

# Human microbiota: The other human genome



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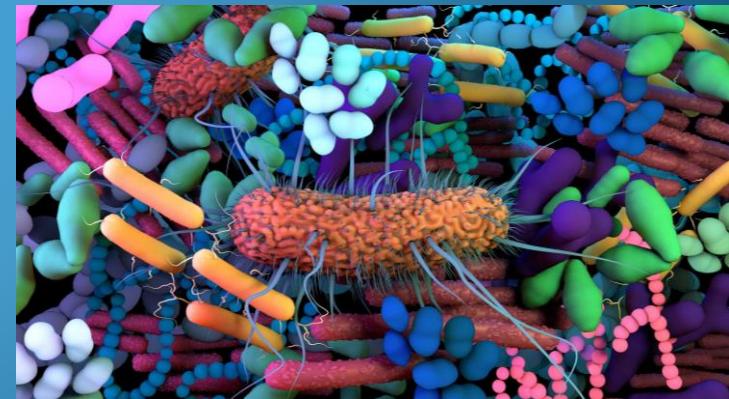
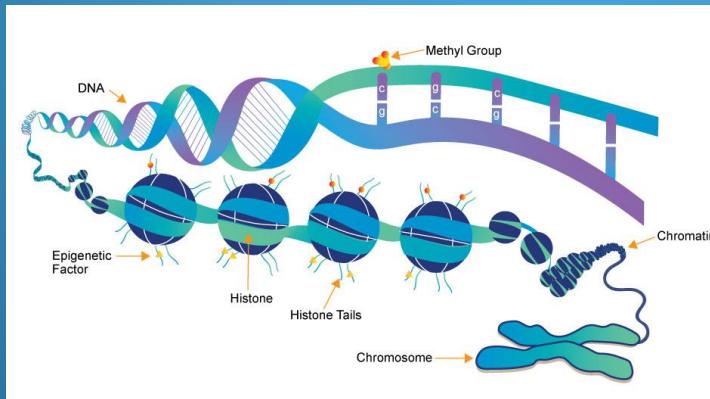
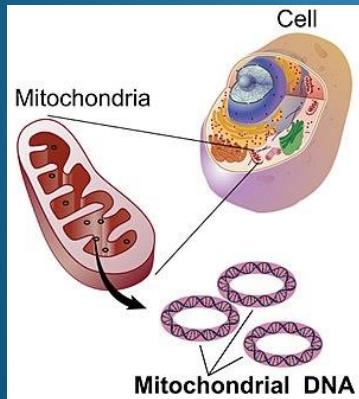


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# Human Genetics

Human genetics has traditionally focussed on the diversity and inheritance of nuclear DNA sequences. However, there are additional forms of DNA inheritance that comprise an “extended genotype”.

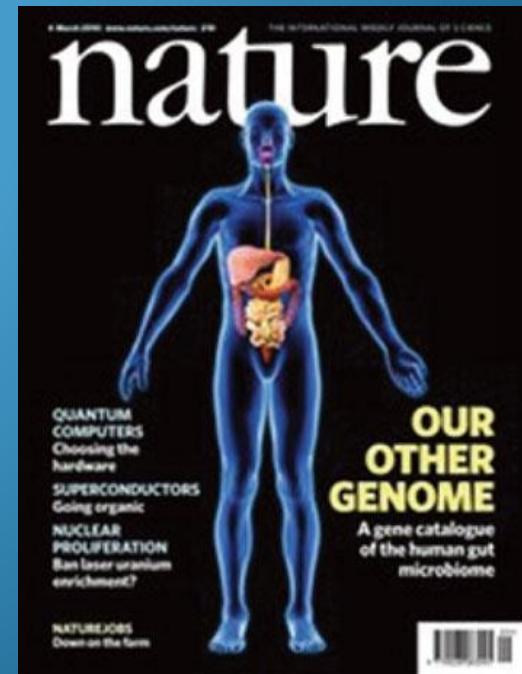
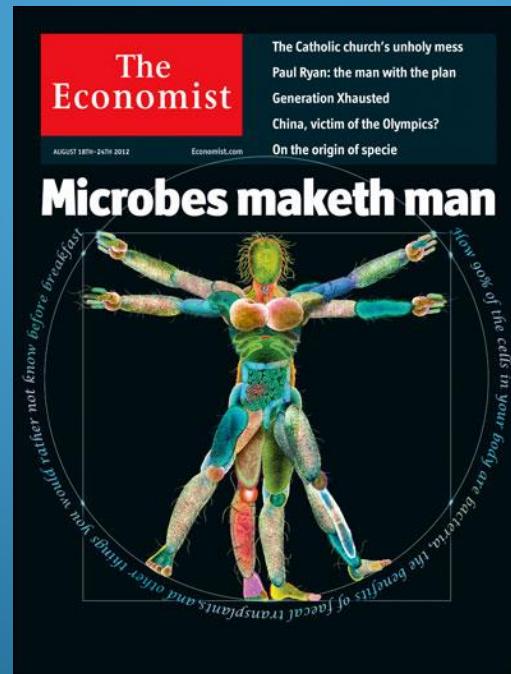
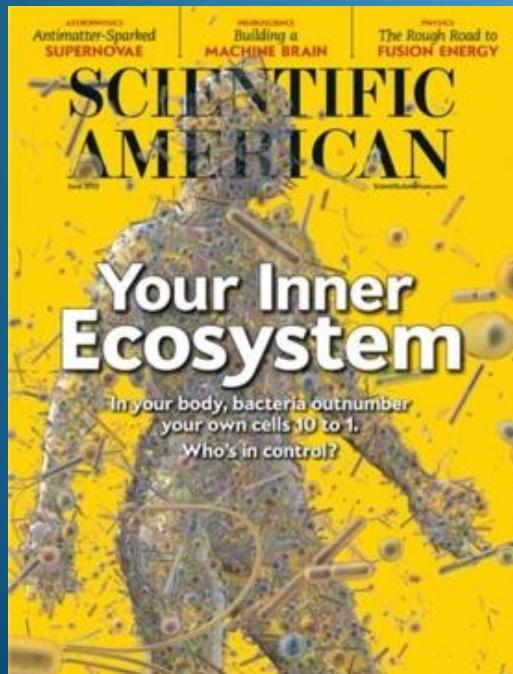
Mitochondrial DNA, Epigenetic marking, and DNA from the microbiota



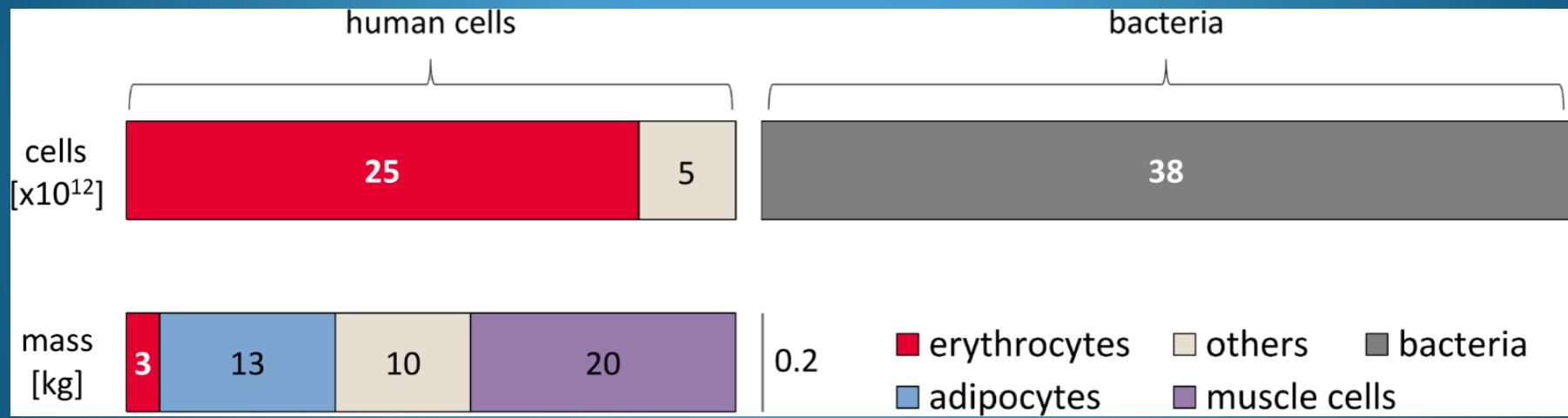
mtDNA: vertical maternal inheritance, asexual; Epigenetic markers: vertical inheritance, transient signal; Microbiome: combination of vertical and horizontal inheritance, enormous genetic diversity.

# Humans and their symbiotic relationships with microorganisms

Each adult has about  $10^{14}$  human cells. The bacterial cells in us, and on us, outnumber our human cells.

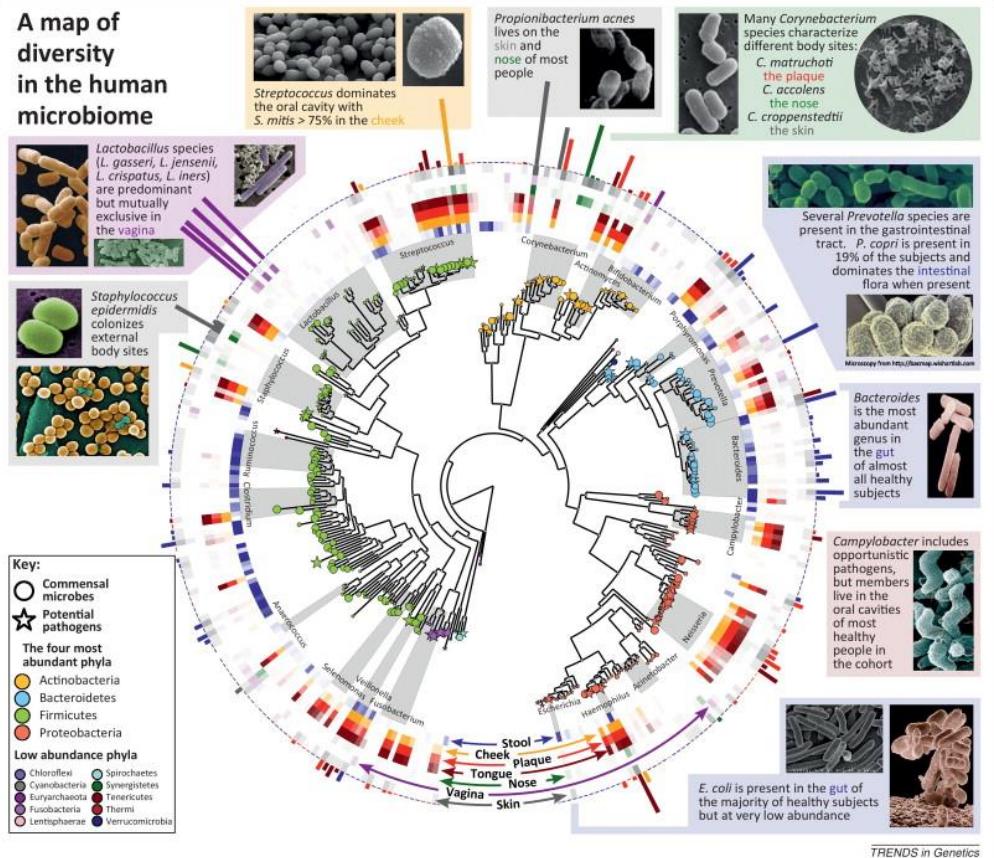
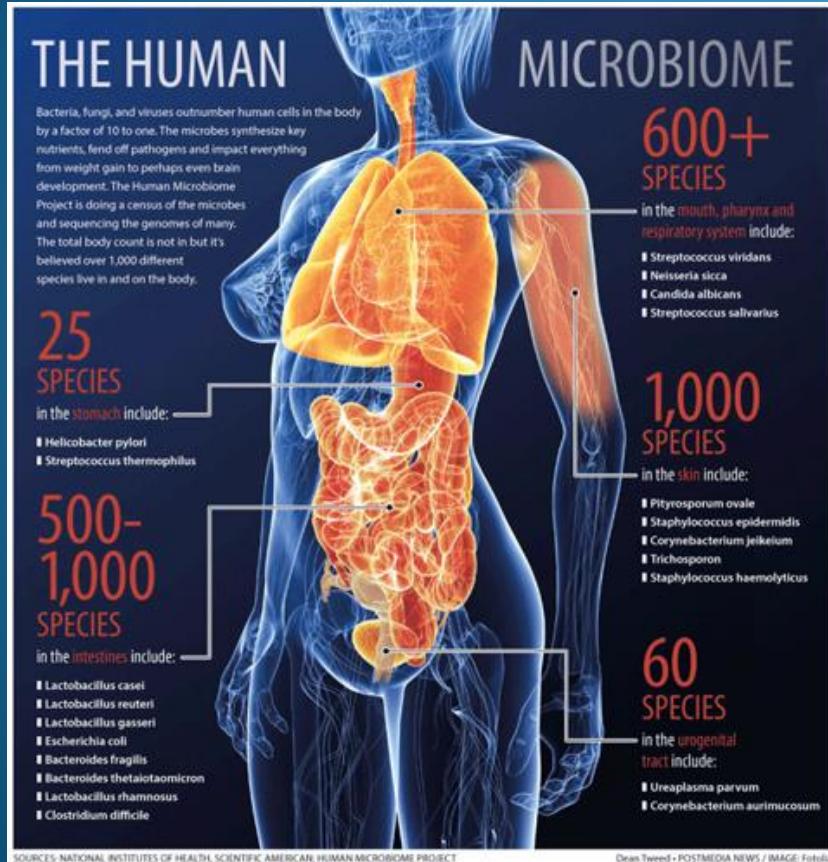


# Bacterial cells outnumber human cells, but their biomass is lower



Distribution of cell number and mass for different cell types in a 70 kg adult. The contribution of bacteria to body mass amounts to about 0.2 kg, which is about 0.3% of body weight.

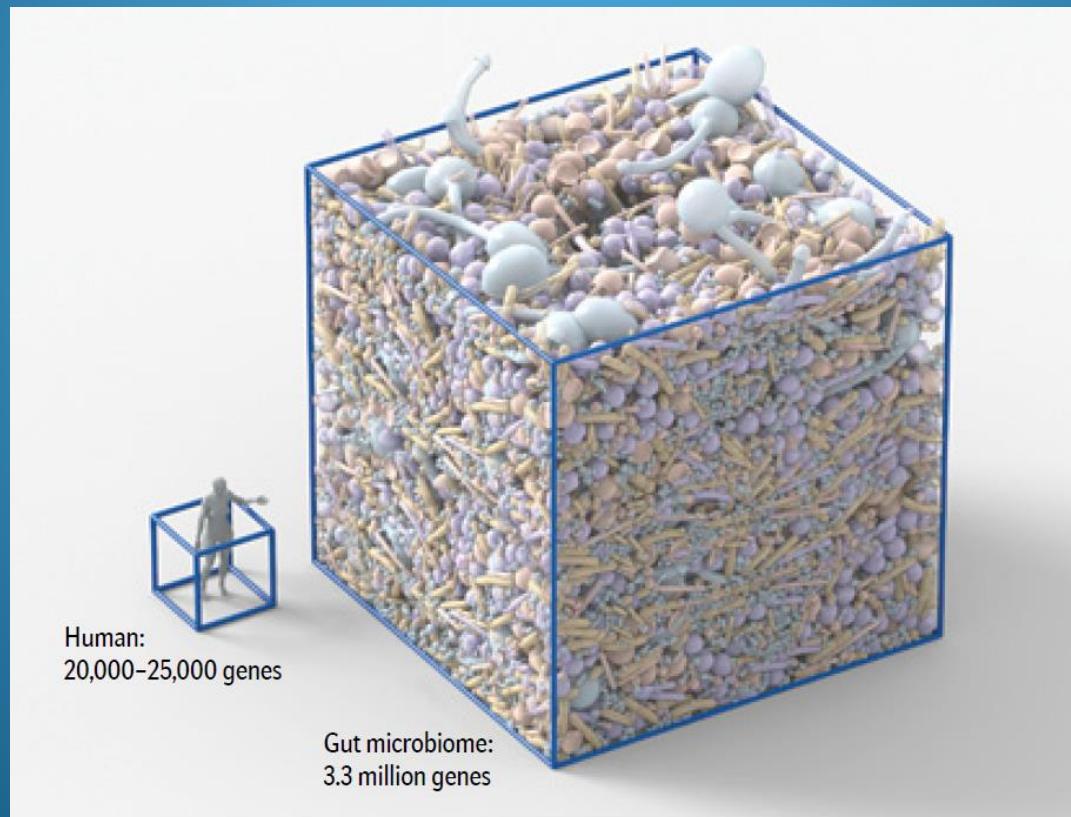
# The Human Microbiota is Diverse



Many thousands of species have been described from the human microbiota

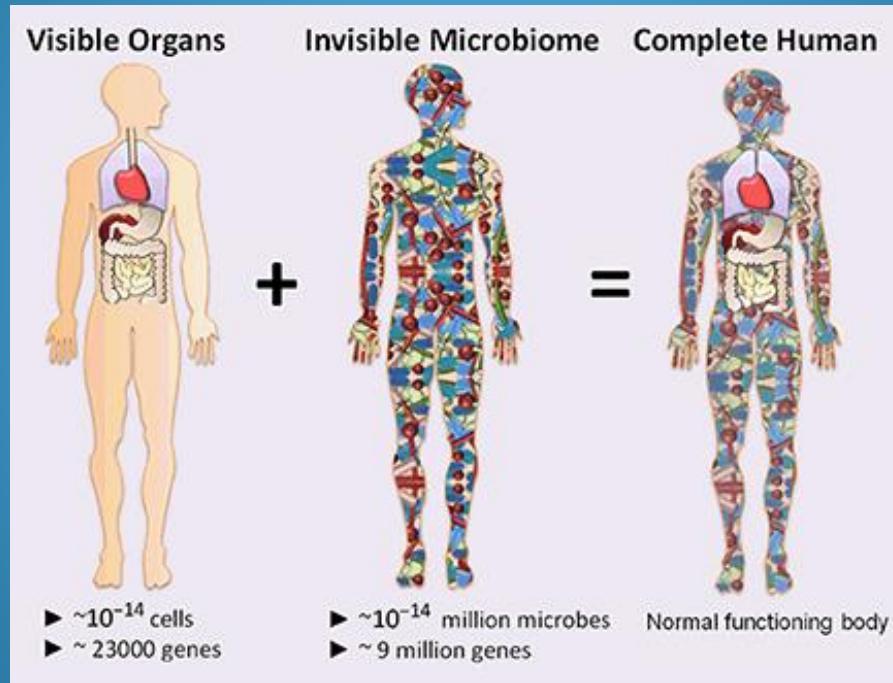
# Genes in the Microbiota

The microbiota encodes enormous functional diversity, and their genes outnumber our human genes 100 to 1. These genes are collectively called the microbiome.



# Human – Bacterial mutualism

The skin, mouth, digestive and urogenital systems all have different, complex microbial communities, dominated by different types of microbes.



These associations are mutualistic, with bacteria gaining nutrients, a stable environment (pH, water, temperature) and transport. Benefits to the human host include nutrition, immune function, development and exclusion of pathogens.

