Probiotika og prebiotika

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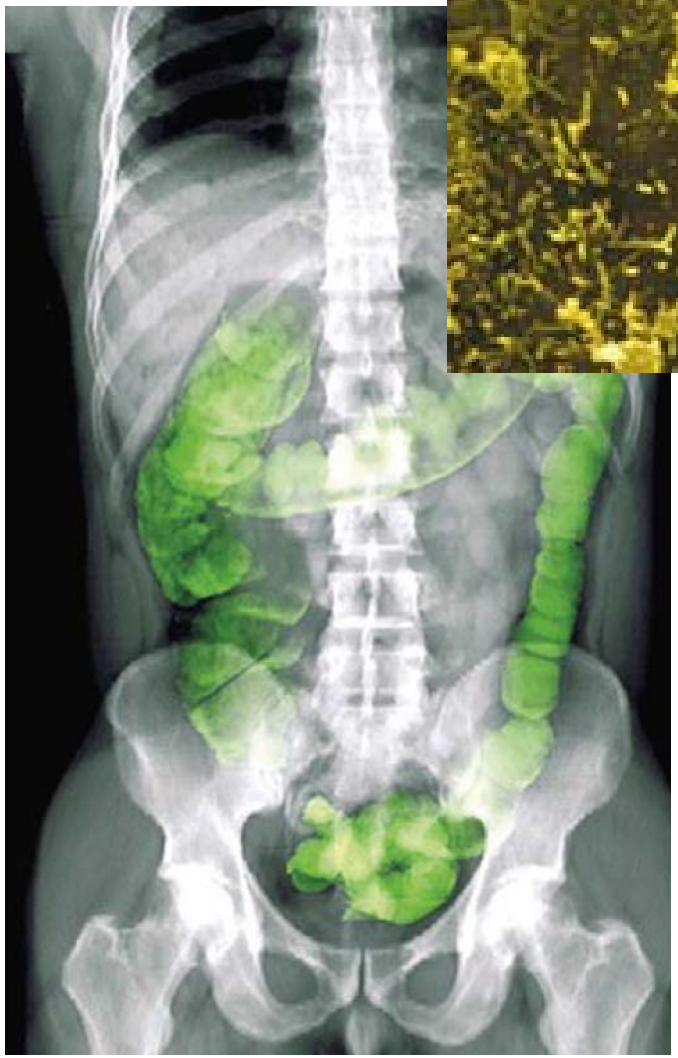
DSKE, Århus, 2. marts 2011

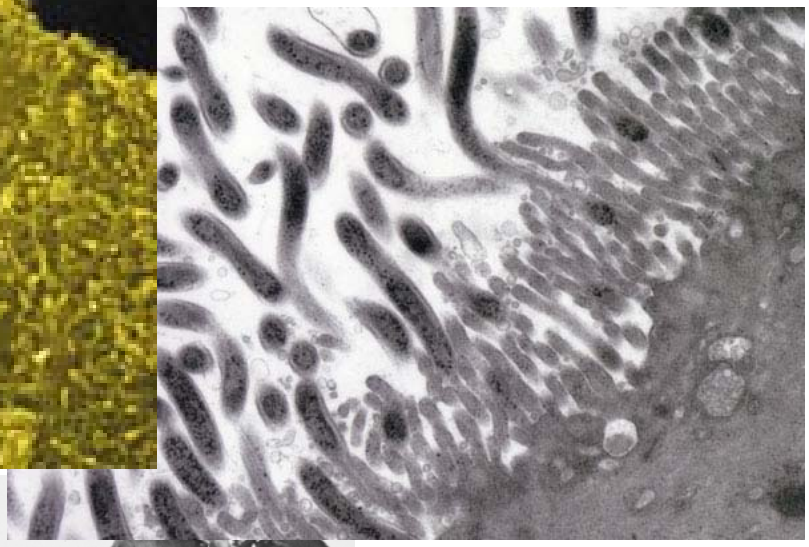
Menu

- Livet i tarmen
- Probiotika
  - Hvad har vi?
  - Hvem skal have det?
- Prebiotika
  - Hvor er det?
  - Hvad kan vi bruge det til?
- Sammenfatning

Livet i tarmen



Protozoer



Parasitter

Svampe

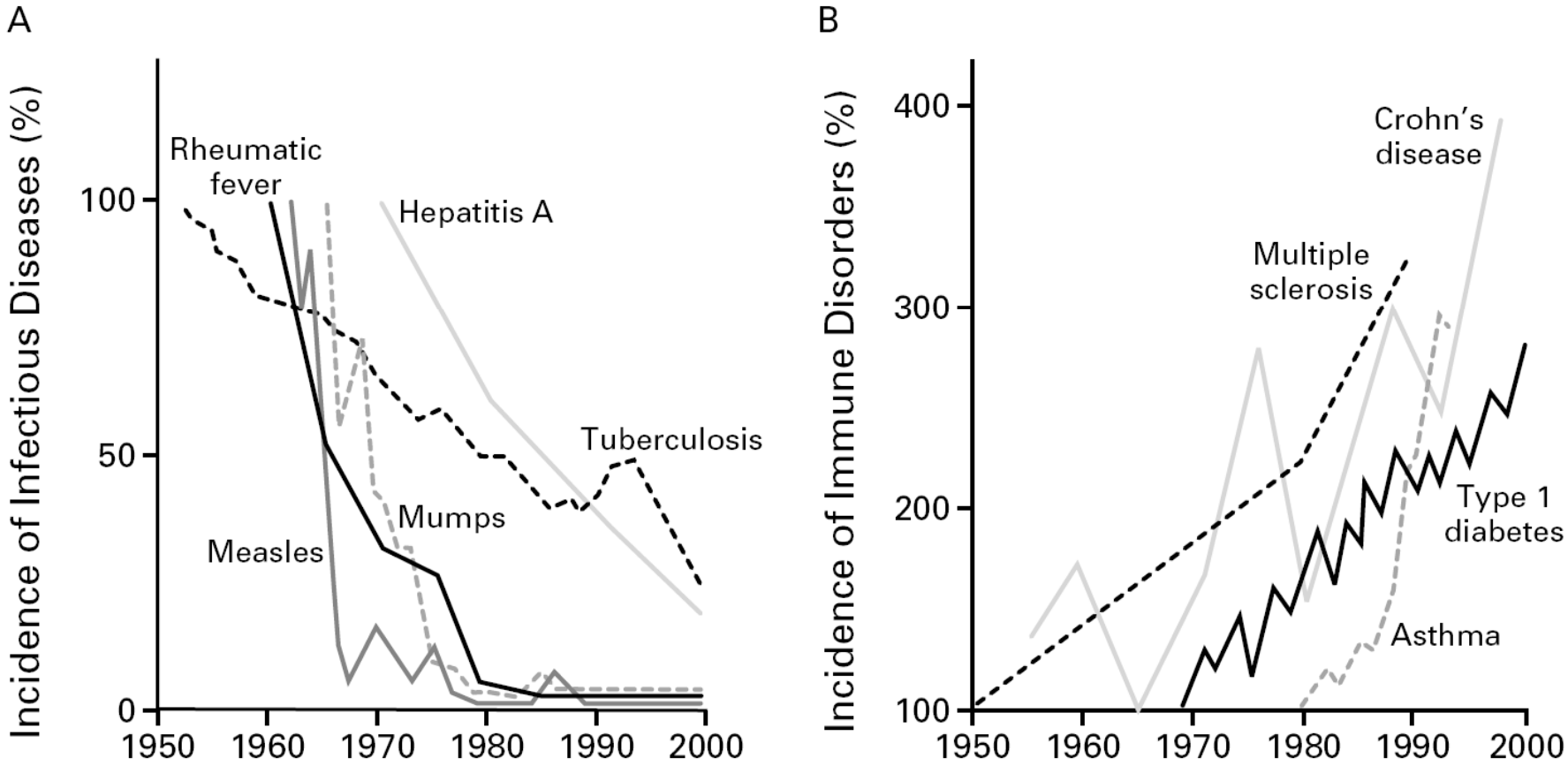
Er det os der går med hunden eller hunden der går med os?

