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Comparison of Two Probiotic Agents**

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Effect of a Probiotic Infant Formula on Infections in Child Care Centers: Comparison of Two Probiotic Agents

Zvi Weizman, MD; Ghaleb Asli, MD; and Ahmed Alsheikh, MD

ABSTRACT. *Objective.* To investigate the effect of 2 different species of probiotics in preventing infections in infants attending child care centers.

Methods. A double-blind, placebo-controlled, randomized trial was conducted from December 1, 2000, to September 30, 2002, at 14 child care centers in the Beer-Sheva area of Israel in healthy term infants 4 to 10 months old. Infants were assigned randomly to formula supplemented with *Bifidobacterium lactis* (BB-12), *Lactobacillus reuteri* (American Type Culture Collection 55730), or no probiotics. Duration of feeding, including follow-up, for each participant was 12 weeks. All infants were fed only the assigned formula and were not breast-fed due to parental decision before recruitment to the study. Probiotic or prebiotic food products or supplements were not allowed. Main outcome measures were number of days and number of episodes with fever (>38°C) and number of days and number of episodes with diarrhea or respiratory illness.

Results. Participants ($n = 201$) were similar regarding gestational age, birth weight, gender, and previous breastfeeding. The controls ($n = 60$), compared with those fed *B lactis* ($n = 73$) or *L reuteri* ($n = 68$), had significantly more febrile episodes (mean [95% confidence interval]: 0.41 [0.28–0.54] vs 0.27 [0.17–0.37] vs 0.11 [0.04–0.18], respectively). The controls also had more diarrhea episodes (0.31 [0.22–0.40] vs 0.13 [0.05–0.21] vs 0.02 [0.01–0.05], respectively) and episodes of longer duration (0.59 [0.34–0.84] vs 0.37 [0.08–0.66] vs 0.15 [0.12–0.18] days, respectively). The *L reuteri* group, compared with BB-12 or controls, had a significant decrease of number of days with fever, clinic visits, child care absences, and antibiotic prescriptions. Rate and duration of respiratory illnesses did not differ significantly between groups.

Conclusions. Child care infants fed a formula supplemented with *L reuteri* or *B lactis* had fewer and shorter episodes of diarrhea, with no effect on respiratory illnesses. These effects were more prominent with *L reuteri*, which was also the only supplement to improve additional morbidity parameters. *Pediatrics* 2005;115:5–9; *probiotics, infant formula, child care, infections.*

ABBREVIATIONS. BB-12, *Bifidobacterium lactis*; CFU, colony-forming units.

Probiotics are viable nonpathogenic bacteria that colonize the intestine and modify the intestinal microflora and their metabolic activities with beneficial effects for the host. Probiotic bacteria beneficially affect the host intestinal microbial balance and may improve immunity.^{1,2}

Breastfed infants develop a probiotic-rich gut microflora with less pathogenic bacteria, compared with formula-fed individuals.³ This effect has been considered one of the mechanisms that decreases the rate of infectious diarrhea in breastfed infants.⁴ It has been demonstrated recently that human milk is a source of lactic acid bacteria for the infant gut.⁵

Infant and follow-up formulas supplemented with probiotics are currently marketed in several countries, aiming to mimic some of the beneficial effects of human milk.⁶

Infants and children attending child care centers demonstrate a higher risk of respiratory and gastrointestinal infections.^{7,8} Several clinical studies have documented the efficacy of probiotic agents in the prevention and treatment of diarrhea,^{9,10} mainly of viral etiology.¹¹ However, only a few studies have been published on the ability of these agents to prevent infectious illnesses in infants and children attending child care. Two of these studies used only 1 strain of a probiotic bacteria,^{12,13} and 1 study used a lysis extract obtained from 8 types of bacteria.¹⁴

The aim of the present study was to compare (using a prospective, well-controlled design) the effect of 2 different species of probiotic bacteria in preventing infectious illnesses in infants attending child care centers.

