everidis
HEALTH SCIENCES

L. reuteri Protectis: A clinically proven probiotic

Scientific Evidence in Infants and Children

L. reuteri Protectis

The microbiota of the infant and child

The newborn infant establishes its intestinal microbiota from the time of delivery and during the next two years. Beneficial bacteria like lactobacilli and bifidobacteria are normally among the first to colonize.[1] Caesarean delivery delays the establishment of favorable bacteria compared to vaginally born infants, which may have significant health consequences.[2]

Breastfeeding supports the foundation of a healthy microbiota as it supplies the bacteria with human milk oligosaccharides in large amounts, which acts as natural prebiotics. A diverse microbiota helps the infant to optimise the development of the digestive tract anatomy and functions.[3]

The microbiota contributes to:

- Enforced gut barrier
- Improved digestion
- Improved motility
- Maturation of gut immune functions

Probiotics and the importance of strain specificity

Probiotics, defined as live strains of bacteria with documented health effects[4], have become a well-recognized option to support the composition of a beneficial microbiota in infants and children. The bacteria species most commonly used as probiotics belong to the genera *Lactobacillus* and *Bifidobacterium*. Different strains of a specific species have different probiotic properties and effects. Hence the benefits of one specific strain cannot be extrapolated to the effects of other probiotics.

Lactobacillus reuteri Protectis is special

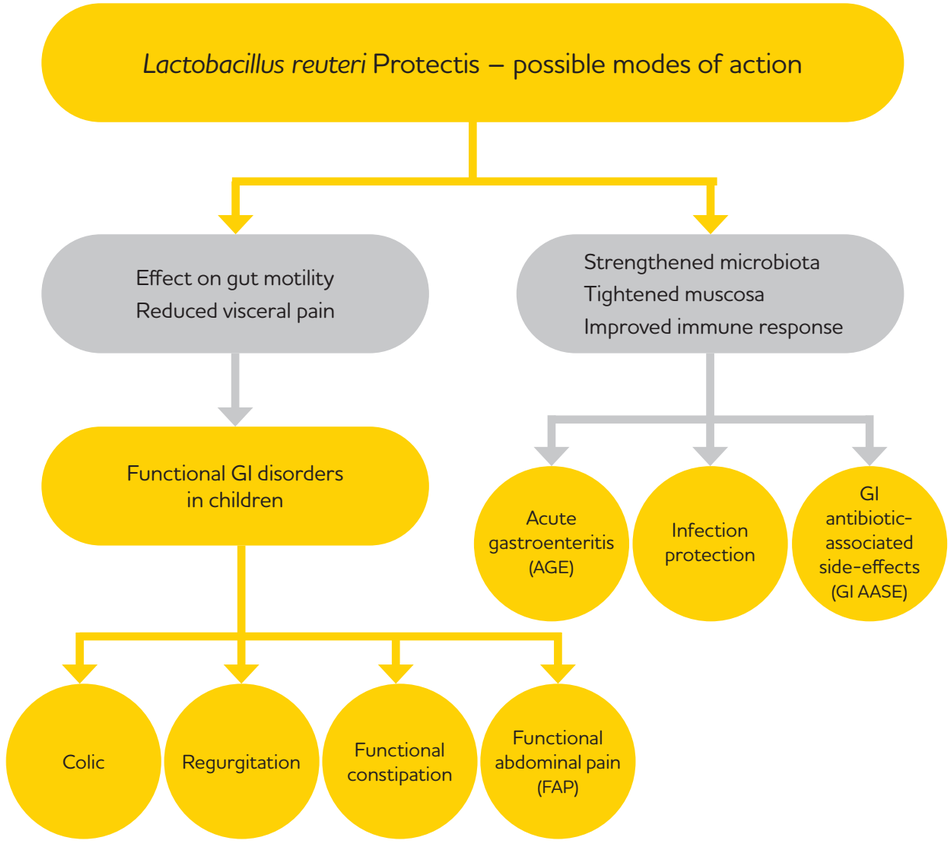
Lactobacillus reuteri Protectis is derived from human mother's milk.[5-7] It is indigenous to the human digestive tract and one of few probiotics that have co-evolved with humans since beginning of time.[8,9]

L. reuteri Protectis is a natural colonizer and has been shown to colonize both the stomach and the small intestine.[10] The probiotic exerts its effects, or modes of action, in many different ways. It has been proven that *L. reuteri* Protectis influences gut motility and may also reduce visceral pain by the release of neuromodulating molecules. Moreover it influences the intestinal microbiota by releasing reuterin, lactic acid and acetic acid, which help promote the growth of other good bacteria, and inhibit pathogens. *L. reuteri* Protectis may also strengthen mucosal integrity by tightening the epithelial barrier and improve immune response.[11-19]

Scientific evidence

Numerous trials have shown the safety and significant effects of *L. reuteri* Protectis on functional gastrointestinal disorders and protection of infections in infants and children, including preterm neonates in intensive care.

- 130 completed studies in 12,300 subjects, whereof:
- 59 studies in infants and children up to 3 years old



Functional gastrointestinal disorders

- Reduced crying time in colicky infants[20-24]
- Improved gut motility and less regurgitation[25-27]
- Reduced constipation[27-29]
- Reduced functional abdominal pain[30-32]

Acute gastroenteritis

- Shortened duration of watery diarrhea and vomiting[33-40]

Infection protection

- Reduced incidence of diarrhea[41-43]
- Improved growth in children with low nutritional status[44]
- Reduced incidence of antibiotic-associated side-effects[45]

Infantile colic

Infantile colic is a common condition, though poorly understood and often frustrating for parents and caregivers. According to the Rome III diagnostic criteria for functional gastrointestinal disorders, a child has infantile colic if it has unexplained episodes of paroxysmal fussing or crying for at least three hours a day, for three days a week or more, for at least one week, and no failure to thrive.[46] This type of crying typically peaks at approximately six weeks of life and ends around the fourth month.[25]

As many as 26% of infants are diagnosed with colic,[47] making the condition one of the most frequent reasons for visits to family practitioners.

