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Literature Review

Are probiotics more efficacious than placebo at preventing radiotherapy-induced diarrhoea in adults with cancer

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Abstract

Background: Patients with cancer undergoing radiotherapy often develop diarrhoea, causing distress and hindering treatment. As probiotics have favourable effects on the gut flora, they are potentially good candidates in the prevention of radiotherapy-induced diarrhoea (RID).

Purpose: The outcome of interest of this systematic review was the efficacy of probiotics in preventing RID.

Materials and methods: Medline and Embase databases were systematically searched. Four randomised controlled trials (RCTs) were finally selected.

Results: Three RCTs showed beneficial results, which were statistically significant. One RCT showed non-beneficial results, which were not statistically significant. The quality of the studies was mixed, and serious limitations were found.

Conclusion: While the indications are towards a benefit of the use of probiotics in preventing RID, more robust evidence is required in the form of well-designed RCTs.

Keywords: diarrhoea; probiotic; radiotherapy

INTRODUCTION

In the United Kingdom, almost four in every ten patients with cancer receive radiotherapy as part of their treatment.[1] When the patient's body volume treated includes part or all of the gastrointestinal tract, a common side effect is diarrhoea.[2]

Radiotherapy-induced diarrhoea (RID) is defined as an inflammatory and degenerative process caused by radiation and affecting the gastrointestinal tract.[2] Usually, diarrhoea starts within the first 2 weeks of treatment; it can be mild and eventually resolve, or can become more serious and chronic.[3] In the United Kingdom, ~80% of patients with cancer undergoing abdominal or pelvic radiotherapy will develop some degree of RID, resulting in patients' distress and potential withdrawal of treatment.[4]

Radiation is thought to cause diarrhoea by creating changes in intestinal bacterial flora, intestinal motility, vascular permeability of the

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mucosal cells and intestinal mucosa malabsorption of lactose and bile acids.[2,5] Treatment often includes medications such as antibiotics, sucralfate, mesalazine, octreotide, loperamide and diphenoxylate.[6,7] While exact statistics are lacking, treatment failure is thought to occur in a large proportion of patients,[8] highlighting the need for novel approaches in the prevention of RID.

In the last few years, probiotics have acquired importance in the prevention and treatment of acute gastrointestinal symptoms.[9–11] A joint report by the Food and Agriculture Organisation of the United Nations and the World Health Organisation defines probiotics as 'live microorganisms which when administered in adequate amounts confer a health benefit on the host'.[12] Probiotics provide their benefit through modulation of intestinal inflammation by altering the composition and the metabolic properties of the indigenous intestinal flora.[7] In experimental and clinical studies, probiotics have been shown to be beneficial in the prevention and treatment of a variety of gastrointestinal disorders, including infectious diarrhoea, clostridium difficile-induced diarrhoea, inflammatory bowel disease, irritable bowel syndrome and ulcerative colitis.[13] This systematic review aims to examine the evidence for a possible efficacy of probiotics in the prevention of RID.

METHOD

The review follows the National Institute for Health and Clinical Excellence (NICE) guidelines manual methodology,[14] and it is designed as a 'mini-review', along the lines suggested by Griffiths.[15] To search for relevant studies, we asked the question: are probiotics more efficacious than placebo at preventing RID in adults with cancer? We searched Medline and Embase databases. Medline has a broad coverage of biomedical literature, whereas Embase has a stronger focus on pharmacology, drug research and European literature.[14,16] Only randomised controlled trials (RCTs) were included, as they are the studies of choice when answering questions of therapeutic efficacy.[17,18] Table 1 reports the inclusion/exclusion criteria used.