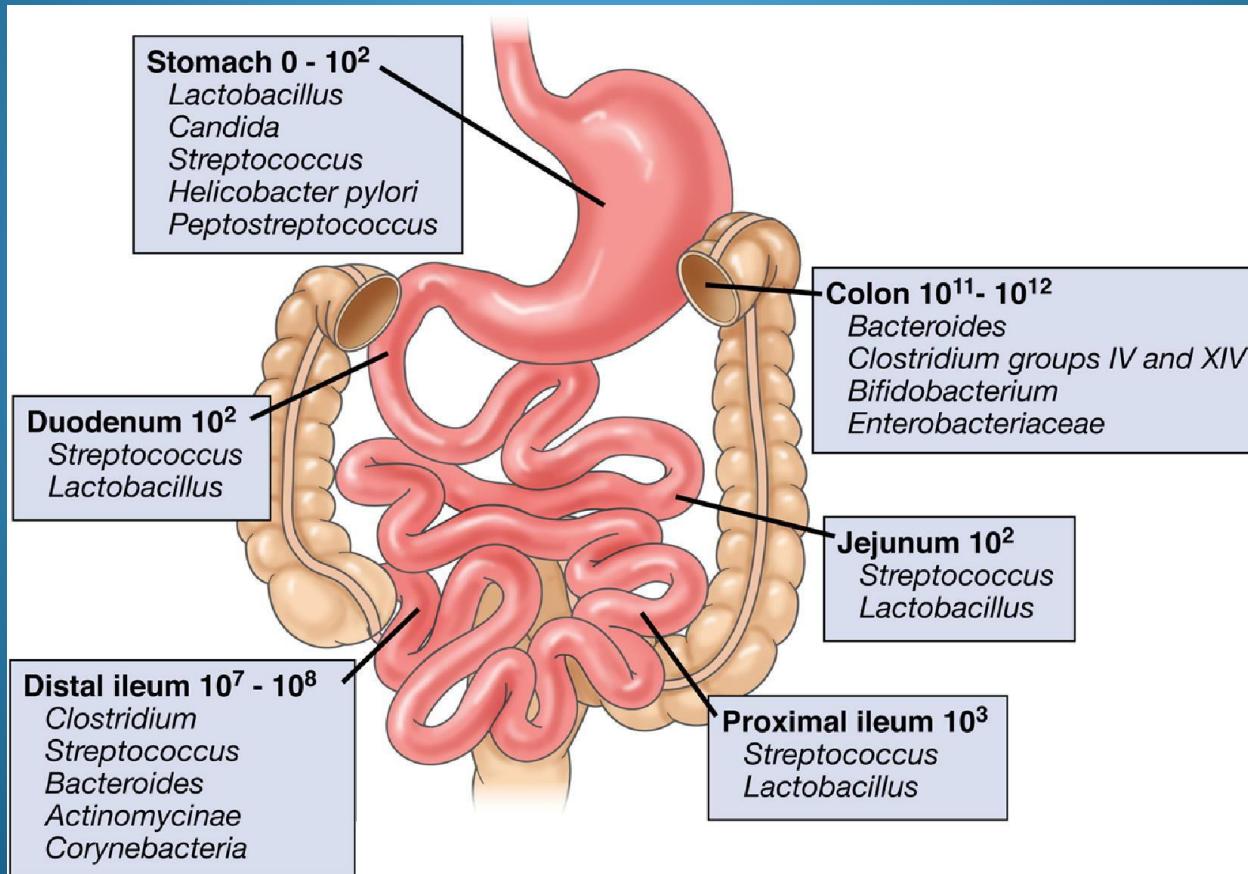
# The large intestine has the greatest numbers of bacteria



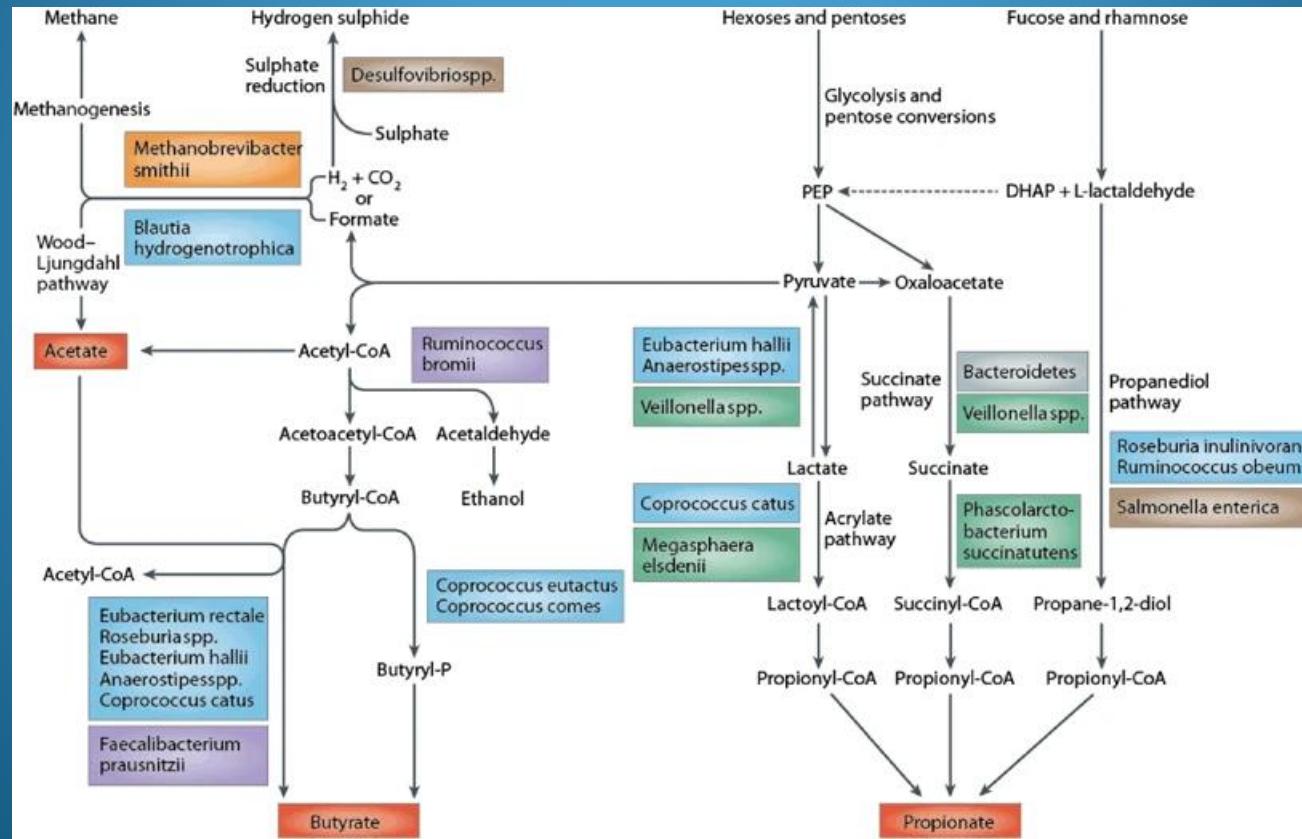
Location	Typical concentration of bacteria <sup>(1)</sup> (number/mL content)	Volume (mL)	Order of magnitude bound for bacteria number
Colon (large intestine)	$10^{11}$	400 <sup>(2)</sup>	$10^{14}$
Dental plaque	$10^{11}$	<10	$10^{12}$
Ileum (lower small intestine)	$10^8$	400 <sup>(5)</sup>	$10^{11}$
Saliva	$10^9$	<100	$10^{11}$
Skin	< $10^{11}$ per m <sup>2</sup> <sup>(3)</sup>	1.8 m <sup>2</sup> <sup>(4)</sup>	$10^{11}$
Stomach	$10^3$ – $10^4$	250 <sup>(5)</sup> –900 <sup>(6)</sup>	$10^7$
Duodenum and Jejunum (upper small intestine)	$10^3$ – $10^4$	400 <sup>(5)</sup>	$10^7$

# Specialization in the digestive system

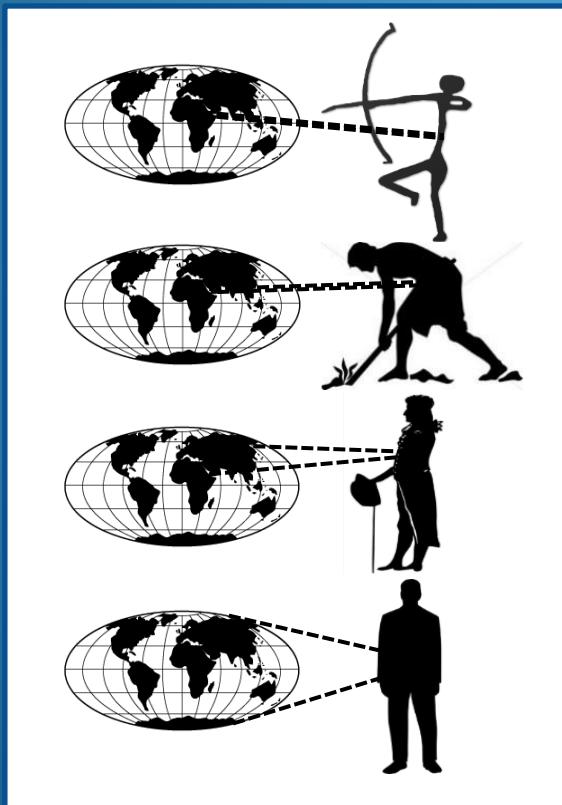
The dominant species change in various regions of the gastrointestinal tract.



# These bacteria integrate with human metabolism



# Evolution of the Human Microbiota



Because the microbiota are so well integrated with human anatomy, physiology and biochemistry, the microbiota has clearly co-evolved with humans.

Can we reconstruct this evolution?

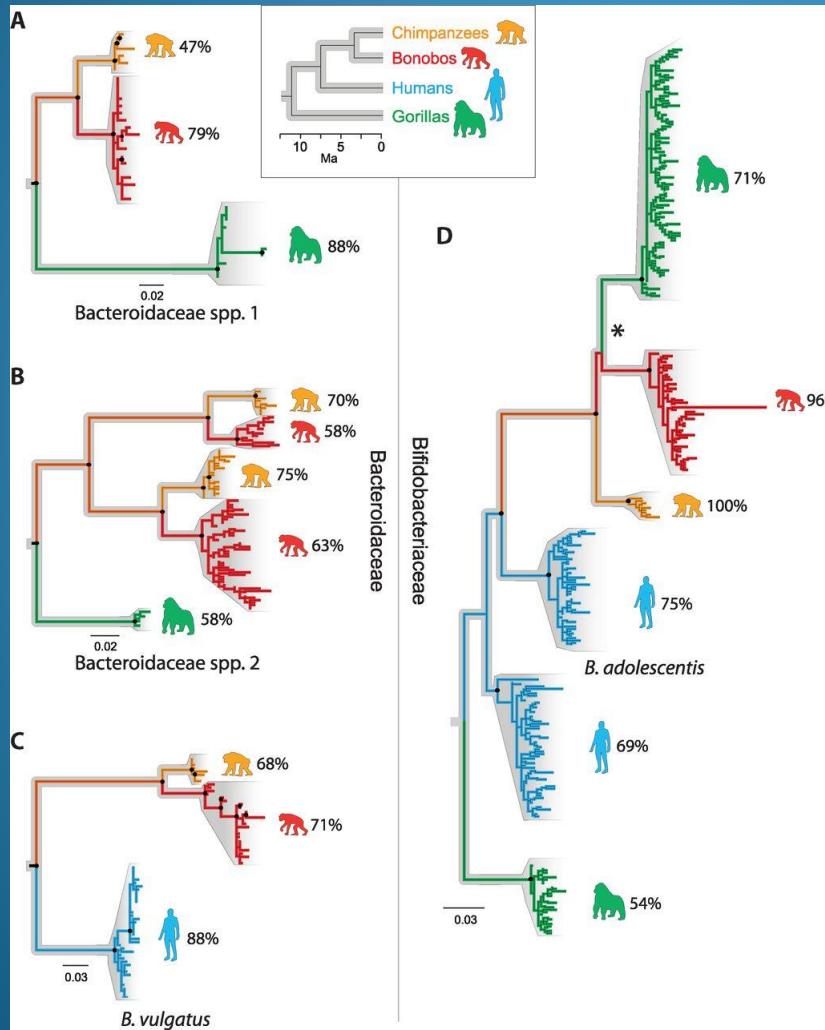
# What was the ‘ancestral’ microbiota like?

There are three ways to address this question:

- Compare humans with other great apes
- Examine fossil microbiota
- Examine microbiota of hunter-gatherers

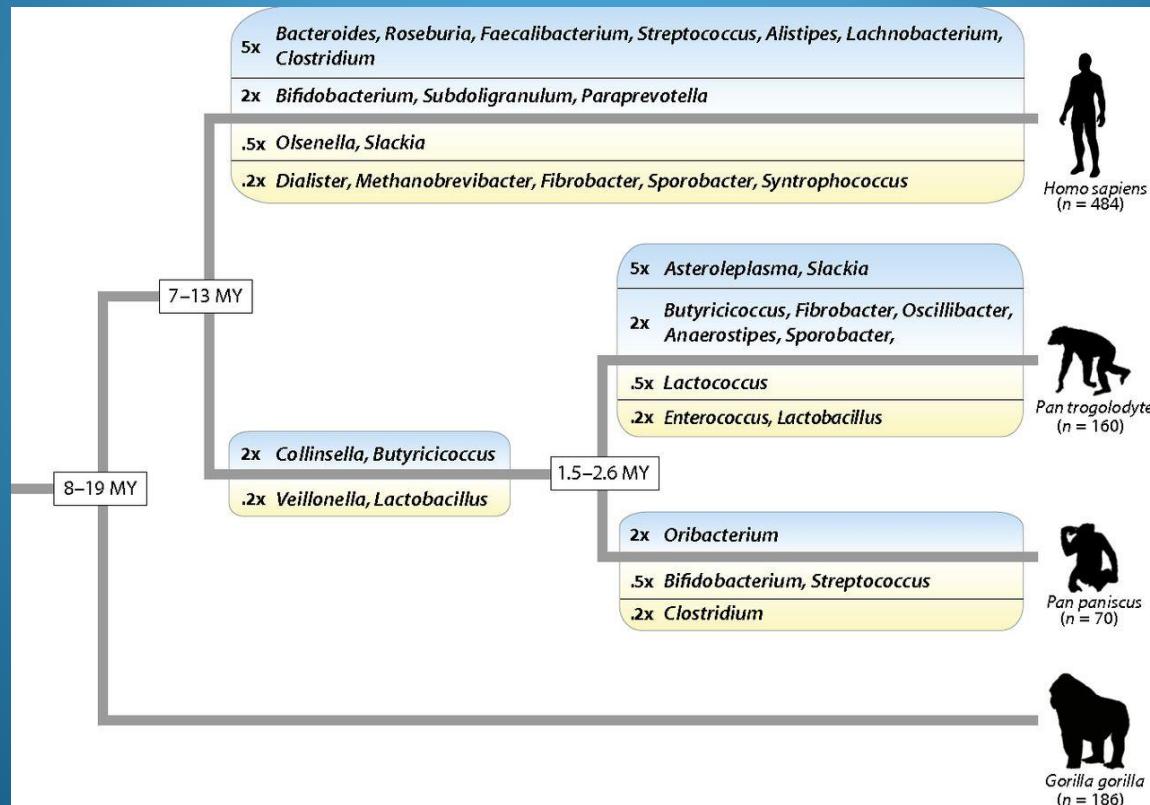


# Bacteria co-speciate with humans

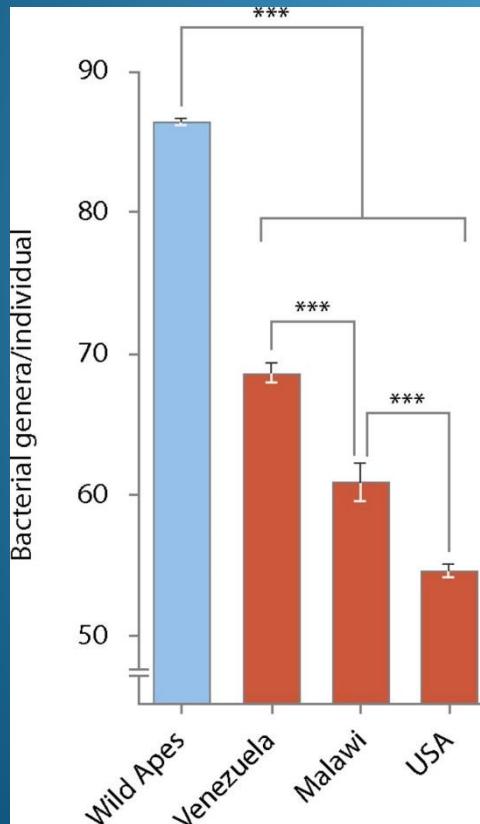


# Microbiota in the great apes

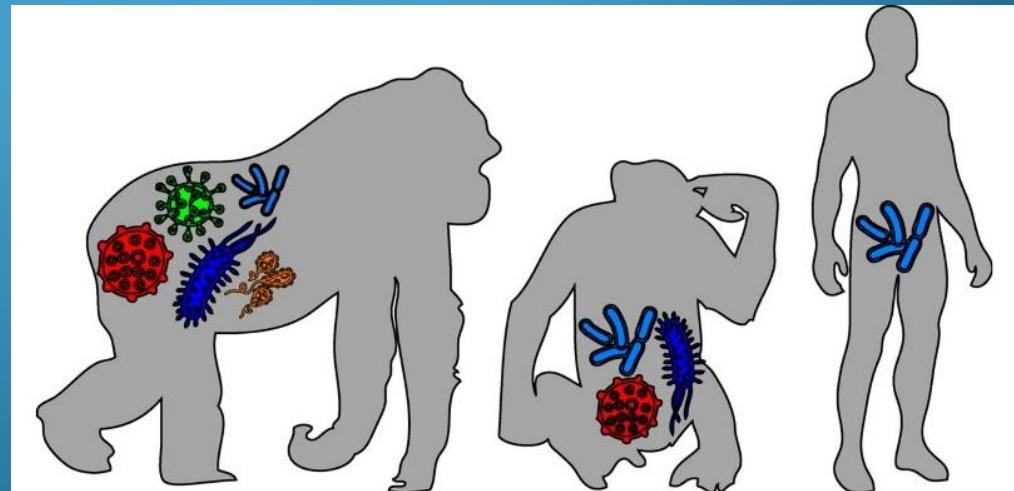
Changes to the composition of gut microbiota in the great apes are clock-like, and consistent with the dates of their evolutionary divergence. However, the human microbiota has evolved more quickly.



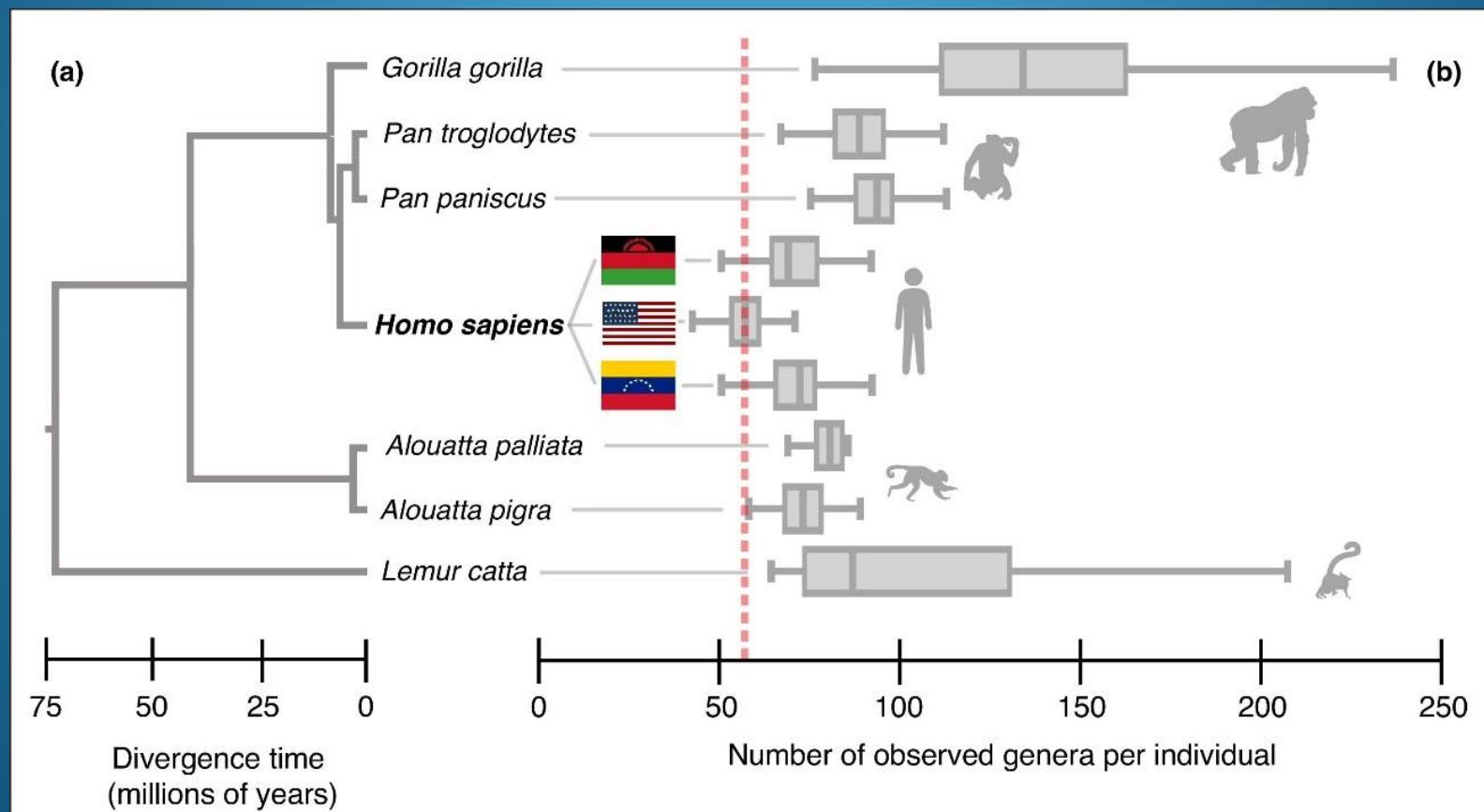
# Human microbiota has lost ancestral diversity



Humans carry significantly fewer bacterial genera than gorillas, chimps and bonobos



# Humans in urban societies have the least diversity

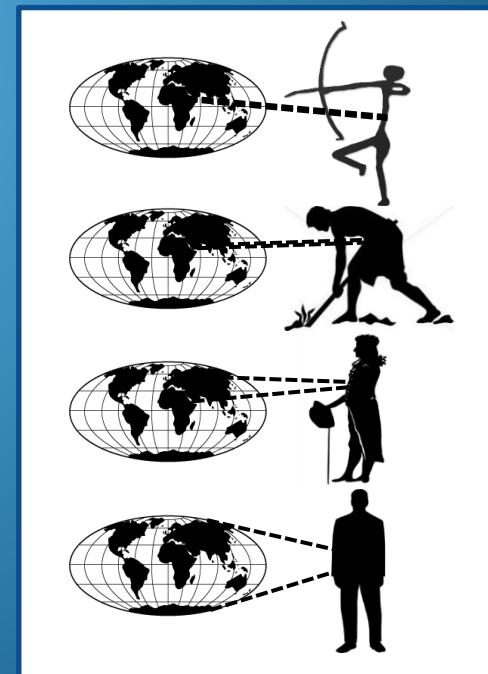


# What causes loss of diversity in the microbiota?

There appear to be multiple stages (and multiple causes) for the loss of diversity from the human microbiota.

