Study summaries BB-12®

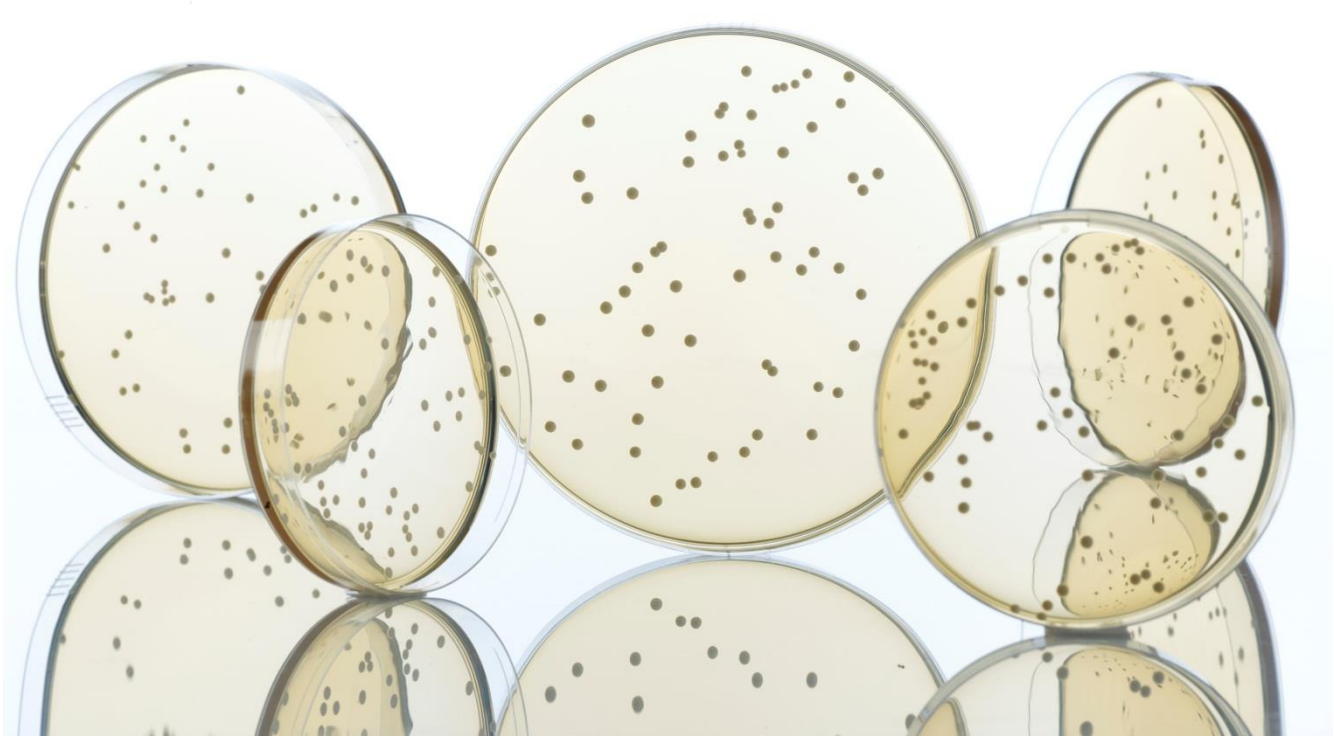
This binder contains summaries of clinical studies performed with with *Bifidobacterium* BB-12® - alone or in combination with other strains.

Clinical studies are performed within Infant & Children's Nutrition – including studies in pre-term infants and pregnant women.

February 2019

Chr. Hansen A/S

Human Health & Nutrition



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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and L. rhamnosus LGG®
Dosage CFU/day: 1 x 10^9 of each

Larnkjær, A., et al. "Effect of probiotics on thymus size and markers of infection in late infancy: a randomized controlled trial". *Pediatric Research*, (January), 1–6 (2020).

Abstract: BACKGROUND: Probiotics are known to stimulate the immune system but the effect on thymus size in late infancy is unknown. We examined the effect of probiotics on thymus size and C-reactive protein (CRP) in healthy Danish infants starting daycare. We further examined associations between thymus size, CRP and recent infections. METHODS: The study included 186 children randomized to a combination of Lactobacillus rhamnosus, LGG® and Bifidobacterium animalis spp. lactis, BB-12® or placebo for 6 months. Thymus size, assessed as thymus index (TI) and thymus weight index (TWI), was measured by ultrasound at baseline and at endpoint. Blood samples were drawn to measure CRP. Infections were parent-reported. RESULTS: There was no significant difference in thymus size between the probiotic group and placebo ($p \geq 0.248$) but TWI tended to be higher in the probiotic group corresponding to 5% higher than placebo ($p = 0.068$) in an adjusted model. There was no effect of probiotics on CRP ($p = 0.331$). At the endpoint, thymus size was inversely associated with CRP ($p \leq 0.040$), diarrhea ($p \leq 0.050$), and TI was also associated with the absence from daycare due to respiratory or gastrointestinal infections ($p = 0.010$). CONCLUSION: The probiotic intervention had no effect on thymus size or CRP in Danish children at the age of starting daycare.

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Research field: Infant and Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and L. rhamnosus LGG®
Dosage CFU/day: 10 billion total

Castro-Mejía, J. L., et al. "Restitution of gut microbiota in Ugandan children administered with probiotics (Lactobacillus rhamnosus GG and Bifidobacterium animalis subsp. lactis BB-12) during treatment for severe acute malnutrition". *Gut Microbes*, *00*(00), 1–13 (2020).

Abstract: Severe acute malnutrition (SAM) is a major challenge in low-income countries and gut microbiota (GM) dysbiosis may play a role in its etiology. Here, we determined the GM evolution during rehabilitation from SAM and the impact of probiotics (Lactobacillus rhamnosus GG and Bifidobacterium animalis subsp. lactis BB-12) supplementation. The GM (16S rRNA gene amplicon sequencing) of children admitted to hospital with SAM showed distinct composition over admission (e.g. Klebsiella spp., and Enterobacteriaceae spp.), discharge (e.g. Clostridiaceae spp., Veilonella dispar) and follow-up (e.g. Lactobacillus ruminis, Blautia spp., Faecalibacterium prausnitzii), reaching similar β- and α-diversity as healthy individuals. Children with diarrhea had reduced distribution of Bacteroidaceae, Lachnospiraceae, increased Enterobacteriaceae and Moraxellaceae, and lower α-diversity. Children suffering from edematous SAM had diminished proportion of Prevotellaceae, Lachnospiraceae, Ruminoccaceae and a higher α-diversity when compared to non-edematous SAM. Supplementation of probiotics did not influence β-diversity upon discharge or follow-up, but it increased ($p < .05$) the number of observed species [SE: > 4.5]. Children where the probiotic species were detected had lower cumulative incidence ($p < .001$) of diarrhea during the follow-up period compared to children receiving placebo and children receiving probiotics, but where the probiotics were not detected. The GM of children with non-edematous and edematous SAM differ in composition, which might have implications for future GM targeted treatments. Probiotics treatment reduced the cumulative incidence of diarrhea during the outpatient phase, with the strongest effect in children where the administered probiotics could be detected in the GM.

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Research field: Maternal Health and Mental Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and L. rhamnosus LGG®
Dosage CFU/day: minimum of 6.5 x 10^9

Dawe, J. P., et al. "Probiotics and Maternal Mental Health: A Randomised Controlled Trial among Pregnant Women with Obesity". *Scientific Reports*, *10*(1), 1–11 (2020).

Abstract: Poor maternal mental health has been associated with a myriad of pregnancy and child health complications. Obesity in pregnancy is known to increase one's risk of experiencing poor maternal mental health and associated physical and mental health complications. Probiotics may represent a novel approach to intervene in poor mental health and obesity. We conducted this pre-specified secondary analysis of the Healthy Mums and Babies (HUMBA) randomised controlled trial to investigate whether probiotics would improve maternal mental health outcomes up to 36 weeks of pregnancy. Two-hundred-and-thirty pregnant women with obesity (BMI ≥ 30.0 kg/m2) were recruited and randomised to receive probiotic (Lactobacillus rhamnosus GG and Bifidobacterium lactis BB12, minimum 6.5 × 109 CFU) or placebo capsules. Depression, anxiety, and functional health and well-being were assessed at baseline (120−176 weeks' gestation) and 36 weeks of pregnancy. Depression scores remained stable and did not differ between the probiotic (M = 7.18, SD = 3.80) and placebo groups (M = 6.76, SD = 4.65) at 36 weeks (p-values > 0.05). Anxiety and physical well-being scores worsened over time irrespective of group allocation, and mental well-being scores did not differ between the two groups at 36 weeks. Probiotics did not improve mental health outcomes in this multi-ethnic cohort of pregnant women with obesity.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU: 10^9 of each strain

Schmidt et al. "Probiotics in late infancy reduce the incidence of eczema : A randomized controlled trial". *Pediatr Allergy Immunol*, *30*(3), 1–6, (2019).

Abstract: Abstract Background: Allergic diseases are common and represent a considerable health and economic burden worldwide. We aimed to examine the effect of a combination of two probiotic strains administered in late infancy and early childhood on the development of allergic diseases and sensitization. Methods: In this double-blind, placebo-controlled intervention trial, participants were randomized to receive a daily mixture of Lactobacillus rhamnosus and Bifidobacterium animalis subsp lactis or placebo—starting prior to attending day care. The intervention period was 6 months, and the parents answered web-based questionnaires on allergic symptoms and doctor's diagnosed allergic disease monthly. IgE was measured at baseline and follow-up. Results: A total of 290 participants were randomized: 144 in the probiotic group and 146 in the placebo group. Mean age at intervention start was 10.1 months. At follow- up (mean age 16.1 months), the incidence of eczema was 4.2% in the probiotic group and 11.5% in the placebo group (P = 0.036). The incidence of asthma and conjunctivitis did not differ between groups, and no children presented with rhinitis. Sensitization was equal in the two groups at intervention start (7.5% and 9.5%, respectively), and two children in each group were sensitized during the intervention. Conclusions: We observed a significantly lower incidence of eczema in the probiotic group compared to the placebo group. The probiotics were administered in late infancy— prior to attending day care—suggesting a broader window of opportunity using probiotics in the prevention of eczema. The incidence of asthma, rhinitis, conjunctivitis, and sensitization did not differ.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day:

Nabukeera-Barungi et al. "Thymus gland size during recovery from complicated severe acute malnutrition: a prospective study of the role of probiotics". Paediatrics and International Child Health, 39(2), 95–103, (2019).

