Probiotics for the Prevention of *Clostridium difficile*–Associated Diarrhea: A Systematic Review and Meta-analysis

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Introduction

- Antibiotic treatment may disturb the colonization resistance of gastrointestinal flora, resulting in a range of symptoms—most notably, antibiotic-associated diarrhea.
- *Clostridium difficile* is the pathogen most often associated with opportunistic proliferation after breakdown of colonization resistance due to antibiotic administration.
  - Asymptomatic intestinal colonization to diarrhea, colitis, pseudomembranous colitis, and death

Introduction

- *Clostridium difficile*–associated diarrhea (CDAD) occurs most often in older, hospitalized adults who are exposed to broad-spectrum antibiotics
  - One third of cases of antibiotic-associated diarrhea can be attributed to *C. difficile*
- In high-income countries, CDAD is the most common cause of hospital-acquired infectious diarrhea, and more than 300000 hospitalized patients in the United States are affected each year

Introduction

- Probiotics are microorganisms that are believed to counteract disturbances in intestinal flora and thereby reduce the risk for colonization by pathogenic bacteria
- If probiotics are effective, their low cost and low incidence of associated adverse events would make them an attractive choice for the prevention of CDAD.

Objective

- Determine the efficacy and safety of probiotics (any strain or dose) for the prevention of CDAD in adults and children receiving antibiotics by conducting a systemic review

Method

Data sources

- The Cochrane Central Register of Controlled Trials from the Cochrane Library (2012, Issue 6)
- MEDLINE (1966 to 2012)
- EMBASE (1980 to 2012)
- CINAHL (1982 to 2012)
- Allied and Complementary Medicine Database (1985 to 2012)
- Web of Science (1945 to 2012)

Data sources

- Gray-literature
- Contacted companies that manufacture probiotic agents and individuals working in the field to identify additional unpublished or ongoing trials

Study selection

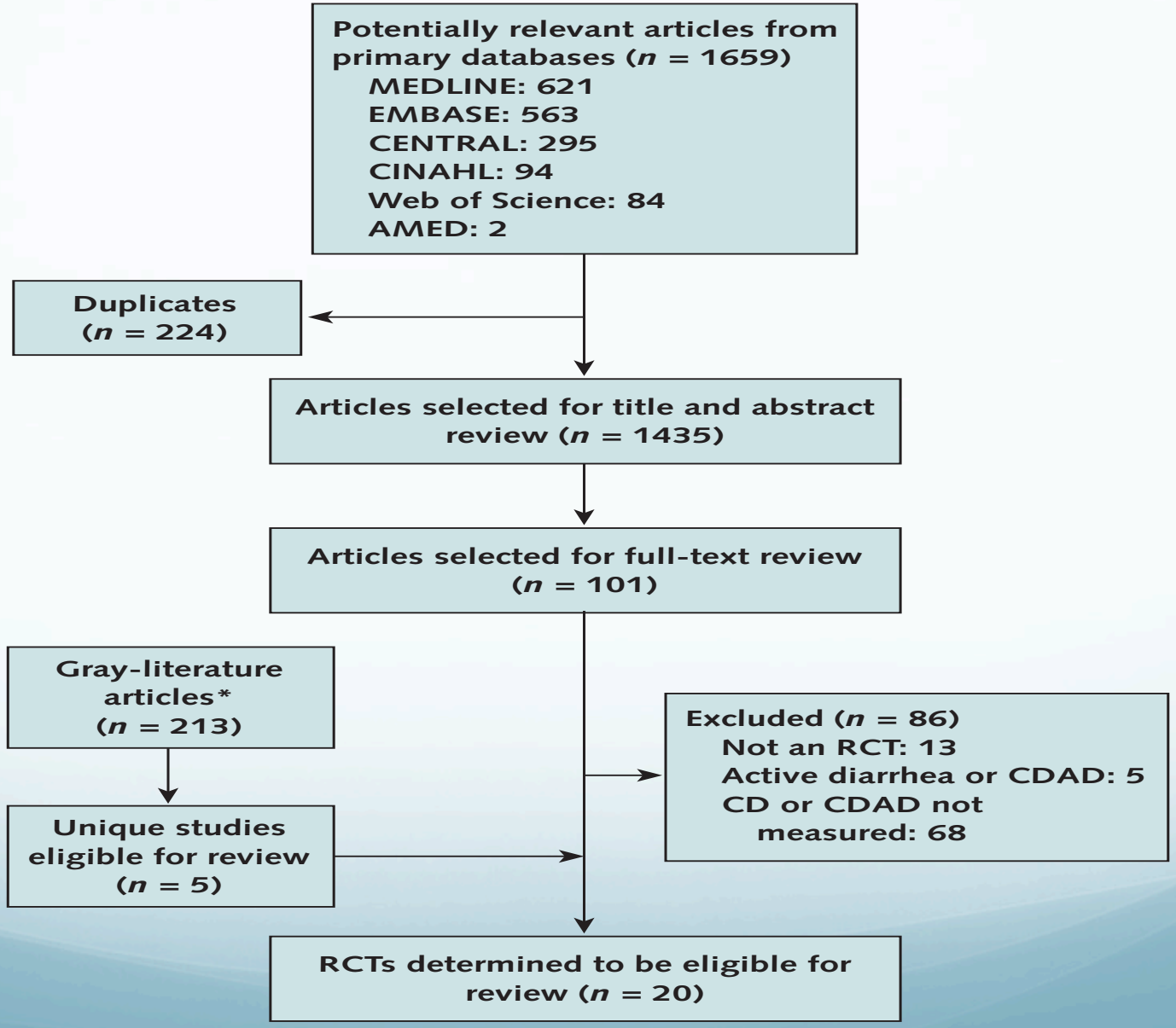
- Included randomized, controlled trials in adult or pediatric patients
  - Treated with antibiotics that compared the effect of any dose of a specified probiotic of any strain with placebo or no treatment
  - Reported the incidence of diarrhea with associated positive stool cytotoxin assay or culture for *C. difficile*.

