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REVIEW PAPER

Lactobacillus rhamnosus for treating irritable bowel syndrome in children – a systematic review with meta-analysis

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ABSTRACT

The objective of the study was to systematically assess whether the oral probiotic *Lactobacillus rhamnosus* (LGG) improves symptoms of irritable bowel syndrome in children. Four randomised clinical trials met the inclusion criteria, a total of 252 patients. Success of treatment was reported in 50 out of 82 patients (58.82%) from the LGG group, compared with 28 from 82 (34.14%) in the placebo group (p = 0.05). The number of pain episodes was lower in the LGG group compared with the placebo group (n = 117, 95% CI: 1.50 [–2.03; –0.97], $p < 0.05$). The use of LGG resulted in a decrease in the perception of pain intensity in the study population overall ($n = 219$, 95% CI: –0.61 [–1.13; –0.09], $p < 0.05$). A higher dosage of LGG was less effective than a lower dosage in improving the overall treatment success ($p = 0.05$). The dosage of LGG was not statistically significant in improving pain severity ($p = 0.12$).

KEY WORDS:
Lactobacillus rhamnosus, microbiota, probiotic, irritable bowel syndrome.

INTRODUCTION

Irritable bowel syndrome (IBS) is one the most common chronic functional gastrointestinal (GI) disorders in the paediatric population [1]. Although considered benign, it has a significant effect on the life quality of affected children and their families and poses a remarkable burden on healthcare systems. The symptoms involve not only diarrhoea, constipation, abdominal distention, bloating, cramping, and urgency to defecate, but are also associated with pain, anxiety, school absenteeism, and frequent visits to a physician [2]. The aetiology of IBS remains unclear, so therapeutic options are limited so far. The disease should be treated based on the predominant symptoms. Antacids, laxatives, antidiarrhea medications, antispasmodics, and antidepressants are just a few of the therapeutic agents [3]. However, few studies have reported the relationship between the gut microbiota and IBS. The faecal microbiota of patients with IBS shows a great homogeneity comprising decreased level of coliforms, lactobacilli and bifidobacterial compared with healthy individuals [4]. Moreover, some studies suggest that factors suspected to imply to the IBS pathogenesis have the capacity to change the intestinal microflora [5].

Clinical application of probiotics, consumed in adequate amounts, is beneficial to the health of the host. One of the probiotic bacterial strains studied in several clinical trials for treating, preventing, and/or alleviating IBS symptoms is *Lactobacillus rhamnosus* GG (LGG). This probiotic strain is naturally found in the GI tract. It can

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survive, and proliferate at gastric acid pH and in medium containing bile and adhere to enterocytes [6]. In addition, LGG can form a biofilm, which mechanically protects the mucosa and secretes postbiotics – soluble factors beneficial to the gut [7, 8]. Probiotics are also believed to prevent overgrowth of pathogenic bacteria and maintain the integrity of the gut mucosal barrier [9].

These beneficial effects of probiotics have been broadly studied in several trials. However, the results of LGG used for treating IBS in children and adolescents are ambiguous. The goal of this study is to systematically overview the available data, compare the results, and assess whether oral administration of the probiotic LGG compared with placebo would improve symptoms of IBS in children.

MATERIAL AND METHODS

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

This review included every relevant randomised controlled trial (RCTs) that compared the effects of LGG administration with the effects of placebo for treating abdominal pain in children with IBS.

As in our earlier report focusing on a single probiotic strain [10], for this systematic review and meta-analysis, the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions [11] and the PRISMA Statement [12] were followed. Electronic databases (see Search strategy) were systematically searched for relevant studies to be included in this review. Only RCTs that compared LGG with placebo or LGG as synbiotic with inulin were eligible for inclusion. The participants were children up to 18 years of age with clinically diagnosed IBS according to Rome II and III criteria. The data presented in the included articles were collected from July 2003 to September 2012.

