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Grupo de Interesse Especial (SIG)

em Farmacologia e Terapêutica

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Uma iniciativa para uso da estrutura de vídeo e web-conferências da Rede Universitária de Telemedicina (RUTE-MCT) ***para reduzir as distâncias geográficas e integrar ações em ensino e pesquisa em farmacologia e terapêutica no Brasil***

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Durante a sessão: A todos os participantes:

Mantenham os **microfones da videoconferência no MUDO enquanto não estiverem falando**, medida que se faz necessária para evitar ruídos e perda de qualidade de áudio durante a conferência.

Perguntas, Comentários ***pelo Chat***

Inscrições para perguntas por audio ***pelo Chat*** (nome, instituição)

Estrutura da sessão

1. Boas vindas – informações gerais : ~2 min
2. Apresentação do tema e palestrante : ~3 min
3. Apresentação do palestrante: ~30 min
4. Debate do tema com participantes: ~40 min
5. Encerramento e Registro Participação: ~5 min

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Impacto da desnutrição na microbiota intestinal: importância de pré e probióticos

Palestrante:
Prof. Dr. Aldo Ângelo Moreira Lima (UFC)

Coordenador Local da Sessão:
Profa. Dra. Flávia Santos (UFC)

Challenges in Child Malnutrition

Malnutrition is the main cause of mortality in the world - 180 mi. children;

Victora et al. Lancet 371:340-357, 2008; Gaayeb et al Am J Trp Med Hyg 90:566-573, 2014; Kosek et al. Am J Trp Med Hyg 88:390-396, 2013; Waber et al. Nutr Neurosci 17:58-64, 2013; Black et al Lancet 382:427-451, 2013.

The mechanisms associated with malnutrition manifestations vary and are the result of persistent abnormalities in growth, immune system and neurocognitive deficit;

Guerrrant et al. Nut Rev 66(9):487-505, 2008.

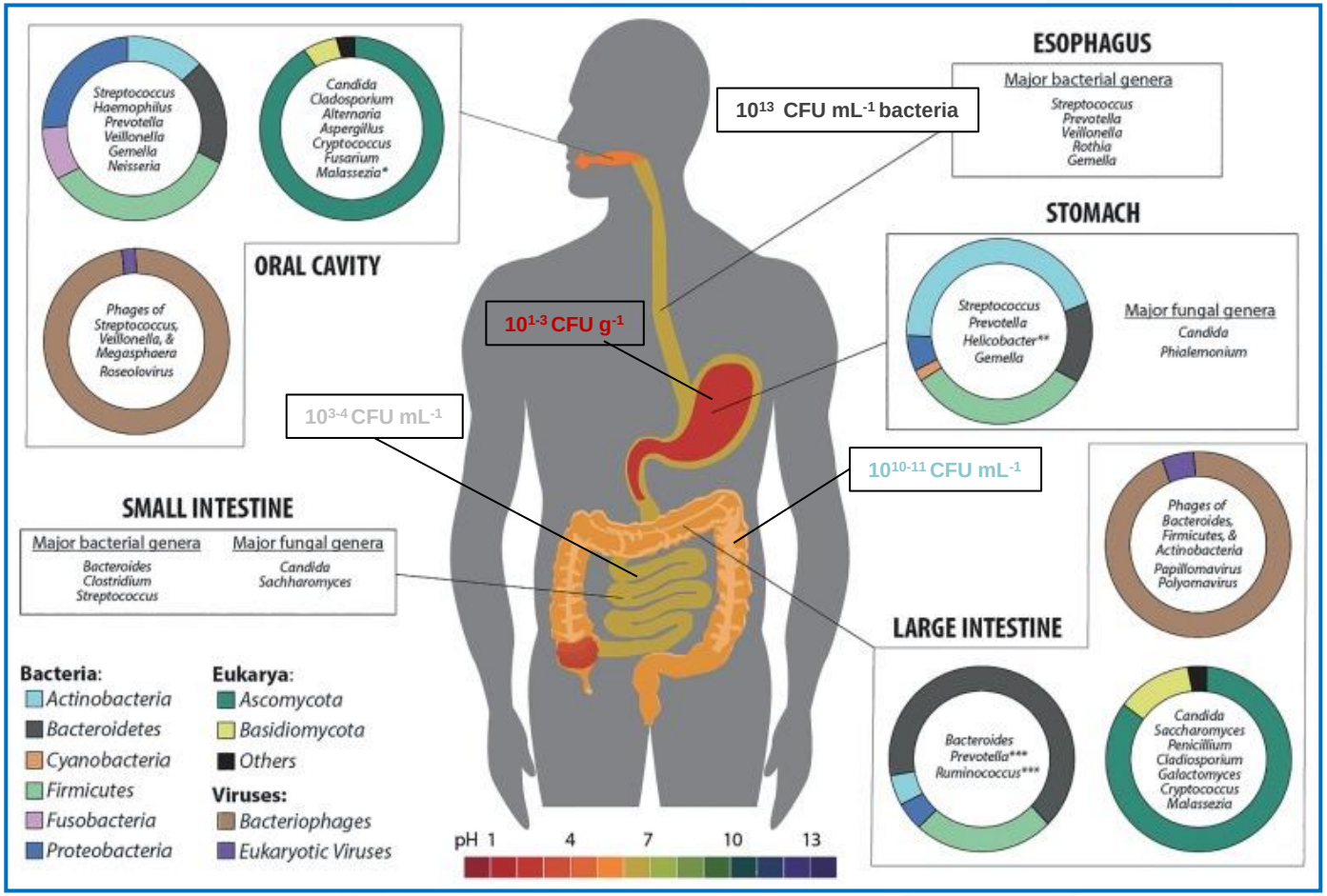
Malnutrition is related to food insecurity, a diet with low nutritional content or bioavailability, load of pathogens and functional gastrointestinal barrier.

Richard et al Clin Infect Dis 59:S255-S260, 2014; Keush et al Clin Infect Dis 59:S207-S212, 2014; Dewey J Nut 143:2050-2054, 2013.

