An overview of probiotic research

(human & mechanistic studies)

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Society of Dairy Technology
15 April 2016

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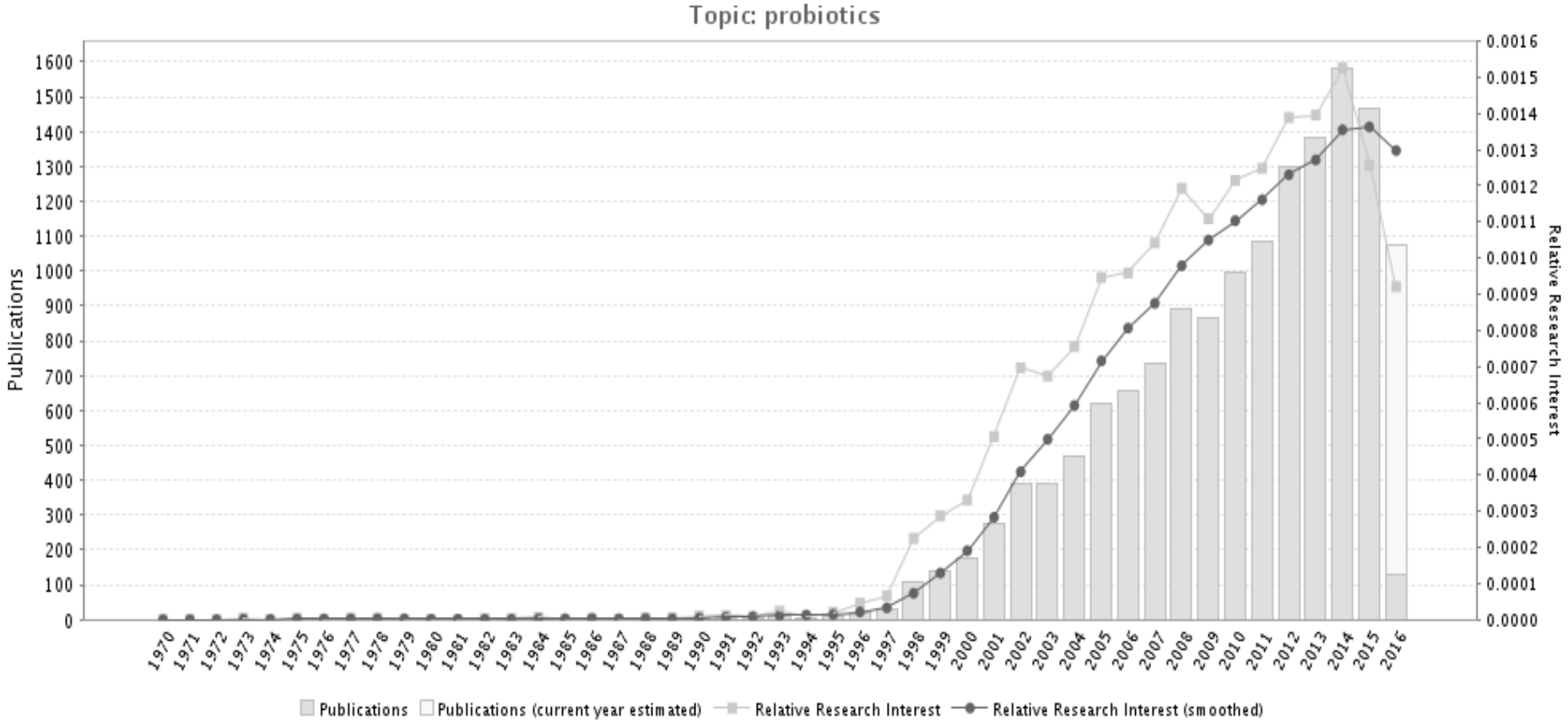
Published papers: ‘probiotics’

www.gopubmed.com



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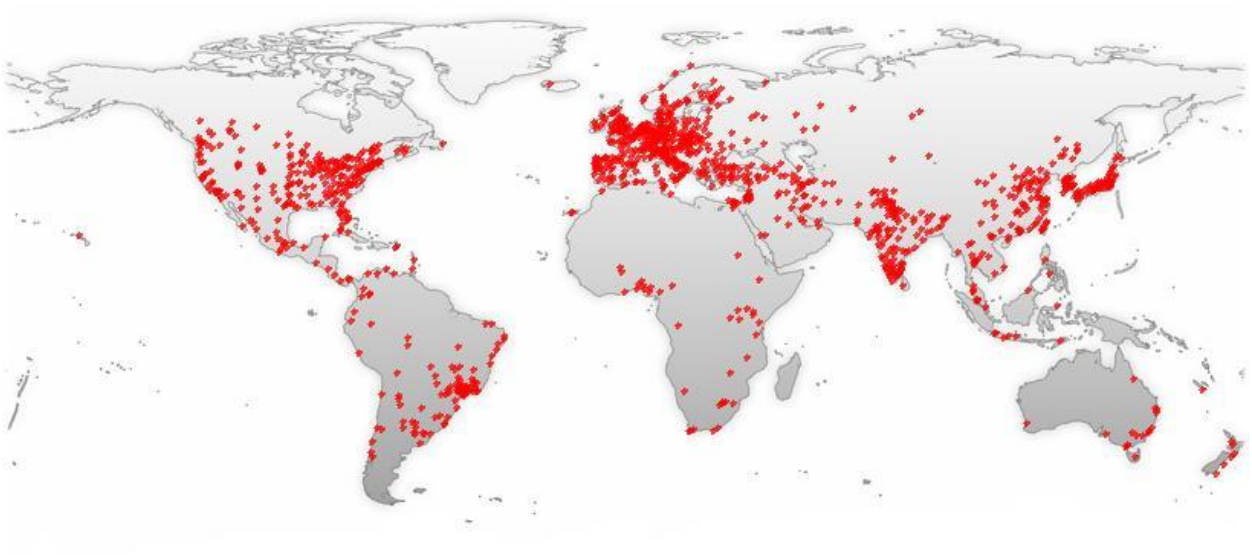
‘Probiotic’ research – who and where?

- Universities & research institutes
- Hospitals, surgeries

- Academics
- Healthcare professionals
- Industry scientists



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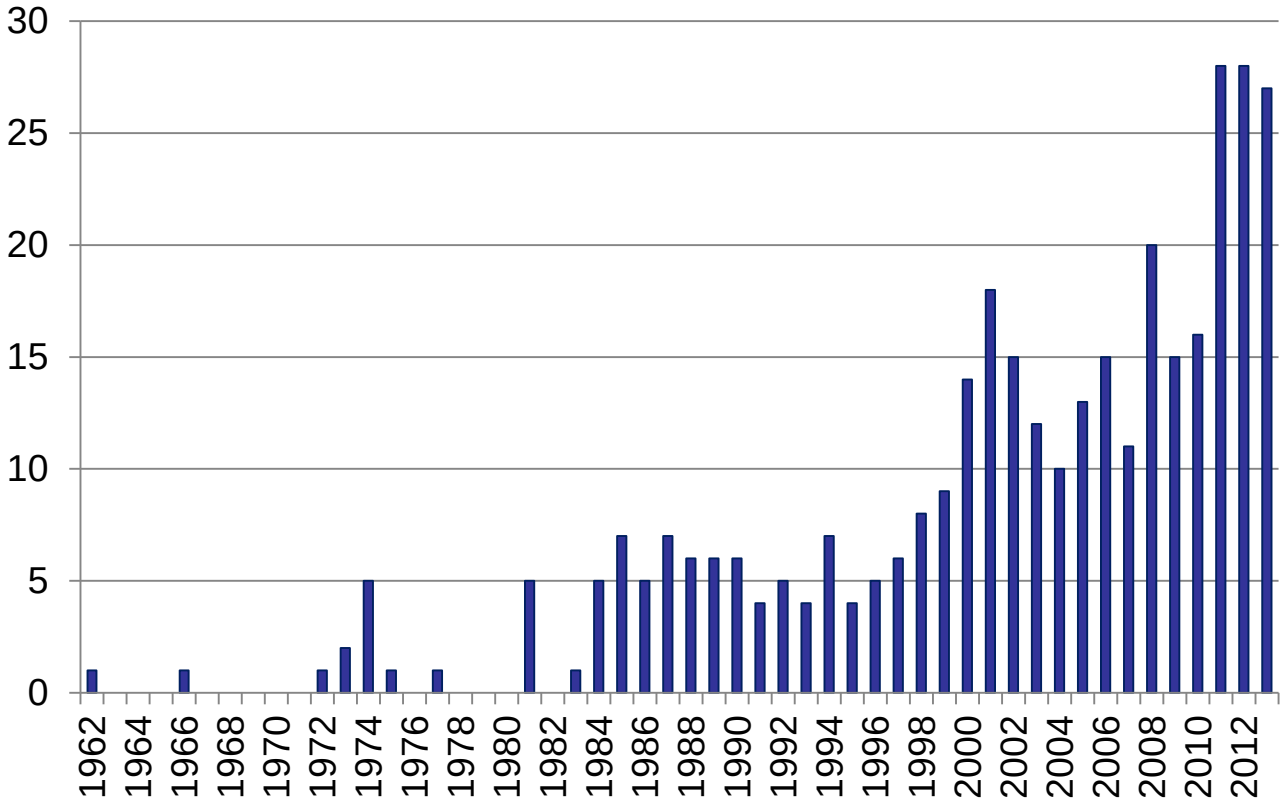
Lactobacillus casei Shirota



