6.2 Enteral Nutrition (Other): Probiotics

Question: Does the addition of probiotics to enteral feeding result in better outcomes in critically ill patients?

Summary of evidence: There were 4 level 1 and 28 level 2 studies that were reviewed. Of the 32 included trials, 21 enrolled heterogeneous critically ill (medical and surgical) ICU patients (Spinder 2008, Barraud 2010, Frohmader 2010, Morrow 2010, Ferrie 2011, Tempe 1983, Heimburger 1994, Bleichner 1997, Kecskes 2003, Jain 2004, Klarin 2005, McNaught 2005. Forestier 2008, Klarin 2008, Knight 2008, Lopez de Toro 2014, Sanaie 2014, Rongrungruang 2015, Malik 2016, Zeng 2016, de Castro Soares 2017), 6 enrolled patients with acute pancreatitis (Besselink 2008, DerSimonian 1986, Li 2007, Olah 2007, Cui 2013, Wang 2013), 1 enrolled trauma patients (Kotzampassi 2006), 1 enrolled head injury patients (Tan 2011, Tan 2013) and 2 enrolled burn patients (Schlotterer 1987, Lu 2004). Three trials studied the effects of the addition of *saccharomyces boulardii* to enteral nutrition, four studied the effects of Lactobacillus plantarum, three studied the effects of Lactobacillus rhamnosus, one studied Lactobacillus casei, three studied the effects of VSL #3, one studied the effects of Trevis ™ (combination of probiotics+ prebiotics), four studied the effects of Synbiotic 2000 (combination of probiotics and prebiotics), one studied Ecologic 641 (probiotics) plus prebiotics (Besselink 2008), one studied Biovicerin (sporulated B. cereus), and eleven studies used probiotics of varying strains . In one study, synbiotics were compared to a prebiotic (vs. placebo/conventional therapy), hence the data from this trial was not included in the meta-analysis (Olah 2007). Bleichner and de Castro Soares only reported on diarrhea while the other studies reported on clinical outcomes. In most of the studies, patients received either enteral or parenteral nutrition, but no further details were provided.

Mortality: Probiotics had no effect on hospital mortality when the data from 17 trials were pooled (RR 0.98, 95% CI 0.82, 1.18, p=0.85, heterogeneity I^2=0%; figure 1) and no effect on ICU mortality pooling results from 7 trials (RR 0.90, 95% CI 0.70, 1.17, p=0.44, heterogeneity I^2=0%; figure 2).

Overall infections and VAP: Infectious complications were reported in 12 trials. Pooled results show that probiotics were associated with a significant reduction in infectious complications (RR 0.82, 95% CI 0.69, 0.97, p=0.02, heterogeneity I^2=41%; figure 3). When the data from the 8 trials reporting VAP were pooled, probiotics were associated with a significant decrease in the incidence of VAP (RR 0.76, 95% CI 0.62, 0.92, p=0.006, heterogeneity I^2=24%; figure 4).

Subgroup analyses: Several subgroup analyses were done to elucidate the effects of probiotics on infections (see figure 5).The details are as follows:

Dose of probiotics: Subgroup analyses showed similar rates of infectious complications in trials using high dose probiotics (≥5 x 10^9 CFU/day) (0.87, 95% CI 0.72, 1.06, p = 0.18) as those using a lower dose (<5 x 10^9 CFU/day) (RR 0.40, 95% CI 0.11, 1.50, p=0.18; p-value for the difference between groups: p=0.25).

Lactobacillus plantarum: Subgroup analyses showed that *L. plantarum,* either alone or in combination with other probiotics, was associated with a significant reduction in overall infections (RR 0.70, 95% CI 0.50, 0.97, p=0.03). However, this was not significantly different from the aggregated results of trials of that did not include *L. plantarum* (RR 0.88, 95% CI 0.72, 1.09, p=0.25; p-value for the difference between groups: p=0.23).

Lactobacillus rhamnosus GG: Subgroup analyses showed that effect of trials using LGG was not different from trials that did not include LGG (RR 0.86, 95% CI 0.67, 1.10 compared to RR 0.76, 95% CI 0.58, 1.01; p-value for the difference between groups: p=0.53).

Higher mortality: The median mortality rate (hospital mortality or ICU mortality if hospital not reported) in the control groups of all studies was 15%. Subgroup analyses showed that probiotics were associated with a significant reduction in overall infections among patients with higher risk of death (>15% mortality in the control group) (RR 0.75, 95 % CI 0.57, 0.98, p=0.03). There was no significant effect in overall infections observed for trials of patients with a lower mortality (≤15% mortality) in the control group (RR 0.88, 95% CI 0.66, 1.18, p=0.40) and the test of subgroup differences was not significant (p-value for the difference between groups: p=0.41).

Methodological score: The median method score was 10. We compared trials with a methods score of less than 10 with those with a score of 10 or more. Trials with a higher score showed no effect on infection (RR 0.93, 95% CI 0.76, 1.15, p=0.51), whereas trials with a lower methods score showed a significant reduction in infectious complications (RR 0.70, 95% CI 0.58, 0.85, p=0.0003, p-value for the difference between groups: p=0.05).

Length of Stay: Probiotics had no impact on hospital LOS when data from 12 trials were pooled (WMD -1.23, 95% CI -4.21, 1.74, p=0.42, heterogeneity I^2=66%; figure not shown). There was a trend towards a decrease in ICU LOS when results of 15 trials were pooled (WMD -3.39, 95% CI -7.55, 0.78, p=0.11, heterogeneity I^2=93%; figure 6).

Other: The impact on diarrhea, reported variably as days of diarrhea, diarrhea rates and/or duration of diarrhea was reported in 14 trials. Pooling results from 9 trials that reported patients who developed diarrhea, probiotics had no effect (RR 0.97, 95% CI 0.82, 1.15, p=0.54; heterogeneity I^2=5%; figure 7). Data were too sparse to aggregate other reported individual infections (see table 1).