Abstract: BACKGROUND: Children with severe acute malnutrition (SAM) are prone to infections due to immune dysfunction including severe thymus atrophy which recovers during nutritional rehabilitation. AIM: To investigate predictors of thymus size recovery, including probiotics during nutritional rehabilitation of children admitted with complicated SAM. METHODS: In this prospective study nested in a randomized controlled trial, children 6-59 months admitted with SAM received standard care and either probiotics or placebo during hospitalization until 8 weeks post-discharge. Thymus size was measured using ultrasound at admission, discharge, 8 weeks post-discharge and among 27 community controls. Predictors of thymus size recovery were assessed using linear regression. RESULTS: Among 388 children with SAM, mean (SD) thymus size was 1.06 cm2 (0.41), 1.24 cm2 (0.48), 2.85 cm2 (1.07) and 4.2 cm2 (0.93) at admission, discharge, follow-up and in the healthy controls respectively ($p < 0.05$).Probiotics did not affect thymus recovery. During both inpatient therapeutic care (ITC) and outpatient therapeutic care (OTC), thymus recovery correlated positively with anthropometry but negatively with caregiver-perceived illness severity and Haemoglobin <8 g/dl. Negative predictors of thymus recovery during ITC included grade 3 oedema (beta -0.13, 95%CI -0.25; -0.01), dermatosis (beta -0.21, 95%CI -0.41; -0.01), C-reactive protein (CRP) >15mg/L (beta -0.13, 95%CI -0.25; -0.02) and neutrophils (beta -0.01, 95%CI -0.02; -0.002). During OTC, HIV negatively predicted thymus recovery. CONCLUSION: Children with SAM failed to regain thymus size at 8 weeks post-discharge. Probiotics did not predict thymus recovery during nutritional rehabilitation. More research is needed to find interventions which can accelerate immune recovery. ABBREVIATIONS: ART, Antiretroviral therapy; BB-12, Bifidobacterium animalis subsp. Lactis; CRP, C-reactive protein; ITC, inpatient therapeutic care; LGG, Lactobacillus rhamnosus; MNU, Mwanamugimu Nutrition Unit; MUAC, mid-upper arm circumference; OTC, outpatient therapeutic care; PCR, Polymerised chain reaction; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; VAS, visual analogue score; WHO, World Health Organization; WHZ, weight-for-height score.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU/day: 6.5 x 10^9

Okesene-Gafa et al, "Effect of antenatal dietary interventions in maternal obesity on pregnancy weight-gain and birthweight: Healthy Mums and Babies (HUMBA) randomized trial". *American Journal of Obstetrics and Gynecology*, *221*(2), 152.e1-152.e13 (2019).

Abstract: Background: Pregnancy interventions that improve maternal and infant outcomes are urgently needed in populations with high rates of obesity. We undertook the Healthy Mums and Babies (HUMBA) randomized controlled trial to assess the effect of dietary interventions and or probiotics in a multiethnic population of pregnant women with obesity, living in an area of high deprivation. Objectives: To determine whether a culturally tailored dietary intervention and or daily probiotic capsules in pregnant women with obesity reduces the co-primary outcomes of (1) excessive gestational weight gain (mean >0.27 kg/week) and (2) birthweight. Study Design: We conducted a 2 × 2 factorial, randomized controlled trial in women without diabetes at pregnancy booking, body mass index ≥30 kg/m 2 , and a singleton pregnancy. At 12 +0 to 17 +6 weeks' gestation, eligible women were randomized to a dietary intervention (4 tailored educational sessions at ≤28 weeks' gestation by a community health worker trained in key aspects of pregnancy nutrition plus text messaging until birth) or to routine dietary advice; and to daily capsules containing either (Lactobacillus rhamnosus GG and Bifidobacterium lactis BB12, minimum 6.5 × 10 9 colony forming units), or placebo, until birth. Analysis was by intention to treat with adjustment for maternal baseline body mass index. Infant outcomes were additionally adjusted for ethnicity, sex, and gestational age at birth. Results: In total, 230 women were recruited between April 2015 and June 2017 (dietary intervention N = 116 vs routine dietary advice N = 114; probiotics N = 115 vs placebo N = 115). Baseline characteristics and demographic variables were similar across all groups. There was no significant difference between intervention groups, for the co-primary outcomes of (1) proportion of women with excessive gestational weight gain (dietary intervention vs routine advice: 79/107 [73.8%] vs 90/110 [81.8%], adjusted relative risk [relative risk, 0.92; 95% confidence interval, 0.80–1.05]; probiotics versus placebo: 89/108 [82.4%] and 80/109 [73.4%], relative risk, 1.14, 95% confidence interval, 0.99–1.31) or (2) birthweight (dietary intervention vs routine advice: 3575 vs 3612 g, adjusted mean difference, −24 g, 95% confidence interval, −146 to 97; probiotics vs placebo: 3685 vs 3504 g, adjusted mean difference, 107 g, 95% confidence interval, −14 to 228). Total maternal weight gain, a secondary outcome, was lower with dietary intervention compared with routine dietary advice (9.7 vs 11.4 kg, adjusted mean difference, −1.76, 95% confidence interval, −3.55 to 0.03). There were no significant differences between intervention groups in other secondary maternal or neonatal outcomes. Conclusion: Although dietary education and or probiotics did not alter rates of excessive gestational weight gain or birthweight in this multiethnic, high-deprivation population of pregnant women with obesity, dietary education was associated with a modest reduction in total weight gain with potential future benefit for the health of mothers and their offspring if sustained.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU/day: 2 x 10^9

Adler Sørensen et al. "Probiotics and the immunological response to infant vaccinations; a double-blind randomized controlled trial". *Clinical Microbiology and Infection*, *25*(4), 511.e1-511.e7, (2019).

Abstract:
Objectives: To examine the effect of a combination of probiotics on the antibody response to pneumococcal and pertussis vaccination in healthy Danish children, aged 8–14 months, at the time of starting day care. Moreover, the cytokine response to lipopolysaccharide of whole blood was assessed. Methods: A total of 290 children were randomly allocated to receive a combination of Bifidobacterium animalis ssp. lactis and Lactobacillus rhamnosus GG daily for a 6-month intervention period, and blood samples were drawn at the start and end of the study. Specific antibody response towards Streptococcus pneumoniae serotypes and Bordetella pertussis toxin, as well as endotoxin-induced interleukin-6 (IL-6) and interferon-γ (IFN-γ) production in blood were analysed by Luminex and ELISA. Results: There was no significant difference between the average individual changes from baseline to end of study in antibody concentrations for S. pneumoniae for both the probiotics (340.4% ± 11.2%) and the placebo group (382.9% ± 10.4%) (p 0.525), nor for B. pertussis toxin in the two groups (probiotics 190.1% ± 12.6% versus placebo 238.8% ± 1.1%, p 0.340). The average individual change in IL-6 concentration was significantly lower in the probiotics versus the placebo group (2.9% ± 10.3% versus 33.7% ± 9.0%, p 0.024), whereas there was no difference in IFN-γ concentration (0.0% ± 0.2% versus −0.2% ± 0.1%, p 0.279). Conclusions: The probiotic intervention did not affect the antibody response against S. pneumoniae and B. pertussis toxin in healthy Danish children.

Research field: Infant and Children´s Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12®
Dosage CFU/day: 1 × 10^9 cfu BB-12® per day

Nocerino et al. *Bifidobacterium animalis* subsp.*lactis* BB-12 is effective in the treatment of infant colic: result of a randomized controlled trial. *Alimentary Pharmacology & Therapeutics*, (December), 1–11, (2019)

Abstract
OBJECTIVES AND STUDY. Infant colic (IC) is a very common affecting up to 20-40% of infants aged <3 m, with a typical peak at about 6 wks of age. The pathophysiology is still poorly defined, but alterations in gut microbiota structure and function seem to be involved. This suggests the potential role of probiotics as therapeutic strategy. We aimed to evaluate the potential efficacy of *Bifidobacterium animalis* subsp.*lactis* BB-12 (BB-12) in babies with IC. Main study outcome was the rate of infants with a reduction of ≥50% of mean daily crying duration at 28 days after intervention. Secondary outcomes were the mean number of crying episodes, occurrence of infectious episodes, number of bowel movements and stool consistency. Gut microbiota structure and function (butyrate production) and fecal level of human beta defensin 2 (HBD-2), cathelicidin (LL-37), secretory IgA (sIgA) and calprotectin (CLP) were also evaluated.
METHODS. A double-blind RCT on otherwise healthy exclusively breastfed infants aged ≤ 7 wks, with IC were performed. Infants were randomly allocated to 2 groups (group A, BB-12 or group B, placebo) according to the randomization list. Study products were provided in drops packed in identical boxes with the same color, weight, smell and taste. Each subject assumed orally 6 drops/day of the assigned product for 28 consecutive days. Patient's parents were provided with a diary to report daily the number and duration of crying episodes, number of bowel movements and stool consistency. All subjects were clinically examined weekly and parents' diary completeness were checked. At baseline and at the end of treatment, a stool sample was collected from all study subjects to assess gut microbiota structure (16sRNA), butyrate production (HPLC-MS), HBD-2, LL-37, sIgA, CLP (ELISA).
RESULTS. 80 infants were randomized, 40 per group; 8 subjects were lost to follow up, and 72 subjects completed the study: 35 in BB-12 group and 37 in placebo group. At baseline, main demographic and clinical features of the 2 study groups were similar. The rate of infants with reduction of ≥50% of duration of crying was significantly higher in infants treated with BB-12 compared to placebo (80% vs 32.5% respectively, $p<0.05$). The mean number of crying episodes significantly decreased in both groups, but with a significant higher effect in BB-12 group
(-4.77±3.43 vs -2.31±2.28 respectively, $p<0.05$). Mean daily stool frequency decreased in both groups but the effect was significant higher in the BB-12 group; stool consistency was similar between the 2 groups. A significant increase in Bifidobacterium abundance, butyrate production, HBD-2, LL-37, sIgA, associated with a decrease in CLP level was observed in BB-12 group. ($p<0.05$).
CONCLUSIONS. The results of this study demonstrate that the oral daily supplementation with BB-12 is effective in managing IC. The effect could derive from multiple immune and non-immune mechanisms associated with a possible modulation of gut microbiota. This RCT studied specific well characterized probiotic strain, dose, and age group. The findings cannot be extrapolated for other probiotic strains.

Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and E. faecium L3
Dosage CFU/day: 2 billion of each strain

Di Pierro, Francesco et al. "Use of a Probiotic Mixture Containing Bifidobacterium Animalis Subsp. Lactis BB12 and Enterococcus Faecium L3 in Atopic Children." Minerva Pediatrica 70.5 (2018): 418–424.

Abstract: BACKGROUND Imbalance of the human gut microbiota in childhood, mainly due to low gut biodiversity and a low bifidobacterial load, has been suggested as a risk factor for atopy. Administration of Enterococcus faecium L3 in infants has been shown to increase the gut bifidobacterial count. The aim was to verify if a mixture of Bifidobacterium animalis subsp. lactis BB12 and E. faecium L3 could reduce the signs, symptoms and need for drugs in atopic children. METHODS We retrospectively analyzed, and compared with controls, clinical outcomes following use of BB12 and L3 strains when administered 3 months before or during the development of signs and symptoms of atopy. RESULTS When administered in the 3 months before the development of atopy, the BB12 and L3 strains significantly reduced ($p<0.001$) rhinitis, watery eyes and cough/bronchospasm. However, reduced efficacy was observed when the mixture was given during the 3 months of atopy. The mixture of strains also significantly reduced the use of oral anti-histamines, inhaled corticosteroids (in the same children in two different years) and oral corticosteroids (in different children in the same year). CONCLUSIONS When administered as a prophylactic, the mixture of BB12 and L3 (iNatal Ped®) statistically decreases the signs and symptoms of atopy and reduces the use of drugs. Administration of the same probiotics as treatment after the appearance of atopy is less effective.

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Research field: Infant and Children´s Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and Lactobacillus acidophilus LA-5 and L. rhamnosus LGG®
Dosage CFU/day: 5×10^{10} cfu of LGG and Bb-12 and 5×10^{9} cfu of La-5 per day

Simpson, Melanie Rae et al. "Breastfeeding-Associated Microbiota in Human Milk Following Supplementation with Lactobacillus Rhamnosus GG, Lactobacillus Acidophilus La-5, and Bifidobacterium Animalis Ssp Lactis Bb-12." Journal of Dairy Science 101.2 (2018): 889–899.

Abstract: Breastfeeding is one of the major factors affecting the early development of the infant gut microbiota, and weaning is associated with a shift in the gut microbiota toward a more adult composition. Through breastfeeding, infants receive bioactive components that shape their microbiota while also being exposed to the breast milk and breast surface microbial communities. Recent studies have suggested the possibility of an entero-mammary route of microbial transfer, opening the possibility of infant gut microbiota modulation through maternal probiotic supplementation. In this study, we have analyzed breast milk samples collected at 10 d and 3 mo postpartum from women participating in the Probiotics in the Prevention of Allergy among Children in Trondheim placebo controlled trial. Women who were randomized to the probiotic arm of the Probiotics in the Prevention of Allergy among Children in Trondheim trial received a fermented milk supplemented with Lactobacillus rhamnosus GG, Lactobacillus acidophilus La-5, and Bifidobacterium animalis ssp. lactis Bb-12, consuming this daily from 4 wk before their expected due date until 3 mo after birth. In total, 472 breast milk samples were assessed for the administered bacteria using quantitative real-time PCR and the microbiota transferred during breastfeeding was analyzed using 16S ribosomal RNA gene sequencing of 142 samples. We found that breastfeeding is unlikely to be a significant source of L. rhamnosus GG, L. acidophilus La-5, and B. animalis ssp. lactis Bb-12 for infants in the probiotic arm of the trial. Furthermore, maternal supplementation did not significantly affect the overall composition of the breast milk microbiota transferred during breastfeeding. We also present a descriptive analysis of this microbiota, which was largely dominated by Streptococcus and Staphylococcus genera at both 10 d and 3 mo postpartum. Samples collected at 3 mo postpartum had a statistically significant lower presence and relative abundance of the Staphylococcus genus. These samples also had a greater number of observed species and diversity, including more operational taxonomic units from the Rothia, Veillonella, Granulicatella, and Methylbacterium genera.

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Research field: Infant and Children´s Nutrition
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12®, Bifidobacterium longum subsp. infantis BB-02 and Streptococcus thermophilus TH-4
Dosage CFU/day: 350 x 10^6, 300x10^6 and 350x10^6 CFU, respectively

Plummer, Erica L. et al. "Gut Microbiota of Preterm Infants Supplemented with Probiotics: Sub-Study of the ProPrems Trial." Bmc Microbiology 18.1 (2018): 184.

Abstract: Background: The ProPrems trial, a multi-center, double-blind, placebo-controlled randomized trial, previously reported a 54% reduction in necrotizing enterocolitis (NEC) of Bell stage 2 or more from 4.4 to 2.0% in 1099 infants born before 32 completed weeks' gestation and weighing < 1500 g, receiving probiotic supplementation (with Bifidobacterium longum subsp. infantis BB-02, Streptococcus thermophilus TH-4 and Bifidobacterium animalis subsp. lactis BB-12). This sub-study investigated the effect of probiotic supplementation on the gut microbiota in a cohort of very preterm infants in ProPrems. Results: Bifidobacterium was found in higher abundance in infants who received the probiotics (AOR 17.22; 95% CI, 3.49–84.99, p < 0.001) as compared to the placebo group, and Enterococcus was reduced in infants receiving the probiotic during the supplementation period (AOR 0.27; 95% CI, 0.09–0.82, p = 0.02). Conclusion: Probiotic supplementation with BB-02, TH-4 and BB-12 from soon after birth increased the abundance of Bifidobacterium in the gut microbiota of very preterm infants. Increased abundance of Bifidobacterium soon after birth may be associated with reducing the risk of NEC in very preterm infants.

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Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU/day:

Tan, Tina P. et al. "Safety of Bifidobacterium Animalis Subsp Lactis (B. Lactis) Strain BB-12-Supplemented Yogurt in Healthy Children." Journal of Pediatric Gastroenterology and Nutrition 64.2 (2017): 302–309.

Abstract: OBJECTIVES: Probiotics are live microorganisms that may provide health benefits to the individual when consumed in sufficient quantities. For studies conducted on health or disease endpoints on probiotics in the United States, the Food and Administration has required those studies to be conducted as investigational new drugs. This phase I, double-blinded, randomized, controlled safety study represents the first requirement of this pathway. The purpose of the study was to determine the safety of Bifidobacterium animalis subsp. lactis (B lactis) strain BB-12 (BB-12)-supplemented yogurt when consumed by a generally healthy group of children. The secondary aim was to assess the effect of BB-12-supplemented yogurt on the gut microbiota of the children.
METHODS: Sixty children ages 1 to 5 years were randomly assigned to consume 4 ounces of either BB-12-supplemented yogurt or nonsupplemented control yogurt daily for 10 days. The primary outcome was to assess safety and tolerability, as determined by the number of reported adverse events.
RESULTS: A total of 186 nonserious adverse events were reported, with no significant differences between the control and BB-12 groups. No significant changes due to probiotic treatment were observed in the gut microbiota of the study cohort.
CONCLUSIONS: BB-12-supplemented yogurt is safe and well-tolerated when consumed by healthy children. The present study will form the basis for future randomized clinical trials investigating the potential effects of BB-12-supplemented yogurt in different disease states.

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Research field: Infant and children´s nutrition and Immune Health
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12® and L. rhamnosus, LGG® **and** Lactobacillus acidophilus La-5.
Dosage CFU/day: 5x10^{10} CFU/day of each strain

Schei et al. "Early Gut Mycobiota and Mother-Offspring Transfer." Microbiome 5.1 (2017): 107

Abstract: BACKGROUND: The fungi in the gastrointestinal tract, the gut mycobiota, are now recognised as a significant part of the gut microbiota, and they may be important to human health. In contrast to the adult gut mycobiota, the establishment of the early gut mycobiota has never been described, and there is little knowledge about the fungal transfer from mother to offspring.
METHODS: In a prospective cohort, we followed 298 pairs of healthy mothers and offspring from 36 weeks of gestation until 2 years of age (1516 samples) and explored the gut mycobiota in maternal and offspring samples. Half of the pregnant mothers were randomised into drinking probiotic milk during and after pregnancy. The probiotic bacteria included Lactobacillus rhamnosus GG (LGG), Bifidobacterium animalis subsp. lactis Bb-12 and Lactobacillus acidophilus La-5. We quantified the fungal abundance of all the samples using qPCR of the fungal internal transcribed spacer (ITS)1 segment, and we sequenced the 18S rRNA gene ITS1 region of 90 high-quantity samples using the MiSeq platform (Illumina).
RESULTS: The gut mycobiota was detected in most of the mothers and the majority of the offspring. The offspring showed increased odds of having detectable faecal fungal DNA if the mother had detectable fungal DNA as well (OR = 1.54, p = 0.04). The fungal alpha diversity in the offspring gut increased from its lowest at 10 days after birth, which was the earliest sampling point. The fungal diversity and fungal species showed a succession towards the maternal mycobiota as the child aged, with Debaryomyces hansenii being the most abundant species during breast-feeding and Saccharomyces cerevisiae as the most abundant after weaning. Probiotic consumption increased the gut mycobiota abundance in pregnant mothers (p = 0.01).
CONCLUSION: This study provides the first insight into the early fungal establishment and the succession of fungal species in the gut mycobiota. The results support the idea that the fungal host phenotype is transferred from mother to offspring.