SEARCH STRATEGY

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, and EMBASE databases were search from inception until February 2022. Grey literature were searched through Google Scholar. The search strategy included the use of a validated filter for identifying RCTs, which was combined with a topic-specific strategy using the following PubMed MeSH terms (children OR child* OR infants OR infant* OR toddler* OR adolescent* OR teenage* OR baby OR preschool children) AND (probiotic OR *Lactobacillus rhamnosus* OR *Lactobacillus rhamnosus* OR *Lactobacillus casei rhamnosus* OR *Lactobacillus* OR LGG) AND (irritable bowel syndrome OR IBS OR (irritable AND bowel AND syndrome) OR functional abdominal pain OR Mucous Colitis OR spastic colon OR irritable colon OR functional bowel OR colonic disease OR gastrointestinal syndrome OR fgid OR functional gastrointestinal disorder OR Colon spasm OR Irritable colon syndrome OR spastic colitis OR unstable colon OR functional colonic disease OR irritable colon syndrome OR functional).

Moreover, reference lists from the original studies and review articles identified were screened. Key researchers on the topic of probiotics were identified by the research team. No language restrictions were imposed. Two registers for clinical trials (www.clinicaltrials.gov; www.clinicaltrialsregister.eu) were screened to identify unpublished and ongoing studies. All potentially relevant articles were retained, and the full text of each of these studies was examined to determine which studies met the inclusion criteria.

The primary outcome was clinical effectiveness of LGG defined as improvement in global IBS symptoms and abdominal pain (as defined by the investigators). Secondary outcomes were the effects of *Lactobacillus rhamnosus* on the course of IBS, particularly on defecatory pattern, GI symptoms, drug-related outcomes (adverse effects of intervention and need for use of other drugs), and health-related quality of life parameters.

SELECTION OF STUDIES

Studies with irrelevant titles and abstracts were excluded; however, we obtained every study with a relevant but insufficient abstract. Disagreements were discussed until researchers achieved a consensus.

DATA EXTRACTION AND MANAGEMENT

Using a standardised form, 5 of the reviewers (JT, LS, BB, JŻ, AH) independently undertook the literature search, data extraction, and quality assessment. Data were extracted as complete (available) case analyses. Data extracted included data on year of publication, study design, number and base characteristic of participants, IBS definition used, LGG dose and duration of the intervention, the comparator intervention, and study outcomes as defined by the authors. All data were compared between the groups to reduce the risk of error. Disagreements were resolved by discussion with another reviewer (MR).

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

The first version of the Cochrane Collaboration's risk-of-bias tool for assessing risk of bias in included trials was used, which assesses randomisation and allocation of participants; blinding of participants, personnel, and outcome assessors; and incomplete or selective reporting. If an item could not be evaluated due to missing information, it was rated as having an unclear risk of bias. Two of the reviewers (JT, JŻ) independently assessed the risk

of bias of the included trials. Disagreements were resolved by a third reviewer (MR).

MEASURES OF TREATMENT EFFECT

The impact of LGG was expressed as an odds ratio (OR) of IBS treatment success compared with control, with 95% confidence interval (CI) or a mean difference of continuous outcomes between experimental and control groups, with 95% CI. If feasible, subgroup analyses were performed.

DEALING WITH MISSING DATA

Corresponding authors were contacted if reports provided insufficient or missing data for our analysis. However, we have not received any response, thus only the available data were analysed.

ASSESSMENT OF HETEROGENEITY

Heterogeneity between studies was assessed using the I^2 statistic, with > 50% considered to be significant heterogeneity, and the χ^2 test, with a p-value < 0.1 indicating statistically significant heterogeneity. Data were pooled using a fixed effects model if heterogeneity between the studies was low. Data of studies with substantial heterogeneity were analysed using the random effects model (if appropriate to pool the data).

STATISTICAL METHODS

Review Manager (RevMan) software [Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020] was used to analyse the data. The binary measure for individual studies and pooled statistics is reported as the OR between the experimental and control groups with 95% CI. Several subgroup analyses were planned based on the dose of LGG, the setting (studies carried out in countries based on the Human Development Index status [very high/high vs. medium/low]), and the type of treatment (outpatient vs. inpatient). However, only 2 subgroups were analysed: the patients with treatment success and improvement of pain.

