

THE LOSS OF MICROBIAL DIVERSITY

UO-CHC 441H/431H: Microbes + Social Equity

Lecture 8

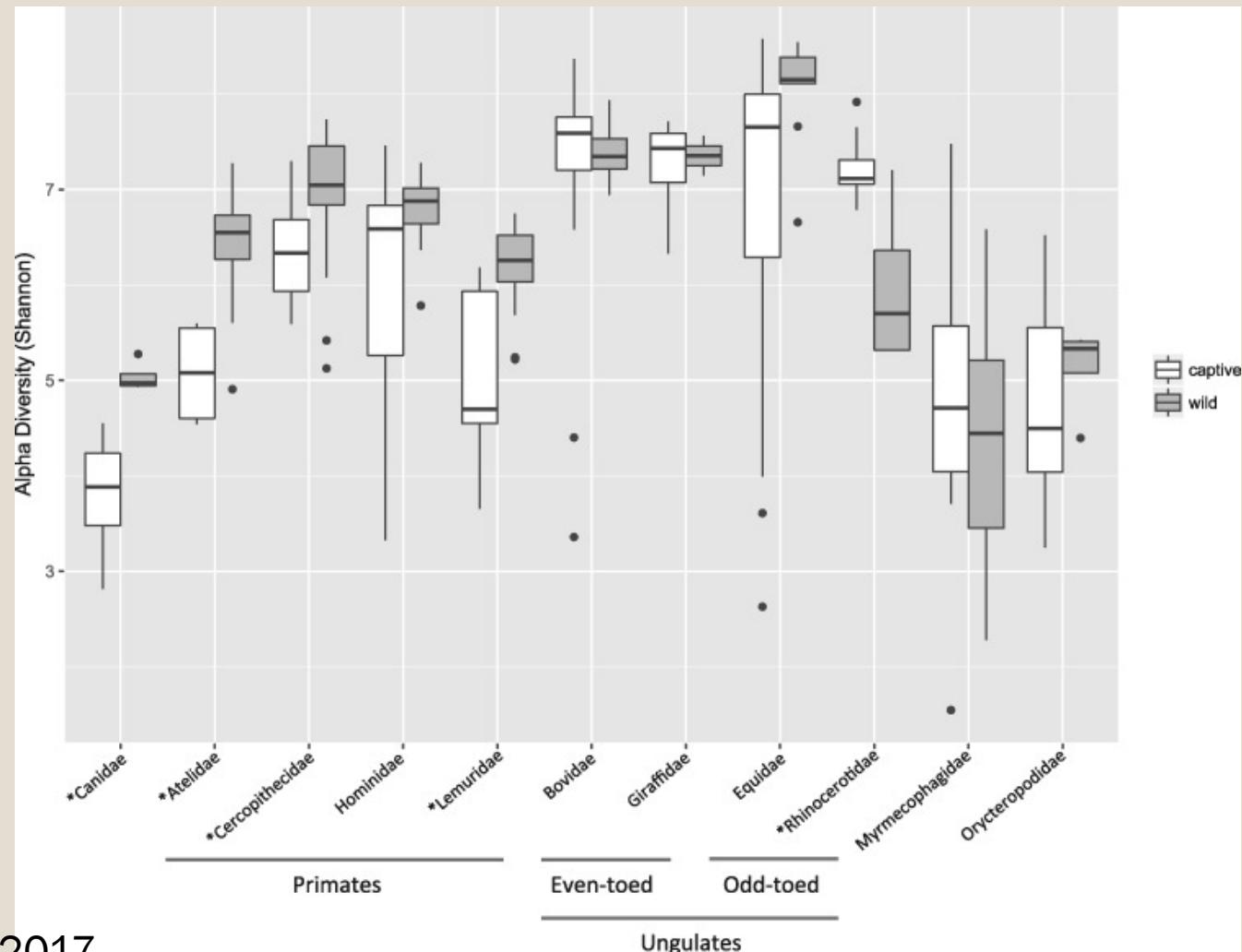
Dr. Sue Ishaq Pellegrini

Learning objectives

- The loss of microbial diversity through
 - *Diet*
 - *Captivity*
- The Hygiene Hypothesis
- The Old Friend's Hypothesis
- The Rewilding Hypothesis
- Precedence for microbial law

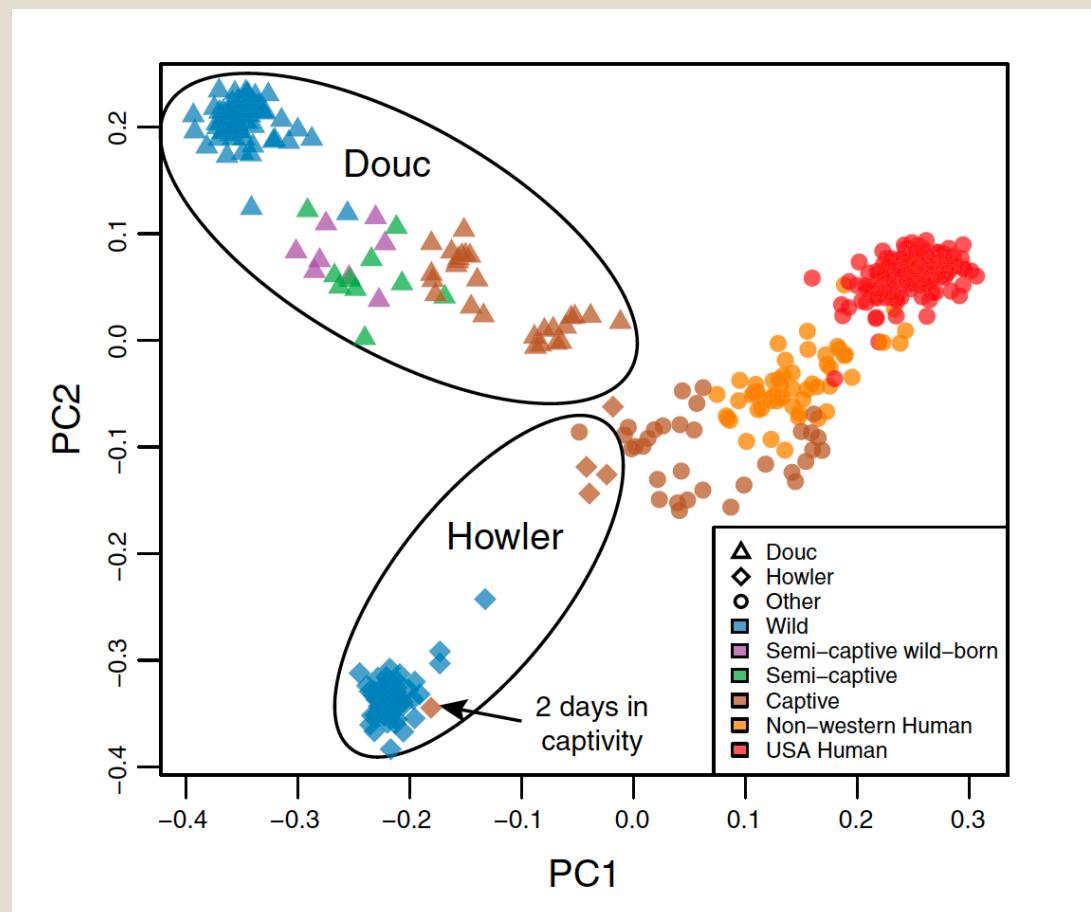
CAPTIVITY AND URBANIZATION

Captivity reduces the diversity of bacterial species in captive primates, canids, and equids