METHODS

Subjects

Healthy term infants, 4 to 10 months old, from 14 child care centers in the Beer-Sheva area of Israel were recruited for this prospective, randomized, double-blind, placebo-controlled trial through meetings with parents. The study lasted 21 months from December 2000 through September 2002, covering 2 winter seasons and 2 summer seasons. Included child care centers were in similar socioeconomic areas. In each center a minimum of 6 infants (2 in each group, recruited during the same season) was required. We excluded infants with prematurity, birth weight <2500 g, congenital anomalies, chronic disease, failure to thrive, allergy or atopic disease, and recent (within the preceding 4 weeks) exposure to probiotics, prebiotics, or antibiotics. All infants were weaned from breastfeeding, due to parental decision, at least 2 weeks before recruitment to the study.

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No conflict of interest declared.

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Intervention

All participants were fed a humanized cow's milk formula (Materna Premium, stage II; Materna Laboratories, Maabarot, Israel). Each infant was assigned randomly to be fed by 1 of the following: the above-mentioned formula supplemented with *Bifidobacterium lactis* (BB-12; CHR Hansen, Hoersholm, Denmark) or *Lactobacillus reuteri* (American Type Culture Collection 55730, also called SD 2112; BioGaia AB, Stockholm, Sweden) or the same formula with no supplement of probiotics. Randomization was performed by the random-digit method on the basis of computer-generated numbers.

The concentration of microorganisms in each supplemented formula was 1×10^7 colony-forming units (CFU) per g of formula powder. Duration of feeding, including follow-up, for each participant was 12 weeks. Infants were fed the enrollment formula in the child care center and at home. Probiotic or prebiotic food products or supplements were not allowed throughout the study. The amount and viability of the probiotic bacteria were monitored every 3 months.

Follow-up Parameters

Each participant underwent a physical examination, including determination of growth parameters (weight, length, and head circumference) at baseline and at 4, 8, and 12 weeks. The parents filled out a daily questionnaire and were instructed to report daily on every symptom. Respiratory symptoms included runny nose, cough, and shortness of breath. Gastrointestinal symptoms included every episode with watery diarrhea. In addition, parents had to report daily every episode of fever ($>38.0^\circ\text{C}$), absence from child care center, visit to the clinic, prescription of any medication including antibiotics, and adverse reactions. The temperature was measured daily rectally. With any episode of fever or illness signs, the child's temperature was taken every 4 hours.

With each illness, each infant was examined daily by a pediatrician on the research team. The respiratory illness group included all patients with upper, lower, or mixed respiratory signs. The gastrointestinal illness group included all patients with ≥ 3 watery stools per day. From each patient with diarrhea a stool sample was analyzed for routine bacterial cultures (including *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* species, excluding toxigenic *Escherichia coli*), rotavirus, and ova and parasites, including *Cryptosporidium*. In addition, each family had a weekly telephone call from the research team to improve compliance and monitoring.

The parents' daily questionnaire included also the following feeding, behavior, and stooling characteristics. Feeding parameters included number of meals per day, response to food (on a 1–5 scale), daily formula volume, and daily number of regurgitation and vomiting episodes. Behavior characteristics included daily number of severe crying attacks, crying nature (on a 1–4 scale), number of night awakenings, and a daily restlessness score (on a 1–5 scale). Stooling parameters included daily number of bowel movements, stooling effort (on a 1–4 scale), stool consistency (on a 1–4 scale), presence of blood in stools, and a daily gas score (on a 1–4 scale).

Outcome Measures

The primary outcome measures included number of episodes of and number of days with fever ($>38^\circ\text{C}$) and number of days with respiratory symptoms or diarrhea and number of episodes with respiratory illness or diarrhea. Additional primary measures included number of visits to the clinic, number of antibiotic prescriptions, and number of child care center absences. Secondary measures were feeding characteristics, growth parameters, changes in behavior and stooling characteristics, and side effects.

