Probiotics in prevention of IgE-associated eczema: A double-blind, randomized, placebo-controlled trial

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Background: An altered microbial exposure may underlie the increase of allergic diseases in affluent societies. Probiotics may alleviate and even prevent eczema in infants.

Objective: To prevent eczema and sensitization in infants with a family history of allergic disease by oral supplementation with the probiotic *Lactobacillus reuteri*.

Methods: Double-blind, randomized, placebo-controlled trial, which comprised 232 families with allergic disease, of whom 188 completed the study. The mothers received *L reuteri* ATCC 55730 (1×10^8 colony forming units) daily from gestational week 36 until delivery. Their babies then continued with the same product from birth until 12 months of age and were followed up for another year. Primary outcome was allergic disease, with or without positive skin prick test or circulating IgE to food allergens.

Results: The cumulative incidence of eczema was similar, 36% in the treated versus 34% in the placebo group. The *L reuteri* group had less IgE-associated eczema during the second year, 8% versus 20% ($P = .02$), however. Skin prick test reactivity was also less common in the treated than in the placebo group, significantly so for infants with mothers with allergies, 14% versus 31% ($P = .02$). Wheeze and other potentially allergic diseases were not affected.

Conclusion: Although a preventive effect of probiotics on infant eczema was not confirmed, the treated infants had less IgE-associated eczema at 2 years of age and therefore possibly run a reduced risk to develop later respiratory allergic disease.

Clinical implication: Probiotics may reduce the incidence of IgE-associated eczema in infancy. (J Allergy Clin Immunol 2007;119:1174-80.)

Key words: *Children, eczema, IgE,* Lactobacillus, *prevention, probiotics, sensitization, skin prick test*

An altered microbial exposure may be partly responsible for the increase of allergic diseases in populations with a western lifestyle.[1] Indeed, several studies show differences in the intestinal microbiota between allergic and nonallergic children[2,3] and between countries with a low and high prevalence of atopic disease.[4,5] For example, infants who later develop allergic disease have been reported to be colonized less often with *Bacteroides* and bifidobacteria[2] and to have lower ratios of bifidobacteria to clostridia.[3] Furthermore, allergic disease seems to be inversely related to having grown up on a farm or with an anthroposophic lifestyle[6] and to endotoxin exposure,[7] and it may be associated with the use of antibiotics in infancy.[8] However, intervention studies are needed to evaluate the relevance of these findings.

Probiotics have been defined as ''living micro-organisms, which, upon ingestion in certain numbers, exert health benefits beyond inherent general nutrition''[9] and have been reported to improve the symptoms in infants with eczema.[10-12] Furthermore, one study has suggested a preventive effect of a probiotic strain on allergic disease. In this study, supplementation with *Lactobacillus rhamnosus* GG (LGG) to pregnant women and their offspring during the first 6 months of life reduced the incidence of eczema in infants with a family history of allergic disease.[13,14] Despite an effect on eczema, LGG had no effect on either sensitization or wheezing and asthma up to 4 years of age. More investigations are needed to confirm these findings and to evaluate whether probiotic strains with other properties may have a preventive effect not only on eczema but also on sensitization.

Lactobacillus reuteri (L reuteri) has anti-inflammatory properties, as demonstrated in animal and human *in vitro* studies.[15-17] For example, *L reuteri* prevents TNF-α–induced IL-8 expression in murine epithelial cells,[15] diminishes inflammatory bowel disease in murine models,[16] and induces human IL-10 producing regulatory T cells by

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Abbreviations used
ARC: Allergic rhinoconjunctivitis
CFU: Colony forming units
LGG: *Lactobacillus rhamnosus* GG
OR: Odds ratio
SCORAD: Scoring Atopic Dermatitis
SPT: Skin prick test

modulating dendritic cell function.[17] Clinical studies have confirmed beneficial effects in acute diarrhea in children,[18-20] reduction of infections in a day-care setting,[21] and in combination with a *L rhamnosus* strain, improvement of childhood eczema.[11]

The aim of the current study was to assess the effect of oral supplementation with *L reuteri* in infancy on eczema development and sensitization during the first 2 years of life.

