AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: the effects of *Lactobacillus rhamnosus* GG supplementation for the prevention of healthcare-associated diarrhoea in children

H. Szajewska, M. Wanke & B. Patro

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

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

Publication data
Submitted 22 July 2011
First decision 7 August 2011
Resubmitted 10 August 2011
Accepted 11 August 2011
EV Pub Online 7 September 2011

SUMMARY

Background
In children, healthcare-associated diarrhoea, in particular, due to rotavirus, may prolong the hospital stay and increase medical costs, prompting interest in effective, low-cost, preventive strategies.

Aim
To review systematically data on the efficacy of administering *Lactobacillus rhamnosus* GG (LGG) for the prevention of healthcare-associated diarrhoea.

Methods
MEDLINE, EMBASE, Health Source: Nursing/Academic Edition, the Cochrane Library, trial registries and proceedings of major meetings were systematically searched for randomised controlled trials (RCTs) performed in children aged 1 month to 18 years that compared administration of LGG with placebo or no intervention. Two reviewers assessed studies for inclusion and risk of bias and extracted the data. Outcome measures included the incidences of healthcare-associated diarrhoea and rotavirus gastroenteritis. If appropriate, meta-analyses were carried out using the fixed effects model.

Results
Three RCTs involving 1092 children were included. Compared with placebo, LGG administration for the duration of hospital stay was associated with significantly lower rates of diarrhoea (two RCTs, $n = 823$, relative risk, RR 0.37, 95% confidence interval, CI 0.23–0.59) and symptomatic rotavirus gastroenteritis (three RCTs, $n = 1043$, RR 0.49, 95% CI 0.28–0.86). There was no significant difference between the LGG and the control groups in the incidence of asymptomatic rotavirus infection, duration of hospitalisation or duration of diarrhoea. LGG was well tolerated, and no harms were reported in any of the trials.

Conclusion
In hospitalised children, the administration of *Lactobacillus rhamnosus* GG compared with placebo has the potential to reduce the overall incidence of healthcare-associated diarrhoea, including rotavirus gastroenteritis.

Aliment Pharmacol Ther 2011; **34:** 1079–1087

doi:10.1111/j.1365-2036.2011.04837.x

BACKGROUND

Healthcare-associated infections, also referred to as 'hospital-acquired', 'nosocomial' or 'hospital-onset' infections, are defined as infections not present and without evidence of incubation at the time of admission to a healthcare setting.[1] Infections occurring more than 48 h after admission are usually considered to be healthcare-associated infections.[2] One of the most common types is healthcare-associated diarrhoea (HAD). In children, rotavirus remains a leading cause of nosocomial gastroenteritis.[3] One study showed that nosocomial rotavirus infection may occur in 27% of hospitalised children.[4] However, the true burden may be underreported due to difficulties in gathering reliable data.[2] HAD results in prolonged hospital stays and increased additional medical costs.[5]

The single most inexpensive procedure to prevent HAD is improved hand washing combined with isolation of infected children, although the effectiveness of these measures is unsatisfactory.[2] For prevention of rotavirus infection, vaccination seems to be the most promising strategy.[6] The availability of two efficacious and safe rotavirus vaccines with high efficacy against severe rotavirus gastroenteritis, combined with consistent recommendations to include these vaccines in national immunisation programmes,[6,7] offers promise in reducing the burden of disease caused by rotavirus. Although the incidence of nosocomial rotavirus diarrhoea has not been an outcome measure in any vaccine trials performed so far, the high efficacy of both vaccines in the prevention of community-acquired rotavirus gastroenteritis makes this secondary benefit very likely. Unfortunately, the high cost of rotavirus vaccines preclude their widespread use in many settings, thus, maintaining interest in simple, effective, low-cost strategies for preventing HAD.

Probiotics are 'live microorganisms which when administered in adequate amounts confer a health benefit on the host'.[8] One of the most studied probiotics is *Lactobacillus rhamnosus* GG (LGG). In children, there is now convincing data to support the use of LGG for the treatment of acute gastroenteritis[3] and the prevention of the antibiotic-associated diarrhoea.[9] Despite some positive evidence, it is unclear whether LGG is also effective for preventing nosocomial diarrhoea. According to the European Food and Safety Authority (EFSA),[10] only one of the three randomised controlled trials (RCTs) evaluated by the EFSA showed an effect of LGG on the incidence or duration of diarrhoea in hospitalised children. The use of 'vote counting' to compare the number of studies with positive results with the number of studies with negative results can be questioned. In the Cochrane Handbook for Systematic Reviews of Interventions, it is clearly stated that 'vote counting might be considered as a last resort in situations when standard meta-analytical methods cannot be applied (such as there is not consistent outcome measure)'.[11] Considering the above, we aimed to systematically assess and pool together, if appropriate, evidence of the effects of LGG compared with placebo on the prevention of HAD, including rotavirus gastroenteritis, to resolve such uncertainty.

METHODS

The guidelines from the Cochrane Collaboration for undertaking and reporting the results of a systematic review and meta-analysis[11] and the PRISMA statement[12] were followed for this systematic review and meta-analysis.

Criteria for considering studies for this review (types of studies, participants, interventions, outcomes)

All randomised controlled trials (RCTs) that compared the effectiveness of LGG to placebo/no intervention for the prevention of HAD in children were included in the analysis. Participants had to be children aged 1 month to 18 years, male or female and of any ethnic group, who were being admitted to the hospital for any reason. We excluded studies with participants at high risk of developing infections (e.g., intensive care unit patients, very low birth weight preterm infants). The intervention group had to receive LGG given at any dose and in any form. The control group had to receive placebo or no intervention. The primary outcome measure was the incidence of HAD, using the primary investigator's definition. The secondary outcome measures were the incidence of rotavirus gastroenteritis, the incidence of asymptomatic rotavirus infection, the duration of diarrhoea, the duration of the hospitalisation and harms.

Search methods for identification of studies

Studies appropriate for inclusion were identified by searching MEDLINE, EMBASE, Health Source: Nursing/Academic Edition and The Cochrane Library through January 2011. The search was repeated in June 2011. Two reviewers independently performed a systematic review. The search strategy included the use of a validated filter for identifying RCTs, which was combined with a topic-specific strategy using the following terms: (prevention OR prevent OR prevent* OR preventive therapy OR prophylaxis) AND (diarrhoea OR diarrhoe* OR diarhe* OR dysenter* OR gastro enteritis OR diarrhoea OR diarrh* OR gastritis OR gastrit* OR

gastroenteritis OR gastroenterocolitis OR vomit* OR intestinal infection* OR gastrointestinal infection* OR rotavirus) AND (probiotics OR probiotic OR lactobacillus OR LGG OR lactobacillus rhamnosus OR lactobacill*) AND (children OR child* OR infants OR infant* OR toddler* OR adolescent* OR teenage* OR baby OR preschool children) AND (Humans[Mesh]). In addition, we searched two trial registries (ClinicalTrials.gov, http://www.clinicaltrials.gov, and EU Clinical Trials Register, http://www.clinicaltrialsregister.eu) and proceedings from major scientific gastrointestinal meetings such as ESPGHAN, NASPGHAN, UEGW and DDW published in the last 3 years.

Data extraction

Using a standardised data extraction form, authors independently extracted the following data items: author, year of publication, language, study setting, methodological design, exclusion criteria for participants, patient characteristics (age, diagnosis), number of patients allocated to each group, type of interventions and outcome measures including their definitions. The reviewers independently carried out data extraction and entered the data into a computer program. The Cochrane Review Manager (RevMan) [Computer program, Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011] was used for statistical analysis and to perform the meta-analysis of the RCTs. The differences between the reviewers were resolved by discussion.

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 and 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.[13]

Measures of treatment effect

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

Dealing with missing data

An available case analysis, i.e. an analysis in which data are analysed for every participant for whom the outcome was obtained, was carried out for all outcomes.

Assessment of heterogeneity

Heterogeneity was quantified by χ^2 and I^2. The latter 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, if it was still considered appropriate to pool the data.

Assessment of reporting biases

To test for publication bias, we planned to use a test for asymmetry of the funnel plot proposed by Egger *et al.*[14] However, the publication bias was not formally assessed using a funnel plot due to the small number of studies (<10) included in the analyses of the primary and secondary outcome measures.

Data synthesis (Statistical methods)

The data were analysed using RevMan. The binary measure for individual studies and pooled statistics is reported as the risk ratio (RR) between the experimental and control groups with a 95% confidence interval (95% CI). Number needed to treat (NNT) with a 95% CI were calculated using STATSDIRECT statistical software (version 2, 7, 8 [2010-03-15]; StatsDirect Ltd., Altrincham, UK).

RESULTS

Description of studies

Figure 1 shows the flow of studies through the selection process. A total of 1685 studies were identified from the primary electronic databases. Independent review of the titles and/or abstracts identified eight potentially relevant studies for full-text review. Authors independently assessed these studies and identified three RCTs that met the inclusion criteria.[15–17] The characteristics of the included trials are presented in Table 1. Excluded studies are described in Table 2. The included trials randomised a total of 1092 patients, of which 1043 were followed up. All included studies were double blind, randomised, placebo-controlled trials and published in the English language. All trials had some methodological limitations,

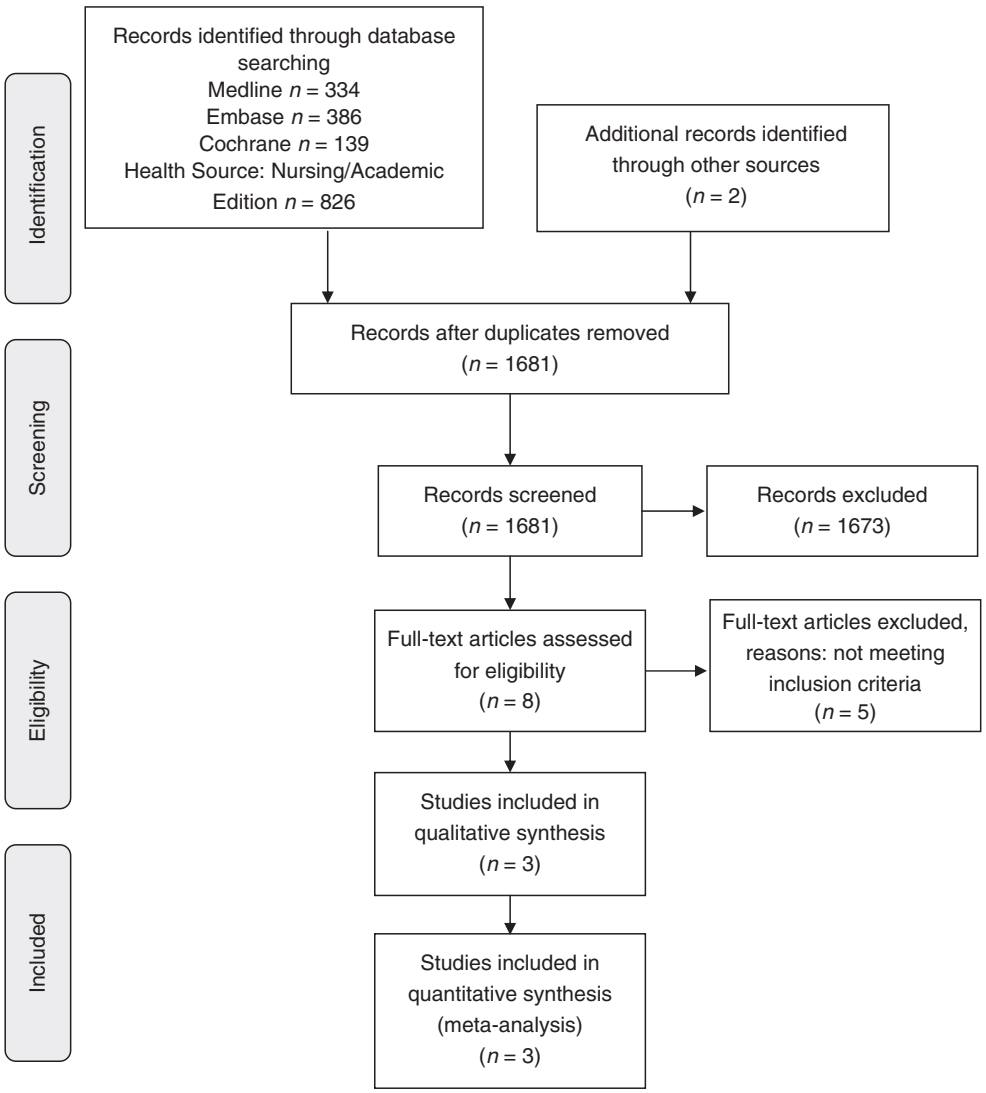

Figure 1 | Identification process for eligible trials.

with unclear allocation concealment applying to all trials. All studies were conducted in Europe (Croatia, Italy, Poland). Patients were hospitalised in paediatric departments for acute or chronic diseases. In two studies,[16,17] the most common reason for hospitalisation was a respiratory tract infection. In the study by Hojsak *et al.*,[15] a respiratory tract infection on admission was an exclusion criterion. Patients' ages ranged from 1 month to 18 years of age. Two RCTs[16,17] included infants and young children only (age below 18 and 36 months respectively); one RCT[15] excluded young infants below the age of 12 months.

The daily dose of LGG ranged from 1×10^9 CFU (Hojsak *et al.*[15]) to 1×10^{10} CFU (Mastretta *et al.*[16]) to 1.2×10^{10} CFU (Szajewska *et al.*[17]). The form of administration of LGG was fermented milk supplemented with LGG or LGG in capsules or sachets. In all included studies, LGG administration lasted for the duration of the hospital stay. In all studies, the probiotic intervention group was compared with a placebo control group. The follow-up period ranged from 3 days[16,17] to 7 days[15] after discharge from the hospital.

In two RCTs,[15,17] the primary outcome measure was the incidence of diarrhoea. While the definitions of this outcome were similar, in the study by Hojsak *et al.*,[15] patients with antibiotic-associated diarrhoea without a positive stool test were excluded from the analyses. In all included RCTs, the incidence of rotavirus gastroenteritis was assessed. In the study by Mastretta *et al.*,[16] this was the primary outcome.

Table 1 | Methodological quality summary and characteristics of included studies

	Methodological quality summary*				Characteristics of included trials					
Author (country)	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete data addressed?	Population	Exp/Cont (Follow-up)	LGG dose	Control	Duration of intervention (follow-up period)	Primary outcome (definition)
Hojsak *et al.* (Croatia)	Yes (computer-generated numbers)	Unclear	Yes (DB)	Yes	>12 months with acute and/or chronic diseases (mean age: 10 ± 5 years)	376/366 (100%)	10^9 CFU daily in 100 mL of fermented milk product	Placebo (post-pasteurized fermented milk product without LGG)	During hospital stay (7 days after discharge)	Gastrointestinal tract infections (diarrhoea with ≥3 loose or watery stools within 24 h with or without vomiting). AAD was not considered.
Mastretta *et al.* (Italy)	No (odd and even random sampling numbers)	Unclear	Yes (DB)	No	1 to 18 months with acute and/or chronic diseases (mean age: 10 months)	134/135 (Follow-up 114/106, i.e. 82%)	2 capsules of 10^{10} CFU on admission, and 1 capsule daily during hospitalisation	Placebo (oligosaccharides)	During hospital stay (3 days after discharge)	Rotavirus infections (diarrhoea defined as ≥3 loose stools at least 24 h after admission with Rotavirus antigen detected in stool sample)
Szajewska *et al.* (Poland)	Unclear (as reported in the paper); computer-generated numbers as clarified by the authors	Unclear	Yes (DB)	Yes	1 to 36 months with acute and/or chronic diseases (mean age: 11 months)	45/36 (100%)	6×10^9 CFU in 1 sachet twice daily	Placebo (maltodextrin)	During hospital stay (3 days after discharge)	Diarrhoea (≥3 loose or watery stools in a 24-h period). AAD was not excluded.

AAD, antibiotic-associated diarrhoea; CFU, colony forming units; DB, double-blinding (participants and investigators).

* In all cases, an answer of 'yes' indicates a low risk of bias, and an answer of 'no' indicates a high risk of bias.

Table 2 | Characteristics of excluded trials

Study (author)	Reason for exclusion
Penna *et al.*[20]	Different probiotic strain used as an intervention (*Lactobacillus delbrueckii* H2B20)
Honneycut *et al.*[21]	Different population (Intensive Care Unit patients)
Saavedra *et al.*[22]	Different probiotic strain used as an intervention (*Bifidobacterium bifidum* and *Streptococcus thermophilus*)
Pancheva *et al.*[23]	Different probiotic strain used as an intervention (combination of *Lactobacillus acidophilus, Lactobacillus delbrueckii* subsp., *bulgaricus* and *Bifidobacterium bifidum*)

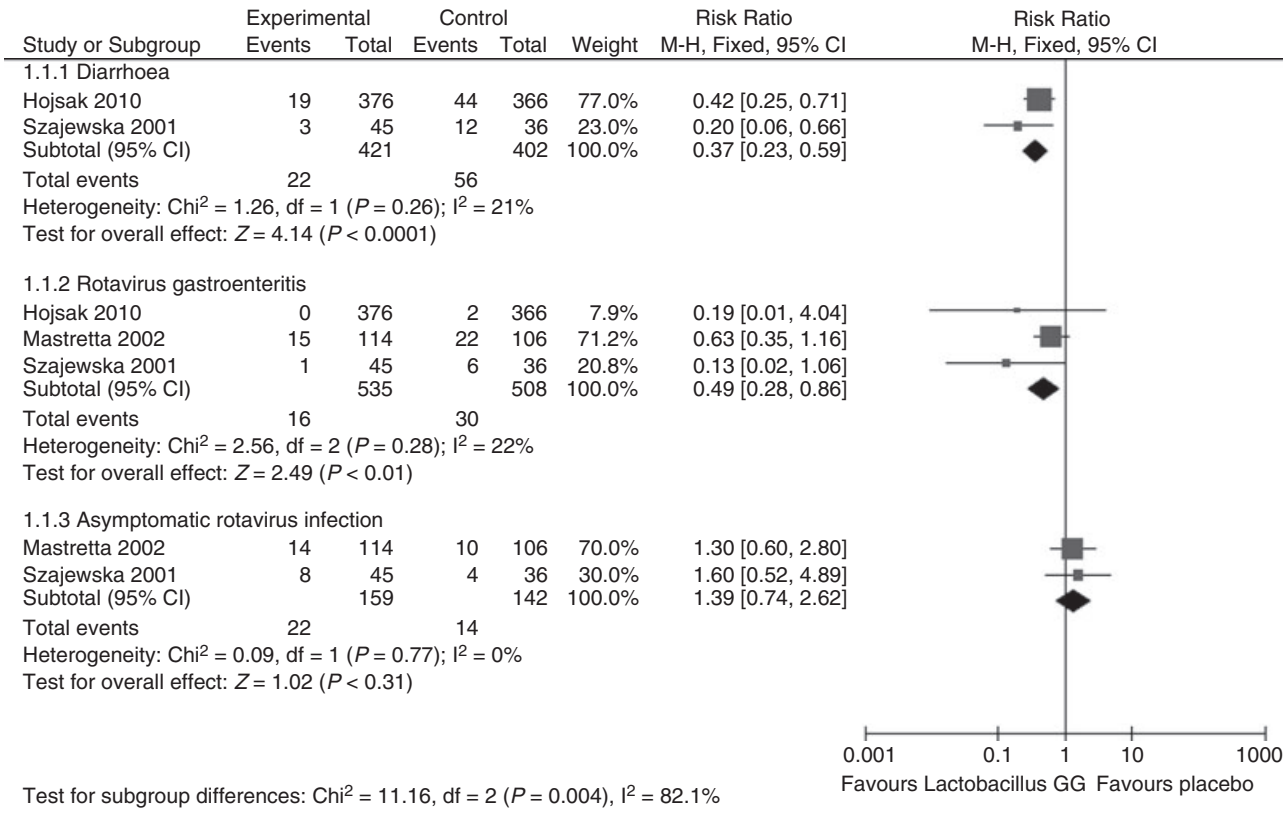

Figure 2 | Effect of *Lactobacillus* GG on healthcare-associated diarrhoea.

Effects of interventions

Diarrhoea. The pooled results showed a significant reduction in the risk of diarrhoea in the LGG group compared with the placebo group (two RCTs,[15,17] n = 823, RR 0.37, 95% CI 0.23–0.59, fixed effects model, NNT 12, 95% CI 8–21). No significant heterogeneity between the trials was detected (χ^2 = 1.26, P = 0.26, I^2 = 21%) (Figure 2).

Rotavirus gastroenteritis. The pooled results of three RCTs involving 1043 children revealed a significant reduction in the risk of symptomatic rotavirus gastroenteritis in the LGG group compared with the placebo group (RR 0.49, 95% CI 0.28–0.86, fixed effects model, NNT 35). No heterogeneity between the trials was found (χ^2 = 2.56, P = 0.28, I^2 = 22%) (Figure 2).

Asymptomatic rotavirus infection. The pooled results showed no significant difference between the LGG and the placebo groups in the incidence of asymptomatic rotavirus infection (two RCTs,[16,17] n = 301, RR 1.39, 95% CI 0.74–2.62, fixed effects model). No heterogeneity between the trials was found (χ^2 = 0.09, P = 0.77, I^2 = 0%) (Figure 2).

Other outcomes. All trials reported data about the duration of hospitalisation. We were not able to perform a meta-analysis regarding the effect of LGG on the

duration of hospitalisation, because of the different presentation of the results (mean with standard deviation,[17] mean with no standard deviation[16] or median[15]). None of these studies showed a significant difference between the LGG group and the placebo group in the duration of hospitalisation. One RCT[17] reported no difference in the duration of diarrhoea between the LGG group and the placebo group (6.3 ± 1.3 days vs. 6.5 ± 2.6 days). In the study by Hojsak *et al.*,[15] in the LGG group compared with the placebo group, there was a reduced risk of episodes of diarrhoea that lasted >2 days (RR 0.4, 95% CI 0.25–0.7).

Harms. *Lactobacillus rhamnosus* GG was well tolerated, and no harms associated with its administration were reported in any of the trials.

DISCUSSION

Summary of main results

In this systematic review and meta-analysis, we have demonstrated that the administration of LGG compared with placebo to hospitalised children reduced the overall incidence of HAD, including rotavirus gastroenteritis, although it did not have an effect on the asymptomatic rotavirus infection. To prevent one case of nosocomial diarrhoea in children, 12 children would need to be treated with LGG.

Overall completeness and applicability of evidence

Although only three RCTs met our inclusion criteria, they involved more than 1000 subjects, half of whom received LGG. With regard to the generalisability of our findings, our inclusion criteria allowed for a wide range of children to be included, including older children. The trial settings, typical children's hospitals, were consistent with those found in clinical practice. Important groups that were not represented in the study populations include immunocompromised, critically ill children, including preterm infants and those in intensive care units with indwelling devices who are at higher risk of developing healthcare-associated infections. Thus, our findings do not apply to patients who are particularly at risk of developing healthcare-associated infections.

