Lactobacillus GG Supplementation on Anti-*Helicobacter pylori* Therapy-Related Side Effects and Eradication Rates: A Meta-Analysis

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Abstract

Background: Concerns still exist with respect to unsatisfactory eradication rates and/or therapy-associated side effects for the use of standard triple therapy in the treatment of *Helicobacter pylori* infection, which prompts considerable interest in new therapy. We systematically reviewed the literature to investigate whether *Lactobacillus* GG as supplementation to standard triple therapy could improve *H. pylori* eradication rates and/or reduce therapy-associated side effects. Methods: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched from their inception to August 4, 2015 for randomized controlled trials (RCTs). The language was restricted to English only. Results: Four RCTs involving a total of 305 participants (including 83 children) were included. *Lactobacillus* GG given along with triple therapy significantly reduced the risk of overall *H. pylori* therapy-related adverse effects (three RCTs, n = 221, RR 0.59, 95% CI 0.45 - 0.78), particularly of diarrhea (four RCTs, n = 285, RR 0.23, 95% CI 0.11 - 0.47), bloating (four RCTs, n = 289, RR 0.61, 95% CI 0.41 - 0.90), and taste disturbance (four RCTs, n = 288, RR 0.38, 95% CI 0.23 - 0.62). There were no significant differences between groups in the risk of other adverse effects. No beneficial effects of *Lactobacillus* GG were observed for *H. pylori* eradication rates (four RCTs, n = 284, RR 0.99, 95% CI 0.88 - 1.13). Conclusion: Current evidence indicates that *Lactobacillus* GG administered along with standard triple therapy is a feasible way to reduce therapy-related side effects, particularly diarrhea, bloating, and taste disturbance. However, *Lactobacillus* GG shows no effects on eradication rates.

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1. Introduction

Helicobacter pylori is the causative agent of chronic gastritis, peptic ulcer, gastric adenocarcinoma, and lymphoma [1]-[3]. The most commonly prescribed triple therapy, composed of proton-pump inhibitor, clarithromycin or levofloxacin, and amoxicillin or tinidazole, remains the first-choice treatment for *H. pylori* infection. However, in recent years, we have witnessed decreasing eradication rates with this standard triple therapy, mainly due to increased resistance to antibiotics [4]. Moreover, about 5% - 30% of patients receiving triple therapy are reported to experience antibiotic-associated side effects, which leads to low compliance and further treatment failure [5]. Strategies targeted to raise eradication rates and improve the treatment tolerability are increasingly needed.

In 2012, the Maastricht IV/Florence Consensus Report stated that certain probiotics as adjuvant treatment could exert beneficial effects on the management of *H. pylori* [6]. A recent meta-analysis [7] also evaluated the effects of supplementation with probiotics on *H. pylori* eradication rates and side effects of anti-*H. pylori* treatment. Thirty-three randomized controlled trials (RCTs) of varying methodological quality involving a total of 4459 patients were identified. These pooled results indicated that probiotic supplementation, when compared with eradication therapy, could increase eradication rates, particularly when antibiotic therapies are relatively ineffective, and reduce therapy-related overall side effects. However, the beneficial effects of probiotics seem to be strain specific, and pooling data on various strains may lead to spurious conclusions. A more appropriate way is to conduct a meta-analysis that evaluates the effects of a clearly defined probiotic microorganism.

Several specific probiotics have been shown to lower *H. pylori* bacterial load and gastric inflammation and reduce antibiotic-associated side effects [8]. Our study focused on a single probiotic microorganism, *i.e.*, *Lactobacillus* GG, to evaluate the probable effects of *Lactobacillus* GG given concomantly with standard eradication therapy on major clinical outcomes related to *H. pylori* eradication and therapy-associated side effects.

2. Methods

This systematic review and meta-analysis was conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) [9], and the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [10].

2.1. Literature Search and Selection Criteria

PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched. We used the following key words: probiotic, probiotics, *Lactobacillus rhamnosus* GG, *Lactobacillus* GG, *LGG*, *Helicobacter pylori*, and *H. pylori*. The language was restricted to English. The last search was conducted in August 4, 2015. The detailed search strategy is shown in **Table 1**. The cited references of retrieved articles and previous reviews were also manually checked to identify any additional eligible studies. All citations were imported into a bibliographic database (EndNote X7; Thomson Reuters) for assessment of eligibility. Two of authors (G-QZ, H-JH) independently carried out literature search, eligibility evaluation, data extraction and quality assessment. Discrepancies between authors were resolved by consensus.