These stages occurred during:

- the Palaeolithic (2.6 mya – 10,000 BC)
- the Holocene (10,000 BC +)
- the Industrial Revolution (1760 +)
- the Anthropocene (1950 +)



# The Palaeolithic

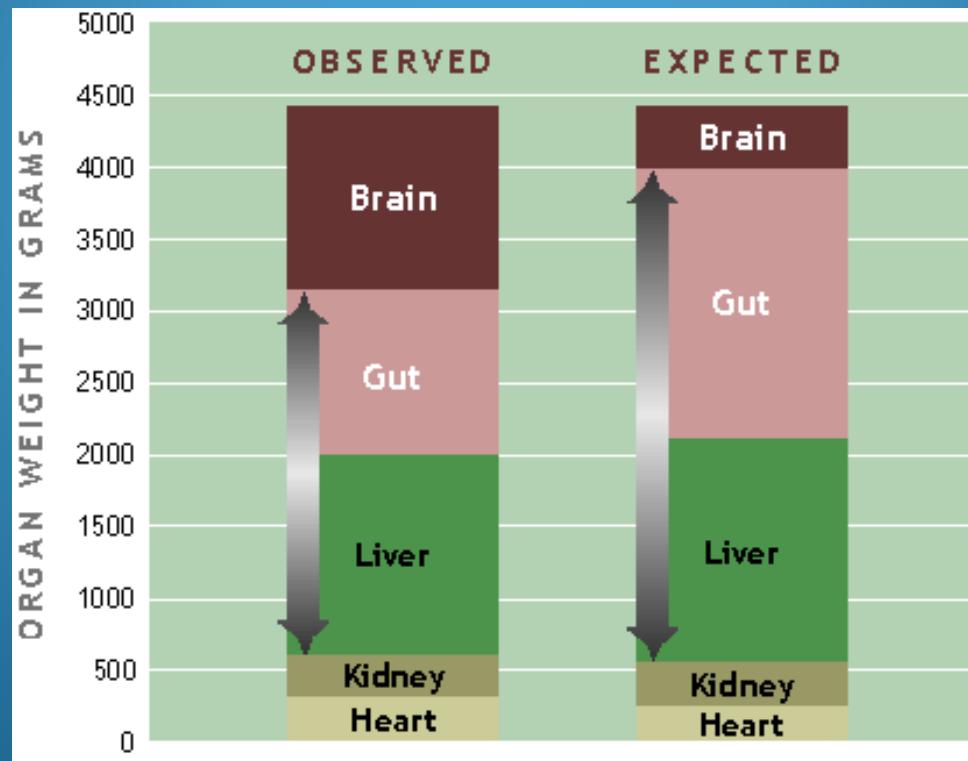
A shift in diet away from plant-based food, towards animal fat and protein, led to a reorganized gut morphology. This reduced the volume of the gut and altered its resident microbiota.



Ferraro *et al.* 2013. Earliest archaeological evidence of persistent hominin carnivory. *PLoS One*, 8(4); Milton 1987. Primate diets and gut morphology: implications for hominid evolution. *Food and evolution: toward a theory of human food habits*, 93-115.

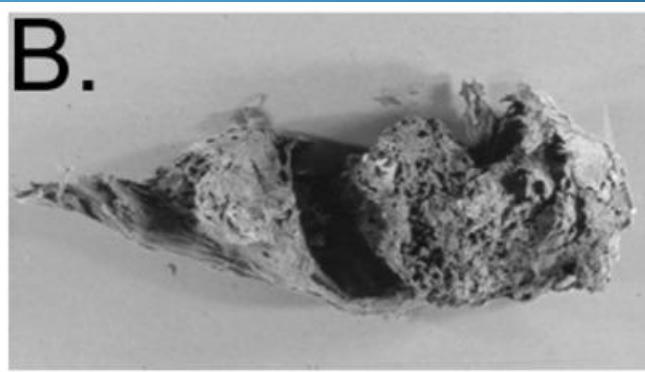
# The use of fire

From 350,000 years ago, the habitual use of fire increased the calories we could obtain from food, lowering the need for a big gut volume, and decreasing the space for microbiota.



# Reconstructing ancient microbiota

Ancient DNA analysis can help reconstruct the ancestral microbiota



Pre-Columbian  
Andean mummy  
with paleofeces

Santiago-Rodriguez *et al.* 2015. Gut microbiome of an 11th century AD pre-Columbian Andean mummy. *PLoS one*, 10(9);  
Tito *et al.* 2012. Insights from characterizing extinct human gut microbiomes. *PLoS one*, 7(12).

# Reconstructing ancient microbiota

Fossils can be used as a source of information about the ancient microbiota. These studies do have to be treated with caution, because of the potential for differences in preservation and modern contamination.



DNA can be obtained from fossil teeth, such as these Neanderthals from Spy-1 and El Sidron caves. Dental calculus preserves evidence of diet and of oral microbiota (note: Neanderthals are not the same species as modern humans).

# Coprolites can tell us about the ancient gut microbiota

Microbial DNA recovered from coprolites has similarities with gut microbiota from modern rural populations, rather than urban populations.



The Lloyds Bank coprolite: A human coprolite from a Viking site at Coppergate, York, England.

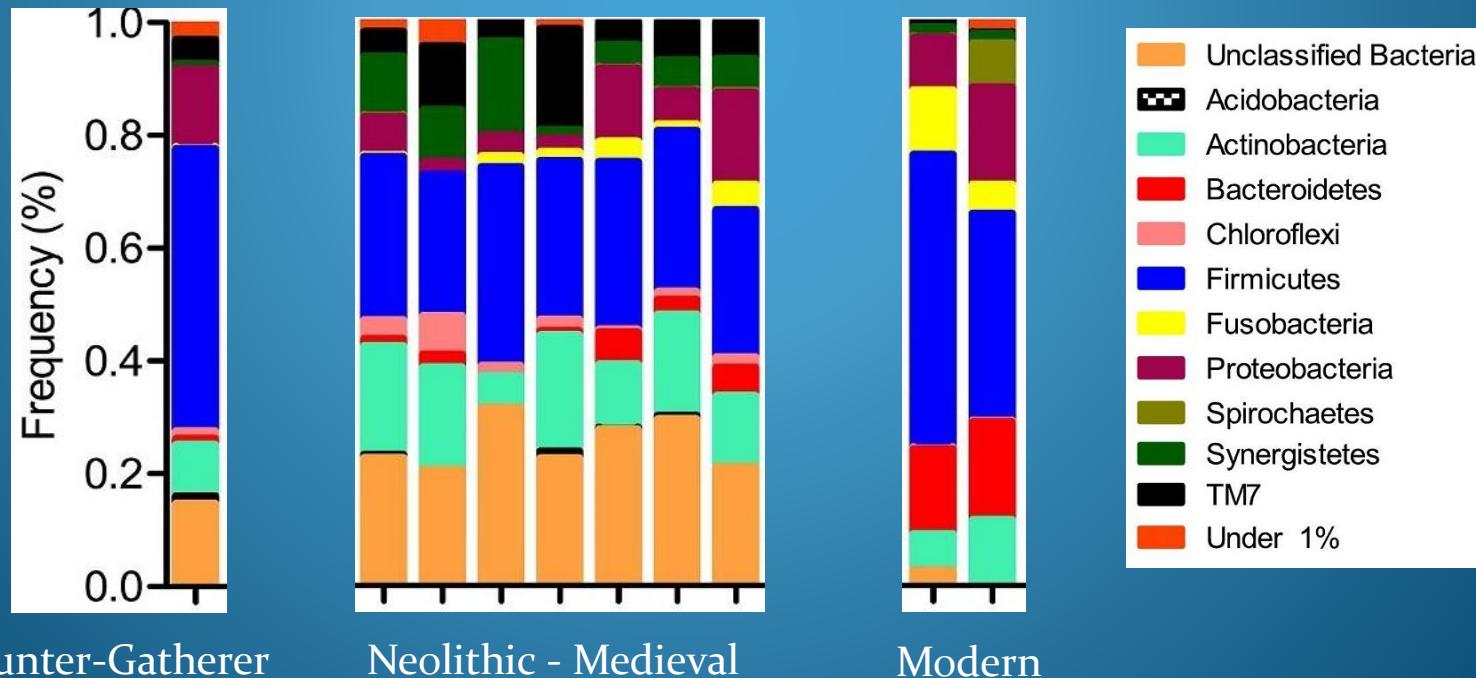
Cano *et al.* 2014. Paleomicrobiology: revealing fecal microbiomes of ancient indigenous cultures. *PLoS one*, 9(9); Tito *et al.* 2012. Insights from characterizing extinct human gut microbiomes. *PLoS one*, 7(12).



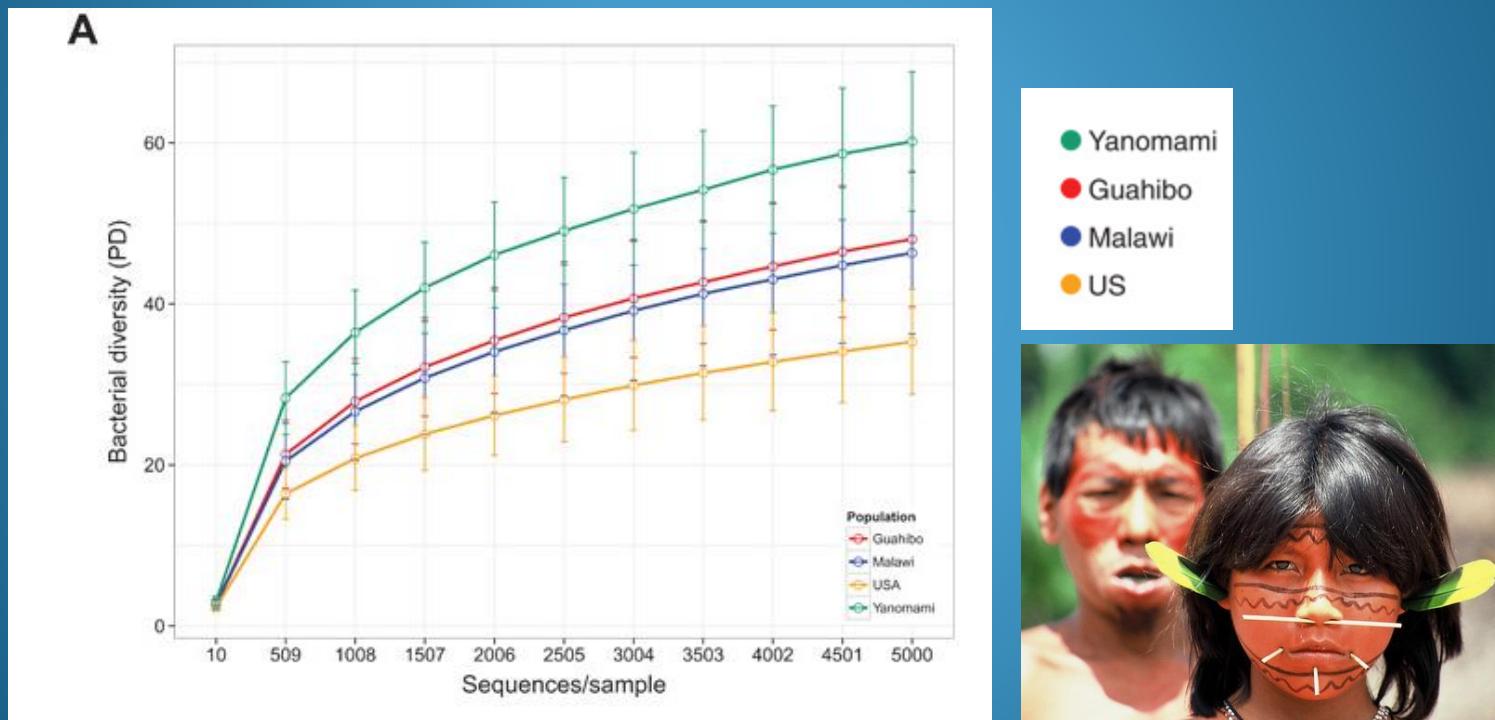
# Agriculture



The human oral microbiota changed significantly from hunter-gatherer to agricultural communities, and then to modern times, corresponding with changes in diet. Modern oral microbiota have many more pathogenic species.

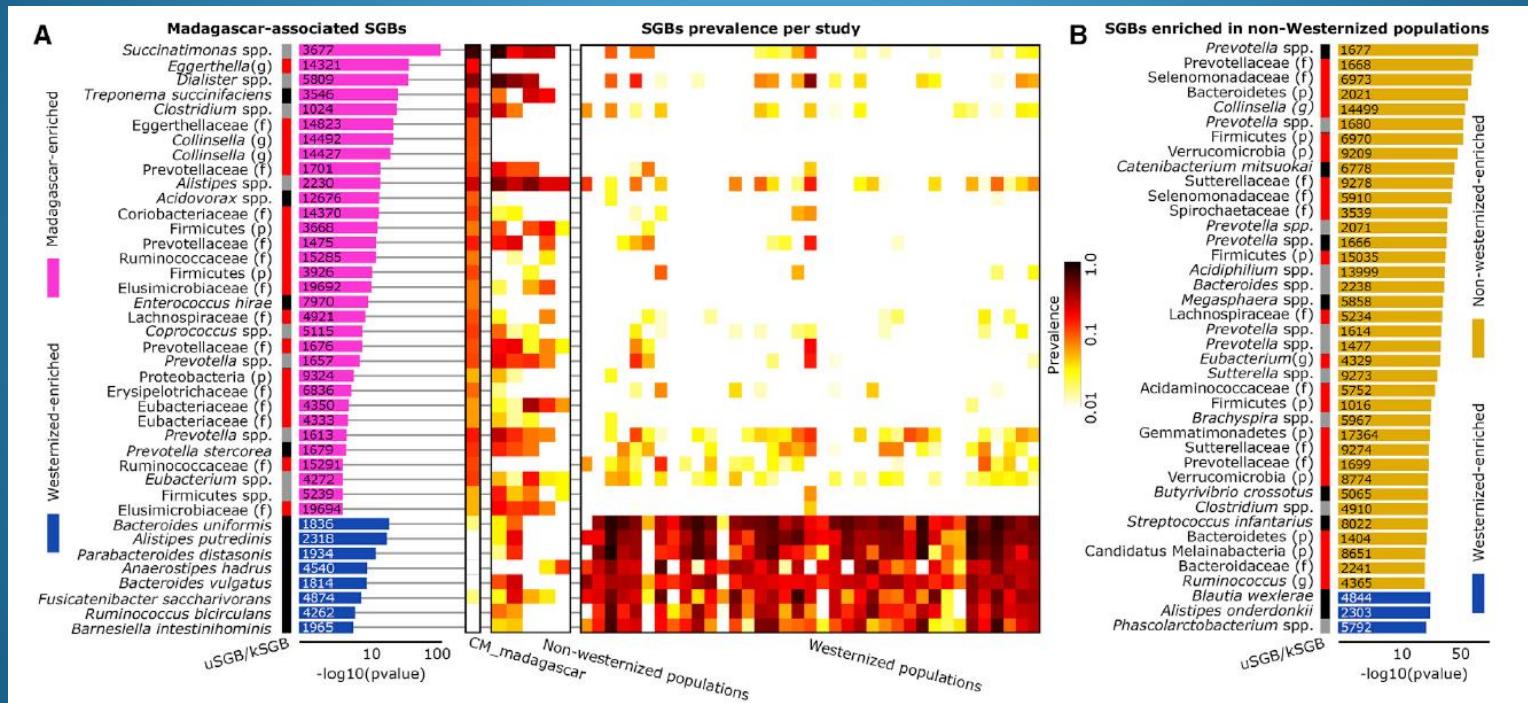


# Examining hunter-gatherer microbiota



Yanomami (hunter-gatherers) have the highest diversity of microbiota (microbial species) and microbiome (microbial genes) ever documented; higher than subsistence farmers and urban populations.

# Significant numbers of microbial taxa are still being discovered



Testing of over 9,000 individuals detected almost 5,000 different bacterial species, 75% of which had never been described before. These new species were mainly found in non-Westernized populations, suggesting modern life causes extinctions.

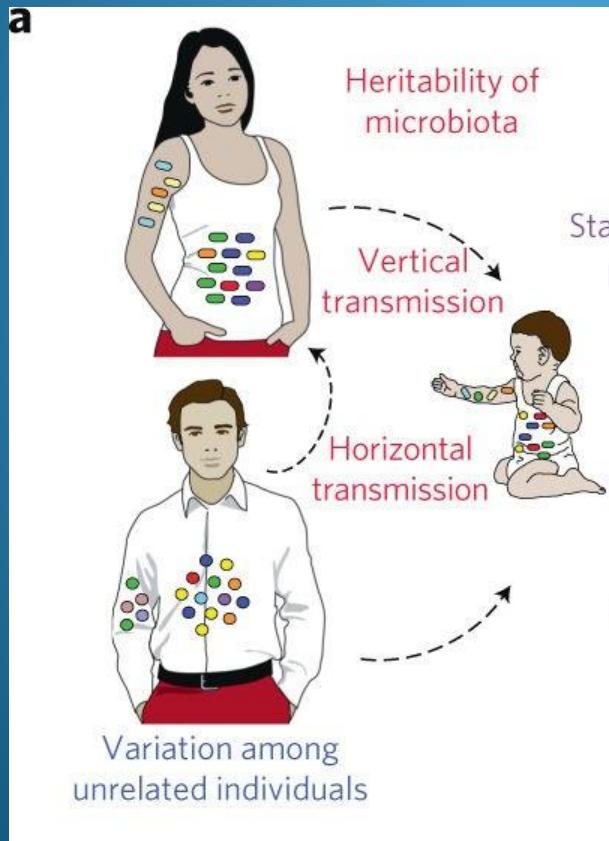
# Significant numbers of taxa are missing in urbanized populations



The gut microbiota of New Guinea highlanders contains many species that are never found in urbanized populations.

# So how do we get our microbiota?

We acquire microbiota from our mothers, our families, and from our environment.



