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Systematic review with meta-analysis: *Lactobacillus reuteri* DSM 17938 for diarrhoeal diseases in children

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SUMMARY

Background
Not all probiotics are equal.

Aim
To investigate the efficacy of *Lactobacillus reuteri* DSM 17938 (*L. reuteri*) in the management of various types of diarrhoeal diseases in children.

Methods
Medline, Embase, the Cochrane Library, trial registries and reference lists of included studies were searched in January 2016, with no language restriction, for randomised controlled trials (RCTs).

Results
Eight RCTs (n = 1229) met the inclusion criteria. In treatment trials, *L. reuteri* administration reduced the duration of diarrhoea (three RCTs, n = 256, mean difference, MD −24.82 h, 95% CI −38.8 to −10.8) and increased the cure rate on day 1 and day 2. However, heterogeneity and wide confidence intervals call for caution in interpreting results. In preventive trials carried out in hospitalised children, based on the findings from two RCTs (n = 290), there was no significant reduction in the risk of nosocomial diarrhoea, rotavirus diarrhoea or diarrhoea of any origin with *L. reuteri* administration. Based on one RCT (n = 97), there was no effect of *L. reuteri* on the risk of antibiotic-associated diarrhoea. However, the evidence is limited because the overall frequency of diarrhoea was surprisingly low. In preventive studies carried out in apparently healthy children, *L. reuteri* reduced diarrhoeal outcomes in one RCT; the evidence from another trial was less convincing.

Conclusions
In therapeutic settings, *L. reuteri* administration reduces the duration of diarrhoea and increases the chance of cure. In preventive settings, *L. reuteri* has the potential to reduce the risk of community-acquired diarrhoea in otherwise healthy children.

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BACKGROUND

Description of the condition

Worldwide, each child younger than 5 years of age experiences on average three episodes of acute diarrhoea per year.[1] Treatment may be generally limited to fluid and electrolyte replacement.[1] Preventive strategies to reduce the risk of diarrheal diseases include exclusive breastfeeding, improved nutrition, personal hygiene, safe water supply, sanitation, personal hygiene, hand-washing, vaccinations (particularly, against rotavirus), and, in some areas, vitamin A and zinc supplementation.[2–4] However, the effectiveness of these strategies is either suboptimal, or, as in the case of vaccines, not always available or affordable, hence, there is interest in alternative interventions to reduce the burden of diarrheal diseases in children.

Description of the intervention

Probiotics are 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'.[5] A number of systematic reviews and meta-analyses have documented that probiotics have both therapeutic and preventive effects in patients with diarrhoeal diseases. However, considering that probiotics have strain-specific effects, focus needs to be on individual probiotic strains, not on probiotics in general. One of the widely available probiotics is *Lactobacillus reuteri* DSM 17938, a hetero-fermentative bacterium that resides in the gastrointestinal tract of humans and animals; this daughter strain of *L. reuteri* ATCC 55730 was obtained by removing resistance traits for tetracycline and lincomycin from the mother strain.[6, 7]

How the intervention might work

There are several mechanisms of action of *L. reuteri* DSM 17938 that influence the health of humans. *L. reuteri* is able to produce reuterin, which is a potent anti-pathogenic compound capable of inhibiting a wide spectrum of microorganisms including Gram-positive bacteria, Gram-negative bacteria, fungi and protozoa.[8] Aggregative and coaggregative abilities of *L. reuteri* help to colonise the gastrointestinal tract and remove pathogens from it.[7] One of the immunomodulatory properties of *L. reuteri* is biofilm production that stimulates tumour necrosis factor production by lipopolysaccharide (LPS)-activated monocytoid cells.[8] *In vitro* studies showed that *L. reuteri* influenced LPS-induced interleukin-8 production in cultured intestinal epithelial cell lines, and in rat intestines, reduced LPS-induced KC/GRO (interleukin-8) production, differentially affected Th1-type and Th2-type cytokines, and improved LPS-induced intestinal morphological damage.[9]

AIM

Previously, we reported that administration of *L. reuteri* DSM 17938 significantly reduced the duration of diarrhoea and increased the chance of cure on day 3 when compared to placebo or no treatment.[10] Since then, new evidence has emerged on the effectiveness of *L. reuteri* DSM 17938. The aim of the review was to update the data on the efficacy of *L. reuteri* DSM 17938 for the treatment and prevention of various types of diarrhoeal diseases in children.

METHODS

We conducted a systematic review following the guidelines developed by the Cochrane Collaboration[11] and the PRISMA statement for reporting[12]; however, the protocol for this review has not been registered.

