

## REVIEW ARTICLE

# A systematic review of prevention and treatment of infantile colic

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**Abstract****Aim:** The aim of this review was to evaluate the evidence for interventions for infantile colic.**Methods:** This was a systematic review based on a literature search in December 2017 for articles published during 2007–2017 about preventive and treatment interventions for infantile colic in infants. The review included original randomised controlled trials (RCTs) and meta-analyses with at least 20 infants in each study group that were assessed according to GRADE criteria.**Results:** The review found moderately strong evidence that administration of *Lactobacillus reuteri* DSM 17938 shortened the crying duration, with positive evidence from three out of four national contexts. There were four RCTs of acupuncture, all with no or minimal effect on crying duration. All studies reviewed with a follow-up until or beyond three months of age show a quite steep decline over time in crying duration in both treatment and control groups.**Conclusion:** *Lactobacillus reuteri* DSM 17938 is a promising treatment for infantile colic with moderately strong evidence in this review, but studies in more populations are needed. Acupuncture is not an effective treatment for infantile colic. Systematic support strategies to parents with infantile colic are important knowledge gaps.**KEYWORDS**

acupuncture, colic, excessive crying, infantile colic, infant, probiotics

## 1 | INTRODUCTION

Infant behaviours such as excessive crying, fussing and sleeping problems are found in approximately 20% of all children and are the most common complaints for which parents seek professional help. Infants referred for persistent crying problems and associated sleeping or feeding problems, so-called 'infant regulation problems', are at increased risk for developing more severe problems later in childhood including ADHD, conduct problems, negative emotionality and academic difficulties.<sup>1</sup>

A varied amount of crying daily is considered normal in typically developing infants, with the duration increasing from birth and peaking at approximately 6 weeks.<sup>2</sup> Infantile colic has been the subject of many investigations, and since 1954, it has been defined as 'crying for at least three hours per day, for at least three days per week, for a period of three weeks or longer in otherwise healthy infants'; typically known as Wessel 'rule of threes'. Recently, the Wessel criteria have been further refined in the Rome classification of functional gastrointestinal disorders (Rome IV), with the replacement of the three weeks duration criterion with a 7-day duration criterion.<sup>3</sup>

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Infantile colic is a common disorder in the first months of life, affecting somewhere between 4% and 28% of infants worldwide, depending on geography and definitions used.<sup>2</sup> Persistent infant colic can contribute to parental fatigue and distress and may result in strained parental relationships and poor parental engagement with their infant.<sup>3</sup>

It has been assumed that the causes of excessive crying/infant colic are multifactorial, with maternal, paternal, infant and environmental factors being implicated.<sup>4</sup> Maternal considerations include stress and postnatal depression, whereas infant factors may include the individual infant's temperament, developmental milestones achieved, the infant's sensory processing capacity and underlying organic causes. Organic causes are thought to include food protein allergy and/or food intolerances.<sup>2</sup>

The aim of this review was to evaluate the evidence for methods for prevention and treatment of excessive crying in infancy and to identify important knowledge gaps that need to be filled in future research.

## 2 | METHODS

We searched MEDLINE, Web of Science and PsycINFO in December 2017 for articles published during 2007–2017 about preventive and treatment interventions for sleep problems and crying/colic in infants. See Appendix S1 for search syntax. A total of 2070 unique records were found and screened through abstracts. When the retrieved articles indicated that the overlap in the literature of treatment of sleep disorders and infantile colic was minimal, it was decided to separate the review into two. The following criteria were used in the review of studies of infantile colic:

1. The article should describe an original randomised control trial (RCT) study. Quasi-randomised studies were also included.
2. Colic/ crying in infants below six months of age should be the target of the intervention.
3. Infant and parental outcomes were accepted.
4. Intervention and control groups should consist of at least 20 infants.
5. Systematic reviews were included only if the studies included fulfilled the above search criteria.

The search flow is described in Figure 1.

All articles were screened by two researchers with the GRADE framework<sup>5</sup> operationalised into a Swedish checklist by the Swedish Agency for Health Technology Assessment and Assessment of Social Services ([https://www.sbu.se/globalassets/ebm/metodbok/mall\\_randomiserade\\_studier.pdf](https://www.sbu.se/globalassets/ebm/metodbok/mall_randomiserade_studier.pdf))

## 3 | RESULTS

There were 476 articles of original studies that were screened in full text. Ten articles that described original intervention studies and two

### Key notes

- One in five infants fulfil the criteria of infantile colic at the age of six weeks.
- There is moderately strong evidence that administration of the probiotic *Lactobacillus reuteri* DSM 17938 can shorten crying duration in infants with colic, while the available evidence does not support acupuncture for colic.
- There is a need for evidence-based parent support strategies for infantile colic. Such strategies should also include the second parent.

that described meta-analyses fulfilled the study criteria described above and were judged to be of moderate or high quality according to the GRADE criteria. These studies included interventions based on principles of education of parents, probiotics, food manipulation of the mother, pain relief and acupuncture. Table 1 provides a summary of the studies included in the results.

