

Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG in the prevention of antibiotic-associated diarrhoea in children and adults

H. Szajewska & M. Kołodziej

Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland.

Correspondence to:

Prof. H. Szajewska, Department of Paediatrics, The Medical University of Warsaw, 01-184 Warsaw, Działdowska 1, Poland.
E-mail: hania@ipgate.pl

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SUMMARY

Background

The effects of probiotics are strain specific. The clinical effects of each strain need to be evaluated separately.

Aim

To evaluate the efficacy of *Lactobacillus rhamnosus* GG (LGG) in the prevention of antibiotic-associated diarrhoea (AAD) in children and adults.

Methods

The Cochrane Library, MEDLINE, and EMBASE databases were searched up to July 2015, with no language restrictions, for randomised controlled trials (RCTs). Reference lists of reviews and included studies were examined. The quality of evidence (QoE) was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.

Results

Twelve RCTs (1499 participants) were included. Treatment with LGG compared with placebo or no additional treatment reduced the risk of AAD in patients treated with antibiotics from 22.4% to 12.3% (11 RCTs, $n = 1308$, relative risk, RR: 0.49, 95% confidence interval, CI: 0.29–0.83, low QoE). However, when children and adults were evaluated separately, the difference was significant in children only (five RCTs, $n = 445$, RR 0.48, 95% CI 0.26–0.89; moderate QoE). In adults, the difference was not significant (six RCTs, $n = 863$, RR 0.48, 95% CI 0.20–1.15; low QoE), except for in a subset of patients receiving antibiotics as part of *Helicobacter pylori* eradication therapy (four RCTs, $n = 280$, RR 0.26, 95% CI 0.11–0.59; low QoE).

Conclusions

This meta-analysis shows that *Lactobacillus rhamnosus* GG is effective in preventing antibiotic-associated diarrhoea in children and adults treated with antibiotics for any reason. However, the quality of evidence is moderate to low.

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INTRODUCTION

The prevalence of antibiotic-associated diarrhoea (AAD), defined as unexplained diarrhoea that occurs in association with antibiotic therapy,¹ varies depending on the criteria used to diagnose it and the age group. In the paediatric population, the incidence of AAD is 5–30%,² and in adults, 5–70%.³ The antibiotics most commonly linked to AAD include cephalosporins, clindamycin, broad-spectrum penicillins, such as amoxicillin and ampicillin, and fluoroquinolones, such as ciprofloxacin and levofloxacin. AAD may occur just a few hours after antibiotic administration or up to several months after its discontinuation.^{4, 5} In the majority of cases of AAD, no infectious agent is found. However, *Clostridium difficile* is responsible for the most severe cases.⁶ AAD is usually self-limiting; however, if it is caused by *C. difficile*, it may lead to life-threatening pseudomembranous colitis.¹

Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'.⁷ The rationale for the use of probiotics is based on the assumption that AAD results from the disruption of the commensal gut microbiota caused by antibiotic therapy.⁸ Evidence from several meta-analyses has consistently shown that most of the tested probiotics significantly reduced the risk of AAD in the general (mainly adult) population. A 2012 meta-analysis pooled data from 63 randomised controlled trials (RCTs) involving almost 12 000 participants, and it indicated a statistically significant reduction in AAD in the probiotic groups compared with the control groups (relative risk, RR: 0.58; 95% confidence interval, CI: 0.50–0.68).⁹ The effects of probiotics are strain specific. The clinical effects of each strain need to be evaluated separately.

A 2005 systematic review evaluated the efficacy of *Lactobacillus rhamnosus* GG (LGG) in the prevention of AAD. Six placebo-controlled RCTs were found. Four of the six trials found that administration of LGG compared with placebo significantly reduced the risk of AAD in patients treated with antibiotics.¹⁰ A number of mechanisms by which LGG may prevent AAD have been suggested, as discussed in detail elsewhere.¹¹ Among others, these mechanisms include the effects of LGG-derived soluble proteins, which enhance LGG adherence to intestinal epithelial cells and protect them from cytokine-induced injury by regulating several signalling pathways. Moreover, seven different peptides were isolated from LGG-conditioned media, which showed anti-Gram-negative and anti-Gram-positive bactericidal activity.¹²

In the last few years, a number of new relevant studies have been published. These studies have prompted

interest in updating current evidence on the efficacy of LGG in the prevention of AAD in children and adults. The choice of the LGG strain was determined by the fact that it is widely available in many countries and is commonly used. This review was initiated as part of the development of guidelines on the use of probiotics for preventing AAD in children.