We developed a PICOS (Patient, Intervention, Comparators, Outcome, and Study design) approach as the

Table 1. Search strategy.

Search terms
1. (probiotic OR probiotics OR *Lactobacillus rhamnosus* GG OR *Lactobacillus* GG OR *LGG*)
2. (*Helicobacter pylori* OR *H. pylori*)
3. controlled trial
4. 1 AND 2 AND 3

eligibility criteria: 1) Population: *H. pylori*-infected subjects of any age, diagnosed by generally accepted methods (*i.e.*, histopathology, the ^{13}C-urea breath test (UBT), the rapid urease test, or measurement of *H. pylori* IgG antibody); 2) Intervention: *Lactobacillus* GG supplementation given during standard triple therapy; 3) Comparators: standard triple therapy without *Lactobacillus* GG; 4) Outcome: the primary outcome was incidence of adverse effects. The adverse effects of interest were any common gastrointestinal adverse effects that occurred during standard triple therapy, including diarrhea, epigastric pain, nausea and/or vomiting, abdominal bloating, flatus, taste disturbance, loss of appetite, constipation, and the need for discontinuation of the anti-*H. pylori* therapy; the secondary outcome was *H. pylori* eradication rate, confirmed by a negative ^{13}C-UBT or other generally accepted method; 5) Study design: only randomized controlled trials were eligible.

2.2. Data Extraction and Quality Assessment

Two of authors (G-QZ, H-JH) independently extracted relevant data from each included study by using a unified data form. Extracted data were entered into a standardized Excel file. The items included in the data form were as follows: source (first author, year of publication, country), number of patients enrolled, eradication regimen, *Lactobacillus* GG (dose, duration), the comparator group, primary and secondary outcomes reported by the authors, follow-up, and methods of checking *H. pylori* status and side effects. The Cochrane Risk of Bias Tool was adopted to assess the risk of bias for each RCT [11].

2.3. Statistical Analysis

To evaluate the effects of probiotics, we calculated relative risks (RRs) with its 95% confidence intervals (CIs) for the outcomes of interest between intervention and control groups. Heterogeneity across studies was tested by using the I^2 statistic [12]. Studies with an I^2 value of greater than 50% were considered to have significant heterogeneity. The random effects model was used to calculate pooled RRs and its 95% CIs if significant heterogeneity existed. Otherwise, the fixed effects model was applied to calculate the pooled RRs. Funnel plot was carried out to investigate publication bias of all the included studies. However, the publication bias was not formally assessed, due to the small number of studies (<10) included in the analyses of the primary and secondary outcome measures. All statistical analyses were performed with RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

3. Results

A total of 193 records were identified by the initial database search. Twenty-eight records were excluded for duplicates, and 159 records were excluded based on the titles and abstracts for various reasons (reviews, letters, experimental studies or irrelevant to our study). The remaining six full-text articles were assessed for eligibility, and two of them were further excluded because of non-English [13] [14]. Finally, four trials met the inclusion criteria [15]-[18]. The selection process is shown in **Figure 1**.

3.1. Characteristics of Included Studies

These trials randomized a total of 305 patients, of which 288 were followed up. The main characteristics of included trials are summarized in **Table 2**. Three studies enrolled only adults [15]-[17], and one RCT [18] (n = 83) was undertaken exclusively in children (age range: 5 - 17 years). In all four included trials, *Lactobacillus* GG was given along with standard triple therapy composed of a proton pump inhibitor and two antibiotics. The daily doses of *Lactobacillus* GG ranged from 1×10^9 CFU (b.i.d) [18] to 6×10^9 CFU (b.i.d) [15]-[17]. Three RCTs were placebo controlled [16]-[18], and there was no additional intervention in the control group in the other one trial [15]. The included studies were conducted in Italy (three RCTs) [15]-[17] and Egypt (one RCT) [18]. **Figure 2** shows the results of the methodological quality assessment. The allocation concealment was unclear in one RCT [17], and another trial [15] was at high risk of binding. The remaining two trials had good methodological quality.

