Study summaries LGG®

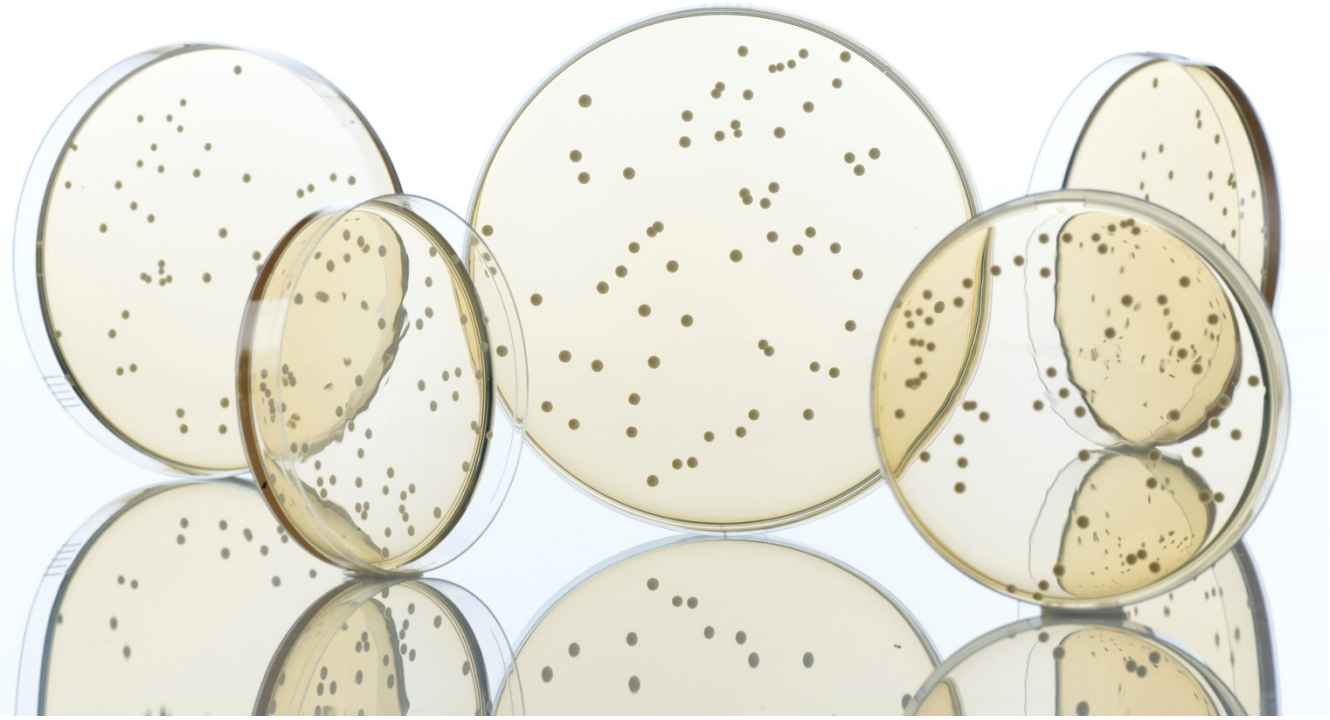
This binder provides you with summaries of selected publications on *L. rhamnosus* LGG® - one of the best documented probiotic strains.

The publications are clinical studies performed in humans documenting the effects in various conditions.

December 2012

Chr. Hansen A/S

Human Health & Nutrition



Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 2 billion
Product formulation: Sticks
Reference number: 1448

Smith, et al. Effect of Lactobacillus rhamnosus LGG(R) and Bifidobacterium animalis ssp. lactis BB-12(R) on health-related quality of life in college students affected by upper respiratory infections. Br.J.Nutr. 2012:1-9

Abstract: College students are susceptible to upper respiratory infections (URI) due to inadequate sleep, stress and close living quarters. Certain probiotic strains modulate immune function and may improve health-related quality of life (HRQL) during URI. The present study recruited apparently healthy college students and assessed the effect of probiotics on HRQL outcomes (i.e. self-reported duration, symptom severity and functional impairment of URI) in those who developed URI. Missed school and work days due to URI were also considered. Subjects (n 231) were apparently healthy college students living on campus in residence halls at the Framingham State University (Framingham, MA, USA), and were randomised to receive placebo (n 117) or probiotic-containing powder (daily dose of minimum 1 billion colony-forming units of each Lactobacillus rhamnosus LGG® (LGG®) and Bifidobacterium animalis ssp. lactis BB-12® (BB-12®); n 114) for 12 weeks. Subjects completed The Wisconsin Upper Respiratory Symptom Survey-21 to assess HRQL during URI. The final analyses included 198 subjects (placebo, n 97 and probiotics, n 101). The median duration of URI was significantly shorter by 2 d and median severity score was significantly lower by 34 % with probiotics v. placebo (P < 0·001), indicating a higher HRQL during URI. Number of missed work days was not different between groups (P = 0·429); however, the probiotics group missed significantly fewer school days (mean difference = 0·2 d) compared to the placebo group (P = 0·002). LGG® and BB-12® may be beneficial among college students with URI for mitigating decrements in HRQL. More research is warranted regarding mechanisms of action associated with these findings and the cost-benefit of prophylactic supplementation.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Other
Research subfield: Metabolic status
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 0756

Aaltonen, et al. Impact of maternal diet during pregnancy and breastfeeding on infant metabolic programming: a prospective randomized controlled study. Eur.J.Clin.Nutr. 2011;65:10-.

Abstract: Objectives:To evaluate the impact of maternal diet and intensive dietary counselling during pregnancy and breastfeeding on the infant's metabolic status.Subjects/Methods:At the first trimester of pregnancy, 256 women were randomized into a control/placebo group and two dietary counselling groups (diet/probiotics and diet/placebo). The counselling, with double-blind randomization to probiotics (Lactobacillus rhamnosus GG and Bifidobacterium lactis BB-12) or placebo, targeted excessive saturated fat and low fibre consumption. Maternal diet was evaluated repeatedly during pregnancy and postpartum by means of 3 days' food diaries. Metabolic markers, serum 32-33 split and intact proinsulin, leptin/adiponectin ratio, skinfold thickness and waist circumference were measured of 194 healthy infants at the age of 6 months, and the high levels were taken to mirror adverse metabolic status.Results:The proportion of infants with a high 32-33 split proinsulin was significantly lower in dietary counselling with probiotics (n=6/62, 9.7%) or placebo (n=7/69, 10.1%) compared with the control/placebo group (n=17/63, 27.0%). The high split proinsulin was associated with larger skinfold thickness, waist circumference and higher leptin/adiponectin ratio in the infants (P<0.05). With respect to maternal diet during pregnancy, the highest and lowest tertiles of fat intake increased the infant's risk of high split proinsulin, whereas those of butter associated correspondingly with the infant's waist circumference. Further, breastfed infants showed a reduced risk of high split proinsulin and leptin/adiponectin ratio compared with formula-fed infants.Conclusions:Modification of maternal diet during pregnancy and breastfeeding may benefit infant metabolic health. High split proinsulin reflects adverse metabolic status in infancy, which can be improved by early dietary counselling.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 1319

Hoppu, et al. Probiotics and dietary counselling targeting maternal dietary fat intake modifies breast milk fatty acids and cytokines. Eur.J.Nutr. 2011:.

Abstract: PURPOSE: Breast milk fatty acids possess immunomodulatory properties, and new intervention strategies beyond supplementation of maternal diet with single oils are called for. The objective of the present study was to evaluate the effect of dietary intervention during pregnancy and breastfeeding on breast milk fatty acid and cytokine composition. METHODS: Pregnant women were randomised into three study groups: dietary intervention with probiotics (diet/probiotic) or with placebo (diet/placebo) and a control group (control/placebo). Dietary intervention included dietary counselling and provision of rapeseed oil-based food products. The probiotics used were Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 in combination. Dietary intake was evaluated by food records at every trimester of pregnancy and 1 month postpartum. Breast milk samples were collected after birth (colostrum) and 1 month after delivery for fatty acid and cytokine analysis (n = 125). RESULTS: Dietary intervention improved the quality of fat in the diet. In breast milk, the proportion of Î±-linolenic acid and total n-3 fatty acids was higher in both dietary intervention groups compared with control group ($p < 0.05$). In the diet/probiotic group, the Î³-linolenic acid content was higher compared with the diet/placebo group ($p < 0.05$). The concentrations of TNF-Î±, IL-10, IL-4 and IL-2 were higher in both dietary intervention groups compared with controls, and furthermore, long-chain n-3 fatty acids were associated with several cytokines in colostrum samples. CONCLUSION: The present intervention demonstrated the possibility of modifying breast milk immunomodulatory factors by dietary means.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic diseases
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. acidophilus LA-5 and L. rhamnosus LGG
Dosage CFU/day: 1 billion LA-5 + 10 billion BB-12 and LGG each
Product formulation: Fermented milk
Reference number: 0855

Dotterud, et al. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. Br.J.Dermatol. 2010;163(3):616-623

Abstract: Summary Background Previous reports have suggested that certain probiotics given to mothers and children at risk of atopy halves the incidence of atopic dermatitis (AD) at 2 years of age. Objectives To examine if probiotics given to pregnant women in a nonselected population could prevent atopic sensitization or allergic diseases during the child's first 2 years. Methods In a randomized, double-blind trial of children from a nonselected maternal population (ClinicalTrials.gov identifier: NCT00159523), women received probiotic milk or placebo from 36 weeks of gestation to 3 months postnatally during breastfeeding. The probiotic milk contained Lactobacillus rhamnosus GG, L. acidophilus La-5 and Bifidobacterium animalis subsp. lactis Bb-12. Children with an itchy rash for more than 4 weeks were assessed for AD. At 2 years of age, all children were assessed for atopic sensitization, AD, asthma and allergic rhinoconjunctivitis. The intention-to-treat (ITT) analysis was enabled by multiple imputations. Results Four hundred and fifteen pregnant women were computer randomized. At 2 years, 138 and 140 children in the probiotic and the placebo groups, respectively, were assessed. In the ITT analysis, the odds ratio (OR) for the cumulative incidence of AD was 0.51 in the probiotic group compared with the placebo [95% confidence interval (CI) 0.30-0.87; P = 0.013]. There were no significant effects on asthma (OR 0.68, 95% CI 0.26-1.80; P = 0.437) or atopic sensitization (OR 1.52, 95% CI 0.74-3.14; P = 0.254). Conclusions Probiotics given to nonselected mothers reduced the cumulative incidence of AD, but had no effect on atopic sensitization.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Infections
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: Fermented milk
Reference number: 0755

Hojsak, et al. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. Pediatrics 2010;125:e1171

Abstract: OBJECTIVE: The incidence of nosocomial infections, predominantly gastrointestinal and respiratory, in children in developed countries is high, ranging from 5% to 44%. There is no effective strategy for preventing these infections. The objective of our study was to investigate the role of Lactobacillus GG (LGG) in preventing nosocomial gastrointestinal and respiratory tract infections at a pediatric hospital. METHODS: We conducted a randomized, double-blind, placebo-controlled trial of 742 hospitalized children. They were randomly allocated to receive for their hospitalization LGG at a dose of 10(9) colony-forming units in 100 mL of a fermented milk product (LGG group, n = 376) or placebo that was the same postpasteurized fermented milk product without LGG (placebo group, n = 366). 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.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Infections
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: Fermented milk
Reference number: 0754

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

Abstract: BACKGROUND & AIMS: The aim of our study was to investigate the role of Lactobacillus GG (LGG) in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers.METHODS: We conducted a 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.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Weight Management
Research subfield: Weight management
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsules
Reference number: 0960

Ilmonen, et al. Impact of dietary counselling and probiotic intervention on maternal anthropometric measurements during and after pregnancy: A randomized placebo-controlled trial. Clin.Nutr. 2010:.

Abstract: BACKGROUND & AIMS: To establish whether probiotic supplemented dietary counselling influences maternal anthropometric measurements during and after pregnancy.METHODS: At the first trimester of pregnancy 256 women were randomly assigned to receive nutrition counselling to modify dietary intake according to current recommendations or as controls; dietary intervention groups were further randomized to receive probiotics Lactobacillus rhamnosus GG (ATCC 53103) and Bifidobacterium lactis (diet/probiotics) or placebo (diet/placebo) capsules in a double-blind manner, whilst the controls received placebo (control/placebo). The intervention lasted until the end of exclusive breastfeeding for up to six months.RESULTS: The risk of central adiposity defined as waist circumference 80 cm or more was lowered in women in the diet/probiotics group compared with the control/placebo group (OR 0.30, 95%CI 0.11-0.85, p = 0.023 adjusted for baseline BMI), whilst the diet/placebo group did not differ from the controls (OR 1.00, 95% CI 0.38-2.68, p = 0.994) at 6 months postpartum. The number needed to treat (NNT) with diet/probiotics to prevent one woman from developing a waist circumference of 80 cm or more was 4. Healthy eating pattern at 12 months postpartum (p = 0.001) and BMI prior to pregnancy (p < 0.001) were strong determinants of BMI at 12 months postpartum when adjusted for dietary intervention and exercise.CONCLUSION: The impact of probiotics-supplemented dietary counselling on central adiposity, may offer a novel means for the prevention and management of obesity. This trial was registered at clinicaltrials.gov as NCT 00167700, section 3.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Other
Research subfield: Growth
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsules
Reference number: 1043

Luoto, et al. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br.J.Nutr. 2010;103(12):1792-1799

Abstract: The perinatal nutritional environment impacts upon the health and well-being of mother and child also in the long term. The aim of the present study was to determine the safety and efficacy of perinatal probiotic-supplemented dietary counselling by evaluating pregnancy outcome and fetal and infant growth during the 24 months' follow-up. Altogether, 256 women were randomised at their first trimester of pregnancy into a control and a dietary intervention group. The intervention group received intensive dietary counselling provided by a nutritionist and were further randomised, double-blind to receive probiotics (Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12; diet/probiotics) or placebo (diet/placebo). Firstly, probiotic intervention reduced the frequency of gestational diabetes mellitus (GDM); 13 % (diet/probiotics) v. 36 % (diet/placebo) and 34 % (control); P = 0.003. Secondly, the safety of this approach was attested by normal duration of pregnancies with no adverse events in mothers or children. No significant differences in prenatal or postnatal growth rates among the study groups were detected. Thirdly, distinctive effects of the two interventions were detected; probiotic intervention reduced the risk of GDM and dietary intervention diminished the risk of larger birth size in affected cases; P = 0.035 for birth weight and P = 0.028 for birth length. The results of the present study show that probiotic-supplemented perinatal dietary counselling could be a safe and cost-effective tool in addressing the metabolic epidemic. In view of the fact that birth size is a risk marker for later obesity, the present results are of significance for public health in demonstrating that this risk is modifiable.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion or or 1000 billion
Product formulation: Other
Reference number: 0783

Basu, et al. Efficacy of high-dose Lactobacillus rhamnosus GG in controlling acute watery diarrhea in Indian children: a randomized controlled trial. J.Clin.Gastroenterol. 2009;43:208-213

Abstract: AIM: To evaluate the effective dose of Lactobacillus rhamnosus GG (LGG) as probiotic in acute watery diarrhea (AWD) in Indian children. SETTING: Hospital-based study. DESIGN: Randomized, controlled, blinded trial. METHODS: All patients of AWD admitted over 1 year were included in the study. They were randomized into 3 groups to receive either only oral rehydration solution (ORS) (group A/control), ORS+LGG powder containing 10(10) colony forming units (CFU) (group B), or ORS+LGG powder containing 10(12) CFU (group C) twice daily for a minimum period of 7 days or until diarrhea stopped along with correction of dehydration. None of them received any other drug such as antibiotic or antidiarrheal medication. The duration and frequency of diarrhea and vomiting were studied. Data were analyzed by SPSS-10 software. RESULTS: The study comprised of 559 patients, group A/controls (n=185), group B (n=188), and group C (n=186). All the groups were similar with respect to age, number of breastfed infants, presentation with dehydration, degree of protein energy malnutrition, and rotavirus infection. 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.