De Eneste To, 2010

Livet i tarmen

- 10^{12} organismer/ml tarmindhold
- **Bakterier**, svampe, parasitter, protozoer
- ~ 1000 arter
- Grundlægges i første levemåneder
- ”Core” microbiota
- Udvikling af immunologisk tolerance

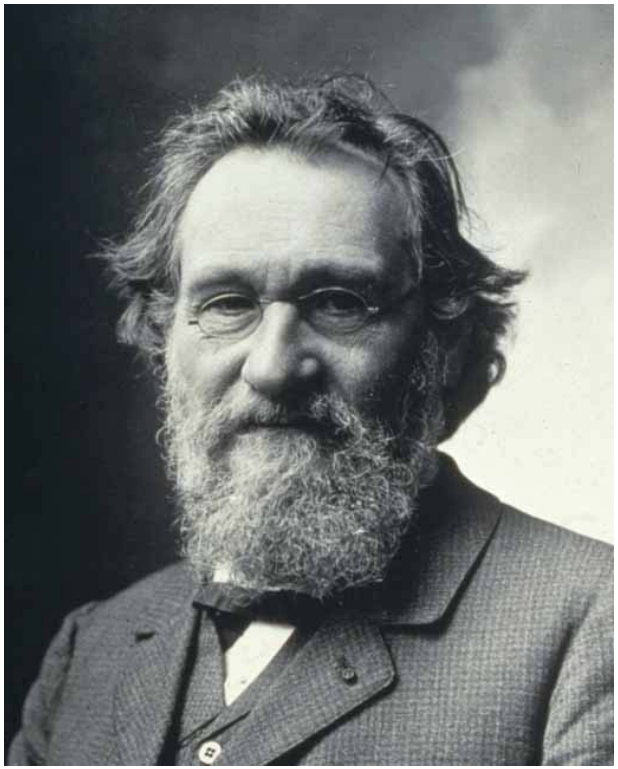
Preidis GA, Gastroenterology 2009;136:2015



Omvendt forhold mellem forekomsten af typiske infektionssygdomme og immunbetingede sygdomme i perioden 1950-2000.