Data Extraction and Quality Assessment

- Two reviewers independently extracted data on patients, methods, interventions, outcomes, missing outcome data (for example, loss to follow-up), and results
- Two reviewers independently assessed the risk of bias, including sequence generation, allocation concealment, blinding, number of patients with missing outcome data, selective outcome reporting, and other sources of bias

Result

Summary of evidence search and selection



Characteristics of included trials

Study, Year (Reference)	Population	Treatment Group		Control Group	
		Participants, *n*	Mean Age (SD or Range)	Participants, *n*	Mean Age (SD or Range)
Arvola et al, 1999 (32)	5 inpatients and 114 outpatients	89	4.7 y (2 wk–11.8 y)	78	4.4 y (2 wk–12.8 y)
Beausoleil et al, 2007 (33)	89 inpatients	44	68.8 y (14.5 y)	45	72.9 y (13.4 y)
Bravo et al, 2008 (34)	86 outpatients	41	49.8 y (20.5 y)	45	51.0 y (17.9 y)
Can et al, 2006 (35)	151 inpatients	73	NS*	78	NS*
Duman et al, 2005 (36)	NS (14-d triple therapy for *Helicobacter pylori* eradication)	204	45.7 y (12.7 y)	185	44.7 y (13.9 y)
Gao et al, 2010 (37)	255 inpatients	171	60.0 y (6.0 y)	84	60.0 y (6.0 y)
Hickson et al, 2007 (38)	135 inpatients	69	73.7 y (11.1 y)	66	73.9 y (10.5 y)
Kotowska et al, 2005 (39)	72 inpatients and 197 outpatients (total, 269)	132	4.9 y (6.2 mo–14.8 y)	137	4.7 y (5.2 mo–15.2 y)
Lönnermark et al, 2010 (40)	137 inpatients and 102 outpatients (total, 239)	118	47 y	121	43 y
McFarland et al, 1995 (41)	193 inpatients	97	40.7 y (16.0 y)	96	42.3 y (17.7 y)
Miller et al, 2008 (47)†	189 inpatients	95	≥18 y	94	≥18 y
Miller et al, 2008 (47)†‡	316 inpatients	157	≥18 y	159	≥18 y
Plummer et al, 2004 (42)	138 inpatients	69	Elderly	69	Elderly
Psaradellis et al, 2010 (48)†	248 inpatients and 189 outpatients (total, 437)	233	59.5 y (18.1 y)§	239	58.1 y (19.1 y)§
Rafiq et al, 2007 (49)†	100 inpatients	45	NS	55	NS
Ruszczyński et al, 2008 (43)	134 inpatients and 106 outpatients (total, 240)	120	4.5 y (3.7 y)	120	4.6 y (3.8 y)
Safdar et al, 2008 (44)	40 inpatients	23	66.6 y (14.5 y)	17	72.5 y (11.0 y)
Selinger et al, 2011 (50)†	124 inpatients	62	NS	62	NS
Surawicz et al, 1989 (45)	318 inpatients	212	48.6 y§	106	45.4 y§
Thomas et al, 2001 (46)	302 inpatients	152	57.2 y (18.0 y)§	150	54.4 y (17.4 y)§