Research field: Other
Research subfield: Glucose regulation
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsules
Reference number: 1012

Laitinen, et al. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br.J.Nutr. 2009;101(11):1679-1687

Abstract: Balanced glucose metabolism ensures optimal fetal growth with long-term health implications conferred on both mother and child. We examined whether supplementation of probiotics with dietary counselling affects glucose metabolism in normoglycaemic pregnant women. At the first trimester of pregnancy 256 women were randomised to receive nutrition counselling to modify dietary intake according to current recommendations or as controls; the dietary intervention group was further randomised to receive probiotics (Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12; diet/probiotics) or placebo (diet/placebo) in a double-blind manner, whilst the control group received placebo (control/placebo). Blood glucose concentrations were lowest in the diet/probiotics group during pregnancy (baseline-adjusted means 4.45, 4.60 and 4.56 mmol/l in diet/probiotics, diet/placebo and control/placebo, respectively; P = 0.025) and over the 12 months' postpartum period (baseline-adjusted means 4.87, 5.01 and 5.02 mmol/l; P = 0.025). Better glucose tolerance in the diet/probiotics group was confirmed by a reduced risk of elevated glucose concentration compared with the control/placebo group (OR 0.31 (95 % CI 0.12, 0.78); P = 0.013) as well as by the lowest insulin concentration (adjusted means 7.55, 9.32 and 9.27 mU/l; P = 0.032) and homeostasis model assessment (adjusted means 1.49, 1.90 and 1.88; P = 0.028) and the highest quantitative insulin sensitivity check index (adjusted means 0.37, 0.35 and 0.35; P = 0.028) during the last trimester of pregnancy. The effects observed extended over the 12-month postpartum period. The present study demonstrated that improved blood glucose control can be achieved by dietary counselling with probiotics even in a normoglycaemic population and thus may provide potential novel means for the prophylactic and therapeutic management of glucose disorders.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Infections
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion of each
Product formulation: Milk powder
Reference number: 0494

Rautava, et al. Specific probiotics in reducing the risk of acute infections in infancy--a randomised, double-blind, placebo-controlled study. Br.J.Nutr. 2009;101(11):1722-1726

Abstract: A randomised, double-blind, placebo-controlled study was conducted to determine whether probiotics might be effective in reducing the risk of infections in infancy. Infants requiring formula before the age of 2 months were recruited from community well-baby clinics. Infant formula supplemented with the probiotics Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb-12 or placebo was administered daily until the age of 12 months. Incidence of early infections (before the age of 7 months) and incidence of recurrent (three or more) infections during the first year of life were recorded as the main outcome measures of the study. During the first 7 months of life, seven out of thirty-two (22 %) infants receiving probiotics and twenty out of forty (50 %) infants receiving placebo experienced acute otitis media (risk ratio (RR) 0.44 (95 % CI 0.21, 0.90); P = 0.014) and antibiotics were prescribed for ten out of thirty-two (31 %) infants receiving probiotics and twenty-four out of forty (60 %) infants receiving placebo (RR 0.52 (95 % CI 0.29, 0.92); P = 0.015). During the first year of life, nine out of thirty-two (28 %) infants receiving probiotics and twenty-two out of forty (55 %) infants receiving placebo encountered recurrent respiratory infections (RR 0.51 (95 % CI 0.27, 0.95); P = 0.022). These data suggest that probiotics may offer a safe means of reducing the risk of early acute otitis media and antibiotic use and the risk of recurrent respiratory infections during the first year of life. Further clinical trials are warranted.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Other
Research subfield: Blood pressure
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: Capsules
Reference number: 0690

Aaltonen, et al. Evidence of infant blood pressure programming by maternal nutrition during pregnancy: a prospective randomized controlled intervention study. J.Pediatr. 2008;152:79-84

Abstract: OBJECTIVES: To evaluate the impact of maternal nutrition during pregnancy on infant blood pressure. STUDY DESIGN: Pregnant women (n = 256) were randomized into 3 groups: modified dietary intake according to current recommendations and probiotics (diet/probiotics), placebo (diet/placebo), and a control/placebo group. In the infants born to these women, blood pressure was recorded at age 6 months using an automated oscillometric DINAMAP R. RESULTS: Despite significant differences in maternal dietary intakes between the study groups, the intervention focusing on maternal fat intake showed no direct impact on infants' blood pressure. Instead, a complex U-shaped interrelationship was uncovered; the highest and lowest quartiles of intakes of specific nutrients, carbohydrate (P = .006 for systolic pressure and P = .015 for diastolic pressure), and monounsaturated fatty acids (P = .029 for diastolic pressure) compared with the middle quartiles resulted in higher blood pressure at age 6 months. The pattern between maternal carbohydrate intake during pregnancy and infants' blood pressure remained significant even after adjustment for breastfeeding and body length. A reverse U-shaped trend again was observed between maternal intake of fruits and infants' systolic blood pressure (P = .077). CONCLUSION: With a view toward programming blood pressure to adulthood, our results suggest an opportunity for dietary counseling to promote child health.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Irritable bowel syndrome
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 2.4 billion
Product formulation: Other
Reference number: 0696

Kajander, et al. Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. Aliment.Pharmacol.Ther. 2008;27:48-57

Abstract: BACKGROUND: Irritable bowel syndrome is the most common diagnosis in gastroenterology. Trials suggest certain probiotics to be beneficial. AIM: To investigate the effects of multispecies probiotic supplementation (Lactobacillus rhamnosus GG, L. rhamnosus Lc705, Propionibacterium freudenreichii ssp. shermanii JS and Bifidobacterium animalis ssp. lactis Bb12) on abdominal symptoms, quality of life, intestinal microbiota and inflammatory markers in irritable bowel syndrome. METHODS: Eighty-six irritable bowel syndrome patients (Rome II criteria) participated in this randomized, placebo-controlled 5-month intervention. Patients were randomized to receive daily either multispecies probiotic supplementation or placebo. Irritable bowel syndrome symptoms, quality of life, microarray-based intestinal microbiota stability (n = 20), serum cytokines and sensitive C-reactive protein were monitored. RESULTS: The composite irritable bowel syndrome score had at 5 months decreased 14 points (95% CI: -19 to -9) from baseline with the multispecies probiotic vs. three points (95% CI: -8 to 1) with placebo (P = 0.0083). Especially, distension and abdominal pain were affected. A stabilization of the microbiota was observed, as the microbiota similarity index increased with the probiotic supplementation (1.9 +/- 3.1), while it decreased with placebo (-2.9 +/- 1.7). No differences were seen in C-reactive protein. CONCLUSIONS: This multispecies probiotic seems to be an effective and safe option to alleviate symptoms of irritable bowel syndrome, and to stabilize the intestinal microbiota.

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 12 billion
Product formulation: NA
Reference number: 0674

Canani, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. BMJ 2007;335(7615):340

Abstract: OBJECTIVE: To compare the efficacy of five probiotic preparations recommended to parents in the treatment of acutediarrhoea in children. Design Randomised controlled clinicaltrial in collaboration with family paediatricians over 12 months. SETTING: Primary care. PARTICIPANTS: Children aged 3-36 months visiting a family paediatrician for acutediarrhoea. INTERVENTION: Children's parents were randomly assigned to receive written instructions to purchase a specific probiotic product: oral rehydration solution (control group); Lactobacillus rhamnosus strain GG; Saccharomyces boulardii; Bacillus clausii; mix of L delbrueckii var bulgaricus, Streptococcus thermophilus, L acidophilus, and Bifidobacterium bifidum; or Enterococcus faecium SF68. MAIN OUTCOME MEASURES: Primary outcomes were duration of diarrhoea and daily number and consistency of stools. Secondary outcomes were duration of vomiting and fever and rate of admission to hospital. Safety and tolerance were also recorded. RESULTS: 571 children were allocated to intervention. Median duration of diarrhoea was significantly shorter (P<0.001) in children who received L rhamnosus strain GG (78.5 hours) and the mix of four bacterial strains (70.0 hours) than in children who received oral rehydration solution alone (115.0 hours). One day after the first probiotic administration, the daily number of stools was significantly lower (P<0.001) in children who received L rhamnosus strain GG and in those who received the probiotic mix than in the other groups. The remaining preparations did not affect primary outcomes. Secondary outcomes were similar in all groups. CONCLUSIONS: Not all commercially available probiotic preparations are effective in children with acutediarrhoea. Paediatricians should choose bacterial preparations based on effectiveness data. TRIAL REGISTRATION NUMBER: Current Controlled Trials ISRCTN56067537 [controlled-trials.com].

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Gastrointestinal symptoms
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 3 billion
Product formulation: Capsules
Reference number: 0539

Gawronska, et al. A randomized double-blind placebo-controlled trial of Lactobacillus GG for abdominal pain disorders in children. Aliment.Pharmacol.Ther. 2007;25:177-184

Abstract: BACKGROUND: Functional abdominal pain disorders (FAPD) are common in school-aged children; however, there is no reliable treatment. AIM: To determine the efficacy of Lactobacillus rhamnosus GG (LGG) for treating FAPD in children. METHODS: 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. CONCLUSION: The LGG appears to moderately increase treatment success, particularly among children with IBS.

Research field: Gastrointestinal Health
Research subfield: Microbiota
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: Capsules
Reference number: 0702

Gronlund, et al. Maternal breast-milk and intestinal bifidobacteria guide the compositional development of the Bifidobacterium microbiota in infants at risk of allergic disease. Clin.Exp.Allergy 2007;37(12):1764-1772

Abstract: BACKGROUND: The sources and the impact of maternal bacteria on the initial inoculum of the intestinal microflora of newborn infants remain elusive. OBJECTIVE: To assess the association between maternal breast-milk and fecal bifidobacteria and infants' fecal bifidobacteria. METHODS: Sixty-one mother-infant pairs were included, special emphasis being placed on the maternal allergic status. Bifidobacteria were analysed by a direct PCR method in fecal samples from mothers at 30-35 weeks of gestation and from infants at 1 month of age and from breast-milk samples 1 month post-partum. RESULTS: Fecal Bifidobacterium adolescentis and Bifidobacterium bifidum colonization frequencies and counts among mother-infant pairs correlated significantly (P=0.005 and 0.02 for frequencies, respectively, and P=0.002 and 0.01 for counts, respectively). Only infants of allergic, atopic mothers were colonized with B. adolescentis. Each of the breast-milk samples contained bifidobacteria [median 1.4 x 10(3) bacterial cells/mL; interquartile range (IQR) 48.7-3.8 x 10(3)]. Bifidobacterium longum was the most frequently detected species in breast-milk. Allergic mothers had significantly lower amounts of bifidobacteria in breast-milk compared with non-allergic mothers [median 1.3 x 10(3) bacterial cells/mL (IQR 22.4-3.0 x 10(3)) vs. 5.6 x 10(3) bacterial cells/mL (1.8 x 10(3)-1.8 x 10(4)), respectively, (P=0.004)], and their infants had concurrently lower counts of bifidobacteria in feces [3.9 x 10(8) bacterial cells/g (IQR 6.5 x 10(6)-1.5 x 10(9)) in infants of allergic mothers, vs. 2.5 x 10(9) bacterial cells/g (6.5 x 10(8)-3.2 x 10(10)) in infants of non-allergic mothers, P=0.013]. CONCLUSIONS: Breast-milk contains significant numbers of bifidobacteria and the maternal allergic status further deranges the counts of bifidobacteria in breast-milk. Maternal fecal and breast-milk bifidobacterial counts impacted on the infants' fecal Bifidobacterium levels. Breast-milk bacteria should thus be considered an important source of bacteria in the establishment of infantile intestinal microbiota.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Infections
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 0.5 billion
Product formulation: Fermented milk
Reference number: 0637

Hatakka, et al. Probiotics reduce the prevalence of oral candida in the elderly--a randomized controlled trial. J.Dent.Res. 2007;86:125-130

Abstract: Overgrowth of oral yeast is a common problem among the elderly. Probiotic bacteria are known to inhibit the growth of pathogenic microbes. We tested the hypothesis that cheese containing probiotic bacteria can reduce the prevalence of oral Candida. During this 16-week, randomized, double-blind, placebo-controlled study, 276 elderly people consumed daily 50 g of either probiotic (n = 136) or control cheese (n = 140). The primary outcome measure was the prevalence of a high salivary yeast count (>or= 10(4) cfu/mL) analyzed by the Dentocult method. The prevalence decreased in the probiotic group from 30% to 21% (32% reduction), and increased in the control group from 28% to 34%. Probiotic intervention reduced the risk of high yeast counts by 75% (OR = 0.25, 95%CI 0.10-0.65, p = 0.004), and the risk of hyposalivation by 56% (OR = 0.44, 95%CI 0.19-1.01, p = 0.05). Thus, probiotic bacteria can be effective in controlling oral Candida and hyposalivation in the elderly.

