BB536® Clinical Evidence

Digestive Support

Bioscience Microflora

Ogata T., et al. Effect of Bifidobacterium longum BB536 administration on the intestinal environment, defecation frequency, and fecal characteristics of human volunteers. 1997. 16(2): 53-58

Topic	**Does *Bifidobacterium longum* BB536 have an effect on intestinal environment, defecation frequency, and fecal characteristics?**
Background	*Bifidobacterium* is a genus of Gram-positive, anaerobic bacteria. They are ubiquitous inhabitants of the gastrointestinal tract, vagina and mouth of mammals and other animals. Many species of bifidobacteria exert a range of beneficial health effects, including the regulation of intestinal microbial homeostasis, the inhibition of pathogens and harmful bacteria that colonize and/or infect the gut mucosa, the modulation of local and systemic immune responses, the repression of procarcinogenic enzymatic activities within the microbiota, the production of vitamins, and the bioconversion of a number of dietary compounds into bioactive molecules. The study investigates BB536, a strain of bifidobacteria used in many dairy products, on intestinal health.
Study Type	Human clinical intervention trial.
Study Design	Placebo-controlled crossover study. Study 1: Volunteers consumed 200 mL of milk per day for 1 week (control period). After an interval period of 2 weeks, they were assigned to group A or group B and served 200 mL of milk containing *B. longum* BB536 at concentrations of either 2 x 10^9 (group A) or 2 x 10^{10} (group B) for 1 week. Parameters of intestinal environment were measured after control period and after treatment period. Study 2: Volunteers consumed 200 mL of milk per day for 1 week (control period). After an interval period of 2 weeks, they were served 200 mL of milk containing *B. longum* BB536 at a concentration of 2 x 10^9 for 3 weeks. Defecation frequency was monitored and visual fecal characteristics were observed during control period and during treatment period.
Subjects	Study 1 - intestinal environment: 12 volunteers Study 2 - defecation frequency and fecal characteristics: 40 female volunteers suffering from constipation
Dosage	2 x 10^9 or 2 x 10^{10} viable *B. longum* BB536 cells daily in 200 mL of milk
Results	The administration of *B. longum* BB536 resulted in the following changes compared with control period: • A significant decrease of fecal ammonia content. • A significant reduction in the activity of some fecal enzymes. • An increase in *Bifidobacterium* percentage in the fecal flora. • A decrease in the number of *Enterobacteriaceae* and *Clostridium perfringens*. • A significant increase in fecal moisture content. • A significant increase in the defecation frequency. • A positive change in the fecal visual characteristics.
Conclusion	"The results indicate that the administration of *B. longum* BB536 improves intestinal environment, defecation frequency, and fecal characteristics."

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Digestive Support

Anaerobe

Odamaki T., et al. Effect of the oral intake of yogurt containing *Bifidobacterium longum* BB536 on the cell numbers of enterotoxigenic *Bacteroides fragilis* in microbiota. 2012. 18(1): 14–18

Topic	**Yogurt supplemented with a probiotic strain, *Bifidobacterium longum*, was examined in humans for the potential of eliminating enterotoxigenic *Bacterioides fragilis* (ETBF) from the microbiota of the human intestinal tract.**
Background	Enterotoxigenic *Bacteroides fragilis* (ETBF) strains have been suggested to be associated with acute and persistent diarrheal disease, inflammatory bowel disease, and colorectal cancer, although further epidemiological studies are needed for clarification. *Bacteroides* is the second-most dominant group of intestinal microbiota after Firmicutes and comprises symbionts that are critical to host nutrition and mucosal immunity. Among *Bacteroides* species, some strains of *B. fragilis* are opportunistic pathogens, being the most common anaerobic isolates in clinical specimens, bloodstream infections, and abdominal abscesses. A possible association of the fecal cell numbers of *Bacteroides fragilis* with the development of some allergic disorders has been proposed. Among strains of *B. fragilis*, some strains were named "enterotoxigenic B. fragilis" (ETBF) because they secrete a 20-kDa zinc-dependent metalloprotease toxin (B. fragilis toxin—BFT). ETBF asymptomatically colonizes a proportion of the human population, but it has also been demonstrated to be involved in the pathogenesis of diarrheal diseases in animal and human studies. It has been suggested that ETBF contributes to conditions including inflammatory bowel disease, necrotizing enterocolitis in neonates, and malnutrition in children in the developing world. Evidence exists for a possible association of ETBF with colorectal cancer.
Study Type	Human clinical intervention trial.
Study Design	A pilot study was performed to examine the effect of the oral administration of yogurt supplemented with a probiotic strain on the cell numbers of fecal ETBF in a healthy population. Among 420 healthy adults, 38 subjects were found to be ETBF carriers, giving a prevalence of approximately 9%. Among them, 32 subjects were enrolled in an open, randomized parallel-group study to ingest yogurt supplemented with a probiotic strain, *Bifidobacterium longum* BB536 (BB536Y group), for 8 weeks, with milk provided to the control group (milk group). The cell numbers of ETBF and the dominant species of the *B. fragilis* group were measured by a quantitative PCR method.
Study Design (cont'd)	Each yogurt contained approximately 1.0 x 10^9 CFU of lactic acid bacteria. The BB536 yogurt contained 4.27 x 10^8 and more than 1.12 x 10^8 CFU of living BB536 after preparation and at the end of the consumption period, respectively.
Subjects	32 adults who were determined to be ETBF carriers.
Dosage	Each group was then randomized to receive 200 mL of ultra-high-temperature pasteurized milk (milk group) or 160 g of yogurt supplemented with *B. longum* BB536 (BB536Y group) daily.
Results	Compared with the baseline values, there was a significant decrease in the cell number of ETBF at week 8 in the BB536Y group but not in the milk group. Linear mixed models analysis for longitudinal data revealed a significant difference in the changes of ETBF cell numbers between the two groups during the intervention phase.
Conclusion	These results imply the potential of probiotic yogurt for eliminating ETBF in the microbiota, but its clinical significance needs to be evaluated in the future. This is the first report of a possible effect of probiotic intake on ETBF in the microbiota.

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Microbial Ecology in Health and Disease

Ogata T., et al. Effect of Bifdobacterium longum BB536 yogurt administration on the intestinal environment of healthy adults. 1999. 11(1): 41-46

Topic	**Does a yogurt made with Bifidobacterium longum BB536 have an effect on fecal microflora, fecal putrefactive substances, fecal enzymatic activities, and fecal properties in healthy adults?**
Background	Bifidobacteria are well-known intestinal bacteria whose number decrease with age. This decrease influences the intestinal environment because bifidobacteria are known to create a favorable intestinal environment by suppressing the proliferation of unfavorable bacteria. B. longum BB536 has been reported to reduce cancer risk, enhance immunity, and increase bone density in animal experiments. The study investigates yogurt made with BB536, a strain of Bifidobacterium on intestinal health.
Study Type	Human clinical intervention trial
Study Design	Placebo-controlled crossover study: After a yogurt-free (control) period of 2 weeks, volunteers were administered 250 mL of yogurt containing BB536 per day for 2 weeks, followed by another 2-week yogurt-free period. The last 2 weeks, volunteers were administered 250 mL/day of standard yogurt. Feces analysis was performed twice during each of the consecutive 2-week periods.
Subjects	6 healthy volunteers
Dosage	5 x 10^9 B. longum BB536 viable cells
Results	Administration of yogurt containing B. longum BB536 resulted in the following changes compared with the control yogurt: • A significant increase in the proportion of Bifidobacterium in the fecal microflora. • A significant increase in the number of Lactobacillus clostridium sp., and total aerobic bacteria in the feces tended to decrease. • A decrease in the level of some putrefactive substances, including ammonia indole and paracresol. • A significant increase in the levels of short-chain and volatile fatty acids. • Urease activity decreased concomitant with the decrease in ammonia levels.
Conclusion	"These findings suggested that administration of yogurt containing B. longum BB536 was effective to improve the intestinal environment. Similar effects were observed with standard yogurt, but they were less evident than in the case of yogurt containing B. longum BB536."

Bioscience Microflora

Yaeshima T., et al. Effect of yogurt containing Bifidobacterium longum BB536 on the intestinal environment, fecal characteristics, and defecation frequency: A comparison with standard yogurt. 1997. 16(2): 73-77

Topic	**Does a yogurt made with Bifidobacterium longum BB536 have an effect on intestinal environment with reference to fecal microflora, ammonia levels, fecal characteristics (color, consistency), and defecation frequency in healthy adults?**
Background	Bifidobacteria found in the fecal microflora of humans have been shown to contribute to the health of the hosts by suppressing unfavorable bacteria and stimulating host immune functions. B. longum BB536 has been reported to have many positive physiological effects. The study investigates yogurt made with BB536, a strain of Bifidobacterium on intestinal health.
Study Type	Human clinical intervention trial
Study Design	Placebo-controlled crossover study: The volunteers were each administered 100 g of standard yogurt per day for 2 weeks. After a 2-week interval period, each subject was administered 100 grams of B. longum BB536 yogurt per day for the subsequent test period. The period of administration of B. longum BB536 yogurt was 2 weeks for testing effects on the intestinal environment and 3 weeks for testing effects on fecal characteristics and defecation frequency.
Subjects	Study 1 – intestinal environment: 11 female volunteers Study 2 – fecal characteristics and defecation frequency: 39 female volunteers
Dosage	2 x 10^7 B. longum BB536 viable cells/mL (2 x 10^9)
Results	Administration of yogurt containing B. longum BB536 resulted in the following changes compared with control yogurt: • Significant increase in the number and relative percentage of fecal bifidobacteria. • Fecal ammonia concentration tended to decrease. • Fecal organic acid content tended to increase. • Significant increase in defecation frequency. • The color of the feces changed to yellow and the consistency changed to soft.
Conclusion	"The administration of Bifidus yogurt was effective to improve the intestinal environment, fecal characteristics, and defecation frequency."

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Journal of Nutritional Food
Yaeshima, T., et al. Effect of sweet yogurt containing Bifidobacterium longum BB536 on the defecation frequency and fecal characteristics of healthy adults: A comparison with sweet standard yogurt. 1998. 1(3/4): 29 - 34

Topic	**Does a yogurt supplemented with *Bifidobacterium longum* BB536 have an effect on fecal characteristics (color, consistency) and defecation frequency in healthy adults?**
Background	Bifidobacteria found in the fecal microflora of humans have been shown to contribute to the health of the hosts by suppressing unfavorable bacteria and stimulating host immune functions. B. longum BB536 has been reported to have many positive physiological effects. The study investigates the effects of yogurt made with BB536, a strain of bifidobacteria, on intestinal health.
Study Type	Human clinical intervention trial
Study Design	Placebo-controlled crossover study: After a yogurt-free (control) period of 2 weeks, volunteers were administered 100 g of sweet yogurt containing BB536 per day for 2 weeks, followed by another 2-week yogurt-free period. The last 2 weeks volunteers were administered 100 g/day of standard sweet yogurt. Defecation frequency and fecal characteristics were observed throughout the test period.
Subjects	41 healthy female volunteers
Dosage	2 x 10^9 viable *B. longum* BB536 cells
Results	Administration of sweet yogurt containing *B. longum* BB536 resulted in the following changes: • Significant increase in the defecation frequency compared with standard yogurt period and yogurt-free period. • The consistency of the feces tended to change to soft, the odor tended to reduce, and the color significantly changed to yellow after consuming *B. longum* BB536 yogurt.
Conclusion	"The administration of BB536 sweet yogurt was effective to improve the defecation frequency and fecal characteristics."

***Journal of Nutritional Food* (Japan)**
Yaeshima T., et al. Effect of non-fermented milk containing *Bifidobacterium longum* BB536 on the defecation frequency and fecal characteristics in healthy adults. 2001. 4(2): 1-6

Topic	**Does *Bifidobacterium longum* BB536 have an effect on defecation frequency and fecal characteristics?**
Background	*Bifidobacterium* is one of the predominant bacteria constituting the human and animal intestinal flora and is known to have a close relationship with the health of the host. The physiological effects of bifidobacteria on the host are mainly brought about by increasing bifidobacteria within the intestine. As a result of improvement of the intestinal flora or intestinal environment, constipation and diarrhea are improved, which probably leads to improvement or prevention of intestinal diseases. In this study, to test the intestinal conditioning effects of nonfermented milk containing *B. longum* BB536, defecation frequency, fecal characteristics, and defecation sensation were investigated.
Study Type	Human clinical intervention trial
Study Design	Placebo-controlled crossover trial: Nonfermented milk containing *Bifidobacterium longum* BB536 was administered for 2 weeks to 43 healthy female volunteers who had constipation tendency. The effects on defecation frequency and fecal characteristics were examined and compared with the effects of a placebo non-fermented milk. The study duration was 8 weeks divided into four consecutive periods: milk-free period 1 (1st and 2nd week), *B. longum* BB536 milk administration period (BB536 milk period: 3rd and 4th week), milk-free period 2 (5th and 6th week), and placebo milk administration period (placebo milk period: 7th and 8th week). During *B. longum* BB536 milk period and placebo milk period, each subject consumed 180 ml of the assigned milk per day.
Subjects	43 female volunteers with constipation tendency
Dosage	>2 x 10^9 *B. longum* BB536 viable cells per serving of milk

Results	The study reported the following results: • A significant increase in defecation frequency was observed following ingestion of *B. longum* BB536 milk. • The number of days with defecation increased significantly during *B. longum* BB536 and placebo milk periods compared with the milk-free periods. • During the *B. longum* BB536 milk period and placebo milk period, the odor of feces was reduced and the sensation after defecation was improved significantly.
Conclusion	"The administration of BB536 milk was effective to improve the defecation frequency, and fecal characteristics."

Japanese Journal of Lactic Acid Bacteria
Xiao J.Z. et al. Effect of yogurt containing *Bifidobacterium* longum BB536 on the defecation frequency and fecal characteristics of healthy adults: A double-blind crossover study. 2007. 18(1): 31-36

Topic	**Can *Bifidobacterium longum* BB536 affect the defecation frequency and fecal characteristics of healthy adults?**
Background	Bifidobacteria is a genus of Gram-positive, anaerobic bacteria. They are ubiquitous inhabitants of the gastrointestinal tract, vagina, and mouth of mammals and other animals. Many species of bifidobacteria exert a range of beneficial health effects, including the regulation of intestinal microbial homeostasis, the inhibition of pathogens and harmful bacteria that colonize and/or infect the gut mucosa, the modulation of local and systemic immune responses, the repression of procarcinogenic enzymatic activities within the microbiota, the production of vitamins, and the bioconversion of a number of dietary compounds into bioactive molecules. The study investigates the effects of BB536, a strain of bifidobacteria used in many dairy products, on intestinal health.
Study Type	Human clinical intervention trial
Study Design	Randomized placebo-controlled double-blind two-way crossover trial: After a 2-week run-in period, subjects were randomly allocated to receive *B. longum* BB536 supplemented drink-type yogurt or a placebo yogurt at 100 grams per day for 2 weeks. After a 2-week washout period, subjects were crossed over to another 2 weeks of intake.
Subjects	55 healthy subjects with constipation tendency
Dosage	100 g yogurt containing >2 x 10^7 CFU/g *B. longum* BB536 (total >2 x 10^9)
Results	The study reported the following results: The defecation frequency was significantly increased during the intake stages of either BB536 or placebo yogurt compared with non-intake periods. Significant increase was also found by administration of BB536 yogurt compared with placebo yogurt. No adverse effects were found due to yogurt intake.
Conclusion	"These results indicate that the administration of BB536 yogurt is effective to improve the defecation frequency."