### 3.1 | Education

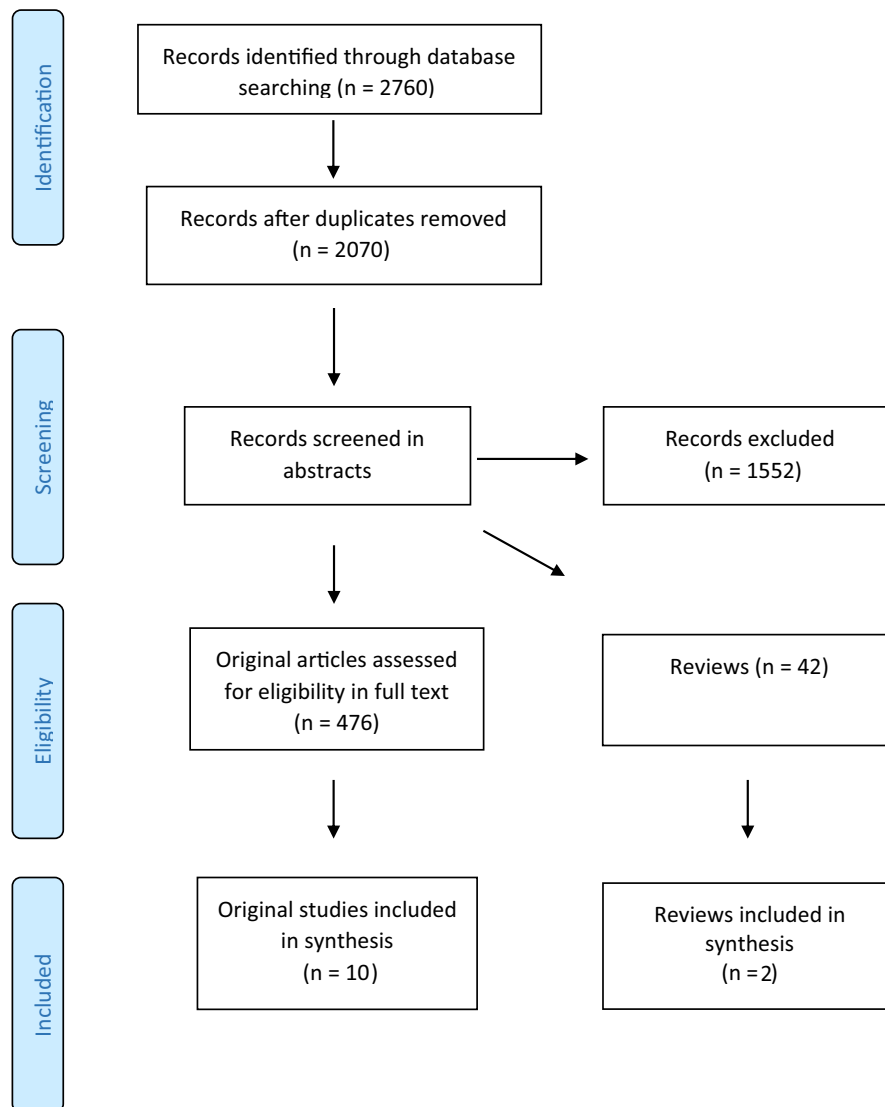
In an intervention delivered by well-baby clinics in Melbourne, Australia, Hiscock et al<sup>6</sup> mailed a 27-page booklet and 23-min DVD to randomised families. Control families received the routine support and information provided by the well-baby clinic. The booklet contained information about normal infant sleep cycles, crying patterns, strategies to promote independent settling and self-care for parents. Intervention families were also offered an individual telephone consultation at infant age 6–8 weeks (ie peak infant crying time) and a 1.5-h parent group session at approximately infant age 12 weeks. The intervention did not have any effect on crying duration in the infants, but mothers in the intervention group had lower levels of clinical cases of depression according to the Edinburgh Parental Depression scale, with adjusted odds ratios (ORs) of 0.57 at the six-month follow-up.

### 3.2 | Probiotics

The developing gastrointestinal microbiota has been suggested to be involved in the causation of excessive crying in children in the age 2 week to 3 months, the typical period when excessive crying peaks and fades. This period is also the period when the previously sterile gut is colonised with bacteria, and it has been hypothesised that this process initially could cause discomfort/pain in some infants.<sup>7</sup>

This hypothesis has been tested in a number of randomised controlled trials with different types of bacteria. The bacteria most consistently found to be linked with decreased crying time is *Lactobacillus reuteri* DSM 17938. In two population-based studies

FIGURE 1 Search flow



in Italy,<sup>8,9</sup> this probiotic was evaluated as a preventive intervention for excessive crying in double-blind RCTs. Both studies favoured the intervention group, but one<sup>9</sup> used indirect measures of excessive crying and thus should be interpreted cautiously. In a Finnish study, Kukkonen et al<sup>10</sup> investigated the effects of a mix of probiotic bacteria, not including *Lactobacillus reuteri* DSM 17938, on the development of allergic disorders, and also recorded the incidence of infantile colic. Very similar rates were found in control and intervention groups.

