Microbes, milk, and the making of a human: Rethinking early life through the gut

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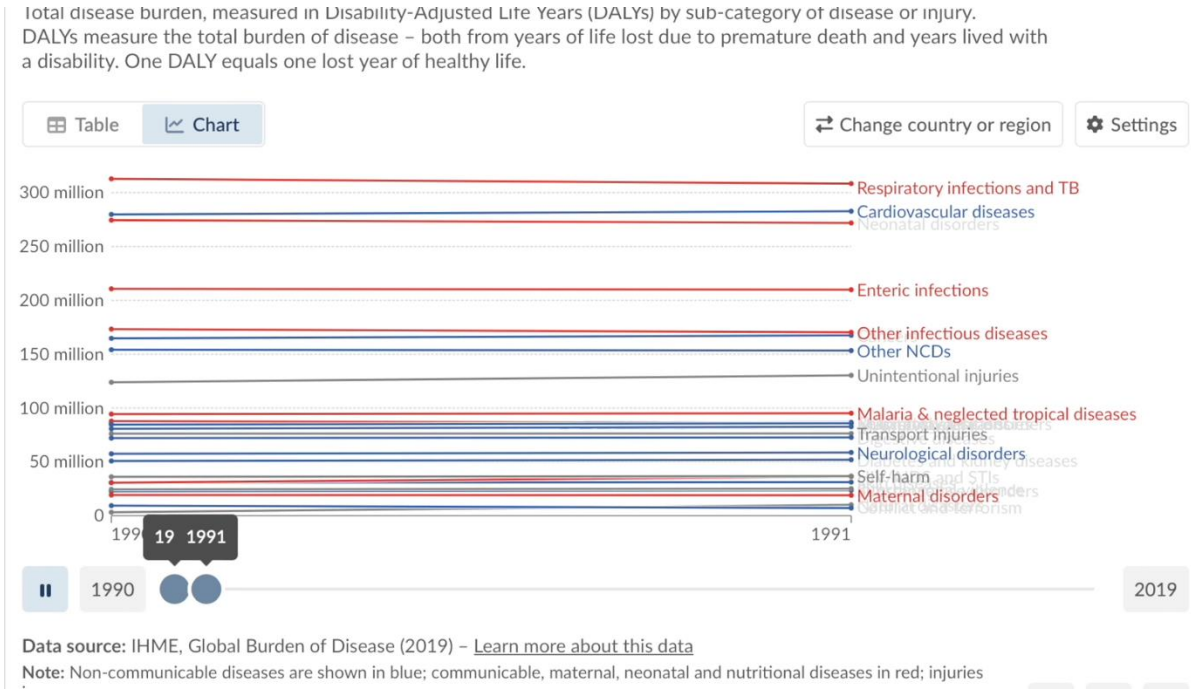
IMPERIAL

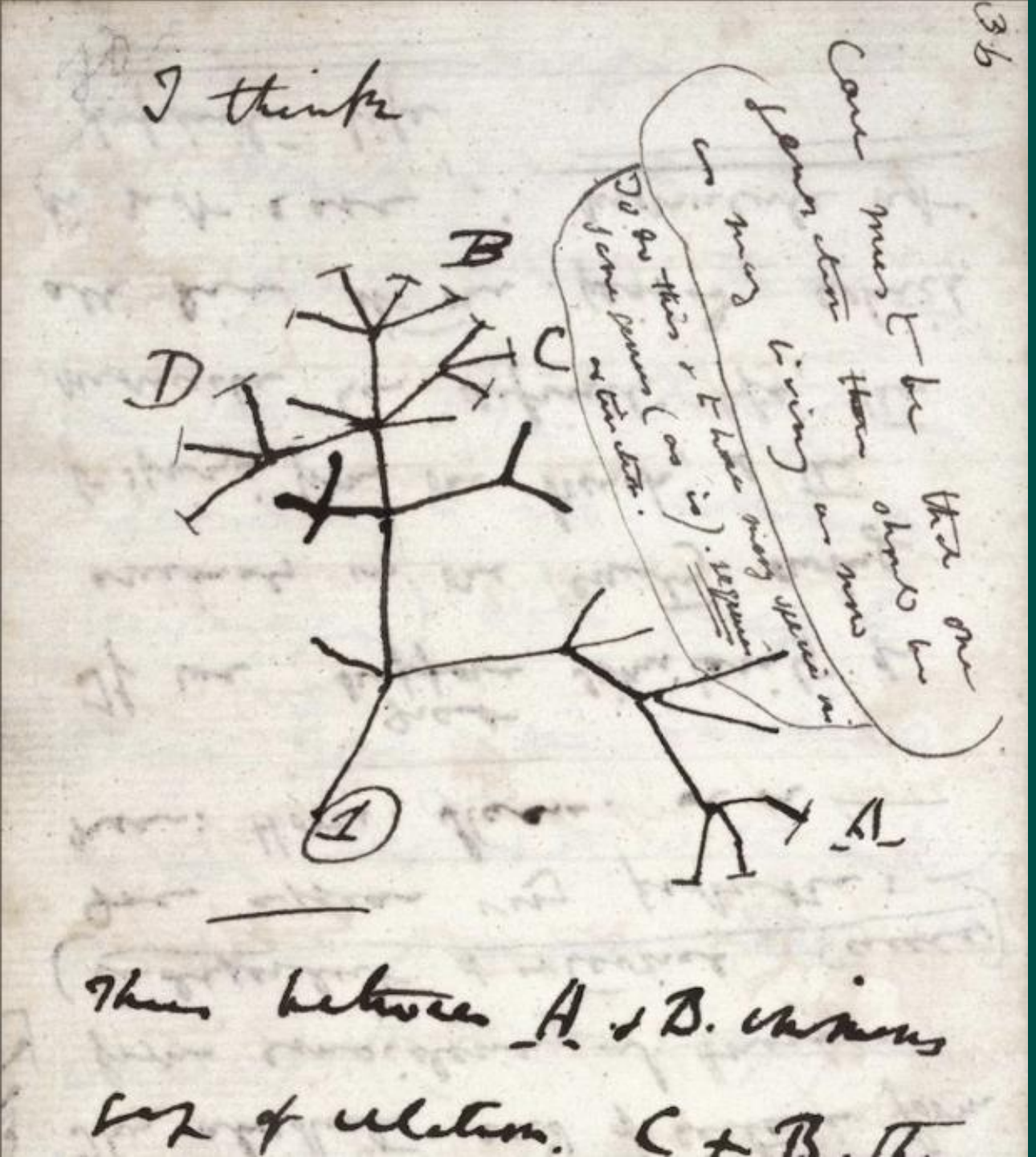
The Baby Friendly Initiative
UNITED KINGDOM
unicef

We *are* living longer: We are *not* living happier



A microbiome

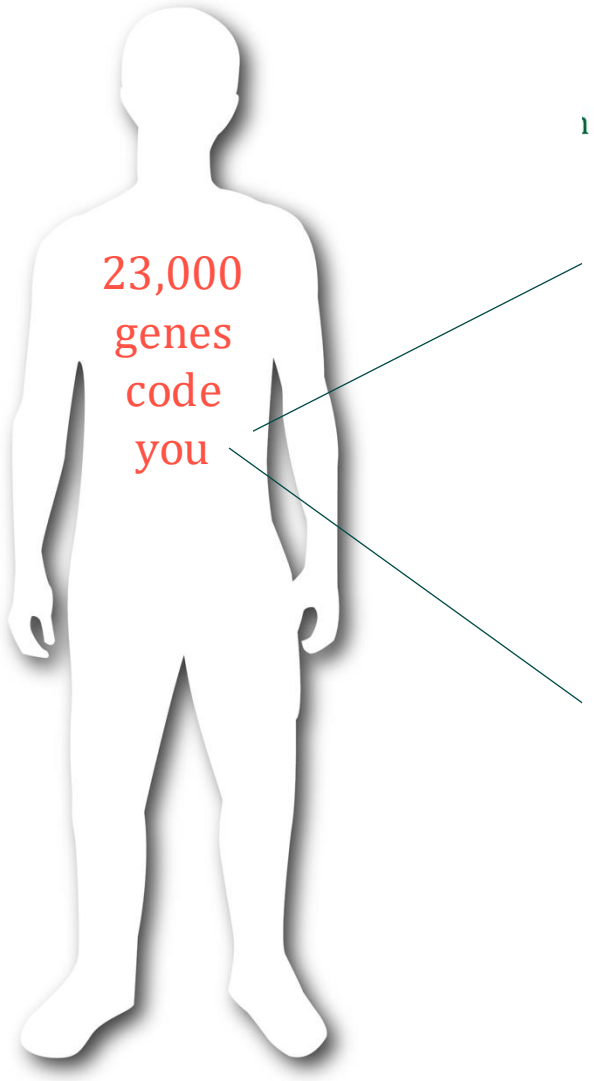
Characterisation of an entire habitat including all microbes, their genomes, and surrounding environmental conditions



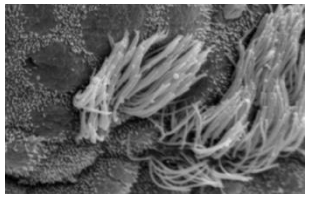
The tree of life

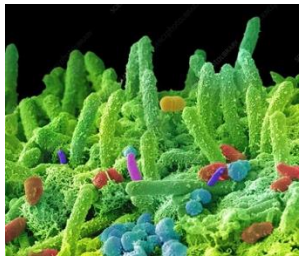
Is dominated by single celled organisms (prokaryotes)

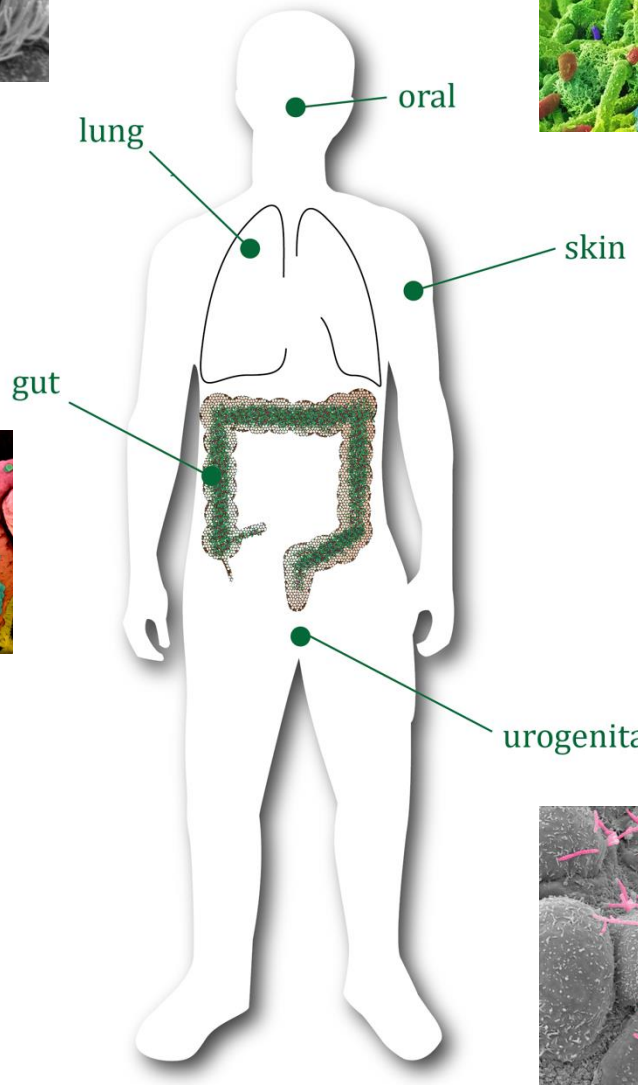
We are 0.001% human at genomic level: YOU are a superorganism

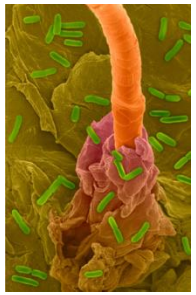


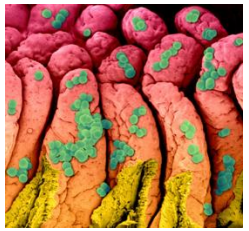
232 million microbial genes

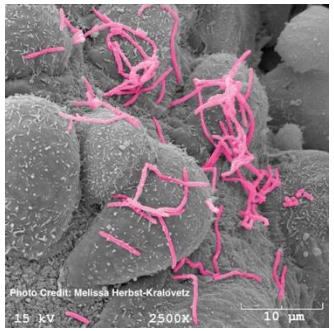












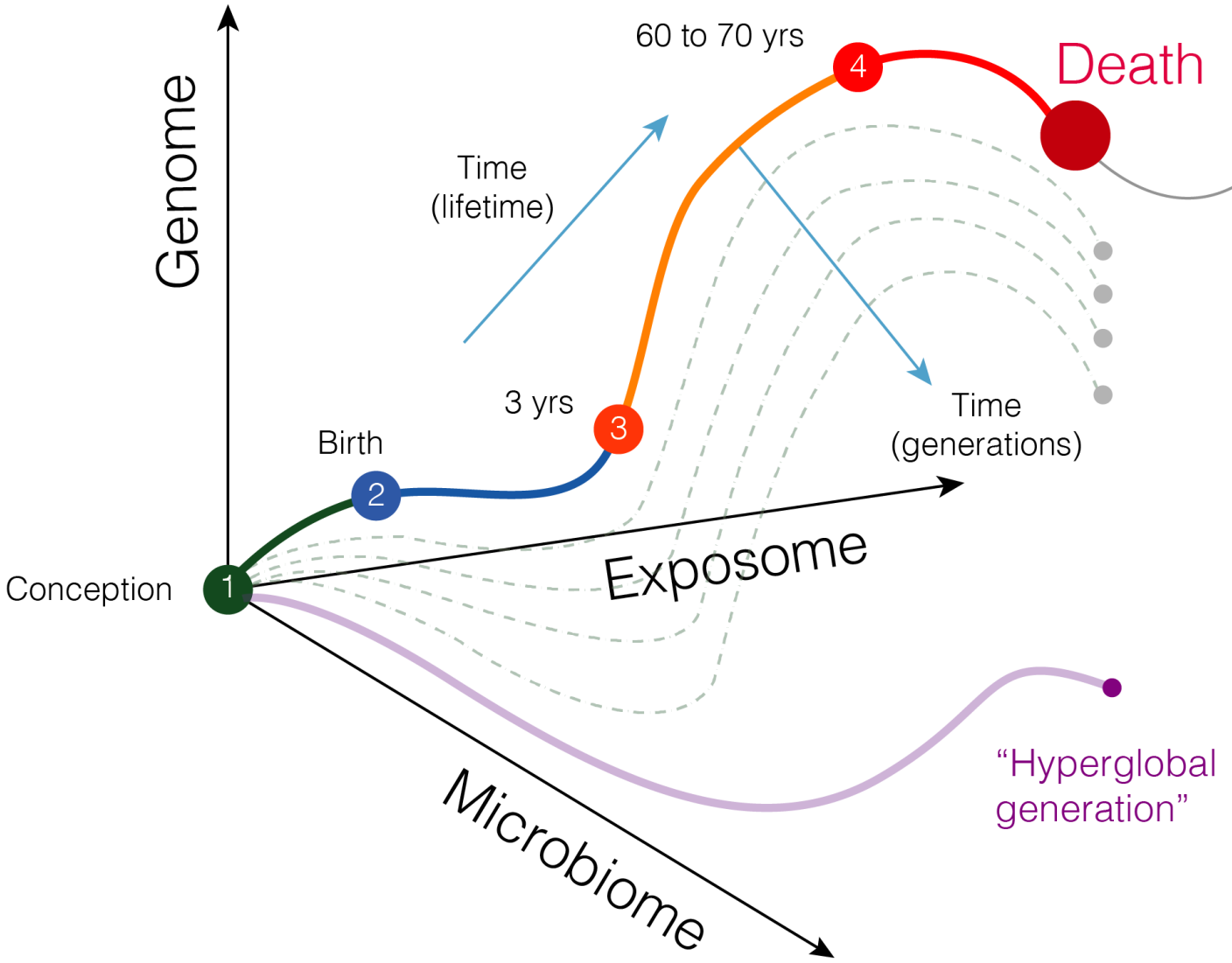
The human microbiome is MASSIVE and UNMAPED