RESULTS

INCLUDED STUDIES

The literature search initially yielded 44 articles, of which 4 RCTs met the inclusion criteria for this systematic review. Figure 1 shows a flow diagram documenting the identification process for the eligible trials. All studies were published in English. Each study [13–16]

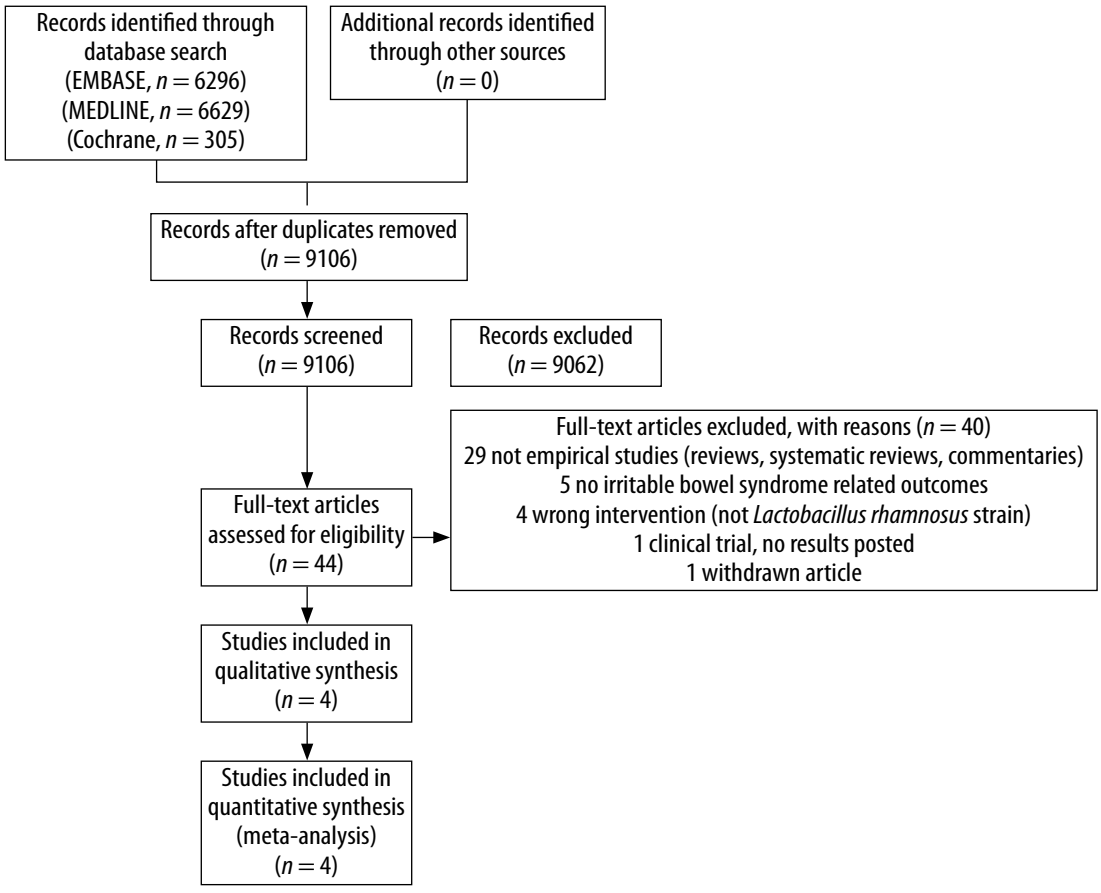

FIGURE 1. Identification process for eligible trials

was a full-text publication published in a peer-reviewed journal.

The included RCTs randomised a total of 252 patients, aged 0–18 years. The diagnoses were made mainly according to the Rome II criteria [13–15]; only in a single RCT [16] were the Rome III criteria used. Sample size calculations were only available in 2 trials [15, 16]. All studies were placebo-controlled trials. Two trials were conducted in Europe [14, 15], one trial was conducted in the US [13], one in Iran [16]. All RCTs were conducted in out-patients. The daily dose of LGG ranged from 3×10^9 [14, 15] to 10^{10} [13, 16] colony forming units administered twice daily. In 2 trials inulin was present in the LGG and in the placebo capsules [13, 16]. Measurement after intervention ranged from 4 weeks [15, 16], through 6 weeks [13], to 8 weeks [14]. In one trial [14], follow-up 8 weeks after the end of intervention was presented and treatment success was reported at different time points; nevertheless, for this meta-analysis the data from the end of intervention were used. The definitions of outcome measures varied. None of the trials was industry supported. Table 1 summarises the characteristics of all included RCTs.

