Diarrhea in Preschool Children and *Lactobacillus reuteri*: A Randomized Controlled Trial

**abstract**

**OBJECTIVES:** To evaluate whether daily administration of *Lactobacillus reuteri* DSM 17938 reduces the frequency and duration of diarrheal episodes and other health outcomes in day school children in Mexico.

**METHODS:** Healthy children (born at term, aged 6–36 months) attending day care centers were enrolled in this randomized, double-blind, placebo-controlled trial. They received *L reuteri* DSM 17938 (dose 10^8 colony-forming unit; n = 168) or identical placebo (n = 168) by mouth, daily for 3 months, after which they were followed-up after a further 3 months without supplementation.

**RESULTS:** Data from all children were included in the final analysis. *L reuteri* DSM 17938 significantly reduced the frequency and duration of episodes of diarrhea and respiratory tract infection at both 3 and 6 months (P < .05). Additionally, the number of doctor visits, antibiotic use, absenteeism from day school and parental absenteeism from work were significantly reduced in the *L reuteri* group (P < .05). A cost-benefit analysis revealed significant reductions in costs in the *L reuteri*-treated children. No adverse events related to the study product were reported.

**CONCLUSIONS:** In healthy children attending day care centers, daily administration of *L reuteri* DSM 17938 had a significant effect in reducing episodes and duration of diarrhea and respiratory tract infection, with consequent cost savings for the community. *Pediatrics* 2014;133:e904–e909

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**KEY WORDS**

*Lactobacillus reuteri* DSM 17938, diarrhea, children

**ABBREVIATIONS**

CFU—colony-forming unit
ICER—incremental cost-effectiveness ratio
RCT—randomized controlled trial
RTI—respiratory tract infection
USD—US dollars

Dr Gutierrez-Castrellon prepared the protocol, submitted it to the ethical research committee, interviewed parents/legal guardians, participated in the follow-up of patients, analyzed outcome data (biostatistical analysis), and drafted the final manuscript for submission; Drs Estevez Jimenez, Parra, and Mancilla-Ramirez interviewed parents/legal guardians, requested written consent, participated in baseline evaluation and follow-up of patients, assessed children with diarrhea, respiratory, or other acute events, and reviewed and revised the manuscript; Mr Jimenez Gutierrez evaluated evidence in the preparation of the protocol, designed the database, participated in the statistical analysis, and reviewed and revised the manuscript; Ms Diaz Garcia evaluated evidence in the preparation of the protocol, participated in the nutrition assessment of children during baseline and follow-up evaluation, and reviewed and revised the manuscript; Mr Lopez-Velazquez requested written consent, participated in follow-up assessments, and reviewed and revised the manuscript; and all authors approved the final manuscript for submission.

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(Continued on last page)
Diarrhea remains an important cause of morbidity and mortality in children around the world, with children in day care centers representing a population with a higher risk of gastrointestinal and respiratory infection. Live bacterial supplementation is emerging as a potentially effective prophylactic intervention in this population to reduce gastrointestinal and other infectious diseases that impact children’s health. In a randomized controlled trial (RCT) in healthy Finnish day care children (1–6 years old), daily supplementation with L rhamnosus ATCC 53013 for 7 months led to fewer days of absence due to illness (4.9 days versus 5.8 days on placebo, \(P = .03\)), and lower incidence of respiratory infection (8.6% absolute reduction versus placebo, \(P = .05\)). A large RCT on Indian children (1–5 years old) who received Lactobacillus casei Shirota daily for 12 weeks demonstrated a 14% absolute reduction in the frequency of acute diarrhea during the 24 week observation period compared with placebo. In Taiwanese preschool children (<5 years of age), Lin et al compared the L casei rhamnosus “Antibiophilus,” L rhamnosus T cell-1, a combination of 12 bacterial strains, and placebo and reported a significant absolute reduction (>40%) in gastrointestinal infections with the multiple strain product and 17% reduction of respiratory infections in children who received L casei rhamnosus. Rautava et al conducted a similar RCT in Finnish children who received either a mixture of Lactobacillus rhamnosus GG and Bifidobacterium lactis BB-12 or placebo up to the age of 12 months. They observed a significant absolute reduction (28%, \(P = .01\)) for acute otitis media and recurrent respiratory infections (27%, \(P = .022\)) in the children who received the bacterial supplement, whereas the incidence of gastrointestinal infections only tended to reduction (absolute reduction of 12%, \(P = .09\)). Further, healthy Israeli children (4–10 months old) supplemented daily with Bifidobacterium lactis BB-12 or Lactobacillus reuteri ATCC 55730 for 12 weeks in an RCT study in the day care setting had less frequent episodes of diarrhea (absolute reduction of 18% and 29%, respectively compared with placebo) and duration (absolute reduction of 22% and 44%, respectively compared with placebo). The incidence and duration of respiratory infections were unaltered by the intervention. More recently, an RCT by Agustina et al in Indonesian children (1–6 years old) reported that a 6-month supplementation with L reuteri DSM 17938 gave a significant absolute reduction (26%) of all reported diarrhea compared with placebo, with a stronger effect seen in malnourished children.