Microbiome composition of Bacteria, Eukarya, and Viruses of the human gastrointestinal tract

Functions of microbiota:

1. **Vitamin production;**
2. **Absorption of ions (Ca^{++}, Mg^{++} and Fe^{++});**
3. **Protection against pathogens;**
4. **Histological development of the GI barrier function;**
5. **Modulation of the imune system; and**
6. **Fermentation of foods to short chain fatty acids.**



Phylum level compositional data are presented where available along with the most common genera in each GI tract location. The colors on the doughnut plots correspond to the legend in the lower left corner; the GI tract is colored according to the pH scale shown at the bottom of the Figure. (* *Malassezia* may vary among studies. ** The abundance of *Helicobacter* may vary greatly between individuals. *** Proportions of these and other colon *genera* vary with age, diet, & geographical location).

Hillman et al. Microbes Environ 32:300-313, 2017.

RESEARCH ARTICLE

MICROBIOME

Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children

Laura V. Blanton,[1] Mark R. Charbonneau,[1] Tarek Salih,[1] Michael J. Barratt,[1] Siddarth Venkatesh,[1] Olga Ilkaveya,[2] Sathish Subramanian,[1] Mark J. Manary,[3,4] Indi Trehan,[3,5] Josh M. Jorgensen,[6] Yue-mei Fan,[7] Bernard Henrissat,[8,9] Semen A. Leyn,[10] Dmitry A. Rodionov,[10,11] Andrei L. Osterman,[11] Kenneth M. Maleta,[4] Christopher B. Newgard,[2,12] Per Ashorn,[7,13] Kathryn G. Dewey,[6] Jeffrey I. Gordon[1]*

Science. 2016 Feb 19;351(6275).

Goals

1. Identify the age-discriminatory rate that is also discriminatory for growth;
2. Repairing impaired growth phenotypes; and
3. Assess whether the culture of the discriminatory microbiota rate repairs the growth deficit.

Methods

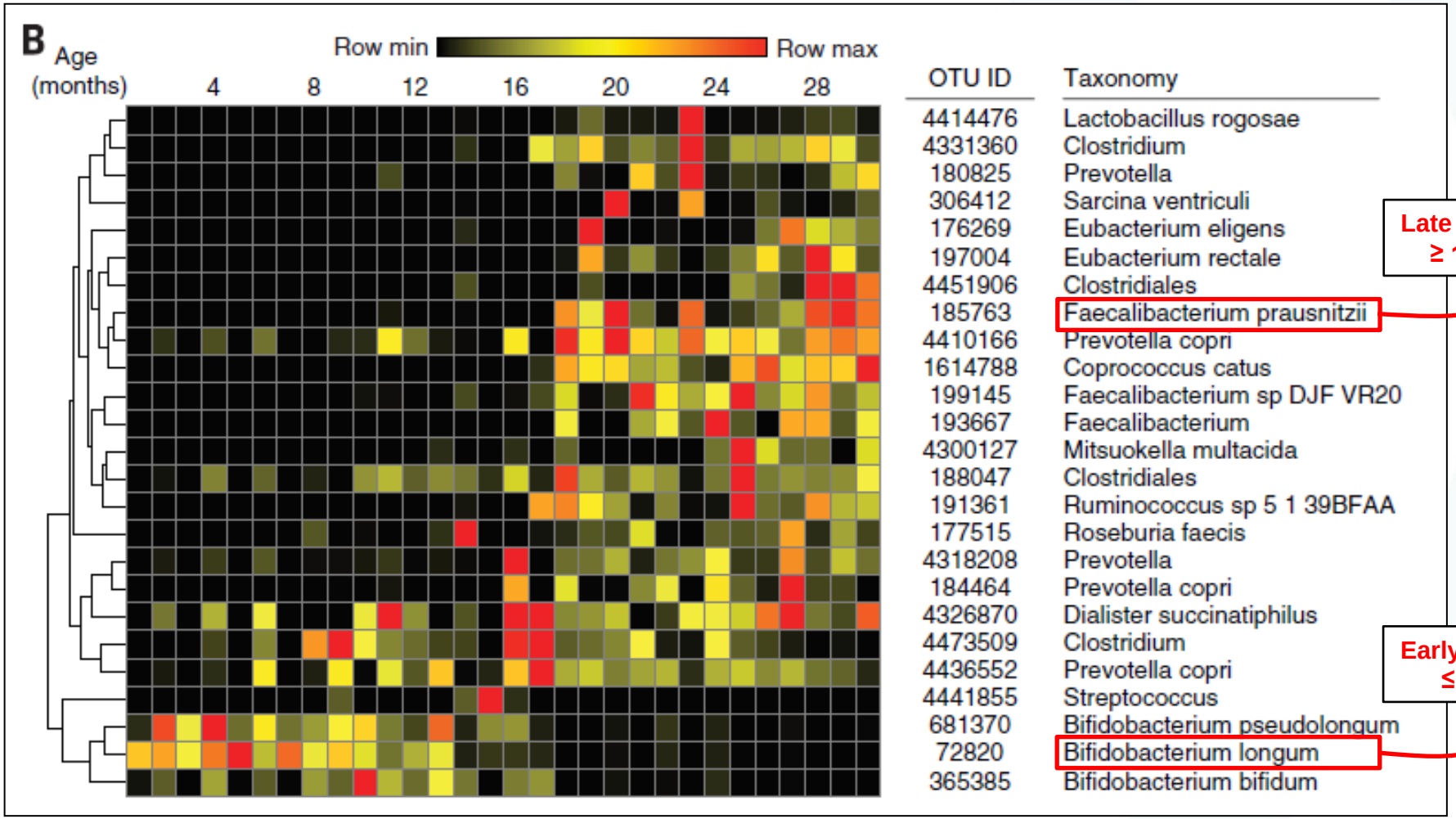
The study involved children from birth to the end of the first two years of age in Mirpur, Bangladesh, with monthly collection of stool samples and **analysis of a V4 variant region of the 16S rRNA combined in a statistical model of Random Forest machine learning algorithm**, revealing the presence of 24 age-discriminating bacterial strains, with relative changes in abundance over time.

Thus defining a normal microbiota maturation program.