Table 1. *Inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
Randomised controlled trial Adult participants (aged 18 or older) Participants might also receive concurrent chemotherapy Presence of diarrhoea included as outcome, or enough data provided to calculate it	Absence of a placebo group Use of probiotics for treatments other than prevention of diarrhoea Not in English

RESULTS

The database search provided 63 original citations. We excluded irrelevant papers by scrutinising the title or abstract, or full copy where there was uncertainty as to whether they met the inclusion criteria (Figure 1, Table 2). Finally, four papers answering the review question and meeting the inclusion criteria were selected.[19–22]

Chitapanarux et al.[22] conducted a randomised, double-blind, placebo-controlled trial to determine whether a probiotic preparation (Infloran) reduced the risk of RID. They recruited 63 adult female patients (two groups)

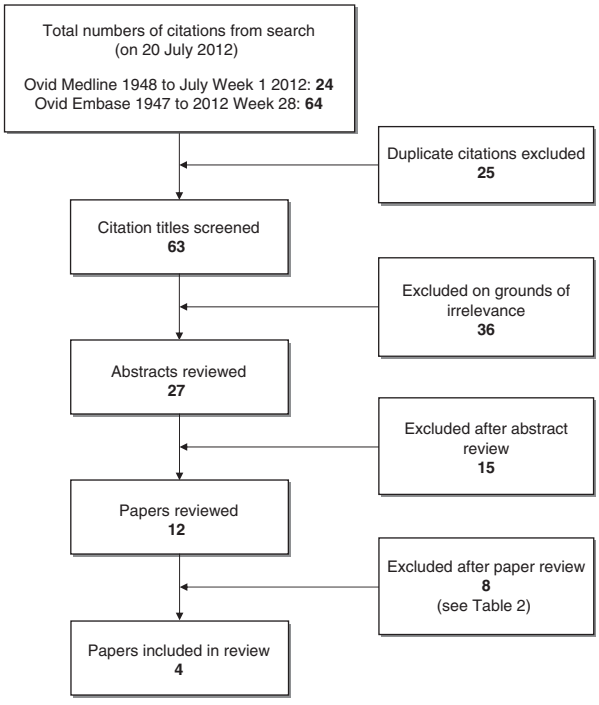

Figure 1. Exclusion of papers.

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Table 2. *Excluded papers*

Paper reference	Reason for exclusion
Delia et al.[48]	Report of pilot study with data used in later larger RCT reported by Delia et al.[19]
Delia et al.[49]	Report of pilot study with data used in later larger RCT reported by Delia et al.[19]
Delia et al.[50]	Reports the same study reported by Delia et al.[19]
Henriksson et al.[51]	Probiotics as treatment of RID, not prevention
Okawa et al.[52]	Probiotics as cancer treatment, not prevention of RID
Salminen et al.[5]	Not placebo controlled
Timko[7]	Not placebo controlled
Urbancsek et al.[11]	Probiotics as treatment of RID, not prevention

Abbreviations: RCT, randomised controlled trial; RID, radiotherapy-induced diarrhoea.

undergoing radiotherapy and concurrent cisplatin chemotherapy for cervical cancer (they did not specify the health-care settings).

Delia et al.[19] investigated the ability of a high-potency probiotic preparation (VSL#3) to prevent RID by conducting a randomised, double-blind, placebo-controlled trial. They recruited 490 adult patients (two groups) attending an Italian radiotherapy outpatient unit, who were receiving radiotherapy for sigmoid, rectal or cervical cancers.

Germain et al.[20] studied the impact of a standard dose and a high dose of a probiotic preparation (Bifilact) on the onset of RID by conducting a randomised, placebo-controlled trial. They recruited 246 adult patients (three groups) of a hospital in Quebec with rectal, cervical, endometrial or prostatic cancer, with some patients having received surgery or chemotherapy.

Giralt et al.[21] ran a randomised, double-blind, placebo-controlled trial to study the efficacy of a fermented liquid yogurt (containing Lactobacillus casei DN-114001) for the prevention of RID. They recruited 118 adult female patients (two groups) receiving radiotherapy and concurrent cisplatin chemotherapy for cervical or endometrial cancer at different Spanish hospitals.

QUALITY ASSESSMENT

As suggested by Huwiler-Muntener et al.,[23] we separately assessed the reporting quality and methodological quality of the four papers. Reporting quality was assessed with the CONSORT RCT checklist.[24] The papers did not describe the randomisation method in detail, nor calculated effect sizes and confidence intervals (CIs). The paper by Delia et al.[19] and Germain et al.[20] published, respectively, as 'rapid communication' and, as a conference proceeding abstract, had the lowest reporting quality, lacking discussion of blinding, statistical methods and study limitations.

