From metagenomics to bacterial therapy.

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RESISTANCE OF THE MOUSE'S INTESTINAL TRACT TO EXPERIMENTAL SALMONELLA INFECTION

I. Factors Which Interfere with the Initiation of Infection by Oral Inoculation*

By MARJORIE BOHNHOFF, C. PHILLIP MILLER, M.D., and WILLIAM R. MARTIN,‡ Ph.D.

(*From the Departments of Medicine and Microbiology, University of Chicago, Chicago*)

(Received for publication, July 2, 1964)

Described below are observations which seem to account, in large part at least, for the normal resistance of the mouse's intestinal tract to infection with *Salmonella enteritidis* introduced by mouth, the natural route of infection. Thus inoculated, about 10^6 microorganisms are required to infect 50 per cent of young adult CF-1 mice (1). Their resistance, however, can be sharply reduced by the oral administration of a single, large dose of streptomycin, for during the following 24 hours, <10 microorganisms of the same strain suffice to initiate infection (2, 3). Of the changes in the mouse's enteric microflora resulting from streptomycin treatment, the most consequential was thought to be the elimination of certain obligate anaerobes belonging to the genus *Bacteroides* (4, 5).

Journal of Experimental Medicine (1964) 120:805-16.

IN VIVO AND IN VITRO ANTAGONISM OF INTESTINAL BACTERIA AGAINST *SHIGELLA FLEXNERI*

I. CORRELATION BETWEEN VARIOUS TESTS*

DAVID J. HENTGES AND ROLF FRETER

From the Department of Microbiology, Stritch School of Medicine, Loyola University, Chicago, Illinois; and the Department of Microbiology, Jefferson Medical College, Philadelphia, Pennsylvania

Antagonism against pathogenic bacteria exerted by microorganisms of the normal human body flora has been the subject of numerous studies ever since the time of Metchnikoff's original ideas on the benefits attributable to the presence of lactobacilli in the intestine. This degree of interest is only natural since, for many different reasons, the ability to control the bacterial flora of patients would be of great value to the physician.

Hentges, D. J. and Freter, R. 1962, J Infect Dis 110:30–37.

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2013

Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

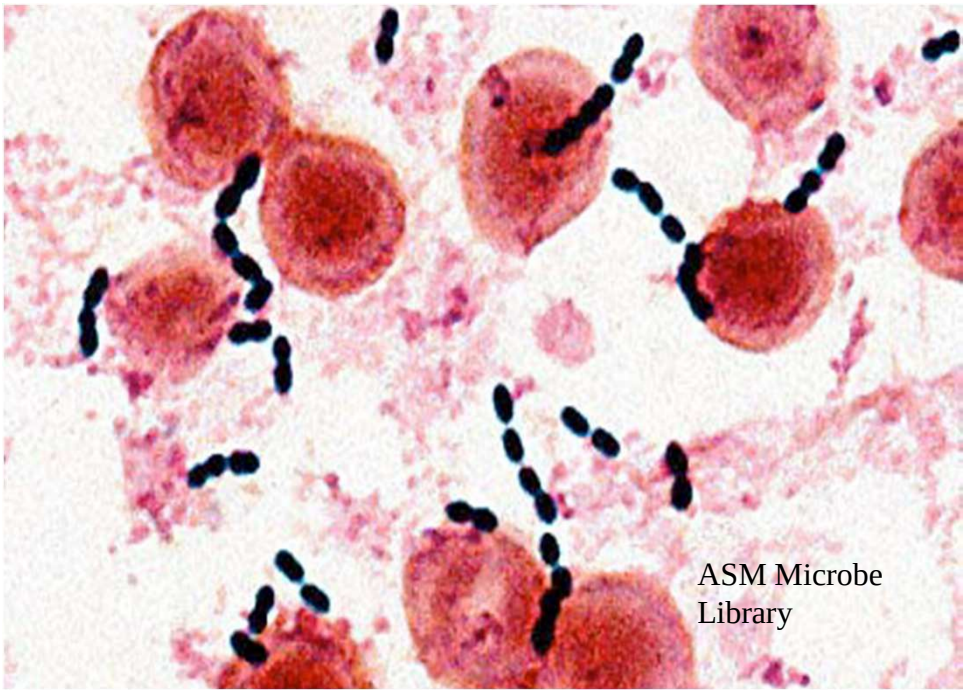
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Vancomycin-resistant enterococcus (VRE)

- Gram positive bacterium
- Increasing prevalence (<1% to 28.5%)
- One of the most common causes of nosocomial bloodstream infections
- High risk for patients receiving broad spectrum antibiotics



Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT)

Pre-transplant conditioning:

- Total body irradiation
- Cytotoxic chemotherapy
- Prophylactic antibiotic administration

