Appendices for American Gastroenterological Association Institute Technical Review on the Role of Probiotics in the Management of Gastrointestinal Disorders

Geoffrey A. Preidis,[1] Adam V. Weizman,[2] Purna C. Kashyap,[3] Rebecca L. Morgan[4]

[1]Section of Gastroenterology, Hepatology & Nutrition, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA; [2]Division of Gastroenterology, Mount Sinai Hospital Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [3]Enteric Neuroscience Program, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA; [4]Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

Contents

Appendix 1: Should probiotics be used as part of the treatment of *Clostridioides difficile* infection? 9

Bibliography 9

Question: *Saccharomyces boulardii* compared to placebo/antibiotics in symptomatic patients with confirmed *C. difficile* infection (1a) 10

Question: *Lactobacillus plantarum* 299v compared to placebo/antibiotics in symptomatic patients with confirmed *C. difficile* infection (1b) .. 13

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo/antibiotics in symptomatic patients with confirmed *C. difficile* infection (1c) 17

Question: *Lactobacillus acidophilus* ATCC 700396 + *Lactobacillus paracasei* subsp. *paracasei* ATCC 335 + *Bifidobacterium animalis* subsp. *lactis* ATCC SD5220 and ATCC SD5219 compared to placebo/antibiotics in symptomatic patients with confirmed *C. difficile* infection (1d) 19

Appendix 2: Should probiotics be used in the prevention of *Clostridioides difficile*-associated diarrhea? 22

Bibliography 22

Question: Probiotics compared to antibiotics alone or antibiotics + placebo in patients receiving antibiotic therapy for any indication with the exception of *C. difficile* infection (2a) 26

Outcomes stratified by species: 38

C. difficile-associated diarrhea 38

Incidence of infection 42

Adverse events 45

Incidence of antibiotic-associated diarrhea 49
Appendix 3: Should probiotics be used in patients with Crohn's disease? 53
Bibliography 53
Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo or standard of care or placebo + standard of care in patients with Crohn's disease (3a) 55
Question: *Escherichia coli* Nissle 1917 compared to placebo in patients with Crohn's disease (3b) 59
Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo +/- mesalamine in patients with Crohn's disease (3c) 61
Question: *Lactobacillus rhamnosus* ATCC 53103 + maintenance therapy compared to placebo + maintenance therapy in patients with Crohn's disease (3d) 65
Question: *Lactobacillus rhamnosus* ATCC 53103 + mesalamine compared to mesalamine alone in patients with Crohn's disease (3e) 67
Question: *Lactobacillus rhamnosus* ATCC 53103 compared to mesalamine in patients with Crohn's disease (3f) 69
Question: *Saccharomyces boulardii* compared to placebo +/- mesalamine alone in patients with Crohn's disease (3g) 71
Question: *Lactobacillus johnsonii* NCC 533 compared to placebo in prevention of endoscopic recurrence after surgery for Crohn's disease (3h) 73
Appendix 4: Should probiotics be used in patients with ulcerative colitis? 75
Bibliography 75
Question: *Bifidobacterium breve* Yakult + *Bifidobacterium bifidum* Yakult + *Lactobacillus acidophilus* compared to placebo in patients with ulcerative colitis (4a) 77
Question: *Bifidobacterium breve* Yakult + *Lactobacillus acidophilus* fermented milk compared to placebo in patients with ulcerative colitis (4b) 79
Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to mesalamine alone in patients with ulcerative colitis (4c) 81
Question: *Bifidobacterium longum* Reuter ATCC BAA-999 compared to placebo in patients with ulcerative colitis (4d) 85

Question: *Escherichia coli* Nissle 1917 compared to placebo +/- mesalamine in patients with ulcerative colitis (4e) 87

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to mesalamine in patients with ulcerative colitis (4f) 90

Question: *Lactobacillus reuteri* ATCC 55730 enema + meslamine compared to placebo + mesalamine in patients with ulcerative colitis (4g) .. 92

Question: *Lactobacillus acidophilus* LA-5 + *Bifidobacterium animalis* subsp. *lactis* Bb12 compared to placebo in patients with ulcerative colitis (4h) 94

Question: *Enterococcus faecalis* T-110 + *Clostridium butyricum* TO-A + *Bacillus mesentericus* TO-A compared to placebo in patients with ulcerative colitis (4i) 96

Appendix 5: Should probiotics be used in patients with pouchitis? 98

Bibliography 98

Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo / standard of care in patients with pouchitis (5a) 99

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo in patients with pouchitis (5b) 103

Question: *Clostridium butyricum* CBM 588 compared to placebo in patients with pouchitis (5c) 105

Question: *Bifidobacterium longum* subsp. *longum* compared to placebo in patients with pouchitis (5d) 107

Appendix 6: Should probiotics be used to improve global response or abdominal pain severity in symptomatic children and adults with irritable bowel syndrome? 109

Bibliography 109

Question: *Saccharomyces boulardii* compared to placebo for adults with IBS (6a) 113

Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo for adults with IBS (6b) 116

Question: *Escherichia coli* Nissle 1917 compared to placebo for adults with IBS (6c) 121

Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo for children with IBS (6d) 123

Question: *Lactobacillus plantarum* 299v compared to placebo for adults with IBS (6e) 126

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo for treatment if IBS in adults (6f) 130

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo for children with IBS (6g) 132

Question: *Bacillus coagulans* MTCC 5856 compared to placebo for treatment of IBS (6h) 136

Question: *Lactobacillus reuteri* compared to placebo for adults with IBS (6i) 139

Question: *Lactobacillus reuteri* DSM 17938 compared to placebo for children with IBS (6j) 141

Question: *Lactobacillus gasseri* BNR17 compared to placebo for treatment of IBS (6k) 142

Question: *Saccharomyces cerevisiae* CNCM I-3856 compared to placebo for treatment if IBS in adults (6l) 143

Question: *Lactobacillus casei* Shirota compared to placebo for adults with IBS (6m) 149

Question: *Lactobacillus rhamnosus* compared to placebo for adults with IBS (6n) 151

Question: *Lactobacillus acidophilus* SDC 2012 and 2013 compared to placebo for adults with IBS (6o) 154

Question: *Bifidobacterium animalis* subsp. *lactis* I-2494 + *Streptococcus salivarius* subsp. *thermophilus* I-1630 + *Lactobacillus delbrueckii* subsp. *bulgaricus* I-1632 and I-1519 compared to placebo for adults with IBS (6p) 156

Question: *Lactobacillus paracasei* subsp. *paracasei* F-19 + *Lactobacillus acidophilus* LA-5 + *Bifidobacterium animalis* subsp. *lactis* Bb12 compared to placebo for adults with IBS (6q) 161

Question: *Escherichia coli* DSM 17252 compared to placebo for adults with IBS (6r) 163

Question: *Streptococcus salivarius* subsp. *thermophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Lactobacillus acidophilus* + *Bifidobacterium longum* subsp. *longum* compared to placebo for adults with IBS (6s) 165

Question: *Bifidobacterium longum* subsp. *longum* LA-101 + *Lactobacillus acidophilus* LA-102 + *Lactococcus lactis* LA-103 + *Streptococcus salivarius* subsp. *thermophilus* LA-104 compared to placebo for adults with IBS (6t) 168

Question: *Bifidobacterium longum* subsp. *longum* NCC 3001 compared to placebo for adults with IBS (6u) 171

Question: *Lactobacillus rhamnosus* NCIMB 30174 + *Lactobacillus plantarum* NCIMB 30173 + *Lactobacillus acidophilus* NCIMB 30175 + *Enterococcus faecium* NCIMB 30176 compared to placebo for adults with IBS (6v) 175

Question: *Lactobacillus acidophilus* NCIMB 30157 and NCIMB 30156 + *Bifidobacterium bifidum* NCIMB 30153 + *Bifidobacterium animalis* subsp. *lactis* NCIMB 30172 compared to placebo for adults with IBS (6w) 180

Question: *Lactobacillus acidophilus* KCTC 11906BP + *Lactobacillus plantarum* KCTC 11867BP + *Lactobacillus rhamnosus* KCTC 11868BP + *Bifidobacterium breve* KCTC 11858BP + *Bifidobacterium animalis* subsp. *lactis* KCTC 11903BP + *Bifidobacterium longum* subsp. *longum* KCTC 11860BP + *Streptococcus salivarius* subsp. *thermophilus* KCTC 11870BP compared to placebo for adults with IBS (6x) 182

Question: *Bifidobacterium bifidum* MIMBb75 compared to placebo for adults with IBS (6y) 185

Question: *Bifidobacterium animalis* subsp. *animalis* DN-173 + *Streptococcus salivarius* subsp. *thermophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* compared to placebo for adults with IBS (6z) 187

Question: *Lactobacillus paracasei* subsp. *paracasei* F-19 + *Lactobacillus acidophilus* LA-5 + *Bifidobacterium animalis* subsp. *lactis* Bb12 + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo for adults with IBS (6aa) 189

Question: *Lactobacillus plantarum* CECT7484 and CECT7485 + *Pediococcus acidilactici* CECT7483 compared to placebo for adults with IBS (6ab) 191

Question: *Bifidobacterium longum* subsp. *infantis* M-63 + *Bifidobacterium breve* M-16V + *B. longum* Reuter ATCC BAA-999 compared to placebo for children with IBS (6ac) 193

Question: *Lactobacillus brevis* KB290 compared to placebo for adults and children with IBS (6ad)..... 195

Question: *Lactobacillus casei* DG compared to placebo for adults with IBS (6ae)..... 197

Question: *Lactobacillus acidophilus* NCFM + *Bifidobacterium animalis* subsp. *lactis* ATCC SD5220 compared to placebo for adults with IBS (6af) 198

Question: *Lactobacillus acidophilus* CL1285 + *Lactobacillus casei* LBC80R + *Lactobacillus rhamnosus* CLR2 compared to placebo for adults with IBS (6ag) 200

Question: *Bacillus subtilis* PXN 21 + *Bifidobacterium bifidum* PXN 23 + *Bifidobacterium breve* PXN 25 + *Bifidobacterium longum* subsp. *infantis* PXN 27 + *B. longum* subsp. *longum* PXN 30 + *Lactobacillus acidophilus* PXN 35 + *Lactobacillus delbrueckii* subsp. *bulgaricus* PXN39 + *Lactobacillus casei* PXN 37 + *Lactobacillus plantarum* PXN 47 + *Lactobacillus rhamnosus* PXN 54 + *Lactobacillus helveticus* PXN 45 + *Lactobacillus salivarius* PXN 57 + *Lactococcus lactis* PXN63 + *Streptococcus salivarius* subsp. *thermophilus* PXN 66 compared to placebo for adults with IBS (6ah) 202

Question: *Bifidobacterium bifidum* BGN4 + *Bifidobacterium animalis* subsp. *lactis* AD011 + *Lactobacillus acidophilus* AD031 + *Lactobacillus casei* IBS041 compared to placebo for adults with IBS (6ai) 205

Question: *Bifidobacterium longum* subsp. *longum* + *Lactobacillus acidophilus* compared to no probiotics for adults with IBS (6aj)..... 207

Question: *Clostridium butyricum* compared to no probiotics for adults with IBS (6ak) 209

Question: *Streptococcus salivarius* subsp. *thermophilus* MG510 + *Lactobacillus plantarum* LRCC5193 compared to no probiotics for adults with IBS (6al) 211

Question: *Bacillus coagulans* Unique IS2 compared to no probiotics for children with IBS (6am) 213

Question: *Lactobacillus acidophilus* + *Lactobacillus rhamnosus* + *Bifidobacterium breve* + *Bifidobacterium animalis* subsp. *lactis* + *Bifidobacterium longum* subsp. *longum* + *Streptococcus salivarius* subsp. *thermophilus* compared to no probiotics for adults with IBS (6an). 215

Question: *Bifidobacterium animalis* subsp. *lactis* Bb12 + *Lactobacillus acidophilus* LA-5 + *Lactobacillus delbrueckii* subsp. *bulgaricus* LBY-27 + *Streptococcus salivarius* subsp. *thermophilus* STY-31 compared to no probiotics for adults with IBS (6ao) 217

Question: *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium bifidum* + *Bifidobacterium animalis* subsp. *lactis* + *Lactobacillus acidophilus* + *Lactobacillus rhamnosus* + *Streptococcus salivarius* subsp. *thermophilus* compared to no probiotics for adults with IBS (6ap) .. 219

Question: *Bifidobacterium animalis* subsp. *lactis* W52 + *Lactobacillus casei* W56 + *Lactobacillus salivarius* W57 + *Lactococcus lactis* W58 + *Lactobacillus acidophilus* ATCC 700396 + *Lactobacillus rhamnosus* W71 compared to placebo for adults with IBS (6aq) 221

Question: *Lactobacillus rhamnosus* ATCC 53103 and LC705 + *Bifidobacterium breve* Bb99 + *Propionibacterium freudenreichii* subsp. *shermanii* JS compared to placebo for adults with IBS (6ar) 223

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to no probiotics for children with IBS (6as) 224

Appendix 7: Should probiotics be used to reduce the duration or severity of diarrhea in children with acute infectious gastroenteritis? 226

Bibliography 226

Question: Probiotics compared to placebo and/or standard care alone for treatment of acute infectious diarrhea in children 233

Question: *Saccharomyces boulardii* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7a) 238

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7b) 241

Question: *Lactobacillus acidophilus* compared to placebo in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7c) 246

Question: *Lactobacillus acidophilus* + *Bifidobacterium bifidum* compared to placebo for the treatment of acute infectious diarrhea in children (7d) 248

Question: *Lactobacillus reuteri* compared to placebo in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7e) 250

Question: *Lactobacillus helveticus* Rosell-52 + *Lactobacillus rhamnosus* Rosell-11 compared to placebo in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7f) 252

Question: *Bifidobacterium animalis* subsp. *lactis* compared to placebo for treatment of acute infectious diarrhea in children (7g) 255

Question: *Streptococcus salivarius* subsp. *thermophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7h) 257

Question: *Enterococcus faecium* SF68 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7i) 259

Question: *Escherichia coli* Nissle 1917 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7j) 261

Question: *Bacillus mesentericus + Clostridium butyricum + Enterococcus faecalis* compared to placebo/standard of care for treatment of acute infectious diarrhea in children (7k) 263

Question: *Lactobacillus acidophilus* + *Lactobacillus rhamnosus* + *Bifidobacterium longum* subsp. *longum* + *Saccharomyces boulardii* compared to placebo for treatment of acute infectious diarrhea (7l) 265

Question: *Lactobacillus rhamnosus* 19070-2 + *Lactobacillus reuteri* DSM 12246 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7m) 267

Question: *Lactobacillus casei* Shirota compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7n) 268

Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7o) 269

Question: *Enterococcus faecalis* + *Clostridium butyricum* + *Bacillus mesentericus* + *Bacillus coagulans* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7p) 271

Question: *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium animalis* subsp. *lactis* + *Lactobacillus acidophillus* + *Lactobacillus rhamnosus* + *Lactobacillus plantarum* + *Pediococcus pentosaceus* compared to placebo for the treatment of acute infectious diarrhea in children (7q) 273

Question: *Lactobacillus paracasei* subps. *paracasei* ST11 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7t) 275

Question: *Lactobacillus acidophilus + Bifidobacterium bifidum + Lactobacillus delbrueckii* subsp. *bulgaricus* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7u)..... 276

Question: *Bifidobacterium ruminatum* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7v)..... 278

Question: *Lactobacillus rhamnosus* 573L/1 and 573L/2 and 573L/3 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7w)..... 279

Question: *Lactobacillus acidophilus* + "Bifidobacter" compared to placebo for the treatment of acute infectious diarrhea in children (7x) 280

Appendix 8: Should probiotics be used in preterm, low birth weight infants?..... 281

Question: Single- and multiple-strain probiotics compared with no probiotics for preterm, low birth weight infants (8a) 281

Appendix 1: Should probiotics be used as part of the treatment of *Clostridioides difficile* infection?

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Question: *Saccharomyces boulardii* compared to placebo/antibiotics in symptomatic patients with confirmed *C. difficile* infection (1a)

Bibliography: McFarland 1994, Surawicz 2000

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. boulardii*	Placebo/Antibiotics	Relative (95% CI)	Absolute (95% CI)		
Cessation of Diarrhea in Patients with initial or recurrent disease												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	42/57 (73.7%)	37/67 (55.2%)	**RR 1.33** (1.02 to 1.74)	**182 more per 1,000** (from 11 more to 409 more)	⨁⨁◯◯ LOW	CRITICAL
Recurrence of Diarrhea in patients with initial or recurrent disease												
1	randomised trials	not serious	not serious	serious [a]	serious [b]	none	15/57 (26.3%)	30/67 (44.8%)	**RR 0.59** (0.35 to 0.98)	**184 fewer per 1,000** (from 291 fewer to 9 fewer)	⨁⨁◯◯ LOW	CRITICAL
Treatment-related Adverse Events in patients with initial or recurrent disease												
1	randomised trials	not serious	not serious	serious [a]	serious [c]	none	Statistically significant increase in thirst (P = 0.02) and constipation (P = 0.03) in patients receiving *S. boulardii* compared to placebo.				⨁⨁◯◯ LOW	CRITICAL
Cessation of diarrhea in patients with recurrent disease only												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. boulardii*	Placebo/Antibiotics	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [d]	serious [b]	none	15/18 (83.3%)	7/17 (41.2%)	**RR 1.67** (0.95 to 2.93)	**276 more per 1,000** (from 21 fewer to 795 more)	⨁⨁◯◯ LOW	CRITICAL

Recurrence of diarrhea in patients with recurrent disease only

1	randomised trials	not serious	not serious	serious [d]	serious [b]	none	3/18 (16.7%)	7/14 (50.0%)	**RR 0.33** (0.10 to 1.06)	**335 fewer per 1,000** (from 450 fewer to 30 more)	⨁⨁◯◯ LOW	CRITICAL

Treatment-related Adverse Events in patients with recurrent disease only

1	randomised trials	not serious	not serious	serious [d]	serious [c]	none	No statistically significant differences in the number or type of adverse events in patients treated with *S. boulardii* or placebo, and that no adverse events occurred during the four-week follow-up period.				⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

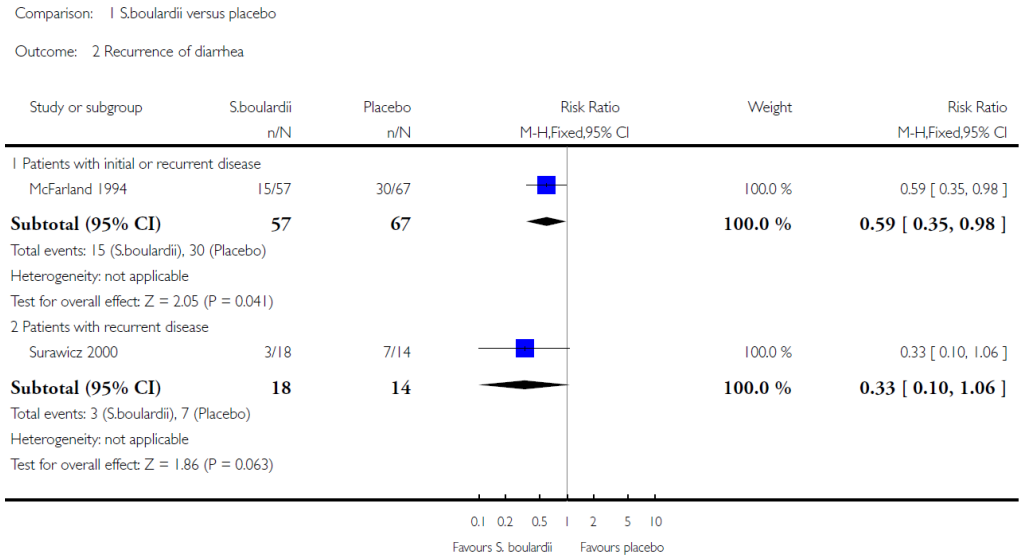
a. Some indirectness identified based on difference in populations with regards to initial and/or recurrent infection (McFarland 1994) or just recurrent infection (Surawicz 2000). Additionally, indirectness identified based on comparators: placebo reported for McFarland 1994 and high dose vancomycin reported for Surawicz 2000.

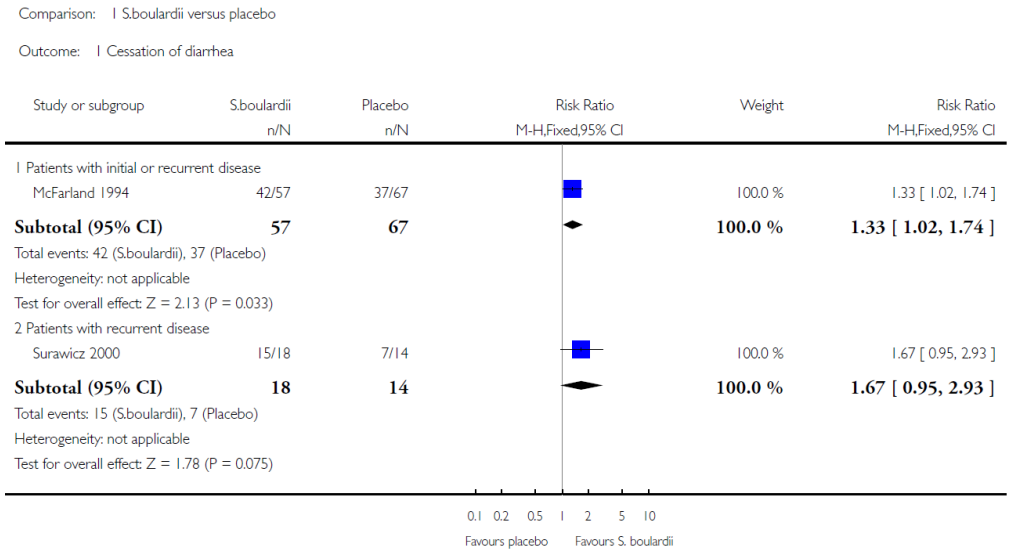
b. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

c. No raw data reported. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

d. Some indirectness identified based on difference in populations with regards to initial and/or recurrent infection (McFarland 1994) or just recurrent infection (Surawicz 2000). Additionally, indirectness identified based on comparators: high dose vancomycin reported for Surawicz 2000.

Forest Plots





Question: *Lactobacillus plantarum* 299v compared to placebo/antibiotics in symptomatic patients with confirmed *C. difficile* infection (1b)

Bibliography: Wullt 2003

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. plantarum* 299v	Placebo/Antibiotics	Relative (95% CI)	Absolute (95% CI)		
Cessation of Diarrhea												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. plantarum* 299v	Placebo/Antibiotics	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	11/12 (91.7%)	9/9 (100.0%)	**RR 0.93** (0.73 to 1.19)	**70 fewer per 1,000** (from 270 fewer to 190 more)	⨁◯◯◯ VERY LOW	CRITICAL

Recurrence of Diarrhea

1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	4/11 (36.4%)	6/9 (66.7%)	**RR 0.55** (0.22 to 1.35)	**300 fewer per 1,000** (from 520 fewer to 233 more)	⨁◯◯◯ VERY LOW	CRITICAL

Bacteriological Cure (Resolution of CDI) (follow up: range 11 days to 13 days; assessed with: Negative assay for C. difficile toxin)

1	randomised trials	not serious	not serious	serious [a]	very serious [b]	none	7/12 (58.3%)	7/9 (77.8%)	**RR 0.75** (0.41 to 1.36)	**194 fewer per 1,000** (from 459 fewer to 280 more)	⨁◯◯◯ VERY LOW	CRITICAL

Treatment-related Adverse Events

1	randomised trials	not serious	not serious	serious [a]	serious [c]	none	0/12 (0.0%)	0/9 (0.0%)	not estimable		⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

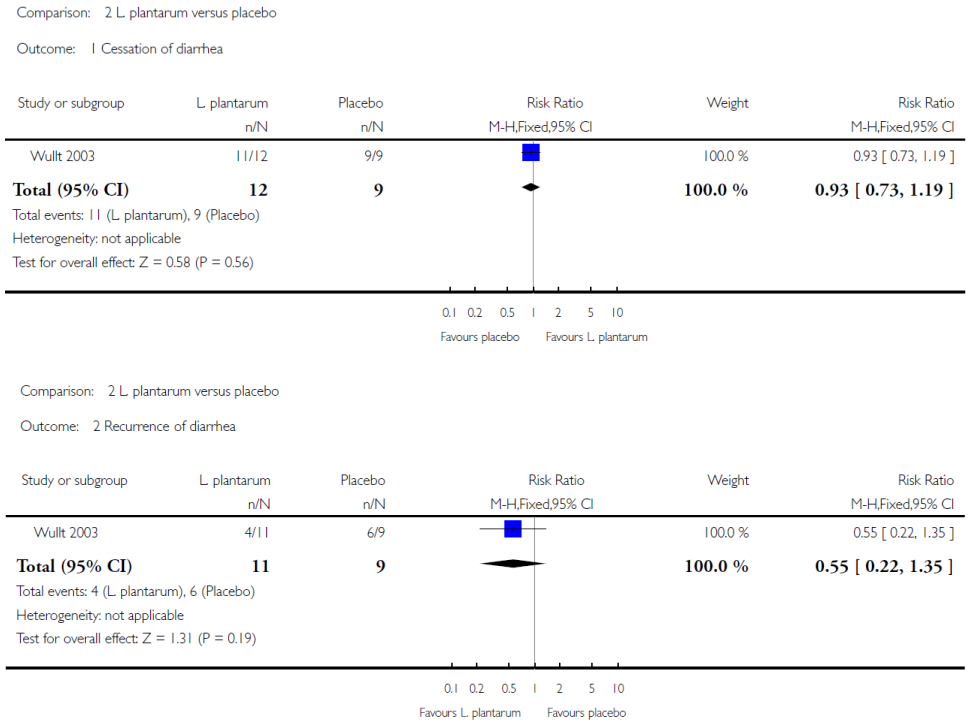
Explanations

a. Study only reports on adults; therefore, these findings may not be generalizable to children.

b. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

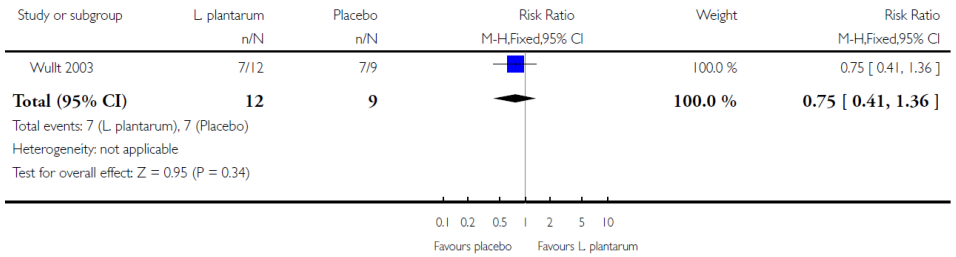
c. No events reported out of small sample.

Forest Plots



Comparison: 2 L. plantarum versus placebo

Outcome: 3 Bacteriological cure



Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo/antibiotics in symptomatic patients with confirmed *C. difficile* infection (1c)

Bibliography: Lawrence 2005

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	Placebo/Antibiotics	Relative (95% CI)	Absolute (95% CI)		
Recurrent C. difficile-associated Diarrhea												
1	randomised trials	not serious [a]	not serious	serious [b]	very serious [c]	none	3/8 (37.5%)	1/7 (14.3%)	**RR 2.63** (0.35 to 19.85)	**233 more per 1,000** (from 93 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment-related Adverse Events												
1	randomised trials	not serious [a]	not serious	serious [b]	serious [d]	none	Mild gastrointestinal upset with bloating (25%) and flatulence (37.5%) reported in patients treated with *L. rhamnosus* ATCC 53103.				⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

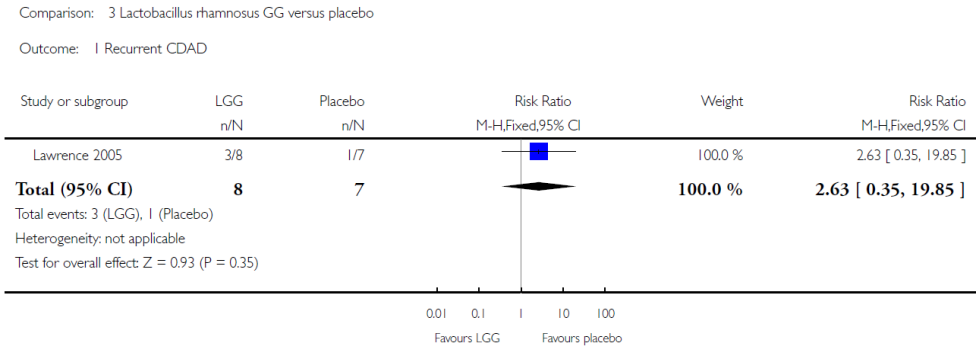
a. Type of antibiotic and duration of antibiotic dosing is unclear.

b. Reported study population includes adults only. May not be generalizable to the entire population.

c. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

d. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots



Question: *Lactobacillus acidophilus* ATCC 700396 + *Lactobacillus paracasei* subsp. *paracasei* ATCC 335 + *Bifidobacterium animalis* subsp. *lactis* ATCC SD5220 and ATCC SD5219 compared to placebo/antibiotics in symptomatic patients with confirmed *C. difficile* infection (1d)

Bibliography: Barker 2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* ATCC 700396 + *L. paracasei* subsp. *paracasei* ATCC 335 + *B. animalis* subsp. *lactis* ATCC SD5220 and ATCC SD5219	Placebo/Antibiotics	Relative (95% CI)	Absolute (95% CI)		
C. difficile infection Recurrence												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	1/15 (6.7%)	1/13 (7.7%)	**RR 0.86** (0.05 to 15.22)	**11 fewer per 1,000** (from 73 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment-related Adverse Events (follow up: 8 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* ATCC 700396 + *L. paracasei* subsp. *paracasei* ATCC 335 + *B. animalis* subsp. *lactis* ATCC SD5220 and ATCC SD5219	Placebo/Antibiotics	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	serious [b,d]	serious [c]	none	12/16 (75.0%)	12/15 (80.0%)	**RR 0.94** (0.64 to 1.37)	**48 fewer per 1,000** (from 288 fewer to 296 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Concerns for risk of bias based on selective reporting and incomplete outcome data.

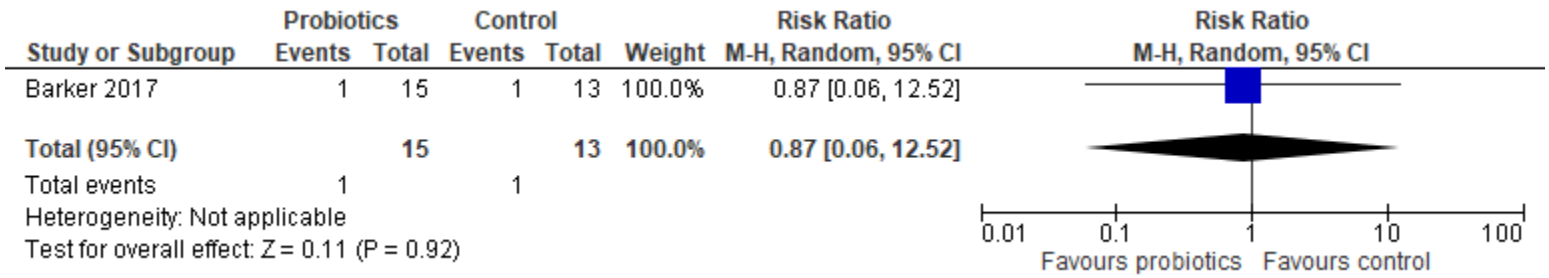
b. Study included only adult population and may not be generalizable to the entire population.

c. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

d. Outcome reports on any GI discomfort experienced by participants; however, does not specify those related to the use of probiotics alone.

Forest Plots

C. difficile Recurrence



Appendix 2: Should probiotics be used in the prevention of *Clostridioides difficile*-associated diarrhea?

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Question: Probiotics compared to antibiotics alone or antibiotics + placebo in patients receiving antibiotic therapy for any indication with the exception of *C. difficile* infection (2a)

Bibliography: Goldenberg 2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics	Antibiotics alone or antibiotics + placebo	Relative (95% CI)	Absolute (95% CI)		
Incidence of C. difficile-associated Diarrhea												
31	randomised trials	serious [a,b]	not serious	serious [c]	not serious	none	70/4535 (1.5%)	164/4147 (4.0%)	**RR 0.40** (0.30 to 0.52)	**24 fewer per 1,000** (from 28 fewer to 19 fewer)	⨁⨁◯◯ LOW	CRITICAL
Incidence of C. difficile Infection												
15	randomised trials	serious [a,b]	not serious	not serious	serious [d]	none	98/633 (15.5%)	99/581 (17.0%)	**RR 0.86** (0.67 to 1.10)	**24 fewer per 1,000** (from 56 fewer to 17 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse Events												
32	randomised trials	serious [a,b]	serious [e]	not serious	not serious	none	620/4329 (14.3%)	677/3976 (17.0%)	**RR 0.83** (0.71 to 0.97)	**29 fewer per 1,000** (from 49 fewer to 5 fewer)	⨁⨁◯◯ LOW	CRITICAL
Incidence of Antibiotic-associated Diarrhea												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Probiotics	Antibiotics alone or antibiotics + placebo	Relative (95% CI)	Absolute (95% CI)		
33	randomised trials	serious [a,b]	serious [f]	not serious	not serious	none	565/4618 (12.2%)	771/4252 (18.1%)	**RR 0.58** (0.48 to 0.70)	**76 fewer per 1,000** (from 94 fewer to 54 fewer)	⨁⨁◯◯ LOW	CRITICAL
Incidence of Antibiotic-associated Diarrhea (Adults)												
23	randomised trials	not serious [g]	serious [h]	serious [i]	not serious	none [j]	476/3694 (12.9%)	583/3342 (17.4%)	**RR 0.62** (0.51 to 0.76)	**66 fewer per 1,000** (from 85 fewer to 42 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Incidence of Antibiotic-associated Diarrhea (Children)												
6	randomised trials	not serious [k]	not serious	serious [l]	not serious	publication bias strongly suspected [m]	56/566 (9.9%)	156/575 (27.1%)	**RR 0.38** (0.29 to 0.49)	**168 fewer per 1,000** (from 193 fewer to 138 fewer)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. 21/31 of the studies included had high or uncertain risk of bias.

b. rating down once for risk of bias covered multiple minor concerns, including publication bias.

c. overall effect estimate was heavily influenced by 5 studies with a baseline risk of CDAD > 15%, studies with a low baseline risk of CDAD did not demonstrate significant risk reduction

d. The 95% CI includes the potential for both benefit and harm.

e. heterogeneity suggested based on an I2 of 49%. Goldenberg 2017 authors suggest that this heterogeneity may be explained by a subgroup effect found between the probiotic species.

f. heterogeneity suggested based on an I2 of 61%. Goldenberg 2017 authors suggest that this heterogeneity may be explained by a subgroup effect from the inclusion of both pediatric vs adult populations.

g. 12/23 studies with unclear or high risk of bias.

h. statistically significant heterogeneity noted between studies (I2 = 59%), may be explained by risk of bias.

i. adults only included and may not be generalizable to the entire population.

j. visual inspection of the funnel plot and statistical assessment via Harbord linear regression test were suggestive of small study effects (e.g. publication bias) (P = 0.02).

k. 2/6 studies with unclear or high risk of bias reported.

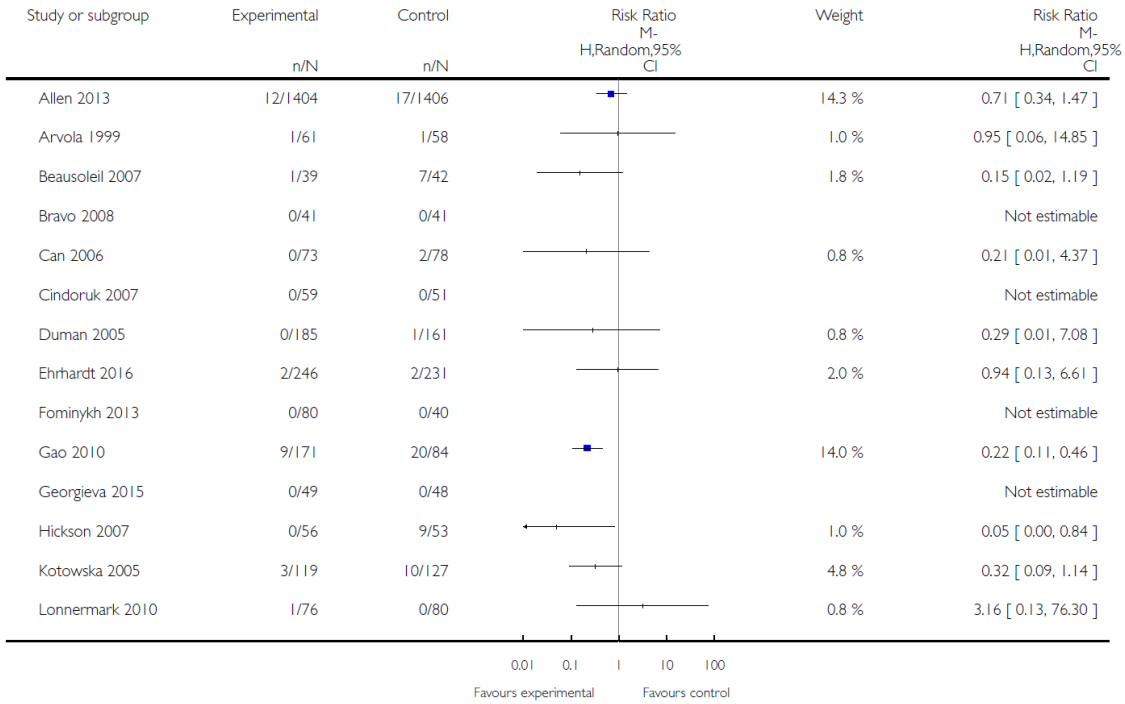
l. children only included and may not be generalizable to the entire population.

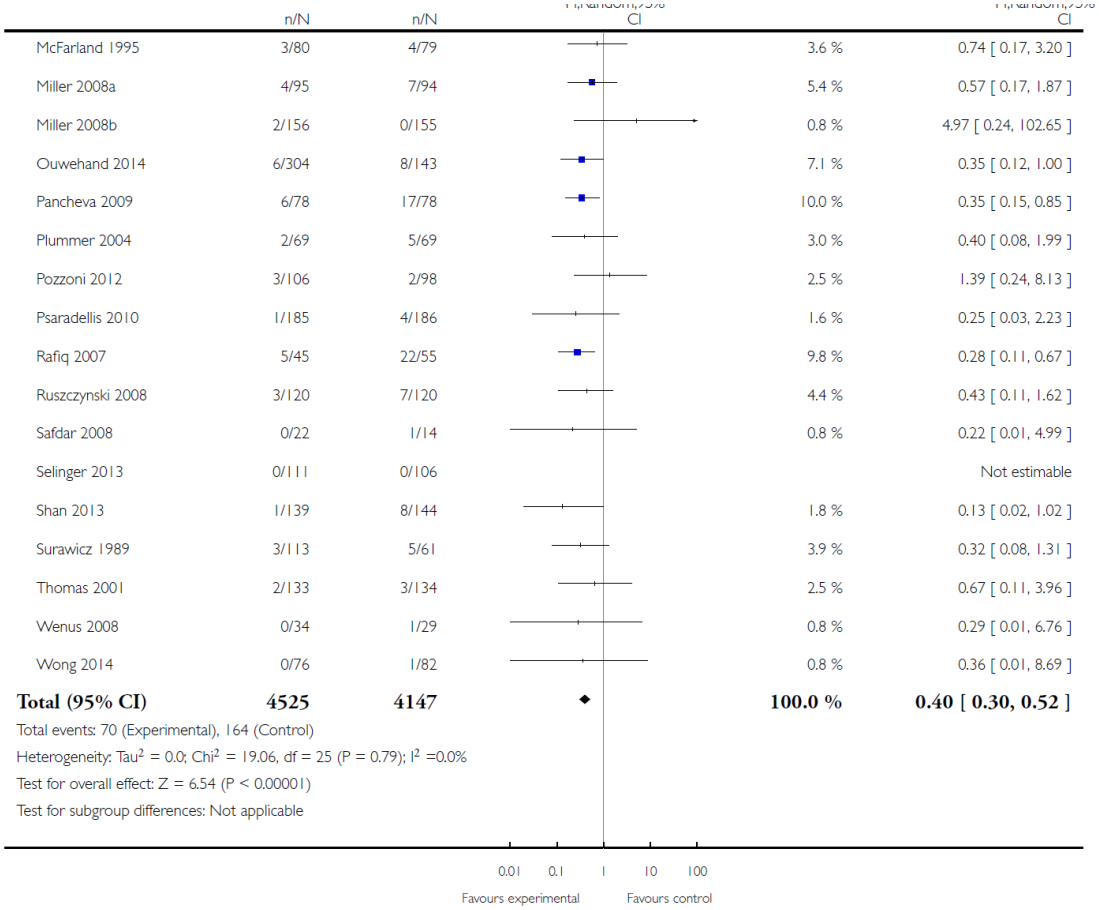
m. with n=6 Harbord's linear regression test is underpowered to detect a significant interaction, however visual inspection of the funnel plot is suspicious for publication bias. Also, due to the review's inclusion criteria specific to CDAD not AAD we worry about the possibility of publication bias here.