1Kg of microbes in the gut

100 trillion bacteria

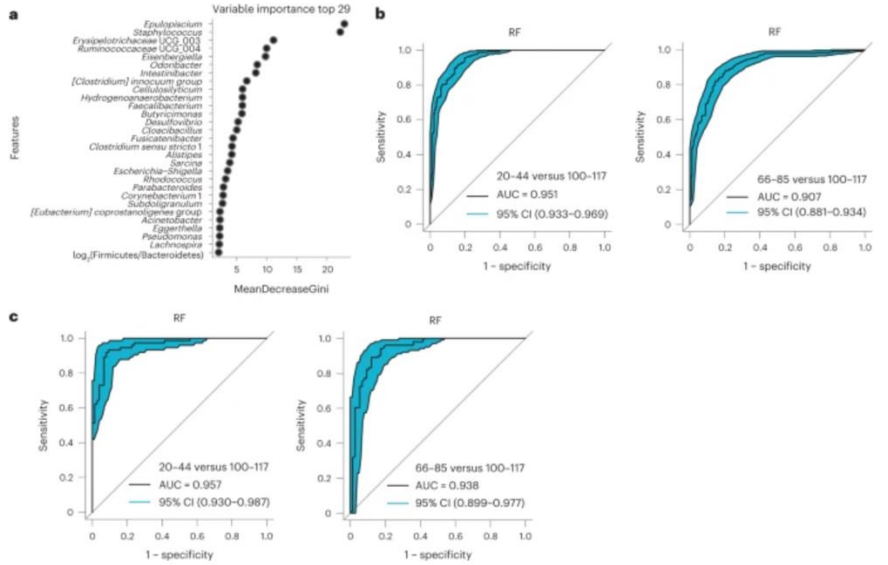
Same number of microbes as cells in the human body

The meta hypothesis: Gene-environment-microbiome (GEM) interactions



necrobiome

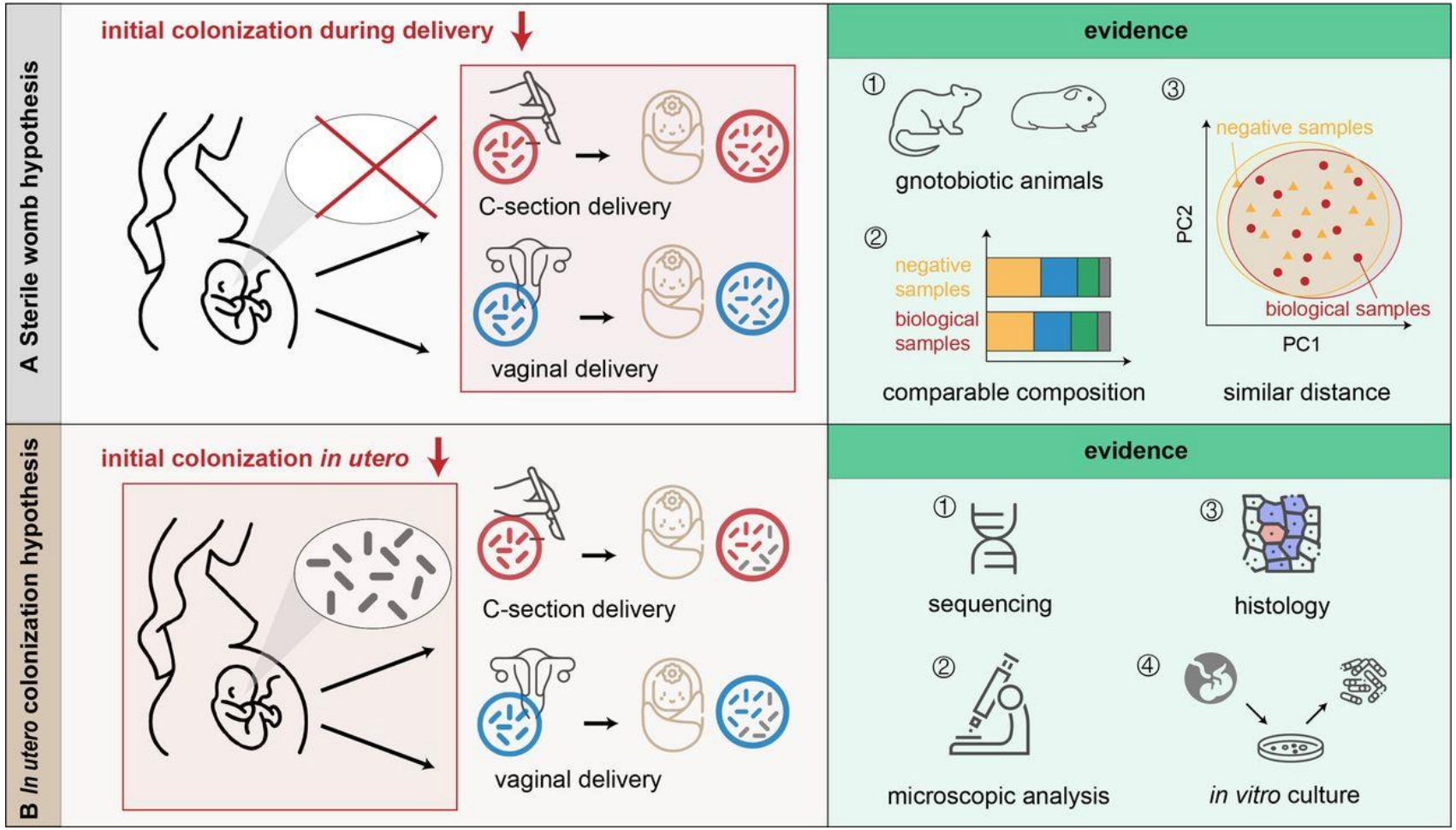
Long-lived individuals show a unique aging pattern of the gut microbiome



centenarians displayed youth-associated features in the gut microbiome characterized by an over-representation of a *Bacteroides*-dominated enterotype

https://doi.org/10.1038/s43587-023-00389-y

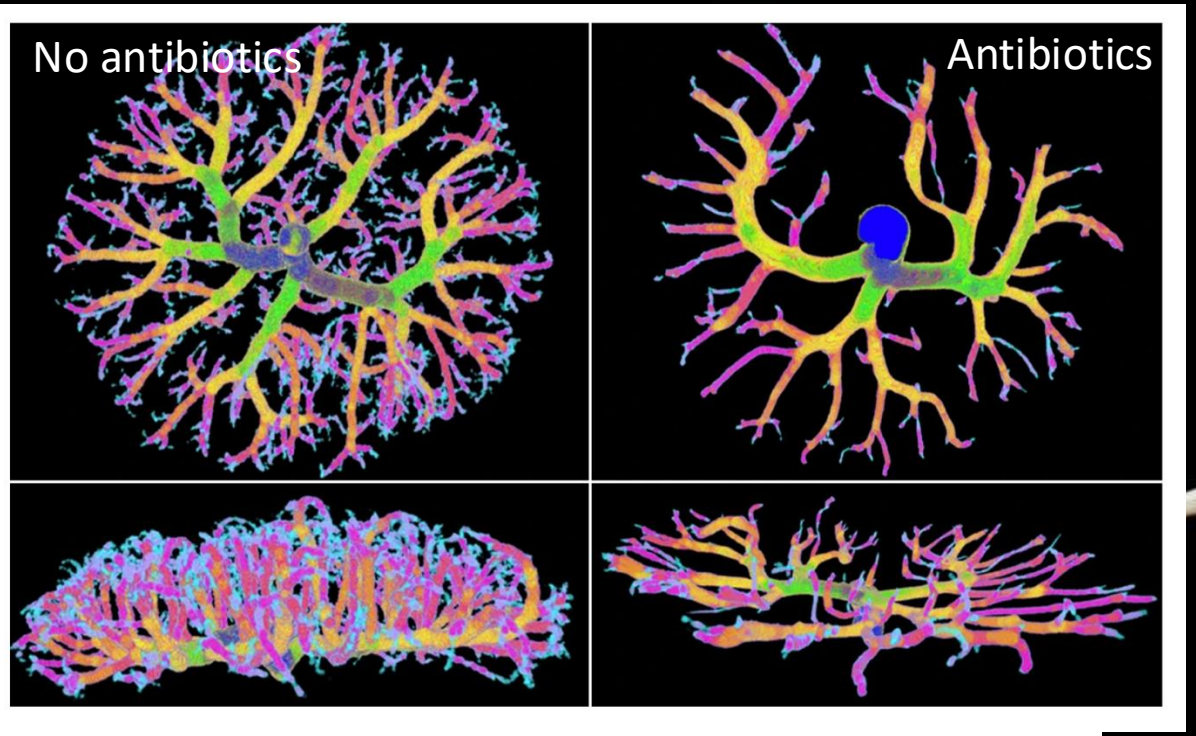
Challenging dogma in human colonisation



- Fetal organs show diverse bacterial genera that can be cultured and propagated

Cell DOI:https://doi.org/10.1016/j.cell.2021.04.039

Placenta does not develop normally without a healthy microbiome



doi: https://doi.org/10.1038/d41586-023-03105-3

Maternal microbial metabolites protect the infant against obesity NCDs and emotional development

DOI: 10.1126/science.aaw8429

Maternal obesity and dietary-microbiome interactions shape CRC risk in offspring

Gut 2022;71:1332-1339

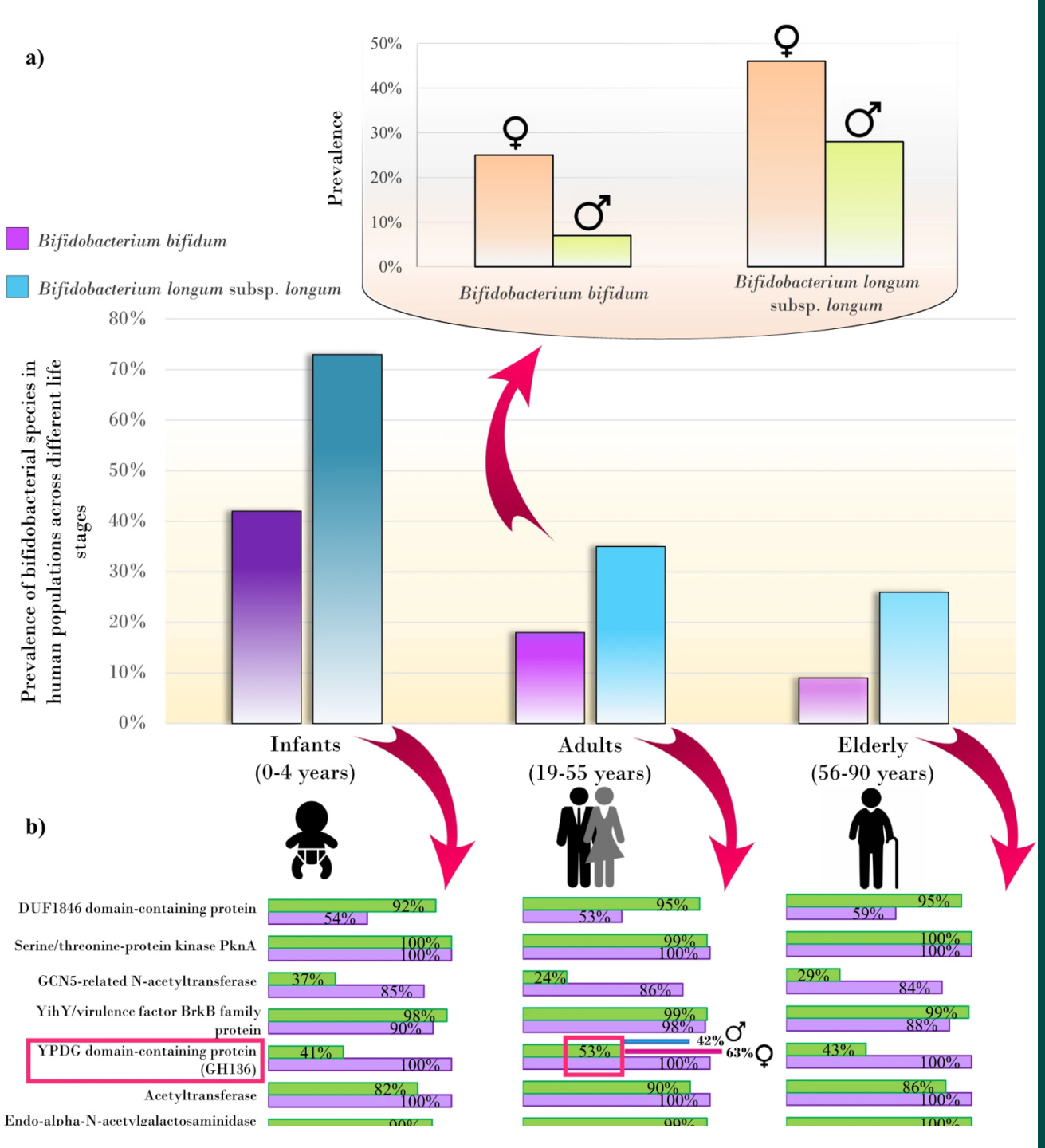
SCI AM

MONET MOUTRIE

Our immune system is not a cold war defense system. It is a collective memory educated by the microbiome.

