

Supplementary Online Content

Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA*. 2012;307(18):1959-1969.

eMaterial

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eReferences. Included RCTs

This supplementary material has been provided by the authors to give readers additional information about their work.

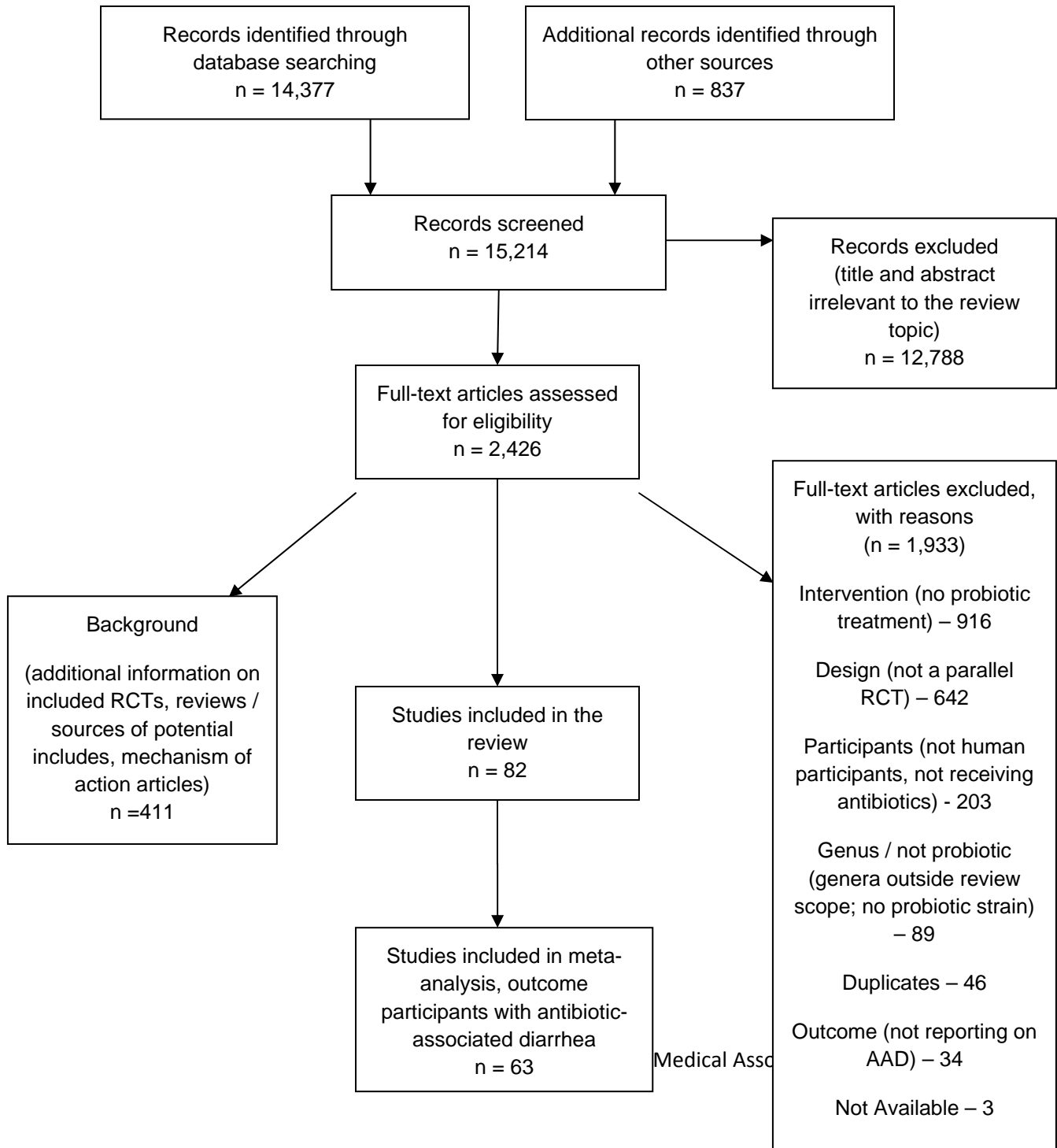
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eFigure 1. PubMed Search Strategy

probiotic* OR prebiotic* OR synbiotic*
NOT
animals NOT humans

Note: The search strategy was designed to find all research studies on probiotics and was not restricted to specific outcomes, study designs, interventions, or genera.

eFigure 2. Flow Diagram



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eTable. Evidence Table Probiotics for AAD

Author, Year	Risk of Bias ^{\$}	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
Adam, 1977 ¹	Unclear	Prevent AAD aim: Yes	Adults; Children; Elderly, mean age n/a	OutPt	Bronchopulmonary or oto-rhino-laryngology infections	Penicillin; Ampicillin; Amoxicillin; other semisynthetics; Cephalosporin; Tetracycline and chloral hydrates; Tetracyclines derivatives; dose and duration vary	Saccharomyces, boulardii, n/a, lyophilized, n/a	4 capsules qd, duration n/a Probiotic	Placebo	Stool index (number of stools, consistency, color; before-after comparison); assessor n/a	N: 199 N with AAD: 9 Other results: Moderate diarrhea: 0	N: 189 N with AAD: 33 Other results: Moderate diarrhea: 15
Armuzzi, 2001 ²	Unclear	Prevent AAD aim: Yes	Adults, mean age 39.27 (2.25)	OutPt	H. pylori	Clarithromycin 500 mg bid; Tinidazole 500 mg bid; for 7 days	Lactobacillus, rhamnosus, GG, lyophilized, 6x10 ⁹ cfu	6x10 ⁹ cfu bid for 14 days Probiotic	Placebo	De Boer questionnaire, self report	N: 30 N with AAD: Other results: 3.3% diarrhea during eradication and 2 follow up weeks	N: 30 N with AAD: Other results: 26.6% diarrhea during eradication, 10% and 6.6% the 2 follow up weeks
Armuzzi, 2001 ³	Unclear	Prevent AAD aim: Yes	Adults, mean age 40 (12)	OutPt	H. pylori	Clarithromycin 500 mg bid; Tinidazole 500 mg bid; for 7 days	Lactobacillus, rhamnosus, GG, lyophilized, 6x10 ⁹ cfu	6x10 ⁹ cfu bid for 14 days Probiotic	Antibiotics-only	De Boer questionnaire, self report	N: 60 N with AAD: Other results: 6.6% diarrhea frequency during eradication and 3.3% the 2	N: 60 N with AAD: Other results: 23.3% diarrhea frequency during eradication, 18.3% and