Forest plots

Comparison: 1 Probiotics versus control

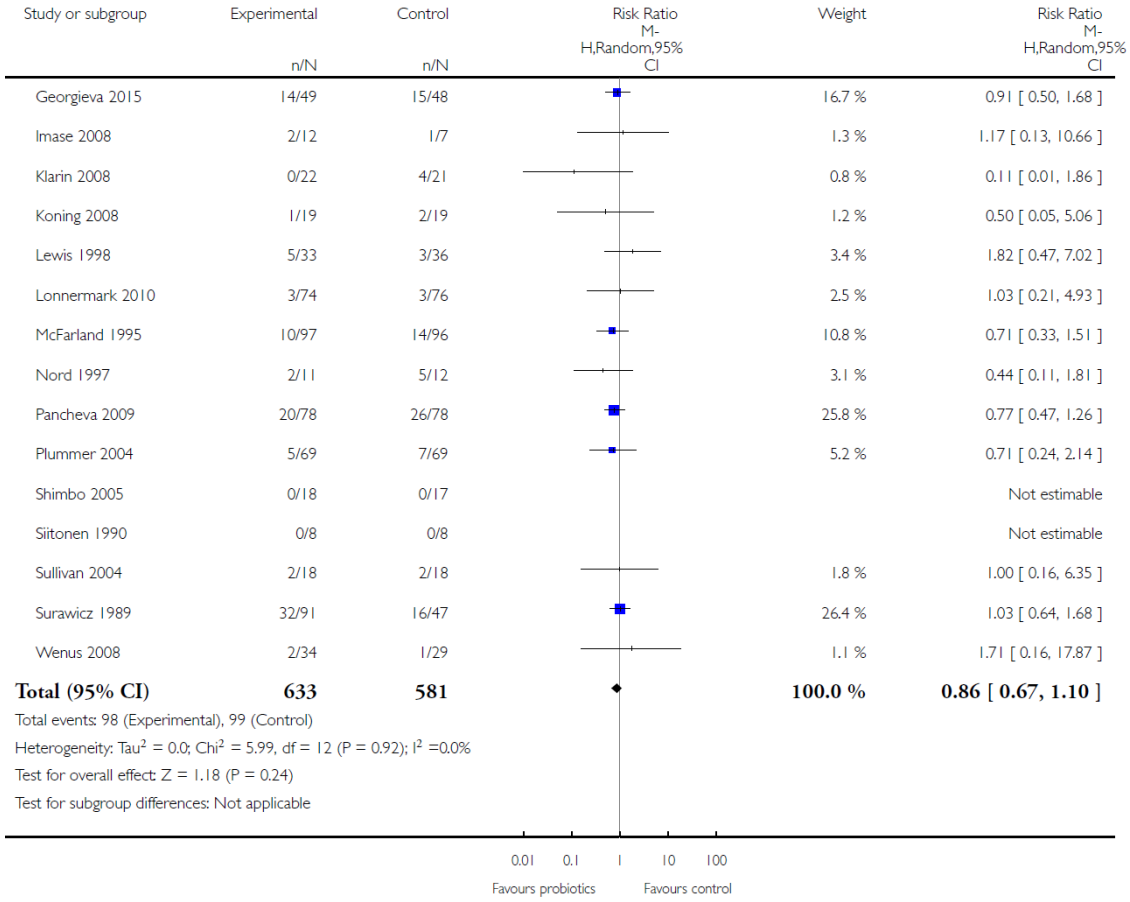
Outcome: 1 Incidence CDAD: complete case




n/N
n/N
CI
CI
McFarland 1995 3/80 4/79 3.6 % 0.74 [0.17, 3.20]
Miller 2008a 4/95 7/94 5.4 % 0.57 [0.17, 1.87]
Miller 2008b 2/156 0/155 0.8 % 4.97 [0.24, 102.65]
Ouwehand 2014 6/304 8/143 7.1 % 0.35 [0.12, 1.00]
Pancheva 2009 6/78 17/78 10.0 % 0.35 [0.15, 0.85]
Plummer 2004 2/69 5/69 3.0 % 0.40 [0.08, 1.99]
Pozzoni 2012 3/106 2/98 2.5 % 1.39 [0.24, 8.13]
Psaradellis 2010 1/185 4/186 1.6 % 0.25 [0.03, 2.23]
Rafiq 2007 5/45 22/55 9.8 % 0.28 [0.11, 0.67]
Ruszczynski 2008 3/120 7/120 4.4 % 0.43 [0.11, 1.62]
Safdar 2008 0/22 1/14 0.8 % 0.22 [0.01, 4.99]
Selinger 2013 0/111 0/106 Not estimable
Shan 2013 1/139 8/144 1.8 % 0.13 [0.02, 1.02]
Surawicz 1989 3/113 5/61 3.9 % 0.32 [0.08, 1.31]
Thomas 2001 2/133 3/134 2.5 % 0.67 [0.11, 3.96]
Wenus 2008 0/34 1/29 0.8 % 0.29 [0.01, 6.76]
Wong 2014 0/76 1/82 0.8 % 0.36 [0.01, 8.69]
Total (95% CI) 4525 4147 100.0 % 0.40 [0.30, 0.52]
Total events: 70 (Experimental), 164 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 19.06, df = 25 (P = 0.79); I² =0.0%
Test for overall effect: Z = 6.54 (P < 0.00001)
Test for subgroup differences: Not applicable
0.01
0.1
1
10
100
Favours experimental
Favours control

Comparison: 1 Probiotics versus control

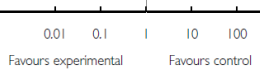
Outcome: 18 Incidence of infection: complete case

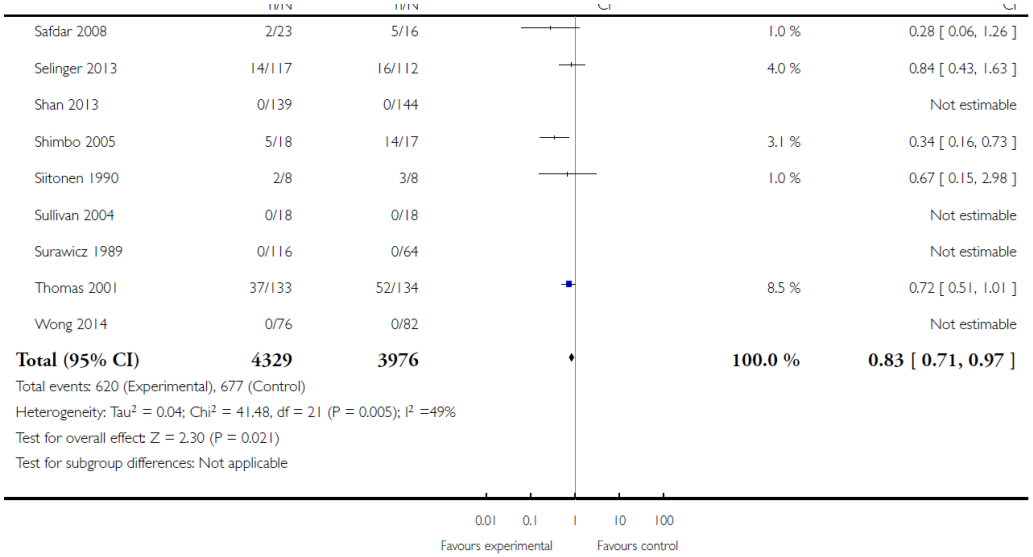


Comparison: 1 Probiotics versus control

Outcome: 24 Adverse Events: complete case

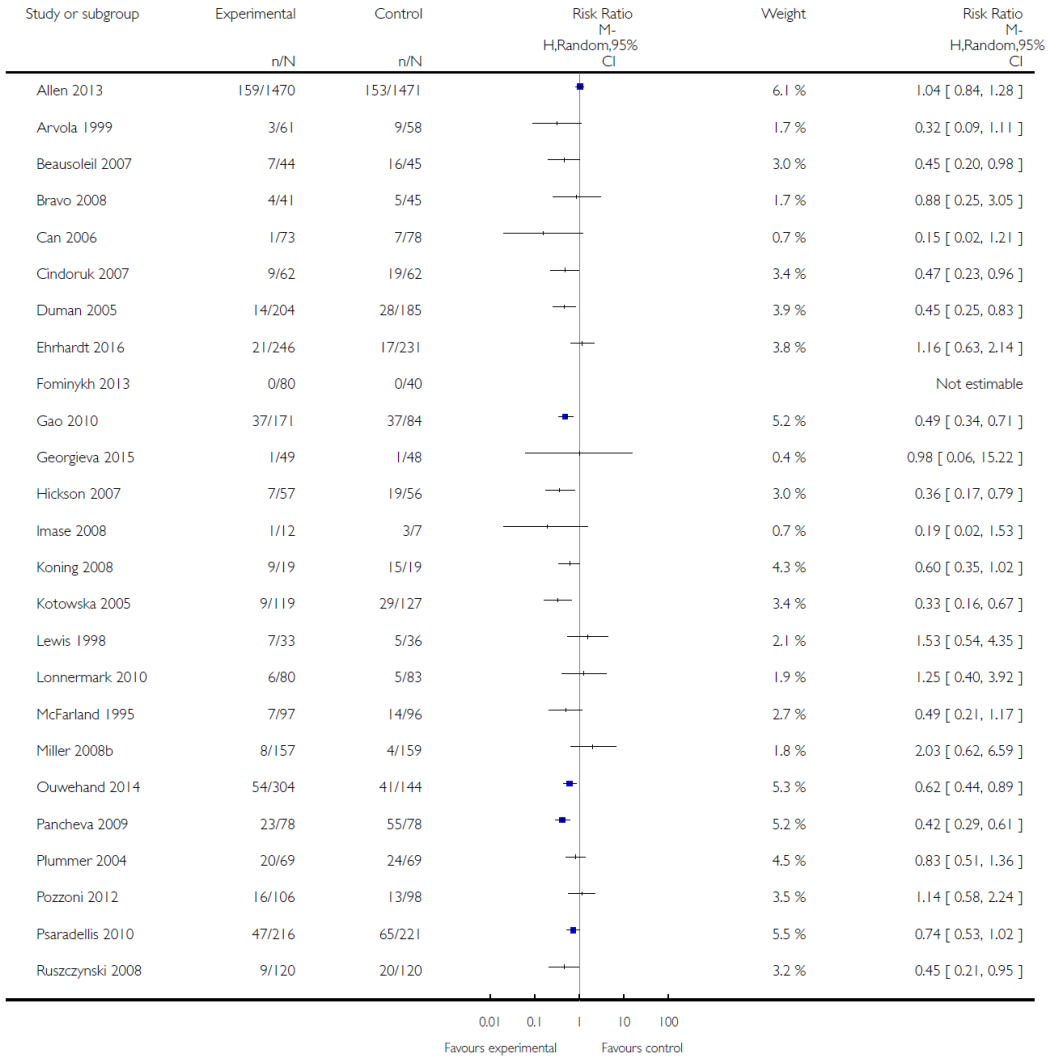
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Allen 2013	294/1470	284/1471		13.1 %	1.04 [0.90, 1.20]
Arvola 1999	0/61	0/58			Not estimable
Beausoleil 2007	21/44	20/45		6.6 %	1.07 [0.68, 1.68]
Bravo 2008	3/41	4/45		1.1 %	0.82 [0.20, 3.46]
Cindoruk 2007	41/62	62/62		12.4 %	0.66 [0.56, 0.79]
Duman 2005	3/196	4/180		1.0 %	0.69 [0.16, 3.04]
Ehrhardt 2016	18/146	12/146		3.7 %	1.50 [0.75, 3.00]
Fominykh 2013	0/80	0/40			Not estimable
Gao 2010	1/171	2/84		0.4 %	0.25 [0.02, 2.67]
Hickson 2007	0/57	0/56			Not estimable
Imase 2008	1/12	3/7		0.5 %	0.19 [0.02, 1.53]
Klarin 2008	0/22	0/22			Not estimable
Koning 2008	15/19	17/19		10.0 %	0.88 [0.67, 1.17]
Kotowska 2005	0/119	0/127			Not estimable
Lonnermark 2010	3/80	3/83		0.9 %	1.04 [0.22, 4.99]
McFarland 1995	0/93	12/92		0.3 %	0.04 [0.00, 0.66]
Miller 2008a	2/95	4/94		0.8 %	0.49 [0.09, 2.64]
Miller 2008b	4/156	0/155		0.3 %	8.94 [0.49, 164.71]
Nord 1997	9/11	10/12		7.9 %	0.98 [0.67, 1.43]
Ouwehand 2014	14/304	12/144		3.4 %	0.55 [0.26, 1.16]
Pozzoni 2012	41/106	35/98		8.3 %	1.08 [0.76, 1.55]
Psaradellis 2010	90/216	103/221		11.6 %	0.89 [0.72, 1.10]
Ruszczynski 2008	0/120	0/120			Not estimable

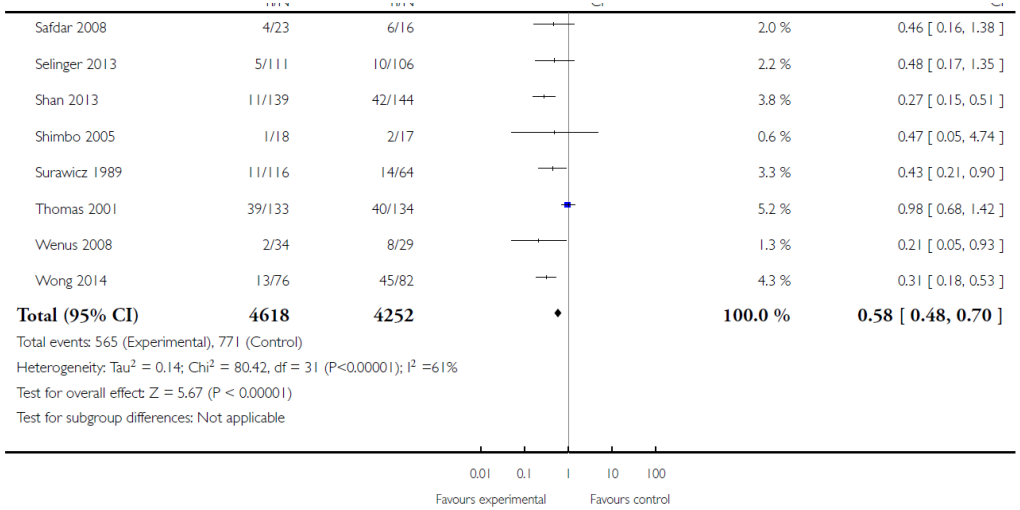



Safdar 2008 2/23 5/16 1.0 % 0.28 [0.06, 1.26]
Selinger 2013 14/117 16/112 4.0 % 0.84 [0.43, 1.63]
Shan 2013 0/139 0/144 Not estimable
Shimbo 2005 5/18 14/17 3.1 % 0.34 [0.16, 0.73]
Siitonen 1990 2/8 3/8 1.0 % 0.67 [0.15, 2.98]
Sullivan 2004 0/18 0/18 Not estimable
Surawicz 1989 0/116 0/64 Not estimable
Thomas 2001 37/133 52/134 8.5 % 0.72 [0.51, 1.01]
Wong 2014 0/76 0/82 Not estimable
Total (95% CI) 4329 3976 100.0 % 0.83 [0.71, 0.97]
Total events: 620 (Experimental), 677 (Control)
Heterogeneity: Tau² = 0.04; Chi² = 41.48, df = 21 (P = 0.005); I² =49%
Test for overall effect: Z = 2.30 (P = 0.021)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control

Comparison: 1 Probiotics versus control

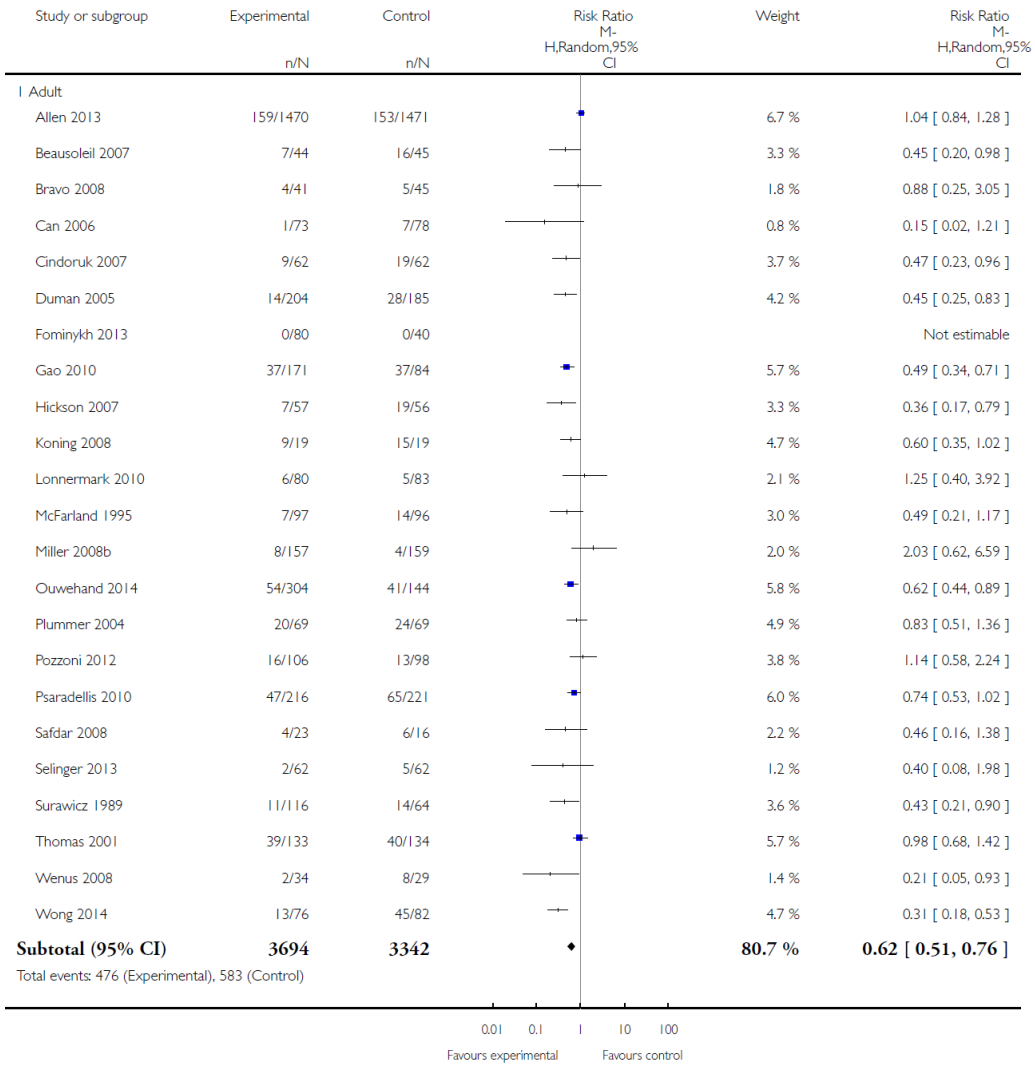
Outcome: 35 Incidence AAD: complete case

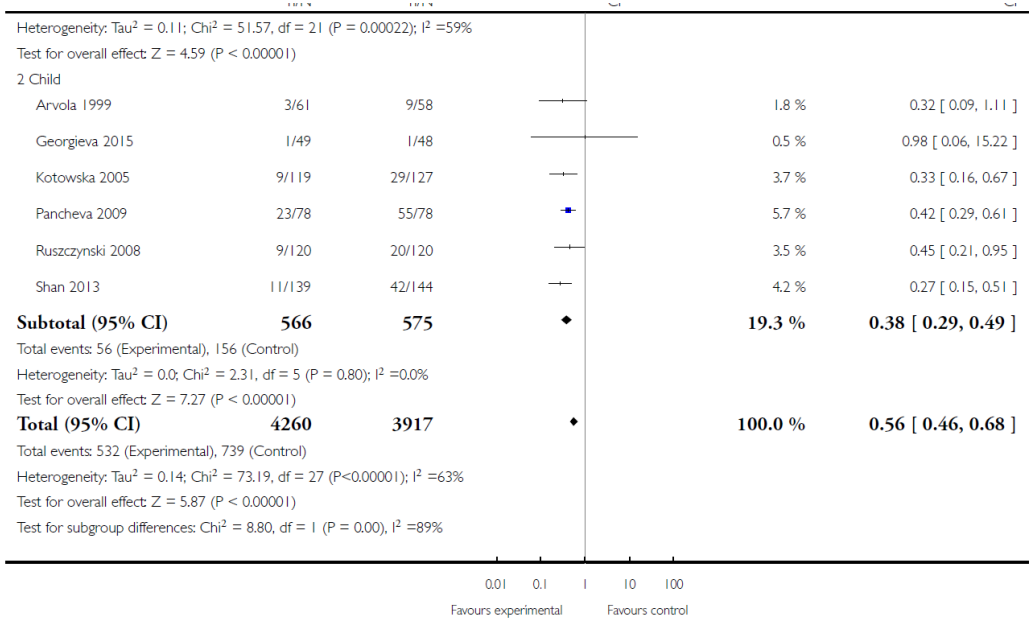



Safdar 2008 4/23 6/16 2.0 % 0.46 [0.16, 1.38]
Selinger 2013 5/111 10/106 2.2 % 0.48 [0.17, 1.35]
Shan 2013 11/139 42/144 3.8 % 0.27 [0.15, 0.51]
Shimbo 2005 1/18 2/17 0.6 % 0.47 [0.05, 4.74]
Surawicz 1989 11/116 14/64 3.3 % 0.43 [0.21, 0.90]
Thomas 2001 39/133 40/134 5.2 % 0.98 [0.68, 1.42]
Wenus 2008 2/34 8/29 1.3 % 0.21 [0.05, 0.93]
Wong 2014 13/76 45/82 4.3 % 0.31 [0.18, 0.53]
Total (95% CI) 4618 4252 100.0 % 0.58 [0.48, 0.70]
Total events: 565 (Experimental), 771 (Control)
Heterogeneity: Tau² = 0.14; Chi² = 80.42, df = 31 (P<0.00001); I² =61%
Test for overall effect: Z = 5.67 (P < 0.00001)
Test for subgroup differences: Not applicable
0.01 0.1 1 10 100
Favours experimental
Favours control

Comparison: 1 Probiotics versus control

Outcome: 45 Incidence AAD: Adult versus child




Heterogeneity: Tau² = 0.11; Chi² = 51.57, df = 21 (P = 0.00022); I² =59%
Test for overall effect: Z = 4.59 (P < 0.00001)
2 Child
Arvola 1999 3/61 9/58 1.8 % 0.32 [0.09, 1.11]
Georgieva 2015 1/49 1/48 0.5 % 0.98 [0.06, 15.22]
Kotowska 2005 9/119 29/127 3.7 % 0.33 [0.16, 0.67]
Pancheva 2009 23/78 55/78 5.7 % 0.42 [0.29, 0.61]
Ruszczynski 2008 9/120 20/120 3.5 % 0.45 [0.21, 0.95]
Shan 2013 11/139 42/144 4.2 % 0.27 [0.15, 0.51]
Subtotal (95% CI) 566 575 19.3 % 0.38 [0.29, 0.49]
Total events: 56 (Experimental), 156 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 2.31, df = 5 (P = 0.80); I² =0.0%
Test for overall effect: Z = 7.27 (P < 0.00001)
Total (95% CI) 4260 3917 100.0 % 0.56 [0.46, 0.68]
Total events: 532 (Experimental), 739 (Control)
Heterogeneity: Tau² = 0.14; Chi² = 73.19, df = 27 (P<0.00001); I² =63%
Test for overall effect: Z = 5.87 (P < 0.00001)
Test for subgroup differences: Chi² = 8.80, df = 1 (P = 0.00), I² =89%
0.01 0.1 1 10 100
Favours experimental
Favours control

Outcomes stratified by species:

C. difficile-associated diarrhea

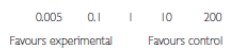
Analysis 1.8. Comparison 1 Probiotics versus control, Outcome 8 Incidence CDAD: Subgroup: Species: all.

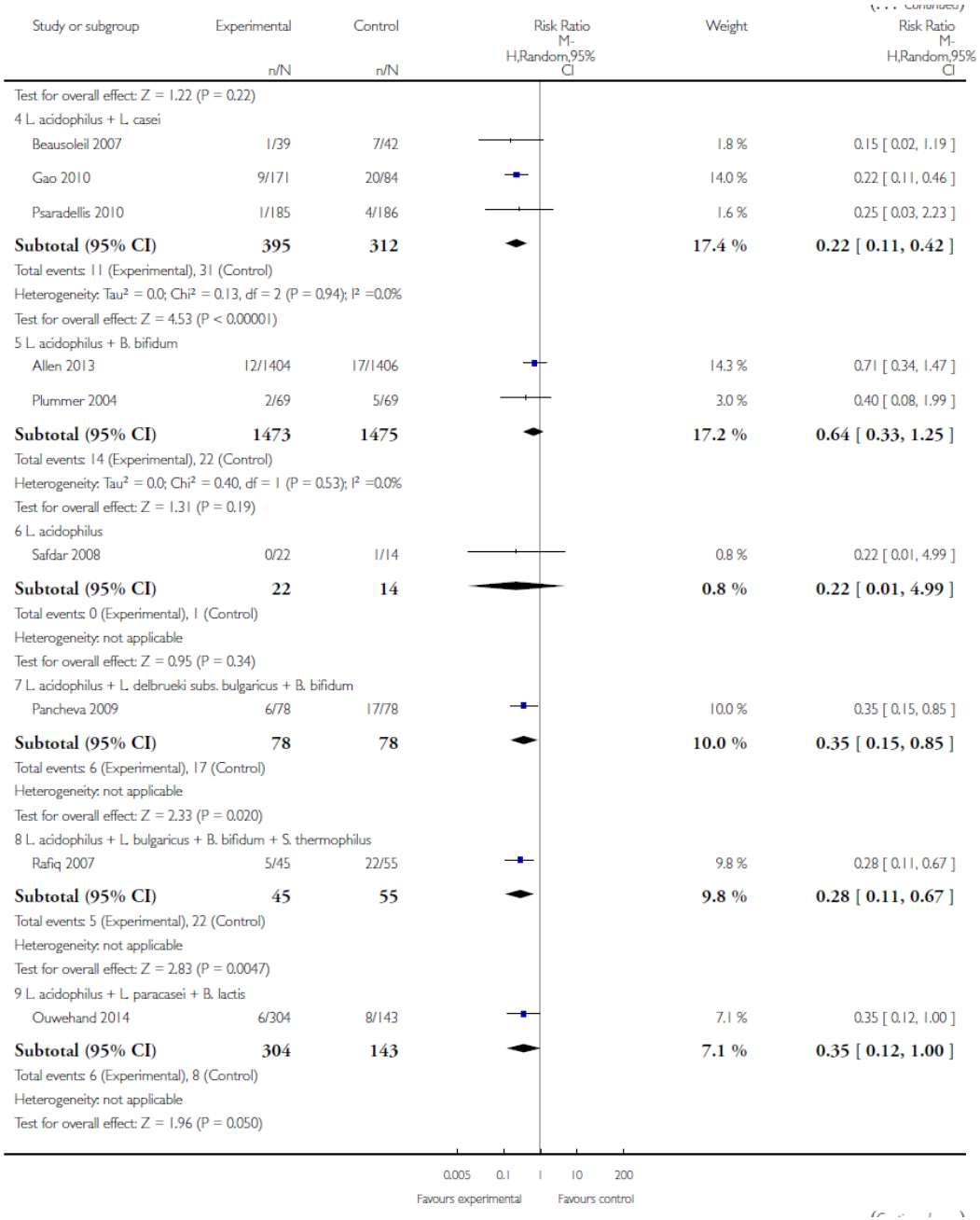
Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

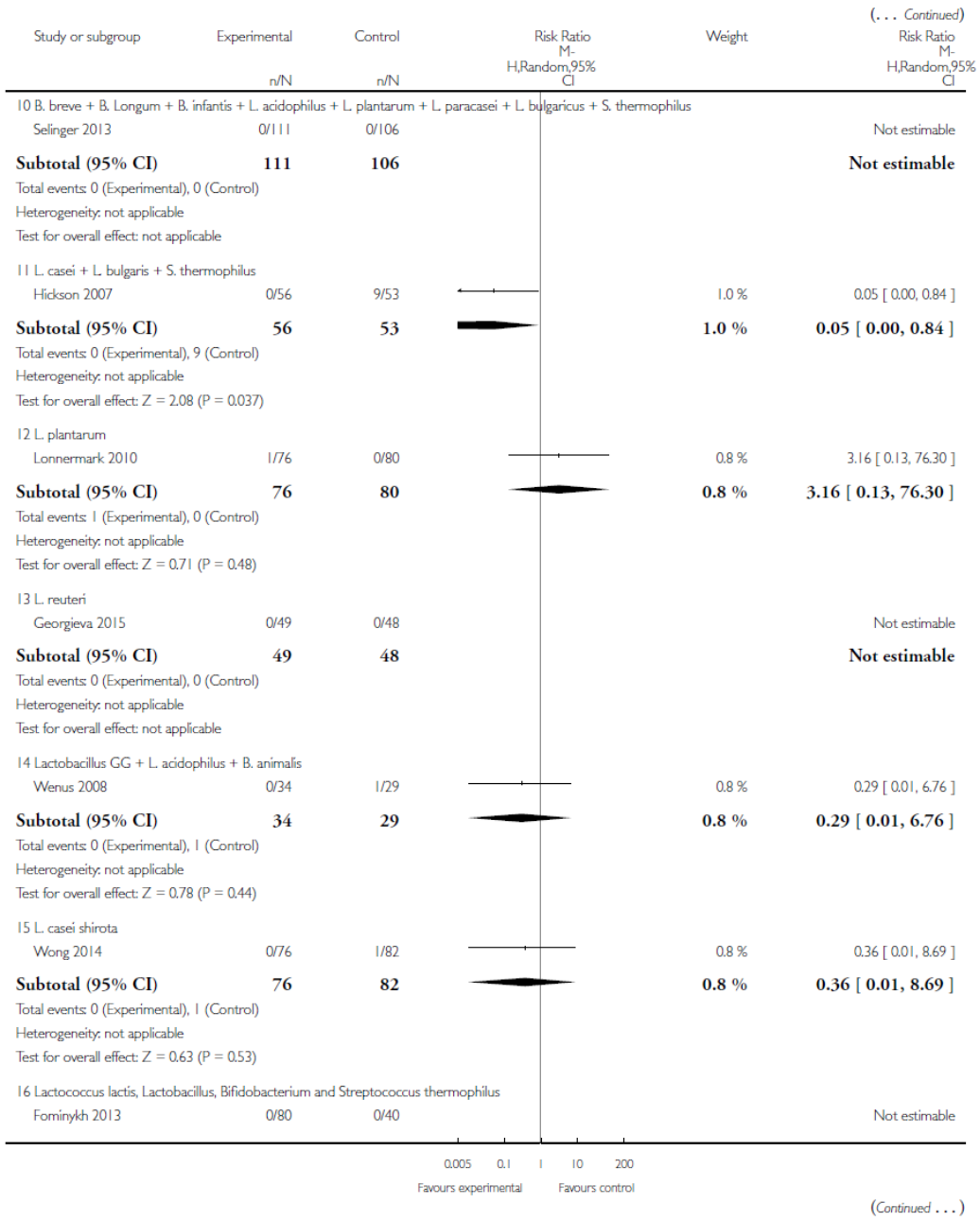
Comparison: 1 Probiotics versus control

Outcome: 8 Incidence CDAD: Subgroup: Species: all

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 S. boulardii					
Bravo 2008	0/41	0/41			Not estimable
Can 2006	0/73	2/78		0.8 %	0.21 [0.01, 4.37]
Cindoruk 2007	0/59	0/51			Not estimable
Duman 2005	0/185	1/161		0.8 %	0.29 [0.01, 7.08]
Kotowska 2005	3/119	10/127		4.8 %	0.32 [0.09, 1.14]
McFarland 1995	3/80	4/79		3.6 %	0.74 [0.17, 3.20]
Pozzoni 2012	3/106	2/98		2.5 %	1.39 [0.24, 8.13]
Shan 2013	1/139	8/144		1.8 %	0.13 [0.02, 1.02]
Surawicz 1989	3/113	5/61		3.9 %	0.32 [0.08, 1.31]
Subtotal (95% CI)	**915**	**840**		**18.2 %**	**0.41 [0.22, 0.79]**
Total events: 13 (Experimental), 32 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.18$, df = 6 (P = 0.65); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.67 (P = 0.0076)					
2 S. cerevisiae					
Ehrhardt 2016	2/246	2/231		2.0 %	0.94 [0.13, 6.61]
Subtotal (95% CI)	**246**	**231**		**2.0 %**	**0.94 [0.13, 6.61]**
Total events: 2 (Experimental), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
3 Lactobacillus GG					
Arvola 1999	1/61	1/58		1.0 %	0.95 [0.06, 14.85]
Miller 2008a	4/95	7/94		5.4 %	0.57 [0.17, 1.87]
Miller 2008b	2/156	0/155		0.8 %	4.97 [0.24, 102.65]
Ruszczynski 2008	3/120	7/120		4.4 %	0.43 [0.11, 1.62]
Thomas 2001	2/133	3/134		2.5 %	0.67 [0.11, 3.96]
Subtotal (95% CI)	**565**	**561**		**14.1 %**	**0.63 [0.30, 1.32]**
Total events: 12 (Experimental), 18 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.26$, df = 4 (P = 0.69); $I^2 = 0.0\%$					




Study or subgroup
Experimental
n/N
Control
n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 1.22 (P = 0.22)
4 L. acidophilus + L. casei
Beausoleil 2007 1/39 7/42 1.8 % 0.15 [0.02, 1.19]
Gao 2010 9/171 20/84 14.0 % 0.22 [0.11, 0.46]
Psaradellis 2010 1/185 4/186 1.6 % 0.25 [0.03, 2.23]
Subtotal (95% CI) 395 312 17.4 % 0.22 [0.11, 0.42]
Total events: 11 (Experimental), 31 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 0.13, df = 2 (P = 0.94); I² =0.0%
Test for overall effect: Z = 4.53 (P < 0.00001)
5 L. acidophilus + B. bifidum
Allen 2013 12/1404 17/1406 14.3 % 0.71 [0.34, 1.47]
Plummer 2004 2/69 5/69 3.0 % 0.40 [0.08, 1.99]
Subtotal (95% CI) 1473 1475 17.2 % 0.64 [0.33, 1.25]
Total events: 14 (Experimental), 22 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 0.40, df = 1 (P = 0.53); I² =0.0%
Test for overall effect: Z = 1.31 (P = 0.19)
6 L. acidophilus
Safdar 2008 0/22 1/14 0.8 % 0.22 [0.01, 4.99]
Subtotal (95% CI) 22 14 0.8 % 0.22 [0.01, 4.99]
Total events: 0 (Experimental), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
7 L. acidophilus + L. delbrueki subs. bulgaricus + B. bifidum
Pancheva 2009 6/78 17/78 10.0 % 0.35 [0.15, 0.85]
Subtotal (95% CI) 78 78 10.0 % 0.35 [0.15, 0.85]
Total events: 6 (Experimental), 17 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.33 (P = 0.020)
8 L. acidophilus + L. bulgaricus + B. bifidum + S. thermophilus
Rafiq 2007 5/45 22/55 9.8 % 0.28 [0.11, 0.67]
Subtotal (95% CI) 45 55 9.8 % 0.28 [0.11, 0.67]
Total events: 5 (Experimental), 22 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.83 (P = 0.0047)
9 L. acidophilus + L. paracasei + B. lactis
Ouwehand 2014 6/304 8/143 7.1 % 0.35 [0.12, 1.00]
Subtotal (95% CI) 304 143 7.1 % 0.35 [0.12, 1.00]
Total events: 6 (Experimental), 8 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.96 (P = 0.050)
0.005
0.1
1
10
200
Favours experimental
Favours control


(. . . Continued)
Study or subgroup
Experimental
n/N
Control
n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
10 B. breve + B. Longum + B. infantis + L. acidophilus + L. plantarum + L. paracasei + L. bulgaricus + S. thermophilus
Selinger 2013 0/111 0/106 Not estimable
Subtotal (95% CI) 111 106 Not estimable
Total events: 0 (Experimental), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: not applicable
11 L. casei + L. bulgaris + S. thermophilus
Hickson 2007 0/56 9/53 1.0 % 0.05 [0.00, 0.84]
Subtotal (95% CI) 56 53 1.0 % 0.05 [0.00, 0.84]
Total events: 0 (Experimental), 9 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.08 (P = 0.037)
12 L. plantarum
Lonnermark 2010 1/76 0/80 0.8 % 3.16 [0.13, 76.30]
Subtotal (95% CI) 76 80 0.8 % 3.16 [0.13, 76.30]
Total events: 1 (Experimental), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.71 (P = 0.48)
13 L. reuteri
Georgieva 2015 0/49 0/48 Not estimable
Subtotal (95% CI) 49 48 Not estimable
Total events: 0 (Experimental), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: not applicable
14 Lactobacillus GG + L. acidophilus + B. animalis
Wenus 2008 0/34 1/29 0.8 % 0.29 [0.01, 6.76]
Subtotal (95% CI) 34 29 0.8 % 0.29 [0.01, 6.76]
Total events: 0 (Experimental), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.78 (P = 0.44)
15 L. casei shirota
Wong 2014 0/76 1/82 0.8 % 0.36 [0.01, 8.69]
Subtotal (95% CI) 76 82 0.8 % 0.36 [0.01, 8.69]
Total events: 0 (Experimental), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
16 Lactococcus lactis, Lactobacillus, Bifidobacterium and Streptococcus thermophilus
Fominykh 2013 0/80 0/40 Not estimable
0.005 0.1 1 10 200
Favours experimental
Favours control
(Continued . . .)

(. . . *Continued*)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**80**	**40**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**4525**	**4147**	◆	**100.0 %**	**0.40 [0.30, 0.52]**
Total events: 70 (Experimental), 164 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 19.06$, df = 25 (P = 0.79); $I^2 = 0.0\%$					
Test for overall effect: Z = 6.54 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 12.13$, df = 12 (P = 0.43), $I^2 = 1\%$					

0.005 0.1 1 10 200

Favours experimental Favours control

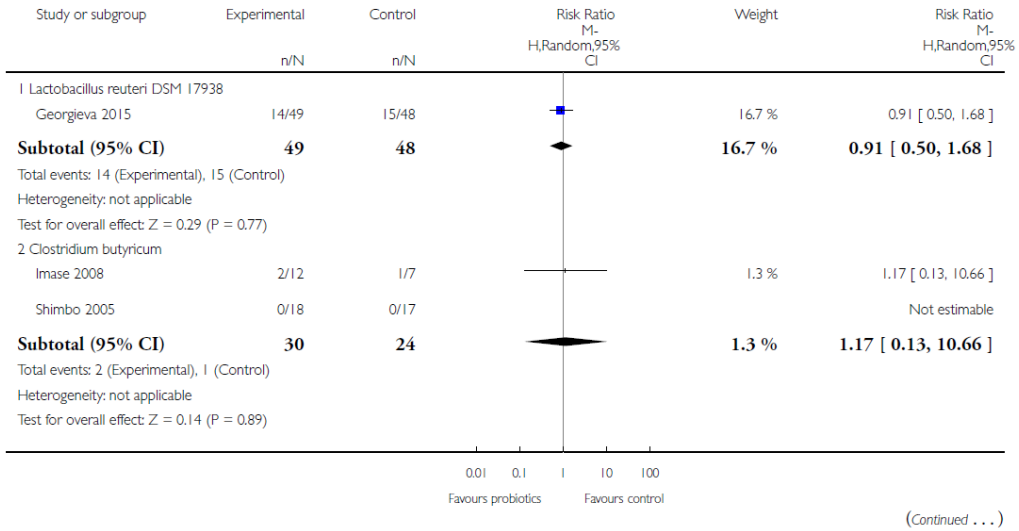
Incidence of infection

Analysis 1.21. Comparison 1 Probiotics versus control, Outcome 21 Incidence of infection: Species: all.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 Probiotics versus control

Outcome: 21 Incidence of infection: Species: all



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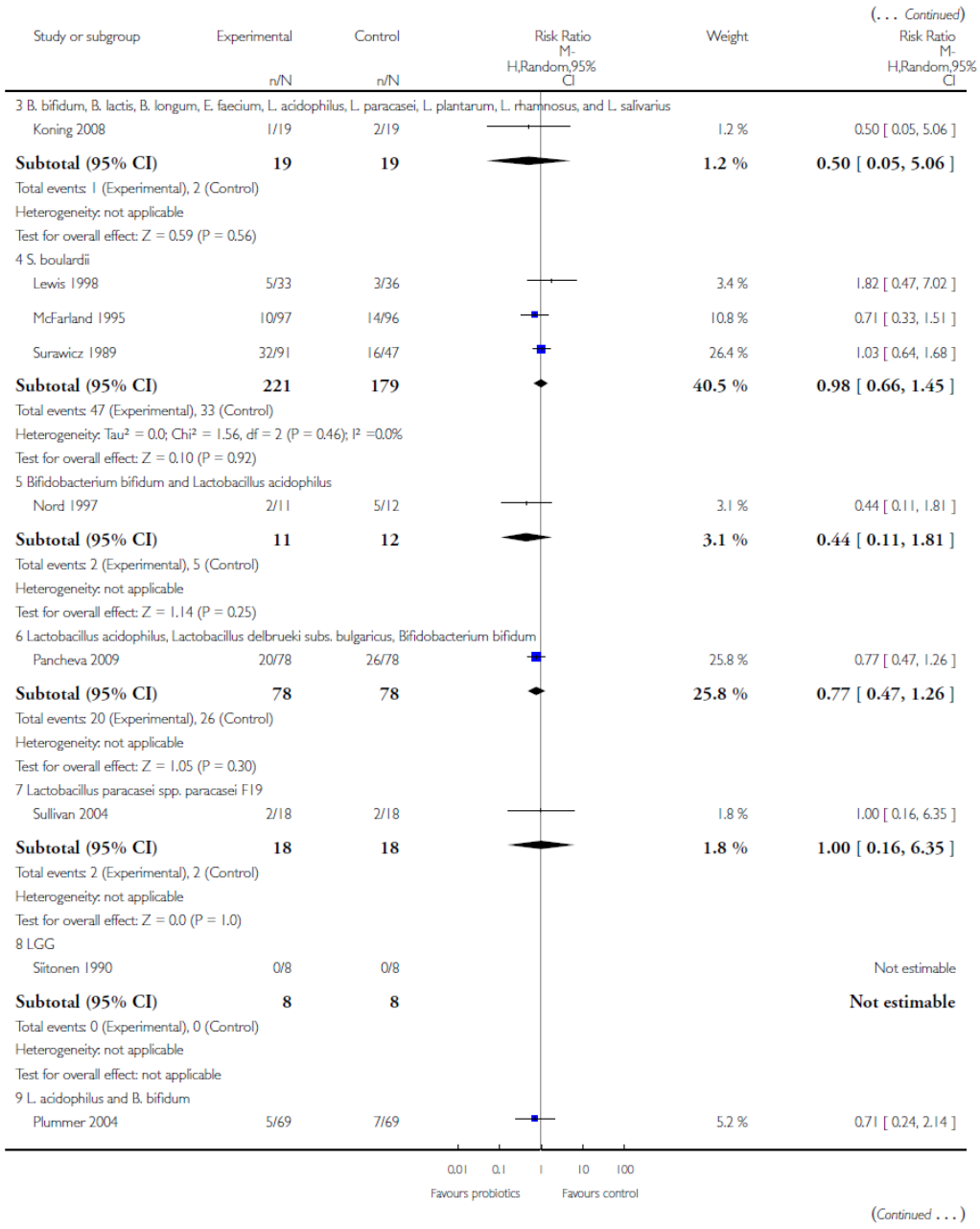
(. . . Continued)
Study or subgroup
Experimental
n/N
Control
n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
3 B. bifidum, B. lactis, B. longum, E. faecium, L. acidophilus, L. paracasei, L. plantarum, L. rhamnosus, and L. salivarius
Koning 2008 1/19 2/19 1.2 % 0.50 [0.05, 5.06]
Subtotal (95% CI) 19 19 1.2 % 0.50 [0.05, 5.06]
Total events: 1 (Experimental), 2 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
4 S. boulardii
Lewis 1998 5/33 3/36 3.4 % 1.82 [0.47, 7.02]
McFarland 1995 10/97 14/96 10.8 % 0.71 [0.33, 1.51]
Surawicz 1989 32/91 16/47 26.4 % 1.03 [0.64, 1.68]
Subtotal (95% CI) 221 179 40.5 % 0.98 [0.66, 1.45]
Total events: 47 (Experimental), 33 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 1.56, df = 2 (P = 0.46); I² =0.0%
Test for overall effect: Z = 0.10 (P = 0.92)
5 Bifidobacterium bifidum and Lactobacillus acidophilus
Nord 1997 2/11 5/12 3.1 % 0.44 [0.11, 1.81]
Subtotal (95% CI) 11 12 3.1 % 0.44 [0.11, 1.81]
Total events: 2 (Experimental), 5 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
6 Lactobacillus acidophilus, Lactobacillus delbrueki subs. bulgaricus, Bifidobacterium bifidum
Pancheva 2009 20/78 26/78 25.8 % 0.77 [0.47, 1.26]
Subtotal (95% CI) 78 78 25.8 % 0.77 [0.47, 1.26]
Total events: 20 (Experimental), 26 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.05 (P = 0.30)
7 Lactobacillus paracasei spp. paracasei F19
Sullivan 2004 2/18 2/18 1.8 % 1.00 [0.16, 6.35]
Subtotal (95% CI) 18 18 1.8 % 1.00 [0.16, 6.35]
Total events: 2 (Experimental), 2 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)
8 LGG
Siitonen 1990 0/8 0/8 Not estimable
Subtotal (95% CI) 8 8 Not estimable
Total events: 0 (Experimental), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: not applicable
9 L. acidophilus and B. bifidum
Plummer 2004 5/69 7/69 5.2 % 0.71 [0.24, 2.14]
0.01 0.1 1 10 100
Favours probiotics
Favours control
(Continued . . .)

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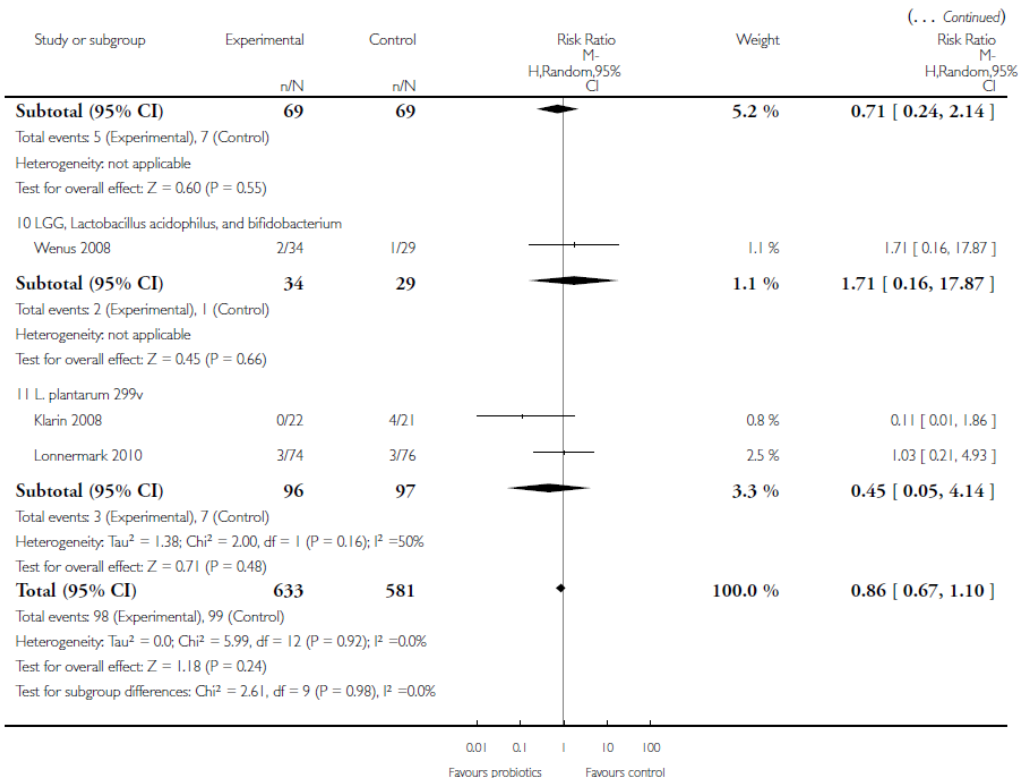
Study or subgroup
Experimental
n/N
Control
n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
Subtotal (95% CI) 69 69 5.2 % 0.71 [0.24, 2.14]
Total events: 5 (Experimental), 7 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.60 (P = 0.55)
10 LGG, Lactobacillus acidophilus, and bifidobacterium
Wenus 2008 2/34 1/29 1.1 % 1.71 [0.16, 17.87]
Subtotal (95% CI) 34 29 1.1 % 1.71 [0.16, 17.87]
Total events: 2 (Experimental), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.45 (P = 0.66)
11 L. plantarum 299v
Klarin 2008 0/22 4/21 0.8 % 0.11 [0.01, 1.86]
Lonnermark 2010 3/74 3/76 2.5 % 1.03 [0.21, 4.93]
Subtotal (95% CI) 96 97 3.3 % 0.45 [0.05, 4.14]
Total events: 3 (Experimental), 7 (Control)
Heterogeneity: Tau² = 1.38; Chi² = 2.00, df = 1 (P = 0.16); I² =50%
Test for overall effect: Z = 0.71 (P = 0.48)
Total (95% CI) 633 581 100.0 % 0.86 [0.67, 1.10]
Total events: 98 (Experimental), 99 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 5.99, df = 12 (P = 0.92); I² =0.0%
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Chi² = 2.61, df = 9 (P = 0.98), I² =0.0%
0.01
0.1
1
10
100
Favours probiotics
Favours control

Adverse events

Analysis 1.30. Comparison 1 Probiotics versus control, Outcome 30 Adverse Events: Species: all.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 Probiotics versus control

Outcome: 30 Adverse Events: Species: all

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 L. plantarum					
Klarin 2008	0/22	0/22			Not estimable
Lonnermark 2010	3/80	3/83		0.9 %	1.04 [0.22, 4.99]
Subtotal (95% CI)	**102**	**105**		**0.9 %**	**1.04 [0.22, 4.99]**
Total events: 3 (Experimental), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
2 LGG					
Arvola 1999	0/61	0/58			Not estimable
Miller 2008a	2/95	4/94		0.8 %	0.49 [0.09, 2.64]
Miller 2008b	4/156	0/155		0.3 %	8.94 [0.49, 164.71]
Ruszczynski 2008	0/120	0/120			Not estimable
Siitonen 1990	2/8	3/8		1.0 %	0.67 [0.15, 2.98]
Thomas 2001	37/133	52/134		8.5 %	0.72 [0.51, 1.01]
Subtotal (95% CI)	**573**	**569**		**10.6 %**	**0.74 [0.48, 1.14]**
Total events: 45 (Experimental), 59 (Control)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 3.18$, df = 3 (P = 0.36); $I^2 = 6\%$					
Test for overall effect: Z = 1.39 (P = 0.17)					
3 SB					
Bravo 2008	3/41	4/45		1.1 %	0.82 [0.20, 3.46]
Cindoruk 2007	41/62	62/62		12.4 %	0.66 [0.56, 0.79]
Duman 2005	3/196	4/180		1.0 %	0.69 [0.16, 3.04]
Kotowska 2005	0/119	0/127			Not estimable
McFarland 1995	0/93	12/92		0.3 %	0.04 [0.00, 0.66]
Pozzoni 2012	41/106	35/98		8.3 %	1.08 [0.76, 1.55]
Shan 2013	0/139	0/144			Not estimable
Surawicz 1989	0/116	0/64			Not estimable
Subtotal (95% CI)	**872**	**812**		**23.1 %**	**0.76 [0.48, 1.19]**