What served as the basis for computing two related parameters :

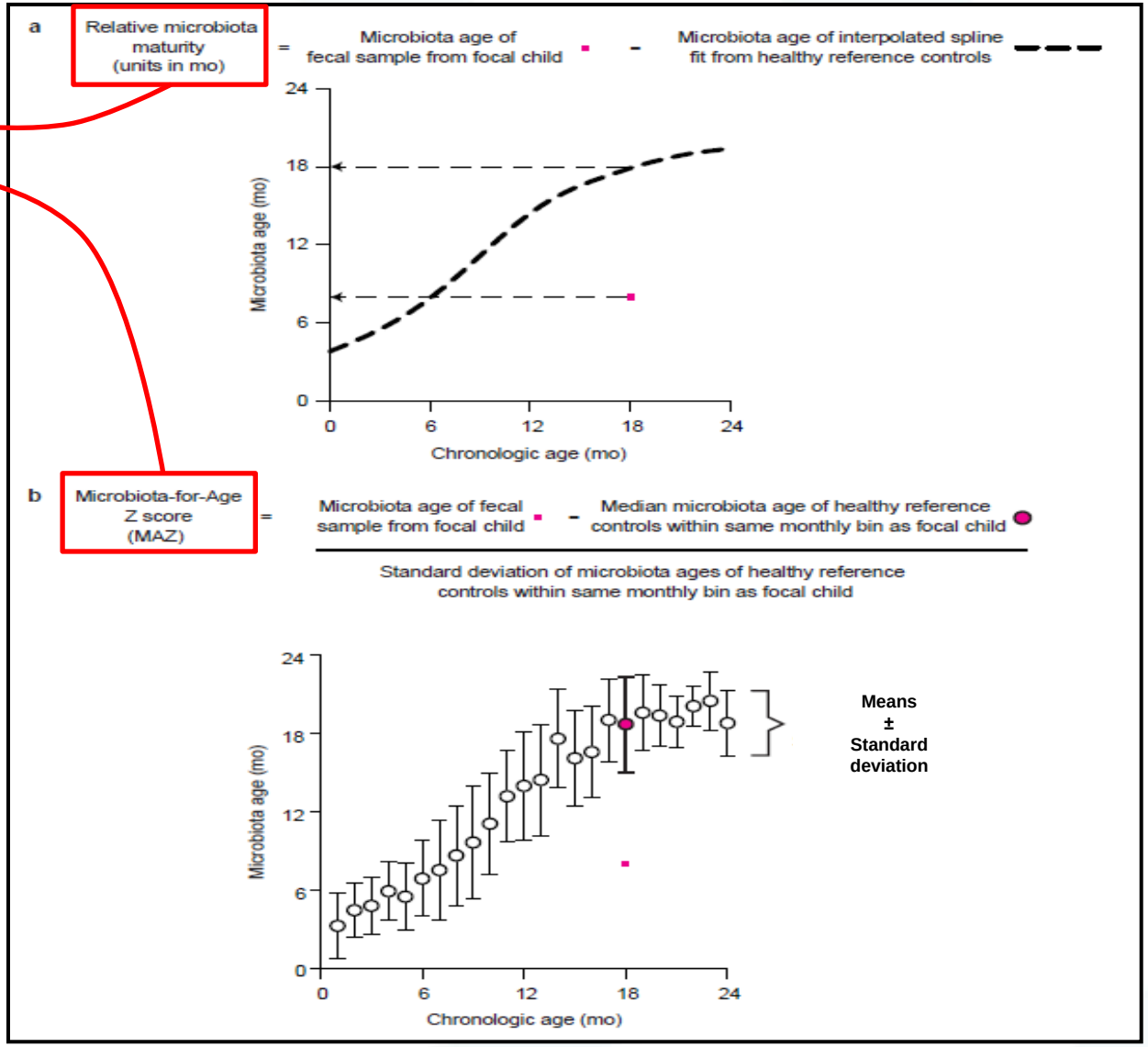
- ***Relative maturity of the microbiota;***
- ***Microbiota by age z-score (MAZ)***

A heat map of changes over time in the relative abundances of the 25 OTUs in fecal microbiota collected from healthy Malawian infants and children constituting the test set (N = 29)

