

L. reuteri Protectis®
Throughout Childhood

True friendship starts with a good gut feeling

BioGaia®

Supporting your invisible heroes

Information to health care professionals

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L. reuteri Protectis®

Probiotic definition: "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host".[5]

The microbiota of the infant and child

The foetus and then the infant, interacts with a complex array of factors linked to epigenome, nutrition and the microbiota. This altogether lays the foundation for health later in life. The newborn infant establishes its intestinal microbiota from the time of delivery and during the first two years of life.[1] Beneficial bacteria like *lactobacilli* and *bifidobacterial* are normally among the first to colonize.[2] Caesarean delivery delays the establishment of favourable bacteria compared to vaginal delivery, which may have health consequences.[3]

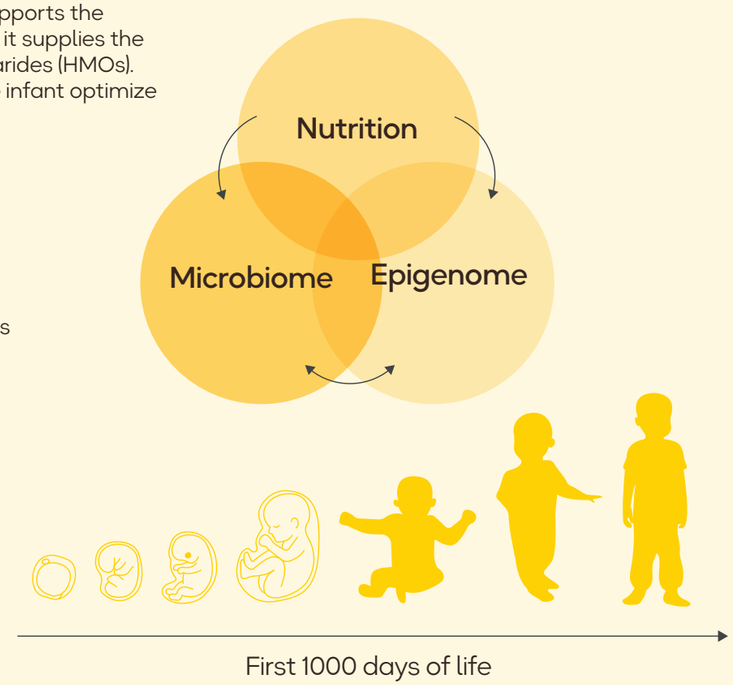
It is well known that breastfeeding supports the foundation of a healthy microbiota as it supplies the bacteria with human milk oligosaccharides (HMOs). Furthermore, the microbiota helps the infant optimize the functioning of the digestive tract.[4]

The microbiota contributes to:

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

Probiotics

Probiotics have become a well-recognized option to support the developing microbiota of infants and children. The species most often used as probiotics belong to the former genera of *Lactobacillus* and *Bifidobacterium*. Different strains of a specific species have different probiotic properties and effects. Hence the benefits of one specific probiotic strain cannot be extrapolated to another probiotic strain.



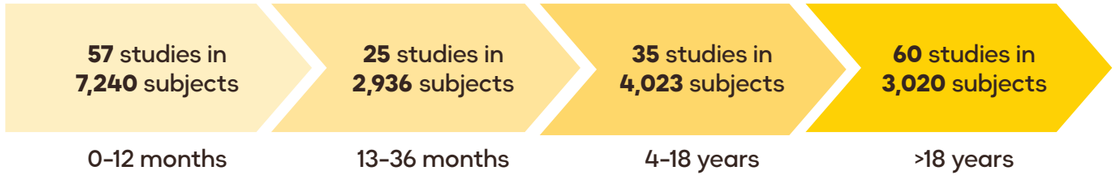
Modified from Indrio F, et al. 2017 [1]

Scientific Evidence

Numerous studies have proven the safety and efficacy of the probiotic *L. reuteri* Protectis.

Clinical studies with *L. reuteri* Protectis® - per age group

177 completed clinical studies in 17 219 individuals



BioGaia Protectis® is special

BioGaia Protectis contains the probiotic strain *Limosilactobacillus reuteri* DSM 17938, formerly known as *Lactobacillus reuteri* DSM 17938. It is derived from human breast milk and has also been isolated from other body sites, including the oral cavity, gastrointestinal tract, urinary tract, and skin. The abundance varies among individuals and is more common in individuals from rural areas. It is indigenous to the human digestive tract and one of few probiotics that have coevolved with humans since beginning of time.[6,7]

L. reuteri Protectis is well tolerated and supplementation result in temporary colonisation.[8] The safety of the strain is confirmed by both the Qualified Presumption of Safety (QPS) list assessed by the European Food Safety Authorities (EFSA) and by being Generally Recognized As Safe by the US Federal Food and Drug (FDA) act.

L. reuteri Protectis is an excellent producer of reuterin, a well-known antimicrobial compound. It also produces several other antimicrobial substances such as lactic and acetic acid and exopolysaccharides.

Exopolysaccharides from *L. reuteri* is important for biofilm formation and adherence of *L. reuteri* to epithelial surfaces thereby preventing pathogenic bacteria from binding to the mucosa. *L. reuteri* Protectis also plays a role in the microbiota-gut-brain axis as it produces different neurotransmitters.[9]

L. reuteri Protectis® - Mode of action

To understand the underlying mechanisms, numerous preclinical (in vitro and animal) studies have been caried out and are used to describe the main modes of action of *L. reuteri* Protectis:

- Reduces visceral pain[10]
- Improves gastrointestinal motility[11]
- Improves epithelial barrier function by tightening the epithelial lining and increasing epithelial cell growth[12,13]
- Supports a balanced microbiota by production of antimicrobial substances.[14]
- Balances the immune function.[15]

Clinical studies support the use of *L. reuteri* Protectis®

Clinical studies have shown several health benefits for *L. reuteri* Protectis, primarily in Functional Gastrointestinal Disorders (FGIDs) also called disorder of the Gut-Brain interaction, but also in acute gastroenteritis, antibiotic associated side effects and in protection of infections. You will find more information on the clinical evidence in the following chapters.

- **Infant Colic**
  Reduced crying time in colicky infants
- **Regurgitation**
  Improved gut motility and less regurgitation
- **Functional Constipation**
  Reduced constipation
- **Functional Abdominal Pain**
  Reduced functional abdominal pain
- **Acute Gastroenteritis**
  Shortened duration of watery diarrhoea and vomiting
- **Infection Protection**
  Reduced incidence and duration of diarrhoea and respiratory tract infections

  Improved growth in children with low nutritional status
- **Antibiotic-Associated Side Effects**
  Reduced incidence of antibiotic associated side-effects

Guidelines Supporting the Use of BioGaia Protectis®

L. reuteri in Infants and Children

- 7 guidelines supporting the use for AGE
- 6 guidelines supporting the use for colic
- 2 guidelines supporting the use for FAP
- 1 guideline supporting the use for infection protection