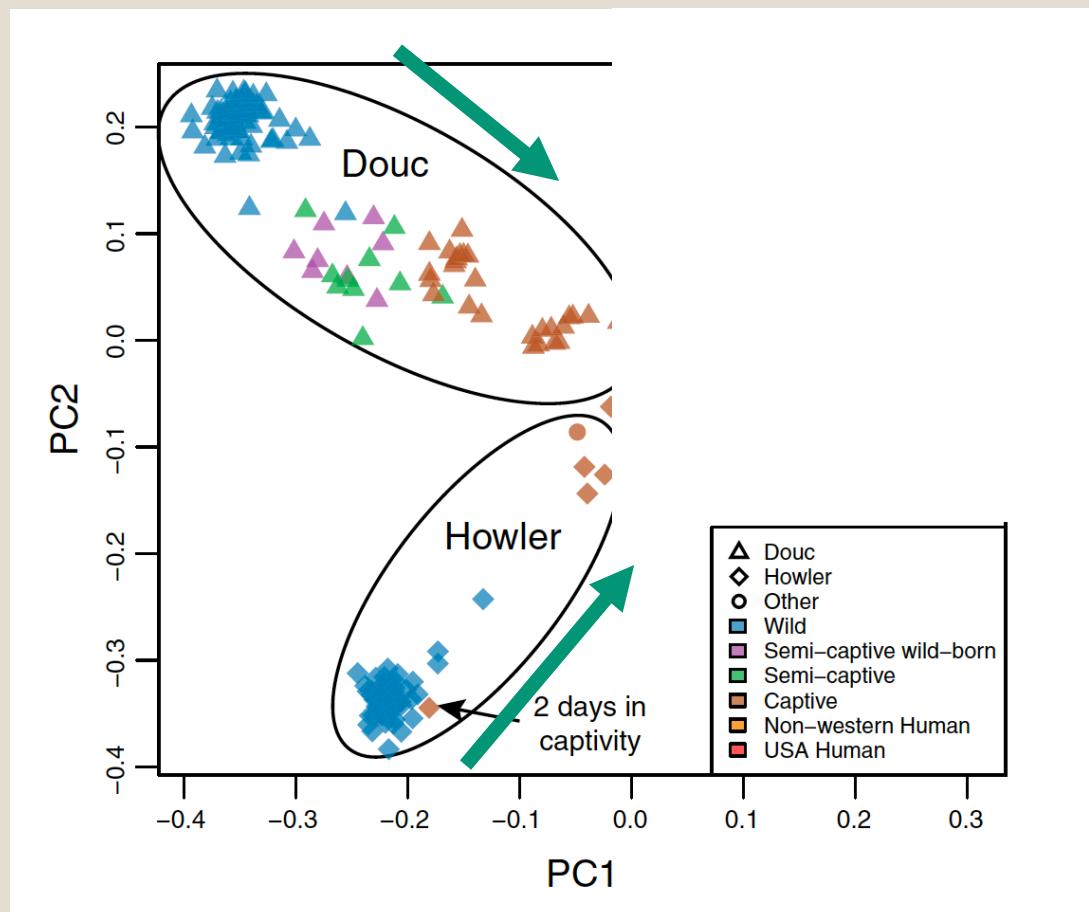
McKenzie et al. 2017

Comparing gut diversity in primates in captivity and humans



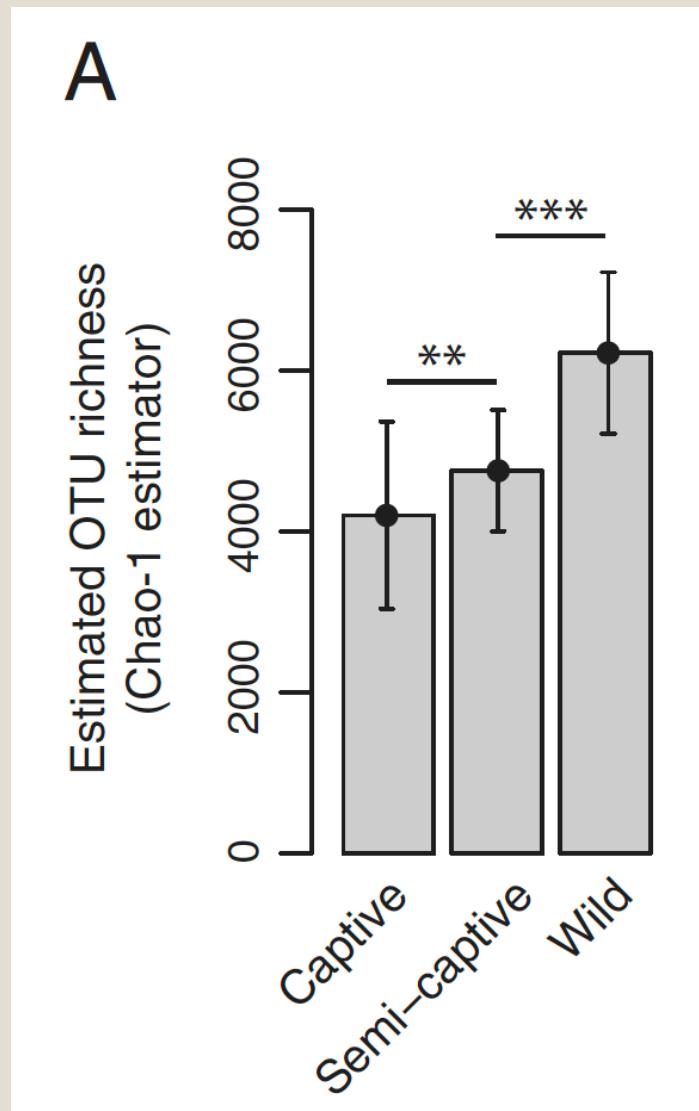
Primates in captivity have reduced gut diversity over time

- The bacterial community in primate gut was changed by being in captivity
- And the bacterial community in their gut starts to look more like the human gut bacterial community
- Clayton et al. 2016



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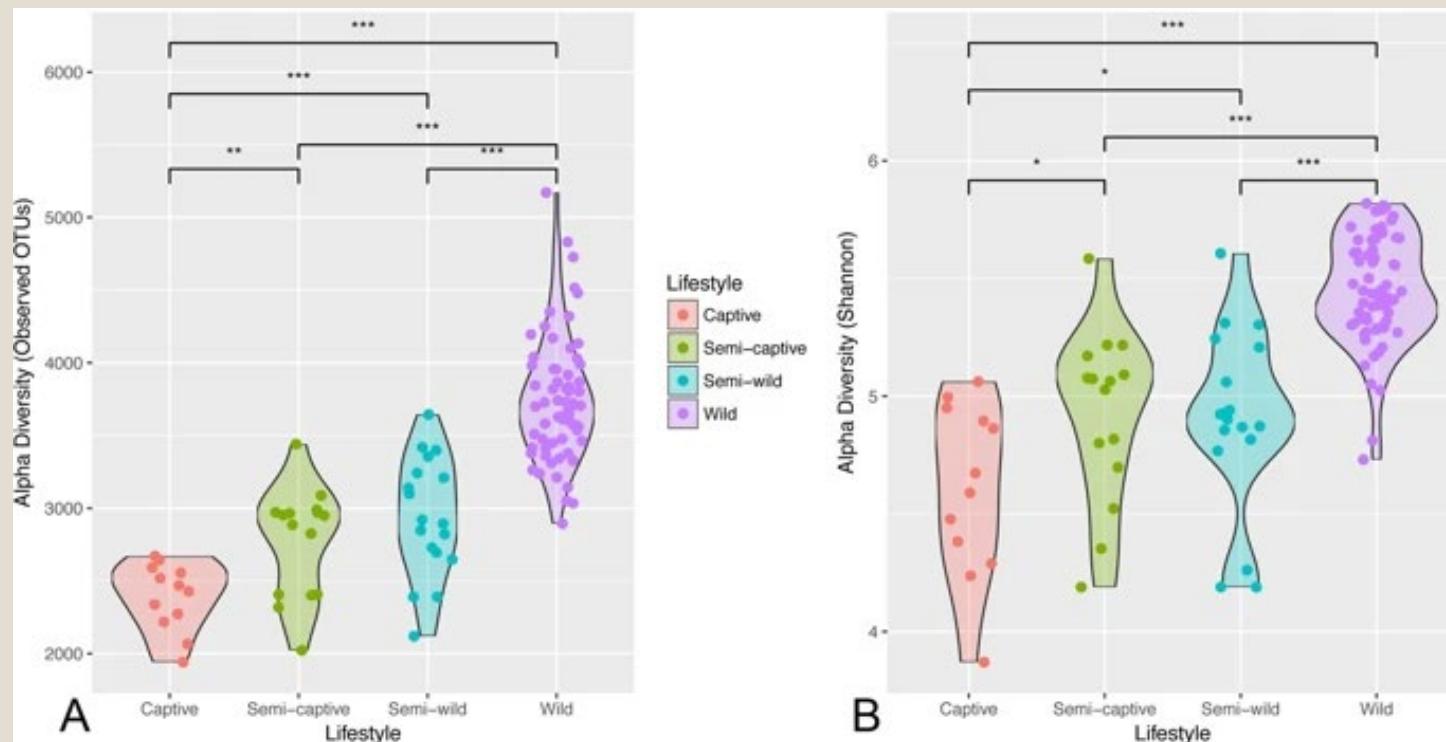


Within a species, low microbial diversity in gut is association with poor health

- Reviewed in Valdes et al. 2018
- Lower bacterial diversity observed in people with:
 - *inflammatory bowel disease* [31](#)
 - *psoriatic arthritis* [32](#)
 - *type 1 diabetes* [33](#)
 - *atopic eczema* [34](#)
 - *coeliac disease* [35](#)
 - *Obesity* [36](#)
 - *type 2 diabetes* [37](#)
 - *arterial stiffness* [38](#)
 - *Crohn's disease, especially smokers* [39](#)

Prevalence of GI problems in captive primates

- Diarrhea is common
- Colitis (long-term gut inflammation) one of main reasons for euthanizing captive primates
- Effect of reduced diet or captivity?

