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Probiotics in the Treatment and Prevention of Acute Infectious Diarrhea in Infants and Children: A Systematic Review of Published Randomized, Double-Blind, Placebo-Controlled Trials

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ABSTRACT

Background: This review was designed to assess the evidence from randomized controlled trials on effects of probiotics in the treatment and prevention of acute infectious diarrhea in infants and children.

Methods: A systematic review of published, randomized, double-blind, placebo-controlled trials on probiotics in the treatment or prevention of acute diarrhea defined as >3 loose or watery stools per 24 hours in infants and children.

Results: The use of probiotics as compared with placebo was associated with a significantly reduced risk of diarrhea lasting >3 days. The pooled estimate risk was 0.43 (95% CI, 0.34–0.53) with a fixed-effect model, and remained significant in a random-effect model (0.40; 95% CI, 0.28–0.57). Only *Lactobacillus* GG showed a consistent effect. Probiotics significantly reduced the duration of diarrhea when compared with placebo, particularly in rotaviral gastroenteritis—the pooled, weighted, mean difference (WMD) assuming the random-effect model was −20.1 hours (95% CI, −26.1 to −14.2) and −24.8 (95% CI, −31.8 to −17.9) respectively. A meta-analysis of the prevention studies was not feasible because of significant clinical and statistical heterogeneity.

Conclusions: There is evidence of a clinically significant benefit of probiotics in the treatment of acute infectious diarrhea in infants and children, particularly in rotaviral gastroenteritis. *Lactobacillus GG* showed the most consistent effect, although other probiotic strains may also be effective. Further research is needed. Clinical and statistical heterogeneity of the prophylactic interventions preclude drawing firm conclusions about the efficacy of probiotics in preventing acute gastroenteritis. ***JPGN 33:S17–S25, 2001.*** **Key Words:** Probiotics—Acute diarrhea—Gastroenteritis—Treatment—Prevention—Systematic review—Double-blind placebo-controlled studies—Children. © 2001 Lippincott Williams & Wilkins, Inc.

Probiotics are live microbial feeding supplements that beneficially affect the host animal by improving its microbial balance (1). They are commonly used in the treatment and prevention of acute diarrhea. The rationale for using probiotics in acute infectious diarrhea is based on the assumption that they act against intestinal pathogens. However, the mechanism by which probiotics work is unclear. The possible mechanisms include the synthesis of antimicrobial substances (2,3), competition for nutrients required for growth of pathogens (4), competitive inhibition of adhesion of pathogens (5–7), modification of toxins or toxin receptors (8,9), and stimulation of nonspecific and specific immune responses to pathogens (10,11). Recently, Mack et al. (12) showed that *Lactobacillus* species (particularly *L. rhamnosus* strain GG [LGG] and *L plantarum* strain 299v) inhibit, in a dose-dependent manner, binding of *E. coli* strains to intestine-derived epithelial cells grown in tissue culture by stimulation of synthesis and increased secretion of mucins. However, the clinical efficacy of probiotics in the treatment and prevention of acute infectious diarrhea has not been fully established. This review was, therefore, designed to assess and quantify the evidence from published, randomized, controlled trials on the effectiveness of probiotics in the treatment and prevention of acute infectious diarrhea in infants and children. To the best of our knowledge, no previously systematic review on this topic has been published.

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METHODS

Inclusion Criteria

The protocol of this study was prepared before searching for relevant trials. The criteria for considering original studies in-

TABLE 1. *Summary of randomized double-blind placebo-controlled treatment trials that met criteria for inclusion*

