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Probiotics for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer (Review)

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[Intervention Review]

Probiotics for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer

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ABSTRACT

Background

Treament-related diarrhoea is one of the most common and troublesome adverse effects related to chemotherapy or radiotherapy in people with cancer. Its reported incidence has been as high as 50% to 80%. Severe treatment-related diarrhoea can lead to fluid and electrolyte losses and nutritional deficiencies and could adversely affect quality of life (QoL). It is also associated with increased risk of infection in people with neutropenia due to anticancer therapy and often leads to treatment delays, dose reductions, or treatment discontinuation. Probiotics may be effective in preventing or treating chemotherapy- or radiotherapy-induced diarrhoea.

Objectives

To evaluate the clinical effectiveness and side effects of probiotics used alone or combined with other agents for prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 7), MEDLINE (1946 to July week 2, 2017), and Embase (1980 to 2017, week 30). We also searched prospective clinical trial registers and the reference lists of included studies.

Selection criteria

We included randomised controlled trials (RCTs) investigating the effects of probiotics for prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer.

Data collection and analysis

Two review authors independently selected studies, extracted data, and assessed risk of bias. We used random-effects models for all meta-analyses. If meta-analysis was not possible, we summarised the results narratively.

Main results

We included 12 studies involving 1554 participants. Eleven studies were prevention studies, of which seven compared probiotics with placebo (887 participants), one compared two doses of probiotics with each other and with placebo (246 participants), and three compared probiotics with another active agent (216 participants).The remaining study assessed the effectiveness of probiotics compared with placebo for treatment of radiotherapy-related diarrhoea (205 participants).

For prevention of radiotherapy (with or without chemotherapy)-induced diarrhoea, review authors identified five heterogeneous placebo-controlled studies (with 926 participants analysed). Owing to heterogeneity, we could not carry out a meta-analysis, except for two outcomes. For occurrence of any diarrhoea, risk ratios (RRs) ranged from 0.35 (95% confidence interval (CI) 0.26 to 0.47) to 1.0 (95% CI 0.94 to 1.06) (three studies; low-certainty evidence). A beneficial effect of probiotics on quality of life could neither be demonstrated nor refuted (two studies; low-certainty evidence). For occurrence of grade 2 or higher diarrhoea, the pooled RR was 0.75 (95% CI 0.55 to 1.03; four studies; 420 participants; low-certainty evidence), and for grade 3 or higher diarrhoea, RRs ranged from 0.11 (95% CI 0.06 to 0.23) to 1.24 (95% CI 0.74 to 2.08) (three studies; low-certainty evidence). For probiotic users, time to rescue medication was 36 hours longer in one study (95% CI 34.7 to 37.3), but another study reported no difference (moderate-certainty evidence). For the need for rescue medication, the pooled RR was 0.50 (95% CI 0.15 to 1.66; three studies; 194 participants; very low-certainty evidence). No study reported major differences between groups with respect to adverse effects. Although not mentioned explicitly, no studies reported deaths, except one in which one participant in the probiotics group died of myocardial infarction after three sessions of radiotherapy.

Three placebo-controlled studies, with 128 analysed participants, addressed prevention of chemotherapy-induced diarrhoea. For occurrence of any diarrhoea, the pooled RR was 0.59 (95% CI 0.36 to 0.96; two studies; 106 participants; low-certainty evidence). For all other outcomes, a beneficial effect of probiotics could be neither demonstrated nor refuted (one to two studies; 46 to 106 participants; all low-certainty evidence). Studies did not address quality of life nor time to rescue medication.

Three studies compared probiotics with another intervention in 213 participants treated with radiotherapy (with or without chemotherapy). One very small study (21 participants) reported less diarrhoea six weeks after treatment when dietary counselling was provided (RR 0.30, 95% CI 0.11 to 0.81; very low-certainty evidence). In another study (148 participants), grade 3 or 4 diarrhoea occurred less often in the probiotics group than in the control group (guar gum containing nutritional supplement) (odds ratio (OR) 0.38, 95% CI 0.16 to 0.89; low-certainty evidence), and two studies (63 participants) found less need for rescue medication of probiotics versus another active treatment (RR 0.44, 95% CI 0.22 to 0.86; very low-certainty evidence). Studies did not address quality of life nor time to rescue medication.

One placebo-controlled study with 205 participants addressed treatment for radiotherapy-induced diarrhoea and could not demonstrate or refute a beneficial effect of probiotics on average diarrhoea grade, time to rescue medication for diarrhoea (13 hours longer in the probiotics group; 95% CI -0.9 to 26.9 hours), or need for rescue medication (RR 0.74, 95% CI 0.53 to 1.03; moderate-certainty evidence). This study did not address quality of life.

No studies reported serious adverse events or diarrhoea-related deaths.

Authors' conclusions

This review presents limited low- or very low-certainty evidence supporting the effects of probiotics for prevention and treatment of diarrhoea related to radiotherapy (with or without chemotherapy) or chemotherapy alone, need for rescue medication, or occurrence of adverse events. All studies were underpowered and heterogeneous. Severe side effects were absent from all studies.

Robust evidence on this topic must be provided by future methodologically well-designed trials.

PLAIN LANGUAGE SUMMARY

Live micro-organisms for prevention or treatment of diarrhoea in people with cancer who are treated with chemotherapy or radiotherapy

Background

Up to 80% of people treated with chemotherapy or radiotherapy for cancer suffer from diarrhoea - one of the most common and troublesome side effects. Severe diarrhoea can lead to dehydration (fluid and salts loss) and malnutrition from changes to digestion and bowel habits and could adversely affect quality of life. It is also associated with increased risk of infection in people with low white cell blood count related to cancer treatment. Diarrhoea often leads to delays in cancer treatment or the need to lower the dose or even discontinue cancer treatment. Foods containing live bacteria or yeast (probiotics) might have a beneficial effect on the occurrence and severity of diarrhoea.

Aim of the review

To evaluate the effects of live micro-organisms (probiotics) in preventing the occurrence or reducing the severity of diarrhoea in people with cancer who are receiving chemotherapy or radiotherapy.

Main findings

Overall, the studies we found do not give a clear answer on whether probiotics reduce the occurrence or severity of diarrhoea, improve quality of life, or reduce the need for other medication. However, an analysis of only well-performed studies demonstrated a beneficial effect for some outcomes.

With regard to prevention of diarrhoea compared with placebo in participants treated with radiotherapy with or without chemotherapy, we are not able to conclude whether use of probiotics would be beneficial based on the five relevant studies.

For prevention of diarrhoea due to chemotherapy alone, three studies suggested that use of probiotics may not reduce diarrhoea, and one study reported use of less rescue medication for diarrhoea.

Three studies that compared probiotics with another agent for preventing diarrhoea in patients treated with radiotherapy with or without chemotherapy found beneficial effects of probiotics for the occurrence and severity of diarrhoea and the need for rescue medication.

With respect to treatment of diarrhoea due to radiotherapy, we found only one study that did not demonstrate a clear effect of probiotics compared with placebo.

No study reported serious adverse events nor deaths related to diarrhoea.

Certainty of the evidence
The quality (certainty) of the evidence in prevention studies was low to very low. For the only study that assessed the effects of probiotics on treatment for diarrhoea, the certainty of the evidence was moderate.

What are the conclusions?
Evidence supporting the effects of probiotics in preventing or treating diarrhoea related to cancer treatment is insufficient. However, probiotics appear to be safe, as no studies have found severe side effects.

Summary of findings for the main comparison. Probiotics compared with placebo for prevention of diarrhoea in participants with cancer treated with radiotherapy (with or without chemotherapy)

Probiotics compared with placebo for prevention of diarrhoea in patients with cancer treated with radiotherapy (with or without chemotherapy)

Patient or population: participants with cancer treated with radiotherapy (with or without chemotherapy)
Setting: secondary care
Intervention: probiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with probiotics				
Any diarrhoea	RRs ranged from 0.35 (95% CI 0.26 to 0.47) to 1.0 (95% CI 0.94 to 1.06)		-	771 (3 RCTs)	⊕⊕⊖⊖ LOW[a,b]	
Quality of life	Mean quality of life was 0	MD 3.7 higher (1.21 lower to 8.61 higher)	-	72 (1 RCT)	⊕⊕⊖⊖ LOW[c,d]	A second study in 226 participants reported that probiotic intake did not affect QoL
Diarrhoea grade 2 or higher	Study population		RR 0.75 (0.55 to 1.03)	420 (4 RCTs)	⊕⊕⊖⊖ LOW[d,e]	
	676 per 1000	507 per 1000 (372 to 696)				
Diarrhoea grade 3 or higher	RRs ranged from 0.11 (95% CI 0.06 to 0.23) to 1.24 (95% CI 0.74 to 2.08)		-	793 (3 RCTs)	⊕⊕⊖⊖ LOW[b,f]	
Diarrhoea grade 4	RRs of standard (81 participants) and high doses (59 participants) of probiotics versus placebo (86 participants) were 0.24 (95% CI 0.05 to 1.06) and 0.65 (95% CI 0.21 to 2.01), respectively		-	226 (1 RCT)	⊕⊖⊖⊖ VERY LOW[g,h]	
Time to rescue medication	Mean time to rescue medication was 0 hours	MD 36 hours higher (34.7 higher to 37.3 higher)	-	482 (1 RCT)	⊕⊕⊕⊖ MODERATE[c]	A second study in 226 participants reported no differences between groups

Requiring rescue medication for diarrhoea	Study population		RR 0.50 (0.15 to 1.66)	194 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[d,i]	A fourth study in 226 participants reported less use of rescue medication in the probiotics group
	323 per 1000	161 per 1000 (48 to 536)				
Adverse events	No study reported major differences between groups. In one study (46 participants), bloating occurred more often in the probiotic group: RR 2.07, 95% CI 1.26 to 3.42		-	902 (5 RCTs)	⊕⊕⊖⊖ LOW[j,k]	
Mortality	Although not mentioned explicitly, no studies reported any deaths, except one study, in which 1 participant in the probiotics group died of myocardial infarction after 3 sessions of radiotherapy		-	902 (5 RCTs)	⊕⊕⊖⊖ LOW[k]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; OIS: optimal information size; QoL: quality of life; RCT: randomised controlled trial; RR: risk ratio; OR: odds ratio.

GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]One study at high risk of selection bias; one study at high risk of attrition bias; one study at unclear risk of bias.
[b]Major indications of heterogeneity between studies.
[c]High risk of attrition bias.
[d]Wide CI that includes no effect; OIS not reached.
[e]One study at high risk of selection bias and one study at high risk of attrition bias, both leaving those out, changes the effect to the null. Remaining two studies, however, at unclear risk of bias; therefore downgrading by one level.
[f]One study at high risk of selection bias; two studies at high risk of attrition bias.
[g]High risk of selection bias.
[h]Wide CIs; OIS not reached.
[i]One study at high risk of attrition bias, but no downgrading because of influence to the null. Downgrading by one level because of unclear risk of bias in another study.
[j]Studies addressed many different adverse events.
[k]OIS not reached.

Summary of findings 2. Probiotics compared with placebo for prevention of diarrhoea in participants with cancer treated with chemotherapy

Probiotics compared with placebo for prevention of diarrhoea in participants with cancer treated with chemotherapy

Patient or population: participants with cancer treated with chemotherapy
Setting: secondary care
Intervention: probiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with probiotics				
Any diarrhoea	Study population		RR 0.59 (0.36 to 0.96)	106 (2 RCTs)	⊕⊕⊖⊖ LOW[a]	In another cross-over study, 6 of 22 suffered from diarrhoea during the probiotic period compared with 10 of 22 during the placebo period (no paired analysis presented)
	491 per 1000	289 per 1000 (177 to 471)				
Quality of life - not measured	-	-	-	-	-	
Diarrhoea grade 2 or higher	Study population		RR 0.67 (0.22 to 2.05)	46 (1 RCT)	⊕⊕⊖⊖ LOW[b,c]	In another cross-over study, 3 of 22 suffered from grade 2 diarrhoea or higher during the probiotic period compared with 7 of 22 during the placebo period (no paired analysis presented)
	261 per 1000	175 per 1000 (57 to 535)				
Diarrhoea grade 3 or higher	Study population		RR 0.11 (0.01 to 1.95)	46 (1 RCT)	⊕⊕⊖⊖ LOW[b,c]	In another cross-over study, 1 of 22 suffered from grade 3 diarrhoea or higher during the probiotic period compared with 4 of 22 during the placebo period (no paired analysis presented)
	174 per 1000	19 per 1000 (2 to 339)				
Diarrhoea grade 4	Study population		RR 0.33 (0.01 to 7.78)	46 (1 RCT)	⊕⊕⊖⊖ LOW[b,c]	
	43 per 1000	14 per 1000 (0 to 338)				
Time to rescue medication - not measured	-	-	-	-	-	

Requiring rescue medication for diarrhoea	Results not quantified. "Participants on probiotic arm used less loperamide and diphenoxylate/atropine compared to participants on placebo arm"	-	46 (1 RCT)	⊕⊕⊖⊖ LOW[c]
Adverse events	Results not quantified. No differences between groups reported	-	106 (2 RCTs)	⊕⊕⊖⊖ LOW[c]
Mortality	Although not mentioned explicitly, no studies reported any deaths	-	128 (3 RCTs)	⊕⊕⊖⊖ LOW[c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; OIS: optimal information size; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]OIS not reached. CI includes irrelevant benefit.
[b]Wide CI that includes both benefit and harm.
[c]OIS not reached.

Summary of findings 3. Probiotics compared with other active treatment for prevention of diarrhoea in participants with cancer treated with radiotherapy (with or without chemotherapy)

Probiotics compared with other active treatment for prevention of diarrhoea in participants with cancer treated with radiotherapy (with or without chemotherapy)

Patient or population: participants with cancer treated with radiotherapy (with or without chemotherapy)
Setting: secondary care
Intervention: probiotics
Comparison: other active treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other active treatment	Risk with probiotics				

Any diarrhoea	Study population		RR 0.30 (0.11 to 0.81)	21 (1 RCT)	⊕⊖⊖⊖ VERY LOW[a,b,c]	
	900 per 1000	270 per 1000 (99 to 729)				
Quality of life - not measured	-	-	-	-	-	
Severity of diarrhoea: grade 3 or higher	Study population		OR 0.38 (0.16 to 0.89)	148 (1 RCT)	⊕⊕⊖⊖ LOW[b,c]	Based on an analysis that addressed the factorial design of this study
	373 per 1000	184 per 1000 (87 to 346)				
Time to rescue medication - not measured	-	-	-	-	-	
Requiring rescue medication for diarrhoea	Study population		RR 0.44 (0.22 to 0.86)	63 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	
	567 per 1000	249 per 1000 (125 to 487)				
Adverse events	No differences between groups in all studies		-	211 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	
Mortality	Although not mentioned explicitly, no studies reported any deaths		-	211 (3 RCTs)	⊕⊕⊖⊖ LOW[c,d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; OIS: optimal information size; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]High risk of detection bias.
[b]High risk of performance bias.
[c]Very small study/studies. OIS not reached.

[d]High risk of bias in all studies. Not downgraded for mortality.

Summary of findings 4. Probiotics compared with placebo for treatment of diarrhoea due to radiotherapy (with or without chemotherapy) in participants with cancer

Probiotics compared with placebo for treatment of diarrhoea due to radiotherapy (with or without chemotherapy) in participants with cancer

Patient or population: participants with cancer treated with radiotherapy (with or without chemotherapy)
Setting: secondary care
Intervention: probiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with probiotics				
Reduction in severity of diarrhoea	"The average diarrhoea grade (rated by the investigators using standard scores ranging from 0 for no diarrhoea to 3 for severe diarrhoea) was 0.7 for the Antibiophilus group and 1.0 for the placebo group at the end of the study (no significant difference between the two groups)"		-	205 (1 RCT)	⊕⊕⊕⊖ MODERATE[a,b]	
Quality of life - not measured	-	-	-	-	-	
Time to rescue medication (in hours)	Mean time to rescue medication (in hours) was 0	MD 13 higher (0.86 lower to 26.86 higher)	-	205 (1 RCT)	⊕⊕⊕⊖ MODERATE[a,b]	
Requiring rescue medication for diarrhoea	Study population		RR 0.74 (0.53 to 1.03)	205 (1 RCT)	⊕⊕⊕⊖ MODERATE[a,b]	
	476 per 1000	352 per 1000 (252 to 490)				
Adverse events	"Serious adverse events were not observed. In the Antibiophilus group, three participants reported mild to moderate gastrointestinal problems; in the placebo group two participants reported moderate to severe gastrointestinal events, and one patient observed a mild labial oedema. All documented events were of a transient nature; in three patients, symptomatic treatment of adverse events was prescribed"		-	205 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	
Mortality	Although not mentioned explicitly, no studies reported any deaths		-	205 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; OIS: optimal information size; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]One study in 205 participants; OIS not reached.
[b]CI includes both benefit and harm.

BACKGROUND

Description of the condition

Diarrhoea is one of the most common and troublesome adverse effects related to cancer chemotherapy or pelvic or abdominal radiotherapy (Benson 2004). The incidence of all grades of diarrhoea during chemotherapy and/or radiotherapy has been reported to be as high as 50% to 80% (Sanguineti 2008). Up to one-third of people experience severe (grade 3 or 4) diarrhoea (Maroun 2007), especially with those regimens that include bolus 5-fluorouracil (5-FU) or irinotecan. Severe treatment-related diarrhoea can lead to fluid and electrolyte losses and nutritional deficiencies from alterations in gastrointestinal transit and digestion, and could adversely affect quality of life (QoL). Diarrhoea is also associated with increased risk of infection in people with treatment-related neutropenia. Diarrhoea often leads to treatment delays, dose reductions, or treatment discontinuation. Furthermore, a small but significant mortality risk is associated with chemotherapy-induced diarrhoea. This level of morbidity reveals the need for a more comprehensive assessment of diarrhoea and a more aggressive and systematic treatment approach. This systematic review defines diarrhoea as three or more loose or liquid stools per day.

Description of the intervention

According to the definition currently adopted by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO), probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (FAO and WHO 2001). Lactic acid bacteria and bifidobacteria are the most common types of microbes used as probiotics, but certain yeasts and bacilli may also be helpful. Probiotics are commonly consumed as part of fermented foods with specially added active live cultures such as yogurt and soy yogurt, or as dietary supplements. Although probiotics are often used to prevent or treat gastrointestinal conditions such as diarrhoea, probiotics themselves can also produce abdominal side effects, such as bloating and flatulence. Side effects of probiotics usually appear to be mild (Eskesen 2015).

How the intervention might work

Probiotics such as *Lactobacillus rhamnosus GG*, which is a strain of *L rhamnosus* isolated in 1983 from the intestinal tract of a healthy human being, are thought to work by stimulating the cell proliferation rate of bowel epithelial cells, thus enhancing repair of mucosa damaged by radiotherapy and/or chemotherapy. Also, these lactobacilli may restore the bacterial equilibrium within the bowel, inhibiting bacterial translocation into the tissues and stimulating the local and systemic immune response to pathogens (Banasaz 2002; Khaled 2003; Mack 2003; Mattar 2001; Vaarala 2003).

Why it is important to do this review

A meta-analysis of randomised controlled trials (RCTs) revealed that co-administration of some probiotics such as *L rhamnosus GG* with standard rehydration therapy reduced the duration of diarrhoea by one day in children younger than five years with acute-onset diarrhoea (Huang 2002). Some RCTs have also shown that probiotics are of benefit for treatment of antibiotic-associated diarrhoea and for prevention of nosocomial (hospital-acquired) diarrhoea in infants (Cremonini 2002; Szajewska 2001). Furthermore, a recent Cochrane review demonstrated that, based on moderate-certainty evidence, probiotics are both safe and effective for prevention of *Clostridium difficile*-associated diarrhoea in adults and children but do not significantly reduce the incidence of *C difficile* infection compared with placebo or no treatment (Goldenberg 2013). It also has been found that nutritional intervention with the probiotic drink containing *Lactobacillus casei DN-114 001* does not reduce the incidence of radiotherapy-induced diarrhoea (Giralt 2008).

Previous studies have demonstrated that probiotic supplementation is well tolerated and may reduce the frequency of severe diarrhoea and abdominal discomfort related to chemotherapy or radiotherapy (Delia 2007; Osterlund 2007; Salminen 1988; Urbancsek 2001). Some trials have found that probiotic lactic acid-producing bacteria offer an easy-to-use, safe, and feasible approach to protecting people with cancer against the risk of chemotherapy- or radiotherapy-induced diarrhoea (Delia 2007; Osterlund 2007; Urbancsek 2001).

Although probiotics are thought to be safe and to have few side effects, people who have intestinal damage, immune problems, or overgrowth of bacteria in the intestines are at risk of having the micro-organisms leave the gastrointestinal tract and possibly cause multiple organ failure. Moreover, it has been reported that *L rhamnosus* and *L casei* may be involved in infections, such as abscesses, meningitis, and septic arthritis (available at www.mayoclinic.org/drugs-supplements/acidophilus/background/hrb-20058615).

