11 February 2020
Use of Probiotics for the Management of Acute Gastroenteritis

Table S1. Summary of methods

Criteria for considering studies	
Type of studies	Systematic reviews and meta-analyses, and subsequently published or not included RCTs, quasi-RCTs. Search date: from September 2013 (end of the last search) to August 2019.
Type of participants	Children with clinically diagnosed acute gastroenteritis, including in- and outpatients, regardless of the location (however, with focus on children living in geographic Europe).
Type of interventions	• Active (e.g., live or viable) and lyophilized forms of probiotics as single ingredients or in combination with other probiotics in all delivery vehicles (and formulations). • Six taxonomic groups (*Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus, Enterococcus,* and *Bacillus*). • Studies in which it could not be verified what group of probiotics was consumed were excluded. • Studies administering yogurt or milk products containing only *Lactobacillus* or *Streptococcus* organisms as starter cultures were not included (regardless whether alone or supplemented with probiotics).
Type of outcome measures	
Outcome(s)	• Duration of diarrhea • Need for hospitalization for outpatients (or duration of hospitalization for inpatients) • The percentage of children recovered by 48 h (or diarrhea on day 2)
Search methods of identification of studies	
Electronic searches	For systematic reviews/meta-analyses: • The *Cochrane Database of Systematic Reviews* • The DARE (*Database of Abstracts of Reviews of Effects)* For systematic reviews/meta-analyses and subsequently published trials (starting from the date of the most recent search in the included reviews). • CENTRAL *(Cochrane Central Register of Controlled Trials).* • PubMed *(National Library of Medicine, includes MEDLINE®).* • EMBASE *(Biomedical and pharmacological bibliographic database).* The search strategy included the use of a validated filter for identifying controlled trials, which was combined with a topic-specific strategy. The search was carried out independently by two reviewers. No language restrictions were imposed (provided the language is known to a member of the group).

Searching other resources	The reference lists from identified studies and key review articles, including previously published meta-analyses.
Data collection and analysis	
Selection of studies	An initial screening of the title, abstract, and keywords of every record identified was performed. The next step was the retrieval of the full text of potentially relevant publications. Two reviewers independently assessed the eligibility of each potentially relevant trial with the use of inclusion criteria. If they had different opinions, these were resolved by discussion with at least one other member of the WG.
Data extraction	The data extracted included baseline characteristics (including the definition of acute gastroenteritis), inclusion criteria, experimental and control treatments, setting, dose, outcomes of interest (with definitions), and funding.
Assessment of risk of bias in included trials	RCT: The Cochrane Collaboration's tool for assessing risk, which includes the following criteria: • adequacy of sequence generation; • allocation concealment; • blinding of participants, personnel and outcome assessors; • incomplete outcome data were addressed.
Measures of treatment effect	If feasible, for dichotomous outcomes, the results for individual studies, and pooled statistics were reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (CI). For continuous outcomes, the results were reported as the mean difference (MD) with 95% CI.
Assessment of heterogeneity	Heterogeneity using the I^2 statistic was assessed. The values of 25%, 50%, and 75% were used as edge limits for low, moderate, and high heterogeneity.
Assessment of reporting biases	When at least 10 RCTs were available, publication bias was assessed using the funnel plot proposed by Egger et al. (75). A P value less than 0.05 implicates publication bias.
Data synthesis	The data were analyzed using Review Manager (RevMan [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All pooled analyses were explicitly performed for the current report.

Table S2. The grades of the certainty of evidence and strength of recommendation set by the GRADE Working Group

GRADE certainty of evidence	
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.
GRADE strength of recommendations	
Strong*	When the evidence showed that the benefit of the intervention clearly outweighs the undesirable effects.
Weak (conditional)*	When the trade-offs were less certain (either because of the low quality of evidence or because the evidence suggests that desirable and undesirable effects are closely balanced).

GRADE: Grading of Recommendations Assessment, Development and Evaluations.

*Interpretation of strong and weak (conditional) recommendations

	Strong recommendation	Weak (conditional) recommendation
For patients:	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Table S3. Wording of recommendations

Strength of recommendation	**Example recommendation**
Strong recommendation *for*	Healthcare professionals should recommend X to Y.
Weak recommendation *for*	Healthcare professionals may recommend X to Y.
No recommendation	There is no recommendation for or against X to Y.
Weak recommendation *against*	Healthcare professionals may not recommend X to Y.
Strong recommendation *against*	Healthcare professionals should not recommend X to Y.

Where X is the intervention and Y is the population.

Table S4. Summary of systematic reviews/meta-analyses and network meta-analyses on probiotics for the management of acute gastroenteritis in children

Review ID	Search date/ databases searched	Population & Age	Intervention	Comparison	Outcomes	Included studies	Definition of acute diarrhea	Results	Comments
Szajewska et al. 2020 (1)	Up to December 2019/ Medline, Embase, Cochrane	Children with acute diarrhea Aged 1 month to 15 years (majority aged 60 months or less)	*Saccharomyces Boulardii*	Placebo/ no treatment	Primary: - Duration of diarrhea - Stool volume Secondary: - Percentages of children with diarrhea at various times intervals – Percentage of children with diarrhea lasting longer than 7 days - Stool frequency - Vomiting - Duration of hospitalizatio n - Adverse effects	29 RCTs	-	Primary: - Reduced duration of diarrhea: MD –1.06 days, 95% CI (-1.32 to -0.79) - Stool volume (no RCTs) Secondary: - Reduced duration of hospitalization: MD -0.85 day, 95% CI (-1.35 to -0.34) - Presence of diarrhea day 2: RR 0.75, 95% CI (0.67 to 0.84)	Additional outcomes reported by the authors: - Presence of diarrhea on days 1,3,4,5, >7 -Vomiting - Adverse events - Stool frequency
Patro et al. 2019 (2)	From January 2016 to August 2019 /Medline, Embase	Children under 18 years Aged 3 months to 5 years	*Lactobacillus reuteri* DSM 17938	Placebo or no treatment	Primary: - Duration of diarrhea (days) - Stool volume Secondary: - Percentages of children	4 RCTs on diarrhea treatmen t	-	- Duration of diarrhea: MD -0.87 days; 95% CI (-1.43 to -0.31) - Stool volume: none of the trials assessed this outcome - Cure on day 2: RR 4.54, 95% CI (2.02 to 10.18) - Duration of hospitalization: MD -0.54 days, 95% CI: (-1.09 to 0.0)	Additional outcomes reported: - Cure on day 1,3,4,5 - Stool output

	Central, others				with diarrhea at various times intervals - Percentage of children with diarrhea lasting longer than 7 days - Duration of hospitalizatio n (days)			- Adverse events: no adverse effects were observed	
Szajewska et al. 2019 (3)	Up to January 2019/ Medline, Embase, Central, others	Children with acute diarrhea Aged 1 month to 7 years	*Lactobacillus rhamnosus GG*	Placebo/ no treatment	Primary: - Duration of diarrhea - Stool volume Secondary: - Percentages of children with diarrhea at various times intervals – Percentage of children with diarrhea lasting longer than 7 days - Duration of hospitalizatio n - Adverse effects	18 RCTs	-	Primary: - Reduced duration of diarrhea: MD −0.85 day, 95% CI (−1.15 to −0.56) - No effect on stool volume: Total stool volume (ml/g): MD 8.97, 95%CI (−86.26 to 104.2) - Stool volume on day 1 (g/kg): MD 13.60, 95%CI (−13.11 to 40.31) - Stool volume on day 2 (g/kg): MD 12.40, 95%CI (−6.39 to 31.19) Secondary: - Presence of diarrhea on day 2: RR 0.37, 95%CI (0.17 to 0.84) - Duration of hospitalization: MD -1.22 days, 95%CI (-2.33 to -0.10)	Additional outcomes reported by the authors (not presented): - Presence of diarrhea on days 3,4,5, >7,>10 - Dose - Setting - Inpatients/ outpatients - Etiology - Rotavirus vaccination status - Clinical severity score - Adverse effects
Ianiro et al. 2018 (4)	Up to October 2017/ Medline,	Children under 18 years of age with	*Bacillus clausii*	Placebo and/or standard of	Primary: - Duration of diarrhea	6 RCTs	≤14 days	Primary: - Duration of diarrhea: MD -9.12 hours, 95% CI (-6.49 to -1.75), p = 0.015	