Mucositis – loss of epithelial integrity

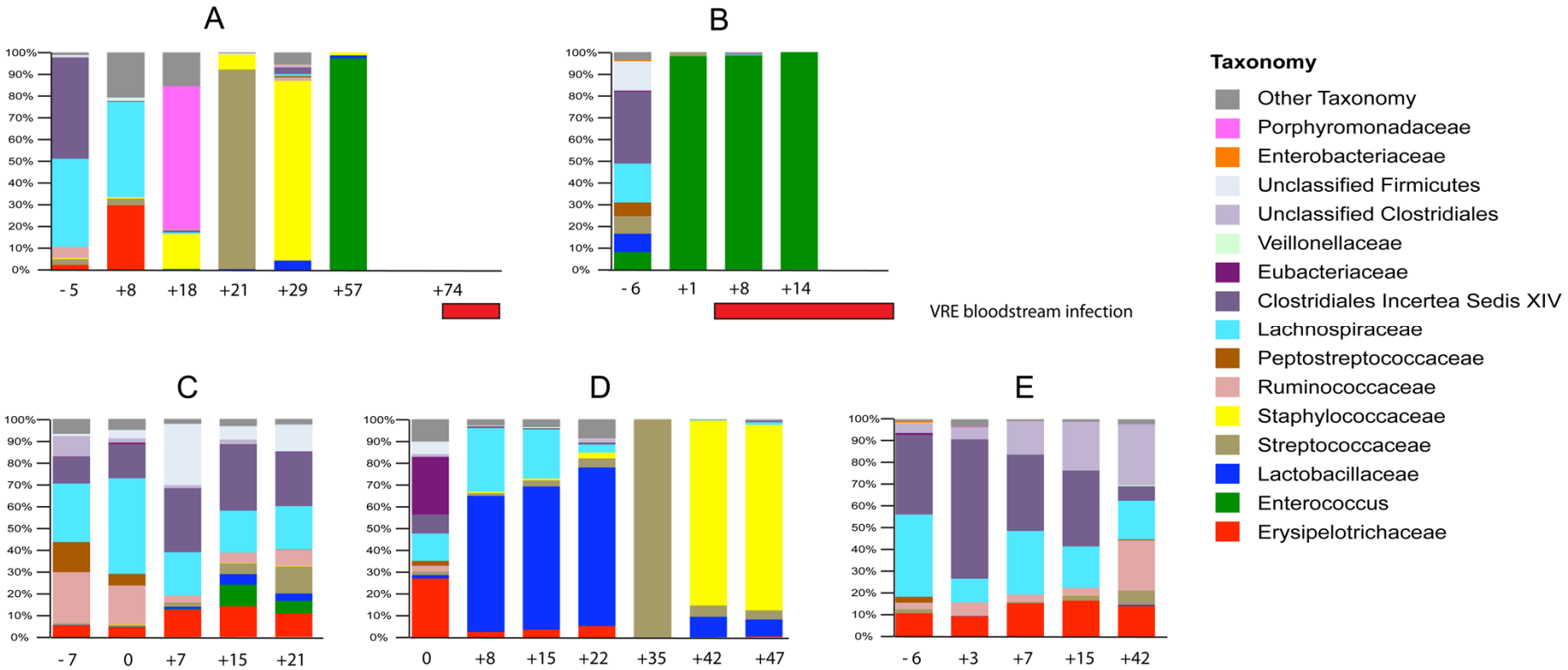
Neutropenia

Monocytopenia

High risk of infection – frequent broad-spectrum antibiotic administration

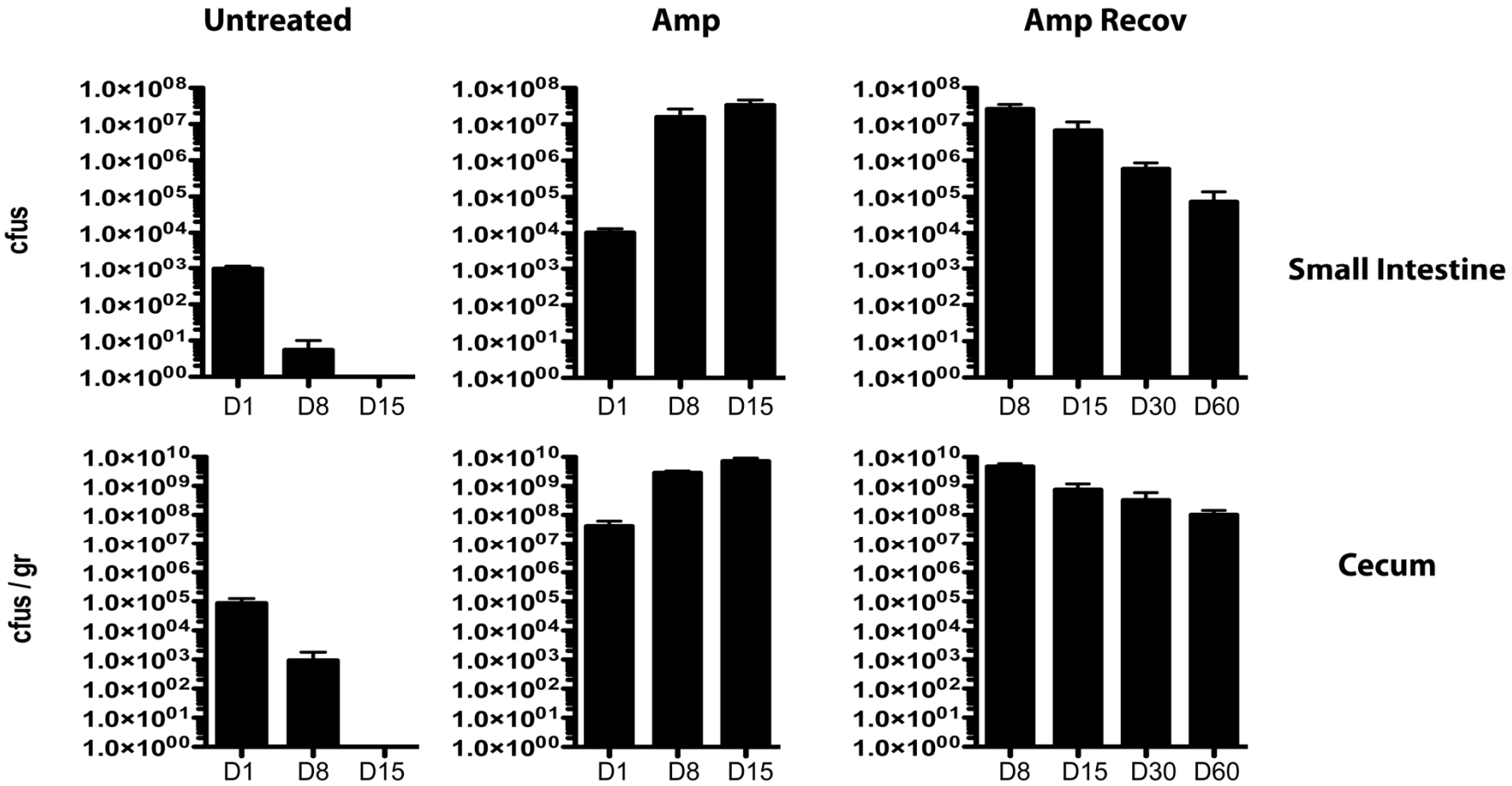
Graft versus host disease

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



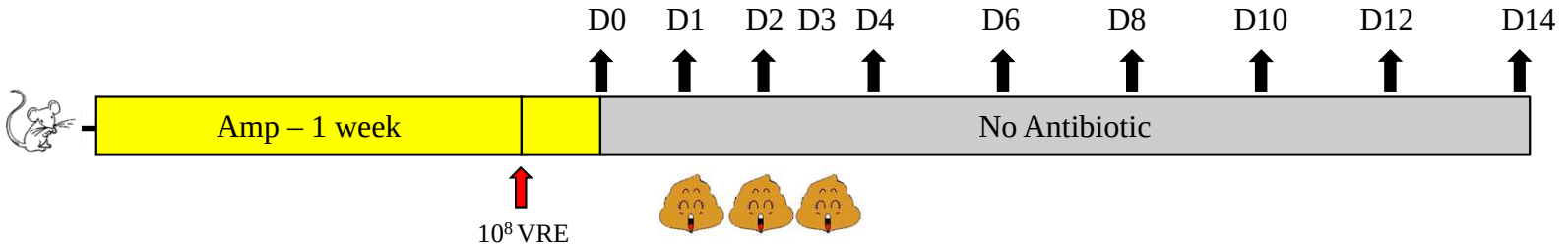
Ubeda et al. (2010) Journal of Clinical Investigation 120:4332.

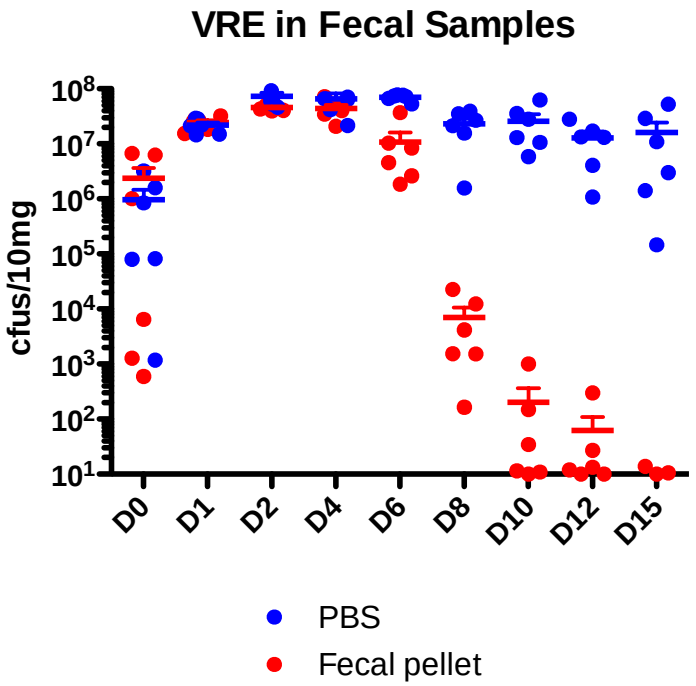
Antibiotic treatment enables VRE Domination of the GI tract in mice.

