Possible role of the microbiome in the development of acute malnutrition and implications for food-based strategies to prevent and treat acute malnutrition

International Symposium on Understanding Moderate Malnutrition in Children for Effective Interventions

Mark Manary MD

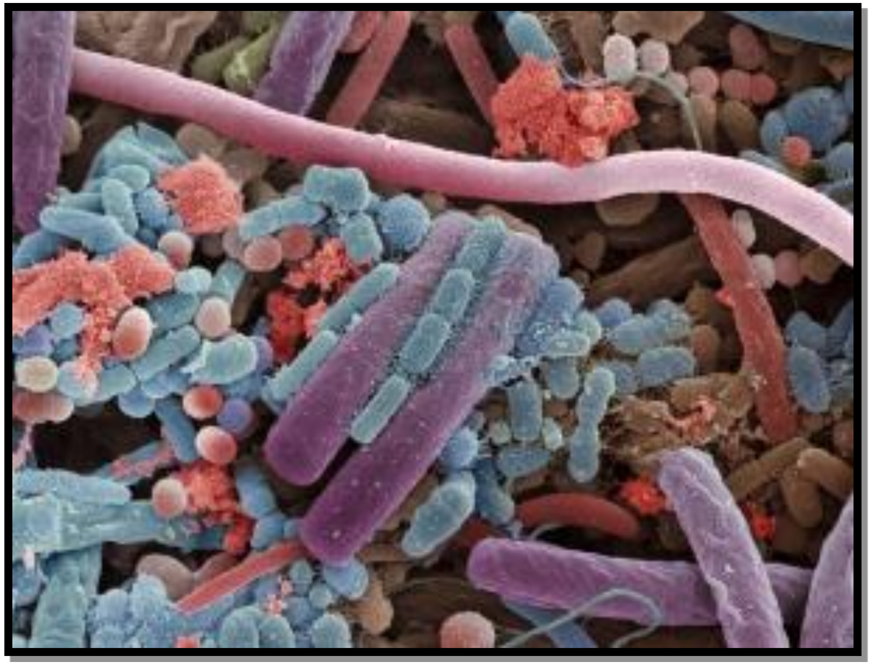
Washington University School of Medicine, USA

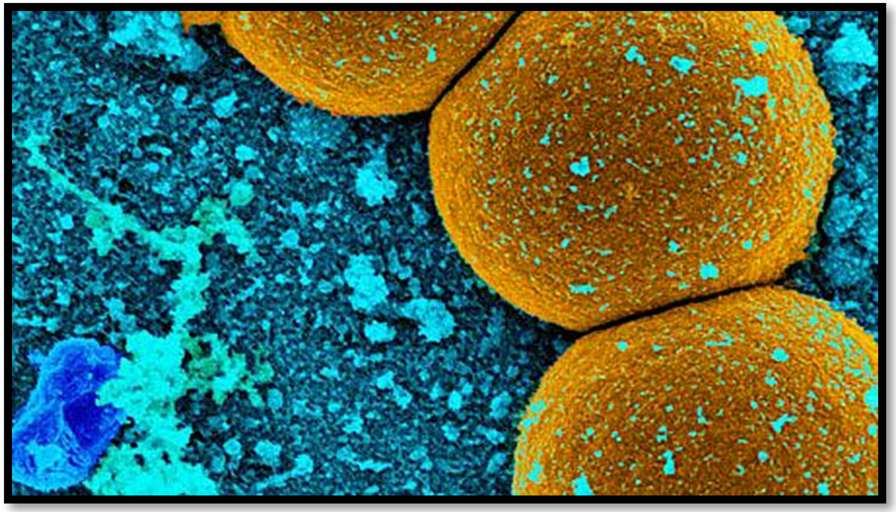
THE MICROBIOME

The microbiome is designed to facilitate the absorption of the foods we eat – and has adapted to diet and environments to help hosts best utilize dietary intakes

The Microbiome

- The ecological community of commensal, symbiotic, and pathogenic microorganisms within our bodies
- 100 trillion micro-organisms
  - Anaerobic bacteria
  - Archaea
  - Yeast
  - Parasites
- Individual “finger-print” specificity – each person has a unique profile of organisms regulating their microbiome
- Complex and dynamic – it is constantly evolving and changing based on exposure





