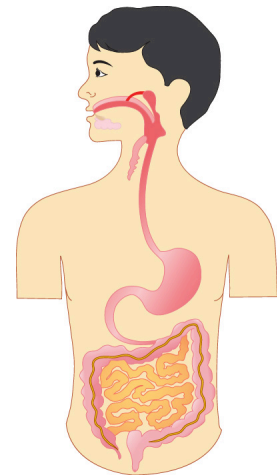


Welcome to a world of probiotics!

What are probiotics?

Probiotics means "for life". Probiotics are live microorganisms that give health benefits when taken in adequate amounts. Common microorganisms used as probiotics are lactic acid bacteria and bifidobacteria.

Probiotics can be taken as food supplement to strengthen the immune system and the gut and oral microflora or to achieve a specific health effect. A condition for the good bacteria to contribute to health is that they survive all the way to the colon. Another important criteria for qualifying as a probiotic is that the health benefits of the bacteria must have been proven in clinical studies (in humans). The studies must have been made with exactly the same strain, or strains, and the same number of bacteria as in the final product.



Why is it important with the right bacteria?

Numerous studies have shown positive effects of different lactic acid bacteria in the gastrointestinal tract. Some general effects are preventing pathogenic bacteria from becoming too many in the gut, strengthening the intestinal mucosa and nourishing the intestinal cells. Lactic acid bacteria also affect the immune system in a positive way, both in the gastrointestinal tract and in the rest of the body.

Probiotics for oral health is a new and highly interesting area. A growing number of clinical studies are showing positive results in diseases such as gingivitis and periodontitis. The general effects in the oral cavity are the same as in the rest of the body.

Lactic acid bacteria are found naturally in various foods such as yogurt, olives and pickled vegetables. In the past lactic acid bacteria were used as a way to preserve various foods, as the low pH prevents other bacteria to destroy the food.

There are different kinds of good bacteria. Most of them belong to the functional group lactic acid bacteria, such as lactobacilli and bifidobacteria. Within these groups there are a large number of different bacterial strains with different properties. The health effects can thus vary depending on the strain.

In the past we got a lot more lactic acid bacteria through our diet, but today our food contains very little of the healthy bacteria, which means that we may need to take lactic acid bacteria as supplements for the stomach, intestines and gums to work well.

Who should take probiotics?

All people, young and old, benefit from taking probiotics to keep pathogenic bacteria away. It is not possible to overdose because the probiotic bacteria are perceived as a natural part of our intestinal and oral flora. In addition, the enormous amount of bacteria that are already established in the gut and oral cavity strive at keeping the system in balance and the number of "newcomers" in check.

In some situations, there is a greater and more urgent need to strengthen the intestinal flora, for example during an antibiotic treatment, when suffering from certain gastrointestinal diseases or when having stomach problems when travelling. As a full 70 per cent of the immune system is located in the intestines, probiotics may have positive effects on the immune system.

Probiotics for children

BioGaia has extensive documentation of its probiotic strain *Lactobacillus reuteri* Protectis (BioGaia ProTectis) in people of all ages, from premature infants to adults. Documentation is important because there are differences between the effects of different bacterial strains. Also, from a security perspective, it is important that the products are thoroughly tested.

There are many studies with BioGaia ProTectis in children that show positive effects, especially in the following areas:

Colic

Infant colic affects up to one in four newborns and is one of the most common reasons for parents to contact health care institutions during the baby's first months.¹ The definition of colic varies, but it is usually described as crying or fussing for at least three hours per day three days in one week or more.

Studies have shown that supplementation with BioGaia ProTectis can reduce colic by 75 per cent and improve the quality of life for the family.²

Regurgitation

Regurgitation is common among infants. It is due to movements in the digestive system and the way food is transported. When the function of nerves and muscles in the gastrointestinal tract is disturbed, the child develops symptoms of regurgitation. The frequency varies with age, with infants up to the first month being more frequently affected. By the first birthday most infants have outgrown their regurgitation. Most infants are happy and healthy even if they frequently spit up or vomit. However, in some cases troublesome regurgitation persist causing unnecessary stress for parents and additional workload for health care professionals.

¹ Rosen LD et al. Complementary Holistic, and Integrative Medicine: Colic. Pediatrics in Review, Vol. Oct 2007;

² Szajewska H et al. *Lactobacillus reuteri* DSM 17938 for the Management of Infantile Colic in Breastfed Infants: a Randomised, Double-Blind, Placebo-Controlled Trial. J Pediatrics 2012; 162:257-262.