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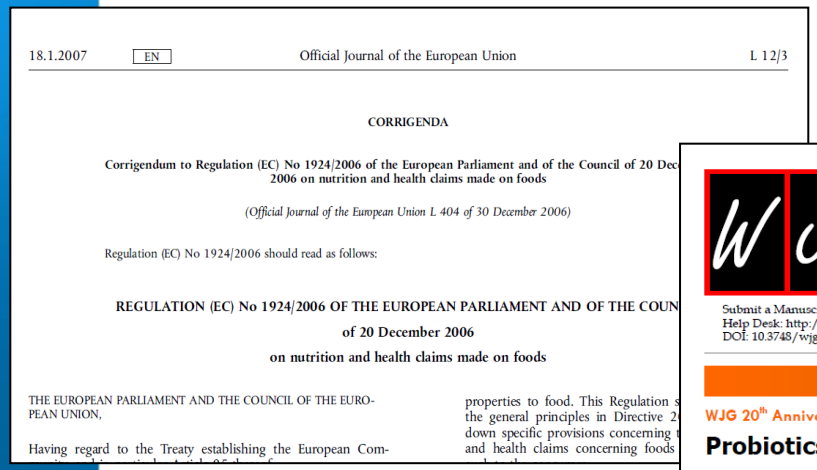
What has driven the research?

- The gut microbiota's influence on health and disease
- Demonstration of health benefits
- Commercial reasons



18.1.2007 EN Official Journal of the European Union L 12/3

CORRIGENDA

Corrigendum to Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 Dec 2006 on nutrition and health claims made on foods

(Official Journal of the European Union L 404 of 30 December 2006)

Regulation (EC) No 1924/2006 should read as follows:

REGULATION (EC) No 1924/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUN

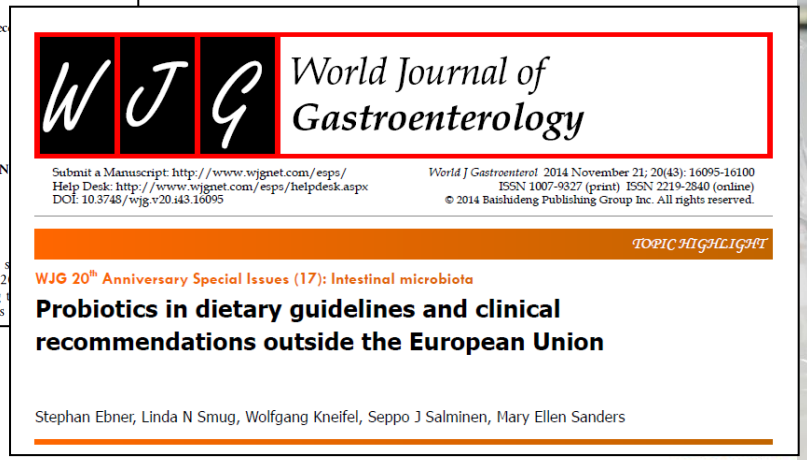
of 20 December 2006

on nutrition and health claims made on foods

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Com-

properties to food. This Regulation s
the general principles in Directive 2
down specific provisions concerning t
and health claims concerning foods



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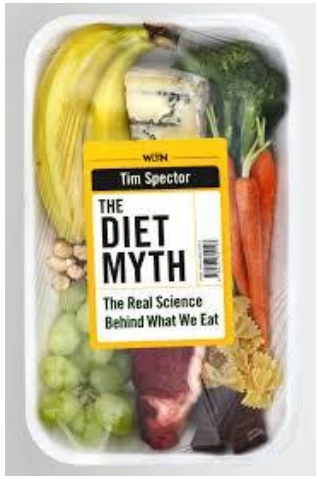
TOPIC HIGHLIGHT

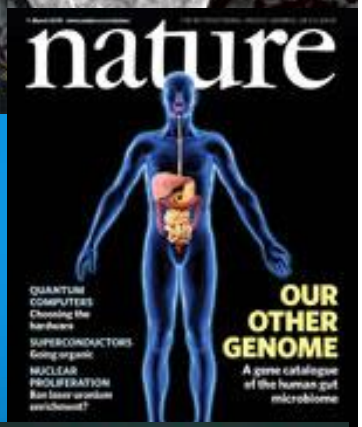
WJG 20th Anniversary Special Issues (17): Intestinal microbiota

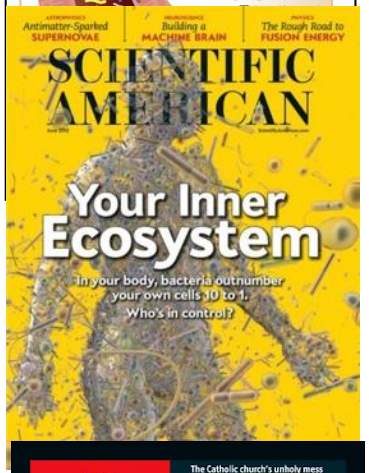
Probiotics in dietary guidelines and clinical recommendations outside the European Union

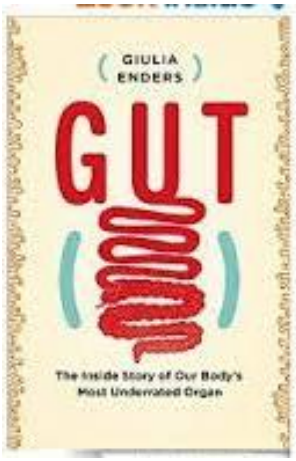
Stephan Ebner, Linda N Smug, Wolfgang Kneifel, Seppo J Salminen, Mary Ellen Sanders

