Selected Lactobacillus rhamnosus GG Research Abstracts

Compiled September 2013
# Lactobacillus rhamnosus GG:
The most clinically studied probiotic

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Introduction

This booklet is educational in nature and is intended to provide a brief overview of probiotics along with specific information about *Lactobacillus rhamnosus* GG. It is not a comprehensive review of probiotics nor of *Lactobacillus rhamnosus* GG. This booklet is provided for guidance and reference purposes only to introduce some of the scientific studies surrounding the benefits of *Lactobacillus rhamnosus* GG for children.

The selected abstracts included in this booklet demonstrate the benefits of the probiotic *Lactobacillus rhamnosus* GG for managing and supporting:

- Diarrhea
- Gastrointestinal discomfort
- Immune health

Symbiosis between the gastrointestinal microbiota and the host is the basis for these health benefits. In exchange for a stable environment and adequate nutrients, the microbiota play a role in maturation of the gastrointestinal tract, provide the host with nutritional contributions and help safeguard the host from harmful microbes. When this symbiosis is disturbed, introduction of naturally occurring intestinal microflora, like *Lactobacillus rhamnosus* GG, can assist in re-establishing homeostasis and optimal function.

Given the copyright nature of the primary literature, we cannot provide the full texts of these studies. The cited articles are available through the US National Library of Medicine, subscription literature databases as well as individual publishers.
The human body is inhabited by a collection of microorganisms, also known as microflora, that coexist and provide mutual benefit (Sekirov et. al. 2010). Although microflora exists in many areas of the human body, the most heavily colonized is the gastrointestinal tract where 70% of all human microbes reside. Colonization of the gastrointestinal tract begins immediately at birth and within a few days the large intestine is home to a complex and dynamic microbial ecosystem, with high densities of living bacteria. By one month, the microflora established in a newborn is predominantly Lactobacilli and Bifidobacteria (Saavedra 2007) and by one year of age the microflora is stabilized resembling that of a young adult (Sekirov 2010). During colonization, bacteria compete for bacterial receptors on the mucosal surface consisting of glycoconjugates, glycoproteins or lipids, lodged within the microvillus membrane. The composition of the glycoconjugates is thought to affect the composition of the microflora based on the fact that different organisms have different affinities for these terminal sugars. Consequently, host genotype appears to be a key determining factor of microbial composition versus overall diet (Bäckhed 2005). By 1 year of age, an individual's microflora is well established and consists of several hundreds of species; however, these species will vary greatly between individuals. In general, the microflora composition within an individual usually remains constant. Fluctuations can result, however, from illness, medication, and diet. Turnover is ongoing, as evidenced by a large proportion of the fecal mass consisting of bacteria (Guarner 2003) as the microflora continually compete for the limited, available glycol-specific proteins and binding sites on the intestinal mucosal surface. Microflora continually forage for available glycogens on food particles, mucus, and epithelial cells while attempting to avoid elimination (Bäckhed 2005). In general, the microflora within the gastrointestinal tract have three major functions - metabolic, protective, and supportive.

Metabolic/Digestion Support

One of the major outcomes from the human-microflora relationship is the ability of the host/human to gain energy in the form of nutrients which would otherwise not be available; and in return, the microflora are provided nutrients and an environment in which they can grow and proliferate (Guarner 2003). Intestinal microflora are responsible for providing the enzymes and biochemical pathways required for humans to obtain nutrients from polysaccharides, the most abundant food source on the planet (Bäckhed 2005). The microflora ferment these non-digestible carbohydrates into absorbable short-chain fatty acids. These microorganisms also affect lipid uptake and deposition (Sekirov et. al. 2010) and are responsible for the synthesis of vitamin K as well as the absorption of nutrients such as calcium, magnesium, and iron.
Approximately 80% of all immunoglobulin-producing cells in the body are located in the gastrointestinal tract, making it the body’s largest site of immunological response (Salminen 1998, Vighi 2008). The gastrointestinal microbiota is key to preventing foreign microbes, benign or otherwise, from becoming permanent residents. The mucosal immune system relies on the integrity of the intestinal epithelial layer as well as the system’s ability to readily discriminate commensal organisms from pathogenic bacteria. To this end, the microbiota are constantly competing for binding sites and food sources within the gastrointestinal tract interfering with colonization by crowding out the adhesion of potential pathogens.

Preservation of the microflora habitat is critical for the integrity of the intestinal epithelium barrier. Optimal function of the intestinal barrier relies on the commensal microbiota, the mucus gel layer, and the intestinal epithelium which form the first line of defense to provide a physical and chemical barrier. The gut bacteria help maintain the intestinal epithelium by supporting cell proliferation and differentiation within the epithelial cells (Guarner 2003). This epithelial cell differentiation is directed by the production of short chain fatty acids generated by the resident microflora in the large and small bowel. Consequently, the commensal microbiota impact the integrity of the physical barrier, influence the metabolic contributions to the host, as well as support the development of the immune system.

**Probiotic Microbiota Support**

Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host (World Health Organization). Probiotics provide numerous health benefits, including intestinal microbiota balance, digestive assistance and immune support, and impart these health benefits through many of the same mechanisms as the endogenous microflora.

Like endogenous microflora, probiotics directly compete with pathogens for epithelial binding sites on the cells as well as the mucus layer to support epithelial barrier integrity (Thomas 2010). Probiotics also help digest compounds to provide various essential nutrients to the host and produce short chain fatty acids that can modulate the luminal pH as well as influence apoptosis and cell diversity. Through apoptosis mitigation and mucin production, probiotics influence aspects of the epithelial barrier function (Gogineni 2013). Probiotics have been shown to directly release antimicrobial substances and to induce host cells to express them (Guarner 2003). All of this activity contributes to the strength of the epithelial barrier which in turn provides a defense against potential toxins and pathogens. Adaptive immune responses are also sensitive to probiotic activity influencing pathogen specific secretory IgA production as well as beneficial cytokine and chemokine production (Saad 2012).

The World Gastroenterology Organization (WGO) Practice Guidelines on Probiotics and Prebiotics concludes that the potential probiotic health benefits “can only be attributed to the strain or strains tested, and not to the species or the whole group of lactic acid bacteria or other probiotics.” It stands to reason that different organisms will have varying abilities to adhere to gastrointestinal mucosa, produce diverse antimicrobial substances, and employ different mechanisms to compete with pathogens among other strain specific features that may lead to overall health benefits. The amount of the probiotic strain delivered to the individual, the product matrix in which the probiotic is consumed, and the probiotic’s ability to survive the gastrointestinal tract are also important variables when evaluating the specific health benefits of probiotics (Ritchie 2012). Thus, acid and bile tolerance, the ability to survive the gastric and intestinal environment, as well as adherence to intestinal cells need to be considered (Goldin 2008) when evaluating probiotic strains.
**Lactobacillus rhamnosus GG**

*Lactobacillus rhamnosus GG* (ATCC 53103, LGG) is the most extensively studied probiotic strain since its identification in 1985 by Sherwood Gorbach and Barry Goldin. Seeking naturally occurring intestinal bacteria that could produce health benefits as a probiotic, *Lactobacillus rhamnosus GG* was the ideal candidate because of its ability to survive stomach acid and bile, adhere to human intestinal epithelial cells, and produce an antimicrobial substance that could support digestive and immune health. These features of *Lactobacillus rhamnosus GG* have been recognized in over 500 hundred scientific studies including over 200 human trials.

Adhesion is fundamental to competitive exclusion with respect to other microorganisms particularly in the case of pathogen competition, and *Lactobacillus rhamnosus GG* has been shown to survive the upper gastrointestinal tract allowing it to attach to intestinal epithelial cells. Several studies not only show that *Lactobacillus rhamnosus GG* survives the gastrointestinal tract but also demonstrate its ability to bind to the mucosal lining of the large intestine (Saxelin et. al. 1991, 1995 and 2010). These studies by Saxelin and colleagues examined the dose dependence of *Lactobacillus rhamnosus GG* survival and colonization (Saxelin 1991) as well as the effects of the delivery matrix (Saxelin 1995, 2010). They also compared other probiotics with respect to oral and fecal recovery (Saxelin 2010). In support of these findings, genomic analysis of *Lactobacillus rhamnosus GG* revealed pili containing a human-mucus binding protein (Kankainen 2009). *In vitro* studies have shown that *Lactobacillus rhamnosus GG* attachment is required for attenuation of the immune response (Lebeer 2012). Putative mechanisms of action for *Lactobacillus rhamnosus GG* include interference with enteropathogen colonization through competition, secretion of antibacterial substances, stimulation of intestinal epithelial cell proliferation and enhanced secretion of protective mucins (Mack 1999, 2003).

*Lactobacillus rhamnosus GG* has targeted and systemic effects on the immune system, all of which are mediated via the gastrointestinal tract. By influencing such processes of the humoral and cell-mediated immune response, along with important features of innate immunity, probiotics impact immune regulation (DiCaro 2005, Kekkonen 2008, Isolauri 2008). From a clinical perspective, *Lactobacillus rhamnosus GG* has been studied extensively in humans for a variety of uses including immune support, gastrointestinal benefits, and the amelioration of diarrhea. It has been found to be both safe and easy to administer. Practical experience from over 25 years of use in 40 countries confirms the large-scale safety and tolerability of *Lactobacillus rhamnosus GG* (Doron 2005).

A few areas in which the probiotic strain, *Lactobacillus rhamnosus GG*, has demonstrated relief include acute diarrhea, antibiotic-associated diarrhea (AAD), and *C. difficile* induced colitis (Goldin 2008). Although there may be many additional benefits, not all gastrointestinal concerns have been clinically tested and/or validated in children. To date, there is no clinical support for the use of *Lactobacillus rhamnosus GG* for constipation (Chmielewska 2010), Crohn’s disease (Bousvaros 2005), or ulcerative colitis (NASPGHAN 2006). This booklet contains selected *Lactobacillus rhamnosus GG* Research Abstracts highlighting research demonstrating its identified benefits for children.
The safety of *Lactobacillus rhamnosus* GG has been more extensively studied than the safety of any other probiotic bacterium. *Lactobacillus rhamnosus* GG, isolated from a healthy adult person, has a safe history of use in foods since 1990. Large epidemiological studies show that rapidly increasing consumption of the strain in Finland did not increase the incidence of *Lactobacillus or Lactobacillus rhamnosus* GG isolates in blood culture samples (Salminen 2002). A guideline document generated by European pediatric associations recommends the use of *Lactobacillus rhamnosus* GG for diarrhea in children (Guarino 2008) and a medical expert group additionally concluded in its report that probiotics are safe (Floch 2008), and that based on current knowledge, there is no need to restrict the use of them in any consumer groups.

The safety of *Lactobacillus rhamnosus* GG is supported by surveillance studies (Luoto 2010, Salminen 2004) that evaluated potential increases in clinical infections with increased probiotic consumption. Such studies showed that during a nine year period, despite a notable increase in *Lactobacillus rhamnosus* GG consumption (~10-fold) in Finland, the number of infections involving *Lactobacillus* species reported to Helsinki health authorities remained at a constant background level of 10-20 cases per year.

Dozens of clinical studies have demonstrated no adverse impact on nutritional, metabolic, or immune parameters. The *Lactobacillus rhamnosus* species has achieved Qualified Presumption of Safety (QPS) status from the Scientific Committee of European Food Safety Authority.

In healthy children, the use of *Lactobacillus rhamnosus* GG is safe and effective. Cases of bacteremia have occurred in patients with underlying immune compromise, chronic disease or debilitation (Whelan 2010). No reports have described sepsis related to probiotic use in otherwise healthy persons (Allen 2010, Gogineni 2013).

**Lactobacillus bacteremia, clinical significance, and patient outcome, with special focus on probiotic *L. rhamnosus* GG.**


*Lactobacillus* bacteremia is a rare entity, and its clinical significance is poorly defined. We have reviewed the risk factors and outcome for 89 case patients with *Lactobacillus* bacteremia. Species characterization was done in 53% of the cases, revealing 25 *L. rhamnosus* strains and 22 other *Lactobacillus* species. In 11 cases, the strain was identical with the probiotic *L. rhamnosus* GG. In 82% of the cases, the patients had severe or fatal comorbidities. Predisposing factors to bacteremia were immunosuppression, prior prolonged hospitalization, and prior surgical interventions. No significant differences were observed in these predisposing factors or clinical features between patients with cases associated with the various *Lactobacillus* species, other than higher C-reactive protein values in patients with *L. rhamnosus* bacteremia. Mortality was 26% at 1 month and was 48% at 1 year. In multivariate analysis, severe underlying diseases were a significant predictor for mortality (odds ratio [OR], 15.8), whereas treatment with antimicrobials effective *in vitro* was associated with lower mortality (OR, 0.22).

**CONCLUSIONS:** We conclude that lactobacilli in blood cultures are of clinical significance and that their susceptibility should guide decisions about antimicrobial treatment.
Lactobacillus bacteremia during a rapid increase in probiotic use of Lactobacillus rhamnosus GG in Finland.


Lactobacilli supposedly have low pathogenicity; they are seldom detected in blood culture. Lactobacillus rhamnosus GG, which originates indigenously in the human intestine, became available for use as a probiotic in 1990 in Finland. We evaluated the possible effects of the increased probiotic use of L. rhamnosus GG on the occurrence of bacteremia due to lactobacilli. Lactobacilli were isolated in 0.02% of all blood cultures and 0.2% of all blood cultures with positive results in Helsinki University Central Hospital and in Finland as a whole, and no trends were seen that suggested an increase in Lactobacillus bacteremia. The average incidence was 0.3 cases/100,000 inhabitants/year in 1995-2000 in Finland. Identification to the species level was done for 66 cases of Lactobacillus bacteremia, and 48 isolates were confirmed to be Lactobacillus strains. Twenty-six of these strains were L. rhamnosus, and 11 isolates were identical to L. rhamnosus GG.

CONCLUSIONS: The results indicate that increased probiotic use of L. rhamnosus GG has not led to an increase in Lactobacillus bacteremia.

Additional Resources: Studies in alternate (vulnerable) populations

Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: A randomised study.

The efficacy and safety of probiotic Lactobacillus rhamnosus GG on prolonged, noninfectious diarrhea in HIV patients on antiretroviral therapy: A randomized, placebo-controlled, crossover study.

Safety of Lactobacillus GG probiotic in infants with very low birth weight: twelve years of experience.
**Use/Indications**

*Lactobacillus rhamnosus* GG meets all the criteria of a probiotic: viable and stable; survives gastric, biliary and pancreatic digestion; colonizes host; and most importantly demonstrates a functional or clinical benefit to the host. The survival and persistence of a probiotic in the gastrointestinal tract is often demonstrated through fecal recovery following consumption. Fecal recovery of *Lactobacillus rhamnosus* GG has been demonstrated in healthy infants following consumption of infant formula supplemented with the strain at one hundred million, one billion and ten billion cfu/day (Petshcow 2005). The strain has also been recovered in healthy children from 1 to 6 years old, when they consumed about one hundred million cfu/day suspended in liquid milk (Hatakka 2001). Additionally, several studies have investigated fecal recovery in adults. One of the most recent studies compared different product forms and different probiotic strains (Saxelin 2010). In this study, there was no difference in the recovery of *Lactobacillus rhamnosus* GG when one billion cfu/day was consumed in yoghurt, cheese or capsule forms. Not only is *Lactobacillus rhamnosus* GG able to survive the gastrointestinal tract, but it actually adheres to the intestinal mucosa and epithelial cells, as demonstrated in biopsy samples taken during and after consumption (Alander 1999).

While these studies demonstrate that *Lactobacillus rhamnosus* GG can reach the large intestine, it may not be necessary for the bacteria to be recovered in feces for benefits to be realized. There is a lack of pharmacokinetic data investigating the ideal amount of supplementation required for a given intervention. When considering the sufficient daily amount of probiotic to evoke health benefits, it is appropriate to reference the demonstrated supplementation amounts used in previous clinical studies. A summary of the supplementation amounts of *Lactobacillus rhamnosus* GG demonstrated in various clinical studies is provided in Table 1.

**TABLE 1: SUMMARY of CLINICALLY DEMONSTRATED SUPPLEMENTATION**
[cfu/day in billions]

<table>
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<tr>
<th>Indication</th>
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<tr>
<td>General Diarrhea</td>
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<td></td>
<td>Hojsak, I., et al., 2010</td>
<td>1</td>
</tr>
<tr>
<td>Acute Diarrhea</td>
<td>Guandalini, S., et al., 2000</td>
<td>30</td>
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<td></td>
<td>Nixon, A.F., et al., 2012</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Basu, S., et al., 2009</td>
<td>20</td>
</tr>
<tr>
<td>Traveler’s Diarrhea</td>
<td>Oksanen, P.J., et al., 1990</td>
<td>2</td>
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<tr>
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<td>Arvola, T., et al., 1999</td>
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<td>Francavilla, R., et al., 2010</td>
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<td>Gawronska A., et al., 2007</td>
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<td></td>
<td>Bruzzese, E., et al., 2007</td>
<td>5</td>
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<td>Kalliomäki, M., et al., 2003</td>
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<tr>
<th>Pollen Allergy</th>
<th>Authors</th>
<th>cfu/day (billion)</th>
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<tbody>
<tr>
<td></td>
<td>Piirainen, L., et al., 2008</td>
<td>20</td>
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Lactobacillus rhamnosus GG: Abstracts
Examining Evidence-Based Clinical Applications
Diarrhea

Diarrhea can result from an imbalance in the normal intestinal microbiota resulting from diet, medications, pathogens, food sensitivities, and many other causes. As shown in numerous clinical trials, *Lactobacillus rhamnosus* GG has been shown to help rebalance such microbiota fluctuations. Selected studies in children are highlighted below.

Acute Infectious Diarrhea

The Effect of *Lactobacillus* GG on Acute Diarrheal Illness in the Pediatric Emergency Department.

*Nixon, A.F., et al., Pediatric Emergency Care, 2012 ; 28(10) : 1048-1051*

OBJECTIVE: The purpose of this study was to evaluate the effectiveness of the probiotic *Lactobacillus* GG (LGG) in reducing the duration of acute infectious diarrhea in the pediatric emergency department.

STUDY DESIGN: A double-blind, randomized controlled trial included children (6 months to 6 years) presenting to the pediatric emergency department with a complaint of diarrhea. Patients were randomized to receive either placebo or LGG powder twice daily for 5 days. With each dose, parents recorded the stool history in a home diary and were followed up daily by a blinded researcher. Groups were compared in terms of time to normal stool and number of diarrheal stools.

RESULTS: Of 155 patients enrolled, 129 completed the study: 63 in the LGG group and 66 in the placebo group. There was no significant difference in the median (interquartile range) time to normal stool (LGG: 60 hours [37–111] vs placebo: 74 hours [43–120]; P = 0.37) or the number of diarrheal stools (LGG: 5.0 [1–10] vs placebo: 6.5 [2–14]; P = 0.19). Among children who presented with more than 2 days of diarrhea, the LGG group returned to normal stool earlier (LGG: 51 hours [32–78] vs placebo: 74 hours [45–120]; P = 0.02), had fewer episodes of diarrheal stools (LGG: 3.5 [1.0–7.5] vs placebo: 7 [3.0–16.3]; P = 0.02), and were 2.2 times more likely to return to normal stool (95% confidence interval, 1.3–3.9; P = 0.01) compared with children in the placebo group.

CONCLUSIONS: *Lactobacillus* GG may reduce the duration of acute diarrheal illness among children presenting with more than 2 days of symptoms.
Diarrhea can result from an imbalance in the normal intestinal microbiota resulting from diet, medications, pathogens, food sensitivities, and many other causes. As shown in numerous clinical trials, Lactobacillus rhamnosus GG has been shown to help rebalance such microbiota fluctuations. Selected studies in children are highlighted below.

**Lactobacillus GG in the Prevention of Nosocomial Gastrointestinal and Respiratory Tract Infections.**

*Hojsak, I., et al., Pediatrics, 2010; 125:e1171-e1177*

**OBJECTIVE:** Investigate the role of LGG in preventing nosocomial gastrointestinal and respiratory tract infections at a pediatric hospital

**STUDY DESIGN:** A randomized, double-blind, placebo-controlled trial included 742 hospitalized children. For the duration of their hospitalization the children received either 10⁹ cfu in 100ml of fermented milk product or fermented milk product without LGG.

**RESULTS:** In the LGG group, compared with the placebo group, we found a significantly reduced risk for gastrointestinal infections (relative risk [RR]: 0.40 [95% confidence interval (CI): 0.25–0.70]; number needed to treat: 15 [95% CI: 9–34]), respiratory tract infections (RR: 0.38 [95% CI: 0.18–0.85]; number needed to treat: 30 [95% CI: 16–159]), vomiting episodes (RR: 0.5 [95% CI: 0.3–0.9]), diarrheal episodes (RR: 0.24 [95% CI: 0.10–0.50]), episodes of gastrointestinal infections that lasted >2 days (RR: 0.40 [95% CI: 0.25–0.70]), and episodes of respiratory tract infections that lasted >3 days (RR: 0.4 [95% CI: 0.2–0.9]). Groups did not differ in hospitalization duration (P = .1).

**CONCLUSIONS:** LGG administration can be recommended as a valid measure for decreasing the risk for nosocomial gastrointestinal and respiratory tract infections in pediatric facilities.

**Acute Infectious Diarrhea**

*The Effect of Lactobacillus GG on Acute Diarrheal Illness in the Pediatric Emergency Department.*

*Nixon, A.F., et al., Pediatric Emergency Care, 2012; 28(10):1048-1051*

**OBJECTIVE:** The purpose of this study was to evaluate the effectiveness of the probiotic Lactobacillus GG (LGG) in reducing the duration of acute infectious diarrhea in the pediatric emergency department.

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**CONCLUSIONS:** Lactobacillus GG may reduce the duration of acute diarrheal illness among children presenting with more than 2 days of symptoms.
Efficacy of high-dose *Lactobacillus rhamnosus* GG in controlling acute watery diarrhea in Indian children: a randomized controlled trial.


**OBJECTIVE:** To evaluate the effective dose of *Lactobacillus rhamnosus* GG (LGG) as probiotic in acute watery diarrhea (AWD) in Indian children.

**STUDY DESIGN:** All hospitalized patients of AWD admitted over 1 year were randomized into 3 groups to receive either only oral rehydration solution (ORS) (group A/control, n=185), ORS+LGG powder containing 10^{10} colony forming units (CFU) (group B, n=188), or ORS+LGG powder containing 10^{12} CFU (group C, n=186) twice daily for a minimum period of 7 days or until diarrhea stopped along with correction of dehydration. The duration and frequency of diarrhea and vomiting were studied.

**RESULTS:** The frequency and duration of diarrhea, requirement for intravenous therapy, and hospital stay were significantly lower in both the intervention groups compared with the controls. There was no significant difference between the 2 intervention groups. No complication was observed from the doses of LGG used.

**CONCLUSIONS:** Both the doses of LGG (10^{10} and 10^{12} CFU) were equally effective to decrease the frequency and duration of diarrhea and reduction in hospital stay in patients of AWD.
Effect of *Lactobacillus rhamnosus* GG in persistent diarrhea in Indian children: a randomized controlled trial.


**OBJECTIVE:** To evaluate the role of *Lactobacillus rhamnosus* GG (LGG) as probiotic in persistent diarrhea (PD) in children of North Bengal, India.

**STUDY DESIGN:** All patients of PD admitted over a period of 2 years were included in the study as per predefined inclusion criteria. For this double-blind, controlled trial the participants were randomized to receive oral rehydration solution (ORS) alone, or ORS plus LGG powder containing 60 million cells, twice daily for a minimum period of 7 days or till diarrhea has stopped along with correction of dehydration with ORS and/or intravenous fluids as per WHO protocol and antibiotics in culture positive patients.

**RESULTS:** The study comprised of 235 patients randomized into 2 groups, cases (117) and controls (118). Both the groups were similar with respect to age, number of breastfed infants, presentation with dehydration, degree of protein energy malnutrition, and distribution of infections. Stool culture was positive in 90 (38.3%) patients, *Escherichia coli* being the commonest organism followed by *Shigella spp.* and *Clostridium difficile*. The mean duration of diarrhea was significantly lower in the cases than in controls (5.3 vs. 9.2 d). The average duration of hospital stay was also significantly lesser in cases. No complication was observed from the dose of LGG used.

**CONCLUSIONS:** LGG (dose of 120 million cfu) could decrease the frequency and duration of diarrhea and vomiting and reduced hospital stay in patients with persistent diarrhea.
**Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial.**  

**OBJECTIVE:** Evaluate the efficacy of *Lactobacillus GG* administered in the oral rehydration solution to patients with acute-onset diarrhea of all causes.

**STUDY DESIGN:** Children 1 month to 3 years of age with acute-onset diarrhea were enrolled in a double-blind, placebo-controlled investigation. Patients were randomly allocated to group A (n=140), receiving oral rehydration solution plus placebo, or group B (n=147), receiving the same preparation but with a live preparation of *Lactobacillus GG* (at least $10^{10}$ CFU/250 ml). After rehydration in the first 4 to 6 hours, patients were offered their usual feedings plus free access to the same solution until diarrhea stopped.

**RESULTS:** Duration of diarrhea after enrollment was 71.9 +/- 35.8 hours in group A versus 58.3 +/- 27.6 hours in group B (mean +/- SD; P = 0.03). In rotavirus-positive children, diarrhea lasted 76.6 +/- 41.6 hours in group A versus 56.2 +/- 16.9 hours in group B (P < 0.008). Diarrhea lasted longer than 7 days in 10.7% of group A versus 2.7% of group B patients (P < 0.01). Hospital stays were significantly shorter in group B than in group A.

**CONCLUSIONS:** Administering oral rehydration solution containing *Lactobacillus GG* to children with acute diarrhea is safe and results in shorter duration of diarrhea, less chance of a protracted course, and faster discharge from the hospital. The effect is more evident in, but not limited to, rotavirus-positive patients.

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**LGG Significantly Reduces the Duration of Diarrhea in Rotavirus-Infected Children**

![Graph showing duration of diarrhea](Guandalini S et al. J Pediatr Gastroenterol Nutr. 2000;30(1):54-60. Subcohort analysis. Please see full explanation in article.)

- 76.6 +/- 41.6 hours (ORS + placebo)
- 52.2 +/- 16.9 hours (ORS + LGG)

P = 0.008
Additional Resources: Reviews, null results, studies of related organisms and additional populations

Szajewska, H., et al., Alimentary Pharmacology and Therapeutics, 2013; 467-476

Review article: the management of acute gastroenteritis in children.

Szajewska, H., et al., Alimentary Pharmacology and Therapeutics, 2011; 1079-1087

Dose-dependent effect of *Lactobacillus rhamnosus* on quantitative reduction of faecal rotavirus shedding in children.

Efficacy of *Lactobacillus rhamnosus* GG in acute watery diarrhea of Indian children: A randomized controlled trial.

Effective prophylaxis against rotavirus diarrhea using a combination of *Lactobacillus rhamnosus* GG and antibodies.

A placebo-controlled trial of *Lactobacillus* GG to prevent diarrhea in undernourished Peruvian children.
Antibiotic-Associated Diarrhea

*Lactobacillus GG* in the prevention of antibiotic-associated diarrhea in children.


**OBJECTIVE:** The objective of this study was to determine the efficacy of *Lactobacillus casei* sps. *rhamnosus* (*Lactobacillus GG*) (LGG) in reducing the incidence of antibiotic-associated diarrhea when coadministered with an oral antibiotic in children with acute infectious disorders.

**STUDY DESIGN:** Two hundred two children between 6 months and 10 years of age were enrolled; 188 completed all phases of the protocol. LGG, $1 \times 10^{10}$ - $2 \times 10^{10}$ colony forming units per day, or comparable placebo was administered in a double-blind randomized trial to children receiving oral antibiotic therapy in an outpatient setting. The primary caregiver was questioned every 3 days regarding the incidence of gastrointestinal symptoms, predominantly stool frequency and consistency, through telephone contact by blinded investigators.

**RESULTS:** Twenty-five placebo-treated but only 7 LGG-treated patients had diarrhea as defined by liquid stools numbering 2 or greater per day. *Lactobacillus GG* overall significantly reduced stool frequency and increased stool consistency during antibiotic therapy by the tenth day compared with the placebo group.

**CONCLUSION:** *Lactobacillus GG* reduces the incidence of antibiotic-associated diarrhea in children treated with oral antibiotics for common childhood infections.

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**LGG Reduces the Incidence of Antibiotic-Associated Diarrhea in Children**

| Percentage of children treated with antibiotics who developed diarrhea |
|-----------------------------|-----------------------------|
| Placebo-treated children    | LGG-treated children        |
| 0                           | 5                           |
| 5                           | 10                          |
| 10                          | 15                          |
| 15                          | 20                          |
| 20                          | 25                          |
| 25                          | 30                          |

Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study.

OBJECTIVE: Evaluate the incidence of diarrhea after antimicrobial treatment in children with no history of antimicrobial use during the previous 3 months. Another aim of this study was to assess the preventive potential of Lactobacillus rhamnosus GG (Lactobacillus GG; American Type Culture Collection 53103), a probiotic strain with a documented safety record and a therapeutic effect in viral gastroenteritis on antibiotic-associated diarrhea.

STUDY DESIGN: Oral antimicrobial agents were prescribed for the treatment of acute respiratory infections at the clinics of the Health Care Center of the City of Tampere or Tampere University Hospital, Finland, to 167 patients who were invited to participate in the study. The final study population consisted of 119 children from 2 weeks to 12.8 years of age (mean: 4.5 years). The patients were randomized to receive placebo or 2 x 10^10 colony-forming units of Lactobacillus GG in capsules given twice daily during the antimicrobial treatment. The parents kept a daily symptom diary and recorded stool frequency and consistency at home for 3 months. In the case of diarrhea, viral (adenovirus, rotavirus, calicivirus and astrovirus) and bacterial (Salmonella, Shigella, Yersinia, Campylobacter, Clostridium difficile, Staphylococcus aureus, and yeasts) analyses were studied in fecal samples. The primary outcome measure was diarrhea during the first 2 weeks after the beginning of the antimicrobial treatment, because this period most likely reflects the effects of antimicrobial use. Secondary outcome measures were the activities of fecal urease, beta-glucuronidase, and beta-glucosidase.

RESULTS: On the entire follow-up, 80% of any gastrointestinal symptoms were reported during the first 2 weeks after the beginning of the antimicrobial treatment. The incidence of diarrhea was 5% in the Lactobacillus GG group and 16% in the placebo group within 2 weeks of antimicrobial therapy (chi(2) = 3.82). The treatment effect (95% confidence interval) of Lactobacillus GG was -11% (-21%–0%). In diarrheal episodes, the viral and bacterial analyses were positive for Clostridium difficile in 2 cases and for Norwalk-like calicivirus in 3 cases. The age of the patients with diarrhea was between 3 months and 5 years in 75% of cases in both groups. The severity of diarrhea was comparable in the study groups, as evidenced by similar stool frequency (mean: 5 per day; range: 3-6) and the duration of diarrhea (mean: 4 days; range: 2-8). The activities of fecal urease and beta-glucuronidase, but not beta-glucosidase, changed significantly after the beginning of the antimicrobial treatment in the Lactobacillus GG group and in the placebo group alike.

CONCLUSIONS: Lactobacillus GG reduces the risk of antibiotic-associated diarrhea in children.
Additional Resources: Reviews, null results

Szajewska, H., et al., Alimentary Pharmacology and Therapeutics, 2013; 467-476

Review article: the management of acute gastroenteritis in children.

Szajewska, H., et al., Alimentary Pharmacology and Therapeutics, 2011; 1079-1087

Randomized, double-blind, placebo-controlled trial: Effect of *Lactobacillus* GG supplementation on Helicobacter pylori eradication rates and side effects during treatment in children.

Clinical Trial: Effectiveness of *Lactobacillus rhamnosus* (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhea in children.
Gastrointestinal Distress

A variety of symptoms associated with gastrointestinal distress have been seen beyond diarrhea. Probiotics, specifically *Lactobacillus rhamnosus* GG, have been shown to assist with abdominal pain in children irrespective of a diagnosis. It is suspected that inflammation may be responsible for these discomforts and that *Lactobacillus rhamnosus* GG may help address the inflammatory response.

Abdominal Pain

A Randomized Controlled Trial of *Lactobacillus* GG in Children with Functional Abdominal Pain.

*Francavilla, R., et al., Pediatrics, 2010; 126(6):e1445-e1452*

**OBJECTIVE:** To determine whether LGG relieves symptoms in children with recurrent abdominal pain

**STUDY DESIGN:** Randomized, double-blind, placebo controlled trial involving 141 children with irritable bowel syndrome or functional pain. Children received LGG (6 x 10⁹ cfu/day) or placebo for 8 weeks, preceded by a 4 week run-in, and followed for an additional 8 weeks.

**RESULTS:** Compared with baseline, LGG caused a significant reduction of frequency (P<0.01) and severity (P<0.01) of abdominal pain. The differences were still significant during follow-up (P<0.02 and P<0.001, respectively). At week 12, LGG demonstrated improvement in 48 children as compared to 37 children in the placebo group (P<0.03). This difference was also significant at the end of the follow-up (week 16, P<0.03). Intestinal permeability test results were significantly improved in the LGG group (P<0.03); mainly in children with IBS.

**CONCLUSIONS:** LGG significantly reduces the frequency and severity of abdominal pain in children with IBS; this effect is sustained and may be secondary to improvement of the gut barrier.
A randomized double-blind placebo-controlled trial of *Lactobacillus GG* for abdominal pain disorders in children.

**OBJECTIVE:** To determine the efficacy of *Lactobacillus rhamnosus* GG (LGG) for treating FAPD in children.

**STUDY DESIGN:** A total of 104 children who fulfilled the Rome II criteria for functional dyspepsia (FD), or irritable bowel syndrome (IBS), or functional abdominal pain (FAP) were enrolled in a double-blind, randomized controlled trial in which they received LGG (n = 52), or placebo (n = 52) for 4 weeks.

**RESULTS:** For the overall study population, those in the LGG group were more likely to have treatment success (no pain) than those in the placebo group (25% vs. 9.6%, relative benefit (RB) 2.6, 95% confidence interval (CI): 1.05-6.6, number needed to treat (NNT) 7, 95% CI: 4-123). For children with IBS (n = 37), those in the LGG group were more likely to have treatment success than those in the placebo group (33% vs. 5%, RB 6.3, 95% CI: 1.2-38, NNT 4, 95% CI: 2-36) and reduced frequency of pain (P = 0.02), but not pain severity (P = 0.10). For the FD group (n = 20) and FAP group (n = 47), no differences were found.

**CONCLUSIONS:** The LGG appears to moderately increase treatment success, particularly among children with IBS.

**Additional Resources:** Reviews, null result
Probiotics in bloating distention and irritable bowel syndrome—from clinical evidence to guidelines.


The Use of *Lactobacillus* GG in Irritable Bowel Syndrome in Children: A double-blind, randomized control trial.
Travelers’ Diarrhea

Prevention of travellers’ diarrhoea by *Lactobacillus GG*.

**OBJECTIVE:** To assess the efficacy of *Lactobacillus GG* in preventing travelers’ diarrhea.

**STUDY DESIGN:** A placebo-controlled double-blind study was conducted on 820 persons (10-80 years of age) travelling to two destinations in southern. The participants were randomized into two groups receiving either *Lactobacillus GG* (2x10⁹ cfu/day) or placebo in identical sachets. On the return flight each participant completed a questionnaire indicating the incidence of diarrhea and related symptoms during the trip.

**RESULTS:** Of the original group 756 (92%) subjects completed the study acceptably. The overall incidence of diarrhea was 43.8% (331 cases). The total incidence of diarrhea in the placebo group was 46.5% and in the *Lactobacillus GG* 41.0% indicating an overall protection of 11.8%. Protection rates varied between two different destinations with the maximum protection rate reported as 39.5%. Among older age groups there was significantly less diarrhea when compared to younger travelers.

**CONCLUSIONS:** *Lactobacillus GG* appeared to be effective in reducing the occurrence of travelers’ diarrhea in one of the two destinations with no side effects.

The Daily Risk of Travel-related Diarrhea is Significantly Reduced When Travelers Take LGG

![Graph showing the daily risk of diarrhea](image)

- Placebo-treated travelers
- LGG-treated travelers

*P = 0.05*
Additional Resources: Review, study of additional populations

Traveling with Infants and Young Children. Part III: Travelers’ Diarrhea.

Efficacy of Lactobacillus GG as a diarrheal preventive in travelers.
It has been estimated that over two thirds of all the lymphocytes of the human body are located in the intestinal epithelial and sub-epithelial layers. The mucosal immune system acts as the first line of defense reducing the need for systemic immunity to help maintain the health of the host. The mucosal immune system has the difficult task of maintaining the balance between supporting the multitude of protective immune responses against infectious agents, and tolerating the load of antigens present in the intestinal lumen. *Lactobacillus rhamnosus* GG has been demonstrated to benefit innate and adaptive immune responses by contributing to the integrity of the intestinal epithelial barrier and to the cellular immune response.

**An Evaluation of the Ability of the Probiotic Strain *Lactobacillus rhamnosus* GG to Eliminate the Gastrointestinal Carrier State of Vancomycin-resistant Enterococci in Colonized Children.**


**OBJECTIVE:** To evaluate the efficacy of *Lactobacillus rhamnosus* GG (LGG) supplementation in eliminating the gastrointestinal carrier state of vancomycin-resistant enterococci (VRE) in colonized children, and to evaluate the effect of the probiotic on *Lactobacillus* spp. counts in the gastrointestinal tract.

**STUDY DESIGN:** A randomized, single-blind, placebo-controlled study. Children (0 to 18 y old) hospitalized at the wards of the children’s hospital who were diagnosed with gastrointestinal carrier state of VRE were randomized to group receiving 3 billion colony forming unit of LGG/day or placebo for 21 consecutive days. A total of 61 children completed the study (32 in the treatment group and 29 in the control group). Rectal swabs for VRE and *Lactobacillus* spp. were collected at baseline, during supplementation at weekly intervals and 1 month after supplementation. Antibiotic supply was controlled throughout the duration of the analysis.

**RESULTS:** A significant difference in the number of children colonized with VRE between the groups was observed at 3 weeks (P=0.002). The VRE carrier state was lost by 20 of 32 participants in the treatment group and 7 of 29 in the control group. We also observed increased gastrointestinal counts of *Lactobacillus* spp. in children receiving LGG. A statistically significant difference in the occurrence of bacteria was observed from week 1 onwards, whereas in the aspect of growth intensity from week 2 onwards.

**CONCLUSIONS:** LGG supplementation temporarily eliminates the VRE carrier state and increases gastrointestinal counts of *Lactobacillus* spp. in children versus placebo.
**Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: A randomized, double-blind, placebo-controlled trial.**

*Hojsak, I., et al., Clin Nutr. 2010; 29:312-316*

**OBJECTIVE:** To investigate the role of *Lactobacillus* GG (LGG) in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers.

**STUDY DESIGN:** Randomized, double-blind, placebo-controlled trial in 281 children who attend day care centers. They were randomly allocated to receive LGG at a dose of $10^9$ colony-forming units in 100ml of a fermented milk product (LGG group, n=139) or placebo that was the same post-pasteurized fermented milk product without LGG (placebo group, n=142) during the 3-month intervention period.

**RESULTS:** Compared to the placebo group, children in the LGG group had a significantly reduced risk of upper respiratory tract infections (RR 0.66, 95% CI 0.52 to 0.82, NNT 5, 95% CI 4 to 10), a reduced risk of respiratory tract infections lasting longer than 3 days (RR 0.57, 95% CI 0.41 to 0.78, NNT 5, 95% CI 4 to 11), and a significantly lower number of days with respiratory symptoms (p<0.001). There was no risk reduction in regard to lower respiratory tract infections (RR 0.82, 95% CI 0.24 to 2.76). Compared with the placebo group, children in the LGG group had no significant reduction in the risk of gastrointestinal infections (RR 0.63, 95% CI 0.38 to 1.06), vomiting episodes (RR 0.60, 95% CI 0.29 to 1.24), and diarrheal episodes (RR 0.63, 95% CI 0.35 to 1.11) as well as no reduction in the number of days with gastrointestinal symptoms (p=0.063).

**CONCLUSION:** LGG administration can be recommended as a valid measure for decreasing the risk of upper respiratory tract infections in children attending day care centers.
Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial.

OBJECTIVE: To examine whether long term consumption of a probiotic milk could reduce gastrointestinal and respiratory infections in children in day care centres.

STUDY DESIGN: Randomised, double blind, placebo controlled study was conducted over seven months in 18 day care centres in Helsinki, Finland. Healthy children (n=571 aged 1-6 years: 282 (mean (SD) age 4.6 (1.5) years) in the intervention group and 289 (mean (SD) age 4.4 (1.5) years) in the control group. Intervention: Milk with or without Lactobacillus GG. Average daily consumption of milk in both groups was 260 ml (1.3 to 2.6x10⁸ cfu/day). Number of days with respiratory and gastrointestinal symptoms, absences from day care because of illness, respiratory tract infections diagnosed by a doctor, and course of antibiotics were assessed.

RESULTS: Children in the Lactobacillus group had fewer days of absence from day care because of illness (4.9 (95% confidence interval 4.4 to 5.5) v 5.8 (5.3 to 6.4) days, 16% difference, \( P=0.03 \); age adjusted 5.1 (4.6 to 5.6) v 5.7 (5.2 to 6.3) days, 11% difference, \( P=0.09 \)). There was also a relative reduction of 17% in the number of children suffering from respiratory infections with complications and lower respiratory tract infections (unadjusted absolute % reduction -8.6 (-17.2 to -0.1), \( P=0.05 \); age adjusted odds ratio 0.75 (0.52 to 1.09), \( P=0.13 \)) and a 19% relative reduction in antibiotic treatments for respiratory infection (unadjusted absolute % reduction -9.6 (-18.2 to -1.0), \( P=0.03 \); adjusted odds ratio 0.72 (0.50 to 1.03), \( P=0.08 \)) in the Lactobacillus group.

CONCLUSIONS: Lactobacillus GG may reduce respiratory infections and their severity among children in day care. The effects of the probiotic Lactobacillus GG were modest but consistently in the same direction.
Effect of *Lactobacillus GG* supplementation on pulmonary exacerbations in patients with cystic fibrosis: a pilot study.


**OBJECTIVE:** To determine the effects of *Lactobacillus GG* (LGG) on pulmonary exacerbations in cystic fibrosis (CF).

**STUDY DESIGN:** A prospective, randomized, placebo-controlled, cross-over study was performed. Nineteen children received LGG for 6 months and then shifted to oral rehydration solution (ORS) for 6 months. In parallel nineteen received ORS and then shifted to LGG. Main outcome parameters were: incidence of pulmonary exacerbations and of hospital admissions, forced expiratory volume (FEV1), and modifications of body weight.

**RESULTS:** Patients treated with LGG showed a reduction of pulmonary exacerbations (Median 1 vs. 2, range 4 vs. 4, median difference 1, CI 95% 0.5-1.5; p=0.0035) and of hospital admissions (Median 0 vs. 1, range 3 vs. 2, median difference 1, CI 95% 1.0-1.5; p=0.001) compared to patients treated with ORS. LGG resulted in a greater increase in FEV1 (3.6% +/- 5.2 vs. 0.9% +/- 5; p=0.02) and body weight (1.5 kg +/- 1.8 vs. 0.7 kg +/- 1.8; p=0.02).

**CONCLUSIONS:** LGG reduces pulmonary exacerbations and hospital admissions in patients with CF. These suggest that probiotics may delay respiratory impairment and that a relationship exists between intestinal and pulmonary inflammation.

**Additional Resources: Studies in alternate populations**

Probiotic intervention has strain-specific anti-inflammatory effects in healthy adults.

Modulation of humoral immune response through probiotic intake.

Enhancement of the circulating antibody secreting cell response in human diarrhea by a human *Lactobacillus* strain.
Effect of *Lactobacillus rhamnosus* GG on rBet v1 and rMal d1 specific IgA in the saliva of patients with birch pollen allergy.

_Piiainen, L., et al., Annals of Allergy, Asthma & Immunology, 2008; 100(4):338-342_  
_Volume 100, Issue 4, April 2008, Pages 338–342_

**OBJECTIVE:** To study the effects of LGG on the oral immune response in adolescents and adults with birch pollen allergy combined with oral allergy syndrome.

**STUDY DESIGN:** Patients received either LGG (n = 19) or a placebo (n = 19) for 5.5 months (from February 8 to August 6, 1999), starting 2.5 months before the birch pollen season. An oral apple challenge test was performed before, during, and after the pollen season. Saliva samples were collected before and after the challenges, and serum samples were collected before the challenges. Total IgA, IgG, and IgM and rBet v1 and rMal d1 specific IgA, IgG, IgG1, and IgG4 levels were measured from saliva with an enzyme-linked immunosorbent assay (ELISA). Serum rBet v1 specific IgE ELISA and birch radioallergosorbent testing were performed.

**RESULTS:** After 5.5 months, rBet v1 and rMal d1 specific IgA levels had increased from baseline in the LGG compared with the placebo group (Δ rBet v1 IgA, 0.319 vs −0.136 relative units; _P_ = .02; Δ rMal d1 IgA, 0.097 vs −0.117, _P_ = .02). rBet v1 specific IgE serum levels did not differ between the groups. In the LGG group, rBet v1 specific IgE levels correlated positively with stimulated total IgA (_P_ = .04) and IgG (_P_ = .003) in saliva. In the placebo group, rBet v1 specific IgE levels correlated negatively with stimulated rBet v1 and rMal d1 IgA levels (_P_ = .009 for both) and IgG (_P_ = .02 and _P_ = .03, respectively).

**CONCLUSIONS:** LGG showed immunostimulating effects on oral mucosa seen as increased allergen specific IgA levels in saliva.
Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial.


OBJECTIVE: To investigate whether the preventive effect of Lactobacillus on atopic disease extends beyond infancy, we re-examined the cohort at the age of 4 years. Perinatal administration of the probiotic Lactobacillus rhamnosus strain GG (ATCC 53103), reduces incidence of atopic eczema in at-risk children during the first 2 years of life (infancy).

STUDY DESIGN: A follow-up study to Kalliomaki, et al. Briefly, mothers were randomly allocated to receive two capsules of placebo (microcrystalline cellulose) or $1 \times 10^{10}$ cfu of LGG daily for 4 weeks before expected delivery then postnatally for 6 months. Atopic disease was diagnosed on the basis of a questionnaire and a clinical examination.

RESULTS: Fourteen of 53 children receiving lactobacillus had developed atopic eczema, compared with 25 of 54 receiving placebo (relative risk 0.57, 95% CI 0.33-0.97).

CONCLUSIONS: Results suggest that the preventive effect of Lactobacillus GG on atopic eczema extends beyond infancy.
Additional Resources: Review, null study and studies in alternate populations

Formula Selection for Management of Children with Cow's Milk Allergy Influences the Rate of Acquisition of Tolerance: A Prospective Multicenter Study.

Effect of *Lactobacillus GG* on tolerance acquisition in infants with cow's milk allergy:A randomized trial.

The Potential Therapeutic Efficacy of *Lactobacillus GG* in Children with Food Allergies.

Helin, T., et al., Allergy, 2002; 57:243-26

Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial.

Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants.

*Lactobacillus GG* effect in increasing IFN-gamma production in infants with cow's milk allergy.

Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial
Conclusion

*Lactobacillus rhamnosus* GG, a naturally occurring strain of intestinal bacteria that was isolated from a healthy adult, is the most researched probiotic strain in the world. As a result of more than 25 years of research, there have been numerous product applications based on *Lactobacillus rhamnosus* GG including supplements, fermented dairy products, and infant formulas. Products containing *Lactobacillus rhamnosus* GG have been on the market since 1990 and have been safely used in the general population. Clinically, *Lactobacillus rhamnosus* GG has been shown to provide immune and digestive support by actively contributing to the intestinal microbiota. Digestive and immune benefits range from improving nutrient absorption to modulating specific immune responses. While the extent of the benefits that *Lactobacillus rhamnosus* GG can provide has not been fully studied in children to date, the positive body of evidence in other populations is compelling and continues to grow. In the following Appendices, additional studies in alternate populations are provided that go beyond conditions studied in children, one to eighteen years old.
APPENDIX A: Selected Resources: *Lactobacillus rhamnosus* GG and related probiotics in Infants and Pregnancy

Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: A prospective multicenter study.

Probiotic Administration in Early Life, Atopy, and Asthma: A Meta-analysis of Clinical Trials

Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by *Lactobacillus* casei GG.

Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial.

Effect of probiotics on vaccine antibody responses in infancy—a randomized placebo-controlled double-blind trial.

Safety of *Lactobacillus* GG probiotic in infants with very low birth weight: twelve years of experience.

Interaction of orally administered *Lactobacillus rhamnosus* GG with skin and gut microbiota and humoral immunity in infants with atopic dermatitis.
Nermes, M., *et al.*, Clinical and Experimental Allergy. 2010; 41:370-377

Specific probiotics in reducing the risk of acute infections in infancy—a randomised, double-blind, placebo-controlled study.

Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant.

Effect of probiotics and breastfeeding on the *Bifidobacterium* and *Lactobacillus*/*Enterococcus* microbiota and humoral immune responses.

Administration of oral probiotic bacteria to pregnant women causes temporary infantile colonization.
Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants.

Growth during the first 6 months of life in infants using formula enriched with Lactobacillus rhamnosus GG: double-blind, randomized trial.

Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome.

APPENDIX B: Selected Resources: Supporting information regarding Lactobacillus rhamnosus GG in Adults

Effect of Lactobacillus GG supplementation on antibiotic-associated gastrointestinal side effects during Helicobacter pylori eradication therapy: a pilot study.

Treatment of relapsing Clostridium difficile diarrhea with Lactobacillus GG.

Probiotic bacteria stimulate virus-specific neutralizing antibodies following a booster polio vaccination.

Effects of Lactobacillus GG on genes expression pattern in small bowel mucosa.

Effect of Lactobacillus ingestion on the gastrointestinal mucosal barrier alterations induced by indometacin in humans.

The effect of probiotics on respiratory infections and gastrointestinal symptoms during training in marathon runners.

Probiotic treatment of vancomycin-resistant enterococci: a randomised controlled trial.
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