METHODS

Study design

This study was a prospective, double-blind, placebo-controlled, multicenter trial conducted at the Department of Paediatrics in the county hospitals of Jönköping, Motala, and Norrköping and the University Hospital in Linköping in southeastern Sweden. Between January 2001 and April 2003, 232 families with allergic disease (1 or more family members with eczema, asthma, gastrointestinal allergy, allergic urticaria, or allergic rhinoconjunctivitis) were recruited at antenatal clinics. The family history of allergic disease was obtained by a structured interview preceding the inclusion of the family. Randomization was stratified for each study center. Each center was provided an allocation list with unique identification numbers for each subject. Before the delivery, each bottle was labeled and randomly mixed by an independent contract manufacturer. The mothers started taking *L reuteri* or placebo 4 weeks before term and continued daily until delivery. After birth, the baby continued with the same study product as the mother daily up to 12 months of age. Children admitted to the neonatal ward during the first week of life were excluded from the study. Families were requested not to use any other probiotic products during the study period and received a list of available probiotics on the market. Compliance to the treatment regimen was assessed by interviews, stool examination, and collecting used study product bottles. Insufficient compliance led to the exclusion of the participant from the study. The mothers were encouraged to breastfeed. At weaning, their babies were offered a hypoallergenic whey hydrolysate, Profylac (ALK, Hørsholm, Denmark), as formula, until 6 months of age. Thirty-nine (41%) in the *L reuteri* and 43 (47%) in the placebo group received Profylac.

The *Lactobacillus* preparation consisted of freeze-dried *L reuteri* (strain American Type Culture Collection 55730; BioGaia AB, Stockholm, Sweden), suspended in three-quarters refined coconut oil and one-quarter refined peanut oil containing cryoprotective components. The refined oil did not contain peanut proteins (detection level <0.005%). As the content of coconut protein was unknown, 8 mothers who reported coconut allergy were not included in the study. The daily intake, 5 oil droplets, corresponded to 1×10^8 colony forming units (CFUs). The placebo consisted of the same oil without any bacteria and was not possible to differentiate from the active product by smell, taste, or visual appearance. The dose chosen leads to efficient colonization of the human intestine[18,22] and reduces gastroenteritis and other infections.[18,20,21] Safety studies have shown that up to 1000-fold higher doses are safe.[18,19,23,24]

TABLE I. Diagnostic criteria for eczema modified from Seymore

Major features*
1. Evidence of pruritic dermatitis
2. Typical facial or extensor eczematous or lichenified or nummular dermatitis
3. Eczema-free skin of nose-mouth area and/or diaper area
4. Family history of eczema

Minor features*
1. Xerosis/ichtyosis/hyperlinear palms
2. Periauricular fissures
3. Chronic scalp scaling
4. Perifollicular accentuation

*At least 2 major and 2 minor criteria must be present.

Clinical investigations

Follow-up was performed by research nurses at 1, 3, 6, 12, and 24 months of age and by structured telephone interviews with parents at 2, 4, 5, 8, 10, and 18 months. A final follow-up was done by a pediatrician at 2 years of age (1 year after the termination of treatment). The visits consisted of structured interviews related to symptoms of allergic disease, adverse events, infections, use of antibiotics, and possible confounding factors as well as an inspection of the skin. The SCORAD index was used to assess the severity of the eczema.[25] Records from primary care units, private pediatricians, and the pediatric clinics were examined if the parents reported that the child had been examined by a physician. All children with suspected eczema were reexamined by a physician belonging to the study team (T.A., T.J., or G.O.).

Skin prick tests (SPTs) were performed on the volar aspects of the forearm with egg white, fresh skimmed cow milk (lipid concentration 0.5%), and standardized cat, birch, and timothy extracts (Soluprick; ALK) at 6, 12, and 24 months of age. Histamine hydrochloride (10 mg/mL) was used as a positive control and albumin diluent as a negative control. The results of the test were regarded as positive if the mean diameter of the wheal was greater than or equal to 3 mm.

Diagnostic criteria

Eczema was defined as a pruritic, chronic, or chronically relapsing non–infectious dermatitis with typical features and distribution, as suggested by Hanifin and Rajka and modified by Seymour for infants.[26] As all infants had a family history of allergic disease, the criteria were further modified as displayed in Table I. Internal workshops were arranged for the investigators in the study before the study commenced in order to achieve uniform diagnostic criteria of eczema in all study centers. Eczema was classified as IgE-associated if the infant was also sensitized.

Wheeze was defined as an episode with obstructive airway symptoms. Asthma was defined as greater than or equal to 3 wheezing episodes, at least once verified by a physician.