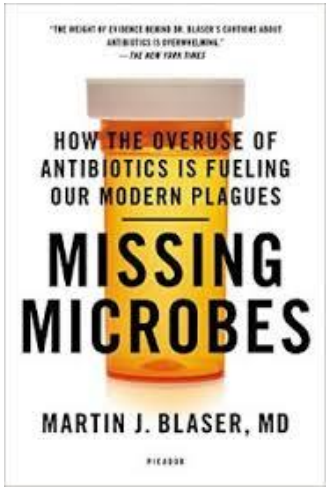
The gut and its microbiome

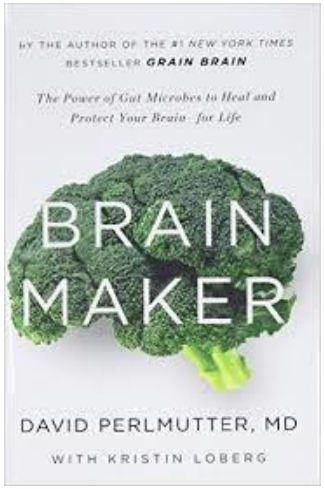


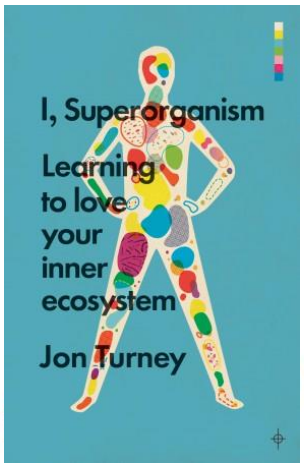












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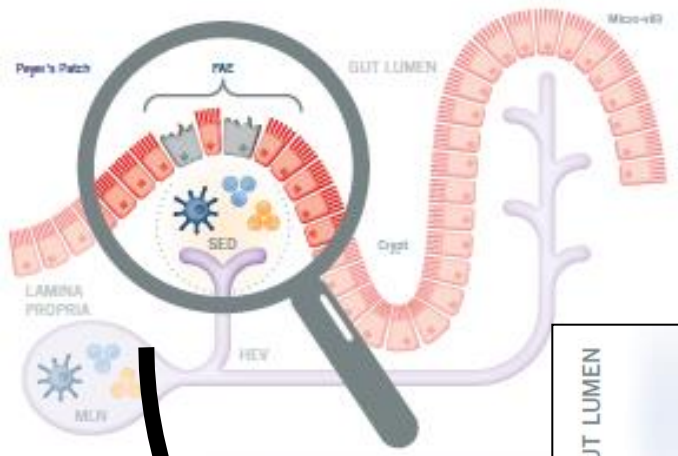
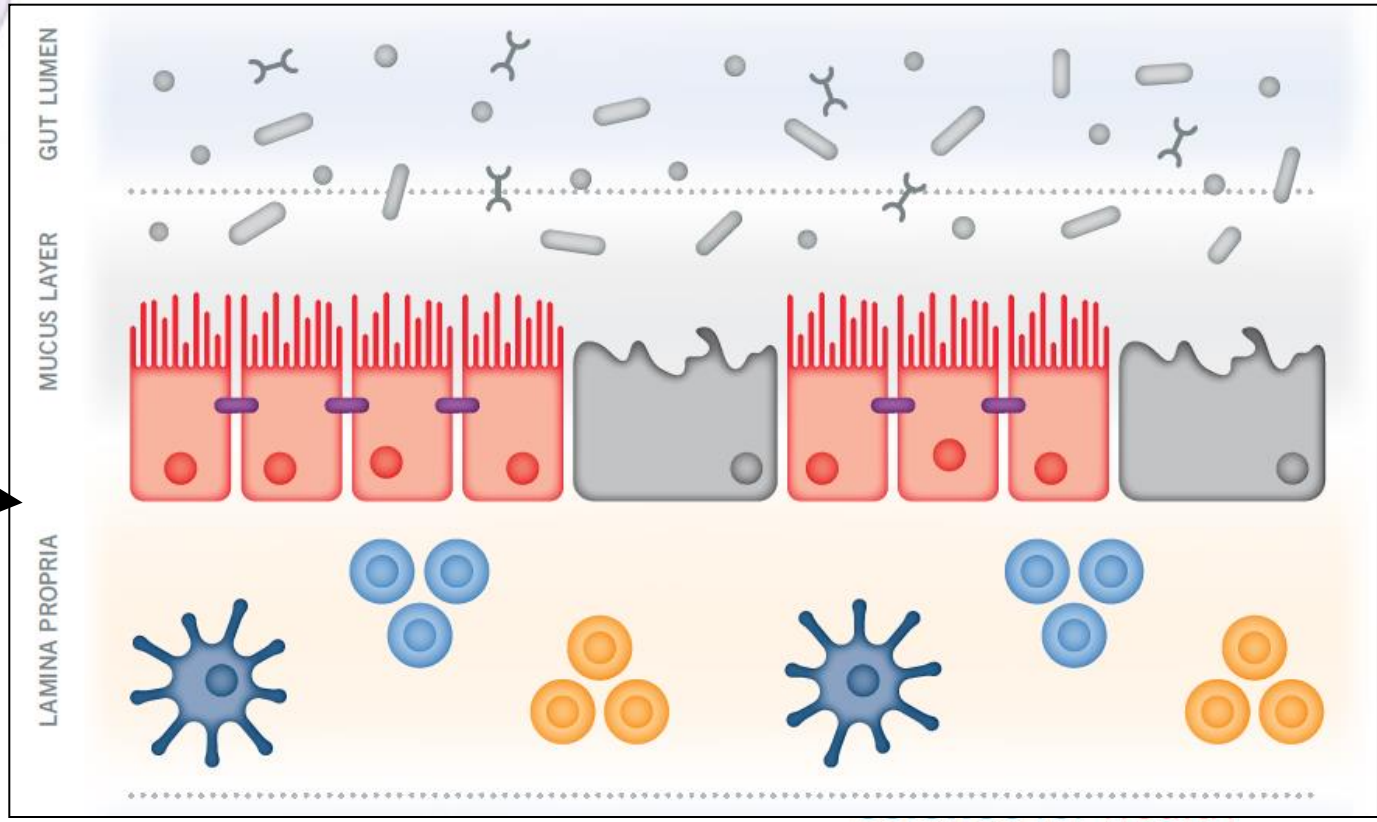
>70% of the immune system is in the gut



Gut-associated lymphoid tissue (GALT)



The gut microbiota

Disease linked to disturbances in the gut microbiota

- Low diversity
- Changed distribution of species
- Change in phyla ratio
- ‘Pathobionts’

Cause or effect?