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Author, Year	Risk of Bias ⁵	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
											following weeks	6.6% the 2 following weeks
Arvola, 1999 ⁴	Unclear	Prevent AAD aim: Yes	Children, mean age 4.7	OutPt	Acute respiratory infections	n/a	Lactobacillus, rhamnosus, GG, form n/a, 2x10 ¹⁰ cfu/capsule	1 capsule bid for 7-10 days Probiotic	Placebo	>=3 loose stools within 24h for >=2 consecutive days; parental report	N: 89 N with AAD: 3 Other results:	N: 78 N with AAD: 9 Other results:
Beausoleil, 2007 ⁵	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 68.8 (14.5)	InPt	Infections needing antibiotics	n/a	Lactobacillus, acidophilus, CL1285, form n/a, >=5x10 ¹⁰ cfu (both strains) Lactobacillus, casei, n/a, form n/a	49 g qd for first 2 days; 98 g qd for rest of antibiotic use Probiotic	Placebo	>=3 liquid stools in a day; medical records	N: 44 N with AAD: 7 Other results: Softened stools (not diarrhea): 8; modified stool color: 1; foul smelling stool: 0	N: 45 N with AAD: 16 Other results: Softened stools (not diarrhea): 9; modified stool color: 2; foul smelling stool: 1
Benhamou, 1999 ⁶	Unclear	Prevent AAD aim: Yes	Children, mean age 2.4 (0.05)	OutPt	Upper and lower respiratory infections	Amoxicillin; Cefadroxil; Diosmectite; Erythromycin; Josamycin; Cefixime; dose and duration vary	Saccharomyces, boulardii, n/a, form n/a, n/a	226 mg qd, duration n/a Probiotic	Diosmectite	>3 liquid bowel movements per day; parental interview	N: 388 N with AAD: 25 Other results: 45 liquid stool observations	N: 391 N with AAD: 16 Other results: 37 liquid stool observations
Bhalla, 2011 ⁷	Unclear	Prevent AAD aim: Yes	n/a, mean age	n/a	Requiring antibiotics for 7 days	n/a (systemic oral antibiotics) for 7 days	Lactobacillus, acidophilus, LA-5, form n/a, n/a Bifidobacterium,	1 techsule bid for 14 days Probiotic	Placebo	n/a, diary card	N: 176 N with AAD: 19 Other results: Diarrhea	N: 167 N with AAD: 26 Other results: Diarrhea

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
							n/a, BB-12, form n/a, n/a				duration 2.32 (SD 2.3) days No SAE	duration 4.58 (SD 3.08) days
Borgia, 1982 ⁸	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 59	InPt	Pulmonary chronic tuberculosis	n/a	Enterococcus, faecium, SF 68, lyophilized, $\geq 7.5 \times 10^7$ cfu	1 capsule qd, duration n/a Probiotic	Antibiotics-only	≥ 2 bowel movements/day of watery stool ≥ 2 days; assessor n/a	N: 40 N with AAD: 2 Other results:	N: 40 N with AAD: 7 Other results:
Bravo, 2008 ⁹	Unclear	Prevent AAD aim: Yes	Adults; Children; Elderly, mean age 49.78 (20.5)	OutPt	Acute infections	Amoxicillin (dose n/a) for 5-10 days	Saccharomyces, boulardii, n/a, lyophilized, 5.1×10^9 cfu/capsule	1 capsule bid for 12 days Probiotic	Placebo	3 loose stools on ≥ 2 consecutive days; self report	N: 41 N with AAD: 3 Other results: Duration of diarrhea: mean 3.5 days SD 1.73; stools per day: mean 1.16, SD 0.41; 1 pt dropped out due to diarrhea on the first day but group unclear No AE associated with probiotics	N: 45 N with AAD: 5 Other results: Diarrhea duration mean 4.2 days, SD 1.3; stools per day: mean 1.16, SD 0.41
Can, 2006 ¹⁰	Unclear	Prevent	Adults, mean	InPt	Chemotherapy but	n/a	Saccharomyces, boulardii, n/a, form	bid, duration	Placebo	n/a; self report	N: 73	N: 78

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		AAD aim: Yes	age		not ICU		n/a, n/a	n/a Probiotic			N with AAD: 1 Other results:	N with AAD: 7 Other results:
Cao, 2005 ¹¹	Unclear	n/a AAD aim: No	Adults, mean age 31.3 (7.3)	n/a	Peptic ulcer	Amoxicillin 1000 mg bid; metronidazole 0.4 (no unit) bid; for 14 days	Bifidobacterium, n/a, n/a, active, n/a Lactobacillus, n/a, n/a, active, n/a Enterococcus, n/a, n/a, active, n/a	420 mg tid for 2 weeks Probiotic	Antibiotics-only	n/a	N: 64 N with AAD: Other results: Alteration of intestinal flora (including: diarrhea, abdominal pain, and fecal changes): 3	N: 64 N with AAD: Other results: Alteration of intestinal flora (including: diarrhea, abdominal pain, and fecal changes): 12
Cimperman, 2011 ¹²	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 51 18	InPt	Hospitalized, most common diagnosis pneumonia	Azithromycin; Ceftriaxone; Moxifloxacin; Vancomycin; Zosyn; Clindamycin; Meropenem; Cefuroxime; Ampicillin/sulbactam; dose and duration vary	Lactobacillus, reuteri, ATCC 55730, form n/a, 10 ^{^8} cfu / tablet	1 tablet bid for 28 days Probiotic	Placebo	>=3 fluffy pieces with ragged edges and a mushy stool or watery and no solid pieces bowel movements per day for 2 consecutive days; self report Bristol stool scale	N: 15 N with AAD: 1 Other results:	N: 16 N with AAD: 5 Other results:
Cindoruk, 2007 ¹³	Unclear	Prevent AAD aim:	Adults, mean age 45.87 (13.35)	OutPt	H. pylori	Clarithromycin 500 mg bid; Amoxicillin 1000 mg bid; for 14 days	Saccharomyces, boulardii, n/a, form n/a, n/a	500 mg bid for 2 weeks	Placebo	De Boer questionnaire, self report	N: 62 N with AAD: 9	N: 62 N with AAD: 19

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		Yes						Probiotic			Other results: No pathogenic growth in stool cultures	Other results:
Contardi, 1991 ¹⁴	Unclear	Prevent AAD aim: Yes	Children, mean age	n/a	Extraintestinal disease	Amoxicillin 50 mg/kg bid for 10 days	Bifidobacterium, bifidum, n/a, active, $\geq 10^6$ cfu/capsule Lactobacillus, acidophilus, n/a, active, $\geq 10^6$ cfu/capsule	1 capsule tid, duration n/a Probiotic	Antibiotics-only	Rating scale, parental report	N: 20 N with AAD: Other results: Number of stools per day: 2 (SD 0.3); fecal consistency: 2 (SD 0.3)	N: 20 N with AAD: Other results: Number of stools per day: 2.7 (SD 0.5); fecal consistency: 2.5 (SD 0.5)
Conway, 2007 ¹⁵	High	Prevent AAD aim: Yes	Adults; Children; Elderly, mean age 37.8 (25.3)	OutPt	n/a	n/a for 7 days	Lactobacillus, acidophilus, n/a, form n/a, 3×10^6 cfu/g Streptococcus, thermophilus, n/a, form n/a, 8×10^8 cfu/g Bifidobacterium, animalis lactis, n/a, form n/a, 5×10^6 cfu/g	150 ml qd for 12 days Probiotic	Antibiotics-only	≥ 3 loose stools per day for ≥ 2 consecutive days; self report	N: 149 N with AAD: 9 Other results: Mean total stool count: 16.1	N: 137 N with AAD: 17 Other results: Mean total stool count: 16.0
Correa, 2005 ¹⁶	Unclear	Prevent	Children, mean	InPt	Receiving	n/a	Bifidobacterium,	≥ 500 ml	Placebo	≥ 3 liquid	N: 87	N: 82