Multifactorial causes and may affect gastrointestinal health later in life

The etiology of infantile colic is multifactorial and not fully understood. Gut dysmotility and visceral hypersensitivity are regarded as main factors behind this condition.[48] In the last decade, the role of the gastrointestinal microbiota has also come into focus. Lower amounts of intestinal lactobacilli as well as increased concentrations of coliform bacteria have been observed in colicky infants compared to non-colicky ones.[49-50]

The immature or dysfunctional intestinal microbiota may lead to a low-grade inflammation and abnormal intestinal metabolism, resulting in colic symptoms.[48] It has been shown that colic in infancy is linked to an increased susceptibility to recurrent abdominal pain, allergic diseases, and psychological disorders later in childhood.[51]

L. reuteri Protectis - the only probiotic with scientific evidence in infantile colic

The possibilities to treat colic have been limited. Simethicone has been widely used in many countries but clinical research has shown that the effect is only equal to placebo.[49]

To date five independent studies with *L. reuteri* Protectis have shown a reduction in crying time in colicky infants.[20-24] The effect of *L. reuteri* Protectis in infantile colic has also been proven in two preventive studies recently published.[27,52] Moreover, eight meta-analyses have been conducted, all with the same conclusion that *L. reuteri* Protectis is the only probiotic with a proven efficacy in infantile colic, especially in breastfed and mixed fed infants.[53-60]

L. reuteri Protectis is the only probiotic with expert recommendations for both treatment and prevention of infantile colic.[61]

Effect of *L. reuteri* Protectis in infantile colic confirmed by five studies

Study	Reduction in crying time by day 7	Reduction in crying time by day 21	Responders by day 7	Responders by day 21
Mi 2015	YES	YES	na	YES**
Chau 2014	YES	YES	ns	YES
Szajewska 2013	YES	YES	YES	YES
Savino 2010	ns	YES	YES	YES
Savino 2007*	YES	YES	na	YES**

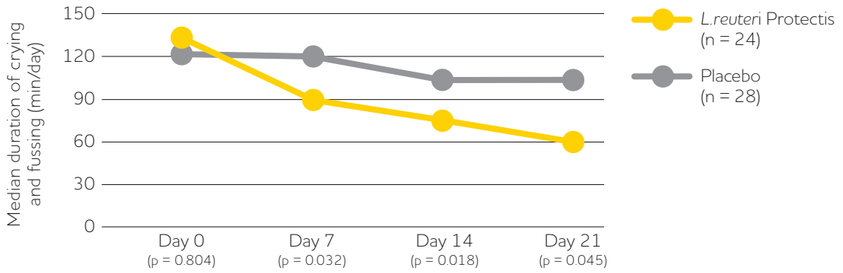
References: *Mi GL et al.* Antonie van Leeuwenhoek 2015;107:1547-1553. *Chau K et al.* J Pediatr. 2014;166:74-78. *Szajewska H et al.* J. Pediatr. 2013;162:257-262. *Savino F et al.* Pediatrics 2010;126:e526-e533. *Savino F et al.* Pediatrics 2007;119:124-130.

YES: Significant compared to placebo
ns: Non-significant
na: Not analysed
* Significant compared to simethicone
** On day 28
Responder: infant with ≥ 50% reduction in average duration of crying and fussing compared to baseline

Less crying and fussing

Compared to placebo, *L. reuteri* Protectis:

- Reduced crying and fussing time with 40 minutes from day 7 and onward
- 71% treatment responders* with *L. reuteri* Protectis after 21 days



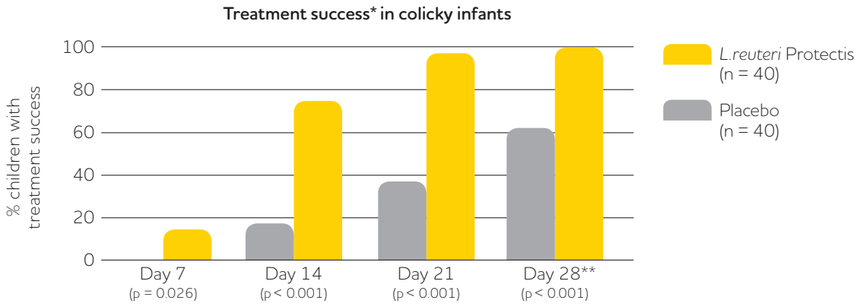
*Infants with 50% or more reduction in daily average crying and fussing time from baseline

Chau K et al. J Pediatr. 2014;166:74-78.

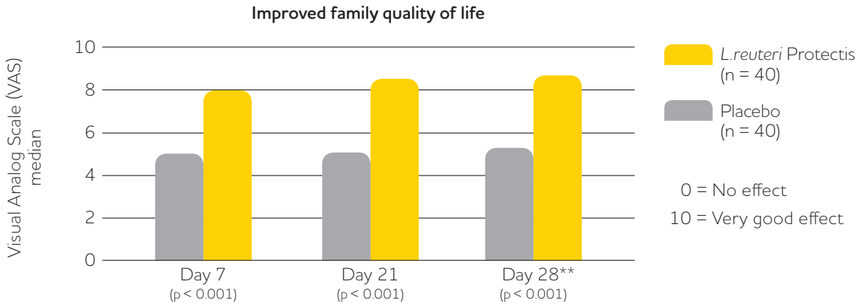
Reduced excessive crying and improved family quality of life

L. reuteri Protectis compared to placebo:

- Effect one week after initiated supplementation
- Reduced daily crying by one hour at day 28
- Improved family quality of life



* ≥ 50% reduction in the daily average crying time
** Follow-up one week after termination of intervention

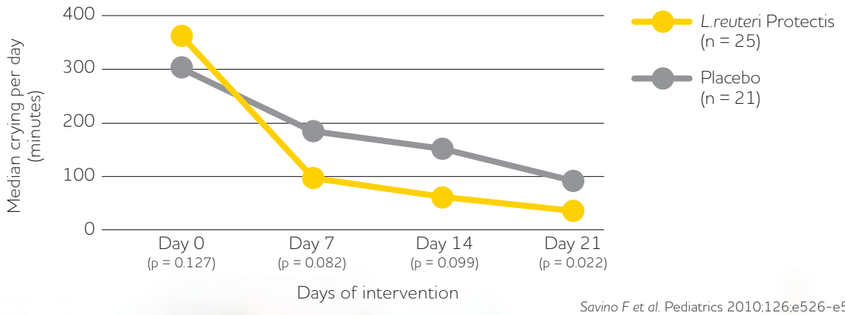


** Follow-up one week after termination of intervention

Szajewska H et al. J. Pediatr. 2013;162:257-262.

