associazione microbiologi clinici italiani
Ente del Terzo Settore

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

CATANZARO - 12 APRILE 2024

GASTROENTERITI INFETTIVE:
NUOVI PERCORSI DIAGNOSTICI

Il ruolo del microbiota nelle gastroenteriti infettive

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Altered **microbiome** as a cause or consequence of disease, or an environmental risk factor or disease modulator

Microbiome provides **biomarkers** that could be tested for risk or presence of disease

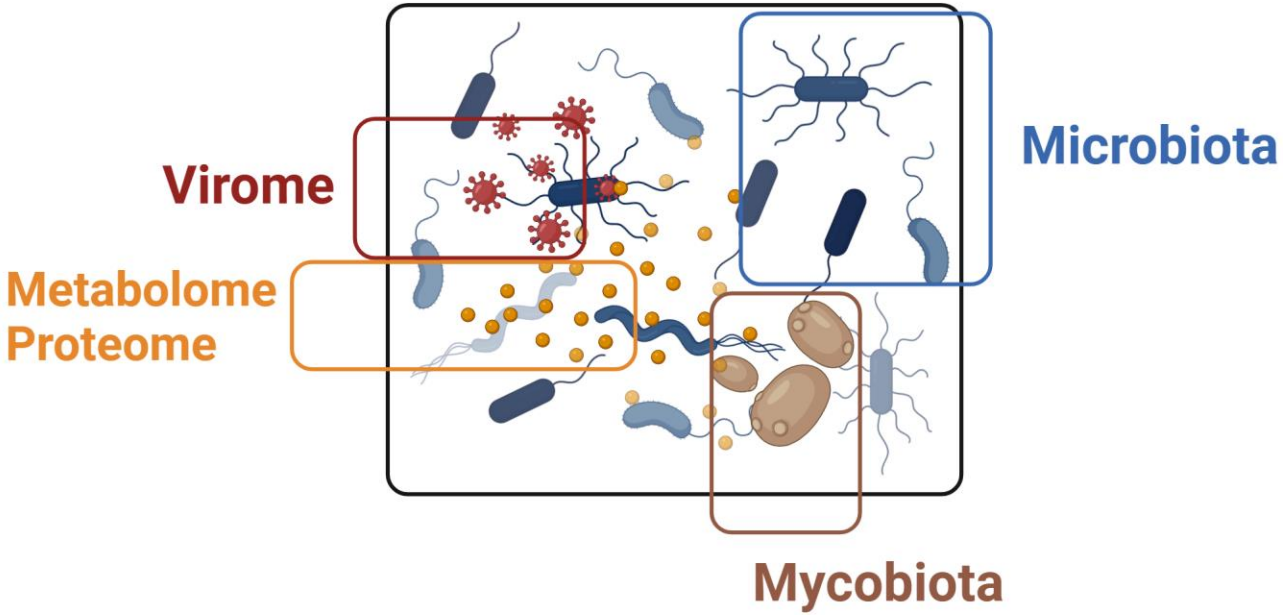
The hunt for a healthy microbiome

Despite evidence of the gut microbiome's role in human health, researchers are still working out what shapes the community of microbes.

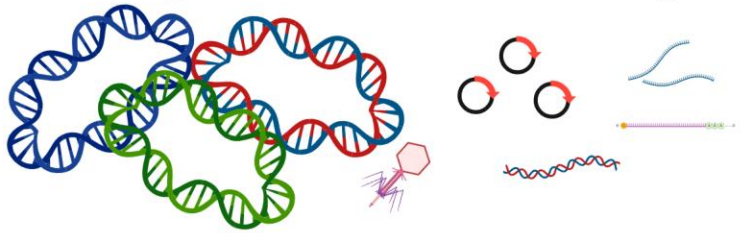
By Michael Eisenstein

Microbiome

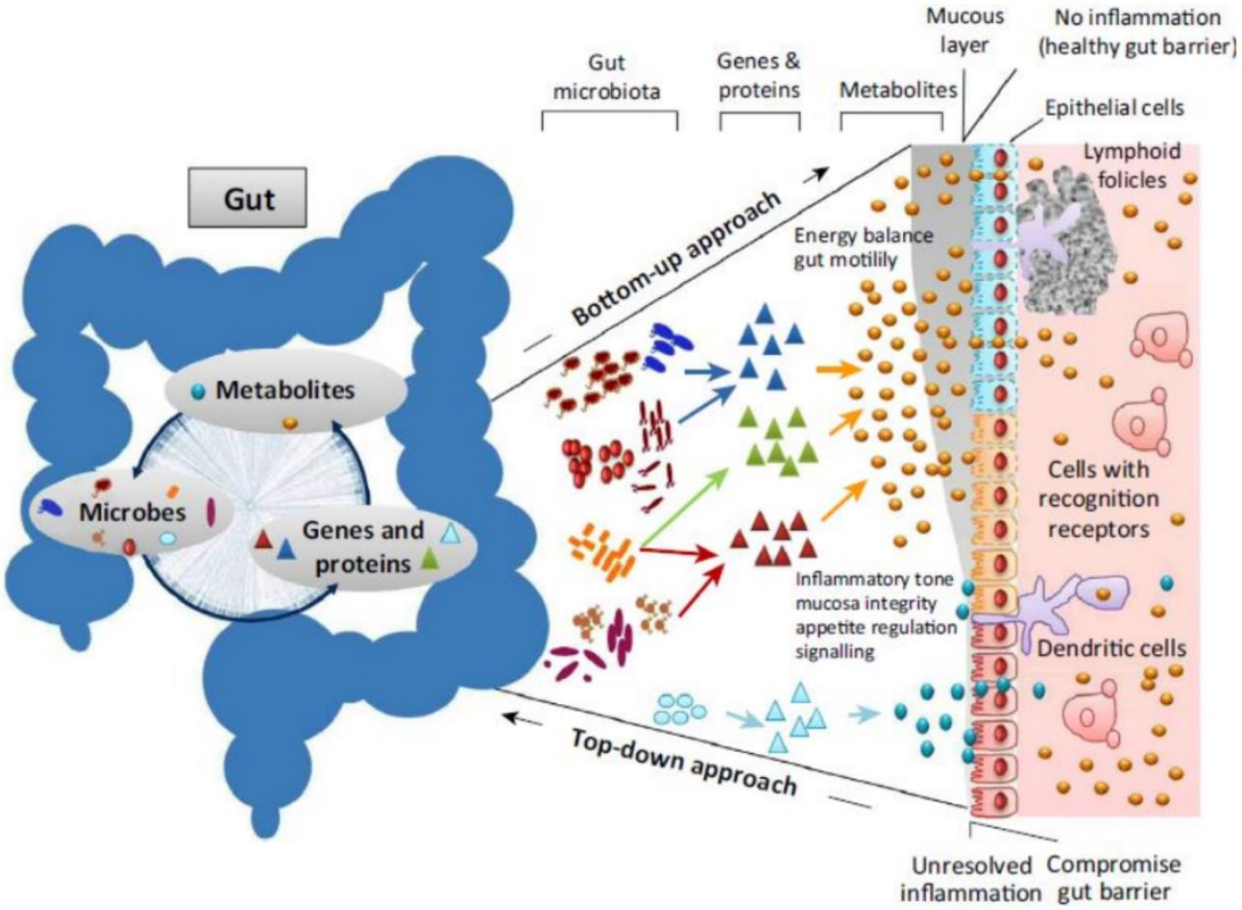
covers not only the microorganisms but also the surrounding environmental conditions.