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Research field: Infant and children´s nutrition and Immune Health
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12® and L. rhamnosus, LGG®
Dosage CFU/day: 10^9 CFU/day

Groele et al. Effects of Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 on beta-cell function in children with newly diagnosed type 1 diabetes: protocol of a randomised controlled trial. Bmj Open 7.10 (2017):

Abstract: INTRODUCTION: Recent evidence has demonstrated that, among other factors, dysbiosis (imbalances in the composition and function of the gut microbiota) may be relevant in the development of type 1 diabetes (T1D). Thus, gut microbiota may be a target for improving outcomes in subjects with T1D. The aim of the study is to examine the effects of Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 on beta-cell function in children with newly diagnosed T1D.
METHODS AND ANALYSIS: A total of 96 children aged 8 to 17 years with newly diagnosed T1D, confirmed by clinical history and the presence of at least one positive autoantibody, will be enrolled in a double-blind, randomised, placebo-controlled trial in which they will receive L. rhamnosus GG and B. lactis Bb12 at a dose of 109 colony-forming units or an identically appearing placebo, orally, once daily, for 6 months. The follow-up will be for 12 months. The primary outcome measures will be the area under the curve of the C-peptide level during 2-hour responses to a mixed meal.
ETHICS AND DISSEMINATION: The Bioethics Committee approved the study protocol. The findings of this trial will be submitted to a peer-reviewed paediatric journal. Abstracts will be submitted to relevant national and international conferences.
TRIAL REGISTRATION NUMBER: NCT03032354; Pre-results.

Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12® and L. rhamnosus, LGG®
Dosage CFU/day:

Rø et al. Reduced Th22 cell proportion and prevention of atopic dermatitis in infants following maternal probiotic supplementation. Clin Exp Allergy. 2017 Aug;47(8):1014-1021

Abstract: BACKGROUND: In the randomized, controlled study Probiotics in the Prevention of Allergy among Children in Trondheim (ProPACT), maternal probiotic supplementation reduced the incidence of atopic dermatitis (AD) in the offspring. In the current study, we hypothesized that the effect was mediated by a shift in the T helper (Th) cells in the children.
OBJECTIVE: To examine whether Th cell proportions were affected by maternal probiotic supplementation and thus could mediate the preventive effect of probiotics on AD.
METHODS: A total of 415 pregnant women were randomized to ingest a combination of Lactobacillus rhamnosus GG (LGG), Bifidobacterium animalis subsp. lactis Bb-12 (Bb-12) and Lactobacillus acidophilus La-5 (La-5) or placebo, and their offspring were assessed for AD during the first 2 years of life. Peripheral blood collected at 3 months of age was analysed for regulatory T cells (n=140) and Th subsets (n=77) including Th1, Th2, Th9, Th17 and Th22.
RESULTS: The proportion of Th22 cells was reduced in children in the probiotic group compared to the placebo group (median 0.038% vs 0.064%, P=.009). The difference between the probiotic and placebo groups was also observed in the children who did not develop AD during the 2-year follow-up. The proportion of Th22 cells was increased in children who developed AD compared to the children who did not develop AD (0.090% vs 0.044%, P<.001). Mediation analysis indicated that the preventive effect of probiotics was partially mediated through the reduction in Th22 cells.
CONCLUSION: Perinatal maternal probiotic supplementation with a combination of LGG, Bb-12 and La-5 reduced the proportion of Th22 cells in 3-month-old children. This may partially explain the preventive effect of probiotics on AD.

Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12®
Dosage CFU/day:

Xinias et al. Innovative Dietary Intervention Answers to Baby Colic. Pediatr Gastroenterol Hepatol Nutr. 2017 Jun;20(2):100-106.

Abstract: PURPOSE: The purpose of this paper is to evaluate the efficacy of a lactose-reduced synbiotic partial whey hydrolysate in formula fed infants presenting with colic and the impact of this dietary intervention in mean crying time and quality of life. METHODS: Forty infants with infantile colic were treated during one month with parental reassurance and the intervention formula (partial whey hydrolysate, reduced lactose, Bifidobacterium lactis BB12 and galacto-oligosaccharides) and were compared to a control group of 20 infants with infantile colic treated with parental reassurance and a standard infant formula. Parents completed a quality of life (QoL) questionnaire assessing the burden of infantile colic. Wilcoxon test, t-test and Mann-Whitney test were used to compare QoL scores before and after intervention as well as between the intervention and control group. RESULTS: At inclusion, duration of crying did not differ between both groups. Crying duration decreased with 2.7 hours (from 3.2 to 0.5 hours) in the intervention group while duration of crying decreased only with 1.2 hours in the control group ($p<0.001$). Stool composition became looser in the intervention group, but defecation frequency did not change. The median scores of the QoL questionnaire improved significantly in the intervention group for all parameters. In the control group, parameters improved significantly also but not for the parent-child and social interaction. The score changes were significantly greater in the intervention than in the control group.
CONCLUSION: The intervention formula (partial whey hydrolysate, synbiotic, reduced lactose) significantly reduced the duration of crying and improved QoL of the parents and infants.

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Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: Bifidobacterium, BB-12® and L. rhamnosus, LGG®
Product formulation:

Laursen et al. Administration of two probiotic strains during early childhood does not affect the endogenous gut microbiota composition despite probiotic proliferation. BMC Microbiol. 2017 Aug 17;17(1):175.

Abstract: BACKGROUND: Probiotics are increasingly applied to prevent and treat a range of infectious, immune related and gastrointestinal diseases. Despite this, the mechanisms behind the putative effects of probiotics are poorly understood. One of the suggested modes of probiotic action is modulation of the endogenous gut microbiota, however probiotic intervention studies in adults have failed to show significant effects on gut microbiota composition. The gut microbiota of young children is known to be unstable and more responsive to external factors than that of adults. Therefore, potential effects of probiotic intervention on gut microbiota may be easier detectable in early life. We thus investigated the effects of a 6 month placebo-controlled probiotic intervention with Bifidobacterium animalis subsp. lactis (BB-12®) and Lactobacillus rhamnosus (LGG®) on gut microbiota composition and diversity in more than 200 Danish infants (N = 290 enrolled; N = 201 all samples analyzed), as assessed by 16S rRNA amplicon sequencing. Further, we evaluated probiotic presence and proliferation by use of specific quantitative polymerase chain reaction (qPCR).
RESULTS: Probiotic administration did not significantly alter gut microbiota community structure or diversity as compared to placebo. The probiotic strains were detected in 91.3% of the fecal samples from children receiving probiotics and in 1% of the placebo treated children. Baseline gut microbiota was not found to predict the ability of probiotics to establish in the gut after the 6 month intervention. Within the probiotics group, proliferation of the strains LGG® and BB-12® in the gut was detected in 44.7% and 83.5% of the participants, respectively. A sub-analysis of the gut microbiota including only individuals with detected growth of the probiotics LGG® or BB-12® and comparing these to placebo revealed no differences in community structure or diversity.
CONCLUSION: Six months of probiotic administration during early life did not change gut microbiota community structure or diversity, despite active proliferation of the administered probiotic strains. Therefore, alteration of the healthy infant gut microbiota is not likely to be a prominent mechanism by which these specific probiotics works to exert beneficial effects on host health.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. rhamnosus, LGG®
Dosage CFU/day: 5 billion each
Product formulation:
Sachet (maltodextrin with or without probiotics)
Reference number: 1739

Grenov, et al. Effect of Probiotics on Diarrhea in Children With Severe Acute Malnutrition: A Randomized Controlled Study in Uganda. J.Pediatr.Gastroenterol.Nutr. 2017;[Epub ahead of print]

Abstract: OBJECTIVES: To assess the effect of probiotics on diarrhea during in- and outpatient treatment of children with severe acute malnutrition (SAM). METHODS: A randomized, double-blind, placebo-controlled study was conducted involving 400 children admitted with SAM. Patients received one daily dose of a blend of Bifidobacterium animalis subsp. lactis (BB-12) and Lactobacillus rhamnosus (LGG) (10 billion colony-forming units, 50:50) or placebo during hospitalization followed by an 8-12 week outpatient treatment period, depending on patients' recovery rate. All outcomes were reported for in- and outpatient treatment separately. The primary outcome was number of days with diarrhea during hospitalization. Secondary outcomes included other diarrhea outcomes, pneumonia, weight gain, and recovery. RESULTS: There was no difference in number of days with diarrhea between the probiotic (n = 200) and placebo (n = 200) groups during inpatient treatment (adjusted difference +0.2 days, 95% CI -0.8 to 1.2, p = 0.69), however during outpatient treatment, probiotics reduced days with diarrhea (adjusted difference -2.2 days 95% CI -3.5 to -0.3, p = 0.025). There were no effects of probiotics on diarrhea incidence and severity or pneumonia, weight gain or recovery during in- or outpatient treatment. Twenty-six patients died in the probiotic versus 20 in the placebo group (p = 0.38). CONCLUSION: BB-12 and LGG had no effect on diarrhea in children with SAM during hospitalization, but reduced the number of days with diarrhea in outpatient treatment by 26%. Probiotics may have a role in follow-up of hospitalized children with SAM or in community based treatment of malnourished children, but further studies are needed to confirm this.This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. http://creativecommons.org/licenses/by-nc-nd/4.0.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® , L. rhamnosus, LGG® ,Lactobacillus paracasei ST11 and Bifidobacterium longum BL999
Dosage CFU/day:

Lundelin, Krista et al. "Long-Term Safety and Efficacy of Perinatal Probiotic Intervention: Evidence from a Follow-up Study of Four Randomized, Double-Blind, Placebo-Controlled Trials." Pediatric Allergy and Immunology 28.2 (2017): 170–175

Abstract: BACKGROUND: Societies worldwide are faced with a progressive increase in immune-mediated health problems such as allergic, autoimmune, and inflammatory diseases, as well as obesity. Perinatal administration of specific probiotic bacteria is an attractive approach in reducing the risk of these conditions, but long-term efficacy and safety data are lacking. The aim here was to evaluate the clinical benefit and long-term safety of specific probiotics administered during the perinatal period.
METHODS: The probiotic strains used were Lactobacillus rhamnosus GG, Bifidobacterium lactis Bb-12, Lactobacillus paracasei ST11, and Bifidobacterium longum BL999. The children involved have subsequently undergone prospective long-term follow-up. In addition to physical examination, data were collected by structured questionnaires on non-communicable diseases and continued probiotic use, and growth data from welfare clinics and school nurses.
RESULTS: Altogether 303 mother-infant pairs were included in the analysis. Seventy-six of 163 (47%) children receiving perinatal probiotics had developed allergic disease compared with 79 of 140 (56%) receiving placebo (OR 0.67, 95% confidence intervals [CI] 0.43-1.06, p = 0.09). Fifty-nine of 133 (44%) children receiving L. rhamnosus GG perinatally had developed allergic disease, OR 0.62, 95% CI 0.38-0.99, p = 0.047, as compared to placebo. We found no differences in growth or non-communicable disease prevalence between children receiving perinatally probiotics or placebo.
CONCLUSIONS: Perinatal probiotic administration is safe in long-term follow-up. Children receiving L. rhamnosus GG perinatally tended to have decreased allergy prevalence.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU/day: 10^9 CFU

Hojsak et al. "Bifidobacterium Animalis Subsp Lactis in Prevention of Common Infections in Healthy Children Attending Day Care Centers - Randomized, Double Blind, Placebo-Controlled Study." Clinical Nutrition 35.3 (2016): 587–591

Abstract: Background & aims: The aim of our study was to investigate the role of Bifidobacterium animalis subsp. lactis (BB-12®) in the prevention of common (gastrointestinal and respiratory) infections in healthy children who attend day care centers. Methods: We conducted a randomized, double-blind, placebo-controlled trial in 210 children who attend day care centers. They were randomly allocated to receive placebo (Placebo group, n = 106) or BB-12®at a dose of 109colony-forming units (CFU) (Intervention group, n = 104) during the 3-month intervention period. Results: Intention to treat analysis was used. There were overall 99 infections in Placebo group and 97 in Intervention group (incidence rate ratio = 1.0014, p = 0.992, Poisson regression model). Overall 65 children (61.3%) in Placebo group and 67 (64.4%) in Intervention group had common infections (p = 0.642). Mean number of infections per child was 0.93 (range 0-3) in Placebo group and 0.93 (range 0-3) in Intervention group (p = 0.898). There was no difference in secondary (duration of symptoms, number of children with gastrointestinal and respiratory tract infections, absence from day care center due to infections, use of antibiotics) and exploratory (type of gastrointestinal and respiratory tract infection) endpoints between groups. Conclusion: Results of performed study show that BB-12®has no effect on the prevention of gastrointestinal and respiratory tract infections in healthy children who attend day care centers.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU/day: -
Product formulation: -
Reference number: 1626

Murakami, et al. Intestinal microbiota in neonates requiring urgent surgery: assessing the role of probiotics using fecal DNA sequencing. Pediatr.Surg.Int. 2016;32(1):37-43

Abstract: PURPOSE: To assess the impact of urgent surgery on neonates and the value of an orally administered probiotic preparation of Bifidobacterium animalis subsp. lactis LKM512 (LKM) using fecal DNA sequencing to analyze intestinal microbiota. METHODS: Subjects for this study were 13 neonates born at our institution. Surgical cases required surgery within 3 days of birth. Groups studied were surgical cases administered LKM (n = 4; LKM+), surgical cases not administered have surgery and were not administered LKM (n = 2; CS), and normal healthy neonates (n = 3; CN). Stool specimens (20 mg) were collected five times (after birth, and on days 3, 7, 10, and 14 after surgery in surgical cases, and after birth, and on days 4, 8, 11, and 15 of life in controls). RESULTS: Clinical data were similar for LKM+ and LKM-. Enterobacteriaceae, Streptococcaceae, Staphylococcaceae and Bifidobacteriaceae were identified in the descending order of abundance in CS stool. Streptococcaceae, Staphylococcaceae, Enterococcaceae and Bifidobacteriaceae were identified in the descending order of abundance in LKM+ stool. Bifidobacteriaceae, Enterobacteriaceae, Staphylococcaceae and Streptococcaceae were identified in the descending order of abundance in LKM- stool. Unexpectedly, Bifidobacteriaceae was significantly more abundant in LKM- than LKM+ ($p < 0.05$). CONCLUSION: Surgical stress appears to affect intestinal microbiota considerably. Probiotic administration in neonates requires clarification.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU/day: 10 billion CFU/day
Product formulation: Other, tablet in a pacifier
Reference number: 1602

Taipale, et al. Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in early childhood. Pediatr.Res. 2016;79(1):65-69

Abstract: BACKGROUND: Specific probiotic bacteria have proven to be effective in the prevention and treatment of infectious diseases in early life in at-risk populations. The impact of administration of Bifidobacterium animalis subsp. lactis BB-12 (BB-12) on the risk of acute infectious diseases was studied in healthy children. METHODS: In this double-blind, placebo-controlled study, 109 one-month-old infants were assigned randomly to a probiotic group receiving a BB-12-containing tablet (n=55) or a placebo (n=54). Test tablets were administered to the infants twice a day (daily dose of BB-12 10 billion CFU) until the age of two years with a novel slow-release pacifier or a spoon. Breastfeeding habits, pacifier use, dietary habits, medications and all signs and symptoms of acute infections were registered in diaries by parents and in questionnaires by trained professionals. RESULTS: The infants receiving BB-12 were reported to have experienced fewer respiratory tract infections (87% vs. 100%; RR 0.87; 95% CI 0.76, 1.00; P=0.033) than the controls. No significant differences between the groups were observed in reported gastrointestinal symptoms, otitis media or fever. The baseline characteristics of the two groups were similar, as was the duration of breastfeeding. CONCLUSION: Administration of BB-12 in early childhood may reduce respiratory tract infections.Pediatric Research (2015); doi:10.1038/pr.2015.174.

Research field: Infant and Children's nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU: $5x10^9$ cfu/ day

Ringel-Kulka, Tamar et al. "Randomized, Double-Blind, Placebo-Controlled Study of Synbiotic Yogurt Effect on the Health of Children." Journal of Pediatrics 166.6 (2015)

Abstract: Objective To assess the effects of daily consumption of a synbiotic yogurt drink on the health, growth, and quality of life of healthy children 12-48 months of age in out-of-home child care. Study design Healthy children attending child care centers were enrolled in a prospective, double-blind, placebo-controlled clinical trial. The intervention was a yogurt drink containing Streptococcus thermophilus, Lactobacillus bulgaricus, and Bifidobacterium animalis subspecies lactis (BB-12) (5 × 109 cfu/100 mL serving), and 1 g of inulin (synbiotic group) vs a similar nonsynbiotic-containing acidified milk drink (placebo group) once daily for 16 weeks. The end points were days of diarrhea, fever, vomiting, symptoms of upper respiratory tract infection, use of antibiotics, physician visits, child care absenteeism, parental work absenteeism, and quality of life (PedsQL 4.0; Mapi Research Trust, Lyon, France). Results Compared with placebo (n = 73), children receiving synbiotic (n = 76) had significantly fewer days of reported fever (1.85 vs 1.95, P

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Research field: Infant and Children's nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. acidophilus, LA-5® and LGG
Dosage CFU/day:

Simpson, Melanie Rae et al. "Perinatal Probiotic Supplementation in the Prevention of Allergy Related Disease: 6 Year Follow up of a Randomised Controlled Trial." Bmc Dermatology 15.1 (2015): 13

Abstract: BACKGROUND Perinatal probiotics supplementation has been shown to be effective in the primary prevention of atopic dermatitis (AD) in early childhood, although the long term effects of probiotics on AD and other allergic diseases is less certain. We have previously reported a significant reduction in the cumulative incidence of AD at 2 years after maternal probiotic supplementation. In this study we present the effects of perinatal probiotics given to women from a general population on allergy related diseases in their offspring at 6 years. METHODS Four hundred and fifteen pregnant women were randomised to receive probiotic or placebo milk in a double-blinded trial from 36 week gestation until 3 months postpartum. Probiotic milk contained Lactobacillus rhamnosos GG, L. acidophilus La-5 and Bifidobacterium animalis subsp. lactis Bb-12. At 6 years, children were re-assessed for AD, atopic sensitisation, asthma and allergic rhinoconjunctivitis (ARC). RESULTS At 6 years, 81 and 82 children were assessed for AD in the probiotic and placebo groups, respectively. In a multiple imputation analysis, there was as trend towards a lower cumulative incidence of AD in the probiotic group compared to the placebo group (OR 0.64, 95 % CI 0.39-1.07, p = 0.086; NNT = 10). This finding was statistically significantly in the complete case analysis (OR 0.48, 95 % CI 0.25-0.92, p = 0.027, NNT = 6). The prevalence of asthma and atopic sensitisation, and the cumulative incidence of ARC were not significantly affected by the probiotic regime at 6 years of age. CONCLUSIONS Maternal probiotic ingestion alone may be sufficient for long term reduction in the cumulative incidence of AD, but not other allergy related diseases. TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT00159523.