Bach, N Engl J Med 2002;347:911

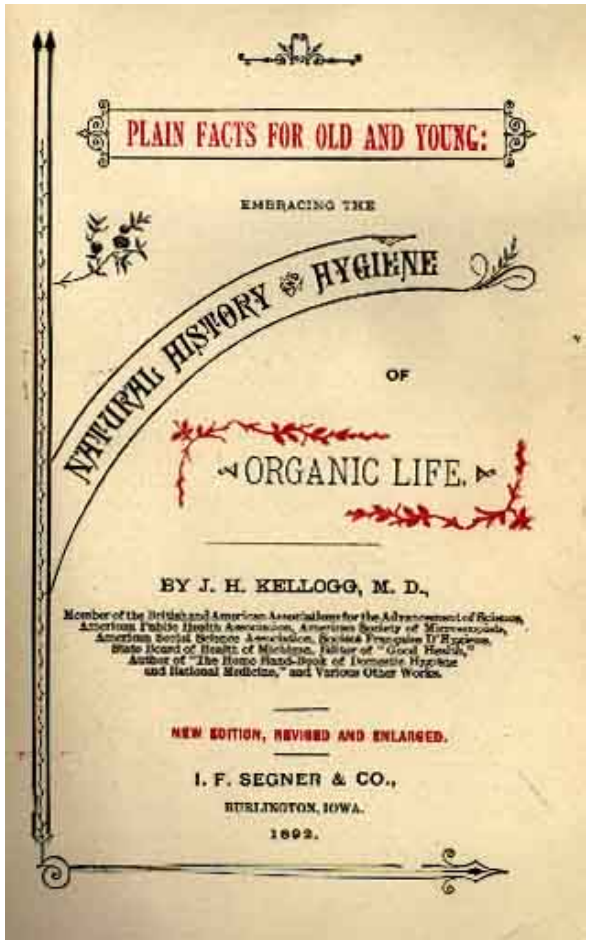
Historie



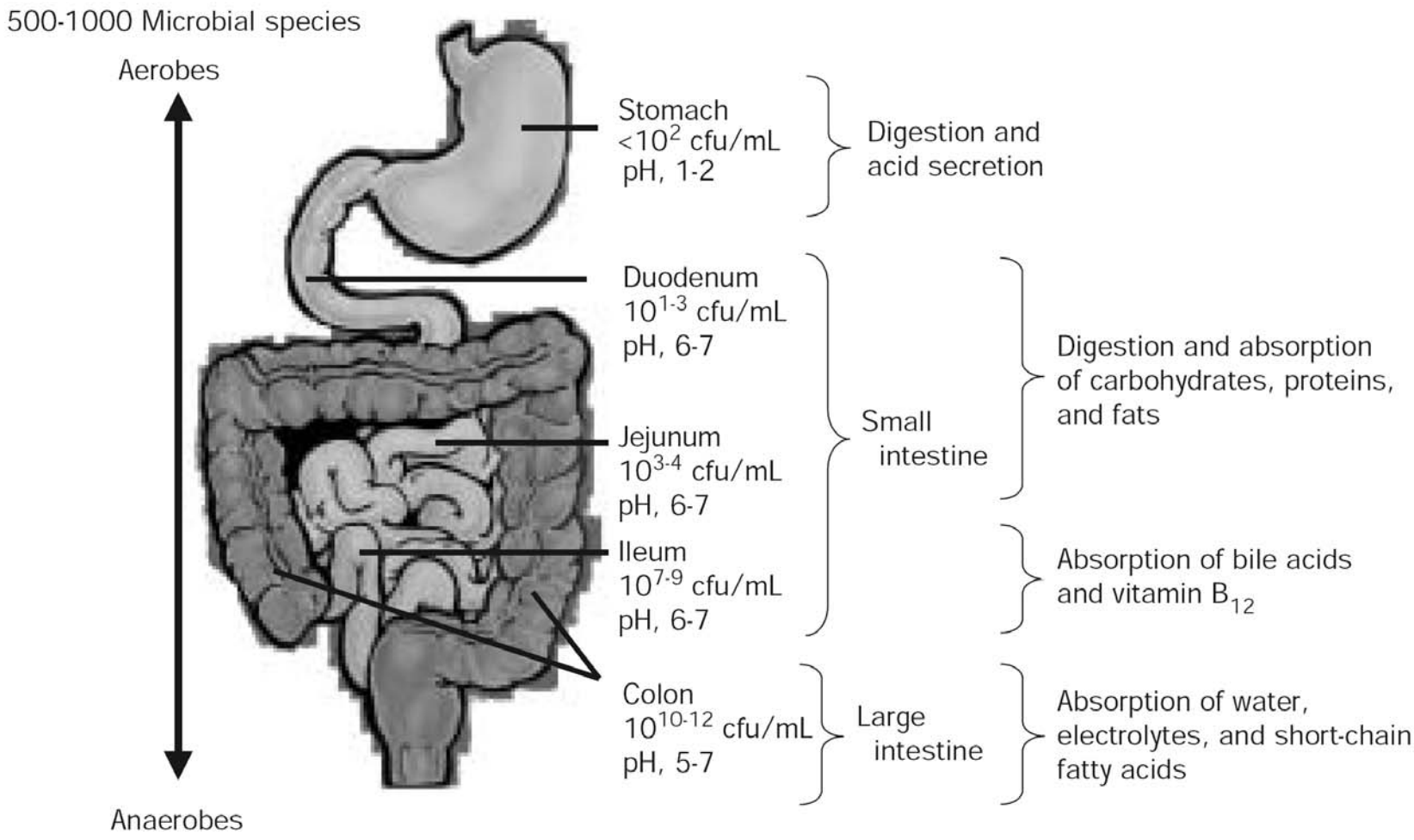
1900

1950

2000

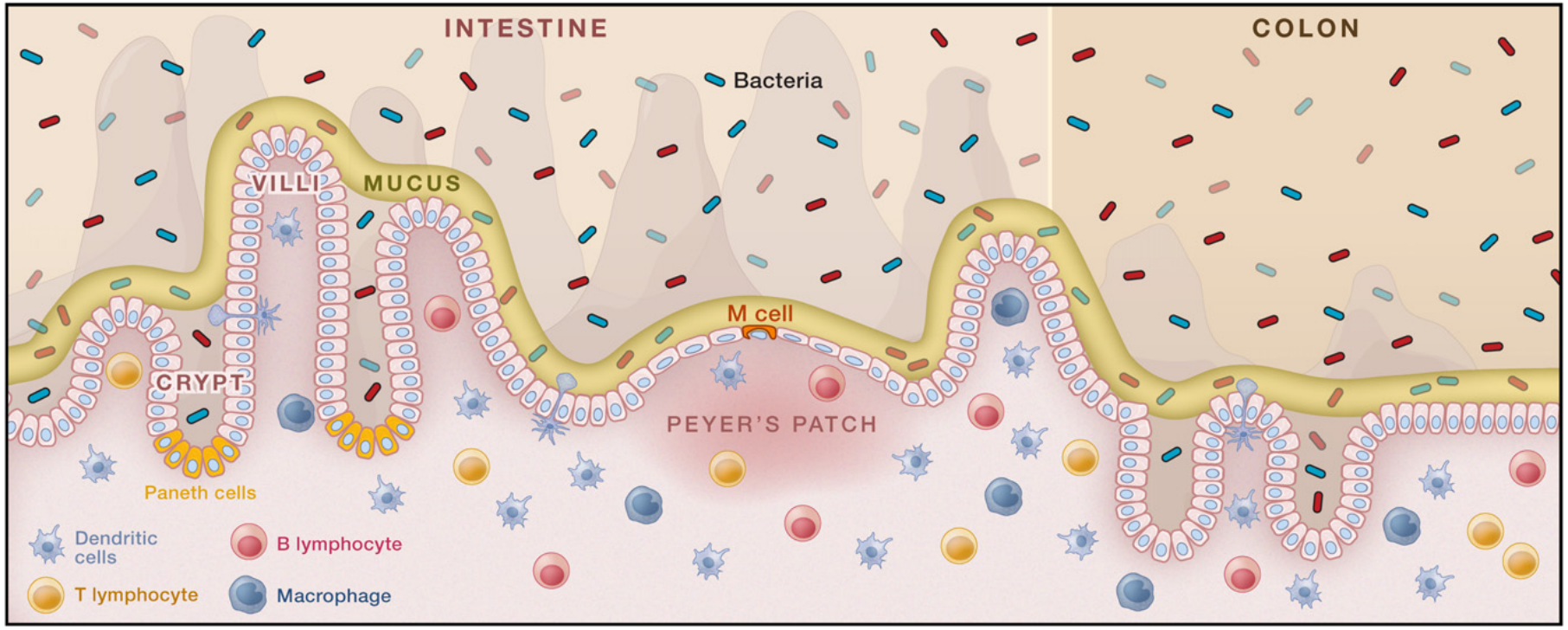


Bakterier i tarmen



DiBaise JK, Mayo Clin Proc 2008;83:460

Tarmen: aktiv barriere



Garrett WS, Cell 2010;140:859

Tarmen i ubalance

- Bakteriel overvækst i tyndtarmen
- *Clostridium difficile* overvækst
- Antibiotika-associeret diaré
- Rejsediaré
- Kronisk inflammatorisk tarmsygdom
- Andre auto-inflammatoriske sygdomme