Supplementation with BioGaia ProTectis can reduce the daily regurgitation by 80 per cent.³

Constipation

The prevalence of constipation among children varies between 7 and 30 per cent.⁴ In almost all cases no organic cause is found⁵ and the constipation is therefore diagnosed as functional. Approximately 40 per cent of children with functional constipation develop symptoms during their first year. The problems often start when changing from breast milk to formula or with the introduction of food. Other frequent starting periods are at the time of toilet training, between two and four years of age, or when the child starts school.⁶⁻⁷ Constipation often leads to long-term problems for the child. Supplementation with BioGaia ProTectis has been shown to normalise stool frequency in infants.⁸

Gastroenteritis

Acute gastroenteritis (AGE) is an inflammation of the gastrointestinal tract. It affects both the gastric mucosa as well as the small intestine and can cause loose or liquid stools several times during a day. The child may have a fever and vomit and the symptoms may persist for 1-2 weeks.⁹

In countries with good child care, the disease is mild and rarely lead to death, but might still require hospitalization, which is often associated with a lot of suffering and high costs.

Several systematic reviews have found probiotics to be effective in reducing the duration of diarrhoea in children.¹⁰ After two days of supplementation with BioGaia ProTectis 74 per cent lost their watery diarrhoea, compared with 19 per cent in the placebo group.¹¹

Good gut health – for both children and adults

Recent studies show that both children and adults strengthen their resistance against gastroenteritis when taking BioGaia ProTectis. A 12-week study of preschool children aged 4-10 months showed that the children who received this probiotic had

³ Indrio F et al. *Lactobacillus reuteri* accelerates gastric emptying and improves regurgitation in infants. Eur J Clin Invest. 2011;41:417-422.

⁴ Van den Berg MM et al. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterology 2006; 101(10):2401-9

⁵ Loening-Baucke V. Chronic constipation in children, Gastroenterology 1993; 105(5):1557-64

⁶ Hyman PE et al. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler, Gastroenterology 2006; 130:1519-26

⁷ Voskuijl WP et al. Use of Rome II criteria in childhood defecation disorders: applicability in clinical and research practice, J Pediatr 2004; 145:213-17

⁸ Coccorullo P et al. *Lactobacillus reuteri* (DSM 17938) in infants with functional chronic constipation: double-blind, randomized, placebo-controlled study. J Pediatrics 2010;157:598-602

⁹ European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases Evidence-based Guidelines for the Management of Acute Gastroenteritis in Children in Europe. Journal of Pediatric Gastroenterology and Nutrition. 2008;46:S81-S184.

¹⁰ Allen SJ et al. Probiotics for treating infectious diarrhoea. Cochrane Database Syst Rev. 2004;CD003048.

¹¹ Shornikova AV et al. *Lactobacillus reuteri* as a therapeutic agent in acute diarrhoea in young children. J Pediatr Gastroenterol Nutr. 1997;24:399-404.

significantly fewer days with illness due to acute diarrhoea compared with children in a control group.¹² The same applied to adults in another study in a larger Swedish workplace that showed that the number of sick days was reduced by 55 per cent in the group that received BioGaia ProTectis compared with the control group.¹³

Treatment with antibiotics

Since antibiotics do not just kill the bad bacteria but also the good ones, the balance of the microflora is affected both during and after the treatment. This may sometimes cause diarrhoea and other stomach problems, a condition known as antibiotic-associated side-effects (AASE). AASE affects approximately 25 per cent of people treated with antibiotics.¹⁴

There is a risk that people, who get stomach problems caused by their antibiotic treatment, discontinue their treatment prematurely. This can lead to reinfection or antibiotic-resistant bacteria. A Swedish study found that 20 per cent of those treated with penicillin do not complete their treatment, because of problems such as diarrhoea.¹⁵

Diarrhoea and abdominal pain during treatment with antibiotics can lead to more sick days than the initial infection caused. For most people the problems are transient, but there are serious cases that require emergency hospitalization. Then, normally, an overgrowth of the toxin-producing bacteria *Clostridium difficile* (*C. difficile*) has been the cause. In the U.S., the number of adults who were hospitalized because of *C. difficile*-related disease doubled between 2000 and 2005.