Trial	Location	Inclusion criteria	Exclusion criteria	Age range
1. Isolauri 1991 (14)	Finland	Acute diarrhea <7 d duration, >3 watery stools during the previous 24 h	No data	4–45
2. Kaila 1992 (10)	Finland	Acute diarrhea <7 d duration	No data	7–37
3. Guandalini 2000 (16)	Poland, Egypt, Croatia, Italy, Slovenia, Holland, Greece, Israel, UK, Portugal	>4 movements per day of liquid or semiliquid stools for 1–5 days	Previous use of probiotics; underlying chronic untreated small bowel disease, IBD, immunosuppressive condition	1–36
4. Shornikova 1997 (15)	Russia	Acute diarrhea <5 d duration, and 1 or more watery stools in previous 24 h	No data	1–36
5. Shornikova 1997 (17)	Finland	Acute diarrhea <7 d duration, and ≥1 watery stools during the preceding 24 h; history of ingesting bovine dairy products	Immunosuppressive therapy; suffering from immune deficiency; history of allergy to bovine milk; serious underlying disease; taken an investigational product during the preceding month	6–36
6. Shornikofa 1997 (18)	Finland	Acute diarrhea <7 d duration, >3 watery stools during the previous 24 h; orally rehydrated	No data	6–36
7. Cetina-Sauri 1994 (21)	France	Acute, non-bloody diarrhea	Concomitant illnesses; other medication; previous treatment with antimicrobial antidiarrheals or drugs influencing intestinal motility; severe electrolyte imbalance or dehydration	3–36
8. Boulloche 1994 (20)	France	Acute diarrhea with at least 5% weight loss	Treatment that could affect diarrhea	1–48
9. Simakahorn 2000 (19)	Thailand	Acute watery diarrhea <5 days and mild to moderate dehydration	Children with mucous bloody stools or major systemic diseases	3–24
10. Pearce 1974 (22)	Canada	Acute-onset diarrhea	Chronic underlying disease; treated with antibiotics	1–36

NA, not available; HRV, human rotavirus; ORS, oral rehydration solution.

cluded 1) reports on the use of probiotics in the treatment or prevention of acute diarrhea defined as >three loose or watery stools in 24 hours lasting not longer than 7 days; 2) randomized, double-blind, placebo-controlled trials; and 3) trials involving infants and children.

Exclusion Criteria

A priori this review was designed to exclude unpublished reports and those available only in an abstract form. In addition, this review excluded trials on prevention or treatment of antibiotic-associated diarrhea and those with pseudo-randomization or comparative studies with no placebo group. If studies had more than one arm, only the comparison of probiotics to placebo was included.

Outcome Measures

All patient outcomes were considered (duration of diarrhea, number of watery stools per day, risk of diarrhea lasting >7

Probiotic strain	Dose	Intervention	Outcomes	Etiology of diarrhea		
				HRV	Bacterial	Undetermined
Lactobacillus GG	$2 \times 10^{10-11}$	Twice daily 5 days Hospitalized patients only	ORS given; weight gain during rehydration; weight gain during realimentation; duration of diarrhea in hospital; hospital stay; watery diarrhea on day 1, 2, 3, 4,5	82%	0%	18%
Lactobacillus GG	10^{10-11}	Twice daily; 5 days Hospitalized patients only	Weight gain during hospitalization; diarrhea stools (% of patients) on day 1, 3; duration of diarrhea	100%	0%	0%
Lactobacillus GG	10^{10}	With ORS until diarrhea stopped 86% hospitalized patients; 14% outpatients	Duration of diarrhea; hospital stay (h); diarrhea >7 days (%)	35%	24%	40%
Lactobacillus GG	5×10^{9}	Twice daily; 5 days Hospitalized patients only	Duration of diarrhea; weight gain by discharge; hospital stay (d)	28%	21%	51%
Lactobacillus reuteri	10^{10-11}	Once daily; 5 days or for the duration of hospitalization, if shorter Hospitalized patients only	Duration of diarrhea in hospital; weight gain after rehydration (g); weight gain by discharge (g); frequency of watery stools and frequency of vomiting	75%	NA	NA
Lactobacillus reuteri	10^{10}	Once daily; max. 5 days Hospitalized patients only	Duration of diarrhea (d); weight gain after rehydration, by discharge; frequency of watery stools and frequency of vomiting episodes	100%	0%	0%
Saccharomyces boulardii	200 mg	Every 8 h	Diarrhea after 2 and 4 days (% of patients)	NA	NA	NA
Lactobacillus acidophilus LB	1 sachet	1 sachet three times daily in the first 24 hours, then 1 sachet twice daily Hospitalized patients only	Mean time since last abnormal bowel movement; mean interval without bowel movement; mean time to produce first normal bowel movement	NA	NA	NA
Lactobacillus acidophilus LB	10^{10}	5 doses Hospitalized patients only	Duration of diarrhea; diarrhea >96 h (%); diarrhea >96 h (%) not receiving antibiotics; diarrhea >24 h (%), watery stools in HRV+ patients (%)	48%	1.5%	50.5%
Str. thermophilus, L. acidophilus, L. bulgaricus	1 capsule = min. 10^{8}	<4 kg—3 capsules per day; 4–10 kg—6 capsules per day; >10 kg—8 capsules per day; until discharge Hospitalized patients only	Duration of diarrhea	NA	NA	NA