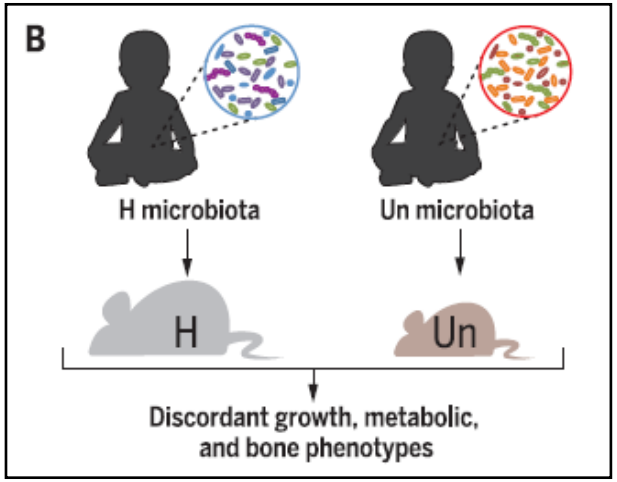


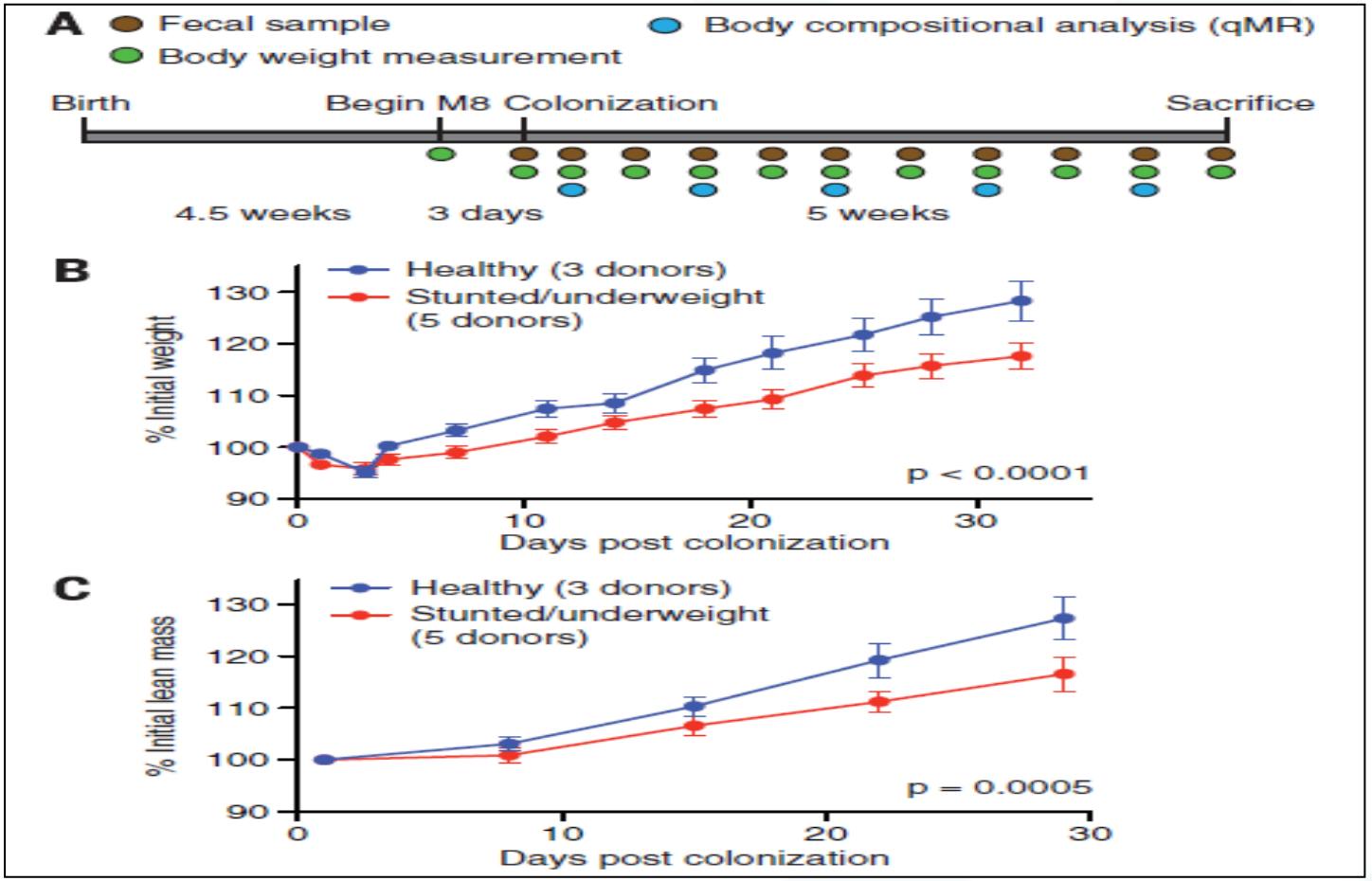
Ilustration of the equations used to calculate ‘relative microbiota maturity’ and ‘microbiota-for-age Z-score’

a, b, The procedure to calculate both microbiota maturation metrics are shown for a single faecal sample from a focal child (pink circle) relative to microbiota age values calculated in healthy reference controls. These reference values are computed in samples collected from children used to validate the **Random-Forests-based sparse 24-taxon model** and are shown in **a**, as a broken line of the interpolated spline fit and in **b**, as median ± s.d. values for each monthly chronologic age bin from months 1 to 24.