METHODS

As in our earlier reports focusing on a single probiotic strain,^{13, 14} for this systematic review and meta-analysis, the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions¹⁵ and the PRISMA Statement¹⁶ 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 no additional intervention were eligible for inclusion. Participants were adults and children who received antibiotics for any reason. The *primary* outcome was the incidence of diarrhoea or AAD (as defined by the investigators). *Secondary* outcomes were the incidence of *C. difficile*-associated diarrhoea; the need for discontinuation of the antibiotic treatment; the need for hospitalisation to manage the diarrhoea (in out-patients); the need for intravenous rehydration in any of the study groups and adverse events.

Search strategy

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE and EMBASE databases were searched for relevant studies published up until July 2015. The main search text word terms and MESH headings used were as follows: diarrhea, diarrhoea, antibiotic-associated, antibiotic associated, *Clostridium difficile*, probiotics, *Helicobacter pylori*, *H pylori*, *Lactobacillus rhamnosus* GG, *Lactobacillus* GG and LGG. Moreover, reference lists from the original studies and review articles identified were screened, and key experts in the field were approached for unpublished material. There were no language restrictions. 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. One reviewer (MK) carried out data extraction, using standard data extraction forms, which was then assessed by the second reviewer (HS). Data were extracted as complete (available) case analyses. Disagreements were resolved by discussion.

The Cochrane Collaboration's 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.¹⁷ If trial methodology was unclear from the published report, an attempt was made to contact the authors for clarification.

Quality of evidence (QoE) for outcomes reported in the included trials was assessed using the GRADE methodology and GRADEpro (Computer program located at www.grade.org, Version, 14 August 2015, McMaster University, 2014). The GRADE system offers four categories of the quality of the evidence (i.e. high, moderate, low and very low).¹⁸

Heterogeneity was quantified by χ^2 and I^2 , which can be interpreted as the percentage of the total variation between studies that are attributable to heterogeneity rather than to chance. For the χ^2 test, $P < 0.15$ indicates significant heterogeneity and for the I^2 statistic, a value $>50\%$ indicates substantial heterogeneity. All analyses were based on the random effects model. To test for publication bias, a test for asymmetry of the funnel plot, as proposed by Egger *et al.*,¹⁹ was used if sufficient (≥ 10) eligible trials were available.

Statistical methods. The Review Manager (RevMan) [Computer program, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014] was used to analyse the data, and StatsDirect (version 3.0.150; StatsDirect Ltd, Sale, Cheshire, UK) was used to generate forests plots and funnel plots. The binary measure for individual studies and pooled statistics is reported as the RR between the experimental and control groups with 95% CI. The number needed to treat (NNT), with the 95% CI, was calculated if there was a significant difference in the dichotomous outcome between the groups, using the formula recommended by the Cochrane Handbook [$\text{NNT} = 1/\text{ACR} \times (1 - \text{RR})$], where ACR, assumed control risk, was an average control group risk.¹⁵ A number of subgroup analyses were planned based on the study population (children and adults), the indication for the antibiotic therapy (common infections and antibiotic therapy as part of *H. pylori* eradication therapy) and the type of antibiotics administered or the indication. However, only the first two analyses were performed.

RESULTS

Twelve RCTs met the inclusion criteria for this systematic review. Among them, eight were full-text publications published in peer-reviewed journals,^{20–27} two were

published abstracts^{28, 29} and two were unpublished abstracts (Miller 2008a,b) identified through a 2013 Cochrane review.³⁰ For a flow diagram documenting the identification process for the eligible trials, see Figure S1. Table S1 summarises the characteristics of all included RCTs, and Table S2 summarises the characteristics of the excluded trials, including the reasons for exclusion.

For the assessment of methodological quality and potential risk of bias, see Figure S2. Only two RCTs were at low risk of bias.^{21, 22} The methodological limitations of trials included unclear sequence generation (five RCTs), unclear allocation concealment (eight RCTs) and no or unclear blinding of participants and personnel (five RCTs) or outcome assessment (six RCTs) or unclear selective reporting (five RCTs). The risk of attrition bias was high or unclear in five RCTs. Two RCTs, published in abstract form only, lacked adequate information to assess the overall risk of bias (an attempt was made to contact trial authors; however, with no success).