Ethics

The study protocol was approved by the local ethics committee of the Soroka University Medical Center and the Ben-Gurion University. A written informed consent was obtained for each infant from both parents.

Estimate of Sample Size

Before the study was conducted, we estimated that for a 2-sided test (at the .05 significance level with a power of 85%) a sample

size of 60 patients in each group would be sufficient to detect a difference of 20% between groups in terms of the number of days with acute illness, based on a previous pilot study.¹⁵

Statistical Analysis

The data from all patients were analyzed on an intention-to-treat basis. For the analysis of the baseline parameters, categorical data were compared by using the χ^2 test, and numerical data were compared by using analysis of variance. For the comparison of the outcome measures we used analysis of variance, and the Tukey test, after appropriate logarithmic transformation to correct for skewness. Means and 95% confidence intervals were back-transformed from log to linear scales for presentation. The analysis was performed with SPSS (standard version 10) software (SPSS Inc, Chicago, IL).

Differences were considered to be significant at the level of $P < .05$. All reported P values are 2-sided. All the statistical data analysis was performed by Ilana Gelernter, from the Statistics Laboratory at Tel-Aviv University (Tel-Aviv, Israel).

RESULTS

A flowchart showing the enrollment and status of patients is presented in Fig 1. Assessed for eligibility were 209 infants, 8 of whom were excluded due to exclusion criteria. Subsequently, the intention-to-treat population consisted of 201 subjects who were assigned randomly to treatment: 60 to the control formula, 73 to the *B lactis* formula, and 68 to the *L reuteri* formula. All 7 failures were the result of poor compliance and violation of the protocol; none of them were formula-related or due to adverse effects.

There were no significant differences between groups at randomization in terms of age at entry, birth weight, gestational age, gender, breastfeeding before the study, mean number of siblings, parental smoking, crowding (>3 persons in a room), and existence of a pet at the household (Table 1).

The mean daily formula volume did not differ significantly between the control, BB-12, and *L reuteri* groups (means [SD]: 636.4 [76.0] vs 645 [59.8] vs 716.9 [123.0] mL, respectively; $P = .288$). Furthermore, no significant differences were observed between groups in terms of other feeding characteristics (daily number of meals, regurgitation and vomiting episodes, and infant compliance).

The results of the primary outcome measures are presented in Table 2. Infants fed a probiotics-free formula, compared with a formula supplemented with *B lactis* or *L reuteri*, had significantly more febrile episodes, and also more episodes of diarrhea, with longer duration. The *L reuteri* group, compared with BB-12 or controls, had significantly fewer days with fever, less visits to the clinic, less absences from the child care unit, and fewer prescriptions of antibiotics. Rate and duration of respiratory illnesses did not differ significantly between groups. There were neither hospitalizations nor outbreaks of diarrhea during the course of the study. The indications for antibiotic therapy were otitis media, pneumonia, and upper respiratory infection, and they did not differ among the groups. No antibiotic-associated episodes of diarrhea were noticed.

Adverse effects were not noticed in any of the participants. Throughout the study, growth parameters (ie, weight, length, and head circumference) were satisfactory, with no significant differences between groups. All the other secondary outcome mea-

