



World Health
Organization

BILL & MELINDA
GATES foundation



National Institute of
Allergy and
Infectious Diseases

Second GVIRF

Global Vaccine

and Immunization Research Forum

Johannesburg, South Africa



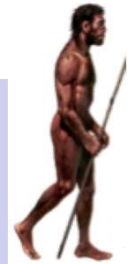
The infant microbiome: Relevance to immune responses

María Gloria Domínguez-Bello
NYU School of Medicine

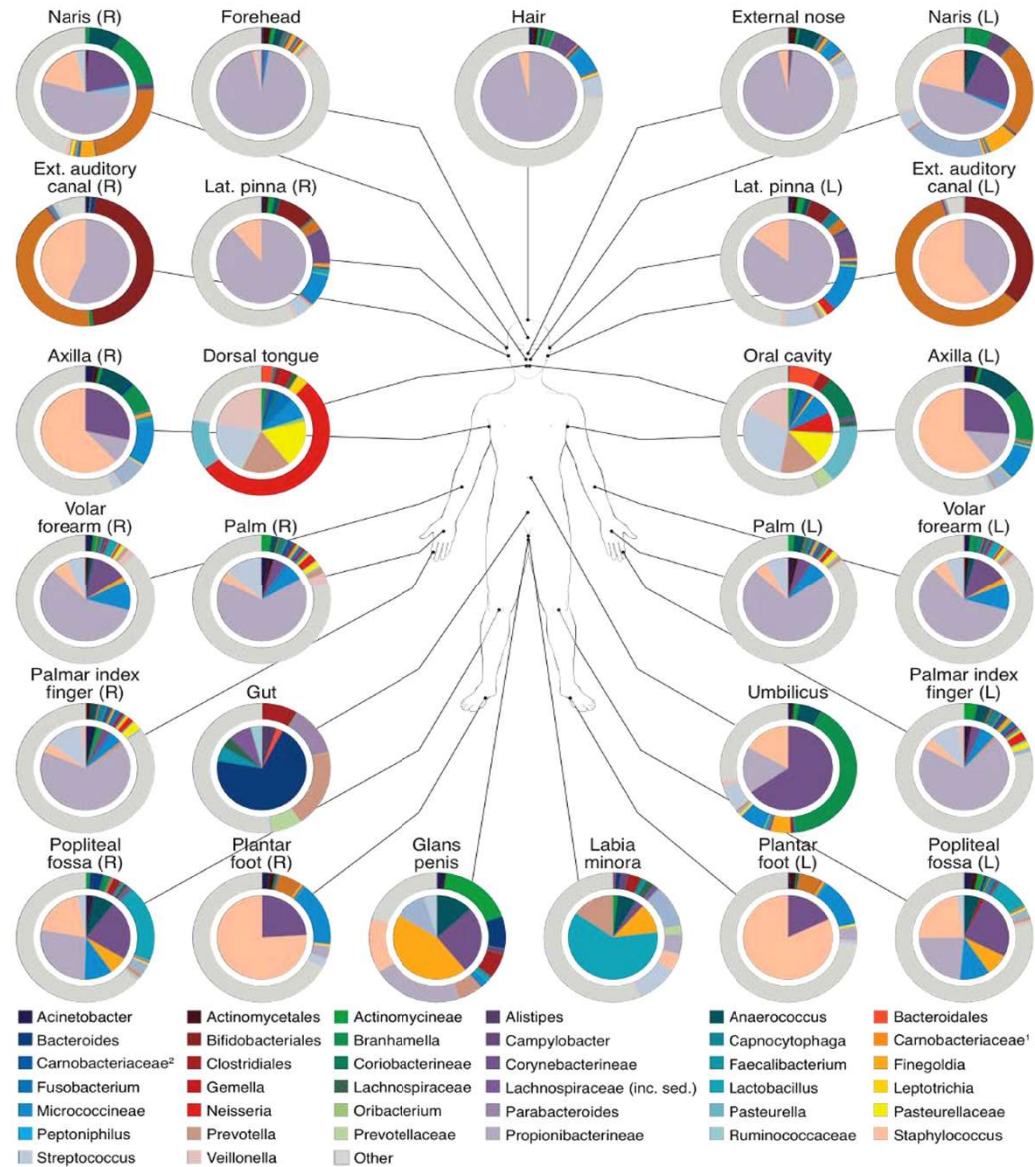


Biology-driven evolution

Origin of Earth 4.8 billion years ago	Origin of first life 3.8 billion years ago BACTERIA	Multicellular life 2.1 billion years ago	Eukaryotes	<i>Homo sapiens</i> 0.2 million years ago
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Human body habitats



Costello et al. 2009, Science

Human Microbiome Project (NIH)

Year = 2007

Initial budget = US\$115 million

Initial aim = development of metagenomics characterization of the microbiome in healthy adults



ARTICLE

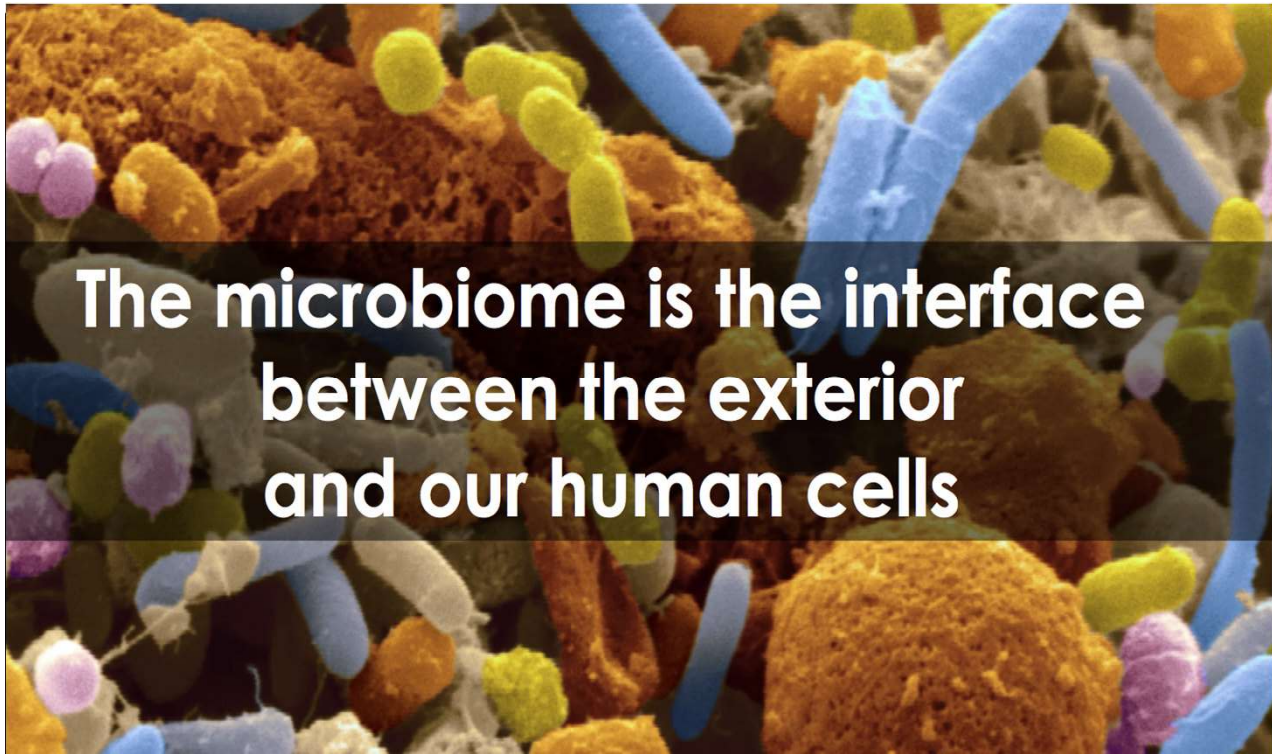
14 JUNE 2012 | VOL 486 | NATURE | 207

[doi:10.1038/nature11234](https://doi.org/10.1038/nature11234)

Structure, function and diversity of the healthy human microbiome

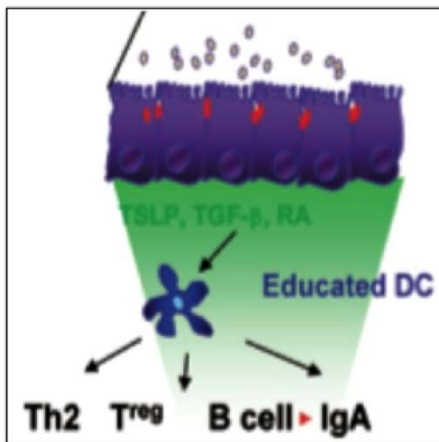
The Human Microbiome Project Consortium*

Studies of the human microbiome have revealed that even healthy individuals differ remarkably in the microbes that occupy habitats such as the gut, skin and vagina. Much of this diversity remains unexplained, although diet, environment, host genetics and early microbial exposure have all been implicated. Accordingly, to characterize the ecology of human-associated microbial communities, the Human Microbiome Project has analysed the largest cohort and set of distinct, clinically relevant body habitats so far. We found the diversity and abundance of each habitat's signature microbes to vary widely even among healthy subjects, with strong niche specialization both within and among individuals. The project encountered an estimated 81–99% of the genera, enzyme families and community configurations occupied by the healthy Western microbiome. Metagenomic carriage of metabolic pathways was stable among individuals despite variation in community structure, and ethnic/racial background proved to be one of the strongest associations of both pathways and microbes with clinical metadata. These results thus delineate the range of structural and functional configurations normal in the microbial communities of a healthy population, enabling future characterization of the epidemiology, ecology and translational applications of the human microbiome.