The included RCTs randomised a total of 1499 patients. Five RCTs were undertaken in children.^{20, 21, 24, 28, 29} Among all of the included studies, five RCTs assessed the effect of LGG during *H. pylori* eradication therapy.^{20, 23, 25–27} Sample size calculations were only available in two trials.^{22, 23} Ten studies were placebo-controlled trials.^{Miller 2008a,b, 20–25, 27, 28} In the remaining studies, there was no intervention in the control group. Six trials were conducted in Europe,^{20, 23–26, 29} three trials were conducted in the US,^{21, 22, 28} two in Canada (Miller 2008a,b) and one in Cuba.²⁷ Six RCTs were conducted in in-patients,^{Miller 2008a,b, 20, 22, 24, 28} and six trials were conducted in out-patients.^{21, 23, 25–27, 29} The daily dose of LGG ranged from 4×10^8 to 12×10^{10} colony forming units (CFU). There was a large variation in the types of antibiotics administered. Follow-up ranged from 10 days to 3 months. In two trials, the exact duration was not mentioned.^{28, 29} The definitions of outcome measures varied, and in 7 RCTs, the definition of diarrhoea was not provided.^{Miller 2008a,b 23, 25–27, 29} Four trials were industry supported.^{Miller 2008a,b, 21, 22}

The GRADE assessment for outcomes related to LGG administration and diarrhoea is presented in Table S3. Using the GRADE, the overall QoE for all assessed outcomes was rated as moderate to very low.

Effects of interventions

Treatment with LGG compared with placebo or no additional treatment reduced the risk of diarrhoea in patients treated with antibiotics from 22.4% to 12.3% (11 RCTs, $n = 1308$, RR 0.49, 95% CI 0.29–0.83, random effect

model; NNT 9, 95% CI 6–26) (Figure 1). However, significant heterogeneity was found ($\chi^2 = 31.81$, $P = 0.0004$, $I^2 = 69\%$).

A pre-planned subgroup analysis based on the study population (children and adults) showed a reduction in the risk of AAD in children only and not in adults. In