This evidence is encouraging, but was obtained with different live bacterial preparations. Two of the studies reveal similar outcome on diarrhea with L reuteri ATCC 55730 and L reuteri DSM 17938 strains, which are closely related, but to establish evidence-based recommendations for the use of L reuteri DSM 17938 for the prevention of infectious disease in day care centers, similar and independent trials with this strain are needed to support a systematic review of outcomes with the same intervention. The current study was designed therefore to evaluate the efficacy of prophylactic use of L reuteri DSM 17938 in reducing the frequency and duration of diarrheal episodes and other health outcomes in Mexican children in the day care setting and further, to assess cost-effectiveness of the intervention.

**METHODS**

This was a prospective, randomized, double-blind, placebo-controlled trial, carried out between April 2011 and June 2012 in 4 different day care centers in southeast Mexico City, close to the National Pediatric Institute of the Ministry of Health. The trial was approved by the Research & Ethics Committee of the National Pediatric Institute at the Ministry of Health. Healthy children of both genders, aged 6 to 36 months, who were born at term (≥36 weeks’ gestation), who belonged to families with similar socioeconomic status, and who were attending the day care centers were eligible for the study. Children were excluded if they had a birth weight <2500 g, chronic disease, failure to thrive, allergy or atopic disease, recent (previous 4 weeks) exposure to probiotics, prebiotics, or antibiotics, or were participating in other clinical trials. At baseline, overcrowding was defined as more than 3 persons living and sleeping in the same bedroom. Initially, parents or legal guardians of potentially eligible children were invited to attend a meeting where the aims and procedures of the study were presented. Informed consent was explained to those who accepted participation of their child, after which written consent was obtained before inclusion of the subject.

The primary outcome was the number of days with diarrhea per child, which was defined as days when 3 or more loose or watery stools were passed within a 24-hour period with or without vomiting. Secondary outcomes were (1) days with a respiratory tract infection (RTI), defined by using international published definitions, (2) days of absence from day care caused by an episode of diarrhea or RTI, (3) days of antibiotic use caused by an episode of diarrhea or RTI, (4) days of medical office or emergency visits caused by an episode of diarrhea or RTI, and (5) total direct and indirect costs to the hospital and to parents/guardians during the study caused by diarrhea and/or RTI. The primary and secondary outcomes were reported for the intervention...
period (0–12 weeks) and for the follow-up period after intervention had stopped (12–24 weeks). Using the outcome data reported by Weizman et al,8 (days with diarrhea: probiotic versus placebo: 0.15 ± 0.03 and 0.59 ± 0.25, respectively, and episodes of diarrhea; 0.02 ± 0.02 and 0.31 ± 0.1, respectively), an α and β error of 0.05 and 0.2, respectively, and an attrition rate of 20%, a minimum sample size of 165 children per arm was calculated by using Stata software version 11.0 for Mac (StataCorp, College Station, TX).

A computer generated allocation sequence and a centralized randomization list (StatsDirect Ltd, StatsDirect statistical software, http://www.statsdirect.com) was made by one of the investigators (Dr Jimenez). To avoid disproportionate numbers of patients in each arm, randomization was performed in balanced blocks of 6 subjects per block (3 receiving active product and 3 receiving placebo) to ensure that each center randomly assigned 50% of children to each treatment. To ensure allocation concealment, a person independent from the study prepared the randomization schedule and oversaw the packaging and labeling of the study products. All study personnel and parents/guardians were unaware of the group assignments, and randomization codes were secured and blinded until all data were analyzed. A master allocation list was held by one of the investigators (Mr Lopez-Velazquez) who was contacted by telephone for the allocation of each patient. Parents were instructed by one of the investigators (Mr Gutierrez-Castrellon, Jimenez, Parra, and Ms Garcia) enrolled patients at the study centers.