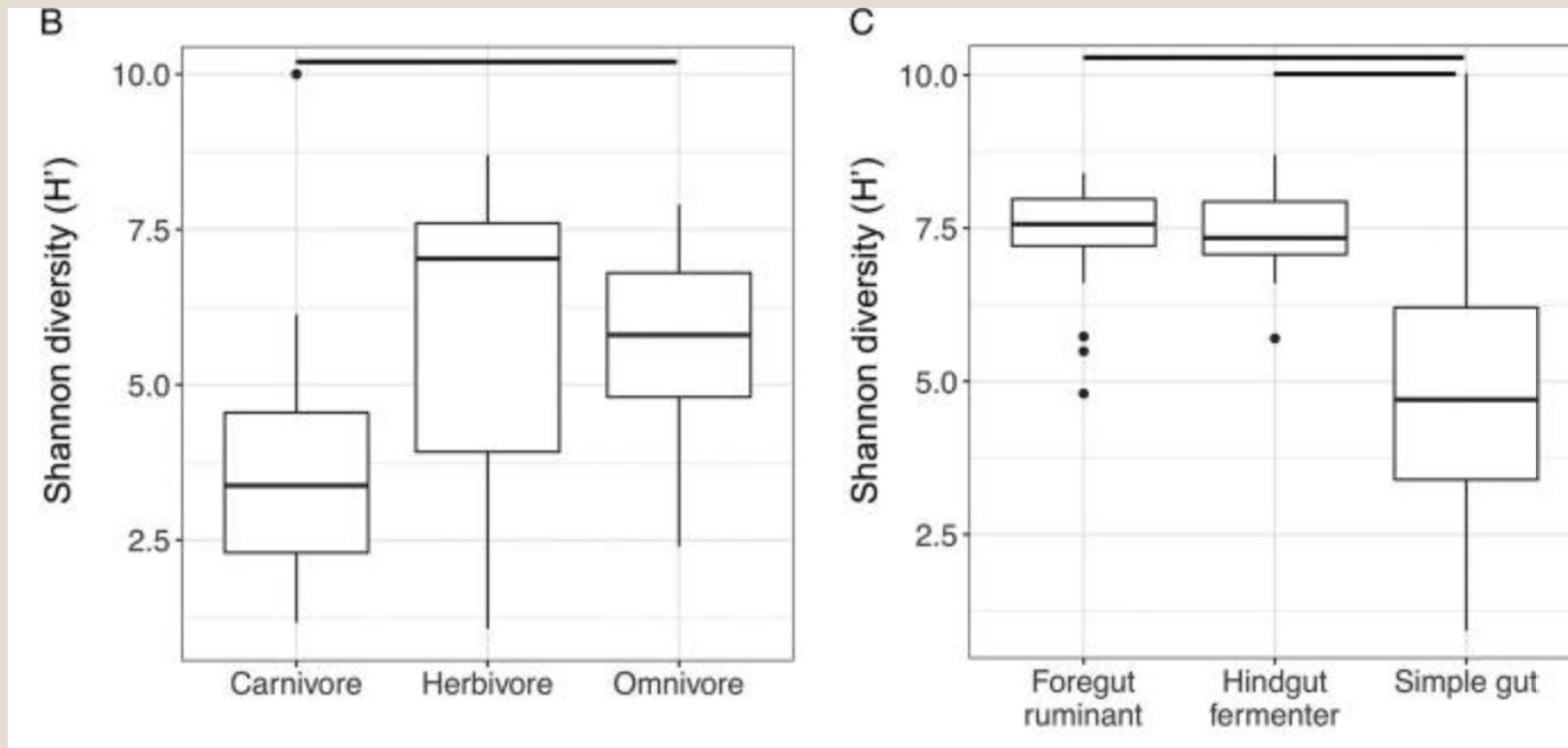


Clayton et al.
2018

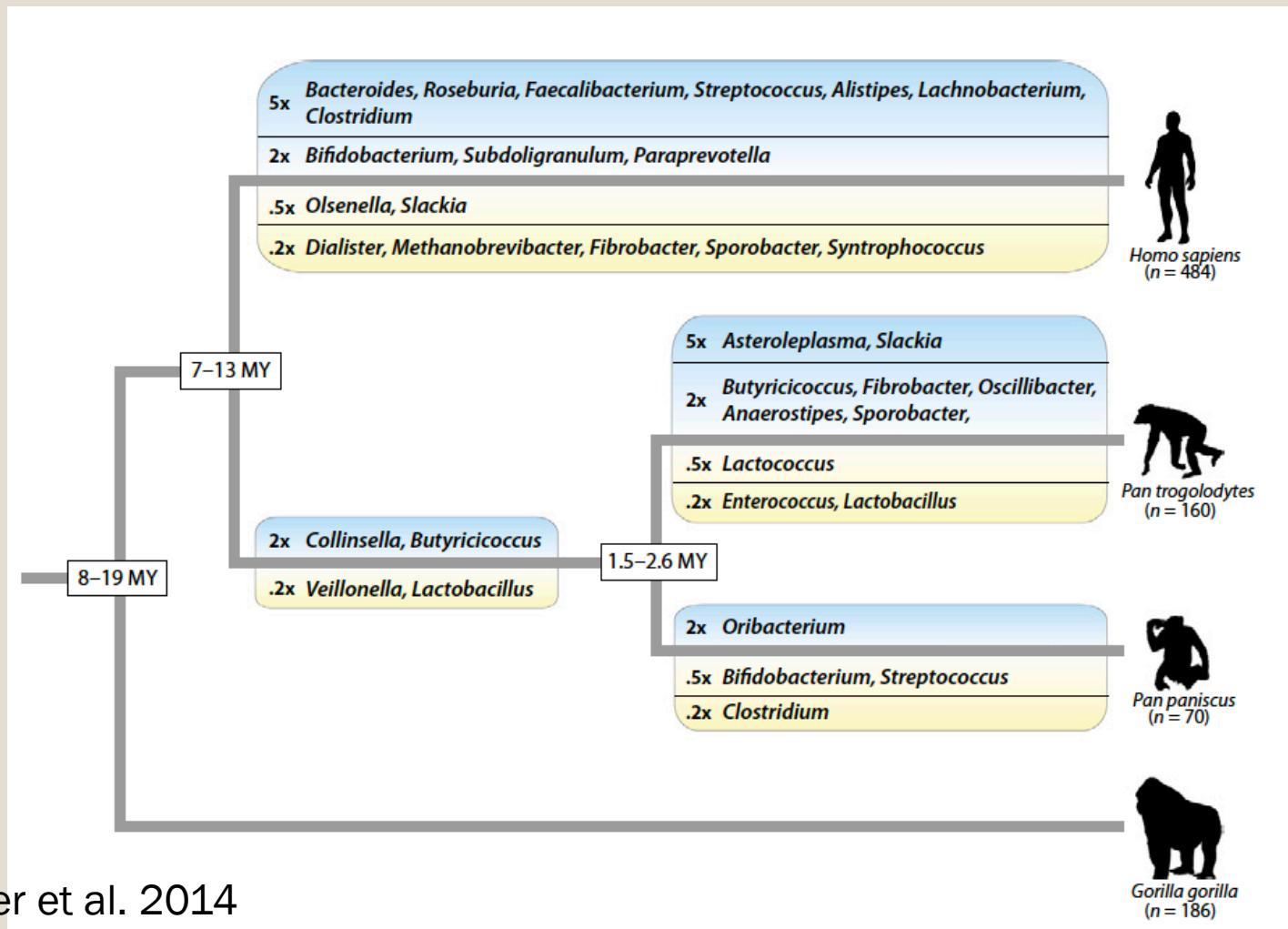
More diversity in diet increases microbial diversity in gut

Reese and Dunn, 2018

Especially if the animal's GI tract supports more microbial fermentation.
Humans have a simple gut

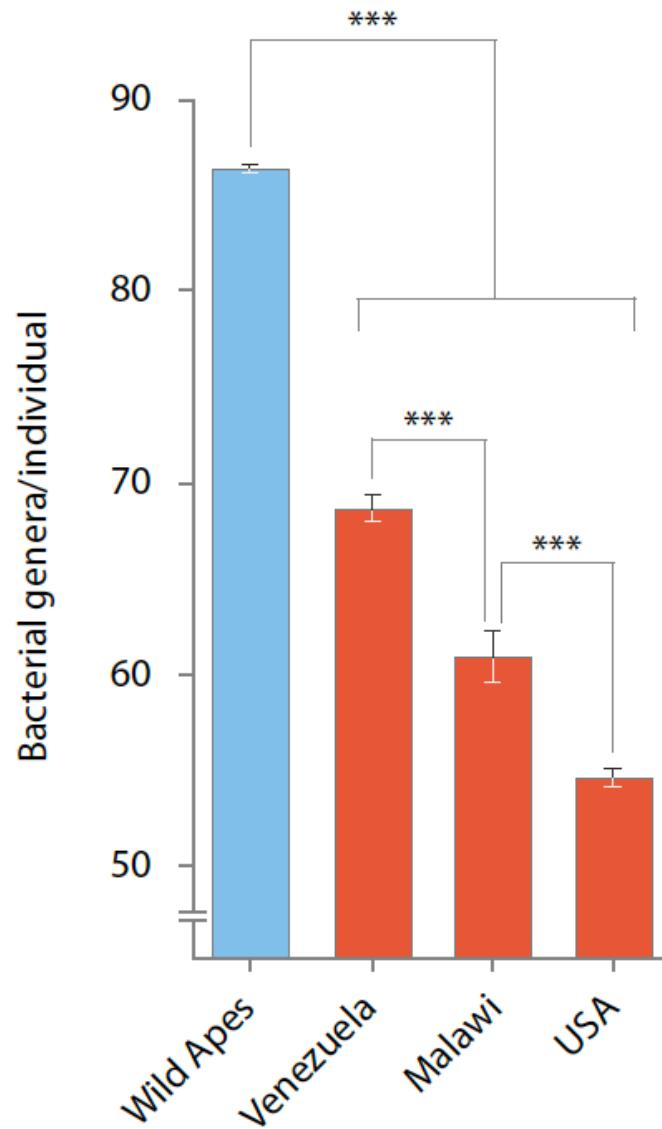


Humans acquired different gut microbiomes as we evolved from our primate ancestors



Moeller et al. 2014

But humans lost
that bacterial
diversity in our
gut as we
urbanized – a
self-imposed
captivity



Moeller et al. 2014

HYGIENE HYPOTHESIS

Development of the Hygiene Hypothesis

- 1989 David Strachan
 - *Is the reduction in childhood infections responsible for the rise in asthma and allergies?*
 - *Children with lots of siblings had fewer allergies later in life*
 - Presumably had more microbial interactions
- Maybe we went overboard with the whole Germ Theory
 - *Could we be too clean?*