Probiotics may provide a beneficial effect for people with chemotherapy- or radiotherapy-induced diarrhoea; therefore, it is important to systematically review the current evidence to assess the effects of probiotic therapy on clinically relevant endpoints in people with cancer receiving chemotherapy, radiotherapy, or both. Previous systematic reviews on this topic have yielded conflicting results. One systematic review found no differences between probiotic supplementation and control in preventing or treating radiotherapy- or chemotherapy-induced diarrhoea (Fuccio 2009). Two other recent systematic reviews concluded that probiotics may provide a beneficial effect for prevention of chemotherapy- or radiotherapy-induced diarrhoea (Liu 2017; Wang 2016), and a fourth systematic review explored the effects of probiotics on the severity and frequency of combined antibiotic-associated and chemotherapy-associated diarrhoea and found a reduction in severity and frequency and in the requirement for medication (Redman 2014).

OBJECTIVES

To evaluate the clinical effectiveness and side effects of probiotics used alone or combined with other agents for prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Adults aged 18 years and over with histologically diagnosed cancer at any stage of disease and receiving chemotherapy or radiotherapy (with or without chemotherapy).

Types of interventions

- Probiotics versus any other intervention (observation, usual care, placebo, or other active agents) for prevention and/or treatment of diarrhoea induced by radiotherapy (with or without chemotherapy) or chemotherapy alone;
- Probiotics combined with other agents versus the same agents without probiotics for prevention and/or treatment of diarrhoea induced by radiotherapy (with or without chemotherapy) or chemotherapy alone;
- One regimen of probiotic administration versus a different regimen of probiotic administration (i.e. different kind of medication, intake, dosage, and timing) for prevention and/or treatment of diarrhoea induced by radiotherapy (with or without chemotherapy) or chemotherapy alone.

We included studies that looked at the following probiotics: lactobacilli (i.e. *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus jensenii*), bifidobacteria (i.e. *Bifidobacterium longum*, *Bifidobacterium breve*,*Bifidobacterium oval*, *Bifidobacterium thermophilum*), and *Saccharomyces buollardii*. We also included studies that combined the use of probiotics with prebiotics (i.e. agents that induce the growth or activity of micro-organisms).

Types of outcome measures

Primary outcomes

- For prevention studies: proportion of participants with diarrhoea
- For treatment studies: reduction in severity of diarrhoea (e.g. according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (NCI 2013; CTCAE 2010).
- Quality of life measured on a scale that is validated through reporting of norms in a peer-reviewed publication (e.g. EORTC-QLQ-C30 (a questionnaire developed to assess the quality of life of people with cancer) or a generic instrument, such as Short Form (SF)-36)

Secondary outcomes

- For prevention studies: severity of diarrhoea (e.g. according to the National Cancer Institute's CTCAE (NCI 2013; CTCAE 2010))
- Time to rescue medication for diarrhoea
- Proportion of participants requiring rescue medication for diarrhoea
- Adverse effects such as sepsis, dysbacteria (microbial imbalance in e.g. the colon or small intestine tested by terminal restriction fragment length polymorphism (T-RFLP)), hypersensitivity (especially in high-risk populations such as those that are immunocompromised or have central lines in situ), abscesses, meningitis, and septic arthritis (as reported by the Mayo Clinic and available at http://www.mayoclinic.org/drugs-supplements/acidophilus/safety/hrb-20058615)
- Mortality related to diarrhoea (if deaths occurred in participants with grade 3 or 4 diarrhoea, we would define them as deaths related to diarrhoea)

We did not define the required time points of outcome measurements in advance, and we extracted the time points at which outcomes were collected as presented by study authors.

We presented 'Summary of findings' tables to report the following outcomes.

- Any diarrhoea.
- Quality of life.
- Diarrhoea.
  - Grade 2 or higher.
  - Grade 3 or higher.
  - Grade 4.
- Time to rescue medication.
- Rescue medication required for diarrhoea.
- Adverse events.
- Mortality.

Search methods for identification of studies

Electronic searches

We conducted a broad search to ensure maximum recall of the relevant literature. We performed a comprehensive search of different electronic databases using a combination of free text and medical subject heading (MeSH) terms to identify potential studies for inclusion in the review. We applied no restrictions on language.

We searched the following databases.

- CENTRAL (2017, Issue 7) (Appendix 1).
- MEDLINE (1946 to July week 2, 2017) (Appendix 2).
- Embase (1980 to July week 30, 2017) (Appendix 3).

Searching other resources

We searched the following prospective trial registers for controlled trials in progress using the key words 'probiotics' AND 'cancer', and we updated this search on 15 June 2017.

- ClinicalTrials.gov (http://clinicaltrials.gov/).
- International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/).

We also screened the reference lists of included studies and used the 'similar articles' feature in PubMed to look for all included studies to identify any additional studies that might have been missed by our search (11 August 2017).

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database and removed duplicates. Two review authors (FvdW, PH) examined the remaining references independently. We excluded studies that clearly did not meet the inclusion criteria (based on screening of titles, abstracts, or both). We obtained the full-text articles of potentially eligible studies, and both review authors independently assessed whether

these studies met the review inclusion criteria. A third review author (RS) arbitrated any differences of opinion. We documented excluded studies and stated reasons for exclusion according to guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (Excluded studies).

Data extraction and management

Two review authors (FvdW, PH) independently extracted data. One review author (FvdW) entered the results into Review Manager 2014, and the other review author (PH) checked them for correctness. DW assisted in processing studies that were published in Chinese.

For each included study, we collected data on characteristics of participants (age, gender distribution, cancer details (e.g. type, stage, grade, histology, performance status), diarrhoea severity, previous treatment including type of cancer treatment), characteristics of interventions (type, formulation, dose, duration, regimen), outcomes that were addressed, and duration of follow-up.

For time-to-event data (mortality related to diarrhoea, time to rescue medication), we extracted the log of the hazard ratio [log(HR)] and its standard error (SE) from trial reports; if these were not reported, we attempted to estimate the log(HR) and its SE using the methods of Parmar 1998.

For dichotomous outcomes (e.g. adverse events, presence of diarrhoea), we extracted the number of participants in each treatment arm who experienced the outcome of interest and the total number of participants assessed at endpoint to estimate a risk ratio (RR).

For continuous outcomes (e.g. QoL measures), we extracted the final mean value and the standard deviation (SD) of the outcome of interest and the total number of participants assessed in each treatment arm at the end of follow-up to estimate the mean difference between treatment arms and its SE.

When possible, we extracted all data relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in the groups to which they were assigned.

We extracted the time points at which outcomes were collected as presented by study authors and, if necessary, analysed them separately.

Assessment of risk of bias in included studies

Two review authors (FvdW, PH) independently assessed the risk of bias of all included RCTs using the Cochrane tool for assessing risk of bias (Higgins 2011); we resolved differences by discussion or by appeal to a third review author (RS). DW assisted with assessment of studies published in Chinese.

We summarised the results in a 'Risk of bias summary'. We interpreted the results of meta-analyses in the light of findings of these risk of bias assessments.

Measures of treatment effect

We expressed treatment effects as RRs with 95% confidence intervals (CIs) for dichotomous outcomes. For time-to-event data, we used the hazard ratio (HR), if possible. For continuous outcomes, we calculated mean differences (MDs) with 95% CIs. When different instruments or scales were used to assess the same outcome, we calculated standardised mean differences (SMDs).

Unit of analysis issues

For meta-analyses in which studies were included that compared more than one intervention with the same control intervention, the denominator of the control intervention was halved. There were no further unit of analysis issues in the included studies.

Dealing with missing data

We did not impute missing outcome data for any outcomes.

Assessment of heterogeneity

We assessed heterogeneity according to guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Besides visual inspection of forest plots, we formally tested for statistical heterogeneity using the natural approximate Chi^2 test, which provides evidence of variation in effect estimates beyond that of chance. Because the Chi^2 test has low power to assess heterogeneity when an analysis includes a small number of participants or trials, we set the P value conservatively at 0.1.

We quantified heterogeneity by using the I^2 statistic, which calculates the percentage of variability due to heterogeneity (differences between studies) rather than chance, with I^2 values of 50% to 90% indicating substantial heterogeneity.

We planned to examine potential sources of clinical heterogeneity by performing subgroup analyses as specified under Subgroup analysis and investigation of heterogeneity. We planned to examine potential sources of methodological heterogeneity by conducting sensitivity analyses, as specified under Sensitivity analysis.

Assessment of reporting biases

We would have used funnel plots to assess the potential for small-study effects, such as selective publication, if more than 10 included studies were available for a comparison. However, this was not the case for any of our analyses.

Data synthesis

We used a random-effects model for all meta-analyses. We separately analysed results for participants treated with radiotherapy (with or without chemotherapy) and those treated with chemotherapy alone. We used Review Manager 2014 for meta-analysis. If meta-analysis was not possible, we summarised the results narratively.

To assess the certainty of the body of evidence for each outcome, we used the GRADE approach as described by the GRADE Working Group and in the *Cochrane Handbook for Systematic Reviews of Interventions* (Guyatt 2011; Higgins 2011), which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. We summarised our judgements in 'Summary of findings' tables.

We downgraded the evidence from 'high' certainty by one level for serious (or by two levels for very serious) concerns for each limitation.

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We had planned to conduct subgroup analyses to investigate possible differences between groups. However, because the data required to perform subgroup analyses by age, stage, and length of follow-up could not be retrieved or did not vary, we were not able to perform these analyses.

Sensitivity analysis

When possible, we performed sensitivity analyses by excluding from the meta-analysis studies at high risk of bias and studies with more than 10% missing outcome data. See Effects of interventions.

RESULTS

Description of studies

Results of the search

We identified 481 studies by searching the primary electronic databases (65 in CENTRAL, 87 in MEDLINE, 329 in Embase). Of these, 124 were duplicates, leaving 357 abstracts and titles identified as original publications. Of these, 37 studies were eligible for full-text review, 12 RCTs met the eligibility criteria (see Characteristics of included studies), and one study (published as a conference abstract) presented an interim analysis of an ongoing RCT in which blinding was still maintained. We classified this study under 'Ongoing studies' (see Characteristics of ongoing studies) (Sharma 2013). We classified another study (also presented as a conference abstract) as 'Awaiting assessment', because it is not clear whether participants in the study received chemotherapy or radiotherapy (see Characteristics of studies awaiting classification) (Theodoropoulos 2013). We excluded the remaining 23 studies and provided reasons for their exclusion under Characteristics of excluded studies. We used the 'similar articles' feature of included studies in PubMed and retrieved a total of 1203 records, but no new studies met eligibility criteria. We present the PRISMA study flow chart in Figure 1.

Figure 1. Study flow diagram (search date 24 July 2017).

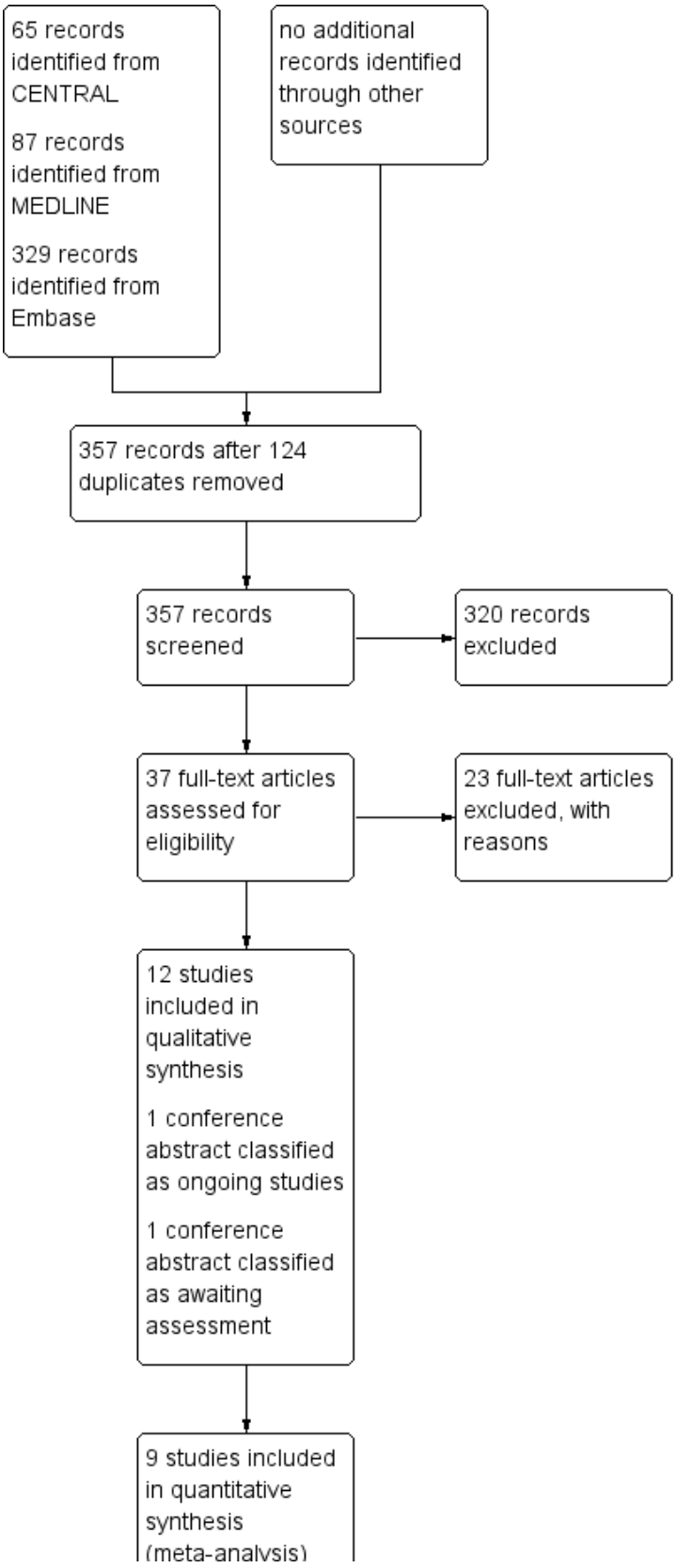
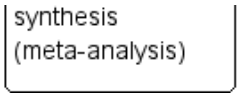


Figure 1. (Continued)



We searched a prospective trial register (https://clinicaltrials.gov/) using the key words 'probiotics' AND 'cancer' and discovered seven additional relevant registered studies, which we have added to the Characteristics of ongoing studies table.

Included studies

Twelve studies involving 1554 participants met the inclusion criteria (Chen 2014; Chitapanarux 2010; Delia 2007; Demers 2014; Giralt 2008; Liu 2000; Mansouri-Tehrani 2016; Mego 2015; Osterlund 2007; Salminen 1988; Timko 2010; Urbancsek 2001). Of these, two studies were published in Chinese (Chen 2014; Liu 2000). Eleven were *prevention* studies, of which seven compared probiotics with placebo (Chen 2014; Chitapanarux 2010; Delia 2007; Giralt 2008; Liu 2000; Mansouri-Tehrani 2016; Mego 2015), one compared two doses of probiotics with each other and with placebo (Demers 2014), and three compared probiotics with another active agent (Osterlund 2007; Salminen 1988; Timko 2010). The remaining study concerned *treatment* of radiotherapy-related diarrhoea and compared probiotics with placebo (see Characteristics of included studies) (Urbancsek 2001).

1. Prevention of diarrhoea

For prevention of diarrhoea, we identified eight placebo-controlled studies and three studies comparing probiotics versus another active intervention or standard therapy.

1.1. Probiotics versus placebo

1.1.1. Patients treated with radiotherapy (with or without chemotherapy)

Five studies compared probiotics with placebo for prevention of diarrhoea in participants undergoing radiotherapy with or without chemotherapy (Chitapanarux 2010; Delia 2007; Demers 2014; Giralt 2008; Mansouri-Tehrani 2016) (Table 1). Of these, one study included some participants who had already developed grade 1 diarrhoea at baseline, and another study addressed prevention of grade 2 or higher diarrhoea (Giralt 2008).

The first study compared a probiotic containing live *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* (n = 32) versus placebo (n = 31) in 63 participants who were undergoing pelvic radiotherapy concurrent with weekly cisplatin. Researchers found no significant differences between the two groups in terms of participant characteristics or pelvic radiotherapy technique at baseline. The study reported on four outcomes of interest: proportion of participants with diarrhoea, severity of diarrhoea, proportion of participants requiring rescue medication, and adverse events. Trialists evaluated these outcomes weekly during radiotherapy.

The second study evaluated the efficacy of a high-potency probiotic preparation for prevention of radiotherapy-induced diarrhoea in people with cancer (Delia 2007). This study involved 490 participants who were randomly assigned to treatment with VSL#3 (n = 245) or identical-appearing placebo (n = 245). VSL#3 contained *Lactobacillus casei, Lactobacillus plantarum, L acidophilus, Lactobacillus delbrueckii* subsp *bulgaricus*, *Bifidobacterium longum, Bifidobacterium breve*, *Bifidobacterium infantis,* and *Streptococcus salivarius* subsp *thermophilus*. One sachet was given three times a day, starting from the first day of radiotherapy until the end of scheduled cycles of radiotherapy. Researchers found no significant differences between the two groups in patient characteristics at baseline. This study reported on five outcomes of interest: proportion of participants with diarrhoea, severity of diarrhoea, time to rescue medication, mortality caused by diarrhoea, and adverse events. Trialists evaluated these outcomes weekly until one month after completion of radiotherapy.

The third study included three intervention arms: a standard dose (twice a day) and a high dose (three times a day) of double-strain Bifilact probiotics (*Lactobacillus acidophilus LAC-361* and *Bifidobacterium longum BB-536*; Virage Santé, Québec, Canada) and placebo (Demers 2014). This study included 229 participants with pelvic (gynaecological, rectal, or prostate) cancer and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 who were to receive radiotherapy at a minimum of 40 Gy at the pelvic level, with or without chemotherapy. Data show no important baseline differences between groups with respect to type of cancer, age, and gender. The study reported on six outcomes of interest: proportion of participants with diarrhoea, severity of diarrhoea, time to rescue medication, proportion of participants needing rescue medication, quality of life, and adverse events. All participants were followed up to a maximum of 10 weeks.

The fourth study compared a probiotic drink (n = 56) with placebo (n = 62) in participants with gynaecological cancer who were undergoing pelvic radiotherapy (45 to 50 Gy, conventional fractionation) for cervical carcinoma (radiotherapy and weekly cisplatin) or endometrial adenocarcinoma (postoperative radiotherapy) (Giralt 2008). The probiotic drink consisted of liquid yogurt containing *Lactobacillus casei DN-114 001* at 108 colony-forming units (CFU)/g. Researchers found no significant differences between the two groups in participant characteristics at baseline. This study reported on four outcomes of interest: severity of diarrhoea (graded weekly according to the CTCAE), proportion of people requiring rescue medication, quality of life, and adverse events. All participants were evaluated weekly by the same investigator and were asked to record the number of bowel movements and stool consistency every day. Each participant was evaluated up to six months.

The fifth study compared use of probiotic capsules (n = 22) versus placebo (n = 24) in participants who were undergoing five weekly fractions of conventional pelvic radiotherapy (total dose: 4000 to 5000 cGy (1.8 Gy/d)) for treatment of pelvic cancer (Mansouri-Tehrani 2016). This review did not discuss a second intervention group that received honey in addition to a probiotic. The probiotic capsules consisted of *L casei, L acidophilus, L rhamnosus, L bulgaricus, B breve, B longum,* and *S thermophilus.* This study reported on four outcomes of interest: severity of diarrhoea (graded weekly according to CTCAE), time to rescue medication, proportion of people requiring rescue medication, and adverse

events. Researchers evaluated these outcomes weekly during four-week radiotherapy.

1.1.2. Patients treated with chemotherapy alone

Three studies compared probiotics with placebo for prevention of diarrhoea in participants undergoing chemotherapy (Chen 2014; Liu 2000; Mego 2015) (Table 2).

The first study compared combined *Clostridium butyricum* and *Bifidobacterium* versus placebo in 70 participants (35 in each group) who underwent surgery for colorectal cancer (Chen 2014). All participants received intravenous chemotherapy during surgery. Both groups were well balanced with respect to tumour location (right or left portion of the colon, or rectum) and tumour stage (stage I to II, 21 versus 23; stage III to IV, 9 versus 7). This study reported on two outcomes of interest: proportion of participants with diarrhoea and adverse events. Study authors did not report the time points of outcome measurement.

The second study was a cross-over study including 22 participants with cancer who received chemotherapy (Liu 2000). Eight participants had lung cancer, five gastric cancer, four colorectal cancer, four breast cancer, and one metastatic neck cancer. *Bifidobacterium* (two capsules, two times a day) with chemotherapy was compared with chemotherapy alone and was administered from one day before chemotherapy to the sixth day of chemotherapy. The washout period lasted about 21 days. This study reported on two outcomes of interest: proportion of participants with diarrhoea and severity of diarrhoea. Study authors did not report the time points of outcome measurement.

The third study compared the Colon Dophilus™ 3*1 capsule per day orally for 12 weeks versus placebo in 46 participants (23 in each group) with colorectal cancer who were about to start chemotherapy based on irinotecan, with ECOG performance status 0 to 1 and life expectancy longer than three months (Mego 2015). Study authors described some baseline differences with respect to gender (more males in the probiotic arm), more participants in the probiotics group with colon cancer (69.6% versus 52.2%), and more participants in the placebo group undergoing resection of the primary tumour. This study reported on four outcomes of interest: incidence and severity of diarrhoea, proportion of participants requiring rescue medication, and adverse events. Study authors did not report the time points of outcome measurement.