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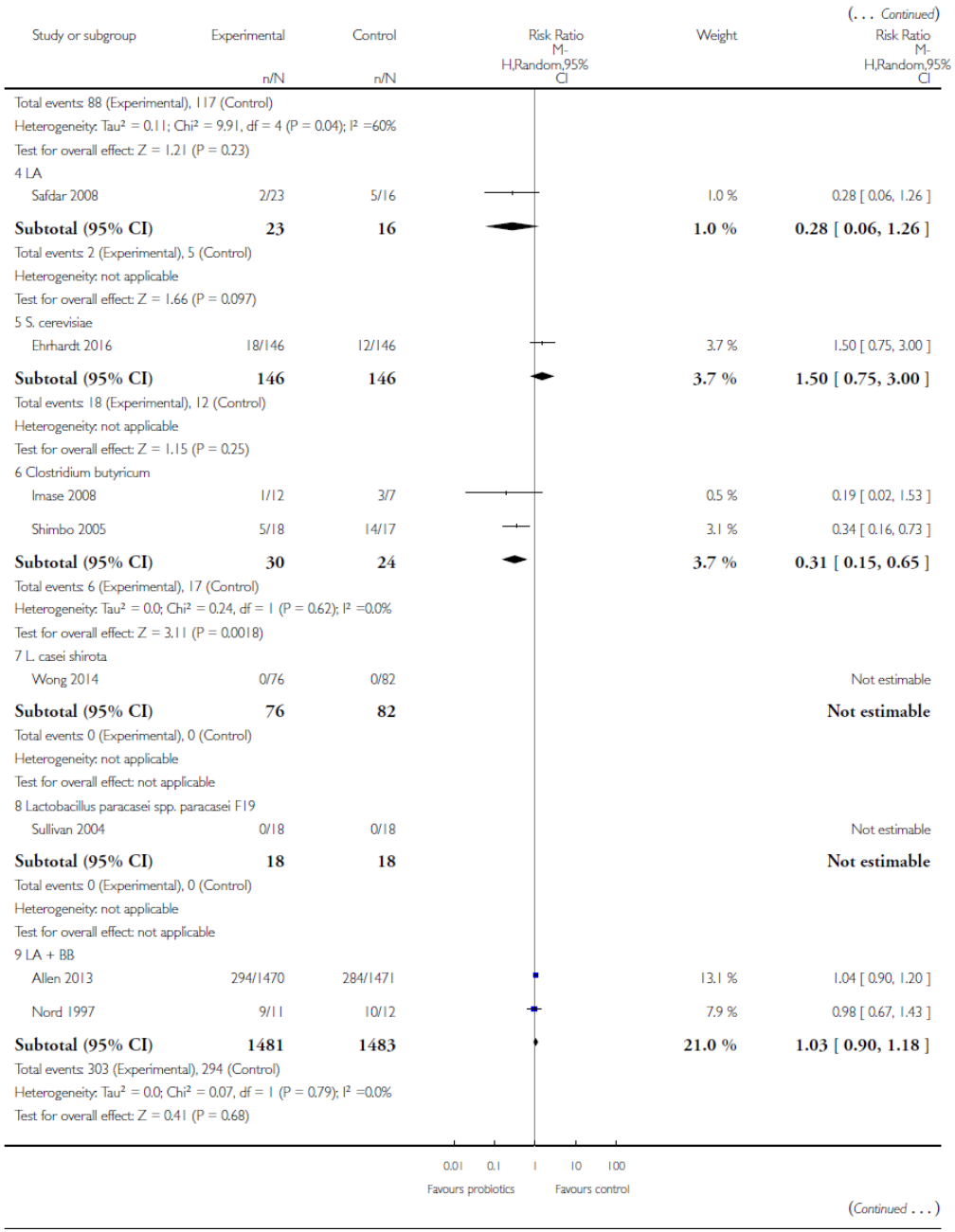

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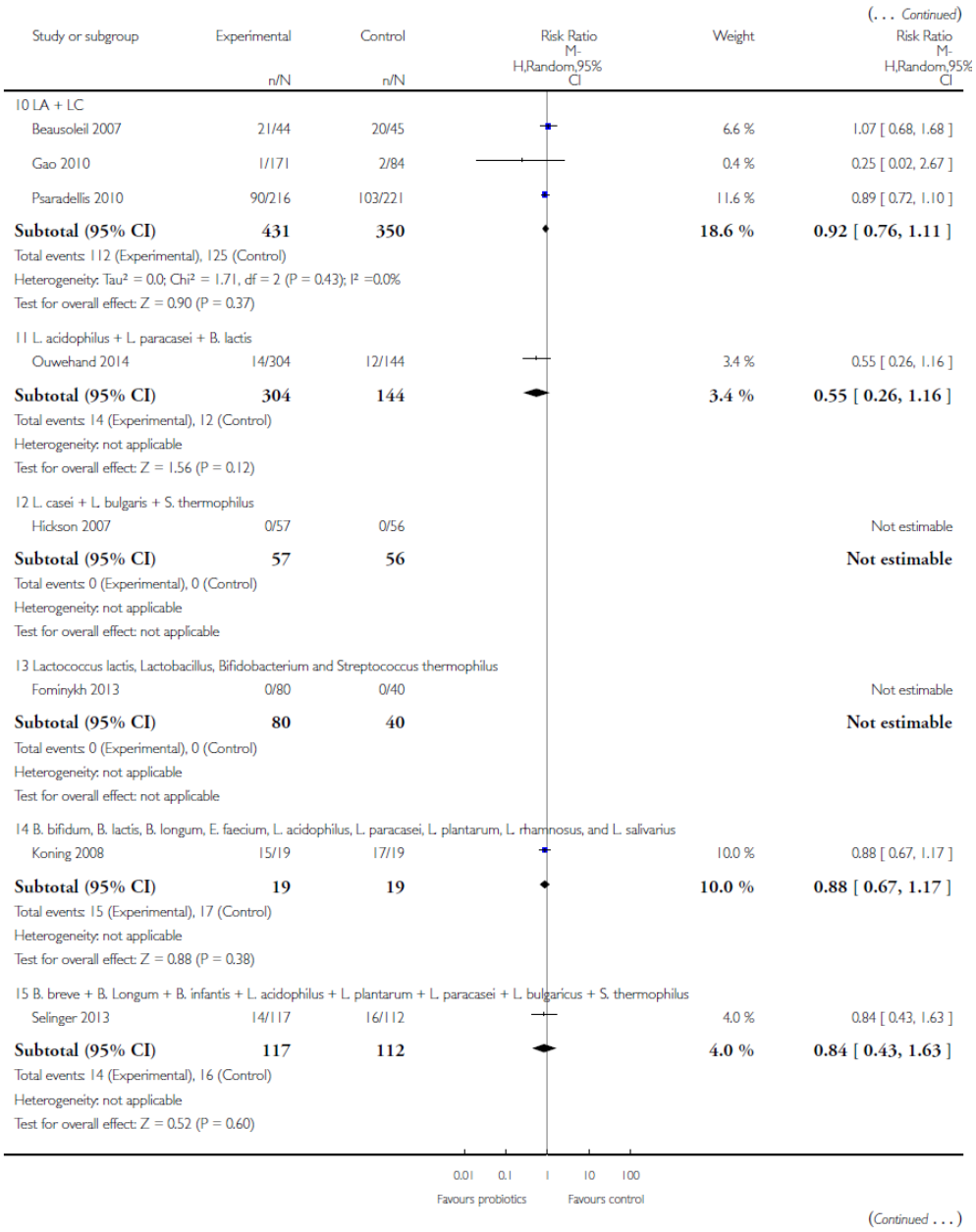

(. . . Continued)
Study or subgroup
Experimental
n/N
Control
n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
10 LA + LC
Beausoleil 2007 21/44 20/45 6.6 % 1.07 [0.68, 1.68]
Gao 2010 1/171 2/84 0.4 % 0.25 [0.02, 2.67]
Psaradellis 2010 90/216 103/221 11.6 % 0.89 [0.72, 1.10]
Subtotal (95% CI) 431 350 18.6 % 0.92 [0.76, 1.11]
Total events: 112 (Experimental), 125 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 1.71, df = 2 (P = 0.43); I² =0.0%
Test for overall effect: Z = 0.90 (P = 0.37)
11 L. acidophilus + L. paracasei + B. lactis
Ouwehand 2014 14/304 12/144 3.4 % 0.55 [0.26, 1.16]
Subtotal (95% CI) 304 144 3.4 % 0.55 [0.26, 1.16]
Total events: 14 (Experimental), 12 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.56 (P = 0.12)
12 L. casei + L. bulgaris + S. thermophilus
Hickson 2007 0/57 0/56 Not estimable
Subtotal (95% CI) 57 56 Not estimable
Total events: 0 (Experimental), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: not applicable
13 Lactococcus lactis, Lactobacillus, Bifidobacterium and Streptococcus thermophilus
Fominykh 2013 0/80 0/40 Not estimable
Subtotal (95% CI) 80 40 Not estimable
Total events: 0 (Experimental), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: not applicable
14 B. bifidum, B. lactis, B. longum, E. faecium, L. acidophilus, L. paracasei, L. plantarum, L. rhamnosus, and L. salivarius
Koning 2008 15/19 17/19 10.0 % 0.88 [0.67, 1.17]
Subtotal (95% CI) 19 19 10.0 % 0.88 [0.67, 1.17]
Total events: 15 (Experimental), 17 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.88 (P = 0.38)
15 B. breve + B. Longum + B. infantis + L. acidophilus + L. plantarum + L. paracasei + L. bulgaricus + S. thermophilus
Selinger 2013 14/117 16/112 4.0 % 0.84 [0.43, 1.63]
Subtotal (95% CI) 117 112 4.0 % 0.84 [0.43, 1.63]
Total events: 14 (Experimental), 16 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
0.01 0.1 1 10 100
Favours probiotics
Favours control
(Continued . . .)

(. . . *Continued*)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**4329**	**3976**	♦	**100.0 %**	**0.83 [0.71, 0.97]**
Total events: 620 (Experimental), 677 (Control)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 41.48$, df = 21 (P = 0.005); $I^2 = 49\%$					
Test for overall effect: Z = 2.30 (P = 0.021)					
Test for subgroup differences: $Chi^2 = 18.95$, df = 10 (P = 0.04), $I^2 = 47\%$					

Incidence of antibiotic-associated diarrhea

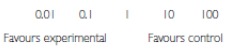
Analysis 1.42. Comparison 1 Probiotics versus control, Outcome 42 Incidence AAD: Species: all.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 Probiotics versus control

Outcome: 42 Incidence AAD: Species: all

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Lactobacillus GG					
Arvola 1999	3/61	9/58		1.6 %	0.32 [0.09, 1.11]
Miller 2008b	8/157	4/159		1.8 %	2.03 [0.62, 6.59]
Ruszczynski 2008	9/120	20/120		3.4 %	0.45 [0.21, 0.95]
Thomas 2001	39/133	40/134		6.5 %	0.98 [0.68, 1.42]
Subtotal (95% CI)	**471**	**471**		**13.3 %**	**0.75 [0.39, 1.43]**
Total events: 59 (Experimental), 73 (Control)					
Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 7.90$, df = 3 (P = 0.05); $I^2 = 62\%$					
Test for overall effect: Z = 0.88 (P = 0.38)					
2 S. boulardi					
Bravo 2008	4/41	5/45		1.6 %	0.88 [0.25, 3.05]
Can 2006	1/73	7/78		0.7 %	0.15 [0.02, 1.21]
Cindoruk 2007	9/62	19/62		3.7 %	0.47 [0.23, 0.96]
Duman 2005	14/204	28/185		4.3 %	0.45 [0.25, 0.83]
Kotowska 2005	9/119	29/127		3.7 %	0.33 [0.16, 0.67]
Lewis 1998	7/33	5/36		2.1 %	1.53 [0.54, 4.35]
McFarland 1995	7/97	14/96		2.8 %	0.49 [0.21, 1.17]
Pozzoni 2012	16/106	13/98		3.9 %	1.14 [0.58, 2.24]
Shan 2013	11/139	42/144		4.3 %	0.27 [0.15, 0.51]
Surawicz 1989	11/116	14/64		3.5 %	0.43 [0.21, 0.90]
Subtotal (95% CI)	**990**	**935**		**30.6 %**	**0.51 [0.36, 0.73]**
Total events: 89 (Experimental), 176 (Control)					
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 17.46$, df = 9 (P = 0.04); $I^2 = 48\%$					
Test for overall effect: Z = 3.67 (P = 0.00024)					
3 Clostridium butyricum					
Imase 2008	1/12	3/7		0.7 %	0.19 [0.02, 1.53]
Shimbo 2005	1/18	2/17		0.5 %	0.47 [0.05, 4.74]
Subtotal (95% CI)	**30**	**24**		**1.2 %**	**0.29 [0.06, 1.34]**



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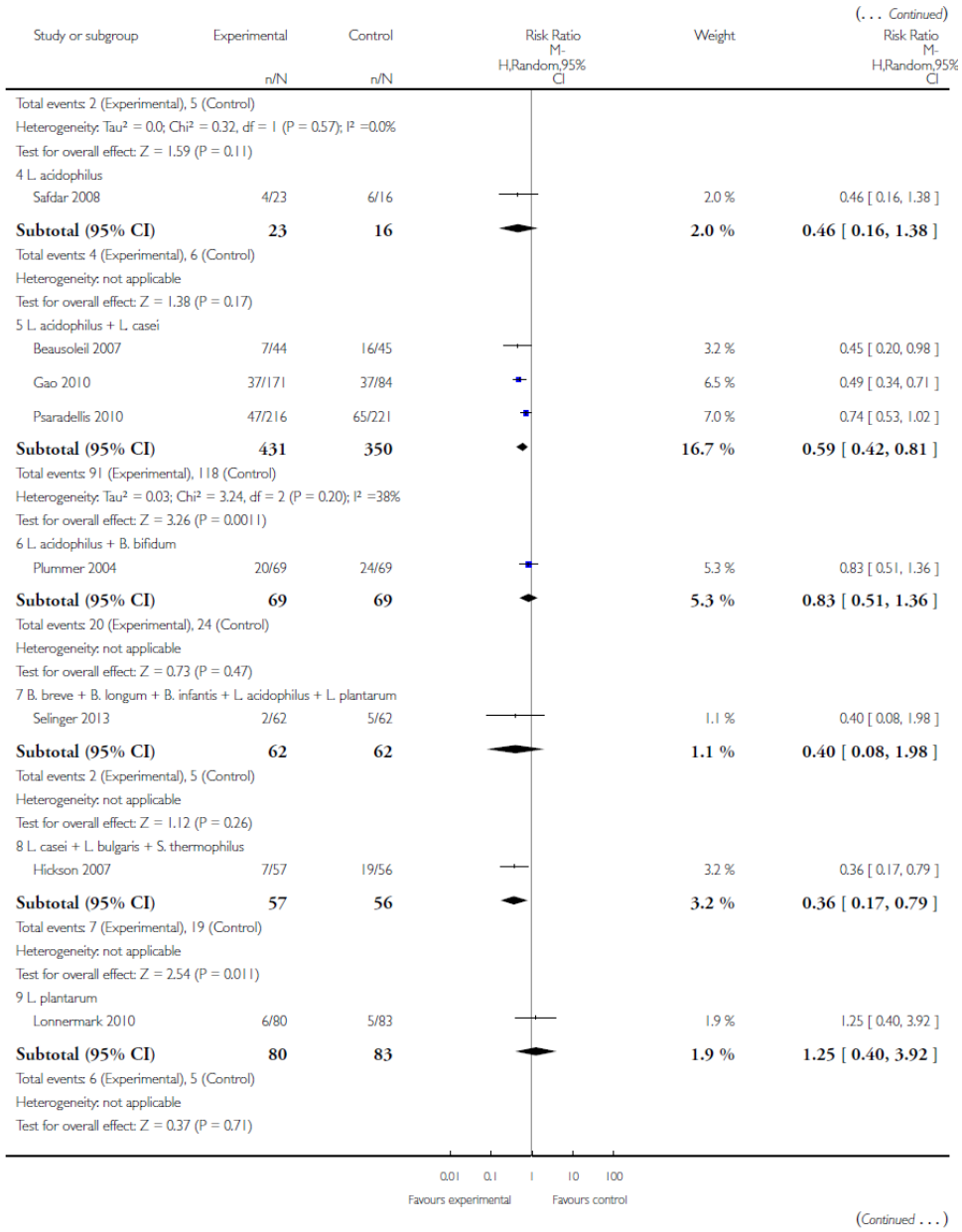
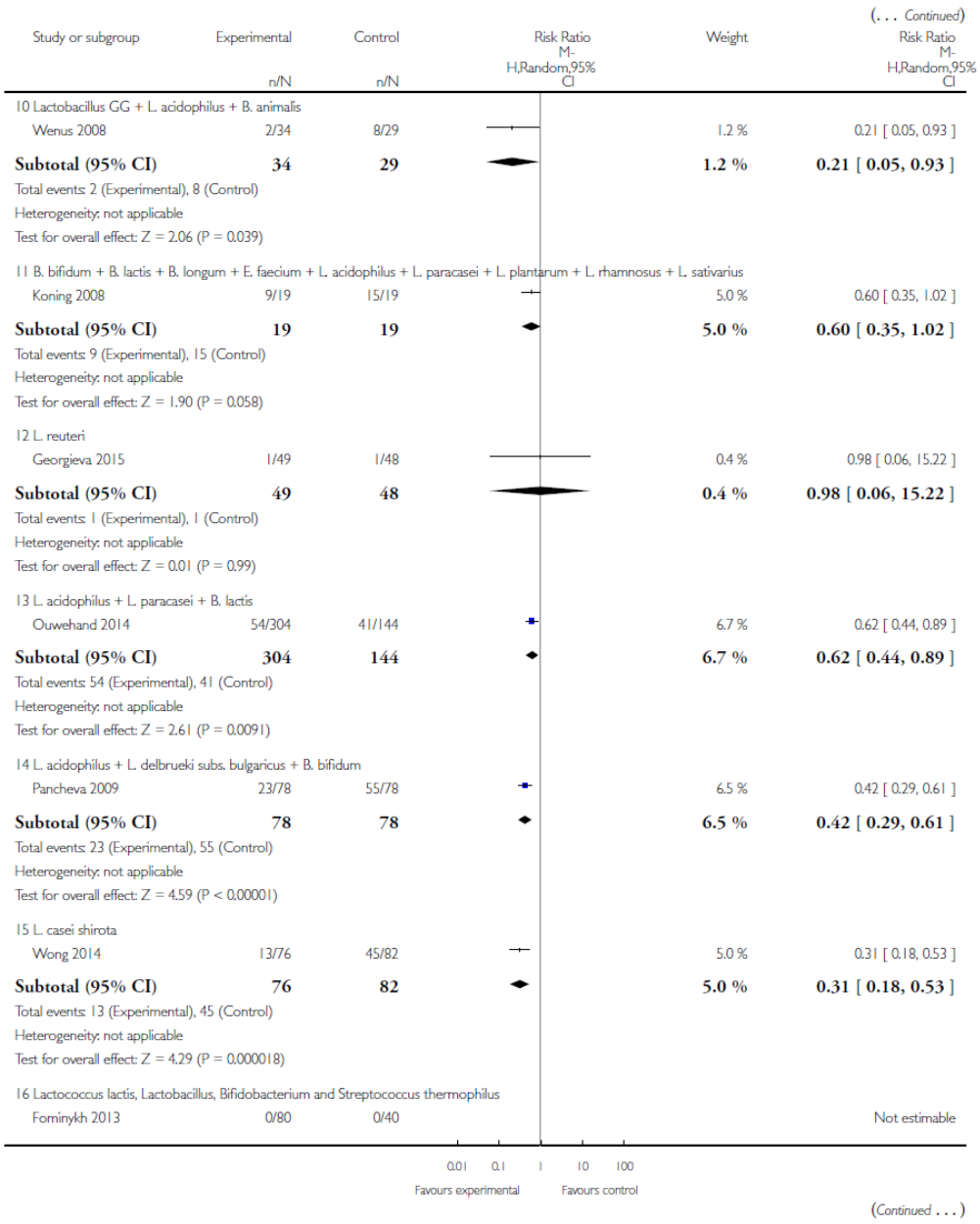

(. . . Continued)
Study or subgroup
Experimental
n/N
Control
n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
Total events: 2 (Experimental), 5 (Control)
Heterogeneity: Tau² = 0.0; Chi² = 0.32, df = 1 (P = 0.57); I² =0.0%
Test for overall effect: Z = 1.59 (P = 0.11)
4 L. acidophilus
Safdar 2008 4/23 6/16 2.0 % 0.46 [0.16, 1.38]
Subtotal (95% CI) 23 16 2.0 % 0.46 [0.16, 1.38]
Total events: 4 (Experimental), 6 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.38 (P = 0.17)
5 L. acidophilus + L. casei
Beausoleil 2007 7/44 16/45 3.2 % 0.45 [0.20, 0.98]
Gao 2010 37/171 37/84 6.5 % 0.49 [0.34, 0.71]
Psaradellis 2010 47/216 65/221 7.0 % 0.74 [0.53, 1.02]
Subtotal (95% CI) 431 350 16.7 % 0.59 [0.42, 0.81]
Total events: 91 (Experimental), 118 (Control)
Heterogeneity: Tau² = 0.03; Chi² = 3.24, df = 2 (P = 0.20); I² =38%
Test for overall effect: Z = 3.26 (P = 0.0011)
6 L. acidophilus + B. bifidum
Plummer 2004 20/69 24/69 5.3 % 0.83 [0.51, 1.36]
Subtotal (95% CI) 69 69 5.3 % 0.83 [0.51, 1.36]
Total events: 20 (Experimental), 24 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
7 B. breve + B. longum + B. infantis + L. acidophilus + L. plantarum
Selinger 2013 2/62 5/62 1.1 % 0.40 [0.08, 1.98]
Subtotal (95% CI) 62 62 1.1 % 0.40 [0.08, 1.98]
Total events: 2 (Experimental), 5 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.12 (P = 0.26)
8 L. casei + L. bulgaris + S. thermophilus
Hickson 2007 7/57 19/56 3.2 % 0.36 [0.17, 0.79]
Subtotal (95% CI) 57 56 3.2 % 0.36 [0.17, 0.79]
Total events: 7 (Experimental), 19 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.54 (P = 0.011)
9 L. plantarum
Lonnermark 2010 6/80 5/83 1.9 % 1.25 [0.40, 3.92]
Subtotal (95% CI) 80 83 1.9 % 1.25 [0.40, 3.92]
Total events: 6 (Experimental), 5 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.37 (P = 0.71)
0.01 0.1 1 10 100
Favours experimental
Favours control
(Continued . . .)


(. . . Continued)
Study or subgroup
Experimental
n/N
Control
n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
10 Lactobacillus GG + L. acidophilus + B. animalis
Wenus 2008 2/34 8/29 1.2 % 0.21 [0.05, 0.93]
Subtotal (95% CI) 34 29 1.2 % 0.21 [0.05, 0.93]
Total events: 2 (Experimental), 8 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.06 (P = 0.039)
11 B. bifidum + B. lactis + B. longum + E. faecium + L. acidophilus + L. paracasei + L. plantarum + L. rhamnosus + L. sativarius
Koning 2008 9/19 15/19 5.0 % 0.60 [0.35, 1.02]
Subtotal (95% CI) 19 19 5.0 % 0.60 [0.35, 1.02]
Total events: 9 (Experimental), 15 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.90 (P = 0.058)
12 L. reuteri
Georgieva 2015 1/49 1/48 0.4 % 0.98 [0.06, 15.22]
Subtotal (95% CI) 49 48 0.4 % 0.98 [0.06, 15.22]
Total events: 1 (Experimental), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.01 (P = 0.99)
13 L. acidophilus + L. paracasei + B. lactis
Ouwehand 2014 54/304 41/144 6.7 % 0.62 [0.44, 0.89]
Subtotal (95% CI) 304 144 6.7 % 0.62 [0.44, 0.89]
Total events: 54 (Experimental), 41 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.61 (P = 0.0091)
14 L. acidophilus + L. delbrueki subs. bulgaricus + B. bifidum
Pancheva 2009 23/78 55/78 6.5 % 0.42 [0.29, 0.61]
Subtotal (95% CI) 78 78 6.5 % 0.42 [0.29, 0.61]
Total events: 23 (Experimental), 55 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 4.59 (P < 0.00001)
15 L. casei shirota
Wong 2014 13/76 45/82 5.0 % 0.31 [0.18, 0.53]
Subtotal (95% CI) 76 82 5.0 % 0.31 [0.18, 0.53]
Total events: 13 (Experimental), 45 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 4.29 (P = 0.000018)
16 Lactococcus lactis, Lactobacillus, Bifidobacterium and Streptococcus thermophilus
Fominykh 2013 0/80 0/40 Not estimable
0.01 0.1 1 10 100
Favours experimental
Favours control
(Continued . . .)

(. . . *Continued*)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**80**	**40**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**2853**	**2506**	◆	**100.0 %**	**0.55 [0.46, 0.65]**
Total events: 382 (Experimental), 596 (Control)					
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 52.78$, df = 29 (P = 0.004); $I^2 = 45\%$					
Test for overall effect: Z = 6.77 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 16.58$, df = 14 (P = 0.28), $I^2 = 16\%$					

Appendix 3: Should probiotics be used in patients with Crohn's disease?

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Included from: Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev 2006:CD004826.

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Van Gossum A, Dewit O, Louis E, et al. Multicenter randomized-controlled clinical trial of probiotics (Lactobacillus johnsonii, LA1) on early endoscopic recurrence of Crohn's disease after lleo-caecal resection. Inflamm Bowel Dis 2007;13:135-42.

Bourreille A, Cadiot G, Le Dreau G, et al. Saccharomyces boulardii does not prevent relapse of Crohn's disease. Clin Gastroenterol Hepatol 2013;11:982-7.

Fedorak RN, Feagan BG, Hotte N, et al. The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. Clin Gastroenterol Hepatol 2015;13:928-35 e2.

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo or standard of care or placebo + standard of care in patients with Crohn's disease (3a)

Bibliography: Prantera 2002, Schultz 2004

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	Placebo or standard of care or placebo+standard of care	Relative (95% CI)	Absolute (95% CI)		
Clinical Remission (follow up: 12 weeks; assessed with: defined as CDAI<150)												
1	randomised trials	serious [a,b]	not serious	serious [c,d]	very serious [e]	none	4/5 (80.0%)	5/6 (83.3%)	**OR 0.80** (0.04 to 17.20)	**33 fewer per 1,000** (from 667 fewer to 155 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse (follow up: 6 months; assessed with: >100 points in CDAI score)												
1	randomised trials	serious [a]	not serious	serious [d]	serious [e]	none	2/4 (50.0%)	3/5 (60.0%)	**RR 0.83** (0.25 to 2.80)	**102 fewer per 1,000** (from 450 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Relapse (follow up: 12 months; assessed with: endoscopy)												
1	randomised trials	serious [f]	not serious	not serious	serious [e]	none	9/18 (50.0%)	6/19 (31.6%)	**RR 1.58** (0.71 to 3.55)	**183 more per 1,000** (from 92 fewer to 805 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	Placebo or standard of care or placebo+standard of care	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow up: 12 months; assessed with: CDAI >150)												
1	randomised trials	serious [f]	not serious	not serious	serious [e]	none	3/18 (16.7%)	2/19 (10.5%)	**RR 1.58** (0.30 to 8.40)	**61 more per 1,000** (from 74 fewer to 779 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events												
1	randomised trials	serious [a,b,f]	not serious	serious [c,d]	serious [e]	none	One study (Schultz 2004) reported mild bloating which occurred in both probiotic and placebo groups. No other adverse events were reported (Schultz 2004). Patients were not withdrawn from the trial which used *L. rhamnosus* ATCC 53103 (2 x 10^9 CFU per day) for 6 months. Prantera 2002a reported there were no adverse events relating solely to the use of the probiotic (*L. rhamnosus* ATCC 53103). Diarrhoea and bloating occurred in a similar proportion of patients receiving probiotic or placebo.				⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio; **RR:** Risk ratio

Explanations

a. Allocation concealment and/or blinding of outcome assessor unclear in Schultz 2004.

b. Use of corticosteroids in both arms of Schultz 2004 could be a confounder.

c. Age of patients and setting was not reported; therefore, it is difficult to speak to the generalizability of the results.

d. Schultz 2004 used antibiotics for 2 weeks prior to intervention, which is not consistent with clinical practice.

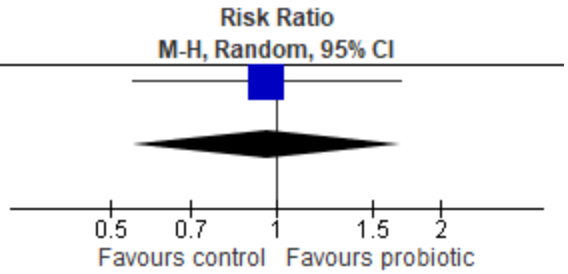
e. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

f. Prantera 2002a had uncertain allocation concealment and loss of 8 subjects in follow up, which is impactful given the few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots

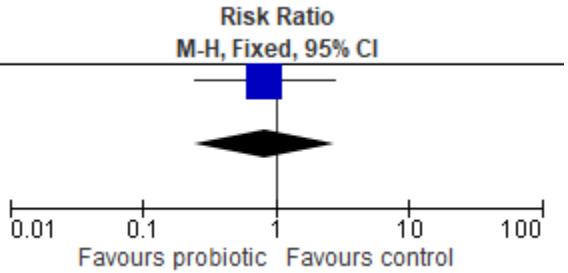
Clinical Remission (follow up: 12 weeks; assessed with: defined as CDAI<150)

	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Schultz 2004	4	5	5	6	100.0%	0.96 [0.55, 1.69]
Total (95% CI)		**5**		**6**	**100.0%**	**0.96 [0.55, 1.69]**
Total events	4		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						



Relapse (follow up: 6 months; assessed with: >100 points in CDAI score)

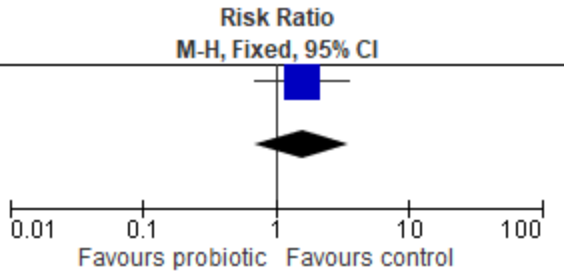
	Experimental		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**
Schultz 2004	2	4	3	5	100.0%	0.83 [0.25, 2.80]
Total (95% CI)		**4**		**5**	**100.0%**	**0.83 [0.25, 2.80]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						



Relapse (follow up: 12 months; assessed with: endoscopy)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Prantera 2002a	9	18	6	19	100.0%	1.58 [0.71, 3.55]
Total (95% CI)		**18**		**19**	**100.0%**	**1.58 [0.71, 3.55]**
Total events	9		6			

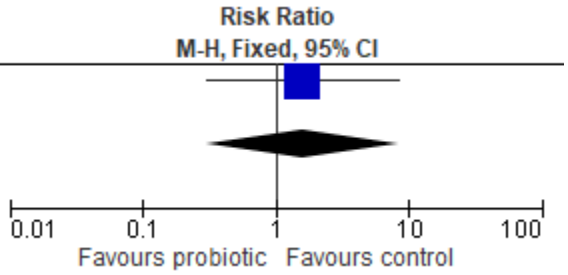
Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)



Relapse (follow up: 12 months; assessed with: CDAI >150)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Prantera 2002a	3	18	2	19	100.0%	1.58 [0.30, 8.40]
Total (95% CI)		**18**		**19**	**100.0%**	**1.58 [0.30, 8.40]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



Question: *Escherichia coli* Nissle 1917 compared to placebo in patients with Crohn's disease (3b)

Bibliography: Malchow 1997

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*E. coli* Nissle 1917	Placebo	Relative (95% CI)	Absolute (95% CI)		
Relapsed at end of treatment (defined as CDAI>150, PCDAI >10, or endoscopically)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	3/10 (30.0%)	7/10 (70.0%)	**RR 0.43** (0.15 to 1.20)	**399 fewer per 1,000** (from 595 fewer to 140 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	0/10 (0.0%)	0/10 (0.0%)	not estimable		⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Allocation generation and concealment unclear for Malchow 1997, missing data of 6 in intervention group and 2 in comparator group. In addition, all patients had active disease at enrollment and received prednisone which could impact lack of difference between the two groups.

b. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

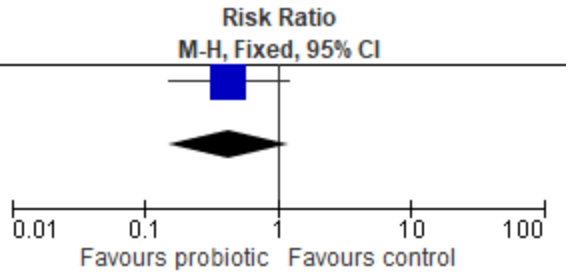
Forest Plots

Relapsed at end of treatment (defined as CDAI>150, PCDAI >10, or endoscopically)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Malchow 1997	3	10	7	10	100.0%	0.43 [0.15, 1.20]
Total (95% CI)		**10**		**10**	**100.0%**	**0.43 [0.15, 1.20]**
Total events	3		7			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.61 (P = 0.11)



Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo +/- mesalamine in patients with Crohn's disease (3c)

Bibliography: Fedorak 2015, Campieri 2010

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo +/- mesalamine	Relative (95% CI)	Absolute (95% CI)		
Relapse of disease endoscopically												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	4/20 (20.0%)	8/20 (40.0%)	**RR 0.50** (0.18 to 1.40)	**200 fewer per 1,000** (from 328 fewer to 160 more)	⨁◯◯◯ VERY LOW	CRITICAL
Severe endoscopic relapse												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo +/- mesalamine	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a,d]	not serious	serious [b]	serious [c]	none	8/63 (12.7%)	16/71 (22.5%)	**RR 0.54** (0.25 to 1.17)	**104 fewer per 1,000** (from 169 fewer to 36 more)	⨁◯◯◯ VERY LOW	CRITICAL

Adverse events

2	randomised trials	serious [a,d]	not serious	serious [b]	serious [c]	none	31/78 (39.7%) [e]	40/82 (48.8%)	**RR 0.83** (0.61 to 1.12)	**83 fewer per 1,000** (from 190 fewer to 59 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Sequence generation and allocation concealment unclear, and only physicians blinded in Campieri 2000.

b. Mesalamine not typically used post-operative in standard care and results may not be generalizable to the research question.

c. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

d. Unclear blinding of outcome assessor in Fedorak 2015.

e. Includes all adverse events reported in Fedorak 2015. Of those, serious adverse events reported are 1 in Probiotic arm and 5 in Placebo arm.

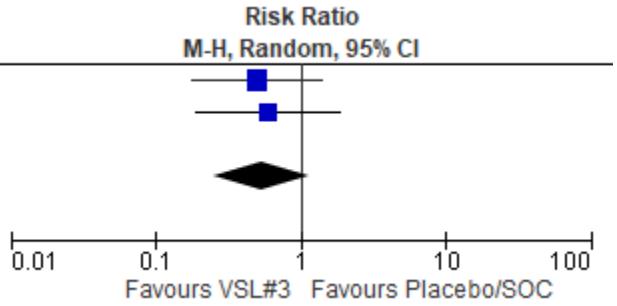
Forest Plots

Severe endoscopic relapse

	VSL#3		Placebo/Standard of care			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Campieri 2000	4	20	8	20	54.7%	0.50 [0.18, 1.40]
Fedorak 2015	4	43	8	51	45.3%	0.59 [0.19, 1.83]
Total (95% CI)		**63**		**71**	**100.0%**	**0.54 [0.25, 1.16]**
Total events	8		16			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%

Test for overall effect: Z = 1.59 (P = 0.11)

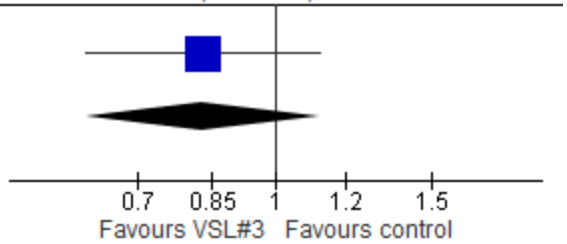


Adverse events

Study or Subgroup	VSL#3 Events	VSL#3 Total	Placebo/Standard of care Events	Placebo/Standard of care Total	Weight	Risk Ratio M-H, Random, 95% CI
campieri 2000	0	20	0	20		Not estimable
fedorak 2015	31	58	40	62	100.0%	0.83 [0.61, 1.12]
Total (95% CI)		**78**		**82**	**100.0%**	**0.83 [0.61, 1.12]**
Total events	31		40			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.22 (P = 0.22)



Question: *Lactobacillus rhamnosus* ATCC 53103 + maintenance therapy compared to placebo + maintenance therapy in patients with Crohn's disease (3d)

Bibliography: Bousvaros 2005

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103 + maintenance therapy	Placebo + maintenance therapy	Relative (95% CI)	Absolute (95% CI)		
Relapse as measured by PCDAI												
1	randomised trials	not serious	not serious	not serious [a]	very serious [b]	none	12/39 (30.8%)	6/36 (16.7%)	**RR 1.85** (0.77 to 4.40)	**142 more per 1,000** (from 38 fewer to 567 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events												
1	randomised trials	not serious	not serious	not serious [a]	very serious [b]	none	7/39 (17.9%)	8/36 (22.2%)	**RR 0.81** (0.33 to 2.00)	**42 fewer per 1,000** (from 149 fewer to 222 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. various maintenance therapies not controlled in Bousvaros 2005.

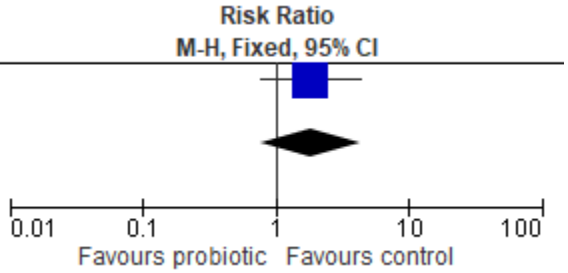
b. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots

Relapse as measured by PCDAI

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bousvaros 2005	12	39	6	36	100.0%	1.85 [0.77, 4.40]
Total (95% CI)		**39**		**36**	**100.0%**	**1.85 [0.77, 4.40]**
Total events	12		6			

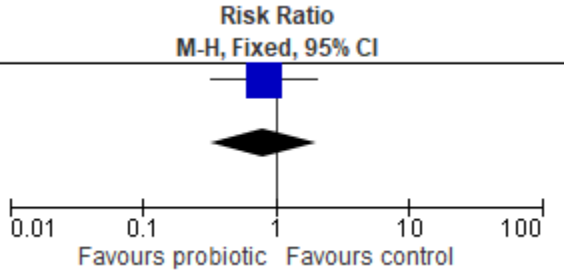
Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)



Adverse Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bousvaros 2005	7	39	8	36	100.0%	0.81 [0.33, 2.00]
Total (95% CI)		**39**		**36**	**100.0%**	**0.81 [0.33, 2.00]**
Total events	7		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)



Question: *Lactobacillus rhamnosus* ATCC 53103 + mesalamine compared to mesalamine alone in patients with Crohn's disease (3e)

Bibliography: Zocco 2003

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103 + mesalamine	Mesalamine alone	Relative (95% CI)	Absolute (95% CI)		
Relapse as measured by CDAI												
1	randomised trials	serious [a]	not serious	serious	very serious [b]	none	2/11 (18.2%)	3/12 (25.0%)	**RR 0.73** (0.15 to 3.57)	**68 fewer per 1,000** (from 213 fewer to 643 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

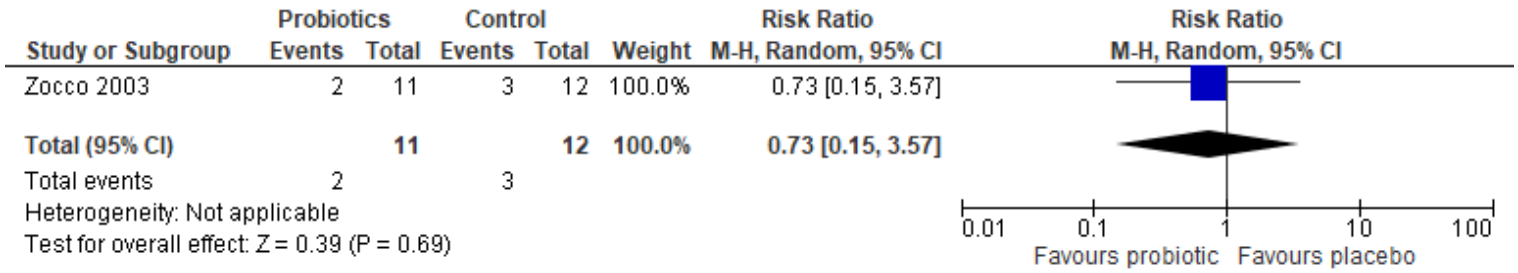
Explanations

a. Sequence generation and allocation concealment unclear, blinding unclear.

b. The 95% CI includes the potential for both benefit and harm.

Forest Plots

Relapse as measured by CDAI


Probiotics
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Zocco 2003 2 11 3 12 100.0% 0.73 [0.15, 3.57]
Total (95% CI) 11 12 100.0% 0.73 [0.15, 3.57]
Total events 2 3
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.69)
0.01
0.1
1
10
100
Favours probiotic
Favours placebo

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to mesalamine in patients with Crohn's disease (3f)

Bibliography: Zocco 2003

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	Mesalamine	Relative (95% CI)	Absolute (95% CI)		
Remission based on CDAI (follow up: 12 months)												
1	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	2/12 (16.7%)	3/12 (25.0%)	**RR 0.67** (0.13 to 3.30)	**82 fewer per 1,000** (from 218 fewer to 575 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. unclear sequence generation, allocation concealment, and blinding.

b. the comparison, mesalamine, is not considered standard of care because of uncertain efficacy, for patients with Crohn's disease.

c. The 95% CI includes the potential for both benefit and harm.

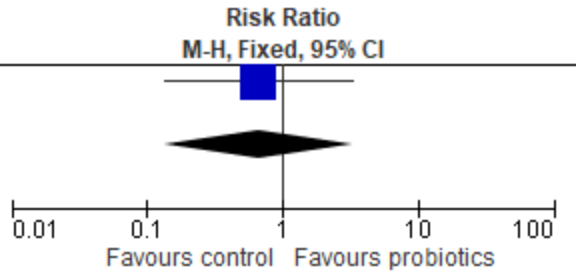
Forest Plots

Remission based on CDAI (follow up: 12 months)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zocco 2003	2	12	3	12	100.0%	0.67 [0.13, 3.30]
Total (95% CI)		**12**		**12**	**100.0%**	**0.67 [0.13, 3.30]**
Total events	2		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.50 (P = 0.62)



Question: *Saccharomyces boulardii* compared to placebo +/- mesalamine alone in patients with Crohn's disease (3g)

Bibliography: Bourreille 2013, Guslandi 2000

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. boulardii*	placebo +/- mesalamine alone	Relative (95% CI)	Absolute (95% CI)		
Relapse as measured by CDAI												
2	randomised trials	serious [a]	not serious	serious [b]	very serious [c]	none	39/96 (40.6%)	48/95 (50.5%)	**RR 0.51** (0.10 to 2.54)	**248 fewer per 1,000** (from 455 fewer to 778 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse events												
1	randomised trials	serious [d]	not serious	serious [b]	serious [c]	none	49/84 (58.3%)	45/81 (55.6%)	**RR 1.05** (0.80 to 1.37)	**28 more per 1,000** (from 111 fewer to 206 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Allocation concealment unclear, unclear physician blinding in Guslandi 2000, and unclear random sequence generation and unclear risk of incomplete reporting for both studies.

b. Use of mesalazine as maintenance therapy in this setting is atypical for treating patients with Crohn's disease. Guslandi 2000 treated intervention arm with low dose mesalazine and compared to mesalazine alone. Both control group and intervention arm receiving same medication in Guslandi 2000.

c. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

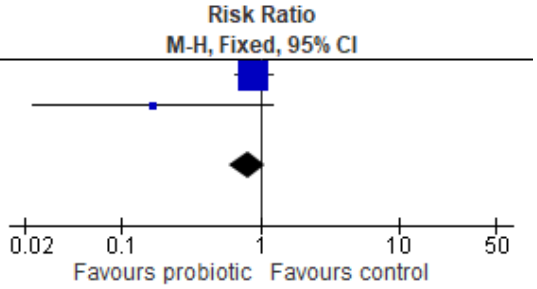
d. Unclear risk of selection, detection, and attrition bias

Forest Plots

Relapse as measured by CDAI

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bourielle 2013	38	80	42	79	87.6%	0.89 [0.66, 1.22]
Guslandi 2000	1	16	6	16	12.4%	0.17 [0.02, 1.23]
Total (95% CI)		**96**		**95**	**100.0%**	**0.80 [0.59, 1.09]**
Total events	39		48			

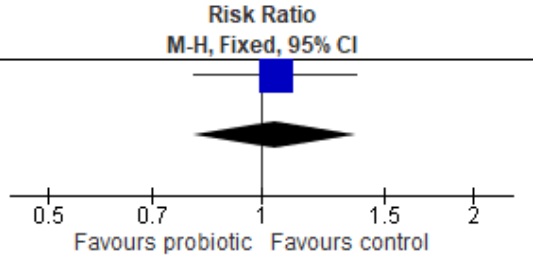
Heterogeneity: Chi² = 2.83, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 1.40 (P = 0.16)



Adverse Events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bourielle 2013	49	84	45	81	100.0%	1.05 [0.80, 1.37]
Total (95% CI)		**84**		**81**	**100.0%**	**1.05 [0.80, 1.37]**
Total events	49		45			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)



Question: *Lactobacillus johnsonii* NCC 533 compared to placebo in prevention of endoscopic recurrence after surgery for Crohn's disease (3h)

Bibliography: Van Gossum 2007, Marteua 2006

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. johnsonii* NCC 533	Placebo	Relative (95% CI)	Absolute (95% CI)		
Severe Endoscopic Relapse												
2	randomised trials	serious [a]	not serious	not serious	serious [b]	none	15/71 (21.1%)	16/74 (21.6%)	**RR 0.97** (0.52 to 1.83)	**6 fewer per 1,000** (from 104 fewer to 179 more)	⊕⊕◯◯ LOW	CRITICAL
Endoscopic Recurrence												
1	randomised trials	serious [c]	not serious	not serious	serious [b]	none	21/43 (48.8%)	30/47 (63.8%)	**RR 0.77** (0.53 to 1.11)	**147 fewer per 1,000** (from 300 fewer to 70 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of random sequence generation and selective reporting

b. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

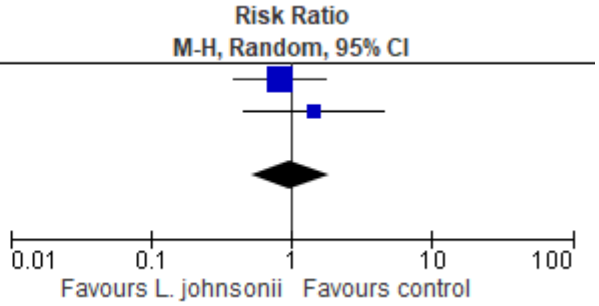
c. unclear risk of selective reporting

Forest plots

Severe Endoscopic Relapse (proportion with severe recurrence i3+i4)

Study or Subgroup	Lactobacillus johnsonii Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Marteau 2006	9	43	12	47	69.6%	0.82 [0.38, 1.75]
Van Gossum 2007	6	28	4	27	30.4%	1.45 [0.46, 4.57]
Total (95% CI)		**71**		**74**	**100.0%**	**0.97 [0.52, 1.83]**
Total events	15		16			

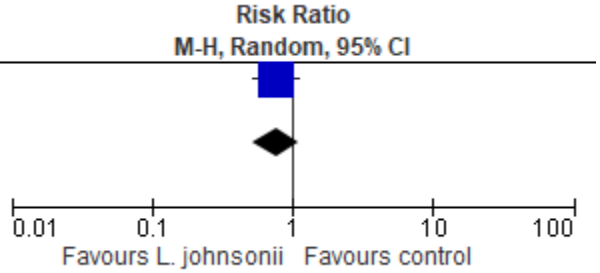
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.93)



Endoscopic Recurrence (endoscopic score >i1)

Study or Subgroup	Lactobacillus johnsonii Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Marteau 2006	21	43	30	47	100.0%	0.77 [0.53, 1.11]
Total (95% CI)		**43**		**47**	**100.0%**	**0.77 [0.53, 1.11]**
Total events	21		30			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)



Appendix 4: Should probiotics be used in patients with ulcerative colitis?

