Meta-analysis: *Lactobacillus GG* for treating acute diarrhoea in children

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**SUMMARY**

**Aim**

To review evidence for the effectiveness of *Lactobacillus GG* (LGG) in treating acute infectious diarrhoea in children.

**Methods**

The following electronic databases were searched through August 2006 for studies relevant to acute infectious diarrhoea and LGG: MEDLINE, EMBASE, CINAHL and The Cochrane Library; additional references were obtained from reviewed articles. Only randomized-controlled trials (RCTs) were included.

**Results**

Eight RCTs (988 participants) met the inclusion criteria. Compared with controls, LGG had no effect on the total stool volume (two RCTs, \(n = 303\)). However, LGG was associated with a significant reduction in diarrhoea duration (seven RCTs, 876 infants, weighted mean difference, WMD \(-1.1\) days (95% confidence interval, CI \(-1.9\) to \(-0.3\)), particularly of rotavirus etiology (WMD \(-2.1\) days, 95% CI \(-3.6\) to \(-0.6\)), risk of diarrhoea >7 days (one RCT, \(n = 287\), relative risk 0.25, 95% CI 0.09–0.75) and duration of hospitalization (three RCTs, \(n = 535\), WMD \(-0.58\), 95% CI \(-0.8\) to \(-0.4\); significance was lost in the random effect model). There was no reduction in the number of stools at any time interval.

**Conclusions**

The use of LGG is associated with moderate clinical benefits in the treatment of acute diarrhoea in children. These findings should be interpreted with caution due to the important methodological limitations and heterogeneity of most of the studies.

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INTRODUCTION

Oral rehydration is the mainstay of therapy for acute gastroenteritis and should continue to be fostered, encouraged and supported. However, despite its proven efficacy, oral rehydration therapy remains underused.\(^1\) The main reason for this is that an oral rehydration solution neither reduces the frequency of bowel movements and fluid loss nor does it shorten the duration of the illness, which decreases its acceptance. As a result, there is an interest on the part of patients, caregivers and practitioners as to simple, safe and effective measures that will visibly reduce the rate of stool loss and/or the duration of diarrhoea. Such a product could, perhaps, be helpful in efforts to reduce the common practice in some settings of treating diarrhoea with ineffective anti-diarrhoeal drugs or unnecessary antibiotics.\(^1\) In this respect, the place of probiotics in the treatment of infectious diarrhoea continues to be evaluated.

Probiotics are living microorganisms that, upon ingestion in certain numbers, exert health benefits beyond inherent general nutrition.\(^2\) Previously, we\(^3\) as well as others\(^4,5,6\) have shown that probiotics significantly reduced the duration of diarrhoea. Critics of using a meta-analytical approach to assess the efficacy of probiotics argue that beneficial effects of probiotics seem to be strain specific, thus, pooling data on different strains may result in misleading conclusions. Even if subgroup analysis based on the probiotic strain is often available, as in the case of our previous meta-analysis\(^3\), sometimes such data are not straightforwardly available to the reader. Furthermore, none of the published meta-analyses addressed the effect of probiotics on stool volume. Finally, many international and local groups of experts when developing guidelines on the management of acute gastroenteritis need data on specific-probiotic strain(s) to decide whether or not they should be routinely used. Given these considerations, the present review was undertaken to review and update data on the effectiveness and safety of only one probiotic strain—*Lactobacillus rhamnosus* GG (LGG), ATCC 53103.

OBJECTIVE

To systematically review the effectiveness of LGG in treating children with acute gastroenteritis.

METHODS

Inclusion and exclusion criteria

We included randomized-controlled trials (RCT) in which the intervention was LGG compared with a placebo or no intervention for children with acute diarrhoea (as defined by the investigators). The primary outcome measures were stool output and duration of diarrhoea. The secondary outcome measures were the percentage of children with diarrhoea at various time intervals (as specified by the investigators), the percentage of children with diarrhoea lasting longer than 7 days, vomiting and adverse effects. In addition to these outcomes, *a priori* we decided to extract other data reported by the investigators if clinically relevant to the current review. We chose one probiotic strain, LGG, to separate our review from other reviews on probiotics, which used all probiotic strains as the starting point for the inclusion criteria. We excluded studies comparing LGG with the control group in which heat-inactivated bacteria or pasteurized yogurt containing some amount of lactic acid bacteria were used. The rationale for such decision is based on data from studies suggesting that some probiotic effects can be achieved by non-viable bacteria and even by isolated bacterial DNA.\(^7,8,9\) As the causes of acute diarrhoea in children differ from those in adults, we excluded studies of adults only. Children could be seen in any setting. Only studies with >80% follow-up were included.

Searches

We searched MEDLINE (1966–August 2006), EMBASE (1980–August 2006), Cumulative Index to Nursing and Allied Health (CINAHL, 1982–August 2006), The Cochrane Database of Systematic Reviews (Issue 3, 2006) and The Cochrane Controlled Trials Register (Issue 3, 2006) for randomized-controlled clinical trials comparing LGG with placebo or no intervention in children with acute diarrhoea (as defined by the investigators) using the following textword terms and MESH headings: diarrhoea /diarrhoea, diarrh*, gastroenteritis, probiotic*, *Lactobacillus* GG, LGG. Furthermore, the reference lists from the original studies and review articles were identified. The pharmaceutical company Dicofarm (Italy) that manufactures LGG was contacted to help identify published and unpublished data. No limit was imposed regarding the language of
publication, but certain publication types (i.e. letters to the editor, abstracts and proceedings from scientific meetings) were excluded.

Data extraction

Each author independently assessed the titles and abstracts of potential papers identified according to the above-described search strategy. All potentially relevant articles were retained and the full text of these studies examined to determine which studies satisfied the inclusion criteria. Data extraction was carried out independently by all reviewers using standard data extraction forms. We compared the extracted data to identify errors. One reviewer (HS) entered the data into The Cochrane Review Manager (RevMan [Computer program]. Version 4.2 for Windows. Oxford, England: The Cochrane Collaboration; 2003) for analysis. Discrepancies between the reviewers were resolved by discussion.

Study quality

The reviewers independently, but without blinding to the authorship or journal, assessed the included trials for: (i) allocation concealment; (ii) blinding of investigators, participants, outcome assessors and data analysts (yes/no/not reported); (iii) intention-to-treat analysis (yes/no); and (iv) comprehensive follow-up. Allocation concealment was considered adequate when the randomization method used did not allow the investigator or the participant to identify or influence the intervention group before the entry of eligible participants into the study. However, the quality of the allocation concealment was considered unclear when randomization was used but no information about the method was available and inadequate, when inappropriate methods of randomization (e.g. alternate medical record numbers, unsealed envelopes and tossing the coin) were used. In regard to the intention-to-treat analysis, an answer of ‘yes’ meant that the authors had specifically reported undertaking this type of analysis and/or that our own study confirmed this finding. Conversely, a ‘no’ meant that authors did not report use of intention-to-treat analysis and/or that we could not confirm its use on study assessment. To evaluate the completeness of patient follow-up, we determined the percentage of participants excluded or lost to follow-up.

Statistical methods

The data was analysed using The Cochrane Review Manager. The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes. The binary measure for individual studies and pooled statistics was reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CI). Number needed-to-treat (NNT) was calculated as the inverse of the pooled absolute risk differences and 95% CI. The weight given to each study was based on the inverse of the variance. Heterogeneity was quantified by $\chi^2$ 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 there was heterogeneity, we present results of both random effects and fixed effects models for the main analysis. For simplicity, if heterogeneity was not revealed, we present results of only the fixed effects model.

For the primary outcomes, when there was statistically significant heterogeneity in outcomes across studies, sensitivity analyses according to each of the four parameters of trial methodological quality were conducted.

To test for publication bias, a test for asymmetry of the funnel plot proposed by Egger et al. was used. This test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the normalized 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.

A priori subgroup analysis based on factors that could potentially influence the magnitude of the treatment response was planned for the following: (i) etiology of diarrhoea; (ii) type of treatment (outpatient vs. inpatient); and (iii) setting (Europe vs. non-European countries).

RESULTS

We initially identified 14 articles. Table 1 summarizes the characteristics of the included trials. Eight RCTs involving 988 participants (494 in the experimental group and 494 in the control group) met our predefined inclusion criteria. All were full peer-reviewed publications. The remaining six studies were
<table>
<thead>
<tr>
<th>No.</th>
<th>Author (Country)</th>
<th>Generation of allocation sequence</th>
<th>Allocation concealment*</th>
<th>Blinding</th>
<th>ITT*</th>
<th>FU†</th>
<th>N (Exp/ Conti)</th>
<th>Inclusion criteria</th>
<th>Age</th>
<th>LGG (dose per day)</th>
<th>Control group</th>
<th>Duration of intervention</th>
<th>Definition of termination of diarrhoea</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Costa-Ribeiro et al. (Brazil; inpatients)</td>
<td>Adequate (code administered sequentially)</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
<td>61/63</td>
<td>≥3 watery or loose stools per 24 h; &lt;72 h; moderate dehydration</td>
<td>1–24 month</td>
<td>10⁹ CFU</td>
<td>Placebo (inulin)</td>
<td>Not specified</td>
<td>From time of randomization until cessation of diarrhoea</td>
<td>RV 50%</td>
</tr>
<tr>
<td>2</td>
<td>Guandalini et al. (Europe–10 centers; in/outpatients)</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>287/323 (89%)</td>
<td>147/140</td>
<td>≥4 liquid or semi-liquid stools for 1–5 days, mild to moderate dehydration</td>
<td>1–36 month</td>
<td>0RS + LGG 10⁹ CFU/250 mL</td>
<td>ORS with no LGG</td>
<td>As tolerated for 4–6 h, then ad libitum</td>
<td>Time in hours until last recorded fluid stool</td>
<td>RV 35%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Guarino et al. (Italy; outpatients)</td>
<td>Adequate (random-number table)</td>
<td>Unclear</td>
<td>No</td>
<td>(open study)</td>
<td>Yes</td>
<td>100%</td>
<td>≥3 watery stools, &lt;48 h</td>
<td>3–36 month</td>
<td>3 × 10⁹ CFU twice daily</td>
<td>No probiotic</td>
<td>5 days</td>
<td>Time to the last loose or liquid stool</td>
<td>RV 61%</td>
</tr>
<tr>
<td>4</td>
<td>Isolauri &amp; Kaila et al. (Finland; inpatients)</td>
<td>Unclear</td>
<td>No</td>
<td>(open study)</td>
<td>Yes</td>
<td>100%</td>
<td>21/21</td>
<td>&gt;3 watery stools during the previous 24 h; &lt;7 days</td>
<td>5–28 month</td>
<td>10⁹ CFU twice daily</td>
<td>No probiotic</td>
<td>5 days</td>
<td>Not defined</td>
<td>RV 100%</td>
</tr>
<tr>
<td>5</td>
<td>Jasinski et al. (Uruguay; outpatients/inpatients)</td>
<td>Unclear</td>
<td>Inadequate</td>
<td>Yes</td>
<td>Yes</td>
<td>100%</td>
<td>45/52</td>
<td>≥3 watery stools during the previous 24 h; &lt;7 days; positive for RV</td>
<td>1–36 month</td>
<td>10⁶ CFU twice daily</td>
<td>No probiotic</td>
<td>Not specified</td>
<td>Time until two first formed stools</td>
<td>RV 40%</td>
</tr>
<tr>
<td>6</td>
<td>Raza et al. (Pakistan; in-patients, undernourished)</td>
<td>Unclear</td>
<td>No</td>
<td>(open study)</td>
<td>Yes</td>
<td>No</td>
<td>36/40 (90%)</td>
<td>&gt;3 watery stools during the previous 24 h; &lt;14 days; at least moderate dehydration</td>
<td>1–24 month</td>
<td>10⁶–11 CFU</td>
<td>Placebo (micro-crystalline cellulose)</td>
<td>2 days</td>
<td>Not measured</td>
<td>No data</td>
</tr>
<tr>
<td>7</td>
<td>Salazar-Lindo et al. (Peru; in-patients)</td>
<td>Random permuted blocks; sealed envelopes</td>
<td>Adequate (number-coded and labeled bottles)</td>
<td>Yes</td>
<td>No</td>
<td>160/179 (89%)</td>
<td>≥3 watery stools; &lt;48 h; no bloody stools; signs of dehydration</td>
<td>3–36 month</td>
<td>Milk formula + LGG 10⁹ CFU/mL 150 mL/kg/day (max. 1 1/2/day)</td>
<td>Placebo (milk with no LGG)</td>
<td>Ad libitum</td>
<td>Time in hours from admission until cessation of diarrhoea</td>
<td>RV 32%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Shornikova et al. (Russia; in-patients)</td>
<td>Randomization schedule</td>
<td>Adequate (randomization numbers sequentially assigned)</td>
<td>Yes</td>
<td>Yes</td>
<td>124/214 (57%) 123/123</td>
<td>≥1 watery stools during the previous 24 h; &lt;5 days</td>
<td>1–36 month</td>
<td>5 × 10⁹ CFU twice daily</td>
<td>Placebo (cellulose powder)</td>
<td>5 days</td>
<td>Last appearance of watery stools</td>
<td>RV 28%</td>
<td></td>
</tr>
</tbody>
</table>

* ITT, intention-to-treat analysis; † FU, completeness of follow-up. RV, rotavirus.
excluded. Table 2 summarizes characteristics of the excluded trials, including the reasons for exclusion.

Six studies were placebo controlled. In the remaining two trials, there was no additional intervention in the control group. Four studies were based in European countries (i.e. EU countries and Russia) and four were based in non-European countries (i.e. Brazil, Pakistan, Peru and Uruguay). The age of the participants ranged from 1 to 36 months. The daily dose of the study product, presentation (LGG in milk or as a capsule) and the duration of the intervention varied. Most of the trials were performed exclusively in in-patients. Except one, all studies provided data on the etiology of the diarrhoea. The definition of the termination of diarrhoea varied among studies. The methodological quality of the trials also varied (Table 1).

Significant heterogeneity was found for total stool volume ($\chi^2 = 4.03, P = 0.04, I^2 = 75.2\%$), duration of diarrhoea ($\chi^2 = 230.13, P < 0.00001, I^2 = 97.4\%$), duration of rotavirus diarrhoea ($\chi^2 = 33.42, P < 0.00001, I^2 = 94\%$), of diarrhoea of unknown cause ($\chi^2 = 13.55, P < 0.0002, I^2 = 92.6\%$) and duration of hospital stay ($\chi^2 = 14.7, P = 0.0006, I^2 = 86.4\%$). However, heterogeneity was not significant for other outcomes.

Stool output

Two RCTs$^{12, 17}$ ($n = 303$) provided data on total stool output; it was defined as total stool output from randomization until cessation of diarrhoea$^{12}$ or the volume of diarrhoea l stools collected from admission until cessation of diarrhoea or for a maximum of 120 h if the diarrhoea continued.$^{17}$ Pooled results for these two RCTs showed no significant difference between the two groups (WMD 24.2 mL/kg, 95% CI $-19.2$ to $67.6$, fixed effects); (8.9 mL/kg, 95% CI $-86$ to $104$, random effects) (Figure 1). Additionally, one RCT$^{16}$ in 36 undernourished boys found no statistically significant difference in stool volume on day 1 (mean difference $13.6$ g/kg, 95% CI $-13.1$ to $40.3$, random effects) or on day 2 (mean difference $12.4$, 95% CI $-6.4$ to $31.2$, random effects). Due to the limited number of RCTs available, no sensitivity analyses were performed.

Duration of diarrhoea

A meta-analysis of seven RCTs$^{12}$ (876 participants) showed a reduction in the duration of diarrhoea (WMD$^{-0.14}$ days, 95% CI $-0.2$ to $-0.08$, fixed effects); ($^{-1.1}$ days, 95% CI $-1.9$ to $-0.3$, random effects) for those treated with LGG compared with placebo (Figure 2); however, the significance was lost on sensitivity analyses except for blinding. Pre-planned subgroup analysis based on setting showed that this finding was significant only for studies carried out in European countries (WMD $^{-1.27}$ days, 95% CI $-2.3$ to $-0.2$, random effects), but was not significant for studies conducted in non-European countries (WMD $^{-0.76}$ days, 95% CI $-1.7$ to $0.2$).

Table 2. Characteristics of excluded trials

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Study design, reason(s) for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Isolauri et al. Pediatrics 1991$^{23}$</td>
<td>RCT. Reallocations of patients after randomization. In the control group, fermented then pasteurized yogurt with some (insignificant) amount of lactic acid bacteria was used.</td>
</tr>
<tr>
<td>2. Kaila et al. Pediatr Res 1992$^{22}$</td>
<td>RCT. In the control group, pasteurised yogurt with $&lt;10^3$ lactic acid bacteria was used.</td>
</tr>
<tr>
<td>3. Kaila et al. Arch Dis Child 1995$^{20}$</td>
<td>RCT, open trial, follow-up 63%. In the control group, killed Lactobacillus species were used.</td>
</tr>
<tr>
<td>4. Majamaa et al. JPGN 1995$^{24}$</td>
<td>RCT, open trial, comparison with other probiotics.</td>
</tr>
<tr>
<td>6. Rautanen et al. Arch Dis Child 1998$^{36}$</td>
<td>RCT, double-blind. Two different simultaneous interventions in the experimental and control groups were studied—hypotonic ORS + Lactobacillus GG vs. ultrahypotonic ORS + Lactobacillus GG. No data presented for placebo group.</td>
</tr>
</tbody>
</table>

ORS, oral rehydration solution; RCT, randomized-controlled trial.
Duration of rotavirus diarrhoea

Based on the results of three RCTs\(^\text{13}\) (\(n = 201\)) to report this outcome, LGG significantly reduced the duration of rotavirus diarrhoea (WMD \(-2\) days, 95% CI \(-2.4\) to \(-1.7\), fixed effects); \((-2.1\) days, 95% CI \(-3.6\) to \(-0.6\), random effects) (Figure 2). One RCT\(^\text{12}\) reported no significant difference in the duration of rotavirus diarrhoea, but no data were given.

Duration of invasive diarrhoea

One RCT\(^\text{13}\) reported data on the duration of diarrhoea in a subset of children (\(n = 53\)) with diarrhoea caused...
by proven invasive enteropathogens; no significant difference was found between the two groups (WMD 0.05 days, 95% CI −0.64–0.74) (Figure 2). Furthermore, Shornikova et al. found no effect (P = 0.42) on diarrhoea in patients in the LGG group (n = 11) compared with the placebo group (n = 15), but no data were reported.

Duration of diarrhoea of unknown cause

Pooled results from two RCTs (n = 124) demonstrated a small effect of LGG on the duration of diarrhoea of unknown cause (WMD −0.84 days, 95% CI −1.32 to −0.36, fixed effects); significance was lost when changing to a random effects model (WMD −1.7, 95% CI −4.2–0.82) (Figure 2).

Diarrhoea on day 2

One small RCT (n = 11) found that LGG reduced the risk of diarrhoea on day 2 (RR 0.37, 95% CI 0.17–0.84) (Figure 3).

Diarrhoea on day 3

A meta-analysis of two RCTs (n = 329) showed reduced risk of the diarrhoea on day 3 in patients receiving LGG. However, this was significant only in the fixed effect model (RR 0.56, 95% CI 0.4–0.78) and was not significant in the random effect model (RR 0.47, 95% CI 0.19–1.12) (Figure 3).

Diarrhoea >7 days

One trial showed a reduction in the risk of diarrhoea lasting >7 days for those treated with LGG compared with control (RR 0.25, 95% CI 0.09–0.75; NNT 5 (95% CI 3–20) (Figure 3).

Diarrhoea >10 days

One trial (n = 97) that provided data on the risk of diarrhoea >10 days showed no significant difference between the groups (RR 0.23, 95% CI 0.03–1.9) (Figure 3).
Hospitalization

Based on the pooled results of three studies (n = 535), there was reduced duration of hospitalization in the LGG group compared with the control group (WMD −0.58 days, 95% CI −0.8 to −0.4, fixed effect); however, this difference was lost on the random effect model (WMD −0.43, 95% CI −1.32 to 0.46) (Figure 4). Based on the results of one RCT (n = 101), hospitalization due to rotavirus diarrhoea was reduced (WMD −0.89 days, 95% CI −1.2 to −0.6).

Vomiting

Based on the results of the only one small RCT (n = 36) to report this outcome, there was no difference in the number of vomiting episodes on day 1 (mean difference −0.2, 95% CI −2 to 1.7); however, there was significant reduction in vomiting episodes in the LGG group on day 2 (mean difference −2, 95% CI −3.4 to −0.6).

Treatment failure

Two RCTs provided data on treatment failure; the outcomes, however, were defined differently, which precluded us from pooling the data together. The first RCT13 (n = 287) defined treatment failure as the need to resort to intravenous rehydration for any reason and demonstrated no difference between groups (RR 1.04, 95% CI 0.5–2.3). In the second RCT17, treatment failure was defined as the proportion of patients in each study group who experienced recurrence or the continued presence of more that 5% dehydration, worsening electrolyte abnormalities, no weight gain, development of an ileus or severe diarrhoea; again, no difference was found between the experimental and control groups (RR 1.2, 95% CI 0.7–1.8).

Adverse events

Investigators in one RCT16 reported myoclonic jerks that occurred in one child in each group. One RCT17 found no adverse effects. Three RCTs12 did not comment on adverse effects.

Publication bias

A funnel plot (Figure 5) and the Egger’s et al. regression asymmetry test (P = 0.09 and 95% CI included 0) did not show any publication or other small sample bias.

DISCUSSION

Principal findings

A meta-analysis of data from RCTs showed that in otherwise healthy infants and children with acute infectious gastroenteritis, the use of LGG was associated with a reduction in the duration of diarrhea, particularly of rotavirus etiology. However, LGG administration did not affect diarrhea caused by invasive enteropathogens nor that of unknown cause. Compared with placebo, LGG reduced the risk of diarrhea >7 days and shortened the duration of hospitalization. On the other hand, the use of LGG compared with control had no effect on stool volume (which by the World Health Organization is considered as the optimal outcome measure for the evaluation of therapeutic agents in the management of acute diarrhea).26 There was no reduction in the number of stools in any time interval studied. Adverse effects were similar in both groups.

Previous studies

Our findings are similar to those of previous systematic reviews on a variety of probiotic strains, including

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>WMD (randcl)</th>
<th>Weight</th>
<th>VMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Guadarrama</td>
<td>147</td>
<td>4.18 (0.93)</td>
<td>149</td>
<td>4.01 (0.89)</td>
<td>0.17</td>
</tr>
<tr>
<td>Shannon</td>
<td>69</td>
<td>2.60 (5.66)</td>
<td>64</td>
<td>2.70 (5.31)</td>
<td>0.33</td>
</tr>
<tr>
<td>51 %</td>
<td>62</td>
<td>3.38 (1.46)</td>
<td>62</td>
<td>3.38 (1.46)</td>
<td>0.00</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>286</td>
<td></td>
<td>286</td>
<td></td>
<td>0.00</td>
</tr>
</tbody>
</table>

Figure 4. Lactobacillus GG vs. control. Hospitalization.
However, this meta-analysis includes more trials than any of the previously published systematic reviews and is the first to focus on only one probiotic strain.

**Effect on rotaviral diarrhoea**

The pronounced effect on rotaviral gastroenteritis potentially could be of the utmost clinical importance, as rotavirus is the leading cause of acute diarrhoea in children worldwide. However, this finding is based on a relatively small number of patients; in total, only 105 children received LGG. Furthermore, at present there are two licensed rotavirus vaccines in Europe (Rotarix and RotaTeq). Both vaccines can be used to control rotavirus disease and have the potential to reduce the burden of rotavirus gastroenteritis. If so, this may question the importance of the use of LGG for treating acute gastroenteritis. On the other hand, at least theoretically, there is a possibility that large-scale use of rotavirus vaccines may result in a shift in prevailing serotypes from those affected by the vaccines to currently less prevalent serotypes (or other viruses), thus, sustaining interest in effective treatments.

**Limitations of the analysis**

Potential sources of bias must be considered. All trials included in our analysis had methodological limitations, including unclear or inadequate allocation concealment, no intention-to-treat analysis and no blinding. Study limitations also included a small sample size in some trials and no widely agreed-on definition of termination of diarrhoea.

The included studies were significantly heterogeneous. The heterogeneity between trials is probably explained by differences in the participants, settings, LGG dose and variability in trial methodological quality, as discussed earlier. Sensitivity analyses using various variables alter the conclusions; however, some of the planned analyses were constrained owing to the limited number of trials available.

The included studies were carried out both in European and non-European countries. Only studies carried out in Europe consistently showed a beneficial effect of LGG. Two out of three trials performed outside of Europe, where infectious agents other than rotavirus are frequently involved, showed no significant reduction in the duration of diarrhoea. In the study by Costa-Ribeiro et al., the mean duration of diarrhoea in the controls was significantly shorter than that reported by the majority of others and additionally the LGG dose used (10^9 CFUs per day) was lower. In the study by Salazar-Lindo et al., the lack of an effect may be explained by three factors. First, lactobacilli appear efficacious especially in rotaviral diarrhoea, and the prevalence of rotavirus in the LGG group was only 24% compared with 39% in controls (P = 0.05). Secondly, the diarrhoea was more severe at study entry in children allocated to the LGG group: 60% had moderate to severe dehydration compared with 46% of controls. Thirdly, LGG was administered only after completing rehydration (there is evidence that early administration is more effective) and in a milk formula containing lactose. Almost 50% of children in both groups showed intolerance to this milk formula at enrollment, thus, possibly masking any favorable effect of the probiotic.

In this systematic review, we excluded trials comparing LGG with a control group in which heat-inactivated bacteria or pasteurized yogurt containing some amount of lactic acid bacteria were used. However, it is noteworthy that with one exception, findings of all excluded trials showed a reduced duration of diarrhoea in children, further confirming the effectiveness of LGG in treating acute gastroenteritis in children.

**Safety**

Based on this review, use of LGG appears to be safe. However, although rarely, the use of LGG is not with-
out risk; complications such as bacteremia have occurred in certain populations.29

CONCLUSIONS
The role of probiotics in the treatment and prevention of infectious diarrhoea continues to be evaluated. The RCTs to date suggest moderate efficacy of LGG. Considering the safety, tolerance and moderate activity of LGG, it is worth a try to use this probiotic strain in the treatment of acute diarrhoea in otherwise healthy infants and young children of developed countries, but this is not a must. On the other hand, as no in-depth diagnostic testing is usually required for managing acute gastroenteritis in children, and as rotavirus is a major cause and introduction of rotavirus vaccine in many countries is likely to reduce the burden of the disease (provided it will be universally available), the significant effect of probiotics in gastroenteritis might become weaker or even disappear.

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REFERENCES