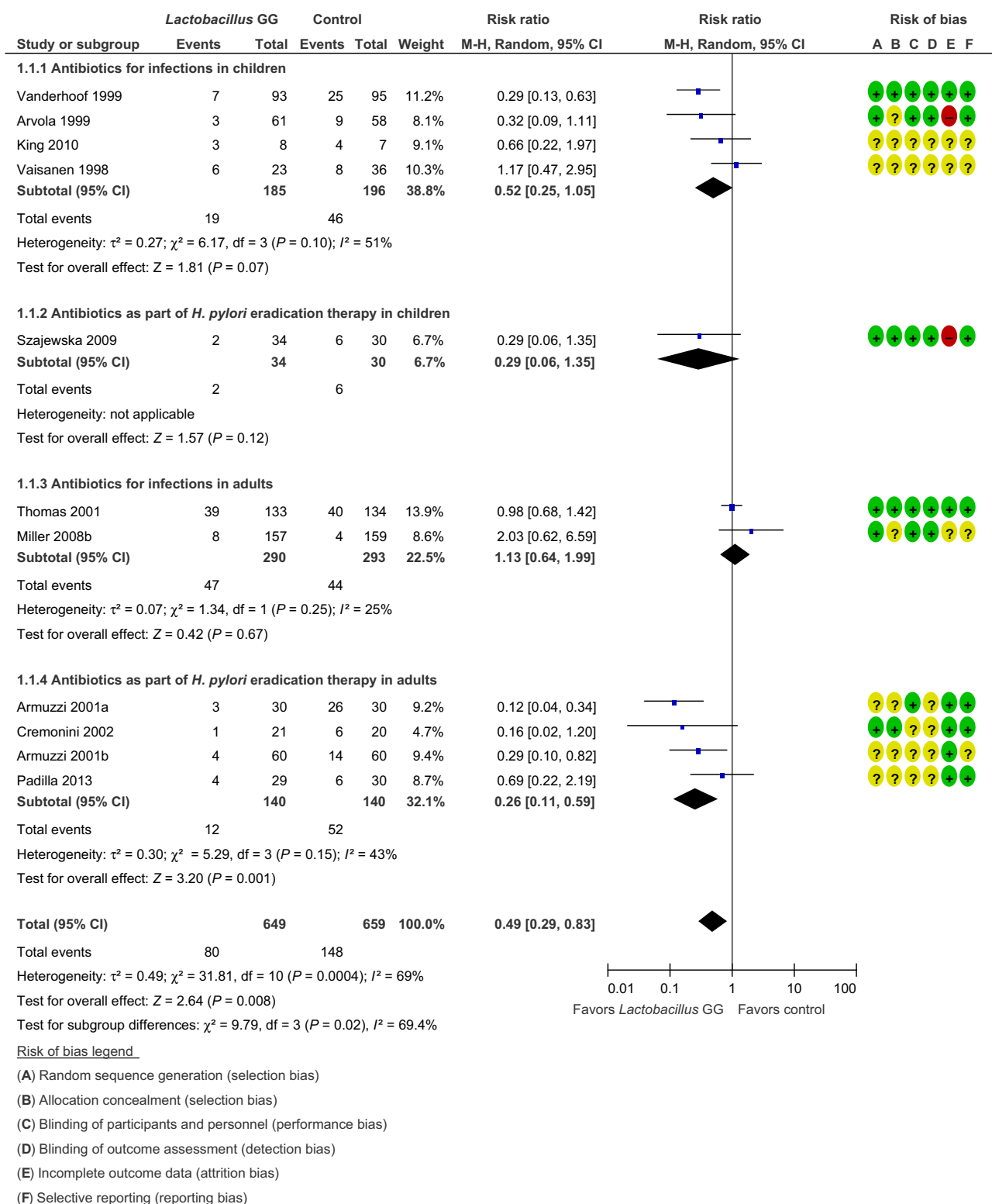


Figure 1 | Effect of *Lactobacillus rhamnosus* GG for preventing antibiotic-associated diarrhoea.

children, compared with placebo or no treatment, LGG administration reduced the risk of AAD from 23% to 9.6% (five RCTs, $n = 445$, RR 0.48, 95% CI 0.26–0.89; NNT 8, 95% CI 6–40). No significant heterogeneity was found ($\chi^2 = 6.61$, $P = 0.16$, $I^2 = 40\%$) (Figure 2).

In adults, compared with placebo or no treatment, LGG administration reduced the risk of AAD from 22.2% to 13.7%; however, the difference was statistically significant in the fixed effects model only (six RCTs, $n = 863$, RR 0.62, 95% CI 0.46–0.82). The significant reduction in the risk of AAD in the LGG group was lost in the random effects model (RR 0.48, 95% CI 0.20–1.15). Significant heterogeneity was found ($\chi^2 = 22.97$, $P = 0.0003$, $I^2 = 78\%$). Another pre-planned subgroup analysis based on the indication for the antibiotic therapy (common infections and antibiotic therapy as part of *H. pylori* eradication therapy) showed a significant reduction

in the risk of AAD in the latter group (four RCTs, $n = 280$, RR 0.26, 95% CI 0.11–0.59; Figure 3).

Four trials ($n = 891$) evaluated the effect of treatment with LGG on the risk of *C. difficile*-associated diarrhoea.^{Miller 2008a,b, 22, 24} The pooled results of these trials revealed no significant difference in risk between the LGG and control groups (RR 0.75, 95% CI 0.31–1.84). No significant heterogeneity was found ($\chi^2 = 1.82$, $P = 0.61$, $I^2 = 0\%$; Figure 4).

Based on the findings from four RCTs,^{20, 21, 25, 26} there was no need for discontinuation of antibiotic treatment, hospital treatment because of diarrhoea in the out-patients or intravenous rehydration in any of the study groups.