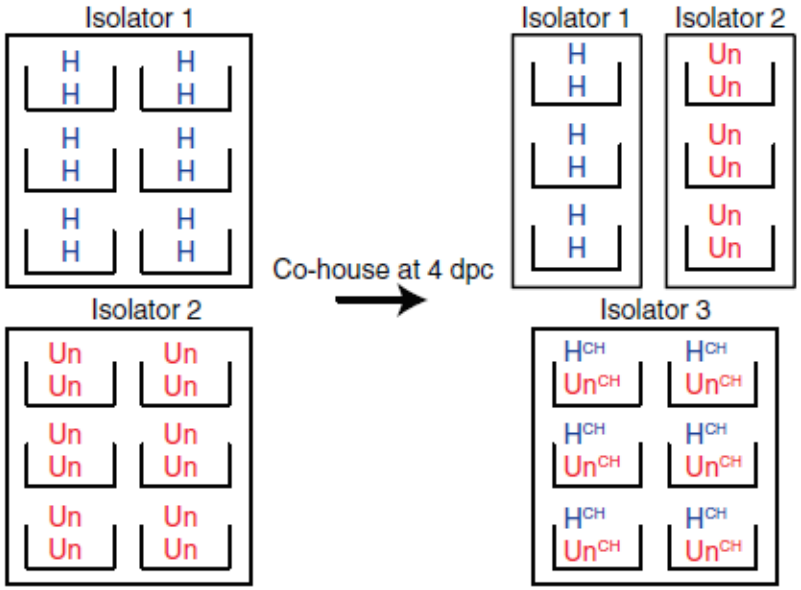


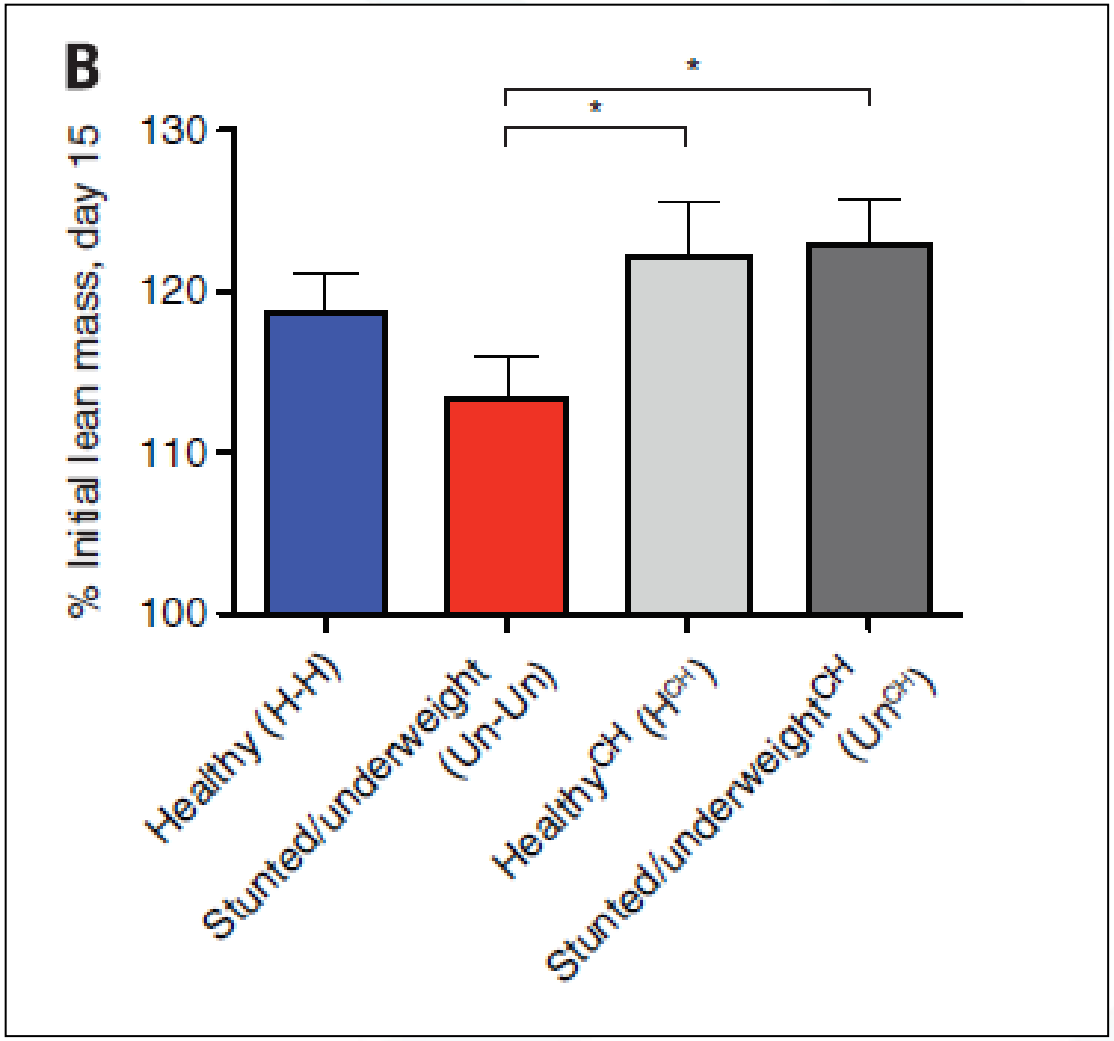
Experimental design of the microbiota screen