Orchestral signaling

The symphony our children listen to is changing

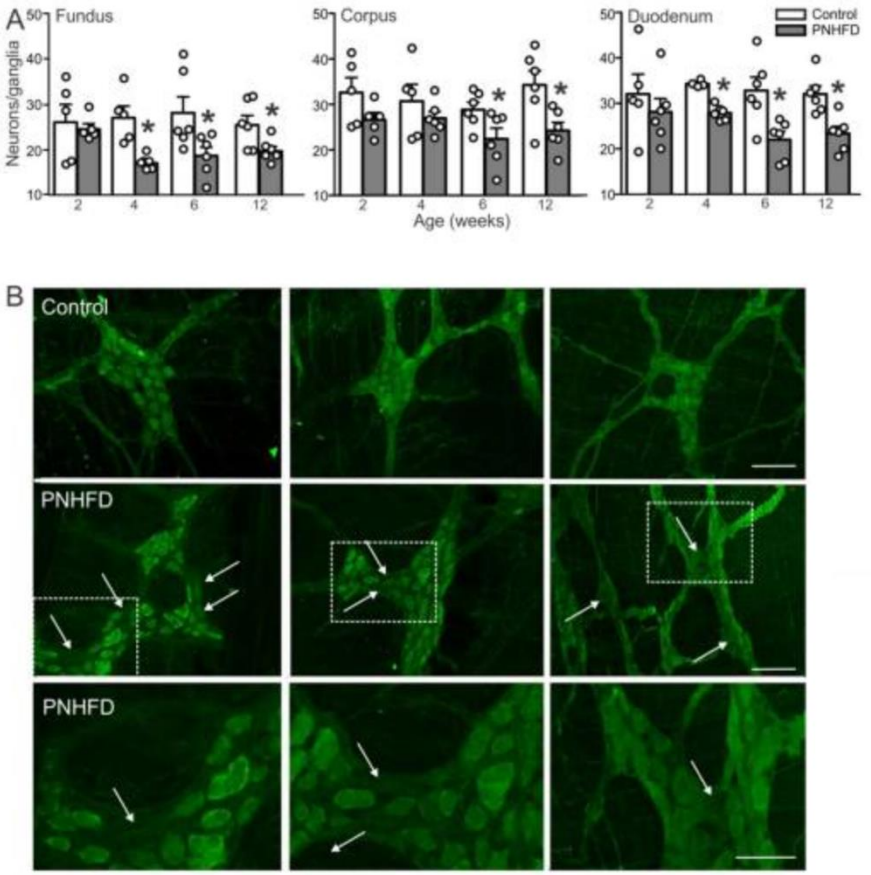


The male and female microbiome is different at all body sites for our whole lives

https://doi.org/10.1038/s41467-023-39931-2

A high fat diet in mothers influences intestinal microbiome and gut function in offspring

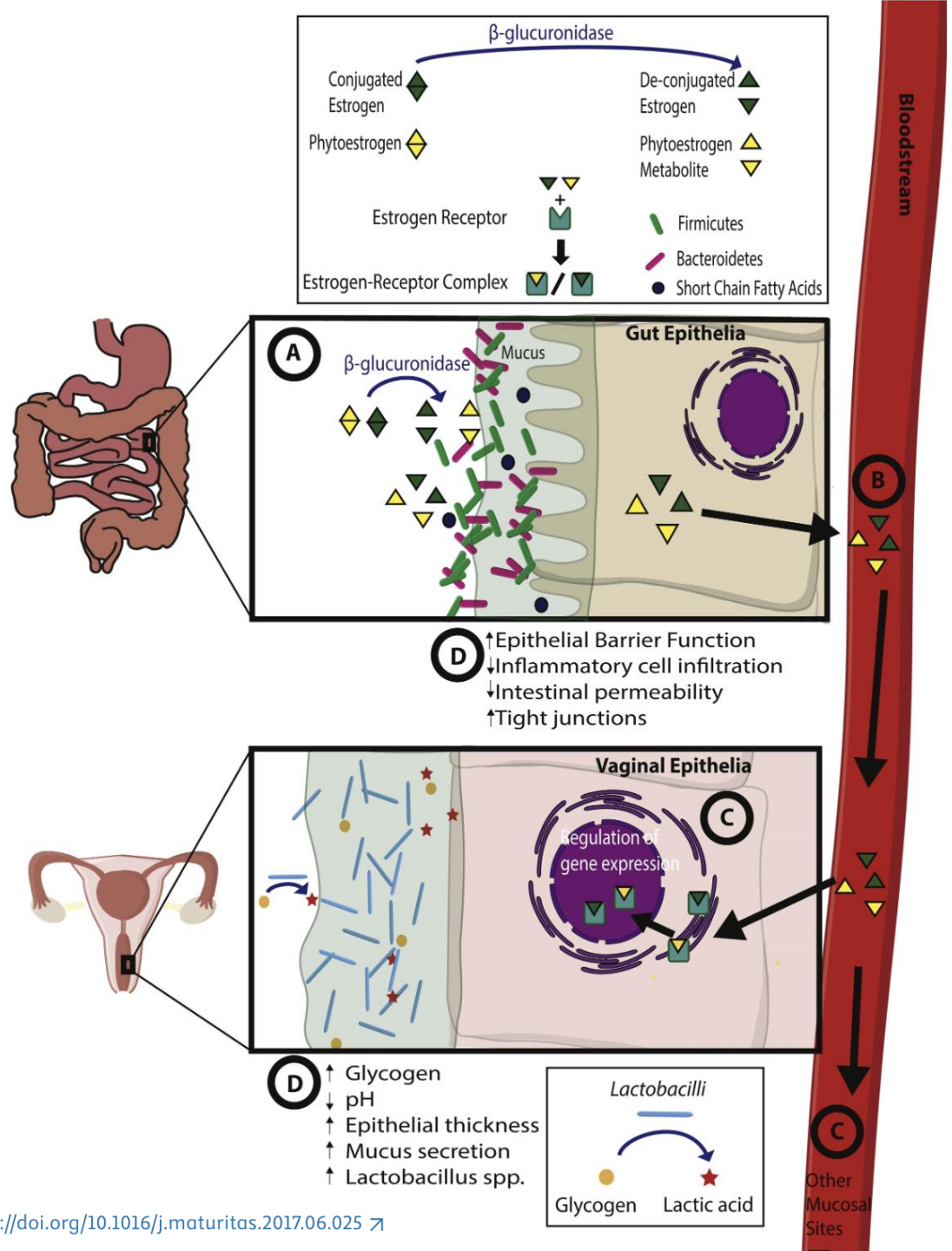
- Dietary fat shapes commensal microbial communities in primates
- A high-fat maternal or postnatal diet, but not obesity per se, structures the offspring's intestinal microbiome
- This in turn modifies intestinal motility in the baby because it modifies the development of the second brain



Number of neurons per ganglia in the fundus (left), corpus (middle) and duodenum (right). PGP-IR neurons per ganglia were significant decreased by 4 weeks of age in the fundus and duodenum, and by 6 weeks of age in the corpus.

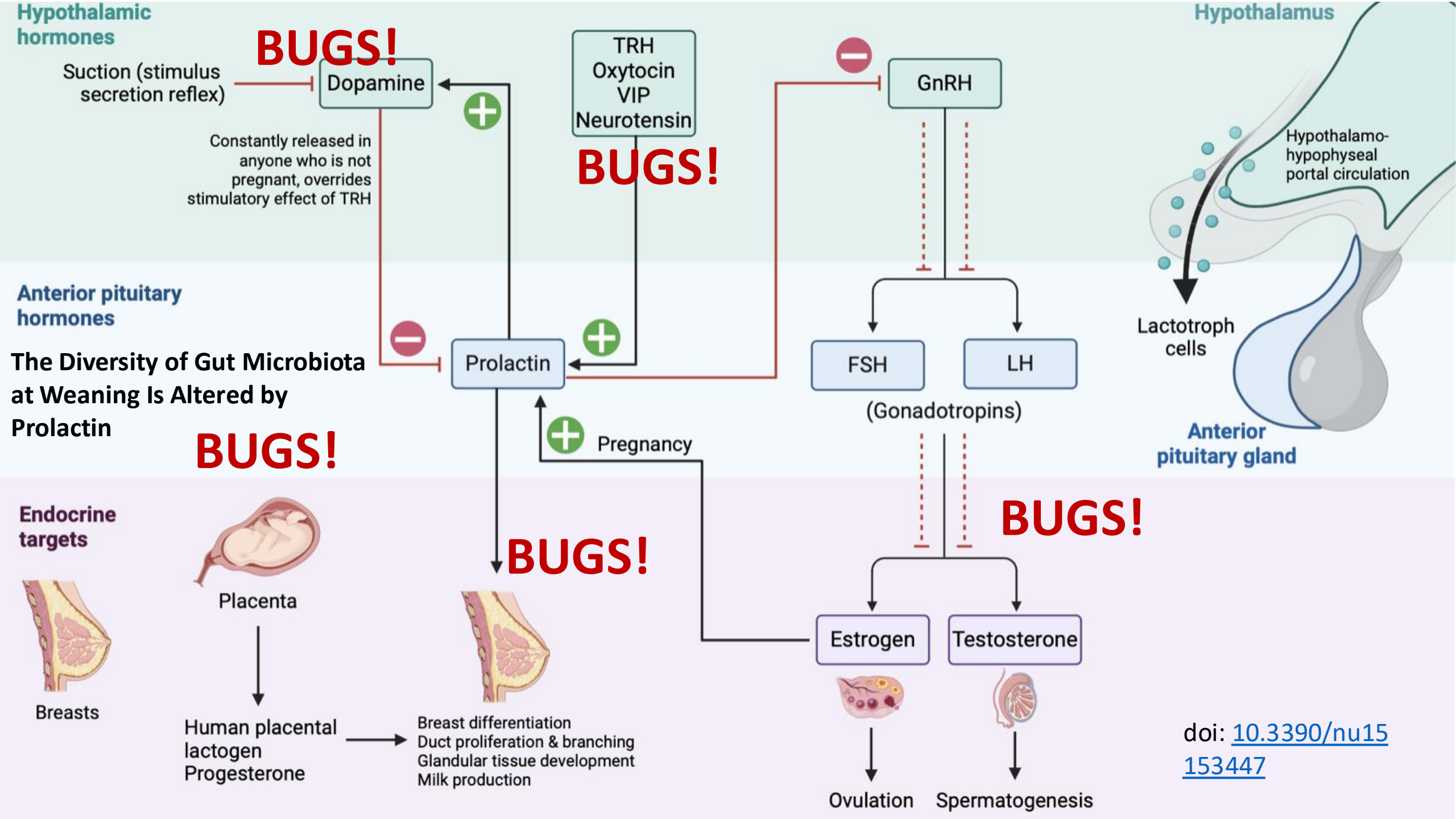
Nat Commun. ; 5: 3889. doi:10.1038/ncomms4889.

Neuroscience. 2018 Nov 21; 393: 369–380.
doi: 10.1016/j.neuroscience.2018.09.033



https://doi.org/10.1016/j.maturitas.2017.06.025 ↗

The "oestrobolome" regulates the amount of free oestrogen in our bodies



The Diversity of Gut Microbiota at Weaning Is Altered by Prolactin

BUGS!

BUGS!

doi: 10.3390/nu15153447

Magical Milk – what we know (it does a lot)

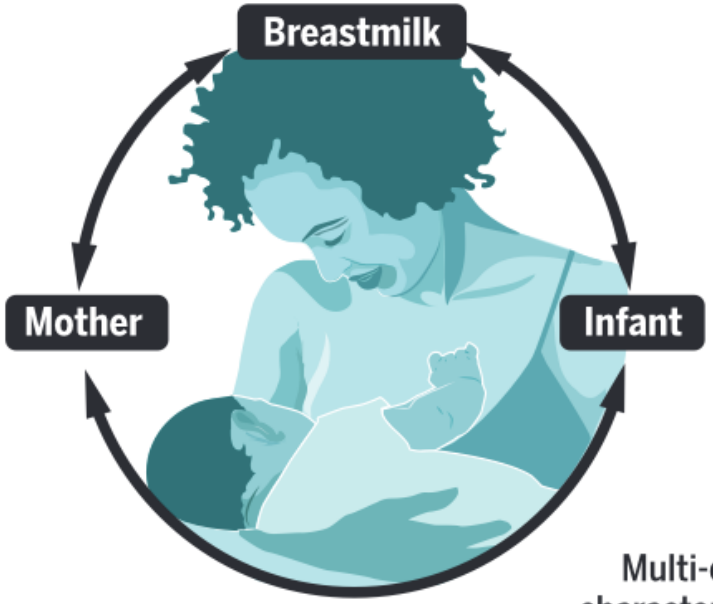
Milk Component	Key Functions	Main Targets / Pathways
HMOs (Human Milk Oligosaccharides)	Feed Bifidobacterium; block pathogens; modulate immunity & gut barrier	Microbiota, immunity; NF-κB, TLR, MAPK, SCFA & tryptophan–serotonin pathways
Lipids & Fatty Acids (incl. DHA, ARA)	Neurodevelopment; immune regulation; metabolic signaling	Neurodevelopment, immunity; PPAR-γ, NF-κB; intracellular lipid-signaling pathways
Bioactive Peptides (lactoferrin, casein peptides, α-lactalbumin)	Antimicrobial defense; iron regulation; gut/immune modulation; serotonin production	Immunity, gut signaling; LRP1, TLR4, TGF-β, opioid receptors; serotonin pathways
MFGM Components	Support brain development; shape microbiota; block pathogens	Neurodevelopment, microbiota; PPAR-γ, NF-κB; EGFR/MAPK, Wnt/β-catenin
Immunoglobulins (IgA, IgG, IgM)	Passive immunity; coat commensals; reduce inflammation	Immune cells; TGF-β & JAK/STAT pathways
MicroRNAs	Regulate gene expression; metabolic programming	Immune & epithelial cells; RNA interference; PI3K/Akt, mTOR
Hormones & Growth Factors (Leptin, Adiponectin, EGF, IGF-1)	Appetite & energy regulation; intestinal maturation; tissue growth	Metabolic & endocrine systems; JAK/STAT, AMPK, EGFR/MAPK, IGF-1–PI3K/Akt
Polyamines	Enhance intestinal growth & homeostasis	Cellular growth pathways (polyamine biosynthesis)
Microbial Metabolism of Bile Acids	Lipid digestion; energy metabolism; microbiota diversity	Microbiota & metabolic regulation; FXR & TGR5 pathways

10^3–10^6 **CFU / mL** of healthy milk

New born babies ingest 10^5–10^9 **bacteria/day**

Coadapting triad

Socioeconomic, cultural, behavioral, and environmental context



Breastmilk components

Gut microbiota components

Multi-omic characterization of infant and maternal physiology

Emerging computational methods

Mechanisms underlying dynamic operations of triad

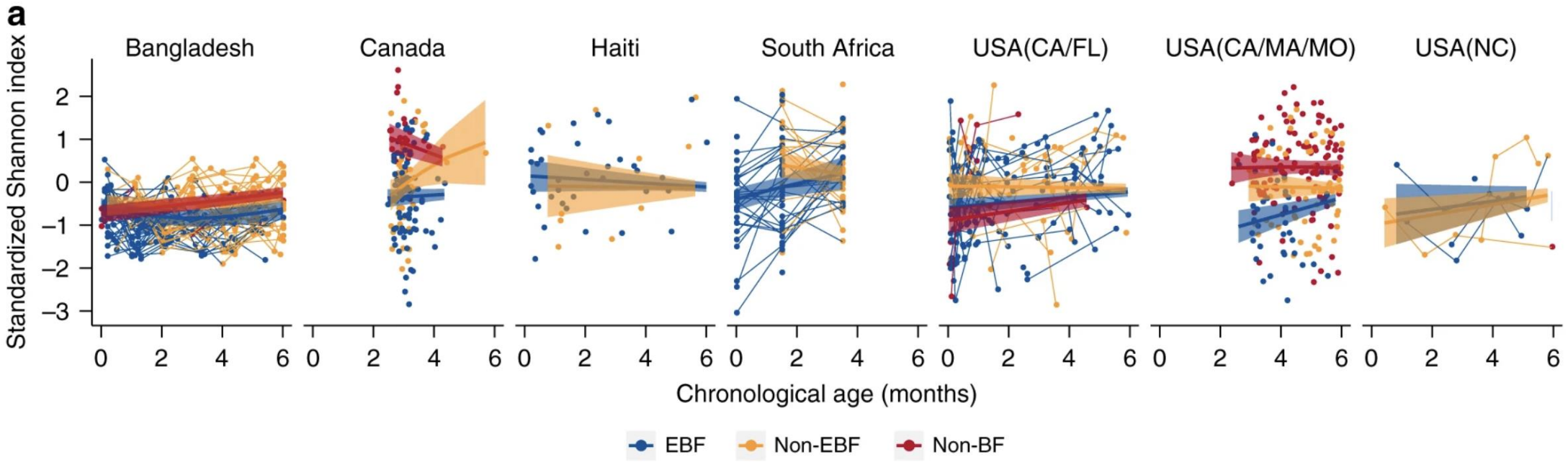
Maternal and infant health status and outcomes: definitions, recommended practices, new therapeutic concepts

https://doi.org/10.1038/s41598-017-13270-x

Home sterilization of collection kits may minimize changes to the HM microbiota during expression.