Transmission and colonization are dynamic and ongoing processes.

Acquisition can be vertical or horizontal, and is subject to change due to environment, diet and age.

# Unborn babies are sterile

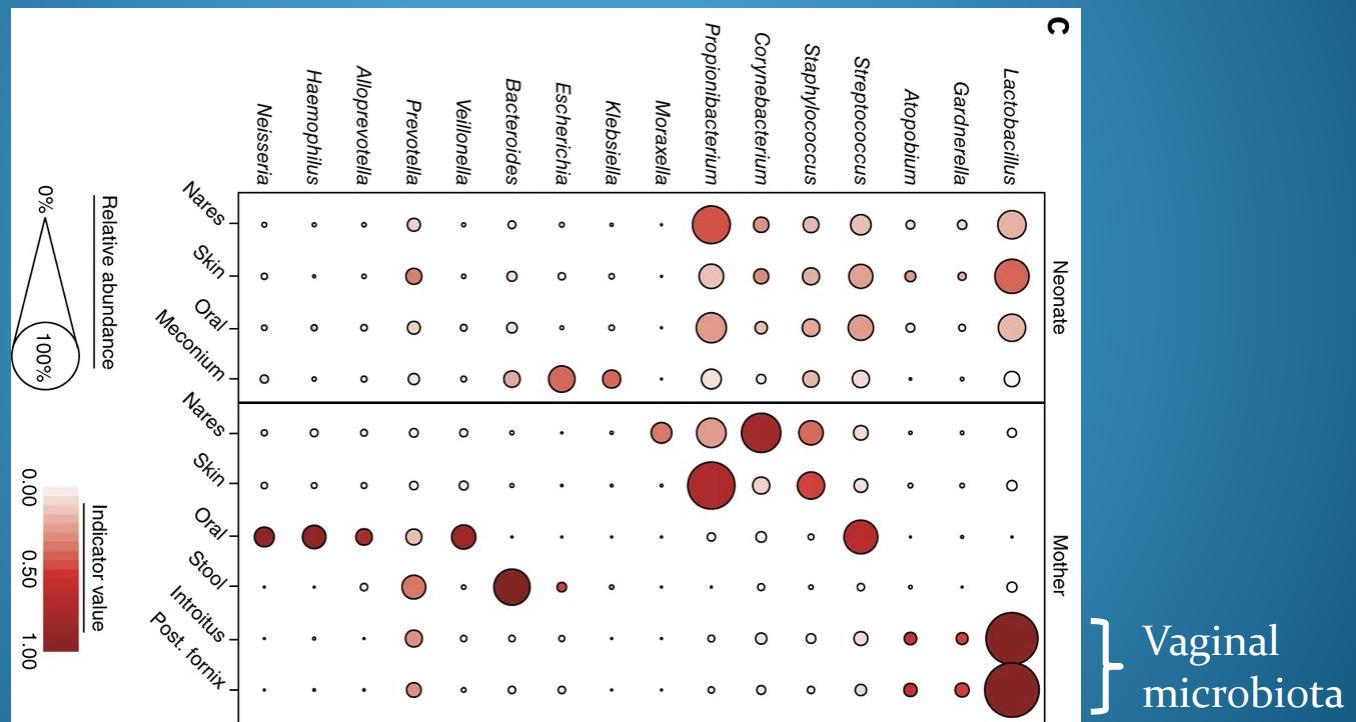
Despite some papers that suggest elements of the microbiota could be present in amniotic fluid and the placenta, these claims have now been largely dismissed.



Willyard 2018. Could baby's first bacteria take root before birth?. *Nature*, 553: 264-266.

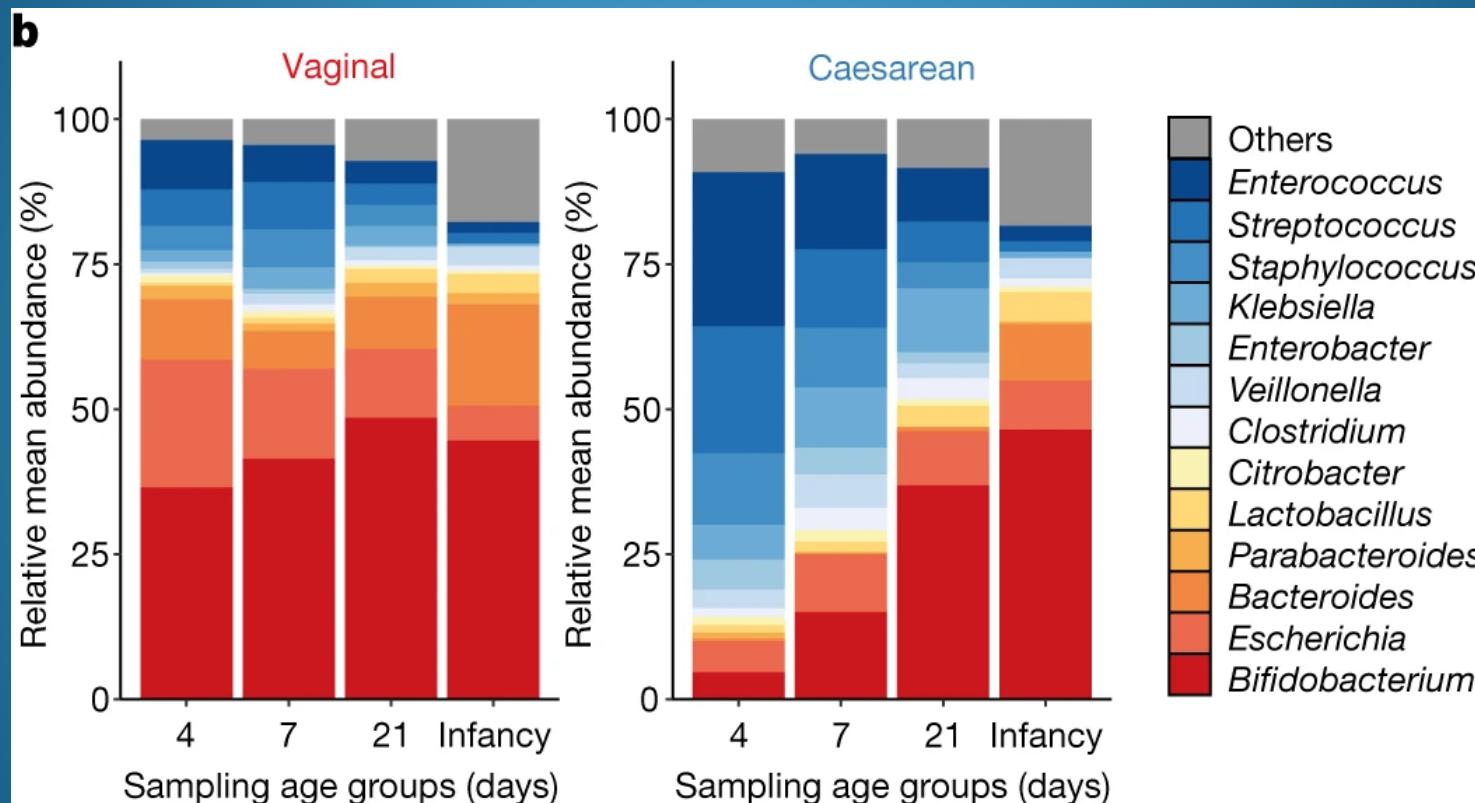
de Goffau *et al.* 2019. Human placenta has no microbiome but can contain potential pathogens. *Nature*, 572: 329-334.

# Newborns acquire maternal microbiota



The microbiota of neonates largely reflects the vaginal and skin microbiota of the mother

# Caesareans alter early colonization



Birth by C-section alters early microbiota. By 4-12 months old, these differences largely disappear, but developmental and physiological changes may have already occurred

# Recolonising Caesarean babies

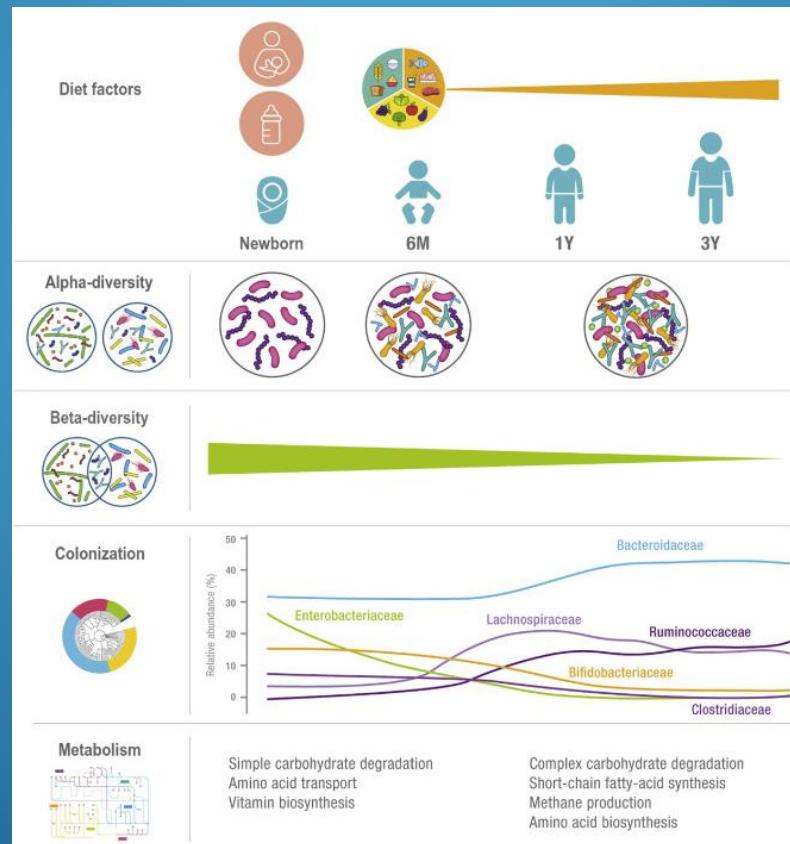
Because of the concerns around microbiota changes in caesarean babies, vaginal swabs have been used to inoculate newborns and restore their ‘natural’ microbiota



Dominguez-Bello et al. 2016 Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer.  
*Nature Medicine* 22: 250-253

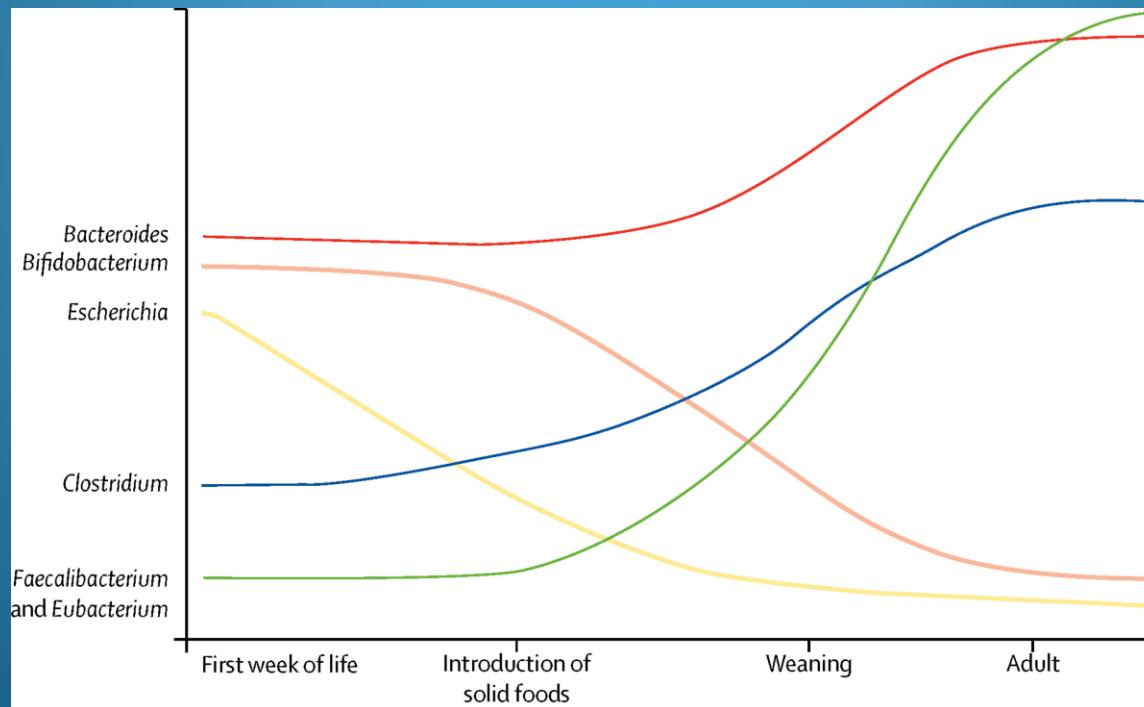
# The infant microbiota is dynamic...

As children grow, their gut microbiota changes with changing diet, becoming more diverse, but more similar between individuals.



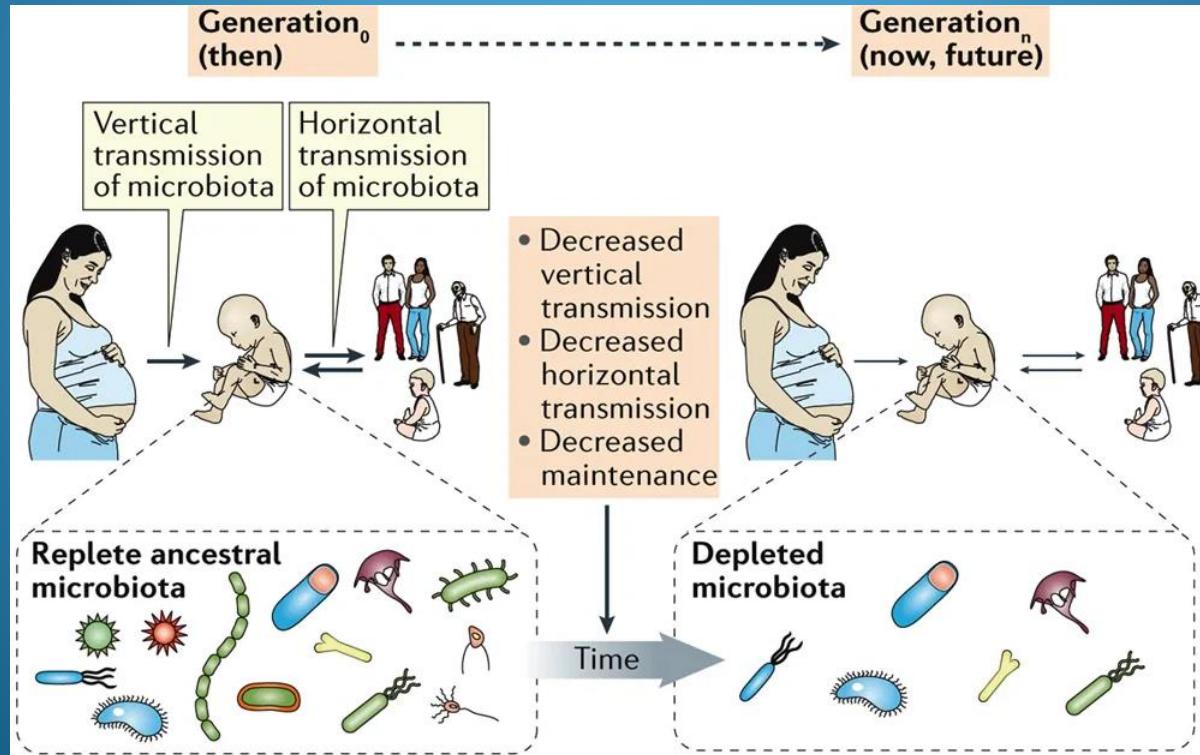
# ....eventually stabilizing in adults

The infant gut is dominated by *Bifidobacterium* and *Escherichia*. In adults, these are replaced by *Bacteroides*, *Clostridium*, *Eubacterium* and *Faecalibacterium*. There are crucial windows for colonization that could influence immune, metabolic and nervous systems.



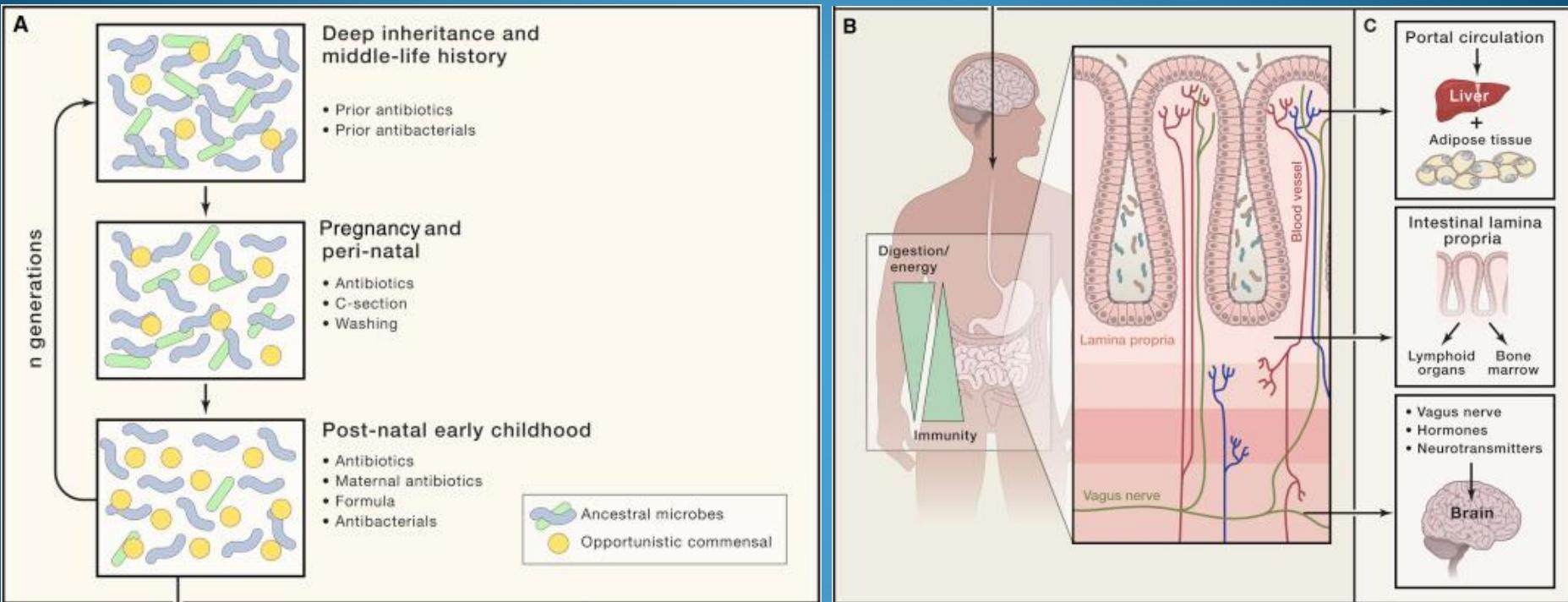
# Are elements of the human gut microbiota becoming extinct?

Evidence suggests a significant loss of diversity in the microbiota of urbanized populations



Blaser 2017. The theory of disappearing microbiota and the epidemics of chronic diseases. *Nature Reviews Immunology*, 17: 461.  
Gillings and Paulsen 2014. Microbiology of the Anthropocene. *Anthropocene*, 5: 1-8.

