63 ° Congr. Nazionale SIGG, Roma, 30 novembre 2018

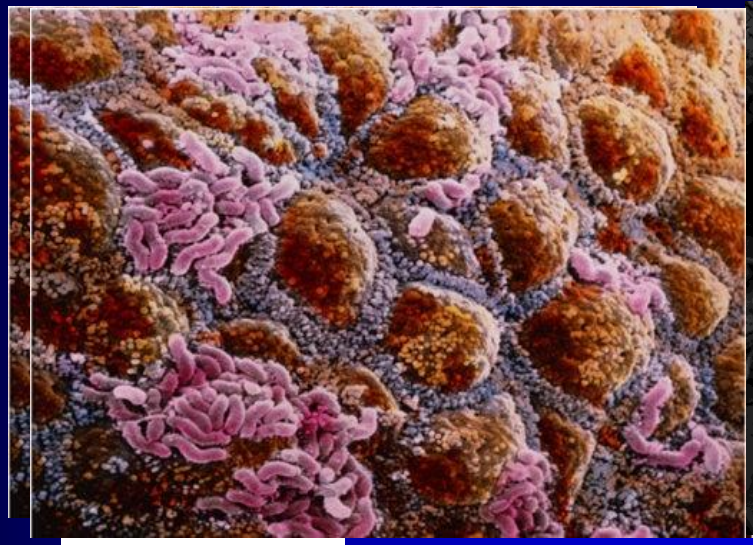
L'INTESTINO SECONDO CERVELLO: COME ASCOLTARLO E ASSISTERLO PEPREPARARE UNA BUONA SALUTE IN ETÀ GERIATRICA?

Giovanni Gasbarrini *

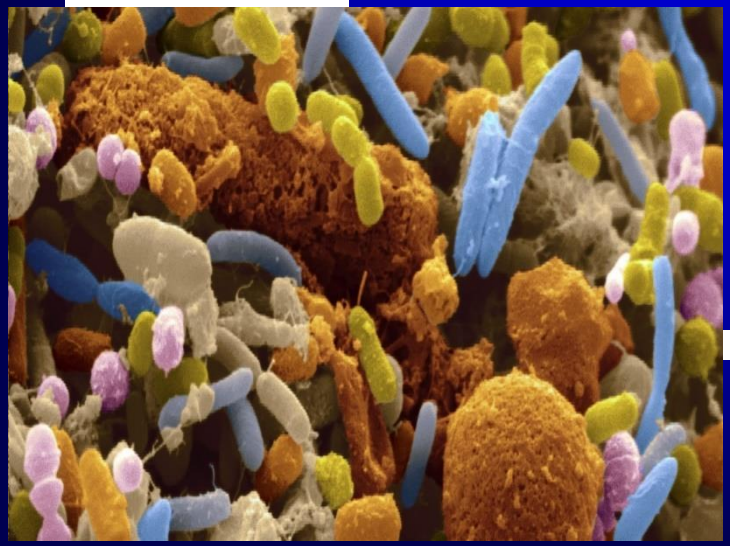
**Professore Emerito di Medicina Interna all' Università Cattolica di Roma*

V. Bahia **

***Tecnico foto*




10 µm

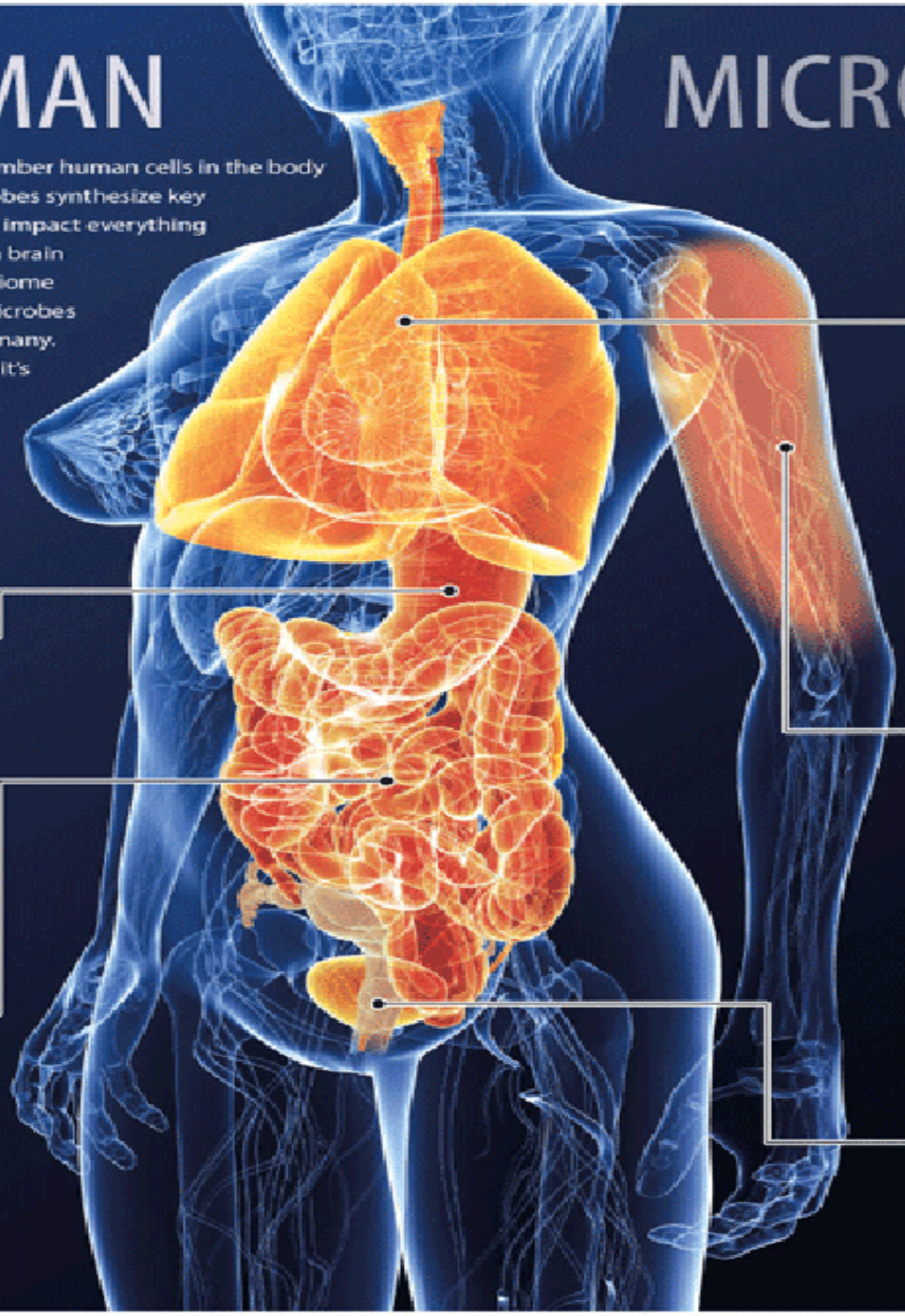


cosa e’

?

THE HUMAN MICROBIOME

Bacteria, fungi, and viruses outnumber human cells in the body by a factor of 10 to one. The microbes synthesize key nutrients, fend off pathogens and impact everything from weight gain to perhaps even brain development. The Human Microbiome Project is doing a census of the microbes and sequencing the genomes of many. The total body count is not in but it's believed over 1,000 different species live in and on the body.



600+ SPECIES

in the mouth, pharynx and respiratory system include:

- Streptococcus viridans
- Neisseria sicca
- Candida albicans
- Streptococcus salivarius

25 SPECIES

in the stomach include:

- Helicobacter pylori
- Streptococcus thermophilus

1,000 SPECIES

in the skin include:

- Pityrosporum ovale
- Staphylococcus epidermidis
- Corynebacterium jeikeium
- Trichosporon
- Staphylococcus haemolyticus

500–1,000 SPECIES

in the intestines include:

- Lactobacillus casei
- Lactobacillus reuteri
- Lactobacillus gasseri
- Escherichia coli
- Bacteroides fragilis
- Bacteroides thetaiotaomicron
- Lactobacillus rhamnosus
- Clostridium difficile

60 SPECIES

in the urogenital tract include:

- Ureaplasma parvum
- Corynebacterium aurimucosum

SOURCES: NATIONAL INSTITUTES OF HEALTH, SCIENTIFIC AMERICAN; HUMAN MICROBIOME PROJECT

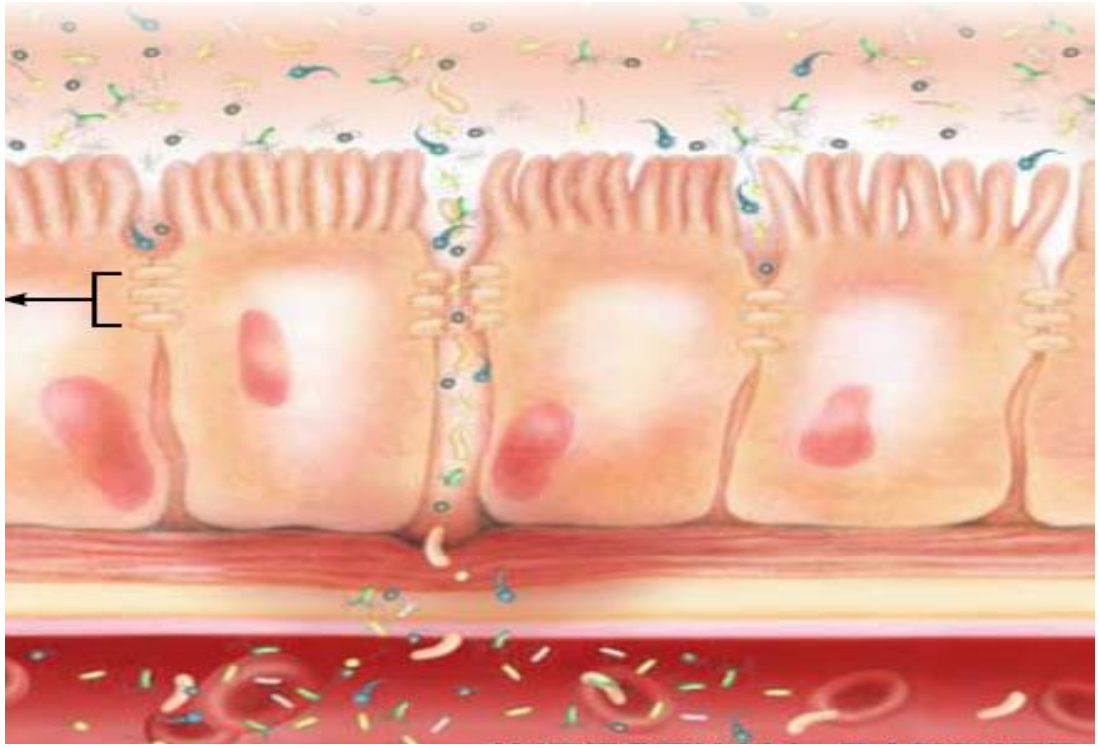
Dean Tweed - POSTMEDIA NEWS / IMAGE: Fotolia

Anatomo-Microbiological barrier

Microbiota

Mucosal Barrier

Epithelial barrier



Endocrine system

Acquired and Innate immunity

Vascular and lymphatic systems

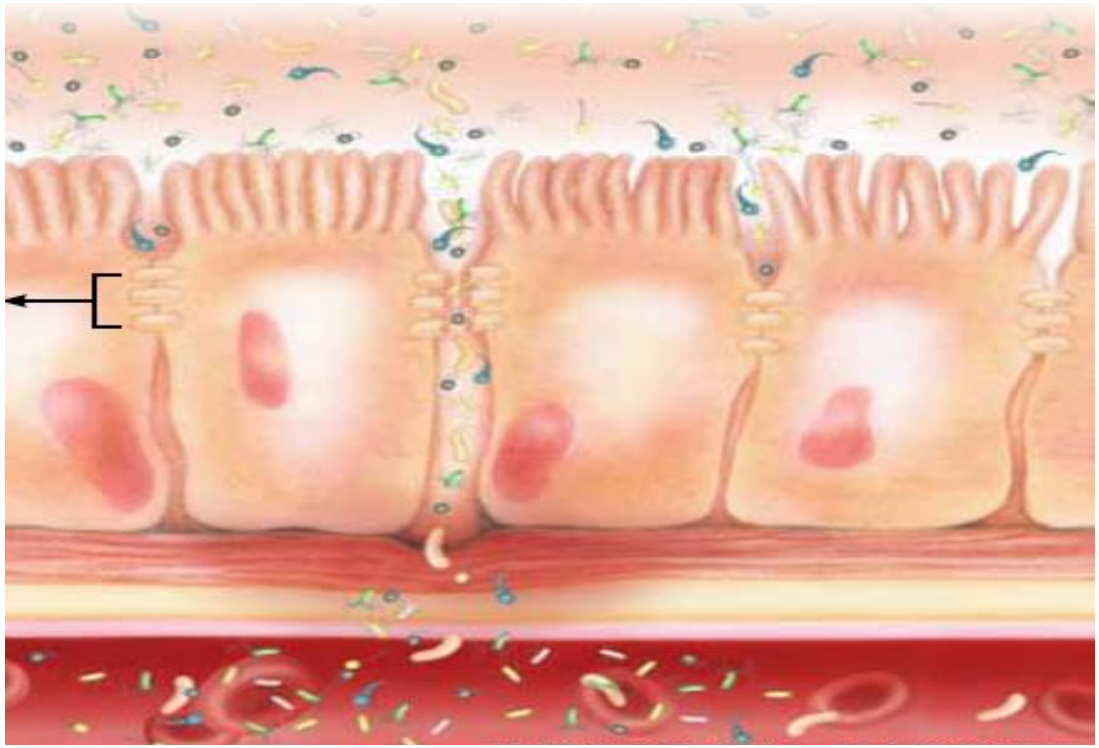
Neuroenteric system

Digestive enzymes

Microbiota has many components

Virus/phages **Bacteria** **Protozoa** **Helminth**

Archea **Micro-eukaryotes** **Yeast** **Parasite**



Mucosal Barrier

Epithelial barrier

Endocrine system

Acquired and Innate immunity

Vascular and lymphatic systems

Neuroenteric system

Digestive enzymes

Gut Bacteriome

Virus/phages

Bacteria

Protozoa

Helminth

Archea

Micro-eukaryotes

Yeast

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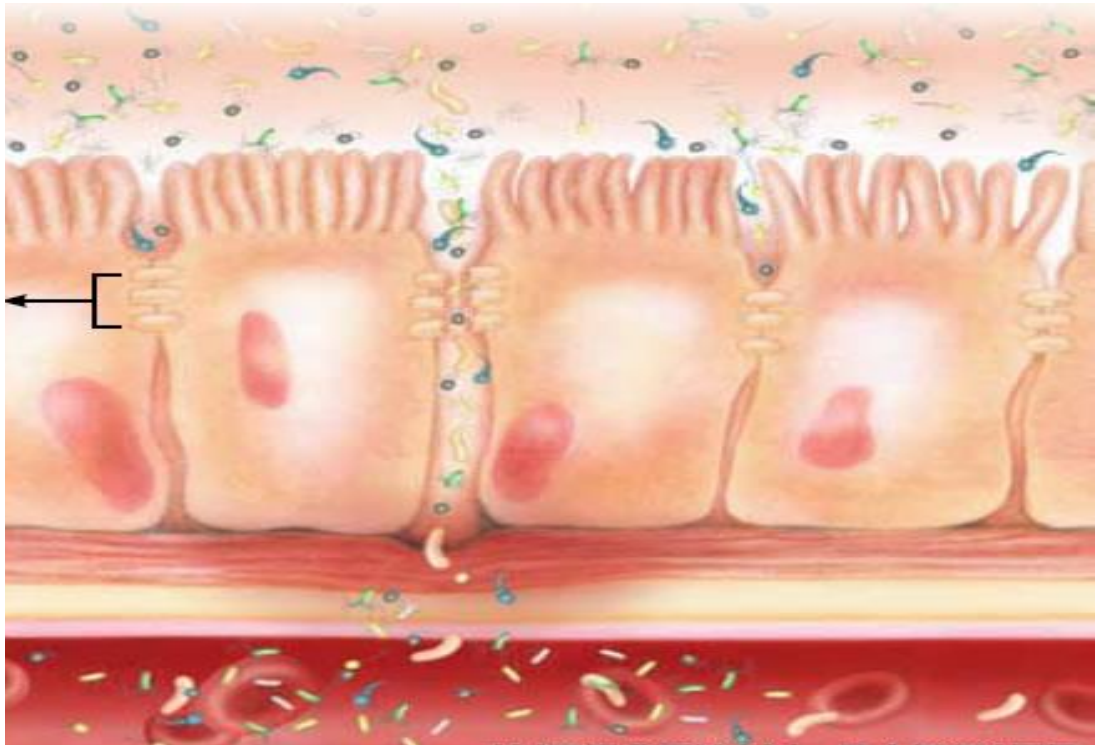


Mucosal Barrier

Epithelial barrier

Acquired and Innate immunity

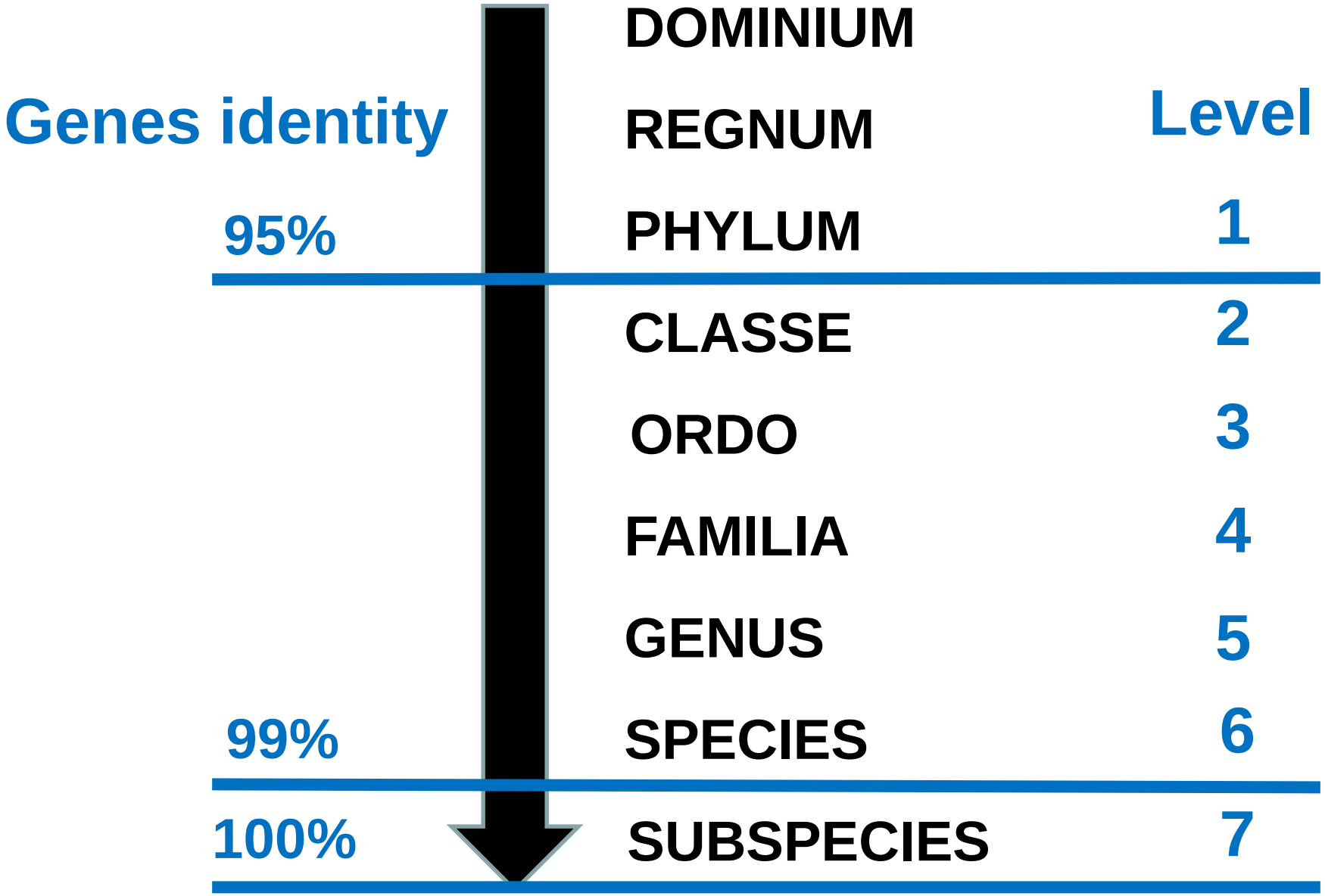
Endocrine system

Vascular and lymphatic systems

Neuroenteric system

Digestive enzymes

Microbial Taxonomic Rank



..HOWEVER, EACH INDIVIDUAL

4-6 phyla

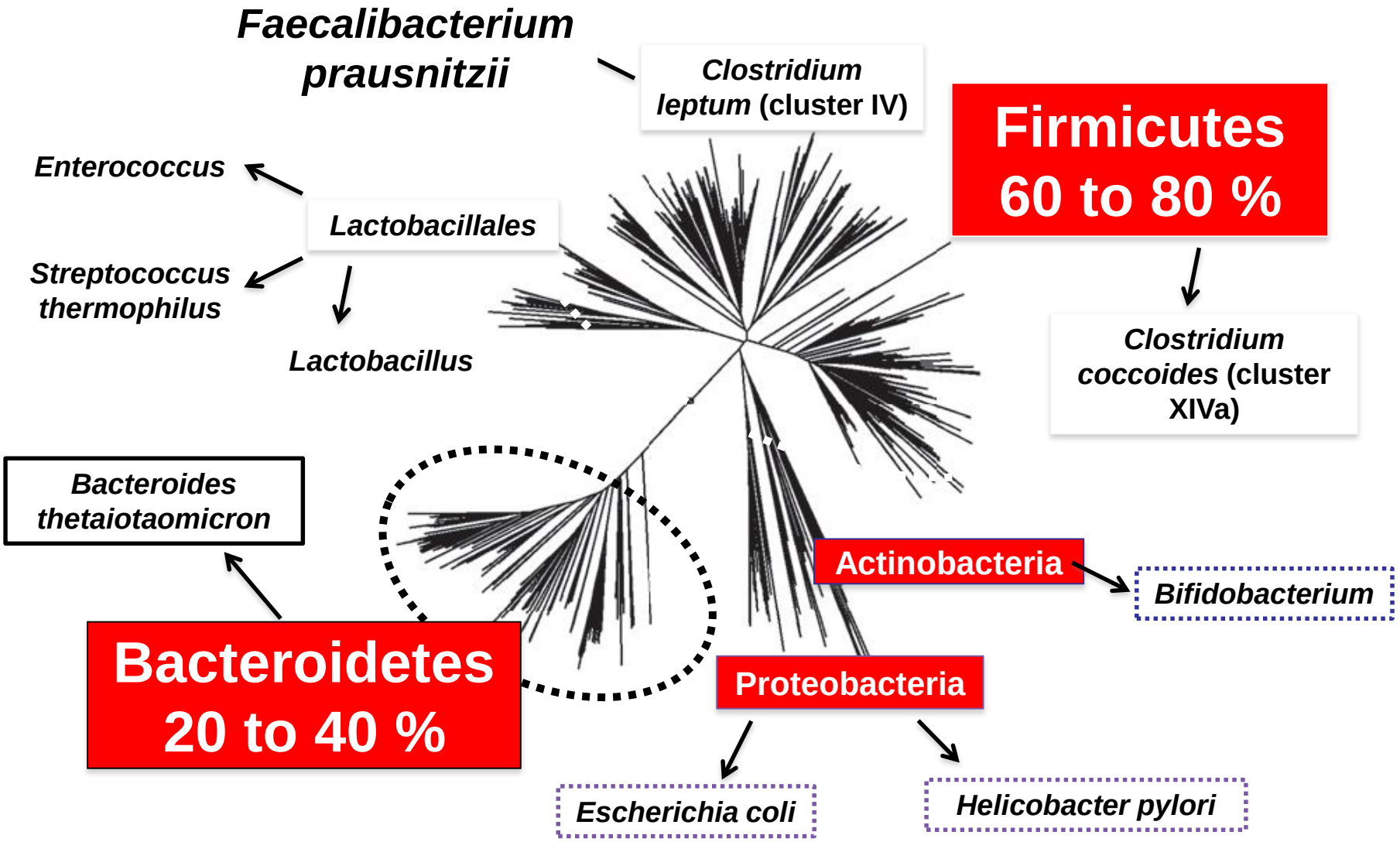
130-150 bacterial species

800-1200 subspecies

800-1000 gr, 3.000.000 genes

Microbiome ⟷ **Metabolome**

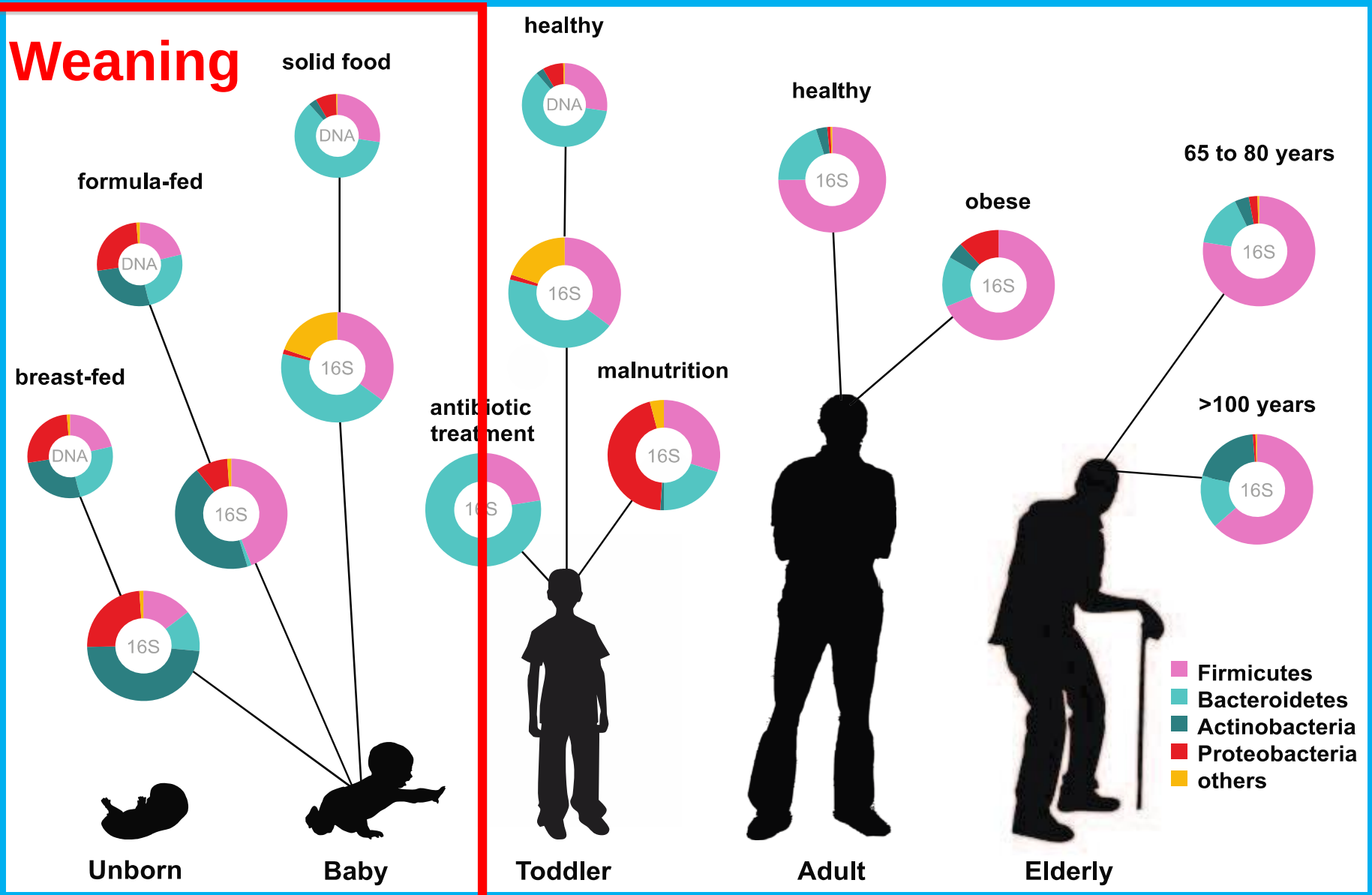
Phylogenetic diversity of human gut Bacteriome