Adverse events. Data regarding therapy-related adverse events were available from eight of the included trials.^{Miller 2008a,b, 20–23, 25, 26} In these trials, LGG was well

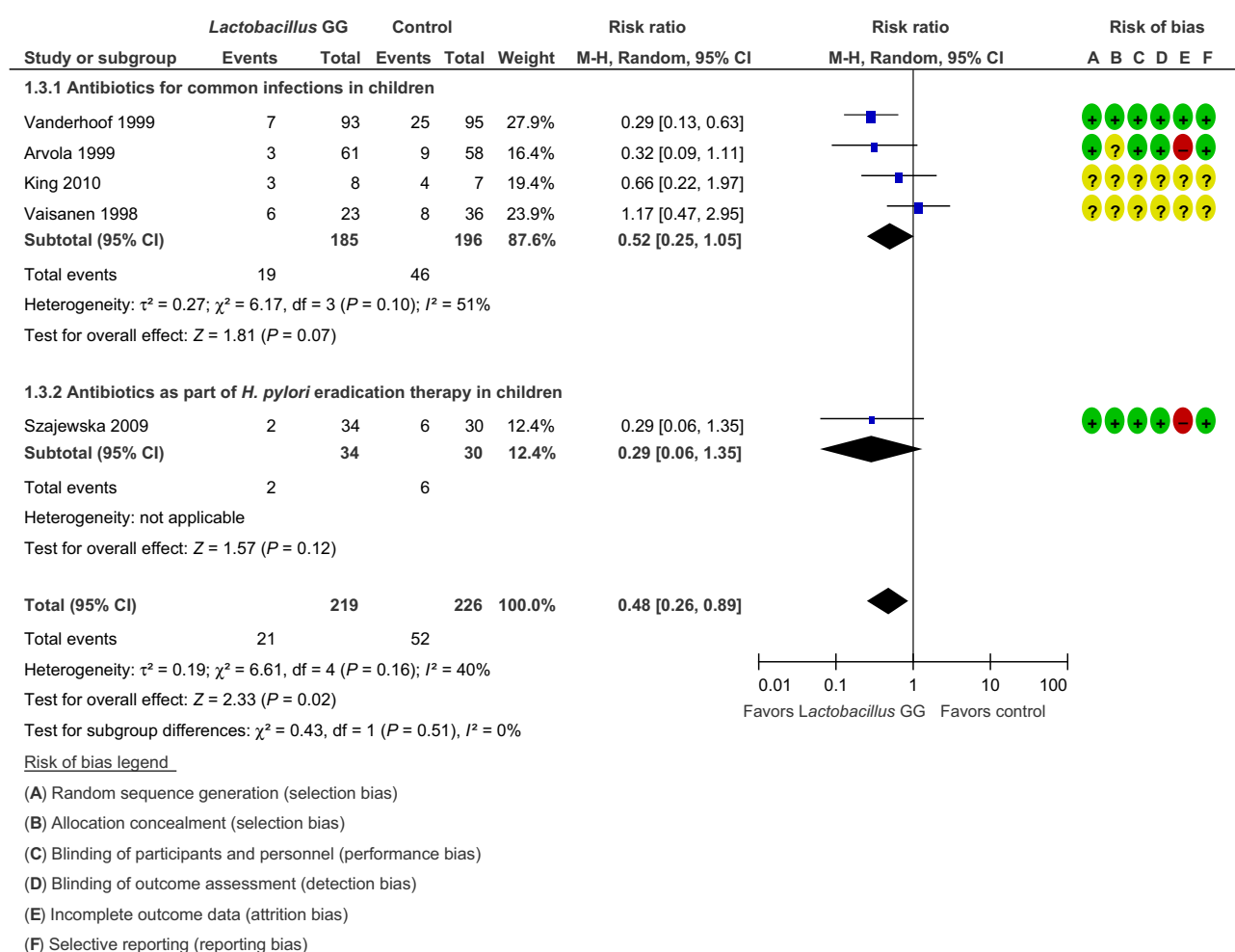


Figure 2 | Effect of *Lactobacillus rhamnosus* GG for preventing antibiotic-associated diarrhea in children.