3.2. Effects of *Lactobacillus* GG

3.2.1. Primary Outcome: Therapy-Associated Side Effects

The incidence of therapy-related adverse effects was reported in all the included trials. A statistically significant
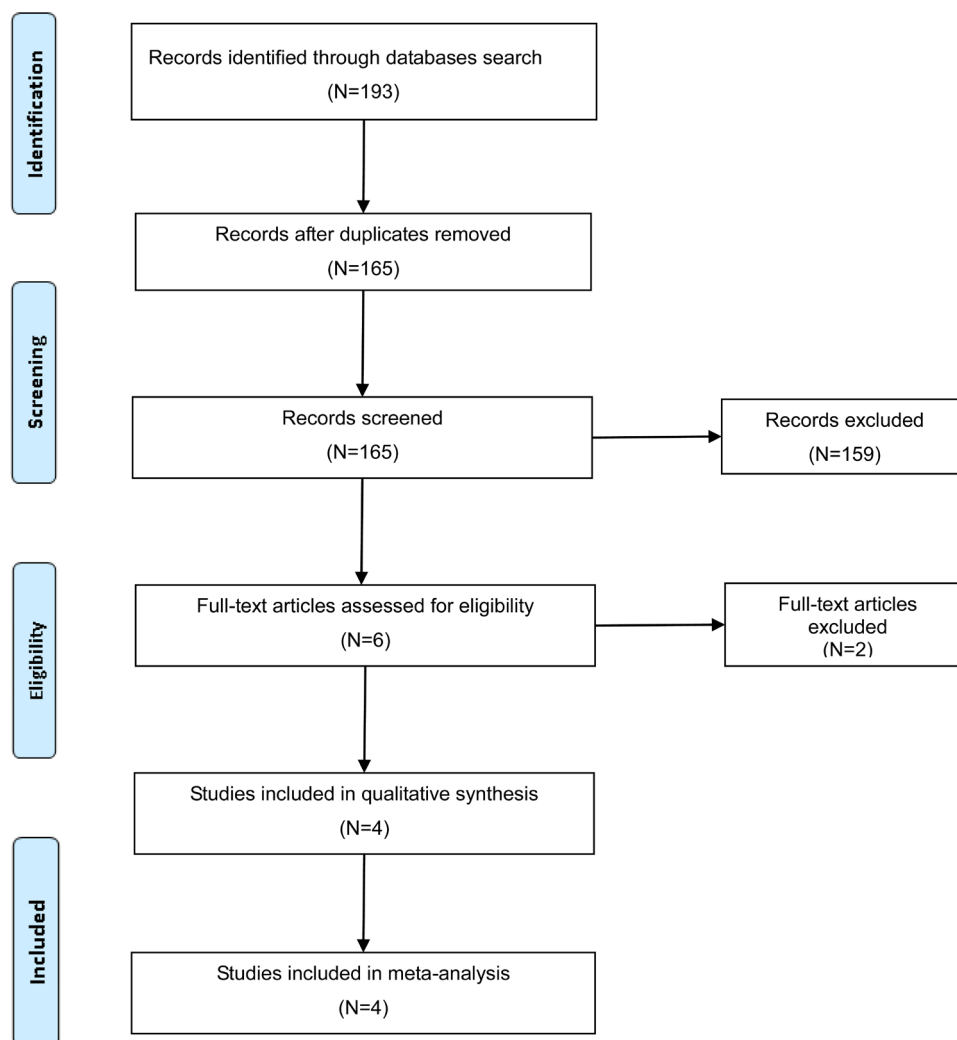
Figure 1. Selection process for the studies included in the meta-analysis.

difference was observed in adults between the *Lactobacillus* GG supplemented group and the control group with regard to the risk of overall adverse effects (three RCTs, n = 221, RR 0.59, 95% CI 0.45 - 0.78), shown in **Figure 3**. The risk of specific therapy-related adverse effects was statistically lower in the *Lactobacillus* GG group compared with the control group, *i.e.*, diarrhea (four RCTs, n = 285, RR 0.23, 95% CI 0.11 - 0.47), bloating (four RCTs, n = 289, RR 0.61, 95% CI 0.41 - 0.90), taste disturbance (four RCTs, n = 288, RR 0.38, 95% CI 0.23 - 0.62), shown in **Figure 4**. No significant difference was observed between groups regarding nausea, vomiting, constipation, epigastric pain, and loss of appetite. The need for discontinuation from the eradication therapy was not reported in any trial.

3.2.2. Secondary Outcome: *H. pylori* Eradication Rates

Data on effects of *Lactobacillus* GG supplementation on *H. pylori* eradication rates were available from all four of the included trials, which reported data from 284 patients (218 adults and 66 children). No significant difference was observed between the *Lactobacillus* GG-supplemented group and the control group with regard to *H. pylori* eradication rates (four RCTs, n = 284, RR 0.99, 95% CI 0.88 - 1.13), shown in **Figure 5**.