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Bifidus (Japan)
Tomoda T., et al. Effect of administration of yogurt containing Bifidobacterium in healthy persons. 1990. 4(1): 21-24

Topic	**Does yogurt containing *Bifidobacterium* have an effect of biochemical markers in the blood, frequency and quality of feces, appetite, and intestinal function?**
Background	A functional improvement of digestive organs by administration of *Bifidobacterium* has been reported in studies with babies, the aged, or sick persons. This study investigates the effect of *Bifidobacterium* on healthy subjects.
Study Type	Human clinical intervention trial.
Study Design	Open-label trial. Subjects were administered 130 grams yogurt made with *Bifidobacterium* for 6 weeks. Subjects reported any improvement of subjective symptoms after administration. A biochemical examination of blood was performed before and after administration. The change of *Bifidobacterium* quantity and ammonia value in feces was further examined.
Subjects	10 healthy volunteers
Dosage	$>10^8$ *Bifidobacterium* viable cells per 1 g ($>1.3 \times 10^{10}$ per dose)
Results	Administration of yogurt containing *Bifidobacterium* resulted in the following changes compared with baseline: • Frequencies and qualities of stool became normal and constipation or diarrhea was not recognized. • Appetite was stimulated. • Intestinal function showed good control. • There were no side effects or discomfort. • Protein, lipid in serum, and liver function before and after were not changed. • The number of *Bifidobacterium* in feces increased more than 10-fold. • Concentration of NH3-N in feces decreased.
Conclusion	"In healthy persons, the administration of *Bifidobacterium* in yogurt showed an improvement of bowel movements, a normalization of digestive function, a stimulation of appetite, and an improvement of intestinal environment."

Bifidobacteria Microflora
Tomoda T., et al. Effect of yogurt and yogurt supplemented with *Bifidobacterium* and/or lactulose in healthy persons: A comparative study. 1991. 10(2): 123-130

Topic	**Does yogurt containing *Bifidobacterium* with or without lactulose have an effect of biochemical markers in the blood, frequency and quality of feces?**
Background	The effect of the administration of supplements containing *Bifidobacterium* and lactulose (a growth factor of *Bifidobacterium*) has been reported in infants, aged persons, and some patients. This study investigated the effect on healthy individuals.
Study Type	Human clinical intervention trial
Study Design	Controlled crossover trial: Subjects were administered 130 grams of four kinds of yogurt: A) plain yogurt; B) yogurt containing lactulose; C) yogurt containing *Bifidobacterium*; D) yogurt containing both *Bifidobacterium* and lactulose. Each yogurt was given for 3–6 weeks, first A, then B, then C, then D, at intervals of 3 months.
Subjects	10 healthy volunteers
Dosage	10^8 *Bifidobacterium longum* viable cells/g yogurt (1.3×10^{10} per serving)
Results	Administration of yogurt containing *Bifidobacterium* and/or lactulose resulted in the following changes compared with control period: • There were no differences in blood chemistry before and after each type of yogurt. • The number of *Bifidobacterium* in the feces increased after administration of yogurt containing *Bifidobacterium* and/or lactulose compared with plain yogurt. • Administered *Bifidobacterium* species and original *Bifidobacterium* species were increased after administration of yogurt containing *Bifidobacterium* and lactulose. • The ammonia content of the feces decreased more after administration of yogurt containing *Bifidobacterium* and/or lactulose compared to plain yogurt.
Conclusion	"Yogurt containing *Bifidobacterium* and/or lactulose seems to be more effective than plain yogurt. The development of many preparations of yogurt can be expected to improve intestinal function in normal persons."

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Digestive Support

Journal of Japanese Society of Nutrition and Food Science
Seki M., et al. The effect of Bifidobacterium cultured milk on the "Regularity" among one aged group. 1978. 31(4): 379-387

Topic	Does cultured milk containing *Bifidobacterium* have an effect on regularity in seniors?
Background	Cultured milk with lactic acid bacteria has been shown to have medicinal benefits. Cultured milk containing *Bifidobacterium* has been reported to improve protein metabolism of cirrhotic patients and stool conditions and increase in quantity of *Bifidobacterium* in feces of patients with constipation. A comparison of fermented milk containing lactic acid bacteria with cultured milk containing *Bifidobacterium* has not been reported and therefore is investigated in this study.
Study Type	Human clinical intervention trial
Study Design	Controlled crossover trial: 126 seniors answered questions regarding their regularity. Subjects who reported constipation to varying degrees were given 100 mL/day of ordinary lactic acid cultured milk (control) for the first 10 days, which were followed by 7 days of the withdrawal period, and then 100mL/day of *Bifidobacterium* cultured milk for 10 days. Daily stool frequency was recorded for each 10 days before and during ingestion of both milk. A fecal specimen was collected in 5 cases through the test period and their microflora was examined.
Subjects	126 senior subjects above age 60 answered questionnaire. 18 participated in ingestion of test milk.
Dosage	20 x 10^8 *Bifidobacterium* viable cells/mL (2 x 10^{10} per serving)
Results	The administration of cultured milk resulted in the following changes: • Stool frequencies tended to increase (12 out of 18 participants) using both cultured milks. • Significant increase in stool frequencies in *Bifidobacterium* cultured milk compared with control milk. • Average number of evacuations in improved participants after *Bifidobacterium* cultured milk was 4.8 per 10 days in pre-ingestion period and 8.4 in the ingestion period, corresponding to normal frequencies. • Not only the CFU of *Bifidobacterium* in feces, but also rates of *Bifidobacterium* both to total bacteria and to *Enterobacteriaceae* were increased by ingestion of *Bifidobacterium* milk.
Conclusion	"*Bifidobacterium* ingestion in cultured milk may improve regularity in seniors with constipation."

Lait
Ballongue J., et al. Effects of Bifidobacterium fermented milks on human intestinal flora 1993. 73: 249-256

Topic	Does *Bifobacterium* cultured milk have an effect on human intestinal flora?
Background	The probiotic effect of cultured milk has been reported. This study attempts to 1) confirm these reports and 2) determine if identified strains of *Bifidobacterium* have a probiotic effect.
Study Type	Human clinical intervention trial
Study Design	Open-label controlled trial: All volunteers (both studies) refrain from eating any fermented dairy products for 2 weeks. During the next 2 weeks, volunteers had feces analysis carried out every 2 days. The next 3 weeks, volunteers go through treatment, followed by another 3-week period in which they stop treatment and have feces analysis done every 2 days. Study 1: Volunteers are divided into four groups (A, B, C, D). Group A is control group and receives no fermented milk. Groups B, C, and D each ingest 3 different types of fermented milk (125 g) 3 times/day. Study 2: Volunteers receive fermented milk with either *B. longum* strain 1) BB536, 2) BB536S15, 3) TCC15707, 4) ATCC15707S42, or 5) fermented milk without *Bifidobacterium*. Feces analysis is done every 2 days.
Subjects	Study 1 – 48 volunteers Study 2 – 45 volunteers
Dosage	10^7 *Bifidobacterium* viable cells/g (1.25 x 10^9 / serving)
Results	Consumption of fermented milk containing various strains of *Bifidobacterium* resulted in these changes: • A scarce increase in *Bifidobacterium* count was observed in feces of volunteers receiving Bifidobacterium of animal origin and increase stops after consumption. • A considerable increase in *Bifidobacterium* count was observed in feces of volunteers receiving fermented milk containing *Bifidobacterium* of human origin. This effect persists for 3 weeks after consumption stops. • Strains of *Bifidobacterium* do not have an equivalent effect on intestinal flora.
Conclusion	"Our study gives evidence that there is a certain difference between the strains of Bifidobacterium from human versus animal origin. In addition, there is a "strain effect," which invalidates the common hypothesis that the bifidogenic factors are responsible for the increase in bifido flora and therefore, the manufacturing of fermented milks cannot be done with undefined strains."

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***Clinical Nutrition* (Japan)**
Ebisawa E., et al. Experience in dosing obstetrical and gynecological inpatients with Bifidobacterium-containing yogurt "La Sante." 1985. 66(7): 805-810

Topic	**Does Bifidobacterium-containing yogurt have an effect on constipation and diarrhea in pregnant women?**
Background	Special precautions against constipation or diarrhea should be taken for obstetrical patients. Imbalance in intestinal microflora is suggested to be one of the causes of diarrhea and constipation. The administration of La Sante yogurt, containing a high content of *Bifidobacterium* (more than 10 billion counts) plus 0.5 grams of lactulose, is considered effective treatment. The dosing of La Sante yogurt to treat diarrhea and constipation in pregnant inpatients is investigated.
Study Type	Human clinical intervention trial
Study Design	Open-label study: 130 grams of La Sante yogurt were served to each patient for 6 days. Questionnaire was given to assess their improvements of symptoms. Comparison of symptoms was made between before and during dosing.
Subjects	110 pregnant volunteers
Dosage	>1 x 10^{10} *Bifidobacterium* viable cells/100g yogurt
Results	Administration of La Sante yogurt resulted in the following changes: • 25% of the tested inpatients felt their gastrointestinal conditions improved. • Flatulence tended to be reduced with continued intake of the yogurt, with a 60% improvement by the 4th day of intake. • 76% improvement in the number of subjects complaining of constipation by 4th day of intake. • 53% improvement in the number of patients complaining of constipation in women in their 20s and 83% improvement in women in their 30s.
Conclusion	"These results suggest the effectiveness of the La Sante yogurt in improving gastrointestinal conditions and properties of feces of the subjects and thus its contribution to improving balance of their intestinal microflora."

***Medicine and Biology* (Japan)**
Tomoda T., et al. The variation and adherence of the species of Bifidobacterium in the intestine during oral administration of Bifidobacterium. 1986. 113(2): 125-128

Topic	**Does *Bifidobacterium longum* colonize and proliferate in the human intestinal tract?**
Background	*Bifidobacterium* has been used clinically to improve digestive function and normalization of bacterial flora in the intestinal tract. This study examines the colonization and proliferation of administered *Bifidobacterium longum* in the intestinal tract.
Study Type	Human clinical intervention trial
Study Design	Open-label trial. 200 mL of cow's milk containing *Bifidobacterium* and *Lactobacillus* was administered daily to volunteers for 3–9 months. Feces were examined before, during, and after administration.
Subjects	3 volunteers with chronic hematological diseases
Dosage	1 x 10^7/ml viable cells of both *Lactobacillus acidophilus* and *Bifidobacterium longum* (2 x 10^9 per serving)
Results	Analysis of feces in volunteers showed the following results: • Prior to administration, residential *Bifidobacterium* was mainly *B. adolescentis*, but 3 months later, all three cases showed increase in *B. longum.* • In the one case that had administration for 9 months, increase in *B. longum* (to where it was predominant over residential *adolescentis*) was observed after 9 months. • In the one case that was administered for 6 months, the species count was equal between *B. longum* and *B. adolescentis.* • The administered *B. longum* colonized and proliferated 1 month after termination for one case.
Conclusion	"Both *B. longum* and *B. adolescentis* increased following *B. longum* administration, and *B. longum* colonized and proliferated for some cases."

Digestive Support

Journal of Dairy Research

Sairanen U., et al. The effect of probiotic fermented milk and inulin on the functions and microecology of the intestine. 2007. 74:367-373

Topic	**Do probiotic fermented milk and inulin have an effect on gastroinstestinal function and microecology?**
Background	Human colonic microbiota may comprise more than 500 bacterial species, and the bacterial concentration varies from 10^{11} to 10^{12} cells/g feces. The most predominant bacteria in the colon are *Clostridium* spp., *Bacteroides* spp., *Bifidobacterium* spp., and *Eubacterium* spp. Bifidobacteria are beneficial bacteria whose increase in the colon is considered desirable. Probiotics are exogenous bacteria that beneficially affect intestinal microbial balance. Prebiotics are indigestible food ingredients that selectively stimulate the growth and activity of beneficial bacteria already available in the colon. This study examines the effect of fermented milk for everyday use with probiotic bacteria on colonic health indicators and whether the prebiotic inulin enhances the effects.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind controlled trial: After a 12-day baseline period, the subjects were randomized to consume, for 3 weeks, 3 x 200 ml daily of either (1) a fermented milk with probiotics (*Bifidobacterium longum* BB536, *Bifidobacterium* spp. 420, and *Lactobacillus acidophilus* 145), (2) a fermented milk with the same probiotics plus 4 grams of inulin, or (3) a control fermented milk. During the last 7 days of the baseline and the intervention periods, the subjects kept a record of their defecation frequency and gastrointestinal symptoms, and collected all their feces. Intestinal transit time, stool weight, and fecal enzyme activities were measured. Thirty-nine subjects were randomized to give fecal samples for analysis of pH and microbes, including lactobacilli, bifidobacteria, coliforms, *Escherichia coli*, *Bacteroides* and *Clostridium perfringens*.
Subjects	66 healthy subjects
Dosage	Fermented milk containing *L. acidophilus* at 8×10^5 CFU/g and *Bifidobacterium* at 3×10^7 to 4×10^6 cfu/g plus 4 grams of inulin.
Results	The study reported the following results: • A significant increase in defecation frequency was observed following ingestion of B. longum BB536 milk. • The number of days with defecation increased significantly during B. longum BB536 and placebo milk periods compared with the milk-free periods. • During the B. longum BB536 milk period and placebo milk period, the odor of feces was reduced and the sensation after defecation was improved significantly
Conclusion	"The probiotic fermented milk product had a positive effect by increasing the number of lactobacilli and bifidobacteria in the colon. Inulin did not alter this effect, but it increased gastrointestinal symptoms."

Restoration of Healthy Microflora

Journal of Antimicrobial Chemotherapy
Orrhage K., et al. Effect of supplements with lactic acid bacteria and oligofructose on the intestinal microflora during administration of cefpodoxime proxetil. 2000. 46:603-611

Topic	**Do *Bifidobacterium longum* BB536, *Lactobacillus acidophilus*, and oligofructose have an effect on intestinal flora in healthy volunteers taking the antibiotic cefpodoxime proxetil?**
Background	The human intestinal microflora is a complex ecosystem with microorganisms living in stable relationships with their host. The equilibrium can be disrupted by treatment of antimicrobial agents and cause overgrowth of pathogens, causing diarrhea and pseudomembraneous colitis. Cefpodoxime proxetil, used to treat upper and lower respiratory tract infections, causes gastrointestinal side effects in 10% of treated patients. Overgrowth of enterococci and yeasts and reduced numbers of enterobacteria are the most pronounced ecological effects in the microflora. Numbers of lactobacilli and bifidobacteria decrease and there is colonization of *Clostridium difficile*. *Bifidobacterium longum* and *Lactobacillus* acidophilus have been used orally to re-establish the balance of microflora during antibiotic therapy. The effect of these two probiotic bacteria on intestinal microflora, fecal pH, and clinical status of healthy
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind parallel group study: All volunteers received two 100 mg cefpodoxime proxetil tablets orally for 7 days. Ten volunteers (Group A) were given 250 mL of fermented milk containing *B. longum* BB536 and *L. acidophilus* NCFB 1748 along with 15 grams of oligofructose for 21 days at the same start time as antimicrobial treatment. Ten volunteers (Group B) received a placebo milk supplement with 15 grams of oligofructose for 21 days. The remaining 10 volunteers (group C) received placebo milk without oligofructose. Stool specimens were collected before administration, on days 2, 4, and 7 of antimicrobial administration and days 2, 4, 7, 14, and 21 after stopping antimicrobial agent.
Subjects	30 healthy volunteers
Dosage	5×10^7 to 2×10^8 *B. longum* BB536 viable cells/mL plus 2×10^8 to 3×10^8 *L. acidophilus* viable cells/mL ($1.25–5 \times 10^{10}$ *B. longum* BB536/serving and $5–7.5 \times 10^{10}$ *L. acidophilus*/serving) plus 15 grams oligofructose.
Results	The study reported the following results: • Supplementation with *B. longum* BB536 and *L. acidophilus* NCFB 1748 and/or oligofructose during administration of cefpodoxime proxetil was well tolerated. • The recovery of these two given strains in fecal samples shows that these microorganisms can survive passage through the intestinal tract. • In the group given microorganisms plus oligofructose, there was a lower frequency of *C. difficile* than in other two groups.
Conclusion	"These observations may be of clinical value for patients at risk of developing *C. difficile* disease."