https://doi.org/10.1186/s12967-025-06967-5

It's a universal observation that breast feeding alters diversity in the infant gut

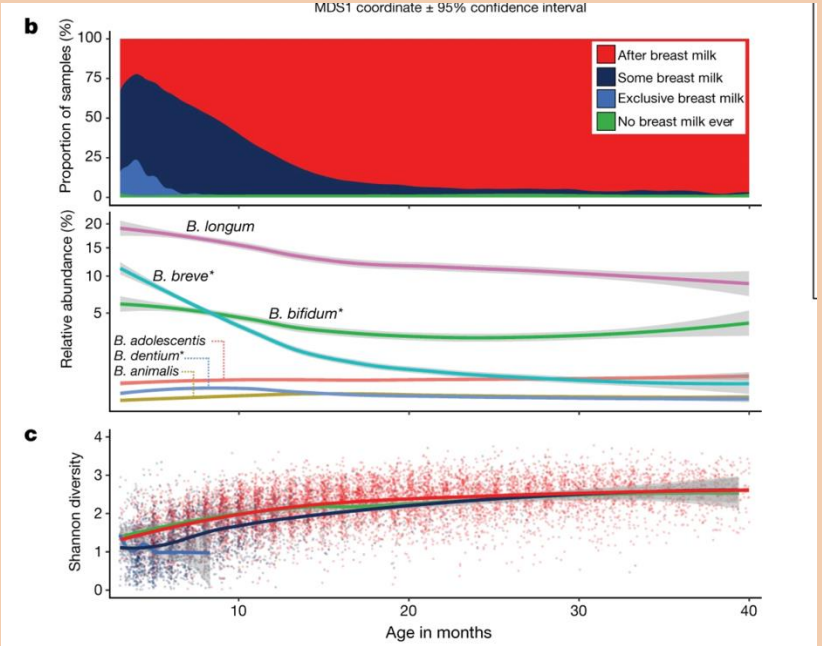


In the first 6 months of life, gut bacterial diversity, microbiota age, relative abundances of Bacteroidetes and Firmicutes, and predicted microbial pathways related to carbohydrate metabolism are consistently higher in non-EBF than in EBF infants, whereas relative abundances of pathways related to lipid metabolism, vitamin metabolism, and detoxification are lower

1825 stool samples from 684 infants

https://doi.org/10.1038/s41467-018-06473-x

The Environmental Determinants of Diabetes in the Young (TEDDY) study



N= 903

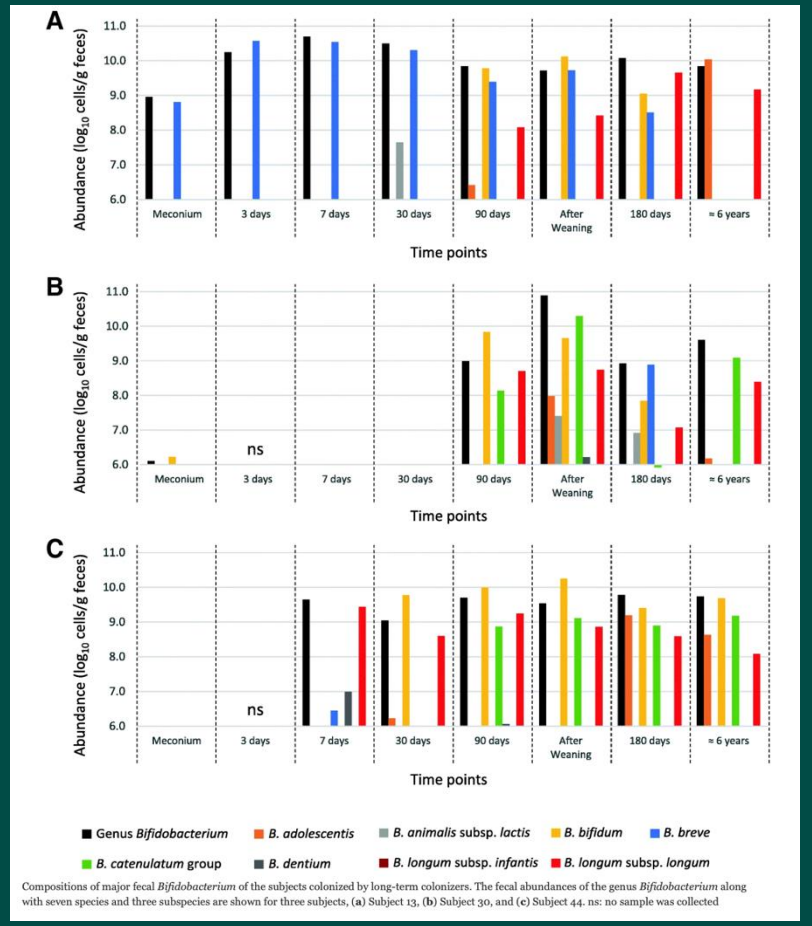
https://doi.org/10.1038/s41586-018-0617-x

Subtle associations between microbial taxonomy and the development of islet autoimmunity or type 1 diabetes

PHASE 2 (Months 15-30)

- Breastfeeding associated with higher levels of *Bifidobacterium* species (*B. breve* and *B. bifidum*)
- Cessation of breast milk resulted in faster maturation of the gut microbiome

Bifs stay in the gut for a long time, but not in all



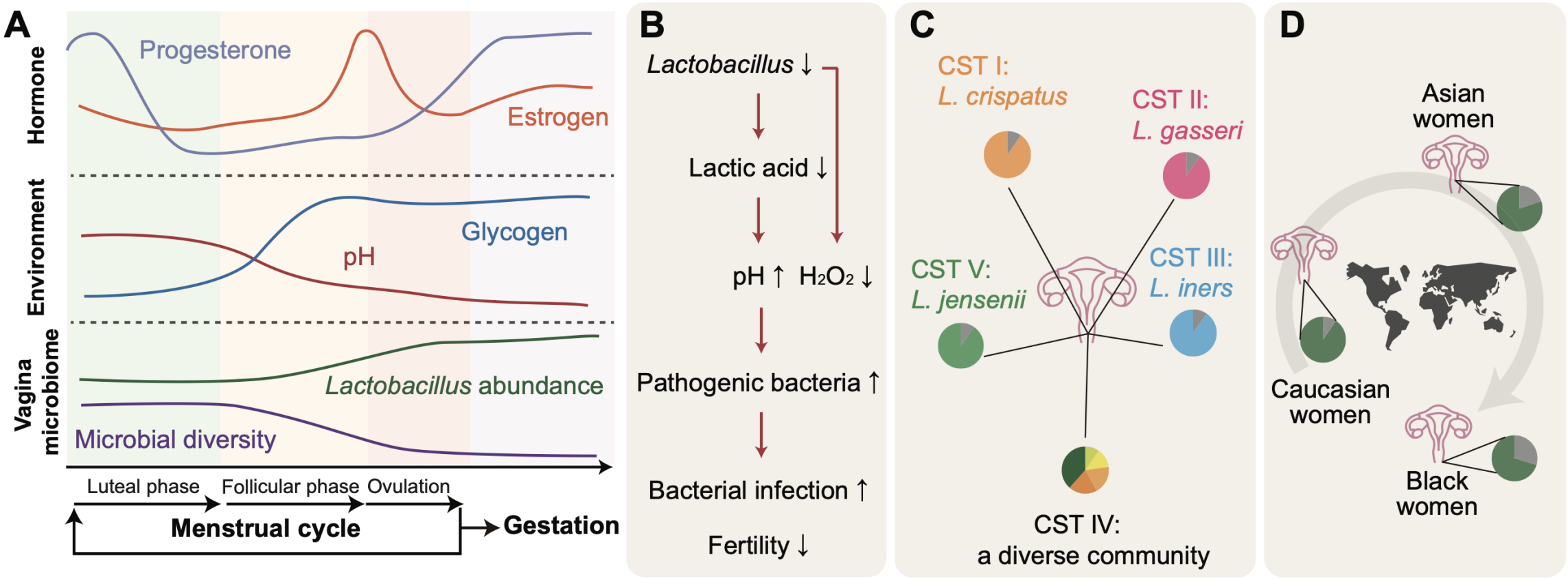
Compositions of major fecal *Bifidobacterium* of the subjects colonized by long-term colonizers. The fecal abundances of the genus *Bifidobacterium* along with seven species and three subspecies are shown for three subjects, (**a**) Subject 13, (**b**) Subject 30, and (**c**) Subject 44. ns: no sample was collected

https://doi.org/10.1186/s12866-018-1358-6

- Hospital versus at-home delivery impacts infant microbiota transmission
- Human milk is a key modulator of infant microbiota during the first year
- Species transmissibility varies across delivery modes and places, except Bifidobacteria

https://doi.org/10.1016/j.chom.2024.05.005

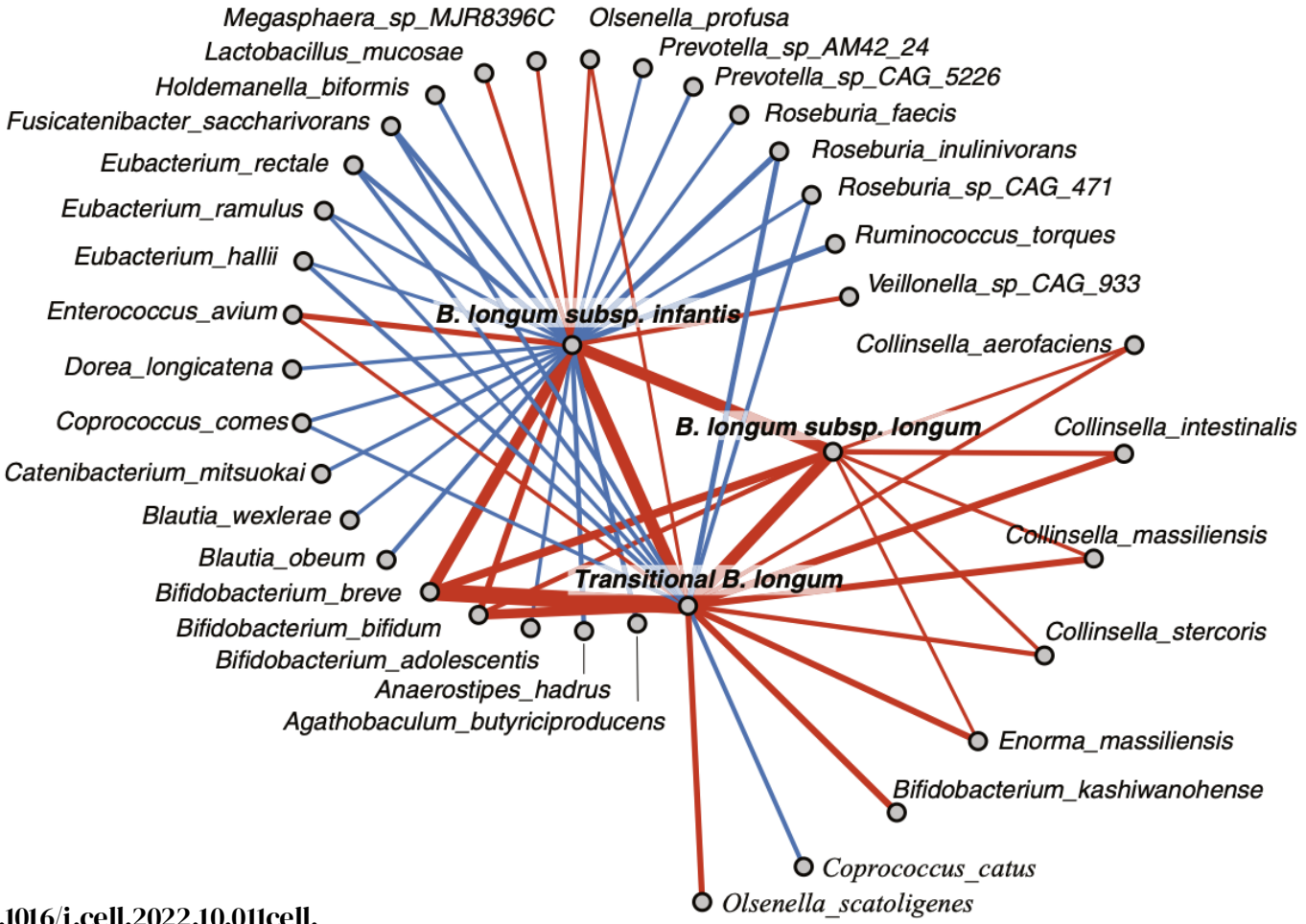
Vaginal microbiome changes during pregnancy

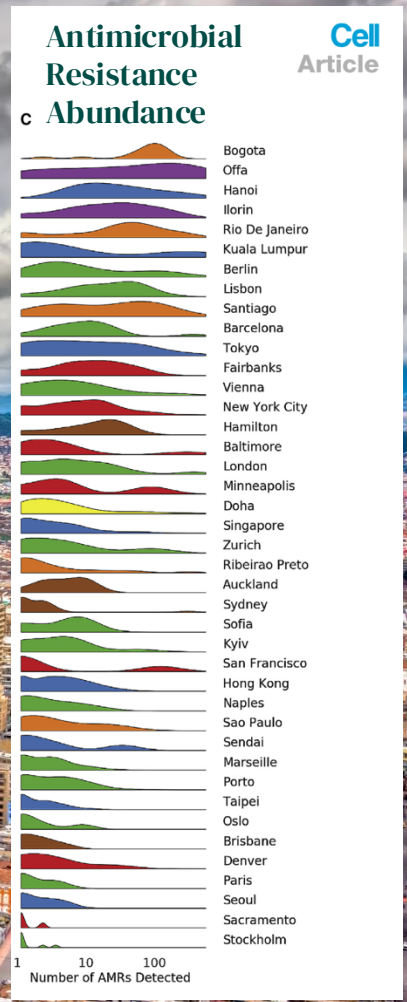


Genomics, Proteomics & Bioinformatics, 2024, Vol. 22, No. 1

Global urban microbiome

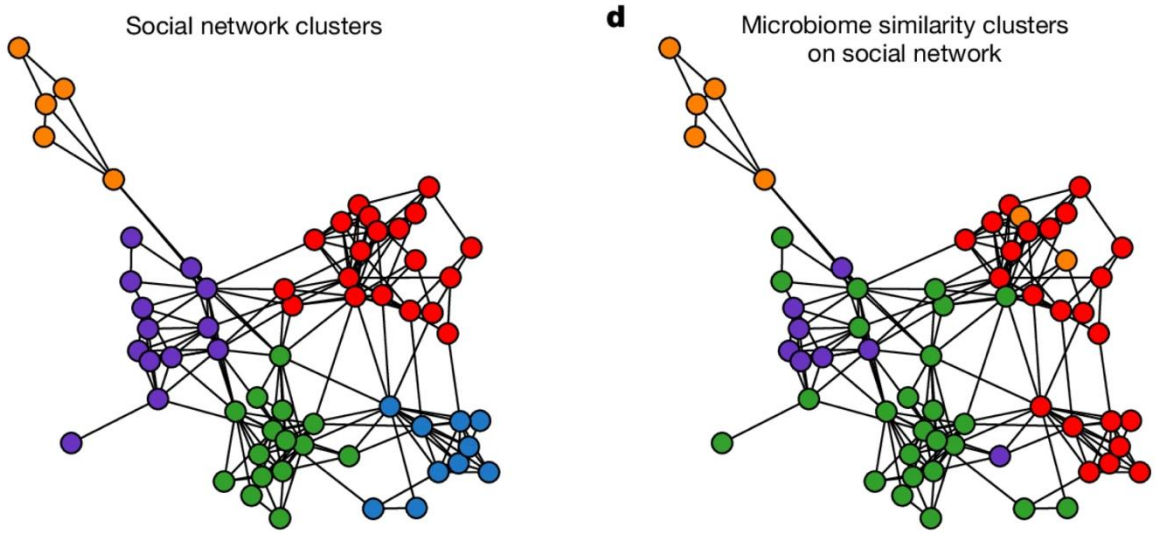
Distinct *Bifidobacterium longum* clade expands with introduction of solid foods and harbours enzymes for utilizing both breast milk and solid food substrates in Bangladeshi children





https://https://doi.org/10.1016/j.cell.2022.10.011cell.