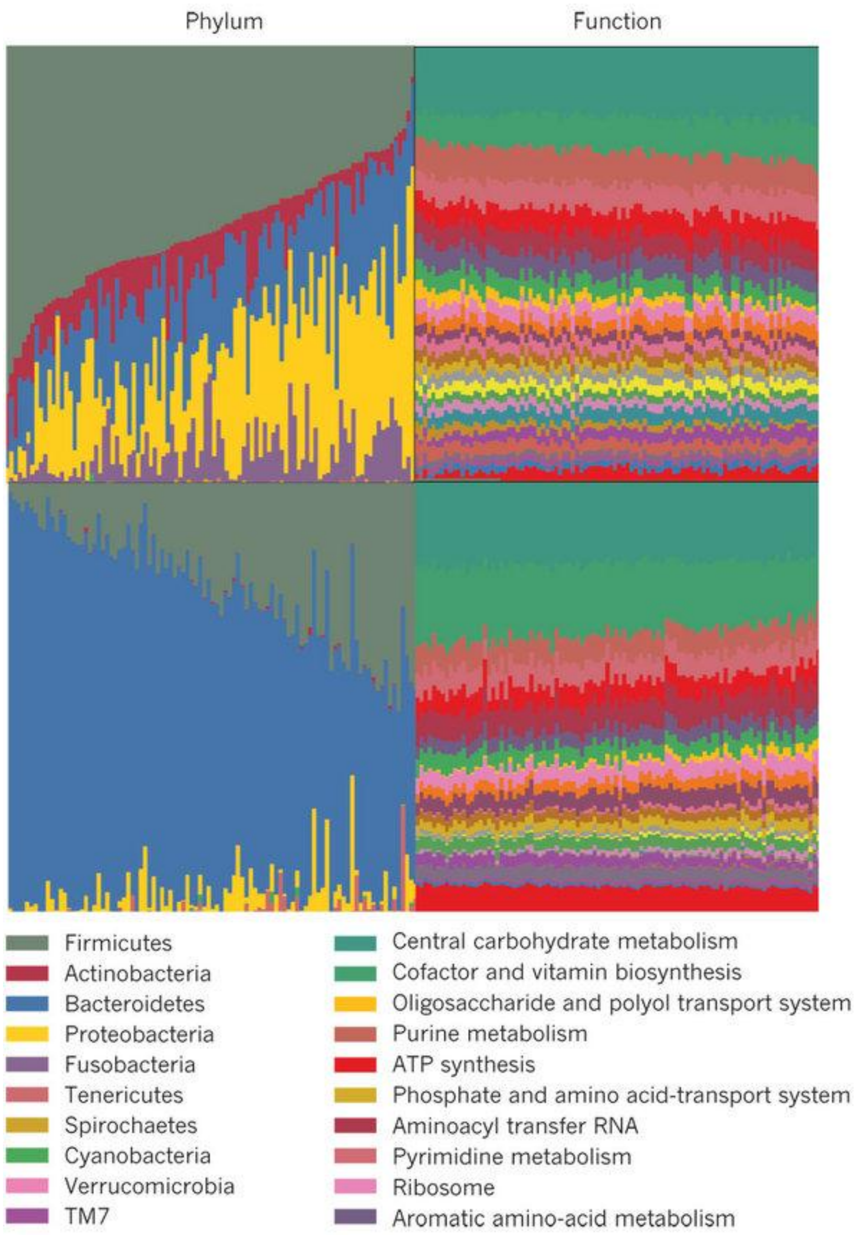
The Role of the Microbiome

Gut microbiota influence the growth and differentiation of gut epithelial cells and play pivotal nutritive, metabolic, immunological and protective functions.

- Efficient extraction of calories from ingested food
  - Fermentation of non-digestible polysaccharides
  - Provision of short-chain fatty acids
- Enzymatic reactions of the microbiome aid in
  - Host homeostasis
  - Food digestion, absorption
  - Synthesis of micronutrients
    - Vitamins K, multiple B vitamins
    - H2, CO2, Methane, Lysine
    - Conversion of Urea to Ammonia
- Detoxification
  - Modulates enterohepatic circulation of compounds detoxified by the liver
- Epithelial development
- Immune function
  - Stimulates the growth of enterocytes
  - Commensal organisms protect from pathogens