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		AAD aim: Yes	age		antibiotics		lactis, n/a, active, 10 ⁷ cfu Streptococcus, thermophilus, n/a, active, 10 ⁶ cfu	as needed for 15 days Probiotic		stools per day for ≥ 2 consecutive days; staff record	N with AAD: 13 Other results: Diarrhea duration: 3.92 (SD 2.47) days No AE judged to be associated with probiotics	N with AAD: 24 Other results: Diarrhea duration: 5 (SD 2.8) days
Cremonini, 2002 ¹⁷	Unclear	Prevent AAD aim: Yes	Adults, mean age	OutPt	H. pylori	Clarithromycin 500 mg bid for 7 days	Lactobacillus, rhamnosus, GG, form n/a, 6x10 ⁹ cfu	1 sachet bid for 14 days Probiotic	Placebo	De Boer questionnaire, self report	N: 21 N with AAD: Other results: Differences in side effects during week 1 (p=0.0025), lower incidence persisted during week 2	N: 21 N with AAD: Other results:
de Bortoli, 2007 ¹⁸	Unclear	Prevent AAD aim: Yes	Adults, mean age 46.1 (10.7)	OutPt	H. pylori	Clarithromycin 500 mg bid; Amoxicillin 1000 mg bid; for 7 days	Lactobacillus, plantarum, n/a, form n/a, 5x10 ⁹ cfu Lactobacillus, reuterii, n/a, form n/a, 2x10 ⁹ Lactobacillus,	5 g bid for 7 days Synbiotic	Antibiotics-only	n/a; self report	N: 105 N with AAD: 1 Other results:	N: 101 N with AAD: 16 Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
							<p>casei rhamnosus, n/a, form n/a, 2x10⁹</p> <p>Bifidobacterium, infantis, n/a, form n/a, 2x10⁹ cfu</p> <p>Bifidobacterium, longum, n/a, form n/a, 2x10⁹</p> <p>Lactobacillus, salivarium, n/a, form n/a, 1x10⁹</p> <p>Lactobacillus, acidophilus, n/a, form n/a, 1x10⁹ cfu</p> <p>Streptococcus, thermophilus, n/a, form n/a, 5x10⁹</p> <p>Bacillus coagulans [Lactobacillus, sporogenes], n/a, form n/a, 1x10⁹</p>					
de Vrese, 2011 ¹⁹	Unclear	Prevent AAD aim:	Adults, mean age	OutPt	H. pylori	Clarithromycin 500mg bid; Amoxicillin 1g bid; for 6 days	Lactobacillus, acidophilus, LA-5, active, >= 10 ⁶	125g bid for 5 weeks	Chemically acidified and curded milk	>= 3 watery stools per day, at least 1 lay within	N: 30 N with AAD: 4 Other results: 4	N: 29 N with AAD: 3 Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		Yes					cfu/g Bifidobacterium, animalis lactis, BB-12, form n/a, >= 10 ⁶ cfu / g Streptococcus, thermophilus, n/a, form n/a, >=10 ⁶ cfu /g	Probiotic		eradication week, questionnaire	days with watery stools, 1 day mean duration of episodes	10 days with watery stools, 4.7 days mean duration of episodes
Duman, 2005 ²⁰	Unclear	Prevent AAD aim: Yes	Adults; Children;Elderly, mean age 45.68 (12.7)	n/a	H. pylori	n/a	Saccharomyces, boulardii, n/a, form n/a, n/a	500 mg bid for 14 days Probiotic	Antibiotics-only	>=3 semi-solid or watery bowel movements per day for >=2 days; self report	N: 204 N with AAD: 14 Other results: Time to the onset of diarrhea (treatment): 4.2 (SD 3.6) days; time to the onset of diarrhea (followup):35 (SD 14.1) days; mucus in stool: 1 "safe"	N: 185 N with AAD: 28 Other results: Time to the onset of diarrhea (treatment): 3.7 (SD 2.6) days; Time to the onset of diarrhea (followup):22.4 (SD 7.3) days; mucus in stool: 9
Engelbrekton,	High	n/a AAD aim:	Adults, mean	OutPt	Healthy	Amoxicillin 875 mg bid for 7	Bifidobacterium, lactis, BI-04,	1 capsule bid for 21	Placebo	n/a; self report	N: 20	N: 20

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
2009 ²¹		No	age 37.2			days	lyophilized, 5x10 ⁹ cfu Bifidobacterium, lactis, bl-07, form n/a, 5x10 ⁹ cfu Lactobacillus, acidophilus, NCFM, form n/a, 5x10 ⁹ cfu Lactobacillus, paracasei, Lpc-37, form n/a, 5x10 ⁹ cfu Bifidobacterium, bifidum, Bb-02, form n/a, 5x10 ⁸ cfu	days (4.1x10 ¹⁰ daily, range 4.3x10 ¹⁰ to 3.6x10 ¹⁰ shown in 12 month product evaluation trial) Probiotic			N with AAD: 3 Other results:	N with AAD: 1 Other results:
Erdeve, 2004 ²²	High	n/a AAD aim: Yes	Children, mean age	OutPt	n/a	Azithromycin (dose n/a) for 10 days (repeated if necessary)	Saccharomyces, boulardii, n/a, form n/a, n/a	dose n/a, duration n/a Probiotic	Antibiotics-only	>=3 watery stools within 1 day; self report	N: 127 N with AAD: 7 Other results:	N: 105 N with AAD: 12 Other results:
Erdeve, 2004 ²³	High	n/a AAD aim: Yes	Children, mean age	OutPt	n/a	Sulbactam-ampicillin (dose n/a) for 10 days (repeated if necessary)	Saccharomyces, boulardii, n/a, form n/a, n/a	dose n/a, duration n/a Probiotic	Antibiotics-only	>=3 watery stools within 1 day; self report	N: 117 N with AAD: 7 Other results:	N: 117 N with AAD: 30 Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
Felley, 2001 ²⁴	High	n/a AAD aim: No	Adults, mean age 30.1	OutPt	H. pylori	Clarithromycin 500 mg bid for 14 days	Lactobacillus, johnsonii, La1, form n/a, >=10 ⁷ cfu/ml	180 ml bid for 3 weeks Probiotic	Placebo	n/a	N: 26 N with AAD: 1 Other results:	N: 27 N with AAD: 0 Other results:
Frigerio, 1986 ²⁵	Unclear	Prevent AAD aim: Yes	n/a, mean age	n/a	n/a	n/a	Enterococcus, faecium, SF 68, form n/a, n/a	2 cps qd for 7 days Probiotic	Placebo	n/a	N: 661 N with AAD: 57 Other results:	N: 662 N with AAD: 107 Other results:
Gao, 2010 ²⁶	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 60 (6)	InPt	Infection	n/a	Lactobacillus, acidophilus, CL1285, form n/a, 5x10 ¹⁰ cfu (both strains combined per capsule) Lactobacillus, casei, LBC80R, form n/a, 5x10 ¹⁰ cfu	1 capsule bid for 5 days, duration n/a Probiotic	Placebo	>=3 liquid stools in a day after antibiotic with no other obvious reason for diarrhea; per Bristol stool form scale per nurse, clinician, or self report	N: 86 N with AAD: 13 Other results: AAD duration: 2.8 (SD 0.8) days	N: 84 N with AAD: 37 Other results: AAD duration: 6.4 (SD 1.8) days
Giovannone, 2007 ²⁷	Unclear	Prevent AAD aim: Yes	n/a, mean age	n/a	H. pylori	Clarithromycin 500 mg bid; Amoxicillin 1 g bid; for 7 days	Lactobacillus, casei, DG, active, 16x10 ⁹ cfu	16x10 ⁹ cfu for 28 days Probiotic	Placebo	Questionnaire, assessor n/a	N: N with AAD: Other results: No differences between groups for diarrhea	N: N with AAD: Other results:
Gotz, 1979 ²⁸	Unclear	Prevent	Adults; Elderly, mean	InPt	n/a	Ampicillin 20 doses	Lactobacillus, acidophilus, n/a,	1 packet qid for 5	Placebo	>=3 more bowel	N: 48	N: 50