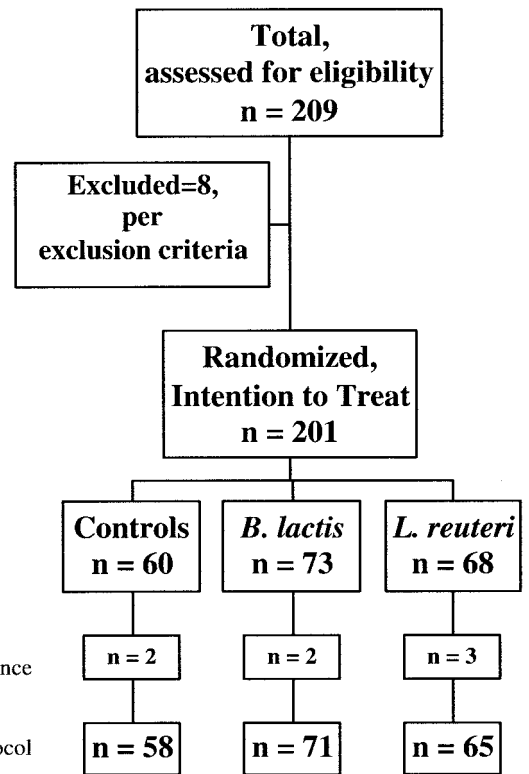


Fig 1. Flow chart showing the enrollment of patients.

TABLE 1. Baseline Characteristics of Participants

Parameter	Controls	BB-12	<i>L reuteri</i>	<i>P</i> Value
<i>n</i>	60	73	68	
Age at entry, mo*	6.7 (1.5)	6.9 (1.6)	6.8 (1.7)	.685
Birth weight, percentiles*	45.2 (28.4)	42.6 (27.1)	47.8 (31.6)	.455
Gestational age, wk*	39.4 (2.1)	38.9 (1.9)	39.6 (2.2)	.644
Male/female, <i>n/n</i>	29/31	34/39	33/35	.711
Previous breastfeeding, %	84	73	76	.866
Number of siblings, <i>n</i>	4.1	3.2	3.6	.665
Parental smoking, %	33	29	39	.477
Crowding, %	24	27	31	.611
Pets at household, %	28	23	32	.784

* Data are means (SD).

TABLE 2. Morbidity Parameters of the 3 Groups

Parameter	Controls	BB-12	<i>L reuteri</i>	<i>P</i> Value
<i>n</i>	60	73	68	
Days with fever	0.83 (0.50–1.16)	0.86 (0.33–1.39)	0.17 (0.04–0.30)	<.001*
Episodes of fever	0.41 (0.28–0.54)	0.27 (0.17–0.37)	0.11 (0.04–0.18)	<.001†
Days with diarrhea	0.59 (0.34–0.84)	0.37 (0.08–0.66)	0.15 (0.12–0.18)	<.001†
Episodes of diarrhea	0.31 (0.22–0.40)	0.13 (0.05–0.21)	0.02 (0.01–0.05)	<.001†
Days with respiratory illness	0.60 (0.31–0.89)	0.68 (0.17–1.19)	0.38 (0.10–0.66)	.169
Respiratory illness episodes	0.24 (0.13–0.35)	0.25 (0.15–0.35)	0.17 (0.08–0.26)	.457
Clinic visits	0.55 (0.42–0.68)	0.51 (0.34–0.68)	0.23 (0.12–0.34)	.002*
Absences from child care	0.43 (0.22–0.64)	0.41 (0.19–0.63)	0.14 (0.07–0.35)	.015*
Prescriptions of antibiotics	0.19 (0.09–0.29)	0.21 (0.12–0.30)	0.06 (0.01–0.12)	.037*

All data are means (95% confidence intervals).

* *L reuteri* versus BB-12 and controls.

† BB-12 and *L reuteri* versus controls.

tures pertaining to behavior and stooling parameters did not reveal any significant differences between groups. There were no cases of bloody stools.

A comparison of stool pathogens in the 3 groups (controls and infants fed formula supplemented with BB-12 or *L reuteri*) did not demonstrate any significant differences regarding rotavirus (38% vs 41% vs

34%, respectively; *P* = .43), positive bacterial cultures (11% vs 7% vs 9%, respectively; *P* = .65), and negative bacterial cultures (51% vs 52% vs 57%, respectively; *P* = .58). Positive bacterial cultures included *Shigella*, *Salmonella*, and *Campylobacter* species in all 3 groups. Stool examination for ova and parasites were negative, excluding 2 cases of *Giardia lamblia* (1

in the control group and 1 in the group fed *L reuteri*-supplemented formula).