days, duration of hospitalization, weight gain; however, the primary outcome measure of interest in treatment trials was the effect of probiotics on the duration of diarrhea, and in prevention studies the primary outcome measure was the incidence rate of diarrhea.

Search Strategy and Study Selection

To identify original trials, a search was made in the MEDLINE database from 1966 until April 2001 and in the Cochrane Controlled Trials Register published in the Cochrane Library (issue 2, 2001; date of latest search, April 2001) for relevant articles using the following key words: probiotics, lactobacillus (LGG, *L. acidophilus, L. rhamnosus, L. plantarum), Bifidobacterium (B. bifidum, B. longum), Streptococcus (S. thermophilus),* enterococcus *(Enterococcus* SF68*), Saccharomyces boulardii AND* (random*, trial*, placebo*, controlled study, double-blind) *AND* (child* *OR* infan* *OR* adolescen* *OR* pediatr* *OR* paediatr*). A separate search also was made

TABLE 2. *Summary of randomized double-blind placebo-controlled prevention trials that met criteria for inclusion*

Trial	Location	Inclusion criteria	Exclusion criteria	Age range
Saavedra 1994 (23)	USA; long-term care facility	Children admitted to hospital	Breast feeding; history of allergy to cow's milk; receiving lactose-free, protein hydrolysate formula	5–24
Szajewska 2001 (25)	Poland; pediatric hospitals	Children admitted to hospital for reasons other than diarrhea	History of probiotics use within 7 d; acute gastroenteritis within 3 days; symptoms suggesting gastroenteritis; underlying intestinal disease; presence of visible blood in the stool; breast-feeding	1–36
Oberhelman 1999 (24)	Peru; peri-urban town	Children with age and with weight-for-age in the lower quartile for the community	Children with second- or third degree malnutrition	1–30

using names of individual authors known to be experts in this field. No limits were imposed as to the language or date of publication. Reference lists to identified review articles and original studies, textbook chapters on acute diarrhea and probiotics, as well as pharmaceutical industry files prepared by manufacturers of probiotics were also hand-searched. One reviewer, who excluded citations that were clearly irrelevant, screened the initial search results using abstracts, titles, and key words, identifying potentially relevant trial reports requiring a full-text review. Articles published in languages other than English were translated when necessary. Then two reviewers independently selected trials for inclusion using the previously defined criteria (see above). They were not blinded to authors, journals, results, or conclusions of individual studies. Agreement was measured using weighted kappa statistics, and any disagreement was resolved by discussion.

Methodologic Quality Assessment and Data Extraction

The methodological quality of each clinical trial was assessed independently by two reviewers using a five-point scale described by Jadad et al. (13) that evaluates the quality of randomization; the quality of blinding; and reasons for withdrawal/dropouts (0 = worst, 5 = best). The measure of agreement between reviewers was calculated using weighted kappa statistics and any disagreement was resolved by consensus.

A single investigator extracted data from eligible trials on a standardized form, which was then checked by a second investigator. No attempt was made to contact the authors of included trials. Of all various outcome measures chosen by the authors of the primary studies, we have used total duration of diarrhea and the presence of diarrhea on day 3 as the two most commonly reported endpoints. In the context of a benign illness, both are clinically relevant outcomes of immediate importance to physicians and parents. Reports on adverse effects of probiotics were also extracted from original studies.

