Dr Warren Hyer
Consultant Paediatric Gastroenterologist

Probiotics – a cure for all?

No conflict of interest to declare

Aims

- To change your opinion of probiotic use in children
- To base your decision on high quality evidence and not studies prejudiced by publication bias
- Have an understanding on the number needed to treat
- Consider other strategies in preference

Outcomes – this is our knowledge so far

In favour of probiotics

✓Prevention and treating viral gastroenteritis

✓ Preventing antibiotic associated diarrhoea

Uncertain benefit

?Preventing NEC

? Treat H pylori

? Treatment for IBS

? Treatment for ulcerative colitis

? Treatment for infantile colic

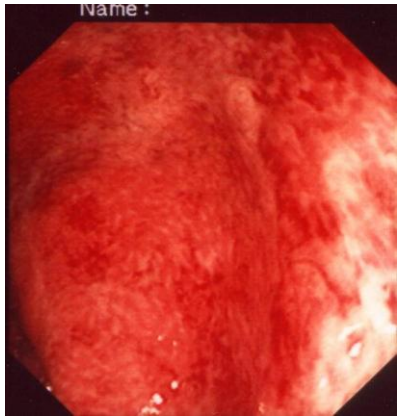
? Preventing atopy

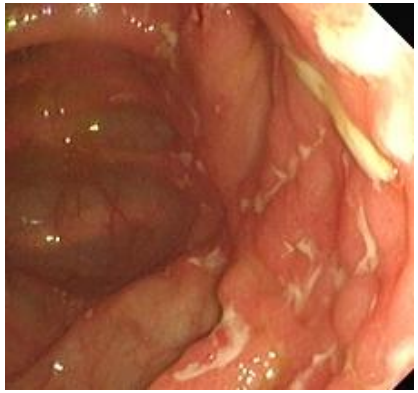
Not proven

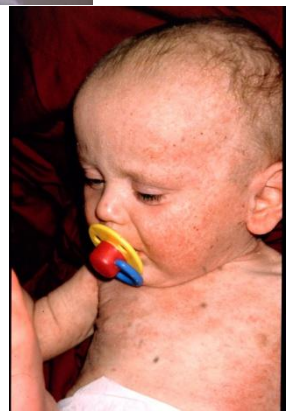
✖Treatment of Crohns disease

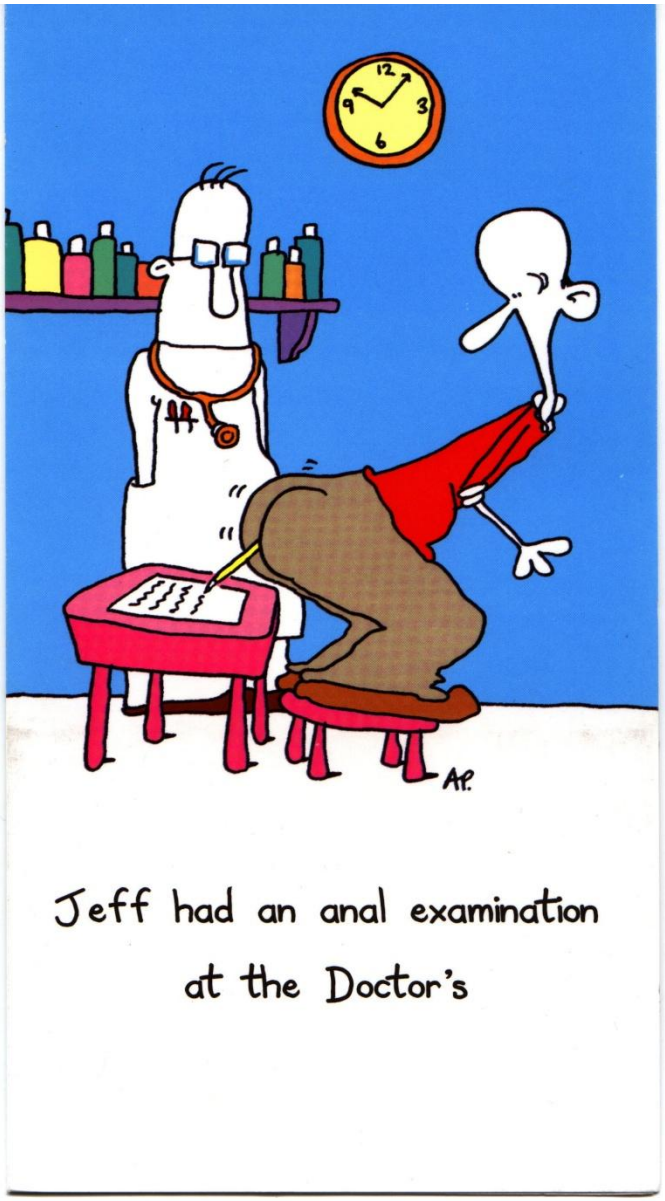
✖ Prevention or treatment for human cancers

Topics we will cover









Bottom line

These are the slides worth remembering

So what are we talking about

Proper probiotics

Lactobacilli
Bifidobacterium
Streptococcus

Not a drinking yoghurt

St. Mark's Hospital and Academic Institute

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

Good versus bad

Good bugs

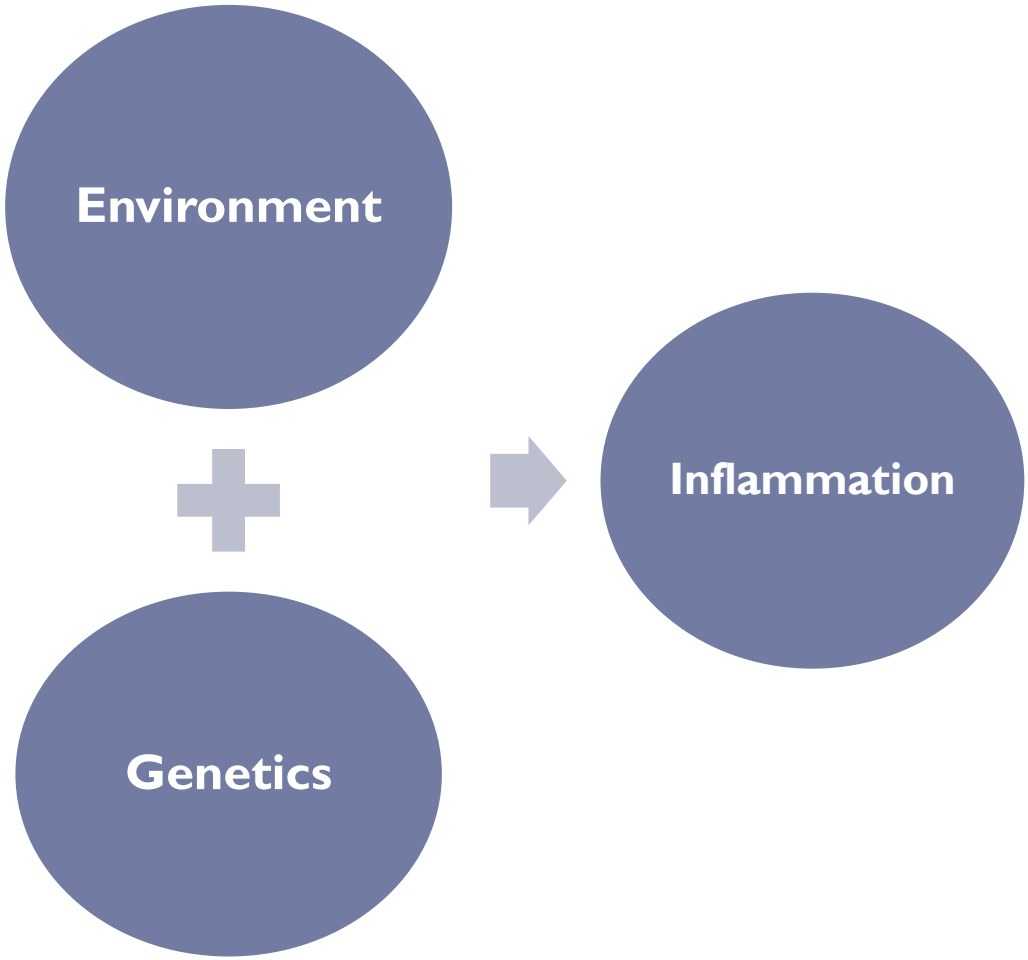
- Lactobacillus rhamnosus
- Bifidobacterium lactis
- Streptococcus thermophilus