1.2. Probiotics versus another active intervention or standard therapy

1.2.1. Patients treated with radiotherapy (with or without chemotherapy)

Three studies compared effects of probiotics versus another active intervention in participants undergoing radiotherapy with or without chemotherapy (Osterlund 2007; Timko 2010; Salminen 1988) (Table 3).

The first study used a factorial design and compared two 5-FU-based regimens and the effects of *Lactobacillus* or fibre supplementation on treatment tolerability (Osterlund 2007). A total of 150 participants received the diagnosis of colorectal cancer and were randomly allocated to receive monthly 5-FU and leucovorin bolus injections or a bimonthly 5-FU bolus plus continuous infusion for 24 weeks as postoperative adjuvant therapy. Participants also were randomised to receive *L rhamnosus GG* supplementation (1 to 2 × 10^{10} per day) or fibre (11 g guar gum per day) during chemotherapy. All participants received dietary counselling. Researchers reported no differences between the two groups in participant characteristics at baseline. This study reported on three outcomes of interest: proportion of participants with diarrhoea, severity of diarrhoea, and adverse events. Trialists evaluated these outcomes four-weekly during chemotherapy and radiotherapy and at protocol-determined intervals (ranging from two to six months) post treatment.

The second study assessed the efficacy of adding live *L acidophilus* cultures to dietary counselling for prevention of intestinal side effects (Salminen 1988). Twenty-four female participants with gynaecological malignancies and scheduled for internal and external irradiation of the pelvic area were randomised to the intervention group (150 mL of a fermented milk test product supplying them with at least 2 × 10^9 live *L acidophilus* bacteria daily and 6.5% lactulose as substrate for the bacteria and dietary counselling recommending a low-fat and low-residue diet during radiotherapy) or to the control group (dietary counselling only). Researchers reported no baseline characteristics. This study reported on three outcomes of interest: proportion of participants with diarrhoea, proportion of participants requiring rescue medication, and adverse events. Trialists evaluated these outcomes during and six weeks after treatment.

The third study assessed the efficacy of a probiotic preparation for prevention of radiotherapy-induced diarrhoea in people with cancer (Timko 2010). Investigators randomised 42 participants who had undergone adjuvant postoperative radiotherapy after abdominal and pelvic cancer to receive either a probiotic preparation with "5"-strain Dophilus (twice per day) containing five probiotic cultures (55% *L rhamnosus,* 20% *B adolescentis,* 5% *L acidophilus,* 5% *B longum,* and 15% *Enterococcus faecium*) or a preparation with Hylak Tropfen Forte (i.e. cell-free fermentation products of *Lactobacillus helveticus* and gut symbionts (100 mL containing 24.95 g *Escherichia coli* metabolita, 12.5 g *Streptococcus faecalis* metabolita, 12.5 g *L acidophilus* metabolita, 49.9 g *L helveticus* metabolita)) at doses of 40 drops, three times per day. Supplementation started on the first day and lasted until completion of radiotherapy. Study authors stated that there were differences between the two groups regarding gender and primary tumour site at baseline (no further details were reported). In addition, during radiotherapy, 27% of participants treated with probiotics required diphenoxylate treatment compared with 55% treated with Hylak Tropfen Forte, and 9% needed administration of antibiotics compared with 25% in the Hylak group. We excluded these participants from the analyses as investigators could not estimate the ways in which these treatments influenced the composition of intestinal bacterial flora. All participants were treated with pelvic radiotherapy with chemotherapy, except for one from the probiotic group. According to study authors, chemotherapy seemed to have resulted in increased toxicity. This study reported on two outcomes of interest: proportion of participants requiring rescue medication and adverse events. Trialists evaluated these outcomes over one to five weeks during radiotherapy.

1.2.2. Patients treated with chemotherapy alone

We found no studies for this group of patients.

2. Treatment of diarrhoea

For treatment of diarrhoea, we identified one placebo-controlled study including participants undergoing radiotherapy (Urbancsek 2001). We identified no studies that included participants with diarrhoea who had received chemotherapy alone. Urbancsek 2001 compared the efficacy and tolerability of *L rhamnosus* (Antibiophilus) versus placebo in 205 participants suffering from mild to moderate diarrhoea induced by radiotherapy (Table 4). Investigators found no differences between the two groups in participant characteristics at baseline. This study reported on four outcomes of interest: severity of diarrhoea, time to rescue medication for diarrhoea, proportion of participants requiring rescue medication, and adverse events. Participants were followed up one week after completion of treatment.

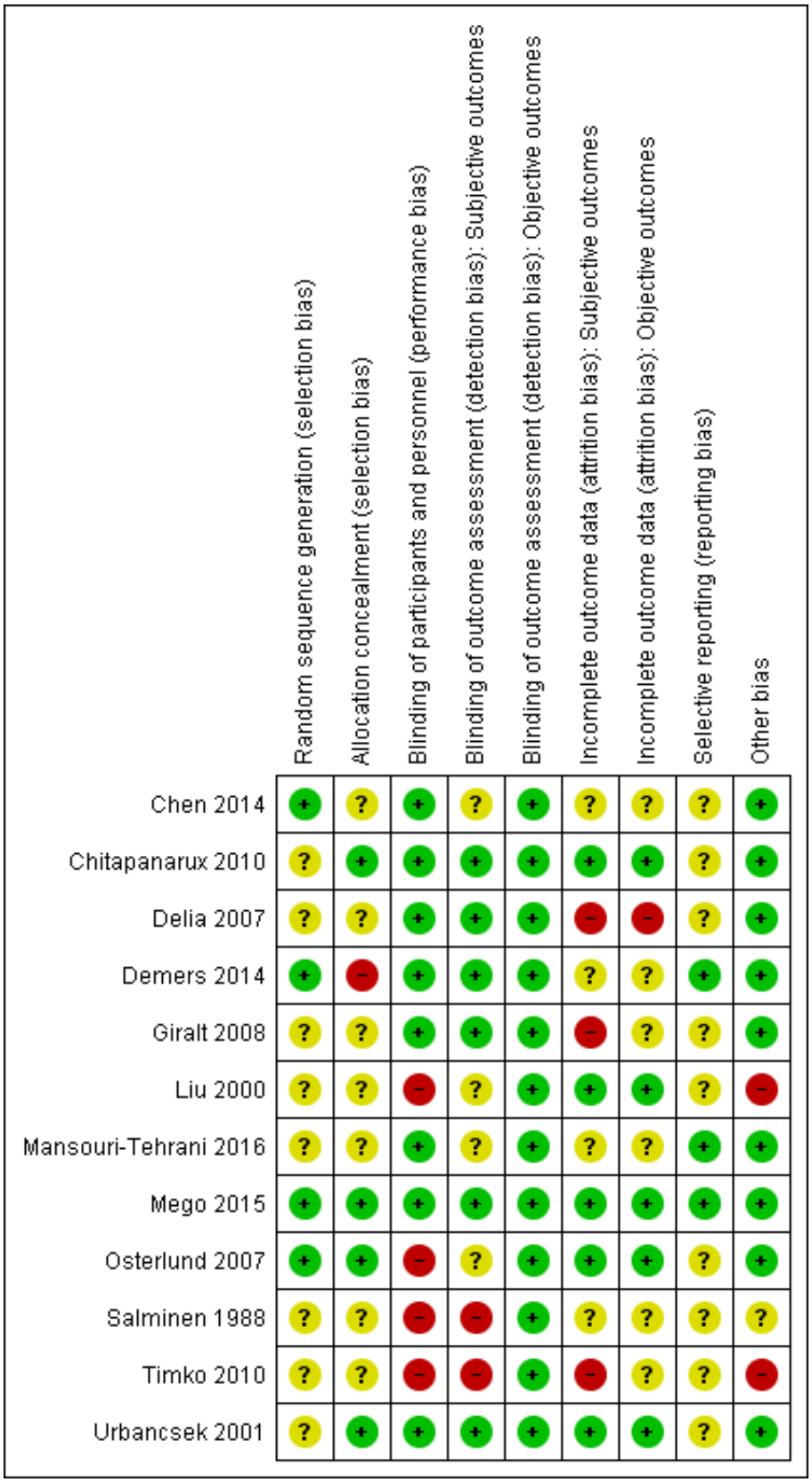
Excluded studies

We excluded 23 studies. Twelve studies were not relevant to our review question, seven were not RCTs, and four were not primary studies. We have presented excluded studies and reasons for exclusion in the Characteristics of excluded studies table.

Risk of bias in included studies

The risk of bias assessment for each study can be found in the 'Risk of bias' tables (see Characteristics of included studies). We have presented a summary of risk of bias assessments in Figure 2. Here, we discuss the overall results of the risk of bias assessments.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Generally, little information was provided on methods used for randomisation or methods used to maintain concealment of allocation, leading to an unclear risk of bias judgement for random sequence generation and allocation concealment. Four studies scored low risk of bias for random sequence generation (Chen 2014; Demers 2014; Mego 2015; Osterlund 2007). We considered four studies to have low risk of bias for allocation concealment (Chitapanarux 2010; Mego 2015; Osterlund 2007; Urbancsek 2001). One study scored high risk of bias regarding allocation concealment because the investigator, who knew the coding system, assigned participants to the different groups (Demers 2014).

Blinding

Four studies scored a high risk of performance bias for participants and/or personnel, as these studies were non-blinded (Liu 2000; Osterlund 2007; Salminen 1988; Timko 2010). We considered two studies to have high risk of detection bias (subjective outcomes) (Salminen 1988; Timko 2010). We assessed four studies as having unclear risk of bias owing to insufficient information (Chen 2014; Liu 2000; Mansouri-Tehrani 2016; Osterlund 2007).

Incomplete outcome data

Three studies scored high risk of attrition bias for subjective outcomes owing to exclusion of participants for intervention-related reasons - as in Delia 2007 - or a substantial number of dropouts (28% (33/118) in Giralt 2008, and 27% and 55% in the intervention and control groups, respectively, in Timko 2010). Another four studies scored unclear risk owing to insufficient information (Chen 2014; Demers 2014; Mansouri-Tehrani 2016) or unclear influence of a relatively large number of dropouts in a small study (Salminen 1988). We judged the remaining studies to have low risk of attrition bias for subjective outcomes. For objective outcomes (mortality), we considered one study to have high risk of attrition bias (Delia 2007), and for six studies, the risk of bias was unclear (Chen 2014; Demers 2014; Giralt 2008; Mansouri-Tehrani 2016; Salminen 1988; Timko 2010).

Selective reporting

In three studies (Demers 2014; Mansouri-Tehrani 2016; Mego 2015), it was clear that there was no selective reporting of data because original study protocols were available. For the other nine studies, the study protocols were not available, and therefore we judged the risk of reporting bias to be unclear.

Other potential sources of bias

One study showed indications of other bias due to possible imbalances in baseline characteristics (Timko 2010). We considered another study to have high risk of bias because investigators ignored the cross-over design in the analyses and in the presentation of results (Liu 2000). In another study, the risk of other bias was unclear because study authors provided insufficient information and no table of baseline characteristics (Salminen 1988). We judged the remaining studies to have low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Probiotics compared with placebo for prevention of diarrhoea in participants with cancer treated with radiotherapy (with or without chemotherapy); **Summary of findings 2** Probiotics compared with placebo for prevention of diarrhoea in participants with cancer treated with chemotherapy; **Summary of findings 3** Probiotics compared with other active treatment for prevention of diarrhoea in participants with cancer treated with radiotherapy (with or without chemotherapy); **Summary of findings 4** Probiotics compared with placebo for treatment of diarrhoea due to radiotherapy (with or without chemotherapy) in participants with cancer

We present results separately for prevention (section 1) and treatment (section 2) of diarrhoea. We discriminated between placebo-controlled studies and studies comparing probiotics with another treatment (subsections 1 and 2, respectively). Finally, because the impact of radiotherapy is considered the most important difference, we presented and analysed studies separately for participants treated with radiotherapy (with or without chemotherapy) and with chemotherapy alone.

1. Prevention of diarrhoea

1.1. Probiotics versus placebo

1.1.1. Participants treated with radiotherapy (with or without chemotherapy)

Five studies with 905 analysed participants compared probiotics with placebo for prevention of radiotherapy (with or without chemotherapy)-related diarrhoea (Chitapanarux 2010; Delia 2007; Demers 2014; Giralt 2008; Mansouri-Tehrani 2016).

Proportion of participants with diarrhoea

Three studies addressed this outcome. Owing to heterogeneity, we did not pool results. One study found that the occurrence of diarrhoea of any grade was significantly reduced with probiotics compared with placebo in 482 participants treated with radiotherapy alone (risk ratio (RR) 0.35, 95% confidence interval (CI) 0.26 to 0.47) (Delia 2007). We observed no significant differences between the two groups among participants treated with chemoradiotherapy in the studies of Chitapanarux 2010 (RR 1.0, 95% CI 0.94 to 1.06; 63 participants) and Demers 2014 (two study arms: RR 0.92, 95% CI 0.82 to 1.02 and RR 0.89, 95% CI 0.78 to 1.02 for standard (167 participants) and high doses (145 participants) of the probiotic, respectively) (Analysis 1.1).

Quality of life

Two studies including participants treated with chemoradiotherapy assessed quality of life by using the EORTC-QLQ-C30 (version 3) instrument (Table 1). The first study (226 participants) reported: "The well-being of patients did change over time. Overall QOL decreased by the end of the treatment, but increased again two weeks post-treatment ($P < 0.0001$). Probiotic intake did not affect the quality of life of patients in this study" (Demers 2014). In the second study (72 participants), QLQ-C30 global scores showed mild improvement compared with baseline in both groups but revealed no significant differences between groups (mean difference (MD) 3.7, 95% CI -1.2 to 8.6) (Giralt 2008).

Severity of diarrhoea

Four studies addressed the occurrence of diarrhoea grade 2 or higher. Among participants treated with radiotherapy (with or without chemotherapy), the pooled RR for the occurrence of grade

2 or higher diarrhoea with probiotics versus placebo was 0.75 (95% CI 0.55 to 1.03; four studies; 420 participants) (Analysis 1.2) (Chitapanarux 2010; Demers 2014; Giralt 2008; Mansouri-Tehrani 2016). One study compared standard-dose and high-dose probiotics versus placebo and included both comparisons separately in the meta-analysis (Demers 2014). We ignored the high value for I^2 (72%) because visual inspection of the forest plot showed sufficient overlap of CIs for the three studies with largest weights, whereas two smaller studies were shown not to influence the results.

Three studies addressed the occurrence of diarrhoea grade 3 or higher; of these, we included intervention groups from one study receiving standard-dose and high-dose probiotics separately (Demers 2014). In 793 participants treated with radiotherapy (with or without chemotherapy), RRs for grade 3 or higher diarrhoea with probiotics versus placebo were heterogeneous (I^2 = 91%) and ranged from 0.11 (95% CI 0.06 to 0.23) to 1.24 (95% CI 0.74 to 2.08) (Analysis 1.3; Summary of findings for the main comparison) (Delia 2007; Demers 2014; Giralt 2008).

One study reported the occurrence of diarrhoea grade 4 in participants treated with both radiotherapy and chemotherapy. The RRs of standard-dose (81 participants) and high-dose (59 participants) probiotics versus placebo (86 participants) were 0.24 (95% CI 0.05 to 1.06) and 0.65 (95% CI 0.21 to 2.01), respectively (Table 1) (Demers 2014).

One study including participants receiving pelvic radiotherapy reported a significantly higher mean diarrhoea grade during weeks 4 and 5 in the placebo group (24 participants) compared with the probiotic group (22 participants; P = 0.007 and P = 0.001, respectively) (Mansouri-Tehrani 2016).

Time to rescue medication for diarrhoea

Two studies in which participants were treated with radiotherapy (with or without chemotherapy) addressed this outcome (Delia 2007; Demers 2014). In one study (482 participants), the mean time to rescue medication was 36 hours longer in the probiotics group than in the placebo group (95% CI 34.7 to 37.3 hours) (Delia 2007). The second study (226 participants) reported: "no difference (P = 0.89) among the groups for the time until the first intake of loperamide" and "The first capsule of loperamide (Imodium) was taken on day 19.7 (placebo), 20.4 (standard dose), and 20.9 (high-dose)" (Table 1) (Demers 2014).

Proportion of participants requiring rescue medication for diarrhoea

Four studies addressed this outcome, of which three could be pooled (Chitapanarux 2010; Giralt 2008; Mansouri-Tehrani 2016). Among participants treated with radiotherapy (with or without chemotherapy), the pooled RR for the need for rescue medication for diarrhoea of probiotics versus placebo was 0.50 (95% CI 0.15 to 1.66; three studies; 194 participants) (Analysis 1.4). Again, we ignored the high value for I^2 (74%) because visual inspection of the forest plot revealed sufficient overlap of CIs from the three studies. The fourth study (226 participants) did not quantify results but reported less use of rescue medication in the probiotics group (Table 1) (Demers 2014).

Adverse events

Five studies addressed this outcome narratively (Table 1) (Chitapanarux 2010; Delia 2007; Demers 2014; Giralt 2008; Mansouri-Tehrani 2016). One study including 63 participants reported no adverse events attributable to the study drug (Chitapanarux 2010). The second study (482 participants) reported that no case of bacteraemia, sepsis, or septic shock due to the probiotic lactobacilli was reported during the treatment period with the probiotic preparation or during the six months beyond active treatment (Delia 2007). In addition, no case of bacteraemia, sepsis, or septic shock due to organisms other than the probiotic lactobacilli was recognised during the period of active treatment. The third study reported no differences between groups with respect to number of hospitalisations, number of treatment interruptions, and reduction in either chemotherapy doses or radiotherapy treatments (226 participants) (Demers 2014). Researchers also reported that intake of the probiotic was well tolerated, and that no septicaemia was recorded, "although a few cases of neutropenia occurred during treatment". The fourth study (85 participants) found no differences in reported complications at six months between treatment groups (Giralt 2008). Study authors stated that the probiotic was well tolerated, and that none of the adverse events reported were considered related to the probiotic. The fifth study reported that during pelvic radiotherapy, three participants belonging to a probiotic group (with or without honey) complained of upper abdominal pain, but that the causal link with probiotic use was not investigated (46 participants) (Mansouri-Tehrani 2016). Bloating occurred more often in the probiotic group (19/22 versus 10/24 participants; RR 2.07, 95% CI 1.26 to 3.42).

Mortality

Not all studies mentioned this explicitly, but no studies reported any deaths (Table 1), except in one study, one participant in the probiotics group died of myocardial infarction after three sessions of radiotherapy; this participant was excluded from the analyses (Delia 2007).

1.1.2. Participants treated with chemotherapy alone

Three studies with 138 participants compared probiotics versus placebo for prevention of diarrhoea after treatment with chemotherapy (without radiotherapy) (Chen 2014; Liu 2000; Mego 2015).

Proportion of participants with diarrhoea

Three studies addressed this outcome. Based on two studies (Chen 2014; Mego 2015), the pooled RR for any diarrhoea of probiotics compared with placebo was 0.59 (95% CI 0.36 to 0.96; 106 participants) in favour of probiotics (Analysis 2.1). The third study was a cross-over study that did not present a paired analysis of the data (Liu 2000). During the probiotic treatment period, six of the 22 participants suffered from any grade of diarrhoea, whereas during the placebo period, 10 participants had diarrhoea (Table 2).

Quality of life

No study addressed this outcome.

Severity of diarrhoea

Two studies addressed the occurrence of diarrhoea grade 2 or higher (Liu 2000; Mego 2015). In one study, the RR of probiotics versus placebo was 0.67 (95% CI 0.22 to 2.05; one study; 46 participants) (Mego 2015). In the other (cross-over) study (Liu 2000), three of the 22 participants suffered from grade 2 or higher diarrhoea during the probiotic treatment period compared with seven in the placebo period (Table 2).

Two studies addressed the occurrence of diarrhoea grade 3 or higher (Liu 2000; Mego 2015). In one study, the RR for grade 3 or higher diarrhoea for probiotics versus placebo was 0.11 (95% CI 0.01 to 1.95; 46 participants) (Mego 2015). In the other (cross-over) study (Liu 2000), one of the 22 participants suffered from grade 3 or higher diarrhoea during the probiotic treatment period compared with four in the placebo period (Table 2).

One study reported the occurrence of diarrhoea grade 4. The RR of probiotics versus placebo was 0.33 (95% CI 0.01 to 7.78; 46 participants) (Mego 2015) (Table 2).

Time to rescue medication for diarrhoea

No study addressed this outcome.

Proportion of participants requiring rescue medication for diarrhoea

One study addressed this outcome in 46 participants (Mego 2015). This study did not quantify the results but reported less use of rescue medication in the probiotics group (Table 2).

Adverse events

Two studies addressed this outcome (Table 2). In the first study (60 participants analysed), the occurrence of various adverse events was similar in both treatment groups, and no differences between groups were found for abdominal distension, systemic inflammatory response syndrome (SIRS), infection of the incisional wound, pulmonary infection, urinary tract infection, duration of fever, and hypoproteinaemia. Researchers observed no side effects relevant to drug use (Chen 2014). The other study (46 participants) reported only that based on study diaries, investigators observed no infections caused by probiotic strains (Mego 2015).

Mortality

Not all studies mentioned this explicitly, but no studies reported any deaths (Table 2).

1.2. Probiotics versus another active intervention or standard therapy

1.2.1. Participants treated with radiotherapy (with or without chemotherapy)

Three studies with 216 participants compared the effects of probiotics versus another active intervention in participants treated with radiotherapy with or without chemotherapy (Osterlund 2007; Timko 2010; Salminen 1988) (Table 3).