BB536® Clinical Evidence

Restoration of Healthy Microflora

Presented at International Conference of Intestinal Bacteriology 2001
de Vrese M., et al. "Effect of yogurt containing *Bifidobacterium longum* BB536 on diarrhea and gastrointestinal symptoms induced by antibiotic administration for eradication of *H. pylori*"

Topic	**Does yogurt containing *Bifidobacterium longum* BB536 have an effect on gastrointestinal symptoms and intestinal microflora induced by the use of antibiotics for the eradication of *H. pylori*?**
Background	The bacterium *H. pylori* was discovered to be at the root of stomach ulcers. Current therapy includes the use of different classes and concentrations of antibiotics, which often induce gastrointestinal symptoms. This study investigated the effect of yogurt containing *B. longum* BB536 on such symptoms.
Study Type	Human clinical intervention trial
Study Design	Open label placebo-controlled trial: Patients were treated with either 125 mL x 2/day placebo yogurt drink or a yogurt drink containing 10^8 *B. longum* BB536/mL for 4 weeks (period I) followed by concurrent yogurt and antibiotic treatment (omeprazole, 20 mg, clarithromycin, 500 mg, amoxicillin, 1g twice/day) for 1 week (period II). Period III consisted of only yogurt administration for an additional 3 weeks. Gastrointestinal symptoms were self-recorded by the volunteers. Feces analysis was performed at start, ends of 4 weeks, 5 weeks, and 8 weeks. .
Subjects	64 patients (test group: 34, placebo group: 30)
Dosage	10^8 *B. longum* BB536 viable cells/mL (2.5 x 10^{10} total daily)
Results	Administration of yogurt containing *B. longum* BB536 resulted in the following changes: • A reduction of incidence of diarrhea and improved gastrointestinal symptoms during antibiotic treatment and facilitation of recovery to normal conditions after antibiotic treatment. • Sample and placebo yogurt lowered CO2 content in breath indicating the lowered activity of *H. pylori*.
Conclusion	"*B. longum* BB536 may be effective as concurrent therapy to reduce gastrointestinal symptoms induced by antibiotics when treating *H. pylori*."

BB536® Clinical Evidence

Restoration of Healthy Microflora

Microbial Ecology in Health and Disease

Orrhage, K, B Brismars, and C Nord. Effect of Supplements with Bifidobacterium longum and Lactobacillus acidophilus on the Intestinal Microbiota during Administration of Clindamycin. 7(1994): 17–25

Topic	**How does supplementation with *Bifidobacterium longum* and *Lactobacillus acidophilus* affect the intestinal microbiota during administration of clindamycin?**
Background	The human gastrointestinal microbiota is stable under circumstances where the microorganisms remain relatively constant. The delicate balance of the ecosystem can, however, be altered by some dietary and environmental factors. The most common and significant cause of disturbances in the gastrointestinal microbiota is the administration of antimicrobial agents. One effect is overgrowth of microorganisms present that are resistant to the antimicrobial agent, such as yeasts, which may cause systemic infections in immunocompromised patients. *Clostridium* may also overgrow and cause diarrhea or pseudomembranous colitis. Clindamycin is an antimicrobial agent used in the treatment of anaerobic infections, especially those caused by *Bacteroides fragilis* or other penicillin-resistant anaerobic bacteria. Clindamycin has been reported to be a potent agent, inducing *C. dificile*–associated diarrhea. Bifidobacteria constitute a major part of the normal intestinal bacteria in humans and are of great importance in the large bowel's resistance to colonization by pathogenic microorganisms. *Bifidobacterium longum* and other species of bifidobacteria have been used as dietary supplements after antibiotic therapy. *Lactobacillus acidophilus* is also a part of the normal intestinal ecosystem in humans. Lactobacilli have also been used as dietary supplements after antibiotic therapy. It is of clinical interest to re-establish, and to maintain, the ecological balance in the intestine during and after antibiotic therapy.
Study Type	Double-blind human intervention study
Study Design	Thirty healthy volunteers in 3 groups participated in a study of the influence of supplements containing *Bifidobacterium longum* and *Lactobacillus acidophilus* on the intestinal microbiota during administration of clindamycin and were divided into 3 groups, each consisting of 7 or 8 women and 2 or 3 men, yielding a total of 10 per group. The mean age was 37 years (range, 21–54 years). None of the volunteers had been treated with antibiotics during the 3 months immediately prior to the study.
Study Design (cont'd)	All groups received clindamycin perorally once a day for 7 days. Group 1 also received a supplement with B. longum and L. acidophilus, group 2 received a supplement with *B. longum*, and group 3 received a placebo, for 21 days. The study analyzed intestinal microbiota, volatile fatty acids, and pH in feces before, during, and after administration of clindamycin with or without supplements of *B. longum* and *L. acidophilus* daily for 21 days starting at the same time as the clindamycin administration. Ten subjects (group 2) received a fermented milk product containing yogurt culture bacteria *L. delbrueckii* subsp. *bulgaricus* LBU108 and *Streptococcus salivarius* subsp. *thermophilus* STH482. Neither of these two latter species is an intestinal microorganism. A 250-mL portion of the fermented milk was given twice a day for 21 days at the same time clindamycin was started. No other medication except clindamycin was allowed during the investigation period.
Subjects	30 healthy volunteers during use of clindamycin
Dosage	5×10^7 to 2×10^8 colony-forming units (CFUs) per mL of *B. longum* BB536 (Nutritional Science Laboratory, Morinaga, Tokyo, Japan) and 2×10^8 to 3×10^8 CFUs per mL of *L. acidophilus* NCFB1748 (Arla, Stockholm, Sweden).
Results	The numbers of anaerobic microorganisms decreased in all groups, but the reduction of *Bacteroides* was significantly smaller in group 1 than in group 3 ($p < 0.05$). No subject in group 3 had any intestinal bifidobacteria on day 7. Significant decreases of volatile fatty acids in fecal specimens were seen ($p < 0.05$). There was a smaller incidence of gastrointestinal discomfort in group 1 than in group 3 ($p < 0.05$).
Conclusion	This study shows that supplementation with a combination of two normal intestinal microorganisms, *B. longum* and *L. acidophilus*, reduced the ecological changes in the intestinal microbiota caused by administration of clindamycin.

Journal of Functional Foods

Chitapanarux, T et al. Effect of Bifidobacterium longum on PPI-based triple therapy for eradication of Helicobacter pylori: A randomized, double-blind placebo-controlled study.
13;March 2015:289–294

Topic	**What is the benefit of Bifidobacterium longum on PPI-based triple therapy for eradication of Helicobacter pylori?**
Background	Probiotics provide a clinical benefit in a variety of gastrointestinal conditions, including inhibition of *Helicobacter pylori (H. pylori)*. This study examined the effect of *Bifidobacterium longum* on *H. pylori* eradication. *H. pylori* infection is found in 70%–90% of the population in developing countries and 25%–50% in developed countries. Eradication of H. pylori is recommended for gastric and duodenal ulcers, gastric cancer, atrophic gastritis, mucosa-associated lymphoma tissue (MALT), lymphoma, and other H. pylori–related complications. Clarithromycin resistance and poor patient compliance are believed to be the major cause of treatment failure. A number of clinical trials have been undertaken based on the theory that probiotic bacteria can inhibit *H. pylori* infection. This study was performed to evaluate whether the addition of *B. longum* to standard PPI-based triple therapy beneficially affects *H. pylori* eradication rates and side effects of triple therapy.
Study Type	Randomized, double-blind, placebo-controlled study
Study Design	Dyspeptic patients with *H. pylori* infection were divided into 2 groups, treated with the standard triple therapy for 7 days, and received *B. longum* or placebo for 4 weeks. Successful eradication therapy was defined as a negative 13C urea breath test 4 weeks after completion of the treatment. *H. pylori*–positive patients were randomly assigned into 2 therapy regimens: patients in the control group received 40 mg of esomeprazole, 1,000 mg of amoxicil1in, and 500 mg of clarithromycin, twice a day for 7 days, and 2 capsules of placebo twice a day for 4 weeks, whereas patients in the test group received the same PPI-based triple therapy for 7 days and 2 capsules of probiotics, Combif AR (*B. longum* BB536, Medinova, Switzerland), twice a day for 4 weeks. A second clinical evaluation was performed 4 weeks after the end of each regimen. Evaluation included a review of the patient's medical history, present symptoms, and concurrent medication, plus a physical examination. Subjects were asked to report any adverse effects of therapy during the treatment period and were given a possible adverse effect list,
Study Design (cont'd)	including epigastric pain, diarrhea, taste disturbance, constipation, and stomatitis. They were also asked to grade each adverse effect according to severity: mild (effect observed, but could be disregarded), moderate (effect sometimes interfered with daily activities), or severe (effect continuously interfered with daily activities). Bacterial eradication was checked in all patients four weeks after treatment by confirming a negative13C urea breath test.
Subjects	63 patients with *H. pylor*i infection (60 completed the study)
Dosage	2 capsules of *Bifidobacteria longum* (CFUs not defined), 2 capsules of probiotics, Combif AR (*B. longum* BB536)
Results	Infection was eradicated in 28 out of 31 patients (90.32%) and 28 out of 30 patients (93.33%) from the test group, and in 22 out of 32 patients (68.75%) and 22 out of 30 patients (73.33%) from the control group, respectively, with significant differences. One (3.23%) patient in the test group and 8 (25%) patients in the control group experienced diarrhea (p = 0.027). After the completion of therapy, 50 of 63 subjects (79.37%) patients tested negative for *H. pylori* on a 13C urea breath test. ITT analysis showed that *H. pylori* was eradicated in 28 of 31 patients in the test group (90.32%) and in 22 of 32 patients in the control group (68.75%). PP analysis showed successful eradication in 28 of 30 (93.33%) patients in the test group and 22 of 30 (73.33%) patients in the control group. Significant differences in *H. pylori* eradication rate were noted between the 2 groups, according to the results of the ITT and PP analyses. In the present randomized controlled study, it was demonstrated that the addition of *B. longum* to a 1-week PPI-based triple therapy led to higher *H. pylori* eradication rate and lower incidence of diarrhea compared with standard PPI based triple therapy in patients with nonulcerous dyspepsia.
Conclusion	The results of the study show that *B. longum* improves eradication of *H. pylori* and reduces anti-H. pylori antibiotic-therapy-associated complications such as diarrhea and other digestive problems. In conclusion, it was confirmed that addition of *B. longum* during standard PPI-based triple therapy is recommended for a better eradication rate and for reduced incidence of anti-*H. pylori* antibiotic-therapy-associated complications.

BB536® Clinical Evidence

Restoration of Healthy Microflora

The Lancet

Colombel J.F., et al. Yoghurt with *Bifidobacterium longum* reduces erythromycin-induced gastrointestinal effects. 1987. 2(8549): 43

Topic	Can *Bifidobacterium longum* prevent antibiotic-associated gastrointestinal effects?
Background	Oral antibiotic therapy often alters the intestinal flora, and this can have serious consequences such as pseudomembraneous colitis. *Bifidobacterium longum* is part of the normal human intestinal microflora and yogurts containing viable bacteria (BA) of this species are available and might re-equilibrate intestinal flora.
Study Type	Human clinical intervention trial
Study Design	Placebo-controlled crossover trial: Volunteers took erythromycin (1 g) by mouth twice daily for two 3-day study periods with a 3-week interval between them. Over each 3-day study period, the volunteers took, together with erythromycin, three BA yogurts or placebo yogurts daily in random order. Stool weight and frequency were noted on the day before (D-1) and on the third day (D-3) of each period. Abdominal disturbances were recorded throughout the study. The composition of the rectal microflora was analyzed on D-1 and D-3.
Subjects	10 healthy volunteers
Dosage	Not reported
Results	The study reported the following results: • Fecal weight, stool frequency, and abdominal complaints were considerably increased when erythromycin was given with placebo yogurt but not when BA yogurt was taken. • Clostridial spores were detected on D-1 of both periods in 8 volunteers during placebo and BA periods. On D-3, clostridial spores were still present in 7 volunteers taking the placebo yogurts, but in only 1 taking BA yogurt.
Conclusion	"The simultaneous intake of BA yogurt with erythromycin reduced the frequency of gastrointestinal disorders seen in volunteers taking erythromycin and placebo yogurt. The sharp fall in clostridial spore count suggests that BA yogurts could reduce antibiotic-induced alterations of the intestinal microflora."

Normal Response to Inflammation

Inflammatory Bowel Disease

Takeda Y., et al. Upregulation of T-bet and tight junction molecules by *Bifidobacterium longum* improves colonic inflammation of ulcerative colitis. 2009. 15(11): 1617-1618

Topic	Can *Bifidobacterium longum* BB536 reduce intestinal inflammation in patients with ulcerative colitis?
Background	Manipulation of the mucosal microbiota to reduce the inflammatory potential of colonizing bacteria is an attractive therapy for patients with ulcerative colitis (UC), and probiotic treatments have been focused on improving intestinal microbial balance. Previous research has shown a significant reduction of proinflammatory cytokines in mucosal biopsies in patients treated with *Bifidobacterium longum* BB536 compared with placebo. This finding was very promising for treatment with UC, but the exact mechanism of BB536 on patients with UC was not elucidated.
Study Type	Human clinical intervention trial
Study Design	OpenlLabel trial: From 2005 to 2007, clinical activity of patients was assessed with the Clinical Activity Index (CAI) prior to BB536 administration. Patients who scored higher than 5 points in CAI were regarded as active phase and were treated with BB536 for 24 weeks. The clinical response was assessed at 24 weeks after administration. Clinical remission was defined as a decrease in the CAI to 4 or less.
Subjects	14 patients with UC who were refractory to more than 2250 mg of 5-aminosalicylate
Dosage	2–3 x 10^{11} freeze-dried viable cells *B. longum* BB536
Results	The study reported the following results: • CAI was reduced in 12 of 14 patients at 24 weeks after starting BB536 therapy. • 67% of patients achieved clinical remission. • The mean CAI significantly decreased at 8, 12, and 24 weeks compared with that before administration of BB536.
Conclusion	"Our pilot study strongly demonstrates that administration of BB536 was well tolerated and effective for inducing remission of patients with UC."

BB536® Clinical Evidence

Healthy Cholesterol Levels

Journal of Dairy Research

Andrade S. and N. Borges. Effect of fermented milk containing *Lactobacillus acidophilus* and *Bifidobacterium longum* on plasma lipids of women with normal or moderately elevated cholesterol. 2009. 76: 469-474

Topic	**What is the effect of milk fermented with *Lactobacillus acidophilus* 145 and *Bifidobacterium longum* BB536 on plasma lipids in a sample of adult women?**
Background	Previous research observed a reduction in serum cholesterol after the ingestion of large amounts (4 to 8 l/d) of milk fermented by a *Lactobacillus* strain. In recent years, clinical trials investigating the effects of fermented milk products on serum lipids have produced conflicting results. The present work aimed to study the effect of fermented milk containing viable *L. acidophilus* and *B. longum* on the serum lipid levels of normal to moderately hypercholesterolemic women.
Study Type	Human clinical intervention trial
Study Design	Double-blind, placebo-controlled, crossover trial: A Crossover trial (two periods of 4 weeks each separated by a 1-week washout period) was performed in two groups of women. Group A consumed 125 grams fermented milk 3 times a day for the first 4 weeks while group B consumed regular yogurt under the same conditions. Groups A and B switched products for the second treatment period.
Subjects	34 women
Dosage	1.4 to 2.1 x 10^8 CFU/g *L. acidophilus* 145 (total 5.3 to 7.9 x 10^{10} daily) and 2.7 x 10^7 to 1.0 x 10^8 CFU/g *B. longum* BB536 (total 1.0 to 3.8 x 10^{10} daily).
Results	The study reported the following results: • Women taking the test product with a baseline total cholesterol above 190 mg/dl showed a significant reduction in LDL cholesterol. • HDL cholesterol was also reduced by the test product.
Conclusion	"We conclude that the fermented milk may help reduce LDL levels in hypercholesterolemic adult women."