2 major phyla: Firmicutes and Bacteroidetes (>70%)

Dethlefsen et al., Nature, 2007 18;449(7164):811-8 Ley et al., Science, 2008, 20;320(5883):1647-51
Tap et al., Environ Microbiol, 2009, 11(10):2574-84

Dysbiosis is a consequence of life events



Ottmann N et al. Front Cell Infect Microb 2012

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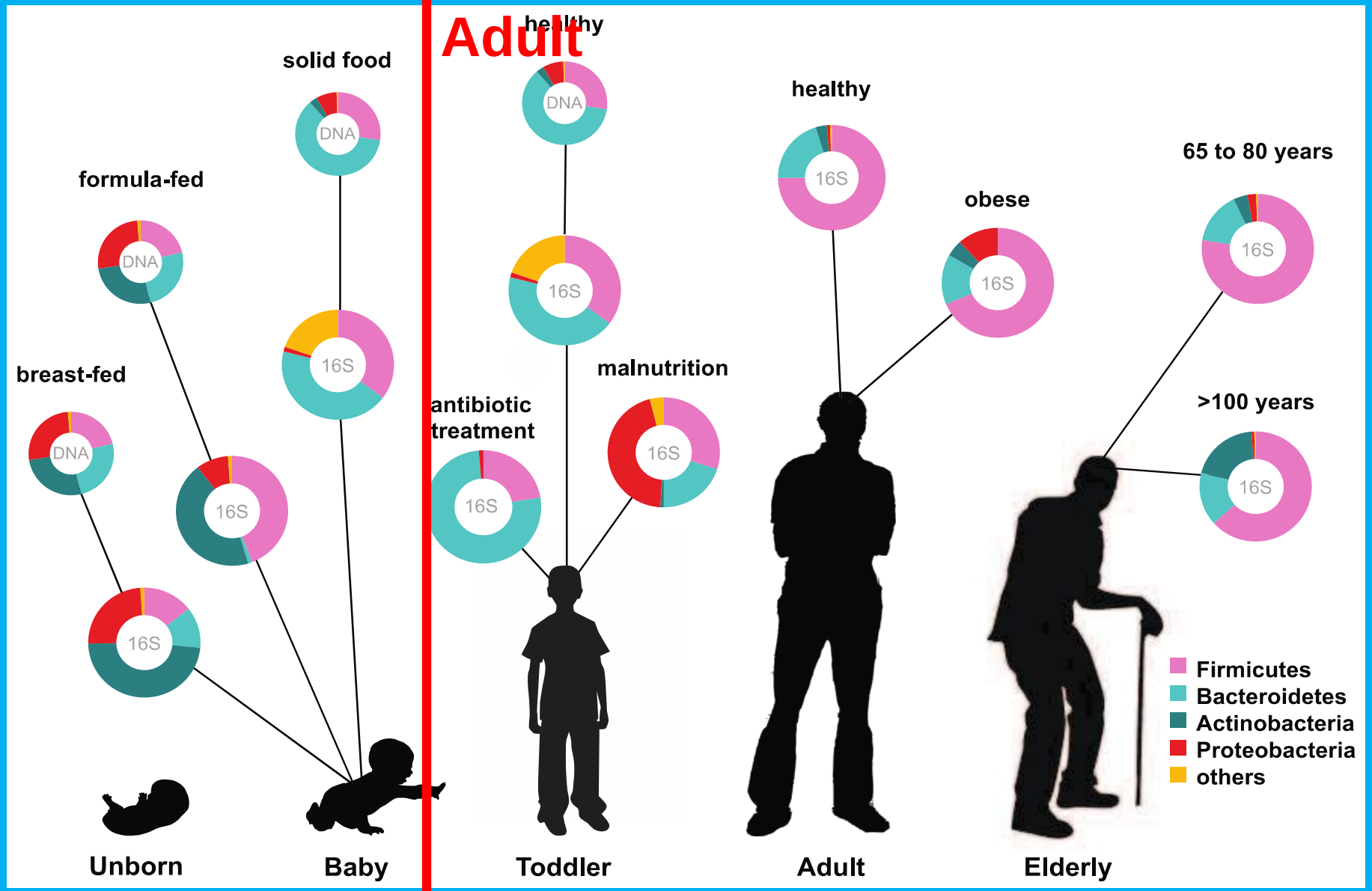
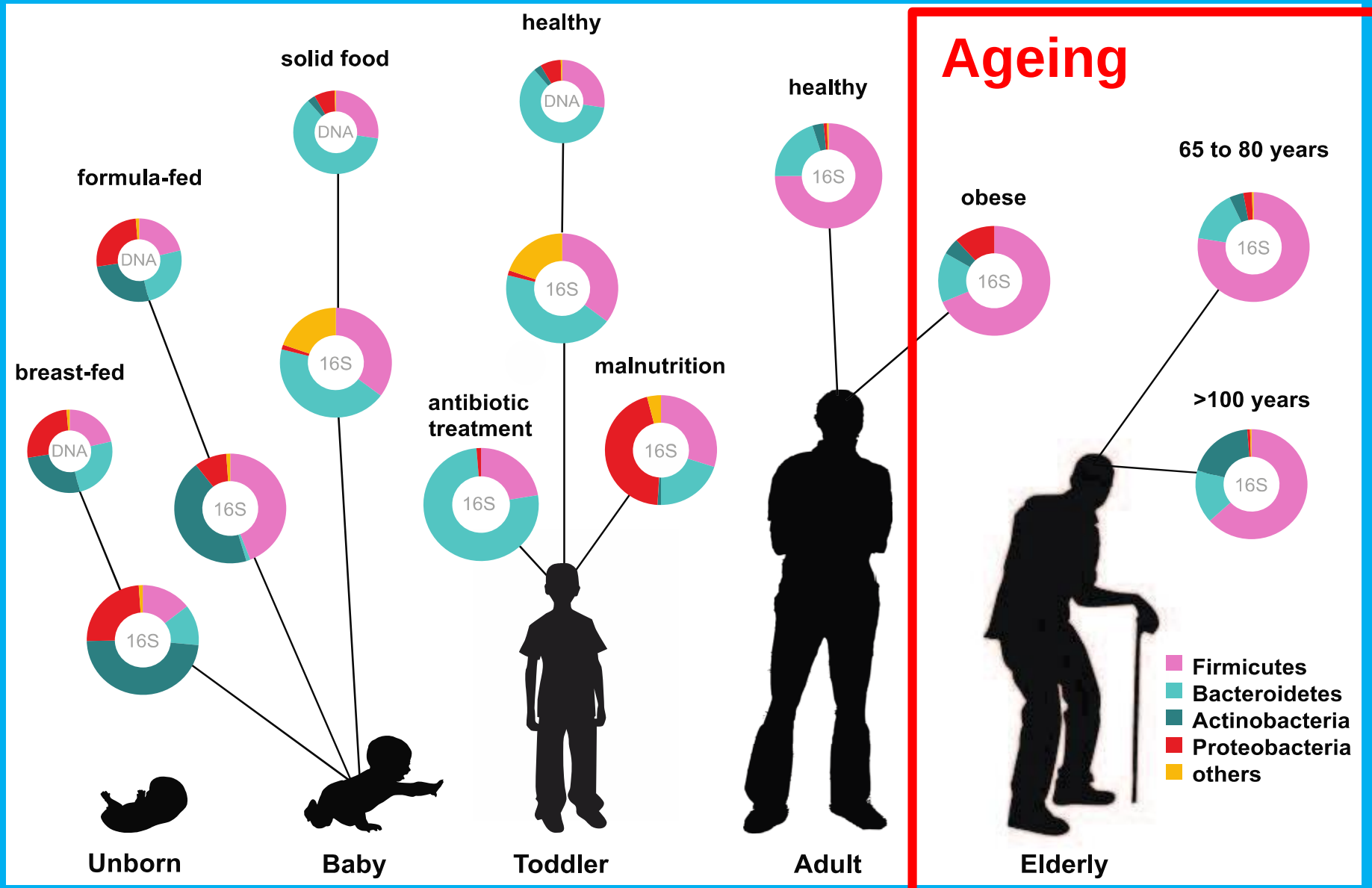


Ottmann N et al. Front Cell Infect Microb 2012

Dysbiosis is caused by several life events



Ottmann N et al. Front Cell Infect Microb 2012

GUT MICROBIOTA AND HOST HEALTH

- **Barrier effect**
- **Immunocompetence/Tolerance**
- **Synthesis**
- **Metabolism**
- **Drug metabolism**
- **Behavior conditioning**

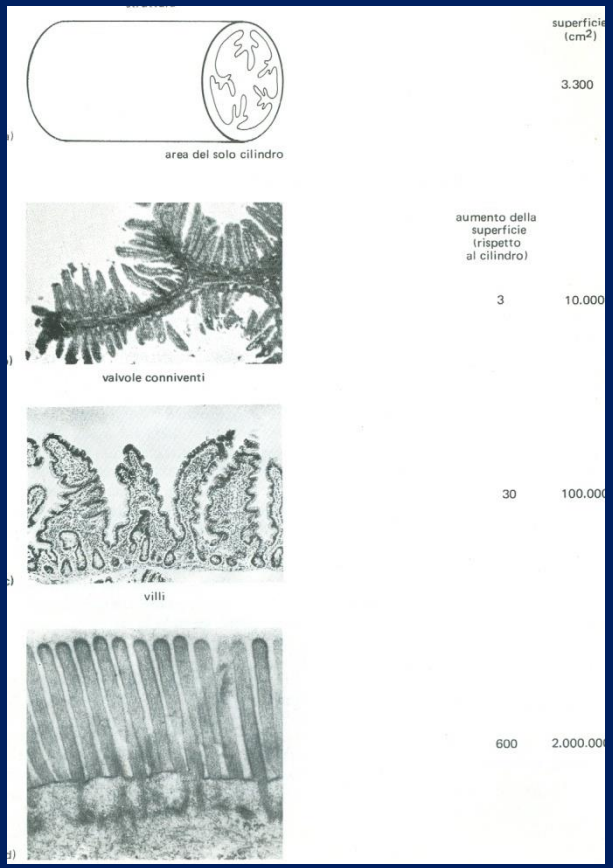
…specific effects in each GI tract!

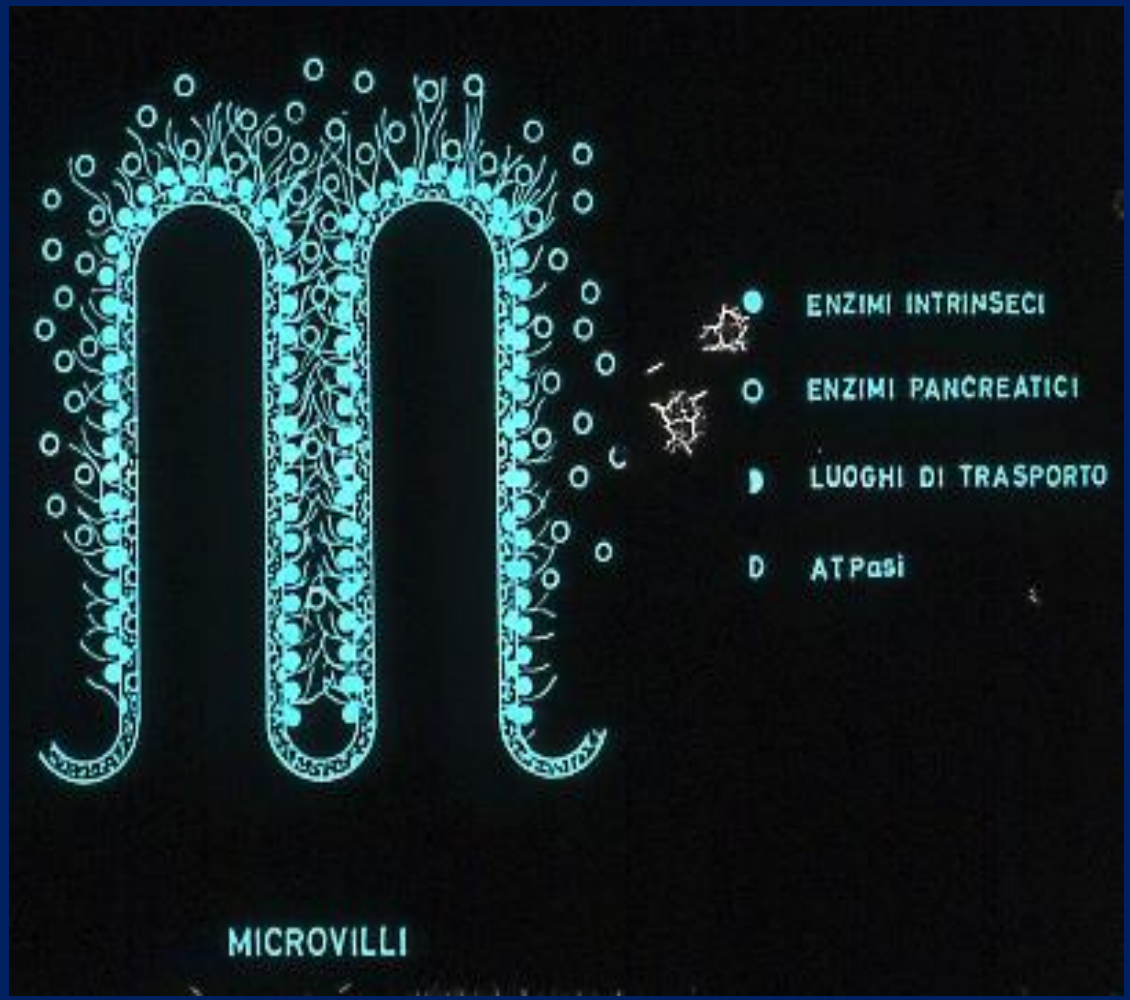
dove sta’

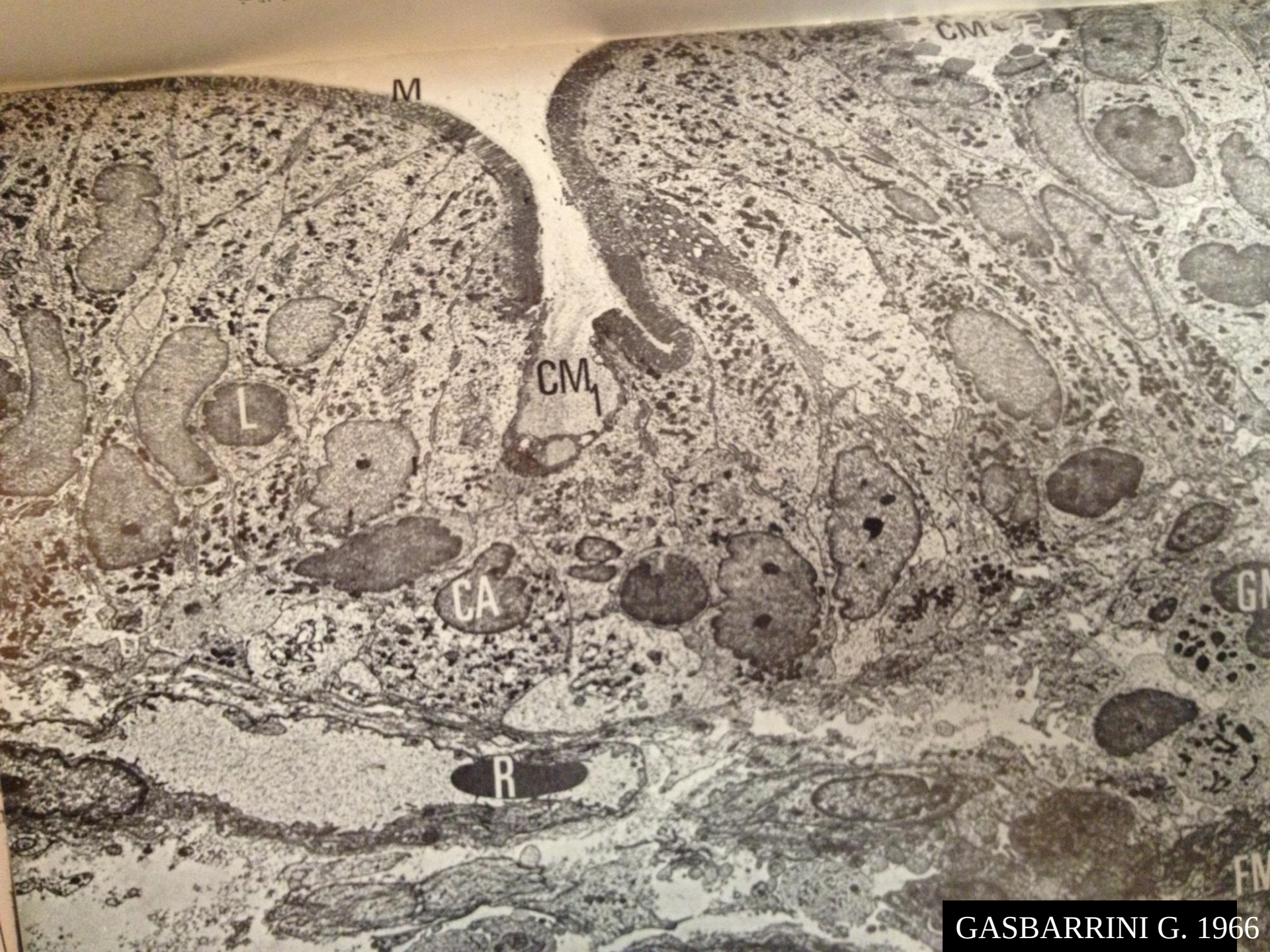
?

MUCOSAL BARRIER: INTEGRITY OF ENTEROCYTES AND BRUSH BORDER

GASBARRINI G. 196


superficie (cm²)
3.300
area del solo cilindro
aumento della superficie (rispetto al cilindro)
3
10.000
valvole conniventi
30
100.000
villi
600
2.000.000

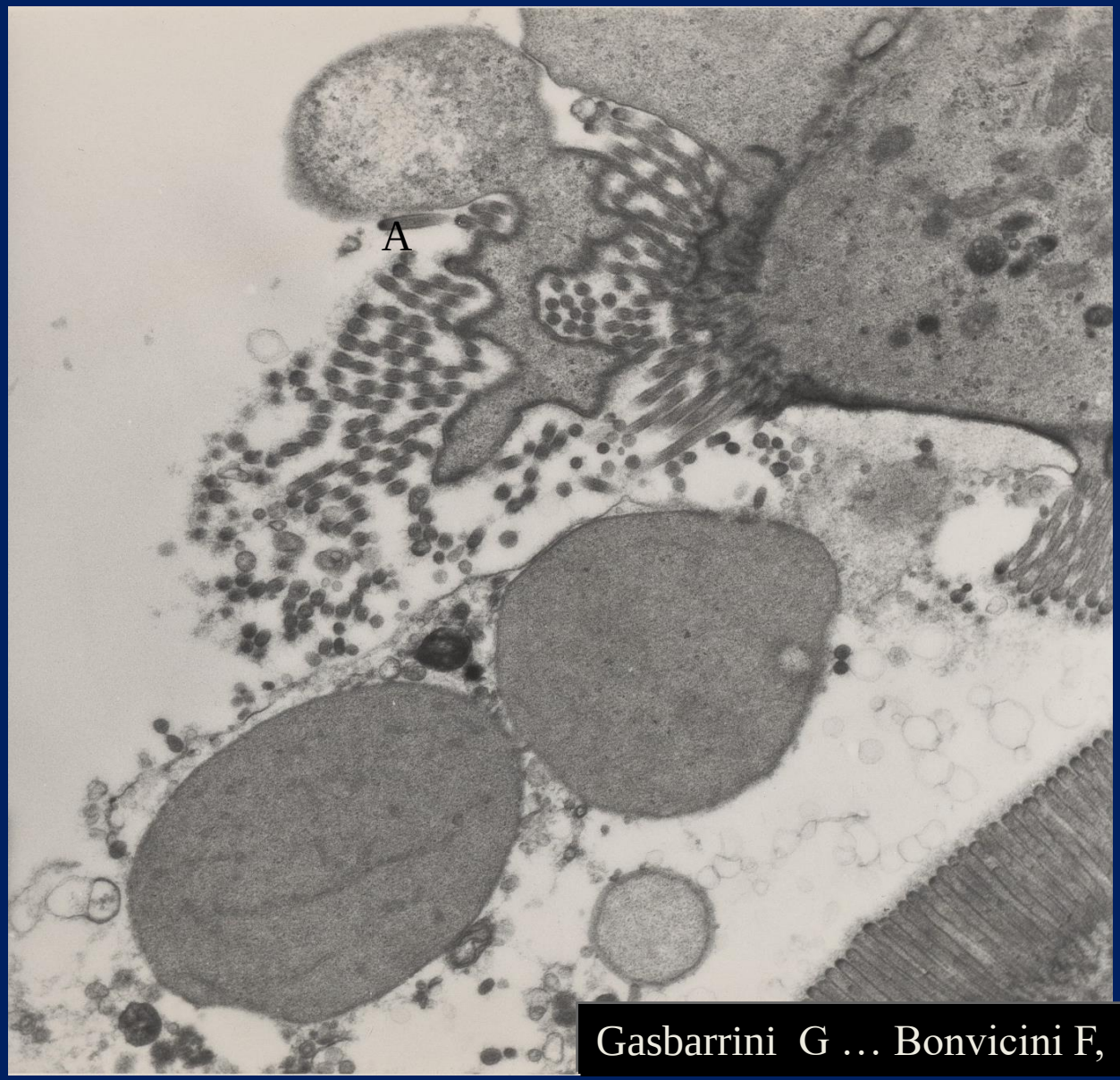

ENZIMI INTRINSECI
ENZIMI PANCREATICI
LUOGHI DI TRASPORTO
D ATPasi
MICROVILLI



GASBARRINI G. 1966

IN GERIATRIA

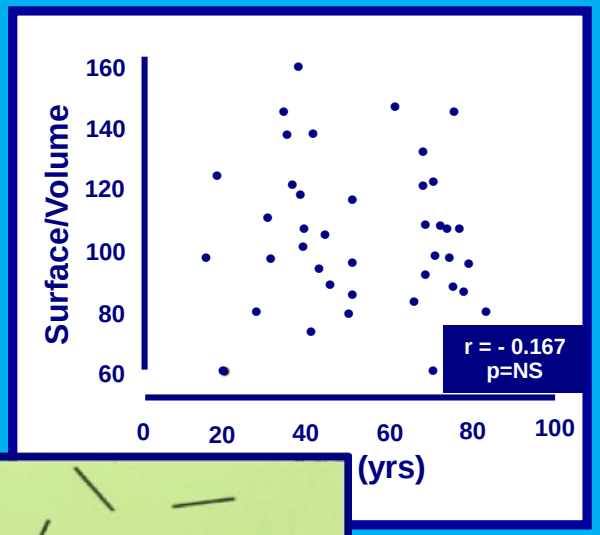
BLEBBING: A PHASE OF PHYSIOLOGIC CELL DEATH WITH EXTRUSION OF APOPTOTIC BODIES

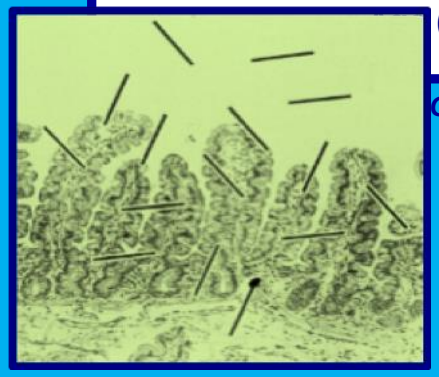


Gasbarrini G … Bonvicini F, 1962

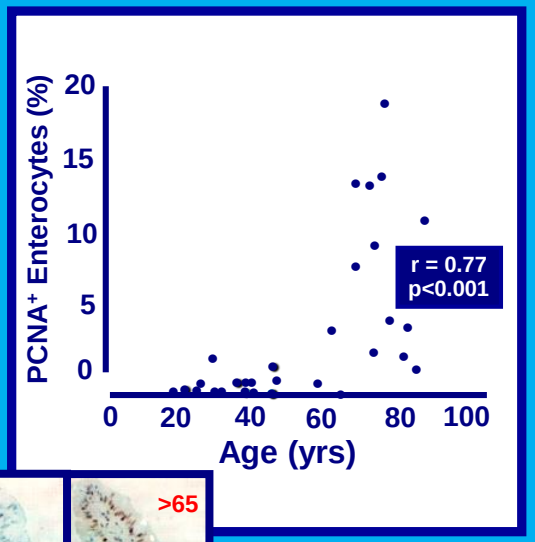
OR LIKE A SILE OF AMERICA'S CUP: *SPINNAKER APOPTOSIS*

