MY SLIDES ARE AVAILABLE THROUGH TODAYS ORGANISERS

Let food be thy medicine

Hippocrates (460-377 BC)

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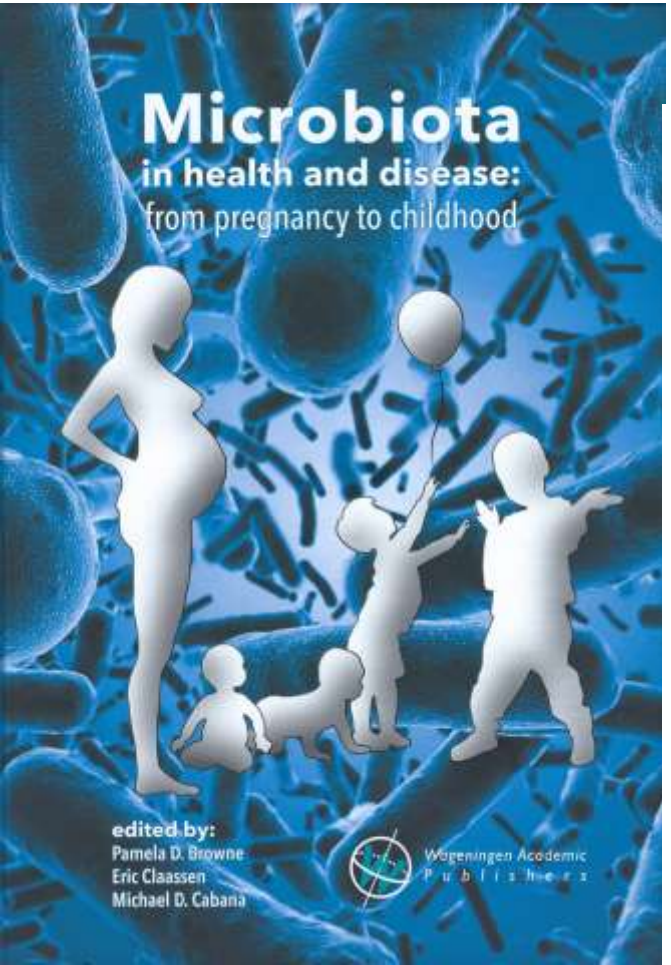
Herewith declared conflict of interest as a non-exclusive and independent expert advisor to numerous industrial, NGO, private and public academic instutions and (EU) consortia (over 155 clients).

MY SLIDES ARE AVAILABLE THROUGH TODAYS ORGANISERS

My day job is starting companies for infectious disease diagnostics and vaccines in a One Health setting mainly for zoonoses (animal to man)

Gerritse, Posno, Schellekens, Boersma & Claassen E. (1990) Oral administration of TNP-lactobacillus conjugates in mice: a model for evaluation of mucosal and systemic immune responses and memory formation elicited by transformed Lactobacilli. Res. Microbiology, 141, 955-962.

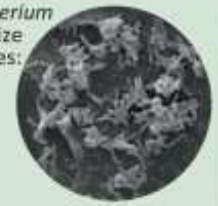


A map of diversity in the human microbiome

Streptococcus dominates the oral cavity with *S. mitis* > 75% in the cheek

Propionibacterium acnes lives on the skin and nose of most people

Many *Corynebacterium* species characterize different body sites:
C. matruchoti the plaque
C. accolens the nose
C. croppenstedtii the skin



Lactobacillus species (*L. gasseri, L. jensenii, L. crispatus, L. iners*) are predominant but mutually exclusive in the vagina

Staphylococcus epidermidis colonizes external body sites

Several *Prevotella* species are present in the gastrointestinal tract. *P. copri* is present in 19% of the subjects and dominates the intestinal flora when present

Microscopy from http://learnmap.wikifortlab.com

Bacteroides is the most abundant genus in the gut of almost all healthy subjects

Campylobacter includes opportunistic pathogens, but members live in the oral cavities of most healthy people in the cohort

E. coli is present in the gut of the majority of healthy subjects but at very low abundance

Key:

- Commensal microbes
- Potential pathogens

The four most abundant phyla

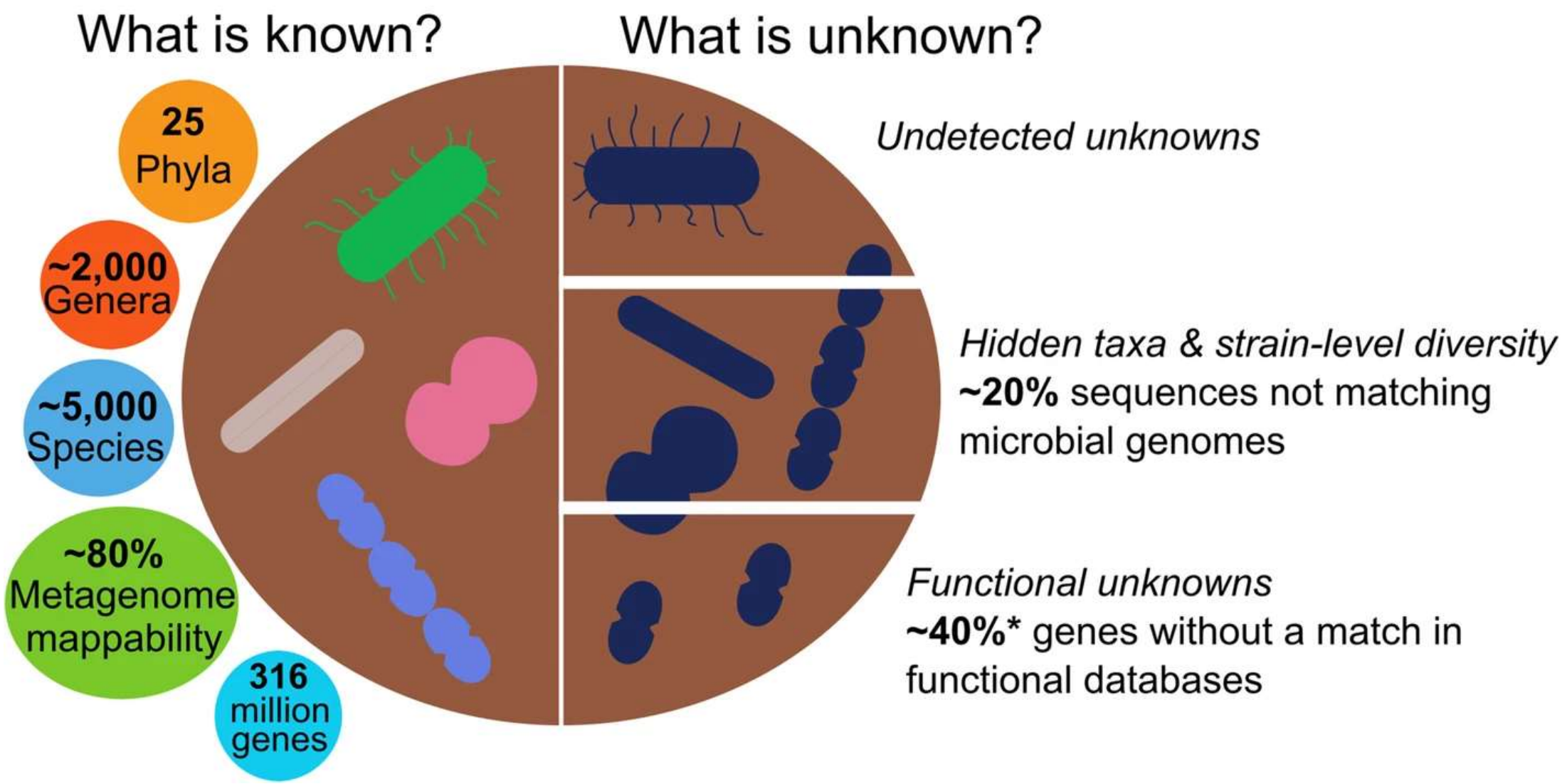
- Actinobacteria
- Bacteroidetes
- Firmicutes
- Proteobacteria

Low abundance phyla

- Chloroflexi
- Cyanobacteria
- Euryarchaeota
- Fusobacteria
- Lentisphaerae
- Spirochaetes
- Synergistetes
- Tenericutes
- Thermi
- Verrucomicrobia

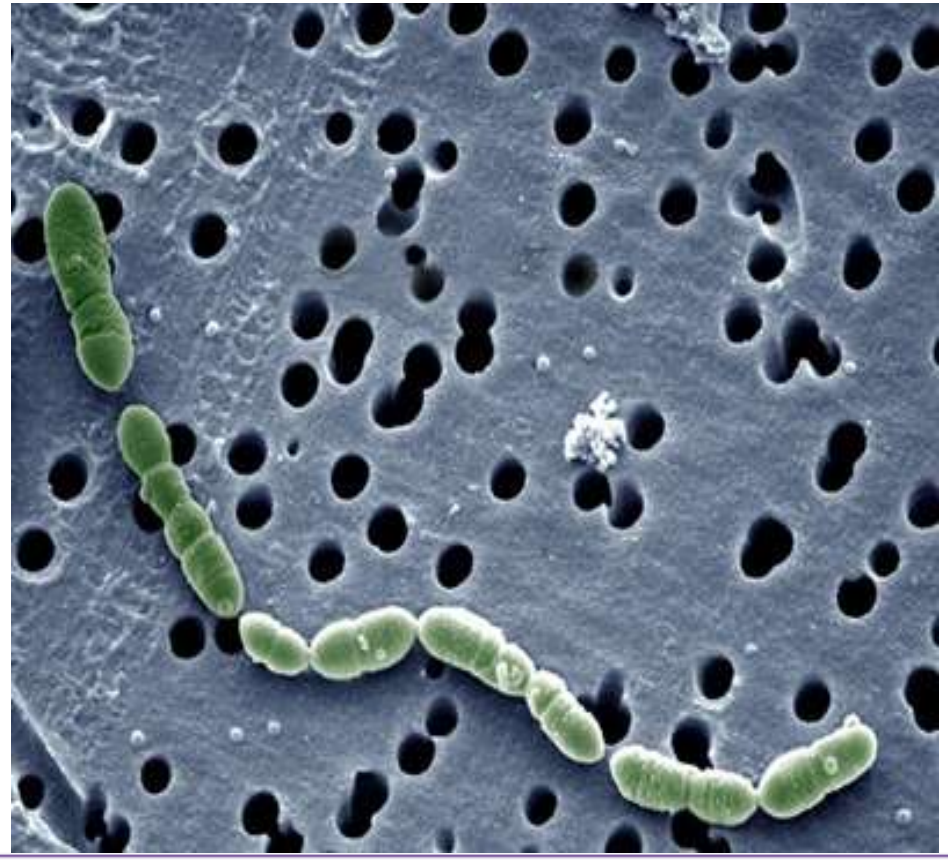
TRENDS in Genetics

The human microbiome



Andrew Maltez Thomas & Nicola Segata BMC Biology 17: 48 (2019)

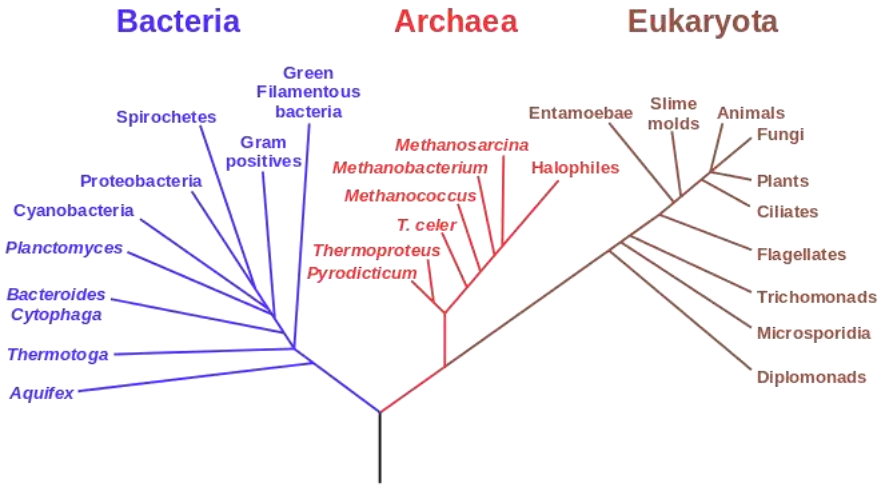
Het humane microbioom heeft 1-10 maal zoveel bacteriën als lichaamscellen!

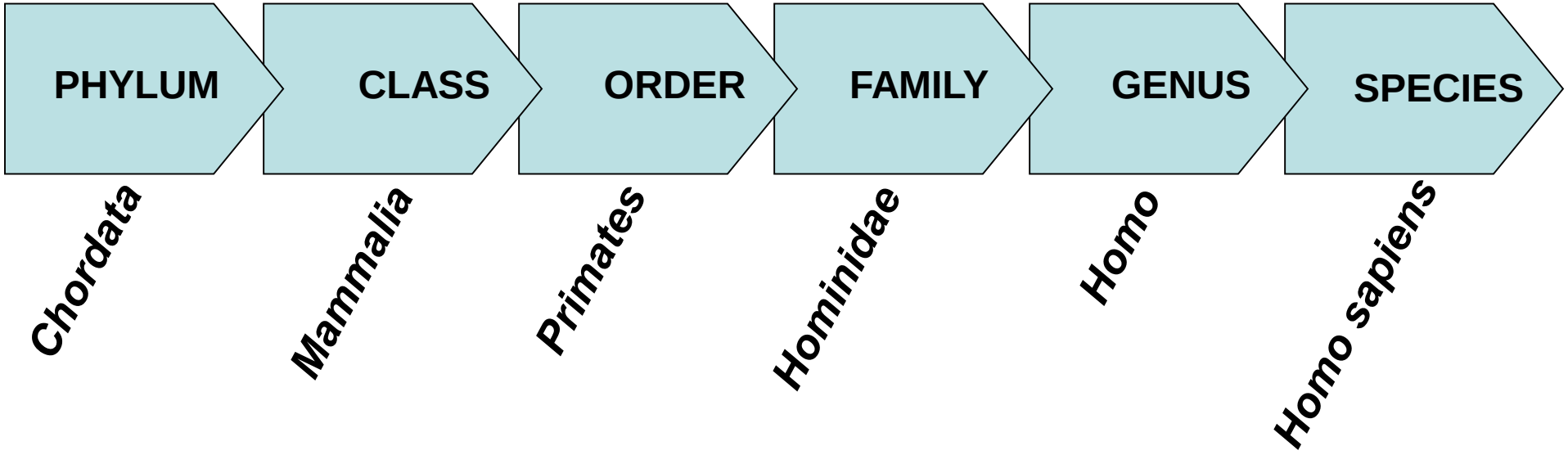


- Er leven ongeveer 10^{14} (honderd-duizend-miljard!) micro-organismen in de mens
- Dat is 1-1½ kilogram per gezonde volwassene
- 100x meer bacteriële genen in vergelijking met humaan genoom

Phylogeny; ‘a reminder….’

Human phylogeny & namegiving

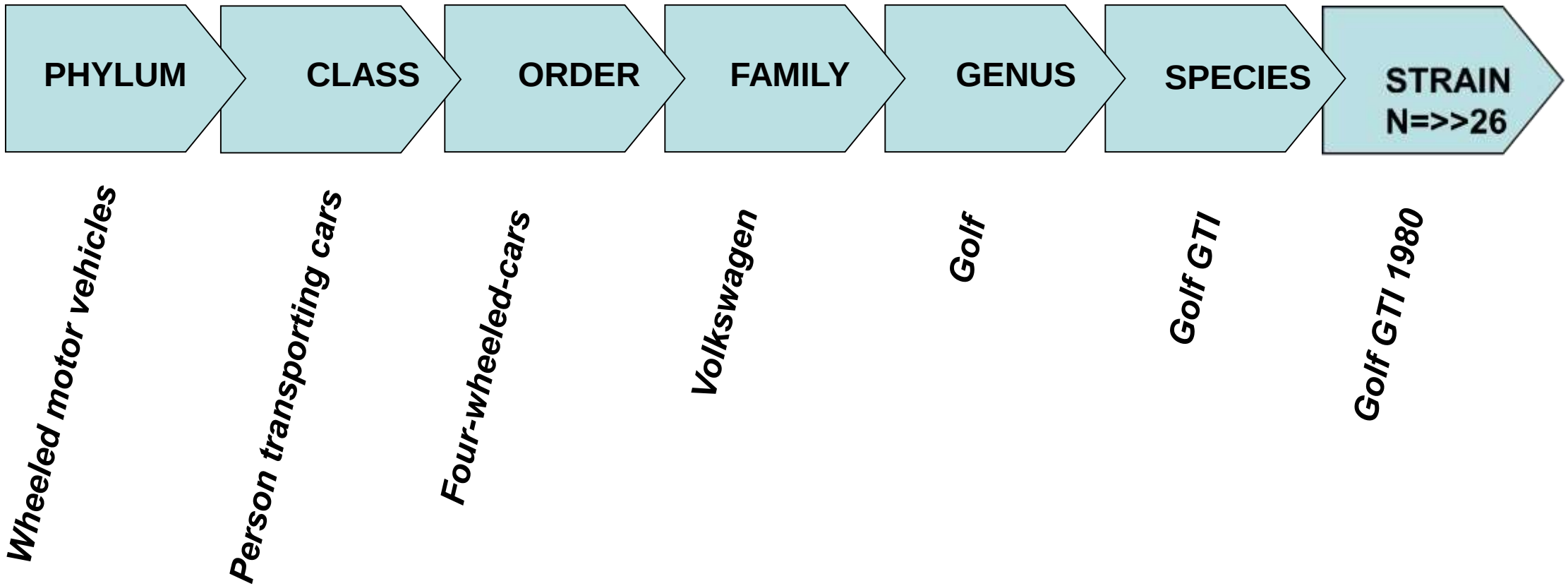




Slide stolen from prof dr Kleerebezem

Phylogeny; ‘a reminder….’

Automobile phylogeny & namegiving ☺

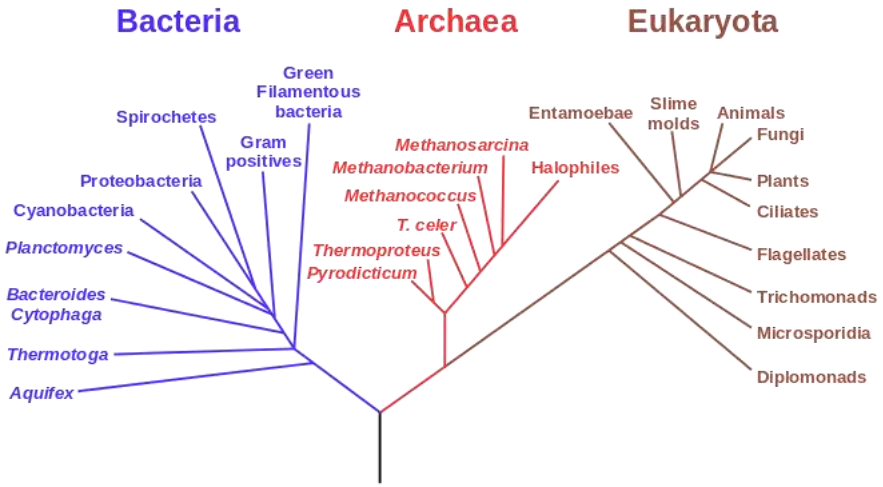


1980

2018

Bacterial phylogeny; ‘a reminder….’

The yoghurt workhorse *S. thermophilus*



PHYLUM	CLASS	ORDER	FAMILY	GENUS	SPECIES (OTU)	STRAIN N=>>26
Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	Streptococcus	S. thermophilus	S. Thermophilus CNRZ 1066

1	Preweaning
2	Weaning
3	Weaned-3 years old
4	4–9 years old
10	10–19 years old
20	20–29 years old
30	30–39 years old
40	40–49 years old
50	50–59 years old
60	60–69 years old
70	70–79 years old
80	80–89 years old
90	90–99 years old
100	Over 100 years old

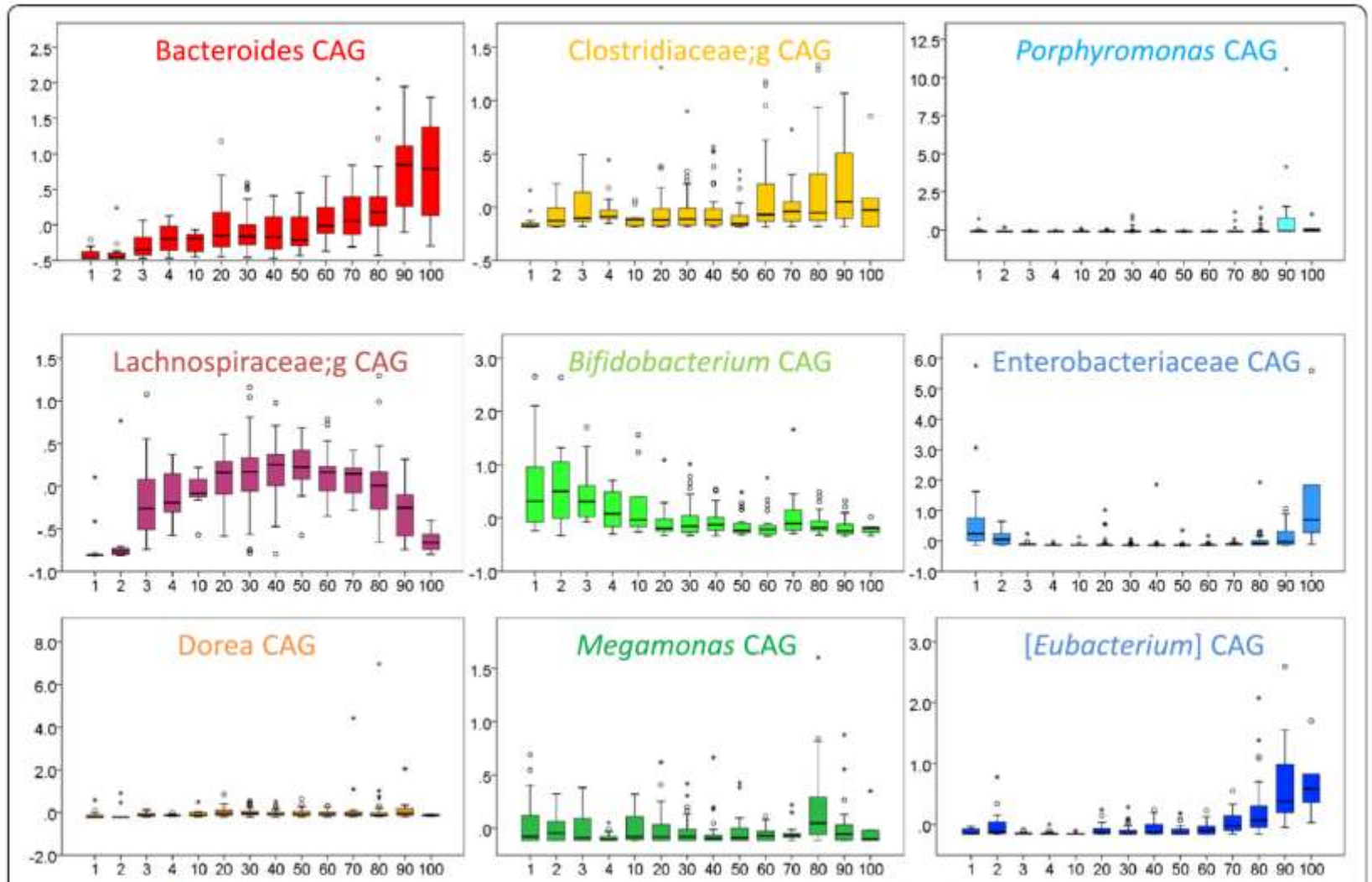
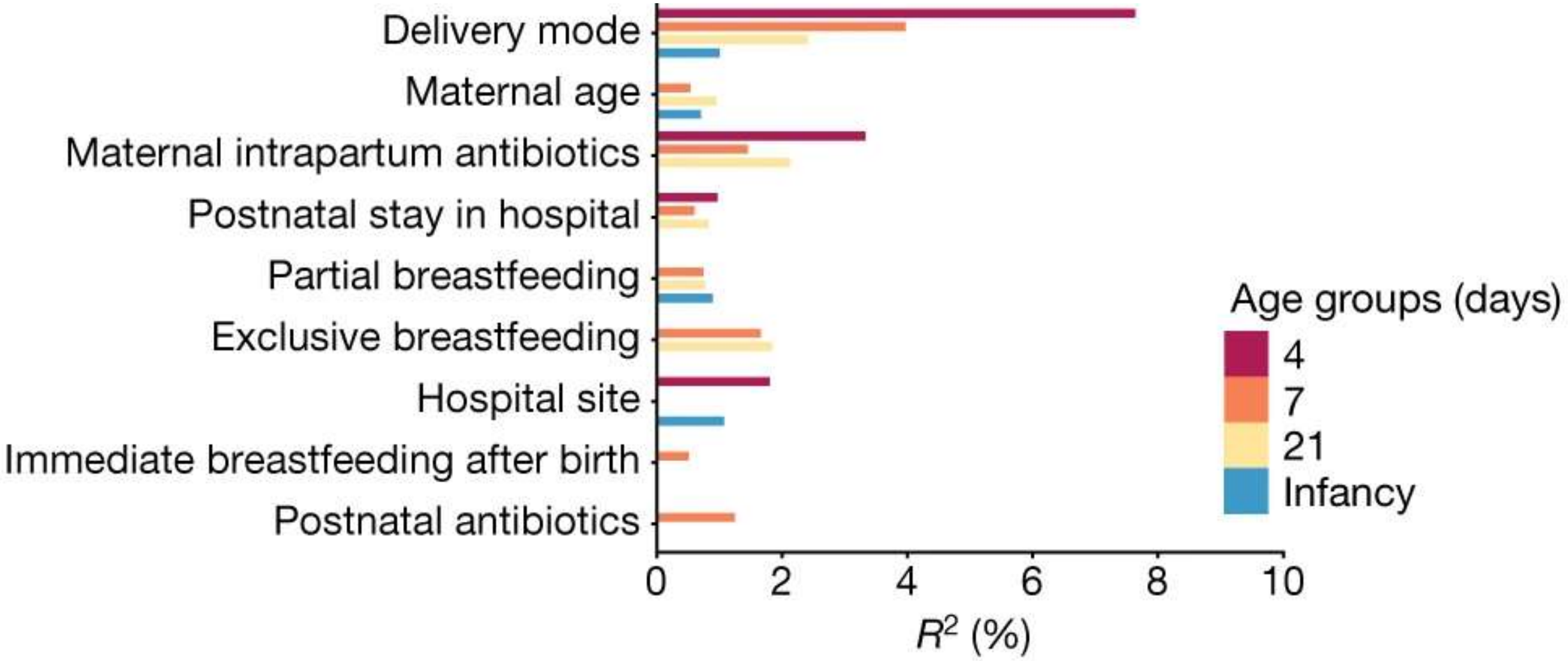


Fig. 3 Transition type of each co-abundance group (CAG) from infant to centenarian. Each number indicates a group as shown in Table 1. Box-plots show the interquartile range (IQR) of the sum of z-scores converted from the relative abundance of genera belonging to the same CAG. Open circles and asterisks indicate outliers from 1.5- to 3.0-fold IQR and over 3.0-fold IQR, respectively

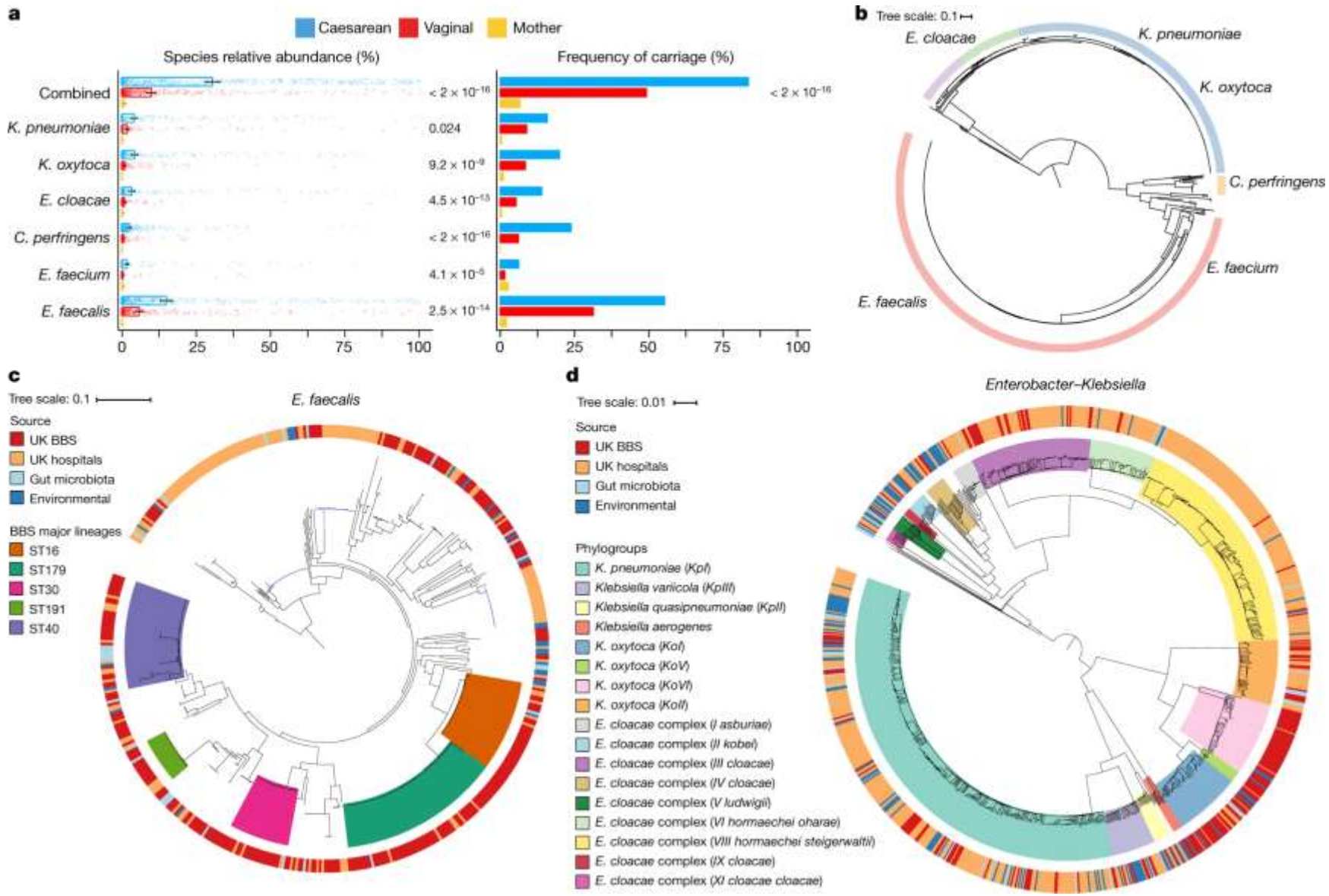
When children are born, they emerge from the relatively sterile environment of the uterus into a world teeming with bacteria . . .