Conclusions:

1) The addition of probiotics to enteral nutrition has no effect on hospital or ICU mortality.
2) The addition of probiotics to enteral nutrition is associated with a reduction in overall infectious complications, though this was only seen in a subgroup of lower quality studies. Probiotic supplementation is associated with a reduction in the incidence of VAP.
3) The addition of probiotics to enteral nutrition has no effect on hospital LOS or diarrhea, but may be associated with a reduction in ICU LOS.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.
Level 2 study: If any one of the above characteristics are unfulfilled

Table 1. Randomized studies evaluating Probiotics in critically ill patients

	Study	Population	Methods Score	Type of Probiotic/Intervention		
				Delivery Vehicle	Intervention/Dose/Duration	Control
1	Tempe 1983	ICU patients N=40	C.Random: yes ITT: yes Blinding: double Score: 10 Viability (intervention): NR	EN tube	EN (unknown) + Ultra-Levure (*Saccharomyces boulardii)*, 10^{10}/1L solution for 11-21 days	EN (unknown) + Placebo (sterile solution)
2	Schlotterer 1987	Burn patients N=18	C.Random: no ITT: no Blinding: double Score: 8 Viability (intervention): NR	NG tube	EN (Polydiet or Nutrigil) + *Saccharomyces boulardi* 500 mg QID for 8-28 days	EN (Polydiet or Nutrigil) + Placebo
3	Heimburger 1994	Mixed ICU patients 83% received antibiotics N=62	C.Random: no ITT: no Blinding: double Score: 9 Viability (intervention): NR	EN tube	EN (standard) + 1g of Lactinex (*Lactobacillus acidophilus & Lactobaccilus bulgaricus*) 2 X 10^6 TID for 5-10 days	EN (standard) + placebo (0.5g dextrose + 0.5g lactose)
4	Bleichner 1997	Mixed ICU patients N=128	C.Random: not sure ITT: yes Blinding: double Score: 13 Viability (intervention): NR	EN tube	EN (unknown) + *Saccharomyces boulardii* 500 mg QID for 21 days or until EN stopped	EN (unknown) + Placebo (powder)
5	Kecskes 2003	ICU patients on antibiotics N=45	C.Random: no ITT: no Blinding: double Score: 8 Viability (intervention): yes	NJ tube	EN (Nutrison fibre) + fermented oatmeal formula with *Lactobacillus plantarum* 299 10^9 BID and fibre for 7 days	EN (Nutrison fibre) + heat killed Lactobacillus plantarum 299 BID + fibre (non-viable)
6	Jain 2004	ICU patients N=90	C.Random: no ITT: yes Blinding: double Score: 10 Viability (intervention): NR	Oral or NG tube	EN or PN + Trevis™ 1 capsule TID + 7.5g Raftilose (oligofructose) BID until hospital discharge	EN or PN + Placebo (powdered sucrose capsules)

7	Lu 2004	Burn patients N=40	C.Random: no ITT: yes Blinding: double Score: 9 Viability (intervention): NR	NR	EN + synbiotics (4 types of probiotics & 4 types of unspecified prebiotics) for 21 days	EN + 4 types of prebiotics
8	Klarin 2005	Critically ill patients on antibiotics N=17	C.Random: no ITT: no Blinding: no Score: 6 Viability (intervention): NR	Mixed in fermented oatmeal, given via NG tube	EN + *Lactobacillus plantarum* 299v, 10^9/day 50ml every 6 hours x 3 days then 25 ml every 6 hours until ICU discharge	EN (Impact or Nutrodrip Fibre). Some patients needed PN
9	McNaught 2005	ICU patients on antibiotics N=130	C.Random: no ITT: yes Blinding: no Score: 7 Viability (intervention): NR	Oral, NJ tube	EN or PN + Proviva, (oatmeal & fruit drink) 5 x 10^7 CFU/ml of L. plantarum 299v X 500 mls until hospital discharge or beyond	EN or PN alone
10	Kotzampassi 2006	Multiple trauma patients from 5 ICUs N=77	C.Random: no ITT: no Blinding: double Score: 8 Viability (intervention): NR VAP determination: clinical	Endoscopic gastrostomy or NG tube	EN or PN + Synbiotic 2000 Forte 10^{11}, 1 sachet/day for 15 days until ICU discharge	EN or PN + Placebo (Maltodextrin), mixed in tap water
11	Alberda 2007	ICU patients N=28	C.Random: no ITT: yes; Blinding: double Score: 10 Viability (intervention): No for VSL # 3; Yes for bacteria sonicates	NG tube	Jevity Plus (EN) (10 g fructooligosaccharides/1000 mL and 12 g of soluble and insoluble fiber blend) + VSL # 3, 1 package BID, 9 x 10^{11}/day for 7 days until ICU discharge or EN discontinuation	Jevity Plus + Placebo
12	Li 2007	Severe acute pancreatitis patients N=25	C.Random: no ITT: yes Blinding: no Score: 7 Viability (intervention): NR	Given enterally	Jinshuangqi (*bifidobacteria, lactobacillus and streptococcus*) 2.0 g TID on basis of traditional treatment Duration: NR	Traditional treatment

13	Olah 2007	Severe acute pancreatitis patients N=83	C.Random: no ITT: no Blinding: no Score: 9 Viability (intervention): NR	NJ tube	EN (Nutricion Fibre) + Synbiotic 2000, 4 X 10^{10} CFU for 7 days	EN (Nutricion Fibre) + 10g plant fibres ((2.5 g each of Betaglucan, Inulin, Pectin & Resistant starch) (Prebiotics) BID for at least 2 days
14	Forestier 2008	Mixed ICU patients, 50% on antibiotics N=208	C.Random: not sure ITT: no Blinding: double Score: 8 Viability (intervention): NR VAP determination: objective	NG tube or Oral (after tube removal)	*Lactobacillus casei rhamnosum*, $10^{9\ CFU}$ BID until ICU discharge	Placebo (growth medium never exposed to bacteria).
15	Besselink 2008	Acute pancreatitis patients from 15 ICUs N=298	C.Random: not sure ITT: yes Blinding: double Score:11 Viability (intervention): NR VAP determination: clinical	NJ tube or Oral	EN (Nutrison Multifibre) + Ecologic 641 10^{10} CFU BID for 28 days	EN (Nutrison Multifibre) + Placebo (cornstarch + maltodextrins)
16	Klarin 2008	ICU patients from 5 ICUs, on antibiotics for c. Difficile N=68	C.Random: yes ITT: no Blinding: double Score: 10 Viability (intervention): NR	Mixed in fermented oatmeal added to enteral feeds NG tube	299 *Lactobacillus plantarum*, 8 x 10^8 CFU/ml given as 6 x 100 ml doses every 12h & after 50 ml given BID until ICU discharge	Same oatmeal gruel mixed with lactic acid
17	Knight 2009	General ICU patients N=300	C.Random: yes ITT: no Blinding: double Score: 10 Viability (intervention): NR VAP determination: clinical	NJ or OG (orogastric) tube	EN (Nutrition Energy) + Synbiotic 2000 FORTE 4 x10^{11} species/sachet BID for 28 days or ICU discharge	EN (Nutrison Energy) + Placebo
18	Barraud 2010	Mechanically ventilated ICU patients, 80% on antibiotics N=167	C.Random: yes ITT: yes; Blinding: double Score: 12 Viability (intervention): NR VAP determination: objective	NG tube	EN (Fresubin) + Ergyphilus 2 x 10^{10} per capsule + potato starch 5 caps/day for 28 days	EN (fresubin) + Placebo capsules (excipient of potato starch)