Criteria for considering studies for this review

Types of studies. Only randomised controlled trials (RCTs) testing the effects of *L. reuteri* DSM 17938 for the treatment or prevention of diarrhoea were considered for inclusion.

Types of participants. Infants and children up to 18 years of age were eligible for inclusion. For therapeutic trials, children with diarrhoea, hospitalised or treated as out-patients, were included. For preventive studies focusing on nosocomial diarrhoea, children hospitalised for any reason other than diarrhoea were eligible for analysis. For studies related to antibiotic-associated diarrhoea, children who received antibiotics for any reason were considered for inclusion. For community-acquired diarrhoea, apparently healthy children before the intervention were of interest.

Types of interventions. We included trials that used *L. reuteri* DSM 17938, irrespective of formulation or dose. Participants in the control group received placebo or no additional intervention.

Types of outcomes. The outcomes for therapeutic studies were as follows: stool volume, duration of diarrhoea, cure on any given day and duration of hospitalisation. The outcomes for preventive studies depended on the type of diarrhoea considered. For prevention of nosocomial diarrhoea, these outcomes included nosocomial diarrhoea, diarrhoea of any origin and rotavirus

diarrhoea. Outcomes of interest for prevention of antibiotic-associated diarrhoea were diarrhoea/antibiotic-associated diarrhoea and *Clostridium difficile*-associated diarrhoea. For prevention of community-acquired diarrhoea, our interest was in outcomes related to the frequency of diarrhoea. For all outcomes, the definitions used by the investigators were accepted. Additionally, adverse events were analysed.

Search methods for identification of studies

Electronic searches. One reviewer (MU) explored Medline, EMBASE and the Cochrane Library databases in October 2015 and again in January 2016. As *L. reuteri* DSM 17938 was formally introduced in 2007, main focus was on publications published since that year.

Terms used as a search strategy were as follows: *lactobacillus* reuteri*, L. reuteri,* DSM 17938, *diarrhea*, diarrhoea*, nosocomial*, pediatric*, paediatric*, child*, infant*, toddler*, adolescent*, newborn**. These searches were combined using the AND Boolean operator. No language restriction was imposed.

Searching other resources. The ClinicalTrials.gov website (http://clinicaltrials.gov/) and EU Clinical Trials Register website (https://www.clinicaltrialsregister.eu) were investigated for trials that were not published. Also, reference lists of included studies were explored for relevant studies.

Data collection and analysis

Selection of studies. One reviewer (MU) carried out the databases search. The selected data were discussed in a face-to-face meeting of all reviewers.

Data extraction and management. One reviewer (MU) extracted the data from RCTs with the use of standard extraction tables for interventional studies. Details of the methods, settings, participants, interventions, outcomes, results and funding were obtained. The extracted data were again discussed in a face-to-face meeting of all reviewers until a consensus was reached. Data were crossed check by another reviewer independently.

Assessment of risk of bias in included studies. The Cochrane Collaboration's tool for assessing risk of bias was used to establish the risk of bias. Type of randomisation method (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias were considered.

Measures of treatment effect. The mean difference (MD) with 95% confidence interval (95% CI) was calculated for continuous outcomes, and relative risk (RR) with 95% CI, for dichotomous outcomes.

Assessment of heterogeneity. χ^2 and I^2 were determined to quantify heterogeneity. For χ^2, a $P < 0.10$ indicated statistical significance for heterogeneity. $I^2 = 0\%$ indicated no observed heterogeneity. $I^2 \geq 50\%$ indicated significant heterogeneity. All analyses were based on the random effects model.

Assessment of reporting biases. We planned to use a test for asymmetry of the funnel plot to assess reporting biases. However, the small number of included studies did not allow us to use this test.

Data synthesis. The data were analysed using the Review Manager (RevMan) [Computer program, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014].

Quality of evidence. The quality of evidence for outcomes reported in the included trials was assessed using the GRADE methodology and GRADEpro (Computer program located at www.gradepro.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).[13]

RESULTS

Results of the search

For a flow diagram documenting the identification process for eligible trials, see Figure S1.

Included studies

The characteristics of the eight included studies involving a total of 1229 participants are presented in Table S1. Moreover, two registered trials were identified. Among them, one RCT was completed but no publication was found (Clinical Trials .gov, NCT02025452, Canada); and one RCT is recruiting yet (ClinicalTrials.gov, NCT01886755, Greece).