TABLE 1. Characteristics of included studies

Study	Participants	Diagnostic criteria	LGG (dose)	Comparison	Primary outcome	Secondary outcomes
Bausserman *et al*. 2005	Children and adolescents (mean age: 12 years, range: 6–17 years)	Rome II criteria for IBS	1 × 10 ^ 10 CFU, twice daily, for 6 weeks	Placebo (inulin)	Change in the abdominal pain severity score	• Number of responders vs. non-responders in each group and changes in the symptoms on the gastrointestinal symptom rating • Scale (15-item GSRS) by syndrome. • Responders were classified as patients with a decrease in abdominal pain severity (1 point or more on the 4-point Likert scale)
Francavilla *et al.* 2010	Children (mean age: 6.4 years, range: 5–14 years)	Rome II criteria for IBS or FAP	3 × 10 ^ 9 CFU, twice daily, for 8 weeks	Placebo	Change in abdominal pain (frequency/ severity) according to the VAS score from baseline to the end of the treatment period	• A decrease of at least 50% in the number of episodes and intensity of pain (treatment success) • A decrease in the perception of children's pain according to their parents • Modification of intestinal permeability
Gawrońska *et al*. 2007	Children (mean age: 11.6 years, range: 6–16 years)	Rome II criteria for IBS, FAP, FD	3 × 109 CFU, twice daily, for 4 weeks	Placebo (maltodextrin)	Treatment success defined as no pain (a relaxed face, score of 0, on the FPS) at the end of the intervention	Improvements defined as a change in: • the FPS by at least 2 faces scores • self-reported severity of pain during the preceding week measured on the FPS • self-reported frequency of pain during the preceding week • use of medication for abdominal pain • school absenteeism because of abdominal pain
Kianifar *et al*. 2015	Children (mean 7.1, range: 4–18 years)	Rome III criteria	1 × 1010 CFU, twice daily for 4 weeks	Placebo (inulin)	Change in abdominal pain according to the Likert pain severity scale from baseline to the end of the treatment period	Change of the functional scale, stool patterns, and associated problems

CFU – colony forming units, FAP – functional abdominal pain, FD – functional dyspepsia, FPS – faces pain scale, GSRS – gastrointestinal symptom rating scale, IBS – irritable bowel syndrome, LGG – Lactobacillus rhamnosus GG, VAS – visual analogue scale

RISK OF BIAS IN INCLUDED TRIALS

For the assessment of potential risk of bias (Figure 2). The methodological limitations of trials included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data (attrition bias), and selective reporting. Every study had good quality; however, the study by Bauserman *et al.* [13] had incomplete data due to over 20% loss to follow-up.

HETEROGENEITY

Heterogeneity among the studies regarding number of pain responders was significant (I^2 = 40%) (χ^2 = 1.67, df = 1 [p = 0.2]). No heterogeneity for number of pain episodes was found (I^2 = 0%)(χ^2 = 0.27, df = 1 [p = 0.60]). Heterogeneity for improvement of pain severity in LGG vs. placebo trials was not found (I^2 = 0%)(χ^2 = 0.02, df = 1 [p = 0.89]). However, in the synbiotic vs. prebiotic trials heterogeneity was significant (I^2 = 79%)(χ^2 = 4.68, df = 1 [p = 0.03]). Due to the low number of available studies, estimating between-study heterogeneity statistic is prone to substantial bias.

In all cases, the observed statistical heterogeneity was not judged to be clinically relevant (i.e. studies consistently reported results in the same direction with clinically insignificant differences between the studies). However, there were too few studies to adequately determine heterogeneity.

EFFECTS OF INTERVENTION – PRIMARY OUTCOME

Treatment success was defined as a change in the abdominal pain severity score [13], a decrease in pain episodes number and pain intensity [14], a lack of pain at the end of intervention [15], and a decrease in Likert pain severity scale score [16].

Success of treatment was reported in 39 patients out of 60 from the LGG group (65%), compared with 18 out of 57 in the placebo group (31.57%), but the difference

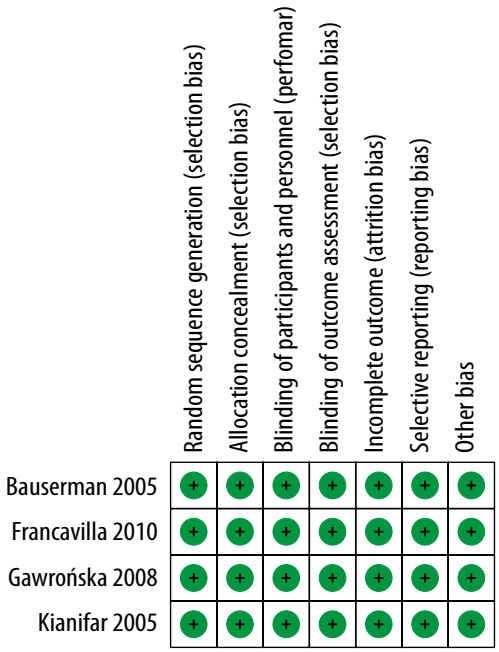

FIGURE 2. Risk of bias summary: review authors' judgments about each item for each included study

was not statistically significant (p = 0.2). Detailed statistics are available in Figure 3.