Real world social networks shape our microbiome



1,787 adults within 18 isolated villages in Honduras

https://doi.org/10.1038/s41586-024-08222-1

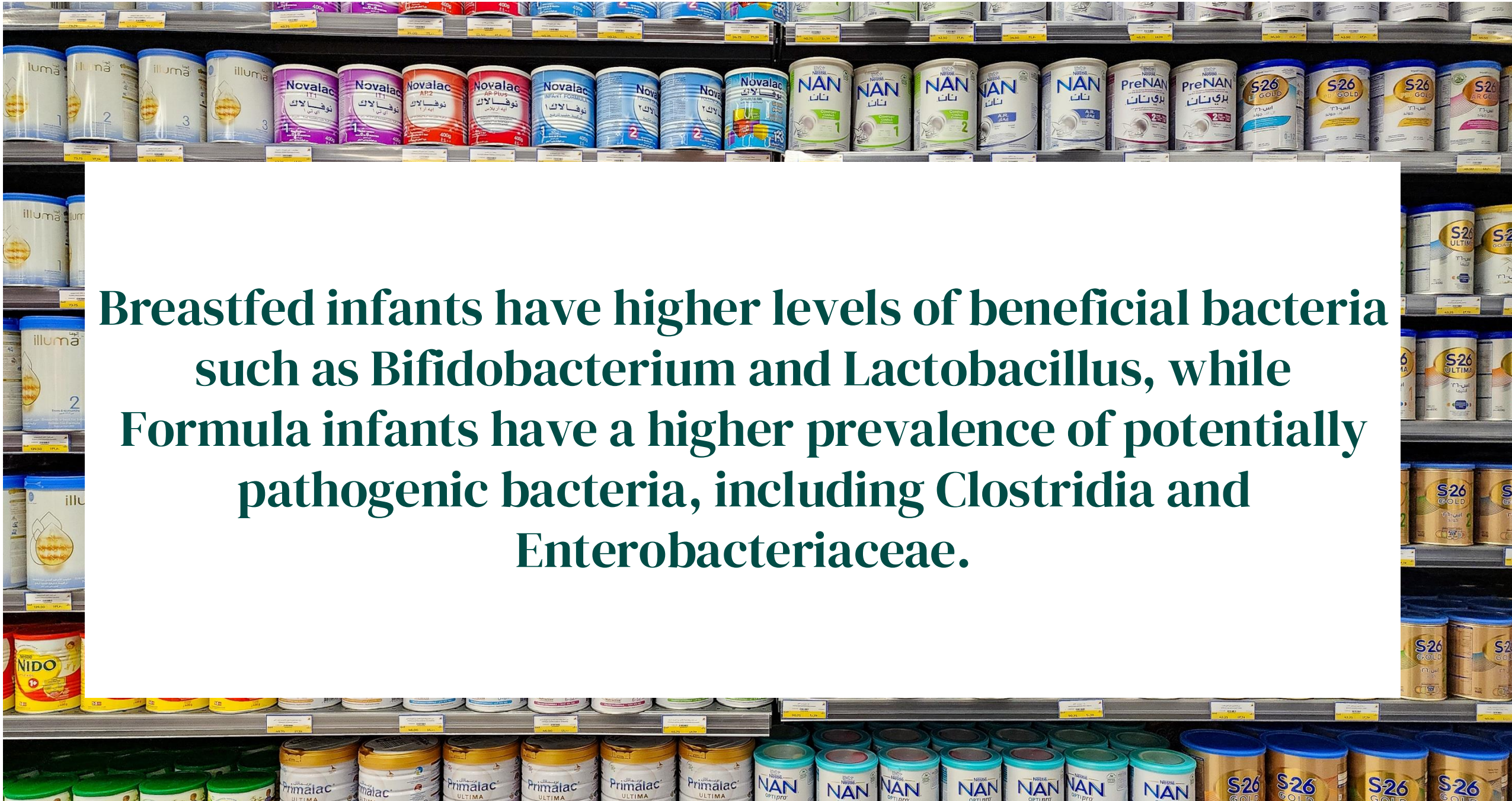
Virome: Even bacteria catch a cold

Transmission of milk phages to the infant GI tract shapes the infant GI microbiome

Early after birth, pioneer bacteria colonize the infant gut and by one month prophage induced from these bacteria provide the predominant population of virus-like particles. By four months of life, identifiable viruses that replicate in human cells become more prominent.

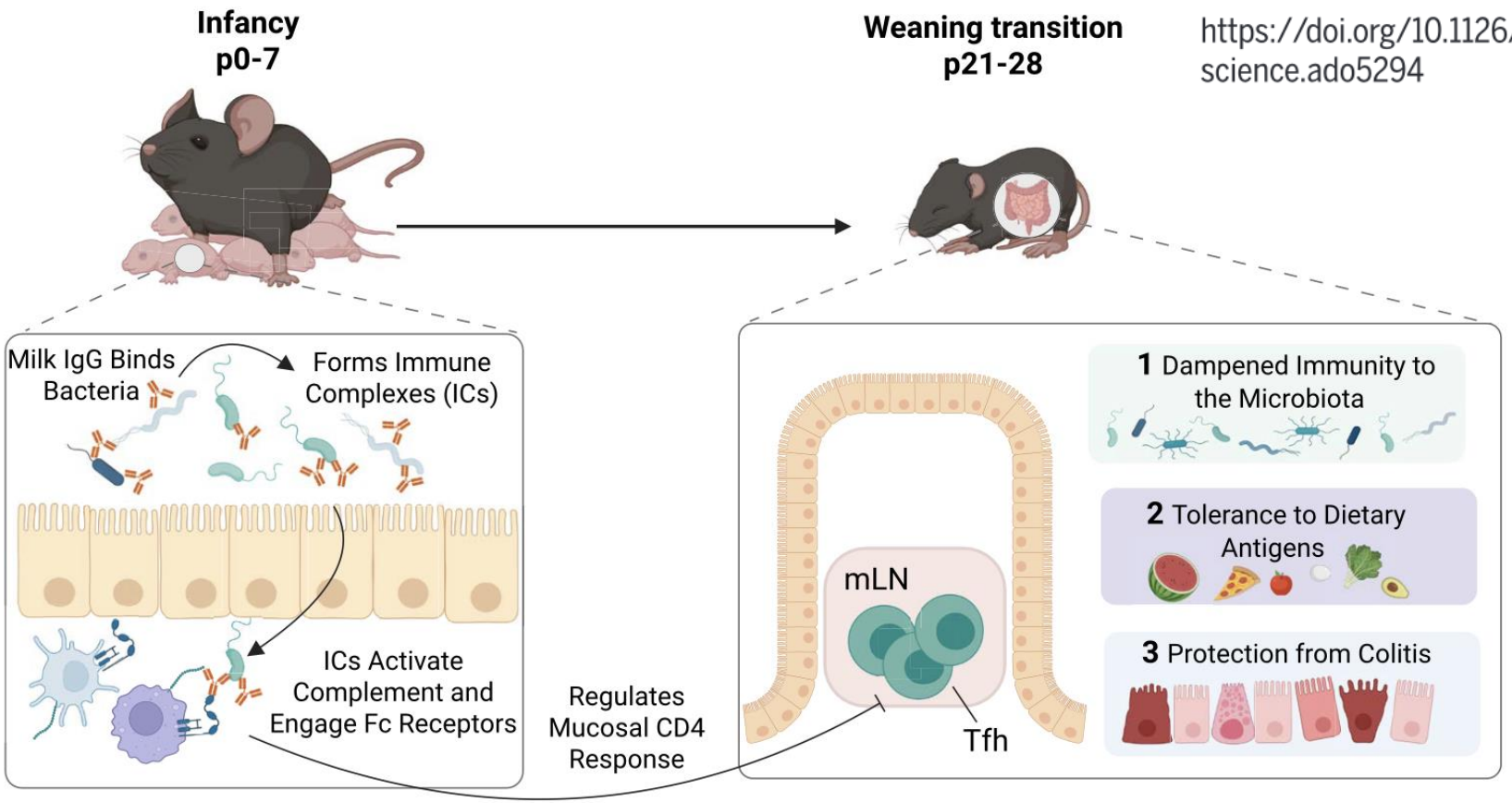
10.1038/s41586-020-2192-1
https://doi.org/10.3389/fmicb.2018.01162

https://youtu.be/V73nEGXUeBY?si=v_3xqNHNM2P174HU



Breastfed infants have higher levels of beneficial bacteria such as Bifidobacterium and Lactobacillus, while Formula infants have a higher prevalence of potentially pathogenic bacteria, including Clostridia and Enterobacteriaceae.

Breast milk immunoglobulins shape the infant immune system



IgG interacts with gut bacteria and antibody-sensing systems in young mice to dampen subsequent immune responses to gut microbial and dietary antigens encountered during weaning

Breast milk antibodies recognize and segregate commensals from the gut epithelium

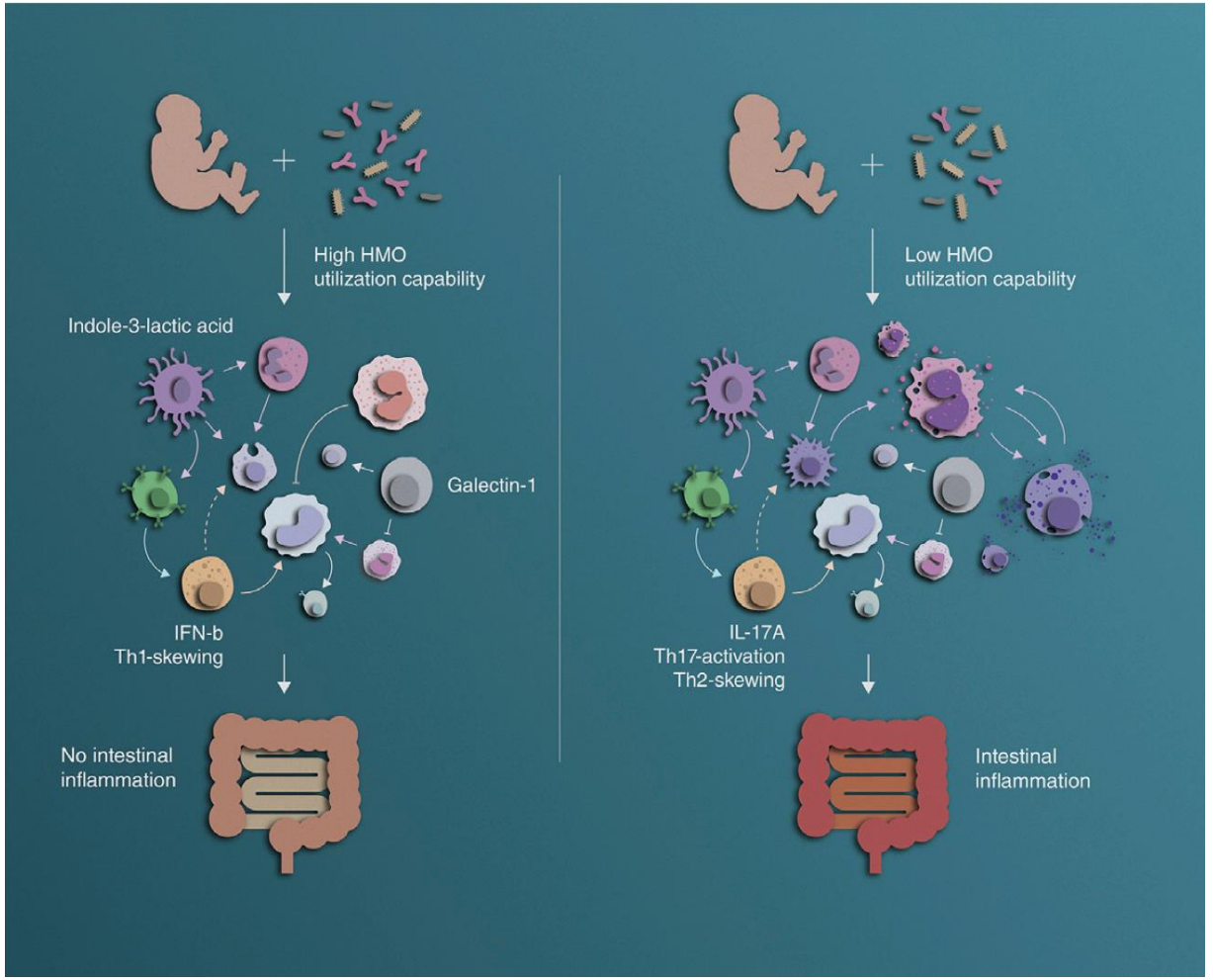
IgG-mediated protection against infection versus IgA-mediated tolerization

IgA instructs Treg cells to delay pathogen clearance during development[2]

Complement in milk selectively culls certain gram-positive microbes in the infant gut[3]

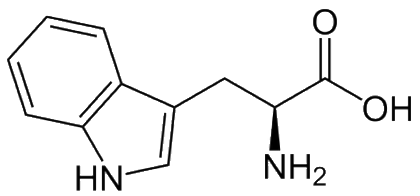
1. https://doi.org/10.1016/j.cell.2021.02.031
2. 10.1016/j.cell.2020.05.030
3. 10.1016/j.cell.2023.12.019