- Faecalibacterium prausnitzii – less abundant in IBD

Bad bugs

- Klebsiella
- Pseudomonas
- Serratia
- Proteus

Role of microbia in GI disease in children – increasing interest



The first opportunity for getting the environment right

Bottom Line

Mode of delivery

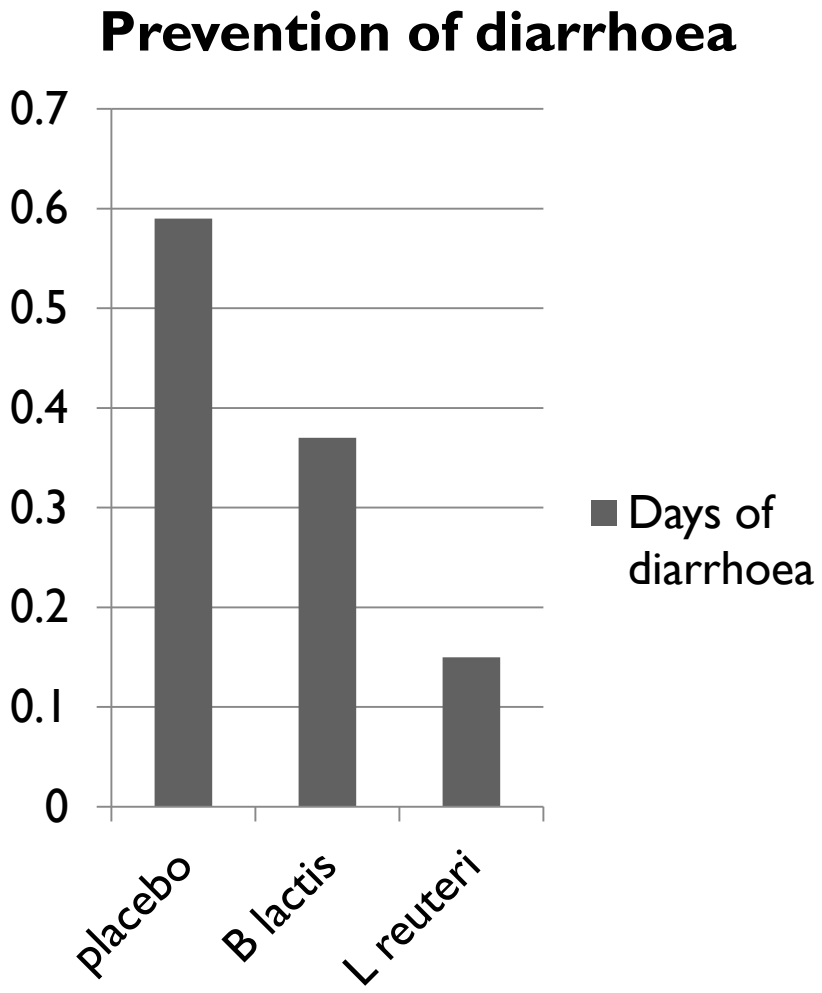
Neonatal antibiotics

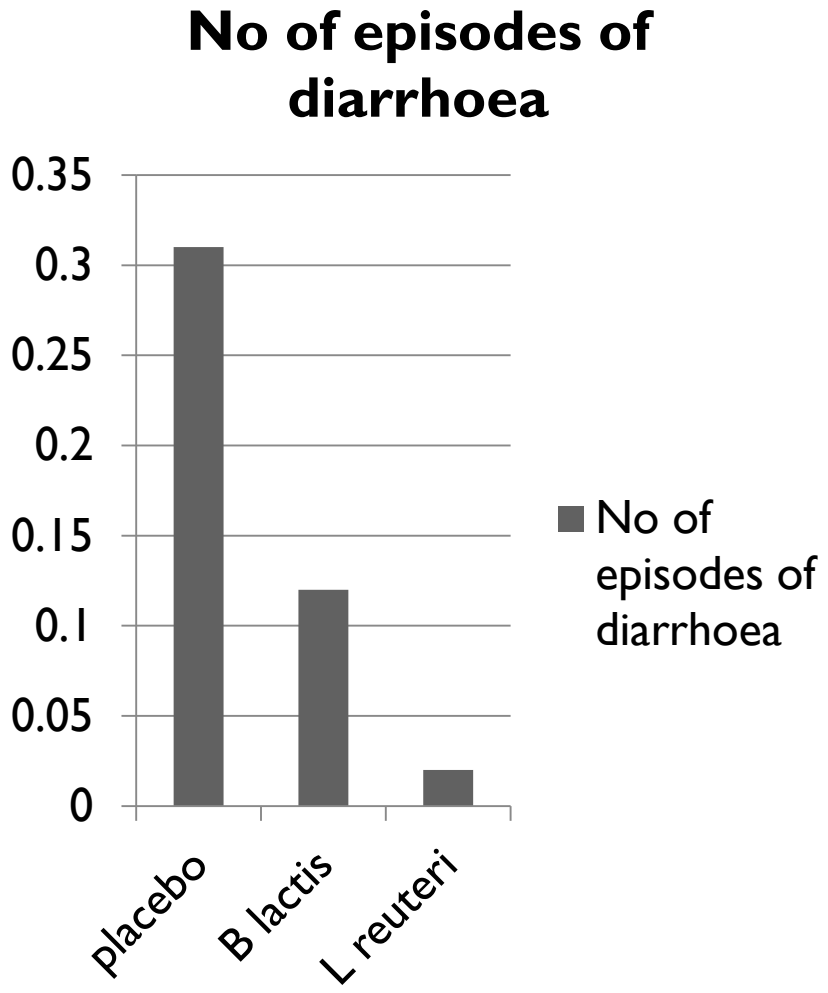
Prematurity

Delays intestinal commensal probiotic bacterial colonisation compared to vaginal delivery

So lets look at the data?

Prevention of nocosomial diarrhoea





Weizman et al Pediatrics 2005

The NEW ENGLAND JOURNAL of MEDICINE

Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis

Guillermo M Ruiz-Palacios, Irene Pérez-Schael, F Raúl Velázquez, Hector Abate, et al. **Boston: Jan2006 Vol. 354, Iss. 1; pg. 11, 14 pgs**

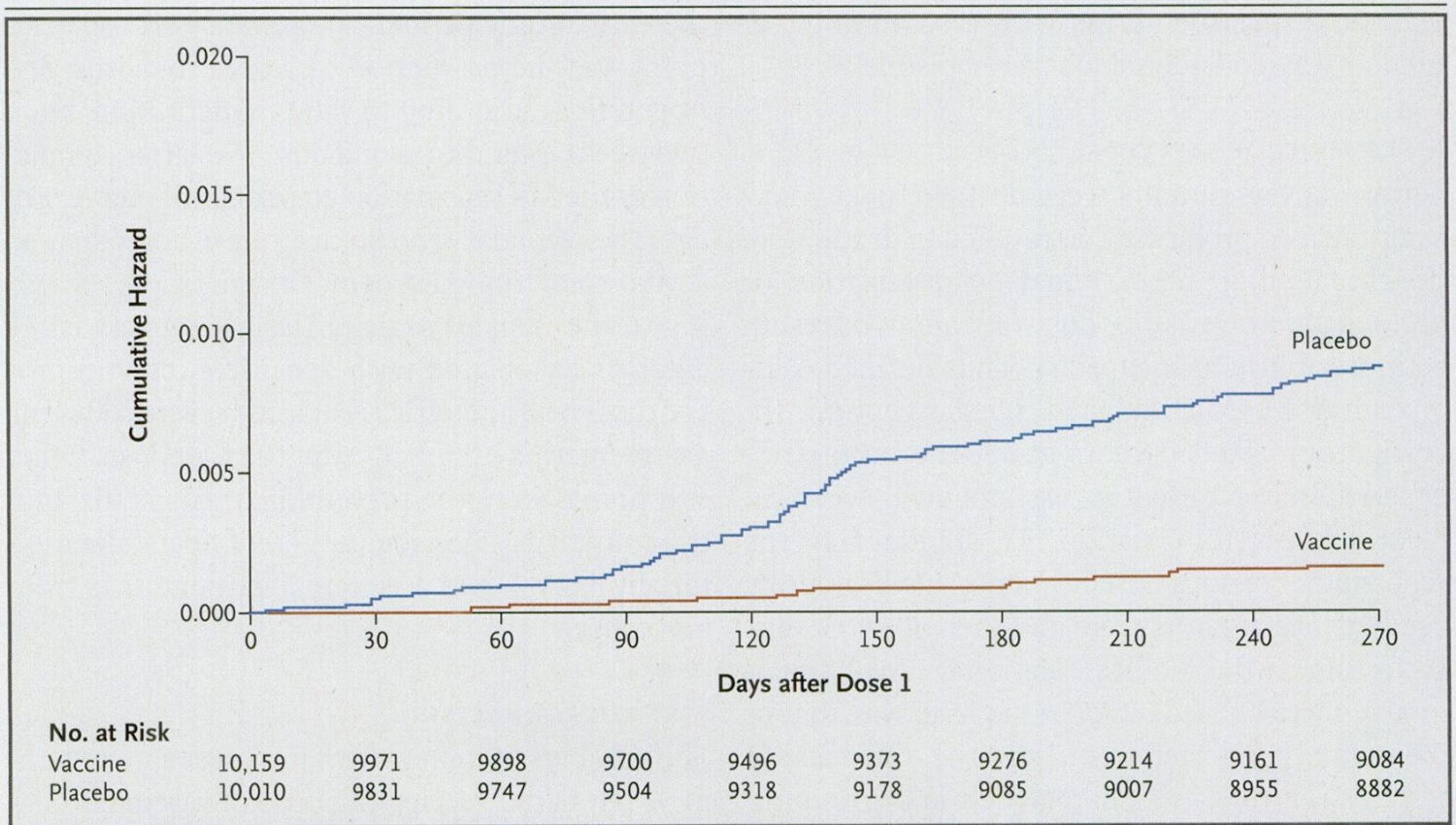


Figure 1. Cumulative Hazard of a First Episode of Severe Gastroenteritis.

The cumulative hazard of a first episode was estimated as a minus-log transformation (of log data to nonlog data) of the Kaplan–Meier survival curve during the period from dose 1 until one year of age among all the infants who received at least one dose of either vaccine or placebo. The difference between receiving placebo and receiving vaccine was significant ($P<0.001$ by the log-rank test).

- After meta analysis:

NNT = 7

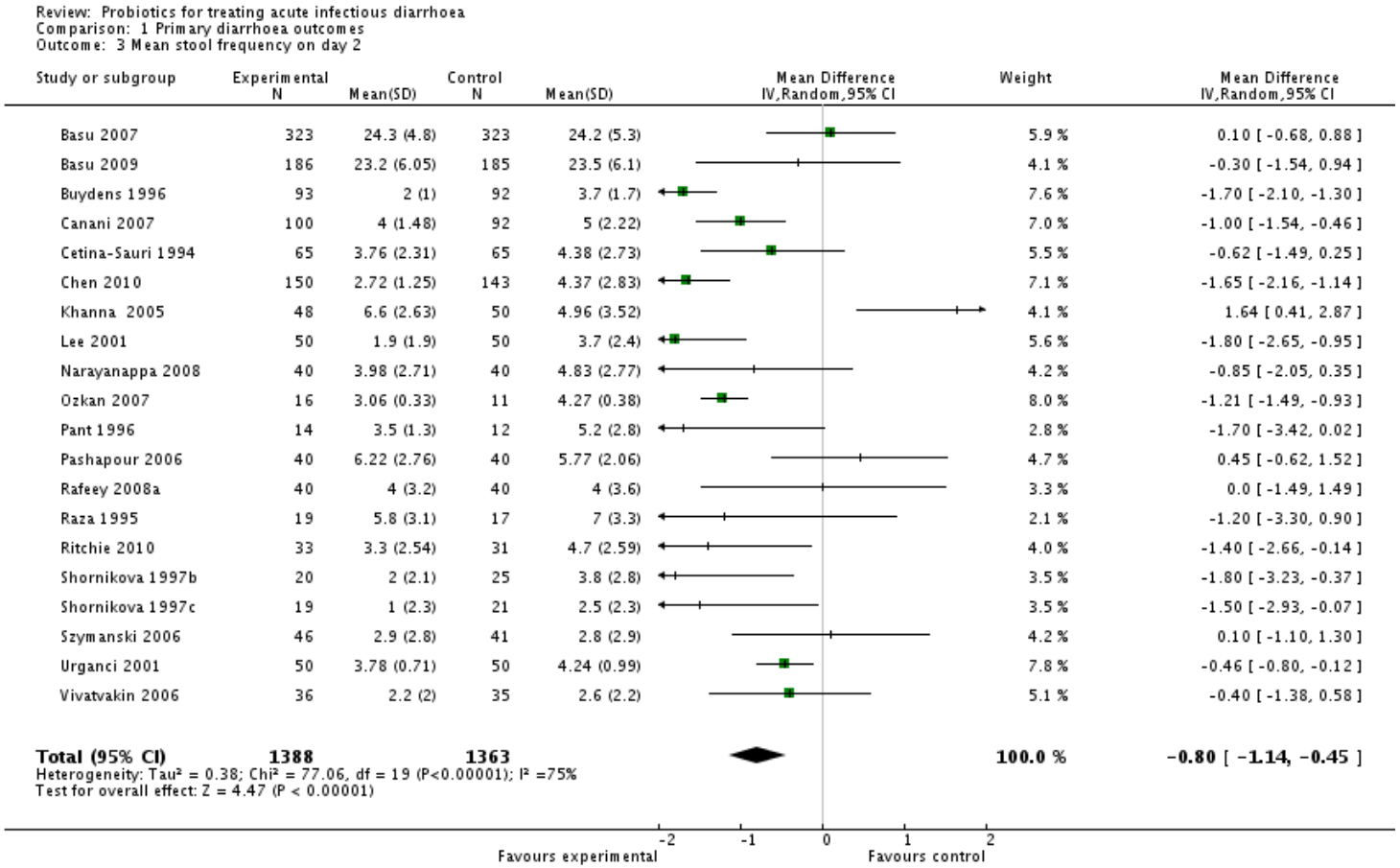
Number needed to treat

7 children would need to have been given LGG to prevent 1 child from developing rotavirus gastroenteritis