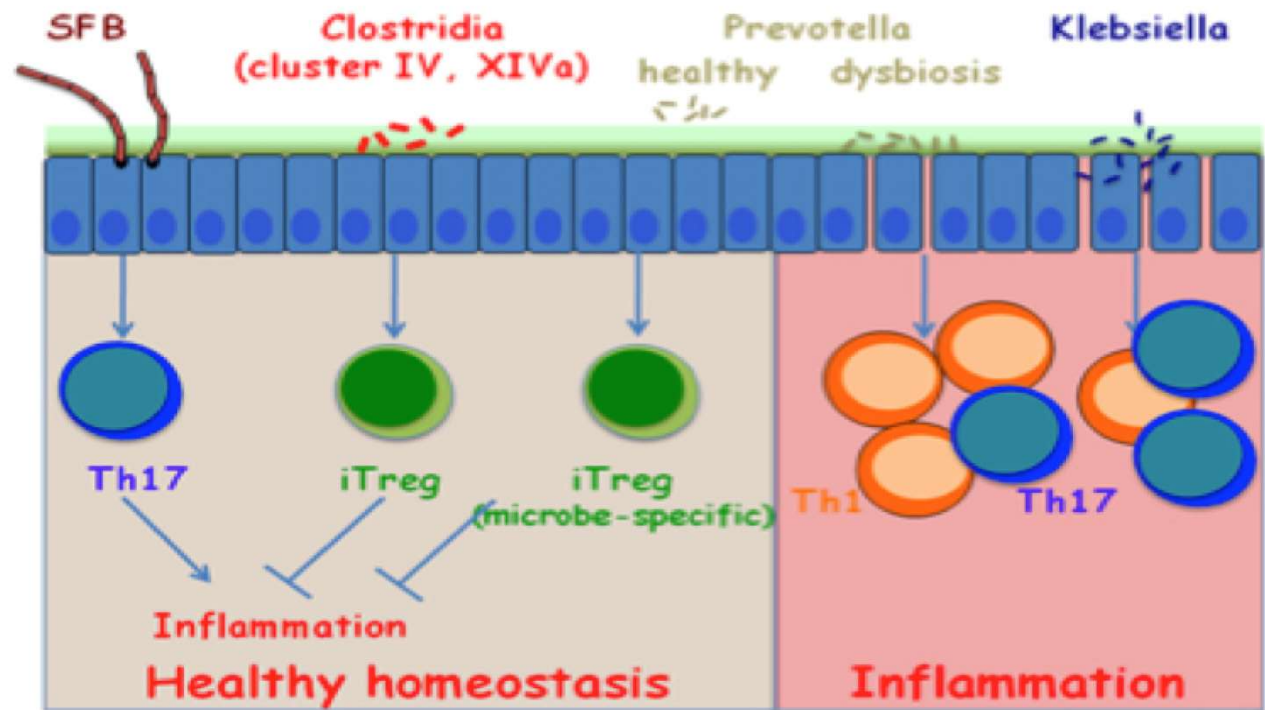


**The microbiome is the interface
between the exterior
and our human cells**

Immune modulation by the gut microbiota

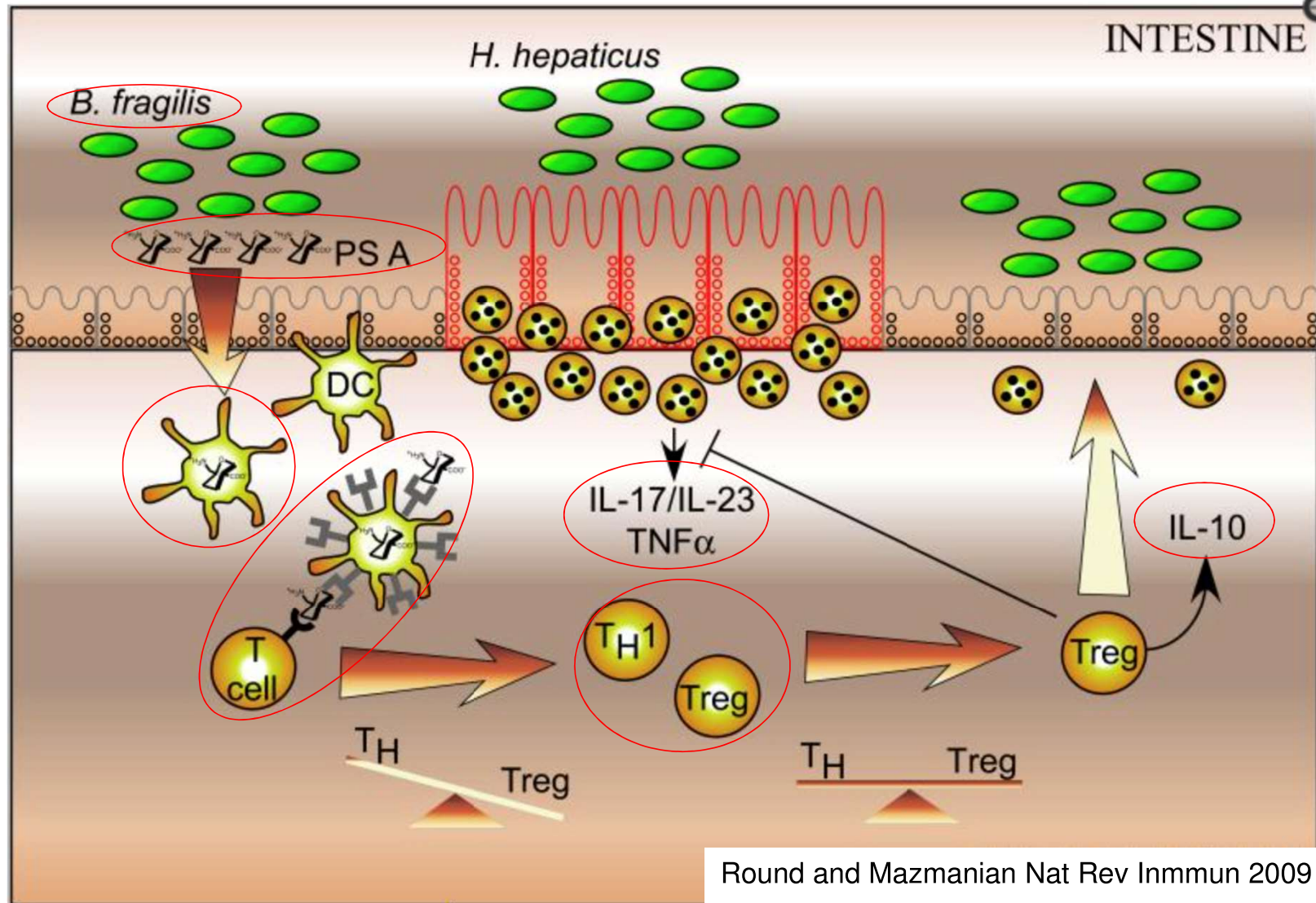


Rescigno, 2009, Biol Rep



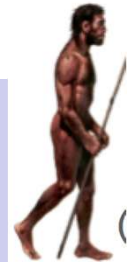
Littman & Pamer 2011, Cell, Host & Microbe

Microbiota control of inflammation



Biology-driven evolution

Origin of Earth 4.8 billion years ago	Origin of first life 3.8 billion years ago BACTERIA	Multicellular life 2.1 billion years ago	Eukaryotes	<i>Homo sapiens</i> 0.2 million years ago
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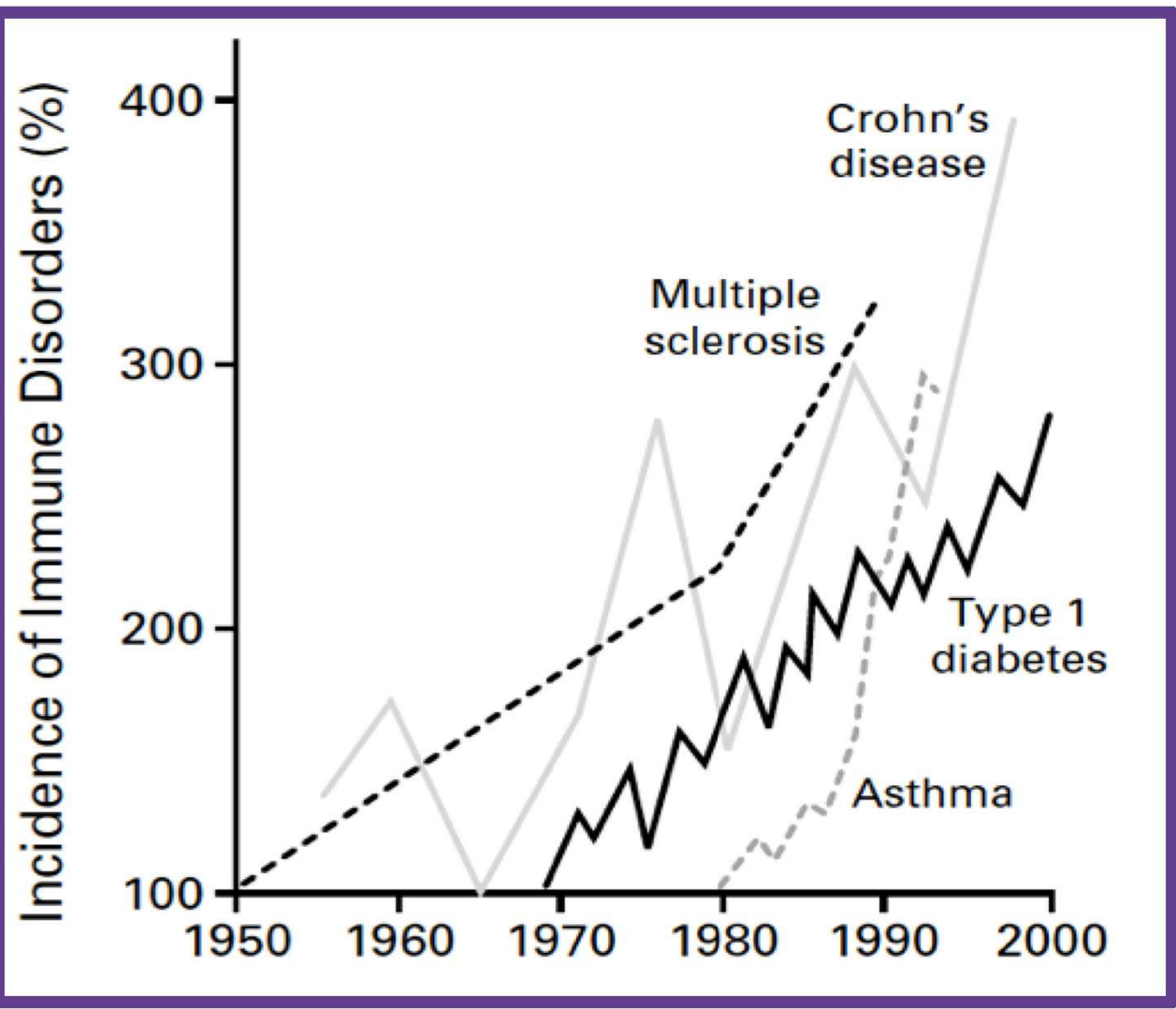


Evolution turns the inevitable
into a necessity

Jacques Monod

Cultural-driven evolution

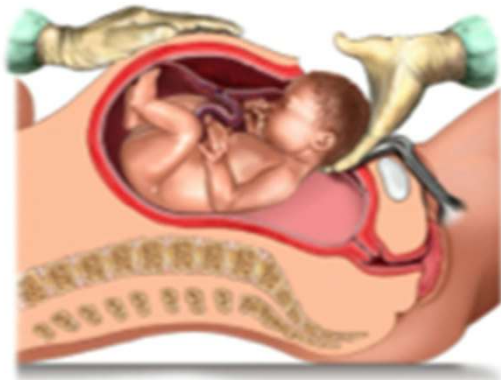




Growing incidence of immune disorders in developed countries

Bach 1999

Diseases associated with C-section



Type 1 diabetes

Algert, McElduff et al. 2009
Aumeunier, Grela et al. 2010
Bonifacio et al. 2012

Celiac disease

Decker, Engelmann et al. 2010
Marild, Stephansson et al. 2012

Asthma

Kero, Gissler et al. 2002
Kero et al. 2002
Thavagnanam et al. 2007
Roduit et al. 2009
Couzin-Frankel 2010
Ege et al. 2011
Azad et al. 2012

Obesity

Huh, Rifas-Shiman, et al. 2012
Blustein et al. 2013
Mueller et al 2014

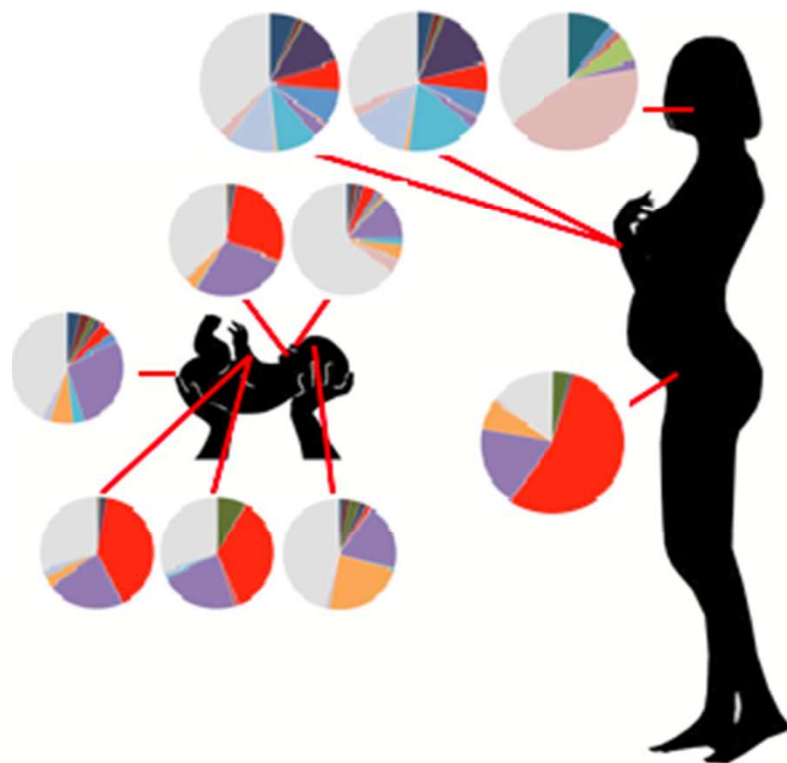
Is the *urbanite* microbiome impacted?