FREQUENCY OF PAIN

Mean difference of pain episodes numbers was significantly lower in the LGG group comparing with placebo group (two RCTs, n = 117, 95% CI: –1.50 (–2.03; –0.97), p < 0.05) (Figure 2).

SEVERITY OF PAIN

Compared with placebo, the use of LGG was associated with a decrease in the perception of pain intensity in the overall study population (2 RCTs, n = 117, 95% CI: –1.07 [–1.72; –0.41], p < 0.05). Detailed statistics are available in Figure 4.

Compared with the use of inulin alone, the use of LGG with inulin was associated with a decrease in

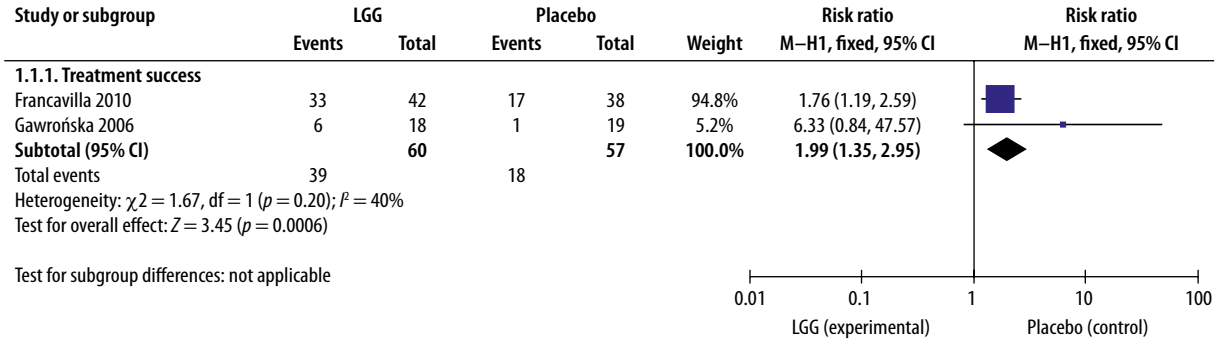

FIGURE 3. Primary outcome: effect of *Lactobacillus rhamnosus* GG on treatment success