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		AAD aim: Yes	age				form n/a, 10 ⁸ cfu/packet (both strains) Lactobacillus, bulgaricus, n/a, form n/a,	days Probiotic		movements than normal; staff report	N with AAD: 3 Other results:	N with AAD: 9 Other results:
Hickson, 2009 ²⁹	Low	Prevent AAD aim: Yes	Adults; Elderly, mean age 73.7 (11.1)	InPt	Respiratory infections, orthopedic surgery, other	n/a	Lactobacillus, casei, DN-114001, active, 10 ⁸ cfu/ml (mean 2.2x10 ⁸ in tests) Streptococcus, thermophilus, n/a, form n/a, 10 ⁸ cfu/ml Lactobacillus, bulgaricus, n/a, active, 10 ⁷ cfu/ml	97 ml bid, duration varies Probiotic	Placebo	>=2 stools per day >= 3 days; staff report	N: 69 N with AAD: 7 Other results: No AE related to the study drinks	N: 66 N with AAD: 19 Other results: No AE related to the study drinks
Hurduc, 2008 ³⁰	High	n/a AAD aim: n/a	Children, mean age 11.5	OutPt	H. pylori	Amoxicillin 50 mg/kg/d qd; Clarithromycin 15 mg/kg/d bid; for 7-10 days	Saccharomyces, boulardii, n/a, form n/a, n/a	250 mg/day bid for 4 weeks Probiotic	Antibiotics-only	n/a	N: 48 N with AAD: Other results: Side effects (e.g., diarrhea) were reduced in the probiotics group	N: 42 N with AAD: Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
Jirapinyo, 2002 ³¹	Unclear	Prevent AAD aim: Yes	Children, mean age	InPt	Sepsis or meningitis	n/a	Lactobacillus, acidophilus, n/a, lyophilized, n/a Bifidobacterium, infantis, n/a, lyophilized,	1 capsule tid for 7 days Probiotic	Placebo	n/a	N: 8 N with AAD: 3 Other results: No unexplained worsening of clinical condition or sepsis due to probiotics	N: 10 N with AAD: 8 Other results: 0
Kim, 2008 ³²	High	n/a AAD aim: Yes	Adults; Elderly, mean age 48.1 (12.4)	OutPt	H. pylori	Clarithromycin 500 mg bid; Amoxicillin 1 g bid; for 7 days	Lactobacillus, acidophilus, HY 2177, form n/a, >10 ⁵ cfu/ml Lactobacillus, casei, HY 2743, form n/a, >10 ⁵ cfu/ml Bifidobacterium, longum, HY 8001, form n/a, >10 ⁶ cfu/ml Streptococcus, thermophilus, B-1, form n/a, >10 ⁸ cfu/ml	150 ml qd for >21 days Probiotic	Antibiotics-only	n/a; self report	N: 168 N with AAD: 16 Other results:	N: 179 N with AAD: 14 Other results:
Klarin, 2008 ³³	Unclear	n/a	Adults;	InPt	Enterally fed,	n/a	Lactobacillus,	50 ml qid	Placebo	n/a	N: 9	N: 8

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		AAD aim: No	Elderly, mean age 70.9		critically ill		plantarum, 299v, form n/a, 10 ⁹ cfu/ml	for 3 days, 25 ml qid for the rest of ICU stay Probiotic			N with AAD: Other results: No difference in diarrhea between groups No infections due to probiotics	N with AAD: Other results:
Klarin, 2005 ³⁴	High	n/a AAD aim: No	Adults; Elderly, mean age 65.5	InPt	ICU	n/a	Lactobacillus, plantarum, 299v, form n/a, 8x10 ⁸ cfu	100 ml bid first 3 days, 50 ml bid n/a (duration) Probiotic	Placebo	n/a; staff report	N: 22 N with AAD: Other results: no C. diff positive sample	N: 22 N with AAD: Other results: 4 C. diff positive samples
Koning, 2008 ³⁵	Unclear	n/a AAD aim: No	Adults; Elderly, mean age	InPt	Chronic obstructive pulmonary with respiratory infection	n/a for 7 days	Bifidobacterium, bifidum, NIZO 3804, form n/a, 10 ⁸ cfu/g Bifidobacterium, lactis, NIZO 3680, form n/a, 10 ⁸ cfu/g Enterococcus, faecium, NIZO 3886, form n/a, 10 ⁸ cfu/g	5 g bid for 2 weeks Probiotic	Placebo	Defecation frequency ≥ 3 per day and/or a faecal consistency (Bristol stool form scale) ≥ 5 /day for ≥ 2 days; n/a	N: 17 N with AAD: 13 Other results: No AE related to the study product	N: 13 N with AAD: 9 Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
							<p>Lactobacillus, acidophilus, NIZO 3678, form n/a, 10⁸ cfu/g</p> <p>Lactobacillus, acidophilus, NIZO 3887, form n/a, 10⁸ cfu/g</p> <p>Lactobacillus, paracasei, NIZO 3672, form n/a, 10⁸ cfu/g</p> <p>Lactobacillus, plantarum, NIZO 3684, form n/a, 10⁸ cfu/g</p> <p>Lactobacillus, rhamnosus, NIZO 3689, form n/a, 10⁸ cfu/g</p> <p>Lactobacillus, salivarius, NIZO 3675, form n/a, 10⁸ cfu/g</p>					
Koning, 2010 ³⁶	High	n/a AAD aim:	Adults, mean age 59.9 (13.3)	OutPt	Healthy	Amoxicillin 500 mg bid for 7 days	Bifidobacterium, bifidum, W23, form n/a, 10 ⁸	5 g bid for 14 days	Placebo	>=3 bowel movements per day >= 2 days and/or	N: 20 N with AAD: 9	N: 21 N with AAD: 17

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Author, Year	Risk of Bias ^s	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		No					cfu/g Bifidobacterium, lactis, W18, form n/a, 10 ⁸ cfu/g Bifidobacterium, longum, W51, form n/a, 10 ⁸ cfu/g Enterococcus, faecium, W54, form n/a, 10 ⁸ cfu/g Lactobacillus, acidophilus, W37, form n/a, 10 ⁸ cfu/g Lactobacillus, acidophilus, W55, form n/a, 10 ⁸ cfu/g Lactobacillus, paracasei, W72, form n/a, 10 ⁸ cfu/g Lactobacillus, plantarum, W62, form n/a, 10 ⁸	Probiotic		consistency >=5 >= 2 days; self report	Other results:	Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
							cfu/g Lactobacillus, rhamnosus, W71, form n/a, 10 ⁸ cfu/g Lactobacillus, salivarius, W24, form n/a, 10 ⁸ cfu/g					
Kotowska, 2005 ³⁷	Unclear	Prevent AAD aim: Yes	Children, mean age	n/a	Otitis media and/or respiratory tract infections	n/a	Saccharomyces, boulardii, n/a, form n/a, n/a	250 mg bid, duration n/a Probiotic	Placebo	>=3 loose or watery stools per day >= 48 hours; self report	N: 132 N with AAD: 9 Other results: including 5 pts with rotavirus diarrhea No AE associated with the therapy	N: 137 N with AAD: 29 Other results: including 7 pts with rotavirus diarrhea 0 AE associated with placebo
La Rosa, 2003 ³⁸	Unclear	Prevent AAD aim: Yes	Children, mean age 6.6	OutPt	Active infections	n/a	Bacillus coagulans [Lactobacillus, sporogenes], n/a, form n/a, 5.5x10 ⁸ cfu/capsule	1 capsule qd for 10 days Synbiotic	Placebo	Scale ranging from normal (0) to liquid (2); self report	N: 60 N with AAD: 14 Other results: Mean duration of diarrhea: 0.7 days (SD 1.4)	N: 60 N with AAD: 31 Other results: Mean duration of diarrhea: 1.6 days (SD 2)
Lewis, 1998 ³⁹	Unclear	Prevent	Elderly, mean	InPt	n/a	n/a	Saccharomyces,	113 mg	Placebo	>=3 loose	N: 33	N: 36