Research field: Infant and Children's nutrition and Oral Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. acidophilus, LA-5®
Dosage CFU/day: 1 million of each strain

Product formulation: Other / ice cream
Reference number: 1586

Ashwin, et al. Effect of Probiotic Containing Ice-cream on Salivary Mutans Streptococci (SMS) Levels in Children of 6-12 Years of Age: A Randomized Controlled Double Blind Study with Six-months Follow Up. J.Clin.Diagn.Res. 2015;9(2):6-9

Abstract: INTRODUCTION: To evaluate the caries risk based on the salivary levels of streptococcus mutans in children of 6-12 years of age group before and after consuming probiotic ice-cream containing Bifidobacterium lactis Bb-12 and Lactobacillus acidophilus La-5. MATERIALS AND METHODS: A double blind, placebo controlled trial was carried out in 60 children aged between 6 to 12 years with zero decayed, missing, and filled teeth (DMFT). They were randomly divided into two equal groups. Saliva sample were collected before the consumption of ice-cream and Streptococcus mutans count was calculated and recorded as baseline data. For the next seven days both the groups were given ice creams marked as A and B. Saliva samples were collected after ice-cream consumption at the end of study period and also after a washout period of 30 days and again after six months. Samples were inoculated and colonies were counted. RESULTS: On statistical evaluation by students paired t-test, probiotic ice-cream brought significant reduction in the Streptococcus mutans count after seven days of ice-cream ingestion ($p<0.001$) and also after 30 d of washout period ($p<0.001$). There was no significant reduction ($p=0.076$) by normal ice-cream consumption. After six months of the study period in both the groups the salivary levels of Streptococcus mutans was similar to the baseline. CONCLUSION: Probiotic ice-cream containing Bifidobacterium lactis Bb-12 and Lactobacillus acidophilus La-5 can cause reduction in caries causative organism. The dosage of the probiotic organisms for the long term or synergetic effect on the oral health are still needed to be explored.

Research field: Infant & Children's Nutrition
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

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Product formulation: Fermented milk
Reference number: 1601

Dotterud, et al. Does Maternal Perinatal Probiotic Supplementation Alter the Intestinal Microbiota of Mother and Child? J.Pediatr.Gastroenterol.Nutr. 2015;61(2):200-207

Abstract: OBJECTIVES Maternal probiotic supplementation has been shown to prevent the development of atopic dermatitis in the offspring. We aimed to investigate whether probiotics in pregnant and breast-feeding mothers altered the colonization pattern and the diversity of the mothers' and children's intestinal microbiota. METHODS In a randomized, double-blind trial, women received probiotic milk or placebo from 36 weeks of gestation up to 3 months postnatally while breast-feeding. The probiotic milk contained Lactobacillus rhamnosus GG, L acidophilus La-5, and Bifidobacterium animalis subsp. lactis Bb-12. Stool samples were collected from the mothers at 30 to 36 weeks of gestation and 3 months after birth, and from the child at age 10 days, 3 months, 1 year, and 2 years, and bacteria were analyzed by quantitative polymerase chain reaction. Additionally, stool samples from 3-month-old and 2-year-old children were characterized using 16S ribosomal RNA gene deep sequencing to estimate the bacterial classes and genera, and the α- and β-diversity. RESULTS Three months after birth, both the prevalence and the relative abundance of the administered probiotic bacteria were significantly increased among the mothers in the probiotic group compared with among those in the placebo group. Only the Lactobacillus rhamnosus GG bacteria colonized the children at 10 days and at 3 months of age. There were no significant differences in the abundance of the administered probiotic bacteria between the groups at 1 and 2 years of age. For the bacterial classes and genera, and α- and β-diversity, there were no significant differences between the groups. CONCLUSIONS Different probiotic bacteria seem to have different ability to transfer from the mother to the child. We found no evidence that the probiotics altered the microbial composition or α- and β-diversity of the children.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. acidophilus, LA-5® and L. rhamnosus, LGG®

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Dosage CFU/day: NA
Product formulation: Fermented milk
Reference number: 1570

Fox, et al. Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study. BMJ Open 2015;5:1-6

Abstract: OBJECTIVE: To estimate the efficacy of a probiotic yogurt compared to a pasteurised yogurt for the prevention of antibiotic-associated diarrhoea in children. DESIGN AND SETTING: This was a multisite, randomised, double-blind, placebo-controlled clinical trial conducted between September 2009 and 2012. The study was conducted through general practices and pharmacies in Launceston, Tasmania, Australia. PARTICIPANTS AND INTERVENTIONS: Children (aged 1-12 years) prescribed antibiotics, were randomised to receive 200 g/day of either yogurt (probiotic) containing Lactobacillus rhamnosus GG (LGG), Bifidobacterium lactis (Bb-12) and Lactobacillus acidophilus (La-5) or a pasteurised yogurt (placebo) for the same duration as their antibiotic treatment. OUTCOMES: Stool frequency and consistency were recorded for the duration of treatment plus 1 week. Primary outcome was stool frequency and consistency, classified at different levels of diarrhoea severity. Due to the small number of cases of diarrhoea, comparisons between groups were made using Fisher's exact analysis. RESULTS: 72 children commenced and 70 children (36 placebo and 34 probiotic) completed the trial. There were no incidents of severe diarrhoea (stool consistency >/=6, >/=3 stools/day for >/=2 consecutive days) in the probiotic group and six in the placebo group (Fisher's exact p=0.025). There was also only one episode of minor diarrhoea (stool consistency >/=5, >/=2 stools/day for >/=2 days in the probiotic group compared to 21 in the placebo group (Fisher's exact p<0.001). The probiotic group reported fewer adverse events (1 had abdominal pain, 1 vomited and 1 had headache) than the placebo group (6 had abdominal pain, 4 had loss of appetite and 1 had nausea). CONCLUSIONS: A yogurt combination of LGG, La-5 and Bb-12 is an effective method for reducing the incidence of antibiotic-associated diarrhoea in children. TRIAL REGISTRATION NUMBER: Australian New Zealand Clinical Trials Registry ACTRN12609000281291.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and S. thermophiles, TH-4® and Lactobacillus paracasei ssp.paracasei CRL-431
Dosage CFU/day: CRL-431 (1,75x10^9CFU), BB-12 (1,75x10^9 CFU), TH-4 (1,50x10^9 CFU) daily

Valsecchi, C. et al. "Evaluation of the Effects of a Probiotic Supplementation with Respect to Placebo on Intestinal Microflora and Secretory IgA Production, during Antibiotic Therapy, in Children Affected by Recurrent Airway Infections and Skin Symptoms." Journal of Biological Regulators and Homeostatic Agents 28.1 (2014): 117–124

Abstract: Antibiotic therapy, especially in pediatric patients, is often associated with significant modifications of the gut microflora, which can lead to intestinal dysbiosis and influence intestinal physiology and immune system functionality. Herein we report the results from a double blind controlled clinical trial in 77 pediatric patients affected by recurrent airway infections, receiving antibiotic therapy with amoxicillin and clavulanic acid. A group was treated with an oral probiotic preparation composed of Lactobacillus paracasei ssp.paracasei CRL-431, Bifidobacterium BB-12, Streptococcus thermophilus TH-4 and a fructooligosaccharide (FOS) during and after antibiotic therapy for seven days, while the other group received placebo. The study revealed a reduction in the Clostridia population, with a contemporary increase in Bifidobacteria and Lactobacilli in fecal samples in the probiotic group and an increase in the Enterobacteria population in the placebo group. Moreover, there was a decreasing trend in secretory IgA production in the probiotic group. Some relevant, but not statistically significant probiotic supplementation effects were identified.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and S. thermophiles, TH-4®
Dosage CFU/day: 1 billion BB-12® and 0.1 billion TH-4®
Product formulation: NA
Reference number: 1532

Ivakhnenko, Nian'kovskii. Effect of probiotics on the dynamics of gastrointestinal symptoms of food allergy to cow's milk protein in infants. Georgian Med.News. 2013;(219)(219):46-52

Abstract: The problem of food allergy to cow's milk protein in children is highly important. The aim of this study was to estimate the effect of Bifidobacterium lactis BB-12 (1small ha, Cyrillic109 CFU) and Streptococcus thermophilus TH-4 (1small ha, Cyrillic108 CFU) administration on gastrointestinal symptoms of cow's milk allergy in infants. We conducted an open randomized prospective clinical study. 60 infants aged of 3-12 months with the diagnosis of atopic dermatitis and allergy to cow's milk protein were enrolled. Children were divided into 2 groups, one of which received probiotics during 4 weeks. Results were estimated after 4 and 8 weeks of study. We found significant impact on reducing the frequency of constipation in infants who received the probiotics in complex treatment. After 4 weeks of treatment constipation was absent in 85.71% infants who received probiotics as compared to 48.15% in the control group (small er, Cyrillic=0.02), after 8 weeks the same numbers were 92.86% vs. 62.96% accordingly (p=0.04). Significant differences between the groups were also determined by the incidences of infantile colic through 4 and 8 weeks and on diarrhea through 8 weeks of studies. It is possible to draw a conclusion that administration of probiotics in addition to elimination diet and base treatment to infants with atopic dermatitis and cow's milk allergy improves clinical symptoms of the disease and decreases gastrointestinal clinical manifestations of cow's milk allergy.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and S. thermophilus TH-4 and B. infantis BB-02
Dosage CFU/day: 1 billion
Product formulation: Other (powder)
Reference number: 1502

Jacobs, et al. Probiotic Effects on Late-onset Sepsis in Very Preterm Infants: A Randomized Controlled Trial. Pediatrics 2013;132(6):1055-1062