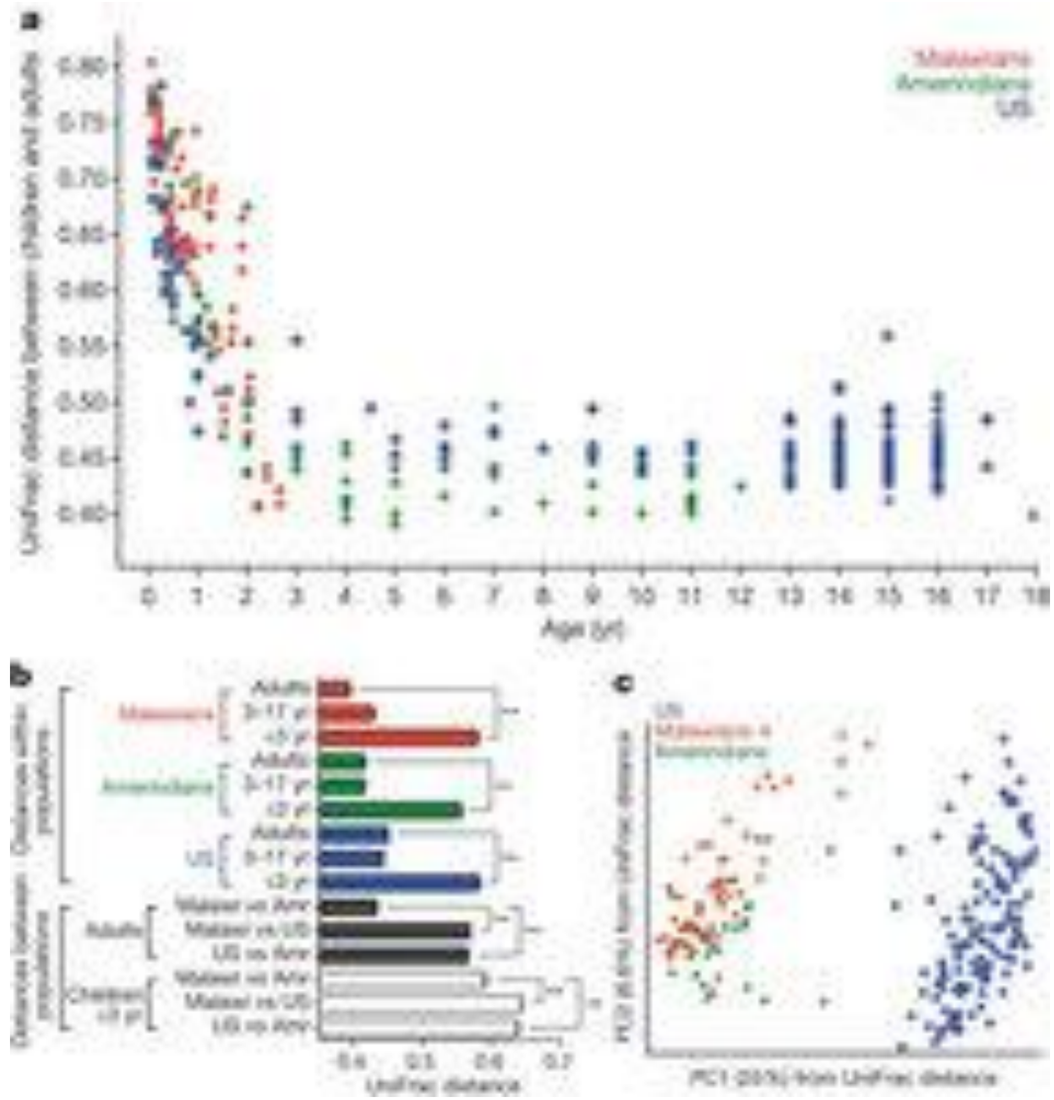
Functionality of the Core Microbiome

- The microbiota is affected by genetic background, age, diet, and health status of the host
- Understanding function
  - Ex-vivo phenotype experimentation
  - DNA
  - Active mRNA, protein and metabolite profiles
- Central, carbohydrate and amino-acid metabolism



Human gut microbiome viewed across age and geography

- Malawi, Venezuela (Amerindian) and US residents
- 326 Total 0-17 yr.
- 202 Adults 18-70
- Analyses were conducted examining each samples microbiomes
  - mRNA sequence