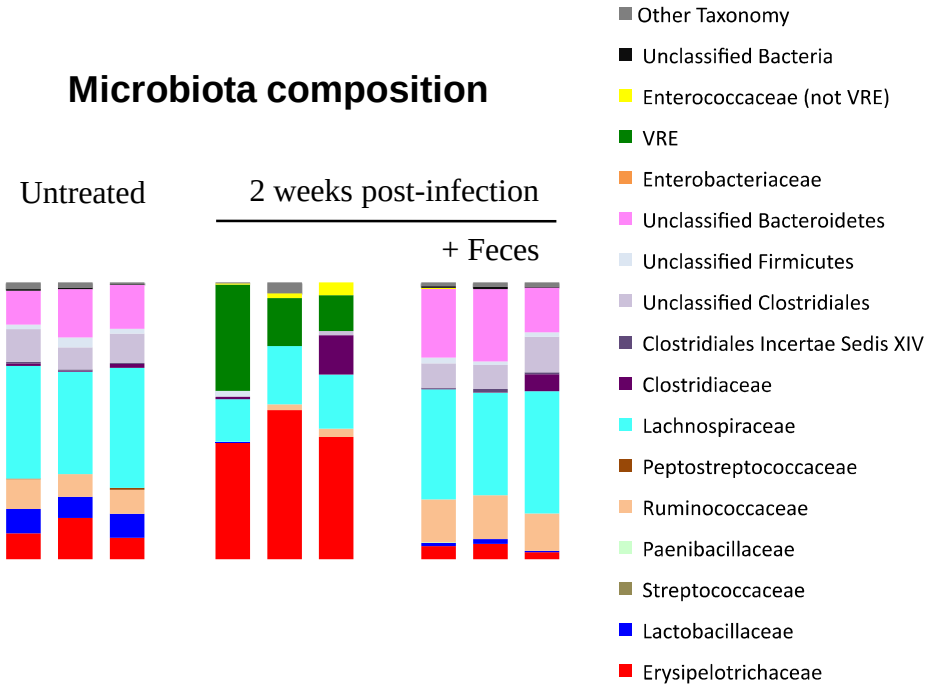


Ubeda et al. (2010) Journal of Clinical Investigation 120:4332.

“Normal” microbiota eliminates persistent VRE



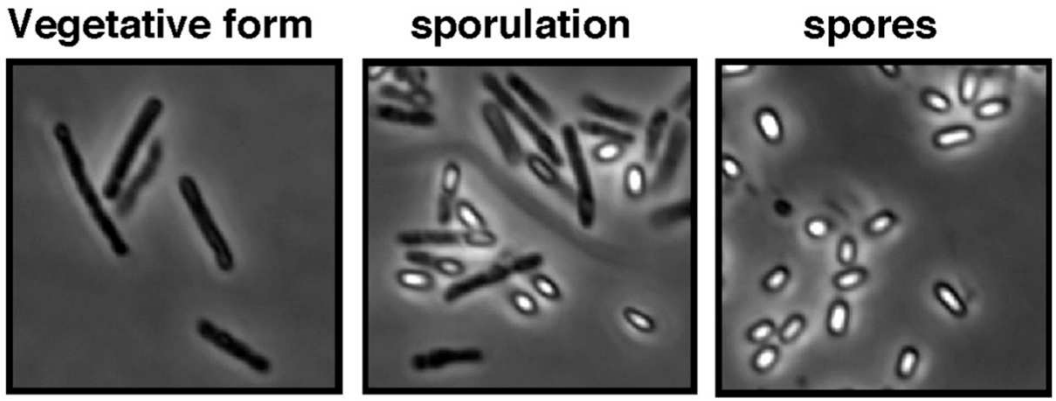




Ubeda et al. (2013) Infection and Immunity

Clostridium difficile (C. dif)

- Gram positive bacillus
- Increasing prevalence in hospitalized patients
- One of the most common causes of diarrhea in hospitalized patients
- High risk for patients receiving broad spectrum antibiotics or chemotherapy



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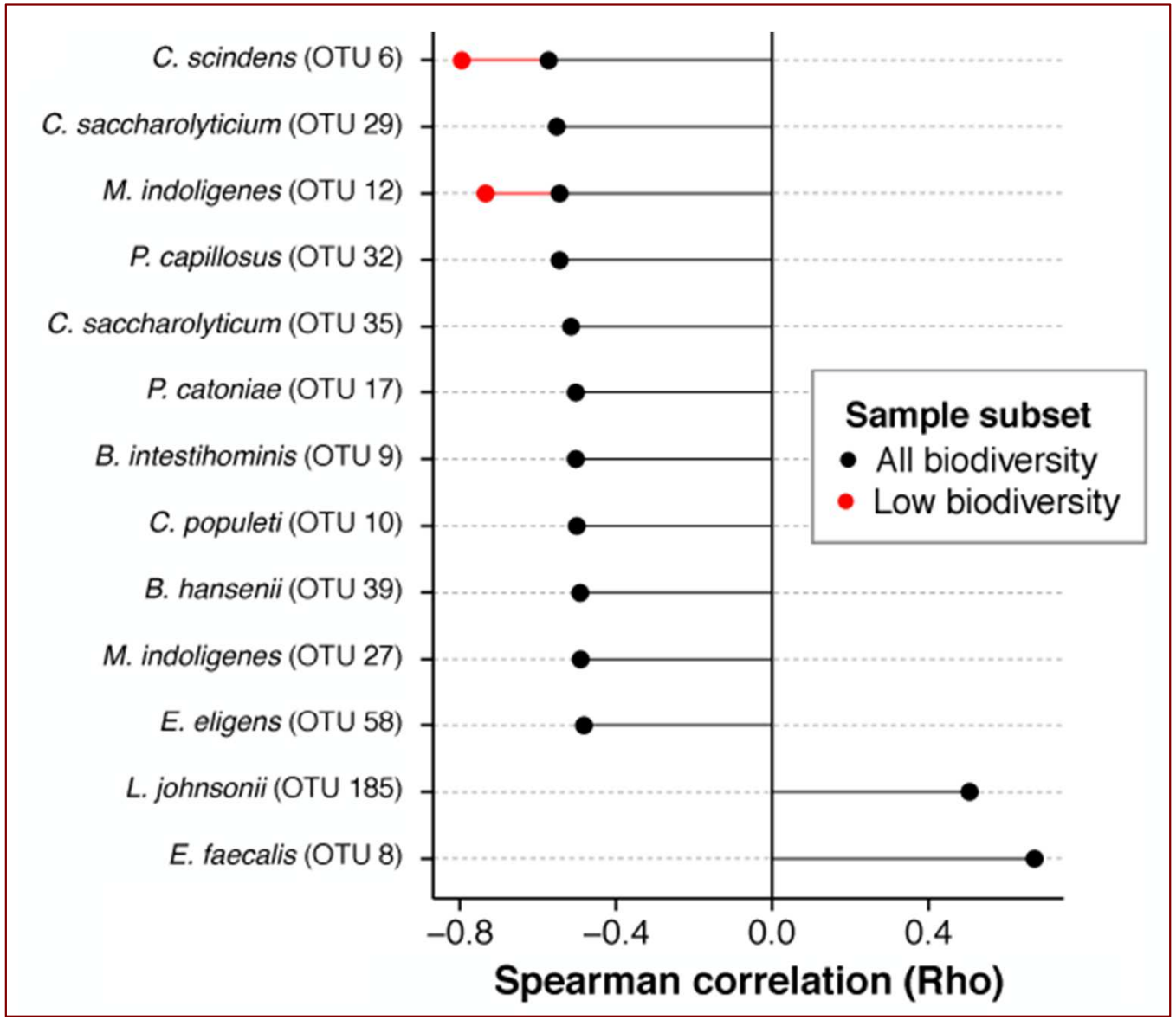
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