Reduced crying time by more than 4.5 hours after one week

- Effect one week after supplementation
- On average 1.5 hours reduction in daily crying compared to placebo

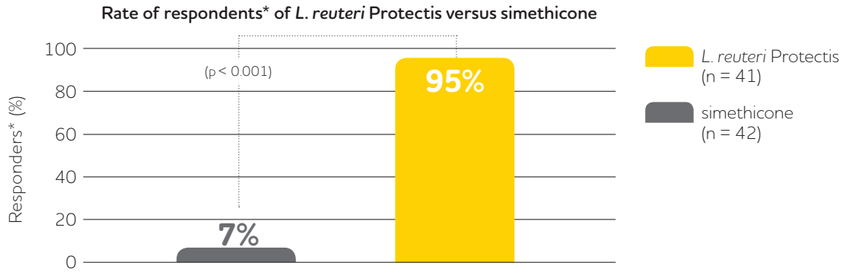


Savino F et al. Pediatrics 2010;126:e526-e533.

95% successfull treatment response

Compared to simethicone, *L.reuteri* Protectis:

- Was superior in reducing daily crying time
- Decreased crying time more than twice as much

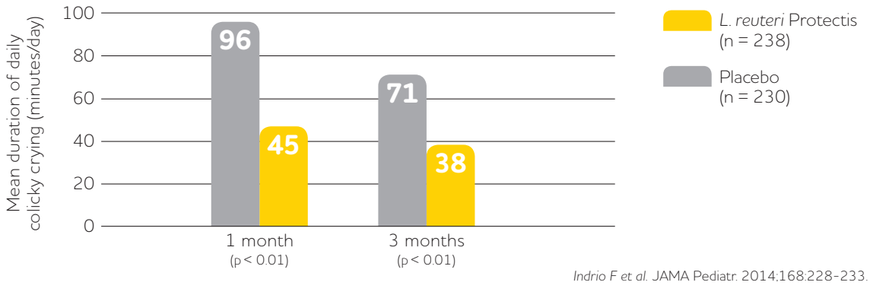


*Infants with 50% or more reduction in daily average crying from baseline

Savino F et al. J. Pediatrics 2007;119:124-130.

Preventive use reduced crying by more than 50%

- After one month, daily inconsolable crying was reduced to 45 minutes in the *L. reuteri* Protectis group compared to more than 1.5 h in the placebo group.
- The difference between the groups persisted to the end of the 3-month intervention.



Indrio F et al. JAMA Pediatr. 2014;168:228-233.

Regurgitation

Regurgitation is defined as the passage of refluxed gastric content into the pharynx or mouth, sometimes with expulsion out of the mouth.[62] An otherwise healthy infant between three weeks and 12 months of age has regurgitation if it meets both criteria:[46]

- Two or more regurgitations times per day for three weeks or more
- No retching, hematemesis, failure to thrive, feeding or swallowing difficulties or abnormal posturing

Uncomplicated regurgitation in otherwise healthy infants is common.[63] The frequency varies with age, with infants up to the first month being more frequently affected.[27] Most infants are happy and healthy even if they frequently spit up or vomit, and by their first birthday most infants have outgrown their regurgitation.

However, from parents perspective regurgitation is often seen as problematic and a health problem which is also reflected by the high frequency of pediatric consultations.[64] The parents worry about their infant getting sufficient food to be able to grow.[65] This may cause unnecessary stress for parents and additional workload for health care professionals.

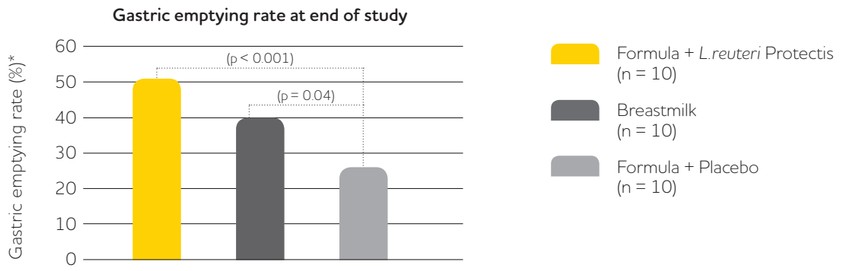
L. reuteri Protectis in the management of regurgitation

L. reuteri Protectis has in both term and preterm infants been shown to significantly increase gastric emptying rate and thereby decrease the number of regurgitations.[25] A recent study on prevention of functional gastrointestinal disorders (FGIDs) in healthy newborns, verified the effect on improved gastric motility and reduced frequency of regurgitation.[27] This study also showed that preventive use of *L. reuteri* Protectis reduced both public and private costs for FGIDs.