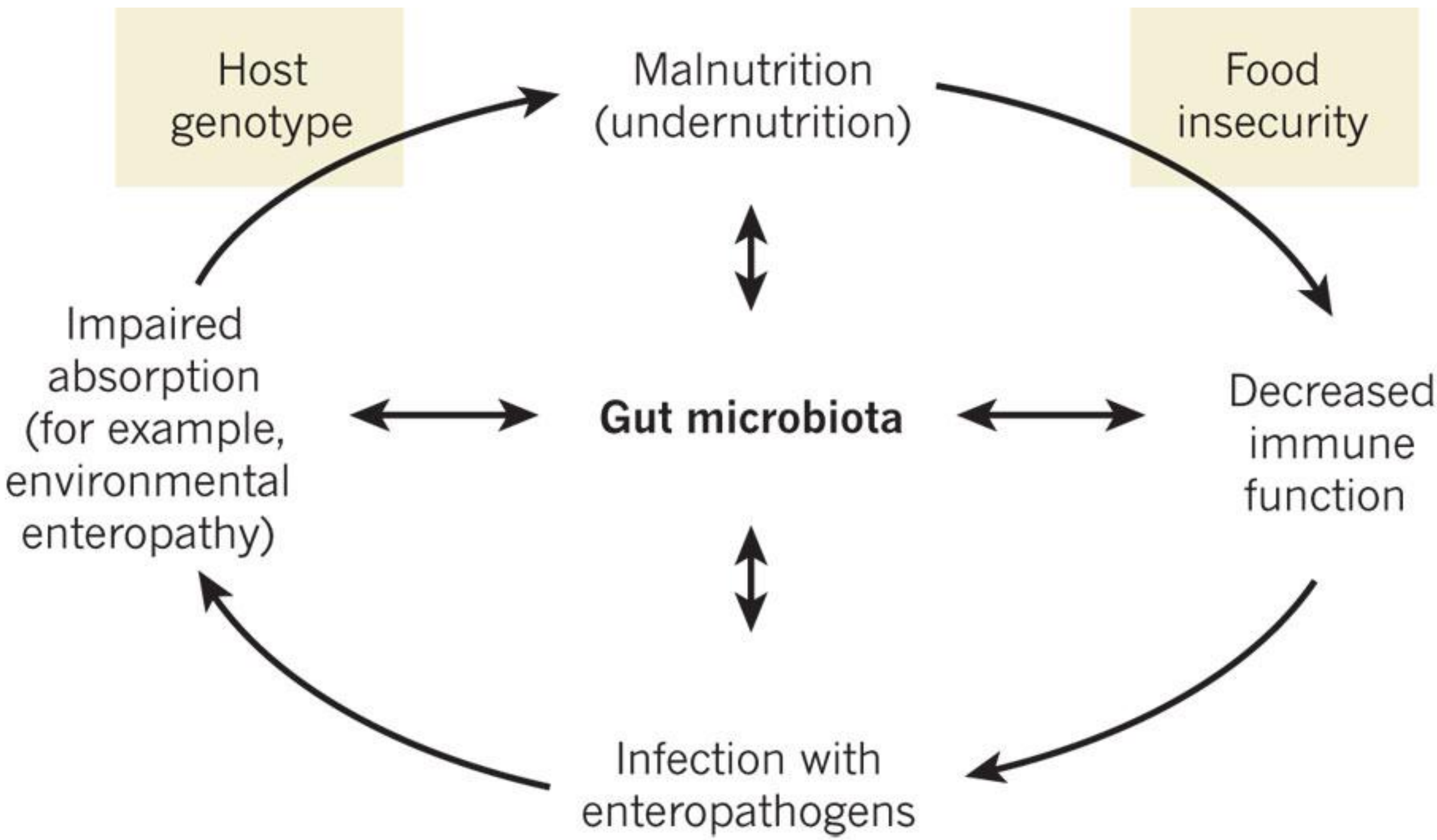


Yatsunekno, T et al. *Nature.* 486, 6.2012.

Human gut microbiome viewed across age and geography

1. Fetal microbiome is sterile
2. Microbiome communities resolve to an adult-like state at 3 yrs
3. Children showed greater interpersonal variation
4. Fecal microbial communities showed geographic variation
    - Staple consumption of carbohydrates (Malawi/Amerindian) vs. fat and protein (US)
5. Bacterial diversity increases with age
6. Microbiome heritability is LOW, as seen in adult twins however environmental similarity is significant

MALNUTRITION AND THE MICROBIOME


Host genotype
Malnutrition (undernutrition)
Food insecurity
Impaired absorption (for example, environmental enteropathy)
Gut microbiota
Decreased immune function
Infection with enteropathogens