Metagenome includes all genomes of the microorganisms



The microbiome as the last human organ



Moya and Ferrer/Trends in Microbiology 2016

Proposed Koch's postulates for NGS

Original[A]	Molecular[B]	Next-generation sequencing[C]
• The microorganism is found in abundance in diseased but not in healthy individuals • The microorganism is able to be isolated from the diseased host and grown in pure culture • The cultured microorganism causes disease when inoculated into a healthy host • The microorganism can be re-isolated from the inoculated host and is the same as the original microorganism • Elimination of the microbe from the host alleviates disease	• The virulence gene is found in pathogenic but not nonpathogenic microbial strains • Deletion or inactivation of the virulence gene leads to loss of microbe pathogenicity • Reactivation or allelic replacement of the gene restores microbe pathogenicity	• Individual microorganisms or communities of microorganisms, as identified by sequencing, differ in abundance, organization, and/or function in diseased vs. healthy individuals • Community virulence or functional consequences may or may not depend on specific, well-defined microbe virulence genes • Community modification and/or elimination of specific community members alleviates the disease state

Wensel et al, The Journal of Clinical Investigation 2022

Gut Microbiota and Gastroenteritis

Infectious diarrhea
3 loose liquid stool per day in patients

1.3 milion deaths yearly (500000 children)

- *Viruses (rotavirus, norovirus)*
- *Bacteria (Campylobacter, Salmonella Shigella, Vibrio, E. coli, Aeromonas, C. difficile)*
- *Parasites (Criptosporidium, Entamoeba, Giardia)*
- *Fungi (Candida)*

1. Pathogenic bacteria inhibits the growth of normal bacteria
2. pathgens produce toxic substances altering gut function and immune response

↓

Major dysbiosis event
Increased bowel movements
Fluids Secretions

Acute disease that requires longitudinal observations to capture rapid changes in microbiota composition

self limiting episodes
oral rehydratation
zinc supplement
probiotics
antimicrobials

highly varied and dynamic
geography
birth term
mode of delivery
breastfeeding
time of weaning
nutritional status

Gut Microbiota and infectious diarrhea

Diarrheagenic bacteria appear transient and/or low abundant

Early phase - diarrhea

symptoms not subsided
3-5 days since disease onset
marked reduction in taxonomic richness and diversity

↓

Significant taxonomic change
Proliferation of fast-growing facultative anaerobes.
Proteobacteria (Enterobacteriaceae/E. coli) and
Streptococcus (Streptococcus salivarius and
Streptococcus gallolyticus)

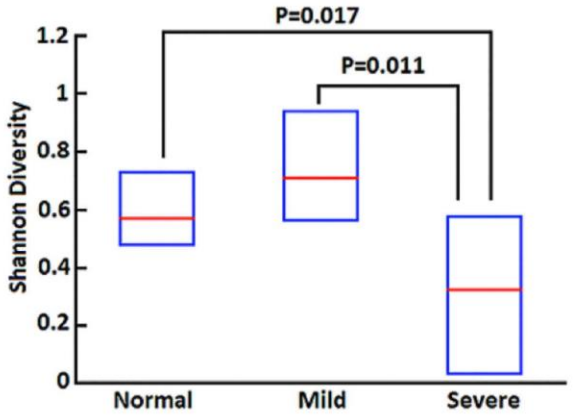
↓

Disappearance of obligate anaerobic gut commensals
(Blautia, Prevotella, Faecalibacterium,
Lachnospiraceae, Ruminococcaceae, etc.)

Adults: often show fecal microbiota similar to healthy controls

In **Children** prevail:
- Bifidobacterium
- Bacteroides
- Streptococcus
- Escherichia

Increase abundance of human oral microbiota (Granulicatella, Gemella, Actinomyces, Rothia, Fusobacterium nucleatum, etc.)



Chen et al, Scientific Reports 2017

Giardia-induced diarrhea was consistently linked to a decrease in **Gammaproteobacteria** and an enrichment of **Prevotella**

During rotavirus infection **Bacteroides** and **Akkermansia** populations (both with mucin-degrading capability)