All included trials were randomised and were either double-blind or single-blind studies. Three RCTs

(n = 256) reported data on the effect of *L. reuteri* DSM 17938 in the treatment of diarrhoea.[14–16] These studies included children aged 3–60 months who were hospitalised[14, 15] or treated as out-patients.[16] *L. reuteri* DSM 17938 was administered at a dose ranging from 1×10^8 colony-forming units (CFU) to 4×10^8 CFU daily for 5–7 days. One trial was placebo controlled. In the two remaining studies, there was no intervention in the control group. Studies were carried out in Italy (one RCT) and Turkey (two RCTs).

Of five included preventive trials, three RCTs assessed the effect of administration of *L. reuteri* DSM 17938 for preventing various types of diarrhoea in hospitalised children. Two RCTs (n = 290) assessed the effect of *L. reuteri* DSM 17938 for the prevention of nosocomial diarrhoea in children aged 1–48 months, hospitalised for reasons other than diarrhoea.[17, 18] Both studies were carried out in Europe (Poland). *L. reuteri* DSM 17938 at a dose of 1×10^8 to 1×10^9 CFU daily or an identically labelled placebo was administered for the duration of hospitalisation. One RCT, carried out in Bulgaria, evaluated the efficacy of *L. reuteri* DSM 17938 for the prevention of antibiotic-associated diarrhoea in hospitalised children.[19] The daily dose of *L. reuteri* DSM 17938 in this study was 1×10^8 CFU, which was given for the duration of antibiotic treatment and 7 days afterwards.

Another two preventive, double-blind, placebo-controlled RCTs reported on the effects of administration of *L. reuteri* DSM 17938 for the prevention of community-acquired diarrhoea in otherwise healthy children.[20, 21] The first trial was carried out in Indonesian children, including malnourished children, and compared, among other interventions, the consumption of regular calcium milk ($\sim$440 mg/day) with or without *L. reuteri* DSM 17938 (5×10^8 CFU/day) for 6 months. Other comparisons, such as with low-calcium milk or regular calcium milk plus *L. casei* CRL431, did not meet our inclusion criteria. The second trial, carried out in 336 otherwise healthy, Mexican children attending day care centres, reported on the consumption of *L. reuteri* DSM 17938 (1×10^8 CFU/day) for 3 months.

Excluded studies

The characteristics of the excluded studies are presented in Table S2.

Risk of bias in included studies

Figure S2 presents the assessment of methodological quality and potential risk of bias in the included RCTs. Only four of the eight included trials were considered as 'low risk of bias'. The major limitations were unclear allocation concealment (three RCTs), lack of blinding (two RCTs) and risk of bias due to incomplete outcome data (one RCT).

Quality of evidence

The GRADE assessment for outcomes related to *L. reuteri* DSM 17938 and diarrhoeal disease is presented in Table S3. Using the GRADE, the quality of evidence for studies assessing the effect of *L. reuteri* for the treatment of diarrhoea was very low, for prevention of nosocomial diarrhoea was high and for preventing antibiotic-associated diarrhoea in children was low.

Effects of interventions

Treatment of acute diarrhoea. *Stool volume.* No RCT evaluated the effects of *L. reuteri* DSM 17938 administration on stool volume.

Duration of diarrhoea (Figure 1). The pooled results from three therapeutic RCTs (N = 256)[14, 15, 16] showed that administration of *L. reuteri* DSM 17938 compared with placebo or no intervention shortened the duration of diarrhoea by 24.82 h (MD 24.82; 95% CI −38.83 to −10.81). Significant heterogeneity was found (χ^2 = 7.27, P = 0.03, I^2 = 73%).

Cure on any given day (Figure 2). Three RCTs (n = 256)[14–16] reported on cure on various days of the intervention. Compared with the placebo or no intervention group, in the *L. reuteri* DSM 17938 group, there was a significantly increased cure rate on day 1 (RR 11.26, 95% CI 2.15–58.84) and day 2 (RR 4.54, 95% CI 2.02–10.18); however, the CIs were very wide, and the results should be interpreted with caution. Additionally, significant heterogeneity was found, especially with regard to data on day 3 (I^2 = 97%). For day 3, no statistical significant difference was found between the *L. reuteri* DSM 17938 group and the placebo group (RR 2.25, 95% CI 0.45–11.23). Similarly, for other days, no significant difference between the groups was found.