Eligible children were randomly assigned to receive either L reuteri DSM 17938 at a dose of 1 × 10^7 colony-forming unit (CFU) or placebo once per day for 12 weeks. Each day, the study product (5 drops [~0.2 mL] of an oil formulation from a dropper bottle) was given to the child directly in the mouth, during the first feed of the day in the home. Each parent was carefully instructed to ensure that the child ingested the drops.

Compliance was assessed by return of the empty bottles to the investigators and by parental reporting of the amount of drops given on a diary report form. The administration of commercially available products containing live bacteria was discouraged by instruction to the parent at recruitment.

The active study product consisted of freeze-dried L reuteri suspended in a mixture of pharmaceutical grade medium chain triglyceride and sunflower oils, whereas the placebo consisted of an identical formulation except without L reuteri. The study products, identical in appearance, taste, and packaging, were supplied by BioGaia AB (Stockholm, Sweden), and stability testing by the manufacturer under stringent conditions guaranteed the viability of the live bacteria at the correct dose under refrigerated storage conditions for the duration of the trial. Parents were instructed to store the study product refrigerated throughout the trial. The manufacturer had no role in the conception, design, or conduct of the study, or in the analysis or interpretation of the outcome data.

Parents or caregivers were trained to report daily stool consistency by using the Bristol scale13 in a diary report form. When liquid or loose stools were observed, parents were instructed to call the principal investigator or study coordinator, who instructed them to take the child to the research center for assessment by one of the pediatricians. An episode of diarrhea was the period from the first to the last observation of the passage of a liquid or semiliquid stool, with each episode being separated by a period of absence of diarrhea for at least 24 hours.14 For confirmed diarrheal episodes where the child was not dehydrated or vomiting, only reduced sodium content (Na 60 mEq/L) oral rehydration solutions (ORS-Na60) were prescribed, and parents were instructed to give their children 60 to 90 mL of ORS-Na60 for each liquid/semiliquid stool passed. The child was sent home, and the parents were instructed to document the episode until resolution. If diarrhea with dehydration was observed, the child was hospitalized, an oral rehydration plan was established, and 100 mL/Kg ORS-Na60 was administered in 4 hours until the child was rehydrated and discharged. Again, parents continued reporting until the diarrheal episode was over.

Parents were trained at the beginning of the study to report any respiratory symptoms, and when they occurred, the principal investigator or coordinator was contacted and the child was assessed at the research center by one of the pediatricians. Depending on the severity of the case, a confirmed diagnosis of RTI led to hospitalization or outpatient care. The medication to treat fever was prescribed by the principal investigator or study coordinator; always using drugs with therapeutic equivalence (paracetamol or ibuprofen) with appropriate doses for age and weight according to published clinical practice guidelines. Antibiotics (amoxicillin with clavulanic acid; 50 mg/kg per day for 7 days) were only prescribed if fever persisted for more than 72 hours, and parents were instructed to report any adverse events (by telephone) and the administered antibiotics in the diary. Parents continued to report symptoms until resolution of the event. Child/parent absenteeism from day care/work was also reported in the diary. During the follow-up period (weeks 12–24), the children were...
monitored in the same way before completing and leaving the study at week 24. Parents returned diaries to the investigators at monthly follow-up visits.

A cost-effectiveness analysis was made by comparing the health outcome and incurred costs between the *L. reuteri* and placebo groups. Using this data, an incremental cost-effectiveness ratio (ICER) was calculated for diarrhea and for RTI, where ICER = (cost of *L. reuteri* supplementation − cost of placebo)/(cost of diarrhea or RTI episodes in *L. reuteri* group − cost of diarrhea or RTI episodes in placebo group). The main analysis was performed from the perspective of the payer, in which only direct costs were considered.

Descriptive statistics were used to report the results. Normal distribution of data was analyzed with the Smirnov-Kolmogorov test, and the *χ²* test was used to compare differences between groups in qualitative variables. Differences in quantitative variables, according to their distribution, were analyzed with the parametric *t* test or the nonparametric Mann-Whitney test. Multiple regressions were performed to determine the effect of supplementation on outcomes, adjusted by covariates like breastfeeding history, type of diet, family allergies, previous use of probiotics, or smoking at home. All statistical analysis was performed with 2-tailed tests, at the 5% significance level, and per protocol. Statistical software SPSS version 17.0 (IBM SPSS Statistics, IBM Corporation) was used.

