AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: *Lactobacillus* GG for treating acute gastroenteritis in children – updated analysis of randomised controlled trials

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Publication data
Submitted 29 May 2013
First decision 8 June 2013
Resubmitted 15 June 2013
Accepted 19 June 2013
EV Pub Online 10 July 2013

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Mr M. Siddiqui.

SUMMARY

Background
The efficacy of each probiotic should be evaluated separately. Previously, we have shown that *Lactobacillus* GG (LGG) is effective in treating acute gastroenteritis (AGE) in children.

Aim
To update our 2007 meta-analysis on the effectiveness of LGG in treating AGE in children.

Methods
The Cochrane Library, MEDLINE and EMBASE databases were searched from August 2006 (end date of last search) to May 2013, with no language restrictions, for randomised controlled trials (RCTs) and meta-analyses.

Results
Fifteen RCTs (2963 participants) met the inclusion criteria in this updated meta-analysis. Combined data from 11 RCTs (n = 2444) showed that LGG significantly reduced the duration of diarrhoea compared with placebo or no treatment (mean difference, MD −1.05 days, 95% CI −1.7 to −0.4). LGG was more effective when used at a daily dose $\geq 10^{10}$ CFU (eight RCTs, n = 1488, MD −1.11 days, 95% CI −1.91 to −0.31) than when used at a daily dose $<10^{10}$ CFU (three RCTs, n = 956, MD −0.9 day, 95% CI −2.5 to 0.69). LGG was effective in children treated in Europe (five RCTs, n = 744, MD −1.27 days, 95% CI −2.04 to −0.49); in the non-European setting, the difference between the LGG group and the control group was of a borderline statistical significance (six RCTs, n = 1700, MD −0.87, 95% CI −1.81 to 0.08).

Conclusions
Lactobacillus GG reduces the duration of diarrhoea. A subset of patients that is more likely to benefit includes subjects treated with a high daily dose of LGG ($\geq 10^{10}$ CFU/day) who are either in-patients or out-patients from geographical Europe. Given the methodological limitations of many of the included trials, the evidence should be viewed with caution.

Aliment Pharmacol Ther 2013; **38**: 467–476

doi:10.1111/apt.12403

INTRODUCTION

Previously, we have shown in a meta-analysis that *Lactobacillus rhamnosus* GG (LGG) is effective in treating acute gastroenteritis (AGE) in children.[1] In brief, compared with controls, although LGG had no effect on the total stool volume, its use was associated with a significant reduction in diarrhoea duration, particularly of rotavirus aetiology, and duration of hospitalisation. There was no reduction in the number of stools at any time interval.

In 2008, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Paediatric Infectious Diseases (ESPID) introduced evidence-based guidelines for the management of AGE in children in Europe. These guidelines, in large part based on the results of this original meta-analysis, stated that probiotics with documented efficacy such as LGG and *Saccharomyces boulardii* may be considered as an adjunct to rehydration for the management of AGE in children.[2] The exact mechanisms by which LGG might exert its actions are not clear. Possible mechanisms include interference with pathogen attachment, interaction with normal microbiota and stimulation or modulation of immune responses, both within the lumen and systemically.[3]

In the last few years, a number of new relevant studies have been published. These studies have prompted interest in updating current evidence, especially in the context of the factors that could potentially influence the magnitude of the treatment response. Among others, these factors are the aetiology of the diarrhoea, the setting (geographical Europe vs. other countries), and the LGG dose. Moreover, the role of LGG in the era of rotavirus vaccination has to be established. Consequently, our aim was to systematically update our 2007 meta-analysis on the effectiveness of LGG in treating AGE in children. We also aimed to evaluate the most effective dose of LGG. This review was initiated as part of the update of the guidelines for the management of AGE in children.[2]

METHODS

The guidelines from the Cochrane Collaboration for undertaking and reporting the results of a systematic review and meta-analysis[4] and the PRISMA statement[5] were followed for this systematic review and meta-analysis.

Criteria for considering studies for this review

All relevant randomised controlled trials (RCTs) that compared use of LGG as a single ingredient (in all delivery vehicles and formulations) with use of placebo or no treatment were eligible for inclusion. The *primary* outcome measures were the stool volume and the duration of diarrhoea. The *secondary* outcome measures were the percentages of children with diarrhoea at various times intervals (as specified by the investigators), the percentage of children with diarrhoea lasting longer than 7 days, the duration of hospitalisation and adverse effects.