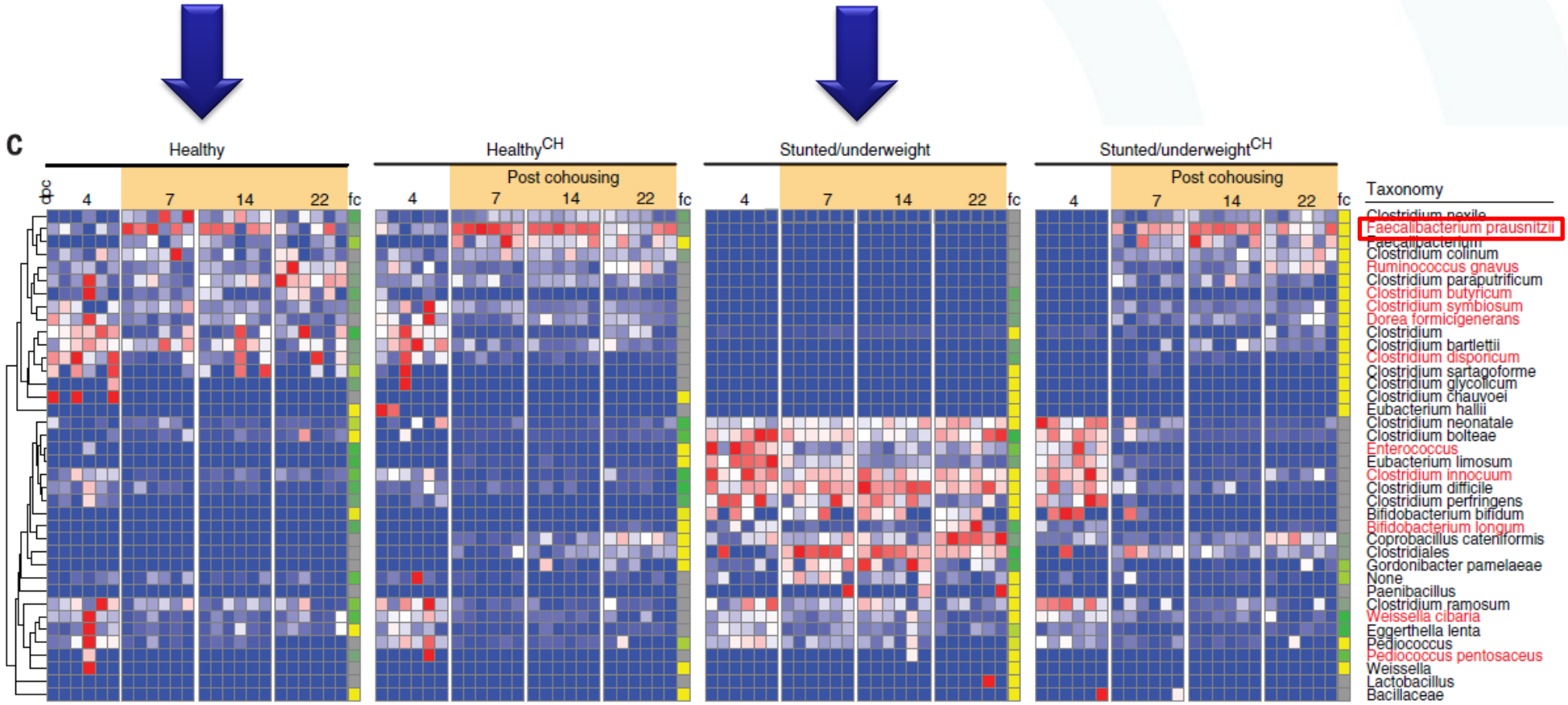


Experimental design for the cohousing experiments



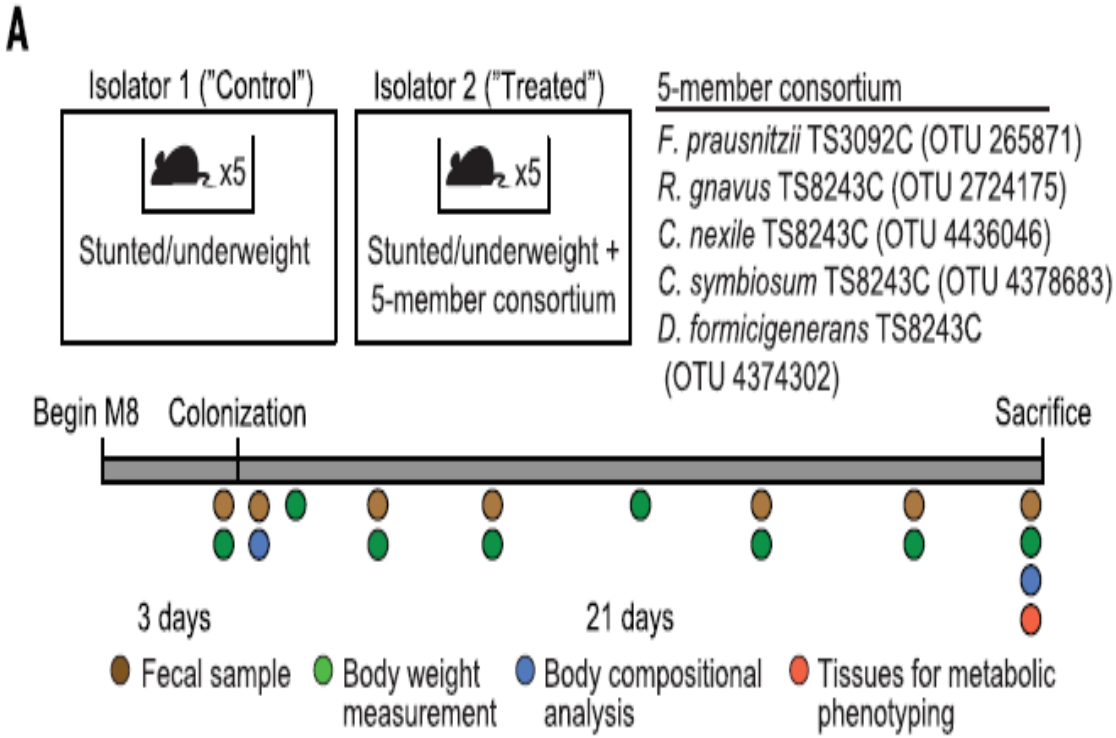


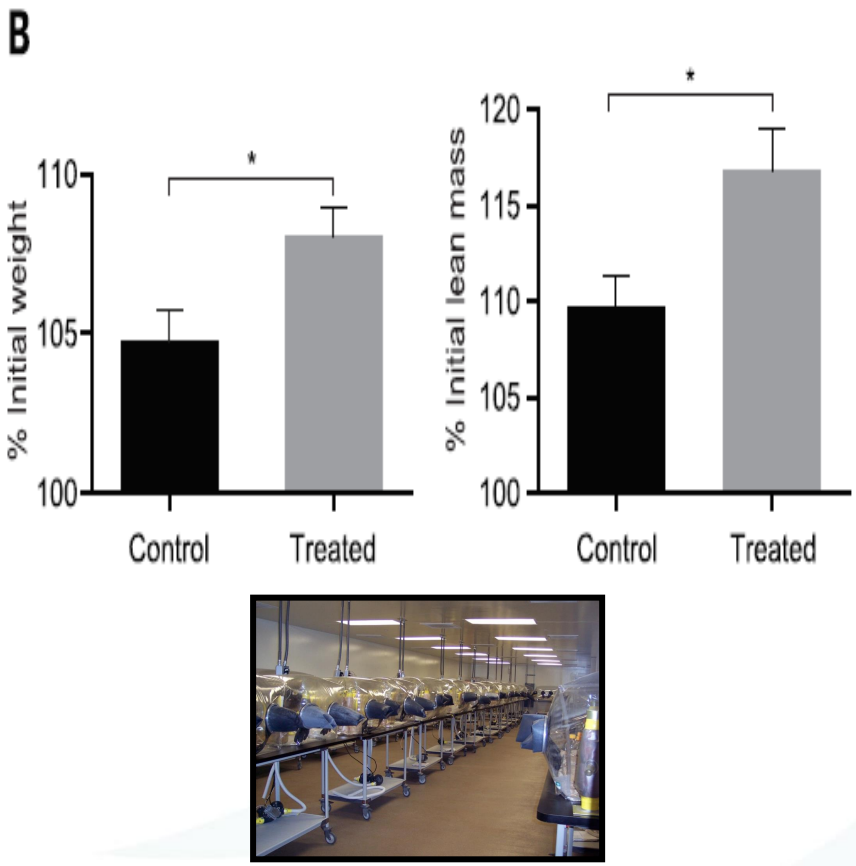
Heat map showing the results of the invasion assay