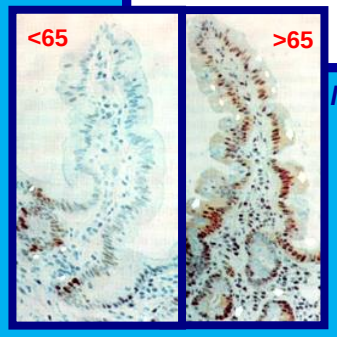
SMALL BOWEL MUCOSA IN THE ELDERLY



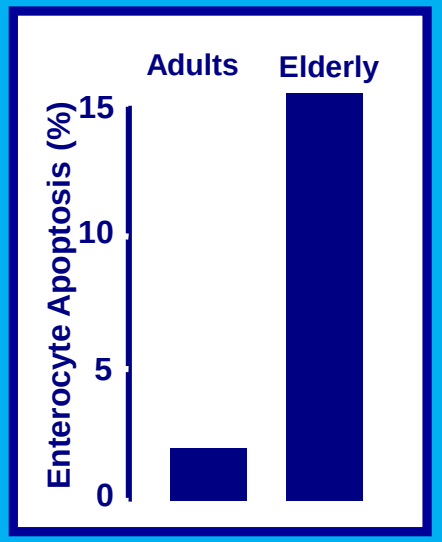


Gerontology 1986





Mech Ageing Dev 1998



Gerontology 2002

THE "AGEING" GUT

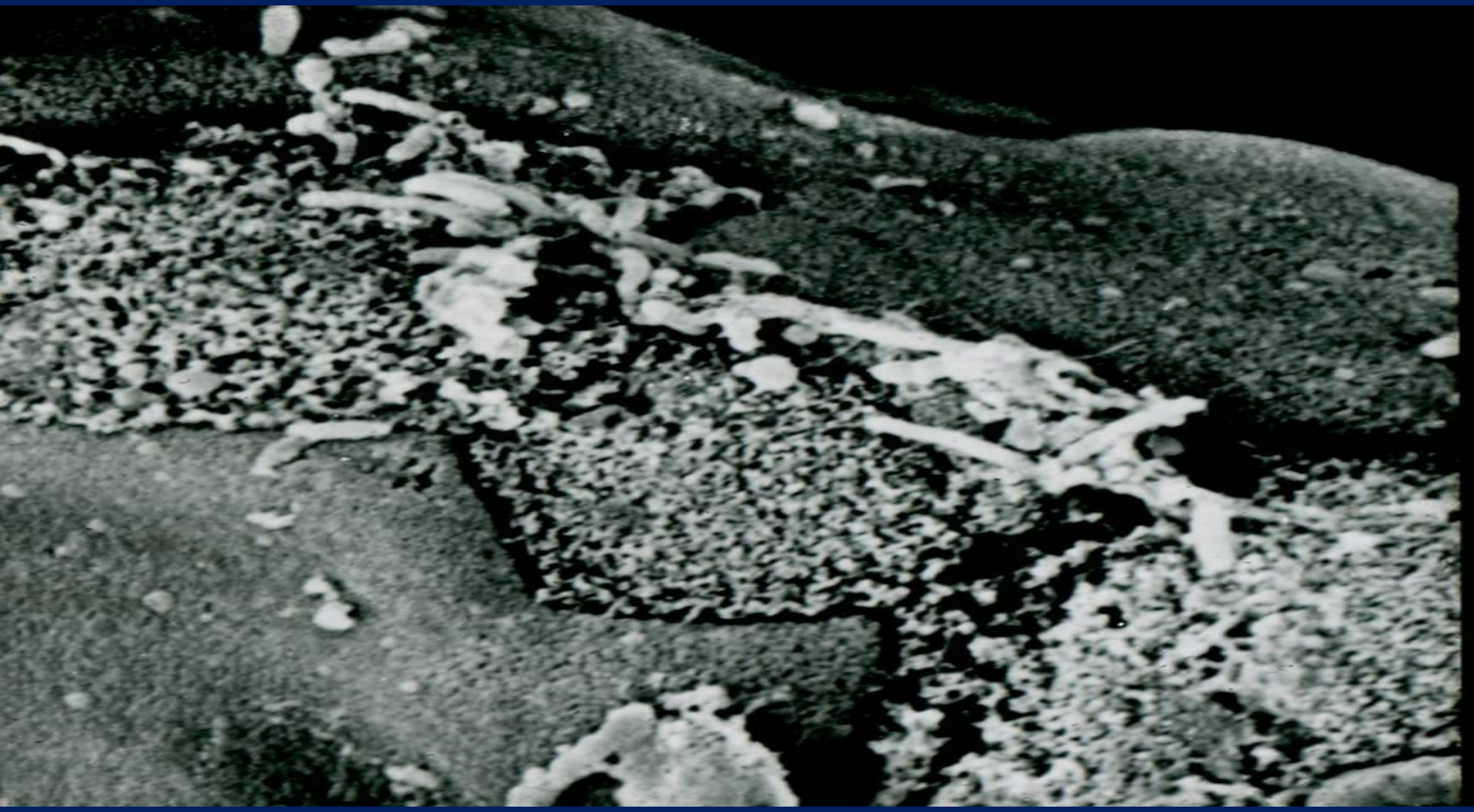
Normal morphology

Increased enterocyte proliferation rate

Malabsorption in stress conditions

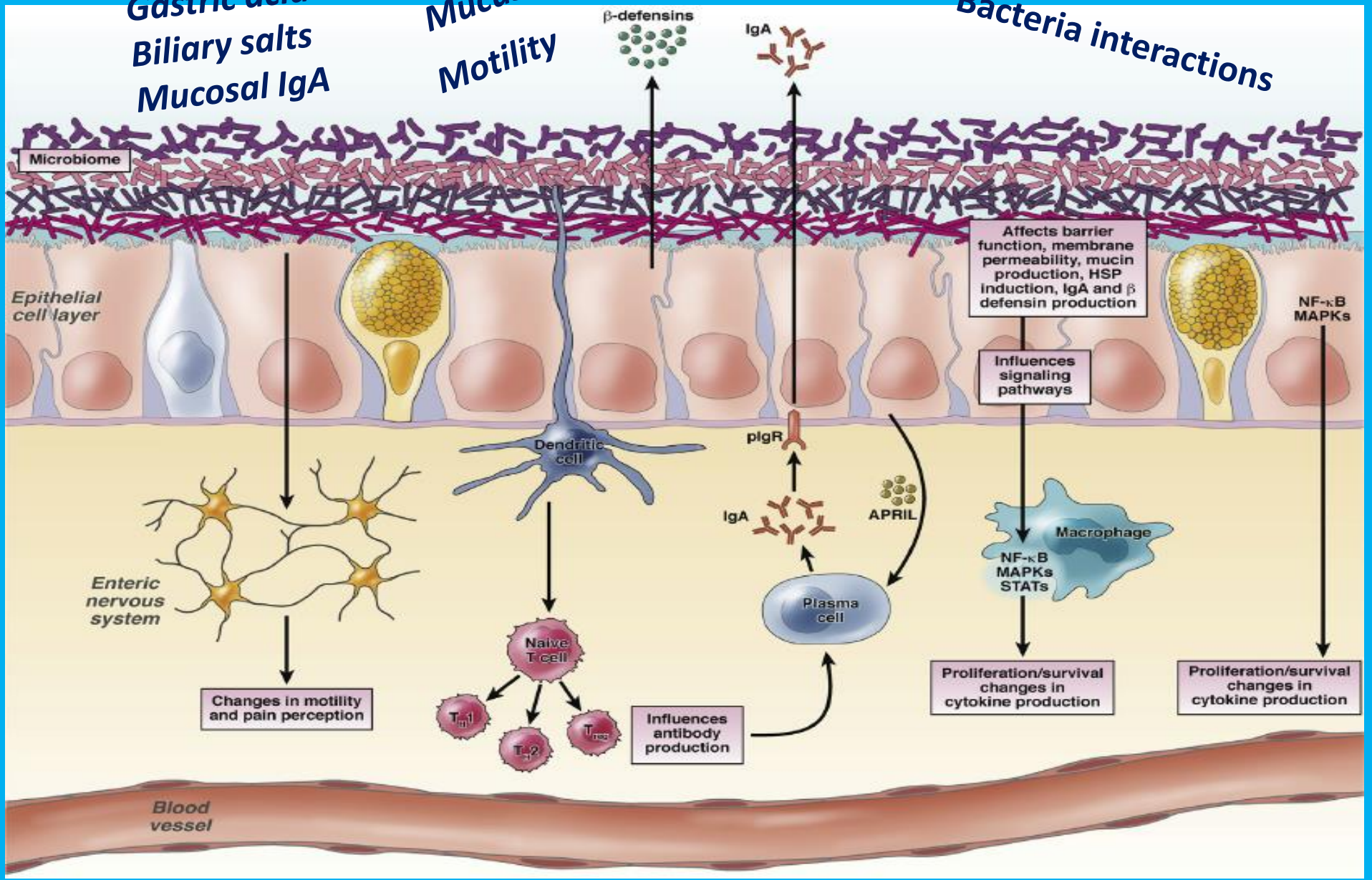
THE ANATOMO-MICROBIOLOGICAL GUT BARRIER

EFFECT OF THE MUCOLYTIC ACTIVITY OF BACTERIA ON THE SURFACE OF ENTEROCYTES



Gasbarrini G et al., SEM, 1985

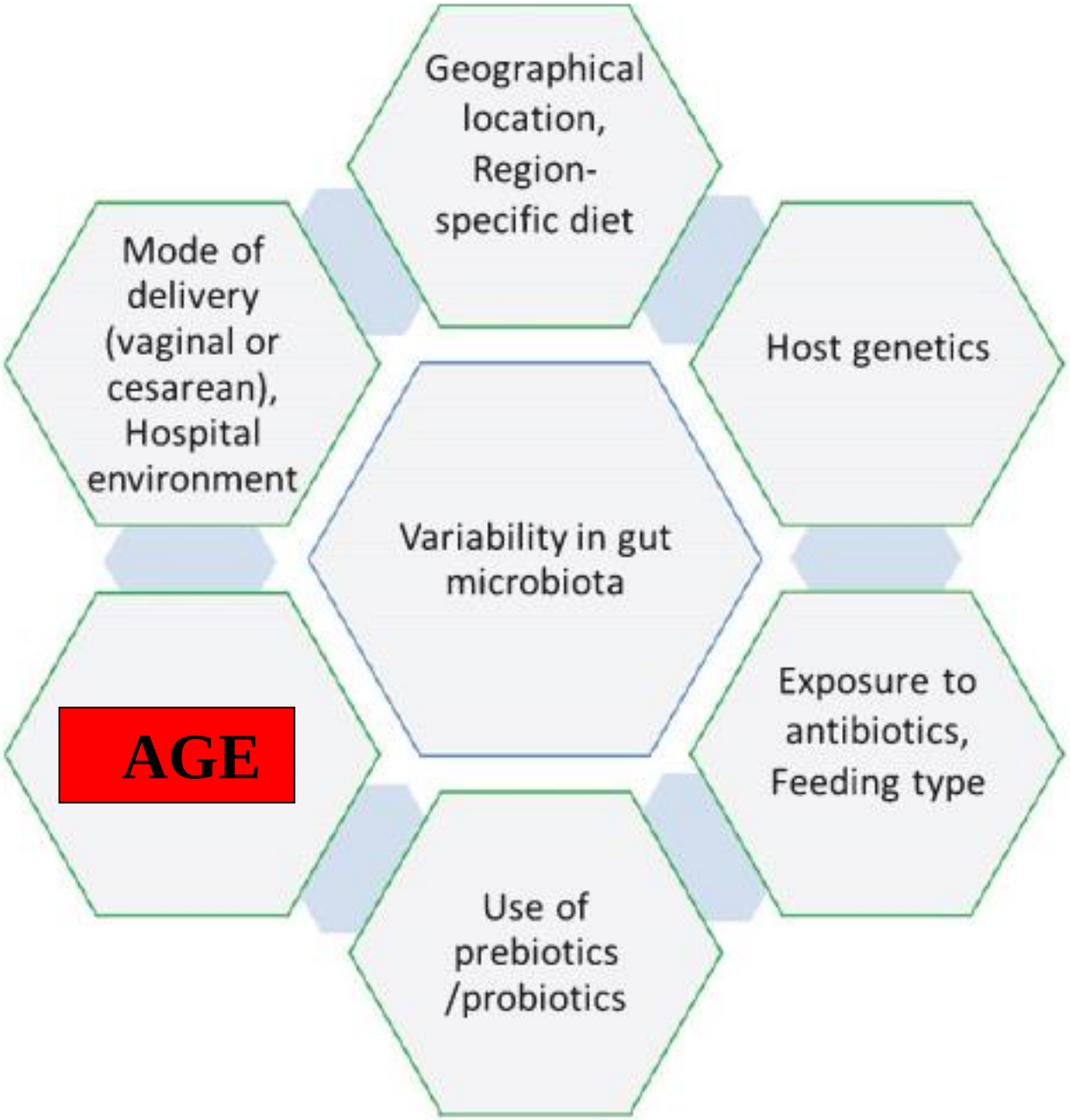
GUT BARRIER INTEGRITY



Hollister EB et al. Gastroenterology 2014

Almost any Digestive and extra-Digestive Diseases have been associated to a DYSBIOTIC and LEAKY GUT

- *Gastrointestinal infections*
- *IBS and IBD*
- *SIBO and CBO*
- *Diverticulosis*
- *Gastro-intestinal Cancers*
- *Food Intolerance/Allergy*
- *Celiac disease*
- *Liver and Pancreatic diseases*
- *Obesity, Diabetes and Metabolic Syndrome*
- *Gynecological, Rheumatological, Cardiovascular, Neuropsichiatric disorders…*



Kumar M et al. Nutrition and Healthy Ageing 2016

Ageing is characterized by the onset of pathophysiological processes which can dramatically compromise the homeostatic equilibrium between microbiota and host

DIGESTION:

- Poor comminution of hard foods due to possible poor dentition and decreased strength of muscles used in chewing and oral processing.
- Diminished production of saliva.
- Possible swallowing difficulties (dysphagia), potentially related to impaired saliva production.
- Possible lower acidity of the stomach, particularly for those with conditions being treated by proton pump inhibitor drugs.
- Diminished production of digestive enzymes.
- Decreased gut motility.

Boland M J Sci Food Agric 2016

Ageing is characterized by the onset of pathophysiological processes which can dramatically compromise the homeostatic equilibrium between microbiota and host

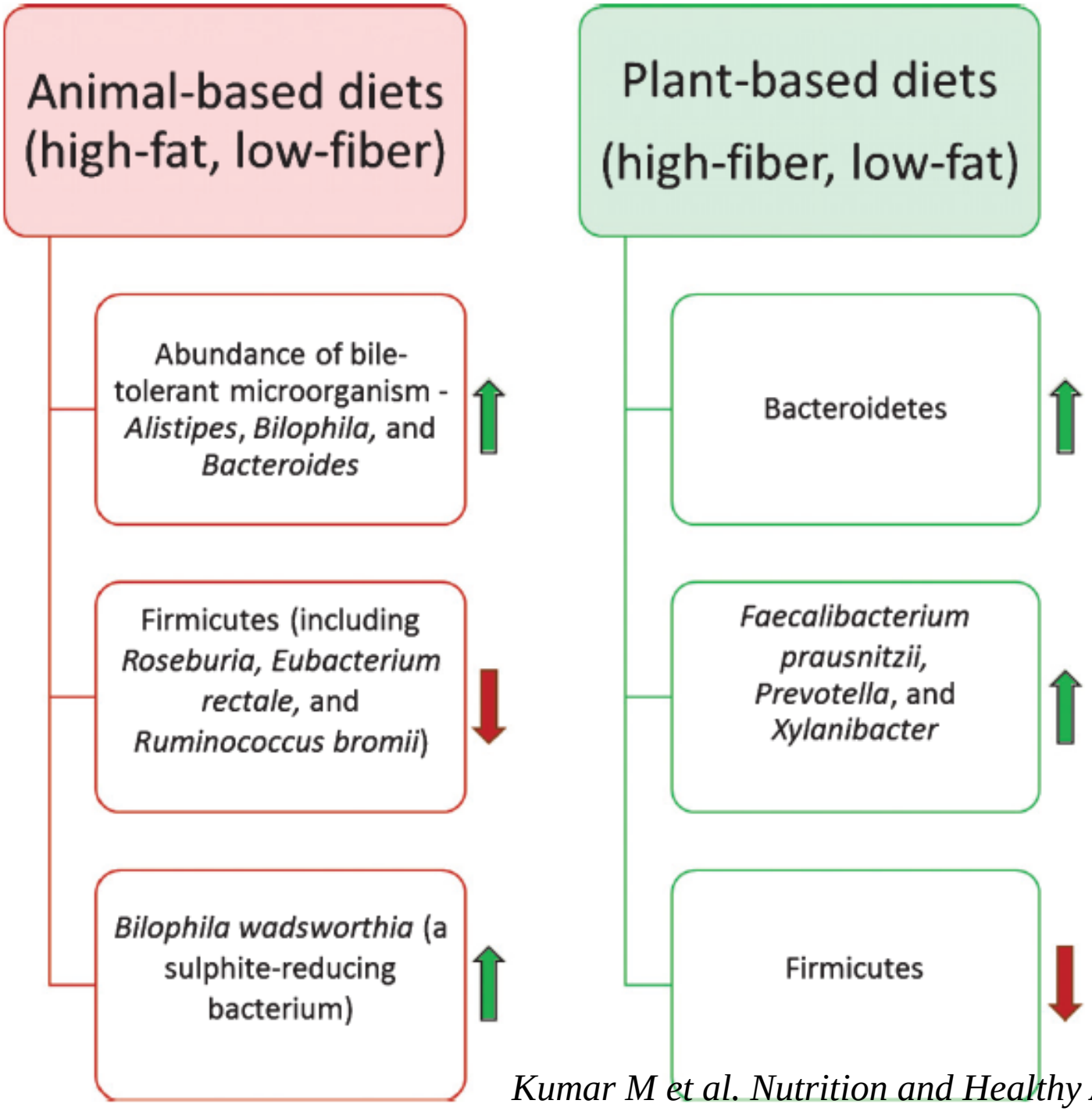
DIET:

• the diet in elderly individuals can change for a number of reasons, including loss of sensation of taste and smell, tooth loss and chewing difficulties.

•elderly have an increased risk of malnutrition

•poor quality of the diet: increased consumption of high sugar/high fat foods and a reduction in the proportion of plant-based foods consumed

Jeffery IB et al. Nutrients 2013



Kumar M et al. Nutrition and Healthy Ageing 2016

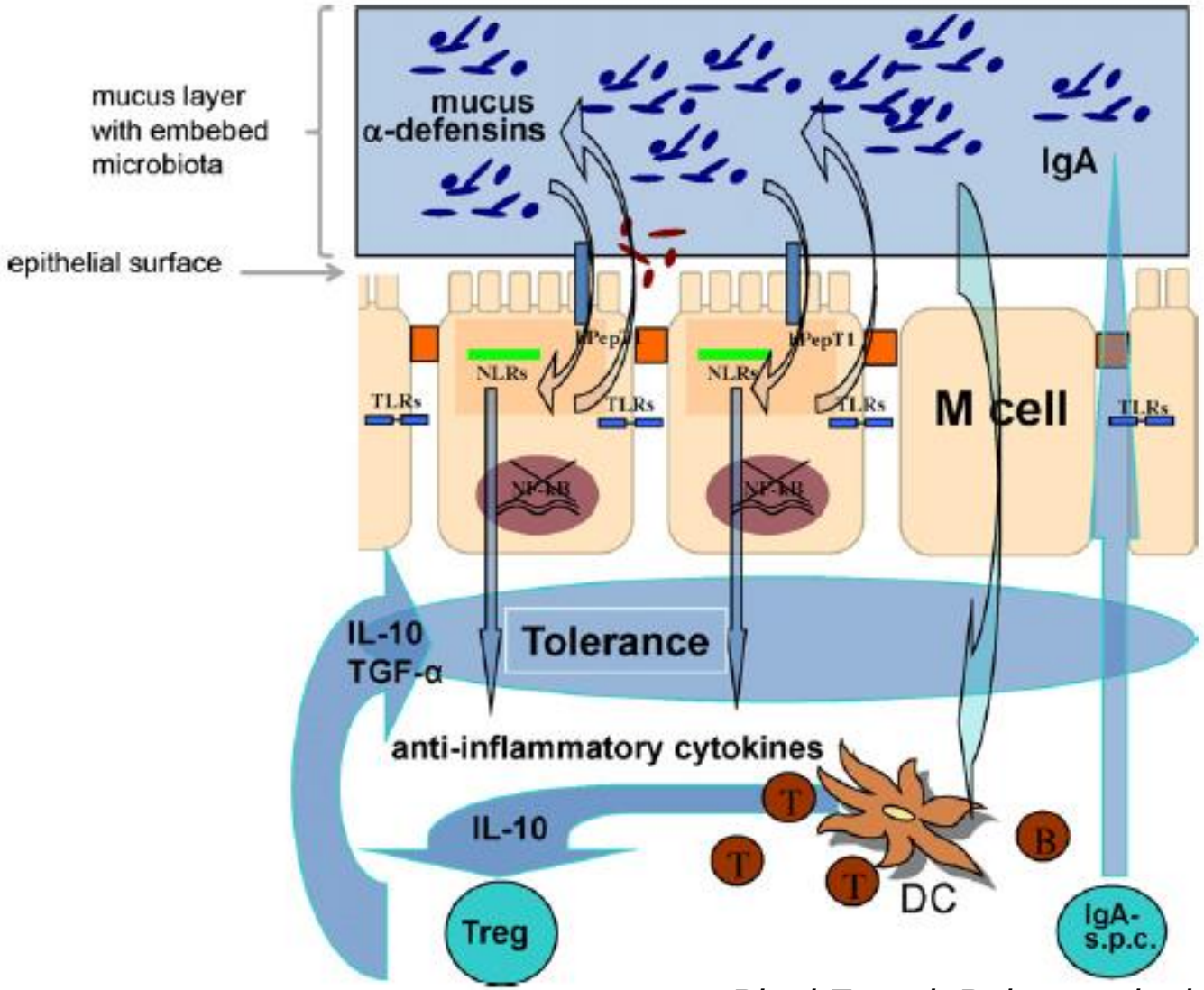
Ageing is characterized by the onset of pathophysiological processes which can dramatically compromise the homeostatic equilibrium between microbiota and host

DETERIORATION OF THE IMMUNE SYSTEM FUNCTION (IMMUNOSENESCENCE)
CAUSE:

- Changes in Innate Immunity
- Changes in Adaptive Immunity
- Inflammaging: a chronic, low-grade, pro-inflammatory condition
- Due to the increase in plasmatic levels and cell capability to produce pro-inflammatory cytokines

Ostan R et al. Neuroimmunomodulation 2008

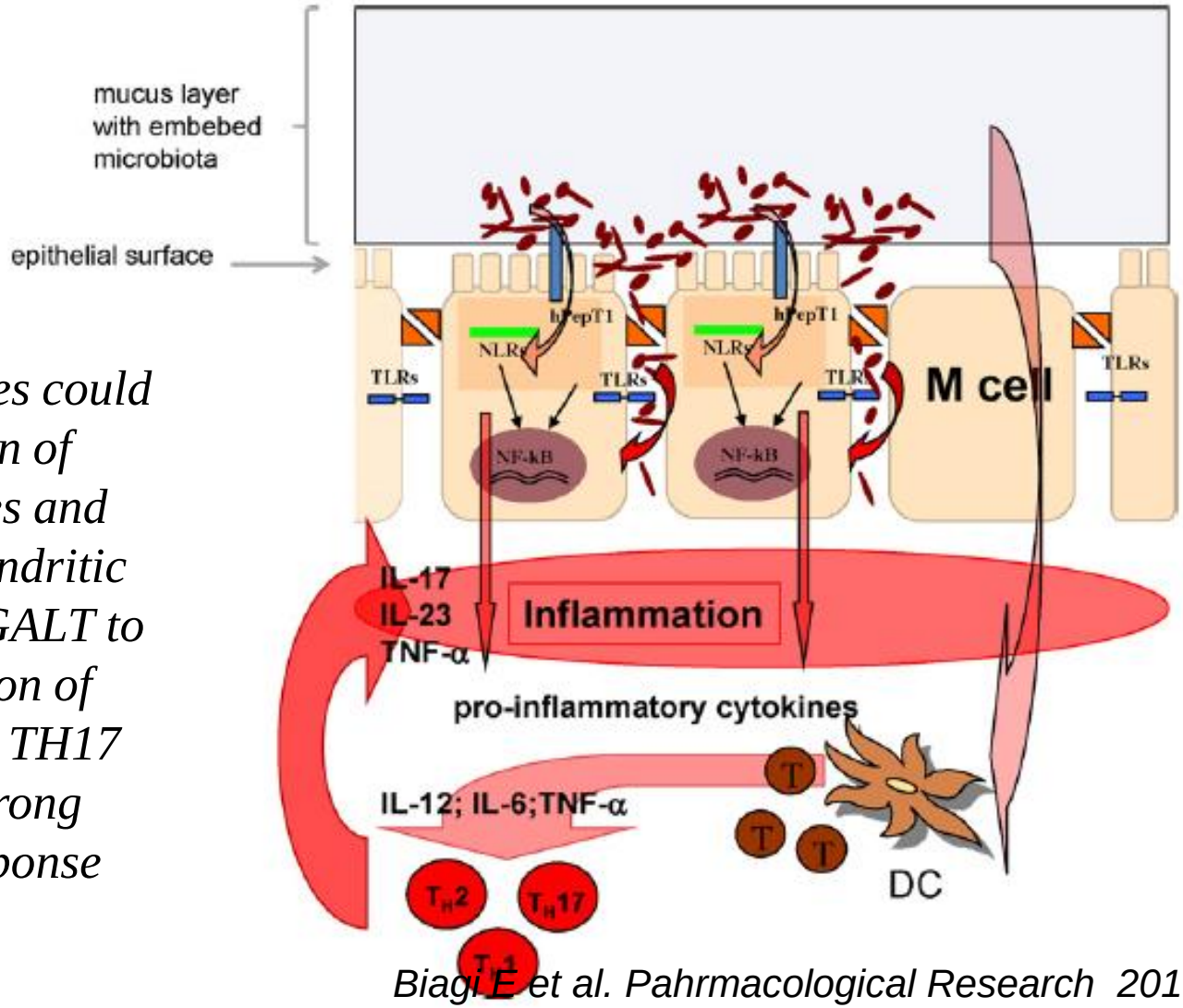
Intestinal microorganisms are kept
under a constant surveillance, to avoid an
excessive bacterial load on the intestinal mucosal surface.