Duration of hospitalisation. Two RCTs assessed this outcome.[14, 15] One RCT showed a reduction in the duration of hospitalisation for those treated with *L. reuteri* DSM 17938 compared with the control group (MD −1.15 days, 95% CI −1.7 to 0.6).[15] Another RCT reported no significant difference between groups in the duration of hospitalisation; however, data were not presented.[14]

Prevention of diarrhoea in hospitalised children. Various types of diarrhoea in hospitalised children were evaluated

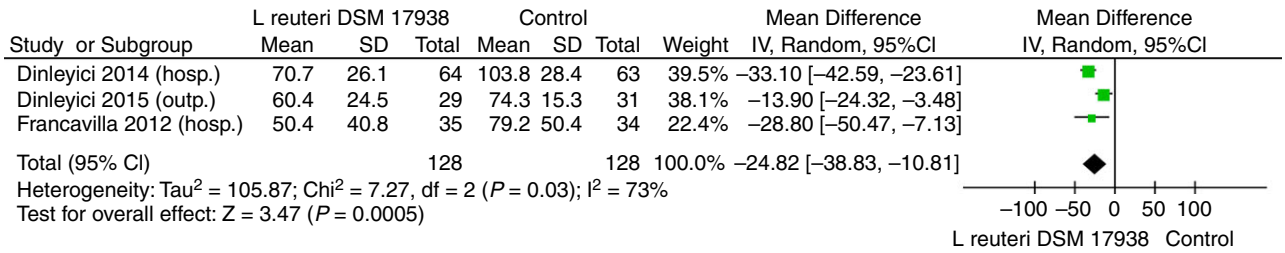

Figure 1 | Effect of *Lactobacillus reuteri* DSM 17938 on the duration of diarrhoea.

in children in the included trials (Figure 3). Compared with placebo, the administration of *L. reuteri* DSM 17938 had no effect on nosocomial diarrhoea (two RCTs,[17, 18] $n = 290$; RR 1.11; 95% CI 0.68–1.81), rotavirus diarrhoea (RR 1.14, 95% CI 0.52–2.52) and any origin diarrhoea (RR 1.22, 95% CI 0.78–1.9). For all outcomes, no significant heterogeneity was found ($I^2 = 0\%$). Based on the findings from one RCT ($n = 97$), there was no significant difference in the risk of antibiotic-associated diarrhoea between the group receiving *L. reuteri* DSM 17938 and the group treated with placebo (RR 0.98, 95% CI 0.06–15.22). However, the overall frequency of diarrhoea was surprisingly low (1 case in each study group).

Prevention of community-acquired diarrhoea. Two RCTs reported on the effects of administration of *L. reuteri* DSM 17938 for preventing community-acquired diarrhoea (Table 1).[20, 21] One RCT performed in 336 healthy Mexican children attending day care centres found that daily administration for 3 months of *L. reuteri* DSM 17938 compared with placebo significantly reduced the number of diarrheal episodes (42 vs. 69, $P = 0.03$), the number of episodes of diarrhoea per child (MD −0.2, 95% CI −0.22 to −0.18), the mean duration of diarrheal episodes ($P = 0.01$) and days with diarrhoea per child ($P = 0.03$).[21]

Another trial carried out in children from Indonesian low-socioeconomic communities found in the group receiving milk supplemented with *L. reuteri* DSM 17938 compared with unsupplemented milk, a significantly reduced incidence of all reported diarrhoea (adj. RR 0.68, 95% CI 0.46–0.99), but there was no significant difference in the incidence between groups when the WHO definition of diarrhoea was applied. Irrespective of the definition used, the administration of *L. reuteri* DSM 17938 reduced the risk of diarrhoea in children with lower nutritional status [defined as below-median weight-for-age *z* score (adj. RR 0.44, 95% CI 0.21–0.92), when the WHO definition of diarrhoea was applied and adj. RR 0.53, 95% CI 0.3–0.92 for all reported diarrhoea]. No significant difference between the groups was found in outcomes such as mean incidence/child/year, the number of episodes and the duration of episodes (no *P* values were given), regardless of the definition of diarrhoea used.[20]

Adverse events

Data regarding therapy-related adverse events were available from eight of the included trials. In these trials, *L. reuteri* DSM 17938 was well tolerated. Adverse event rates were similar in the experimental and control groups, except for in the study by Agustina *et al.*[20] Compared to regular milk, administration of *L. reuteri*-supplemented milk resulted in a change in bowel habits (2/126 vs. 9/124 children, respectively; RR 4.57, 95% CI 1.01–20.74). However, the very wide CI calls for caution when interpreting this finding.