Improved gastric motility in healthy preterm infants

Compared to placebo, *L. reuteri* Protectis:

- Increased gastric emptying rate
- Reduced the number of regurgitation to half as much



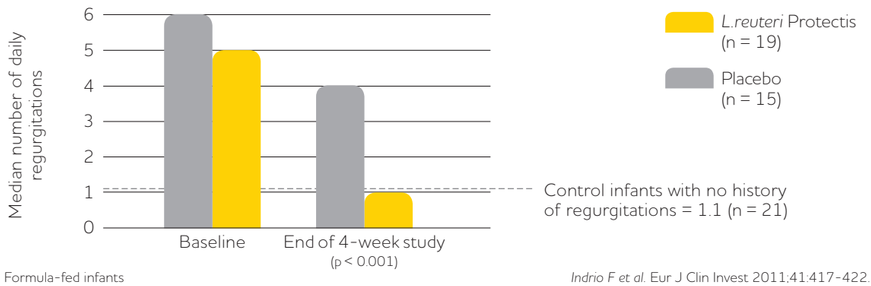
* In each patient the gastric emptying rate was expressed as percent reduction in antral cross sectional area from time 0 to 120 minutes after the meal ingestion.

Indrio F et al. J. Pediatr. 2008;152:801-806.

80% reduction in daily regurgitations*

Compared to placebo *L. reuteri* Protectis:

- Increased gastric emptying rate
- Reduced the number of regurgitations

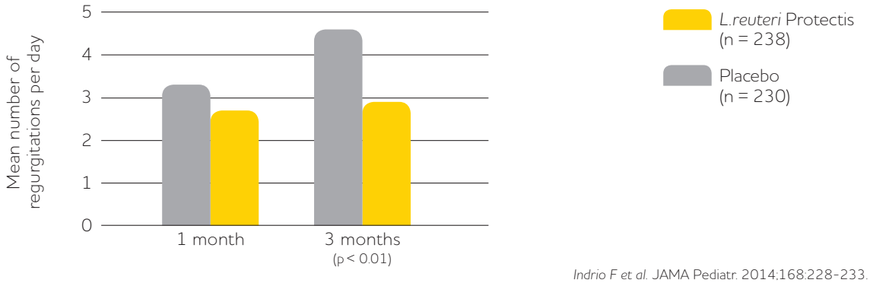


* Formula-fed infants

Indrio F et al. Eur J Clin Invest 2011;41:417-422.

Preventive use reduced the number of regurgitations by 37%

- *L. reuteri* improved gut motility, leading to significant reduction in daily regurgitations compared to placebo



Indrio F et al. JAMA Pediatr. 2014;168:228-233.

Constipation

Constipation is a common and distressing problem all over the world with a prevalence among children up to 30%.[66] In almost no cases can an organic cause be found[67] and the constipation is therefore diagnosed as functional. Today researchers believe functional constipation in children may be caused by gut dysmotility and a disturbed microbiota, rather than bacterial overgrowth.[28]

A child up to four years of age is diagnosed with constipation if it meets at least two of the following criteria for one month:[46]

- Two or fewer defecations per week
- At least one episode per week of incontinence after the acquisition of toileting skills
- History of excessive stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large-diameter stools that may obstruct the toilet

Approximately 40% 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 solid food. Other frequent onset periods are during toilet training, between two and four years of age, or when the child starts school.[46, 68]

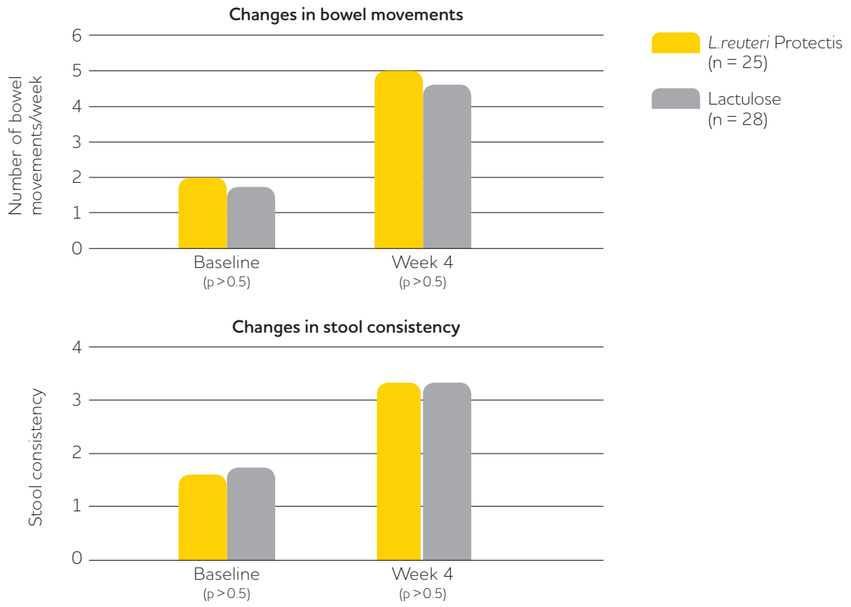
Constipation is often a long-term problem for the child. Only 60% of constipated children are successfully treated with laxatives and many still have symptoms as teenagers and adults.[69]

Proven effects with *L. reuteri* Protectis

L. reuteri Protectis is the only probiotic that has been shown to significantly increase the frequency of bowel movements in infants with functional constipation.[28,71] Moreover, in a recent study it was shown that *L. reuteri* Protectis, besides being as effective as lactulose, reduced abdominal pain and flatulence to a significantly greater extent. In a study on prevention of gastrointestinal functional disorders in healthy newborns, it was verified that *L. reuteri* Protectis improved gut motility, leading to significantly more daily evacuations.[27]

L. reuteri Protectis as effective as lactulose

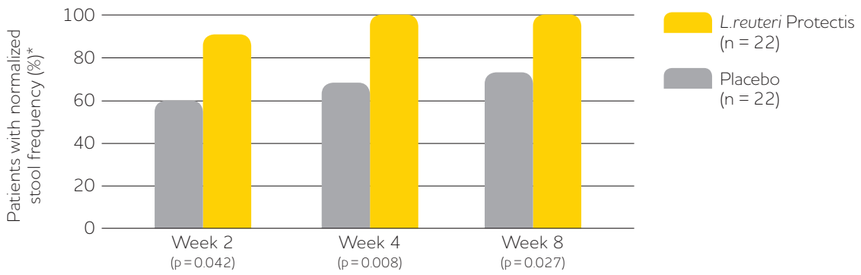
- *L. reuteri* Protectis was equivalent to lactulose in effects on functional constipation
- Abdominal pain and flatulence were reduced by *L. reuteri* Protectis vs. lactulose
- Quality of life increased in both treatment groups to the level of the healthy controls



Olgaç MAB et al. Çocuk Sağlığı ve Hastalıkları Dergisi [Journal of Child Health and Disease] 2013;56: 1-7.