Biagi E et al. Pahrmacological Research 2013

In the elderly, the impairment of the GALT capacity to efficiently synthesize strain-specific secretory IgA, together with the reduced efficiency of the innate immune defences, may result in the failure to control the resident microbiota.

In this context enterocytes could engage the activation of inflammatory cytokines and chemokines, forcing dendritic cells in the underlying GALT to drive the differentiation of effector TH1, TH2 and TH17 cells that induce a strong pro-inflammatory response



Biagi E et al. Pahrmacological Research 2013

EUBIOSIS

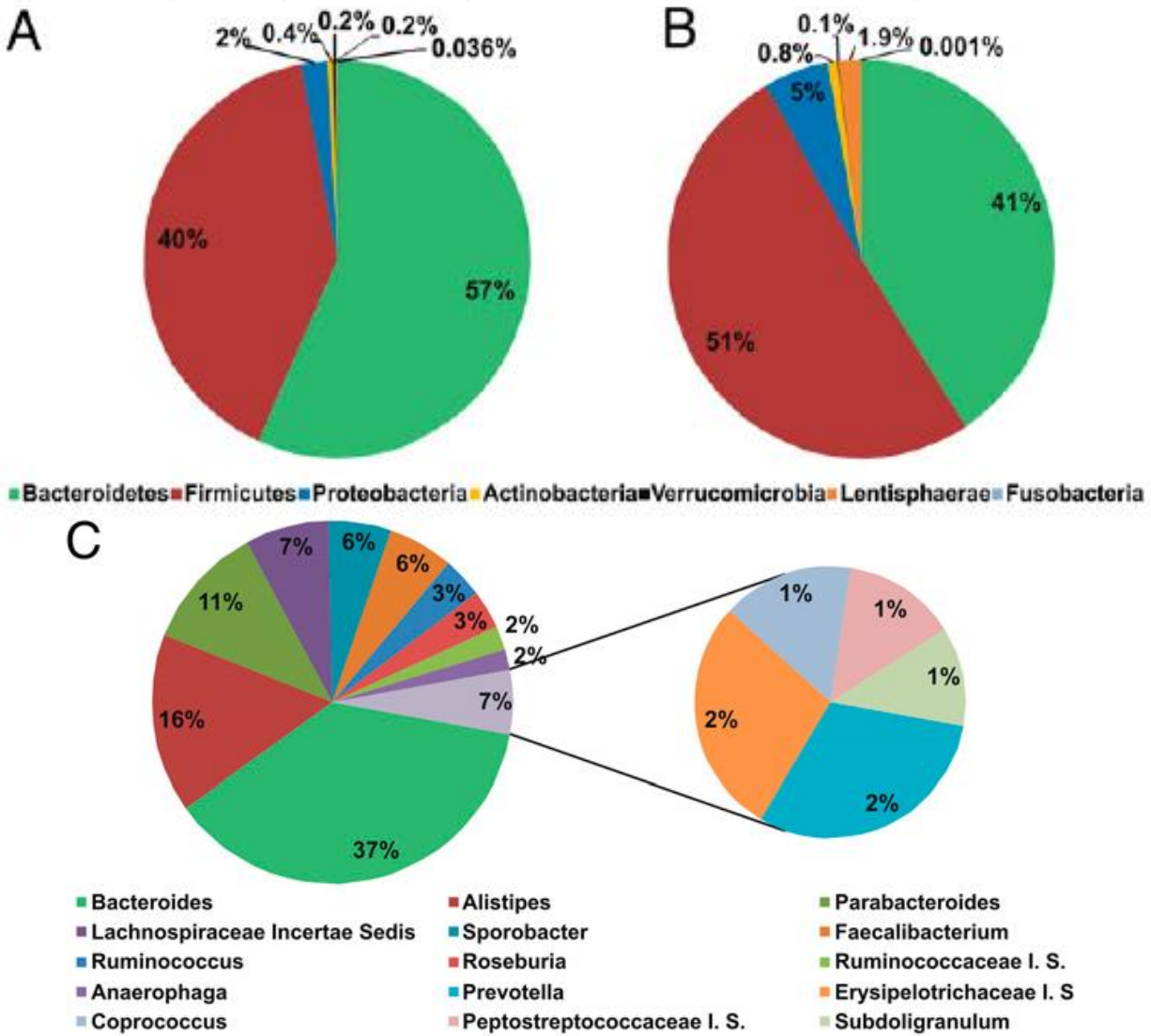
Modification of MICROBIOTA-HOST equilibrium during lifetime

Quali-quantitative alteration of gut microbiota and its functions

“AGED” GUT MICROBIOTA

Composition, variability, and temporal stability of the intestinal microbiota of the elderly

Marcus J. Claesson[a,b], Siobhán Cusack[a], Orla O'Sullivan[c], Rachel Greene-Diniz[a], Heleen de Weerd[d], Edel Flannery[e], Julian R. Marchesi[b,f], Daniel Falush[g], Timothy Dinan[b,h], Gerald Fitzgerald[a,b], Catherine Stanton[b,c], Douwe van Sinderen[a,b], Michael O'Connor[i,j], Norma Harnedy[i,j], Kieran O'Connor[j,k,l], Colm Henry[k,l], Denis O'Mahony[i,j,m], Anthony P. Fitzgerald[e,n], Fergus Shanahan[b,m], Cillian Twomey[i,j,m], Colin Hill[a,b], R. Paul Ross[b,c], and Paul W. O'Toole[a,b,1]



ELDERLY IRISH SUBJECTS:

- Different Fecal Core Microbiota compared toYounger and Older Adults
- Bacteroidetes-Dominant Interindividual Variability
- Increased abundance of *Faecalibacterium spp.*

Claesson et al, PNAS 2010

Gut microbiota composition correlates with diet and health in the elderly

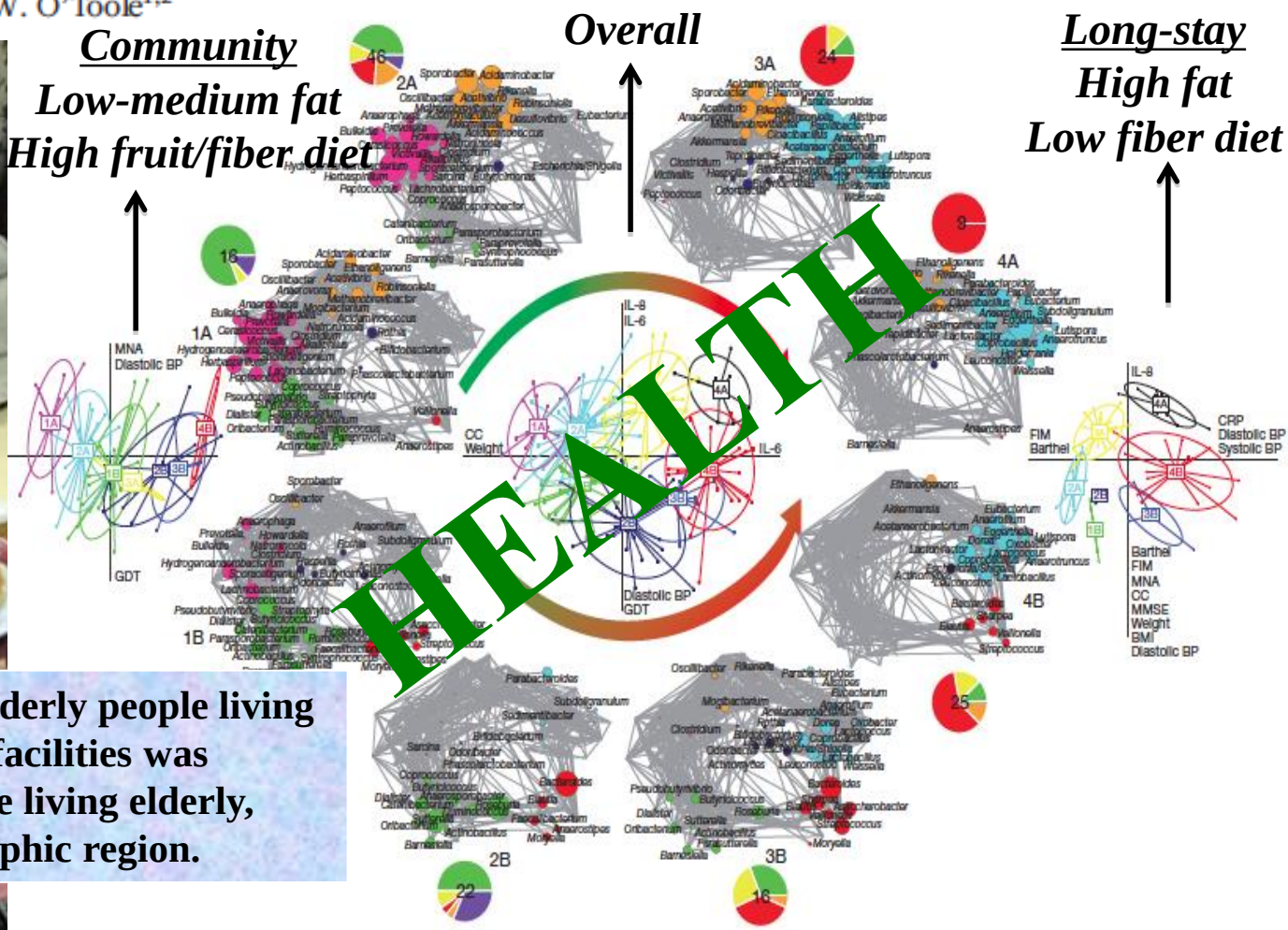
178 | NATURE | VOL 488 | 9 AUGUST 2012

Marcus J. Claesson[1,2]*, Ian B. Jeffery[1,2]*, Susana Conde[3], Susan E. Power[1], Eibhlís M. O'Connor[1,2], Siobhán Cusack[1], Hugh M. B. Harris[1], Mairead Coakley[4], Bhuvaneswari Lakshminarayanan[4], Orla O'Sullivan[4], Gerald F. Fitzgerald[1,2], Jennifer Deane[1], Michael O'Connor[5,6], Norma Harnedy[5,6], Kieran O'Connor[6,7,8], Denis O'Mahony[5,6,8], Douwe van Sinderen[1,2], Martina Wallace[9], Lorraine Brennan[9], Catherine Stanton[2,4], Julian R. Marchesi[10], Anthony P. Fitzgerald[3,11], Fergus Shanahan[2,12], Colin Hill[1,2], R. Paul Ross[2,4] & Paul W. O'Toole[1,2]

Community
Low-medium fat
High fruit/fiber diet

Overall

Long-stay
High fat
Low fiber diet



Microbiota composition in elderly people living in long-stay residential care facilities was different from that of the free living elderly, within the same ethnogeographic region.

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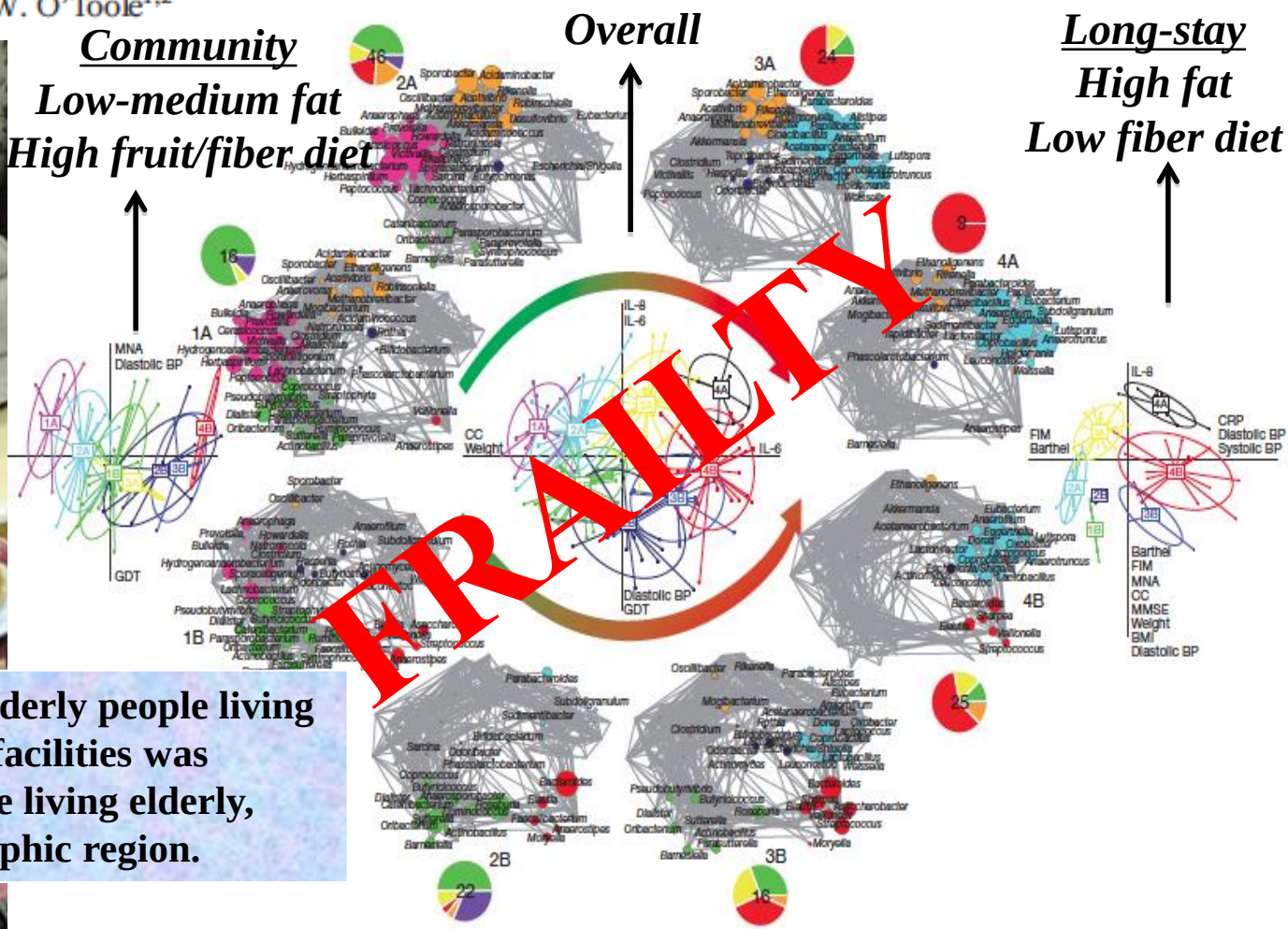


Microbiota composition in elderly people living in long-stay residential care facilities was different from that of the free living elderly, within the same ethnogeographic region.

Gut microbiota in the elderly

- "long-stay" associated microbiota group:
  ↑frailty, ↑consumption of sugars and fats, ↓nutritional status

↓

mostly found in long-term care facilities, but were also detectable in the community in people with similar signs of biological aging

- "diversity-associated" microbiota group:
  more healthy, healthy diet

↓

usually community-dwelling elderly volunteers

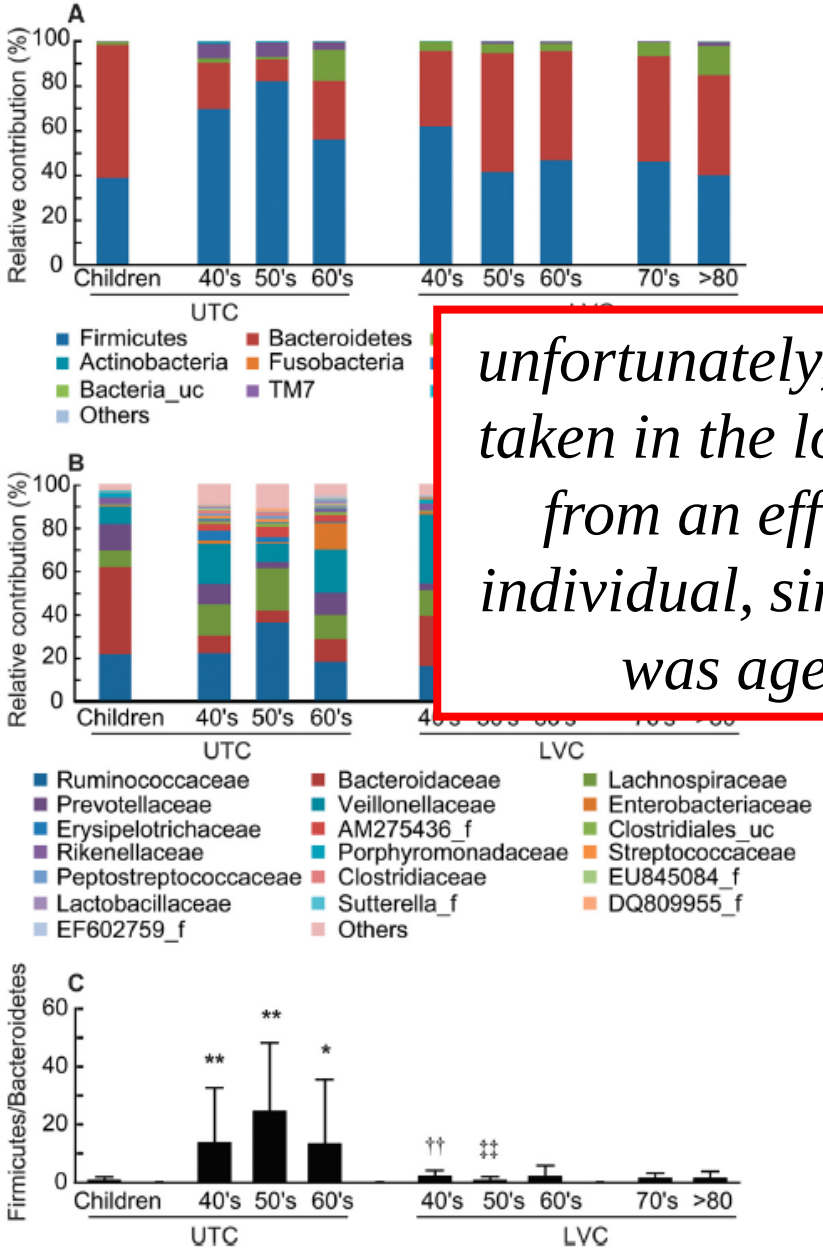
Community associated microbiota configurations were impacted more by the use of antibiotics than the microbiota of individuals in long-term care (more pronounced decrease-recovering process)

Jeffery IB et al. ISME J 2015

Comparative analysis of gut microbiota in elderly people of urbanized towns and longevity villages

Se-Hoon Park[1†], Kyung-Ah Kim[2†], Young-Tae Ahn[1†], Jin-Ju Jeong[2], Chul-Sung Huh[3] and Dong-Hyun Kim[2*]

BMC Microbiology



Gut microbiota of elderly people of urbanized town communities (UTC) vs. longevity village communities (LVC)

The ratio of Firmicutes to Bacteroidetes in the gut
TC adults than in UTC
he population levels of
nd Lachnospira were
than in UTC, but the
igranulum, Megamonas,
36_g were lower in LVC

unfortunately, none of the samples taken in the longevity villages was from an effectively longevous individual, since the elderly group was aged 80±9 years!

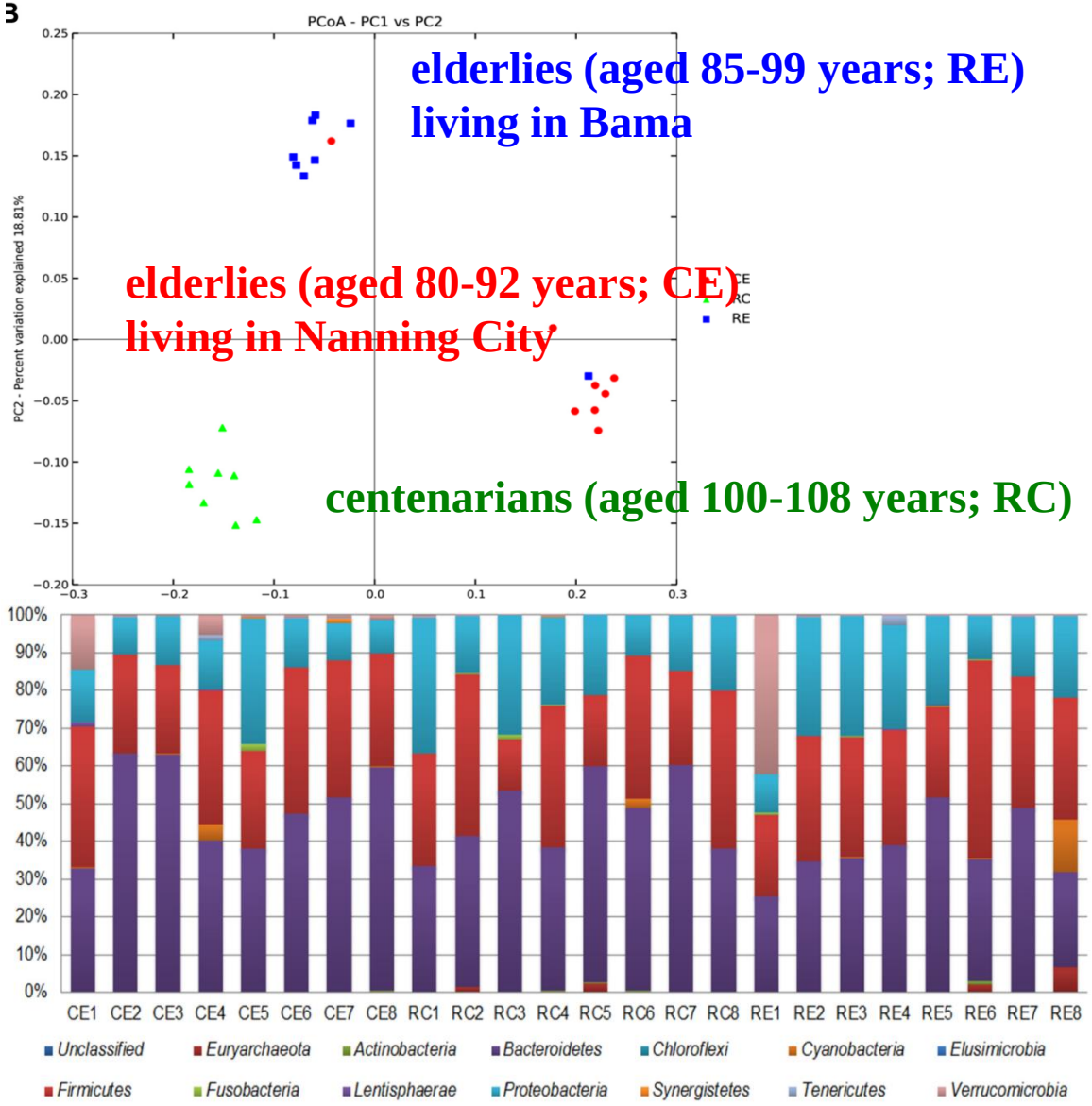
Although most of the species detected in LVC were detected in UTC, **some Bacteroides spp. and Faecalibacterium spp. were detected only in LVC.**

These findings suggest that maintaining gut microbiota, including Faecalibacterium spp. play an important role in preserving residents' health in LVC.