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Question: *Bifidobacterium breve* Yakult + *Bifidobacterium bifidum* Yakult + *Lactobacillus acidophilus* compared to placebo in patients with ulcerative colitis (4a)

Bibliography: Kato 2004

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. breve* Yakult + *B. bifidum* Yakult + *L. acidophilus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Remission (clinical, endoscopic, or histologic)												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	3/10 (30.0%)	4/10 (40.0%)	**RR 0.64** (0.10 to 4.10)	**144 fewer per 1,000** (from 360 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical improvement												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	3/10 (30.0%)	7/10 (70.0%)	**RR 0.18** (0.03 to 1.24)	**574 fewer per 1,000** (from 679 fewer to 168 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

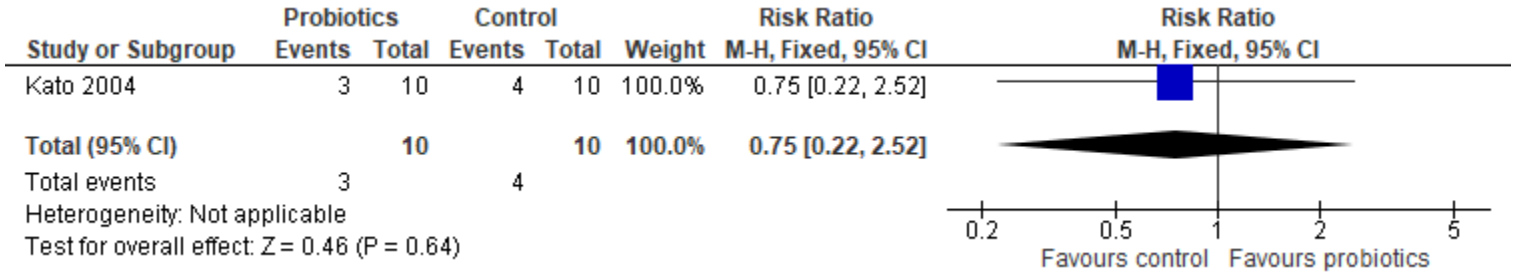
Explanations

a. Allocation concealment unclear and patients and physicians not blinded

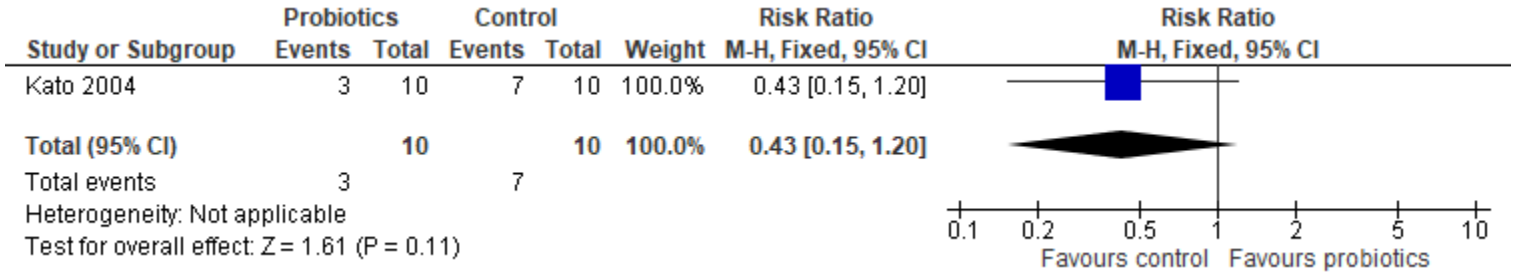
b. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots

Remission



Clinical improvement



Question: *Bifidobacterium breve* Yakult + *Lactobacillus acidophilus* fermented milk compared to placebo in patients with ulcerative colitis (4b)

Bibliography: Matsuoka 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. breve* Yakult + *L. acidophilus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical Relapse												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	22/98 (22.4%)	19/97 (19.6%)	**RR 1.15** (0.66 to 1.98)	**29 more per 1,000** (from 67 fewer to 192 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment-related Adverse Events (bloating, stress, body odor)												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	1/98 (1.0%)	1/97 (1.0%)	**RR 0.99** (0.06 to 15.60)	**0 fewer per 1,000** (from 10 fewer to 151 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of blinding of outcome assessor.

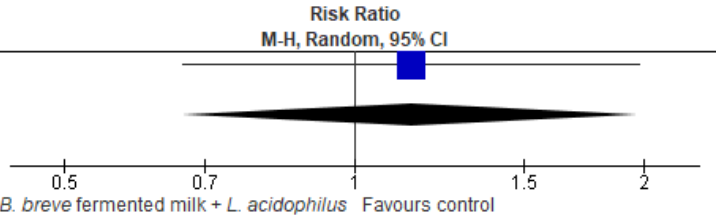
b. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots

Clinical Relapse

Study or Subgroup	*B. breve* fermented milk + *L. acidophilus* Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Matsuoka 2018	22	98	19	97	100.0%	1.15 [0.66, 1.98]
Total (95% CI)		**98**		**97**	**100.0%**	**1.15 [0.66, 1.98]**
Total events	22		19			

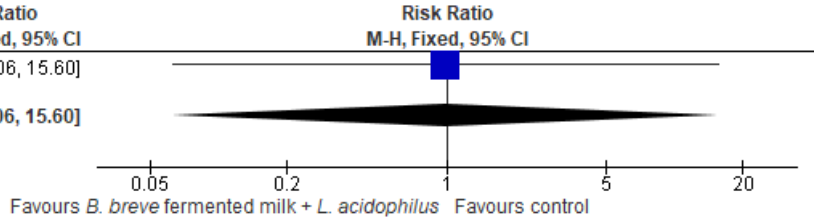
Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)



Treatment-related adverse events

Study or Subgroup	*B. breve* fermented milk + *L. acidophilus* Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Matsuoka 2018	1	98	1	97	100.0%	0.99 [0.06, 15.60]
Total (95% CI)		**98**		**97**	**100.0%**	**0.99 [0.06, 15.60]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to mesalamine alone in patients with ulcerative colitis (4c)

Bibliography: Mallon 2007, Sood 2009, Tursi 2004, Tursi 2010

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	***L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus***	**mesalamine alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Remission (clinical)												
4	randomized trials	serious [a]	serious [b]	not serious [c]	very serious [d]	none	98/186 (52.7%)	62/181 (34.3%)	**RR 1.72** (0.89 to 3.32)	**247 more per 1,000** (from 38 fewer to 795 more)	⨁◯◯◯ VERY LOW	CRITICAL
Adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	mesalamine alone	Relative (95% CI)	Absolute (95% CI)		
4	randomized trials	serious [a]	serious [b]	not serious [c]	very serious [d]	none	22/172 (12.8%)	9/168 (5.4%)	**RR 4.05** (0.08 to 198.28)	**163 more per 1,000** (from 49 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Clinical Response												
2	randomized trials	serious [a]	not serious	not serious [c]	serious [e]	none	66/142 (46.5%)	36/136 (26.5%)	**RR 2.88** (1.49 to 5.57)	**498 more per 1,000** (from 130 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Some studies report not blinded or blinding not clear, 1 study with high risk attrition bias, Tursi 2004 unclear allocation concealment.

b. Serious heterogeneity observed (I^2 = 86%).

c. Interventions vary across studies: Tursi 2004 compares probiotics + balsalazide vs balsalazide; Miele 2009 both groups receive mesalamine maintenance therapy.

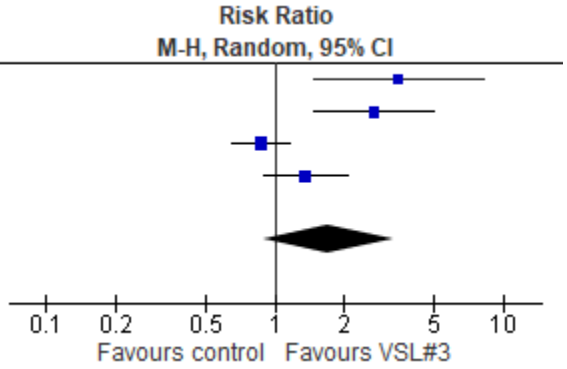
d. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

e. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Clinical Remission:

	VSL#3		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Miele 2009	13	14	4	15	20.1%	3.48 [1.49, 8.16]
Sood 2009	33	77	11	70	24.2%	2.73 [1.50, 4.97]
Tursi 2004	21	30	24	30	28.6%	0.88 [0.65, 1.17]
Tursi 2010	31	65	23	66	27.1%	1.37 [0.90, 2.08]
Total (95% CI)		**186**		**181**	**100.0%**	**1.72 [0.89, 3.32]**
Total events	98		62			

Heterogeneity: Tau² = 0.37; Chi² = 21.92, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 1.61 (P = 0.11)

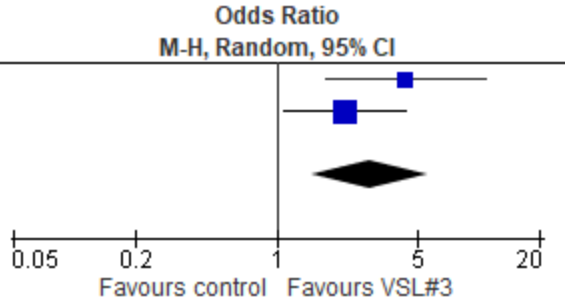


Clinical Response:

Study or Subgroup	VSL#3 Events	VSL#3 Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Sood 2009	25	77	7	70	40.4%	4.33 [1.73, 10.80]
Tursi 2010	41	65	29	66	59.6%	2.18 [1.08, 4.39]
Total (95% CI)		**142**		**136**	**100.0%**	**2.88 [1.49, 5.57]**
Total events	66		36			

Heterogeneity: Tau² = 0.06; Chi² = 1.37, df = 1 (P = 0.24); I² = 27%

Test for overall effect: Z = 3.13 (P = 0.002)

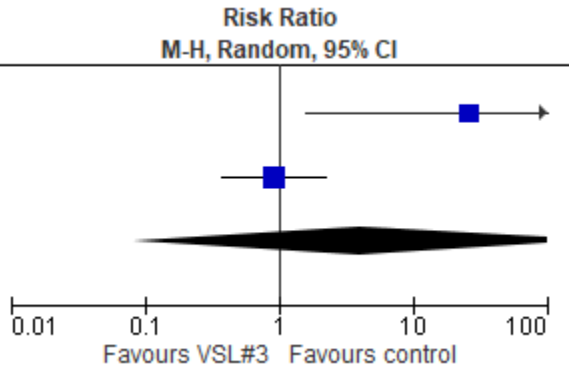


Adverse Events

Study or Subgroup	VSL#3 Events	VSL#3 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Miele 2009	0	14	0	15		Not estimable
Sood 2009	14	77	0	70	44.3%	26.40 [1.60, 434.44]
Tursi 2004	0	10	0	10		Not estimable
Tursi 2010	8	71	9	73	55.7%	0.91 [0.37, 2.24]
Total (95% CI)		**172**		**168**	**100.0%**	**4.05 [0.08, 198.28]**
Total events	22		9			

Heterogeneity: Tau² = 6.86; Chi² = 7.10, df = 1 (P = 0.008); I² = 86%

Test for overall effect: Z = 0.70 (P = 0.48)



Question: *Bifidobacterium longum* Reuter ATCC BAA-999 compared to placebo in patients with ulcerative colitis (4d)

.**Bibliography**: Tamaki 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* Reuter ATCC BAA-999	placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical Remission (follow up: 8 weeks; assessed with: UCDAI ≤2)												
1	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	15/28 (53.6%)	12/28 (42.9%)	**RR 1.54** (0.54 to 4.42)	**231 more per 1,000** (from 197 fewer to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious Adverse Events												
1	randomized trials	serious [a]	not serious	not serious	serious [c]	none	0/24 (0.0%)	0/23 (0.0%)	not estimable		⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Tamaki 2016 has unclear allocation concealment, blinding of outcome assessor, and selective reporting of outcomes.

b. The 95% CI includes the potential for both benefit and harm.

c. No events reported out of a small sample.

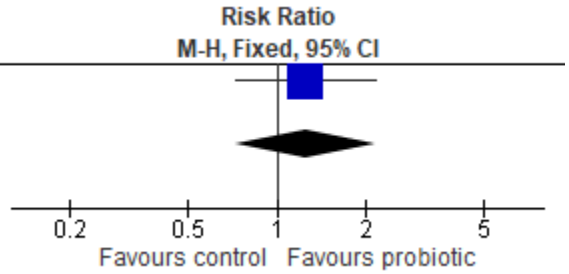
Forest Plots

Clinical Remission

Study or Subgroup	Bifidobacterium longum 536 Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tamaki 2016	15	28	12	28	100.0%	1.25 [0.72, 2.17]
Total (95% CI)		**28**		**28**	**100.0%**	**1.25 [0.72, 2.17]**
Total events	15		12			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.80 (P = 0.43)



Question: *Escherichia coli* Nissle 1917 compared to placebo +/- mesalamine in patients with ulcerative colitis (4e)

Bibliography: Mallon 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*E. coli* Nissle 1917	placebo +/- mesalamine	Relative (95% CI)	Absolute (95% CI)		
Rate of relapse after successful induction[a]												
3	randomized trials	serious [b,c]	not serious	not serious	serious [d]	none	145/271 (53.5%)	122/275 (44.4%)	**RR 1.20** (1.01 to 1.42)	**89 more per 1,000** (from 4 more to 186 more)	⨁⨁◯◯ LOW	CRITICAL
Adverse events												
4	randomized trials	serious [b,c,d]	not serious	serious [d]	very serious [d]	none	90/296 (30.4%)	86/300 (28.7%)	**RR 1.09** (0.86 to 1.38)	**26 more per 1,000** (from 40 fewer to 109 more)	⨁◯◯◯ VERY LOW	CRITICAL
Remission at End of Study Period												
2	randomized trials	serious [b,d]	serious [e]	not serious	very serious [f]	none	49/82 (59.8%)	64/84 (76.2%)	**RR 0.86** (0.49 to 1.49)	**107 fewer per 1,000** (from 389 fewer to 373 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Kruis 1997 defines relapse as CAI > 4; Kruis 2004 defines relapse as CAI > 6 or Endoscopic index > 4.

b. Rembacken 1999 did not report on technique of randomization, allocation concealment unclear, and personnel blinded during the study not described. Additionally, overall withdrawal rates were 8.9% for Rembacken 1999. After study entry, patients received gentamicin 80 mg TID, which is not standard of care.

c. Allocation concealment unclear for all studies, sequence generation unclear for Kruis 1997. Kruis 2004 reported high dropout rate (46.5%).

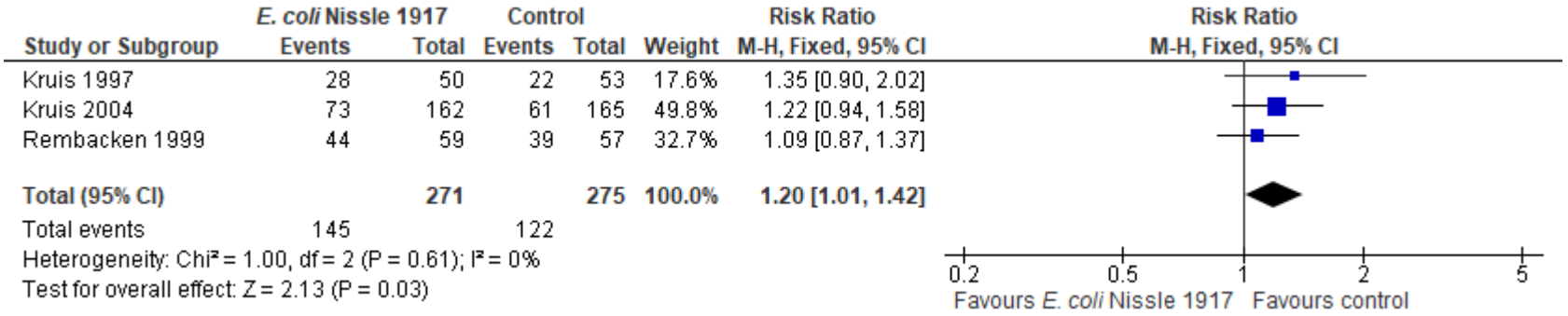
d. In Petersen 2014, all patients received prednisone, which may confound the effects of patients receiving *E. coli* Nissle.

e. Heterogeneity among studies (i2 79%)

f. The 95% CI includes the potential for both benefit and harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots

Rate of Relapse After Successful Induction

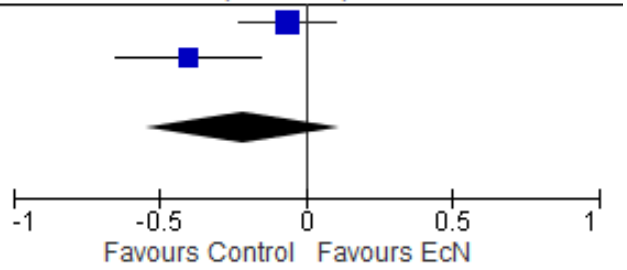


Remission at End of Study Period

Study or Subgroup	EcN Events	EcN Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Rembacken 1999	39	57	44	59	53.9%	-0.06 [-0.23, 0.10]
Petersen 2014	10	25	20	25	46.1%	-0.40 [-0.65, -0.15]
Total (95% CI)		**82**		**84**	**100.0%**	**-0.22 [-0.55, 0.11]**
Total events	49		64			

Heterogeneity: Tau² = 0.05; Chi² = 4.98, df = 1 (P = 0.03); I² = 80%

Test for overall effect: Z = 1.29 (P = 0.20)

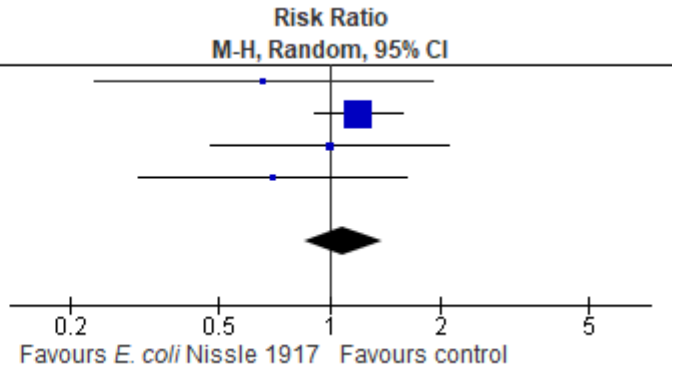


Adverse Events

Study or Subgroup	*E. coli* Nissle 1917 Events	*E. coli* Nissle 1917 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Kruis 1997	5	50	8	53	5.2%	0.66 [0.23, 1.89]
Kruis 2004	68	162	58	165	76.0%	1.19 [0.91, 1.57]
Petersen 2014	9	25	9	25	10.5%	1.00 [0.48, 2.09]
Rembacken 1999	8	59	11	57	8.3%	0.70 [0.30, 1.62]
Total (95% CI)		**296**		**300**	**100.0%**	**1.09 [0.86, 1.38]**
Total events	90		86			

Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 3 (P = 0.49); I² = 0%

Test for overall effect: Z = 0.69 (P = 0.49)



Question: *Lactobacillus rhamnosus* ATCC 53103 compared to mesalamine in patients with ulcerative colitis (4f)

Bibliography: Naidoo 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	mesalamine	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow up: range 12 weeks to 12 months; assessed with: clinical +/- endoscopic)[a]												
1	randomized trials	very serious [b]	not serious	not serious	serious [c]	none	10/65 (15.4%)	12/60 (20.0%)	**RR 0.77** (0.36 to 1.65)	**46 fewer per 1,000** (from 128 fewer to 130 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Zocco 2006 defines relapse as CAI > 4.

b. Allocation concealment unclear for all studies, sequence generation unclear for Zocco 2006, and Zocco 2006 study open label with no blinding.

c. The 95% CI includes the potential for both benefit and harm.

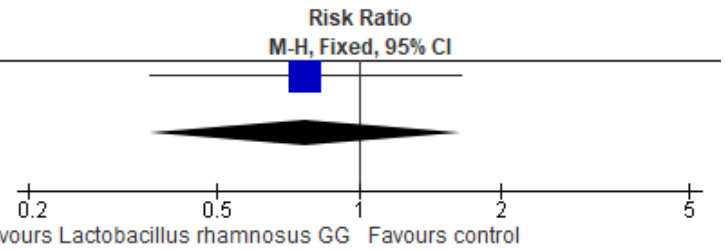
Forest Plots

Relapse

Study or Subgroup	*Lactobacillus rhamnosus* GG Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zocco 2006	10	65	12	60	100.0%	0.77 [0.36, 1.65]
Total (95% CI)		**65**		**60**	**100.0%**	**0.77 [0.36, 1.65]**
Total events	10		12			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.67 (P = 0.50)



Question: *Lactobacillus reuteri* ATCC 55730 enema + meslamine compared to placebo + mesalamine in patients with ulcerative colitis (4g)

Bibliography: Oliva 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. reuteri* ATCC 55730 enema + meslamine	placebo + mesalamine	Relative (95% CI)	Absolute (95% CI)		
Clinical Response (follow up: 8 weeks; assessed with: reduction in the DAI of >/=2 points)												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	16/16 (100.0%)	8/15 (53.3%)	**RR 1.83** (1.14 to 2.92)	**443 more per 1,000** (from 75 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Clinical Remission (follow up: 8 weeks; assessed with: DAI score of <2.0 points)												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	5/16 (31.3%)	0/15 (0.0%)	**RR 10.35** (0.62 to 172.55)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear blinding and selective reporting.

b. The 95% CI includes the potential for both benefit and harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

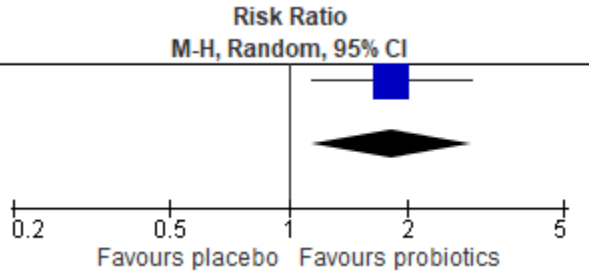
Forest Plots

Clinical response

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Oliva 2012	16	16	8	15	100.0%	1.83 [1.14, 2.92]
Total (95% CI)		**16**		**15**	**100.0%**	**1.83 [1.14, 2.92]**
Total events	16		8			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.53 (P = 0.01)

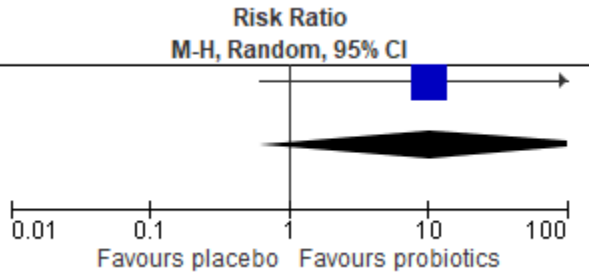


Clinical remission

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Oliva 2012	5	16	0	15	100.0%	10.35 [0.62, 172.55]
Total (95% CI)		**16**		**15**	**100.0%**	**10.35 [0.62, 172.55]**
Total events	5		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.63 (P = 0.10)



Question: *Lactobacillus acidophilus* LA-5 + *Bifidobacterium animalis* subsp. *lactis* Bb12 compared to placebo in patients with ulcerative colitis (4h)

Bibliography: Naidoo 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* LA-5 + *B. animalis* subsp. *lactis* Bb12	Placebo	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow up: 12 months; assessed with: SCCAI score > 4 +/- histological changes)												
1	randomized trials	not serious [a]	not serious	not serious	very serious [b]	none	15/20 (75.0%)	11/12 (91.7%)	RR 0.82(0.6 to 1.11)	**165 fewer per 1,000** (from 367 fewer to 101more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Unclear allocation concealment reported for Wildt 2011.

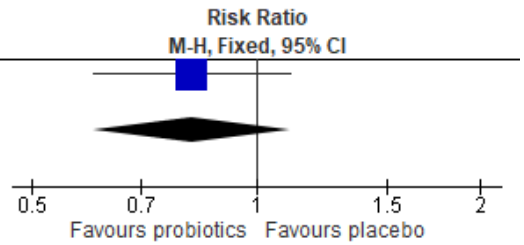
b. The 95% CI includes the potential for both benefit and harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots

Relapse

Study or Subgroup	*L. acidophilus* LA-5 + *B. animalis* subsp. *lactis* BB12 Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wildt 2011	15	20	11	12	100.0%	0.82 [0.60, 1.11]
Total (95% CI)		**20**		**12**	**100.0%**	**0.82 [0.60, 1.11]**
Total events	15		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)



Question: *Enterococcus faecalis* T-110 + *Clostridium butyricum* TO-A + *Bacillus mesentericus* TO-A compared to placebo in patients with ulcerative colitis (4i)

Bibliography: Yoshimatsu 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*E. faecalis* T-110 + *C. butyricum* TO-A + *B. mesentericus* TO-A	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical Remission (follow up: 12 months)												
1	randomized trials	serious [a]	not serious	not serious	serious [b]	none	16/23 (69.6%)	12/23 (52.2%)	**RR 1.33** (0.83 to 2.15)	**172 more per 1,000** (from 89 fewer to 600 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

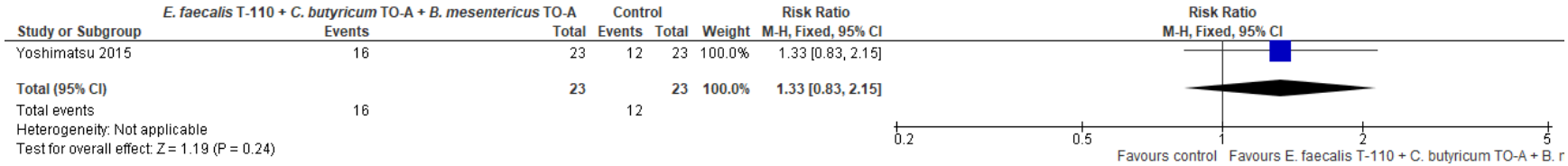
Explanations

a. Unclear risk of allocation concealment, blinding, and selective reporting.

b. The 95% CI includes the potential for both benefit and harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots

Clinical remission


E. faecalis T-110 + C. butyricum TO-A + B. mesentericus TO-A
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Yoshimatsu 2015 16 23 12 23 100.0% 1.33 [0.83, 2.15]
Total (95% CI) 23 23 100.0% 1.33 [0.83, 2.15]
Total events 16 12
Heterogeneity: Not applicable
Test for overall effect: Z = 1.19 (P = 0.24)
0.2
0.5
1
2
5
Favours control
Favours E. faecalis T-110 + C. butyricum TO-A + B. r

Appendix 5: Should probiotics be used in patients with pouchitis?

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Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo / standard of care in patients with pouchitis (5a)

Bibliography: Gionchetti 2000, Gionchetti 2003, Mimura 2004, Pronio 2008

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo / standard of care	Relative (95% CI)	Absolute (95% CI)		
Maintenance of Remission												
2	randomised trials	not serious	not serious	not serious	very serious [a]	none	34/40 (85.0%)	1/36 (2.8%)	**RR 20.24** (4.28 to 95.81)	**534 more per 1,000** (from 91 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo / standard of care	Relative (95% CI)	Absolute (95% CI)		
Adverse Events												
2	randomised trials	not serious	not serious	not serious	very serious [a]	none	1/40 (2.5%)	0/36 (0.0%)	**RR 2.43** (0.11 to 55.89)	**25 more per 1,000** (from 23 fewer to 73 fewer)	⨁⨁◯◯ LOW	CRITICAL
No Episodes of Acute Pouchitis												
2	randomised trials	serious [b]	not serious	not serious [c]	very serious [a]	none	34/36 (94.4%)	23/32 (71.9%)	**RR 1.29** (1.03 to 1.61)	**208 more per 1,000** (from 22 more to 438 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

b. Pronio 2008 is an open-label trial of probiotics versus no treatment.

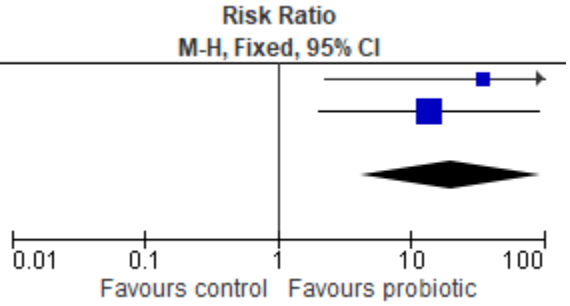
c. The pooled studies feature different comparisons: Pronio 2008 compares probiotics against no treatment and Gionchetti 2003 compares probiotics against placebo.

Forest Plots

Maintenance of Remission

	Probiotics		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Gionchetti 2000	17	20	0	20	31.0%	35.00 [2.25, 544.92]
Mimura 2004	17	20	1	16	69.0%	13.60 [2.02, 91.53]
Total (95% CI)		**40**		**36**	**100.0%**	**20.24 [4.28, 95.81]**
Total events	34		1			

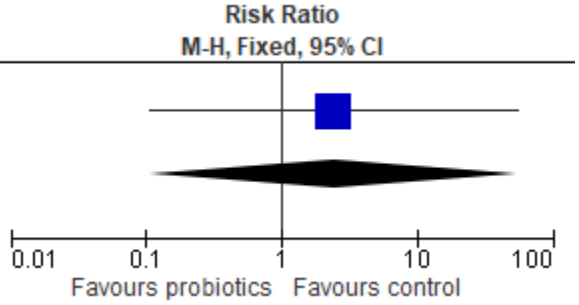
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.79 (P = 0.0001)



Adverse Events

	Probiotics		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Gionchetti 2000	0	20	0	20		Not estimable
Mimura 2004	1	20	0	16	100.0%	2.43 [0.11, 55.89]
Total (95% CI)		**40**		**36**	**100.0%**	**2.43 [0.11, 55.89]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)

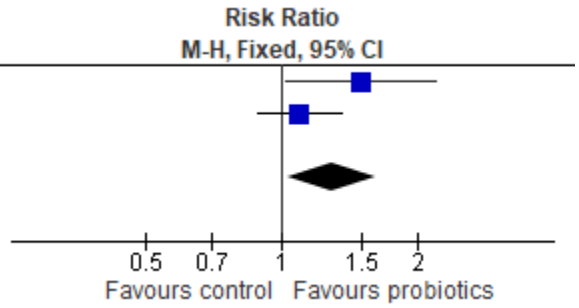


No Episodes of Pouchitis

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gionchetti 2003	18	20	12	20	47.9%	1.50 [1.02, 2.21]
Pronio 2008	16	16	11	12	52.1%	1.10 [0.89, 1.36]
Total (95% CI)		**36**		**32**	**100.0%**	**1.29 [1.03, 1.61]**
Total events	34		23			

Heterogeneity: Chi² = 2.81, df = 1 (P = 0.09); I² = 64%

Test for overall effect: Z = 2.23 (P = 0.03)



Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo in patients with pouchitis (5b)

Bibliography: Singh 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	Placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical Improvement												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/10 (10.0%)	0/10 (0.0%)	**RR 3.00** (0.14 to 65.90)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Kuisma 2003 had unclear risk of bias for random sequence generation and allocation concealment.

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

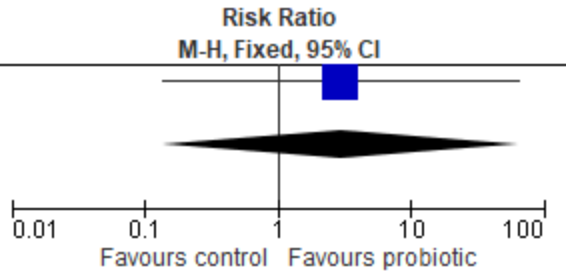
Forest Plots

Clinical Improvement

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kuisma 2003	1	10	0	10	100.0%	3.00 [0.14, 65.90]
Total (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14, 65.90]**
Total events	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.70 (P = 0.49)



Question: *Clostridium butyricum* CBM 588 compared to placebo in patients with pouchitis (5c)

Bibliography: Yasueda 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*C. butyricum* CBM 588	Placebo	Relative (95% CI)	Absolute (95% CI)		
Relapse (follow up: 24 months)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/9 (11.1%)	4/8 (50.0%)	**RR 0.22** (0.03 to 1.60)	**390 fewer per 1,000** (from 485 fewer to 300 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment-related Adverse Events												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	0/9 (0.0%)	0/8 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

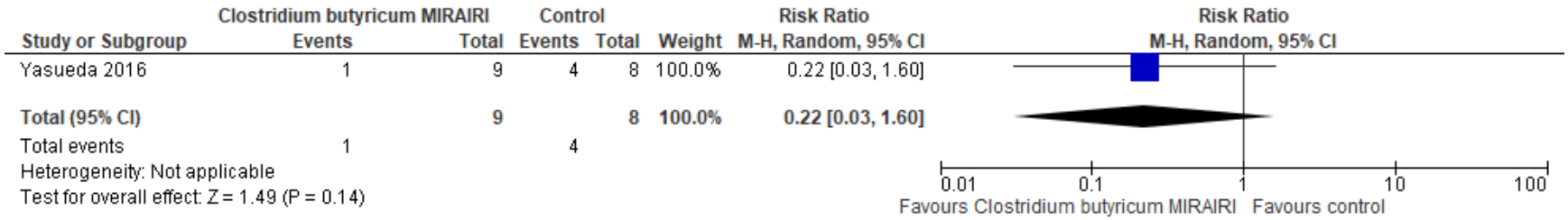
Explanations

a. Unclear risk of blinding, random sequence generation and allocation concealment.

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Forest Plots

Relapse


Clostridium butyricum MIRAIRI
Control
Risk Ratio
Risk Ratio
Study or Subgroup
Events
Total
Events
Total
Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
Yasueda 2016 1 9 4 8 100.0% 0.22 [0.03, 1.60]
Total (95% CI) 9 8 100.0% 0.22 [0.03, 1.60]
Total events 1 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)
0.01
0.1
1
10
100
Favours Clostridium butyricum MIRAIRI
Favours control

Question: *Bifidobacterium longum* subsp. *longum* compared to placebo in patients with pouchitis (5d)

Bibliography: Singh 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *longum*	placebo	Relative (95% CI)	Absolute (95% CI)		
No Episodes of Pouchitis												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	6/7 (85.7%)	3/5 (60.0%)	**RR 1.43** (0.66 to 3.11)	**258 more per 1,000** (from 204 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Brown 2004 has unclear risk for random sequence generation, allocation concealment.

b. The 95% CI includes the potential for both benefit and harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

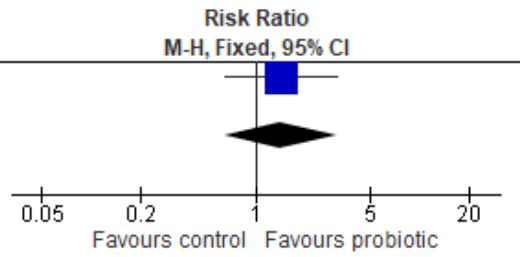
Forest Plots

No episodes of pouchitis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brown 2004	6	7	3	5	100.0%	1.43 [0.66, 3.11]
Total (95% CI)		**7**		**5**	**100.0%**	**1.43 [0.66, 3.11]**
Total events	6		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.90 (P = 0.37)



Appendix 6: Should probiotics be used to improve global response or abdominal pain severity in symptomatic children and adults with irritable bowel syndrome?

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Question: *Saccharomyces boulardii* compared to placebo for adults with IBS (6a)

Bibliography: Abbas 2014, Choi 2011, Kabir 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. boulardii*	placebo	Relative (95% CI)	Absolute (95% CI)		
Abdominal pain subscale (follow up: range 4 weeks to 6 weeks)												
3	randomised trials	serious [a]	not serious	not serious	very serious [b,c,d]	none	117	115	-	SMD **0.26 SD higher** (0.09 lower to 0.61 higher)	⨁◯◯◯ VERY LOW	CRITICAL
IBS symptom scale (follow up: 4 weeks; Scale from: 0 to 6)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b,c]	none	45	45	-	MD **0.1 lower** (0.43 lower to 0.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **SMD:** Standardized mean difference; **MD:** Mean difference

Explanations

a. Unclear risk of reporting bias in all studies

b. The 95% CI includes the potential for both benefit and harm.

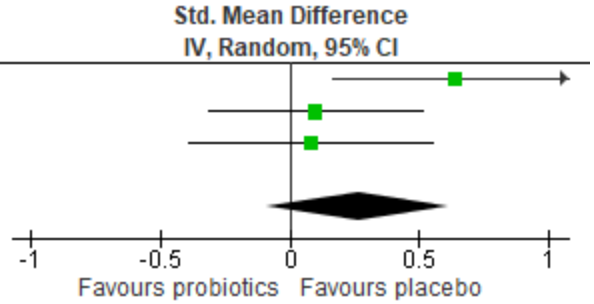
c. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

d. May not provide a clinically meaningful estimate based on the interpretation of the SMD.

Abdominal pain subscale (assessed at end of study)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abbas 2014	1.079	1.021	37	0.546	0.555	35	31.5%	0.64 [0.16, 1.11]
Choi 2011	1.3	1.1	45	1.2	0.9	45	36.6%	0.10 [-0.31, 0.51]
Kabir 2011	0.47	0.72	35	0.41	0.74	35	31.9%	0.08 [-0.39, 0.55]
Total (95% CI)			**117**			**115**	**100.0%**	**0.26 [-0.09, 0.61]**

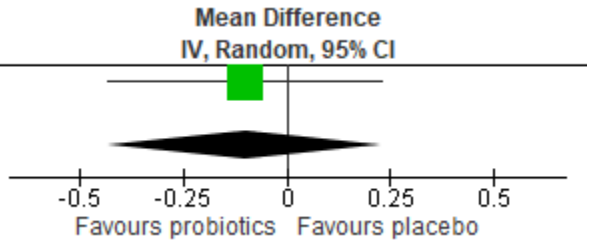
Heterogeneity: Tau² = 0.04; Chi² = 3.56, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 1.48 (P = 0.14)



IBS symptom scale (7-point scale)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Choi 2011	1.2	0.8	45	1.3	0.8	45	100.0%	-0.10 [-0.43, 0.23]
Total (95% CI)			**45**			**45**	**100.0%**	**-0.10 [-0.43, 0.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)



Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo for adults with IBS (6b)

Bibliography: Kim 2003, Kim 2005, Michail 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Urgency (mean VAS measured by difference in groups at end of study)												
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	36	37	-	mean **3 lower** (4.06 lower to 1.94 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Abdominal Pain (mean VAS measured by difference in groups at end of study)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a]	not serious	serious [b]	serious [c]	none	36	37	-	mean **3.78 lower** (4.93 lower to 2.62 lower)	⊕◯◯◯ VERY LOW	CRITICAL

Overall Response (mean VAS measured by difference in groups at end of study)

1	randomised trials	serious [a]	not serious	not serious	very serious [c,d]	none	12	13	-	mean **18 lower** (28.62 lower to 7.38 lower)	⊕◯◯◯ VERY LOW	CRITICAL

Global GSRS Score

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [f]	not serious	not serious	serious [c]	none	15	9	-	mean **0.2 higher** (0.74 higher to 0.34 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

a. unclear risk of selection, reporting bias in all studies

b. IBS subtypes varied across studies

c. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

d. The 95% CI includes the potential for both benefit and harm.

e. Unclear risk of reporting bias in all studies

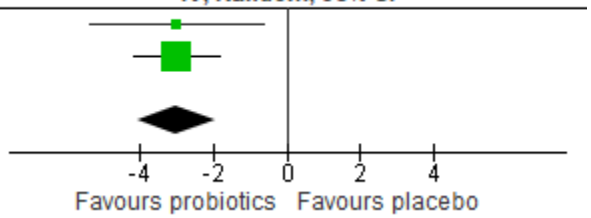
f. Unclear risk of detection and reporting bias

g. Unclear risk of selection, detection, and reporting bias

Mean VAS for Urgency (measured by difference in groups at end of study)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kim 2003	30	3	12	33	3	13	20.3%	-3.00 [-5.35, -0.65]
Kim 2005	19.7	2.1	24	22.7	2.1	24	79.7%	-3.00 [-4.19, -1.81]
Total (95% CI)			**36**			**37**	**100.0%**	**-3.00 [-4.06, -1.94]**

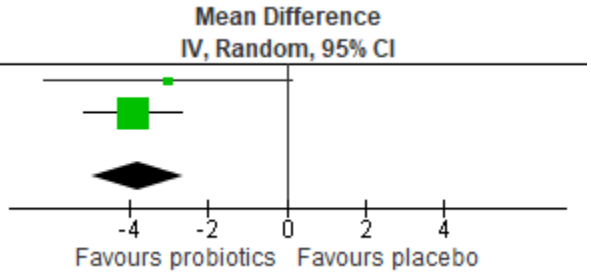
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 5.54 (P < 0.00001)



Mean VAS for Abdominal Pain (measured by difference in groups at end of study)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kim 2003	23	4	12	26	4	13	13.6%	-3.00 [-6.14, 0.14]
Kim 2005	23	2.2	24	26.9	2.2	24	86.4%	-3.90 [-5.14, -2.66]
Total (95% CI)			**36**			**37**	**100.0%**	**-3.78 [-4.93, -2.62]**

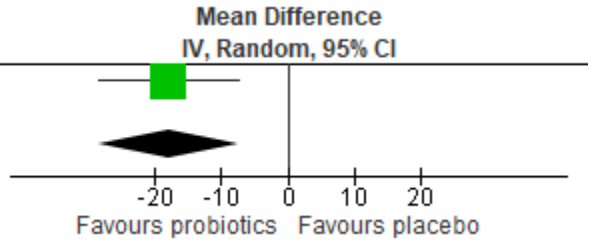
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 6.40 (P < 0.00001)



Overall VAS Score (measured by difference in groups at end of study)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kim 2003	103	14	12	121	13	13	100.0%	-18.00 [-28.62, -7.38]
Total (95% CI)			**12**			**13**	**100.0%**	**-18.00 [-28.62, -7.38]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.32 (P = 0.0009)

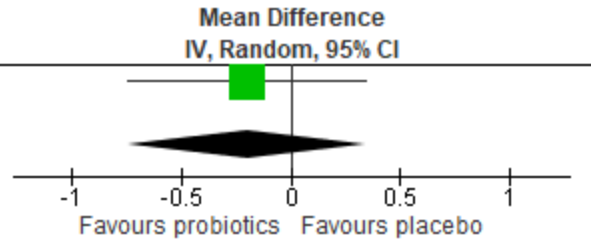


Global GSRS Score at End of Study (lower = better)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Michail 2011	1.5	0.3	15	1.7	0.8	9	100.0%	-0.20 [-0.74, 0.34]
Total (95% CI)			**15**			**9**	**100.0%**	**-0.20 [-0.74, 0.34]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.72 (P = 0.47)



Question: *Escherichia coli* Nissle 1917 compared to placebo for adults with IBS (6c)

Bibliography: Kruis 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*E. coli* Nissle 1917	placebo	Relative (95% CI)	Absolute (95% CI)		
Adverse Events												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	30/60 (50.0%)	27/60 (45.0%)	**RR 1.11** (0.76 to 1.62)	**50 more per 1,000** (from 108 fewer to 279 more)	⨁◯◯◯ VERY LOW	CRITICAL
Overall Clinical Response (measured by difference in groups at end of study)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	27/51 (52.9%)	23/48 (47.9%)	**RR 1.10** (0.75 to 1.64)	**48 more per 1,000** (from 120 fewer to 307 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

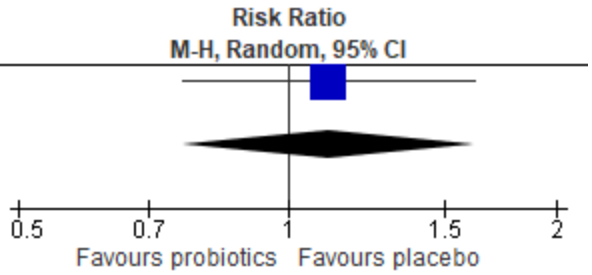
a. Unclear risk of detection bias.

b. The 95% CI includes the potential for both benefit and harm.