LGG – Lactobacillus rhamnosus

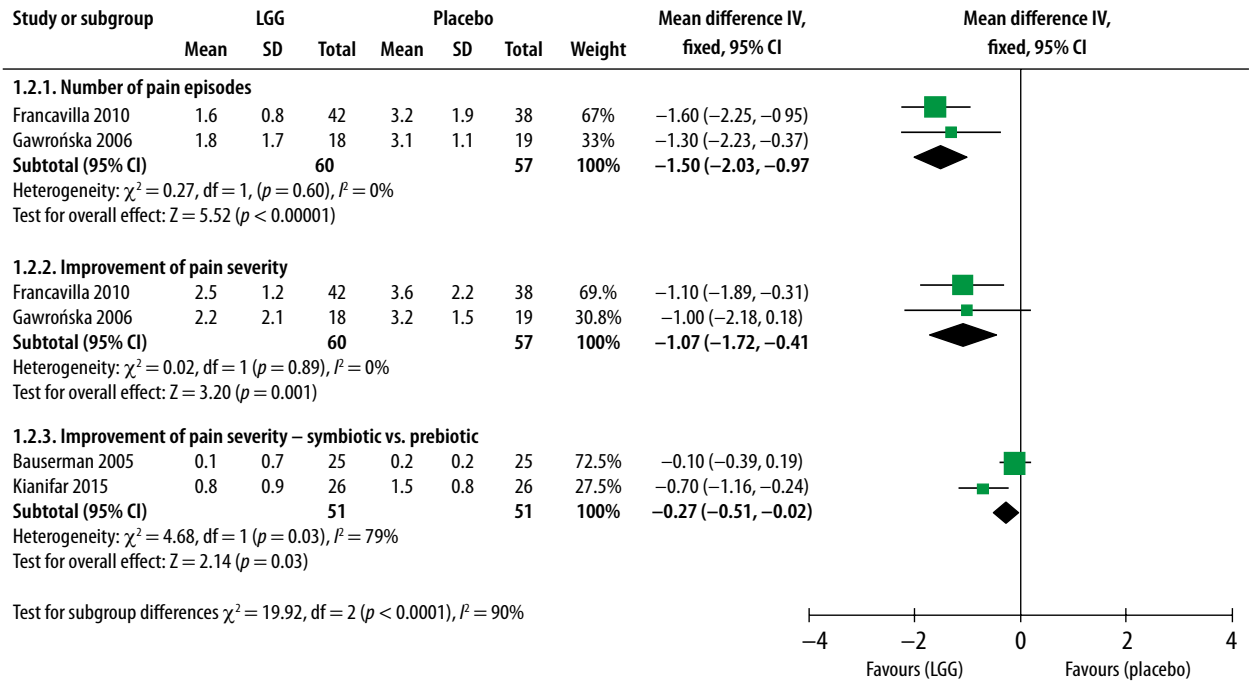

FIGURE 4. Primary outcome: effect of *Lactobacillus rhamnosus* GG on number of pain episodes and improvement of pain severity in *Lactobacillus rhamnosus* GG vs. placebo and synbiotic vs. prebiotic

LGG – Lactobacillus rhamnosus, SD – standard deviation

the perception of pain intensity in the overall study population (2 RCTs, n = 102, 95% CI: −0.27 [−0.51; −0.02], p = 0.03). Detailed statistics are available in Figure 4.

SECONDARY OUTCOMES

Due to the lack of comparable secondary outcomes in the presented trials it was not feasible to assess the impact of LGG on defecatory pattern, GI symptoms, drug-related outcomes (adverse effects of intervention and need for use of other drugs), and health-related quality of life parameters.

ADVERSE EVENTS

Data regarding therapy-related adverse events were available from 4 of the included trials [13–16]. The *Lactobacillus rhamnosus* was well tolerated and no adverse effects were reported.

DISCUSSION

SUMMARY OF MAIN EVIDENCE

This systematic review and meta-analysis provide a summary of current data regarding the effect of *Lactobacillus rhamnosus*, a single probiotic microorganism, in paediatric patients suffering from IBS. Analysing the limited evidence available, we found that the use of the LGG (in synbiotic or alone), compared to the prebiotic or placebo, can result in treatment success. This was defined as a decrease in the abdominal severity score, a decrease in the number of pain episodes and pain intensity, lack of pain at the end of the intervention, and a decrease in Likert severity score in children with IBS. Moreover, LGG reduced the mean number of pain episodes amid the treatment period. Even though the effects were positive and statistically significant, they were clinically modest.

OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

Three major databases (CENTRAL, the Cochrane Library; MEDLINE and EMBASE) were searched with no language restrictions. The data were systematically searched, extracted, and their validity was assessed independently by 5 reviewers (JT, LS, BB, JŻ, AH) to decrease the likelihood of reviewer error or bias. Moreover, the risk of bias was then independently assessed by 2 reviewers (JT, JŻ), and all the disagreements were resolved by a third reviewer (MR). However, the possibility of publication bias cannot be fully excluded, which is a significant threat to the validity of systematic reviews and can be only avoided with the registration of all the RCTs.

One strength of our review distinguishes it from other reviews: our meta-analysis focuses on only one probiotic microorganism. The supplementation of the probiotics is not a homogeneous intervention. Collecting data from different genera, species, strains, or doses of the probiotics may lead to misguided conclusions.

QUALITY OF EVIDENCE

The quality of any systematic review depends on the constituent studies. The included RCTs must have met

the inclusion criteria with adequate randomisation, allocation concealment, blinding, and follow-up, all of which was of sound methodology. Only one study, Bauserman *et al.* [13] had incomplete data due to over 20% loss to follow-up. The second potential limitation is that there were few trials included in the review. The included studies focused on small sample sizes, which is typical for evaluation of the subgroup of patients with specific diagnoses. Nonetheless, to increase power is why the meta-analysis is executed within a systematic review.