Characteristics of included trials

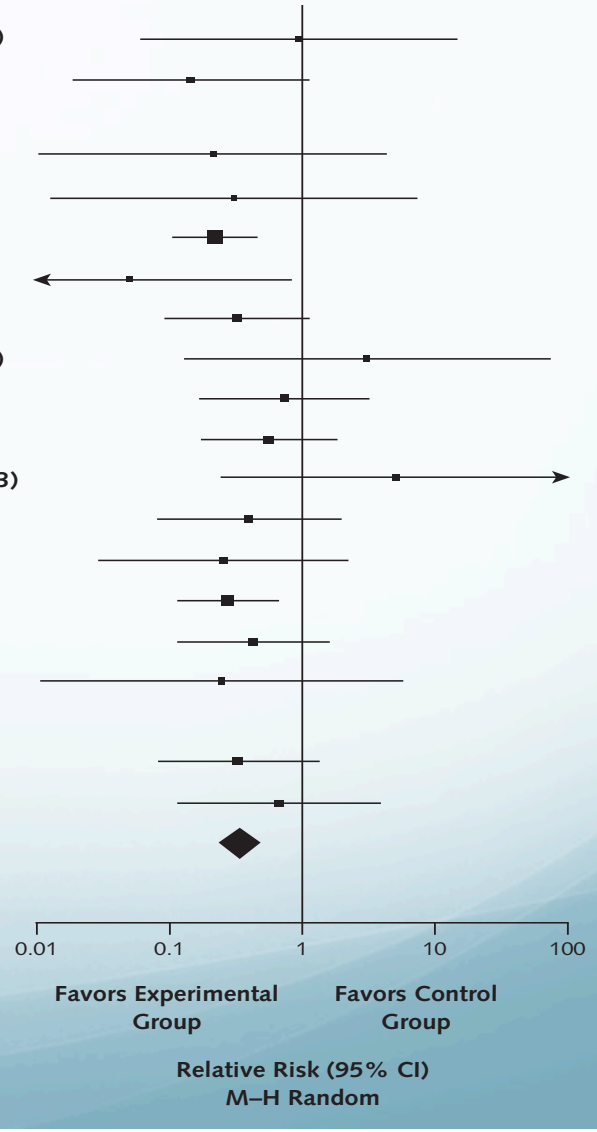
Probiotic	Control (Risk for CDAD, %)	Duration of Follow-up
L. rhamnosus GG 53103, 40 × 10^9 CFU/d for the duration of the antibiotic course	Placebo (2)	3 mo after first antibiotic dose
L. acidophilus CL1285 and *L. casei,* 25 × 10^9 CFU/d for 2 d, then 50 × 10^9 CFU/d for the duration of the antibiotic course	Placebo (16)	21 d after last study drug dose
S. boulardii, 10.2 × 10^9 CFU/d for 12 d; duration of antibiotic course, 5–10 d	Placebo (0)	9 d after last study drug dose
S. boulardii lyophilized 20 × 10^9 CFU/d ≤ 48 h of antibiotic start dose (duration of study drug course NS)	Placebo (3)	4 wk after last antibiotic dose
S. boulardii, 30 × 10^9 CFU/d for 14 d (duration of antibiotic course 14 d)	No treatment (1)	4 wk after last study drug dose
Pro1: *L. acidophilus* CL1285 and *L. casei* LBC80R, 50 × 10^9 CFU/d Pro2: *L. acidophilus* CL1285 and *L. casei* LBC80R, 100 × 10^9 CFU/d, within 36 h of starting antibiotic therapy until 5 d after discontinuation	Placebo (24)	21 d after last study drug dose
L. casei immunitas DN-114 001, 19 × 10^9 CFU/d; *L. bulgaricus,* 1.9 × 10^9 CFU/d; and *S. thermophilus,* 19 × 10^9 CFU/d within 48 h of starting antibiotic therapy until 7 d after discontinuation	Placebo (17)	4 wk after last antibiotic or study drug dose
S. boulardii, 10 × 10^9 CFU/d for the duration of the antibiotic course	Placebo (8)	2 wk after last study drug dose
L. plantarum 299v, 10 × 10^9 CFU/d, within 48 h of starting antibiotic therapy until 7 d after discontinuation	Placebo (0)	≥1 wk after last study drug dose
S. boulardii lyophilized, 30 × 10^9 CFU/d within 72 h of starting antibiotic therapy until 3 d after discontinuation	Placebo (4)	7 wk after last study drug dose
L. rhamnosus GG, 40 × 10^9 CFU/d within 72 h of starting antibiotic therapy, then for 14 d (duration of antibiotic course ≤14 d)	Placebo (7)	30 d after last study drug dose
L. rhamnosus GG, 120 × 10^9 CFU/d within 72 h of starting antibiotic therapy, then for 14 d (duration of antibiotic course ≤14 d)	Placebo (0)	30 d after last study drug dose
L. acidophilus and *B. bifidum,* 20 × 10^9 CFU/d within 36 h of starting antibiotic therapy, then for 20 d	Placebo (7)	Last day of study drug dose
L. acidophilus CL1285 and *L. casei,* 25 × 10^9 CFU/d for 2 d then 50 × 10^9 CFU/d until 5 d after discontinuation of antibiotic	Placebo (2)	21 d after last study drug dose
L. acidophilus, 80%; *L. bulgaricus,* 10%; *B. bifidum,* 5%, and *S. thermophilus,* 5%, 3 g/d with start of antibiotic therapy until hospital discharge	NS (40)	NS
L. rhamnosus GG (2593, 2594, 2595), 2 × 10^{10} CFU/d for the duration of the antibiotic course	Placebo (6)	2 wk after last study drug dose
L. acidophilus, 60 × 10^9 CFU/d during and 14 d after antibiotic course	Placebo (6)	NS
VSL #3 (*B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. bulgaricus, S. thermophilus*), 900 × 10^9 CFU/d during and 7 d after the antibiotic course	Placebo (0)	21 d after last study drug dose
S. boulardii lyophilized, 20 × 10^9 CFU/d within 48 h of starting antibiotic therapy until 2 wk after discontinuation	Placebo (8)	Mean, 17.3 d (SD, 8.6)‡
L. rhamnosus GG, 20 × 10^9 CFU/d within 24 h of starting antibiotic therapy, then for 14 d	Placebo (2)	7 d after last study drug dose