Methodological quality was assessed with the NICE RCT methodology checklist[25] combined with the GRADE risk of bias criteria for individual studies.[26] The assessment aimed at checking for sources of systematic bias[27] for the presence of diarrhoea (Table 3). Owing to lack of clarity regarding their selection methods, all four studies showed risk of selection bias. The study by Chitapanarux et al.[22] was the only study with no risk of attrition bias, as there were no withdrawals among participants and intention to treat analysis was used.[28] The study by Giralt et al.[21] had the highest risk of attrition bias, with 27% attrition ratio and per protocol analysis. Moreover, attrition ratio was imbalanced, with 34% and 21% withdrawals for placebo and treatment group, respectively, increasing risk for bias.[26] The study by Chitapanarux et al.[22] had the least risk of detection bias, as stool consistency was assessed objectively. The study by Germain et al.[20] may be prone to systematic bias, as it lacked clarity in the randomisation process and blinding in the study design, as well as in how diarrhoea was defined (Table 4).

Of the four studies, Chitapanarux et al.[22] and Delia et al.[19] were the most robust; the study by Giralt et al.[21] was the least robust, and the robustness of the study by Germain et al.[20] could not be estimated.

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Table 3. Risk of systematic bias for the presence of diarrhoea[a]

Study	Randomisation and allocation concealment (selection bias)	Blinding (performance bias)	Loss to follow-up Intention to treat or per protocol analysis (attrition bias)	Outcome measure (detection bias)
Chitapanarux et al.[22]	Unclear	Unclear Described as double-blind Placebo identical appearance Blind pre-packaging of study medication	0% placebo 0% intervention 0% overall, intention to treat	Stool samples objectively assessed for consistency by laboratory technician (likely blinded)
Delia et al.[19]	Unclear	Unclear Described as double-blind Placebo identical appearance	2·5% placebo 0·9% intervention 1·7% overall, protocol	Unclear how diarrhoea was defined Data obtained from participants' diary Unclear how diarrhoea was defined
Germain et al. [20]	Unclear	Unclear Described as placebo controlled	Not reported	Patients discussed symptoms weekly with physician and dietitian
Giralt et al.[21]	Unclear	Unclear Described as double-blind Placebo identical appearance	34% placebo 21% intervention 27% overall, protocol	Stool consistency subjectively assessed by participants using Bristol Stool Scale Data obtained from participants' diary

Note: [a] Adapted from Guyatt et al.[26]

FINDINGS AND DISCUSSION

Tables 4 and 5 report features and findings of the studies. Effect sizes and their CIs were calculated as number needed to treat (NNT).[29,30] NNT, endorsed in the GRADE system,[31] is an absolute measure of effects conveying both statistical and clinical significance.[32] The NNT was calculated from the absolute risk reduction (ARR), which is also reported (Table 5). When the ARR is negative, which occurs when the treatment has a harmful effect, the NNT is also negative. A positive (beneficial) NNT is indicated as NNTB and a negative (harmful) NNT as NNTH, and both have a positive sign.[33]

A beneficial effect of their probiotic preparation was found by Chitapanarux et al.[22] (NNTB 2·2, 95% CI 1·5–4·1) and by Delia et al.[19] (NNTB 5, 95% CI 3·5–8·6) and both results were statistically significant. Germain et al.[20] found a beneficial effect for both standard dose group (NNTB 5·5, 95% CI 3·2–19·5), which was statistically significant, and high dose group (NNTB 10·3, 95% CI NNTH 35 to ∞ to NNTB 4·5), which did not reach statistical significance. These results have a high clinical significance: very few patients (the NNTB value) needed to be treated to prevent one additional case of diarrhoea. Probiotics are considered safe, and although adverse events such as probiotic bacteraemias exist they are very rare.[34] Only the study by Giralt et al.[21] found an unfavourable effect of the treatment, which was not statistically significant (NNTH 10·4, 95% CI NNTH 3·3 to ∞ to NNTB 9·3). None of the four studies reported adverse events.