With regard to the intervention, one feature of our review, which distinguishes it from other reviews, is that it focuses on only one probiotic microorganism, LGG. The findings do not apply to other probiotic microorganisms, as the beneficial effects of probiotics are considered to be strain specific.

According to the current definition, a healthcare-associated infection is an infection that occurs after more than 48 h of hospital treatment in a patient admitted for a problem, probably not related to the microbial pathogen. None of the included trials adopted this strict timing in defining nosocomial infections. Initial negative microbiological stool tests on the first day of hospitalisation would be desirable to define nosocomial acquisition. In practice, patients are not routinely screened; this does not reflect everyday practice, and such screening would incur additional costs. No such testing was used in any of the included trials. Given these considerations, data from the trials included in this review demonstrate that LGG has the potential to reduce the burden of both overall diarrhoea and rotavirus gastroenteritis, as defined by the investigators.

For diarrhoea, based on the definition used by the investigators, it was not always possible to distinguish between infectious vs. non-infectious causes of diarrhoea. For clinical practice, however, this is not important as, in principle, the management of diarrhoea is the same regardless of its aetiology and the focus is on rehydration. The low risk of rotavirus infection and the lack of an effect of LGG on rotavirus gastroenteritis in the study by Hojsak *et al.*[15] is not surprising, as the mean age of the participants was 10 ± 5 years; the peak incidence of rotavirus gastroenteritis occurs particularly in children between 6 and 24 months of age.[18]

Although no adverse effects of LGG supplementation were observed in any of the included trials, the administration of probiotics, including LGG, is not without risk. A recent systematic review[19] documented that some probiotic products, namely *Lactobacillus* GG and *S. boulardii*, have been shown to increase the risk of complications in specific patient groups. It needs to be emphasised that most complications have occurred in immunocompromised patients or in patients with other life-threatening illnesses managed in intensive care units.

Quality of the evidence

The methodological quality and the quality of reporting results were variable. Potential limitations include unclear allocation concealment, which increases the risk of selection bias, and a lack of sample size calculations in two trials.[16,17] While the lack of sample size calculations is an obvious limitation of any study, it is noteworthy that one of the reasons why a meta-analysis is performed within a systematic review is to increase power.

Potential biases in the review process

We followed the Cochrane Collaboration guidelines for conducting this systematic review and meta-analysis. Strengths of our review include the searching of several databases with no language restrictions. Study selection, assessment of risk of bias, and data extraction were performed by two reviewers, which reduced the risk of error and bias. Although efforts were made to collect relevant data, the possibility of missing data cannot be excluded. Publication bias remains a possible source of important bias.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews on this topic.

Implications for practice

The current data are promising. The use of LGG appears to be an effective strategy for preventing or reducing the risk of healthcare-associated diarrhoea, including that of rotavirus origin, in the paediatric setting.

Implications for research

Further studies are recommended to address the cost-effectiveness of using LGG for the prevention of HAD. While LGG was unable to reduce the duration of hospital stay, other possible positive outcomes deriving from this intervention are possible such as a reduction in costs related to medications or procedures or additional laboratory testing. Furthermore, research is needed to provide conclusive evidence of the preventive effects of LGG in a patient population that is highly susceptible to infection, such as critically ill children. Finally, it should be emphasised that with the introduction of rotavirus vaccination in many countries, the burden of nosocomial diarrhoea and responsible pathogens may change over time. Therefore, there will be a need to re-evaluate the incidence and aetiology of diarrhoea and the most effective preventive strategies.

ACKNOWLEDGEMENTS

Declaration of personal interests: HS served as a speaker for Dicopharm and Vitispharma, the manufacturer/distributor of *Lactobacillus* GG. Two remaining authors declare no conflict of interest. *Declaration of funding interests*: This study was funded in full by The Medical University of Warsaw.

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