19	Morrow 2010	ICU patients N=146	C.Random: no; ITT: yes; Blinding: double; Score:10 Viability (intervention): yes VAP determination: objective	Oropharynx and NG tube	EN (routine care) + *Lactobacillus rhamnosus* GG, $2X10^9$ BID as lubricant and mixed with water until extubation	EN (routine care) + inert plant starch inulin (prebiotic) BID as as lubricant and mixed with water
20	Frohmader 2010	General ICU patients on antibiotics N=45	C.Random: yes ITT: yes Blinding: double Score: 11 Viability (intervention): yes	NG or NJ tube	EN (Standard) + VSL #3 mixed in nutritional supplement (Sustagen), BID until hospital discharge	EN (Standard) + placebo mixed in nutritional supplement (Sustagen), BID
21	Ferrie 2011	Critically ill patients with diarrhea, N=36	C.Random: no ITT: yes Blinding: double Score: 10 Viability (intervention): yes	NG tube	EN (Standard) + Culturelle *(Lactobacillus rhamnosus GG),* 10^{10} species/capsule + 280 mg inulin powder for 7 days	EN (Standard) + Raftiline, gelatin capsule with 280 mg inulin powder (prebiotic)
22	Sharma 2011	Acute pancreatitis patients N=50	C.Random: yes ITT: yes Blinding: double Score:11 Viability (intervention): yes	Oral, NJ or NG	EN (standard) or oral 4 sachets each $2.5 X 10^9$ *Lactobacillus acidophilus, Bifidobacterium longus*, *Bifidobacterium bifidum* & *Bifidobacterium infantalis* + 25 gms fructose for 7 days	EN (Standard) + placebo
23	Tan 2011	Closed head injury patients N=52	C.Random: yes ITT: yes Blinding: single Score:10 Viability (intervention): yes VAP determination: clinical	NG tube	EN (standard) total of 10^9 bacteria i.e. 7 sachets each $0.5 x 10^8$ *Bifidobacterium longum,* $0.5 X 10^71$ *Lactobacillus bulgaricus* and $0.5 X 10^7$ *Streptococcus thermophilus* for 21 days	EN (standard)
24	Cui 2013	Severe acute pancreatitis N=70	C.Random: no ITT: yes Blinding: no Score:9 Viability (intervention): yes	EN	EN + bifidobacterium, 4 capsules (each 210 mg, $2.604 x 10^9$) every 12 hours, given through nasal gastric tube. Total dose per day $20.832 x 10^9$.	EN

25	Tan 2013	Severe craniocerebral trauma	C.Random: no ITT: other Blinding: no Score:11 Viability (intervention): yes	NG tube	EN + 1×10^9 bacteria of viable probiotics (Golden Bifid, 3.5 g for 3 times per day) per day for 21 days.	EN (standard)
26	Wang 2013	Severe acute pancreatitis with intestinal ileus or abdominal distention. N=183	C.Random: no ITT: yes Blinding: no Score: 6 Viability (intervention): NR	SBFT	EN (standard) + capsules 0.5g TID containing Bacillus subtilis and Enterococcus faecium (5.0×10^7 Bacillus subtilis and 4.5×10^8 Enterococcus faecium per 250 g capsule). Unclear timeframe.	EN (standard)
27	Lopez de Toro 2014	Medical and surgical ICU pts with multi-organ failure N=89	C.Random: yes ITT: yes Blinding: no Score:11 Viability (intervention): NR	EN	EN + symbiotic drink with streptococcus thermophilus, lactobacillus bulgaricus, lactobacillus casei, lactobacillus acidophilus, bifidobacterium, Escherichia coli, coliformes x 7 days (max 4.8×10^9 UFC/ml).	EN and PN
28	Sanaie 2014	Critically ill pts, SIRS, expected LOS $\geq$7 days N=40	C.Random: yes ITT: yes Blinding: double Score:9 Viability (intervention): yes	NG tube	EN (standard) + 2 sachets VSL#3 BID x 7 days.	EN (standard) + placebo
29	Rongungruang 2015	Critically ill medical pts, no VAP at enrollment N=150	C.Random: no ITT: no Blinding: no Score:4 Viability (intervention): NR	EN and oral	80 ml fermented dairy product (8×10^9 cfu Lactobacillus casei [Shirota strain]) for oral care + 80 ml of the fermented dairy product via EN once daily for 28 days after extubated. EN feeding NR.	Standard care
30	Zeng 2016	Mixed ICU patients. N=250	C.Random: no ITT: no Blinding: single Score:8 Viability (intervention): yes	NG tube	EN + probiotic capsules 0.5g 3 times a day (active Bacillus subtilis and Enterococcus faecalis, concentration 4.5×10^9 per 0.25g and 0.5×10^9 per 0.25 g, respectively)	EN (standard)

31	Malik 2016	Mixed ICU patients, not taking microbial cell preparation prior to enrollment N=60	C.Random: yes ITT: no Blinding: double Score:9 Viability (intervention): NR	NG tube	EN + 3g packet (30 billion colony forming units of highly compatible, acid and bile resistant strains of Lactobacillusacidophilus, Lactobacilluscasei, Lactobacillus lactis, Bifidobacteriumbifidium, Bifidobacteriumlongum, Bifidobacteriuminfantus. Given twice daily.	EN + placebo
32	De Castro Soares 2017	ICU pts with diarrhea receiving antibiotics N=60	C.Random: yes ITT: no Blinding: double Score:8 Viability (intervention): NR	Feeding tube	EN + four vials of B. cereus (Biovicerin) q6h (each vial contains $5x10^6$ sporulated B cereus in liquid suspension.	EN + fibre (30g/day [10g q8h] of soluble fibre with 60% guar gum and 40% inulin.