4. Discussion

This meta-analysis of RCTs provides a summary of current knowledge regarding the effects of a single probiotic microorganism, *Lactobacillus* GG, in patients infected by *H. pylori*. With the limited evidence available, addition

Table 2. Characteristics of randomized controlled trials included in our meta-analysis.

Source	Participants	Exp/Cont	Eradication regimen (daily dose)	LGG group dose, duration	Control group	Outcomes	Diagnosis of *Hp* (initial/re-checking)	Follow-up	Score system for assessing side effects
Armuzzi et al., 2001a[15] (Italy)	*Hp*-positive asymptomatic adults	60/60	Pantoprazole (40 mg b.i.d) Clarithromycin (500 mg b.i.d) Tinidazole (500 mg b.i.d) all for 7 days	6×10^9 CFU, b.i.d, for 14 days	No *LGG*	Side effects, eradication rate	UBT, *Hp* IgG antibody/UBT	6 weeks	Questionnaire by De Boer et al.
Armuzzi et al., 2001b[16] (Italy)	*Hp*-positive asymptomatic adults	30/30	Rabeprazole (20 mg b.i.d) Clarithromycin (500 mg b.i.d) Tinidazole (500 mg b.i.d) all for 7 days	6×10^9 CFU, b.i.d, for 14 days	Placebo	Side effects, eradication rate	UBT, *Hp* IgG antibody/UBT	6 weeks	Questionnaire by De Boer et al.
Cremonini et al., 2002[17] (Italy)	*Hp*-positive asymptomatic adults	21/21	Rabeprazole (20 mg b.i.d) Clarithromycin (500 mg b.i.d) Tinidazole (500 mg b.i.d) all for 7 days	6×10^9 CFU, b.i.d, for 14 days	Placebo	Side effects, eradication rate	UBT/UBT	5 - 7 weeks	Questionnaire by De Boer et al.
Szajewska et al., 2009[18] (Poland)	*Hp*-positive asymptomatic children	44/39	Omeprazole (0.5 mg/kg b.i.d) Clarithromycin (10 mg/kg b.i.d) Amoxicillin (25 mg/kg b.i.d) all for 7 days	1×10^9 CFU, b.i.d, for 7 days	Placebo	Eradication rate, side effects	UBT, histology, rapid urease test/UBT	4 weeks	Diary to record the therapy-related side effects

Figure 2. Assessment of risk of bias of all studies included in the meta-analysis.
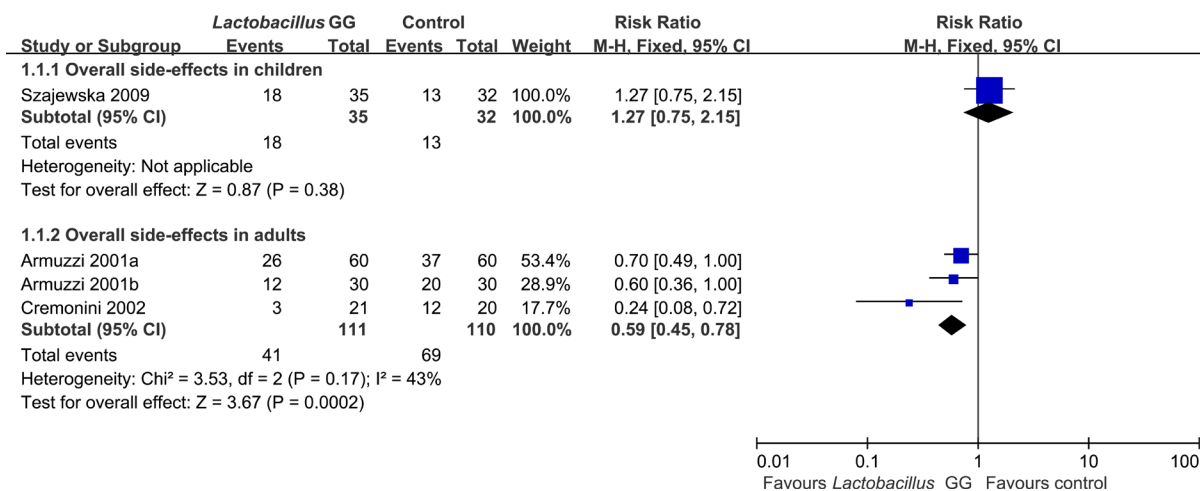

Figure 3. Relative risk (95% CI) of *Lactobacillus* GG on overall side-effects during therapy.

of *Lactobacillus* GG to triple therapy could reduce therapy-related adverse effects, such as diarrhea, bloating, and taste disturbance. However, *Lactobacillus* GG shows no beneficial effects on eradication rates. Because a majority of included patients were adults, our results may be applicable primarily to such a population.