- The microbiome is not just a response to diet
- The microbiota and immune systems co-evolve
- Malnutrition affects innate and adaptive immune system
- Responds to and modulates absorption based on exposure and response to pathogenic microbes
- The microbiota is a barrier to entero-pathogen infection; disruptions can be caused and progressed by malnutrition

Gut Microbiomes of Malawian Twin Pairs Discordant for Kwashiorkor

- 317 twin pairs followed during the first 3 years of life
  - 50% of the twin pairs did not develop acute malnutrition
  - 43% of pairs became discordant (one with malnutrition, one without)
  - 7% of pairs developed acute malnutrition
- Both children in twin pairs discordant for kwashiorkor were treated with a peanut-based RUTF
- Microbiome assessments of health twins and of discordant twins
- 13 discordant kwashikor twin pairs and 9 healthy pairs

Smith et al. Science. 2013.

Gut Microbiomes of Malawian Twin Pairs Discordant for Kwashikor

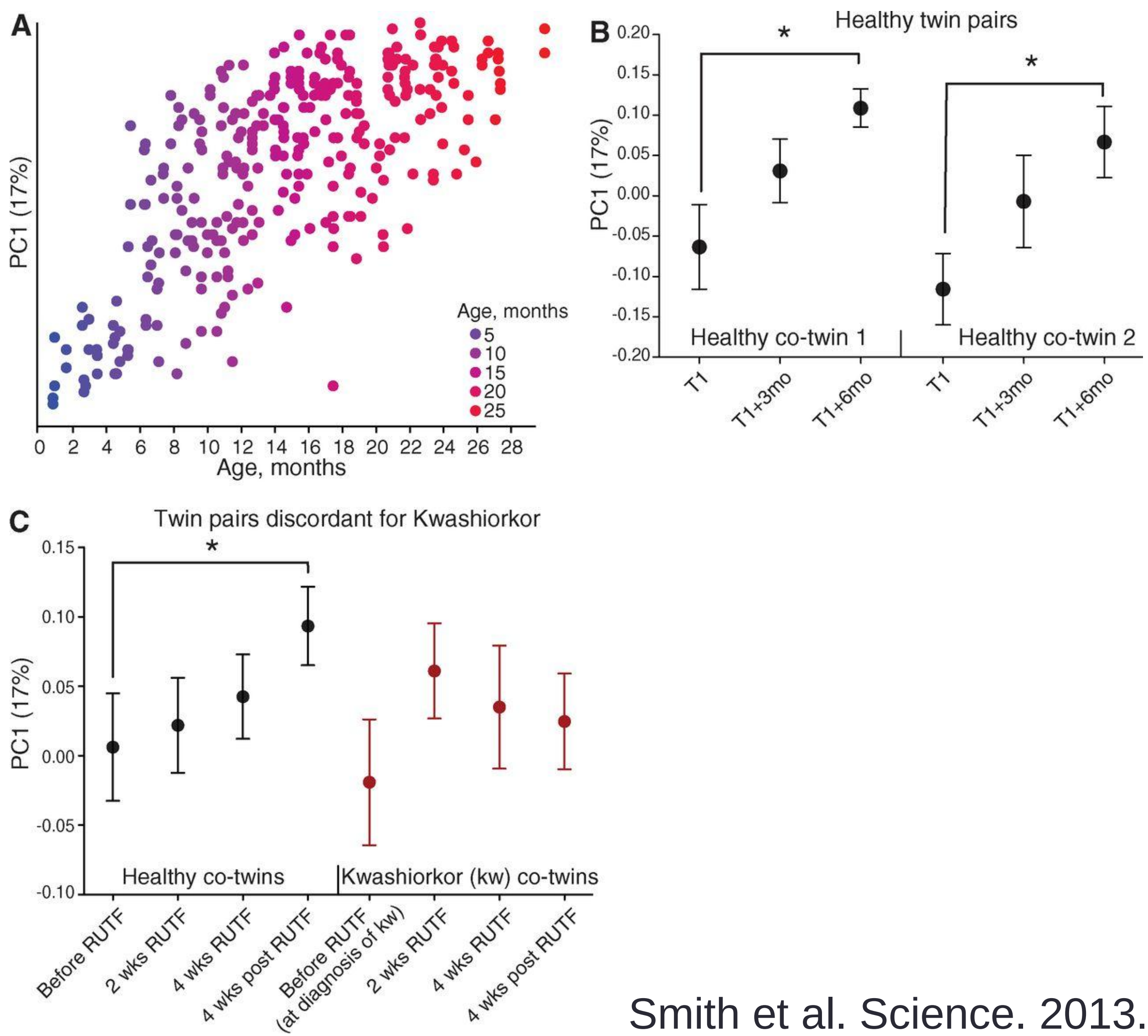
Functional development of the gut microbiomes of healthy twin pairs and twin pairs discordant for kwashiorkor