C Random: concealed randomization
EN: enteral nutrition
NJ: nasojejunal
NG: nasogastric
OG: orogastric
FOS: fructooligosaccharides
CFU: Colony forming units
NR: not reported

Trevis™: 1 capsule= *Lactobacillus acidophilus La5, Bifidobacterium lactis Bb12, Streptococcus thermophilus, Lactobacillus bulgaricus, 4 x 10^9/total*

Synbiotic 2000 Forte: 10^{11} CFU of each: *Pediococcus pentoseceus 5-33:3, Leuconostoc mesenteroides 32-77:1, L. paracasei ssp paracasei 19, L. plantarum* 2362 & 2.5 g each of: inulin, oat bran, pectin and resistant starch

Ergyphilus: 10^{10} *Lactobaccilus rhamnosus GG, Lactobacillus casei, Lactobacillus acidophilus, Bifidobacterium bifidus,*

VSL # 3: > 10^{10} *Bifidobacterium longum, Bifidobacterium breve, >$10^{10/g}$ Bifidobacterium infantis, >$10^{11/g}$ Lactobacillus acidophulus, plantarum, casei, bulgaris & Streptococcus thermophilus*

Jinshuangqi: *Bifidobacterium longum > $10^{7\ CFU}$, Lactobacillus bulgaricus > $10^{6\ CFU}$ & Streptococcus Thermophilus > $10^{6\ CFU}$*

Ecologic 641: *Lactobacillus acidophilus, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum & Bifidobacterium lactis*

Synbiotic 2000: *10^{10} CFU of each: Pediococcus pentoseceus 5-33:3, Leuconostoc mesenteroides 32-77:1, L. paracasei ssp paracasei 19, L. plantarum 2362 &* 2.5 g each of: betaglucan, inulin, pectin and resistant starch

Golden Bifid: *Bifidobacterium bifidum, Lactobacillus bulgaricus and Streptococcus thermophilus triple human probiotics supplemented oligosaccharides FOS (bifidus factor)*

Table 1. Randomized studies evaluating Probiotics in critically ill patients (continued)

	Study	Mortality		Infections		Length of Stay		Diarrhea	
		Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control
1	Tempe 1983	3/20 (15)	3/20 (15)	NR	NR	NR	NR	Diarrhea days 34/389 (9)	Diarrhea days 63/373 (17)
2	Schlotterer 1987	NR	NR	NR	NR	NR	NR	Diarrhea days 3/150 (2)	Diarrhea days 19/143 (13)
3	Heimburger 1994	NR	NR	NR	NR	NR	NR	Diarrhea 5/16 (31)	Diarrhea 2/18 (11)
4	Bleichner 1997	NR	NR	NR	NR	NR	NR	Diarrhea 18/64 (28)[i] Days w/ diarrhea 91/648 (14)	Diarrhea 24/64 (38) Days w/ diarrhea 134/683 (20)
5	Kecskes 2003	Hospital 1/22 (5)	Hospital 2/23 (9)	Septic Compl 1/22 (5)	Septic Compl 7/23 (30)	Hospital 13.7 ± 8.7	Hospital 21.4 ± 17.9	NR	NR
6	Jain 2004	Hospital 22/45 (49)	Hospital 20/45 (45)	Septic Compl 33/45 (73)	Septic Compl 26/45 (58)	Hospital 24.0 ± 31.5 ICU 11.9 ± 13.1	Hospital 18.7 ± 13.5 ICU 9.0 ± 8.9	NR	NR
7	Lu 2004	Hospital 2/20 (10)	Hospital 1/20 (5)	Infectious Compl 8/20 (40)	Infectious Compl 11/20 (55)	NR	NR	NR	NR
8	Klarin 2005	Hospital 2/8 (25) ICU 1/8 (12)	Hospital 2/7 (29) ICU 2/7 (29)	NR	NR	Hospital 48.3 ± 30.4 ICU 14.2 ± 10.6	Hospital 34.3 ± 15.4 ICU 16.3 ± 15.7	NR	NR
9	McNaught 2005	18/52 (35)	18/51 (35)	Septic morbidity 21/52 (40)	Septic morbidity 22/51 (43)	ICU 5 (2-9)	ICU 4 (2-7)	NR	NR

10	Kotzampassi 2006	ICU 5/35 (14)	ICU 9/30 (30)	Infections 22/35 (63) VAP 19/35 (54) Septic Compl 17/35 (49) Central venous line infections 13/35 (37) Wound Infections 6/35 (17) UTI 6/35 (17)	Infections 27/30 (90) VAP 24/30 (80) Septic Compl 23/30 (77) Central venous line infections 20/30 (66) Wound Infections 8/30 (26) UTI 13/30 (43)	ICU 27.7 ± 15.2	ICU 41.3 ± 20.5	Diarrhea 5/35 (14)	Diarrhea 10/30 (30)
11	Alberda 2007	ICU 1/10 (10)	ICU 1/9 (11)	NR	NR	NR	NR	Diarrhea 1/10 (14)	Diarrhea 2/9 (23)
12	Li 2007	NR	NR	Infections 8/14 (58)	Infections 10/11 (91)	Hospital 42 ± 5.0	Hospital 49 ± 6.8	NR	NR
13	Olah 2007	Hospital 2/33 (6)	Hospital 6/29 (21)	Infections 9/33 (27) Septic Compl 7/33 (12) Pancreatic Abscess 2/33 (6) Infected Pancreatic Necrosis 2/33 (6) UTI 3/33 (9)	Infections 15/29 (52) Septic Compl 17/29 (28) Pancreatic Abscess 2/29 (7) Infected Pancreatic Necrosis 6/29 (21) UTI 3/33 (9)	Hospital 14.9 ± 3.3	Hospital 19.7 ± 4.5	NR	NR
14	Forestier 2008	NR	NR	VAP 19/102 (19)	VAP 21/106 (20)	ICU 22.5 ± 20.6	ICU 19.7 ± 16.7	NR	NR