Preventive supplementation with probiotics has, according to several studies, been shown to reduce stomach problems caused by antibiotics.¹⁶

Gum disease – a silent epidemic

Three out of four adults will experience gum disease in their lifetime. Gingivitis, or bleeding gums, affects 50-90 per cent of the population worldwide.¹⁷ It is caused by microorganisms in the oral biofilm that adheres to the tooth surfaces. If gingivitis is not treated in time, it may progress to periodontitis, tooth loss. The progression of

¹² Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. *Pediatrics*. 2005 Jan;115(1):5-9.

¹³ Increasing work-place healthiness with the probiotic *Lactobacillus reuteri*: A randomised, double-blind placebo-controlled study. Py Tubelius, Vlaicu Stan and Anders Zachrisson. *Environmental Health: A Global Access Science Source* 2005, 4:25 doi:10.1186/1476-069X-4-25.

¹⁴ Doron SI, Hibberd PL, Gorbach SL. D "Probiotics for prevention of antibiotic-associated diarrhea". *J Clin Gastroenterol*. (2008)

¹⁵ A Swedish study by TEMO on behalf of the Medical School (2006) shows that two out of ten (from 16 years and up) interrupt on-going antibiotic treatment earlier than the prescription because they feel healthy or because of side effects.

¹⁶ Vidlock EJ, Cremonini F. Meta-analysis: Probiotics in antibiotic-associated diarrhoea. *Aliment Pharmacol Ther*. 2012;35:1355-1369.

¹⁷ Albandar JM, Rams TE. Global epidemiology of periodontal diseases. *Periodontol* 2000. 2002;29:7-10.

periodontitis is slow and often takes place over several years without any apparent symptoms. Professional intervention is necessary to treat periodontitis, otherwise the process will continue and eventually lead to loosening and subsequent loss of teeth. 5-30 per cent of adults suffer from periodontitis.¹⁸

Among patients with deep dental pockets (periodontitis) who received BioGaia ProDentis, the number of tooth surfaces in need of surgery was reduced by 47 per cent, compared to patients in the placebo group.¹⁹ BioGaia ProDentis has also been shown to reduce bleeding and inflammation (gingivitis) by 85 per cent compared to placebo.²⁰

What is *Lactobacillus reuteri*?

BioGaia's probiotics contain *Lactobacillus reuteri*. It is one of the most well researched probiotic species, especially in the very young. To date 126 clinical studies using BioGaia's human strains of *Lactobacillus reuteri* have been performed in more than 10 700 individuals of all ages. Results are published in 97 articles in scientific journals (May 2014).

Studies in humans have been performed in the following areas:

- Infant colic and digestive health in children
- Antibiotic-associated side-effects
- Acute diarrhoea (gastroenteritis)
- Gingivitis (inflammation of the gums)
- Periodontal disease (periodontitis)
- *Helicobacter pylori* infection.

Origin of BioGaia's strains of *Lactobacillus reuteri*

What distinguishes *Lactobacillus reuteri* from other probiotic bacteria is the fact that it is a natural coloniser in humans from birth. It is also one of very few species of *Lactobacillus* whose natural habitat is the oral cavity and gastrointestinal tract of humans. *Lactobacillus reuteri* is therefore especially well adapted to thrive in this kind of environment and establishes a symbiotic relationship with the body. It also produces antimicrobial substances that inhibit the growth of several pathogenic microorganisms.

Studies have shown that probiotics of human origin tend to survive, colonise and be more efficient in humans than strains from other mammals or plants.²¹ The strain of *Lactobacillus reuteri* used in most of BioGaia's products with focus on

¹⁸ Oliver RC, Brown LJ, Loe H. Periodontal diseases in the United States population. J Periodontol. 1998. Feb; 69 (2): 269-78.

¹⁹ Teughels W, Durukan A, Ozcelik O, Pauwels M, Quirynen M, Haytac MC. (2013) Clinical and microbiological effects of *Lactobacillus reuteri* probiotics in the treatment of chronic periodontitis: a randomized placebo-controlled study. J Clin Periodontol. 40:1025–1035.