Results:

DNA sequencing

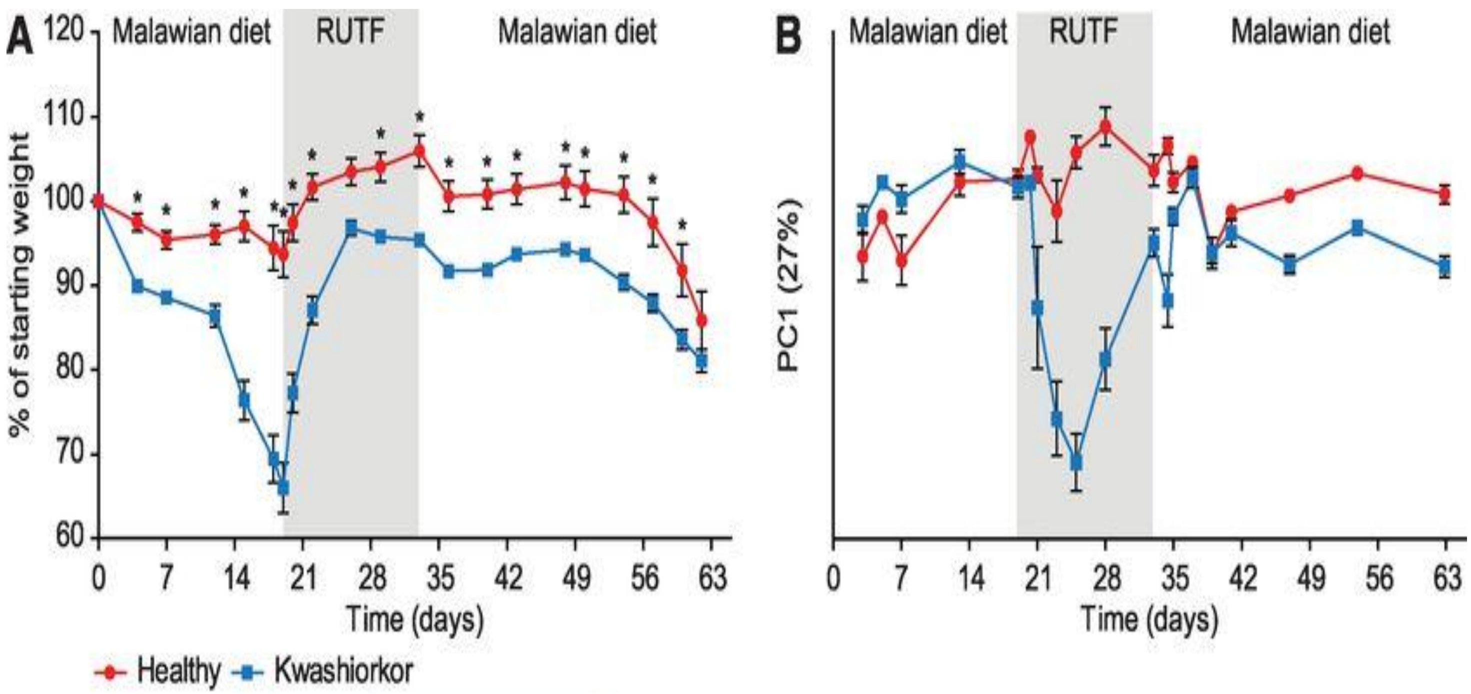
308 samples are plotted against age

The microbiomes of twins with kwashiorkor manifested a **significant decrease in Actinobacteria**



Smith et al. Science. 2013.

Gut Microbiomes of Malawian Twin Pairs Discordant for Kwashiorkor



- Weight loss observed in mice that received fecal microbiota kwashiorkor twin compared to non-malnourished twin

Smith et al. Science. 2013.

