Appendix 1. Published randomised controlled trials (RCTs) about treatment of infantile colic with probiotic vs placebo (past 10 years)

Authors (year)	Sample	Design (country)	Intervention	Outcome	Effective?	SORT
Szajewska H et al (2013)[22]	**Intervention** n = 40 **Control** n = 40 Inclusion criteria: • Infants aged <5 months with infant colic. • Exclusively or predominantly breastfed.	RCT (Poland)	Infants were randomly assigned to receive *Lactobacillus reuteri* DSM 17938 (1×10^8 CFU) or an identically appearing and tasting placebo, orally, five drops once daily, for 21 days.	Crying time reduced significantly in the parental perception of colic severity in the probiotic group when compared with the placebo group. No adverse events were reported. Comment: Absence of an objective way of assessing the crying duration.	Yes	2
Sung V et al (2014)[10]	**Intervention** n = 85 **Control** n = 82 Inclusion criteria: • Infants aged <3 months meeting Wessel's criteria. • Breastfed infants or formula-fed infants.	RCT (Australia)	Infants were randomly assigned to receive *L. reuteri* DSM 17938 (1×10^8 CFU) or an identically appearing and tasting placebo, orally, five drops once daily, for a one-month period.	At the end of the study, the infants in the probiotic group cried or fussed 49 minutes more than the placebo group. This increase only occurred in the formula-fed infants. No adverse events were reported. Comment: Most of the infants were recruited from an emergency or urgent care setting.	No	2
Chau K et al (2015)[23]	**Intervention** n = 24 **Control** n = 28 Inclusion criteria: • Infants aged <6 months with modified Wessel's criteria. • Exclusively breastfed infants.	RCT (Canada)	Infants were randomly assigned to receive five drops orally daily of *L. reuteri* DSM 17938 (1×10^8 CFU) or placebo for 21 days. Daily crying and fussing times were recorded in a structured diary.	*Lactobacillus reuteri* was superior to placebo in reducing daily crying and fussing times. The difference was statistically significant as early as seven days after initiation of the probiotic therapy. Comment: The measure to assess the crying duration and fussing times in infants with colic relied solely on the mothers' reports of the crying duration and fussing episodes in the maternal diaries. Small sample.	Yes	2
Mi GL et al (2015)[24]	**Intervention** n = 21 **Control** n = 21 Inclusion criteria: • Infants aged <4 months with infant colic. • Exclusively or predominantly breastfed infants.	RCT (China)	Participants were assigned to receive *L. reuteri* at a dose 1×10^8 CFU or placebo with an identical formulation without live micro-organisms. Treatment was given to participants for 21 days, and they were monitored for a period of four weeks.	Mean daily crying time had a significantly greater reduction in the probiotic group when compared with the placebo group. Comment: Small sample and single blind trial.	Yes	2

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Authors (year)	Sample	Design (country)	Intervention	Outcome	Effective?	SORT
Fatheree NY et al (2017)[17]	**Intervention** n = 11 **Control** n = 5 Inclusion criteria: • Infants with colic aged three weeks to three months. • Breastfed infants.	RCT (USA)	The participants received either a dose of *L. reuteri* strain DSM 17938 (approximately 5 × 10^8 CFU) or placebo for 42 days and were monitored for 134 days.	Crying and fussing time declined in both groups during treatment with no significant differences between them. Comment: Small sample.	No	2
Tatari M et al (2017)[11]	**Intervention** n = 49 **Control** n = 49 Inclusion criteria: • Infants aged 15–120 days with infant colic. • Breastfed neonates.	RCT (Iran)	Infants were randomly assigned to receive *L. reuteri* daily or a placebo that looked like the probiotic (in terms of shape, size and colour). Treatment lasted for 21 days.	There was a significant decrease in crying time in the intervention group when compared with the control group. Comment: This was a single-blind trial and reports were provided by the mothers in measuring the outcomes.	Yes	2
Savino F et al (2018)[5]	**Intervention** n = 18 **Control** n = 16 Inclusion criteria: • Infants aged <60 days with infant colic.	RCT (Italy)	Infants with colic were randomly assigned to receive oral daily *L. reuteri* DSM 17938 (1 × 10^8 CFU) or placebo for 28 days.	After *L. reuteri* administration for 28 days in infants with colic, the researchers observed a significant decrease in daily crying time. Comment: Small sample.	Yes	2
Ahmadipour S et al (2020)[14]	**Intervention** n = 48 **Control** n = 24 Inclusion criteria: • Infants aged <3 months who met Wessel's criteria. • Breastfed infants.	RCT (Iran)	Supplement containing 1 × 10^9 CFU of *L. reuteri, Lactobacillus rhamnosus, Bifidobacterium infantis* probiotics and fructo-oligosaccharide vs placebo. Both groups were assigned to receive five drops daily.	Probiotic therapy significantly reduced the frequency and duration of crying. Comment: Small sample size. Additionally, the researchers identified difficulties of some parents in reporting the exact crying duration and frequency of their infant.	Yes	2
Nocerino R et al (2020)[8]	**Intervention** n = 35 **Control** n = 37 Inclusion criteria: • Infants aged <7 weeks with infant colic. • Exclusively breastfed infant.	RCT (Italy)	Infants were randomly allocated to receive *Bifidobacterium animalis* subsp. *lactis* BB-12 (1 × 10^9 CFU) or placebo (similar in colour, taste and smell), six drops once daily, for 28 days.	The mean daily crying duration rate was reduced by ≥50%, and reduction was even greater for infants treated with BB 12, starting at the end of the second week. The mean number of crying episodes decreased in both groups, but with a higher effect in the BB 12 group. Comment: Small sample.	Yes	2

CFU, colony-forming units; SORT, strength of recommendation taxonomy