Children's Health

Acta Pediatr

Bennet R., et al. Transient colonization of the gut of newborn infants by orally administered bifidobacteria and lactobacilli. 1992. 81: 784-787

Topic	**Could orally administered bifidobacteria and/or lactobacilli be cultured from the feces of infants after antibiotic treatment?**
Background	Bifidobacteria and lactobacilli have been thought to beneficially affect the local microflora if they are present in high numbers in the gut. A lack of *Bifidobacterium* is seen in vulnerable infants. This study investigates whether lyophilized bacteria could colonize full-term newborn infants immediately after antibiotic treatment, when their intestinal anaerobic bacterial microflora is strongly suppressed.
Study Type	Human clinical intervention trial
Study Design	Open-label trial: Lyophilized *Bifidobacterium longum* BB536, *B. breve* BB576, *Lactobacillus acidophilus* LAC-343, or a mixture of all three strains, were fed to subjects three times daily at mealtimes. Treatment was started the first day after antibiotic treatment and was continued for 5 days.
Subjects	11 infants ages 0–8 weeks
Dosage	3 x 10^9 viable cells of one strain, or a mixture of all three strains 3x10^9 cells each
Results	The bacterial species were isolated as follows (positive culture/total number of cultures after 0, 5, and 15 days): • B. breve – 3/3, 2/3, and 0/1. • *B. longum* – 1/3, 1/3, and 0/3. • *L. acidophilus* – 3/3, 3/3, and 1/3. • Mixture – 2 (1 *L. acidophilus*, 1 *B. breve*)/2, 1 (*B. breve*)/1, and 1(*L. acidophilus*)/2. • No side effects were noted.
Conclusion	"We have shown that it is possible to manipulate the microflora of newborn infants in a controlled way."

Children's Health

Acta Neonatologica Japonica

Akiyama K., et al. Effects of administration of *Bifidobacterium* in extremely premature infants: Development of intestinal microflora by orally administered *Bifidobacterium longum* (in comparison with *Bifidobacterium* breve). 1994. 30: 257-263

Topic	**Does administration of *Bifidobacterium longum* have an effect on the development of intestinal microflora on extremely premature infants?**
Background	The intestinal bacterial flora in premature infants, especially extremely premature infants, is disturbed and an abnormal flora lasts for several months after birth. During this period, pathogenic bacteria, such as *Enterobacteriacea*, proliferate abnormally, commonly resulting in infections. Viable bifidobacteria and lactobacilli preparations have been used in infants for the purpose of improving a transient abnormal intestinal flora that resulted from infectious diarrhea or antibiotic therapy. However, there is no documented use of these preparations for prevention of infection due to abnormal intestinal bacteria during early neonatal period. This study investigated the effect of *B. longum* on intestinal microflora of premature infants.
Study Type	Human clinical intervention trial
Study Design	Randomized placebo-controlled study: Between October 1991 and June 1992, 10 extremely premature infants were randomly assigned a preparation of *B. longum* or a control (n=5 treatment, n=5 control). Administration began at same time as initiation of breast-feeding and was once per day until 8 weeks after birth. At 1, 2, 4, 6, 8, and 12 weeks after birth, fecal samples were collected by rectal stimulation and the intestinal microflora was analyzed.
Subjects	10 extremely premature infants
Dosage	5 x 10^8 viable cells of *B. longum*
Results	The study reports the following results: • In the *B. longum* group, *Bifidobacterium* was found from 2 weeks after birth and a *Bifidobacterium*-predominant flora was established early after birth. In the control group, the formation of *Bifidobacterium* flora was delayed and was established at 8 weeks.
Results (cont'd)	• In the *B. longum* group, the administered strain was the main strain isolated from 2 to 4 weeks after birth, but this strain was replaced from 6 weeks after birth to *B. breve*, which was the putative resident *Bifidobacterium* in the neonatal intensive care unit of this hospital.
Conclusion	"In extremely premature infants who are at high risk of infection, administration of bifidobacteria early after birth has great clinical significance in the improvement of a disturbed intestinal bacterial flora during the initial two months after birth."

BB536® Clinical Evidence

Children's Health

Nutrition

Puccio G., et al. Clinical evaluation of a new starter formula for infants containing live *Bifidobacterium longum* BL999 and prebiotics. 2007. 23:1-8

Topic	**Is *Bifidobacterium longum* (BL999) combined with galacto- and fructo-oligosaccharides safe and tolerated by formula-fed infants?**
Background	The larger number of Bifidobacteria in the intestine of breast-fed infants has been associated with their better health compared with formula-fed infants. The microbiota of breast-fed infants not only has a greater concentration of bifidobacteria, but also contains fewer potentially pathogenic bacteria than that of infants fed with conventional formula. This may partly explain the reduced incidence of morbidity and mortality in breast-fed infants. Therefore, for infants who cannot be breast-fed, there may be a rationale to adapt infant formulas to promote establishment of an intestinal microbiota resembling that of breast-fed infants. The mixture of pro- and prebiotics has been suggested to have a synergistic effect by ensuring the viability of the delivered probiotic bacteria and stimulating the growth of the endogenous bacteria. This trial assesses the safety and tolerability of a new starter formula combining *B. longum* and prebiotics galacto- and fructo-oligosaccharides (GOS/FOS).
Study Type	Human clinical intervention trial
Study Design	Randomized, reference-controlled, double-blind prospective study: 138 infants who were not breast fed after the 14th day of birth were enrolled and assigned to receive the control or experimental formula until they were 112 days old. Mean weight gain (primary outcome) and recumbent length, head circumference, tolerability (gastrointestinal symptoms), and overall morbidity (secondary outcomes) were measured at 14, 28, 56, 84, and 112 days of age.
Subjects	138 infants who were not breast-fed after 14th day of birth
Dosage	2 x 10^7 CFU *B. longum* BL999* plus 4g/L mixture of GOS and FOS (90% and 10%)
Results	The study reported the following results: • No statistically significant difference in recumbent length, head circumference, or incidence of adverse events was found between the two groups. • Infants in the experimental group had fewer incidences of constipation and had stool characteristics that suggest that the experimental formula was tolerated well. Furthermore, these infants showed a trend toward fewer respiratory tract infections.
Conclusion	"The starter formula containing BL999 and galacto- and fructo-oligosaccharides is safe and well tolerated."

**BL999 is the same as BB536, but was referenced as BL999 in the published study*

BB536® Clinical Evidence

Children's Health

American Journal of Clinical Nutrition

Chouraqui J.P. et al. Assessment of the safety, tolerance and protective effect against diarrhea of infant formulas containing mixtures of probiotics or probiotics and prebiotics in a randomized controlled trial. 2008. 87:1365-1373

Topic	**Are infant formulas containing probiotics and synbiotics (combinations of probiotics and prebiotics) safe and tolerated?**
Background	Breast-fed infants are generally healthier than formula-fed infants, especially with respect to their ability to fend off infections. Some of the health benefits of human milk have been attributed partly to factors that modulate the development of a normal gut microbiota. These factors, which include complex oligosaccharides, are thought to selectively stimulate the growth of bacteria considered to be beneficial, such as bifidobacteria and lactobacilli, and inhibit the growth of potentially pathogenic bacteria. The development of improved infant formulas has focused on emulating the beneficial effects of breast milk by, among other approaches, supplementing formulas with specific probiotics or oligosaccharides (prebiotics) that selectively stimulate the growth or metabolic activity of potentially beneficial indigenous bacteria such as bifidobacteria. A number of clinical studies in which the formula of infants was supplemented with probiotics suggest that some probiotics may indeed have beneficial effects in managing and preventing gastrointestinal (GI) infections and diarrhea, prevent the onset of allergy, and be useful in the treatment of atopic disease. The combination of probiotics and prebiotics (synbiotics) has been proposed to have a synergistic effect by both ensuring survival of delivered probiotics and stimulating the growth of selected indigenous bacteria. However, clinical studies showing the effects of feeding synbiotics to infants are scarce.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind controlled prospective study: Healthy full-term infants were exclusively fed a control formula or study formulas containing a) *Bifidobacterium longum* BL999* + *Lactobacillus rhamnosus* LPR; b) BL999 + LPR + 4 g/L of 90% galacto-oligosaccharide/10% short-chain fructo-oligosaccharide (GOS/SCFOS); c) BL999 + *Lactobacillus paracasei* ST11 + 4 g/L GOS/SCFOS from ≤2 to 16 weeks of age (treatment period). Safety and tolerance were assessed based on weight gain during the treatment period (primary outcome) as well as recumbent length, head circumference, digestive tolerance, and adverse events (secondary outcomes), which were evaluated at 2, 4, 8, 12, 16, and 52 weeks of age.
Subjects	284 infants
Dosage	a) 1.29 x 10^8 BL999 CFU/100 mL + 6.45 x 10^8 LPR CFU/100 mL b) 1.29 x 10^8 BL999 CFU/100 mL + 6.45 x 10^8 LPR CFU/100 mL + 0.4 g GOS/SCFOS/100 mL c) 2.58 x 10^8 BL999 CFU/100 mL + 2.58 x 10^8 ST11 CFU/100 mL + 0.4 g GOS/SCFOS/100 mL
Results	The study reported the following results: • During the treatment period, difference in mean weight gain between control and study formula groups in both the intention-to-treat and per-protocol populations was within the predefined equivalence boundaries of ±3.9 g/d, indicating equivalent weight gain. • Secondary outcomes did not show significant differences between groups during the treatment period.
Conclusion	"Infants fed formulas containing probiotics or synbiotics show a similar rate in weight gain compared with those fed a control formula and tolerate these formulas well."

**BL999 is the same as BB536, but was referenced as BL999 in the published study*

BB536® Clinical Evidence

Children's Health

American Journal of Clinical Nutrition

Rouge C., et al. Oral supplementation with probiotics in very-low-birth-weight preterm infants: a randomized, double-blind, placebo-controlled trial. 2009. 89:1828–1835

Topic	**Does probiotic supplementation have an effect on preterm infants born with a very low or extremely low birth weight?**
Background	In neonatal intensive care units, the immaturity of intestinal function, frequent use of broad-spectrum antibiotics, delay in initiating enteral feeding, infection control procedures, and sterilization of milk limit the exposure of preterm infants to normal commensal microorganisms. As a consequence, very-low-birth weight (<1500 g) preterm infants experience a delayed and abnormal pattern of gut colonization, particularly with regard to bifidobacteria and lactobacilli, normally dominant in healthy full-term infants. This impaired intestinal colonization may predispose preterm infants to necrotizing enterocolitis and increase the risk of bacterial translocation. Although recent reports suggest that supplementation with probiotics may enhance intestinal function in premature infants, the mechanisms are unclear, and questions remain regarding the safety and efficacy of probiotics in extremely low-birth-weight infants (< 1000 g).
Study Type	Human clinical intervention trial
Study Design	Bicentric, double-blind, randomized controlled trial: The infants were randomly assigned to the placebo or the probiotic group and randomization was stratified on the basis of neonatal intensive care unit (NICU) center and birth weight category (<1000 g and >1000 g). Infants were fed human and/or preterm formula and were randomly assigned to receive 4 daily capsules of a supplement containing either maltodextrin alone (placebo group) or 108 lyophilized cells per unit of the probiotics *L. rhamnosus* GG and *B. longum* BB536 and maltodextrin (probiotic group) beginning on the day when enteral feeding started until discharge. Stool samples were collected from the first 24 infants enrolled in each NICU for the follow-up of intestinal microbiota and fecal calprotectin. The primary endpoint was the percentage of infants receiving >50% of their nutritional needs via enteral feeding on the 14th day of life.
Subjects	94 infants with a gestational age <32 weeks and a birth weight <1500 g (n=45 probiotic group, n=49 placebo group)
Dosage	4 capsules each containing 10^8 of *B. longum* BB536 and *Lactobacillus rhamnosus* GG (LGG). (4 x10^8 total probiotics daily)
Results	The study reported the following results: The primary endpoint was not significantly different between the probiotic (57.8%) and placebo (57.1%) groups. However, in infants who weighed > 1000g, probiotic supplementation was associated with a shortening in the time to reach full enteral feeding.
Conclusion	"Supplementation with BB536-LGG may not improve the gastrointestinal tolerance to enteral feeding in very-low-birth weight infants but may improve gastro-intestinal tolerance in infants weighing >1000 g."

BB536® Clinical Evidence

Children's Health

Pediatric Research

Mah KW, et al. Effect of a milk formula containing probiotics on the fecal microbiota of Asian infants at risk of atopic diseases. 2007. 62(6): 674-679

Topic	**Does milk formula containing probiotics *Bifidobacterium longum* BB536 and *Lactobacillus rhamnosus* GG have an effect on fecal microbiota of Asian infants with allergic disorders?**
Background	The hygiene hypothesis states that lack of exposure to pathogens or certain commensal bacteria in early life may predispose some individuals toward manifestation of allergic disorders. The gut microbiota plays an important role in the regulation of immune deviation, and an imbalance in itscomposition may lead to an increased susceptibility toward allergies. The use of probiotic bacteria as prophylactic agents from birth may, however, serve as a means to reverse the imbalance. This study investigates whether the dynamics of bacterial colonization of the infant gut would be altered by administration, during the first 6 months of life, of a probiotic product containing bifidobacteria and lactobacilli.
Study Type	Human clinical intervention trial
Study Design	Randomized, double-blind placebo-controlled trial: Newborns were randomized into blocks of 6 subjects to receive either 60 mL daily infant formula supplemented with *Bifidobacterium longum* BB536 and *Lactobacillus rhamnosus* GG (LGG) or standard formula as control for the first 6 months. Fecal samples were collected on day 3, and at 1, 3, and 12 months after birth.
Subjects	37 newborns (probiotic: 20, control: 17) meeting following inclusion criteria with first-degree relative with history of allergic disorder
Dosage	Minimum 60 mL of formula containing 1 x 10^7 CFU/g of *B. longum* BB536 and 2 x 10^7 CFU/g of *Lactobacillus* rhamnosus GG (LGG). At least 10^9 total probiotics daily.
Result	The study reported the following results: • Bifidobacteria increased markedly with a parallel decrease in *Enterobacteriaceae* and *Bacteroides–Prevotella* populations. *Eubacterium rectale–Clostridium coccoides* and *Atopobium* groups also gradually increased. This overall pattern was unaffected by probiotic administration.
Results (cont'd)	• *B. longum* and *L. rhamnosus* were detected more frequently in probiotic group during supplementation, but no difference after supplementation had ceased. • Cultured lactic acid bacteria were also more numerous in the probiotic-administered babies during treatment period.
Conclusion	"Our results indicate that supplemented strains could be detected but did not persist in the bowel once probiotic administration had ceased."