Gut Microbiota Community and Its Assembly Associated with Age and Diet in Chinese Centenarians

J. Microbiol. Biotechnol. (2015), 25(8), 1195–1204

Fang Wang[1], Ting Yu[1], Guohong Huang[1,2], Da Cai[1], Xiaolin Liang[1], Haiyan Su[1], Zhenjun Zhu[1], Danlei Li[3], Yang Yang[4], Peihong Shen[4], Ruifeng Mao[1], Lian Yu[1], Mouming Zhao[1*], and Quanyang Li[1*]



Centenarians-related OTUs:
Ruminococcaceae
Clostridiaceae

High-fiber diet-related OTUs:
Ruminococcaceae

The age and high-fiber diet were concomitant with changes in the gut microbiota of centenarians, suggesting that age and high-fiber diet can establish a new structurally balanced architecture of gut microbiota that may benefit the health of centenarians.

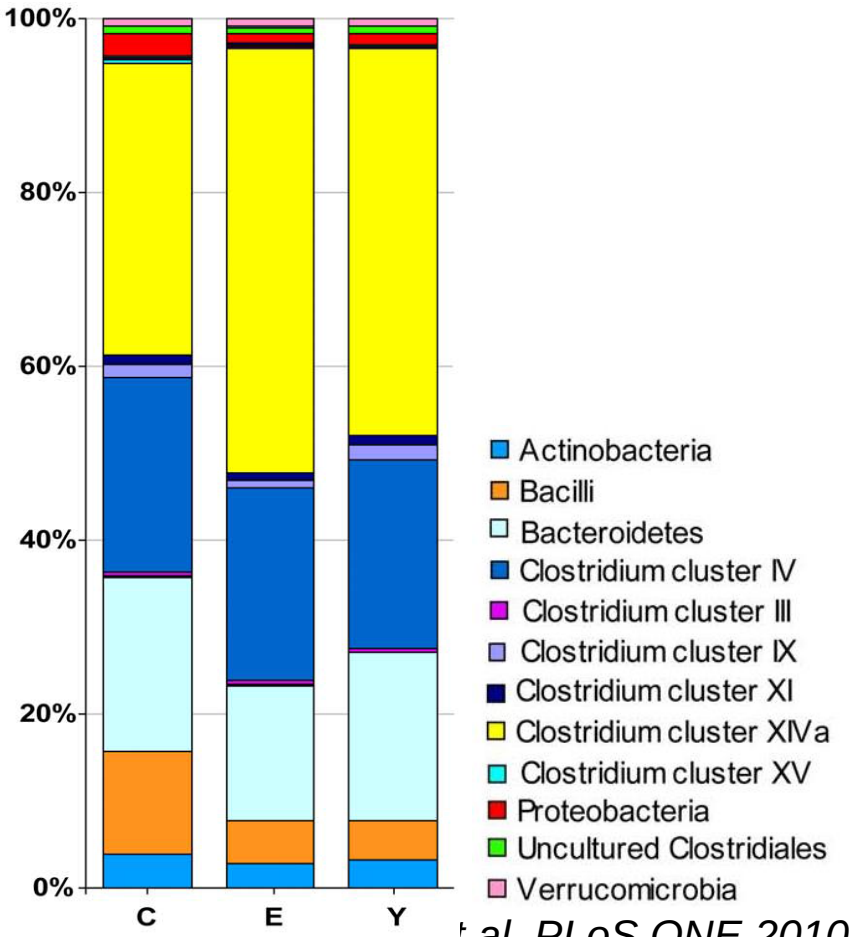
OPEN ACCESS Freely available online

PLoS one

Through Ageing, and Beyond: Gut Microbiota and Inflammatory Status in Seniors and Centenarians

Elena Biagi[1]*, Lotta Nylund[2,3], Marco Candela[1], Rita Ostan[4], Laura Bucci[4], Elisa Pini[4], Janne Nikkïla[3], Daniela Monti[5], Reetta Satokari[2], Claudio Franceschi[4], Patrizia Brigidi[1], Willem De Vos[3,6]

A low diversity in terms of species composition was observed in centenarians (Simpson index =127). **Bacteroidetes and Firmicutes still dominate the gut microbiota** of extremely old people (representing over 93% of the total bacteria). However changes in the relative proportion of Firmicutes subgroups were observed, with **a decrease in the contributing Clostridium cluster XIVa, an increase in Bacilli, and a rearrangement of the Clostridium cluster IV** composition. Moreover, the gut microbiota of centenarians is **enriched in Proteobacteria, a group containing many of those bacteria recently redefined as "pathobionts"**



Biagi, E et al. PLoS ONE 2010

Cell Reports
Article

The Gut Microbiota of Rural Papua New Guineans: Composition, Diversity Patterns, and Ecological Processes

Asaro and Suasi (Papua Nuova Guinea populations):

-live in traditional settings

-no sewage, wastewater, or drinking water treatment facilities exist, drinking water is derived primarily from rivers, streams, or rainwater and is mainly consumed without boiling or any other treatments

-both communities rely on subsistence agriculture for their food supply, with households having their own gardens
-under-nutrition is rare in PNG, as carbohydrate sources are generally available.

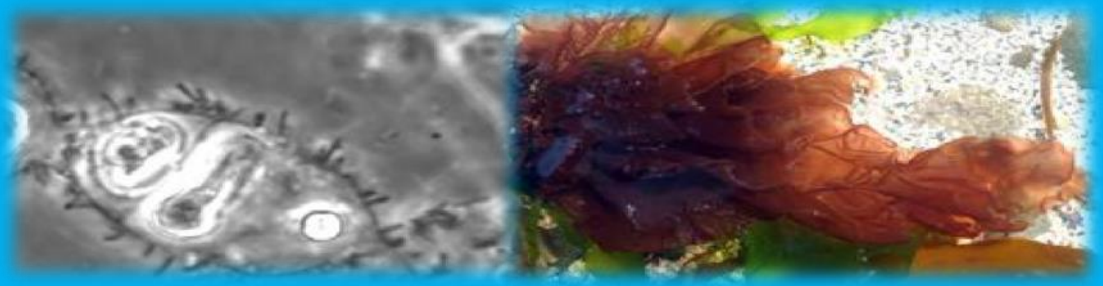
-staple foods are sweet potato, taro, and plantain, which are traditionally cooked in open fires and meat-derived protein (principally pork and fish) is consumed less frequently

-antibiotic use is high due to the high burden of infectious diseases, poorly regulated administration, and the lack of diagnostic capacity, which leads to empirical treatments.

Martinez I et al. Cell Press 2015

Diet and gut bacteria

"A special gift for sushi eaters"



Zobellia galactanivorans is a marine Bacteroidetes able to metabolize the polysaccharide porphyran from marine red algae. Metagenomics revealed that porphyranases were common in the Japanese population but absent in North American individuals.

In Japan, the genome of the gut bacterium Bacteroides plebeius revealed presence of a porphyran utilization locus upstream of genes for conjugative DNA transfer, acquired by horizontal gene transfer from sea-weed-associated bacteria found in sushi.

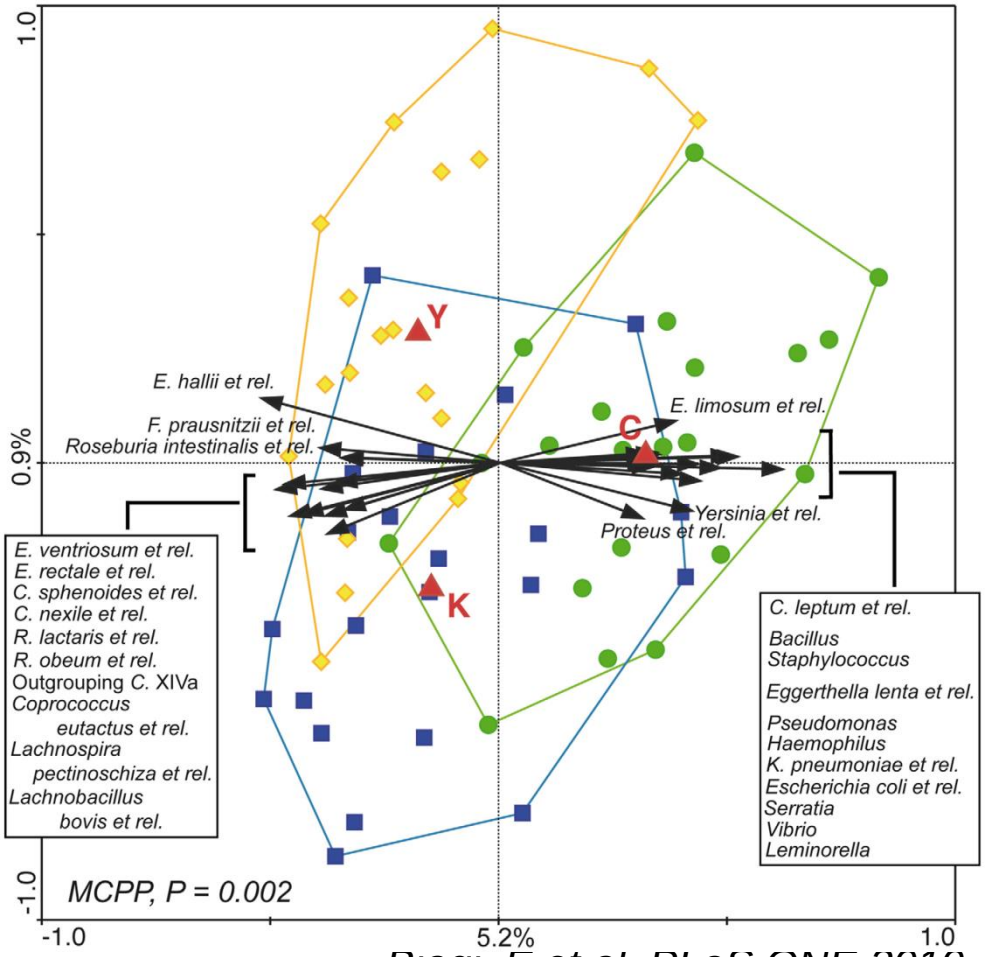
Heheann JH et al. Nature 2010

Several butyrate producers were found in lower amounts in centenarians (*Ruminococcus obeum* et rel., *Roseburia intestinalis* et rel., *E. ventriosum* et rel., *E. rectale* et rel., *E. hallii* et rel. (all belonging Clostridium cluster XIVa), and *Papillibacter cinnamovorans* et rel., and *F. prausnitzii* et rel. (Clostridium cluster IV)). The **decrease of *F. prausnitzii*** in centenarians is of interest as this species is known to affect the gut inflammation processes.

Conversely, the butyrate producers *Anaerotruncus colihominis* et rel. (Clostridium cluster IV), and *Eubacterium limosum* et rel. (Clostridium cluster XV) increased in centenarians.

The increase of *E. limosum* is high (approximately 15- fold), and could point to a group of bacteria characteristic of the long life.

A **decrease in bifidobacteria** and **increased levels of the mucin degrading *A. muciniphila*** were also detected in aged people if compared to the young adults.



Biagi, E et al. PLoS ONE 2010

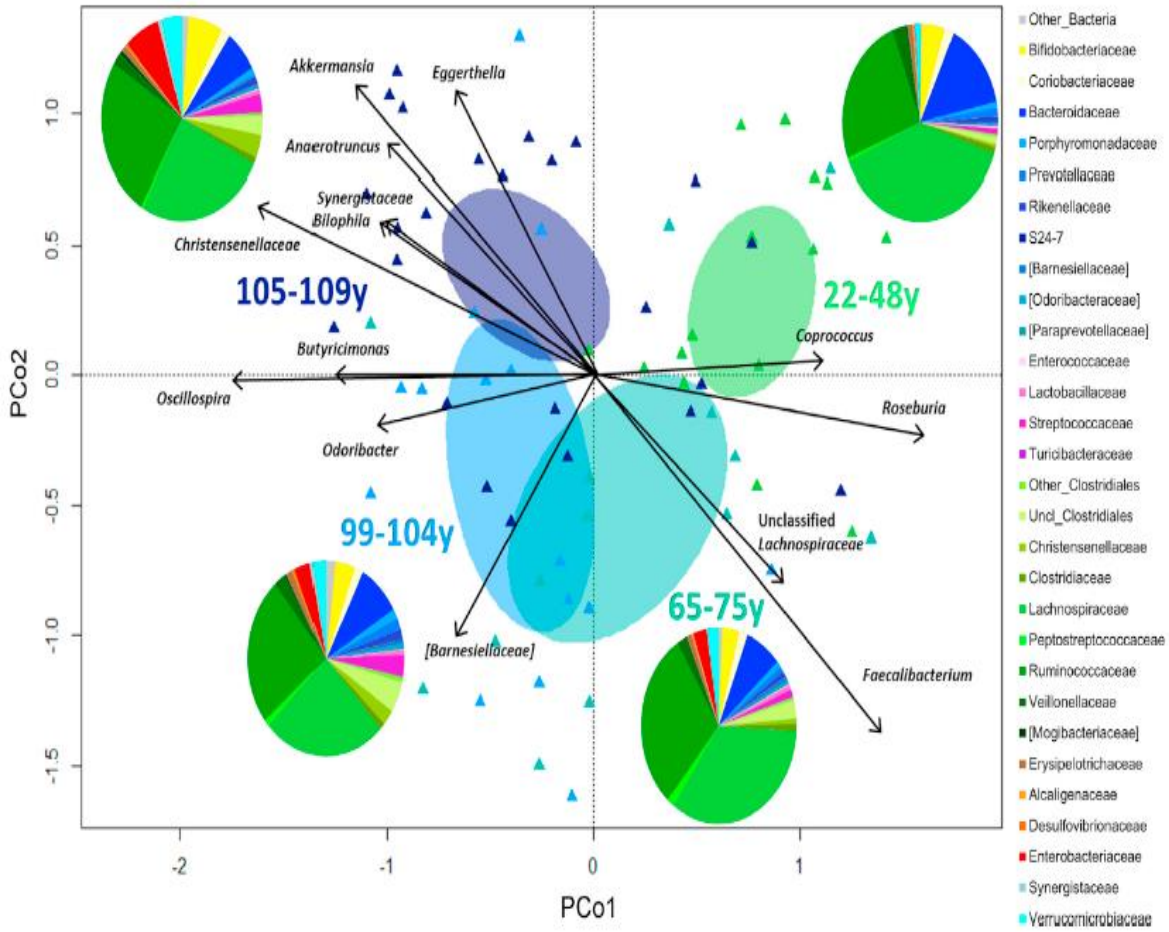
“Aged” gut microbiota:
…only deranged or a trajectory towards a different stability?

Gut Microbiota and Extreme Longevity

Current Biology 26, 1–6, June 6, 2016

Elena Biagi,[1,*] Claudio Franceschi,[2,3,4] Simone Rampelli,[1] Marco Severgnini,[5] Rita Ostan,[2,3] Silvia Turroni,[1] Clarissa Consolandi,[5] Sara Quercia,[1] Maria Scurti,[2,3] Daniela Monti,[6] Miriam Capri,[2,3] Patrizia Brigidi,[1] and Marco Candela[1,*]

young adults (30 years old in average) vs. "young elderly" (aged 65-75 years) vs. long-living subjects, subdivided into a group of 15 centenarians (99-104 years old) and a group of 24 semi-supercentenarians (105-109 years old), all enrolled in a restricted geographic area in Italy



typical signs of an elderly-type gut microbiota: **decrease in saccharolytic butyrate producers** (Faecalibacterium, Coprococcus, Roseburia), **increase in possibly opportunistic bacteria** (Enterobacteriaceae, Desulfovibrionaceae)

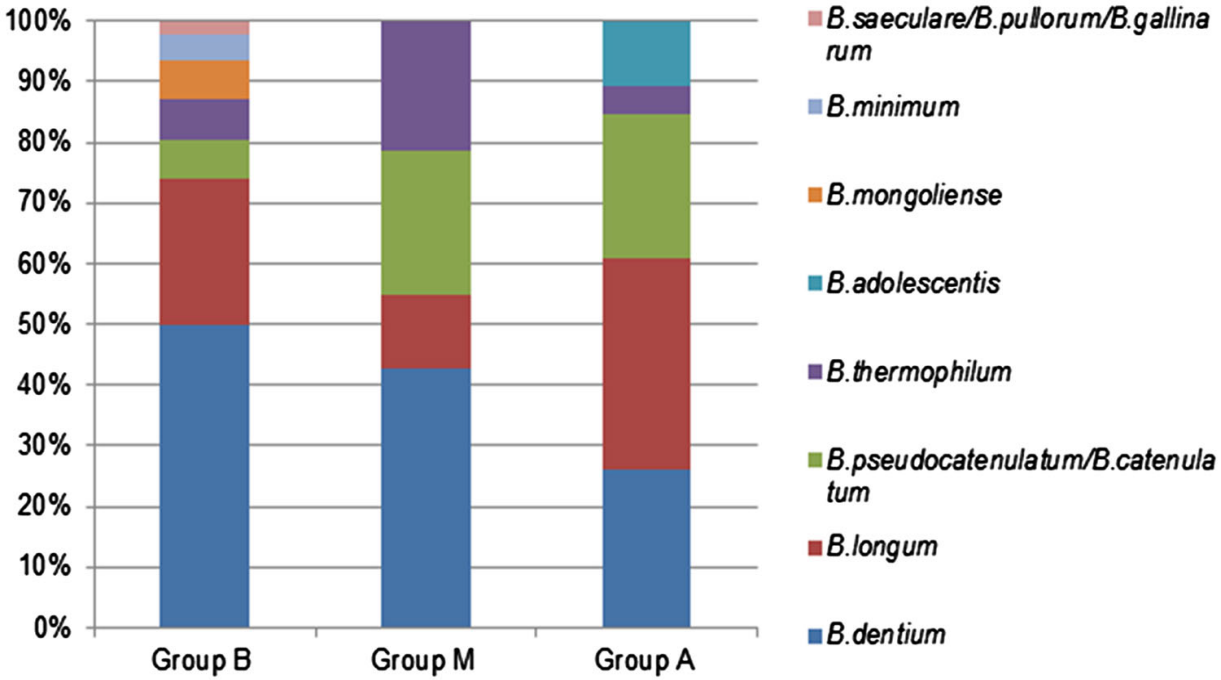
centenarians and, especially, semi-supercentenarians showed an **unexpected increase in bacteria possibly linked to good immunological and metabolic health, such as Christensenellaceae, Akkermansia, Bifidobacterium.**

Qualitative and Semiquantitative Analysis of Fecal *Bifidobacterium* Species in Centenarians Living in Bama, Guangxi, China

Curr Microbiol (2015) 71:143–149

Fang Wang[1] · Guohong Huang[1,2] · Da Cai[1] · Danlei Li[3] · Xiaolin Liang[1] · Ting Yu[1] · Peihong Shen[4] · Haiyan Su[1] · Jidong Liu[1] · Hongcang Gu[5] · Mouming Zhao[1] · Quanyang Li[1]

Centenarians tend to have more complex fecal Bifidobacterium species than young elderlies from different regions.



Bama centenarians

Bama younger elderlies

Nanning elderlies

B. minimum, B. saecularmay/B. pullorum/B. gallinarum, and B. mongoliense were found in centenarians but were absent in the younger elderlies. In addition, Bifidobacterium species found in centenarians were different from those found in Bama young elderly and Nanning young elderly

"Aged" gut microbiota:
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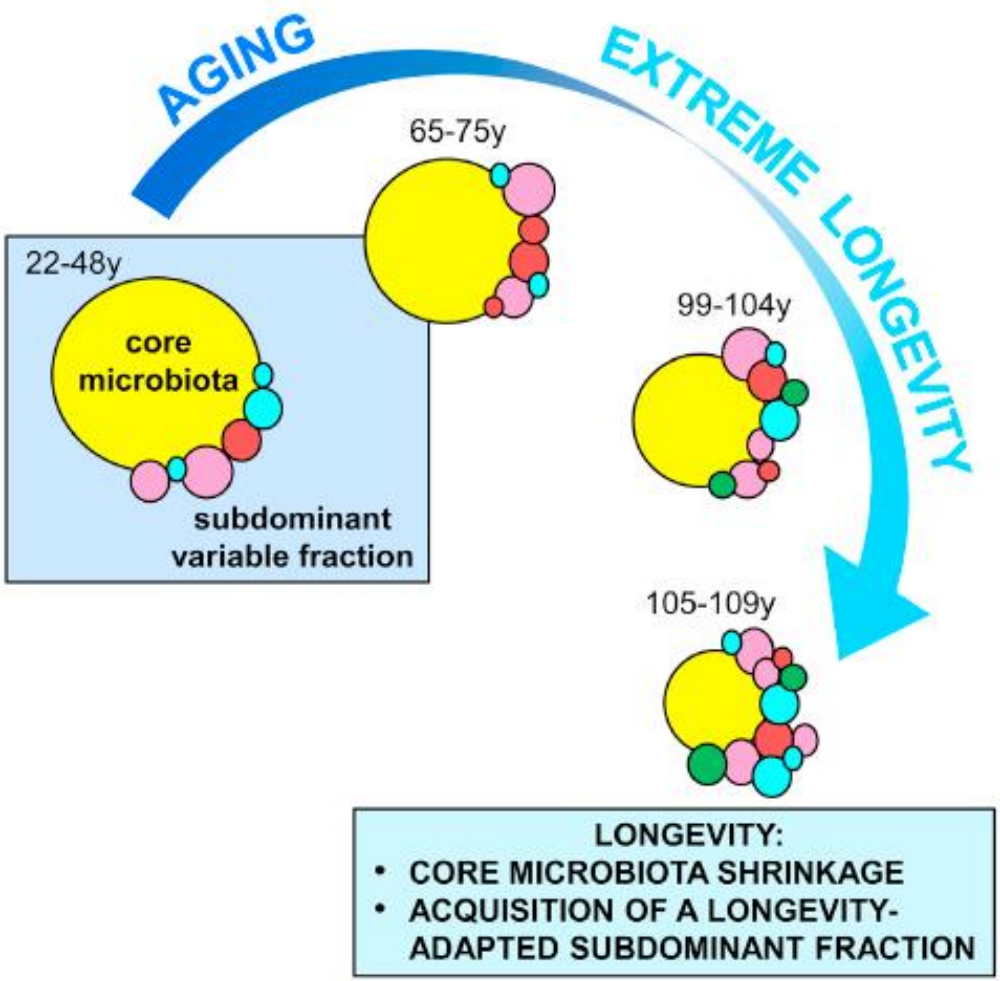


Accommodating opportunistic and allochthonous bacteria might possibly support health maintenance during aging, such as an enrichment and/or higher prevalence of health associated groups (e.g., Akkermansia , Bifidobacterium , and Christensenellaceae).

Gut microbiota signatures of longevity

Fanli Kong[1,2,4], Yutong Hua[1,4],
Bo Zeng[1], Ruihong Ning[1], Ying Li[1,3,5,*],
and Jiangchao Zhao[2,5,6,*]

CellPress

168 individuals from Dujiangyan and Ya'an, Sichuan province, China

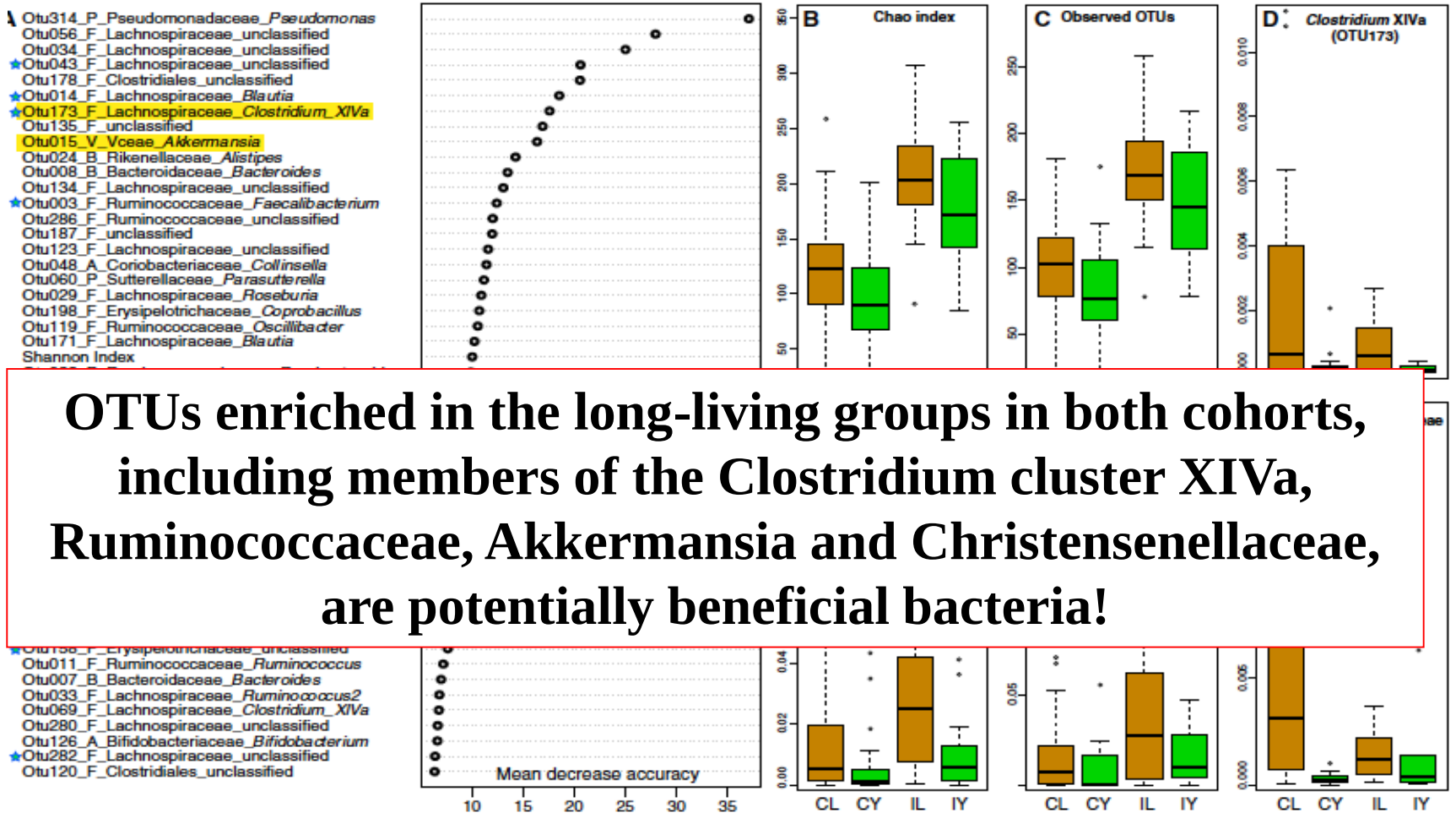
67: long-living group (90 years old),
54: elderly
47: young adults

Greater community richness (number of taxa), including both expected (Chao) and observed numbers of OTUs, were observed in the long-living group (p 0.001). Although not listed as one of the top predictors, community diversity (Shannon index) was also greater in the long-living group than in the younger group (p = 0.012).