100% normalization of stool frequency

- Significant improvement of bowel movements with *L. reuteri* Protectis
- 91% of infants normalized their stool frequency within 2 weeks and 100% within 4 weeks



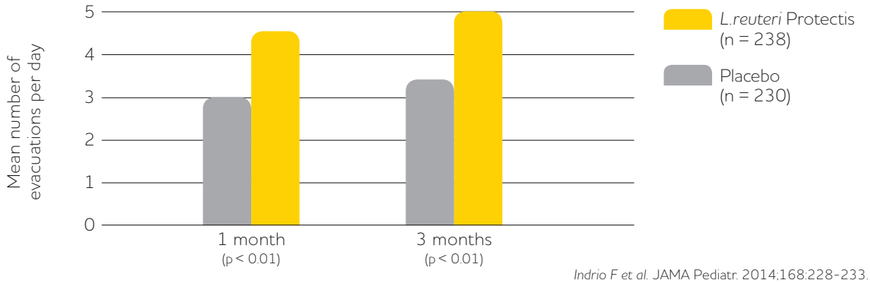
*Normalized stool frequency was defined as ≥3 defecation per week

Coccorullo P et al. J Pediatrics 2010;157:598-602.

Preventive use increased the daily number of evacuations by 43%

Placebo controlled, preventive use of *L.reuteri* Protectis:

- Reduced the onset of constipation in healthy newborns
- Improved gut motility and number of bowel movements



Indrio F et al. JAMA Pediatr. 2014;168:228-233.

Functional abdominal pain

Functional abdominal pain (FAP) disorders affects 10 – 20% of all school-aged children, and is one of the most commonly diagnosed medical problems in pediatrics.[72,30]

In the Rome IV diagnostic guidelines the term functional abdominal pain – not otherwise specified (FAP-NOS) substitutes for the Rome III terms FAP and FAP Syndrome.[73] According to the Rome IV criteria a child suffers from FAP-NOS if the following criteria are fulfilled at least 4 times per month for the last 2 months prior to diagnosis:[73]

- Episodic or continuous abdominal pain
- Insufficient criteria for other functional GI disorders
- Not explained by another medical condition

A complex problem, difficult to treat

Functional abdominal pain may have a great impact on the child's life, interfering with family and social life, participation at school, sports and other activities.

A child with functional abdominal pain often:

- has significantly lower quality of life[74]
- stays home from school – abdominal pain is the second cause of school absenteeism[75]
- seeks medical advice frequently
- goes through worrying investigations
- has long term vulnerability to anxiety disorders[74]
- has persisting pain longer than 5 years despite frequent medical attention[76]

Current treatment options for FAP-NOS are quite few and have limited clinical data in children. In recent years, the interest in the role of probiotics in FAP-NOS has grown, both in terms of research on the clinical efficacy and the underlying mechanisms linked to the disorder.

L. reuteri Protectis – the only probiotic with clinical efficacy in functional abdominal pain

Three double blind, randomized, controlled treatment trials have demonstrated that *L. reuteri* Protectis reduced both the frequency and severity of abdominal pain in children with FAP-NOS compared to placebo.[30-32] The children with *L. reuteri* Protectis had also significantly more days without pain.[32]

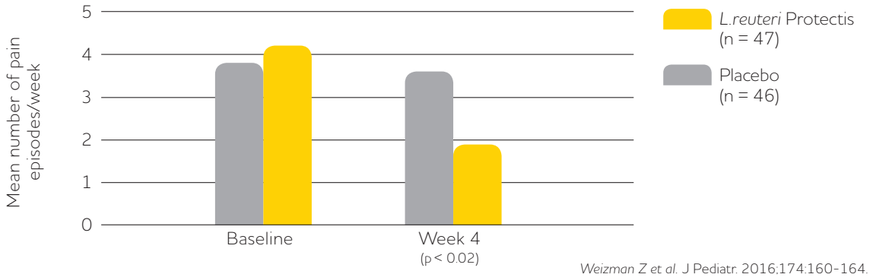
Moreover, a systematic review shows that *L. reuteri* Protectis is the only probiotic with proven efficacy in functional abdominal pain (FAP).[78]

Study	Probiotic strain	Pain relief (FAP)	Supplementation (n)	Age (years)
Weizman 2014/2016	*L. reuteri* Protectis	YES	4 weeks (93)	6 – 15
Romano 2014	*L. reuteri* Protectis	YES	4 weeks (52)	6 – 16
Francavilla 2010	*L. rhamnosus* GG	NO	8 weeks (136)	5 – 14
Gawronska 2007	*L. rhamnosus* GG	NO	4 weeks (104)	6 – 16

FAP = Functional Abdominal Pain

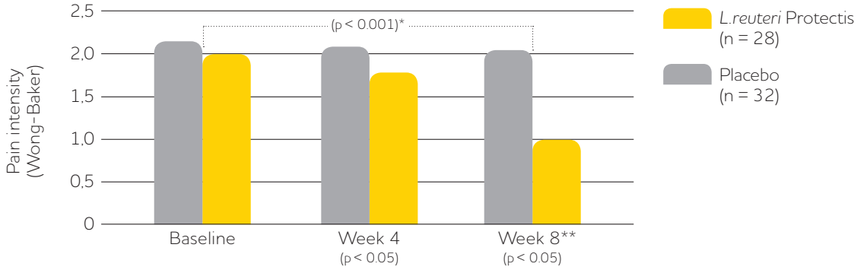
Table modified from *Weizman Z et al.* JPGN 2014;58 (Suppl. 1):430, abstract PO-N-0248.