POSSIBLE INTERVENTIONS AND TREATMENTS

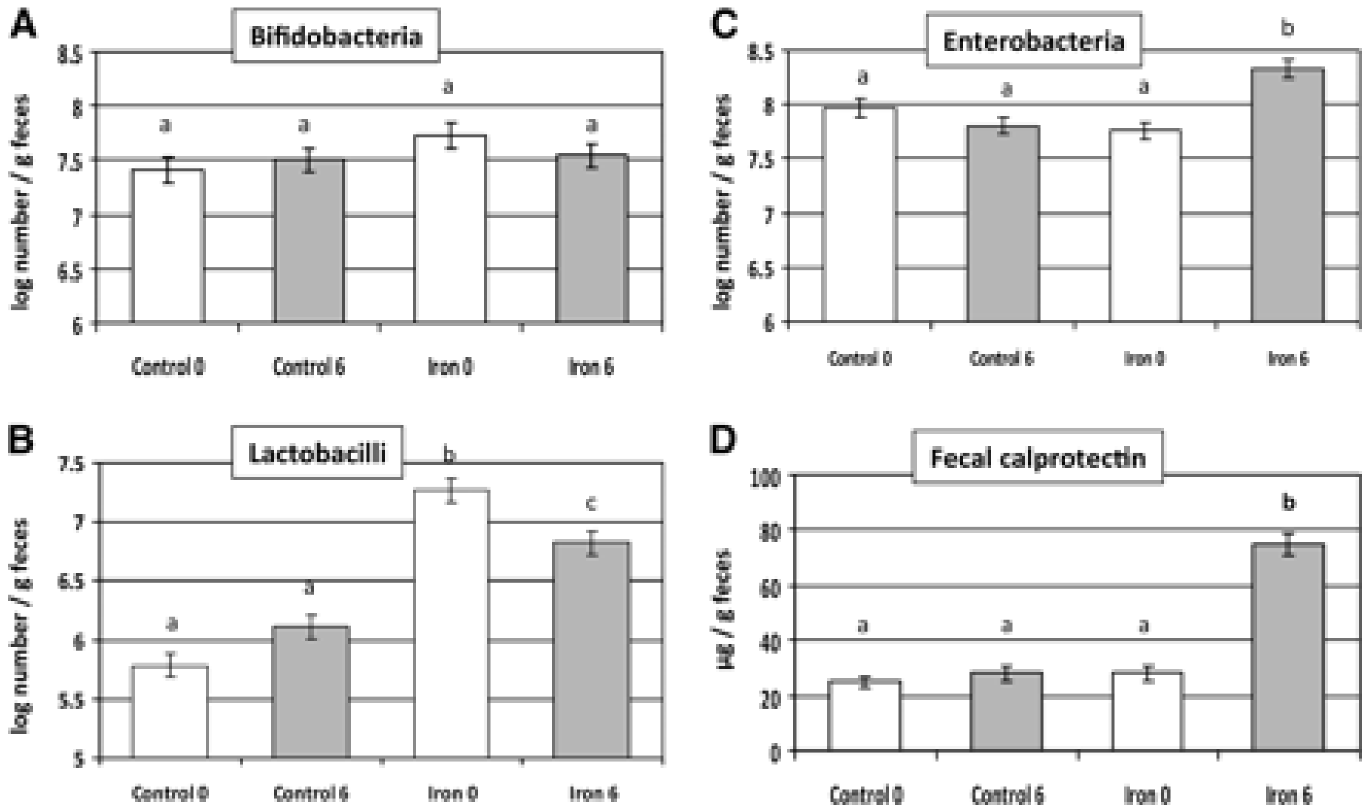
Iron fortification, prebiotics, probiotics, immunoglobbins, zinc, albendazole, antibiotics

The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire

- Iron is essential for the growth and virulence of pathogenic enterobacteria
- Effect of iron fortification on gut microbiota and inflammation
- Could an increase in dietary iron via fortification and supplementation modify the microbiome colonization equilibrium and favor the growth of pathogenic strains
- 139 6-14 Ivorian children received 20 mg Fe/d, 4 times/wk
- Measure: hemoglobin concentration, inflammation, iron status, helminths, diarrhea, fecal calprotectin concentrations, **microbiota diversity/composition** and prevalence of pathogens in the microbiome
  - 74 children to iron group, 73 to control

Zimmerman, et al. The American Journal of Clinical Nutrition. 2010.

The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire



•No sig. change in # of bacteria at 0 to 6 mos, *Bacteroides* and bifidobacteria
•Increase in enterobacteria in the iron group and a reduction in lactobacilli

Zimmerman, et al. The American Journal of Clinical Nutrition. 2010.