BB536® Clinical Evidence

Children's Health

Therapeutics (Japan)

Sekine I., et al. Effects of *Bifidobacterium* containing milk on chemiluminescence reaction of peripheral leukocytes and mean corpuscular volume of red blood cells–A possible role of *Bifidobacterium* on activation of macrophages. 1985. 14(5): 691-695

Topic	**Does *Bifidobacterium longum* BB536 have an effect on nonspecific macrophages in immunocompromised children and does it have an effect on hematogenous mechanism of red blood cells?**
Background	It is well known that various infectious diseases can complicate many cancers, such as infantile leukemia. Such complications are presumed to be attributed to the disruption of the normal hematogenous mechanisms of basic diseases, inhibition of multiplication of immunocompetent cells, and their destruction by various antitumor drugs. *Bifidobacterium* is known to be an immunostimulant by normalizing intestinal flora, reducing pH in intestinal tracts and thereby preventing secondary infection by harmful enterobacteria. It is suggested that the preventative functions of *Bifidobacterium* with regard to infection are through the intermediary of nonspecific macrophages. This study investigates this claim.
Study Type	Human clinical intervention trial
Study Design	Open-label controlled trial: Subjects were administered TM-1, a powdered milk containing *B. longum* BB536. Children aged 4–6 received 7 grams per day and older children received 10 g/day for a period of 1 year. Nonspecific macrophages were measured by chemiluminescence (CL), as well as mean corpuscular volume (MCV) of peripheral red blood cells after 1 year.
Subjects	8 children aged 4–12 (6 with acute lymphocytic leukemia (ALL); 1 with non-Hodgkins lymphoma (NHL); 1 with malignant teratoma) along with age-matched control cases (9 for chemiluminescence and 5 for measurement of MCV)
Dosage	10^8 *B. longum* BB536 viable cells/g (10^9 per serving)
Results	TM-1 milk dosed with *B. longum* BB536 resulted in the following changes • Higher values in first and second peaks of CL analysis compared with control group, suggesting an enhancement effect of nonspecific macrophages against monocytic cells. • Reduction of MCV of red blood cells.
Conclusion	"These results 'strongly suggest' the activation of monocyte-macrophage cell population in group treated with *B. longum* BB536. A significant reduction of MCV of red blood cells was also noted compared with nontreated group."

Anaerobe

Grzeskowiak L., et al. The impact of perinatal probiotic intervention on gut microbiota: Double-blind placebo-controlled trials in Finland and Germany. 2012. 18(1): 7–13

Topic	**To analyze the impact of probiotic administration to mother or infant on gut microbiota composition in 6-month-old infants.**
Background	Specific probiotic combinations given during early feeding, via the mother or incorporated in early formula feeding, influence the intestinal microbiota composition in infants. Intestinal colonization of a newborn starts at birth and continues during infancy. Microbiota development depends on the first inoculum, the mother's microbiota, mode of delivery, and the environment, including feeding practices. Bifidobacteria constitute up to 60%–70% of the total microbiota of healthy breast-fed infants, with *Bifidobacterium longum*, *Bifidobacterium infantis*, and *Bifidobacterium breve* as the most predominant species in different geographic areas. Deviations in microbiota composition such as low numbers or aberrant species of bifidobacteria have been associated with a higher risk of allergic and infectious diseases and obesity.
Study Type	Human clinical intervention trial
Study Design	Double-blind placebo-controlled trials randomized with 3 groups in each country. In Finland, probiotics were given to mothers for 2 months prior to and 2 months after delivery. In Germany, probiotics were started in infants at weaning, at the latest at 1 month of age, and continued for 4 months. A breast-fed group of 6-month-old infants from Finland and Germany were compared. Gut microbiota were analyzed by FCM-FISH and qPCR methods. In Finland, 28 mothers received a probiotic product consisting of *Lactobacillus rhamnosus* LPR (CGMCC 1.3724) with *B. longum* BL999* (ATCC: BAA-999), (LPR + BL999), 29 mothers received *Lactobacillus paracasei* ST11 (CNCM 1-2116) with *B. longum* BL999 (ST11 + BL999), and 22 placebo. The control and formula were based on product Pro Natal. In Germany, 24 infants received partially hydrolyzed formula supplemented with *L. rhomnosus* LPR and *B. longum* BL999* (LPR + BL999). Twenty-five received partially hydrolyzed formula with *B. longum* BL999, and 32 received partially hydrolyzed formula. The control and formulas were based on Beba HA (= Nan-HA), the partially hydrolyzed 100% whey formula. The probiotic and placebo formulas were administered to the infants when they went

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Subjects	In Finland, probiotics were given to 79 mothers for 2 months prior to and 2 months after delivery. In Germany, probiotics were started in infants (81) at weaning, at the latest at 1 month of age, and continued for 4 months. A breast-fed group of 6-month-old infants (22 from Finland, 8 from Germany) were compared.
Dosage	The dose to the mother was 10^9 CFU/day of each probiotic strain provided in one sachet of 7 g per day (powder form) diluted in a glass of water. In the German study, the dose of the probiotic was at least 10^9 CFU/day of each strain provided in metallic tins, each containing 400 g of study formula.
Results	In breast-fed infants, a trend toward higher counts of bifidobacteria was detected in Finland ($p = 0.097$) as against Germany, where a more diverse microbiota was reflected in higher Akkermansia ($p = 0.003$), *Clostridium histolyticum* ($p = 0.035$), and Bacteroides-Prevotella ($p = 0.027$) levels and a higher percentage of Akkermansia ($p = 0.004$). In Finish infants, bifidobacteria were found to be the dominant bacteria, with 100% colonization rate and the highest counts. Finnish LPR + BL999 intervention group (*Lactobacillus rhamnosus* LPR and *Bifidobacterium longum* BL999) had higher percentages of fecal *Lactobacillus-Enterococcus* (9.0% vs. 6.1% placebo, $p = 0.003$) and lower bifidobacteria levels (10.03 log cells/g vs. 10.68 log cells/g placebo, $p = 0.018$). In German infants, bifidobacteria were dominant at 6 months of age in all test groups. The proportions of the major bacterial groups in the fecal microbiota were not influenced by probiotic treatment.
Conclusion	Probiotic treatment had different impacts on gut microbiota composition in Finnish and German infants due to differences in mode of feeding and the early commensal microbiota. Feeding probiotics to mothers before and after birth and breast-feeding resulted in more beneficial bacteria and fewer harmful strains in infants compared with the formula-fed infants who were given strains only after birth.

**BL999 is the same as BB536, but was referenced as BL999 in the published study*

J Pediatr Gastroenterol Nutr. (JPGN)

Simakachorn N., et al. Tolerance, safety, and effect on the fecal microbiota of an enteral formula supplemented with pre- and probiotics in critically ill children. 2011. 53(2): 174–181

Topic	**The aim of this study was to demonstrate the tolerance and safety of an enteral formula containing prebiotics/probiotics, and its effect on the fecal microbiota in critically ill children.**
Background	Young patients under mechanical ventilation requiring enteral feeding were randomized to receive either a test formula containing a synbiotic blend (composed of 2 probiotic strains [*Lactobacillus paracasei* NCC 2461 and *Bifidobacterium longum* NCC3001], fructo-oligosaccharides [FOS], inulin, and acacia gum) or a control formula. Patients remained in the intensive care unit for 7 days and were examined at day 14. Tolerance was assessed by overall caloric intake and time to reach caloric goal. Safety was assessed by abdominal distention, vomiting, and stool frequency. Microbiota was analysed by culture- and molecular-based methods. Enteral nutrition (EN) is the preferred route for nutritional support of critically ill patients in intensive care units (ICUs). Complications associated with EN by tube feeding are not uncommon and reduce the delivery of nutritional requirements to ICU patients. EN has been associated with alterations in the intestinal luminal environment, disturbing the resident microbiota and favoring overgrowth of pathogens. Supplementation of EN formula with fructo-oligosaccharides (FOS) may prevent such adverse changes. A potential solution to manage intestinal microbial disturbances is to provide healthy live microorganisms, known as probiotics, to modulate the gut ecosystem, in combination with prebiotics, to selectively promote the growth and metabolic activity of beneficial bacteria, for example, bifidobacteria. Such a combination of pre- and probiotics is more likely to be effective in regulating the luminal microbial environment all along the gut and providing complementary benefits on the gut physiology.
Study Type	Human clinical intervention trial
Study Design	The study was a controlled double-blind randomized clinical trial of 2 parallel groups conducted in 2 medical centers. Patients between 1 and 3 years old under mechanical ventilation requiring enteral feeding were randomized to receive either a test formula containing a synbiotic blend (composed of 2 probiotic strains [*Lactobacillus paracasei* NCC 2461

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Study Design (cont'd)	and *Bifidobacterium longum* NCC 3001], fructo-oligosaccharides [FOS], inulin, and acacia gum) or a control formula. Patients remained in the intensive care unit for 7 days and were examined at day 14. Tolerance was assessed by overall caloric intake and time to reach caloric goal. Safety was analysed by culture- and molecular-based methods.
Subjects	Ninety-four patients between 1 and 3 years old in intensive care unit.
Dosage	The patients were assigned to 1 of the 2 treatment groups: (1) test group (n = 47): enteral formula supplemented with 2 probiotic strains (*L. paracasei* NCC 2461 [5 x 10^6 CFU/g], *B. longum* BB536 from Morinaga, Japan, coded at the Nestlé Culture Collection to be NCC 3001 [2 x 10^6 CFU/g]), prebiotics (oligofructose/inulin [2.6g/L], acacia gum [2.8g/L]), and DHA [43mg/L]; or (2) control group (n = 47): same enteral formula without added pre- and probiotics or DHA.
Results	Overall caloric intake and time to reach caloric goal were similar between groups (noninferiority was shown). Abdominal distention, vomiting, and stool frequency were not affected by the supplementation with pre- and probiotics. Fecal bifidobacteria were higher in the test group at the end of the study. A similar trend was observed for total lactobacilli. *L. paracasei* NCC 2461 and *B. longum* NCC 3001 were detected in 80.4% and 17% of the test group patients, respectively. Enterobacteria levels remained unchanged during hospitalization in the control group but diminished in the test group.
Conclusion	The enteral formula supplemented with symbiotics was well tolerated by children in intensive care units; it was safe and produced an increase in fecal bacterial groups of previously reported beneficial effects.

J Pediatr Gastroenterol Nutr. (JPGN)

Hascoet J.-M., et al. Effect of formula composition on the development of infant gut microbiota. 2011. 52(6): 756–762

Topic	**This randomized double-blind controlled trial aimed to evaluate the bifidogenic effect of a mainly whey protein study formula low in phosphate and protein, allowing a composition closer to that of human milk.**
Background	Breast-feeding induces a gut microbiota rich in bifidobacteria, whereas formula-fed babies have a more diverse colonization. This ecosystem contributes to the development of the immune response and the lower incidence of diarrhea and allergy in breast-fed infants.
Study Type	Human clinical intervention trial
Study Design	This was a single-center, randomized double-blind controlled trial in which infants were fed 1 of 3 infant formulas. A group of exclusively breast-fed infants served as a reference. Healthy newborn infants were randomly assigned at enrollment to receive the study formula, containing *Bifidobacterium longum* BL999* (ATCC: BAA-999 designation BB536, Morinaga, Japan: NCC3001), or control formula. The study formula had low protein and phosphate content, high lactose, and contained predominantly whey protein compared with the control formula. One hundred ninety healthy infants exclusively received study formula with or without *Bifidobacterium longum* BL999, or a control formula for up to 4 months. Breast-fed infants served as a reference population. Stool samples collected at 2 months of age were analyzed for bacterial counts (log colony-forming units [CFU]/g). Growth measurement, stool IgA, digestive tolerance, and adverse events were investigated.
Subjects	190 healthy infants
Dosage	2 x 10^7 CFU/g of *B. longum* BL999. The infants were exclusively fed the assigned formula ad libitum from the ages of 4 days to 4 months.

Results	Bifidobacteria counts were significantly higher in infants receiving the study formula alone (10.0 [0.8], p < 0.0001, median [interquartile range]) or with BL999 (9.8 [1.4], p < 0.01) than control (9.2 [3.5]), and were similar to breast-fed infants (10.1 [0.4], p > 0.05). The difference between the 2 study groups was 0.16 log CFU/g (90% confidence interval [CI] [0–0.4]), within the predefined equivalence margin. Microbiota profile, as a percentage of total bacteria counts, showed about 50% bifidobacteria, 8% enterobacteria, and <10% clostridia in study formulae and breast-fed infants versus 22%, 13%, and 19% in controls, respectively. There were no significant differences in growth measurements, digestive tolerance, and adverse events between groups.
Conclusion	This study showed that infant formula closer resembling human milk was more bifidogenic than the control formula and led to a microbiota profile similar to that for breast-fed infants.

**BL999 is the same as BB536, but was referenced as BL999 in the published study*

Asia Pac J Clin Nutr

Firmansyah A. et al. Improved growth of toddlers fed a milk containing synbiotics. 2011. 20(1): 69–76

Topic	**Comparison of growth and development of toddlers fed milk containing synbiotics (*Bifidobacterium longum* BL999*, *Lactobacillus rhamnosus* LPR, and prebiotics) and long-chain polyunsaturated fatty acids (LCPUFA) or a control milk.**
Background	Bifidobacteria and lactobacilli form the predominant bacterial species of the gastrointestinal (GI) tract in breast-fed infants, and have been associated with decreased morbidity, especially due to infections. Studies have suggested that both bifidobacteria and lactobacilli may be involved in reducing diarrhea and GI infections. This has formed the basis for their selection for use as probiotics in milks for infants and toddlers. Probiotics protect against GI infections by stimulating the immune system, create an environment in the GI tract that is unsuitable for growth of pathogens (low pH), and compete for binding sites on the epithelia. Some probiotics (mostly combinations of *Lactobacillus* and *Bifidobacterium* species) have also been shown to play an important role in curbing allergy development in high-risk infants. Prebiotics selectively stimulate the growth of certain beneficial bacteria, such as bifidobacteria, in the colon, and may improve the viability of probiotics. Synbiotics, the combination of probiotics and prebiotics, have thus been proposed to have synergistic health effects. There have also been suggestions that LCPUFA may be involved in the modulation of the immune system. However, considering that these lipids are integral components of cell membranes, their addition to milks may contribute to improved health in toddlers.
Study Type	Human clinical intervention trial
Study Design	Randomized controlled double-blind parallel group study. The aim of the current study was to evaluate the effects of milk containing synbiotics and LCPUFA on growth of healthy 12-month-old toddlers who were fed this milk for 4 months. We compared the effect of a milk containing *Bifidobacterium longum* BL999*, *Lactobacillus rhamnosus* LPR, inulin and fructo-oligosaccharide (prebiotics), and LCPUFA with that of a control milk lacking these components, with the hypothesis that the health benefits of the synbiotic plus LCPUFA milk would

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Study Design (cont'd)	be demonstrated by better growth in toddlers fed milk containing these components. We also explored possible effects of this milk on immune response to vaccination and on neurodevelopment. Both the synbiotics and control milks were cow's-milk-based and contained protein, carbohydrate, fat, vitamins, and minerals in amounts sufficient for normal growth of toddlers ages 12–24 months as supplementary food. In addition, the synbiotics milk also contained the probiotics *Bifidobacterium longum* BL999 (ATCC: BAA 999) and *Lactobacillus rhamnosus* LPR (CGMCC 1.3724), the prebiotics inulin (30%) and fructo-oligosaccharide (70%), and the LCPUFA, arachidonic acid (AA) and docosahexaenoic acid (DHA). One hundred milliliters of the reconstituted milk contained 14.4 g of this combination. Anthropometric measurement, gastrointestinal, tolerance (stool characteristics), stool bacterial counts, safety, antivaccine IgG, and neurodevelopment were observed.
Subjects	Three hundred and ninety-three healthy 12-month-old toddlers were enrolled and randomized into the synbiotics (n = 199) and the control milk (n = 194) groups
Dosage	Approximately 400 mL/day for 12 months. The test milk (powder form) was supplemented with 1 x 10^7 CFU/g of *B. longum* BL999 and 2 x 10^7 CFU/g of *L. rhamnosus*.
Results	Weight gain between 12 and 16 months was significantly greater in the synbiotics group (mean t/- SD, 7.57 +/- 4. 13 g/day) compared with the control group (6.64 +/- 4.08 g/day). There was a significant increase in lactobacilli and enterococci counts between 12 months and 16 months in the synbiotic group.
Conclusion	This shows that 4 months of feeding milk containing synbiotics and LCPUFA led to higher weight gain in toddlers compared with those fed a control milk lacking these components. However, an effect on neurodevelopmental measures was not observed. There was an increase in colonization with lactobacilli and enterococci in the synbiotics milk group but not in the control group.