Probiotics for the prevention of *Clostridium difficile*–associated diarrhea

Study, Year (Reference)	Experimental Group, *n*		Control Group, *n*		Weight, %	Relative Risk (95% CI) M–H Random
	Events	Total	Events	Total		
Arvola et al, 1999 (32)	1	61	1	58	1.7	0.95 (0.06–14.85)
Beausoleil et al, 2007 (33)	1	44	7	45	3.0	0.15 (0.02–1.14)
Bravo et al, 2008 (34)	0	41	0	45	–	Not estimable
Can et al, 2006 (35)	0	73	2	78	1.4	0.21 (0.01–4.37)
Duman et al, 2005 (36)	0	196	1	180	1.2	0.31 (0.01–7.47)
Gao et al, 2010 (37)	9	171	20	84	23.0	0.22 (0.11–0.46)
Hickson et al, 2007 (38)	0	56	9	53	1.6	0.05 (0.00–0.84)
Kotowska et al, 2005 (39)	3	119	10	127	7.9	0.32 (0.09–1.14)
Lönnermark et al, 2010 (40)	1	80	0	83	1.3	3.11 (0.13–75.26)
McFarland et al, 1995 (41)	3	97	4	96	5.9	0.74 (0.17–3.23)
Miller et al, 2008 (47)	4	95	7	94	8.9	0.57 (0.17–1.87)
Miller et al, 2008 (47)*	2	157	0	159	1.4	5.06 (0.25–104.63)
Plummer et al, 2004 (42)	2	69	5	69	4.9	0.40 (0.08–1.99)
Psaradellis et al, 2010 (48)	1	216	4	221	2.7	0.26 (0.03–2.27)
Rafiq et al, 2007 (49)	5	45	22	55	16.1	0.28 (0.11–0.67)
Ruszczyński et al, 2008 (43)	3	120	7	120	7.2	0.43 (0.11–1.62)
Safdar et al, 2008 (44)	0	23	1	17	1.3	0.25 (0.01–5.79)
Selinger et al, 2011 (50)	0	62	0	62	–	Not estimable
Surawicz et al, 1989 (45)	3	116	5	64	6.5	0.33 (0.08–1.34)
Thomas et al, 2001 (46)	2	133	3	134	4.0	0.67 (0.11–3.96)
Total (95% CI)		1974		1844	100.0	0.34 (0.24–0.49)
Total events, *n*	40		108			