A diagnosis of allergic rhinoconjunctivitis (ARC) required watery discharge at least twice in contact with the same allergen and no signs of infection. Urticaria was defined as allergic when appearing at least twice in conjunction with a certain food. A diagnosis of gastrointestinal allergy required vomiting, diarrhea, or systemic reaction after ingestion of a potentially allergenic food and a confirmation by challenge, unless there was a clear history of a severe systemic reaction.

Infants were regarded as sensitized if they had at least 1 positive SPT and/or detectable circulating allergen specific-IgE antibodies.

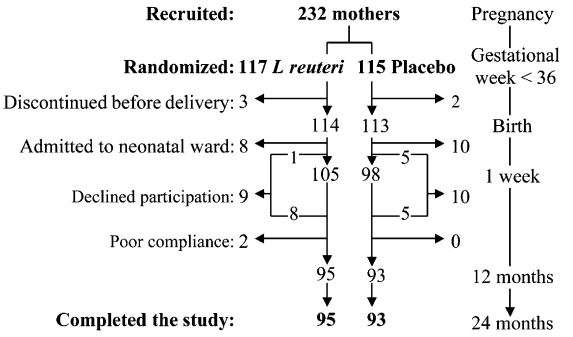

FIG 1. Participation rate and reason for discontinuation. Families were excluded if their baby was admitted to the neonatal ward during the first week of life or if they had a poor compliance. A total of 16 of 19 families declining participation gave no reason, whereas 3 (2 in the *L reuteri* group) did so because of abdominal discomfort/colic.

IgE antibody analyses

Venous blood samples were drawn at 6, 12, and 24 months of age. Circulating IgE antibodies to egg white and cow's milk were analyzed at 6, 12, and 24 months of age (UniCap Pharmacia CAP System; Pharmacia Diagnostics, Uppsala, Sweden). The cutoff level was 0.35 kU/L, according to the protocol of the manufacturer. In addition, circulating IgE to a mixture of food allergens, including egg white, cow's milk, cod, wheat, peanut, and soybean, was analyzed at 6, 12, and 24 months of age (UniCap Pharmacia CAP System, fx5, Pharmacia Diagnostics).

Statistical analysis

The power calculation to estimate the sample size needed to detect true differences between the *L reuteri* and the placebo group was made based on an anticipated 40% frequency of allergic disease in the placebo group at 2 years. With at least 91 subjects in each group, a 50% reduction in frequency of allergic disease could be detected at a 5% level of significance with 80% power. With a dropout frequency of 20%, a total sample size of 228 families was desirable. The χ^2 test was used to compare the prevalence of outcome variables and background factors between the groups. The Fisher exact test was used when the expected frequency for any cell was less than 5. Logistic regression was made for adjusting for the influence on prevalence figures from possible confounders. As SCORAD scores are not normally distributed, the groups were compared using the Mann-Whitney *U* test for these analyses. Only families that completed the study were included in the analyses. As the mother received the study product in late pregnancy, the effect of the treatment was also assessed by stratifying by parental status of allergic disease. A probability level of less than .05 was considered to be statistically significant. The calculations were performed with the computer program Stata version 8.2 (StataCorp LP, College Station, Tex).

Ethical aspects

An informed consent was obtained from both parents before inclusion. Pain connected with blood sampling was minimized with topical anesthesia. The Regional Ethics Committee for Human Research at Linköping University approved the study.

RESULTS

The participation rate and the reason for discontinuation are displayed in Fig 1. One dropout infant belonging to the *L reuteri* group had an episode of wheezing at 2 months of age. This dropout infant was the only one having any suspected symptoms potentially associated with allergic disease before discontinuation. The compliance was high among the participants according to interviews and collected study product bottles. Only 2 infants, both from the *L reuteri* group, were excluded because of poor compliance not caused by any adverse events. Baseline characteristics in families completing the study were similar in the 2 groups (Table II).