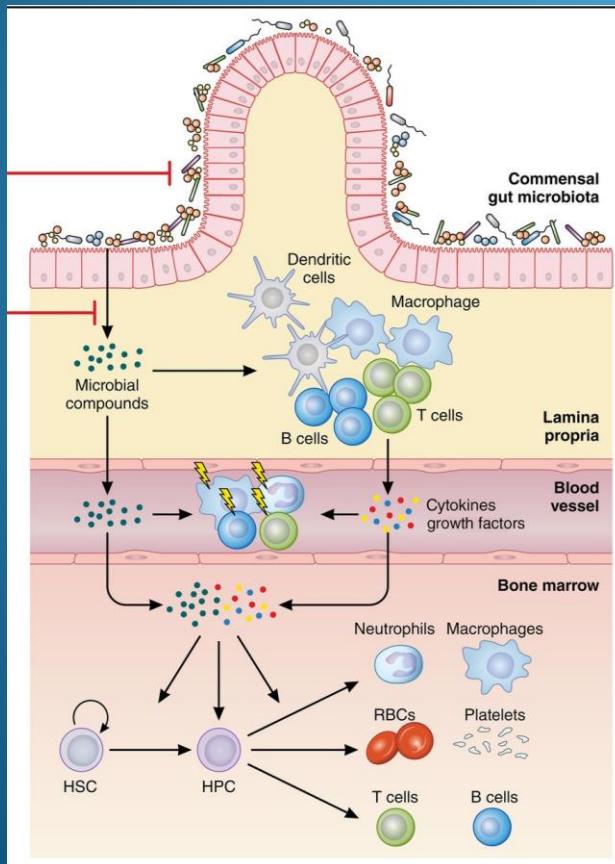
# Avoiding the extinction vortex



Generation by generation loss of microbial diversity leads to depauperate microbiomes, with serious consequences for health and well-being

# What do the microbiota do?

Microbiota have a role in the development and education of the immune system



Gut microbiota have a role in the production of blood cells. Compounds from the commensal gut microbiota stimulate production of lymphocytes, macrophages, and dendritic cells, and also maintain activity of stem cells, lymphocytes, monocytes, and neutrophils.

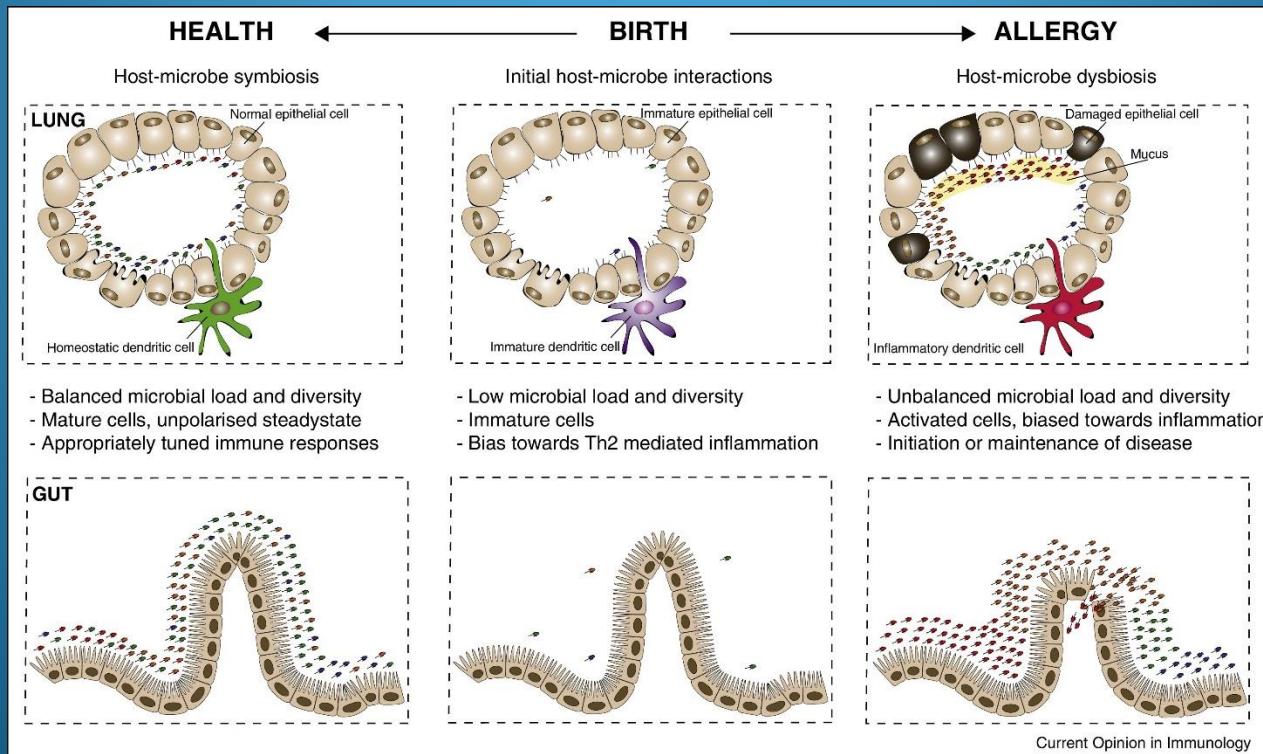
Microbial compounds consequently promote activity of the innate and adaptive immune system against bacterial and viral infections.

HSC = hematopoietic stem cells

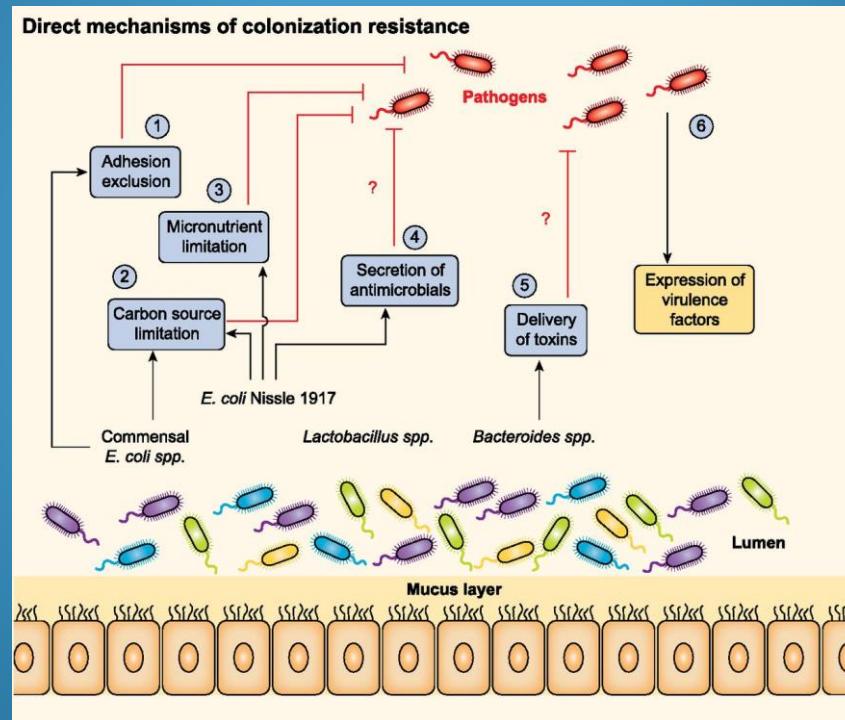
HPC = hematopoietic progenitor cells

# Changes in colonization can change immune responses

Changes to microbial populations in the respiratory system or the gut can lead to chronic and inappropriate inflammatory responses, such as asthma and allergy.

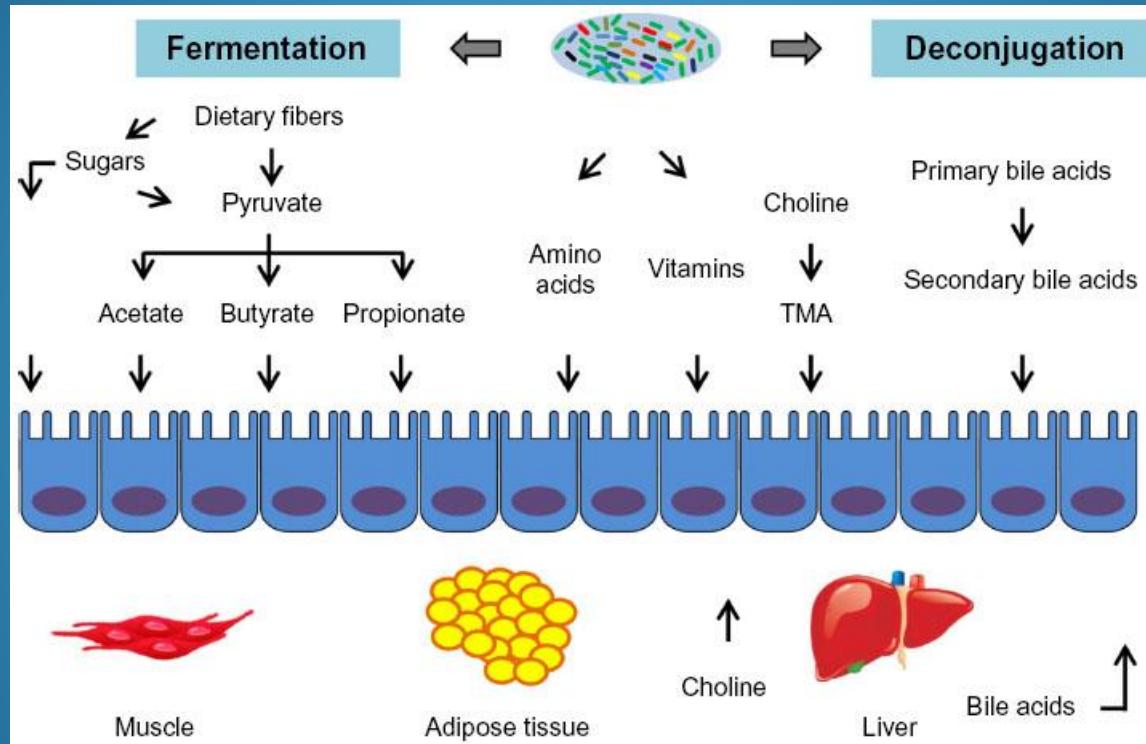


# The microbiota actively exclude colonization by pathogens



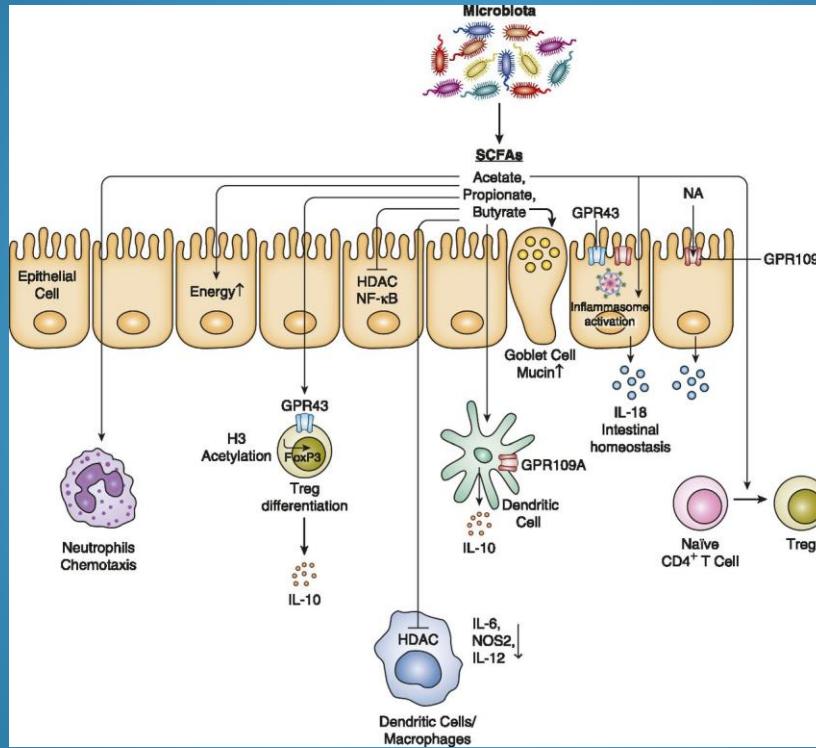
Commensal bacteria actively exclude pathogens by occupying niches, rapidly using up nutrients, and by secreting antimicrobials and toxins

# Microbiota contribute metabolites....



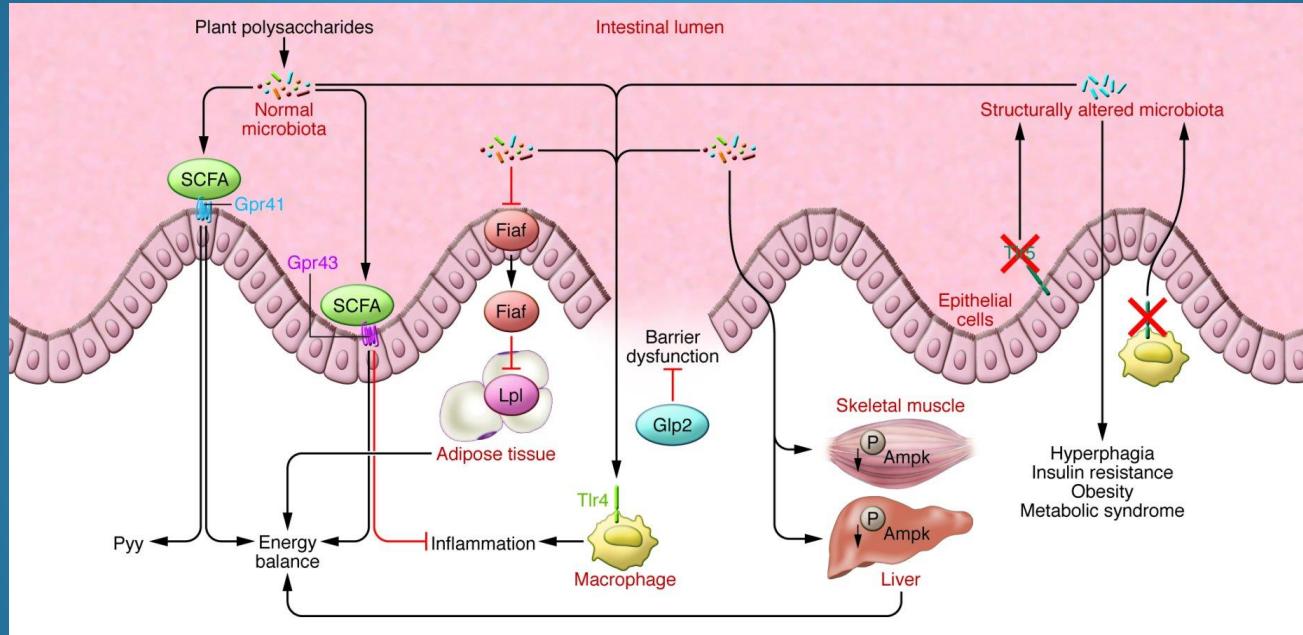
Gut microbiota contribute to metabolism via anaerobic fermentation, vitamin biosynthesis, and bile acid metabolism. Polysaccharides are converted by gut microbiota into short-chain fatty acids: acetate, propionate, and butyrate. Microbes synthesize amino acids and vitamins B and K. Bile acids can be deconjugated by gut microbiota.

# ...which can shape immune responses....



Microbiota-associated metabolites shape mucosal immunity. Short chain fatty acids (SCFA) affect multiple facets of the immune response (macrophage and dendritic cell function, cytokine secretion, differentiation of regulatory T-cells, secretion of mucin from goblet cells, and neutrophil chemotaxis).

# ....and help regulate metabolism



Gut microbiota produce short chain fatty acids (SCFA) that bind to G-protein receptors (Gpr), thus influencing energy balance via peptide YY (Pyy). Microbial signals regulate the release of Fasting-induced adipose factor (Fiaf), influencing peripheral fat storage. The microbiota help regulate appetite, weight gain and insulin sensitivity, and also affect energy usage in the liver and muscle tissue, via poorly characterized mechanisms.

# What aspects of modern life might affect our microbiota?



Caesarean birth



Bottle feeding



Antimicrobials

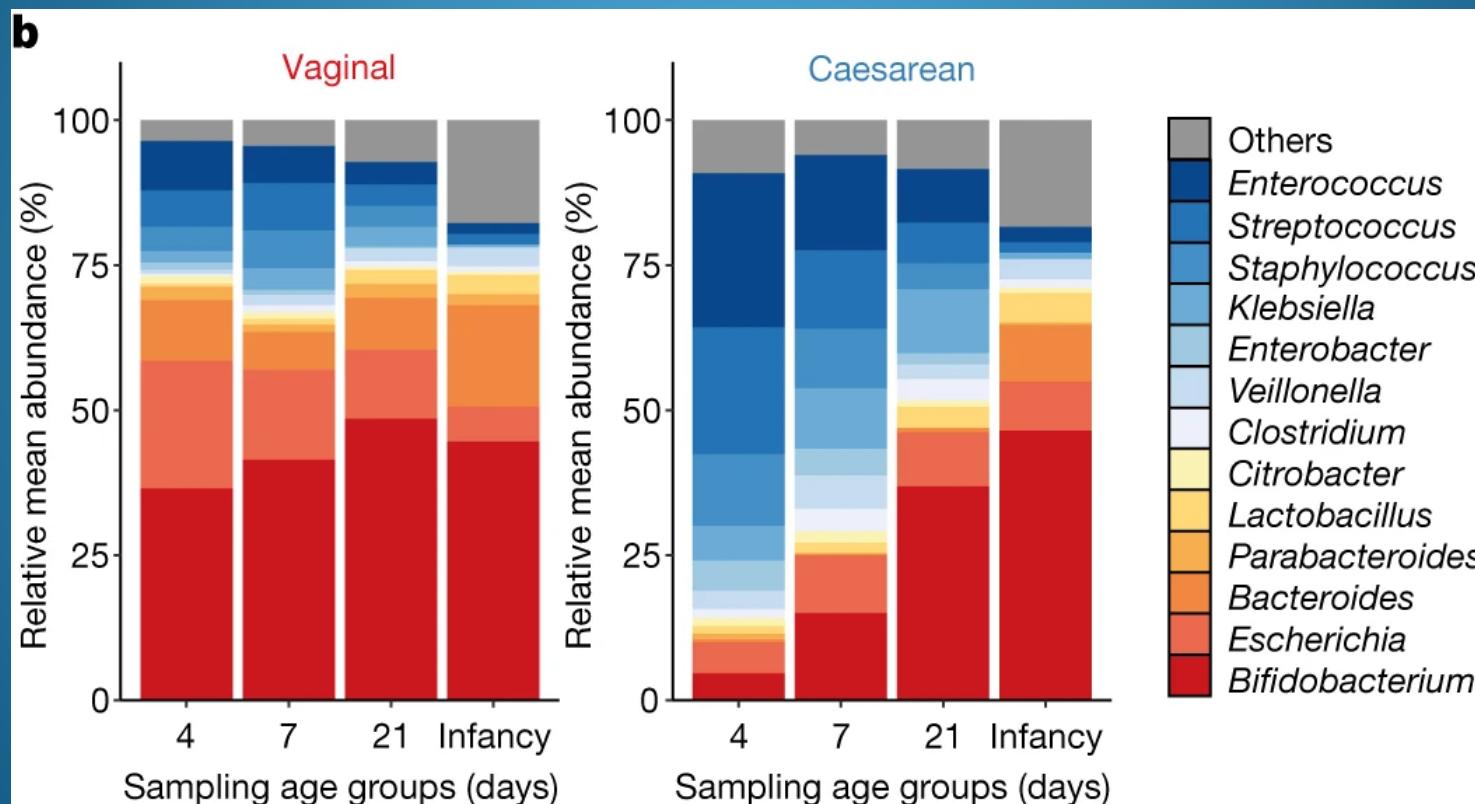
Diet



Host genetics

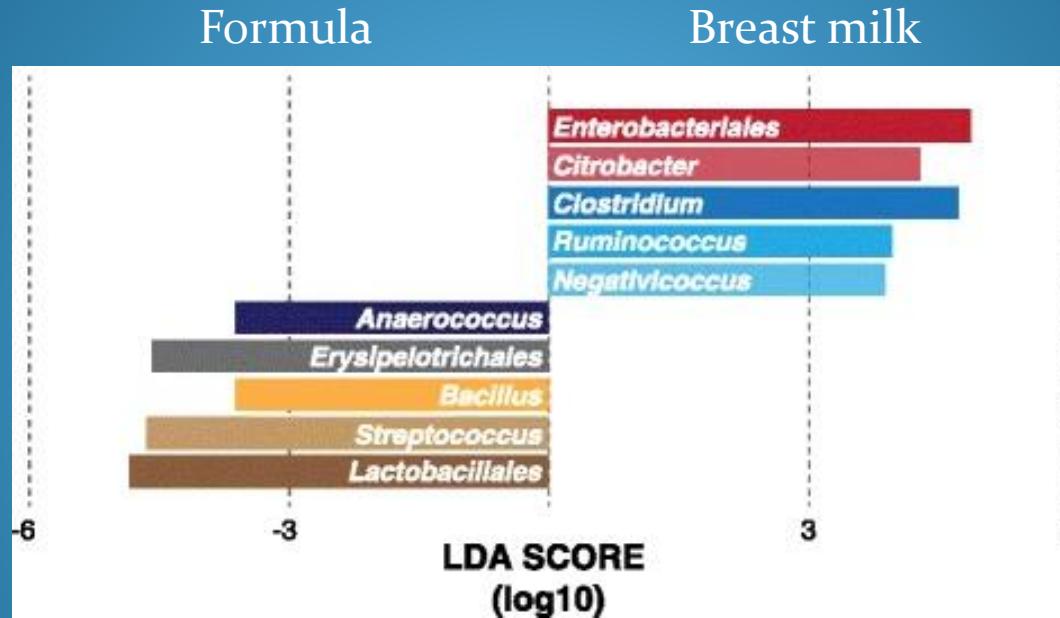
Dominguez-Bello et al. 2016 *Nature Medicine* **22**: 250-253; Gillings et al. 2015 *Genes*, **6**: 841-857;  
Ardeshir et al. 2014 *Science Translational Medicine* **6**: 252ra120; Dethlefsen & Relman 2011 *PNAS*, **108**: 4554-4561

# Caesarean delivery alters early colonization



Birth by C-section alters early microbiota. By 4-12 months old, these differences largely disappear, but developmental and physiological changes may have already occurred

# Formula feeding in humans.....



Preterm infants fed breast milk had higher initial diversity of microbiota, and accumulated additional diversity in a predictable succession. This acquisition and succession was perturbed in formula fed infants.

