Supplementary Material 5: Tolerability results of probiotics for antibiotic-associated diarrhea and publication bias

Table S5.1. Network and traditional meta-analysis results for total occurrence of adverse events, and quality of evidence.

Interventions	Total occurrence of adverse events			
	Network meta-analysis OR (95% CI)	Quality of evidence	Pairwise meta-analysis OR (95% CI)	Quality of evidence
Multi-genera II vs. Placebo	0.49 (0.28, 0.87)	Low*†§ψ	0.80 (0.68, 0.94)	Low*†§ψ
Multi-genera III vs. Placebo	0.98 (0.46, 2.08)	Moderate*	1.33 (0.98, 1.80)	Moderate*
LGG vs. Placebo	0.35 (0.14, 0.86)	Moderate*ψ	0.27 (0.14, 0.52)	Moderate*ψ
L. rhamnosus vs. Placebo	0.47 (0.05, 4.35)	Low†‡ψ	0.39 (0.05, 2.80)	Low†‡ψ
L. casei vs. Placebo	0.47 (0.14, 1.61)	Moderate†ψ	0.48 (0.22, 1.04)	Moderate‡ψ
L. acidophilus vs. Placebo	0.70 (0.29, 1.68)	Moderate*	0.95 (0.67, 1.34)	Moderate*
L. reuteri vs. Placebo	0.22 (0.03, 1.58)	Low*†ψ	0.25 (0.06, 0.94)	Low*†ψ
L. plantarum vs. Placebo	1.04 (0.13, 8.37)	Low*‡	1.04 (0.20, 5.28)	Moderate*
B. clausii vs. Placebo	0.40 (0.09, 1.87)	Moderate*ψ	0.42 (0.19, 0.91)	Moderate*ψ
S. boulardii vs. Placebo	0.43 (0.21, 0.86)	Moderate†ψ	0.51 (0.36, 0.74)	Moderate†ψ
Multi-genera III vs. Multi-genera II	1.98 (0.81, 4.82)	Very low*†§	0.65 (0.23, 1.84)	Very low*†‡§
LGG vs. Multi-genera II	0.71	Low*†	1.33	Moderate*†ψ

	(0.25, 1.99)		(0.26, 6.83)	
L. rhamnosus vs. Multi-genera II	0.96 (0.10, 9.43)	Very low*†‡	NA	NA
L. casei vs. Multi-genera II	0.95 (0.24, 3.68)	Low*†	NA	NA
L. acidophilus vs. Multi-genera II	1.41 (0.50, 3.97)	Low*†	NA	NA
L. reuteri vs. Multi-genera II	0.44 (0.05, 3.46)	Low*†‡ψ	NA	NA
L. plantarum vs. Multi-genera II	2.10 (0.24, 18.21)	Low*†‡ψ	NA	NA
B. clausii vs. Multi-genera II	0.82 (0.16, 4.18)	Very low*†‡	NA	NA
S. boulardii vs. Multi-genera II	0.87 (0.36, 2.08)	Very low*†§	1.00 (0.18, 5.63)	Low*†§ψ
LGG vs. Multi-genera III	0.36 (0.11, 1.16)	Moderate*ψ	NA	NA
L. rhamnosus vs. Multi-genera III	0.48 (0.05, 5.03)	Moderate*‡ψ	NA	NA
L. casei vs. Multi-genera III	0.48 (0.11, 2.03)	Moderate*†ψ	NA	NA
L. acidophilus vs. Multi-genera III	0.71 (0.23, 2.24)	Moderate*	NA	NA
L. reuteri vs. Multi-genera III	0.22 (0.03, 1.86)	Moderate*‡ψ	NA	NA
L. plantarum vs. Multi-genera III	1.06 (0.12, 9.75)	Low*‡	NA	NA
B. clausii vs. Multi-genera III	0.41 (0.08, 2.28)	Moderate*‡ψ	NA	NA
S. boulardii vs. Multi-genera III	0.44 (0.16, 1.22)	Moderate*†ψ	NA	NA
L. rhamnosus vs. LGG	1.35 (0.12, 14.73)	Moderate‡	NA	NA
L. casei vs. LGG	1.33 (0.29, 6.14)	High	NA	NA