TABLE II. Baseline characteristics in children completing the study until 2 years of age

	Lactobacillus reuteri	Placebo
Birth weight	3.658 kg	3.603 kg
Birth length	51.3 cm	50.8 cm
	% (n)	% (n)
Boys	56 (53)	48 (45)
First born	48 (46)	58 (54)
Caesarean delivery	11 (10)	15 (14)
Parental smoking	7 (7)	12 (11)
Furred pets	15 (14)	9 (8)
Family history of		
Eczema	57 (54)	58 (54)
Asthma	49 (47)	47 (44)
ARC* and food allergy	96 (91)	90 (84)
Parental allegic disease†		
Mother	72 (71)	77 (72)
Father	66 (63)	64 (60)
Both parents	44 (42)	44 (41)
None‡	3 (3)	2 (2)

*Allergic rhinoconjunctivitis.
†Eczema, asthma, gastrointestinal allergy, allergic urticaria, or ARC.
‡At least 1 sibling with allergic disease.

The cumulative incidence of eczema was similar in the *L reuteri* and the placebo groups (36% vs 34%, Table III). IgE-associated eczema, however, was less common in the *L reuteri* group, although the difference was only statistically significant during the second year of life (8% vs 20%, $P = .02$, Fig 2). This result was true even when limiting the definition of IgE- associated eczema to only include infants with eczema and a positive SPT result (4% vs 14%, $P = .02$). Adjusting for potential confounders, that is, breastfeeding, antibiotics, sex, birth order, cesarean delivery, parental smoking, furred pets, and family history for eczema, ARC, and food allergy, did not affect this result significantly (crude odds ratio [OR] for IgE-associated eczema at 12-24 months 0.35, $P = .026$, adjusted OR 0.36, $P = .047$). Generally, the eczema was mild. The median SCORAD points in affected infants were 12 in the *L reuteri* versus 9 in the placebo group at 12 months, and 11 versus 8 at 24 months. The cumulative incidence of wheeze was also similar in the 2 groups, 8% versus 12% at 0-12 months and 18% versus 16% at 0-24 months. The figures for the other possible manifestations of allergic disease were low (Table III).

The cumulative incidence of any positive SPT tended to be lower in the *L reuteri* group, 18%, compared with the

placebo group, 29% ($P = .07$, Table III). This trend remained after adjusting for breastfeeding, antibiotics, sex, birth order, cesarean delivery, parental smoking, furred pets, and family history of ARC and food allergy (crude OR = 0.53, $P = .07$, adjusted OR 0.53, $P = .09$). Circulating IgE to egg white was less often detected in the *L reuteri* group, although only significantly so at 2 years of age, (7% vs 17%, $P = .047$). No other differences in circulating IgE to food allergens were observed between the groups (Table III). The infants in the *L reuteri* group tended to be less sensitized at 2 years of age (23% vs 34%, $P = .096$). Overall, 37% and 48% of the infants in the treated and placebo groups, respectively, were sensitized; they had either a positive SPT and/or circulating IgE to food allergens, during the study period.

The prevalence of breastfeeding was high in the 2 study groups (Table IV), and the duration tended to be longer in the placebo group (7.6 vs 8.4 months, $P = .08$). Infections were equally common between the groups, 11.4 occasions in the *L reuteri* and 10.8 occasions in the placebo group until 2 years of age. Acute otitis media tended to be more common in the *L reuteri* group, 25%, compared with the placebo group, 15% ($P = .08$, Table IV). Antibiotics were more often prescribed in the *L reuteri* group during the first year of life (Table IV), and acute otitis media was the indication for 70% of the prescriptions. As antibiotics might have an impact on the effect of *L reuteri* treatment, the clinical outcome was adjusted for antibiotics separately. This adjustment did not affect any comparisons significantly (data not shown), however. Attendance to day-care centers was also similar in the 2 groups (data not shown).

No difference was found in the cumulative incidence of mild adverse events such as spitting-up, colic, and constipation during the first 12 months of age (Table IV). At 1 and 2 months of age, however, more infants in the *L reuteri* group were reported having spitting-ups than in the placebo group (26% vs 14%, $P = .04$, at 1 month, and 33% vs 19%, $P = .04$, at 2 months), but no differences were found when the parents were asked whether their infants had any gastrointestinal problems (13% vs 9%, $P = .37$, at 1 month, and 6% vs 11%, $P = .28$, at 2 months). Furthermore, the infants were heavier in the *L reuteri* than the placebo group at 3 months (6.4 kg vs 6.1 kg, $P = .03$, *t*-test), but not at any other time points The cumulative incidence of infants reported to have gastrointestinal problems during the first 12 months was 21% in the *L reuteri* group and 23% in the placebo group. No severe adverse events were reported.