Gut Microbiota and infectious diarrhea

Post diarrhea

Increase in taxonomic richness and diversity

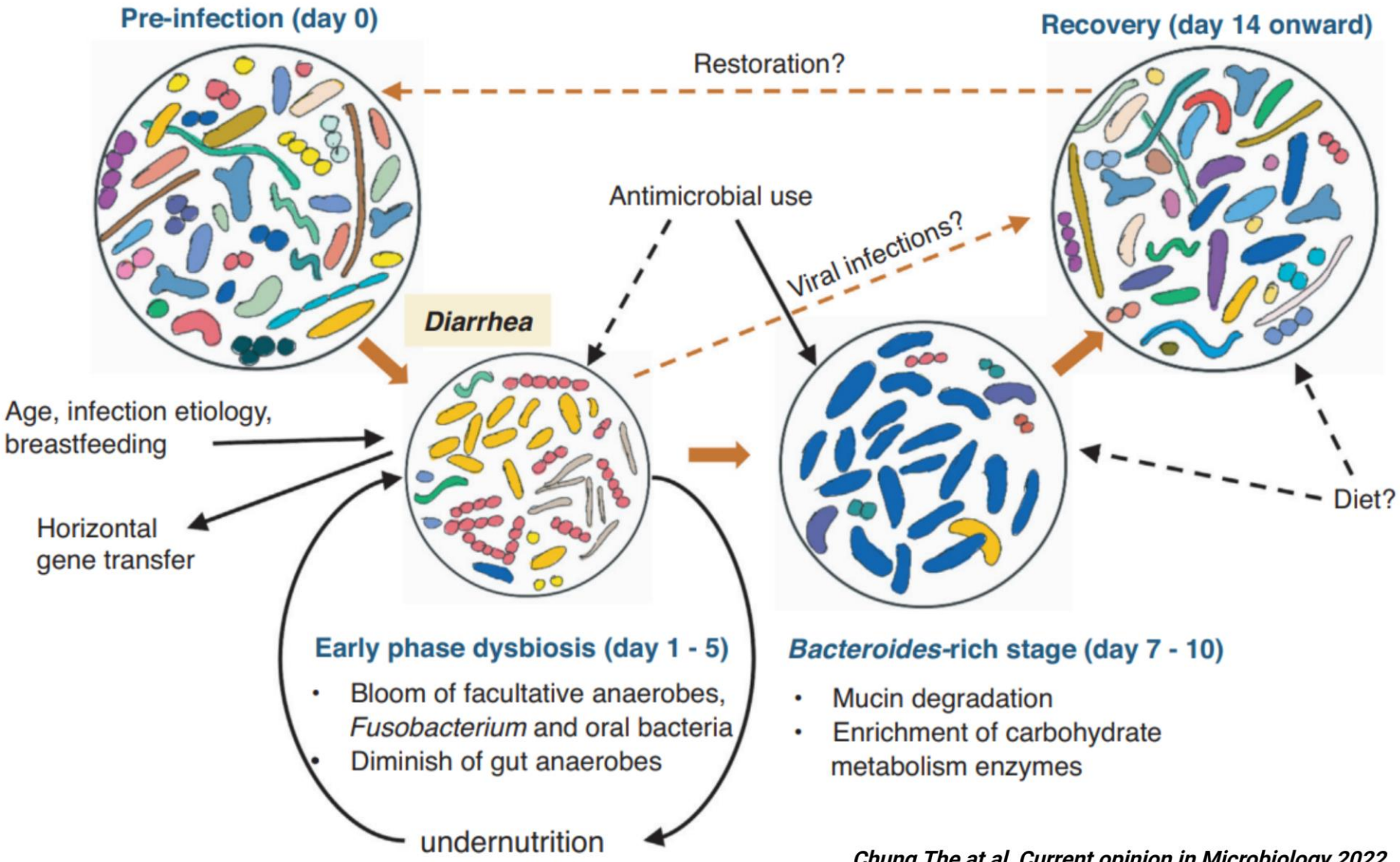
↓

Mid-stage is specifically characterized by a sizable abundance of Bacteroides (occurring as early as day 7 since disease onset)
Late-stage harbors a greater abundance and diversity of Prevotella and SCFA-producing Firmicutes

↓

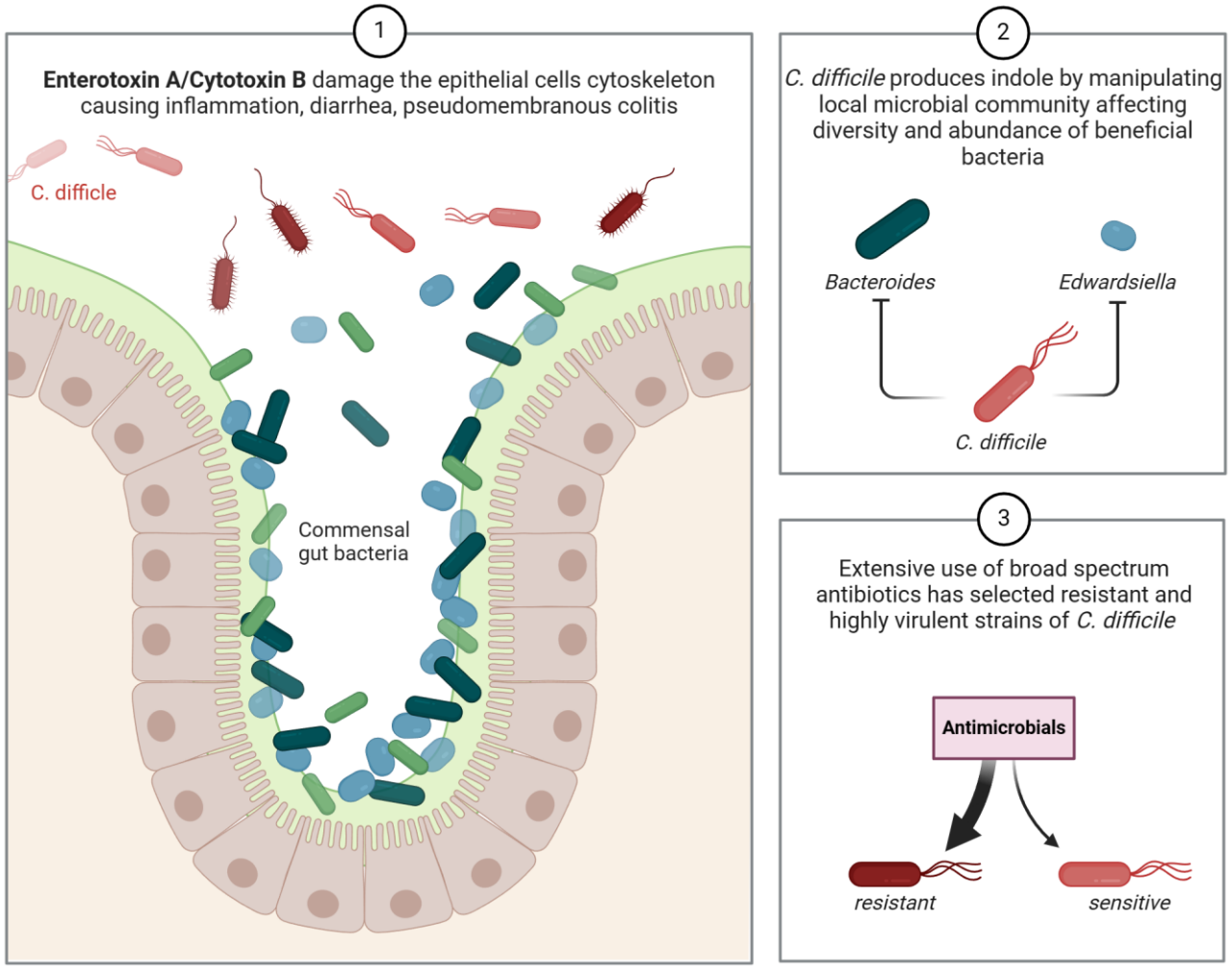
Increase **Bacteroides** relative abundance
Subsequently initiates a complex network of cross-feeding to expedite the repopulation of other anaerobic and SCFA producing commensals (**Bifidobacterium, Roseburia, Faecalibacterium**, etc.), thus establishing a taxonomically and functionally diverse community

Gut Microbiota and infectious diarrhea: Summary

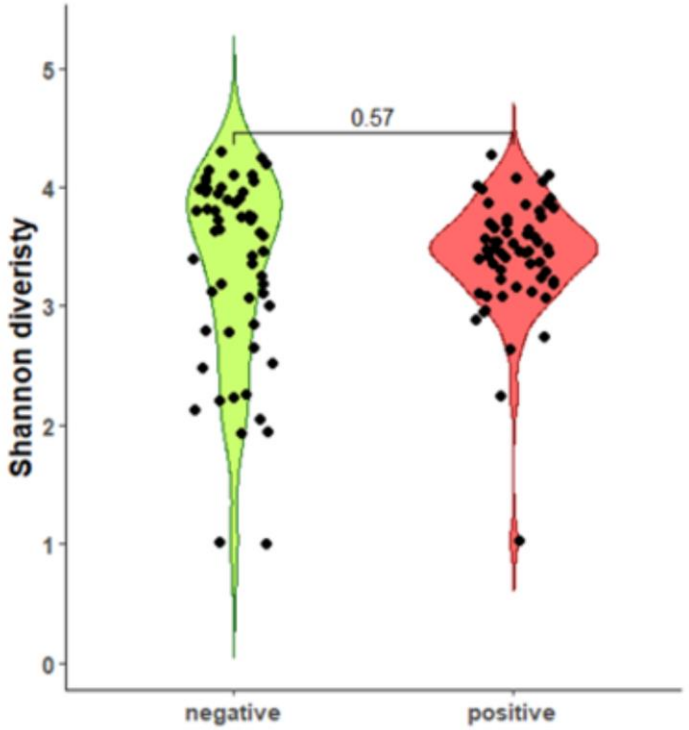


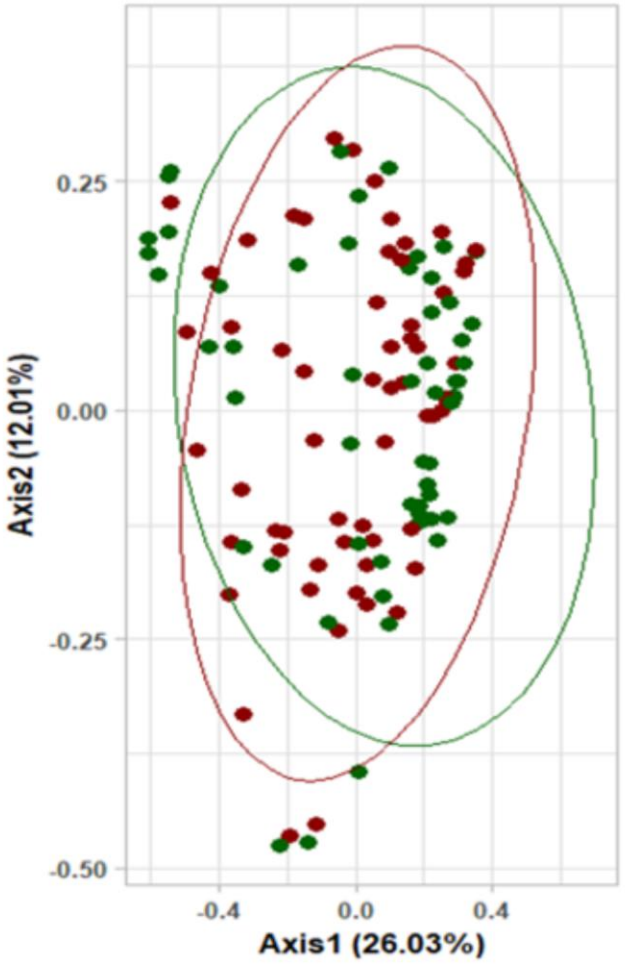
Chung The at al, Current opinion in Microbiology 2022

CDI pathogenesis: impact on gut microbiota



Gut Microbiota at CDI onset

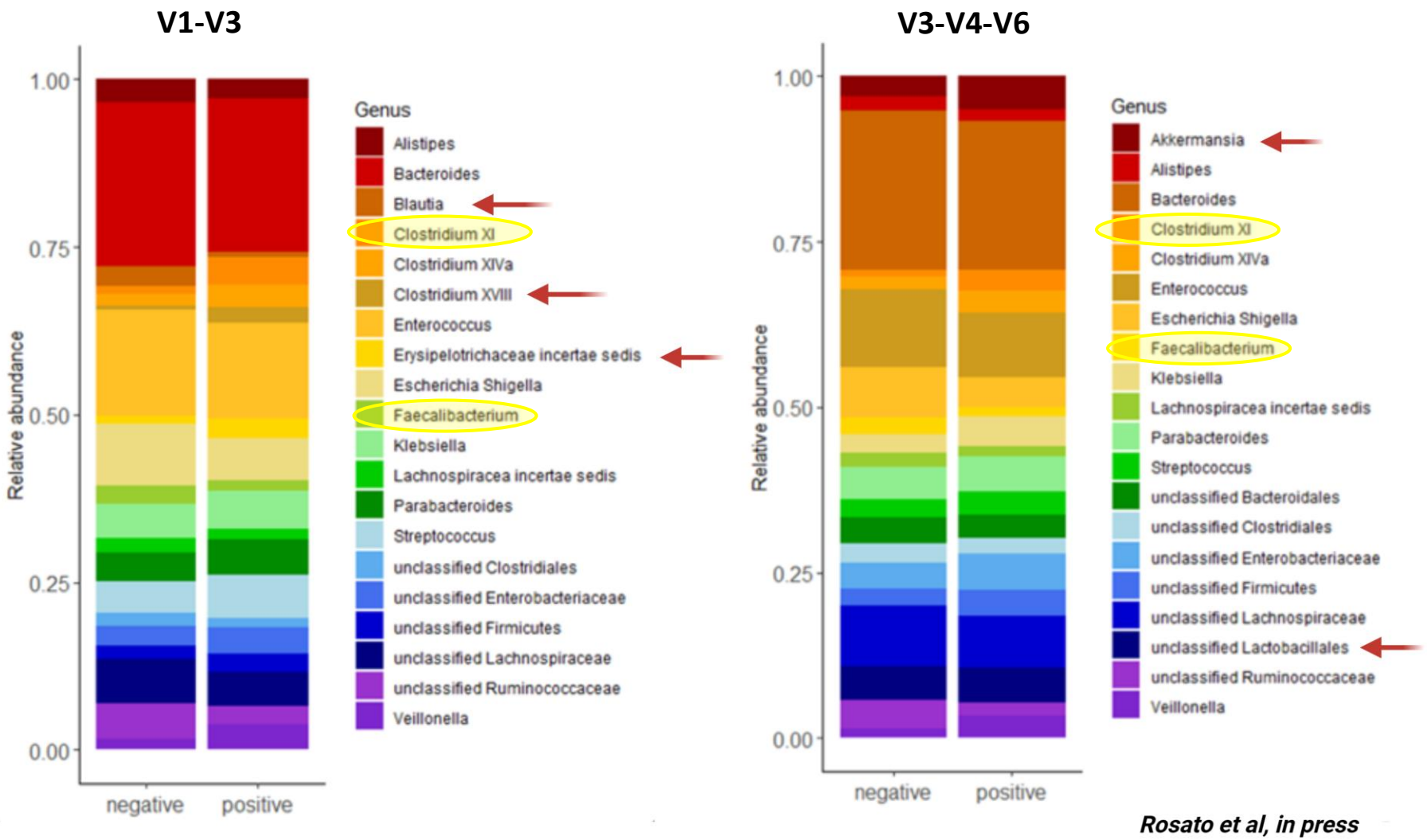




Rosato et al, in press

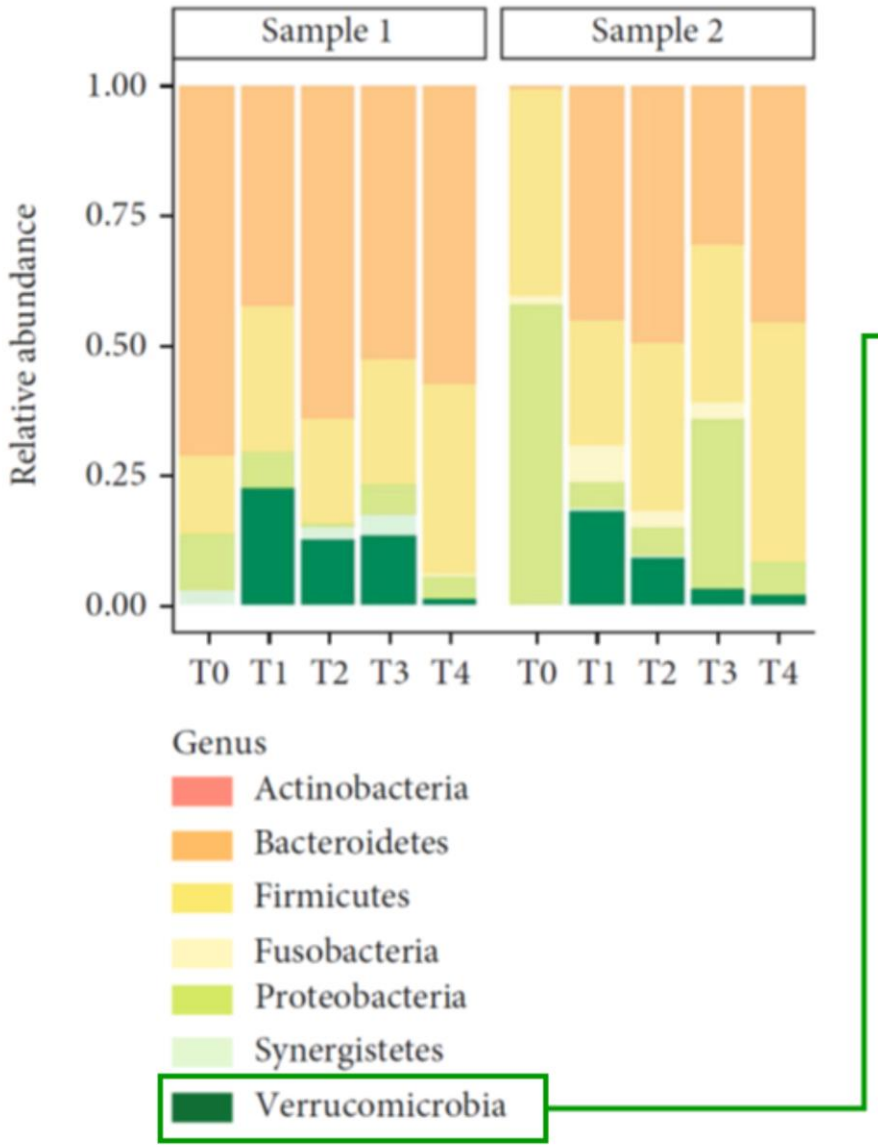
No changes in alpha and beta diversity are detected at the CDI onset compared to control group

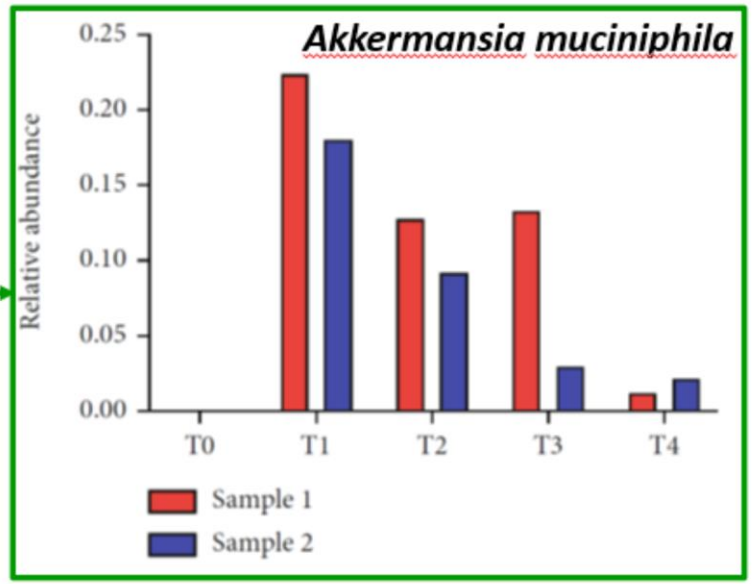
Microbiota characterization: application



Rosato et al, in press

Microbiota characterization: application



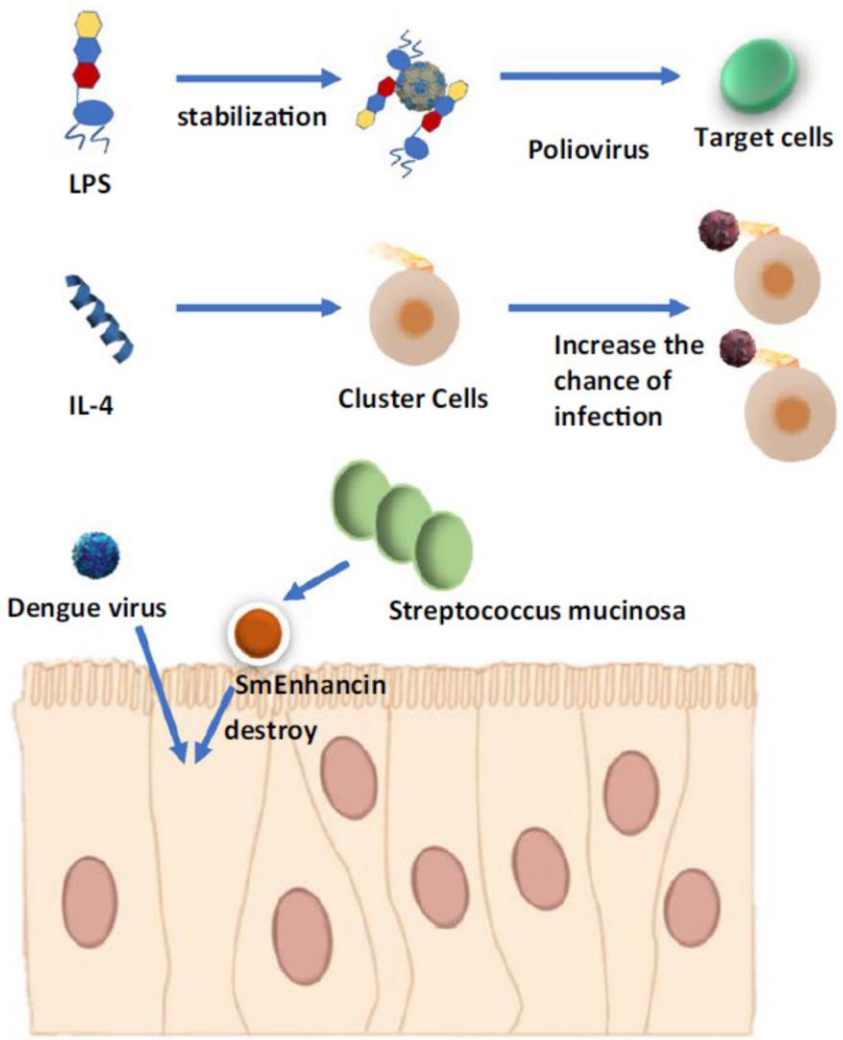


Quaranta et al, BioMed Research International 2022

Metagenomics data revealed an "awakening" by microbial species absent or low abundant at time T0 and acquired after the infusion

The infusion of selected bacteria would act as a trigger factor for "bacterial repopulation" representing an innovative treatment in patients with CDI.