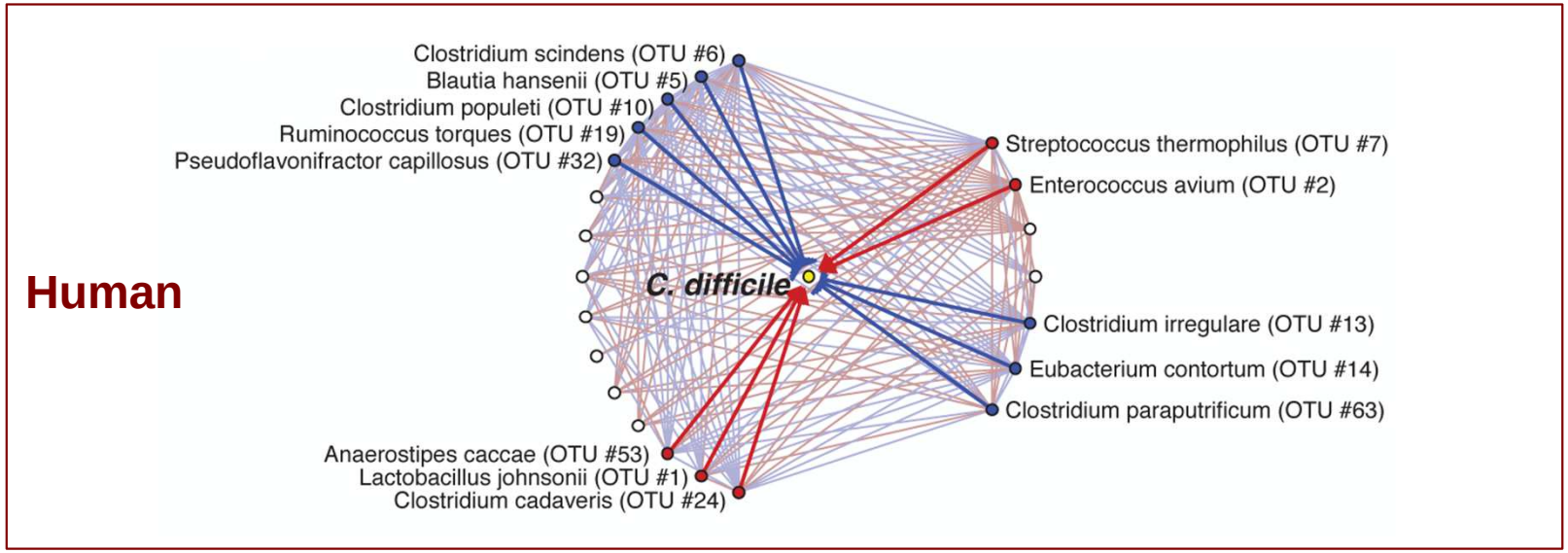
Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf,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

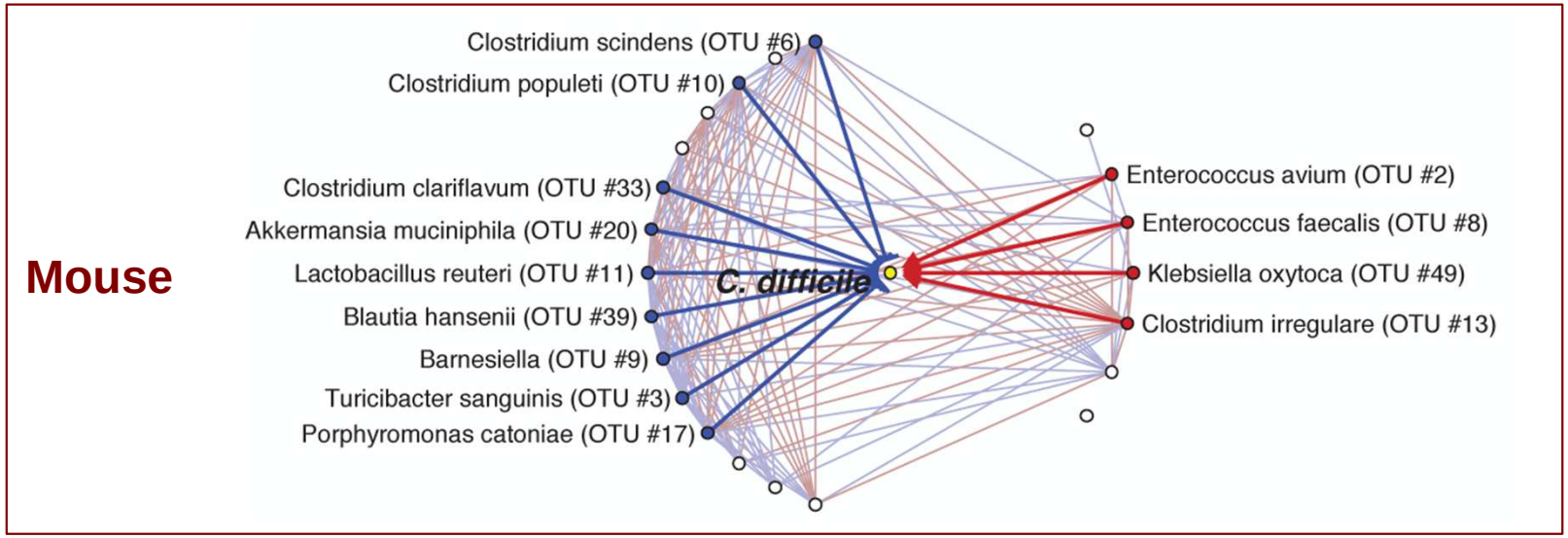
Correlating microbiota components & CDI resistance