Adverse events

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kruis 2012	30	60	27	60	100.0%	1.11 [0.76, 1.62]
Total (95% CI)		**60**		**60**	**100.0%**	**1.11 [0.76, 1.62]**
Total events	30		27			

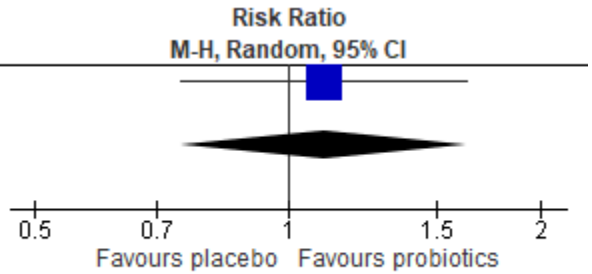
Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)



Clinical Response (measured by difference in groups at end of study)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kruis 2012	27	51	23	48	100.0%	1.10 [0.75, 1.64]
Total (95% CI)		**51**		**48**	**100.0%**	**1.10 [0.75, 1.64]**
Total events	27		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)



Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo for children with IBS (6d)

Bibliography: Guandalini 2010

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo	Relative (95% CI)	Absolute (95% CI)		

Reduction in Abdominal Pain Scores at 6 weeks (higher is better)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	59	59	-	mean **0.5 higher** (0.43 higher to 0.57 higher)	⊕⊕◯◯ LOW	CRITICAL

Reduction in Abdominal Bloating Scores at 6 weeks (higher is better)

1	randomised trials	very serious [a]	not serious	not serious	not serious [b]	none	59	59	-	mean **0.85 higher** (0.74 higher to 0.96 higher)	⊕⊕◯◯ LOW	

CI: Confidence interval

Explanations

a. High risk of attrition bias

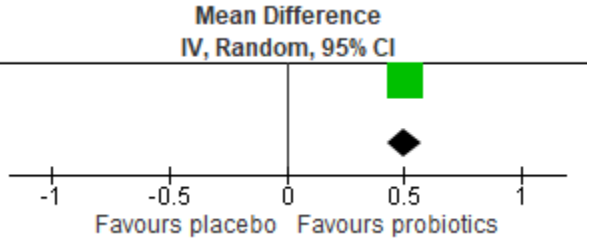
b. Same patients crossed over; improvement noted over time even with placebo

*Guandilini 2010 – of note, patients crossed over. All patients received either placebo or probiotics, then switched over to receive the other. Total 59 subjects

Reduction in Abdominal Pain scores at 6 weeks (measured by change from baseline to week 6)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Guandalini 2010	1	0.2	59	0.5	0.2	59	100.0%	0.50 [0.43, 0.57]
Total (95% CI)			**59**			**59**	**100.0%**	**0.50 [0.43, 0.57]**

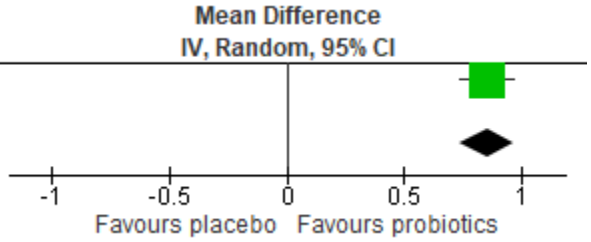
Heterogeneity: Not applicable
Test for overall effect: Z = 13.58 (P < 0.00001)



Reduction in Bloating scores at 6 weeks (measured by change from baseline to week 6)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Guandalini 2010	1.35	0.4	59	0.5	0.2	59	100.0%	0.85 [0.74, 0.96]
Total (95% CI)			**59**			**59**	**100.0%**	**0.85 [0.74, 0.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 14.60 (P < 0.00001)



Question: *Lactobacillus plantarum* 299v compared to placebo for adults with IBS (6e)

Bibliography: Stevenson 2014, Ducrotte 2012, Niedzielen 2001

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. plantarum* 299v	Placebo	Relative (95% CI)	Absolute (95% CI)		
Severity Score as per Francis Score at End of Study (0-100; higher is more severe)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	54	27	-	mean **23.78 higher** (23.08 lower to 70.64 higher)	⊕⊕◯◯ LOW	CRITICAL
Overall QOL-IBS questionnaire (1-5; higher is more severe)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	54	27	-	mean **8.59 higher** (3.76 lower to 20.94 higher)	⊕⊕◯◯ LOW	CRITICAL
Abdominal Pain Severity as per VAS (higher is more severe)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. plantarum* 299v	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	serious [d]	none	108	106	-	mean **0.24 lower** (0.39 lower to 0.09 lower)	⨁⨁◯◯ LOW	CRITICAL

Improvement in Abdominal Pain at Study End

1	randomised trials	serious [c]	not serious	not serious	serious [d]	none	20/20 (100.0%)	11/20 (55.0%)	**RR 1.78** (1.20 to 2.64)	**429 more per 1,000** (from 110 more to 902 more)	⨁⨁◯◯ LOW	CRITICAL

Overall Improvement at Study End

1	randomised trials	serious [c]	not serious	not serious	serious [d]	none	19/20 (95.0%)	3/20 (15.0%)	**RR 6.33** (2.22 to 18.06)	**800 more per 1,000** (from 183 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The 95% CI includes the potential for both benefit and harm.

b. Unclear risk of detection and reporting bias

c. Unclear risk of selection, detection, attrition, and reporting bias

d. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

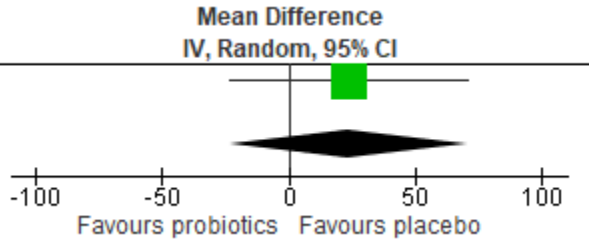
e. Unclear risk of selection, detection, performance, and reporting bias

f. No S.D. included

Francis Severity Score at the end of study

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Stevenson 2014	209.08	110.63	54	185.3	96.52	27	100.0%	23.78 [-23.08, 70.64]
Total (95% CI)			**54**			**27**	**100.0%**	**23.78 [-23.08, 70.64]**

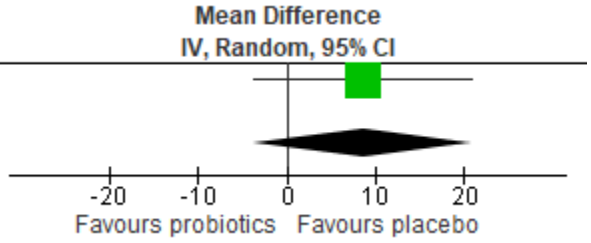
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)



Overall QOL-IBS questionnaire (lower = better)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Stevenson 2014	41.81	27.28	54	33.22	26.47	27	100.0%	8.59 [-3.76, 20.94]
Total (95% CI)			**54**			**27**	**100.0%**	**8.59 [-3.76, 20.94]**

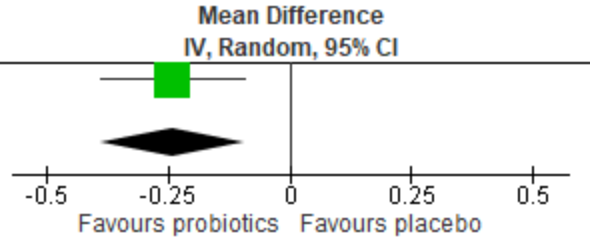
Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.17)



Abdominal Pain Severity as per VAS (measured by mean score reduction)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ducrotte 2012	0.68	0.53	108	0.92	0.57	106	100.0%	-0.24 [-0.39, -0.09]
Total (95% CI)			**108**			**106**	**100.0%**	**-0.24 [-0.39, -0.09]**

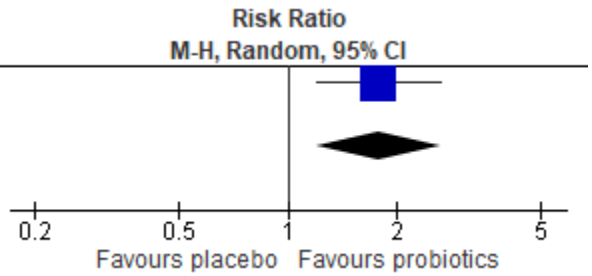
Heterogeneity: Not applicable
Test for overall effect: Z = 3.19 (P = 0.001)



Improvement in Abdominal Pain at end of Study

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Niedzielin 2001	20	20	11	20	100.0%	1.78 [1.20, 2.64]
Total (95% CI)		**20**		**20**	**100.0%**	**1.78 [1.20, 2.64]**
Total events	20		11			

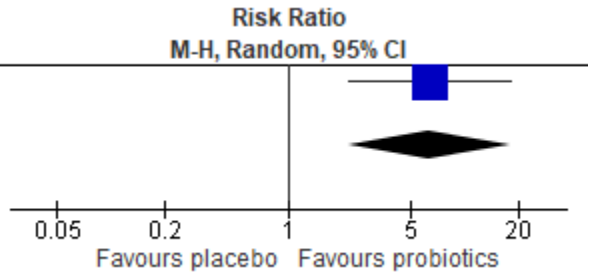
Heterogeneity: Not applicable
Test for overall effect: Z = 2.87 (P = 0.004)



Overall Improvement at End of Study (partial or complete improvement)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Niedzielin 2001	19	20	3	20	100.0%	6.33 [2.22, 18.06]
Total (95% CI)		**20**		**20**	**100.0%**	**6.33 [2.22, 18.06]**
Total events	19		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.45 (P = 0.0006)



Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo for treatment if IBS in adults (6f)

Bibliography: O'Sullivan 2000

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Bloating Scores												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	24	24	-	mean **0.1 lower** (0.21 lower to 0.01 higher)	⊕⊕◯◯ LOW	CRITICAL
Mean Pain Scores												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	24	24	-	mean **0.2 lower** (0.14 lower to 0.26 lower)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

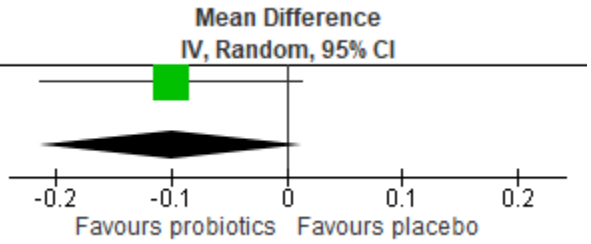
a. Unclear risk of selection, performance, detection, attrition, and reporting bias

b. Cross over study

Mean Bloating Scores (lower = better)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
O'Sullivan 2000	1.5	0.2	24	1.6	0.2	24	100.0%	-0.10 [-0.21, 0.01]
Total (95% CI)			**24**			**24**	**100.0%**	**-0.10 [-0.21, 0.01]**

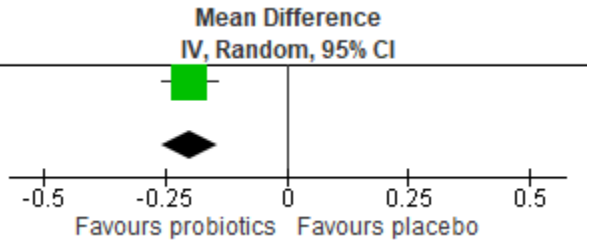
Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)



Mean Pain Scores (lower = better)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
O'Sullivan 2000	1.2	0.1	24	1.4	0.1	24	100.0%	-0.20 [-0.26, -0.14]
Total (95% CI)			**24**			**24**	**100.0%**	**-0.20 [-0.26, -0.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 6.93 (P < 0.00001)



Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo for children with IBS (6g)

Bibliography: Francavilla 2010, Bausserman 2005

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	Placebo	Relative (95% CI)	Absolute (95% CI)		
Response in Diarrhea as per GSRS												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	2/17 (11.8%)	0/18 (0.0%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Response in Constipation as per GSRS												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	1/20 (5.0%)	3/22 (13.6%)	not estimable		⊕◯◯◯ VERY LOW	CRITICAL
Number of Pain Episodes												
1	randomised trials	serious [c]	not serious	not serious	serious [b]	none	42	38	-	mean **1.6 lower** (2.25 lower to 0.95 lower)	⊕⊕◯◯ LOW	CRITICAL
Intensity Pain Scores												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [c]	not serious	not serious	serious [b]	none	42	38	-	mean **1.1 lower** (1.89 lower to 0.31 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

a. Unclear risk of reporting bias

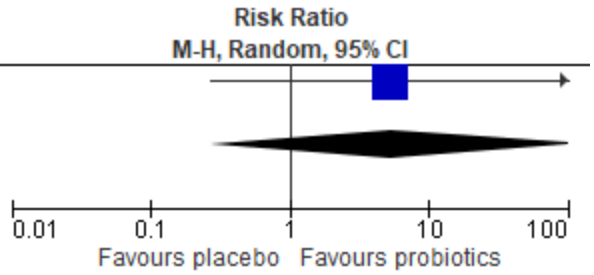
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

c. Unclear risk of detection bias

Response in Diarrhea as per GSRS (more = better)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bausserman 2005	2	17	0	18	100.0%	5.28 [0.27, 102.58]
Total (95% CI)		**17**		**18**	**100.0%**	**5.28 [0.27, 102.58]**
Total events	2		0			

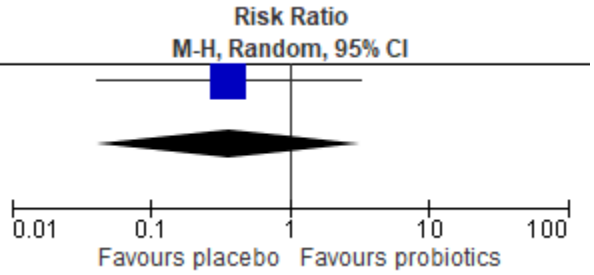
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



Response in Constipation as per GSRS (more = better)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bausserman 2005	1	20	3	22	100.0%	0.37 [0.04, 3.25]
Total (95% CI)		**20**		**22**	**100.0%**	**0.37 [0.04, 3.25]**
Total events	1		3			

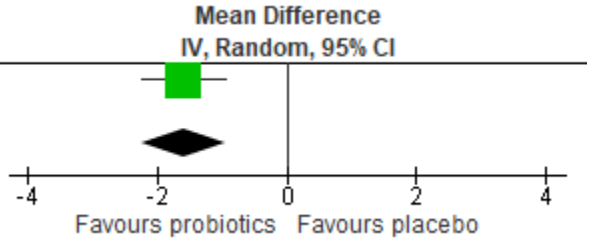
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



Number of Pain Episodes (measured at weeks 5-12)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Francavilla 2010	1.6	0.8	42	3.2	1.9	38	100.0%	-1.60 [-2.25, -0.95]
Total (95% CI)			**42**			**38**	**100.0%**	**-1.60 [-2.25, -0.95]**

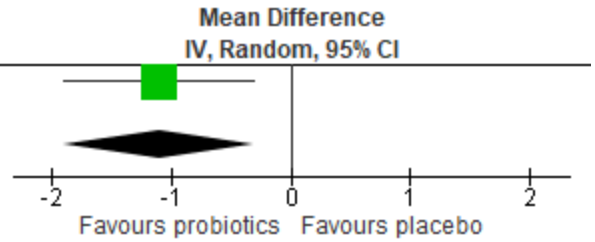
Heterogeneity: Not applicable
Test for overall effect: Z = 4.82 (P < 0.00001)



Intensity of Pain Scores (measured at weeks 5-12)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Francavilla 2010	2.5	1.2	42	3.6	2.2	38	100.0%	-1.10 [-1.89, -0.31]
Total (95% CI)			**42**			**38**	**100.0%**	**-1.10 [-1.89, -0.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.74 (P = 0.006)



Question: *Bacillus coagulans* MTCC 5856 compared to placebo for treatment of IBS (6h)

Bibliography: Majeed 2016, Majeed 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. coagulans* MTCC 5856	Placebo	Relative (95% CI)	Absolute (95% CI)		
IBS-QOL Score at End of Study												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	20	20	-	mean **28 lower** (48.46 lower to 7.54 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Abdominal Pain Scores at End of Study												
1	randomised trials	serious [c]	not serious	not serious	very serious [d]	none	18	18	-	mean **4.11 lower** (4.36 lower to 3.86 lower)	⊕◯◯◯ VERY LOW	CRITICAL
Diarrhea Score at End of Study												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. coagulans* MTCC 5856	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [c]	not serious	not serious	very serious [d]	none	18	18	-	mean **2.68 lower** (3.00 lower to 2.36 lower)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

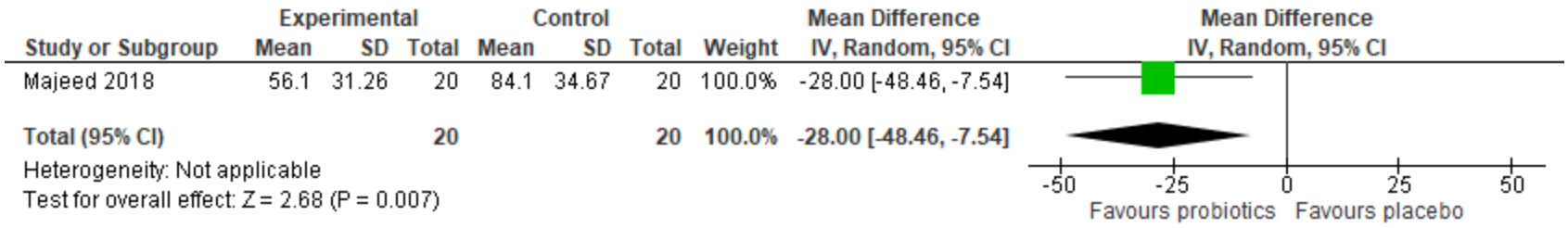
a. Unclear detection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

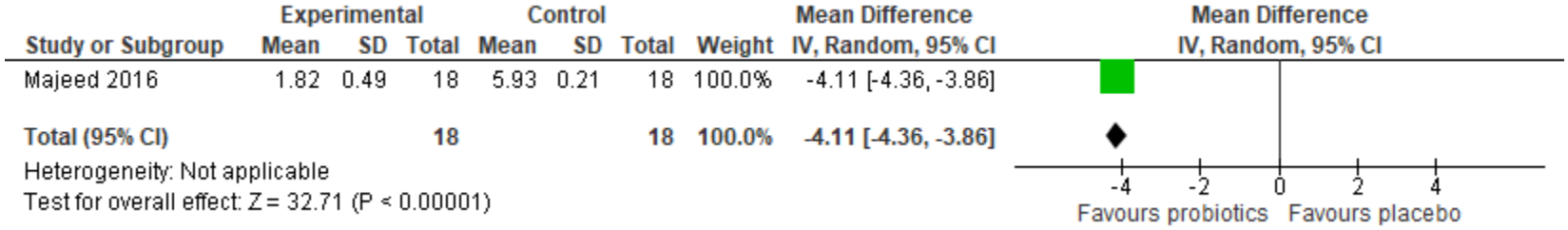
c. Unclear risk of detection, selection, and performance bias

d. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

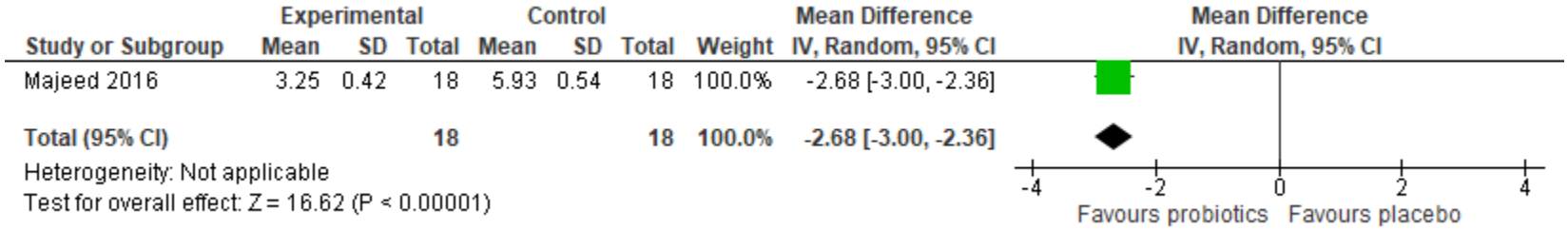
IBS-QOL Score at End of Study (lower = better)



Abdominal Pain Scores at End of Study



Diarrhea Score at End of Study



Question: *Lactobacillus reuteri* compared to placebo for adults with IBS (6i)

Bibliography: Amirimani 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. reuteri*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Abdominal Pain												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	41	31	-	mean **0.46 higher** (0.23 lower to 1.15 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Mean Stool Frequency												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	41	31	-	mean **0.29 lower** (0.87 lower to 0.29 higher)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

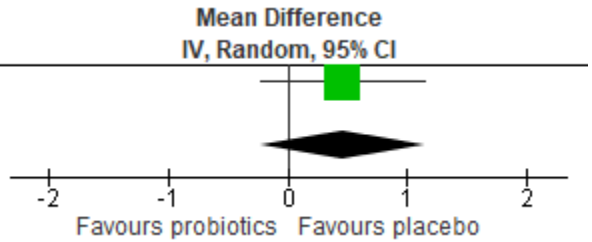
a. High risk of selection, detection, performance, and attrition bias. Symptom scores appear unbalanced at baseline, therefore measurement at end of study also unbalanced (i.e., mean stool frequency reflects an increase from baseline for probiotic group and a decrease from baseline in placebo group).

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Abdominal pain Scores at end of treatment

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Amirimani 2013	1.57	1.71	41	1.11	1.26	31	100.0%	0.46 [-0.23, 1.15]
Total (95% CI)			**41**			**31**	**100.0%**	**0.46 [-0.23, 1.15]**

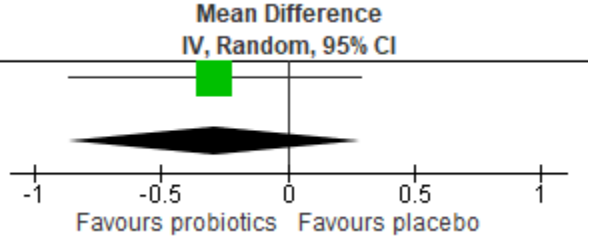
Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)



Mean Stool Frequency at end of treatment

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Amirimani 2013	1.54	1.18	41	1.83	1.28	31	100.0%	-0.29 [-0.87, 0.29]
Total (95% CI)			**41**			**31**	**100.0%**	**-0.29 [-0.87, 0.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.32)



Question: *Lactobacillus reuteri* DSM 17938 compared to placebo for children with IBS (6j)

Bibliography: Jadrešin 2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. reuteri* DSM 17938	placebo	Relative (95% CI)	Absolute (95% CI)		
Median Number of Days Without Pain												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	Probiotic 89.5 (5-108 days; n=26), placebo 51 (0-107 days; n=29)				⨁◯◯◯ VERY LOW	CRITICAL
Severity of Abdominal Pain at 4 months												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	Probiotic 0.21 (0-1.7; n=26), placebo 0.6 (0.2 n=29)				⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. High risk of attrition bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Question: *Lactobacillus gasseri* BNR17 compared to placebo for treatment of IBS (6k)

Bibliography: Shin 2018, Kim 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. gasseri* BNR17	Placebo	Relative (95% CI)	Absolute (95% CI)		
Change in Abdominal Pain Scores from Baseline												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	Shin 2018 reports abdominal pain score reduction in probiotic arm of 2.4 (from 3.6 to 1.2; n=24) compared with placebo arm of 1.8 (from 4.7 to 2.9; n=27) at week 8. Kim 2018 suggests benefit in intervention arm (n=55)				⊕◯◯◯ VERY LOW	CRITICAL
Change in Disturbed Daily Life Scores												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	Shin 2018 reports abdominal pain score reduction in probiotic arm of 2 (from 6.8 to 4.8; n=24) compared with placebo arm of 2 (from 5.5 to 3.5; n=27) at week 8.				⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. High risk of selection and attrition bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate; the narrative suggests there may not be a meaningful difference between groups.

Question: *Saccharomyces cerevisiae* CNCM I-3856 compared to placebo for treatment if IBS in adults (6l)

Bibliography: Pineton 2015, Spiller 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. cerevisiae* CNCM I-3856	Placebo	Relative (95% CI)	Absolute (95% CI)		
Change in Abdominal Pain from Baseline (IBS all subtypes)												
1	randomised trials	serious [a]	not serious	not serious	serious [c]	none	86	93	-	mean **0.35 lower** (0.75 lower to 0.05 higher)	⊕⊕◯◯ LOW	CRITICAL
Response to Treatment												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	57/177 (32.2%)	47/175 (26.9%)	**RR 1.20** (0.87 to 1.66)	**54 more per 1,000** (from 35 fewer to 177 more)	⊕⊕◯◯ LOW	CRITICAL
Abdominal Pain Scores at Study End in IBS-C												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. cerevisiae* CNCM I-3856	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	82	98	-	mean **0.3 lower** (0.67 lower to 0.07 higher)	⊕⊕◯◯ LOW	CRITICAL

Abdominal Pain Scores at Study End in IBS-D

1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	41	38	-	mean **0.1 higher** (0.54 lower to 0.74 higher)	⊕⊕◯◯ LOW	CRITICAL

Bloating Scores at Study End IBS-C

1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	82	98	-	mean **0.5 lower** (0.87 lower to 0.13 lower)	⊕⊕◯◯ LOW	CRITICAL

Bloating Scores at Study End IBS-D

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. cerevisiae* CNCM I-3856	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	41	38	-	mean **0 higher** (0.64 lower to 0.64 higher)	⊕⊕◯◯ LOW	CRITICAL

Composite Score IBS -C

1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	82	98	-	mean **1.3 lower** (2.59 lower to 0.01 lower)	⊕⊕◯◯ LOW	CRITICAL

Composite Score IBS -D

1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	41	38	-	mean **0.5 higher** (1.65 lower to 2.65 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear reporting, detection bias

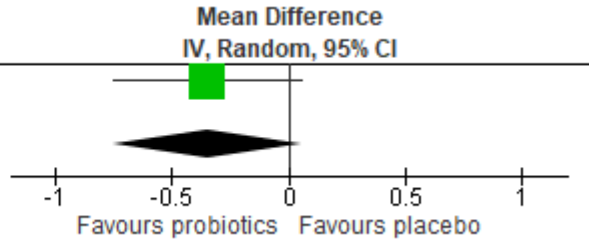
b. Unclear detection bias

c. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Change in Abdominal Pain from Baseline (IBS all subtypes; lower = better)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Pineton 2015	-1.2	1.31	86	-0.85	1.44	93	100.0%	-0.35 [-0.75, 0.05]
Total (95% CI)			**86**			**93**	**100.0%**	**-0.35 [-0.75, 0.05]**

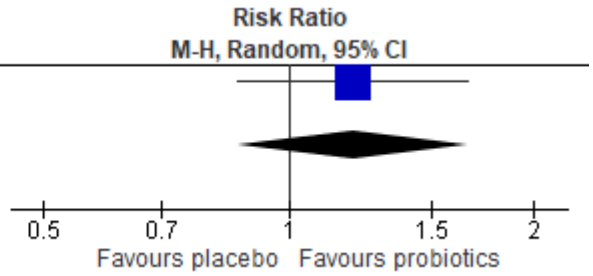
Heterogeneity: Not applicable
Test for overall effect: Z = 1.70 (P = 0.09)



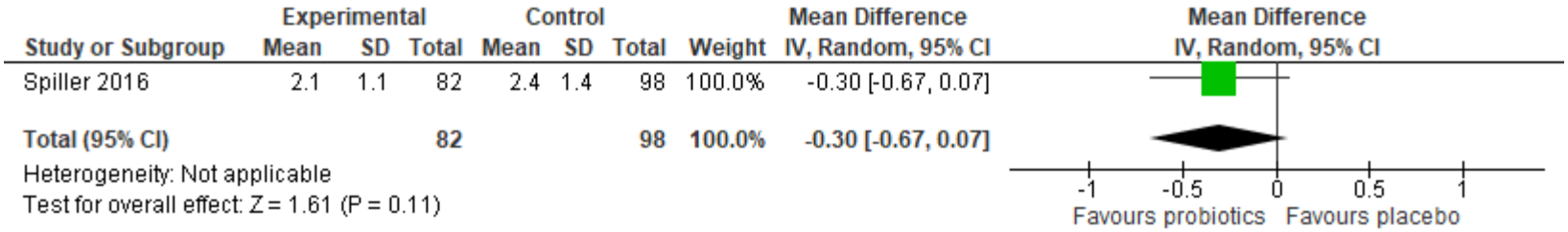
Response to treatment

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Spiller 2016	57	177	47	175	100.0%	1.20 [0.87, 1.66]
Total (95% CI)		**177**		**175**	**100.0%**	**1.20 [0.87, 1.66]**
Total events	57		47			

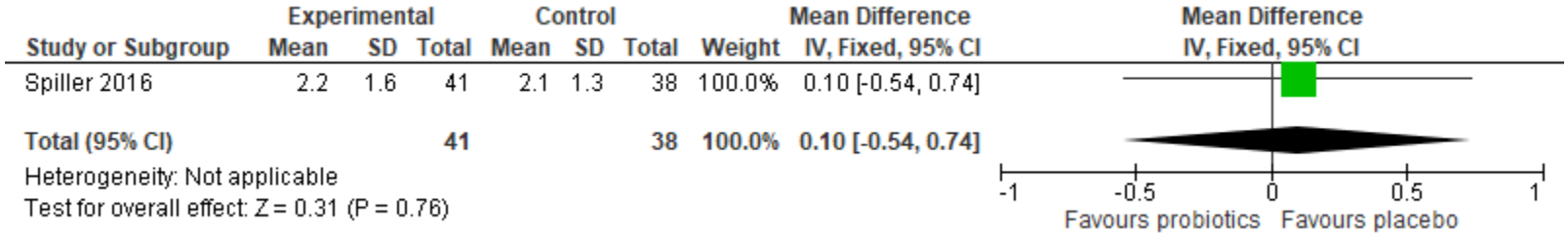
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)



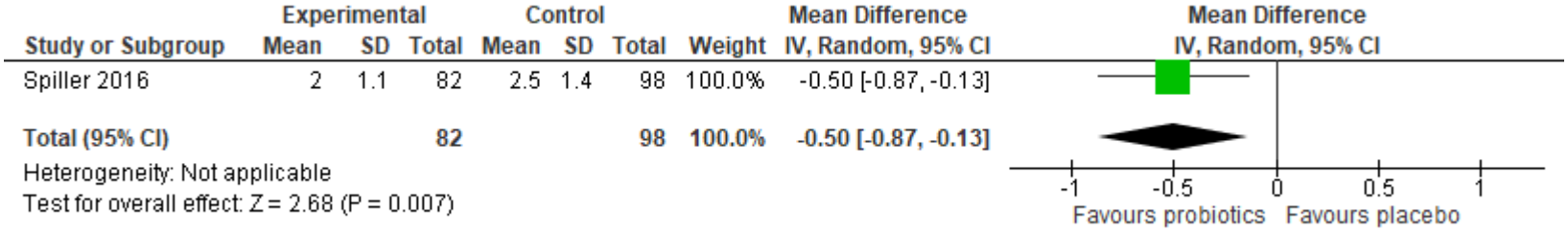
Abdominal Pain Scores at Treatment End in IBS-C (lower = better)



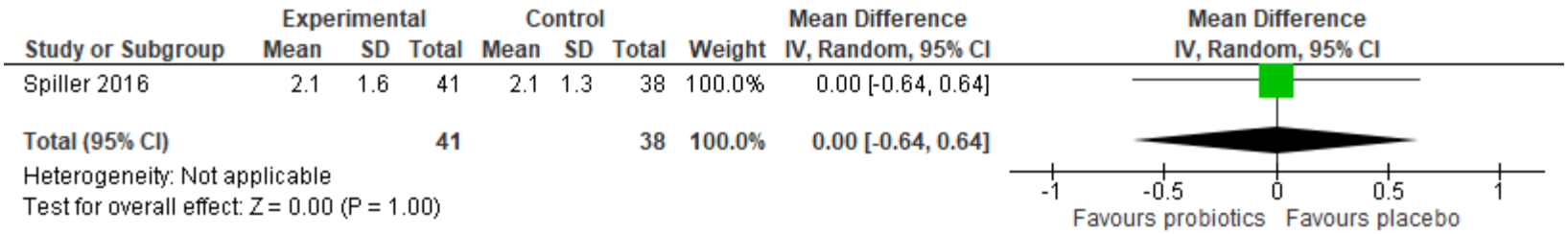
Abdominal Pain Scores at Treatment End in IBS-D (lower = better)



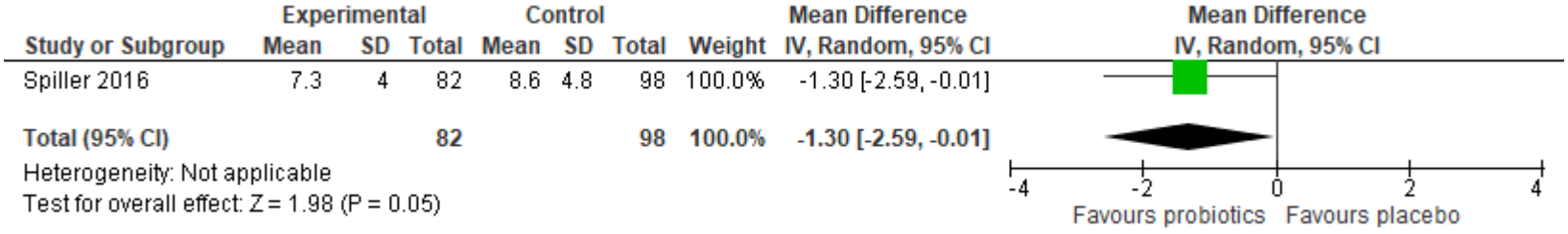
Bloating Scores at Study End IBS-C (lower = better)



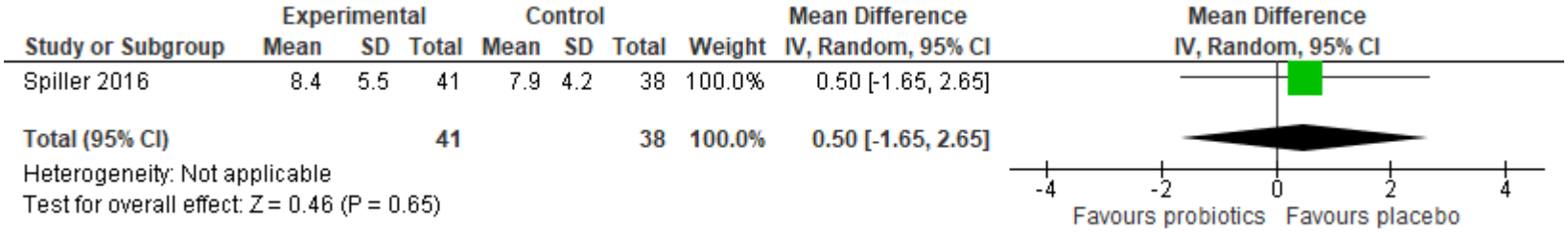
Bloating Scores at Study End IBS-D (lower = better)



Composite Score IBS-C (lower = better)



Composite Score IBS-D (lower = better)



Question: *Lactobacillus casei* Shirota compared to placebo for adults with IBS (6m)

Bibliography: Thijssen 2016

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. casei*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Composite QOL at end of treatment												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	39	41	-	mean **0** (1.75 lower to 1.75 higher)	⊕⊕◯◯ LOW	CRITICAL
Mean Number of Symptom Free Days at end of treatment												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	39	41	-	mean **0.2 SD lower** (1.91 lower to 1.51 higher)	⊕⊕◯◯ LOW	CRITICAL
Overall Response at End of Treatment												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	14/39 (35.9%)	12/41 (29.3%)	**RR 1.23** (0.65 to 2.31)	**67 more per 1,000** (from 102 fewer to 383 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

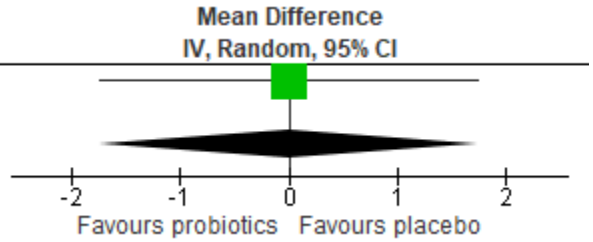
Explanations

a. Unclear risk of selection, performance, and detection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

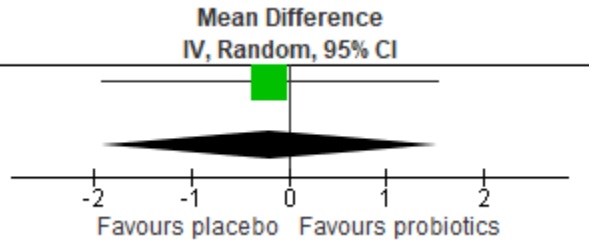
Composite QOL at end of treatment (higher = better; week 8)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Thijssen 2016	43	4	39	43	4	41	100.0%	0.00 [-1.75, 1.75]
Total (95% CI)			**39**			**41**	**100.0%**	**0.00 [-1.75, 1.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								



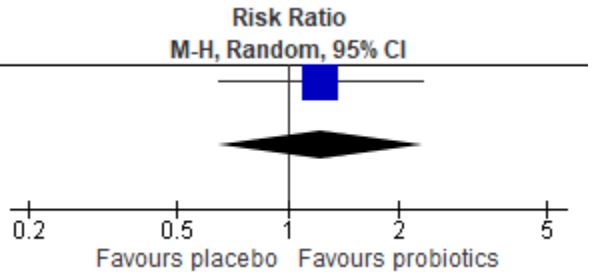
Mean Number of Symptom Free Days at end of treatment (week 8)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Thijssen 2016	2.6	3.5	39	2.8	4.3	41	100.0%	-0.20 [-1.91, 1.51]
Total (95% CI)			**39**			**41**	**100.0%**	**-0.20 [-1.91, 1.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.23 (P = 0.82)								



Overall Response at End of Treatment

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Thijssen 2016	14	39	12	41	100.0%	1.23 [0.65, 2.31]
Total (95% CI)		**39**		**41**	**100.0%**	**1.23 [0.65, 2.31]**
Total events	14		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						



Question: *Lactobacillus rhamnosus* compared to placebo for adults with IBS (6n)

Bibliography: Dapoigny 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Change in IBS Severity Score from Baseline for *L. rhamnosus* in IBS-C												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4	7	-	mean **52.60 higher** (28.69 lower to 133.89 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Change in IBS Severity Score from Baseline for *L. rhamnosus* in IBS-D												
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	7	8	-	mean **103.1 lower** (214.18 lower to 7.98 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Proportion of Patients with severe symptoms at end of treatment (*L. rhamnosus*)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	very serious [b]	none	4/25 (16.0%)	5/25 (20.0%)	**RR 0.80** (0.24 to 2.64)	**40 fewer per 1,000** (from 152 fewer to 328 more)	⨁◯◯◯ VERY LOW	CRITICAL

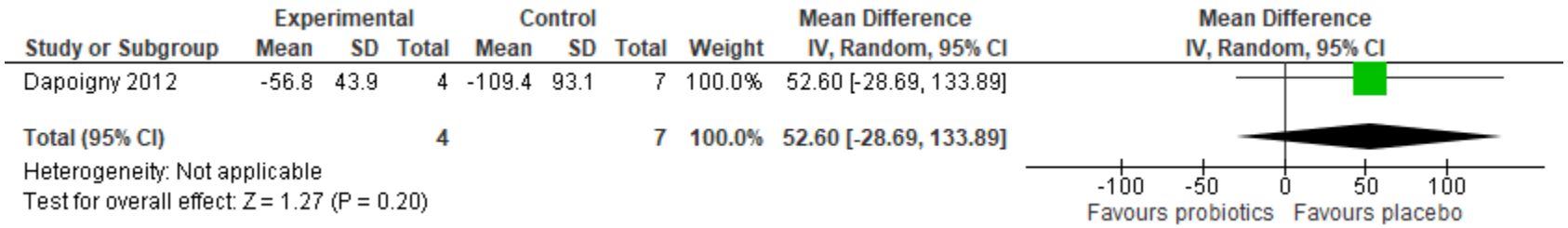
CI: Confidence interval; **RR:** Risk ratio

Explanations

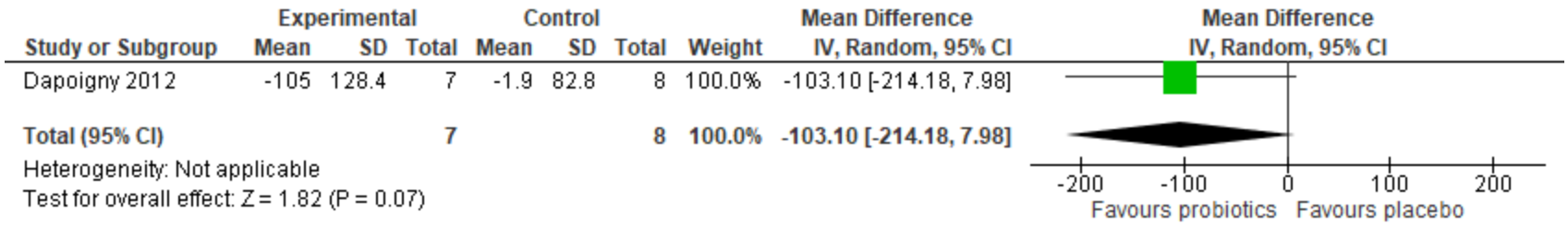
a. High risk selection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

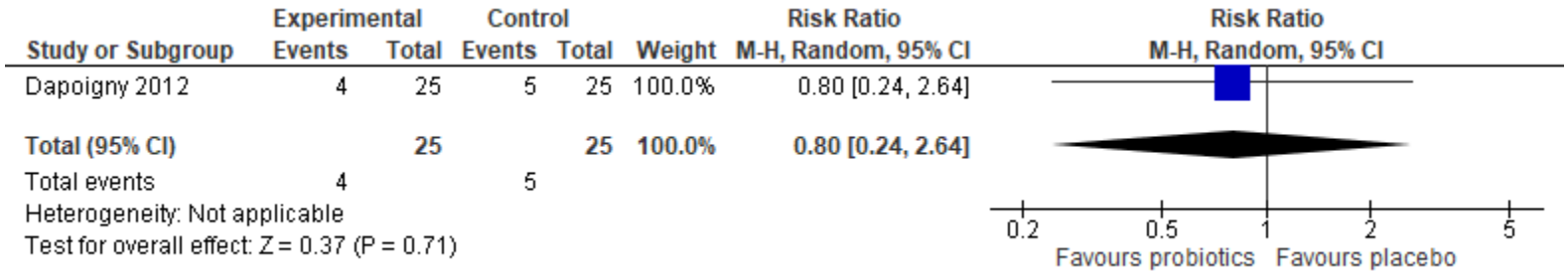
Change in IBS Severity Score from Baseline for *L. rhamnosus* in IBS-C



Change in IBS Severity Score from Baseline for *L. rhamnosus* in IBS-D



Proportion of Patients with severe symptoms at end of treatment (*L. rhamnosus*)



Question: *Lactobacillus acidophilus* SDC 2012 and 2013 compared to placebo for adults with IBS (6o)

Bibliography: Sinn 2008

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* SDC 2012 and 2013	Placebo	Relative (95% CI)	Absolute (95% CI)		
Abdominal pain symptom response												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	16/20 (80.0%)	7/20 (35.0%)	**RR 2.29** (1.21 to 4.32)	**451 more per 1,000** (from 73 more to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of detection and reporting bias

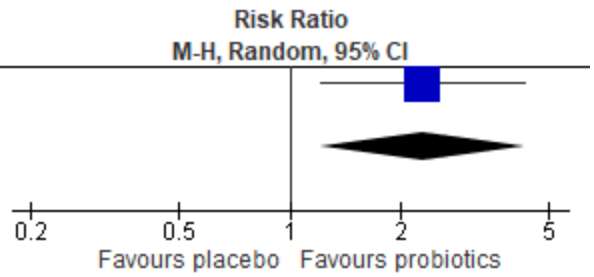
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Proportion of Response (i.e. improvement) of Abdominal Pain

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Sinn 2008	16	20	7	20	100.0%	2.29 [1.21, 4.32]
Total (95% CI)		**20**		**20**	**100.0%**	**2.29 [1.21, 4.32]**
Total events	16		7			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.55 (P = 0.01)



Question: *Bifidobacterium animalis* subsp. *lactis* I-2494 + *Streptococcus salivarius* subsp. *thermophilus* I-1630 + *Lactobacillus delbrueckii* subsp. *bulgaricus* I-1632 and I-1519 compared to placebo for adults with IBS (6p)

Bibliography: Roberts 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. animalis* subsp. *lactis* I-2494 + *S. salivarius* subsp. *thermophilus* I-1630 + *L. delbrueckii* subsp. *bulgaricus* I-1632 and I-1519	Placebo	Relative (95% CI)	Absolute (95% CI)		
Symptom relief at Week 4												
1	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	34/60 (56.7%)	26/49 (53.1%)	**RR 1.07** (0.76 to 1.51)	**37 more per 1,000** (from 127 fewer to 271 more)	⊕⊕◯◯ LOW	CRITICAL
Mean Change from Baseline to Week 4 in IBS Symptom Severity Score												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. animalis* subsp. *lactis* I-2494 + *S. salivarius* subsp. *thermophilus* I-1630 + *L. delbrueckii* subsp. *bulgaricus* I-1632 and I-1519	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	41	44	-	mean **22.24 lower** (56.43 lower to 11.95 higher)	⊕⊕◯◯ LOW	CRITICAL

Mean Change from Baseline to Week 4 in Birmingham IBS Symptoms Scale

1	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	60	49	-	mean **2.18 lower** (6.32 lower to 1.96 higher)	⊕⊕◯◯ LOW	CRITICAL

Mean Change in IBD QOL at Week 4

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. animalis* subsp. *lactis* I-2494 + *S. salivarius* subsp. *thermophilus* I-1630 + *L. delbrueckii* subsp. *bulgaricus* I-1632 and I-1519	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious [a,b]	none	60	50	-	mean **1.91 higher** (2.54 lower to 6.36 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

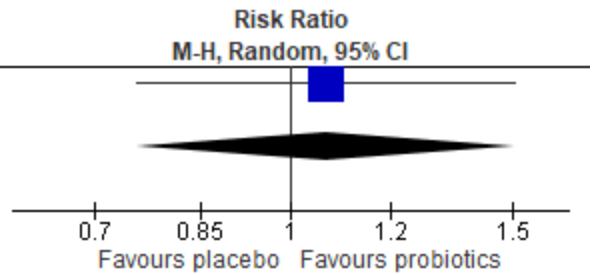
Explanations

a. The 95% CI includes the potential for both benefit and harm.
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Symptom relief at week 4

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Roberts 2013	34	60	26	49	100.0%	1.07 [0.76, 1.51]
Total (95% CI)		**60**		**49**	**100.0%**	**1.07 [0.76, 1.51]**
Total events	34		26			

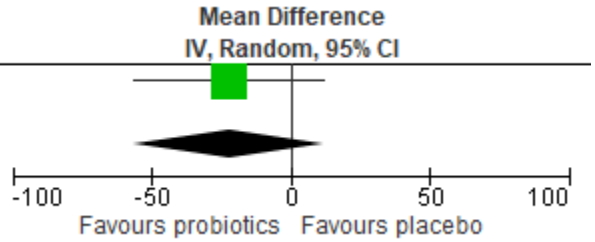
Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)



Mean Change from Baseline to Week 4 in IBS Symptom Severity Score (higher score = greater burden)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Roberts 2013	-53.35	81.98	41	-31.11	78.57	44	100.0%	-22.24 [-56.43, 11.95]
Total (95% CI)			**41**			**44**	**100.0%**	**-22.24 [-56.43, 11.95]**

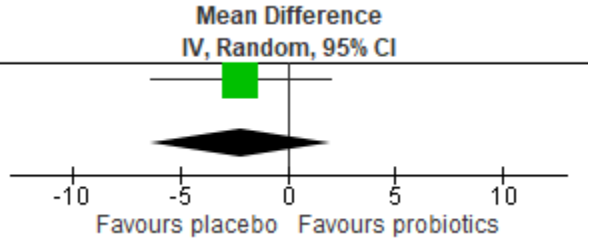
Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)



Mean Change from Baseline to Week 4 in Birmingham IBS Symptoms Scale – Total score (higher score = better QoL)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Roberts 2013	6.1	10.83	60	8.28	11.1	49	100.0%	-2.18 [-6.32, 1.96]
Total (95% CI)			**60**			**49**	**100.0%**	**-2.18 [-6.32, 1.96]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

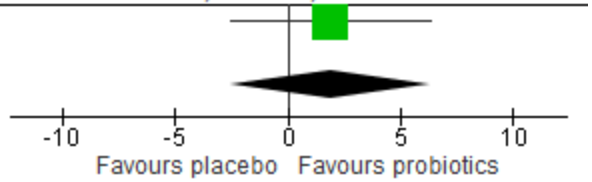


Mean Change in IBD QOL at Week 4 (higher score = better QoL)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Roberts 2013	7.6	10.88	60	5.69	12.6	50	100.0%	1.91 [-2.54, 6.36]
Total (95% CI)			**60**			**50**	**100.0%**	**1.91 [-2.54, 6.36]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.84 (P = 0.40)



Question: *Lactobacillus paracasei* subsp. *paracasei* F-19 + *Lactobacillus acidophilus* LA-5 + *Bifidobacterium animalis* subsp. *lactis* Bb12 compared to placebo for adults with IBS (6q)

Bibliography: Begtrup 2013

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* F-19 + *L. acidophilus* LA-5 + *B. animalis* subsp. *lactis* Bb12	Placebo	Relative (95% CI)	Absolute (95% CI)		
Proportion with Response of Symptoms												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	35/67 (52.2%)	26/64 (40.6%)	**RR 1.29** (0.88 to 1.87)	**118 more per 1,000** (from 49 fewer to 353 more)	⊕⊕◯◯ LOW	CRITICAL
IBD QOL Scores at end of 6 months of treatment												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	59	49	-	mean **0** (6.08 lower to 6.08 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

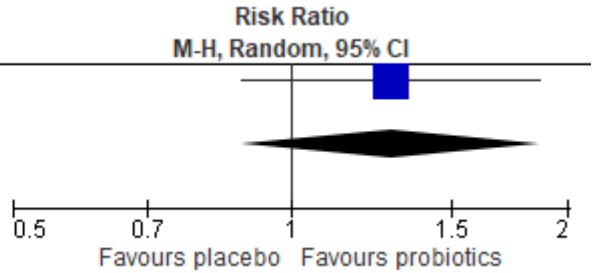
Explanations

a. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Proportion with Response of Symptoms

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Begtrup 2013	35	67	26	64	100.0%	1.29 [0.88, 1.87]
Total (95% CI)		**67**		**64**	**100.0%**	**1.29 [0.88, 1.87]**
Total events	35		26			