Harb et al<sup>11</sup> performed a meta-analysis of six double-blind RCTs of the *Lactobacillus reuteri* DSM 17938 as treatment for infantile colic in infants with breastfeeding in populations from three European countries and Australia. Effects were estimated data at 21 days of treatment, because this was the common data collection point for these studies. Overall, *Lactobacillus reuteri* DSM 17938 reduced crying time in the infants studied (pooled MD  $-55.9$  min/day, 95% CI  $-64.4$  to  $-47.3$ ,  $P < .001$ ). It should be noted, however, that the largest study, a study from Australia

by Sung et al<sup>12</sup>, did not find any effect of the probiotic. In the GRADE terminology, the evidence was categorised as moderately strong rather than strong, because of this heterogeneity between populations.

Kianifar et al<sup>13</sup>, in Iran, examined the effects of a mixture of 6 species of microbiota, not including *Lactobacillus reuteri* DSM 17938, plus fructo-oligosaccharide on infants with infantile colic in a double-blind RCT, with a significant treatment effect on crying duration on the seventh day of the intervention.

### 3.3 | Diet

In a French double-blind RCT of formula-fed infants, Dupont et al<sup>14</sup> investigated the effects on crying duration in infants with infantile colic of an experimental formula enriched with probiotics (other than *Lactobacillus reuteri* DSM 17938) and reduced in protein and starch. No effect on crying duration was demonstrated.

TABLE 1 Overview of articles included in review of prevention and treatment for excessive crying/infantile colic

Authors/year	Sample	Setting and delivery	Intervention details	Outcome	Was the programme effective?
<b>Information/education</b>					
Hiscock et al (2014)	<p><b>Intervention</b> N = 273 families</p> <p><b>Control</b> N = 274 families</p> <p>Mothers and their child born at 32 weeks' gestation or later, with enough English and no known chronic disorder</p> <p><b>Attrition:</b> 55%</p>	<p><b>Design</b> RCT</p> <p><b>Setting</b> 42 well-child clinics in Melbourne, Victoria, Australia</p>	<p>Mothers were recruited at the first home visit by their Maternal and Child Health (MCH) nurse</p> <p>Intervention families were mailed a 27-page booklet and 23-min DVD. The booklet contained information about normal infant sleep cycles, crying patterns, strategies to promote independent settling and self-care for parents. Intervention families were also offered an individual telephone consultation at infant age 6–8 weeks (ie peak infant crying time 15) and a 1.5-h parent group session at approximately infant age 12 weeks</p> <p><b>Control group</b>—The control group received usual well-child care</p>	<p>Infant outcomes were measured by postal survey at approximately 4 and 6 months of age. Caregivers were asked if they had experienced a problem (yes/no) with infant day sleep, crying or feeding, and if they responded in the affirmative, to rate the severity of each problem on a 7-point Likert scale, from 1 = 'hardly any problem' to 7 = 'a severe problem'</p> <p>There were no differences between groups in caregiver report of infant sleep, crying, or feeding problems at follow-up at 4 and 6 months of age</p> <p>Levels of maternal depression, however, were lower in the intervention group at the 6-month, but not 4-month follow-up</p>	<p>No on infant crying</p> <p>Inconclusive, on maternal mental health</p>
<b>Probiotics Prevention</b>					
Indrio et al (2014)	<p><b>Intervention</b> N = 468 families</p> <p><b>Control</b> N = 471 families</p> <p>Inclusion criteria were (1) gestational age more than 37 to less than 41 weeks, (2) age less than 1 week on entry into the study, (3) birthweight adequate for gestational age, (4) Apgar score of more than 8 at 10 min, (5) no congenital disorders and/or clinical or physical alterations at clinical examination and (6) no antibiotic or probiotic administration before inclusion</p> <p><b>Attrition:</b> 20%</p>	<p><b>Design</b> RCT</p> <p><b>Setting</b> 9 Paediatric clinics in Italy</p>	<p>Recruitment at nine paediatric clinics. Age at recruitment or reasons for attending the clinic are not documented in the article. Infants were randomly allocated to receive either L reuteri DSM 17938 or placebo. Five drops of the formulation, delivering a dose of <math>1 \times 10^8</math> colony-forming units of L reuteri DSM17938, were administered to the newborns each day for 90 days</p>	<p>Parents were asked to record minutes per day of inconsolable crying from recruitment up to age 3 months</p> <p>At 3 months of age, the mean duration of crying time (38 vs 71 min; <math>P &lt; .01</math>) for the L reuteri DSM17938 and placebo groups, respectively, was significantly different</p> <p>Comment: Outcomes were not analysed separately for formula and breastfed children</p>	<p>Yes</p>

(Continues)

TABLE 1 (Continued)

Authors/year	Sample	Setting and delivery	Intervention details	Outcome	Was the programme effective?
Kukkonen et al (2014)	<b>Intervention</b> N =461 families <b>Control</b> N =464 families <b>Attrition:</b> 8%	<b>Design</b> RCT <b>Setting</b> 42 well-child clinics in Melbourne, Victoria, Australia	Mothers took capsules containing a mixture of <i>Lactobacillus rhamnosus</i> GG and LC705, <i>Bifidobacterium breve</i> Bb99 and <i>Propionibacterium freudenreichii</i> ssp <i>shermanii</i> JS (8–9 _ 109 colony-forming units in each capsule) or a placebo twice daily for 4 weeks before delivery. For 6 months after birth, the infants received daily 1 opened capsule of the same probiotics and 0.8 g of GOSs (of bovine origin) in liquid form or placebo (microcrystalline cellulose plus sugar syrup)	Questionnaire at 3 months Infantile colic, defined as crying at least 4 h per day for at least 3 days per week occurred in 4% and similar but less frequent crying (once or twice per week) occurred in 10% of each group Comment: Recording of colic not very detailed, main purpose of study is prevention of allergies	No
Savino et al (2015)	<b>Intervention</b> N =51 children <b>Control</b> N =54 children Inclusion criteria: Healthy term infants < 10 days <b>Attrition:</b> 7%	<b>Design</b> RCT <b>Setting</b> 3 GP offices and one paediatric clinic in Genova and Turin, Italy	Patients were randomly assigned to receive five drops containing the probiotic <i>L. reuteri</i> DSM 17938 (108 cfu) with 400 UI of vitamin D3 or only 400 UI of vitamin D3 daily (vitamin D is routinely administered to all newborns). The treatment group received a suspension of freeze-dried <i>L. reuteri</i> DSM 17938 in a mixture of sunflower oil and medium-chain triglyceride oil supplied with added vitamin D3, in a 5-mL dark bottle fitted with a dropper cap. The control product was a suspension of olive oil with cholecalciferol (vitamin D) 2.5 mg (100,000 UI/mL), in a 10-mL dark bottle with a dropper cap. The two liquids looked and smelled similar	The use of pain-relieving agents (simethicone, cimetropium bromide) was reported each day by parents during the intervention period into the 'diary' and was assessed and reported in the table data by a study team member. The paediatrician noted the number of phone calls and visits due to infantile colic. All outcomes favoured the intervention group Comment: Indirect measures of crying	Yes
<i>Treatment</i> Harb 2016	<b>Meta-analysis based on (N intervention/N control):</b> Chau 2015 (52/52) in Ontario, Canada Mi 2015 (39/39) in Zhengzhou, China Savino 2010 (46/46) in North-West Italy Savino 2007 (83/83) in North-West Italy Sung 2014 (127/68) in Melbourne, Australia Szajewska (80/69) in Warsaw, Poland	<b>Design</b> RCT <b>Setting</b>	All studies are double-blind RCTs of the probiotic <i>L. reuteri</i> . The studies include infants with exclusive and partial breastfeeding but exclude studies with formula-fed infants	Crying time recorded in diaries in all included studies Five of the six studies favoured the intervention. The summarised effect was a reduction of 54 min crying time per day Comment: The largest study, by Sung et al in Australia showed no effect of the intervention	Yes

(Continues)

TABLE 1 (Continued)

Authors/year	Sample	Setting and delivery	Intervention details	Outcome	Was the programme effective?
Kianfar 2014	<p><b>Intervention</b> N =25 children</p> <p><b>Control</b> N =20 children</p> <p>Inclusion criteria: Term infants, aged 3 weeks to 3 months, weaned (formula-fed), with normal growth and with more than 3 weeks of crying periods, at least 3h per day, 3 days per week (Wessel et al., 1954)</p> <p><b>Attrition:</b> 10%</p>	<p><b>Design</b> RCT</p> <p><b>Setting</b> Teaching hospital in Iran</p>	<p>Intervention infants received a symbiotic sachet containing 1 billion CFU of <i>L. casei</i>, <i>L. rhamnosus</i>, <i>Streptococcus thermophilus</i>, <i>Bifidobacterium breve</i>, <i>L. acidophilus</i>, <i>B. infantis</i>, <i>L. bulgaricus</i> and <i>FOS</i> (Protexin Healthcare, Somerset, UK). The control group received placebo that was matched for size, volume, shape and manufactured by the same company. Both synbiotics and placebo were dispensed by hospital pharmacist</p> <p>Intervention was concealed from study investigators, pharmacist and parents to minimise treatment bias</p>	<p>Outcome measures were (1) reduction in the daily crying time &gt; 50%, yes/no, (2) reduction in the daily crying time &gt; 90% (yes/no) and (3) Mean daily crying time</p> <p>All three outcomes favoured the intervention at day 7</p>	Yes
<b>Other nutritional</b>					
Dupont 2010	<p><b>Intervention</b> N =30 children</p> <p><b>Control</b> N =32 children</p> <p>Inclusion criteria: healthy breastfed infants aged 2 weeks to 4 months with infant colic defined as per Wessel's criteria</p> <p><b>Attrition:</b> 26%</p>	<p><b>Design</b> RCT</p> <p><b>Setting</b> ?</p>	<p>A prospective, multicentre randomised, double-blind, placebo-controlled study compared two Infant Formulas, during 1 month, in colicky formula-fed children. The experimental formula (EF, Modilac Digest 1) was a-lactalbumin-enriched and probiotics supplemented (<i>Lactobacillus rhamnosus</i>, <i>Bifidobacterium infantis</i>), reduced in protein and lactose content, and thickened with corn starch. The control formula (CF) was not enriched in a-lactalbumin, had a higher quantity of proteins and lactose, and neither probiotics nor starch</p>	<p>The crying duration decreased similarly with time in control and intervention group</p>	No
Hill 2015	<p><b>Intervention</b> N =47 children</p> <p><b>Control</b> N =43 children</p> <p>Maternal atopy was present in around 50% in both intervention and control groups</p> <p>Inclusion criteria: Healthy breastfed infants with infant colic defined as per Wessel's criteria. Mean age at start of intervention: 5.5 weeks</p> <p><b>Attrition:</b> 11% in intervention group and 20% in control group</p>	<p><b>Design</b> RCT</p> <p><b>Setting</b> Well-baby clinics in Melbourne, Australia</p>	<p>The effects of 2 maternal diet programmes, that is a low-allergen diet that excluded major food allergens and a control diet that included these foods, were compared. Both diets avoided food preservatives, colours and additives. Intervention mothers were instructed to exclude all foods containing dairy products, soy, wheat, eggs, peanuts, tree nuts and fish from their diet. Their diet included a rice milk drink, meats, vegetables, fruits and cereals (corn and rice). A calcium supplement (1.2 g/day) was prescribed</p>	<p>Reduction in crying time after one week was more prominent in children with mothers on the elimination diet, particularly for moderate reduction</p> <p>Comment: Not blinded, very high level of atopy in mothers, reduction by atopy was not reported, adherence to diet was poor in control group</p>	Yes

(Continues)

TABLE 1 (Continued)

Authors/year	Sample	Setting and delivery	Intervention details	Outcome	Was the programme effective?
<b>Pain relief</b>					
Biagioli 2016	Cochrane Review of randomised controlled trials (RCTs) and quasi-RCTs evaluating the effects of pain-relieving agents given to infants with colic, satisfying the Wessel criteria. The review included 18 RCTs involving 1014 infants	<b>Design</b> RCTs and quasi-RCTs <b>Setting</b>	Three studies compared simethicone with placebo, and one with <i>Mentha piperita</i> ; four studies compared herbal agents with placebo; two compared sucrose or glucose with placebo; five compared dicyclomine with placebo; and two compared cimetropium—one against placebo and the other at two different dosages. One multiple-arm study compared sucrose and herbal tea vs no treatment	<b>Simethicone.</b> Comparison with placebo revealed no differences with placebo <b>Herbal agents.</b> Low and moderate quality evidence suggesting that herbal agents reduced the duration of crying compared with placebo <b>Sucrose.</b> One very low-quality study involving 35 infants reported that sucrose reduced hours spent crying compared with placebo (MD 1.72, 95% CI 1.38 to 2.06) <b>Dicyclomine.</b> One study met quality criteria, showing an effect of RR 2.50, 95% CI 1.17 to 5.34, compared with placebo. Two of five studies reported relevant adverse effects (longer sleep 4%, wide-eyed state 4%, drowsiness 13%) <b>Cimetropium bromide.</b> One very low-quality study showed reduced crying duration compared with placebo	No Inconclusive Inconclusive
<b>Acupuncture</b>					
Reinthal et al (208)	<b>Intervention</b> N = 20 children <b>Control</b> N = 20 <b>Attrition:</b> 0% reported	<b>Design</b> RCT <b>Setting</b> Private acupuncture clinic	A prospective quasi-randomised single-blind control study The structured programme of four treatments over a period of two weeks was delivered in a private acupuncture clinic, with referral from 21 child health clinics. The infants allocated to have acupuncture subsequently received light needling at point LI4 of the hand's first dorsal interosseal muscle	Pain diary divided into 4–6 h periods. For each period a rating between 0 and 10 was made. Frequency and crying duration were also recorded No difference in reduction of crying duration between intervention and control groups Comment: This is a small study with multiple outcomes	No

(Continues)

TABLE 1 (Continued)

Authors/year	Sample	Setting and delivery	Intervention details	Outcome	Was the programme effective?
Landgren et al (2010)	<p><b>Intervention</b> N = 43 children</p> <p><b>Control</b> N = 38</p> <p>Inclusion criteria: healthy infants, born after gestational week 36, not treated with dicyclomine and fulfilling the modified Wessel criteria for colic: 'crying/fussing for at least 3 h a day, occurring 3 days or more in the same week'</p> <p><b>Attrition:</b> 10%</p>	<p><b>Design</b> RCT</p> <p><b>Setting</b> Private acupuncture clinic</p>	<p>The randomisation procedure divided the infants into an intervention group with a structured programme including acupuncture (acupuncture group) or to the same structured programme not including acupuncture (control group)</p> <p>The study was double-blind as neither the parents who registered the infants crying nor the nurse who met the parents knew to which group the infant belonged. Two closed doors separated the parents from the treatment room and music was always played. Parents were informed that the needle was very thin, usually caused no bleeding or visible marks and that acupuncture does not necessarily provoke crying</p> <p>The structured programme was delivered in a private acupuncture clinic and consisted of a total of six biweekly visits to the acupuncture clinic. The infants allocated to have acupuncture subsequently received minimal, standardised acupuncture with a sterilised, disposable acupuncture needle, Vinco MicroClean, 0.20 × 13 mm. The needle was inserted unilaterally and left in place for 2 s at an approximate depth of 2 mm at point LI4 of the hand's first dorsal interosseal muscle</p>	<p>Parents reported infants' fussing, crying and colicky crying in a standardised diary form</p> <p>Intervention and control groups had similar improvement over time with regard to crying time. During the second week fussing and colicky crying was slightly lower in the intervention group</p> <p>Comment: Solely breastfeeding rates were slightly lower in control group, 66% vs 74%</p>	No

(Continues)



TABLE 1 (Continued)

Authors/year	Sample	Setting and delivery	Intervention details	Outcome	Was the programme effective?
Landgren et al (2017)	<p><b>Intervention</b> Group A = 47 children Group B = 49 children</p> <p><b>Control</b> 48 children</p> <p>Inclusion criteria: Eligible infants were between 2 and 8 weeks of age who, according to their parents' records in a diary, cried and/or fussed &gt; 3 h/day for &gt; 3 days during the baseline week (BL). Before inclusion they also needed to have tried a diet excluding cow's milk protein from breastfeeding mothers and/or appropriate formula for at least 5 days. The exclusion criteria included being born before 37 weeks' gestation, taking any kind of prescribed medication or having previously tried acupuncture</p> <p><b>Attrition:</b> 2%</p>	<p><b>Design</b> RCT</p> <p><b>Setting</b> Four well-baby clinics in Sweden</p>	<p>A multicentre three-armed RCT conducted. Infants were randomly allocated to either A. standardised minimal acupuncture at point LI4 of the hand's first dorsal interosseal muscle; B. semi-standardised individualised acupuncture inspired by traditional Chinese; or C. regular support from CHC</p>	<p>Parents reported infants' fussing and crying in a standardised diary form. Intervention and control groups had similar improvement over time with regard to crying time. Colicky crying was slightly lower in intervention groups at follow-up</p> <p>Comment: Analysis of success of blinding showed that 72% of intervention parents but only 21% had understood which group their child was included in</p>	No
Skeije et al (2013)	<p><b>Intervention</b> N = 38 children with diaries N = 44 children with parental interviews Mean age 6 weeks at the start of the intervention</p> <p><b>Control</b> N = 41 with diaries Mean age 6 weeks at the start of the diaries</p> <p>Inclusion criteria: Term infant who fulfilled the Wessel criteria for colic: 'crying/fussing for at least 3h a day, occurring 3 days or more in the same week'</p> <p><b>Attrition:</b> 10%</p>	<p><b>Design</b> RCT</p> <p><b>Setting</b> 13 GP's offices in Norway</p>	<p>The randomisation procedure divided the infants into an intervention group with a structured programme including acupuncture (acupuncture group) and a control group with no treatment. Both groups visited the GP office on the day of the inclusion and day 4 and day 5</p> <p>The GP was alone in the treatment room with the infant during the intervention. Identical procedure, except for the needle insertions, was performed on each infant in the treatment and no-treatment control group</p>	<p>The primary outcome was difference in changes in crying time in the registration period</p> <p>Intervention and control groups had similar improvement over time with regard to crying time. The blinding was evaluated and found to be successful</p>	No

### 3.4 | Pain relief

In a Cochrane review by Biagoli et al<sup>15</sup>, a number of pain relief medications and herbal agents, that had been studied in RCTs and quasi-RCTs of infants with infant colic, were analysed. Three studies examined simethicone and found no effect compared with a control group. No conclusive evidence for treatment effects was found for herbal agents, sucrose nor cimetropium bromide. Biagoli et al<sup>15</sup> also reports one RCT of moderate quality of Dicyclomine. In this study, more of the infants given dicyclomine responded with less crying than those given placebo. Major adverse effects of the drug, however, were reported, with longer sleep 4%, wide-eyed state 4% and drowsiness 13%.

### 3.5 | Acupuncture

Four Scandinavian studies investigated acupuncture as treatment for infantile colic (according to the Wessel criteria); three RCTs and one quasi-RCT. Three Swedish studies used light needling at the hand's first dorsal interosseal muscle. Two of these studies were made in private acupuncture clinics<sup>16,17</sup>, while Landgren et al<sup>18</sup> investigated acupuncture as an intervention in well-baby clinics in Malmö, with nurses delivering the acupuncture. The decrease in crying duration over time was similar in control and study groups in all of these three intervention studies. The intention in all these three studies was to blind whether the infant had received acupuncture or not, but in the one study that investigated the quality of the blinding, it was found that many parents in the acupuncture group had understood that their infant was in the treatment group. In a Norwegian study, Skeije et al<sup>19</sup> applied acupuncture below the patella in the office of GPs in a blinded RCT. The blinding was found to be successful, but no positive treatment effect was identified.

## 4 | DISCUSSION

In this study, we have reviewed original studies and meta-analyses published during 2007–2017 of prevention and treatment interventions for infantile colic. We found several different strategies for interventions with an infant-centred focus; probiotics, acupuncture, pain relief and herbal medicines. A few studies had a parent-focused approach based on dietary manipulation of breastfeeding mothers or education of parents.

The review showed moderately strong evidence that the administration of *Lactobacillus reuteri* DSM 17938 can shorten the crying duration in infants with infantile colic. RCTs conducted in three different countries in south and east Europe have shown significant reductions in crying time in infants with infantile colic. This conclusion is further supported by a also supported by two recent meta-analyses by Sung et al<sup>20</sup> and Gutiérrez-Castrellón et al<sup>21</sup>. There is less evidence for a positive effect in formula-fed infants, as concluded in the meta-analysis by Sung et al<sup>20</sup>, and no evidence of an effect

in infants with colic in Australia. It has been suggested that the effect of *Lactobacillus reuteri* DSM 17938 is dependent on the infant gut microbiota and that differences between the effect on crying duration in breastfed and formula-fed infants are explained by differences in microbiota<sup>7,22</sup>. It is possible that infant gut microbiota also differs between national populations and that results of effects of *Lactobacillus reuteri* DSM 17938 from one population therefore may not be transferrable to other national contexts.<sup>23</sup> This could potentially explain the lack of effect of *Lactobacillus reuteri* DSM 17938 on infants with colic in Australia. *Lactobacillus reuteri* DSM 17938 has also been investigated as a preventive measure on the population level, but here solid evidence is lacking, as concluded in a recent Cochrane review by Ong et al.<sup>24</sup> More preventive studies are needed in sufficiently large study population to enable detection of the low-grade effects that can be expected in such trials.

With regard to pain relief, simethicone has been investigated in several RCTs, but without any clinically relevant treatment effects.<sup>15</sup> There is some, albeit limited, evidence for dicyclomine as a pain relief for colicky infants, but the reported adverse effects were so severe that the drug was retrieved from the market in the early 1990s.<sup>25</sup>

Building on experimental evidence from a Swedish study on the association of maternal intake of cow milk to crying in colicky infants,<sup>26</sup> breastfeeding mothers with colicky infants are often given the advice to eliminate cow milk from their diet.<sup>27</sup> Unfortunately, there was no RCT in this review that tested this hypothesis. It should be remembered, however, that cow milk allergy is a fairly common organic cause of infant colic that should always be considered in the medical examination of a colicky infant.<sup>3</sup>

Acupuncture as treatment for infant colic had been investigated in four controlled studies in Scandinavia, where three were RCTs and at least one was successfully blinded. The effects were minimal at the most. Further presentation of data from these studies also shows considerable pain associated with the treatment sessions.<sup>28</sup> Acupuncture can thus not be recommended as a treatment for infant colic.

### 4.1 | Limitations

This study used a limited time window from 2007 to 2017, thus not taking into account studies published before or after that date. Publication bias should always be considered in evaluation of treatment studies and particularly when economic incentives are involved. *Lactobacillus reuteri* DSM 17938 is a commercial product, and the possibility of such bias thus cannot be excluded for this treatment.

## 5 | FUTURE STUDIES

The lack of evidence for interventions for infantile colic in formula-fed infants makes such studies a high priority in this field. As has

been mentioned above, there is also a need for further studies of this probiotic as a preventive intervention for colic. Manipulation of maternal diets are often suggested as interventions for colic in breastfed infants in clinical practice, but evidence for this from more than single RCT is lacking.<sup>21</sup>

All studies reviewed with a follow-up until or beyond three months showed a quite steep decline over time in crying duration in both treatment and control groups. A review by Wolke et al<sup>29</sup> found a mean population prevalence of around 20% for infantile colic during the first 6 weeks of life, 11% at 8–9 weeks of age and less than one per cent at 10–12 weeks of age. The primary challenge is thus not to cure infants with excessive crying during their first months, but to alleviate stress during these months to prevent secondary effects in the family. There was only one study in this review<sup>6</sup> that explored this line of thought in a study with an educational strategy with positive effects on maternal depression. A recent Cochrane review by Gordon et al in 2019<sup>30</sup> on parent training programmes for infantile colic, with broader inclusion criteria than this review, similarly found limited evidence for positive effects. Further studies are needed to develop and evaluate such strategies of support, with the inclusion also of the second parent.

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#### CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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#### REFERENCES

- Crncec R, Matthey S, Nemeth D. Infant sleep problems and emotional health: a review of two behavioural approaches. *J Reprod Infant Psychol*. 2010;28:44–54.
- St James-Roberts I. Helping parents to manage infant crying and sleeping: a review of the evidence and its implications for services. *Child Abuse Rev*. 2007;16:47–69.
- Zeevenhooven J, Browne PD, L'Hoir MP, de Weerth C, Benninga MA. Infant colic: mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2018;15(8):479–496.
- Kaley F, Reid V, Flynn E. The psychology of infant colic: a review of current research. *Infant Ment Health J*. 2011;32:526–541.
- Alonso-Coello P, Schünemann HJ, Moberg J, et al. Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*. 2016;353:i2016.
- Hiscock H, Cook F, Bayer J, et al. Preventing early infant sleep and crying problems and postnatal depression: a randomized trial. *Pediatrics*. 2014;133:e346–e354.
- Dubois NE, Gregory KE. Characterizing the intestinal microbiome in infantile colic: findings based on an integrative review of the literature. *Biol Res Nurs*. 2016;18(3):307–315.
- Indrio F, Di Mauro A, Riezzo G, et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial. *JAMA Pediatr*. 2014;168:228–233.
- Savino F, Ceratto S, Poggi E, Cartosio ME, Cordero di Montezemolo L, Giannattasio A. Preventive effects of oral probiotic on infantile colic: a prospective, randomised, blinded, controlled trial using *Lactobacillus reuteri* DSM 17938 DSM 17938. *Benef Microbes*. 2015;6:245–251.
- Kukkonen K, Savilahti E, Haahtela T, et al. Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. *Pediatrics*. 2008;122:8–12.
- Harb T, Matsuyama M, David M, Hill RJ. Infant colic-what works: a systematic review of interventions for breast-fed infants. *J Pediatr Gastroenterol Nutr*. 2016;62:668–686.
- Sung V, Hiscock H, Tang MLK, et al. Treating infant colic with the probiotic *Lactobacillus reuteri* DSM 17938: double blind, placebo controlled randomised trial. *BMJ (Clinical research ed)*. 2014;348:g2107.
- Kianifar H, Ahanchian H, Grover Z, et al. Synbiotic in the management of infantile colic: a randomised controlled trial. *J Paediatr Child Health*. 2014;50:801–805.
- Dupont C, Rivero M, Grillon C, Belaroussi N, Kalindjian A, Marin V. Alpha-lactalbumin-enriched and probiotic-supplemented infant formula in infants with colic: growth and gastrointestinal tolerance. *Eur J of Clin Nutr*. 2010;64:765–767.
- Biagioli E, Tarasco V, Lingua C, Moja L, Savino F. Pain-relieving agents for infantile colic. *Cochrane Database Syst Rev*. 2016;9:CD009999.
- Landgren K, Kvorning N, Hallstrom I. Acupuncture reduces crying in infants with infantile colic: a randomised, controlled, blind clinical study. *Acupunct Med*. 2010;28:174–179.
- Reinthal M, Andersson S, Gustafsson M, et al. Effects of minimal acupuncture in children with infantile colic - a prospective, quasi-randomised single blind controlled trial. *Acupunct Med*. 2008;26:171–182.
- Landgren K, Hallstrom I. Effect of minimal acupuncture for infantile colic: a multicentre, three-armed, single-blind, randomised controlled trial (ACU-COL). *Acupunct Med*. 2017;35(3):171–179.
- Skjeie H, Skonnord T, Fetveit A, Brekke M. Acupuncture for infantile colic: a blinding-validated, randomized controlled multicentre trial in general practice. *Scand J Prim Health Care*. 2013;31:190–196.
- Sung V, D'Amico F, Cabana MD, et al. *Lactobacillus reuteri* DSM 17938 to treat infant colic: a meta-analysis. *Pediatrics*. 2018;141:e20171811.
- Gutiérrez-Castrellón P, Indrio F, Bolio-Galvis A, Jiménez-Gutiérrez C, Jiménez-Escobar I, López-Velázquez G. Efficacy of *Lactobacillus reuteri* DSM 17938 for infantile colic. *Medicine*. 2017;96(51):e937522.
- Rautava S, Luoto R, Salminen S, Isolauri E. Microbial contact during pregnancy, intestinal colonization and human disease. *Nat Rev Gastroenterol Hepatol*. 2012;9:565–576.
- St James-Roberts I. Is it time to recommend *Lactobacillus* for colic? Not Necessarily. *Pediatrics*. 2018;141:e20173445.
- Ong TG, Gordon M, Banks SS, Thomas MR, Akobeng AK. Probiotics to prevent infantile colic. *Cochrane Database Syst Rev*. 2019;3:CD012473.

25. Crotteau CA, Wright ST, Eglash A. Clinical inquiries. What is the best treatment for infants with colic? *J Fam Pract.* 2006;55:634–636.
26. Lothe L, Lindberg T, Jakobsson I. Macromolecular absorption in infants with infantile colic. *Acta Paediatr Scand.* 1990;79:417–421.
27. Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics.* 1989;83:262–266.
28. Skjeie H, Skonnord T, Brekke M, et al. Acupuncture treatments for infantile colic: a systematic review and individual patient data meta-analysis of blinding test validated randomised controlled trials. *Scand J Prim Health Care.* 2018;36(1):56–69.
29. Wolke D, Bilgin A, Samara M. Systematic review and meta-analysis: fussing and crying durations and prevalence of colic in infants. *J Pediatr.* 2017;185(55–61):e4.
30. Gordon M, Gohil J, Banks SS. Parent training programmes for managing infantile colic. *Cochrane Database Syst Rev.* 2019;12:CD012459.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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