Gregory *et al.* 2016. Influence of maternal breast milk ingestion on acquisition of the intestinal microbiome in preterm infants. *Microbiome*, 4: 68; Ardesir *et al.* 2014. Breast-fed and bottle-fed infant rhesus macaques develop distinct gut microbiotas and immune systems. *Science Translational Medicine*, 6: 252ra120

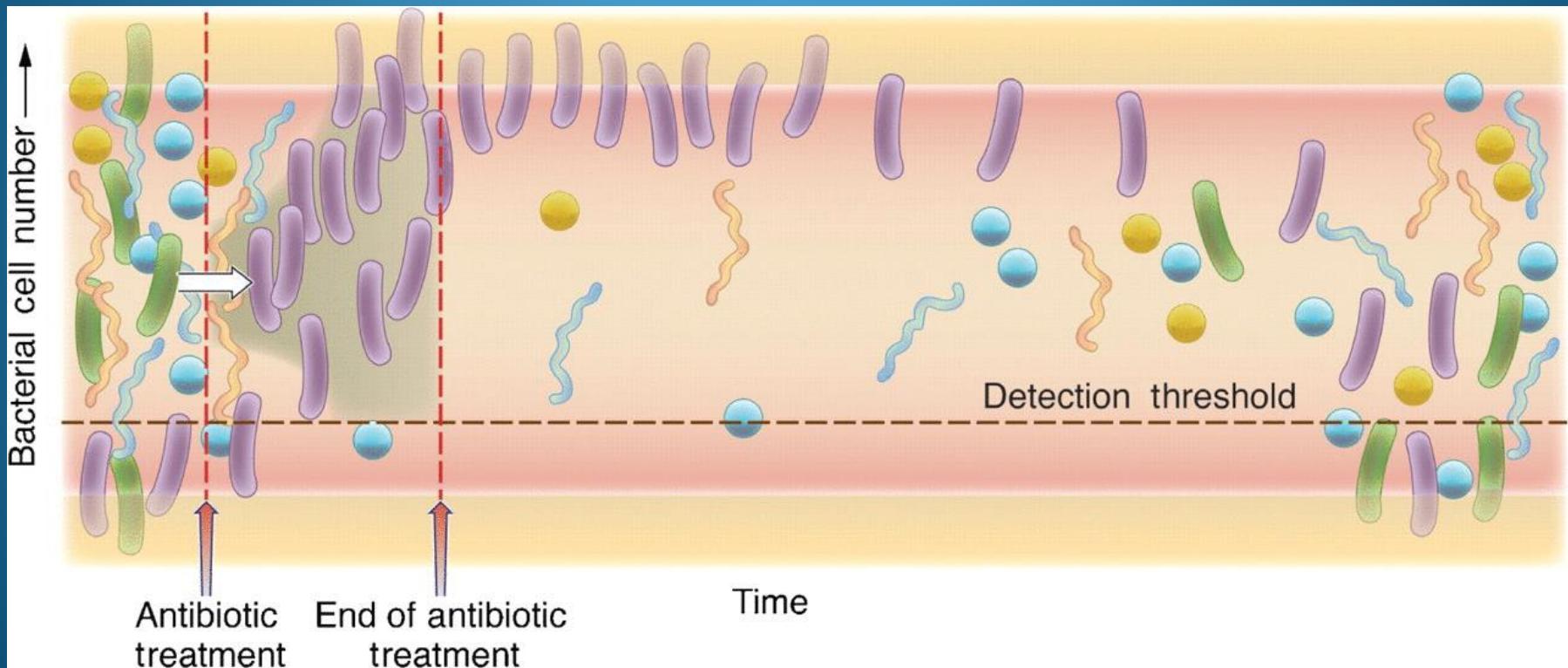
# Antimicrobial agents cause declines in microbiota diversity



Agents such as mercury, arsenic, sulfa drugs, antibiotics and disinfectants kill microbiota indiscriminately. Treated individuals may never recover their original diversity

# Antibiotic treatment

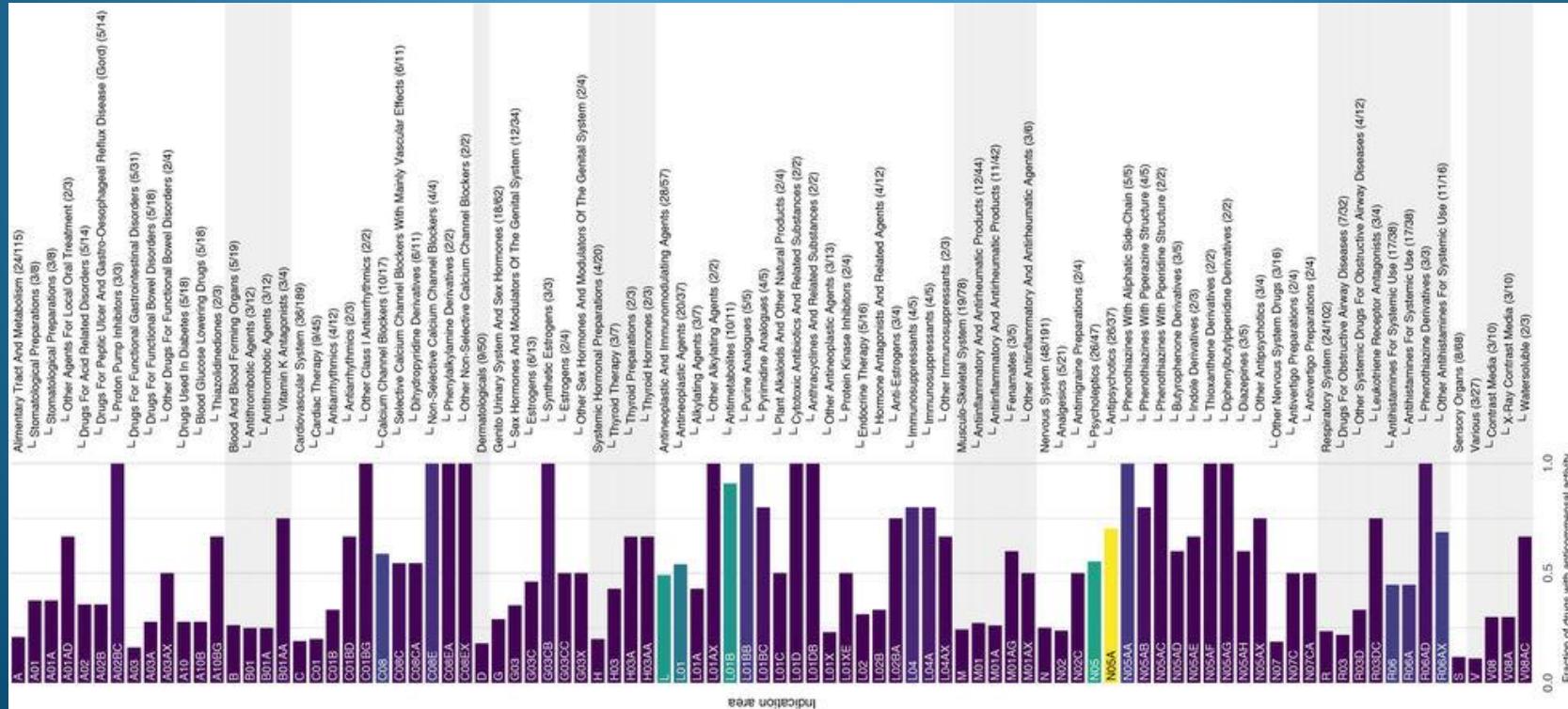
It can take up to 2 years to recover diversity in the microbiota



Jernberg *et al.* 2010. Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology*, 156: 3216-3223;  
Dethlefsen and Relman 2011. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proceedings of the National Academy of Sciences*, 108(Supplement 1): 4554-4561

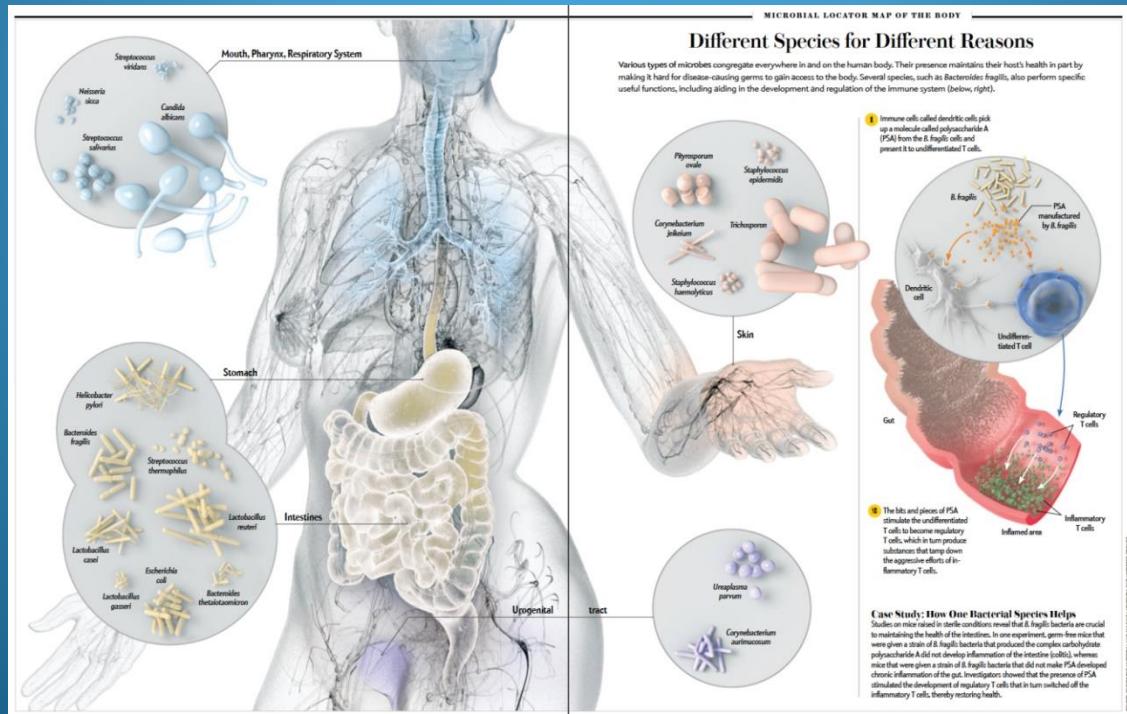
# Pharmaceuticals also affect gut microbiota

Significant proportions of all classes of pharmaceuticals affect the gut microbiota. Are their effects mediated through influencing the microbiota, rather than human cells?



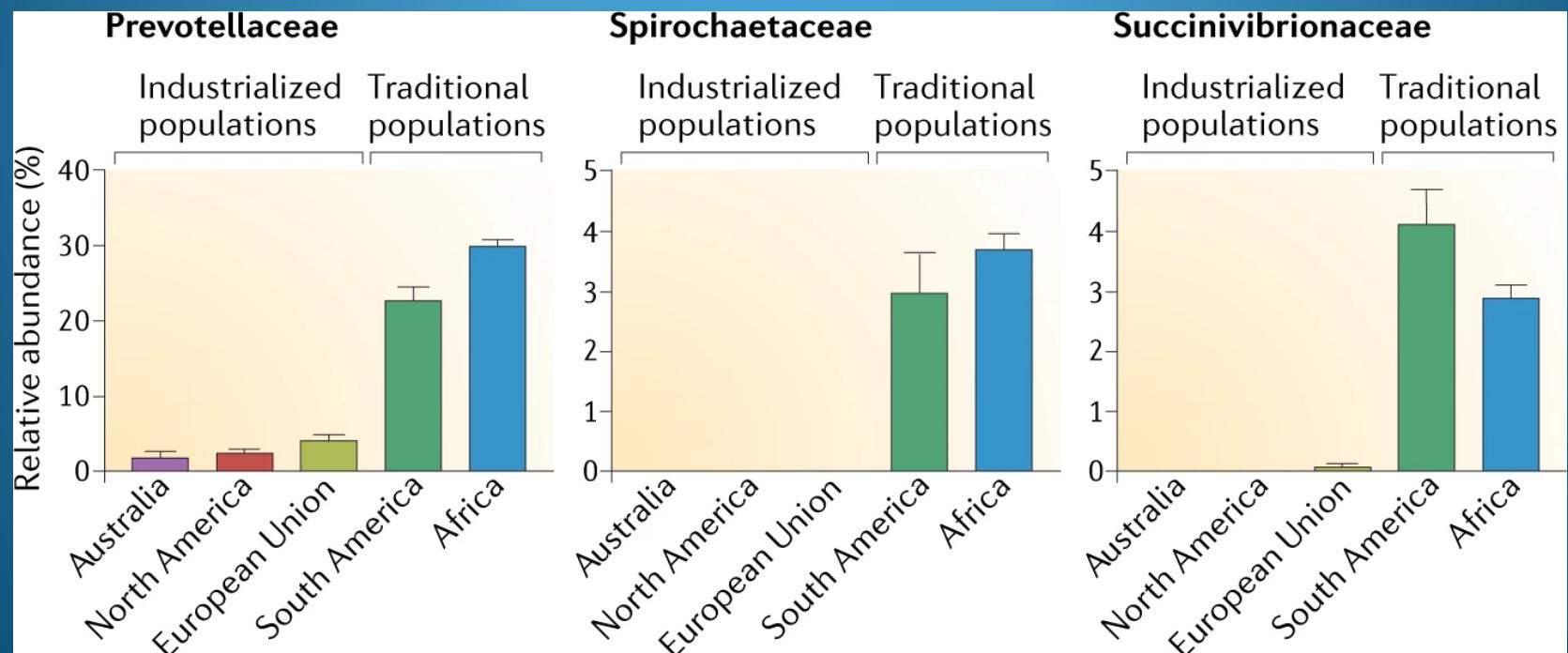
# So, we have damaged our own internal microbial ecosystems....

The human microbiota is under environmental pressures, and similar to all other ecosystems, is degrading.



# ....and elements of the microbiota are becoming extinct

A number of taxa are essentially absent in the gut microbiota of urbanized and industrial populations.



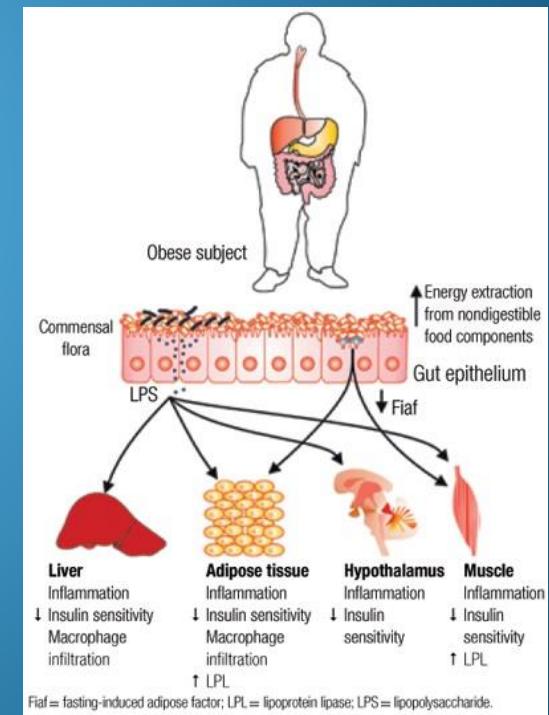
# Diseases associated with dysbiosis are surprisingly diverse

Multiple factors adversely affect microbial diversity and the balance of microbial communities. These imbalances (dysbiosis) are increasingly being associated with disease



# Microbiota and obesity

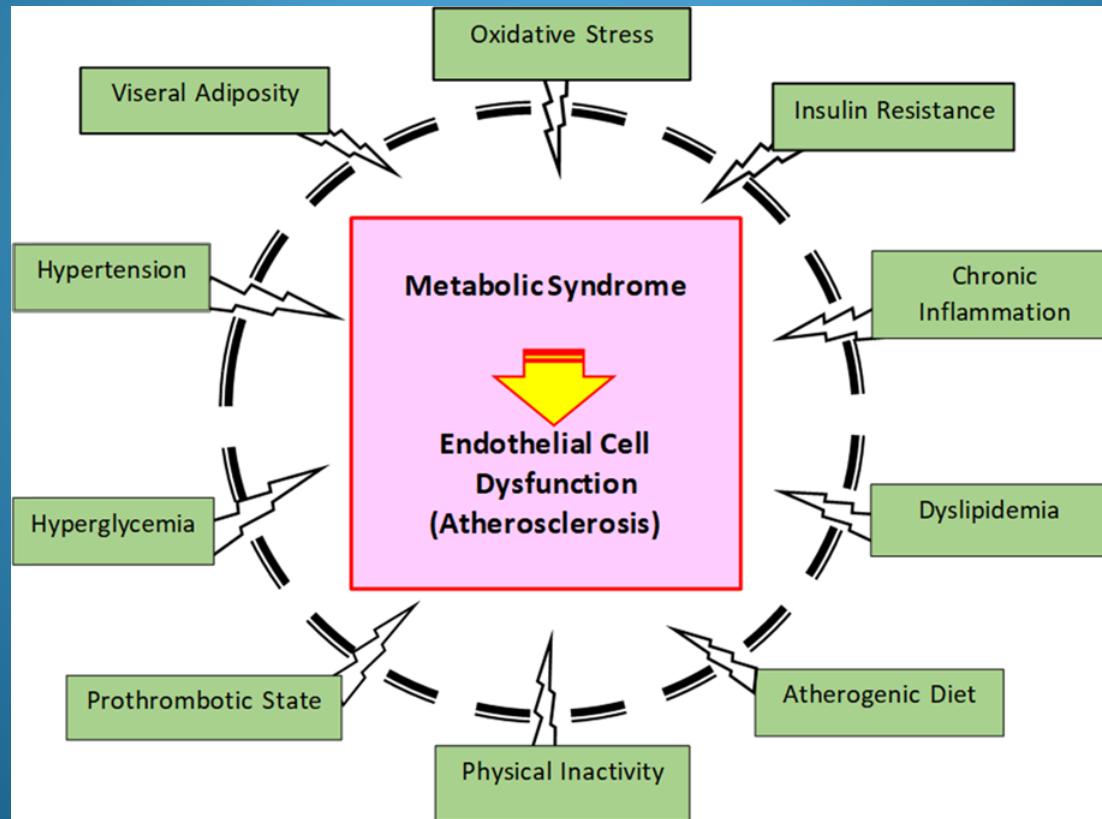
Obese mice differ from lean mice in the ratio of Bacteroidetes to Firmicutes in their gut microbiota. Transplanting the ‘obese’ microbiota into germ-free mice makes them fat. Similar differences are found in lean and obese humans.



Turnbaugh *et al.* 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, 444: 1027; Schwietz *et al.* 2010. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity*, 18: 190-195; Cho and Blaser 2012. The human microbiome: at the interface of health and disease. *Nature Reviews Genetics*, 13: 260-270.