Statistical Methods

The data were analyzed using StatsDirect software (version 1.9.2, I.E. Buchan). The binary outcome measure (presence of diarrhea on day 3) of individual studies and pooled statistics are reported as risk ratio (RR) between the experimental (treated with probiotics) and placebo groups with 95% confidence intervals (95% CI). The continuous outcome (total duration of diarrhea in hours) is presented as weighted mean difference (WMD) between the treatment and placebo groups with 95% CI. The weights given to each study are based on the inverse of the variance. Heterogeneity among pooled estimates was tested with Q test (chi-square statistics) using an alpha of 0.10. Sensitivity and subgroup analyses were performed to identify sources of heterogeneity, if present. Both fixed- and random-effect models are reported throughout for confirmation of pooled results. A priori subgroup analysis was planned based on two factors that could potentially influence the magnitude of treatment response: 1) type of probiotic; 2) etiology of diarrhea (viral vs. bacterial). The number needed to treat was calculated, when appropriate, as the inverse of pooled risk difference and 95% CI.

To allow a rough comparison of the efficacy of probiotics in the prevention studies, data derived from published articles were expressed as patient-month (number of patients × time of observation) and incidence rate of diarrhea (diarrheal cases per patient-month) in the experimental and placebo groups (outcome measures). Then the incidence rate ratio (IRR) was calculated using the following formula: IRR = incidence rate of diarrhea in the experimental (treated) group ÷ incidence rate of diarrhea in the placebo group.

RESULTS

Study Inclusion and Characteristics

A total of 13 papers met the inclusion criteria and qualified for analysis (10,14–25). Details of 10 treatment trials are summarized in Table 1 and 3 prevention trials are characterized in Table 2. All treatment studies involved hospitalized patients, except one (16) that also included a minor group of outpatients, and most were conducted in developed countries. The probiotic strains studied were LGG, *L. reuteri*, *L. acidophilus* LB, *Saccharomyces boulardii, Streptococcus thermophilus lactis, L. acidophilus,* and *L. bulgaricus.* The participants' ages ranged from 1 to 48 months (Table 1).

TABLE 2. *Continued.*

Probiotic strain	Dose	Intervention	Outcomes	Type of diarrhea
Bifidobacterium bifidum, Str. thermophilus	BB 1.9×10^9 ST 0.14×10^8/g of formula	For the duration of hospital stay with formula	Episodes of disease; duration of episode; no of stools per episode; stool weight (g); rotavirus shedding: prevalence, shedding during diarrhea	Nosocomial
Lactobacillus GG	6×10^9	Twice daily; for the duration of hospital stay	Incidence of diarrhea; age of children with diarrhea; onset time of diarrhea after admission; duration of diarrhea; no of watery stools per 24 h in children with diarrhea	Nosocomial
Lactobacillus GG	3.7×10^{10}	Once daily; 6 days a week; for 15 months	Episodes of diarrhea; duration of episodes	Community acquired

The prevention studies evaluated either LGG, or a combined preparation of *Streptococcus thermophilus* and *Bifidobacterium bifidum.* Two were carried out in hospitals in developed countries, and one was a community-based trial in a developing country and included undernourished children (Table 2).

Ten trials were excluded (11,26–34) for the following reasons: lack of blinding (26), comparative study without placebo group (11,28–30,33), incomplete follow-up (31,32), incomplete data reporting (31), or two different simultaneous interventions in experimental and control subjects (34).

Quality Assessment

The kappa score for agreement between reviewers for selection was 0.72 (good agreement). The overall kappa score for agreement between reviewers for trial quality was 0.78 (good agreement). Disagreement was predominantly caused by slight differences in interpretation. Consensus was reached in all cases. The quality score ranged from 3 to 5 (median, 4) points out of 5 possible.

Effect of Probiotics on the Risk of Diarrhea Lasting >3 Days

Eight trials involving 731 children reported data on the presence of diarrhea lasting >3 days. There was no evidence of statistical heterogeneity ($P = 0.12$) across those studies. The use of probiotics as compared with placebo was associated with a significantly reduced risk of diarrhea lasting >3 days. The pooled estimate RR was 0.43 (95% CI, 0.34–0.53; $P < 0.0001$) with the fixed-effect model, and remained significant in the random-effect model (RR, 0.40; 95% CI, 0.28–0.57; $P < 0.0001$). The results of subgroup analysis for individual probiotic strains as well as pooled estimate are presented in Figure 1. Only LGG showed a consistent effect on the reduction in risk of diarrhea lasting >3 days in fixed and random effects models. It was calculated, assuming the more conservative random effect model, that 4 (95% CI, 3–9) patients need to be treated with LGG to avoid one case of diarrhea lasting >3 days. Based on the results of the only study included, number needed to treat for *Saccharomyces boulardii* was 2 (95% CI, 2–3). A similar subgroup analysis based on etiology of diarrhea was not feasible because of the lack of relevant data that could be extracted from the included original studies.