Baseline characteristics of intervention and control groups had no significant differences in each of the three studies that reported relevant details,[19,21,22] providing good internal validity. Participants' total radiation dose was similar across the three studies that reported it.[19,21,22] Some of the participants in all studies but those in Delia et al.[19] also received chemotherapy. However, the study samples were considerably different. Chitapanarux et al.[22] studied 63 women treated for cervical cancer, and Giralt et al.[21] recruited 118 women with cervical and endometrial cancer. Delia et al.[19] studied 482

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Table 4. *Features of included studies*[a]

Reference	Study type	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Chitapanarux et al.[22]	Randomised, double-blind, placebo-controlled trial	Strengths Nil attrition ratio, intention to treat analysis, objective detection of diarrhoea Weaknesses Small sample	63 randomised (31 comparison, 32 intervention), all participants completed the study Inclusion criteria Adults with FIGO stage IIB-IIB squamous cell carcinoma of cervix, receiving external radiotherapy and brachytherapy with weekly cisplatin, ECOG performance status 0–1 and negative anti-HIV Exclusion criteria Past history of pelvic radiotherapy or abdominal surgery and diarrhoea before beginning of the study, patients with gastrointestinal disease, pregnant and lactating patients	Setting not specified Age, stage of disease, performance status and whole pelvis radiotherapy technique did not show significant difference between the groups Patients received 56 Gy of external beam radiotherapy, 28 Gy dose of brachytherapy and weekly cisplatin 40 mg/m^2 for 6 weeks	Infloran capsules (2 billion of viable lyophilised bacteria: Lactobacillus acidophilus plus Bifidobacterium bifidum) Administered twice a day, morning and evening before meals, from 7 days before start of radiotherapy to last day of radiotherapy	Identical appearing placebo administered with the same schedule	Weekly follow-up during radiotherapy Follow-up after completion not specified	No details
Delia et al.[19]	Randomised, double-blind, placebo-controlled trial	Strengths Large sample, very low attrition ratio Weaknesses Per protocol analysis, subjective detection of diarrhoea	490 randomised (245 each group), 239 participants in comparison group completed the study, 243 in intervention group Inclusion criteria Adult receiving adjuvant radiation therapy after surgery for sigmoid, rectal or cervical cancers, no contraindication for probiotic, antibiotic or radiation therapy Exclusion criteria Karnofsky performance score $\leq$70, life expectancy $\leq$1 year, persistent vomiting or diarrhoea, fistulising disease, Crohn's disease or ulcerative colitis, intra-abdominal abscesses or temperature $>$37·5°C, sepsis syndrome, use of antibiotics in preceding 2 weeks	Outpatient clinic based Groups balanced in terms of gender, age, nodal involvement, tumour grade and size, local invasion at operation and histology, postoperative complications Patients received a total X-ray dose between 60 and 70 Gy	VSL#3 sachets (450 billions of viable lyophilised bacteria: Lactobacillus (L.) casei, L. plantarum, L. acidophilus, L. delbruekii subsp. bulgaricus, Bifidobacterium (B.) longum, B. breve, B. infantis, Streptococcus salivarius subs. thermophilus) Administered from first day of radiotherapy, one sachet three times a day	Identical appearing placebo administered with the same schedule	Weekly follow-up during radiotherapy and 1 month after completion	No details

Table 4. Continued

Reference	Study type	Study quality	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Source of funding
Gemain et al.[20]	Placebo-controlled trial	Strengths Moderate sample Weaknesses Subjective detection of diarrhoea	246 randomised in three groups: placebo, normal dose, high dose Attrition rate not specified Inclusion criteria Patients with rectal, cervical, endometrial or prostatic cancer. Some patients had surgery before radiotherapy and some received chemotherapy Exclusion criteria Not specified	Hospital in Quebec Characteristics not reported	Bifilact capsules Normal dose: two capsules of 1·3 billion of Lactobacillus acidophilus and Bifidobacterium longum High dose: three capsules of 10 billion of same strains Administration schedule not specified	Placebo not described	Weekly follow-up during radiotherapy for 60 days	No details
Giralt et al.[21]	Randomised, double-blind, placebo-controlled trial	Strengths Weaknesses High and unbalanced attrition rate, per protocol analysis Subjective detection of diarrhoea	118 randomised (62 comparison, 56 intervention), 41 participants in comparison group completed the study, 44 in intervention group Inclusion criteria Female aged 18 or above, Eastern Cooperative Oncology Group functional status <2, endometrial adenocarcinoma requiring post-operative pelvic radiotherapy or advanced cervical squamous cell carcinoma treated with pelvic radiotherapy and concomitant weekly cisplatin Exclusion criteria Other types of pelvic tumours, chemotherapy other than cisplatin, previous chemotherapy or radiotherapy, antimicrobial or immunosuppressors treatment, presence of acute or chronic gastrointestinal condition with diarrhoea in the month before recruitment	Various hospitals in Spain Age, weight, height, quality of life and performance status did not show significant difference between the groups Patients received 45–50·4 Gy of external beam radiotherapy and cervical cancer patients received weekly cisplatin 40 mg/m^2 for 5–6 weeks	Fermented liquid yogurt (10^8 CFU/g of Lactobacillus (L.) casei DN-114001 plus Streptococcus thermophilus and L. deblrueckii, subsp. bulgaricus) Administered three times a day, from 7 days before start of radiotherapy to last day of radiotherapy	Identical appearing placebo obtained from sterilisation of the active product, administered with the same schedule	Weekly evaluation during radiotherapy Follow-up 6 months after recruitment	No details