²⁰ Twetman S, Derawi B, Keller M, Ekstrand K, Yucel-Lindberg T, Stecksén-Blicks C. (2009) Short-term effect of chewing gums containing probiotic *Lactobacillus reuteri* on the levels of inflammatory mediators in gingival crevicular fluid. Acta Odontol Scand. 67:19-24.

gastrointestinal health was originally isolated from breast milk of a Peruvian mother. The bacteria was identified and characterized at the Agrarian University in Lima, Peru and deposited in a bioresource centre, from where the master cell stock of *Lactobacillus reuteri* used for production, is still retrieved. Accordingly, one of the strains used in BioGaia's oral health products is a natural habitant of the oral cavity. This strain was originally isolated from a Japanese woman with an exceptional oral status.

Lactobacillus reuteri:

- Strains of human origin (breast milk and saliva)
- Uniquely adapted to colonise in the gastrointestinal tract in humans
- Produces substances that inhibit pathogenic microorganisms
- Well-documented health benefits
- Fights harmful bacteria without impairing the balance of the microflora.

In BioGaia's bioresource centre there is a large number of strains of *Lactobacillus reuteri*. These can be divided into two main groups:

- Strains with immunostimulatory properties, such as *Lactobacillus reuteri* DSM 17938 (*Lactobacillus reuteri* Protectis), for digestive health and immune system related to the gastrointestinal tract.
- Strains with anti-inflammatory properties: for example, *Lactobacillus reuteri* ATCC PTA 5289, which in combination with *Lactobacillus reuteri* DSM 17938 is called *Lactobacillus reuteri* Prodentis and used for oral health, and *Lactobacillus reuteri* ATCC PTA 6475, which in combination with *Lactobacillus reuteri* DSM 17938 is called *Lactobacillus reuteri* Gastrus (for control of *Helicobacter pylori* infection).

BioGaia ProTectis

BioGaia's ProTectis is a well-documented product. More than 96 studies in humans have been performed with the probiotic strain *Lactobacillus reuteri* Protectis, which is the strain used in all BioGaia ProTectis products, and there is on-going research all over the world. It is the only probiotic that has shown to be effective in infants with colic.

Main products:

- BioGaia ProTectis baby drops
- BioGaia ProTectis baby drops with vitamin D₃
- BioGaia ProTectis tablets with lemon and strawberry flavour
- BioGaia ProTectis tablets with vitamin D₃ and orange flavour
- BioGaia ProTectis ORS (Oral Rehydration Solution) with neutral and orange flavour

Please visit www.biogaia.com/products to find out which products are available in your country.

Lactobacillus reuteri Protectis is the only probiotic shown in studies to colonize the entire gastrointestinal tract, even in the stomach and small intestine.

One tablet or five drops of a BioGaia ProTectis product contains 100 million live bacteria, which is the dose shown in scientific studies to be effective for this strain. BioGaia guarantees that all products contain live bacteria and can be stored at room temperature (max. 25C).

BioGaia ProDentis

BioGaia ProDentis is the first and only probiotic specifically formulated to promote healthy gums. It is a combination of two complementary strains of *Lactobacillus reuteri* that were originally isolated from human breast milk and saliva, specifically selected for their documented anti-pathogenic and anti-inflammatory effects in the oral cavity. BioGaia ProDentis has a well-proven safety and efficacy through more than 20 clinical trials.

Products:

- BioGaia ProDentis lozenges
- BioGaia ProDentis chewing gum
- BioGaia ProDentis drops (for in-clinic use)

All products have a refreshing mint flavour.

Please visit www.biogaia.com/products to find out which products are available in your country.

One lozenge, chewing gum or five drops of a BioGaia ProDentis product contains 200 million live bacteria, which is the dose shown in scientific studies to be effective for this strain combination. BioGaia guarantees that all products contain live bacteria. BioGaia ProDentis lozenges and chewing gum can be stored at room temperature (max. 25C). BioGaia ProDentis drops needs to be refrigerated.



About BioGaia

BioGaia is an innovative Swedish health care company with more than 20 years experience of developing, market and sell probiotic products with documented health benefits. The products are primarily based on different strains of the lactic acid bacterium *Lactobacillus reuteri*, whereof the most important ones are *Lactobacillus reuteri* Protectis for gastrointestinal health and *Lactobacillus reuteri* Prodentis for oral health.

BioGaia has a global network of leading, independent researchers and specialists, in-house experts and commercial partners active in around 80 markets worldwide.

Read more about BioGaia at www.biogaia.com/about-biogaia.