The rotavirus vaccine is superior

Treatment of diarrhoea

Allen et al Probiotics for treating infectious diarrhoea. Cochrane 2010



- But by how much do they improve the episode

- ONE DAY
- And does that prevent hospital admission

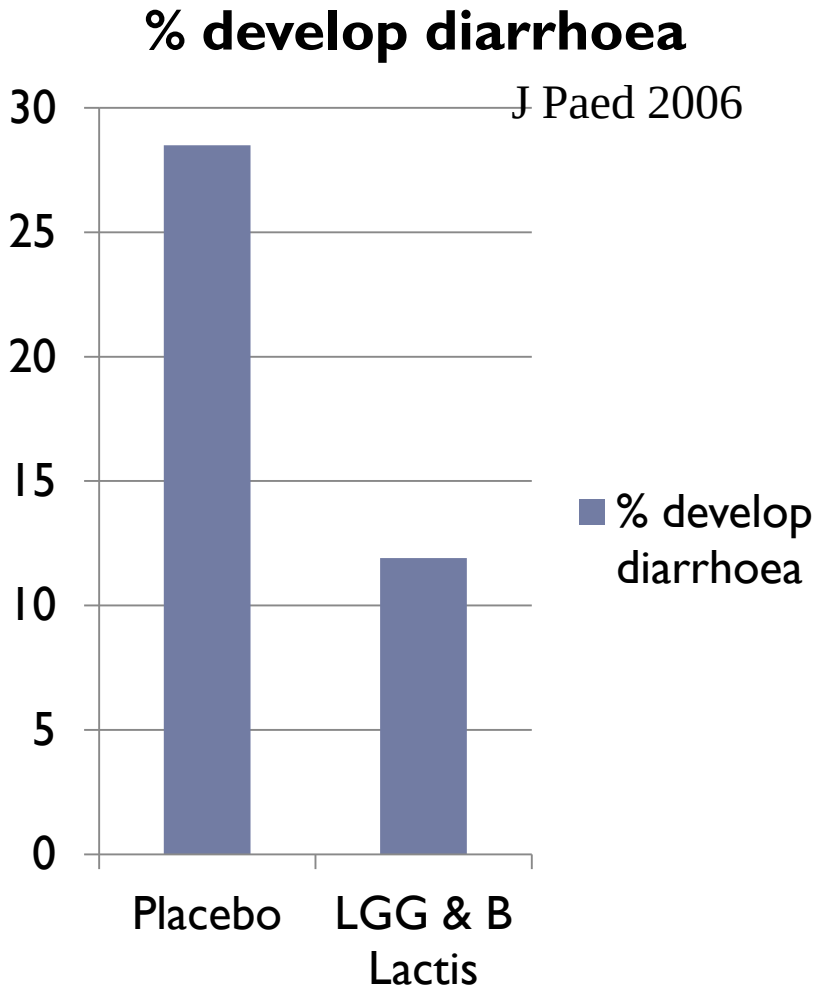
Not worth it

Strain dependent

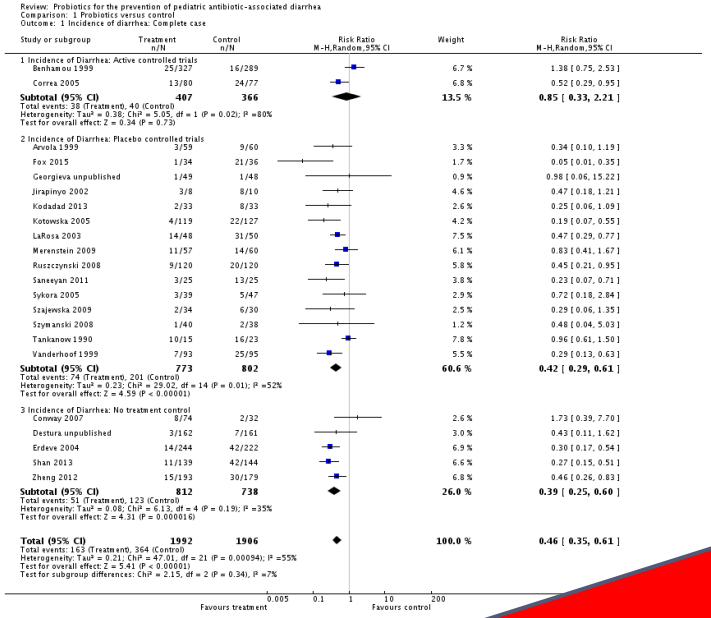
Have to be given early

Only help in healthy children

Antibiotic associated diarrhoea

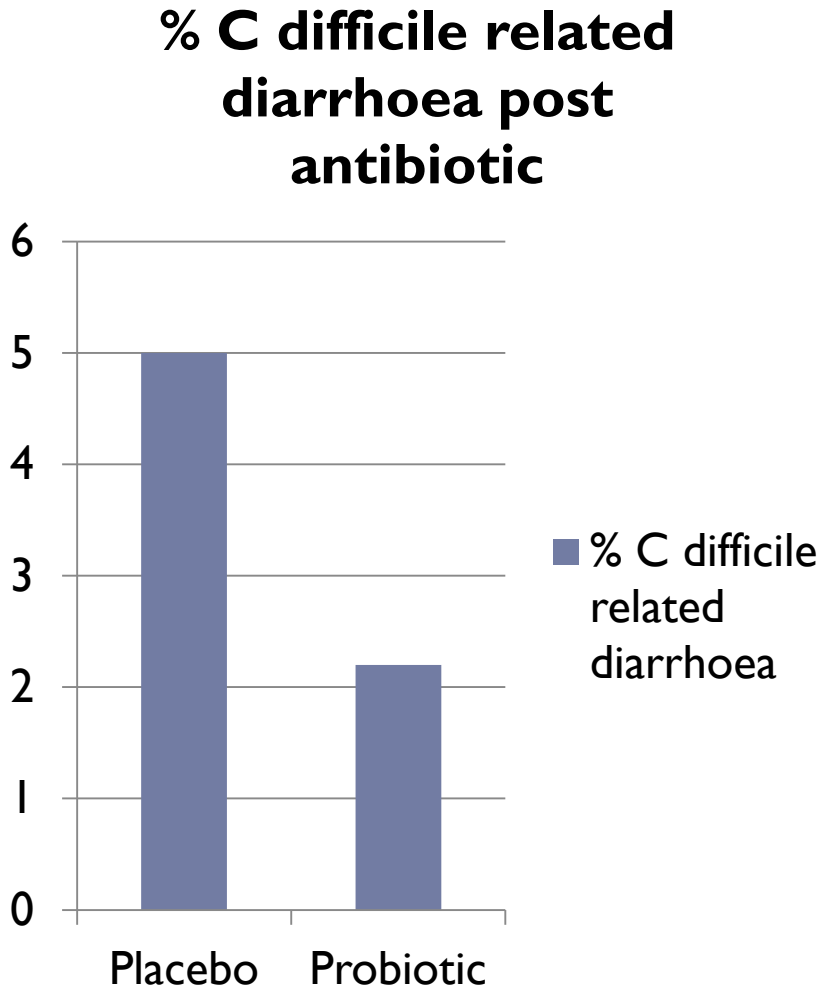


- Metaanalysis- Goldenburg 2015 Cochrane



NNT =10

Preventing C difficile infection post anti biotics



- Probiotics reduce risk of C difficile associated diarrhoea post antibiotics by 64%

Goldenberg
Cochrane database 2013

- Antibiotic use worldwide is rising
- Antibiotic resistance escalates
- Vaccination regimes prevent sepsis
- Probiotics are effective in reducing risk of Clostridium difficile

Just give less antiobitics

Better education about fever

Complete vaccination schedules

Avoid PPI's

Wash hands

Use less broad spectrum antibiotic

The Bottom Line

Necrotising enterocolitis

AlFaleh Probiotics for prevention of NEC Cochrane 2014

Summary of data

- 24 RCT
- Probiotic group vs placebo had reduced risk of NEC (n=5520). RR 0.43
- Probiotic group reduced mortality (n=5112)
  RR 0.65
- Sepsis rate identical
- Reduced time to feeding

So they work?

- So probiotics confer benefit:

1. Reduce mortality
2. Reduce morbidity

- What is the optimal probiotic formulation?
- We do not know about the safety and efficacy of probiotics in VLBW?
- What is the duration?
- In formula or human milk
- Studies do not have the same end point?

Studies on individual strains are still promising: (Review JPEN 2015)

- L reuteri:
- Reduced time to full feeds (by 1.34 days)
- Risk of late onset sepsis (RR 0.66)
- Duration of hospitalisation by 11 days

For NEC

I concede, the data supports use of probiotics as a prevention strategy.

- Studies on individual strains are still promising: (review JPEN 2015)

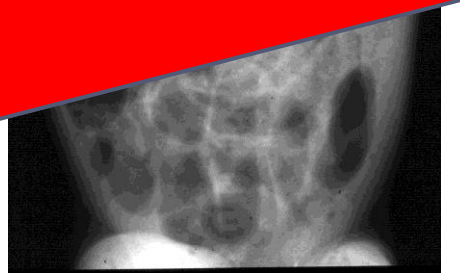
- L reuteri:
- Reduced time to full feeds (by 1.34 days)
- Risk of late onset
- Dur

For NEC

I concede, the data supports use of

Number needed to prevent one case of NEC is between 21 and 27

But why not have more effective ways of preventing NEC?