Half the number of pain episodes



Weizman Z et al. J Pediatr. 2016;174:160-164.

50% less pain intensity

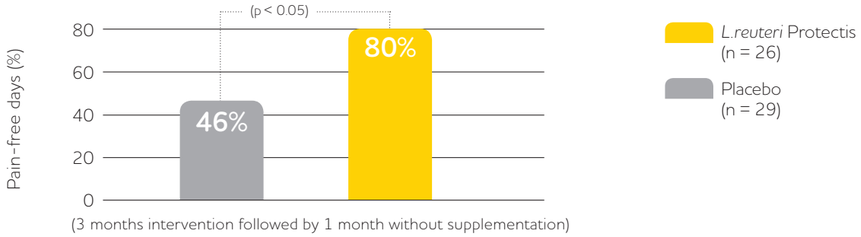


* Significantly reduced pain intensity from week 0 to week 8 in the *L reuteri* Protectis group.

** Follow-up 4 weeks after termination of intervention.

Romano C et al. Paediatr Child Health. 2014;50(10):E68-E71.

More pain-free days with *L. reuteri* Protectis



(3 months intervention followed by 1 month without supplementation)

Jadresin O et al. J Pediatr Gastroenterol Nutr., online 30 Nov 2016, doi: 10.1097/MPG.0000000000001478.

Acute gastroenteritis

Acute gastroenteritis (AGE) manifests as an inflammation of the gastrointestinal tract, affecting the stomach lining as well as that of the small intestine. General symptoms are loose or liquid stools and/or an increase in the frequency of evacuations (≥3 in 24 hours), with or without fever or vomiting. Typically, the diarrhea lasts less than seven days and not longer than 14 days.[79]

AGE is a worldwide problem

AGE is a major cause of morbidity and mortality in children around the world. The vast majority of deaths occur in developing countries, but even in the developed world AGE is associated with a substantial number of hospitalizations and high costs. The causes of AGE include a range of viruses, bacteria and parasites. Viruses remain the most common cause by far, and rotavirus is the most important viral pathogen worldwide. By the age of five all children, regardless of homeland, have had a rotavirus infection.[80,81]

The main clinical feature of AGE is dehydration, which generally reflects disease severity. Infants are especially susceptible to dehydration. In addition, they depend on others to provide them with enough water and nutrition.

Rehydration solutions

Oral rehydration solution (ORS) is recommended worldwide as first-line therapy for children with mild to moderate gastroenteritis. This is based on the results of dozens of randomized, controlled trials and several large meta-analyses.[79,82-85]

Early administration of ORS can reduce complications and the number of clinic visits and hospitalizations. This can result in less suffering for the child and family, reduced risk of spreading and catching disease, and reduced economic burden. Based on studies showing a reduction of the intensity and duration of diarrhea, it is now also recommended that zinc should be given to all children with AGE.[85]

L. reuteri Protectis in the treatment of AGE

Several studies with *L. reuteri* Protectis as adjunct to ORS treatment, have shown significantly less vomiting and reduced duration and severity of acute diarrhea.[86,33-38] The earlier the onset of probiotic treatment, the faster the recovery.[87,88]

Moreover, the beneficial effects of *L. reuteri* Protectis in AGE is stated in a recent meta-analysis, and also indicated from ESPGHAN* as one of few probiotics that may have a positive treatment effect in AGE.[39,40]

Faster recovery with *L. reuteri* Protectis

Study	Significant reduction of			
	Duration of diarrhea	Diarrhea at 48h of treatment	Vomiting at 48h of treatment	Duration of hospital stay
Dinleyici 2015	YES	YES	na	na
Dinleyici 2014	YES	YES	na	YES
Francavilla 2012	YES	YES	ns	ns
Eom 2005	ns*	YES	YES	YES
Shornikova 1997a	ns*	YES	YES	na
Shornikova 1997b	YES	YES	na	ns

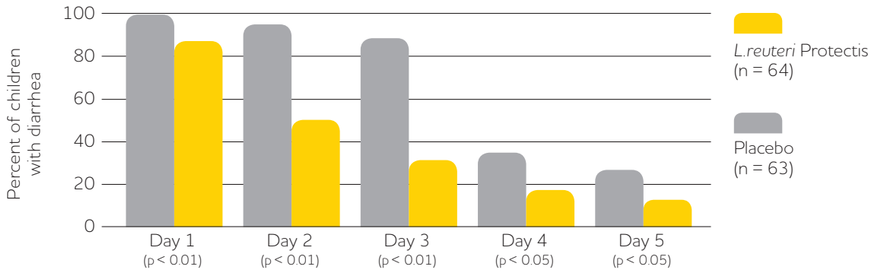
References: *Dinleyici EC et al.*, J Pediatr 2015;91:392-396. *Dinleyici EC et al.*, Acta Paediatrica 2014;103:e300-e305. *Francavilla R et al.* Aliment Pharmcol Ther. 2012;36:363-369. *Eom et al.* Korean J Pediatr 2005;48: 986-989. *Shornikova AV et al.* J Pediatr Gastroenterol Nutr. 1997;24:399-404. *Shornikova AV et al.* Pediatr Infect Dis J. 1997;16:1103-1107.