KEIZERSNEDE GEEFT MICROBIOTA ACHTERSTAND



Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth

Yan Shao, Samuel C. Forster, Evdokia Tsaliki, Kevin Vervier, Angela Strang, Nandi Simpson, Nitin Kumar, Mark D. Stares, Alison Rodger, Peter Brocklehurst, Nigel Field & Trevor D. Lawley **Nature (2019)**



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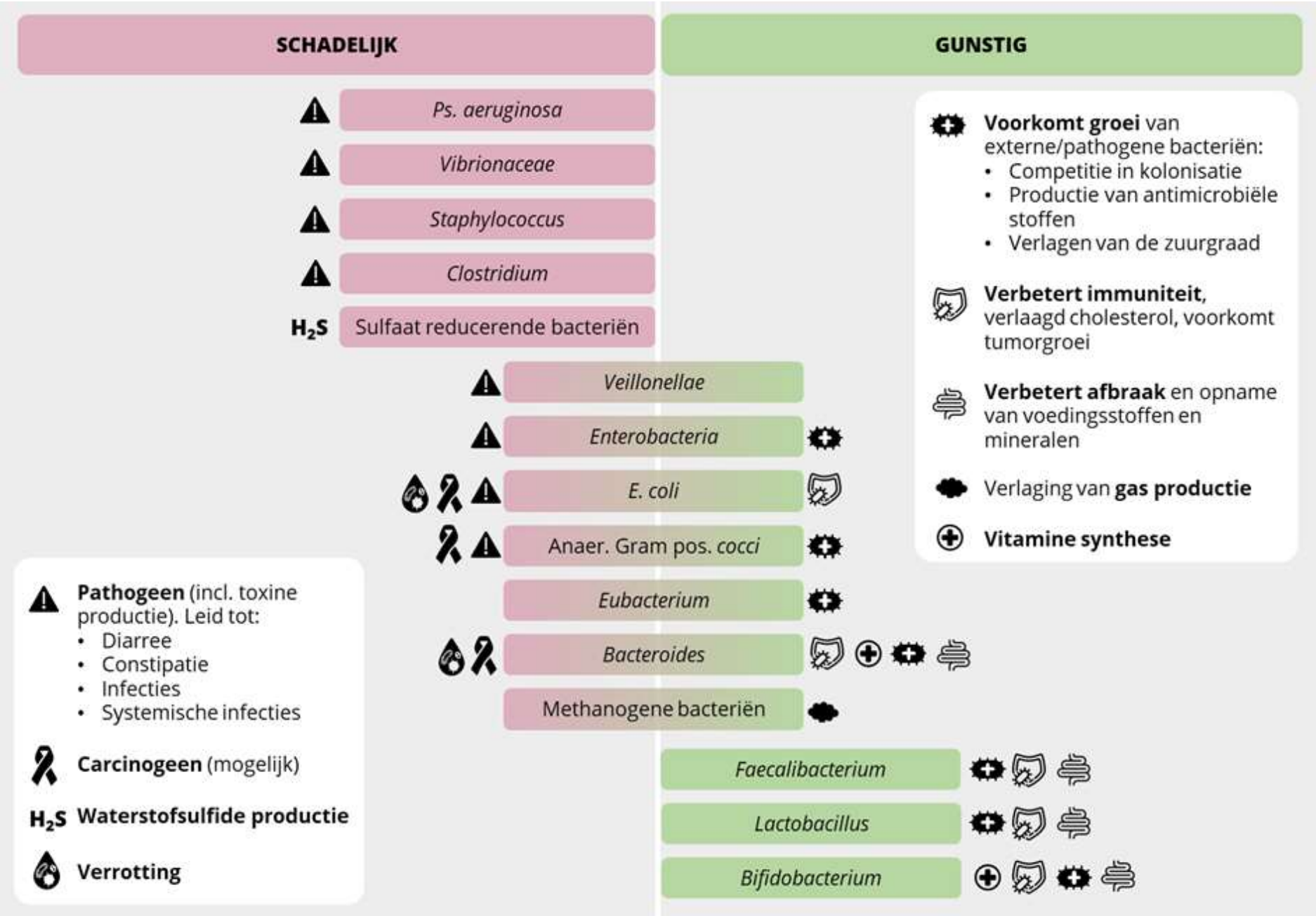
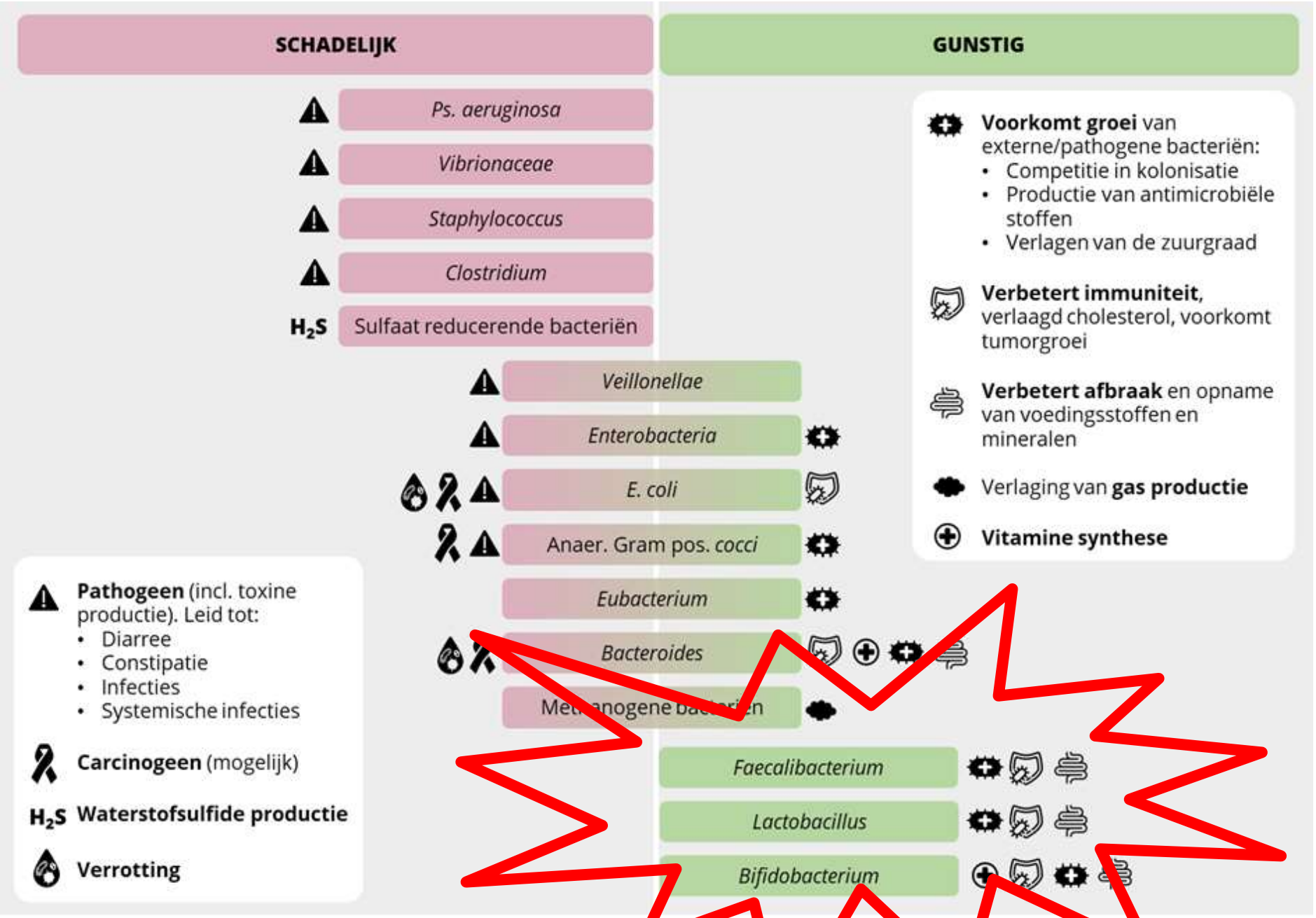


Nieuwboer, Claassen et al 2019, in druk

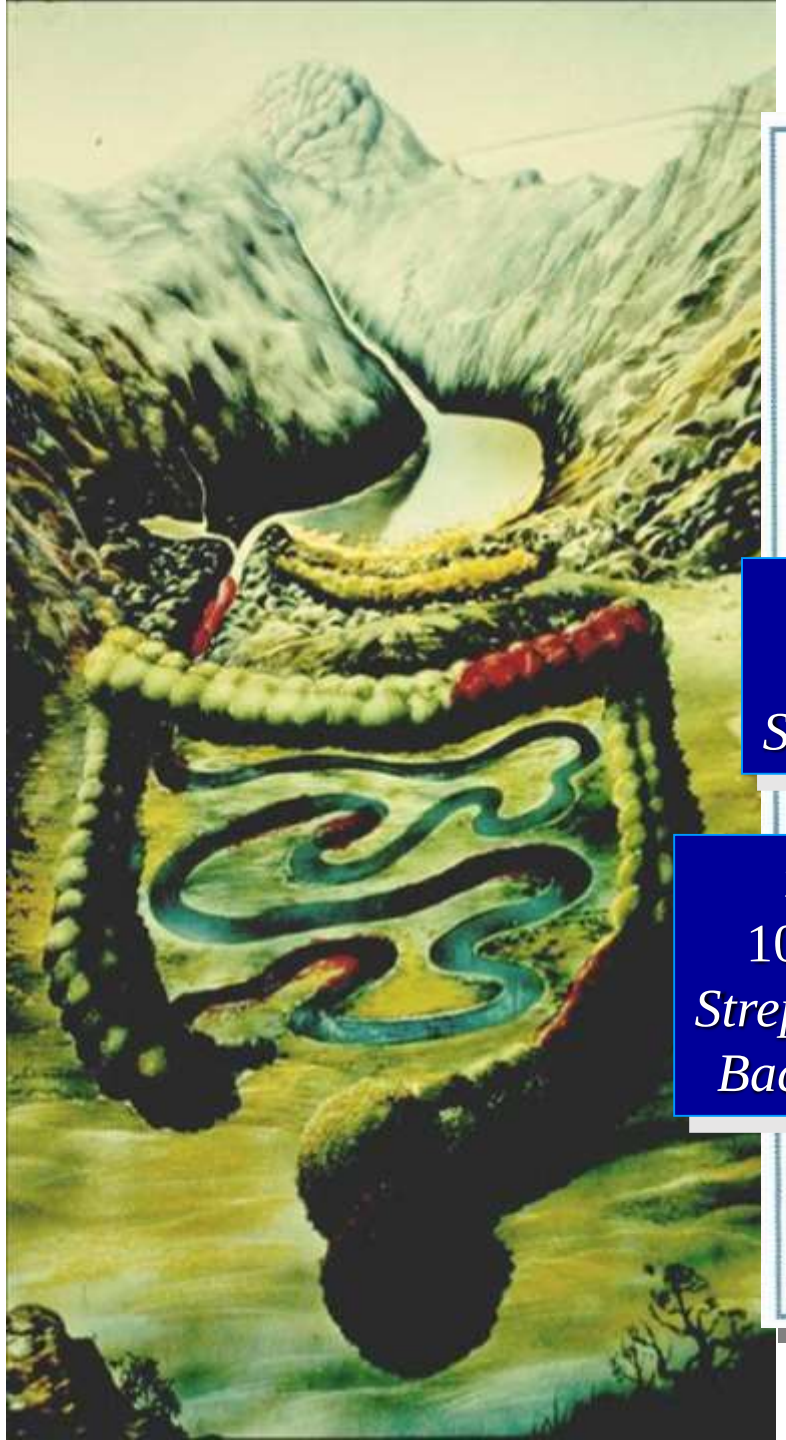


Nieuwboer, Claassen et al 2019, in druk

Darmvlokken (*villi*) geven oppervlakte vergroting

- De totale oppervlakte van de ‘uitgespreide darm’ komt daarmee op meer dan 300 vierkante meter

- Dat is een tennisveld



Mouth
$10^5 – 10^7$
polymorph germs

stomach
$10^2 – 10^3$
Streptococcus

duodenum
$< 10^{4-5}$
Streptococcus

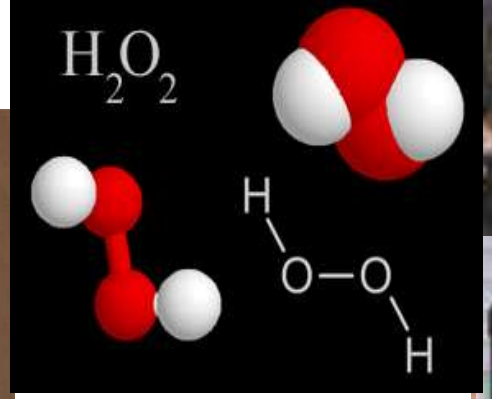
jenunum
$10^5 – 10^6$
Streptococcus

ileum
$10^3 – 10^7$
Streptococcus
Bacteroides

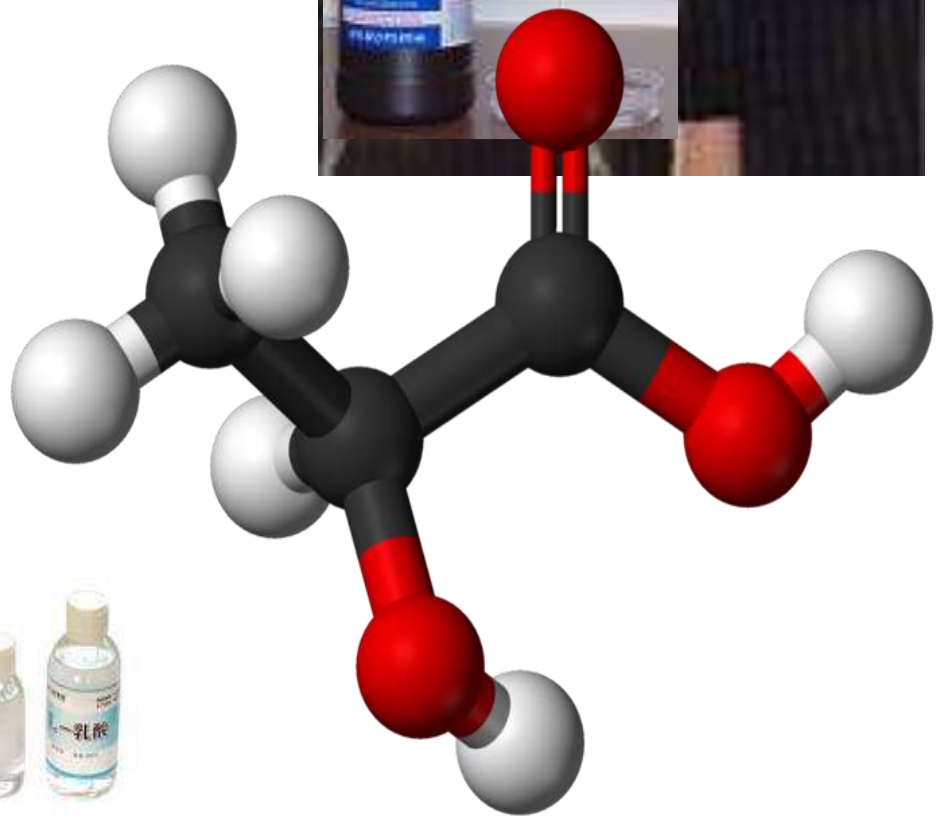
colon
$10^9 – 10^{11}$
Bacteroides
Clostridum
Streptococcus
Bifidobacteria
Enterobacteria

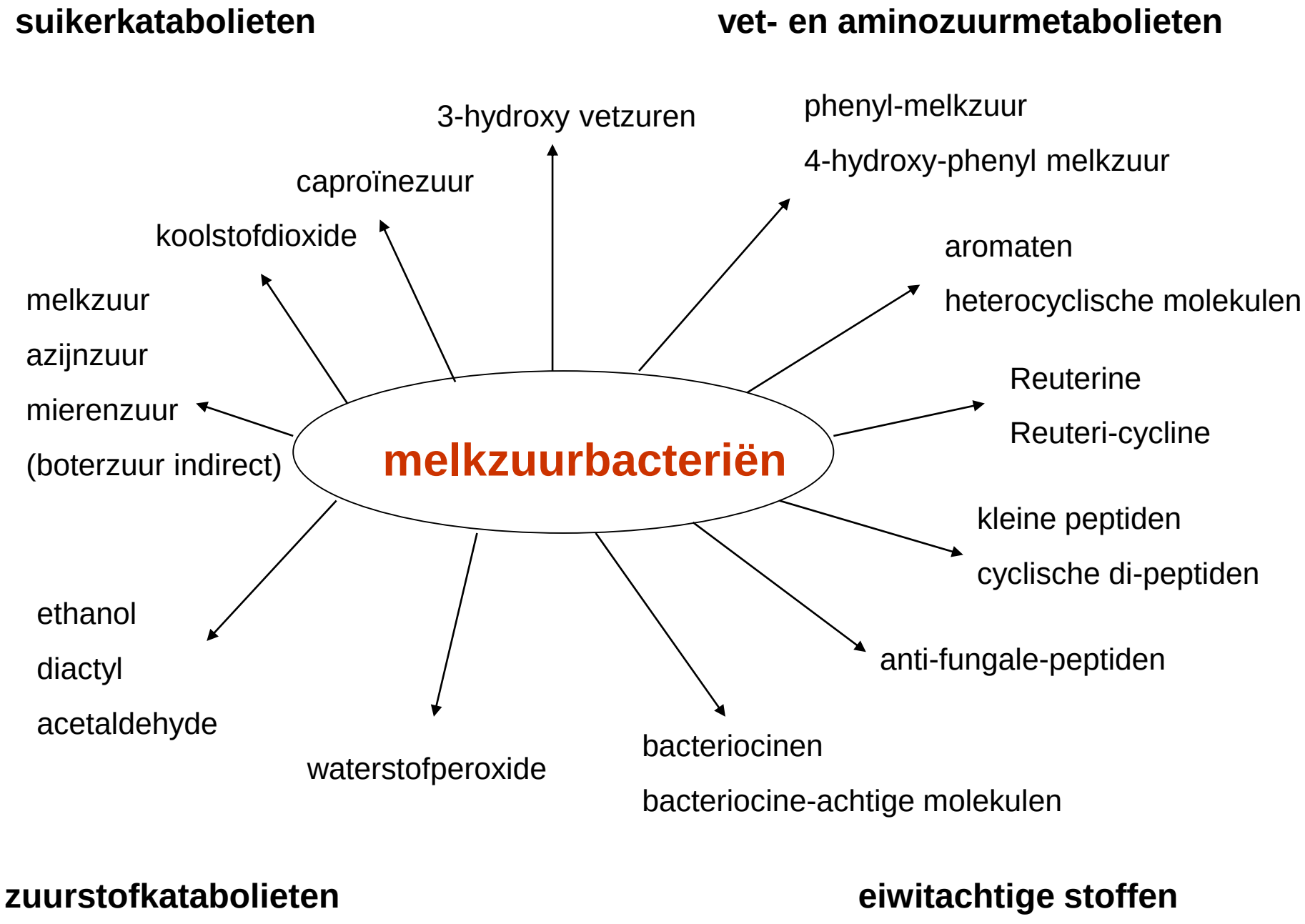

Hier zit uw
BROODJE met uw
levende bacteriële
gasten!!

Bacterieen moeten aanhechten aan darm eptiheel om te koloniseren: competitie

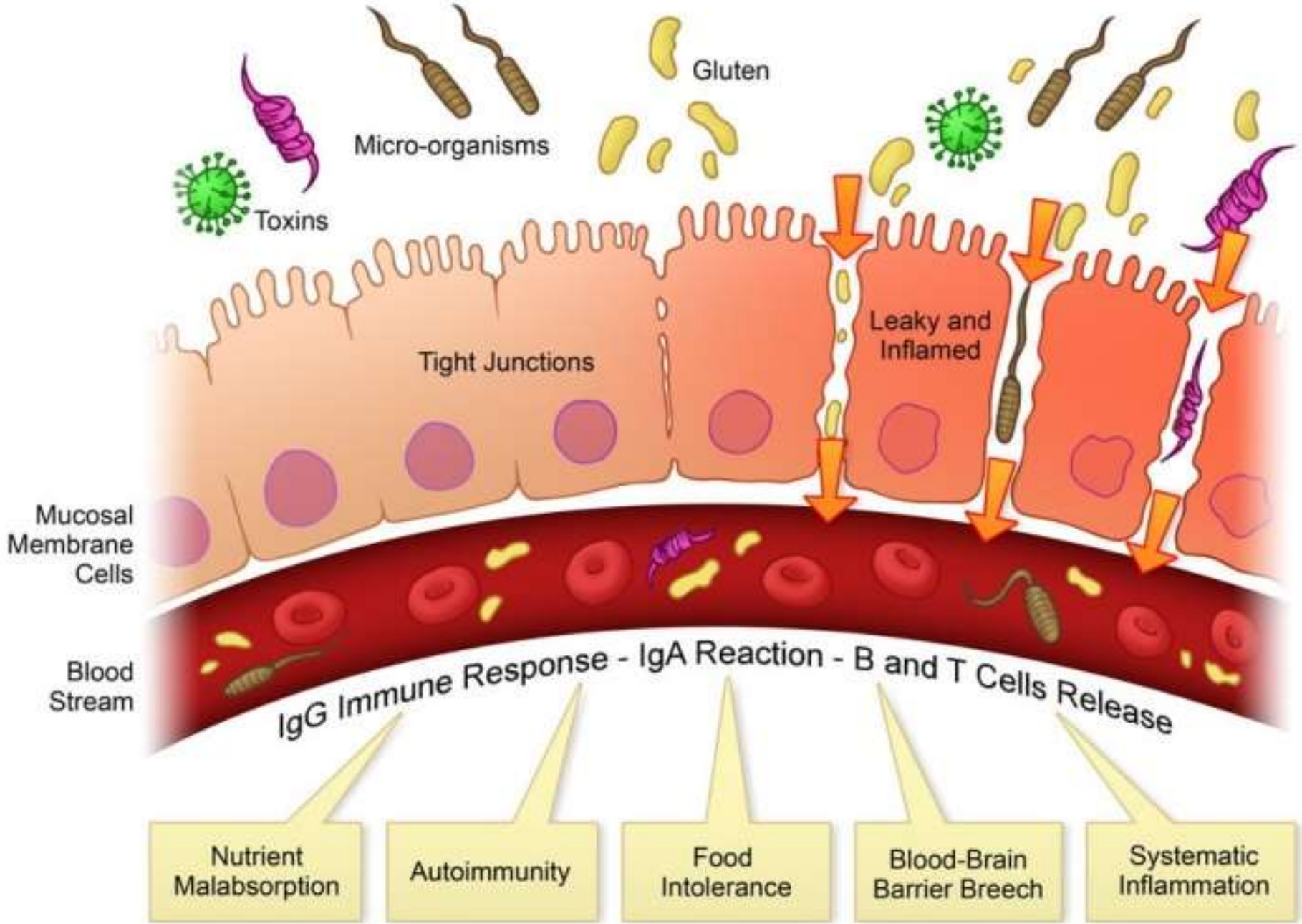

H_2O_2
H
O—O
H


BLONDIE

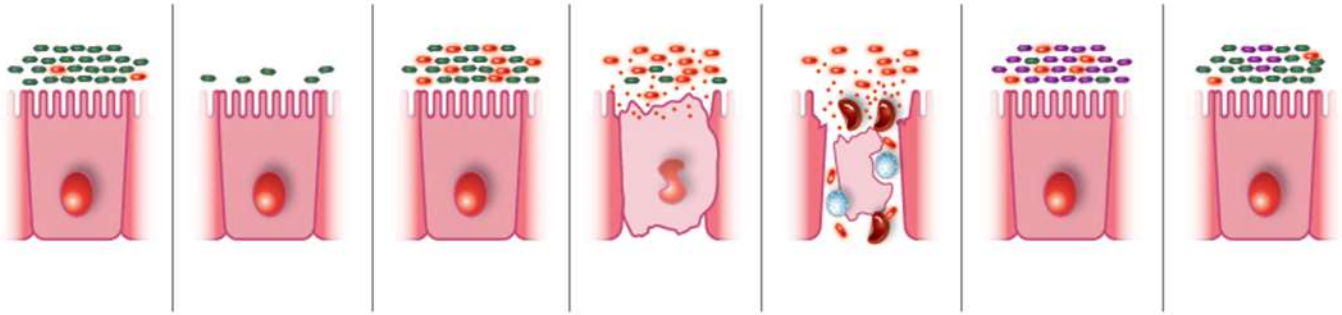



suikerkatabolieten
vet- en aminozuurmetabolieten
3-hydroxy vetzuren
caproïnezuur
koolstofdioxide
melkzuur
azijnzuur
mierenzuur
(boterzuur indirect)
phenyl-melkzuur
4-hydroxy-phenyl melkzuur
aromaten
heterocyclische molekulen
Reuterine
Reuteri-cycline
kleine peptiden
cyclische di-peptiden
anti-fungale-peptiden
melkzuurbacteriën
ethanol
diactyl
acetaldehyde
waterstofperoxide
bacteriocinen
bacteriocine-achtige molekulen
zuurstofkatabolieten
eiwitachtige stoffen

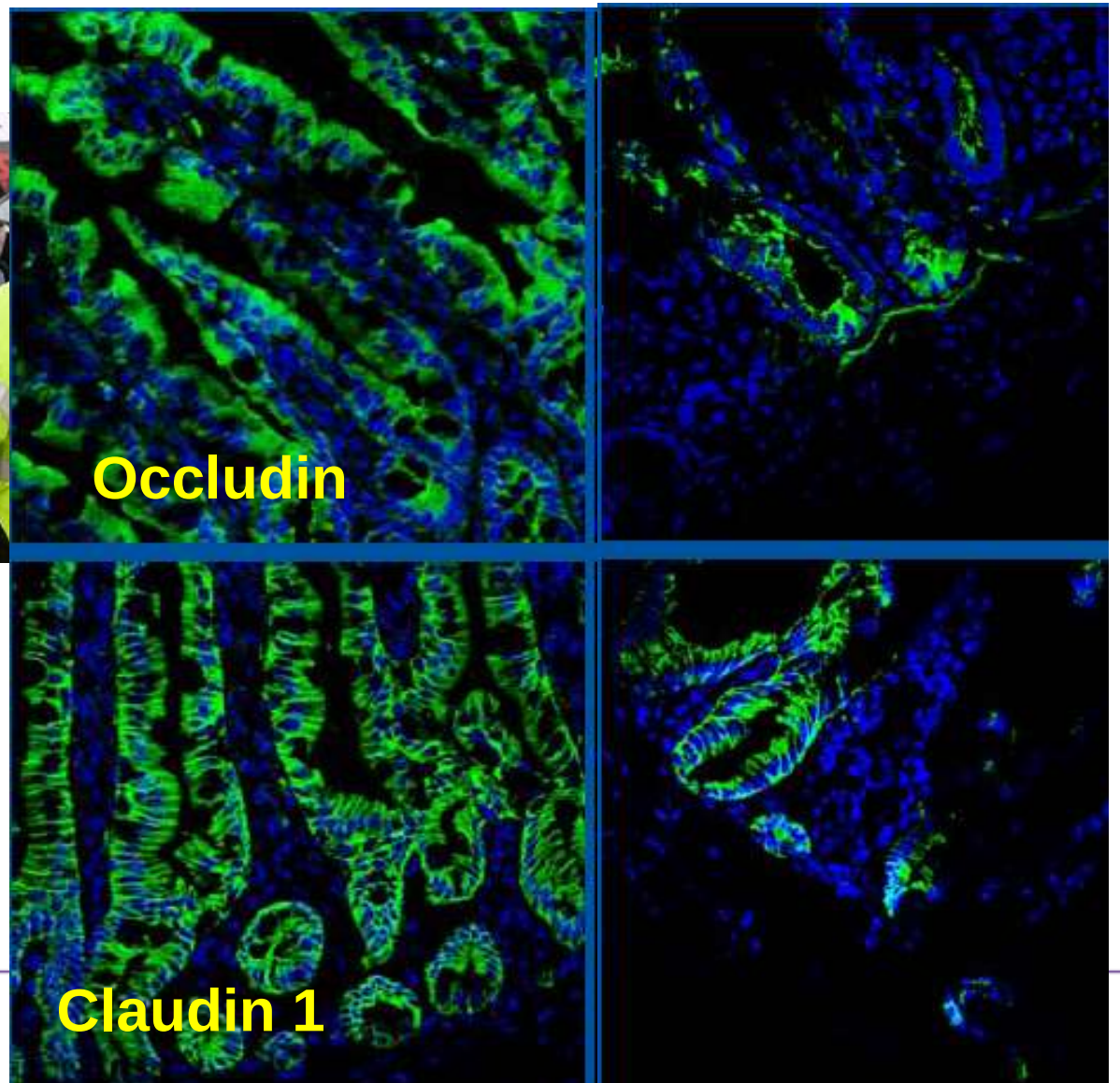
Darmwand en gezond epitheel is een barriere


Gluten
Micro-organisms
Toxins
Tight Junctions
Leaky and Inflamed
Mucosal Membrane Cells
Blood Stream
IgG Immune Response - IgA Reaction - B and T Cells Release
Nutrient Malabsorption
Autoimmunity
Food Intolerance
Blood-Brain Barrier Breech
Systematic Inflammation

Afbraak van de barriere functie -> opportunisten & ontsteking

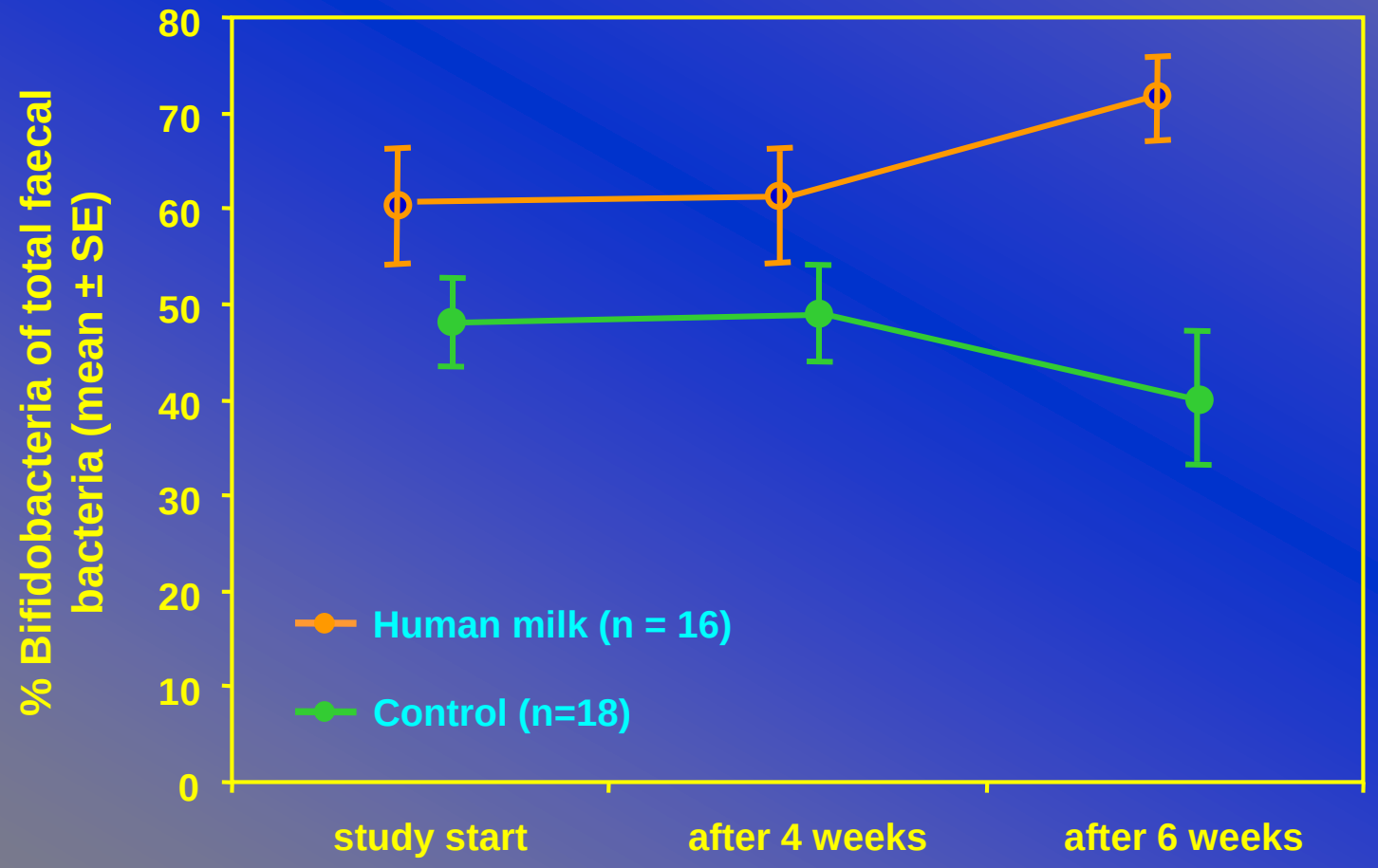


Lactobacilli versterken tight junctions



Clinical Studies: Effects of the Prebiotic GOS/FOS Mixture in Infants 4-12 Weeks

- Bifidogenicity -



Knol et al., 2002

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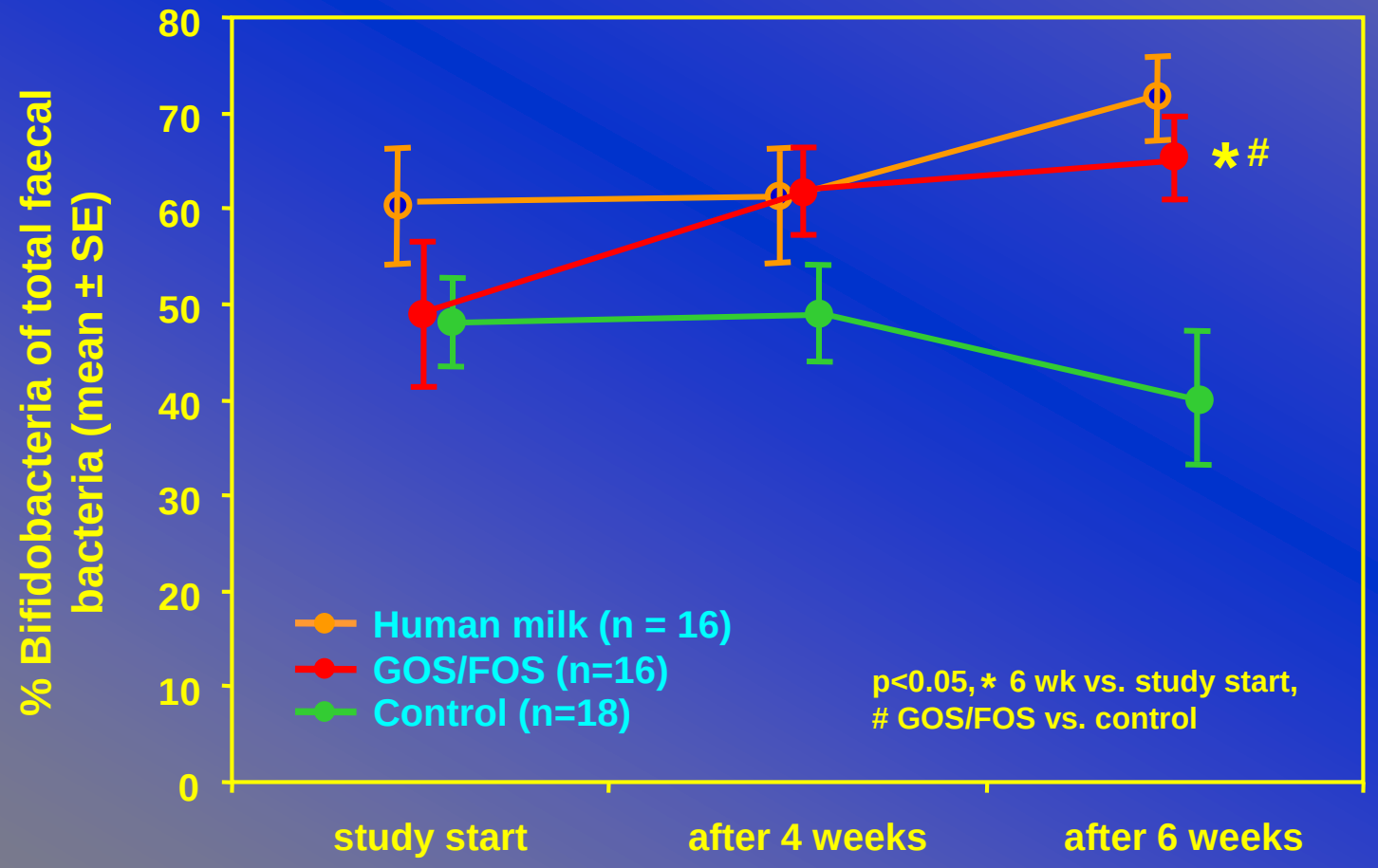
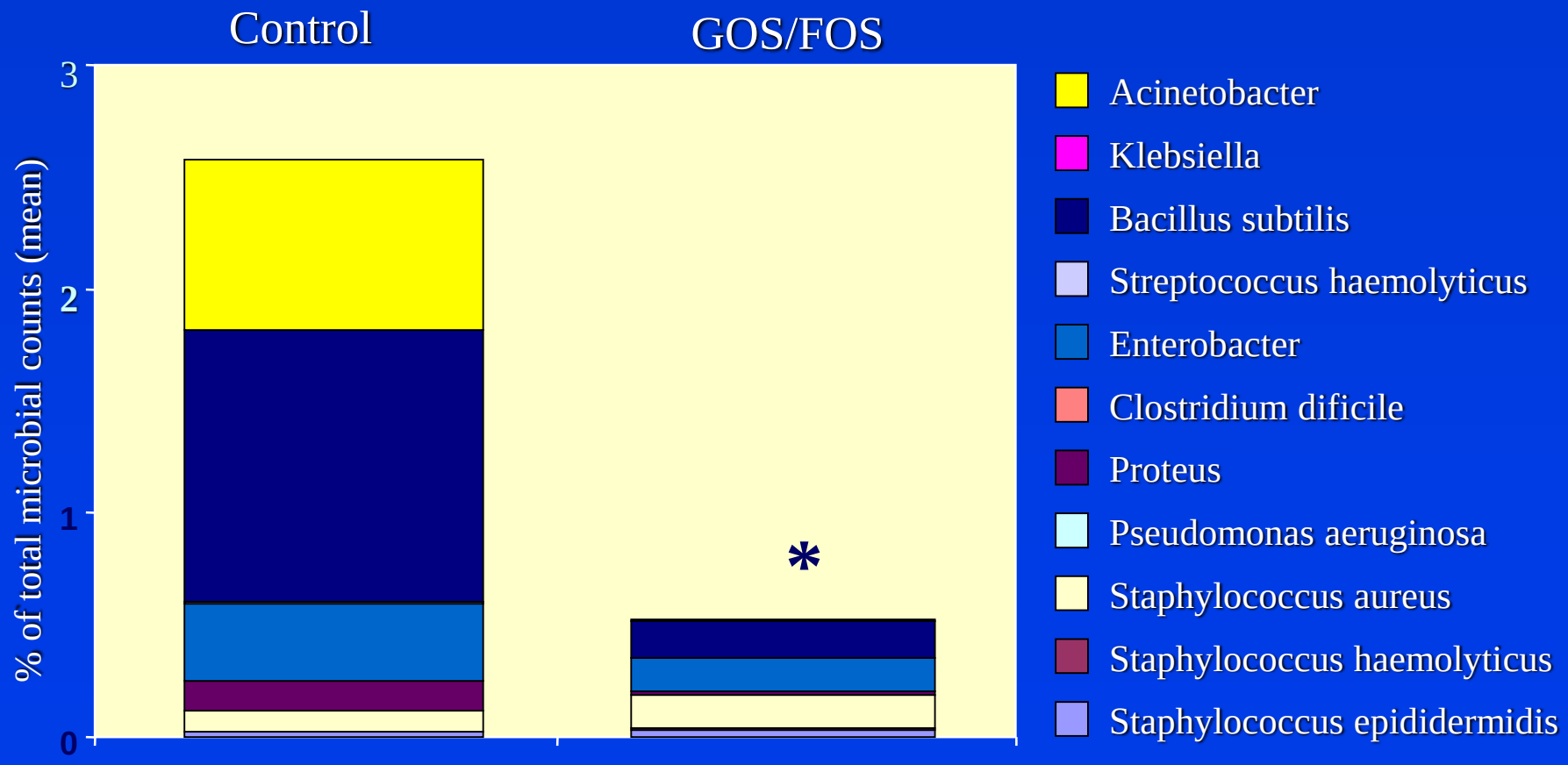


Knol et al., 2002

Reduction of pathogens in the gut after GOS&FOS

Difference group
Mann-Whitney U-test:
Sum of all pathogens:
* p=0.01 vs. Control

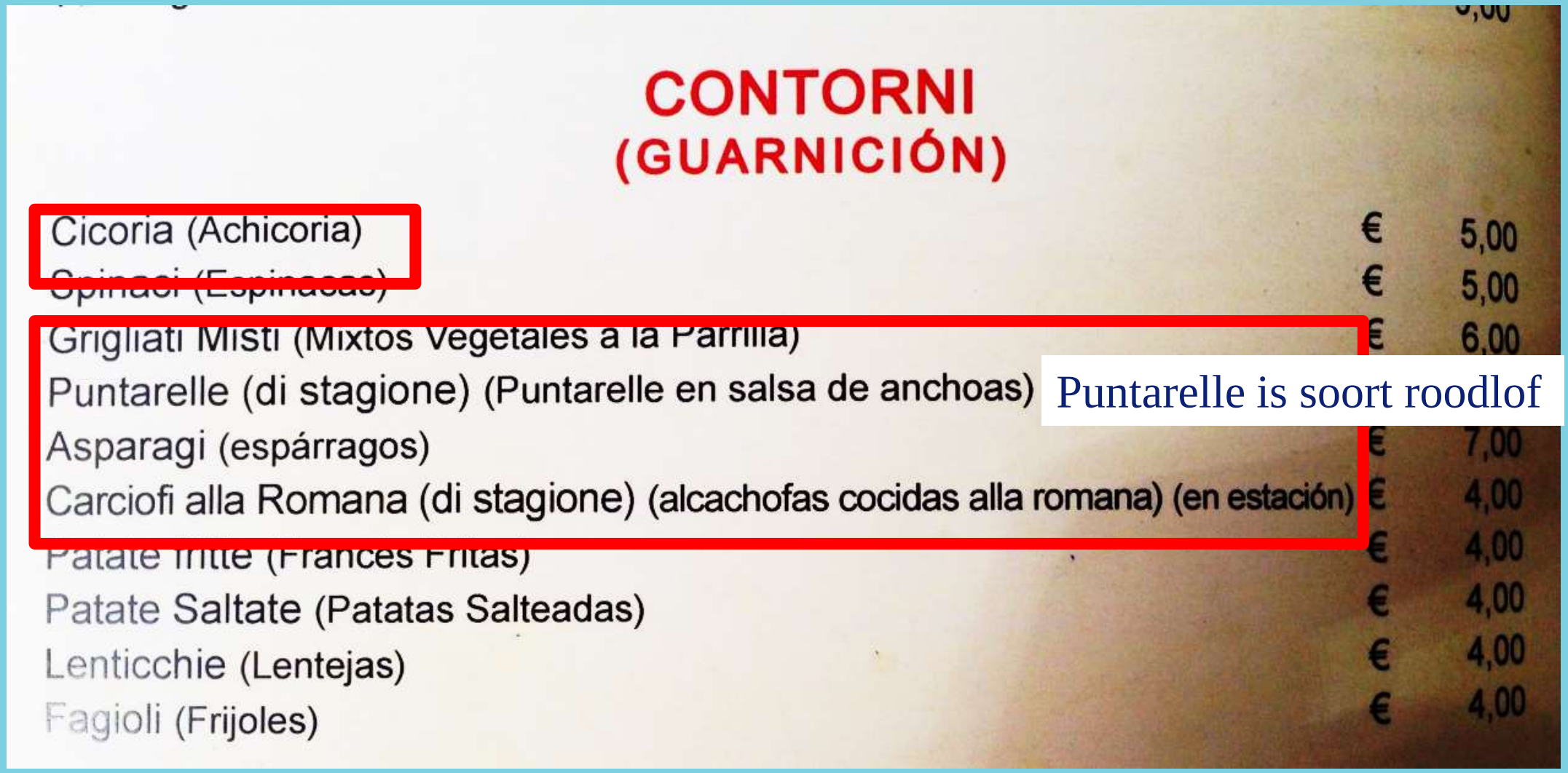


Boehm et al., JPGN, 2003

Slide from Yvan van den Plas

Citation: Claassen E (2014) Cost-benefit relation of diet and probiotics in iatrogenic bowel irregularity (IBI). Front. Pharmacol. 5:14. doi: 10.3389/fphar.2014.00014

	% w/w (vers)
Witlof / Cichorei	15-20
Knoflook	9 - 16
Schorseneer	4 - 10
Prei	3 - 10
Ui	2 - 6
Artisjok	2 - 6
Asperge	2 - 3
Tarwemeel	1 – 4
Borstvoeding Mens	0.5 - 1.5
Haver	0.5 - 1.5
Banaan	0.3 - 0.7
Zoogdier melk	0.01 - 0.1



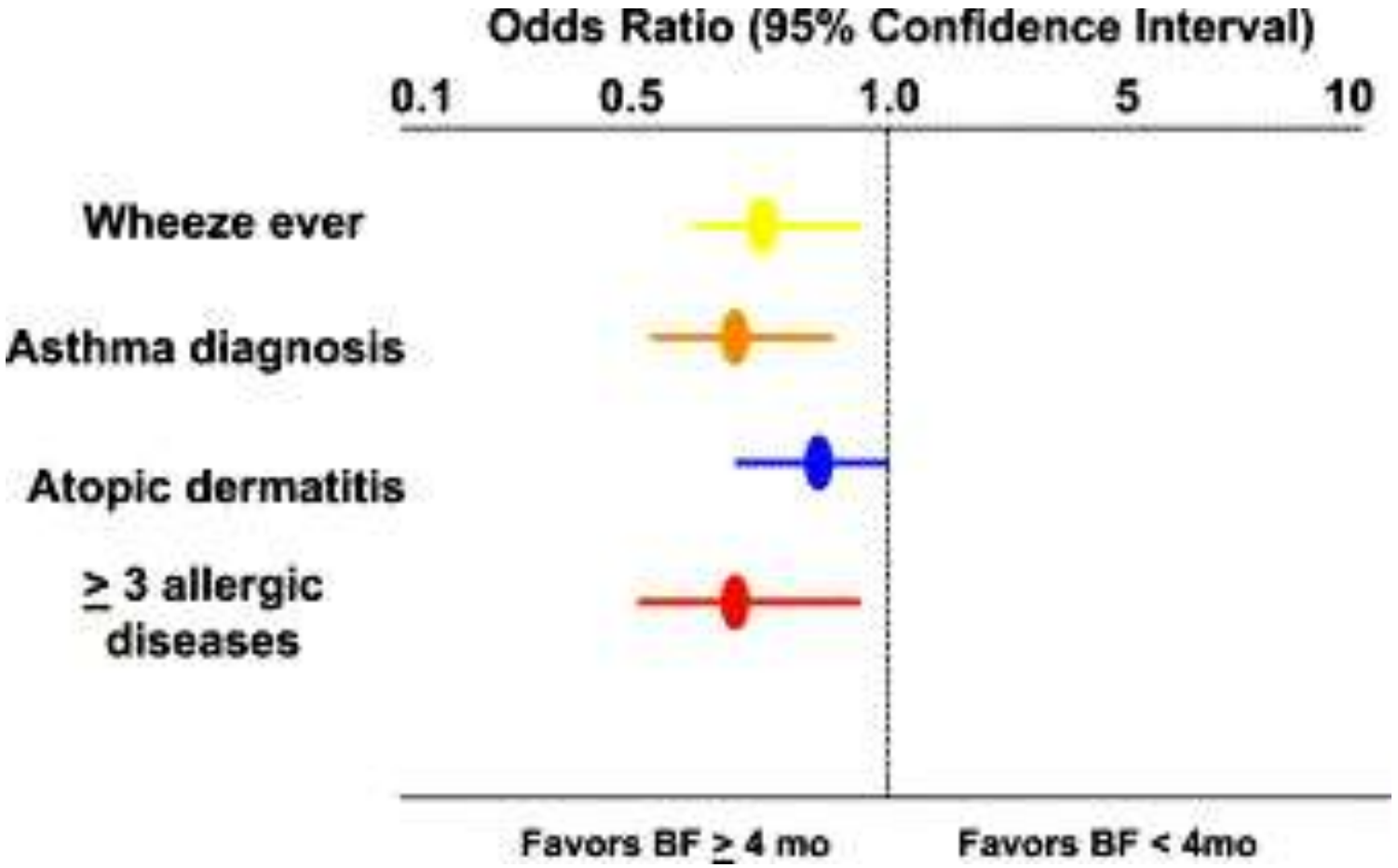
Puntarelle is soort roodlof

From Holland witlof
designed © by slappo

Breast is Best

Xenia Warrior Princess

Breastfeeding reduces chance on allergy

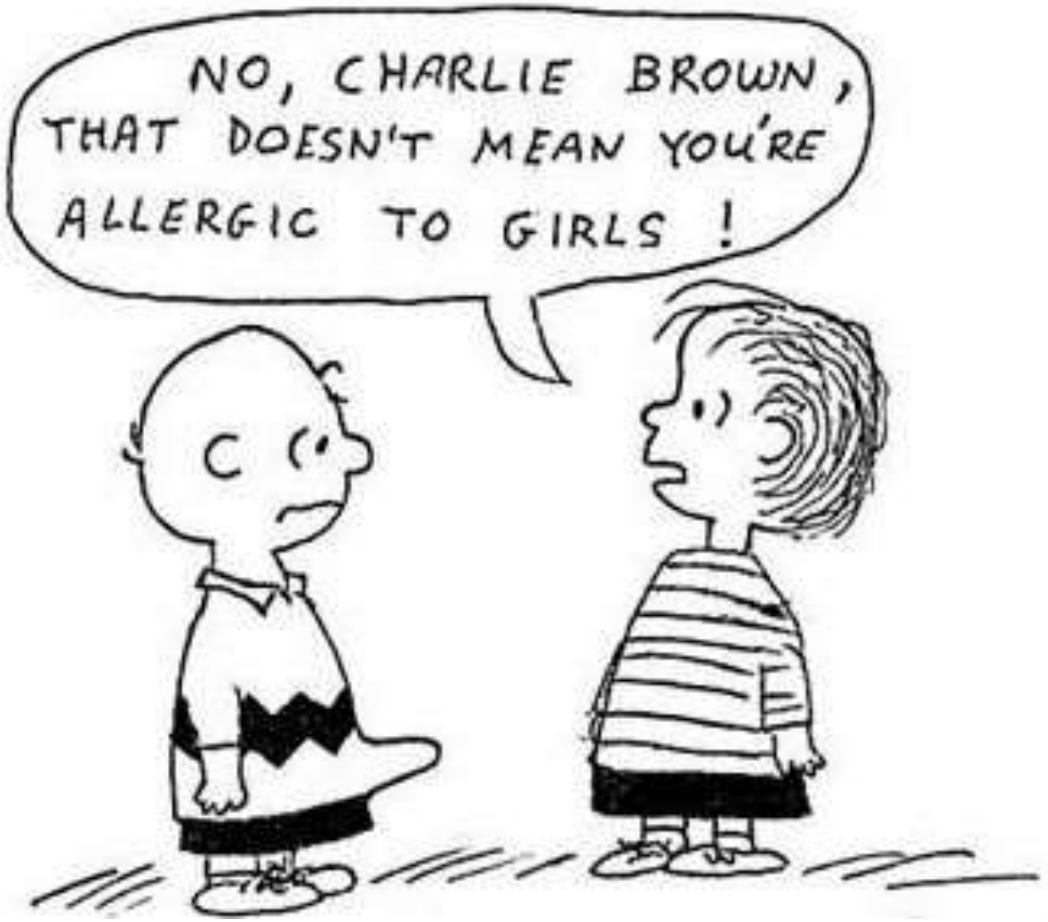


Friedman & Zeiger (2005) J Allergy Clin Immunol 115: 1238-48

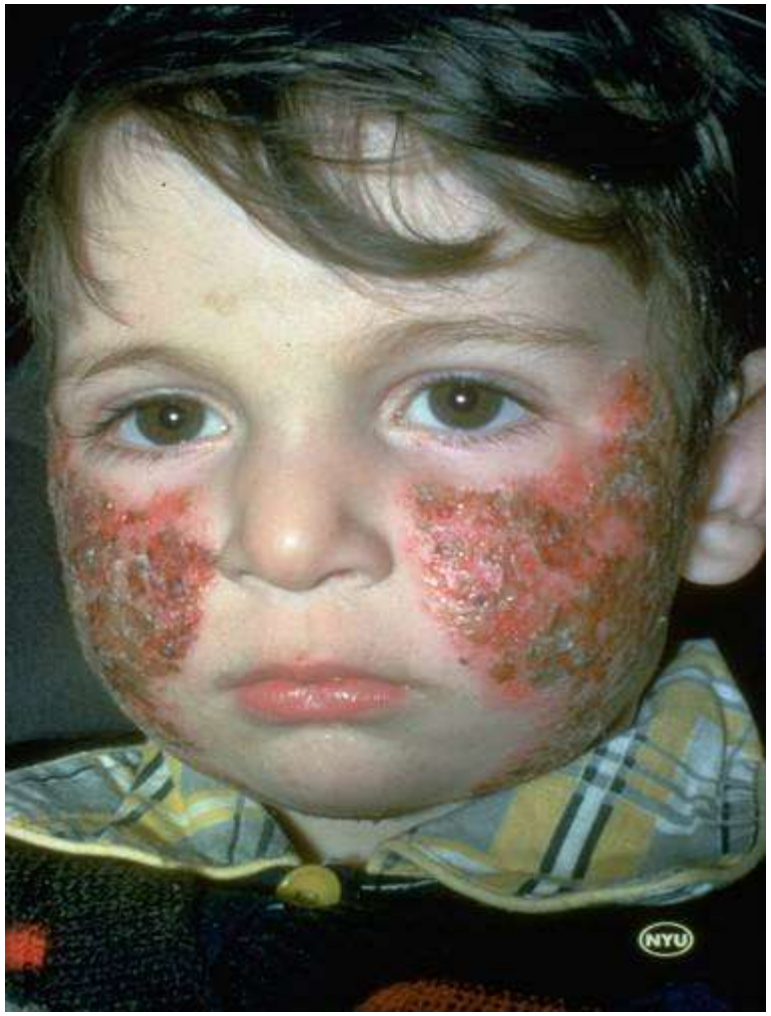
Allergisch meisje of?

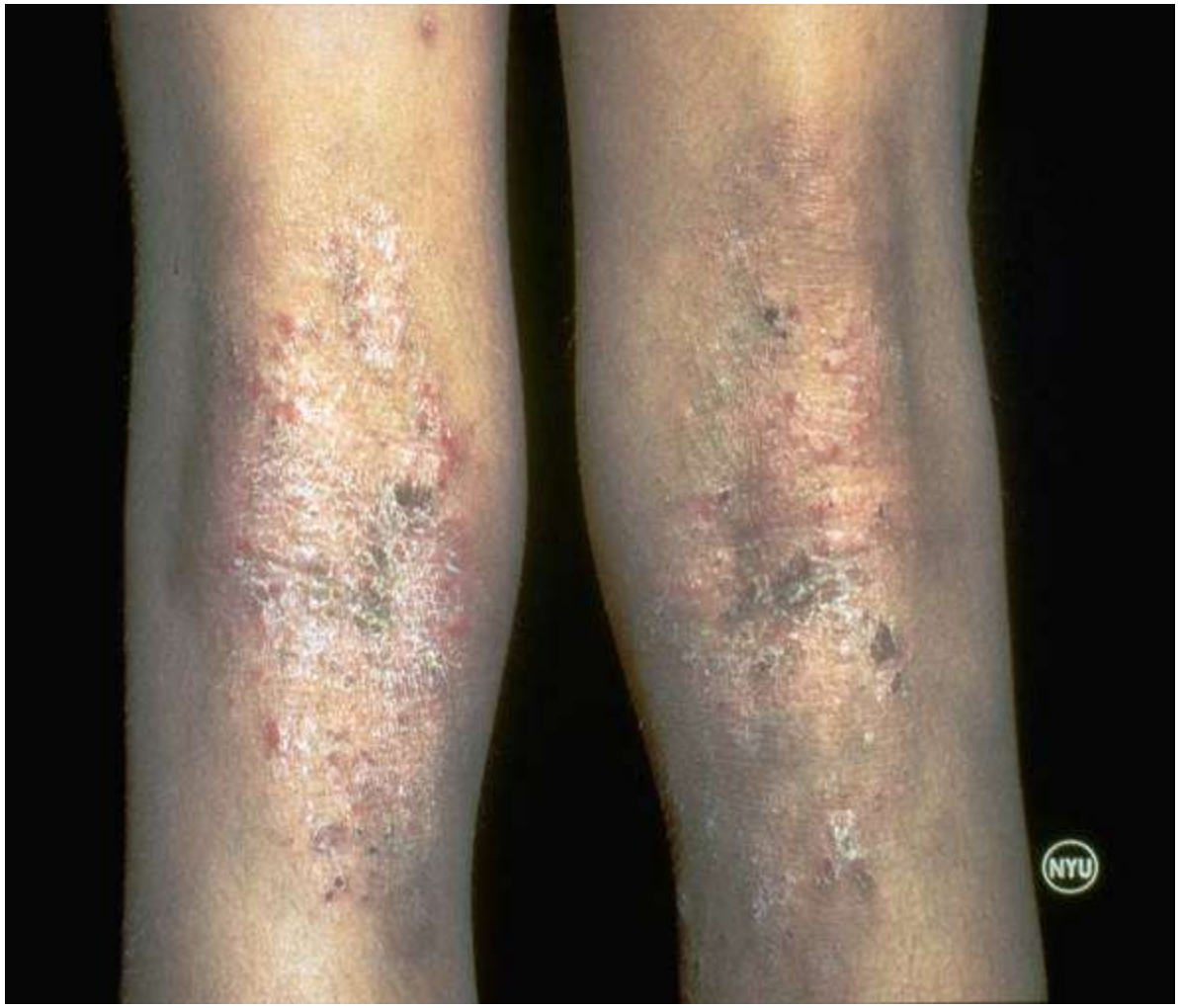
STICHTING Darmgezondheid

Allergisch voor meisjes?



Examples Atopic / Constitutional Eczema





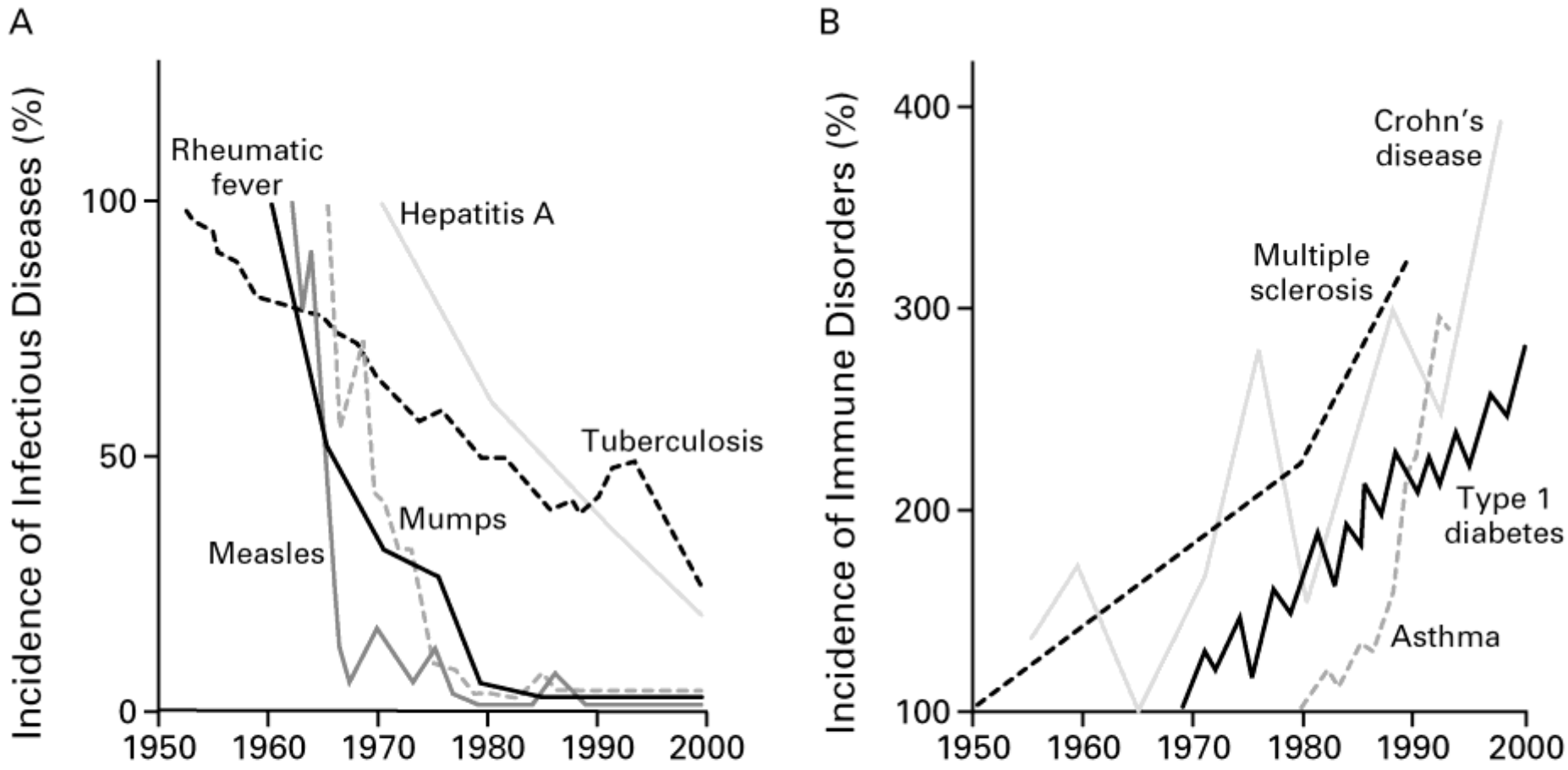
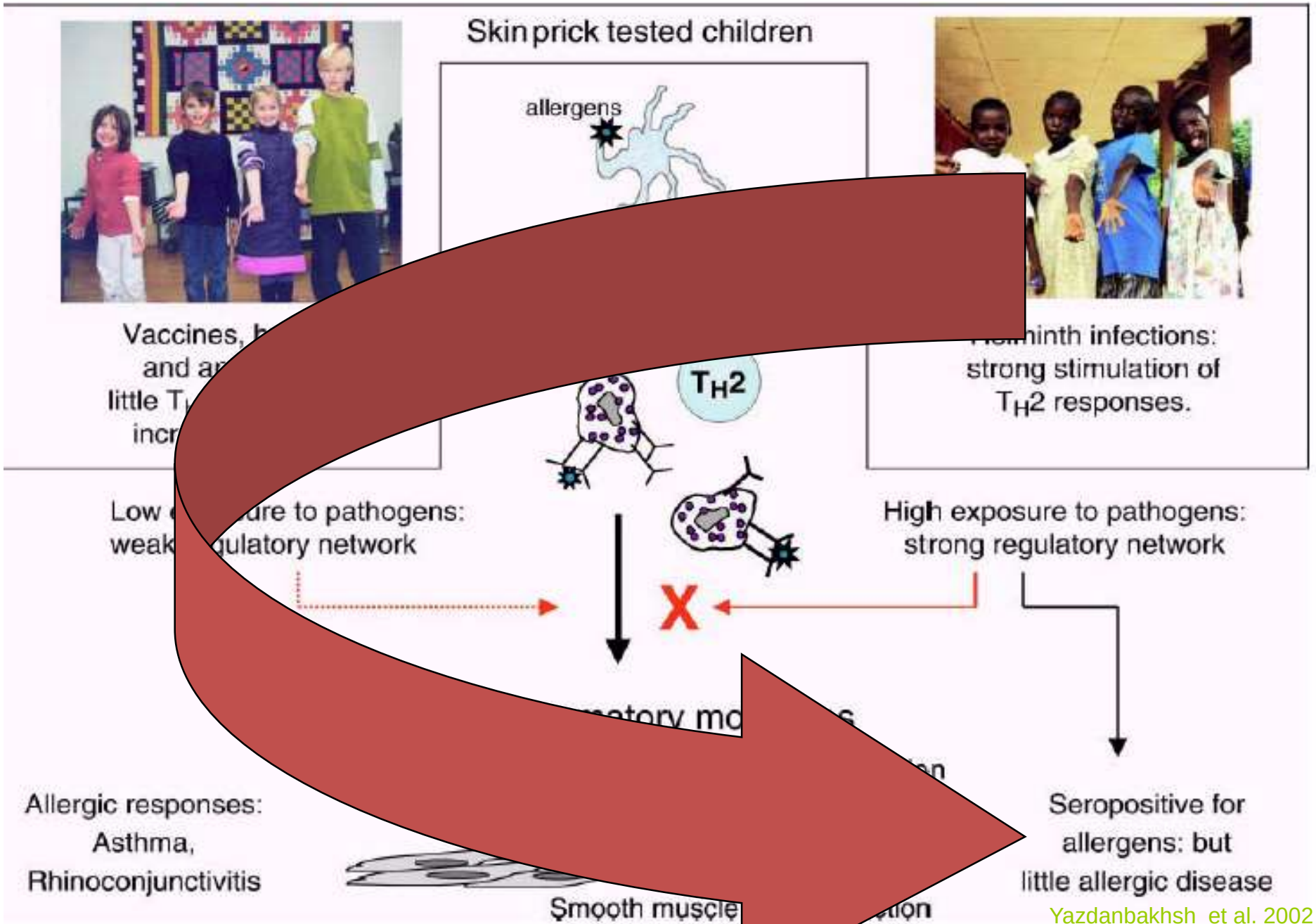


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussemet et al.[12] In Panel B, data on immune disorders are derived from Swarbrick et al.,[10] Dubois et al.,[13] Tuomilehto et al.,[14] and Pugliatti et al.[15]

The Africa Paradox and the hygiënehypothesis



Yazdanbakhsh et al. 2002

'Old friends trigger regulation through innate dendritic cell receptors'

Mechanisms of Disease: the hygiene hypothesis revisited

Francisco Guarner*, Raphaëlle Bourdet-Sicard, Per Brandtzaeg, Harsharnjit S Gill, Peter McGuirk, Willem van Eden, James Versalovic, Joel V Weinstock and Graham AW Rook

NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY

MAY 2006 VOL 3 NO 5

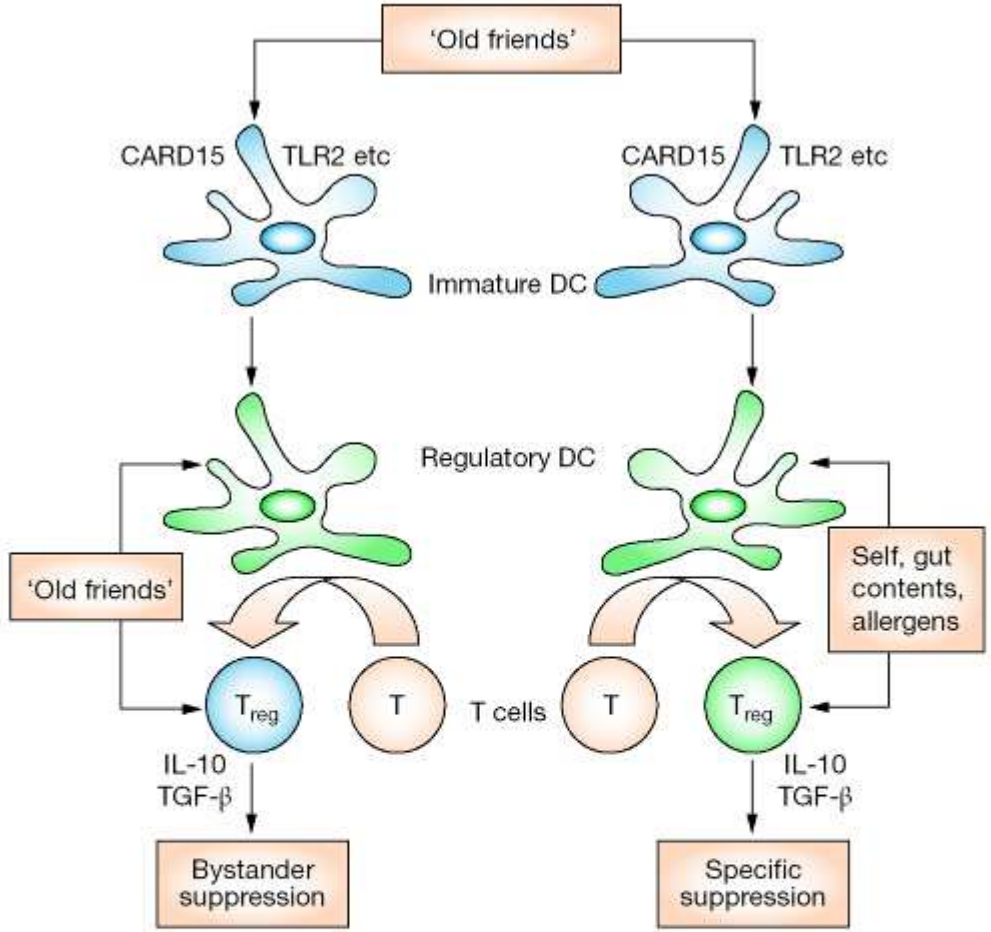


Figure 3 The 'old friends' hypothesis. Organisms recognized as harmless by the innate immune system (through pattern-recognition receptors, such as CARD15 and Toll-like receptor 2) cause dendritic cells to mature into regulatory dendritic cells that drive regulatory-T-cell polarization. Some of these cells will recognize the 'old friends' themselves, and so provide a continuous background bystander regulation. Regulatory dendritic cells, however, might also process and present epitopes from self, allergens and gut content (antigens, bacterial DNA motifs, microbial heat-shock proteins) and so drive specific immunoregulation.
DC, dendritic cells; IL, interleukin; TGF-β, transforming growth factor-β; TLR2, Toll-like receptor 2; T_{reg}, regulatory T cell.

Scout senses no danger (sees “old friends”): info to officer “steady state of tolerance”
“Hold your fire”

Allergy: Scout senses danger & no old friends: info to officer and command to fire

The possible link between de-worming and the emergence of immunological disease

JOEL V. WEINSTOCK, ROBERT W. SUMMERS, DAVID E. ELLIOTT, KHURRAM QADIR, JOSEPH F. URBAN, JR, and ROBIN THOMPSON

IOWA CITY, IOWA, and BELTSVILLE, MARYLAND

A major objective of our laboratory is the study of the various complex host immunological responses to helminths. Helminths are a group of worm-like organisms, some of which live in the intestinal lumen or host tissue. Helminths include

experimental data from both human and animal research now provide substantial support for this hypothesis.

Exposu partici- stock: "We're opening up
potential tive and the possibility of whole
the immu ry bowel new classes of drugs."

Man and his worm. Joel Weinstock holds a dose of eggs from *Trichuris suis* (*inset*), which he is using to treat inflammatory bowel disease.

children ir
with the
haematob
lergic to h
for asthma
free of w
concentrat
uct of reg
higher in i

HYGIËNE

Vroeger: minder hygiëne en minder allergie

Beetje vies is gezond

Disturbance microbiota (=dysbiosis)

World Health Organization

Directly linked to gut dysbiosis

- Inflammatory Bowel Disease (IBD)
- Irritable Bowel Syndrome (IBS)
- Diarrhea
- Antibiotic associated diarrhea
- Travelers diarrhea
- Infantile diarrhea (Rotavirus)
- Caused by food pathogens
- Constipation
- Helicobacter pylori infections

Food and Agriculture Organization of the United Nations

Indirectly linked to gut dysbiosis

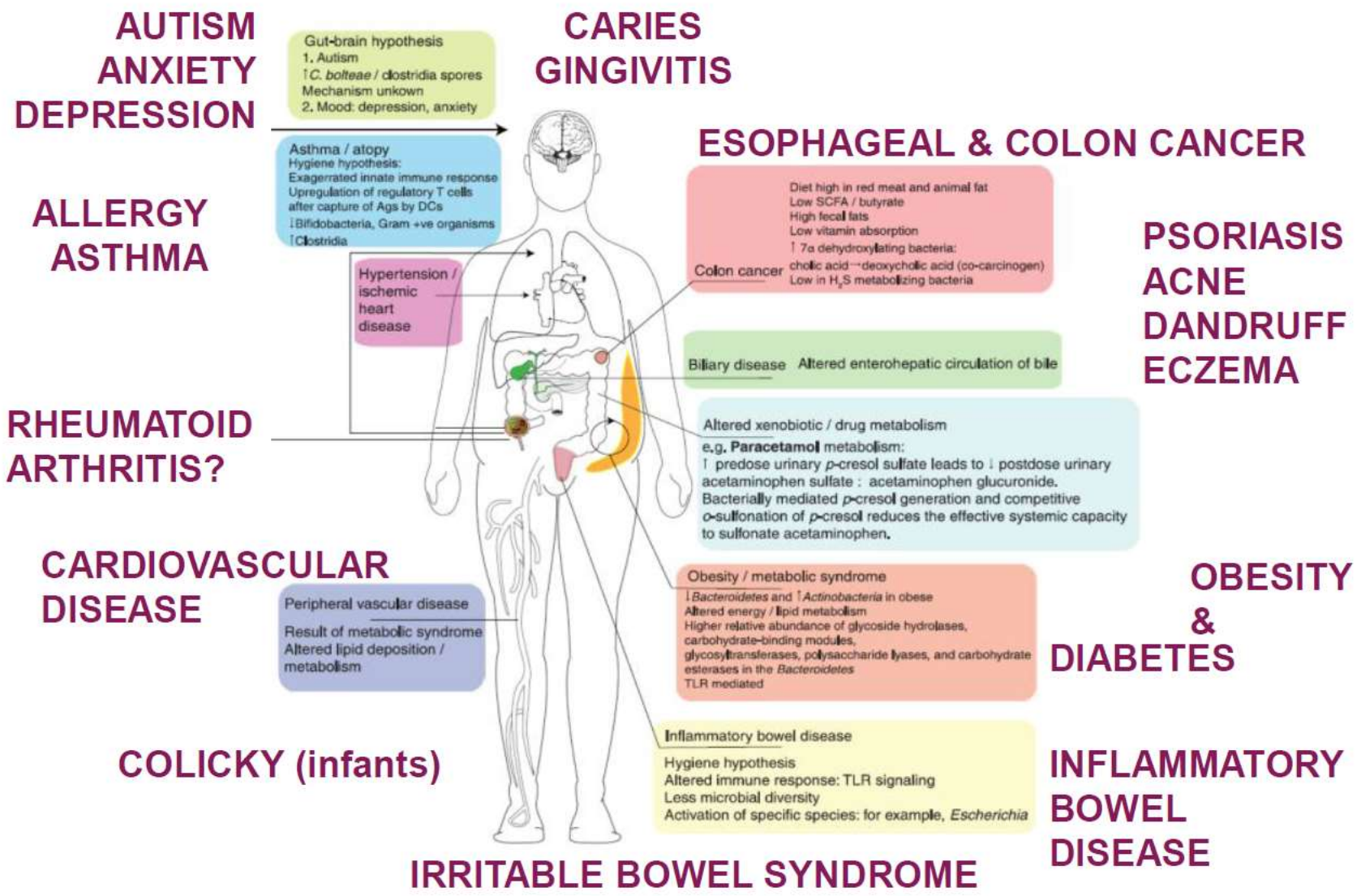
- Allergies
- Cancer
- Cardiovascular disease
- Urinary tract infections
- Bacterial vaginosis
- Upper respiratory tract infections

OPEN ACCESS

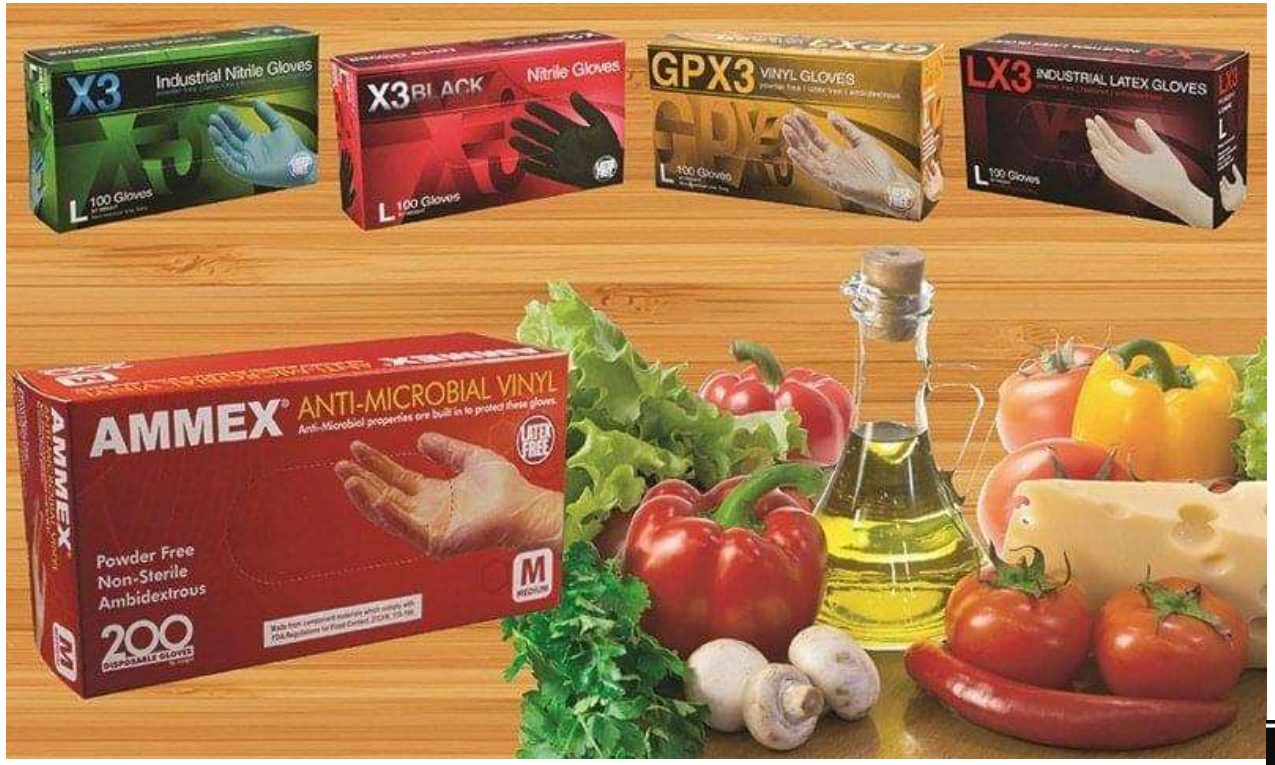
An update on the use and investigation of probiotics in health and disease

Mary Ellen Sanders,[1] Francisco Guarner,[2] Richard Guerrant,[3] Peter R Holt,[4] Eamonn MM Quigley,[5,6] R Balfour Sartor,[7] Philip M Sherman,[8] Emeran A Mayer[9]

The human microbiota
In health and disease



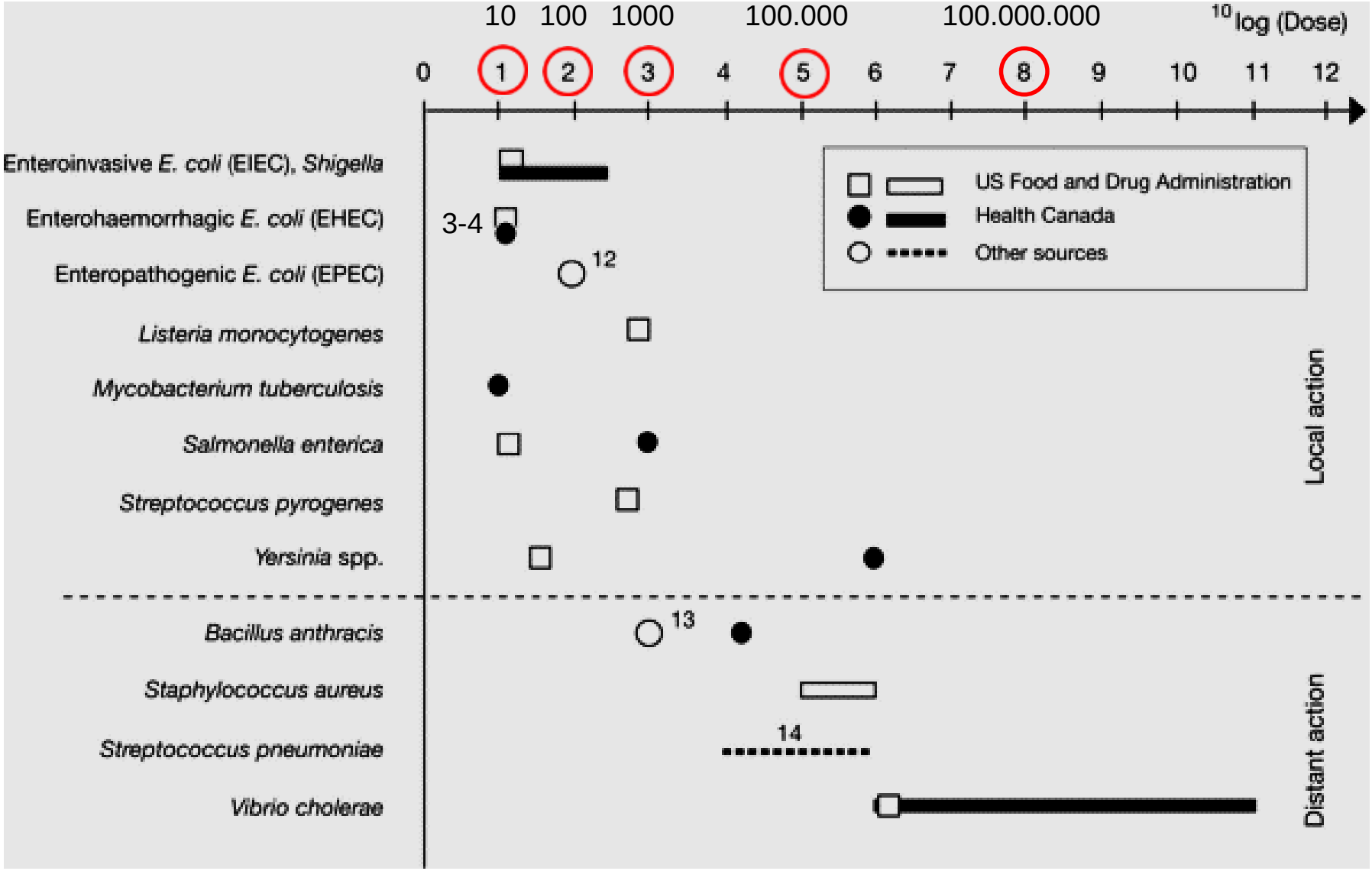
With increased food safety our food has also became more and more sterile



Every advantage has its disadvantage.

— Johan Cruijff —

VAN 4 EHEC KIEMEN KUN JE AL DOOD GAAN



ER KUNNEN WEL 100 MILJARD KIEMEN NODIG ZIJN OM CHOLERA TE KRIJGEN

The history of probiotics: the untold story.
Ozen M, Dinleyici EC

Probiotic, a word derived from Latin, means 'for life'. A long time before the awareness of probiotic microorganisms, fermented products, such as beer, bread, wine, kefir, kumis and cheese had been very frequently used for nutritional and **therapeutic** purposes.

Yoghurt is most likely resulted from a fermentation process within the animal skin bags used for transportation of water and milk in regions with low humidity and high temperatures (Middle Asia and Middle East).

The history of probiotics goes parallel with the evolution of human race and, thanks to the sophisticated techniques at the moment, can be traced back to the ancient times, nearly **10,000 years ago**.

History of Health Claims

- Persian version of the Old Testament (Genesis 18:8) states " Abraham owed his longevity to the consumption of sour milk."
- In 76 BC the Roman historian Plinius recommended the administration of fermented milk products for treating gastroenteritis .

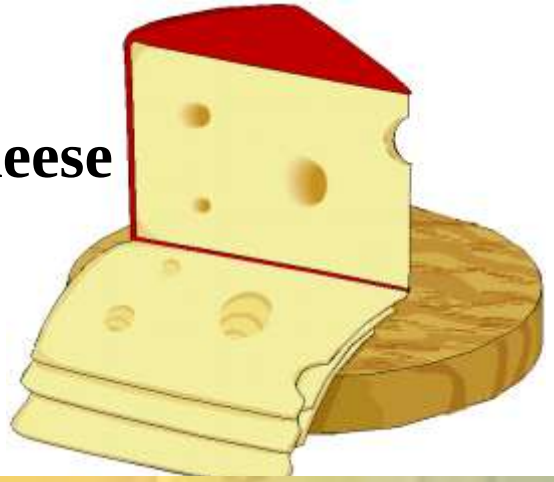

Astérix
Panoramix

Volume 156, Issue 3, September *1979*, Pages 309-319

Cellular and Humoral Adjuvant Activity of A Mistletoe Extract

Nanne Bloksma, HansVan Dijk, PieterKorst & Jan M.Willers

Cheese



Yogurt

Sauerkraut

Sourdough bread

cured ham

Salami and pickles

Vinegar

GEFERMENTEERDE VOEDING BEVAT TUSSEN 10 EN 10.000.000.000 MELKZUURBACTERIEEN PER ML/G

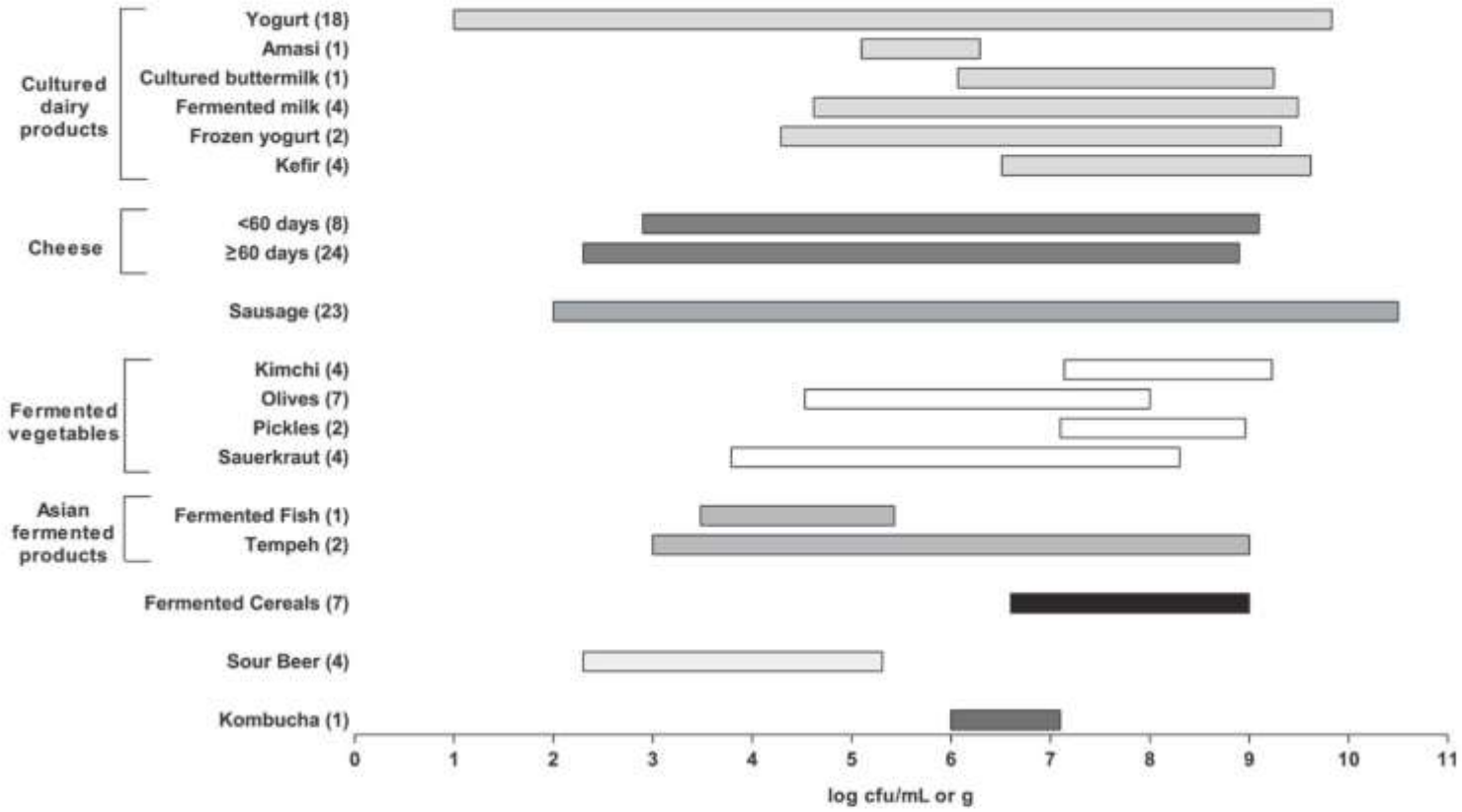


FIGURE 1 | Summary of lactic acid bacteria (LAB) counts in all fermented foods as reported in **Tables 1–8**. The bar plots represents a range (minimum to maximum) of counts found across the studies surveyed. The number of studies used here for each fermented food is shown in brackets. Products were excluded if they had no viable counts or when LAB counts were not reported. For yogurt, initial counts were used for products that had counts for more than one timepoint. For cheese, the products were divided by aging time (60 days) and were excluded if aging time was not reported.

Fermented Foods as a Dietary Source of Live Organisms

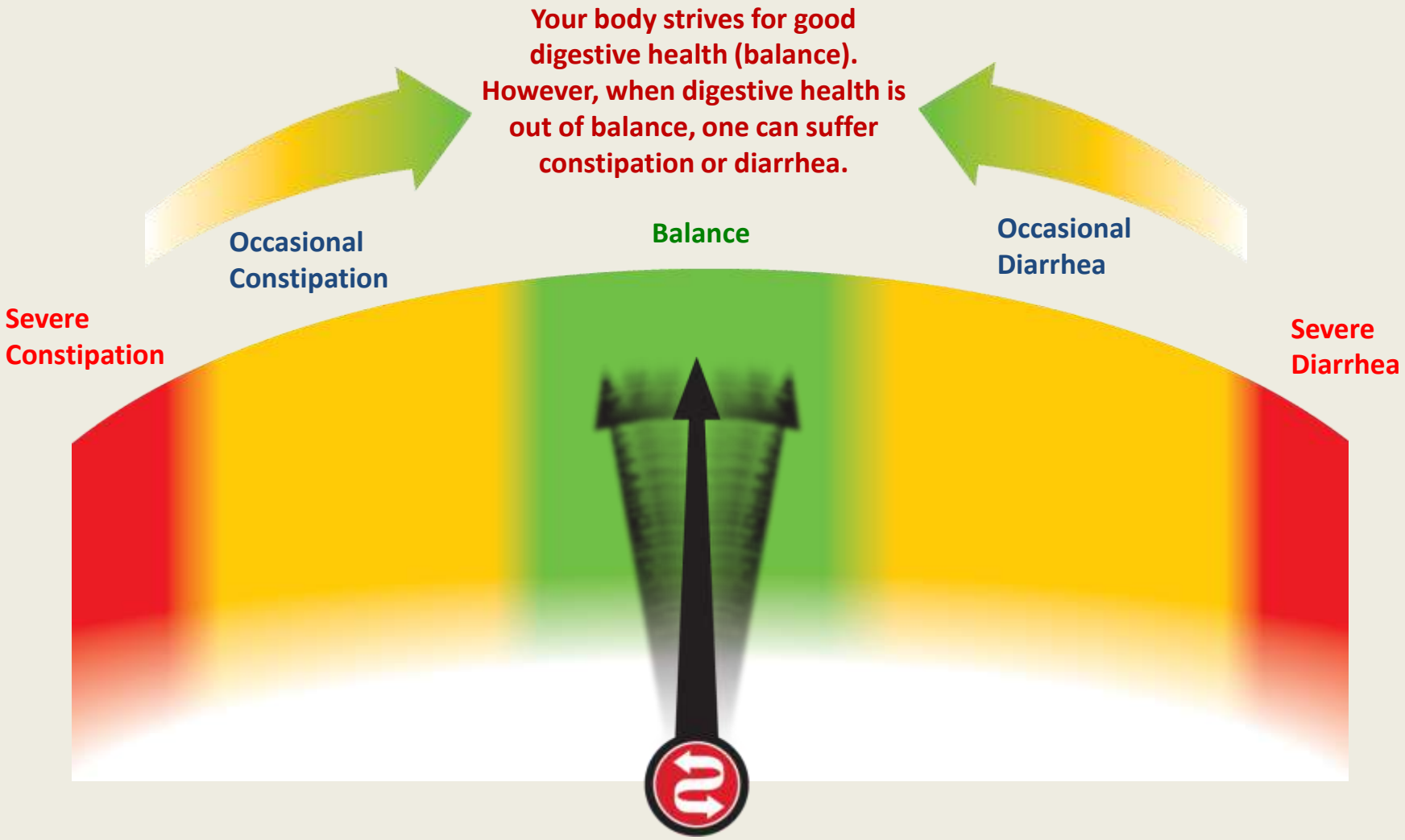
*Shannon Rezac, Car Reen Kok, Melanie Heermann and Robert Hutkins**


Al en toe zit er poep in mijn ontlasting, dokter.
Ontlasting is poep, mevrouw van der Wal.
Nee echt?
Gatsie.

Bristol Stool Chart

Type 1		Losse harde keutels, zoals noten (moeilijk uit te scheiden)
Type 2		Als een worst, maar klonterig
Type 3		Als een worst, maar met barstjes aan de buitenkant
Type 4		Als een worst of slang, glad en zacht
Type 5		Zachte keutels met duidelijke randen (makkelijk uit te scheiden)
Type 6		Zachte stukjes met gehavende randen, een papperige uitscheiding
Type 7		Waterig, geen vaste stukjes. Helemaal vloeibaar

Lower GI Digestive Health Segments



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

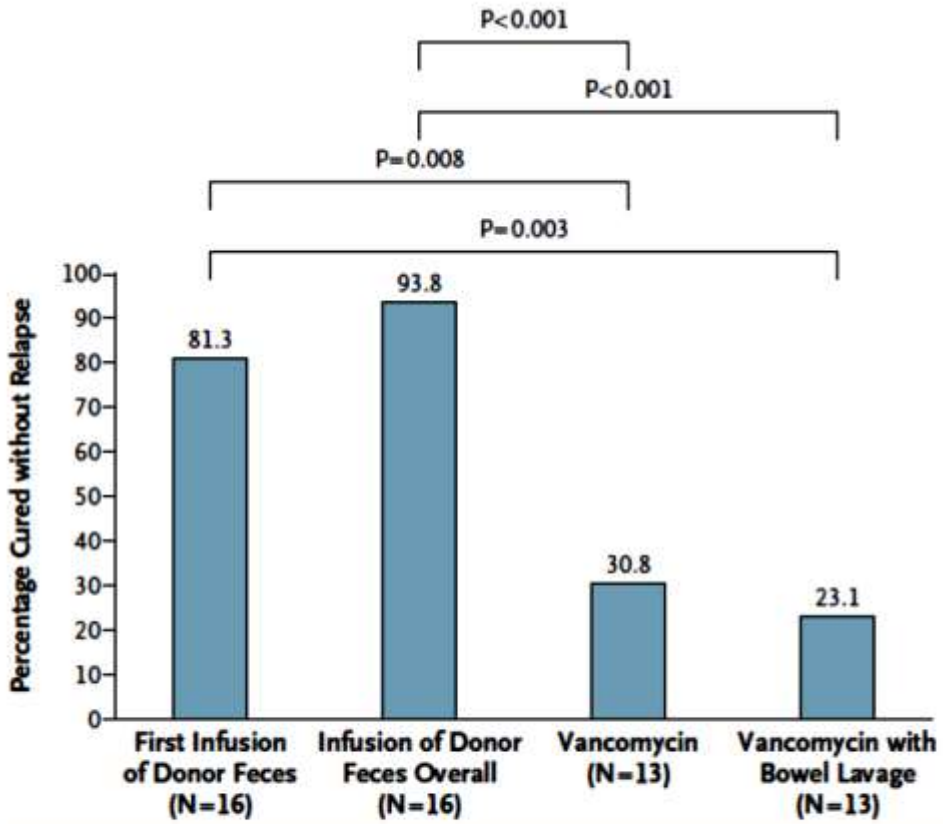


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

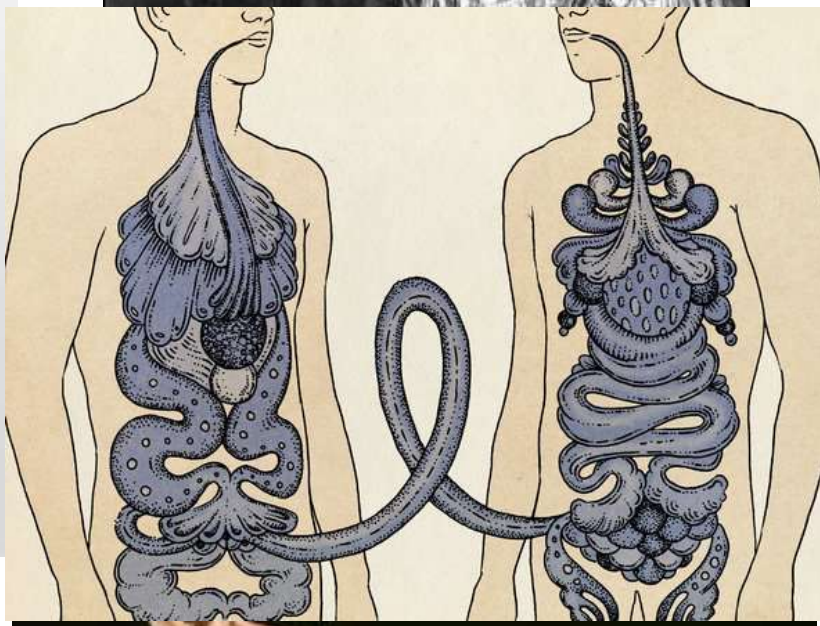
Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

* Adverse events that were reported on the day of donor-feces infusion and those that were reported during follow-up are listed separately. NA denotes not applicable.

† During follow-up, one patient with recurrent urinary tract infections had a urinary tract infection for which antibiotics were prescribed. Another patient had fever during hemodialysis for which antibiotics were prescribed; cultures remained negative.

History

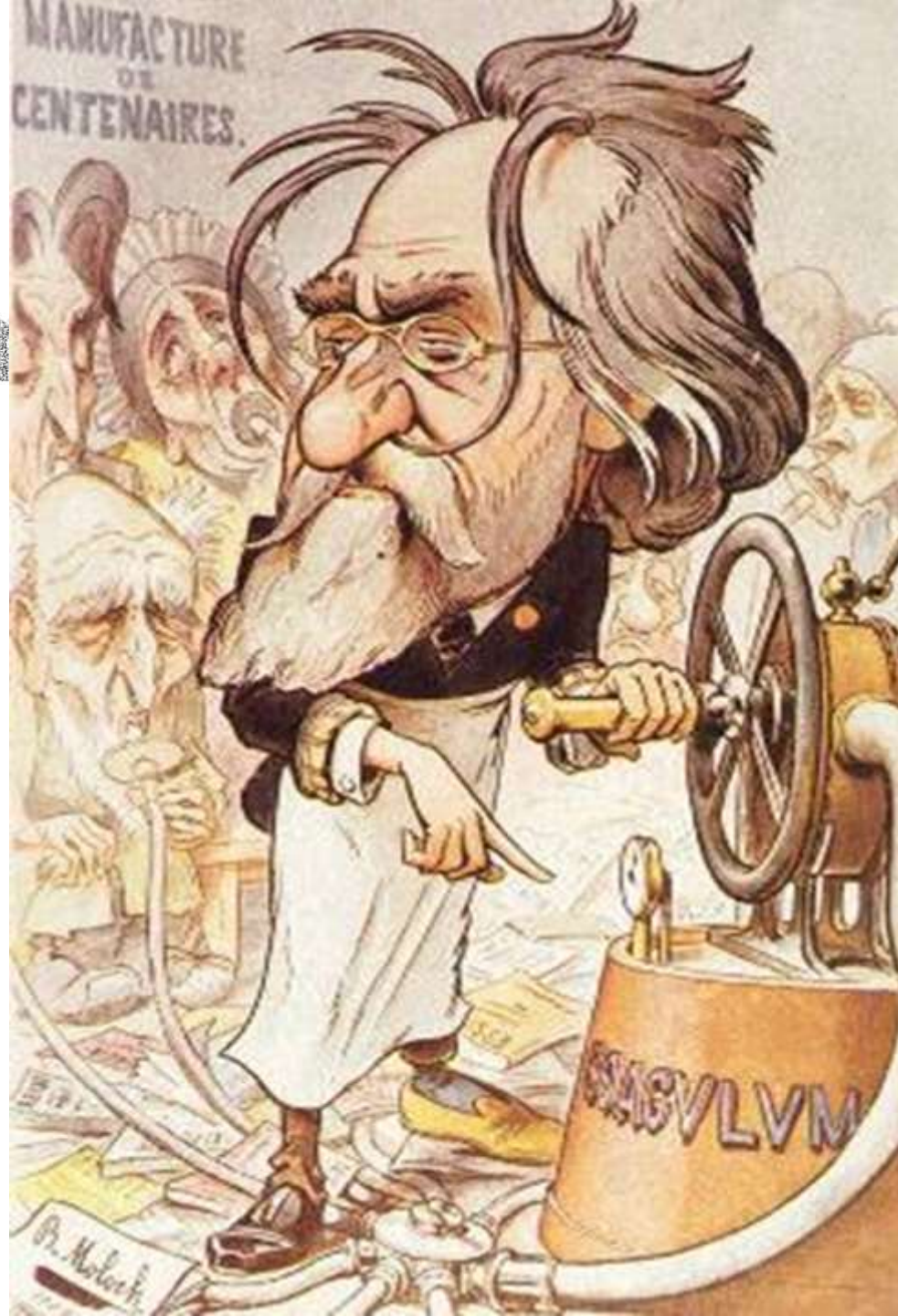
- First documented in 4th Century China as "Yellow Soup"
- In some countries, maternal feces is inserted into the newborn's mouth to "jumpstart" the colon
- June 17th, 2013: FDA approved the procedure for recurrent C. diff.
- 0 documented serious side effects
- 92% - 95% success rate



The New York Times
Published: January 21, 1912

METCHNIKOFF CONFIRMED IN HIS THEORY OF LONG LIFE

Baba Vasilka Tudor Vasilka



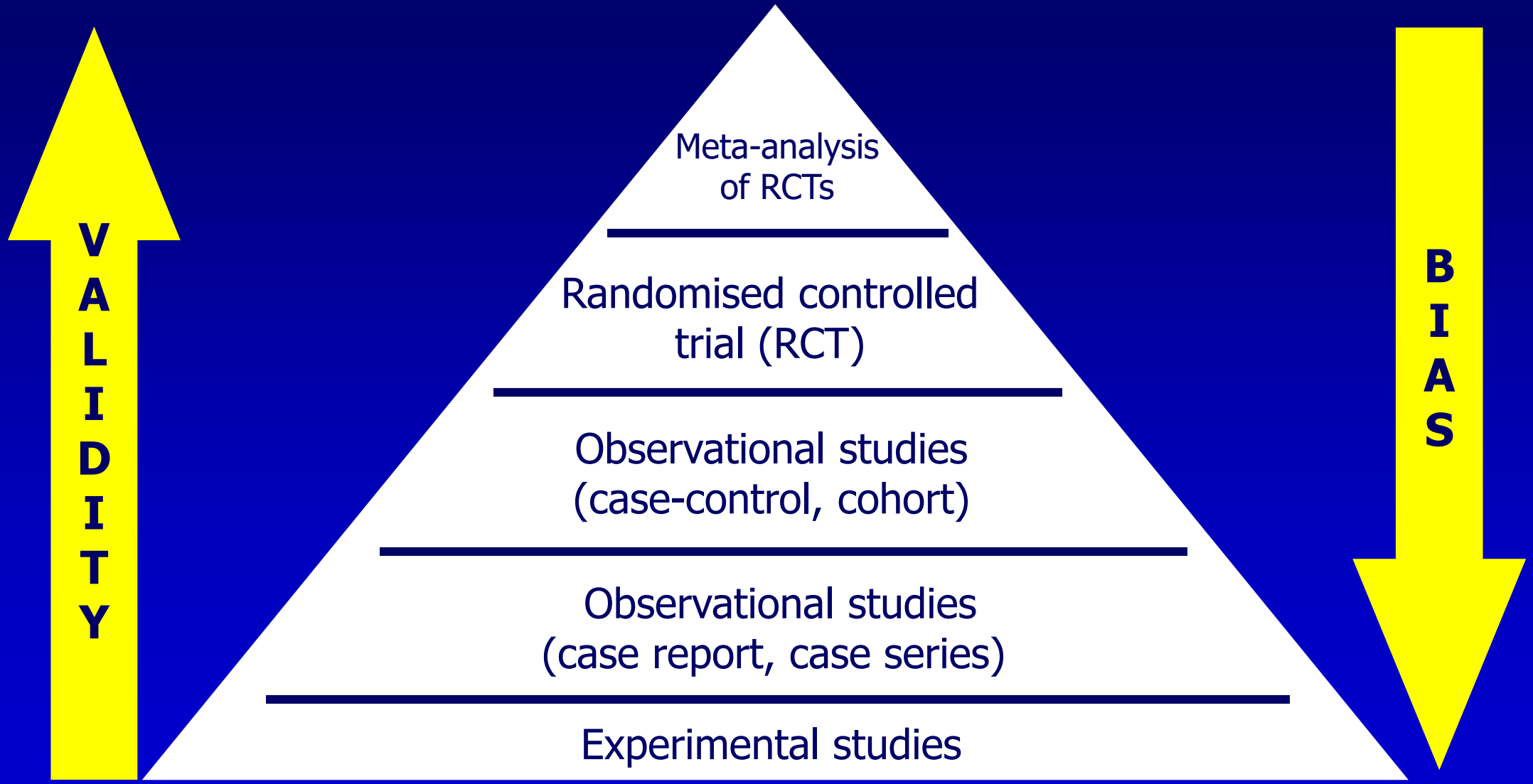
1935

concept of probiotic in medicine

“biotherapy”

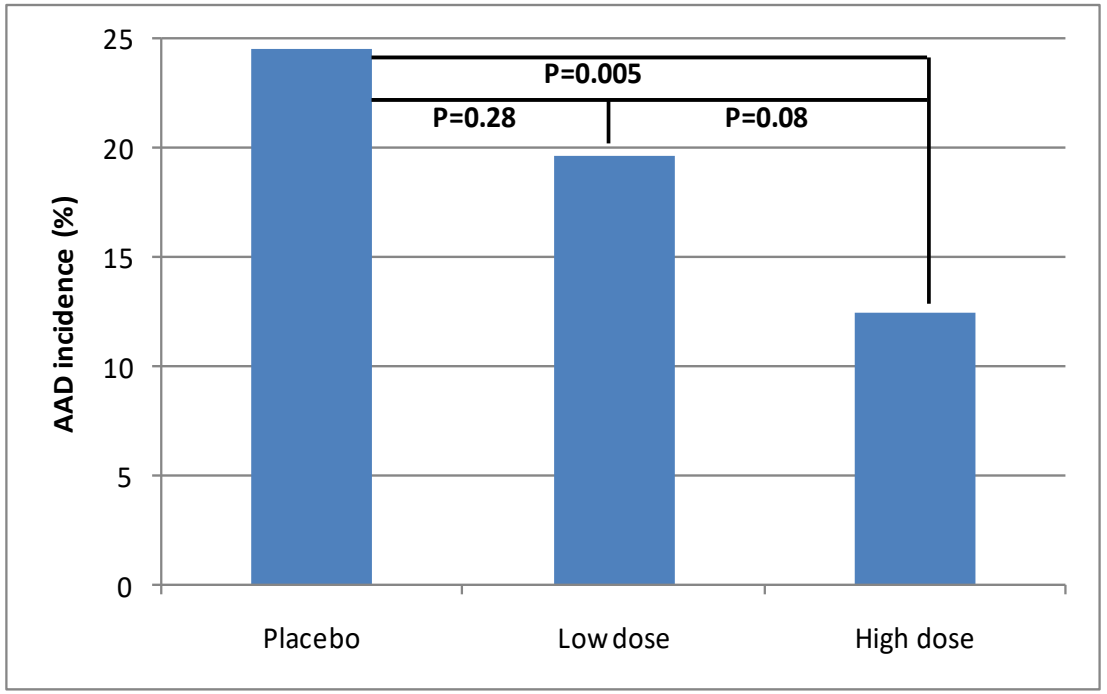
Hierarchy of evidence

For questions about the effectiveness of an intervention



First Overpowered study 2012: 500+ AAD Volunteer study

Ouwehand et al., in press



Antibiotic-associated diarrhea (AAD) incidence by study group. Low dose 4.17×10^{9} colony forming units (CFU), High-dose: 1.70×10^{10} CFU, Placebo: microcrystalline cellulose.

Meta-analysis: probiotics in antibiotic-associated diarrhoea

Study or subgroup	Probiotic Events	Probiotic Total	Placebo Events	Placebo Total	Weight	Risk ratio M–H, Random, 95% CI
Armuzzi 2001	1	30	8	30	0.7%	0.13 [0.02, 0.94]
Arvola 1999	3	61	9	58	1.7%	0.32 [0.09, 1.11]
Beausoliel 2007	7	44	16	45	3.2%	0.45 [0.20, 0.98]
Can 2006	1	73	7	78	0.7%	0.15 [0.02, 1.21]
Cimperman 2011	1	13	5	10	0.8%	0.15 [0.02, 1.12]
Cindoruk 2007	9	62	19	62	3.6%	0.47 [0.23, 0.96]
Correa 2005	13	80	24	77	4.4%	0.52 [0.29, 0.95]
Cremonini 2002	3	63	6	20	1.6%	0.16 [0.04, 0.58]
Gao 2010	37	171	37	84	6.1%	0.49 [0.34, 0.71]
Gotz 1979	3	36	9	43	1.7%	0.40 [0.12, 1.36]
Hickson 2007	7	57	19	56	3.2%	0.36 [0.17, 0.79]
Jirapinyo 2002	3	8	8	10	2.5%	0.47 [0.18, 1.21]
Koning 2008	9	19	15	19	4.9%	0.60 [0.35, 1.02]
Koning 2010	13	17	9	13	5.5%	1.10 [0.71, 1.73]
Kotowska 2005	9	119	29	127	3.7%	0.33 [0.16, 0.67]
LaRosa 2003	14	48	31	50	5.1%	0.47 [0.29, 0.77]
Lewis 199[illegible]	7	33	5	36	[illegible]2%	1[illegible]3 [0.5[illegible], 4.35]
Lin[illegible]erm[illegible] 20[illegible]	6	80	5	83	[illegible]%	1[illegible]5 [0.[illegible]40, [illegible]92]
McFa[illegible]ld [illegible]99[illegible]	7	97	[illegible]4	96	[illegible]%	0[illegible]9 [[illegible]21, [illegible]17]
M[illegible]llyl[illegible]ma 200[illegible]	4	2[illegible]	[illegible]4	2[illegible]	1.1%	2[illegible] [[illegible]42, 10.[illegible]2]
Nista 2004	5	50	15	50	2.6%	0.33 [0.13, 0.85]
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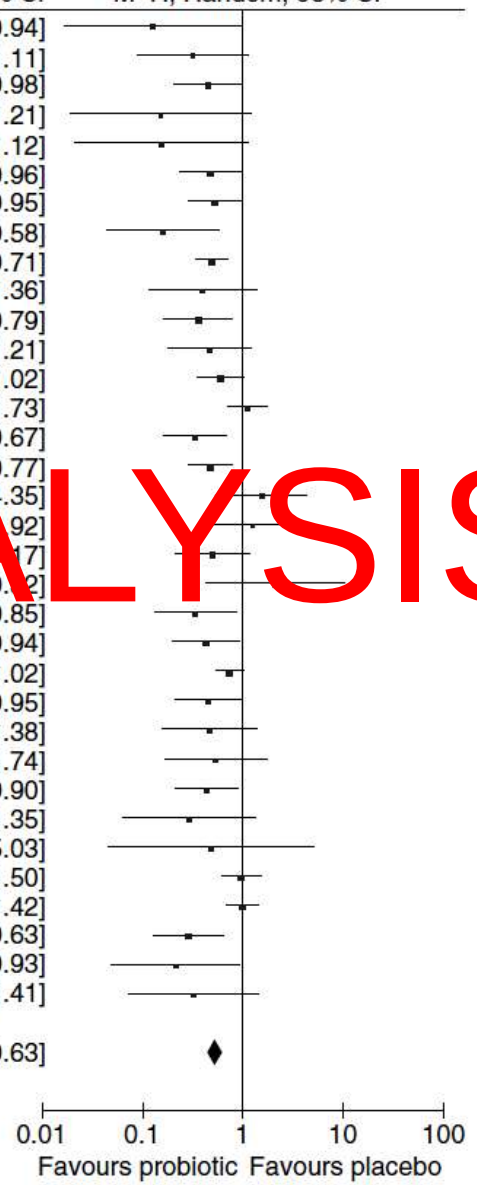
Psaradellis 2010	47	216	65	221	6.5%	0.74 [0.53, 1.02]
Rusczczynski 2008	9	120	20	120	3.4%	0.45 [0.21, 0.95]
Safdar 2008	4	23	6	16	2.1%	0.46 [0.16, 1.38]
Song 2010	4	103	8	111	1.9%	0.54 [0.17, 1.74]
Surawicz 1989	11	116	14	64	3.5%	0.43 [0.21, 0.90]
Szajewska 2009	2	34	6	30	1.2%	0.29 [0.06, 1.35]
Szymanski 2008	1	40	2	38	0.5%	0.47 [0.04, 5.03]
Tankanow 1990	10	15	16	23	5.5%	0.96 [0.61, 1.50]
Thomas 2001	39	133	40	134	6.2%	0.98 [0.68, 1.42]
Vanderhoof 1999	7	93	25	95	3.2%	0.29 [0.13, 0.63]
Wenus 2008	2	34	8	29	1.3%	0.21 [0.05, 0.93]
Wunderlich 1989	2	23	6	22	1.3%	0.32 [0.07, 1.41]
Total (95% CI)		2154		1984	100.0%	0.53 [0.44, 0.63]
Total events	306		515			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 58.86$, df = 33 ($P = 0.004$); $I^2 = 44\%$

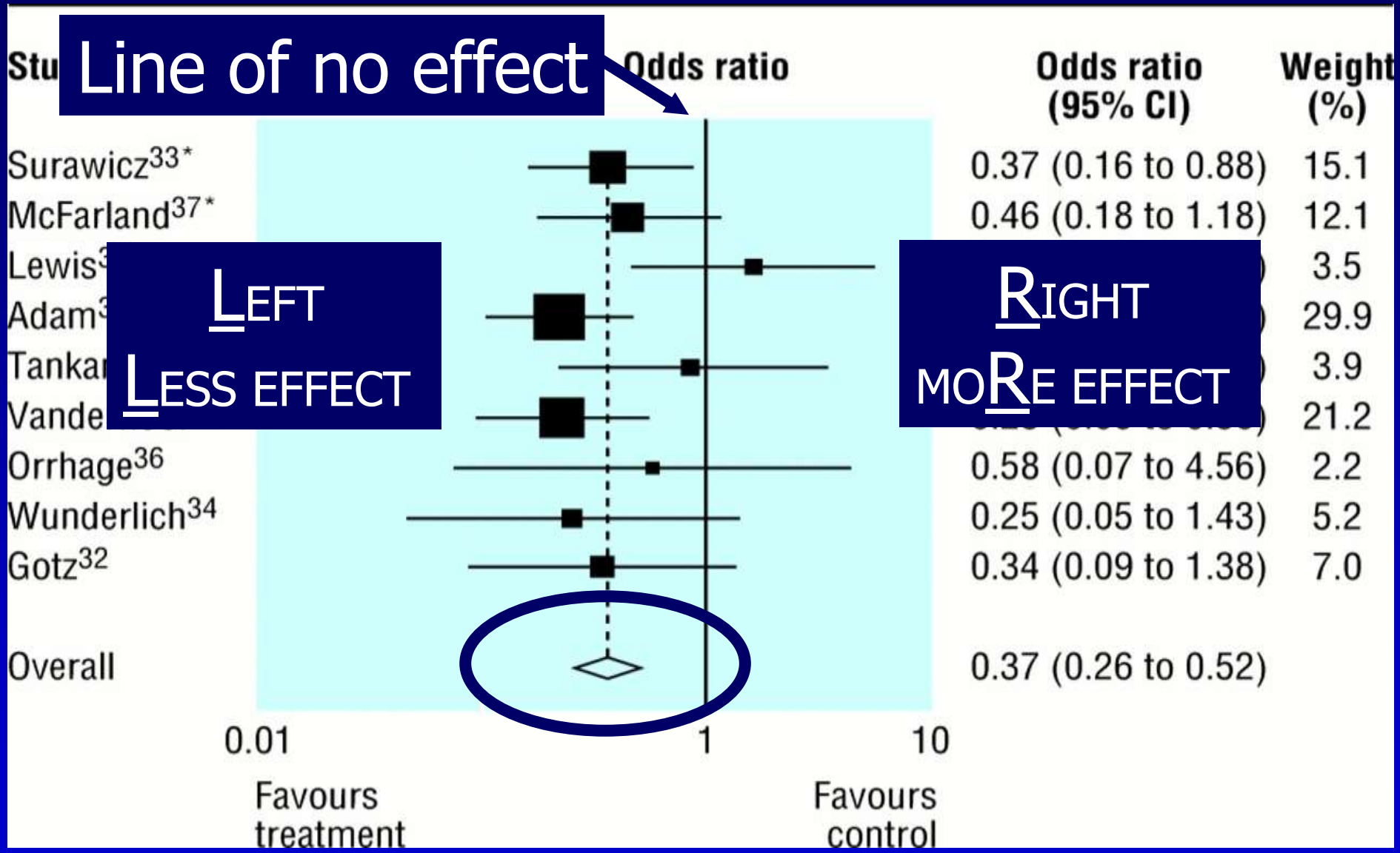
Test for overall effect: $Z = 6.91$ ($P < 0.00001$)



META ANALYSIS

Aliment Pharmacol Ther 2012; 35: 1355–1369

The forest plot



D'Souza AL. et al. BMJ 2002; 324: 361-4

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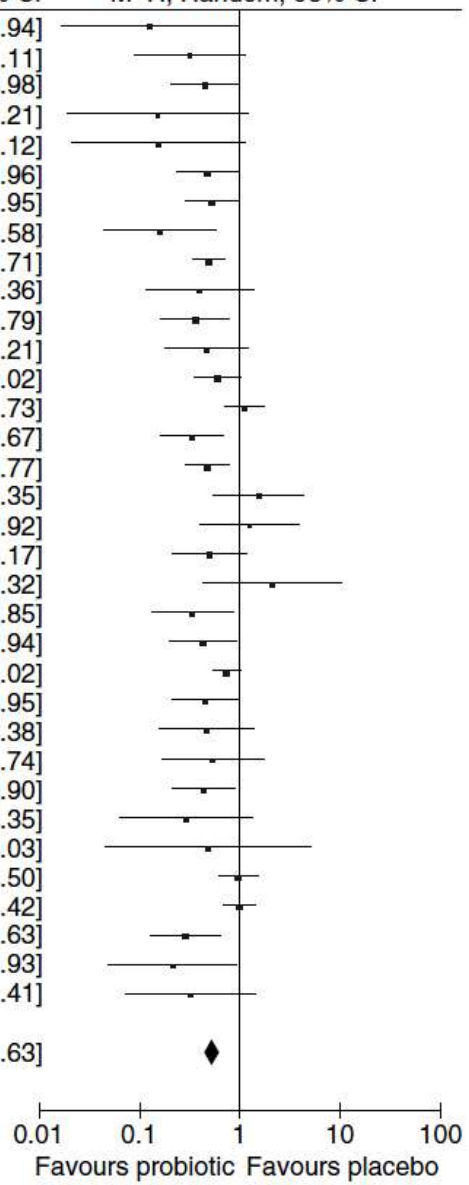
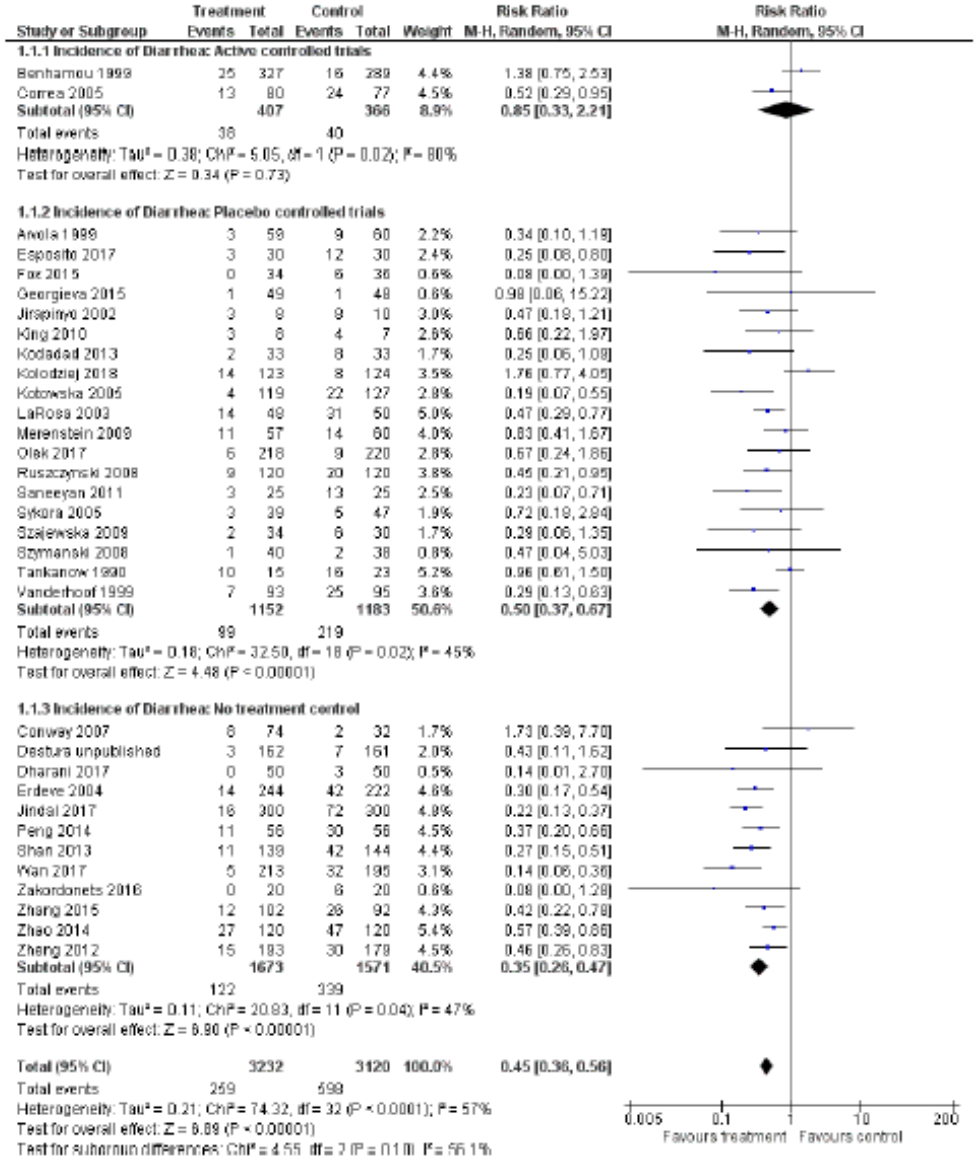


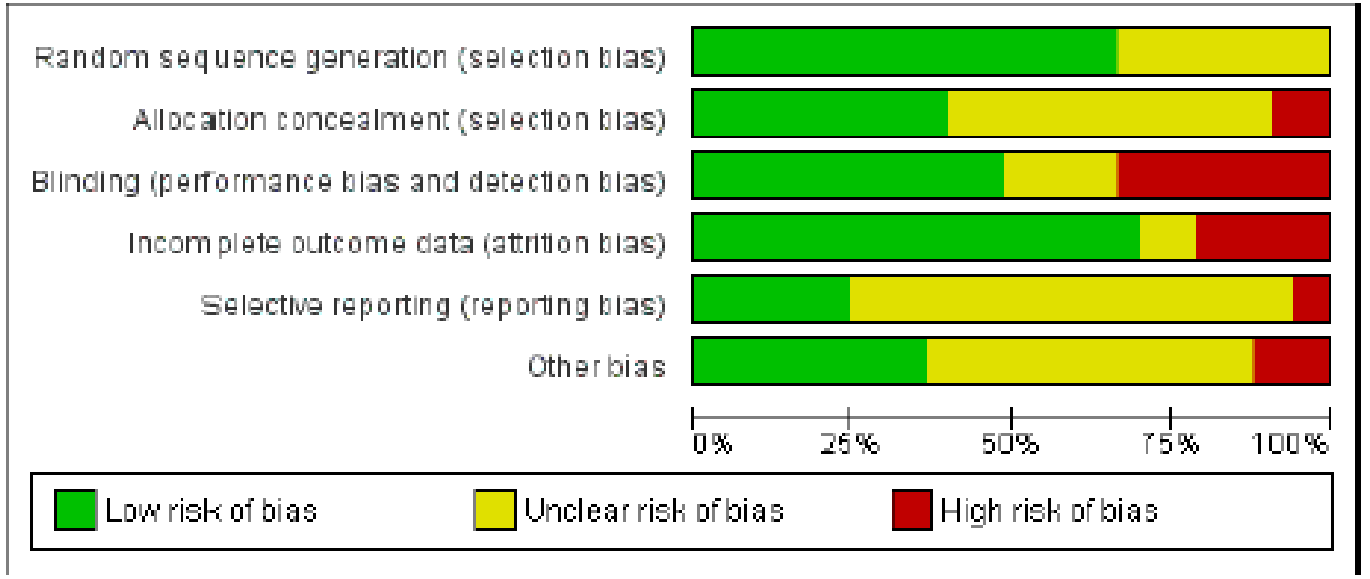
Aliment Pharmacol Ther 2012; 35: 1355–1369

Figure 6. Forest plot of comparison: 1 Probiotics versus control, outcome: 1.1 Incidence of diarrhea: Complete case.



Cochrane forest plot 2019

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database of Systematic Reviews **2019**, Issue 4. Art. No.: CD004827. DOI: 10.1002/14651858.CD004827.pub5.

The overall evidence suggests a moderate protective effect of probiotics for preventing AAD (NNTB 9, 95% CI 7 to 13). Using five criteria to evaluate the credibility of the subgroup analysis on probiotic dose, the results indicate the subgroup effect based on high dose probiotics (≥ 5 billion CFUs per day) was credible. Based on high-dose probiotics, the NNTB to prevent one case of diarrhea is 6 (95% CI 5 to 9). The overall certainty of the evidence for the primary endpoint, incidence of AAD, based on high dose probiotics was moderate due to the minor issues with risk of bias and inconsistency related to a diversity of probiotic agents used. Evidence also suggests that probiotics may moderately reduce the duration of diarrhea, a reduction by almost one day. The benefit of high dose probiotics (e.g. Lactobacillus rhamnosus or Saccharomyces boulardii) needs to be confirmed by a large well-designed multi-centered randomized trial. It is premature to draw firm conclusions about the efficacy and safety of 'other' probiotic agents as an adjunct to antibiotics in children. Adverse event rates were low and no serious adverse events were attributable to probiotics.

Guo Q, Goldenberg JZ, Humphrey C, El Dib R, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database of Systematic Reviews **2019**

Not all probiotics are equal

1. **Optifit** Naturel CEB6 (€1,20)

2. **Pro.X** Probiotic Drink Naturel (€1,20)

3. **Campina** Vifit Drink Perzik (€0,89)

4. **Yakult** (€2,60)

5. **Danone** Actimel (€1,60)

6. **Danone** Activia Muesli (€1,70)

7. **Pharma Nord** Bio-Flora (€16,50)

11. **A. Vogel** A[illegible]ce (€13,50)

12. **Proviact** Probiotic Breakfast Drink [illegible]pple (€0,79)

13. **Solgar** ABC Dophilus Powder (€26,50)

14. **De Tuinen** Acidophilus 90mg met pectine (€20)

15. **TopPharm** DarmConditioner (€9,90)

16. **Optimax** O-care (€15)

17. **Orthica** Orthiflor Start (€17)

18. **Jacob Hooy** Probiotic (€20)

19. **Orthica** Orthiflor Plus (€37)

(€17)

22. **Arkopharma** Arkocaps Acidophilus (€7,50)

23. **Natufood** Probiotica Naturel (€13)

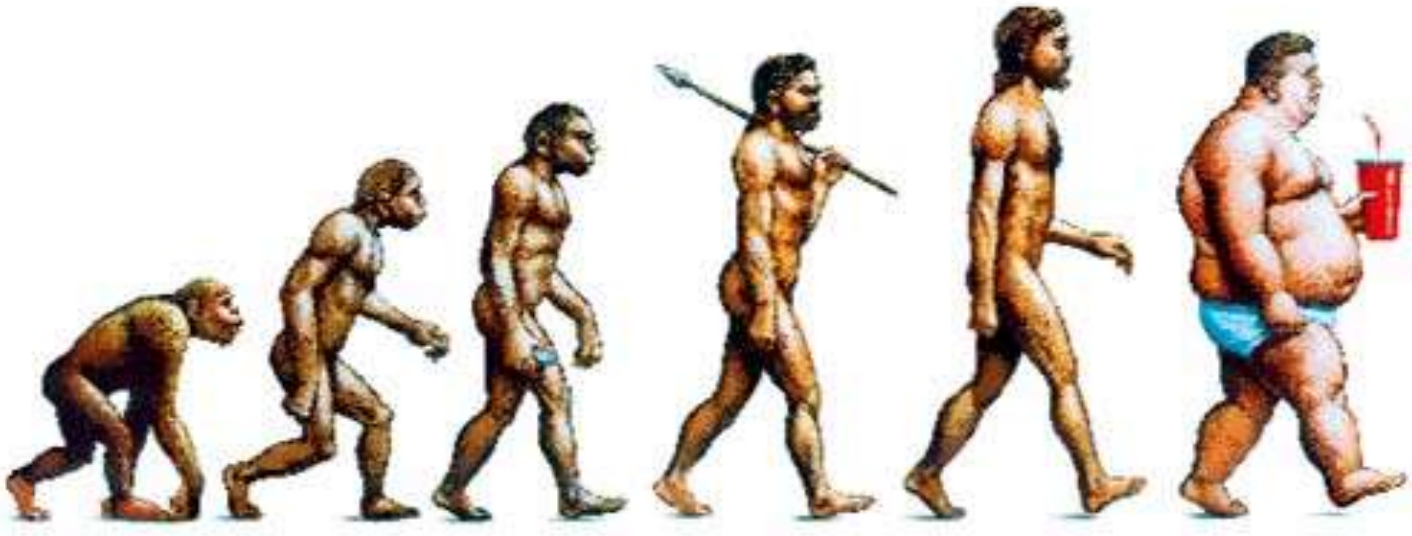
24. **Hema** Darm verzorging (€4,50)

25. **Bloem** Darmflora Balans (€13)

26. **Etos** Darmconditie met lactobacillus (€8)

27. **Lucovitaal** Cranberry+X-tra Forte (€20)

28. **Good for You** Lactobacillus+ (€14)




♂
30 tot 40 jaar
11%
40 tot 50 jaar
23%
50 tot 60 jaar
32%
60 tot 70 jaar
40%
♀
30 tot 40 jaar
28%
40 tot 50 jaar
33%
50 tot 60 jaar
44%
60 tot 70 jaar
58%

Beneficial Microbes, March 2014; 5(1): 19-28

Wageningen Academic Publishers

The development of probiotic treatment in obesity: a review

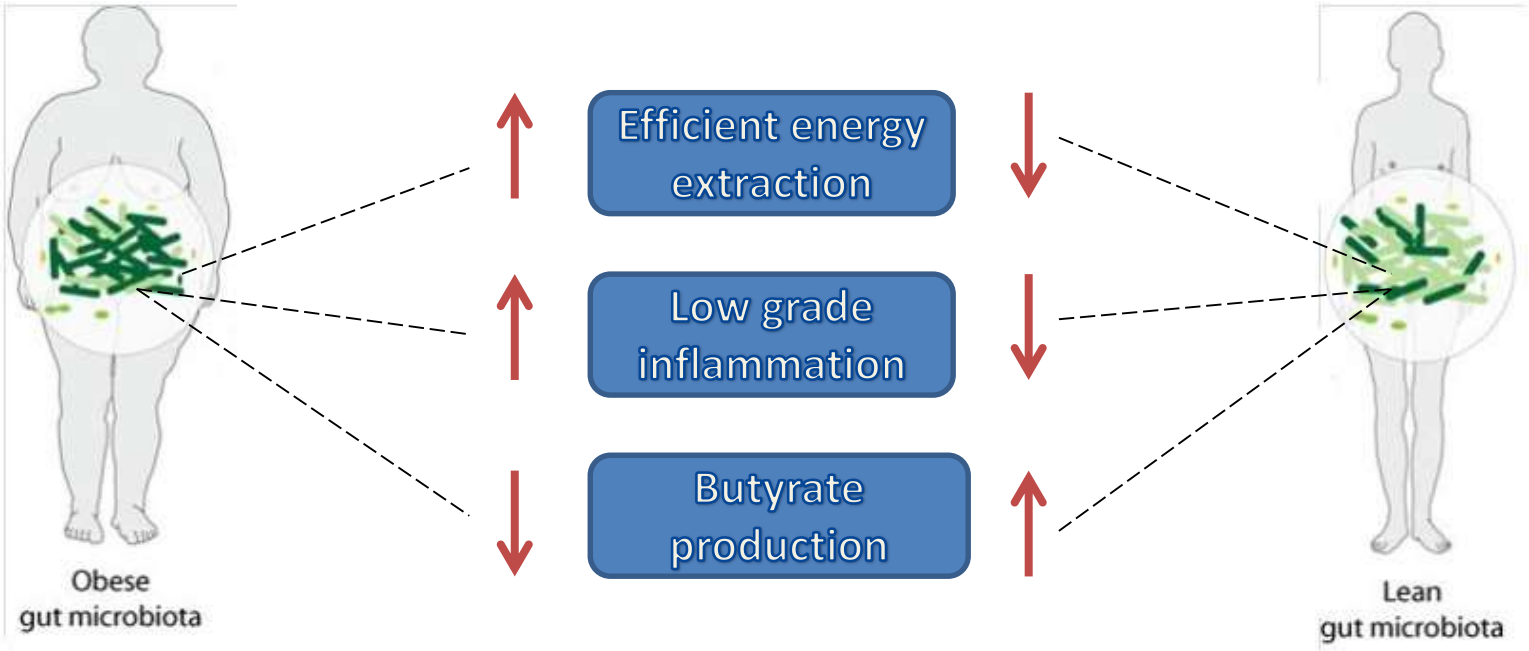
M.C. Mekkes[1*], T.C. Weenen[2,3*], R.J. Brummer[4] and E. Claassen[1,3]

*[1]VU University Amsterdam, Athena Institute, De Boelelaan 1085, 1081 HV Amsterdam, the Netherlands; [2]Erasmus School of Economics Rotterdam, Burgemeester Oudlaan 50, 3062 PA Rotterdam, the Netherlands; [3]Erasmus Medical Center Rotterdam, Dr. Molewaterplein 50, 1315 GE Rotterdam, the Netherlands; [4]School of Health and Medical Sciences, Örebro University, 701 82 Örebro, Sweden; marcel.mekkes@gmail.com; *Co-first author*

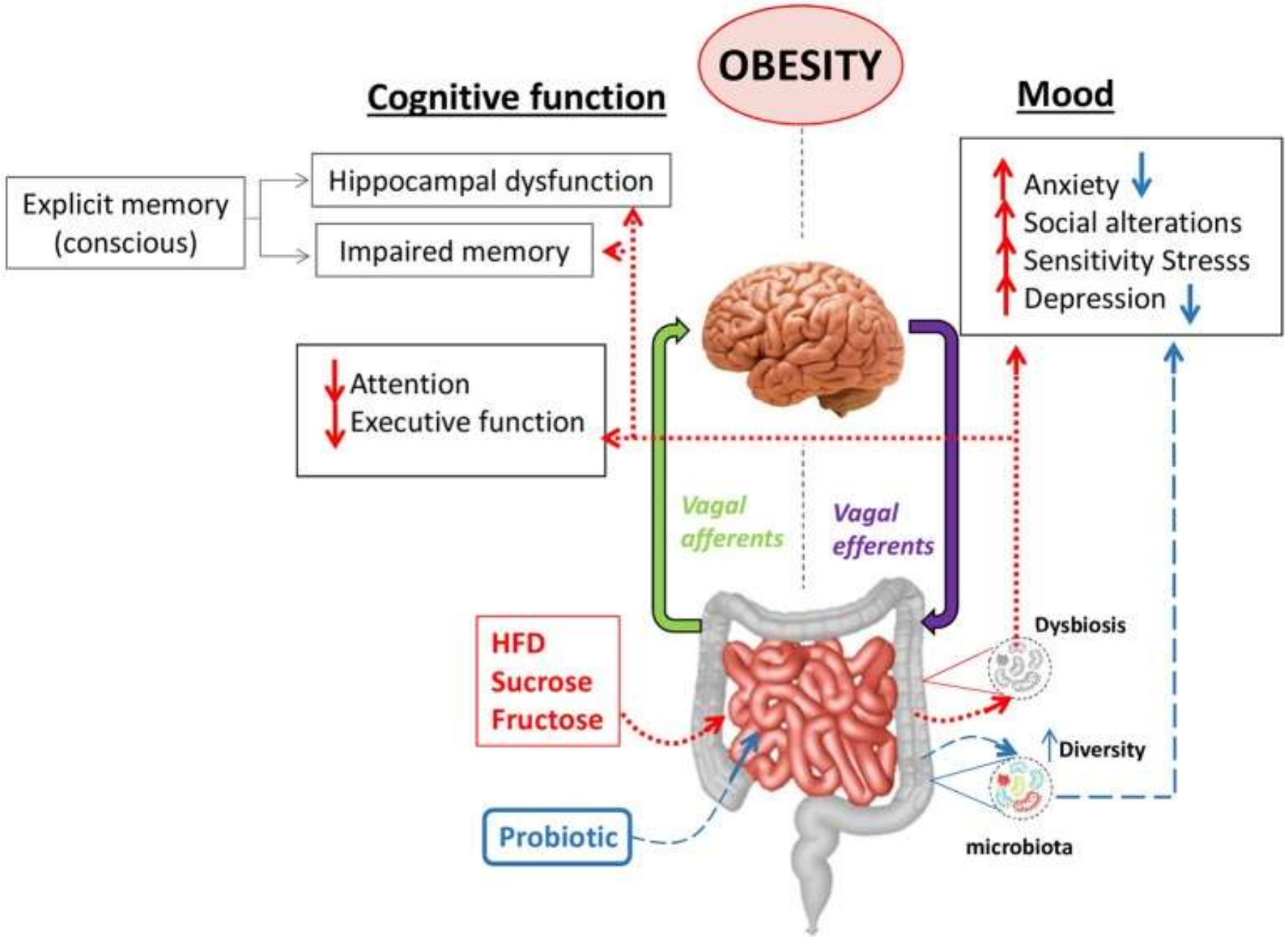
Received: 18 December 2012 / Accepted: 3 March 2013

REVIEW ARTICLE

The influence on metabolism



- This explains the differences in metabolic mechanisms
- These insights are a base to understand the Mechanism Of Action (MOA) of future probiotic treatment
- Probiotic microorganism might manipulate these mechanisms
  - Reducing effect on weight and weight gain

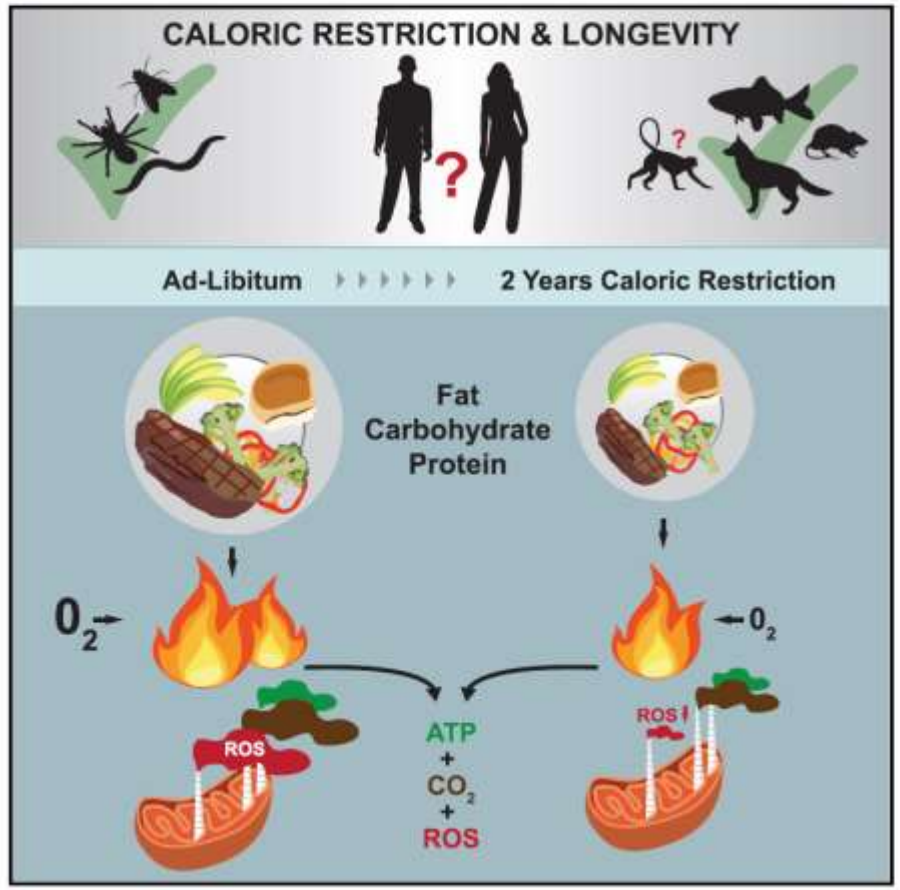

OBESITY
Cognitive function
Mood
Explicit memory (conscious)
Hippocampal dysfunction
Impaired memory
Attention
Executive function
Anxiety
Social alterations
Sensitivity Stresss
Depression
Vagal afferents
Vagal efferents
HFD
Sucrose
Fructose
Probiotic
Dysbiosis
Diversity
microbiota

Clinical and Translational Report

Cell Metabolism

Metabolic Slowing and Reduced Oxidative Damage with Sustained Caloric Restriction Support the Rate of Living and Oxidative Damage Theories of Aging

Graphical Abstract



Authors

Leanne M. Redman, Steven R. Smith, Jeffrey H. Burton, Corby K. Martin, Dora Il'yasova, Eric Ravussin

Correspondence

leanne.redman@pbrc.edu

In Brief

Calorie restriction (CR) has been shown to have health benefits and to extend lifespan in diverse species. Redman et al. conducted a 2-year CR trial in healthy, non-obese humans and found evidence that prolonged CR enhances resting energy efficiency, resulting in decreased systemic oxidative damage.

HARA HACHI BU

The influence of a probiotic milk drink on the development of gingivitis: a pilot study

Staab B, Eick S, Knöfler G, Jentsch H. The influence of a probiotic milk drink on the development of gingivitis: a pilot study. J Clin Periodontol 2009; 36: 850–856. doi: 10.1111/j.1600-051X.2009.01459.x.

Table 2. Interproximal plaque index (API) for all teeth

	Test group ($n = 25$)		Control group ($n = 25$)		*U*-test
	mean	standard deviation	mean	standard deviation	*p*
Baseline	39.2	19.1	38.9	6.9	0.846
Beginning of experimental gingivitis (1)	27.8	14.9	31.3	14.4	0.419
End of experimental gingivitis (2)	93.1	8.8	96.6	8.0	0.093
Friedman test *p*	<0.001		<0.001		
Wilcoxon test *p* baseline – 1	0.160		0.021		
Wilcoxon test *p* 1 – 2	<0.001*		<0.001*		
Wilcoxon test *p* baseline – 2	<0.001*		<0.001*		

*Significant after Bonferroni adjustment.

Table 3. Plaque index (PI) for all teeth

	Test group ($n = 25$)		Control group ($n = 25$)		*U*-test
	mean	standard deviation	mean	standard deviation	*p*
Baseline	0.76	0.23	0.68	0.23	0.217
Beginning of experimental gingivitis (1)	0.98	0.32	0.82	0.34	0.053
End of experimental gingivitis (2)	2.52	0.61	2.14	0.30	0.001
Friedman test *p*	<0.001		<0.001		
Wilcoxon test *p* baseline – 1	0.001*		0.044		
Wilcoxon test *p* 1 – 2	<0.001*		<0.001*		
Wilcoxon test *p* baseline – 2	<0.001*		<0.001*		

*Significant after Bonferroni's adjustment.

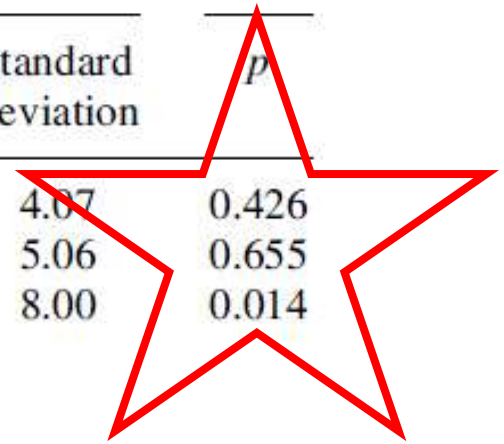
Table 4. Papilla bleeding index (PBI) for all teeth

	Test group ($n = 25$)		Control group ($n = 25$)		*U*-test
	mean	standard deviation	mean	standard deviation	*p*
Baseline	0.67	0.30	0.80	0.27	0.127
Beginning of experimental gingivitis (1)	0.99	0.34	0.89	0.36	0.308
End of experimental gingivitis (2)	1.17	0.57	1.12	0.36	0.985
Friedman test *p*	<0.001		<0.001		
Wilcoxon test *p* baseline – 1	0.001*		0.061		
Wilcoxon test *p* 1 – 2	0.071		0.003		
Wilcoxon test *p* baseline – 2	<0.001*		<0.001*		

Decrease of gingival inflammation markers

Table 6. Myeloperoxidase activity (MPO, μU) in the gingival crevicular fluid

	Test group ($n = 25$)		Control group ($n = 25$)		*U*-test
	mean	standard deviation	mean	standard deviation	*p*
Baseline	2.66	4.86	3.83	4.07	0.426
Beginning of experimental gingivitis (1)	4.43	5.18	4.92	5.06	0.655
End of experimental gingivitis (2)	3.58	5.27	8.50	8.00	0.014
Friedman test *p*	0.326		0.024		
Wilcoxon test *p* baseline – 1	0.339		0.563		
Wilcoxon test *p* 1 – 2	0.427		0.036		
Wilcoxon test *p* baseline – 2	0.382		0.015*		



European Journal of Clinical Nutrition (2011), 1–7

0954-3007/11
www.nature.com/ejcn

ORIGINAL ARTICLE

Probiotics affect the clinical inflammatory parameters of experimental gingivitis in humans

S Slawik[1,3], I Staufenbiel[2,3], R Schilke[2], S Nicksch[2], K Weinspach[2], M Stiesch[1] and J Eberhard[1]

PI & Bleeding on Probing

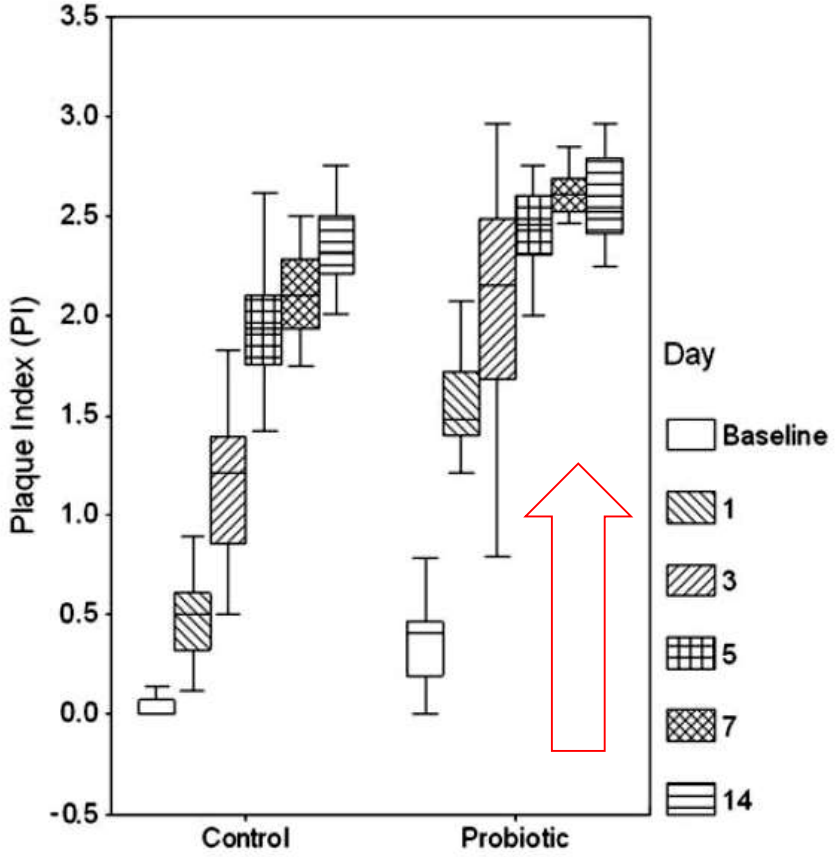


Figure 1 PI values shown as box plots at baseline, days 1, 3, 5, 7 and 14.

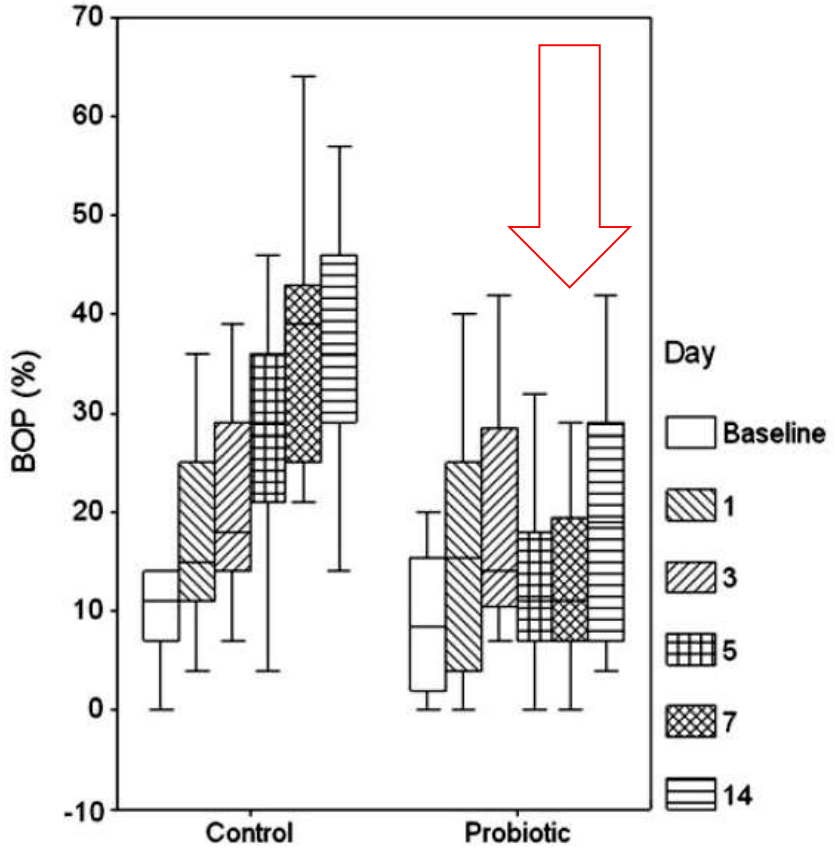


Figure 4 BOP values shown as box plots at baseline, days 1, 3, 5, 7 and 14.

Caries Research

Caries Res 2001;35:412–420

Received: November 20, 2000
Accepted after revision: June 11, 2001

Effect of Long-Term Consumption of a Probiotic Bacterium, *Lactobacillus rhamnosus* GG, in Milk on Dental Caries and Caries Risk in Children

L. Näse[a] K. Hatakka[b] E. Savilahti[c] M. Saxelin[b] A. Pönkä[e] T. Poussa[f]
R. Korpela[b] J.H. Meurman[a,d]

[a]Institute of Dentistry, University of Helsinki; [b]Valio Ltd., R & D, Helsinki; [c]Hospital for Children and Adolescents and [d]Department of Oral and Maxillofacial Diseases, Helsinki University Central Hospital, [e]Center of the Environment, Helsinki, and [f]Stat-Consulting, Tampere, Finland

LGG PROBIOTIC

CONTROL

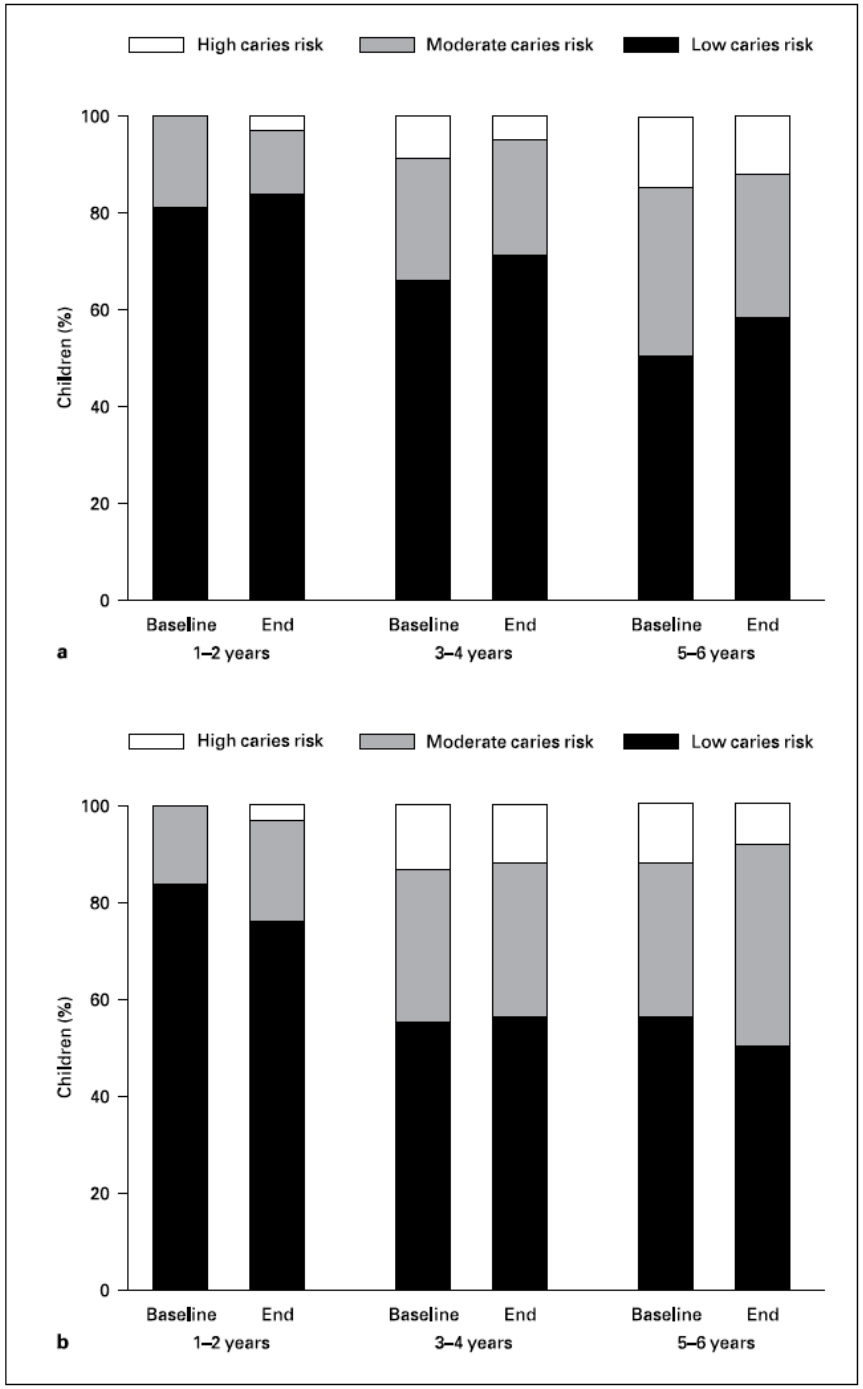


Fig. 2. Effects of LGG milk (**a**) and control milk (**b**) on caries risk in day-care children in three age groups, at baseline and at the end

STICHTING Darmgezondheid

EFFECT OF DAIRY PRODUCTS ON THE LIFETIME OF PROVOX2 VOICE PROSTHESES IN VITRO AND IN VIVO

Leonora Q. Schwandt, MD,[1,2] Ranny van Weissenbruch, MD, PhD,[1] Henny C. van der Mei, PhD,[2] Henk J. Busscher, PhD,[2] Frans W. J. Albers, MD, PhD[1]

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Published online 11 April 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20180

Lifetime +376% Replacements – 40%

Table 2. Differences in lifetime and number of voice prostheses replaced during 6 months before entering the study and during 6 months using Yakult Light fermented milk drink in a patient group requiring frequent replacement.

Patient no.	Lifetime before YL, d*	No. replacements before YL	Lifetime with YL, normalized†	No. replacements with YL	+1 SD	+2 SD
1	64 ± 15 (0.24)	3	0.66 ± 0.11	4	0	0
2	33 ± 5 (0.17)	7	1.05 ± 0.38	4	2	2
3	21 ± 7 (0.34)	7	2.06 ± 1.57	6	0	3
4	43 ± 26 (0.6)	4	1.26 ± 0.29	3	1	0
5	31 ± 14 (0.44)	5	2.27 ± 1.78	3	1	1
6	35 ± 17 (0.48)	5	1.82 ± 0.61	2	1	1
7	23 ± 12 (0.51)	10	2.38 ± 3.5	4	0	2
8	12 ± 5 (0.42)	13	1.93 ± 1.89	9	1	3
9	10 ± 3 (0.24)	6	23.04 ± 0‡	1	0	1
10	60 ± 34 (0.57)	4	1.14 ± 0.87	3	1	0
Mean	33 ± 18 (0.26)	64	3.76§ ± 1.1	39§	7	13

Abbreviations: YL, Yakult Light fermented milk drink; SD, standard deviation.
Note. For every patient, the lifetime was normalized by dividing the lifetime per replaced voice prosthesis by the mean lifetime in days before using YL. The normalized mean lifetime before using YL was therefore 1.00 for each patient. Also included are the numbers of voice prostheses replaced during drinking YL, which were longer than 1 or 2 SD in situ with respect to the mean in situ lifetime and SD before entering the study.
**Standard deviations were indicated by ±. The first digit represents the SD in days; the number in parentheses is the normalized SD.*
†For every patient the control was set at 1.00 (mean in situ lifetime before entering study).
‡This patient required no new voice prosthesis during the experimental period.
§Significant differences (paired Student's t test, $p < .01$) from the control.

Peventie van biofilm vorming op voice prothese

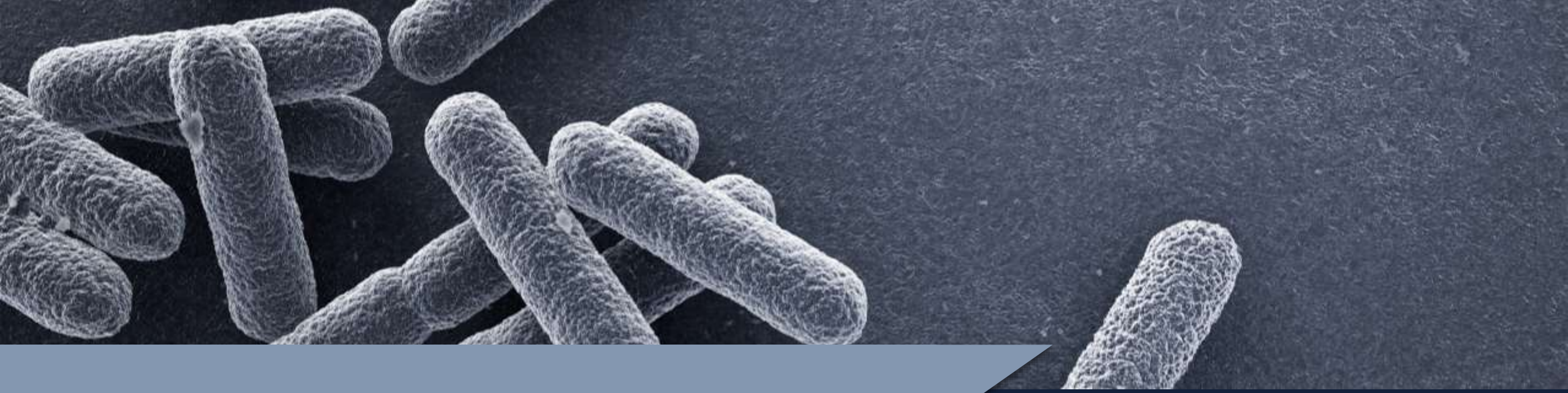
- **In vitro** (R. Free *et al*. 2000,L. Schwandt et al. 2004)
- Vermindering van bacteriën na spoelen met karnemelk, Yakult, Yakult Light, Vifit, halfvolle melk en verschillende soorten magere yoghurt.
- Soms vermeerdering van gisten
- Grootste effect met karnemelk, Yakult en Yakult Light.

- **In vivo** (L. Schwandt *et al.* 2005)
- Geen effect karnemelk
- Yakult Light geeft vermindering biofilm en verlengde levensduur van de prothese met factor 3.7.

Probiotica en Halitose

- Kang et al zagen een vermindering van vluchtige sulfide verbindingen na gebruik van *Weisella cibaria.* Waarschijnlijk is het mechanisme gebaseerd op waterstofperoxide productie door *W. cibaria*

- *Streptococcus salivarius* onderdrukt ook vluchtige zwavelcomponent productie, waarschijnlijk door competitie voor kolonisatiegebieden met zwavelverbinding producerende bacterien



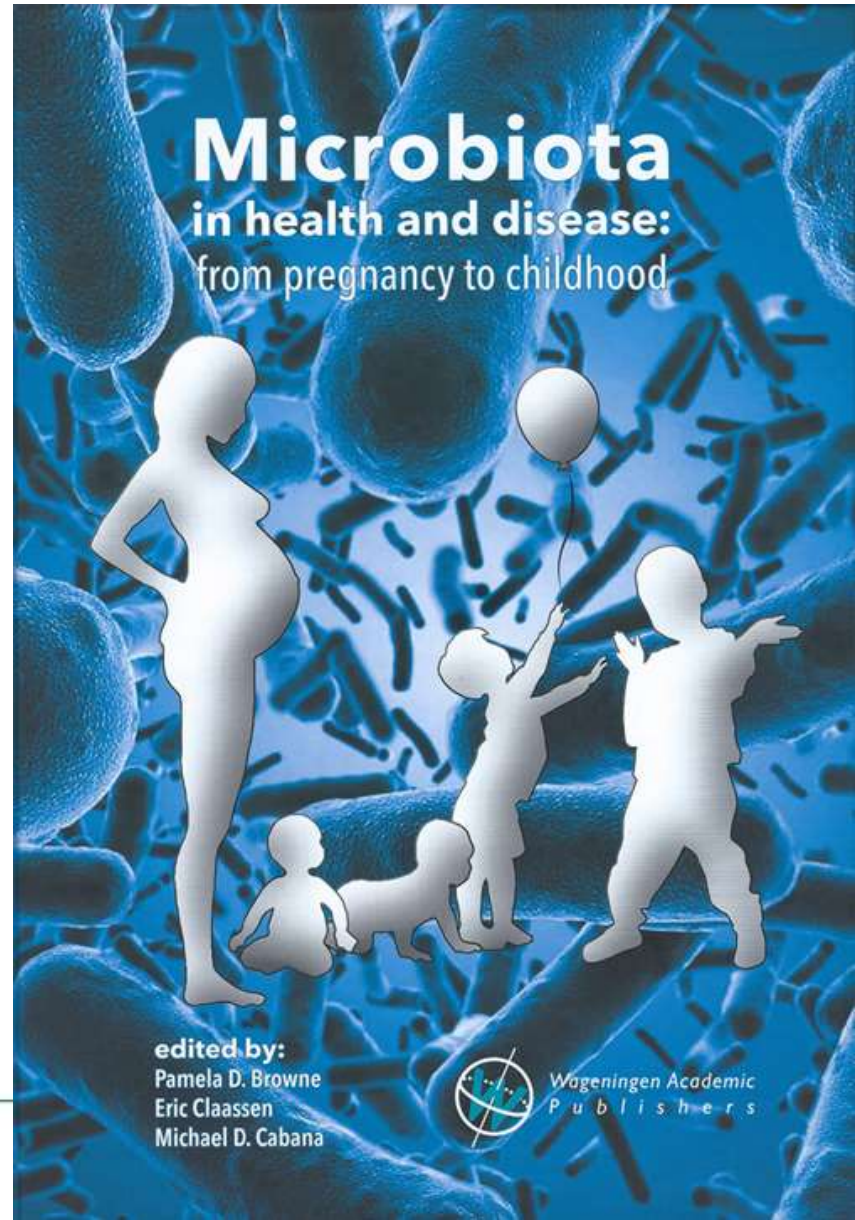
DEALING WITH THE REMAINING CONTROVERSIES OF PROBIOTIC SAFETY

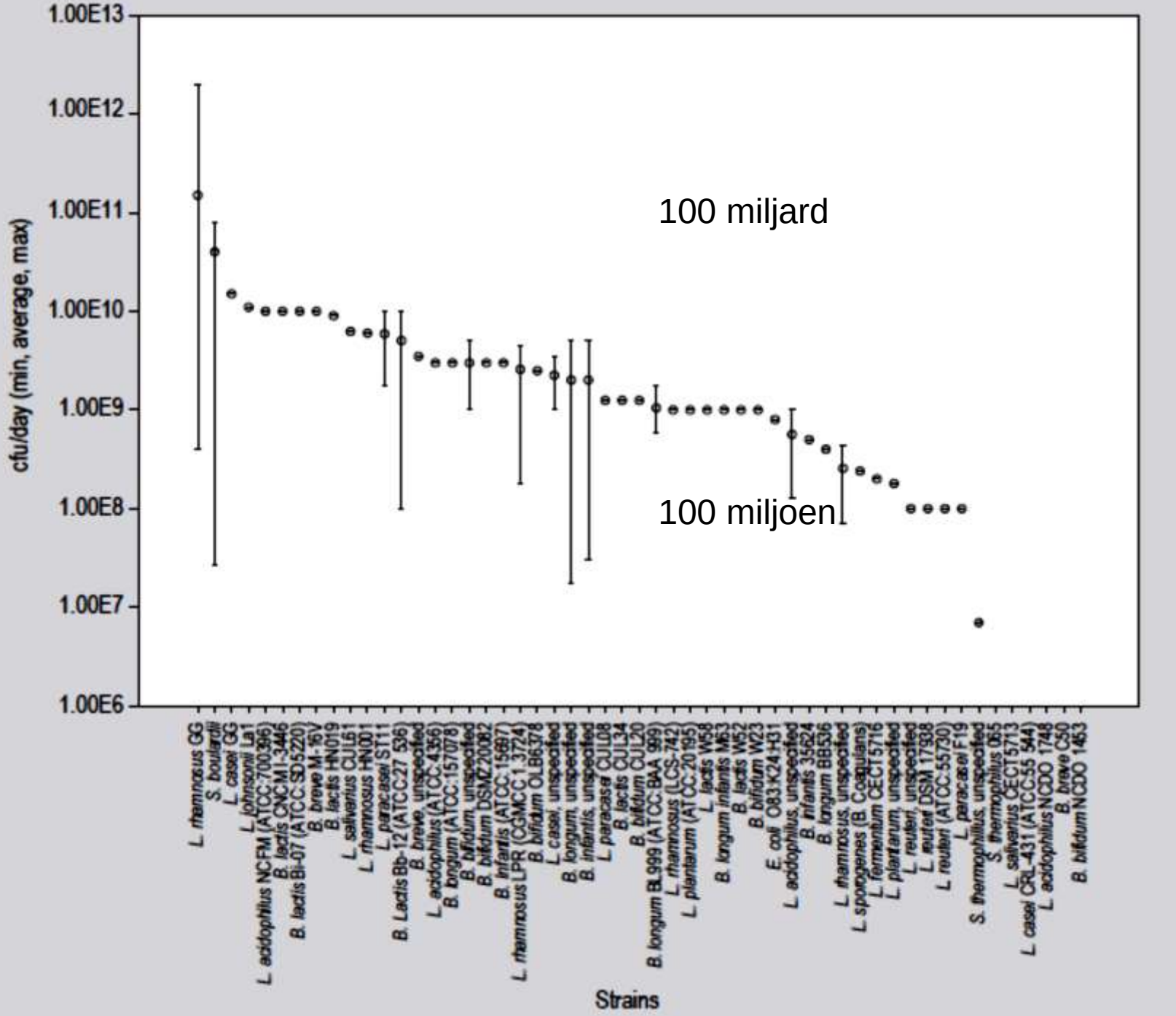
M. van den Nieuwboer and E. Claassen. Beneficial Microbes

Beneficial Microbes, March 2014; 5(1): 45-60

Probiotic and synbiotic safety in infants under two years of age

M. van den Nieuwboer[1,2], E. Claassen[1,3], L. Morelli[4], F. Guarner[5] and R.J. Brummer[6]




1.00E13
1.00E12
1.00E11
1.00E10
1.00E9
1.00E8
1.00E7
1.00E6
cfu/day (min, average, max)
100 miljard
100 miljoen
L. rhamnosus GG
S. boulardii
L. casei GG
L. johnsonii La1
L. acidophilus NCFM (ATCC 700396)
B. lactis CNCM I-3446
B. lactis Bi-07 (ATCC SD5220)
B. breve M-16V
B. lactis HN019
L. salivarius CUL61
L. rhamnosus HN001
L. paracasei ST11
B. Lactis Bb-12 (ATCC 27 536)
B. breve, unspecified
L. acidophilus (ATCC 4356)
B. longum (ATCC 15708)
B. bifidum, unspecified
B. bifidum DSMZ 20082
B. infantis (ATCC 15697)
L. rhamnosus LPR (CGMCC 1.3724)
B. bifidum OLB6378
L. casei, unspecified
B. longum, unspecified
B. infantis, unspecified
L. paracasei CUL08
B. lactis CUL34
B. bifidum CUL20
B. longum BL999 (ATCC BAA 999)
L. rhamnosus (LGS-742)
L. plantarum (ATCC 20195)
L. lactis W58
B. longum infantis M63
B. lactis W52
B. bifidum W23
E. coli O83:K24:H31
L. acidophilus, unspecified
B. infantis 35624
B. longum BB536
L. rhamnosus, unspecified
L. sporoganes (B. Coagulans)
L. fermentum CECT5716
L. plantarum, unspecified
L. reuteri, unspecified
L. reuteri DSM 17938
L. reuteri (ATCC 55730)
L. paracasei F19
S. thermophilus, unspecified
S. thermophilus 065
L. salivarius CECT5713
L. casei CRL-431 (ATCC 55 544)
L. acidophilus NCDO 1748
B. breve C50
B. bifidum NCDO 1453
Strains

Niet alle probiotica zijn gelijk!

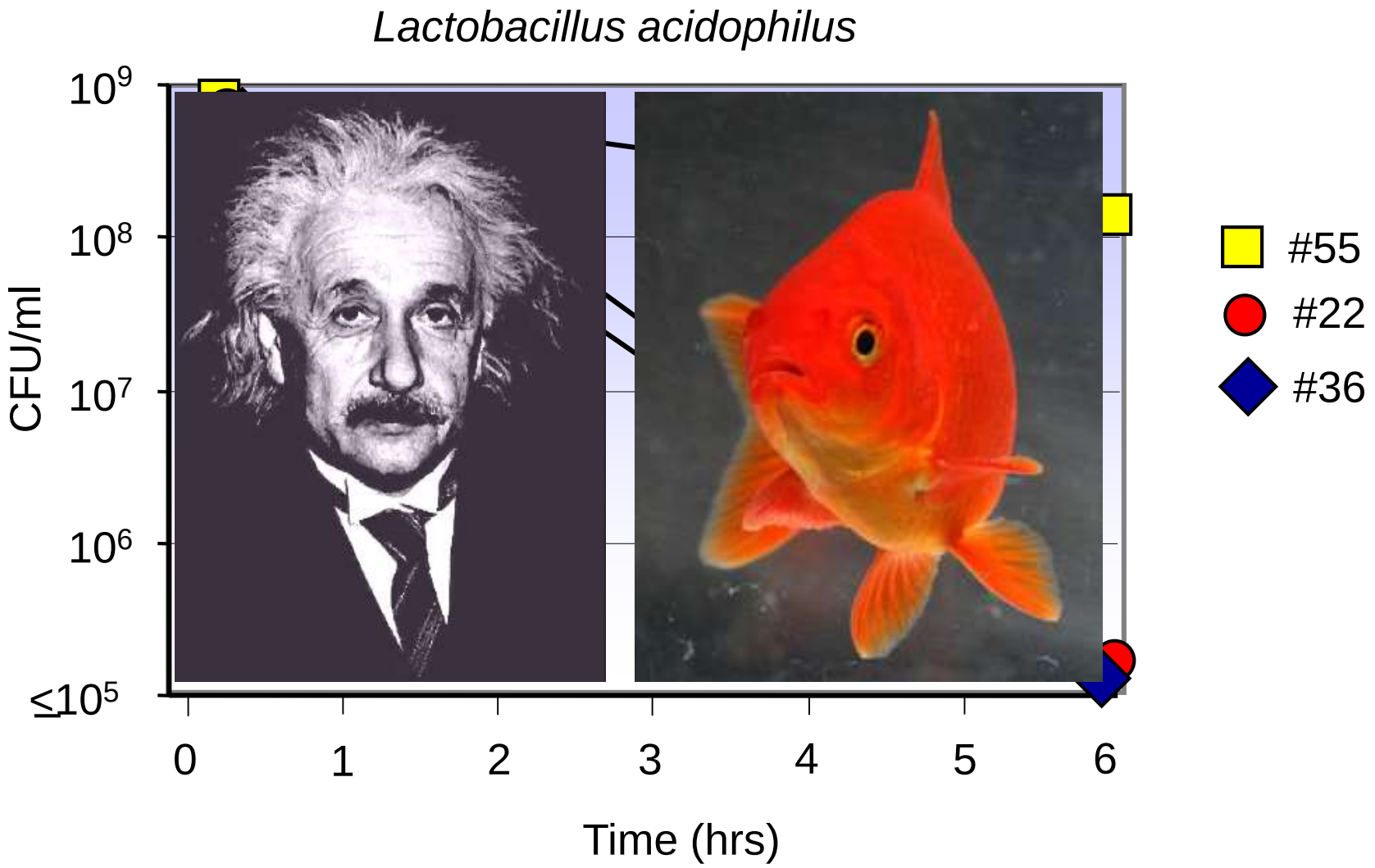


Table 1. Common terminology clinical adverse events (CTCAE) v 4.0

Category	Designation
Blood and lymphatic system disorders	I
Cardiac disorders	II
Congenital, familial and genetic disorders	III
Ear and labyrinth disorders	IV
Endocrine disorders	V
Eye disorders	VI
Gastrointestinal disorders	VII
General disorders and administration site conditions	VIII
Hepatobiliary disorders	IX
Immune system disorders	X
Infections and infestations	XI
Injury, poisoning and procedural complications	XII
Investigations	XIII
Metabolism and nutrition disorders	XIV
Musculoskeletal and connective tissue disorders	XV
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	XVI
Nervous system disorders	XVII
Pregnancy, puerperium and perinatal conditions	XVIII
Psychiatric disorders	XIX
Renal and urinary disorders	XX

Van den Nieuwboer *et al*., 2014

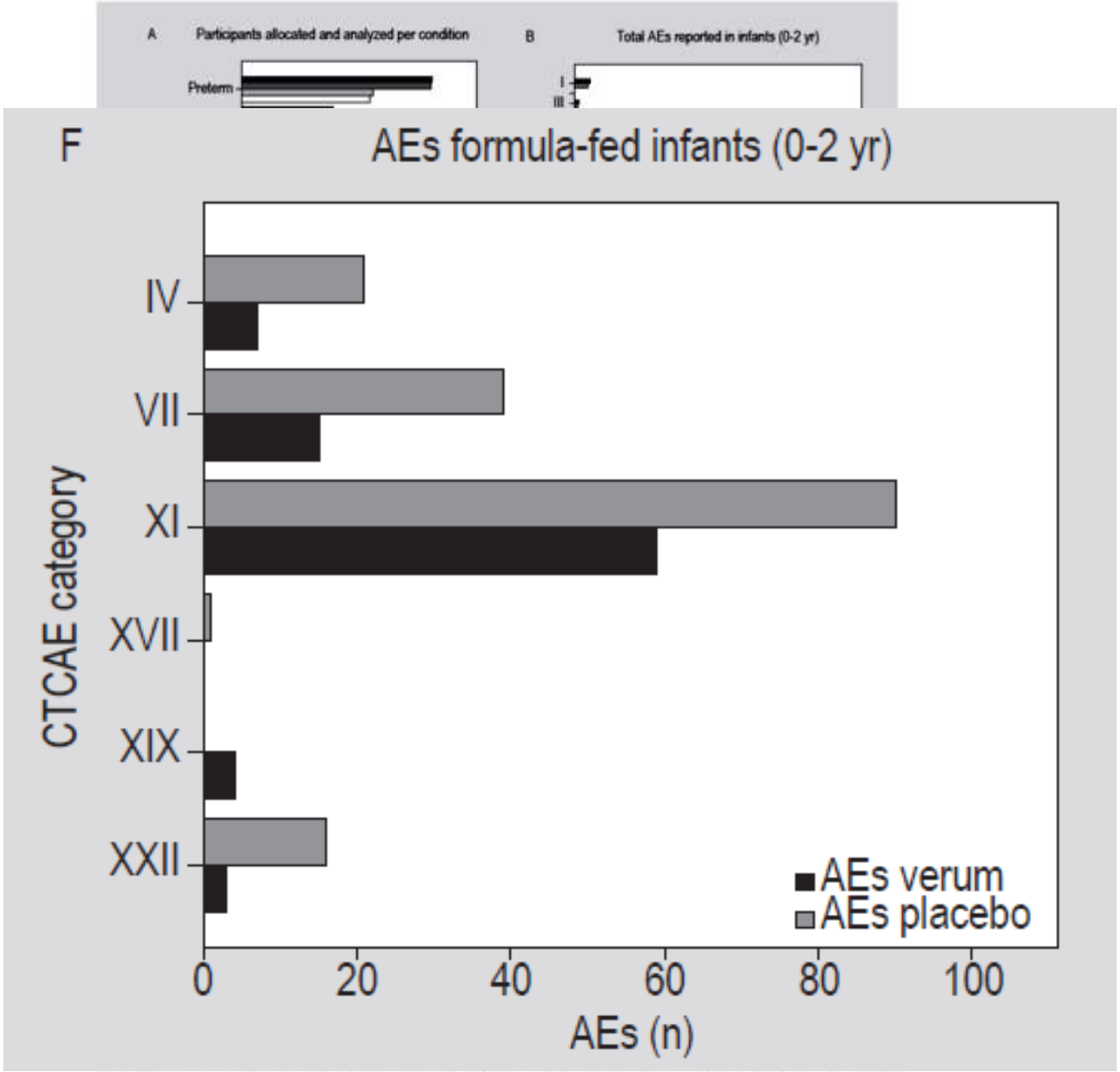


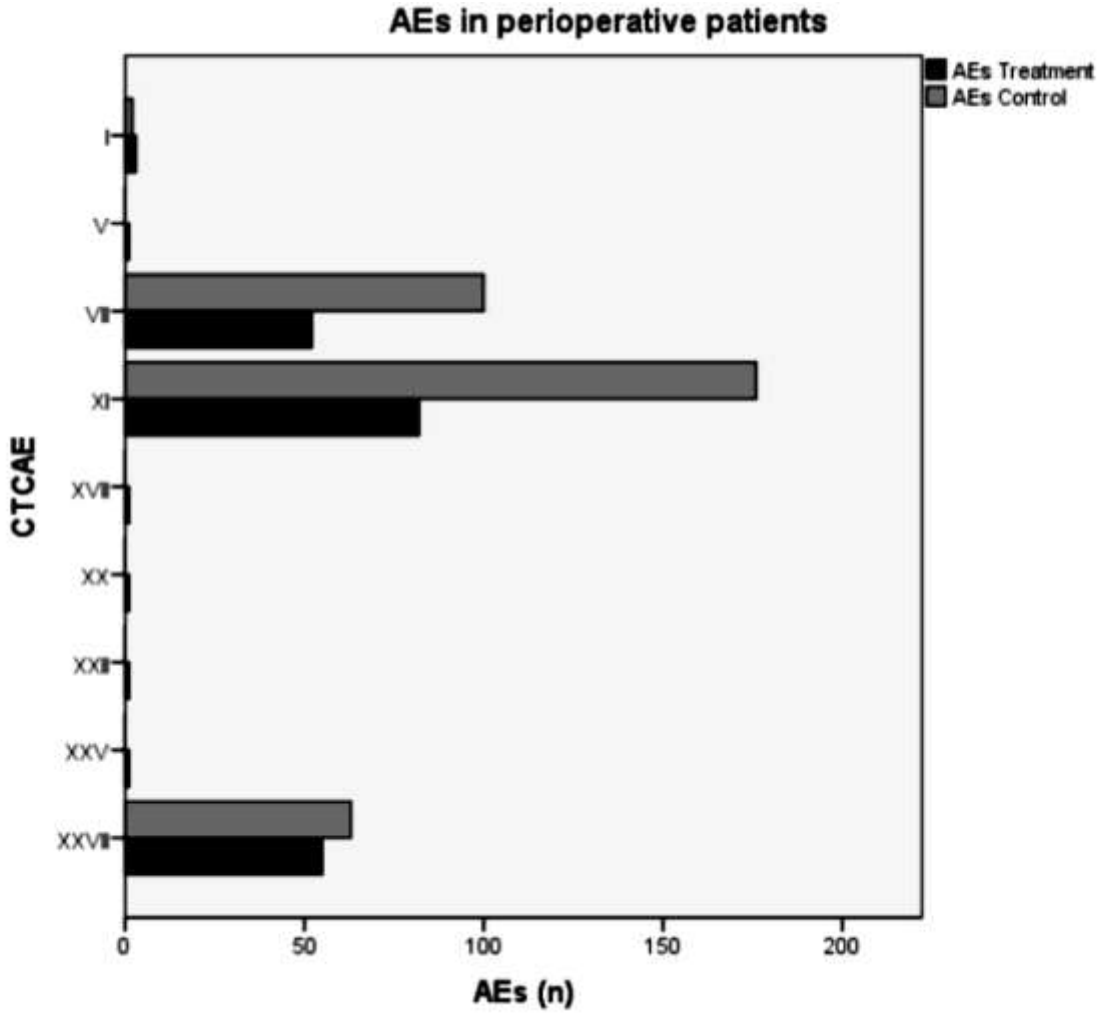
Figure 6. (A) Participants allocated and analysed per protocol of the verum and placebo group for each health condition. (B) The total adverse events (AEs) reported of all studies, comparing placebo and verum group and categorised according to the Common Terminology Clinical Adverse Events (CTCAE). (C) Reported AEs categorised according to CTCAE analysed for preterm infants, (D) infants with diarrhoea, (E) infants with dermatitis, and (F) formula-fed infants.

The administration of Probiotics and Synbiotics in Immune Compromised Adults: is it Safe?

Van den Nieuwboer, M.[1], Brummer, R.J. [2] , Guarner, F.[3], Morelli, L. [4], Cabana, M. [5], and Claassen, E

This study aimed to systematically evaluate safety of probiotics and synbiotics in immune compromised adults (≥ 18 years). Safety was analysed using the Common Terminology Clinical Adverse Events (CTCAE version 4.0) classification, thereby providing an update on previous reports using the most recent available clinical data (2008-2013). Safety aspects are represented and related to number of participants per probiotic strain/culture, study duration, dosage, clinical condition and selected afflictions. Analysis of 57 clinical studies indicates that probiotic and/or synbiotic administration in immune compromised adults is safe with regard to the current evaluated probiotic strains, dosages and duration.

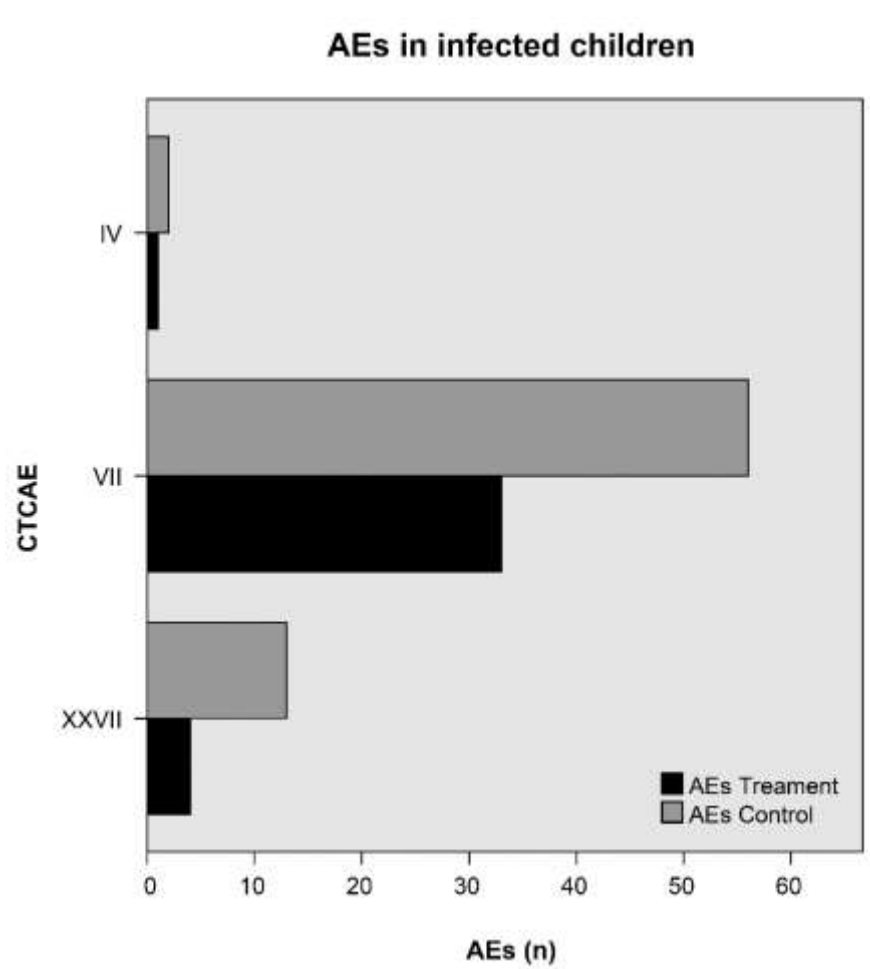
Beneficial Microbes: 2016, in press

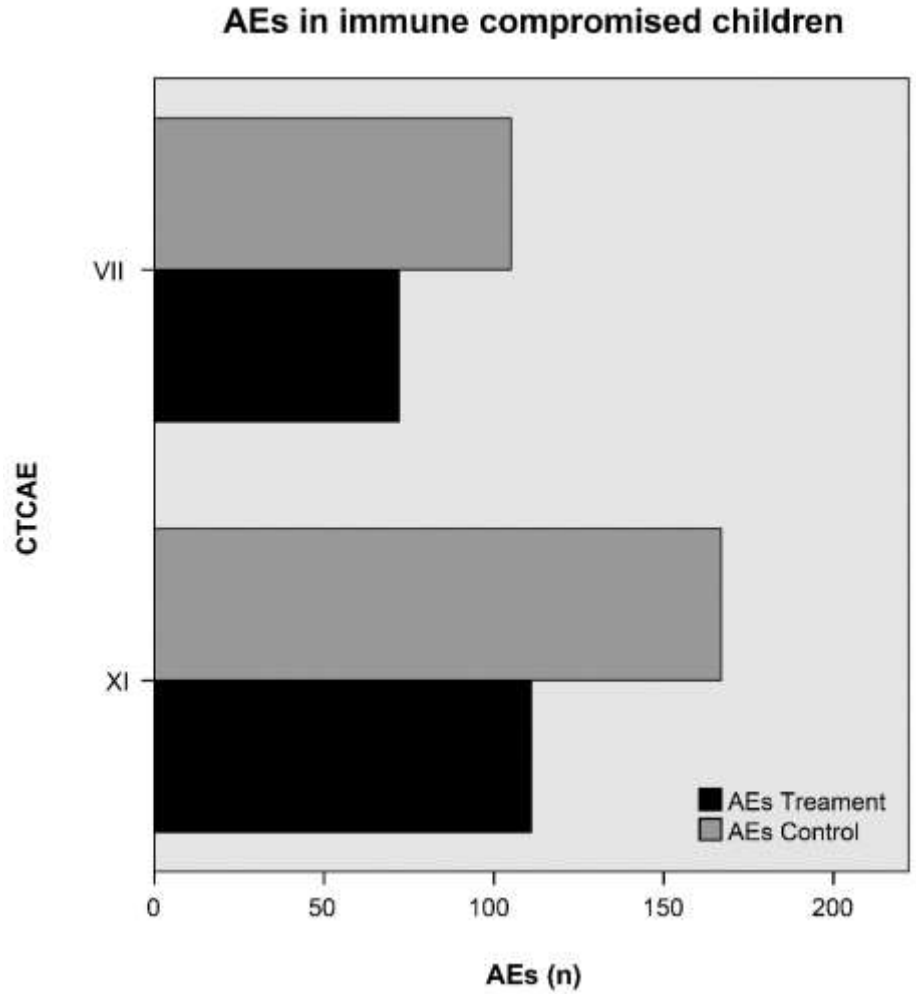

AEs in perioperative patients
AEs Treatment
AEs Control
CTCAE
I
V
VII
XI
XVII
XX
XXII
XXV
XXVII
0
50
100
150
200
AEs (n)

Safety of Probiotics and Synbiotics in Children Under 18 Years of Age

Van den Nieuwboer, M., Brummer, R.J., Guarner, F., Morelli, L., Cabana, M. , and Claassen, E.

Beneficial Microbes 2015 March online


AEs in infected children
CTCAE
IV
VII
XXVII
0
10
20
30
40
50
60
AEs (n)
AEs Treament
AEs Control


AEs in immune compromised children
CTCAE
VII
XI
0
50
100
150
200
AEs (n)
AEs Treament
AEs Control

PROBIOTICS REDUCE COMPLICATIONS

REDUCED COMPLICATIONS - Probiotic intake is associated with a reduction in symptoms and AEs compared to the placebo. Examples are:

- ✓ In the prevention of *Clostridium difficile* associated diarrhoea, probiotics reduce the risk of **AEs by 17%**
- ✓ Probiotic intake for preventing necrotizing enterocolitis is associated with fewer infections and gastrointestinal symptoms and **50% reduced mortality rate**
- ✓ **Lower rates of respiratory and gastrointestinal infections** in healthy infants as a result of probiotic intake
- ✓ **Reduced incidence of catheter related bloodstream infections** in mechanically ventilated individuals
- ✓ **Lower incidence of complications** after surgery with probiotic intake.

Due to **heterogeneity and publication bias**, the evidence for this reduction in adverse events is low. In order to make these general conclusions, additional data is required.

- It is difficult for an investigator to discriminate whether an AE is a result of the patient condition or from the investigated product.
- Effects of probiotics can be widespread, exerting a subtle positive influence extending far beyond the gut
- Experienced AEs in placebo and probiotic groups are often a result of the health condition of the individual

PharmaNutrition 6 (2018) 198–206

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journal homepage: www.elsevier.com/locate/phanu

Economic potential of probiotic supplementation in institutionalized elderly with chronic constipation

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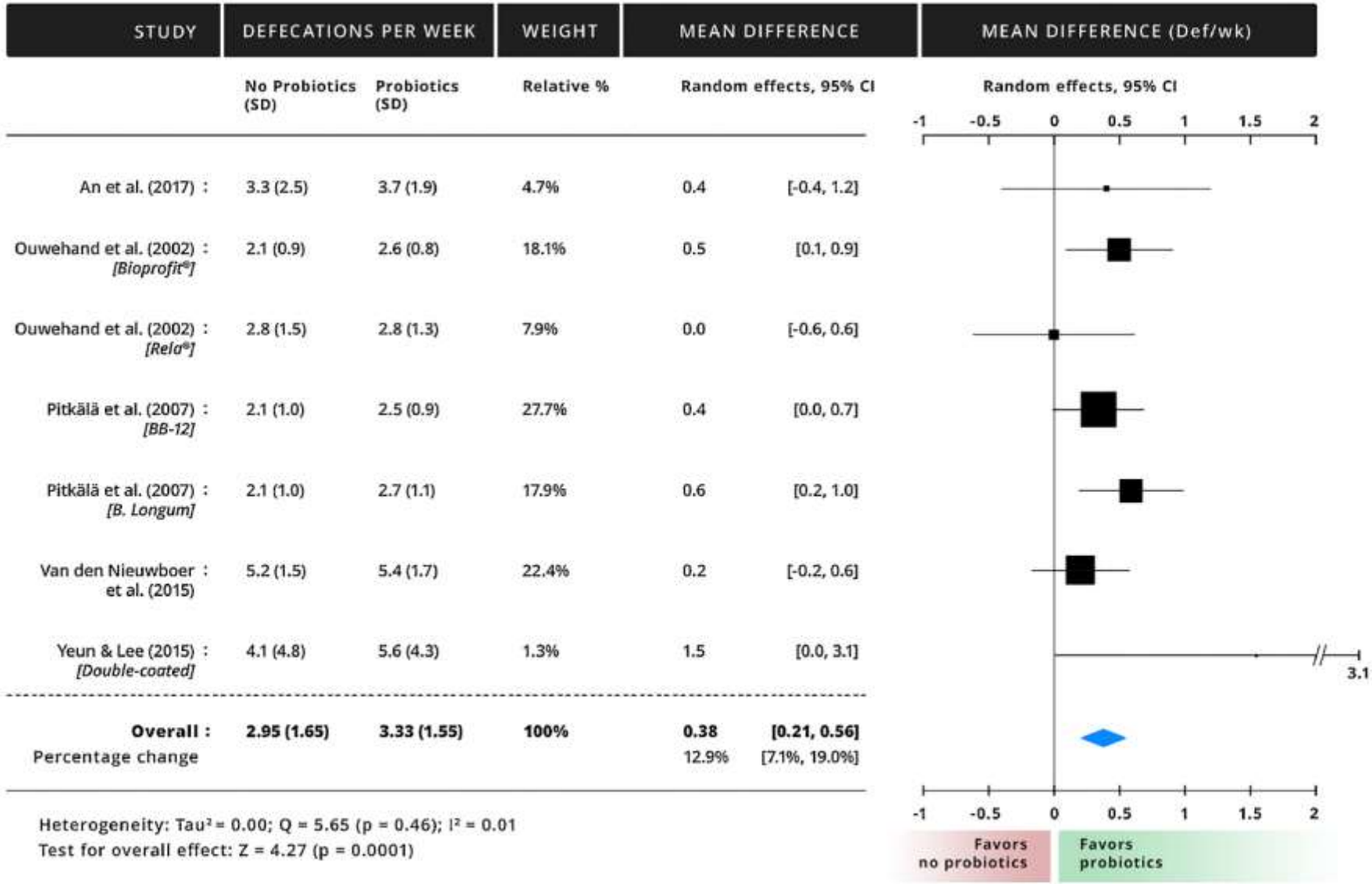

Fig. 5. Probiotics increase defecation frequency of institutionalized elderly by 13%.
This figure portrays the results of a random effects analysis on the defecation frequency of institutionalized elderly following probiotic supplementation. The overall effect is given as the difference Δ in days (0.38), followed by the percentage change (12.9%). Values of Pitkälä et al. [38] are calculated from the percentage of days with bowel movements. Values of Yeun and Lee [39] are estimated from the median and interquartile range according to the method described by Wan et al [45].

Probiotics & elderly care: Costs perspective

- Saving potential probiotics AAD: £ 399 per hospitalized patient over age of 65 years and treated with antibiotics
- Mean total costs chronic constipation direct medical costs in first year after diagnosis: € 310 ± 845

Lenoir Wijnkoop, Nijten, Craig, Butler, Frontiers in Pharmacology 2014, 5(13), 1-9
Dik, Siersema, Joseph, Hodgkins, Smeets, van Oijen, European J. Gastr. & Hepatol. 2014, 26: 1260-1266

SCIENTIFIC REPORTS

OPEN

The mechanistic link between health and gut microbiota diversity

Olaf F. A. Larsen & Eric Claassen

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Accepted: 12 January 2018
Published online: 01 February 2018

Although numerous reports link a decreased diversity of the gut microbiota to a declined health status, to date no mechanistic motivation for this exists. Here, we show by applying first principles basic graph theory on small networks that higher diversity within such a netw systems and redundancy. Our results quantitatively support earl gut microbiota richness with respect to these parameters. Our si diversity leads to higher resilience within small microbiological e microbiota. This notion should provide an ingredient when devel within the domain of microbiota management.

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Towards a rational design of faecal transplant analogues

Olaf F. A. Larsen[1], Anton H. J. Koning[2], Peter J. van der Spek[2] & Eric Claassen[1]

Received: 10 October 2018
Accepted: 21 March 2019
Published online: 03 April 2019

Faecal transplants (microbiota transfer) have shown to be promising therapies having a wide range of therapeutic applications. However, current safety considerations hamper further valorisation. As such, well designed faecal transplant analogues provide an interesting alternative to minimize possible safety aspects. However, to date little knowledge on how to rationally design such analogues exists. Here, we show by applying first order basic graph theory that such analogues dedicated to restoring a specific physiological functionality (a microbial guild) should consist of 5–6 species to maximize stability, efficiency, and minimize safety issues and production costs.

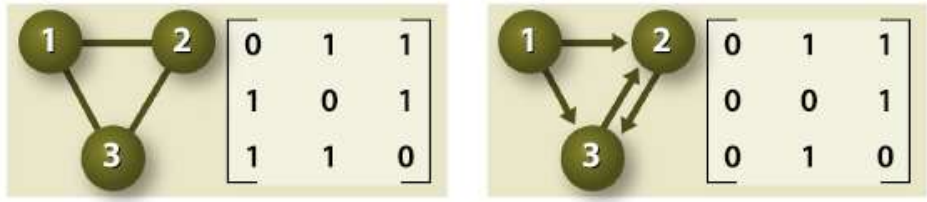
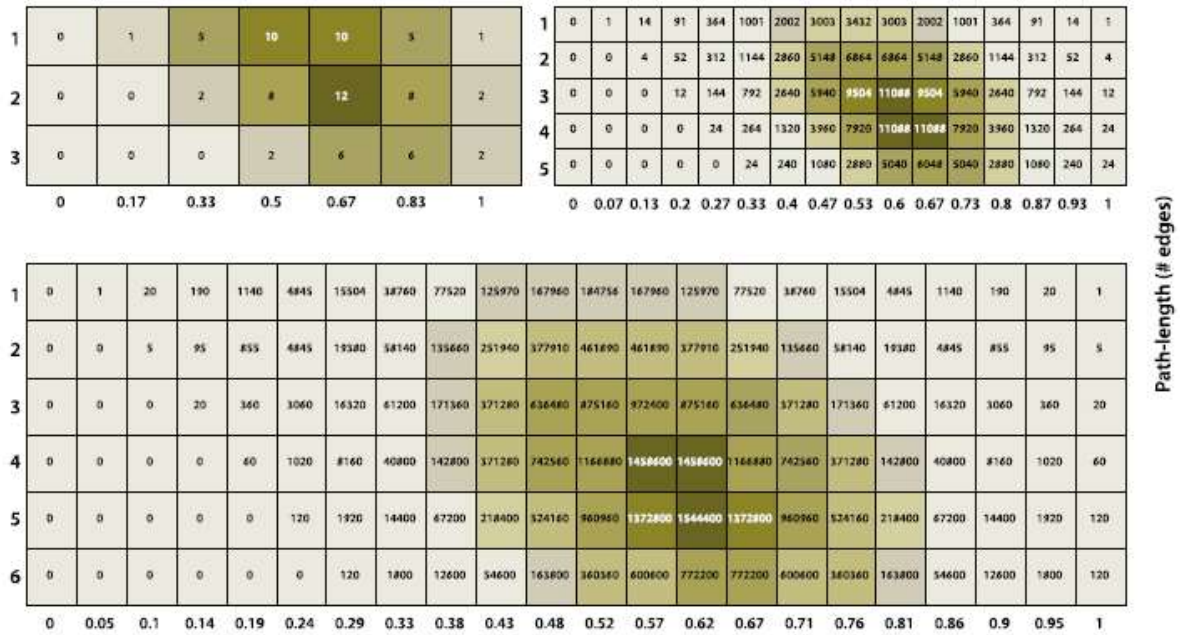


Figure 1. Schematic representations of two systems comprising three microbial species. The circles ("nodes") represent the three species, whereas the lines ("edges") represent the signalling connections between the species. In the left panel, the signals are undirected. As such, the presence or absence of an edge between two species simply represents communication or no communication at all between the respective species. In the right panel, the edges are directed. In this example, species 1 can exert a signal to species 2 and 3. Species 2, however, cannot exert a signal to species 1, but can exert a signal to species 3, and species 3 can again exert a signal to species 2. For each graphical representation, the respective adjacency matrix is given as well, with both row- and column-numbers representing nodes 1, 2 and 3, respectively. Each matrix element represents either a connection ("1") or no connection ("0") between the species. As an example, for the left adjacency matrix, elements (1, 2) and (2, 1) indicate a connection between species 1 and 2. The right adjacency matrix indicates that there is a signal going from species 1 to species 2, element (1, 2), but there is no signalling "back" possible from species 2 to species 1, element (2, 1). In our simulations, no connection of a species with itself is possible, hence the diagonal elements are all zero. In the case of undirected edges, the matrix is obviously symmetric (left example).



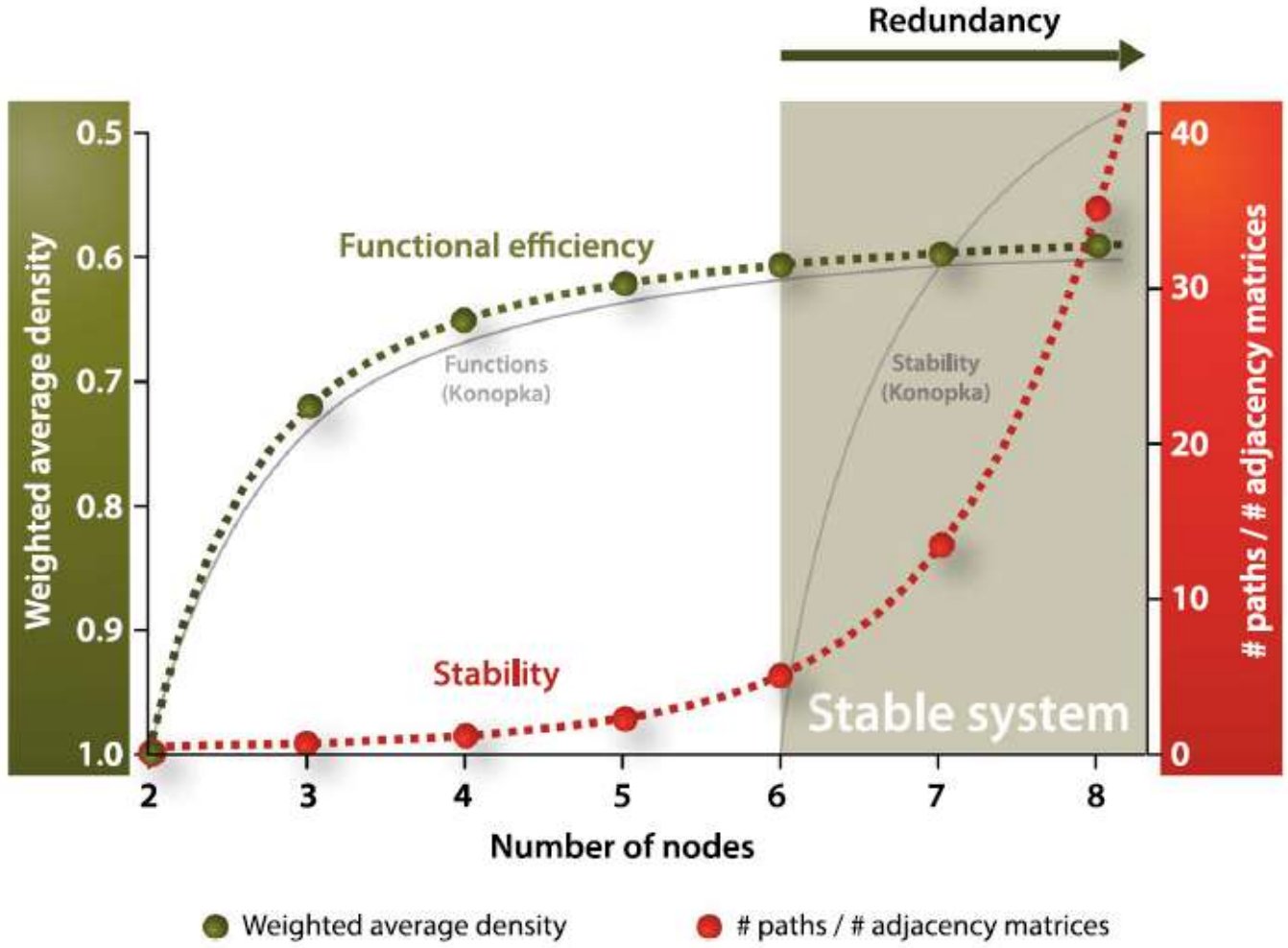
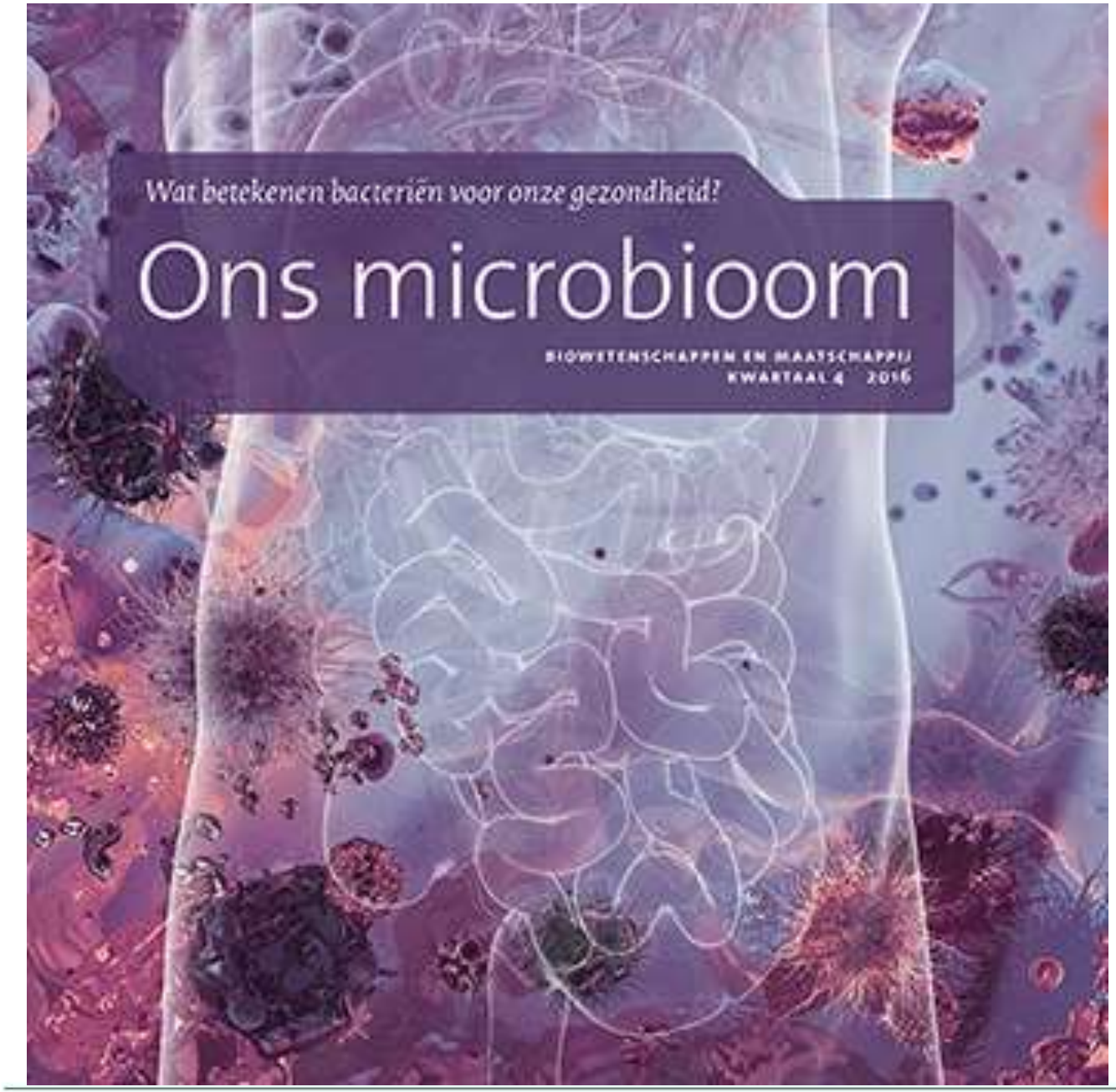


Figure 4. Graphical summary of our findings (adapted from Konopka[14]). Green: weighted average density reflecting functional efficiency. Red: number of paths divided by the number of adjacency matrices, reflecting stability. Grey: trends as proposed earlier by Konopka[14].



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STICHTING Darmgezondheid

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NEXT SLIDES FOR DISCUSSION

Health Maintenance of Athletes with Probiotics

Marta Oliveira

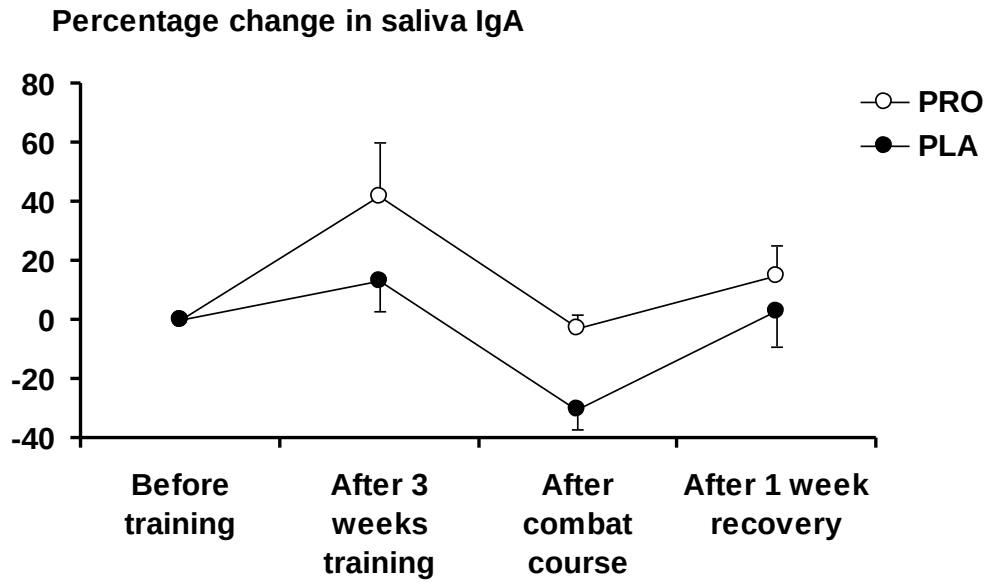
School of Sport, Exercise & Health Sciences
Loughborough University, UK

TEAM GB

The Official Preparation Camp Headquarters for Team GB

EFFECT OF A PROBIOTIC ON RESPIRATORY INFECTIONS AND SALIVA IGA DURING INTENSE MILITARY TRAINING

- 47 army cadets
- Daily 100 ml *L. casei DN-114 001* probiotic drink or placebo for 3 weeks training, followed by a 5-day combat course
- No difference in incidence of respiratory illness
- Significant saliva IgA decrease only in placebo group



Tiollier et al 2007 Military Med 172: 1006-1011

Environmental Health: A Global Access Science Source

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Research

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Increasing work-place healthiness with the probiotic *Lactobacillus reuteri*: A randomised, double-blind placebo-controlled study

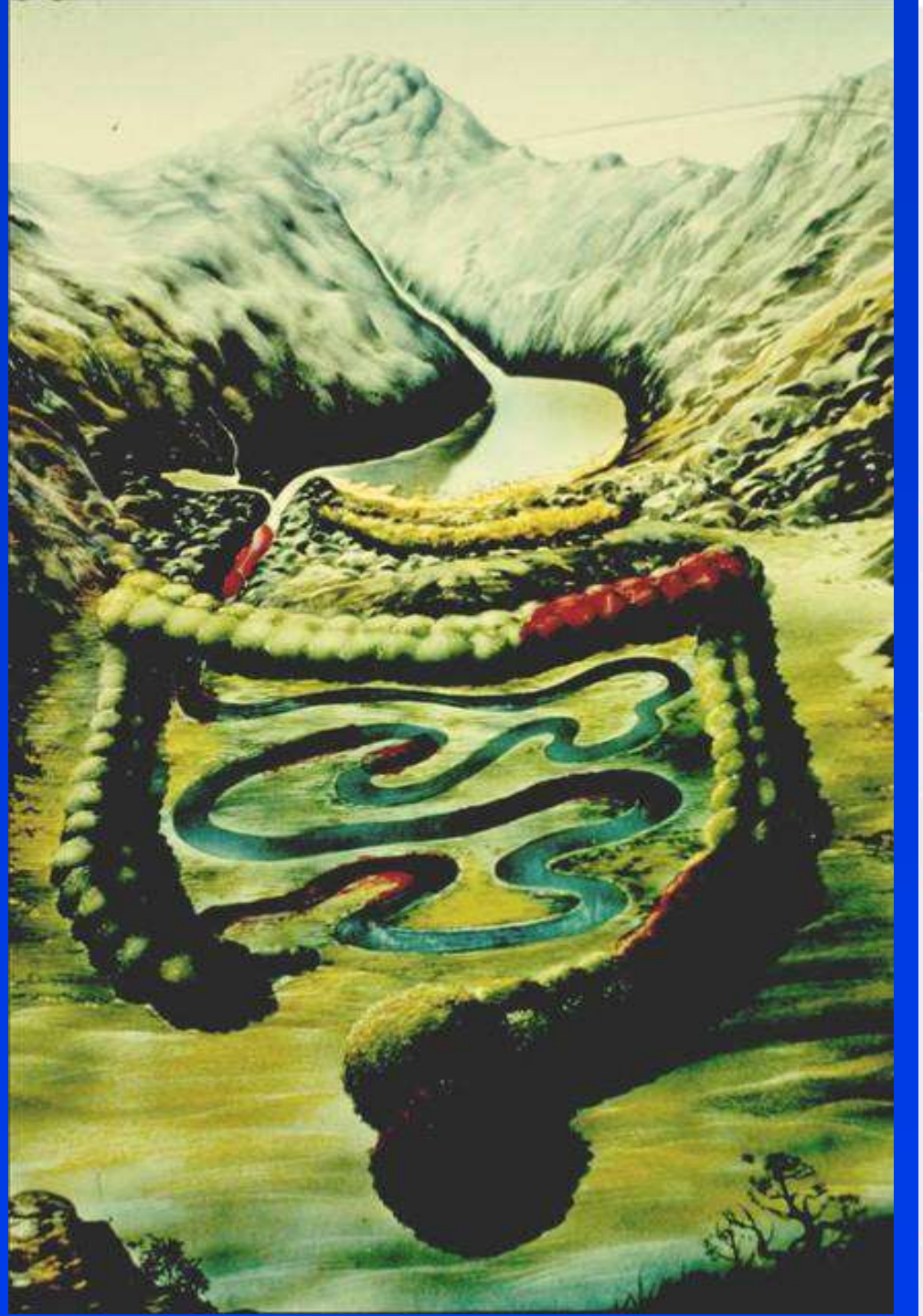
Py Tubelius[1], Vlaicu Stan[1] and Anders Zachrisson*[2]

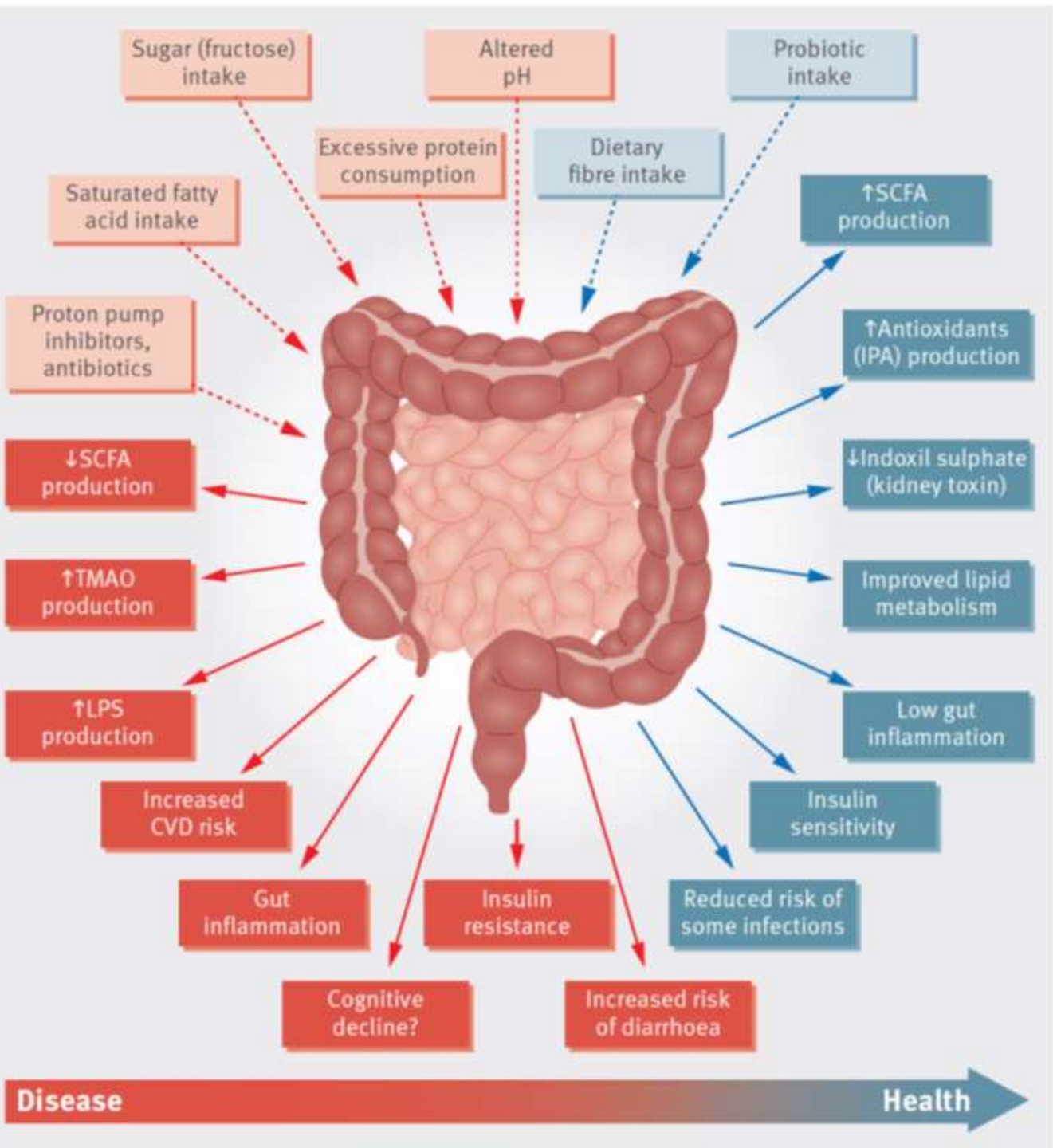
- 'Healthy' Shift-workers Probiotics and resistance to infections
  - Gastro-intestinal and respiratory

Published: 07 November 2005

Environmental Health: A Global Access Science Source 2005, **4**:25 doi:10.1186/1476-069X-4-25

Received: 22 August 2005
Accepted: 07 November 2005

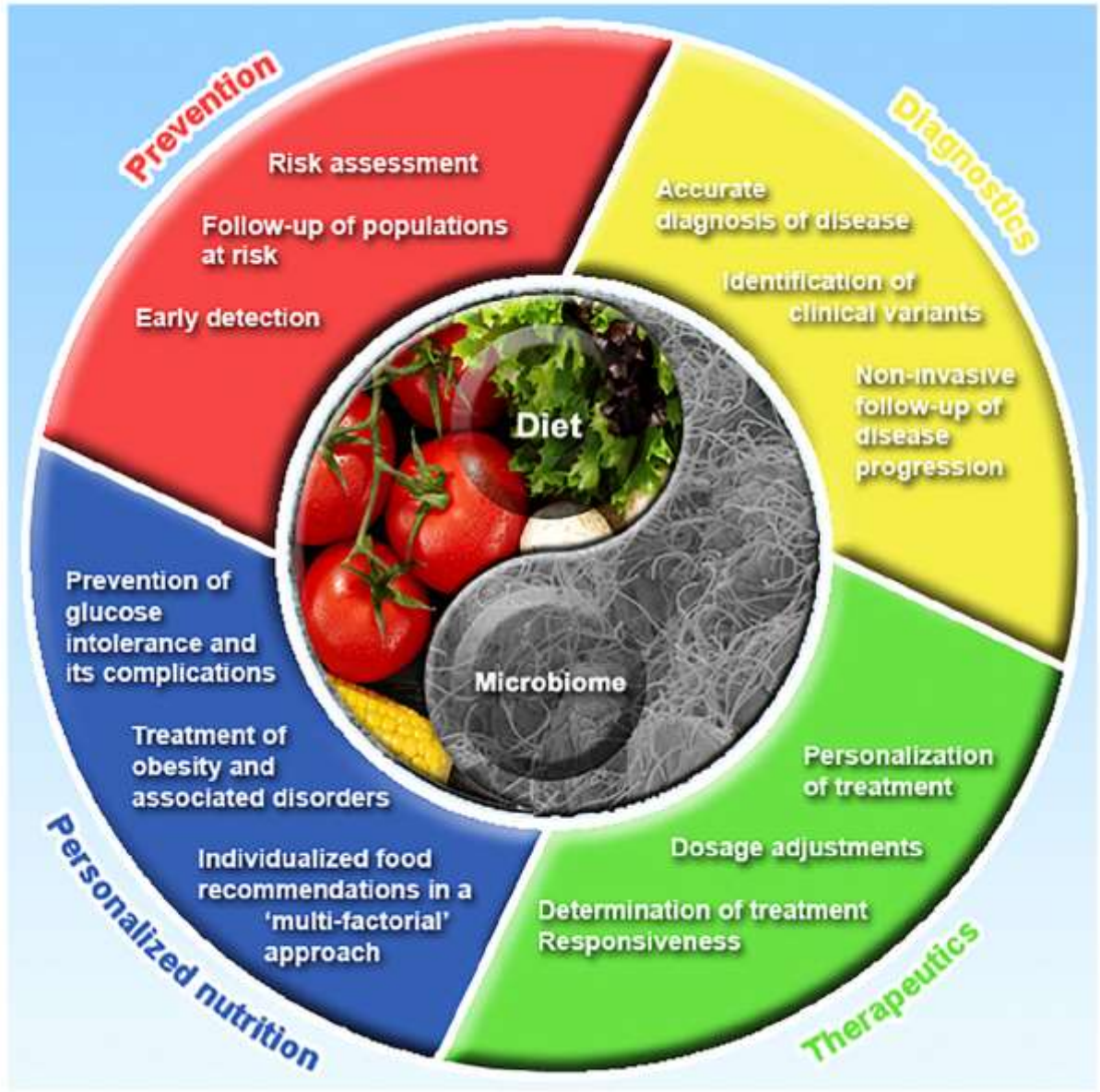



Sugar (fructose) intake
Altered pH
Probiotic intake
Excessive protein consumption
Dietary fibre intake
Saturated fatty acid intake
↑SCFA production
Proton pump inhibitors, antibiotics
↑Antioxidants (IPA) production
↓SCFA production
↓Indoxil sulphate (kidney toxin)
↑TMAO production
Improved lipid metabolism
↑LPS production
Low gut inflammation
Increased CVD risk
Insulin sensitivity
Gut inflammation
Insulin resistance
Reduced risk of some infections
Cognitive decline?
Increased risk of diarrhoea
Disease
Health

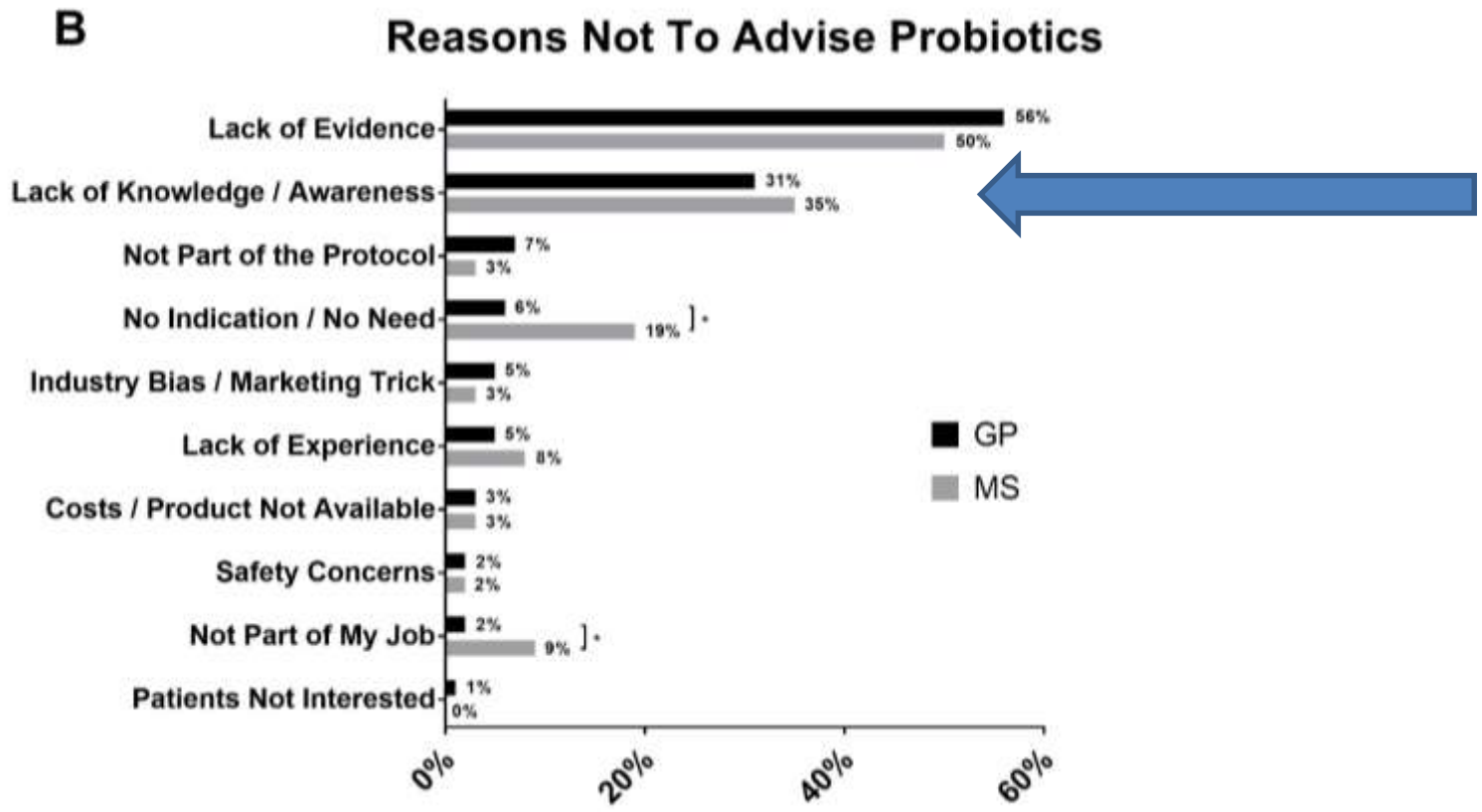
water – YLT – melk – YOR – dubbelfris – fruitshoot

fristi – ijsthee – drinkontbijt – ijskoffie cappuccino – jus d’orange – appelsap

energy drank – cassis – druivensap – cola – chocolademelk – sportdrank

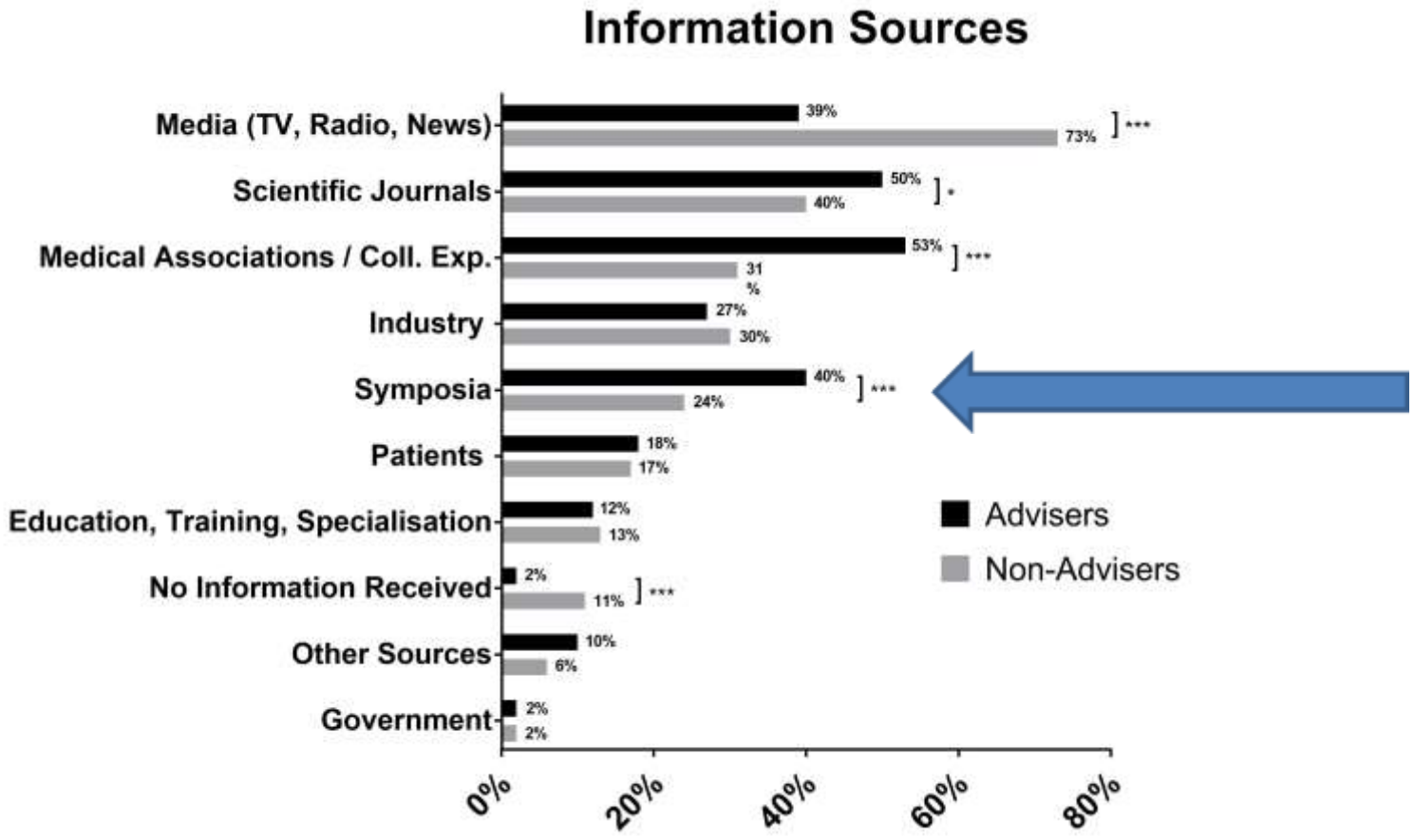

Prevention
Risk assessment
Follow-up of populations at risk
Early detection
Diagnostics
Accurate diagnosis of disease
Identification of clinical variants
Non-invasive follow-up of disease progression
Diet
Microbiome
Therapeutics
Personalization of treatment
Dosage adjustments
Determination of treatment Responsiveness
Personalized nutrition
Prevention of glucose intolerance and its complications
Treatment of obesity and associated disorders
Individualized food recommendations in a 'multi-factorial' approach

Medical Doctors: reasons not to advice



Flach, Dias, Rademaker, Van der Waal, Claassen & Larsen, PharmaNutrition 5 (2017) 103–108

Medical Doctors: information sources



Flach, Dias, Rademaker, Van der Waal, Claassen & Larsen, PharmaNutrition 5 (2017) 103–108

Recommendations for Probiotic Use or: ‘A’ claims (Floch et al., 2015)

- Infectious diarrhea children (treatment)
- AAD (antibiotic associated diarrhea; prevention)
- Pouchitis (prevention and maintenance of remission)
- Ulcerative Colitis (maintenance only)
- Immune response
- Atopic Eczema ass. with Cow milk allergy (prev.& treat.)

Voedingsadvies

- **Groente en fruit zijn de basis van dagelijkse voeding**
- **Verwen je darm eet witlof, asperge, artisjok, ui, knoflook, prei**
- **Eet gefermenteerde producten**
- **Eet elke dag een handje ongezouten noten**
- **Eet ten minste 2x per week vette vis**
- **Eet matig vlees (gevogelte is beter dan rood) en altijd met groene groente**
- **Let op en beperk je suiker inname waar je maar kunt**
- **Drink water/koffie/thee in plaats van fris- of fruitdrank**
- **Wees zuinig met zetmeel (brood, pasta, rijst, aardappelen)**
- **Gebruik liever altijd volkoren graanproducten (met mate)**
- **Gebruik volvette melkproducten, vooral yoghurt, kwark en kaas**
- **Vermijd industrieel geproduceerde voedingsmiddelen**
- **Gebruik olijfolie als dressing en om te braden**

NOTABLE EXCEPTIONS HIGH DOSE CLINICALLY TESTED SUPERMARKET PRODUCTS

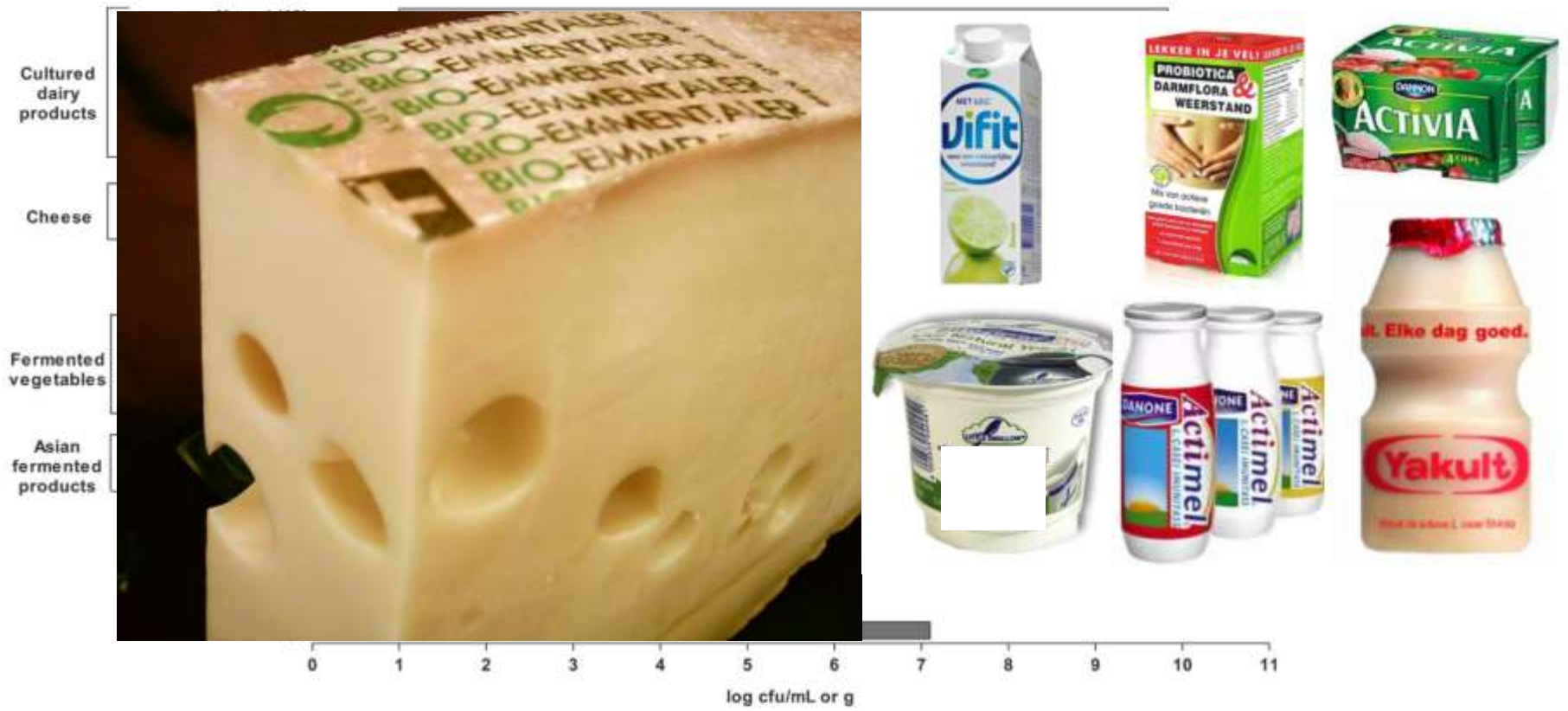


FIGURE 1 | Summary of lactic acid bacteria (LAB) counts in all fermented foods as reported in **Tables 1–8**. The bar plots represents a range (minimum to maximum) of counts found across the studies surveyed. The number of studies used here for each fermented food is shown in brackets. Products were excluded if they had no viable counts or when LAB counts were not reported. For yogurt, initial counts were used for products that had counts for more than one timepoint. For cheese, the products were divided by aging time (60 days) and were excluded if aging time was not reported.

Fermented Foods as a Dietary Source of Live Organisms

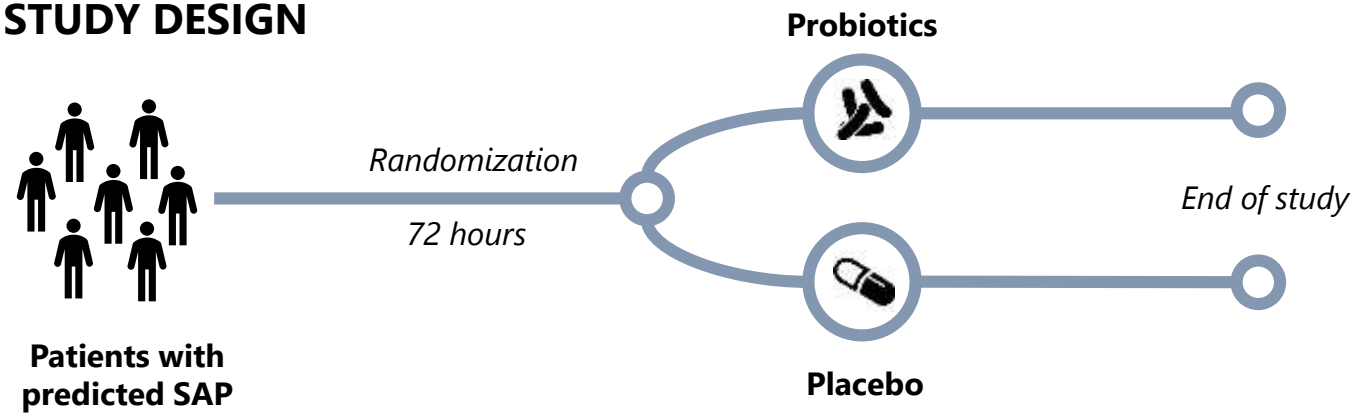
*Shannon Rezac, Cor Roen Kok, Melanie Heermann and Robert Hutkins**

probiotisch	10 log CFU/gr-ml		referentie
NB gefermenteerd en niet gepasteuriseerd	9-12	dagelijkse dosis bij dieet rijk aan gefermenteerde voeding	15
		belangrijke actieve ingredient(en)	
sommige kazen	3-9	*Propionibacterium freudenreichii* (Emmentaler)	16
'levende' yoghurt	1-10	*Lactobacillus, Bifidobacterium, Lactocccus, Streptococcus* (alle spp.)	17
gefermenteerde zuivel	4-9	*Lactobacillus, Bifidobacterium, Lactocccus, Streptococcus* (alle spp.)	18
kimchi, augurken en dergelijke	6-10	*Lactobacillus plantarum, Leuconostoc sp*	19
tempeh	3-9	*Rhizopus spp, Fusarium spp.* (plus gisten en melkzuurbacteriën)	20
miso en natto	2-7	*Penicillium spp.* en *Aspergillus spp.*	21
kefir (incl. kefiran)	6-9	melkzuur- en azijnzuurbacteriën en gisten op een polysacharide matrix	22
echt zuurdesembrood	6-8	*Lactobacilus casei, Bifidobacterium pseudocatelunatum*	18
zuurkool en olijven	4-8	*Lactobacillus spp, Leuconostoc spp.*	23
salami en ham	2-11	Lactobacillus plantarum spp.	24
gefermenteerde salsa	5-7	Lactobacillus fermentum	25
'levende' wijn	2-5	*Saccharomyces cerevisiae* (en soms ook melkzuurbacteriën)	26
'levend' bier	2-5	melkzuurbacteriën (bijv. Lambiek en Geuze)	27
gefermenteerde cacao	3-8	*Saccharomyces boulardii; Lactobacillus fermentum, L. plantarum*	28
kombucha	6-7	*Pichia; Bretanomyces; Zygosaccharomyces, Komagataeibacter, Gluconobacter*	29
prebiotisch			
		vorming microbioom (bij kinderen) met oplosbare vezels	30
cichorei en witlof	0.15-0.2 g/g	MAC (microbiotatoegankelijke koolhydraten, bijv. GOS en FOS)	31, 32
knoflook	0.09-0.16 g/g	MAC (microbiotatoegankelijke koolhydraten, bijv. GOS en FOS)	31
prei en schorseneer	0.04-0.1 g/g	MAC (microbiotatoegankelijke koolhydraten, bijv. GOS en FOS)	31
ui, asperge en artisjok	0.02-0.06 g/g	MAC (microbiotatoegankelijke koolhydraten, bijv. GOS en FOS)	31
tarwe	0.01-0.04 g/g	MAC (microbiotatoegankelijke koolhydraten, bijv. GOS en FOS)	31
aardappel en mais	n.a.		33
zoete aardappel		anthocyanines en fenolzuren resulteren in korteketenvetzuren	34
boerenkool en kruisvormigen		glucosinolaat geeft isothiocyanaat (rauw beter i.v.m. myrosinase)	35
avocado		oplosbare vezels	36
kombucha (thee)		glucuronzuur, azijnzuur, polyfenolen, fenolen, B-complex vitamines en foliumzuur	37
bosbes, thee en Koffie		polyfenolen	38
hennep en chiazaden		antioxidanten en flavonoïden,	39
walnoten		antioxidanten en bevordering boterzuurproductie door het microbioom	40
quinoa		antioxidanten en verlaging van de pH door productie korteketenvetzuur	41
paardenbloem en moerbeibes		microbioom versnelt ethanolafbraak en glucosemetabolisme	42
bonen		antioxidanten	43
fruit		oplosbare vezels, pectine en resistent zetmeel	44

Tabel 1. Voedingsproducten die een positieve werking kunnen hebben op het microbioom.

PROPATRIA - TRIAL

STUDY DESIGN



MULTI-STRAIN PROBIOTIC PRODUCT

- *Lactobacillus acidophilus* W70
- *Lactobacillus casei* W56
- *Lactobacillus salivarius* W24
- *Lactococcus lactis* W58
- *Bifidobacterium bifidum* W23
- *Bifidobacterium lactis* W52

These strains inhibit bacterial growth for all well-known pathogens that play a role in the necrosis of the pancreas

WHAT WENT WRONG?

- ✓ The mortality was significantly higher in the probiotic arm compared to the placebo arm (**16% vs. 6%** respectively)
- ✓ **Skewed randomization** – Patient were in a worse condition when allocated to the probiotic group
- ✓ **Poor timing** - bacterial overgrowth occurs within 24 hours after onset of symptoms, patients were allocated after 72 hours
- ✓ **Administrative** and **procedural** issues in the trial

WHAT WENT RIGHT?

- ✓ Mortality was within the expected range of **11-18%**
- ✓ Mortality in the placebo arm was **relatively low**
- ✓ **No infections** were confirmed to be caused by any of the probiotic strains administered
- ✓ An **independent monitoring committee** was installed to monitor safety of patients.
- ✓ **Underlying causal relationship** between the administered probiotics and the higher mortality rate observed in the PROPATRIA trial is lacking*

* Refs:
van Baal, M.C., 2014.

SAFETY OF PROBIOTICS

HYPOTHETICAL RISKS

- **Bacterial translocation** leading to systemic infections
- **Transfer of antimicrobial resistances genes** to more pathogenic bacteria
- Aberrant short- and long-term **immune stimulation** in susceptible populations
- Unwanted **metabolic activities** (e.g. lactic acidosis)

ACTUAL RISKS

- **No reports** of sepsis related to probiotic use in healthy persons
- Bacteraemia has been observed in isolated cases in patients with **severe underlying diseases**
- **No clinical evidence** in humans of transfer of antimicrobial resistance has ever been observed
- Adverse effects with probiotic consumption are limited to mild gastrointestinal symptoms, such as nausea, diarrhoea, flatulence (not statistically different compared to placebo).

622 *Studies*

24.615 participants receiving probiotics

- ✓ **No indication** that the number of reported adverse events (AEs) was increased in short-term probiotic intervention compared to the placebo
- ✓ **RR** 0.98; 95% CI: 0.93-1.04

57 *Studies*

5.642 infants (0-2y) receiving probiotics

- ✓ **No significant difference** in the number of AEs between probiotic and control groups.
- ✓ **Even at very high dosages**, study products were generally well tolerated (10^{12} cfu/day)

74 *Studies*

8.472 children (0-18y) receiving probiotics

- ✓ **No significant difference** between reported AEs in the probiotic and control group
- ✓ There were **no events of infection**, bacteraemia or sepsis associated with the administered probiotics

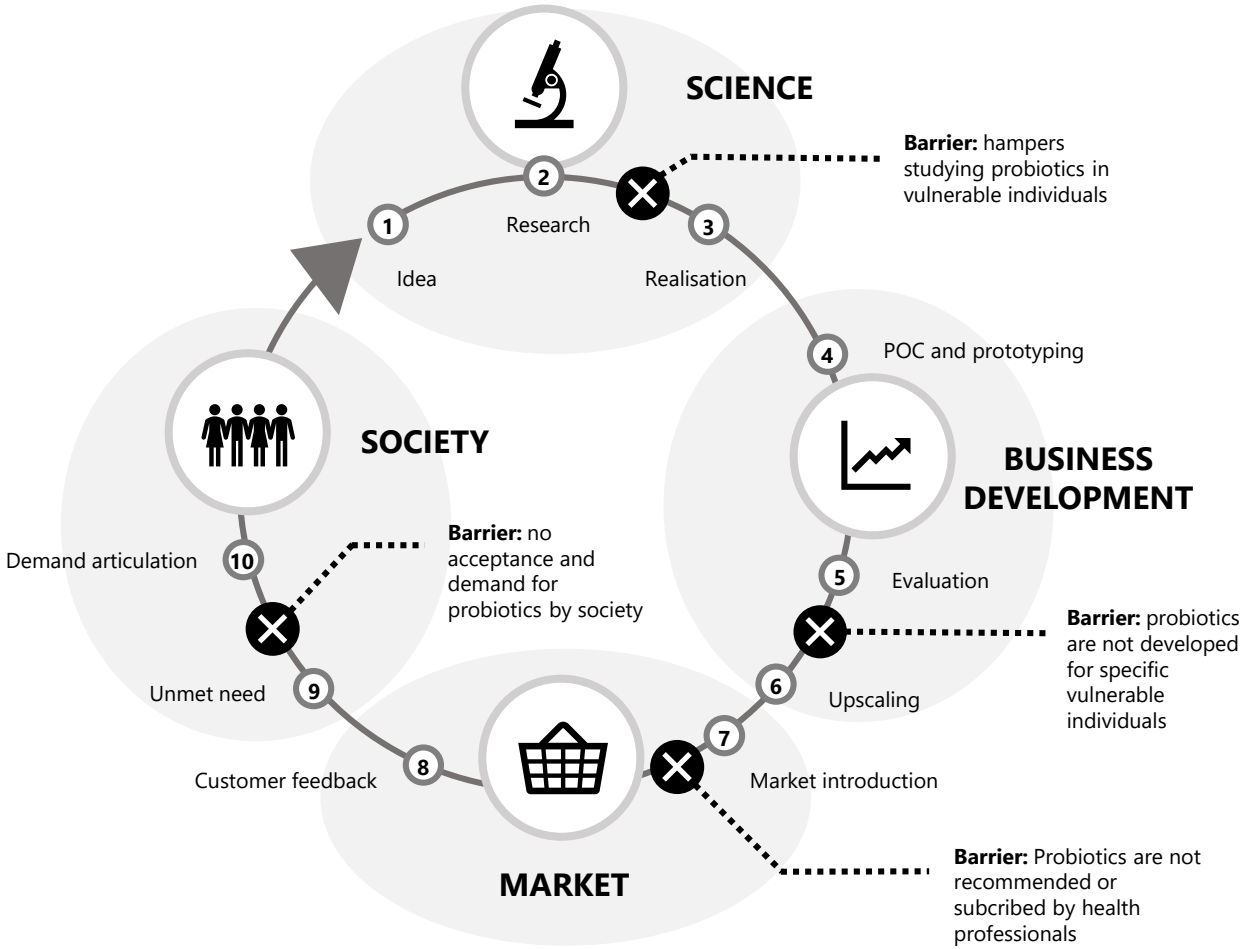
57 *Studies*

2.563 immune compromised adults receiving probiotics

- ✓ **None of the serious AEs** were related, or suspected to be related, to the probiotic product

Refs:
- van den Nieuwboer *et al.* 2014a, b, 2015
- Hempel *et al.* 2011

NEED FOR STANDARDIZATION



- Intake of probiotics is **not associated** with increased health risks
- **Structural- and/or incorrect safety reporting** limits making definitive conclusions
- The poor documentation of AEs does not mean probiotics are unsafe
- The lack of a clear safety profile **hampers innovation** in each domain of the valorisation cycle
- **Consensus is needed** amongst stakeholders regarding a standardized manner to document and report adverse events
- We suggest using the **Common Terminology Criteria for Adverse Events** (CTCAE) Version 5.0 (2017) → can be utilized for Adverse Event reporting and provides a grading (severity) scale for each AE term.