Effect of Probiotics on Duration of Diarrhea

The duration of diarrhea was analyzed in 8 trials involving 773 children (405 in experimental and 368 in control groups). Probiotics significantly reduced the duration of diarrhea compared with placebo—the pooled WMD assuming the random-effect model was −18.2 hours (95% CI, −26.9 to −9.5; $P < 0.0001$). However, significant statistical heterogeneity was detected across the included studies ($P = 0.015$). A subgroup analysis based on the type of probiotic strain and sensitivity analysis revealed the phenomenon to be that reported in Pearce J. et al. (22), i.e., no significant effect of a preparation containing unspecific strains of *Streptococcus thermophilus*, *L. acidophilus,* and *L. bulgaricus* (WMD, 14.4 hours; 95% CI, −6.6–35.4). The exclusion of this trial resulted in a homogenous group of 7 studies involving 679 children ($P = 0.3$). Individual and pooled results of this subgroup analysis for three different probiotic strains are presented in Figure 2.

An attempt was made to extract data on the effect of probiotics on the duration of diarrhea of viral and bacterial etiology from original studies, although only Guandalini et al. (16) reported relevant results. Thus we combined the results of four studies involving predominantly young children with confirmed rotaviral gastroenteritis—Isolauri et al. (14), 82% human rotavirus (HRV), no cases of invasive enteric infections; Kaila M. et al. (10),