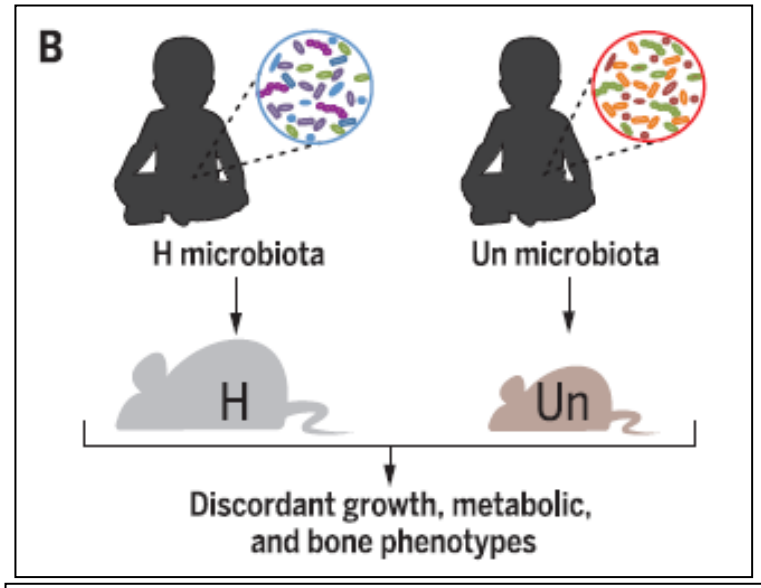
(A) Experimental design, including the composition of the five-member consortium of cultured bacterial strains; and

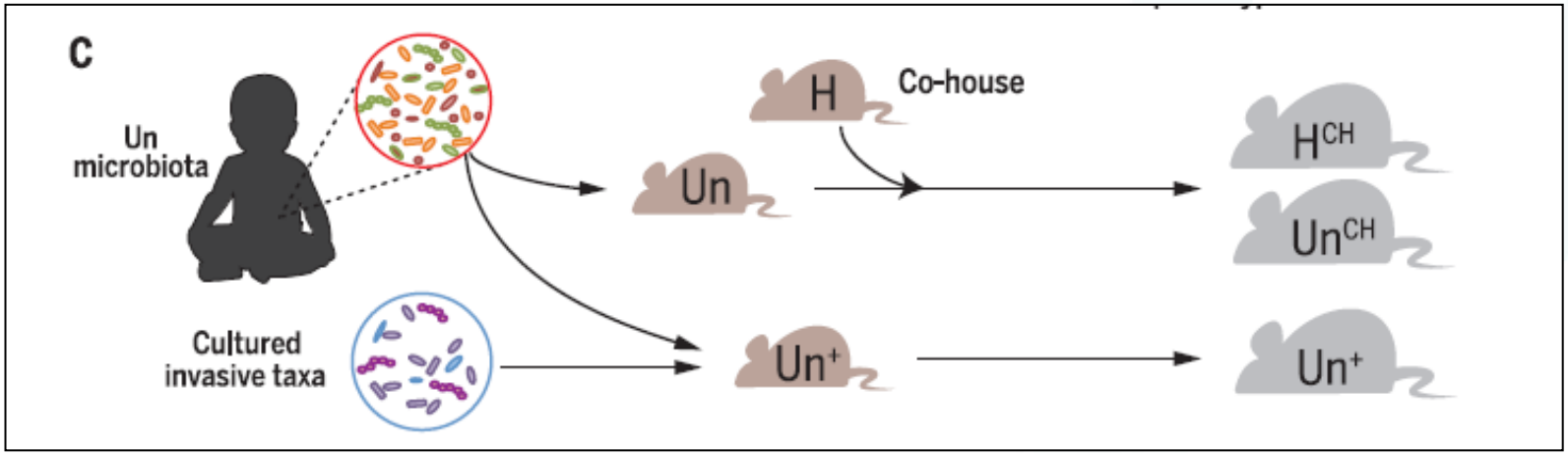
(B) Weight gain and lean mass gain (21 days after gavage) of mice colonized with the donor microbiota, with (treated) or without (control) the cultured consortium





***Summary*: Preclinical evidence that gut microbiota immaturity is causally related to childhood undernutrition**





RESEARCH ARTICLE SUMMARY

MICROBIOME

A Sparse Co-Varying Unit of the Human Gut Microbiota that Describes Healthy and Impaired Community Development

Arjun S. Raman, Jeanette L. Gehrig, Sathish Subramanian, Siddarth Venkatesh, Gagandeep Kang, Pascal O. Bessong, Aldo A.M. Lima, Margaret Kosek, William A. Petri Jr., Sayeeda Huq, Ishita Mostafa, Munirul Islam, Mustafa Mahfuz, Rashidul Haque, Tahmeed Ahmed, Michael J. Barratt, and Jeffrey I. Gordon*

Science 365, 12 July 2019

Goals

To describe an “ecogroup” of 15 intestinal bacteria interact in the children's microbiota resulting in an indicator of healthy or inadequate development;

To determine the effect of therapeutic food designed to target the microbiota in the “ecogroup” profile compared with that of healthy children.

Original study names and number of children participating

	Study name	Internet Identity	Number of children studied
1	**Field Studies of Amebiasis in Bangladesh**	ClinicalTrials.gov identifier NCT02734264	629
2	**Interactions of Enteric Infections and Malnutrition and the Consequences for ChildHealth and Development - MAL-ED Cohort Study**	ClinicalTrials.gov identifier NCT02441426	1.796
3	**Trial study of microbiota-directed complementary food (MDCF) prototypes conducted in Dhaka, Bangladesh**	ClinicalTrials.gov identifier NCT03084731	180
4	**Development and Field Testing of Ready-to-Use Therapeutic Foods Made of Local Ingredients in Bangladesh for the Treatment of Children with SAM**	ClinicalTrials.gov identifier NCT01889329	490
Total			3.095

Raman et al. Science 365, 140 (2019) 12 July 2019

MAL-ED Network Field Sites

Iquitos, Peru	Bhaktapur, Nepal
Fortaleza. Brazil*	Mirpur, Bangladesh*
Haydom, Tanzania	Naushero Feroz, Pakistan
Limpopo, S. Africa	Vellore, India

- Collaborating Institution
- Longitudinal Cohort Site Institution
- Case-Control Site

The MAL-ED Network CID 59 Suppl. 4, 2014.