L. acidophilus vs. LGG	1.99 (0.56, 6.99)	High	NA	NA
L. reuteri vs. LGG	0.61 (0.07, 5.74)	Moderate*	NA	NA
L. plantarum vs. LGG	2.96 (0.31, 28.65)	Low*‡	NA	NA
B. clausii vs. LGG	1.15 (0.20, 6.80)	Moderate*	NA	NA
S. boulardii vs. LGG	1.22 (0.41, 3.66)	Moderate†	0.75 (0.15, 3.84)	High†ψ
L. casei vs. *L. rhamnosus*	0.99 (0.08, 12.56)	Low†‡	NA	NA
L. acidophilus vs. *L. rhamnosus*	1.48 (0.14, 16.07)	Moderate‡	NA	NA
L. reuteri vs. *L. rhamnosus*	0.46 (0.02, 9.01)	Moderate*‡ψ	NA	NA
L. plantarum vs. *L. rhamnosus*	2.20 (0.10, 46.18)	Low*‡	NA	NA
B. clausii vs. *L. rhamnosus*	0.86 (0.06, 12.69)	Low*‡	NA	NA
S. boulardii vs. *L. rhamnosus*	0.91 (0.09, 9.30)	Low†‡	NA	NA
L. acidophilus vs. *L. casei*	1.49 (0.33, 6.78)	High	NA	NA
L. reuteri vs. *L. casei*	0.46 (0.04, 4.81)	Moderate*†ψ	NA	NA
L. plantarum vs. *L. casei*	2.22 (0.20, 25.08)	Very low*†‡	NA	NA
B. clausii vs. *L. casei*	0.86 (0.12, 6.19)	Very low*†‡	NA	NA
S. boulardii vs. *L. casei*	0.92 (0.22, 3.79)	Moderate†	NA	NA
L. reuteri vs. *L. acidophilus*	0.31 (0.03, 2.73)	Highψ	NA	NA
L. plantarum vs. *L. acidophilus*	1.49	Moderate‡	NA	NA

	(0.15, 14.32)			
B. clausii vs. *L. acidophilus*	0.58 (0.10, 3.39)	Moderate‡	NA	NA
S. boulardii vs. *L. acidophilus*	0.62 (0.20, 1.88)	Moderate†	NA	NA
L. plantarum vs. *L. reuteri*	4.82 (0.27, 86.32)	Moderate*‡ψ	NA	NA
B. clausii vs. *L. reuteri*	1.88 (0.15, 23.20)	Low*‡	NA	NA
S. boulardii vs. *L. reuteri*	1.99 (0.24, 16.46)	Moderate†	NA	NA
B. clausii vs. *L. plantarum*	0.39 (0.03, 5.18)	Moderate*‡ψ	NA	NA
S. boulardii vs. *L. plantarum*	0.41 (0.05, 3.73)	Moderate†‡ψ	NA	NA
S. boulardii vs. *B. clausii*	1.06 (0.20, 5.71)	Low†‡	NA	NA

Abbreviations: OR=odds ratio; CI=confidence interval; NA=not applicable.

*Limitations in study design or execution (risk of bias); †Inconsistency in results; ¶Indirectness of evidence; ‡Imprecision of results; §Publication bias; ψMagnitude of the effect.

Table S5.2. Traditional meta-analysis results for total occurrence of adverse events.

Interventions	Trails	Partici pants	Effect Estimate OR (95% CI)	Heterogeneity
Multi-genera II vs. Placebo	8	4204	0.80 (0.68, 0.94)	P=0.00, I^2=69.0% (35.3%, 85.2%), tau^2=0.33
Multi-genera III vs. Placebo	6	1132	1.33 (0.98, 1.80)	P=0.19, I^2=33.9% (0.0%, 72.9%), tau^2=0.09
LGG vs. Placebo	3	305	0.27 (0.14, 0.52)	P=0.60, I^2=0.0%, tau^2=0.00
L. rhamnosus vs. Placebo	2	412	0.39 (0.05, 2.80)	P=0.97, I^2=0.0%, tau^2=0.00
L. casei vs. Placebo	2	156	0.48 (0.22, 1.04)	P=0.20, I^2=36.9% (0.0%, 80.0%), tau^2=0.16
L. acidophilus vs. Placebo	5	904	0.95 (0.67, 1.34)	P=0.33, I^2=13.8% (0.0%, 58.3%), tau^2=0.05
L. reuteri vs. Placebo	1	40	0.25 (0.06, 0.94)	NA
L. plantarum vs. Placebo	1	163	1.04 (0.20, 5.28)	NA
B. clausii vs. Placebo	1	100	0.42 (0.19, 0.91)	NA
S. boulardii vs. Placebo	6	1118	0.51 (0.36, 0.74)	P=0.07, I^2=45.0% (0.0%, 70.7%), tau^2=0.18
Multi-genera III vs. Multi-genera II	1	249	0.65 (0.23, 1.84)	NA
LGG vs. Multi-genera II	1	43	1.33 (0.26, 6.83)	NA
S. boulardii vs. Multi-genera II	1	42	1.00 (0.18, 5.63)	NA
S. boulardii vs. LGG	1	43	0.75 (0.15, 3.84)	NA

Abbreviations: OR=odds ratio; CI=confidence interval; NA=not applicable.