Search methods for identification of studies

The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), MEDLINE, and EMBASE databases were searched from August 2006 (end of last search) to May 2013. The principal search text word terms and MESH headings used were as follows: diarrhea/diarrhoea, diarrh*, gastroenteritis, probiotic*, *Lactobacillus rhamnosus* GG, *Lactobacillus* GG, LGG. No language restrictions were imposed. The reference lists from identified studies and key review articles, including previously published systematic reviews with or without a meta-analysis, were also searched to identify any other relevant studies. The ClinicalTrials.gov website was also searched for RCTs that were registered but not yet published. Certain publication types (i.e. letters to the editor, abstracts, proceedings from scientific meetings) were excluded, unless a full set of data was obtained from the authors. We contacted one author (Nixon[6]) for further information, who by email provided missing information regarding the dose of LGG.

Data collection and analysis

Three (AS, MR, DGB) reviewers using a standardised approach independently undertook the literature search, data extraction and quality assessment. The data sought included baseline characteristics of the participants, details related to the use of experimental and control interventions (including dose and duration), setting and funding. Any disagreements were resolved by discussion with the fourth reviewer (HS).

In one RCT (*Basu et al. 2009*[7]), participants were randomly assigned to three groups: an intervention group that received oral rehydration solution (ORS) plus LGG at a daily dose of 2×10^{10} colony-forming units (CFU), another intervention group that received ORS plus LGG at a daily dose of 2×10^{12} CFU, or a control group that received ORS only. Because the objective of our review was to compare supplementation with placebo or no supplementation, we combined both experimental arms into a single experimental group according to the method of *Hogg and Craig*.[8] In the study by *Misra*

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et al.,[9] missing standard deviations were obtained by multiplying standard errors of means by the square root of the sample size: s.d. = S.E. × √N.[10]

Assessment of risk of bias in included studies

The reviewers independently, but without being blinded to the authors or journal, assessed the risk of bias in the studies that met the inclusion criteria. The Cochrane Collaboration's tool for assessing risk of bias was used, which includes the following criteria: adequacy of sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; and extent of loss to follow-up, i.e. the proportion of patients in whom the investigators were not able to determine outcomes (incomplete outcome data). In all cases, an answer of '*yes*' indicates a low risk of bias, and an answer of '*no*' indicates a high risk of bias.[11]

Measures of treatment effect

The dichotomous outcomes, the results for individual studies and pooled statistics are reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CI). The continuous outcomes are reported as the mean difference (MD) between the treatment and control groups with 95% CI.

Dealing with missing data

We assessed pooled data using available case analysis, i.e. an analysis in which data are analysed for every participant for whom the outcome was obtained, rather than intention-to-treat analysis with imputation.[12]

Assessment of heterogeneity

Heterogeneity was quantified by χ^2 and I^2, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. If heterogeneity was not revealed, we present results of only the fixed effects model. If there was substantial heterogeneity (over 50%), all analyses were based on the random effects model.

Assessment of reporting biases

To test for publication bias, we used a test for asymmetry of the funnel plot proposed by Egger *et al.*[13] This test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the normalised effect estimate (estimate divided by its standard error) against precision (reciprocal of the standard error of the estimate) weighted by the reciprocal of the variance of the estimate (on StatsDirect; StatsDirect Ltd. StatsDirect statistical software. http://www.statsdirect.com. England: StatsDirect Ltd. 2008. Version 2.7.9 (2012.07.09).