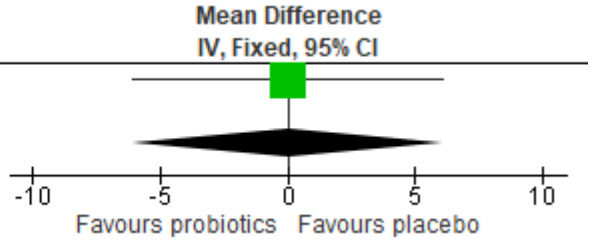
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)



IBD QOL Scores at end of 6 months of treatment

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Begtrup 2013	78	15.6	59	78	16.4	49	100.0%	0.00 [-6.08, 6.08]
Total (95% CI)			**59**			**49**	**100.0%**	**0.00 [-6.08, 6.08]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Question: *Escherichia coli* DSM 17252 compared to placebo for adults with IBS (6r)

Bibliography: Enck 2009

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*E. coli* DSM 17252	Placebo	Relative (95% CI)	Absolute (95% CI)		
Response Rate GSS												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	27/148 (18.2%)	7/150 (4.7%)	**RR 3.91** (1.76 to 8.70)	**136 more per 1,000** (from 35 more to 359 more)	⊕⊕◯◯ LOW	CRITICAL
Response Rate APS												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	28/148 (18.9%)	10/150 (6.7%)	**RR 2.84** (1.43 to 5.63)	**123 more per 1,000** (from 29 more to 309 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

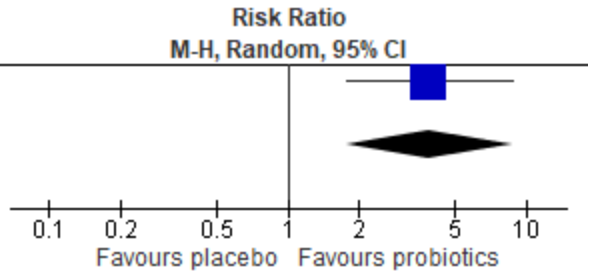
Explanations

a. Unclear risk of bias in all domains with the exception of attrition bias (low risk)
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Response Rate GSS

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Enck 2009	27	148	7	150	100.0%	3.91 [1.76, 8.70]
Total (95% CI)		**148**		**150**	**100.0%**	**3.91 [1.76, 8.70]**
Total events	27		7			

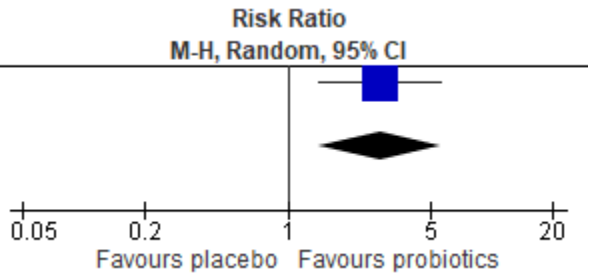
Heterogeneity: Not applicable
Test for overall effect: Z = 3.34 (P = 0.0008)



Response Rate APS

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Enck 2009	28	148	10	150	100.0%	2.84 [1.43, 5.63]
Total (95% CI)		**148**		**150**	**100.0%**	**2.84 [1.43, 5.63]**
Total events	28		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.98 (P = 0.003)



Question: *Streptococcus salivarius* subsp. *thermophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Lactobacillus acidophilus* + *Bifidobacterium longum* subsp. *longum* compared to placebo for adults with IBS (6s)

Bibliography: Zeng 2008

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. salivarius* subsp. *thermophilus* + *L. delbrueckii* subsp. *bulgaricus* + *L. acidophilus* + *B. longum* subsp. *longum*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Global IBS Symptoms												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	14	15	-	mean **1.54 lower** (2.53 lower to 0.55 lower)	⨁◯◯◯ VERY LOW	CRITICAL
VAS Abdominal Pain												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. salivarius* subsp. *thermophilus* + *L. delbrueckii* subsp. *bulgaricus* + *L. acidophilus* + *B. longum* subsp. *longum*	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	14	15	-	mean **9.31 lower** (14.34 lower to 4.28 lower)	⊕◯◯◯ VERY LOW	CRITICAL

VAS Bloating

1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	14	15	-	mean **2.43 higher** (0.66 lower to 5.52 higher)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

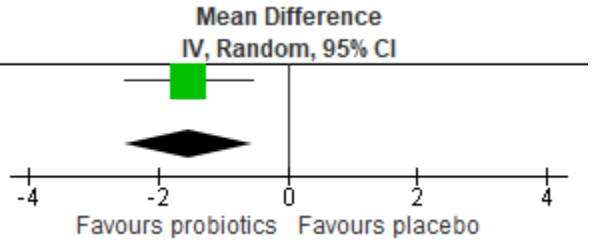
a. High risk of detection and performance bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Global IBS Symptoms (lower = better; measured at week 4)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Zeng 2008	7.64	1.24	14	9.18	1.48	15	100.0%	-1.54 [-2.53, -0.55]
Total (95% CI)			**14**			**15**	**100.0%**	**-1.54 [-2.53, -0.55]**

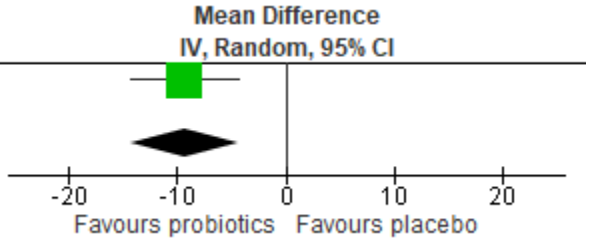
Heterogeneity: Not applicable
Test for overall effect: Z = 3.04 (P = 0.002)



VAS Abdominal Pain (lower = better; measured at week 4)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Zeng 2008	30.11	7.71	14	39.42	5.92	15	100.0%	-9.31 [-14.34, -4.28]
Total (95% CI)			**14**			**15**	**100.0%**	**-9.31 [-14.34, -4.28]**

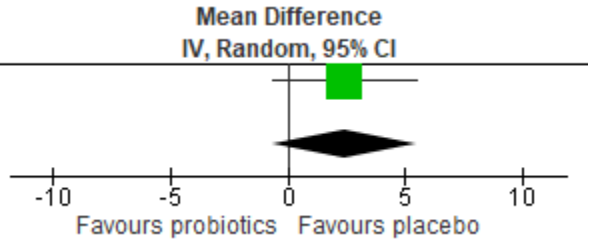
Heterogeneity: Not applicable
Test for overall effect: Z = 3.63 (P = 0.0003)



VAS Bloating (lower = better; measured at week 4)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Zeng 2008	32.1	4.53	14	29.67	3.91	15	100.0%	2.43 [-0.66, 5.52]
Total (95% CI)			**14**			**15**	**100.0%**	**2.43 [-0.66, 5.52]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)



Question: *Bifidobacterium longum* subsp. *longum* LA-101 + *Lactobacillus acidophilus* LA-102 + *Lactococcus lactis* LA-103 + *Streptococcus salivarius* subsp. *thermophilus* LA-104 compared to placebo for adults with IBS (6t)

Bibliography: Drouault-Holowacz 2008

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *longum* LA-101 + *L. acidophilus* LA-102 + *L. lactis* LA-103 + *S. salivarius* subsp. *thermophilus* LA-104	Placebo	Relative (95% CI)	Absolute (95% CI)		
Relief of Symptoms												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	21/48 (43.8%)	22/52 (42.3%)	**RR 1.03** (0.66 to 1.62)	**13 more 1,000** (from 144 fewer to 262 more)	⊕⊕◯◯ LOW	CRITICAL
Decrease in Abdominal Pain Score (Lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *longum* LA-101 + *L. acidophilus* LA-102 + *L. lactis* LA-103 + *S. salivarius* subsp. *thermophilus* LA-104	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	48	52	-	mean **17.70 lower** (36.46 lower to 1.06 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

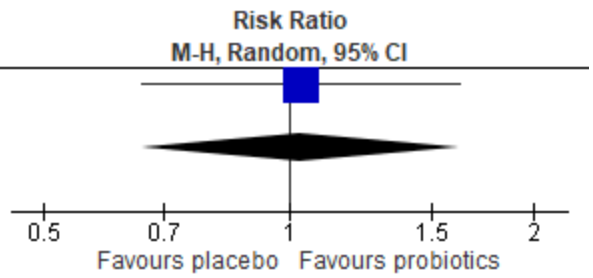
a. Unclear risk of reporting, detection, and performance bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Relief of Symptoms

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Drouault-Holowacz 2008	21	48	22	52	100.0%	1.03 [0.66, 1.62]
Total (95% CI)		**48**		**52**	**100.0%**	**1.03 [0.66, 1.62]**
Total events	21		22			

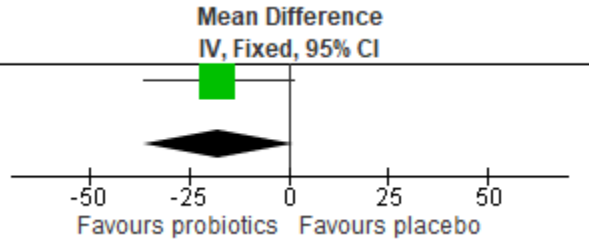
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)



Decrease in Abdominal Pain Scores (lower is better)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Drouault-Holowacz 2008	-41.9	44.6	48	-24.2	51.1	52	100.0%	-17.70 [-36.46, 1.06]
Total (95% CI)			**48**			**52**	**100.0%**	**-17.70 [-36.46, 1.06]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.85 (P = 0.06)



Question: *Bifidobacterium longum* subsp. *longum* NCC 3001 compared to placebo for adults with IBS (6u)

Bibliography: Pinto-Sanchez 2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *longum* NCC 3001	Placebo	Relative (95% CI)	Absolute (95% CI)		
IBS Birmingham Total												
1	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	22	22	-	mean **3.8 lower** (9.24 lower to 1.64 higher)	⊕⊕◯◯ LOW	CRITICAL
Birmingham Constipation												
1	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	22	22	-	mean **1.7 lower** (3.31 lower to 0.09 lower)	⊕⊕◯◯ LOW	CRITICAL
Birmingham Diarrhea												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *longum* NCC 3001	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	22	22	-	mean **0.6 lower** (3.62 lower to 2.42 higher)	⊕⊕◯◯ LOW	CRITICAL

Birmingham Pain

1	randomised trials	not serious [a]	not serious	not serious	very serious [b]	none	22	22	-	mean **1.5 lower** (3.75 lower to 0.75 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

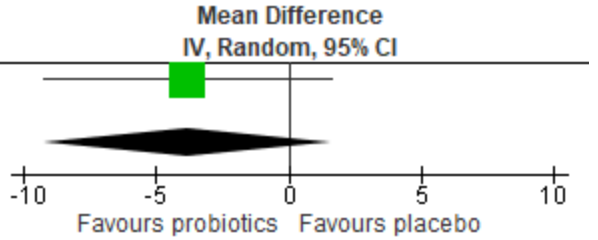
a. Unclear risk of detection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

IBS-Birmingham Total (lower = better; measured at 6 weeks)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Pinto-Sanchez 2017	8.8	9.2	22	12.6	9.2	22	100.0%	-3.80 [-9.24, 1.64]
Total (95% CI)			**22**			**22**	**100.0%**	**-3.80 [-9.24, 1.64]**

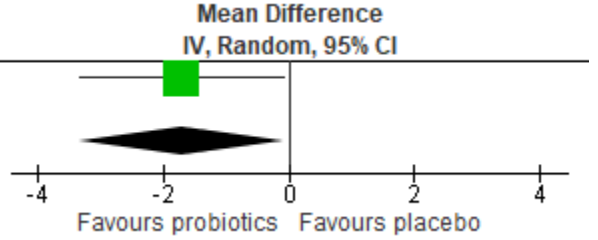
Heterogeneity: Not applicable
Test for overall effect: Z = 1.37 (P = 0.17)



Birmingham Constipation (lower = better; measured at 6 weeks)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Pinto-Sanchez 2017	1.4	1.6	22	3.1	3.5	22	100.0%	-1.70 [-3.31, -0.09]
Total (95% CI)			**22**			**22**	**100.0%**	**-1.70 [-3.31, -0.09]**

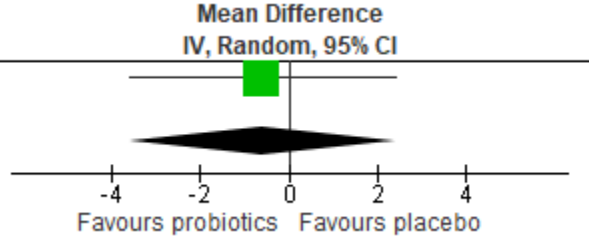
Heterogeneity: Not applicable
Test for overall effect: Z = 2.07 (P = 0.04)



Birmingham Diarrhea (lower = better; measured at 6 weeks)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Pinto-Sanchez 2017	4.1	5.8	22	4.7	4.3	22	100.0%	-0.60 [-3.62, 2.42]
Total (95% CI)			**22**			**22**	**100.0%**	**-0.60 [-3.62, 2.42]**

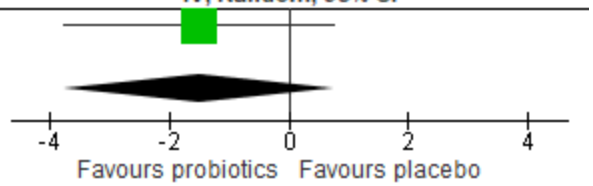
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)



Birmingham Pain (lower = better; measured at 6 weeks)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Pinto-Sanchez 2017	3.4	3.5	22	4.9	4.1	22	100.0%	-1.50 [-3.75, 0.75]
Total (95% CI)			**22**			**22**	**100.0%**	**-1.50 [-3.75, 0.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.31 (P = 0.19)



Question: *Lactobacillus rhamnosus* NCIMB 30174 + *Lactobacillus plantarum* NCIMB 30173 + *Lactobacillus acidophilus* NCIMB 30175 + *Enterococcus faecium* NCIMB 30176 compared to placebo for adults with IBS (6v)

Bibliography: Sisson 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* NCIMB 30174 + *L. plantarum* NCIMB 30173 + *L. acidophilus* NCIMB 30175 + *E. faecium* NCIMB 30176	Placebo	Relative (95% CI)	Absolute (95% CI)		
IBS-SSS Total												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	124	62	-	mean **31.8 lower** (63.68 lower to 0.08 higher)	⊕◯◯◯ VERY LOW	CRITICAL
IBS-SSS Pain												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* NCIMB 30174 + *L. plantarum* NCIMB 30173 + *L. acidophilus* NCIMB 30175 + *E. faecium* NCIMB 30176	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	124	62	-	mean **18.9 lower** (35.57 lower to 2.23 lower)	⊕◯◯◯ VERY LOW	CRITICAL

IBS-SSS Bloating

1	randomised trials	very serious [a]	not serious	not serious	not serious	none	124	62	-	mean **3.8 lower** (12.51 lower to 4.91 higher)	⊕⊕◯◯ LOW	CRITICAL

IBS QoL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* NCIMB 30174 + *L. plantarum* NCIMB 30173 + *L. acidophilus* NCIMB 30175 + *E. faecium* NCIMB 30176	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious [a]	not serious	not serious	not serious	none	124	62	-	mean **2.2 higher** (4 lower to 8.4 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

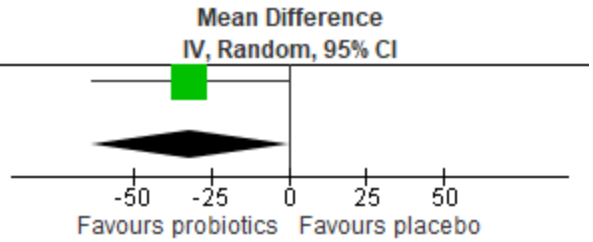
a. High risk of attrition bias

b. The 95% CI includes the potential for both benefit and harm.

IBS-SSS Total (lower = better; measured at 12 weeks)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sisson 2014	240.2	109.18	124	272	102.17	62	100.0%	-31.80 [-63.68, 0.08]
Total (95% CI)			**124**			**62**	**100.0%**	**-31.80 [-63.68, 0.08]**

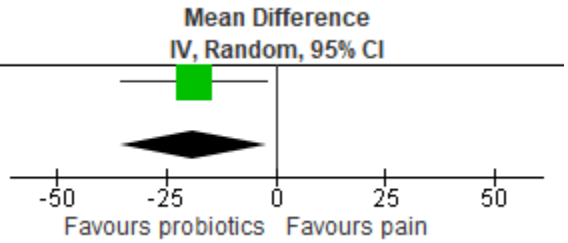
Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)



IBS-SSS Pain (lower = better; measured at 12 weeks)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sisson 2014	81.9	56.46	124	100.8	53.78	62	100.0%	-18.90 [-35.57, -2.23]
Total (95% CI)			**124**			**62**	**100.0%**	**-18.90 [-35.57, -2.23]**

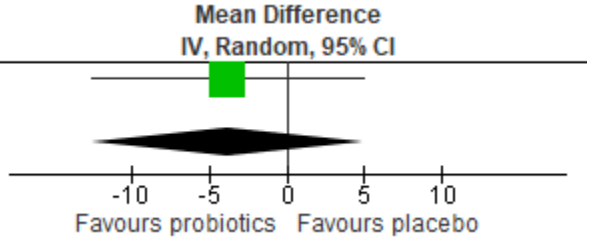
Heterogeneity: Not applicable
Test for overall effect: Z = 2.22 (P = 0.03)



IBS-SSS Bloating (lower = better; measured at 12 weeks)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sisson 2014	44.4	29.17	124	48.2	28.27	62	100.0%	-3.80 [-12.51, 4.91]
Total (95% CI)			**124**			**62**	**100.0%**	**-3.80 [-12.51, 4.91]**

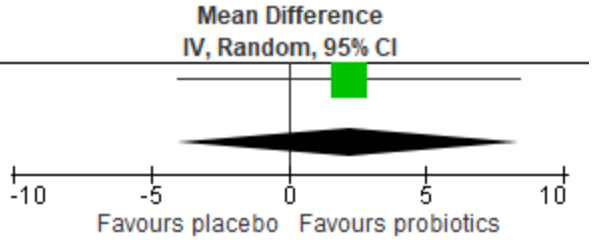
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)



IBS QoL (higher = better; measured at 12 weeks)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sisson 2014	53.4	20.52	124	51.2	20.24	62	100.0%	2.20 [-4.00, 8.40]
Total (95% CI)			**124**			**62**	**100.0%**	**2.20 [-4.00, 8.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)



Question: *Lactobacillus acidophilus* NCIMB 30157 and NCIMB 30156 + *Bifidobacterium bifidum* NCIMB 30153 + *Bifidobacterium animalis* subsp. *lactis* NCIMB 30172 compared to placebo for adults with IBS (6w)

Bibliography: Williams 2009

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* NCIMB 30157 and NCIMB 30156 + *B. bifidum* NCIMB 30153 + *B. animalis* subsp. *lactis* NCIMB 30172	Placebo	Relative (95% CI)	Absolute (95% CI)		
IBS SSS at 8 weeks												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	28	24	-	mean **21.77 lower** (76.64 lower to 33.1 higher)	⨁◯◯◯ VERY LOW	CRITICAL

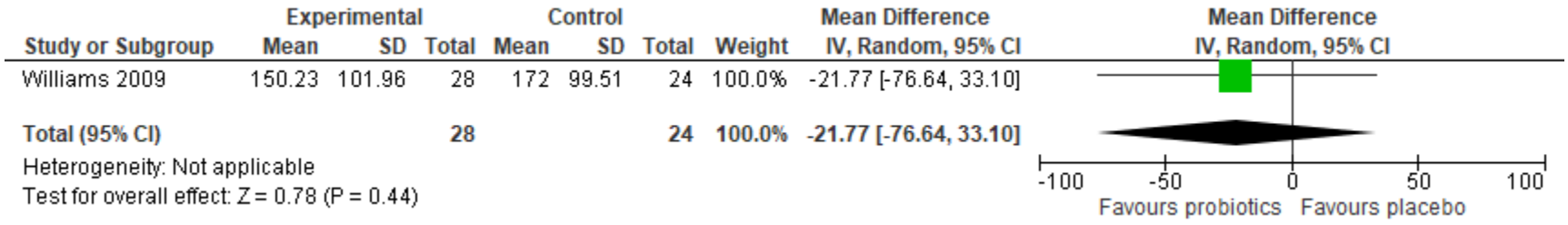
CI: Confidence interval

Explanations

a. High risk of selection and attrition bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

IBS SSS at 8 weeks (lower = better; measured at 8 weeks)



Question: *Lactobacillus acidophilus* KCTC 11906BP + *Lactobacillus plantarum* KCTC 11867BP + *Lactobacillus rhamnosus* KCTC 11868BP + *Bifidobacterium breve* KCTC 11858BP + *Bifidobacterium animalis* subsp. *lactis* KCTC 11903BP + *Bifidobacterium longum* subsp. *longum* KCTC 11860BP + *Streptococcus salivarius* subsp. *thermophilus* KCTC 11870BP compared to placebo for adults with IBS (6x)

Bibliography: Ki Cha 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* KCTC 11906BP + *L. plantarum* KCTC 11867BP + *L. rhamnosus* KCTC 11868BP + *B. breve* KCTC 11858BP + *B. animalis* subsp. *lactis* KCTC 11903BP + *B. longum* subsp. *longum* KCTC 11860BP + *S. salivarius* subsp. *thermophilus* KCTC 11870BP	Placebo	Relative (95% CI)	Absolute (95% CI)		

Adequate Relief of IBS Symptoms

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* KCTC 11906BP + *L. plantarum* KCTC 11867BP + *L. rhamnosus* KCTC 11868BP + *B. breve* KCTC 11858BP + *B. animalis* subsp. *lactis* KCTC 11903BP + *B. longum* subsp. *longum* KCTC 11860BP + *S. salivarius* subsp. *thermophilus* KCTC 11870BP	Placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	12/25 (48.0%)	3/25 (12.0%)	**RR 4.00** (1.28 to 12.47)	**360 more per 1,000** (from 34 more to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

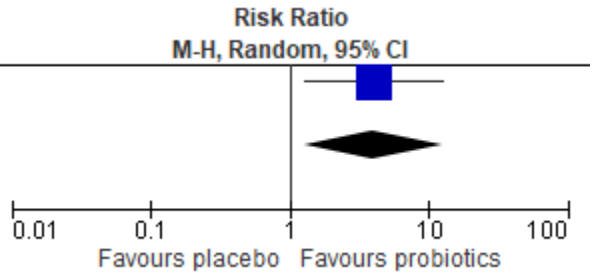
a. Unclear risk of detection and reporting bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Adequate Relief of IBS Symptoms

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Ki Cha 2012	12	25	3	25	100.0%	4.00 [1.28, 12.47]
Total (95% CI)		**25**		**25**	**100.0%**	**4.00 [1.28, 12.47]**
Total events	12		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)



Question: *Bifidobacterium bifidum* MIMBb75 compared to placebo for adults with IBS (6y)

Bibliography: Guglielmetti 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. bifidum* MIMBb75	Placebo	Relative (95% CI)	Absolute (95% CI)		
Response Rate as per SGA												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	35/60 (58.3%)	13/62 (21.0%)	**RR 2.78** (1.64 to 4.72)	**373 more per 1,000** (from 134 more to 780 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of detection and reporting bias

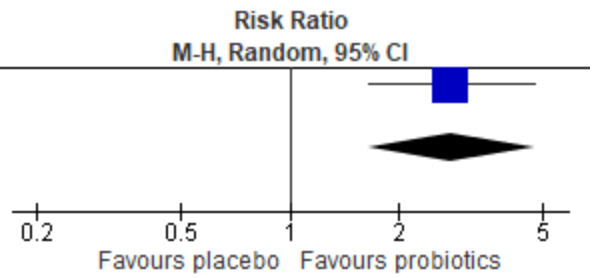
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Overall Response Rate as per SGA

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Guglielmetti 2011	35	60	13	62	100.0%	2.78 [1.64, 4.72]
Total (95% CI)		**60**		**62**	**100.0%**	**2.78 [1.64, 4.72]**
Total events	35		13			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.79 (P = 0.0001)



Question: *Bifidobacterium animalis* subsp. *animalis* DN-173 + *Streptococcus salivarius* subsp. *thermophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* compared to placebo for adults with IBS (6z)

Bibliography: Guyonnet 2007

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. animalis* subsp. *animalis* DN-173 + *S. salivarius* subsp. *thermophilus* + *L. delbrueckii* subsp. *bulgaricus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Quality of Life Responder Rate												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	88/135 (65.2%)	63/132 (47.7%)	**RR 1.37** (1.10 to 1.70)	**177 more per 1,000** (from 48 more to 334 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of selection performance, and detection bias

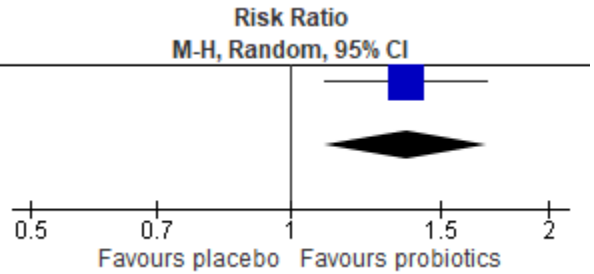
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Quality of Life Responder Rate

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Guyonnet 2007	88	135	63	132	100.0%	1.37 [1.10, 1.70]
Total (95% CI)		**135**		**132**	**100.0%**	**1.37 [1.10, 1.70]**
Total events	88		63			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.82 (P = 0.005)



Question: *Lactobacillus paracasei* subsp. *paracasei* F-19 + *Lactobacillus acidophilus* LA-5 + *Bifidobacterium animalis* subsp. *lactis* Bb12 + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo for adults with IBS (6aa)

Bibliography: Simren 2010

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* F-19 + *L. acidophilus* LA-5 + *B. animalis* subsp. *lactis* Bb12 + *L. delbrueckii* subsp. *bulgaricus* + *S. salivarius* subsp. *thermophilus*	Placebo	Relative (95% CI)	Absolute (95% CI)		
Adequate Relief of Symptoms												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	14/37 (37.8%)	10/37 (27.0%)	**RR 1.40** (0.72 to 2.74)	**108 more per 1,000** (from 76 fewer to 470 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of reporting and detection bias

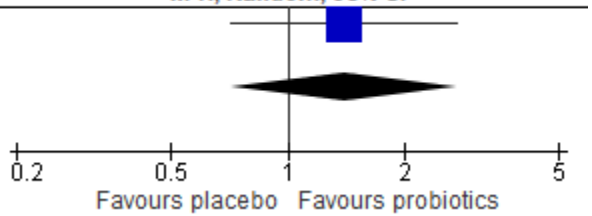
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Adequate Relief of Symptoms

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Simren 2010	14	37	10	37	100.0%	1.40 [0.72, 2.74]	
Total (95% CI)		**37**		**37**	**100.0%**	**1.40 [0.72, 2.74]**	
Total events	14		10				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.98 (P = 0.33)



Question: *Lactobacillus plantarum* CECT7484 and CECT7485 + *Pediococcus acidilactici* CECT7483 compared to placebo for adults with IBS (6ab)

Bibliography: Lorenzo-Zuniga 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. plantarum* CECT7484 and CECT7485 + *P. acidilactici* CECT7483	Placebo	Relative (95% CI)	Absolute (95% CI)		
Proportion with Good Response												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	26/47 (55.3%)	4/24 (16.7%)	**RR 6.19** (1.83 to 20.92)	**865 more per 1,000** (from 138 more to 1,000 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of detection and reporting bias

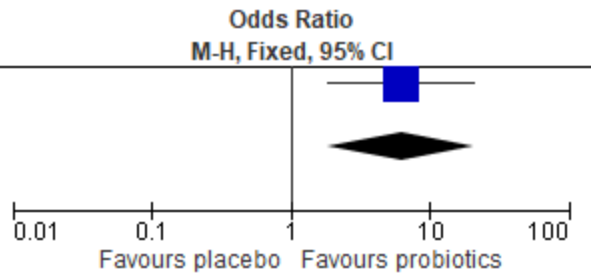
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Proportion with Good Response (i.e. change in IBS-QoL ≥15)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lorenzo-Zuniga 2014	26	47	4	24	100.0%	6.19 [1.83, 20.92]
Total (95% CI)		**47**		**24**	**100.0%**	**6.19 [1.83, 20.92]**
Total events	26		4			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.93 (P = 0.003)



Question: *Bifidobacterium longum* subsp. *infantis* M-63 + *Bifidobacterium breve* M-16V + *B. longum* Reuter ATCC BAA-999 compared to placebo for children with IBS (6ac)

Bibliography: Giannetti 2017

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *infantis* M-63 + *B. breve* M-16V + *B. longum* Reuter ATCC BAA-999	Placebo	Relative (95% CI)	Absolute (95% CI)		
Proportion with Resolution of Abdominal Pain												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	20/48 (41.7%)	5/25 (20.0%)	**RR 2.08** (0.89 to 4.89)	**216 more per 1,000** (from 22 fewer to 778 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

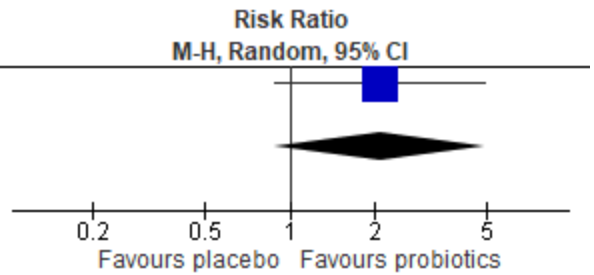
a. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Proportion with Resolution of Abdominal Pain

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Giannetti 2017	20	48	5	25	100.0%	2.08 [0.89, 4.89]
Total (95% CI)		**48**		**25**	**100.0%**	**2.08 [0.89, 4.89]**
Total events	20		5			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.69 (P = 0.09)



Question: *Lactobacillus brevis* KB290 compared to placebo for adults and children with IBS (6ad)

Bibliography: Murakami 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. brevis* KB290	Placebo	Relative (95% CI)	Absolute (95% CI)		
Overall Health QOL (lower score is better)												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	23	23	-	mean **0.1 lower** (0.56 lower to 0.36 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

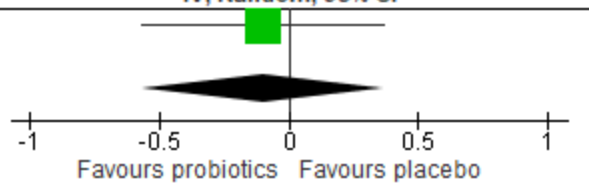
a. Unclear risk of bias in all domains

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Overall Health QOL (lower = better)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Murakami 2012	2.8	0.8	23	2.9	0.8	23	100.0%	-0.10 [-0.56, 0.36]
Total (95% CI)			**23**			**23**	**100.0%**	**-0.10 [-0.56, 0.36]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)



Question: *Lactobacillus casei* DG compared to placebo for adults with IBS (6ae)

Bibliography: Cremon 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. casei* DG	Placebo	Relative (95% CI)	Absolute (95% CI)		
Proportion of Responders for Abdominal Pain												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	15/40 (37.5%)	12/40 (30.0%)	**RR 1.25** (0.67 to 2.32)	**75 more per 1,000** (from 99 fewer to 396 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

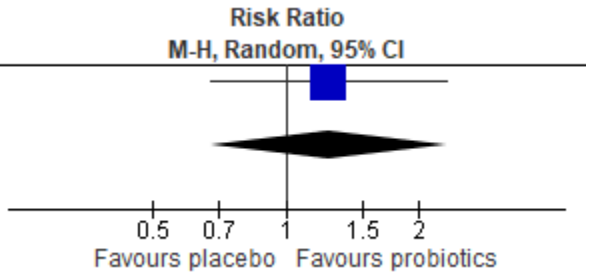
Explanations

a. Unclear risk of detection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Proportion of Response of Abdominal Pain

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Cremon 2018	15	40	12	40	100.0%	1.25 [0.67, 2.32]
Total (95% CI)		**40**		**40**	**100.0%**	**1.25 [0.67, 2.32]**
Total events	15		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						



Question: *Lactobacillus acidophilus* NCFM + *Bifidobacterium animalis* subsp. *lactis* ATCC SD5220 compared to placebo for adults with IBS (6af)

Bibliography: Ringel 2011

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* NCFM + *B. animalis* subsp. *lactis* ATCC SD5220	Placebo	Relative (95% CI)	Absolute (95% CI)		
Bloating Severity Scores in IBS Subgroup												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	17	16	-	mean **2.49 lower** (4.54 lower to 0.44 lower)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

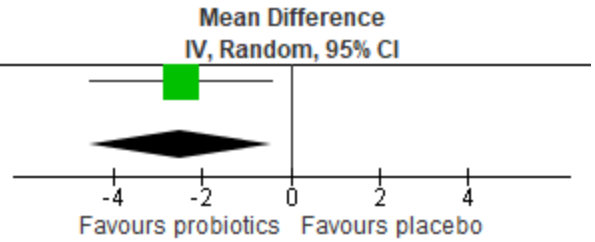
Explanations

a. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Bloating Severity Scores in IBS Subgroup (lower = better)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ringel 2011	4.24	3	17	6.73	3	16	100.0%	-2.49 [-4.54, -0.44]
Total (95% CI)			**17**			**16**	**100.0%**	**-2.49 [-4.54, -0.44]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.38 (P = 0.02)



Question: *Lactobacillus acidophilus* CL1285 + *Lactobacillus casei* LBC80R + *Lactobacillus rhamnosus* CLR2 compared to placebo for adults with IBS (6ag)

Bibliography: Preston 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* CL1285 + *L. casei* LBC80R + *L. rhamnosus* CLR2	Placebo	Relative (95% CI)	Absolute (95% CI)		
Improvement in QOL Score												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	58	27	-	mean **5.57 higher** (4.89 lower to 16.03 higher)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

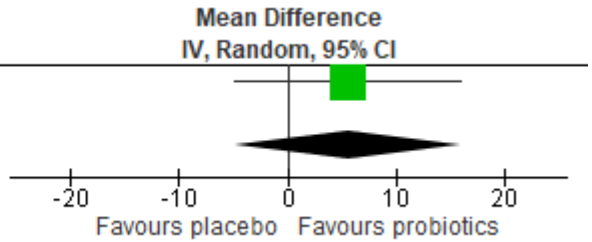
a. unclear risk of selection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

Improvement in QOL Score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Preston 2018	24.01	22.39	58	18.44	23.15	27	100.0%	5.57 [-4.89, 16.03]
Total (95% CI)			**58**			**27**	**100.0%**	**5.57 [-4.89, 16.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)



Question: *Bacillus subtilis* PXN 21 + *Bifidobacterium bifidum* PXN 23 + *Bifidobacterium breve* PXN 25 + *Bifidobacterium longum* subsp. *infantis* PXN 27 + *B. longum* subsp. *longum* PXN 30 + *Lactobacillus acidophilus* PXN 35 + *Lactobacillus delbrueckii* subsp. *bulgaricus* PXN39 + *Lactobacillus casei* PXN 37 + *Lactobacillus plantarum* PXN 47 + *Lactobacillus rhamnosus* PXN 54 + *Lactobacillus helveticus* PXN 45 + *Lactobacillus salivarius* PXN 57 + *Lactococcus lactis* PXN63 + *Streptococcus salivarius* subsp. *thermophilus* PXN 66 compared to placebo for adults with IBS (6ah)

Bibliography: Ishaque 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. subtilis* PXN 21 + *B. bifidum* PXN 23 + *B. breve* PXN 25 + *B. longum* subsp. *infantis* PXN 27 + *B. longum* subsp. *longum* PXN 30 + *L. acidophilus* PXN 35 + *L. delbrueckii* subsp. *bulgaricus* PXN39 + *L. casei* PXN 37 + *L. plantarum* PXN 47 + *L. rhamnosus* PXN 54 + *L. helveticus* PXN 45 + *L. salivarius* PXN 57 + *L. lactis* PXN63 + *S. salivarius* subsp. *thermophilus* PXN 66	Placebo	Relative (95% CI)	Absolute (95% CI)		
Overall IBS-SSS Score at 5 months												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	181	179	-	mean **66 lower** (84 lower to 48 lower)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

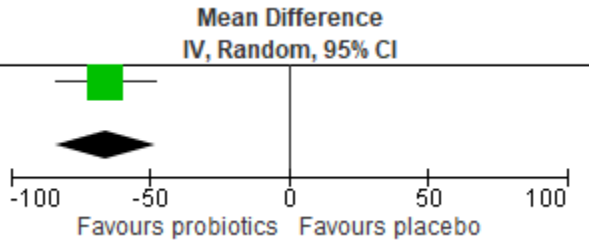
a. high risk of attrition and reporting bias

b. The 95% CI includes the potential for both benefit and harm.

Overall IBS-SSS Score at 5 months

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ishaque 2018	110	71.8	181	176	100	179	100.0%	-66.00 [-84.00, -48.00]
Total (95% CI)			**181**			**179**	**100.0%**	**-66.00 [-84.00, -48.00]**

Heterogeneity: Not applicable
Test for overall effect: Z = 7.19 (P < 0.00001)



Question: *Bifidobacterium bifidum* BGN4 + *Bifidobacterium animalis* subsp. *lactis* AD011 + *Lactobacillus acidophilus* AD031 + *Lactobacillus casei* IBS041 compared to placebo for adults with IBS (6ai)

Bibliography: Hong 2009

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. bifidum* BGN4 + *B. animalis* subsp. *lactis* AD011 + *L. acidophilus* AD031 + *L. casei* IBS041	Placebo	Relative (95% CI)	Absolute (95% CI)		
Response Rate for Pain												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	23/36 (63.9%)	15/34 (44.1%)	**RR 1.45** (0.92 to 2.27)	**199 more per 1,000** (from 35 fewer to 560 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

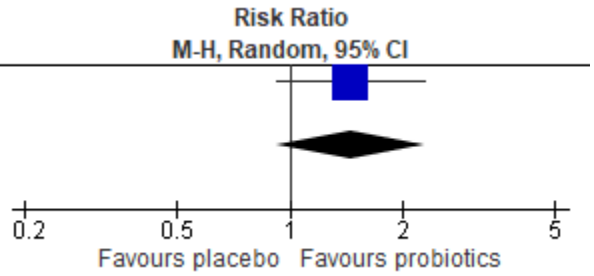
a. unclear risk of reporting and detection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Pain Response Rate

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hong 2009	23	36	15	34	100.0%	1.45 [0.92, 2.27]
Total (95% CI)		**36**		**34**	**100.0%**	**1.45 [0.92, 2.27]**
Total events	23		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)



Question: *Bifidobacterium longum* subsp. *longum* + *Lactobacillus acidophilus* compared to no probiotics for adults with IBS (6aj)

Bibliography: Cui 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *longum* + *L. acidophilus*	No probiotics	Relative (95% CI)	Absolute (95% CI)		
Frequency of effective response to abdominal pain												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	23/35 (65.7%)	6/20 (30.0%)	**RR 2.19** (1.08 to 4.46)	**357 more per 1,000** (from 24 more to 1,000 more)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear reporting of methods.

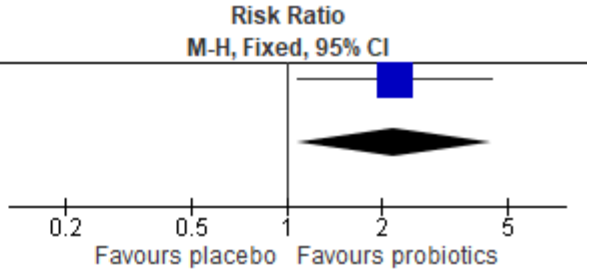
b. The 95% CI may not include a clinically meaningful difference. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Frequency of abdominal pain (measured by response in effectiveness)

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cui 2012	23	35	6	20	100.0%	2.19 [1.08, 4.46]
Total (95% CI)		**35**		**20**	**100.0%**	**2.19 [1.08, 4.46]**
Total events	23		6			

Heterogeneity: Not applicable

Test for overall effect: Z = 2.16 (P = 0.03)



Question: *Clostridium butyricum* compared to no probiotics for adults with IBS (6ak)

Bibliography: Sun 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*C. butyricum*	No probiotics	Relative (95% CI)	Absolute (95% CI)		
IBS symptoms (assessed at 4 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	85	81	-	MD **23.20 lower** (44.06 lower to 2.34 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	85	81	-	MD **2.47 higher** (1.81 lower to 6.75 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

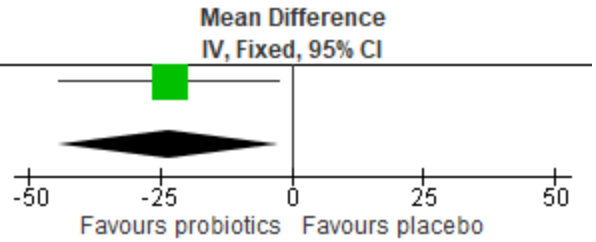
a. Serious concerns with randomization and allocation concealment.

b. The 95% CI may not include a clinically meaningful difference. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

IBS symptoms (lower = better; week 4)

Study or Subgroup	Probiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sun 2018	166.4	66.56	85	189.6	70.36	81	100.0%	-23.20 [-44.06, -2.34]
Total (95% CI)			**85**			**81**	**100.0%**	**-23.20 [-44.06, -2.34]**

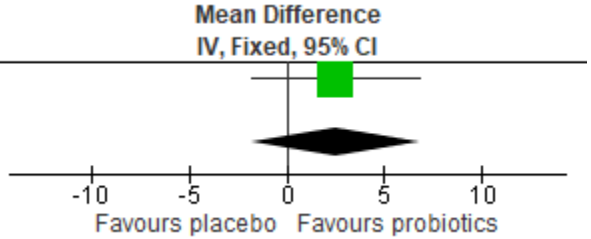
Heterogeneity: Not applicable
Test for overall effect: Z = 2.18 (P = 0.03)



Quality of life (higher = better; week 4)

Study or Subgroup	Probiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sun 2018	88.51	14.4	85	86.04	13.74	81	100.0%	2.47 [-1.81, 6.75]
Total (95% CI)			**85**			**81**	**100.0%**	**2.47 [-1.81, 6.75]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)



Question: *Streptococcus salivarius* subsp. *thermophilus* MG510 + *Lactobacillus plantarum* LRCC5193 compared to no probiotics for adults with IBS (6al)

Bibliography: Yoon 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. salivarius* subsp. *thermophilus* MG510 + *L. plantarum* LRCC5193	No probiotics	Relative (95% CI)	Absolute (95% CI)		
Stool consistency assessed with BSS												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	88	83	-	MD **0.6 higher** (0.27 higher to 0.93 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (measured at 4 weeks)												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	88	83	-	MD **2.1 lower** (4.65 lower to 0.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

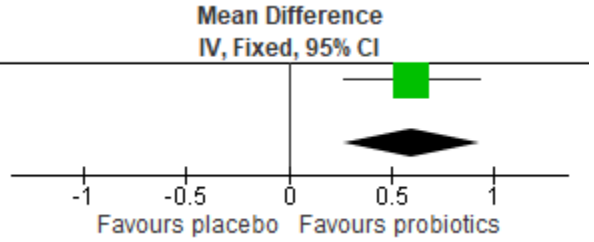
a. Serious concerns with loss to follow-up.

b. The 95% CI may not include a clinically meaningful difference. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Stool consistency assessed with BSS

	Probiotics			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Yoon 2018	3.7	1.1	88	3.1	1.1	83	100.0%	0.60 [0.27, 0.93]
Total (95% CI)			**88**			**83**	**100.0%**	**0.60 [0.27, 0.93]**

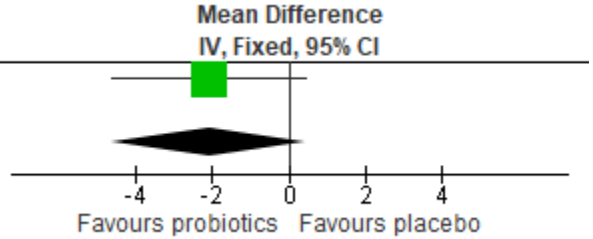
Heterogeneity: Not applicable
Test for overall effect: Z = 3.56 (P = 0.0004)



Quality of life (lower = better)

	Probiotics			Placebo				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Yoon 2018	10.2	9	88	12.3	8	83	100.0%	-2.10 [-4.65, 0.45]
Total (95% CI)			**88**			**83**	**100.0%**	**-2.10 [-4.65, 0.45]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)



Question: *Bacillus coagulans* Unique IS2 compared to no probiotics for children with IBS (6am)

Bibliography: Sudha 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. coagulans* Unique IS2	No probiotics	Relative (95% CI)	Absolute (95% CI)		
Abdominal pain intensity (assessed with: higher score indicates greater reduction in pain)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	72	69	-	MD **3.39 higher** (2.99 higher to 3.79 higher)	⨁⨁◯◯ LOW	CRITICAL
Abdominal discomfort												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	72	69	-	MD **1.9 lower** (2.24 lower to 1.56 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

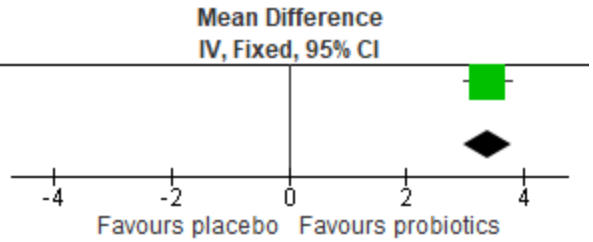
Explanations

a. The 95% CI may not include a clinically meaningful difference. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Reduction in pain intensity (8 weeks)

Study or Subgroup	Probiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sudha 2018	7.62	0.98	72	4.23	1.4	69	100.0%	3.39 [2.99, 3.79]
Total (95% CI)			**72**			**69**	**100.0%**	**3.39 [2.99, 3.79]**

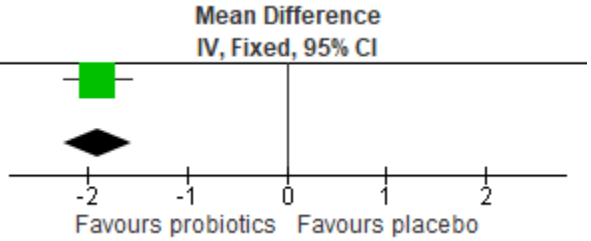
Heterogeneity: Not applicable
Test for overall effect: Z = 16.59 (P < 0.00001)



Abdominal discomfort (lower = better; 8 weeks)

Study or Subgroup	Probiotics Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Sudha 2018	0.5	0.82	72	2.4	1.19	69	100.0%	-1.90 [-2.24, -1.56]
Total (95% CI)			**72**			**69**	**100.0%**	**-1.90 [-2.24, -1.56]**

Heterogeneity: Not applicable
Test for overall effect: Z = 10.99 (P < 0.00001)



Question: *Lactobacillus acidophilus* + *Lactobacillus rhamnosus* + *Bifidobacterium breve* + *Bifidobacterium animalis* subsp. *lactis* + *Bifidobacterium longum* subsp. *longum* + *Streptococcus salivarius* subsp. *thermophilus* compared to no probiotics for adults with IBS (6an)

Bibliography: Yoon 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* + *L. rhamnosus* + *B. breve* + *B. animalis* subsp. *lactis* + *B. longum* subsp. *longum* + *S. salivarius* subsp. *thermophilus*	No probiotics	Relative (95% CI)	Absolute (95% CI)		
Adequate symptom relief												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	29/39 (74.4%)	26/42 (61.9%)	**RR 1.20** (0.89 to 1.62)	**124 more per 1,000** (from 68 fewer to 384 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Serious concerns from loss to follow-up and selective reporting.