Note: [a] Adapted from the evidence table for interventions studies in NICE.[25]

Table 5. Findings of included studies for the presence of diarrhoea and calculated effect sizes

Reference	Study findings[a]	*p*-value	Calculated effect size[b]	Comments
Chitapanarux et al.[22]	I: 6/32 C: 20/31 No harm caused by probiotics	<0·001	ARR 46% (95% CI 24–67%) NNTB 2·2 (95% CI 1·5–4·1)	Statistical significance, very high clinical significance and high precision
Delia et al.[19]	I: 77/243 C:124/239 No harm caused by probiotics	<0·001	ARR 20% (95% CI 12–29%) NNTB 5 (95% CI 3·5–8·6)	Statistical significance, high clinical significance and high precision
Germain et al.[20]	I_1: 65% (standard dose group)	<0·05	ARR_1 18% (95% CI 5–31%)[c] $NNTB_1$ 5·5 (95% CI 3·2–19·5)[c]	Statistical significance and high clinical significance
	I_2: 73% (high dose group) C: 83%	=0·19	ARR_2 10% (95% CI −3 to 22%) $NNTB_2$ 10·3 (95% CI NNTH 35 to ∞ to NNTB 4·5)	Moderate clinical significance and no statistical significance
Giralt et al.[21]	I: 30/44 C: 24/41	Not significant	ARR -10% (95% CI −30 to 11%) NNTH 10·4 (95% CI NNTH 3·3 to ∞ to NNTB 9·3)	Moderate clinical significance and no statistical significance

Notes: [a] Study findings expressed as risk of diarrhoea, shown as ratio between number of patients with diarrhoea in a group and total number of patients in that group, for both intervention group (I) and control group (C).
[b] The number needed to treat (NNT) is calculated as the inverse of the absolute risk reduction (ARR). For each study, ARR was calculated as the risk of diarrhoea in the control group minus the risk of diarrhoea in the treatment group. When the ARR is negative (i.e., treatment is worse than placebo), the NNT is also negative. A positive NNT is indicated as NNTB (benefit) and a negative NNT is indicated as NNTH (harm), both with a positive sign.
[c] Germain et al.[20] reported only the percentage of participants with diarrhoea in each group; therefore, to estimate the boundaries of the confidence intervals, the groups were assumed to be of equal number of participants, that is, 246/3 = 82.

adults of both genders treated for various cancers, thereby being more representative of the larger population of patients undergoing abdominal and pelvic radiotherapy, and therefore having higher external validity. Similarly, Germain et al.[20] investigated 246 adults of both genders treated for various cancers.

Chitapanarux et al.[22] showed low detection bias. An independent laboratory technician established stool consistency as loose (diarrhoea) and soft or formed (normal stool). However, the much larger study[19] had risk of detection bias, as presence of diarrhoea was assessed through participants' diary and diarrhoea was not clearly defined. For similar reasons detection bias was showed by Germain et al.[20] and Giralt et al.[21]

Results are also inconsistent. Chitapanarux et al's[22] lower NNTB indicates higher efficacy of their treatment, but with a probiotic (Infloran) two orders of magnitude-less potent, containing less bacterial strains and administered less frequently than the probiotic (VSL#3) used by Delia et al.[19] This could be because of the small sample size, reflected in the wider CI, by which the true efficacy could be near the CI higher boundary. Similarly, even if less strikingly, Germain et al's[20] standard-dose group showed an effect size comparable with that by Delia et al.[19] but with a probiotic two orders of magnitude-less potent. Moreover, Germain et al.[20] showed internal dose–effect inconsistency, as the standard-dose group had higher benefit (NNTB = 5·5) than the high-dose group (NNTB = 10·3).

