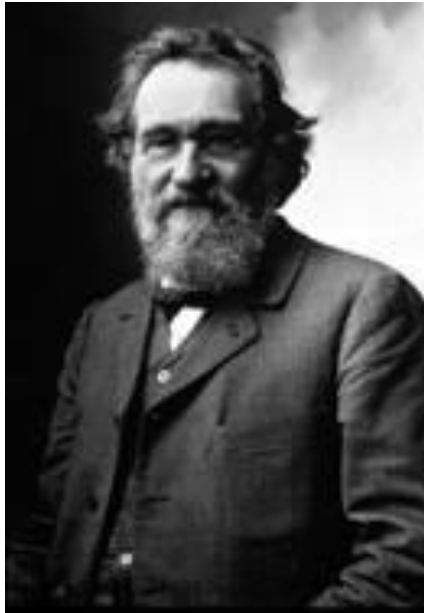


ProVen: Probiotics

Probiotic History



Elie Metchnikoff (1845-1916)



The Lab4 Consortium

Lab4 consists of four specially selected types of friendly probiotic bacteria:

- Lactobacillus acidophilus – strain 1
- Lactobacillus acidophilus – strain 2
- Bifidobacterium bifidum
- Bifidobacterium animalis (var lactis)



Lactobacillus acidophilus



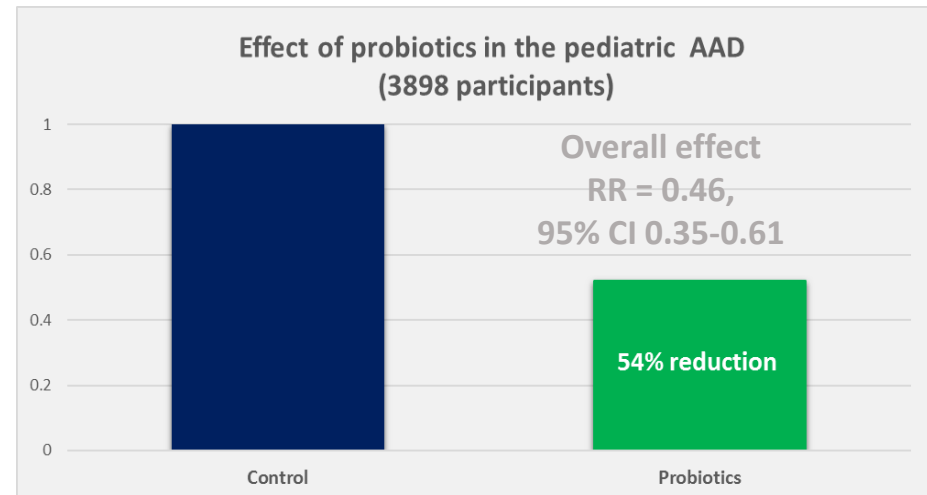
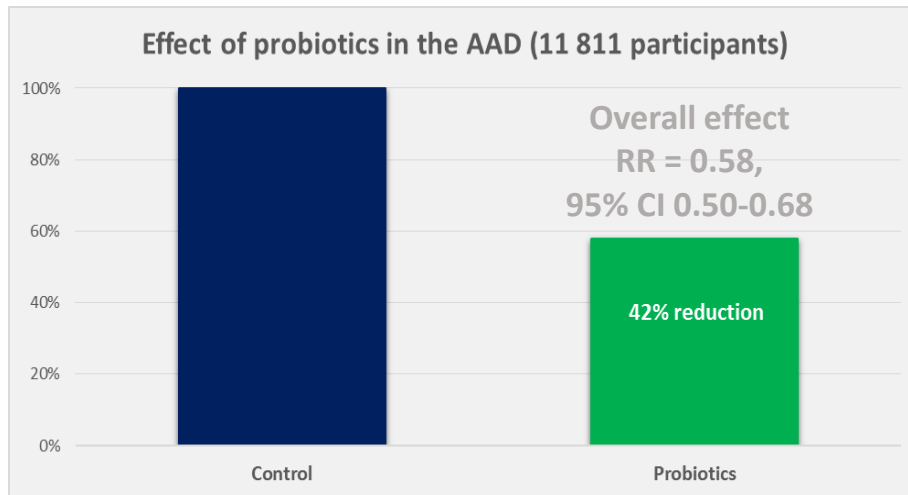
Bifidobacterium bifidum

Antibiotics and Associated Diarrhoea

- AAD – common adverse event with global prevalence of AAD ranges from 3.2% to 29%
- Among all AAD cases, 10-20% are associated with CDAD
- There are about 2000 new cases of CDAD in Ireland annually.
- Recurrence of CDAD occurs in approx. 30% of patients who initially responded to antibiotic therapy
- A more virulent strain of C. difficile (NAP1) emerged in 2000 and has spread throughout North America and Europe

A Review of Human Clinical Trials Performed with ProVen Probiotics Over the Last 12 Years

Probiotics and Antibiotic Associated Diarrhoea (AAD)



Probiotics and Antibiotic Associated Diarrhoea (AAD)

Trial type: Double blind placebo controlled

Location: Addenbrookes Hospital U.K

Aim: Use ProVen Adult to prevent or reduce *Clostridium difficile* infection and associated diarrhoea in patients receiving antibiotics.