Guidelines supporting the use of BioGaia Probiotics

New! Guidelines for Infants and Children	Description	Region	Strain	Indication
Szajewska H, 2023[16] Probiotics for the management of pediatric gastrointestinal disorders: position paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications.	The ESPGHAN Special Interest Group on Gut Microbiota and Modifications provides updated recommendations for the use of probiotics for the management of selected pediatric gastrointestinal disorders.	Europe	*L. reuteri* DSM 17938	Acute gastroenteritis, Functional abdominal pain, Management of Infant colic in breastfed infants
Indrio F, 2021[17] Management of the Most Common Functional Gastrointestinal Disorders in Infancy: The Middle East Expert Consensus.	During a consensus meeting, a locally relevant approach for treating common FGIDs such as infant regurgitation, infant colic, and functional constipation was discussed and approved by 14 regional experts.	Middle Eastern countries	*L. reuteri* DSM 17938	Infant colic
Guarino A, 2018[18] Universal Recommendations for the Management of Acute Diarrhea in Nonmalnourished Children.	The Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition (FISPGHAN) Working Group (WG) selected care protocols on the management of acute diarrhea in infants and children, and developed overall agreements based on this.	Global	*L. reuteri* DSM 17938	Acute gastroenteritis
Hojsak I, 2018[19] Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups.	Guidelines for using probiotics in paediatric health care, conducted by an expert panel that was convened by the European Paediatric Association.	Europe	*L. reuteri* DSM 17938	Infant colic
Iramain R, 2017[20] Consensus Guideline on Acute Gastroenteritis in the Emergency Department. Emergency Medicine Committee of SLACIP (Latin American Society of Pediatric Intensive Care).	Recommendations for the diagnosis and management of acute gastroenteritis in pediatrics from the Latin American Society of Pediatric Intensive Care.	Latin America	*L. reuteri* DSM 17938 & 55730	Acute gastroenteritis
Cameron D, 2017[21] Probiotics for gastrointestinal disorders: Proposed recommendations for children of the Asia-Pacific region.	Recommendations for probiotics in pediatric gastrointestinal diseases in the Asia-Pacific region, developed by a working group of international experts in adult and pediatric gastroenterology from Asia-Pacific countries, as well as from countries outside the region.	Asia-Pacific region	*L. reuteri* DSM 17938	Infant colic, Acute gastroenteritis
Guarner F, 2017[22] World Gastroenterology Organisation Global Guidelines Probiotics and prebiotics	Evidence-based recommendations for probiotics and prebiotics from the World Gastroenterology Organisation (WGO).	Global	*L. reuteri* DSM 17938	Infant colic management, Infant colic prevention, Functional abdominal pain, Acute gastroenteritis, Infections in children attending day-care centers
Lo Vecchio A, 2016[23] An international consensus report on a new algorithm for the management of infant diarrhoea.	Evidence-based recommendations of the European Society of Gastroenterology, Hepatology and Nutrition and the European Society of Pediatric Infectious Diseases and an updated review of the literature.	Europe	*L. reuteri* DSM 17938	Acute gastroenteritis
Cruchet S, 2015[24] The use of probiotics in pediatric gastroenterology: a review of the literature and recommendations by Latin-American experts.	Guidelines based on discussions of a Latin American (LATAM) expert consensus group. Relevant clinical questions were used as a basis for discussion and topics were divided between authors according to their field of expertise in various childhood diseases.	Latin America	*L. reuteri* DSM 17938	Infant colic, Acute gastroenteritis

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Infant Colic

Colic is a common condition that is distressing and worrisome for parents and caregivers. It involves long periods of crying and hard-to-soothe behaviour without apparent cause. Globally up to 20% of infants experience colic, making the condition one of the most frequent reasons for visits to family practitioners.[1]

Colic is defined by Rome IV diagnostic criteria for Functional Gastrointestinal Disorders as:

- An infant who is <5 months of age when the symptoms start and stops
- Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers
- No evidence of infant failure to thrive, fever, or illness[1]

Colic impacts the whole family. Having a colicky baby is linked to maternal anxiety and depression and can affect family quality of life. It can also interfere with breastfeeding and disrupt the establishment of the mother-baby bond.[2]

Additionally, long term follow-up studies indicate that colic may be associated with future health problems such as recurrent abdominal pain, allergic diseases, or psychological disorders.[3]

Etiology of colic

The etiology of colic is multifactorial and not yet fully understood. However, research indicate that the condition is related to an immaturity of the gastrointestinal tract which is linked to problems with gut motility, imbalanced microbiota, and a low-grade inflammation.[2]

Studies have shown that newborns who later develop infant colic have a lower relative abundance of *Lactobacillus* in the first stool compared to those who remain healthy.[4] Furthermore, low levels of *Lactobacillus* and *Bifidobacteria* and high levels of *E. coli* have been observed more frequently in colicky infants compared to non-colicky infants.[5]

The possibilities to treat colic are limited. Simethicone is widely used but clinical research has shown that the effect is equal to placebo.[6] Numerous studies have shown that colic may be alleviated, and excessive crying reduced by supplementation with probiotics. *L. reuteri* Protectis is the most studied probiotic for the management of infant colic.[7]

The proposed pathogenesis for colic is shown in figure 1. The figure shows how the Immaturity of the gastrointestinal tract can lead to disturbed intestinal motility. The disturbed motility (1) results in poor absorption of nutrients, leakage of fermentable nutrients (2), giving rise to both increased gas production and dysbiosis (3). The dysbiosis triggers an inflammation (4) noticed by a leaky gut epithelium. The inflammation, leaky epithelium and gas production are all believed to trigger pain and discomfort also called visceral pain (5) in infants through the gut-brain communication axis resulting in excessive inconsolable crying.

Proposed pathogenesis for colic

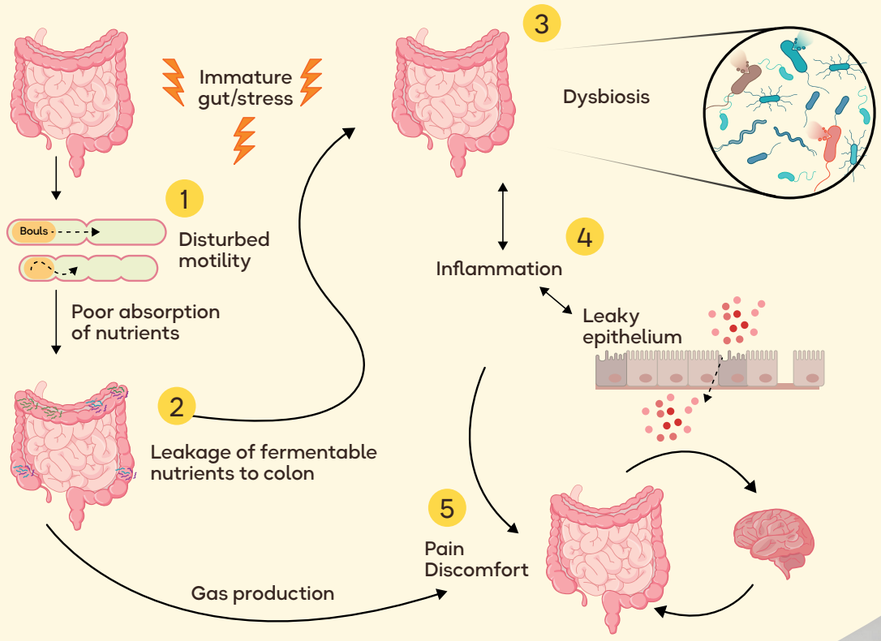


Figure 1.



Mode of action of the strain *L. reuteri* Protectis®

L. reuteri Protectis positively affects the immature gut by slowing down the propagation in the small intestine, enabling proper digestion and absorption of nutrients. It also decreases the leakage of fermentable carbohydrates to the colon. In the colon, *L. reuteri* Protectis increases intestinal motility, which speeds up transportation of the remaining contents resulting in reduced gas formation and reduced dysbiosis.[8] The improved microbial balance[9] subsequently leads to a reduction in inflammation[10] and a reduced leakage by epithelial cells.[11,12]

Finally, *L. reuteri* Protectis blocks the pain receptor TRPV-1 leading to reduced nerve firing and reduced pain.[13] Together, these effects may explain the reduced crying in colicky babies.

L. reuteri Protectis® – the most researched probiotic for colic

L. reuteri Protectis is the most researched probiotic strain for infant colic.[7] It's proven to reduce crying and fussing in colicky babies and to improve family quality of life. To date the positive effect has been proven in 8 randomised controlled studies. Furthermore, two prevention studies have shown reduced crying time when *L. reuteri* was used prophylactic. Twelve meta-analyses confirm the efficacy and 6 international guidelines has a positive recommendation for *L. reuteri* Protectis for the management of colic.

8
colic treatment studies[14–21]

L. reuteri Protectis®:

- Significantly reduced daily inconsolable crying time
- Improved the well-being of mom and baby
- Improved QoL for the family

2
colic prevention studies[22, 23]

L. reuteri Protectis®:

- Significantly reduced daily inconsolable crying time
- Reduced formula use
- Improved breastfeeding rates
- Saved families money

12
meta-analyses[6, 24–34]

L. reuteri Protectis®: effective in infant colic, especially in exclusively or predominantly breastfed infants

6
international clinical guidelines[5, 35–39]

Supports the use of *L. reuteri* Protectis® for management of infant colic in breastfed infants

References:
Colic treatment: (Savino, 2019) (Chau K, 2014), (Savino F, 2007), (Savino F, 2010), (Szajewska H, 2013), (Mi GL, 2015), (Savino F, 2018b), (Savino F, 2018a)
Colic prevention: (Indrio F, 2014), (Savino F, 2015)
Meta-analyses: (Harb T, 2016), (Anabrees, 2013), (Sung V, 2013), (Urbańska M, 2014), (Sung V, 2018), (Gutiérrez-Castrellón P, 2017), (Schreck Bird A, 2017), (Sung V, 2015), (Xu M, 2015), (Dryl R, 2018), (Dos Reis Buzzo Zermiani AP 2021), (Ellewood J, 2019), (Skonieczna-Żydecka K, 2020)
Guidelines: (Cruchet S, 2015), (Szajewska H, 2023), (Indrio F, 2021), Hojsak I, 2018), (Guarner F, 2017), (Cameron D, 2017), (Cruchet S, 2015)



Effects of *L. reuteri* Protectis® in colic confirmed by eight studies

Publication	Reduction in crying time by day 7	Reduction in crying time by day 21	Reduction in crying time by day 28 or 30	Responders[1] by day 7	Responders[1] by day 21	Numbers needed to treat
Savino F et al. 2019	na	na	✓	na	na	3
Savino F et al. 2018a	na	na	✓	na	na	2
Savino F et al. 2018b	na	na	✓	na	na	na
Mi GL et al. 2015	✓	✓	✓	na	✓	1
Chau K et al. 2015	✓	✓	✓	ns	✓	2
Szajewska H et al. 2013	✓	✓	✓	✓	✓	2
Savino F et al. 2010	ns	✓	✓	✓	✓	4
Savino F et al. 2007	✓	✓	✓	na	na	1

ns: *not significant*
na: *not analysed*

[1]*Responder: reduction in crying time by ≥50% compared to baseline*

Reduction in crying and fussing

A double blind placebo controlled trial in 52 infants showed that *L. reuteri* Protectis (1x10^8 CFU/day) compared to placebo:

- Significantly reduced crying and fussing time from day 7 and onwards
- After 21 days reduced the daily crying time compared to baseline with at least 50% in 71% of infants

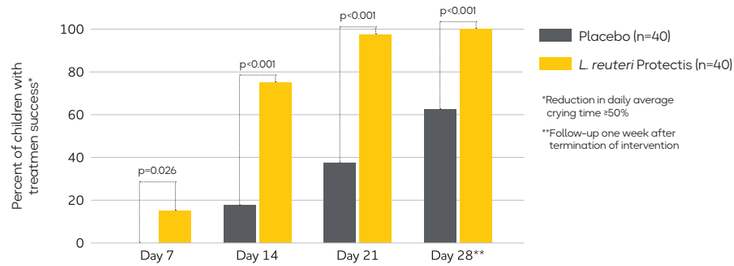


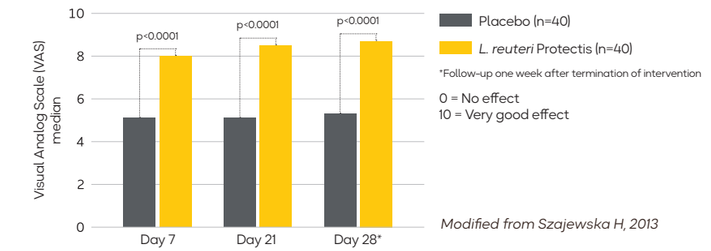
Modified from Chau K, 2014

Decreased crying time and improved family quality of life

In a randomised, double-blind, placebo-controlled study in 80 exclusively or predominately breastfed colicky infants *L. reuteri* Protectis was shown to significantly reduce crying time by day 14. Furthermore, *L. reuteri* Protectis significantly improved family quality of life measured by Visual Analog Scale (VAS) throughout the study.

The infants received five drops (1x10^8 CFU/day) of *L. reuteri* Protectis (n=40) or placebo (n=40) for 21 days.



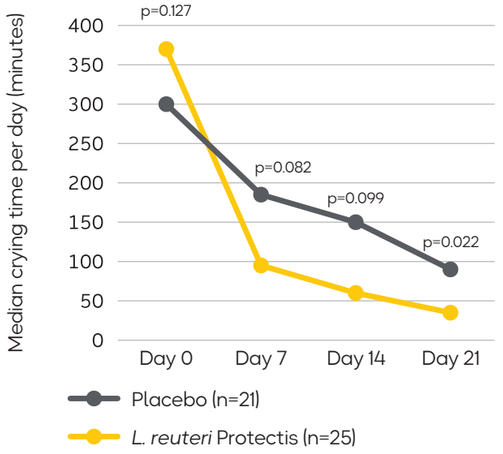


Modified from Szajewska H, 2013

Reduced daily crying

In a Randomised, double-blind, placebo controlled trial in 50 infants *L. reuteri* Protectis reduced crying time with more than 4.5 hours after one week. The infants were supplemented with five drops ($1x10^8$ CFU/day) of *L. reuteri* DSM 17938 (n=25) or placebo (n=25) for 21 days.

- Crying decreased with 4.5 hours per day after one week of supplementation.

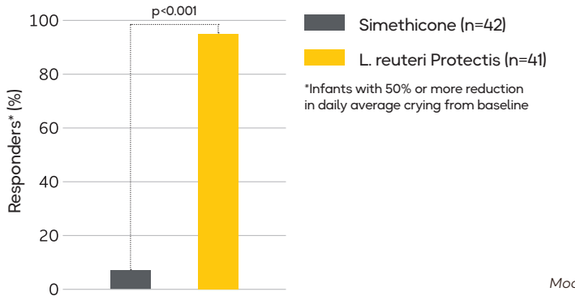


Modified from Savino F et al. 2010

BioGaia Protectis® superior to simethicone

In a prospective, randomised study, 90 breastfed colicky infants were supplemented with five drops of *L. reuteri* Protectis ATCC 55730 $1x10^8$ CFU/day (n=45) or simethicone 60 mg/day (n=45) for 28 days. Compared to simethicone, *L. reuteri* Protectis:

- Significantly reduced daily crying time starting from day 7



Modified from Savino, 2007

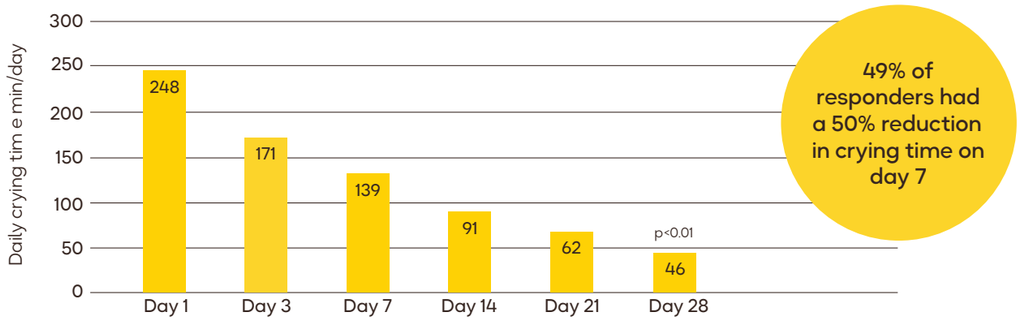


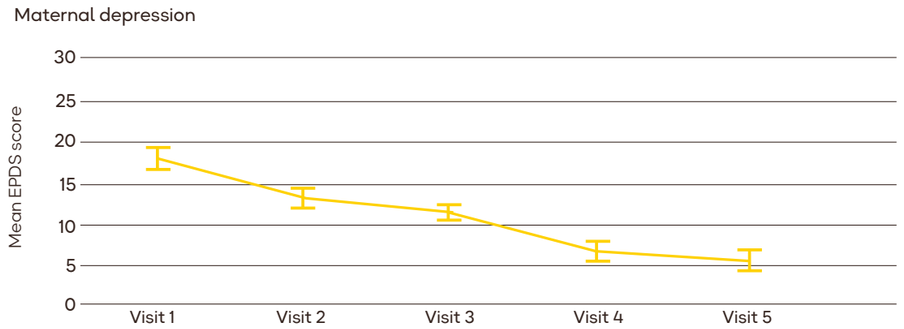
Decreased crying time and improved quality of life

In a prospective, observational multi-centre study, 120 infants <5 months exclusively or predominantly breastfed, were supplemented with 5 drops of *L. reuteri* DSM 17938 (1x10^{8}CFU/day) for 5 weeks.

Supplementation with *L. reuteri* DSM 17938 resulted in a significant reduction from baseline to end of study in:

- crying time
- parental perception of the severity of colic
- intensity of unexplained fussiness
- maternal depression





Maternal depression was assesed by the Edinburgh's postnatal depression scale (EPDS)

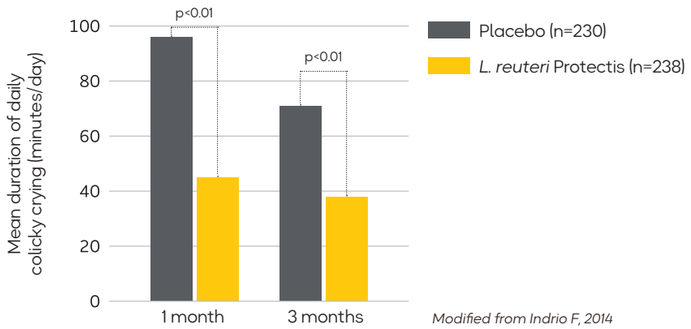
Modified from Wadhwa A, 2022



Preventive use of BioGaia Protectis® reduced crying time

In a prospective, multicenter, double-blind, placebo-controlled randomised trial 589 infants <1 week were included. The infants received either five drops per day of *L. reuteri* DSM 17938 (1x10^8 CFU, n=238) or placebo (n=230) for 90 days.

- After one month, daily inconsolable crying was reduced to 45 minutes/day in the *L. reuteri* Protectis group whereas it was still more than 90 minutes/day in the placebo group.
- The difference between the groups persisted to the end of the 3-month intervention.



Modified from Indrio F, 2014

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Regurgitation

Regurgitation is defined as the passage of refluxed gastric content into the pharynx or mouth, sometimes with expulsion out of the mouth.[1] It occurs most often during transient relaxations of the lower oesophageal sphincter unaccompanied by swallowing, which permit gastric content to flow into the oesophagus.[2]

The Rome IV diagnostic criteria for FGIDs[3] define that an otherwise healthy infant between three weeks and 12 months of age has regurgitation if it meets and experience:

- Two or more regurgitations/day for 3 weeks or more.
- No retching, haematemesis, failure to thrive, no feeding, swallowing, or respiratory problems.
- No abnormal posturing.

Uncomplicated regurgitation in otherwise healthy infants is common.[4] The frequency varies with age, with infants up to the first month being more frequently affected.[5] Most infants are happy and healthy even if they frequently spit up or vomit, and by their first birthday most of them have outgrown regurgitation.

From a parent perspective regurgitation is often seen as problematic and the health problem is reflected by the high frequency of paediatric consultations.[6] The parents worry about their infant getting sufficient food to be able to grow.[7] This may cause unnecessary stress for parents and additional workload for healthcare professionals. Therefore, a preventive strategy could be beneficial for both the parents and the community.

L. reuteri Protectis® in the management of regurgitation

L. reuteri Protectis has been shown to significantly increase gastric emptying rate in infants and thereby decrease the number of regurgitations.[8]

A study on prevention of functional gastrointestinal disorders (FGIDs) in healthy newborns, verified the effect on improved gastric motility and reduced frequency of regurgitation.[9] This study also showed that preventive use of *L. reuteri* Protectis reduced both public and private costs for FGIDs.

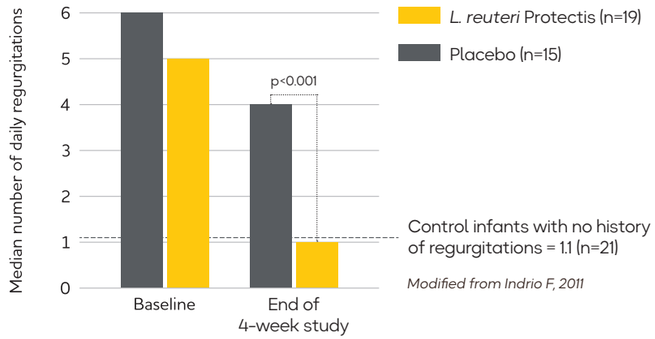
	Treatment	Prevention	Increased gastic mobility	Reduced number of regurgitations
Indrio, 2011	√		√	√
Indrio, 2014		√		√

Reduced number of daily regurgitations

A randomised, double-blind, placebo-controlled pilot study enrolled 42 infants. Also a control group with 21 infants matched for age and weight, with no history of regurgitation and fulfilling the inclusion criteria, were recruited to assess the cut off value of normal range of gastric emptying rate.

Compared to placebo *L. reuteri* Protectis:

- Increased gastric emptying rate
- Reduced the number of regurgitations



Modified from Indrio F, 2011

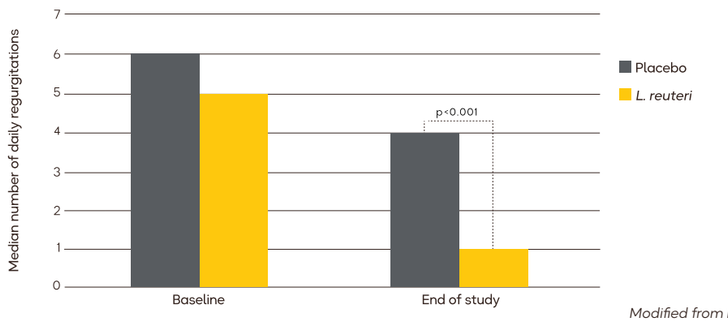


Prevent the number of regurgitations

A prospective, multicenter, double-blind, placebo-controlled randomised prevention trial included 589 infants <1 week. The infants received either five drops per day of *L. reuteri* DSM 17938 ($1x10^8$ CFU, n=238) or placebo (n=230) for 90 days.

Compared to placebo *L. reuteri*:

- improved gut motility
- significantly reduced the number of daily regurgitations
- reduced both private and public cost due to less visits to the paediatrician



Modified from Indrio F, 2014

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Functional Constipation

Constipation is a common and distressing problem all over the world. If no organic cause can be found it is classified according to the Rome IV criteria as functional constipation.[1]

According to the Rome IV diagnostic criteria for FGIDs[1]: a child up to 4 years has functional constipation if it meets at least 2 of the following criteria in one month:

- ≤2 defecations/week
- ≤1 episode/week of incontinence after the acquisition of toilet skills
- History of excessive stool retention
- History of painful or hard bowel movements
- Presence of large faecal mass in rectum
- History of large-diameter stools

Prevalence and etiology

The prevalence of functional constipation is around 3 % in the first year of life and increases to around 10% in the second year of life. It is often a result of repeated attempts of withholding faeces by a child who have fears associated with evacuation.[1] Withholding behaviour leads to stool retention that leads to more water being absorbed and making the stool hard and painful to evacuate.[2] For infants the problems often start when changing from breast milk to formula or with the introduction of solid food. For older children the onset periods are often during toilet training, or when the child starts school.[1,3]

Constipation is often a long-term problem and the goal of treatment is to produce soft, painless stools and to prevent reaccumulating faeces. Education, behavioural modification, daily maintenance stool softeners and dietary modification are all important components of therapy.[4]

Proven effects with *L. reuteri* Protectis®

L. reuteri Protectis has been shown to significantly increase the frequency of bowel movements in infants with functional constipation.[5] Furthermore, in a prevention study of functional gastrointestinal disorders in healthy newborns, it was demonstrated that *L. reuteri* Protectis improved gut motility, leading to significantly more daily evacuations.[6]

	Comparison group	Improved stool frequency	Improved stool consistency	n	Age
Cocorullo, 2010	Placebo	√	No	44	6–12 months
Olgaç, 2013	Lactulose	√	√	103	4–16 years
Kubota, 2020	Magnesium Oxide (MgO) & placebo	√	No	60	6 months–6 years

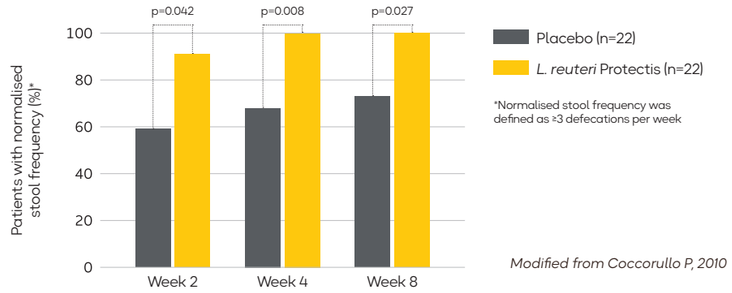
Normalisation of stool frequency

A double-blind, placebo-controlled, randomised study in 44 infants > 6 months with functional chronic constipation showed an increase in the frequency of bowel movements per week after supplementation with *L. reuteri* DSM 17938.

The children received 1x10^8 CFU/day of *L. reuteri* DSM 17938 (n=22) or placebo (n=22) for 8 weeks.

Compared to placebo *L. reuteri* Protectis:

- Significantly improved the frequency of bowel movements
- 91% of infants normalised their stool frequency within 2 weeks and 100% within 4 weeks

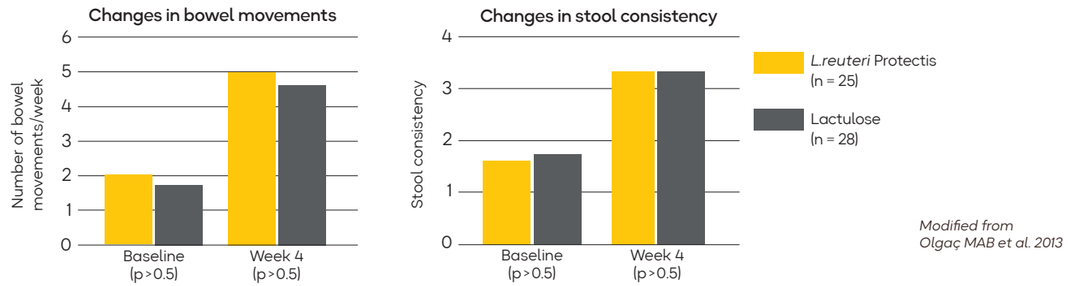


Modified from Coccorullo P, 2010

L. reuteri Protectis® as effective as lactulose

In an open, randomised study in 103 children, 53 with functional constipation and 50 healthy, were randomised to receive either 1x10^8 CFU of *L. reuteri* DSM 17938 (n=25) or lactulose 1 ml/kg (n=28) daily for 4 weeks. The study showed that *L. reuteri* Protectis was equivalent to lactulose in the effects on functional constipation:

- Improved stool consistency
- Increased number of bowel movements



Modified from Olgaç MAB et al. 2013

The study further more showed that abdominal pain and flatulence were significantly reduced by *L. reuteri* Protectis compared to lactulose and the quality of life increased in both treatment groups to the level of the healthy controls.

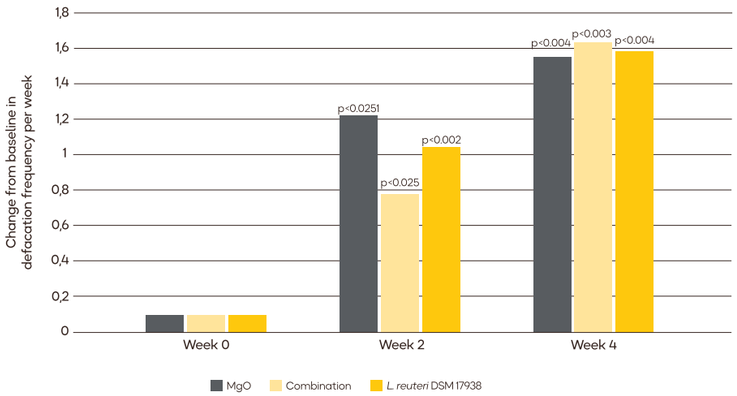
L. reuteri Protectis® as effective as magnesium oxide

A prospective double-blind, placebo-controlled, randomised, and parallel-group trial were performed in 60 children, 6 months to 6 years, with a diagnosis of functional constipation.

L. reuteri DSM 17938 was given twice a day for 4 weeks (2x10^8 CFU/day).

L. reuteri Protectis was equivalent to magnesium oxide (MgO) in increasing defecation frequency:

- No synergistic effect of the combination of *L. reuteri* Protectis and MgO
- *L. reuteri* Protectis did not cause imbalance in the gastrointestinal microbiome which were seen in the magnesium oxide group

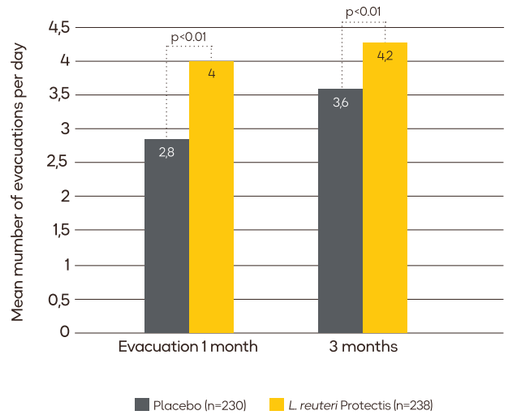


Modified from Kubota M, 2020

Prevention of constipation in infants

A prospective, multicenter, double-blind, placebo-controlled randomised prevention trial included 589 infants <1 week. The infants received either five drops per day of *L. reuteri* DSM 17938 (1x10^8 CFU, n=238) or placebo (n=230) for 90 days.

The study showed a 43 % increase in evacuations already after one month of supplementation with *L. reuteri* DSM 17938 in healthy infants.



Modified from Indrio F, 2014

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Functional Abdominal Pain

Functional Abdominal Pain (FAP) disorders affect 10–20% of all school-aged children, and is one of the most diagnosed medical problems in pediatrics.[1,2]

In the Rome IV diagnostic guidelines, the term functional abdominal pain – not otherwise specified (FAP-NOS) substitutes the Rome III terms FAP and FAP Syndrome.[3]

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:[3]

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

Etiology of FAP

FAP is a complex condition and the exact mechanisms are still unclear, but it seems to be an interplay between genetic, physiological and psychosocial factors. The prevailing discussion is that a disturbed gut-brain communication and visceral hypersensitivity may be caused by a combination of genetic predisposition and early life events and physiological factors like poor gastric emptying and gut motility, a low-grade inflammation and alteration of gut microbiota.

The outcome of FAP is also influenced by different psychosocial factors like depression, anxiety, and stress.[4,5]

True pain and lower quality of life

Although there is no organic cause behind FAP, the pain that the child experiences is still very real. FAP also affects the child's psychological health, social life, and general well-being, which may ignite feelings of self-doubt, alienation, and depression.[4]

Management of FAP

Current treatment options for FAP are few but the interest in the role of probiotics in FAP has grown, both in terms of research on the clinical efficacy and the underlying mechanisms linked to the disorder. *L. reuteri* DSM 17938 has shown clinical effect in FAP. This might be explained by the mode of actions of this specific strain since it affects some of the potential factors behind the condition. As described previously *L. reuteri* DSM 17938 has been shown to have a positive effect on mucosal inflammation, gastrointestinal motility, pain perception and the composition of the microbiota.

L. reuteri Protectis® – recommended for functional abdominal pain

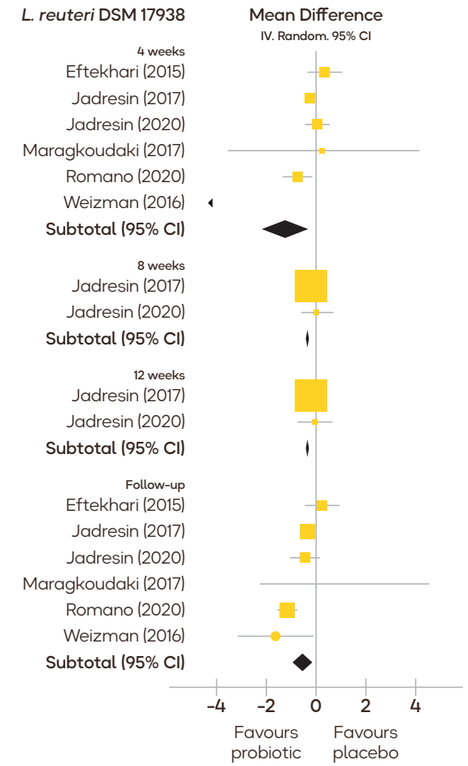
Four double blind, randomized, controlled treatment trials have demonstrated that *L. reuteri* Protectis reduced both the frequency and severity of abdominal pain in children with FAP compared to placebo.[1,6,7,8] The children supplemented with *L. reuteri* Protectis also experienced significantly more days without pain.[7]

A systematic review by Weizman Z et al from 2014[9] and a review with meta-analysis by Trivić et al from 2020[10] shows that *L. reuteri* Protectis is the only probiotic with proven efficacy in FAP. Moreover, World Gastro organisation and the ESPGHAN Special Interest Group on Gut Microbiota and Modifications recommend *L. reuteri* Protectis for the management of FAP.[11,12]

Randomised clinical trial	Decreased pain frequency	Decreased pain intensity	Duration	N	Age (years)
Romano, 2014	No	√	4 weeks	93	6–15
Weizman, 2016	√	√	4 weeks	52	6–16
Jadrešin, 2017	√	√	12 weeks	55	4–18
Jadrešin, 2020	√	√	12 weeks	46	4–18

Decreased pain intensity with long-term use

In a systematic review and meta-analysis by Trivić, nine randomised placebo-controlled trials on children with FAP were included. Three with *L. rhamnosus* GG and six with *L. reuteri* DSM 17938. The review showed that *L. reuteri* DSM 17938 can be effective in reducing pain intensity and in increasing the number of days without pain, whereas no effect was seen for LGG in FAP. As shown in the forest plot, long-term use was efficient in decreasing pain intensity. The boxes show the effect estimates from the single studies, and the diamonds show the pooled result.



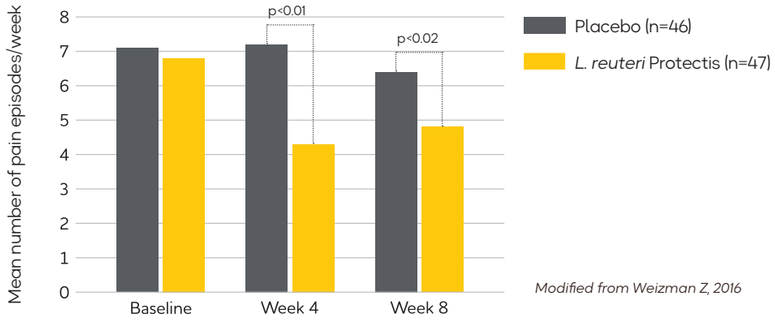
Modified from Trivić I, 2020

Reduced number of pain episodes

In a randomised double-blind, placebo-controlled study in 93 children, 6-15 years, fulfilling the Rome III criteria for FAP, the efficacy of *L. reuteri* DSM 17938 were studied. The children received one chewable tablet 1x10^8 CFU/day of *L. reuteri* DSM 17938 (n=47), or placebo (n=46) for 4 weeks followed by a 4 week follow-up period without supplementation.

Compared to placebo *L. reuteri*:

- Reduced the number of pain episodes
- Decreased the pain intensity



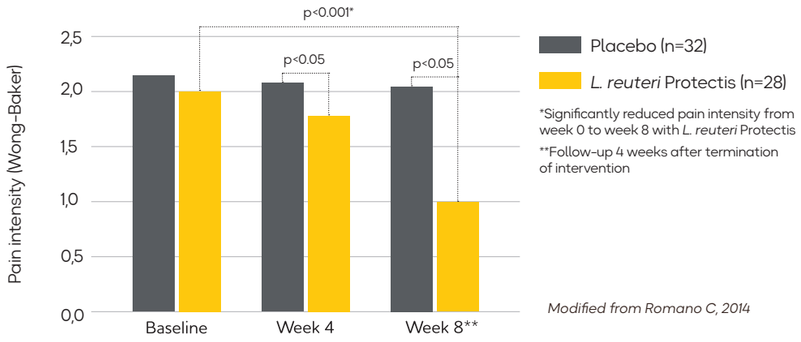
Modified from Weizman Z, 2016

Reduction in pain intensity

In 2014 Romano published a study showing reduced pain intensity in children with FAP after supplementation of *L. reuteri* DSM 17938. The effect increased even in the follow-up period. The study was a double-blind, randomised, placebo-controlled trial in 56 children with FAP aged 6 to 16 years. The children received 2 x 10^8 CFU/day of *L. reuteri* Protectis or placebo for 4 weeks followed by a 4-week follow-up period without supplementation.

Compared to placebo *L. reuteri*:

- Significantly reduced the pain intensity



*Significantly reduced pain intensity from week 0 to week 8 with *L. reuteri* Protectis

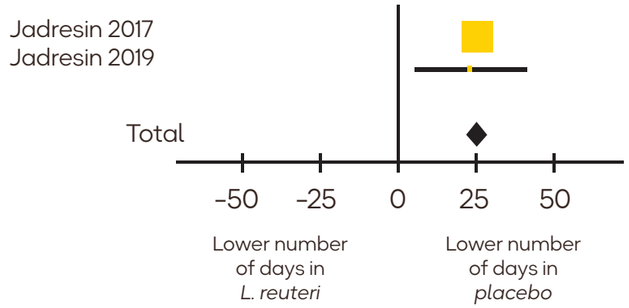
**Follow-up 4 weeks after termination of intervention

Modified from Romano C, 2014

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

Jadresin and co-workers investigated the effectiveness of *L. reuteri* DSM 17938 in the treatment of children with FAP and IBS in a prospective, randomised, double-blind, placebo-controlled parallel study in 55 children, aged 4-18 years, diagnosed with FAP. The children were supplemented with one chewable BioGaia Protectis tablet 1x10^8 CFU/day, or placebo, for 12 weeks followed by a follow-up period of 4-weeks without supplementation. Due to slow inclusion rate, an interim analysis was performed and published in 2017.[7] Based on its positive results, a second study was undertaken, results were published in 2020, including a meta-analysis of the two studies.[8]

The meta-analysis of the two studies demonstrates that children given *L. reuteri* DSM 17938 experienced significantly less severity of pain and more pain-free days, compared to the placebo group of children.



Modified from Trivić I, 2020

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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 diarrhoea lasts less than seven days and no longer than 14 days.[1]

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 hospitalisations 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 birthplace have had a rotavirus infection.[2,3]

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.[1,4,5,6,7]

Early administration of ORS can reduce complications and the number of clinic visits and hospitalisations. 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 diarrhoea, it is now also recommended that zinc should be given to all children with AGE.[7]



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 diarrhoea.[8,9,10,11,12,13,14] The earlier the onset of probiotic treatment, the faster the recovery.[15,16] Also, a published review recommends starting the use of *L. reuteri* Protectis directly in the emergency room to speed up remission of symptoms, reduce the recovery period, and promote the safe discharge of patients.[17]

Moreover, the beneficial effects of *L. reuteri* Protectis in AGE is stated in a meta-analysis[18] and several clinical guidelines have listed *L. reuteri* Protectis as one of few probiotics that may have a positive treatment effect in AGE.[1,19–26]

Faster recovery with *L. reuteri* Protectis®
Scientific overview

Trial	REDUCTION significant compared to placebo				Product information	
First author, year of publication and number of subjects	Duration of diarrhoea	Day 2: % of subjects w diarrhoea	Hospitalization	Duration of intervention	Product and daily dose*	Strain
Francavilla 2012[12], n=69	√	√	ns	7 days	Drops $4x10^8$	DSM 17938
Dinleyici 2014[9], n=127	√	√	√	5 days	Drops $1x10^8$	DSM 17938
Dinleyici 2015[10], n=60	√	√	outpatients	5 days	Drops $1x10^8$	DSM 17938
Szymanski 2019[27], n=91	ns	ns	√	5 days	Drops $2x10^8$	DSM 17938
Shornikova 1997a[13], n=40	ns	√	not analysed	up to 5 days	Powder** $1x10^{10}$– $1x10^{11}$	ATCC 55730
Shornikova 1997b[14], n=66	√	√	ns	5 days	Powder** $1x10^7$ or $1x10^{10}$	ATCC 55730
Eom 2005[11], n=50	ns	√	√	up to 5 days	Powder** $2x10^8$	ATCC 55730
Ruzhentsova 2018[28], n=60	√	not analysed	not analysed	Until cessation of AGE	ORS powder Individual dosage	DSM 17938
Maragkoudaki 2018[29], n=51	ns	ns	outpatients	5 days	ORS powder Individual dosage	DSM 17938

ns: non-significant

**) Daily dose in CFU, colony forming units*
***) Freeze-dried culture mixed with other dry ingredients*

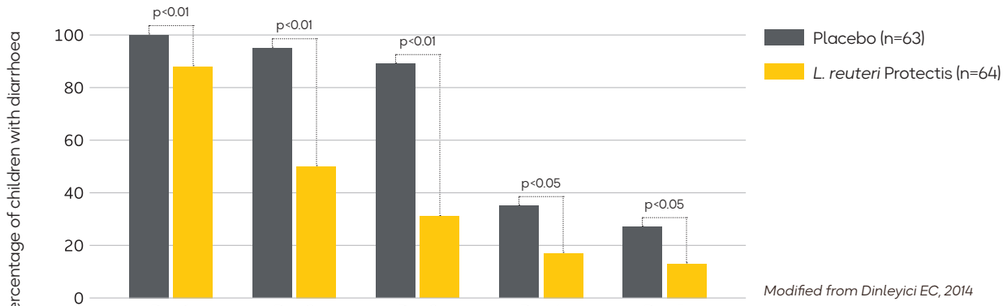


Effect of *L. reuteri* Protectis® after 24 hours

In a controlled, randomised, single blinded study in 127 infants and children hospitalised for acute diarrhoea lasting 12-72 hours, the effectiveness of *L. reuteri* DSM 17938 as an effective adjunct to oral rehydration therapy was confirmed. The children in the *L. reuteri* group received 1x10^8 CFU/day of *L. reuteri* DSM 17938 (n=64) for 5 days and ORS / intravenous rehydration. The control group (n=63) were treated with only ORS / intravenous rehydration.

The advantageous effect was seen already after 24 hours.

- Significant reduction in percentage of children with diarrhea in the *L. reuteri* group
- The total duration of diarrhoea in the *L. reuteri* group was reduced by 33 hours compared to the control group
- Mean length of hospital stay was shortened by 1.2 days compared to the control group
- Prolonged diarrhoea after 7 days was only observed in the control group

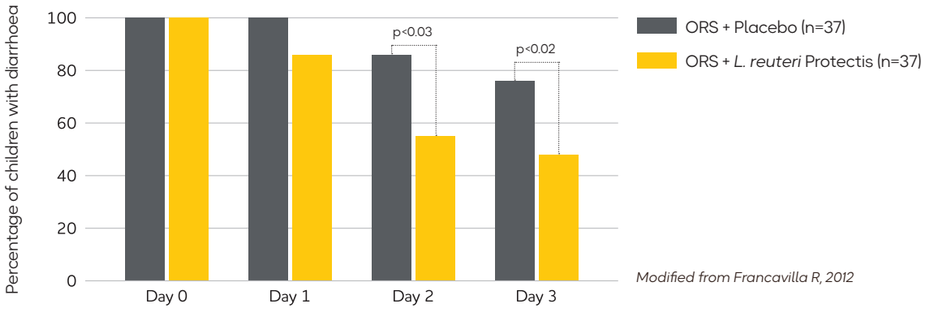


Modified from Dinleyici EC, 2014

Faster recovery from watery diarrhoea

In a double-blind, placebo-controlled study 69 children, 6-36 months old with acute diarrhoea and with clinical signs of mild to moderate dehydration, were randomised to either five drops of *L. reuteri* DSM 17938 (n=35) or placebo (n=34), twice per day for 7 days. The actual dose of *L. reuteri* DSM 17938 was 2x10^8 CFU/day.

- After two days of supplementation, 45% of the children in the *L. reuteri* group were free from watery diarrhoea compared to 14% in the placebo group.



Modified from Francavilla R, 2012

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Infection Protection

Diarrhoea and respiratory tract infections are major causes of illness among young children worldwide.[1,2] Young children are more prone to infections due to an immature immune system and are particularly challenged when children gather in groups, for example at day care and school.[3]

Today the role of the intestinal microbiota in health and disease is well known. Eighty percent 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 microbiota with more beneficial bacteria and less pathogenic ones compared to formula-fed infants.

As breastmilk is a source of lactobacilli, this mechanism has been considered one of the explanations to why breastfed infants demonstrate a decreased rate of infectious diarrhoea.[4]

L. reuteri Protectis® – an effective protector

There are strong indications that probiotics can influence gastrointestinal health in Children.[5] Three trials with *Limosilactobacillus reuteri* Protectis have shown positive effects on prevention of infection in children.[3,4,5]

In addition, it has been shown that preventive use of *L. reuteri* Protectis reduced the costs linked to infections for both family and community.[6]

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

Study	Significant fewer days				
	With diarrhoea	With antibiotic use	With fever	Absent from day care	With respiratory tract infection
Gutierrez 2014[6] (n = 336)	√	√	√	√	√
Weizman 2005[3] (n = 128)	√	√	√	√	ns
Augustina 2012[6] (n = 250)	√	√	na	na	ns

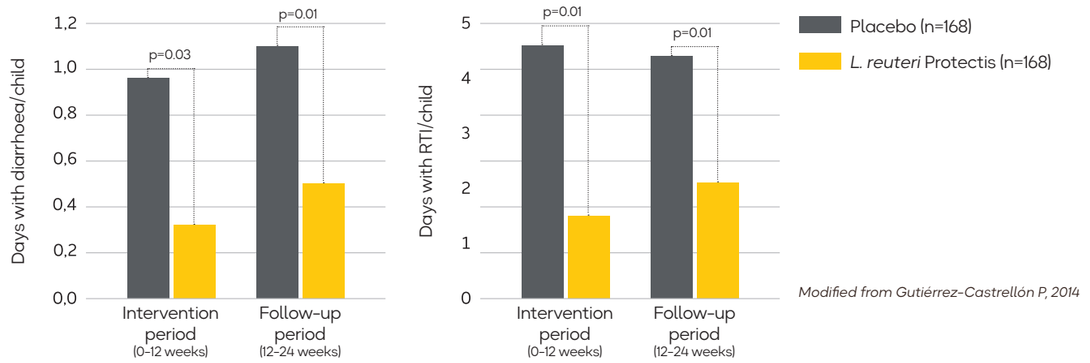
√ = Significant compared to placebo
ns: non-significant
na: not analysed

Less infections with preventive use

In a prospective, randomized, double-blind, placebo-controlled trial in 336 healthy children, 6-36 months attending day care centres, prophylactic use of *L. reuteri* DSM 17938 in reducing the frequency and duration of diarrhoeal episodes as well as other health outcomes were investigated. The children received either *L. reuteri* DSM 17938 drops (1x10^8 CFU/day) or placebo for three months followed by three months without supplementation.

Preventive use of *L. reuteri* Protectis:

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

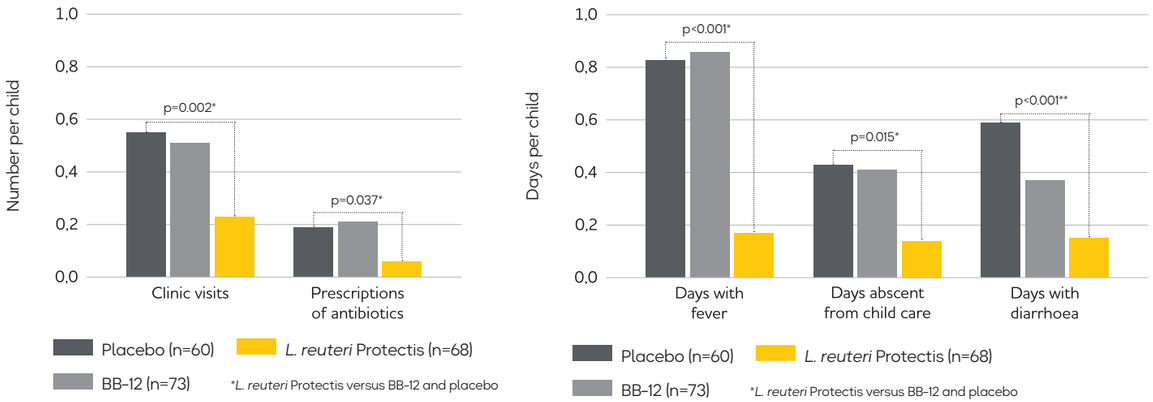


Modified from Gutiérrez-Castrellón P, 2014

Shorter duration of sickness

In a prospective, randomised, double blind and placebo-controlled study, it was investigated whether the prophylactic use of *L. reuteri* Protectis affected the occurrence of infections in infants attending day care. 201 healthy children, aged 4–10 months, were studied for 12 weeks in three different groups: formula with *L. reuteri* ATCC 55730, *Bifidobacterium lactis* BB-12 or without probiotics (placebo).

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

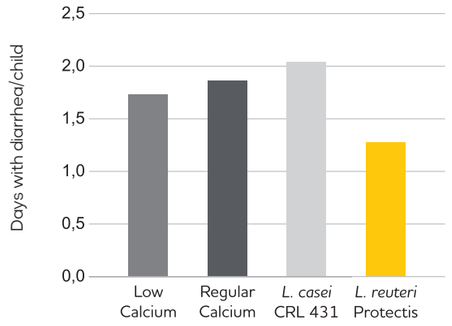


Modified from Weizman Z, 2005

Reduced incidence of diarrhoea

A double-blind, placebo-controlled study performed in 494 healthy children aged one to six years. It was investigated if the addition of probiotics (*L. casei* CRL431 5x10^8 CFU/day or *L. reuteri* Protectis 5x10^8 CFU/day) to milk with regular calcium content would have an effect on the incidence and duration of diarrhoea and/or on acute respiratory tract infections.

- *L. reuteri* Protectis prevented diarrhoea and improved growth (weight and height) during the six-month study period.
- Regular calcium milk alone or with L. casei did not reduce the incidence of diarrhoea.



Modified from Agustina R, 2012

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Antibiotic-Associated Side Effects

Antibiotic-associated side effects are common and usually affect the gastrointestinal system. Symptoms may include diarrhoea, nausea, vomiting, bloating and abdominal pain.[1] These manifestations appear when antibiotics disturb the balance of "good" and "bad" bacteria causing pathogenic bacteria to multiply beyond their normal numbers.

Up to 40% of children receiving broad-spectrum antibiotics get diarrhoea.[2] The high prevalence of side effects might lead to treatment discontinuation with the risk of treatment failure and possible development of antibiotic resistance.

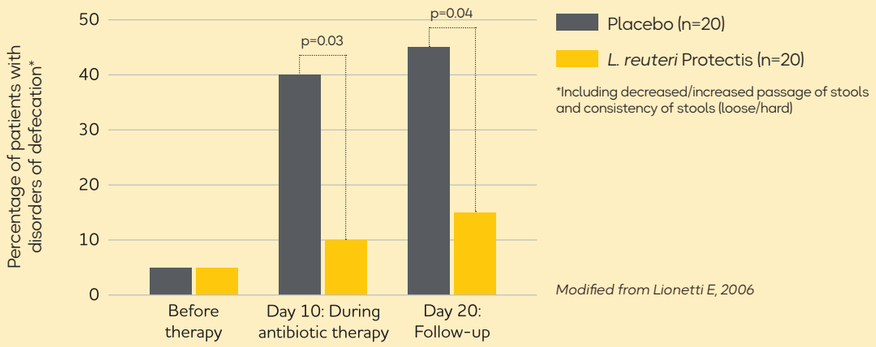
Probiotics are regarded as effective in controlling the overgrowth of potentially pathogenic microorganisms and may help prevent or lower the incidence of antibiotic-associated side effects. Patients are often unwilling to start or comply with any antibiotic therapy if they have previous experience of 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.[3]

75% fewer with defecation disturbances

In a double-blind, placebo-controlled study 69 children, 6-36 months old with acute diarrhoea and with clinical signs of mild to moderate dehydration, were randomised to either five drops of *L. reuteri* DSM 17938 (n=35) or placebo (n=34), twice per day for 7 days. The actual dose of *L. reuteri* DSM 17938 was $2x10^8$ CFU/day.

- *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



Modified from Lionetti E, 2006

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