**RESULTS**

Between April 2011 and June 2012, 562 children were assessed for eligibility, with 536 enrolled and randomly assigned to the *L. reuteri* group (*n* = 168) or placebo group (*n* = 168; Fig 1). There were no dropouts, losses to follow-up, or breaches of protocol, and all 336 children completed the study. The baseline characteristics were similar between the 2 groups (Table 1). We found no differences between children included at the different day care centers.

The number of days with diarrhea per child was reduced by *L. reuteri* supplementation from 0.96 (0.2) to 0.32 (0.1), *P* = .03 during the intervention period (0–12 weeks) and from 1.1 (0.1) to 0.5 (0.2), *P* = .01 during follow-up (12–24 weeks) (Table 2). Significant reductions in the number of episodes and the duration of diarrhea by *L. reuteri* supplementation were also observed during the intervention and follow-up periods (Table 2). During the combined intervention and follow-up period (0–24 weeks), a total of 99 and 152 episodes of diarrhea were reported in the *L. reuteri* and placebo groups, respectively (*P* = .01), and the average duration of diarrhea episodes was 1.6 ± 0.9 days and 2.7 ± 1.1 days, respectively (*P* = .02).

The number of days with RTI per child was reduced by *L. reuteri* supplementation from 4.6 (1.8) to 1.5 (0.6), *P* = .01 during the intervention period and from 4.4 (1.1) to 2.1 (0.8), *P* = .01 during follow-up (Table 2). Significant reductions in episodes and duration of RTI by *L. reuteri* supplementation were also observed in both periods (Table 2). The number of days of absence from school, the number of medical visits, and the number of days of antibiotic

**TABLE 1 Baseline Characteristics of Children**

<table>
<thead>
<tr>
<th>Parameter</th>
<th><em>L. reuteri</em> (<em>n</em> = 168)</th>
<th>Placebo (<em>n</em> = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry, mo</td>
<td>20.6 (4.1)</td>
<td>21.1 (4.2)</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.02 (0.48)</td>
<td>3.01 (0.41)</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>39.3 (0.4)</td>
<td>39.9 (0.6)</td>
</tr>
<tr>
<td>Boy/girl</td>
<td>52/48</td>
<td>53/47</td>
</tr>
<tr>
<td>Exclusively breastfed at 6 mo, %</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Breast milk and infant formula at 12 mo, %</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>History of probiotics use in diet 5 wk or earlier before entrance in study, %</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Smoking at home, %</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Overcrowding, %</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Family history of atopy, %</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or as percent of children in the group. *P* > .05 for all parameters.
use were significantly reduced in the *L. reuteri* group during both the intervention and the follow-up periods, although emergency visits were unaffected by supplementation (Table 2). Weight, height, and stool frequency during the study were not significantly affected by the intervention (Table 2).

During the study, parents/guardians reported 34 cases of exanthematic disease (18 cases of rubella and 16 cases of exanthema subitum) and 22 cases of minor trauma. None of these adverse events were deemed by the principal investigator to be related to the study products, and no related serious adverse events were reported in either group. The prophylactic use of *L. reuteri* was associated with a reduction of $36 US dollars (USD) for each case of diarrhea and $37 USD for each case of RTI (Table 3).

### DISCUSSION

This adequately powered and controlled RCT provides evidence that healthy children attending day care centers have significantly reduced risk for contracting diarrhea or RTI when they are given a daily supplement of 10^8 CFU *L. reuteri* DSM 17938. Further, supplementation reduced the duration of observed diarrhea or RTI episodes. These results are in agreement with other studies in children who attend day care centers.4–7,11

To our knowledge, this is the first study to assess the cost-effectiveness of the prophylactic use of a live bacterial supplement in healthy children with the demonstration of an economic benefit to parents and community of using *L. reuteri* DSM 17938 to prevent diarrhea and respiratory infection in day care centers.

The strengths of our study include adequate randomization and power to test the hypothesis (1−β = 0.8), the use of a double-blind design, comprehensive follow-up strategy, and per protocol analysis, all of which minimize the risk of bias. Our inability to be able to evaluate the etiology of the diarrhea or RTI in the study population, related to the difficulties in Mexico City to obtain fecal samples represents 1 weakness of the study.