Our study has several strengths. First, we systematically searched three major databases and no restriction of publication date was imposed. Second, to minimize the reviewers' error or bias, the searching, assessment of eligibility of studies and extraction of relevant data were performed independently by two of authors in a blinded manner. Third, the beneficial effects of probiotics seem to be strain specific and pooling data on various strains could probably lead to spurious conclusions. Hence, our meta-analysis used only one probiotic microorganism
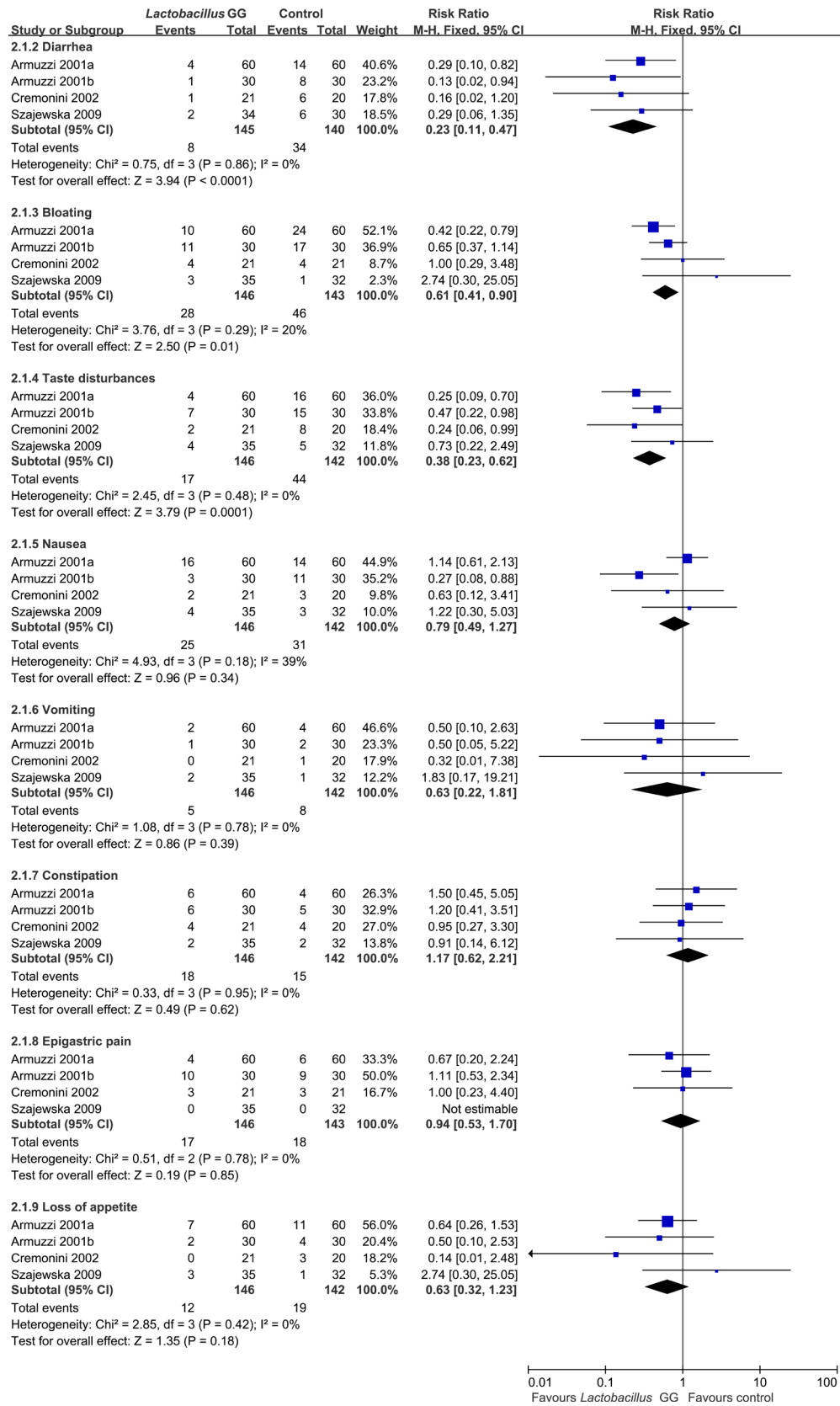
Figure 4. Relative risk (95% CI) of *Lactobacillus* GG on specific side-effects during therapy.
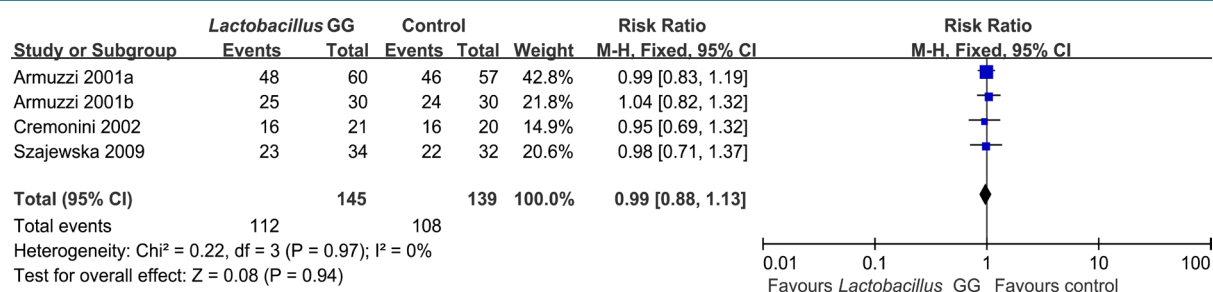
Figure 5. Relative risk (95% CI) of *Lactobacillus* GG on *H. pylori* eradication rates.