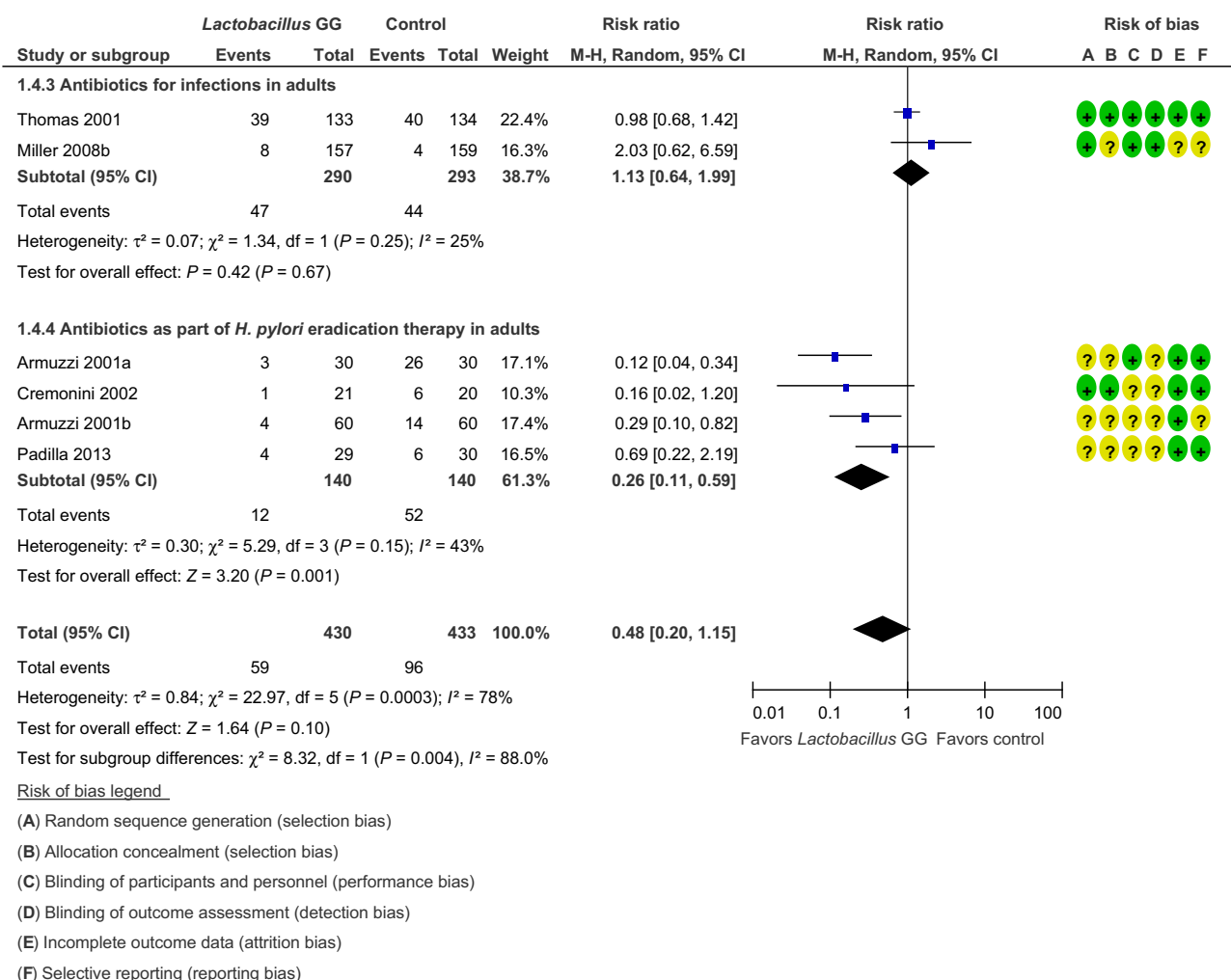


Figure 3 | Effect of *Lactobacillus rhamnosus* GG for preventing antibiotic-associated diarrhoea in adults.

tolerated. Adverse event rates were similar in the experimental and control groups.

Publication bias. There was no evidence of publication bias among trials on LGG and AAD (Figure S3).

DISCUSSION

Summary of evidence

In this systematic review and meta-analysis of 12 RCTs, we showed that LGG, compared with placebo or no treatment, is effective in preventing AAD in the overall population of adults and children treated with antibiotics for any reason. The NNT to avoid one case of AAD was 9. The GRADE assessment revealed moderate to very low QoE. A reduction in the risk of AAD also was revealed when children and adults were evaluated sepa-

rately; however, the difference was statistically significant in children only. In adults, there was a significant difference between the LGG and control groups only in a subset of patients receiving antibiotic therapy as part of *H. pylori* eradication therapy. There was no difference in the risk of *C. difficile*-associated diarrhoea between the LGG and control groups. LGG was well tolerated. Adverse event rates were similar in the LGG and control groups.