Dose–effect inconsistency between Delia et al.[19] and Chitapanarux et al.[22] could be due to a true effect. Delia et al.[19] administered treatment only during radiotherapy, whereas Chitapanarux et al.[22] commenced treatment 7 days before starting radiotherapy, perhaps conferring increased prophylaxis. Moreover, Infloran capsule form might have superior gastric resistance compared with VSL#3 sachets, possibly decreasing potency discrepancy. Final formulation has an important effect on probiotic

Table 6. Clinical evidence profile: probiotics for the prevention of radiotherapy-induced diarrhoea in adults[a]

Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Presence of diarrhoea							
4	RCT	Serious[b]	Serious[c]	No serious indirectness	No serious imprecision	None	Low

Notes: [a] Adapted from the modified GRADE profile[25]. A summary of findings is not included as the effect sizes of the individual studies (Table 5) were not combined with a meta-analysis.
[b] The largest study, accounting for 55% of the total number of patients, has serious risk of detection bias, as stool consistency was subjectively assessed and diarrhoea was not clearly defined.
[c] There is a dose/effect inconsistency between studies and within a study.
Abbreviation: RCT, randomised clinical trial.

therapy efficacy.[35,36] In addition, Giralt et al.[21] were the only investigators who found a non-beneficial effect of probiotics, albeit with no statistically significant results, and used a probiotic of one order of magnitude-less potent than the one used by Chitapanarux et al.[22] and Germain et al.[20] Therefore, Giralt et al's[21] results are consistent with a dose/effect argument.

Heterogeneity of effects is not surprising considering that probiotics include a plethora of microorganism species, with different behaviour in the intestine, and subject to diverse manufacturing methods. This leads to multiple treatment options, including strains used, potency, formulation and therapeutic regimen.

The probiotic preparations used in the included papers have been studied in connection with the treatment of other conditions. Infloran efficacy has been shown in paediatric settings for the treatment of acute diarrhoea[37,38] and prevention of necrotising enterocolitis.[39] The efficacy of VSL#3 has been shown in the prevention of pouchitis,[40] in the treatment maintenance of ulcerative colitis[34,41] and in the reduction of diarrhoea in enterically fed patients.[42] The British National Formulary lists VSL#3 for pouchitis prevention.[43] Lactobacillus casei DN-114001 has showed efficacy in preventing or reducing the severity of infectious diarrhoea.[44–46] Bifilact has not received much attention in the literature.

CONCLUSIONS

When the above considerations are applied to the GRADE system of evidence quality rating,[47] there is low-quality evidence that probiotics are beneficial in RID prevention: the large effects and their precision would suggest a high quality of the evidence, but this is downgraded by effect inconsistency and risk of detection bias (Table 6).

Some of the probiotics investigated in the included studies have been shown to be effective in other gastrointestinal conditions, but this evidence cannot be immediately transferred to RID. Before advising towards the clinical use of probiotics in RID prevention, further trials, especially involving the promising VSL#3 and Infloran, are essential. Where appropriate, trials should describe randomisation, use intention to treat analysis, report effect sizes and assess diarrhoea objectively.

This review had limited scope and objectivity could not be improved without a second reviewer. Making sense of the disparate range of interventions in studies on probiotics is challenging. A meta-analysis on the prevention of RID with probiotics was intentionally avoided. Rather than numerically combining the disparate alternatives of this heterogeneous area of therapy, studies were considered in their own merit, to highlight meaningful results of individual studies and provide directions for future trials.

The studies did not assess participants' perceived benefits, failing to provide further insight into probiotics efficacy. Moreover, patients with RID might develop chronic gastrointestinal symptoms, requiring long-term and often expensive treatment.[4] Long-term follow-up of trial participants are needed to assess probiotic potential in reducing chronic complications and to provide insight of true probiotics clinical cost-effectiveness.

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