(*Lactobacillus* GG). However, several potential limitations should be taken into consideration when interpreting the results. First, one study reported unclear or inadequate allocation concealment and another trial was at high risk of binding process, although the other two trials seemed methodologically sound with respect to allocation concealment, binding, and >90% follow-up. Reassuringly, most included studies reported the effects of *Lactobacillus* GG for therapy-related adverse effects and eradication rate in the same direction, regardless of the methodological shortcomings. Second, we did not perform a statistical test for publication bias because statistical tests for the detection of publication bias have very low power in the meta-analysis of only a few trials [19]. Therefore, the possibility of publication bias still cannot be fully excluded. Third, a small number of studies with small sample sizes were included in our study, especially when subgroups of therapy-related adverse effects were evaluated. However, to increase power is one of the reasons why we conducted this meta-analysis [20].

Our findings with respect to therapy-related diarrhea are consistent with previously published meta-analyses on the effects of *Lactobacillus* GG in preventing antibiotic-associated diarrhea in children and adults [21] [22]. Overall, these data support the use of *Lactobacillus* GG for the prevention of antibiotic-associated diarrhea, regardless of the reason for which the antibiotics were used. Of note, in contrast to several previous systematic reviews [5] [7] [23], we observed a lack of beneficial effect of *Lactobacillus* GG on *H. pylori* eradication rates, although *Lactobacillus* GG was shown to inhibit *H. pylori* adhesion *in vitro* study [24]. Moreover, the results of included studies were consistent and no heterogeneity was observed across studies. Experimental studies regarding the exact mechanisms of action of *Lactobacillus* GG are scant. While the use of *Saccharomyces boulardii* along with standard triple therapy was reported to increase the eradication rates and decrease overall therapy-related side effects [25], our study indicated that *Lactobacillus* GG was not capable of altering the eradication rates. Thus, we speculate that not all probiotics are created equal and that each strain must be evaluated individually in future studies.

Lactobacillus GG seems to be a good candidate for a large multicenter trial in patients with *H. pylori* infection. Since the exact mechanisms by which *Lactobacillus* GG reduces therapy-related side effects are unclear, experimental studies are desirable. As a majority of included patients are adults, studies in children are needed. Moreover, whether other probiotic strains, except *Lactobacillus* GG, have such effects needs to be explored in future experimental and clinical studies.

5. Conclusion

Current evidence indicates that *Lactobacillus* GG supplementation is a safe and effective way to decrease therapy-related side effects, particularly diarrhea, bloating, and taste disturbance, but has no effects on eradication rates. However, the results should be viewed with caution due to the methodological shortcomings of included studies and small sample sizes. High-quality and adequately powered RCTs are still warranted. Because a majority of included participants were adults, studies in children are also needed.

Acknowledgements

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