The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire

- Anemic African children carry an unfavorable ratio of fecal enterobacteria to bifidobacteria and lactobacilli, the unfavorable ratio is increased by iron fortification.
- Iron fortification in this population produces a potentially more pathogenic gut microbiota profile, and this profile is associated with increased gut inflammation.

Zimmerman, et al. The American Journal of Clinical Nutrition. 2010.

Probiotics and prebiotics for severe acute malnutrition: A double-blind efficacy randomized controlled trial in Malawi

- 795 Malawian SAM children
  - 399 Synbiotic2000 + RUTF
    - Four different probiotic lactic acid bacteria (10^{11} colony-forming units of bacteria total)
    - Four prebiotic fermentable bioactive fibers
    - Provides 10^{10} lactic acid bacteria per day
  - 396 RUTF

	Synbiotic (n=399)	Control (n=396)	Relative risk (discrete variables) (95% CI)	p value
Primary outcome				
Nutritional cure (total)	215/399 (53·9%)	203/396 (51·3%)	1·06 (0·93 to 1·21)	0·40
HIV-seropositive cures	66/170 (38·8%)	71/192 (37·0%)	1·05 (0·81 to 1·37)	0·71
HIV-seronegative cures	145/203 (71·4%)	131/190 (68·9%)	1·04 (0·91 to 1·18)	0·59
Secondary outcomes				
Death (total)*	108/399 (27·1%)	119/396 (30·0%)	0·90 (0·72 to 1·12)	0·31
Outpatient defaulters or ward absconders	27/399 (6·8%)	36/396 (9·0%)	0·74 (0·46 to 1·20)	0·23
Failures of nutritional treatment	14/399 (3·5%)	14/396 (3·5%)	0·99 (0·48 to 2·05)	0·98
Readmissions	27/399 (6·8%)	16/396 (4·0%)	1·67 (0·92 to 3·06)	0·08
Other (transfers out; final outcome unknown)	8/399 (2·0%)	8/396 (2·0%)	1·12 (0·44 to 2.86)	0·81
Rate of weight gain (g/kg/day)	4·18 (4·0)	4·14 (4·1)	0·04 (–0·53 to 0·61)†	0·65
Length of stay in programme (days to cure)	37 (34 to 48)	38 (34 to 47)	..	0·42
Outcomes stratified by treatment phase‡				
Deaths (inpatient, during first admission)	61/399 (15·3%)	52/396 (13·1%)	1·16 (0·83 to 1·64)	0·38
Deaths (any time during remainder of study)	47/338 (13·9%)	67/344 (19·4%)	0·71 (0·51 to 1·00)	0·05
Total deaths during all inpatient treatment episodes (including readmissions)	78/486 (16·1%)	74/467 (15·9%)	1·01 (0·76 to 1·36)	0·93
Total deaths during all outpatient treatment episodes (including readmissions)	30/394 (7·6%)	45/387 (11·6%)	0·65 (0·42 to 1·02)	0·06

Data are number (%), mean (SD), or median (IQR). *Children who died during outpatient treatment, or at any time during subsequent admission episodes during the study, were classified under the total death category. †Mean difference (continuous variables). ‡See webappendix p 4 for further details.

Table 2: **Main outcomes**

Kerac et al. The Lancet. 2009

Probiotics and prebiotics for severe acute malnutrition: A double-blind efficacy randomized controlled trial in Malawi

- Nutritional cure (WHZ > 80%) was similar
  - Synbiotic 53.9 vs control groups 51.3%
  - Total deaths similar between groups
  - Other secondary outcomes were similar
  - Less than 10% default
- Synbiotic2000 Forte did not significantly improve SAM outcomes
- Synbiotic group had greater incidence of vomiting, diarrhea, cough
  - Could be by chance?
  - Increased severe diarrhea might be due to the osmotic effect of pre-biotics.
- Antibiotic interactions?

Kerac et al. The Lancet. 2009

Future Directions

- Characterize the entire microbiome genome – understanding the bacterial diversity of the microbiome would help to identify abnormal pathologies
- Harness the microbiota to improve therapeutic and supplementary foods that assist in healing the microbiome while alleviating malnutrition
- Use antibiotics and other interventions to improve the microbiome
- Develop methodologies to make age and cultural comparisons
- Understanding the microbiome is a key step in furthering the treatment of malnutrition