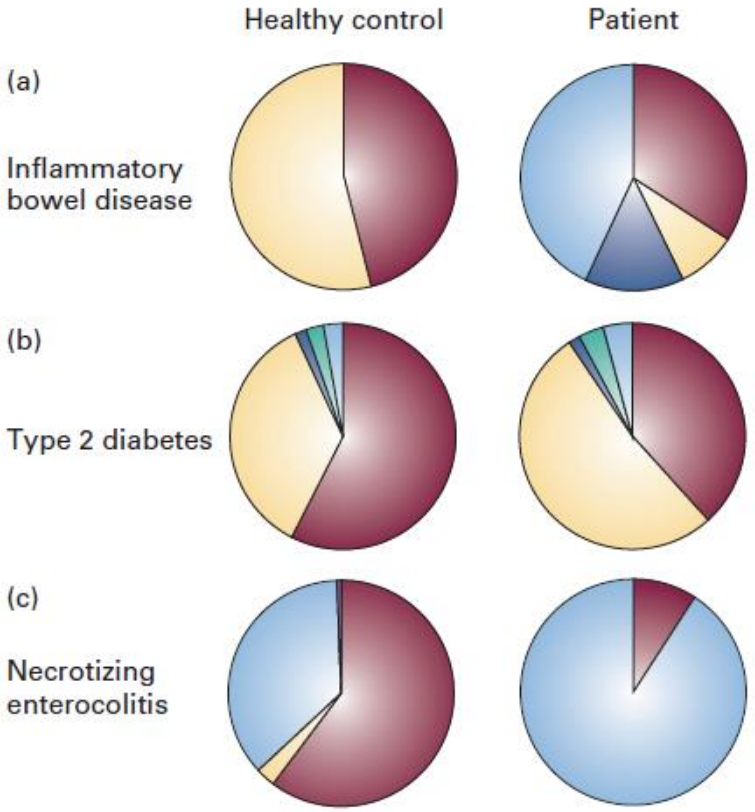
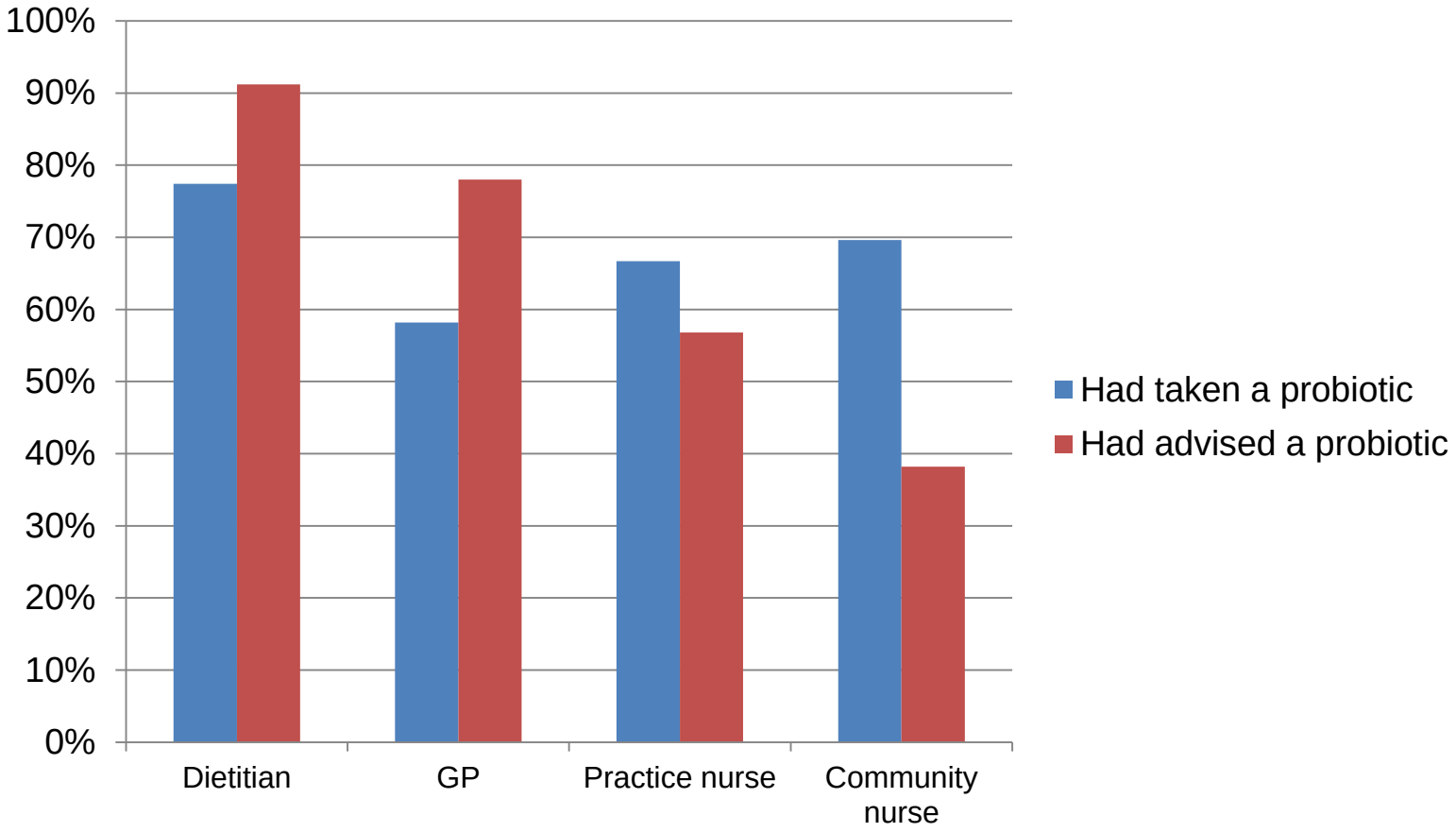


Fig. 6. Gut dysbiois associated with disease. Cause or effect? Microbial analysis of samples from patients and healthy controls showing relative abundance of predominant bacterial phyla. (a) Caecal samples and inflammatory bowel disease; (b) faecal samples and type 2 diabetes; (c) faecal samples and necrotising enterocolitis ■, *Firmicutes*; □, *Bacteroidetes*; ■, *Fusobacteria*; ■, *Actinobacteria*; ■, Verrucomicrobia; ■, *Proteobacteria*. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Microbiology, from Spor *et al.* [54], copyright 2011.

Primary care HCP and probiotics

Jordan et al (2015) *Practice Nursing* 26 (11):402-405



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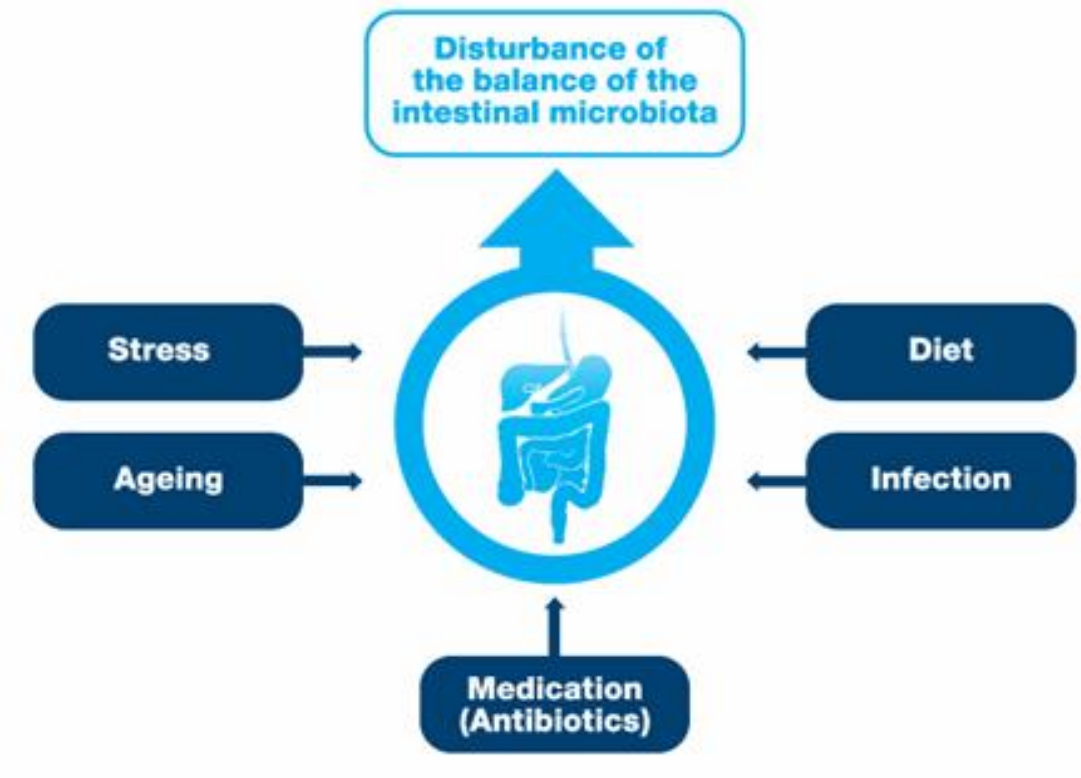
Probiotic recommendations by HCP

Johnson et al (2016) *Gastrointestinal Nursing* 14 (1):27-32

Advising patient to take a probiotic	
During/after antibiotics	63%
IBS symptoms	62%
Diarrhoea	37%
Generally run-down/vulnerable to infection	33%
Constipation	18%
Diverticulitis	17%
Ulcerative colitis	15%
Before travel abroad	13%
Elderly patients	13%
Mothers/babies with allergy risk	5%