In all the included RCTs, the intervention with a probiotic strain lasted a minimum of 4 weeks, which is the recommended duration in the ROME Foundation guidance document for the design of treatment trials in patients with familial glucocorticoid deficiency [17]. However, there is a lack of recommended extended follow-up time in the evaluated studies.

All of the included studies used validated tools – the Likert scale [13, 16], visual analogue scale [14], and the faces pain scale [15], which are objective in such a subjective syndrome as pain itself.

Another essential requirement for interventional studies of IBS is a placebo-controlled study. Two RCTs met this criterion, while another 2 RCTs used LGG in combination with inulin in the experimental group and inulin in the control group; therefore, the outcome could be affected because of the prebiotic potential of inulin. This alleged impact was not observed in our analysis; however, this should be taken into account while designing future studies.

AGREEMENT AND DISAGREEMENT WITH OTHER STUDIES OR REVIEWS

Several preceding systematic reviews, including a Cochrane review by Wallace *et al.* [18], revealed the positive effects of probiotics and synbiotics on functional abdominal pain disorders, confirming that probiotics and synbiotics (as a class of drugs) may be beneficial in alleviating GI symptoms among children, but the evidence is of low certainty. Probiotics may achieve more treatment success when compared with placebo at the end of the treatment, with 50% success in the probiotic group vs. 33% success in the placebo group (RR 1.57, 95% CI: 1.05–2.36; 554 participants; 6 studies; I2 = 70%; low-certainty evidence). Synbiotics may result in more treatment success at the study end when compared with placebo, with 47% success in the probiotic group vs. 35% success in the placebo group (RR 1.34, 95% CI: 1.03 to 1.74; 310 participants; 4 studies; I2 = 0%; low certainty).

In another systematic review and meta-analysis conducted by Trivić *et al.* [19] *Lactobacillus reuteri* was proven to decrease the pain intensity in children with functional abdominal pain. *Lactobacillus rhamnosus* GG and *Lactobacillus reuteri* DSM 17938 were the only 2 probiotic strains investigated; however, neither of them significantly increased the number of children in whom symptoms completely ceased after the intervention.

In principle, results of the Cochrane meta-analysis are consistent with our review. However, subgroup analysis of specific probiotic strains in each clinical entity was not performed in the previously mentioned meta-analysis. Our study fills this gap by evaluating one specific strain in one exclusive clinical condition.

Nevertheless, previous meta-analyses have not provided conclusive evidence to recognise LGG as an effective agent in the management of IBS. We identified one systematic review with a meta-analysis conducted by Horvath *et al.* in 2010 [10], which was focused exclusively on one type of clearly defined probiotic microorganism: *Lactobacillus rhamnosus* GG. Our study was performed to update this. The added value of our systematic review was the longer screening period (over 11 years), identification of one unique RCT conducted by Kianifar *et al.* [16], and providing evidence synthesis only for children with irritable bowel syndrome, because other available systematic reviews provide evidence only for functional abdominal pain disorders as a group, not for FAPD subtypes. Our meta-analysis of RCTs confirms the results of the 2010 meta-analysis and strengthens the evidence of LGG efficacy in the management of abdominal pain-related functional GI disorders (IBS in this case) in childhood.

IMPLICATIONS FOR PRACTICE

The results of this systematic review present preliminary evidence that LGG as a probiotic may be useful in treating children with IBS, particularly in lowering pain severity, decreasing the number of pain episodes, and reducing pain intensity. It is too soon to recommend this routine use in clinical practice; however, the good safety profile and promising efficacy demonstrated in our study may encourage clinicians to consider using probiotics (LGG in particular) in a clinical setting.

IMPLICATIONS FOR RESEARCH

Despite promising results of the 2010 systematic review [10] and over 11 years since its publication, only one new RCT met the criteria and was feasible for inclusion in the meta-analysis. Our study highlights the need to conduct large multi-centred trials devoted to the use of probiotics in functional GI disorders, which may strengthen the evidence and legitimise the use of LGG in the management of IBS in children. Due to the remarkably high heterogeneity among published studies, upcoming trials are desired to provide more unified and consistent methodology, and standardised outcomes and definitions. The impact of dosage or ethnicity on therapeutic success and cost-effectiveness are important but still unanswered issues that need to be further evaluated.

DISCLOSURE

The authors declare no conflict of interest.

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