Abstract: BACKGROUND AND OBJECTIVE:Late-onset sepsis frequently complicates prematurity, contributing to morbidity and mortality. Probiotics may reduce mortality and necrotizing enterocolitis (NEC) in preterm infants, with unclear effect on late-onset sepsis. This study aimed to determine the effect of administering a specific combination of probiotics to very preterm infants on culture-proven late-onset sepsis.METHODS:A prospective multicenter, double-blinded, placebo-controlled, randomized trial compared daily administration of a probiotic combination (Bifidobacterium infantis, Streptococcus thermophilus, and Bifidobacterium lactis, containing 1 x 109 total organisms) with placebo (maltodextrin) in infants born before 32 completed weeks' gestation weighing <1500 g. The primary outcome was at least 1 episode of definite late-onset sepsis.RESULTS:Between October 2007 and November 2011, 1099 very preterm infants from Australia and New Zealand were randomized. Rates of definite late-onset sepsis (16.2%), NEC of Bell stage 2 or more (4.4%), and mortality (5.1%) were low in controls, with high breast milk feeding rates (96.9%). No significant difference in definite late-onset sepsis or all-cause mortality was found, but this probiotic combination reduced NEC of Bell stage 2 or more (2.0% versus 4.4%; relative risk 0.46, 95% confidence interval 0.23 to 0.93, P = .03; number needed to treat 43, 95% confidence interval 23 to 333).CONCLUSIONS:The probiotics B infantis, S thermophilus, and B lactis significantly reduced NEC of Bell stage 2 or more in very preterm infants, but not definite late-onset sepsis or mortality. Treatment with this combination of probiotics appears to be safe.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: 0,1 Billion
Product formulation: Milk powder
Reference number: 1395

Holscher, et al. Bifidobacterium lactis Bb12 Enhances Intestinal Antibody Response in Formula-Fed Infants: A Randomized, Double-Blind, Controlled Trial. JPEN J.Parenter.Enteral Nutr. 2012;36(1 Suppl):106S-17S

Abstract: Background: Addition of probiotics to infant formula may positively affect immune function in nonexclusively breastfed infants. This study aimed to investigate the effect of infant starter formula containing the probiotic Bifidobacterium animalis subspecies lactis (Bb12) on intestinal immunity and inflammation. Methods: Six-week-old healthy, full-term infants (n = 172) were enrolled in a prospective, randomized, double-blind, controlled clinical trial with 2 groups studied in parallel to a breastfed comparison group. Formula-fed (FF) infants were randomized to partially hydrolyzed whey formula (CON) or the same formula containing 10(6) colony-forming units (CFU) Bb12/g (PRO) for 6 weeks. Fecal secretory IgA (sIgA), calprotectin, lactate, and stool pH were assessed at baseline, 2 weeks, and 6 weeks. Anti-poliovirus-specific IgA and anti-rotavirus-specific IgA were assessed at 2 and 6 weeks. Results: Among vaginally delivered FF infants, PRO consumption increased (P < .05) fecal sIgA compared to CON. Anti-poliovirus-specific IgA concentration increased (P < .05) in all infants consuming PRO, whereas anti-rotavirus-specific IgA tended to increase (P = .056) with PRO consumption in cesarean-delivered infants. Anthropometrics and tolerance did not differ significantly between FF infants. Conclusions: Infants consuming formula with Bb12 produced feces with detectable presence of Bb12 and augmented sIgA concentration. Furthermore, cesarean-delivered infants consuming Bb12 had heightened immune response, as evidenced by increased anti-rotavirus- and anti-poliovirus-specific IgA following immunization. These results demonstrate that negative immune-related effects of not breastfeeding and cesarean delivery can be mitigated by including Bb12 in infant formula, thereby providing infants a safe, dietary, immune-modulating bacterial introduction.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: 10 billion
Product formulation: Other
Reference number: 1213

Taipale, et al. Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in infancy. Br.J.Nutr. 2011;105:409-16

Abstract: The impact of controlled administration of Bifidobacterium animalis subsp. lactis BB-12 (BB-12) on the risk of acute infectious diseases was studied in healthy newborn infants. In this double-blind, placebo-controlled study, 109 newborn 1-month-old infants were assigned randomly to a probiotic group receiving a BB-12-containing tablet (n 55) or to a control group receiving a control tablet (n 54). Test tablets were administered to the infants twice a day (daily dose of BB-12 10 billion colony-forming units) from the age of 1-2 months to 8 months with a novel slow-release pacifier or a spoon. Breastfeeding habits, pacifier use, dietary habits, medications and all signs and symptoms of acute infections were registered. At the age of 8 months, faecal samples were collected for BB-12 determination (quantitative PCR method). The baseline characteristics of the two groups were similar, as was the duration of exclusive breastfeeding. BB-12 was recovered (detection limit log 5) in the faeces of 62 % of the infants receiving the BB-12 tablet. The daily duration of pacifier sucking was not associated with the occurrence of acute otitis media. No significant differences between the groups were observed in reported gastrointestinal symptoms, otitis media or use of antibiotics. However, the infants receiving BB-12 were reported to have experienced fewer respiratory infections (65 v. 94 %; risk ratio 0.69; 95 % CI 0.53, 0.89; P = 0.014) than the control infants. Controlled administration of BB-12 in early childhood may reduce respiratory infections.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. paracasei subsp. paracasei L. casei 431
Dosage CFU/day: 1 billion
Product formulation: Milk powder
Reference number: 1253

Vlieger, et al. Tolerance and safety of Lactobacillus paracasei ssp. paracasei in combination with Bifidobacterium animalis ssp. lactis in a prebiotic-containing infant formula: a randomised controlled trial. Br.J.Nutr. 2009;102:869-875

Abstract: The addition of probiotics to infant formula has been shown to be an efficient way to increase the number of beneficial bacteria in the intestine in order to promote a gut flora resembling that of breast-fed infants. The objective of the present study was to evaluate the safety and tolerance of a combination of two probiotic strains in early infancy. A group of 126 newborns were randomised to receive a prebiotic-containing starter formula supplemented with Lactobacillus paracasei ssp. paracasei and Bifidobacterium animalis ssp. lactis or the same formula without probiotics for the first 3 months of life. A total of eighty infants continued the study until they were aged 6 months. Growth measurements were taken monthly at healthy baby clinics. Diaries were used to monitor behaviour, infections, use of antibiotics, as well as stool characteristics. Normal growth occurred in all infants and no statistically significant differences were detected between the probiotics group and the control group for gain in weight, length and head circumference. Infants in the probiotics group produced softer and more frequent stools during the first 3 months of life. No differences were found in crying and sleeping hours, number of parent-diagnosed infections, antibiotic use, visits to the general practitioner and number of adverse events. The use of a prebiotic-containing starter formula supplemented with L. paracasei ssp. paracasei and B. animalis ssp. lactis in early infancy is safe, well tolerated and has no adverse effects on growth and infant behaviour.

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Research field: Infant & Children's Nutrition
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.

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Research field: Infant & Children's Nutrition
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.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and S. thermophilus TH-4
Dosage CFU/day: Approx. 1 and 10 billion
Product formulation: Milk powder
Reference number: 0719

Mao, et al. Effect of a lactose-free milk formula supplemented with bifidobacteria and streptococci on the recovery from acute diarrhoea. Asia Pac.J.Clin.Nutr. 2008;17:30-34

Abstract: Probiotics have been proposed for the management and prevention of acute diarrhoea in infants. A double-blind, randomised, placebo controlled study was carried out in 224 Chinese infants 6 to 36 months of age with severe acute diarrhoea and free from moderate or severe malnutrition. After oral or parenteral rehydration, they were allocated to one of three groups: a lactose-free formula (Control); the same formula but with viable 10(8)CFU B. lactis Bb12 and 5x10(7)CFU St. thermophilus TH4 per gram of powder and, the same formula with the same microorganisms, but with 10(9)CFU/g and 5x10(8)CFU, respectively. Anthropometric parameters, duration of the diarrhoea and rotavirus shedding were evaluated. Eighty seven percent of the episodes were associated with rotavirus infection. The duration of the diarrhoea was not influenced by the intake of probiotics. However, a decrease of rotavirus shedding was observed in infants fed the formula with 10(9) Bb12/g, a finding of probable epidemiological importance in the transmission of this agent.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: Approx. 0.1 billion
Product formulation: Milk powder
Reference number: 0437

Chouraqui, et al. Acidified milk formula supplemented with bifidobacterium lactis: impact on infant diarrhea in residential care settings. J.Pediatr.Gastroenterol.Nutr. 2004;38:288-292

Abstract: OBJECTIVES: Probiotics may be useful in preventing acute infectious diarrhea. Bifidobacteria are particularly attractive as probiotics agent because they constitute the predominant colonic flora of breastfed infants and are thought to play a role in the decreased incidence of diarrhea in breastfed infants. METHODS: This was a multicenter, double-blind, controlled study to evaluate the efficacy of a milk formula supplemented with viable Bifidobacterium lactis strain Bb 12 (BbF) in the prevention of acute diarrhea in infants younger than 8 months living in residential nurseries or foster care centers. RESULTS: Ninety healthy children received either the BbF or a conventional formula (CF) daily. The mean duration of the stay in the residential center was similar (137 v 148 days). At enrollment, there were no differences between the two groups with respect to age (3.7 +/- 2.1 months), gender, anthropometric data, history of allergy or gastrointestinal disease, frequency of breast-feeding in the neonatal period or timing of introduction of solid food. Altogether, 28.3% of the BbF infants had diarrhea during the study compared with 38.7% of controls (NS). There was a statistically insignificant trend for shorter episodes of diarrhea in the BbF group (5.1 +/- 3.3 days v 7 +/- 5.5 days, NS). The number of days with diarrhea was 1.15 +/- 2.5 in the BbF group with a daily probability of diarrhea of 0.84 versus 2.3 +/- 4.5 days and 1.55, respectively, in the CF group (P = 0.0002 and 0.0014). Feeding infants with the BbF reduced their risk of getting diarrhea by a factor of 1.9 (range, 1.33-2.6). Analysis of the cumulative incidence of diarrheal episodes showed a trend that the first onset of diarrhea occurred later in the BbF group. CONCLUSION: These results provide some evidence that viable Bifidobacterium lactis strain Bb 12, added to an acidified infant formula, has some protective effect against acute diarrhea in healthy children.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and S. thermophilus TH-4
Dosage CFU/day: Mean daily consumption of BB-12 was 41 million per kg bodyweight of child in the high supplementation group and 3.7 million in the low supplemented group.
Product formulation: Milk powder
Reference number: 0435