Proportion of participants with diarrhoea

One study including 24 participants (21 participants for analysed) reported this outcome (Salminen 1988). Trialists found differences between the two groups for the proportion of participants with diarrhoea in favour of probiotics at all three follow-up measurements during treatment (exact timing was not reported by study authors) and six weeks after treatment: during treatment, RR 0.34, 95% CI 0.12 to 0.94; RR 0.20, 95% CI 0.06 to 0.72; and RR 0.23, 95% CI 0.06 to 0.83, respectively; six weeks after treatment, RR 0.30, 95% CI 0.11 to 0.81.

Quality of life

No study reported on quality of life.

Severity of diarrhoea

One study including 148 participants reported this outcome (with the odds ratio as the measure of treatment effect) (Osterlund 2007). Compared with those in the control group (guar gum containing nutritional supplement), fewer participants in the *Lactobacillus* group had grade 3 to 4 diarrhoea (odds ratio (OR) 0.38, 95% CI 0.16 to 0.89).

Time to rescue medication for diarrhoea

No study reported time to rescue medication for diarrhoea.

Proportion of participants requiring rescue medication for diarrhoea

Two studies reported this outcome (Salminen 1988; Timko 2010). The pooled RR for the need for rescue medication of probiotics versus other active treatment was 0.44 (95% CI 0.22 to 0.86; 63 participants) (Analysis 3.1).

Adverse events

All three studies reported this outcome. In the first study, which reported the odds ratio as the measure of treatment effect (Osterlund 2007), study authors reported no significant differences for any of the studied adverse events amongst 148 participants.

- Any adverse event grade 3 to 4: OR 0.77 (95% CI 0.35 to 1.72).
- Stomatitis grade 3 to 4: OR 0.59 (95% CI 0.26 to 1.35).
- Neutropenia grade 3 to 4: OR 2.00 (95% CI 0.74 to 4.89).
- Neutropenic infection grade 3 to 4: OR 2.62 (95% CI 0.53 to 13.00).
- Hand-foot syndrome grade 3: 2/97 versus 1/51 (OR: no convergence).

The second study including 21 participants reported no differences in the incidence of vomiting, nausea, abdominal pain, loss of appetite, or weight loss between the two groups, but the probiotics group experienced more flatulence than was reported by the dietary counselling group (Salminen 1988).

The third study (42 participants) stated that abdominal pain was reported by 25% of participants in the probiotic group and 22% of those in the Hylak group (Timko 2010).

Mortality

Not all studies mentioned this explicitly, but no studies reported any deaths (Table 3).

1.2.2. Participants treated with chemotherapy alone

We found no studies for this group of participants.

2. Treatment of diarrhoea

2.1. Probiotics versus placebo

2.1.1. Participants treated with radiotherapy (with or without chemotherapy)

One study compared the efficacy and tolerability of *Lactobacillus rhamnosus* (Antibiophilus) versus placebo in 205 participants with mild to moderate diarrhoea induced by radiotherapy (Table 4) (Urbancsek 2001).

Reduction in severity of diarrhoea

The average diarrhoea grade (rated by investigators using standard scores ranging from 0 for no diarrhoea to 3 for severe diarrhoea) was 0.7 for the Antibiophilus group and 1.0 for the placebo group at the end of the study (no significant differences between the two groups). Patients' self-ratings with regard to diarrhoea grade and faeces consistency showed a difference in treatment-by-time interaction (P < 0.001), but it is unclear how this result should be interpreted.

Quality of life

This study did not report on quality of life.

Time to rescue medication for diarrhoea

Time to rescue medication for diarrhoea (derived from patients' diaries) was longer in the probiotics group than in the placebo group (MD 13 hours, 95% CI -0.86 to 26.86; 205 participants).

Proportion of participants requiring rescue medication for diarrhoea

The proportion of participants requiring rescue medication for diarrhoea showed no significant differences between groups (RR 0.74, 95% CI 0.53 to 1.03; 205 participants).

Adverse events

Study authors reported that they observed no serious adverse events and "In the Antibiophilus group, three participants reported mild to moderate gastrointestinal problems; in the placebo group, two participants reported moderate to severe gastrointestinal events, and one patient observed a mild labial oedema. All documented events were of a transient nature; in three patients, symptomatic treatment of adverse events was prescribed".

Mortality

Although not mentioned explicitly, no study reported any deaths (Table 4).

2.1.2. Participants treated with chemotherapy alone

We found no studies for this group of participants.

2.2. Probiotics versus another active intervention or standard therapy

2.2.1. Participants treated with radiotherapy (with or without chemotherapy)

We found no studies for this group of participants.

2.2.2. Participants treated with chemotherapy alone

We found no studies for this group of participants.

Sensitivity analyses

When we excluded studies at high risk of bias from the analyses, one study was left in Analysis 1.1, and the RR for the occurrence of diarrhoea for probiotics versus placebo became 1.00 (95% CI 0.94 to 1.06). In Analysis 1.2, the RR for diarrhoea grade 2 or higher changed from 0.75 (95% CI 0.55 to 1.03) to 0.35 (95% CI 0.17 to 0.73), and for Analysis 1.4, the RR for the need for rescue medication changed from 0.50 (95% CI 0.15 to 1.66) to 0.27 (95% CI 0.11 to 0.67). In the latter two cases, two studies at unclear risk of bias remained in the meta-analysis. For all other analyses, we could not perform sensitivity analyses because all studies that were included in the (meta-)analysis were at high or low risk of bias.

Only one study had more than 10% missing outcome data (Chen 2014). The RR for any diarrhoea changed from 0.59 (95% CI 0.36 to 0.96) to 0.64 (95% CI 0.35 to 1.18; one study; Analysis 2.1).

DISCUSSION

In this review, we summarised available evidence from randomised controlled trials (RCTs) assessing the effects of probiotics for prevention or treatment of radiotherapy (with or without chemotherapy)- or chemotherapy-related diarrhoea. We included 12 studies involving 1554 participants. Eleven were prevention studies; seven of these compared probiotics with placebo (887 participants), one compared two doses of probiotics with each other and with placebo (246 participants), and three compared probiotics with another active agent (216 participants). The remaining study examined treatment for radiotherapy-related diarrhoea and compared probiotics versus placebo (205 participants).

Summary of main results

For prevention of radiotherapy-induced diarrhoea (with or without chemotherapy), we identified five studies including 905 participants (Summary of findings for the main comparison). Researchers could neither demonstrate nor refute a beneficial effect of probiotics compared with placebo on occurrence of diarrhoea, quality of life, severity of diarrhoea, or the proportion of participants requiring rescue medication (low to very low certainty of evidence). However, sensitivity analyses that omitted studies at high risk of bias revealed a beneficial effect for the occurrence of grade 2 or higher diarrhoea and the proportion of participants requiring rescue medication but showed no effect on the occurrence of any diarrhoea. In one study, time to rescue medication was on average 36 hours longer for probiotic users (95% confidence interval (CI) 34.7 to 37.3), but another study reported no difference (moderate certainty of evidence). No studies reported serious adverse events or diarrhoea-related deaths (low certainty of evidence).

For prevention of chemotherapy-induced diarrhoea, researchers described a beneficial effect of probiotics compared with placebo for occurrence of any diarrhoea (risk ratio (RR) 0.59, 95% CI 0.36 to 0.96; two RCTs; 106 participants), which was confirmed in a third cross-over study including 22 participants (low certainty of evidence) (Summary of findings 2). For severity of diarrhoea and the need for rescue medication, trialists could neither demonstrate nor refute a difference in effect (low certainty of evidence; one RCT; 46 participants). No studies reported serious adverse events or diarrhoea-related deaths (low certainty of evidence). No studies reported on quality of life nor time to rescue medication.

The three studies comparing probiotics versus another active agent in participants treated with radiotherapy (with or without chemotherapy) found differences between the two groups in favour of probiotics for the proportion of participants with diarrhoea six weeks after treatment (very low certainty of evidence; RR 0.30, 95% CI 0.11 to 0.81; one RCT; 21 participants), the occurrence of grade 3 or 4 diarrhoea (low certainty of evidence; odds ratio (OR) 0.38, 95% CI 0.16 to 0.89; one RCT; 148 participants), and the proportion of participants requiring rescue medication (very

low certainty of evidence; RR 0.44, 95% CI 0.22 to 0.86; two RCTs; 63 participants) (Summary of findings 3). No studies reported differences in the occurrence of serious adverse events (very low certainty of evidence), and no studies reported any deaths (low certainty of evidence). Researchers did not examine quality of life nor time to rescue medication.

The remaining study examined treatment for radiotherapy-related diarrhoea (Summary of findings 4). This study compared probiotics versus placebo in 205 participants. Study authors could not demonstrate nor refute a beneficial effect of probiotics on average diarrhoea grade, time to rescue medication for diarrhoea (13 hours longer in the probiotics group; 95% CI -0.9 to 26.9 hours), or need for rescue medication (RR 0.74, 95% CI 0.53 to 1.03) (moderate certainty of evidence). They reported no difference in the occurrence of serious adverse events (moderate certainty of evidence) and no diarrhoea-related deaths. These researchers did not examine quality of life.

Overall completeness and applicability of evidence

For prevention of radiotherapy-induced diarrhoea (with or without chemotherapy), five placebo-controlled studies with 902 participants are currently available, but the number of participants included in the three studies evaluating prevention of chemotherapy-induced diarrhoea is limited. Relevance to participants of some beneficial effects, such as delayed requirement for rescue medication by 36 hours, is questionable. Although some analyses suggest benefit from preventative probiotics, these limitations preclude any firm recommendations in favour of preventative probiotics. In addition, the effects of probiotics are strain-specific (Rijkers 2011). Therefore, these results cannot be extrapolated to other strains of probiotics.

Comparisons of probiotics versus other active treatments are scarce and were performed in studies with few participants and providing evidence of low to very low certainty. Although for some outcomes, trialists reported a beneficial effect of probiotics compared with an alternative treatment, these studies do not permit firm conclusions regarding the choice between available treatment options.

For treatment of diarrhoea, we identified only one study. This study investigated treatment for mild diarrhoea, and the results allow firm conclusions regarding a beneficial effect. This study did not examine quality of life.

Quality of the evidence

The 'Summary of findings' tables for each comparison show that review authors downgraded the certainty (quality) of evidence for most outcomes using GRADE. Except for the only study that addressed treatment for radiotherapy-induced diarrhoea (moderate certainty of evidence for all outcomes), the certainty of evidence was low to very low for most of the outcomes of prevention studies. We downgraded the certainty of evidence mainly for imprecision (e.g. wide 95% CIs that included both beneficial and harmful effects, optimal information size (OIS) not reached) and various types of study limitations. This implies that uncertainty about the effectiveness of probiotics remains.

Potential biases in the review process

We performed a comprehensive search of several electronic databases; however we did not search for conference abstracts. Therefore, it is possible that we missed some unpublished trials or data. In an attempt to overcome this, we searched prospective trial registries. In addition, we performed study selection, data extraction, and risk of bias assessment in duplicate to prevent bias in the review process.

For studies that were retrieved, we could not obtain from publications all the data required to make judgements for all risk of bias items.

Agreements and disagreements with other studies or reviews

We found four similar systematic reviews that evaluated effects of prevention or treatment of diarrhoea or both for participants undergoing radiotherapy or chemotherapy. Authors of the oldest review found no differences between probiotics and control for prevention of diarrhoea or for treatment of radiotherapy- or chemotherapy-induced diarrhoea (Fuccio 2009). A second systematic review assessed the efficacy and safety of probiotics in people with cancer (Redman 2014). Review authors concluded that probiotics may reduce the severity and frequency of diarrhoea (both antibiotic-associated and chemotherapy-associated diarrhoea) and the requirement for antidiarrhoeal medication for patients with cancer. The third review reported an overall beneficial effect of probiotics for prevention of chemoradiotherapy-induced diarrhoea, especially grade 2 or higher (Wang 2016). The most recent review addressed the effects of probiotics for prevention of radiotherapy-induced diarrhoea (Liu 2017); review authors concluded that probiotics may be beneficial for preventing radiotherapy-induced diarrhoea. However, it is not clear what definition trial authors used for the outcome diarrhoea. Review authors included one extra, small study (apparently a conference abstract) that we did not identify, but they made no reference to this study in their report. In our review, we included one study - Mansouri-Tehrani 2016 - that was not (yet) identified by Liu 2017. Finally, we were more stringent in our risk of bias assessments and in refraining from pooling for some outcomes in the presence of heterogeneity.

AUTHORS' CONCLUSIONS

Implications for practice

Prevention of diarrhoea

Overall, available evidence regarding the use of probiotics to prevent radiotherapy- or chemotherapy-induced diarrhoea remains inconclusive. Randomised controlled trials (RCTs) could not deliver proof of clear benefit, as studies were underpowered or were at risk of bias. Moreover, for some outcomes, heterogeneity between studies was considerable and benefits, if any, were small.

However, for prevention of diarrhoea in patients receiving radiotherapy to the pelvis (without chemotherapy), investigators in a well-powered RCT have compared probiotics versus placebo. This study suggests that use of probiotics may decrease the incidence and severity of diarrhoea, and a recent small study has confirmed these results (TCTR20170314001). As in the other studies, these two studies observed no severe side effects of probiotics. Although

the first study had high risk of bias and the second study unclear risk of bias, based on these results, preventative probiotics could be considered for people undergoing radiotherapy, as associated adverse events are limited.

For prevention of chemotherapy-induced diarrhoea, results suggest that probiotics may prevent diarrhoea. However, no firm conclusions can be drawn because the included studies were very small, and only one was judged to be at low risk of bias.

Treatment of diarrhoea

Available evidence shows that the benefit of probiotics for treatment of radiotherapy-induced diarrhoea could be neither demonstrated nor refuted. For chemotherapy-induced diarrhoea, we found no evidence.

Implications for research

For prevention of chemotherapy- or radiotherapy-related diarrhoea, current evidence is of low to very low certainty. Future studies should be designed to minimise potential biases that have been inherent in previous studies and should ensure sufficient power by calculating a sample size in advance that also addresses the rate of loss to follow-up.

Currently available evidence is insufficient for judgement of the efficacy of probiotics for treatment of radiotherapy-induced diarrhoea. Future researchers may wish to focus on mild to moderate diarrhoea and probiotics as an add-on to more active treatment, and new studies should examine treatment for chemotherapy-induced diarrhoea.

All studies should adhere to CONSORT reporting guidelines to enable assessment of the design and conduct of studies, and consideration should be given to agreement on important core outcome sets, as different studies use different measures, introducing heterogeneity, which prevents meta-analysis. Agreed important core outcomes should be measured in a standardised way to allow pooling of results.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chen 2014

Methods	Study design: randomised controlled trial

Chen 2014 *(Continued)*

	Duration of the study, recruitment: 2006 to 2010 Country: China
Participants	Participants with colorectal cancer: age, mean ± SD: intervention group: 60.3 ± 17.2, control group: 59.8 ± 18.7
Interventions	Intervention (n = 35): combined *Clostridium butyricum* and *Bifidobacterium* capsule: 3 capsules, 3 times a day, administered from 5 days before to 7 days after surgery Control (n = 35): placebo All participants received intravenous chemotherapy (calcium folinate 300 mg, fluorouracil 500 mg) during surgery
Outcomes	Proportions of diarrhoea, all-cause mortality, several other clinical outcomes (first postoperative exhaust time, first defecation time, incidence of abdominal distension, incidence of systematic inflammatory response syndrome (SIRS), time of intraperitoneal catheter drain, incidence of infection of incisional wound, incidence of pulmonary infection, incidence of urinary tract infection, time of fever, incidence of hypoproteinaemia, length of consumption of antibiotics, length of hospital stay, side effects relevant to drug), biochemical indices
Notes	Article written in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random sequence was generated through a random number table
Allocation concealment (selection bias)	Unclear risk	No relevant information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled trial with similar packaging of capsules
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	Insufficient information for judgement
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	Five participants in each group were excluded because of metastasis or non-adherence to treatment strategy. Reasons for dropout were not specified per group
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Five participants in each group were excluded because of metastasis or non-adherence to treatment strategy. Reasons for dropout were not specified per group
Selective reporting (reporting bias)	Unclear risk	No study protocol was available, but all outcomes prespecified in the methods section were reported in the results section
Other bias	Low risk	No indications of other bias

Chitapanarux 2010

Methods	Study design: parallel-group RCT Duration of the study: 2007 to 2009 Median overall treatment time: 48 versus 51 days Country: Thailand
Participants	Participants aged ≥ 18 and ≤ 65 years old, with FIGO stage IIB to IIIB squamous cell carcinoma of the cervix, who were planned to receive standard treatment for locally advanced cervical cancer of external beam whole pelvis radiotherapy and brachytherapy plus weekly cisplatin 40 mg/m^2, with ECOG performance status 0 to 1 and negative anti-HIV status Stage of cervical cancer, n (%): • IIB: 17 (53.1) versus 18 (58.1) • IIIB: 15 (46.9) versus 13 (41.9) ECOG performance status, n (%): • 0: 24 (75.0) versus 29 (93.5) • 1: 8 (25.0) versus 2 (6.5) Median age, years: 47 versus 52 Sex: female "Age, stage of disease, performance status, and whole pelvis radiotherapy technique did not show any difference between the two groups"
Interventions	Intervention (n = 32): 2 × 10^9 units of *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* (equivalent to 2 capsules) 2 times a day before meals (morning and evening), beginning 7 days before the start of radiotherapy and continuing every day during radiotherapy Control (n = 31): identical-appearing placebo administered on the same schedule All participants were scheduled for external pelvic radiotherapy at a dose of 200 cGy per fraction, 5 fractions per week. All participants received weekly cisplatin 40 mg/m^2 for 6 weeks during radiotherapy
Outcomes	Occurrence of diarrhoea (graded weekly according to the Common Toxicity Criteria (CTC) system), need for antidiarrhoeal medication, stool consistency, white and red blood cell count in stool
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study, yet method of randomisation not described.
Allocation concealment (selection bias)	Low risk	"Pre-packaged (blinded) study medication differing solely in the patient numbers on the medication package was provided by the sponsor"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was described to be 'double-blind': neither the patient nor the treating physician knew if the patient was on study drug or placebo

Chitapanarux 2010 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment allocation: low risk for assessment of subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	All 63 participants were eligible and assessable
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	All 63 participants were assessed
Selective reporting (reporting bias)	Unclear risk	No study protocol was available, but all outcomes prespecified in the methods section were reported in the results section
Other bias	Low risk	No indications of other bias

Delia 2007

Methods	Study design: parallel-group RCT Duration of the study: 1995 to 2005 Follow-up: "The study subjects were followed up weekly during the scheduled cycle of radiation therapy and then 1 month after completion of radiation therapy" Country: Italy
Participants	Participants received adjuvant postoperative radiotherapy after surgery for sigmoid, rectal, or cervical cancers and had no contraindication for probiotic or antibiotic therapy or radiotherapy Median age, years: not reported Sex: not reported "The randomization was balanced between treatment groups in terms of sex, age, nodal involvement, tumor grade and size, local invasion at operation, invasion of contiguous structures at histology, and postoperative complications"
Interventions	Intervention (n = 245): VSL#3 (VSL Pharmaceuticals, Fort Lauderdale, MD) Control (n = 245): VSL#3-identical-appearing placebo Radiotharapy: total X-ray dose between 60 and 70 Gy
Outcomes	Incidence and severity of radiotherapy-induced diarrhoea, time from start of the study to use of loperamide as rescue medication, daily number of bowel movements
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Delia 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomised study, yet method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Double-blind, placebo-controlled trial: low risk for assessment of subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Double-blind, placebo-controlled trial: low risk for assessment of objective outcomes (mortality)
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	Intervention group (n = 2 dropouts): 1 participant withdrew his consent after the first session of radiotherapy, and 1 died of myocardial infarction after 3 sessions of radiotherapy; both participants were excluded from analysis of results Control group (n = 6 dropouts): 6 participants were withdrawn after a few sessions of radiotherapy owing to the occurrence of severe diarrhoea resistant to loperamide and the usual standard of care; these participants were excluded from analysis of results. No intention to treat
Incomplete outcome data (attrition bias) Objective outcomes	High risk	Intervention group (n = 2 dropouts): 1 participant withdrew his consent after the first session of radiotherapy, and one died of myocardial infarction after 3 sessions of radiotherapy; both participants were excluded from analysis of results Control group (n = 6 dropouts): 6 participants were withdrawn after a few sessions of radiotherapy owing to the occurrence of severe diarrhoea resistant to loperamide and the usual standard of care; these participants were excluded from analysis of results. No intention to treat
Selective reporting (reporting bias)	Unclear risk	No study protocol was available, but all outcomes prespecified in the methods section were reported in the results section
Other bias	Low risk	No indications of other bias

Demers 2014

Methods	Study design: placebo-controlled RCT, 3 parallel groups Duration of the study, recruitment: 2006 to 2010 Follow-up: maximum duration of follow-up was 10 weeks Country: Canada
Participants	Participants (≥ 18 years old) with pelvic (gynaecological, rectal, or prostate) cancer and ECOG performance status of 0 or 1 who were to receive radiotherapy treatments at a minimum of 40 Gy at the pelvic level, with or without chemotherapy