DISCUSSION

The present controlled study is the first to compare 2 different species of probiotic microorganisms and their efficacy in the prevention of common infectious illnesses in child care infants. Because lactobacilli and bifidobacteria are the most commonly used and reported probiotics, we selected 1 representative of each group to be included in the present study.

In most of the parameters studied, the differences were consistently in favor of *L reuteri*. Lactobacilli may influence the incidence of infections by stimulating nonspecific immunity or enhancing humoral and cellular immune mechanisms.¹⁶ This immunostimulatory effect of bacteria has been shown to prevent recurrent infections in children attending child care centers.¹⁴ *L reuteri*, 1 of the few indigenous *Lactobacillus* species in the human gastrointestinal tract, has been used safely for many years as a probiotic dietary supplement.¹⁷ Its positive effects on intestinal disorders such as diarrhea and constipation have been demonstrated in several studies.^{18,19} This agent has been shown to modulate immune responses in a series of animal models.¹⁸ In the human gastrointestinal tract, this probiotic agent successfully induced colonization and was able to grow in situ on gastric, duodenal, and ileal biopsies. At the human ileum epithelium, this microorganism was able to induce immunomodulatory activity, including recruitment of CD4⁺ T-helper cells.²⁰

Some of the statistically significant differences in morbidity parameters between groups were minor in clinical terms. For instance, differences in duration of fever and diarrhea were <1 day. We believe that this tendency might have been more prominent in an optimal therapy setting. Future large-scale and long-term studies should establish preferred modes of therapy (ie, duration, dosage, etc) for better clinical effects.

In the present study, no fecal analysis of intestinal colonization was conducted. Based on the average daily intake of formula, the mean daily ingested dose of probiotic microorganisms was 1.2×10^9 CFU/day, and according to a recent study, oral administration of lactobacilli at levels ranging from 10^8 to 10^{10} CFU/day has led to transient colonization of the infant gastrointestinal tract.²¹

Additional limitations of the present study are the lack of testing stool for other enteric viruses besides rotavirus and the relatively short course of therapy, which may have missed associated adverse events.

Most of the stool pathogens in our series were probably viral. Fecal analysis for rotavirus was positive in 34% to 41%, and the other 51% to 57% of stool samples were negative for routine bacterial cultures. We assume that other enteric viruses, for which stool was not tested, were involved.

This finding is in accordance with many previous studies demonstrating that probiotic agents are able to prevent or treat intestinal infections, mainly of viral etiology.^{22,23}

The mechanisms by which probiotic agents might

exert their protective or therapeutic effect against viral pathogens in particular are mostly unknown. In 1 study, an increased humoral response, including an increase in IgA-specific antibody-secreting cells against rotavirus, was described in children with acute rotaviral diarrhea who received *Lactobacillus* GG.²⁴ More mechanistic studies assessing in vitro and in vivo effects of these agents against different viral pathogens are needed.

To be widely used, a probiotic must also be safe. Lactobacilli and bifidobacteria are generally regarded as nonpathogenic, because they occur naturally in the intestine. In many clinical trials these 2 agents seem to be safe for the general adult and pediatric populations.^{25,26} In addition, the safety of these 2 particular bacteria in infancy has been documented recently in another study by our group.¹⁵

Data comparing probiotic species in a systematic and broad-based way have been scant and mostly derived from animal and laboratory studies. There are almost no controlled clinical studies assessing various species of probiotic microorganisms for a specific indication. The present study compares, in a controlled manner, the clinical efficacy of 2 different probiotic agents for 1 particular clinical application and is unique in this respect. Different types of probiotic bacteria exert different effects based on specific capabilities and enzymatic activities, even within 1 species.²⁷ Therefore, in vitro selection criteria for probiotic bacteria of human origin looking at correlation with in vivo findings are required.²⁸ When the great variety of species and strain characteristics are considered, it becomes clear that a proven probiotic effect of 1 strain or species cannot be transferred to another. Therefore, more controlled clinical studies comparing different types of bacteria for a specific indication are warranted.

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