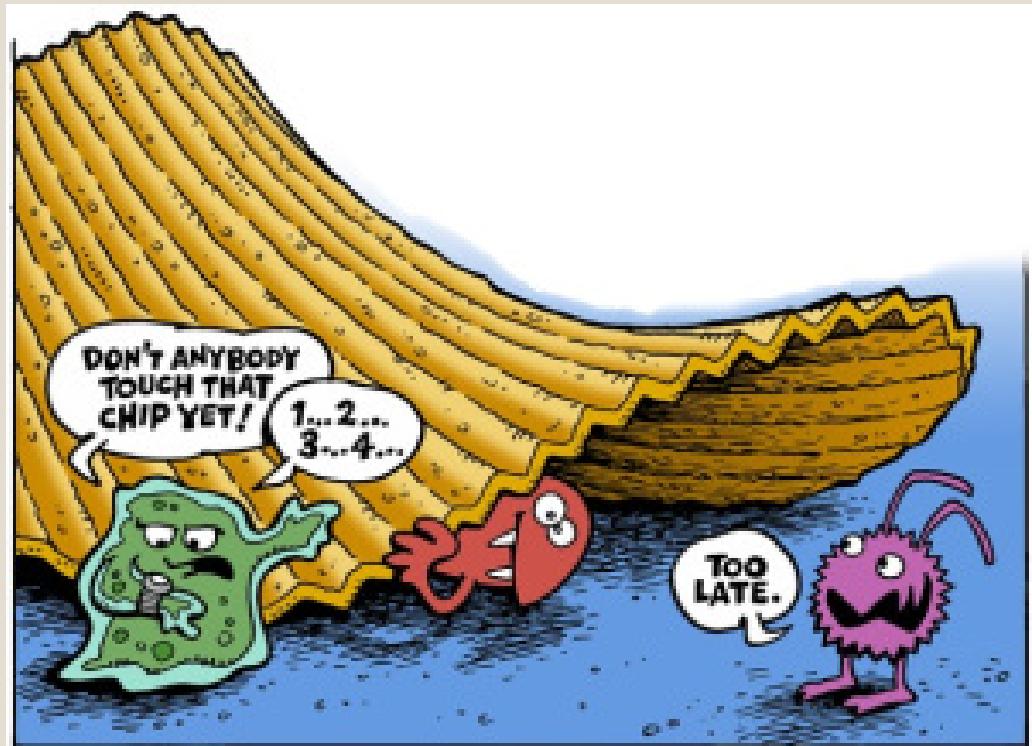
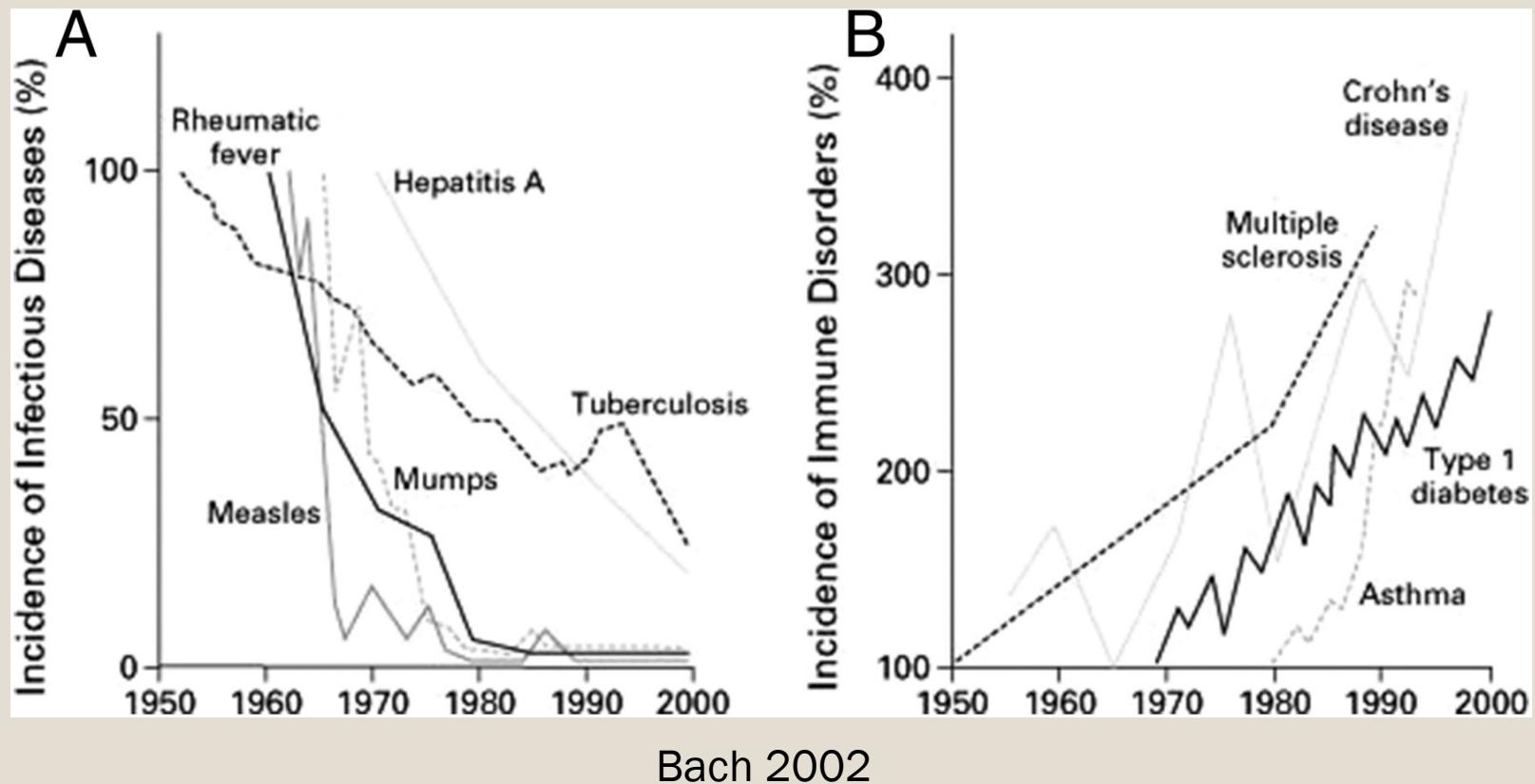


Image: Greg Williams' WikiWorld.

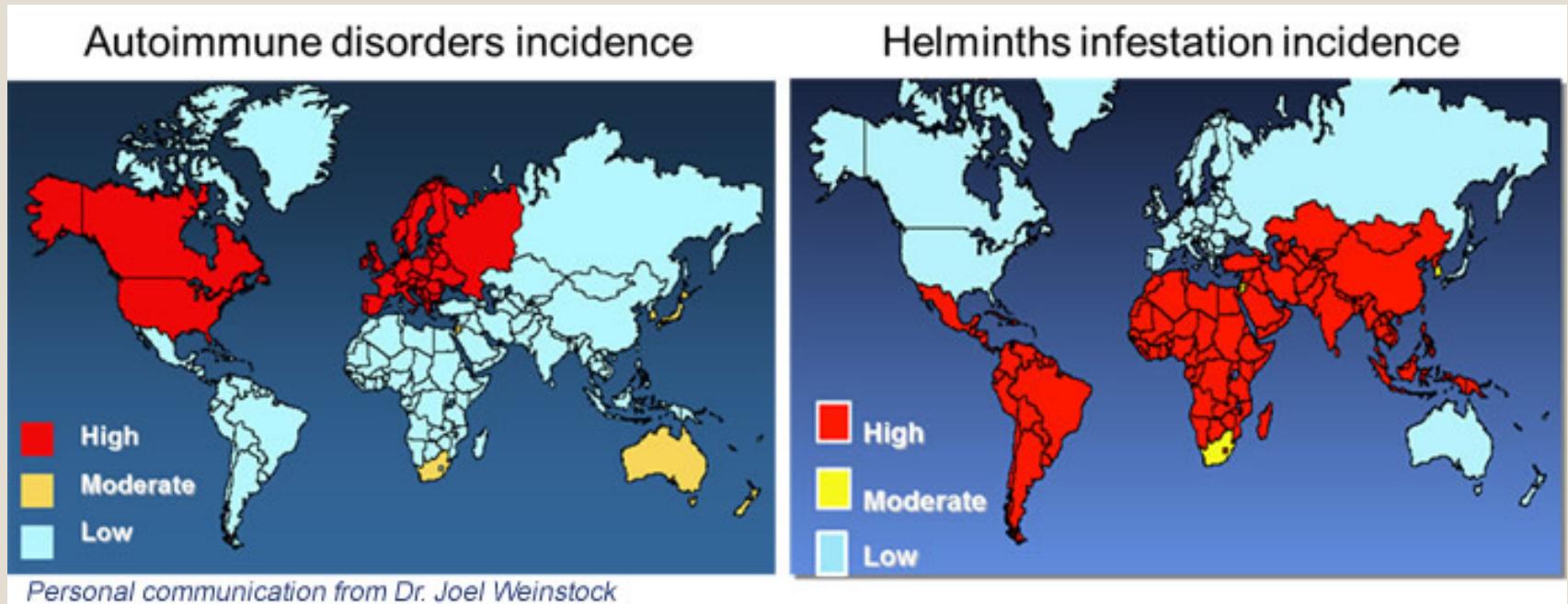
Hygiene Hypothesis

- Also called
 - *Biome depletion theory*
 - *Lost friend's theory*
- Hygiene Hypothesis: A lack of microbial exposure (infectious or symbiotic) at a young age suppresses the development of the immune system and results in dysbiosis later in life
 - *Trouble tolerating microorganisms*
 - *Allergies (over active immune system)*

Reduction in infections and a rise in autoimmune disease: correlation or causation?



Link between autoimmune diseases and helminth (worm) infections?