Biodiversitet

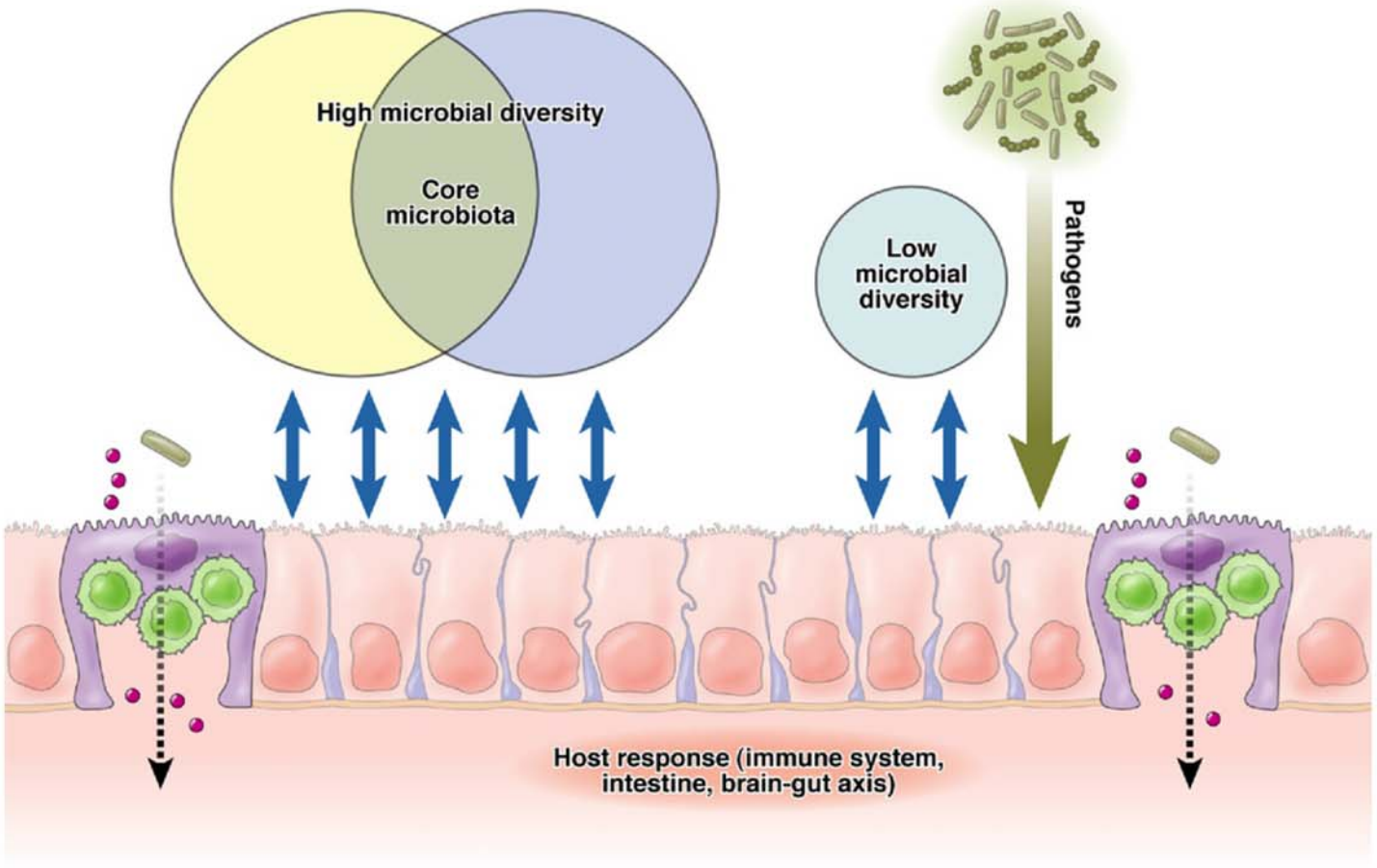
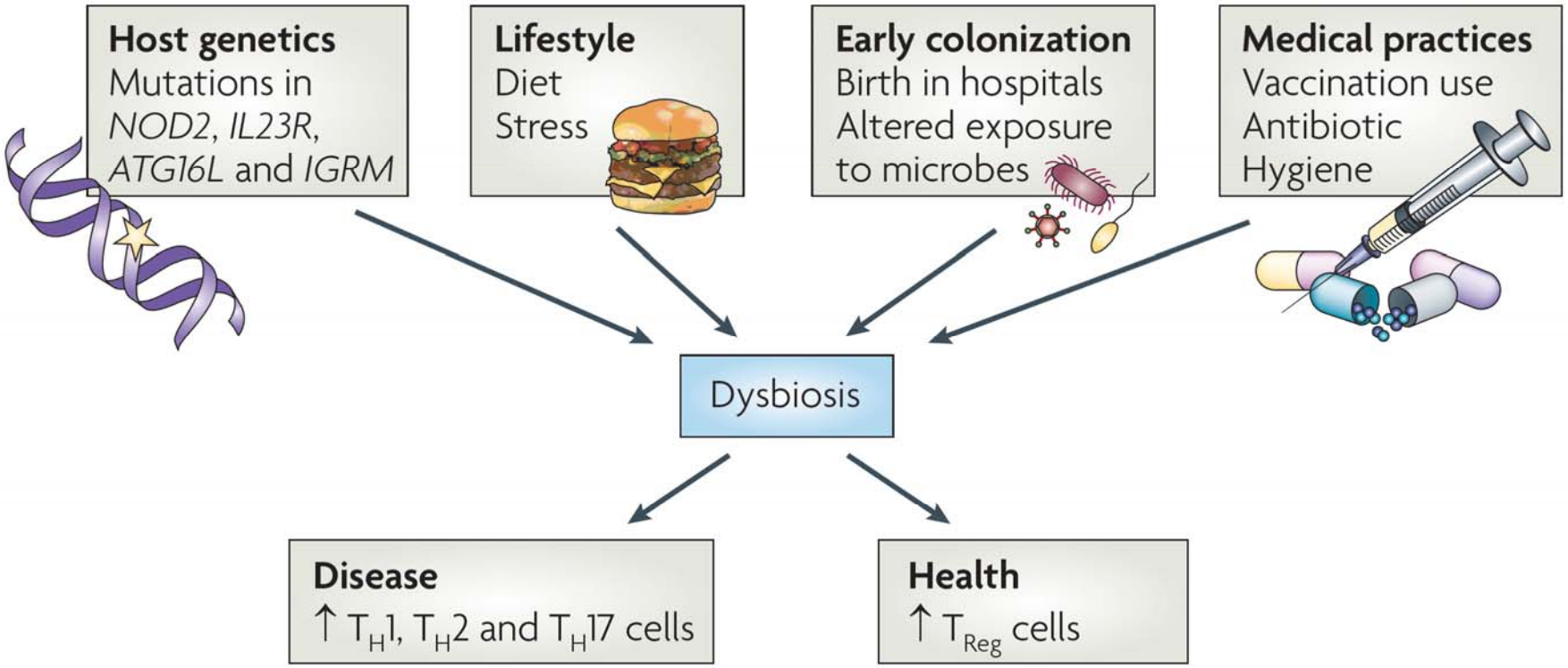


Figure 2. Importance of biodiversity within the gut. In contrast to a low microbial diversity, a high microbial biodiversity provides optimal input to the developing digestive and immune systems and maximal competitive advantage against potential pathogenic challenge.