	Embase, Central, others	acute diarrhea		care/or no treatment	- Stool frequency after intervention - Hospitalization duration Secondary: - Vomiting episodes - Quality of life - Adverse events			- Stool frequency after intervention: MD -0.19 diarrheal motions, 95% CI (-0.43 to -0.06), p= 0.14 - Duration of hospitalization MD -0.85 days, 95% CI (-1.56 to -0.15), p = 0.017 Secondary: - Vomiting: No difference - No serious adverse events - Quality of life not reported	
Florez et al. 2018 (5) Network meta-analysis	Up to May 2017/ Medline, Embase, Cochrane, others	Children under 18 years with acute diarrhea	Probiotics	Placebo and/or standard treatment	Primary: - Diarrhea duration Secondary: - Stool frequency at day 2 - Diarrhea on day 3 - Vomiting - Adverse events	46 RCTs (probiotics) among 174 studies included	-	- Diarrhea duration: All Probiotics: MD -19.4 hours, 95% Credible Interval (-23.7 to -15.1) *LGG (all):* MD -22.7 hours, 95% Credible Interval (-28.8 to -16.7) *LGG* (high- income countries): MD -38 hours, 95% Credible Interval (-45.4; -30.5) *LGG* (low-middle-income countries): MD -11.7 hours, 95%(-19.7 to -3.8) *Saccharomyces boulardii* MD -16.5 hours, 95% Credible Interval (-23.3 to -9.7) Secondary outcomes: - Stool frequency at day 2: All probiotics MD -0.96, 95% Credible Interval (-1.76 to -0.15) - Diarrhea at day 3: Standard vs. all probiotics OR 2.87, 95%Credible Interval (1.78 to 4.55) Standard vs. *Sacharomyces boulardii*	Additionally assessed for diarrhea duration: *S boulardii*+ Zn LGG+smectite Zn+Probiotics LCF+probiotics

								OR 5.55, 95%Credible Interval (3.09 to 10.11) - Vomiting: -Standard vs. all probiotics OR 1.36, 95% Credible Interval (0.56 to 3.60) - Standard vs. LGG OR 1.30, 95% Credible Interval (0.72 to 2.39) - Standard vs. *Sacharomyces boulardii* OR 1.69, 95%Credible Interval (0.65 to 4.48)	
Padayache e et al. 2018 (6)	From April 2014 up to January 2015/ Medline, Embase, Central, others	Hospitalized children with rotavirus acute gastroenterit is <16 years old	*Saccharomyces Boulardii*	Control	Primary: - Duration of diarrhea (days) - Mean number of stools passed per day - Mean number of episodes of diarrhea at follow up - Frequency of diarrhea at start, mid-point, end of intervention-Stool frequency - Changes in stool consistency post intervention Secondary:	10 RCTs	≥ 3 unformed stools in the last 24 h and of ≤ 48 h duration	- Duration of diarrhea: MD –0.57 days, 95% CI (–0.83 to –0.30) - Mean number of stools passed per day: MD -0.97, 95% CI (-1.56 to -0.39) - Frequency of diarrhea: RR 0.66, 95% CI (0.35 to 1.23) - Number having <3 stools per day RR 1.13, 95% CI (0.97 to 1.31) - Duration of hospital stay: MD -0.12 days, 95% CI (-1.90 to 1.65)	

					- Duration of hospital stay (days				
Sniffen et al. 2018 (7)	Up to June 2018/Pubmed, Embase, Cochrane, others	Children aged 1-18 years with acute diarrhea	Probiotics	Control	- Percent cured - Duration of diarrhea (days)	59 RCTs in pediatric acute diarrhea treatment among 155 treatment RCTs	New onset of acute infectious gastroenteritis symptoms (< 7 days duration) due to viral or bacterial etiologies but may be idiopathic	Seven of the eight probiotic types had strong evidence for this disease indication	
Zorzela et al. 2017 (8)	Up to February 2017/ Medline, Embase, Central, others	Children or adults using modified probiotics for either treatment or prophylaxis	Inactivated form of probiotics	Control group of either the identical living strain or strains of the probiotic or a placebo/standard treatment control, or both types of controls	- Efficacy - Adverse events	6 Pediatric RCTs among 26 treatment RCTs	-	- Treatment of acute diarrhea: modified *L acidophilus* vs. control SMD -0.81, 95% CI (-1.44 to -0.17)	Adverse events described in original publication
Freedman et al. 2015 (9)	Up to April 2012/ Medline, Embase, Central, others	Children under 18 years with acute diarrhea	Probiotics among other interventions	Placebo or alternative	Primary: - Any subsequent healthcare visit (7 days) Secondary: - Administratio	6 RCTs among (5 probiotics 1 synbiotic)	-	Primary outcome: 1 study reported no difference between groups in terms of return for additional ED care Secondary: -Hospitalization:	RCTs conducted in developed countries only

					n of intravenous rehydration - Hospitalization - Adverse effects	31 RCTs included		No difference for hospitalization within 7 days RR 0.53, 95% CI (0.26 to 1.07) - Need to administer intravenous rehydration within 7 days	When analyzed by individual probiotic product, most comparisons included a single RCT and reported no significant differences between groups
Gutierrez-Castrellon et al. 2015 (10) Network meta-analysis	Up to February 2014/ Medline, Embase, Central, others	Children under 5 years with acute diarrhea	*Lactobacillus GG* , *Saccharomyces Boulardii* (among other interventions to reduce diarrhea in children)	Placebo	Primary: - Diarrhea duration (hours) Secondary: - Stool output 48-72 hours - Adverse events	19 RCTs among 51 RCTs included	-	- Diarrhea duration: *Lactobacillus GG* > 10^{10} CFU vs. placebo: SMD: –0.82, 95% CI (–1.31 to –0.34) *Lactobacillus GG* ≤ 10^{10} CFU vs. placebo: SMD –0.88, 95%CI (–1.97 to 0.20) *Saccharomyces boulardii* vs. placebo: SMD: -0.81, 95%CI (–1.07 to –0.55) *Lactobacillus reuteri* vs. placebo: SMD: –1.11, 95%CI (–1.45 to –0.77) SUCRA analysis showed racecadotril as the first option followed by smectite and *Lactobacillus reuteri* Secondary outcomes not reported	
Ahmadi et al. 2015 (11)	Up to June 2013/Pubmed, Central, Ovid	Infants and children with rotavirus diarrhea Age range 1-72 months	Probiotic strains	Placebo	Duration of diarrhea	14 RCTs (lactobacillus GG, non-lactobacillus GG, all)	-	- All probiotics: SMD -0.41, 95% CI (-0.56 to –0.25, p<0.001)	Lactobacillus GG subgroup and non-LGG: presentation of results unclear

Feizizadeh et al. 2014 (12)	Up to September 2013/ Pubmed, Central, Embase, others	Children with acute diarrhea Aged 1 month to 15 years	*Saccharomyces Boulardii*	Placebo or no control	Primary: - Duration of diarrhea - Diarrhea lasting ≥4 days - Stool frequency on day 2 after intervention Secondary: - Diarrhea lasting ≥3 days - Stool frequency on day 3 after intervention - Harms	22 trials	≤14 days	Primary: - Reduction of diarrhea duration: MD -19.7 hours, 95% CI (-26.05 to -13.34), P <0.001 - Reduction of stool frequency on day 2: MD --0.74, 95% CI (-1.38 to -0.10), P = 0.023 - Diarrhea on day 4 after intervention compared with the control: RR 0.38, 95% CI (0.24 to 0.59), P<0.001 - Reduced stool frequency on day 3: MD -1.24, 95% CI (-2.13 to -0.35), P = 0.006 - Diarrhea lasting ≥3 days: RR 0.41, 95% CI (0.27 to 0.60), P=0.001	Randomized and non-randomized trials Additional outcomes: - Vomiting duration - Duration of hospitalization - Weight gain
Applegate et al. 2013 (13)	Up to December 2012/ PubMed, Cochrane Library, WHO Regional Databases, Web of Science, Biosis, Popline, Global Health, Scopus, and Embase	Community-acquired acute diarrhea among children < 5 years of age	Probiotics	Suitable control group	Diarrhea duration Stool frequency on the 2nd day Risk of diarrhea hospitalization Diarrhea mortality	8 RCTs	3 loose or watery stools per day	- Diarrhea duration reduction: 14.0%, 95% CI (3.8 to 24.2%) - Stool frequency reduction on the 2nd day: 13.1%, 95% CI (0.8 to 25.3%) - Risk of diarrhea hospitalization: no difference - Diarrhea mortality: no studies identified	
Dinleyici et al. 2012 (14)	Up to October 2011/Pub	Adults and children	*Saccharomyces Boulardii*	placebo or active	Duration of diarrhea	19 RCTs	-	- Duration of diarrhea: pooled WMD -0.99 day (approximately 24 h, 95% CI (-1.40 to -0.58)	Additional outcomes:

	Med, Embase, Central, others	with acute diarrhea		control or no treatment)	Reducing percentage of children with diarrhea Duration of hospitalizatio n Mean number of stools at different time intervals	17 RCTs in children		- Diarrhea at day 3: RR 0.52, 95% CI (0.42 - 0.65)	- Duration of hospitalizat ion; - Diarrhea on days 2;4;5;6;7; - Mean number of stools reported on days 1;2;3,4;5;6;7
Salari et al. 2012 (15)	Search dates not reported/ Pubmed, Scopus, Cochrane, ISI	Children with diarrhea	Probiotics	Placebo	Duration of diarrhea (days) - Number of stools per day - Duration of fever - Duration of hospitalizatio n - Duration of vomiting	20 RCTs	-	- Duration of diarrhea: WMD -0.67 day, 95% CI (-0.95 to -0.38), P<0.0001 - Number of stools per day WMD -0.81, 95% CI (-2.05 to 0.44), P= 0.20	
Allen et al. 2010 (16)	Up to July 2010/ PubMed, Embase, Central, others	Adults and children with acute diarrhea	Specific probiotic	Placebo or no probiotic	Primary: - Duration of diarrhea - Diarrhea lasting ≥4 days - Stool frequency on day 2 after intervention Secondary:	57 RCTs in children among 63 RCTs	Duration < 14 days. Was proven or presumed to be caused by an infectious agent	Primary: - Duration of diarrhea: MD -24.76 hours, 95% CI (-15.9 to -33.6) - Diarrhea lasting ≥4 days: RR 0.41, 95% CI (0.32 to 0.53) - Stool frequency on day 2: MD -0.80, 95% CI (-0.45 to -1.14) Secondary: - Diarrhea lasting ≥3 days: RR 0.62, 95% CI (0.56 to 0.70) - Mean stool frequency on day 3: MD -0.63, 95% CI (-1.18 to -0.07)	

					- Diarrhea lasting ≥3 days - Stool frequency on day 3 after intervention				

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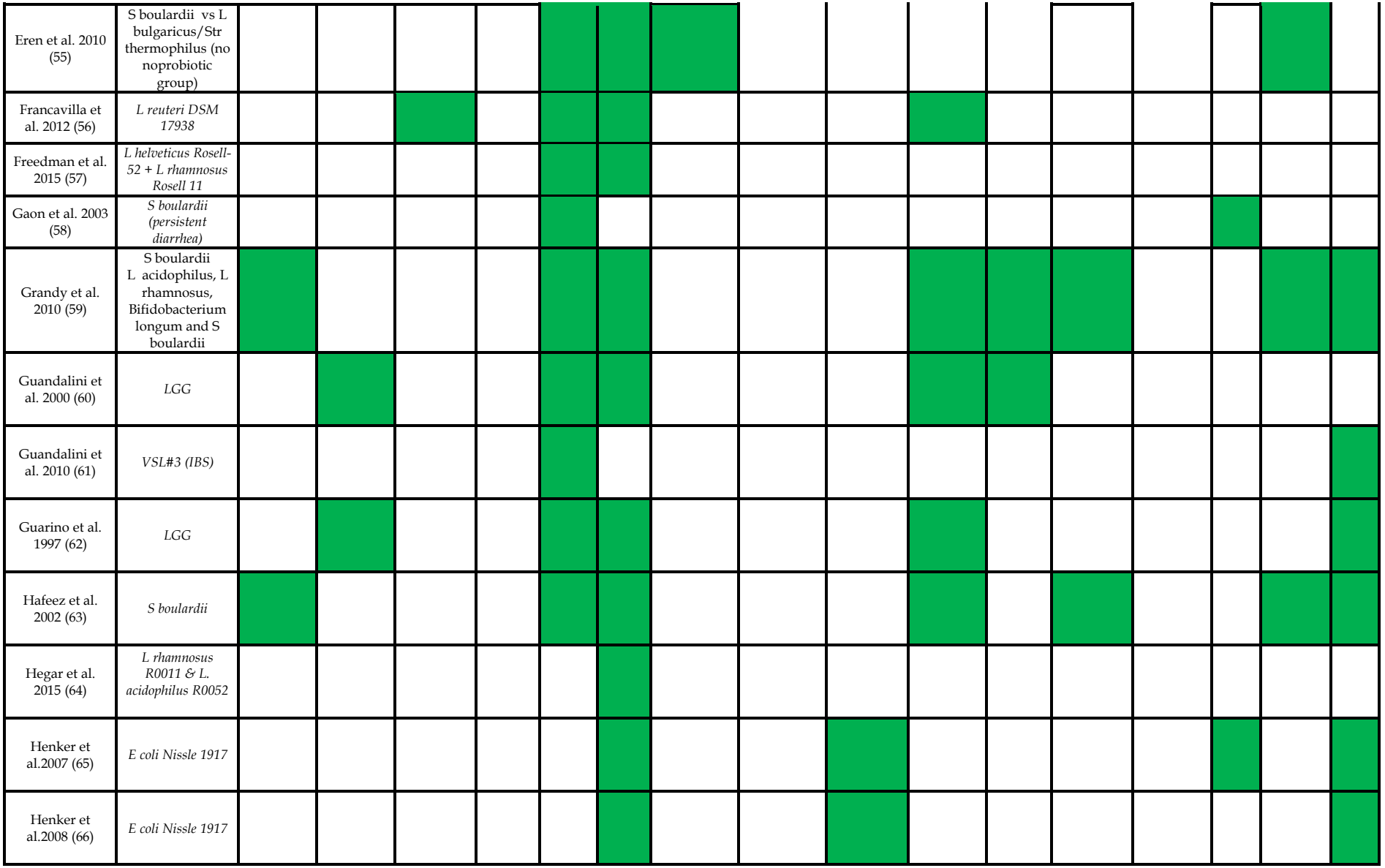
Table S5. Randomized controlled trials (RCTs) in children comparing probiotics with placebo/no intervention included in various systematic reviews/meta-analyses (A) and additionally identified (B).

A. RCTs included in the systematic reviews/meta-analyses

Study ID	Probiotic strain	Szajewska et al. 2020[*S boulardii*] (1)	Szajewska et al. 2019 [*LGG*] (2)	Patro et al. 2019 [*L reuteri DSM 17938*] (3)	Ianiro et al. 2018 [*Bacillus clausii*] (4)	Sniffen et al. 2018 (5)	Florez et al. 2018 (6)	Padayachee et al. 2018 [*S boulardii*] (7)	Zorzela et al. 2017 [inactivated probiotics] (8)	Freedman et al. 2015 (9)	Gutierrez-Castrellon et al. 2015 (10)	Ahmadi et al. 2015 (11)	Feizizadeh et al. 2014 [*S boulardii*] (12)	Applegate et al. 2013 (13)	Salari et al. 2012 (14)	Dinleyici et al. 2012 [*S boulardii*] (15)	Allen et al. 2010 (16)
Abbaskhaniyan et al. 2012 (17)	Fermented yoghurt											■					
Agarwal et al. 2001 (18)	Yoghurt *L casei DN 114001*					■											
Agarwal et al. 2002 (19)	Yoghurt *L casei DN 114001*					■											
Aggarwal et al. 2014 (20)	*LGG*		■														
Agustina et al. 2007 (21)	*L rhamnosus LMG P-22799* + inulin, dietary fiber (soy polysaccharides+ zinc+iron)														■		
Azim et al. 2014 (22)	*S boulardii*	■															
Basu et al. 2007 (23)	*LGG*		■			■	■				■				■		■
Basu et al. 2009 (24)	*LGG*		■				■				■				■		■
Bhat et al. 2018 (25)	*B clausii* *S boulardii*	■															
Bhatnagar et al. 1998 (26)	Yoghurt formula																■
Billoo et al.2006 (27)	*S boulardii*	■				■	■	■			■		■		■	■	■

Boudraa et al. 2001 (28)	*L bulgaricus* and *S thermophilus*																
Boulloche et al. 1994 (29)	*L acidophilus LB strain*																
Burande et al. 2013 (30)	*S boulardii*																
Burki et al. 2017 (31)	*S boulardii*																
Canani et al.2007 (32)	*LGG, S boulardii, L delbrueckii var bulgaricus, L acidophilus, Streptococcus thermophilus, B bifidum; B clausii; Enterococcus faecium SF 68*																
Caragueorendain et al. 1999 (33)	*Lactobacillus acidophilus and bifidus*																
Castaneda et al. 1995 (34)	*S boulardii* chronic diarrhea																
Cetina-Sauri et al. 1994 (35)	*S boulardii*					1989											
Chapoy et al. 1985 (36)	*S boulardii*																
Chen et al. 2010 (37)	*Bacillus mesentericus, Enterococcus faecalis, Clostridium butyricum*																
Chouraqui et al. 1995 (38)	*S boulardii*																
Costa-Ribeiro et al. 2003 (39)	*LGG*																
Correa et al. 2011 (40)	*S boulardii*																