Data synthesis (statistical methods)

The data were analysed using Review Manager (RevMan) [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Subgroup analysis and sensitivity analyses

For the primary outcomes, *a priori* subgroup analyses based on factors that could potentially influence the magnitude of the treatment response were planned for the following: (i) Dose of LGG [high dose ($\geq 10^{10}$ CFU/day) vs. lower dose ($<10^{10}$ CFU/day)]. The optimal dose and treatment duration of LGG therapy have not been clearly established. However, the cut-off of 10^{10} CFU/day has been previously suggested in the literature with a postulated larger effect in trials administering a larger dose of probiotic[14–16]; (ii) Setting (studies carried out in geographical Europe vs. non-European countries). In the case of diarrhoeal diseases, consideration of the study location is important, as factors such as pathogens, access to clean water and sanitation, or comorbidities may have an impact on outcomes; (iii) Type of treatment (out-patient vs. in-patient); (iv) Aetiology of diarrhoea; (v) Vaccination against rotavirus status. In addition, when there was statistically significant heterogeneity in the primary outcome across studies, sensitivity analyses were performed to determine the impacts of allocation concealment (adequate vs. inadequate and/or unclear), blinding (open trial vs. double-blind trials) and attrition (<20% vs. ≥20%).

RESULTS

The literature search yielded 27 articles, of which 12 were reviewed in full text. Of these studies, seven RCTs met the inclusion criteria. Thus, in addition to the previously identified eight RCTs (n = 988),[17–24] seven new RCTs were found.[6, 7, 9, 25–28] For a flow diagram documenting the identification process for eligible trials, as well as the characteristics of the included and excluded trials, with reasons for exclusion (most studies included additional strains or prebiotics, in addition to LGG), see online Supporting Information. Two ongoing RCTs were identified via ClinicalTrials.gov (NCT01130792, and NCT01773967).

The 15 selected studies recruited a total of 2963 patients (1603 in the experimental group and 1360 in the control group). The sample size ranged from 36 to 662 participants. Six studies were performed in geographical Europe or largely in Europe. For example, the study by *Guandalini et al.*[18] was performed mainly in Europe (77%), but a subset of patients (23%) was recruited in Israel and Egypt. Nine RCTs were performed in other countries. Except for two multi-centre trials,[18, 24] the included studies were single-centre trials. There was clinical heterogeneity among the trials in type of treatment (in-patients and/or out-patients); 10 RCTs were carried out in in-patients; three, in out-patients; and two, in both in-patients and out-patients. The daily doses of LGG ranged from 1.2×10^8 CFU[25] to 2×10^{12} CFU.[7] In all studies, LGG was used in addition to rehydration therapy consisting of an oral rehydration solution and/or intravenous rehydration. Notably, in three RCTs, LGG was dissolved in ORS,[7, 18, 24] and in one RCT, LGG was administered in infant formula.[22] Ten RCTs were placebo controlled; in the remaining five trials, there was no additional intervention in the control group (see online Supporting Information).

Risk of bias in included studies

All included trials had a number of methodological limitations (see online Supporting Information). The major limitations were unclear randomisation (five trials), no or unclear allocation concealment (eight trials), and no or unclear blinding (five trials). In none of the trials was attrition >20%.

Heterogeneity and publication bias

Significant heterogeneity ($I^2 \geq 50\%$) was found for both primary outcomes [i.e. total stool volume ($I^2 = 75\%$), duration of diarrhoea ($I^2 = 98\%$)], and for all secondary outcomes ranging from $I^2 = 56\%$ (presence of diarrhoea on day 3) to $I^2 = 99\%$ (duration of hospitalisation). The publication bias was formally assessed only in the analysis of the duration of diarrhoea. There was no significant funnel plot asymmetry [Egger test −5.6 (95% CI = −11.5–0.3; $P = 0.06$); see funnel plot in online Supporting Information]. For other outcomes, the publication bias was not formally assessed using a funnel plot due to the small number of studies (<10) included in the analyses.

Effects

A summary of all the results is presented in Table 1 and online (Supporting Information). Here, we report only those outcomes for which new data were available.

Duration of diarrhoea. A meta-analysis of 11 RCTs,[7, 9, 17–20, 23–26, 28] which included 2444 participants, showed a reduction in the duration of diarrhoea of −1.05 days (95% CI −1.7 to −0.4) for those treated with LGG compared with placebo or no treatment (Figure 1). The included trials were significantly heterogeneous ($I^2 = 98\%$). Pre-planned sensitivity analyses based on trial methodological quality were performed. Statistically significant between-study heterogeneity persisted in sensitivity analyses, suggesting that the differences in outcomes between studies were caused by factors other than differences in methodological quality (see online Supporting Information).

In addition, data on the duration of diarrhoea were reported in two other trials; however, the data were reported in a format that did not allow pooling of data.