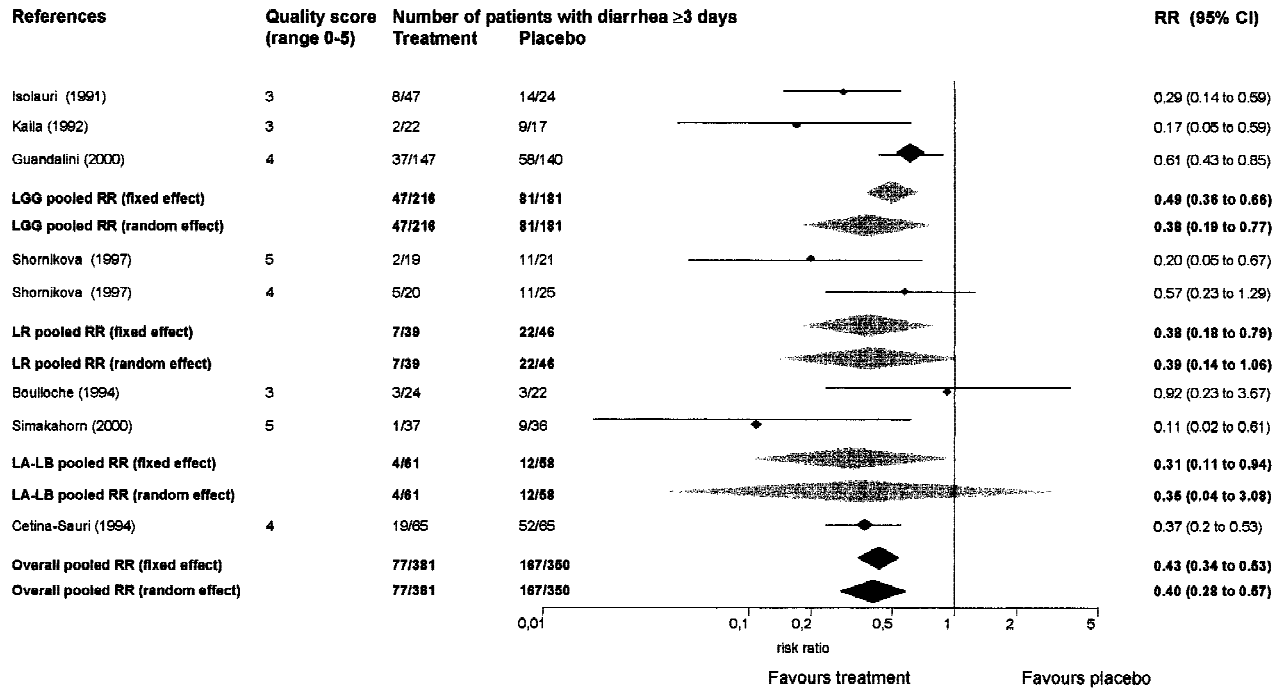

FIG. 1. Efficacy of probiotics in the treatment of acute diarrhea measured as reduction in risk of diarrhea lasting 3 days or more. RR, relative risk; CI, confidence interval; LGG, *Lactobacillus* GG; LA-LB, *Lactobillus acidophilus* LB.

100% HRV; Shornikova et al. (17), 75% HRV, no cases of invasive enteric infections; Shornikova et al. (17), 100% HRV—and a subset of children with rotavirus infection extracted from the study by Guandalini et al. (16). This procedure resulted in a group of 297 children (165 in experimental and 132 in control groups) with no evidence of statistical heterogeneity ($P = 0.82$). In these patients probiotics (LGG, *L. reuteri*) significantly re-

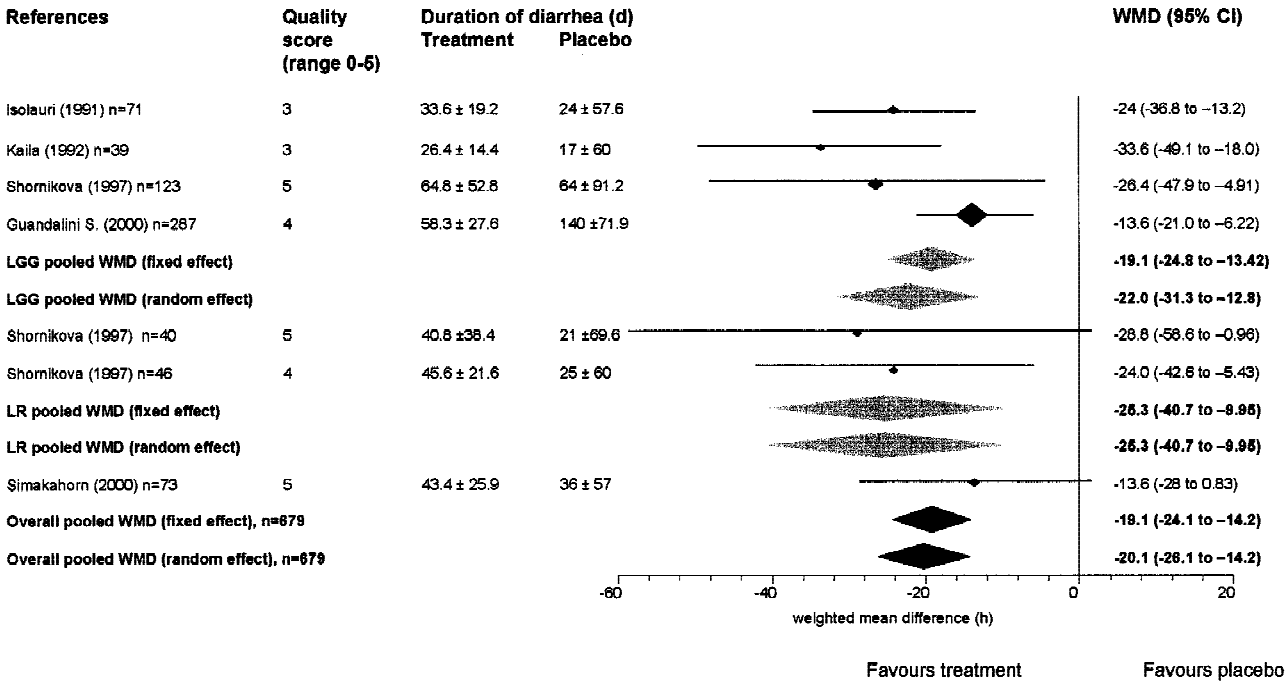

FIG. 2. Weighted mean differences (WMD; in hours) in the duration of diarrhea between treatment with probiotics and placebo. CI, confidence interval; LGG, *Lactobacillus* GG; LR, *Lactobacillus reuteri.*

duced the duration of diarrhea as compared with placebo (WMD, −24.8 hours; 95% CI, −31.8 to −17.9; $P < 0001$; Fig. 3), whereas such effect was absent in a subset of 53 children with invasive enteric infections reported by Guandalini et al. (16) (WMD, 1.3 hours; 95% CI, −15.3 to 17.9).