**BL999 is the same as BB536, but was referenced as BL999 in the published study*

Clinical Et Experimental Allergy

Sho S. E. et al. Probiotic supplementation in the first 6 months of life in at-risk Asian infants — effects on eczema and atopic sensitization at the age of 1 year. 2009. 39: 571–578

Topic	**The role of probiotics in allergy prevention remains uncertain but has been shown in some studies to have a possible protective effect on eczema. Assessment of the effect of probiotic supplementation in the first 6 months of life on eczema and allergic sensitization at 1 year of age in Asian infants at risk of allergic disease.**
Background	Probiotic supplementation in early life is considered an attractive strategy for the primary prevention of allergic diseases. It has an excellent safety record. Its use is supported by the observation that early-life gut microbiota plays an important immunoregulatory role, and an "imbalance" in its composition may increase susceptibility toward allergies. In vitro and animal studies have shown that probiotic bacteria promote immunoregulatory functions by inducing T cells bearing TGF-β and increasing the production of IL-10 regulatory cytokines. The eventual test of such a strategy lies in intervention studies in the form of clinical trials.
Study Type	Human clinical intervention trial
Study Design	A double-blind placebo-controlled randomized study was conducted to assess the effect of probiotic supplementation in the first 6 months of life on the incidence of eczema and allergen sensitization in the first year in Asian infants at risk of allergic disease. This study assessed the effect of administration of a probiotic (*Bifidobacterium longum* and *Lactobacillus rhamnosus*) supplemented cow's-milk-based infant formula from the first day of life for 6 months on the prevention of eczema and allergic sensitization in the first year of life in Asian infants at risk of allergic disease. The inclusion criteria were: a first-degree relative with a doctor diagnosis of asthma, allergic rhinitis, or eczema and a positive skin-prick test (SPT) to dust mites. Subjects received at least 60 mL (9.26 g) a day of commercially available cow's-milk-based infant formula (Nan 1®), with either probiotic supplementation [*B. longum* BL999* (ATCC: BAA-999 designation BB536, Morinaga, Japan) 1 x 10^7 colony forming units (CFU)/g and *L. rhamnosus* LPR (CGMCC 1.3724) 2 x 10^7 CFU/g] or without, initiated within 12 hours for the first 6 months of life. The infants in the probiotic group, therefore,

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Study Design (cont'd)	received at least 2.8 x 10^8 CFU of probiotic bacteria per day. Mothers were then free to decide whether to make up the remainder of the baby feeds either with the trial formula, or to supplement with breast milk, or another infant formula. Clinical evaluation was performed at 1, 3, 6, and 12 months of age, with serum total IgE measurement and skin-prick tests conducted at the 12-month visit. The primary clinical outcome measure was the incidence of eczema, and the secondary outcome measure was allergen sensitization.
Subjects	124 families in the probiotic arm and 121 families in the placebo arm
Dosage	>2.8 x 10^8 CFU of probiotic bacteria per day.
Results	This randomized-controlled trial, a first in an Asian cohort, did not show a protective effect of probiotic supplementation for the first 6 months of life on eczema or allergen sensitization at 1 year of age. The incidence of eczema in the probiotic (n = 27/124; 22%) group was similar to that in the placebo group (n = 30/121; 25%). In subjects with eczema, the median SCORAD score at 12 months was 17.10 in the probiotic group and 11.60 in the placebo group The rate of sensitization to common allergens (probiotic = 24% vs. placebo = 19%), showed no difference. Total IgE geometric mean was 18.76 kU/L in the probiotic group and 23.13 kU/L in the placebo group. Atopic eczema (with sensitization) in the probiotic group (7.3%) was similar to that in the placebo group (5.8%).
Conclusion	The study does not support the role of early-life probiotic supplementation as a modality for primary eczema prevention. An extended period of follow-up of this cohort is intended to determine longer-term outcomes and effect on other manifestations of allergy in this population.

**BL999 is the same as BB536, but was referenced as BL999 in the published study*

Allergology International

Enomoto, T et al. Effect of Bifidobacterial Supplementation to Pregnant Women and Infants in the Prevention of Allergy Developments in Infants and on Fecal Microbiota: 2014;63:575–585

Topic	**What is the effect on infants of bifidobacterial supplementation in pregnant Japanese women and their infants who develop allergic diseases at birth?**
Background	Probiotics may help prevent allergies in infants, though efficacy is uncertain.
Study Type	Human intervention, open label study
Study Design	In an open trial, *Bifidobacterium breve* M-16V and *Bifidobacterium longum* BB536 were given prenatally to 130 mothers beginning 1 month prior to delivery and postnatally to their infants for 6 months. Beginning approximately 4 weeks before the date of expected delivery, the participants were advised to ingest the bifidobacterial powder by drinking it with milk or water. Another 36 mother-infant pairs served as controls and did not receive the bifidobacteria. Development of allergic symptoms in the infants was assessed at 4, 10, and 18 months of age. Fecal test samples were collected from the mothers and infants to measure bacteria. After delivery, the infants were given one sachet of the same bifidobacterial powder to be consumed daily in breast milk or water for breast-feeding infants or in formula or water for formula-feeding infants beginning approximately 1 week after birth and continuing for 6 months.
Subjects	130 mothers
Dosage	Pregnant women received 2 sachets daily of bifidobacterial powder (approximately 1 g per sachet, each containing approximately 5 × 10^9 colony-forming units of *B. longum* BB536 [ATCC BAA-999] and *B. breve* M-16V [LMG 23729]). After delivery, the infants were given 1 sachet of the same bifidobacterial powder.

Results	The risk of developing eczema/atopic dermatitis (AD) in infants during the first 18 months of life was significantly reduced in the bifido group (OR: 0.231 [95% CI: 0.084–0.628] and 0.304 [0.105–0.892] at 10 and 18 months of age, respectively). Pyrosequencing analyses indicated an altered composition of the fecal microbiota at 4 months for infants who developed eczema/AD at 4 and 10 months of age. The proportion of Proteobacteria was significantly lower ($p = 0.007$) in mothers at the time of delivery who received probiotics when compared with the control group and was positively correlated ($r = 0.283$, $p = 0.024$) with infants at 4 months of age. No adverse effects were found with the use of probiotics.
Conclusion	These data suggest that the prenatal and postnatal supplementation of bifidobacteria is effective in primary prevention of allergic diseases. Some degree of limited changes in the composition of fecal microbiota by the bifidobacterial supplementation was found.

Anaerobe

Ishizeki, S, M Sugita, M Takata, T Yaeshima. Effect of administration of bifidobacteria on intestinal microbiota in low-birth-weight infants and transition of administered bifidobacteria: a comparison between one-species and three-species administration. 2013 Oct;23:38–44

Topic	**What was the effect of administration of bifidobacteria on the intestinal microbiota in low-birth-weight infants, and the transition of each strain of administered bifidobacteria?**
Background	The development of the infant immune system and protection from infection is critically influenced by bifidobacteria. Low-birth-weight infants have delay in the formation of intestinal microbiota, especially bifidobacteria. This increases the risk of intestinal infections, including necrotizing enterocoltitis. It also affects the growth of infants who are born prematurely. A beneficial effect has been found for supplementation of infants with these species of probiotics.
Study Type	Human intervention study, open label, with control group
Study Design	A single strain of *Bifidobacterium breve* M-16V (5×10^8 CFUs; one-species group) or a mixture of three species composed of *B. breve* M-16V, *Bifidobacterium longum* subsp. *infantis* M-63, and *B. longum* subsp. *longum* BB536 (5×10^8 CFUs of each strain; three-species group) was administered daily for 6 weeks. The control group received breast milk or a combination of breast milk and formula without the added strains of *Bifidobacterium*.
Subjects	46 infants
Dosage	5×10^8 CFUs daily
Results	Bifidobacterial administration significantly increased the detection rates and cell numbers of bifidobacteria in the feces during weeks 1 through 6. The proportion of bifidobacteria was significantly higher in the one-species group at weeks 1 through 4, and in the three-species group at weeks 1 through 6 compared with the control group. Furthermore, the proportion of bifidobacteria in the three-species group was significantly higher than that in the one-species group at weeks 1 and 6. The proportion of infants with bifidobacteria-predominant microbiota also was significantly higher in the three-species group than in the control group. Detection rates of Clostridium were lower in the bifidobacteria-administered groups.

Results (cont'd)	The proportions of Enterobacteriaceae were significantly lower in the three-species group compared with the other groups (weeks 4 and 6). Among the three strains administered, B. breve M-16V and Bifidobacterium infantis M-63 were detected in 85% or more of the infants during the administration period, while B. longum BB536 was detected in 40% or less.
Conclusion	Compared with administration of one species, giving three species of bifidobacteria resulted in earlier formation of bifidobacteria-predominant fecal microbiota and maintenance of the microbiota..

Journal of Allergy and Clinical Immunology

Rautava, S, E Kainonen, S Salminen, E Isolauri. Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant. 2012 Dec;130(6):1355–60

Topic	**What is the benefit of giving probiotic supplementation to the mother during pregnancy and breast-feeding on reducing the risk of eczema in the infant?**
Background	Probiotics have shown promising potential in reducing the risk of eczema in infants; however, the optimal probiotic intervention regimen remains to be determined. It was investigated whether maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of developing eczema in high-risk infants. Clinical trials associate specific probiotic supplementation in early life with decreased risk of developing eczema. On the basis of available evidence, it appears that probiotic intervention is most effective in reducing the risk of eczema in the infant if started during pregnancy. Seven published studies showed efficacy in reducing disease risk for both prenatal maternal and postnatal probiotic supplementation. Previously provided data suggest that *Lactobacillus rhamnosus* GG administered to the pregnant and breast-feeding mother significantly reduces the risk of developing eczema in high-risk infants. The present study was to investigate whether exclusively maternal probiotic intervention without direct probiotic supplementation to the infant during the last 2 months of pregnancy and the first 2 months of breast-feeding is effective in reducing the risk of developing eczema in high-risk infants identified objectively as those with mothers with allergic disease and atopic sensitization.
Study Type	A double-blind, randomized, placebo-controlled trial
Study Design	Mothers with allergic disease and atopic sensitization were randomly assigned to receive 1) *Lactobacillus rhamnosus* LPR and *Bifidobacterium longum* BL999* (LPR+BL999), 2) L. paracasei ST11 and B. longum BL999 (ST11+BL999), or 3) placebo, beginning 2 months before delivery and during the first 2 months of breast-feeding. The infants were followed until the age of 24 months. Skin-prick tests were performed at the ages of 6, 12, and 24 months.
Subjects	205 mother-infant pairs
Dosage	1. 3 × 10^9 CFUs provided in 1 sachet of 7 g/d (powder form) which was diluted in a glass of water. The same dietary supplement without probiotics served as a placebo.

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Results	The risk of developing eczema during the first 24 months of life was significantly reduced in infants of mothers receiving *Lactobacillus rhamnosus* LPR+ *Bifidobacterium longum* BL999 (odds ratio [OR], 0.17; 95% CI, 0.08–0.35; p < .001) and ST11+BL999 (OR, 0.16; 95% CI, 0.08–0.35; p < .001). The respective ORs for chronically persistent eczema were 0.30 (95% CI, 0.12–0.80; p = .016) for *Lactobacillus rhamnosus* and 0.17 (95% CI, 0.05–0.56; p = .003) for *Bifidobacterium longum* BL999. Probiotics had no effect on the risk of atopic sensitization in the infants. No adverse effects were related to the use of probiotics.
Conclusion	A preventive regimen with specific probiotics given to the pregnant and breast-feeding mother, prenatally and postnatally, is safe and effective in reducing the risk of eczema in infants with allergic mothers positive for a skin-prick test demonstrating atopic predisposition.

**BL999 is the same as BB536, but was referenced as BL999 in the published study*

Skin

Department of Dermatology, School of Medicine, Wakayama Medical University, Wakayama, Japan

Yonezawa, S, J Xiao, Y Yamamoto, F Furukawa. Effect of milk supplemented with bifidobacteria on skin condition in healthy adult women. Food Science and Technology Institute, Morinaga Milk Industry Co., Ltd., 2014

Topic	**What is the effect of milk supplemented with bifidobacteria on the skin condition in healthy adult women?**
Background	Bifidobacteria are known to possess physiological functions, including the effect of regulating intestinal health. When women who had skin problems such as atopic dermatitis, acne, and dry skin, together with constipation consumed milk supplemented with bifidobacteria continuously for 8 weeks, the frequency of bowel movements and skin condition were improved. Skin can be improved by consuming foods supplemented with bifidobacteria, one of the mechanisms of action likely involving regulation of intestinal function such as elimination. *Bifidobacterium longum* BB536 (Bifidus BB536), a *Bifidobacterium* strain isolated from a healthy infant by Morinaga Milk Industry, has been reported to exhibit various physiological functions based on the regulation of intestinal activity. In the present study, subjects with constipation and skin problems were administered food supplemented with Bifidus BB536 to examine the effects on constipation and these skin problems. *Bifidobacterium* and galacto-oligosaccharide consumption of the fermented milk significantly reduced serum phenol levels and prevented decrease in skin moisture during the dry winter season. Although phenols are produced in the intestines, they accumulate in the skin via blood circulation and disrupt keratinocyte differentiation, which may be one of the causes of skin problems such as dryness.
Study Type	Human intervention study
Study Design	Twenty-eight women (mean age, 40.7 years: range, 30–62 years) who had skin problems such as atopic dermatitis, acne, and dry skin, together with a bowel movement frequency of three times or fewer per week were recruited. Subjects consumed 1 bottle per day of milk supplemented with Bifidus BB536 (180 mL containing 2×10^9 colony-forming units (CFUs) of bifidobacteria) every day for 8 weeks. Subjective scores of skin condition (questionnaire, visual analog scale (VAS) for itchiness, and Skindex-16) and defecation status were investigated before consumption at week 1 and at week 4 and week 8 of consumption. The skin condition was examined by a dermatologist and microscopic photographs were recorded at week 0, week 4 and week 8.

BB536® Clinical Evidence

Skin

Study Design (cont'd)	In an exploratory analysis of the relationship between subjective scores of skin condition and quality of defecation, a significant positive correlation was found in the improvement of acne severity with the improvement of bowel movements.
Subjects	28 women
Dosage	180 mL containing 2×10^9 CFUs of bifidobacteria
Results	In subjects consuming milk supplemented with Bifidus BB536, defecation frequency was increased, and fecal health as well as the sensation of complete defecation were improved. Regarding skin conditions, subjective symptoms including glossiness, firmness, skin porosity, redness, dryness, suitability of cosmetics, number of acnes, and severity of acne improved. Changes in VAS score for itchiness also showed significant improvement. Microscopic photographs of the skin surface also demonstrated improvements in skin texture and dryness. Effects have been attributed to the immunomodulatory function of probiotics in regulating the Th1/Th2 balance.
Conclusion	In the study, beneficial effects on the skin condition resulting from consumption of foods containing bifidobacteria were shown. The effect may be owing to the improvement of the intestinal environment and possible direct effects on the skin. Further studies are necessary to clarify these mechanisms and provide additional evidence.

Cellular Health

Bifidobacteria Microflora

Tomoda T., et al. Intestinal *Candida* overgrowth and *Candida* infection in patients with leukemia: Effect of *Bifidobacterium* administration. 1988. 7(2): 71-74

Topic	**Does *Bifidobacterium* have an effect on intestinal *Candida* in patients with leukemia receiving chemotherapy?**
Background	Leukemia patients receiving chemotherapy have higher number of intestinal *Candida* than normal subjects. The number of intestinal *Candida* is correlated with incidence of *Candida* infections such as respiratory infections and urinary infections. The effect of *Bifidobacterium* administration on the growth of Candida is examined.
Study Type	Human clinical intervention trial
Study Design	Open-label controlled trial: Leukemia patients were treated with chemotherapy, and the number of intestinal *Candida* was calculated. Forty-nine of the 100 patients had more than 10^5 *Candida*/g feces (while control patients had less than 10^4). Twenty-eight of the 49 were fed *Bifidobacterium* for more than 3 months (either 3 g/day of Levenin® or 200 mL/day of Morinaga Bifidus®). The number of *Candida* was calculated and incidences of infections were monitored.
Subjects	100 patients with leukemia and 34 normal patients (control)
Dosage	10^7 viable cells each *Bifidobacterium longum*, *L. acidophilus*/mL (Morinaga Bifidus) or 10^7 of *Bifidobacterium infantis*, *L. acidophilus*, *Enterococcus faecalis*/g (Levenin)
Results	When *Bifidobacterium*-treated patients were divided into two groups (A: those that continued to excrete more than 10^5 *Candida*/g and B: those that excreted less than 10^4 *Candida*/g), a significant difference was apparent in the incidence of *Candida* infection in patients with $<10^4$ *Candida*/g.
Conclusion	The present study clarified that an increased number of intestinal *Candida* is one of the causes of opportunistic infection by *Candida*. The usefulness of *Bifidobacterium* administration is demonstrated."

BB536® Clinical Evidence

Cellular Health

Medicine and Biology (Japan)

Kageyama T., et al. Comparative study on oral administrations of some *Bifidobacterium* preparations. 1987. 115(2): 65-68

Topic	**Does *Bifidobacterium* have an effect on bacterial quantity and variation in species in patients with leukemia or cancer?**
Background	There is an imbalance in residential intestinal flora during administration of oral anticancer or immunosuppressive drugs. A few findings reported on the utility of administration of *Lactobacillus* preparation to prevent this imbalance. This study compares several *Bifidobacterium* preparations for a similar effect.
Study Type	Human clinical intervention trial
Study Design	Open-label trial: Once per day for 6 months, one patient received 200 mL cow's milk containing *Bifidobacterium*, one patient received 2 bags x 1 gram of bacterial powder, and one patient received both treatments. Fecal flora was counted and classified before administration and after 2, 4, and 6 months of *Bifidobacterium* administration.
Subjects	3 patients with leukemia
Dosage	Cow's milk: 10^7/mL viable cells each *Bifidobacterium* and *Lactobacillus* Bacterial powder: 10^9 to 10^{10} viable cells *Bifidobacterium* plus 1 g lactulose/bag
Results	*Bifidobacterium* supplementation resulted in the following changes: • Cow's milk with *Bifidobacterium*: a decrease in *Bacteroides*. • Bacterial powder: a decrease in *Bacteroides*, *Candida*, and *E. coli*. • Both treatments: a decrease in *Bacteroides*, *Candida*, and *E. Coli*.
Conclusion	"The effect of various *Bifidobacterium* administration methods on the imbalance in bacterial flora in the intestinal tract of patients with leukemia under treatment showed the proliferation of *Bacteroides*, *Candida*, and *E. coli* could be inhibited during *Bifidobacterium* administration" anti-leukemic therapy."

***Medicine and Biology* (Japan)**

Tomoda T., et al. Variation in small groups of constant intestinal flora during administration of anticancer or immunosuppressive drugs. 1981. 103 (1): 45-49

Topic	**Do probiotics have an effect on bacterial quantity and variation in species in patients with leukemia or cancer?**
Background	There is an imbalance in residential intestinal flora during administration of oral anticancer or immunosuppressive drugs. The present study examines variations in bacterial species and quantity in intestinal bacteria with administration of probiotics.
Study Type	Human clinical intervention trial
Study Design	Open-label controlled trial: Patients received either no treatment or treatment with 200 mL cow's milk containing *Lactobacillus* acidophilus and *Bifidobacterium*. Treatment was administered daily for 2 to 6 months (varying by case). Intestinal flora in feces were examined monthly.
Subjects	60 patients with acute myelogenous leukemia or chronic myelogenous leukemia or solid cancers (all taking anticancer drugs) and 10 healthy subjects as controls
Dosage	Cow's milk: 10^7/mL viable cells each *Bifidobacterium* and *Lactobacillus*
Results	The study reported the following results: • Patients receiving anticancer drugs showed increase in *Klebsiella*, *Citrobacter*, *Pseudomonas*, *P. vulgaris*, and *Candida*, compared with the control. • Administration of the probiotic cow's milk suppressed the proliferation pf *Pseudomonas*, *P. vulgaris*, *and Candida*.
Conclusion	"Administration of probiotics in cow's milk suppressed the proliferation of *Pseudomonas*, *P. vulgaris*, and *Candida* in patients receiving anticancer drugs."

BB536® Clinical Evidence

Cellular Health

Bifidobacteria Microflora

Kageyama T., et al. The effect of *Bifidobacterium* administration in patients with leukemia. 1984. 3(1): 29-33

Topic	**Does *Bifidobacterium* have an effect on populations of intestinal bacteria and *Candida* on patients with leukemia?**
Background	It is well known that patients with leukemia are prone to infectious diseases that are caused by microorganisms found in the oral cavity, pharynx, larynx, and digestive tract. These infections are often fatal. The intestinal flora of patients with leukemia is often changed by chemotherapy, which allows for growth of pathogenic bacteria. *Bifidobacterium* is investigated to counteract this imbalance of intestinal microorganisms.
Study Type	Human clinical intervention trial
Study Design	Open-label controlled trial: Patients received anti-leukemic drugs, followed by supplementation with 200 mL milk containing *Bifidobacterium* and *Lactobacillus*, or nothing (non administration group) daily for 3 months. Following administration of anti-leukemia drugs and after 3 months, intestinal bacteria were isolated, counted, and classified from feces.
Subjects	56 patients with leukemia
Dosage	10^7 *Bifidobacterium* and 10^7 *Lactobacillus* viable cells/mL (2 x 10^9 of each per serving)
Results	Supplementation resulted in the following significant changes: • Significant increases were seen in *E. coli*, *Bacteroides*, and *Veillonella* after anti-leukemic drugs. After administration of *Bifidobacterium*, the intestinal bacteria returned to normal. • The numbers of *Klebsiella*, *Citrobacter*, *Pseudomonas*, or *Proteus vulgaris* were greater in nonadministration group. • *Bifidobacterium* administration decreased the number of Candida in patients compared with nonadministration group. • *Bifidobacterium* administration reduced the extent of urine indicant and blood endotoxin positive reactions.
Conclusion	"It has been demonstrated that *Bifidobacterium* administration can be used for the purpose of prophylaxis of many infections and improvement of secondary metabolic disturbance due to the intestinal bacteria in leukemic patients undergoing anti-leukemic therapy."

Journal of Clinical Nutrition

Demers, M, A Dagnault, and J Desjardins. A randomized double-blind controlled trial: impact of probiotics on diarrhea in patients treated with pelvic radiation. 2014 Oct;33(5):761–7

Topic	**What is the effect of the probiotic Bifilact® on moderate and severe treatment-induced diarrhea during pelvic radiation?**
Background	Radical radiation therapy is commonly used for treatment of pelvic cancer, and up to 80% of patients receiving radiotherapy will develop acute radiation-induced diarrhea. The primary aim of this study is to evaluate the effect of the probiotic Bifilact on moderate and severe treatment-induced diarrhea during pelvic radiation. Patients with pelvic cancers were treated between 2006 and 2010 at L'Hôtel-Dieu de Québec, University Health Center.
Study Type	Randomized, double-blind controlled trial
Study Design	Patients were split into 2 groups: some who had surgery before pelvic radiotherapy, and some who had received chemotherapy. A total of 246 patients were randomized to receive a placebo or either of two regimens of double-strain Bifilact probiotics (Lactobacillus acidophilus LAC361 and Bifidobacterium longum BB536). A standard dose twice a day (1.3 billion CFUs) or a high dose 3 times a day for a total of 10 billion CFUs consumed. Patients were instructed to record their digestive symptoms every day throughout the day with a standardized scale and met a registered dietitian and radiation oncologist every week during treatment. The main analysis compared time to first appearance of grade ≥ 2-3-4 diarrhea using Kaplan-Meier curves as measured by proportion of patients without moderate and severe diarrhea.
Subjects	229 patients with pelvic cancer (17 out of 246 patients were excluded)
Dosage	A standard dose twice a day (1.3 billion CFUs) or a high dose 3 times a day for a total of 10 billion CFUs.

Results	The differences between groups for all types of diarrhea were not statistically significant (p = 0.13). At 60 days, the proportion of patients without moderate and severe diarrhea in the standard-dose group (35%) was more than twice as high as that of the placebo group (17%), with a hazard ratio of 0.69 (p = 0.04). In patients who had surgery, the probiotics standard-dose group had a better proportion of patients without very severe diarrhea than the placebo group, respectively 97% and 74% (p = 0.03). In all groups, the average number of bowel movements per day during treatment was fewer than 3 soft stools (p = 0.80) and the median abdominal pain less than 1 based on the National Cancer Institute scale (p = 0.23).
Conclusion	The standard dose of 1.3 billion CFUs of Bifilact may reduce radiation-induced grade 2-3-4 diarrhea at the end of the treatment in patients with pelvic cancer. In patients operated on before radiation therapy, a standard dose of probiotics may reduce radiation-induced grade 4 diarrhea. Nutritional interventions by a registered dietitian seemed to reduce global digestive symptoms.

Clinical and Experimental Allergy

Xiao J.Z. et al. Probiotics in the treatment of Japanese cedar pollinosis: a double-blind placebo-controlled trial. 2006. 36:1425-1435

Topic	**Does *Bifidobacterium longum* BB536 have an effect in the treatment of Japanese cedar pollinosis?**
Background	Japanese cedar pollinosis (JCPsis) is an immunoglobin E (IgE)-mediated type I allergy caused by exposure to Japanese cedar pollen. It is the most common allergic disease in Japan, with increasing prevalence over the past decade. Probiotic microorganisms have been shown to be effective in the treatment of allergic inflammation and food allergy, but their efficacy remains controversial. This study investigates whether the probiotic *Bifidobacterium longum* BB536 can relieve clinical symptoms and modulate plasma cytokine levels of Japanese cedar pollinosis during the pollen season.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind, placebo-controlled trial: Subjects were given *B. longum* BB536 powder or placebo powder twice daily for 13 weeks. Subjective symptoms and self-care measures were recorded daily and blood samples were taken before and during the intervention (at weeks 4, 9, and 13) to measure the blood parameter levels related to JCPsis.
Subjects	44 subjects with a clinical history of JCPsis
Dosage	5 x 10^{10} viable cells *B. longum* BB536/ 2 grams
Results	*B. longum* BB536 supplementation resulted in the following changes compared with placebo powder: • *B. longum* BB536 intake was associated with a significant reduction in number of subjects prematurely terminated due to severe symptoms and pollinosis medication. • Subjective symptom scores indicated significant decreases in rhinorrhea, nasal blockage, and composite scores. • Comparison of medical scores showed marked improvements in all symptoms on *B. longum* BB536 intake. • A T-helper type 2 (TH2)-skewed immune response occurring along with pollen dispersion was observed. • *B. longum* BB536 significantly suppressed increases in plasma thymus- and activation-regulated chemokine and tended to suppress elevations of Japanese cedar pollen (JCP)-specific IgE.
Conclusion	"These results suggest the efficacy of BB536 in relieving JCPsis symptoms, probably through the modulation of TH2-skewed immune response."

BB536® Clinical Evidence

Seasonal Relief

Journal Investig Allergol Clin Immunol

Xiao J.Z. et al. Effect of probiotic *Bifidobacterium longum* BB536 in relieving clinical symptoms and modulating plasma cytokine levels of Japanese cedar pollinosis during the pollen season. A randomized double-blind, placebo-controlled trial. 2006. 16(2): 86-93

Topic	Does *Bifidobacterium longum* BB536 have an effect in the treatment of Japanese cedar pollinosis?
Background	Japanese cedar pollinosis (JCPsis) is an immunoglobin E (IgE)-mediated type I allergy caused by exposure to Japanese cedar pollen. It is the most common allergic disease in Japan, with increasing prevalence over the past decade. Probiotic microorganisms have been shown to be effective in the treatment of allergic inflammation and food allergy, but their efficacy remains controversial. This study investigates whether the probiotic *Bifidobacterium longum* BB536 can relieve clinical symptoms and modulate plasma cytokine levels of Japanese cedar pollinosis during the pollen season.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind, placebo-controlled trial: Subjects were given yogurt either containing *B. longum* BB536 (BB536 yogurt) or without BB536 (placebo yogurt) at 2 x 100 g per day for 14 weeks. Subjective symptoms and self-care measures were recorded daily and blood samples were taken before and during the intervention (at weeks 4, 9, and 14) to measure the blood parameter levels related to JCPsis.
Subjects	40 subjects with a clinical history of JCPsis
Dosage	2 x 10^9 *B. longum* BB536 viable cells/serving of yogurt
Results	*B. longum* BB536 supplementation resulted in the following changes compared with placebo yogurt: • Significantly alleviated eye symptoms. • Nasal symptoms such as itching, rhinorrhea, and blockage, as well as throat symptoms tended to be relieved. • Tendency to suppress the decreasing blood levels of interferon-gamma (IFN-y) and the increasing blood eosinophil rates. • A decreased trend in the difference from baseline levels of JCP-specific IgE levels was observed at week 4 in the BB536 group.
Conclusion	"In conclusion, these results suggest that intake of BB536-supplemented yogurt may relieve JCPsis symptoms, probably through a modulating effect on TH (T-helper) balance."

Allergology International

Xiao J.Z. et al. Clinical efficacy of probiotic *Bifidobacterium longum* for the treatment of symptoms of Japanese cedar pollen allergy in subjects evaluated in an environmental exposure unit. 2007. 56(1): 67-75

Topic	Does *Bifidobacterium longum* BB536 have an effect in the treatment of Japanese cedar pollinosis?
Background	Japanese cedar pollinosis (JCPsis) is an immunoglobin E (IgE)-mediated type I allergy caused by exposure to Japanese cedar pollen. It is the most common allergic disease in Japan, with increasing prevalence over the past decade. Probiotic microorganisms have been shown to be effective in the treatment of allergic inflammation and food allergy, but their efficacy remains controversial. This study investigates whether the probiotic *Bifidobacterium longum* BB536 can relieve clinical symptoms using an environmental exposure unit.
Study Type	Human clinical intervention trial
Study Design	Double two-way crossover trial: After a 1-week run-in period, subjects were randomly allocated to receive *B. longum* BB536 powder or placebo twice a day for 4 weeks. After a 2-week washout period, subjects were crossed over to another 4 weeks of intake. At the end of each intake period, subjects received controlled JCP exposure for 4 hours in the Environmental Exposure Unit. Symptoms were self-rated 30 minutes before and every 30 minutes during the exposures. From the first day of exposure through the next 5 successive days, participants self-rated their delayed symptoms and medication uses. Blood samples were taken before the exposures. The mean JCP levels for exposures were 6500 to 7000 grains/m3 air.
Subjects	24 subjects with a clinical history of JCPsis
Dosage	5 x 10^{10} viable cells *B. longum* BB536/serving
Results	*B. longum* BB536 supplementation resulted in the following changes compared with placebo powder: • A significant reduction in the ocular symptom scores during JCP exposures. • Evaluating delayed symptoms after exposures indicated that scores for disruption of normal activities were significantly lower. • Prevalence of medication use was markedly reduced by *B. longum* BB536 intake.
Conclusion	"These results suggest the potential beneficial effect of BB536 in relieving symptoms of JCP allergy."