Nixon et al.[6] reported that among US children, there was no significant difference in the median time until normal stool between the LGG and placebo groups [60 h (interquartile range: 37–111) vs. 74 h (43-120), respectively, $P = 0.37$]. However, among children who presented with more than 2 days of diarrhoea, the LGG group compared with the placebo group returned to normal stool earlier [51 h (32–78) vs. 74 h (45–120), respectively, $P = 0.02$].

Czerwionka-Szaflarska *et al.*[27] found in Polish children a significantly shorter duration of treatment (definition of treatment was not specified) in the LGG plus ORS group compared to the ORS only group (3.7 vs. 5.0 days, $P = 0.006$). However, there was no significant difference in the duration of treatment between the LGG only group and the ORS only group (4.0 vs. 5.0 days, $P = 0.59$) or between the LGG only group and the LGG plus ORS group (4 vs. 3.71 days, $P = 0.23$).

Moreover, one study *(Salazar-Lindo et al.*[22]*)* reported the duration of diarrhoea only in children who responded to the treatment within 5 days of admission. Children with ongoing diarrhoea were not further considered. For this reason, the data from this study are not included in our analysis.

As planned, a number of pre-planned subgroup analyses were performed. These analyses showed that LGG was more effective when used at a higher daily dose ($\geq 10^{10}$ CFU/day) compared with a lower daily dose ($<10^{10}$ CFU) (Figure 1). A reduction in the duration of diarrhoea was found both in studies carried out in Europe and in non-European settings. However, the difference between the LGG group and the control group in the duration of diarrhoea was statistically significant in Europe only (five RCTs, $n = 744$; MD −1.27 days, 95% CI

