

Is probiotic treatment useful for infantile eczema?

Human breast milk is rich in pre and probiotics and may play an important role in infant health and development. Proper nutrition and prevention in the early stages of life may lead to better health later on. There are many facets involving the benefits of probiotics, specifically, including the bacterium *Lactobacillus* that have recently been explored for the first time. The article, “*Lactobacillus* GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial,” examines the possible benefits of *Lactobacillus* that is found in human breast milk. Pregnant mothers who were carrying infants who were at a high risk of allergic disease were recruited for this study. Through a randomized control trial mothers were given probiotic supplementation from week 36 gestation up until delivery. The infants were assessed after delivery through the first year for allergic sensitization and eczema. The umbilical cord and breast milk was also examined to determine their probiotic levels. However, the study resulted in not providing sufficient evidence for prevention of eczema and thus preventing allergic response. This leads us to our question: what health benefits does the probiotic *Lactobacillus* have in immune response and what is their involvement in infant, and therefore adult, health?

Reference: Boyle RJ, Ismail IH, Kivivuori S, Licciardi PV, Robins-Browne RM, Mah L-J, Axelrad C, Moore S, Donath S, Carlin JB, Lahtinen SJ, Tang MLK. *Lactobacillus* GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. *Allergy* 2011; 66: 509–516

AND Evidence Analysis Worksheet I

Citation	West C, Hammarstrom M, Hernell O. Probiotics during weaning reduce the incidence of eczema. <i>Pediatr Allergy Immunol.</i> 2009; 20, 430-437.
Study Design	Double-blind, placebo-controlled, randomized trial
Class	A
Research Purpose	The purpose of this study is to find how affective the introduction of probiotics, specially the effects of <i>Lactobacillus paracasei</i> ssp. <i>paracasei</i> strain F19 (LF19) during infant weaning is in reducing the incidence of eczema.
Inclusion Criteria	Infants were born healthy, full term, have a birth weight of more than 2,500 grams, born vaginally, and have no allergic manifestation or medication that could affect gut microflora. Parents had to sign written consent.
Exclusion Criteria	Infants who were excluded include those who appeared to have allergies, those who were given medication that could affect bacteria in the gut, born pre-term, compromised health, delivered by cesarean section, and who have a low birth weight.
Description of Study Protocol	<ul style="list-style-type: none"> • For the intervention the infants were randomly put in two different groups: intervention and placebo. The parents were instructed to feed their infant the cereal that was given to them. One serving of cereal contained 1×10^8 colony forming units of LF19. The parents were instructed to not feed their infant any products that contain probiotics. They infant's stools were tested for LF19 and verified by amplified polymerase chain reaction (RAPD-PCR). This was to test compliance. • Intervention group of 89 participants received rice (from 4-6 months) and wheat based (6-13 months) cereals

	<p>supplemented with LF19.</p> <ul style="list-style-type: none"> • Placebo group of 90 participants received rice and wheat based cereals not supplemented with LF19 • The different cereals were in colored cartons that were either blue or yellow. Neither the parents nor the investigators knew which carton was supplemented with LF19 until the analysis was completed. • Nursing mothers were asked to keep a daily diary of the number of breast feedings per day. They were also asked to record if the infant showed any symptom of allergic response on their skin or their airways. Eczema was based on the questionnaires as a itchy rash for at least two weeks and/or a doctor diagnosis. • These records were reviewed monthly by the appointed nurse for the research. After the monthly review the parents were then asked to complete a interview and a questionnaire related to asthmatic symptoms, diagnoses, prescriptions, or any another drug or supplement being administered to the infant. A doctor’s diagnosis of asthma defined asthma for this study. • Venous blood was being drawn from infants at 5 ½ months and 13 month of age using Vacutainer brand tubes. • Plasma and serum were collected and measured for IgE. The total/ specific concentrations were measured when the infant was 13 months old. • At both 5 ½ and 13 months old the IFN-γ, IL-4, and IFN-γ/IL-4 mRNA ratios were determined.
<p>Data Collection Summary</p>	<p>Independent variables</p> <ul style="list-style-type: none"> • One group received supplementation of LF19 cereals (probiotic group). The other group, the placebo group, did not receive cereals that were supplemented with LF19

Dependent variables:

- Incidence of eczema, IgE concentrations/ratios, incidence of asthma, IFN- γ /IL4 mRNA levels after T-cell stimulation (cytokine mRNA expression), and incidence of rhino-conjunctivitis.

Confounding variables:

- Some of the confounding variables include exposure to pets at home who have fur, relation to at least one person with an allergy, gender, gestational age, birth weight, older siblings, day care attendance, or exposure to smoking in the home. Those who have a relative with an allergy were classified as high-risk. Infants who were in the placebo group were prescribed antibiotics more than those in the intervention group.
- The primary outcome measure was the cumulative incidence of eczema at 13 months of age. The secondary outcome measure was the cumulative incidence of asthma, allergic rhino-conjunctivitis, concentrations of IgE and cytokine mRNA expression levels at 13 months of age.

Statistics used:

- The data from eligible infants in this study were analyzed using an intention-to-treat (ITT) basis.
- A chi-square test was used for comparing proportions and the Fisher's exact test was used as needed.
- The statistical method of logistic regression was used to adjust the clinical outcome measures to take confounding variables into consideration.
- The Student's t-test was used to analyze breastfeeding duration.
- The Mann-Whitney U-test was used to compare the ratios of IgE and cytokine mRNA due to the log-transformation not

	<p>leading to normal distribution.</p> <ul style="list-style-type: none"> • Total RNA was extracted using a method called acid guanidium-thiocyanate-phenol-cholorform. Levels of this mRNA for IL4 and IFN-γ were used to determine assays (utilized with the <i>TaqMan</i> EZ technology) for PCR with RNA copy standards that developed in the lab. • IgE (total and specific) concentrations were determined with a system called Pharmacia CAP System. Values above 0.35 were considered to be a sign of sensitization.
<p>Summary of Results</p>	<ul style="list-style-type: none"> • There were no differences between the groups at baseline regarding the confounding factors. • 171 infants were able to complete the trial and were included in the ITT analysis. • It was found that the incidence of eczema at 13 months of age was 11 % in the probiotic group and 22% in the placebo group. 9/84. Incidence of eczema in the high-risk group was 11% in the probiotic group and 26% in the placebo group. • In the probiotic group 2% of the infants were diagnosed with asthma and 6% of the placebo group was diagnosed with asthma ($p= 0.4$). All of these infants had a family history of allergies. Only one infant that belonged in the probiotic group was diagnosed with allergic rhino-conjunctivitis. • It was found that there were no statistically significant differences in concentrations serum IgE at 13 months of age. • There were no statistically significant differences between the two groups in their IFN-γ or IL4 mRNA levels or ratio at 5.5 and 13 months of age. It was found that the probiotic group infants after 9 months of age had an increase in IFN-γ mRNA and decrease in the IL4 mRNA levels compared to the placebo group. At risk infants had their ratios higher at 13 months of

	<p>age. The p values for these findings are 0.4. Also these statistics are not included in the report.</p> <ul style="list-style-type: none"> • It was found that infants with eczema (43%) had higher extent of symptoms from environmental allergens than the infants who did not have eczema (22%) [p= 0.023]. However the IgE concentrations did not differ in probiotic group (11.6) compared to the placebo group (7.7) [p= 0.3].
<p>Author Conclusion</p>	<ul style="list-style-type: none"> • Lactobacillus F19 demonstrated preventive effects in food during weaning on the incidence of infant eczema. It is proposed that this mechanism could possibly be mediated by involving a higher Th1/Th2 ratio in the infants who are receiving LF19. • The author states that follow-up studies on these infants are necessary to have a full understanding of this trial. For instance, a long-term study is needed to see how the infants are affected by respiratory allergies as they age. Also, there needs to be more studies in order to understand how allergy prevention can be achieved with other probiotic strains.
<p>Reviewer Comments</p>	<ul style="list-style-type: none"> • One strength that the study had is that is very thorough. They took many factors into consideration, such as infant risk of allergies due to family history, while completing the study. Also, there are not many confounding factors that affect the integrity of the study. • One limitation that the study has is that not many infants were involved in the study. A higher number of participants may have been better in order to include a wider variety of people. <p>Concerns:</p> <ul style="list-style-type: none"> • There were no concerns in regards to validity and generalizability of the study.

	<p>Funding source:</p> <ul style="list-style-type: none"> This study was supported by Semper AB, Sweden, Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning; Swedish Agency for Innovation Systems; Swedish Research Council, Medicine and Natural and Engineering Sciences; the Västerbotton country council; Ronald McDonald Fund; Swedish Nutrition Foundation and Oskar-fonden.
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AND Evidence Analysis Worksheet II

Citation	Boyle RJ, Ismail IH, Kivivuori S. Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. <i>Allergy</i> 2011; 66, 509-516.
Study Design	Double-blind, placebo-controlled, randomized trial
Class	A
Research Purpose	The purpose of this study was to determine if prenatal treatment with a probiotic called <i>Lactobacillus rhamnosus</i> GG (LGG) could influence infantile risk of eczema.
Inclusion Criteria	Participants must be pregnant women who are either affected by a doctor-diagnosed allergy, such as asthma, eczema, food allergy, or allergic rhinitis, or have a partner to a previous child who is affected by such conditions.
Exclusion Criteria	Women with multiple pregnancies, fetal abnormality or maternal immune deficiencies, or already take probiotic supplements.
Description of Study Protocol	<p>Intervention:</p> <ul style="list-style-type: none"> 250 pregnant women were recruited for this study. They were randomly chosen to be in one of two groups: the probiotic group (n= 125) and the placebo group (n= 125). The participants in the probiotic group were instructed to take 1.8×10^{10} cfu LGG every morning beginning in their 36th

week of pregnancy until they delivered.

- The placebo group was instructed to take a maltodextrin placebo.

Outcomes:

- Mothers completed a questionnaire regarding allergy and eczema symptoms were included in the examinations.
- Outcomes were measured in infants at 3, 6, and 12 months of age.
- Incidence of eczema was measured in the infants. Eczema was defined by the criteria held by The UK Eczema Working Party which includes: itchy skin, scratching, rubbing, family history of atopic disease, history of skin rash on flexures, outer surfaces of the limbs or cheeks, history of dry skin, visible dermatitis on the flexures, outer surfaces of the limbs or cheeks, or the onset of rash under the age of two.
- At 12 months of age a skin prick test was performed on the infants back. A wheal diameter was used to define atopy.
- Atopy was defined as a skin prick test wheal diameter more than or equal to 3 mm more than the negative control to a single allergen.
- IgE-associated eczema was defined when a positive skin prick test and an eczema occurrence during the first 12 months were both present.
- Severity of eczema was determined using a Scoring Atopic Dermatitis (SCORAD) scale.
- Asthma was defined according to a proposal by Castro-Rodriguez.
- Colic occurrence was also measured and was defined by the infant crying or being fussy without any obvious reason for more than or equal to 3 hours on more than or equal to 3 days per week for more than 3 consecutive weeks.

	<ul style="list-style-type: none"> • All assessments were conducted by either the research nurse (CA) or the appointed pediatric allergist (RJB).
<p>Data Collection Summary</p>	<p>Independent variables:</p> <ul style="list-style-type: none"> • The probiotic group who received supplements of LGG from week 36 in pregnancy to delivery. • The placebo group who received a maltodextrin placebo. <p>Dependent variables:</p> <ul style="list-style-type: none"> • Incidence of infantile eczema, allergic sensitization, IgE-associated eczema, severity of eczema, respiratory and gastrointestinal symptoms. <p>Confounding variables:</p> <ul style="list-style-type: none"> • Possible confounding factors may include: genetic background, diet, intestinal microbiota, paternal or maternal eczema, smoking in the household, gender, gestation, birthweight, delivery method, maternal age, antibiotic use during pregnancy, and probiotic intake during pregnancy. <p>Outcomes:</p> <ul style="list-style-type: none"> • The primary outcome measure was the cumulative incidence of infantile eczema within the first year. • The secondary outcome measure was allergic sensitization, IgE-associated eczema, severity of eczema, respiratory and gastrointestinal symptoms. <p>Statistics:</p> <ul style="list-style-type: none"> • A two-group continuity-corrected χ^2 test with two-sided significance of 0.05 was used to detect eczema risk between the two treatment groups. • A t-test was also used for the continuous data that was normally distributed. • A rank sum test was used for data that was skewed. • A chi-square test was used for category data.

	<ul style="list-style-type: none"> • A Fisher’s exact test was used when expected frequencies were more than or equal to 5. • Data was analyzed using the STATA 11.
<p>Summary of Results</p>	<ul style="list-style-type: none"> • 212 out of the original 250 (85%) participants completed the study to the 1 year follow up. Two of the infants passed away perinatally; 30 participants were unable to contact or moved away; 6 participants withdrew; 2 had adverse reactions of treatment. • Capsules were returned 195 of the participants (98 from the probiotic group and 97 from the placebo) and were counted and revealed that 87% (91% from the probiotic and 84% from the placebo) too more than or equal to 80% of the expected dose. • There were no statistically significant differences in the confounding factors in this study. <p>Eczema and allergic sensitization</p> <ul style="list-style-type: none"> • There was no difference in the prevalence of eczema in infants between the probiotic (34%) and placebo group (39%). IgE-associated eczema also had no differences with incidence being 18% in the probiotic group and 19% in the placebo group. • Incidence of eczema ever was 34% in the probiotic group and 39% in the placebo group. P-value was 0.44. • There was no difference in the prevalence of IgE-associated eczema or allergic sensitization or in the severity of the eczema during the first 12 months after birth. • Incidence of atopic eczema: 18% in the probiotic group and 19% in the placebo. <p>LGG on GI and respiratory outcomes</p> <ul style="list-style-type: none"> • There was not any statistical significance in the difference of

	<p>outcomes and adverse in the placebo or probiotic group. This includes adverse gastrointestinal symptoms during the prenatal intervention portion wheezing, asthma, gastroenteritis, colic, vomiting, and hospital admission.</p> <ul style="list-style-type: none"> • CBMC (cord blood mononuclear cells) samples were taken from only 77 of the participants and were cryopreserved within 12 hours. • Immune parameters were measured and there was not a difference between the probiotic and the placebo group. • These parameters were measured with either LPS(lipopolysaccharide) or LTA (lipoteichoic acid). • The CBMC samples were measured for the following cytokines: IL-10, IL-13, IFN-γ, TNFα, and TF-B1. These cytokines are associated with increased risk of eczema. It was found that there was no difference in the levels of these cytokines after a 48-hour period or a 24-hour period between the two groups.
<p>Author Conclusion</p>	<ul style="list-style-type: none"> • Prenatal supplement of <i>Lactobacillus rhamnosus</i> GG did not prevent infantile eczema. There was also no effect on the immune response of the newborns. In fact, the prenatal treatment with LGG led to a decreased amount of breast milk sCD14 and IgA levels. It is noted that postnatal treatment, a longer duration of prenatal treatment, or a different probiotic strain might have offered a positive effect.
<p>Reviewer Comments</p>	<p>Strengths:</p> <ul style="list-style-type: none"> • The strengths of the study were that they were very thorough in the assessment of infantile eczema by using blood samples, skin prick tests, questionnaires, and by having a trained nurse

	<p>and allergist to confirm symptoms.</p> <p>Limitations:</p> <ul style="list-style-type: none"> • The limitations in this study include losing a large number of participants and short intervention time span (about 4 weeks). Had the intervention began earlier in the pregnancies it might have made a larger difference. Another limitation was that the gut microflora of the pregnant women was not investigated and may have had an impact on the effectiveness of LGG supplementation. • Women who took probiotic supplements were excluded from the study but their diet was not evaluated. Their diet while being pregnant may have had an impact of the LGG supplements as well. <p>Concerns:</p> <ul style="list-style-type: none"> • There were no concerns in regards to validity and generalizability of the study. <p>Funding source:</p> <ul style="list-style-type: none"> • The Jack Brockhoff Foundation, the Murdoch Children’s Research Institute, the Australian National Health and Medical Research Council and the Ilhan Food Allergy Foundation, a scholarship from the University of Melbourne Baillieu, a Murdoch Children’s Research Institute Postgraduate Scholarship, the National Institute for Health Research Comprehensive Biomedical Research Centre, a scholarship from the Ministry of Higher Education, Malaysia, Universiti Putra Malaysia, Applied Biosciences Graduate School, and Elintarvikkeiden Tutkimussaatio, Finland.

AND Evidence Analysis Worksheet III

Citation	Kukkonen K, Savilahti E, Haahtela T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. <i>J Allergy Clin Immunol.</i> 2007;119(1):192-8.
Study Design	Randomized Clinical Trial.
Class	A
Research Purpose	To determine if use of pre- and probiotics reduces allergic disease in babies.
Inclusion Criteria	<ul style="list-style-type: none"> • Pregnant mothers carrying children with an increased risk for developing allergies from Helsinki. • At least one parent of the unborn child had a physician-diagnosed allergic disease, which was evaluated by telephone interviews by trained personnel. • Target dates of birth were between November 2000 and March 2003.
Exclusion Criteria	<ul style="list-style-type: none"> • Infants born who were gestated fewer than 37 weeks, • Infants born with major malformations, and • B-twins.
Description of Study Protocol	<ul style="list-style-type: none"> • The double-blind intervention included two parallel groups of women who were in the last two to four weeks of their pregnancies. <ul style="list-style-type: none"> ○ One group was given a probiotic capsule twice daily, and the other a placebo capsule twice daily, through the completion of their pregnancies, and then their infants were given a capsule supplement, once daily, for the next six months. <ul style="list-style-type: none"> ▪ Probiotic Group: The probiotic supplements given to the study group comprised of one capsule containing Lactobacillus rhamnosus, (5 10⁹ colony-forming units [cfu]); L rhamnosus, (5 10⁹ cfu); Bifidobacterium breve), 2 10⁸ cfu; and Propionibacterium freudenreichii ssp. shermanii, (2 10⁹ cfu). The infants were given one opened capsule containing the same probiotics mixed with 20 drops of sugar syrup containing 0.8 g of galacto-oligosaccharides. ▪ Placebo Group: The placebo group of mothers was given capsules containing microcrystalline cellulose, with the infants received sugar syrup without galacto-oligosaccharides. • Parent(s) were given questionnaires at 3 months regarding pregnancy, birth, and parental education. Parents responded to another questionnaire at 3, 6, 12, and 24 months regarding nutrition, symptoms of infant colic, symptoms of allergic

	<p>diseases, infections, antibiotic use, family size, day care, parental smoking, environment, and household pets.</p> <ul style="list-style-type: none"> • Compliance to treatment was also evaluated at 3 and 6 months, determined by doses not given and number of pills returned to the researchers. • In the event that breastfeeding was insufficient for the infant, normal adapted cow's milk-based formula was given, and if the infants were allergic to cow's milk, a hypoallergenic formula was used.
<p>Data Collection Summary</p>	<p>Independent</p> <ul style="list-style-type: none"> ▪ Probiotic and prebiotic supplement versus placebo <p>Dependent</p> <ul style="list-style-type: none"> • Cumulative incidence of any allergic disease <ul style="list-style-type: none"> ○ Food allergy (diagnosed with 2 week food challenge with improved symptoms) ○ Asthma ○ Allergic rhinitis with antigen-specific sensitivity (history of 2 or more symptoms) ○ Cumulative incidence of IgE associated disease, including IgE associated eczema 925 <ul style="list-style-type: none"> ▪ Assessed at 6 months by skin prick test (measuring wheal size at 15 minutes >3mm) ▪ Assessed at 2 years by immunoassay using centrifuged serum (concentration of IgE >0.7kU/L) • Eczema (atopic/IgE and nonatopic) diagnosed using UK Working Party definition <p>Confounders</p> <ul style="list-style-type: none"> • Sex • Delivery by cesarean section • Breast-feeding • Use of antibiotics during the intervention • Regular (daily or >2 days a week) use of probiotics after the intervention <p>Statistical Analysis</p> <ul style="list-style-type: none"> ▪ Multivariable logistic regression to adjust outcome for confounds ▪ <i>Mann-Whitney U</i> test ▪ X² test ▪ The n (population) initially participating was 1,223. The probiotic group n=610 and the placebo group n=613. Due to drop-out and adverse reactions, the final population at 2 years for the probiotic group was n=461 and the placebo

	<p>group n=464 (925 total). This is a >24% loss from the initial population.</p>
<p>Summary of Results</p>	<ul style="list-style-type: none"> • Not significant: <ul style="list-style-type: none"> ○ The participants of the study in both the probiotic and the placebo groups were evenly distributed (<3% difference) in gender, birth weight, delivery by cesarean section, maternal allergy, paternal allergy, both parents allergic, breast-fed or not, age at initiation of day care, and furred pets at home ○ No overall prevention of allergic disease (p<.159) prevention by use of probiotic/prebiotic supplement by age of 2 years ○ Sensitization not significant at 2 years (p<.184), from 31% to 28% • May be significant: <ul style="list-style-type: none"> ○ Maternal smoking differed 3% between the two groups: <ul style="list-style-type: none"> ▪ 16% in the probiotic group and 13% in the placebo group ○ Firstborn child in the family participating differed 6%: <ul style="list-style-type: none"> ▪ 58% in the probiotic group and 52% in the placebo group ○ Antibiotics during intervention differed % between the two groups: <ul style="list-style-type: none"> ▪ 23% in the probiotic group and 28% in the placebo group ○ Some overall prevention of IgE-associated allergic disease (p<.022) by age of 2 years (odds ratio=0.71, 95% confidence index) ○ Reduction of eczema (p<.015), from 32% to 26% ○ Significant reduction of atopic (IgE-associated) eczema (p<.012), from 18% to 12%
<p>Author Conclusion</p>	<ul style="list-style-type: none"> ▪ Pregnant women with increased chances of producing children with early allergic diseases who are treated with probiotics not likely to reduce the overall occurrence of allergic disease in their children. ▪ An inverse relationship occurs between the use of probiotics during pregnancy and infant feedings and the infants developing eczema. This relationship is stronger with reduction of atopic or IgE-associated eczema in infants. ▪ The reduction of IgE-associated diseases is greater in male infants than in female infants, leaving room to research these differences in another study. ▪ The specific probiotic <i>L rhamnosus</i> weakly stimulates dendritic cell maturation, which influence the expression of regulatory

	cytokines so they effectively prevent or reduce eczema.
Reviewer Comments	<p>This study brings up questions about whether the information obtained could be applied to correlation with later allergic conditions, and displays the disparities in results between male and female infants. While the authors discuss criteria for other allergic disease states considered during the study, they weren't included in the results, concentrating on the subject while leaving questions for future studies. This study was held in Finland and may not be representative of other populations due to its exclusive population. As this was a recruited study from the suburban area of Helsinki, it's possible that the people who ultimately participated may not show a true cross-section of the country's population.</p> <p>Possible conflicts of interest could come from the study's funding, which was supported by the Helsinki University Central Hospital Research Funds and Valio Ltd, Helsinki, Finland. Valio owns dairy producers and one of the authors (K. Kukkonen) has received grant funding from Valio, while R. Korpela and T. Tuure are employed by Valio's R and D department, which is listed as a potential conflict of interest. This study utilized cow milk products as a vehicle for some of the probiotics, as well as the prebiotics, which are derived from dairy.</p>

AND Evidence Analysis Worksheet IV

Citation	Soh SE, Aw M, Gerez I, et al. Probiotic supplementation in the first 6 months of life in at risk Asian infants--effects on eczema and atopic sensitization at the age of 1 year. Clin Exp Allergy. 2009;39(4):571-8.
Study Design	Randomized Clinical Trial.
Class	A
Research Purpose	To determine if probiotic use plays a role in reducing eczema development in Asian infants
Inclusion Criteria	<ul style="list-style-type: none"> • First degree relative with doctor-diagnosed asthma/allergic rhinitis/eczema, and a positive skin prick test (SPT) to dust mites

	<ul style="list-style-type: none"> • Gestational age of >35 weeks • Birth weight > 2kg • Absence of major congenital malformation or illness
Exclusion Criteria	<ul style="list-style-type: none"> • Parent is assessed to be mentally or legally incapable of informed consent • Parents choosing to breast-feed exclusively
Description of Study Protocol	<ul style="list-style-type: none"> • Double-blind intervention on infants >35 weeks gestational age, divided into two parallel groups. <ul style="list-style-type: none"> ○ Both groups were given 60mL a day of a commercially available cow's milk-based infant formula with either a probiotic supplement or without (placebo). Formula supplementation was initiated within 12 hours of birth until the subject was 6 months old. After the infants had consumed the daily allotment of formula, their parents were allowed to give them more formula, breast milk, or another formula of their choice. <ul style="list-style-type: none"> ▪ Probiotic group: (n=126) were given formula fortified with specific species of bacteria so that the concentration was 2.8×10^8 CFU. ▪ Placebo group: (n=127) were given the same base formula as the probiotic group, so that it looked and tasted the same, but without the probiotics. • Parental daily diaries and biweekly phone calls were used to assess compliance for the first 6 months • Consumption of less than 60mL of formula a day for 3 days

	<p>considered non-compliance.</p> <ul style="list-style-type: none"> • Weaning to solids occurred between 4-6 months with parents advised to avoid feeding potentially allergenic foods, such as eggs, shellfish, and peanuts until their 1st birthday. • Infants were evaluated by study pediatricians at 1, 3, 6, and 12 months of age, when they took detailed histories, anthropometric data, and conducted clinical exams, especially looking for the presence of eczema. Questionnaires were used to evaluate clinical disease and environmental exposures such as day care, number of siblings, use of antibiotics, second-hand smoke, and pets.
<p>Data Collection Summary</p>	<p>Independent</p> <ul style="list-style-type: none"> • Probiotic versus placebo <p>Dependent</p> <ul style="list-style-type: none"> • Incidence of eczema – defined as a pruritic rash over the face and/or arms with chronic presence or series of relapses as defined by Hanifin and Rajka, adjusted for infants by Seymour. This was objectified by the Scoring Atopic Dermatitis (SCORAD) index to determine the severity each incidence of atopic dermatitis. • Rate of sensitization to common allergens – determined by measurement of IgE in serum samples from cord blood and samples drawn at 1 year. The IgE was measured by fluoroenzymeimmunoassay with a detection limit of 0.35 kU/L. Additionally, skin prick testing was performed at 12 months using standardized techniques and testing common allergen

extracts, including soy, milk, egg yolk, egg white, and two species of dust mites. Weals >3mm in diameter greater than the negative control were considered positive.

Confounders

- Gender
- Birth Order
- Prenatal maternal smoking
- Passive smoking exposure
- Smoking exposure
- Household pets
- Housing types
 - Public
 - Private (condominiums)
 - Landed
- Feeding history (birth-6 months)
 - Near total breastfeeding
 - Any breastfeeding
 - Total formula
- Age at weaning (months)
- Use of antibiotics by 6 months
- Day care attendance by 12 months

	<p>Statistical Analysis</p> <ul style="list-style-type: none"> • X^2 test • <i>Mann-Whitney U</i> test • Multivariable logistic regression to adjust outcome for confounds • The n (population) participating was n=253, and after the 12 month study, the final was n=245. This is a <4% loss from the selected group.
<p>Summary of Results</p>	<ul style="list-style-type: none"> • The participants of the study in both the placebo and probiotic groups both showed similar distribution, by percent, of the following characteristics: gestational age, ethnicity, mode of delivery (caesarean section/vaginal delivery), birth weight, family history of eczema, and paternal atopy. Some variation occurred in the distribution of gender, birth order, asthma, allergic rhinitis, and maternal atopy (greater than 5%). • The characteristics of sensitization of the subjects at 12 months were not dissimilar between placebo and probiotic groups, including skin prick test results for common allergens, and inhalant allergens. • Of all the confounders considered, only passive smoke exposure in households, breastfeeding and total formula intake by subjects differed between the two groups. (37% placebo versus 46% probiotic) • Incidence of eczema in placebo group (n=30/121; 25%) versus probiotic group (n=27/124; 22%) not significantly different. Multivariable logistic regression was performed to account for any confounding effects influencing atopic propensity but feeding history between treatment groups did not significantly

	<p>affect the findings.</p> <p>Despite a couple of differences between the distribution of the two groups, there does not appear to be any significant association between probiotic use in infants and reduction of eczema.</p> <ul style="list-style-type: none"> • Incidence of eczema in the probiotic group was 22%, similar to that of the placebo group, which was 25% • Allergic sensitization was not shown to be significantly different, with the probiotic group at 24% and placebo at 19% • Atopic eczema in the probiotic group was 7.3% while 5.8% in the placebo group.
<p>Author Conclusion</p>	<ul style="list-style-type: none"> • Administration of probiotics in early life via cow's milk formula appeared to show no effect on the prevention of eczema and allergic sensitization in the first year of life for those infants of Asian descent at risk of developing allergic disease. • Previous studies considering the incidence of a relationship between probiotic use and eczema reduction have been mixed. This study addressed discrepancies between the ways the previous studies were conducted, and no studies had considered an all Asian population before. The findings of this study mirrored the results of two other clinical trials before which involved Australian and German populations. • The unique feature of this study is that it attempts to mirror real life as opposed to other studies, in that it allows for traditional feeding styles, such as breast feeding and retail formula supplementation rather than relying

	<p>completely on the study formula. This was intended to allow for greater compliance. It also relies on cow milk formula rather than hypoallergenic, which introduced cow dairy to the study participants, who didn't show increased cow milk allergy.</p> <ul style="list-style-type: none"> • According to ISAAC Phase 3 studies, schoolchildren of the Singapore cohort have significantly less eczema than the other studies ethnic groups. Review of these other studies suggest that probiotics are less likely to make an impact on populations already unlikely to develop eczema.
<p>Reviewer Comments</p>	<p>This study tries to determine whether previous studies on specific populations are indicative of probiotic influence on the potential for developing eczema in infants. While it considers various confounds and the likelihood for a population to be predisposed for eczema, the authors seem to approach the subject from the perspective that there will not be a positive association between probiotic use and prevention of eczema. While this bias might not show in the development of the study, the discussion indicates a belief that the only previous studies, of which there were five, may all be debunked for various reasons, such as study design and population studied. The one element of the study that seems to be consistent with bias is the actual delivery of the probiotics, which includes using a possibly confounding type of milk which is one of the eight top allergens.</p>

Summary of Evidence

AND Evidence Analysis Worksheet I

In a double-blind, placebo-controlled, randomized trial, *Probiotics during weaning reduce the incidence of eczema*, West et al (2009) studied the effects of eczema incidence while supplementing *Lactobacillus* F19 in infant cereal fed to 171 healthy, full term infants, which were divided into two groups, probiotic (n=84) and placebo (n=87), from birth to 13 months of age. Each serving of cereal contained 1×10^8 colony forming units of LF19. The ratio of interferon- γ to interleukin 4 mRNA expression in peripheral blood T cells was measured from the infants blood and assessed along with IgE serum levels, and incidence of asthma and allergic rhino-conjunctivitis. It was found that there was a difference in the incidence of eczema between the probiotic (11%) and the placebo (22%) group; incidence of eczema in the high-risk group was 11% in the probiotic group and 26% in the placebo group; there no difference in IgE serum concentrations in either group; no difference was found in incidence of asthma between the probiotic (2%) and the placebo (6%) group. There were no differences between the groups at baseline values. In this trial the serving size of cereal for each feeding should have been considered when assessing the effects on infantile eczema.

Conclusion

Lactobacillus F19 (1×10^8 colony forming units of LF19/ serving) given as a supplement in a rice/wheat based cereal for infants was useful in preventing infantile eczema by 10% but did not make a difference in IgE serum concentrations or asthma in healthy, full-term infants that had no difference in baseline characteristics.

Grade II

AND Evidence Analysis Worksheet II

In a double-blind, placebo-controlled, randomized trial, *Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial*, Boyle et al (2011) studied the effects of treating 125 pregnant women with 1.8×10^{10} cfu of *Lactobacillus rhamnosus* GG as a probiotic group and treating 125 women with a placebo during the last 4 weeks of pregnancy and the influence on the risk of infantile eczema. It was found that there was no difference in the prevalence of eczema among the probiotic (34%) and placebo group (39%) in 212 healthy, full term infants as well as no difference between the probiotic (18%) and placebo (19%) groups regarding incidence of atopic eczema and IgE-associated eczema. There was also no difference in the following cytokines: IL-10, IL-13, IFN- γ , TNFalpha, and TF-B1 and the effect on increased risk of eczema. It may have been beneficial to increase the time of intervention as well as the microflora already present in the pregnant mother's GI tract seeing as these factors may greatly impact the result.

Conclusion:

Supplements of *Lactobacillus rhamnosus* GG (1.8×10^{10}) in capsule form given to pregnant women did not prevent infantile eczema or decrease eczema causing cytokines in their healthy, full-term infants who had no differences in baseline characteristics.

Grade II

AND Evidence Analysis Worksheet III

Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases

In a high quality randomized, double-blind, placebo-controlled trial by Kukkonen et al (2007), researchers looked at 925 infants and found that supplemental administration of a proprietary compounded pre- and probiotic given to pregnant women in their last few weeks of pregnancy and then to their infants for the first six months of their life demonstrated a significant decrease in atopic eczema, and to a lesser degree, decreased incidence of other IgE eczema and IgE associated disease. This was most strongly correlated during the first few months of life and by the 2 year assessment, the correlation had ceased to be significant. The primary outcome indicates an adjusted 35% reduction in IgE associated allergic disease and a secondary outcome showing an adjusted 31% and 39% decrease in eczema and atopic eczema, respectively, in the pre- and probiotic group. Disparities between male and female infants results may indicate genetic disparity between gender. All participants were from Helsinki and of Finnish descent, which may not be representative of the general population.

Grade II

AND Evidence Analysis Worksheet IV

Probiotic supplementation in the first 6 months of life in at risk Asian infants – effects on eczema and atopic sensitization at the age of 1 year

This high quality randomized, double-blind, clinical trial by Soh et al (2009) reviewed the results of previous similar studies and selected an Asian population as one had not been previously studied in probiotic studies aimed at determining their effect on infant eczema. 253 high-risk for allergic disease infants were divided into probiotic and placebo groups before birth, with the mothers ingesting assigned supplements up to 4 weeks before birth and continuing to deliver the assigned supplement daily for the first 6 months of each infant's life. Assessments were given at throughout the first year of their life but no significance of probiotic use versus placebo was seen. The study's limitations may include the specific strain of probiotic and dose as well as the lack of exposure to the probiotic during early fetal development where it may have more impact. This study otherwise indicates there is no benefit to using probiotic to decrease future development of allergic disease and eczema.

Grade II

Conclusion

Supplementation with strains of probiotic in the last trimester of gestation and the first six months of infant life may or may not have an effect as to whether children at risk because of allergic parents develop allergic disease, especially eczema. While a study conducted in Finland indicated positive correlation between probiotic use and reduction of atopic eczema and some IgE mediated allergic disease, a similar study conducted on Asian infants showed no correlation between probiotic use and reduction of allergic disease. Different strains were emphasized in the two studies and the Finnish study also incorporated galactooligosaccharide prebiotics, which could present differences in outcomes, though testing of infants in both studies at 6 months and 1 year showed no significant populations of these bacteria in their guts. Additionally, the Finnish study incorporated nearly four times the subjects into their results, making their sample broader and more representative of their population.

Overall Grade II

References

Boyle RJ, Ismail IH, Kivivuori S. Lactobacillus GG treatment during pregnancy for the prevention of eczema: a randomized controlled trial. *Allergy* 2011; 66, 509-516.

Boyle R, Mah L, Chen A, Kivivuori S, Robins-Browne R, Tang M. Effects of lactobacillus GG treatment during pregnancy on the development of fetal antigen-specific immune responses. *Clin Exp Allergy*. 2008; 38, 1882-1890.

Kukkonen K, Savilahti E, Haahtela T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol*. 2007; 119:192-198.

West C, Hammarstrom M, Hernell O. Probiotics during weaning reduce the incidence of eczema. *Pediatr Allergy Immunol*. 2009; 20, 430-437.