-mediated defense against antibiotic-resistant bacterial infections.

Complex microbial networks in the gut provide colonization resistance; the indirect and direct mechanisms remain incompletely defined.

Microbiota-mediated modification of bile acids contributes to host resistance to intestinal pathogens.

Commensal microbes inhibit antibiotic-resistant pathogens by secreting bacteriocins (e.g. lantibiotics) and producing SCFAs.

Microbiota diversity predicts survival following allogeneic hematopoietic stem cell transplantation.

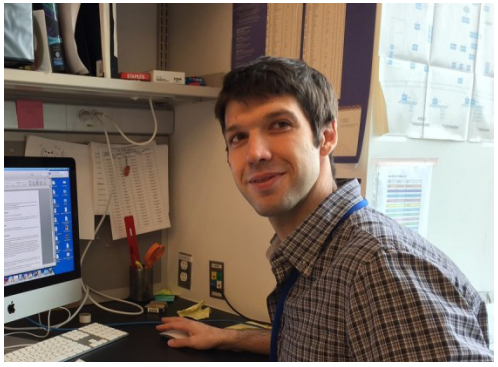
Reconstitution of mucosal bacterial populations following antibiotic therapy using FMT or specific commensal microbes provides an alternative approach to treat and prevent infections in an era of decreasing antibiotic susceptibility.

Joao Xavier

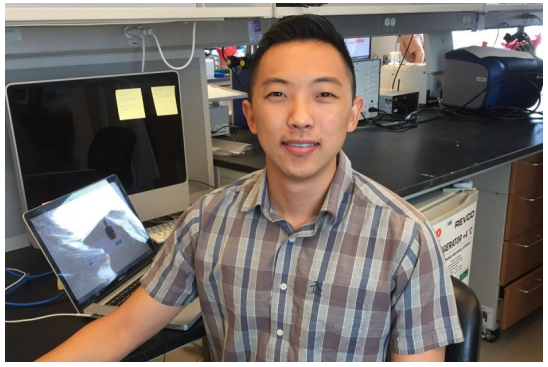
Ying Taur

Marcel van den Brink

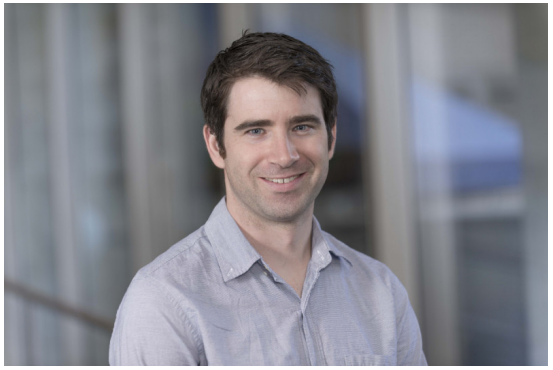
Bastiaan Haak



Simone Becattini



Sohn Kim



Matthew Sorbara

Thomas Moody

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