Mode of birth and the primary microbiota

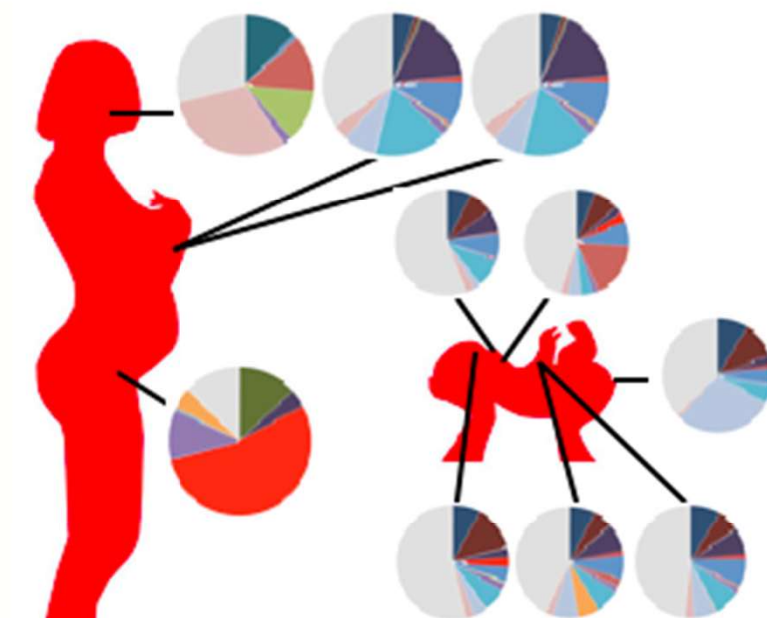
- Acinetobacter
- Bacillales
- Coriobacterineae
- Corynebacterineae
- Haemophilus
- Lactobacillus
- Micrococcineae
- Neisseria
- Pasteurellaceae
- Prevotella
- Propionibacterineae
- Sneathia
- Staphylococcus
- Streptococcus
- Other

Vaginal

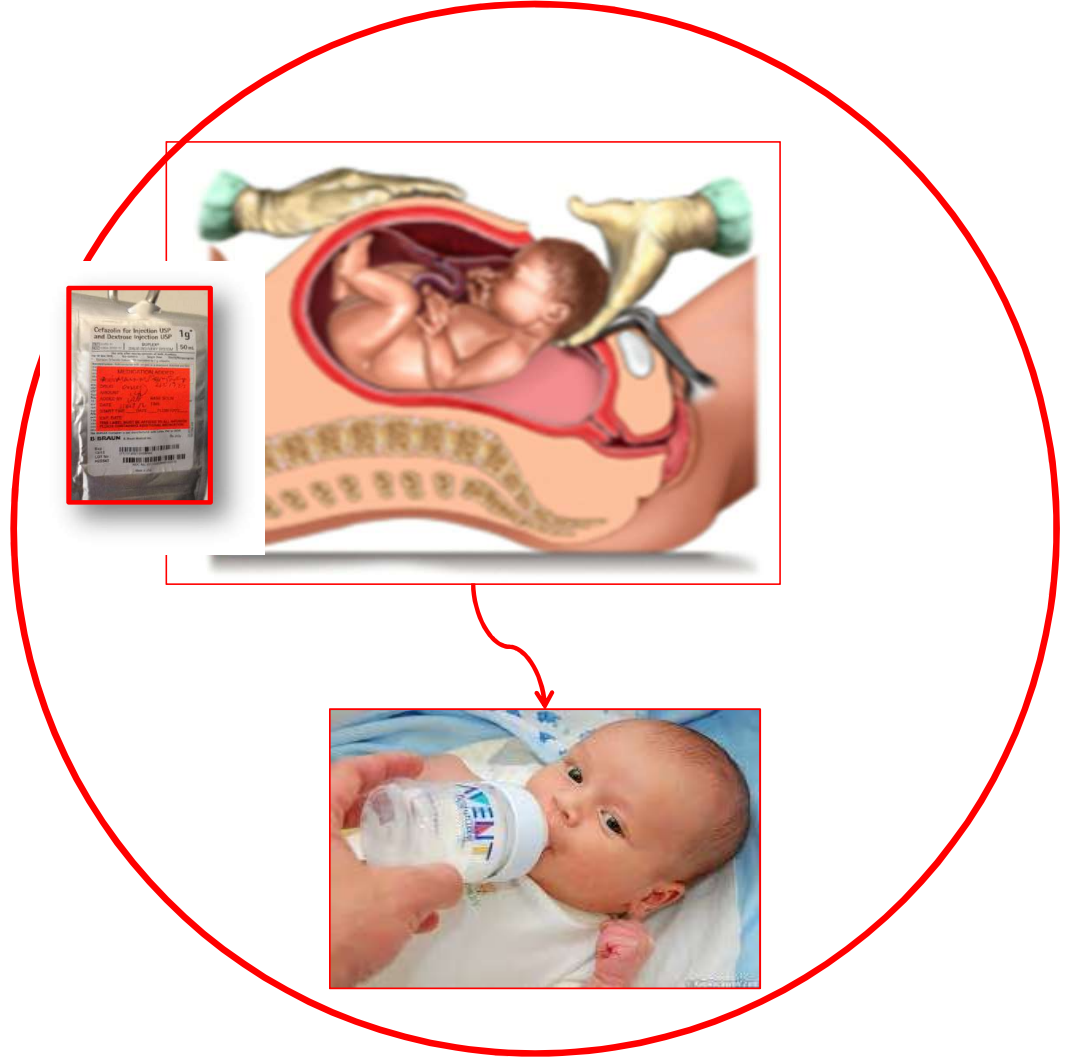


n=4

C-section



N=5





Age-associated changes in infant microbiota

43 infants followed for 2 years

23 did not have antibiotics during this time:

13	Vaginal- 70% breastfed
10	C-section- 70% formula suppl

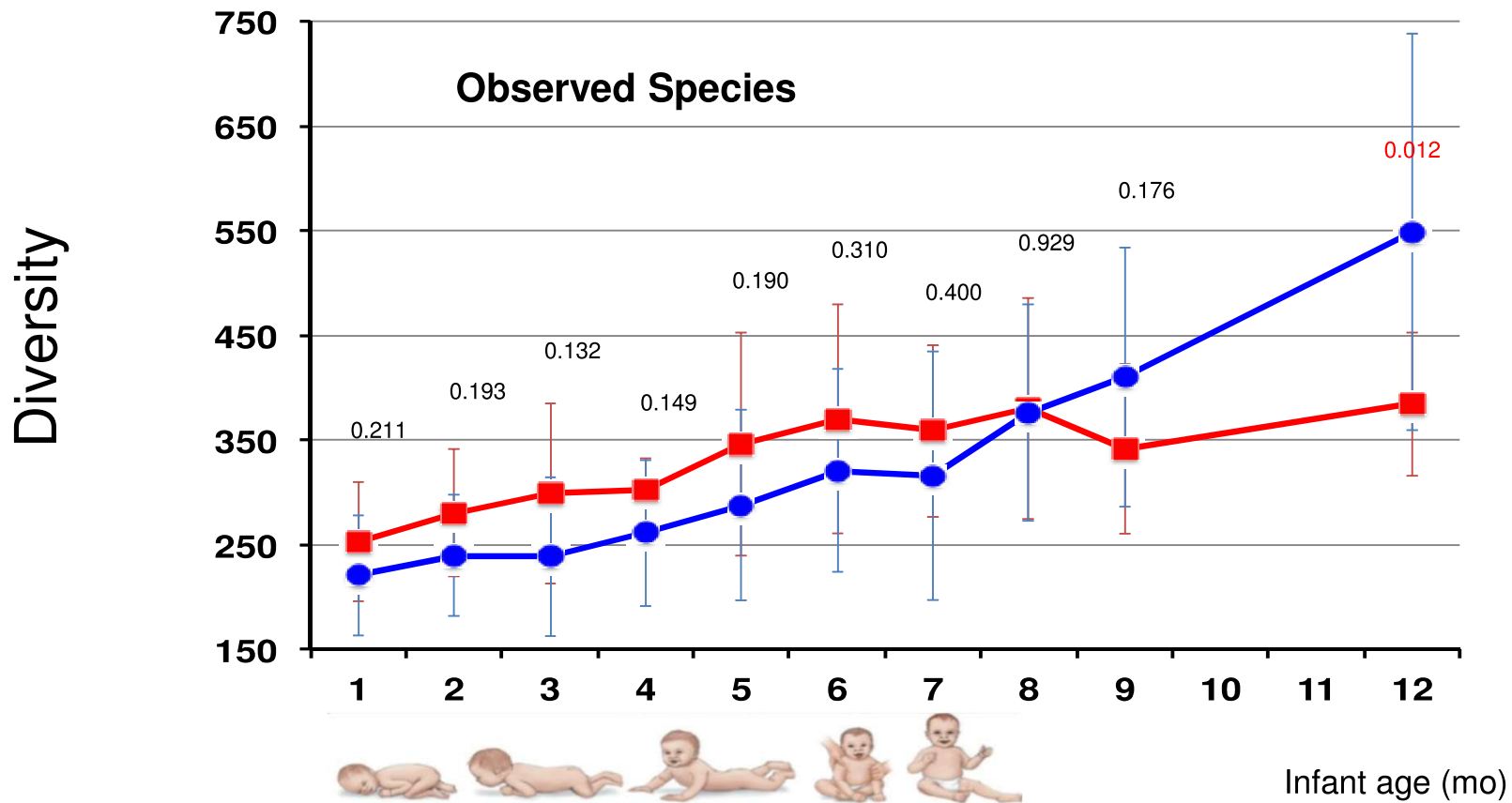
Infants not exposed to antibiotics in year 1
Nonparametric p-values calculated using 10,000
Monte Carlo permutations

Infant age (mo)

ECAM study



Reduction of diversity in C-section formula-fed infants



13 Vaginal- 70% breastfed
10 C-section- 70% formula suppl

Infants not exposed to antibiotics in year 1
Nonparametric p-values calculated using 10,000
Monte Carlo permutations