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		AAD aim: Yes	age 75				boulardii, n/a, form n/a, n/a	bid, duration n/a Probiotic		stools within 24 hours; staff report	N with AAD: 7 Other results: No AE attributable to probiotics	N with AAD: 5 Other results:
Li, 2010 ⁴⁰	High	Prevent AAD aim: Yes	Elderly, mean age	InPt	Hospitalized with infections	n/a	Bacillus, licheniformis, n/a, active, 1.5x10 ⁹ cfu	tid for 1 week Probiotic	Antibiotics-only	n/a	N: 122 N with AAD: 15 Other results: no AE	N: 125 N with AAD: 34 Other results:
Lighthouse, 2004 ⁴¹	High	n/a AAD aim: No	Adults; Elderly, mean age	n/a	HCV-related Child B liver cirrhosis	Rifaximin 400 mg tid for 1 week in treatment, for 2 weeks in control group	Lactobacillus, acidophilus, n/a, form n/a, n/a Lactobacillus, helveticus, n/a, form n/a, n/a Bifidobacterium, n/a, n/a, form n/a, n/a	10 ml tid for 5 weeks Synbiotic	Antibiotics-only	n/a	N: 10 N with AAD: 1 Other results: No AE due to the treatment schedules	N: 10 N with AAD: 0 Other results: No AE due to the treatment schedules
Ligny, 1976 ⁴²	Unclear	Treat AAD aim: Yes	Adults, mean age 47	n/a	Chronic diarrhea due to antibiotics	n/a	Saccharomyces, Hansen, CBS 5926, form n/a, n/a	3-4 capsules qd for 1 month Probiotic	Placebo	Stool normalization and no consumption of Papaverine; assessor n/a	N: 20 N with AAD: 3 Other results: Potential improvements:	N: 20 N with AAD: 16 Other results: Potential improvements:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
											2 Product was safe, very well tolerated, no contra-indications	3
Lionetti, 2006 ⁴³	Unclear	Prevent AAD aim: Yes	Children, mean age 12.3	OutPt	H. pylori	Amoxicillin 50 mg/kg/d; Clarithromycin 15 mg/kg/d; Tinidazole 20 mg/kg/d; for 5 days	Lactobacillus, reuteri, ATCC 55730, lyophilized, 10 ⁸ cfu	1 pill qd for 20 days Probiotic	Placebo	n/a; self report	N: 20 N with AAD: Other results: Disorders of defecation: 3 No AE reported	N: 20 N with AAD: Other results: Disorders of defecation: 9
Lonnermark, 2010 ⁴⁴	Unclear	Prevent AAD aim: Yes	Adults, mean age	n/a	Infection	n/a	Lactobacillus, plantarum, n/a, form n/a, 5x10 ⁷ cfu/ml	200 ml qd, duration n/a Probiotic	Placebo	>=3 loose or watery stools per day >=2 consecutive days; self report	N: 118 N with AAD: 6 Other results:	N: 121 N with AAD: 5 Other results:
Martinez, 2009 ⁴⁵	Unclear	n/a AAD aim: No	Adults; Children, mean age 29.1 (7.5)	OutPt	Vulvovaginal candidiasis	Fluconazole 150 mg 1 time	Lactobacillus, rhamnosus, GR-1, active, 10 ⁹ cfu Lactobacillus, reuteri, RC-14, active, 10 ⁹ cfu	2 capsules qd for 28 days Probiotic	Placebo	n/a	N: 29 N with AAD: Other results: Light stool: 1	N: 26 N with AAD: Other results: Light stool: 0
McFarland, 1995 ⁴⁶	Unclear	Prevent AAD aim:	Adults; Elderly, mean age 40.7 (16)	InPt	n/a	Beta-lactams; dose and duration n/a	Saccharomyces, boulardii, n/a, form	500 mg bid, duration	Placebo	>=3 loose stools/day >= 2 consecutive	N: 97 N with AAD: 7	N: 96 N with AAD: 14

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		Yes					n/a, 3x10 ¹⁰ cfu/g	n/a Probiotic		days associated with ≥1 b-lactam with no other etiology of diarrhea; self report	Other results: Duration of AAD (during treatment): 3.0 days; duration of AAD (posttreatment): 2.5 days; diarrhea severity (mean stools/day): 4.9 (SD 2.2)	Other results: Duration of AAD (during treatment): 4.0 days; duration of AAD (posttreatment): 18.0 days; diarrhea severity (mean stools/day): 5.2 (SD 1.2)
Merenstein, 2009 ⁴⁷	Unclear	Prevent AAD aim: Yes	Children, mean age 2.9 (1.5)	OutPt	Upper respiratory infections	n/a	Lactobacillus, acidophilus, n/a, form n/a, n/a Bifidobacterium, breve, n/a, form n/a, n/a Bifidobacterium, longum, n/a, form n/a Saccharomyces, florentinus, n/a, form n/a and Lactococcus lactis, plantarum, rhamnosus, casei; and Leuconostoc	≥75 ml qd for 10 days Probiotic	Heat killed organisms	n/a; self report	N: 61 N with AAD: 11 Other results:	N: 64 N with AAD: 14 Other results:

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Author, Year	Risk of Bias ^s	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
							cremoris					
Monteiro, 1981 ⁴⁸	Unclear	Prevent AAD aim: Yes	n/a, mean age	n/a	Infections	Tetracycline; Betalactamines; dose and duration n/a	Saccharomyces, boulardii, n/a, form n/a, n/a	1 capsule qid for 6 days Probiotic	Placebo	>2 defecations >=3 times a day; n/a	N: 121 N with AAD: 19 Other results:	N: 119 N with AAD: 33 Other results:
Myllyluoma, 2005 ⁴⁹	Unclear	n/a AAD aim: Yes	Adults; Elderly, mean age	OutPt	H. pylori	Clarithromycin 500 mg bid; Amoxicillin 1 g bid; for 7 days	Lactobacillus, rhamnosus, GG, form n/a, 6x10 ⁸ cfu/ml (2 L. strains combined; microbial quality assessed regularly) Lactobacillus, rhamnosus, LC, form n/a Bifidobacterium, breve, Bb99, form n/a, 7x10 ⁶ cfu/ml And Propionibacterium, freudenreichii, shermanii JS	65 ml bid for 7 days, 65 ml qd for 3 weeks Probiotic	Placebo	>= 3 watery or loose stools per day for >= 2 consecutive days; self report, De Boer modified	N: 23 N with AAD: 4 Other results:	N: 24 N with AAD: 2 Other results: Epigastric pain: 7; bloating: 7; flatulence: 7
Nista, 2004 ⁵⁰	Unclear	Prevent AAD aim:	Adults, mean age 46 (13)	OutPt	H. pylori	Clarithromycin 500 mg bid; Amoxicillin 1 g bid; for 7 days	Bacillus, clausii, n/a, form n/a,	1 vial tid for 14 days	Placebo	De Boer questionnaire,	N: 60 N with AAD:	N: 60 N with AAD:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		Yes					2x10 ⁹ spores	Probiotic		self report	Other results: 10% diarrhea first week, 4% second	Other results: 30% diarrhea first week, 8% second
Ozkinay, 2005 ⁵¹	High	n/a AAD aim: No	Adults, mean age 42 (10)	OutPt	Vaginal infection	n/a	Lactobacillus, acidophilus, n/a, active, 10 ⁷ cfu	1 tablet qd for 6-12 days Synbiotic	Placebo	n/a	N: 240 N with AAD: 1 Other results:	N: 120 N with AAD: Other results: 2 cases of AE (nausea, diarrhea)
Park, 2007 ⁵²	Unclear	n/a AAD aim: No	Adults; Elderly, mean age 21.67	OutPt	H. pylori	Amoxicillin 1000 mg bid; Clarithromycin 500 mg bid; for 7 days	Bacillus, subtilis, n/a, lyophilized, 2.5x10 ⁹ cfu/g Streptococcus, faecium, n/a, lyophilized, 22.5x10 ⁹ cfu/g	2 capsules tid for 8 weeks Probiotic	Antibiotics-only	n/a	N: 176 N with AAD: 2 Other results:	N: 176 N with AAD: 17 Other results:
Plummer, 2004 ⁵³	High	Prevent AAD aim: Yes	Elderly, mean age	InPt	n/a	n/a	Lactobacillus, acidophilus, n/a, form n/a, 2x10 ¹⁰ cfu (both strains combined) Bifidobacterium, bifidum, n/a, form n/a, 2x10 ¹⁰ cfu	1 capsule qd for 20 days Probiotic	Placebo	n/a; staff record	N: 69 N with AAD: 15 Other results: C. diff positive: 11; toxin positive: 5	N: 69 N with AAD: 15 Other results: C. diff positive: 9; toxin positive: 7
Reid, 1992 ⁵⁴	Unclear	n/a	Adults, mean	OutPt	Lower urinary tract	Norfloxacin 400 mg bid for 2	Lactobacillus,	1 capsule	Placebo	n/a; self report	N: 19	N: 21

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		AAD aim: No	age 23 (4.4)		infections	days or Trimethoprim/sulfamethoxazole 160mg/800mg qd for 3 days	rhamnosus, GR-1, lyophilized, 1.6x10 ⁷ cfu (combined) Lactobacillus, fermentum, B-54, lyophilized	bid for 2 weeks and at the end of each of the next 2 months Probiotic			N with AAD: 0 Other results:	N with AAD: 0 Other results:
Ruszczynski, 2008 ⁵⁵	Low	Prevent AAD aim: Yes	Children, mean age	n/a	Common infections	n/a	Lactobacillus, rhamnosus, Pen, form n/a, 2x10 ⁹ cfu (all strains combined) Lactobacillus, rhamnosus, E/N, form n/a, 2x10 ⁹ cfu Lactobacillus, rhamnosus, Oxy, form n/a, 2x10 ⁹ cfu	2x10 ⁹ cfu bid for duration of antibiotics Probiotic	Placebo	>= 3 loose or watery stools per day for >=48 hours and caused by C. difficile or unexplained diarrhea; self report	N: 120 N with AAD: 20 Other results: Duration of diarrhea: 4.4 days (SD 2.2); 5 rotavirus diarrhea, 0 adenovirus diarrhea No AE observed	N: 120 N with AAD: 9 Other results: Duration of diarrhea: 4.1 days (SD 2.1); 10 rotavirus diarrhea, 1 adenovirus diarrhea No AE observed
Safdar, 2008 ⁵⁶	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 66.56 (14.53)	InPt	Infection	n/a	Lactobacillus, acidophilus, n/a, form n/a, 2x10 ¹⁰ cfu/capsule	1 capsule tid for 14 days Probiotic	Placebo	Bowel movement consistency on the Stool consistency continuum listed as 1, 2, or 3 for >=2	N: 23 N with AAD: 4 Other results:	N: 17 N with AAD: 6 Other results:

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Author, Year	Risk of Bias ^s	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
										consecutive days; research team + self report (after discharge)		
Sahagun-Flores, 2007 ⁵⁷	Unclear	n/a AAD aim: No	Adults, mean age 45.19 (8.8)	OutPt	H. pylori	Amoxicillin 1 g; Clarithromycin 500mg; for 7 days	Lactobacillus, casei, Shirota, lyophilized, 8 x 10 ⁹ cfu	1 dose tid for 7 days Probiotic	Antibiotics-only	n/a	N: 35 N with AAD: Other results: 4 pts dropped out due to diarrhea, metallic taste and abdominal discomfort, family problems and other reasons	N: 36 N with AAD: Other results:
Sampalis, 2010 ⁵⁸	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 59.5 18.1	n/a	Respiratory, skin, urogenital tract, or other infections	Beta-lactams; Quinolones; Macrolides; Clindamycin; Metronidazole; Septra; Tetracycline; Tobramycin; Vancomycin; Linezolid; for a minimum of 3 days	Lactobacillus, acidophilus, CL1285, form n/a, 50x10 ⁹ cfu (both strains per 3.5oz. bottle) Lactobacillus, casei, n/a, form n/a, 50x10 ⁹ cfu	49 g/qd for 2 days, 98 g/qd for 27-38 days Probiotic	Placebo	>= 1 episode of unformed / liquid stool in 24 h, diary cards	N: 233 N with AAD: 47 Other results: Mean number of days with diarrhea: 0.67 None of the SAE were related to the treatment product	N: 239 N with AAD: 65 Other results: Mean number of days with diarrhea: 1.19