Czerwionka-Szaflarska et al. 2009 (41)	*LGG*		■				■										■
D'Apuzzo 1982 (42)	*Streptococcus faecium*																■
Dalgic et al. 2011 (43)	*S boulardii*	■				■	■	■			■	■	■			■	
Das et al. 2016 (44)	*S boulardii*	■					■										
Dash et al. 2016 (45)	*S boulardii*	■															
Dinleyici et al. 2009 (46)	*S boulardii (Entamoeba histolytica)*	■				■							■			■	
Dinleyici et al. 2011 (47)	*S boulardii (Blastocystis hominis)*					■											
Dinleyici et al. 2014 (48)	*L reuteri DSM 17938*			■		■	■										
Dinleyici et al. 2015 (49)	*S boulardii*	■				■	■										
Dinleyici et al. 2015 (50)	*L reuteri DSM 17938*			■		■	■										
Dubey et al. 2008 (51)	*L acidophilus, L paracasei, L bulgaricus, L plantarum, B breve, B infantis, B longum, S thermophilus (VSL#3)*																■
Dutta et al. 2011 (52)	*L sporogenes (B coagulans)*						■					■					
El-Soud et al.2015 (53)	Milk formula supplemented with *B lactis*						■										
Erdogan et al. 2012 (54)	S boulardii	■				■		■					■				


Eren et al. 2010 (55)
S boulardii vs L bulgaricus/Str thermophilus (no noprobiotic group)
Francavilla et al. 2012 (56)
L reuteri DSM 17938
Freedman et al. 2015 (57)
L helveticus Rosell-52 + L rhamnosus Rosell 11
Gaon et al. 2003 (58)
S boulardii (persistent diarrhea)
Grandy et al. 2010 (59)
S boulardii L acidophilus, L rhamnosus, Bifidobacterium longum and S boulardii
Guandalini et al. 2000 (60)
LGG
Guandalini et al. 2010 (61)
VSL#3 (IBS)
Guarino et al. 1997 (62)
LGG
Hafeez et al. 2002 (63)
S boulardii
Hegar et al. 2015 (64)
L rhamnosus R0011 & L. acidophilus R0052
Henker et al.2007 (65)
E coli Nissle 1917
Henker et al.2008 (66)
E coli Nissle 1917

Hernandez et al. 1998 (67)	*S boulardii*					■	■						■				■
Htwe et al. 2008 (68)	*S boulardii*	■				■	■	■			■		■			■	■
Huang et al. 2012 (conference presentation) (69)	*E faecalis, C butyricum* and *B mesentericus*						■										
Huang et al. 2014 (full paper of Huang et al. 2012) (70)	*E faecalis, C butyricum* and *B mesentericus*						■										
Huseynova et al. 2011 (71)	*S boulardii*												■				
Isolauri et al. 1991 (72)	*LGG fermented milk* *LGG*					■	■										
Isolauri et al. 1994 (73)	*LGG*		■			■	■				■						■
Javeed et al. 2018 (74)	*S boulardii*	■															
Jasinski et al. 2002 (75)	*LGG*		■								■						■
Kaila et al. 1992 (76)	*LGG*					■						■					
Kaila et al. 1995 (77)	*LGG* (viable vs inactivated *LGG)*					■			■								
Khan et al. 2012 (78)	*S boulardii*	■				■	■						■				
Khanna et al. 2005 (79)	Tyndalized (heat-killed)						■		■						■		■

	Lactobacilus acidophilus																
Kianifar et al. 2009 (80)	*L acidophilus & B bifidum*																
Kowalska-Duplaga et al. 1999 (81)	*Bifidobacterium ruminatum*																
Kowalska-Duplaga et al. 2004 (82)	*L acidophilus, B bifidum, L bulgaricus*																
Kumar et al. 2018 (83)	*S boulardii*																
Kurugol et al. 2005 (84)	*S boulardii*																
Lahiri et al. 2008 (clinical study report NCT00457353) (85)	*B clausii*																
Lahiri et al. 2011 (conference abstract) (86)	*B clausii*																
Lahiri et al. 2015 (87)	*B clausii*																
Lahiri et al. 2015 (88)	*B clausii O/C, SIN, N/R, T*																
Lee et al. 2001 (89)	*L. acidophilus & Bifidobacteria infantis*																
Lee et al. 2015 (90)	*Bifidobacterium longum, Bifidobacterium lactis, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus plantarum, Pediococcus pentosaceus*																
Le Luyer et al. 2010 (91)	*S boulardii* (infant formula)																

Lievin-Le Moal et al. 2007 (92)	*L acidophilus LB*					■			■								■
Majamaa et al. 1995 (93)	*LGG*					■	■										
Manyal et al. 2015 (94)	*Lactobacillus sporogenes* + Zinc						■										
Mao et al. 2008 (95)	Milk formula + *Streptococcus thermophilus, Bifidobacterium lactis*														■		■
Maugo et al. 2012 (96)	*B claussi*				■												
Miele et al. 2009 (97)	*VSL#3* (ulcerative colitis)					■											
Misra et al. 2009 (98)	*LGG*		■				■				■			■			■
Moal et al. 2007 (99)	*L acidophilus LB*						■								■		
Narayanappa et al. 2008 (100)	*Bifilac* (no strain specification)						■					■			■		■
Nixon et al. 2012 (101)	*LGG*		■				■			■							
Oandasan et al.1999 (102)	*L acidophilius and L bifidus*						■										■
Ozkan et al. 2007 (103)	*S boulardii*	■				■	■	■					■			■	■
Pant et al. 1996 (104)	*LGG* [Data reported only for a subset of recruited subjects with watery diarrhoea (26/40, 65%). No data for children with bloody stools]					■	■										■
Pashapour et al. 2006 (105)	Pasteurized cow's milk yogurt (*L*														■		■

	bulgaricus & S thermophilus)																
Phavichitr et al. 2013 (106)	*Lactobacillus acidophilus* + *Bifidobacterium bifidum* viv. lyophilisat with lactose + magnesium stearate as excipients																
Pedone et al. 1999 (107)	Fermented milk *L casei DN 114 001*																
Pociecha et al. 1998 (108)	*L rhamnosus E/N, Oxy, and Pen* + smectite vs *L rhamnosus E/N, Oxy, and Pen* only																
Raafey et al. 2008 (109)	*Lactobacillus acidophilus*																
Raza et al. 1995 (110)	*LGG*																
Rerksuppaphol et al. 2010 (111)	*Lactobacillus acidophilus* + *Bifidobacterium bifidum* at 4 Celsius *Lactobacillus acidophilus* + *Bifidobacterium bifidum a*t room temperature																
Riaz et al. 2012 (112)	*S boulardii*																
Ritchie et al. 2010 (113)	*LGG*																
Rosenfeldt et al. 2002 (hospitalized) (114)	*L rhamnosus 19070-2 and L reuteri DSM 12246*																
Rosenfeldt et al. 2002 (non hospitalized) (115)	L rhamnosus 19070-2 and L reuteri DSM 12246																

Salazar-Lindo et al. 2007 (116)	*LGG*		■			■			■						■		
Savas-Erdeve & Gokay 2009 (117)	*S boulardii* (amebiasis)	■				■							■			■	
Sarker et al. 2005 (118)	Lactobacillus paracasei *ST11*						■					■			■		■
Schnadower et al. 2018 (119)	*LGG*		■														
Sepp et al. 1995 (120)	*L casei GG* + *trimethoprim*																■
Shan et al. 2013 (121)	*S boulardii* (part of AAD study)					■											
Sharif et al. 2016 (122)	*S boulardii*	■															
Shornikova et al. 1997 (123)	*LGG*		■				■				■	■					■
Shornikova et al. 1997 (124)	*L reuteri*						■				■						■
Shornikova et al. 1997 (125)	*L reuteri*						■				■	■					■
Simakachorn et al. 2000 (126)	*L acidophilus LB*					■	■		■			■					■
Sindhu et al. 2014 (127)	*LGG*		■			■	■										
Sirsat et al. 2017 (128)	*S boulardii*	■															

Sugita et al. 1994 (129)	*L casei*																■
Szymański et al. 2006 (130)	*L rhamnosus strains (573L/1; 573L/2; 573L/3)*						■					■			■		■
Szymański et al. 2019 (131)	*L reuteri DSM 17938*			■													
Taborska et al. 1997 (132)	*L acidophilus ND*																■
Teran et al. 2009 (133)	*L acidophilus, L rhamnosus, B longum, S boulardii*						■								■		■
Thibault et al. 2004 (134)	Infant formula with *Bifidobacterium breve c50 & Streptococcus thermophilus 065*														■		
Tlaskal et al. 1995 (135)	*L acidophilus (helveticum R52) + L rhamnosus R11*					■											
Tlaskal et al. 2005 (136)	*L acidophilus /helveticum R52 + L rhamnosus R11*					■											
Upadhyay et al. 2014 (137)	*LGG*						■										
Urganci et al. 2001 (138)	*S boulardii*					■	■						■				■
Urtula and Dacula 2008 (139)	*B clausii*				■												
Vandenplas et al. 2007 (140)	*S boulardii*	■				■							■			■	
Villarruel et al. 2007 (141)	*S boulardii*	■				■	■				■		■		■	■	■
Veereman-Wauters et al. 2009 (142)	*LGG, L acidophilus, L casei, L plantarum, B infantis*													■			
Vidjadevan et al. 2017/2018 (143) (144)	*B clausii S boulardii*	■															