Shanahan F, Gastroenterology 2010;139;1808

”Dysbiotisk” mikroflora



Round JL, Nat Rev Immunol 2009;9:313

”Godt” for tarmen

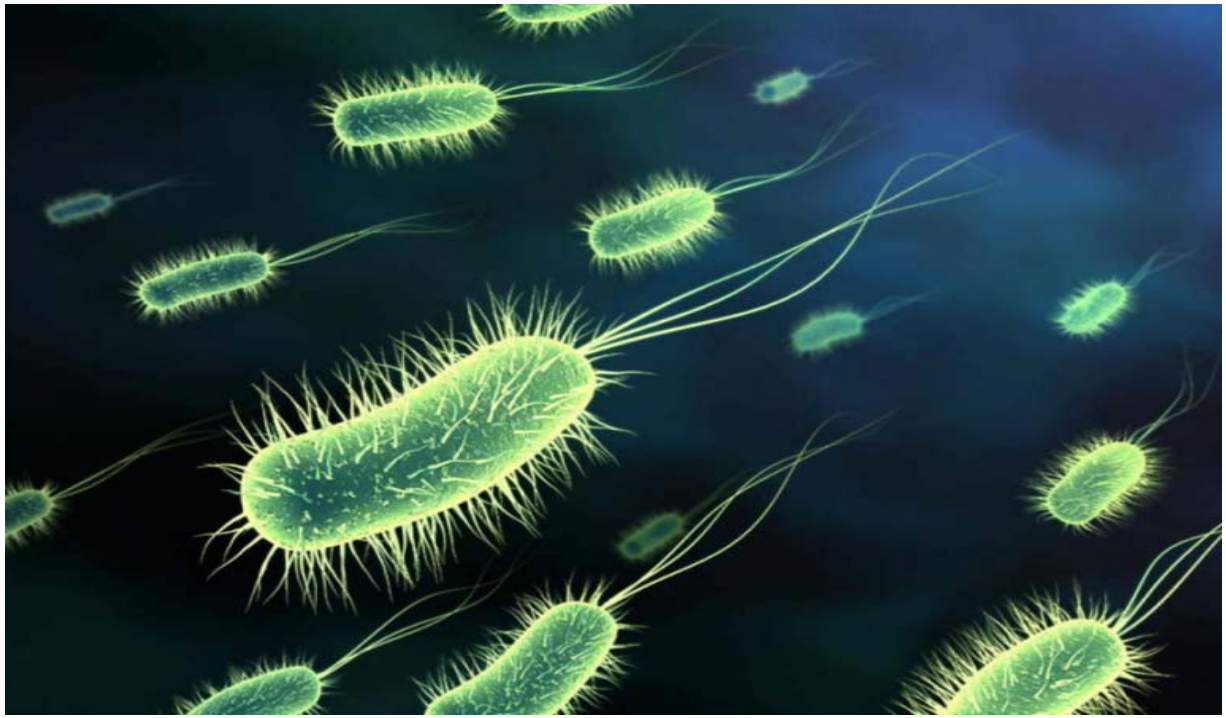
- Øget biodiversitet
- Mucosal barriere
  - Mucus
  - Butyrat
  - Antimikrobielle peptider
- Påvirkning af immunsystemet
  - Styrke regulatoriske celler

Garrett WS, Cell 2010;140:859

Påvirkning af tarmfloraen

- Livsstil
- Kostfibre
  - Komplekse ufordøjelige polysaccharider, (lignin)
- Antibiotika
  - Hæmmer vækst af mikroorganismer
- Probiotika
  - Aktivt virkende mikroorganismer
- Prebiotika
  - Stoffer der fremmer vækst af bestemte mikroorganismer

Probiotika – bakterier til tarmen



Probiotika

- Live microorganisms which, when administered in adequate amounts, confer a health benefit to the host

FAO/WHO, 2001

- Specific live or inactivated microbial cultures that have documented targets in reducing the risk of human disease or in their nutritional management

Isolauri, 2002

- Farmabiotika: Microbial components which manipulate host-microbe-dietary interactions

Shanahan F, Gastroenterology 2010;139:1808


VSL#3®
The Living Shield™
All-natural live lactic acid bacteria supplement
450 billion yogurt bacteria per packet


DANONE
Actim
Actimel


MUTAFLOR 100 mg
MUTAFLOR 100 mg


CULTURA
hindbær drik
CULTURA
fersken/ passion drik


Gefilus
Evolus
Benecol
teho juoma


Yomogi


60 kapsler
Symbioflor
Præparat med gavnlige mælkesyre-bakterier for optimal tarmflora og tarmfunktion.
Fri for gær, gluten, lactose og sukker.
MT nr.: 6120593

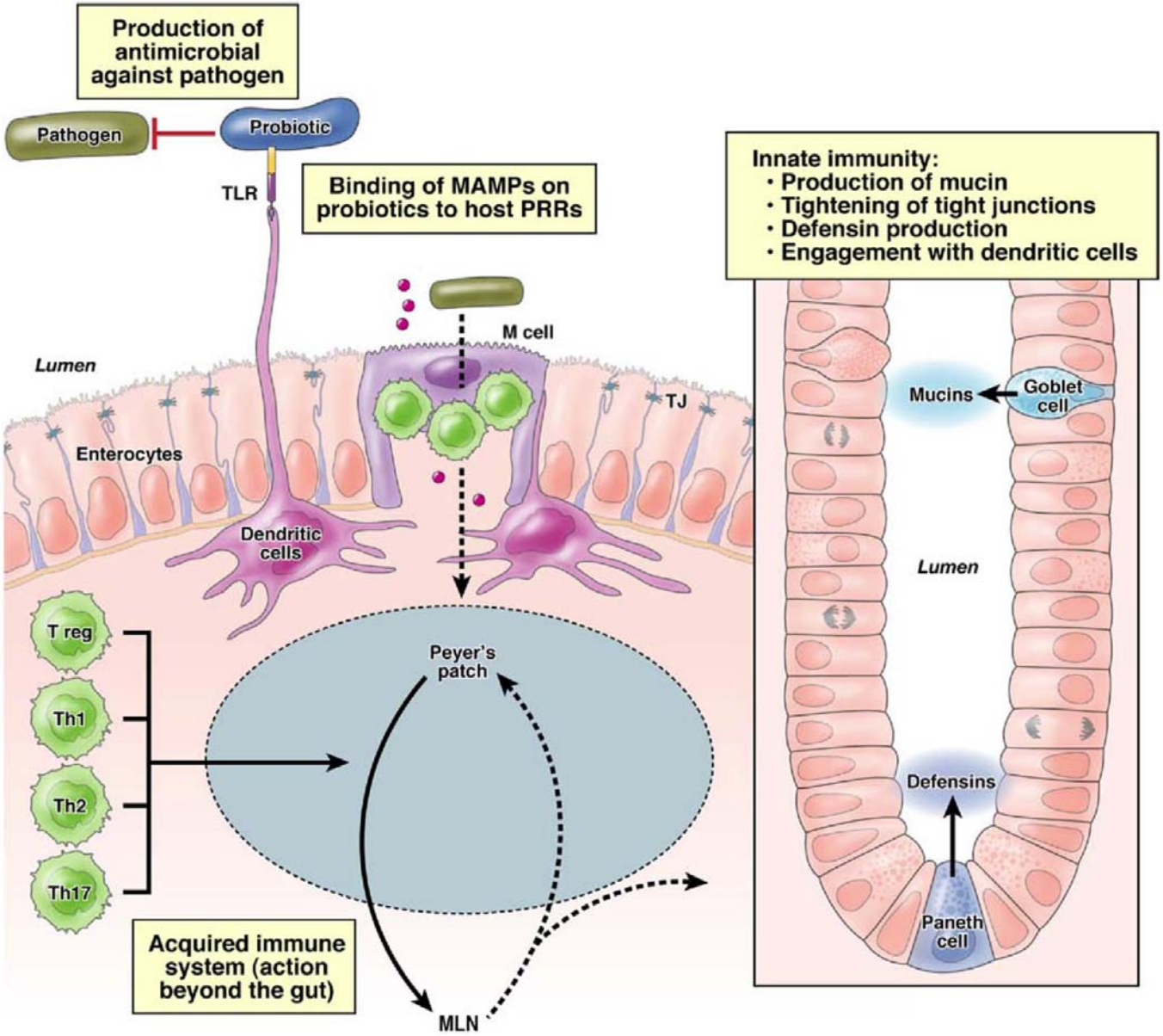

Gaio
Gaio


Acido
Ymer
ØKOLOGISK
Acido
ØKOLOGISK
Ymer


TWINLAB
YEAST FIGHTERS


ProViva
Active


BIFOLAC
DIARRÉ
BIFOLAC



chanisms of probiotic action: within the lumen, at the mucosal surface, and by stimulation of innate and acquired immunity. The echanism varies among different probiotic strains and is dependent on the clinical indication.