- Parasitic infections and allergies both trigger host to produce antibody type IgE (immunoglobulin E)
- Parasitic infections and allergies both trigger host to T-helper 2 (Th2) cells

Maybe Hygiene Hypothesis doesn't explain everything (Scudellari, 2017)

- Long-term helminth (worm) infections cause lots of Th2 production (van den Biggelaar et al. 200)
 - *but also an anti-inflammatory molecule called interleukin-10 (IL10)*
 - *IL10 inversely correlated with allergy*
 - *Constant immune challenge prevents immune system overreaction*
- Autoimmune disorders and irritable bowel disease aren't caused by the same immune system reactions
- Measles and many respiratory diseases not to be protective against allergic disease (Benn et al. 2004)
 - *may increased the risk*

OLD FRIENDS HYPOTHESIS

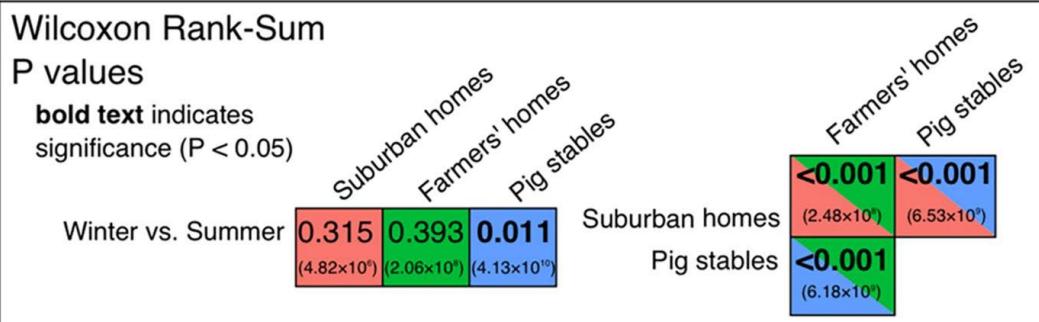
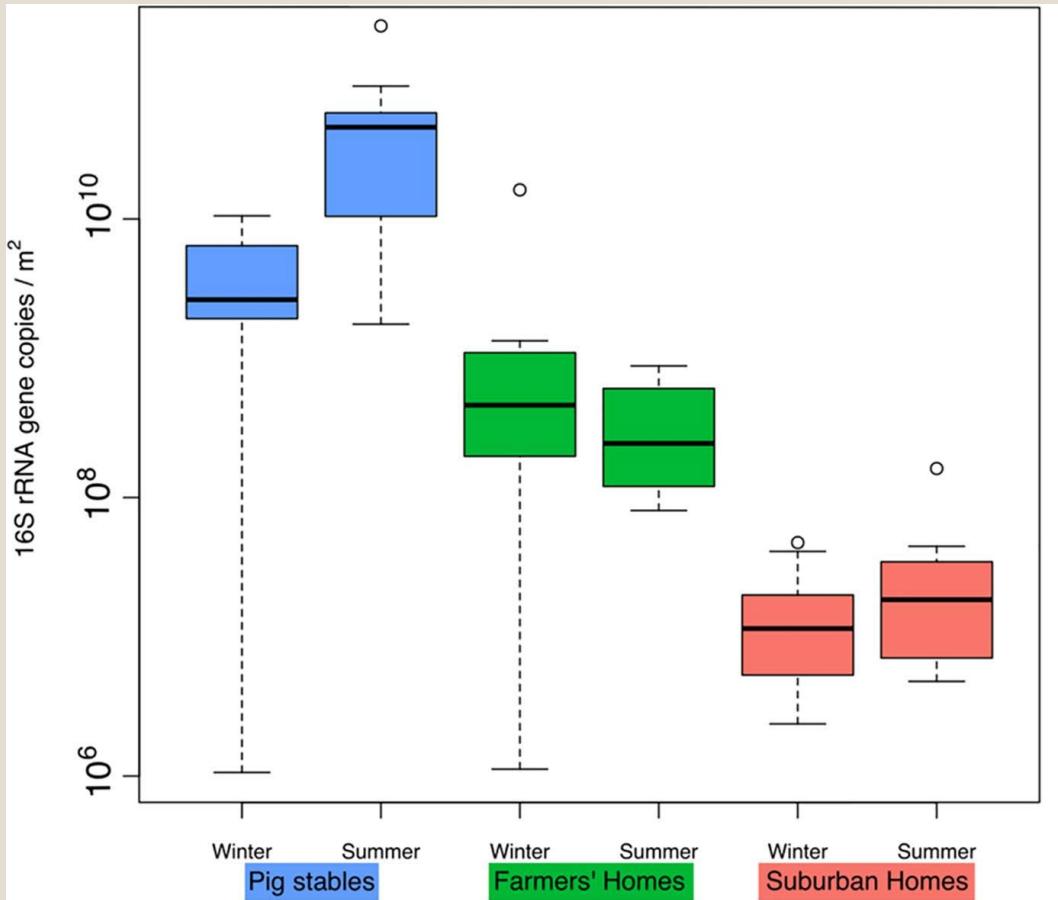
Old Friends Hypothesis

- proposed by Graham Rook in 2003
 - <http://www.grahamrook.net/OldFriends/oldfriends.html>
 - *Refined version of Hygiene Hypothesis*
- Old Friends Hypothesis: beneficial microbial exposures do not occur through infection disease (especially viral epidemics) but through the microorganisms present over the course of primate development which are adapted to host ecosystems.

Where are we losing our Old Friends?

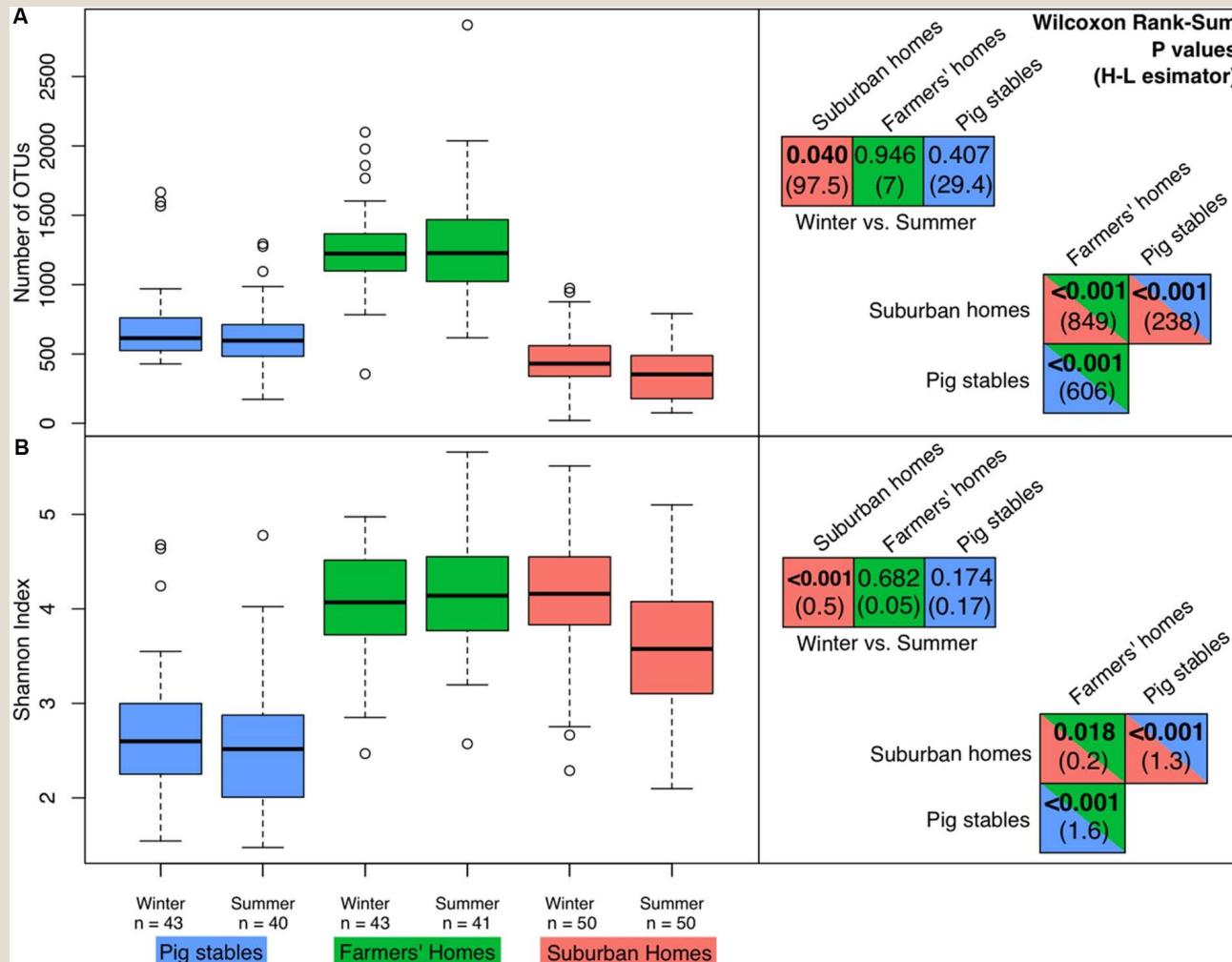
- Cesarean section
- Formula feeding
- Fewer siblings or less family contact
 - 1989 *David Strachan*
- Less exposure to animals, including pets and livestock
- Urbanization and loss natural environment
- Reviewed in Bloomfield et al. 2016