ECAM study

Paine et al 1998, Ecosystems

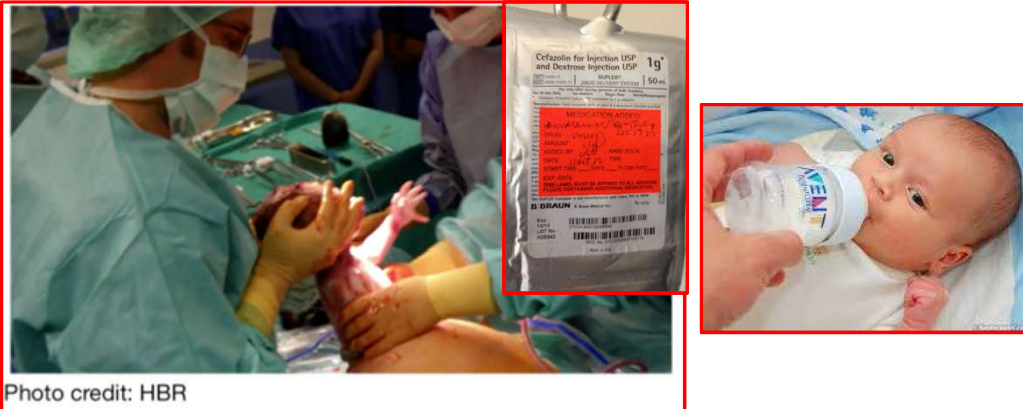
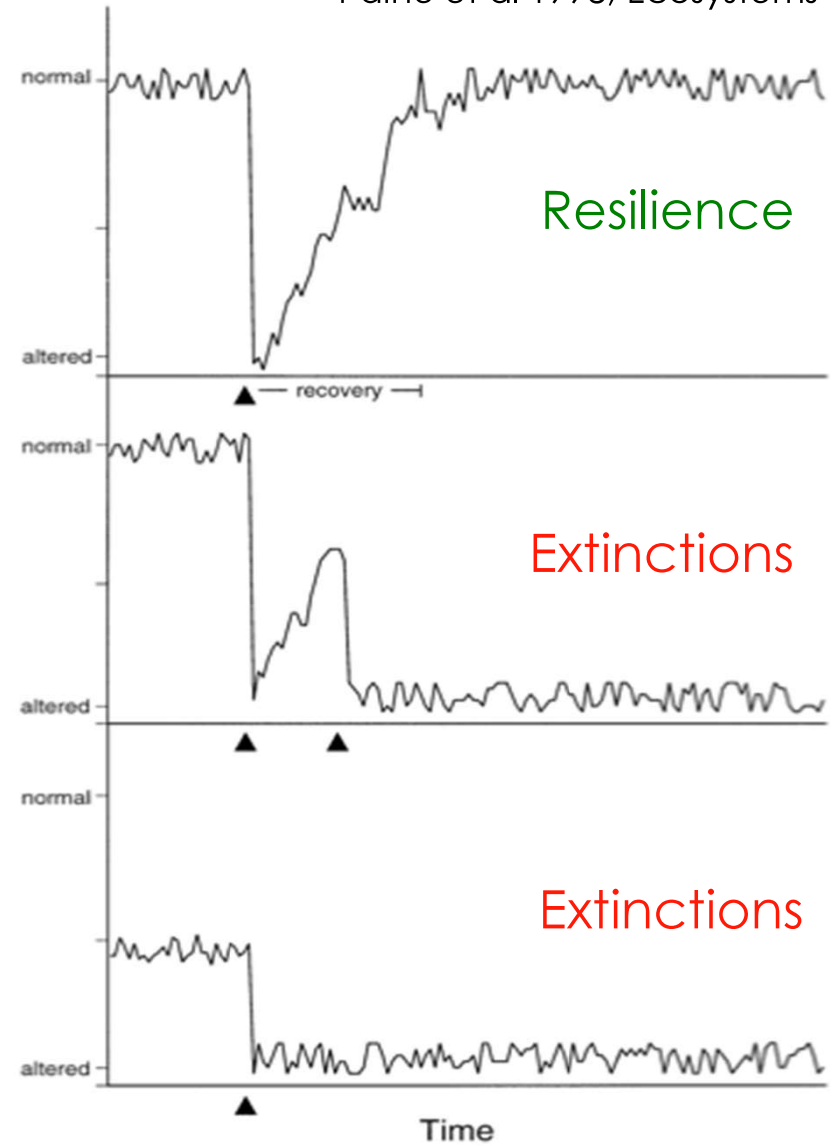
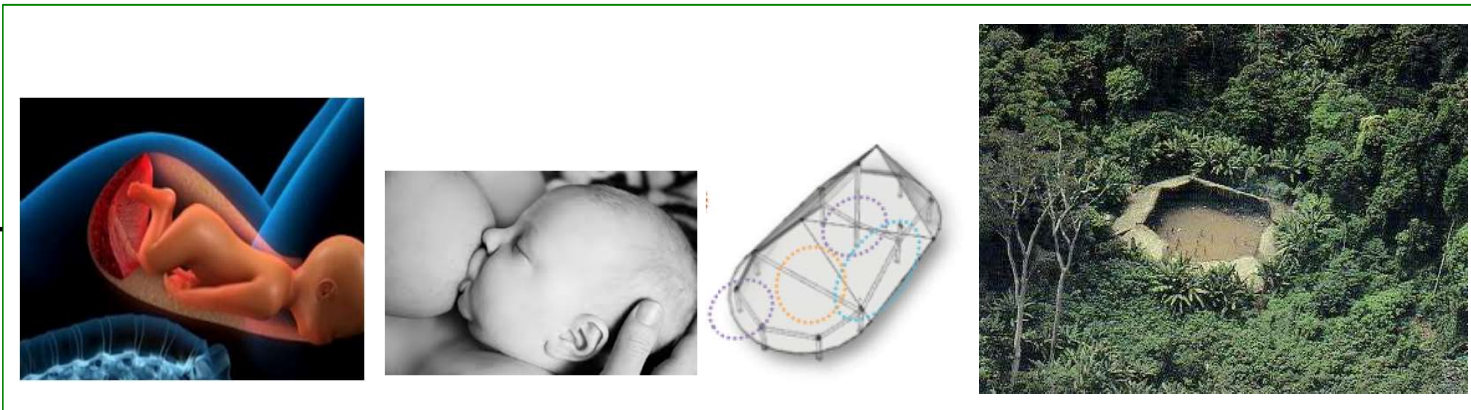
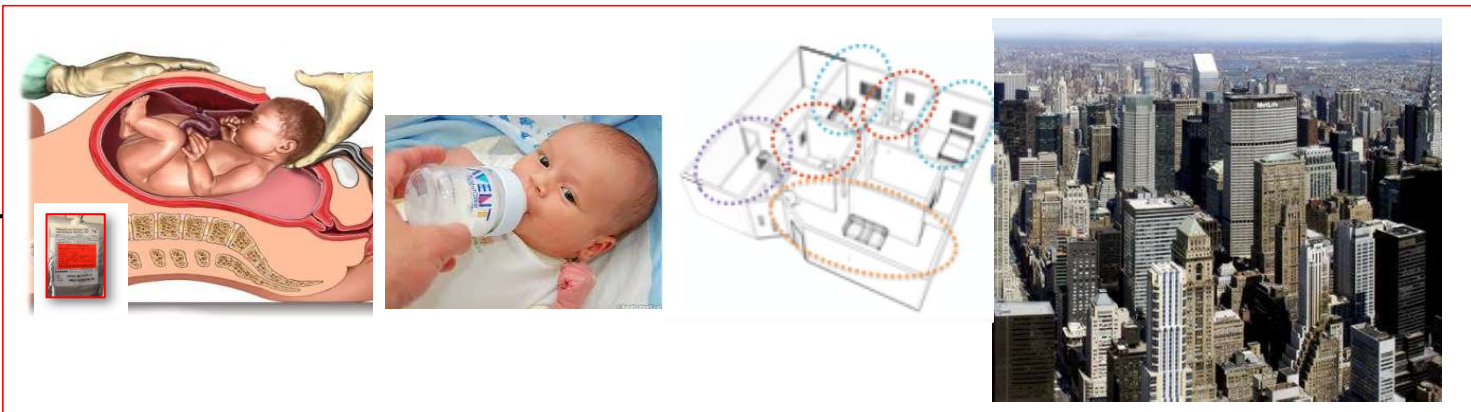