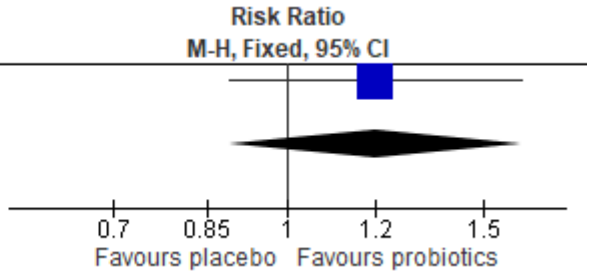
b. The 95% CI may not include a clinically meaningful difference. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Adequate symptom relief

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Yoon 2015	29	39	26	42	100.0%	1.20 [0.89, 1.62]
Total (95% CI)		**39**		**42**	**100.0%**	**1.20 [0.89, 1.62]**
Total events	29		26			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.20 (P = 0.23)



Question: *Bifidobacterium animalis* subsp. *lactis* Bb12 + *Lactobacillus acidophilus* LA-5 + *Lactobacillus delbrueckii* subsp. *bulgaricus* LBY-27 + *Streptococcus salivarius* subsp. *thermophilus* STY-31 compared to no probiotics for adults with IBS (6ao)

Bibliography: Jafari 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. animalis* subsp. *lactis* Bb12 + *L. acidophilus* LA-5 + *L. delbrueckii* subsp. *bulgaricus* LBY-27 + *S. salivarius* subsp. *thermophilus* STY-31	No probiotics	Relative (95% CI)	Absolute (95% CI)		
Mild-to-moderate degree of GI symptoms												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	6/54 (11.1%)	8/54 (14.8%)	**RR 0.75** (0.28 to 2.02)	**37 fewer per 1,000** (from 107 fewer to 151 more)	⊕⊕◯◯ LOW	CRITICAL
Relief of general symptoms												
1	randomised trials	not serious	not serious	not serious	very serious [b]	none	46/54 (85.2%)	25/54 (46.3%)	**RR 1.84** (1.35 to 2.50)	**389 more per 1,000** (from 162 more to 694 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

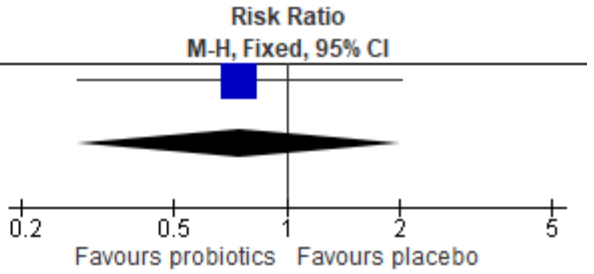
a. The 95% CI includes the potential for benefits and harms.

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Increase in mild-to-moderate degree of GI symptoms

	Probiotics		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Jafari 2014	6	54	8	54	100.0%	0.75 [0.28, 2.02]
Total (95% CI)		**54**		**54**	**100.0%**	**0.75 [0.28, 2.02]**
Total events	6		8			

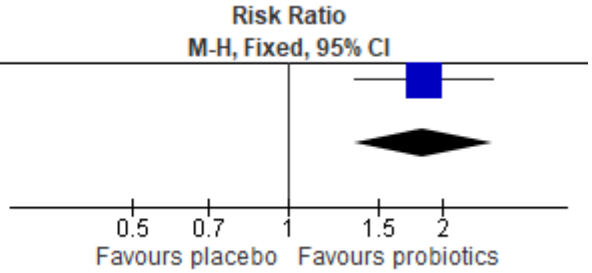
Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)



Relief of general symptoms

	Probiotics		Placebo			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Jafari 2014	46	54	25	54	100.0%	1.84 [1.35, 2.50]
Total (95% CI)		**54**		**54**	**100.0%**	**1.84 [1.35, 2.50]**
Total events	46		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.88 (P = 0.0001)



Question: *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium bifidum* + *Bifidobacterium animalis* subsp. *lactis* + *Lactobacillus acidophilus* + *Lactobacillus rhamnosus* + *Streptococcus salivarius* subsp. *thermophilus* compared to no probiotics for adults with IBS (6ap)

Bibliography: Yoon 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *longum* + *B. bifidum* + *B. animalis* subsp. *lactis* + *L. acidophilus* + *L. rhamnosus* + *S. salivarius* subsp. *thermophilus*	No probiotics	Relative (95% CI)	Absolute (95% CI)		
Global relief of IBS symptoms												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	17/25 (68.0%)	9/24 (37.5%)	**RR 1.81** (1.01 to 3.25)	**304 more per 1,000** (from 4 more to 844 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

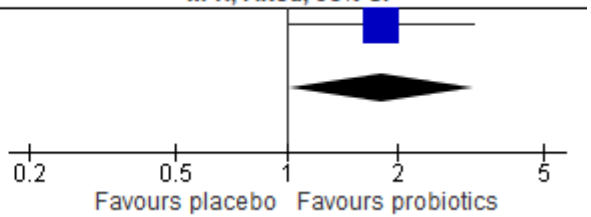
a. Serious concerns due to unclear methods for blinding and reporting.

b. The 95% CI may not include clinically meaningful benefits. Small sample suggests fragility in the estimate.

Global relief of IBS symptoms

	Probiotics		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Yoon 2014	17	25	9	24	100.0%	1.81 [1.01, 3.25]	
Total (95% CI)		**25**		**24**	**100.0%**	**1.81 [1.01, 3.25]**	
Total events	17		9				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)



Question: *Bifidobacterium animalis* subsp. *lactis* W52 + *Lactobacillus casei* W56 + *Lactobacillus salivarius* W57 + *Lactococcus lactis* W58 + *Lactobacillus acidophilus* ATCC 700396 + *Lactobacillus rhamnosus* W71 compared to placebo for adults with IBS (6aq)

Bibliography: Ludidi 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. animalis* subsp. *lactis* W52 + *L. casei* W56 + *L. salivarius* W57 + *L. lactis* W58 + *L. acidophilus* ATCC 700396 + *L. rhamnosus* W71	Placebo	Relative (95% CI)	Absolute (95% CI)		
Number of hypersensitive patients(6 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	16/21 (76.2%)	14/19 (73.7%)	**RR 1.03** (0.72 to 1.48)	**22 more per 1,000** (from 206 fewer to 354 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

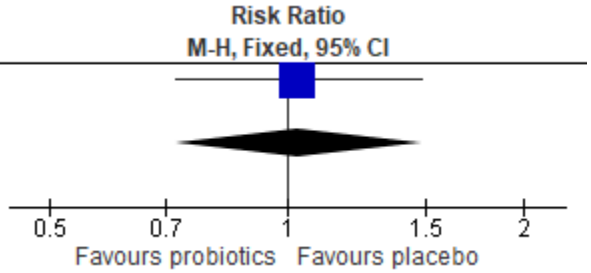
Explanations

a. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Number of hypersensitive patients (6 weeks)

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ludidi 2014	16	21	14	19	100.0%	1.03 [0.72, 1.48]
Total (95% CI)		**21**		**19**	**100.0%**	**1.03 [0.72, 1.48]**
Total events	16		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)



Question: *Lactobacillus rhamnosus* ATCC 53103 and LC705 + *Bifidobacterium breve* Bb99 + *Propionibacterium freudenreichii* subsp. *shermanii* JS compared to placebo for adults with IBS (6ar)

Bibliography: Kajander 2005

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103 + *L. rhamnosus* LC705 + *B. breve* Bb99 + *P. freudenreichii* subsp. *shermanii* JS	Placebo	Relative (95% CI)	Absolute (95% CI)		
Symptom score (abdominal pain, distension, flatulence, borborygmi) (assessed with: difference from baseline)												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	52	51	-	SMD **7.7 SD lower** (13.9 lower to 1.6 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **SMD:** Standardized mean difference

Explanations

a. The 95% CI includes values that may not be clinically meaningful. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Question: *Lactobacillus rhamnosus* ATCC 53103 compared to no probiotics for children with IBS (6as)

Bibliography: Gawronska 2007

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	No probiotics	Relative (95% CI)	Absolute (95% CI)		
Treatment success												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	6/18 (33.3%)	1/19 (5.3%)	**RR 6.33** (0.84 to 47.57)	**281 more per 1,000** (from 8 fewer to 1,000 more)	⨁⨁◯◯ LOW	CRITICAL
Improvement in symptoms												
1	randomised trials	not serious	not serious	not serious	very serious [a]	none	10/18 (55.6%)	6/19 (31.6%)	**RR 1.76** (0.81 to 3.84)	**240 more per 1,000** (from 60 fewer to 897 more)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

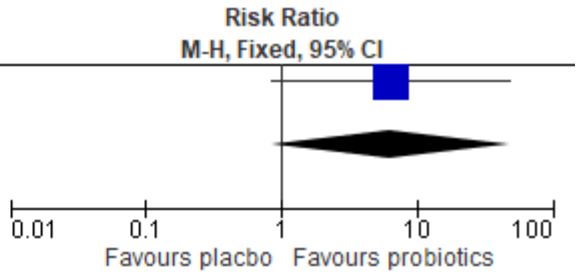
Explanations

a. The 95% CI includes the potential for both appreciable benefit as well as appreciable harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Treatment success

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gawronska 2007	6	18	1	19	100.0%	6.33 [0.84, 47.57]
Total (95% CI)		**18**		**19**	**100.0%**	**6.33 [0.84, 47.57]**
Total events	6		1			

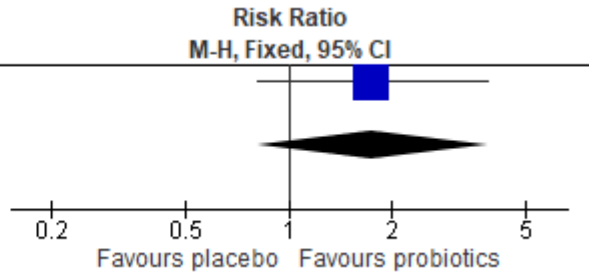
Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)



Improvement in symptoms

Study or Subgroup	Probiotics Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gawronska 2007	10	18	6	19	100.0%	1.76 [0.81, 3.84]
Total (95% CI)		**18**		**19**	**100.0%**	**1.76 [0.81, 3.84]**
Total events	10		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)



Appendix 7: Should probiotics be used to reduce the duration or severity of diarrhea in children with acute infectious gastroenteritis?

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Question: Probiotics compared to placebo and/or standard care alone for treatment of acute infectious diarrhea in children

Bibliography: Allen 2010 + 23 studies

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	probiotics	placebo and/or standard care alone	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
58	randomised trials	serious [a,b]	serious [c]	not serious	not serious	none	4662	4556	-	mean 21.91 lower (27.64 lower to 16.17 lower)	⊕⊕◯◯ LOW	CRITICAL
Diarrhea Lasting > 4 days												
29	randomised trials	serious [a,b]	serious [c]	not serious	not serious	none	312/1607 (19.4%)	615/1532 (40.1%)	**RR 0.50** (0.40 to 0.62)	**201 fewer per 1,000** (from 241 fewer to 153 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mean Stool Frequency on Day 2												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	probiotics	placebo and/or standard care alone	Relative (95% CI)	Absolute (95% CI)		
20	randomised trials	serious [a,b]	serious [c]	not serious	not serious	none	1388	1363	-	MD 0.8 lower (1.14 lower to 0.045 lower)	⊕⊕◯◯ LOW	CRITICAL
Diarrhea Lasting > 3 days												
30	randomised trials	serious [a,b]	serious [c]	not serious	not serious	none	558/1516 (36.8%)	888/1506 (59.0%)	**RR 0.62** (0.56 to 0.70)	**224 fewer per 1,000** (from 259 fewer to 177 fewer)	⊕⊕◯◯ LOW	CRITICAL
Mean Stool Frequency on Day 3												
14	randomised trials	serious [a,b]	serious [c]	not serious	not serious	none	1194	1173	-	MD 0.63 lower (1.18 lower to 0.07 lower)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

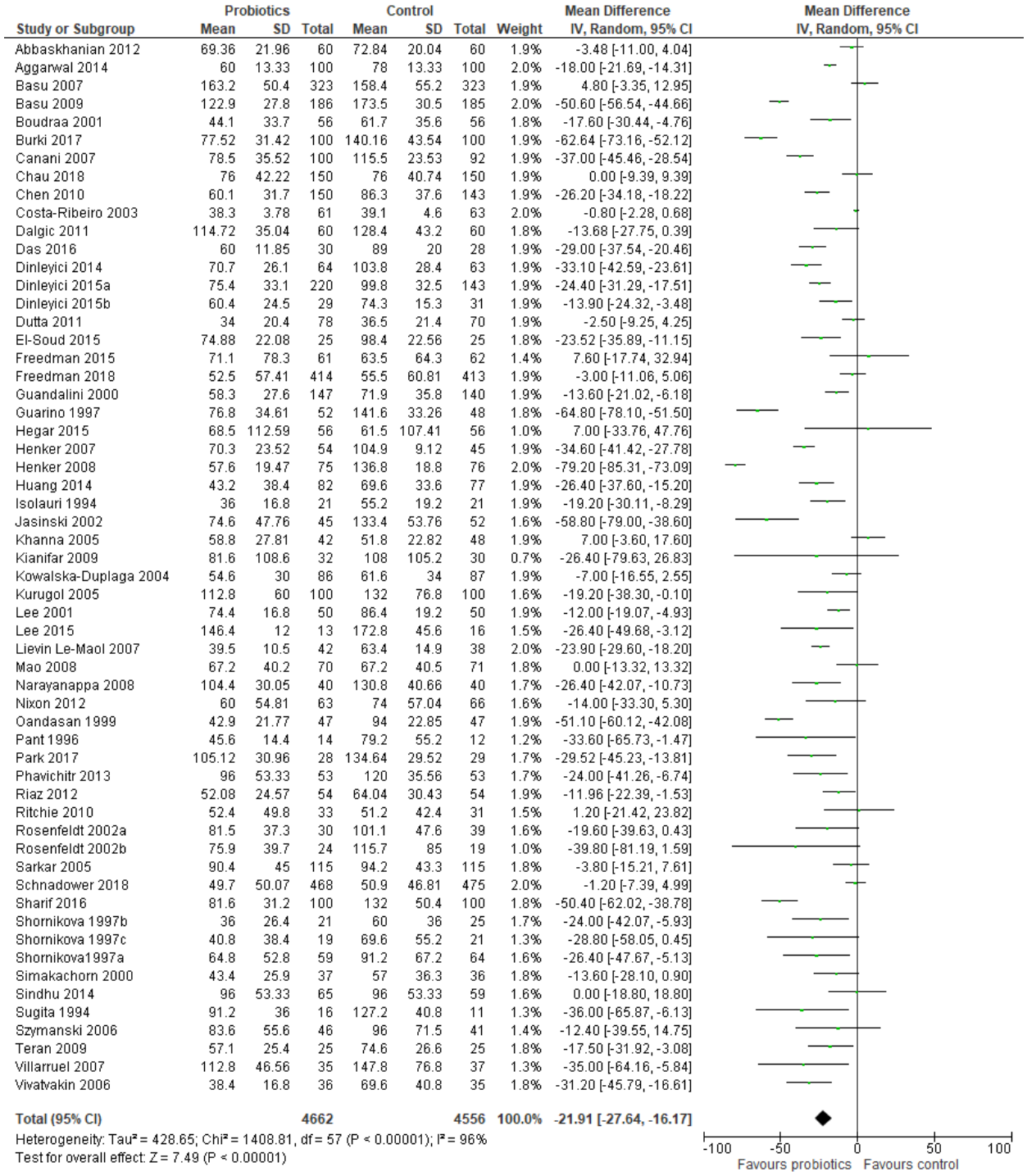
Explanations

a. Several studies with unclear sequence generation, allocation concealment, or open with no blinding (some without placebo)

b. Several studies with follow up < 90%

c. Significant heterogeneity across studies due to difference in study design, probiotic strains used, single vs. combination of probiotics, age of participants, and setting

Mean Duration of Diarrhea:

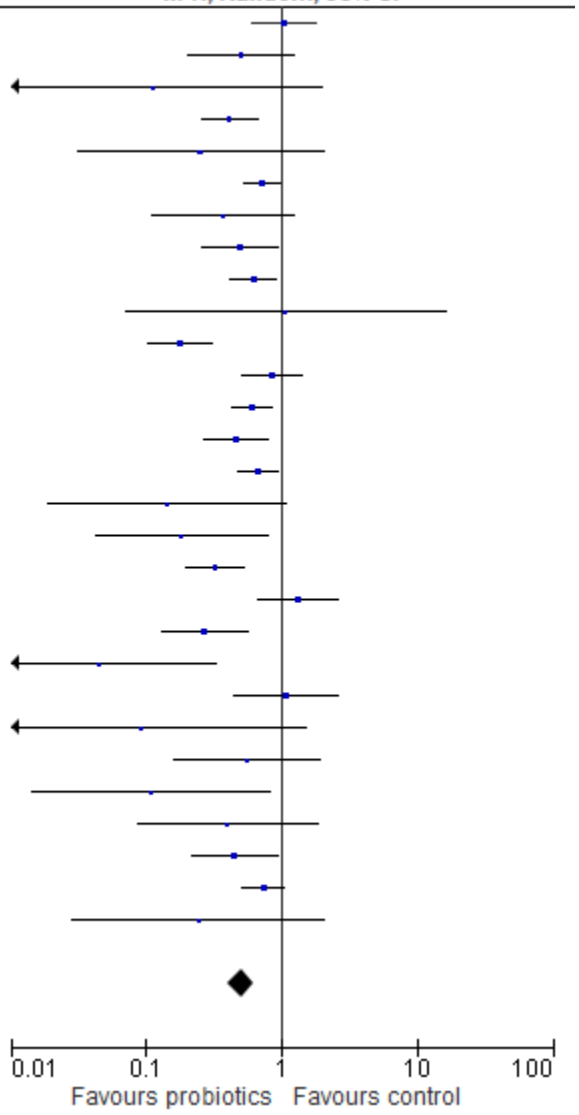

Probiotics
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Abbaskhanian 2012 69.36 21.96 60 72.84 20.04 60 1.9% -3.48 [-11.00, 4.04]
Aggarwal 2014 60 13.33 100 78 13.33 100 2.0% -18.00 [-21.69, -14.31]
Basu 2007 163.2 50.4 323 158.4 55.2 323 1.9% 4.80 [-3.35, 12.95]
Basu 2009 122.9 27.8 186 173.5 30.5 185 2.0% -50.60 [-56.54, -44.66]
Boudraa 2001 44.1 33.7 56 61.7 35.6 56 1.8% -17.60 [-30.44, -4.76]
Burki 2017 77.52 31.42 100 140.16 43.54 100 1.9% -62.64 [-73.16, -52.12]
Canani 2007 78.5 35.52 100 115.5 23.53 92 1.9% -37.00 [-45.46, -28.54]
Chau 2018 76 42.22 150 76 40.74 150 1.9% 0.00 [-9.39, 9.39]
Chen 2010 60.1 31.7 150 86.3 37.6 143 1.9% -26.20 [-34.18, -18.22]
Costa-Ribeiro 2003 38.3 3.78 61 39.1 4.6 63 2.0% -0.80 [-2.28, 0.68]
Dalgic 2011 114.72 35.04 60 128.4 43.2 60 1.8% -13.68 [-27.75, 0.39]
Das 2016 60 11.85 30 89 20 28 1.9% -29.00 [-37.54, -20.46]
Dinleyici 2014 70.7 26.1 64 103.8 28.4 63 1.9% -33.10 [-42.59, -23.61]
Dinleyici 2015a 75.4 33.1 220 99.8 32.5 143 1.9% -24.40 [-31.29, -17.51]
Dinleyici 2015b 60.4 24.5 29 74.3 15.3 31 1.9% -13.90 [-24.32, -3.48]
Dutta 2011 34 20.4 78 36.5 21.4 70 1.9% -2.50 [-9.25, 4.25]
El-Soud 2015 74.88 22.08 25 98.4 22.56 25 1.8% -23.52 [-35.89, -11.15]
Freedman 2015 71.1 78.3 61 63.5 64.3 62 1.4% 7.60 [-17.74, 32.94]
Freedman 2018 52.5 57.41 414 55.5 60.81 413 1.9% -3.00 [-11.06, 5.06]
Guandalini 2000 58.3 27.6 147 71.9 35.8 140 1.9% -13.60 [-21.02, -6.18]
Guarino 1997 76.8 34.61 52 141.6 33.26 48 1.8% -64.80 [-78.10, -51.50]
Hegar 2015 68.5 112.59 56 61.5 107.41 56 1.0% 7.00 [-33.76, 47.76]
Henker 2007 70.3 23.52 54 104.9 9.12 45 1.9% -34.60 [-41.42, -27.78]
Henker 2008 57.6 19.47 75 136.8 18.8 76 2.0% -79.20 [-85.31, -73.09]
Huang 2014 43.2 38.4 82 69.6 33.6 77 1.9% -26.40 [-37.60, -15.20]
Isolauri 1994 36 16.8 21 55.2 19.2 21 1.9% -19.20 [-30.11, -8.29]
Jasinski 2002 74.6 47.76 45 133.4 53.76 52 1.6% -58.80 [-79.00, -38.60]
Khanna 2005 58.8 27.81 42 51.8 22.82 48 1.9% 7.00 [-3.60, 17.60]
Kianifar 2009 81.6 108.6 32 108 105.2 30 0.7% -26.40 [-79.63, 26.83]
Kowalska-Duplaga 2004 54.6 30 86 61.6 34 87 1.9% -7.00 [-16.55, 2.55]
Kurugol 2005 112.8 60 100 132 76.8 100 1.6% -19.20 [-38.30, -0.10]
Lee 2001 74.4 16.8 50 86.4 19.2 50 1.9% -12.00 [-19.07, -4.93]
Lee 2015 146.4 12 13 172.8 45.6 16 1.5% -26.40 [-49.68, -3.12]
Lievin Le-Maol 2007 39.5 10.5 42 63.4 14.9 38 2.0% -23.90 [-29.60, -18.20]
Mao 2008 67.2 40.2 70 67.2 40.5 71 1.8% 0.00 [-13.32, 13.32]
Narayanappa 2008 104.4 30.05 40 130.8 40.66 40 1.7% -26.40 [-42.07, -10.73]
Nixon 2012 60 54.81 63 74 57.04 66 1.6% -14.00 [-33.30, 5.30]
Oandasan 1999 42.9 21.77 47 94 22.85 47 1.9% -51.10 [-60.12, -42.08]
Pant 1996 45.6 14.4 14 79.2 55.2 12 1.2% -33.60 [-65.73, -1.47]
Park 2017 105.12 30.96 28 134.64 29.52 29 1.7% -29.52 [-45.23, -13.81]
Phavichitr 2013 96 53.33 53 120 35.56 53 1.7% -24.00 [-41.26, -6.74]
Riaz 2012 52.08 24.57 54 64.04 30.43 54 1.9% -11.96 [-22.39, -1.53]
Ritchie 2010 52.4 49.8 33 51.2 42.4 31 1.5% 1.20 [-21.42, 23.82]
Rosenfeldt 2002a 81.5 37.3 30 101.1 47.6 39 1.6% -19.60 [-39.63, 0.43]
Rosenfeldt 2002b 75.9 39.7 24 115.7 85 19 1.0% -39.80 [-81.19, 1.59]
Sarkar 2005 90.4 45 115 94.2 43.3 115 1.8% -3.80 [-15.21, 7.61]
Schnadower 2018 49.7 50.07 468 50.9 46.81 475 2.0% -1.20 [-7.39, 4.99]
Sharif 2016 81.6 31.2 100 132 50.4 100 1.8% -50.40 [-62.02, -38.78]
Shornikova 1997b 36 26.4 21 60 36 25 1.7% -24.00 [-42.07, -5.93]
Shornikova 1997c 40.8 38.4 19 69.6 55.2 21 1.3% -28.80 [-58.05, 0.45]
Shornikova1997a 64.8 52.8 59 91.2 67.2 64 1.6% -26.40 [-47.67, -5.13]
Simakachorn 2000 43.4 25.9 37 57 36.3 36 1.8% -13.60 [-28.10, 0.90]
Sindhu 2014 96 53.33 65 96 53.33 59 1.6% 0.00 [-18.80, 18.80]
Sugita 1994 91.2 36 16 127.2 40.8 11 1.3% -36.00 [-65.87, -6.13]
Szymanski 2006 83.6 55.6 46 96 71.5 41 1.4% -12.40 [-39.55, 14.75]
Teran 2009 57.1 25.4 25 74.6 26.6 25 1.8% -17.50 [-31.92, -3.08]
Villarruel 2007 112.8 46.56 35 147.8 76.8 37 1.3% -35.00 [-64.16, -5.84]
Vivatvakin 2006 38.4 16.8 36 69.6 40.8 35 1.8% -31.20 [-45.79, -16.61]
Total (95% CI) 4662 4556 100.0% -21.91 [-27.64, -16.17]
Heterogeneity: Tau² = 428.65; Chi² = 1408.81, df = 57 (P < 0.00001); I² = 96%
Test for overall effect: Z = 7.49 (P < 0.00001)
-100 -50 0 50 100
Favours probiotics Favours control

Proportion with Diarrhea ≥ 4 days:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhatnagar 1998	17	47	17	49	5.1%	1.04 [0.61, 1.79]
Boudraa 2001	6	56	12	56	3.2%	0.50 [0.20, 1.24]
Caragüe-Orendain	0	35	4	35	0.5%	0.11 [0.01, 1.99]
Cetina-Sauri 1994	16	65	39	65	5.5%	0.41 [0.26, 0.66]
Chapoy 1985	1	19	4	19	0.9%	0.25 [0.03, 2.04]
Costa-Ribeiro 2003	31	61	45	63	6.6%	0.71 [0.53, 0.95]
D'Apuzzo 1982	3	21	7	18	2.3%	0.37 [0.11, 1.22]
Dinleyici 2014	11	64	22	63	4.5%	0.49 [0.26, 0.93]
Dinleyici 2015a	37	220	39	143	6.0%	0.62 [0.41, 0.92]
Dinleyici 2015b	1	29	1	31	0.6%	1.07 [0.07, 16.31]
Dubey 2008	12	113	67	111	5.0%	0.18 [0.10, 0.31]
Francavilla 2012	15	35	17	34	5.3%	0.86 [0.52, 1.43]
Guandalini 2000	37	147	58	140	6.3%	0.61 [0.43, 0.85]
Henker 2007	13	55	30	58	5.1%	0.46 [0.27, 0.78]
Henker 2008	30	75	46	76	6.4%	0.66 [0.47, 0.92]
Hernandez 1998	1	25	7	25	1.0%	0.14 [0.02, 1.08]
Htwe 2008	2	50	11	50	1.7%	0.18 [0.04, 0.78]
Jasinski 2002	12	45	43	52	5.3%	0.32 [0.20, 0.53]
Kowalska-Duplaga 1999	13	33	9	30	4.2%	1.31 [0.66, 2.62]
Kurugol 2005	8	100	30	100	4.0%	0.27 [0.13, 0.55]
Oandasan 1999	1	47	22	47	1.0%	0.05 [0.01, 0.32]
Ritchie 2010	8	33	7	31	3.3%	1.07 [0.44, 2.61]
Shornikova 1997b	0	21	6	25	0.5%	0.09 [0.01, 1.52]
Shornikova 1997c	3	19	6	21	2.1%	0.55 [0.16, 1.91]
Simakachorn 2000	1	37	9	36	1.0%	0.11 [0.01, 0.81]
Teran 2009	2	25	5	25	1.5%	0.40 [0.09, 1.87]
Urganci 2001	8	50	18	50	4.0%	0.44 [0.21, 0.93]
Villarruel 2007	22	44	30	44	6.2%	0.73 [0.51, 1.05]
Vivatvakin 2006	1	36	4	35	0.9%	0.24 [0.03, 2.07]
Total (95% CI)		**1607**		**1532**	**100.0%**	**0.50 [0.40, 0.62]**
Total events	312		615			

Heterogeneity: Tau² = 0.16; Chi² = 73.84, df = 28 (P < 0.00001); I² = 62%

Test for overall effect: Z = 6.36 (P < 0.00001)



Question: *Saccharomyces boulardii* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7a)

Bibliography: Burki 2017, Cetina-Sauri 1994, Chapoy 1985, Das 2016, Dinleyici 2015, Erdogan 2012, Hernandez 1998, Htwe 2008, Kurugol 2005, Riaz 2012, Sharif 2016, Urganci 2001, Villarruel 2007, Grandy 2010

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. boulardii*	placebo and/or standard care	Relative (95% CI)	Absolute (95% CI)		
Diarrhea Lasting > 4 days												
8	randomised trials	very serious [a]	serious [b]	not serious	serious [c]	none	95/501 (19.0%)	169/425 (39.8%)	**RR 0.45** (0.32 to 0.64)	**219 fewer per 1,000** (from 270 fewer to 143 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Duration of Diarrhea												
10	randomised trials	very serious [a]	serious [d]	not serious	serious [e]	none	745	667647	-	mean 28.77lower (40.35 lower to 17.18 lower)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Most studies have at least one source of high risk of bias including lack of blinding (open study), sequence generation, or allocation concealment

b. Heterogeneity among studies (I^2 = 57%) due to differences in study design, participant age, and setting

c. CI crossing 1 in several studies including study with weight of 25%

d. Heterogeneity among studies (I^2 = 89%) due to differences in study design, participant age, and setting

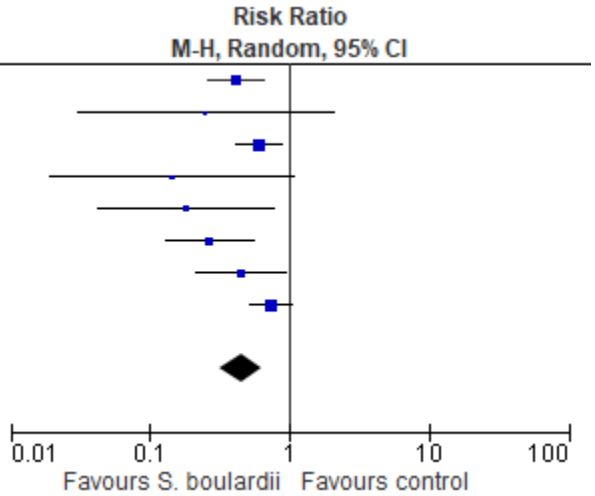
e. The 95% CI includes the potential for both benefit and harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Duration ≥ 4 days

Study or Subgroup	S. boulardii Events	S. boulardii Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Cetina-Sauri 1994	16	65	39	65	19.5%	0.41 [0.26, 0.66]
Chapoy 1985	1	19	4	19	2.5%	0.25 [0.03, 2.04]
Dinleyici 2015a	37	148	30	72	22.0%	0.60 [0.41, 0.89]
Hernandez 1998	1	25	7	25	2.6%	0.14 [0.02, 1.08]
Htwe 2008	2	50	11	50	4.7%	0.18 [0.04, 0.78]
Kurugol 2005	8	100	30	100	12.9%	0.27 [0.13, 0.55]
Urganci 2001	8	50	18	50	12.8%	0.44 [0.21, 0.93]
Villarruel 2007	22	44	30	44	23.0%	0.73 [0.51, 1.05]
Total (95% CI)		**501**		**425**	**100.0%**	**0.45 [0.32, 0.64]**
Total events	95		169			

Heterogeneity: Tau² = 0.10; Chi² = 13.94, df = 7 (P = 0.05); I² = 50%

Test for overall effect: Z = 4.55 (P < 0.00001)

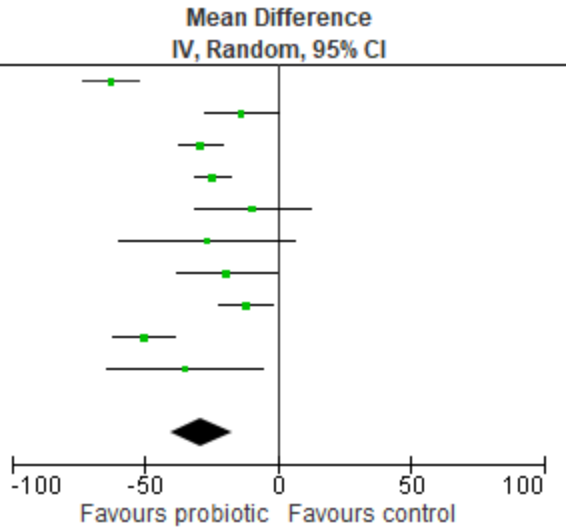


Mean Duration of Diarrhea:

Study or Subgroup	S. boulardii Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Burki 2017	77.52	31.42	100	140.16	43.54	100	11.4%	-62.64 [-73.16, -52.12]
Dalgic 2011	114.72	35.04	60	128.4	43.2	60	10.6%	-13.68 [-27.75, 0.39]
Das 2016	60	11.85	30	89	20	28	11.8%	-29.00 [-37.54, -20.46]
Dinleyici 2015a	75.4	33.1	220	99.8	32.5	143	12.1%	-24.40 [-31.29, -17.51]
Erdogan 2012	158.4	40.8	25	168	38.4	25	8.7%	-9.60 [-31.56, 12.36]
Grandy 2010	58	30.37	21	84.5	69.63	20	6.2%	-26.50 [-59.67, 6.67]
Kurugol 2005	112.8	60	100	132	76.8	100	9.4%	-19.20 [-38.30, -0.10]
Riaz 2012	52.08	24.57	54	64.04	30.43	54	11.5%	-11.96 [-22.39, -1.53]
Sharif 2016	81.6	31.2	100	132	50.4	100	11.2%	-50.40 [-62.02, -38.78]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	7.0%	-35.00 [-64.16, -5.84]
Total (95% CI)			**745**			**667**	**100.0%**	**-28.77 [-40.35, -17.18]**

Heterogeneity: Tau² = 276.43; Chi² = 72.74, df = 9 (P < 0.00001); I² = 88%

Test for overall effect: Z = 4.87 (P < 0.00001)



Question: *Lactobacillus rhamnosus* ATCC 53103 compared to placebo in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7b)

Bibliography: Aggarwal 2014, Basu 2007, Basu 2009, Canani 2007, Costa-Ribeiro 2003 , Guandalini 2000, Guarino 1997, Isolauri 1994, Jasinski 2002, Nixon 2012, Pant 1996, Raza 1995, Ritchie 2010, Schnadower 2018, Shornikova 1997a, Sindhu 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
14	randomised trials	serious [a]	serious [b]	not serious	not serious	none	1672	1672	-	mean 23.13 lower (33.94 lower to 12.33 lower)	⨁⨁◯◯ LOW	CRITICAL
Severe Infection (According to Vesikari Scale)												
2	randomised trials	serious [c]	not serious	not serious	serious [d]	none	74/533 (13.9%)	75/534 (14.0%)	**RR 0.98** (0.73 to 1.32)	**3 fewer per 1,000** (from 38 fewer to 45 more)	⨁⨁◯◯ LOW	CRITICAL
Hospitalization												
3	randomised trials	serious [c]	not serious	not serious	serious [d]	none	31/633 (4.9%)	32/626 (5.1%)	**RR 0.96** (0.60 to 1.54)	**2 fewer per 1,000** (from 20 fewer to 28 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* ATCC 53103	placebo	Relative (95% CI)	Absolute (95% CI)		
Diarrhea > 4 days												
4	randomised trials	serious [a]	serious [b]	not serious	not serious	none	88/286 (30.8%)	153/286 (53.5%)	**RR 0.38** (0.27 to 0.54)	**332 fewer per 1,000** (from 391 fewer to 246 fewer)	⨁⨁◯◯ LOW	CRITICAL
Mean Stool Frequency Day 2												
6	randomised trials	serious [a]	serious [b]	not serious	not serious	none	675	660	-	mean 0.75 lower (1.13 lower to 0.37 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Several studies noted to have high risk of bias for either lack of blinding, low follow up rate, sequence generation, or allocation concealment

b. Significant heterogeneity among studies due to differences in study design, participant age, and setting

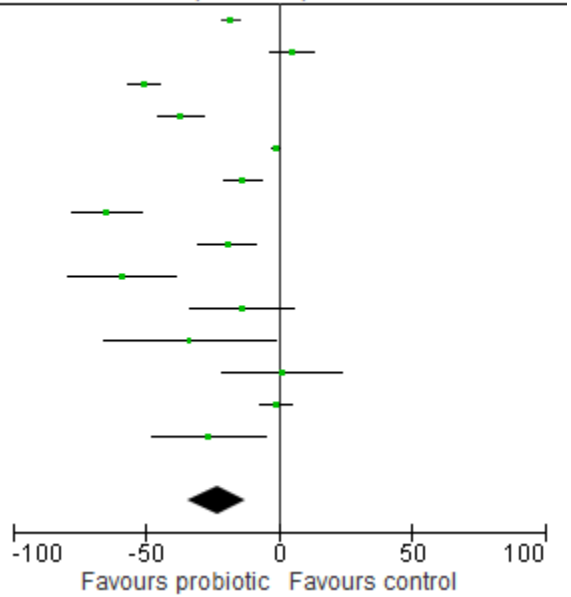
c. High risk of reporting bias with 1 study

d. The 95% CI includes the potential for both benefit and harm.

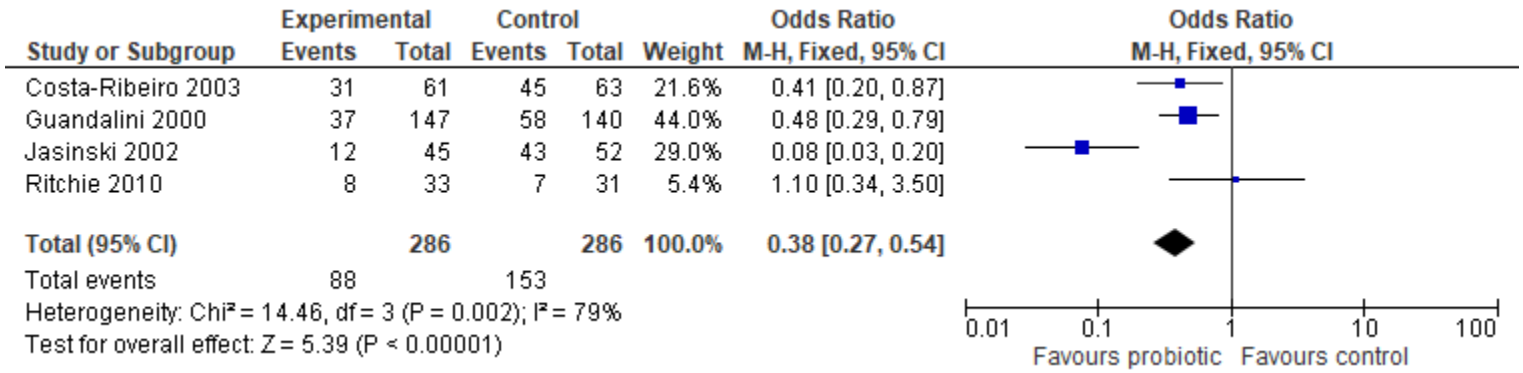
Mean Duration of Diarrhea:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aggarwal 2014	60	13.33	100	78	13.33	100	8.1%	-18.00 [-21.69, -14.31]
Basu 2007	163.2	50.4	323	158.4	55.2	323	7.8%	4.80 [-3.35, 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	8.0%	-50.60 [-56.54, -44.66]
Canani 2007	78.5	35.52	100	115.5	23.53	92	7.8%	-37.00 [-45.46, -28.54]
Costa-Ribeiro 2003	38.27	3.78	61	39.09	4.6	63	8.1%	-0.82 [-2.30, 0.66]
Guandalini 2000	58.3	27.6	147	71.9	35.8	140	7.8%	-13.60 [-21.02, -6.18]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	7.3%	-64.80 [-78.10, -51.50]
Isolauri 1994	36	16.8	21	55.2	19.2	21	7.5%	-19.20 [-30.11, -8.29]
Jasinki 2002	74.64	47.76	45	133.44	53.76	52	6.3%	-58.80 [-79.00, -38.60]
Nixon 2012	60	54.81	63	74	57.04	66	6.5%	-14.00 [-33.30, 5.30]
Pant 1996	45.6	14.4	14	79.2	55.2	12	4.7%	-33.60 [-65.73, -1.47]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	6.0%	1.20 [-21.42, 23.82]
Schnadower 2018	49.7	50.07	468	50.9	46.81	475	7.9%	-1.20 [-7.39, 4.99]
Shornikova1997a	64.8	52.8	59	91.2	67.2	64	6.2%	-26.40 [-47.67, -5.13]
Total (95% CI)			**1672**			**1672**	**100.0%**	**-23.13 [-33.94, -12.33]**

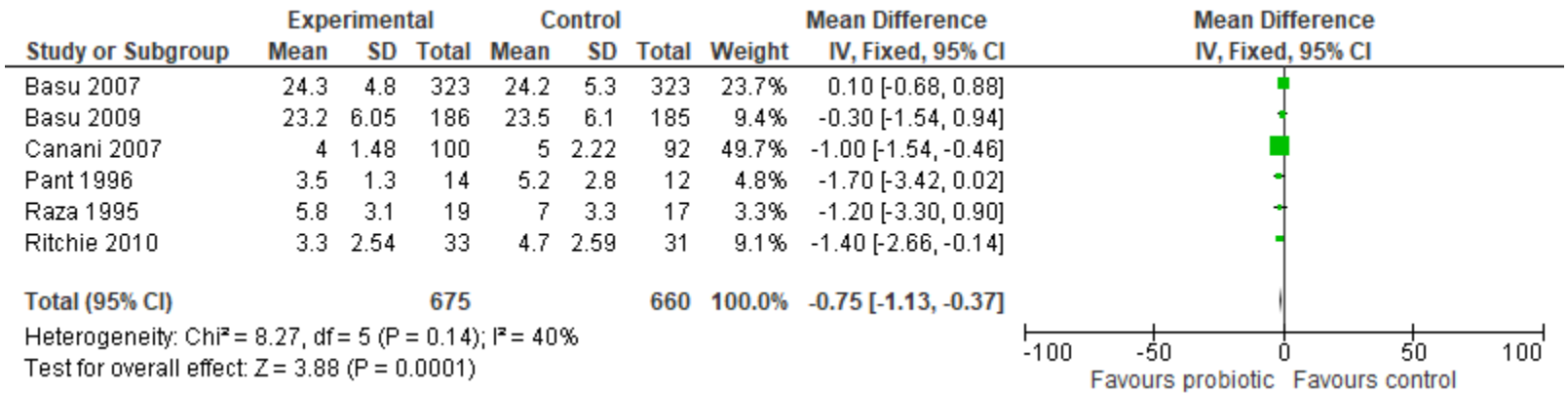
Heterogeneity: Tau² = 372.92; Chi² = 480.17, df = 13 (P < 0.00001); I² = 97%
Test for overall effect: Z = 4.20 (P < 0.0001)



Diarrhea ≥ 4 days



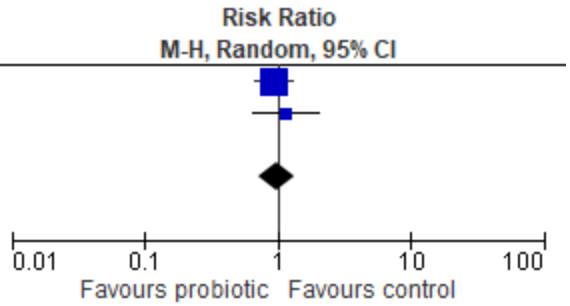
Mean Stool Frequency Day 2



Severe infection as per Vesikari scale:

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Schnadower 2018	55	468	60	475	74.0%	0.93 [0.66, 1.31]
Sindhu 2014	19	65	15	59	26.0%	1.15 [0.65, 2.05]
Total (95% CI)		**533**		**534**	**100.0%**	**0.98 [0.73, 1.32]**
Total events	74		75			

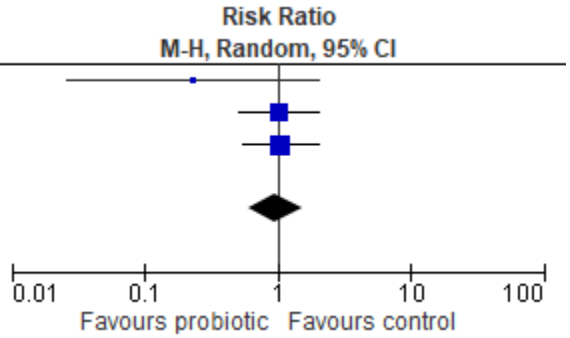
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)



Hospitalization:

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Canani 2007	1	100	4	92	4.6%	0.23 [0.03, 2.02]
Schnadower 2018	15	468	15	475	44.1%	1.01 [0.50, 2.05]
Sindhu 2014	15	65	13	59	51.2%	1.05 [0.54, 2.01]
Total (95% CI)		**633**		**626**	**100.0%**	**0.96 [0.60, 1.54]**
Total events	31		32			

Heterogeneity: Tau² = 0.00; Chi² = 1.78, df = 2 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)



Question: *Lactobacillus acidophilus* compared to placebo in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7c)

Bibliography: Boulloche 1994, Khanna 2005, Lievein Le-Maol 2007, Simakachorn 2000, Chau 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus*	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
4	randomised trials	serious [a]	serious [b]	not serious	serious [c]	none	271	272	-	mean 7.79 lower (23.85 lower to 8.28 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Diarrhea Lasting >3days												
4	randomised trials	serious [d]	not serious	not serious	serious [e]	none	22/159 (13.8%)	37/156 (23.7%)	**RR 0.59** (0.33 to 1.05)	**97 fewer per 1,000** (from 159 fewer to 12 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear or high risk of selection bias

b. Studies have different direction of effect, I2 92%

c. The 95% CI includes the potential for both benefit and harm.

d. Unclear or high risk of selection bias and/or performance bias

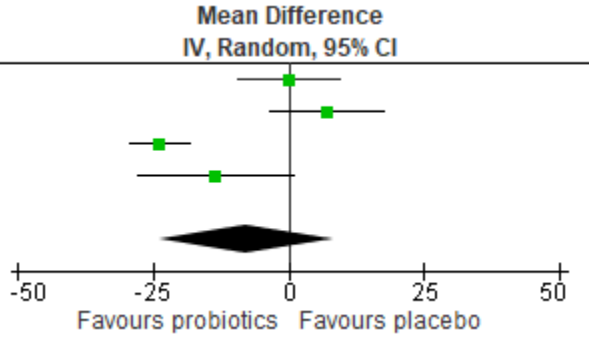
e. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Mean Duration of Diarrhea (Hours):

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Chau 2018	76	42.22	150	76	40.74	150	25.5%	0.00 [-9.39, 9.39]
Khanna 2005	58.8	27.81	42	51.8	22.82	48	24.9%	7.00 [-3.60, 17.60]
Lievin Le-Maol 2007	39.5	10.5	42	63.4	14.9	38	26.9%	-23.90 [-29.60, -18.20]
Simakachorn 2000	43.4	25.9	37	57	36.3	36	22.7%	-13.60 [-28.10, 0.90]
Total (95% CI)			**271**			**272**	**100.0%**	**-7.79 [-23.85, 8.28]**

Heterogeneity: Tau² = 240.88; Chi² = 35.06, df = 3 (P < 0.00001); I² = 91%

Test for overall effect: Z = 0.95 (P = 0.34)

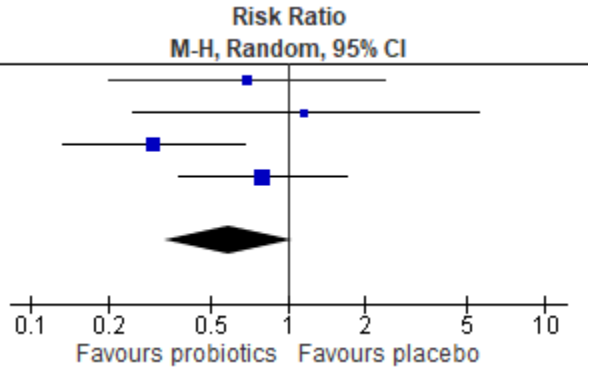


Diarrhea Lasting ≥ 3 days:

	Experimental		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Boulloche 1994	4	38	5	33	18.0%	0.69 [0.20, 2.38]
Khanna 2005	3	42	3	49	12.2%	1.17 [0.25, 5.48]
Lievin Le-Maol 2007	6	42	18	38	33.1%	0.30 [0.13, 0.68]
Simakachorn 2000	9	37	11	36	36.6%	0.80 [0.38, 1.69]
Total (95% CI)		**159**		**156**	**100.0%**	**0.59 [0.33, 1.05]**
Total events	22		37			

Heterogeneity: Tau² = 0.09; Chi² = 4.04, df = 3 (P = 0.26); I² = 26%

Test for overall effect: Z = 1.79 (P = 0.07)



Question: *Lactobacillus acidophilus* + *Bifidobacterium bifidum* compared to placebo for the treatment of acute infectious diarrhea in children (7d)

Bibliography: Kianifar 2009, Lee 2001, Oandasan 1999, Phavichitr 2013, Rerksuppaphol 2010, Vivatvakin 2006

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus + B. bifidum*	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean duration of diarrhea (assessed with: hours)												
6	randomised trials	serious [b]	serious [a]	not serious	not serious	none	241	237	-	MD 28.44 hours lower (45.72 lower to 11.15 lower)	⨁⨁◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Some inconsistency suspected based on visual inspection of the forest plot and high I^2 of 89%.