Demers 2014 *(Continued)*

	Exclusion criteria: previous radiotherapy treatment in the pelvic or abdominal region, medical history of gastrointestinal disorders, pregnancy, breastfeeding, neutropenia, probiotic intolerance Participant characteristics (standard dose versus higher dose versus placebo), n (%): • Prostate: 26 (32) versus 22 (37) versus 27 (30) • Endometrium: 10 (12) versus 5 (8) versus 11 (12) • Cervix: 8 (10) versus 4 (7) versus 14 (16) • Rectum: 36 (45) versus 24 (41) versus 36 (41) • Others: 1 (1) versus 4 (7) versus 1 (1) Mean age, years: 61.4 versus 62.0 versus 60.6 Male sex, n (%): 58 (72) versus 39 (66) versus 56 (63) "The data reveal that the participants were well distributed among groups and protocol fidelity exceeded 90% in each of the three groups"
Interventions	Intervention 1 (n = 91 randomised, n = 81 analysed): standard dose of double-strain Bifilact probiotics (*Lactobacillus acidophilus LAC-361* and *Bifidobacterium longum BB-536*) twice a day (1.3 billion CFU) Intervention 2 (n = 64 randomised, n = 59 analysed): high dose of double-strain Bifilact probiotics (*Lactobacillus acidophilus LAC-361* and *Bifidobacterium longum BB-536*) 3 times a day (10 billion CFU) Control group: placebo (n = 91 randomised, n = 86 analysed)
Outcomes	Proportion of participants with diarrhoea, quality of life (EORTC-QLQ-C30), need for antidiarrhoeal medication, number of bowel movements, abdominal pain, stool consistency, compliance, number of hospitalisations, number of treatment interruptions, and reduction in chemotherapy doses or radiotherapy treatments as a result of severe diarrhoea or abdominal pain
Notes	Trial registration: NCT01839721; number analysed in the control group (86) based on Table 2 of the study report

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were block-randomised by the research nurse according to the random list generated by blocks of 2, 4,or 6 patients, according to random permutations [...] another random block using higher probiotics dosage to the randomization was added with preservation of the double blind. New random lists were generated for each stratum with a 3:1:1 ratio (higher dose, standard dose, placebo) to compensate for the late start of the higher dose group"
Allocation concealment (selection bias)	High risk	"All the bottles had a similar appearance; they were all identified by the commercial brand Bifilact. Also the group, either A, B or C, was circled on that bottle, depending on whether that bottle belonged to the placebo group, standard dose group, or high dose group. Only the nurse knew the coding system, the nurse also assigned the patient to a group, according to the randomization list"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The two registered dieticians and caregivers were blinded to these processes to preserve the double blind" Participants were blinded as well
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	"The two registered dieticians and caregivers were blinded to these processes to preserve the double blind"

Demers 2014 *(Continued)*

		Participants were blinded as well
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	n = 17 dropped out before first radiotherapy (standard-dose group n = 10, high-dose group n = 5, placebo group n = 2) and were excluded from the analysis. Not clear whether this may have influenced the results n = 7 discontinued intervention (standard-dose group n = 1, high-dose group n = 3, placebo group n = 3); however all were analysed in the group to which they were randomised
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Survival status of 17 excluded participants was unknown
Selective reporting (reporting bias)	Low risk	Outcomes reported in publication correspond to outcomes prespecified in study protocol
Other bias	Low risk	No indication of other bias

Giralt 2008

Methods	Study design: placebo-controlled parallel-group RCT Duration of the study, recruitment: November 2002 to December 2005 Follow-up: 6 months Country: Spain
Participants	Female gender, age ≥ 18 years, good performance status (ECOG functional status < 2), and diagnosis of endometrial adenocarcinoma requiring postoperative pelvic RT or advanced cervical squamous cell carcinoma treated with pelvic RT and concomitant weekly cisplatin Primary tumour site: • Endometrium: 37/56 versus 37/62 • Cervix: 19/56 versus 25/62 ECOG performance status: • 0: 38/56 versus 45/62 • 1: 18/56 versus 17/62 Mean age, years (SD): 60.9 (11.8) versus 59.3 (12.8) Sex: all female "Both groups were well matched according to standard variables at baseline"
Interventions	Intervention (n = 44): 96 mL 3 times daily of a fermented liquid yogurt containing approximately 10^8 CFU/g of *Lactobacillus casei DN-114 001*, in addition to the standard starters *Streptococcus thermophilus* and *Lactobacillus delbrueckii*, subsp *bulgaricus* Control (n = 41): same amount of matching placebo, prepared by sterilising the active product with 4 kGy administered for 5 minutes

Giralt 2008 *(Continued)*

	Total radiation dose was 45 to 50 Gy, conventional fractionation. Participants with cervical cancer received a weekly intravenous dose of cisplatin 40 mg/m^2 during external beam RT. Antiemetic treatment was provided with 5-HT$_3$ blockers to maintain oral tolerability, as required
Outcomes	Reduction of the incidence of diarrhoea, defined by a Common Toxicity Criteria grade ≥ 2 or the need for loperamide
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was done in blocks and was stratified by tumour type
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled trial
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Double-blind, placebo-controlled trial: low risk for assessment of subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	118 participants were randomly allocated to the active product or placebo. Subsequent review determined that 33 of the total number of participants were ineligible and were excluded from the study. Of these 33 participants, 17 withdrew prematurely for personal reasons, 11 were excluded for protocol violations, and 5 were excluded for lack of compliance. The remaining 85 participants constituted the study group. Of these 85 participants, 44 received the active product, and 41 placebo
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Survival status of excluded participants not reported
Selective reporting (reporting bias)	Unclear risk	No study protocol was available, but all outcomes prespecified in the methods section were reported in the results section
Other bias	Low risk	No indications of other bias

Liu 2000

Methods	Study design: randomised cross-over trial Duration of the study, recruitment: no information Country: China

Liu 2000 *(Continued)*

Participants	22 participants with cancer (8 with lung cancer, 5 with gastric cancer, 4 with colorectal cancer, 4 with breast cancer, 1 with neck metastatic carcinoma) 13 males and 9 females Age, median (range): 59 (35 to 73) years
Interventions	Intervention (n = 11): *Bifidobacterium* combined with chemotherapy Control (n = 11): chemotherapy alone *Bifidobacterium* capsule (2 capsules per time, 2 times a day) was taken from 1 day before chemotherapy to the sixth day of chemotherapy in each phase. Length of the washout period was about 21 days
Outcomes	Severity of diarrhoea
Notes	Article written in Chinese

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	During the control phase, no treatment was provided
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	No details provided
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	No loss to follow-up
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	No study protocol available; however all outcomes prespecified in the methods section were reported in the results section
Other bias	High risk	Cross-over design ignored in the analyses

Mansouri-Tehrani 2016

Methods	Study design: placebo-controlled RCT with 3 parallel groups

Mansouri-Tehrani 2016 *(Continued)*

	Duration of the study, recruitment: October 2012 to May 2013 Follow-up: 5 weeks Country: Iran
Participants	78 participants between 20 and 85 years of age with diagnosis of pelvic cancer (colorectal, prostate, endometrial, bladder, ovarian, cervical, bone sarcoma) who were about to receive radiotherapy (11 participants dropped out) Exclusion criteria: opioid usage, antimicrobial treatment, presence of any acute or chronic gastrointestinal condition associated with diarrhoea for ≥ 1 month before inclusion Mean age ± SD: 63.7 ± 15.1 versus 57.9 ± 17.5 versus 64.2 ± 11.7 years Male/female: 14/8 versus 8/13 versus 17/7 Cancer site, n: • Colorectal: 6 versus 9 versus 9 • Prostate: 6 versus 3 versus 6 • Endometrium: 3 versus 5 versus 2 • Bladder: 4 versus 0 versus 4 • Ovary: 2 versus 1 versus 1 • Cervix: 1 versus 1 versus 2 • Bone sarcoma: 0 versus 2 versus 0
Interventions	Probiotics: 'LactoCareOD' (Zist Takhmir Company, Tehran, Iran) containing *Lactobacillus casei* 1.5 × 10^9 CFU, *Lactobacillus acidophilus* 1.5 × 10^{1o} CFU, *Lactobacillus rhamnosus* 3.5 × 10^9 CFU, *Lactobacillus bulgaricus* 2.5 × 10^8 CFU, *Bifidobacterium breve* 1 × 10^{1o} CFU, *Bifidobacterium longum* 5 × 10^8 CFU, and *Streptococcus thermophilus* 1.5 × 10^8 CFU per 500 mg Intervention group 1 (n = 22): 2 probiotic capsules per day after consumption of 150 grams of low-fat yogurt Intervention group 2 (n = 21): 2 probiotic capsules and 30 grams honey per day after consumption of 150 grams of low-fat yogurt and 15 grams of honey at night Placebo group (n = 24): 2 placebo capsules per day after consumption of 150 grams of low-fat yogurt All participants received conventional radiotherapy for 4 to 5 weeks (total dose from 4000 to 5000 cGy (1.8 Gy/d))
Outcomes	Severity of diarrhoea according to the Common Toxicity Criteria of the National Cancer Institute, stool consistency according to an adapted Bristol Scale, daily number of bowel movements, need for antidiarrhoeal medication, bloating
Notes	Trial registration: IRCT2015030421338N1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A randomized, placebo-controlled study was performed"/"Simple randomization was used to allocate patients to three groups"
Allocation concealment (selection bias)	Unclear risk	No details provided

Mansouri-Tehrani 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	No details provided, but group 1 received probiotics and group 3 (control group) received similar medication with placebo capsules
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	"The patients evaluated for the daily number of bowel movement (defecation), diarrhea grade, stool consistency score, the need for antidiarrheal medication and bloating weekly by one person" Not sure whether this person was unaware of the treatment group
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	Double-blind, placebo-controlled trial: low risk for assessment of objective outcomes (mortality)
Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	"Among 78 patients involved in this study, 11 patients were excluded for failure to follow up" Reasons for dropout and intervention group of dropouts not presented
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	"Among 78 patients involved in this study, 11 patients were excluded for failure to follow up" Reasons for dropout and intervention group of dropouts not presented
Selective reporting (reporting bias)	Low risk	Outcomes presented according to trial registration form (IRCT2015030421338N1); laboratory outcomes reported in another paper
Other bias	Low risk	No indications of other bias

Mego 2015

Methods	Study design: placebo-controlled RCT, conducted at 6 cancer centres Duration of the study, recruitment: between January 2011 and December 2013 Follow-up: not reported Country: Slovakia
Participants	Inclusion criteria: age ≥ 18 years, histologically proven colorectal cancer, starting new line of chemotherapy based on irinotecan, ECOG performance status 0 or 1, life expectancy > 3 months; no psychological, familial, sociological or geographical condition potentially hampering compliance with study protocol and follow-up schedule Exclusion criteria: impossible to take oral medication, active infection treated by antibiotic therapy, ileostomy, hypersensitivity to study drug, any concurrent malignancy other than non-melanoma skin cancer, other cancer in past 5 years, serious concomitant systemic disorders or diseases incompatible with the study (at the discretion of investigator) Median age (range): 62 (45 to 75) versus 64 (42 to 81) years Male gender, n (%): 14 (60.9) versus 12 (52.2) Primary tumour site, n (%): • Colon 16 (69.6) versus 12 (52.2) • Rectum 7 (30.4) versus 11 (47.8) Karnofsky performance status, n (%): • 100%: 13 (56.5) versus 11 (47.8)

Mego 2015 *(Continued)*

- 90%: 8 (34.8) versus 8 (34.8)
- 80%: 2 (8.7) versus 3 (13.0)

Type of chemotherapy, n (%):

- Irinotecan weekly: 14 (60.9) versus 14 (60.9)
- Irinotecan every 2 or 3 weeks: 9 (39.1) versus 9 (39.1)
- 5-Fluorouracil: 12 (52.2) versus 12 (52.2)
- Capecitabine: 0 (0) versus 2 (8.7)

Biological therapy, n (%):

- Cetuximab: 4 (17.4) versus 5 (21.7)
- Bevacizumab: 6 (26.1) versus 7 (30.4)

Interventions	Intervention (n = 23): probiotic formula Colon Dophilus™ (produced by Harmoniom International, Inc., Mirabel, Canada) 3*1 capsule per day orally for 12 weeks "Each capsule contained $10*10^9$ CFU of bacteria. Each capsule contained 10 lyophilized probiotic strains including *Bifidobacterium breve HA-129* (25%), *Bifidobacterium bifidum HA-132* HA (20%), *Bifidobacterium longum HA-135* (14.5%), *Lactobacillus rhamnosus HA-111* (8%), *Lactobacillus acidophilus HA-122* (8%), *Lactobacillus casei HA-108* (8%), *Lactobacillus plantarum HA-119* (8%), *Streptococcus thermopilus HA-110* (6%), *Lactobacillus brevis HA-112* (2%), *Bifidobacterium infantis HA-116* (0.5%)" Control (n = 23): placebo Participants received full supportive care during irinotecan-based chemotherapy including antidiarrhoeal drugs (loperamide, diphenoxylate/atropine) treatment, antiemetics, and analgesics when appropriate as a standard of care
Outcomes	Grade 3 or 4 toxicity or SAE-related toxicity according to NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) Any grade gastrointestinal symptoms (enteritis, colitis, constipation, abdominal distension, bloating, flatulence, gastritis, dyspepsia, nausea, vomiting) according to NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE)
Notes	Trial registration: NCT01410955

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were centrally randomised in ratio 1:1" "Participants were allocated to one of the treatment groups (probiotic or placebo) based on preformed randomization table" "Random allocation sequence was generated using random number table. Participants were stratified according to center, treatment with cetuximab, and irinotecan regimen (weekly versus every 2 to 3 weeks)"
Allocation concealment (selection bias)	Low risk	"After signing of informed consent, each patient received study number and investigator called to randomization center" "Investigator received the identification number of containers for randomised patient, and patient received corresponding containers" "Patients, investigators and statisticians were blinded to treatment allocation. All containers with probiotics/placebo looked the same and were sequentially numbered"

Mego 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients, investigators and statisticians were blinded to treatment allocation. All containers with probiotics/placebo looked the same and were sequentially numbered"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	No loss to follow-up
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the prospective trial register seem to have been presented (although it is not clear whether the 2-year time frame was applied)
Other bias	Low risk	"The study was prematurely terminated due to slow accrual, when only 49 of 220 planned participants were accrued"

Osterlund 2007

Methods	Study design: open-label, prospective, randomised, single-institution, 2 × 3 factorial design study Duration of the study, recruitment: November 1997 to August 2001 Follow-up: 4-weekly during chemotherapy and radiotherapy and at protocol-determined intervals (ranging from 2 to 6 months) post treatment Country: Finland
Participants	Study participants had either Dukes' B or C colorectal cancer (n = 126) or metastatic colorectal cancer that had been rendered free from all overt metastases by surgery (Dukes' D; n = 24) Site, n (%) • Colon: 59 (60) • Rectum: 39 (40) Dukes' stage, n (%) • B: 27 (28) versus 13 (25) • C: 55 (56) versus 31 (60) • D*: 16 (16) versus 8 (15) *Patients were rendered free from all macroscopic cancer by surgery Median age, years (range): 60 (31 to 75) Sex (M/F): 51/47 versus 25/27

Osterlund 2007 *(Continued)*

	"The treatment arms were balanced with gender, the WHO performance status, primary tumour site, Dukes' stage, and radiation therapy given"
Interventions	Intervention (n = 98):*Lactobacillus rhamnosus GG* (administered orally as gelatin capsules twice daily at a dose of 1 to 2 × 10^{10} per day during 24 weeks of adjuvant cancer chemotherapy Control (n = 52): guar gum containing nutritional supplement (contains 11 g guar gum and 550 kcal or 2300 kJ), administered daily, on cycle days 7 to 14, for 8 days per month Chemotherapy: monthly 5-FU and leucovorin bolus injections (the Mayo regimen) or a bimonthly 5-FU bolus plus continuous infusion (the simplified de Gramont regimen) for 24 weeks as postoperative adjuvant therapy. Pelvic radiotherapy for rectal cancer was administered to a total cumulative dose of 50.4 Gy in 1.8-Gy daily fractions over 5.5 weeks (except for participants who underwent abdominoperineal resection, when the dose was limited to 45 Gy). All participants received dietary counselling
Outcomes	Frequency of grade 3 and 4 diarrhoea; treatment-related adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation to study treatments was performed by a computerised minimisation technique and 1 out of 6 chances. Participants were randomly allocated at a 1:1 ratio to receive the simplified de Gramont regimen or the Mayo regimen as adjuvant chemotherapy. Participants were also randomly assigned to receive or not receive at a 2:1 ratio *Lactobacillus rhamnosus GG* and at a 1:2 ratio fibre-containing nutritional support (guar gum)
Allocation concealment (selection bias)	Low risk	"The allocation group was concealed until interventions had been assigned" Yet, not described how
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The study was not placebo-controlled nor blinded to administration of the dietary supplements"
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	"The study was not placebo-controlled nor blinded to administration of the dietary supplements, which may or may not have influenced assessment of subjective outcomes such as adverse effects"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	None of the participants were lost to follow-up: study was analysed according to the intention-to-treat principle. Sixteen (11%) subjects did not complete the scheduled 6 months of adjuvant chemotherapy because of adverse events (n = 7, 6 of whom received bolus 5-FU), cancer recurrence (n = 5), or concomitant disease (n = 4). Two participants (both in the continuous 5-FU group) who did not receive any of the study treatments owing to postoperative complications were not included in safety or efficacy analyses, leaving 148 participants for inclusion in these analyses
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	No participants were lost to follow-up

Osterlund 2007 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	"Outcome was analysed as defined in the study protocol" No study protocol was available, but all outcomes prespecified in the methods section were reported in the results section
Other bias	Low risk	No indications of other bias

Salminen 1988

Methods	Study design: 2-group parallel RCT Duration of the study: not reported; follow-up until 6 weeks after completion of treatment Country: Finland
Participants	Participants with the diagnosis of cervix or uterus carcinoma were included in this study Age: 40 to 75 years Sex: female
Interventions	Intervention (n = 11): both dietary counselling and a daily dose of ≥ 2×10^9 live *Lactobacillus acidophilus* bacteria in the form of a yogurt-type product 150 mL of the product daily for 5 days before radiotherapy, daily throughout the radiotherapy period including the interval, and then for 10 days after completion of the therapy regimen Control (n = 10): dietary counselling only Sum of internal and external radiation was 8000 cGy for the tumour and 5000 cGy for the pelvic area
Outcomes	Frequency and severity of radiotherapy-induced diarrhoea, intestinal side effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised study, yet method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding: probably not performed
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	No information on blinding: probably not performed. High risk of detection bias for subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced

Salminen 1988 *(Continued)*

Incomplete outcome data (attrition bias) Subjective outcomes	Unclear risk	Two participants were excluded from the control group because of changes in the radiotherapy regimen. One participant from the test group was excluded because she had no pause during radiotherapy. All other participants in the test group tolerated the yogurt treatment well and completed the prescribed treatment regimen Owing to the relatively large numbers of dropouts in this small study, we scored 'unclear'
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Owing to the relatively large numbers of dropouts in this small study, we scored 'unclear'
Selective reporting (reporting bias)	Unclear risk	Study was published in 1988, and no study protocol is available. Yet, all outcomes prespecified in the methods section were reported in the results section
Other bias	Unclear risk	No baseline characteristics are reported in Table 1. As treatment groups are small, baseline differences could have been present by chance

Timko 2010

Methods	Study design: randomised parallel-group non-placebo-controlled trial Duration of the study, recruitment: June 2005 to March 2006 Country: Slovakia
Participants	Oncology participants underwent adjuvant postoperative radiotherapy in the abdominal and pelvic region, with or without chemotherapy. Absence of gastrointestinal disorders Median age, years (range): 62 (34 to 82) versus 67 (43 to 83) Sex (male/female): 12/10 versus 16/4
Interventions	Intervention (n = 22): L-Group - Probiotic preparation "5"-strain Dophilus (55% *Lactobacillus rhamnosus*, 20% *Bifidobacterium adolescentis*, 5% *Lactobacillus acidophilus*, 5% *Bifidobacterium longum*, 15% *Enterococcus faecium*) with a count of 6 billion active bacteria/capsule at a daily dosage of 2 × 1 capsule Control (n = 20): H-Group - Hylak Tropfen Forte preparation (i.e. cell-free fermentation products of *Lactobacillus helveticus* and gut symbionts (100 mL containing 24.95 g *Escherichia coli* metabolita, 12.5 g *Streptococcus faecalis* metabolita, 12.5 g *Lactobacillus acidophilus* metabolita, 49.9 g *Lactobacillus helveticus* metabolita)) at a dose of 40 drops, 3 times per day Radiation total cumulative dose of 50 Gy (2 Gy/d). High-risk patients (e.g. patients with prostate cancer) received dosage of 6567 Gy (2 Gy/d)
Outcomes	Incidence and severity of radiotherapy-induced diarrhoea
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Timko 2010 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomised study, yet method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No information on blinding: probably not performed; no placebo had been used
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	No information on blinding and no placebo: probably not performed. High risk of detection bias for subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	High risk	During RT, 27% of participants in L-Group required diphenoxylate treatment compared with 55% in H-Group, and 9% in L-Group needed administration of antibiotics compared with 25% in H-Group. As we could not estimate the way in which these treatments influenced the composition of intestinal bacterial flora, we excluded these participants from our comparisons
Incomplete outcome data (attrition bias) Objective outcomes	Unclear risk	Survival status of excluded participants was unknown
Selective reporting (reporting bias)	Unclear risk	No study protocol was available, but all outcomes prespecified in the methods section were reported in the results section
Other bias	High risk	Treatment arms were not balanced by gender and primary tumour site