Treatment of H pylori

- Probiotics – increased eradication rate OR 1.95
  - But does not get eradication up to 90%
- Probiotics reduced risk of side effects RR 0.32
- Maastricht consensus Gut 2012:
- "certain probiotics show promising results as adjuvant treatment in reducing side effects"

H pylori

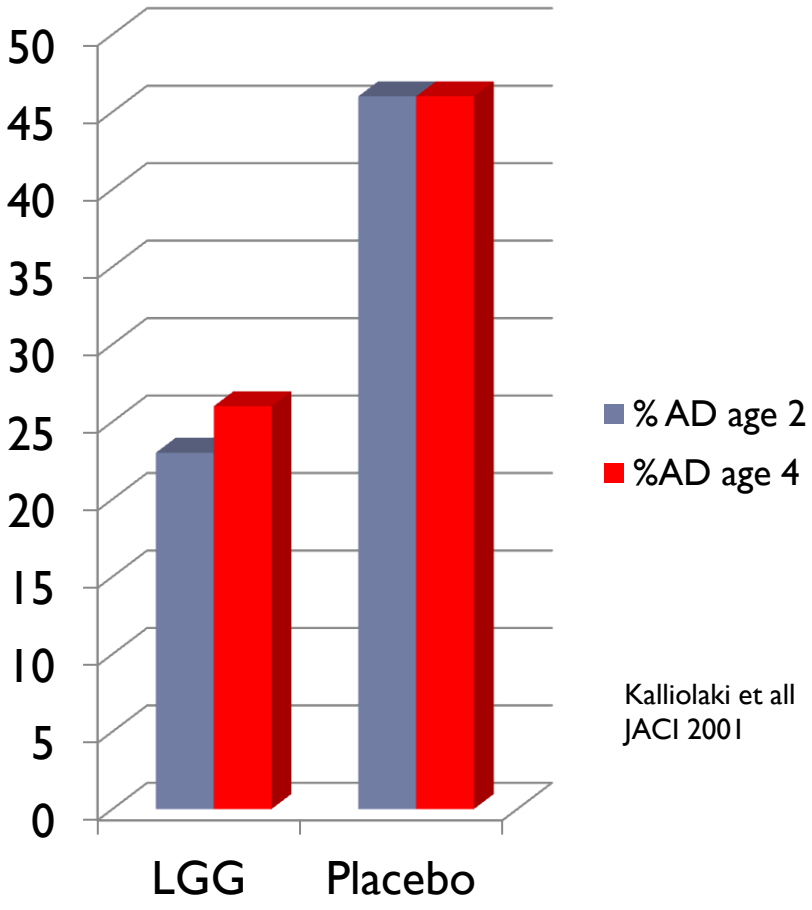
May improve eradication rate

May improve risk of side effects

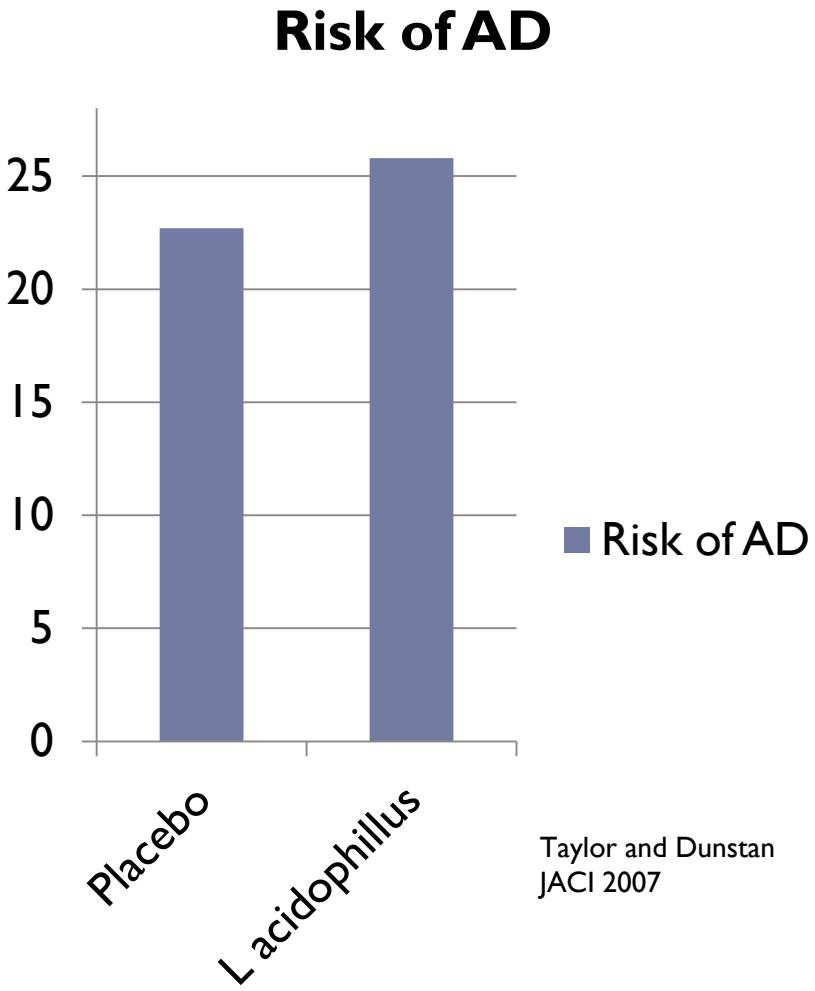
But does it matter?

Does it improve compliance?

Prevention of atopic disease

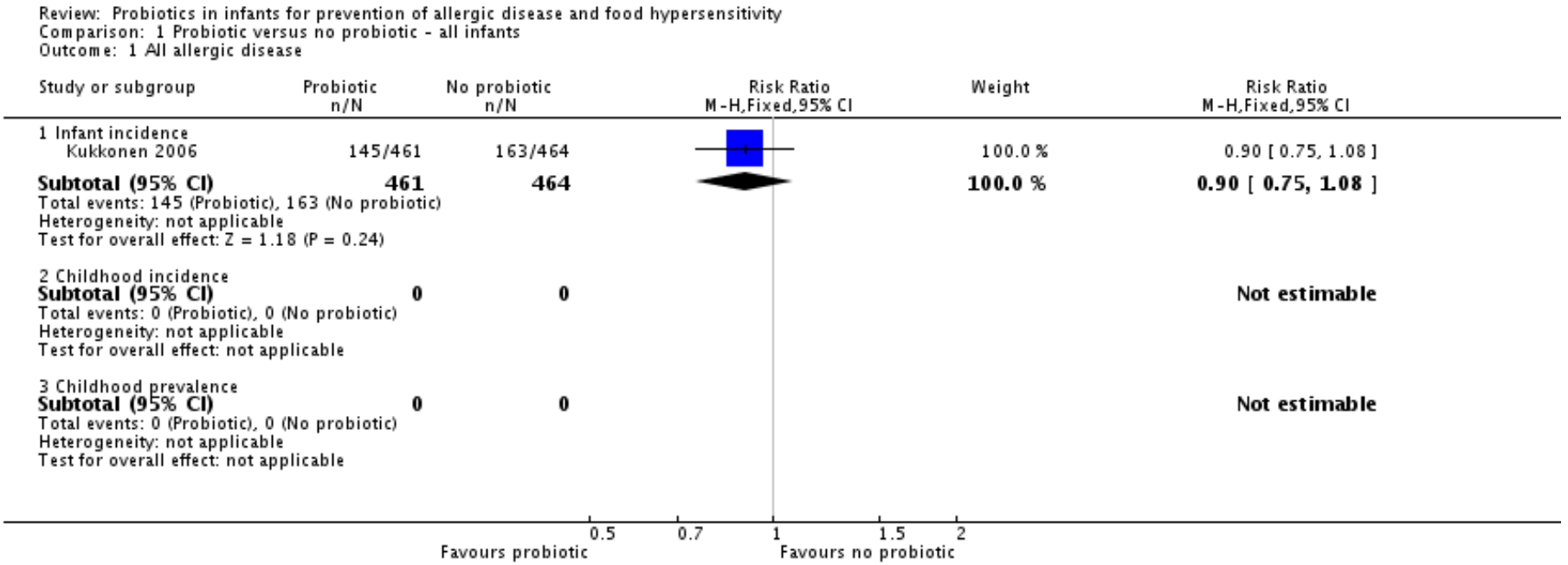


Kalliolaki et all
JACI 2001



Taylor and Dunstan
JACI 2007

Cochrane conclusion



- Instead of use probiotics, why not strive for a vaginal delivery and breast feed?

Insufficient

"There is insufficient evidence to recommend the addition of probiotics to infant feeds for prevention of allergic disease or food hypersensitivity. Although there was a reduction in clinical eczema in infants, this effect was not consistent between studies"

- European Academy of Allergy and Clinical Immunology (EAACI) 2014
  - There is no evidence to support use of probiotics for food allergy prevention

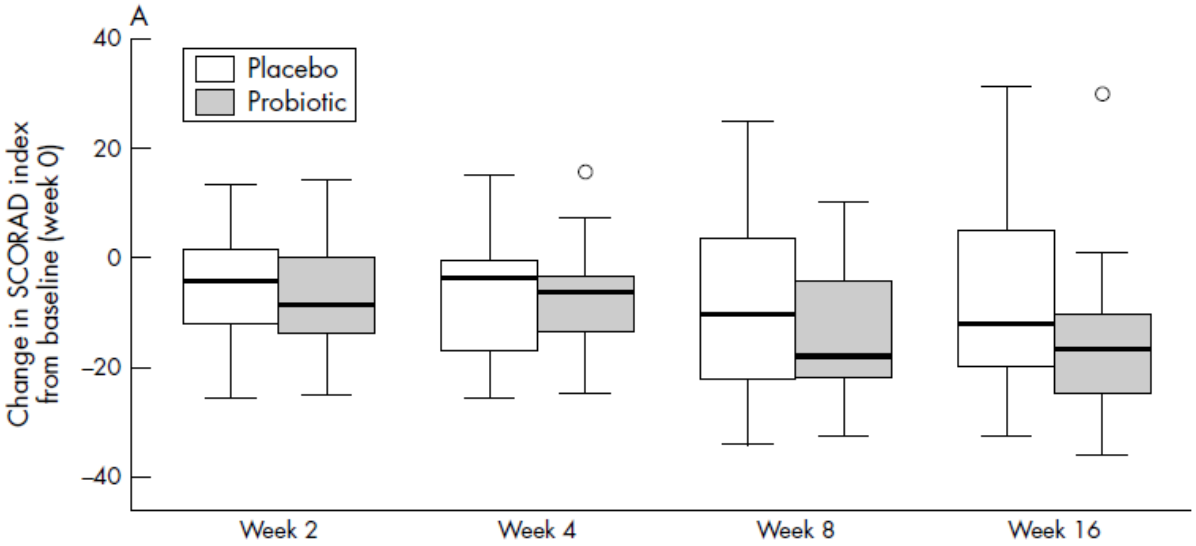
- World Allergy Organisation 2015 (WAO)
  - Significant benefit of probiotic supplement in reducing the risk of eczema when used in the last trimester (RR 0.57 if given to mother; RR 0.8 if given to infant).

Bottom line

Confused?

And as for treating atopic disease.....

- SCORAD eczema score
- Weston et al 2004 Arch Dis Child

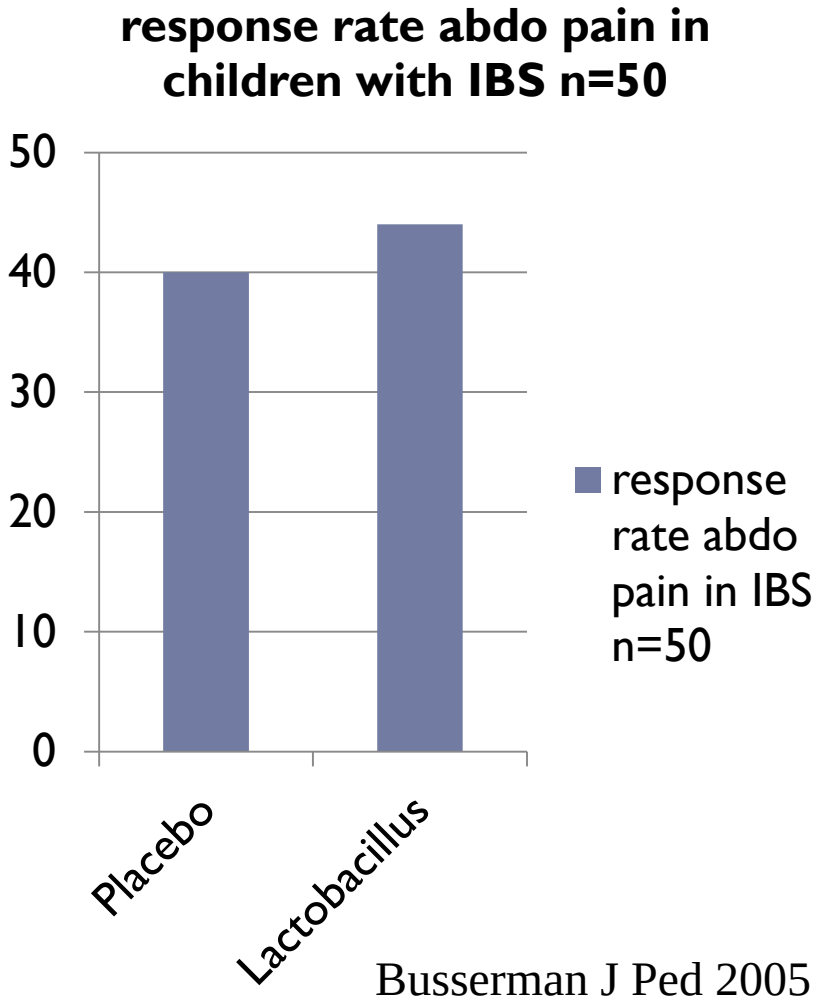


To treat his eczema: that degree of change is hardly going to change his eczema….you would be better off changing his milk

For treatment:

Not proven to be effective

Irritable bowel syndrome



Busserman J Ped 2005

Adult practice

- Moderate benefit only
- Variable end points
- Often mixed with constipation studies

NNT = 4

IBS

There are so many better tools for managing IBS:

Hypnotherapy

FODMAP reduction

Herbal therapy

Drug therapies

thebmj

STATE OF THE ART REVIEW

Irritable bowel syndrome: new and emerging treatments

Magnus Halland, Yuri A Saito

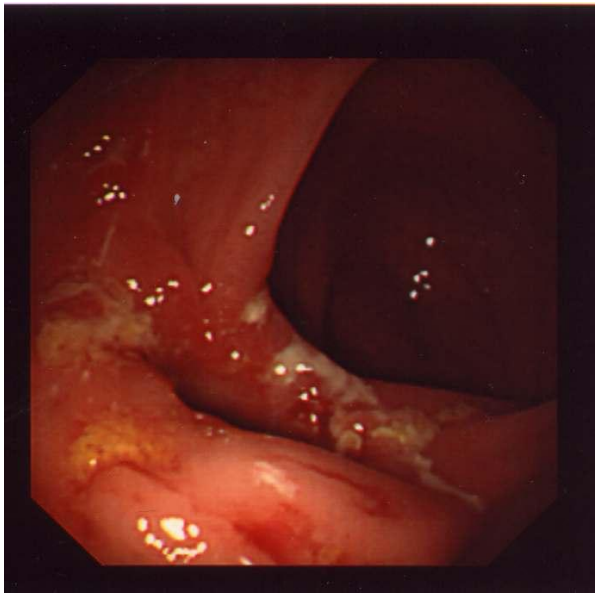
Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN 55905, USA
Correspondence to: Y A Saito
saito.yuri@mayo.edu

Cite this as: *BMJ* 2015;350:h1622
doi: 10.1136/bmj.h1622

ABSTRACT

Irritable bowel syndrome is one of the most common gastrointestinal disorders in developed nations. It is characterized by abdominal pain, altered bowel habits, and bloating. Several non-pharmacological and pharmacological agents, which target

With the concurrent use of antibiotics and rise in prevalence of IBD and relationship to Westernised medicines



- Lack of biodiversity
- Cause or effect
- Linked to Westernised lifestyle
- Imbalance in normal gut microbiota due to antbiotic use might have sustained effect on GI immune tolerance

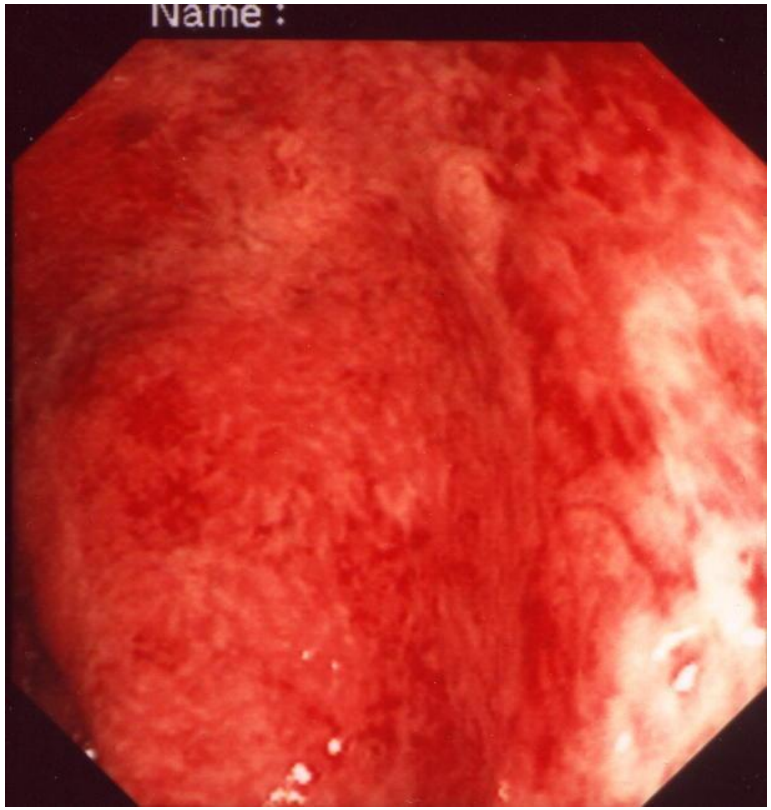
Gut microbiota

ORIGINAL ARTICLE

Geographical patterns of the standing and active human gut microbiome in health and IBD

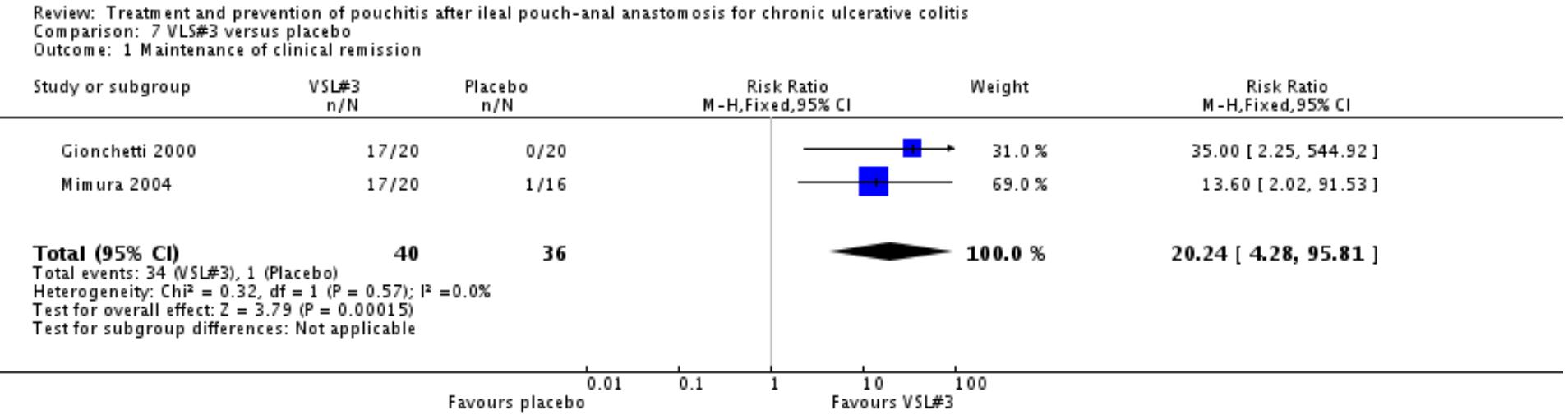
Ateequr Rehman,[1] Philipp Rausch,[2,3] Jun Wang,[2,3] Jurgita Skieceviciene,[1,4]

Ulcerative colitis



- 40% of children use alternative therapies
- There is good reason to consider probiotics might work

Adult studies are promising especially in pouchitis



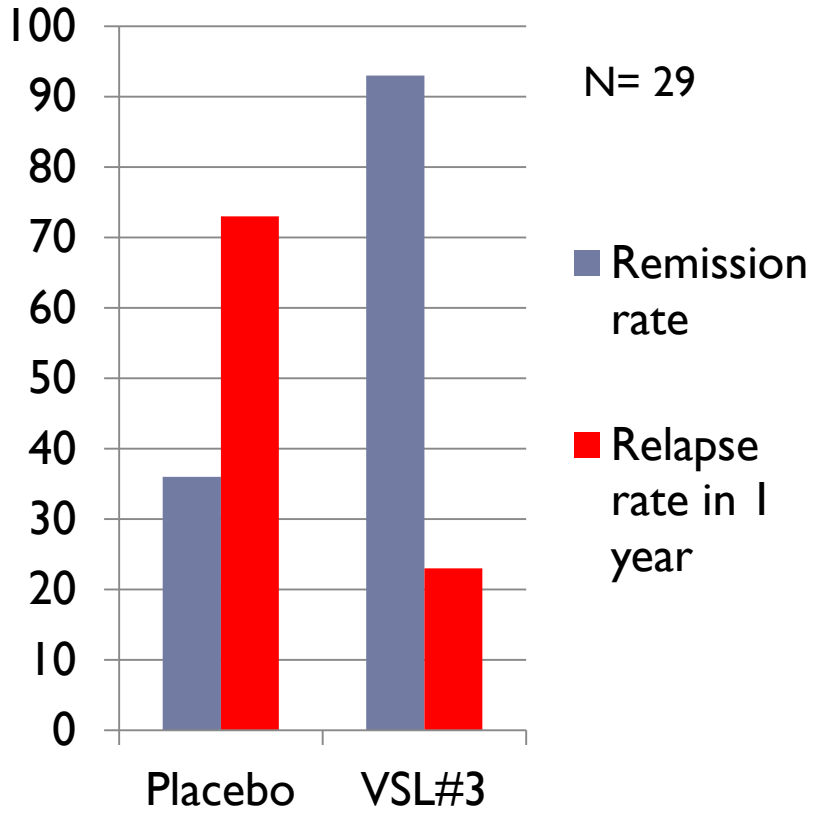
2.4 Probiotics

ECCO Statement 6G

E coli Nissle is an effective alternative to 5-ASA for maintenance [EL1b, RG A]

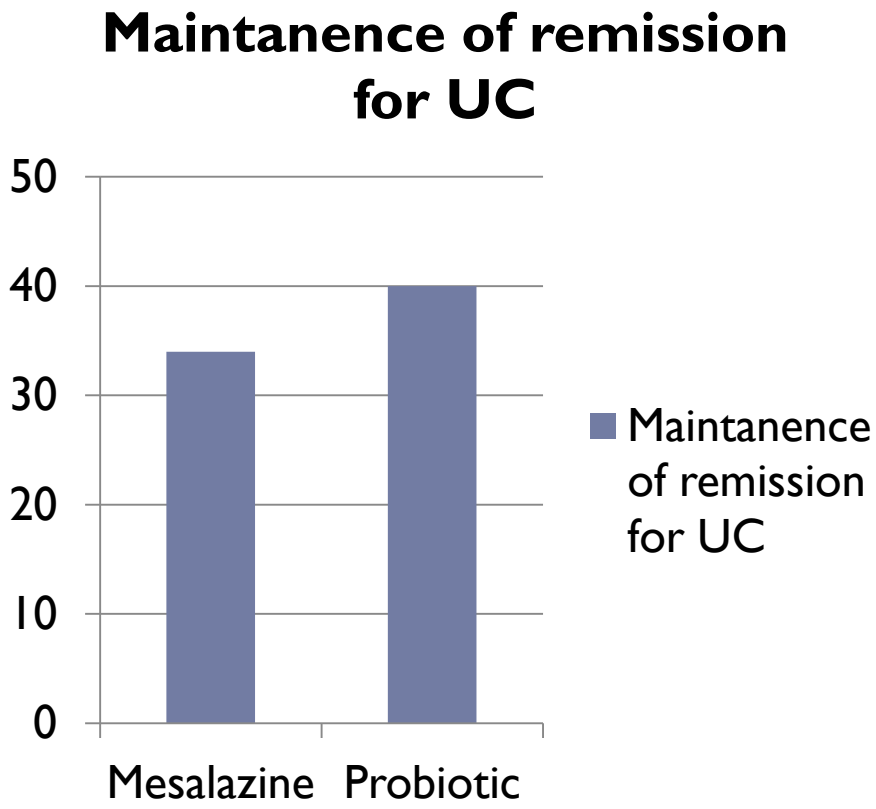
In ulcerative colitis

Children study

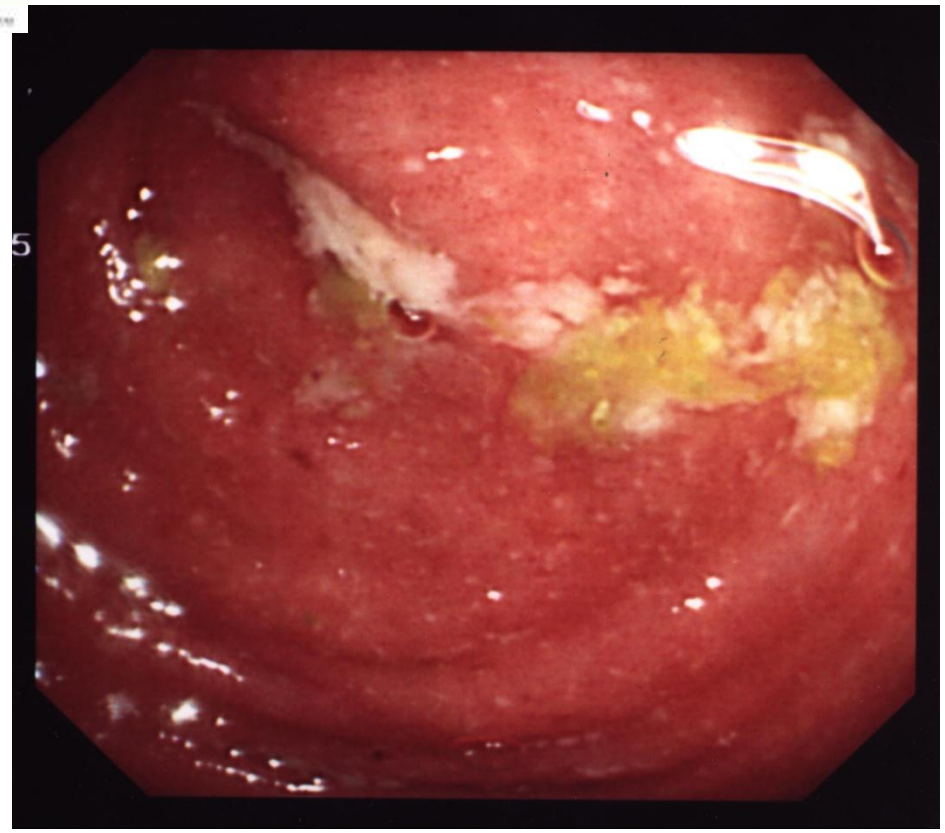


Miele AM J Gastr 2009

Adult study



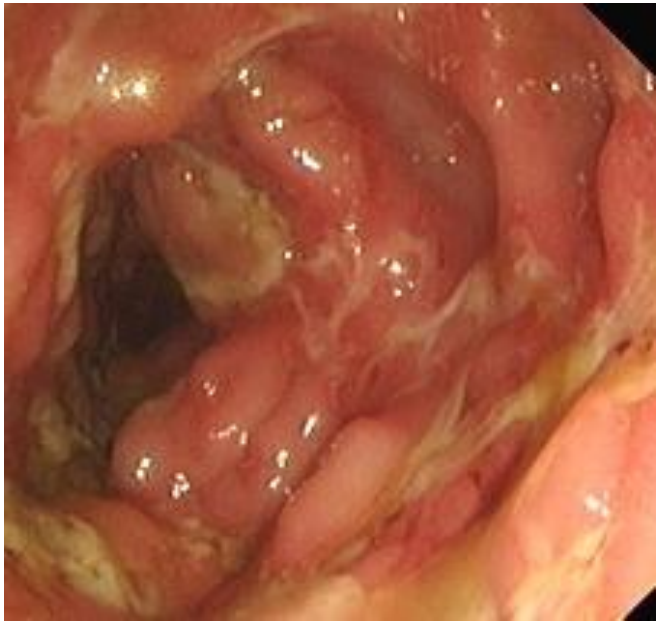
Naidoo Cochrane 2011



For UC

Probiotics cannot be **generally** recommended for ulcerative colitis

But ECCO states there is a role in the adult consensus statement



Crohn disease

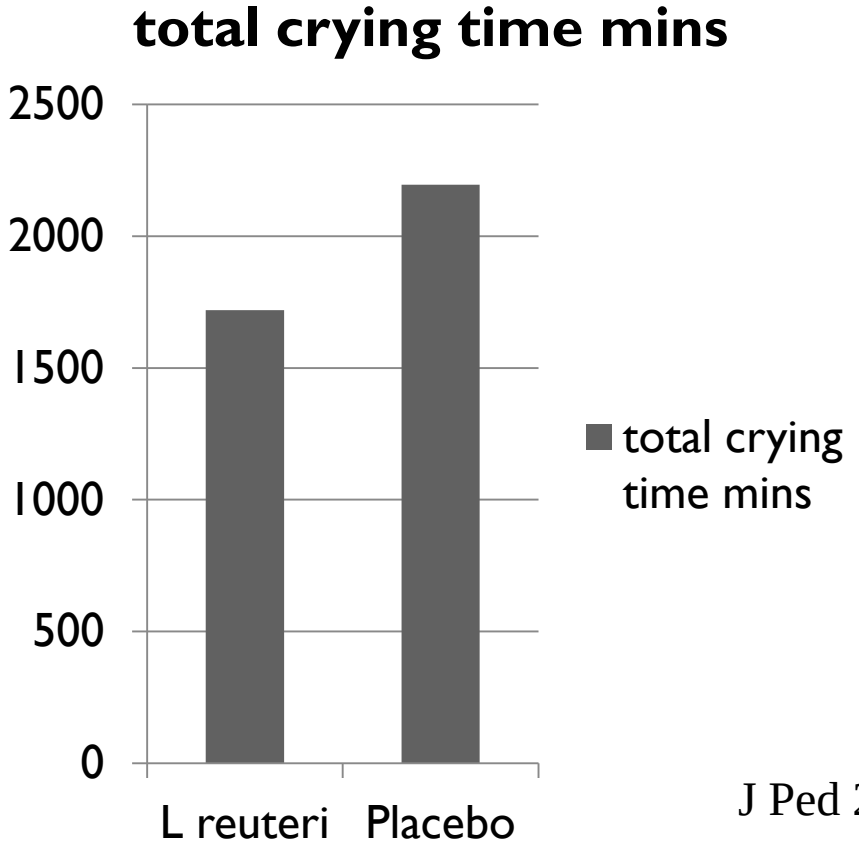
No role. No evidence

3.7 Probiotics

Statement 21

Probiotics are not recommended for maintenance of remission [EL3 (pediatrics) EL2 (adults)]

Infantile colic



- Hardly striking
- n=50
- Another 3 studies show the same reduced crying times

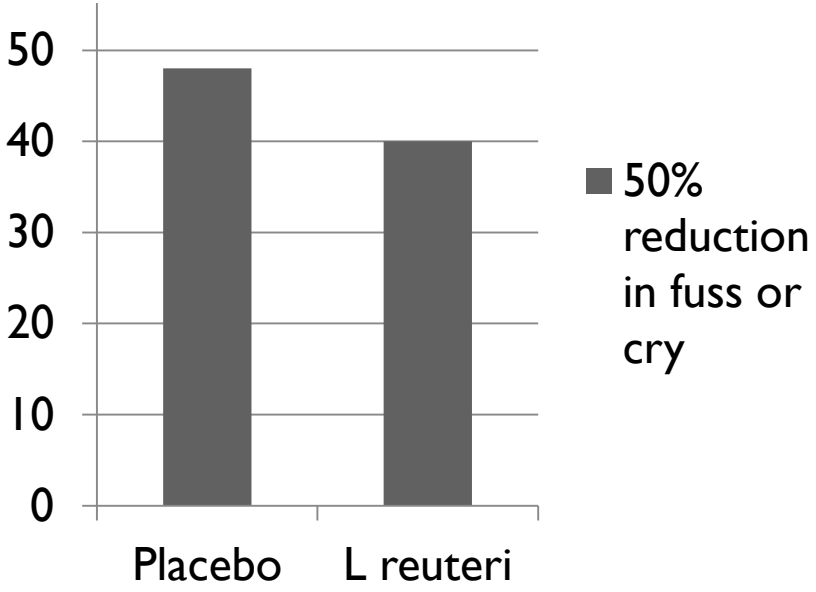
J Ped 2015

BMJ 2014;348:g2107 doi: 10.1136/bmj.g2107 (Published 1 April 2014)

167 breast fed infants

RESEARCH

Treating infant colic with the probiotic *Lactobacillus reuteri*: double blind, placebo controlled randomised trial



St. Mark's Hospital and Academic Institute

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

thebmj

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click for updates

BMJ 2014;348:g2107 doi: 10.1136/bmj.g2107 (Published 1 April 2014)

167 breast fed infants

RESEARCH

Treating infant colic with the probiotic *Lactobacillus reuteri*: double blind, placebo controlled randomised

Contradictory study, in breast fed, n=589,

JAMA Paediatric 2014

Reducing crying time by 51 mins per day by 1 month

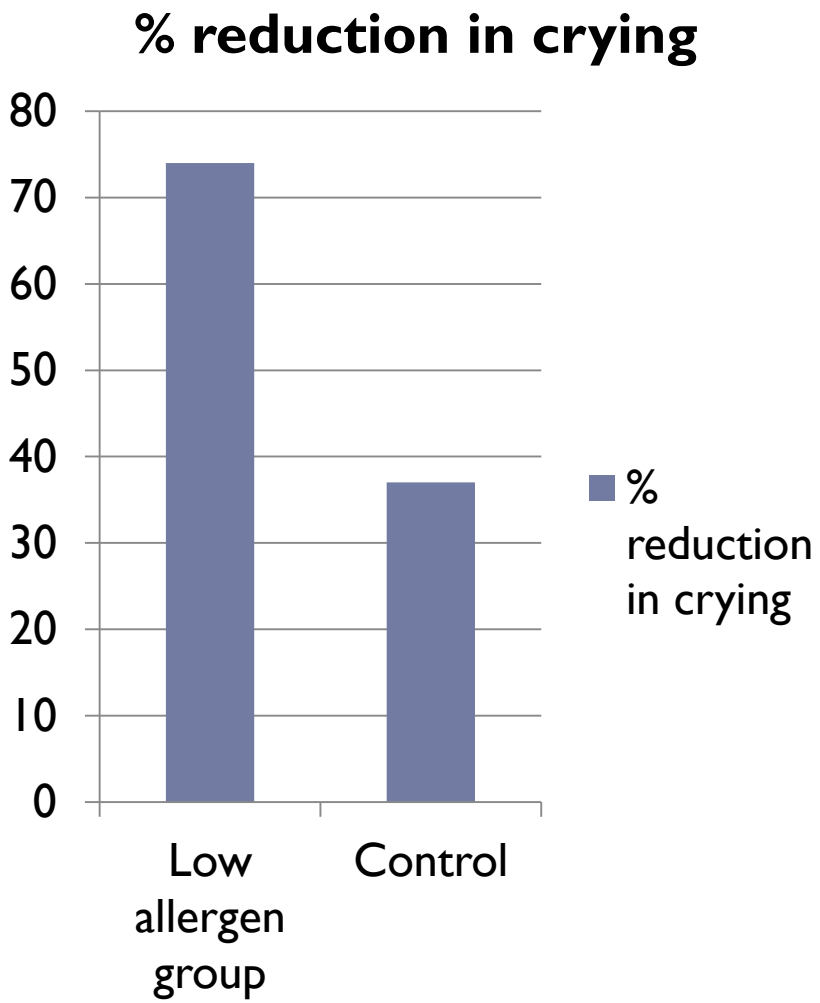
0

Placebo L reuteri

What about changing mother's diet?

- Reduction in cry fuss duration by 25%

Iacovou et al Mat Child Health 2012



How many allergic foods to reduce?
Vit D and dietician

Diet change

Has more value than reflux medicines

Don't over restrict maternal diet

Change infant formula for 2 weeks – then re offer regular CMF

BMJ

BMJ 2014;348:g2286 doi: 10.1136/bmj.g2286 (Published 1 April 2014)

EDITORIALS

Probiotics and infant colic

Still a hammer in search of a nail

So, with such a dearth of good evidence, perhaps the more important question is: "Should we be treating infant colic at all?" A great deal of accumulated clinical experience tells us that children with colic incur no serious long term effects from the disorder, and that symptoms abate with time. The potential harm associated with diagnostic testing and treatment of infants is likely to surpass the harm from colic itself.

Probiotics

Hardly a striking difference

Might reduce crying times

But there are other strategies that may work better – see infantile colic session

Controversial use of probiotics

Obesity

Non alcoholic steato-hepatitis

ORIGINAL ARTICLE: HEPATOLOGY AND NUTRITION

Probiotics to Adolescents With Obesity: Effects on Inflammation and Metabolic Syndrome

Probiotics did not impact on metabolic markers.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Gut Microbiota, the Genome, and Diet in Atherogenesis

Joseph Loscalzo, M.D., Ph.D.

olism. Changes in the microbial population within the gut can lead to alterations in normal metabolism that can potentially promote the development of obesity, the metabolic syndrome, and type 2 diabetes mellitus.[2] Cotter and colleagues[3] have recently defined this interaction between the genome and microbiome as a coordinated "supraorganismal" metabolism (a term

But I ask Krish

Do you really believe probiotics can get you from this to this? These are lifestyle choices, not gut flora?

Other conditions where these is no evidence probiotics are effective

- Constipation
- Prevention of extra-intestinal infections in children
- Cancer prevention

Bottom lines

? In favour of probiotics

✓ Treating viral gastroenteritis

✓ Preventing antibiotic associated diarrhoea

Uncertain benefit

? Preventing NEC

? Treat H pylori

✖ Treatment for IBS

? Treatment for ulcerative colitis

✖ Treatment for infantile colic

✖ Preventing atopy

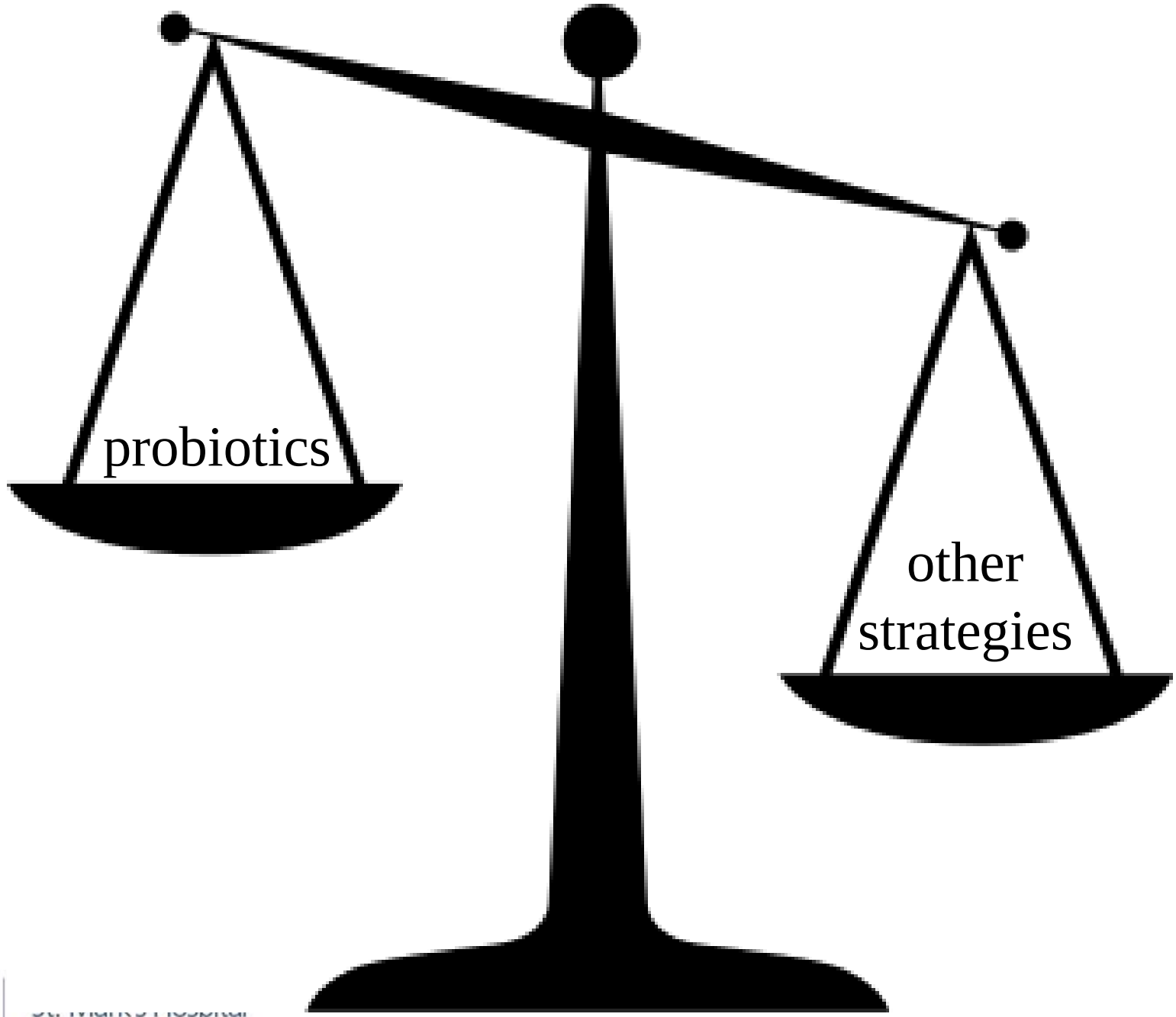
Not proven

✖Treatment of Crohns disease

✖ Prevention or treatment for human cancers

But it's the wrong question

Don't ask do probiotics work -
But ask if there is a better strategy for that illness/ symptom


probiotics
other
strategies

Probiotics or con?

Science Photo Library

See Comment page 634
See Articles page 651

Online publication during the past week of two randomised trials of probiotics will intensify debate about their role as nutritional supplements. In the largest study of probiotics to date, the Dutch Acute Pancreatitis Study Group, writing in *The Lancet*, showed that a combination of lactobacilli and bifidobacteria more than doubled mortality compared with placebo in 298 patients with predicted severe acute pancreatitis. By contrast, David Pyne and colleagues report in the *British Journal of Sports Medicine*, that another species of lactobacillus halved the frequency of respiratory infections in 20 high-performance distance runners.

How these findings translate to the 2 million people who consume probiotics regularly in the UK and who are neither world-class athletes, nor have acute pancreatitis is not clear. Though many studies have attributed benefit to probiotics, most have involved specific illnesses in hospital settings. The benefits of different strains and their mechanisms of action in typical consumers are uncertain. Indeed, the validity of advertised health benefits is being examined by a court in California, USA.

Regulation of the worldwide US$4 billion probiotic market is disjointed, since substantiation of claims must satisfy different local criteria depending on whether the products are considered foods, supplements, or drugs. Since July, 2007, the European Union requires scientific evidence to support claims of benefit. But labelling is often incomplete and misleading, despite recommendations by the Food and Agriculture Organization in 2002 to specify strain details, number of viable bacteria, storage conditions, and consumer information. For instance, a UK survey in 2006 found that half of 50 probiotics tested did not contain the specified strain or stated concentration.

By raising questions of safety and efficacy, the above trials should generate further probiotic research, which concerned consumers will want extended to community studies. Meanwhile, the WHO definition that probiotics confer a health benefit on the host might need revision, because after the Dutch group's results, it is no longer tenable to regard probiotics as risk-free. ■ *The Lancet*

For the **paper by Pyne et al** see the *British Journal of Sports Medicine* 2008; published online Feb 13. DOI:10.1136/bjsm.2007.044628

Probiotics or con?

Science Photo Library

See Comme
See Arti

Online publication during the past week of two randomised trials of probiotics will intensify debate about their role as nutritional supplements. In the largest study of probiotics to date, the Dutch Acute

Inadequate strain in the assay
$4-8 billion market
Storage
Survival in the stomach
And is it risk free?

benefits is being examined by a court in California, USA.

Regulation of the worldwide US$4 billion probiotic market is disjointed, since substantiation of claims must satisfy different local criteria depending on whether the

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BMJ 2016;352:i227 doi: 10.1136/bmj.i227 (Published 23 February 2016)

EDITORIALS

"Vaginal seeding" of infants born by caesarean section

How should health professionals engage with this increasingly popular but unproved practice?

- 25% of babies born by Caesarean section
- Modest increase risk in obesity, asthma and autoimmune disease
- Alteration in microbiota
- Neonatal antibiotics increase risk of atopy

Probiotics

We are just trying to reproduce normal gut flora.

Can we avoid changing the flora?

2.4 antibiotic courses before age 2 years in the US

Faecal transplantation in UC

- Effective in C difficile infection (NICE approved)
- Use in ulcerative colitis
- Can be used to maintain UC remission

For C difficile treatment

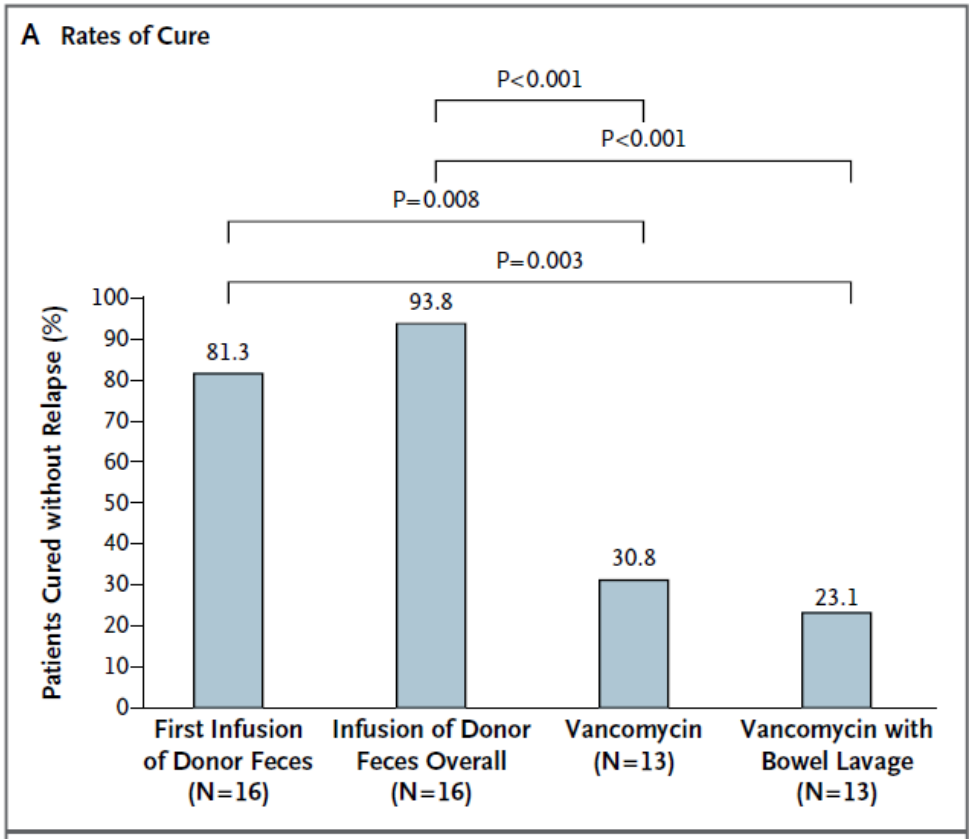
The NEW ENGLAND JOURNAL of MEDICINE

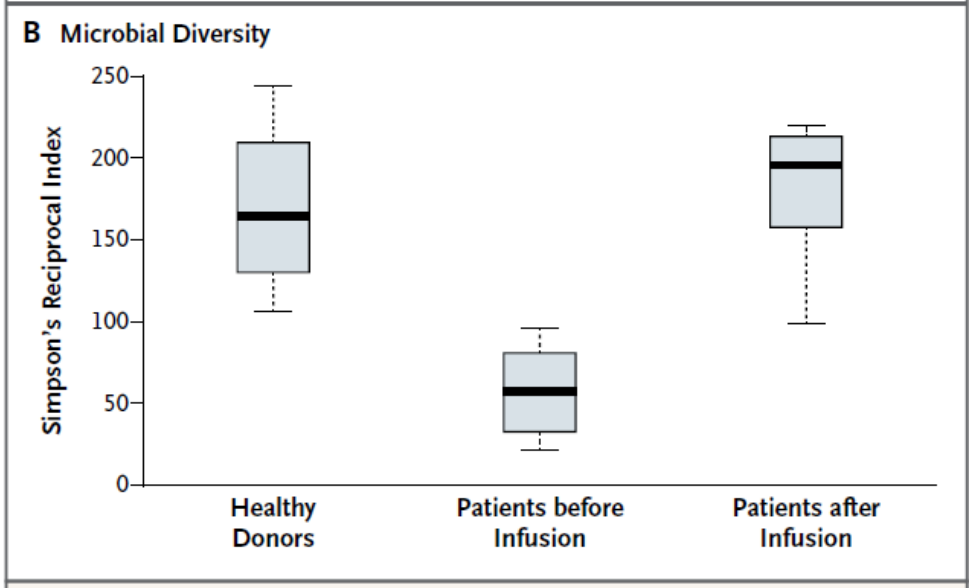
REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Clostridium difficile Infection

Daniel A. Leffler, M.D., and J. Thomas Lamont, M.D.





St. Mark's Hospital and Academic Institute

The irony of westernised living

The New England Journal of Medicine

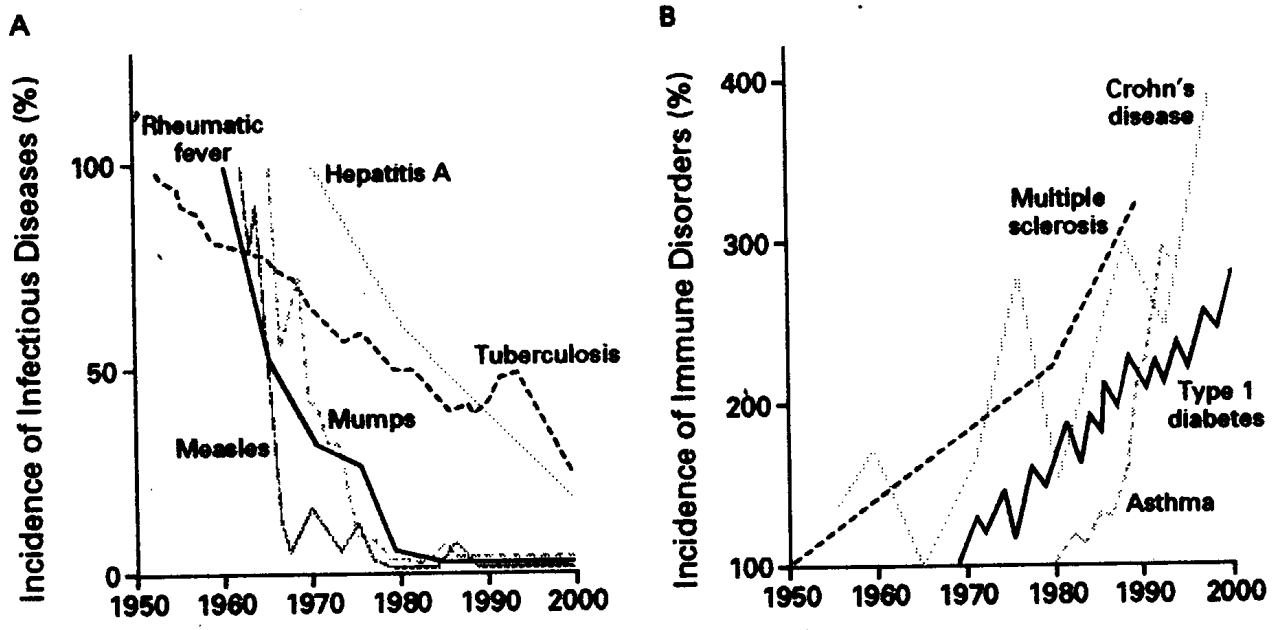


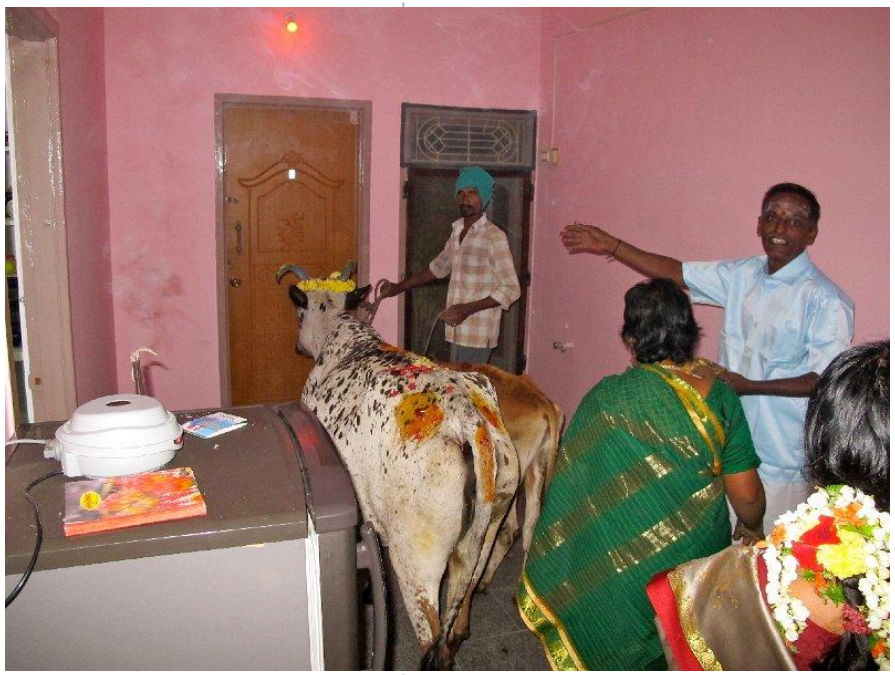
Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

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]

- Reduction in risk of atopic disease

Bring the cow, and filth back into the kitchen

Reduce urbanisation



Lancet 2001

The first opportunity for getting the environment right

Bottom Line

Mode of delivery

Neonatal antibiotics

Prematurity

Delays intestinal commensal probiotic bacterial colonisation compared to vaginal delivery

The Bottom Line

Do the probiotics work

In favour of probiotics

✓ Prevention and treating viral gastroenteritis

✓ Preventing antibiotic associated diarrhoea

Uncertain benefit

✓ Preventing NEC

✓ Treat H pylori

? Treatment for IBS

✓ Treatment for ulcerative colitis

? Treatment for infantile colic

? Preventing atopy

Not proven

✖ Treatment of Crohns disease

✖ Prevention or treatment for human cancers

But are they worth giving?

In favour of probiotics

- 👎 Prevention and treating viral gastroenteritis
- 👎 Preventing antibiotic associated diarrhoea

Uncertain benefit

- 👎 Preventing NEC
- 👎 Treat H pylori
- 👎 Treatment for IBS
- 👎 Treatment for ulcerative colitis
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- 👎 Preventing atopy

Not proven

- ✖ Treatment of Crohns disease
- ✖ Prevention or treatment for human cancers

👎 = **there is a better way**

Aims

- To change your opinion of probiotic use in children ✓
- To base your decision on high quality evidence and not studies prejudiced by publication bias ✓
- Have an understanding on the number needed to treat ✓
- Consider other strategies in preference ✓