Table 1 | Overview of the results

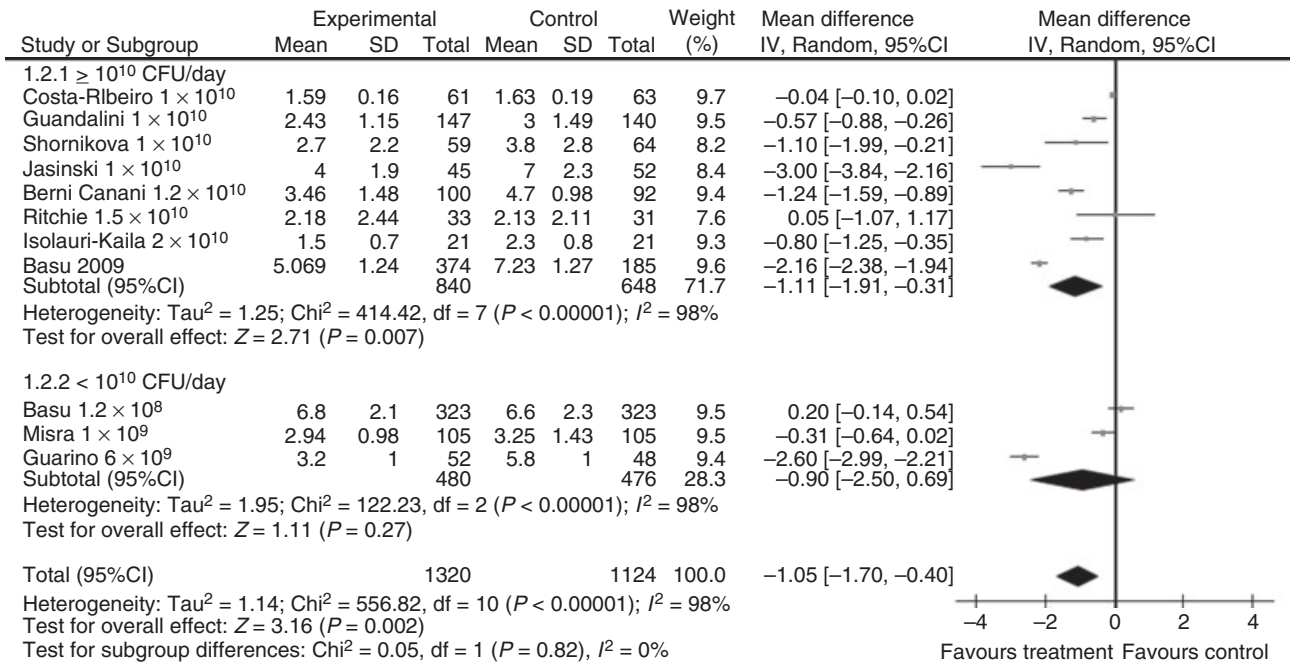
Outcome or subgroup	RCT	Participants	Statistical method, random effect model	Effect estimate (95% CI)	Significance	I^2	New data*
Total stool volume (mL/g)	2	303	MD	8.97 (−86.26 to 104.2)	NS	75%	No
Europe	No data						
Non-Europe	2	303	MD	8.97 (−86.26 to 104.2)	NS	75%	No
Stool volume	2	303	MD	8.97 (−86.26 to 104.2)	NS	75%	No
On day 1 (non-Europe) (g/kg)	1	36	MD	13.60 (−13.11 to 40.31)	NS	N/A	No
On day 2 (non-Europe) (g/kg)	1	36	MD	12.40 (−6.39 to 31.19)	NS	N/A	No
Duration of diarrhoea (days)	11	2444	MD	−1.05 (−1.7 to −0.40)	–	98%	Yes
Daily dose of LGG (CFU)							
$\geq 10^{10}$	8	1488	MD	−1.11 (−1.91 to −0.31)	–	98%	Yes
$<10^{10}$	3	956	MD	−0.90 (−2.5 to 0.69)	NS	98%	Yes
Setting							
Studies carried out in Europe (exclusively or largely)	5	744	MD	−1.27 (−2.04 to −0.49)	–	94%	Yes
Studies carried out in non-Europe	6	1700	MD	−0.87 (−1.81 to 0.08)	NS	99%	Yes
In-patients							
Europe	2	165	MD	−0.86 (−1.27 to −0.46)	–	0%	No
Non-Europe	5	1603	MD	−0.48 (−1.46 to 0.51)	NS	99%	Yes
Out-patients							
Europe	2	292	MD	−1.92 (−2.35 to −0.58)	–	96%	No
Non-Europe	No data						No
Both in-/outpatients (Europe and non-Europe)	2	384	MD	−1.75 (−4.13 to 0.63)	–	96%	No
Aetiology							
Rotavirus	3	201	MD	−2.05 (−2.39 to −1.71)	–	94%	No
Invasive pathogen	1	43	MD	0.05 (−0.64 to 0.74)	NS	N/A	No
Unknown cause	2	124	MD	−0.84 (−1.32 to −0.36)	–	93%	No
Presence of diarrhoea							
On day 2	1	36	RR	0.37 (0.17 to 0.84)	–	N/A	No
On day 3	3	393	RR	0.64 (0.36 to 1.13)	–	56%	No
On day 4	1	64	RR	1.07 (0.44 to 2.61)	NS	N/A	Yes
On day 5	1	179	RR	1.17 (0.65 to 2.13)	NS	N/A	No
>7 days	1	294	RR	0.27 (0.09 to 0.78)	–	N/A	No
>10 days	1	97	RR	0.23 (0.03 to 1.91)	NS	N/A	No
Duration of hospital stay (days)	4	1615	MD	−1.42 (−3.05 to 0.21)	NS	99%	Yes

MD, mean difference; N/A, not applicable; NS, nonsignificant; RR, relative risk.

* Compared with 2007 meta-analysis (Ref. 1).

−2.04 to −0.49); in the non-European setting, the difference between groups in the duration of diarrhoea was of borderline statistical significance (six RCTs, $n = 1700$; MD −0.87; 95% CI −1.81–0.08) (Figure 2). A reduction in the duration of diarrhoea was found in studies carried out in in-patients and out-patients. However, the difference between the LGG group and the control group was statistically significant in out-patients only (two RCTs, $n = 292$; MD −1.92 days, 95% CI −3.25 to −0.58); in in-patients, the difference between groups in the duration of diarrhoea was of borderline statistical significance (seven RCTs, $n = 1768$; MD −0.61 day, 95% CI −1.4–0.19) (see online Supporting Information).

With regard to the aetiology, as previously reported by us, LGG was particularly effective in treating diarrhoea of rotavirus aetiology (two RCTs, $n = 201$; MD −2.08, 95% CI −3.55 to −0.6) (see online Supporting Information). No studies were identified that evaluated the effectiveness of LGG in children vaccinated against rotavirus.