Saavedra, et al. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. Am.J.Clin.Nutr. 2004;79:261-267

Abstract: BACKGROUND: Nonpathogenic live bacteria are consumed as food by many children, particularly in the form of yogurt. The tolerance and safety of long-term consumption of specific types and strains of probiotic bacteria are not well documented. OBJECTIVE: The goal was to evaluate tolerance to formulas containing 2 levels of probiotic supplementation and effects on growth, general clinical status, and intestinal health in free-living healthy infants. DESIGN: This was a prospective, double-blind, randomized, placebo-controlled study of healthy infants aged 3-24 mo. Infants were assigned to receive a standard milk-based formula containing 1 x 10(7) colony-forming units (CFU)/g each of Bifidobacterium lactis and Streptococcus thermophilus, formula containing 1 x 10(6) CFU/g each of B. lactis and S. thermophilus, or unsupplemented formula. Clinical outcomes included formula intake, gastrointestinal tolerance, anthropometric measures, daycare attendance, and history of illness. RESULTS: One hundred eighteen infants aged (+/- SD) 7.0 +/- 2.9 mo at enrollment consumed formula for 210 +/- 127 d. There were no significant differences in age, sex, formula consumption, or length of study between groups. The supplemented formulas were well accepted and were associated with a lower frequency of reported colic or irritability ($P < 0.001$) and a lower frequency of antibiotic use ($P < 0.001$) than was the unsupplemented formula. There were no significant differences between groups in growth, health care attention seeking, daycare absenteeism, or other health variables. CONCLUSION: Long-term consumption of formulas supplemented with B. lactis and S. thermophilus was well tolerated and safe and resulted in adequate growth, reduced reporting of colic or irritability, and a lower frequency of antibiotic use.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: ≥ 12 billion
Product formulation: Milk powder
Reference number: 0411

Nopchinda, et al. Effect of bifidobacterium Bb12 with or without Streptococcus thermophilus supplemented formula on nutritional status. J.Med.Assoc.Thai. 2002;85(Suppl 4):1225-1231

Abstract: Acute diarrhea is a common cause of infant morbidity and mortality. Probiotic supplemented infant formula is one of the effective methods for prevention of rotavirus diarrhea. Other benefits of the probiotics supplemented formula were evaluated by monitoring the growth of the children. A double-blind, placebo-controlled trial was done in 148 children aged 6-36 months. They were divided into 3 groups: the Bb12 group, 51 children received infant formula with Bifidobacteria Bb12 supplement; the Bb12+ST group, 54 children received infant formula with Bb12 and Streptococcus thermophilus supplement; and the control group, 43 children received infant formula without supplement. The mean weight Z-score according to WHO reference standard of the Bbl2 group was -1.8 +/- 0.12, the Bb12+ST group was -1.4 +/- 0.11 and the control group was -1.8 +/- 0.13 at entry. The mean weight Z-score of children after 6 month showed that the children in the Bbl2+ST group had the highest increase in weight which was increased from -1.4 +/- 0.11 to -0.9 +/- 0.12 compared to the Z-score of the Bb12 group which had increased from -1.8 +/- 0.12 to -1.2 +/- 0.13 and in the control group from -1.8 +/- 0.13 to -1.7 +/- 0.25. In terms of the mean height Z-score, the Bb12 group was -2.7 +/- 0.14 to -1.7 +/- 0.16 which was higher than the Bb12+ST group (- 2.2 +/- 0.13 to -1.7 +/- 0.13) but was not different from the control group. However, the mean weight/height Z-score of the Bbl2+ST group had approached the reference standard (Bb12 group -0.1 +/- 0.11 to -0.1 +/- 0.13, Bb12+ST group -0.1 +/- 0.10 to 0.3 +/- 0.17, control group -0.4 +/- 0.12 to -0.1 +/- 0.16). Data showed that children who received the probiotics supplement formula had better growth during the 6 month period.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 30-80 billion
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.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: NA
Product formulation: Milk powder
Reference number: 0413

Phuapradit, et al. Reduction of rotavirus infection in children receiving bifidobacteria-supplemented formula. J.Med.Assoc.Thai. 1999;82 Suppl 1:S43

Abstract: This study was conducted at Pakkred Babies Home, Bangkok, Thailand; with the hypothesis that children receiving probiotic-supplemented milk-based formula may be protected from developing diarrheal diseases. Salivary rotavirus-specific IgA antibody was used as an indicator of rotavirus infection. One hundred and seventy-five children, aged 6-36 months, were enrolled in the study. They were divided into 3 groups according to the type of formula given. There were 81 episodes of diarrhea during an 8-month study period, most of which were caused by bacterial enteropathogens. Ninety-seven pairs of salivary samples were adequate for the analysis of rotavirus antibody. Among 23 children receiving milk-based follow-up formula and serving as control group, 30.4 per cent of them had > or = 4-fold increase in the antibody titre, indicating subclinical rotavirus infection. The majority of children in the other 2 study groups, receiving the same formula supplemented with either Bifidobacterium Bb12 alone or together with Streptococcus thermophilus, had no significant change in the antibody titres between the two time points. The results of this study support our hypothesis that children receiving bifidobacteria-supplemented milk-based formula may be protected against symptomatic rotavirus infection.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: 1 billion
Product formulation: Milk powder
Reference number: 0332

Fukushima, et al. Effect of a probiotic formula on intestinal immunoglobulin A production in healthy children. Int.J.Food Microbiol. 1998;42:39-44

Abstract: The anti-infectious effect of probiotics has recently been reported and one mechanism may be the non-specific stimulation of immunity. This study was performed to elucidate the influence of a probiotic formula on intestinal microflora and local immunity in healthy children. A follow-up formula containing viable bifidobacteria was given to seven healthy Japanese children (15 to 31 months old) for 21 days. During intake of the formula, the administered strain was detected in feces from five subjects (71%) and total fecal bifidobacteria slightly increased. Fecal levels of total IgA and anti-poliovirus IgA during intake of the formula were significantly higher than those before intake ($P < 0.05$). The increase in local IgA levels resulting from ingestion of the probiotic formula may contribute to enhancement of the mucosal resistance against gastrointestinal infections.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: > 0.6 billion
Product formulation: Milk powder
Reference number: 0285

Fukushima, et al. Effect of follow-up formula containing bifidobacteria (NAN BF) on fecal flora and fecal metabolites in healthy children. Bioscience Microflora 1997;16:65-72

Abstract: 7 healthy children age 15-31 months received follow-up formulas with BB-12 for 21 days. The effect on fecal flora and metabolic products were studied. BB-12 was detected in fecal samples in 71% of the subjects. Fecal bifidobacteria tended to increase, while clostridia decreased ($P<0.05$). Fecal putrefactive products were significantly reduced ($P<0.01$), and acetic acid increased ($P<0.05$). The formulas was well-accepted by all children. Results suggest that the formula with BB-12 is beneficial in improving the intestinal flora and maintaining the healthy intestinal condition of children during and after weaning.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: Approx. 0.1 billion
Product formulation: Milk powder
Reference number: 0221

Langhendries, et al. Effect of a fermented infant formula containing viable bifidobacteria on the fecal flora composition and pH of healthy full-term infants. J.Pediatr.Gastroenterol.Nutr. 1995;21:177-181

Abstract: We assessed the growth, tolerance, and acceptability as well as fecal flora composition and stool pH of 20 healthy full-term infants fed with a fermented whey-adapted infant formula containing viable bifidobacteria (10(6)/g of powder) during the first 2 months of life. This fermented infant formula, first biologically acidified by Streptococcus thermophilus and Lactobacillus helveticus, was compared to a whey-adapted, nonacidified, low-phosphate infant formula in a double-blind, randomized controlled study. The results were compared to a control group (n = 14) of fully breast-fed infants. The fermented whey-adapted formula containing viable bifidobacteria induced a prevalence of colonization with bifidobacteria at 1 month of age similar to that of breast-fed infants (12/20 versus 8/14) but significantly higher than in the group fed the standard infant formula (4/20). The mean bacterial count of bifidobacteria was similar in all colonized infants; however, fecal pH was significantly lower in the breast-fed infants than in the nonacidified bottle-fed infants. This kind of infant formula was well tolerated and promoted a normal growth during the first 2 months.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and S. thermophilus TH-4
Dosage CFU/day: >10 billion
Product formulation: Milk powder
Reference number: 0200

Saavedra, et al. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. Lancet 1994;344(8929):1046-1049

Abstract: Acute diarrhoea is a serious cause of infant morbidity and mortality, and the development of preventive measures remains an important goal. Bifidobacteria (which constitute the predominant intestinal flora of breastfed infants), as well as other lactic-acid-producing organisms such as Streptococcus thermophilus, are thought to have a protective effect against acute diarrhoeal disease. However, their efficacy has not been assessed in controlled trials. In a double-blind, placebo-controlled trial, infants aged 5-24 months who were admitted to a chronic medical care hospital were randomised to receive a standard infant formula or the same formula supplemented with Bifidobacterium bifidum and S thermophilus. Patients were evaluated daily for occurrence of diarrhoea, and faecal samples, obtained weekly, were analysed for rotavirus antigen by enzyme immunoassay. Faecal samples were also obtained during an episode of diarrhoea for virological and bacteriological analyses. 55 subjects were evaluated for a total of 4447 patient-days during 17 months. 8 (31%) of the 26 patients who received the control formula and 2 (7%) of 29 who received the supplemented formula developed diarrhoea during the course of the study ($p = 0.035$, Fisher's exact test, two-tailed). 10 (39%) of the subjects who received the control formula and 3 (10%) of those who received the supplemented formula shed rotavirus at some time during the study ($p = 0.025$). The supplementation of infant formula with B bifidum and S thermophilus can reduce the incidence of acute diarrhoea and rotavirus shedding in infants admitted to hospital.

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