Heterogeneity: $\tau^2 = 0.00$; chi-square = 12.09; $P = 0.79$; $I^2 = 0\%$

Test for overall effect: $Z = 5.87$; $P < 0.001$

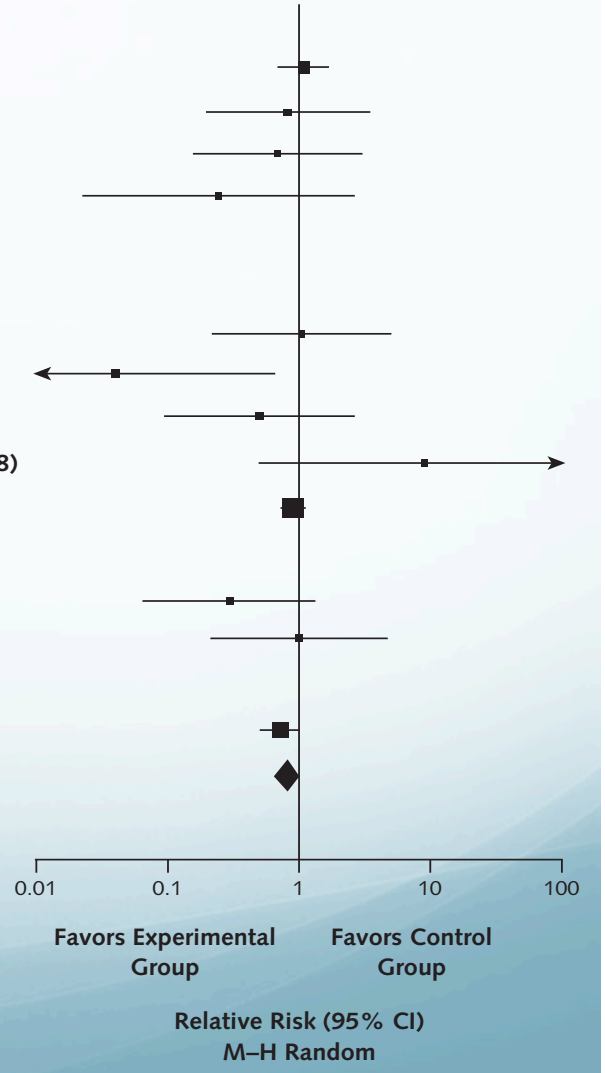


Risk for adverse effects with probiotics

Study, Year (Reference)	Experimental Group, *n*		Control Group, *n*		Weight, %	Relative Risk (95% CI) M–H Random
	Events	Total	Events	Total		
Arvola et al, 1999 (32)	0	61	0	58	–	Not estimable
Beausoleil et al, 2007 (33)	21	44	20	45	18.9	1.07 (0.68–1.68)
Bravo et al, 2008 (34)	3	41	4	45	2.6	0.82 (0.20–3.46)
Duman et al, 2005 (36)	3	196	4	180	2.5	0.69 (0.16–3.04)
Gao et al, 2010 (37)	1	171	2	84	1.0	0.25 (0.02–2.67)
Hickson et al, 2007 (38)	0	56	0	53	–	Not estimable
Kotowska et al, 2005 (39)	0	119	0	127	–	Not estimable
Lönnermark et al, 2010 (40)	3	80	3	83	2.2	1.04 (0.22–4.99)
McFarland et al, 1995 (41)	0	93	12	92	0.7	0.04 (0.00–0.66)
Miller et al, 2008 (47)	2	95	4	94	2.0	0.49 (0.09–2.64)
Miller et al, 2008 (47)*	4	157	0	159	0.7	9.11 (0.49–167.88)
Psaradellis et al, 2010 (48)	87	216	99	221	38.8	0.90 (0.72–1.12)
Ruszczyński et al, 2008 (43)	0	120	0	120	–	Not estimable
Safdar et al, 2008 (44)	2	23	5	17	2.4	0.30 (0.06–1.35)
Selinger et al, 2011 (50)	3	62	3	62	2.2	1.00 (0.21–4.76)