DISCUSSION

Summary of evidence

This review aimed to investigate the potential benefits of *L. reuteri* DSM 17938 administration in the management of diarrheal diseases in children. In treatment trials, based on the finding from three RCTs, *L. reuteri* DSM 17938 reduced the duration of diarrhoea by approximately 1 day and increased the cure rate on day 1 and day 2. However, the findings are weakened by the heterogeneity and very wide confidence intervals around the estimates of the treatment effect. In preventive trials carried out in hospitalised children, based on the findings from two RCTs, there was no significant reduction in the risk of nosocomial diarrhoea, rotavirus diarrhoea or diarrhoea of any origin with administration of *L. reuteri* DSM 17938. Based on one RCT, there was no

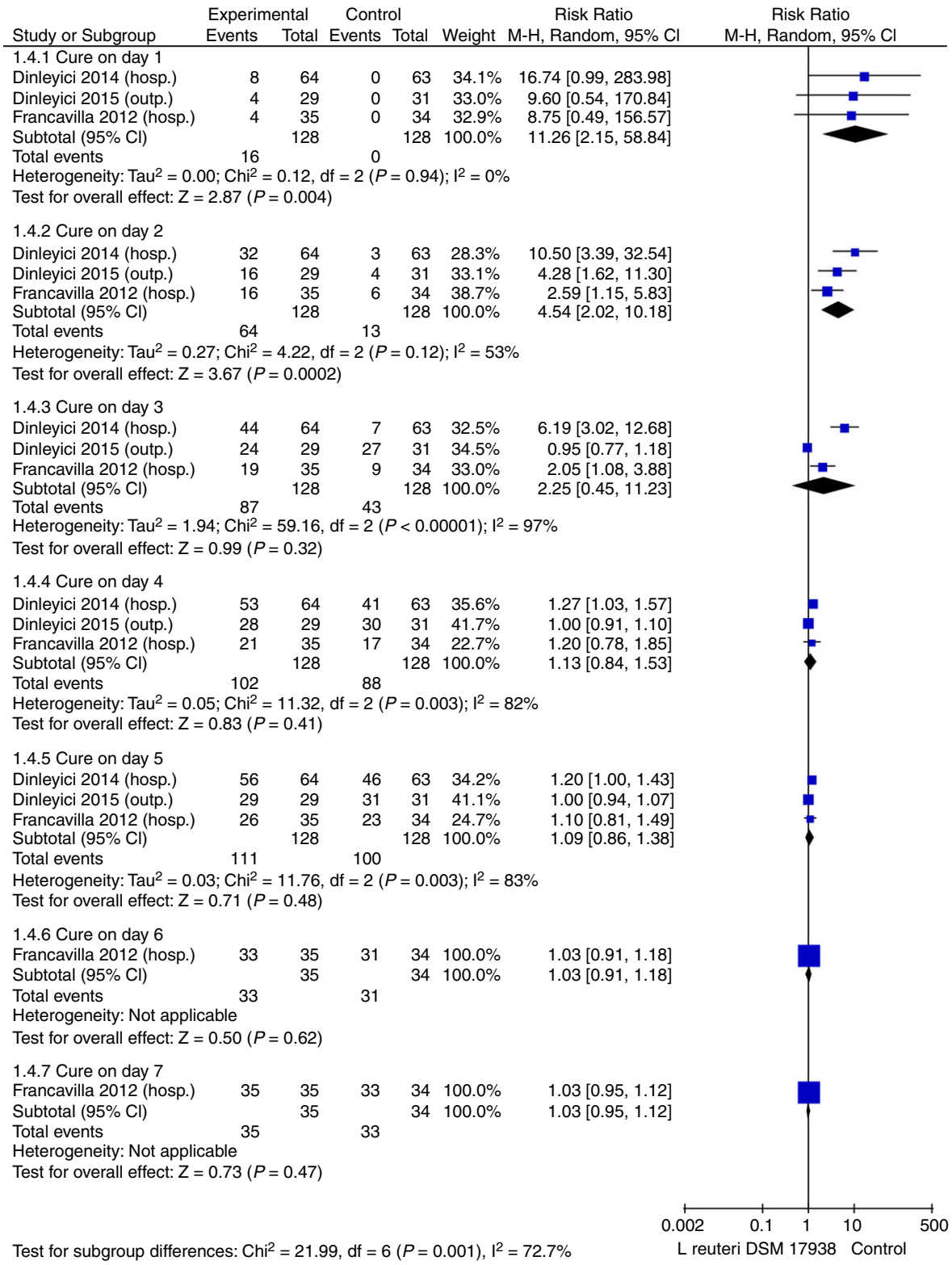

Figure 2 | Effect of *Lactobacillus reuteri* DSM 17938 on cure of acute diarrhoea on any given day of intervention.