Buffie et al. (2015) Nature 517:205

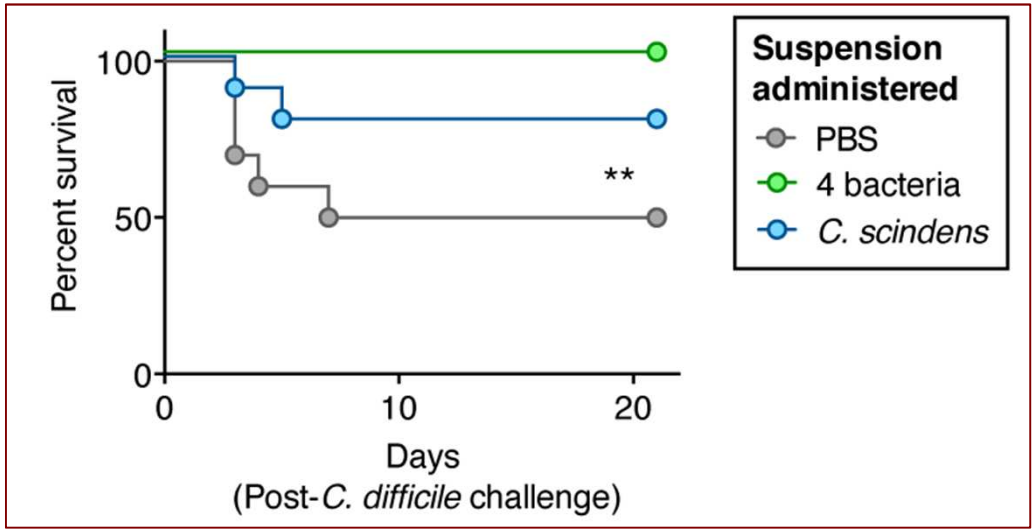
Shared microbial taxa associated with *C. difficile* inhibition in murine and human lower GI tracts, as determined by inference.