Validation by comparison with the Italian dataset from Biagi et al.

Kong F et al. Curr Biol 2016

Among the top 50 features that differentiate the Chinese long-living people from the younger groups, 11 were also listed as the top 50 in the Italian dataset, including community richness (Chao index and observed OTUs), members of Blautia (OTU014), Clostridium XIVa (OTU173), Faecalibacterium (OTU003), Escherichia_Shigella (OTU005), unclassified Lachnospiraceae (OTU043, 028 and 282), Ruminococcaceae (OTU018), and Erysipelotrichaceae (OTU158)



OTUs enriched in the long-living groups in both cohorts, including members of the Clostridium cluster XIVa, Ruminococcaceae, Akkermansia and Christensenellaceae, are potentially beneficial bacteria!

Kong F et al. Curr Biol 2016

Consequences of gut microbiota ageing

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- Susceptibility to C. difficile infection
- Increased inflammatory status

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- Susceptibility to C. difficile infection
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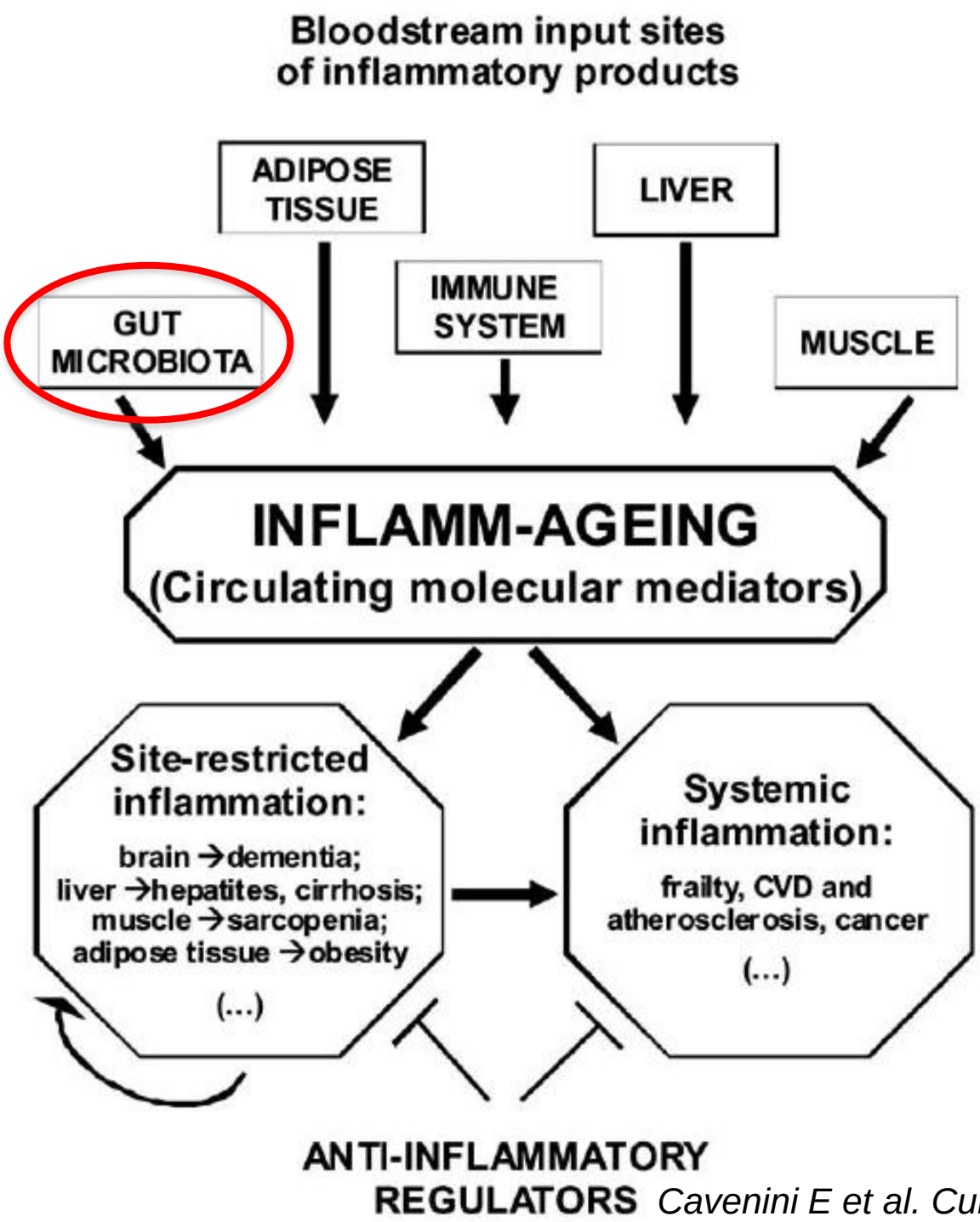


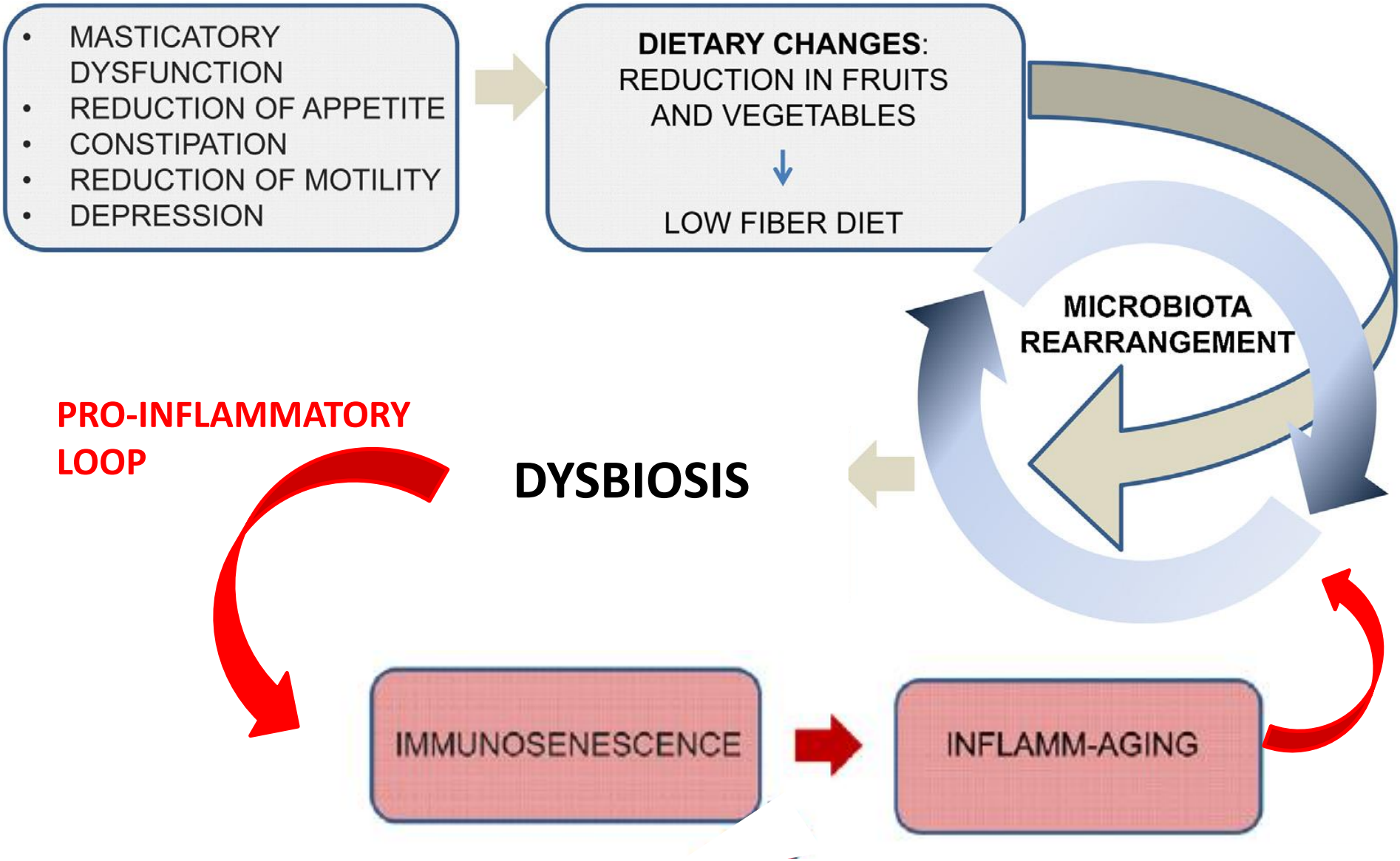
Cavenini E et al. Currt Pharm Des 2010

INFLAMM-AGEING CONSEQUENCES:

- Progression of chronic diseases
- Metabolic alterations such as insulin resistance and muscle
- catabolism (sarcopenia or cachexia).
- The lymphocyte cell cycle can be altered within an inflammatory microenvironment, this may explain the higher frequency of autoimmune phenomena
- A sustained inflammatory response can induce the compensatory production of immunosuppressor mediators that can tip the balance to a relatively hyporeactive immune system.

Ostan R et al. Neuroimmunomodulation 2008

Ageing inevitably affects gut microbiome



Candela M et al. Mech Ageing Dev 2013

LIMITATIONS OF GUT MICROBIOME RESEARCH IN AGEING:

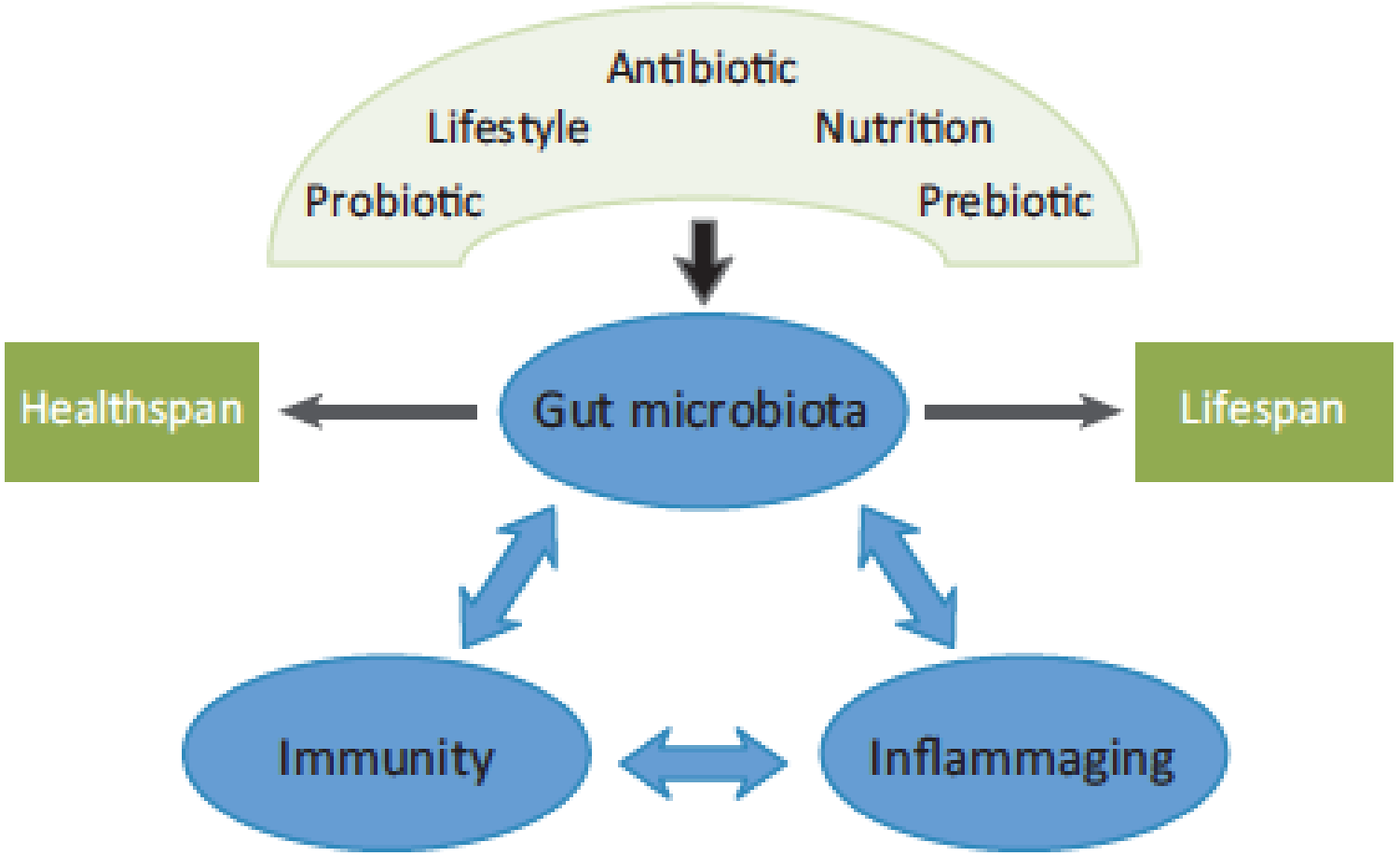
- Unfeasibility of longitudinal studies to assess the "real" evolution of gut microbiome throughout life
- Limitations of studies conducted in different Countries (different diet/lifestyle)
- Lack of consensus on the definition of "elderly"

However, once a large number of microbiota studies focused on subjects of different age, including longliving individuals, will be available from several different countries, a comparative unconstrained approach of NGS data will be useful to isolate microbiota signatures of longevity independent of the nationality of the involved subjects.

Describing a sort of "universal" longevity dynamics may help in unraveling how the gut microbial ecosystem could affect our lifespan and, more importantly, healthspan.

Biagi E et al. Mechanisms of Ageing and Development 2016

In the future, the age-tailored and personalized modulation of the gut microbiome composition will be aimed at maintaining the microbial profile **with the highest probability to help the host in preventing diseases and promoting health in that specific stage of life**



Nikoletopoulou V et al. Trend in Endocrinology and Metabolism 2014

Consequences of gut microbiota ageing

- Susceptibility to C. difficile infection
- Increased inflammatory status

C DIFF INFECTION
Socio-economic burden in EU

Wien Klin Wochenschr. 2014 Jul;126(13-14):427-30. doi: 10.1007/s00508-014-0549-x. Epub 2014 Jun 6.

Severe Clostridium difficile infection: incidence and risk factors at a tertiary care university hospital in Vienna, Austria.

Starzengruber P[1], Segagni Lusignani L, Wrba T, Mitteregger D, Indra A, Graninger W, Presterl E, Diab-Elschahawi M.

5.23 CDI /10.000 patient-days
4.41 severe CDI /10.000 patient-days

84.5% severe CDI according to ESCMID guidelines

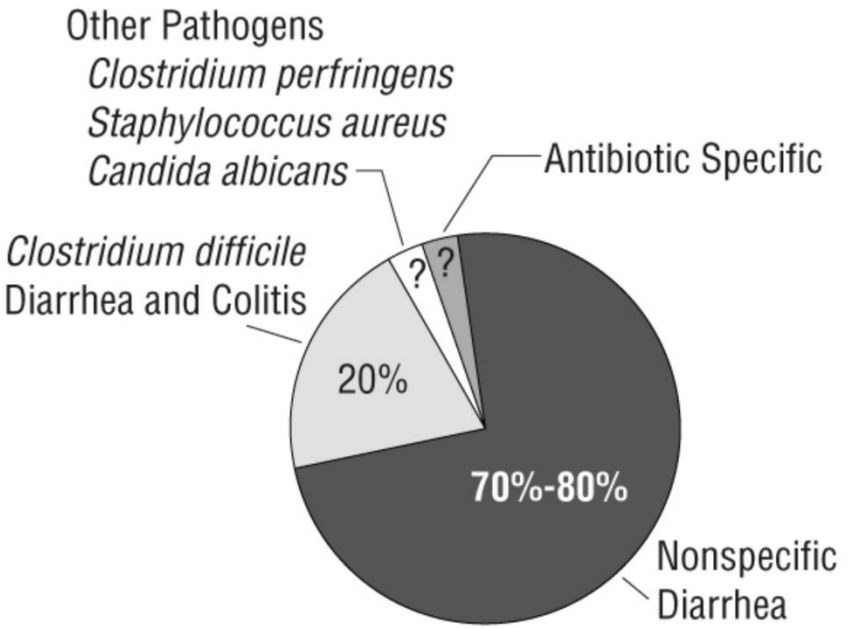
Infection. 2014 Jun;42(3):585-9. doi: 10.1007/s15010-014-0597-1. Epub 2014 Feb 13.

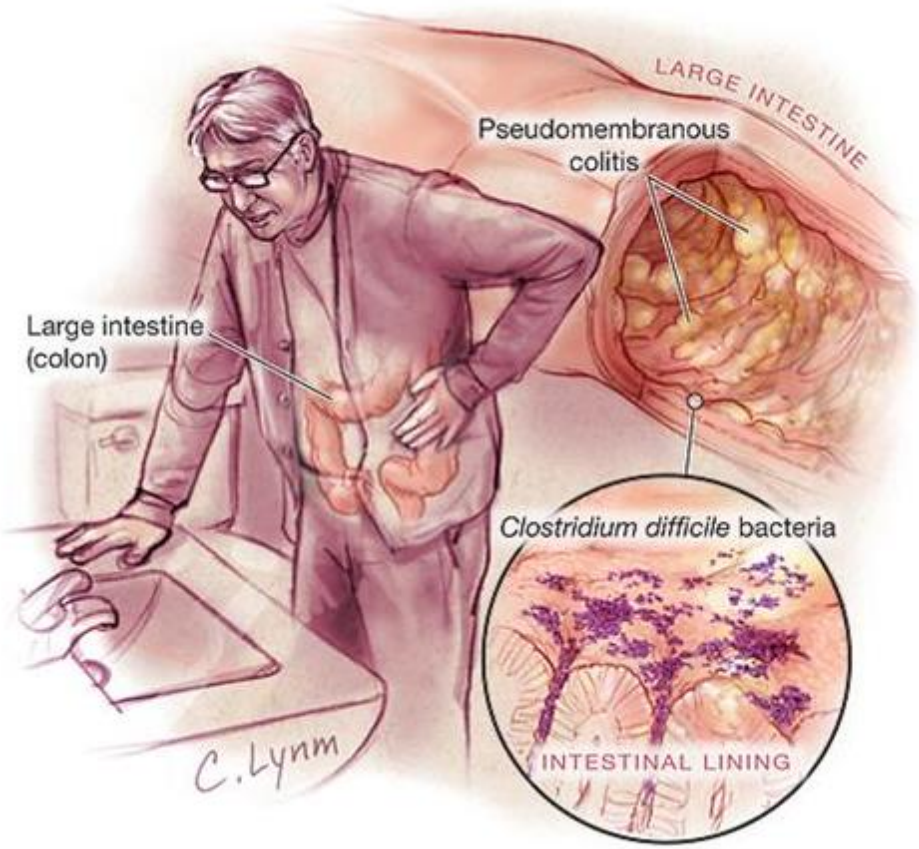
A cluster of fulminant Clostridium difficile colitis in an intensive care unit in Italy.

Guastalegname M[1], Grieco S, Giuliano S, Falcone M, Caccese R, Carfagna P, D'ambrosio M, Taliani G, Venditti M.

2,61/1.000 admissions in 2013 vs 1,26/1.000 admissions in 2012

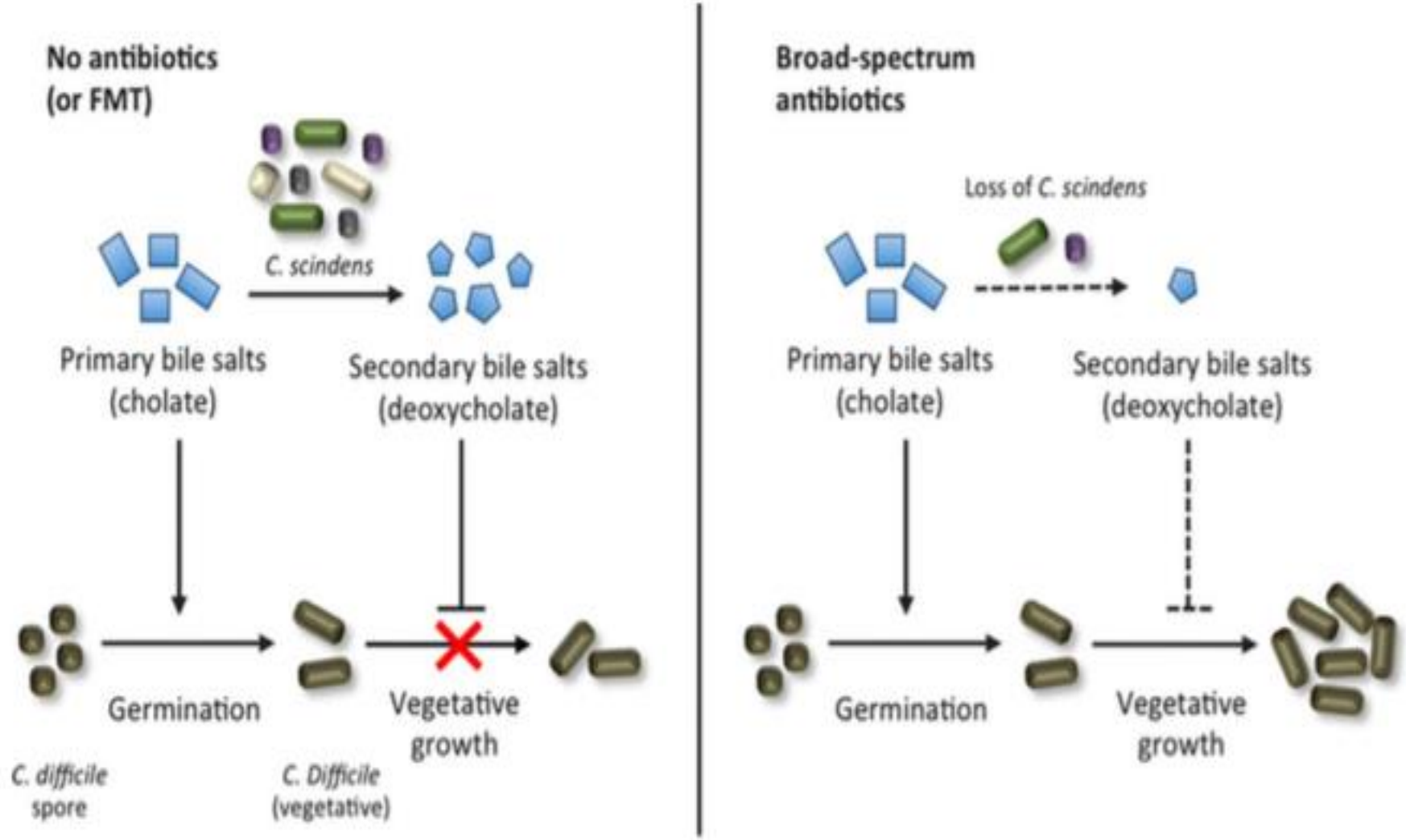
C. difficile, antibiotics and diarrhoea





Hurley BW Jama 2002

Antibiotics, *C. difficile* and diarrhoea



Tanya M. Monaghan et al, Inflamm Bowel Dis 2015

Gut microbiota composition and *Clostridium difficile* infection in hospitalized elderly individuals: a metagenomic study

Christian Milani[1,*], Andrea Ticinesi[2,3,*], Jacoline Gerritsen[4], Antonio Nouvenne[2,3], Gabriele Andrea Lugli[1], Leonardo Mancabelli[1], Francesca Turroni[1], Sabrina Duranti[1], Marta Mangifesta[1], Alice Viappiani[5], Chiara Ferrario[1], Marcello Maggio[3,6], Fulvio Lauretani[2], Willem De Vos[4], Douwe van Sinderen[7], Tiziana Meschi[2,3] & Marco Ventura[1]

hospitalized elderly patients (age ≥ 65) under standard diet: 25 CDI-positive (CDI group), 29 CDI-negative exposed to antibiotic treatment (AB+ group) and 30 CDI-negative subjects not on antibiotic treatment (AB− group).

CDI was associated with a significant **under-representation of gut commensals with putative protective functionalities,** including Bacteroides, Alistipes, Lachnospira and Barnesiella, and over-representation of opportunistic pathogens.

In CDI- patients, antibiotic treatment was associated with significant depletion of few commensals like Alistipes, but not with a reduction in species richness

Sci Rep 2016

European Consensus Conference on Faecal Microbiota Transplantation in Clinical Practice

FMT for recurrent *Clostridium difficile* infection

Statement: FMT is recommended as a highly effective and safe treatment option for both mild and severe rCDI. Its implementation in **clinical practice is recommended**

Quality of evidence: high **Strength of recommendation:** strong

FMT for refractory *Clostridium difficile* infection

Statement: FMT can be considered as a treatment option for **refractory CDI**

Quality of evidence: high **Strength of recommendation:** strong

FMT for the first episode of *Clostridium difficile* infection

Statement: There is insufficient evidence to recommend FMT as a treatment for the first episode of CDI. Additional studies are needed to determine if **FMT could have an advantage over antibiotics for this indication**

Quality of evidence: low **Strength of recommendation:** weak

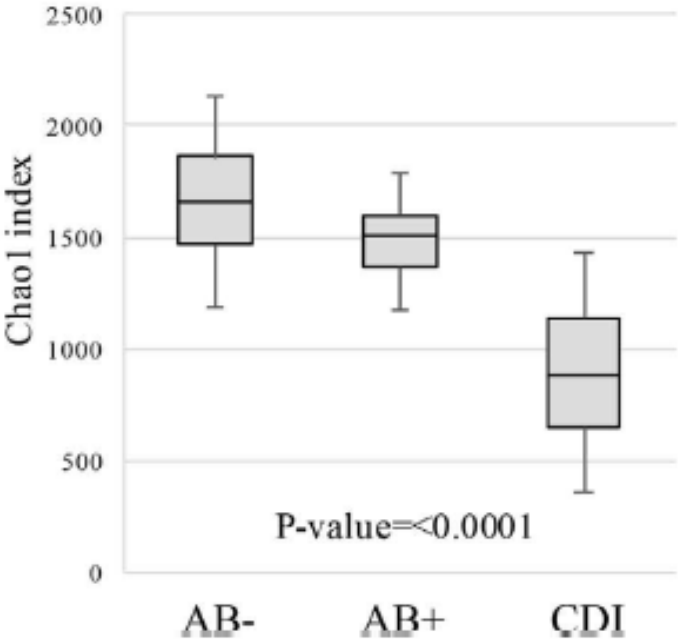
Cammarota et al – Gut 2016

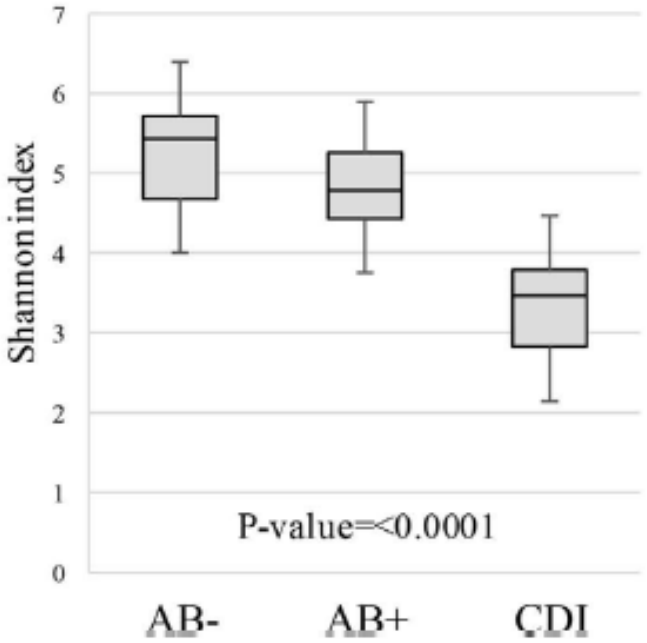
Gut microbiota composition and *Clostridium difficile* infection in hospitalized elderly individuals: a metagenomic study

Christian Milani[1,*], Andrea Ticinesi[2,3,*], Jacoline Gerritsen[4], Antonio Nouvenne[2,3], Gabriele Andrea Lugli[1], Leonardo Mancabelli[1], Francesca Turroni[1], Sabrina Duranti[1], Marta Mangifesta[1], Alice Viappiani[5], Chiara Ferrario[1], Marcello Maggio[3,6], Fulvio Lauretani[2], Willem De Vos[4], Douwe van Sinderen[7], Tiziana Meschi[2,3] & Marco Ventura[1]

hospitalized elderly patients (age ≥ 65) under standard diet: 25 CDI-positive *(CDI group)*, 29 CDI-negative *exposed to* ***antibiotic treatment (AB+*** *group) and* 30 CDI-negative *subjects not on* ***antibiotic treatment (AB−*** *group).*

A significantly lower microbial diversity was detected in CDI samples, whose microbiomes clustered separately from CDI-negative specimens





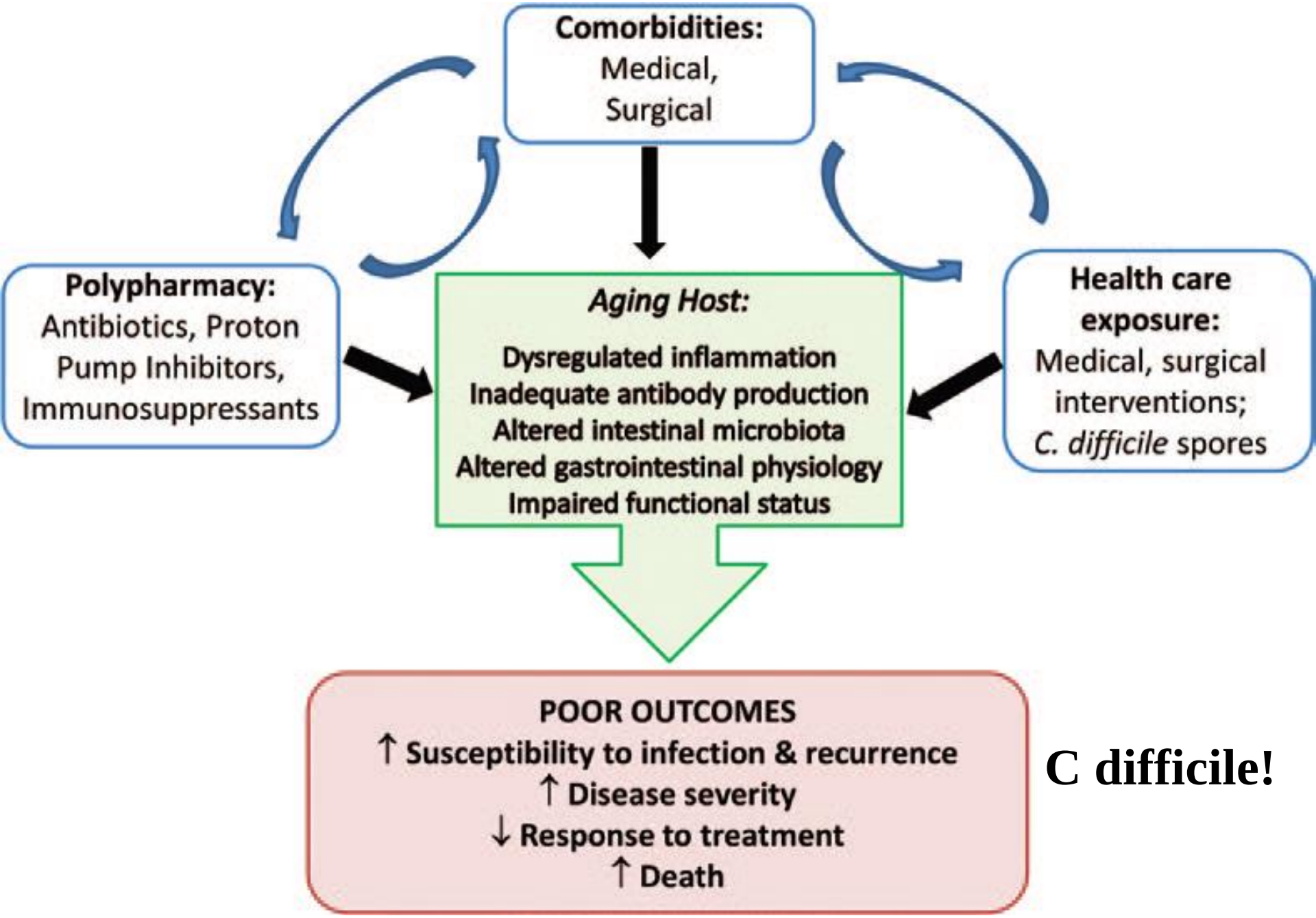
Sci Rep 2016

Preliminary Communication

Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection

- **20 pts with rCDI received 15 FMT capsules by healthy volunteers on 2 consecutive days and were followed up for symptom resolution and adverse events for up to 6 months**
- **Resolution of diarrhea in 14 patients (70%; 95%CI, 47%-85%) after a single capsule-based FMT**
- **All 6 non-responders were re-treated; 4 had resolution of diarrhea, resulting in an overall 90% rate of clinical resolution of diarrhea (18/20)**
- **No serious adverse events attributed to FMT**

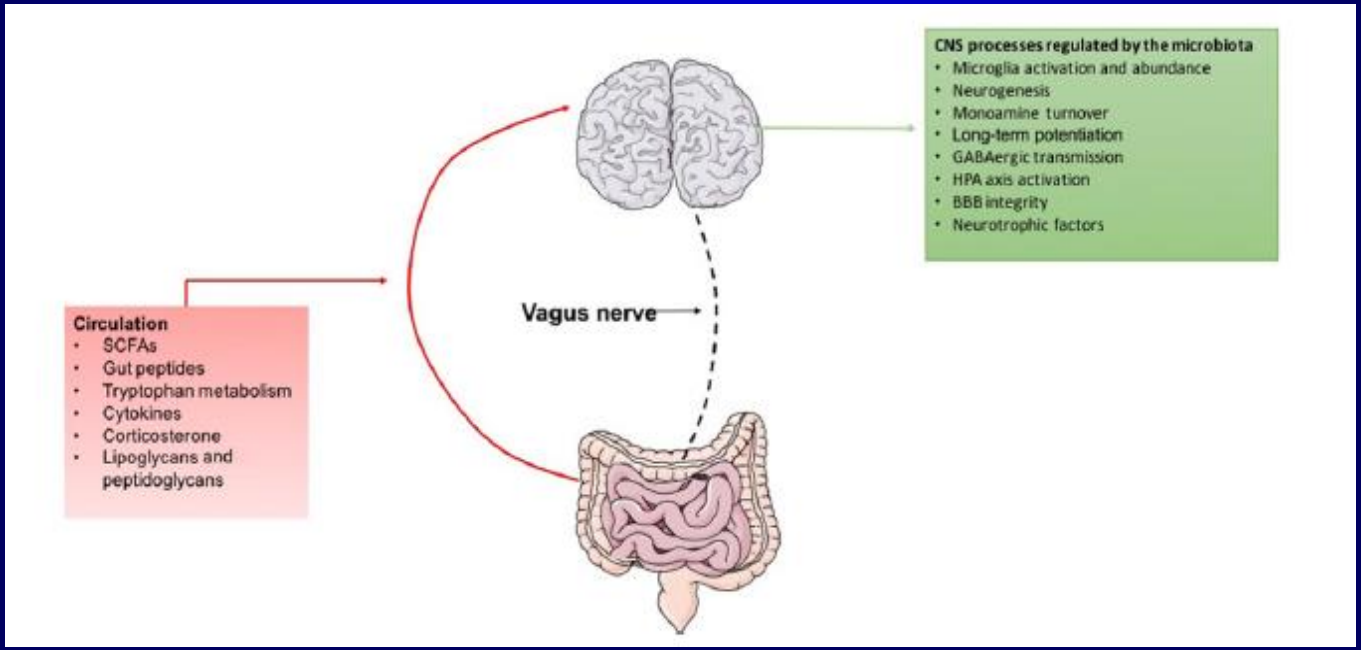
Youngster – JAMA 2014



C difficile!

Shin JH et al. J Gerontol A Biol Sci Med Sci, 2016

MICROBIOTA-GUT-BRAIN AXIS



Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

MICROBIOTA-GUT-BRAIN AXIS

- Neurotransmitters synthesis
- Modulation of the immune system
- Neuroactive metabolites production
- Vagus pathway
- Modulation of key dietary amino-acids (TRP)

- Neuroinflammation
- Stress
- Neurotransmission
- Neurogenesis
- Modulation of complex behaviors

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

GUT MICROBIOTA ⟷ NEUROLOGIC DISEASES

- Parkinson's disease (PD)
- Alzheimer's disease (AD)
- Cerebrovascular diseases
- Affective disorders
- Alcohol addiction

- Autism spectrum disorders
- Multiple Sclerosis

} Not typical of the elderly

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

GUT MICROBIOTA IN PARKINSONIAN PATIENTS

- Reduced abundance of Prevotella species, which produce mucin ⟶ increase in intestinal permeability and bacterial translocation
- Increased Akkermansia muciniphila
- Lower levels of anti-inflammatory-associated bacteria (Blautia, Roseburia)
- Lower levels of acetate, butyrate and propionate
- Small intestine bacterial overgrowth

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

PARKINSON'S DISEASE AND HELICOBACTER PYLORI

- H. pylori may contribute to the developement of parkinsonian symptoms through degeneratig dopaminergic neurons in the brain
- H. pylori eradication ehnances the onset time of levodopa and improves tremor, and walking ability
- rigidity

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

STROKE AND BRAIN INJURY

- Alterations to the human microbiota following stroke have been observed, with specific decreases observed in the Bacteroides fragilis group and increases in an Atopobium cluster noted
- Microbial metabolism was also affected by stroke, with decreases in fecal concentration of acetic acide and increases in valeric acid and isovaleric acid.

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

STROKE AND BRAIN INJURY – PRECLINICAL DATA

- Depletion of gut bacteria through antibiotic administration worsened the survival rate of mice following the induction of ischemia
- In the middle cerebral artery occlusion, cerebral ischemia is associated with a dysregulation of the murine microbiota, with a reduction in bacterial α-diversity, intestinal motility and intestinal barrier dysfunction (=increased permeability)
- Microbial-derived metabolites may influence stroke susceptibility through modulat infectivation platelet a and thrombosis.

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

STROKE AND BRAIN INJURY – PRECLINICAL DATA

- The gut microbiota modulates immune signaling and influences the pathological outcome during stroke
- An increased activation of the sympathetic nervous system may also influence dysregulation to the microbiota following stroke
- The gut microbiota may influence the severity of post-stroke infections, a complication associated with stroke

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

ALZHEIMER'S DISEASE

Accumulation of amyloid plaques, tau fibrils and neuroinflammation widespread

- Higher levels of Shigella/Escherichia
- Increased of hematic IL-1β and CXCL2

} Systemic inflammation

- Higher levels of LPS and Escherichia coli K99 pilli protein in brain parenchyma and blood vessels of Alzheimer's patients

- LPS was found to colocalize with Aβ 1-40 in amyloid plaques

} Bacterial components translocation

- Molecular mimicry may also play a role in Alzheimer's disease neurodegeration

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

DEPRESSION

Depressed patients usually have a dysregulatedicrobiota
(reduction in species richness and microbial diversity)

↓

Transplantation of these patients' microbiota into microbiota-depleted rats, they developed a depression behavioral phenotype. They also had an elevated kynurenne/tryptophan ratio, indicating that perhaps the depressed microbiota facilitates the conversion of tryptophan into kynurenine, a deleterious metabolite

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

THE ROLE OF AMYLOID IN NEURODEGENERATION

- Why are the neurodegenerative disorders so closely related to age?

↓

The late onset of Alzheimer and Parkinson's disease allows for minute alterations in proteostasis and inflammation to have cumulative effects

- What are the principal sources of microbial amyloid in humans?

Friedland RP et al. The role of microbial amyloid in neurodegeneration. PLoS Pathog. 2017 Dec 21;13(12):e1006654. doi: 10.1371/journal.ppat.1006654. eCollection 2017 Dec.

ALCOHOL ADDICTION

The psychological status of alcoholics with increased intestinal permeability was worse than that of controls and alcoholics with regular intestinal permeability

↓

A dysregulated microbiota-gut-brain axis facilitates the psychological symptoms observed in alcoholics

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

AUTISM

- Growing evidences suggest that the gut microbiota composition may affect some facets of social behaviors in mammals
- In many animal models of autism spectrum disorders there is an altered microbiota composition
- Recent evidence suggests that the modulation of the gut microbiota (through diet, probiotics and microbiota transfer) may affect some behaviors typical of autism spectrum disorders
- The relationship between the host's genetics and the gut microbiota in affecting the behavior is still to clarify.

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

PANS / PANDAS AND GUT MICROBIOTA

Pediatric acute-onset neuropsychiatric syndrome (**PANS**)

Pediatric autoimmune neuropsychiatric disorders associated with streptococcical infections (**PANDAS**)

Sudden developement of tics, obsessive-compulsive disorder and behavioral symptoms

In a cohort of 30 PANS/PANDAS patients, it has been demonstrated the **presence of an altered intestinal bacterial community structure** comparing to controls.

Quagliariello A…Gasbarrini A. et al. Gut Microbiota Profiling and Gut-Brain Crosstalk in Children Affected by Pediatric Acute-Onset Neuropsychiatric Syndrome and Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. Front Microbiol. 2018 Apr 6;9:675. doi: 10.3389/fmicb.2018.00675. eCollection 2018.

PANS / PANDAS AND GUT MICROBIOTA

- PANS/PANDAS patients aged 4-8 showed a strong increase in *Bacteroidetes* (*Bacteroides, Odoribacter, Oscillospira*) and in many pathways regarding the antibody response to gut inflammation, while pathways concerning brain functions resulted to be decreased.
- In PANS/PANDAS patients older than 9 it was not possible to identify a distinct biomarker in the bacterial population; however, a negative correlation emerged between *Firmicutes* and *anti-streptolysin O titer*, with a positive correlation with *Odoribacter*.

Streptococcal infection can lead the gut microbiota composition to a pro-inflammatory status through the selection of bacterial strains associated with gut inflammation and immune activation.

Quagliariello A …Gasbarrini A.et al. Gut Microbiota Profiling and Gut-Brain Crosstalk in Children Affected by Pediatric Acute-Onset Neuropsychiatric Syndrome and Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections. Front Microbiol. 2018 Apr 6;9:675. doi: 10.3389/fmicb.2018.00675. eCollection 2018.

MULTIPLE SCLEROSIS

Autoimmune disease caused by the progressive demyelination of the axons

- Increased intestinal permeability in patients with relapsing/remitting MS

- Increased circulating LBP in patients with remitting/relapsing MS → Gram negative transocation from the intestinal lumen

- Reductions in Faecalibacterium, Prevotella and Anaerostiples; it us still to be determined whether these alterations are comorbid consequences of multiple sclerosis or play an active role in the development of the disease

- In mice, the gut microbiota influences myelination within the prefrontal cortex and the composition of the gut microbiota may determine the severity of the disease.

Sherwin E et al, Recent developments in understanding the role of the gut microbiota in brain health and disease. Ann N Y Acad Sci. 2017 Aug 2. doi: 10.1111/nyas.13416.

nella pratica clinica

?

Doctor, should I eat yogurth?

Yogurt. Per la legge è *latte fermentato* con due specifici batteri, il *Lattobacillus bulgaricus* e lo *Streptococcus thermophilus*, il cui compito è quello di fermentare il lattosio ad acido lattico (la cui acidità fa coagulare il latte per la precipitazione della caseina) e di dare gusto attraverso la trasformazione dei grassi e delle proteine in sostanze aromatiche. Alla fine della fermentazione lattica si registra anche un aumento dell'acido folico e della niacina. Di norma il latte utilizzato è quello vaccino.

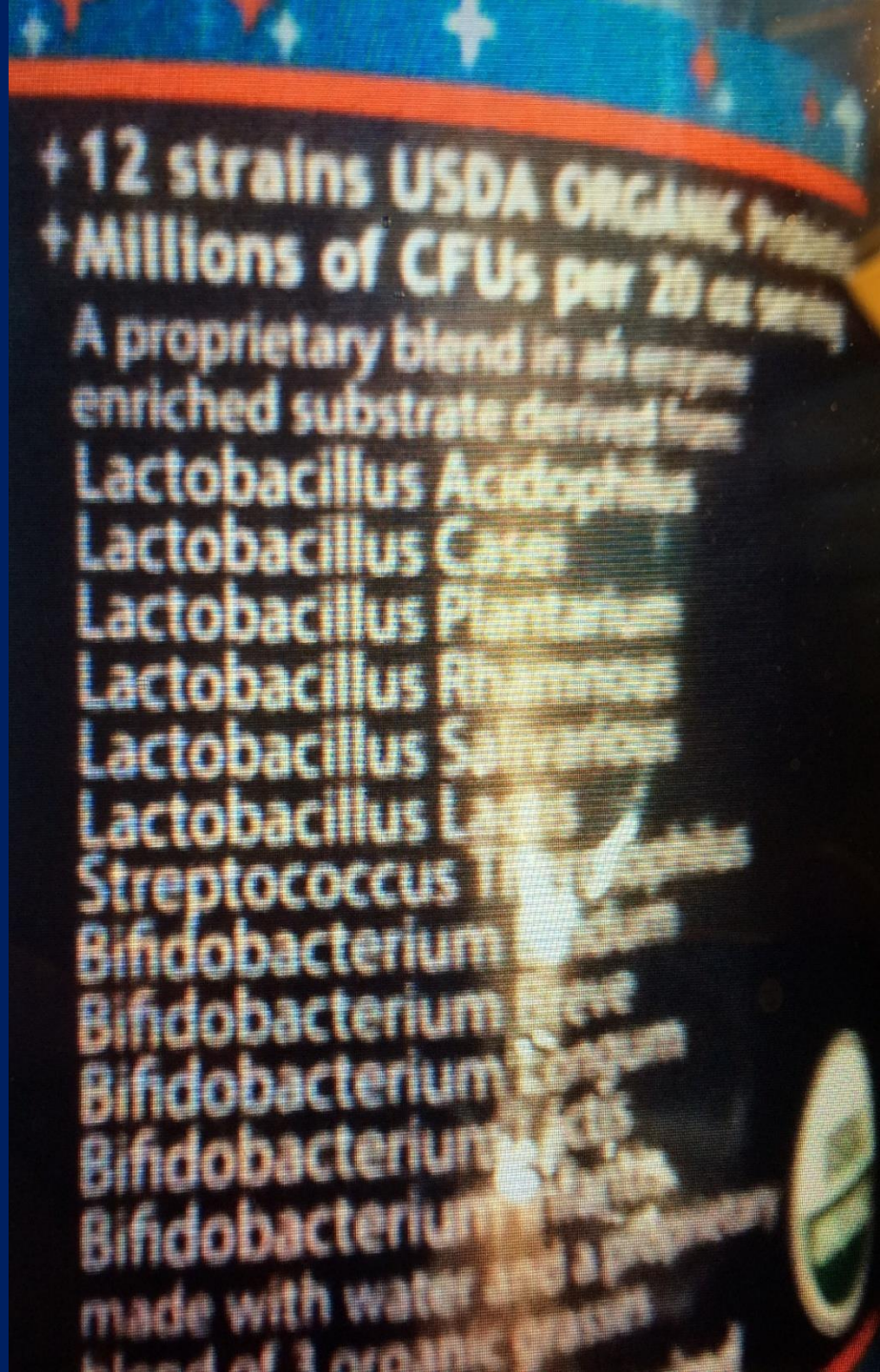
Latte fermentato. Questa denominazione viene riportata in etichetta quando il latte è fermentato con microrganismi diversi da quelli usati per lo yogurt.

‘

Ne fate uso

?