Probiotic relevance today

- Our relationship with bacteria
- Life expectancy and health risks



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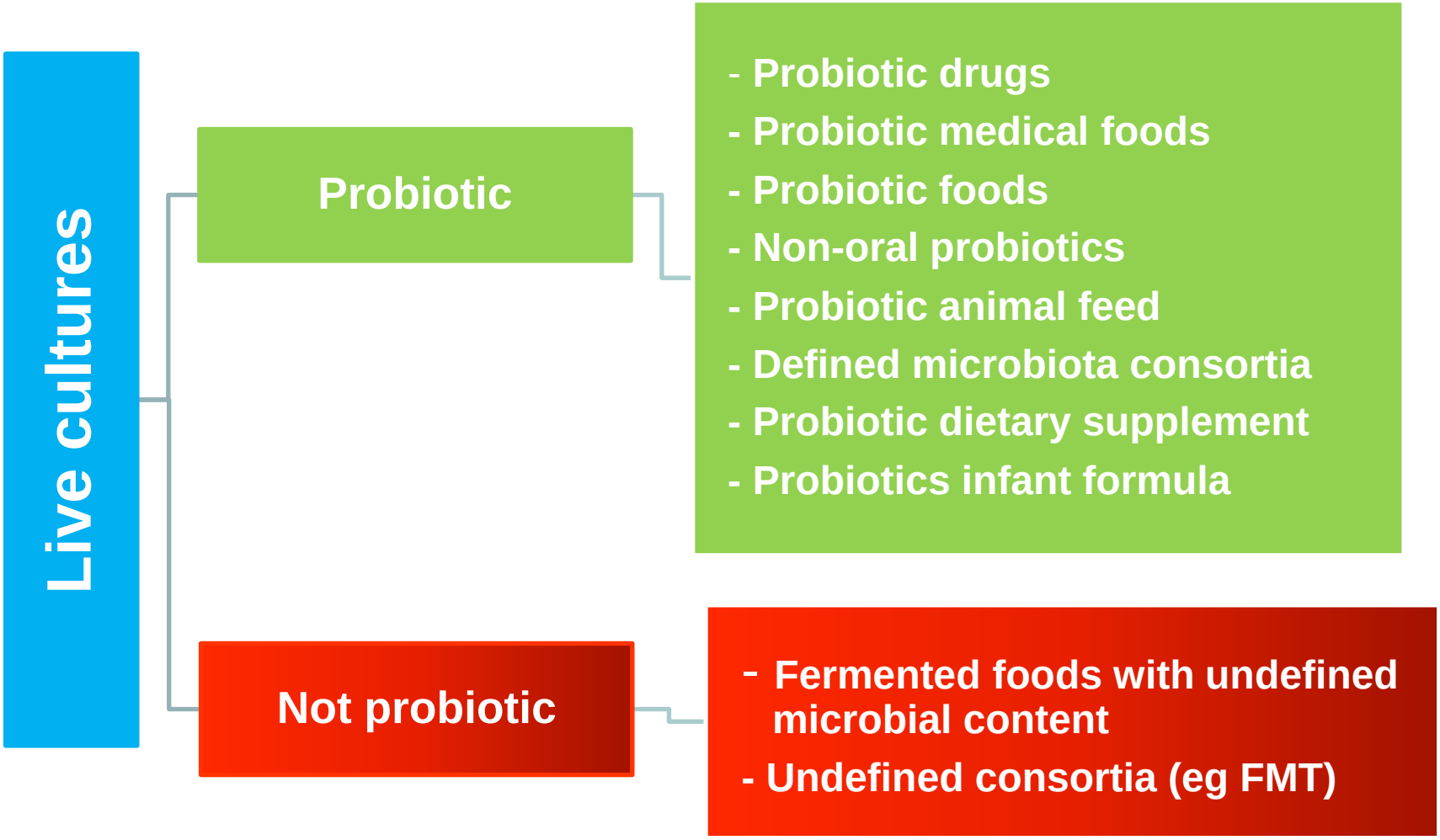
Scientific evidence

- *In vitro* studies
- *In vivo* (animal studies)
- Human studies
  - *Ex vivo*; observational
  - RCT and other intervention studies
  - Epidemiological studies
- Meta-analyses and systematic analyses
- HCP guidelines; economic reviews

Suggested framework for probiotic products

Hill et al (2014) *Nature Reviews Gastro Hepatol*



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Important criteria

- Safety
- Quality
- Gut survival
- Efficacy

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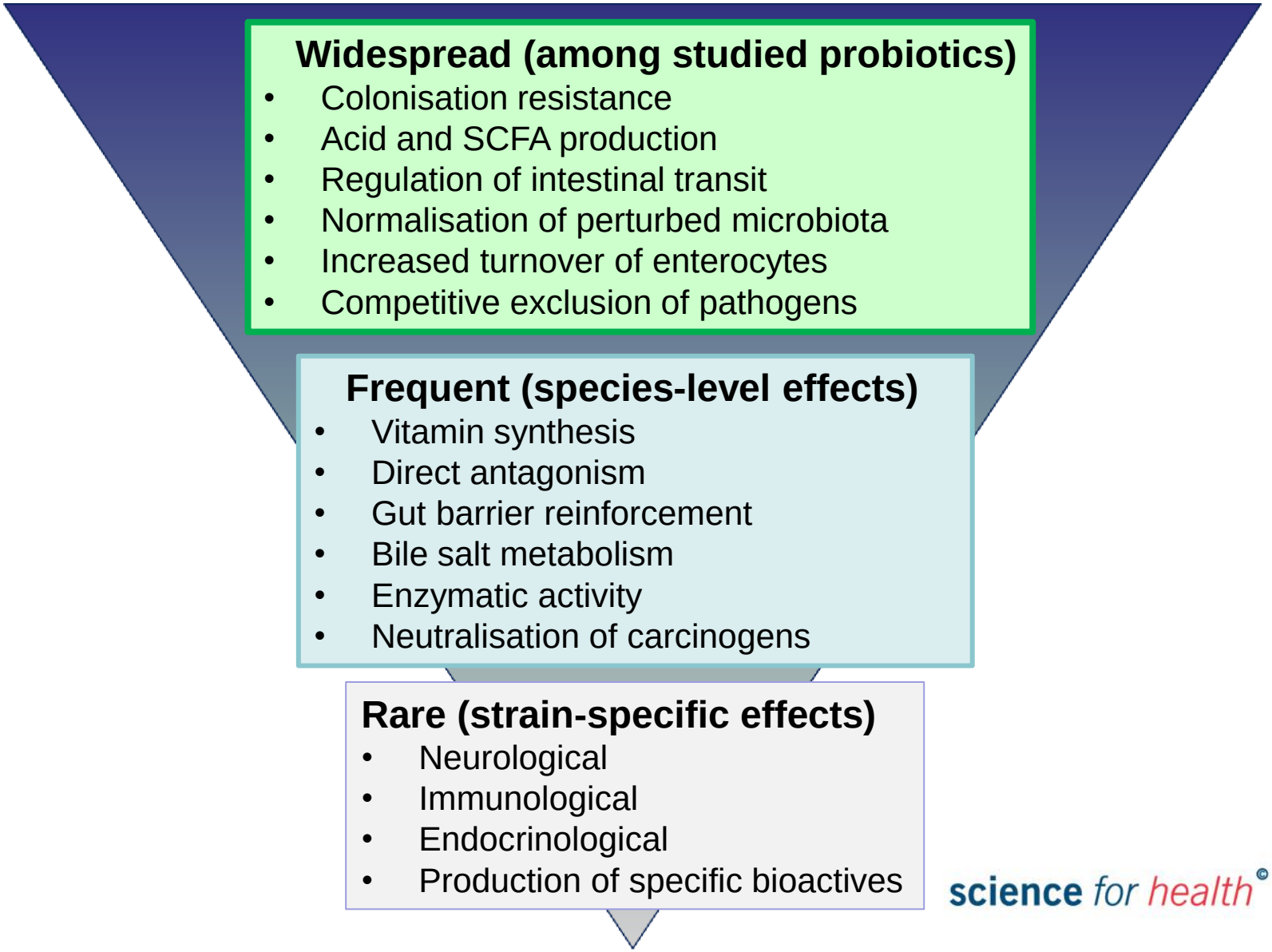
Probiotic mechanisms of activity