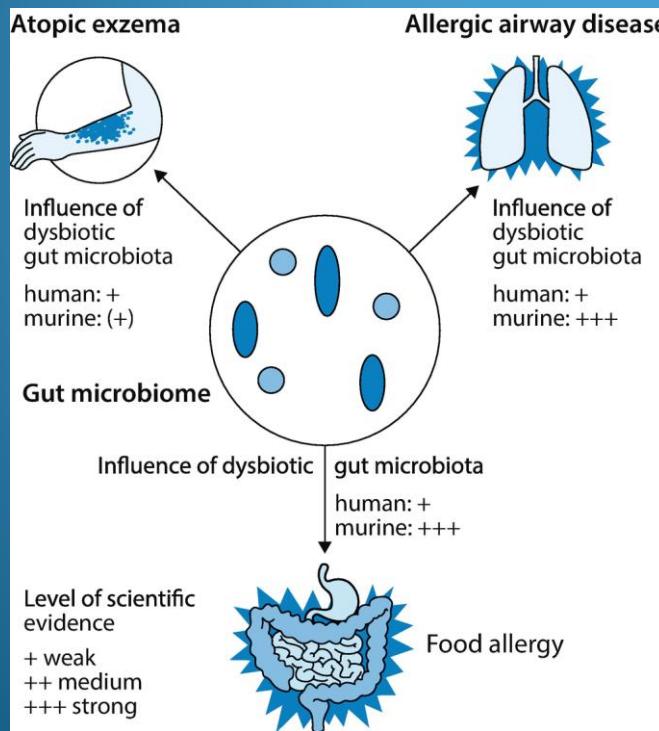
# Metabolic syndrome

A chronic inflammatory disease manifested by symptoms including cardiovascular disease, insulin resistance and type 2 diabetes. Dysbiosis is increasingly being investigated as a driving factor.



# Immune system disorders

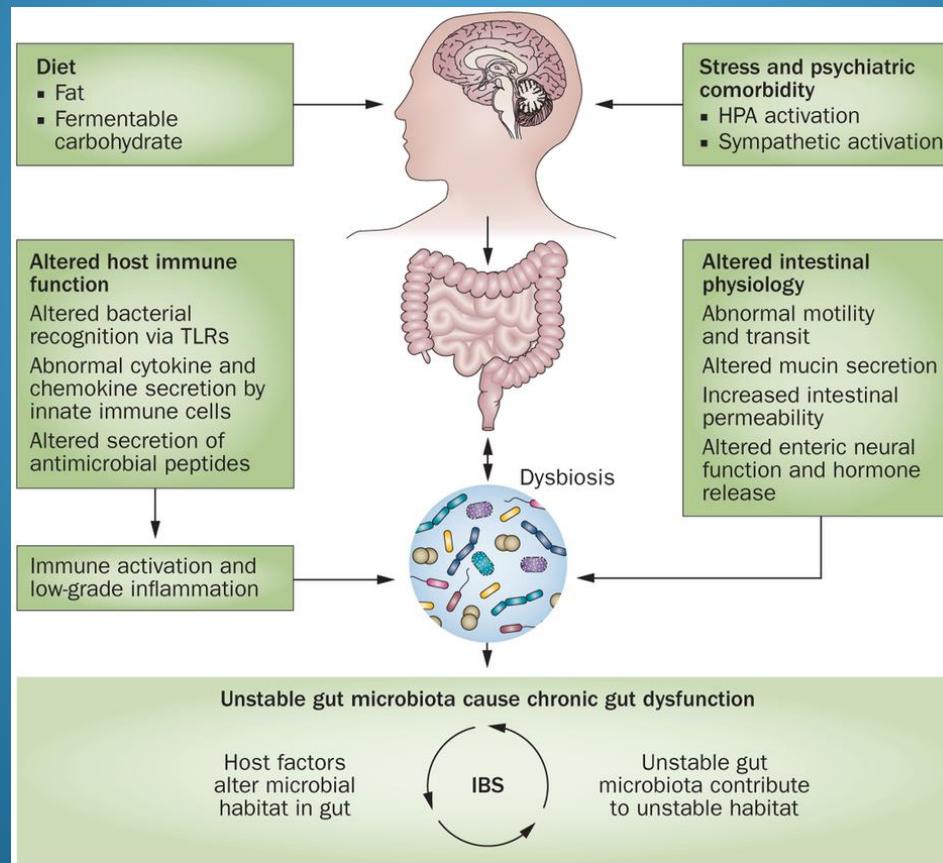
Exposure to microbiota in the early postnatal period affects immune homeostasis and disease susceptibility. Caesarean and pre-term babies may have increased susceptibility to dysfunction of the immune system, manifesting as eczema, asthma and allergies.



BUT – the evidence is still being accumulated, and there is a strong publication bias towards studies that show effects

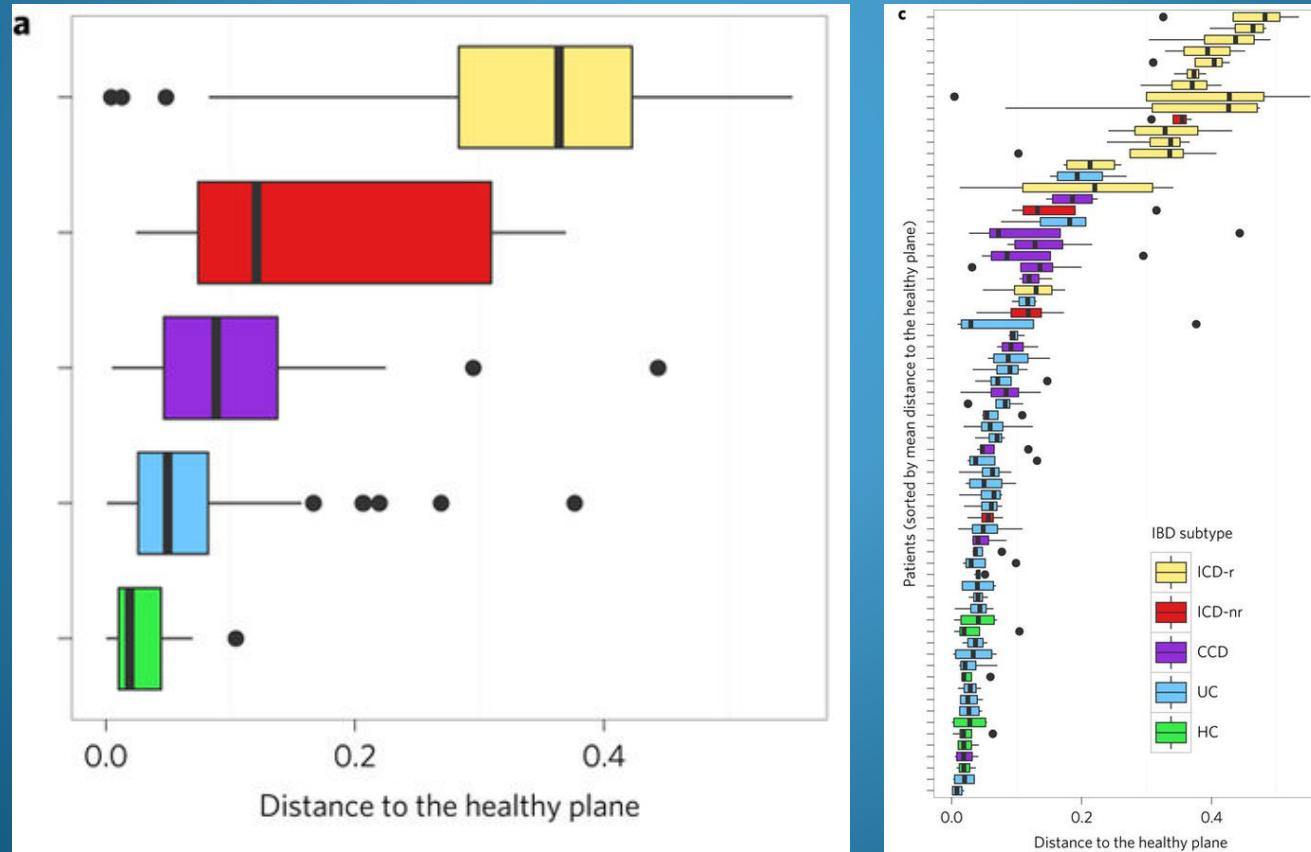
# Irritable bowel syndrome

Complex feedback loops between environment, diet, host immune function and microbial communities alter the functioning of the human gut



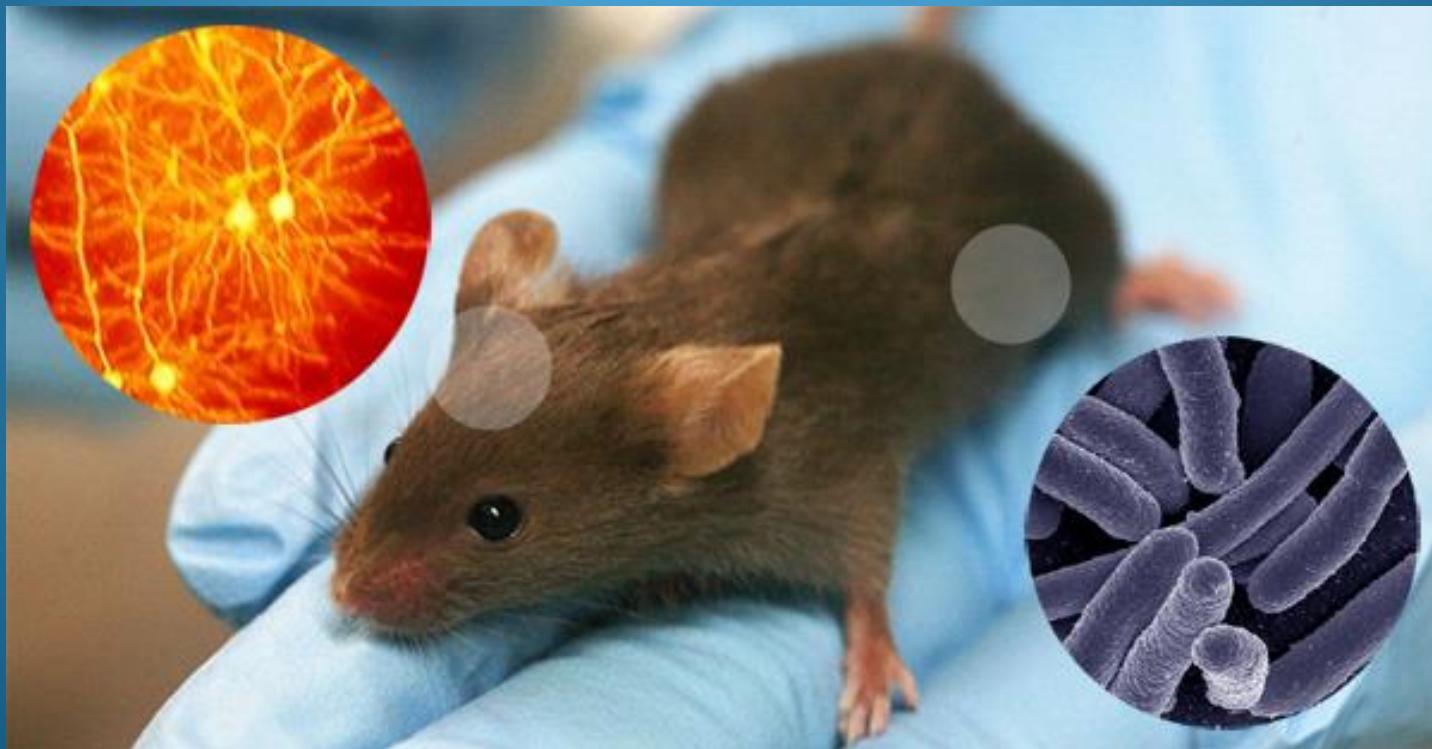
# Inflammatory bowel diseases

Microbial composition of patients with ileal Crohn's disease (yellow and red), colonic Crohn's disease (purple), or ulcerative colitis (blue) differs significantly from healthy controls (green)



# The gut-brain axis

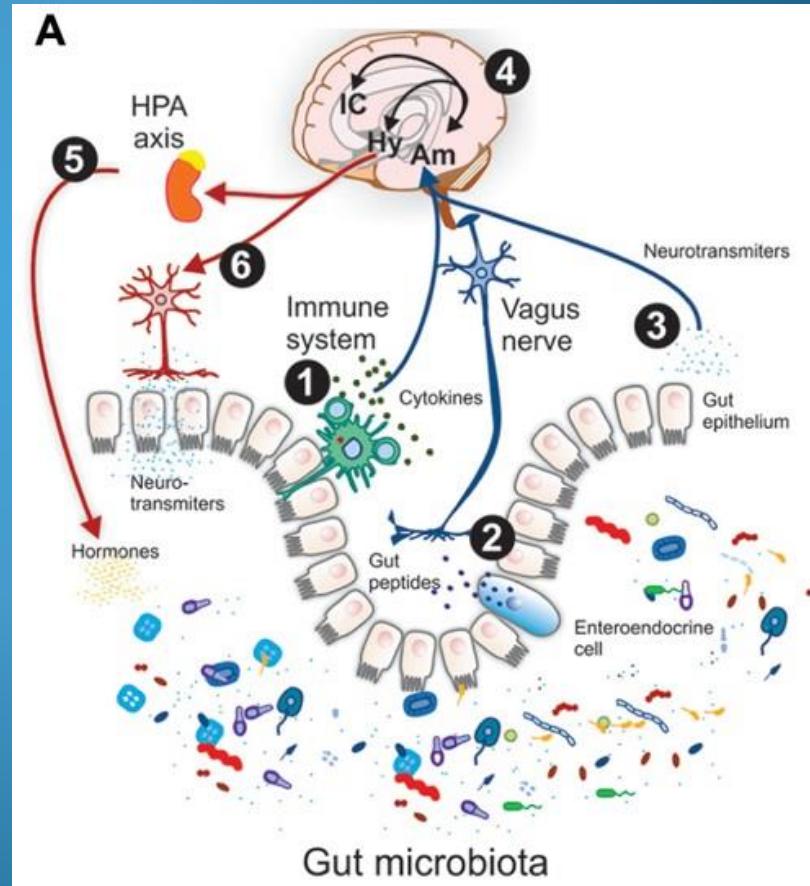
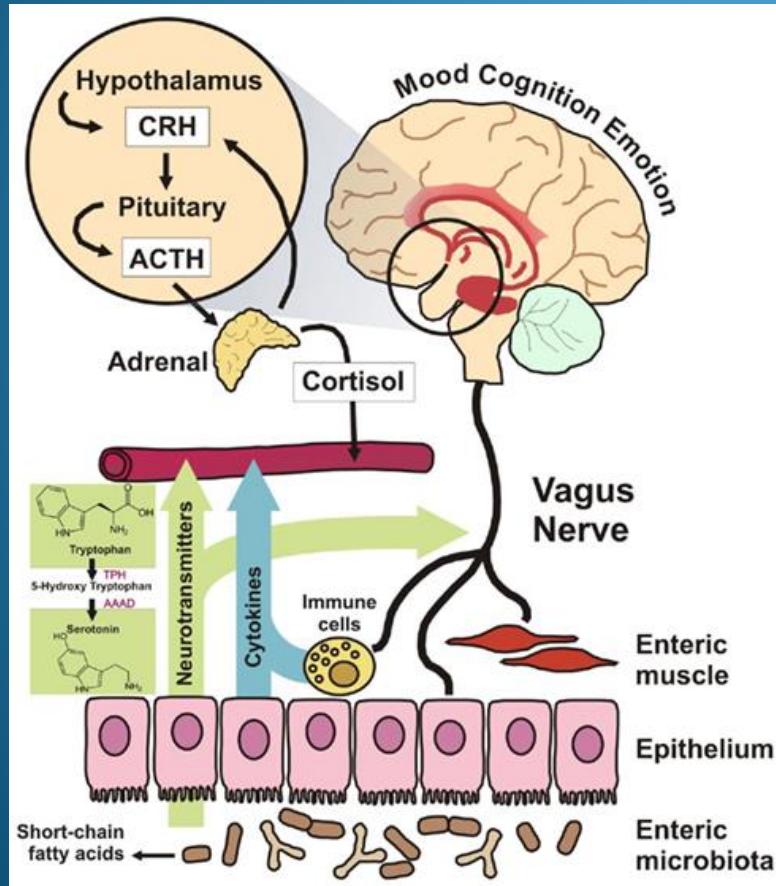
The gut microbiota influences brain development in mammals, and gut microbes have effects on brain activity. There is good evidence for an association between dysbiosis and anxiety/depression.



Bravo *et al.* 2011. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proceedings of the National Academy of Sciences*, 108: 16050-16055; Heijtz *et al.* 2011. Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences*, 108: 3047-3052..

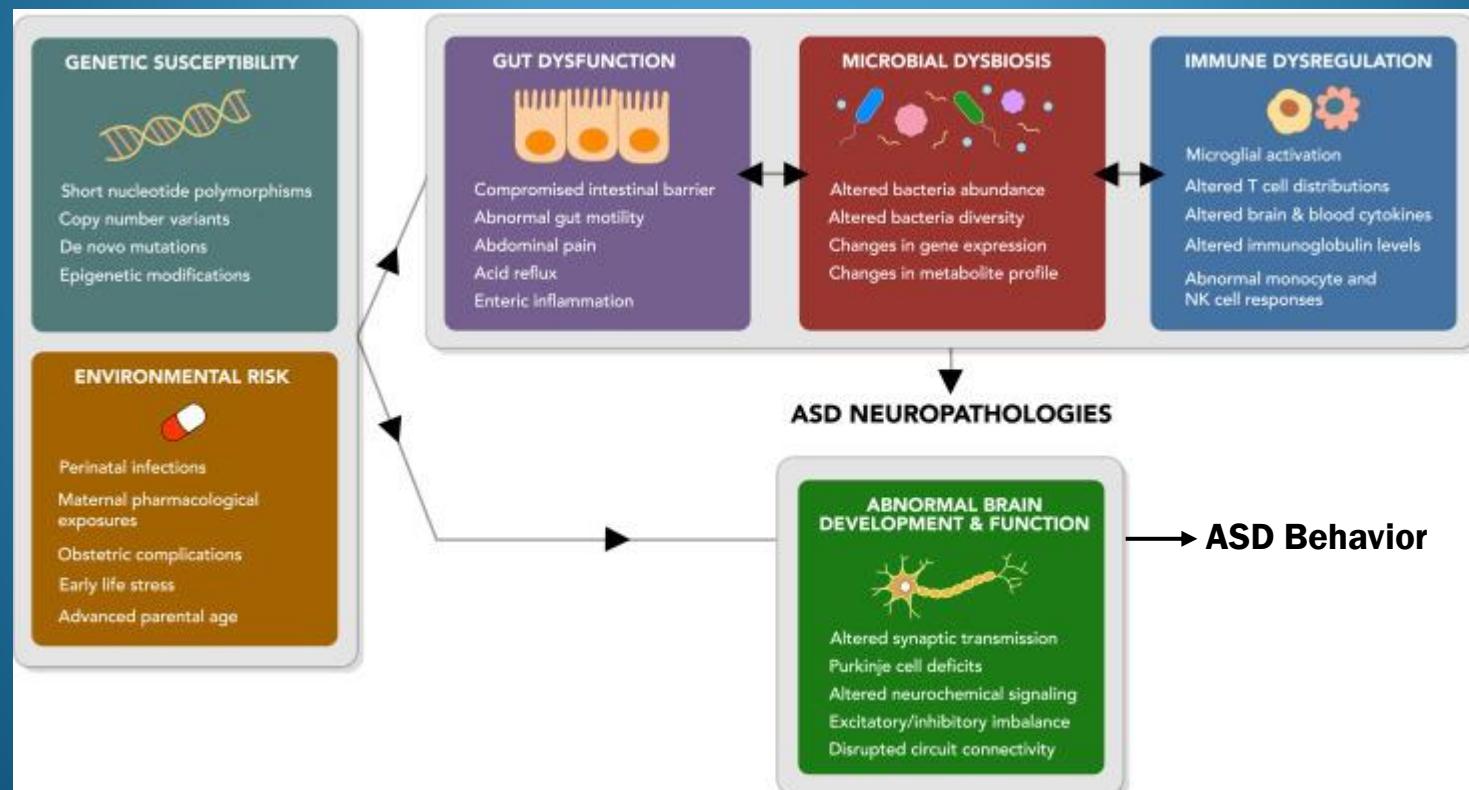
# Microbiota and the brain

There is complex cross-talk between the intestinal microbiota and the brain



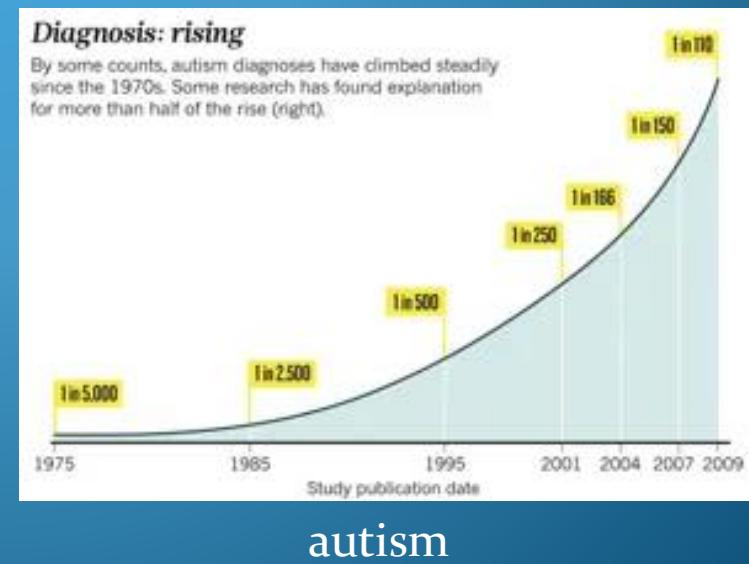
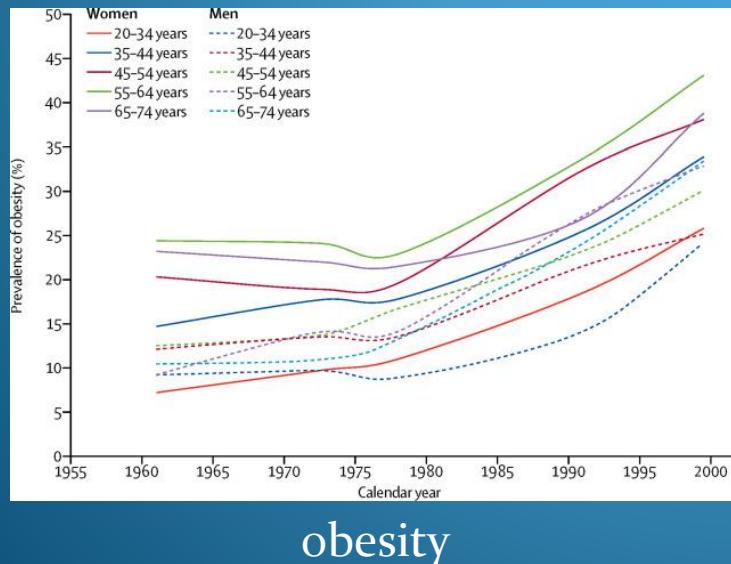
# The microbiota and autism