Stool samples were taken at 1 week and at 1, 3, 6, 12, and 24 months. As *L reuteri* was also detected in some stool samples in the placebo group, as reported in a separate communication (T. R. Abrahamsson, G. Sinkiewicz, T. Jakobsson, M. Fredrikson, and B. Björkstén, unpublished data, February 2007), assessments were repeated, excluding these infants from the placebo group. The difference in the prevalence of IgE-associated eczema remained significant, 8% in the *L reuteri* and 21% in the placebo group ($P = .04$). No other assessments became significant (data not shown).

As the mother received the study product in late pregnancy, the effect of the treatment was also assessed depending on the parental atopic status. Indeed, the effect of the treatment was more pronounced, when only infants whose mothers had allergic disease were included. The effect on IgE-associated eczema, SPT reactivity, and sensitization became statistically significant (Table V).

TABLE III. The cumulative incidence of allergic disease, SPT ≥3 mm, specific IgE levels >0.35 kU/L, and use of topical corticosteroids in infants completing the study until 2 years of age

	Lactobacillus reuteri % (n)	Placebo % (n)
Eczema	36 (34)	34 (32)
IgE-associated eczema*	17 (13)	28 (21)
Asthma	7 (7)	11 (10)
Wheeze including asthma	18 (17)	16 (15)
ARC†	1 (1)	4 (4)
Gastrointestinal allergy	2 (2)	2 (2)
Allergic urticaria	3 (3)	1 (1)
SPT (≥3 mm)		
Egg	14 (13)	23 (21)
Milk	4 (4)	7 (6)
Cat	2 (2)	5 (5)
Birch	2 (2)	4 (4)
Grass	0 (0)	1 (1)
Any allergen	18 (17)	29 (27)
Specific IgE (>0.35 kU/L)		
Ovalbumin	16 (12)	27 (20)
Betalactoglobulin	19 (14)	13 (9)
Food allergens (fx5)	34 (26)	36 (26)
Sensitized‡	37 (28)	48 (36)
Topical corticosteroids	41 (39)	49 (46)

*Infants were excluded from subanalyses if data were missing from any time point. Sensitized infants with eczema.
†Allergic rhinoconjunctivitis.
‡Infants with either a positive SPT and/or circulating IgE to food allergens.

DISCUSSION

Although no preventive effect on infant eczema occurred in this study, there was less IgE-associated eczema at 2 years of age in infants receiving *L reuteri*. The cumulative incidence of any positive SPT was also lower, and fewer infants were sensitized at 2 years of age in the *L reuteri* group. The effect was more pronounced when only infants whose mothers have allergic disease were included, which may implicate significance of the supplementation to the mothers in late pregnancy. The effect of *L reuteri* treatment may also have become more evident in infants of mothers with allergic disease, as they run an increased risk for allergic disease.[27] As sensitized infants with eczema are at increased risk for later development of allergic asthma and rhinoconjunctivitis,[28,29] these observations warrant continued clinical follow-up.

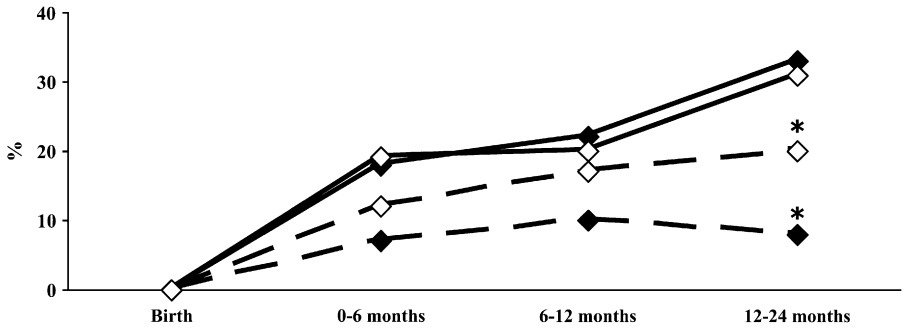

FIG 2. Prevalence of any eczema *(solid lines)* and IgE-associated eczema *(hatched lines)* during the first 24 months of life in infants receiving daily oral supplementation of *L reuteri (closed symbols)* or placebo *(open symbols)* during the first 12 months of life. *$P = .02$ with χ^2 test.