Effects of Probiotics on Diarrhea Prevention

Three prevention trials involving 340 children were available for the analysis. The prevention trials differed considerably in their subject selection, setting (hospital vs. field trial) and type of diarrhea (nosocomial vs. community), type and duration of intervention, exposures to HRV, as well as in reported outcome measures. Because of significant clinical and statistical heterogeneity, the reviewers decided that a metaanalysis of the prevention studies was not feasible. Only one study (25) showed that the use of probiotics (LGG) significantly reduced the incidence of diarrhea in the study population (Table 3). Both significant clinical and statistical heterogeneity ($P = 0.007$) of studies included in this systematic review precludes drawing firm conclusions about the efficacy of probiotics in prevention of acute diarrhea in children.

Side Effects of Probiotics

No adverse reactions were reported.

DISCUSSION

Evidence suggested a modest but clinically significant benefit of probiotics in the *treatment* of acute gastroenteritis in infants and children, particularly of LGG, which showed a consistent effect in reducing the duration of diarrhea. Other probiotic strains may also be effective, but further research is needed. Clinical and statistical heterogeneity of the prophylactic interventions precludes the drawing of firm conclusions about the efficacy of probiotics in *prevention* of acute infectious gastroenteritis. No obvious adverse effects of probiotics were observed.

The predefined inclusion criteria confined this systematic review only to controlled, published trials. This review evaluated trials in infants and children only. It does not provide any evidence for or against the use of probiotics in adults. Although in children, rotavirus is the single most common cause of acute gastroenteritis, especially in developed countries where most of the included studies were performed, the etiology of diarrhea in adults differs, which may influence the efficacy of probiotics.

Limitations of the Study

Searching exclusively the Medline database for relevant articles (and not other medical databases), as well as evaluating published trials only, is the limitation of the