Think of your gut like a barrier reef



Tryptophan metabolism

Dietary tryptophan



Intestinal cells

Microbiota

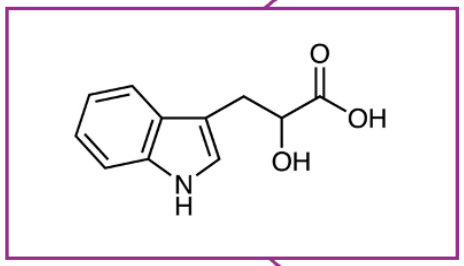
IDO1

TpH1

Bifidobacteria spp
Lactobacillus spp

Kyurenine metabolites

Serotonin (5-HT), N-acetylserotonin and Melatonin



Prebiotics for AhR producing bacteria

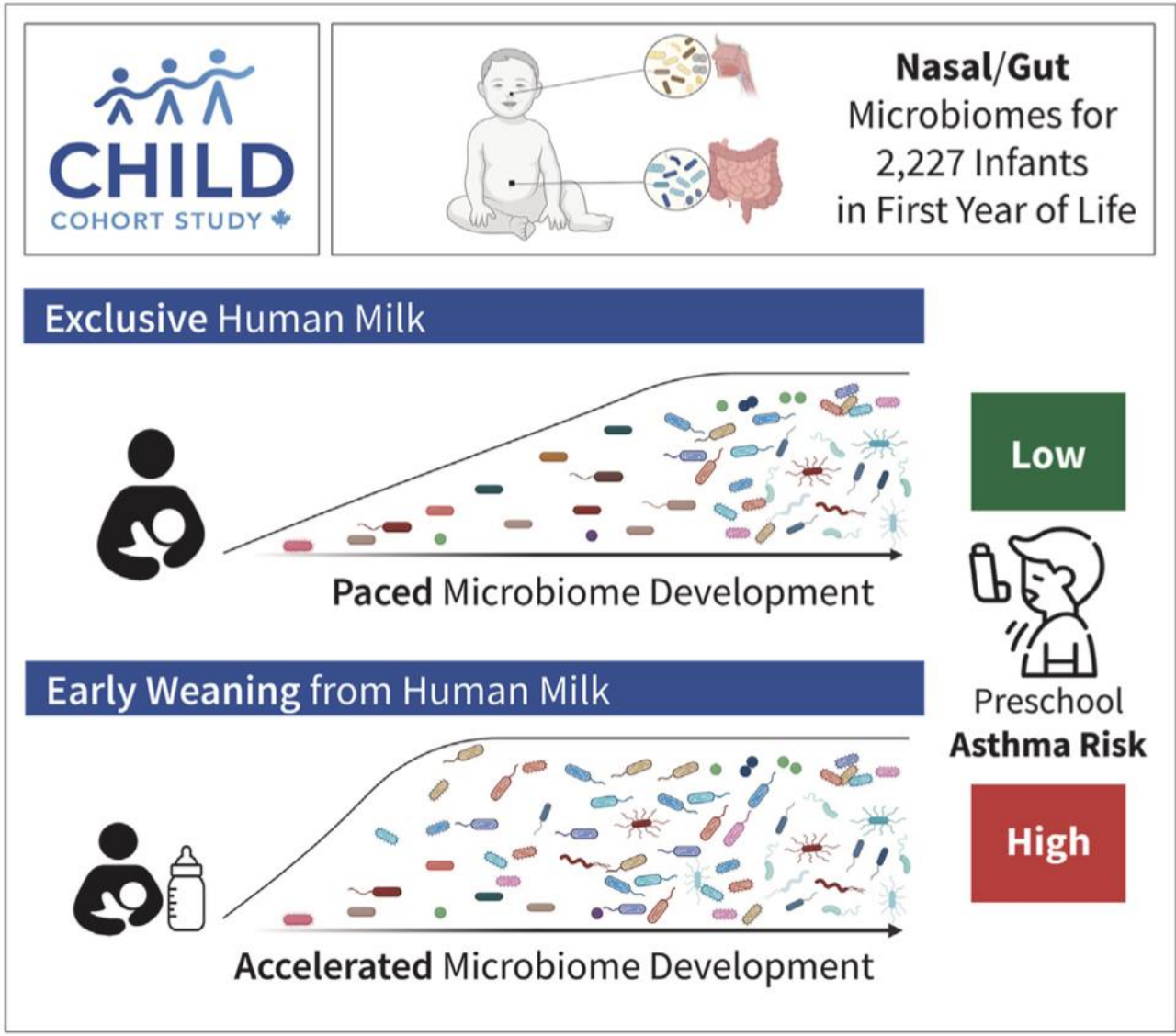
Inflammation

NEC

Breast feeding *Superbloom*

Breast milk is a 'pacemaker' indirectly protecting against asthma by regulating nasal and gut microbiome development during the first year of life

https://doi.org/10.1016/j.cell.2024.07.022



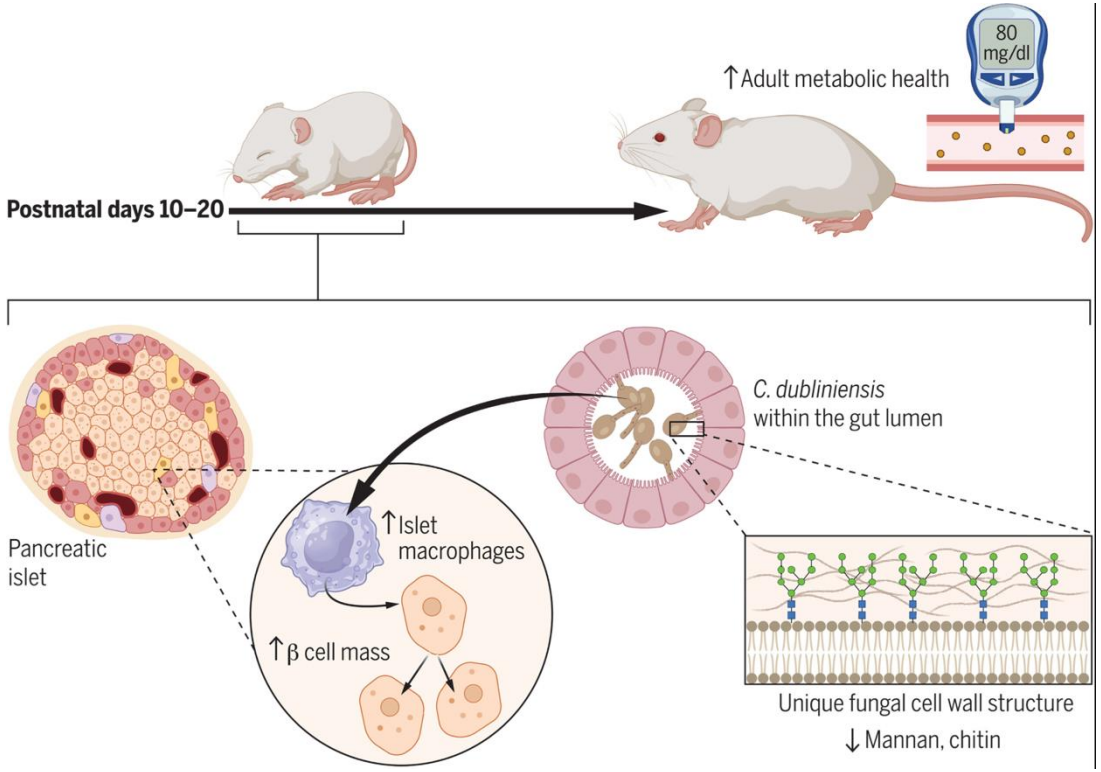
Ruminococcus gnavus and tryptophan biosynthesis drives asthma risk

Mycobiome also defines metabolic health

Candida dubliniensis

DOI: 10.1126/science.adn0953

Science



"If the developmental window is missed (e.g. in germ-free mice) or if the microbiota are disrupted during the developmental window, there is reduced beta cell development and compromised metabolic function reverberates throughout the life of the animal"

DAILY STAR

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News › Weird News › Dogs

Dogs should be encouraged to lick their owners all over

Dr James Kinross admits it 'might be seen as gross' (Image: Getty Images)

them fight bacteria

Comments 1

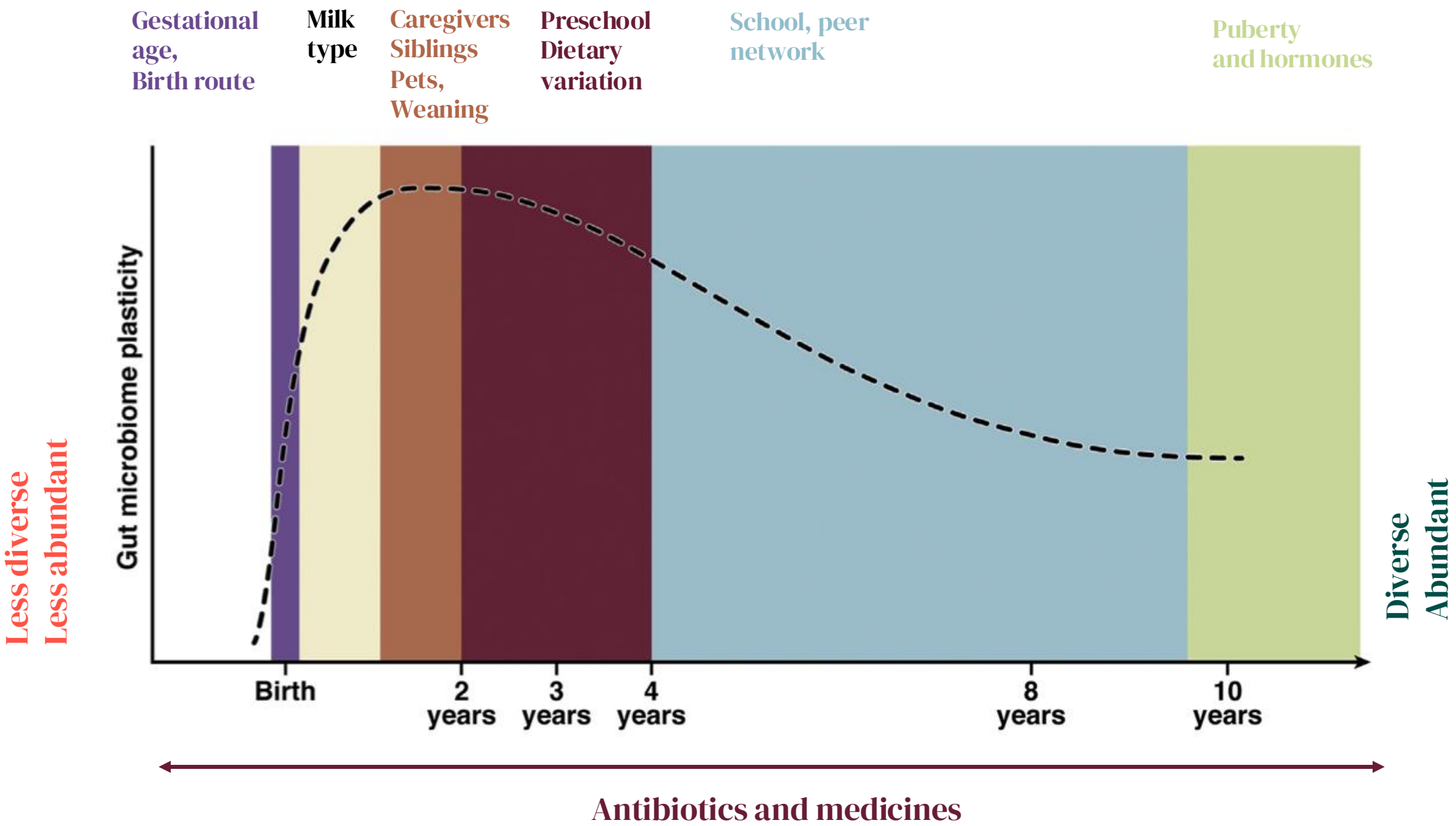
ORIGINAL ARTICLE

The impact of prenatal dog keeping on infant gut microbiota development

Ariane R. Panzer, Alexandra R. Sitarik, Doug Fadrosh, Suzanne L. Havstad, Kyra Jones, Brent Davidson, Salvatore Finazzo, Ganesa R. Wegienka, Kimberley Woodcroft, Nicholas W. Lukacs ... See all authors

First published: 14 March 2023 | https://doi.org/10.1111/cea.14303 | Citations: 30

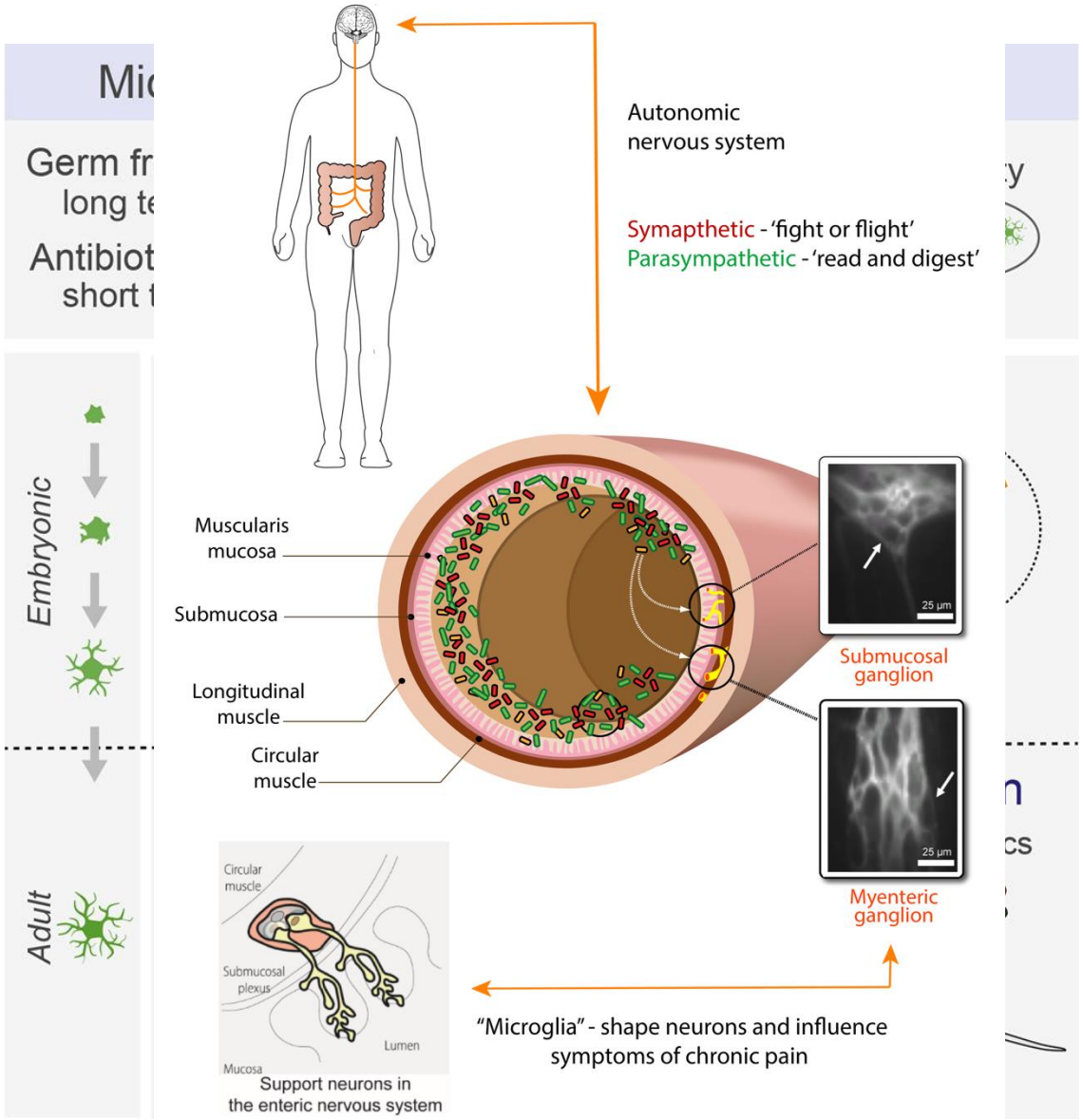
Stool samples from dog-exposed infants were microbially more diverse ($p = .041$) through age 18 months with enhanced diversity most apparent between 3 and 6 months of age.