15	Besselink 2008	24/152 (16)	9/144 (6)	Infections 46/152 (30) VAP 24/152 (16) Bacteremia 33/152 (22) Infected necrosis 21/152 (14) Urosepsis 1/52 (2)	Infections 41/144 (28) VAP 16/144 (11) Bacteremia 22/144 (15) Infected necrosis 14/144 (10) Urosepsis 2/144 (1)	Hospital 28.9 ± 41.5 ICU 6.6 ± 17	Hospital 23.5 ± 25.9 ICU 3.0 ± 9.3	Diarrhea 25/152 (16)	Diarrhea 28/144 (19)
16	Klarin 2008	Hospital 3/22 (5) ICU 2/22 (9)	Hospital 2/22 (0) ICU 2/22 (9)	c. difficile+ fecal samples 0/71	c. difficile+ fecal samples 4/80	Hospital 25.8 ± 19.4 ICU 8.0 ± 5.4	Hospital 50.3 ± 75.2 ICU 11.6 ± 14	NR	NR
17	Knight 2009	Hospital 35/130 (27) ICU 28/130 (22)	Hospital 42/129 (33) ICU 34/129 (26)	VAP 12/130 (9)	VAP 17/129 (13)	ICU 6 (3-11)	ICU 7 (3-14)	Diarrhea 7/130 (5)	Diarrhea 9/129 (7)
18	Barraud 2010	ICU 21/87 (24) 28 days 22/87 (25) 90 days 27/87 (31)	ICU 21/80 (26) 28 days 19/80 (24) 90 days 24/80 (30)	All infections 30/87 (34) Infection > 96 hr 26/87 (30) VAP 23/87 (26) Catheter related BSI 3/87 (4) UTI 4/87 (5)	All infections 30/80 (38) Infection > 96 hr 29/80 (36) VAP 15/80 (19) Catheter related BSI 11/80 (14) UTI 4/89 (5)	Hospital 26.6 ± 22.3 ICU 18.7 ± 12.4	Hospital 28.9 ± 26.4 ICU 20.2 ± 20.8	Diarrhea 48/87 (55)	Diarrhea 42/80 (53)
19	Morrow 2010	12/68 (18)	15/70 (21)	VAP 13/73 (18)	VAP 28/73 (38)	Hospital 21.4 ± 14.9 ICU 14.8 ± 11.8	Hospital 21.7 ± 17.4 ICU 14.6 ± 11.6	Non C. Difficile Diarrhea 42/68 (62) C. difficile diarrhea 4/68 (6)	Non C. Difficile Diarrhea 44/70 (63) C. difficile diarrhea 13/70 (19)

20	Frohmader 2010	5/20 (25)	3/25 (12)	NR	NR	ICU 7.3 ± 5.7	ICU 8.1 ± 4	Diarrhea episodes/pt/day 0.53 ± 0.54	Diarrhea episodes/pt/day 1.05 ± 1.08
21	Ferrie 2011	Hospital 2/18 (11) 6 months 7/18 (39)	Hospital 2/18 (11) 6 months 5/18 (28)	Infections 14/18 (78)	Infections 16/18 (89)	Hospital 54.50 ± 31.26 ICU 32.04 ± 24.46	Hospital 59.04 ± 33.92 ICU 29.75 ± 18.81	Duration of Diarrhea 3.83 ± 2.39 Loose stools/day 1.58 ± 0.88	Duration of Diarrhea 2.56 ± 1.85 Loose stools/day 1.10 ± 0.79
22	Sharma 2011	Hospital 2/24 (8)	Hospital 2/26 (8)	NR	NR	Hospital 13.23 ± 18.19 ICU 4.94 ± 9.54	Hospital 9.69 ±9.69 ICU 4.0 ± 5.86	NR	NR
23	Tan 2011	28 day 3/26 (12)	28 day 5/26 (19)	Infections 9/26 (35) VAP 7/26 (27)	Infections 15/26 (58) VAP 13/26 (50)	ICU 6.8 ± 3.8	ICU 10.7 ± 7.3	NR	NR
24	Cui 2013	Hospital 1/23 (4)	Hospital 1/25 (4)	N/A	N/A	Hospital 10.4 ± 3.9 (23)	Hospital 13.4 ± 5.2 (25)	NR	NR
25	Tan 2013	28 day 23/26 (12)	28 day 5/26 (19)	NR	NR	ICU 6.8 ± 3.8 (26)	ICU 10.7 ± 7.3 (26)	NR	NR
26	Wang 2013	Unspecified 1/62 (8.1)	Unspecified 3/61 (9.8)	Pancreatic sepsis 8/62 (13) MODS 7/62 (11.3)20 14.16	Pancreatic sepsis 13/61 (21) MODS 15/61 (25)	NR	NR	NR	NR
27	Lopez de Toro 2014	Hospital 19/46 (41) ICU 15/46 (33)	Hospital 18/43 (42) ICU 14/43 (33)	Hospital acquired infections 9/46 (20)	Hospital acquired infections 13/43 (30)	Hospital 18.5 (10-36) ICU 9 (3-19)	Hospital 24.5 (10-38) ICU 8 (2.5-16.5)	NR	NR

28	Sanaie 2014	28 day 2/20 (10)	28 day 5/20 (25)	Bacteremia 2/20(10)	Bacteremia 5/20(25)	ICU 13.85 ± 6.96	ICU 14.16 ± 5.97	NR	NR
29	Rongungruang 2015	28 day 18/75 (24) 90 day 25/75 (33)	28 day 17/75 (23) 90 day 26/75 (35)	VAP 18/75 (24)	VAP 22/75 (29)	ICU 30.5 (4-98) Hospital 20 (2-106)	ICU 19 (5-30) Hospital 19 (3-171)	19/75 (25)	14/75 (19)
30	Zeng 2016	Hospital 11/103 (11) – excludes ICU deaths ICU 15/118 (13)	Hospital 16/108 (15) – excludes ICU deaths ICU 9/117 (8)	Clinically diagnosed VAP 48/118 (41) Micro confirmed VAP 43/118 (36)	Clinically diagnosed VAP 62/117 (53) Micro confirmed VAP 59/117 (50)	ICU 18 [IQR 14-32] Hospital, after ICU admission 13.5 ± 12.4	ICU 22 [IQR 11-56] Hospital, after ICU admission 10.6 ± 10.2	NR	NR
31	Malik 2016	NR	NR	NR	NR	ICU 10.9 ± 3.9 (24)	ICU 15.8 ± 7.8 (25)	NR	NR
32	De Castro Soares 2017	NR	NR	NR	NR	NR	NR	Days to cease Diarrhea 2.5 ± 1.3	Days to cease Diarrhea 3.7 ± 1.1 P=0.011

NR: Not Reported
VAP: Ventilator Associated Pneumonia
UTI: Urinary Tract Infection
ICU: Intensive Care Unit
BSI: Blood Stream Infection