Research field: Gastrointestinal Health
Research subfield: Microbiota
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 8-9 billion
Product formulation: Capsules
Reference number: 0652

Kajander, et al. Effects of multispecies probiotic supplementation on intestinal microbiota in irritable bowel syndrome. Aliment.Pharmacol.Ther. 2007;26:463-473

Abstract: BACKGROUND: A multispecies probiotic has shown beneficial effects in irritable bowel syndrome. In addition, certain other probiotics have demonstrated advantageous effects, but the mechanisms behind this are poorly understood. AIM: To investigate the mode of action of a multispecies probiotic consisting of Lactobacillus rhamnosus GG, Lactobacillus rhamnosus Lc705, Propionibacterium freudenreichii ssp. shermanii JS and Bifidobacterium breve Bb99 by monitoring its effects on intestinal microbiota and markers of microbial activity. METHODS: A total of 55 irritable bowel syndrome patients participated in this placebo-controlled double-blind trial. Subjects received either multispecies probiotic or placebo supplementation daily during a 6-month period. The composition of intestinal microbiota was analysed with real-time polymerase chain reaction, short-chain fatty acids with gas chromatography and enzymes with spectrophotometer. RESULTS: Each supplemented probiotic strain was detected in faecal samples. Intestinal microbiota remained stable during the trial, except for Bifidobacterium spp., which increased in the placebo group and decreased in the probiotic group (P = 0.028). No changes in short-chain fatty acids occurred. A decrease in ss-glucuronidase activity was detected in 67% of the subjects in the probiotic group vs. 38% in the placebo group (P = 0.06). CONCLUSIONS: Factors other than the microbial groups and metabolites studied herein seem responsible for the alleviation of irritable bowel syndrome symptoms by the multispecies probiotic.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Other
Research subfield: Other
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 2 billion
Product formulation: Capsules
Reference number: 0689

Kaplas, et al. Dietary counseling and probiotic supplementation during pregnancy modify placental phospholipid fatty acids. Lipids 2007;42:865-870

Abstract: It has previously been shown that maternal nutrition affects the fetal environment, with consequences for the infant's health. From early pregnancy onwards participants here received a combination of dietary counseling and probiotics (Lactobacillus GG and Bifidobacterium lactis Bb12; n = 10), dietary counseling with placebo (n = 12), or placebo alone (n = 8). The major differences in placental fatty acids were attributable to a higher concentration of n-3 polyunsaturated fatty acids in both intervention arms than in controls. Further, dietary counseling with probiotics resulted in higher concentrations of linoleic (18:2n-6) and dihomo-gamma-linolenic acids (20:3n-6) compared with dietary counseling with placebo or controls.

Research field: Immune Health
Research subfield: Infections
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: Milk-based fruit drink: 40 billion, capsules: 10 billion
Product formulation: Capsules or other
Reference number: 0684

Kekkonen, et al. The effect of probiotics on respiratory infections and gastrointestinal symptoms during training in marathon runners. Int.J.Sport Nutr.Exerc.Metab. 2007;17:352-363

Abstract: Heavy exercise is associated with an increased risk of upper respiratory tract infections. Strenuous exercise also causes gastrointestinal (GI) symptoms. In previous studies probiotics have reduced respiratory tract infections and GI symptoms in general populations including children, adults, and the elderly. These questions have not been studied in athletes before. The purpose of this study was to investigate the effect of probiotics on the number of healthy days, respiratory infections, and GI-symptom episodes in marathon runners in the summer. Marathon runners (N = 141) were recruited for a randomized, double-blind intervention study during which they received Lactobacillus rhamnosus GG (LGG) or placebo for a 3-mo training period. At the end of the training period the subjects took part in a marathon race, after which they were followed up for 2 wk. The mean number of healthy days was 79.0 in the LGG group and 73.4 in the placebo group (P = 0.82). There were no differences in the number of respiratory infections or GI-symptom episodes. The duration of GI-symptom episodes in the LGG group was 2.9 vs. 4.3 d in the placebo group during the training period (P = 0.35) and 1.0 vs. 2.3 d, respectively, during the 2 wk after the marathon (P = 0.046). LGG had no effect on the incidence of respiratory infections or GI-symptom episodes in marathon runners, but it seemed to shorten the duration of GI-symptom episodes.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic diseases
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: >1 billion
Product formulation: Milk powder
Reference number: 0701

Mah, et al. Effect of a milk formula containing probiotics on the fecal microbiota of asian infants at risk of atopic diseases. Pediatr.Res. 2007;62:674-679

Abstract: The fecal microbiota of 37 infants with (n = 20) or without (n = 17) probiotic administration was evaluated on D 3, and at 1, 3, and 12 mo by fluorescence in situ hybridization-flow cytometry (FISH-FC), PCR, and bacteriological culture methods. They represent consecutive subjects of an ongoing double-blind, placebo-controlled trial on a probiotic formula (LGG and Bifidobacterium longum) administered during the first 6 mo of life. Despite varying composition in each baby, there was a general bacterial colonization pattern in the first year. Bifidobacteria increased markedly (p = 0.0003) with a parallel decrease in Enterobacteriaceae (p 0.05). B. longum (p = 0.005) and Lactobacillus rhamnosus (p 0.05). Cultured lactic acid bacteria were also more numerous in the probiotic-administered babies during treatment period (log CFU/g 8.4 versus 7.4; p = 0.035). Our results indicate that supplemented strains could be detected but did not persist in the bowel once probiotic administration had ceased.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: H. pylori
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG and L. rhamnosus LC705 and P. freudenreichii JS
Dosage CFU/day: 2.5 billion
Product formulation: Other
Reference number: 0634

Myllyluoma, et al. Probiotic intervention decreases serum gastrin-17 in Helicobacter pylori infection. Dig.Liver Dis. 2007;39:516-523

Abstract: BACKGROUND: Previously we showed that a probiotic combination with L. rhamnosus GG was beneficial as an adjuvant therapy during H. pylori eradication. AIM: To evaluate whether probiotic combination with LGG adheres to the upper gastrointestinal mucosa and modifies H. pylori colonisation and H. pylori induced inflammation. METHODS: Thirteen patients referred for gastroduodenoscopy received a drink consisting of equal doses (2.5x10(9)CFU) of LGG, L. rhamnosus LC705, Propionibacterium freudenreichii JS and Bifidobacterium lactis Bb12 daily. Recovery of probiotics in biopsies (antrum, corpus, duodenum) and faecal samples was evaluated by strain-specific quantitative polymerase chain reaction. H. pylori colonization and gastric inflammation was investigated by urease activity ((13)C-urea breath test), histology and serum pepsinogen I, II and gastrin-17 measurements. RESULTS: Twelve patients were fully investigated; of these three of the patients had LGG adhering to the biopsies at end of the intervention. Other probiotic strains were not detected, even though the recovery of all individual probiotic strains from the faeces was significantly increased ($p<0.01$). After the treatment, the level of (13)C-urea breath test ($p=0.063$) and gastrin-17 ($p=0.046$) decreased. CONCLUSIONS: The decreases in (13)C-urea breath test and gastrin-17 indicate that the probiotic combination exerts a beneficial effect on gastric mucosa in H. pylori infected patients. LGG showed marginal ability to adhere to the upper gastrointestinal tract mucosa.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10-20 billion
Product formulation: Other
Reference number: 0695

Osterlund, et al. Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study. Br.J.Cancer 2007;97:1028-1034

Abstract: 5-Fluorouracil (5-FU)-based chemotherapy is frequently associated with diarrhoea. We compared two 5-FU-based regimens and the effect of Lactobacillus and fibre supplementation on treatment tolerability. Patients diagnosed with colorectal cancer (n=150) were randomly allocated to receive monthly 5-FU and leucovorin bolus injections (the Mayo regimen) or a bimonthly 5-FU bolus plus continuous infusion (the simplified de Gramont regimen) for 24 weeks as postoperative adjuvant therapy. On the basis of random allocation, the study participants did or did not receive Lactobacillus rhamnosus GG supplementation (1-2 x 10(10) per day) and fibre (11 g guar gum per day) during chemotherapy. Patients who received Lactobacillus had less grade 3 or 4 diarrhoea (22 vs 37%, P=0.027), reported less abdominal discomfort, needed less hospital care and had fewer chemotherapy dose reductions due to bowel toxicity. No Lactobacillus-related toxicity was detected. Guar gum supplementation had no influence on chemotherapy tolerability. The simplified de Gramont regimen was associated with fewer grade 3 or 4 adverse effects than the Mayo regimen (45 vs 89%), and with less diarrhoea. We conclude that Lactobacillus GG supplementation is well tolerated and may reduce the frequency of severe diarrhoea and abdominal discomfort related to 5-FU-based chemotherapy.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Other
Research subfield: Probiotic characteristics
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: NA
Reference number: 0605

Gueimonde, et al. Effect of maternal consumption of lactobacillus GG on transfer and establishment of fecal bifidobacterial microbiota in neonates. J.Pediatr.Gastroenterol.Nutr. 2006;42:166-170

Abstract: BACKGROUND: Establishment of the gut microbiota at birth provides a substantial source of microbial stimuli for the maturation of the immune system. Deviations in this process precede the development of specific diseases providing the rationale for the use of probiotics to counteract them. OBJECTIVE: This study was designed to characterize both the mother-infant bifidobacteria transfer at birth and the development of bifidobacteria microbiota during the first weeks of life in infants whose mothers received Lactobacillus rhamnosus GG or placebo. METHODS: Species-specific PCR was used to assess the fecal bifidobacterial composition of mothers before and after delivery and in infants at 5 days and 3 weeks of age. RESULTS: Bifidobacterium longum was the species most commonly found in the mothers. Bifidobacterium catenulatum was the most prevalent group in infants at 5 days of age and B. longum the predominant species at 3 weeks. At 5 days of age, infants whose mothers received L. rhamnosus GG showed a significantly higher occurrence of B. breve and lower of B. adolescentis than those from the placebo group. In addition, L. rhamnosus GG consumption increased the bifidobacterial diversity in infants and reduced the Bifidobacterium microbiota similarity between mother and infant. CONCLUSIONS: These results indicate that specific changes in the transfer and initial establishment of bifidobacteria in neonates take place as consequence of the consumption of L. rhamnosus GG by the mothers.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Irregular bowel movements
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 15 billion
Product formulation: Fermented milk
Reference number: 0613

Hongisto, et al. A combination of fibre-rich rye bread and yoghurt containing Lactobacillus GG improves bowel function in women with self-reported constipation. Eur.J.Clin.Nutr. 2006;60:319-324

Abstract: OBJECTIVE: The aim of the study was to investigate the effects of fibre-rich rye bread and yoghurt containing Lactobacillus GG (LGG) on intestinal transit time and bowel function, and to test whether they have an interaction in cases of self-reported constipation. DESIGN: The study was carried out as a two-by-two factorial design. SETTING: Free-living subjects. SUBJECTS: A total of 59 healthy women with self-reported constipation, recruited by advertisement. INTERVENTIONS: After a baseline period, the subjects were randomized into four diet groups: (1) rye bread+LGG yoghurt, (2) rye bread, (3) LGG yoghurt, and (4) control. The 3-week dietary intervention was followed by a 3-week follow-up period. During each period, total intestinal transit time was measured and the subjects recorded faecal frequency and consistency, difficulty in defecation and gastrointestinal symptoms. RESULTS: The rye bread shortened total intestinal transit time (mean difference, -0.7; CI(95), -1.1 to -0.2; P=0.007), increased faecal frequency (0.3; CI(95), 0.1 to 0.5; P=0.001), softened faeces (-0.3; CI(95), -0.4 to -0.2; P<0.001) and made defecation easier (-0.4; CI(95), -0.5 to -0.2; P<0.001), but also increased gastrointestinal symptoms (1.6; CI(95), 0.7 to 2.4; P<0.001) compared to the low-fibre toast consumed in the LGG and control groups. There were fewer symptoms in the rye bread+LGG group compared to the rye bread group (-1.3; CI(95), -2.4 to -0.2; P=0.027). CONCLUSIONS: Fibre-rich rye bread can be recommended in the treatment of constipation, and the simultaneous consumption of LGG yoghurt relieves the adverse gastrointestinal effects associated with increased intake of fibre.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion BB-12 and 10 billion LGG
Product formulation: Milk powder
Reference number: 0509

Rautava, et al. Specific probiotics in enhancing maturation of IgA responses in formula-fed infants. Pediatr.Res. 2006;60:221-224

Abstract: The first months of life represent a critical period for the maturation of the infant's immune system and, thus, a window of opportunity for measures to reduce the risk of disease. We hypothesized that specific probiotics might promote mucosal immunologic maturation in formula-fed infants. The numbers of cow's milk-specific and total IgA-secreting cells were measured at 3, 7, and 12 mo of age in a double-blind placebo-controlled study of 72 infants with early artificial feeding. The infants consumed infant formula supplemented with specific probiotics (Lactobacillus GG and Bifidobacterium lactis Bb-12) or placebo during the first year of life. Further analyses of the serum concentrations of the IgA-inducing cytokine TGF-beta2 and the soluble innate microbial receptor sCD14 were conducted. The numbers of cow's milk-specific IgA secreting cells were significantly higher in infants receiving probiotics compared with those receiving placebo ($p = 0.045$, ANOVA for repeated measures). At 12 mo of age, the serum concentrations of sCD14 were 1479 pg/mL [95% confidence interval (CI) 1373-1592] in infants receiving probiotics and 1291 pg/mL (95% CI 1152-1445) in infants receiving placebo ($p = 0.046$). Administration of the probiotics Lactobacillus GG and Bifidobacterium lactis Bb-12 at the time of introduction of cow's milk in the infant's diet results in cow's milk-specific IgA antibody responsiveness that may be the result of increased production of sCD14.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Microbiota
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: Milk powder
Reference number: 0607