Vivatvakin et al. 2006 (145)	*L acidophilus, Bifidobacterium infantis*																

B. RCTs meeting the inclusion criteria but not included in the systematic reviews

Study ID	**Probiotic strain**
Freedman 2018 (146)	*Lactobacillus rhamnosus R0011 and L. helveticus R0052*
Hamid et al. 2019 (147)	*B clausii*
Houeiss et al. 2018 (148)	*B clausii* *L acidophilus* + *B lactis*
Hong Chau et al. 2018 (149)	*L acidophilus*
Hung-Hsiang Lai et al. 2019 (150)	*Lactobacillus casei*
Sudha et al. 2019 (151)	*B clausii UBBC-07*

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Use of Probiotics for the Management of Acute Gastroenteritis

Figure S1. *Saccharomyces boulardii* vs. control. Duration of diarrhea & Duration of hospitalization

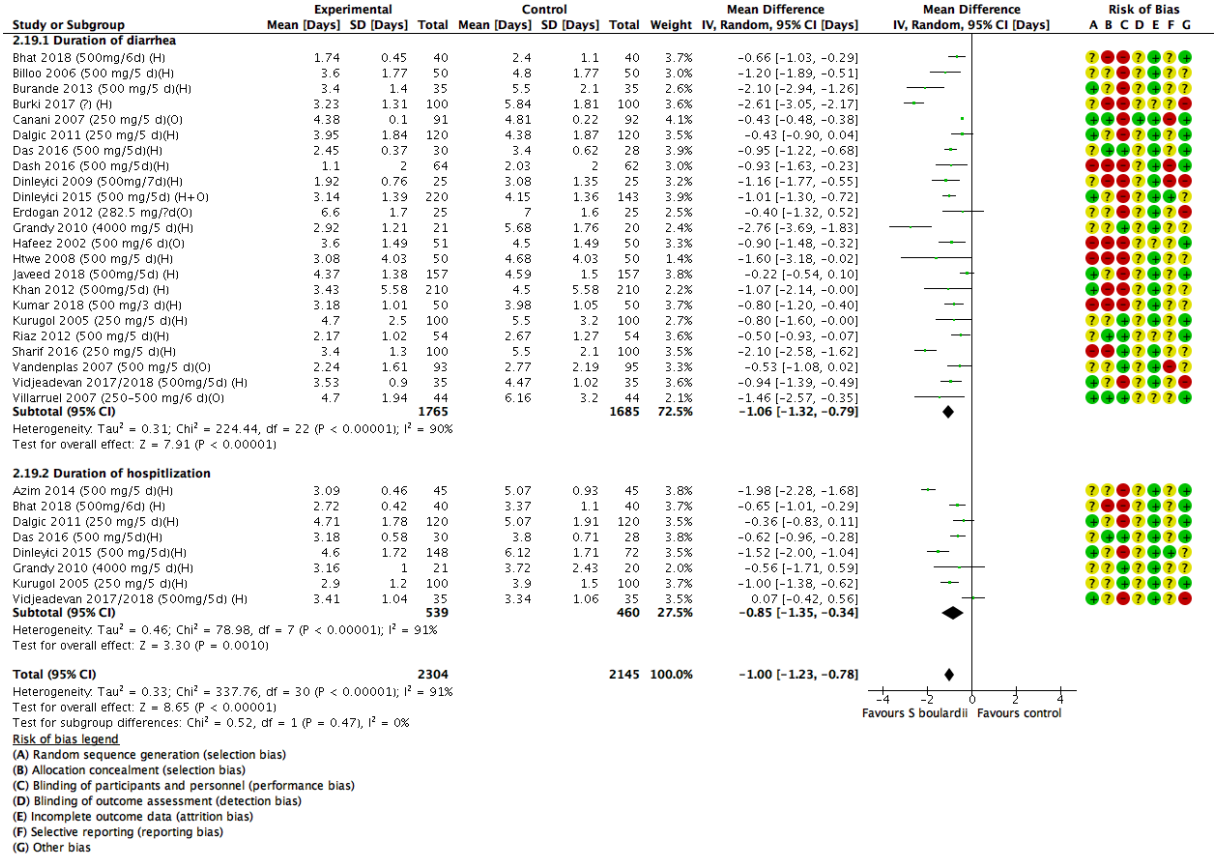


Figure S2. *Saccharomyces boulardii* vs. control. Need for hospitalization in outpatients.

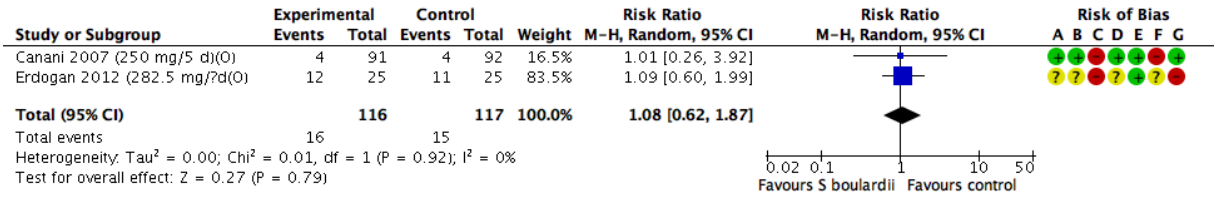
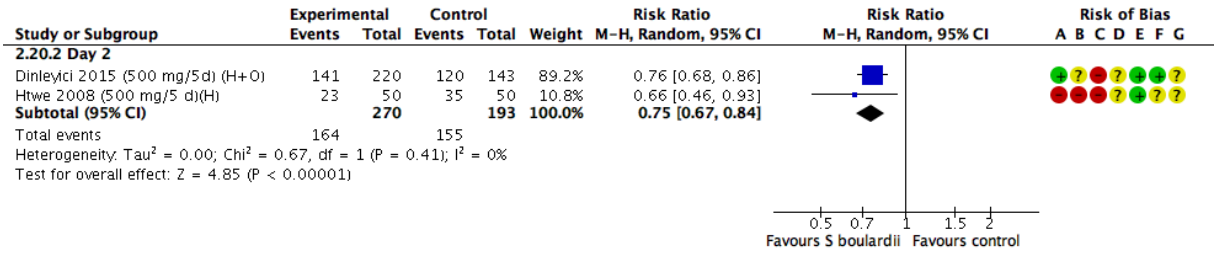


Figure S3. ***Saccharomyces boulardii*** **vs. control. Diarrhea on day 2.**



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure S4. *Lactobacillus rhamnosus* GG vs. control. Duration of diarrhea