Strengths and limitations

Our meta-analysis has some strengths. The methodology developed by the Cochrane Collaboration was followed. Several methods to reduce reviewer error and bias were implemented (i.e. comprehensive literature search, pre-specified criteria for methodological assessment and analysis, no restrictions by language or year of publication,

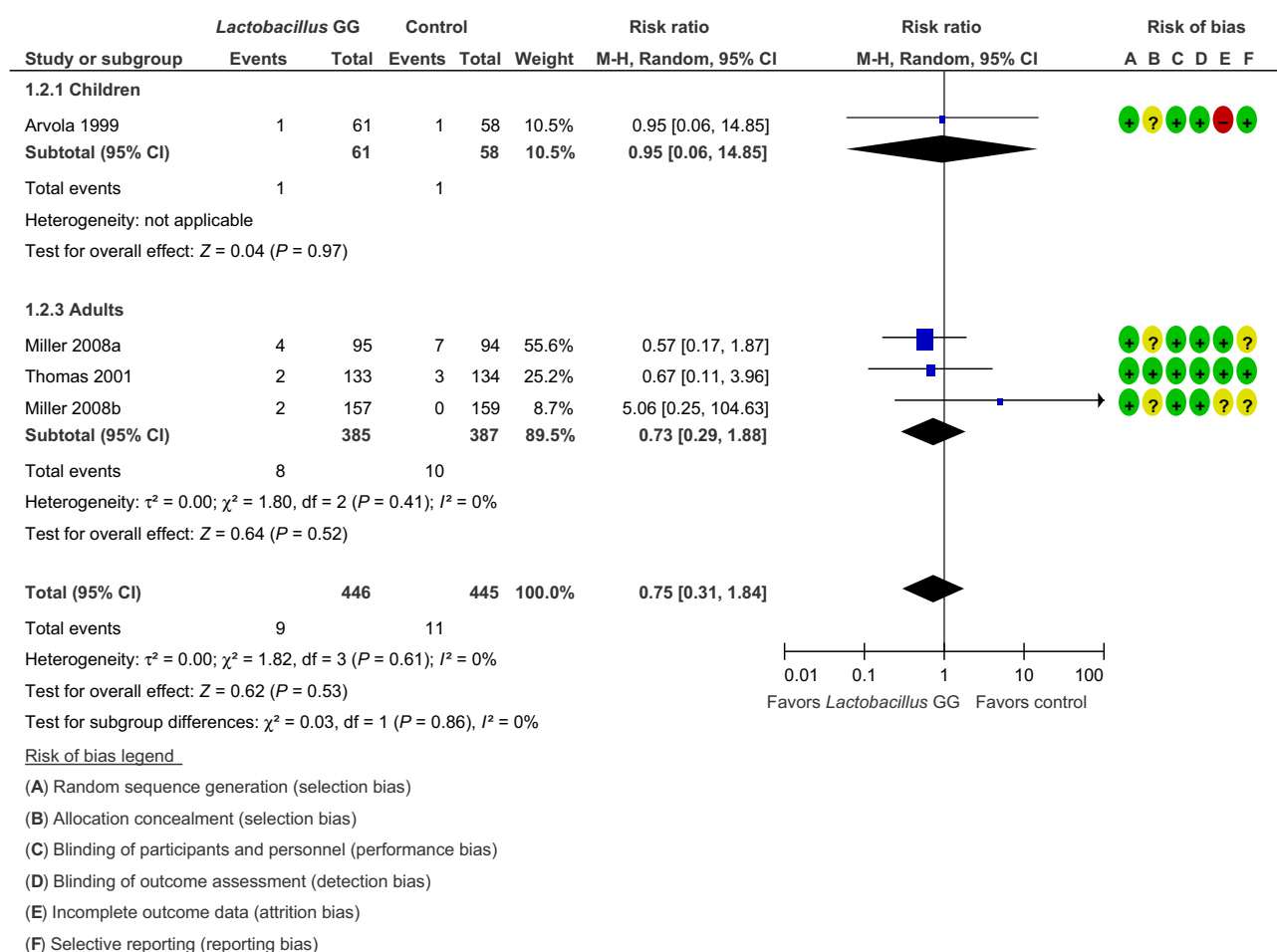


Figure 4 | Effect of *Lactobacillus rhamnosus* GG for preventing *Clostridium difficile*-associated diarrhoea.

attempts to identify unpublished trials). Risk of bias was assessed. However, methodological limitations of the included trials were apparent. For instance, in most of the trials, there was unclear random sequence generation and unclear allocation concealment, which increase the risk of selection bias. Although, with one exception, all RCTs were described as double-blinded trials, most had unclear risk of bias for blinding of participants and personnel or outcome assessment, which increases the risk of performance and detection biases. Sample size calculations were not carried out in many trials; however, the total sample size in the meta-analysis was sufficient to allow us to draw reliable conclusions.