Trial Design:

- 150 patients initiating antibiotic therapy were randomly assigned to probiotic 3 capsules of ProVen Adult daily or placebo group for 20 days with faecal sample taken at day 0 and 20
- Incidence of the following were monitored:
 - 1) Presence of *C.difficile*
 - 2) Presence of *C.difficile* toxin
 - 3) Incidence of diarrhoea

The Cambridge Clostridium difficile AAD Study

RCT with 150 patients initiating antibiotic therapy were randomly assigned to probiotic 1 capsule daily or placebo group for 20 days.

Outcomes

1) Incidence of *C.difficile*:

Placebo: 13.0%

ProVen: 15.9%

2) Incidence of *C.difficile* toxin:

Placebo: 78% of positives

ProVen: 46% of positives (sig diff)

3) Development of *C.difficile* associated diarrhoea:

Placebo: 67% of positives (7patients)

ProVen: 18% of positives (2 patients) (sig diff)

Plummer S et al 2004 International Microbiology 7: 59-62

The Cambridge Lab4 Antibiotic Trial 1 - Opportunistic Pathogen Re-growth Following Antibiotic Therapy

To investigate the following:

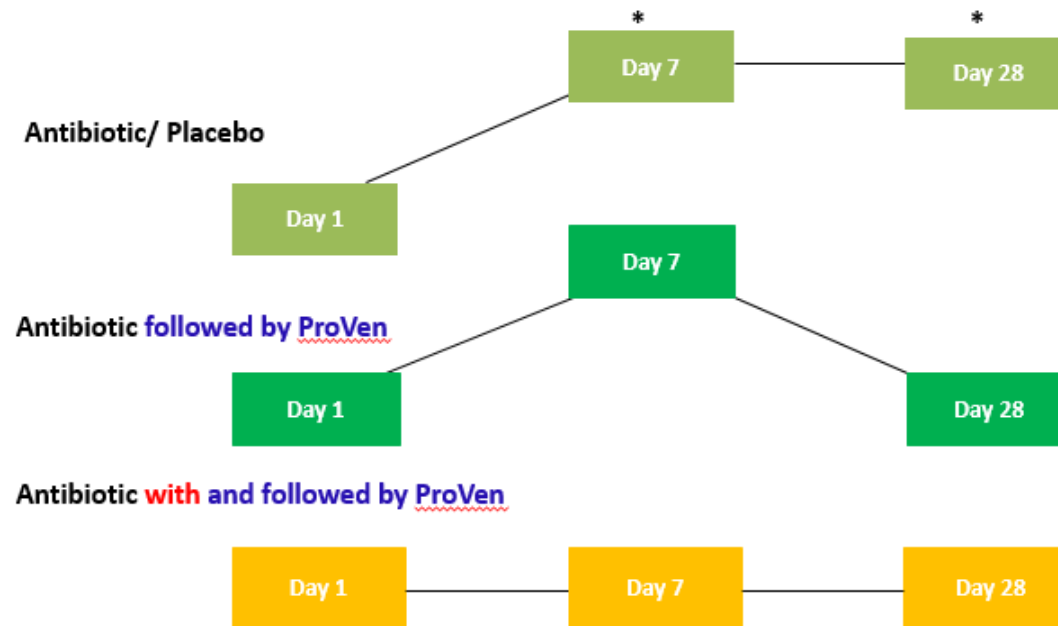
- Effects of antibiotics on re-growth of opportunistic pathogens
- Effects of probiotics on this opportunistic pathogen re-growth
- Two capsules of ProVen Adult per day for either 7 or 14 days

Cambridge Lab4 trial 1

| Group | Days | Treatment |
|--------------|-------------------------------|---|
| 1 | 1 – 7 8 – 15 | Antibiotic/Placebo Placebo |
| 2 | 1 – 7 8 – 15 | Antibiotic/Placebo Lab 4 |
| 3 | 1 – 7 8 – 15 | Antibiotic /Lab4 /Lab4 |

Samples: Days 1 (control), 7, 12, 17 and 28

Populations Effects of Antibiotics and ProVen Probiotics on the Population of Enterobacter, Enterococcal and Staphylococcal



