
Proeldoper
MEDICAL TRAINING SLIDES

Introduction

- Diarrhea refers to the abrupt onset of three or more loose or liquid stools per day.
- Acute diarrhea is defined as an abnormally frequent discharge of semi-solid or fluid fecal matter from the bowel, lasting less than 14 days.
- Although preventable, acute diarrhea remains a major cause of morbidity and mortality in children worldwide,
- Resulting in 525,000 deaths per year among those younger than five years.
- Most of these mortalities occur in developing countries.

Beaugerie L et al. Presse Med. 2013 Jan;42(1):52-9.

Introduction conti..

- Other direct consequences of diarrhea in children include Impaired growth, malnutrition, and impaired cognitive development.
- Acute diarrhea in children is caused by a wide range of pathogens:
  - Viral,
  - Bacterial,
  - Protozoal Pathogens
- which makes overcoming the high disease burden a large challenge.

Beaugerie L et al. Presse Med. 2013 Jan;42(1):52-9.

Treatment guideline..

- Currently, the World Health Organization (WHO) recommends:

Oral rehydration salts (ORS) and continued feeding for the prevention and treatment of dehydration, as well as zinc supplementation to shorten the duration and severity of the diarrheal episode.

https://www.who.int/elena/titles/bbc/zinc_diarrhoea/en/

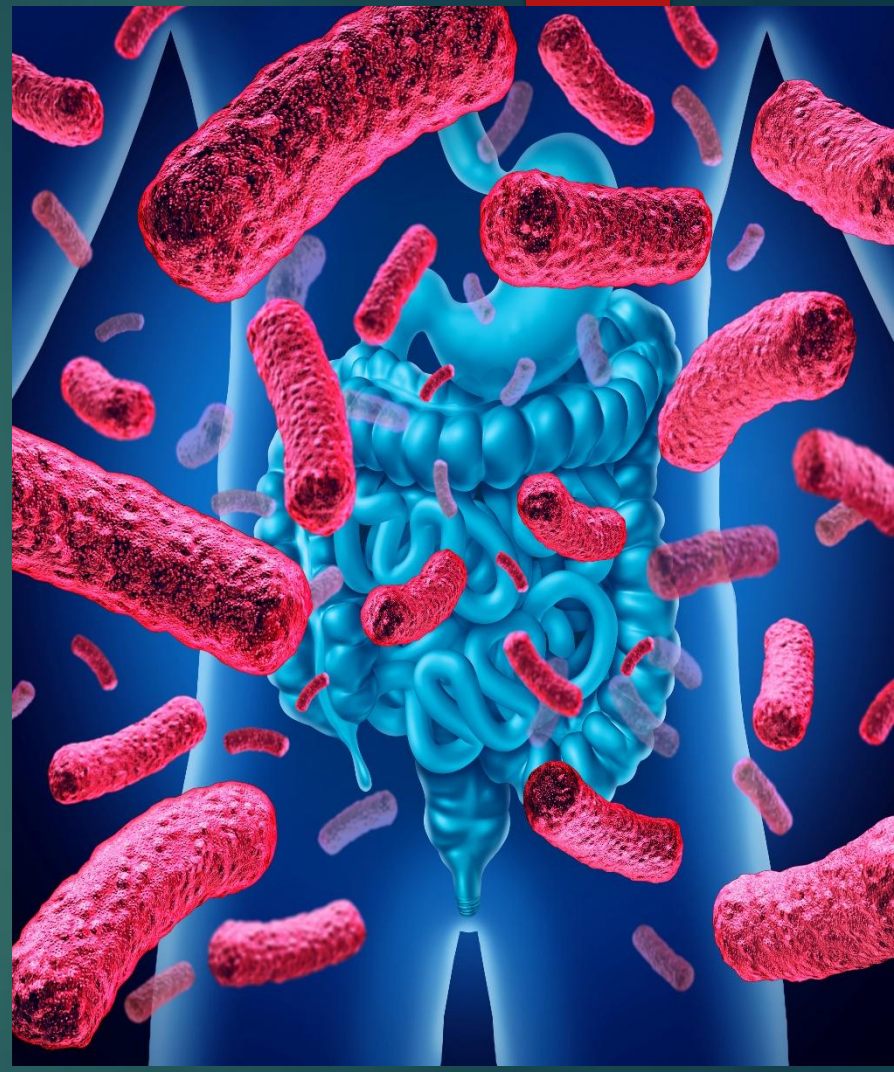
Probiotics

- "Probiotic" is derived from Latin word **'pro' –for and Greek word "biotic" – life**.
- Probiotics are living micro-organisms that, upon ingestion in certain numbers, exert health benefits beyond inherent general nutrition.

Tarvade S et al. Indian Journal of Basic and Applied Medical Research: June 2014:3(3):434-445

Probiotics

- Probiotics can play an important role in immunological, digestive and respiratory functions and could have a significant effect in alleviating infectious disease in children and adults.
- It has been suggested that probiotics
  - Modulate the immune response,
  - Produce antimicrobial agents, and
  - Compete in nutrient uptake and adhesion sites with pathogens.



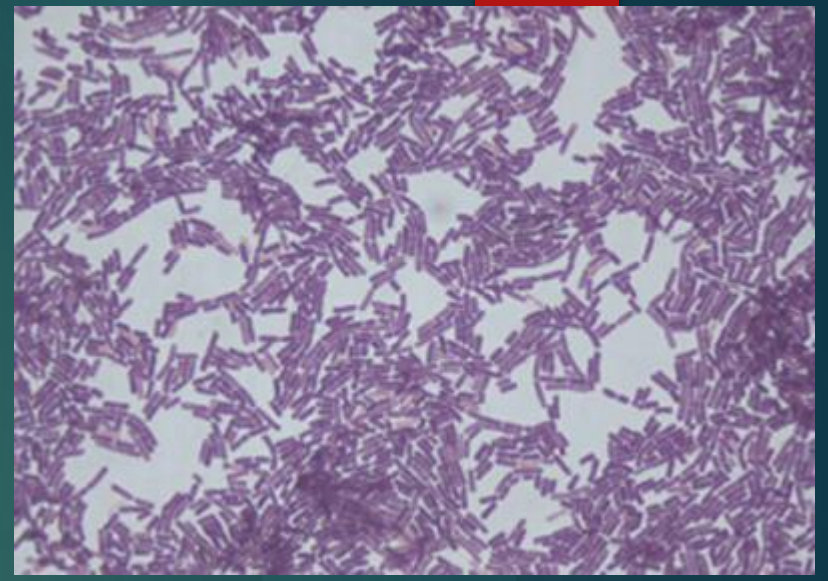
Tarvade S et al. Indian Journal of Basic and Applied Medical Research: June 2014:3(3):434-445

Classification of Probiotics

Lactobacillus Spp.	*Acidophilus* *Plantarum* *Rhamnosus* *Paracasei* *Fermentum*	Reuteri Johnsonii Brevis Casei Lactis Delbrueckii Gasseri
Bifidobacterium Spp.	*Breve* *Infantis* *Longum* *Bifidum* *Thermophilum* *Adolescentis* *Animalis* *Lactis*	
Bacillus Spp.	*Coagulans* ***Clausii***	
Streptococcus Spp.	*Thermophilus*	
Enterococcus Spp.	*Faecium*	
Saccharomyces Spp.	*Cerevisiae*	

Khalighi A et al. IntechOpen 2016. DOI: 10.5772/63646. Available from: https://www.intechopen.com/books/probiotics-and-prebiotics-in-human-nutrition-and-health/probiotics-a-comprehensive-review-of-their-classification-mode-of-action-and-role-in-human-nutrition

Bacillus clausii



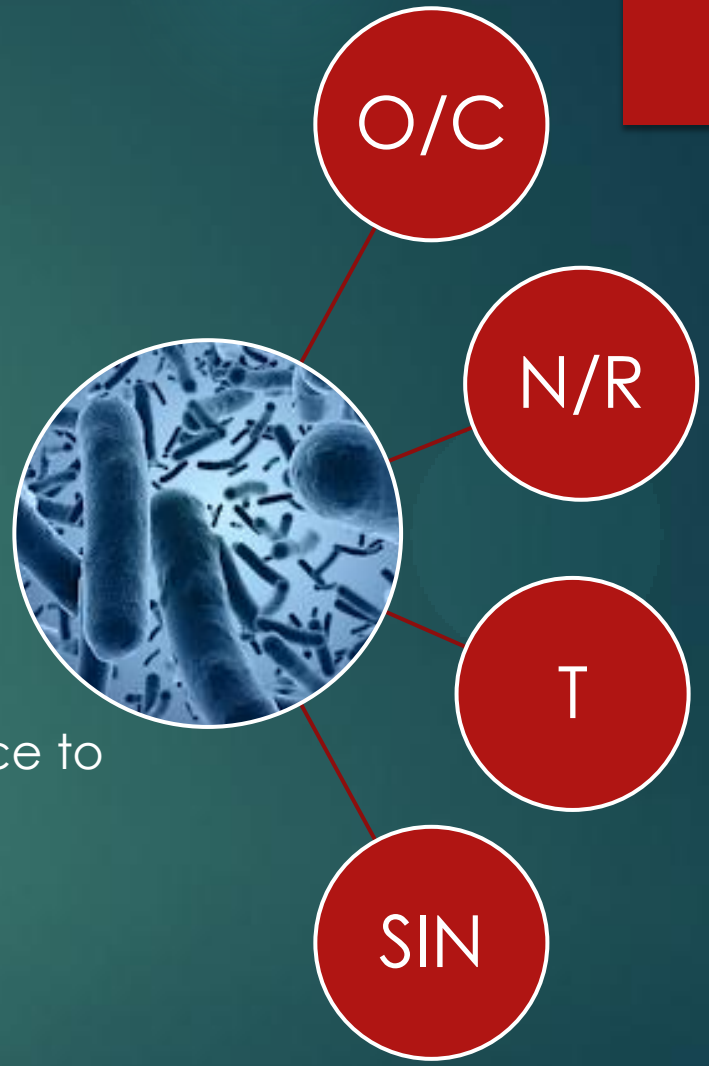
Characteristics

- *Bacillus clausii* is a
  - Rod-shaped,
  - Non-pathogenic,
  - Spore-forming,
  - Aerobic,
  - Gram-positive Bacterium
- Able to survive transit through the acidic environment of the stomach and colonize the intestine even in the presence of antibiotics.

Marseglia GL et al. Ther Clin Risk Manag. 2007 Mar; 3(1): 13–17

Bacillus clausii strains

There are 4 commonly used strains:



The designations of these strains are derived from their resistance to diverse antibiotics:

- O/C is resistant to chloramphenicol,
- N/R is resistant to Novobiocin and Rifampin,
- T is resistant to Tetracycline, and
- SIN is resistant to neomycin and streptomycin

Senesi S et al. Appl Environ Microbiol. 2001 Feb; 67(2): 834–839

Mechanism of action of Probiotics

1. Production of growth substrates for the growth of good bacteria
2. Competition for binding sites with pathogenic bacteria
3. Improved barrier function
4. Reduction of inflammation, thus altering intestinal properties for colonization
5. Stimulation of innate immune response (by unknown mechanisms)

Khalighi A et al. IntechOpen 2016. DOI: 10.5772/63646. Available from: https://www.intechopen.com/books/probiotics-and-prebiotics-in-human-nutrition-and-health/probiotics-a-comprehensive-review-of-their-classification-mode-of-action-and-role-in-human-nutrition

Antimicrobial and Immunomodulatory activities of the *B. clausii* probiotic strains.

- In vitro each of the four *B. clausii* probiotic strains **stimulated the production of IFN- γ** by murine spleen cells.

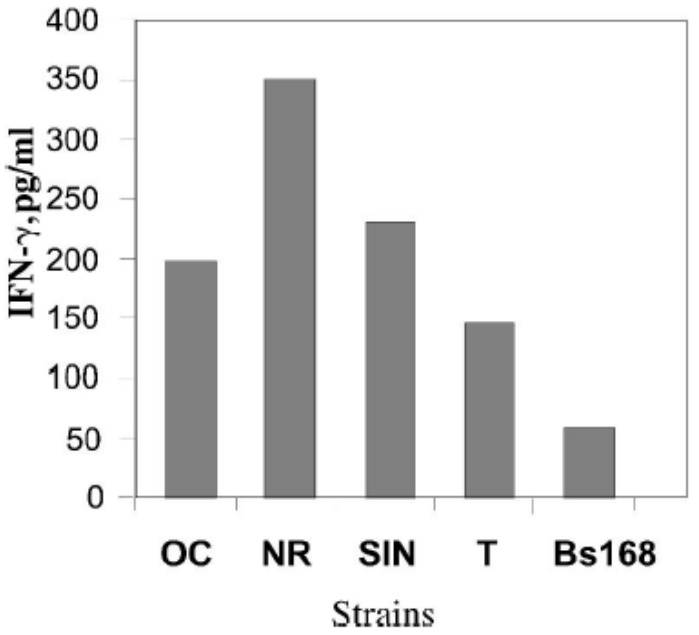


FIGURE 2. Stimulation of IFN-γ production by murine spleen cells induced with *B. clausii* probiotic strains. Spleen cells were isolated from C57BL/6j mice and cocultured with probiotic strain *B. clausii* OC (O/C), *B. clausii* NR (N/R), *B. clausii* SIN (SIN), *B. clausii* T (T), or reference strain *B. subtilis* 168 (Bs168). Analysis of IFN-γ production by murine spleen cells was realized 72 hours later using ELISA.

Urdaci MC et al. J Clin Gastroenterol. 2004;38(2): S86-S90

Antimicrobial and Immunomodulatory activities of the *B. clausii* probiotic strains.

- Moreover, all these strains induced the **proliferation of murine CD4+ T cells** in the presence of Antigen Presenting Cells.

TABLE 2. *B. clausii* Probiotic Strains Stimulate Proliferation of Murine $CD4^+$ T Cells

Strain/Immunostimulater	Stimulation of Murine $CD4^+$ T Cell* Proliferation, Index of Stimulation
B. clausii OC	2.5
B. clausii NR	3.8
B. clausii SIN	2.7
B. clausii T	2.9
B. subtilis 168	1.9
Con A, 2 µg/mL†	3.4

*A total of 5×10^5 CFU bacteria was used for stimulation of 2×10^5 $CD4^+$ T cells in the presence of irradiated (3300 rad) naive murine spleen cells (5×10^5 cells). Spleen and $CD4^+$ T cells were isolated from C57Bl/6j mice.

†Concanavalin A was used as a positive control for $CD4^+$ T-cell stimulation.

Urdaci MC et al. J Clin Gastroenterol. 2004;38(2): S86-S90

Antimicrobial and Immunomodulatory activities of the *B. clausii* probiotic strains.

- The exact mechanisms are not fully understood but the **above changes seem to have an antibacterial effect**

TABLE 1. Inhibitory Activity Produced by *B. clausii* OC Supernatant for Different Pathogenic and Nonpathogenic Intestinal Bacteria and Other Microorganisms

Strain Tested	Activity*
S. aureus CIP† 350 53 156	++
Enterococcus faecium LMBA‡ 27323	+
E. faecium LMBA 27323	+
Micrococcus sp LMBA 26	++
Lactococcus lactis ATCC§ 11454	+
L. lactis LMBA 374	+
Clostridium difficile 514¶	++
Escherichia coli LMBA 20684	–
Salmonella enterica serovar; S. typhimurium ATCC 29629	–
S. flexneri LMBA 12225	–
Vibrio cholerae NCTC** 8021	–
V. parahaemolyticus ATCC 17802	–
Pseudomonas fluorescens LMBA BE1	–
Fusarium oxysporum ox52††	–

*Antimicrobial activity determined by agar diffusion test.

Urdaci MC et al. J Clin Gastroenterol. 2004;38(2): S86-S90

Table 2. Graded recommendations for probiotic formulations for the prevention or treatment of 19 different types of diseases.

Type of disease	No. of study arms	Strong evidence* (no. + RCTs/no. negative RCTs)	Moderate evidence* (no. + RCTs/no. negative RCTs)	Weak to not effective* (no. + RCTs/no. negative RCTs)
Prevention				
Pediatric acute diarrhea	61	*S. boulardii* I-745 (25+/4-) *L. rhamnosus* GG (10+/3-) *L. reuteri* 17938 (3+/0-) *L. acidophilus* LB (3+/1-) *L. casei* DN114001 (3+/0-) *Bac. clausii* mix (O/C, N/R84, T84, Sin8 (3 +/1-) 8-strain mix (2+/0-)	LhLr (2+/1-)	None

LhLr mix, L. helveticus R52 (CNCM I-1722) + L. rhamnosus R11 (CNCM I-1720),

Sniffen JC et al. PLoS ONE 2018; 13(12):e0209205

Proeldoper

Proeldoper

Composition

- Each 5 ml oral suspension contains:
- *Bacillus clausii* spores 2 x 10^9 spores

Dosage

- Adults 2-3 mini bottles a day
- Childre 1-2 mini bottles a day

Proeldoper

Therapeutic indications

- For the treatment of alterations in the intestinal bacterial flora.
- **DCGI Date of approval:** 28-01-2005

Proeldoper

- Proeldoper is a preparation of **Bacillus clausii spores**, normal inhabitants of the intestine, with no pathogenic properties.
- Administered orally, Bacillus clausii spores, due to their **high resistance to both chemical and physical agents,** cross the barrier of the acid gastric juices and reach the intestinal tract.
- In the intestinal tract they are **transformed form spores into metabolically active organisms.**

Proeldoper

- The administration of Proeldoper contributes to the **recovery of the intestinal microbial flora** altered during the course of intestinal microbial imbalance of diverse origin.
- Furthermore, since the Bacillus clausii is **capable of producing various vitamins**, in particular group B vitamins, it contributes to correcting the dysvitaminosis caused by antibiotics and chemotherapeutic agents in general.

Proeldoper

- Proeldoper can be administered in the interval between two doses of antibiotic.
- The antibiotic-resistance refers to:

  - Penicillin,
  - the Cephalosporins,
  - Tetracyclines,
  - Macrolides,
  - Aminoglycosides,
  - Novobiocin,
  - Chloramphenicol,
  - Thiamphenicol,
  - Lincomycin,
  - Isoniazid,
  - Cycloserine,
  - Rifampicin,
  - Nalidixic acid
  - Pipemidic acid.

Side effects

- Hypersensitivity reactions, including rash urticaria and angioedema have been reported

Precautions for use

- During antibiotic therapy, the product should be administered in the interval between one dose of antibiotic and the next.

Pregnancy and lactation

- There are no contraindications regarding the use of the product during pregnancy and lactation.

Clinical studies

Bacillus clausii as adjunctive treatment for acute community-acquired diarrhea among Filipino children: a large-scale, multicenter, open-label study (CODDLE)

Methods:

- A total of 3178 patients (median age of 2 years) were enrolled
- Treated with one to two vials of *Bacillus clausii* in the following bacterial stains: O/C, SIN, N/R, and T (oral suspension of 2 billion spores per 5-mL vial)
- Duration: 5 to 7 days.

Castro et al. Tropical Diseases, Travel Medicine and Vaccines 2019; 5:14

Bacillus clausii as adjunctive treatment for acute community-acquired diarrhea among Filipino children: a large-scale, multicenter, open-label study (CODDLE)

In more than half of the per-protocol population (1535/2916; 52.6%), **diarrhea was resolved within the first 3 days** of treatment with *Bacillus clausii*.

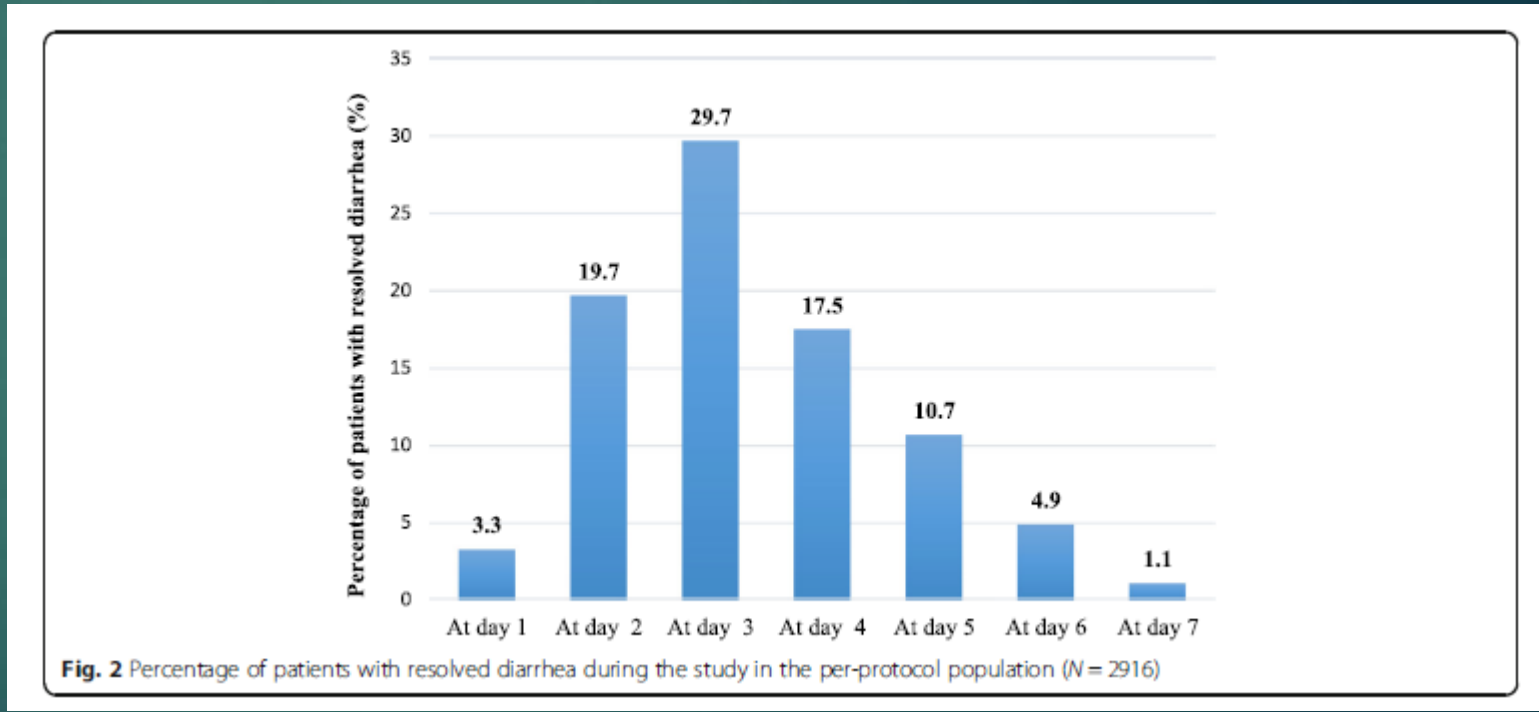


Fig. 2 Percentage of patients with resolved diarrhea during the study in the per-protocol population ($N = 2916$)

Castro et al. Tropical Diseases, Travel Medicine and Vaccines 2019; 5:14

Bacillus clausii as adjunctive treatment for acute community-acquired diarrhea among Filipino children: a large-scale, multicenter, open-label study (CODDLE)

There was no significant difference (p = 0.297) in mean **diarrhea duration** between patients with either antibiotic-associated (3.3 ± 1.3 days) or viral diarrhea (3.4 ± 1.3 days).

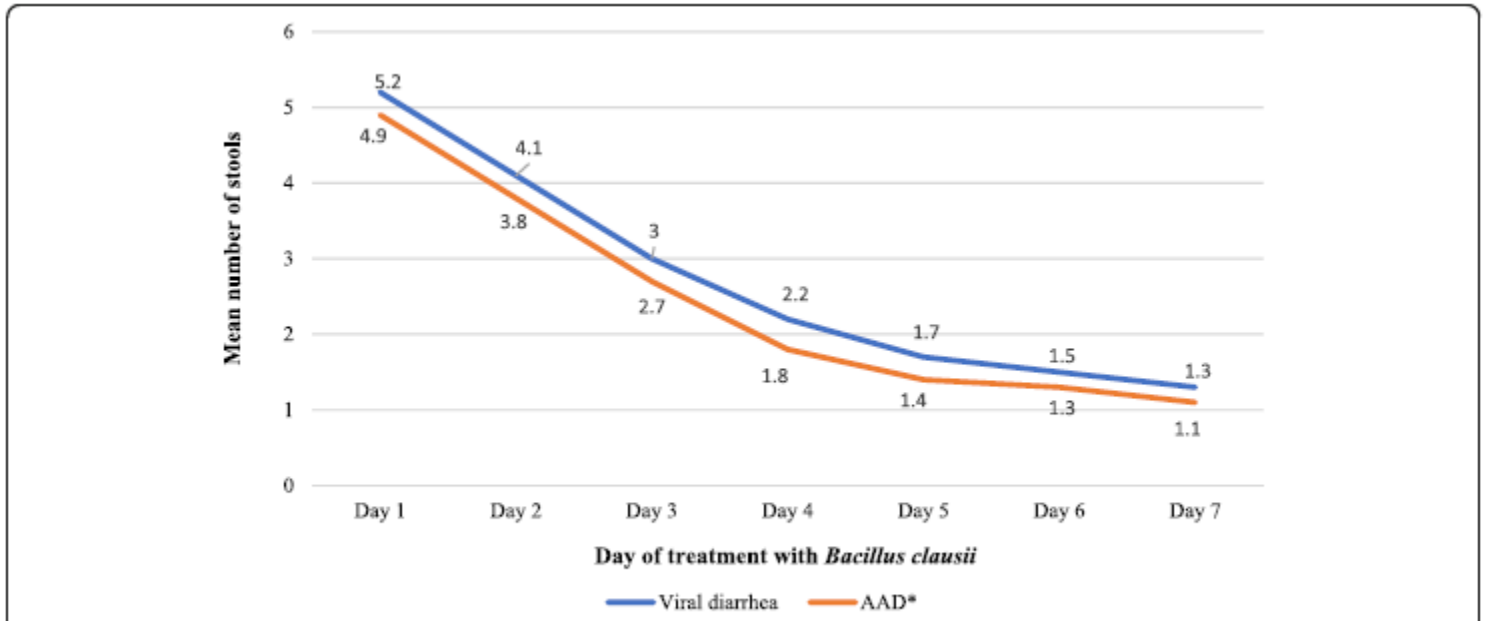


Fig. 3 Mean number of stools per day of treatment, according to the cause of diarrhea. *AAD, antibiotic-associated diarrhea. Repeated measures analysis of variance: viral diarrhea versus AAD: $p = 0.938$

Castro et al. Tropical Diseases, Travel Medicine and Vaccines 2019; 5:14

Bacillus clausii as adjunctive treatment for acute community-acquired diarrhea among Filipino children: a large-scale, multicenter, open-label study (CODDLE)

GI symptoms before and after *B.clausii* administration showed **significant decrease**

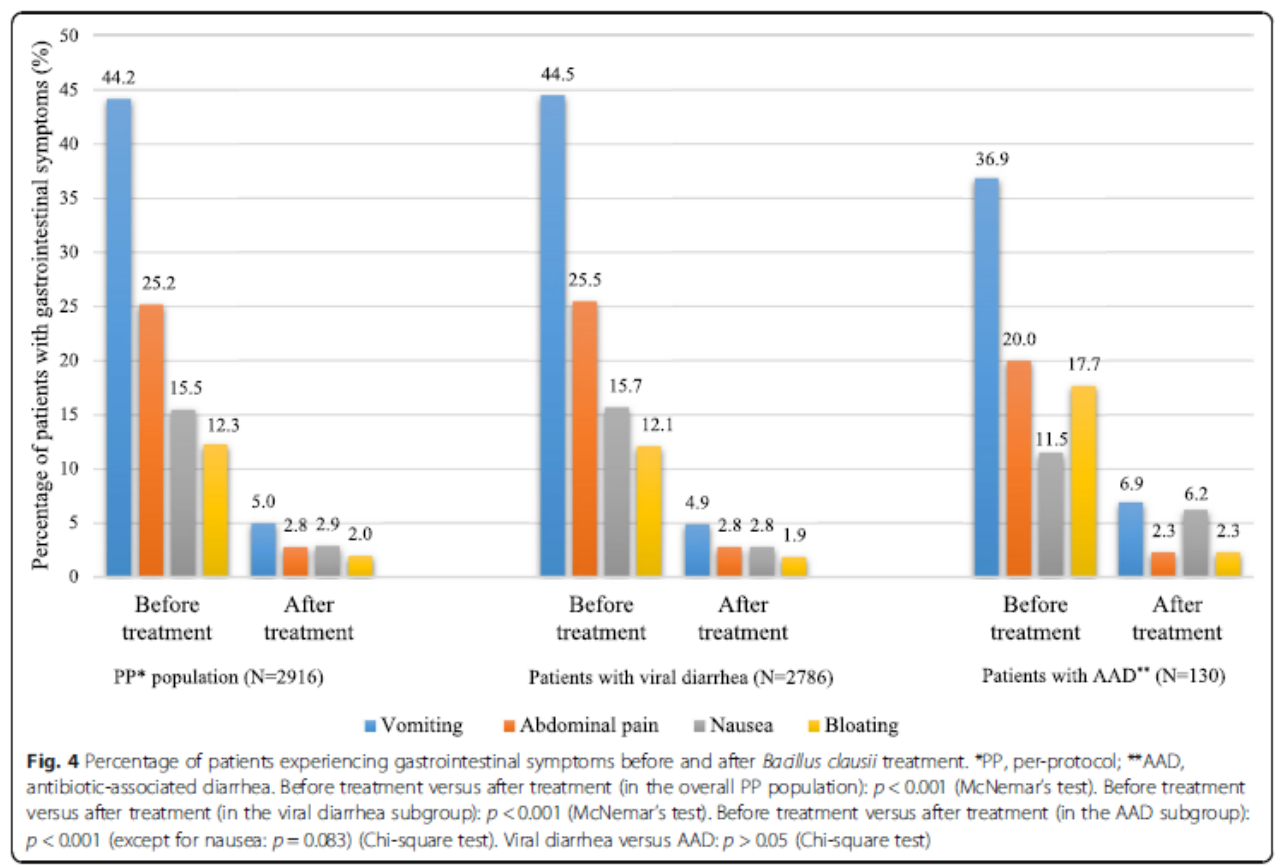


Fig. 4 Percentage of patients experiencing gastrointestinal symptoms before and after *Bacillus clausii* treatment. *PP, per-protocol; **AAD, antibiotic-associated diarrhea. Before treatment versus after treatment (in the overall PP population): $p < 0.001$ (McNemar's test). Before treatment versus after treatment (in the viral diarrhea subgroup): $p < 0.001$ (McNemar's test). Before treatment versus after treatment (in the AAD subgroup): $p < 0.001$ (except for nausea: $p = 0.083$) (Chi-square test). Viral diarrhea versus AAD: $p > 0.05$ (Chi-square test)

Castro et al. Tropical Diseases, Travel Medicine and Vaccines 2019; 5:14

Bacillus clausii as adjunctive treatment for acute community-acquired diarrhea among Filipino children: a large-scale, multicenter, open-label study (CODDLE)

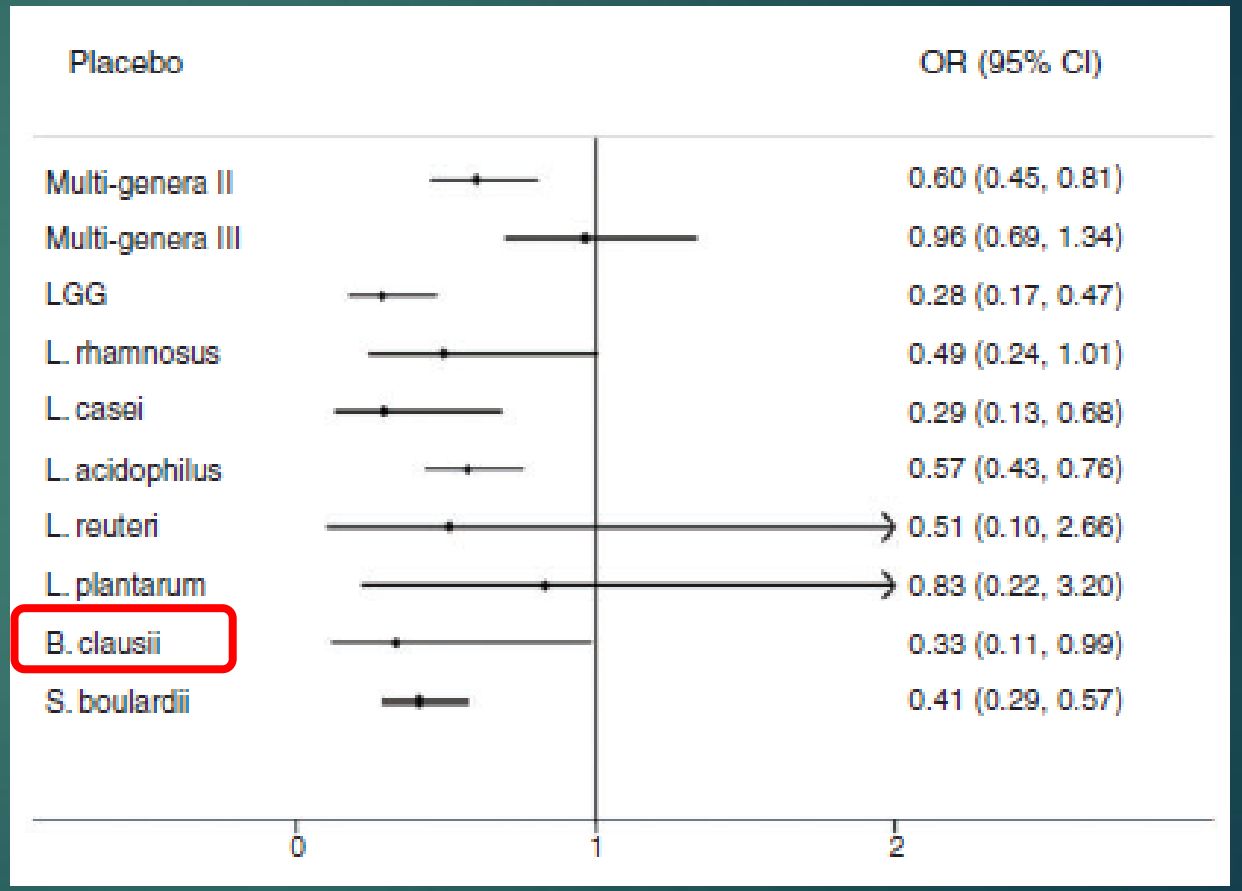
Outcomes:

- Therapy with *Bacillus clausii* was **well-tolerated**, and the adverse event rate was very low (0.09%).
- *Bacillus clausii* significantly **reduced the mean number of stools per day**, from 5.2 ± 2.0 stools at baseline to 1.2 ± 0.6 stools at study end ($p < 0.001$).
- Similarly, the proportion of patients with loose stools decreased from 81.6% at baseline to 9.2% at end of treatment period.
- **Acceptability** of *Bacillus clausii* therapy was high.

Castro et al. Tropical Diseases, Travel Medicine and Vaccines 2019; 5:14

Meta-analysis: Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea

Incidence of diarrhea was less with *B.Clausii*

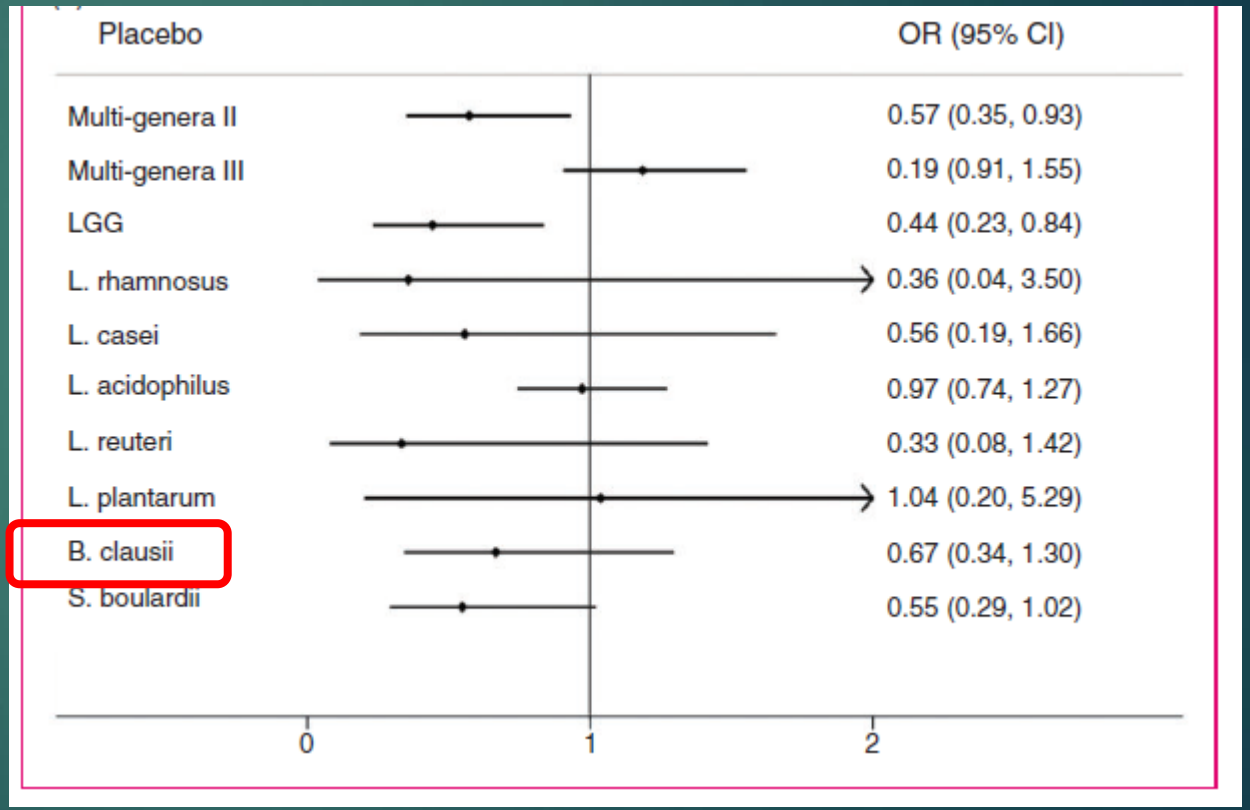


Forest plot of network meta-analysis for the incidence of diarrhea compared with placebo arm.

Cai et al. United European Gastroenterology Journal 2018;6(2): 169–180

Meta-analysis: Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea

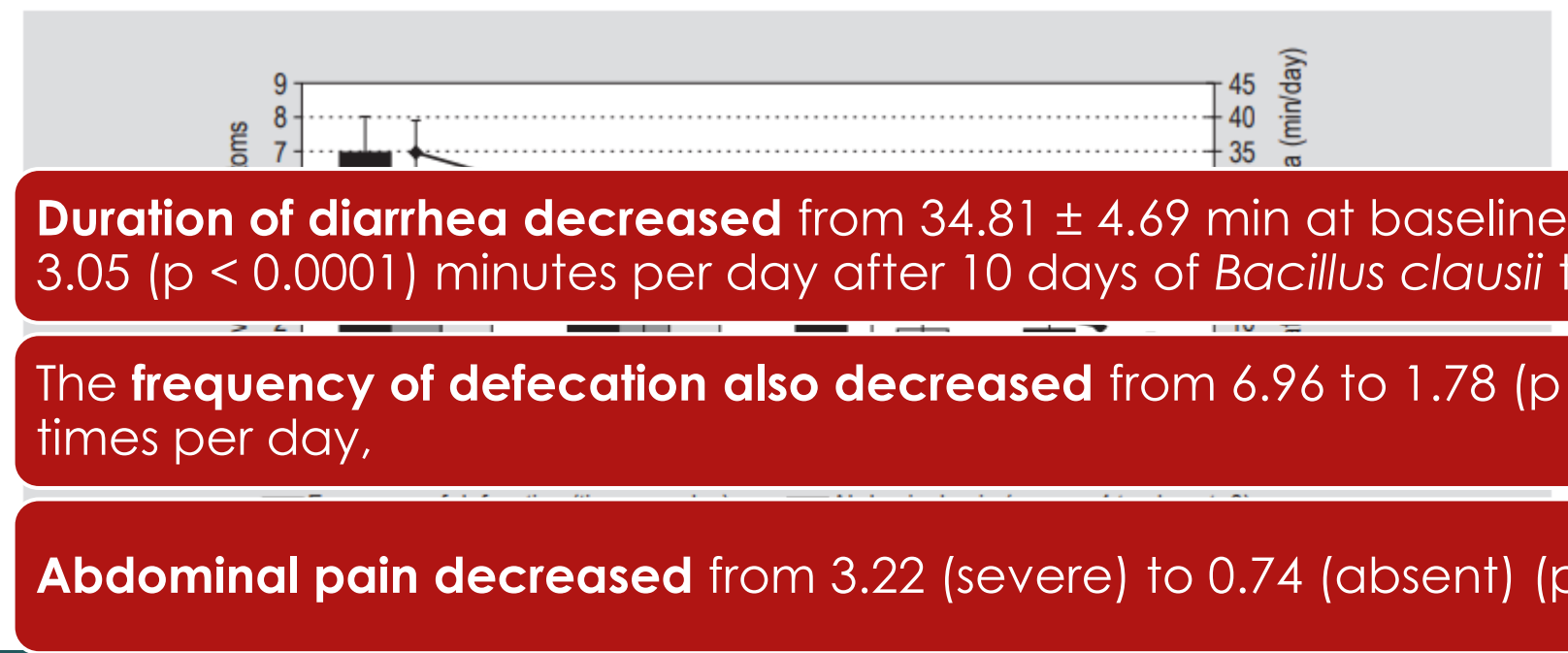
B.Clausii had less adverse events and was well tolerated



Forest plot of network meta-analysis for total occurrence of adverse events compared with placebo arm.

Cai et al. United European Gastroenterology Journal 2018;6(2): 169–180

Efficacy of *Bacillus clausii* in the treatment of patients suffering from acute diarrhoea



Duration of diarrhea decreased from 34.81 ± 4.69 min at baseline to 9.26 ± 3.05 ($p < 0.0001$) minutes per day after 10 days of *Bacillus clausii* therapy.

The **frequency of defecation also decreased** from 6.96 to 1.78 ($p < 0.0001$) times per day,

Abdominal pain decreased from 3.22 (severe) to 0.74 (absent) ($p < 0.0001$).

Stool consistency improved from 3.93 (watery) to 1.22 (soft) ($p < 0.0001$).

Sudha MR et al. Beneficial Microbes, June 2013; 4(2): 211-216

Bacillus Clausii As An Adjuvant Therapy In Acute Childhood Diarrhoea

- **Study design**: Open-label, prospective, randomized, controlled
- **Intervention/Control sample size**: 69/62
- **Median Age**: 6 months to 12 years
- **Treatment regimen**: $2x10^9$ CFU of ***Bacillus clausii*** **bid + ORS + zinc, for 5 days vs. ORS + zinc** for 5 days
- **Follow up**: At 6, 12, 24, 36, 48, 60, and 72 h
- **Outcome**:
  - **Mean duration of diarrhea 22.64 h and mean duration of hospital stay 2.78 days** in the Bacillus clausii group vs. 47.05 h and 4.30 days, respectively, in the control group ($p < 0.01$ for diarrhea duration).
  - Treatment with ***Bacillus clausii*** **reduced total treatment costs by 472 Indian rupees** compared to ORS alone.

Lahiri K et al. IOSR-JDMS 2015;14:74–76.

Beneficial Role of Probiotic in Acute Childhood Diarrhea

- **Study design**: Open-label, prospective, randomized, controlled
- **Intervention/Control sample size**: 80/80
- **Median Age**: Up to 6 Years
- **Treatment regimen**: 2x109 CFU of ***Bacillus clausii*** **bid + ORS + zinc, for 5 days vs. ORS + zinc for 5 days**
- **Follow up**: At 6, 12, 24, 36, 48, 60, and 72 h
- **Outcome**: Mean (SD) **duration of diarrhea 22.26 h and mean stool frequency** 1.15 in the *Bacillus clausii* group was significantly less compared to control group (34.16 h and 1.70, respectively)

Lahiri K et al. Res. Med. Health Sci. 2015;2: 26–30

Bacillus clausii in Reducing Duration Acute Diarrhoea in Children 6–59 Months of Age with Severe Dehydration.

- **Study design**: Randomized, double-blind, placebo controlled.
- **Intervention/Control sample size**: 51/51
- **Median Age**: Mean (SD): *Bacillus clausii* group: 11.3 (5.3) and control group: 11.9 (6.4) months
- **Treatment regimen**: $2x10^9$ CFU of ***Bacillus clausii*** **bid + ORS + zinc sulfate, for 5 days vs. zinc sulfate + ORS + 1 vial bid of a placebo** packaged in identical looking vials containing sterile water, for 5 days
- **Follow up**: Day 1 to day 7

Maugo, B.M et al. 2018 Available online: http://erepository.uonbi.ac.ke/bitstream/handle/11295/8325/DR._MAUGO_BRIAN_MAUGO_M.MED_PAEDS_2012.pdf?sequence=1 (accessed on 14 Jan 2019).

Bacillus clausii in Reducing Duration Acute Diarrhoea in Children 6–59 Months of Age with Severe Dehydration.

Outcome:

- Mean (SD) **duration of diarrhea in *Bacillus clausii* group was shorter** (77.59 (34.10) h) than placebo group (86.74 (40.16) h)
- **Significant decrease in mean number of diarrheal motions** on day 3 and day 4 between *Bacillus clausii* group vs. placebo group (p = 0.018)

Maugo, B.M et al. 2018 Available online: http://erepository.uonbi.ac.ke/bitstream/handle/11295/8325/DR._MAUGO_BRIAN_MAUGO_M.MED_PAEDS_2012.pdf?sequence=1 (accessed on 14 Jan 2019).

Bacillus clausii an Adjunct Treatment for Pediatric Patients with Acute Non-Bloody Diarrhea: An RCT

- **Study design**: Monocentric, randomized, controlled.
- **Intervention/Control sample size**: 35/35
- **Median Age**: 18 months
- **Treatment regimen**: $2x10^9$ or $4x10^9$ CFU of ***Bacillus clausii*** **per day + ORS, for 3 days vs. ORS for 3 days**
- **Follow up**: After day 3 of therapy, and upon discharge
- **Outcome**:
  - Mean (SD) **duration of diarrhea significantly shorter in the *Bacillus clausii*** group (69.84 (16.84) h) than in control group (83.76 (22.05) h) (p = 0.005
  - **Mean duration of hospital stay was also shorter favoring *Bacillus clausii*** group (59.0 h vs. 76.8 h) (p = 0.063).

Urtula RP et al. 2018. Available online: http://arl4.library.sk/arl-sllk/en/detail-sllk_un_cat-0013574-Bacillus-clausii-an-adjunct-treatmentfor- pediatric-patients-with-acute-nonbloody-diarrhea-a-rando/ (accessed on 19 April 2018).

GMA-CO Clinical Study Report: ENTER_L_01486

- **Study design**: Randomized, double-blind, placebo controlled.
- **Intervention/Control sample size**: 51/51
- **Mean (SD) age**: *Bacillus clausii* group: 11.3 (5.3) and control group: 11.9 (6.4) months
- **Treatment regimen**: 2x109 CFU of ***Bacillus clausii* bid + ORS + zinc sulfate, for 5 days vs. zinc sulfate + ORS + 1 vial bid of a placebo** packaged in identical looking vials containing sterile water, for 5 days
- **Follow up**: Day 1 to day 7
- **Outcome**: Mean (SD) duration of diarrhea in *Bacillus clausii* group was shorter (77.59 (34.10) h) than placebo group (86.74 (40.16) h). **Significant decrease in mean number of diarrhea episodes** on day 3 and day 4 ($p<0.05$) in the *Bacillus clausii* group vs. placebo group.

Lahiri, K.R. GMA-CO Clinical Study Report: ENTER_L_01486. Sanofi-Aventis. Available online: https://www.sanofi.com/media/Project/One-Sanofi-Web/sanofi com/common/docs/clinicalstudy-results/ENTER_L._01486_summary.pdf (accessed on 14 Jan 2019).

Probiotics for treatment of acute diarrhoea in children: Randomised clinical trial

- **Study design**: Prospective, multicenter, single-blind, randomized, controlled.
- **Intervention/Control sample size**: 100/92
- **Median Age**: 18 months
- **Treatment regimen**: 1 x10^9 CFU of ***Bacillus clausii*** **bid for 5 days + ORS for 3 to 6 h vs. ORS for 3 to 6 h** (followed by full strength formula of lactose or cows' milk, in both groups)
- **Follow up**: Day 1 to day 7
- **Outcome**: Median duration of diarrhea in patients receiving *Bacillus clausii* (118 h) similar to control group (115 h), with an estimated difference of 1 h between both groups (p = 0.76). All other outcomes were also similar in both groups. *Bacillus clausii* was well tolerated, with no observed adverse events.

Canani RB et al. BMJ 2007; 335: 340.

Summary of RCTs

Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea

- Reduced the duration of diarrhea

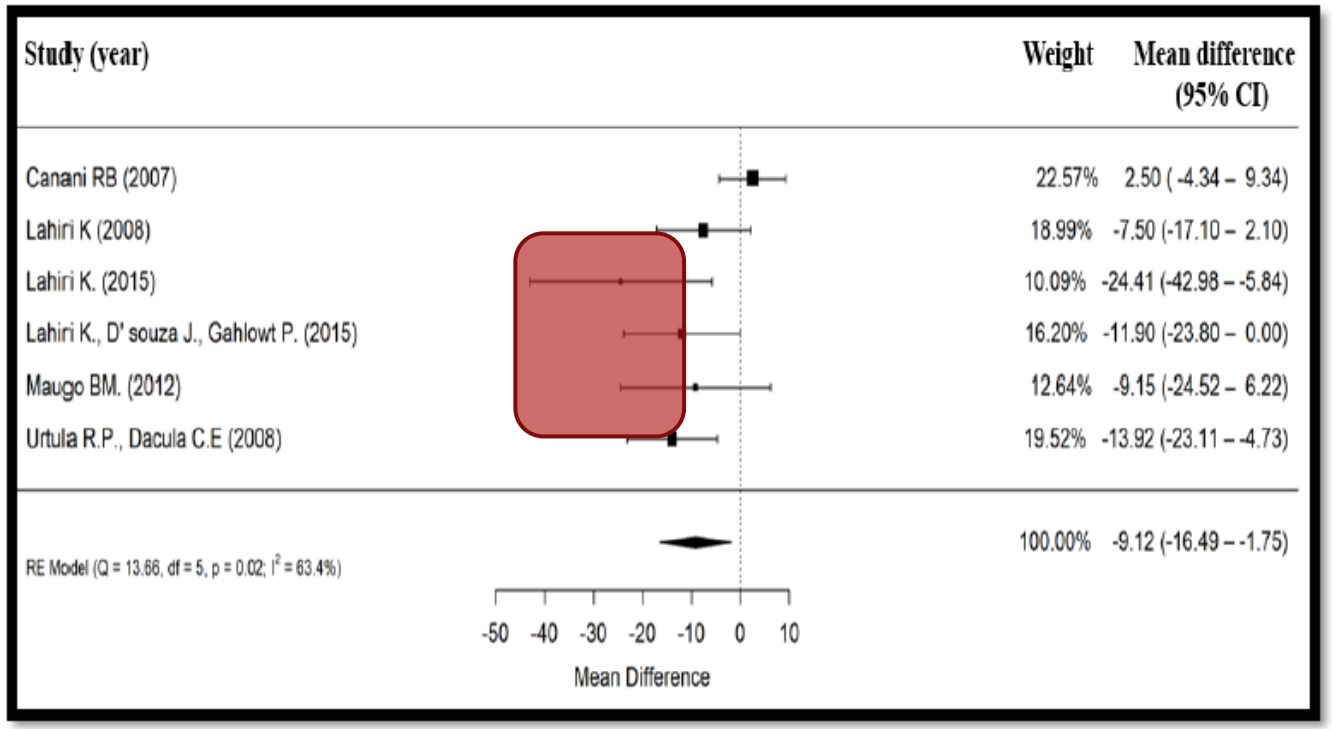


Figure 2. Forest plot showing effect of *Bacillus clausii* on mean duration of diarrhea. CI, confidence interval, RE, random effects.

Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea

- Reduced stool frequency

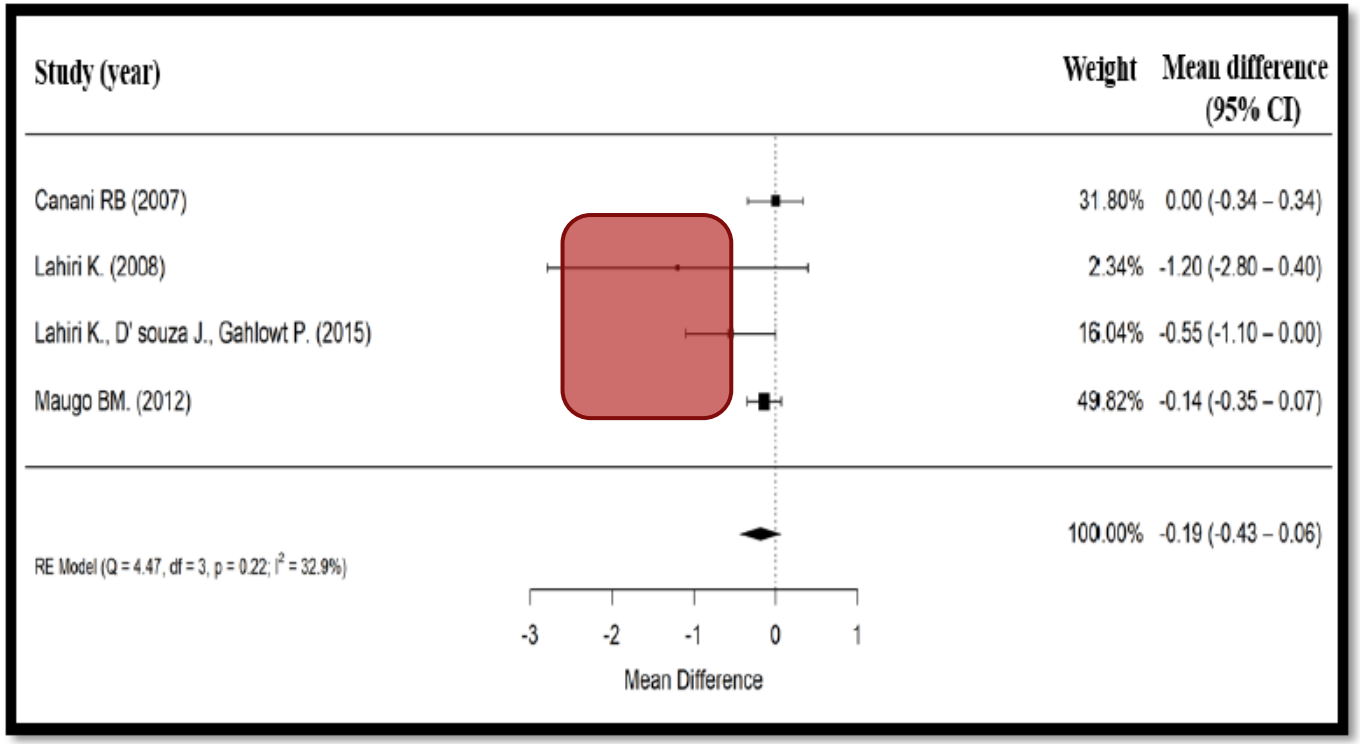


Figure 3. Forest plot showing effect of *Bacillus clausii* on mean stool frequency. CI, confidence interval, RE, random effects.

Ianiro G et al. Nutrients 2018;10(1074):1-1

Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea

- Reduced duration of Hospitalization

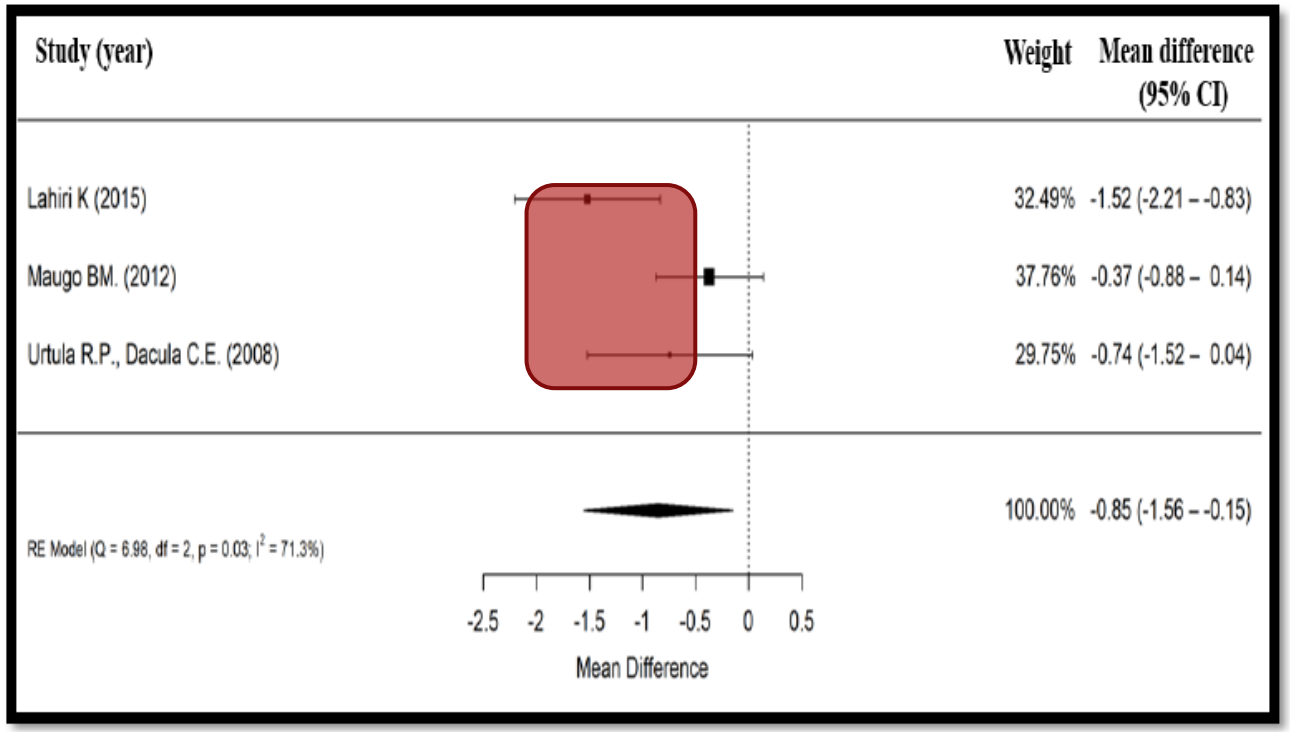


Figure 4. Forest plot showing effect of *Bacillus clausii* on mean duration of hospitalization. CI, confidence interval, RE, random effects.

Ianiro G et al. Nutrients 2018;10(1074):1-1

Bacillus clausii therapy to reduce side-effects of anti-Helicobacter pylori treatment: An RCT

- **Aim**: To evaluate the effect of Bacillus clausii, a probiotic, on incidence (primary variable) and severity of antibiotic-associated side-effects during anti-H. pylori therapy.
- **Results**: **Incidence and Intensity of nausea and diarrhoea in patients treated with *B. clausii* was significantly lower** than in placebo group. There were no differences in adherence to treatment and H. pylori eradication rates between groups.
- **Conclusion**: In symptom-free, H. pylori-positive subjects ***B. clausii* bacterio-therapy reduces the incidence of the most common side-effects related to anti-H. pylori antibiotic therapy** compared with placebo

Nista EC et al. Aliment Pharmacol Ther 2004; 20: 1181–118

Salient features

- Many strains of *B. clausii* are **considered antibiotic resistant** and hence they are **recommended for use along with antibiotics**.
- Antibiotic resistance genes are present in chromosomal DNA which is intrinsic and not transfer-able. Hence ***B. clausii* cannot transfer its resistance to any other organism**.
- **Safety** of *B.Clausii* has been very good
- *Bacillus clausii* to **possess antimicrobial and immunomodulatory activities** which may explain the effect of *Bacillus clausii* against acute childhood diarrhea.

Senesi S et al. Appl. Environ. Microbiol. 2001;67(2):834–839.

Salient features

- Moreover, *Bacillus clausii* strains were found to **release antimicrobial substances** in the medium, these substances are active against Gram-positive bacteria, in particular against *Staphylococcus aureus, Enterococcus faecium, and Clostridium difficile*.
- *Bacillus clausii* spores **can germinate** during gastrointestinal transit and grow as vegetative cells both in the **presence of bile and under limited oxygen** availability

Senesi S et al. Appl. Environ. Microbiol. 2001;67(2):834–839.

thank you

Dysbiosis

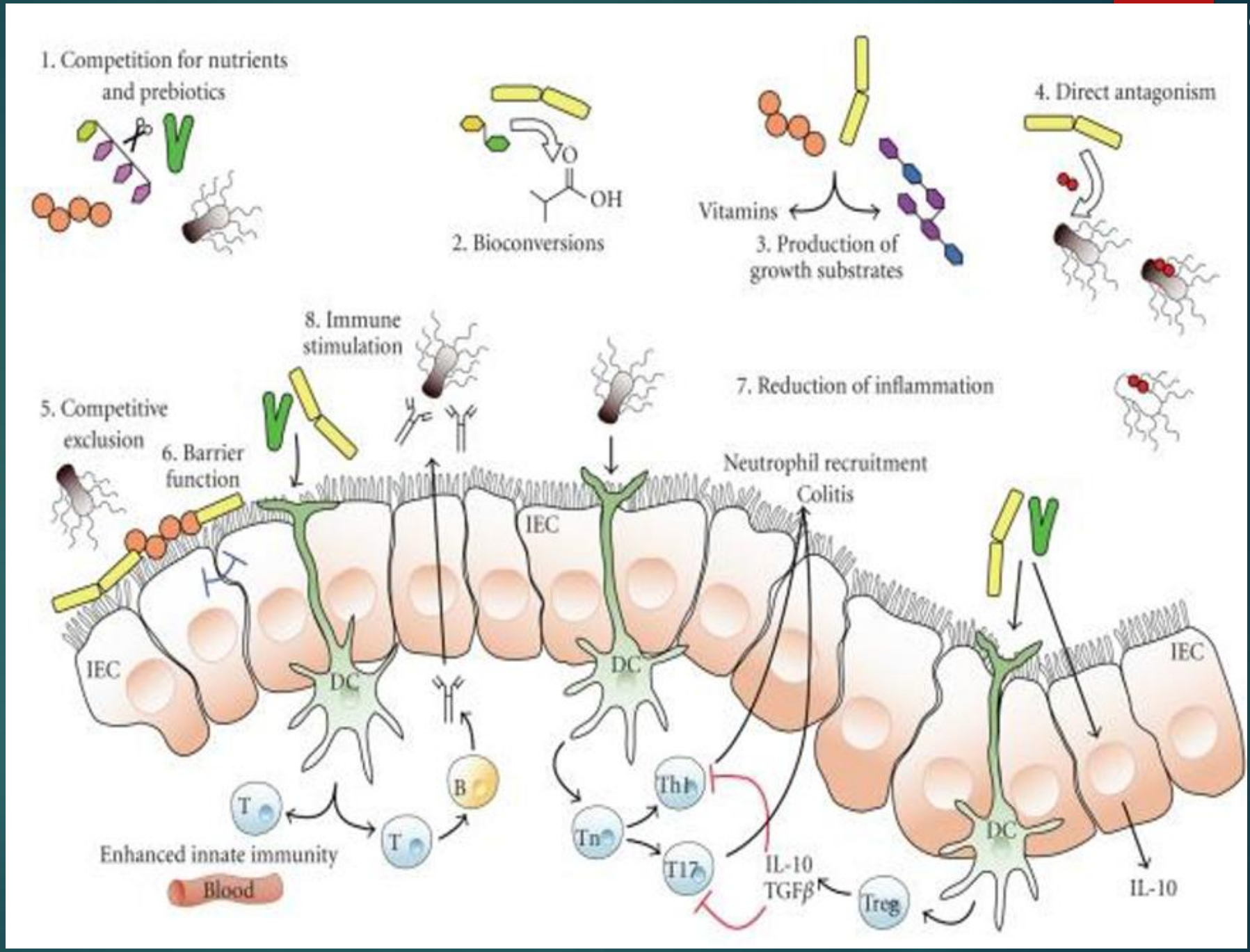
- Dysbiosis can be defined through the loss or gain of bacteria that either promote health or disease, respectively.

or

- Loss of bacteria that promote health or gain of bacteria that promote disease

Wilkins LJ et al. Sci Rep 2019; 9:12918

ells, T:T-c

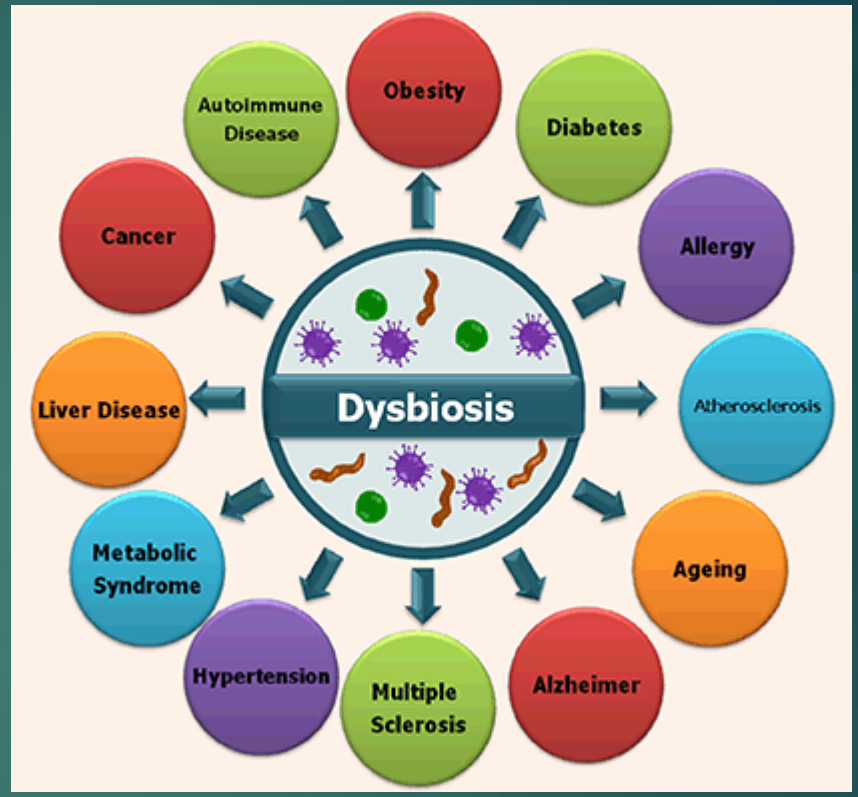


Khalighi A et al. IntechOpen 2016. DOI: 10.5772/63646. Available from: https://www.intechopen.com/books/probiotics-and-prebiotics-in-human-nutrition-and-health/probiotics-a-comprehensive-review-of-their-classification-mode-of-action-and-role-in-human-nutrition

Causes of Dysbiosis

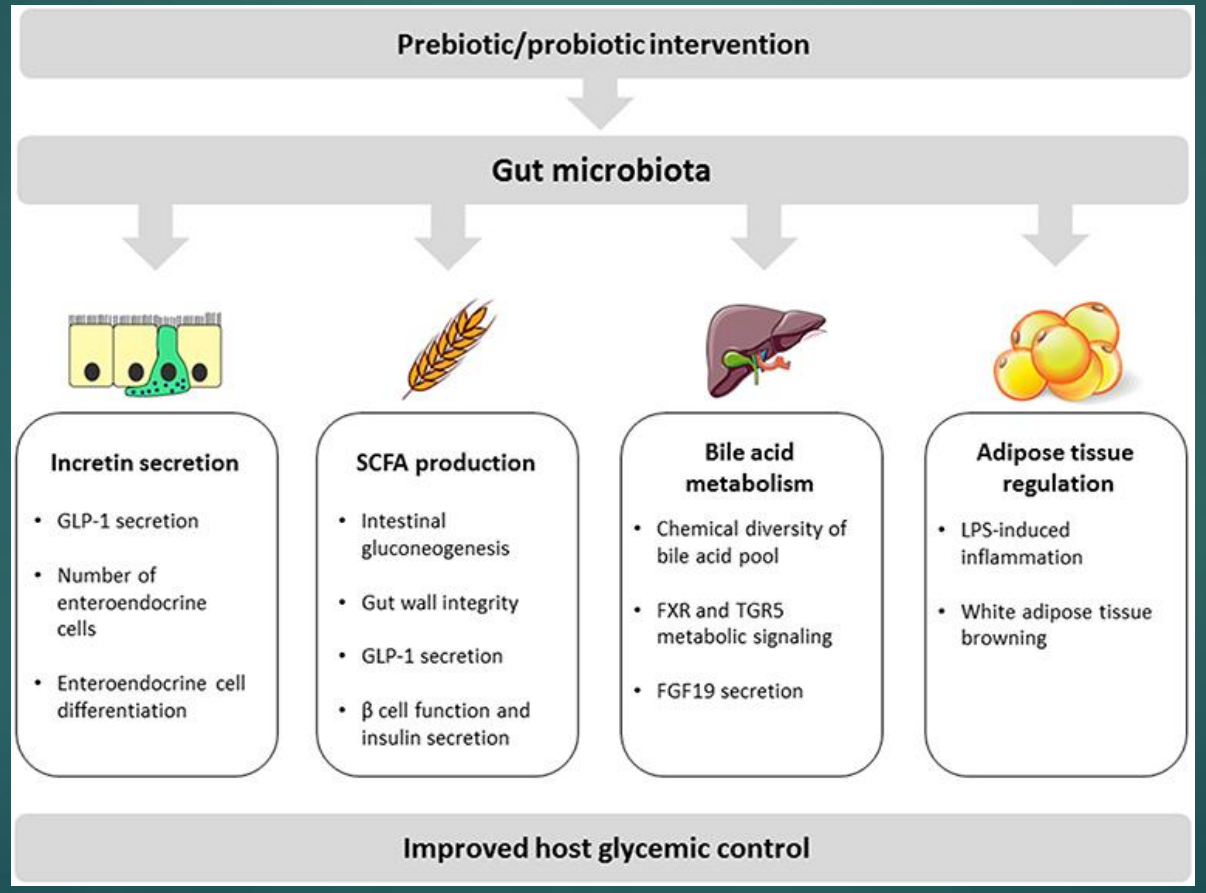
Appanna VD. Human Microbes - The Power Within 2018: 81-122.

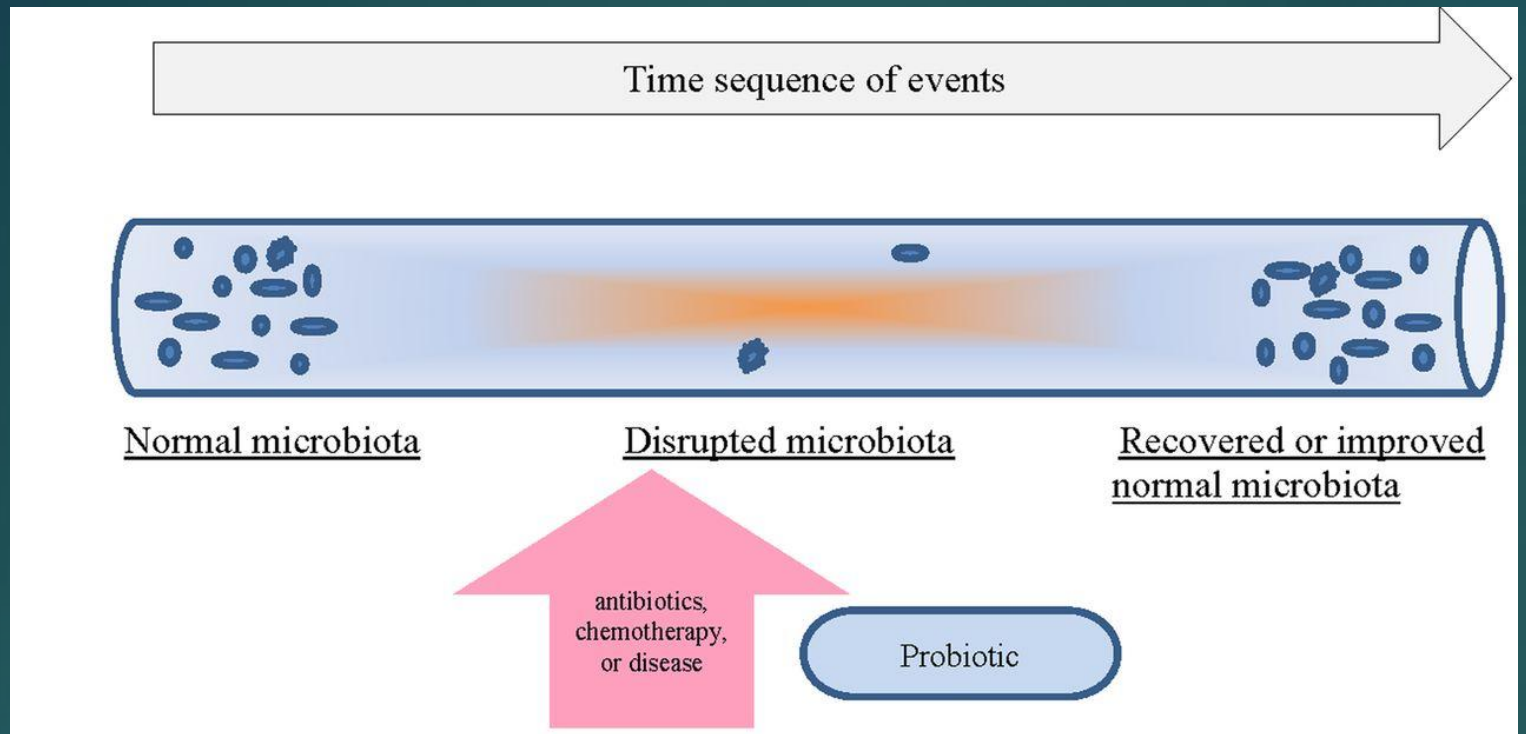
Complications of Dysbiosis



Appanna VD. Human Microbes - The Power Within 2018: 81-122.

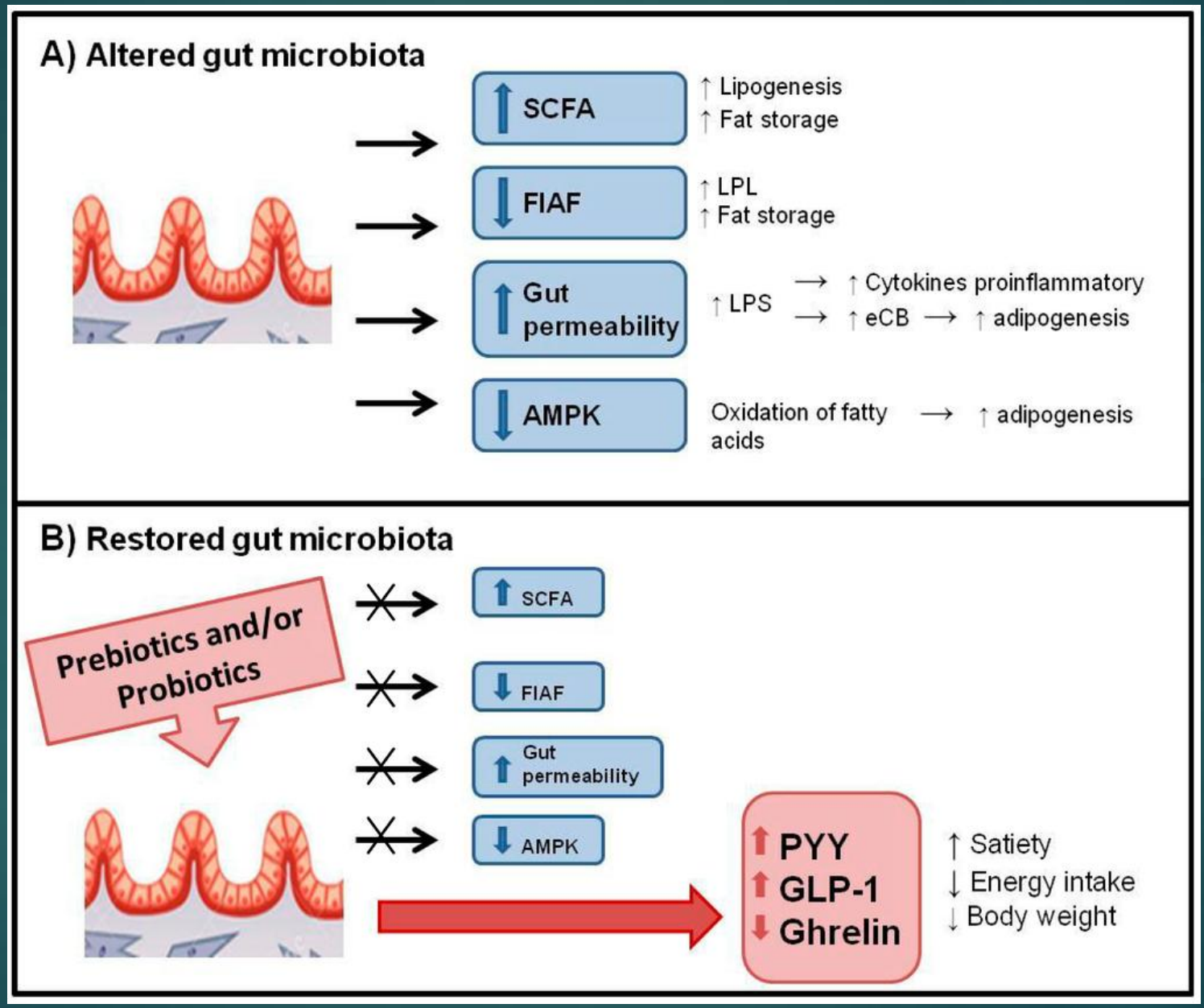
Health of gut microbiota





Model	Type of population enrolled	Dysbiosis at baseline	Time microbiota disrupted	Probiotic or control intervention	Potential outcomes
A	Healthy volunteers or at-risk patients	no	post-baseline	preventive	restoration
B	Patients with active disease at enrollment	yes	pre-baseline	treatment	altered or improved
C	Healthy volunteers	no	not disrupted	preventive	altered

4:e005047.



Sanchez M et al. Int. J. Environ. Res. Public Health 2015; 12: 162-175.