Shanahan F, Gastroenterology 2010;139;1808

Probiotika produkter

Præparat	Mikroorganisme	CFU per enhed	Daglig dosis
Paraghurt®	*Streptococcus faecium*	1 x 10^6/kapsel	**8 x 10^6**
Bifolac®	*Lact. rhamnosus, Bif. longum*	2 x 10^6/kapsel	**8 x 10^6**
Acido tykmælk	*Lactobacillus acidophilus*	1 x 10^6/ml	**2 x 10^8**
Idoform®	*1 Entero, 1 Bifido*	1 x 10^9/kapsel	**1 x 10^9**
Symbioflor	*1 Strepto, 1 Lacto, 1 Bifido*	1,5 x 10^9/kapsel	**3 x 10^9**
Dicoflor	*Lactobacillus rhamnosus GG*	6 x 10^9/kapsel	**1,2 x 10^{10}**
Sacchaflor®	*Saccharomyces Boulardii*	5 x 10^9/kapsel	**1 x 10^{10}**
Actimel®	*Lactobacillus casei defensis*	1 x 10^9/ml	**1 x 10^{11}**
Cultura®	*2 Lacto, 1 Bifido, 1 strep*	1 x 10^9/ml	**1 x 10^{11}**
Mutaflor®	*E. Coli Nissle* 1917	1 x 10^{10}/kapsel	**2 x 10^{10}**
VSL#3®	4 *Lacto*, 3 *Bifido*, 1 *Strep*	4,5 x 10^{11}/brev	**9 x 10^{11}**

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Probiotika anvendelse

- Rejsediaré og kortvarig diaré hos børn

Canani RB, BMJ 2007;335:340
Cochrane systematic review 2004(2):CD003048

- Antibiotika-associeret diaré
  - Kapsel- eller mælkebaseret højdosis multikultur; *L. GG*
  - Clostridium difficile diaré: Sacchaflor®

Hickson M, BMJ 2007;335:80
McFarland LV, Am J Gastroenterol 2006;101:812

- Colitis ulcerosa:
  - Forebyggelse af opblussen: Mutaflor®
  - Pouchitis: VSL#3®

Kruis W, Gut 2004;53:1617
Gionchetti, Gastroenterology 2003;124:1202

- Colon irritabile
  - Især bifidobakterier

Haller D, J Nutr 2010;140:690S
Brenner DM, Am J Gastroenterol 2009;104:1033

Prebiotika – mad til bakterierne

Prebiotika

- Ufordøjelige fermenterbare fødevarer, som via selektiv vækst/aktivitets-fremning af en eller få bakteriearter gavner værten

Gibson GR, J Nutr 1995,125:1401

Quigley EM, Pharm Res 2010;61:213

- Fructo-oligosaccharider (FOS)
  - Inulin, oligo-fructose
- Galacto-oligosaccharider (GOS)
  - Human milk oligosaccharid (kun i ammemælk)
- Gluco-macropeptider?

Prebiotika

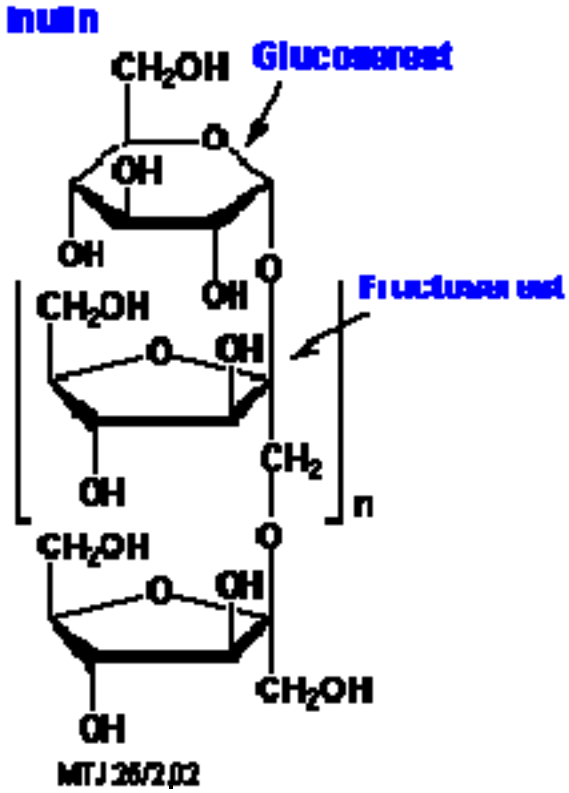
Cikorie

Jordskok

Mælkebøtte

Inulin

- Fructo-oligosaccharid med 2-60 fructoserester efter glucoserest.
- Forekommer i rødder af kurvblomst-planter
  - lægealant (*Inula Helenium*)
  - Cikorie, jordskok, mælkebøtte
  - skorzoner, endivie
  - løg, porre



BioSite.dk

FOS indhold i fødevarer

Fødevare	F-oligosaccharid%	6 gram FOS opnås ved
Cikorierod	64,6%	9,3
Jordskok	31,5%	19
Mælkebøtterod	24,3%	25
Hvidløg	17,5%	34
Porre	11,7%	51
Løg, rå	8,6%	70
Løg, tilberedt	5%	120
Asparges	5%	120
Hvede, fuldkorn	5%	120
Banan	1%	600

Moshfegh AJ, J Nutr 1999;129:1407S

Prebiotika anvendelse

- Substrat for egne bifidobakterier
  - Colon irritabile
  - Forebyggelse af coloncancer
- Fermentering til butyrat (smørsyre)
  - Protektive egenskaber mod cancer?
- Tilsætning til probiotika (=synbiotika)
  - Synergistisk effekt?
  - Kliniske indikationer?
- Øget mæthed, ændrede tarmhormoner
  - Betydning for adipositas hos mennesker?

Konklusioner

- Tarmen en aktiv barriere
  - Bakterier i colon manipulerbare
  - Antimikrobielle peptider oa beskyttende faktorer
  - Aktiv påvirkning fra kost, bakterier, specifikke tilskud
- Probiotika
  - Valg af stamme, koncentration, medium (mælk/pulver)
  - Specifikke virkningsmekanismer
- Prebiotika
  - Oprenset tilskud af oligosaccharider
  - Mulig anvendelse som substrat til bakterier
- Fremtid: – synbiotika – farmabiotika

Loppefrøskaller *(psyllium husks)*

- *Psyllium = plantago ovata = isphagula = isabgol*
- *Komplekst ufordøjeligt xylose-holdigt polysaccharid*
- *ringe fermenterbart*
- *Gel-dannende*

Actimel og Cultura ”shots”

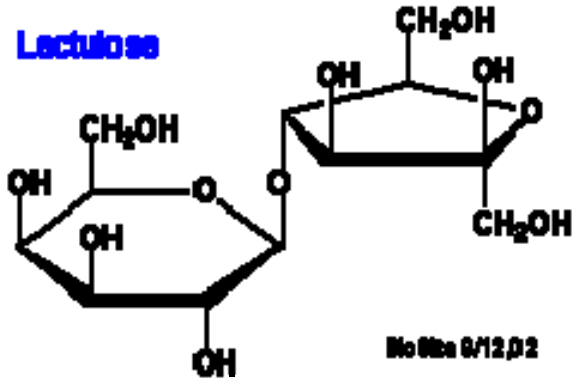
	Actimel	Cultura
Energi	327 kJ	240 kJ
Protein	2,7 g	3,0 g
Kulhydrat	12,4 g	9,0 g
Fedt	1,5 g	0,4 g
Probiotika	*L. casei defensis*	*L. casei F19, L. acidophilus LA-5, B. BB-12, S. termophilus*
Prebiotika	-	Inulin 2,5 g

www.actimel.dk

www.arla.dk

Laktulose

- Di-saccharid: Galactose og fructose
- Ufordøjeligt
- Osmotisk virkende laksans



VSL#3

- 3 x 10^{11} bakterier per gram
- Daglig dosis 6 gram (1800 millarder bakterier)
- 8 bakteriestammer
  - *Lactobacillus casei*
  - *Lactobacillus plantarum*
  - *Lactobacillus acidophilus*
  - *Lactobacillus delbrueckii ssp. bulgaricus*
  - *Bifidobacterium longum*
  - *Bifidobacterium breve*
  - *Bifidobacterium infantis*
  - *Streptococcus salivarius ssp.thermophilus*

Gionchetti. Gastroenterology 2000; 119: 305

Probiotika: Hvad er der i?

Summary of isolation and identification results

Description	Food supplements	Dairy products
Number of products	30	25
* from which no viable strains could be isolated	11 (37%)	0
* containing all claimed species	4/30 (13%)	2 (8%)
* containing other species than those claimed	9/19 (47%)	10 (40%)
* claiming more species than found	22/30 (73%)	16 (64%)
Most frequently claimed species	*Lb. acidophilus*	*Lb. acidophilus*
Most frequently isolated species	*E. faecium*, *Lb. rhamnosus*	*S. thermophilus*, *Lb. acidophilus*

Temmerman R, Appl Environ Microbiol 2003;69:220

Probiotika ved diaré

Table 3 | Primary outcome index: duration of diarrhoea (hours) in study groups

Group	Treatment	Median (IQR) duration (hours)	Estimated difference (95% CI)*	P value†
1	Oral rehydration solution alone	115.5 (95.2-127)	—	—
2	*Lactobacillus casei* subsp *rhamnosus* GG	78.5 (56.5-104.5)	−32 (−41 to −23)	<0.001
3	*Saccharomyces boulardii*	105.0 (90-104.5)	−5 (−13 to 5)	0.38
4	*Bacillus clausii*	118.0 (95.2-128.7)	1 (−7 to 8)	0.76
5	*L delbrueckii* var *bulgaricus*, *L acidophilus*, *Streptococcus thermophilus*, *B bifidum*	70.0 (49-101)	−37 (−47 to −25)	<0.001
6	*Enterococcus faecium* SF 68	115.0 (89-144)	2 (−5 to 11)	0.61

IQR=interquartile range.
*Compared with oral rehydration solution alone.
†Mann-Whitney U test. P value for comparison with oral rehydration solution alone.

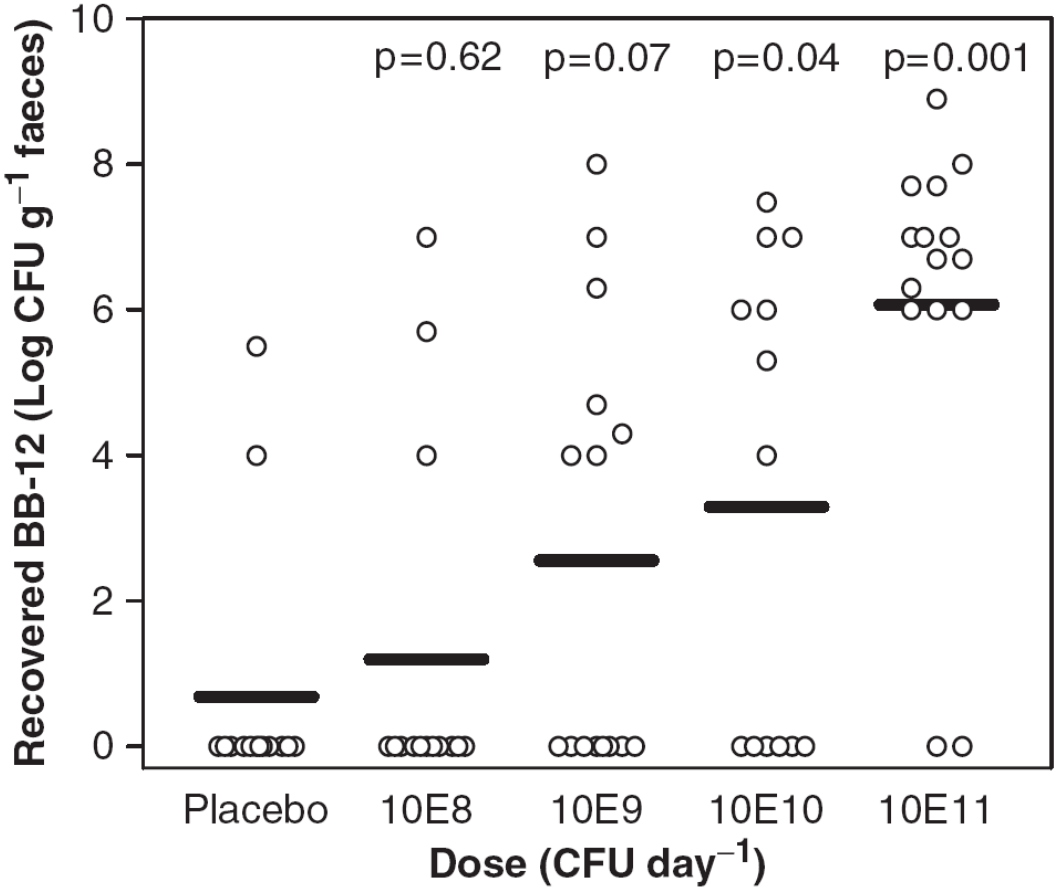
Table 1 | Micro-organism load (according to product label when the study was performed), administration, and main characteristics of preparations analysed

Groups	Micro-organisms	Strains	Dose (twice daily)	Brand*	Price (€)
2	*Lactobacillus casei*	Rhamnosus GG	6×10^9 CFU/dose	Dicoflor 60	10.50
3	*Saccharomyces boulardii*	*S boulardii* lt	5×10^9 live micro-organisms/dose	Codex†	8.50
4	*Bacillus clausii*	O/C84, N/R84, T84, SIN84	10^9 CFU/dose	Enterogermina†	6.50
5	*L delbrueckii* var *bulgaricus*, *L acidophilus*, *Streptococcus thermophilus*, *B bifidum*	LMG-P17550, LMG-P 17549, LMG-P 17503, LMG-P 17500	10^9 CFU, 10^9 CFU, 10^9 CFU, 5×10^8 CFU/dose	Lactogermina†	10.50
6	*Enterococcus faecium*	SF 68	7.5×10^7 CFU/dose	Bioflorin†	10.50

CFU=colony forming units.
*All sold in coloured cardboard boxes.
†Composition, brand name, and costs of these probiotic preparations have changed since study ended.

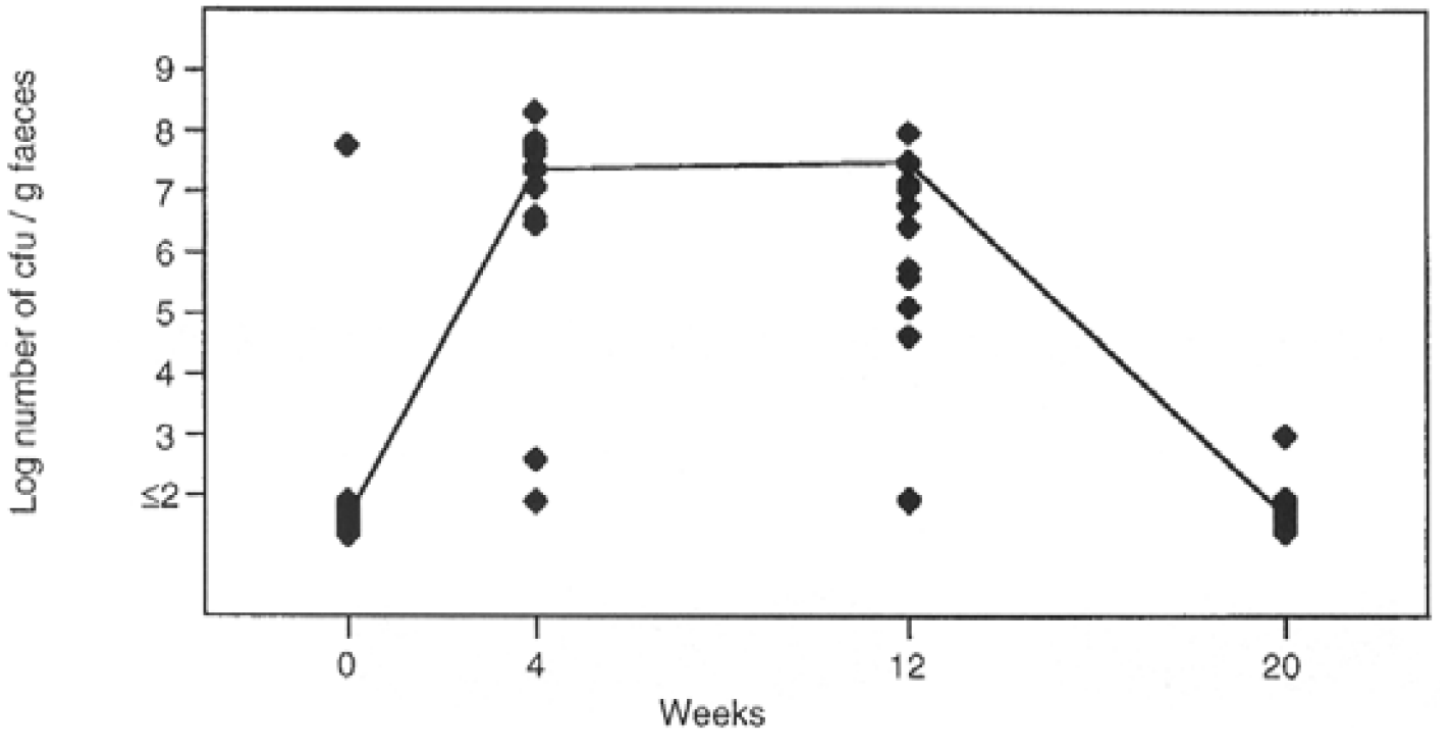
Canani RB, BMJ 2007;335:340

Dosis probiotika



Christensen HR, FEMS 2006;47:380

Kolonisering af tarmen



Forekomst af *Lactobacillus F19* i afføring fra 13 ældre voksne før, under og efter 12 ugers behandling.

Sullivan A, Microbial Ecol Health Dis 2002;S3:17

Probiotika ved IBS

Review: probiotics for IBS
Comparison: 01 probiotics vs placebo
Outcome: 01 risk of IBS not improving

Study or subcategory	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 *Lactobacillus*					
Nobaek 00	21/30	25/30		12.86	0.84 (0.63 to 1.12)
Niedzielin 01	11/20	17/20		9.91	0.65 (0.42 to 1.00)
Sinn 08	4/20	13/20		4.11	0.31 (0.12 to 0.78)
Subtotal (95% CI)	70	70		26.88	0.64 (0.41 to 1.02)
Total events: 36 (treatment), 55 (control)					
Test for heterogeneity: $\chi^2 = 5.48$, df = 2 (p = 0.06), $I^2 = 63.5\%$					
Test for overall effect: Z = 1.87 (p=0.06)					
02 combination					
Kim 03	8/12	8/13		7.51	1.08 (0.60 to 1.95)
Tsuchiya 04	7/34	30/34		6.44	0.23 (0.12 to 0.46)
Kajander 05	21/52	34/51		10.91	0.61 (0.41 to 0.89)
Drouault-Holowacz 08	33/53	31/53		12.37	1.06 (0.78 to 1.45)
Subtotal (95% CI)	151	151		37.23	0.66 (0.36 to 1.20)
Total events: 69 (treatment), 103 (control)					
Test for heterogeneity: $\chi^2 = 20.92$, df = 3 (p = 0.0001), $I^2 = 85.7\%$					
Test for overall effect: Z = 1.36 (p = 0.17)					
03 *Bifidobacterium*					
Long 06	13/30	21/30		9.31	0.62 (0.39 to 0.99)
Whorwell 06	143/270	54/92		14.35	0.90 (0.74 to 1.11)
Subtotal (95% CI)	300	122		23.66	0.80 (0.56 to 1.13)
Total events: 156 (treatment), 75 (control)					
Test for heterogeneity: $\chi^2 = 2.07$, df = 1 (p = 0.15), $I^2 = 51.7\%$					
Test for overall effect: Z = 1.29 (p = 0.20)					
04 *Streptococcus*					
Gade 89	20/32	19/22		12.23	0.72 (0.53 to 0.99)
Subtotal (95% CI)	32	22		12.23	0.72 (0.53 to 0.99)
Total events: 20 (treatment), 19 (control)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.01 (p = 0.04)					
Total (95% CI)	553	365		100.00	0.71 (0.57 to 0.88)
Total events: 281 (treatment), 252 (control)					
Test for heterogeneity: $\chi^2 = 28.33$, df = 9 (p = 0.0008), $I^2 = 68.2\%$					
Test for overall effect: Z = 3.12 (p = 0.002)					

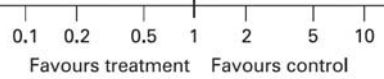


Figure 2 Forest plot of trials comparing probiotics with placebo reporting a dichotomous outcome. IBS, irritable bowel syndrome.