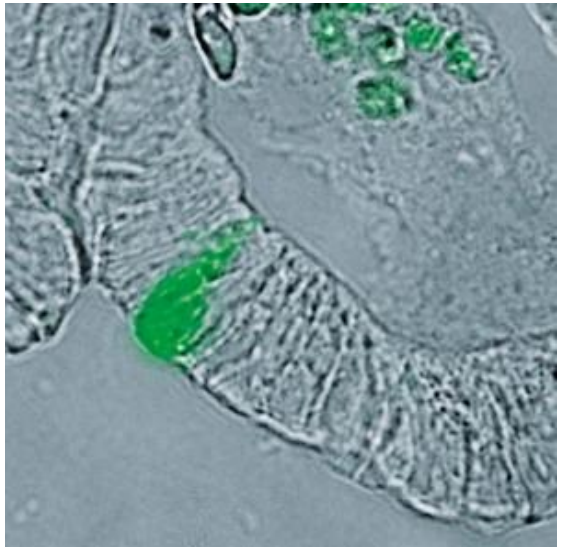
Gastroenterology 2021;160:495–506

Our second brain has its own immune system

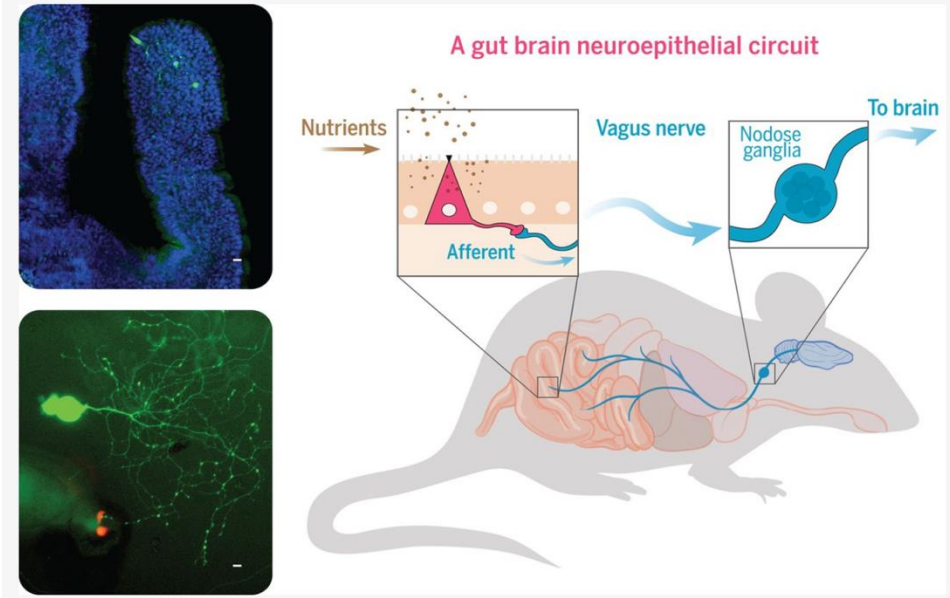
Bacteria shape our sensitivity to pain and gut motility in a sex dependent manner



Microbes talk to us through hormones



- Enterochromaffin cells only make up 1% of the gut, but these cells produce >90% of the body's serotonin
- They literally “taste” the world around us and they are hard wired into our nervous system



The neuropod cells.
(Top left) Neuropod cells synapse with sensory neurons in the small intestine, as shown in a confocal microscopy image. Blue indicates all cells in villus; green indicates green fluorescent protein (GFP) in neuropod cell and sensory neurons. (Bottom left) This neural circuit is recapitulated in a coculture system between organoids and vagal neurons. Green indicates GFP in vagal neuron; red indicates td-Tomato red fluorescence in neuropod cell. (Right) Neuropod cells transduce fast sensory signals from gut to brain. Scale bars, 10 μm.

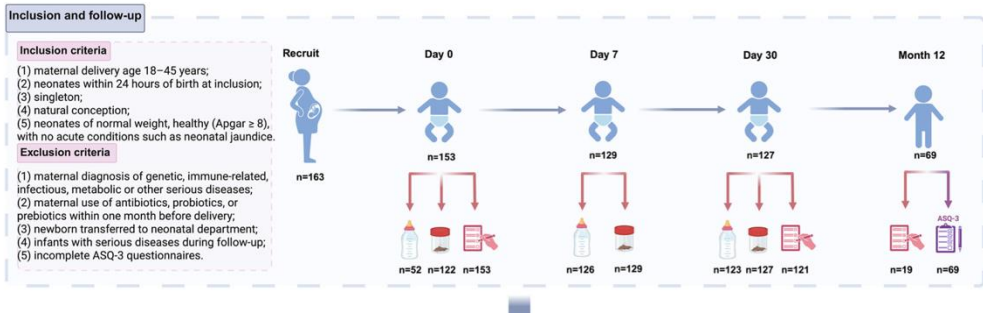
Science

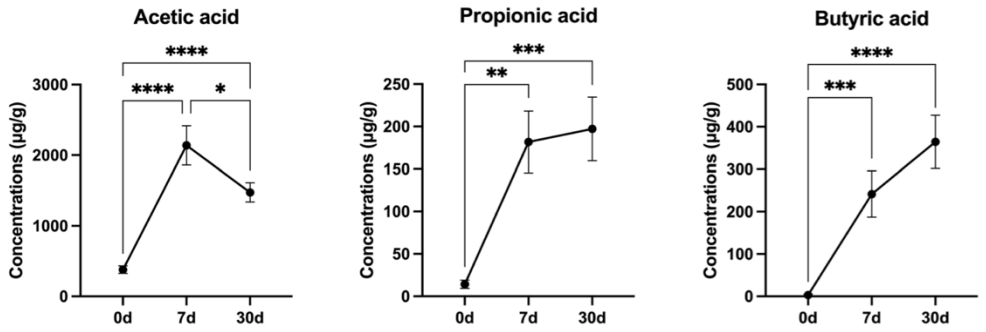
DOI: 10.1126/science.aat5236

The consequence of a misassembled microbiome is an unhappy brain

"Faecal microbiome transplant of autistic children can lead to autistic-like behaviours, different microbial community structures, and altered tryptophan and serotonin metabolism in mice."

https://doi.org/10.1038/s41522-025-00790-y





In early-life stable and unique maternal milk may influences long-term neurodevelopment by dynamically modulating IGM and SCFAs

Microbes influence our risk of depression in a sex dependent manner

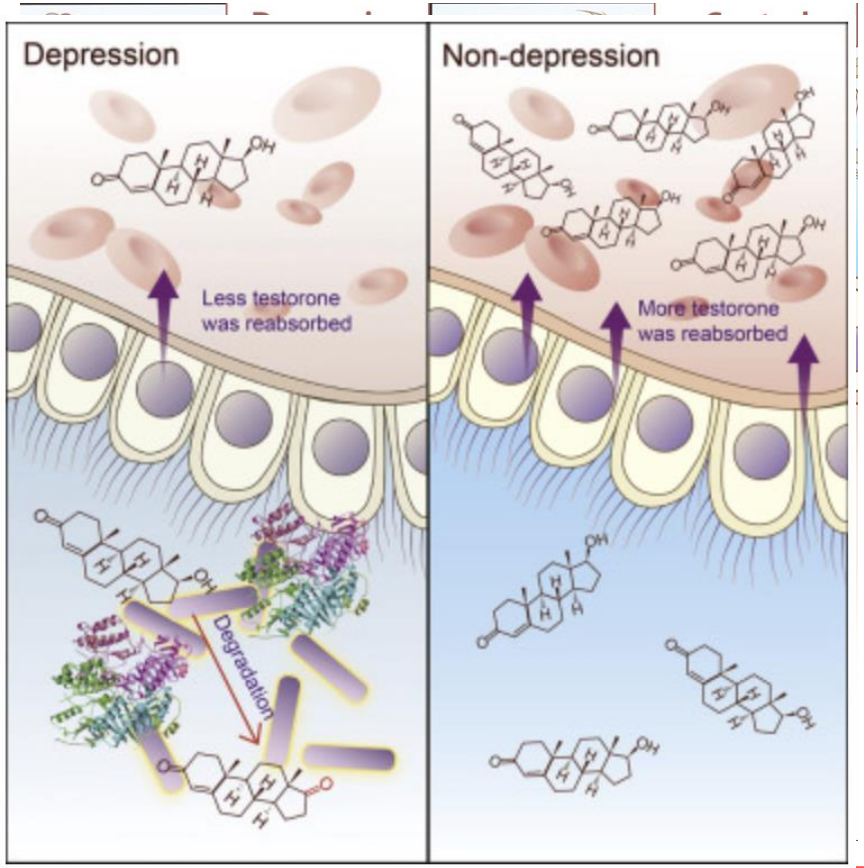
Premenopausal females with depression have *Klebsiella* dominant fecal microbiota

Klebsiella degrades testosterone

Mice given bacteria from depressed women experience estradiol decline and depression-like behaviors

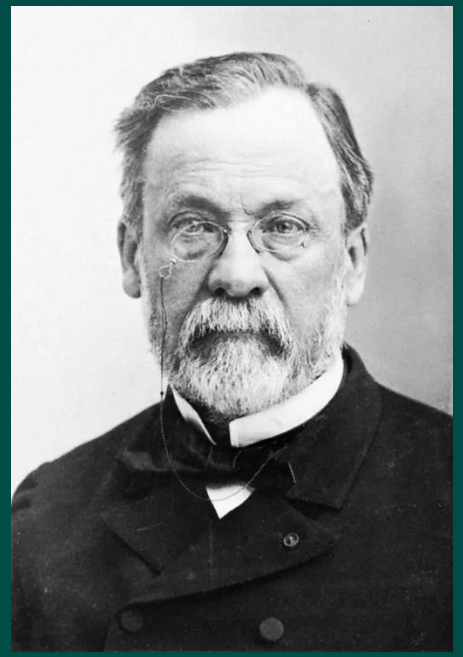
Mycobacterium neoaurum in depression degrades testosterone in feces

When this bacteria are transplanted into rats the bacteria lowers testosterone and induces depression behaviors

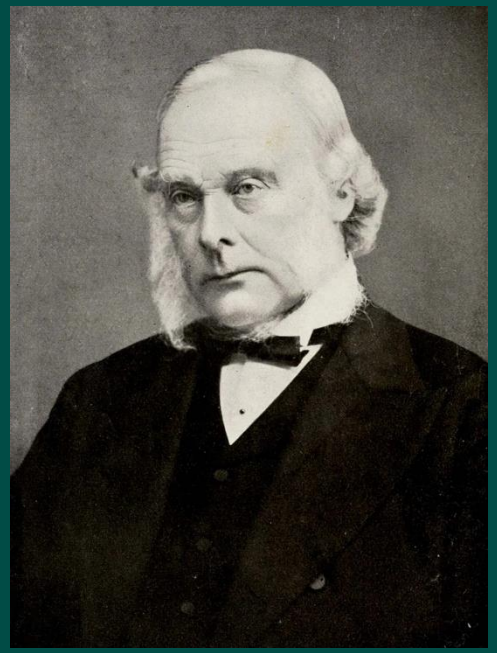


DOI:https://doi.org/10.1038/s41579-022-00703-2

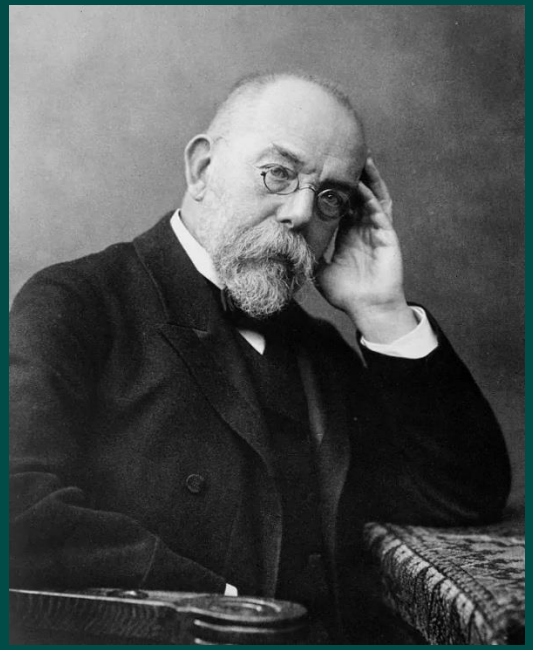
The war on bugs



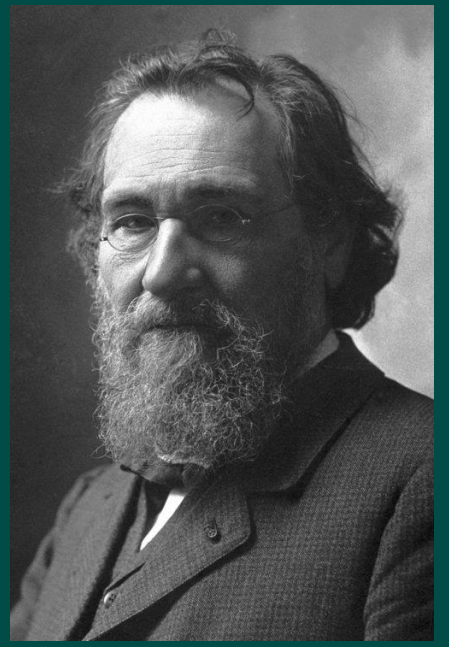
Louis Pasteur 1822-1895



Joseph lister 1827-1912

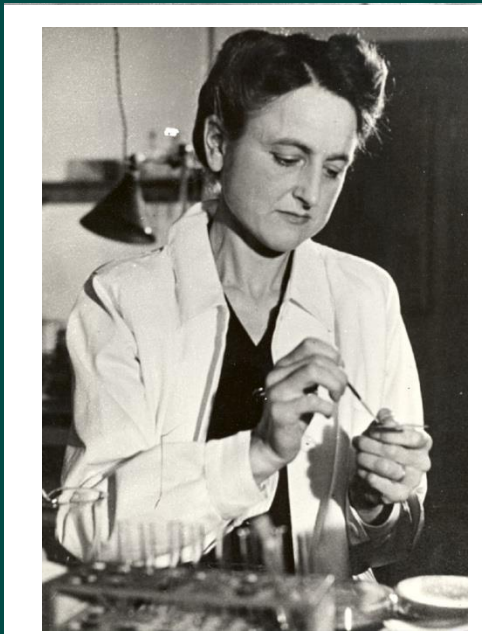


Robert Koch 1843-1910



Eli Metchnikoff
1844-1916

Margaret Jennings
(1904-1994)



Alexander Fleming
1881-1955

Intra-partum antibiotics changes the breast milk microbiome

> Medicamenta (Madr). 1948 Feb 10;6(142):85.