Farms have more total bacterial cells in the air



Vestergaard et al. 2018

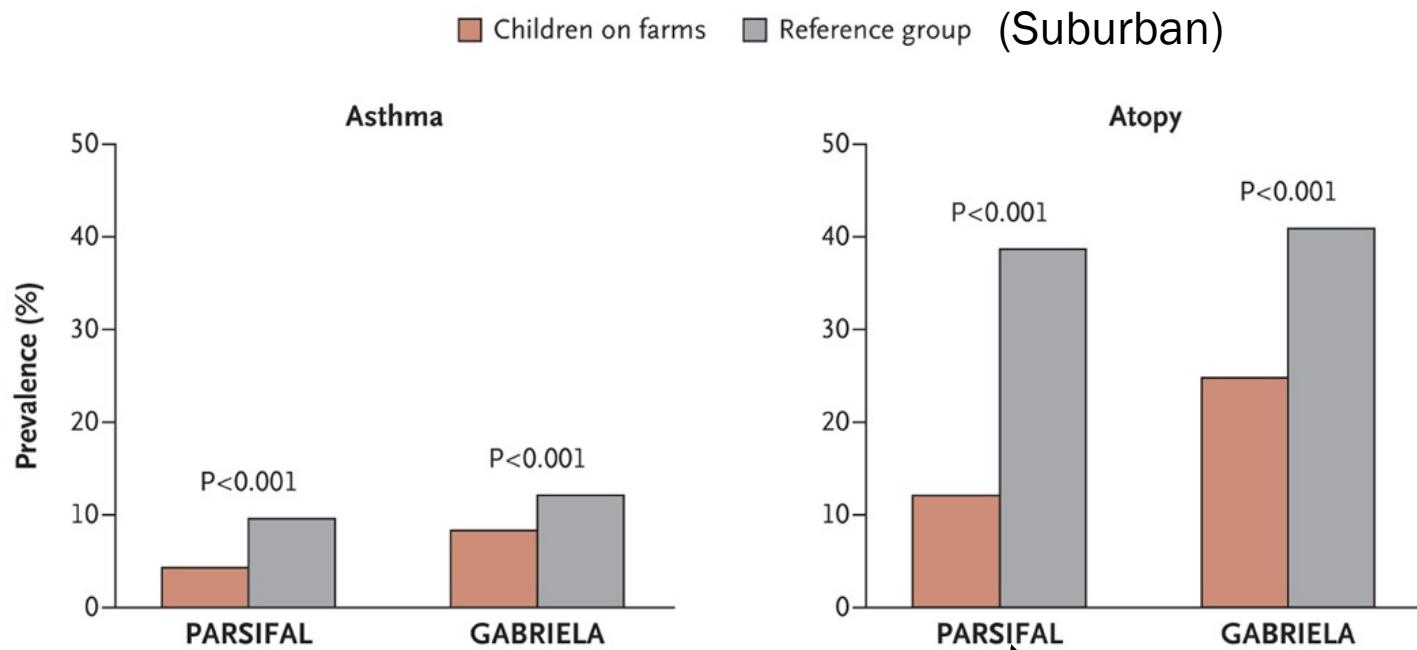
Farm homes had more bacterial diversity (mixing of outdoor bacteria and indoor/human bacteria)



Vestergaard et al. 2018

Rural vs. urban and good microbial exposure

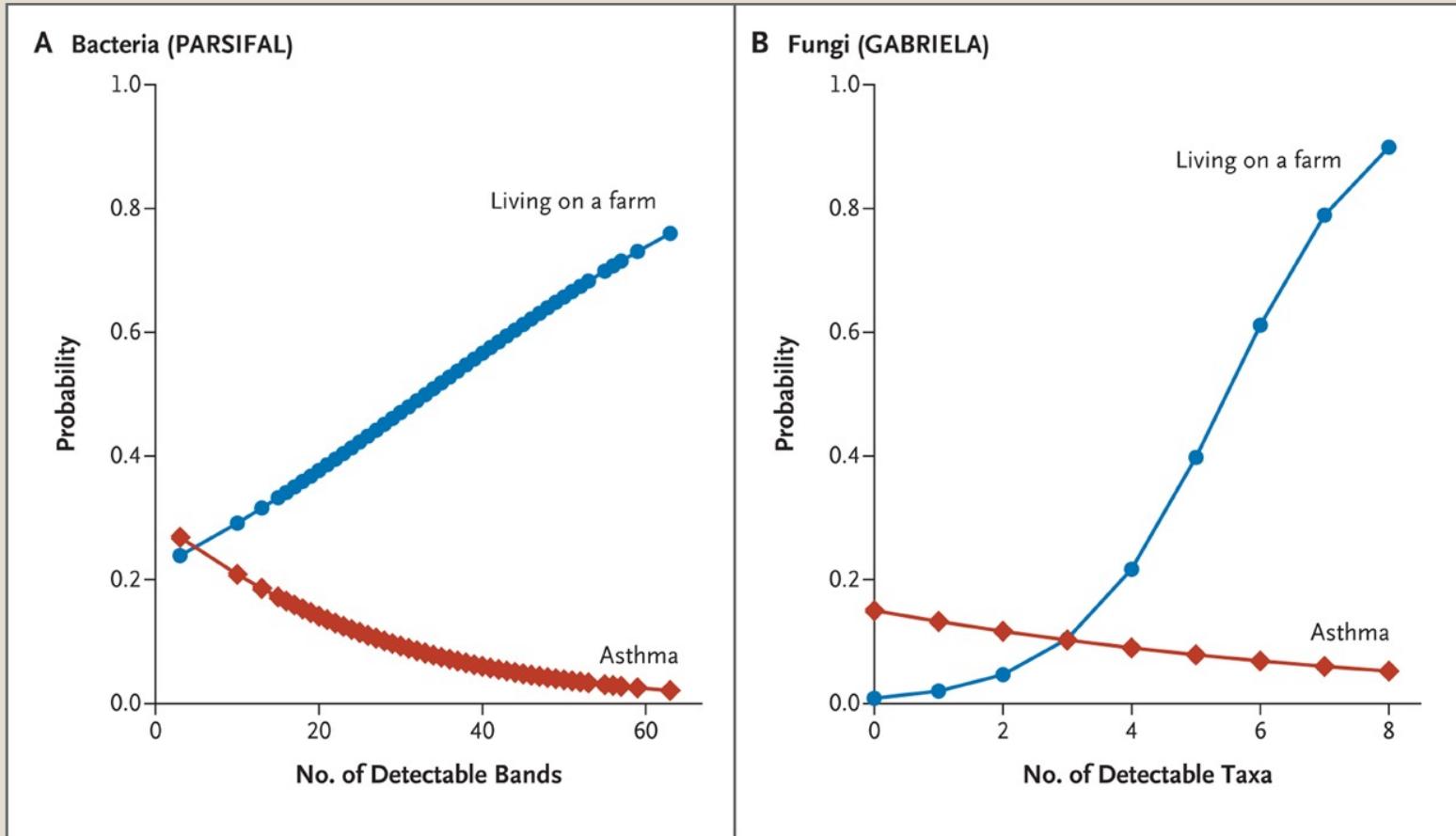
Studied 16,500 children in Germany



Ege et al. 2011

Names of the cohorts

Rural vs. urban and good microbial exposure



Ege et al. 2011

Microbial exposure not always good: Air around landfills has lots of bacteria and fungi

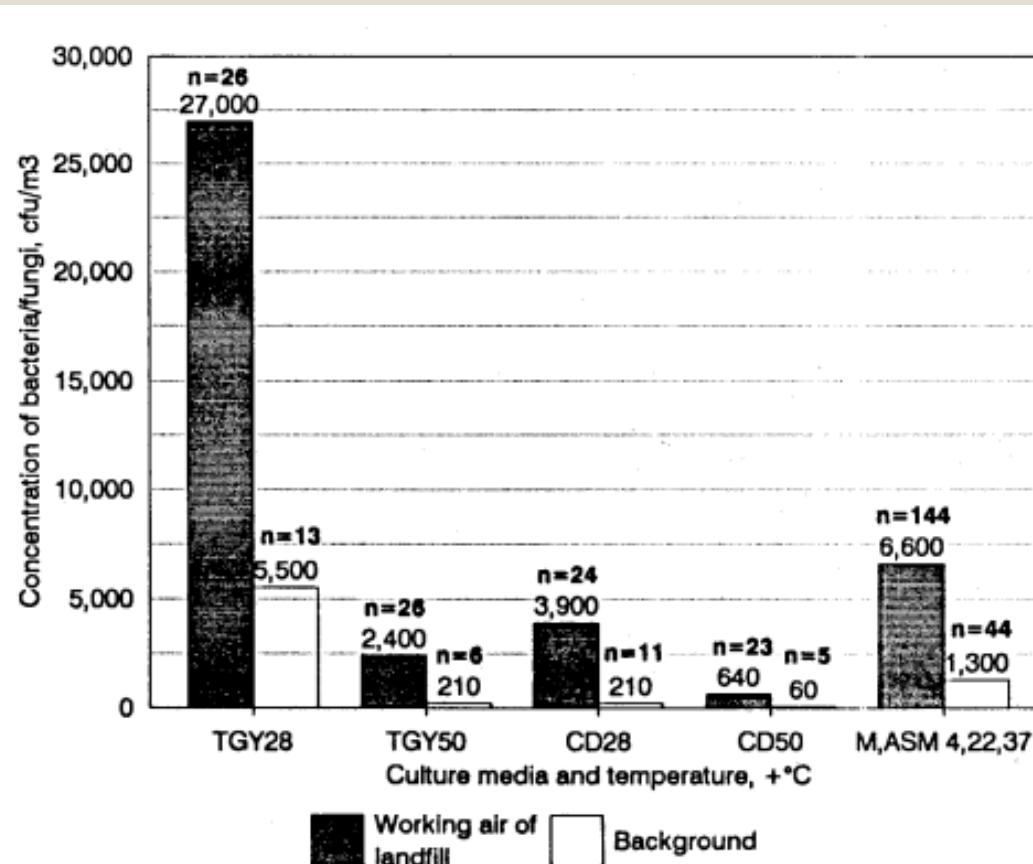


FIGURE 1. Concentrations of microbes in the working air of the landfills and in the background air.