Vendt, et al. Growth during the first 6 months of life in infants using formula enriched with Lactobacillus rhamnosus GG: double-blind, randomized trial. J.Hum.Nutr.Diet. 2006;19:51-58

Abstract: BACKGROUND: Probiotic bacteria have beneficial effects on the immune system and gastrointestinal tract, but the impacts of their long-term consumption on health and growth in early infancy are not well documented. The aim of this study was to evaluate the influence of Lactobacillus rhamnosus GG (LGG)-enriched formula on growth and faecal microflora during the first 6 months of life in normal healthy infants. MATERIALS AND METHODS: One hundred and twenty healthy infants (up to 2 months) received LGG-supplemented formula or regular formula in a double-blind, randomized manner until the age of 6 months. Weight, length and head circumference were measured monthly and transformed into standard deviation scores (SDS). Faecal samples were obtained from a random sample of infants (n=25) at entry and at the end of the study. RESULTS: One hundred and five infants (51 in the LGG group) completed the study. Children receiving LGG-supplemented formula grew better: their changes in their length and weight SDS (DeltaSDS) at the end of the study were significantly higher than those receiving regular formula (0.44+/- 0.37 versus 0.07+/- 0.06, P< 0.01 and 0.44+/- 0.19 versus 0.07+/- 0.06, P< 0.005, respectively). The LGG group had a significant, higher defecation frequency 9.1+/-2.06 versus 8.0+/- 2.8 (P<0.05). More frequent colonization with lactobacilli was found in the LGG group, 91% versus 76% (P<0.05) at the end of the study. CONCLUSIONS Infants fed with LGG-enriched formula grew better than those fed with regular formula. Further studies are necessary to clarify the mechanism of LGG in infant growth.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Cancer
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: NA
Reference number: 0497

Collins, et al. The influence of synbiotic consumption on cancer risk biomarkers in previously resected colon cancer subjects. Journal of Biotechnology 2005

Abstract: 37 colon cancer subjects who had undergone curative resection were supplemented with BB-12, L.GG and raftilose for 12 weeks. Fecal and blood samples were obtained before, midway through (6 weeks) and following intervention (12 weeks). Rectal biopsies were obtained at T1 and T3. Fecal flora was determined using plating techniques. Genotoxic and cytotoxic potential of Fecal Water was determined. Cytokine production was estimated in vitro. Flow cytometry was used to determine NK cell cytotoxic activity as well as the phagocytic and respiratory burst activity of monocytes. In the synbiotic group fecal numbers of bifidobacteria increased significantly ($p>0.001$), lactobacilli increased (ns $p=0.0674$) while coliforms decreased ($p<0.05$). In the placebo group bifidobacteria decreased ($p<0.001$), the other bacterial groups were unaffected. Genotoxic damage was increased in placebo biopsies but unchanged in the probiotic group. The geno- and cytotoxic potential of FW was unaltered. IFN-gamma production was significantly increased in synbiotic group but IL-2, IL-10, IL-12 and TNF-alpha production was unaffected. In conclusion synbiotic consumption of BB-12, L.GG and raftilose beneficially altered the composition of the gut flora and protected against genotoxic damage in vivo suggesting a protective effect against colon carcinogenesis.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG and L. paracasei subsp. paracasei L. casei 431
Dosage CFU/day: 10 billion
Product formulation: Fermented milk
Reference number: 0462

de Vrese, et al. Probiotic bacteria stimulate virus-specific neutralizing antibodies following a booster polio vaccination. Eur.J.Nutr. 2005;44(7):406-413

Abstract: BACKGROUND: Orally ingested probiotic bacteria may modulate the immune response and increase antibody titers against enteric infections by bacteria or viruses. Even though positive effects of probiotics on respiratory tract infections have been reported, overall only few studies have examined effects on virus infections concerning organs other than the gastrointestinal tract. AIM OF THE STUDY: It was the aim of the study to investigate whether and how probiotics affect the immune response to a standardized enterovirus challenge (polio) and infections not limited to the gastrointestinal tract in healthy adults. METHODS: In a randomized, controlled and double-blind study 64 volunteers consumed for 5 weeks chemically acidified clotted milk without bacteria or with 10(10)/serving (Lactobacillus rhamnosus) GG or Lactobacillus acidophilus CRL431 added. In the second week subjects were vaccinated orally against polio 1, 2 and 3. Polio virus neutralizing serum activity, the primary parameter, was determined by the standard neutralization test (WHO) before and three times after vaccination. Polio-specific IgA, IgG and IgM were detected by ELISAs. RESULTS: Probiotics increased poliovirus neutralizing antibody titers (NT) and affected the formation of poliovirus-specific IgA and IgG in serum. The maximum increase after immunization was about 2, 2.2, or 4-fold higher, respectively, for NT, IgG or, IgA, in volunteers consuming probiotics instead of placebo. No consistent difference was noted between bacterial strains. CONCLUSIONS: Probiotics induce an immunologic response that may provide enhanced systemic protection of cells from virus infections by increasing production of virus neutralizing antibodies.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Recovery
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: Control:0 - low: 0.1 billion - medium: 1 billion- high: 10 billion
Product formulation: Milk powder
Reference number: 0583

Petschow, et al. Effects of feeding an infant formula containing Lactobacillus GG on the colonization of the intestine: a dose-response study in healthy infants. J.Clin.Gastroenterol. 2005;39:786-790

Abstract: OBJECTIVES: This study aimed to determine whether feeding Lactobacillus GG (LGG) at varying levels (10 to 10 cfu/day) would result in colonization, defined as > or =1,000 cfu of LGG per gram of stool in 3 of 5 samples collected during the feeding period. METHODS: Infants received unsupplemented formula during a 7-day baseline, 1 of 4 formulas containing 0 (control), 10 (low), 10 (medium), or 10 (high) cfu of LGG per day during a 2-week test, and unsupplemented formula during a 2-week follow-up. Baseline, test, and follow-up stool samples were evaluated for levels of viable LGG. RESULTS: During test, supplemented infants were colonized, compared with control ($P < 0.05$). Median stool counts of LGG (log10 cfu/g) in colonized infants were 5.24 (low), 6.05 (medium), and 5.97 (high). LGG persisted in the stools for 7 to 14 days after discontinuing LGG. No differences were observed among groups in stool consistency, flatulence, fussiness, or adverse events. CONCLUSION: A 2-week oral administration of 10 to 10 cfu/day LGG was well tolerated; all levels successfully colonized the intestinal tract of healthy, term infants.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 billion
Product formulation: Milk powder
Reference number: 0668

Rinne, et al. Effect of probiotics and breastfeeding on the bifidobacterium and lactobacillus/enterococcus microbiota and humoral immune responses. J.Pediatr. 2005;147:186-191

Abstract: OBJECTIVE: To assess impact of probiotics and breastfeeding on gut microecology. STUDY DESIGN: Mothers were randomized to receive placebo or Lactobacillus rhamnosus GG before delivery, with treatment of the infants after delivery. We assessed gut microbiota, humoral immune responses, and measured soluble cluster of differentiation 14 (sCD14) in colostrum in 96 infants. RESULTS: Fecal Bifidobacterium and Lactobacillus/Enterococcus counts were higher in breastfed than formula-fed infants at 6 months; P <.0001 and P=.01, respectively. At 3 months, total number of immunoglobulin (Ig)G-secreting cells in breastfed infants supplemented with probiotics exceeded those in breastfed infants receiving placebo; P=.05, and their number correlated with concentration of sCD14 in colostrum. Total numbers of IgM-, IgA-, and IgG-secreting cells at 12 months were higher in infants breastfed exclusively for at least for 3 months and supplemented with probiotics as compared with breastfed infants receiving placebo; P=.005, P=.03 and P=.04, respectively. Again, sCD14 in colostrum correlated with numbers of IgM and IgA cells; P=.05 in both. CONCLUSIONS: We found an interaction between probiotics and breastfeeding on number of Ig-secreting cells, suggesting that probiotics during breastfeeding may positively influence gut immunity.

Research field: Immune Health
Research subfield: Atopic eczema
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: a: 5 billion LGG b: 5 billion LGG + 5 billion LC705 + 0.2 billion Bb99 + 2 billion JS
Product formulation: Other
Reference number: 0576

Viljanen, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. Allergy 2005;60:494-500

Abstract: BACKGROUND: Probiotic bacteria are suggested to reduce symptoms of the atopic eczema/dermatitis syndrome (AEDS) in food-allergic infants. We aimed to investigate whether probiotic bacteria have any beneficial effect on AEDS. METHODS: Follow-up of severity of AEDS by the Severity Scoring of Atopic Dermatitis (SCORAD) index in 230 infants with suspected cow's milk allergy (CMA) receiving, in a randomized double-blinded manner, concomitant with elimination diet and skin treatment, Lactobacillus GG (LGG), a mixture of four probiotic strains, or placebo for 4 weeks. Four weeks after the treatment, CMA was diagnosed with a double-blind placebo-controlled (DBPC) milk challenge in 120 infants. RESULTS: In the whole group, mean SCORAD (at baseline 32.5) decreased by 65%, but with no differences between treatment groups immediately or 4 weeks after the treatment. No treatment differences were observed in infants with CMA either. In IgE-sensitized infants, however, the LGG group showed a greater reduction in SCORAD than did the placebo group, -26.1 vs-19.8 (P=0.036), from baseline to 4 weeks after the treatment. Exclusion of infants who had received antibiotics during the study reinforced the findings in the IgE-sensitized subgroup. CONCLUSION: Treatment with LGG may alleviate AEDS symptoms in IgE-sensitized infants but not in non-IgE-sensitized infants.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic eczema
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: a: 5 billion LGG b: 5 billion LGG + 5 billion LC705 + 0.2 billion Bb99 + 2 billion JS
Product formulation: Other
Reference number: 0578

Pohjavuori, et al. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. J.Allergy Clin.Immunol. 2004;114:131-136

Abstract: BACKGROUND: Probiotic bacteria are potentially beneficial to maturation of the infant's immune system. OBJECTIVE: To examine the role of probiotic bacteria in treatment of cow's milk allergy (CMA) and IgE-associated dermatitis, we investigated the immunologic effects of Lactobacillus rhamnosus GG (LGG) and a mixture of 4 bacterial species (MIX). METHODS: In a randomized, double-blind study design, concomitantly with elimination diet and skin treatment, LGG, MIX, or placebo was given for 4 weeks to infants with suspected CMA. After anti-CD3 (OKT3) and anti-CD28 stimulation of PBMCs, IFN-gamma, IL-4, IL-5, and IL-12 levels were measured in culture supernatants by ELISA. Intracellular IFN-gamma, IL-4, and IL-5 production on CD4 lymphocytes was analyzed with fluorescence-activated cell sorting. RESULTS: Secretion of IFN-gamma by PBMCs before the treatment was significantly lower in infants with CMA (P=.016) and in infants with IgE-associated CMA (P=.003) than in non-CMA infants. Among the infants who received LGG, the level of secreted IFN-gamma increased in those with CMA (P=.006) and in those with IgE-associated dermatitis (P=.017) when compared with the placebo group. Secretion of IL-4 increased significantly in infants with CMA in the MIX (P=.034) but not in the LGG group. CONCLUSION: Deficiency in IFN-gamma response appears to be related to CMA. LGG raises IFN-gamma production of PBMC in infants with CMA and in infants with IgE-associated dermatitis and may thus provide beneficial TH1 immunomodulatory signals. MIX, although containing LGG, appears to modulate the immune responses differently.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic eczema
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 billion
Product formulation: Capsules
Reference number: 0573

Kalliomaki, et al. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 2003;361(9372):1869-1871

Abstract: 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). We have therefore assessed persistence of the potential to prevent atopic eczema at 4 years. Atopic disease was diagnosed on the basis of a questionnaire and a clinical examination. 14 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). Skin prick test reactivity was the same in both groups: ten of 50 children previously given lactobacillus compared with nine of 50 given placebo tested positive. Our results suggest that the preventive effect of lactobacillus GG on atopic eczema extends beyond infancy.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic eczema
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: Milk powder
Reference number: 0580

Kirjavainen, et al. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. J.Pediatr.Gastroenterol.Nutr. 2003;36:223-227

Abstract: OBJECTIVES: The aim of this study was to assess the efficacy of oral supplementation of viable and heat-inactivated probiotic bacteria in the management of atopic disease and to observe their effects on the composition of the gut microbiota. METHODS: The study population included 35 infants with atopic eczema and allergy to cow's milk. At a mean age of 5.5 months, they were assigned in a randomized double-blind manner to receive either extensively hydrolyzed whey formula (placebo group) or the same formula supplemented with viable (viable LGG group) or heat-inactivated Lactobacillus GG (heat-inactivated LGG group), respectively. The changes in symptoms were assessed by the SCORAD method and the presence of some predominant bacterial genera in the feces detected with 16S rRNA-specific probes. RESULTS: The treatment with heat-inactivated LGG was associated with adverse gastrointestinal symptoms and diarrhea. Consequently, the recruitment of patients was stopped after the pilot phase. Within the study population, atopic eczema and subjective symptoms were significantly alleviated in all the groups; the SCORAD scores (interquartile range) decreased from 13 (range, 4-29) to 8 (range, 0-29) units in the placebo group, from 19 (range, 4-47) to 5 (range, 0-18) units in the viable LGG group, and from 15 (range, 0-29) to 7 (range, 0-26) units in the heat-inactivated LGG group. The decrease in the SCORAD scores within the viable LGG group tended to be greater than within the placebo group. The treatments did not appear to affect the bacterial numbers within the genera enumerated. CONCLUSIONS: Supplementation of infant formulas with viable but not heat-inactivated LGG is a potential approach for the management of atopic eczema and cow's milk allergy.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Microbiota
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 - 40 billion
Product formulation: Capsules
Reference number: 0598