Hill et al (2014) *Nature Reviews Gastro Hepatol*



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The main research areas

Human trials and mechanistic studies

- Infections
  - Diarrhoea (including antibiotic-associated)
  - Other infectious disease (bacterial, viral, protozoal, adjuvant effects)

- Gut disorders
  - IBS, constipation, IBD, diverticulitis, short bowel syndrome
  - NEC, pre-term, infant colic

- Emerging areas of research
  - Allergy/atopy
  - Liver disease
  - Obesity-related /metabolic disease
  - Hypertension; CVD
  - Cancer
  - Urogenital
  - Gut-brain axis
  - Multi-drug resistant pathogens

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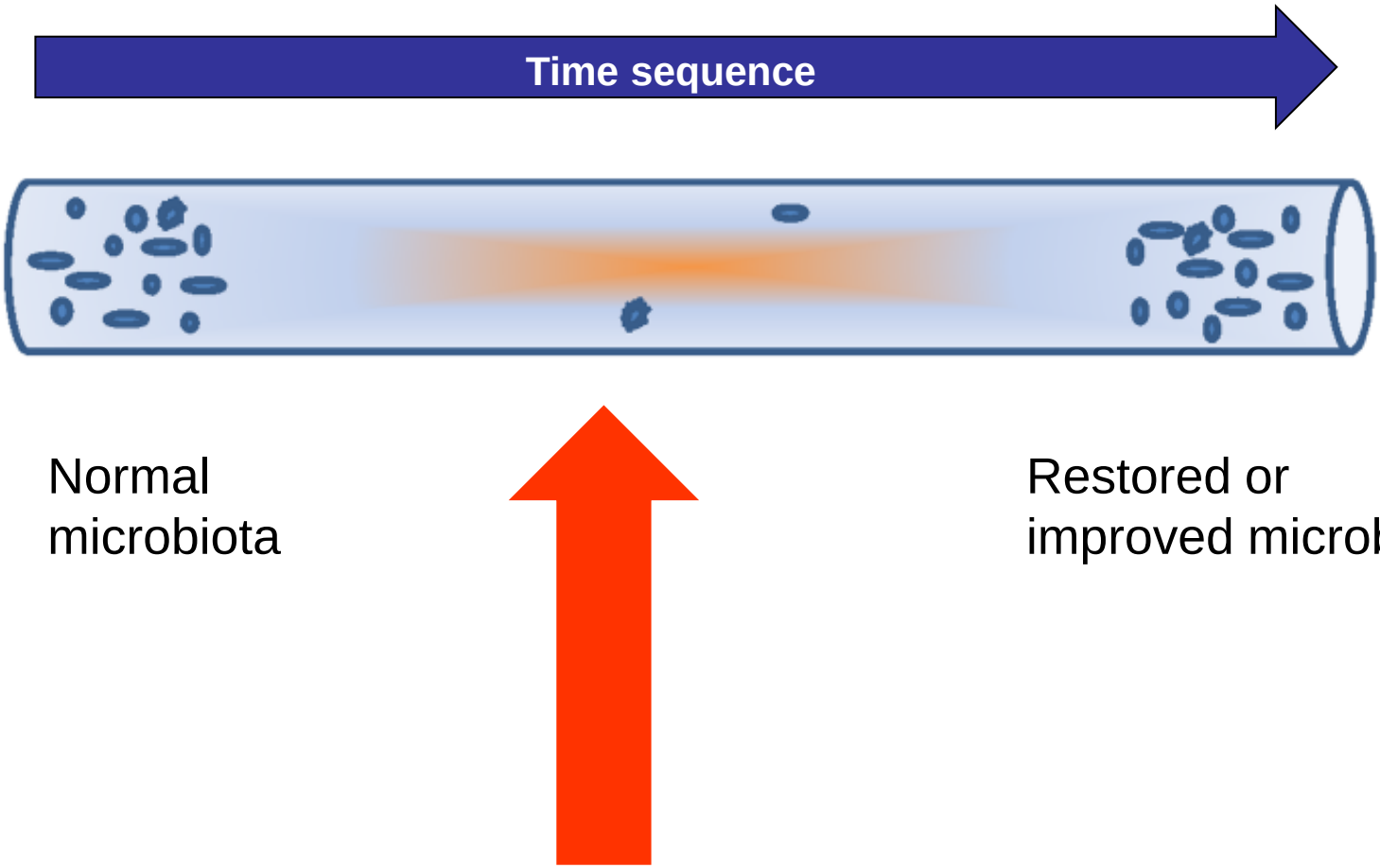
Antibiotic-associated diarrhoea (AAD)

McFarland LV (2014) *BMJ Open* 4:e005047



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AAD and *Clostridium difficile*

- A range of human studies: most (but not all positive)
  - heterogeneity of factors

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REVIEW

Probiotics for antibiotic-associated diarrhea: Do we have a verdict?

Iyad Issa, Rami Moucari

Most published RCT and meta-analyses suggest benefit

- Probiotics are available, low cost and safe
- Perhaps prophylactic use for specific populations
  - patients with history of AAD
  - patients with risk factors for development of CDAD.

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C. difficile & AAD: example study

Pirker et al (2013) *Food & Agric Immunol* 24(3): 315-330

- Open label trial, elderly patients on 3 wards at a general hospital
  - 340 patients on ABx: 1 bpd probiotic FMD during ABx + 3 d
  - 338 patients on ABx in matched control gp: not given probiotic

Endpoint	Probiotic group	Control group	Relative risk reduction with probiotic	*P*
AAD	17/340 (5%)	63/338 (18.6%)	73.2%	<0.001
CDI	1/340 (0.3%)	21/338 (6.2%)	95.3%	<0.001

Faecal analysis

- ABx reduced microbial diversity and decreased bifidobacteria
- LcS intervention reversed this & increased abundance of lactobacilli

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Recurrent *Clostridium difficile*

Lee L et al (2013) *IJPP* 8(4): 145-148

- Single-site, cohort-control study at Milton Keynes Hospital
- Patients (median age 78 years; 33% male) who had original *C. difficile* infection treated with:
  - ABx alone [n= 35]
  - or ABx + probiotic FMD [n=31]

Endpoint	Probiotic group	Control group	*P*
Recurrence of *C. difficile* infection	**3.2%**	**20.0%**	**0.007**

- Readmission to hospital for diarrhoea within 3 months:
  - 19.4% in probiotic group vs 35.1% in control group

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Infectious diarrhoea

Probiotic as treatment?

- Acute rotavirus diarrhoea in children: positive effect in reducing the duration (Ahmadi et al, 2015)
- Community acquired diarrhoea in children: may be efficacious in reducing duration and stool frequency during a diarrhoea episode (Applegate et al, 2013)
- Persistent diarrhoea in children: limited evidence suggesting effective in treating (Aponte et al, 2013)
- Acute infectious diarrhoea: used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. (Allen et al, 2010)

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Infectious diarrhoea

Probiotic as prevention?