Rahkonen et al. 1989

Children living in slums near landfills produced more breath methane

- Living in slum next to landfill = more likely to produce measurable breath methane
- Living in slum next to landfill = produced more methane

	Slum near the landfill	Slum away from the landfill	High socioeconomic group	P
Breath CH ₄ producer prevalence	53.1% (59/111) ^a	31.4% (11/35) ^b	21.9% (7/32) ^b	0.001 ²
CH ₄ in breath CH ₄ producers ppm	24 (18.0–35.0) ^a	17.0 (10.0–31.0) ^b	17 (11.0–19.0) ^b	0.007 ¹

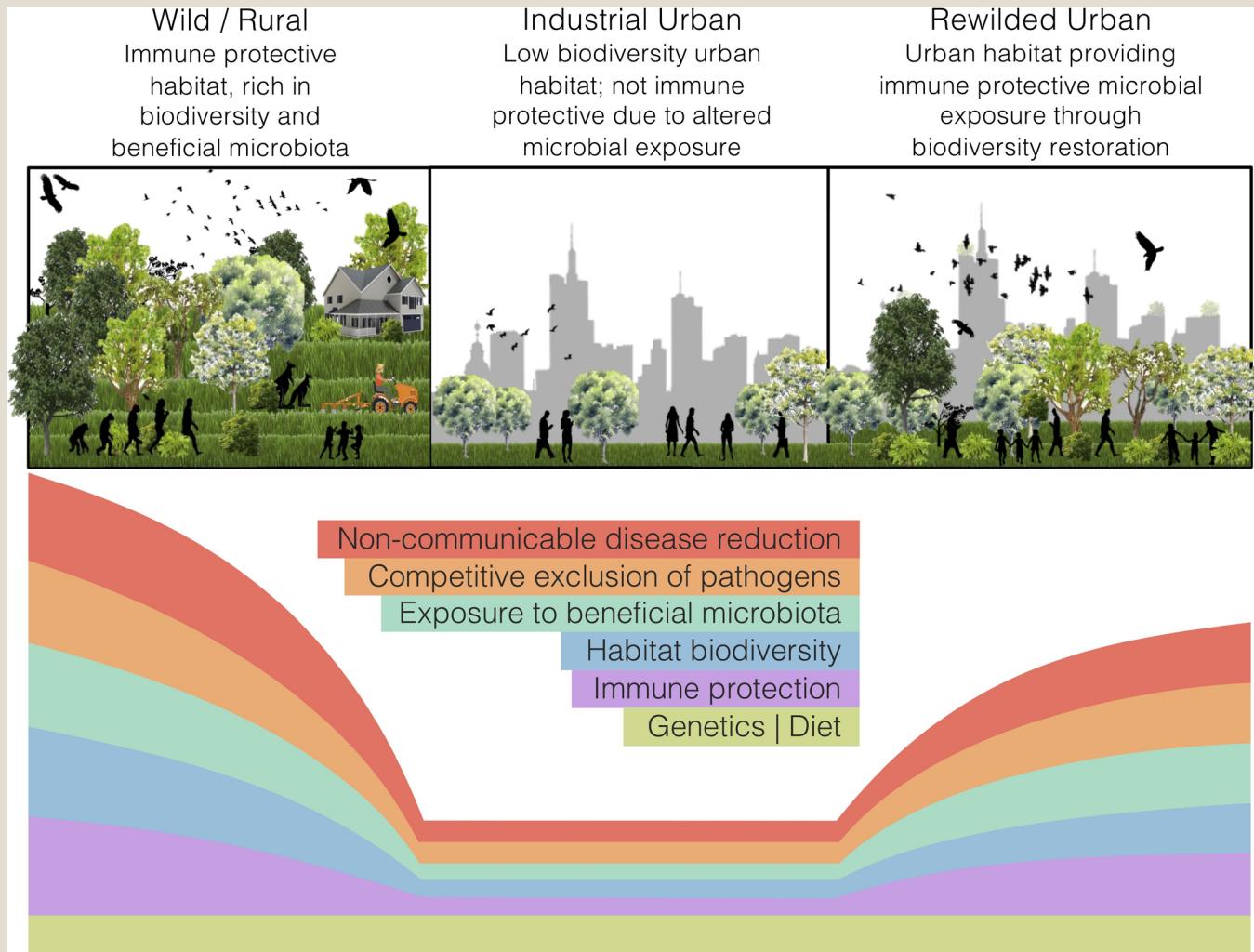
Bezerra de Araujo Filho et al. 2014

THE REWILDLING HYPOTHESIS

Using natural environments to increase microbial diversity

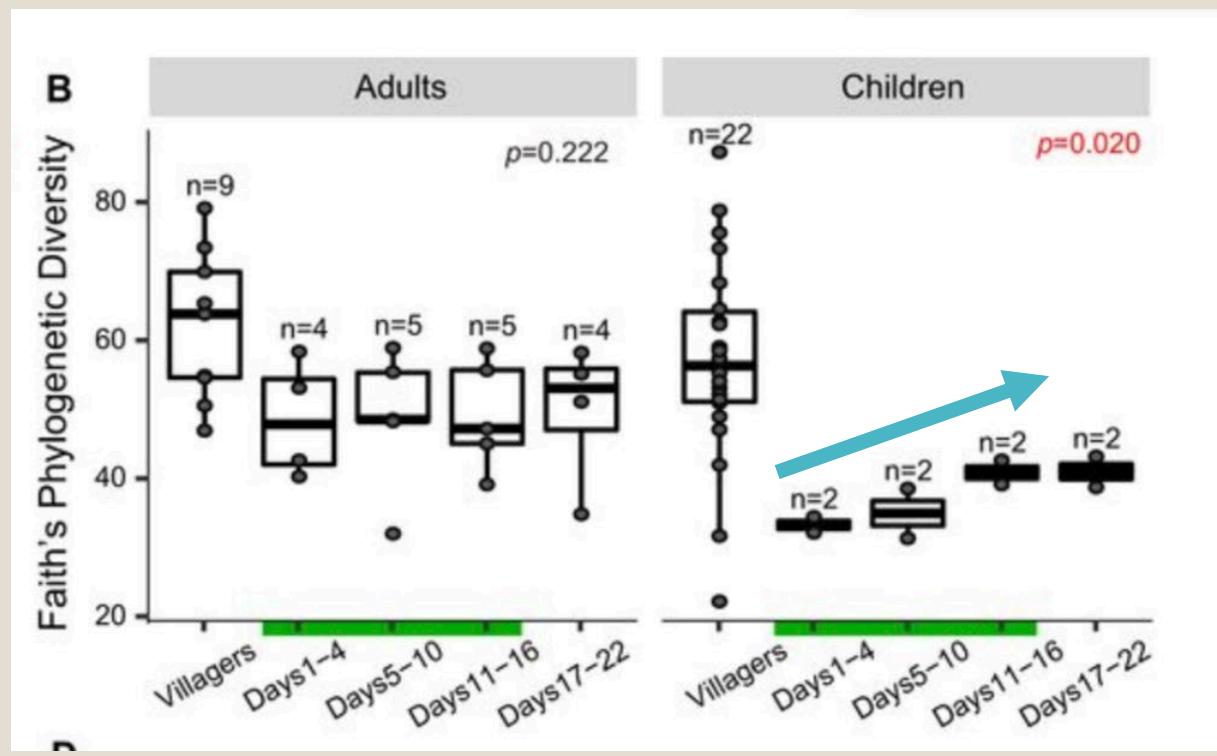
- Proposed by Mills et al. 2019 (I reviewed)
- Microbiome Rewilding Hypothesis—restoring biodiverse habitats in urban green spaces can rewild the environmental microbiome to a state that helps prevent human disease as an ecosystem service.