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
Saneeyan, 2011 ⁵⁹	Unclear	n/a AAD aim: No	Children, mean age 8.2 (2.1)	OutPt	H. pylori	Amoxicillin 25mg per kg bid, max. 1.5g; Claritromycin 10mg per kg bid, max. 1g per day; Omeprazol 0.5mg bid; for 2 weeks	Lactobacillus, casei, n/a, form n/a, 10 ⁹ cfu / sachet (strains combined) Lactobacillus, acidophilus, n/a, form n/a, Lactobacillus, reuteri, n/a, form n/a, Lactobacillus, bulgaricus, n/a, form n/a, Streptococcus, cremoris, n/a, form n/a, Bifidobacterium, bifidum, n/a, form n/a, Bifidobacterium, infantis, n/a, form n/a,	qd for 2 weeks Probiotic	Antibiotics-only	>=3 times soft or watery stool per day for 48 hours; assessor n/a	N: 25 N with AAD: 3 Other results:	N: 25 N with AAD: 13 Other results:
Schrezenmeir, 2004 ⁶⁰	Unclear	Prevent AAD aim:	Children, mean age 4.16 (0.13)	OutPt	Tonsillitis, pharyngitis, otitis media, or bronchitis/mild	n/a	Lactobacillus, acidophilus, n/a, form n/a, 10 ⁹ cfu/g (both strains	120 ml tid (1-3 years old), 120 ml qid (4-6	Placebo	n/a; self report	N: 50 N with AAD: 2 Other results:	N: 43 N with AAD: 0 Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		Yes			pneumonia		combined) Bifidobacterium, n/a, n/a, form n/a	years old); for antibiotic treatment duration Synbiotic			No significant changes from baseline for stool consistency, stool frequency, and diarrhea	No significant changes from baseline for stool consistency, stool frequency, and diarrhea
Selinger, 2011 ⁶¹	Unclear	Prevent AAD aim: Yes	n/a, mean age	InPt	Hospitalized on systemic antibiotics	n/a (systemic antibiotics), dose and duration vary	Lactobacillus, n/a, n/a, form n/a, n/a Bifidobacterium, n/a, n/a, form n/a, n/a Streptococcus, n/a, n/a, form n/a, n/a	1 sachet bid for the length of the antibiotic course Probiotic	Placebo	n/a	N: 62 N with AAD: 0 Other results: No drug-related SAE	N: 62 N with AAD: 4 Other results:
Sheu, 2002 ⁶²	High	n/a AAD aim: No	Adults, mean age 47.8	OutPt	H. pylori	Amoxicillin 1 g bid; Clarithromycin 500 mg bid; for 7 days	Lactobacillus, n/a, n/a, active, 5x10 ⁹ cfu / bottle (all combined) Bifidobacterium, n/a, n/a, active, 5x10 ⁹ cfu/bottle (all combined)	200 ml bid for 1 week Probiotic	Antibiotics-only	n/a	N: 80 N with AAD: 2 Other results:	N: 80 N with AAD: 10 Other results:
Sitonen, 1990 ⁶³	Unclear	Prevent AAD aim: Yes	Adults, mean age	OutPt	Healthy	Erythromycin 400 mg tid for 7 days	Lactobacillus, rhamnosus, GG, active, n/a	125 ml bid for 7 days Probiotic	Placebo	n/a; self report	N: 6 N with AAD: Other results:	N: 6 N with AAD: Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
											Diarrhea duration: 2 days	Diarrhea duration: 8 days
Simakachorn, 2011 ⁶⁴	Unclear	n/a AAD aim: No	Children, mean age 1.98 0.95	InPt	Critically ill	n/a	Lactobacillus, paracasei, NCC 2461, form n/a, 5x10 ⁶ cfu / g Bifidobacterium, longum, BB 536 (NNC 3001), form n/a, 2x10 ⁶ cfu / g	estimated 10 ⁹ cfu per day, for 14 days Synbiotic	Placebo	n/a	N: 47 N with AAD: Other results: No difference between groups in AE (including diarrhea) No reported secondary infections associated with the administered probiotics	N: 47 N with AAD: Other results:
Song, 2010 ⁶⁵	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 61 15	OutPt	Respiratory tract infection	Cephalosporins; Macrolides; Fluoroquinolones; Antituberculosis drugs; Clindamycin; Penicillin; Aminoglycosides; Metronidazole; Sulfamethoxazole/trimethoprim; Glycopeptides; dose and duration vary	Lactobacillus, rhamnosus, R0011, form n/a, 2x10 ⁹ cfu (both strains combined) Lactobacillus, acidophilus, R0052, form n/a	1 capsule bid for 14 days Probiotic	Placebo	Loose / watery stool > 3 per day for 2 consecutive days; > 2 loose stools for 2 days	N: 103 N with AAD: 11 Other results: 28 pts with increased bowel frequency on > 3 of 14 days	N: 111 N with AAD: 14 Other results: 38 pts with increased bowel frequency on > 3 of 14 days
Song, 2010 ⁶⁶	High	n/a AAD aim:	Adults; Children; Elderly,	OutPt	H. pylori	Amoxicillin 1000 mg bid; Clarithromycin 500 mg bid; for	Saccharomyces, boulardii, n/a, form	1 capsule tid for 4	Antibiotics-	n/a	N: 330	N: 331

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
		No	mean age 49.76 (11.7)			7 days	n/a, 3x10 ¹⁰ cfu/g	weeks Probiotic	only		N with AAD: 11 Other results:	N with AAD: 20 Other results:
Stein, 2007 ⁶⁷	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 50.5 (17.7)	InPt	n/a	n/a	Lactobacillus, acidophilus, n/a, form n/a, 1.5x10 ⁹ cfu Bifidobacterium, bifidum, n/a, form n/a, 1.5x10 ⁹ cfu Lactobacillus, bulgaricus, n/a, form n/a, 1.5x10 ⁹ cfu Streptococcus, thermophilus, n/a, form n/a, 1.5x10 ⁹ cfu	1 capsule tid, duration n/a Probiotic	Placebo	>=2 watery stools within 24 hours; assessor n/a	N: 21 N with AAD: 3 Other results:	N: 21 N with AAD: 1 Other results:
Sullivan, 2003 ⁶⁸	Unclear	n/a AAD aim: No	Adults, mean age 28	OutPt	Healthy	Clindamycin 150 mg qid for 7 days	Lactobacillus, acidophilus, NCFB 1748, form n/a, 10 ⁸ cfu/ml (all strains combined) Lactobacillus, paracasei subsp. paracasei, F 19, form n/a	250 ml bid for 14 days Probiotic	Placebo	n/a; self report	N: 12 N with AAD: 1 Other results: Looser stool: 1	N: 12 N with AAD: 0 Other results: Looser stool: 0

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
							Bifidobacterium, lactis, Bb12, form n/a					
Surawicz, 1989 ⁶⁹	Unclear	Prevent AAD aim: Yes	Adults; Elderly, mean age 47.8 (20.1)	n/a	n/a	n/a	Saccharomyces, boulardii, n/a, lyophilized, n/a	250 mg bid, duration n/a Probiotic	Placebo	>=3 loose or watery stools per day for >=2 days; staff and self report	N: 116 N with AAD: 11 Other results: Bowel movements average per day: 5.2; diarrhea duration: 5.2 days No side effects	N: 64 N with AAD: 14 Other results: Bowel movements average per day: 3.7; diarrhea duration: 4.0 days No side effects
Sykora, 2005 ⁷⁰	Unclear	n/a AAD aim: No	Children, mean age 12.6 (3.3)	OutPt	H. pylori	Amoxicillin 25 mg/kg bid; clarithromycin 7.5 mg/kg bid; for 7 days	Lactobacillus, casei, DN-114001, form n/a, 10 ⁸ cfu/ml	100 ml qd for 1 week Probiotic	Placebo	Questionnaire, self report	N: 39 N with AAD: Other results: Differences in side effects (including e.g., diarrhea) were not statistically significant	N: 47 N with AAD: Other results:
Szajewska, 2009 ⁷¹	Unclear	Prevent AAD aim: Yes	Children, mean age 12.3 (2.7)	InPt	H. pylori	Amoxicillin 25 mg/kg bid; Clarithromycin 10 mg/kg bid; for 7 days	Lactobacillus, rhamnosus, GG, form n/a, 10 ⁹ cfu	10 ⁹ cfu bid for 7 days	Placebo	>= 3 loose or watery stools per day for >= 2	N: 44 N with AAD: 2	N: 39 N with AAD: 6