Our study further provides support and confirmation of the findings of Agustina et al9 with *L. reuteri* DSM 17938 in Indonesian children where daily supplementation with this specific live bacterial strain also gave significant effect on the

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**TABLE 2 Outcome Analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intervention Period</th>
<th>After Intervention Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>L. reuteri</em> Group</td>
<td>Placebo Group</td>
</tr>
<tr>
<td>0–12 wk (n = 168)</td>
<td>12–24 wk (n = 168)</td>
<td>0–12 wk (n = 168)</td>
</tr>
<tr>
<td>Number of diarrhea episodes</td>
<td>42</td>
<td>69</td>
</tr>
<tr>
<td>Episodes of diarrhea per child</td>
<td>0.2 (0.1)</td>
<td>0.4 (0.1)</td>
</tr>
<tr>
<td>Mean duration of diarrhea episodes, d</td>
<td>1.4 (1.0)</td>
<td>2.5 (0.9)</td>
</tr>
<tr>
<td>Days with diarrhea per child</td>
<td>0.32 (0.1)</td>
<td>0.36 (0.2)</td>
</tr>
<tr>
<td>Number of RTI episodes</td>
<td>93</td>
<td>204</td>
</tr>
<tr>
<td>Episodes of RTI per child</td>
<td>0.6 (0.2)</td>
<td>1.2 (0.4)</td>
</tr>
<tr>
<td>Mean duration of RTI episodes, d</td>
<td>2.5 (1.1)</td>
<td>3.8 (0.9)</td>
</tr>
<tr>
<td>Days with RTI per child</td>
<td>1.5 (0.6)</td>
<td>4.6 (1.8)</td>
</tr>
<tr>
<td>Episodes of fever per child</td>
<td>0.4 (0.1)</td>
<td>1.1 (0.3)</td>
</tr>
<tr>
<td>Days with fever per child</td>
<td>1.2 (0.5)</td>
<td>2.8 (0.8)</td>
</tr>
<tr>
<td>Days of school absenteeism per child</td>
<td>1.9 (0.7)</td>
<td>3.4 (1.2)</td>
</tr>
<tr>
<td>Days of work absenteeism for parent per child</td>
<td>1.2 (0.3)</td>
<td>2.2 (0.2)</td>
</tr>
<tr>
<td>Number of medical visits per child</td>
<td>1.0 (0.2)</td>
<td>1.5 (0.3)</td>
</tr>
<tr>
<td>Number of emergency visits per child</td>
<td>0.06 (0.02)</td>
<td>0.1 (0.01)</td>
</tr>
<tr>
<td>Days using antibiotics per child</td>
<td>2.7 (0.9)</td>
<td>4.1 (1.3)</td>
</tr>
<tr>
<td>Mean weight gain during study period, cm</td>
<td>2.6 (0.9)</td>
<td>2.4 (1.1)</td>
</tr>
<tr>
<td>Stool frequency (movement/day per child)</td>
<td>2.0 (1.2)</td>
<td>2.0 (0.9)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) as indicated.

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**TABLE 3 Cost-effectiveness Analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intervention (L. reuteri versus placebo)</th>
<th>Placebo (n = 168), USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of intervention (L. reuteri)</td>
<td>6461.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Cost of diarrhea episodes (99 vs 152)</td>
<td>8486.0</td>
<td>13 053.0</td>
</tr>
<tr>
<td>Cost of respiratory infections (222 vs 421)</td>
<td>15 805.0</td>
<td>29 706.0</td>
</tr>
<tr>
<td>Cost of school or work absenteeism</td>
<td>7162.1</td>
<td>11 522.4</td>
</tr>
<tr>
<td>Incremental cost effectiveness ratio for diarrhea</td>
<td>$-35.7 (ICER = (14 947.5 – 15 053.0) / (99 – 152))$</td>
<td></td>
</tr>
<tr>
<td>ICER for respiratory infections</td>
<td>$-37.4 (ICER = (22 286 – 29 706) / (222 – 421))$</td>
<td></td>
</tr>
</tbody>
</table>
incidence of diarrhea, and further extends the finding to a different ethnic group of children. This allows analysis of multiple independent studies (present study, Weizman et al,8 and Agustina et al9) on the same intervention with similar protocols to establish evidence-based recommendations for the use of L reuteri DSM 17938 for the prevention of infectious disease in day care centers.

CONCLUSIONS
Healthy children attending day care centers have a significantly reduced risk for contracting diarrhea or RTI when given a daily supplement of 10^8 CFU L reuteri DSM 17938 with consequent cost savings for the community. This study adds independent support to previously published evidence that can now be used in systematic reviews to establish evidence-based recommendations for the use of L reuteri DSM 17938 in the prevention of infectious diseases in day care centers.

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