Table S5.3. SUCRA values and effectiveness ranking for occurrence of adverse event subtypes.

Interventions	Abdominal or epigastric pain Network meta-analysis: OR (95% CI)	SUCRA value	Mean rank #	Constipation Network meta-analysis: OR (95% CI)	SUCRA value	Mean rank#	Flatulence Network meta-analysis: OR (95% CI)	SUCRA value	Mean rank#	Vomiting Network meta-analysis: OR (95% CI)	SUCRA value	Mean rank#	Nausea Network meta-analysis: OR (95% CI)	SUCRA value	Mean rank#
Placebo	Reference	26.0	6.9	Reference	41.9	5.1	Reference	26.8	6.1	Reference	59.2	3.9	Reference	18.8	6.7
Multi-genera II	0.65 (0.37, 1.16)	56.1	4.5	0.32 (0.09, 1.09)	87.9	1.8	1.01 (0.79, 1.28)	34.6	5.6	0.49 (0.14, 1.75)	78.0	2.5	0.91 (0.43, 1.94)	29.9	5.9
Multi-genera III	0.61 (0.32, 1.16)	40.2	5.8	1.12 (0.50, 2.49)	37.9	5.3	0.92 (0.59, 1.43)	37.3	5.4	0.68 (0.23, 2.03)	30.3	5.9	0.70 (0.30, 1.63)	47.0	4.7
LGG	1.21 (0.41, 3.61)	22.7	7.2	1.20 (0.47, 3.02)	36.8	5.4	0.63 (0.41, 0.97)	74.7	2.8	0.40 (0.04, 4.25)	77.7	2.6	0.48 (0.17, 1.35)	74.6	2.8
L. rhamnosus	0.97 (0.17, 5.36)	36.8	6.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
L. casei	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
L. acidophilus	0.46	70.2	3.4	0.93	49.6	4.5	0.63	66.9	3.3	2.25	29.5	5.9	0.65	51.4	4.4

	OR (95% CI)	SUCRA	Rank	OR (95% CI)	SUCRA	Rank	OR (95% CI)	SUCRA	Rank	OR (95% CI)	SUCRA	Rank	OR (95% CI)	SUCRA	Rank
	(0.21, 1.00)			(0.55, 1.57)			(0.28, 1.42)			(0.18, 27.80)			(0.18, 2.37)		
L. reuteri	0.20 (0.05, 0.77)	91.3	1.7	2.35 (0.86, 6.39)	4.2	7.7	0.30 (0.08, 1.07)	91.6	1.6	0.63 (0.05, 8.75)	66.2	3.4	0.43 (0.10, 1.76)	69.2	3.2
L. plantarum	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
B. clausii	0.44 (0.13, 1.49)	69.3	3.5	0.49 (0.20, 1.20)	80.4	2.4	0.66 (0.30, 1.47)	35.5	5.5	0.21 (0.04, 1.11)	27.5	6.1	0.34 (0.11, 1.09)	56.3	4.1
S. boulardii	0.89 (0.24, 9.02)	37.4	6.0	0.50 (0.12, 2.20)	61.3	3.7	0.97 (0.55, 1.52)	32.5	5.7	1.53 (0.23, 10.30)	31.6	5.8	0.64 (0.28, 1.46)	52.8	4.3

Abbreviations: CI=confidence interval; OR=odds ratio; NA=not applicable; SUCRA=surface under the cumulative ranking curve.

[#]Rank was derived from occurrence rate values of adverse event subtypes for all studies, 1=best tolerance.

Table S5.4. Summary table of all outcomes for efficacy and tolerability.

Interventions	Trials	Participants	Effect Estimate OR (95% CI)
Treatment efficacy			
Incidence of diarrhea	51	9569	0.44 (0.36, 0.54)
C. difficile infection rate	21	6623	0.36 (0.25, 0.53)
Fever rate	5	1206	0.57 (0.35, 0.90)
Dehydration rate	3	769	0.31 (0.15, 0.67)
Treatment tolerability			
Total occurrence rates of adverse reactions	35	8157	0.51 (0.38, 0.68)
Abdominal or epigastric pain	25	5902	0.60 (0.45, 0.82)
Constipation	19	2377	0.86 (0.61, 1.21)
Flatulence	24	5988	0.85 (0.71, 1.01)
Vomiting	18	4664	0.56 (0.36, 0.88)
Nausea	22	5195	0.57 (0.39, 0.84)
Loss of appetite	10	523	0.34 (0.22, 0.54)
Taste disturbance	7	527	0.83 (0.60, 1.25)

Abbreviations: OR=odds ratio; CI=confidence interval.

Figure S5.1. Forest plot of network meta-analysis for the tolerability outcomes compared with placebo arm.

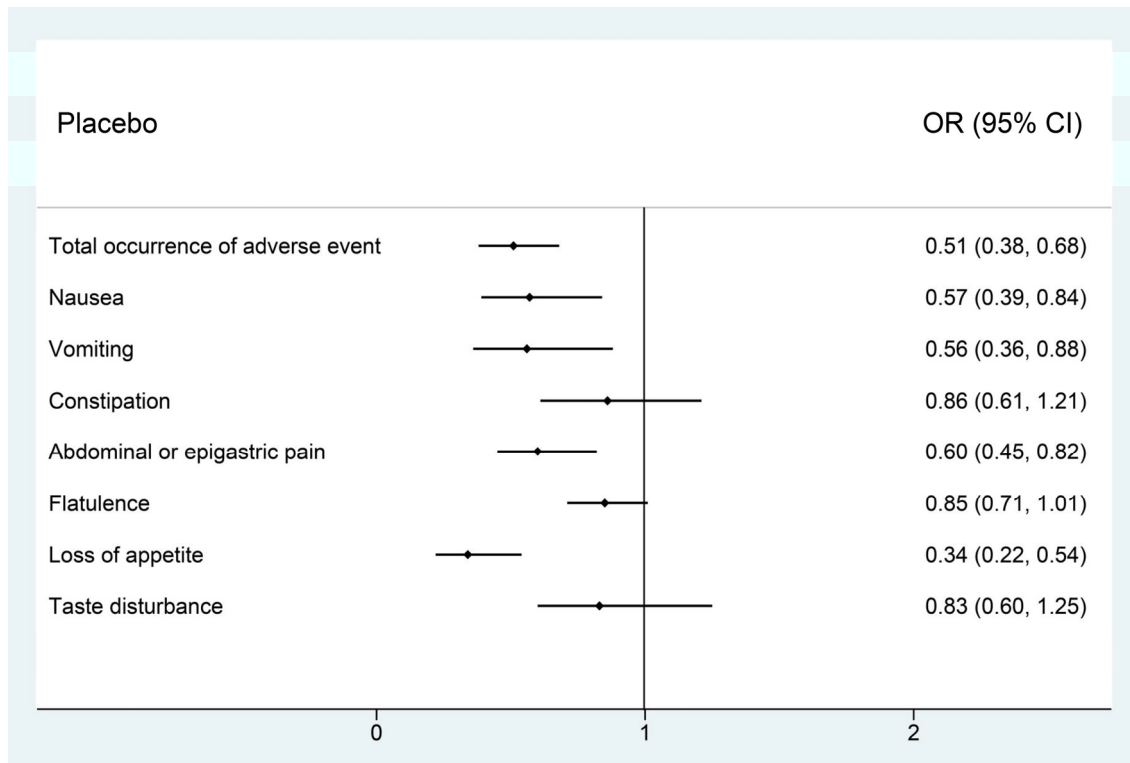| Placebo	OR (95% CI)
Total occurrence of adverse event	0.51 (0.38, 0.68)
Nausea	0.57 (0.39, 0.84)
Vomiting	0.56 (0.36, 0.88)
Constipation	0.86 (0.61, 1.21)
Abdominal or epigastric pain	0.60 (0.45, 0.82)
Flatulence	0.85 (0.71, 1.01)
Loss of appetite	0.34 (0.22, 0.54)
Taste disturbance	0.83 (0.60, 1.25)

Figure S5.2. Comparison-adjusted funnel plot of network analysis for total occurrence of adverse events compared with placebo arm.