Figure 1. Hospital Mortality

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Tempe 1983	3	20	3	20	1.5%	1.00 [0.23, 4.37]	1983
Kecskes 2003	1	22	2	23	0.6%	0.52 [0.05, 5.36]	2003
Jain 2004	22	45	20	45	16.4%	1.10 [0.71, 1.71]	2004
Lu 2004	2	20	1	20	0.6%	2.00 [0.20, 20.33]	2004
Klarin 2005	2	8	2	7	1.1%	0.88 [0.16, 4.68]	2005
McNaught 2005	18	52	18	51	11.6%	0.98 [0.58, 1.66]	2005
Olah 2007	2	33	6	29	1.4%	0.29 [0.06, 1.34]	2007
Besselink 2008	14	152	9	144	5.0%	1.47 [0.66, 3.30]	2008
Klarin 2008	3	22	2	22	1.1%	1.50 [0.28, 8.12]	2008
Knight 2009	35	130	42	129	22.7%	0.83 [0.57, 1.21]	2009
Frohmader 2010	5	20	3	25	1.9%	2.08 [0.56, 7.68]	2010
Morrow 2010	12	68	15	73	6.9%	0.86 [0.43, 1.70]	2010
Sharma 2011	2	24	2	26	0.9%	1.08 [0.17, 7.10]	2011
Ferrie 2011	2	18	2	18	0.9%	1.00 [0.16, 6.35]	2011
Cui 2013	1	23	1	25	0.4%	1.09 [0.07, 16.39]	2013
Lopez de Toro 2014	19	46	18	43	13.3%	0.99 [0.60, 1.61]	2014
Zeng 2016	26	118	25	117	13.6%	1.03 [0.63, 1.68]	2016
Total (95% CI)		**821**		**817**	**100.0%**	**0.98 [0.82, 1.18]**	
Total events	169		171				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.84$, df = 16 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 0.19 (P = 0.85)

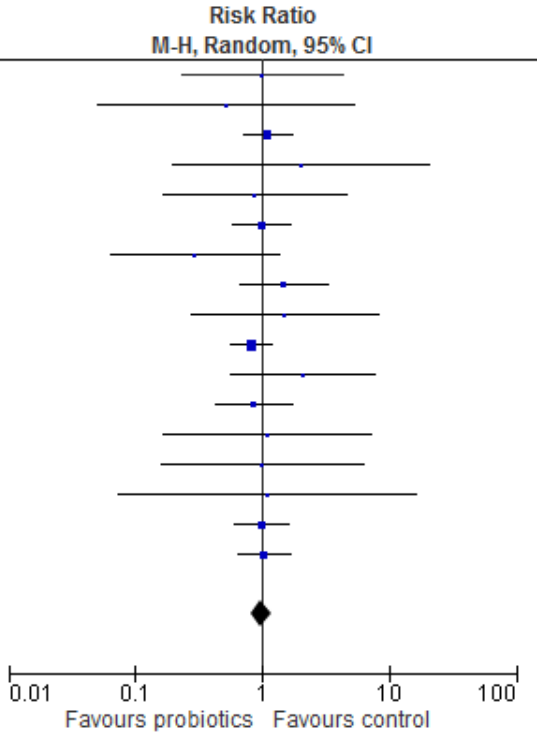


Figure 2. **ICU Mortality**

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Klarin 2005	1	8	2	7	1.4%	0.44 [0.05, 3.85]	2005
Kotzampassi 2006	5	35	9	30	7.0%	0.48 [0.18, 1.27]	2006
Alberda 2007	1	10	1	9	1.0%	0.90 [0.07, 12.38]	2007
Klarin 2008	2	22	2	22	1.9%	1.00 [0.15, 6.48]	2008
Knight 2009	28	130	34	129	34.9%	0.82 [0.53, 1.26]	2009
Barraud 2010	21	87	21	80	24.4%	0.92 [0.54, 1.55]	2010
Lopez de Toro 2014	15	46	14	43	18.6%	1.00 [0.55, 1.82]	2014
Zeng 2016	15	118	9	117	10.8%	1.65 [0.75, 3.63]	2016
Total (95% CI)		**456**		**437**	**100.0%**	**0.90 [0.70, 1.17]**	
Total events	88		92				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.68$, $df = 7$ ($P = 0.70$); $I^2 = 0\%$
Test for overall effect: $Z = 0.77$ ($P = 0.44$)

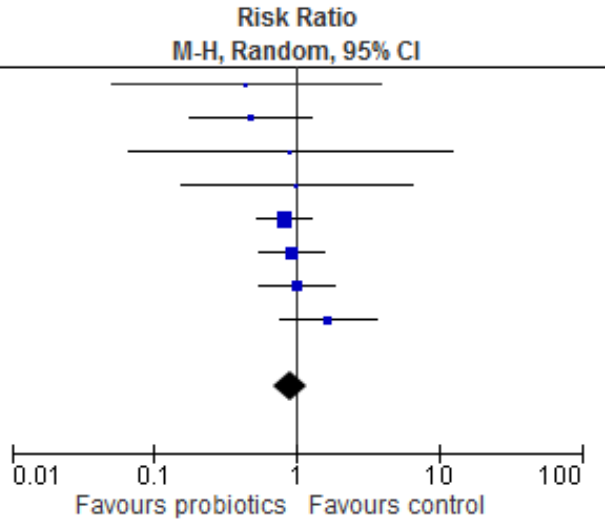


Figure 3. **Infections**

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kecskes 2003	1	22	7	23	0.7%	0.15 [0.02, 1.12]	2003
Jain 2004	33	45	26	45	13.3%	1.27 [0.93, 1.72]	2004
Lu 2004	8	20	11	20	5.2%	0.73 [0.37, 1.42]	2004
McNaught 2005	21	52	22	51	8.8%	0.94 [0.59, 1.48]	2005
Kotzampassi 2006	22	35	27	30	14.2%	0.70 [0.53, 0.93]	2006
Li 2007	8	14	10	11	8.0%	0.63 [0.38, 1.03]	2007
Olah 2007	9	33	15	29	5.3%	0.53 [0.27, 1.02]	2007
Besselink 2008	46	152	41	144	11.6%	1.06 [0.75, 1.51]	2008
Barraud 2010	26	87	29	80	9.3%	0.82 [0.53, 1.27]	2010
Ferrie 2011	14	18	16	18	13.6%	0.88 [0.65, 1.18]	2011
Tan 2011	9	26	15	26	5.7%	0.60 [0.32, 1.12]	2011
Lopez de Toro 2014	9	46	13	43	4.4%	0.65 [0.31, 1.36]	2014
Total (95% CI)		**550**		**520**	**100.0%**	**0.82 [0.69, 0.97]**	
Total events	206		232				

Heterogeneity: Tau² = 0.03; Chi² = 18.55, df = 11 (P = 0.07); I² = 41%
Test for overall effect: Z = 2.31 (P = 0.02)