ALKALIZE
ENERGY
Probiotics
Organic Hydration


+12 strains USDA ORGANIC
+Millions of CFUs per
A proprietary blend
enriched substrate
Lactobacillus
Lactobacillus
Lactobacillus
Lactobacillus
Lactobacillus
Streptococcus
Bifidobacterium
Bifidobacterium
Bifidobacterium
Bifidobacterium
Bifidobacterium
made with

Human diet shapes bacteria ENTEROTYPES

“feeding” our microbiota

biotin and riboflavin

Proteolytic bacteria:
Bacteroides, *Streptococcus, Staphylococcus, Proteus, Escherichia, some species of Clostridium, Fusobacteria, Bacillus, Propionibacterium…*

thiamine and folate

Saccharolytic bacteria
Prevotella, *Bifidobacterium, Lactobacillus, Eubacterium, Propionibacterium, Escherichia, Enterococcus, Peptostreptococcus, Fusobacteria…*

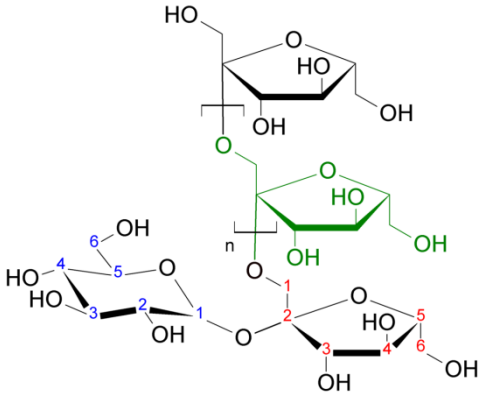
Wu et al. Science 2011

Fermentation

Prebiotic fibres: FOS, GOS and inulin

The highest level of butyrate are seen with prebiotic fibres: **FOS, GOS and inulin**

- Prebiotics fibres are totally fermented, producing **SCFA**
- **FOS**, **GOS** and **inulin** selctively
  - Stimulate proliferation of bifidobacteria and lactobacilli
  - Inhibition patogenic Gram + and Gram – bacteria
  - **Reduce intestinal permeability**, **LPS** and metabolic endotoxiemia

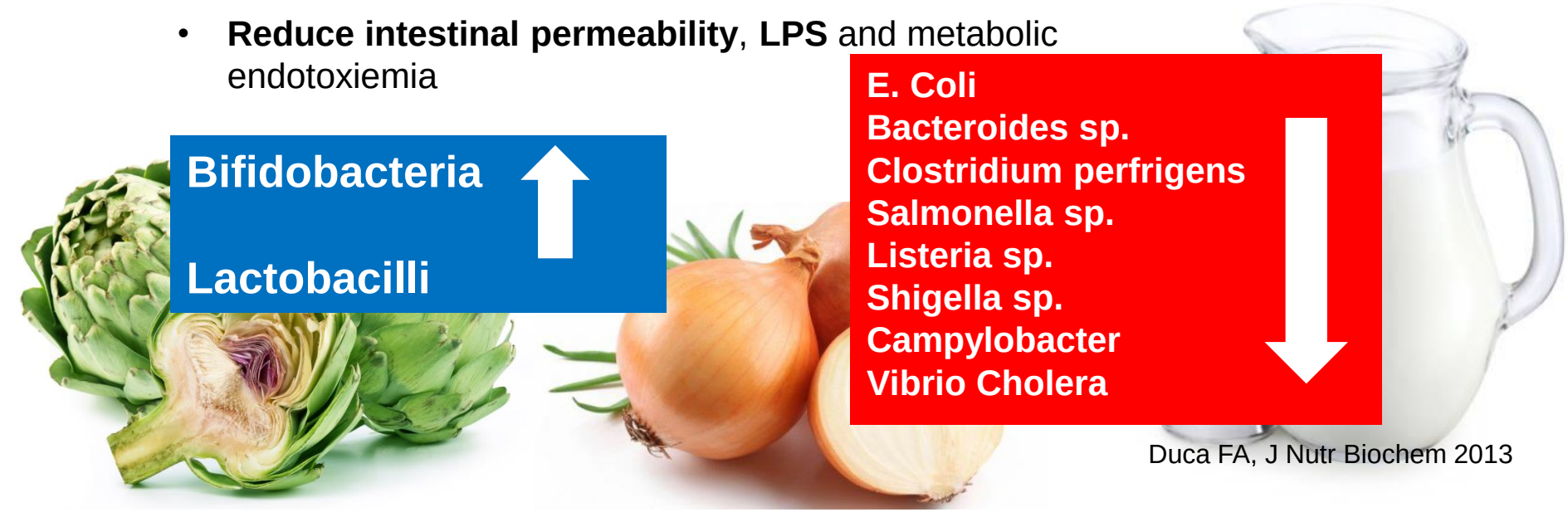


Bifidobacteria ↑

Lactobacilli

E. Coli
Bacteroides sp.
Clostridium perfrigens
Salmonella sp.
Listeria sp.
Shigella sp.
Campylobacter
Vibrio Cholera

↓



Duca FA, J Nutr Biochem 2013

PROBIOTICI TINDALIZZATI NON VITALI lactobacillus acidophilus HA-122

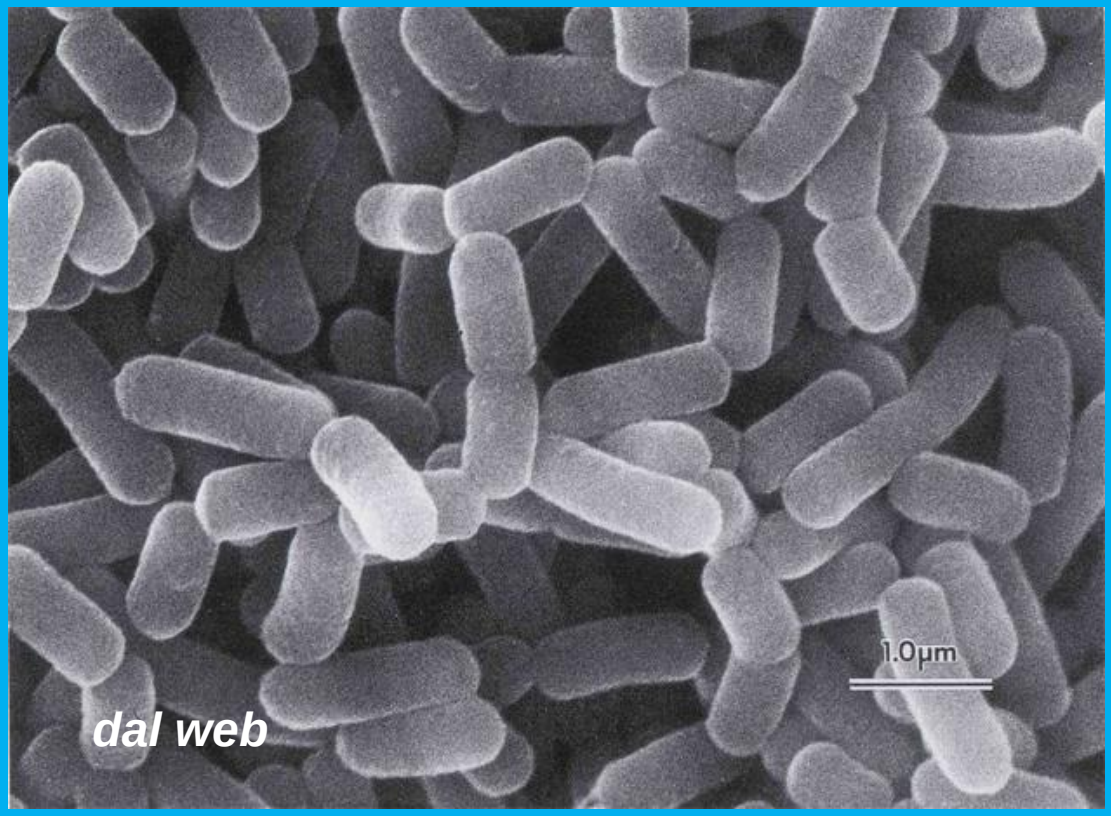
- INULINA
- AMINOACIDI (glicina, glutammina)
- VIT D3 (colecalciferolo)
- ZINCO

NO GLUTINE , NO LATTOSIO

LACTOBACILLUS ACIDOPHILUS

Presente in bocca, intestino, vagina.
Produce acido lattico attraverso l'enzima lattasi.

Contenuto nello yogurt e prodotti caseari vari, e nei cibi fermentati



dal web

INDICAZIONI

- **Infezioni vaginali**
- **Infezioni polmonari nel bambino**
- **Diarrea da antibiotici**
- **Meteorismo**
- **Eczema dei bambini (l'uso oraleda parte di donne in gravidanza e allattamento, e bambini previene la dermatite atopica**
- **Ipercolesterolemia**

INULINA
Fibra vegetale solubile
CARBOIDRATO OTTENUTO DA CICORIA E CARCIOFO
non digerita , non assorbita, fermentata dai batteri intestinali che se ne nutrono (**PREBIOTICO**)
Proposta per favorire la flora batterica eubiotica, nella stipsi.
Non ancoraprovata la sua utilità nelle iperlipemie, obesità, diabete.

GLUTAMMINA sintetizzata a partire dall'acido glutammico, è **l'aminoacido prevalente (60%)** nel corpo umano. Concentrata nei ***muscoli, nel liquido cefalo-rachidiano e nel plasma. Stress fisico-psichico, invecchiamento ne richiedono l'integrazione alimentare. Se carente, viene sottratta dai muscoli e dalla cute che perdono tonicità e compattezza.***
Importante substrato energetico per le cellule in rapido turnover come i linfociti. Fondamentale per il **sistema immunitario**, l'integrità delle **cellule intestinali**, dei **follicoli dei capelli.**
Favorisce l'equilibrio acido-basse.

GLICINA produce immunoglobuline, previene l'apoptosi cellulare prematura. Importante per il **sistema immunitario**. Come componente del glutatione regola I **processi infiammatori**.

VIT D_3

FUNZIONI BIOLOGICHE CLASSICHE

Endocrina: 1-25 $(OH)_{2:}$ colecalciferolo (calcitriolo):

- assorbimento di calcio e fosforo intestinale e renale
- regolazione **recettori della Vit D nelle paratiroidi** e della loro risposta al calcio sotto il controllo del paratormone. DEFICIT = iperplasia delle paratiroidi e aumento del paratormone
- Controllo della propria omeostasi attraverso le idrossilasi renali

VIT D_3

FUNZIONI BIOLOGICHE NON CLASSICHE

Immunità: riduzione del rischio di malattie infiammatorie croniche, autoimmunitarie. Possibile protezione in m. neoplastiche.

Controllo della differenziazione e maturazione **neuronale,**
del rischio di **deficit cognitivi** e di **depressione**.

DEFICIT VIT D_3: carenza <20 ng/ml ; insufficienza 20-30 ng/ml

Alterazione immunità, aumentata incidenza di m. cardiovascolari

Aumento del rischio di cadute e fratture:

- Riduzione della forza del quadricipite femorale
- Riduzione della stabilità posturale e delle performance muscolari funzionali
- Riduzione della velocità di conduzione dei motoneuroni, dei tempi di reazione e della sintesi di fattori neurotrofici

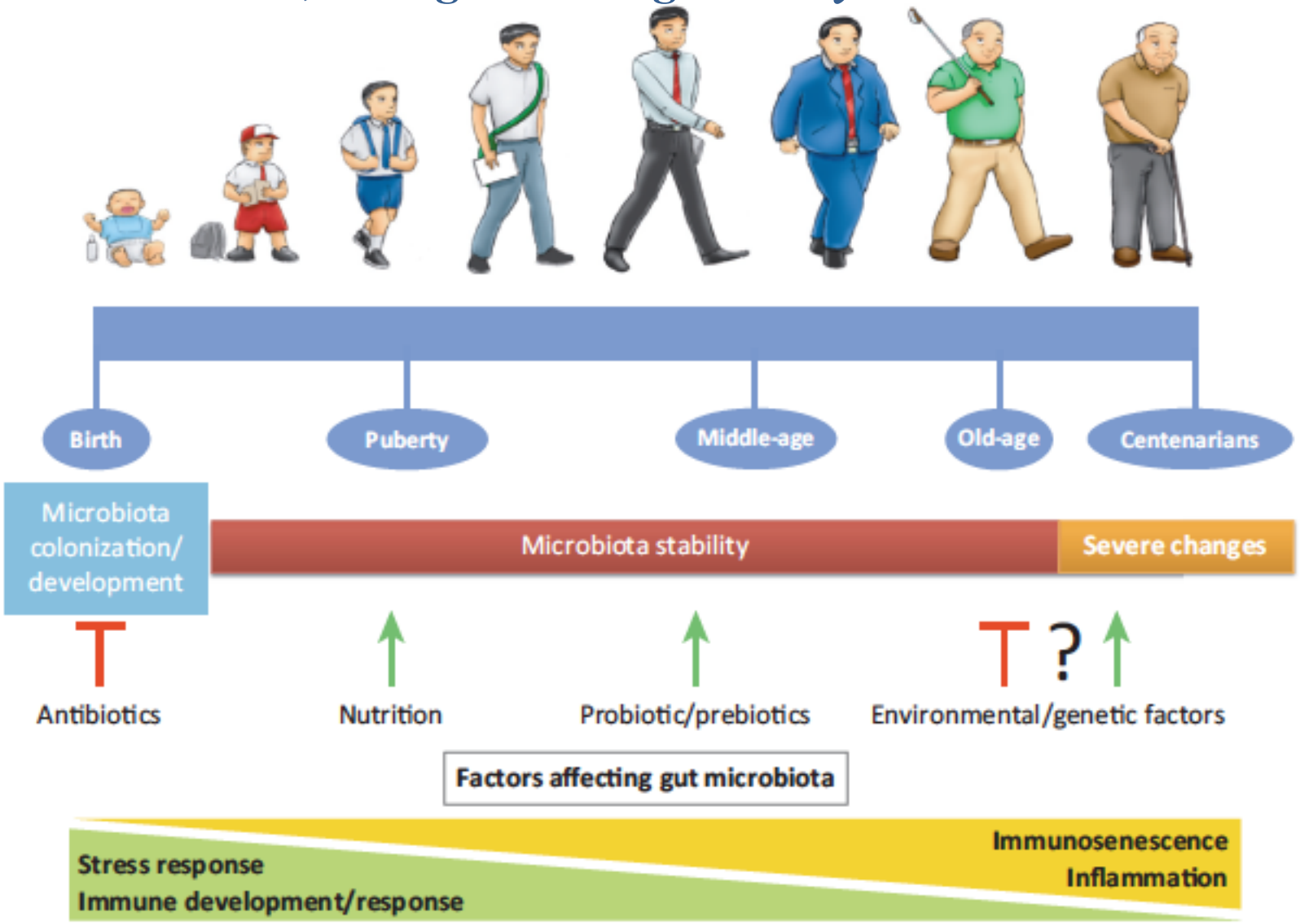
ZINCO

Molluschi (ostriche), carne rossa, ceci e lenticchie, cereali integrali, uova, funghi, semi di zucca, noci, mandorle, pinoli, lievito di birra, cioccolato

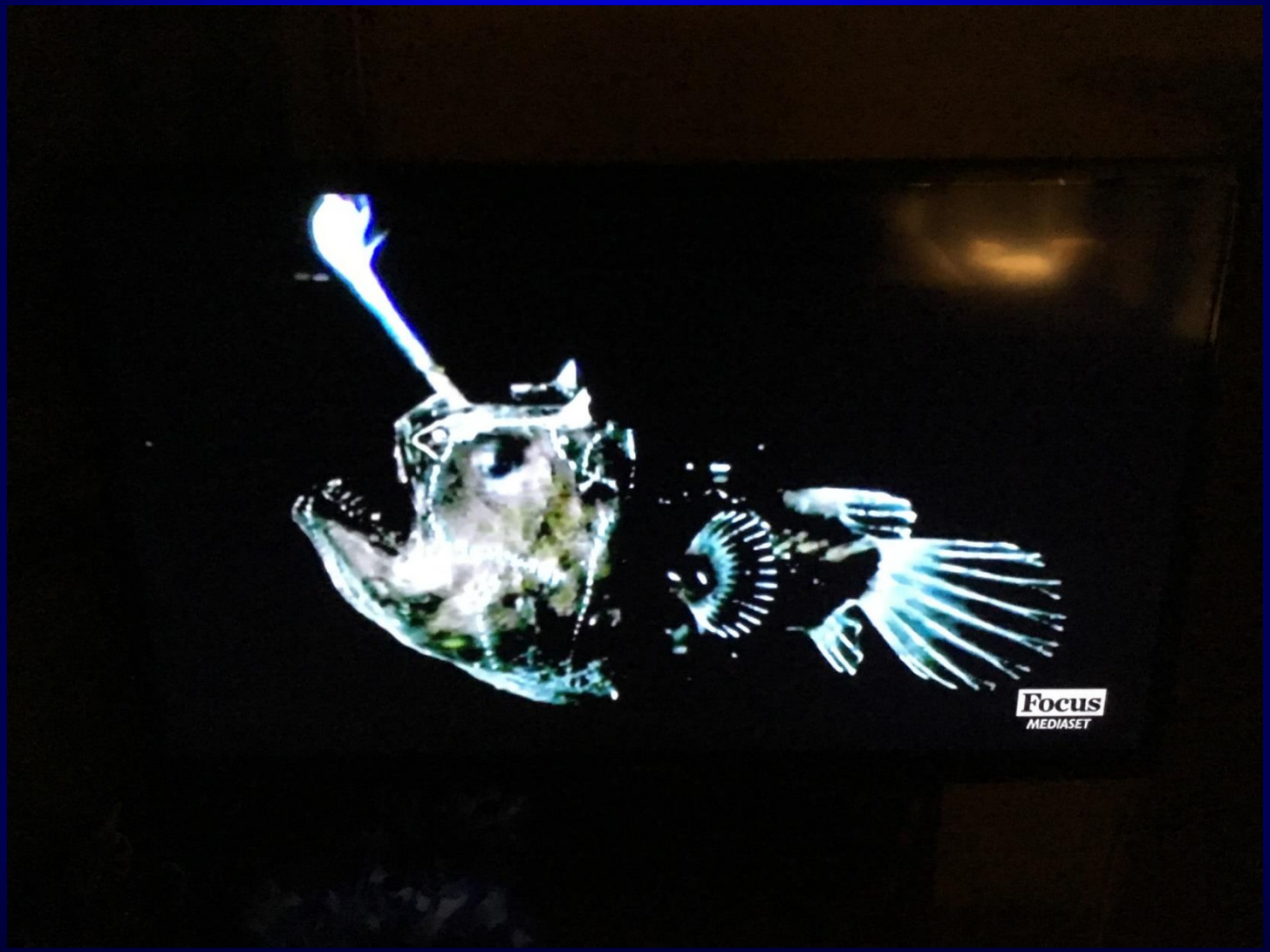
FUNZIONI FONDAMENTALI PER L'ORGANISMO

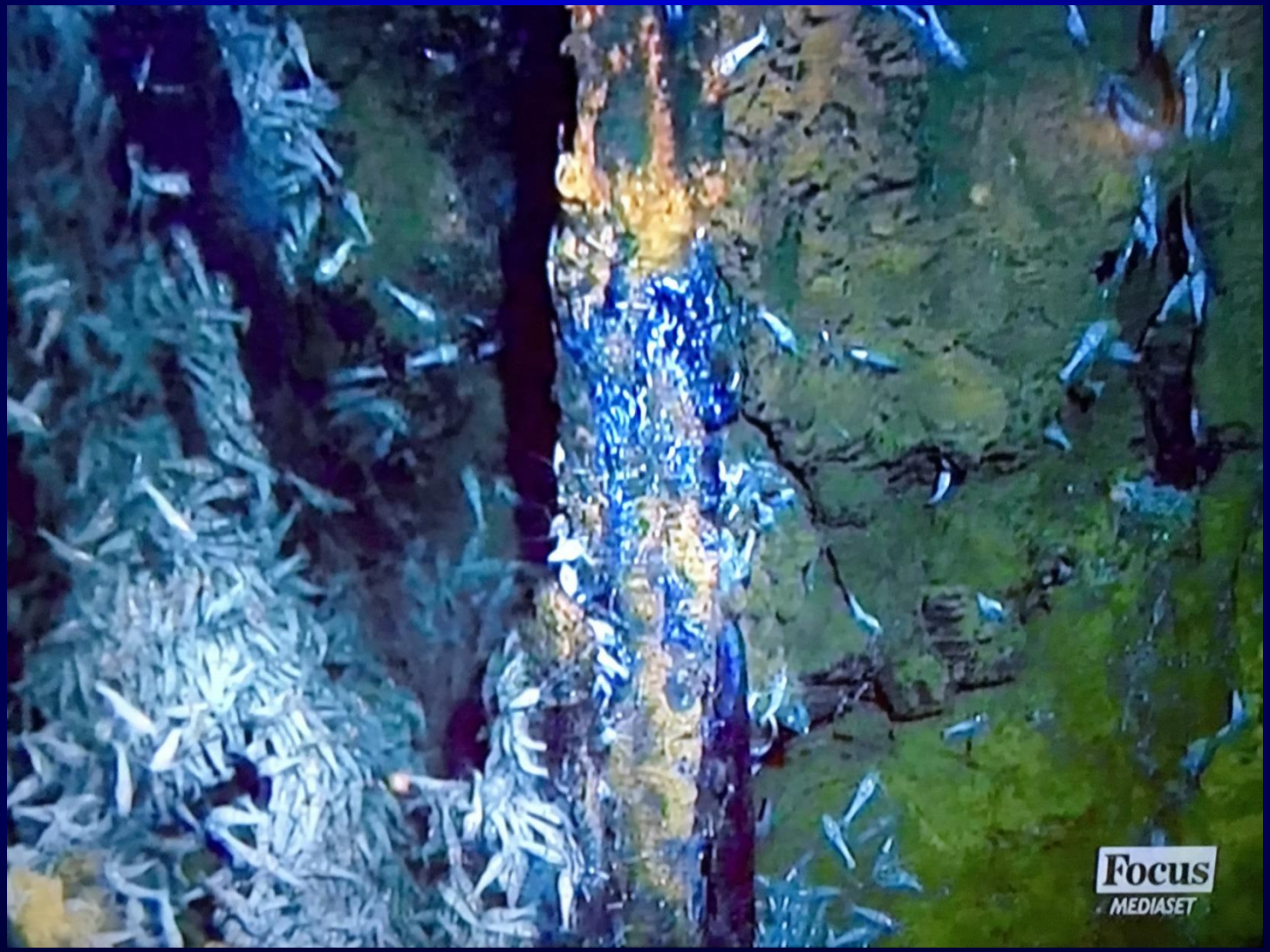
- Immagazzinato in muscoli , fegato, ossa, capelli
- Antiossidante
- Attiva numerosi enzimi
- Attiva ormoni sessuali, della crescita, insulina
- Attiva sistema immunitario
- Favorisce vista, olfatto, memoria
- Favorisce cicatrizzazione delle ferite
- Previene e cura la degenerazione maculare
- Favorisce crescita dei capelli e delle unghie
- Utile nel diabete
- Necessario per l'apparato riproduttivo

There is no chronological threshold or age at which the composition of the microbiota suddenly alters; rather, changes occur gradually with time…

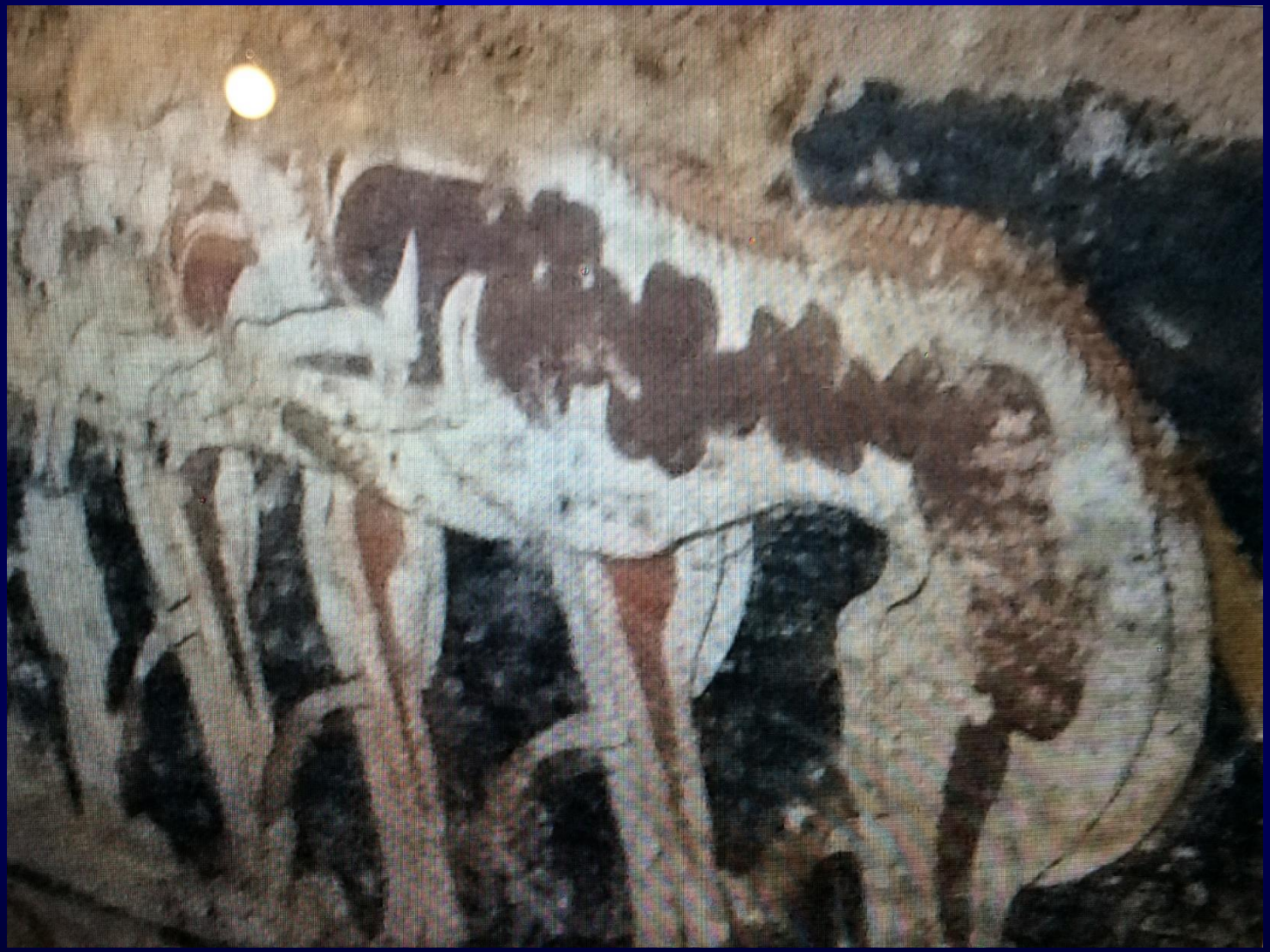


Nikoletopoulou V et al. Trend in Endocrinology and Metabolism 2014


Focus
MEDIASET


Focus
MEDIASET

Archeologia



GASBARRINI G., Dig.Dis. Hepatol., 2018