YES: Significant compared to placebo
ns: non-significant
na: not analysed
* p = 0.07

* ESPGHAN: The European Society for Paediatric Gastroenterology, Hepatology and Nutrition

Effect of *L. reuteri* Protectis after 24 hours

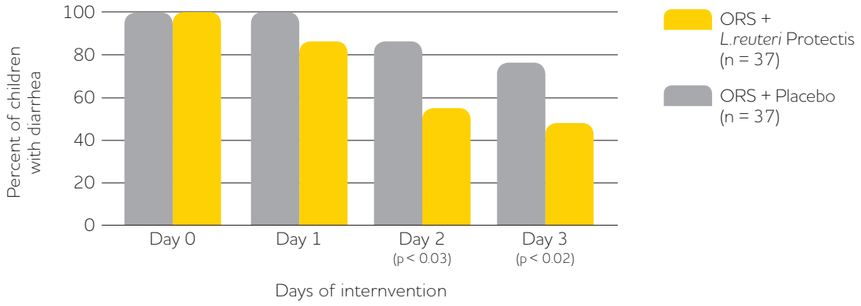
- Duration of diarrhea was reduced by 33 hours compared to the control group
- The advantageous effect was seen already 24 hours after start of intervention
- Mean length of hospital stay was shortened by 1.2 days compared to the control group
- Prolonged diarrhea after 7 days was only observed in the control group



Dinleyici EC et al. Acta Paediatrica 2014;103:e300-e305

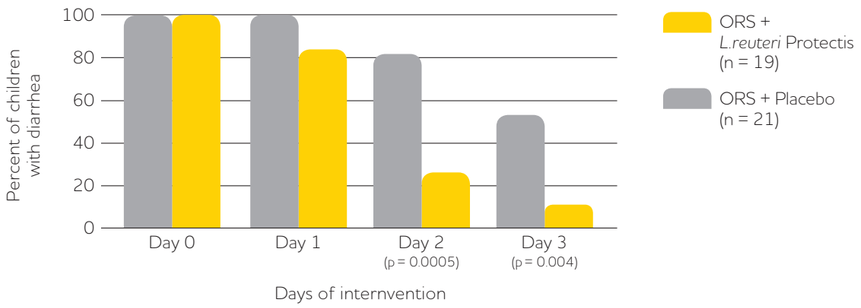
Faster recovery from watery diarrhea

- *L. reuteri* Protectis reduced watery diarrhea in 45% of children on the second day of treatment



Francavilla R et al. Aliment Pharmcol Ther. 2012;36:363-369.

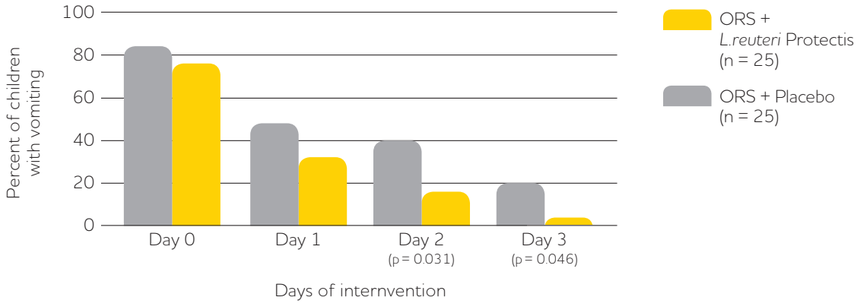
74% free from watery diarrhea on day two



Shornikova AV et al. J Pediatr Gastroenterol Nutr. 1997;24:399-404.

84% free from vomiting on day two

- Reduced vomiting and diarrhea
- Effects seen already on the second day of treatment



Eom et al. Korean J Pediatr 2005;48: 986-989.

Infection protection

Diarrhea and respiratory tract infections are major causes of illness and death among young children worldwide.[89,90] Young children are more prone to infections due to an undeveloped immune system. It is particularly challenged when children gather in groups, for example at day care and school.[43]

Today the role of the intestinal microbiota in health and disease is well known. 80% of the immune system can be directly linked to the gastrointestinal wall which makes a healthy intestinal mucosa and a balanced microbiota essential for a well functioning immune system.

Breastfed infants have been shown to develop a more diverse microbiota with more beneficial bacteria and less pathogenic ones compared to formula-fed infants. As breast-milk is a source of lactobacilli, this mechanism has been considered one of the explanations to why breastfed infants demonstrate a decreased rate of infectious diarrhea.[41]

L. reuteri Protectis - an effective protector

Moreover, there are strong indications that probiotics can influence gastrointestinal health in children.[4] Three trials with *Lactobacillus reuteri* Protectis have shown positive effects on prevention of disease in children.[41-43]

In addition, it has been shown that preventive use of *L. reuteri* Protectis reduced the costs linked to infections for both family and community.[42]

Less infections and fewer sick days with *L. reuteri* Protectis

Study	Significantly fewer days				
	With diarrhea	With antibiotic use	With fever	Absent from day care	With respiratory tract infection
Gutierrez 2014 (n = 336)	YES	YES	YES	YES	YES
Weizman 2005 (n = 128)	YES	YES	YES	YES	ns
Agustina 2012 (n = 250)	YES	YES	na	na	ns

References: *Gutiérrez-Castrellón P et al.* Pediatrics 2014;133:4 e904-e909. *Weizman Z et al.* Pediatrics. 2005;115:5-9. *Agustina R et al.* Pediatrics 2012;129: e1155-e1164.

YES: Significant compared to placebo
ns: non-significant
na: not analysed

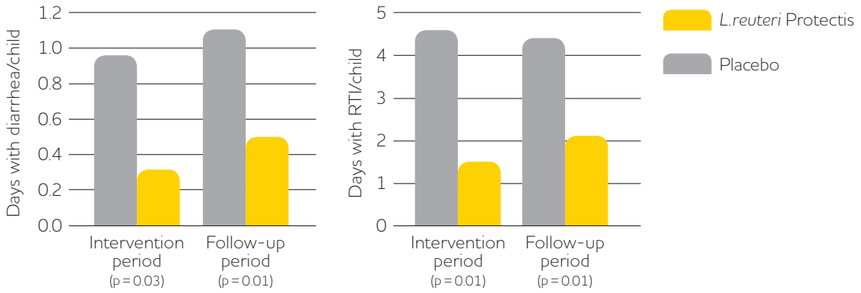
Less infections with preventive use

Preventive use of *L. reuteri* Protectis:

- Reduced the number of days with diarrhea and respiratory tract infection (RTI) by 67%
- Reduced the need of antibiotics
- Reduced direct and indirect costs for both family and community

Days with diarrhea and respiratory tract infection

Intervention period = 0 – 12 weeks; Follow-up period = 12 – 24 weeks

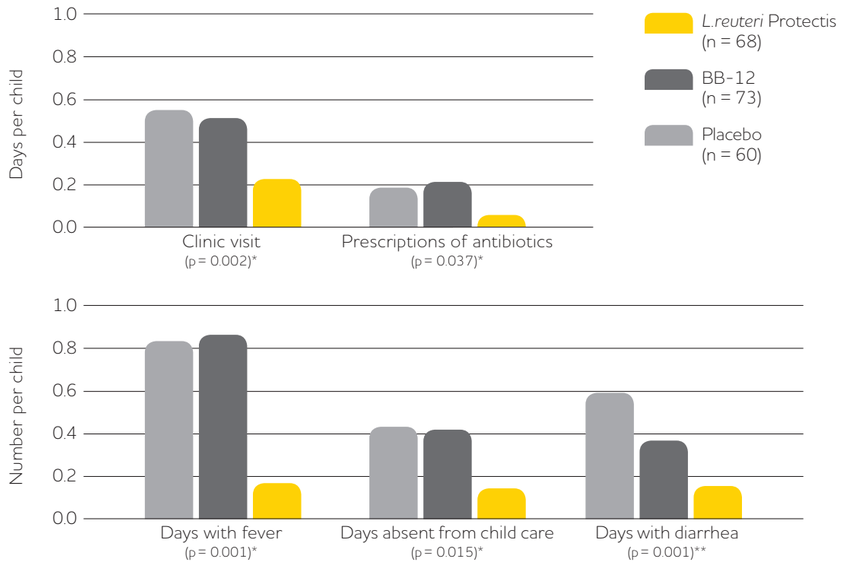


Gutiérrez-Castrellón P et al. Pediatrics 2014;133:4 e904-e909.

Shorter time of sickness and less absence from day care

- Supplementation of *L. reuteri* Protectis led to fewer days with fever, less absence from day care and fewer prescriptions of antibiotics compared to both BB-12 and the placebo group
- Days and episodes of diarrhea were significantly reduced compared to placebo

Days with diarrhea, antibiotic prescriptions and absence from day care for *L. reuteri* Protectis, BB-12 and placebo at end of intervention



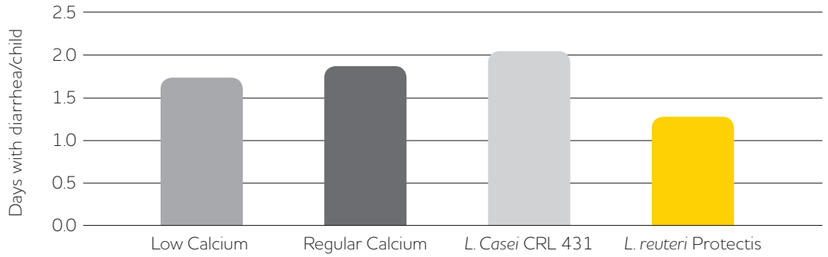
* *L reuteri* Protectis versus BB-12 and placebo
** BB-12 and *L reuteri* Protectis versus placebo

Weizman Z et al. Pediatrics. 2005;115:5-9.

32% reduction in the incidence of diarrhea

- *L. reuteri* Protectis prevented diarrhea and improved growth (weight and height) during the six-month study period
- Regular calcium milk alone or with *Lactobacillus casei* did not reduce the incidence of diarrhea. Neither of the two tested probiotics had any effect on reduced risk of acute respiratory infections

Mean incidence of all diarrhea*



* ≥ 2 loose/liquid stools in 24 hours

Agustina R et al. Pediatrics 2012;129: e1155-e1164.
Agustina R et al. J. Nutr. 2013;143:1184-1193.

Antibiotic-associated side-effects

Antibiotic-associated side-effects are common and usually affect the gastrointestinal system and may include diarrhea, nausea, vomiting, bloating and abdominal pain.[92] These manifestations appear when antibiotics disturb the balance of the "good" and "bad" bacteria causing pathogenic bacteria to multiply beyond their normal numbers.

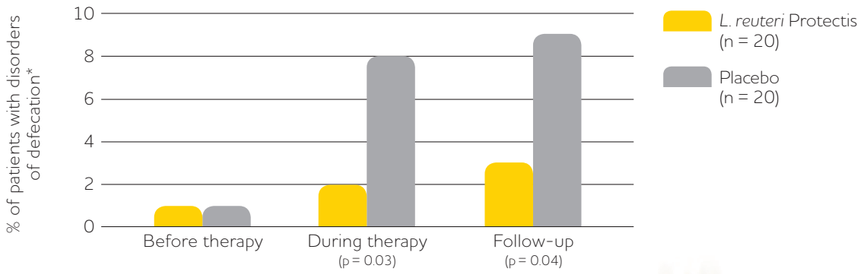
Up to 40 % of children receiving broad-spectrum antibiotics get diarrhea.[93] The high prevalence of side-effects might lead to treatment discontinuation with the risk of treatment failure and possible development of antibiotic resistance.

Probiotics are regarded as effective for controlling the overgrowth of potentially pathogenic microorganisms and may help to prevent or lower the incidence of antibiotic-associated side-effects. Patients are often unwilling to start or comply with any antibiotic therapy if they previously have experienced adverse events. An option to avoid this problem could be adjunctive probiotic administration.

L. reuteri Protectis has been studied in children as an adjunct to antibiotic treatment, and successfully reduced antibiotic-associated side-effects.[45]

75% less defecation disturbances

- *L. reuteri* Protectis reduced antibiotic-associated side-effects compared to placebo
- The effects on GI symptoms were evident both during the course of antibiotics and the follow-up period



* Including decreased/increased passage of stools and consistency of stools (loose/hard)

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