Kuisma, et al. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. Aliment.Pharmacol.Ther. 2003;17:509-515

Abstract: BACKGROUND: Preliminary trials of probiotics in preventing recurrent chronic pouchitis have been encouraging. AIM: To investigate the efficacy of Lactobacillus GG supplementation as primary therapy for ileal pouch inflammation, and its effect on the microbial flora. METHODS: Twenty patients, with a previous history of pouchitis and endoscopic inflammation, were recruited for a prospective, randomized, double-blind, placebo-controlled trial of Lactobacillus GG supplementation (10 LGG, 10 placebo) in two gelatine capsules [(0.5-1) x 10(10) colony-forming units/capsule] b.d. for 3 months. Quantitative bacterial culture of fresh faecal samples and biopsies taken from the pouch and afferent limb was performed before and after supplementation. RESULTS: Lactobacillus GG supplementation changed the pouch intestinal flora by increasing the ratio of total faecal lactobacilli to total faecal anaerobes (P = 0.03) and enhancing the frequency of lactobacilli-positive cultures in the pouch and afferent limb mucosal biopsy samples. However, only 40% of patients were colonized with Lactobacillus GG. No differences were observed between the groups with regard to the mean pouchitis disease activity index or the total anaerobes or aerobes of faecal or tissue biopsy samples. CONCLUSIONS: A single-strain probiotic bacterium supplement of Lactobacillus GG changed the pouch intestinal bacterial flora, but was ineffective as primary therapy for a clinical or endoscopic response. More clinical trials are needed to evaluate the right placement and dosage of probiotics within a treatment regimen for pouchitis.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: H. pylori
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 12 billion
Product formulation: Other
Reference number: 0555

Cremonini, et al. Effect of different probiotic preparations on anti-helicobacter pylori therapy-related side effects: a parallel group, triple blind, placebo-controlled study. Am.J.Gastroenterol. 2002;97(11):2744-2749

Abstract: OBJECTIVES: Several studies show that probiotics may prevent side effects during therapy against Helicobacter pylori (H. pylori). Other reports indicate competitive interaction between some probiotics and H. pylori. We compared efficacy of two different probiotics and one probiotic combination with placebo for preventing anti-H. pylori therapy-related side effects and for improving the eradication rate. METHODS: A total of 85 H. pylori positive, asymptomatic patients were randomized in four groups to receive probiotic or placebo both during and for 7 days after a 1-wk triple therapy scheme (rabeprazole 20 mg b.id., clarithromycin 500 mg b.i.d., and tinidazole 500 mg b.i.d.). Group I (n = 21) received Lactobacillus GG; group II (n = 22), Saccharomyces boulardii; group III (n = 21), a combination of Lactobacillus spp. and biphidobacteria; and group IV (n = 21), placebo. Subjects filled in weekly symptom questionnaires for 4 wk. Blinded investigators collected and analyzed data. H. pylori status was rechecked after 5-7 wk. RESULTS: Side effects occurred mainly during the eradication week. None of them caused therapy discontinuation. In all probiotic-supplemented groups, there was a significantly lower incidence of diarrhea and taste disturbance during the eradication week with respect to the placebo group. Overall assessment of tolerability was significantly better in the actively treated patients than in the placebo group. No differences in the incidence of side effects between the probiotic groups were observed. The H. pylori eradication rate was almost identical between the probiotic and placebo groups. CONCLUSIONS: All the probiotics used were superior to placebo for side effect prevention, but were not associated with better compliance with antibiotic therapy. The effect of probiotic supplementation on side effects during anti-H. pylori regimens seemed to be independent of the probiotic species used.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic eczema
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 billion
Product formulation: Other
Reference number: 0587

Rautava, et al. Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant. J.Allergy Clin.Immunol. 2002;109:119-121

Abstract: The prevalence of atopic diseases is increasing throughout the Western world, and means of primary prevention are needed to reverse this trend. The role of breast-feeding, the best source of infant nutrition, in protection against atopic disease remains elusive. In this double-blinded, placebo-controlled study of 62 mother-infant pairs, it is shown that administering probiotics to the pregnant and lactating mother increased the immunoprotective potential of breast milk, as assessed by the amount of anti-inflammatory transforming growth factor beta2 (TGF-beta2) in the milk (2885 pg/mL [95% CI, 1624-4146] in mothers receiving probiotics vs 1340 pg/mL [95% CI, 978-1702] in mothers receiving placebo; P =.018). The risk of developing atopic eczema during the first 2 years of life in infants whose mothers received probiotics was significantly reduced in comparison with that in infants whose mothers received placebo (15% and 47%, respectively; relative risk, 0.32 [95% CI, 0.12-0.85]; P =.0098). Maternal atopy was a clear risk factor for atopic eczema in the infant. The infants most likely to benefit from maternal probiotic supplementation were those with an elevated cord blood IgE concentration. Administering probiotics during pregnancy and breast-feeding thus offers a safe and effective mode of promoting the immunoprotective potential of breast-feeding and provides protection against atopic eczema during the first 2 years of life.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: H. pylori
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 12 billion
Product formulation: Other
Reference number: 0554

Armuzzi, et al. The effect of oral administration of Lactobacillus GG on antibiotic-associated gastrointestinal side-effects during Helicobacter pylori eradication therapy. Aliment.Pharmacol.Ther. 2001;15:163-169

Abstract: BACKGROUND: One-week triple therapy is currently considered the golden standard against Helicobacter pylori. However, gastrointestinal side-effects are among the major pitfalls in such regimens. Probiotic supplementation might help to prevent or reduce such drug-related manifestations. AIM: To determine whether adding the probiotic Lactobacillus GG to an anti-H. pylori regimen could help to prevent or minimize the gastrointestinal side-effects burden. METHODS: Sixty healthy asymptomatic subjects screened positive for H. pylori infection were randomized to 1 week rabeprazole (20 mg b.d.), clarithromycin (500 mg b.d.), tinidazole (500 b.d.) and the probiotic Lactobacillus GG for 14 days or to the same regimen with a placebo preparation. Patients completed validated questionnaires during the week of treatment and during the following 3 weeks, to determine the type and severity of side-effects and an overall judgement of tolerability. RESULTS: Diarrhoea, nausea and taste disturbance were significantly reduced in the Lactobacillus GG supplemented group (relative risk=0.1, 95% CI: 0.1-0.9; relative risk=0.3, 95% CI: 0.1-0.9; relative risk=0.5, 95% CI: 0.2-0.9, respectively). An overall assessment of treatment tolerability showed a significant difference in favour of the Lactobacillus GG supplemented group (P=0.04). CONCLUSIONS: Lactobacillus GG supplementation showed a positive impact on H. pylori therapy-related side-effects and on overall treatment tolerability.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: H. pylori
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 12 billion
Product formulation: Capsules
Reference number: 0553

Armuzzi, et al. Effect of Lactobacillus GG supplementation on antibiotic-associated gastrointestinal side effects during Helicobacter pylori eradication therapy: a pilot study. Digestion 2001;63

Abstract: BACKGROUND: One-week triple therapy is currently regarded as the reference of anti-Helicobacter pylori treatment. However, antibiotic-associated gastrointestinal side effects are among the major pitfalls of such regimens. Probiotic supplementation may be regarded as a therapeutic tool to prevent or reduce these troublesome drug-related manifestations. AIM: To determine whether the addition of the probiotic Lactobacillus GG to an anti-H. pylori standard triple therapy could help to prevent or minimize the occurrence of gastrointestinal side effects. METHODS: One hundred and twenty healthy asymptomatic subjects screened positive for H. pylori infection and deciding to receive eradication therapy were randomized either to 1-week pantoprazole (40 mg b.i.d.), clarithromycin (500 mg b.i.d.), tinidazole (500 mg b.i.d.) or to the same regimen supplemented with Lactobacillus GG for 14 days. Patients filled in validated questionnaires during follow-up to determine the type and severity of side effects and to judge overall tolerability. RESULTS: Bloating, diarrhea and taste disturbances were the most frequent side effects during the eradication week and were significantly reduced in the Lactobacillus GG-supplemented group (RR = 0.4, CI 0.2-0.8; RR = 0.3, CI 0.1-0.8; RR = 0.3, CI 0.1-0.7, respectively). The same pattern was observed throughout the follow-up period. Overall assessment of treatment tolerability showed a significant trend in favor of the Lactobacillus GG-supplemented group (p = 0.03). CONCLUSIONS: Lactobacillus GG supplementation beneficially affects H. pylori therapy-related side effects and overall treatment tolerance.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Infections
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 130 - 260 million
Product formulation: Fermented milk
Reference number: 0574

Hatakka, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. BMJ 2001;322(7298):1327

Abstract: OBJECTIVE: To examine whether long term consumption of a probiotic milk could reduce gastrointestinal and respiratory infections in children in day care centres. DESIGN: Randomised, double blind, placebo controlled study over seven months. SETTING: 18 day care centres in Helsinki, Finland. PARTICIPANTS: 571 healthy children 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. MAIN OUTCOME MEASURES: 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. 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.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic diseases
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 billion
Product formulation: Capsules
Reference number: 0572

Kalliomaki, et al. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001;357(9262):1076-1079

Abstract: BACKGROUND: Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of Lactobacillus GG (which is safe at an early age and effective in treatment of allergic inflammation and food allergy). METHODS: In a double-blind, randomised placebo-controlled trial we gave Lactobacillus GG prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Chronic recurring atopic eczema, which is the main sign of atopic disease in the first years of life, was the primary endpoint. FINDINGS: Atopic eczema was diagnosed in 46 of 132 (35%) children aged 2 years. Asthma was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0.51 [95% CI 0.32-0.84]). The number needed to treat was 4.5 (95% CI 2.6-15.6). INTERPRETATIONS: Lactobacillus GG was effective in prevention of early atopic disease in children at high risk. Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics, for prevention of atopic disease.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Oral Health
Research subfield: Caries
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 130 - 260 million
Product formulation: Fermented milk
Reference number: 0575

Nase, et al. Effect of long-term consumption of a probiotic bacterium, Lactobacillus rhamnosus GG, in milk on dental caries and caries risk in children. Caries Res. 2001;35:412-420

Abstract: Lactobacillus rhamnosus GG, ATCC (LGG), has shown antagonism to many bacteria including mutans streptococci. This randomized, double-blind, placebo-controlled intervention study was designed to examine whether milk containing LGG has an effect on caries and the risk of caries in children when compared with normal milk. 594 children, 1-6 years old, from 18 municipal day-care centres were included. The children received the milk with meals from coded containers 5 days a week in the day-care centres for 7 months. The children's oral health was recorded at baseline and at the end, using WHO criteria. The caries risk was calculated based on clinical and microbiological data, comprising mutans streptococcus levels from dental plaque and saliva. The risk was classified as high if the child had a dmft/DMFT or initial caries score >0, and a mutans streptococcus count > or = 10(5) CFU/ml. The results showed less dental caries in the LGG group and lower mutans streptococcus counts at the end of the study. LGG was found to reduce the risk of caries significantly (OR = 0.56, p = 0.01; controlled for age and gender, OR = 0.51, p = 0.004). The effect was particularly clear in the 3- to 4-year-olds. Thus, milk containing the probiotic LGG bacteria may have beneficial effects on children's dental health.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 12 billion
Product formulation: Other
Reference number: 0559

Szajewska, et al. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. J.Pediatr. 2001;138:361-365

Abstract: OBJECTIVE: Nosocomial diarrhea is a major problem in pediatric hospitals worldwide. We evaluated the efficacy of orally administered Lactobacillus GG (LGG) in the prevention of this disease in young children. STUDY DESIGN: Eighty-one children aged 1 to 36 months who were hospitalized for reasons other than diarrhea were enrolled in a double-blind trial and randomly assigned at admission to receive LGG (n = 45) at a dose of 6 x 10(9) colony-forming units or a comparable placebo (n = 36) twice daily orally for the duration of their hospital stay. RESULTS: LGG reduced the risk of nosocomial diarrhea (> or =3 loose or watery stools/24 h) in comparison with placebo (6.7% vs 33.3%; relative risk: 0.2; [95% CI: 0.06-0.6]; number needed to treat: 4 [95% CI: 2-10]). The prevalence of rotavirus infection was similar in LGG and placebo groups (20% vs 27.8%, respectively; relative risk: 0.72; 95% CI: 0.33-1.56). However, the use of LGG compared with placebo significantly reduced the risk of rotavirus gastroenteritis (1/45 [2.2%] vs 6/36 [16.7%], respectively; relative risk: 0.13; 95% CI: 0.02-0.79; number needed to treat: 7; 95% CI: 3-40). CONCLUSIONS: Prophylactic use of LGG significantly reduced the risk of nosocomial diarrhea in infants, particularly nosocomial rotavirus gastroenteritis.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 40 billion LGG, 34 billion L. lactis
Product formulation: NA
Reference number: 0611

Fang, et al. Modulation of humoral immune response through probiotic intake. FEMS Immunol.Med.Microbiol. 2000;29:47-52

Abstract: Thirty healthy volunteers were randomised into three different treatment groups and consumed Lactobacillus GG, Lactococcus lactis or placebo (ethyl cellulose) for 7 days. On days 1, 3 and 5, an attenuated Salmonella typhi Ty21a oral vaccine was given to all subjects to mimic an enteropathogenic infection. All subjects responded well to the vaccine, but no significant differences were observed in numbers of IgA-, IgG- and IgM-secreting cells among the different groups. There was a trend towards a greater increase in specific IgA among the subjects receiving the vaccine in combination with Lactobacillus GG. Those receiving L. lactis with their vaccine evinced significantly higher CR3 receptor expression on neutrophils than those receiving either the placebo or Lactobacillus GG. These results indicate that probiotics may influence differently the immune response to oral S. typhi vaccine and that the immunomodulatory effect of probiotics is strain-dependent.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 45 billion
Product formulation: Other
Reference number: 0565