effect of *L. reuteri* DSM 17938 administration on the risk of antibiotic-associated diarrhoea; however, the evidence is very limited because the overall frequency of diarrhoea in this trial was surprisingly low. In preventive studies carried out in apparently healthy children, *L. reuteri* DSM 17938 administration consistently reduced

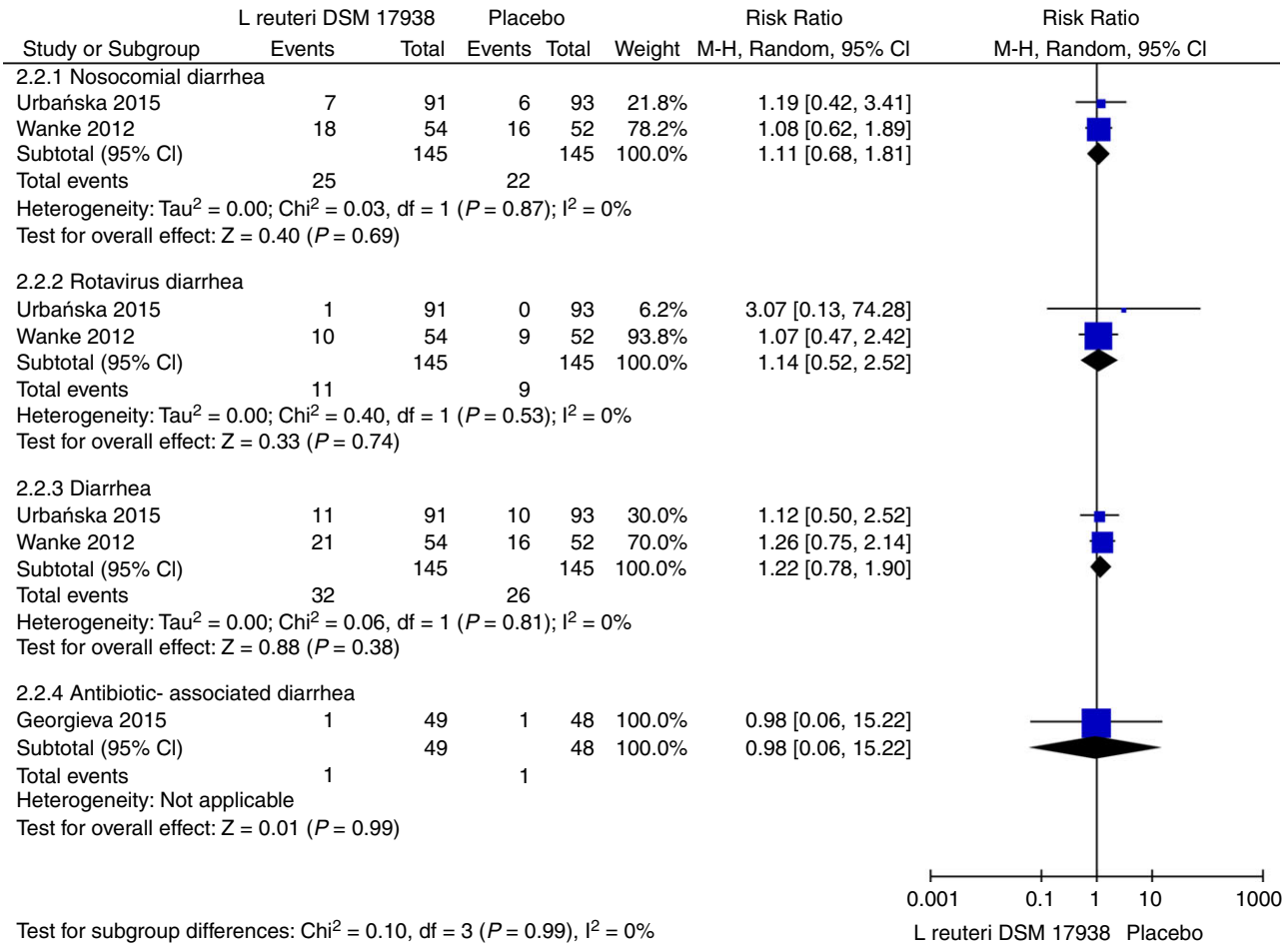

Figure 3 | Effect of *Lactobacillus reuteri* DSM 17938 for preventing various type of diarrhoea in hospitalised children.