Seasonal Relief

J Investig Allergol Clin Immunol.
Odamaki T., et al. Fluctuation of fecal microbiota in individuals with Japanese cedar pollinosis during the pollen season and influence of probiotic intake. 2007. 17(2): 92-100

Topic	**Does *Bifidobacterium longum* BB536 have an effect on fecal microbiota during pollen season?**
Background	Japanese cedar pollinosis (JCPsis) is an immunoglobin E (IgE)-mediated type I allergy caused by exposure to Japanese cedar pollen. It is the most common allergic disease in Japan, with increasing prevalence over the past decade. Clinical trial has previously shown the intake of yogurt supplemented with a probiotic strain, *Bifidobacterium longum* BB536, alleviates symptoms and affects blood parameters in individuals with JCPsis during the pollen season. This study investigates whether the probiotic *Bifidobacterium longum* BB536, which has been shown to relieve clinical symptoms and modulate plasma cytokine levels of Japanese cedar pollinosis during the pollen season, has an effect on fecal microflora balance in patients with JCPsis.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind, placebo-controlled trial: After a 2-week run-in period, participants were randomly assigned to groups that ingested 2 x100 g of yogurt daily either with *B. longum* BB536 or without BB536 for 14 weeks (comprising 4 weeks before and 10 weeks during pollen season). Subjective symptoms were recorded daily and blood samples were taken before and during (at weeks 4, 9, and 14) the intervention to measure levels of blood parameters related to JCPsis. Fecal samples were obtained from 23 subjects (placebo group, n=13; BB536 group, n=10) before and during the intervention (weeks 4, 9, and 13), and fecal microbiota were analyzed using terminal restriction fragment length polymorphism and real-time polymerase chain reaction (PCR) methods.
Subjects	40 subjects with a clinical history of JCPsis
Dosage	3.5 x 10^8 viable cells *B. longum* BB536/serving

Results (cont'd)	The study reported the following results: • Real-time PCR analyses indicated that the cell numbers of the *B. fragilis* group increased significantly along with pollen dispersion in both *B. longum* BB536 and placebo groups. • Cell numbers of bifidobacteria were significantly higher in the *B. longum* BB536 group compared with the placebo group. • The ratio of cell numbers of the *B. fragilis* group to bifidobacteria increased significantly during the pollen season in the placebo group but not in the BB536 group. • An *in vitro* study using peripheral blood mononuclear cells from JCPsis subjects indicated that strains of the *B. fragilis* group induced significantly more helper T cell (TH) type 2 cytokines (interleukin [IL]-6) but fewer TH1 cytokines (IL-12 and interferon) compared with those of bifidobacteria.
Conclusion	"These results suggest a relationship between fluctuation in intestinal microbiota and pollinosis allergy. Furthermore, intake of BB536 yogurt appears to exert positive influences on the formation of anti-allergic microbiota."

Seasonal Relief

Int Arch Allergy Immunol

Xiao J.Z. et al. Changes in plasma TARC levels during Japanese cedar pollen season and relationships with symptom development. 2007. 144(2): 123-127

Topic	**Does *Bifidobacterium longum* BB536 have an effect in the treatment of Japanese cedar pollinosis?**
Background	Japanese cedar pollinosis (JCPsis) is an immunoglobin E (IgE)-mediated type I allergy caused by exposure to Japanese cedar pollen. It is the most common allergic disease in Japan, with increasing prevalence over the past decade. Blood thymus and activation-regulated chemokine (TARC) levels are well known as an objective parameter for disease severity for several allergic disorders. The probiotic *Bifidobacterium longum* has been shown to relieve clinical symptoms and modulate plasma cytokine levels of Japanese cedar pollinosis during the pollen season. The present study aims to evaluate the relationship between TARC levels and disease symptoms during the pollen season in a clinical trial aiming to evaluate the effect of the probiotic *B. longum* BB536 in the treatment of JCPsis.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind, placebo-controlled trial: Subjects were given *B. longum* BB536 powder or placebo powder twice daily for 13 weeks. Subjective symptoms and self-care measures were recorded daily and blood samples were taken before and during the intervention (at weeks 4, 9, and 13) to measure the blood parameter levels related to JCPsis, including plasma TARC levels.
Subjects	42 subjects with a clinical history of JCPsis
Dosage	5 x 10^{10} viable cells *B. longum* BB536/2 grams
Results	The study reported the following results: • Significant increases in plasma TARC levels were observed in subjects receiving placebo, but not in subjects receiving BB536. • Increased plasma TARC levels were markedly greater in subjects who experienced severe symptoms and were thus excluded early from the intervention.
Results (cont'd)	• Significant differences were found in changes from baseline TARC levels in February and March between the subjects in which treatment was terminated early and the remaining ones. Among the remaining subjects, significant positive correlations were found as regards changed values of TARC compared with baseline in March and April with symptom scores recorded in the pollen season.
Conclusion	"Changed values of blood TARC in the pollen season may offer promising parameters for assessing disease severity and monitoring treatment."

Seasonal Relief

Journal of Medical Microbiology

Odamaki, T., et al. Influence of *Bifidobacterium longum* BB536 intake on fecal microbiota in individuals with Japanese cedar pollinosis during the pollen season. 2007. 56: 1301-1308

Topic	**Does *Bifidobacterium longum* BB536 have an effect on fecal microbiota during pollen season?**
Background	It has been reported that intake of yogurt or powder supplemented with the *B. longum* BB536 probiotic strain alleviated subjective symptoms and affected blood markers of allergy in individuals with Japanese cedar pollinosis (JCPsis) during the pollen seasons of 2004 and 2005, based on randomized double-blind, placebo-controlled trials. Furthermore, the 2004 study found that intestinal bacteria such as the *Bacteroides fragilis* group significantly fluctuated during the pollen season in JCPsis individuals, and intake of *B. longum* BB536 yogurt tended to suppress these fluctuations. The present study investigated fecal microbiota to examine whether any changes occurred during the pollen season and whether any influence was exerted by intake of BB536 powder in the 2005 pollen season, which happened to be a heavy season, to confirm the 2004 findings and to evaluate the relationship of microbiota with symptom development.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind placebo-controlled trial: Subjects received *B. longum* BB536 or a placebo twice daily for 13 weeks during the pollen season. To study changes in fecal microbiota during the pollen season, 14 healthy volunteers (JCP-specific IgE-negative and with no prior history of spring allergic rhinitis) were administered placebo powder during the same intervention stage in an identical manner to JCPsis subjects. Fecal samples were collected before (week 0), during (weeks 4, 8, and 13) and after (week 17) intervention, and out of JCP season (week 28). Fecal microbiota was analyzed using terminal-RFLP (T-RFLP) and real-time PCR methods.
Subjects	44 subjects with a clinical history of JCPsis
Dosage	5 x 10^{10} viable cells *B. longum* BB536/serving
Results	The study reported the following results: • Principal component analysis based on T-RFLP indicated distinct patterns of microbiota between healthy subjects and JCPsis subjects in the placebo group, but an intermediate pattern in the *B. longum* BB536 group at week 13, the last stage of the pollen season.
Results (cont'd)	• The coordinate of principal component 1 at week 13 correlated with composite scores of JCPsis symptoms recorded during the pollen season. • *Faecalibacterium prausnitzii* and the *Bacteroides fragilis* group were identified as the main contributors to microbiotal fluctuations. • Real-time PCR indicated that *B. longum* BB536 intake suppressed increases in the *Bacteroides fragilis* group compared with the placebo.
Conclusion	"These results suggest that fecal microbiota in JCPsis subjects, but not healthy subjects, fluctuates at the end of the pollen season and that BB536 intake plays a role in maintaining normal microbiota."

Seasonal Relief

Applied and Environmental Microbiology
Odamaki T., et al. Distribution of different species of the *Bacteroides fragilis* group in individuals with Japanese cedar pollinosis. 2008. 74(21): 6814-6817

Topic	**Does *Bifidobacterium longum* BB536 have an effect on distribution of *Bacteroides fragilis* in subjects with Japanese cedar pollinosis?**
Background	Japanese cedar pollinosis (JCPsis), an immunoglobulin E (IgE)-mediated type I allergy caused by exposure to Japanese cedar pollen (JCP), represents a public health issue affecting over 16% of the Japanese population. In clinical studies evaluating the effects of a probiotic strain, *B. longum* BB536, on JCPsis, we found that administration of *B. longum* BB536 significantly alleviated some subjective symptoms and affected blood markers in individuals with JCPsis. Furthermore, fluctuations were observed in the *Bacteroides fragilis* group among individuals with JCPsis in the pollen season, with administration of *B. longum* BB536 suppressing these fluctuations. The *Bacteroides fragilis* group has been suggested to be associated with allergic disease in several clinical studies. This study uses samples from a previous clinical study evaluating the effects of *B. longum* BB536 on clinical symptoms of JCPsis to evaluate the association of a species of *Bacteroides fragilis* with allergic disease.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind, placebo-controlled trial: JCPsis subjects were given *B. longum* BB536 powder or placebo powder twice daily for 13 weeks. An additional 14 healthy adults who were JCP specific, IgE negative, and without prior history of spring allergic rhinitis were administered placebo powder during the same intervention period in an identical manner to JCPsis subjects. Participants were instructed to collect fecal specimens, which were analyzed.
Subjects	44 subjects with a clinical history of JCPsis, 14 healthy adults
Dosage	5 x 10^{10} viable cells *B. longum* BB536/serving
Results	The study reported the following results: • Cell numbers of *Bacteroides fragilis* and *Bacteroides intestinalis* were significantly higher in the JCPsis group than in the non-JCPsis group.
Results (cont'd)	• Compared to the pre-pollen season, totals of nine, six, and two species of the *Bacteroides fragilis* group were increased significantly after the pollen season in the placebo, BB536, and healthy groups, respectively. • Comparing cell numbers after pollen season, significant intergroup differences were found for *Bacteroides fragilis* and *Bacteroides intestinalis* between the placebo and healthy groups and significant intergroup differences were found for *Bacteroides fragilis* between the placebo and *B. longum* BB536 groups.
Conclusion	"Our data suggest that prevalence of *Bacteroides fragilis* and *Bacteroides intestinalis* might represent risk factors for JCPsis. In addition, no significant change was observed in cell numbers of *Bacteroides fragilis* or *Bacteroides intestinalis* in the BB536 group, suggesting that intake of *B. longum* BB536 may play a role in stabilizing the microbiota, which might in turn exert suppressive effects on sensitization to pollen and/or symptom development."

JPEN Journal of Parenteral Enteral Nutrition

Akatsu, H. et al. Clinical effects of Probiotic B. longum BB536 on immune function and intestinal microbiota in elderly patients receiving enteral tube feeding. 2013 Sep;37(5):631–40

Topic	**What is the clinical effect of probiotic Bifidobacterium longum BB536 on im mune function and intestinal microbiota in elderly patients receiving enteral tube feeding?**
Background	Immune system function declines with age, therefore the effects of supplementation with the probiotic Bifidobacterium longum BB536 on immune function and intestinal microbiota were investigated in the elderly. The decline of immune function associated with aging in the elderly contributes to poor vaccine efficacy and an increased risk of influenza virus infection and bacterial infections. Studies suggest that probiotics can modulate both innate and adaptive immune function. Effects of a probiotic Bifidobacterium strain, BB536, on the immune responses of elderly patients receiving enteral nutrition were investigated. Intestinal microbiota are the largest source of microbial stimulation in the body and affect both mucosal and systemic immunity. The composition of the intestinal microbiota in elderly people differs from that of younger adults and the number of bifidobacteria decreases with age. Bifidobacteria in intestinal microflora have been suggested to exert beneficial effects, including antagonism against pathogens, and immune modulation. Probiotics are thought to help in preventing infections since usage has been shown to reduce the incidence and duration of infection in children and adults during the winter season and to enhance the effects of influenza vaccination. Probiotic bacteria have been reported to elicit cellular immunity in phagocytes and natural killer (NK) cells and to promote the secretion of immunoglobulin A (IgA) into feces and saliva, suggesting that probiotics can modulate both innate and adaptive immune function. In mice, oral administration of BB536 was effective in protecting against influenza virus infection and pathogenic bacterial infection. In humans, the intake of BB536 alleviated the symptoms of certain allergies, such as Japanese cedar pollinosis.
Study Type	Double-blind human intervention study
Study Design	In a double-blind study, 45 elderly patients fed by enteral tube (mean [SD] age 81.7 [8.7] years) were given BB536 (n = 23) or a placebo powder (n = 22) for 12 weeks and were observed for an additional 4 weeks posttreatment. At week 4, all patients received an influenza vaccination (A/H1N1, A/H3N2, and B). Clinical data were assessed, including body temperature, bowel movements, fecal microbiota, and immunological biomarkers in blood.
Subjects	45 elderly patients
Dosage	BB536 powder (approximately 5×10^{10} colony-forming units/2 g) twice daily for 12 weeks
Results	BB536 intake significantly increased cell numbers of bifidobacteria in fecal flora. There was a tendency toward an increase ($p = .085$ at week 4 and $p = .070$ at week 16) of serum secretory IgA in the BB536 group compared with the placebo group. Natural killer (NK) cell activity decreased significantly in the placebo group during the intervention but not in the BB536 group. Among those subjects with low NK cell activity (< 55%, n = 10 for each group), a significant intergroup difference ($p < .05$) was observed in the changed values from base line of NK cell activity at weeks 8 and 12.
Conclusion	These results show the potential of long-term ingestion of BB536 in increasing the cell number of bifidobacteria in intestinal microbiota and modulating immune function in the elderly.

Healthy Immune Support

Biosci. Biotechnol. Biochem

Namba K., et al. Effect of *Bifidobacterium longum* BB536 administration on influenza infection, influenza vaccine antibody titer, and cell-mediated immunity in the elderly. 2010. 74(5): 939-945

Topic	**Does *Bifidobacterium* BB536 have an effect on elderly rates of infections, including influenza?**
Background	*Bifidobacterium longum* BB536 is a human bifidobacterial strain that has been used in various kinds of commercial products since 1977. Also, BB536 has been investigated for its clinical effects, including improvement of intestinal conditions, prevention of diarrhea, immunopotentiating effects, reduction of cancer risk, and safety by many scientists in the world, so more than 40 scientific literatures have been already published in many journals. Recently, a new effect of *B. longum* BB536 on influenza virus has been reported. This study investigates the effect of *B. longum* BB536 on influenza infection in the elderly.
Study Type	Human clinical intervention trial
Study Design	Randomized double-blind placebo-controlled trial. Subjects were administered 2 grams of *B. longum* BB536 powder (in a sachet) daily for 6 weeks and vaccinated with the influenza vaccine at the 3rd week of *B. longum* BB536 powder administration. After assessment for levels of antibody titers to influenza vaccine at the 5th week, the subjects were divided into two groups (BB536 and placebo groups) at week 6. The administration of *B. longum* BB536 powder continued for 14 more weeks in the BB536 group, and the subsequent incidence of influenza, fever, antibiotics administration, and levels of antibody titers to influenza vaccine was then recorded during 14 weeks.
Subjects	27 elderly volunteers over 65 years of age and living in nursing homes
Dosage	1 x 10^{11} *B. longum* BB536 viable cells/2 grams
Results	*B. longum* BB536 supplementation resulted in the following significant changes compared with placebo group: • No subjects in the BB536 group contracted influenza during the observation period. Five subjects from the placebo group contracted influenza. • Fewer subjects in the BB536 group developed temperatures of 38°C or above than in the placebo (2 versus 8).
Results (cont'd)	• Fewer subjects treated with antibiotics for infections in the BB536 group than in the placebo group (2 versus 8). • The results of the blood analysis showed significantly higher bactericidal activity of neutrophils and higher NK cell activity at the 5th week of *B. longum* BB536 administration, compared with preadministration. These effects persisted for 20 weeks in the BB536 group but diminished in the placebo group by the 20th week.
Conclusion	"These results suggest that *B. longum* BB536 stimulates the body's immune system and activates NK cells and neutrophils, thereby reducing infections among the elderly, such as influenza."