Basu (2009): 2 experimental arms in which LGG was administered at a daily dose of 2 x 10^{10} CFU and 2 x 10^{12} CFU were combined into a single experimental group (see text for more details).

Figure 1 | *Lactobacillus* GG vs. control. Duration of diarrhoea. High dose and low dose.

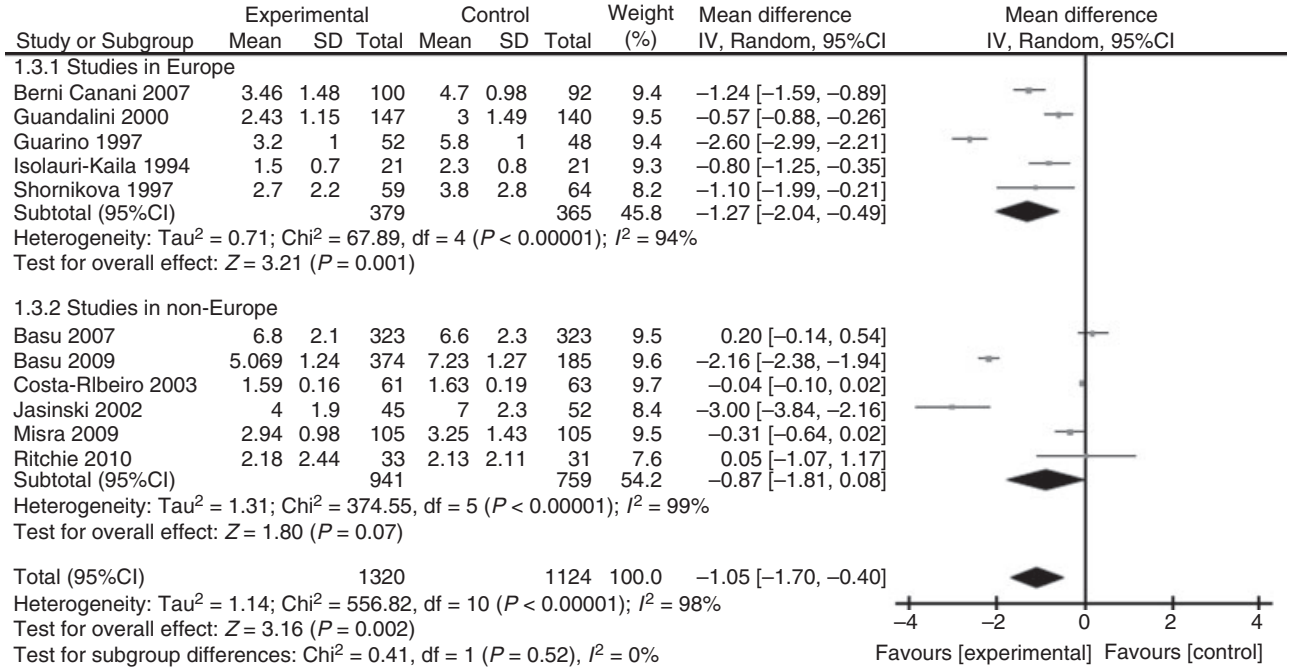


Figure 2 | *Lactobacillus* GG vs. control. Duration of diarrhoea. Setting (Europe and non-Europe).

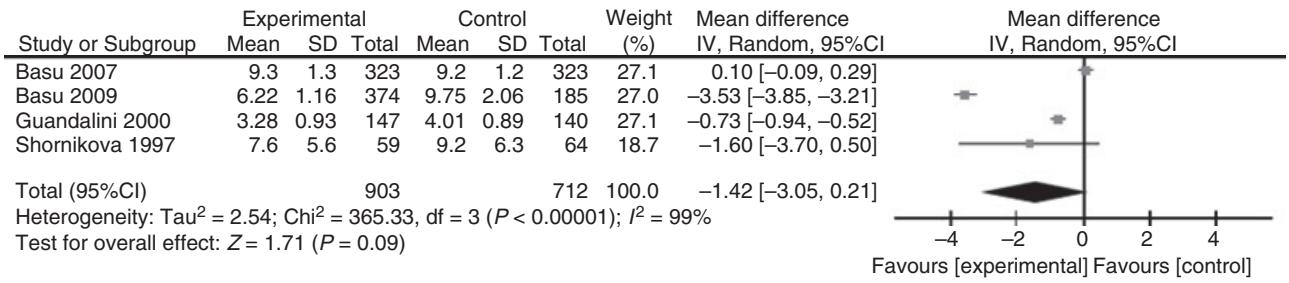


Figure 3 | *Lactobacillus* GG vs. control. Hospitalisation.