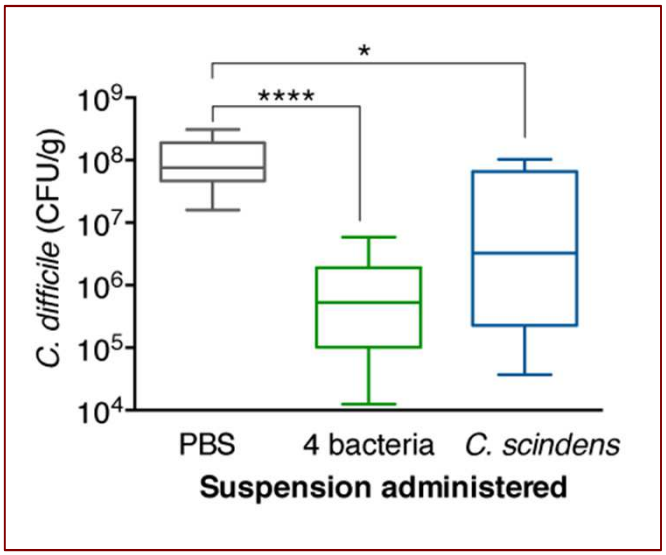


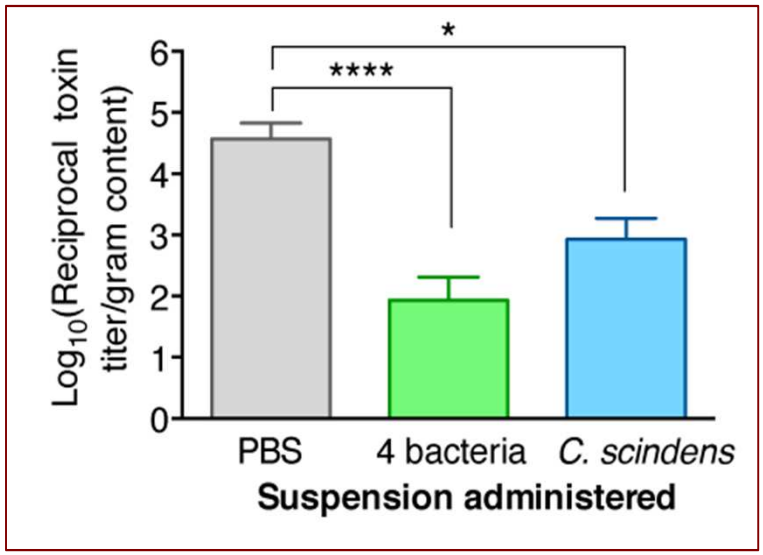


Buffie et al. (2015) Nature 517:205

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

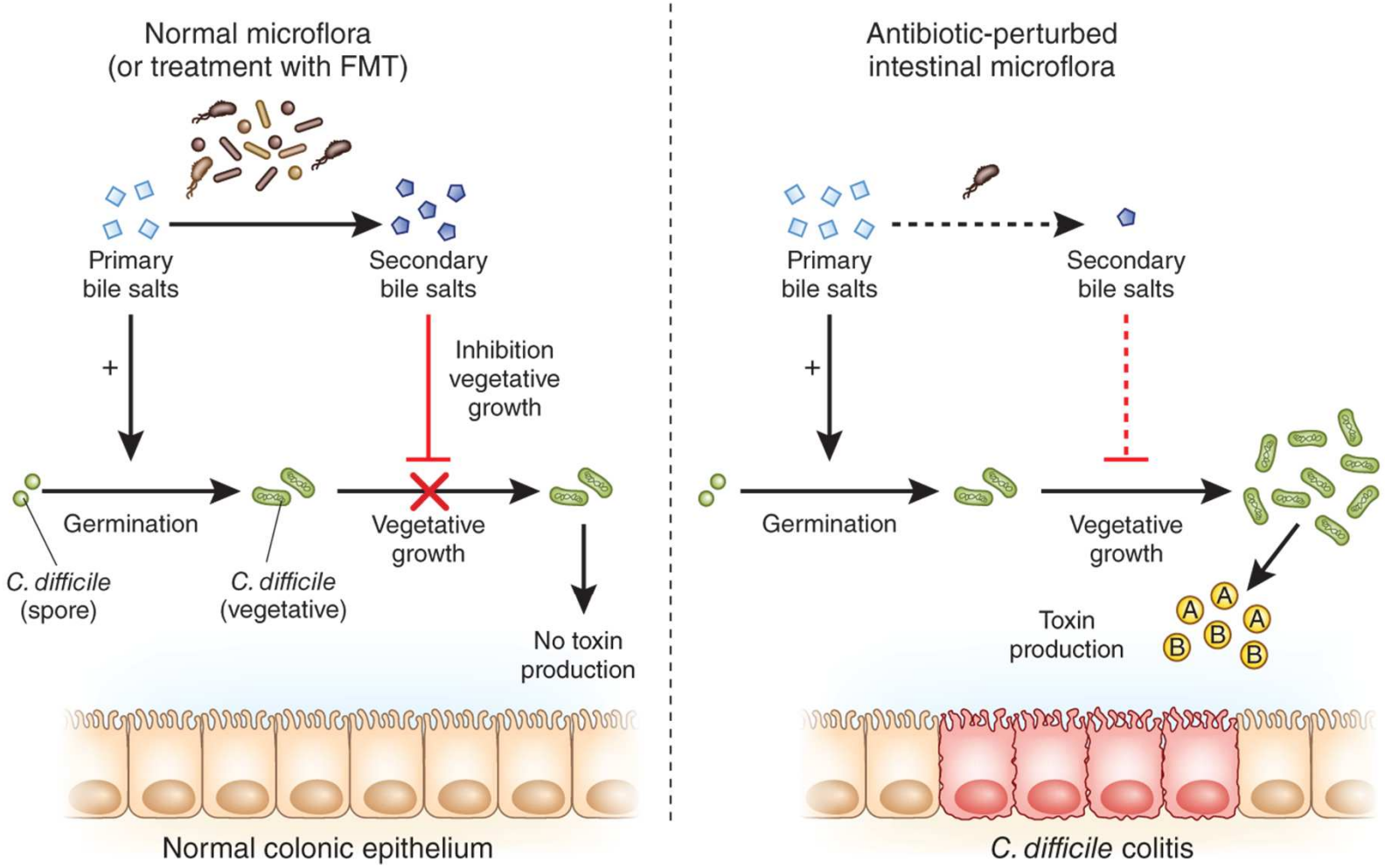






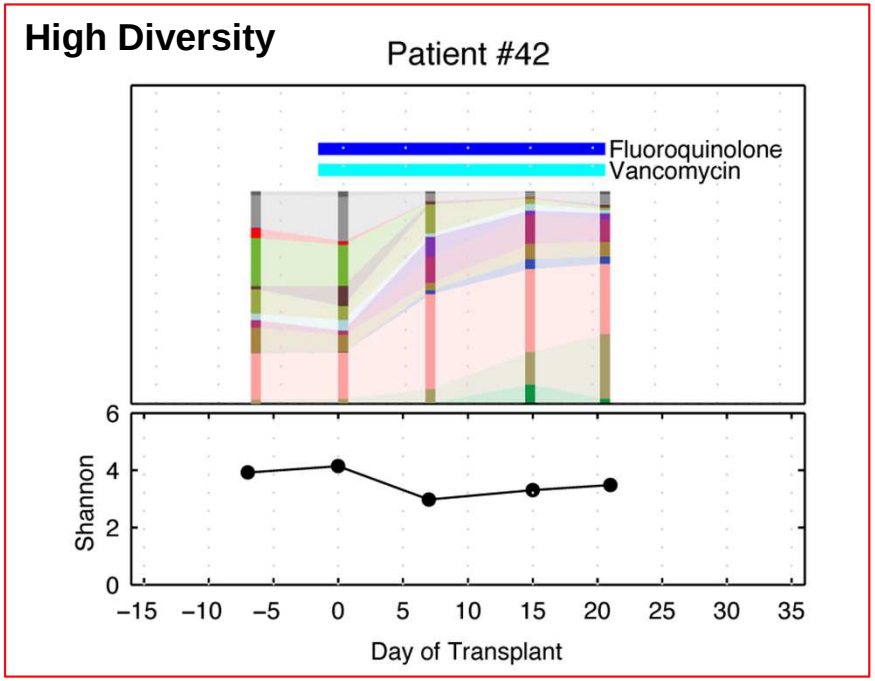
Buffie et al. (2015) Nature 517:205

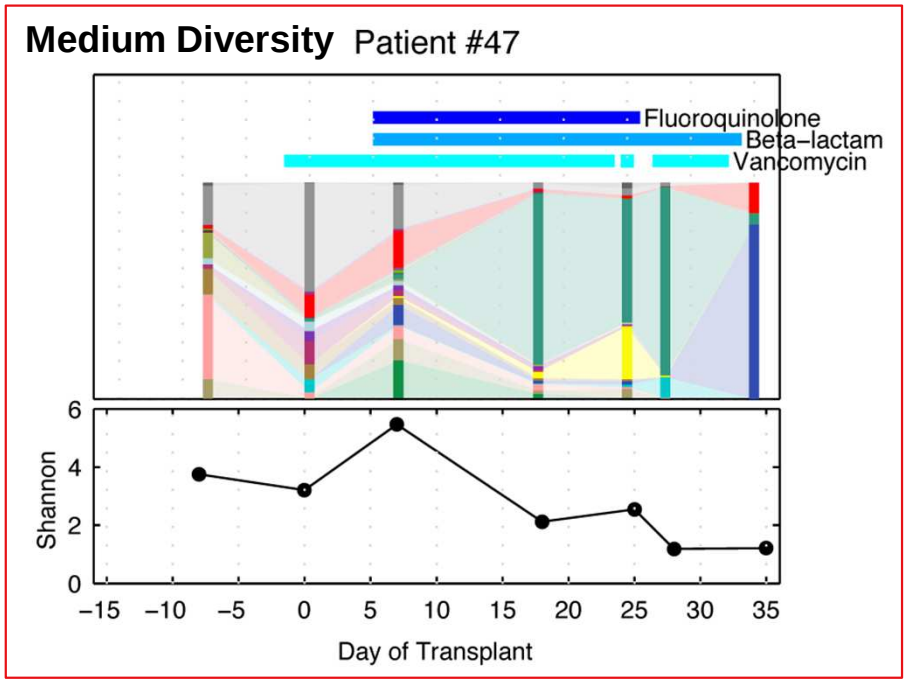
Secondary bile salt-mediated inhibition of *Clostridium difficile* growth