Sur et al (2010) *Epidemiol Infect* 139:919-926

- DBPCRT in India
- N=3758 children, one to five years old
- One bottle a day for 12 weeks;
- Assessment for a further 12 weeks

Results

- ↓ incidence of diarrhoea (0.88 cases/child/year vs 1.029)
  - equivalent to reduction of diarrhoea risk of 14% ($P<0.01$)
- Range of pathogens detected in faeces
  - ↓ *Aeromonas* and *Cryptosporidium*

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Immune modulation

Van Baarlen et al (2011) PNAS 108 (Suppl1): 456204569

- DBPCRT: 6 h consumption, biopsies from duodenum; RNA hybridised to whole genome expression arrays
- Direct demonstration of modulation of cellular pathways
- Each strain induced differential gene-regulatory networks and pathways in the human mucosa
- Large person to person variation

Strain	Mucosal responses involved:
L. acidophilus **Lafti-L10**	regulation of immune response, hormone regulation of tissue growth and development, ion homeostasis
L. casei **CRL-431**	proliferation, Th1-Th2 balance, hormonal regulation of blood pressure
L rhamnosus **GG**	wound healing, IFN response, and ion homeostasis

Upper respiratory tract infection

Gleeson et al (2011) *Int J Sport Nutr Exercise Metab* 21:55-64

- 86 elite athletes at Lougborough University
- 58 completed 16 weeks of probiotic or placebo

Endpoint	Probiotic group	Placebo group	*P*
Proportion subjects with ≥ 1 week URTI symptoms	0.66	0.90	0.021
Mean number of URTI episodes	1.2 ± 1.0	2.1 ± 1.2	< 0.01

Hao et al (2015; Cochrane review). Moderate quality evidence that probiotics:

- ↓ number of people who develop a URTI (OR: 0.57; 95% CI: 0.37-0.76).
- also probably ↓ URTI duration by ca. 2 days

Healthcare costs

Lenoir-Wijnkoop et al (2015) *PlosOne* 10(4):e0122765

- Rationale: probiotics reduce duration and number of common respiratory tract infections and associated antibiotic prescriptions.

- Health economic analysis in France
  - Virtual age- and gender- standardised population model. Compared generalised probiotic use vs none during winter, using results from two previous reviews, and based on 2011-2012 flu season

- Generalised probiotic use estimated to save

	Cochrane data	YHEC data
CRTI-days	6.6M	2.4M
Antibiotic courses	473,000	291,000
Sick leave days	1.5M	581,000

- Economic impact on NHS. Estimated savings of
  - €37.7 M (Cochrane)
  - €14.6 M (YHEC)

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IBS symptoms & probiotics

- The link between the gut microbiota and IBS
- The range of IBS trials (Mazurak et al al, 2015)
- Example systematic review: management of lower GI symptoms in clinical practice (Hungin et al 2013)
  - **High evidence** : specific probiotics help reduce overall symptom burden and abdominal pain in some patients
  - **Moderate evidence:** specific probiotics help relieve overall symptom burden in some patients with IBS-D, and reduce bloating/distension and improve bowel movement frequency/consistency in some IBS patients. Sometimes led to improvement in quality of life.
- Clinical guidelines

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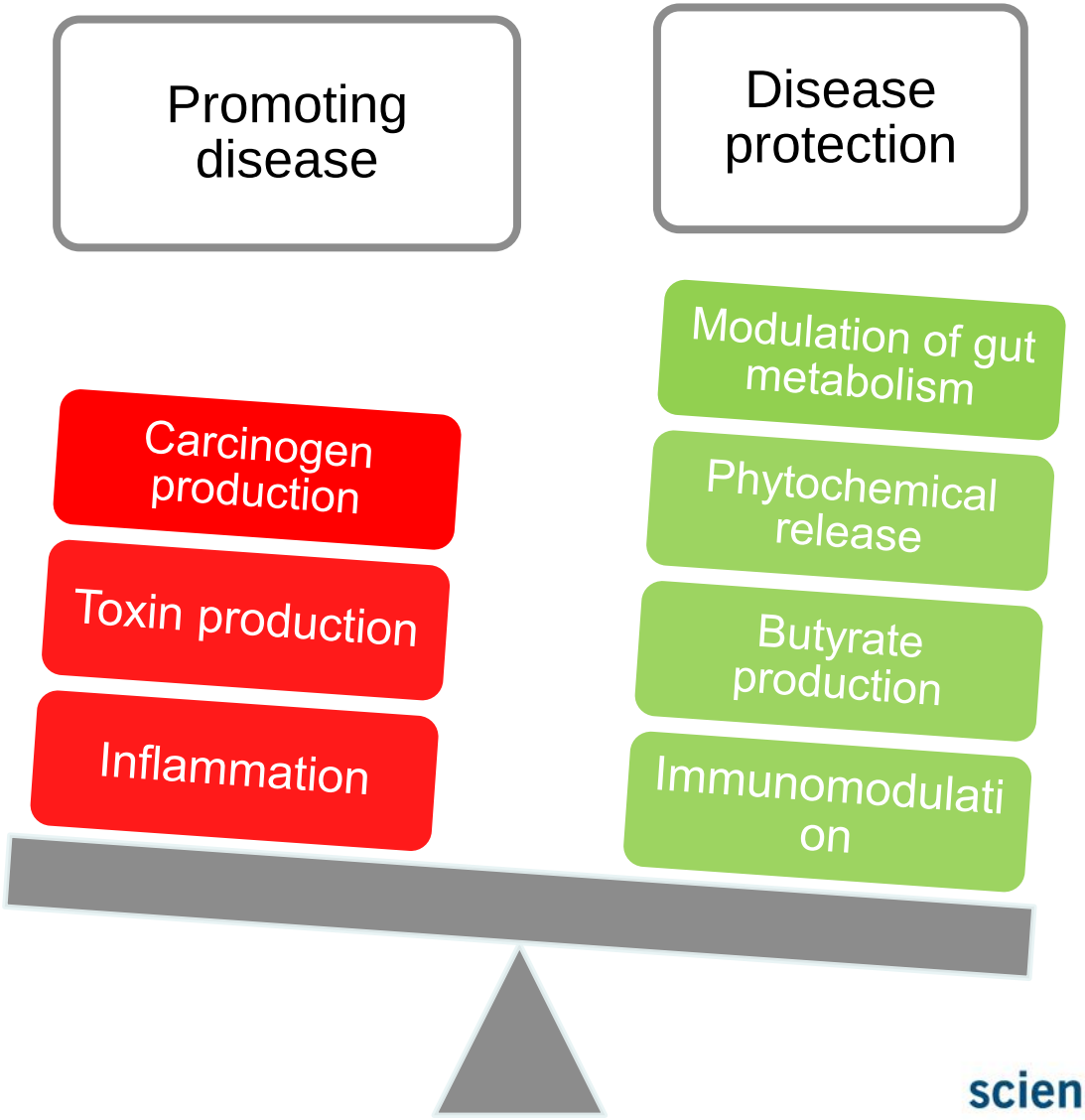
The gut microbiota and cancer

Friend or foe? (after Flint et al, 2012)