Photo credit: HBR

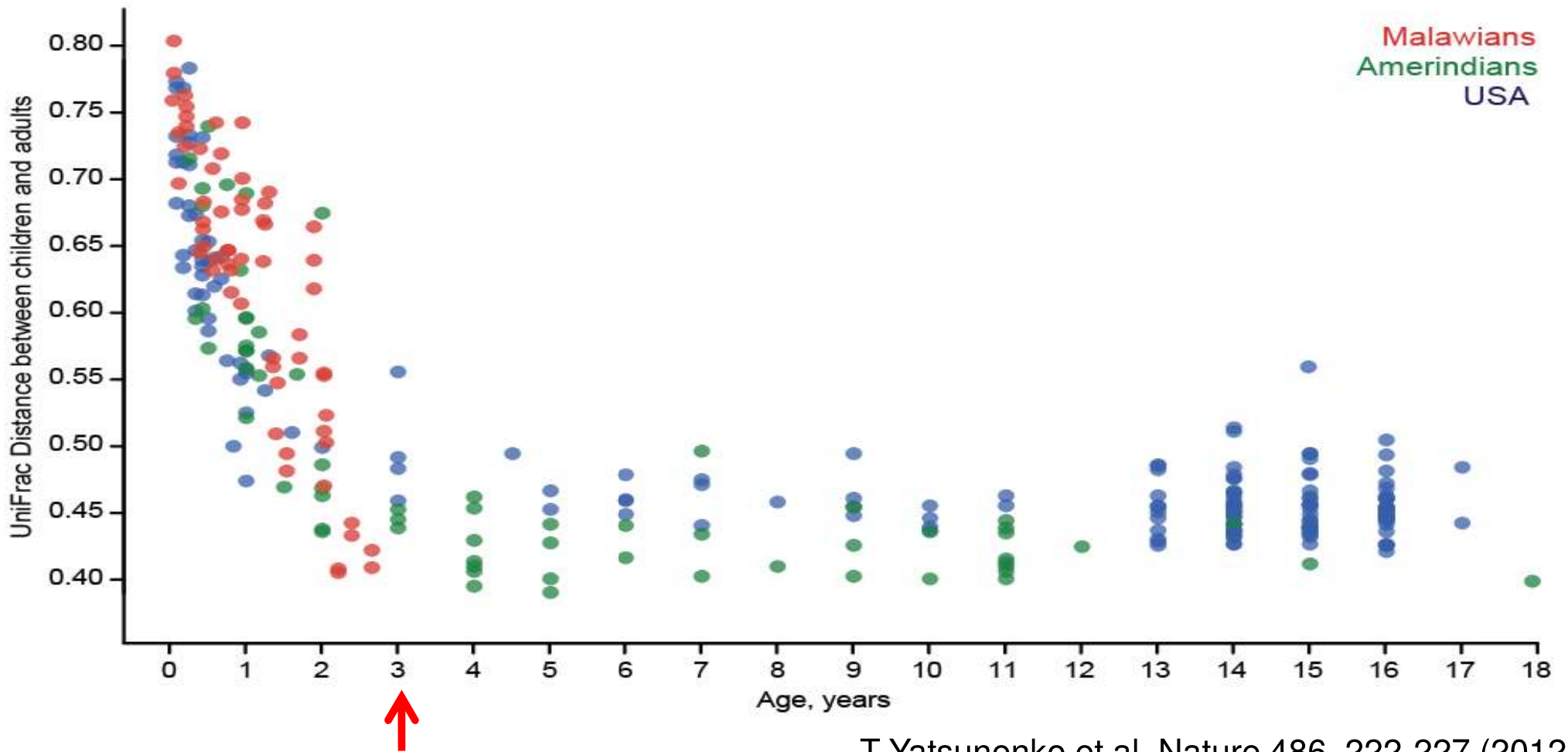
Compounded C-section factors



Urban vs traditional microbiome

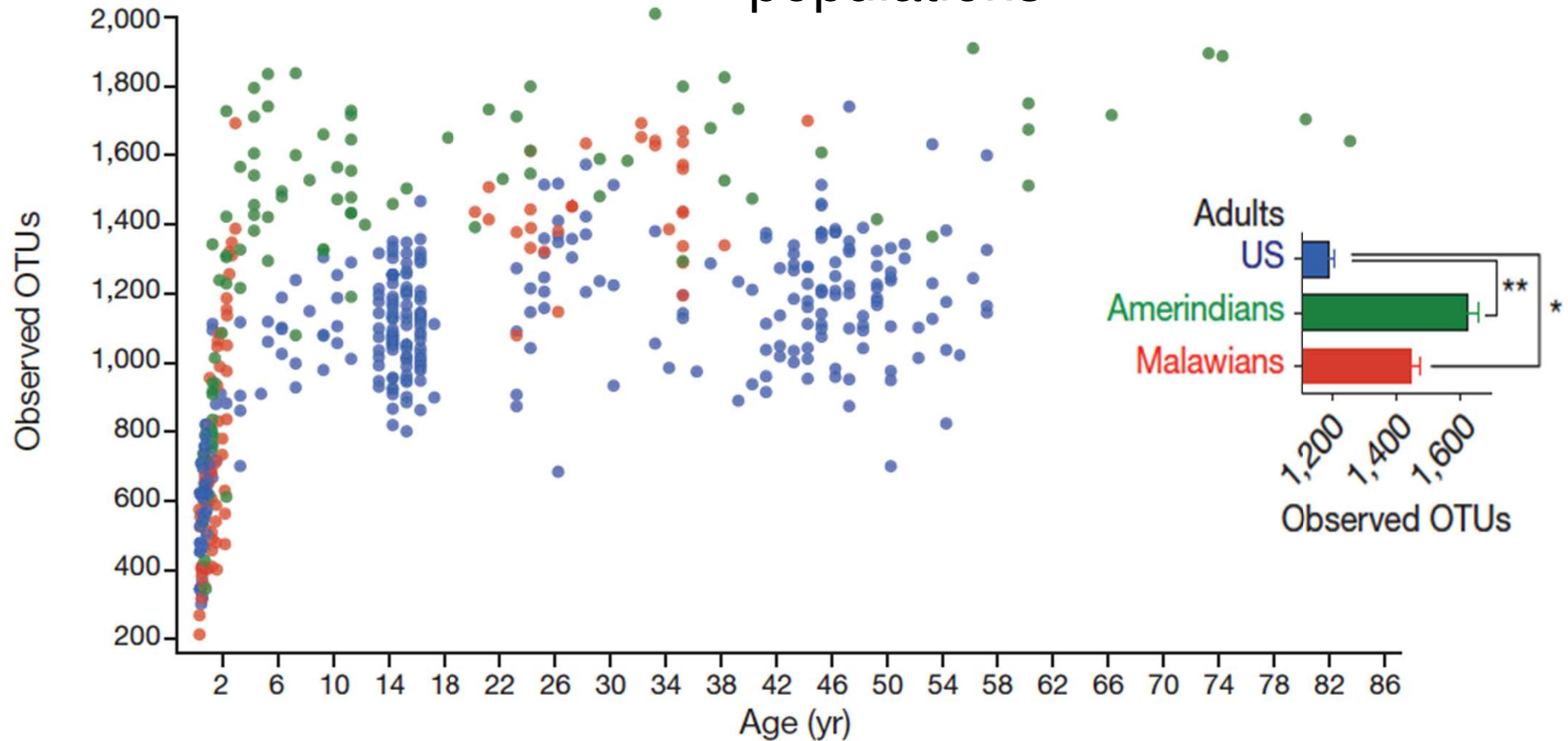


Maturation of the human gut microbiome



T Yatsunenko et al. Nature 486, 222-227 (2012)

Fecal microbiota diversity in adults from three human populations



Yatsunencko et al. 2012, Nature

Most Isolated peoples



Photo: Maria G Dominguez-Bello

REPÚBLICA BOLIVARIANA DE VENEZUELA



Ministerio del Poder Popular
para la Salud

MEMORIA 2008

Se conformaron cinco equipos itinerantes, los cuales participaron en tres operativos realizados a comunidades Yanomami de difícil acceso, logrando acceder a 11 comunidades (Kopariwe, Pisisipiwei, Hokoto, Maiyotheri, Kohoroshiwe, kaiperipowei, Rashakami, Hashimu, Toshamoshi, Shokopruru, Shukumina) de las cuales algunas eran desconocidas para el SPNS y otras no habían sido contactadas en varios años, atendiendo un total de 1.150 indígenas.

1975

The New York Times

February 17, 2013



Napoleon Chagnon

A Yanomami leader, Krihisiwa, encounters a helicopter for the first time, 1975.

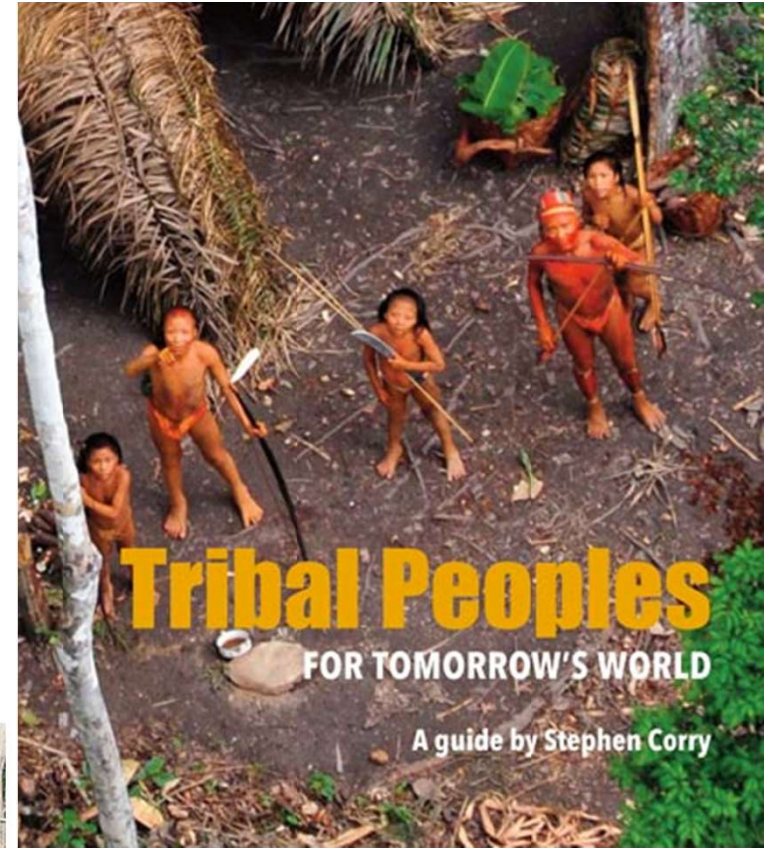
Venezuela

First contacted

2008



Paraguay



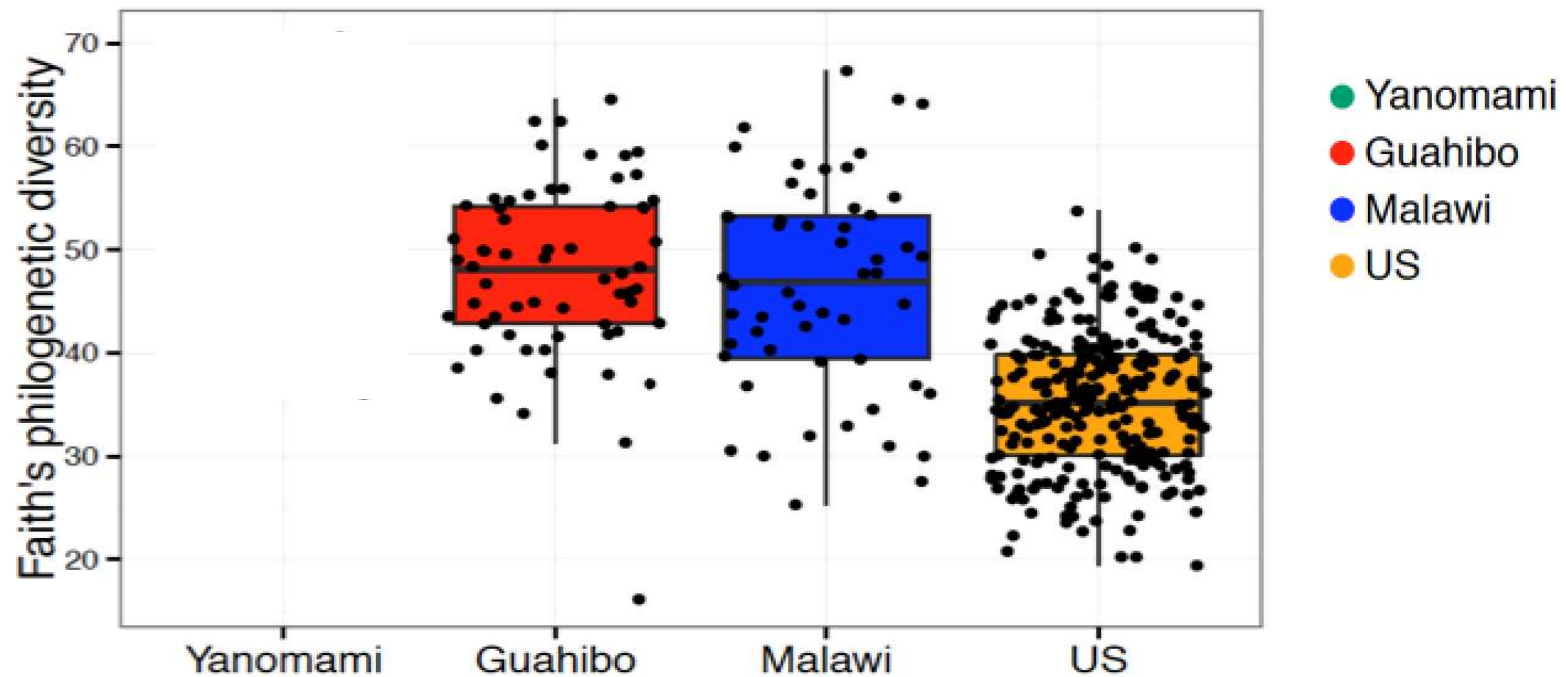
Brazil

Yanomami village – first contact



Photos:
Oscar Noya
2008

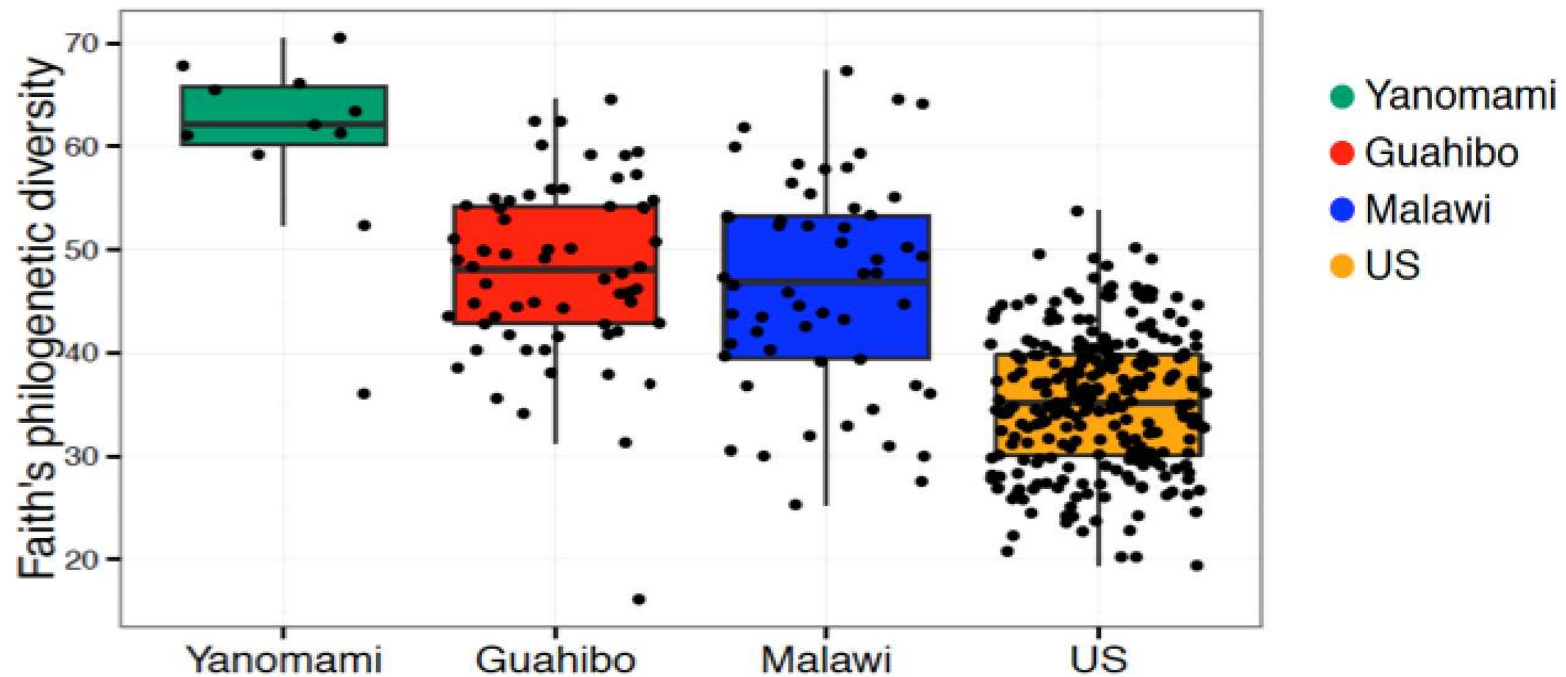
Fecal microbiome alpha diversity across cultures



Westernization

Clemente et al. 2015 Science Advances

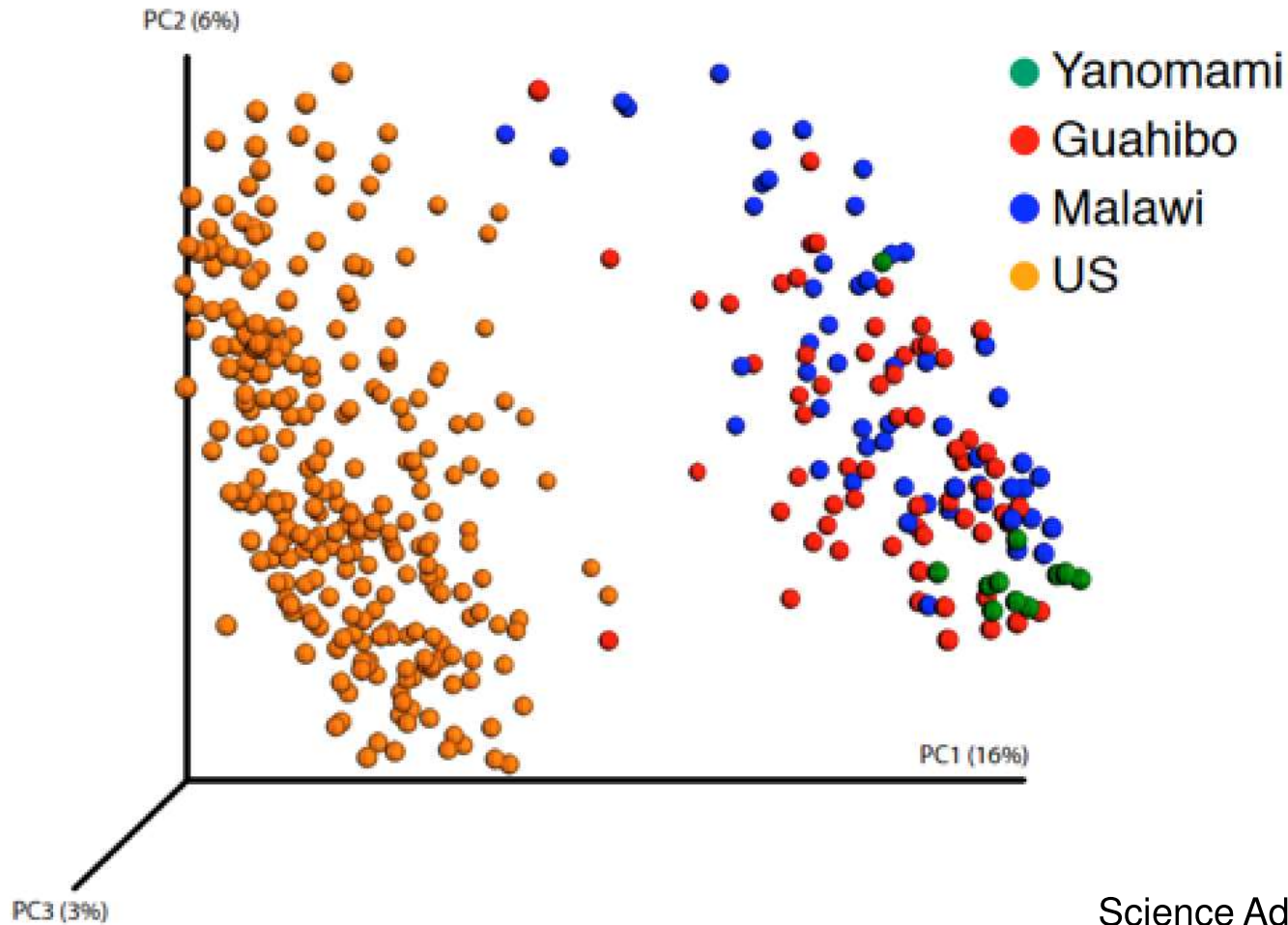
Fecal microbiome alpha diversity across cultures



Westernization

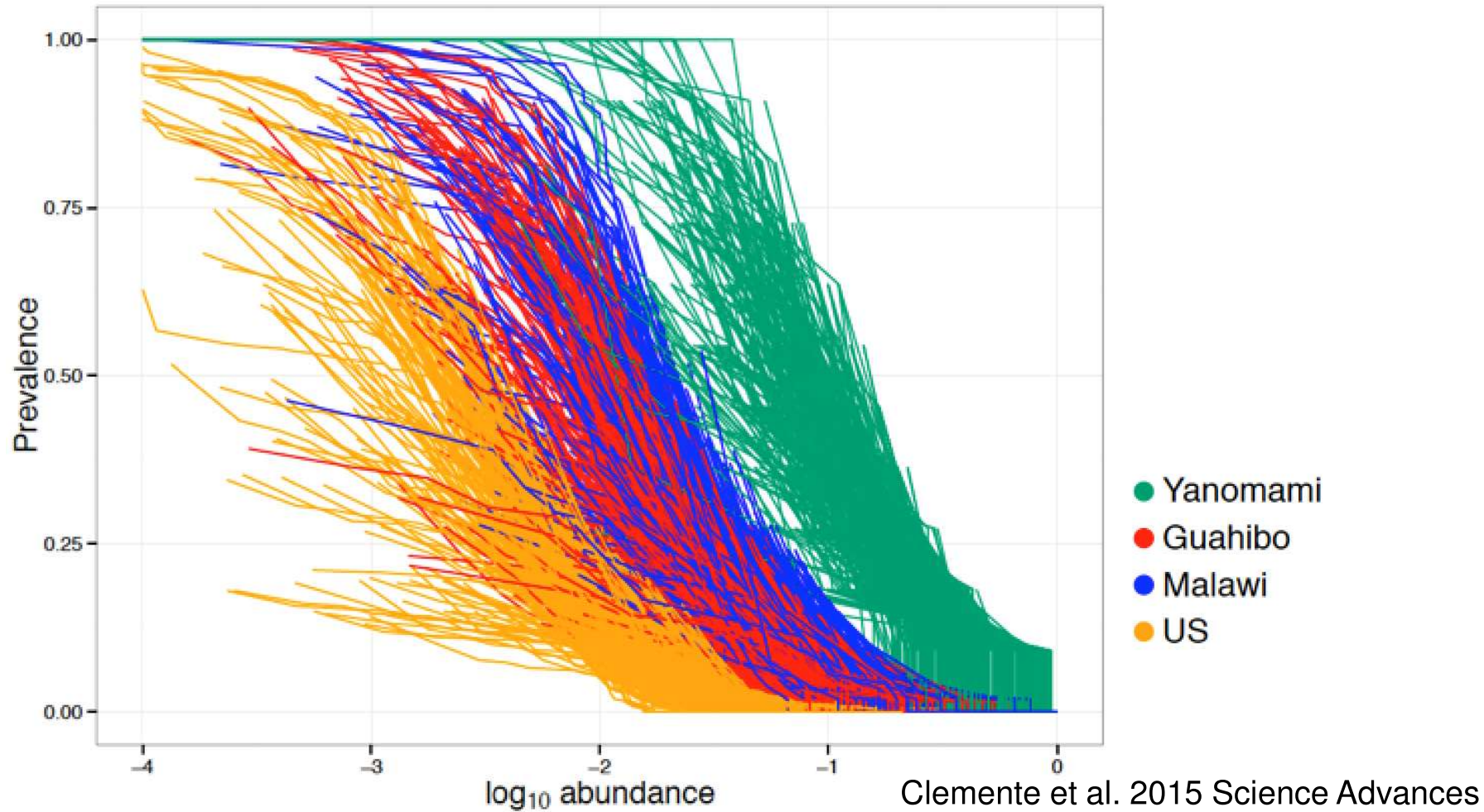
Clemente et al. 2015 Science Advances

Fecal microbiome beta-diversity across cultures



Science Advances, 2015

Prevalence/abundance curves of individual fecal bacteria in human populations



The microbiome and impact of Western practices

- Modern lifestyle practices reduce the gut microbiota diversity
- Bacterial diversity in the gut is rendered as a good attribute.
- Early microbiota impacts might be associated with abnormal inflammatory responses

Impacted *urbanite* microbiome





Seattle, USA,

Urbanite lifestyles



Belem-Iquitos, Peru



Caracas, Venezuela



URBANIZATION → SOCIAL STRATIFICATION



Checherta



P. Almendras



Iquitos



Manaus



The microbiome of the urban poor ? ? ?

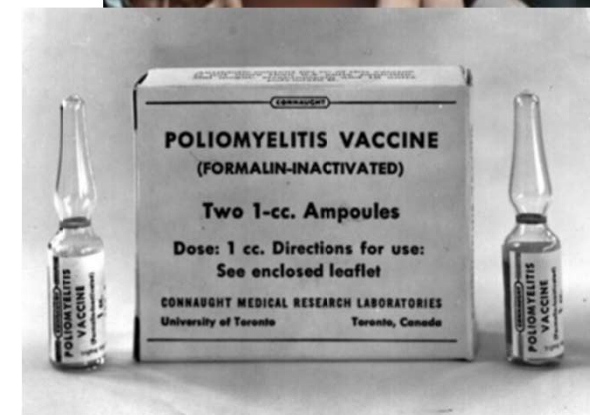
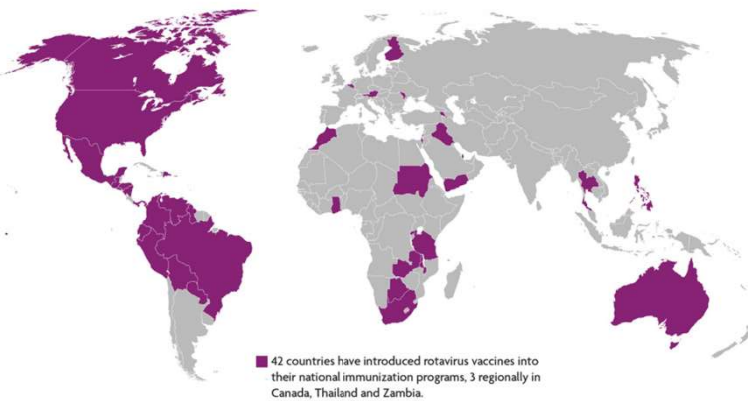


Very few studies!

ICDDR,B worker recruiting a mother in Mirpur, a slum in Dhaka, Bangladesh

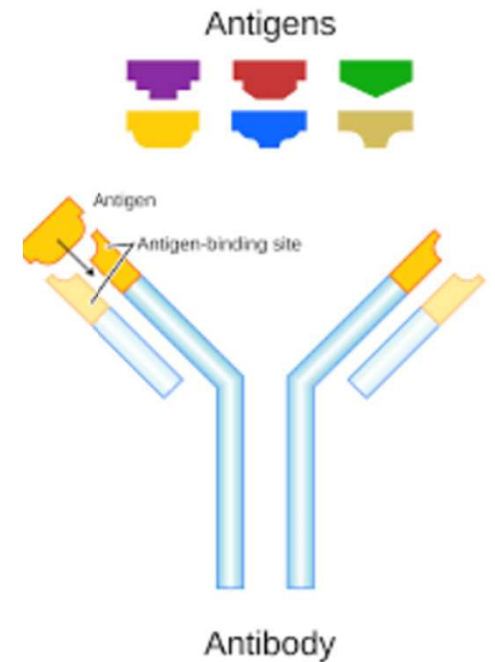
Photo: William Petri Jr.