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Author, Year	Risk of Bias ^s	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
								Probiotic		days; self report	Other results:	Other results:
Szymanski, 2008 ⁷²	Unclear	Prevent AAD aim: Yes	Children, mean age	n/a	Acute otitis media, respiratory tract infection, urinary tract infection	n/a	Bifidobacterium, longum, PL03, form n/a, 10 ⁸ cfu (all strains combined) Lactobacillus, rhamnosus, KL53A, form n/a Lactobacillus, plantarum, PL02, form n/a	10 ⁸ cfu bid, duration n/a Probiotic	Placebo	>=3 loose or watery stools per day for >=2 days; self reported	N: 40 N with AAD: 1 Other results: Stools per day: 1 (SD 0.4) No AE were reported	N: 38 N with AAD: 2 Other results: Stools per day: 1.3 (SD 0.6) No AE were reported
Tankanow, 1990 ⁷³	High	Prevent AAD aim: Yes	Children, mean age	OutPt	Disease requiring amoxicillin	Amoxicillin dose and duration vary	Lactobacillus, acidophilus, n/a, form n/a, 5.1x10 ⁸ cfu (both strains combined per packet) Lactobacillus, bulgaricus, n/a, form n/a,	1 packet qid for 10 days Probiotic	Placebo	>=1 abnormally loose bowel movements per day; parental report	N: 15 N with AAD: 10 Other results:	N: 23 N with AAD: 16 Other results:
Thomas, 2001 ⁷⁴	Low	Prevent AAD aim: Yes	Adults; Elderly, mean age	InPt	Infection	n/a	Lactobacillus, rhamnosus, GG, active, 10 ¹⁰ cfu/capsule (viability tested in sample)	1 capsule bid for 14 days Probiotic	Placebo	Watery or liquid stools (1, 2, 3 on Stool Consistency Continuum) for >= 2	N: 152 N with AAD: 39 Other results:	N: 150 N with AAD: 40 Other results:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
										consecutive days or ≥ 3 BM $>$ pt's normal; self report		
Tursi, 2004 ⁶⁵	Unclear	n/a AAD aim: Yes	Adults; Elderly, mean age 58.2	OutPt	H. pylori	Amoxicillin 1 g tid; Tinidazole 500 mg bid; for 10 days	Lactobacillus, casei casei, DG, lyophilized, 8×10^6 cfu	750 mg qd for 10 days Probiotic	Antibiotics-only	n/a; self report	N: 35 N with AAD: 0 Other results: slight black feces: 1	N: 35 N with AAD: 5 Other results: slight black feces: 3
Vanderhoof, 1999 ⁷⁶	High	Prevent AAD aim: Yes	Children, mean age	OutPt	Acute infectious disease	n/a	Lactobacillus, rhamnosus, GG, active, 10^{10} cfu/capsule	1-2 capsules qd for 10 days Probiotic	Placebo	≥ 2 liquid stools per day on ≥ 2 days; primary care giver report	N: 93 N with AAD: 7 Other results: Duration of diarrhea: 4.7 days; stool consistency score < 4 : 17%; No drop-out resulting from untoward effects of LGG or placebo	N: 95 N with AAD: 25 Other results: Duration of diarrhea: 5.88 days; stool consistency score < 4 : 48%;
Wenus, 2008 ⁷⁷	High	Prevent AAD aim: Yes	Adults; Elderly, mean age 58.8 (16.5)	InPt	n/a	n/a	Lactobacillus, rhamnosus, GG, form n/a, $> 10^8$ cfu	250 ml qd for 14 days Probiotic	Heat killed organisms	≥ 3 fluid stools/day ≥ 2 days; self report	N: 46 N with AAD: 2 Other results: C. diff culture	N: 41 N with AAD: 8 Other results: C. diff culture

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
							Lactobacillus, acidophilus, La-5, form n/a, $\geq 10^7$ cfu Bifidobacterium, animalis lactis, Bb12, form n/a, $> 10^8$ cfu				positive without AAD: 1; toxin A positive without AAD: 1 (out of 55 samples from both groups)	positive: 1
Witsell, 1995 ⁷⁸	High	Prevent AAD aim: Yes	Adults; Children; Elderly, mean age 34	OutPt	Infections (ear, sinus or throat)	Amoxicillin/clavulanate 250 or 500 mg tid (duration n/a)	Lactobacillus, acidophilus, n/a, form n/a, 10^7 cfu/tablet (2 strains combined) Lactobacillus, bulgaricus, n/a, form n/a	3 tablets qid, duration n/a Probiotic	Antibiotics-only	Questionnaire, self report	N: 12 N with AAD: Other results: ≥ 1 gastrointestinal complaint with antibiotics: 10; diarrhea score (1-5): 1.58 (SD 0.5)	N: 15 N with AAD: Other results: ≥ 1 gastrointestinal complaint with antibiotics: 10; diarrhea score (1-5): 1.00 (SD 0.24)
Wunderlich, 1989 ⁷⁹	Unclear	Treat AAD aim: Yes	Adults, mean age 33	OutPt	Acute diarrhea while on antibiotics	n/a	Enterococcus, faecium, SF 68, lyophilized, 7.5×10^7 cfu/capsule	1 capsule bid for 7 days Probiotic	Placebo	≥ 2 liquid or semi-liquid stools per day; self report	N: 23 N with AAD: 2 Other results: Moderate diarrhea: 0 No side effects were reported	N: 22 N with AAD: 6 Other results: Moderate diarrhea: 1 No side effects were reported

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
Yasar, 2010 ⁸⁰	Unclear	n/a AAD aim: Yes	Adults, mean age 38.32 10.66	OutPt	H. pylori	Amoxicillin, 1000mg bid; Clarithromycin, 500mg bid; for 14 days	Bifidobacterium, animalis, DN-173 010-1010, form n/a, 10 cfu/g	125ml qd for 14 days Probiotic	Antibiotics-only	AAD absent, mild, moderate, or severe, self report	N: 38 N with AAD: 14 Other results:	N: 38 N with AAD: 15 Other results:
Yoon, 2011 ⁸¹	Unclear	n/a AAD aim: Yes	Adults; Elderly, mean age 53.7 11.1	OutPt	H. pylori	Moxifloxacin, 400 mg qd; Amoxicillin, 1000mg bid, for 2 weeks	Lactobacillus, acidophilus, HY 2177, form n/a, >10 ⁵ cfu/ml Lactobacillus, casei, HY 2743, form n/a, >10 ⁶ cfu/ml Bifidobacterium, longum, HY 8001, form n/a, >10 ⁶ cfu / ml Streptococcus, thermophilus, B-1, form n/a, >10 ⁸ cfu/ml	150ml qd for 4 weeks Probiotic	Antibiotics-only	n/a, self-report, interview	N: 151 N with AAD: 20 Other results:	N: 186 N with AAD: 17 Other results:
Zoppi, 20013 ⁸²	High	Prevent AAD aim: Yes	Children, mean age 5.1	InPt	Febrile respiratory tract infections	Ceftriaxone 50 mg/kg qd (duration n/a)	Bifidobacterium, bifidum, n/a, active, 10 ⁹ cfu Lactobacillus, acidophilus, n/a, active, 10 ⁹ cfu	2 capsules tid, duration n/a Probiotic	Antibiotics-only	n/a	N: 7 N with AAD: Other results: No difference in intestinal complaints; stools per day:	N: 5 N with AAD: Other results: No difference in intestinal complaints; stools per day:

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Author, Year	Risk of Bias [§]	Prevention vs. Treatment Aim	Age group; mean (SD)	Setting	Condition	Antibiotics, Dose, Duration	Probiotics: Genus, Species, Strain, Form, Potency	Dose	Comparator	Diarrhea Definition, Assessment	Intervention group results	Control group results
											1 (SD 1)	3 (SD 1)

Note: §: Risk of bias assessment based on Cochrane Risk of Bias tool dimensions 'Sequence generation; Blinding of participants, personnel and outcome assessors; Incomplete outcome data; Selective outcome reporting; Other sources of bias', Determination of strain, Power calculation, Absence of conflict of interest; n/a: not available, not applicable; AAD: antibiotic-associated diarrhea; AAD aim: prevention or treatment of AAD reported is an explicit aim of study; qd: once a day; bid: twice a day; tid: three times a day; qid: four times a day; cfu = colony forming unit; InPt: Inpatients, OutPt: Outpatients; n/a: not available, not applicable; pts: participants; SAE: serious adverse event; SD: standard deviation

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