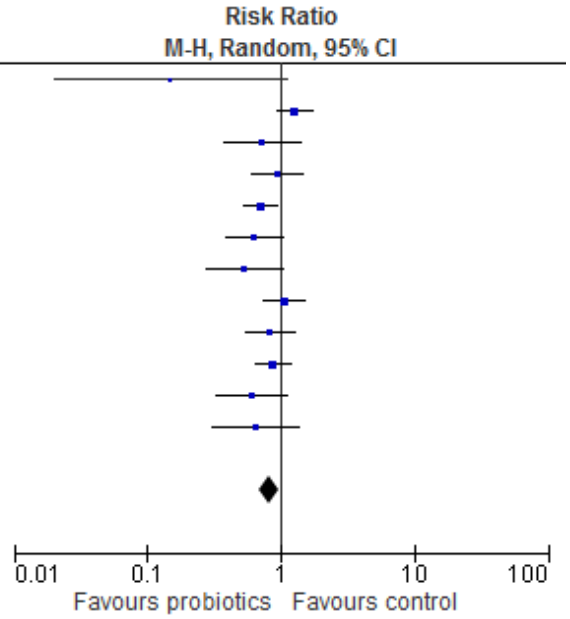


Figure 4. **VAP**

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kotzampassi 2006	19	35	24	30	19.8%	0.68 [0.48, 0.97]	2006
Forestier 2008	19	102	21	106	10.2%	0.94 [0.54, 1.64]	2008
Knight 2009	12	130	17	129	7.0%	0.70 [0.35, 1.41]	2009
Barraud 2010	23	87	15	80	9.7%	1.41 [0.79, 2.51]	2010
Morrow 2010	13	73	28	73	9.8%	0.46 [0.26, 0.82]	2010
Tan 2011	7	26	13	26	6.3%	0.54 [0.26, 1.13]	2011
Rongrungruang 2015	18	75	22	75	10.9%	0.82 [0.48, 1.40]	2015
Zeng 2016	48	118	62	117	26.2%	0.77 [0.58, 1.01]	2016
Total (95% CI)		**646**		**636**	**100.0%**	**0.76 [0.62, 0.92]**	
Total events	159		202				

Heterogeneity: Tau² = 0.02; Chi² = 9.23, df = 7 (P = 0.24); I² = 24%
Test for overall effect: Z = 2.77 (P = 0.006)

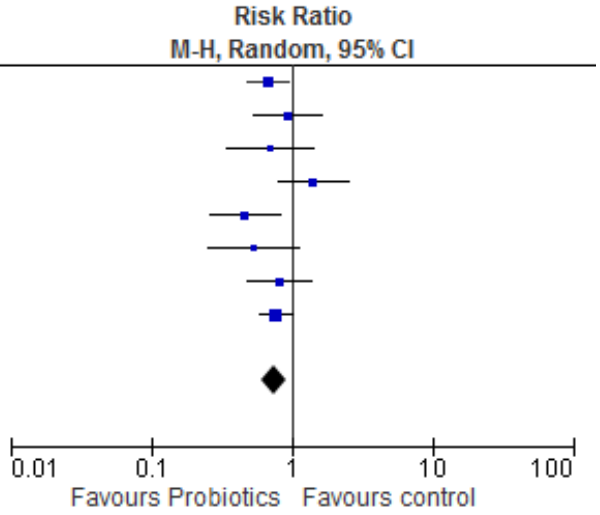
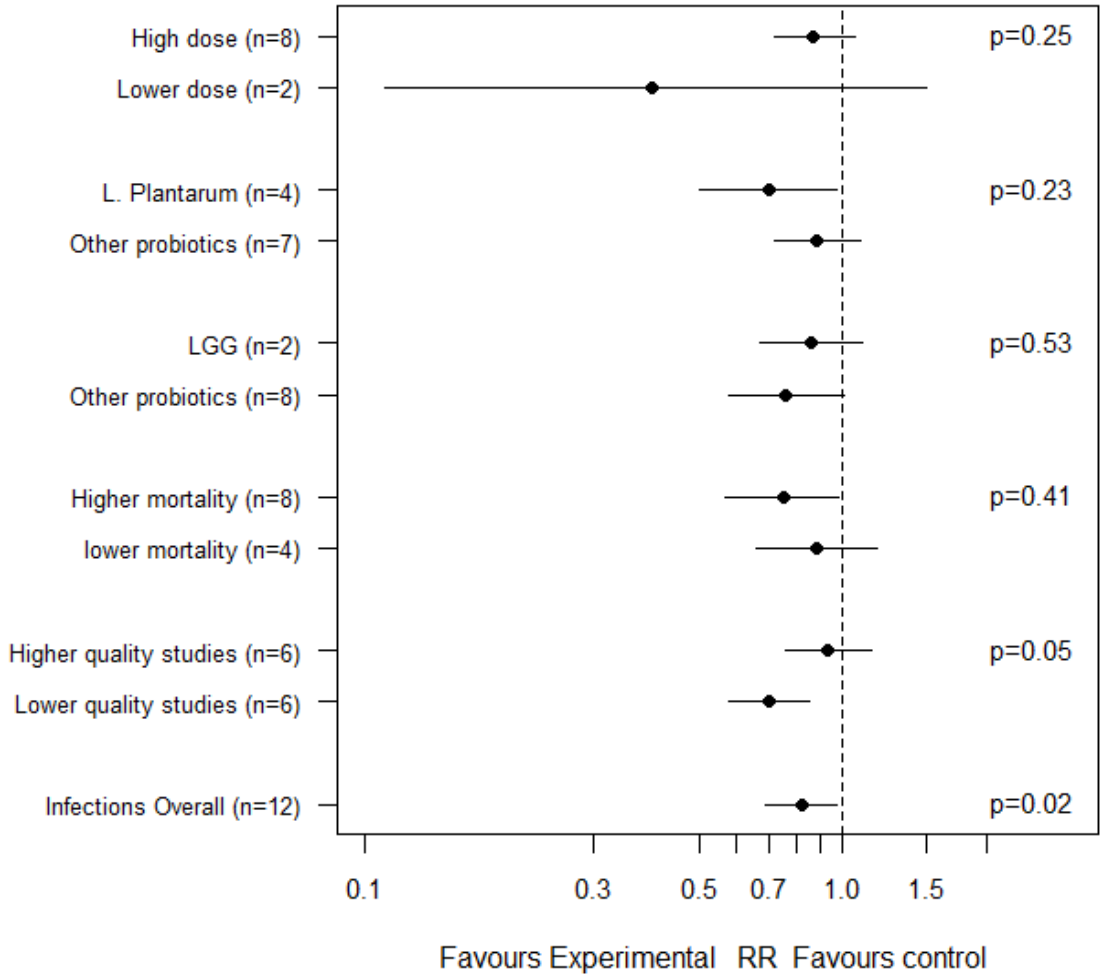
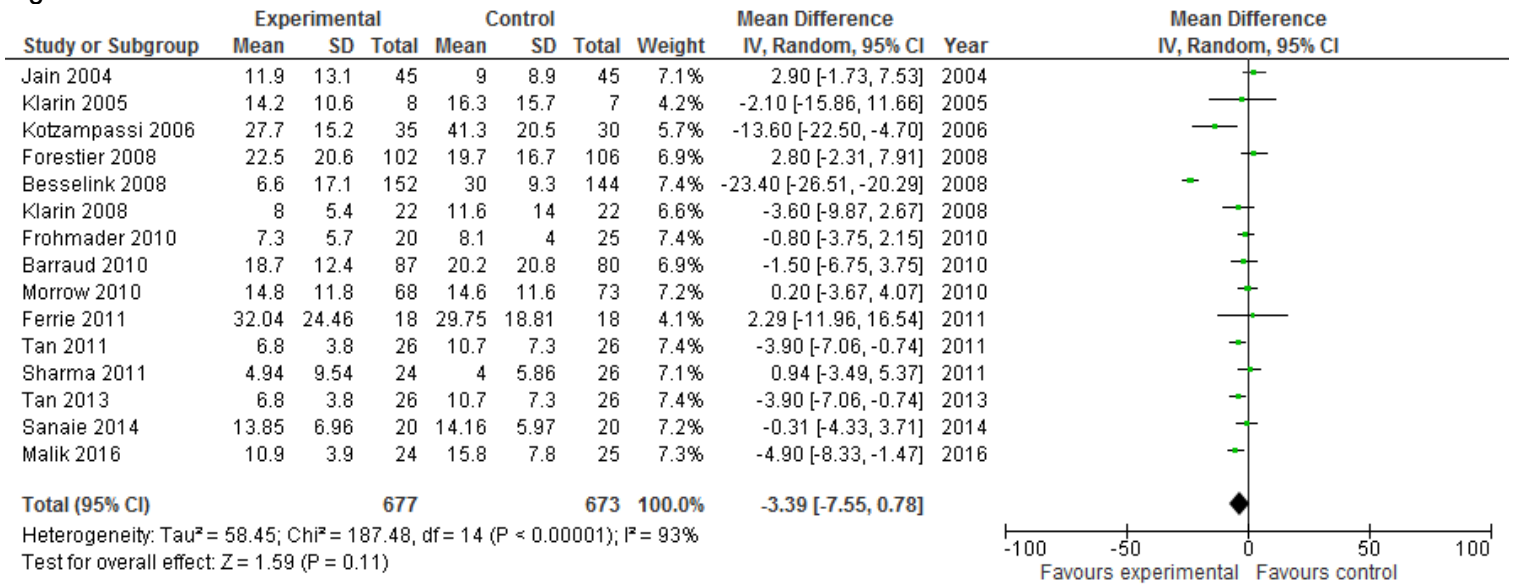