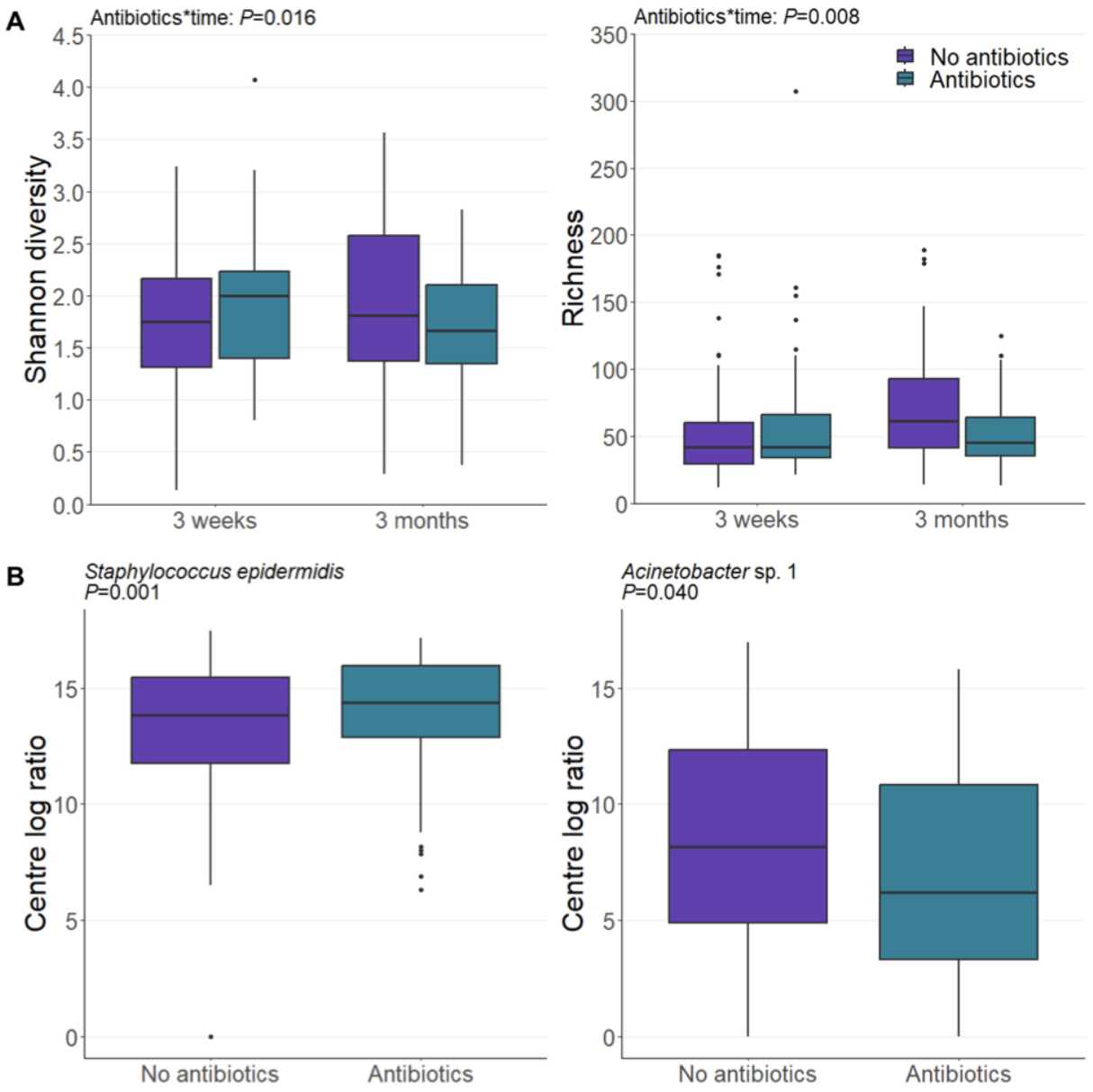
[Does Penicillin Have An Inhibitory Action On Lactation?]

[Article in Spanish]

R CERES RODRIGUEZ

266 milk samples collected from 208 mothers at 3 weeks and 3 months postpartum from the Growing Up in Singapore Toward healthy Outcomes (GUSTO) study.

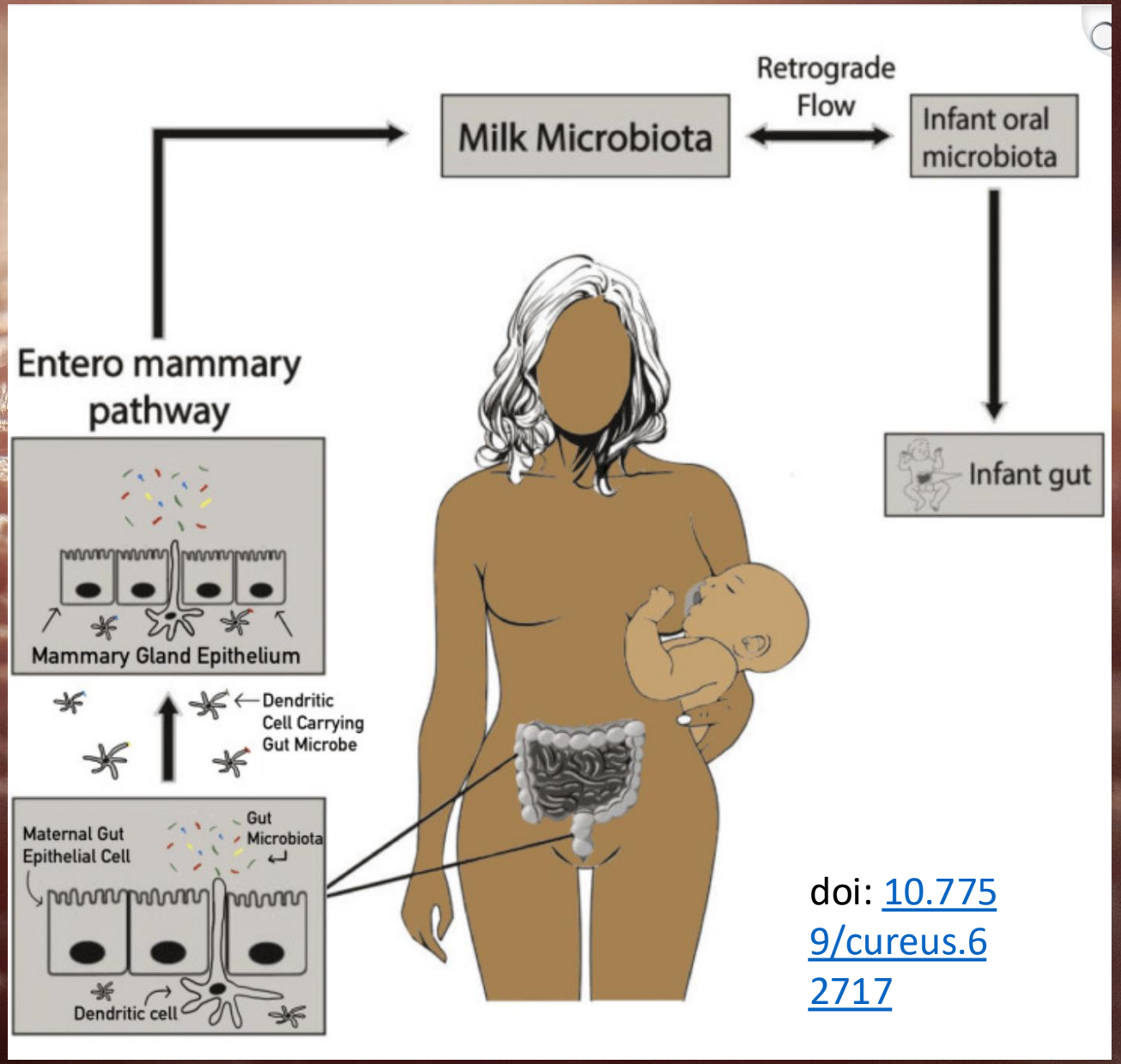
10.1128/msystems.00677-25



Mastitis

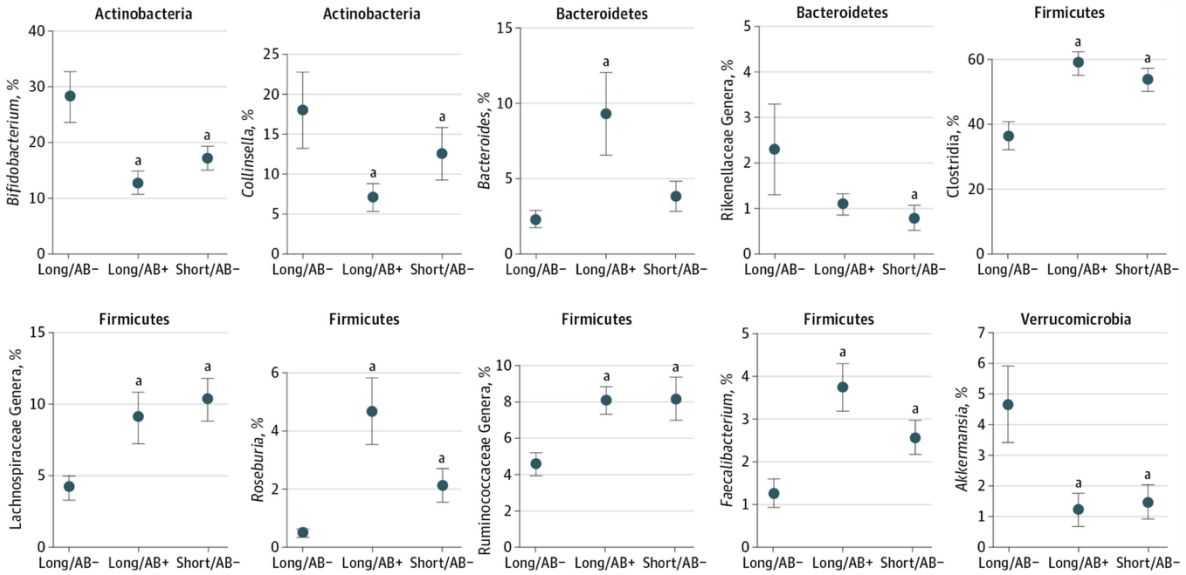
The Skin's immune system has set points that are defined by the dual action of sex hormones and the microbiota.

Sex hormones control the strength of local immunity and microbiota calibrate its tone



doi: 10.7759/cureus.62717

Antibiotic use in a child during breastfeeding weakens the beneficial effects of long breastfeeding duration and increases the risk of obesity



doi:10.1001/jamapediatrics.2016.0585

Antibiotics have profoundly reshaped the infant microbiome

Antibiotics cause weight gain

THE EFFECT OF AUREOMYCIN ON UNDERNOURISHED AFRICAN CHILDREN

by

LORNA G. MACDOUGALL, M.B., CH.B., D.C.H.*

(*King George VI Hospital, Nairobi, Kenya*)

INTRODUCTION

Growth rate and control of infection. The use of antibiotics as a supplement in the feeding of young animals has been the subject of much research in recent years and has proved a valuable means of increasing the growth rate, preventing mortality and reducing the incidence of infection (MARTIN, 1942 ; MOORE et al., 1946 ; HARNED et al., 1948 ; KNOEBEL and BLACK, 1952 ; BLACK and BRATZLER, 1952 ; JUKES et al., 1950 ; STOKSTAD and JUKES, 1950).

Owing to the more rapid growth of experimental animals, their response to antibiotics has been easier to assess than that of human beings, and, so far, few trials have been undertaken in the latter, and only one in grossly undernourished children in whom the maximum response might be expected (LEWIS et al., 1956).

A clinical trial by ROBINSON (1952) with premature infants showed that there was an increase in the rate of growth and a reduction in mortality from infection when aureomycin, in small doses, was given daily, but a similar response was not obtained by COODIN (1953) using terramycin. In the supplementation of school diets with terramycin, streptomycin and penicillin, WETZEL and HOPWOOD (1954) found an improved rate of growth among the children treated and also that subclinical infections had less growth inhibitory effect in the antibiotic supplemented group.

Multiple trials in school children by SCRIMSHAW et al. (1954) with aureomycin and penicillin showed widely varying weight gains over periods of 2 - 3 years, irrespective of treatment. There was, however, an initial increase in height, and sometimes weight, among the aureomycin-treated groups during the first six months. A survey by CARTER (personal communication) among mentally defective, spastic children, showed that the prolonged administration of aureomycin produced a significant increase in the annual weight gain, and greatly reduced the incidence of gastrointestinal disorders. HAIGHT and PIERCE (1954) in a trial with young naval recruits found that antibiotics in small doses produced a significant weight increase in this age group also.

Drug Resistance. As a result of the widespread and often indiscriminate use of antibiotics in the treatment of human disease, the problem of drug resistant organisms and allergies has become increasingly common. It might be expected, therefore, that the prolonged administration of antibiotics associated with animal feeding experiments would eventually produce deleterious side effects, but so far this has not proved the case. The improved growth rate of treated animals has been maintained and disease epidemics largely eradicated, with the subsequent improvement in growth rate of unsupplemented animals in the same environment which has been attributed to the reduction in " disease potential " of their surroundings (LIBBY and SCHAIBLE, 1955).

* I wish to express my thanks to the Director of Medical Services, Kenya Colony, for permission to publish this article, to Mr. Pearson of the Medical Research Laboratory, Nairobi, for the serological work, to Dr. O. B. Tandon of the Institute of Nutrition of Central America and Panama, for the statistical analysis of results, and to Lederle Laboratories, Pearl River, New York, for the supply of aureomycin and placebos.

“Crapsule”

Science

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RESEARCH ARTICLE

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

VANESSA K. RIDAURA, JEREMIAH J. FAITH, FEDERICO E. REY, JIYE CHENG, ALEXIS E. DUNCAN, ANDREW L. KAU, NICHOLAS W. GRIFFIN, VINCENT LOMBARD, BERNARD HENRISSAT, [...], AND JEFFREY I. GORDON +15 authors Authors Info & Affiliations

SCIENCE • 6 Sep 2013 • Vol 341, Issue 6150 • DOI: 10.1126/science.1241214

Milk microbes can be transplanted too!

Applied Microbiology and Biotechnology (2024) 108:74
https://doi.org/10.1007/s00253-023-12965-8

APPLIED MICROBIAL AND CELL PHYSIOLOGY

Check for updates

Milk microbiome transplantation: recolonizing donor milk with mother's own milk microbiota

Lisa F. Stinson[1] · Jie Ma[1] · Ching Tat Lai[1] · Alethea Rea[2] · Sharon L. Perrella[1] · Donna T. Geddes[1]

Received: 6 September 2023 / Revised: 29 November 2023 / Accepted: 10 December 2023 / Published online: 9 January 2024

- Mother's own milk microbiome can be successfully transplanted into donor human milk.
- Recolonization is equally successful in UV-C-treated and Holder-pasteurized milk.
- Recolonization time should be restricted due to rapid bacterial growth

HIT 1

HIT 2

HIT 3

Exposome (e.g. microplastics, smoking)

Antibiotics

OR = 1.48, 95% CI = 1.01-2.17, P = .046) and adenomas (OR = 1.40, 95% CI = 1.17-1.68, P < .001 doi: 10.1002/ijc.34648

Antibiotics

1.49 (95% CI 1.07, 2.07), $p = 0{\cdot}018$; ≥50 years doi.org/10.1038/s41416-021-01665-7

Metabolism

Neonatal microbiome

BREAST FEEDING incomplete microbiome assembly INITIATION

Substrate dependent luminal microbiome (Adenoma formation)

Obesity, Atopy, autoimmune dx, etc..

Bowel cancer

Cancer

Chronic inflammation PROMOTION

Passenger microbes (e.g. *Fusobacterium nucleatum*)

Maternal microbiome

Antibiotics

HR 4.40 (95% CI 1.63, 11.88) for long-acting sulfonamides. doi: 10.1093/ije/dyad004.

Globalised diet, alcohol, low fibre, UPFs

Cancer risk varies with the resilience of the microbiome


We are experiencing an internal climate crisis

Germ Theory

19th century

Microbiome Theory

21st century

A healthy maternal microbiome should be a human right

Conclusions

- The parental microbiome influences infant health from the moment of conception
- The gut-breast axis defines the immunological potential of human breast milk
- There is no substitute for breast milk, because it is PERSONALISED
- Breast feeding seeds the microbiome in the infant gut with life long consequences for their risk of non-communicable disease
- We are only just begining to understand this

Thankyou!

www.dark-matter.org.uk