Surawicz et al, 1989 (45)	0	116	0	64	–	Not estimable
Thomas et al, 2001 (46)	37	133	52	134	26.0	0.72 (0.51–1.01)
Total (95% CI)		1783		1638	100.0	0.82 (0.65–1.05)
Total events, *n*	166		208			

Heterogeneity: $\tau^2 = 0.03$; chi-square = 13.27; $P = 0.28$; $I^2 = 17\%$

Test for overall effect: $Z = 1.58$; $P = 0.11$

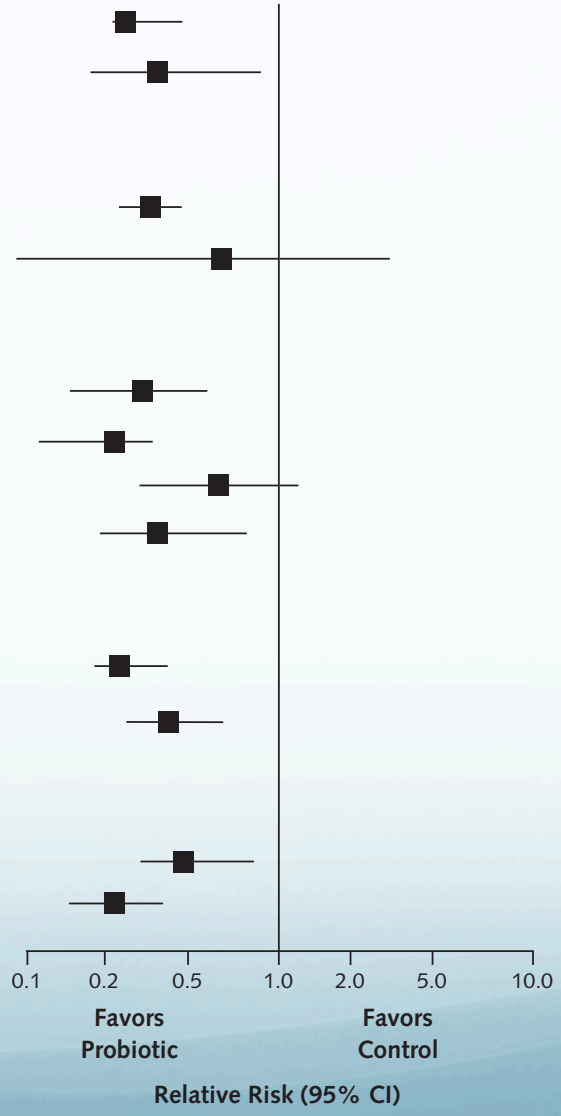


Probiotics to Prevent Clostridium difficile–Associated Diarrhea

Outcome	Assumed Risk: Control Group†	Corresponding Risk: Probiotic Group (95% CI)‡	RR (95% CI)	Participants (Studies)	Quality of the Evidence§
Incidence of CDAD (complete case) Diarrhea as defined by authors + cytotoxin assay or culture Follow-up: end of antibiotic treatment to 3 mo after antibiotic therapy was discontinued	**Study Population**		0.34 (0.24–0.49)	3818 (20)	Moderate
	59 per 1000 persons	20 per 1000 persons (14–29)			
	Moderate‖				
	50 per 1000 persons	17 per 1000 persons (12–25)			
Adverse events (complete case), as reported by patients	**Study Population**		0.82 (0.65–1.05)	3421 (17)	Moderate
	129 per 1000 persons	106 per 1000 persons (84–135)			
	Moderate‖				
	36 per 1000 persons	30 per 1000 persons (23–37)			

