Clinical Trials with BioGaia Probiotics

BioGaia®

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Welcome to the new edition of Clinical Trials with BioGaia Probiotics. It has been updated with new relevant publications on BioGaia strains published in 2021. In addition, we have added links to all publications that will take you directly to the online abstract.

Enjoy!

Clinical Trials Supporting the Use of BioGaia Probiotics With *Limosilactobacillus* reuteri*

Including:

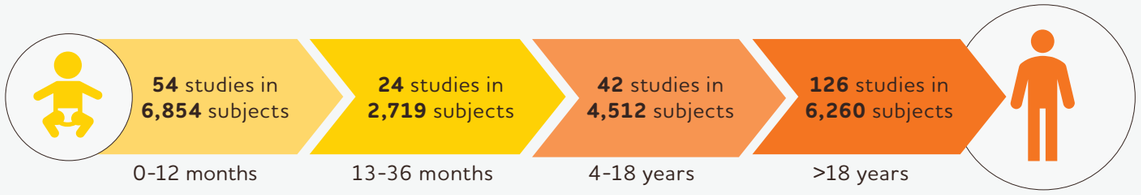
- *L. reuteri* **DSM 17938** = *L. reuteri* Protectis**
- *L. reuteri* **ATCC PTA 5289** + *L. reuteri* **DSM 17938** = *L. reuteri* Prodentis**
- *L. reuteri* **ATCC PTA 6475** + *L. reuteri* **DSM 17938** = *L. reuteri* Gastrus**
- *L. reuteri* **ATCC PTA 4659** = *L. reuteri* **Colus**

** Previously named Lactobacillus*

*** L. reuteri DSM 17938 is derived from L. reuteri ATCC 55730. By removal of two plasmids carrying tet (W) tetracycline and lnu (A) lincosamide resistance genes, the new daughter strain is free from potentially transferable resistance genes.*

Clinical Trials with All BioGaia Probiotics – Per Age Group

246 completed clinical trials in 20 345 individuals



Guidelines Supporting the Use of BioGaia Probiotics

Guidelines for infants and children	Infant colic
The Middle East Expert Consensus, Indrio F et al. 2021	✓
European guidance by EPA/UNEPSA, Hojsak I et al. 2018	✓
World Gastroenterology Organisataion Global guidelines, Guarner F et al. 2017	✓
Asia-Pacific recommendations, Cameron D et al. 2017	✓
Latin America recommendations, Cruchet S et al. 2015	✓

Guidelines for children	Functional abdominal pain
World Gastroenterology Organisation Global guidelines, Guarner F et al. 2017	✓
Management guideline, Korterink J et al. 2015	✓

Guidelines for infants & children	Acute gastroenteritis
ESPGHAN Recommendation update, Szajewska H et al. 2020	✓
FISPGHAN Universal recommendation, Guarino A et al. 2018	✓
World Gastroenterology Organisation Global guidelines, Guarner F et al. 2017	✓
Asia-Pacific recommendations, Cameron D et al. 2017	✓
Latin-America, Emergency Consensus guideline, Iramain R et al. 2017	✓
Latin-America recommendations, Cruchet S et al. 2015	✓
International consensus report, Lo Vecchio A et al. 2016	✓

Guideline for infants & children	Infections in children attending day-care centers
World Gastroenterology Organisation Global guidelines, Guarner F et al. 2017	✓

Guideline for adults	Functional constipation	Antibiotic-associated diarrhoea	*Helicobacter pylori* infection (adjuvant therapy)
World Gastroenterology Organisation Global guidelines, Guarner F et al. 2017	✓	✓	✓

New
Clickable links!

Infant Colic - Treatment

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Mi G-L, 2015 China	Evaluate the effects of *L. reuteri* DSM 17938 on colicky infants < 4 months old, exclusively or predominantly breastfed: on rate of treatment success, reduction in daily crying time, parent satisfaction and maternal depression.	R, DB, PC 4 weeks	*L. reuteri*: 20 ($1x10^8$ CFU) Placebo: 19	Significant effects compared to placebo: · Treatment success (≥ 50% reduction of crying time vs. baseline) was 100% in the *L. reuteri* group vs. 16% in the placebo group. · Reduction in mean daily crying time (from 201 to 32 min/d in the *L. reuteri* group vs. 201 to 121 min/d in the placebo group). Differences were significant at each weekly evaluation. · Parental satisfaction (100% vs 16% in the placebo group). · Improved maternal depression scores throughout the study period (Edinburgh postnatal depression scale). · No report of adverse effects in any of the groups.
Chau K, 2015 Canada	Investigate the efficacy of *L. reuteri* DSM 17938 for the treatment of infant colic in breastfed infants ≤ 6 months.	R, DB, PC 21 days	*L. reuteri*: 24 ($1x10^8$ CFU) Placebo: 28	Compared to placebo: · *L. reuteri* significantly improved colic symptoms by reducing median crying and fussing times at days 7, 14 and 21. · The rate of responders (50% reduction in daily crying time) was significantly higher in the *L. reuteri* group compared with the control group at day 21.
Szajewska H 2013 Poland	Efficacy of *L. reuteri* DSM 17938 on infant colic in infants younger than 5 months, exclusively or predominantly breastfed. Effect on screaming intensity and family quality of life. The trial included follow-up one week after termination of ingestion of the study product.	R, DB, PC 21 days + 7 days follow-up	*L. reuteri*: 40 ($1x10^8$ CFU) Placebo: 40	· *L. reuteri* significantly reduced daily crying time compared to placebo · Significantly more responders on day 7, 14, 21 and 28 (follow-up) compared to placebo · Parents' rating of screaming intensity and family quality of life was significantly decreased and increased, respectively, atall time points
Savino F, 2010 Italy	To study the effect of *L. reuteri* DSM 17938 on infant colic in infants 2–16 weeks old, and investigate changes in the faecal microbiota.	R, DB, PC 21 days	*L. reuteri*: 25 ($1x10^8$ CFU) Placebo: 21	· *L. reuteri* significantly reduced daily crying time compared to placebo · Significantly more responders on day 7, 14 and 21 compared to placebo · Reduced faecal *E. coli* and increased counts of lactobacilli in the *L. reuteri* group only
Savino F, 2021 Italy New!	To examine urinary metabolomic fingerprints and crying time in colicky breastfed infants.	R, DB, PC 28 days.	*L. reuteri*: 16 ($1x10^8$ CFU) Placebo: 16	Compared to placebo *L. reuteri* significantly reduced daily crying time from day 0 to day 28. Furthermore, *L. reuteri* was linked to an increase of urinary metabolites that might be related to an improvement of gut absorption.
Savino F, 2019 Italy	To investigate CC-Chemokine Receptor 7 (CCR7) and interleukin 10 (IL-10) expression in breastfed colicky infants treated with *L. reuteri* DSM 17938. The secondary outcome was to evaluate crying time.	R, DB, PC 28 days	*L. reuteri*: 21 ($1x10^8$ CFU) Placebo: 25	Compared to placebo *L. reuteri* significantly: · Increased expression of CCR7 · Reduced crying time No difference was observed for IL-10 after the study period in either group. The increased expression of CCR7 could be a response to the probiotic treatment, suggesting that this could be part of the mechanism for the positive effects on colic by *L. reuteri*.
Savino F, 2018a Italy	To evaluate crying time, changes in mRNA levels of transcription factors RORγ (Th17 cell marker) and FOXP3 (Treg marker), and to investigate gut microbiota and faecal calprotectin in infants treated with *L. reuteri* DSM 17938 for infant colic.	R, DB, PC 30 days	*L. reuteri*: 32 ($1x10^8$ CFU) Placebo: 28	Compared to placebo *L. reuteri* significantly: · Reduced crying time · Increased FOXP3 concentration, resulting in a decreased RORγ/FOXP3 mRNA ratio · Reduced faecal calprotectin
Savino F, 2018b Italy	To investigate levels of Treg cells and TLR2 and TLR4 mRNA expression in infants with and without colic (<60 days old). The secondary outcome was the impact of *L. reuteri* DSM 17938 on Treg and TLR mRNA expression.	R, DB, PC 28 days	Control group without colic: 25 With colic: *L. reuteri*: 18 ($1x10^8$ CFU) Placebo: 16	· At baseline there were no differences in mRNA levels of Treg cells, TLR2 or TLR4 between infants with or without colic. · *L. reuteri* significantly decreased crying time (302.3±19.86 min/day on day 0 vs 76.75±22.15 min/day on day 28, P=0.001) and increased FoxP3 mRNA expression. · TLR2 and TLR4 mRNA expression increased in both groups.
Sung V, 2014 Australia	Efficacy of *L. reuteri* DSM 17938 on infant colic in infants < 3 months, with mixed feeding types. Colic defined as daily combined screaming or fussing of 180 minutes or more. Maternal mental health and family quality of life (QoL) were also studied.	R, DB, PC 28 days + follow-up at 6 months	*L. reuteri*: 67 ($1x10^8$ CFU) Placebo: 60 Other probiotics than *L. reuteri* were allowed for mothers and/or infants, and also use of proton pump inhibitor	Compared to placebo: · At day 28 mean values: 49 min more daily screaming + fussing time in the *L. reuteri* group ($p<0.02$), due to more fussing time in this group · At day 28 median values: no difference · No difference in duration of screaming time · No difference in number of episodes of screaming/fussing, or in sleeping time · No difference between groups in family QoL or maternal mental health
Savino F, 2007 Italy	Efficacy on infant colic in infants 11–80 days old.	R, open 28 days	*L. reuteri*: 41 ($1x10^8$ CFU) Simethicone: 42	· *L. reuteri* significantly reduced daily crying time compared to simethicone · On day 28, 95% were responders in the probiotic group vs. 7% in the simethicone group

Infant Colic - Treatment

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Martinelli M, 2017 Italy	To compare the effectiveness of three alternative treatments of infant colic: A) a mixture of standardized extract of *Matricaria chamomilla* L., *Melissa officinalis* L. and tyndallized *Lactobacillus acidophilus* (H122) compared with B) *Lactobacillus reuteri* DSM 17938, and C) simethicone.	R, Open, multi-centre, 21 days + 7 days of follow-up	*L. reuteri*: 45 ($1x10^8$ CFU) Herbs + tyndallized *L. acidophilus*: 45 Simethicone: 43	· Rate of treatment success was significantly greater in Group A and B, 30/45 and 31/45, respectively vs. 19/43 in group C. · Mean daily crying time was significantly reduced in both Group A (from 211.3 ± 40 min/day to 69.6 ± 59 min/day) and in Group B (from 201.6 ± 32.5 min/day to 58.1 ± 48.9 min/day) vs. Group C (from 199.5 ± 32 min/day to 106 ± 56.5 min/day). · No significant difference was observed between Group A and B ($p = 0.4$). · No adverse events were reported in any of the groups.
Karadag N, 2012 (abstract) Turkey	Efficacy on infant colic and mother's postpartum depression comparing *L. reuteri* DSM 17938 with herbal drops and sterile water. Baby massage was practiced in all three groups.	R, open 21 days + follow-up of mother's mental health after 2 months	*L. reuteri*: 25 ($1x10^8$ CFU) Herbal drops: 24 Sterile water: 25	· *L. reuteri* and sterile water significantly reduced daily crying time compared to herbal drops at three weeks · At three weeks the daily crying time was 35 minutes in the *L. reuteri* group compared to 188 minutes in the sterile water group and 300 min in the herbal drops group · A significant drop in depression and anxiety scores were seen only for mothers in the *L. reuteri* group at the follow-up at two months

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Twelve Meta-Analyses Support the Efficacy in Infant Colic

Reviews with meta-analysis of *L. reuteri* effects	Number of trials	Effect in breastfed infants	Effect in mixed fed infants	Effect in formula-fed infants	Safe to use
Dos Reis Buzzo Zermiani AP et al. 2021	8	✓	NA	No	✓
Ellwood J et al. 2020	32[1]	✓	No statement	No	✓
Skonieczna-Żydecka K et al. 2020	16	✓	✓	No	✓
Sung V et al. 2018 (Individual participant data meta-analysis, IPDMA)	4	✓	✓	No	✓
Gutiérrez-Castrellón P et al. 2017	5[1]	✓[2]	✓[2]	✓[2]	Not evaluated
Dryl R, Szajewska H 2017	5	✓	✓	No	Not evaluated
Schreck Bird A et al. 2017	5	✓	✓	More studies needed	✓
Harb T et al. 2016	6[1]	✓	✓	More studies needed	✓
Xu M et al. 2015	5	✓	No statement	More studies needed	✓
Urbańska M, Szajewska H 2014	3	✓	✓	More studies needed	✓
Sung V et al. 2013	3	✓	No statement	More studies needed	✓
Anabrees J et al. 2013	3	✓	Possibly	More studies needed	✓

[1] *Analysis includes different managements of infant colic*
[2] *No subgroup analysis according to feeding mode*

Infant Colic - Prevention

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Indrio F, 2014 Italy	Investigate if oral supplementation with *L. reuteri* DSM 17938 during the first 3 months of life can reduce the onset of colic, gastroesophageal reflux, and constipation in term newborns, and in addition reduce the socio-economic impact of these conditions.	R, DB, PC 90 days Multicentre study	*L. reuteri*: 238 ($1x10^8$ CFU) Placebo: 230	Compared to placebo: · Daily administration of *L. reuteri* early in life reduced the duration of daily inconsolable type of crying, frequency of regurgitation, and incidence of functional constipation in the first 3 months of life · Private and public costs for the management of these conditions were significantly reduced for infants receiving *L. reuteri*
Savino F, 2015a Italy	Test the preventive effect of *L. reuteri* DSM 17938 combined with vitamin D, on infant colic.	12 weeks Randomized, open label study, blinded outcome analyst. Commercial vitamin D drop product as the comparator.	*L. reuteri* + vit. D: 51 ($1x10^8$ CFU) Vit. D only: 54	Prevention of colic was significantly more successfully achieved in the *L. reuteri* group compared with the control group. The effect was indirectly measured, and demonstrated by significantly less use of pain-relieving agents, contacts with doctor (calls and visits due to symptoms of colic), and change of feeding to partially or exclusively infant formula.

Functional Abdominal Pain (FAP) in Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Jadrešin O, 2020 Croatia	To investigate the effect of *L. reuteri* DSM 17938 in the treatment of functional abdominal pain (FAP) in children aged 4-18 years. This study was performed after interim analysis of Jadrešin 2017 in order reach the initial targeted sample size.	R, DB, PC 3 months + 1 month follow up	*L. reuteri*: 24 ($1x10^8$ CFU) Placebo: 22	Compared to placebo, *L. reuteri* significantly: · increased days without pain · reduced intensity of pain at 4 months Pooled data from both studies confirmed increased days without pain and reduced severity of pain.
Weizman Z, 2016 Israel	To assess the efficacy of *L. reuteri* DSM 17938 on functional abdominal pain (FAP) in children aged 6-15 years, with the primary outcomes frequency and intensity of abdominal pain. Intensity measured by Hicks face scoring system, ranking 0=no pain and 10=very severe pain.	R, DB, PC 4 weeks + 4 weeks of follow-up	*L. reuteri*: 47 ($1x10^8$ CFU) Placebo: 46	Compared to placebo: · Frequency of pain was significantly reduced at 4 weeks with 1.9 vs. 3.6 episodes/week in the *L. reuteri* and placebo group, respectively. · Intensity of pain was significantly reduced during the supplementation: 4.3 vs. 7.2 on Hicks scale. This effect that was sustained at the follow-up at 8 weeks: 4.8 vs. 6.4. · For other GI symptoms there was a significant reduction in the incidence of abdominal distention and bloating in the *L. reuteri* group.
Romano C, 2014 Italy	To study if *L. reuteri* DSM 17938 affect functional abdominal pain in children aged 6-16 years.	R, DB, PC 4 weeks suppl.+ 4w follow-up	*L. reuteri*: 30 ($2x10^8$ CFU) Placebo: 26	· Significantly reduced severity of abdominal pain during *L. reuteri* intake ·Reduction in pain sustained up to 4 weeks after cessation of *L. reuteri* · Pain frequency decreased significantly during the 8 weeks in both groups
Rahmani P, 2020 India	To investigate the effect of *L. reuteri* DSM 17938 in the treatment of Recurrent Abdominal Pain in children 6 to 16 years.	R, DB, PC 4 weeks	*L. reuteri*: 65 ($2x10^8$ CFU) Placebo: 60	Compared to placebo, *L. reuteri* significantly: · decreased the frequency, severity and duration of abdominal pain · improved the pain pattern
Jadrešin O, 2017 Croatia	To investigate the effect of *L. reuteri* DSM 17938 in the treatment of functional abdominal pain (FAP) and irritable bowel syndrome (IBS) in children aged 4-18 years.	R, DB, PC 3 months + 1 month of follow-up	*L. reuteri*: 26 ($1x10^8$ CFU) Placebo: 29	Results of interim analysis of the study: · Significant increase in days free of pain in the *L. reuteri* group compared to placebo: 80% vs. 46% of study days. · Both groups showed significant reduction in severity of pain compared to baseline. · Results suggest an effect of *L. reuteri* also in children with IBS.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Functional Abdominal Pain (FAP) in Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Maragkoudaki M, 2017 Greece, Slovenia, Poland	Multicenter trial to assess the effect of *L. reuteri* DSM 17938 in children with functional abdominal pain, mean age 9y. Primary outcome was pain frequency and intensity. Secondary outcomes: other GI symptoms, need for drugs to relieve pain, child school and adult work absenteeism, treatment success (> 50% reduction in pain score).	R, DB, PC 4 weeks + 4 weeks follow-up	*L. reuteri*: 27 ($2x10^8$ CFU) Placebo: 27	Compared to baseline, *L. reuteri* significantly decreased child school and adult work absenteeism as well as the use of drugs to relieve pain. This was not seen in the placebo group. Comment: The study was underpowered for detection of significant differences between the two groups, due to premature closure of the study based on very slow inclusion rate.
Eftekhari K, 2015 Iran	To assess the effect of *L. reuteri* DSM 17938 in the treatment of functional abdominal pain (FAP) in children aged 4-16 years.	R, DB, PC 4 weeks + 4 weeks of follow-up	*L. reuteri*: 40 ($1x10^8$ CFU) Placebo: 40	There were no differences between the groups in pain frequency, pain severity or 'associated gut symptoms' during the intervention and the follow-up periods. Within both groups, there was a significant reduction in pain frequency and severity from baseline to end of the intervention period. Study limitations: There is no account of type of placebo, and report of outcomes is not consistent.

Functional Abdominal Pain in Children - Meta-Analysis

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Trivić I, 2020 Crotatia	Evaluate strain-specific probiotic effects on functional abdominal pain in children.	9 RCTs: Gawronska 2007, Francavilla 2010, Romano 2010, Sabbi 2011, Eftekhari 2015, Weizman 2016, Jadrešin 2017, Maragkoudaki 2017, Jadrešin 2020	Systematic review and meta-analysis *L. rhamnosus* GG (LGG) and *L. reuteri* DSM 17938 were the only probiotic strains evaluated.	· Compared to placebo, *L. reuteri* DSM 17938 significantly reduce pain intensity and increase number of days without pain · No significant benefit of LGG supplementation in the treatment of FAP · Further trials regarding long-term outcomes, possibly involving longer interventions, are needed

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Regurgitation in Infants

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Indrio F, 2011 Italy	To evaluate the efficacy of *L. reuteri* DSM 17938 on gastric function in full term formula-fed infants with ≥ 4 regurgitation episodes/day.	R, DB, PC 30 days	*L. reuteri*: 19 (1x10^8 CFU) Placebo: 15	· *L. reuteri* significantly reduced regurgitation episodes by 50% · *L. reuteri* significantly increased gastric emptying rate at 30 days compared to baseline
Papagaroufalis K, 2014 Greece	To assess the safety of infant formula containing *L. reuteri* DSM 17938 during the first month of life, with special reference to D-lactic acid, in comparison to infants fed a control formula. Other outcomes were GI tolerance, sleeping and crying behaviour, growth and occurrence of adverse events.	R, DB, PC 28 days Follow-up on days 112 and 168	*L. reuteri*: 36 (1x10^8 CFU) Control: 35 31 infants in each group took part in the follow-up on days 112 and 168	Compared to control formula: · Regurgitation episodes were significantly fewer in the *L. reuteri* group · The probiotic group had significantly lower frequency of hard stools and higher percentage of soft stools at day 28
Indrio F, 2017 Italy	To evaluate the efficacy of a partially hydrolyzed whey protein formula containing additional starch and *L. reuteri* (Lr) on frequency of regurgitation and gastric emptying in infants with functional regurgitation. Gastric emptying rate (GErate), measured by ultrasound, was defined as reduction in antral cross-sectional area in relation to ingestion of meal, at time 0 and after 120 min.	R, DB, PC 4 weeks	Thickened, partially hydrolyzed formula + *L. reuteri*: 37 (2.8x 10^6 CFU/g powder) Standard formula: 35	Compared to control, *L. reuteri* significantly reduced daily regurgitations (baseline vs. day 28): · 7.4 vs. 2.6 in the Lr group · 7.5 vs. 5.3 in control group GErate percentage change between week 0 and week 4 was significantly higher in the *L. reuteri* group compared to controls: median 12.3% and 9.1%, respectively.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Functional Gastrointestinal Disorders (FGIDs)

Functional Constipation in Infants and Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Coccorullo P, 2010 Italy	To evaluate the effect of *L. reuteri* DSM 17938 in 6-12 months old infants with chronic functional constipation.	R, DB, PC 8 weeks	*L. reuteri*: 22 (1x10^{8}CFU) Placebo: 22	*L. reuteri* significantly improved: · Defecation frequency compared to placebo · Faecal consistency compared to baseline
Kubota M, 2020 Japan	To evaluate the efficacy of *L. reuteri* DSM 17938 and MgO on chronic functional constipation in children 6 months to 6 years.	R, DB, PC parallel-group, 4 weeks	1) *L. reuteri* + MgO placebo: 20 2) *L. reuteri* + MgO: 19 3) MgO + *L. reuteri* placebo: 21 (*L. reuteri*: 2x10^{8}CFU; MgO: 30 mg/kg bw)	All groups experienced a significant improvement in defecation frequency at week 4. *L. reuteri* and MgO were equally effective in the management of functional constipation in young children.
Contreras AAG, 2020 Mexico	To assess the efficacy of a probiotic (*L. reuteri* DSM 17938), a prebiotic (agave inulin) or symbiotic (both), on stool characteristics in children with cerebral palsy (CP) and chronic constipation, aged 14 to 60 months.	R, DB, PC 28 days	1) *L. reuteri* + agave inulin placebo: 10 2) Agave inulin + *L. reuteri* placebo: 10 3) *L. reuteri* + agave inulin: 10 4) *L. reuteri* placebo + agave inulin placebo: 7 (*L. reuteri*: 1x10^8 CFU; agave inulin: 4 g)	Both *L. reuteri* and agave inulin improved stool characteristics and constipation in children with CP. In addition, *L. reuteri* improved intestinal motility and lowered stool pH.
Olgac B, 2013 Turkey	To evaluate the effects of *L. reuteri* DSM 17938 and lactulose, respectively, on functional constipation in children aged 4-16 years. In addition, Quality of life (QoL) and perception of disease was assessed at baseline and at the end of treatment by both the children and parents, and compared to QoL of a healthy group of children.	R, open 4 weeks	*L. reuteri*: 25 (1x10^{8}CFU) Lactulose: 28 (1mg/kg/d) Control group of healthy children for comparison of QoL: 50	*L. reuteri* was equal to lactulose in significant improvement compared to baseline, in: · Frequency of defecation · Stool consistency · Abdominal pain, painful defecation and stool-withholding behaviour *L. reuteri* was significantly more effective compared to lactulose in reduction of: · Abdominal pain · Flatulence From the parents' perspective, QoL and perception of disease was significantly improved in the lactulose group but not in the *L. reuteri* group. Children's scores of QoL and perception of disease were significantly increased in both groups, and to the level of healthy children.
Zaja O, 2021 Croatia **New!**	To investigate the effect of *L. reuteri* DSM 17938 on constipation in children and adolescents with anorexia nervosa (AN).	R, DB, PC 12 weeks + 12w follow-up	*L. reuteri*: 15 (1x10^8 CFU) Placebo: 16	· At 12 weeks, stool was normalized in the majority of patients of both groups, without statistical difference. · At follow-up, significantly more subjects in the Lr group had normalized frequency of defecation and body weight (93% and 63%, respectively, p=0.04). · Recovery of bone health and serum vit. D levels showed a stronger positive trend in the Lr group vs. the placebo group.
Papagaroufalis K, 2014 Greece	To assess the safety of infant formula containing *L. reuteri* DSM 17938 during the first month of life, with special reference to D-lactic acid, in comparison to infants fed a control formula. Other outcomes were GI tolerance, sleeping and crying behaviour, growth and occurrence of adverse events.	R, DB, PC 28 days Follow-up on days 112 and 168	*L. reuteri*: 36 (1x10^8 CFU) Control: 35 31 infants in each group took part in the follow-up on days 112 and 168	Compared to control formula: · Regurgitation episodes were significantly fewer in the *L. reuteri* group · The probiotic group had significantly lower frequency of hard stools and higher percentage of soft stools at day 28
Wegner A, 2018 Poland	Assess if functional constipation in children aged 2-7y, with prior failure of ordinary constipation treatment, could be relieved by use of *L. reuteri* DSM 17938 as an adjunct to treatment with macrogole (=PEG, polyethylene glycol).	R, DB, PC 8 weeks	*L. reuteri* + PEG: 59 (1x10^8 CFU) Placebo + PEG: 62	*L. reuteri* had no additional effect to the treatment with macrogole on mean number of bowel movements (BM) per week (7.5±3.3 vs 6.9±2.5, in the active and placebo group, respectively) or number of patients who increased their frequency of BM. The incidence of constipation-related GI symptoms was the same between groups.
Jadrešin O, 2018 Croatia	Investigate the additional effect of *L. reuteri* to lactulose in the treatment of functional constipation.	R, DB, PC 12 weeks + 4 weeks follow-up	*L. reuteri* + lactulose: 18 Placebo + lactulose: 15 (*L. reuteri*: 1x10^8 CFU; lactulose: 1-3 ml/kg/day)	No additional benefit of *L. reuteri* together with lactulose in the treatment of functional constipation. Due to slow recruitment rate the study was terminated prematurely, and therefore the results should be interpreted with caution.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Prevention of FGIDs in Infants

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Indrio F, 2014 Italy	Investigate if oral supplementation with *L. reuteri* DSM 17938 during the first 3 months of life can reduce the onset of colic, gastroesophageal reflux, and constipation in term newborns, and in addition reduce the socio-economic impact of these conditions	R, DB, PC 90 days Multicentre study	*L. reuteri:* 238 ($1x10^8$ CFU) Placebo: 230	Compared to placebo: · Daily administration of *L. reuteri* early in life reduced daily inconsolable type of crying, frequency of regurgitation, and incidence of functional constipation in the first 3 months of life · Private and public costs for the management of these conditions were significantly reduced for infants receiving *L. reuteri*

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Constipation in Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Riezzo G, 2018 Italy	To study the effect of a 15-week supplementation of *L. reuteri* DSM 17938 in adults with chronic functional constipation and normal colonic transit time. Primary outcome was change in Constipaq score (constipation symptoms and quality of life). Secondary outcomes were constipation symptom item's scores. Mean age 44 years.	R, DB, PC 105 days	*L. reuteri:* 28 (Induction period, 15 days: $4x10^8$ CFU=4 tablets Standard dose, 90 days: $2x10^8$ CFU=2 tablets) Placebo: 28	Compared to the placebo group at day 105, *L. reuteri* significantly: · Reduced the Constipaq score, which includes quality-of-life evaluation ($p<0.0001$) · Reduced symptoms related to gas production and dysbiosis (incomplete defecation, abdominal discomfort, pain, and bloating) · Reduced the need of laxatives *L. reuteri* had no effect on stool consistency.
Riezzo G, 2019 (substudy of Riezzo 2018) Italy	To evaluate pathophysiological aspects = serum concentrations of GI neuropeptides serotonin (5-HT) and brain-derived neurotrophic factor (BDNF) and their association with changes in symptoms and quality-of-life scores during intake of *L. reuteri* DSM 17938 or placebo in adults with chronic functional constipation (FC). Results on symptoms and quality of life (QoL) in this cohort of patients are previously published in Riezzo et al. 2018.	R, DB, PC 105 days	See information above. Additional group of healthy controls, n= 20, for comparison of serum levels of 5-HT and BDNF	· Baseline serum levels of 5-HT were significantly higher in FC subjects compared to healthy controls · 5-HT and BDNF were significantly reduced compared to placebo at the end of intervention (day 105) · 5-HT in the Lr group was reduced by 24% ($p<0.008$) to a level non-significant from that of healthy controls, and significantly different from placebo ($p<0.04$), on day 105. · Neither 5-HT nor BDNF serum levels showed correlation with the symptoms or QoL scores.
Ojetti V, 2014 Italy	The effect of *L. reuteri* DSM 17938 on functional constipation in adults of mean age 35.6 (± 15) years	R, DB, PC 4 weeks	*L. reuteri:* 20 ($2x10^8$ CFU) Placebo: 20	· Frequency of defecation per week was significantly increased at week 4 compared to placebo · Stool consistency was somewhat improved but without significant difference compared to baseline or compared to placebo
Ojetti V, 2017 Italy	The effect of *L. reuteri* DSM 17938 on production of methane (CH_4) in adults with functional constipation. Methane production of >5 ppm during a H_2/CH_4 lactulose breath test (LBT). Mean age 36y.	Open, no control group 4 weeks	*L. reuteri:* 20 ($2x10^8$ CFU)	· Compared to baseline, there was a significant reduction in the CH_4 production by *L. reuteri:* 8.9 ± 8.6 ppm vs. 20.8 ± 15 ppm, and on AUC value (Area Under the Curve): 2128.4 vs. 5101.5. · 11 patients (55%) ceased to produce methane (<5 ppm). · Bowel movements/week were significantly increasedcompared to baseline: 6.4 ± 0.7 vs. 4.1 ± 1.2.

Irritable Bowel Syndrome (IBS)

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Niv E, 2005 Israel	To evaluate *L. reuteri* for treatment of mixed type IBS in adults.	R, DB, PC 6 months	*L. reuteri:* 27 ($2x10^8$ CFU) Placebo: 27	Compared to placebo, *L. reuteri* showed strong tendency to effect on: · Reduced gases · Reduced constipation Study limitations: underpowered, due to only one study center of two started and completed the study

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

AGE Treatment in Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Ruzhentsova TA, 2018 Russia	Comparison of BioGaia ORS with *L. reuteri* DSM 17938 and zinc vs. ORS product Rehydron + *Bifidobacterium bifidum*, for treatment of acute gastroenteritis in hospitalized children, 5 mo -13y. In addition to ORS, intestinal sorbents, antimicrobial and antipyretic therapy were used.	R, open Product ingested until cessation of diarrhoea	*L. reuteri*: 30 ($1x10^9$ CFU/ sachet/250mL individualized dosage) Rehydron: 30 individualized dosage *B. bifidum:* <1y: $1x10^8$ CFU 2-3 times/d, >1y: $5x10^8$ 2-3 times/d	Compared to Rehydron + *B. bifidum*, BioGaia ORS: · Significantly reduced duration of diarrhoea by 0.9 days 2.2 vs. 3.1 days) · Abdominal pain ended significantly faster in the BioGaia ORSgroup: 0.3 days vs. 1.9 days. · Acceptance of the BioGaia ORS was 100% vs. 73% (22/30) of Rehydron
Dinleyici EC, 2014 Turkey	The efficacy of *L. reuteri* DSM 17938 in children aged 3 – 60 mo, and hospitalized for acute diarrhoea. Both groups of children received conventional rehydration therapy, but the control group received no probiotic.	R, single blinded (effects analyst) 5 days	*L. reuteri*: 64 ($1x10^8$ CFU) Control: 63	Compared to controls: · *L. reuteri* significantly reduced the duration of diarrhoea · The proportion of children with watery diarrhoea after 48h and 72h was significantly reduced · Duration of hospital stay was significantly reduced · Prolonged diarrhoea was only reported in the control group of children
Dinleyici EC, 2015 Turkey	The efficacy of *L. reuteri* DSM 17938 in children aged 3 – 60 mo, and treated as outpatients for acute diarrhoea. Both active and control group of children received conventional rehydration therapy, but the control group received no probiotic.	R, single blinded (effects analyst) 5 days	*L. reuteri*: 29 ($1x10^8$ CFU) Control: 31	Compared to controls: · *L. reuteri* significantly reduced the duration of diarrhoea · At 48h the proportion of children with watery diarrhoea was significantly reduced From the 72nd hour of intervention, there was no difference between the two groups in the percentage of children with watery diarrhoea
Francavilla R, 2012 Italy	Effect on acute gastroenteritis caused by rotavirus in children 6-36 months old, and hospitalized due to clinical signs of mild to moderate dehydration.	R, DB, PC 7 days	*L. reuteri*: 35 ($2x10^8$ CFU) Placebo: 34	Compared to placebo *L. reuteri* significantly: · reduced the duration of diarrhoea by 1.2 days · the frequency of watery diarrhoea was significantly reduced on treatment days 2 and 3 · the number of children with normal stool consistency was significantly higher on days 2 and 3
Eom T-H, 2005 South Korea	Reduction of symptoms in children hospitalized for acute gastroenteritis and aged 6 mo – 3y.	R, DB, PC 5 days or until discharged	*L. reuteri*: 25 ($2x10^8$ CFU) Placebo: 25	*L. reuteri* significantly reduced: · frequency of watery diarrhoea · frequency of vomiting · hospital stay
Shornikova A, 1997a Finland	Treatment of children hospitalized for acute gastroenteritis and aged 6 mo – 3y.	R, DB, PC 5 days or until discharged	*L. reuteri*: 19 ($1x10^{10}$–$1x10^{11}$ CFU) Placebo: 21	*L. reuteri* significantly reduced: · frequency of watery diarrhoea · frequency of vomiting
Shornikova A, 1997b Finland	Treatment of children hospitalized for acute rotavirus gastroenteritis and aged 6 mo – 3y.	R, DB, PC 5 days or until discharged	*L. reuteri*: 21 ($1x10^{10}$ CFU) *L. reuteri*: 20 ($1x10^7$ CFU) Placebo: 25	*L. reuteri* in the high dose significantly reduced: · duration of watery diarrhoea · frequency of diarrhoea Positive, but non-significant, effects were seen also in the low dose group compared to placebo
Pernica JM, 2017 Botswana	Pilot trial to verify the feasibility of a trial designed to measure the benefits of rapid enteric diagnostic testing (REDT) and *L. reuteri* DSM 17938 on acute gastroenteritis, recurrence of diarrhoea and growth in children aged 2-60 mo. and admitted to hospital. In addition, the children were treated with standard rehydration therapy, zinc, and targeted antimicrobial treatment if indicated.	R, DB, PC 60 days	1. *L. reuteri* + REDT: 18 ($1x10^8$ CFU = 5 drops/d) 2. Placebo + RETD: 17 3. *L. reuteri* + standard care: 15 ($1x10^8$ CFU = 5 drops/d) 4. Placebo + standard care: 20	Rapid enteric diagnostic testing and *L. reuteri* supplementation for 60 days was associated with a significant increase in 60-day adjusted standardized height and significantly less recurrent diarrhoea compared to standard care and placebo treatment. Conclusions: Rapid diagnostics and *L. reuteri* DSM 17938 therapy hold promise for the treatment of gastroenteritis and the prevention of stunting in children living in high-burden settings.
Maragkoudaki M, 2018 Greece	The efficacy of an oral rehydration solution (ORS) enriched with *L. reuteri* DSM 17938 and zinc, in children treated as outpatients for acute diarrhoea. The control group received an ORS of similar osmolarity but without the probiotic and zinc. Mean age of the children was 1.8 years.	R, DB, PC 5 days	*L. reuteri*: 28 ($\approx 7x10^8$ CFU/first 4 hours*) Control: 23 * 1 sachet of the probiotic ORS contained $1x10^9$ CFU, to be blended with 250 mL of water	All of the outcomes showed a trend to superiority in the *L. reuteri* + zinc-ORS group without reaching statistical significance compared to control for any of them. The study enrolled too few subjects to be able to show any statistically significant differences between groups.
Szymański H 2019 Poland	Effects of *L. reuteri* DSM 17938 as an adjunct to oral rehydration therapy of children younger than 5 years, hospitalized for acute diarrhoea lasting ≤ 5 days.	R, DB, PC 5 days Followed-up for 3 days to investigate any recurrence of diarrhoea	*L. reuteri*: 44 ($2x10^8$ CFU) Control: 47	Compared to placebo, the effects of *L. reuteri* were: · Duration of diarrhoea was unaffected · Duration of hospital stay was significantly reduced by 6h. This effect was more pronounced in children unvaccinated against rotavirus (75% of the study population) with a reduction of almost 10h ($p<0.025$). · No difference in other outcomes including adverse events

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Acute Gastroenteritis (AGE)

AGE Treatment in Children - Meta-Analysis

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Patro-Gołąb B, 2019	To systematically update evidence on the effectiveness of *L. reuteri* DSM 17938 in the treatment of AGE in children. The review was initiated as part of the update of the guidelines for the use of probiotics in the management of AGE in children.	4 RCTs: Dinleyici 2014, Dinleyici 2015, Francavilla 2012, Szymański H 2019	Meta-analysis	The addition of *L. reuteri* DSM 17938 to standard rehydration therapy (compared with placebo or no intervention): · reduced duration of diarrhoea by 21h · reduced hospitalization with 13h The findings may inform guideline development groups about the efficacy of *L. reuteri* DSM 17938 for treating children with AGE.

AGE Prevention in Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Gutiérrez-Castrellón P, 2014 Mexico	Evaluate if daily administration of *L. reuteri* DSM 17938 reduces the frequency and duration of diarrhoea episodes and respiratory tract infections (RTI) in Mexican day school children aged 6-36 months. A cost-effectiveness analysis was also made.	R, DB, PC 3 months of intervention, follow-up at 6 months	*L. reuteri*: 168 ($1x10^8$ CFU) Placebo: 168	Compared to placebo: · *L. reuteri* significantly reduced the frequency and duration of episodes of diarrhoea and respiratory tract infection at both 3 and 6 months · he number of doctor visits, antibiotic use, absenteeism from day school and parental absenteeism from work were significantly reduced · The use of *L. reuteri* was associated with a reduction of costs by 36 US dollars (USD) for each case of diarrhoea, and by 37 USD for each case of RTI
Weizman Z, 2005 Israel	Prevention of common infections in day-care children 4–10 months old.	R, DB, PC 12 weeks	*L. reuteri*: 68 ($1.2x10^9$ CFU) Bb-12: 73 ($1.2x10^9$ CFU) Control: 60	*L. reuteri* significantly reduced (compared to Bb-12 and control): · Days with fever · Need to consult doctor and need of antibiotics · Absence from day-care Both probiotics significantly reduced: · Episodes with fever · Episodes and days with diarrhoea
Agustina R, 2012a Indonesia	To investigate milk with low and regular calcium content, respectively, and the addition of probiotics (*L. reuteri* DSM 17938 or *L. casei* CRL431) to milk with regular calcium content, on the incidence and duration of diarrhoea and acute respiratory infections in healthy Indonesian children, 1–6y old.	R, DB, PC 6 months	*L. reuteri*: 124 ($5x10^8$ CFU) *L. casei*: 120 ($5x10^8$ CFU) Low calcium milk: 124 Regular calcium milk: 126	Only *L. reuteri* significantly reduced: · Incidence of diarrhoea in children with lower nutritional status, irrespective of definition of diarrhoea · Incidence of diarrhoea in all children when diarrhoea was defined as ≥ 2 loose/liquid stools/24h instead of ≥ 3 loose/liquid stools/24h The interventions had no effect on incidence or duration of acute respiratory infection
Agustina R, 2012b (substudy of Agustina 2012a) Indonesia	To investigate milk with low and regular calcium content, respectively, and the addition of probiotics (*L. reuteri* DSM 17938 or *L. casei* CRL431) to milk with regular calcium content, on the incidence and duration of acute diarrhoea due to rotavirus or other causes in healthy Indonesian children, 1–6y old.	R, DB, PC 6 months	*L. reuteri*: 124 ($5x10^8$ CFU) *L. casei*: 120 ($5x10^8$ CFU) Low calcium milk: 124 Regular calcium milk: 126	· *L. reuteri* significantly reduced the duration of diarrhoea in affected children · Rotavirus-positive episodes were significantly shortened by *L. reuteri* and by calcium · *L. casei* shortened the duration of rotavirus-negative episodes
Wanke M, 2012 Poland	The efficacy of *L. reuteri* DSM 17938 in prevention of nosocomial diarrhoea in hospitalized children, 1–48 months old.	R, DB, PC During hospital stay	*L. reuteri*: 54 ($1x10^8$ CFU) Placebo: 52	*L. reuteri* did not affect the incidence of hospital-acquired diarrhoeal disease.
Urbanska M, 2016 Poland	The efficacy of *L. reuteri* DSM 17938 in prevention of nosocomial diarrhoea in hospitalized children, 1–48 months old. A repeat of Wanke's trial with a 10 times higher dose.	R, DB, PC During hospital stay	*L. reuteri*: 91 ($1x10^9$ CFU) Placebo: 93	*L. reuteri* did not affect the incidence of hospital-acquired diarrhoeal disease. There was also no difference between the *L. reuteri* and placebo groups for any of the secondary outcomes, including adverse effects. Rotavirus vaccination status had no impact on the results.
Weizman Z, 2009 (abstract, follow-up of Weizman, 2005) Israel	To evaluate if day-care infants acquire a long-term protection against common infections, following a probiotic supplementation period.	R, DB, PC Follow-up after 12 weeks	*L. reuteri*: 66 ($1.2x10^9$ CFU) Bb-12: 69 ($1.2x10^9$ CFU) Control: 59	· Protection only observed during supplementation period · No long-term protection against common infections for any of the probiotics compared to control

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Acute Gastroenteritis (AGE)

AGE Treatment in Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Dumitru IM, 2009 Romania	To study *L. reuteri* DSM 17938 as an adjunct to oral rehydration and antimicrobial therapy, on duration of acute diarrhoea in adults with HIV/AIDS	R, open 7 days	*L. reuteri*: 50 ($1x10^8$ CFU) Control: 50	· *L. reuteri* significantly reduced duration of diarrhoea in adults with HIV/AIDS compared to control · *L. reuteri* DSM 17938 was well tolerated

AGE Prevention in Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Tubelius P, 2005 Sweden	To study prevention of short-term illness, cold or GI infection, in healthy adults at a work place.	R, DB, PC 80 days	*L. reuteri*: 94 ($1x10^8$ CFU) Placebo: 87	*L. reuteri* significantly reduced short-term sick leave due to cold or GI infection compared to placebo: 10.6% and 26.4%, respectively, reported sick-leave. Among the in total 53 shift-workers, the frequency was 0 vs. 33%.
Schröder C, 2015 Germany	The effect of regular intake of *L. reuteri* DSM 17938 on the number of days of sick leave caused by respiratory and/or gastrointestinal diseases among male steelworkers.	R, DB, PC 90 days	*L. reuteri*: 79 ($1x10^8$ CFU) Placebo: 80 Randomized: 242	*L. reuteri* significantly reduced the incidence of diarrhoea, which was reported on 0.60 days for subjects of the *L. reuteri* group vs. 1.33 days in the placebo group. There was no difference in primary outcome of number of sick days due to respiratory or gastrointestinal symptoms. The drop-out rate of randomized subjects was 34%.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Common Infections, Prevention and Treatment

Infection Protection in Infants and Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
New! Maya-Barrios A, 2021 Mexico	To evaluate the safety and efficacy of *L. reuteri* ATCC PTA 5289 combined with *L. reuteri* DSM 17938, as an adjuvant to non-steroidal anti-inflammatory drug (NSAID) in children with upper respiratory tract infections (URTIs) aged 6 months to 5 years.	R, DB, PC, 10 days	*L. reuteri* : 35 ($4x10^8$ CFU) Placebo: 35	Compared to placebo the supplement containing *L. reuteri* significantly reduced: · Days with fever · Duration of symptoms · Severity of sore throat · Rhinorrhea · Average cost per child · Nasal congestion · TNF-α
Gutiérrez-Castrellón P, 2014 Mexico	Evaluate if daily administration of *L. reuteri* DSM 17938 reduces the frequency and duration of diarrhoea episodes and respiratory tract infections (RTI) in Mexican day school children aged 6-36 months. A cost-effectiveness analysis was also made.	R, DB, PC 3 months of intervention, follow-up at 6 months	*L. reuteri*: 168 ($1x10^8$ CFU) Placebo: 168	Compared to placebo: · *L. reuteri* significantly reduced the frequency and duration of episodes of diarrhoea and respiratory tract infection at both 3 and 6 months · The number of doctor visits, antibiotic use, absenteeism from day school and parental absenteeism from work were significantly reduced · The use of *L. reuteri* was associated with a reduction of costs by 36 US dollars (USD) for each case of diarrhoea, and by 37 USD for each case of RTI
Agustina R, 2012a Indonesia	To investigate milk with low and regular calcium content, respectively, and the addition of probiotics (*L. reuteri* DSM 17938 or *L. casei* CRL431) to milk with regular calcium content, on the incidence and duration of diarrhoea and acute respiratory infections in healthy Indonesian children, 1–6y old.	R, DB, PC 6 months	*L. reuteri*: 124 ($5x10^8$ CFU) *L. casei*: 120 ($5x10^8$ CFU) Low calcium milk: 124 Regular calcium milk: 126	Only *L. reuteri* significantly reduced: · Incidence of diarrhoea in children with lower nutritional status, irrespective of definition of diarrhoea · Incidence of diarrhoea in all children when diarrhoea was defined as ≥ 2 loose/liquid stools/24h instead of ≥ 3 loose/liquid stools/24h The interventions had no effect on incidence or duration of acute respiratory infection
Agustina R, 2013 (substudy of the Agustina 2012 trial) Indonesia	To investigate the hypotheses that cow's milk with added probiotics *L. reuteri* DSM 17938 or *L. casei* CRL431 would improve growth and iron and zinc status of Indonesian children, whereas milk calcium alone would improve growth but reduce iron and zinc status. A 6-mo. randomized trial was conducted in low-socioeconomic urban communities, in healthy children, 1–6y old.	R, DB, PC 6 months	*L. reuteri*: 124 ($5x10^8$ CFU) *L. casei*: 120 ($5x10^8$ CFU) Low calcium milk: 124 Regular calcium milk: 126	· Changes in underweight, stunting, anaemia prevalence, and iron and zinc status were similar between groups. · Regular milk calcium in itself did not affect growth or iron and zinc status. Compared with Regular calcium group: · *L. casei* CRL 431 modestly improved monthly weight velocity. · *L. reuteri* DSM 17938 modestly improved growth by increasing weight gain, changes in weight-for-age Z-score over 6 mo., and monthly weight and height velocity.
Weizman Z, 2005 Israel	Prevention of common infections in day-care children 4–10 months old.	R, DB, PC 12 weeks	*L. reuteri*: 68 ($1.2x10^9$ CFU) Bb-12: 73 ($1.2x10^9$ CFU) Control: 60	*L. reuteri* significantly reduced (compared to Bb-12 and control): · Days with fever · Need to consult doctor and need of antibiotics · Absence from day-care Both probiotics significantly reduced: · Episodes with fever · Episodes and days with diarrhoea
Di Nardo G, 2014 Italy	The aim of this study was to evaluate the effect of *L. reuteri* DSM 17938 in patients with cystic fibrosis, with mild-to-moderate lung disease and aged 6–29y (median age 18y), on the rate of respiratory exacerbations and of infections of the upper respiratory and the GI tracts. NOTE: The right designation of the probiotic strain of this trial is *L. reuteri* DSM 17938, not ATCC 55730 as stated in the paper.	R, DB, PC 6 months	*L. reuteri*: 30 ($1x10^8$ CFU) Placebo: 30	Compared to placebo, *L. reuteri* significantly: · Reduced the frequency of pulmonary exacerbations · Reduced the number of upper respiratory tract infections = otitis The groups did not differ statistically in the mean number and duration of hospitalizations for pulmonary exacerbations and gastrointestinal infections. There was no effect on lung function (mean delta value of FEV1), faecal calprotectin concentration, and tested cytokines (tumour necrosis factor-α and interleukin-8) between the two groups.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Common Infections, Prevention and Treatment

Infection Protection in Infants and Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Wanke M, 2012 Poland	The efficacy of *L. reuteri* DSM 17938 in prevention of nosocomial diarrhoea in hospitalized children, 1-48 months old.	R, DB, PC During hospital stay	*L. reuteri:* 54 ($1x10^8$ CFU) Placebo: 52	*L. reuteri* did not affect the incidence of hospital-acquired diarrhoeal disease.
Urbanska M, 2016 Poland	The efficacy of *L. reuteri* DSM 17938 in prevention of nosocomial diarrhoea in hospitalized children, 1-48 months old. A repeat of Wanke's trial with a 10 times higher dose.	R, DB, PC During hospital stay	*L. reuteri:* 91 ($1x10^9$ CFU) Placebo: 93	*L. reuteri* did not affect the incidence of hospital-acquired diarrhoeal disease. There was also no difference between the *L. reuteri* and placebo groups for any of the secondary outcomes, including adverse effects. Rotavirus vaccination status had no impact on the results.
Georgieva M, 2015 Bulgaria	To evaluate the preventive effect of *L. reuteri* DSM 17938 on antibiotic-associated diarrhoea and *Clostridium difficile*-related infections in hospitalized children, 3-12 years old.	R, DB, PC Study product ingested during the antibiotic course and 7 days thereafter. Follow-up at 21 days post-antibiotic treatment	*L. reuteri:* 49 ($1x10^8$ CFU) Placebo: 48	The incidence of diarrhoea was unexpectedly low with only one case in each group. Hence, the study was underpowered to be able to detect any statistical differences between groups. There were no *Cl. difficile*-related infections, and no differences between groups on proportion of subjects who were positive for *Cl. difficile* toxin A and B at baseline and on day 21, respectively. There were no differences between groups on the incidence of other GI-related symptoms. The study products were well tolerated and there was no report of any adverse events.
Savino F, 2015b Italy	To evaluate the effects of early administration of *L. reuteri* DSM 17938 on microbial composition in faecal samples of newly hospitalized, exclusively formula-fed infants below 6 mo. of age. Infants given *L. reuteri* during at least one month preceding hospitalization were compared to matched controls not given any probiotic.	A case-control observational study	*L. reuteri:* 30 ($1x10^8$ CFU) Control: 30	Compared to the control group: · Infants with previous consumption of *L. reuteri* DSM 17938 (Lr) had significantly lower total counts of anaerobic Gram-neg. bacteria, *enterobacteriaceae* and enterococci. The Lr group had significantly higher total counts of anaerobic Gram-pos. bacteria. There was no difference in total counts of lactobacilli and bifidobacteria. · Infants of the Lr group were negative for atypical enteropathogenic *E. coli*, *Salmonella* spp., *Cronobacter sakazakii* and *Serratia odorifera.* · The Lr group had significantly less of *Hafnia alvei* and *Klebsiella oxytoca.*
Weizman Z, 2009 (abstract, substudy of Weizman, 2005) Israel	To evaluate if day-care infants acquire a long- term protection against common infections, following a probiotic supplementation period.	R, DB, PC Follow-up after 12 weeks	*L. reuteri:* 66 ($1.2x10^9$ CFU) Bb-12: 69 ($1.2x10^9$ CFU) Control: 59	· Protection only observed during supplementation period · No long-term protection against common infections for any of the probiotics compared to control
Oncel MY, 2015 Turkey	To compare the efficacy of orally administered *L. reuteri* DSM 17938 vs. the anti-fungal nystatin in prevention of fungal colonisation and invasive candidiasis in very low birth weight infants ≤1,500 g	R, open	*L. reuteri:* 150 ($1 x10^8$ CFU) Nystatin: 150	Prophylactic *L. reuteri* was equal to nystatin in reduction of *Candida* colonisation and invasive candidiasis. Secondary outcomes, compared to nystatin *L. reuteri* significantly reduced: · frequency of proven sepsis · rates of feeding intolerance · duration of hospital stay None of the positive blood cultures grew *L. reuteri.* No other adverse events related to *L. reuteri* were noted.
Romeo MG, 2011 Italy	To study effects of *L. reuteri* and another probiotic on *Candida* colonisation and of late-onset sepsis in premature newborns in intensive care. Neurological outcome at 12 months of age.	R, open 6 weeks or until discharged from intensive care	*L. reuteri:* 83 ($1x10^8$ CFU) LGG: 83 ($6x10^9$ CFU) Control: 83	· *L. reuteri* significantly reduced the incidence of GI problems, need of antibiotics and halved the hospital stay, compared to both LGG and control group Both probiotics compared to control group: · Significantly reduced incidence of high faecal levels of *Candida*

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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Common Infections, Prevention and Treatment

Infection Protection in Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Tubelius P, 2005 Sweden	To study prevention of short-term illness, cold or GI infection, in healthy adults at a work place.	R, DB, PC 80 days	*L. reuteri*: 94 ($1x10^8$ CFU) Placebo: 87	*L. reuteri* significantly reduced short-term sick leave due to cold or GI infection compared to placebo: 10.6% and 26.4%, respectively, reported sick-leave. Among the in total 53 shift-workers, the frequency was 0 vs. 33%.
Di Nardo G, 2014 Italy	The aim of this study was to evaluate the effect of *L. reuteri* DSM 17938 in patients with cystic fibrosis, with mild-to-moderate lung disease aged 6-29y (median age 18y), on the rate of respiratory exacerbations and of infections of the upper respiratory and the GI tracts. NOTE: The right designation of the probiotic strain of this trial is *L. reuteri* DSM 17938, not ATCC 55730 as stated in the paper.	R, DB, PC 6 months	*L. reuteri*: 30 ($1x10^8$ CFU) Placebo: 30	Compared to placebo, *L. reuteri* significantly: · Reduced the frequency of pulmonary exacerbations · Reduced the number of upper respiratory tract infections = only otitis The groups did not differ statistically in the mean number and duration of hospitalizations for pulmonary exacerbations and gastrointestinal infections. There was no effect on lung function (mean delta value of FEV1), faecal calprotectin concentration, and tested cytokines (tumour necrosis factor-a and interleukin-8) between the two groups.
Schröder C, 2015 Germany	The effect of regular intake of *L. reuteri* DSM 17938 on the number of days of sick leave caused by respiratory and/or gastrointestinal diseases among male steelworkers.	R, DB, PC 90 days	*L. reuteri*: 79 ($1x10^8$ CFU) Placebo: 80 Randomized: 242	*L. reuteri* significantly reduced the incidence of diarrhoea, which was reported on 0.60 days for subjects of the *L. reuteri* group vs. 1.33 days in the placebo group. There was no difference in primary outcome of number of sick days due to respiratory or gastrointestinal symptoms. The drop-out rate of randomized subjects was 34%.

Treatment of Urinary Tract Infection in Women

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Vidal-Vazquez P, 2018 (abstract) Mexico	A proof-of-concept study to evaluate the efficacy of *L. reuteri* DSM 16666 and DSM 17938 in combination with cranberry PAC (proanthocyanidin) and zinc for the treatment of urinary tract infections in premenopausal women.	R, DB, PC 12 days + 18 days follow-up	*L. reuteri*: 922 ($4x10^8$ CFU) Placebo: 24	*L. reuteri* significantly reduced clinical symptoms of urinary tract infection. Proportion of women reporting negative to mild severity of symptoms was 91% in the *L. reuteri* group vs. 54% in the placebo group ($p<0.05$). The frequency of adverse events was similar between the groups.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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Treatment of Allergic Symptoms in Children and Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Miniello VL, 2010 Italy	To study if oral intake of *L. reuteri* could modify the cytokine production in the lung in 4-10 year old children with atopic dermatitis (AD) and non-allergic dermatitis.	R, DB, PC 8 weeks	*L. reuteri*: 26 (1x10^8 CFU) Placebo: 25	· In AD patients only *L. reuteri* significantly increased the IFN-gamma production and decreased IL-4 levels in exhaled breath condensate. The Th2/Th1 cytokines quotient was thereby modified in a positive way. · No changes in clinical scores of eczema
Miraglia del Giudice M, 2012 Italy	The effect of *L. reuteri* in children 6-14y with well-controlled asthma, on airway inflammation as measured by certain inflammatory parametaers, and clinically.	R, DB, PC 60 days	*L. reuteri*: 22 (1x10^8 CFU) Placebo: 21	Compared to placebo *L. reuteri* significantly reduced airway inflammation, shown as changed levels in exhaled breath condensate: · reduction of exhaled nitric oxide (FeNO) · reduction of the cytokine IL-2 · increase of the cytokine IL-10 Clinical parameters, FEV1 and children's asthma control test (C-ACT), did not differ within or between groups during the treatment.
Miraglia del Giudice M, 2016 Italy	To test the effects of *L. reuteri* DSM 17938 in combination with vitamin D, on airway inflammation in vit. D-deficient children (6-14y) with well-controlled asthma, and allergy to house dust mite. Primary outcome was bronchial inflammation and secondary outcomes were asthma control measured by questionnaire (Childhood Asthma Control Test [C-ACT]), and lung function evaluated by spirometry.	R, DB, PC 90 days + follow-up after another 30 days	*L. reuteri*: 14 (1x10^8 CFU + vit D. 400 IU/ 10µg) Placebo: 15	Compared to placebo, *L. reuteri* + vit. D significantly: · Reduced bronchial inflammation assessed by fractional exhaled nitric oxide · the effect was sustained during the follow-up month In addition, there was a reduced response to bronchodilation in actively-treated children. These findings were associated with significant increase in serum vit. D3 concentration in the active group.
Ciprandi G, 2015 Italy	Pilot study to evaluate adjuvant effect of drops with *L. reuteri* DSM 17938 + vitamin D3, ingested concomitantly with sublingual immunotherapy (SLIT), in adults with seasonal rhinitis due to Parietaria pollen.	Open, non-ranomized *L. reuteri* + vit D3 ingested during the first (of three) month of SLIT. Patients' perception of symptom severity and medication use were assessed and compared in retrospect to the previous pollen season.	*L. reuteri*: 15 (2x10^8 CFU) + 800 IU vit. D3 + SLIT Control=SLIT only: 15	There were significant reductions in symptom severity and use of medications, both within and between groups. The study is limited by few patients included, no randomization and use of placebo, and the comparison to the previous year's pollen season made in retrospect. It is thereby difficult to make firm conclusions from the study results.
Gromert N, 2009 (abstract) Sweden	Study on *L. reuteri* as an adjunct to standard treatment of atopic eczema in 3 months–4 year old children.	R, DB, PC 12 months	*L. reuteri*: 25 (1x10^8 CFU) Placebo: 25	*L. reuteri* significantly reduced: · Extension of the eczema · Itching and loss of sleep · Skin prick test reaction to peanut allergen Total IgE at 12 months was at steady state, while it was significantly increased in the placebo group
Cirillo AI, 2005 (abstract) Italy	To reduce risk of worsening of atopic eczema during period with cow's milk intake, in 3–5 year old children.	Open 3 months	*L. reuteri*: 8 (2x10^8 CFU) Control: 7	· Atopic eczema relief in all children on *L. reuteri* · Control: all children got worse in their eczema

Allergy Prevention in Infants

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Huoman J, 2021 Sweden New!	To investigate epigenome-wide DNA methylation patterns from a sub-group of children from an on-going allergy prevention trial using pre- and postnatal combined *L. reuteri* and ω-3 fatty acid treatment.	Sub-group of children in on-going R, DB, PC trial.	1) *L. reuteri* + ω-3 PUFA: n = 18 2) probiotics + placebo: n = 16, 3) ω-3 + placebo: n = 15, 4) double placebo: n = 14	Prenatal *L. reuteri* and/or ω-3 fatty acid treatment resulted in hypermethylation and affected immune- and allergy-related pathways in neonatal T helper cells. The results show potential synergistic effects between the interventions.
Forsberg A, 2020 Sweden	To investigate how maternal peripheral immunity is affected by pregnancy, and by probiotic and ω-3 fatty acid supplementation.	R, DB, PC From gestational week 20 until birth	1) *L. reuteri* + ω-3 PUFA: 22 2) ω-3 PUFA + placebo: 21 3) placebo + ω-3 PUFA:22 4) placebo capsules + placebo oil: 23 (*L. reuteri*: 1x10^9 CFU, 20 droplets × 2 daily; ω-3 PUFA: 3840 mg)	Probiotic supplementation to the mother during the second half of pregnancy resulted in immunomodulatory effects among activated and resting Treg cells. Furthermore, several systemic immune modifying effects of pregnancy were observed.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Immune-Related Disorders and Immune Modulation

Allergy Prevention in Infants

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Forsberg A, 2020 (Substudy of Abrahamsson, 2007) Sweden	To assess the effects of pre-and postnatal *L. reuteri* supplementation on DNA methylation in relation to immune maturation and allergy development.	R, DB, PC Women were supplemented from gestational week 36, children were supplemented for the first year of life	*L. reuteri*: 95 (1x10^8 CFU) Placebo: 93	Maternal *L. reuteri* supplementation during pregnancy alters DNA methylation patterns in CD4+ T cells towards enhanced immune activation at birth, which may affect immune maturation and allergy development.
Abrahamsson T, 2007 Sweden	Prevention of atopic eczema in infants 0–2 years old.	R, DB, PC 12 months + Substudy at 24 months	*L. reuteri*: 95 (1x10^8 CFU) Placebo: 93	· Significantly fewer in the *L. reuteri* group with IgE-associated eczema at 2 years of age · Skin prick test reactivity to allergens was less common in the *L. reuteri* vs. the placebo group, significantly so for infants with mothers with allergies · The overall incidence of eczema was the same in the two groups at 2 years of age.
Abrahamsson T, 2011 (Substudy of Abrahamsson 2007) Sweden	Prevention of allergy/atopic eczema in infants 0-2 years old.	R, DB, PC 12 months + follow-up at 24 months	*L. reuteri*: 95 (1x10^8 CFU) Placebo: 93	Infants with faecal *L. reuteri* the first week of life had a less allergy-prone chemokine profile in their blood at 6 months of age.
Abrahamsson TR, 2013 (Follow-up of Abrahamsson 2007) Sweden	In a study on prevention of allergy in newborns, *L. reuteri* ATCC 55730 reduced the incidence of IgE-associated allergic disease in infancy. This treatment might therefore also reduce the risk of asthma and allergic rhino conjunctivitis in school age (at the age of 7), which this follow-up study set out to investigate. It also evaluated whether this supplementation was associated with any long-term side effects.	Original study: R, DB, PC	*L. reuteri*: 94 (1x10^8 CFU) Placebo: 90 In the 2007 trial 232 infants were randomized and 188 completed	For the allergic disease outcomes there were no differences between groups: · The prevalence of asthma was 15% in the *L. reuteri* vs. 16% in placebo group · Allergic rhino conjunctivitis: 27% vs. 20% · Eczema: 21% vs. 19% · Skin prick test reactivity: 29% vs. 26%
Ceratto S, 2014 (abstract, follow- up of Savino 2010) Italy	If probiotic treatment for infant colic may prevent atopic diseases (cow's milk allergy and atopic dermatitis), asthma and migraine at the age of five, and effects on growth.	Original study: R, DB, PC	*L. reuteri*: 25 (1x10^8 CFU) Placebo: 23	· The prevalence of atopic disorders was significantly lower in the *L. reuteri* group compared to placebo, with an odds ratio of 0.16. · Asthma was absent in both groups and there was one case of migraine, in the placebo group. · Growth was equal in the two groups, measured as BMIZ-score.

Modulation of Immune Parameters in Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Valeur N, 2004 Denmark	To evaluate effect on immune cells in the gut epithelium in healthy adults.	Open 28 days + 28d follow-up	*L. reuteri*: 19 (4x10^8 CFU)	*L. reuteri* significantly increased/stimulated CD4+ T-lymphocytes in the small intestine (ileum)
Böttcher MF, 2008 Sweden (Mothers of the infants of Abrahamsson's prevention-of-allergy study of 2007)	To evaluate effect on the immunological composition of breast milk. Pregnant women ingested *L. reuteri* before giving birth.	R, DB, PC 4 weeks before delivery, follow-up after 1 month	*L. reuteri*:54 (1x10^8 CFU) Placebo: 55	· Colostrum content of the cytokine TGF-beta2 was significantly reduced while its content of the anti-inflammatory cytokine IL-10 increased · The effect was not retained at follow-up
Mangalat N, 2012 USA	Primary objective was to investigate the safety of the *L. reuteri* Protectis drops in healthy adults. Secondary aim was changes in some specific immune factors.	R, DB, PC 2 months with follow-up after 1 and 4 months	*L. reuteri*: 30 (1x10^8 CFU) Placebo: 10	2 months of *L. reuteri* intake had no significant effect on: · subclasses of PBMC (peripheral blood mononuclear cells) · regulatory T cells (Tregs) · TLRs (toll like receptors) 2 and 4 expression · cytokine expression by stimulated PBMCs There was a small, significant increase in the faecal calprotectin level, within the normal clinical range

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Cystic Fibrosis in Children and Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
del Campo R, 2014 Spain	To assess the effects of *L. reuteri* DSM 17938 in subjects with cystic fibrosis, aged 8–44y (mean age 18y), on GI and overall health (measured by validated questionnaires), the effect on gut inflammation and the composition of the gut microbiota.	R, DB, PC, crossover 2 parallel groups 6 mo pro-biotic 6 mo placebo	30 in total *L. reuteri*: 30 (1x10^8 CFU) Placebo: 30	Compared to the placebo test period: · GI health score was significantly improved after 6 mo with *L. reuteri*, measured by the GIQLI questionnaire · Gut inflammation, measured as faecal calprotectin levels, was significantly reduced by *L. reuteri* After 6 months with *L. reuteri*, the composition of the gut microbiota was modulated to a less dense and a more diverse one, with 31% reduction of high numbers of Proteobacteria. There was a considerable increase of *Firmicutes* and *Bacteroidetes*. The microbiota thereby became more similar to the one of healthy persons.
Di Nardo G, 2014 Italy	The aim of this study was to evaluate the effect of *L. reuteri* DSM 17938 in patients with cystic fibrosis, with mild-to-moderate lung disease and aged 6–29y (median age 18y), on the rate of respiratory exacerbations and of infections of the upper respiratory and the GI tracts. NOTE: The right designation of the probiotic strain used in this trial is *L. reuteri* DSM 17938, not ATCC 55730 as stated in the paper.	R, DB, PC 6 months	*L. reuteri*: 30 (1x10^8 CFU) Placebo: 30 NOTE: The dose was 5 drops, which is equivalent to 1x10^8 CFU, not 1x10^{10}, as stated in the article.	Compared to placebo, *L. reuteri* significantly: · Reduced the frequency of pulmonary exacerbations · Reduced the number of upper respiratory tract infections = otitis The groups did not differ statistically in the mean number and duration of hospitalizations for pulmonary exacerbations and gastrointestinal infections. There was no effect on lung function (mean delta FEV1), faecal calprotectin concentration, tested cytokines (tumour necrosis factor-alfa and interleukin-8) between the two groups.
del Campo R, 2009 (abstract) Spain	To evaluate the effect on gastrointestinal and general health in cystic fibrosis (CF) patients aged 4–44 year, after six months of supplementation with *L. reuteri* DSM 17938 or the multi-strain product VSL#3.	R, open 6 months	40 in total *L. reuteri*: not stated (1x10^8 CFU) VSL#3: not stated (9x10^{11} CFU)	· Significantly improved subjective GI health in children and adults with CF during intake of *L. reuteri* or VSL#3 · No difference in effect between groups

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Inflammatory Bowel Disease in Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Oliva S, 2012 Italy	Efficacy of *L. reuteri* administered as a daily rectal enema in children with distal ulcerative colitis, 6–18 years old. The disease was mild to moderate in activity at entry, and mesalazine was concomitant treatment	R, DB, PC 8 weeks	*L. reuteri*: 16 Placebo: 15 (1x10^{10} CFU)	Compared to baseline values, the Mayo Disease Activity Index was significantly decreased in the *L. reuteri* group compared to placebo at 8 weeks. Within the *L. reuteri* group the histological score of rectal epithelium was significantly decreased. The levels of proinflammatory cytokines were downregulated while the anti-inflammatory IL-10 was upregulated.

Diverticulitis

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
New! Ojetti V, 2022 Italy	To evaluate the efficacy of *L. reuteri* ATCC PTA 4659 in the treatment of acute uncomplicated diverticulitis. Primary outcome was reduction of abdominal pain (Visual Analogue Scale, VAS) and inflammatory markers (C-reactive protein, CRP, and calprotectin). Secondary outcome was duration of hospitalisation. All patients recieved fluids (Isolyte 2000 for 24h) and bowel rest (for 48h) upon admission to the hospital.	R, DB, PC 10 days	*L. reuteri*: 61 (1x10^9 CFU) Placebo: 58	Compared to placebo, *L. reuteri* (Lr) significantly reduced: · CRP level: 72h after admission the CRP value was reduced by 58.8% in the Lr group, and by 40% in the placebo group ($p<0.05$). · Calprotectin: 72h after admission the calprotectin level was reduced by 17% in the Lr group, and by 10.6% in the placebo group ($p<0.05$). Both groups had a mean reduction of 4 points in VAS score 72 h after admission (from 7 to 3). · Mean hours of hospitalisation were 75.5 in the Lr group, and 83.5 in the placebo group.
Petruzziello C, 2019 Italy	To evaluate the efficacy of *L. reuteri* ATCC PTA 4659, in association with standard antibiotic therapy, in the treatment of acute uncomplicated diverticulitis. Primary outcome was reduction of abdominal pain (Visual Analogue Scale, VAS) and in C-reactive protein (CRP, marker of inflammation). Secondary outcome was duration of hospitalisation.	R, DB, PC 10 days	*L. reuteri* + antibiotics: 44 (1x10^9 CFU) Placebo + antibiotics: 44	Compared to placebo, *L. reuteri* (Lr) significantly reduced: · Abdominal pain: The mean delta reduction in abdominal pain during days 1 – 3 was 4.5 and 2.3 VAS points in the Lr and placebo group, respectively ($p< 0.0001$). Baseline value of 8.2 and 7.9, respectively (non-significant). The reduction in pain was significantly larger in the Lr group throughout the study period. · CRP: 72 h after admission, the reduction in CRP was 45.4 mg/L and 27.5 mg/L in the Lr and control group, respectively, ($p<0.0001$), from a baseline value of 68 and 71 mg/L, respectively (non-significant difference). · Mean hours of hospitalisation were 93 in the Lr group, and 113 in the placebo group ($p<0.0001$).

Lactose Intolerance in Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Ojetti V, 2010 Italy	To evaluate the effects of lactase, *L. reuteri* and placebo on reduction of H_2 breath excretion and gastrointestinal (GI) symptoms in lactose intolerant adults.	R, PC, open 10 days	*L. reuteri*: 20 (4x10^8 CFU) Lactase: 20 Placebo: 20	Compared to baseline *L. reuteri* significantly reduced: · H_2 breath excretion and GI symptoms Best effect was seen with lactase while placebo had no effect

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Antibiotic-Associated Side Effects in Children and Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Cimperman L, 2011 USA	Prevention of antibiotic-associated diarrhoea or infectious in hospitalized adults, mean age 51y.	R, DB, PC 4 weeks + 2w follow-up	*L. reuteri*: 13 ($2x10^8$ CFU) Placebo: 10	Significantly reduced incidence of diarrhoea: 7.7% in *L. reuteri* group and 50% in placebo
Kołodziej M, 2018 Poland	Efficacy of drops with *L. reuteri* DSM 17938 in prevention of antibiotic-associated (AAD) or other diarrhoea in hospitalized children <18y. Episode of diarrhoea defined in three ways based on severity (≥3 or loose or watery stools/24h for a minimum of 48h or 24h, and ≥ 2 loose or watery stools/24h for a minimum of 24h). AAD was diarrhoea caused by *Clostridium difficile* or otherwise unexplained diarrhoea.	R, DB, PC 9 days (mean) in both groups = during antibiotic therapy (oral or intravenous). Follow-up at day 7 post-antibiotic.	*L. reuteri*: 123 ($2x10^8$ CFU) Placebo: 124	· Incidence of AAD by the strictest definition was 11.4% and 6.5% in the *L. reuteri* and placebo group, respectively, and 13% and 13.7%, respectively, for AAD by any of the other two definitions. · Incidence and type of adverse events were similar · Median age of subjects was 4 mo, mean age was 26 mo
Francavilla R, 2008 Italy	Evaluate if pre-treatment with *L. reuteri* ATCC 55730 may reduce GI symptoms and bacterial load, and increase eradication rate in *H. pylori* (Hp)-infected dyspeptic adults.	R, DB, PC 28 days with *L. reuteri* followed by 10d Hp eradication therapy	*L. reuteri*: 20 ($1x10^8$ CFU) Placebo: 20	*L. reuteri* for 4 weeks significantly: · Reduced the load of *H. pylori* · Improved GI health scores There was no additional effect on eradication rate
Georgieva M, 2015 Bulgaria	To evaluate the preventive effect of *L. reuteri* DSM 17938 on antibiotic-associated diarrhoea and *Clostridium difficile*-related infections in hospitalized children, 3–12 years old.	R, DB, PC Study product ingested during the antibiotic course and 7 days thereafter. Follow-up at 21 days post-antibiotic treatment	*L. reuteri*: 49 ($1x10^8$ CFU) Placebo: 48	The incidence of diarrhoea was unexpectedly low with only one case in each group. Hence, the study was underpowered to be able to detect any statistical differences between groups. There were no *Cl. difficile*-related infections, and no differences between groups on proportion of subjects who were positive for *Cl. difficile* toxin A and B at baseline and on day 21, respectively. There were no differences between groups on the incidence of other GI-related symptoms. The study products were well tolerated and there was no report of any adverse events.
Lionetti E, 2006 Italy	To evaluate side-effects of 10-day eradication therapy of *H. pylori* in children 3–18 years old.	R, DB, PC 20 days from start of eradication treatment	*L. reuteri*: 20 ($1x10^8$ CFU) Placebo: 20	*L. reuteri* significantly reduced the frequency of: · Stomach distension · Stomach pain · Belching · Constipation/diarrhoea
Ojetti V, 2012 Italy	Increase the eradication rate of *H. pylori* and reduce side-effects of 7 days of second line eradication treatment in adults	R, open 14 days + 6w follow-up	*L. reuteri*: 45 ($3x10^8$ CFU for 14d) Control: 45	*L. reuteri* significantly reduced the incidence and severity of the treatment side-effects diarrhoea and nausea

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Cancer Treatment-Related Diarrhoea

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Aiello RA, 2008 (abstract) Italy	To study incidence of diarrhoea and abdominal pain in adults treated with chemotherapy for colon cancer, and safety of *L. reuteri*.	R, open 60 days	*L. reuteri*: 58 ($1x10^8$ CFU) Control: 58	*L. reuteri*: · Significantly reduced incidence and severity of diarrhoea · Was safe to use

Proton Pump Inhibitor Side Effects

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Belei O, 2018 Romania	To evaluate small intestinal bacterial overgrowth (SIBO) in children with gastroesophageal reflux disease (GERD) after treatment with proton pump inhibitor (PPI), with or without the addition of *L. reuteri* DSM 17938. Glucose hydrogen breath test (GHBT) was used for assessment of SIBO. Healthy children, who did not receive any treatment, served as comparison group for the GHBT.	Open 12 weeks GHBT was performed before and after 12 weeks of treatment.	*L. reuteri*: + PPI: 64 ($1x10^8$ CFU) Placebo + PPI: 64 Healthy controls: 120	No GERD patient had SIBO before treatment. After 12 weeks of treatment, there was a significant difference in rate of SIBO: · Placebo + PPI: 56% (36/64) · *L. reuteri* + PPI: 6% (4/64) · Healthy controls: 5% (6/120) · The rate of GI symptoms related to SIBO was 64% in the placebo + PPI group vs. 0% in the *L. reuteri* + PPI, and the healthy control group, respectively.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Helicobacter pylori Infection

Helicobacter pylori Infection in Children and Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Poonyam P, 2019 Thailand	Evaluate the efficacy of *L. reuteri* DSM 17938 + ATCC PTA 6475 (Gastrus) and quadruple therapy (bismuth, metronidazole, tetracycline, dexlansoprazole) on *H. pylori* eradication in adults (mean age 54y).	R, DB, PC 7 and 14 days	*L. reuteri*: 7 d: 25 ($4x10^8$ CFU) Placebo, 7 d: 25 *L. reuteri* 14 d: 25 ($4x10^8$ CFU) Placebo, 14 d: 25	After 14 days of treatment, the eradication rate was 96% with *L. reuteri* Gastrus and 88% with placebo (non-significant difference). *L. reuteri* Gastrus significantly reduced the side-effects nausea/vomiting, abdominal discomfort and bitter taste after 14 days of treatment.
Moreno Márquez C, 2021 Spain New!	Evaluate the efficacy of *L. reuteri* DSM 17938 + ATCC PTA 6475 in reducing gastrointestinal symptoms during bismuth-containing quadruple therapy (bismuth, metronidazole, tetracycline and omeprazole) in *H. pylori*-positive adults. Gastrointestinal symptoms were assed by Gastrointestinal Symptom Rating Scale (GSRS) score.	R, DB, PC 10 days	*L. reuteri* + antibiotics: 44 ($1x10^9$ CFU) Placebo + antibiotics: 44	Compared to placebo, *L. reuteri* (Lr) significantly reduced: · Abdominal pain: The mean delta reduction in abdominal pain during days 1 – 3 was 4.5 and 2.3 VAS points in the Lr and placebo group, respectively ($p< 0.0001$). Baseline value of 8.2 and 7.9, respectively (non-significant). The reduction in pain was significantly larger in the Lr group throughout the study period. · CRP: 72 h after admission, the reduction in CRP was 45.4 mg/L and 27.5 mg/L in the Lr and control group, respectively, $p<0.0001$), from a baseline value of 68 and 71 mg/L, respectively (non-significant difference). · Hours of hospitalisation: mean duration of 93 vs. 113 hours in the Lr and control group, respectively ($p<0.0001$).
Francavilla R, 2014 Italy	To assess the effects of *L. reuteri* (Lr) DSM 17938 + ATCC PTA 6475 in *H. pylori*-infected and treatment naive, symptomatic adults, on eradications rates, and clinical and pathological parameters. Study products were administered before, during and after the 7-day treatment with omeprazole, amoxicillin and clarithromycin.	R, DB, PC 96 days w Lr and in 3 phases: d 0–28=pre-eradication, d 29–35=eradication therapy, d 36–96=follow-up	*L. reuteri*: 43 ($2x10^8$ CFU) Placebo: 43	Compared with placebo, *L. reuteri* significantly: · Reduced the incidence of the side effect symptoms abdominal and epigastric pain, abdominal distension/bloating and diarrhoea · Reduced serum levels of the inflammatory marker gastrin-17
Emara MH, 2013 Egypt	To test if the addition of *L. reuteri* (Lr) DSM 17938 + ATCC PTA 6475 (Gastrus) to standard triple therapy (omeprazole, amoxicillin and clarithromycin) improves the eradication rates, and clinical and pathological parameters in *H. pylori*-infected and treatment naive, symptomatic adults, aged 18–60y.	R, DB, PC Lr: 4 weeks Triple therapy: 2 weeks Follow-up at 8 weeks after start of interventions	*L. reuteri*: 35 ($2x10^8$ CFU) Placebo: 35	Compared to placebo, *L. reuteri* Gastrus significantly reduced: · GSRS (Gastrointestinal Symptom Rating Scale) · gastritis inflammatory cell score · diarrhoea and taste disorders The rate of eradication of *H. pylori* was 74.3% (26/35) and 65.7% (23/35) in the *L. reuteri* Gastrus and placebo group, respectively (non-significant difference).
Francavilla R, 2008 Italy	Evaluate if pre-treatment with *L. reuteri* may reduce GI symptoms and bacterial load and increase eradication rate in *H. pylori* (Hp)-infected dyspeptic adults.	R, DB, PC 28 days with *L. reuteri* followed by 10d Hp eradication therapy	*L. reuteri*: 20 ($1x10^8$ CFU) Placebo: 20	*L. reuteri* for 4 weeks significantly: · Reduced the load of *H. pylori* · Improved GI health scores There was no additional effect on eradication rate
Lionetti E, 2006 Italy	Evaluate effects on side-effects of 10-day eradication therapy of *H. pylori* in children 3–18 years old.	R, DB, PC 20 days from start of eradication treatment	*L. reuteri*: 20 ($1x10^8$ CFU) Placebo: 20	Eradication of *H. pylori* was equally successful in both groups: 17/20 in the probiotic group vs. 16/20 in the placebo group. There were no dropouts because of treatment side-effects.
Kotzev, 2015 Bulgaria	Evaluate if pre-treatment with the combination of omeprazole (PPI) and *L. reuteri* (Lr) (strains DSM 17938 + ATCC PTA 6475 (Gastrus) may reduce the bacterial load on its own, and increase eradication rate in *H. pylori* (Hp)-infected dyspeptic adults.	R, DB, PC 28 days of PPI + Lr. Thereafter 10-d. triple eradication therapy for those still positive for Hp. Follow-up at day 90 after initiation of intervention.	*L. reuteri*: 25 ($2x10^8$ CFU + omeprazole) Placebo + omeprazole: 28 ($2x10^8$ CFU + omeprazole)	Compared to baseline, there was a decline in the proportion of patients positive for Hp infection both one week after the end of the 28-day supplementation period and at the follow-up at day 90, but with no significant difference between groups. At day 90, compared to baseline, the overall presence and severity of GI symptoms had improved to the same extent in the two groups, measured by GSRS (Gastrointestinal Symptoms Rating Score).
Imase K, 2007 Japan	Evaluate the effect of *L. reuteri* (Lr) ATCC 55730 on infection load in non-symptomatic *H. pylori*-infected adults.	R, DB, PC 4 arms crossover 4 + 4 weeks	Lr → Placebo: 15 ($4x10^8$ CFU) Placebo → Lr: 15 ($4x10^8$ CFU) Lr → Lr: 5 ($4x10^8$ CFU) Placebo → placebo: 5	· *L. reuteri* significantly reduced *H. pylori* bacterial load measured by urea breath test · The suppressive effect was sustained another 4 weeks in the group testing Lr first and then placebo
Ojetti V, 2012 Italy	Increase the eradication rate of *H. pylori* and reduce side-effects of 7 days of second line eradication treatment in adults	R, open 14 days + 6w follow-up	*L. reuteri*: 45 ($3x10^8$ CFU) Control: 45	*L. reuteri* supplementation significantly increased the eradication rate of *H. pylori* to 80% compared to 60% in the control group
Dore MP, 2016 Italy	Investigate if the eradication rate of *H. pylori* in adults is improved by *L. reuteri* DSM 17938, administered during the eradication therapy and for 10 days thereafter.	Open 10 days of eradication the-rapy, *L. reuteri* for 10+10 days	*L. reuteri*: 45 ($1x10^8$ CFU)	The rate of eradication was 93.3% (42/45). In 2/4 (50%) previously treated for *H. pylori* the infection was also eradicated. Side effects were reported in 8 patients: mild diarrhoea for a few days (5), and abdominal discomfort (3).

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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Bone Health

Osteopenia

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Nilsson AG, 2018 Sweden	To investigate if *L. reuteri* ATCC PTA 6475 has an effect on bone loss in older women with low bone mineral density. Primary outcome was relative change in volumetric bone mineral density (vBMD) after 12 months.	R, DB, PC 12 months	*L. reuteri*: 45 ($1x10^{10}$ CFU) Placebo: 45	*L. reuteri* significantly reduced bone loss compared to placebo ($p=0.047$). Change in vBMD was -0.83% in the *L. reuteri* group and -1.85% in the placebo group.

Oral Health

Gingivitis

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Schlagenhauf U, 2020 Germany	Investigate the effect of *L. reuteri* Prodentis on gingival inflammation in healthy adults	R, DB, PC	*L. reuteri* (2 tabl/d): 36 ($4x10^8$ CFU) Placebo (2 tabl/d): 36	Compared to placebo, *L. reuteri* significantly improved bleeding of probing (primary outcome), as well as gingival index, plaque control record, probing pocket depth and probing attachment level (secondary outcomes).
Schlagenhauf U 2016 Germany	Influence of *L. reuteri* Prodentis lozenges on plaque control and gingival inflammation in pregnant women.	R, DB, PC During 3rd trimester and the first days after delivery	*L. reuteri:* 24 ($4x10^8$ CFU) Placebo: 21	Compared to placebo, *L. reuteri* Prodentis significantly reduced: · Plaque index · Gingival index There was no effect on the inflammation marker TNF-α (in serum).
Bravo J, 2018 Chile	To evaluate the efficacy of *L. reuteri* Prodentis lozenges in the treatment of gingivitis in young adults (~19y).	R, DB, PC 3 months	*L. reuteri:* 15 ($2x10^8$ CFU) Placebo: 15	Only the *L. reuteri* group had a significant reduction in number of sites with severe inflammation. However, both the groups had significant improvements in gingival index, plaque index and bleeding on probing.
Sabatini S, 2017 Italy	Pilot trial to evaluate the effect of *L. reuteri* Prodentis lozenges on gingivitis in diabetic patients (adults).	R, SB, open 30 days	*L. reuteri:* 40 ($4x10^8$ CFU) Control: 40	Compared to control, *L. reuteri* significantly reduced: · Plaque index · Bleeding on probing
Twetman S, 2009 Denmark	To investigate the effect of *L. reuteri* Prodentis chewing gums on gingival inflammation and the levels of selected pro- and anti-inflammatory cytokines in gingival crevicular fluid, in adults.	R, DB, PC 2 weeks + 2w follow-up	*L. reuteri* (2 gums): 13 ($4x10^8$ CFU) *L. reuteri* (1 gum) + placebo (1 gum): 13 ($2x10^8$ CFU) Placebo (2 gums): 12	*L. reuteri* significantly: · Decreased bleeding on probing and reduced the volume of gingival crevicular fluid · Dose-dependently decreased proinflammatory oral cytokines
Krasse P, 2006 Sweden	To study the effect of a probiotic chewing gum on gingivitis and dental plaque in adults, and the occurrence of the probiotic in saliva.	R, DB, PC 14 days	*L. reuteri* LR-1: 20 ($2x10^8$ CFU) *L. reuteri* LR-2: 21 ($2x10^8$ CFU) Placebo: 18	*L. reuteri* significantly reduced gingivitis and dental plaque in patients with moderate to severe gingivitis. Both strains were shown to colonize the saliva.
Stensson M, 2014 (follow-up of the population of Abrahamsson's prevention of allergy study of 2007) Sweden	To evaluate the effect on oral health, at age 9 years, of daily oral supplementation with the probiotic *L. reuteri* ATCC 55730, to mothers during the last month of gestation and to children throughout the first year of life.	R, SB, PC Multi-center Clinical and radiographic examination of the primary dentition and carious lesions, plaque and gingivitis were recorded. Saliva and plaque samples were analysed for mutans streptococci (MS) and lactobacilli (LB). Salivary secretory IgA (sIgA) was determined.	*L. reuteri* (5 drops/d): 60 ($1x10^8$ CFU) Placebo (5 drops/d): 53 Attrition rate of 40% compared to the initial 188 infants of Abrahamsson's trial (2007). Loss to follow-up was mainly due to family move from the area.	Compared to placebo, *L. reuteri* significantly: · Increased the proportion of caries free children: 82% vs. 58% · Decreased the prevalence of approximal caries: 0.67 vs. 1.53 tooth surfaces · Decreased the number of sites with gingivitis No statistically significant intergroup differences were found with respect to mutans streptococci or lactobacilli in saliva or plaque. There was a non-significant trend towards higher sIgA in the probiotic group compared to placebo.
Iniesta M, 2012 Spain	To investigate the effect of *L. reuteri* Prodentis lozenges on clinical and microbiological outcomes in adults with gingivitis.	R, DB, PC 8 weeks	*L. reuteri:* 20 ($2x10^8$ CFU) Placebo: 20	*L. reuteri* reduced numbers of selected periodontal pathogens in the subgingival microbiota, but without any associated clinical impact.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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Gingivitis

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Hallström H, 2013 Sweden	Effect of *L. reuteri* Prodentis lozenges on experimental gingivitis, specific cytokines of gingival crevicular fluid (GCF) and supragingival plaque microbiota in healthy, adult females.	R, DB, PC, crossover 3 weeks, separated by 2-week run-in and washout periods. Participants refrained from cleaning four of their lateral teeth during the experimental periods	18 subjects in total *L. reuteri*: 18 ($2x10^8$ CFU, twice/d) Placebo: 18	· All subjects presented a local plaque accumulation and all but one developed manifest gingivitis at the test sites during the intervention periods. There were no differences in clinical parameters between the two types of test products. · The volume of GCF increased in both groups but was statistically significant only after the placebo period. · The concentrations of IL1 -β and IL-18 increased significantly, while IL-8 and MIP-1β decreased. No differences were displayed between test and placebo. · The microbial composition did not differ between the groups.
Tran LL, 2012 (abstract) USA	Effects of *L. reuteri* Prodentis in healthy adults where gingivitis was experimentally induced by refraining from all oral hygiene measures.	R, DB, PC 14 days	*L. reuteri* : 26 ($2x10^8$ CFU) Placebo: 27	In both groups the gingival and plaque indices increased significantly compared to baseline values, and to the same extent. *L. reuteri* was detected in the saliva of 40% in the probiotic group, while it was absent in the entire placebo group.

Periodontitis

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Laleman I, 2020 Belgium	To evaluate the effect of *L. reuteri* Prodentis lozenges as an adjunct to mechanical debridement on residual pockets in patients with periodontitis.	R, DB, PC 12 weeks with follow-up at 24 weeks	*L. reuteri* (2 tabl/d): 20 ($4x10^8$ CFU) Placebo (2 tabl/d): 19	At 24 weeks, the overall probing pocket depth in the *L. reuteri* Prodentis group was significantly lower compared to the placebo group (p=0.034). This difference was even more pronounced in moderate (4–6mm) and deep (≥7mm) pockets.
Pelekos G, 2020 China	Sub-analysis of data from a previous study evaluating the effect of *L. reuteri* Prodentis as an adjunct to Scaling and Root Surface Debridement (S/RSD). This study evaluated changes at molars with deep pockets (PPD≥5mm).	R, DB, PC 28 days	*L. reuteri* (2 tabl/d): 21 ($4x10^8$ CFU) Placebo (2 tabl/d): 20	Compared to placebo, *L. reuteri* significantly improved CAL and conferred a higher probability of shallow residual pocket depth.
Grusovin MG, 2019 Italy	Pilot study to evaluate the effect of *L. reuteri* Prodentis as an adjunct to Full Mouth Guided Biofilm Therapy (FM-GBT) in patients with severe and advanced forms of periodontitis (stage III and IV, grade C).	R, DB, PC 3 months + 3 months washout + 3 months + 3 months washout (1 year in total)	*L. reuteri*: (2 tabl/d): 10 ($4x10^8$ CFU) Placebo (2 tabl/d): 10	*L. reuteri* Prodentis significantly reduced mean probing pocket depth at all time-points (3, 6, 9, and 12 months), sites with BOP at 6 and 9 months, and increased probing attachment level at 6 months, compared to placebo. No complications or adverse events were reported.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Periodontitis

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Teughels W, 2013 Turkey	To evaluate the effects of *L. reuteri* Prodentis lozenges on clinical and microbiological parameters, as an adjunct to scaling and root planing (SRP) in adults with chronic periodontitis (mean age 46y).	R, DB, PC 12 weeks	*L. reuteri* (2 tabl/d): 15 ($4x10^8$ CFU) Placebo (2 tabl/d): 15	At week 12, all clinical parameters were significantly reduced in both groups. Compared to placebo, subjects in the *L. reuteri* group showed significant effects on: · More pocket depth reduction and attachment gain in moderate and deep pockets · Number of subjects with a high and low risk for disease progression, respectively · Number of subjects in need of surgery on ≥3 teeth · Larger reduction in counts of *Porphyromonas gingivalis* in sub-, supragingival and saliva samples at 12 weeks
Vicario M, 2013 Spain	Effect of short-term use of *L. reuteri* Prodentis lozenges on initial to moderate chronic periodontitis in non-smoking and otherwise healthy adults.	R, DB, PC 30 days	*L. reuteri*: 10 ($2x10^8$ CFU) Placebo: 9	*L. reuteri* Prodentis significantly decreased: · Plaque index · Bleeding on probing · Pocket probing depths of 5–6 mm and ≥6 mm All indices increased in the placebo group, although non-significantly. No adverse effects were recorded in any of the groups.
Vivekananda MR, 2010 India	To investigate the effect of *L. reuteri* Prodentis lozenges on chronic periodontitis, alone or in combination with scaling and root planing (SRP).	R, DB, PC Day 0–21 = SRP only, day 22–42 study product added	*L. reuteri* (2 tabl/d): 15 ($4x10^8$ CFU) Placebo (2 tabl/d): 15	· *L. reuteri* Prodentis alone and in combination with SRP significantly inhibited chronic periodontitis inflammation, plaque formation and counts of oral pathogens · The combined treatments significantly reduced clinical attachment level and probing pocket depth
Tekce M, 2015 Turkey	Investigation of short- and long-term effects on clinical and microbiological parameters of *L. reuteri* Prodentis (Lr) as an adjunct to initial treatment with scaling and root planing in subjects with chronic periodontitis, aged 35–50 years. The colonisation ability of *L. reuteri* in the periodontal pockets was also assessed.	R, DB, PC 3 weeks, with follow-up at days 21, 90, 180 and 360	*L. reuteri* (2 tabl/d): 20 ($4x10^8$ CFU) Placebo (2 tabl/d): 20	Significant effects for *L. reuteri* Prodentis compared to placebo were shown as: · Consistently greater reductions in pocket depths (primary outcome) from baseline to days 21, 90, 180 and 360 · Significantly fewer patients in need of surgery at day 360. The proportion of teeth in need of surgery at day 360 was 0.8% and 41.2%, respectively After one year, the total viable cell counts of bacteria and proportions of obligate anaerobes had returned to the baseline levels in both groups after initial significant reductions. In the probiotic group Lr was found in subgingival pockets in 6 and 11 patients on day 21 and 90, respectively. All patients completed until follow-up at day 360, and without any adverse reactions.
Ince G, 2015 (subgroup analysis of Tekce 2015 trial) Turkey	Investigation of short- and long-term effects on clinical and micro-biological parameters of *L. reuteri* Prodentis (Lr) as an adjunct to initial treatment with scaling and root planing in subjects with chronic periodontitis, aged 35–50 years.	R, DB, PC 3 weeks, with follow-up at days 21, 90, 180, 360	*L. reuteri* (2 tabl/d): 15 ($4x10^8$ CFU) Placebo (2 tabl/d): 15	Compared to the placebo group, subjects in the *L. reuteri* Prodentis group had significant changes in the inflammation-associated markers in the gingival crevicular fluid up to day 180: there was a decrease in the level of MMP-8 (matrix metalloproteinases-8) and increase in the TIMP-1 (tissue inhibitor of metalloproteinases-1). For the clinical markers, the effect compared to placebo was sustained up to day 360.
Szkaradkiewicz AK, 2014 Poland	To assess if supplementation with *L. reuteri* Prodentis (Lr) can improve clinical and inflammatory parameters in subjects with moderate chronic periodontitis, aged 31–46y, and previously untreated for periodontitis.	Open. Lr was admin. from two weeks (for an unknown period of time) after professional cleaning and treatment to subjects with low response to the professional treatment. Subjects with good clinical response at this time point remained as a control group.	*L. reuteri* (2 tabl/d): 24 ($4x10^8$ CFU) Control: 14	18/24 (75%) of subjects given *L. reuteri* evaluated 2 weeks after stopping the use of the probiotic, had significant decrease in severity of periodontitis by the clinical measures bleeding on probing, pocket probing depth and clinical attachment level. The levels of the pro-inflammatory cytokines TNF-α, IL-1β and IL-17 in the crevicular fluid were also significantly decreased in these 18 subjects. The remaining 6 of the intervention group showed no response, and their levels of the different parameters were similar to the 14 control group subjects at the same time point.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Peri-Implant Mucositis and Peri-Implantitis

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Alqahtani F, 2021 (New!)	To compare the efficay of *L. reuteri* Prodentis with antibiotics as an adjunct to mechanical debridement in the treatment of peri-implant mucositis. Primary outcomes were plaque index, bleeding on probing, probing depth and crestal-bone-loss, recorded at baseline and at 3-and 6-months follow-up.	R, Open Lr: 21 days Antibiotics: 7 days	1) MD + *L. reuteri* ($4x10^8$ CFU) 2) MD + antibiotics 3) MD	At 3 months, peri-implant plaque index, bleeding on probing and probing depth were significantly lower in the probiotic group compared to the placebo group. However, at 6 months no differences were seen between the groups.
Alqahtani F 2019 Saudi Arabia	To evaluate the effect of *L. reuteri* Prodentis as adjuvant to mechanical debridement (MD) in the treatment of peri-implant mucositis in smoking and non-smoking patients.	R, open 3 weeks + follow-up at 3- and 6 months	80 in total. 40 smokers and 40 non-smokers *L. reuteri* (2 tabl/d): 40 (20 in each group) ($4x10^8$ CFU)	In non-smokers, the mean pocket depth, plaque index and bleeding on probing were significantly lower in the subjects that received *L. reuteri* Prodentis as adjunct to MD, compared to those who received MD alone at the 3 months' follow-up. At the 6 months' follow-up, there were no sign differences between the groups. In smokers, there were no significant differences at any of the time points.
Peña M, 2019 Spain	To evaluate the additional effect of *L. reuteri* Prodentis after mechanical debridement and 0.12% chlorhexidine in the treatment of peri-implant mucositis, compared to mechanical debridement and chlorhexidine alone.	R, DB, PC 1 month + 3 months follow-up	*L. reuteri*: 25 ($2x10^8$ CFU) Placebo: 25	The administration of *L. reuteri* did not provide any additional effect on clinical or microbiological parameters after treatment with mechanical debridement and 0.12% chlorhexidine.
Galofré M, 2018 Spain	To evaluate the clinical and microbiological effect of *L. reuteri* Prodentis as adjuvant to non-surgical mechanical therapy in implants with mucositis or peri-implantitis.	R, DB, PC 1 month + 2 months follow-up	*L. reuteri*: : 22 ($2x10^8$ CFU) Placebo: 22	*L. reuteri* significantly decreased probing pocket depth in implants with mucositis or peri-implantitis. In addition, bleeding on probing decreased in implants with peri-implantitis, and general bleeding on probing in patients with mucositis. *L. reuteri* had limited effect on the peri-implant microbiota, although a significant decrease of was found in implants with mucositis.
Tada H, 2018 Japan	To evaluate the effect of *L. reuteri* Prodentis, as an adjunct to antibiotics, on clinical and microbiological parameters in patients with mild to moderate peri-implantitis.	R, DB, PC 6 months	*L. reuteri* : 15 ($2x10^8$ CFU) Placebo: 15	· *L. reuteri* significantly reduced modified bleeding index compared to placebo · Significant improvements in probing pocket depth in the *L. reuteri* group, but not in the placebo group · No significant differences in bleeding on probing. However, number of patients with high bleeding on probing scores were fewer in the *L. reuteri* group · No significant differences in bacterial numbers
Hallström H, 2016 Sweden	To investigate if *L. reuteri* Prodentis, administered as oil and lozenges, has any additive effect to mechanical treatment on clinical parameters, microbiota and crevicular fluid around implants with peri-implant mucositis, in adults 24–85y old	R, DB, PC 3 months Topical oil was applied at the baseline cleaning session, the subjects thereafter used the study lozenges	*L. reuteri* (2 tabl): 22 ($4x10^8$ CFU) Placebo (2 tabl): 24 Follow-up at 6 mo.	*L. reuteri* did not add any benefit to conventional therapy in this study: all clinical variables improved over a 6-month period in both groups. The study groups harboured low-to-moderate levels of the main pathogens associated with periodontitis, and a single topical application of *L. reuteri* Prodentis oil, followed by a daily oral administration of lozenges, did not affect the profile of the subgingival microbiota. The levels of inflammatory mediators IL-1β, IL-8, CCL5 and TNF-α were reduced by 40–50% compared with baseline after 4 weeks in both groups, with no difference between them.
Flichy-Fernández AJ, 2015 Spain	To assess clinical and immune system effects of *L. reuteri* Prodentis in edentulous adult patients with tooth implants, comparing a group with healthy implants to a group with peri-implant mucositis at one or more implants.	R, DB, PC crossover 1 mo. with active product, followed by 7 mo. of washout period, then 1 mo. with placebo product and 7 mo. of follow-up	A) *L. reuteri* + healthy implants (1 tabl): 22 ($2x10^8$ CFU) B) *L. reuteri* + peri-implant mucositis (1 tabl): 12	After 1 month with *L. reuteri* Prodentis, the decreases in plaque, probing depth, gingival index and crevicular fluid were significantly greater than with placebo in both group A and B. The effects were, however, more pronounced in group B, who had peri-implant mucositis. The pro-inflammatory immune parameters IL-1β, IL-6 and IL-8 were all improved after the probiotic supplementation, but to a greater extent in the peri-implantitis group.
Flichy-Fernández AJ, 2012 (abstract) Spain	Effect of *L. reuteri* Prodentis lozenges on counts of periodontal pathogens in adults with 1-2 dental implants and in comparison with teeth in the same individual.	R, DB, PC, crossover 28 days per product	30 in total *L. reuteri*: 30 ($2x10^8$ CFU) Placebo: 30	Compared to placebo the counts of *P. gingivalis, T. denticola* and of total bacterial load were significantly reduced in dental implants. In the teeth there was a significant reduction in counts of *T. forsythia, T. denticola* and total bacterial load.
Ata-Ali J, 2012 (abstract) Spain	Effect of *L. reuteri* Prodentis lozenges on counts of periodontal pathogens at dental implants in smoking and non-smoking adults.	Open 28 days	54 in total, 37 non-smokers and 17 smokers *L. reuteri*: 54 ($2x10^8$ CFU)	In both smokers and non-smokers *L. reuteri* reduced the counts of *T. forsythia, P. gingivalis* and *T. denticola* at the implants. *A. actinomycetemcomitans* was not detected in any group. Total bacterial load was reduced in non-smokers but not in smokers.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Caries-Associated Risk Factors

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Alamoudi NM, 2018 Saudi Arabia	To evaluate the effect of *L. reuteri* Prodentis lozenges on caries-associated salivary bacterial counts (mutans streptococci and lactobacilli), dental plaque accumulation, and salivary buffer capacity in preschool children (3–6y).	R, DB, PC 28 days	*L. reuteri*: 90 ($4x10^8$ CFU) Placebo: 88	*L. reuteri* significantly reduced mutans streptococci and lactobacilli, compared to placebo. However, there was no difference in plaque accumulation or buffer capacity between the groups.
Alforaidi S, 2021 Sweden (New!)	Evaluate the effect of drops containing *L. reuteri* Prodentis on plaque pH and the number of *S. mutans* and lactobacilli in orthodontic patients.	*R, DB, PC 3 weeks	*L. reuteri*: 13 Placebo: 14 (rinse w 5 drops diluted in 1 ml wter, 2x/d)	Significant increase in plaque pH at three weeks in the probiotic group ($p<0.05$), while insignificant changes in the pH value were found for the placebo group in comparison to baseline ($p > 0.05$). No difference in the number of *S. mutans* and lactobacilli between the groups.
Caglar E, 2006 Turkey	To study the effect of *L. reuteri* ATCC 55730 in two non-dairy delivery systems, on mutans streptococci and lactobacilli in adults.	R, DB, PC 3 weeks	*L. reuteri* drinking straw: 30 ($1x10^8$ CFU) Placebo drinking straw: 30 *L. reuteri* chewable tablet: 30 ($1x10^8$ CFU) Placebo chewable tablet: 30	*L. reuteri* delivered in a drinking straw or as a chewable tablet significantly reduced the counts of mutans streptococci compared to placebo.
Caglar E, 2007 Turkey	To compare the effect of chewing gums with xylitol or *L. reuteri* Prodentis, or a combination thereof, on counts of mutans streptococci and lactobacilli in the saliva of young adults.	R, DB, PC 3 weeks	*L. reuteri*: 20 ($6x10^8$ CFU) *L. reuteri* + xylitol: 20 ($4x10^8$ CFU) Xylitol: 20	· Three weeks' daily consumption of either 3 *L. reuteri* Prodentis chewing gums or 6 xylitol chewing gums reduced the counts of mutans streptococci · Total lactobacilli levels were unaffected
Caglar E, 2008 Turkey	To evaluate the effect of *L. reuteri* Prodentis lozenges on *Streptococcus mutans* in young adults with high counts thereof.	R, DB, PC 10 days	*L. reuteri*: 10 ($2x10^8$ CFU) Placebo: 10	· *L. reuteri* significantly reduced the counts of *Streptococcus mutans* · Total number of lactobacilli was unaffected
Cannon M, 2013 USA	To evaluate and compare microbiological anti-caries effects of two probiotics: PerioBalance (=*L. reuteri* Prodentis) lozenges (Lr) and EvoraKids chewable tablets (EvK, blend of three streptococci strains), in children aged 6–12y and with moderate to high risk of caries. Both healthy and medically compromised children were included.	R, open 28 days with Lr 30 days with EvK Evaluation 8 weeks after start of intervention	*L. reuteri* (1 tabl/d): 30 ($2x10^8$ CFU) probiotic mix* (2 tabl/d): 30 * Str. uberis KJ2, Str. oralis KJ3, Str. rattus JH145 (EvoraKids, >100 million cfu)	Both probiotics suppressed the level of mutans streptococci and lactobacilli, compared to baseline. The difference between the two probiotics was non-significant. (The CRT (Caries Risk Test) Bacteria Kit was applied for microbiological evaluations. It allows simultaneous determination of mutans streptococci and lactobacilli counts in saliva by means of selective agars.)
Cildir S, 2012 Turkey	To study effects on salivary mutans streptococci and lactobacilli in 4–12y old children with cleft lip/palate by use of *L. reuteri* Prodentis drops.	R, DB, PC, crossover 25 days per product	19 subjects in total *L. reuteri*: 19 ($2x10^8$ CFU) Placebo: 19	*L. reuteri* Prodentis drops did not reduce the salivary counts of mutans streptococci or total lactobacilli.
Gizani S, 2016 Greece	To evaluate the effect of daily intake of *L. reuteri* Prodentis on white spot lesion (WSL) formation as well as on salivary lactobacilli (LB) and mutans streptococci (MS) counts, in patients undergoing orthodontic treatment with fixed appliances.	R, DB, PC 17 months with start 6 months after bonding	*L. reuteri*: 42 ($4x10^8$ CFU) Placebo: 43	There were no differences in the incidence of WSL between the groups at debonding. The levels of salivary LB were significantly reduced in both groups at the time of debonding compared with baseline, while no alterations of the MS counts were unveiled. The patients had generally a neglected oral hygiene, both at baseline and at the follow-up.
Marttinen A, 2012 Finland	Effect of*L. reuteri* Prodentis lozenges and tablets with *Lactobacillus GG* (LGG) on the production of lactic acid in supragingival dental plaque. Detection rate of probiotic strains, and counts of total lactobacilli and mutans streptococci in dental plaque.	R, DB, crossover 2 weeks per product	13 subjects in total *L. reuteri*: 13 ($4x10^8$ CFU) LGG: 13 (2 tablets per day)	Lactic acid production in plaque was unaffected after use of either two probiotics for 2 weeks. *L. reuteri* was detected more frequently in dental plaque than LGG. Mutans streptococci levels were unchanged during both treatments, comparing baseline and after two weeks. Total lactobacilli in plaque were increased during use of *L. reuteri* but non-significantly so during LGG use.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Caries-Associated Risk Factors

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Keller MK, 2012b Sweden + Denmark	The effect on regrowth of oral bacteria after a 3-day full-mouth disinfection with chlorhexidine in young adults with moderate to high salivary counts of *S. mutans*.	R, DB, PC 6 weeks + 6 weeks follow-up	*L. reuteri* (2 tabl/d): 32 ($4x10^8$ CFU) Placebo (2 tabl/d): 30	The intake of lozenges with *L. reuteri* did not affect the regrowth rate of salivary mutans streptococci after full-mouth disinfection with chlorhexidine, nor the counts of other bacteria associated with oral health.
Keller MK, 2012c Denmark	To study the effects of *L. reuteri* Prodentis on lactic acid formation in supragingival dental plaque and changes in counts of *S. mutans* and total lactobacilli in young, healthy adults with moderate to high counts of salivary mutans streptococci.	R, DB, PC, crossover 2 weeks per product and 3-week washout between the two periods	18 subjects in total *L. reuteri* (3 tabl/d): 18 ($6x10^8$ CFU) Placebo (3 tabl/d): 18	There was no increase in plaque acidity after use of *L. reuteri* for two weeks. Scores for growth of *S. mutans* remained the same within groups, while total lactobacilli increased significantly during the test period.
Keller MK, 2014 Denmark	To investigate the effect of *L. reuteri* Prodentis on early caries lesions in adolescents, aged 12-17 years, as measured by quantitative light-induced fluorescence.	R, DB, PC 12 weeks	*L. reuteri* (2 tabl/d): 19 ($4x10^8$ CFU) Placebo (2 tabl/d): 17	There were no statistically significant differences in fluorescence values and lesion area between the groups, neither at baseline, nor at the follow-up. Compared to baseline, there was a significant decrease in fluorescence at 12 weeks in the test group but not in the placebo group.
Nikawa H, 2004 Japan	To investigate the effect of *L. reuteri* ATCC 55730, delivered in yoghurt, on mutans streptococci and lactobacilli in young healthy adults.	R, PC, crossover, 2 weeks per product	40 subjects in total *L. reuteri:* 40 (CFU not stated) Placebo: 40	· Reduction of the counts of *Streptococcus mutans* in both groups · In the group with *L. reuteri* during the first test period, the inhibiting effect of *L. reuteri* was sustained also during the placebo period
Romani Vestman N, 2013 (additional results of the study by Keller et al. 2012b) Sweden + Denmark	To determine the prevalence of *L. reuteri* Prodentis' strains DSM 17938 and ATCC PTA 5289 in saliva during and after a 6-week intervention preceded by full-mouth disinfection with chlorhexidine, compared with placebo, and investigate whether the persistence of these probiotic strains affected the re-growth of mutans streptococci (MS) in young, healthy adults.	R, DB, PC 6 weeks follow-up at 3 and 6 months	*L. reuteri* (2 tabl/d): 31 ($4x10^8$ CFU) Placebo (2 tabl/d): 28	The strain *L. reuteri* DSM 17938 was detected in 60–70% of test group subjects during intervention, but it was cultivable in only a few individuals after termination of the intervention. The presence of DNA from *L. reuteri* DSM 17938 in saliva seemed to delay the regrowth of caries-associated MS.
Stensson M, 2014 (follow-up of the population of Abrahamsson's prevention-of-allergy study of 2007) Sweden	To evaluate the effect on oral health, at age 9 years, of daily oral supplementation with the probiotic *L. reuteri* ATCC 55730, to mothers during the last month of gestation and to children throughout the first year of life.	R, SB, PC Multi-center Clinical and radiographic examination of the primary dentition and carious lesions, plaque and gingivitis were recorded. Saliva and plaque samples were analysed for mutans streptococci (MS) and lactobacilli (LB). Salivary secretory IgA (sIgA) was determined.	*L. reuteri* (5 drops/d): 60 ($1x10^8$ CFU) Placebo (5 drops/d): 53 Attrition rate of 40% compared to the initial 188 infants of Abrahamsson's trial (2007). Loss to follow-up was mainly due to family move from the area.	Compared to placebo, *L. reuteri* significantly: · Increased the proportion of caries free children: 82% vs. 58% · Decreased the prevalence of approximal caries: 0.67 vs. 1.53 tooth surfaces · Decreased the number of sites with gingivitis No statistically significant intergroup differences were found with respect to mutans streptococci or lactobacilli in saliva or plaque. There was a non-significant trend towards higher sIgA in the probiotic group compared to placebo.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Oral Health

Immune Parameters in Saliva

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Ericson D, 2013 Sweden	To investigate whether ingestion of *L. reuteri* Prodentis could influence salivary IgA levels, specific anti-mutans streptococci IgA levels and specific antibodies towards the ingested probiotic bacterium.	R, DB, PC 12 weeks + follow-up 1 month thereafter	*L reuteri* (2 gums/d): 11 ($2x10^8$ CFU) Placebo (2 gums/d): 12	The total level of salivary IgA increased significantly within the test group. Specific IgA towards the ingested *L. reuteri* ATCC PTA 5289, as well as against *S. mutans* and *S. sobrinus*, decreased in the test group and the levels tended to return to pre-treatment values after the 4-week washout period. No changes were seen in the control group during the trial.
Jørgensen MR, 2016 Denmark	To evaluate the effect of daily ingestion of *L. reuteri* Prodentis on the levels of secretory IgA (sIgA) and the cytokines interleukin (IL)-1β, IL-6, IL-8 and IL-10 in whole saliva of healthy young adults, aged 18–32y.	R, DB, PC, crossover 3 weeks of intervention with 3 weeks of washout between, follow-up 3 weeks post-intervention	41 subjects in total *L reuteri* (2 tabl/d): 41 ($4x10^8$ CFU) Placebo (2 tabl/d): 41	No significant differences in the concentrations of salivary sIgA or cytokines were recorded between the *L. reuteri* and placebo interventions or between baseline and 3 weeks post-intervention levels. No side- or adverse effects were reported.
Braathen G, 2017 Denmark (substudy of Jørgensen 2016)	Saliva from the subjects of the Jørgensen 2016 trial, who ingested *L. reuteri* Prodentis, was further analysed for the presence of *L. reuteri,* the concentration of total protein, salivary IgA and selected cytokines. Results were compared between individuals who harbored *L. reuteri* after the probio-tic intervention (PCR-positive) and those who displayed sub-detection levels (PCR-negative).	R, DB, PC, crossover 3 weeks of intervention with 3 weeks of washout between, follow-up 3 weeks post-intervention	41 subjects in total *L reuteri* (2 tabl/d): 41 ($4x10^8$ CFU) Placebo (2 tabl/d): 41	At baseline, 27% of the individuals displayed presence of *L. reuteri* and 42% were positive immediately after the three-week probiotic intervention. Those with *L. reuteri* in saliva had significantly higher concentrations of salivary IgA and higher %IgA/protein ratio at the termination of the probiotic intake compared with subjects with non-presence of *L. reuteri*. No differences in the cytokine levels were observed.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Oral Health

Other Oral Health Trials

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Keller MK, 2012a Denmark	To evaluate the effect of *L. reuteri* Prodentis chewing gums on oral malodour.	R, DB, PC, crossover, 14 days per product	25 subjects in total *L. reuteri* (2 gums/d): 25 ($4x10^8$ CFU) Placebo (2 gums/d): 25	The probiotic chewing gums significantly decreased oral malodour assessed by organoleptic scores after the probiotic period compared to the placebo gum period. There was no effect on volatile sulphur compounds.
Keller MK, 2018 Denmark	A pilot study to investigate the effect of *L. reuteri* Prodentis lozenges on recurrent candidiasis in oral lichen planus patients.	R, DB, PC 16 weeks + 36 weeks follow-up	*L. reuteri* (3 tabl/d): 10 ($6x10^8$ CFU) Placebo (2 tabl/day): 13	No difference between the groups during the intervention or follow-up in terms of recurrent oral candidiasis. The study experienced recruitment problems and was therefore underpowered.
Kraft-Bodi E, 2015 Sweden	To investigate the effect of a daily intake of the probiotic *L. reuteri* Prodentis on the prevalence and counts of oral *Candida* in frail elderly patients living in nursing homes, and aged 60–102 years and mean age 88y.	R, DB, PC Multi-center 12 weeks Study product was taken at the same time as medicines, morning and early evening	*L. reuteri* (2 tabl/d): 84 ($4x10^8$ CFU) Placebo (2 tabl/d): 90	Compared to placebo, the *L. reuteri* group had a statistically significant reduction in the prevalence of high *Candida* counts (primary outcome), and the difference was statistically significant in both saliva and plaque ($P < 0.05$). No significant differences between the groups were noted concerning clinical signs of gingivitis, i.e. the levels of supragingival plaque or bleeding on probing. No adverse events related to the study products were reported.
Romani Vestman N, 2015 Sweden	To assess the impact on saliva and tooth biofilm microbiota composition and species richness of *L. reuteri* Prodentis ingestion for four weeks, in healthy adult volunteers, aged 20–66.	R, DB, PC 12 weeks follow-up at 1 and 6 mo. after termination of intervention	*L. reuteri* 2 tabl/d): 21 ($4x10^8$ CFU) Placebo (2 tabl/d): 20	· The microbiota composition shifted but species richness remained unaffected · The shift normalized within 1 month after terminating exposure · The *L. reuteri* strains were detected in approximately 70% of the participants during daily administration and in approx. 24% at the 1-month follow-up
Twetman S, 2018 Denmark	Pilot study to investigate the effect of *L. reuteri* Prodentis lozenges , together with *L. reuteri* Prodentis topical oil, on oral wound healing.	R, DB, PC, crossover 1-week run-in period. Biopsy taken with a standardized punch, followed by 8 days intervention. 4-week wash-out period, all procedures were repeated a second time..	10 subjects in total *L. reuteri* (2 tabl/d) + topical oil (1 drop/d): 10 (tabl. $4x10^8$ CFU; oil, $4x10^7$ CFU) Placebo (2 tabl/d) + topical oil (1 drop/d): 10	Tendency of improved wound healing in the *L. reuteri* group at the 2-and 5-day check-ups, but not significant compared to placebo. Higher, but non-significant expressions of TNF superfamily ligands and IL-8 in the probiotic group. The salivary levels of oxytocin were significantly lower ($p<0.05$) in the placebo group at the 8-day follow-up.
Wälivaara D-Å, 2019 Sweden	Investigation of the effect of *L. reuteri* Prodentis lozenges on oral wound healing, swelling, pain and discomfort after surgical removal of mandibular third molars in adults above 18y. A diary was filled out 14 days post-operatively by patients to record pain, swelling, any sleep disturbance, sick leave from work, use of analgesics, adverse events or side effects.	R, DB, PC 2 weeks	*L. reuteri:* (3 tabl/d): 30 ($6x10^8$ CFU) Placebo (3 tabl/d): 31	On day 14, compared to placebo: · Significant reduction in Lr patients' self-reported data on sense of swelling, number of nights with disturbed sleep and days with sick-leave from work ($p<0.05$). · No difference between groups in regard to objective wound healing scores, concentration of oxytocin in saliva and growth of specific bacteria in wound exudate. · No side effects or adverse events were reported
Pedersen AML, 2019 Denmark	Pilot trial to investigate the effect of *L. reuteri* Prodentis lozenges on recurrent aphthous ulcers in adults aged 18–30y, evaluated by Ulcer Severity Score (USS) and subjective pain reported by a Visual Analogue Pain Scale.	R, DB, PC 90 days	*L. reuteri* (2 tabl/d): 10 ($4x10^8$ CFU) Placebo (2 tabl/d): 9	Day 90, end of intervention: · Tendency to greater improvement (difference in lesions by USS) compared to placebo ($p<0.07$). · Significant improvement in USS within the *L. reuteri* group only. · Subjective pain score was improved but without difference between groups. · No report on any side effects or adverse events.
Sinkiewicz G, 2010 Sweden	To investigate the presence of *L. reuteri* in saliva after daily use of *L. reuteri* Prodentis chewing gum, and the effect on plaque index and supra- and subgingival microbiota, in healthy adults.	R, DB, PC 12 weeks + 4w follow-up	*L. reuteri:* 11 ($4x10^8$ CFU) Placebo: 12	· Both strains in *L. reuteri* Prodentis were found in the saliva in the test group after 1 week, but were washed out after cessation of chewing gum usage · Plaque index did not change in the *L. reuteri* group while it increased significantly in the placebo group · *L. reuteri* Prodentis had no significant effect on the composition of the supra- or subgingival microbiota

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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Diabetes Type 2

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Mobini R, 2017 Sweden	To evaluate metabolic effects of *L. reuteri* DSM 17938, in standard or high dose, in adults with type 2 diabetes on insulin treatment. Primary outcome was changes in glycated hemoglobin, secondary outcomes were insulin sensitivity (assessed by glucose clamp), liver fat content, body composition, body fat distribution, faecal microbiota composition and serum bile acids.	R, DB, PC 12 weeks	*L. reuteri*: 15 ($1x10^8$ CFU) *L. reuteri*: 14 ($1x10^{10}$ CFU) Placebo: 15	· Compared to baseline, subjects in the high dose group exhibited increases in insulin sensitivity index (ISI) and serum levels of the secondary bile acid deoxycholic acid (DCA). · Compared to placebo there was no difference in outcomes at the end of the study period. · Post hoc analysis showed that subjects who responded with increased ISI after ingestion of *L. reuteri* had higher microbial diversity at baseline, and increased serum levels of DCA after supplementation. In addition, increases in DCA levels correlated with improved insulin sensitivity in the probiotic recipients.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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Metabolism and Nutrition

Iron Deficiency Anaemia

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Manoppo J, 2019 Indonesia	To determine whether *L. reuteri* DSM 17938 plays a role in the absorption of iron preparations containing 300mg Sulfas Ferrous (SF) in children with iron deficiency anaemia.	R, quasi experimental, SB, controlled 14 days	*L. reuteri*: 34 ($3x10^8$ CFU) & 300mg SF Control: 32 300mg SF	Intervention with iron preparations and *L. reuteri* DSM 17938 in children with iron deficiency anaemia leads to a higher increase in levels of Reticulocyte hemoglobin equivalent than does intervention with iron preparations only. *L. reuteri* DSM 17938 has a beneficial role in the absorption of iron from the intestinal mucosa.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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Colonisation and Microbiota Trials

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Valeur N, 2004 Denmark	Colonisation and effect on immune cells of the gut epithelium in healthy adults.	Open 28 days + 28d follow-up	*L. reuteri*: 19 ($4x10^8$ CFU)	Colonisation verified after 4 weeks by biopsies from the gastric mucosa and the small intestine (duodenum and ileum) and by faecal analyses
Abrahamsson T, 2009 (Substudy of Abrahamsson 2007) Sweden	Prevalence of *L. reuteri* in infant feces after oral supplementation, and influence on the microbial ecology in infants 0-2 years old.	R, DB, PC 12 months + follow-up at 24 months	*L. reuteri*: 95 ($1x10^8$ CFU) Placebo: 93	· *L. reuteri* was detected in the feces of most infants after oral supplementation during the first year of life · Treatment with antibiotics did not reduce the levels of *L. reuteri*
Björkman P, 1999 Finland	Colonisation of the large intestine in healthy adults.	Open 12 days	*L. reuteri*: 10 ($>10^9$ CFU)	Colonisation verified after 12 days by biopsies from the large intestine and by faecal analyses
Rosander A, 2008 Sweden	To verify the safety and colonisation of *L. reuteri* (Lr) DSM 17938 in healthy adults, and also in high dose.	R, DB, PC 28 days + 28d follow-up	Lr DSM 17938: 4 ($8x10^8$ CFU) Lr DSM 17938: 5 ($6.5x10^{10}$ CFU) Lr ATCC 55730: 3 ($8x10^8$ CFU) Placebo: 4	Colonisation of *L. reuteri* DSM 17938 verified in faecal samples, and to the same extent as for *L. reuteri* ATCC 55730
Egervärn M, 2010 Sweden	To evaluate the risk of transfer of plasmid borne antibiotic resistance in *L. reuteri* ATCC 55730 to other gut microbes.	R, DB 14 days + 14d follow-up	*L. reuteri* ATCC 55730: 7 ($5x10^8$ CFU) *L. reuteri* DSM 17938: 7 ($5x10^8$ CFU)	*L. reuteri* DSM 17938 colonized to the same extent as *L. reuteri* ATCC 55730
Savino F, 2010 Italy	To study the effect of *L. reuteri* DSM 17938 on infant colic in infants 2-16 weeks old, and investigate changes in the faecal microbiota.	R, DB, PC 21 days	*L. reuteri*: 25 ($1x10^8$ CFU) Placebo: 21	· 13 infants from each group had faecal samples analysed for *L. reuteri* DSM 17938, and on day 21 it was detected in 12 of 13 infants in the probiotic group, at a mean number of $2.8x10^4$ CFU/g. · There was no *L. reuteri* DSM 17938 detected in the feces of the infants in the placebo group.
Roos S, 2013 (Substudy of Savino 2010) Italy	To analyze the global faecal microbial composition, using large-scale DNA sequencing of 16 S rRNA genes, in a subsample of a population of colicky, breastfed infants given *L. reuteri* DSM 17938 or placebo.	R, DB, PC Faecal samples were collected on days 1 and 21 (last day of intervention)	*L. reuteri*: 15 ($1x10^8$ CFU) Placebo: 14	· The infants' faecal microbiota were composed of *Proteobacteria, Firmicutes, Actinobacteria* and *Bacteroidetes* as the four main phyla. Infants with colic had very high inter-individual variability with *Firmicutes/Bacteroidetes* ratios varying from 4000 to 0.025. On an individual basis, the microbiota was, however, relatively stable over time. · *L. reuteri* did not change the global composition of the microbiota, but responders to treatment had an increased relative abundance of the phyla *Bacteroidetes* and genus *Bacteroides* at day 21 compared with day 0 vs. non-responders. · The phyla composition of the infants at day 21 could be divided into three enterotype groups, dominated by *Firmicutes, Bacteroidetes*, and *Actinobacteria*, respectively.
Dommels YEM, 2009 The Netherlands	To evaluate the faecal detection rate of *L. reuteri* DSM 17938 and another probiotic when ingested in a low-fat spread.	R, DB, PC 3 weeks	*L. reuteri*: 13 ($1x10^9$ CFU) LGG: 16 ($5x10^9$ CFU) Placebo: 13	*L. reuteri* DSM 17938 showed good survival in the GI tract when ingested in a low-fat spread
Smith TJ, 2011 USA	To study colonisation and persistence of *L. reuteri* DSM 17938 in healthy adults after daily or alternate-day probiotic dosing in a vanilla pudding. Colonisation was measured as faecal counts of *L. reuteri* All subjects were non-colonized by *L. reuteri* on day 0.	Open 7 days	Daily *L. reuteri*: 9 ($1x10^9$ CFU) Alternate day *L. reuteri*: 9 ($1x10^9$ CFU)	Alternate-day compared to daily probiotic intake achieved equivalent colonisation. Faecal levels on days 2-4 were of the same magnitude as on days 5-7 in both groups. Colonisation declined rapidly once dosing stopped. Whether alternate day dosing had any effect on clinical outcome measures was not studied.
Glintborg B, 2006 Denmark	To reduce bacterial load and gastric inflammation in *H. pylori*-infected dyspeptic adults.	Open 6 months	*L. reuteri*: 7 ($4x10^8$ CFU)	Colonisation of the gastric mucosa verified at 6 months in all subjects by biopsies
Handschur M, 2007 South Africa	To test identification methods for detection and persistence of *L. reuteri* in the feces of 4-12 months old infants hospitalized for diarrhoea.	Open, PC 3 days	*L. reuteri*: 4, whereof 2 HIV-pos. ($1x10^{10}$ CFU) Placebo: 3, whereof 1 HIV-pos.	*L. reuteri* was detected in feces after 3 days of supplementation to infants with diarrhoea and treated with antibiotics

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Colonisation and Microbiota Trials

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Papagaroufalis K, 2014 Greece	To assess the safety of infant formula containing *L. reuteri* DSM 17938 during the first month of life, with special reference to D-lactic acid, in comparison to infants fed a control formula. Other outcomes were GI tolerance, sleeping and crying behavior, growth and occurrence of adverse events.	R, DB, + control formula 28 days Follow-up on days 112 and 168	36 ($6.6x10^8$ CFU) Control: 35 31 infants in each group took part in the follow-up on days 112 and 168	Compared to control formula: · On day 14 and at 4 months the faecal detection rate of *Bifidobacterium, Lactobacillus,* and *L. reuteri* was significantly higher in the probiotic group · There was no difference in the detection rate of *Enterobacteriaceae* or in total bacteria levels
Garcia Rodenas CL, 2016 (substudy of Papagaroufalis 2014) Greece	To assess the response of newborn infants' microbiota depending on C-section- (C) or vaginally-delivered (V) and ingesting a formula containing *L. reuteri* DSM 17938, in comparison to a similar formula without the probiotic.	R, DB, + control formula (Ct) Stool samples were collected at 2 weeks and 4 months of age. Microbial DNA was extracted, amplified and pyrosequenced	*L. reuteri* (V-Lr): 9 *L. reuteri* (C-Lr): 11 ($1x10^9$ CFU/L of formula) Control (V-Ct): 10 Control (C-Ct): 10	At two weeks, feeding of the *L. reuteri* formula induced changes in the microbiota of C-section-delivered infants to a composition more like the one in vaginally born infants, whether given *L. reuteri* or not. This C-section group had significantly increased abundance and occurrence of *Bifidobacterium* compared to the C-Ct group. *Enterobacteriaceae* abundance was largely decreased. By contrast, the levels of clostridia and *Enterococcus* were similarly high in both C-Ct and C-Lr when compared to the vaginally born groups. *Enterobacter* in C-Lr was not significantly different from C-Ct or from the vaginal delivery groups. At four months the differences between groups were gone, except for *Lactobacillus*, which was increased at both study ages in the Lr groups, regardless of mode of delivery.
Karvonen A, 2001 (abstract) Finland	Safety and colonisation in newborn term infants.	R, DB, PC 30 days	*L. reuteri*: 12 (10^5 CFU) *L. reuteri*: 25 (10^7 CFU) *L. reuteri*: 25 (10^9 CFU) Placebo: 28	No child had any faecal *L. reuteri* on day 0. Thereafter *L. reuteri* colonized in a dose-dependent manner.
del Campo R, 2014 Spain	To assess the effects of *L. reuteri* DSM 17938 in subjects with cystic fibrosis, aged 8-44y (mean age 18y), on GI and overall health (measured by validated questionnaires), the effect on gut inflammation and the composition of the gut microbiota.	R, DB, PC, cross-sover 2 parallel groups 6 mo probiotic 6 mo placebo	30 in total *L. reuteri*: 30 ($1x10^8$ CFU) Placebo: 30	Compared to the placebo test period: · GI health score was significantly improved after 6 mo with *L. reuteri*, measured by the GIQLI questionnaire · Gut inflammation, measured as faecal calprotectin levels, was significantly reduced by *L. reuteri* After 6 months with *L. reuteri* the composition of the gut microbiota was modulated to a less dense and a more diverse one, with 31% reduction of high numbers of *Proteobacteria*. There was a considerable increase of *Firmicutes* and *Bacteroidetes*. The microbiota thereby became more similar to the one of healthy persons.
Mangalat N, 2012 USA	Primary aim was to investigate the safety of drops with *L. reuteri* DSM 17938 in healthy adults. Secondary aim was to study changes in some immune factors.	R, DB, PC 2 months with follow-up after 1 and 4 months	*L. reuteri*: 30 (5 drops/d = $5x10^8$ CFU) Placebo: 10	The numbers of faecal *L. reuteri* as analysed by qPCR differed almost significantly compared to placebo after 1 and 2 months of ingestion. Generally, the numbers of *L. reuteri* were low in the treatment group.
Rattanaprasert M, 2014 USA	To test substrate-directed synbiotic strategies to enhance the persistence and metabolic activity of *L. reuteri* DSM 17938 in the human gut, in a human crossover trial. The prebiotics were galactooligosaccharide (GOS) and/or rhamnose, with maltodextrin as the control. Faecal samples were analysed for numbers of *L. reuteri* and its metabolic activity.	R, SB, PC, cross-over. 4 study periods of 28d each: 11d run-in/ washout period + 7d with ingestion of study product + 10d test-of-persistence period with ingestion of each prebiotic only.	*L. reuteri* (Lr): 15 ($5x10^8$ CFU) 4 study periods: 1. Lr + GOS (2 g) 2. Lr + rhamnose (2 g) 3. Lr + (GOS+rhamnose, 1+1g) 4. Lr + maltodextrin	After 7 days of ingestion of the synbiotic preparations and of *L. reuteri* + maltodextrin, the faecal numbers were 10^8 cfu/g but declined rapidly thereafter. As a single substrate, rhamnose had no effect on metabolic activity. When it was combined with GOS, this synbiotic preparation contributed to the stimulation of metabolic activity of *L. reuteri* n most subjects. The synbiotic preparations, as well as the prebiotics on their own, were well tolerated.
Frese S, 2012 USA	Compare survival and persistence rates of autochthonous (indigenous) and allochthonous (transient) *Lactobacillus* strains in healthy, young adults. Autochthonous strains: *L. reuteri* ATCC PTA 6475 and *L. mucosae* FSL-04. Allochthonous: *L. acidophilus DDS1.*	R, SB, crossover 7 days with 15 days follow-up	12 subjects in total *L. reuteri*: 12 ($1x10^9$ CFU) *L. mucosae*: 12 ($1x10^9$ CFU) *L. acidophilus*: 12 ($1x10^9$ CFU)	*L. reuteri* and *L. mucosae* were detected in more subjects after administration, and these strains also reached about ten times higher cell numbers in faecal samples when compared to *L. acidophilus.* The autochthonous strains were more efficiently established, which is of importance when selecting probiotic strains for human use.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Safety in Infants and Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Abrahamsson T, 2007 Sweden	Prevention of atopic eczema in infants 0-2 years old.	R, DB, PC 12 months	*L. reuteri*: 95 (1x10^8 CFU) Placebo: 93	No clinical tolerance problems during the 12 months supplementation or at follow-up at 2 years of age
Abrahamsson TR, 2013 (Substudy of Abrahamsson 2007) Sweden	In a study on prevention of allergy in newborns, *L. reuteri* ATCC 55730 reduced the incidence of IgE-associated allergic disease in infancy. This treatment might therefore also reduce the risk of asthma and allergic rhino conjunctivitis in school age, which this follow-up study set out to investigate. It also evaluated whether this supplementation was associated with any long-term side effects. The age at follow-up was 7y.	Original study: R, DB, PC	*L. reuteri*: 94 (1x10^8 CFU) Placebo: 90 In the 2007 trial 232 infants were randomised and 188 completed	· Growth indices and gastrointestinal symptoms were similar in the two groups · No severe adverse events were reported
Connolly E, 2005 Sweden	To investigate if levels of D(-)-lactic acid levels in the blood is a safety issue in infants who get *L. reuteri* ATCC 55730 as a long-term daily supplement from birth.	R, DB, PC 12 months	*L. reuteri*: 14 (1x10^8 CFU) Placebo: 10	· All infants had very low levels of D(-)-lactic acid (20-130µM) as measured after 6 and 12 months, i.e. far below levels associated with D(-)-lactic acidosis · This D(-)-lactic acid producing probiotic can be safely given to infants
Kosek MN, 2019 Peru	A phase I study to assess the safety and tolerability of *L. reuteri* DSM 17938 in oil suspension in healthy children, 2-5y old, before doing a phase II/III treatment-of-diarrhoea study in children.	R, DB, PC 5 days follow-up until day 28, and at 6 mo post-enrollment	*L. reuteri*: 41 (1x10^8 CFU) Placebo: 19	Results support no reason for safety concern of use of *L. reuteri*. No difference in markers for iron status, liver, kidney and immune functions. Same incidence of fever and diarrhoeal episodes, but days with diarrhoea, rash or pruritus were fewer in Lr group, based on parental reporting for 28 days. No difference in rates of adverse events between groups, all evaluated as non-related to study products. No serious adverse events.
Gutiérrez-Castrellón P, 2014 Mexico	Evaluate if daily administration of *L. reuteri* DSM 17938 reduces the frequency and duration of diarrhoea episodes and respiratory tract infections in Mexican day school children aged 6-36 months. A cost-effectiveness analysis was also made.	R, DB, PC 3 months of intervention, follow-up at 6 months	*L. reuteri*: 168 (1x10^8 CFU) Placebo: 168	During the study, parents/guardians reported 34 cases of exanthematous disease (18 cases of rubella and 16 cases of exanthema subitum) and 22 cases of minor trauma. None of these adverse events were deemed to be related to the study products, and no related serious adverse events were reported in any group.
Indrio F, 2014 Italy	Investigate if oral supplementation with *L. reuteri* DSM 17938 during the first 3 months of life can reduce the onset of colic, gastro-esophageal reflux, and constipation in term newborns, and in addition reduce the socio-economic impact of these conditions	R, DB, PC 90 days Multicentre study	*L. reuteri*: 238 (1x10^8 CFU) Placebo: 230	Adverse events were monitored by weekly telephone calls that also monitored compliance to study products. No adverse events were reported that were related to the trial.
Savino F, 2010 Italy	To study the effect of *L. reuteri* DSM 17938 on infant colic in infants 2-16 weeks old, and investigate changes in the faecal microbiota.	R, DB, PC 21 days	*L. reuteri*: 25 (1x10^8 CFU) Placebo: 21	· Infants in both groups increased their growth parameters significantly during the 3-week study, with no statistical differences between groups. · The study products were well tolerated. 5 adverse events were reported, whereof one in the probiotic group. All were evaluated as unrelated to the study product.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

L. reuteri and Safety

Safety in Infants and Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Fatheree NY, 2017 USA	A phase 1 study that investigated the safety and tolerability of *L. reuteri* DSM 17938 in healthy breastfed infants with colic, aged 3 weeks to 3 months. Secondary outcomes were effect on crying and fussing time, inflammatory biomarkers and microbiota composition.	R, DB, PC 42 days + 134 days follow-up	*L. reuteri*: 12 (1x10^8 CFU) Placebo: 7 NOTE: The dose was 5 drops, equivalent to 1x10^8 CFU, not 5x10^8 CFU, as stated in the article.	Adverse events were monitored strictly based on the FDA Adverse Events Response System and clinical severity index. · No severe adverse events were reported · ÅNo significant differences between *L. reuteri* and placebo in any of the outcomes
Urbanska M, 2016 Poland	The efficacy of *L. reuteri* DSM 17938 in prevention of nosocomial diarrhoea in hospitalized children, 1-48 months old. A repeat of Wanke's trial but with a 10 times higher dose.	R, DB, PC During hospital stay	*L. reuteri*: 91 (1x10^9 CFU) Placebo: 93	*L. reuteri* did not affect the incidence of hospital-acquired diarrhoeal disease. There was also no difference between the *L. reuteri* and placebo groups for any of the secondary outcomes, including adverse effects. Rotavirus vaccination status had no impact on the results.
Handschur M, 2007 South Africa	To test identification methods for detection and persistence of *L. reuteri* ATCC 55730 in the feces of 4-12 months old infants hospitalized for diarrhoea.	Open, PC 3 days	*L. reuteri*: 4, whereof 2 HIV-pos. (1x10^{10} CFU) Placebo: 3, whereof 1 HIV-pos.	*L. reuteri* was detected in feces after 3 days of supplementation to infants with diarrhoea and treated with antibiotics. There was no report of any adverse events.
Hoy-Schulz YE, 2016 Bangladesh	A phase I study that investigated the safety and acceptability of two probiotics: drops with *L. reuteri* DSM 17938 (Lr) and powder with *B. longum* ssp *infantis* 35624 (Bi), in healthy infants aged 4 to 12 weeks, from urban slums in Bangladesh. Gastrointestinal and respiratory symptoms as well as breastfeeding rates, hospitalizations, differential withdrawals, and caretakers' perception of probiotic use were compared among arms. Primary outcome was proportion of days with symptoms.	R, DB, controlled 1 month's invention + follow-up after 2 additional months. Randomized to 1 of 3 different dosing arms (daily, weekly, biweekly – once every two weeks) over one month, or to a 4th arm that received no probiotics.	Lr+Bi daily: 35 (29 doses) Lr+Bi weekly: 35 (5 doses) Lr+Bi biweekly: 35 (3 doses) Control: 32 (Lr: 1x10^8 CFU + Bi: 1x10^9 CFU)	The ingestion of the combination of these two probiotics was found safe, also if given daily: they did not cause sudden reactions, increase symptom rates, or diminish breastfeeding rates. They were acceptable to the infants and no problems administering the probiotics were identified. No differences in rates of any reported symptoms were observed among arms; additionally, no sudden adverse or allergic reactions were found after probiotic administration, and no hospitalizations were deemed related to the study products.
Karvonen A, 2001 (abstract) Finland	Safety and colonisation in newborn term infants of *L. reuteri* ATCC 55730	R, DB, PC 30 days	*L. reuteri* 12 (1x10^5 CFU) *L. reuteri*: 25 (1x10^7 CFU) *L. reuteri*: 25 (1x10^9 CFU) Placebo: 28	· No clinical tolerance problems · Reduction in frequency of watery stools compared to placebo
Weizman Z, 2006 Israel	Safety of *L. reuteri* ATCC 55730 in healthy infants 3-65 days old.	R, DB, PC 4 weeks	*L. reuteri*: 20 (1.2x10^9 CFU) Bb-12: 20 (1.2x10^9 CFU) Control: 19	Infant formulas with added probiotics were safe, well tolerated and did not negatively affect growth, defecation habits or infant behaviour.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

Safety in Infants and Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Papagaroufalis K, 2014 Greece	To assess the safety of starter infant formula containing *L. reuteri* DSM 17938 during the first month of life, with special reference to D-lactic acid, in comparison to infants fed a control starter formula. Other outcomes were GI tolerance, sleeping and crying behaviour, growth and occurrence of adverse events.	R, DB, controlled 28 days Follow-up on days 112 and 168	*L. reuteri*: 36 (6.6 x 10^8 CFU) Control: 35 31 infants in each group took part in the follow-up on days 112 and 168	· Median urinary D-lactate levels were higher in the *L. reuteri* group than in the control group at 7 and 14 days, but lower at 28 days. Results were consistent with normal ranges of D-lactate previously reported for healthy infants, and far below pathological ranges described in adults. · The occurrence of serious and non-serious AEs was comparable between the two groups. Non-serious AEs were reported in 20% of infants in the probiotics group and 23% of infants in the control group. In both groups, most of these (5 in the probiotics group and 6 in the control group) were respiratory system disorders. None was related to the study products. · In all, 5% of infants in each group had a serious AE during the study · Growth was normal, without differences between groups · There were no differences in the duration of crying or night time sleep
Cekola PL, 2015 USA	To assess the safety of a partially hydrolysed infant formula with added *L. reuteri* DSM 17938 (Lr) in comparison to a similar product without any probiotic (Con), in healthy full-term neonates, with growth as primary outcome. The formulas differed only with regard to the proportion of carbohydrate sources: lactose:maltodextrin ratio was 70:30 in Con + added prebiotic (GOS), while the ratio was 30:70 and no GOS in the Lr formula.	R, DB, controlled Infants ingested the formula from day 14 after birth to day 112=14 weeks	*L. reuteri* 60 (1x10^8 CFU) Placebo: 62	Infants assigned to either formula had normal and similar rates and patterns of growth. Overall, between groups, there were no significant differences in formula intake, stool frequency, colour, consistency, flatulence, frequency of spit-up/vomiting, mood, sleep, or incidence of adverse events (AEs). In both groups a few of the AEs were evaluated as having 'probable' relationship to study product.
Lee LY, 2015 Singapore	To establish safety in healthy, full term infants of starter infant formula containing *L. reuteri* DSM 17938, and *L. reuteri* same strain) plus prebiotics FOS/GOS, respectively, assessed against WHO Growth Standards (CGS). GI tolerance and urinary L- and D-lactate were also investigated.	R, DB, controlled 6 months Follow-up at 2 and 4 mo	*L. reuteri* : 68 *L. reuteri* + FOS/GOS: 72 (1x10^8 CFU)	· Both groups gained weight in accordance with WHO CGS. Other growth parameters were similar between the two groups. · Excretion of urinary L- and D-lactate were similar in the groups · GI tolerance and morbidity were similar in the two groups

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L. reuteri and Safety

Long Term Follow-up Data of Trials in Infants and Children

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Abrahamsson TR, 2013 (Substudy of Abrahamsson 2007) Sweden	In a study on prevention of allergy in newborns, *L. reuteri* ATCC 55730 reduced the incidence of IgE-associated allergic disease in infancy. This treatment might therefore also reduce the risk of asthma and allergic rhino conjunctivitis in school age, which this follow-up study set out to investigate. It also evaluated whether this supplementation was associated with any long-term side effects. The age at follow-up was 7y.	Original study: R, DB, PC	*L. reuteri*: 94 (1x10^8 CFU) Placebo: 90 In the 2007 trial 232 infants were randomised and 188 completed	· Growth indices and gastrointestinal symptoms were similar in the two groups · No severe adverse events were reported
Stensson M, 2014 (Substudy of Abrahamsson 2007) Sweden	To evaluate the effect on oral health, at age 9 years, of daily oral supplementation with the probiotic *L. reuteri* ATCC 55730, to mothers during the last month of gestation and to children throughout the first year of life.	R, SB, PC Multi-center	*L. reuteri* (5 drops/d): 60 (1x10^8 CFU) Placebo (5 drops/d): 53 Attrition rate of 40% compared to the initial 188 infants. Loss to follow-up was mainly due to family move from the area.	Compared to placebo, *L. reuteri* significantly: · Increased the proportion of caries free children: 82% vs. 58% · Decreased the prevalence of approximal caries: 0.67 vs. 1.53 tooth surfaces · decreased the number of sites with gingivitis
Ceratto S, 2014 (abstract, substudy of Savino 2010) Italy	If probiotic reatment with *L. reuteri* DSM 17938 for infant colic may prevent atopic diseases (cow's milk allergy and atopic dermatitis), asthma and migraine at the age of five, and effects on growth.	Original study: R, DB, PC	*L. reuteri*: 25 (1x10^8 CFU) Placebo: 23 In 2010 50 were randomised at baseline and 46 analysed	Growth was similar in the two groups, measured as BMI Z-score.

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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Safety in Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Abrahamsson T, 2007 Sweden	To evaluate prevention of atopic eczema in infants 0–2 years old where pregnant women ingested *L. reuteri* ATCC 55730 before giving birth.	R, DB, PC 4 weeks before delivery, follow-up after 1 month	*L. reuteri*: 95 ($1x10^8$ CFU) Placebo: 93	No report of any adverse events in women receiving *L. reuteri* during the last month of pregnancy
Böttcher MF, 2008 (Substudy of Abrahamsson 2007) Sweden	To evaluate effect on the immunological composition of breast milk (as part of a study on allergy prevention in the offspring). Pregnant women ingested *L. reuteri* ATCC 55730 before giving birth.	R, DB, PC 4 weeks before delivery, follow-up after 1 month	*L. reuteri*: 54 ($1x10^8$ CFU) Placebo: 55	· Colostrum content of the cytokine TGF-beta2 was significantly reduced while its content of the anti-inflammatory cytokine IL-10 increased · The effect was not retained at follow-up · Development of eczema during the first 24 months of life was not associated with any of the analysed breast milk parameters
Egervärn M, 2010 Sweden	To evaluate the risk of transfer of plasmid borne antibiotic resistance in *L. reuteri* ATCC 55730 to other gut microbes.	R, DB 14 days + 14d follow-up	*L. reuteri* ATCC 55730: 7 ($5x10^8$ CFU) *L. reuteri* DSM 17938: 7 ($5x10^8$ CFU)	· No clinical safety or tolerance problems · There was no transfer of antibiotic resistance to other gut bacteria species
Schlagenhauf U, 2016 Germany	Influence of *L. reuteri* Prodentis lozenges on plaque control and gingival inflammation in pregnant women	R, DB, PC During 3rd trimester and until the first days after delivery	*L. reuteri:* 24 ($4x10^8$ CFU) Placebo: 21	Compared to placebo, *L. reuteri* Prodentis significantly reduced: · plaque index · gingival index There was no effect on the inflammation marker TNF-α (in serum). There is no report of any adverse events.
Mangalat N, 2012 USA	To investigate the safety of drops with *L. reuteri* DSM 17938, according to FDA's policies of Investigational New Drug, administered to healthy adults for 2 months. Changes in some immune factors were also monitored.	R, DB, PC 2 months with follow-up after 1 and 4 months	*L. reuteri*: 30 (5 drops/d = $5x10^8$ CFU) Placebo: 10	*L. reuteri* drops were safe to consume and well tolerated. There was no increased risk of adverse events or differences in adverse events reported in the probiotic vs. the placebo group. None of the adverse events were related to the probiotic. No severe adverse events were reported.
Oberhelman RA, 2014 Peru	A phase I study to assess the safety and tolerability of *L. reuteri* DSM 17938 in oil suspension in healthy adult volunteers.	R, DB, PC 5 days + follow-up until day 36 and at 6 months after start of study	*L. reuteri*: 30 ($1x10^8$ CFU) Placebo: 15	· There was no evidence of invasive infection due to *L. reuteri* administration and no differences between groups for laboratory parameters, vital signs, clinical tolerance, or symptoms reported. · The frequency of subject-reported symptoms on the daily log sheets was similar between study groups. · The frequency of adverse events was similar between study groups, and no serious adverse events were reported.
Rosander A, 2008 Sweden	To verify the safety and colonisation of *L. reuteri* (Lr) DSM 17938 in healthy adults, and also in high dose.	R, DB, PC 28 days + 28d follow-up	Lr DSM 17938: 4 ($8x10^8$ CFU) Lr DSM 17938: 5 ($6.5x10^{10}$ CFU) Lr ATCC 55730: 3 ($8x10^8$ CFU) Placebo: 4	No clinical safety or tolerance problems with any of the dosages or *L. reuteri* strains
Wolf BW, 1998 USA	Safety and tolerance in immunocompromised, i.e. HIV-positive adults. The subjects were 23–50yr, the majority men, and not using antiretroviral therapy. They consumed high dose of freeze-dried *L. reuteri* SD2112 (=ATCC 55730) powder in sachets.	R, DB, PC 21 days + 14d follow-up Physical examination, serum chemistries, hematology, urinalysis, and faecal fat: at baseline, day 21 and 35. Faecal total *Lactobacillus* and *L. reuteri* were analysed every week, including baseline. Any GI symptoms were reported in a daily diary.	*L. reuteri*: 15 ($1x10^{10}$ CFU) Placebo: 20	There were no clinical safety or tolerance problems compared to placebo. · Blood analyses showed no growth of bacteria. · Faecal numbers of *L. reuteri* and total *Lactobacillus* were unusually low in the active group, though *L. reuteri* tended to increase in the active group. The lifestyle of most subjects, being homosexual men, might explain this deviation from the results of the safety trial in healthy men (Wolf 1995).

** R= randomized, DB = double blind, SB = single blind, PC= placebo controlled*

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L. reuteri and Safety

Safety in Adults

Reference	Study Objectives	Study Design*	Subjects and (Daily Dose)	Results
Wolf BW, 1995 USA	Safety and tolerance in healthy adult males consuming a capsule with powder of freeze-dried *L. reuteri* SD2112 (=ATCC 55730) in high dose.	R, DB, PC 21 days + 7d follow-up Serum chemistries, hematology, urinalysis, urinary indican excretion, faecal fat and faecal total *Lactobacillus* and *L. reuteri, were* analysed every week, including baseline. Physical examination: day 0, 21 and 28. Any GI symptoms were reported in a daily diary. Faecal level of *L. reuteri* was checked also at day 77 after first day of probiotic consumption.	*L. reuteri*: 15 ($1x10^{11}$ CFU) Placebo: 15	The incidence of subjective tolerance factors was infrequent and similar for both treatments. Serum chemistry associated with heart, liver, and kidney function, protein balance, and bone maintenance was analysed: although significant differences were observed for a few of the serum chemistry and hematology variables, all of the values remained within the normal range for healthy adult males. Subjects consuming *L. reuteri* had increased ($p<0.01$) levels of *L. reuteri* in their feces on day 7, 14, 21, and 28. Colonisation was lost within 2 months. Total *Lactobacillus* numbers did not differ between groups during the study. Conclusion: *L. reuteri* at this high dosage was safe to use and with good tolerance.

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