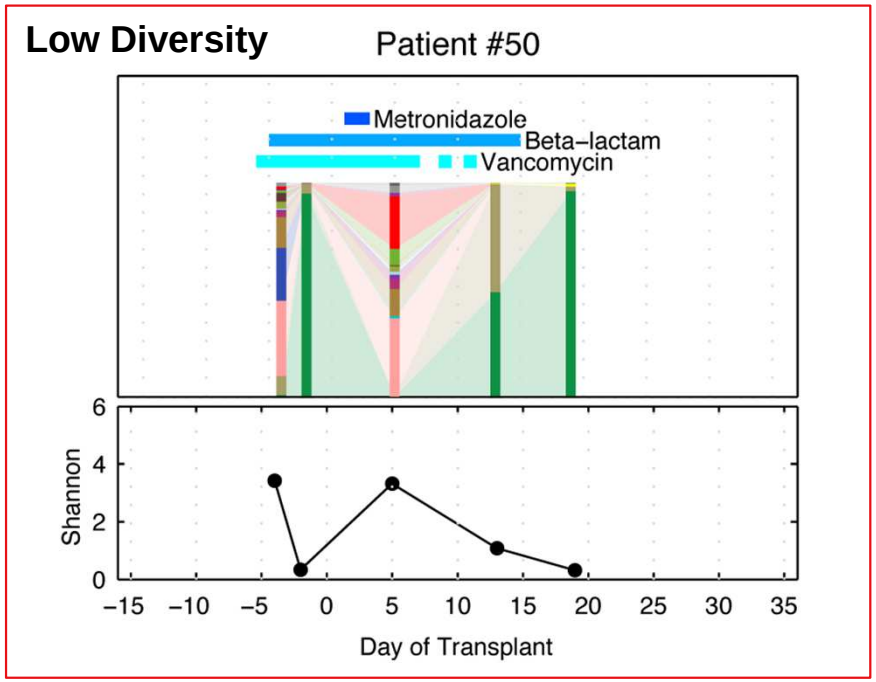


Taur & Pamer (2014) Nature Medicine

Loss of microbiota diversity following allo-HSCT is variable

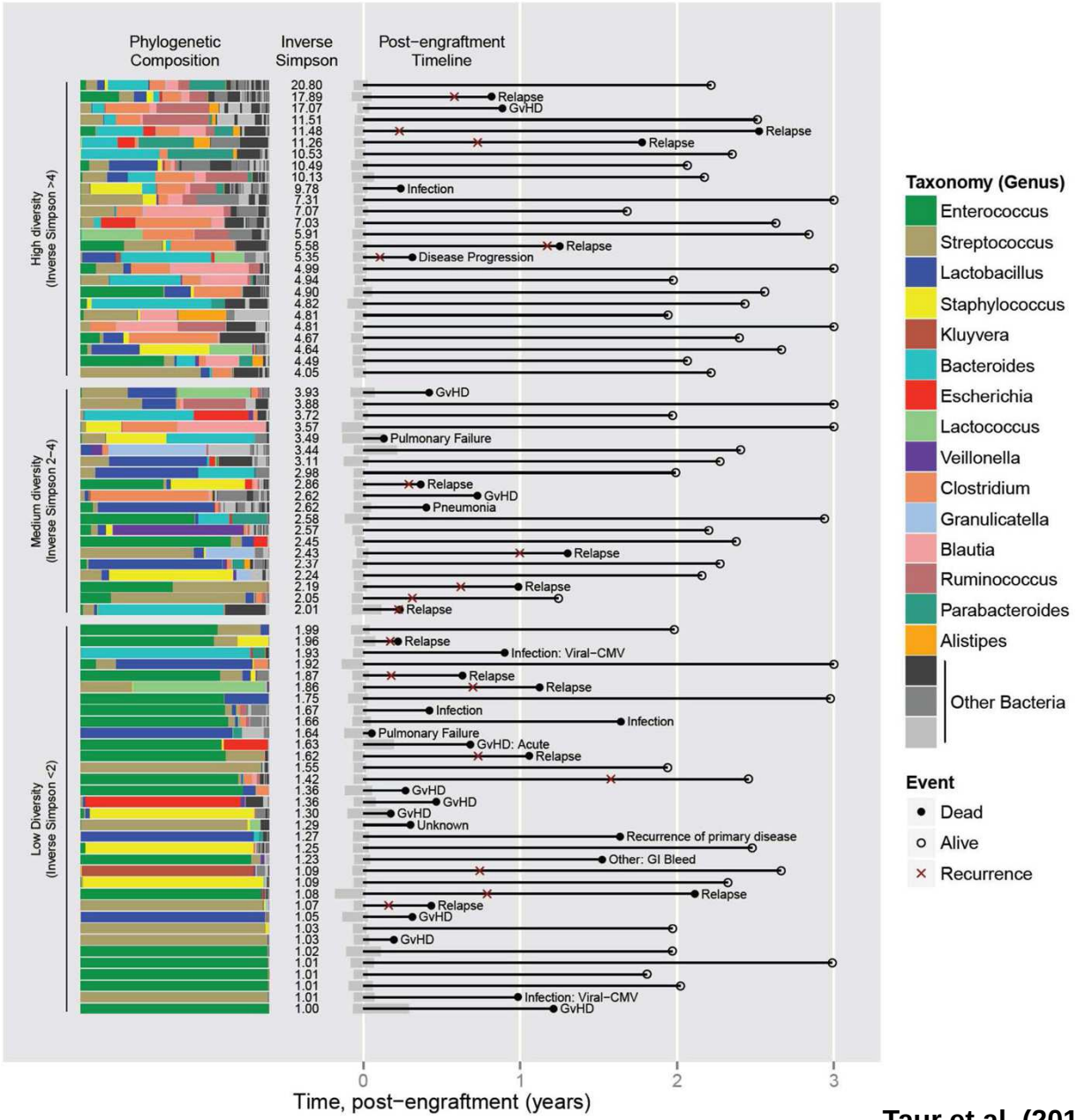






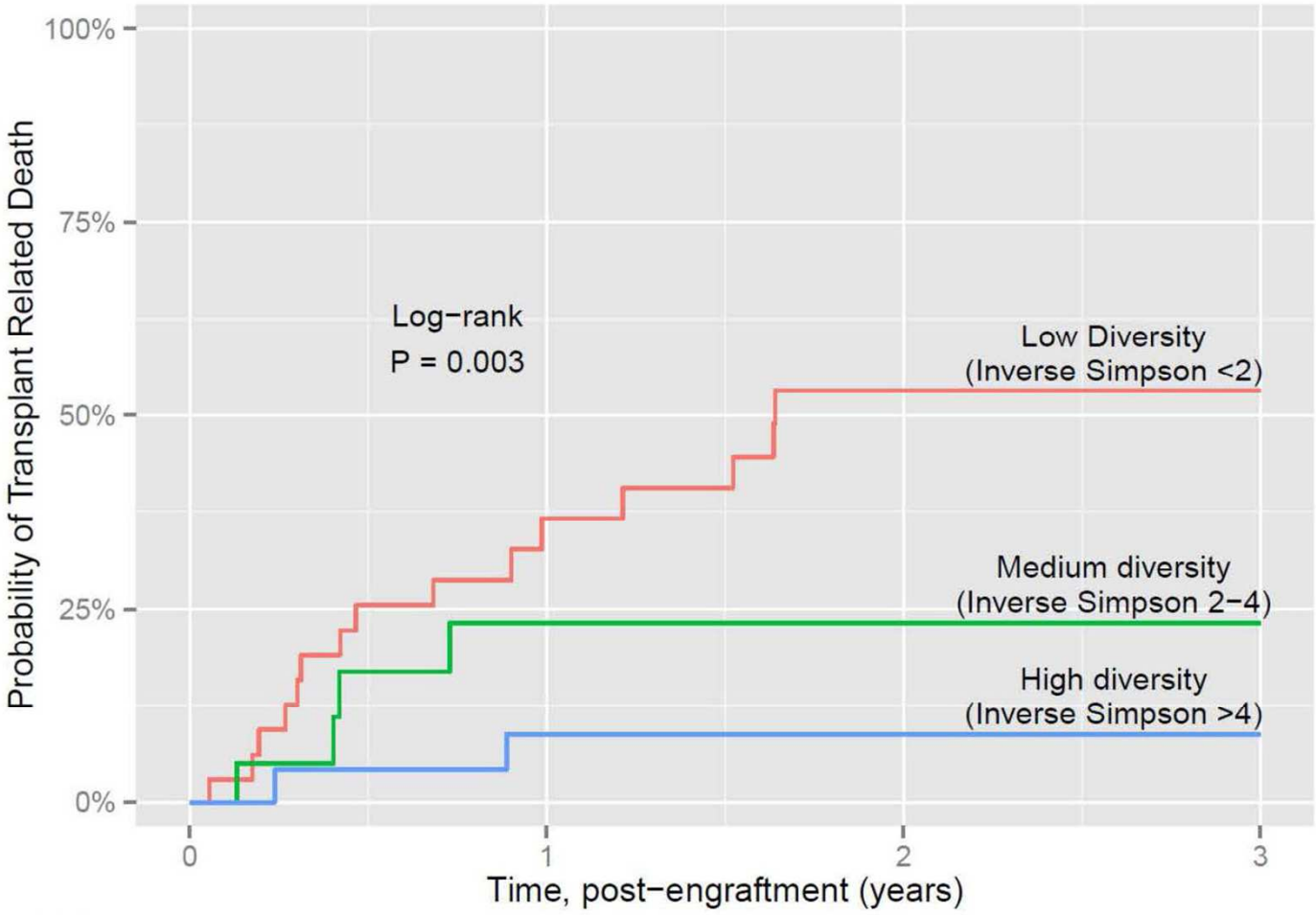
Taur et al. (2014) Blood 124:1174-82.