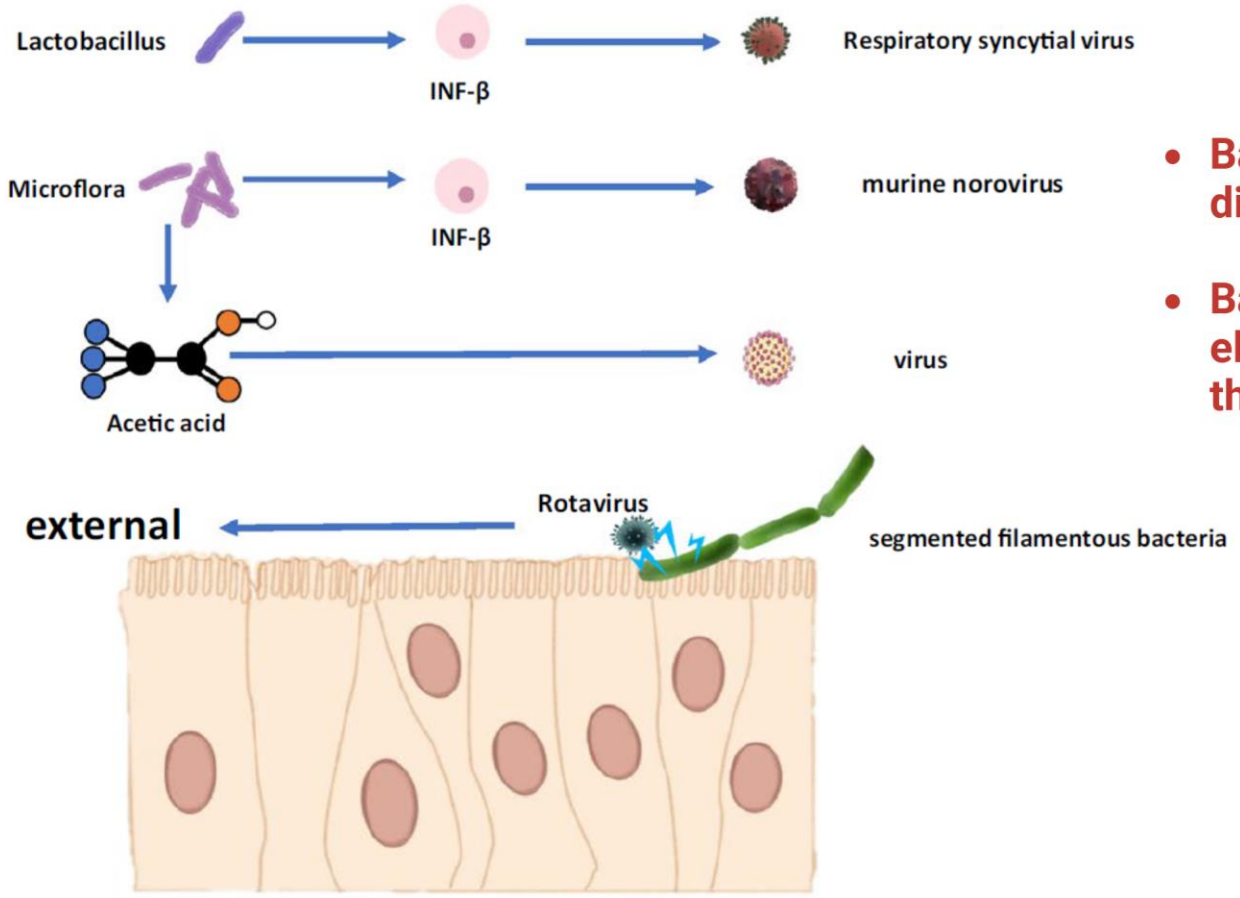
Viral gastroenteritis and gut microbiota



Lv et al, Current Microbilogy 2021

- **Enhance the infectivity of virus (stabilize the structure of virus and increase the differentiation of target cells)**
- **Modify the host immune response and weaken the defence against virus.**