Dysbiosis of the intestinal microbiota, and the immune and gastrointestinal symptoms seen in Autism Spectrum Disorders can influence neurodevelopment, neural activity, and the manifestation of behaviours characteristic of ASD.



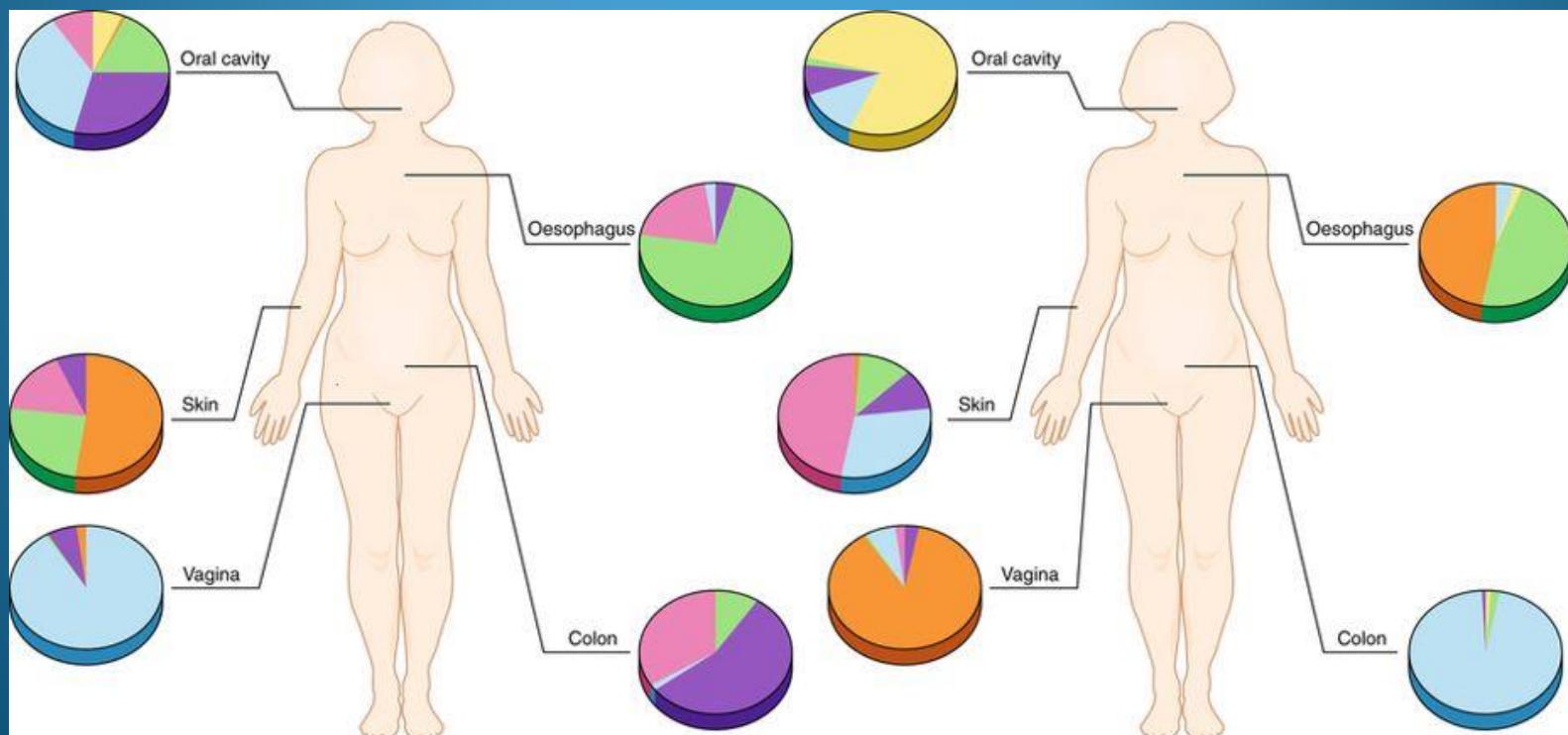
# Diseases caused by dysbiosis should have common characteristics

- difficulty ascribing a simple cause (a gene, a pathogen)
- variable presentation in severity and timing
- rapid increase in frequency after 1950-1970



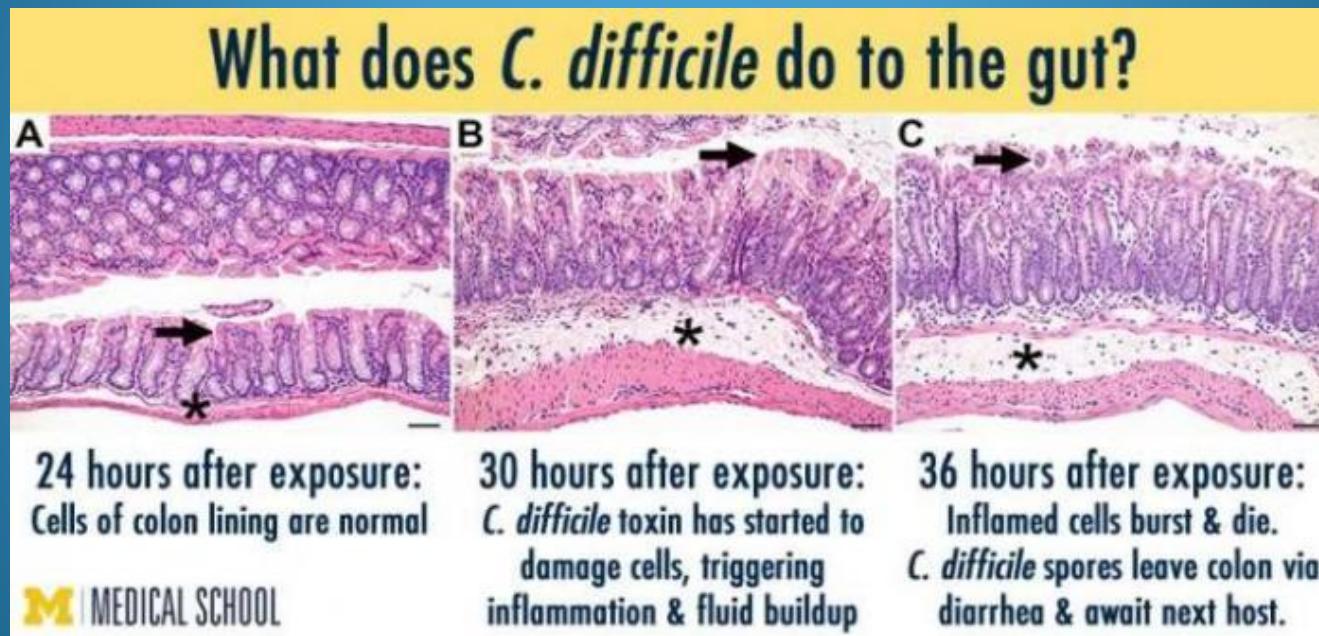
# The Challenges

Understanding how the microbiota affects health and disease is complicated by the fact that individuals can carry unique microbiota



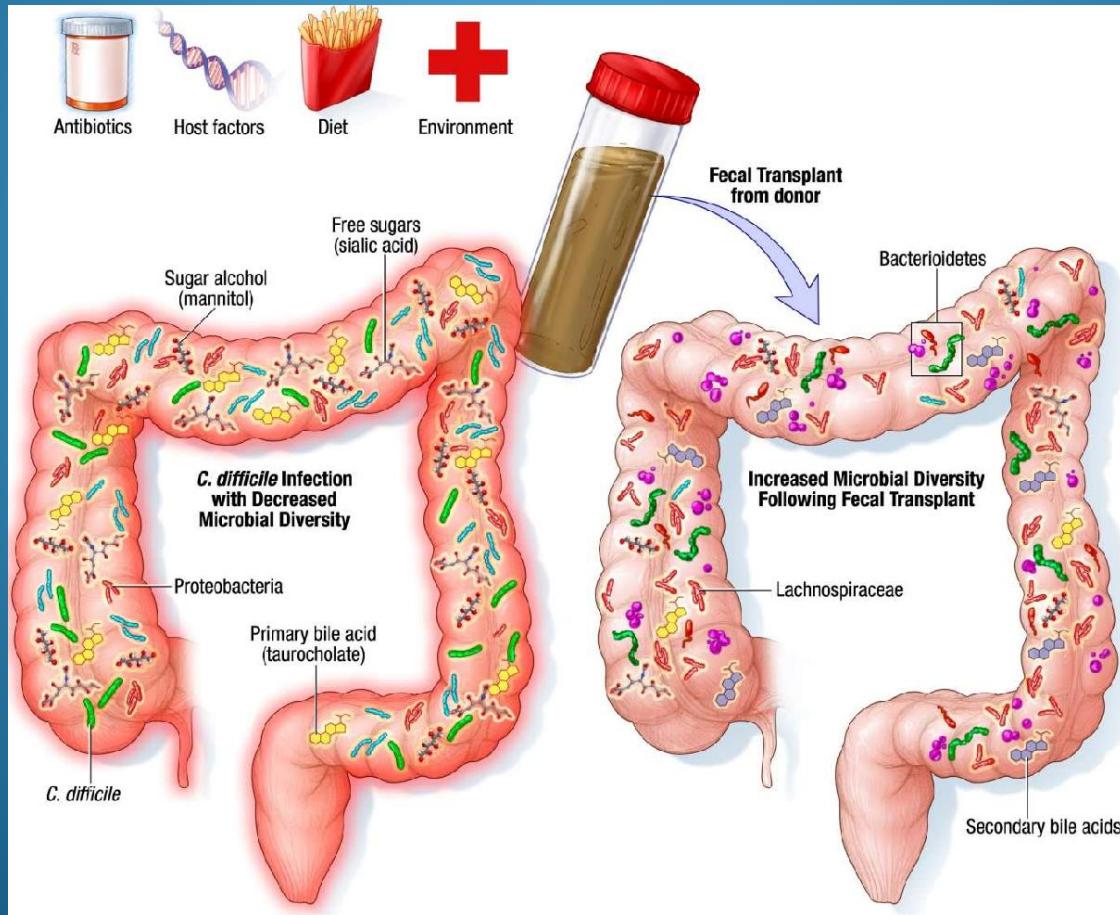
# The Challenges

Understanding the complex microbial ecosystems that inhabit every organism, and managing these ecosystems when they become degraded is a major challenge.



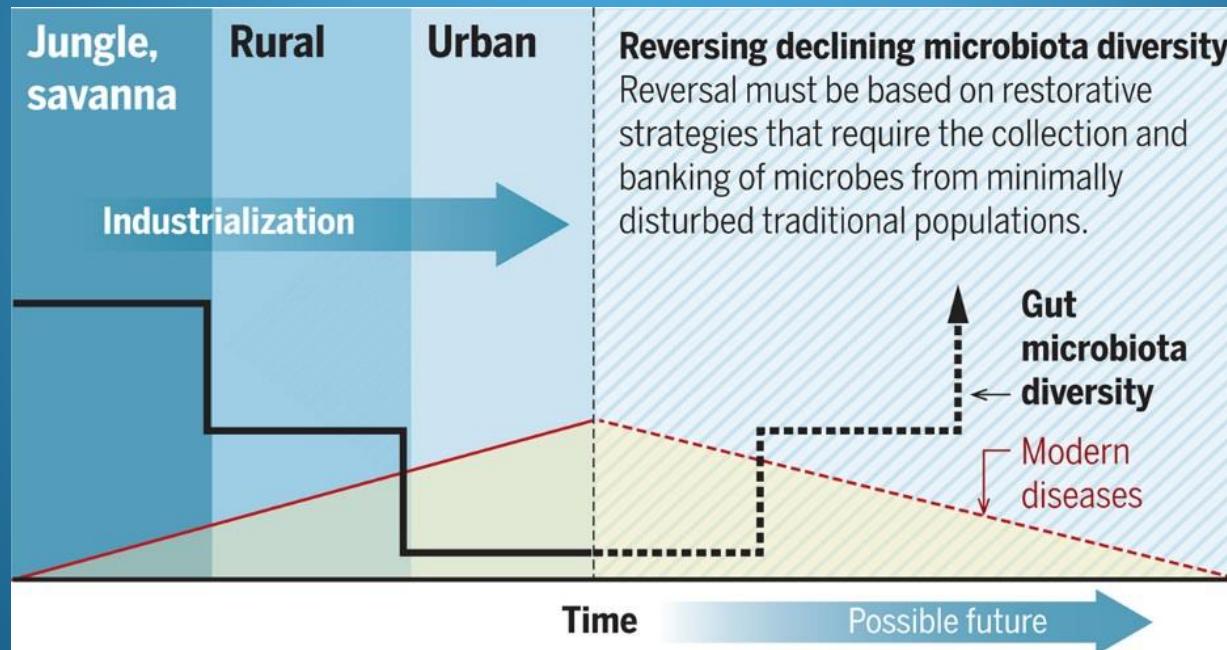
An example: *Clostridium difficile* invades the human gut, like a weed invades degraded land. The cure is similar to bush regeneration – ‘Poo transplants’ from healthy volunteers.

# But we need to avoid over-enthusiasm and hype.....



# Avoiding the extinction vortex

Generation by generation loss of microbial diversity leads to depauperate microbiomes, with serious consequences for health and well-being



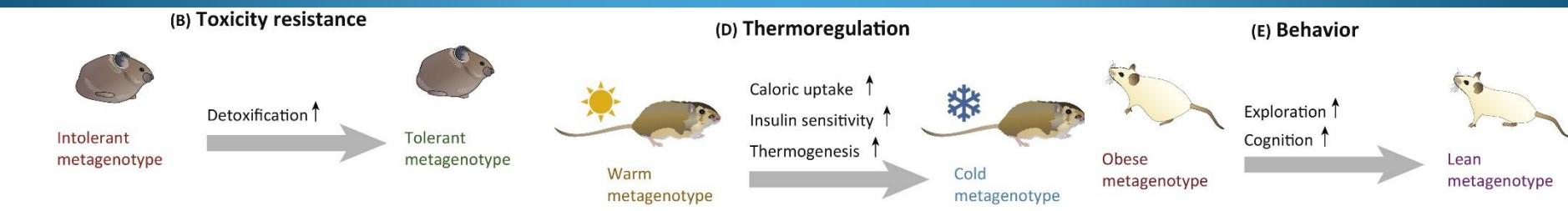
# Microbial conservation?

Will groups such as the Yanomami become the last custodians of microbial species that are otherwise extinct in the developed world?



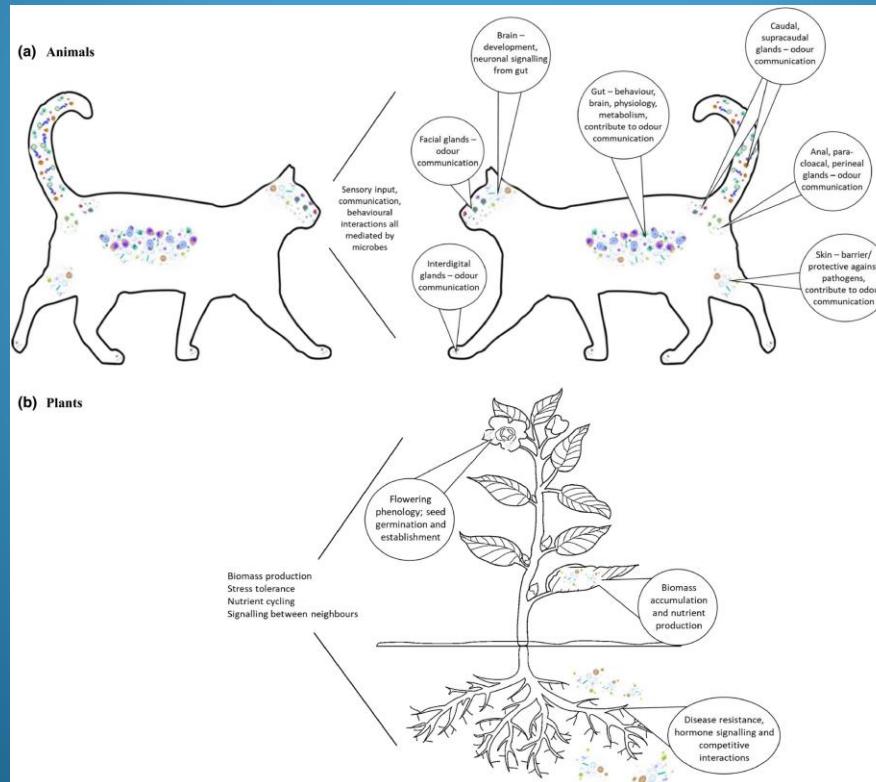
# Microbial genes are part of an ‘extended genotype’

Microbial genes offer an opportunity for rapid acquisition of phenotypes, or for generating variability with little expense to the host. Microbiota are just as important for plants and animals.



Changes to the meta-genotype allow rapid adaptation to environmental change. Similarly, diverse signals of individuality could be generated using microbial metabolites, without increasing the size and complexity of the host genome.

# To conserve the natural world, and to protect human health, we need to conserve microorganisms



# Thanks for your attention

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Emma V Lab Facebook

<https://www.facebook.com/profile.php?id=100009142133231>

The Conversation

<https://theconversation.com/bad-times-for-good-bacteria-how-modern-life-has-damaged-our-internal-ecosystems-47689>