Orally delivered vaccines display lower efficacy in low income countries



Reasons for lower vaccine efficacy

Maternal antibodies neutralizing?
(breast milk controversy
with polio vaccine)



Malnutrition?



Reasons for lower vaccine efficacy

Environmental enteropathy?

Constant inflammation

Infections

Malnutrition

Hooper et al 2012, Science
Keusch et al. 2013 Food Nutr Bull
Korpe et al 2012, Trends Mol Med
Cooper et al. 2000, JID
MAL ED Network 2014, JID



Desensitization of
antigenic responses?

Healthy Intestine



- Healthy villi
- Absorb nutrients
- Pathogen barrier

Environmental Enteropathy



- Villous atrophy
- Malabsorption
- “Leaky” intestine

Several vaccinations are given during infancy



Early microbiome may be important in vaccine efficacy

Commensal bacteria



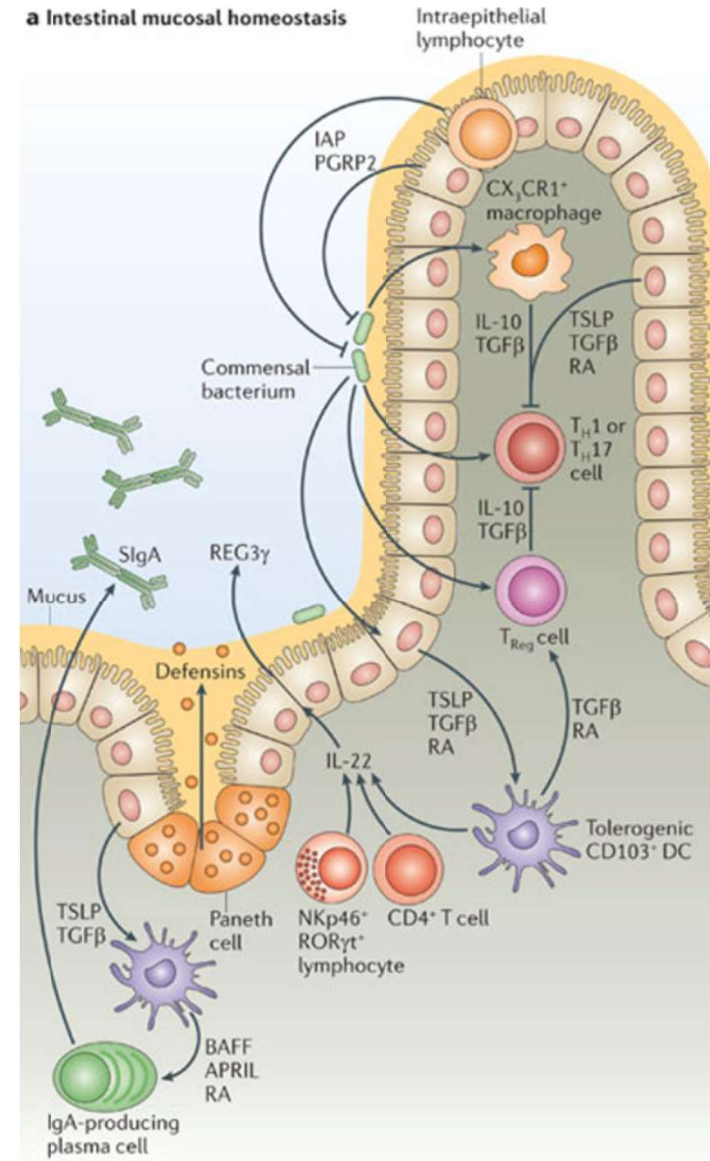
Differentiation of B cells



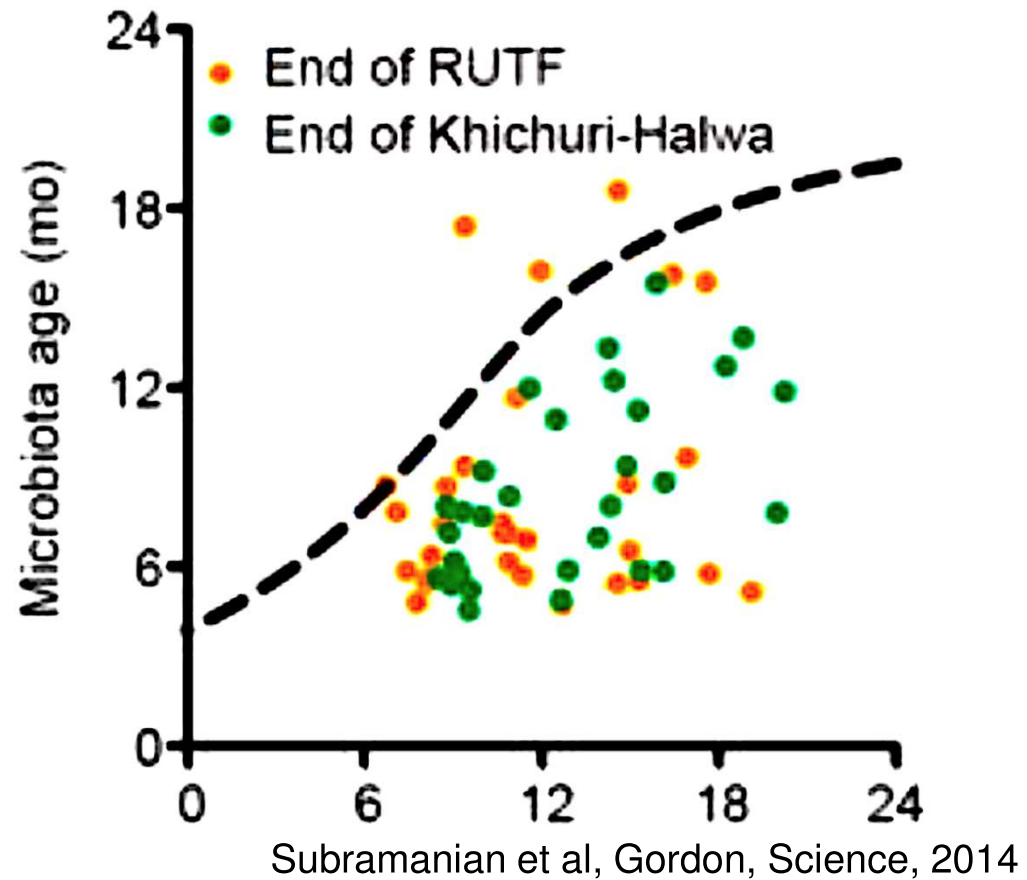
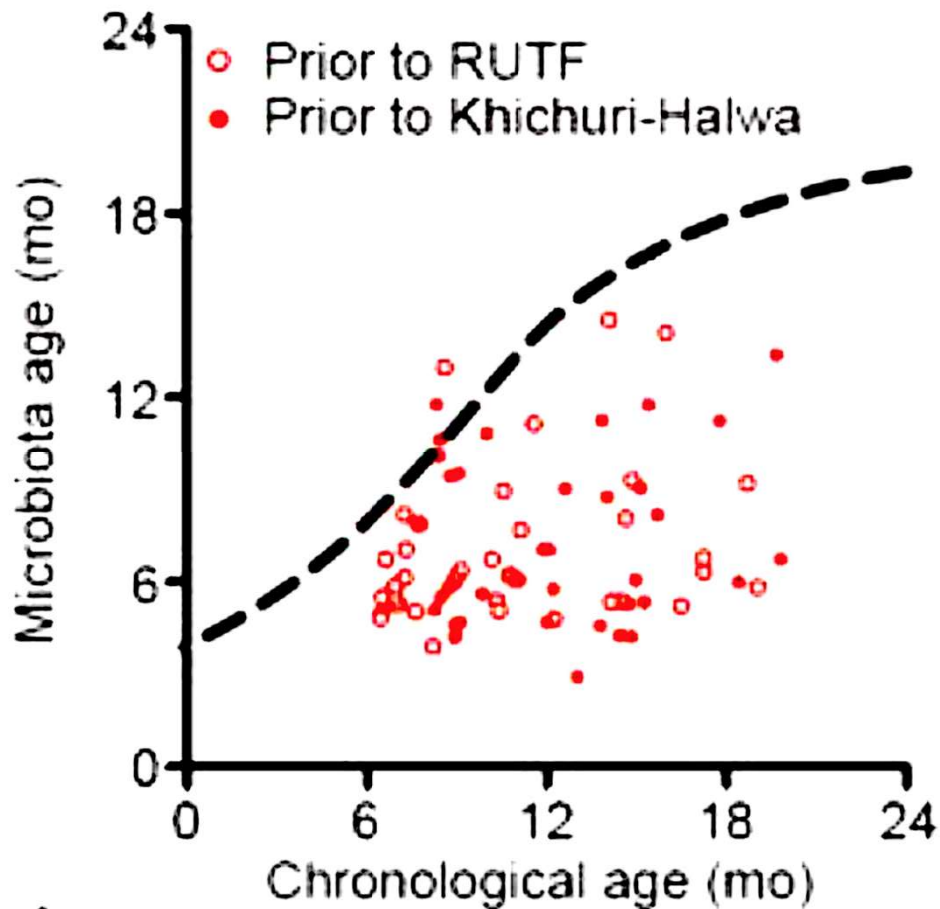
IgA



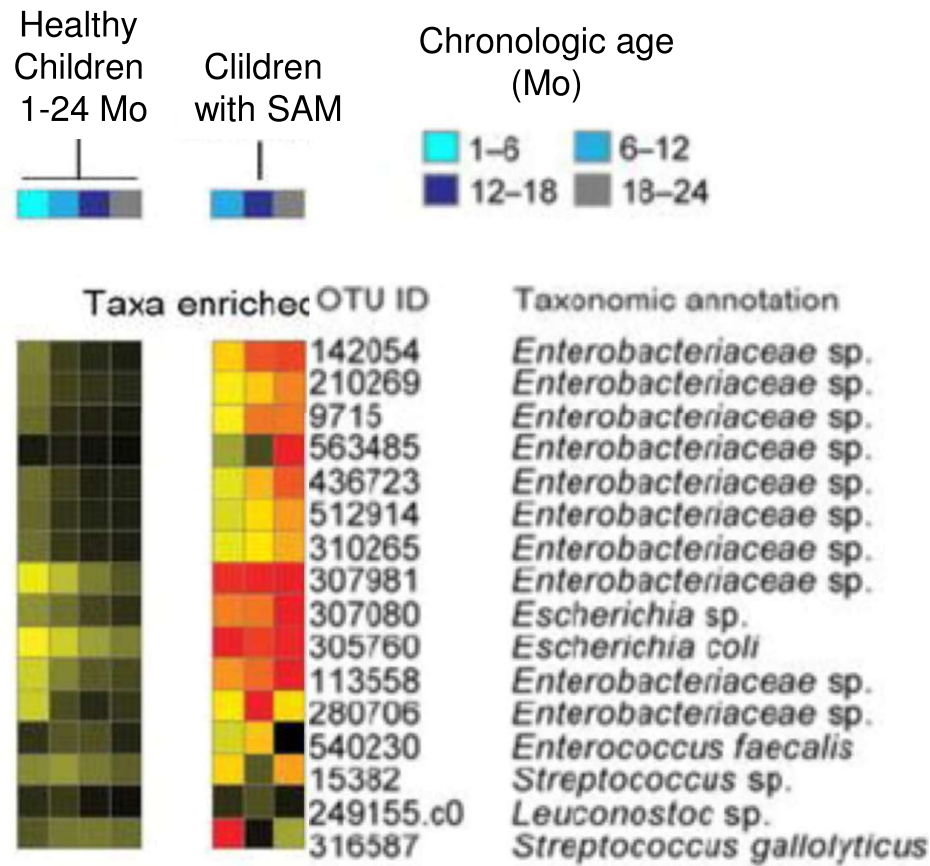
Intestinal mucosa IgA-secreting plasma cells.



Severe acute malnutrition effect on early microbiome maturity and efficacy of dietary interventions

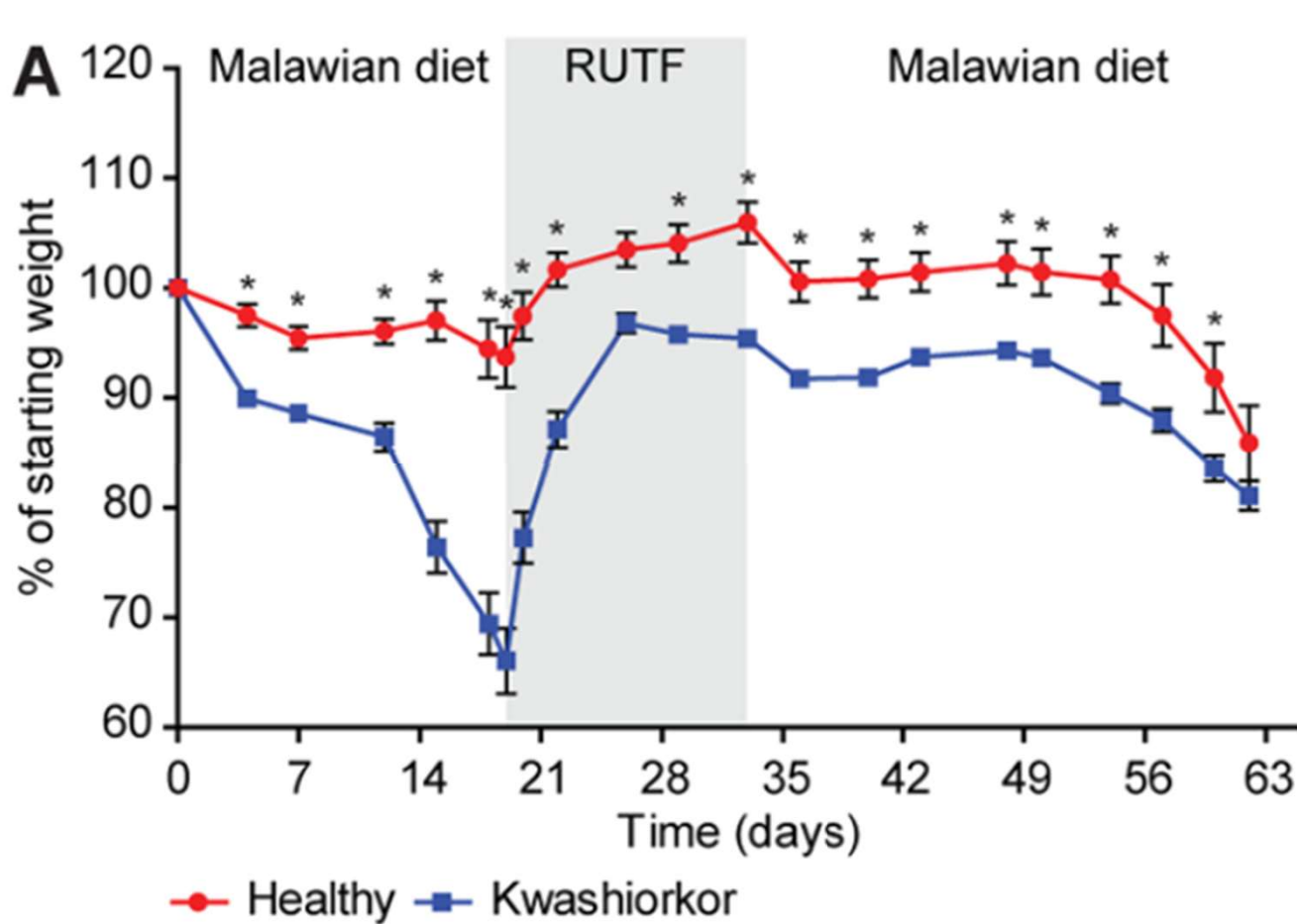


Overrepresented fecal taxa in severe acute malnutrition



Subramanian et al, Gordon, Science, 2014

Weight in GF mice humanized with fecal microbiota from kwashiorkor and healthy co-twins*

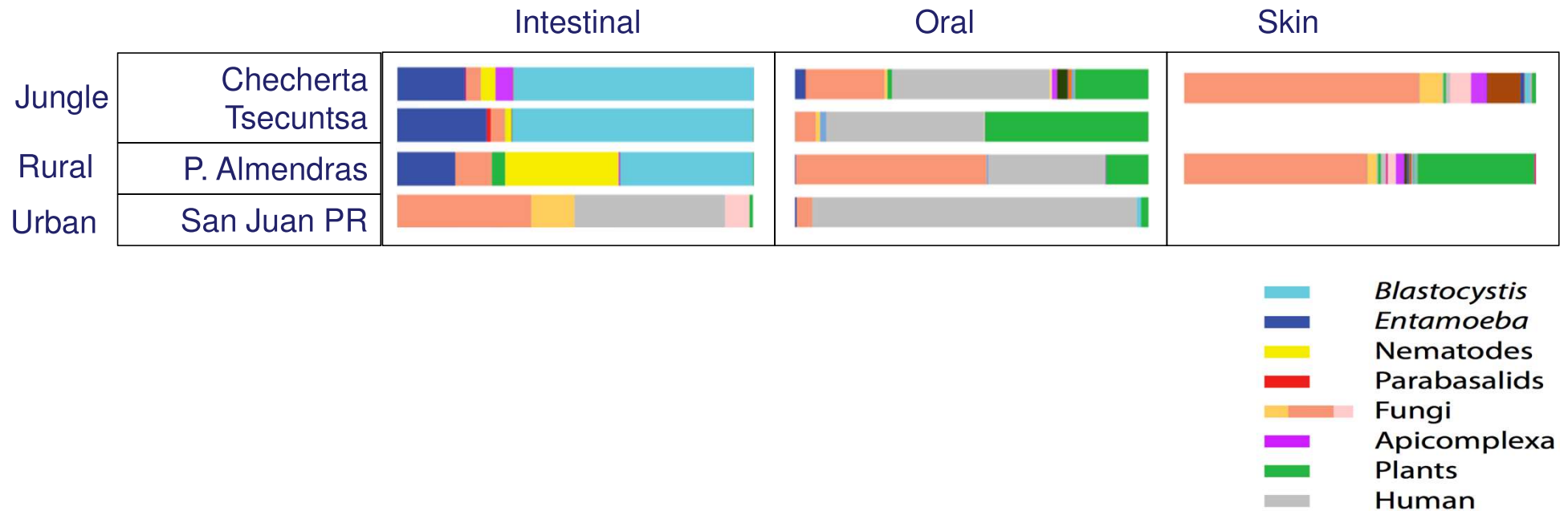


* <math>< 3</math> years

Kwashiorkor
microbiota
weight loss on
Malawi diet



Eukaryotes as part of the microbiome?



(18S rRNA gene sequences)



Laura Wegener Parfrey
University of British Columbia

Albendazole-treated children



greater interferon (IFN)- γ and IL-2 levels
(Cooper PJ et al. 2011 BMC Infect Dis.)

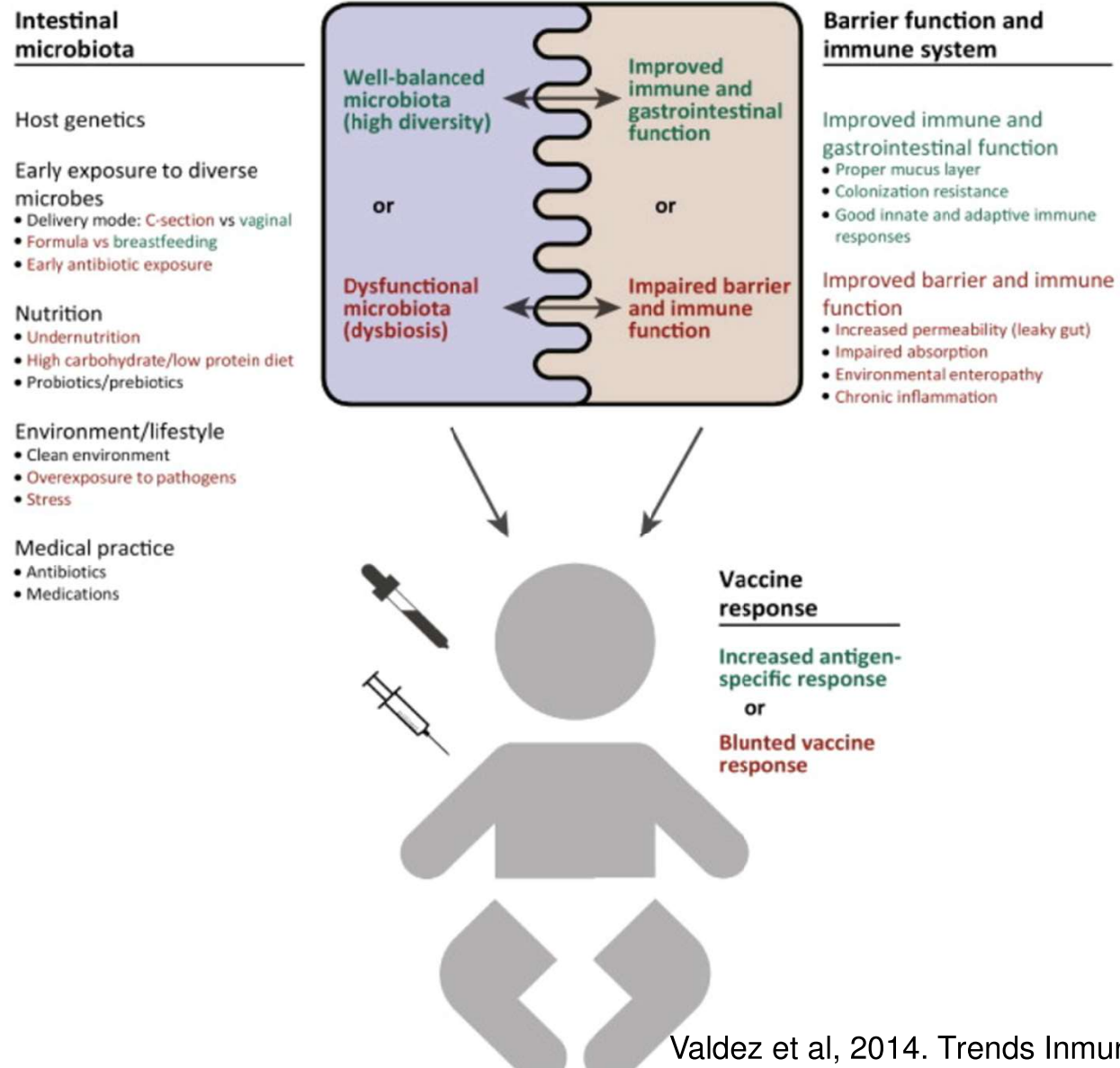
Microbiome effect?

More research needed to characterize the early microbiome and immune responses of children

- 1. Including eukaryotes and viruses**
- 2. In different body epithelia**
- 3. Across cultures and geographies**



Understanding of the **microbiome and vaccine responses** will lead to better future vaccination strategies





**ALFRED P. SLOAN
FOUNDATION**

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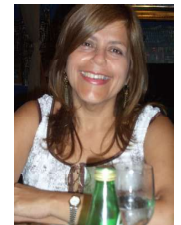
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