Viral gastroenteritis and gut microbiota

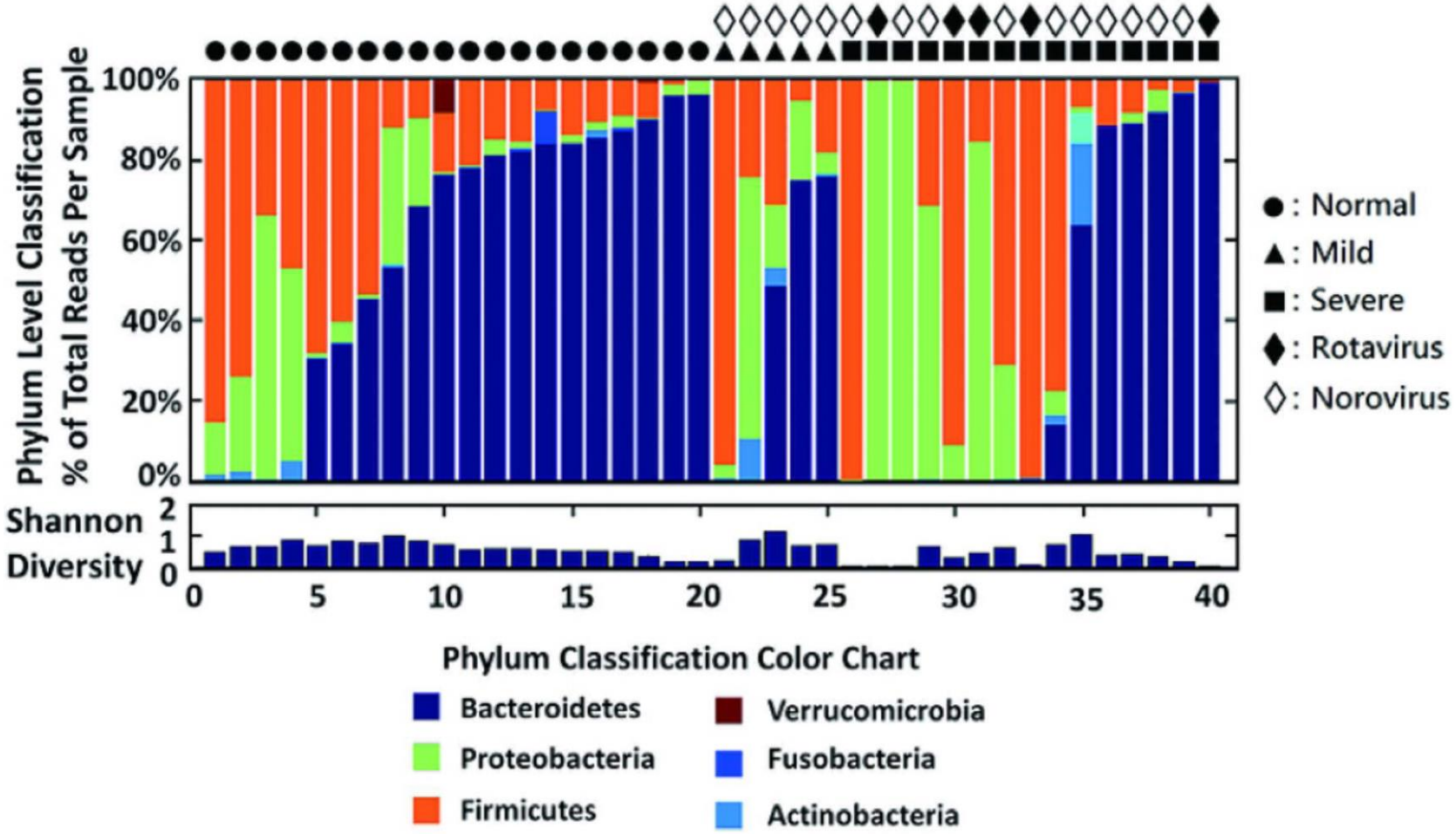


Lv et al, Current Microbilogy 2021

- **Bacteria and their metabolites directly fight viruses**
- **Bacteria and their metabolites eliminate viruses by mobilizing the body's immune system**

Viral gastroenteritis and gut microbiota

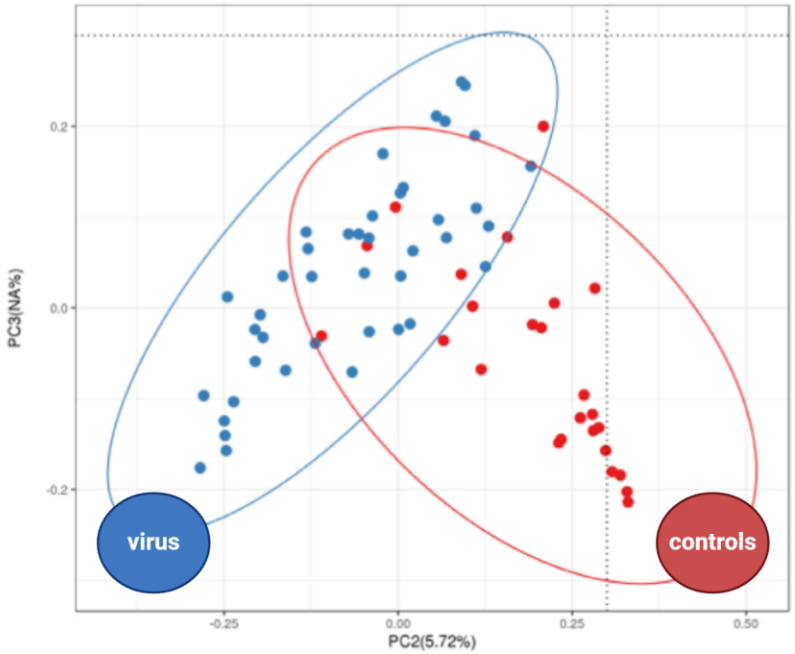
Greater richness in *Campylobacteraceae, Neisseriaceae, Methylobacteriaceae, Sphingomonadaceae* and *Enterobacteriaceae* in patients with acute viral gastroenteritis

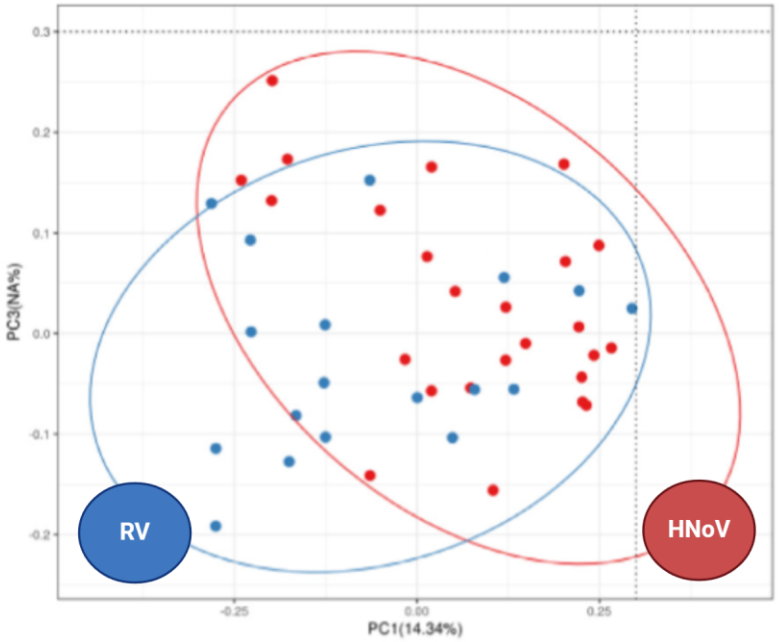


Chen et al, Scientific Reports 2017

Viral gastroenteritis and gut microbiota

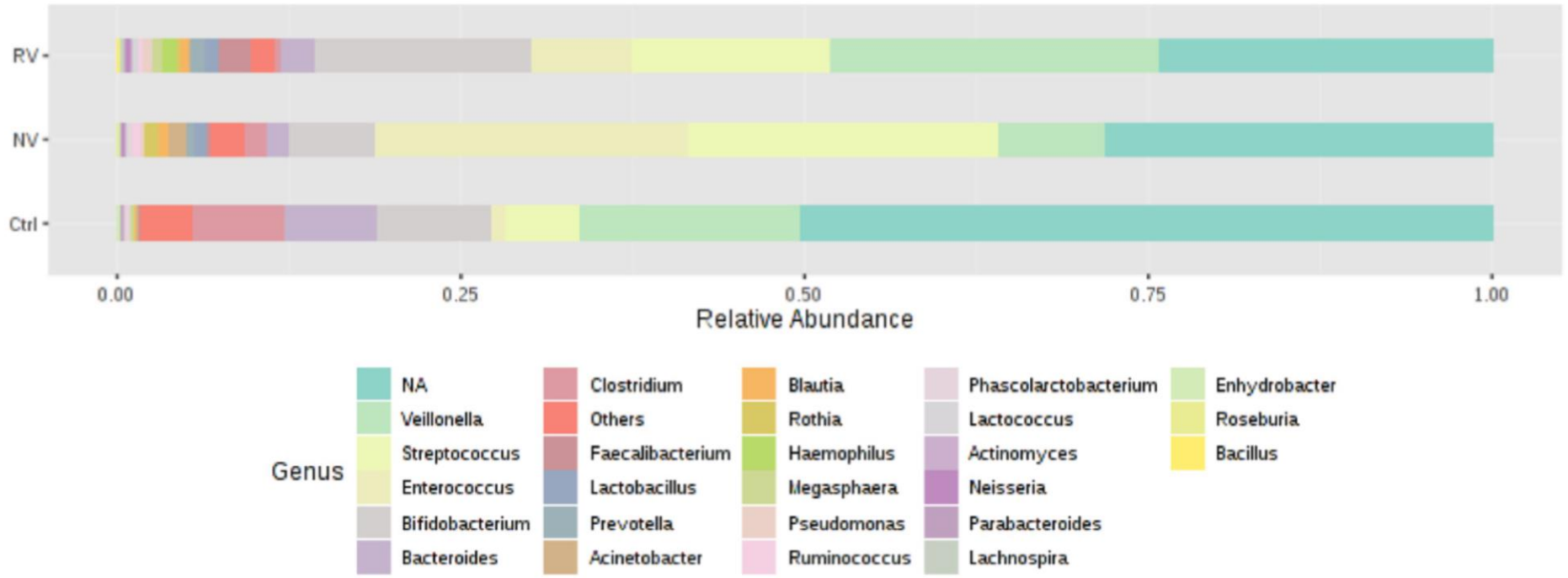
Chao1 index for the HNoV group was higher compared with the control group, while it was lower for the RV group compared with the HNoV group





Xiong et al, International Journal of Infectious Diseases 2021

Viral gastroenteritis and gut microbiota



RV group: *Actinobacteria - Bifidobacterium spp., Streptococcus spp., Enterococcus spp. and Lactobacillus spp*
HNoV group: *Fusobacteriaand Cyanobacteria - Enterococcus spp. and Streptococcus spp.*
***Bacillus* appears the characteristic genus in infected infant**

Xiong et al, International Journal of Infectious Diseases 2021

Microbiota restoration

Probiotics

- *Bifidobacterium breve* and *Bifidobacterium pseudocatenulatum DSM20439* inhibit the expression of intestinal Shiga toxin EHEC (Asahara et al., 2004)
- Lactobacillus LGG reduces the incidence of diarrhea in children and shorten the course of diarrhea a (Li et al., 2019)
- Lactobacillus rhamnosus GG regulates the maturation and differentiation of dendritic cells (DCs) and the secretion of inflammatory factors preventing diarrhea caused by Rotavirus (Jiang et al., 2017).

Prebiotics

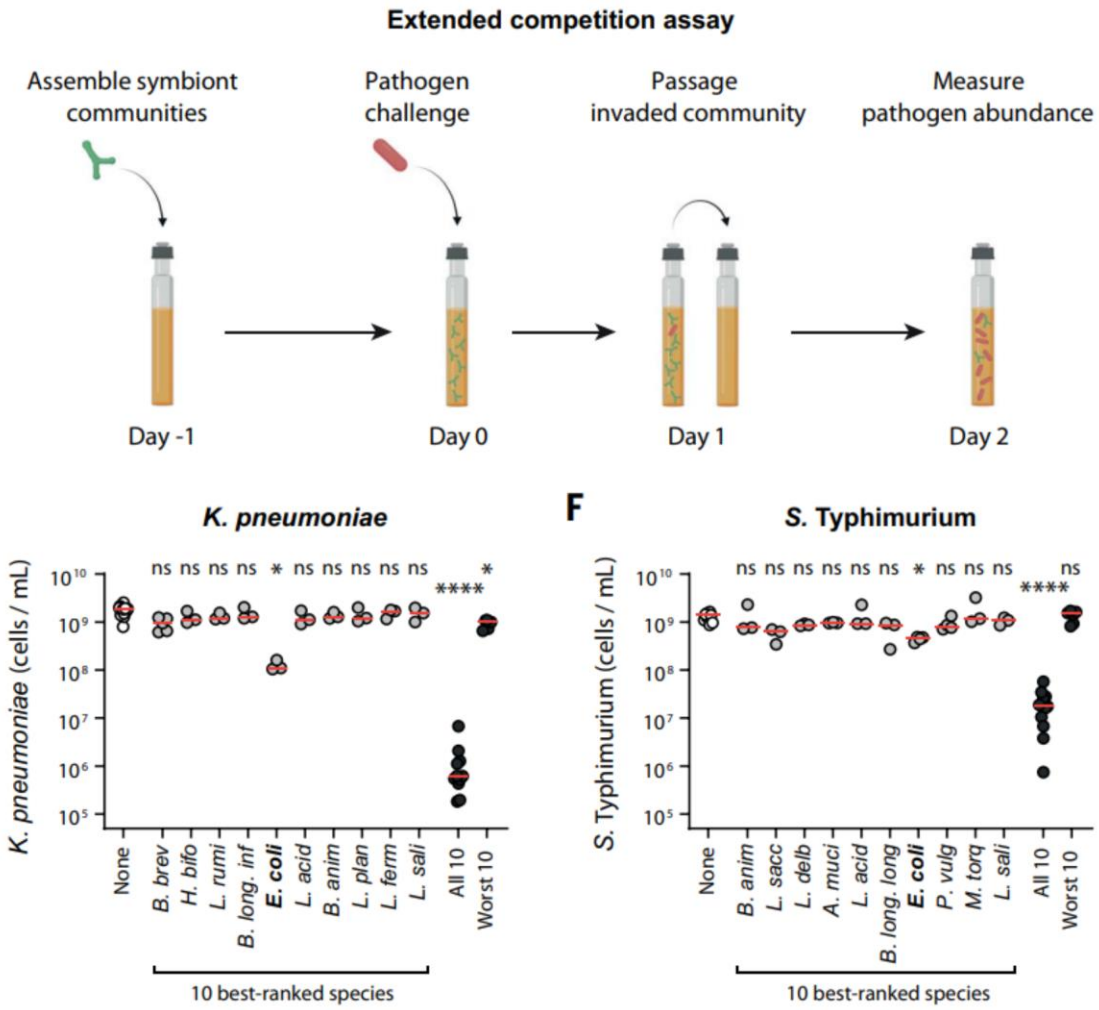
FMT

To standardize:
donor selection, ethics, operation method, and the follow-up

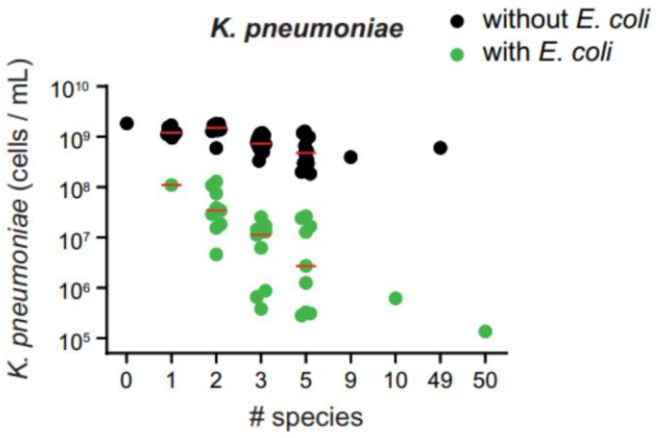
- **regulation of the balance of gut microbiota**
- **improvement immunity**
- **manipulation of intestinal defense barrier**
- **metabolites**

- **Microbial quorum sensing investigation**
- **Knowledge of the mechanisms of probiotics-mediated diarrheal pathogen clearance**
- **Nutritional regulation (impact of personalized diets)**

Microbiota restoration



Single species do not provide robust colonization resistance, but a diverse community can, depending on its composition



Spragge et al, Science 2023

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