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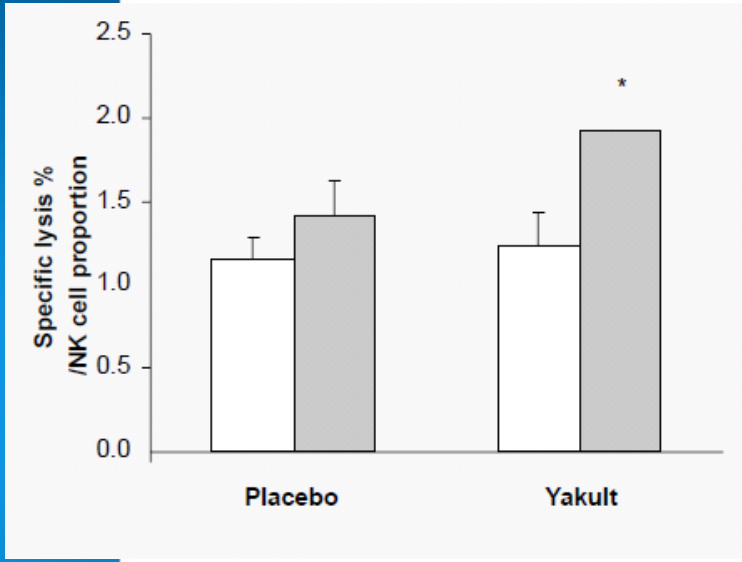
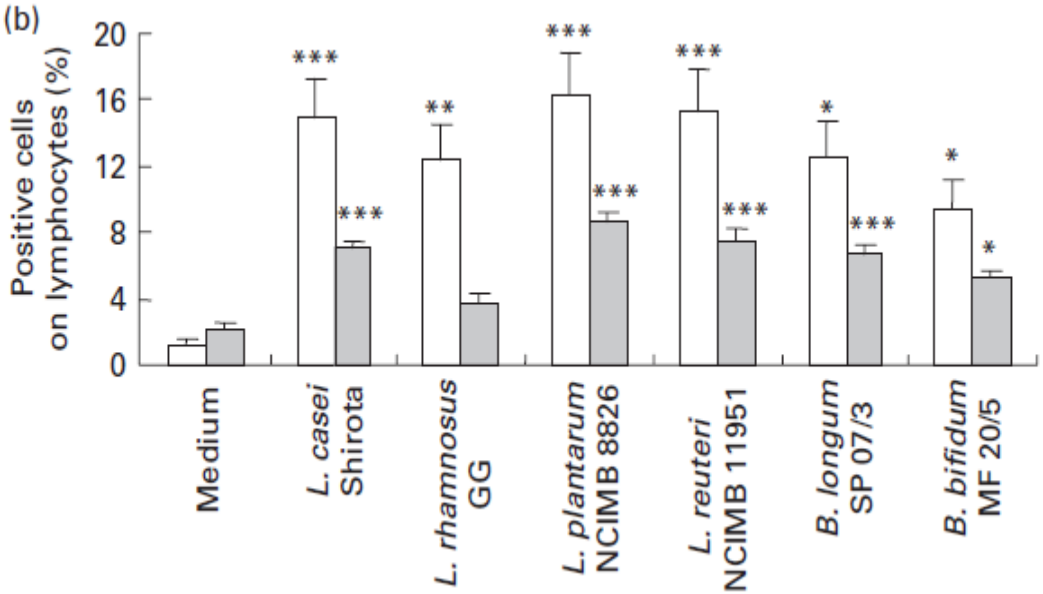
Natural killer cell activity

Dong et al (2013) *Eur J Nutr* 52:1853-1863
Dong et al (2012) *Br J Nutr* 108:459-470





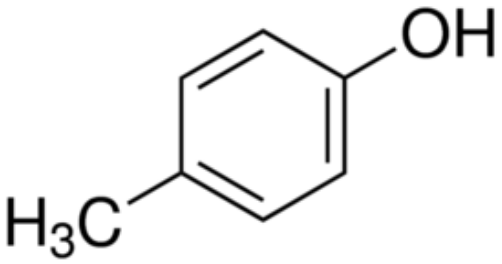
Metabolism in the gut

De Preter et al (2007) *Am J Physiol* 292: 358-368

- Placebo-controlled, crossover study in healthy people (n=20) given 4 weeks interventions with either:
  - Prebiotic (oligofructose enriched inulin)
  - *Lactobacillus casei* Shirota
  - *Bifidobacterium breve* Yakult

- Quantification of potentially toxic metabolites in the colon
  - MS of urine following consumption of stable radioactive isotope – labelled biomarker: (lactose [$^{15}N^{15}N$]ureide)
  - MS of faeces: Measurement of *p*-cresol

- Probiotic associated with
  - Significant reduction in *p*-cresol
  - Trend for reduced urinary ^{15}N excretion



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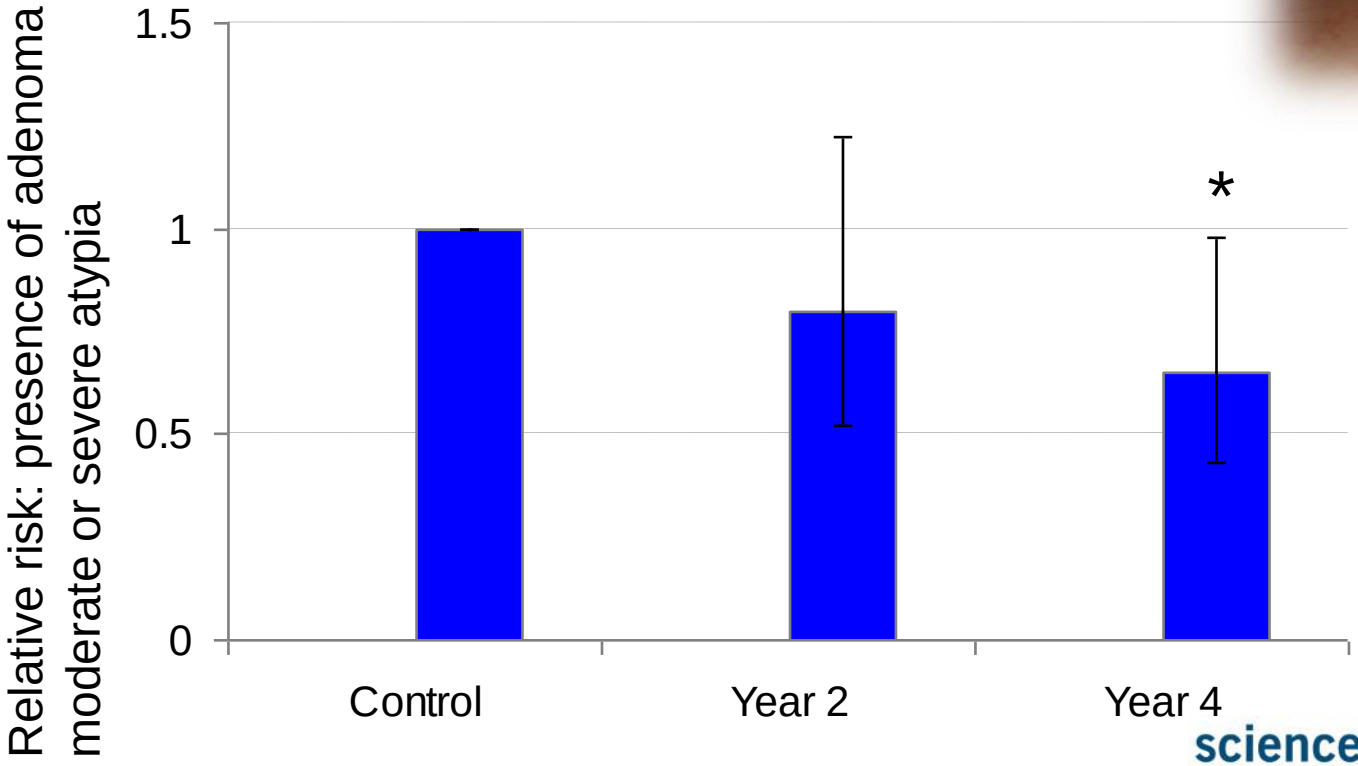
Colorectal cancer

Ishikawa et al (2005) *Int J Cancer* 116: 762-767

- Patients with previous surgical removal of ≥ 2 CRC tumours
- Four year interventions:
  - Probiotic +/- wheat bran cf. no intervention



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Cancer: case control population studies

Breast cancer (Toi et al (2013) *Curr Nutr Food Sci* 9:194-200)

- 306 adult patients cf. 662 matched controls
  Diet, lifestyle etc assessed (questionnaire & interview)

- ORs associated with *L. casei* Shirota beverage consumption (≥ x4 per wk cf < 4): 0.65 (p=0.048)

Superficial bladder cancer (Ohashi et al (2002) *Urol Int* 68:273-280)

- 180 cases (mean age 67 y) from 7 hospitals vs 445 gender/age matched controls

- ORs for superficial bladder cancer
  - Smoking: 1.61 (CI 1.10-2.36)
  - Previous intake of fermented milk drink (10-15 y ago)
    - 1-2 times per week: 0.46 (0.27 – 0.79)

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