Table 1 | Effect of *Lactobacillus reuteri* DSM 17938 for preventing community-acquired diarrhoea

Reference (country)	Outcome	Regular milk	Regular milk + *L. reuteri*	Comment
Agustina 2012; Indonesia[20]	Diarrhoea (WHO definition ≥3 loose/liquid stools/24 h)			
	Mean incidence/child/year	0.86	0.67	N.S.*
	No. of episodes	0.38 ± 0.78	0.30 ± 0.56	N.S.*
	Adjusted RR (95% CI)	1 (ref.)	0.76 (0.46–1.25)	N.S.*
	Duration of episodes (days)	2.94 ± 3.25	2.68 ± 3.05	N.S.*
	All diarrhoea (2 and ≥3 loose/liquid stools/24 h)			
	Mean incidence/child/year	1.86	1.28	N.S.*
	No. of episodes	0.77 ± 1.38	0.56 ± 0.77	N.S.*
	Adjusted RR (95% CI)	1 (ref.)	0.68 (0.46–0.99)	
	Duration of episodes (days)	2.03 ± 2.84	1.91 ± 2.52	N.S.*
		Placebo	*L. reuteri*	
Gutierrez-Castrellon 2014[21]; Mexico	No. of diarrheal episodes	69	42	$P = 0.03$
	Episodes of diarrhoea per child	0.4 ± 0.1	0.2 ± 0.1	$P = 0.02$
	Mean duration of diarrheal episodes	2.5 ± 0.9	1.4 ± 1.0	$P = 0.01$
	Days with diarrhoea per child	0.96 ± 0.2	0.32 ± 0.1	$P = 0.03$

* *P* value not reported.

diarrheal outcomes in one RCT; the evidence from another trial is less convincing.

Strengths and limitations

Our systematic review has a number of strengths. The review was based on the methodology developed by the Cochrane Collaboration and reported according to the PRISMA statement. Multiple efforts were made to decrease the risk of biases (e.g. no language or date restrictions imposed, searching for not yet published trials). The risk of bias in the included trials also was assessed. Finally, our review focused on a singe probiotic, which is available in many countries, thus, the findings are applicable to practice.

However, we are aware of some limitations. While the analyses were defined *a priori,* the protocol of the review has not been registered. The number of included trials related to any specific type of diarrhoea is limited. Moreover, particularly in the case of two therapeutic trials, there was a risk of performance and/or detection biases due to lack of blinding. In contrast to the therapeutic trials, evidence from the preventive trials focused on community-acquired diarrhoea may be rated as high quality, as none of the trials have major flaws. However, the strength of some conclusions, such as in case of the effect of *L. reuteri* DSM 17938 on antibiotic-associated diarrhoea, is limited by the small number of trials (only one RCT was available) and extremely small number of events (overall two cases) in this trial. Moreover, for some outcomes, the confidence interval of the summary estimate was very wide, resulting in uncertainty. Thus, while some findings appear promising, they must be interpreted with caution.

Agreement and disagreement with other studies or reviews

In addition to *L. reuteri* DSM 17938, two other well-studied probiotics are *Lactobacillus rhamnosus GG* (LGG) and *Saccharomyces boulardii (S. boulardii).* A recent meta-analysis of RCTs showed that administration of LGG, compared with placebo or no treatment, significantly reduced the duration of diarrhoea in children by approximately 1 day (11 RCTs; $n = 2444$; MD −1.05 days, 95% CI −1.7 to −0.4).[22] Similarly, compared with placebo, administration of *S. boulardii* reduced the duration of diarrhoea by 1 day (7 RCTs; $n = 944$; MD −1.08 day, 95% CI −1.64 to −0.53).[23] Thus, the effect of *L. reuteri* DSM 17938 for the management of acute diarrhoea is similar to the effect of LGG and *S. boulardii,* although evidence is more limited.