Urbancsek 2001

Methods	Study design: randomised, double-blind, parallel-group design Duration of the study: August 1996 to end of June 1998 Country: Hungary
Participants	People with cancer in the age range 19 to 75 years developing diarrhoea within 4 weeks after receiving radiotherapy (median cumulative radiation dose 50 Gy per patient) in the abdominal region, patients with clinical evidence of severe diarrhoea-induced dehydration, and patients with bloody diarrhoea were not eligible Mean age, years (range): 59 (28 to 81) versus 60 (33 to 86) Sex, % (male/female): 25/75 versus 26/76
Interventions	Intervention (n = 102): *Lactobacillus rhamnosus* (Antibiophilus, each sachet containing 1.5 g of *Lactobacillus rhamnosus* equivalent to 1.5×10^9 CFU) 3 times a day Control (n = 103): identical-appearing sachets of placebo, each containing 700 mg corn starch, 797 mg microcrystalline cellulose, 1.37 mg iron oxide, 1.13 mg dispersed orange (colouring agent), and 1 mg caramel aroma, 3 times a day

Urbancsek 2001 *(Continued)*

Outcomes	Time to and frequency of rescue medication per participant. Documentation of any possible adverse reactions was provided on a volunteer basis. Secondary efficacy endpoints included average number of daily bowel movements, diarrhoea grading, and faeces consistency ratings
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised study, yet method of randomisation not described
Allocation concealment (selection bias)	Low risk	Pre-packaged (blinded) study medication differing solely in patient numbers on the medication package was provided to investigators by the sponsor
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was described to be 'double-blind': neither the patient nor the treating physician knew if the patient was receiving study drug or placebo
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	Participants were blinded to treatment allocation: low risk for assessment of subjective outcomes
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	No information; however it is unlikely that assessment of objective outcomes (mortality) would have been influenced
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	Intention-to-treat analysis was performed
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	Intention-to-treat analysis was performed
Selective reporting (reporting bias)	Unclear risk	No study protocol is available, but all outcomes prespecified in the methods section were reported in the results section
Other bias	Low risk	No indications of other bias

5-FU: 5-fluorouracil
5-HT_3: 5-hydroxytryptamine receptor
CFU: colony-forming units
CTC: Common Toxicity Criteria
CTCAE: Common Terminology Criteria for Adverse Events
ECOG: Eastern Cooperative Oncology Group
EORTC-QLQ-C30: questionnaire developed to assess the quality of life of patients with cancer
FIGO: International Federation of Gynaecology and Obstetrics
NCI: National Cancer Institute
RCT: randomised controlled trial
RT: radiotherapy
SAE: serious adverse event
SD: standard deviation
SIRS: systemic inflammatory response syndrome
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amital 2003	Editorial
Aso 1995	Study about prophylaxis for recurrence of superficial bladder cancer
Delia 2002	No RCT
Delia 2002a	Letter to the editor
Dugas 1999	No RCT
Fuccio 2012	Irrelevant to our review question; no RCT
Fuccio 2013	Letter to the editor
Garcia-Peris 2016	Comparison of prebiotics versus placebo
Horowitz 2003	No RCT
Lacouture 2016	Combined intervention of probiotic and topical alclometasone that was not randomly allocated
Liu 2011	Participants receiving preoperative chemotherapy or radiotherapy were excluded
Liu 2013	Participants receiving preoperative chemotherapy or radiotherapy were excluded
Marteau 2001	Irrelevant to our review question
Marteu 2001	Narrative review
McFarland 1994	Population irrelevant to our review question
Mettler 1973	No RCT
Narayan 2010	Not cancer-related diarrhoea; no RCT
Ohigashi 2011	No RCT
Okawa 1989	Outcomes irrelevant to our review question
Osterlund 2004	Comparison not of interest
Sasidharan 2016	Prebiotics
Visich 2010	No RCT
Zheng 2006	Children

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Theodoropoulos 2013

Methods	Single-centre double-blind RCT
Participants	Participants underwent colectomy for cancer No mention of participants undergoing chemotherapy or radiotherapy
Interventions	Synbiotics (combination of prebiotics and probiotics) (n = 38) Placebo (n = 35) Administration at the day participants were able to tolerate PO liquid diet and for 15 days thereafter
Outcomes	Primary endpoints: gastrointestinal function-related quality of life at 1, 3, and 6 months postoperatively (using validated questionnaire GIQLI (Gastrointestinal Quality of Life Index)) Secondary endpoints: assessment of functional bowel disorders (diarrhoea, constipation) based on respective domains of the validated instrument EORTC-QLQ-C30
Notes	Clintrial.Gov trial ID NCT01479907 No mention of participants undergoing chemotherapy or radiotherapy Trial may be excluded in a future update

EORTC-QLQ-C30: questionnaire developed to assess the quality of life of patients with cancer, version 3.
GIQLI: Gastrointestinal Quality of Life Index.
PO: by mouth.
RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2015-000868-34-DE

Trial name or title	Study for investigating the effects of a probiotic on diarrhea caused by chemotherapy in patients with gastric, colon, and rectum cancer
Methods	Allocation: randomised controlled trial Control: placebo Study endpoint classification: efficacy study Intervention model: parallel Number of arms: 2 Masking: double-blind (masked roles: subject, investigator, outcomes assessor) Primary purpose: prevention Study phase: 3
Participants	Gastric or colorectal cancer, for which treatment with 5-fluorouracil and 1 further chemotherapeutic remedy (irinotecan or a platinum-based chemotherapeutic remedy) is planned Inclusion criteria: • Male or female adults; patients with gastric or colorectal cancer (stage III or IV), for which treatment with 5-fluorouracil and 1 further chemotherapeutical remedy (irinotecan or a platinum-based chemotherapeutical remedy) is planned • Addition of bevacizumab antibody is allowed as well; life expectancy of at least the trial duration

EUCTR2015-000868-34-DE *(Continued)*

	• First administration of the product under investigation must take place 72 hours before or after the beginning of the chemotherapeutical treatment, ideally at the same time • Inclusion into the study is possible only at the beginning of the first chemotherapeutic cycle • Fertile female patients (aged 49 years or younger, last menstruation occurred within last 2 years), surgically sterilised or using the same highly effective method of contraception for ≥ 3 months • Willingness to refrain from other probiotics or probiotic yogurts; a systematic change in eating behaviour should not be planned • Sufficient knowledge of German language and sufficient psychological state to complete questionnaires and assessment scales • Informed written consent Exclusion criteria: • Participation in other clinical trials (currently or within past 30 days) • Intolerance against ingredients of the product under investigation; pregnancy or lactation • Not able to orally consume the product under investigation • Antidiarrhoeal therapy with antibiotics • Alcohol or drug abuse within past 6 months • Any health condition (including abnormal blood parameters) that prevents patient from taking part in the study according to the opinion of the investigator
Interventions	Intervention group: Mutaflor Suspension. Oral suspension Placebo group: oral suspension
Outcomes	Primary outcome measures: • Common toxicity criteria (CTC) for diarrhoea Secondary outcome measures: • Quality of life (according to SF-12 and FACIT-D) • Stool consistency according to the Bristol Stool Scale • Anthropometry (body mass index (BMI)) • Bioelectrical impedance analysis (BIA) • Blood parameters (C-reactive protein, haematocrit) • Stool parameters (α1-antitrypsin, calprotectin)
Starting date	ClinicalTrials.gov Identifier: EUCTR2015-000868-34-DE Study start date: 9 April 2015
Contact information	Contact: Clinical Trials Information info@zkes-gmbh.de
Notes	

NCT00197873

Trial name or title	Randomised, double-blind, placebo-controlled, cross-over phase II study on the effects of *Lactobacillus rhamnosus GG* supplementation in patients on 1st line XELOXA treatment for metastatic colorectal cancer
Methods	Allocation: randomised Endpoint classification: efficacy study

NCT00197873 *(Continued)*

	Intervention model: cross-over assignment Masking: double-blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: prevention
Participants	Estimated enrolment: 84 Ages eligible for study: ≥ 18 years (adult, senior) Genders eligible for study: both Accepts healthy volunteers: no Inclusion criteria: • Patients with histologically confirmed diagnosis of CRC, chemotherapy naïve for metastatic disease (prior adjuvant chemotherapy for CRC allowed), scheduled to start capecitabine treatment as first-line chemotherapy for metastatic disease • Age ≥ 18 years • Measurable or non-measurable metastatic disease • ECOG performance status 0 to 2 • Life expectancy > 3 months • Thrombocytes ≥ 100,000/µL, neutrophils ≥ 1500/µL, aspartate amino transferase/alanine amino transferase ≤ 2.5 × upper limit of normal (ULN) (< 5 × ULN if liver metastases present), alkaline phosphatase ≤ 2.5 × ULN (< 5 × ULN if liver metastases present), serum bilirubin ≤ 1.5 × ULN, serum creatinine ≤ 1.5 × ULN, urine dipstick of proteinuria < 2+ (or U-Prot < 100 mg/dL). Patients discovered to have 2+ or greater proteinuria on dipstick urinalysis at baseline must undergo a 24-hour urine collection and must have ≤ 1 g of protein/24 hours • Women of childbearing potential must have a negative serum pregnancy test done before administration of bevacizumab. Patients and their partners should prevent pregnancy (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) up to at least 6 months after last treatment completion or last drug dose, whichever happens first • Signed written informed consent according to ICH/GCP and local regulations (approved by independent ethics committee (IEC)) will be obtained before any study-specific screening procedures are performed • Patient must be able to comply with the protocol Exclusion criteria: • Prior treatment with first-line chemotherapy for metastatic CRC • Adjuvant treatment with bevacizumab within 12 months • Acute or chronic diarrhea or colostomy • Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before day 0 (patients must have recovered from any major surgery) • Near future planned radiotherapy for underlying disease (prior completed radiotherapy treatment allowed) • Clinical or radiological evidence of CNS metastases • Past or current history within past 5 years of malignancy, except for the indication under this study and curatively treated basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix • Serious non-healing wound or ulcer • Evidence of bleeding diathesis or coagulopathy • Uncontrolled hypertension • Clinically significant (i.e. active) cardiovascular disease, for example, cerebrovascular accidents (≤ 6 months), myocardial infarction (≤ 6 months), unstable angina, New York Heart Association (NYHA) grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication

NCT00197873 *(Continued)*

	• Treatment with any investigational drug (including IMMP, EGFR inhibitors) or participation in another investigational study within 30 days before enrolment • Evidence of other disease, metabolic dysfunction, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates the treatment, or patient at high risk of treatment complications • Ongoing treatment with aspirin (> 325 mg/d), continuous high-dose NSAIDs or other medications known to predispose to gastrointestinal ulceration • Pregnancy (positive serum pregnancy test) and lactation • Any other serious or uncontrolled illness that, in the opinion of the investigator, makes it undesirable for the patient to enter the trial
Interventions	*Lactobacillus rhamnosus* supplementation: *Lactophilus* supplementation is administered during chemotherapy Placebo is administered during chemotherapy
Outcomes	Primary outcome measures: effect on treatment-related grade 2 to 4 diarrhoea [Time Frame: 18 weeks] [Designated as safety issue: No] Secondary outcome measures: effect on treatment-related toxicity other than diarrhoea [Time Frame: 18 weeks] [Designated as safety issue: No] Association between supplementation and response [Time Frame: 18 weeks] [Designated as safety issue: No] • Effect on resectability of liver metastases [Time Frame: 1 year] [Designated as safety issue: No] • Effect on serum growth factor levels [Time Frame: 18 weeks] [Designated as safety issue: No]
Starting date	ClinicalTrials.gov Identifier: NCT00197873 Study start date: September 2005 Estimated primary completion date: October 2016
Contact information	Heikki Joensuu, Professor, Helsinki University
Notes	

NCT01790035

Trial name or title	A phase I and randomised controlled phase II trial of the probiotic LGG for prevention of side effects in patients undergoing chemoradiation for gastrointestinal cancer
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double-blind (subject, investigator) Primary purpose: treatment
Participants	Estimated enrolment: 120 Ages eligible for study: ≥ 18 years (adult, senior) Genders eligible for study: both

NCT01790035 *(Continued)*

Accepts healthy volunteers: no

Inclusion criteria:

- Current diagnosis of a gastrointestinal, abdominal, or pelvic cancer for which the use of continuous definitive or adjuvant external beam RT to the abdomen or pelvis at a minimum dose of 4500 cGy is planned
- Scheduled to receive concurrent administration of fluoropyrimidine chemotherapy (5-FU or capecitabine) during radiotherapy
- Age ≥ 18 years
- Life expectancy ≥ 6 months
- Negative pregnancy test done ≤ 7 days before registration (for women of childbearing potential only)
- The following laboratory values obtained ≤ 28 days before registration: haemoglobin ≥ 9.0 g/dL, WBC ≥ 3500, absolute neutrophil count ≥ 1500, platelets ≥ 100,000
- ECOG performance status (PS) 0, 1, or 2
- Willingness to abstain from ingestion of yogurt products and/or any product containing probiotics during study drug treatment
- Ability to complete questionnaire(s) alone or with assistance
- Ability to understand and willingness to sign informed consent

Exclusion criteria:

- Previous bowel resection, which, in the opinion of the investigator, would decrease the benefit of the probiotic. Patients who have undergone recent bowel surgeries that would not decrease the benefit of the probiotic are eligible provided they are more than 30 days from surgery with no serious complications
- Known allergy to a probiotic preparation
- Any history of inflammatory bowel disease
- Grade 3 or 4 diarrhoea, rectal bleeding, abdominal cramping, or incontinence of stool ≤ 7 days before registration
- Any medical condition that may interfere with ability to receive protocol treatment
- Prior abdominal or pelvic RT
- Use of probiotics ≤ 2 weeks before registration
- Use of antibiotics ≤ 3 days before registration
- Planned continuous antibiotic treatment during RT
- History of gastrointestinal or genitourinary obstruction or porphyria
- History of irritable bowel syndrome (IBS)
- History of hypersensitivity to all of the following antibiotics: penicillin, erythromycin, clindamycin, and any fluoroquinolone

Interventions	Intervention: LGG Comparator: placebo

Outcomes	Primary outcome measures:
	
	• Efficacy (randomised phase II trial) [Time Frame: Up to 6 months following the last dose of LGG or placebo] [Designated as safety issue: No]
	  ◦ Compare the proportion of patients receiving abdominal or pelvic chemoradiation with a fluoropyrimidine treated with the probiotic LGG who develop CTCAE grade 2 or greater diarrhea to the proportion of patients receiving abdominal or pelvic chemoradiation with a fluoropyrimidine treated with placebo who develop CTCAE grade 2 or greater diarrhoea
	• Safety (phase I safety lead-in) [Time Frame: Up to 30 days following completion of treatment] [Designated as safety issue: Yes]
	  ◦ Determine the safety and tolerability of LGG in patients receiving abdominal or pelvic chemoradiation with a fluoropyrimidine. The DSMC will review the data as part of an interim analysis when the last patient has had 30 days of follow-up. The DSMC will ensure that ≥ 18 participants

NCT01790035 *(Continued)*

	have had follow-up at 30 days (with expected 10% dropout). Accrual to the randomised portion of the trial will occur only if there are no episodes of *Lactobacillus*-associated septicaemia. Additionally, if ≥ 2 serious adverse events of a similar nature occur and a causal relationship to the investigational product cannot be excluded, accrual to the randomised portion will not occur
	
	Secondary outcome measures:
	
	• Diarrhoea subscale score [Time Frame: Up to 5 years after completion of treatment] [Designated as safety issue: No]
	  ◦ Average AUC of the FACIT-D diarrhoea subscale scores will be compared between the 2 treatment groups using a 2-sample t-test. The FACIT-D will be completed at baseline, weekly during radiotherapy, for the 2 weeks following completion of radiotherapy, 12 months following the end of radiotherapy, and at years 2 to 5 following completion of radiotherapy
	• Need for antidiarrhoeal medication [Time Frame: Up to 2 weeks after completion of treatment] [Designated as safety issue: No]
	  ◦ Need for use of an antidiarrhoeal medication (loperamide) will be evaluated at a binary endpoint (Use or No Use). Comparison will be made using Fisher's exact test as previously described (Chitapanarux 2010)
	• Grade 3 or greater diarrhoea [Time Frame: Up to 6 months following the last dose of LGG or placebo] [Designated as safety issue: No]
	  ◦ In patients receiving abdominal or pelvic chemoradiotherapy with a fluoropyrimidine, compare the proportion of patients who develop diarrhoea ≥ grade 3 (by CTCAE version 4.0) among those treated with the probiotic LGG to the proportion of those receiving placebo
	• Fecal calprotectin [Time Frame: Up to 2 weeks following the completion of treatment] [Designated as safety issue: No]
	  ◦ Determine whether faecal calprotectin correlates with onset, duration, and/or severity of diarrhoea during chemoradiotherapy
	• Serum citrulline [Time Frame: Up to 2 weeks following the completion of treatment] [Designated as safety issue: No]
	  ◦ Determine whether serum citrulline correlates with onset, duration, and/or severity of diarrhoea during chemoradiotherapy

Starting date	ClinicalTrials.gov Identifier: NCT01790035 Study start date: August 2014 Estimated primary completion date: October 2021
Contact information	Matthew Ciorba, MD; 314-362-9054; mciorba@wustl.edu
Notes	

NCT02169388

Trial name or title	Effects of gut microflora on the immune and nutritional status of CRC patients after chemotherapy
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double-blind (subject, caregiver, investigator) Primary purpose: supportive care
Participants	Estimated enrolment: 30 Ages eligible for study: 18 to 80 years (adult, senior)

NCT02169388 *(Continued)*

	Genders eligible for study: both Accepts healthy volunteers: no Inclusion criteria: • Scheduled for chemotherapy after radical resection of colorectal cancer Exclusion criteria: • Palliative resection of colorectal cancer • Antibiotic, probiotic, or prebiotic usage within 1 month • Other malignancy • History of other abdominal surgery • Coagulopathy or bleeding disorders • Pregnant or breast-feeding (for females) • Impaired liver or renal function
Interventions	Experimental: probiotic (microbial composition using probiotic, 3 capsules/times, 2 times/d for 4 weeks) Placebo comparator: placebo (Microbiota modulation using placebo, 3 capsules/times, 2 times/d for 4 weeks)

Outcomes	Primary outcome measures:
	
	• Composition of micro-organisms in stool after probiotic intervention [Time Frame: 5 months] [Designated as safety issue: No]
	  ◦ Primary coordination of faecal samples: 16s rDNA (ribosomal DNA) will be compared between 2 groups using Bray-Curtis distance-based primary co-ordination analysis (PCoA)
	• Short-chain fatty acids in faeces of patients after chemotherapy [Time Frame: 5 months] [Designated as safety issue: No]
	  ◦ The total concentration of short-chain fatty acids in the faeces of patients after chemotherapy
	• Frequency and severity of adverse effects during chemotherapy [Time Frame: 5 months] [Designated as safety issue: No]
	  • Adverse effects include vomiting, nausea, diarrhoea, and abdominal pain
	
	Secondary outcome measures:
	
	• Observed changes in immune status after chemotherapy [Time Frame: 5 months] [Designated as safety issue: No]
	  ◦ Immune status indexes include percentage of neutrophils, total lymphocytes, lymphocyte subgroups, plasma immunoglobulin level, CRP (C-reactive protein)
	• Observed changes in nutritional status after chemotherapy [Time Frame: 5 months] [Designated as safety issue: No]
	  ◦ Nutritional status indexes include BMI, percentage of body weight changes, plasma albumin, and prealbumin

Starting date	ClinicalTrials.gov Identifier: NCT02169388 Study start date: June 2014 Estimated primary completion date: January 2015
Contact information	Contact: Yanqing Li, MD, PhD; 86-531-82169236 ext 82169508; liyanqing@sdu.edu.cn
Notes	

NCT02351089

Trial name or title	Probiotics in radiation-treated gynecologic cancer
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Masking: double-blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: prevention
Participants	Estimated enrolment: 200 Ages eligible for study: ≥ 18 years (adult, senior) Genders eligible for study: female Accepts healthy volunteers: no Inclusion criteria: • Women with diagnosis of cancer in the small pelvis and waiting to receive radiotherapy as primary or secondary treatment following surgery. Chemotherapy may or may not be part of the treatment regimen • Age older than 18 years • Agreement for participation in the study by signed written informed consent Exclusion criteria: • Previously treated with irradiation of the pelvic area • Reluctance to refrain from using other probiotic products during participation in the study
Interventions	Probiotic low dose: capsules containing probiotic powder and corn starch Probiotic high dose: capsules containing probiotic powder and corn starch Placebo: capsules containing corn starch
Outcomes	Primary outcome measures: change in incidence of loose/watery stools [Time Frame: Baseline and 10 weeks later] [Designated as safety issue: No]
Starting date	ClinicalTrials.gov Identifier: NCT02351089 Study start date: February 2015 Estimated primary completion date: December 2016 (final data collection date for primary outcome measure)
Contact information	Contact: Maria Bjurberg, MD, PhD; maria.bjurberg@skane.se
Notes	

NCT02819960

Trial name or title	Prevention of irinotecan-induced diarrhea by probiotics
Methods	Allocation: randomised