Subgroup analysis

Subgroup	Events/Patients, *n/n*		Relative Risk (95% CI)	*P* Value fo Test of Interactio
	Probiotic Group (*n* = 1974)	Control Group (*n* = 1844)		
Age				
Adults	33/1674	90/1539	0.22 (0.23–0.49)	
Children	7/300	18/305	0.40 (0.17–0.96)	0.69
Probiotic dosage				
>10 billion CFU/d	36/1775	98/1634	0.34 (0.23–0.49)	
≤10 billion CFU/d	4/199	10/210	0.61 (0.08–4.60)	0.57
Species				
Other (mixed) species	8/335	37/339	0.30 (0.15–0.61)	
L. acidophilus + *L. casei*	11/431	31/350	0.21 (0.11–0.42)	0.34
L. rhamnosus	12/566	18/565	0.63 (0.30–1.33)	0.15
S. boulardii	9/642	22/590	0.39 (0.19–0.82)	0.84
Risk of bias				
Low	17/695	52/613	0.27 (0.16–0.46)	
High or unclear	23/1279	56/1231	0.42 (0.26–0.68)	0.24
Species				
Single	21/1208	40/1155	0.50 (0.29–0.84)	
Multiple	19/766	68/689	0.25 (0.15–0.41)	0.06



Publication bias

- Found no graphical or statistical evidence of publication bias

Discussion

Review of this study

- Large relative risk reduction in the incidence of CDAD (relative risk, 0.34 [CI, 0.24 to 0.49]) from 20 randomized trials testing the effect of probiotics (*Bifidobacterium*, *Lactobacillus*, *Saccharomyces*, or *Streptococcus* species) in patients receiving antibiotics
- The evidence warrants moderate confidence in this large relative risk reduction

Review of the study

- Results were similar in adults and children, with lower and higher doses, among trials administering similar probiotic species (for example, *S. boulardii* vs. *L. rhamnosus*), and in studies at higher and lower risk of bias
- Trials using multiple species showed larger effects (relative risk, 0.25 [CI, 0.15 to 0.41]) than those using a single species (relative risk, 0.50 [CI, 0.29 to 0.84])

Review of the study

- Of 17 trials reporting adverse events, none reported a serious adverse event deemed attributable to probiotics, with the pooled estimate virtually excluding any increase in adverse events (relative risk, 0.82 [CI, 0.65 to 1.04]
- These results were be considered to warrant moderate confidence that short-term probiotic use in persons who are not immunodeficient or severely debilitated does not result in important side effects

Comparison with other studies

	This study	JAMA. 2012;307: 1959-69	CMAJ. 2005;173:167-70
No. of trial	20	14	5
Effect (RR, 95% CI)	0.34 (0.24-0.49)	0.29 (0.17-0.48)	Only systemic review: studies conducted to date provide insufficient evidence for the routine clinical use of probiotics to prevent or treat CDAD.
Safety	No difference	-	-

Limitation

- Total sample size (3878) not meet optimal information size (5676)
- 13 trials excluded patients who were immunodeficient or who were receiving immunosuppressive therapy

Strengths

- Comprehensive search strategy
- No publication bias
- Applied GRADE criteria to interpret results

Conclusion

- Moderate-quality evidence supports a large protective effect of probiotics in preventing CDAD.
- Given the low cost of probiotics and the moderate-quality evidence suggesting the absence of important adverse effects, there seems little reason not to encourage the use of probiotics in patients receiving antibiotics who are at appreciable risk for CDAD.

Miyarisan

- 菌種：*Clostridium butyricum*
- 菌數：10^7-10^8 / pack
- 單價：NTD 15 / pack

Comparison

	Miyarisan	C. Diff toxin test	Metronidazole	Vancomycin
單價	15	800	1.76	382
一療程總價	630	-	197	5348