TABLE IV. Breast-feeding, antibiotics, infections, and adverse events in children completing the study

	Lactobacillus reuteri % (n)	Placebo % (n)
Breast-feeding		
3 mo, exclusive	69 (66)	76 (71)
6 mo, partial	84 (80)	84 (78)
Antibiotics		
0-12 mo	37 (35)*	20 (19)*
12-24 mo	43 (41)	42 (39)
0-24 mo	58 (61)	48 (45)
Acute otitis media		
0-12 mo	25 (24)	15 (14)
12-24 mo	35 (33)	28 (26)
0-24 mo	47 (45)	35 (33)
Gastroenteritis		
0-12 mo	29 (28)	30 (28)
12-24 mo	45 (43)	40 (37)
0-24 mo	60 (57)	54 (58)
Mild adverse events		
Spitting-up 0-12 mo	54 (51)	46 (43)
Colic 0-12 mo	12 (11)	11 (10)
Constipation 0-12 mo	4 (4)	6 (6)

*$P = .013$ with χ^2 test.

Besides a suggested preventive effect,[13] administration of probiotic bacteria (*L reuteri, L rhamnosus*, and *L fermentum*) to children has previously also been reported to improve symptoms of eczema.[10-12,30] The effect was more pronounced for IgE-associated eczema in 2 of these studies.[11,30] In a recent treatment study with LGG, neither eczema nor specific-IgE levels were affected, however.[31] Proposed modes of action by probiotics include improved intestinal barrier function, degradation of macromolecules, and influence on the gut immune system.[31] Earlier studies on the effect of lactobacilli on immune cells in animal or *in vitro* models have shown promotion of Th1-like responses with IFN-γ, IL-12, and IL-18 activation, which inhibites development of a Th2-like deviation in infants.[32] *L reuteri* has displayed a slightly different profile than other probiotic bacteria and seems to possess more pronounced anti-inflammatory properties, as demonstrated in animal and human *in vitro* studies.[15-17,33] For example, *L reuteri* prevents TNF-α–induced IL-8 expression in murine epithelial cells,[15] diminishes inflammatory bowel disease in murine models,[16] and induces human IL-10 producing regulatory T cells by modulating dendritic cell function *in vitro*.[17] The effect of *L reuteri* on the development of IgE-associated eczema and sensitization in the current study may be caused by such anti-inflammatory properties. Another mode of action of *L reuteri* could be an indirect effect through an influence on the composition of the intestinal microbiota, as *L reuteri* strains produce the antimicrobial metabolite reuterin and inhibit pathogenic bacteria, without inhibiting normal bacterial residents of the gastrointestinal tract *in vitro*.[34]

In the previous prevention study with LGG by Kalliomäki et al, the effect was restricted to eczema and no reduction in the incidence of sensitization, or respiratory allergic disease, occurred either at 2 or 4 years of age.[13,14] Furthermore, no effect was found on IgE-associated eczema. Naturally, the divergent results between these 2 trials raises questions over whether different probiotic strains might have different properties critical for an effect on allergic diseases.[17,32,33] Our study differs from the study by Kalliomäki et al, not only because different probiotic strains were used but also in other aspects. The daily dose was lower in our study (1×10^8 CFU) compared with the Finnish study (1×10^{10} CFU). In a previous study on gastroenteritis, the effect of *L reuteri* was dose dependent.[18] It cannot, therefore, be excluded that a higher dose of *L reuteri* may also have led to an effect on eczema in non–sensitized infants and not only in sensitized ones as in our study. On the other hand, the infants received the study product for 12 months in our study, whereas in the Kalliomäki study, either the mother or the infant received lactobacilli for 6 months. This finding is important, because examination of the breast milk in our study revealed that only 12 % of the mothers receiving *L reuteri* during pregnancy had *L reuteri* in their colostrum 1-3 days after delivery (T. R. Abrahamsson, G. Sinkiewicz, T. Jakobsson, M. Fredrikson, and B. Björkstén, unpublished data, February 2007).

Very recently, Taylor et al[35] reported the outcome of an allergy prevention study with a probiotic strain of *L*

TABLE V. Eczema, IgE-associated eczema, wheeze, asthma, SPT ≥3 mm, and sensitization in infants, depending on parental status of allergic disease

	Mother with allergic disease*		Father with allergic disease*	
	L reuteri % (n)	Placebo % (n)	*L reuteri* % (n)	Placebo % (n)
Eczema				
0-6 mo	14 (10)	24 (17)	22 (14)	17 (10)
6-12 mo	21 (15)	26 (19)	29 (18)	20 (12)
12-24 mo	32 (23)	38 (27)	38 (24)	33 (20)
0-24 mo	34 (24)	40 (29)	43 (27)	35 (21)
IgE-associated eczema†				
0-6 mo	5 (3)	15 (10)	9 (5)	11 (6)
6-12 mo	6 (4)‡	22 (14)‡	13 (8)	15 (8)
12-24 mo	7 (5)‡	23 (15)‡	11 (6)	20 (11)
0-24 mo	13 (8)§	32 (19)§	21 (11)	28 (13)
Any positive SPT				
6 mo	7 (5)	15 (11)	13 (8)	12 (7)
12 mo	13 (9)	25 (18)	21 (13)	20 (12)
24 mo	7 (5)§	20 (14)§	13 (8)	18 (11)
0-24 mo	14 (10)§	31 (22)§	23 (14)	28 (17)
Sensitized‖				
6 mo	13 (8)	21 (14)	23 (13)	18 (10)
12 mo	19 (13)	32 (21)	33 (20)	28 (15)
24 mo	18 (12)‡	39 (26)‡	30 (17)	31 (17)
0-24 mo	28 (17)‡	52 (31)‡	46 (24)	45 (21)
Wheeze including asthma				
0-12 mo	8 (6)	10 (7)	11 (7)	15 (9)
0-24 mo	18 (13)	15 (11)	21 (13)	17 (10)
Asthma				
0-12 mo	1 (1)	3 (2)	3 (2)	5 (3)
0-24 mo	8 (6)	10 (7)	10 (6)	13 (8)

*A total of 71 mothers and 63 fathers in the *L reuteri*, and 72 mothers and 66 fathers in the placebo group had an allergic disease, that is, eczema, asthma, gastrointestinal allergy, allergic urticaria, or allergic rhinoconjunctivitis.
†Infants were excluded from subanalyses if data were missing from any time point. Sensitized infants with eczema.
‡$P < .01$ with χ^2 test.
§$P < .05$.
‖Infants with either a positive SPT and/or circulating IgE to food allergens.

acidophilus. The results in that study differ significantly from our's and Kalliomäki et al's,[13] in that IgE-associated eczema and sensitization were more common in infants receiving probiotics, whereas the incidence of any eczema was not affected. Besides the use of a different bacterial strain, their study design differed from our's and the Finnish study in that the mothers were not supplemented with the study product during pregnancy. The results of the 3 prevention studies may therefore suggest that the supplementation to the mothers in late pregnancy is of a crucial importance.

Rosenfeldt et al[11] reported lower SCORAD scores among sensitized infants with eczema treated with an *L reuteri* and an *L rhamnosus* strain. In contrast, the scores were not affected in our study, which could possibly be explained by the fact that the scores were much lower in our study than the study by Rosenfeldt et al, which examined infants referred to specialists for eczema. In our study, the infants were diagnosed early and treated before severe illness had developed, because they were under close surveillance from birth.

Oral supplementation with the *L reuteri* strain used in the current study has been reported to decrease febrile episodes, episodes with diarrhea, and antibiotic prescriptions but not respiratory illness in Israeli infants in child care centers.[21] In contrast, in our study, antibiotics were prescribed more often in the *L reuteri* group during the first year of life, although the infection rate was similar in the 2 groups. Antibiotics were mostly prescribed for acute otitis media in the current study, and a difference in the infection panorama in the 2 countries with a higher incidence of gastrointestinal infection in Israel may probably explain the different outcomes. Although it cannot be excluded completely, it is not likely that oral supplementation with *L reuteri* increases the risk for acute otitis media. On the other hand, antibiotics have been associated with a higher risk for allergic disease in previous studies.[8] This higher risk, however, was restricted to broad spectrum antibiotics,[8] which seldom are prescribed for acute otitis media in Sweden. This finding may explain why the adjustments for antibiotics did not affect the effect of *L reuteri* in our study.

In summary, this intervention study on infants with a family history of allergic disease could not confirm a preventive effect of probiotics on infant eczema. The prevalence of IgE-associated eczema during the second year and the cumulative incidence of SPT reactivity, were, however, lower in the treated group. The effect was more pronounced among infants with mothers with allergies. As sensitized infants with eczema have increased risk for later development of allergic asthma and rhinoconjunctivitis, studies on the outcome in older children, as well as possible mechanisms behind this effect, are warranted.

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