Guandalini, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J.Pediatr.Gastroenterol.Nutr. 2000;30:54-60

Abstract: BACKGROUND: The probiotic Lactobacillus GG is effective in promoting a more rapid recovery of acute, watery diarrhea in children with rotavirus enteritis. Very limited information is available, however, on the potential role of such agents in non-rotaviral diarrheal episodes. Furthermore, no evidence is available concerning the efficacy of Lactobacillus GG administered in the oral rehydration solution during oral rehydration therapy. A multicenter trial was conducted to evaluate the efficacy of Lactobacillus GG administered in the oral rehydration solution to patients with acute-onset diarrhea of all causes. METHODS: 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, receiving oral rehydration solution plus placebo, or group B, 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: One hundred forty children were enrolled in group A, and 147 in group B. There were no differences at admission between the groups in age, sex, previous types of feeding, previous duration of diarrhea, use of antibiotics, weight, height, weight-height percentile, prevalence of fever, overall status, degree of dehydration, and percentage of in- versus outpatients. 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 groups 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.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic eczema
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: Child-dependent
Product formulation: Milk powder
Reference number: 0388

Isolauri, et al. Probiotics in the management of atopic eczema. Clin.Exp.Allergy 2000;30(11):1604-1610

Abstract: BACKGROUND: Over the last two decades the incidence of allergic diseases has increased in industrialized countries, and consequently new approaches have to be explored. OBJECTIVE: The potential of probiotics to control allergic inflammation at an early age was assessed in a randomized double-blind placebo-controlled study. METHODS: A total of 27 infants, mean age 4.6 months, who manifested atopic eczema during exclusive breast-feeding and who have had no exposure to any infant or substitute formula were weaned to probiotic-supplemented, Bifidobacterium lactis Bb-12 or Lactobacillus strain GG (ATCC 53103), extensively hydrolysed whey formulas or to the same formula without probiotics. The extent and severity of atopic eczema, the growth and nutrition of infants, and concentrations of circulating cytokines/chemokines and soluble cell surface adhesion molecules in serum and methyl-histamine and eosinophilic protein X in urine were determined. RESULTS: The SCORAD score reflecting the extent and severity of atopic eczema was 16 (7-25) during breast-feeding, median (interquartile range). After 2 months, a significant improvement in skin condition occurred in patients given probiotic-supplemented formulas, as compared to the unsupplemented group; chi(2) = 12.27, P = 0.002. SCORAD decreased in the Bifidobacterium lactis Bb-12 group to 0 (0-3.8), and in the Lactobacillus GG group to 1 (0.1-8.7), vs unsupplemented 13.4 (4.5-18.2), median (interquartile range), in parallel with a reduction in the concentration of soluble CD4 in serum and eosinophilic protein X in urine. CONCLUSION: The results provide the first clinical demonstration of specific probiotic strains modifying the changes related to allergic inflammation. The data further indicate that probiotics may counteract inflammatory responses beyond the intestinal milieu. The combined effects of these probiotic strains will guide infants through the weaning period, when sensitization to newly encountered antigens is initiated. The probiotic approach may thus offer a new direction in the search for future foods for allergy treatment and prevention strategies.

Research field: Immune Health
Research subfield: Inflammation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 billion
Product formulation: Capsules
Reference number: 0577

Pessi, et al. Interleukin-10 generation in atopic children following oral Lactobacillus rhamnosus GG. Clin.Exp.Allergy 2000;30(12):1804-1808

Abstract: Oral Lactobacillus rhamnosus GG ingestion for 5 days to 4 weeks has been shown to alleviate clinical symptoms of gastrointestinal inflammation and atopic dermatitis. To determine whether oral Lactobacillus rhamnosus GG may act by generating immunosuppressive mediator in atopic children. Lactobacillus rhamnosus GG (ATCC 53103) at a daily dose of 2 x 1010 cfu was added for 4 weeks to the diets of nine children (mean age, 21 months) with atopic dermatitis. Blood and faecal samples were collected before supplementation and at early (2 weeks) and late stage (4 and 8 weeks from the beginning). The concentrations of interleukin-6 (IL-6), IL-10, IL-12, tumour necrosis factor-alpha (TNFalpha) and interferon-gamma (IFNgamma) in sera, as well as the production of IL-2, IL-4, IL-10 and IFNgamma in mitogen-induced peripheral blood mononuclear cells, were assessed. Secretory IgA and TNFalpha were also determined in faeces. The serum IL-10 concentration differed significantly between before, early and late samples ($P < 0.001$) due to the elevation of serum IL-10 in the later phase of oral Lactobacillus rhamnosus GG ingestion. The enhancement of IL-10 production in mitogen-induced cultures preceded the rise in serum IL-10. The enhanced IL-10 generation in vivo substantiates the anti-inflammatory properties of specific probiotic bacteria strains, and provides an additional reason for considering such treatments for patients with intestinal inflammation.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Recovery
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 60 billion
Product formulation: Fermented milk
Reference number: 0602

Alander, et al. Persistence of colonization of human colonic mucosa by a probiotic strain, Lactobacillus rhamnosus GG, after oral consumption. Appl.Environ.Microbiol. 1999;65:351-354

Abstract: Lactobacillus rhamnosus GG is one of the most thoroughly studied probiotic strains. Its advantages in the treatment of gastrointestinal disorders are well documented. The aim of the present study was to demonstrate with colonic biopsies the attachment of strain GG to human intestinal mucosae and the persistence of the attachment after discontinuation of GG administration. A whey drink fermented with strain GG was fed to human volunteers for 12 days. Fecal samples were collected before, during, and after consumption. L. rhamnosus GG-like colonies were detected in both fecal and colonic biopsy samples. Strain GG was identified by its characteristic colony morphology, a lactose fermentation test, and PCR. This study showed that strain GG was able to attach in vivo to colonic mucosae and, although the attachment was temporary, to remain for more than a week after discontinuation of GG administration. The results demonstrate that the study of fecal samples alone is not sufficient in evaluating colonization by a probiotic strain.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 40 billion
Product formulation: Capsules
Reference number: 0550

Arvola, et al. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. Pediatrics 1999;104:e64

Abstract: OBJECTIVES: Antimicrobial treatment may disturb the colonization resistance of gastrointestinal microflora, which may induce clinical symptoms, most commonly diarrhea. The severity of antibiotic-associated diarrhea may range from a brief, self-limiting disease to devastating diarrhea with electrolyte disturbances, dehydration, crampy abdominal pain, pseudomembranous colitis, toxic megacolon, or even death. The incidence of diarrhea in children receiving a single antimicrobial treatment is unclear. In addition to more critical use of antimicrobials, adjunctive preventive measures to antibiotic-associated diarrhea are needed. The objective of this study was to 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. METHODS: 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. Of the patients, 48 were lost to follow-up; therefore, the final study population consisted of 119 children from 2 weeks to 12. 8 years of age (mean: 4.5 years). All study subjects met the inclusion criteria: they had not received any antimicrobial medication during the previous 3 months, they did not suffer from gastrointestinal disorders, and they did not need intravenous antimicrobial treatment. 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. Lactobacillus GG and placebo capsules were indistinguishable in appearance and taste. The parents kept a daily symptom diary and recorded stool frequency and consistency at home for 3 months. Diarrhea was defined as at least three watery or loose stools per day for a minimum of 2 consecutive days. 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 metabolic activity of the gut microflora was assessed by analysis of fecal urease, beta-glucosidase, and beta-glucuronidase activities. 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. (ABSTRACT TRUNCATED)

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: Capsules
Reference number: 0571

Jung. Lactobacillus GG augments the immune response to typhoid vaccination: A double-blinded, placebo-controlled study. FASEB J. 1999;13:A872-.

Abstract: DESIGN: In a double-blind randomised controlled trial, 30 healthy volunteers receiving oral typhoid vaccine, were randomized to receive either LGG or placebo as capsules two wk prior to vaccination. RESULTS: LGG augments the immune response to concurrently administered vaccine and its effect is not due to a non-specific enhancement of the antibody response. LGG group showed a significantly higher IgG response to the vaccine at 2 and 5 wk. At 5 wk, IgA response was also increased. There was no change in existing antibody titer to tetanus in either group.

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 37 billion
Product formulation: Capsules
Reference number: 0558

Oberhelman, et al. A placebo-controlled trial of Lactobacillus GG to prevent diarrhea in undernourished Peruvian children. J.Pediatr. 1999;134:15-20

Abstract: OBJECTIVE: Lactobacillus GG (L-GG), an acid- and bile-resistant strain that colonizes the intestinal mucosa, has been used to manage diarrhea in children. Our objective was to evaluate the prophylactic use of L-GG to prevent diarrhea in children at high risk from a developing country in a randomized, placebo-controlled trial. STUDY DESIGN: Two hundred four undernourished children 6 to 24 months old from an indigent peri-urban Peruvian town received either L-GG or placebo in flavored gelatin once daily, 6 days a week, for 15 months. Episodes of diarrhea were documented by daily home visits, and diagnostic studies were done in a subset of cases. Recovery of L-GG in stool from subjects and from family contacts was examined. RESULTS: Subjects in the L-GG group had significantly fewer episodes of diarrhea (5.21 episodes diarrhea/child/year ['ecy'] L-GG group, 6. 02 ecy placebo group; P =.028). The decreased incidence of diarrhea in the L-GG group was greatest in the 18- to 29-month age group (P =. 004) and was largely limited to nonbreastfed children (Breastfed: 6. 59 ecy L-GG, 6.32 ecy placebo, P =.7; Nonbreastfed: 4.69 ecy L-GG, 5. 86 ecy placebo, P =.005). The duration of diarrhea episodes and the causes of diarrhea were similar in both groups, except adenovirus was more common in the placebo group. CONCLUSION: L-GG supplementation may be useful as a prophylactic measure to control diarrhea in undernourished children at increased risk, especially nonbreastfed children in the toddler age group.; PIP: This article features a placebo-controlled trial of Lactobacillus GG (L-GG) for diarrhea prevention in undernourished children in Peru. The purpose of the study was to evaluate the use of L-GG as prophylactic treatment for diarrhea. The study population included 204 undernourished children aged 6-24 months, 99 of which were on L-GG and 105 on placebo. Subjects were followed by daily home visits to document diarrhea episodes and diagnostic studies were conducted. Results revealed that children receiving L-GG experienced fewer episodes of diarrhea, which were more pronounced among 18-29 month old children and largely limited to non-breast-fed children. Moreover, the duration of diarrhea episodes and its causes were similar in both groups, except that adenovirus was detected more frequently in the placebo group. In conclusion, L-GG supplementation would decrease diarrhea incidence in high-risk children.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 2 billion
Product formulation: NA
Reference number: 0595

Schultz, et al. Oral therapy with Lactobacillus GG alters the immune response towards bacteroides sp. (Abstract). Eur.J.Clin.Invest. 1999;29 suppl 1:78

Abstract: DESIGN: It was investigated whether a therapy with LGG would alter the immune response towards own and foreign bacterial antigens. Healthy volunteers received LGG or nothing (controls) for 4 weeks. Whole blood and CD4+ T-lymphocytes were stimulated with LPS, PHA-P and LGG and with own or foreign Bacteroides ovatus for five days. RESULTS: Colonization with LGG was confirmed by stool culture. Oral therapy with LGG significantly reduced the proliferative response ($P<0.05$) compared to controls. Thus, an adjuvant probiotic therapy of patients with Irritable Bowel Disease (IBD) might therefore reduce the aggressive immune response towards the resident luminal flora.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10-20 billion
Product formulation: Capsules
Reference number: 0551

Vanderhoof, et al. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. J.Pediatr. 1999;135:564-568

Abstract: 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 x 10(10) - 2 x 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.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic eczema
Study type: In-vitro study and human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: NA
Reference number: 0347

Kankaanpaa, et al. Results on clinical demonstration of probiotics on children. Presented at Functional Food Research in Europe, Third Workshop, PROBDEMO 1998:.

Abstract: DESIGN: The immunomodulatory effects of BB-12 and Lactobacillus rhamnosus LGG were investigated in in vitro and in vivo (clinical) studies. In vitro, lymphocyte proliferation tests were performed with 5 healthy blood donors and phytohemagglutinin-induced proliferation was studied in cultures containing a probiotic extract or dexamethasone. In the clinical study, 49 atopic patients received the elimination diet supplemented with BB-12, LGG or placebo, and the severity of skin symptoms was measured before and after supplementation. RESULTS: In vitro results indicated the suppressive effect of BB-12 on lymphocyte proliferation, the effect comparable to dexamethasone. In the clinical study, the clinical symptoms of atopic dermatitis were significantly alleviated in the group after receiving BB-12 ($P<0.008$) compared to after receiving the placebo ($P<0.18$). The effect of L-GG was similar to BB-12 in both studies. These findings implicate the potential use of these specific probiotics as immunomodulatory agents in the management of allergic inflammation.