Duration of hospitalisation. A meta-analysis of four RCTs (n = 1615) showed a reduction in the duration of hospitalisation for those treated with LGG compared with the control group (MD −0.82 day, 95% CI −0.95 to −0.69). However, changing our meta-analysis model from fixed to random effects (due to significant heterogeneity) changed the results, and no significant difference was found between the groups (MD −1.42 days, 95% CI −3.05–0.21) (Figure 3).

Adverse effects. Adverse effects were similar in experimental and control groups.

DISCUSSION

Summary of evidence

This updated meta-analysis of RCTs confirms the results of our previous analysis. That is, in children with AGE, addition of LGG to standard rehydration therapy compared with placebo or no intervention reduced the duration of diarrhoea by approximately 1 day. A subset of patients that is more likely to benefit includes subjects treated with a high daily dose of LGG ($\geq 10^{10}$ CFU/day) who are both in-patients and out-patients from geographical Europe. Limited evidence from trials in which the aetiology of diarrhoea was assessed suggests that LGG was more effective in treating diarrhoea of rotavirus origin.

Strengths and limitations

This meta-analysis is based on the largest number of studies, and it focuses on a single probiotic. A limitation of our meta-analysis is that only some of the studies seemed methodologically sound. Potential limitations included unclear or inadequate allocation concealment and no blinding in some trials. Both can introduce systematic bias by overestimating the effect and skewing the results in favour of either treatment, depending on the biases of the investigators. Included trials used different definitions of diarrhoea and reported outcomes, namely the duration of diarrhoea. Such heterogeneity among RCTs on acute diarrhoea in respect to diarrhoeal definitions and primary outcomes was previously reported by *Johnston et al.*[29] In 138 analysed RCTs, 64 unique definitions of diarrhoea, 69 unique definitions of diarrhoea resolution and 46 unique primary outcomes were used. To address these problems, recently, the Consensus Group on Outcome Measures Made in Paediatric Enteral Nutrition Clinical Trials (COMMENT) was established. The COMMENT agreed that consensus on a core set of outcomes with agreed definitions, including those related to acute diarrhoea, should be reached and that these outcomes should be measured and reported in nutritional trials.[30]

Agreement and disagreement with other studies or reviews

A number of previous meta-analyses, including a Cochrane review by Allen *et al.*,[31] showed the effect of probiotics (as a class of agents) in the management of children with AGE. In contrast, our work focused exclusively on one type of a clearly defined, single-organism, probiotic microorganism, specifically LGG, as it has been repeatedly questioned whether it is appropriate to pool data on different probiotic microorganisms. The risk is that pooling data from different genera, species, strains and doses of probiotics obtained in different settings and/or populations, presumably with variations in their native intestinal microbiota, may result in misleading conclusions. The results could be erroneously extrapolated to other probiotics, including those that have not been adequately studied.

One of the remaining unsolved questions is what dose of LGG should be applied. Two studies by *Basu et al.*[7, 25] included in our review are of interest as they document the importance of the dose of a probiotic In these double-blind, placebo-controlled RCTs, three dif-

ferent doses of LGG were evaluated, i.e. 1.2×10^7 CFU (showing no effect of LGG); 2×10^{10} CFU, and 2×10^{12} CFU (both showed a positive effect). These results indicate that a minimum daily dose of LGG is needed; however, once the optimum is reached, a further increase in dose is not needed.

In some of the studies, LGG was administered together with ORS. In all the studies administering LGG in ORS, there was a reduction in the duration of diarrhoea. Whether or not this way of administration of ORS (i.e. early in the course of the disease) contributed to the beneficial effect of LGG on the duration of diarrhoea is not clear, but it could not be excluded.

The benefit of using LGG in the management of AGE, i.e. a reduction in the duration of diarrhoea by approximately 1 day, often raises the question of whether this treatment is worthy. AGE places a substantial economic burden on the families of affected children and on the healthcare system.[32] Given the economic impact of the disorder, country-specific studies to examine the cost-effectiveness of using LGG for the treatment of AGE are needed. While no such reports on LGG have been published, some preliminary data suggest a cost/benefit of using probiotics and prebiotics (synbiotics) in the management of AGE.[33]

A recent systematic review[34] documented that some probiotic products, particularly LGG and *Saccharomyces boulardii*, have been shown to increase the risk of complications in specific patient groups. Notably, most complications have occurred in immune-compromised subjects or in patients with other life-threatening illnesses managed in intensive care units. It was also stated that all case reports that detailed infections caused by certain probiotics (i.e. LGG or *S. boulardii*) are likely to reflect their wider use in the clinical setting rather than their increased virulence. Overall, probiotics are safe for use in otherwise healthy populations, but caution should be taken in patients with risk factors for adverse events (e.g. patients with central venous catheters or increased bacterial translocation).[34]

While it was not a subject of our analysis, one of the challenges in transferring the results of clinical trials with probiotics includes the microbiological quality and labelling of many probiotic products. These have often been questioned. Only some of the products meet the definition of probiotics, i.e. contain viable, defined microorganisms in sufficient numbers.[35] An additional challenge comes from the regulatory issues. For example, the European Food Safety Authority (EFSA) has so far expressed only a negative opinion about health claims for probiotics. Consequently, many clinicians have concerns regarding the reliability of some of the products currently on the market. Some of the issues, also issues worth addressing when planning clinical trials on probiotics, were recently discussed elsewhere.[3]

CONCLUSIONS AND FUTURE RESEARCH

This updated systematic review and meta-analysis of RCTs has confirmed that LGG, a probiotic currently supported by ESPGHAN/ESPID, reduces the duration of diarrhoea, particularly in children from geographical Europe, treated with a high dose of LGG ($\geq 10^{10}$ CFU/day), both as in-patients and out-patients. However, given the methodological limitations of many of the included trials, the evidence should be viewed with caution. The role of probiotics in the treatment of AGE in the era of rotavirus vaccination has yet to be established. Recent evidence indicates that since the introduction of rotavirus vaccines, norovirus, at least in US children, has become the leading cause of medically attended AGE.[36] If so, the efficacy of LGG in treating norovirus AGE needs to be confirmed. Country-specific studies to examine the cost-effectiveness of using LGG for the treatment of AGE are needed.

AUTHORSHIP

Guarantor of the article: None.

Author contributions: HS initially conceptualised this study. All authors contributed to the initial protocol of the study. All 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. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

Declaration of personal interests: H. Szajewska served as a speaker for Dicofarm and VitisPharma, the manufacturers of LGG. H. Szajewska is one of the investigators in a clinical trial on LGG included in this review. The remaining authors declare no conflict of interest.

Declaration of funding interests: This study was funded in full by The Medical University of Warsaw.

SUPPORTING INFORMATION

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

Table S1. Characteristics of included studies.

Table S2. Characteristics of excluded trials.

Figure S1. Identification process for eligible trials (since August 2006, i.e. the date of the last search).

Figure S2. *Lactobacillus* GG vs. control. Stool volume.

Figure S3. *Lactobacillus* GG vs. control. Duration of diarrhoea. In-patients and out-patients.

Figure S4. *Lactobacillus* GG vs. control. Duration of diarrhoea. Aetiology of diarrhoea.

Figure S5. *Lactobacillus* GG vs. control. Duration of diarrhoea (definition of diarrhoea).

Figure S6. *Lactobacillus* GG vs. control. Presence of diarrhoea.

Figure S7. *Lactobacillus* GG vs. control. Methodology. Randomisation.

Figure S8. *Lactobacillus* GG vs. control. Methodology. Allocation concealment.

Figure S9. *Lactobacillus* GG vs. control. Methodology. Blinding.

Figure S10. Funnel plot of comparison: *Lactobacillus* GG vs. control. Duration of diarrhoea. High dose vs. low dose of *Lactobacillus* GG.

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