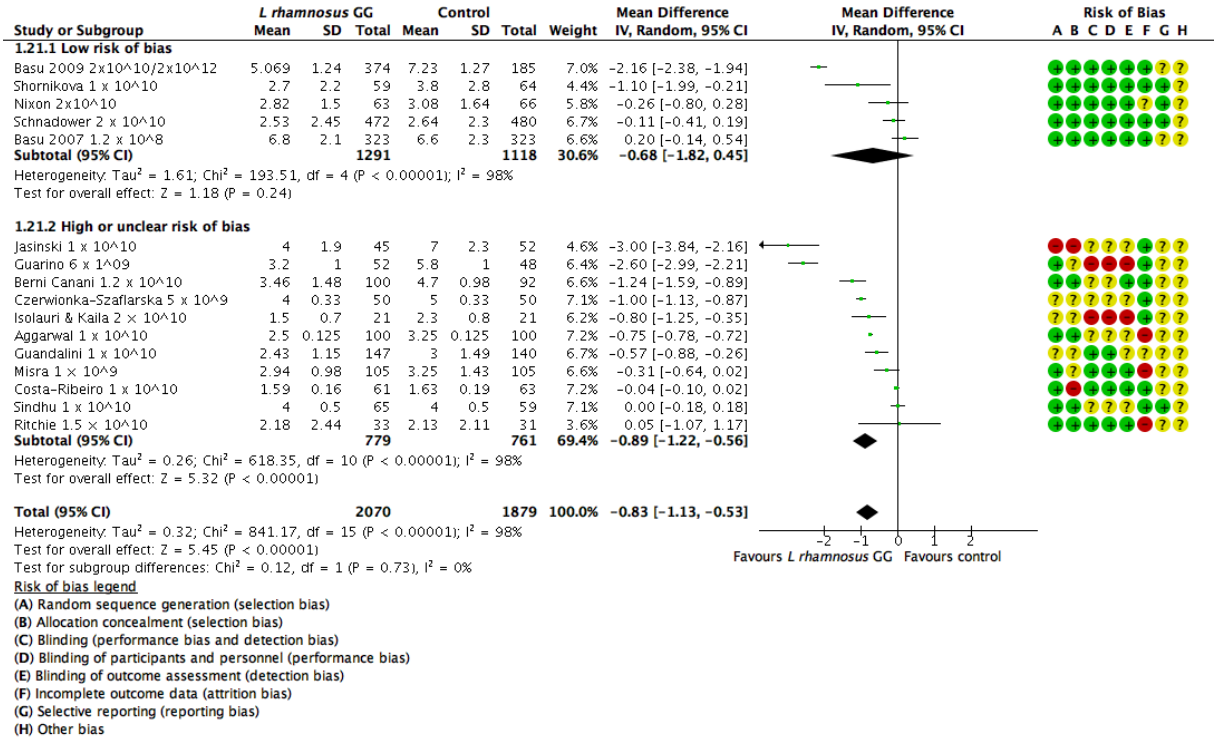


Figure S5. *Lactobacillus rhamnosus* GG vs. control. Duration of hospitalization.

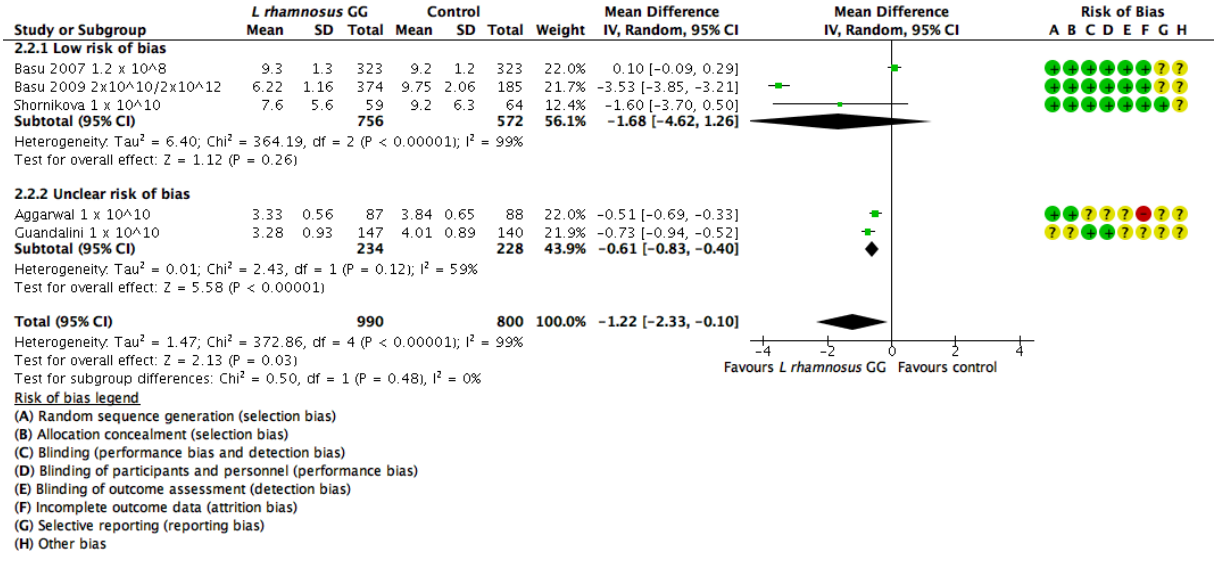
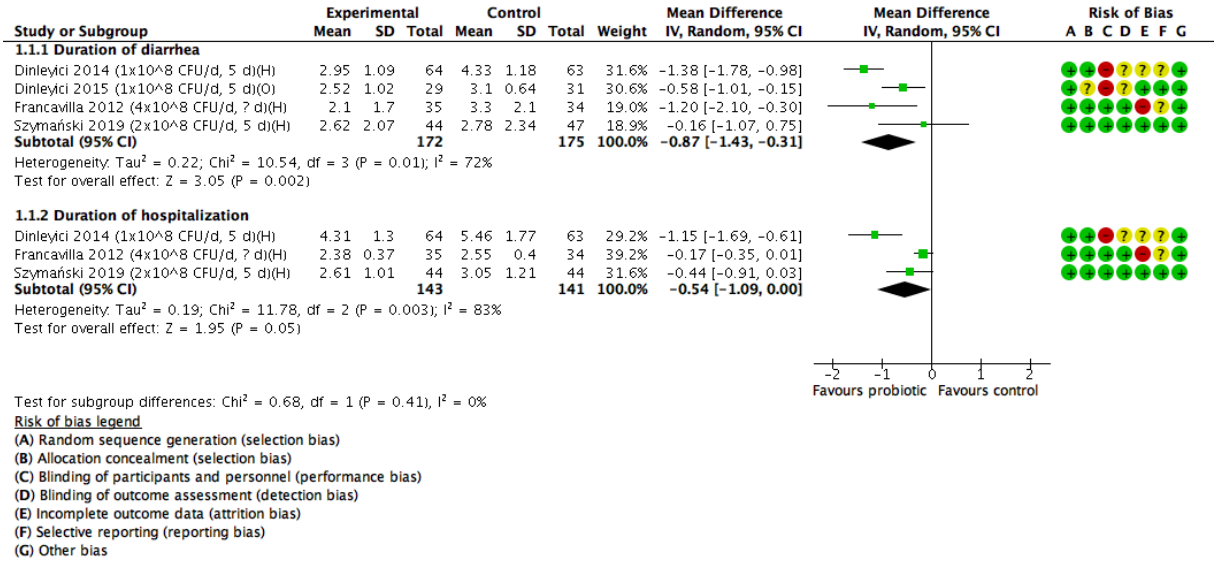


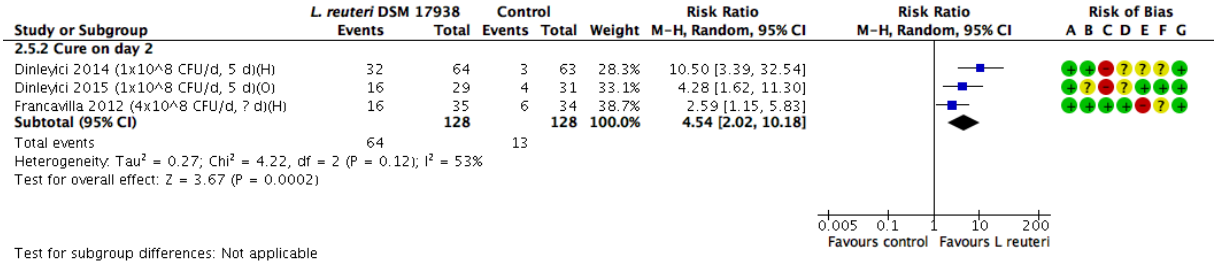
Figure S6. *Lactobacillus reuteri* DSM 17938 vs. control. Duration of diarrhea & Duration of hospitalization



Test for subgroup differences: Chi² = 0.68, df = 1 (P = 0.41), I² = 0%

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

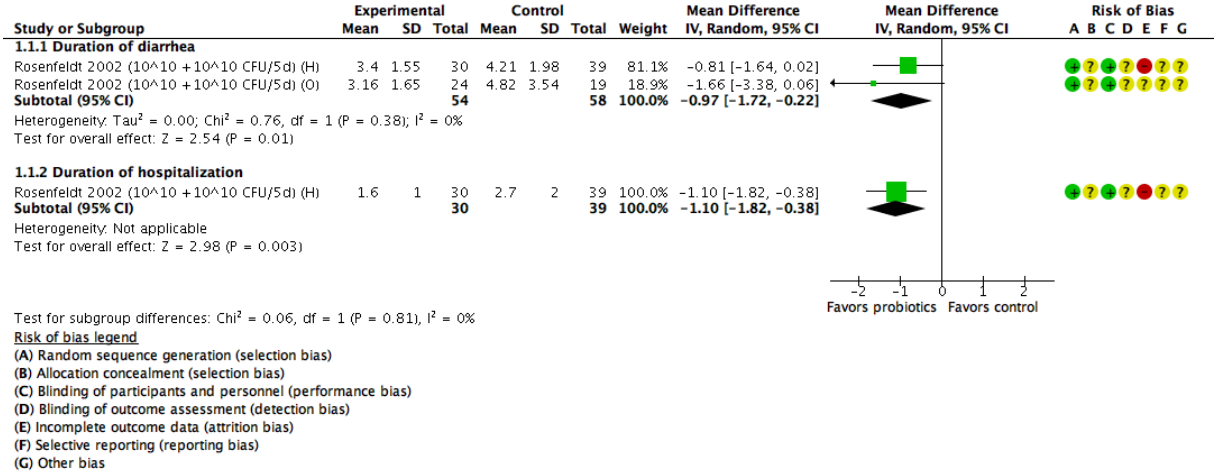
Figure S7. *Lactobacillus reuteri* DSM 17938 vs. control. Cure on day 2.



Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure S8. *L. rhamnosus* 19070-2 & *L. reuteri* DSM 12246 vs control. Duration of diarrhea & Duration of hospitalization

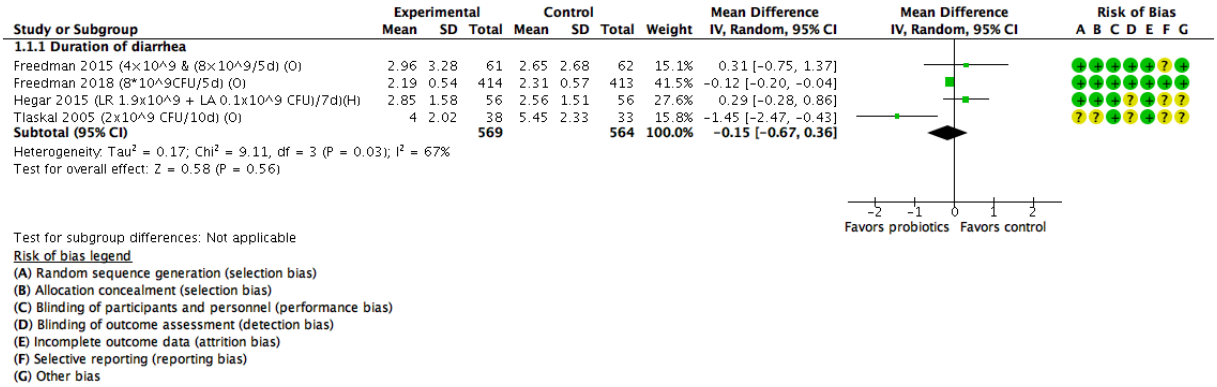


Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure S9. *L helveticus* R0052 & *L rhamnosus* R0011 vs control. Duration of diarrhea

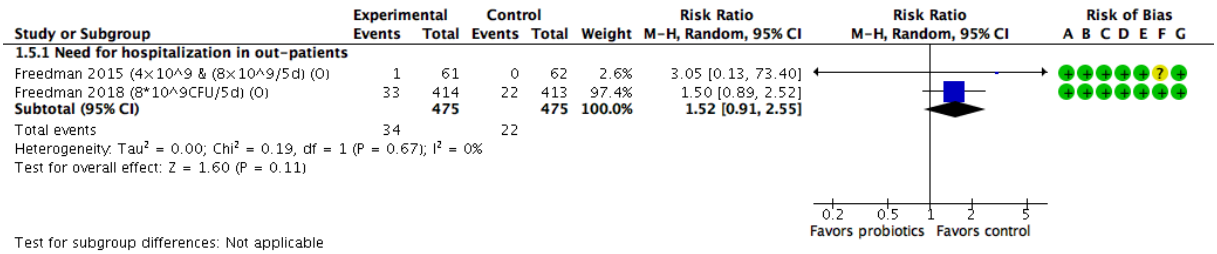


Test for subgroup differences: Not applicable

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure S10. *L helveticus* R0052 & *L rhamnosus* R0011 vs placebo. Need for hospitalization in out-patients.



Test for subgroup differences: Not applicable

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure S11. *Bacillus clausii* O/C, SIN, N/R, and T vs control. Duration of diarrhea

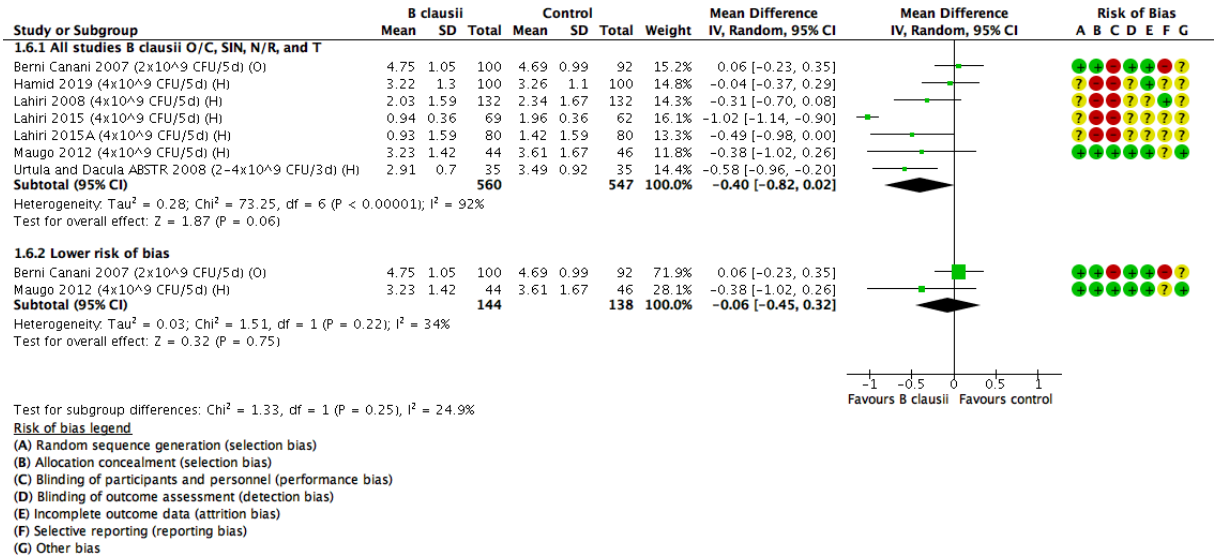
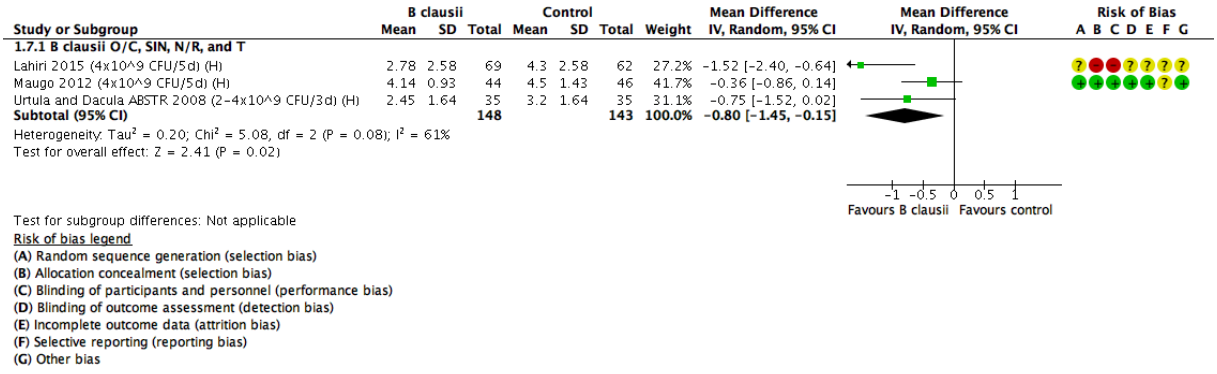


Figure S12. *Bacillus clausii* O/C, SIN, N/R, and T. Duration of hospitalization.



Comment: Urtula & Dacula 2008. Published as an abstract only.

Use of Probiotics for the Management of Acute Gastroenteritis

Question: Lactobacillus GG compared to controls for acute diarrhea

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactobacillus GG	controls	Relative (95% CI)	Absolute (95% CI)		
Lactobacillus GG vs. control. Duration of diarrhea.												
16	randomized trials	serious [a]	serious [b]	serious [c]	serious [d]	none	2070	1879	-	MD 0.83 days lower (1.13 lower to 0.53 lower)	⨁◯◯◯ VERY LOW	
Lactobacillus GG vs. control. Hospitalization.												
5	randomized trials	serious [a]	serious [b]	not serious	serious [d]	none	990	800	-	MD 1.22 days lower (2.33 lower to 0.1 lower)	⨁◯◯◯ VERY LOW	
Lactobacillus GG vs. control. Duration of diarrhea. Low risk of bias studies only												
5	randomized trials	not serious	serious [b]	serious [c]	serious [d]	none	1291	1118	-	MD 0.68 days lower (1.82 lower to 0.45 higher)	⨁◯◯◯ VERY LOW	
Lactobacillus GG vs. control. Presence of diarrhea. Diarrhea on day 2												
1	randomized trials	serious [e]	not serious	serious [f]	very serious [d,g]	none	5/19 (26.3%)	12/17 (70.6%)	RR 0.37 (0.17 to 0.84)	445 fewer per 1 000 (from 586 fewer to 113 fewer)	⨁◯◯◯ VERY LOW	

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

Explanations

a. Unclear risk of bias in some studies
b. Large heterogeneity I^2=98% ($p<0.05$)
c. Different definitions of diarrhea
d. The recommendation would be altered if the lower versus the upper boundary of the CI represented the true underlying effect (based on the assumption that 1-day reduction is clinically important)
e. Unclear: random sequence generation and allocation concealment
f. Non-European population
g. Small sample size

Question: Lactobacillus reuteri DSM 17938 compared to placebo/ no treatment for acute gastroenteritis in children

Setting:

Bibliography: . [Intervention] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactobacillus reuteri DSM 17938	placebo/ no treatment	Relative (95% CI)	Absolute (95% CI)		
Lactobacillus reuteri DSM 17938 vs. control. Duration of diarrhea (days)												
4	randomized trials	serious [a]	serious [b]	serious [c]	serious [d]	none	172	175	-	MD 0.87 days lower (1.43 lower to 0.31 lower)	⊕◯◯◯ VERY LOW	
Lactobacillus reuteri DSM 17938 vs. control. Cure on day 2												
3	randomized trials	serious [a]	not serious	serious [e]	not serious	none	64/128 (50.0%)	13/128 (10.2%)	RR 4.54 (2.02 to 10.18)	360 more per 1 000 (from 104 more to 932 more)	⊕⊕◯◯ LOW	
Lactobacillus reuteri DSM 17938 vs. control. Duration of hospitalization												
3	randomized trials	serious [f]	serious [g]	serious [e]	serious [d]	none	143	141	-	MD 0.54 days lower (1.09 lower to 0)	⊕◯◯◯ VERY LOW	

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

Explanations

a. 2 out of 4 studies open label
b. Large heterogeneity I^2=74% (p<0.05)
c. Differences in dosage across studies; 2 out of 4 included studies in non-European population
d. The recommendation would be altered if the lower versus the upper boundary of the CI represented the true underlying effect (based on the assumption that 1-day reduction is clinically important)
e. Population differences (European and non-European).
f. No blinding in 1 out of 3 studies
g. Test for heterogeneity p<0.05; I^2 =83%

Question: Saccharomyces boulardii compared to placebo/ no treatment for acute gastroenteritis in children

Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Saccharomyces boulardii	placebo/no treatment	Relative (95% CI)	Absolute (95% CI)		
Saccharomyces boulardii vs. control. Duration of diarrhea												
23	randomized trials	serious [a]	serious [b]	serious [c]	serious [d]	none	1765	1685	-	MD 1.06 days lower (1.32 lower to 0.79 lower)	⨁◯◯◯ VERY LOW	
Saccharomyces boulardii vs. control. Duration of hospitalization												
8	randomized trials	serious [a]	serious [e]	serious [f]	serious [d]	none	539	460	-	MD 0.85 days lower (1.35 lower to 0.34 lower)	⨁◯◯◯ VERY LOW	
Saccharomyces boulardii vs. control. Need for hospitalization												
2	randomized trials	serious [g]	not serious	not serious	very serious [h]	none	16/116 (13.8%)	15/117 (12.8%)	RR 1.08 (0.62 to 1.87)	10 more per 1000 (from 49 fewer to 112 more)	⨁◯◯◯ VERY LOW	
Saccharomyces boulardii vs. control. Diarrhea on day 2												
2	randomized trials	serious [g]	not serious	serious [i]	not serious	none	164/270 (60.7%)	155/193 (80.3%)	RR 0.75 (0.67 to 0.84)	201 fewer per 1000 (from 265 fewer to 128 fewer)	⨁⨁◯◯ LOW	

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

Explanations

a. In most studies, no blinding ensured
b. Substantial heterogeneity I^2=90% (p<0.05), not explained by the subgroup analyses
c. A different definition of diarrhoea across the studies; only one study from the European population
d. The recommendation would be altered if the lower versus the upper boundary of the CI represented the true underlying effect (based on the assumption that 1-day reduction is clinically important)
e. Large heterogeneity (>=90%; p<0.05)
f. Origin of most of the trials outside from Europe
g. No blinding ensured
h. As there are few events and the CI includes appreciable benefit and harm - rated down the quality of evidence by two levels for imprecision.
i. Non-European population

Question: Bacillus clausii O/C, SIN, N/R, and T compared to placebo/no treatment for acute gastroenteritis in children

Author(s):
Question: Bacillus clausii compared to placebo for acute gastroenteritis in children
Setting:
Bibliography: . [Intervention] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bacillus clausii	placebo	Relative (95% CI)	Absolute (95% CI)		
Duration of diarrhoea (strain specifications) - B clausii O/C, SIN, N/R, and T												
7	randomised trials	very serious [a]	serious [b]	serious [c]	serious [d]	none	560	547	-	MD 0.4 days lower (0.82 lower to 0.02 higher)	⨁◯◯◯ VERY LOW	
Duration of hospitalization (strain specification - B clausii O/C, SIN, N/R, and T												
3	randomised trials	very serious [e]	not serious	serious [f]	serious [d]	none	148	143	-	MD 0.8 lower (1.45 lower to 0.15 lower)	⨁◯◯◯ VERY LOW	
Duration of diarrhea (B clausii O/C, SIN, N/R, and T)) - Lower risk of bias												
2	randomised trials	serious [g]	not serious	serious [c]	serious [d]	none	144	138	-	MD 0.06 lower (0.45 lower to 0.32 higher)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; MD: Mean difference

Explanations

a. Only one study with blinding ensured; one study - data based on the published systematic review (no access to abstract) - not possible to assess the risk of bias); Unclear randomization in most included trials.
b. Large, unexplained heterogeneity I2=92%; p<0.05
c. Only one RCT from the European setting
d. The recommendation would be altered if the lower versus the upper boundary of the CI represented the true underlying effect.
e. Only one study with blinding ensured; one study - data based on the published systematic review (no access to abstract) - not possible to assess the risk of bias)
f. All included trials from non-European populations
g. One RCT- two domains with high risk of bias

Question: L helveticus R0052 & L rhamnosus R0011 compared to placebo / no treatment for acute gastroenteritis in children

Setting:

Bibliography: . [Intervention] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	L helveticus R0052 & L rhamnosus R0011	placebo / no treatment	Relative (95% CI)	Absolute (95% CI)		
Should L helveticus R0052 & L rhamnosus R0011 vs. control. Duration of diarrhea (follow up: range 5 days to 10 days)												
4	randomized trials	not serious	serious [a]	not serious	not serious	none	569	564	-	MD 0.15 days lower (0.67 lower to 0.36 higher)	⊕⊕⊕◯ MODERATE	CRITICAL
Should L helveticus R0052 & L rhamnosus R0011 vs. control. Need for hospitalization in out-patients												
2	randomized trials	not serious	not serious	not serious	serious [b]	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	

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

Explanations

a. Minimal or no overlap of confidence intervals, which suggests variation is more than what one would expect by chance alone (1 RCT); heterogeneity 67%; heterogeneity p<0.05; some variation in effect.
b. The recommendation would be altered if the lower versus the upper boundary of the CI represented the true underlying effect

Question: L rhamnosus 19070-2 & L reuteri DSM 12246 compared to placebo/no treatment for acute gastroenteritis in children

Setting:

Bibliography: . [Intervention] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

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/no treatment	Relative (95% CI)	Absolute (95% CI)		
L. rhamnosus 19070-2 & L. reuteri DSM 12246 vs. control. Duration of diarrhea												
2	randomized trials	serious [a]	not serious	not serious	very serious [b]	none	54	58	-	MD 0.97 days lower (1.72 lower to 0.22 lower)	⨁◯◯◯ VERY LOW	
L. rhamnosus 19070-2 & L. reuteri DSM 12246 vs. control. Duration of hospitalization												
1	randomized trials	serious [c]	not serious	not serious	very serious [b]	none	30	39	-	MD 1.1 days lower (1.82 lower to 0.38 lower)	⨁◯◯◯ VERY LOW	

CI: Confidence interval; MD: Mean difference

Explanations

a. Unclear information about allocation concealment in included trials - can potentially lower confidence in the estimate of effect
b. Downgraded due to small sample size. The recommendation would be altered if the lower versus the upper boundary of the CI represented the true underlying effect (based on the assumption that 1-day reduction is clinically important)
c. Unclear information on allocation concealment; high risk of attrition bias