MAL-ED

Timeline of test, specimen or survey collection, 0-24 Months

	Months																	
	0	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	
Gut integrity				X			X			X				X				
Gut inflammation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Incidence and prevalence of enteric pathogens	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diarrhea incidence	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anthropometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Nutrition	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Micronutrients								X						X				
Cognitive function							X							X				
Household/maternal assessment	X						X							X				
Vaccine response								X						X				
Other illness surveillance	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Sample types
Urine
Stool
Blood
Interview

MAL-ED

A Sparse Co-Variable Unit of the Human Intestine Microbiota that Describes Healthy and Impaired Community Development

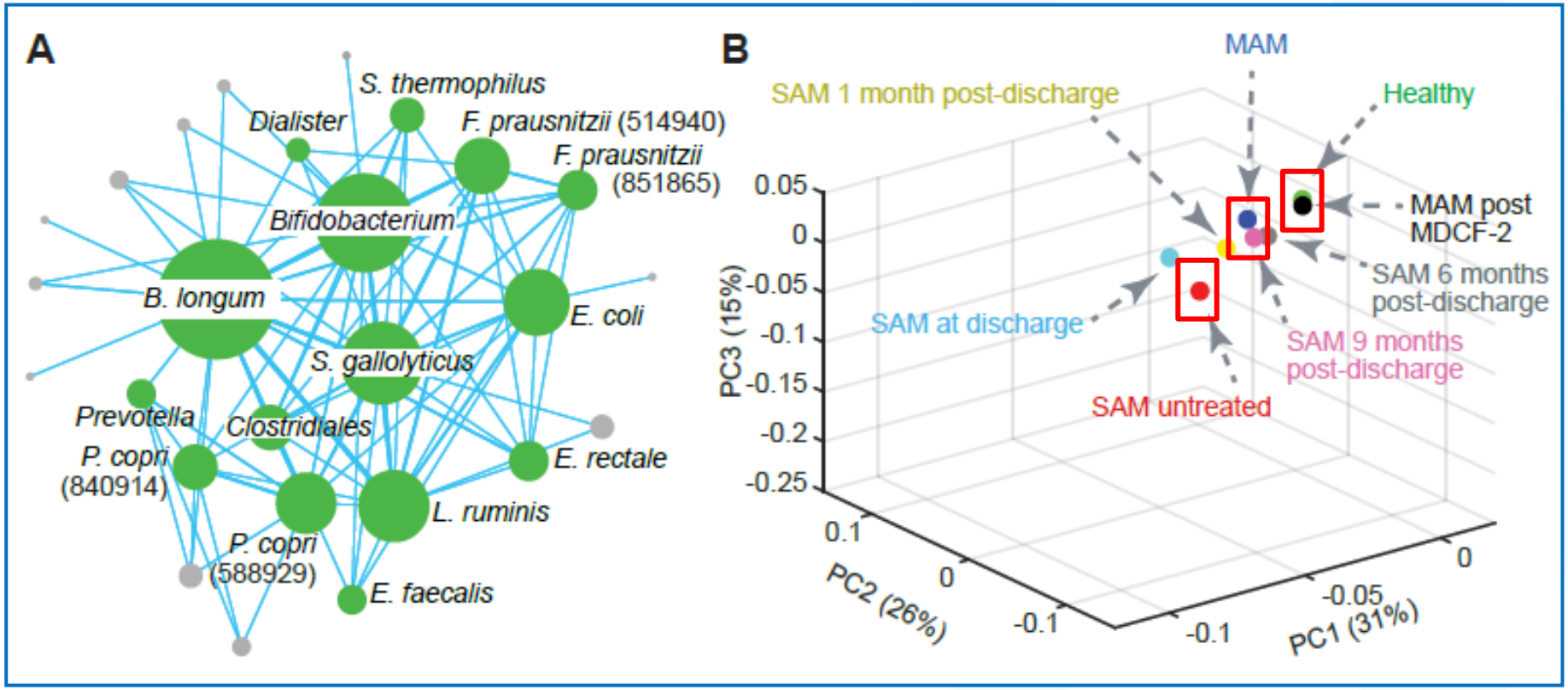


Figure - Ecogroup as a concise description of the shape in the human microbiota. (A) network diagram of the co-variable rate, where the color of the node (taxon) indicates the ecogroup (green) or the non-ecogroup (gray), the size of the node indicates the number of taxa that interact with each other, and the connection indicates the covariance between two rates. (B) Measuring the representation of ecogroup rates reveals that children with severe acute malnutrition (SAM) treated with standard therapeutic foods have an ecogroup profile like that of children with moderate acute malnutrition (MAM) untreated, indicating persistent disorders in their intestinal community compared to healthy. In contrast, children with MAM treated with a therapeutic food designed for microbiota (MDCF-2) have an ecogroup profile that almost entirely overlaps that of healthy children.

Science 365, 12 July 2019

Conclusions I

- ✓ **Malnourished children have impaired intestinal microbiota development;**
- ✓ **The transplanted microbiota from healthy or malnourished Malawian donors aged 6 and 18 months into germ-free young mice fed a Malawian diet revealed that the immature microbiota of malnourished babies and children transmits impaired growth phenotypes;**
- ✓ **The representation of various age-discriminatory rates in recipient animals was correlated with the gain of lean body mass; hepatic, muscular and cerebral metabolism; and bone morphology;**

Conclusions II

- ✓ **The mouses were cohabited shortly after receiving microbiota from healthy children or with short stature and low weight; age-discriminating taxa and growth of the former's microbiota were able to invade the latter, which prevented growth deficiencies in recipient animals;**

- ✓ **The addition of two invasive species, *Ruminococcus gnavus* and *Clostridium symbiosum*, to the microbiota of malnourished donors also improved growth and metabolic abnormalities in recipient animals. These results provide evidence that the immaturity of the microbiota is causally related to malnutrition and reveals potential targets and therapeutic agents.**

International collaboration program

Federal University of Ceará, Brazil

University of Virginia, VA

Thank you!

Financial support: NIAID-ICIDR, MAL-ED, BMGF, FNIH, FIC, CNPq, CAPES, FINEP and FUNCAP.

Jeffrey I Gordon
Wash. Univ., St. Louis, MO

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