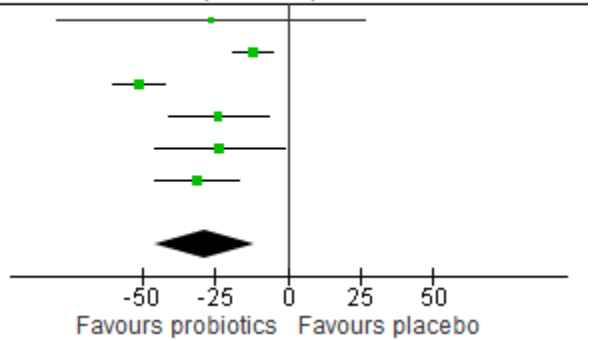
b. Risk of bias assessment identified unclear and high concerns among all included studies.

Mean Duration of Diarrhea:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kianifar 2009	81.6	108.6	32	108	105.2	30	7.1%	-26.40 [-79.63, 26.83]
Lee 2001	74.4	16.8	50	86.4	19.2	50	20.7%	-12.00 [-19.07, -4.93]
Oandasan 1999	42.9	21.77	47	94	22.85	47	20.3%	-51.10 [-60.12, -42.08]
Phavichitr 2013	96	53.33	53	120	35.56	53	17.7%	-24.00 [-41.26, -6.74]
Rerksuppaphol 2010	28	32	23	51.5	44	22	15.7%	-23.50 [-46.06, -0.94]
Vivatvakin 2006	38.4	16.8	36	69.6	40.8	35	18.6%	-31.20 [-45.79, -16.61]
Total (95% CI)			**241**			**237**	**100.0%**	**-28.44 [-45.72, -11.15]**

Heterogeneity: Tau² = 362.67; Chi² = 45.22, df = 5 (P < 0.00001); I² = 89%

Test for overall effect: Z = 3.22 (P = 0.001)



Question: *Lactobacillus reuteri* compared to placebo in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7e)

Bibliography: Shornikova 1997b, Shornikova 1997c, Dinleyici 2015a, Dinleyici 2014, Francavilla 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. reuteri*	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
4	randomised trials	serious [a]	not serious [b]	not serious	not serious	none	133	140	-	mean 24.36 lower (35.55 lower to 13.17 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Diarrhea Lasting > 3 days												
4	randomised trials	serious [c]	not serious	not serious	not serious	none	47/149 (31.5%)	96/153 (62.7%)	**RR 0.67** (0.47 to 0.95)	**207 fewer per 1,000** (from 333 fewer to 31 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Several studies with high risk of either performance bias, detection bias, or attrition bias

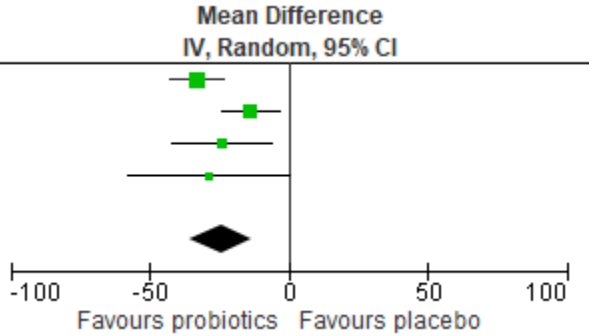
b. Some heterogeneity among studies (I^2 = 58%); however, all are in the same direction.

c. Some studies with high risk of performance bias, detection bias, or selection bias

Mean Duration of Diarrhea:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	34.8%	-33.10 [-42.59, -23.61]
Dinleyici 2015b	60.4	24.5	29	74.3	15.3	31	33.1%	-13.90 [-24.32, -3.48]
Shornikova 1997b	36	26.4	21	60	36	25	21.0%	-24.00 [-42.07, -5.93]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	11.1%	-28.80 [-58.05, 0.45]
Total (95% CI)			**133**			**140**	**100.0%**	**-24.36 [-35.55, -13.17]**

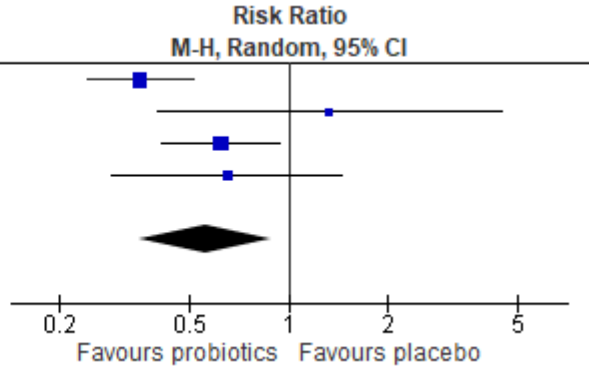
Heterogeneity: Tau² = 70.24; Chi² = 7.22, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 4.27 (P < 0.0001)



Diarrhea Lasting > 3 days:

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dinleyici 2014	20	64	56	63	35.7%	0.35 [0.24, 0.51]
Dinleyici 2015b	5	29	4	31	11.1%	1.34 [0.40, 4.50]
Francavilla 2012	16	35	25	34	33.9%	0.62 [0.41, 0.94]
Shornikova 1997b	6	21	11	25	19.3%	0.65 [0.29, 1.46]
Total (95% CI)		**149**		**153**	**100.0%**	**0.56 [0.35, 0.89]**
Total events	47		96			

Heterogeneity: Tau² = 0.12; Chi² = 7.39, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 2.47 (P = 0.01)



Question: *Lactobacillus helveticus* Rosell-52 + *Lactobacillus rhamnosus* Rosell-11 compared to placebo in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7f)

Bibliography: Freedman 2015, Freedman 2018, Hegar 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. helveticus* Rosell-52 + *L. rhamnosus* Rosell-11	placebo	Relative (95% CI)	Absolute (95% CI)		
Hospitalization												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	34/475 (7.2%)	22/475 (4.6%)	**RR 1.52** (0.91 to 2.55)	**24 more per 1,000** (from 4 fewer to 72 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Adverse Events												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	140/475 (29.5%)	164/475 (34.5%)	**RR 0.85** (0.71 to 1.02)	**52 fewer per 1,000** (from 100 fewer to 7 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Duration of Diarrhea												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. helveticus* Rosell-52 + *L. rhamnosus* Rosell-11	placebo	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious [b]	not serious	not serious	serious [a]	none	531	531	-	mean 1.72 lower (9.27 lower to 5.83 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

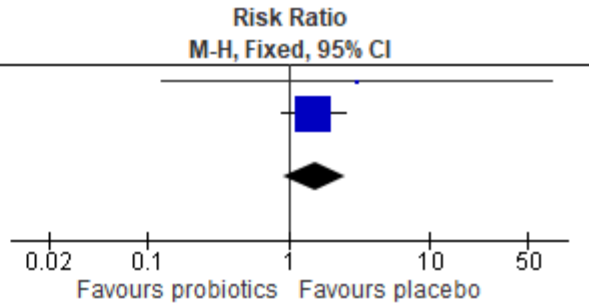
a. The 95% CI includes the potential for both benefit and harm. The 95% CI includes the potential for both benefit and harm.

b. Unclear risk of performance, detection, and reporting bias in Hegar 2015

Hospitalization:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Freedman 2015	1	61	0	62	2.2%	3.05 [0.13, 73.40]
Freedman 2018	33	414	22	413	97.8%	1.50 [0.89, 2.52]
Total (95% CI)		**475**		**475**	**100.0%**	**1.53 [0.92, 2.56]**
Total events	34		22			

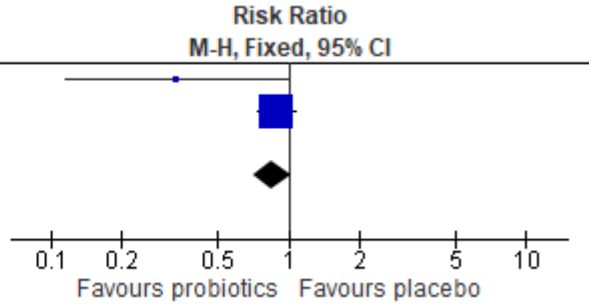
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.62 (P = 0.10)



Adverse Events:

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Freedman 2015	4	61	12	62	7.3%	0.34 [0.12, 0.99]
Freedman 2018	136	414	152	413	92.7%	0.89 [0.74, 1.08]
Total (95% CI)		**475**		**475**	**100.0%**	**0.85 [0.71, 1.02]**
Total events	140		164			

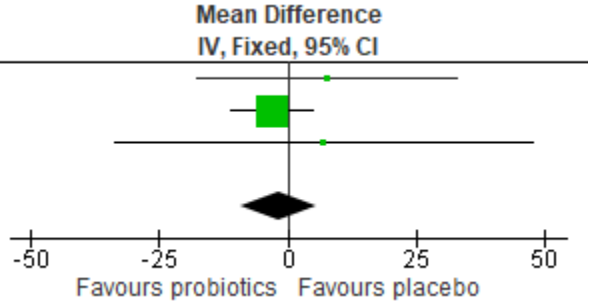
Heterogeneity: Chi² = 3.06, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.70 (P = 0.09)



Mean Duration of Diarrhea:

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Freedman 2015	71.1	78.3	61	63.5	64.3	62	8.9%	7.60 [-17.74, 32.94]
Freedman 2018	52.5	57.41	414	55.5	60.81	413	87.7%	-3.00 [-11.06, 5.06]
Hegar 2015	68.5	112.59	56	61.5	107.41	56	3.4%	7.00 [-33.76, 47.76]
Total (95% CI)			**531**			**531**	**100.0%**	**-1.72 [-9.27, 5.83]**

Heterogeneity: Chi² = 0.79, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.66)



Question: *Bifidobacterium animalis* subsp. *lactis* compared to placebo for treatment of acute infectious diarrhea in children (7g)

Bibliography: El-Soud 2015, Erdogan 2012, Mao 2008

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. animalis* subsp. *lactis*	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
3	randomised trials	very serious [a]	serious [b]	not serious	serious [c]	none	120	121	-	mean 1.88 lower (3.68 lower to 0.08 lower)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. Erdogan has high risk of performance bias and all studies have uncertain risk of selection, detection, and reporting bias

b. Heterogeneity among studies (I2 94%)

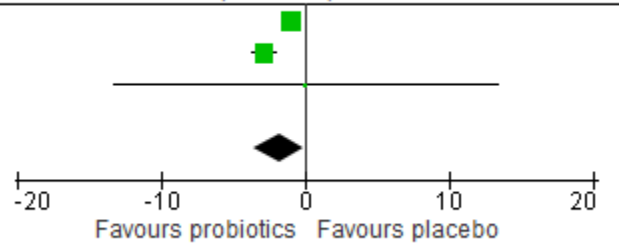
c. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Mean Duration of Diarrhea:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
El-Soud 2015	3.12	0.92	25	4.1	0.94	25	50.6%	-0.98 [-1.50, -0.46]
Erdogan 2012	4.1	1.3	25	7	1.6	25	47.7%	-2.90 [-3.71, -2.09]
Mao 2008	67.2	40.2	70	67.2	40.5	71	1.8%	0.00 [-13.32, 13.32]
Total (95% CI)			**120**			**121**	**100.0%**	**-1.88 [-3.68, -0.08]**

Heterogeneity: Tau² = 1.60; Chi² = 15.46, df = 2 (P = 0.0004); I² = 87%

Test for overall effect: Z = 2.04 (P = 0.04)



Question: *Streptococcus salivarius* subsp. *thermophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7h)

Bibliography: Bhatnagar 1998, Boudraa 2001

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*S. salivarius* subsp. *thermophilus* + *L. delbrueckii* subsp. *bulgaricus*	placebo	Relative (95% CI)	Absolute (95% CI)		
Diarrhea > 4 days												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	23/103 (22.3%)	29/105 (27.6%)	**RR 0.82** (0.51 to 1.30)	**50 fewer per 1,000** (from 135 fewer to 83 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mean Duration of Diarrhea												
1	randomised trials	very serious [a]	not serious	not serious	serious [c]	none	56	61	-	mean **17.6 lower** (30.16 lower to 5.04 lower)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

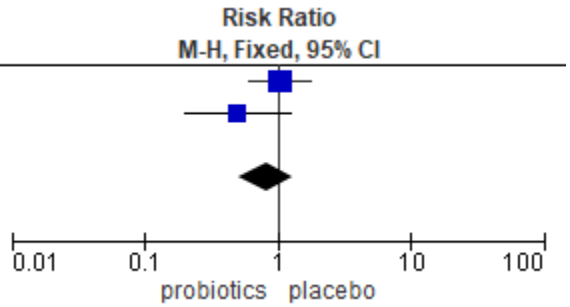
Explanations

a. High risk of detection and attrition bias in one study
b. Low event rate
c. The 95% CI includes the potential for both benefit and harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Diarrhea > 4days

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhatnagar 1998	17	47	17	49	58.1%	1.04 [0.61, 1.79]
Boudraa 2001	6	56	12	56	41.9%	0.50 [0.20, 1.24]
Total (95% CI)		**103**		**105**	**100.0%**	**0.82 [0.51, 1.30]**
Total events	23		29			

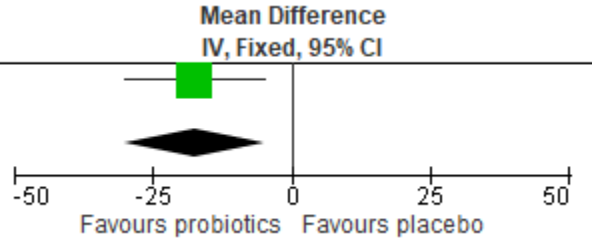
Heterogeneity: Chi² = 1.91, df = 1 (P = 0.17); I² = 48%
Test for overall effect: Z = 0.86 (P = 0.39)



Mean duration of diarrhea (hours)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Boudraa 2001	44.1	33.7	56	61.7	35.6	61	100.0%	-17.60 [-30.16, -5.04]
Total (95% CI)			**56**			**61**	**100.0%**	**-17.60 [-30.16, -5.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.75 (P = 0.006)



Question: *Enterococcus faecium* SF68 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7i)

Bibliography: D'Apuzzo 1982

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*E. faecium* SF68	placebo	Relative (95% CI)	Absolute (95% CI)		
Diarrhea > 4days												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	3/21 (14.3%)	7/18 (38.9%)	**RR 0.37** (0.11 to 1.22)	**245 fewer per 1,000** (from 346 fewer to 86 more)	⨁⨁◯◯ LOW	CRITICAL

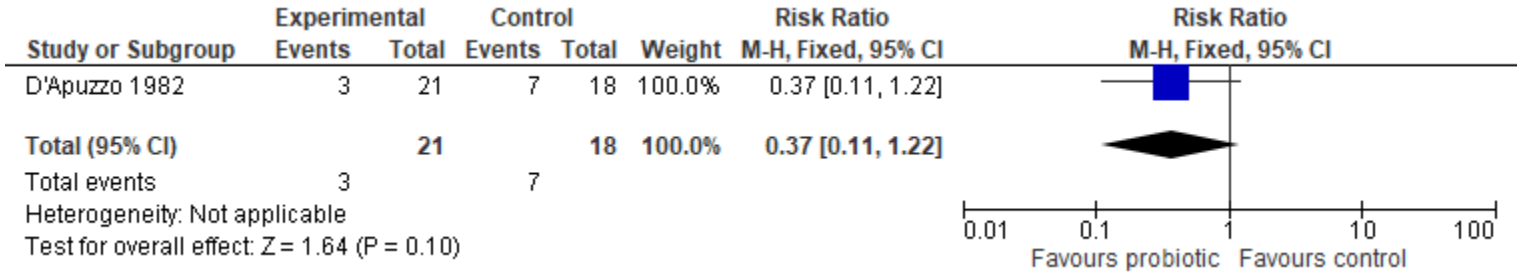
CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of selection and detection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Diarrhea > 4 days



Question: *Escherichia coli* Nissle 1917 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7j)

Bibliography: Henker 2007a, Henker 2008

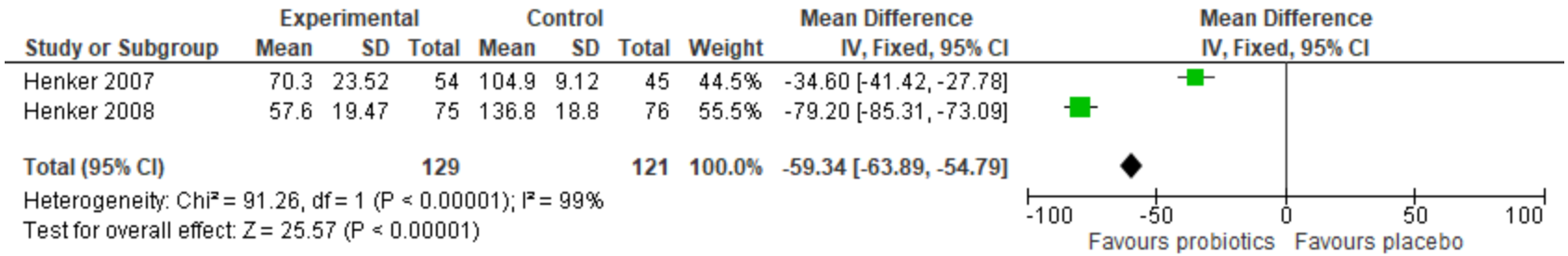
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*E. coli* Nissle 1917	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
2	randomised trials	very serious [a]	not serious	not serious	not serious	none	129	121	-	mean 59.34 lower (63.89 lower to 54.79 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

a. High risk of attrition bias

Mean duration of diarrhea (hours)


Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Henker 2007 70.3 23.52 54 104.9 9.12 45 44.5% -34.60 [-41.42, -27.78]
Henker 2008 57.6 19.47 75 136.8 18.8 76 55.5% -79.20 [-85.31, -73.09]
Total (95% CI) 129 121 100.0% -59.34 [-63.89, -54.79]
Heterogeneity: Chi² = 91.26, df = 1 (P < 0.00001); I² = 99%
Test for overall effect: Z = 25.57 (P < 0.00001)
-100
-50
0
50
100
Favours probiotics
Favours placebo

Question: *Bacillus mesentericus + Clostridium butyricum + Enterococcus faecalis* compared to placebo/standard of care for treatment of acute infectious diarrhea in children (7k)

Bibliography: Chen 2010, Huang 2014

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. mesentericus + C. butyricum + E. faecalis*	placebo/standard of care	Relative (95% CI)	Absolute (95% CI)		
Mean Stool Frequency Day 3												
2	randomised trials	serious [a]	serious [b]	not serious	not serious [c]	none	232	220	-	mean 1.46 lower (1.82 lower to 1.1 higher)	⨁⨁◯◯ LOW	CRITICAL
Length of Stay												
2	randomised trials	serious [a]	serious [b]	not serious	not serious [c]	none	232	220	-	mean 0.94 days fewer (1.27 fewer to 0.61 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

a. Unclear risk of selection and reporting bias and high risk of bias in Huang 2014 for performance, detection, and attrition bias

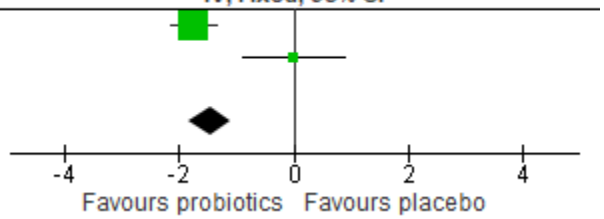
b. High heterogeneity (I2 >90%) and opposite direction of effect

c. OIS is met for continuous outcomes (>400).

Mean Stool Frequency Day 3:

	Experimental			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Chen 2010	1.48	1.2	150	3.23	2.1	143	83.5%	-1.75 [-2.14, -1.36]	
Huang 2014	3.1	2.9	82	3.1	2.8	77	16.5%	0.00 [-0.89, 0.89]	
Total (95% CI)			**232**			**220**	**100.0%**	**-1.46 [-1.82, -1.10]**	

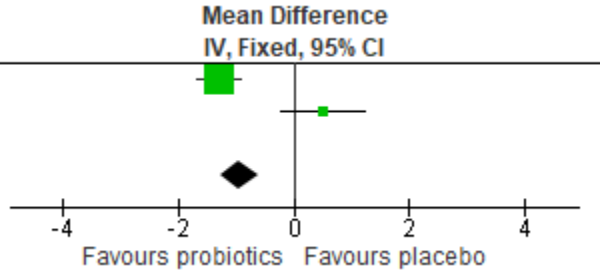
Heterogeneity: Chi² = 12.51, df = 1 (P = 0.0004); I² = 92%
Test for overall effect: Z = 7.95 (P < 0.00001)



Length of Stay (days)

	Experimental			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**	**IV, Fixed, 95% CI**
Chen 2010	2.9	0.8	150	4.2	2.1	143	79.8%	-1.30 [-1.67, -0.93]	
Huang 2014	5.7	2.4	82	5.2	2.3	77	20.2%	0.50 [-0.23, 1.23]	
Total (95% CI)			**232**			**220**	**100.0%**	**-0.94 [-1.27, -0.61]**	

Heterogeneity: Chi² = 18.62, df = 1 (P < 0.0001); I² = 95%
Test for overall effect: Z = 5.60 (P < 0.00001)



Question: *Lactobacillus acidophilus* + *Lactobacillus rhamnosus* + *Bifidobacterium longum* subsp. *longum* + *Saccharomyces boulardii* compared to placebo for treatment of acute infectious diarrhea (7l)

Bibliography: Grandy 2010, Teran 2009

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* + *L. rhamnosus* + *B. longum* subsp. *longum* + *S. boulardii*	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea (measured in hours)												
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	68	46	-	17.93 hours fewer (from 31.90 fewer to 3.95 greater)	⊕◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

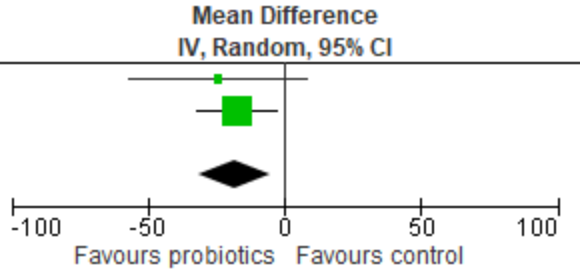
a. Unclear risk of selection and performance bias

b. The 95% CI includes the potential for both benefit and harm. Few events reported do not meet the optimal information size and suggest fragility in the estimate. Mean duration of diarrhea (hours)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Grandy 2010	60	29.63	23	84.5	69.63	20	16.2%	-24.50 [-57.33, 8.33]
Teran 2009	57.1	25.4	25	74.6	26.6	25	83.8%	-17.50 [-31.92, -3.08]
Total (95% CI)			**48**			**45**	**100.0%**	**-18.63 [-31.83, -5.43]**

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%

Test for overall effect: Z = 2.77 (P = 0.006)



Question: *Lactobacillus rhamnosus* 19070-2 + *Lactobacillus reuteri* DSM 12246 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7m)

Bibliography: Rosenfeldt 2002, Rosenfeld 2002a

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* 19070-2 + *L. reuteri* DSM 12246	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea (hours)												
2	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	54	58	-	mean 23.43 lower (41.47 lower to 5.4 lower)	⨁◯◯◯ VERY LOW	CRITICAL

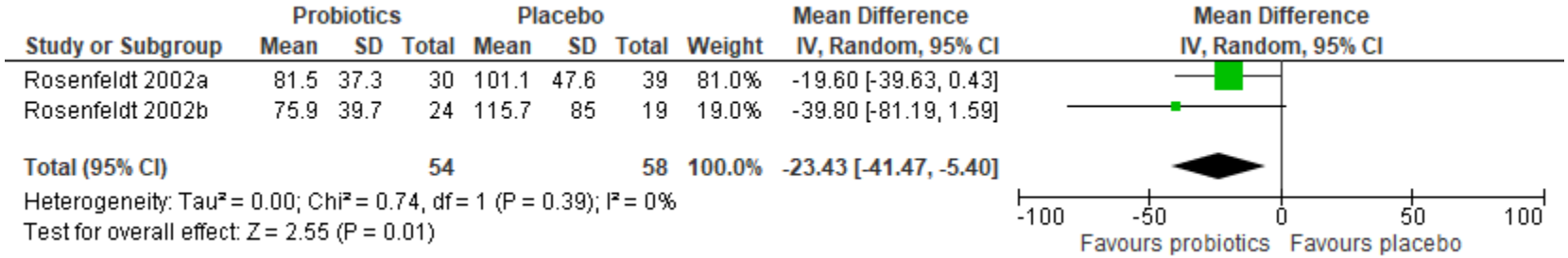
CI: Confidence interval

Explanations

a. High risk of attrition bias in both studies

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

Mean duration of diarrhea (hours)



Question: *Lactobacillus casei* Shirota compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7n)

Bibliography: Sugita 1994

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. casei* Shirota	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean duration of diarrhea (hours)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	16	11	-	mean 36 lower (65.87 lower to 6.13 lower)	⨁◯◯◯ VERY LOW	CRITICAL

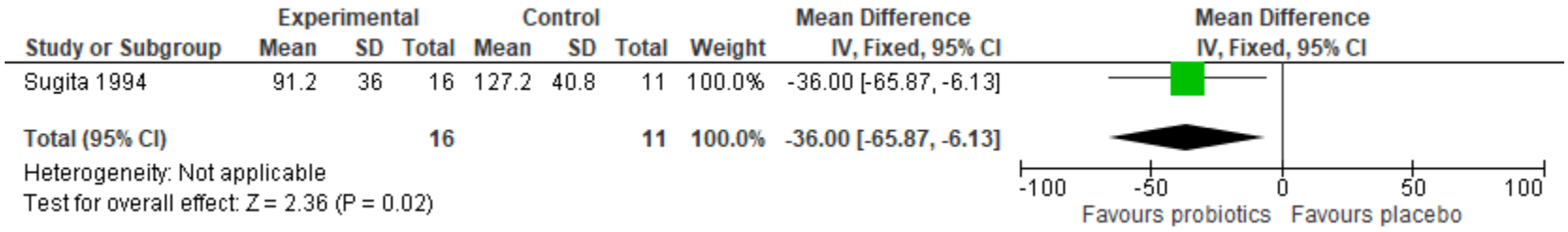
CI: Confidence interval

Explanations

a. High risk of bias in all domains

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

Mean duration of diarrhea (hours)



Question: *Lactobacillus paracasei* subsp. *paracasei* + *Lactobacillus plantarum* + *Lactobacillus acidophilus* + *Lactobacillus delbrueckii* subsp. *bulgaricus* + *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium breve* + *B. longum* subsp. *infantis* + *Streptococcus salivarius* subsp. *thermophilus* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7o)

Bibliography: Dubey 2008

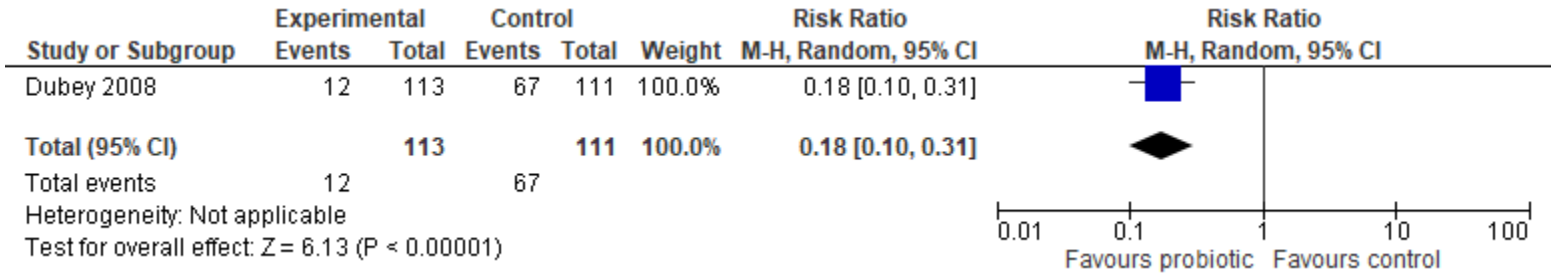
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* + *L. plantarum* + *L. acidophilus* + *L. delbrueckii* subsp. *bulgaricus* + *B. longum* subsp. *longum* + *B. breve* + *B. longum* subsp. *infantis* + *S. salivarius* subsp. *thermophilus*	placebo	Relative (95% CI)	Absolute (95% CI)		
Diarrhea > 4 days												
1	randomised trials	serious [a]	not serious	serious [b]	not serious	none	12/113 (10.6%)	67/111 (60.4%)	**RR 0.18** (0.10 to 0.31)	**495 fewer per 1,000** (from 543 fewer to 416 fewer)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of selection bias
b. Lack of standardized formula

Diarrhea > 4 days



Question: *Enterococcus faecalis* + *Clostridium butyricum* + *Bacillus mesentericus* + *Bacillus coagulans* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7p)

Bibliography: Narayanappa 2008

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*E. faecalis* + *C. butyricum* + *B. mesentericus* + *B. coagulans*	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	40	40	-	mean 26.4 lower (42.07 lower to 10.73 lower)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

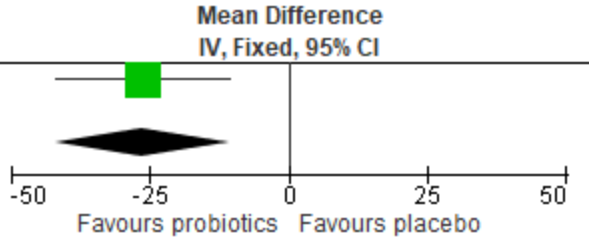
a. Unclear risk of selection and detection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

Mean duration of diarrhea (hours)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	100.0%	-26.40 [-42.07, -10.73]
Total (95% CI)			**40**			**40**	**100.0%**	**-26.40 [-42.07, -10.73]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.30 (P = 0.0010)



Question: *Bifidobacterium longum* subsp. *longum* + *Bifidobacterium animalis* subsp. *lactis* + *Lactobacillus acidophillus* + *Lactobacillus rhamnosus* + *Lactobacillus plantarum* + *Pediococcus pentosaceus* compared to placebo for the treatment of acute infectious diarrhea in children (7q)

Bibliography: Lee 2015

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. longum* subsp. *longum* + *B. animalis* subsp. *lactis* + *L. acidophillus* + *L. rhamnosus* + *L. plantarum* + *P. pentosaceus*	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	13	16	-	MD 1.1 days lower (2.07 lower to 0.13 lower)	⊕◯◯◯ VERY LOW	CRITICAL

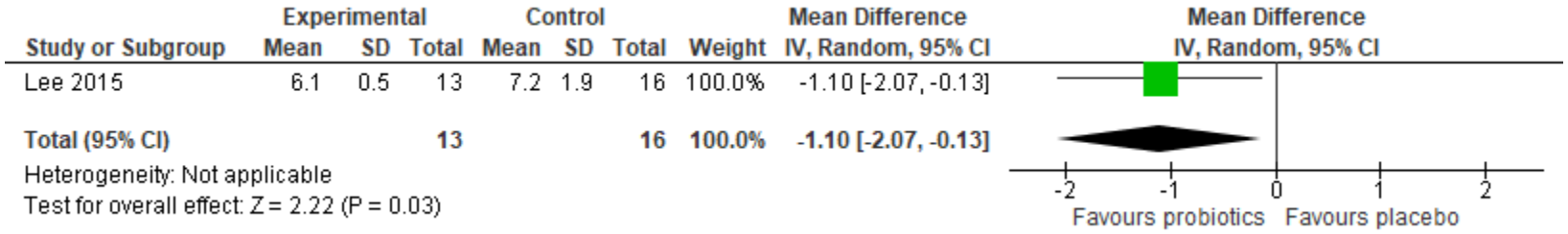
CI: Confidence interval

Explanations

a. Unclear risk of selection bias, performance bias, detection bias, and reporting bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Mean Duration of Diarrhea (Days)



Question: *Lactobacillus paracasei* subps. *paracasei* ST11 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7t)

Bibliography: Sarkar 2005

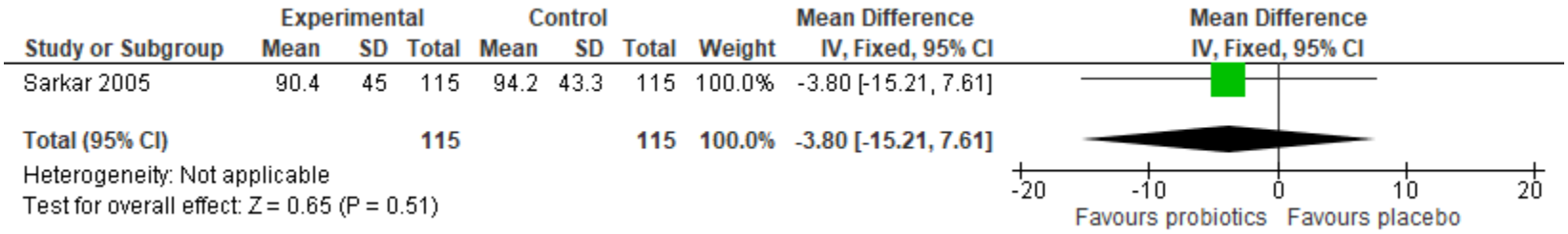
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. paracasei* subsp. *paracasei* ST11	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
1	randomised trials	not serious	not serious	not serious	Very serious [a,b]	none	115	115	-	mean 3.8 lower (15.21 lower to 7.61 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

a. The 95% CI includes the potential for both benefit and harm.
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Mean duration of diarrhea (hours)



Question: *Lactobacillus acidophilus + Bifidobacterium bifidum + Lactobacillus delbrueckii* subsp. *bulgaricus* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7u)

Bibliography: Kowalska-Duplaga 2004

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus + B. bifidum + L. delbrueckii* subsp. *bulgaricus*	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean duration of diarrhea (hours)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	86	87	-	mean 7 lower (16.55 lower to 2.55 higher)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

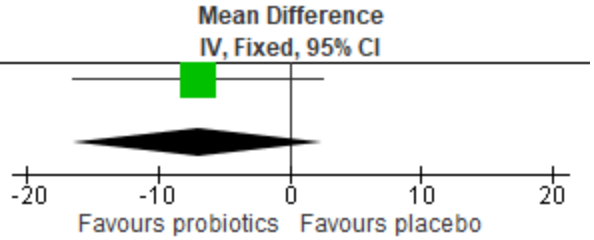
a. High risk of selection bias

b. The 95% CI includes the potential for both benefit and harm.

Mean duration of diarrhea (hours)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Kowalska-Duplaga 2004	54.6	30	86	61.6	34	87	100.0%	-7.00 [-16.55, 2.55]
Total (95% CI)			**86**			**87**	**100.0%**	**-7.00 [-16.55, 2.55]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)



Question: *Bifidobacterium ruminatum* compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7v)

Bibliography: : Kowalska-Duplaga 1999

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*B. ruminatum*	placebo	Relative (95% CI)	Absolute (95% CI)		
Diarrhea > 4 days												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	none	13/33 (39.4%)	9/30 (30.0%)	**RR 1.31** (0.66 to 2.62)	**93 more per 1,000** (from 102 fewer to 486 more)	⨁⨁◯◯ LOW	CRITICAL

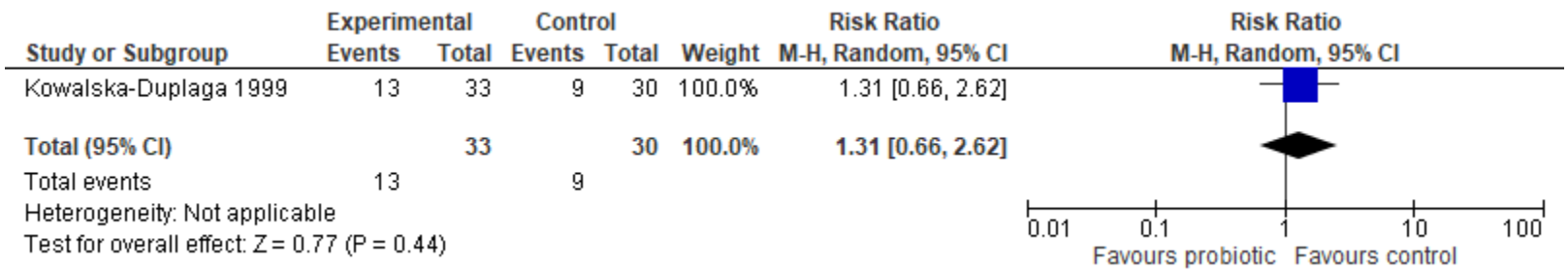
CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Unclear risk of selection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Duration of Diarrhea > 4 days



Question: *Lactobacillus rhamnosus* 573L/1 and 573L/2 and 573L/3 compared to placebo and/or standard care in patients with signs and/or symptoms suggestive of acute infectious gastroenteritis (7w)

Bibliography: Szymanski 2006

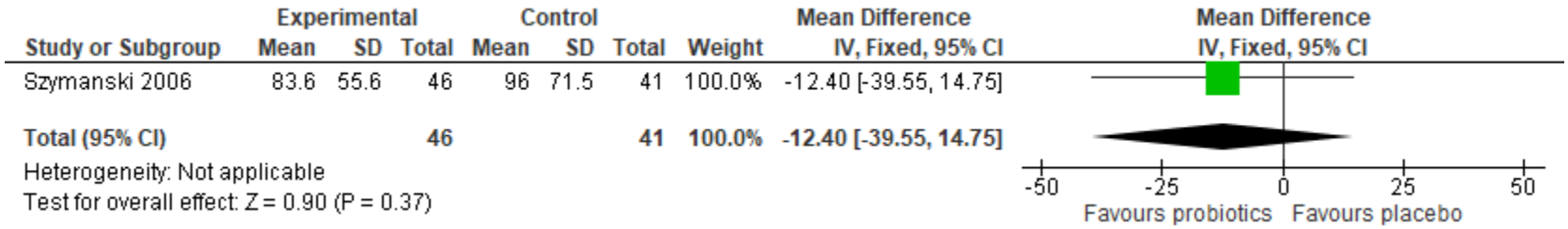
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. rhamnosus* 573L/1 and 573L/2 and 573L/3	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean Duration of Diarrhea												
1	randomised trials	not serious	not serious	not serious	Very serious [a,b]	none	46	41	-	mean 12.4 lower (39.55 lower to 14.75 higher)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval

Explanations

a. The 95% CI includes the potential for both benefit and harm.
b. Few events reported do not meet the optimal information size and suggest fragility in the estimate.

Mean duration of diarrhea (hours)



Question: *Lactobacillus acidophilus* + "Bifidobacter" compared to placebo for the treatment of acute infectious diarrhea in children (7x)

Bibliography: Abbaskhanian 2012

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*L. acidophilus* + "Bifidobacter"	placebo	Relative (95% CI)	Absolute (95% CI)		
Mean duration of diarrhea												
1	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	60	60	-	MD 3.48 lower (11 lower to 4.04 higher)	⨁◯◯◯ VERY LOW	CRITICAL

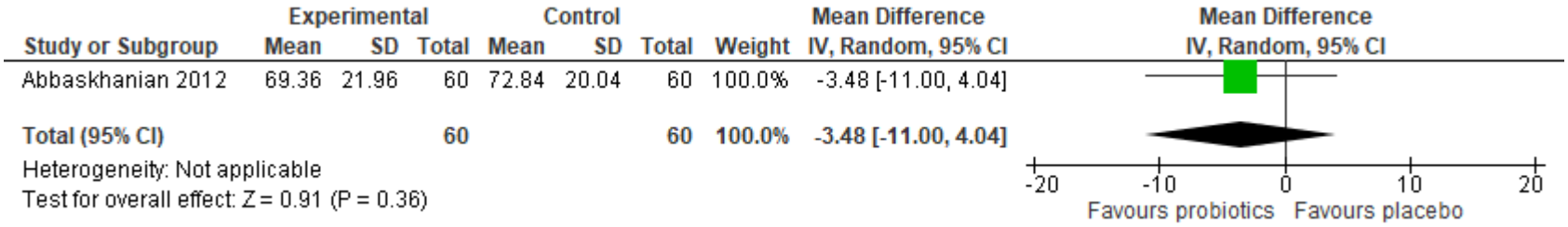
CI: Confidence interval; **MD:** Mean difference

Explanations

a. Unclear risk of bias due to selective reporting and detection bias

b. Few events reported do not meet the optimal information size and suggest fragility in the estimate. The 95% CI includes the potential for both benefit and harm.

Mean Duration of Diarrhea:



Appendix 8: Should probiotics be used in preterm, low birth weight infants?

Question: Single- and multiple-strain probiotics compared with no probiotics for preterm, low birth weight infants (8a)

	All-cause Mortality OR (95% CI)	NEC (stage ≥ II) OR (95% CI)	Culture proven sepsis OR (95% CI)	Feed intolerance OR (95% CI)	Reduction in days to reach full feed MD (95% CI)	Reduction in days of hospitalization MD (95% CI)
***Lactobacillus* spp. & *Bifidobacterium* spp.**	**0.56 (0.39,0.80)**	**0.35 (0.20,0.59)**	0.87 (0.60,1.27)	-	**-2.15 (-3.78,-0.51)**	-2.84 (-6.21,0.54)
Bifidobacterium animalis* subsp. *lactis	0.43 (0.16,1.15)	**0.31 (0.13,0.74)**	0.73 (0.38,1.43)	0.10 (0.00,2.29)	-	**-13.00 (-22.71,-3.29)**
Lactobacillus reuteri	0.77 (0.51,1.17)	**0.55 (0.34,0.91)**	0.71 (0.41,1.26)	0.26 (0.06,1.10)	**-2.62 (-4.53,-0.71)**	**-7.89 (-11.60,-4.17)**
Lactobacillus rhamnosus	0.84 (0.33,2.12)	**0.44 (0.21,0.90)**	0.84 (0.45,1.57)	0.75 (0.11,5.35)	0.02 (-3.29,3.32)	-1.85 (-7.62,3.91)
***Lactobacillus* spp. & *Bifidobacterium* spp. & *Enterococcus* spp.**	0.78 (0.23,2.62)	**0.28 (0.16,0.49)**	0.43 (0.17,1.07)	0.23 (0.02,3.07)	-	-6.00 (-19.53,7.53)
Bifidobacterium* spp. & *Streptococcus salivarius* subsp. *thermophilus	0.84 (0.51,1.40)	**0.38 (0.19,0.75)**	1.04 (0.52,2.06)	-	-1.35 (-4.66,1.95)	-2.75 (-10.00,4.50)
***Bacillus* spp. & *Enterococcus* spp.**	0.95 (0.02,48.18)	**0.23 (0.08,0.63)**	-	-	-	-
Lactobacillus* spp. & *Bifidobacterium* spp. & *Saccharomyces boulardii	1.05 (0.51,2.17)	0.73 (0.29,1.85)	0.54 (0.28,1.04)	0.47 (0.04,5.04)	**-3.30 (-5.91,-0.69)**	-3.20 (-8.38,1.98)
Lactobacillus acidophilus	0.29 (0.03,3.12)	1.00 (0.02,53.66)	-	-	-	20.70 (-12.55,53.95)
B. animalis* subsp. *lactis* & *Bifidobacterium longum* subsp. *longum	0.39 (0.04,4.18)	1.42 (0.37,5.42)	0.77 (0.23,2.57)	-	-	-
B. longum* subsp. *longum	0.77 (0.11,5.35)	0.25 (0.03,2.30)	0.75 (0.23,2.50)	-	-	-
Lactobacillus* spp. & *Bifidobacterium* spp. & *S. salivarius* subsp. *thermophilus	0.40 (0.12,1.30)	0.42 (0.16,1.13)	0.68 (0.35,1.30)	0.68 (0.06,7.70)	5.75 (-0.33,11.83)	7.25 (-5.83,20.33)
Bifidobacterium adolescentis	0.93 (0.02,47.20)	0.13 (0.01,2.51)	-	-	-	-
Bacillus coagulans	0.91 (0.38,2.15)	0.58 (0.20,1.65)	1.15 (0.41,3.21)	0.47 (0.04,5.02)	-1.00 (-5.78,3.78)	4.50 (-4.33,13.33)
Bifidobacterium bifidum	4.31 (0.20,90.52)	0.85 (0.02,43.14)	0.49 (0.13,1.85)	-	-1.10 (-5.31,3.11)	-0.60 (-13.61,12.41)
Bacillus clausii	0.83 (0.37,1.87)	0.98 (0.14,7.10)	0.70 (0.20,2.45)	0.81 (0.06,11.00)	-	-
Bifidobacterium breve	0.92 (0.63,1.34)	0.92 (0.64,1.32)	0.87 (0.48,1.55)	-	-1.53 (-4.30,1.24)	1.18 (-5.88,8.24)
S. boulardii	1.01 (0.46,2.23)	0.81 (0.42,1.55)	0.77 (0.40,1.45)	0.53 (0.08,3.40)	-1.02 (-3.64,1.61)	-1.86 (-6.65,2.92)

Footnote: OR = odds ratio; MD = mean difference. Results are the mean difference, or odds ratio, and associated 95% confidence intervals (95% CIs) between the intervention and placebo from the network meta-analysis. Mean difference values < 0 indicates the

treatment is more effective than placebo. An OR > 1 indicates the treatment is superior to placebo; Underlined numbers in bold represent statistically significant results.

Table legends and description of color gradients:

	Statistically significant difference with placebo and at least one other tx	Statistically significant difference with placebo	Statistically no difference with placebo
High or moderate certainty evidence	**Among the most effective**	**Inferior to the most effective, but superior to placebo**	**No more effective than placebo**
Low or very low certainty evidence	**May be among the most effective**	**May be inferior to the most effective, but superior to placebo**	**May be no more effective than placebo**