Current evidence does not allow one to reach a conclusion regarding the effect of administration of *L. reuteri* DSM 17938 for preventing antibiotic-associated diarrhoea in children. However, one small RCT ($n = 31$) conducted in adults showed that compared with placebo, the administration of *L. reuteri* ATCC 55730, the mother strain of *L. reuteri* DSM 17938, significantly reduced the risk of antibiotic-associated diarrhoea (50% vs. 7.7%, respectively, $P = 0.02$).[24] With regard to other probiotics, compared with placebo or no additional treatment, LGG administration significantly reduced the risk of antibiotic-associated diarrhoea in children treated with antibiotics (five RCTs, $n = 445$, RR 0.48, 95% CI 0.26–0.89).[25] Likewise, compared to placebo or no additional treatment, administration of *S. boulardii* reduced the risk of antibiotic-associated diarrhoea in children treated with antibiotics (six RCTs, $n = 1653$, RR 0.43, 95% CI 0.3–0.6).[26] In line with current guidelines, these two probiotics may be considered for preventing antibiotic-associated diarrhoea in children.[27]

A number of probiotics have been evaluated with regard to their efficacy for preventing nosocomial diarrhoea. A 2011 meta-analysis documented that, compared with placebo, administration of LGG reduced the risk of nosocomial diarrhoea (two RCTs, $n = 823$, RR 0.37, 95% CI 0.23–0.59) and symptomatic rotavirus gastroenteritis (three RCTs, $n = 1043$, RR 0.49, 95% CI 0.28–0.86).[28] Limited data showed that administration of *Bifidobacterium bifidum & Streptococcus thermophilus* compared with placebo reduced the risk of nosocomial diarrhoea (one RCT, $n = 55$, RR 0.22, 95% CI 0.05–0.96) and rotavirus gastroenteritis (one RCT, $n = 55$, RR 0.27, 95% CI 0.08–0.87).[29] In contrast, a recent, large ($n = 727$), double-blind, placebo-controlled RCT demonstrated that administration of *B. animalis* subsp. *lactis* BB-12 was not effective in preventing nosocomial infections (gastrointestinal and respiratory infections) occurring >48 h after admission in hospitalised children older than 1 year.[30] Taken together, these findings document that not all probiotics are equally effective for preventing nosocomial diarrhoea.

Our finding of a beneficial effect of *L. reuteri* DSM 17938 for preventing community-acquired diarrhoea is in line with earlier findings for *L. reuteri* ATCC 55738. One double-blind RCT ($n = 201$) showed a significant reduction in the number of days with diarrhoea in the *L. reuteri* ATCC 55738–supplemented formula group compared with the control formula group (0.15, 95% CI 0.12–0.18 vs. 0.59, 95% CI 0.34–0.84, respectively; $P < 0.001$), as well as a significant reduction in the

number of episodes of diarrhoea (0.02, 95% CI 0.01–0.05 vs. 0.31, 95% CI 0.22–0.4, respectively; $P < 0.001$).[31]

Our review found that *L. reuteri* DSM 17938 was generally well tolerated. In line with a recent review by Hempel *et al.*,[32] overall, probiotics are safe for use in otherwise healthy populations. However, rare adverse events do occur and are difficult to assess due to the lack of assessment and reporting of adverse events in many probiotic intervention studies. Caution should be exercised in using probiotics in specific patient groups in which risk factors for adverse events exist such as immunosuppression, prematurity, critical illness, central venous catheter placement or structural heart disease. Of note, the Food and Drug Administration applied to a number of probiotics, including *L. reuteri* DSM 17938, the Generally Recognized as Safe (GRAS) status.[33]

Conclusions and implications for practice

This review confirms the beneficial effect of *L. reuteri* DSM 17938 for the treatment of acute diarrhoea. In line with current European guidelines, the use of *L. reuteri* DSM 17938 may be considered in the management of acute diarrhoea, although the quality of evidence is low.[1] Regardless of the dose used, *L. reuteri* DSM 17938 is not effective for preventing nosocomial diarrhoea. Current limited evidence does not allow one to reach a conclusion on the effect of *L. reuteri* DSM 17938 for preventing antibiotic-associated diarrhoea. *L. reuteri* DSM 1738 is likely to reduce the risk of community-acquired diarrhoea, however, further research is needed.

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.

Table S1. Characteristics of the included studies.

Table S2. Characteristics of the excluded studies.

Table S3. GRADE evidence profile summarising the effect of *L. reuteri* DSM 17938 supplementation vs. placebo or no intervention in the treatment and prevention of diarrhoea in children.

AUTHORSHIP

Guarantor of the article: HS.

Author contributions: HS and MU initially conceptualised the study. MU contributed in data collection, analysis and interpretation as well as the drafting of the manuscript. DGB contributed to data analysis and preparation of the report. MU assumed the main responsibility for the writing of the first draft of the manuscript. All authors contributed to (and agreed upon) the final version.

All authors approved the final version of the manuscript.

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Declaration of funding interests: None.

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