NCT02819960 *(Continued)*

	Intervention model: parallel assignment Masking: double-blind (participant, care provider) Primary purpose: prevention
Participants	Estimated enrolment: 100 Ages eligible for study: ≥ 18 years (adult, senior) Genders eligible for study: female Accepts healthy volunteers: no Inclusion criteria: • Signed written informed consent • Age > 18 years • Patients with histologically proven colorectal cancer starting new line of chemotherapy based on irinotecan • ECOG PS 0 or 1 at study entry • Life expectancy > 3 months • Absence of any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule Exclusion criteria: • Not possible to take oral medication • Active infection treated by antibiotic therapy • Ileostoma • Hypersensitivity to study drug • Any concurrent malignancy other than non-melanoma skin cancer, no other cancer in past 5 years • Serious concomitant systemic disorder or disease incompatible with the study (at the discretion of the investigator)
Interventions	Probiotic group: probiotic formula PROBIO-FIX INUM will be administered at a dose of 3 × 1 cps per day orally for 6 weeks. No premedication or patient monitoring after administration of probiotic formula is required. Probiotic formula may be taken after meals or snacks to reduce stomach upset. Swallow the capsule, or in case of problems with swallowing, capsule can be opened and content mixed with small amount of food. Food must not be hot Placebo group: maltodextrin will be used for placebo group and will be administered at a the same dose as active formula (3 × 1 cps per day orally for 6 weeks)

Outcomes	Primary outcome measures:
	
	• Prevention of grade 3 or 4 diarrhoea induced by irinotecan-based chemotherapy [Time Frame: first 6 weeks of irinotecan-based chemotherapy]
	  ◦ To determine efficacy (as measured by prevention of grade 3/4 diarrhoea) of probiotic formula PROBIO-FIX INUM given orally to patients with colorectal cancer starting new line of irinotecan-based chemotherapy. Response will be defined as prevention of grade 3/4 diarrhoea according to definition of NCI CTC version 4.0
	
	Secondary outcome measures:
	
	• Progression-free survival [Time Frame: 1 year]
	  ◦ Progression-free survival period will be evaluated according to standard protocol
	• Prevention of diarrhoea of any grade [Time Frame: 6 weeks]
	  ◦ To determine the efficacy (as measured by prevention of grade 1/2 diarrhoea) of probiotic formula PROBIO-FIX INUM given orally to patients with colorectal cancer during first 6 weeks

NCT02819960 *(Continued)*

	of irinotecan-based chemotherapy. Response will be defined as prevention of grade 1/2 diarrhoea according to definition of NCI CTC version 4.0
	• Prevention of other gastrointestinal symptoms [Time Frame: 6 weeks]
	  ◦ To determine the efficacy (as measured by prevention of enterocolitis) of probiotic formula PROBIO-FIX INUM given orally to patients with colorectal cancer starting new line of irinotecan-based chemotherapy. Response will be defined as prevention of enterocolitis during first 6 weeks of irinotecan-based chemotherapy according to definition of NCI CTC version 4.0
	• Incidence of treatment-emergent adverse events [Safety and Toxicity] [Time Frame: 6 weeks]
	  ◦ Safety and toxicity will be evaluated according to NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE) (see Appendix D; http://www.fda.gov/cder/cancer/toxicityframe.htm)

Starting date	ClinicalTrials.gov Identifier: NCT02819960 Study start date: March 2016 Estimated primary completion date: March 2018 (final data collection date for primary outcome measure)
Contact information	Contact: Michal Mego, MD misomego@gmail.com
Notes	

Sharma 2013

Trial name or title	A phase II/III, randomised, double-blind, placebo-controlled study to investigate the efficacy of a probiotic VSL#3 on chemotherapy-induced diarrhea in people with cancer receiving fluoropyrimidines and/or irinotecan (interim analysis) Clinical Trial Registry number: CTRI/2009/091/001042
Methods	Randomised, parallel-group, placebo-controlled trial Country: India
Participants	Participants ≥ 18 years with histologically confirmed diagnosis of cancer, treated with fluoropyrimodines and/or irinotecan-based chemotherapy; ECOG ≤ 2 Participants with recurrent disease must have completed last chemotherapy 4 weeks before enrolment in the study
Interventions	VSL#3 sachets; 1 sachet bid for 12 to 16 weeks. Each sachet contains 900 billion CFU Placebo sachets; 1 sachet bid for 16 weeks
Outcomes	Primary outcome: incidence and duration of grade 3 and 4 diarrhoea caused by fluoropyrimidines and/or irinotecan Secondary outcomes: • Reduction in use of rescue medications (loperamide, antibiotics for diarrhoea) • Weight loss • Frequency of use of TPN (total parenteral nutrition) • Frequency of use of IV fluids • Incidence and duration of all grades of diarrhoea • Assessment of health-related quality of life

Sharma 2013 *(Continued)*

	• Incidence of oral mucositis • Incidence of grade III or IV neutropenia • Stool consistency (Bristol Stool Chart) • Chemotherapy dose modification • Chemotherapy treatment delays Time points: at all chemotherapy cycles, that is, cycles 1, 2, and 3 of chemotherapy and at the follow-up visit (i.e. 2 weeks after third cycle of chemotherapy)
Starting date	27/7/2010
Contact information	Dr Atul Sharma; atul1@hotmail.com
Notes	Conference abstract (limited reporting of interim analysis without unblinding)

TCTR20170314001

Trial name or title	Effect of probiotics for the prevention of acute radiation-induced diarrhea among cervical cancer patients
Methods	Allocation: randomised controlled trial Control: placebo Study endpoint classification: efficacy study Intervention model: parallel Number of arms: 2 Masking: double-blind (masked roles: subject, investigator, outcomes assessor) Primary purpose: prevention Study phase: 2
Participants	Radiotherapy-induced diarrhoea
Interventions	Probiotic group: probiotic group was given 1 capsule 3 times daily (each capsule contains functional yogurt 300 mg containing 1.75 billion lyophilised live *Lactobacillus acidophilus LA-5* plus *Bifidobacterium animalis* subsp *lactis BB-12*), beginning from the first day of radiotherapy, continuing every day until the end of radiotherapy Placebo group: placebo group received placebo capsules (containing starch of equal weight as the study drug), which had identical colour and size as the study drug. Treatment schedule was the same as that of the study group
Outcomes	Primary outcome measures: • Severity of radiotherapy-induced diarrhoea • Incidence of radiotherapy-induced diarrhoea Secondary outcome measures: • Onset of radiotherapy-induced diarrhoea • Use of antidiarrhoeal medication • Dose of loperamide • Time to use of loperamide from start of radiation

TCTR20170314001 *(Continued)*	• Severity of abdominal pain • Episode of abdominal pain in days • Interruption in radiotherapy due to diarrhoea
Starting date	ClinicalTrials.gov Identifier: TCTR20170314001 Study start date: 2 May 2016 Primary completion date: 29 November 2016
Contact information	Contact: Ye Htut Linn, MB, BS, MMedSc dryehtutlinn@gmail.com
Notes	

5-FU: 5-fluorouracil
AUC: area under the curve
BIA: bioelectrical impedance analysis
BMI: body mass index
CFU: colony-forming units
CNS: central nervous system
CRC: colorectal cancer
CRP: C-reactive protein
CTC: Common Toxicity Criteria
CTCAE: Common Terminology Criteria for Adverse Events
DSMC: Data and Safety Monitoring Committee
ECOG PS: Eastern Cooperative Oncology Group Performance Status
EGFR: epidermal growth factor receptor
FACIT-D: Functional Assessment of Chronic Illness Therapy for Patients With Diarrhoea
GCP: Guideline for Good Clinical Practice
IBS: irritable bowel syndrome
ICH: International Conference on Harmonisation
IEC: independent ethics committee
IMMP: no formal explanation was provided; IMMP are a series of new investigational drugs including IMP321, IMP731, IMP701, etc. produced by Immuptep limited
IV: intravenous
NCI: National Cancer Institute
NSAIDs: non-steroidal anti-inflammatory drugs
NYHA: New York Heart Association
PCoA: Bray-Curtis distance-based primary co-ordination analysis
rDNA: ribosomal DNA
RT: radiotherapy
SF-12: 12-item Short Form Health Survey
TPN: total parenteral nutrition
ULN: upper limit of normal
WBC: white blood cell

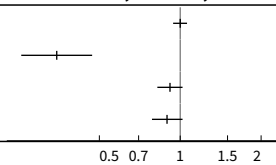
DATA AND ANALYSES

Comparison 1. Probiotics versus placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any diarrhoea	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Diarrhoea grade 2 or higher	4	420	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.03]
3 Diarrhoea grade 3 or higher	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Requiring rescue medication for diarrhoea	3	194	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.15, 1.66]
4.1 New subgroup	3	194	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.15, 1.66]

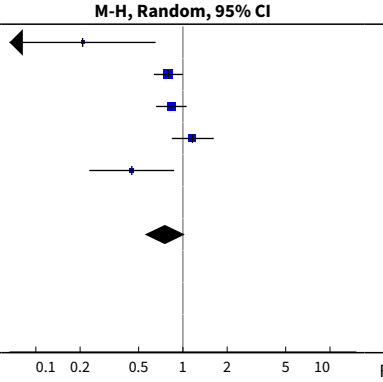
Analysis 1.1. Comparison 1 Probiotics versus placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy), Outcome 1 Any diarrhoea.

Study or subgroup	Probiotic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Chitapanarux 2010	32/32	31/31		1[0.94,1.06]
Delia 2007	42/243	119/239		0.35[0.26,0.47]
Demers 2014	69/81	80/86		0.92[0.82,1.02]
Demers 2014	49/59	80/86		0.89[0.78,1.02]



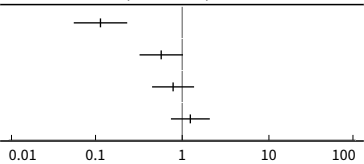
Analysis 1.2. Comparison 1 Probiotics versus placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy), Outcome 2 Diarrhoea grade 2 or higher.

Study or subgroup	Probiotic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chitapanarux 2010	3/32	14/31		6.19%	0.21[0.07,0.65]
Demers 2014	51/81	34/43		28.2%	0.8[0.63,1]
Demers 2014	39/59	34/43		27.77%	0.84[0.66,1.06]
Giralt 2008	30/44	24/41		24.38%	1.16[0.84,1.62]
Mansouri-Tehrani 2016	7/22	17/24		13.45%	0.45[0.23,0.87]
Total (95% CI)	**238**	**182**		**100%**	**0.75[0.55,1.03]**
Total events: 130 (Probiotic), 123 (Placebo)					
Heterogeneity: Tau^2=0.08; Chi^2=14.16, df=4(P=0.01); I^2=71.75%					
Test for overall effect: Z=1.75(P=0.08)					



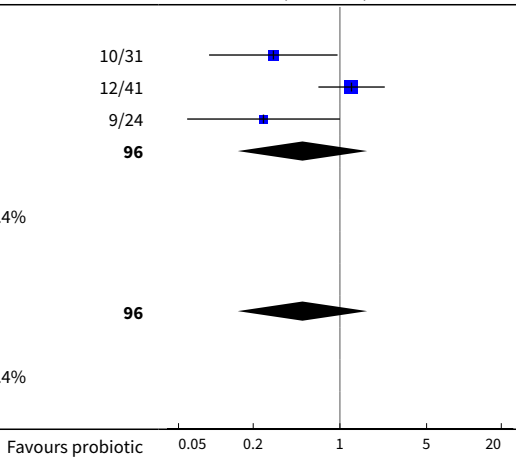
Analysis 1.3. Comparison 1 Probiotics versus placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy), Outcome 3 Diarrhoea grade 3 or higher.

Study or subgroup	Probiotic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Delia 2007	8/243	69/239		0.11[0.06,0.23]
Demers 2014	14/81	26/86		0.57[0.32,1.02]
Demers 2014	14/59	26/86		0.78[0.45,1.37]
Giralt 2008	20/44	15/41		1.24[0.74,2.08]



Analysis 1.4. Comparison 1 Probiotics versus placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy), Outcome 4 Requiring rescue medication for diarrhoea.

Study or subgroup	Probiotic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 New subgroup					
Chitapanarux 2010	3/32	10/31		31.46%	0.29[0.09,0.96]
Giralt 2008	16/44	12/41		40.68%	1.24[0.67,2.3]
Mansouri-Tehrani 2016	2/22	9/24		27.86%	0.24[0.06,1]
Subtotal (95% CI)	**98**	**96**		**100%**	**0.5[0.15,1.66]**
Total events: 21 (Probiotic), 31 (Placebo)					
Heterogeneity: Tau^2=0.83; Chi^2=7.81, df=2(P=0.02); I^2=74.4%					
Test for overall effect: Z=1.13(P=0.26)					
Total (95% CI)	**98**	**96**		**100%**	**0.5[0.15,1.66]**
Total events: 21 (Probiotic), 31 (Placebo)					
Heterogeneity: Tau^2=0.83; Chi^2=7.81, df=2(P=0.02); I^2=74.4%					
Test for overall effect: Z=1.13(P=0.26)					

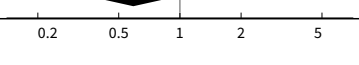


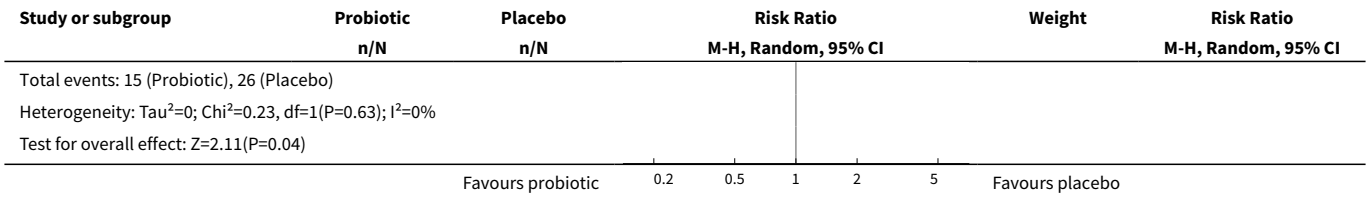
Comparison 2. Probiotics versus placebo for prevention of diarrhoea induced by chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any diarrhoea	2	106	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.36, 0.96]

Analysis 2.1. Comparison 2 Probiotics versus placebo for prevention of diarrhoea induced by chemotherapy alone, Outcome 1 Any diarrhoea.

Study or subgroup	Probiotic n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2014	6/30	12/30		34.27%	0.5[0.22,1.16]
Mego 2015	9/23	14/23		65.73%	0.64[0.35,1.18]
Total (95% CI)	**53**	**53**		**100%**	**0.59[0.36,0.96]**

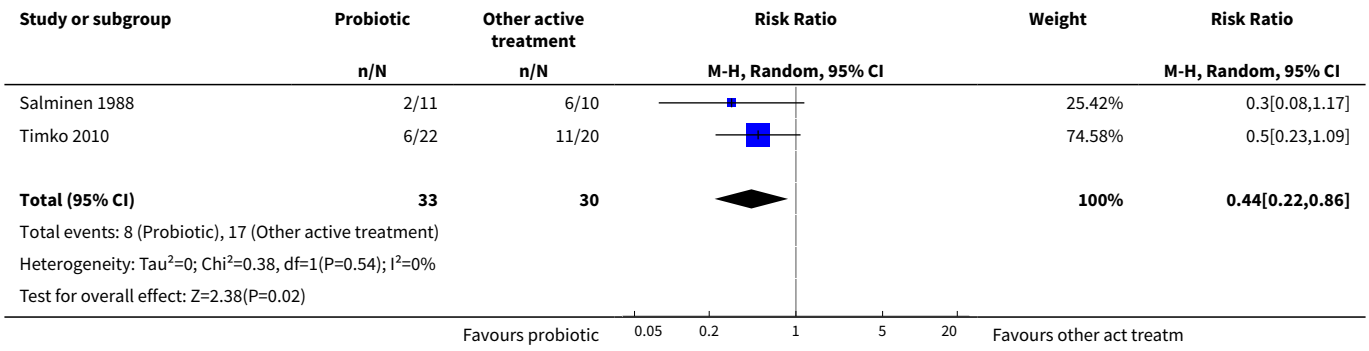




Comparison 3. Probiotics versus another active treatment for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Requiring rescue medication for diarrhoea	2	63	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.22, 0.86]

Analysis 3.1. Comparison 3 Probiotics versus another active treatment for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy), Outcome 1 Requiring rescue medication for diarrhoea.



ADDITIONAL TABLES

Table 1. Probiotics vs placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy)

Study ID and participants	Intervention(s)	Results
Chitapanarux 2010 Participants undergoing whole pelvis radiotherapy and brachytherapy plus weekly cisplatin 40 mg/m²	Intervention: 2 × 10^9 units of *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* (equivalent to 2 capsules) 2 times a day before meals (morning and evening), beginning 7 days before the start of radiotherapy and continuing every day during radiotherapy (n = 32)	Proportion of participants with diarrhoea: "During irradiation, diarrhoea occurred in all patients" Quality of life: not assessed Severity of diarrhoea: grades 2/3: 3/32 versus 14/31 (RR 0.21, 95% CI 0.07 to 0.65) Time to rescue medication for diarrhoea: not assessed Proportion of participants requiring rescue medication for diarrhoea: 3/32 versus 10/31 (RR 0.29, 95% CI 0.09 to 0.96)

Table 1. Probiotics vs placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy) *(Continued)*

	Control: Identical-appearing placebo on the same schedule (n = 31)	Adverse events: "There were no adverse events attributable to the study drug" Mortality: study authors reported no deaths
Delia 2007 Participants who underwent adjuvant postoperative radiotherapy after surgery for sigmoid, rectal, or cervical cancer	Intervention: VSL#3, 1 sachet tid (each sachet containing 450 billions/g of viable lyophilised bacteria, including 4 strains of *Lactobacillus* (*L casei, L plantarum, L acidophilus, and L delbrueckii* subsp *bulgaricus*), 3 strains of *Bifidobacterium* (*B longum, B breve, and B infantis*), and 1 strain of*Streptococcus salivarius* subsp*thermophilus*) from first day of radiotherapy until end of scheduled cycles of radiotherapy (n = 245) Control: VSL#3-identical-appearing placebo (n = 245)	Proportion of participants with diarrhoea: 42/243 versus 119/239 (RR 0.35, 95% CI 0.26 to 0.47) Quality of life: not assessed Severity of diarrhoea: grade 3/4: 8/243 versus 69/239 (RR 0.11, 95% CI 0.06 to 0.23) Time to rescue medication (loperamide) for diarrhoea, mean in hours (SD): 122 (8) versus 86 (6) (MD 36, 95% CI 34.74 to 37.26) Proportion of participants requiring rescue medication for diarrhoea: not reported Adverse events: "No case of bacteremia, sepsis, or septic shock due to the probiotic lactobacilli was reported among the VSL#3 recipients during the treatment period with the probiotic preparation or during the six months beyond active treatment. Likewise, no case of bacteremia, sepsis, or septic shock due to organisms other than the probiotic lactobacilli was recognized during the period of active treatment. We did not recognize any other toxicity reasonably attributable to VSL#3" Mortality: "No tumor- or treatment-related deaths or deaths from other causes were recorded in either group during the period of radiation therapy" NB: One participant in the probiotics group died of myocardial infarction and was excluded from the analyses
Demers 2014 Participants with pelvic cancer who were to receive radiotherapy treatments, with or without chemotherapy	Intervention group 1: standard dose of double-strain Bifilact probiotics (*Lactobacillus acidophilus LAC-361* and *Bifidobacterium longum BB-536*) twice a day (1.3 billion CFU) (n = 91 randomised, n = 81 analysed) Intervention group 2: high dose of double-strain Bifilact probiotics (*Lactobacillus acidophilus LAC-361* and *Bifidobacterium longum BB-536*) 3 times a day (10 billion CFU) (n = 64 randomised, n = 59 analysed) Control group: placebo (n = 91 randomised, n = 89 analysed)	Proportion of participants with diarrhoea: Standard 69/81 versus 80/86 (RR 0.92, 95% CI 0.81 to 1.03) High 49/59 versus 80/86 (RR 0.89, 95% CI 0.78 to 1.03) Quality of life (EORTC-QLQ-C30): "The wellbeing of participants did change over time. Overall QoL decreased by the end of the treatment, but increased again two weeks post-treatment (P<0.0001). Probiotic intake did not affect the quality of life of participants in this study" Severity of diarrhoea: Grade 2+: Standard 51/81 versus 68/86 (RR 0.80, 95% CI 0.63 to 1.00) High 39/59 versus 68/86 (RR 0.84, 95% CI 0.66 to 1.06) Grade 3+: Standard 14/81 versus 26/86 (RR 0.57, 95% CI 0.32 to 1.02) High 14/59 versus 26/86 (RR 0.78, 95% CI 0.45 to 1.37) Grade 4: Standard 2/81 versus 9/86 (RR 0.27, 95% CI 0.05 to 1.39)

Table 1. Probiotics vs placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy) *(Continued)*