Madden et al 2005, Int Immunopharm 5; 1091-97

Cambridge Antibiotic Resistance Trial 2

Effect of ProVen on Antibiotic Resistance in the Re-growth Microbiota

The emergence of antimicrobial drug resistance adversely affects patient care and threatens the management of public health infectious diseases globally. (WHO World Health Report 2007: a safer future)

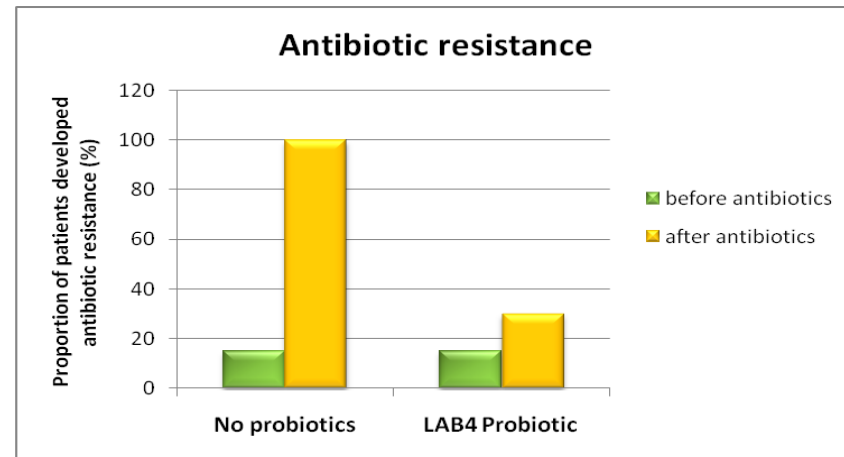
Antibiotic resistance will eventually result in all antibiotics being ineffective against virtually all pathogens. This is probably the most important problem to face global healthcare in the coming century.

Aim of DBPC Trial:

Patients requiring antibiotic therapy received two capsules of ProVen Adult (25 billion/day) or placebo daily for 21 days in conjunction with antibiotics.

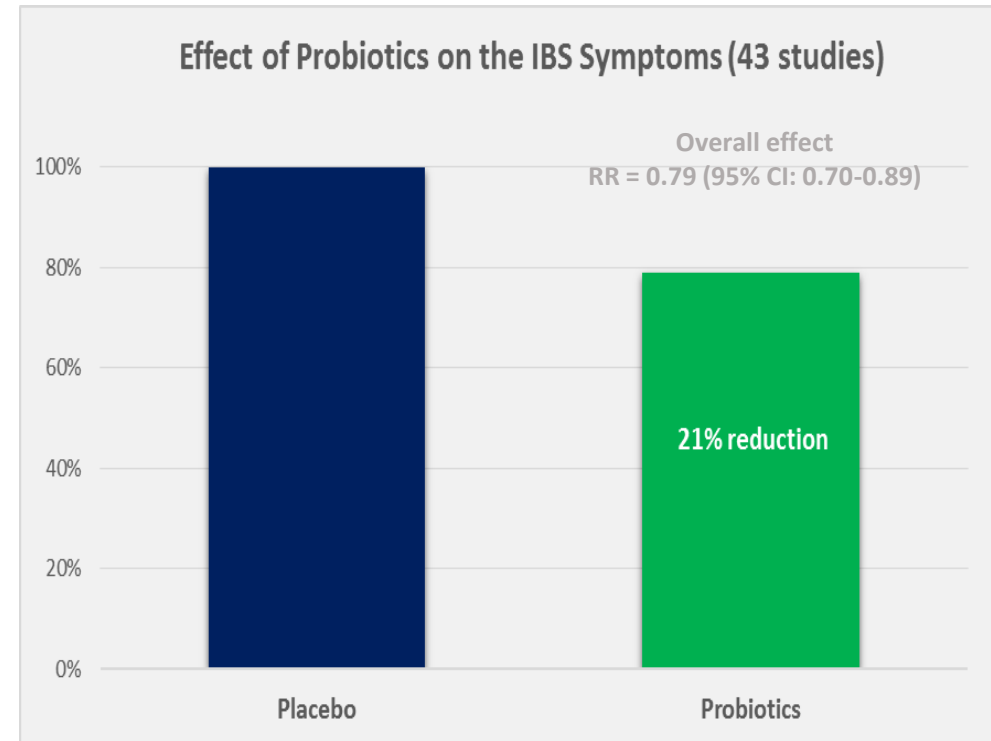
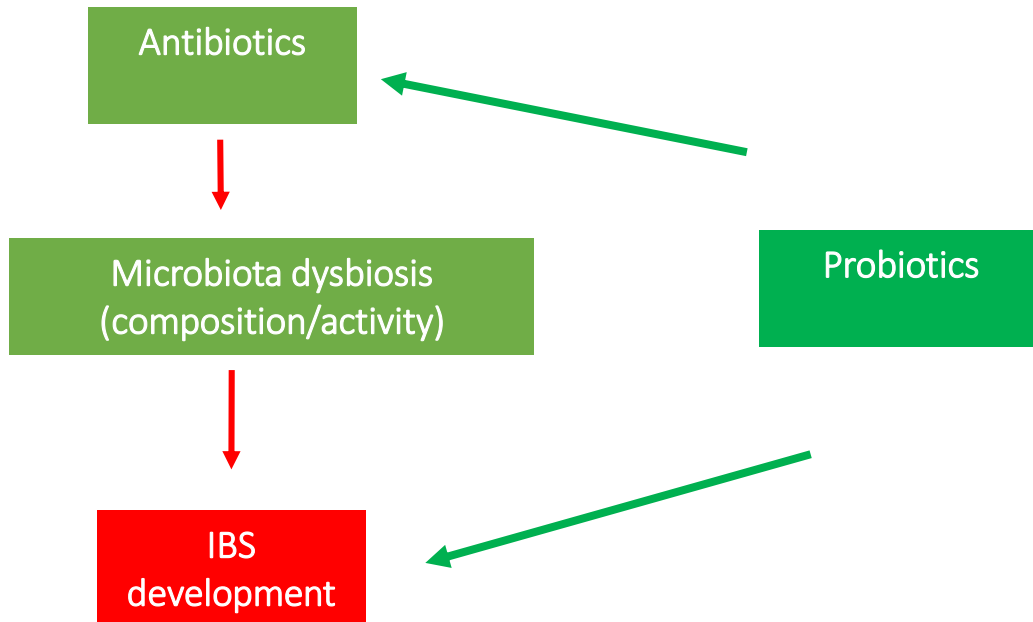
Plummer et al 2005, Int J Antimicrob Agents 26