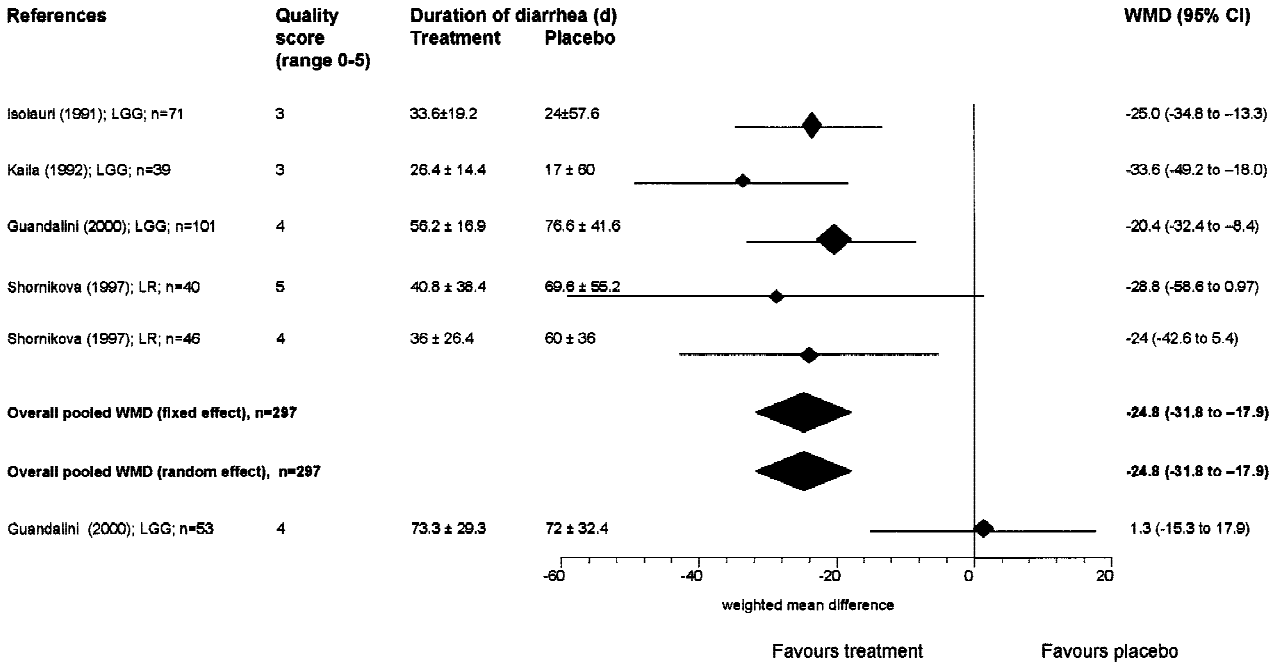

FIG. 3. Weighted mean differences (WMD; in hours) in the duration of rotaviral gastroenteritis between treatment with probiotics and placebo. For comparison, the effect of *Lactobacillus* GG (LGG) in invasive bacterial diarrhea is shown at the bottom of the forest plot. CI, confidence interval; LR, *Lactobacillus reuteri.*

TABLE 3. *Efficacy of probiotics in the prevention of acute gastroenteritis*

	Probiotic group		Placebo group		
Reference	Cases (n)	Patient-month	Cases (n)	Patient-month	IRR (95% CI)
Saavedra 1994	2	76.5	8	71.8	0.23 (0.02–1.18)
Szajewska 2001	3	14.25	12	9.96	0.17 (0.03–0.65)
Oberhelman 1999	490	1085.9	464	992.3	0.97 (0.85–1.1)

Data expressed as patient-month (number of patients × time of observation) and incidence rate of diarrhea (diarrheal cases per patient-month) in the probiotic treated and placebo groups. IRR (incidence rate ratio) = incidence rate of diarrhea in the treated with probiotics group/incidence rate of diarrhea in the placebo group.

present study. However, we believe that the risk of not properly selecting published trials is low. It has been suggested that exploration of databases other than Medline and "grey literature" (e.g. theses, internal reports, non–peer reviewed journals, etc.) may be of greater relative importance when trials outside the medical mainstream, such as physiotherapy or alternative medicine, are looked at (35,36). Publication bias is another potent threat to the validity of systematic reviews.

The primary outcome measure analyzed in this systematic review was the duration of diarrhea, which is not optimal for making conclusions on the efficacy of probiotics (or any other drug) in acute diarrhea. As with the World Health Organization recommendations (37), the main criterion should be effect on stool output. However, none of the studies that met the inclusion criteria evaluated stool output. Consequently, until further studies are available that address this outcome measure, no firm conclusion can be drawn on the effect of probiotics on stool output in acute diarrhea.

Sources of Heterogeneity

Significant statistical heterogeneity was detected across studies evaluating the effect of probiotics on the duration of diarrhea. The incompatibility of the results reported in the Pearce et al. (22) trial may be explained by properties of the probiotic strains used. Moreover, the dosage of probiotics used in this study was 100 times smaller than the dosage in the other included studies. This incompatibility also could be because of the time of reintroduction of oral feeds (late feeding in the study of Pearce et al. vs. early feeding in all other studies).

The investigation of possible sources of heterogeneity of the prevention studies revealed considerable clinical and methodological heterogeneity. The trials differed considerably in their subject selection (undernourished vs. chronically hospitalized children vs. children hospitalized for acute diseases); inclusion of breast-fed infants; and type of diarrhea (nosocomial vs. community acquired). There were also differences in the duration of the interventions as well as in reported outcome measures. It seems likely that these substantial clinical and methodological differences have lead to the heterogeneity in the observed results.

Future Research

Systematic review of published, randomized, controlled trials showed that only a limited number of trials were available for analysis. Further research is required. Future trials should evaluate carefully selected, precisely defined probiotic strains. A standardized scientific methodology should be implemented (randomized, double-blind, placebo-controlled trials). The incorporation of a standard set of outcome measures, including stool output, may greatly contribute to defining the overall role of probiotics, as well as of individual probiotic strains, in the treatment and prevention of acute gastroenteritis.

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