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 0.26 billion
Product formulation: Other
Reference number: 0585

Pelto, et al. Probiotic bacteria down-regulate the milk-induced inflammatory response in milk-hypersensitive subjects but have an immunostimulatory effect in healthy subjects. Clin.Exp.Allergy 1998;28(12):1474-1479

Abstract: BACKGROUND: Probiotic bacteria can influence immune responses both specifically by stimulating antibody production and nonspecifically by enhancing phagocytosis of pathogens and modifying cytokine production. OBJECTIVE: The authors hypothesized that probiotic bacteria can alleviate hypersensitivity by influencing phagocytes. The modulation of phagocytes may be different in healthy subjects compared with hypersensitive subjects. SUBJECTS AND METHODS: In a double-blind, cross-over study, challenges with milk in milk-hypersensitive and healthy adults with or without an intestinal bacterial strain, Lactobacillus GG (ATCC 53103) were performed. The challenge-induced immunoinflammatory response was recorded by measuring the expression of phagocytosis receptors prior to and after the challenge using flow cytometry. RESULTS: In milk-hypersensitive subjects, milk challenge increased significantly the expression of CR1, FcgammaRI and FcalphaR in neutrophils and CR1, CR3 and FcalphaR in monocytes. Milk with Lactobacillus GG prevented the increase of the receptor expression. In healthy subjects, milk challenge did not influence receptor expression while milk with Lactobacillus GG increased significantly the expression of CR1, CR3, FcgammaRIII and FcalphaR in neutrophils. CONCLUSION: Probiotic bacteria appear to modulate the nonspecific immune response differently in healthy and hypersensitive subjects. This is seen as an immunostimulatory effect in healthy subjects, and as a down-regulation of immunoinflammatory response in milk-hypersensitive subjects.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Other
Reference number: 0600

Rautanen, et al. Management of acute diarrhoea with low osmolarity oral rehydration solutions and Lactobacillus strain GG. Arch.Dis.Child. 1998;79:157-160

Abstract: Two hypotonic oral rehydration solutions with osmolarities of 224 mosmol/l (Na+ 60 mmol/l, glucose 84 mmol/l) and 204 mosmol/l (Na+ 60 mmol/l, glucose 64 mmol/l), respectively, and oral treatment with Lactobacillus GG were evaluated in a double blind trial in children aged 6-36 months hospitalised for acute diarrhoea. Early administration of Lactobacillus GG at the start of oral rehydration resulted in the shortest duration of diarrhoea, best weight gain, and fastest correction of acidosis. A reduced osmolarity oral rehydration solution (224 mosmol/l) combined with early administration of Lactobacillus GG is an effective treatment for acute diarrhoea in young children; further reduction of osmolarity may not be beneficial.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: Ad libitum
Product formulation: Other
Reference number: 0563

Guarino, et al. Oral bacterial therapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea. J.Pediatr.Gastroenterol.Nutr. 1997;25:516-519

Abstract: BACKGROUND: Oral administration of live Lactobacillus casei strain GG is associated with the reduction of duration of diarrhea in children admitted to the hospital because of diarrhea. The purposes of this work were to investigate the clinical efficacy of oral administration of Lactobacillus in children with mild diarrhea who were observed as outpatients, and to see whether Lactobacillus GG can reduce the duration of rotavirus excretion. METHODS: Duration of diarrhea was recorded in 100 children seen by family pediatricians and randomly assigned to receive oral rehydration or oral rehydration followed by the administration of lyophilized Lactobacillus casei, strain GG. Rotavirus was looked for in the stools of all children and in those in whom results were positive, stools were examined again 6 days after the onset of diarrhea. RESULTS: In 61 children results were positive for rotavirus and in 39 results were negative. Duration of diarrhea was reduced from 6 to 3 days in children receiving Lactobacillus GG, with a similar pattern in rotavirus-positive and -negative children. Six days after the onset of diarrhea, stools in only 4 out of 31 children that received Lactobacillus GG were positive for rotavirus compared with positive findings in 25 out of 30 control subjects. CONCLUSIONS: Oral administration of Lactobacillus GG is effective in rotavirus-positive and rotavirus-negative ambulatory children with diarrhea. Furthermore, it reduces the duration of rotavirus excretion.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 2 billion
Product formulation: Capsules
Reference number: 0557

Hilton, et al. Efficacy of Lactobacillus GG as a Diarrheal Preventive in Travelers. J.Travel Med. 1997:41-43

Abstract: Traveler's diarrhea can be a debilitating problem for individuals on international trips. Retrospective and prospective studies have shown the incidence of traveler's diarrhea to range from 15-56%. 1,2A placebo-controlled, double-blinded study in Finnish travelers found that the probiotic Lactobacillus GG decreases the incidence of traveler's diarrhea.3 Lactobacillus GG, initially isolated from healthy humans, is remarkable in its ability to resist acid and bile degradation and to adhere to the intestinal mucosa.4 To assess the efficacy of Lactobacillus GG in preventing diarrhea in American tourists, a study was conducted at the Travel and Immunization Center of the Long Island Jewish Medical Center (LIJMC).

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Atopic eczema
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 40 billion
Product formulation: Milk powder
Reference number: 0579

Majamaa, Isolauri. Probiotics: a novel approach in the management of food allergy. J.Allergy Clin.Immunol. 1997;99:179-185

Abstract: BACKGROUND: The gastrointestinal microflora is an important constituent of the gut mucosal defense barrier. We have previously shown that a human intestinal floral strain, Lactobacillus GG (ATCC 53103), promotes local antigen-specific immune responses (particularly in the IgA class), prevents permeability defects, and confers controlled antigen absorption. OBJECTIVE: The aim of this study was to evaluate the clinical and immunologic effects of cow's milk elimination without (n = 14) and with (n = 13) the addition of Lactobacillus GG (5 x 10(8) colony-forming units/gm formula) in an extensively hydrolyzed whey formula in infants with atopic eczema and cow's milk allergy. The second part of the study involved 10 breast-fed infants who had atopic eczema and cow's milk allergy. In this group Lactobacillus GG was given to nursing mothers. METHODS: The severity of atopic eczema was assessed by clinical scoring. The concentrations of fecal alpha 1- antitrypsin, tumor necrosis factor-alpha, and eosinophil cationic protein were determined as markers of intestinal inflammation before and after dietary intervention. RESULTS: The clinical score of atopic dermatitis improved significantly during the 1-month study period in infants treated with the extensively hydrolyzed whey formula fortified with Lactobacillus GG. The concentration of alpha 1-antitrypsin decreased significantly in this group (p = 0.03) but not in the group receiving the whey formula without Lactobacillus GG (p = 0.68). In parallel, the median (lower quartile to upper quartile) concentration of fecal tumor necrosis factor-alpha decreased significantly in this group, from 709 pg/gm (91 to 1131 pg/gm) to 34 pg/gm (19 to 103 pg/gm) (p = 0.003), but not in those receiving the extensively hydrolyzed whey formula only (p = 0.38). The concentration of fecal eosinophil cationic protein remained unaltered during therapy. CONCLUSION: These results suggest that probiotic bacteria may promote endogenous barrier mechanisms in patients with atopic dermatitis and food allergy, and by alleviating intestinal inflammation, may act as a useful tool in the treatment of food allergy.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 billion
Product formulation: NA
Reference number: 0608

Malin, et al. Dietary therapy with Lactobacillus GG, bovine colostrum or bovine immune colostrum in patients with juvenile chronic arthritis: evaluation of effect on gut defence mechanisms. Inflammopharmacology 1997:219-236

Abstract: The effect of dietary therapy with a human Lactobacillus strain GG (ATCC 53103), bovine colostrum, or bovine immune colostrum with specific antibodies against anaerobic intestinal bacteria on gut defence mechanisms were studied in juvenile chronic arthritis. Thirty patients with juvenile chronic arthritis were randomly allocated to receive a freeze-dried powder of Lactobacillus GG, or bovine colostrum, or bovine immune colostrum, for a two-week period. Immunologic and non-immunologic gut defence mechanisms were indirectly investigated in blood and faecal samples. In patients receiving Lactobacillus GG, the median (interquartile range) frequency of immunoglobulin-secreting cells, determined by enzyme-linked immunospot assay, increased in the IgA class from 1840 (690-2530) to 3480 (1030-13 170)/10(6) cells; p=0.02. Likewise the median (interquartile range) frequency of specific antibody-secreting cells against dietary antigens increased during the Lactobacillus GG therapy in the IgM class from 3.8 (1.4-5.0) to 11.2 (5.0-30.0)/10(6) cells; p=0.02. In addition, Lactobacillus GG therapy decreased the median (interquartile range) activity of faecal urease, which has been associated with mucosal tissue damage, from 40.3 (21.7-54.3) to 28.6 (24.5-49.4) nmol. min(-1) (mg protein)(-1); p=0.10, while, in patients receiving bovine colostrum, faecal urease activity increased (from 42.2 to 80.6; p=0.04). All findings were transient. We suggest that gut defence mechanisms are disturbed in juvenile chronic arthritis and we further suggest that orally administered Lactobacillus GG has a potential to reinforce the mucosal barrier mechanisms in juvenile chronic arthritis.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Other
Reference number: 0564

Shornikova, et al. A trial in the Karelian Republic of oral rehydration and Lactobacillus GG for treatment of acute diarrhoea. Acta Paediatr. 1997;86:460-465

Abstract: In a controlled trial in Petrozavodsk, Karelia, the effects of oral rehydration and Lactobacillus strain GG (LGG) on recovery from acute diarrhoea (27% rotavirus, 21% bacterial aetiology) were studied in 123 children aged between 1 and 36 months of age. On admission to hospital, the patients were first randomized to receive either isotonic oral rehydration solution (ORS) with osmolarity 311 mosmol/l and sodium 90 mmol/l (WHO-ORS), or a hypotonic ORS with osmolarity 224 mosmol/l and sodium 60 mmol/l (Light-ORS), and thereafter randomized to receive either 5 x 10(9) colony forming units of LGG or a matching placebo. The two ORS performed equally for acute rehydration, and oral rehydration with either ORS was associated with a shorter duration of diarrhoea than intravenous rehydration (p = 0.036). Patients receiving LGG had a significantly shorter duration of watery diarrhoea [mean (SD) 2.7 (2.2) days] than those receiving the placebo [3.7 (2.8) days, p = 0.03]. LGG significantly shortened the duration of rotavirus diarrhoea but not diarrhoea with confirmed bacterial aetiology.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20-200 billion
Product formulation: Other
Reference number: 0568

Pant, et al. Lactobacillus GG and acute diarrhoea in young children in the tropics. J.Trop.Pediatr. 1996;42:162-165

Abstract: A prospective, placebo controlled, triple blind clinical trial was undertaken in Thailand to determine the effect of Lactobacillus GG on recovery from acute diarrhoea in children. Thirty-nine children (mean age = 8 months) were enrolled and following rehydration received either oral Lactobacillus GG (n = 20) as a freeze-dried preparation or placebo (n = 19) twice daily for 2 days. The clinical characteristics of the study groups were similar. There was no significant difference overall in clinical response detected between the study groups. When only those with acute non-bloody diarrhoea (n = 26) were considered, the mean duration of diarrhoea was significantly shorter in the lactobacillus group (1.9 days) than in the placebo group (3.3 days) (P < 0.055). Stool frequency was less on the second day in the lactobacillus group (P < 0.05). The results suggest that Lactobacillus GG accelerates recovery from acute watery diarrhoea in young children in a tropical setting.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1.25 billion
Product formulation: Other
Reference number: 0584

Biller, et al. Treatment of recurrent Clostridium difficile colitis with Lactobacillus GG. J.Pediatr.Gastroenterol.Nutr. 1995;21:224-226

Abstract: DESIGN: Four children (aged 5-70 mo) with bloody diarrhea and abdominal cramping, and with positive Clostriduim difficile cytotoxin assays were treated with LGG for 2 weeks. RESULTS: LGG was successful in the treatment of four children with C. difficile colitis. All four children responded clinically within 5-7 days, with a marked decrease in stool frequency and cramping. All four children were all asymptotic at the end of the 2-week, and with negative C. difficile cytotoxin assays. However, two children became toxin-positive and had diarrhea, and were retreated with LGG. Thereafter, all children remained asympotic and toxin-negative. No side effects were noted.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Immune Health
Research subfield: Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 100 billion
Product formulation: NA
Reference number: 0620

Isolauri, et al. Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by Lactobacillus casei GG. Vaccine 1995;13:310-312

Abstract: In a search for new strategies to improve oral vaccination, the effect of orally administered Lactobacillus casei strain GG (LGG) in conjunction with D x RRV rhesus-human reassortant live oral rotavirus vaccine was tested in 2-5-month-old infants. Infants who received LGG showed an increased response with regard to rotavirus-specific IgM secreting cells, measured using an ELISPOT technique, on day 8 after vaccination. In infants receiving LGG or placebo, respectively, a rotavirus IgM seroconversion was detected in 26/27 (96%), versus 23/27 (85%) cases ($p = 0.15$) and rotavirus IgA seroconversion was detected in 26/28 (93%) versus 20/27 (74%) cases ($p = 0.05$). These findings suggest that LGG has an immunostimulating effect on oral rotavirus vaccination. The clinical significance of LGG-enhanced immune responses to oral vaccines should be further evaluated.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health and Immune Health
Research subfield: Diarrhea / Immune stimulation
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: Other
Reference number: 0582

Kaila, et al. Viable versus inactivated lactobacillus strain GG in acute rotavirus diarrhoea. Arch.Dis.Child. 1995;72:51-53

Abstract: The effect of viable or heat inactivated human Lactobacillus casei strain GG on rotavirus immune responses in patients with rotavirus diarrhoea was assessed. Rotavirus serum IgA enzyme immunoassay antibody responses were higher in infants treated with viable L casei strain GG than in those treated with inactivated L casei strain GG. There was a significant difference at convalescence with rotavirus specific IgA secreting cells found in 10/12 infants receiving viable but only 2/13 infants receiving inactivated L casei strain GG. The results indicate that viable L casei strain GG stimulate rotavirus specific IgA antibody responses, theoretically significant in the prevention of reinfections.

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 billion
Product formulation: Other
Reference number: 0566

Majamaa, et al. Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. J.Pediatr.Gastroenterol.Nutr. 1995;20:333-338

Abstract: We compared different lactic acid bacteria for their effect on the immune response to rotavirus in children with acute rotavirus gastroenteritis. After initial oral rehydration, 49 children aged 6 to 35 months with rotavirus gastroenteritis randomly received either Lactobacillus casei subsp. casei strain GG (LGG), L. casei subsp. rhamnosus (Lactophilus), or a combination of Streptococcus thermophilus and L. delbruckii subsp. bulgaricus (Yalacta) twice daily for 5 days. Serum antibodies to rotavirus, total number of immunoglobulin-secreting cells (ISC), and specific antibody-secreting cells (sASC) to rotavirus were measured at the acute stage and at convalescence. The mean (SD) duration of diarrhea was 1.8 (0.8) days in children who received LGG, 2.8 (1.2) days in those receiving Lactophilus, and 2.6 (1.4) days in those receiving Yalacta (F = 3.3, p = 0.04). The ISC response was comparable in the three study groups, but the rotavirus-specific immune responses were different. LGG therapy was associated with an enhancement of IgA sASC to rotavirus and serum IgA antibody level at convalescent stage. We conclude that certain strains of lactic acid bacteria, particularly LGG, promote serum and intestinal immune responses to rotavirus, and thus may be important in establishing immunity against rotavirus reinfections.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20-200 billion
Product formulation: Other
Reference number: 0562

Raza, et al. Lactobacillus GG promotes recovery from acute nonbloody diarrhea in Pakistan. Pediatr.Infect.Dis.J. 1995;14:107-111

Abstract: A prospective, placebo-controlled, triple blind clinical trial was carried out in Pakistan to determine the effect of Lactobacillus GG on the course of acute diarrhea in hospitalized children. Forty children (mean age, 13 months) were enrolled and after rehydration received either oral Lactobacillus GG (n = 21) or placebo (n = 19) twice daily for 2 days, in addition to the usual diet. The clinical course of diarrhea was followed during the treatment period. Features on admission into the study groups were similar and were characterized by severe diarrhea, malnutrition and inappropriate management before presentation. Response was evident on Day 2 when the frequency of both vomiting and diarrhea was less in the Lactobacillus group. In those who had presented with acute nonbloody diarrhea (n = 32), the percentage of children with persistent watery diarrhea at 48 hours was significantly less in the Lactobacillus group: 31% vs. 75% (P < 0.01). No significant difference was observed by 48 hours in those presenting with bloody diarrhea. The relevance of this finding to the management of diarrhea in the tropics is discussed.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20 billion
Product formulation: Other
Reference number: 0567

Isolauri, et al. Oral bacteriotherapy for viral gastroenteritis. Dig.Dis.Sci. 1994;39(12):2595-2600

Abstract: The effect of orally administered lactobacilli on acute rotavirus diarrhea was tested in 42 well-nourished children ages 5-28 months. After oral rehydration, the patients were randomized to a study group, receiving human Lactobacillus casei strain GG 10(10) colony-forming units twice daily for five days, or a control group not given lactobacilli. Lactobacillus GG was found in the feces in 83% of the study group. The diarrheal phase was shortened in that group. Dietary supplementation with lactobacilli significantly influenced the bacterial enzyme profile: urease activity during diarrhea transiently increased in the control group but not in the study group; F = 8.6, P = 0.01. No intergroup differences were found in beta-glucuronidase, beta-glucosidase, and glycocholic acid hydrolase levels. We suggest that rotavirus infection gives rise to biphasic diarrhea, the first phase being an osmotic diarrhea and the second associated with overgrowth of specifically urease-producing bacteria. Oral bacteriotherapy appears a promising means to counteract the disturbed microbial balance.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Recovery
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 0.2 billion
Product formulation: Milk powder
Reference number: 0596

Millar, et al. Enteral feeding of premature infants with Lactobacillus GG. Arch.Dis.Child. 1993;69:483-487

Abstract: The objectives of this study were to determine whether or not the probiotic Lactobacillus GG can colonise the immature bowel of premature infants and if so, does colonisation result in a reduction of the size of the bowel reservoir of nosocomial pathogens such as enterobacteriaceae, enterococci, yeasts or staphylococci, and does colonisation with Lactobacillus GG have any effect on the clinical progress and outcome. Twenty preterm infants with a gestational age of 33 weeks or less who were resident on a neonatal unit were studied from the initiation of milk feeds until discharge. The infants were randomised to receive either milk feeds or milk feeds supplemented with Lactobacillus GG 10(8) colony forming units twice a day for two weeks. The clinical features of the two groups of infants were similar. Orally administered Lactobacillus GG was well tolerated and did colonise the bowel of premature infants. However, colonisation with Lactobacillus GG did not reduce the faecal reservoir of potential pathogens and there was no evidence that colonisation had any positive clinical benefit for this particular group of infants.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Recovery
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: Tablets: 1 billion, 4 billion, 8 billion. Fermented milk: 2.1 billion, 12 billion
Product formulation: Fermented milk or tablets
Reference number: 0601

Saxelin, et al. Dose response on the faecal colonisation of Lactobacillus strain GG administered in two different formulations. Microb.Ecol.Health Dis. 1993:119-122

Abstract: DESIGN: Fecal colonization of LGG in human subjects were studied after oral administration of LGG was given to 44 20- to 55-y-old healthy volunteers for 7 days as enterocoated tablets and in fermented milk. RESULTS: Fermented milk and enterocoated tablets are good carriers for administrating LGG. All 44 volunteers excreted LGG by day 3 of the test period and continued to do so during the test period. There was no statistical difference between the tablet groups in mean fecal LGG contents. With fermented milk, there was a marked, statistically significant increase in mean fecal LGG content when the administration was 12 billion cfu/d compared to 2.1 billion cfu/d.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Other
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 0.2 billion
Product formulation: Milk powder
Reference number: 0603

Stansbridge, et al. Effects of feeding premature infants with Lactobacillus GG on gut fermentation. Arch.Dis.Child. 1993;69:488-492

Abstract: The study aimed to find out whether gut colonisation of premature babies with a probiotic, Lactobacillus GG, modified enteric carbohydrate fermentation. Twenty preterm infants were randomised to receive Lactobacillus GG 10(8) colony forming units twice a day for two weeks or to a control group. Faecal short chain fatty acids (SCFAs), ethanol, and urinary 2,3-butanediol, were measured in parallel with microbiological studies. Lactobacillus GG colonised nine babies. From 1-28 days of age faecal SCFAs did not differ significantly from controls. Median and ranges were (treated and controls, respectively): acetic acid: 173 (trace-799), 166 (trace-700); propionic acid: 44 (trace-169), 37 (11-229); butyric acid: 31 (5-107), 37 (2-118) mumol/g dry weight. Ethanol was detected in more faecal samples from treated babies (65% v 37%), and at higher concentration (6.3 (trace-40) v 3.3 (0.6-8.8; one 229) mumol/g). 2,3-Butanediol was found in 66% of urine samples from treated babies and 58% from controls. On 83% of these occasions Klebsiella sp, Enterobacter sp, or Serratia sp were cultured from faeces. Lactobacillus GG had no obvious adverse effects on nutritionally important SCFAs. The small increase in ethanol excretion is unlikely to have clinical significance.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Recovery
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: a: 40 billion b: 360 billion c: 160 billion
Product formulation: Fermented milk
Reference number: 0593

Goldin, et al. Survival of Lactobacillus species (strain GG) in human gastrointestinal tract. Dig.Dis.Sci. 1992;37:121-128

Abstract: A newly isolated strain of a species of Lactobacillus of human origin, designated GG (Lactobacillus GG), has been studied to determine its ability to survive in the human gastrointestinal tract. When fed to 76 volunteers as a frozen concentrate or as a fermented preparation in milk or whey, Lactobacillus GG was recovered in the feces of all subjects receiving the fermented milk or whey and in 86% receiving the frozen concentrate when a single fecal specimen was cultured. The organism was also present in the feces of subjects concurrently receiving ampicillin. After terminating feeding of the organism, Lactobacillus GG persisted in the feces of 87% of volunteers four days later and in 33% of subjects seven days later. Lactobacillus GG lowered fecal bacterial beta-glucuronidase activity by approximately 80% in volunteers given the organism for four weeks. These studies demonstrate that Lactobacillus GG can survive and temporarily colonize the human gastrointestinal tract and can affect the metabolic activity of the resident microflora.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20-200 billion
Product formulation: Fermented milk
Reference number: 0561

Kaila, et al. Enhancement of the circulating antibody secreting cell response in human diarrhea by a human Lactobacillus strain. Pediatr.Res. 1992;32:141-144

Abstract: Human Lactobacillus sp strain GG (Lactobacillus GG) administered during acute rotavirus diarrhea has been shown to promote clinical recovery. To elucidate the immune mechanisms behind such a favorable outcome, the ELISPOT (solid phase enzyme-linked immunospot) assay of Ig- and specific antibody-secreting cells among circulating lymphocytes was used, giving indirect evidence of the immunologic events in the gut. After rehydration, 39 children with acute rotavirus diarrhea, mean age 16 (SD 6) mo, randomly received either a Lactobacillus GG fermented milk product (study group) or a pasteurized yogurt (placebo group). The duration of diarrhea was significantly shorter in the study group than in the placebo group [mean 1.1 (SD 0.6) versus 2.5 (SD 1.4)d, p = 0.001]. Lactobacillus GG therapy was associated with a significantly enhanced nonspecific humoral response during the acute phase of the infection, reflected in the IgG, IgA, and IgM Ig-secreting cell numbers. At convalescence, 90% of the study group versus 46% of the placebo group had developed an IgA specific antibody-secreting cell response to rotavirus (p = 0.006). The results indicate that Lactobacillus GG promotes recovery from rotavirus diarrhea via augmentation of the local immune defense. Furthermore, specific IgA response to rotavirus is endorsed, which is possibly relevant in protection against reinfections.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 20-200 billion
Product formulation: Other
Reference number: 0560

Isolauri, et al. A human Lactobacillus strain (Lactobacillus casei sp strain GG) promotes recovery from acute diarrhea in children. Pediatrics 1991;88:90-97

Abstract: To determine the effect of a human Lactobacillus strain (Lactobacillus casei sp strain GG, Gefilac) on recovery from acute diarrhea (82% rotavirus), 71 well-nourished children between 4 and 45 months of age were studied. After oral rehydration, the patients randomly received either Lactobacillus GG-fermented milk product, 125 g (10(10-11) colony-forming units) twice daily (group 1); Lactobacillus GG freeze-dried powder, one dose (10(10-11) colony-forming units) twice daily (group 2); or a placebo, a pasteurized yogurt (group 3) 125 g twice daily; each diet was given for 5 days, in addition to normal full diet otherwise free of fermented dairy products. The mean (SD) duration of diarrhea after commencing the therapy was significantly shorter in group 1 (1.4 [0.8] days) and in group 2 (1.4 [0.8] days) than in group 3 (2.4 [1.1] days); F = 8.70, P less than 0.001. After rehydration, each dietary group maintained a positive weight trend. The urinary lactulose-mannitol recovery ratios (means [95% confidence intervals]) on admission were 0.09 (0.03, 0.24) in group 1, 0.12 (0.07, 0.22) in group 2, and 0.08 (0.04, 0.18) in group 3; no significant alterations in intestinal permeability were observed at retesting after 2 days of realimentation. The result indicates that early nutritional repletion after rehydration causes no mucosal disruption and is beneficial for recovery from diarrhea. It is further suggested that Lactobacillus GG in the form of fermented milk or freeze-dried powder is effective in shortening the course of acute diarrhea.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Recovery
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1.5 million, 15 million, 0.15 billion, 1.5 billion, 15 billion, or 150 billion
Product formulation: Other
Reference number: 0594

Saxelin, et al. Dose response colonisation of faeces after oral administration of Lactobacillus casei strain GG. Microb.Ecol.Health Dis. 1991:209-214

Abstract: DESIGN: In order to examine the fecal colonization properties of LGG, 39 healthy volunteers, aged 18-55 y, were given one of six different levels of LGG (freeze-dried powder) orally for 7 days. RESULTS: No LGG was detected in the fecal samples of the volunteers prior to the study. With the doses 15 billion cfu/d and 150 billion cfu/d, all volunteers were colonized.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 2 billion
Product formulation: Other
Reference number: 0556

Oksanen, et al. Prevention of travellers' diarrhoea by Lactobacillus GG. Ann.Med. 1990;22:53-56

Abstract: A placebo-controlled double-blind study was conducted on the efficacy of Lactobacillus GG in preventing travellers' diarrhoea. Altogether 820 persons travelling on holiday to southern Turkey to two destinations were randomized into two groups receiving either Lactobacillus GG or placebo in identical sachets. On the return flight each participant completed a questionnaire indicating the incidence of diarrhoea and related symptoms during the trip. Of the original group 756 (92%) subjects completed the study acceptably. The overall incidence of diarrhoea was 43.8% (331 cases). The total incidence of diarrhoea 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 diarrhoea when compared to younger travellers. Lactobacillus GG appeared to be effective in reducing the occurrence of travellers' diarrhoea in one of the two destinations with no side effects.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: Fermented milk
Reference number: 0552

Siitonen, et al. Effect of Lactobacillus GG yoghurt in prevention of antibiotic associated diarrhoea. Ann.Med. 1990;22:57-59

Abstract: The efficacy of Lactobacillus GG yoghurt in preventing erythromycin associated diarrhoea was studied. Sixteen healthy volunteers were given erythromycin acistrate 400 mg t.i.d for a week. The volunteers were randomly assigned into two groups taking twice daily 125 ml of either Lactobacillus GG fermented yoghurt or pasteurized regular yoghurt as placebo during the drug treatment. Subjects receiving Lactobacillus GG yoghurt with erythromycin had less diarrhoea than those taking pasteurized yoghurt. Other side effects of erythromycin, such as abdominal distress, stomach pain and flatulence, were less common in the GG yoghurt group than in the placebo yoghurt group. The subjects receiving Lactobacillus GG yoghurt were colonized with these bacteria even during erythromycin treatment as measured by faecal counts of total Lactobacillus GG. No Lactobacillus GG was found in the faecal samples of volunteers in the group taking pasteurized yoghurt.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com

Research field: Gastrointestinal Health
Research subfield: Diarrhea
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: NA
Reference number: 0623

Gorbach, et al. Successful treatment of relapsing Clostridium difficile colitis with Lactobacillus GG. Lancet 1987(8574):1519

Abstract: DESIGN: LGG was given for 5-10 days to five patients, aged 35-93 years, with relapsing C. difficile colitis, despite use of normal drugs (metronidazole, vancomycin, bacitracin, cholestyramine). RESULTS: Four patients had an immediate satisfactory result with termination of diarrhea and no further relapses. One patient had initial improvement, but relapsed 3 days later with diarrhea, was then treated again with metronidazole, followed by LGG treatment, after which there were no further relapses.

Chr. Hansen A/S -10-12 Bøge Allé – DK-2970 Hørsholm, Denmark - Phone: +45 45 74 74 74 - Fax: +45 45 74 88 88 - www.chr-hansen.com