Figure 5. Effect of Probiotics on Infections: Subgroup Analyses



Legend: Numbers in brackets indicate the number of studies.
RR: Risk ratio
p values for the subgroups indicate the differences in the subgroup effect of probiotics on infections.
LGG= *Lactobacillus rhamnosus* GG

Figure 6. ICU LOS



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Jain 2004	11.9	13.1	45	9	8.9	45	7.1%	2.90 [-1.73, 7.53]	2004
Klarin 2005	14.2	10.6	8	16.3	15.7	7	4.2%	-2.10 [-15.86, 11.66]	2005
Kotzampassi 2006	27.7	15.2	35	41.3	20.5	30	5.7%	-13.60 [-22.50, -4.70]	2006
Forestier 2008	22.5	20.6	102	19.7	16.7	106	6.9%	2.80 [-2.31, 7.91]	2008
Besselink 2008	6.6	17.1	152	30	9.3	144	7.4%	-23.40 [-26.51, -20.29]	2008
Klarin 2008	8	5.4	22	11.6	14	22	6.6%	-3.60 [-9.87, 2.67]	2008
Frohmader 2010	7.3	5.7	20	8.1	4	25	7.4%	-0.80 [-3.75, 2.15]	2010
Barraud 2010	18.7	12.4	87	20.2	20.8	80	6.9%	-1.50 [-6.75, 3.75]	2010
Morrow 2010	14.8	11.8	68	14.6	11.6	73	7.2%	0.20 [-3.67, 4.07]	2010
Ferrie 2011	32.04	24.46	18	29.75	18.81	18	4.1%	2.29 [-11.96, 16.54]	2011
Tan 2011	6.8	3.8	26	10.7	7.3	26	7.4%	-3.90 [-7.06, -0.74]	2011
Sharma 2011	4.94	9.54	24	4	5.86	26	7.1%	0.94 [-3.49, 5.37]	2011
Tan 2013	6.8	3.8	26	10.7	7.3	26	7.4%	-3.90 [-7.06, -0.74]	2013
Sanaie 2014	13.85	6.96	20	14.16	5.97	20	7.2%	-0.31 [-4.33, 3.71]	2014
Malik 2016	10.9	3.9	24	15.8	7.8	25	7.3%	-4.90 [-8.33, -1.47]	2016
Total (95% CI)			**677**			**673**	**100.0%**	**-3.39 [-7.55, 0.78]**	

Heterogeneity: Tau² = 58.45; Chi² = 187.48, df = 14 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.59 (P = 0.11)

Figure 7. Diarrhea

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Heimburger 1994	5	16	2	18	1.2%	2.81 [0.63, 12.54]	1994
Bleichner 1997	18	64	24	64	10.5%	0.75 [0.45, 1.24]	1997
Kotzampassi 2006	5	35	10	30	3.0%	0.43 [0.16, 1.12]	2006
Alberda 2007	1	10	2	9	0.6%	0.45 [0.05, 4.16]	2007
Besselink 2008	25	152	28	144	11.1%	0.85 [0.52, 1.38]	2008
Knight 2009	7	130	9	129	3.0%	0.77 [0.30, 2.01]	2009
Morrow 2010	42	68	44	73	33.4%	1.02 [0.79, 1.33]	2010
Barraud 2010	48	87	42	80	29.9%	1.05 [0.79, 1.39]	2010
Rongrungruang 2015	19	75	14	75	7.2%	1.36 [0.74, 2.50]	2015
Total (95% CI)		**637**		**622**	**100.0%**	**0.97 [0.82, 1.15]**	
Total events	170		175				

Heterogeneity: Tau² = 0.00; Chi² = 8.44, df = 8 (P = 0.39); I² = 5%
Test for overall effect: Z = 0.34 (P = 0.74)