Microbiome Rewilding Hypothesis



Fecal microbial diversity in urban-dwelling children increased by 2-week hunter-gatherer trip

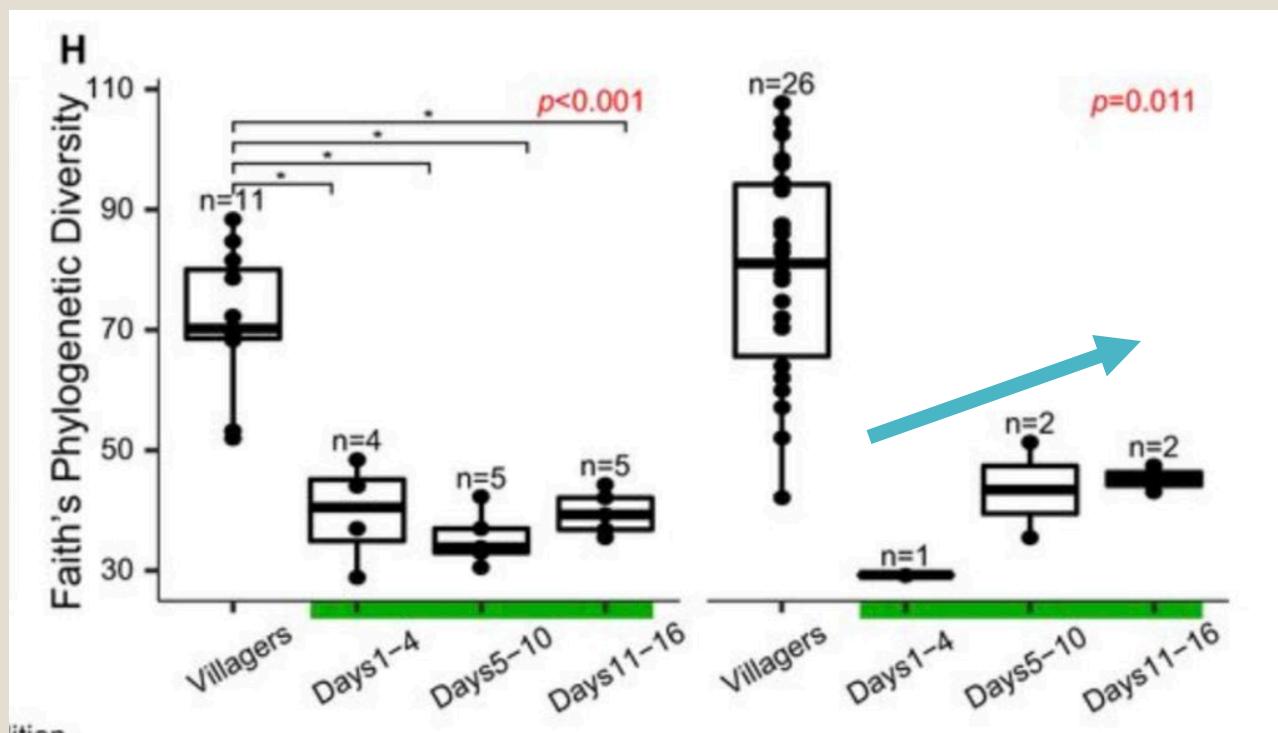
- Living in Caracas, Venezuela traveled to rain forest
- Huge limitation: only 2 city kids studied
- Trend in urban children but not urban adults



Ruggles et al. 2018

Skin microbial diversity in urban-dwelling children increased by 2-week hunter-gatherer trip

- Living in Caracas, Venezuela, traveled to rain forest
- Huge limitation: only 2 city kids studied
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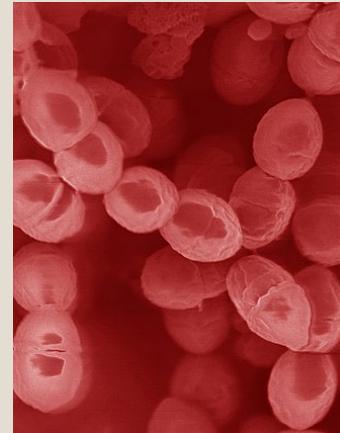
Ruggles et al. 2018

LAW & TAXONOMIC ORDER

State Microbes

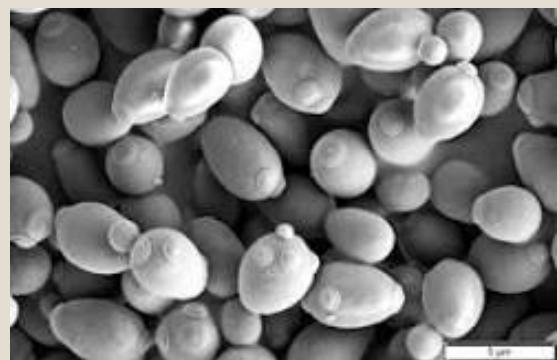
Wisconsin, 2009

- *Lactobacillus lactis*
- cheesemaking, \$3 billion industry in WI
- Failed to pass. But a state pastry was voted in



Hawai'i, failed to pass

- 2013, *Flavobacterium akiainvivens*
- 2014, *Aliivibrio fischeri*



Oregon, 2013 first to pass

- *Saccharomyces cerevisiae*
- Brewer's yeast, \$2 billion industry in OR



New Jersey, 2019

- *Streptomyces griseus*
- Soil, makes streptomycin

Images:
Wikipedia

Food safety regulations

- Historically used biological agents (microbes) in food which have no record of harm are categorized as ok to use
 - “*Generally recognized as safe*” (*GRAS*) *in the U.S.*
 - Is a legal status
 - Food business operator owns burden of proof
 - “*qualified presumption of safety*”, (*QPS*) *in the E.U.*
 - Is not a legal status
 - Governing agency owns burden of proof
 - Brodmann et al. 2017

Federal Drug Administration oversight

“Pre-market System”

- Products that are: “food additive”, “new drug”, “biological product”
 - *Supplier/maker is responsible for proving it's SAFE and EFFECTIVE*

“Postmarket” system

- *Manufacturers can put products on the market WITHOUT full approval from FDA*
- *Most dietary supplements fall under this category and have not been proven SAFE and EFFECTIVE*

http://cid.oxfordjournals.org/content/46/Supplement_2/S133.full

https://wwwnc.cdc.gov/eid/article/16/11/10-0574_article



Post-market systems/Supplements

- As long as they don't cause HARM they will not be pulled from shelves
- Complaints for any FDA-regulated product can get reported to FAERS
 - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm>
- Studies have shown 80% don't contain the ingredients on their labels
 - *Contains legumes and wheat instead*
 - O'Connor, Anahad. "New York Attorney General Targets Supplements at Major Retailers." New York Times, 3 February 2015.
 - Lockwood 2011

Probiotics Guidelines

- 2001 guidelines were developed
 - *Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics*
-
1. *identification of the genus and species of the probiotic*
 1. combination of phenotypic and genotypic tests as clinical evidence suggesting that the health benefits of probiotics may be strain specific
 2. *in vitro testing to delineate the mechanism of the probiotic effect*
 3. *substantiation of the clinical health benefit of probiotic agents with *human trials**

Precedent to legislating microbes

■ Health

- *Knowingly spreading a sexually transmitted disease can be claimed as ‘battery’ for civil claims in all states*
- *For criminal claims in some states*
- *Usually for incurable diseases*
- *Louis A. Alexander, Liability in Tort for the Sexual Transmission of Disease Genital Herpes and the Law , 70 Cornell L. Rev. 101 (1984) Available at:
<http://scholarship.law.cornell.edu/clr/vol70/iss1/5>*

The right to bodily integrity

- From Wikipedia, apparently the most accessible site for legal information...
- “The United States Constitution does not contain any specific provisions regarding the rights one has with respect to his or her physical body or the specific extent to which the state can act upon bodies.^[12] However, the U.S. Supreme Court has upheld right to privacy, which, as articulated by Julie Lane, often protects rights to bodily integrity. In Griswold v. Connecticut (1965) the Court supported women's rights to obtain birth control (and thus, retain reproductive autonomy) without marital consent. Similarly, a woman's right to privacy in obtaining abortions was protected by Roe v. Wade (1973). In McFall v. Shimp (1978), a Pennsylvania court ruled that a person cannot be forced to donate bone marrow, even if such a donation would save another person's life.
- Conversely, the Supreme Court has also protected the right of governmental entities to infringe upon bodily integrity. Examples include laws prohibiting the use of drugs, laws prohibiting euthanasia, laws requiring the use of seatbelts and helmets, strip searches of prisoners, and forced blood tests.^[13]
- https://en.wikipedia.org/wiki/Bodily_integrity

Thoughts for next discussion

- Are microbes part of the human body?
- Do we have a right to microbes?
- Does the physical wellbeing of someone include microbial wellbeing?

HOMEWORK

Homework

- **Reading (pick 1):**
 - *Clayton_2016_captivity primate microbiome*
 - *Moeller_2014_human gut microbiome*
 - *Scudellari_ 2017_cleaning up hygiene hypothesis*
 - *8_Morar_2019_concept of microbiome*
- **Assignment (12 pts):** Write a minimum 1-page, single-spaced essay on the importance of microbes and gut health and why this is a public health/social equity issue.
 - *Due 7/8.*
 - *Include > 3 citations, and line numbers.*
 - *You may choose any relevant, credible scientific article, review, or reference.*

Citations

Bach 2002 <https://www.ncbi.nlm.nih.gov/pubmed/12239261?dopt=Abstract>

Benn et al. 2004

https://www.bmjjournals.org/content/328/7450/1223?ijkey=08826f54f581ff9ec55fae454e5a7b33d1466d2f&keytype2=tf_ipsecsha

Brodmann et al. 2017 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5601064/>

Clayton et al. 2018 <https://www.nature.com/articles/s41598-018-29277-x>

Ege et al. 2011 <https://www.nejm.org/doi/full/10.1056/NEJMoa1007302>

Lockwood 2011 <https://onlinelibrary.wiley.com/doi/full/10.1111/j.2042-7158.2010.01159.x>

McKenzie et al. 2017 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5978021/>

Mills et al. 2019 <https://www.frontiersin.org/articles/10.3389/fmicb.2019.00550/full>

Moeller et al. 2014 <https://www.pnas.org/content/111/46/16431>

Reese and Dunn, 2018 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6069118/>

Ruggles et al. 2018 <https://msphere.asm.org/content/3/4/e00193-18>

Scudellari 2014 <http://www.pnas.org/content/114/7/1433#ref-1>

Valdes et al. 2018 <https://www.bmjjournals.org/content/361/bmj.k2179>

Van den Biggelaar et al. 2000 <https://www.ncbi.nlm.nih.gov/pubmed/11095260?dopt=Abstract>

Vestergaard et al. 2018 <https://www.ncbi.nlm.nih.gov/pubmed/29765370>