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



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

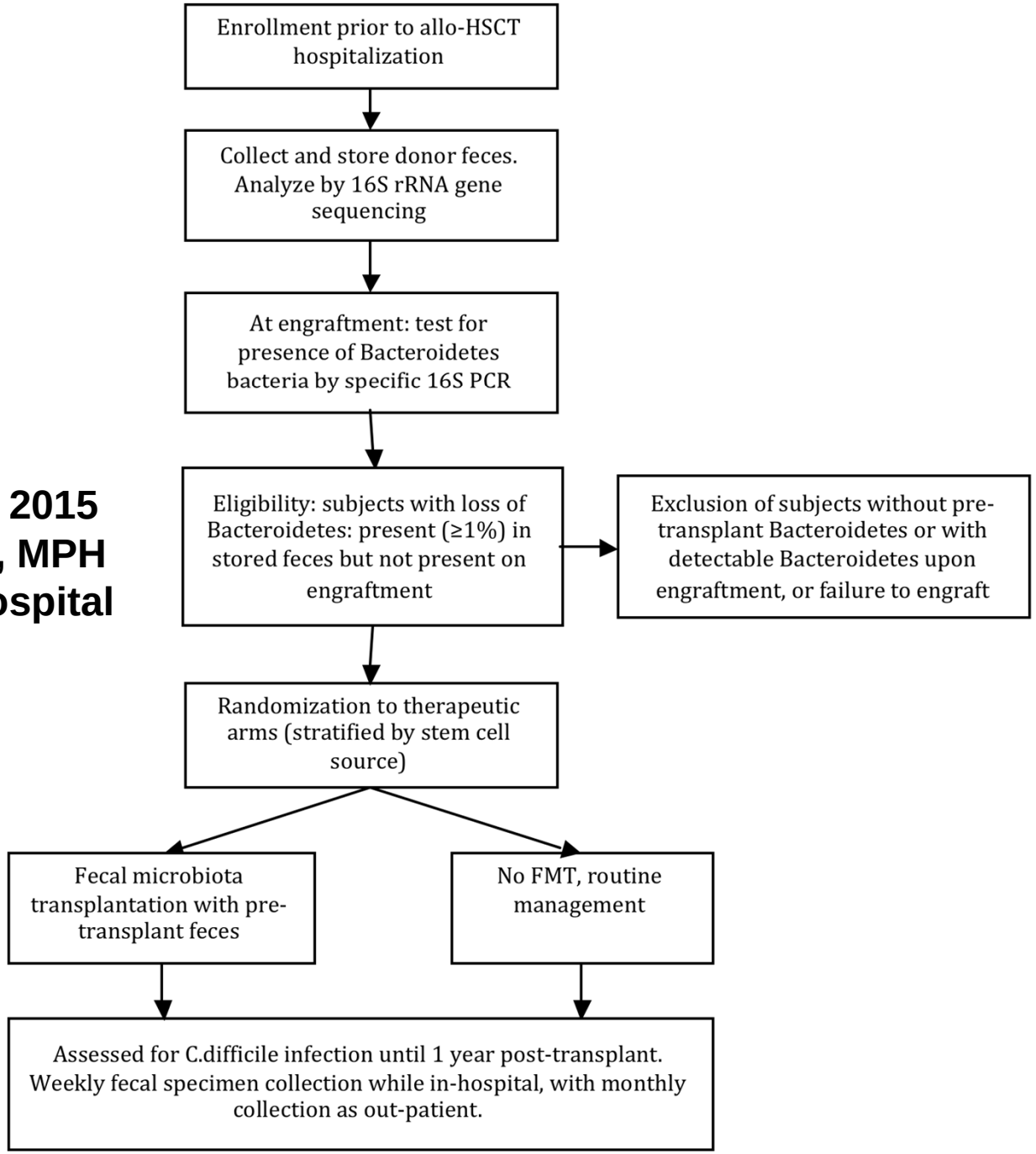
Transplant-related mortality is markedly reduced in patients with a diverse microbiota following engraftment



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

MSKCC Auto-FMT Clinical Trial

Opened: January 2015
PI: Ying Taur, MD, MPH
Site: Memorial Hospital



Microbiota-mediated defense against antibiotic-resistant bacterial infections.

Microbial populations in the gut stimulate antimicrobial mechanisms that reduce the ability of pathogens to colonize the gut.

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

Bacterial populations that confer resistance can be defined by metagenomic analyses and include obligate anaerobic bacteria.

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

Microbiota diversity predicts survival following allogeneic hematopoietic stem cell transplantation.

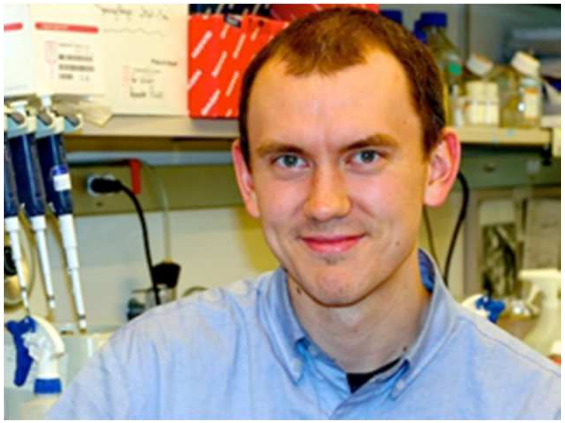
Reconstitution of mucosal bacterial populations following antibiotic therapy using FMT or specific commensal microbes provides an alternative approach to treat and prevent infections in an era of decreasing antibiotic susceptibility.

Joao Xavier

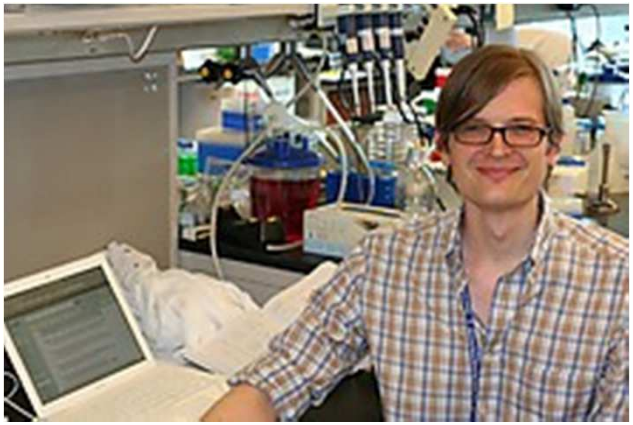
Ying Taur

Rob Jenq

Marcel van den Brink



Charlie Buffie



Peter McKenney

Carles Ubeda

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Charlie Buffie
Silvia Caballero
Dane Samilo
Krista Dubin
Brittany Lewis
Ingrid Leiner
Boze Susac
Rebecca Carter
Lilan Ling

Computational Biology
Joao Xavier
Jonas Schluter
Kat Coyte

Genomics Core Laboratory
Agnes Viale

Infectious Diseases
Ying Taur
Eric Littmann
Mergim Gjonbalaj