This systematic review and meta-analysis focuses exclusively on LGG. However, in the included trials, the probiotic daily dose and timing of follow-up varied, as well as the definition of AAD. For some outcomes, statistical heterogeneity of studies was significant, as evidenced by the high I^2 statistic; therefore, these findings

should be interpreted with caution. No evidence of publication bias was found; however, this is a possible limitation of any systematic review.

For completeness, we included trials in which antibiotics were used for any reason, including *H. pylori* eradication therapy. Data in adults were obtained noticeably from studies in which antibiotics were used as part of the *H. pylori* eradication therapy. In contrast, there was only one such trial conducted in children; most of the data were obtained from trials in which antibiotics were used for common paediatric infections. However, with the current data, we could not identify differential efficacy according to indications for the use of antibiotics, if it matters at all.

Agreement and disagreement with other studies or reviews

Our findings stand in line with the results of previously published meta-analyses.^{9, 31–33} All consistently showed

that probiotics compared with placebo or no treatment reduced the risk of AAD in children and adults. However, in large part, these meta-analyses pooled data on various probiotics. One recent exception is our 2015 single-strain meta-analysis on the effectiveness of *S. boulardii* in preventing AAD in children and adults.¹³ Of note, both LGG and *S. boulardii* showed a similar reduction in the risk of AAD (51% vs. 53% respectively).

Compared with a 2005 systematic review focusing on LGG only,¹⁰ we included more trials (12 vs. 6 respectively) involving more patients (1499 vs. 692 respectively). We also conducted a meta-analysis of the extracted data. Thus, our analysis more precisely defines the role of LGG in preventing AAD.

Conclusions and implications for practice

The best treatment regimens remain to be determined. Based on the published trials, it seems appropriate to start LGG administration early, preferably simultaneously with antibiotic treatment, before modification of the gut microbiota and overgrowth of pathogens occur. It also seems appropriate to continue the administration of LGG for the duration of antibiotic treatment. However, it remains unclear how long to continue LGG after the cessation of antibiotic treatment. The optimal dose of LGG for preventing AAD remains unclear. In children, the best effect (reduction in the risk of AAD by 71%) was achieved with the highest dose ($1-2 \times 10^{10}$ CFU).²¹ However, a similar effect size was not achieved in another trial using the same dose,²⁴ perhaps because of a lower baseline risk of AAD. In adults, there was no clear link between the effect size and the LGG dose. As a matter of fact, a better effect was achieved with a lower dose. Identifying populations most likely to benefit from LGG administration during antibiotic treatment would be desirable. For example, patients of extreme ages or patients with life-threatening illnesses managed in intensive care units need further assessment.

One recent meta-analysis, although focusing on probiotics in general, not on LGG, concluded that probiotics may not reduce the risk of AAD and *C. difficile*-associated diarrhoea in older patients.³⁴

In summary, current evidence justifies the use of LGG for preventing AAD, although a number of questions remain unanswered and the QoE calls for caution.

AUTHORSHIP

Guarantor of the article: HS.

Author contributions: HS initially conceptualised this study. Both authors were responsible for data collection, data analysis, data interpretation and preparation of the report. HS assumed the main responsibility for the writing of this manuscript. Both authors contributed to (and agreed upon) the final version.

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Declaration of personal interests: HS has served as a speaker for Dicofarm, the manufacturer of LGG. MK declares no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Identification process for eligible trials.

Figure S2. Assessment of methodological quality and potential risk of bias.

Figure S3. Funnel plot for publication bias.

Table S1. Characteristics of the included trials.

Table S2. Characteristics of the excluded studies.

Table S3. GRADE evidence profile summarising the effect of *Lactobacillus rhamnosus* GG supplementation vs. placebo or no intervention on antibiotic-associated diarrhoea.

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