Cambridge Antibiotic Resistance Trial – Results



- The types measured were the Enterobacteria
- At the start, about 18% of patients had detectable levels of antibiotic resistant Enterobacteria
- After the trial, the control group 100% of patients developed detectable levels of antibiotic resistant Enterobacteria, whereas only 30% of the probiotic group had detectable levels of antibiotic resistant Enterobacteria,

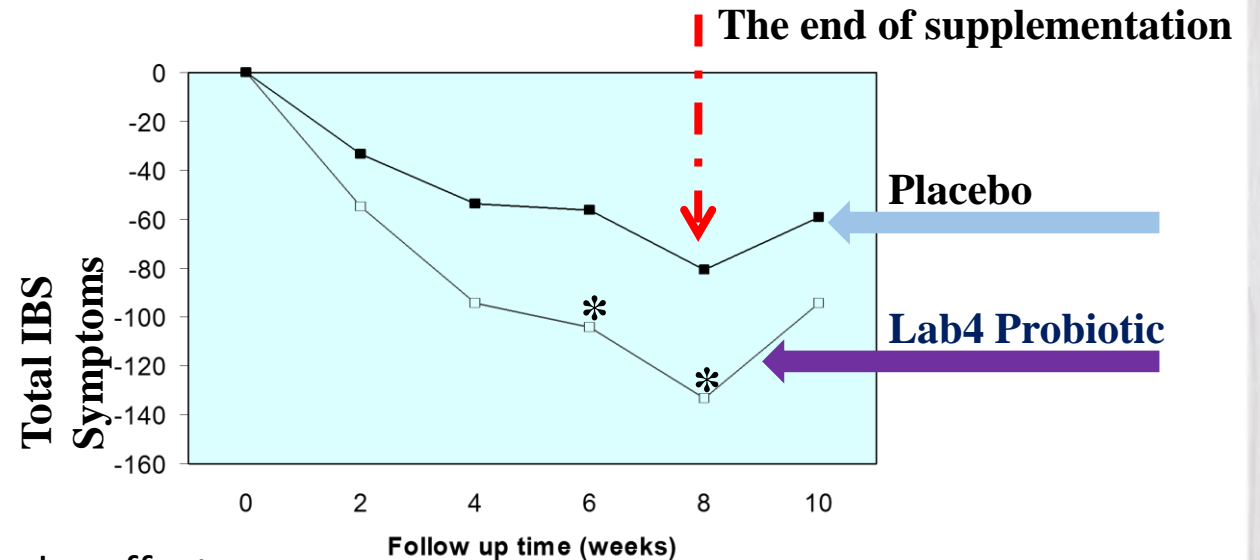
Probiotics and the Treatment of IBS



Summary Results of Sheffield LAB4 IBS Trial

Significant reduction of Total IBS Symptoms comprising:

- number of days with pain
- severity of pain
- bloating
- satisfaction with bowel habit
- quality of life



- Significant difference observed despite strong placebo effect
- Continuous supplementation is necessary to sustain the effect