		High 4/59 versus 9/86 (RR 0.58, 95% CI 0.17 to 2.04) Time to rescue medication (loperamide) for diarrhoea, mean in days (SD): "There was no significant difference (P = 0.89) among groups for the time until first intake of loperamide. The first capsule of loperamide (Imodium) was taken on days 19.7 (placebo), 20.4 (standard dose), and 20.9 (high-dose)" Proportion of participants requiring rescue medication for diarrhoea: "The percentage of participants that took loperamide was 42.5% for the placebo group, 30.2% for the standard-dose group, and 27.4% for the high-dose group, but this difference was not significant (P = 0.30)" Adverse events: "Other variables analyzed as a part of this study were the number of hospitalizations, the number of treatment interruptions and the reduction of either chemotherapy doses or radiotherapy treatments as a result of severe diarrhoea or abdominal pain. None of these variables differed among the groups after statistical analyses. Intake of Bifilact was well tolerated. No septicemia was recorded although a few cases of neutropenia occurred during treatment" Mortality: study authors reported no deaths
Giralt 2008 Women with endometrial or cervical carcinoma requiring postoperative pelvic radiotherapy with or without concomitant weekly cisplatin The same investigator weekly evaluated all participants and asked all to record the number of bowel movements and stool consistency every day. Evaluation for each participant took up to 6 months	Intervention: 96 mL 3 times daily of a fermented liquid yogurt containing approximately 10^8 CFU/g of *Lactobacillus casei DN-114 001*, in addition to the standard starters *Streptococcus thermophilus* and *Lactobacillus delbrueckii*, subsp *bulgaricus* (n = 56) Control: same amount of matching placebo, prepared by sterilising the active product with 4 kGy administered for 5 minutes (n = 62)	Proportion of participants with diarrhoea: not reported Quality of life: QLQ-C30 global score (change from baseline), mean (SD): 4.28 (11.02) versus 0.58 (10.22) (MD 3.70, 95% CI -1.21 to 8.61) Severity of diarrhoea: Grade ≥ 2: 30/44 versus 24/41 (RR 1.16, 95% CI 0.84 to 1.62) Grade ≥ 3: 20/44 versus 15/41 (RR 1.24, 95% CI 0.74 to 2.08) Time to rescue medication for diarrhoea: not assessed Proportion of participants requiring rescue medication for diarrhoea: 16/44 versus 12/41 (RR 1.24, 95% CI 0.67 to 2.30) Adverse events: "No differences were found with regard to the complications reported at 6 months. In >80% of cases, the participants and physicians reported an increase in bowel movements and changes in stool consistency; however, most changes were minimal. A pathologic increase in fecal calprotectin was observed in 1 patient of the 12 analyzed in the active group versus. 3 of the 11 analyzed in the placebo group. The study product was well tolerated, and none of the adverse events reported were considered related" Mortality: study authors reported no deaths
Mansouri-Tehrani 2016 Participants with pelvic cancer. All participants received conventional radiotherapy (5 fractions weekly for 4 to 5 weeks)	Intervention group 1: 2 probiotic capsules containing *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum,* and *Streptococcus thermophilus* per day after consumption of 150 grams of low-fat yogurt (n = 22)	Proportion of participants with diarrhoea: not reported Quality of life: not addressed Severity of diarrhoea: Grade 2 + 3: 7/22 versus 17/24 (RR 0.45, 95% CI 0.23 to 0.87) "Mean diarrhea grade in weeks 4 and 5 was significantly higher in the placebo group than the probiotic [and probiotic plus honey] groups (p = 0.007 and 0.001 for probiotic and p < 0.001 and p = 0.001 for probiotic plus honey in weeks 4 and 5 respectively)" Time to rescue medication for diarrhoea: not addressed

Table 1. Probiotics vs placebo for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy) *(Continued)*

	Intervention group 2 (not used in this review): 2 probiotic capsules and 30 grams honey per day after consumption of 150 grams of low-fat yogurt and 15 grams honey at night (n = 21) Control group: 2 placebo capsules per day after consumption of 150 grams of low-fat yogurt (n = 24)	Proportion of participants requiring rescue medication for diarrhoea: 2/22 versus 9/24 (RR 0.24, 95% CI 0.06 to 1.00) Adverse events: "During pelvic radiotherapy, three patients (they belonged to probiotic user; with or without honey) complained of upper abdominal pain. The causal link between the complaint and the probiotic was not investigated" Bloating: 19/22 versus 10/24 (RR 2.07, 95% CI 1.26 to 3.42) "The results of the Chi-square test showed that the number of patients with bloating in the probiotic groups (alone or plus honey) was significantly higher than the placebo group (P=0.002 and 0.021 for the probiotic and the probiotic plus honey groups, respectively)" Mortality: study authors reported no deaths

CFU: colony-forming units.
CI: confidence interval.
EORTC-QLQ-C30: questionnaire developed to assess the quality of life of patients with cancer, version 3.
MD: mean difference.
QoL: quality of life.
RR: risk ratio.
SD: standard deviation.

Table 2. Probiotics vs placebo for prevention of diarrhoea induced by chemotherapy

Study ID and participants	Intervention(s)	Results
Chen 2014 Participants with colorectal cancer undergoing intravenous chemotherapy	Intervention: combined *Clostridium butyricum* and *Bifidobacterium* capsule (n = 35) Control: placebo (n = 35) Both interventions (3 capsules, 3 times a day) were administered from 5 days before surgery for colorectal cancer to 7 days after surgery in each group. All participants received intravenous chemotherapy (calcium folinate 300 mg, fluorouracil 500 mg) during surgery	Proportion of participants with diarrhea: 6/30 versus 12/30 (RR 0.50, 95% CI 0.22 to 1.16) Quality of life: not assessed Severity of diarrhoea: not assessed Time to rescue medication for diarrhoea: not assessed Proportion of participants requiring rescue medication for diarrhoea: not assessed Adverse events: abdominal distension: 18/30 versus 11/30 (RR 1.64, 95% CI 0.94 to 2.85) Systemic inflammatory response syndrome (SIRS): 7/30 versus 9/30 (RR 0.78, 95% CI 0.33 to 1.82) Infection of incisional wound: 3/30 versus 3/30 (RR 1.0, 95% CI 0.22 to 4.56) Pulmonary infection: 2/30 versus 2/30 (RR 1.0, 95% CI 0.15 to 6.64) Urinary tract infection: 2/30 versus 2/30 (RR 1.0, 95% CI 0.15 to 6.64) Duration of fever (days): 4.5 ± 1.0 versus 4.6 ± 1.2 (MD -0.10 days, 95% CI -0.66 to 0.46) Hypoproteinaemia: 5/30 versus 4/30 (RR 1.25, 95% CI 0.37 to 4.21)

Table 2. Probiotics vs placebo for prevention of diarrhoea induced by chemotherapy *(Continued)*

		Side effects relevant to drug: 0/30 versus 0/30 Mortality: study authors reported no deaths
Liu 2000 Participants with cancer of the lung, stomach, colon, rectum, or breast or with metastatic neck carcinoma who were to receive chemotherapy	Cross-over study with 22 participants Intervention: *Bifidobacterium* combined with chemotherapy Control: chemotherapy alone *Bifidobacterium* capsule (2 capsules per time, 2 times a day) was taken from 1 day before chemotherapy to the sixth day of chemotherapy in each phase. Length of the washout period in this cross-over study was about 21 days	Proportion of participants with diarrhoea: 6/22 versus 10/22 (no paired analysis presented) Quality of life: not assessed Severity of diarrhoea: Grade 2+: 3/22 versus 7/22 (no paired analysis presented) Grade 3+: 1/22 versus 4/22 (no paired analysis presented) Time to rescue medication: not assessed Proportion of participants requiring rescue medication for diarrhoea: not assessed Adverse events: not assessed Mortality: study authors reported no deaths
Mego 2015 Participants with colorectal cancer starting a new line of chemotherapy	Intervention: probiotic formula Colon Dophilus™ 3*1 capsule per day orally for 12 weeks "Each capsule contained 10*109 CFU of bacteria. Each capsule contained 10 lyophilized probiotic strains including *Bifidobacterium breve HA-129* (25%), *Bifidobacterium bifidum HA-132* HA (20%), *Bifidobacterium longum HA-135* (14.5%), *Lactobacillus rhamnosus HA-111* (8%), *Lactobacillus acidophilus HA-122* (8%), *Lactobacillus casei HA-108* (8%), *Lactobacillus plantarum HA-119* (8%), *Streptococcus thermopilus HA-110* (6%), *Lactobacillus brevis HA-112* (2%), *Bifidobacterium infantis HA-116* (0.5%) (n = 23)" Control: placebo (n = 23). "Each capsule with placebo contained only inactive ingredients without probiotic bacteria, and placebo capsules were prepared by the central pharmacy. The placebo was indistinguishable from the capsule with probiotics in terms of color, appearance, taste, smell, size, shape, and other properties and contained the same additives as probiotic capsule"	Proportion of participants with diarrhoea: 9/23 versus 14/23 (RR 0.64, 95% CI 0.35 to 1.18) Quality of life: not assessed Severity of diarrhoea: Grade 2+: 4/23 versus 6/23 (RR 0.67, 95% CI 0.22 to 2.05) Grade 3+: 0/23 versus 4/23 (RR 0.11, 95% CI 0.01 to 1.95) Grade 4: 0/23 versus 1/23 (RR 0.33, 95% CI 0.01 to 7.78) Time to rescue medication for diarrhoea: not assessed Proportion of participants requiring rescue medication for diarrhoea: "participants on probiotic arm used less loperamide and diphenoxylate/atropine compared to participants on placebo arm" Adverse events: "We received filled study diaries from 38 (82.6%) of patients. ….. We did not observe any infection caused by probiotic strains used in this study" Mortality: study authors reported no deaths

CI: confidence interval.
RR: risk ratio.
SIRS: systemic inflammatory response syndrome.

Table 3. Probiotics vs active treatment for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy)

Study ID and participants	Intervention(s)	Results

Table 3. Probiotics vs active treatment for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy) *(Continued)*

Osterlund 2007 Participants with Dukes' B or C colorectal cancer or metastatic colorectal cancer who underwent chemotherapy and radiotherapy	Intervention:*Lactobacillus rhamnosus GG* (administered orally as gelatin capsules twice daily at a dose of 1 to 2 × 10^{10} per day during 24 weeks of adjuvant cancer chemotherapy (n = 98) Control: guar gum containing nutritional supplement (contains 11 g guar gum and 550 kcal or 2300 kJ), administered daily, on cycle days 7 to 14, for 8 days per month (n = 52) All participants received dietary counselling	Proportion of participants with diarrhoea: not reported Quality of life: not assessed Severity of diarrhoea: grade 3-4 OR 0.38 (95% CI 0.16 to 0.89) Time to rescue medication for diarrhoea: not assessed Proportion of participants requiring rescue medication for diarrhoea: not assessed Adverse events (Common Toxicity Criteria of the National Cancer Institute of Canada scale version 2): Any adverse event grade 3 or 4: OR 0.77 (95% CI 0.35 to 1.72) Stomatitis grade 3 or 4: OR 0.59 (95% CI 0.26 to 1.35) Neutropenia grade 3 or 4: OR 2.00 (95% CI 0.74 to 4.89) Neutropenic infection grade 3 or 4: OR 2.62 (95% CI 0.53 to 13.00) Hand-foot syndrome grade 3: 2/97 versus 1/51 (OR: no convergence) Mortality: study authors reported no deaths
Salminen 1988 Participants with carcinoma of the cervix or uterus who were to receive radiotherapy	Intervention: dietary counselling recommending a low-fat and low-residue diet during radiotherapy and a daily dose of at least 2 × 10^{9} live *Lactobacillus acidophilus* bacteria in the form of a yogurt-type product (150 mL of a fermented milk test product) and 6.5% lactulose as substrate for the bacteria; 150 mL of the product daily for 5 days before radiotherapy, daily throughout the radiotherapy period including the interval, and then for 10 days after completion of the therapy regimen (n = 12) Control: dietary counselling only recommending a low-fat and low-residue diet during radiotherapy (n = 12)	Proportion of participants with diarrhoea: "All subjects in the control group suffered from diarrhoea during the radiotherapy" During treatment, control time 2: 3/11 versus 8/10 (RR 0.34, 95% CI 0.12 to 0.94) During treatment, control time 3: 2/11 versus 9/10 (RR 0.20, 95% CI 0.06 to 0.72) During treatment, control time 4: 2/11 versus 8/10 (RR 0.23, 95% CI 0.06 to 0.83) Six weeks after treatment: 3/11 versus 9/10 (RR 0.30, 95% CI 0.11 to 0.81) "The incidence of diarrhoea was significantly smaller in the yoghurt group than in the control group (P<0.01)" Quality of life: not assessed Severity of diarrhoea: not assessed Time to rescue medication for diarrhoea: not assessed Proportion of participants requiring rescue medication for diarrhoea: 2/11 versus 6/10 (RR 0.30, 95% CI 0.08 to 1.17) Adverse events: "There were no differences in the incidence of vomiting, nausea, abdominal pain, loss of appetite or weight loss between the groups. However, the yoghurt group experienced more flatulence than the controls" Mortality: study authors reported no deaths

Table 3. Probiotics vs active treatment for prevention of diarrhoea induced by radiotherapy (with or without chemotherapy) *(Continued)*

Timko 2010 Participants with cancer who underwent adjuvant postoperative radiotherapy therapy in the abdominal and pelvic region, with or without chemotherapy	Intervention: probiotic preparation "5"-strain Dophilus (55% *Lactobacillus rhamnosus,* 20% *Bifidobacterium adolescentis*, 5% *Lactobacillus acidophilus*, 5% *Bifidobacterium longum*, 15% *Enterococcus faecium*) with a count of 6 billion active bacteria/capsules at a daily dosage of 2 × 1 capsule (n = 22) Control: Hylak Tropfen Forte preparation (i.e. cell-free fermentation products of *Lactobacillus helveticus* and gut symbionts (100 mL containing: 24.95 g *Escherichia coli* metabolita, 12.5 g *Streptococci faecalis* metabolita, 12.5 g *Lactobacillus acidophilus* metabolita, 49.9 g *Lactobacillus helveticus* metabolita) in doses of 40 drops, 3 times per day (n = 20)	Proportion of participants with diarrhoea: not assessed Quality of life: not assessed Severity of diarrhoea: not assessed Time to rescue medication for diarrhoea: not assessed Proportion of participants requiring rescue medication for diarrhoea (diphenoxylate): RR 0.50, 95% CI 0.23 to 1.09 Adverse events: Abdominal pain: 25% versus 22% "All these participants were being treated with pelvic radiotherapy with chemotherapy, except for one patient of L-Group. Chemotherapy thus seemed to result in increased toxicity" "None of the participants discontinued treatment for gastrointestinal toxicity" Mortality: study authors reported no deaths

CI: confidence interval.
OR: odds ratio.
RR: risk ratio.

Table 4. Probiotics vs placebo for treatment of diarrhoea induced by radiotherapy

Study ID and participants	Intervention(s)	Results
Urbancsek 2001 Participants with cancer who developed diarrhoea within 4 weeks after receiving radiotherapy in the abdominal region	Intervention: *Lactobacillus rhamnosus* (Antibiophilus, with each sachet containing 1.5 g of *Lactobacillus rhamnosus* equivalent to 1.5×10^9 colony-forming units) 3 times a day (n = 102) Control: identical-appearing sachets of placebo, each containing 700 mg corn starch, 797 mg microcrystalline cellulose, 1.37 mg iron oxide, 1.13 mg dispersed orange (colouring agent), and 1 mg caramel aroma 3 times a day (n = 103)	Proportion of participants with diarrhoea: not reported Quality of life: not assessed Severity of diarrhea: average grade rated by investigators using standard scores of 0 for none, 1 for mild, 2 for moderate, and 3 for severe diarrhoea: Study start: 2.0 versus 2.2 Study end: 0.7 versus 1.0 Time (hours) to rescue medication for diarrhoea: 138 (SE = 5) versus 125 (SE= 5) (MD 13, 95% CI -0.86 to 26.86) Proportion of participants requiring rescue medication for diarrhoea: RR 0.74, 95% CI 0.53 to 1.03 Adverse events: "Serious adverse events (in GCP terms) were not observed in this study. In both study groups, three participants reported adverse events. In the Antibiophilus1 group, three participants reported gastrointestinal problems (mild to moderate); in the placebo group, two participants reported gastrointestinal events (moderate to severe), and one patient observed a mild labial oedema. All documented events were of a transient nature; in three patients, symptomatic treatment of adverse events was prescribed"

Table 4. Probiotics vs placebo for treatment of diarrhoea induced by radiotherapy *(Continued)*

	Mortality: study authors reported no deaths

CI: confidence interval.
GCP: Good Clinical Practice.
MD: mean difference.
RR: risk ratio.

APPENDICES

Appendix 1. The Cochrane Library (CENTRAL) search strategy

#1 MeSH descriptor Neoplasms explode all trees
#2 neoplasm* or cancer* or tumor* or tumour* or malignan* or carcinom*
#3 (#1 OR #2)
#4 MeSH descriptor Diarrhea explode all trees
#5 diarrh*
#6 antidiarrh*
#7 anti-diarrh*
#8 (#4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Probiotics explode all trees
#10 probiotic*
#11 MeSH descriptor Prebiotics explode all trees
#12 prebiotic*
#13 MeSH descriptor Lactobacillus explode all trees
#14 lactobacillus
#15 MeSH descriptor Bifidobacterium explode all trees
#16 bifidobacterium
#17 saccharomyces boulardii
#18 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19 (#3 AND #8 AND #18)

Appendix 2. MEDLINE (Ovid) search strategy

1 exp Neoplasms/
2 (neoplasm* or cancer* or tumor* or tumour* or malignan* or carcinom*).mp.
3 1 or 2
4 exp Diarrhea/
5 diarrh*.mp.
6 antidiarrh*.mp.
7 anti-diarrh*.mp.
8 6 or 4 or 7 or 5
9 exp Probiotics/
10 probiotic*.mp.
11 Prebiotics/
12 prebiotic*.mp.
13 exp Lactobacillus/
14 lactobacillus.mp.
15 Bifidobacterium/
16 bifidobacterium.mp.
17 saccharomyces boulardii.mp.
18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 3 and 8 and 18
21 controlled clinical trial.pt.
22 randomized.ab.
23 placebo.ab.
24 drug therapy.fs.
25 randomly.ab.
26 trial.ab.
27 groups.ab.

28 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 19 and 28

key:
mp=title, original title, abstract, name of substance word, subject heading word, unique identifier; pt=publication type; ab=abstract; fs=floating subheading

Appendix 3. Embase (Ovid) search strategy

1 exp neoplasm/
2 (neoplasm* or cancer* or tumor* or tumour* or malignan* or carcinom*).mp.
3 1 or 2
4 exp diarrhea/
5 diarrh*.mp.
6 antidiarrh*.mp.
7 anti-diarrh*.mp.
8 4 or 5 or 6 or 7
9 exp probiotic agent/
10 probiotic*.mp.
11 prebiotic agent/
12 prebiotic*.mp.
13 Lactobacillus/
14 lactobacillus*.mp.
15 exp Bifidobacterium/
16 bifidobacterium.mp.
17 saccharomyces boulardii.mp.
18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 3 and 8 and 18
20 crossover procedure/
21 double-blind procedure/
22 randomized controlled trial/
23 single-blind procedure/
24 random*.mp.
25 factorial*.mp.
26 (crossover* or cross over* or cross-over*).mp.
27 placebo*.mp.
28 (double* adj blind*).mp.
29 (singl* adj blind*).mp.
30 assign*.mp.
31 allocat*.mp.
32 volunteer*.mp.
33 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 19 and 33
35 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
36 34 not 35

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

CONTRIBUTIONS OF AUTHORS

Amending the protocol, selecting studies, assessing risk of bias, extracting data, performing analysis, applying GRADE criteria, and writing the draft review: Dang Wei, Pauline Heus, Fleur van de Wetering, and Rob Scholten.

Commenting on draft protocol and review, and providing content for the discussion and implications sections: Geertjan van Tienhoven and Leen Verleye.

DECLARATIONS OF INTEREST

Dang Wei: none known.
Pauline Heus: none known.
Fleur T van de Wetering: none known.
Geertjan van Tienhoven: none known.

Leen Verleye: none known.
Rob JPM Scholten: none known.

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  The Belgian Health Care Knowledge Centre (KCE) commissioned and supported a series of systematic reviews for the guideline "Supportive treatment for cancer. Part 2: prevention and treatment of adverse events related to chemotherapy and/or radiotherapy for adults with cancer". This protocol was one of the research questions for this guideline.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The current review author team prepared this review based on a protocol that was written by another group of review authors. During the review process, editors and peer referees provided quite a few suggestions for amendments. This resulted in post hoc amendments to the methods section and to the presentation of results.

Based on advice to reduce the number of primary outcomes, we moved the following primary outcomes, which were listed in the protocol, to secondary outcomes: severity of diarrhoea (for prevention studies), time to rescue medication, proportion of participants requiring rescue medication, and mortality related to diarrhoea.

With respect to types of interventions, because radiotherapy (with or without chemotherapy) and chemotherapy have major different effects on the occurrence of diarrhoea, we decided to perform all analyses for these two intervention types separately. Consequently, subgroup analysis according to type of intervention was no longer applicable. We did not perform other predefined subgroup analyses for age, stage, and length of follow-up, as data could not be retrieved or did not vary.

INDEX TERMS

Medical Subject Headings (MeSH)

Diarrhea [complications] [prevention & control] [*therapy]; Neoplasms [*drug therapy] [*radiotherapy]; Placebos [therapeutic use]; Probiotics [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans