

# Infant Colic—What works: A Systematic Review of Interventions for Breast-fed Infants

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## ABSTRACT

**Objectives:** To determine the strength of evidence for commonly used interventions for colic in breast-fed and mixed-fed infants younger than 6 months.

**Methods:** Searches of PubMed, CINAHL, Embase, AMED, and Web of Science databases were conducted from July 2014 to July 2015. Included studies were randomised controlled trials involving mothers and their colicky infants younger than 6 months; assessed colic against the Wessel or modified Wessel criteria; and included phytotherapies, prescription medicines, and maternal dietary interventions. Studies with <16 participants were excluded. Meta-analyses were conducted where data were sufficient to enable pooling. Quality was assessed against the Cochrane Risk Bias Assessment Tool.

**Results:** A total of 17 articles met the inclusion criteria for this review. The 6 studies included for subgroup meta-analysis on probiotic treatment, notably *Lactobacillus reuteri*, demonstrated that probiotics appear an effective treatment, with an overall mean difference in crying time at day 21 of  $-55.8$  min/day (95% CI  $-64.4$  to  $-47.3$ ,  $P = 0.001$ ). The 3 studies included for subgroup meta-analysis on preparations containing fennel suggest it to be effective, with an overall mean difference of  $-72.1$  min/day (95% CI  $-126.4$  to  $-17.7$ ,  $P < 0.001$ ).

**Conclusions:** Probiotics, in particular *L reuteri*, and preparations containing fennel oil appear effective for reducing colic, although there are limitations to these findings. The evidence for maternal dietary manipulation, lactase, sucrose, glucose, and simethicone is weak. Further well-designed clinical trials are required to strengthen the evidence for all of these interventions.

**Key Words:** fussiness, herbal teas, infant colic, irritability, *L reuteri*, maternal diet, medication, probiotics, reflux, simethicone, sucrose

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The term “infant colic” is often used by health care professionals to describe a collection of symptoms, including persistent crying and fussiness, with the affected infant unable to

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## What Is Known

- A universally accepted definition of infant colic would enhance the effectiveness of research in this area and enable more studies to be compared for a more meaningful outcome of any further systematic reviews.
- Colic is considered multifactorial in nature.
- Maternal dietary manipulation, probiotics, and some nonprescription remedies may be of benefit for breast-fed colicky infants.

## What Is New

- Meta-analysis of 6 randomised controlled trials of *Lactobacillus reuteri* demonstrated an overall positive effect for colicky breast-fed infants.
- Meta-analysis of preparations containing fennel demonstrated positive effect for colicky breast-fed infants.
- The significant heterogeneity demonstrated here may be addressed through the adoption of standardised case definitions and data collection methodologies.

settle or self sooth and sometimes unable to feed properly. It is recognised as a functional gastrointestinal disorder of infancy by the Rome III classification (1). Persistent infant colic can contribute to parental fatigue and distress and may result in strained parental relationships, and poor parental engagement with their infant (2).

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 (3–5). Infant colic has been the subject of many investigations, and since 1954 it has been defined as “crying for >3 hours per day, for >3 days per week, for a period of 3 weeks or longer in otherwise healthy infants”; typically known as Wessel “rule of threes” (6,7). The Rome III Criteria of Childhood Functional Gastrointestinal Disorders: Neonate/Toddler defined infant colic as crying for >3 hours per day, for >3 days per week, for at least 1 week, with no failure to thrive (1).

Establishing an accurate prevalence for infant colic has been problematic due to the various definitions of colic used in research. Canivet et al (8) cite a prevalence of 9% to 60% internationally, depending on the definitions and research methodologies used. Interestingly, their research revealed that when 4 distinct definitions were used the prevalence varied from 3.3% to 17.1%, with the prevalence in the Wessel group to be 9.3% (8). Other research suggests prevalence varies between 4% and 28% when defined by modified Wessel criteria (9,10). More recently, Vandenplas et al

(11) in their worldwide survey of paediatric health professionals together with their study of the literature estimated the overall prevalence for colic to be in the order of 20%; however, they concede that the actual prevalence remains uncertain. The importance of using a standardised definition of infant colic for research purposes has been emphasised by Reijneveld et al (9), because it is more likely to result in a rigorous study that can be compared with other research through systematic review. These findings strengthen the case for standardising the definition of colic, perhaps with the Rome III criteria, which would enable a more accurate prevalence to be established.

It has been widely recognised that the causes of infant colic are multifactorial, with maternal, paternal, infant, and environmental factors being implicated. Maternal considerations include stress and postnatal depression (12), whereas infant factors may include the individual infant’s temperament, developmental milestones achieved, the infant’s sensory processing capacity, and underlying organic causes (7,13). Environmental causes, such as exposure to tobacco smoke, have also been implicated in infant colic (14). The role of the infant gastrointestinal microbiota has recently come into focus, with several randomised controlled trials investigating the efficacy of *Lactobacillus reuteri* as a treatment option (15–20). Organic causes are thought to include food protein allergy (21,22) and/or food intolerances (23).

Parents of unsettled infants often seek medical assistance to determine the cause of their infant’s distress, resulting in high utilisation of health services (24,25). There is an excess of information for parents on the Internet; a recent Google search using the search term “infant colic” yielded >1.5 million results; however, much of this advice is conflicting and possibly contributes to parental confusion. The question remains as to how much of the information is evidence based. There have been a number of reviews of treatments for infant colic since 2000 (26–37), some narrative and some systematic (Table 1). The review herein differs from previous reviews in that we focussed our review around narrow inclusion criteria, which increases its strength. Our review considers studies that include exclusively breast-fed and mixed-fed infants, whereas 11 of the 12 previous reviews (26–33,35–37) considered studies of exclusively formula fed in addition to exclusively breast-fed and mixed-fed infants. Our review considers only studies with experimental design, whereas, 7 of the 12 prior reviews (26,27,31–35) included studies of experimental and observational design, which may reduce their rigour. In addition, our review considers studies which define infant colic as Wessel or modified Wessel criteria, whereas 10 of the 12 previous reviews (26–35) considered studies using Wessel, modified Wessel criteria, as well as unspecified or another definitions of colic. Using a narrow definition of infant colic strengthens our review. Our review also includes meta-analyses, whereas, only 2 of the previous reviews (28,36) were able to pool data for meta-analysis for probiotics (*L reuteri*). Our review provides a rigorous examination of commonly used interventions that are easily accessed by parents of colicky infants and aims to provide up to date evidence on the efficacy of common treatments for infant colic for health professionals to convey to the parents of breast-fed and mixed-fed colicky infants.

**METHODS**

**Inclusion/Exclusion Criteria**

This systematic review was compliant with the Preferred Reporting Items of Systematic Reviews and Meta-analysis framework (38). Studies for inclusion were required to be of experimental design, either randomised-controlled or randomised crossover trials, and published after 1 January, 1980. The participants were mothers of colicky fully breast-fed or partially breast-fed infants younger than six months. Studies included in this review defined

TABLE 1. A selection of reviews of interventions for infant colic published since 2000

Author	Method	Feeding mode	Colic definition	Interventions	Study types	Outcome
Cohen-Silver and Ratnapalan 2009	Narrative literature review	EBF EFF Breast-fed	Wessel criteria Unspecified	Maternal diet eHf Simethicone	RCTs Reviews	<i>Breast-fed infants:</i> eliminating cow’s milk protein from maternal diet should be considered for children with blood in their stools <i>Formula-fed infants:</i> hypoallergenic formulas should be considered. <i>All infants:</i> families of colicky infants should receive education about the condition and the different treatment options as well as counselling and encouraged to try behaviour modification to help reduce maternal stress. The use of probiotics, glucose, or herbal remedies could be considered for those infants not responding to behavioural or dietary interventions
Cowie 2013	Narrative literature review	Formula-fed Mixed-fed Breast-fed	Wessel criteria	Glucose Herbal preparations Chiropractic Behavioural Probiotic Behavioural	RCTs	<i>Breast-fed infants:</i> no specific recommendations made for breast-fed infants

(continued)

TABLE 1. (continued)

Author	Method	Feeding mode	Colic definition	Interventions	Study types	Outcome
Garrison and Christakis 2000	Systematic review without meta-analysis	Formula-fed	Modified Wessel criteria	eHf	Case control	<i>Formula-fed infants</i> : hydrolysed formulas may be useful for colicky formula-fed infants
		Mixed-fed	Unspecified	Chiropractic	Medical record audits	<i>All infants</i> : behavioural interventions with supportive home visiting, increasing parental skill and competence may be of use for managing colicky infants. Further research is required to determine effective parental support systems
		EFF	Wessel criteria	Osteopathic Sucrose Glucose Herbal tea Massage Behavioural	Reviews	
Hall et al 2012	Systematic review without meta-analysis	Breast-fed	Modified Wessel criteria	Maternal diet	Cross over trials	<i>Formula-fed infants</i> : hydrolysed formula and soy formula may be of benefit; however, more research is required
		Formula-fed	Other	eHf		<i>All infants</i> : varying definitions of colic are problematic for research. Some interventions are effective; however, more rigorous research is needed
		EBF	Wessel criteria	Pharmaceutical Soy formula Lactase Sucrose Naturopathic Pharmacological	RCTs	<i>Breast-fed infants</i> : there is some evidence for low allergen maternal diets, further research is required
Iacovou et al 2012	Systematic review without meta-analysis	EFF	Modified Wessel criteria	Fibre-enriched formula	Cross over trials	<i>Formula-fed infants</i> : there is some evidence for the use of a casein hydrolysed formula, further research is required
		Breast-fed	Other	eHf	Cohort	<i>All infants</i> : the following interventions have very little evidence to support their use for infant colic: simethicone, dicyclomine hydrochloride, cimetropium bromide, lactase, added fibre, or behavioural interventions
		Formula-fed	Unspecified	Maternal diet Lactase Behavioural	Pilot studies Quasi-experimental	
Iacovou et al 2012	Systematic review without meta-analysis	EBF	Wessel criteria	Maternal diet	RCTs	<i>Breast-fed infants</i> : hypoallergenic diet may be useful; however, this may be difficult for mothers to follow
		EFF	Modified Wessel criteria	eHf formula	Cohort	<i>Formula-fed infants</i> : the strongest evidenced is for hydrolysed formula and some evidence that soy formula may be useful

	Breast-fed	Other	Soy formula	Case control	All infants: a universal definition and agreement on symptoms and data collection methods would help improve evidence
Joanna Briggs Institute 2008	Formula-fed EBF EFF Mixed	Wessel criteria Modified Wessel criteria Other	Fibre-enriched formula Carbohydrate Maternal diet eHF Soy formula	Cross sectional RCTs Reviews	<i>Breast-fed infants:</i> low allergen maternal diets may be of use for treating colic, more well-designed trials are needed <i>Formula-fed infants:</i> hydrolysed formula may be of benefit for treating colic; there is no evidence for the use of soy formula in treating colic <i>All infants:</i> there was no or very limited evidence for the following interventions: simethicone, lactase, low lactose formula, increased carrying, car-ride simulators, behavioural interventions, and parental counselling. There is some evidence to suggest that herbal tea may be of benefit; however, caution should be used, because overuse can lead to nutritional inadequacy. Sucrose was found to be of benefit; however, the benefit was short lived
Lucaassen 2010	EBF EFF Breast-fed Formula-fed	Wessel criteria Modified Wessel criteria Other	Lactase Simethicone Herbal tea Sucrose Behavioural Maternal diet eHF Soy formula	RCTs	<i>Breast-fed infants:</i> no specific recommendation <i>Formula-fed infants:</i> no specific recommendation
Savino and Tarasco 2010	EBF	Wessel criteria	Reduced stimulation Chiropractic Osteopathy Crib vibrator Massage Behavioural Pharmaceutical Herbal Probiotics	RCTs	<i>All infants:</i> insufficient RCT evidence for the use of hydrolysed milk to replace breast milk or standard cow's milk formula, soy formula, or low lactose formula to reduce crying time in infants. RCTs with simethicone are of insufficient quality to determine the efficacy for colic. RCT for reduced stimulation, infant massage, simethicone, osteopathy, counseling, or chiropractic were inconclusive <i>Breast-fed infants:</i> probiotics ( <i>L. reuteri</i> ) may be of benefit; hypoallergenic maternal diet may be of benefit

(continued)

TABLE 1. (continued)

Author	Method	Feeding mode	Colic definition	Interventions	Study types	Outcome
		EFF	Modified Wessel criteria	Maternal diet	Reviews	<i>Formula-fed infants</i> : hydrolysed formula may be of benefit. No evidence for the use of soy formulas. Some evidence for the use of probiotic-supplemented formulas
		Breast-fed	Other	eHF	Pilot studies	<i>All infants</i> : no evidence for complementary and alternative therapies. Chiropractic manipulation has demonstrated only short-term effect, and the majority of the claims from this field are not supported by evidence. Behavioural interventions including car-ride simulators and increased carrying are not supported by evidence. Herbal teas containing fennel may be of use; however, their usage is cautioned as overuse may lead to nutritional inadequacy. The usefulness of simethicone is unsupported
		Formula-fed		Herbal Behavioural Pharmacological Probiotics	Cohort Case control	
Savino 2014	Narrative literature review	EBF	Wessel criteria		RCTs	<i>Breast-fed infants</i> : maternal hypoallergenic diet may be of benefit. Probiotics ( <i>L reuteri</i> ) may also be of benefit
		EFF	Modified Wessel criteria	Maternal diet	Reviews	<i>Formula-fed infants</i> : hydrolysed formula may be of benefit. No evidence for the use of soy formulas. Some evidence for the use of probiotic-supplemented formulas
		Breast-fed	Other	eHF	Pilot studies	<i>All infants</i> : no evidence for complementary and alternative therapies. Chiropractic manipulation has demonstrated only short-term effect, and the majority of the claims from this field are not supported by evidence. The evidence for acupuncture is inconclusive. Behavioural interventions including car-ride simulators and increased carrying are not supported by evidence. Herbal teas containing fennel may be of use; however, their usage is cautioned because overuse may lead to nutritional inadequacy. The usefulness of simethicone is unsupported
		Formula-fed		Pharmacological Chiropractic Acupuncture Herbal Behavioural	Cohort Case control	
Sung 2013	Systematic review with meta-analysis (probiotics only)	EBF	Without colic	Probiotics <i>L reuteri</i> , <i>L animalis</i> , <i>L rhamnosus GG</i> , <i>B longum</i> , <i>B breve</i> , <i>B lactis</i>	RCTs	<i>Breast-fed infants</i> : <i>L reuteri</i> may be effective for treating colic; however, evidence for its use in treating and preventing colic is insufficient. Larger and more rigorous trials are required to determine the strength of the evidence

EFF	Wessel criteria	Formula-fed infants: insufficient evidence for <i>L. reuteri</i> 's use to treat and prevent colic, particularly in formula-fed infants All infants: so specific findings are reported			
EBF	Modified Wessel criteria Other Modified Wessel criteria	Breast-fed infants: evidence from RCTs suggest probiotics containing <i>L. reuteri</i> are effective for reducing colic in breast-fed infants; however, a larger RCT in Australia contradicts this evidence, and further research is required in this area Formula-fed infants: there is limited evidence for the use of <i>L. reuteri</i> in reducing colic in formula-fed infants, and it cannot be recommended to treat or prevent colic All infants: so specific findings are reported	Probiotics <i>L. reuteri</i>	RCTs	
EFF					
Mixed-fed EBF	Modified Wessel criteria	Breast-fed infants: <i>L. reuteri</i> is likely to reduce crying time in colicky breast-fed and predominately breast-fed infants; however, more trials are needed Formula-fed infants: <i>L. reuteri</i> is unlikely to reduce crying time in colicky formula-fed infants All infants: the above recommendations apply to all infants	Probiotics <i>L. reuteri</i>	RCTs	
EFF					
Mixed-fed					

EBF = exclusively breast-fed; EFF = exclusively formula-fed; eHF = extensively hydrolysed formula; RCT = randomised controlled trial.

colic as either Wessel criteria (6), or a modified Wessel criteria, as per the Rome III criteria. Included studies also demonstrated the following intervention types: maternal diet; pharmacotherapies, both prescription and over the counter; phytotherapies; and probiotics. Studies were excluded if the sample size was <16 participants, because n = 16 is the minimum number of participants required to show a difference of 1 standard deviation. Outcome measures for included studies were changes in crying duration and response rates as measured by a reduction in symptoms. Table 2 details the Population, Intervention, Comparison and Outcome (PICO) statement for this systematic review, with inclusion and exclusion criteria.

### Literature Search

An extensive search of the following 5 databases was conducted from July 2014 to 31 July, 2015: PubMed, CINAHL, Embase, AMED, and Web of Science. Search terms included MeSH headings and search strings, and were informed by prior reading of the literature for treating infant colic. They included the following: Feeding OR Breastfeeding AND Colic OR Irritability OR fussiness AND crying; Infant AND Colic; Maternal diet AND Colic AND Breastfed infants; Infant AND Colic AND Diet; Infant AND Colic AND Reflux; Infant AND Colic AND Medication; Infant AND Colic AND PPIs; Infant AND Colic AND Simethicone; Infant AND Colic AND Probiotics; Infant AND Colic AND Herbal teas; Infant AND Colic AND Sucrose. These search strings were chosen as prior examination of the literature on treating colic suggested that they represent the most common treatment options.

### Study Selection Process

Studies were scrutinised based on the inclusion and exclusion criteria by T.H. and M.M. independently. Consensus was reached before excluding any studies at each key step in the selection process. Consensus regarding the final list of studies for inclusion was reached by T.H., M.M., and R.H.

### Data Extraction Process and Assessment of Bias

The data extraction process was completed by T.H. and independently verified by M.M. and R.H. Where possible, authors were contacted for any data that were missing. Where studies had reported crying times at baseline and during or after the intervention, these were extracted. Crying times were often reported as mean with standard deviation in minutes per day. Where crying was reported in hours per day, these were converted to minutes per day. Where data were reported in original publications as medians and interquartile ranges, these were converted to means and standard deviations using the formulae in Hozo et al 2005 (39), because these formulae made no assumptions about the original data. In addition, where numbers, or percentages of infants responding to treatment were reported, these data were extracted. The quality of the included studies were assessed using the Cochrane Risk of Bias Assessment Tool, published in the *Cochrane Handbook for Systematic Reviews of Interventions* (40).

### Data Analysis Process

Separate subgroup meta-analyses were conducted for studies investigating probiotics and studies examining the effectiveness of fennel oil, where these studies reported sufficient outcome data to enable pooling for meta-analysis. Studies of other interventions did not contain sufficient data for subgroup meta-analysis. Mean differences (MDs) with standard deviations for continuous outcomes

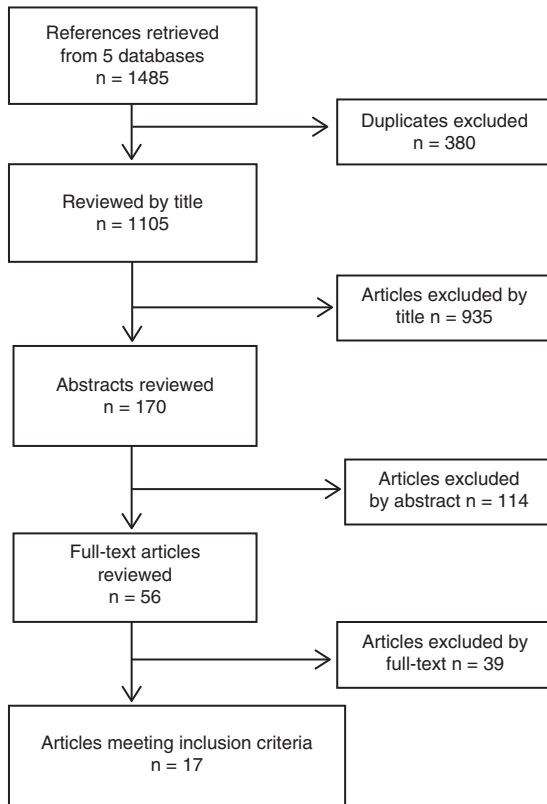


FIGURE 1. Study selection process.

were calculated from stated baseline and outcome measures of crying duration. For 1 study (41), the data on herbal tea containing fennel were extracted, compared with the control pre- and post-intervention, and these data were then available to be considered in the meta-analysis for tea containing fennel. All of the data were analysed with STATA/SE 13.1 (StataCorp LP, College Station, TX) statistical software, using random effects model. Heterogeneity was assessed using the  $I^2$  statistic. Publication bias was assessed using log odds ratio and funnel plot.

## RESULTS

### Study Selection

Initial searches resulted in the extraction of 1485 titles. After 380 duplicates were excluded, 1105 articles were reviewed by title. Of these, 935 were excluded by title. The remaining 170 abstracts were reviewed. Of these abstracts, 114 were excluded, leaving 56 full-text articles to be retrieved for review. Of the 56 full-text articles, 39 were excluded on the basis of not meeting the inclusion criteria. This process is detailed in Fig. 1. Studies using dicyclomine HCL and cimetropium bromide were excluded at this stage because it became evident that these products were no longer available in a range of countries, with dicyclomine HCL being contraindicated for infants younger than 6 months in many countries. Studies were also excluded at this stage in which more information was sought from authors, and none was available, or the authors were unable to be contacted.

### Study Characteristics and Assessment of Bias Risk

Seventeen studies were included in this systematic review, all examining the effects of a treatment on infant colic in fully or

TABLE 2. PICO inclusion/exclusion criteria

Criteria	Types of studies	Study participants	Types of interventions	Types of outcome measures	Language
Inclusion	Randomised controlled trials and randomised crossover trials	Mothers and their colicky breast-fed or mixed-fed infants <6 mo. Studies may have a formula-fed cohort if a breast-fed cohort was also included; the results were combined with a breast-fed cohort; and the same intervention was given. Studies must also have n ≥ 16 in each group. Colic defined by Wessel or modified Wessel criteria, including Rome III	Maternal dietary intervention, probiotics, pharmacotherapies, and phytotherapies	Studies reporting crying times, or number of infants responding to treatment	Studies published in English only
Exclusion	Observational and case studies	Mothers and their noncolicky infants, or with colic but >6 months. Exclusively formula-fed infants. Colic defined by any other criteria than Wessel or modified Wessel criteria	Osteopathic, chiropractic, behavioural, formula only, and interventions contraindicated for infants <6 mo	Studies not reporting crying times or response rates	Studies in languages other than English

PICO = Population, Intervention, Comparison, Outcome.

partially breast-fed babies. The interventions included: probiotics/synbiotics (N=7), maternal dietary interventions (N=1), preparations containing fennel (N=3), or other nonprescription remedies (N=6). Of the 17 studies selected, 12 were randomised controlled trials (15–18,20,41–47) and the remaining 5 were randomised crossover trials (48–52). The randomised crossover trials examined the effects of over the counter remedies including sucrose, glucose, lactase, peppermint, and simethicone. The ingredients of each intervention and placebo are detailed at Table 4. The quality of the 17 included studies were assessed using the Cochrane Risk of Bias Assessment Tool (40) (Table 3).

### Probiotics/Synbiotics

A subgroup meta-analysis of MDs in crying times for the probiotic *L reuteri* was performed on data at 21 days of treatment (Fig. 2), because this was the common data collection point for these studies. Overall, *L reuteri* reduced crying time in the infants studied (pooled MD -55.9 min/day, 95% CI -64.4 to -47.3,  $P < 0.001$ ) (Figure 2).

The study by Kianifar et al (44) examined the effects of a synbiotic mixture that contained 6 species of microbiota (*Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium infantis*, *Lactobacillus bulgaricus*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*) plus fructo-oligosaccharide, and despite the availability of crying data pre and post intervention, it was not included in the subgroup meta-analysis because the preparation did not contain *L reuteri* and was considered not directly comparable to the studies using *L reuteri*.

### Preparations Containing Fennel

A subgroup meta-analysis was conducted on the 3 studies testing the efficacy of fennel on reducing crying time in infants (Fig. 3). Overall, preparations containing fennel demonstrated effectiveness with a pooled MD of -72.1 min/day (95% CI -126.4 to -17.7,  $P < 0.01$ ). The Alexandrovich et al (42) study included 125 infants of 2 to 12 weeks, with response rates and cumulative crying being the reported outcomes. The authors reported response to treatment rates for 65% of infants, whereas 23.7% also responded to the placebo, demonstrating a significant placebo effect in this study.

Arikan et al (41) studied 4 intervention groups and a control group with no intervention. Infants in treatment group 3 (n=35) were given tea containing fennel. Baseline mean crying time for the fennel tea group was 306.6 min/day ( $\pm 85.8$ ), and at the end of the intervention it had reduced to 192.0 min/day ( $\pm 73.8$ ). When compared with the other 2 studies in this subgroup meta-analysis, the MD was -109.2 min/day (95% CI -219.1 to 0.7,  $P = ns$ ). Because of the large confidence interval and it crossing the line of no effect, the study was, however, considered of limited value.

Savino et al 2005 (45) examined the effects of a commercially available phytotherapeutic agent containing fennel (ColiMil), with simethicone used as the comparator (n=88). The study outcomes were reported as crying durations and response rates. Mean crying duration at baseline in the treatment group was 201.2 min/day ( $\pm 18.3$ ), reducing to 76.9 min/day ( $\pm 23.5$ ) at day 7, equating to a mean reduction of crying of -124.3 min/day ( $\pm 11.8$ ),  $P < 0.001$ . This study reported a response rate in the treatment group of 85.4% and 48.9% for the placebo, which is a high placebo response. In the subgroup meta-analysis, the ColiMil containing fennel appeared to be an effective treatment for infant colic, with an MD in crying time of -95.5 min/day, (95% CI -100.9 to -90.2,  $P < 0.001$ ). ColiMil, however, contains 4 herbal ingredients and it is unclear how much of the preparation's effectiveness was due to the fennel, other

TABLE 3. Study characteristics

Author/country	Study design	Inclusion criteria	Age, wk	No. of CI, %	No. of BF, %	Treatment	Control	Outcomes	Results	Risk for bias CRBAT <sup>3</sup>
Probiotics/synbiotics Chau et al 2014/Canada	Double-blind RCT	Modified Wessel	3–26	52 (100%)	52 (100%)	Probiotic: <i>L reuteri</i>	Placebo	Crying time, reported as median (IQR), converted to mean ( $\pm$ SD) min/day; responders defined as reduced crying time $\geq$ 50% from baseline	Treatment group: day-21 crying time reduced from 123.8 ( $\pm$ 149.8) to 63.5 ( $\pm$ 18.6); response rate of 71% at 21 days  Control group: day-21 crying time reduced from 123.8 ( $\pm$ 163.9) to 103.3 ( $\pm$ 25.1); response rate of 21% at 21 days	Low

(continued)



TABLE 3. (continued)

Author/country	Study design	Inclusion criteria	Age, wk	No. of CI, %	No. of BF, %	Treatment	Control	Outcomes	Results	Risk for bias CRBAT <sup>3</sup>
Kianifar et al 2014/Iran	Double-blind RCT	Wessel	2	45 (90%)	45 (100%)	Synbiotic	Placebo	Crying time mean ( $\pm$ SD) min/day; responders defined as reduced crying time $\geq$ 50% from baseline	<i>Treatment group: day-30</i> crying time reduced from 193.0 ( $\pm$ 26.0) to 28.8 ( $\pm$ 9.7); response rate of 87% at 30 days <i>Control group: day-30</i> crying time reduced from 185.0 ( $\pm$ 24) to 63.46 ( $\pm$ 10); response rate of 46% at 30 days	Low
Mi et al 2015/China	Single-blind RCT	Modified Wessel	4	39 (93%)	39 (100%)	Probiotic: <i>L Reuteri</i>	Placebo	Crying time mean ( $\pm$ SD) min/day; responders defined as reduced crying time $\geq$ 50% from baseline	<i>Treatment group: day-21</i> crying time reduced from 200.9 ( $\pm$ 6.3) to 82.2 ( $\pm$ 17.1); response rate of 90% at 21 days <i>Placebo group: day-21</i> crying time reduced from 200.7 ( $\pm$ 8.3) to 137.1 ( $\pm$ 18.3); response rate of 5.2% at 21 days	Low
Savino et al 2007/Italy	Prospective RCT	Modified Wessel	3–13	83 (92%)	83 (100%)	Probiotic: <i>L Reuteri</i>	Simethicone	Crying time reported as median (IQR) min/day, converted to mean ( $\pm$ SD); responders defined as reduced crying time $\geq$ 50% from baseline	<i>Treatment group: day-21</i> crying time reduced from 212.5 ( $\pm$ 29.1) to 80.5 ( $\pm$ 30.3); response rate of 95% at 28 days <i>Control group: day-21</i> crying time reduced from 213.0 ( $\pm$ 29.4) to 147.5 ( $\pm$ 41.1); response rate of 7% at 28 days	Low
Savino et al 2010/Italy	Double-blind RCT	Modified Wessel	2–16	46 (92%)	46 (100%)	Probiotic: <i>L Reuteri</i>	Placebo	Crying time reported as median (IQR) min/day, converted to mean ( $\pm$ SD); responders defined as reduced crying time $\geq$ 50% from baseline	<i>Treatment group: day-21</i> crying time reduced from 370.0 ( $\pm$ 34.6) to 35.0 ( $\pm$ 24.5); response rate of 84% at 21 days	Low

Sung et al 2014/ Australia	Double-blind RCT	Modified Wessel	0–12	127 (76%)	68 (54%)	Probiotic: <i>L. Reuteri</i>	Placebo	Crying time mean (±SD) min/day; responders defined as reduced cry/fuss time ≥50% from baseline	<p><i>Control group:</i> day-21 crying time reduced from 300 (±43.3) to 90.0 (±42.7); response rate of 43% at 21 days</p> <p><i>Treatment group:</i> day-21 crying time reduced from 328.0 (±152.0) to 217.0 (±130.0); response rate of 40% at 1 month</p> <p><i>Control group:</i> day-21 crying time reduced from 329 (±126.0) to 207 (±93.0); response rate of 48% at 1 month</p> <p><i>Treatment group:</i> day-21 crying time reduced from 240.0 (±19.6) to 75.0 (±9.3); response rate was 98% at 21 days</p>	Low
Szajewska et al 2013/Poland	Double-blind RCT	Modified Wessel	0–20	80 (98%)	69 (86%)	Probiotic: <i>L. Reuteri</i>	Placebo	Crying time reported as median (IQR) min/day, converted to mean (±SD); responders defined as reduced crying time ≥50% from baseline	<p><i>Control group:</i> day-21 crying time reduced from 240.3 (±21.7) to 130.5 (±9.9); response rate of 38% at 21 days</p> <p><i>Treatment group:</i> 64% of infants improved</p>	High
Phytotherapies Akcam et al 2006/Turkey	Double-blind randomised crossover trial	Wessel	9.1	25 (83%)	10 (40%)	Glucose solution	Placebo	Subjective parental reported symptom improvement scale	<p><i>Control group:</i> 48% of infants improved.</p> <p><i>Treatment group:</i> day-7 crying time reduced from 115.7 (±15.4) to 75.4 (±10.3); response rate of 65%</p> <p><i>Control group:</i> day-7 crying time reduced from 110.6 (±13.7) to 105.4 (±12.9); response rate of 24%</p>	Medium
Alexandrovich et al 2003/ Russia	Double-blind RCT	Wessel	2-12	121 (97%)	91 (75%)	Fennel oil	Placebo	Crying time mean (±SD) min/day; responders defined by a reduction in cumulative crying to <540min/week		

(continued)

TABLE 3. (continued)

Author/country	Study design	Inclusion criteria	Age, wk	No. of CI, %	No. of BF, %	Treatment	Control	Outcomes	Results	Risk for bias CRBAT <sup>3</sup>
Alves et al 2012/Brazil	Double-blind randomised crossover trial	Wessel	2–8	27 (90%)	27 (100%)	Mint	Simethicone	Crying time mean ( $\pm$ SD) min/day; responders defined by mother's opinion and daily episodes of colic	<i>Treatment group:</i> day-17 crying time reduced from 192.0 ( $\pm$ 51.6) to 111.0 ( $\pm$ 28.0); response rate of 60% in treatment and control groups. Crying episodes reduced from 3.9 ( $\pm$ 1.1)/day to 1.7 ( $\pm$ 0.5)/day at 17 days <i>Control group:</i> day-17 crying episodes reduced from 3.9 ( $\pm$ 1.1)/day to 1.5 ( $\pm$ 0.6)/day	Low
Arikan et al 2008/Turkey	Prospective RCT of 5 groups, including fennel tea and control	Wessel	4–12	70 (100%)	70 (100%)	Fennel tea	Control: no intervention	Crying time mean ( $\pm$ SD) min/day	<i>Treatment group:</i> day-21 crying times reduced from 306.6 ( $\pm$ 85.8) to 192.0 ( $\pm$ 73.8); response rates not reported <i>Control group:</i> day-21 crying times reduced from 198.7 ( $\pm$ 16.9) to 165.3 ( $\pm$ 20.7)	High
Markestad 1997/Norway	Double-blind randomised crossover trial	Wessel's	0–12	19 (95%)	17 (89%)	Sucrose solution	Placebo	No crying times reported; responders defined by parents on a scale of 1–5	<i>Treatment group:</i> response rate of 63%	Medium
Savino et al 2005/Italy	Double-blind RCT	Wessel's	3–8.6	88 (95%)	88 (100%)	ColiMil	Placebo	Crying time mean ( $\pm$ SD) min/day; responders defined as reduced crying time $\geq$ 50% from baseline	<i>Control group:</i> response rate of 5% <i>Treatment group:</i> day-7 crying time reduced from 201.2 ( $\pm$ 18.3) to 76.9 min/day ( $\pm$ 23.5); response rate of 85% <i>Control group:</i> day-7 crying time reduced from 198.7 ( $\pm$ 16.9) to 169.9 ( $\pm$ 23.1); response rate of 49%	Medium

Weizman et al 1993/Israel	Double-blind RCT	Wessel's	2-8	68 (94%)	47 (69%)	Herbal tea	Placebo	No crying times reported; responders defined as a colic improvement score	<i>Treatment group:</i> day-14 colic improvement score of 1.7 ( $\pm 0.3$ ); response rate of 57%. <i>Control group:</i> day-14 colic improvement score of 0.7 ( $\pm 0.5$ ); response rate of 26%	Medium
Maternal diet Hill et al/2005 Australia	RCT	Modified Wessel	8-6	90 (84%)	90 (100%)	Maternal elimination diet	Control	Crying time geometric mean min/2 days (range); responders defined as reduced fuss/ cry crying time $\geq 25\%$ from baseline	<i>Treatment group:</i> day-10 crying reduced from 345.0 (249.0-482.0) to 215.0 (126.0-371.0); response rate of 74%  <i>Control group:</i> day-10 crying reduced from 316.0 (217.0-463.0) to 245.0 (135.0-477.0); response rate of 37%	Low
Simethicone Metcalif et al 1994/USA	Double-blind randomised crossover trial	Wessel	2-8	83 (90%)	22 (27%)	Simethicone	Placebo	No crying times reported; responders defined by parents on a 5-point scale	<i>Treatment group:</i> response rate of 28%  <i>Control group:</i> response rate of 37%. 20% responded to both treatments	High
Lactase Kanabar et al 2001/Ireland	Double-blind randomised crossover trial	Modified Wessel	3-13	46 (87%)	Not reported	Lactase	Placebo	Postintervention crying time median (min/day); responders defined as reduced crying time >45% from baseline	<i>Treatment group:</i> day-10 per protocol crying time was reduced to a median crying time of 520.0  <i>Control group:</i> day-10 per protocol crying time was reduced to a median of 872.5. The overall response rate was 26%, and 38% in the compliant group	Low

BF% = percentage of breast-fed infants; CI = completing infants; CMP = cow's milk protein; CRBAT = Cochrane Risk Bias Assessment Tool; RCT = randomised controlled trial; SD = standard deviation.

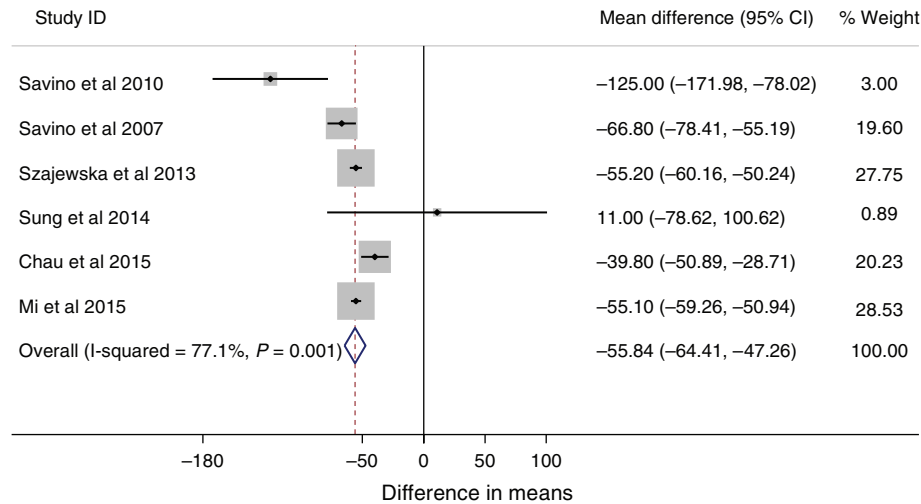


FIGURE 2. Subgroup meta-analysis of the effect of probiotics (*L. reuteri*) at 21 days.

TABLE 4. Table of ingredients in the active or placebo preparations used in the studies outlined in Table 3

Study	Treatment/dose	Placebo/dose
<b>Probiotics/synbiotics</b>		
Chau et al 2014, Canada	<i>Treatment:</i> probiotic drops: $1 \times 10^8$ CFU drops of <i>L. reuteri</i> DSM 17938 suspended in sunflower oil, MCT, and silicon dioxide <i>Dose:</i> 5 drops orally once per day for 21 days	<i>Placebo:</i> sunflower oil, MCT, and silicon dioxide <i>Dose:</i> 5 drops orally once per day for 21 days
Kianifar et al 2014, Iran	<i>Treatment:</i> synbiotic 1 billion ( $10^9$ ) CFU of <i>L. casei</i> , <i>L. acidophilus</i> , <i>B. infantis</i> , <i>L. bulgaricus</i> , <i>L. rhamnosus</i> , <i>S. thermophilus</i> , <i>B. Breve</i> , and Fructo-Oligosaccharide <i>Dose:</i> 1 dose daily from a sealed sachet	<i>Placebo:</i> unspecified, matched for colour, size, and shape and was manufactured by the same company as the symbiotic <i>Dose:</i> same volume in the sachet as treatment
Mi et al 2015, China	<i>Treatment:</i> oil-based suspension containing $10^8$ CFU <i>L. reuteri</i> DSM 17938 in oil suspension for 28 days <i>Dose:</i> daily dose of $10^8$ cfu <i>L. reuteri</i>	<i>Placebo:</i> unspecified oil-based placebo, identical formulation without active probiotic for 28 days <i>Dose:</i> unspecified
Savino et al 2007, Italy	<i>Treatment:</i> probiotic containing <i>L. reuteri</i> American type Culture Strain 55730, $1 \times 10^8$ CFU/day; all mothers followed cow's milk-free diet <i>Dose:</i> 5 drops daily of commercially available probiotic	<i>Placebo:</i> simethicone administered 30 mins after feeding daily for 28 days <i>Dose:</i> 60 mg/day in 15 drops twice daily after feeding for 28 days; all mothers followed cow's milk free diet
Savino et al 2010, Italy	<i>Treatment:</i> probiotic containing a suspension of freeze dried <i>L. reuteri</i> DSM 17938 in a mix of sunflower oil and MCT oil $1 \times 10^8$ CFU/day <i>Dose:</i> 5 drops, 1/day prefeed for 21 days	<i>Placebo:</i> sunflower oil and MCT oil <i>Dose:</i> same dose and duration as active treatment
Sung et al 2014, Australia	<i>Treatment:</i> <i>L. reuteri</i> DSM 17938, $1 \times 10^8$ CFU in oil suspension for 1 month <i>Dose:</i> 5 drops daily for 1 month	<i>Placebo:</i> Maltodextrin in the same oil suspension as treatment, had same colour, appearance, and taste and was package identically as treatment <i>Dose:</i> 5 drops daily for 1 month
Szajewska et al 2013, Poland	<i>Treatment:</i> Probiotic containing $1 \times 10^8$ CFU <i>L. reuteri</i> DSM 17938 in suspension with oil <i>Dose:</i> 5 drops/day for 21 days	<i>Placebo:</i> same oil suspension identical in taste <i>Dose:</i> 5 drops daily for 21 days
<b>Phytotherapies</b>		
Akcam et al 2006, Turkey	<i>Treatment:</i> 30% glucose solution <i>Dose:</i> 1ml/day administered for 4 days	<i>Placebo:</i> distilled water <i>Dose:</i> 1 mL/day administered for 4 days
Alexandrovich et al 2003, Russia	<i>Treatment:</i> 0.1% fennel seed oil + 0.4% polysorbate <i>Dose:</i> mean ( $\pm$ SD) 48.9 ( $\pm$ 6.3) ml per day	<i>Placebo:</i> 0.4% polysorbate and water <i>Dose:</i> mean ( $\pm$ SD) 52.5 ( $\pm$ 7.4) mL/day
Alves et al 2012, Brazil	<i>Treatment:</i> peppermint <i>Dose:</i> 1 drop/kg body weight per day, for 7 days with a 3-day washout period	<i>Placebo:</i> simethicone <i>Dose:</i> 2.5mg/Kg body weight/day for 7 days each with a 3-day washout period
Arikan et al 2008, Turkey	<i>Treatment:</i> G1: massage: 2/day for 25 mins duration each; G2: sucrose 12% solution; G3: fennel tea; G4: exclusive formula group consumed eHf formula	<i>Placebo:</i> no intervention

TABLE 4. (continued)

Study	Treatment/dose	Placebo/dose
	<i>Dose:</i> G2: 2 mL, twice daily; G3: 35 mL dose, max 150mL/day	<i>Dose:</i> nil
Markestad 1997, Norway	<i>Treatment:</i> of 12% solution of sucrose, 12% in distilled water	<i>Placebo:</i> distilled water
	<i>Dose:</i> 2 mL orally on episode of colic, 2 crossover periods at 3–4 day intervals	<i>Dose:</i> 2 mL orally on episode of colic, 2 crossover periods at 3–4 day intervals
Savino et al 2005, Italy	<i>Treatment:</i> Colimil provides <i>Matricariae recutita</i> L 71.10 mg · kg <sup>-1</sup> · day <sup>-1</sup> , <i>Foeniculum vulgare</i> M var. dulce 65.71 mg · kg <sup>-1</sup> · day <sup>-1</sup> , and <i>Melissa officianalis</i> L 38.75 mg · kg <sup>-1</sup> · day <sup>-1</sup>	<i>Placebo:</i> water, fructose, pineapple flavour citric acid, and sorbate potassium
	<i>Dose:</i> 2mL · kg <sup>-1</sup> · day <sup>-1</sup> administered in 2 doses at 5 pm and 8 pm for 7 days	<i>Dose:</i> 2 mg administered daily at 5 and 8pm for 7 days
Weizman et al 1993, Israel	<i>Treatment:</i> Herbal tea (given for 7 days), containing chamomile, vervain, liquorice, fennel, and balm-mint	<i>Placebo:</i> glucose powder and natural flavours dissolved in water
	<i>Dose:</i> Up to 150 mL per colic episode, with a maximum of 3 × 150 mL/day	<i>Dose:</i> up to 150 mL per colic episode, with a maximum of 3 × 150 mL/day
Maternal Diet		
Hill et al 2005, Australia	<i>Treatment:</i> Maternal dietary elimination of egg, cow's milk, soy, wheat peanuts, tree nuts and fish, food preservatives, colours, and additives	<i>Placebo:</i> Control diet contained all the eliminated proteins but no food preservatives, colours, and additives
	<i>Dose:</i> daily for 7 days	<i>Dose:</i> 200 mL soy and 300 mL cow's milk powder, 1 serving peanuts, 1 serving of wheat, and 1 chocolate muesli bar per day for 7 days
Lactase		
Kanabar et al 2001, Ireland	<i>Treatment:</i> lactase drops	<i>Placebo:</i> unspecified
	<i>Dose:</i> 2 drops of for formula-fed infants, 4 drops lactase incubated in expressed foremilk per feed for breast-fed infants, for a period of 10 days, with a 5-day washout period	<i>Dose:</i> 2 drops per feed for formula-fed infants, with 4 drops placebo, incubated in expressed foremilk per feed for breast-fed infants, for a period of 10 days, with a 5-day washout period
Simethicone		
Metcalf et al 1994, USA	<i>Treatment:</i> simethicone	<i>Placebo:</i> unspecified
	<i>Dose:</i> 0.3 mL with each feeding for an average of 7 days duration	<i>Dose:</i> 0.3 mL with each feeding for an average of 7 days duration

CFU = colony forming unit; DSM = Daughter Strain of *L. reuteri* ATCC 557730 strain; MCT = Medium Chain Triglyceride.

ingredients, or the synergistic effect of the combination of the 4 herbal ingredients.

Interestingly, the study by Weizman et al 1993 (47) also found that a herbal tea containing fennel was effective compared with a placebo. It was, however, unable to be included in the subgroup analysis because no crying data at baseline or posttreatment were available.

## Low Allergen Maternal Diet

Because only 1 study on maternal diet was included in this review (43), it was, therefore, not possible to conduct a subgroup meta-analysis on the effects of maternal dietary elimination on crying time. The authors, however, reported a greater reduction in cry/fuss time in the maternal low allergen diet group, with an adjusted geometric mean ratio of 0.79 (95% CI 0.63–0.97) over a 48-hour period.

## Simethicone

Three studies examined simethicone (17,49,51). The Alves et al (49) and Savino et al (17) studies used simethicone as the control intervention, whereas the Metcalf et al (51) study aimed to

determine the effect of simethicone on infant colic. The Metcalf et al (51) study found no significant difference when simethicone was compared with a placebo. Interestingly, the Alves et al study (49) showed no differences in the infant's response to the active treatment (peppermint) when compared with simethicone as the control, demonstrating that the treatment and placebo had similar effect. Savino et al (17) also used simethicone as the control (vs *L reuteri*), which was found to be of limited use for relieving infant colic. Overall, it appears that simethicone is not an effective treatment for infant colic.

## Glucose and Sucrose

Two studies, Arikan et al (41) and Markestad (50), testing the effectiveness of sucrose, and 1 study, Akcam et al (48), testing the effectiveness of glucose, were included. The Arikan et al study (41), a randomised controlled trial, examined the effect of 4 treatments and a control (no intervention), with *n* = 35 in each group. One treatment arm used a sucrose solution (12% in distilled water), and crying duration in the sucrose group reduced significantly from 342.6 min/day (102.6) to 236.4 min/day (90.6), with an MD of 100.8 min/day (16.8), *P* < 0.001.

The Markestad study (50) was a small crossover trial study (*n* = 19), again testing the effectiveness of a 12% sucrose solution.

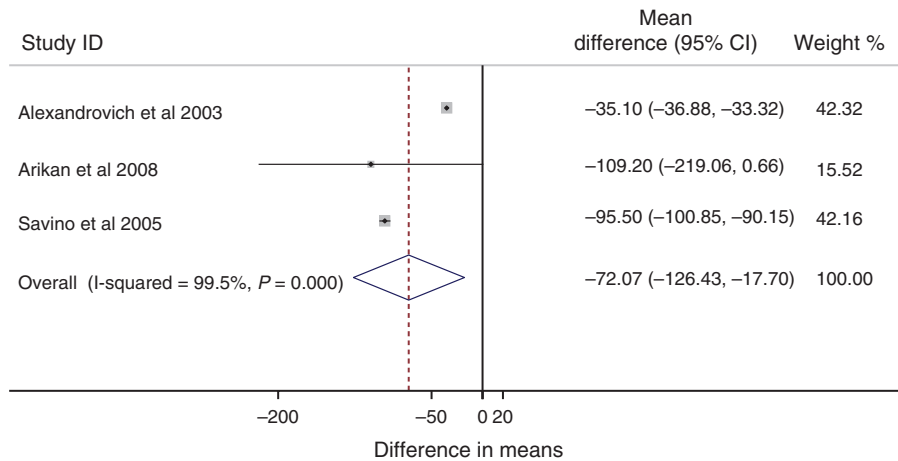


FIGURE 3. Subgroup meta-analysis of the effect of preparations containing fennel at 7 days. CI = confidence interval.

The author reported only response rates, and in the sucrose group this was 63%, which appears to show its effectiveness for reducing infant colic.

Akcam et al (48) tested the effectiveness of glucose for reducing infant colic with a 30% solution in sterile water in a small crossover trial (n = 25). Outcomes were reported as response rates, with 64% responding to the glucose solution and 48% responding to the placebo.

**Lactase**

Kanabar et al (52) reported a crossover trial (n = 53), with an intervention period of 10 days duration and included a 5-day washout period. The authors reported outcomes as response rates for both intention to treat (ITT) analysis (26%, 95% CI 12.9–44.4) and for per protocol (PP) analysis for compliant participants (38%, 95% CI 18.8–59.4). The reported reduction in crying duration between the lactase and placebo groups for ITT was 22.4%, P = ns, and for PP 40.4%, P < 0.01.

**Heterogeneity**

There was considerable heterogeneity between the studies examined here. In terms of subgroups meta-analyses, heterogeneity

was considerable for both probiotics (*L reuteri*) and tea containing fennel, with I<sup>2</sup> = 77.1%, P = 0.001, and I<sup>2</sup> = 99.5%, P < 0.01, respectively, albeit much more pronounced for fennel tea; thus random effects models were chosen for these analyses. This was expected because each of the studies within each subgroup analysis considered here differed in many ways, and the limitations will be further discussed in this review.

**Publication Bias**

Publication bias was assessed with a funnel plot (Fig. 4) and was demonstrated in this review, as evidenced by a high level of heterogeneity between studies (53); differences in methodological quality between studies contributing to the funnel plot’s asymmetry and publication bias, that is, some studies (41,48,51) examined have been assessed as high risk of bias; 40% of the studies (16,17,19,20,50,51) are presenting as outliers in the funnel plot; and not all studies in this review reporting their findings in a way that was useful for future meta-analyses. Unpublished studies and grey literature were not considered in this review and may partially explain the reason for the obvious publication bias demonstrated here.

**DISCUSSION**

This systematic review has achieved its aim of determining the strength of evidence for treatments for infant colic in breast-fed and predominately breast-fed infants younger than 6 months. A range of systematic and literature reviews on treatments for infant colic have been published since 2000 (26,28–37,54). This review differs greatly from these other previously published reviews with respect to its targeted approach. This systematic review was conducted with a narrow set of inclusion criteria, which examined randomised trials of maternal elimination diets, probiotics/synbiotics, over the counter and prescription remedies, and some herbal preparations. Studies were only included if they defined colic as per Wessel or modified Wessel criteria; studies were conducted with 16 or more participants and involved breast-fed infants, mixed-fed infants, or formula-fed infants in which these infants were given the same intervention as the breast- or mixed-fed infants. Some previous reviews did not report their inclusion criteria, or study selection methods (32). Although many reviews limited their investigation to studies defining colic as Wessel or modified Wessel criteria (28,29,31,35,36), some included studies with varying definitions of colic (26,30,33).

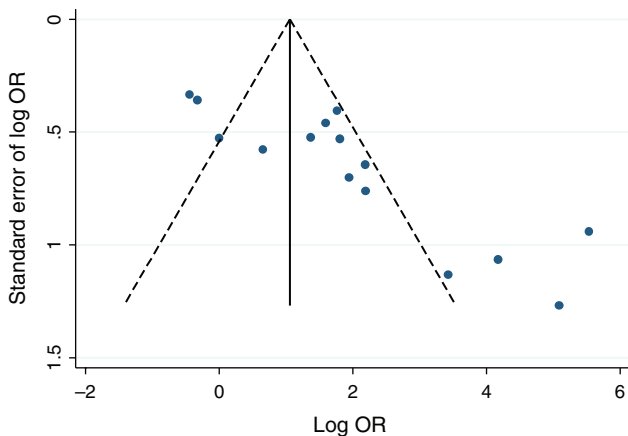


FIGURE 4. Funnel plot with pseudo 95% confidence limits. OR = odds ratio.

With regard to probiotics/synbiotics, our review, with its inclusion of 3 additional studies since previously published meta-analyses of probiotics for treating infant colic (28,36), strengthens the evidence for probiotics/synbiotics in alleviating infant colic, in particular, *L reuteri*. Several earlier reviews (28,31,32,35,36,54) support this. For example, Sung et al (28) included 3 of the studies that feature in our present review (17,18,20). Their meta-analysis concluded that *L reuteri* was effective for reducing colic. In a more recent review, Sung (37) concluded that *L reuteri* appears effective for breast-fed infants only, and that only a subset of colicky infants (no formula feedings and no diagnosis of gastro-oesophageal reflux) may benefit from supplementation with *L reuteri*, and that it cannot be recommended for formula-fed infants at this time. The authors, however, caution that the studies they examined were potentially affected by bias. Our meta-analysis also supports that *L reuteri* is effective for the treatment of infant colic, for exclusively breast-fed infants, and, the studies meeting our strict inclusion/exclusion criteria showed low risk of bias. We also, however, found that *L reuteri* was effective for mixed-fed and formula-fed infants.

Further well-designed studies, with standardised definitions of colic are needed to strengthen the evidence base for colic interventions. Presently, there is significant heterogeneity between studies, and several limitations exist within the intervention studies examined herein.

### Limitations of Studies Using Probiotics/Synbiotics

The results of the Sung et al study (19) are contrary to the finding of the others included in this review regarding the usefulness of *L reuteri* in treating infant colic; this has generated some international controversy. In their original study, Sung et al (19) suggest that their controversial findings may be due to their study having a larger sample size, compared with previous work in this area; atopy and allergy status of the participants; and/or the possibility of regional differences in endemic gut flora. With respect to the latter, regional differences have been found in gut microbiota, correlated with latitude. The Sung et al study (19) was conducted in Australia, whereas the other studies are Italian (17,18), Canadian (15), and Polish (20), and apparent regional differences in gut microbiota may serve to explain Sung et al's findings (19). Interestingly, when we performed a sensitivity analysis, removing the effect of the Sung et al study (19), this made minimal difference to the overall effectiveness for treating infant colic (MD in crying time  $-56.4$  min/day, 95% CI  $-64.8$  to  $-47.9$ ,  $P < 0.001$ ). All of the studies of probiotics/synbiotics examined were assessed as low risk for bias.

### Limitations of Studies Using Preparations Containing Fennel

Alexandrovich et al (42) offer a possible mechanism of action for the efficacy of fennel oil. The fennel plant contains many biologically active compounds of unknown effect, and these may have a spasmolytic effect on the smooth muscle of the intestine. Although the authors report a 65% response rate in the fennel group, they also report a higher than expected response rate (23.7%) in the placebo group, noting a significant placebo effect in this study. A similar placebo effect was reported in the Weizman et al study (47), in which 26% responded to the placebo, compared with 57% in the fennel group. Interestingly, the response rate for the placebo group of infants in the Savino et al study (45) was even higher at 48.9%, compared with 85.4% in the ColiMil group, again, representing a significant placebo effect. The treatment period in all

of these studies using preparations containing fennel was 7 days, and perhaps if the treatment period was longer a greater effect in the treatment group may have been observed.

Consideration of the role of the placebo effect is important, because 5 of the studies examined in our review demonstrated little or no more effect than the placebo they were compared with (19,48,49,51,55). The placebo effect has been widely investigated, and it has been recognised as neurobiological (56,57), meaning that the expectation of a treatment or placebo being effective creates a biological effect. It is feasible that parents with irritable infants will find any treatment or placebo effective because their participation in any investigation may create an expectation. Interestingly, the validity of the placebo effect has been demonstrated in a recently published study by Partty et al (58), in which 2 data collection methods were used to collect crying data, notably, parental interviews, and validated baby diaries. They found that when parents were asked at interview whether their infants had responded to treatment, 87% reported yes, whereas analysis of the baby diaries showed 0% responded to treatment; this demonstrates a very high-perceived difference by the parents.

There were several methodological issues with the studies investigating fennel. Randomisation in the study of Alexandrovich et al (42) was conducted on an individual basis, and allocation methods were not clearly reported. This contributed to the bias risk score of medium. The Arikian et al study (41) was not blinded, and there were several additional aspects of the study that contributed to the overall rating as high risk for bias, for example, allocation was not clearly stated, sample size calculations were not included, and compliance checks were not stated. In the study by Savino et al (45), sample size calculations were not specified, compliance checking was not stated, and the balance of ITT and PP analyses were not clear; these issues contributed to the overall rating of medium risk of bias. Weizman et al (47) methodology was poorly reported and many aspects contributed to an overall rating of medium risk of bias. For example, blinding was stated as double-blind, but very little information on allocation and concealment was reported to substantiate this. Furthermore, a subjective parental colic improvement score was used, which may be problematic considering the placebo effect, and sample size calculations were not reported. Considering all of the studies examining the effects of preparations containing fennel demonstrated methodological issues, and the aforementioned high placebo response demonstrated that any conclusion regarding the effectiveness of fennel must be drawn with caution.

### Limitations of Studies Using Low Allergen Maternal Diet

Two studies on maternal dietary interventions were identified to be meeting the inclusion criteria for this review (43,55); however, 1 of these studies also met the exclusion criteria and was removed from the review. Hill et al (55) included both breast-fed and formula-fed infants, but applied different interventions for each group. The formula-fed infants were randomised to receive either hydrolysed formula or a placebo of standard cow's milk formula as their dietary intervention, whereas the breast-fed infants underwent maternal dietary intervention. This study was unable to be included in our review because the data were reported for both groups combined, with no information given separately for breast-fed infants. As such, these authors reported findings for 2 completely different interventions, in 2 different populations, as a combined response rate. Therefore, it was not possible to determine whether maternal dietary intervention was an effective treatment option for reducing infant colic in breast-fed infants with the study of Hill et al (55).



With respect to a study from Hill et al (43), maternal dietary intervention was found to be effective; however, poor compliance with the dietary intervention in the control group was a major limitation. Only 59% of mothers in the control group were compliant with their intervention, the remaining 41% were partially compliant. This may have skewed the control crying data; however, we cannot be certain of how this has affected the results. In addition, the intervention duration of 1 week may not have been sufficient to eliminate maternal allergens from breast milk, because other studies have shown that some allergens may be present in human breast milk for 9 days and beyond post elimination (59–61). It is clear that more well-designed randomised controlled trials of maternal dietary interventions that are of sufficient duration need to be conducted for exclusively breast-fed infants to determine whether this simple noninvasive approach to treating infant colic is effective.

### Limitations of Studies Using Lactase

One study investigating lactase, by Kanabar et al (52), was included in this review. Although these authors did not report baseline crying data, they reported a difference in crying times between the treatment and placebo groups. In addition, they reported response rates overall; however, they did not indicate rates for treatment and placebo groups separately, and as such, this study was unable to be included in the overall meta-analysis of any treatment versus placebo. It was included in the narrative section of this review, because it met the inclusion criteria specified by the PICO statement. Although this study was assessed as low risk for bias based on its methodology, the poor reporting of their findings has contributed to insufficient evidence for lactase as an effective treatment for infant colic.

The study of Miller et al (62) also investigated the effectiveness of lactase, however, was excluded because it did not meet the criteria specified by the PICO statement. This study was a small crossover trial (n=15), with a 7-day intervention period and no washout period. No response rates or differences in crying durations between baseline and at the end of treatment were reported. The results of hydrogen breath testing were, however, reported, and it was found that concentrations of hydrogen in the breath did not differ significantly between the lactase and the control groups, being indicative of a lack of response to treatment. The authors report that no significant difference in crying duration was demonstrated between the lactase group when compared with the placebo group.

### Limitations of the Crossover Design Studies

A major limitation with crossover trials is the length of time allocated for any washout period, where inadequate or nonexistent washout periods may cause carry over effects from the initial treatment. Any carryover effects can introduce bias into the study (63,64). Of the 5 crossover trials (48–52), the Kanabar et al study (52) reported a 5-day washout period, the Alves et al study (49) reported a 3-day washout period, and the Metcalf et al study (51) reported a 1-day washout period, which may not have been adequate for the colic to reappear before the second treatment round. Two studies that did not specify a washout period (48,50) involved saccharides, 1 of these studies (50) also repeated the crossover intervention and the author conceded that the nature of this repeated crossover design may have contributed to the findings.

### Future Directions

Further well-designed randomised controlled trials or randomised crossover trials with appropriate washout periods are

needed to strengthen the evidence for colic interventions. Any future research methodology should seek to address the high levels of heterogeneity within the present body of research for infant colic. This could be achieved by ensuring a standardised definition of colic, which could be based on the internationally agreed Rome III criteria. Data collection methods should also be standardised, this could include the use of validated tools that capture infant crying in real time, either paper-based or in electronic format to ensure consistency of the data, and ease of data collection for mothers participating in research. Also, a consistent approach to measuring the rates of responding infants would ensure less heterogeneity, this could be achieved by researchers reaching consensus on defining what is meant by a “responder” to treatment by standardising the percentage of reduced crying time to either 25% and more or 50% and more, for example. In addition, standardised reporting of crying data in mean minutes per day, with standard deviations, would be useful to assist with comparisons across similar interventions.

With regard to probiotics/synbiotics, more well-designed trials with this *L reuteri*, particularly in the Southern hemisphere, would be useful in addressing the present controversy surrounding the findings of Sung et al (19), thereby strengthening the emerging body of research.

With regard to future research investigating maternal dietary interventions for colic, heterogeneity can be reduced by ensuring that the infants of participating mothers are exclusive or fully breast-fed, and that the mothers are subject to only 1 intervention, for example, a hypoallergenic diet or another type of diet, and that these diets are well managed by the inclusion of a clinical dietitian in the research team.

## CONCLUSIONS

The evidence presented in this review suggests that probiotics containing *L reuteri* appear to be an effective treatment option for colic in breast-fed infants younger than 6 months. All of the studies selected for this review testing the effectiveness of probiotics were assessed as low risk for bias against the Cochrane Risk Bias Assessment Tool (40) and were considered high quality investigations. Although meta-analysis presented evidence for the effectiveness of preparations containing fennel, this evidence must be viewed with caution because the included studies were of variable quality, had methodological issues, and were assessed as medium or high risk of bias. There was limited evidence for the use of glucose, sucrose, lactase, and simethicone as effective treatments for infant colic in breast-fed infants. The studies presented herein were not without methodological issues and were of variable quality. The high level of heterogeneity between the studies examined is a limiting factor to this analysis. There is limited evidence for the efficacy of maternal dietary manipulation through randomised controlled trials, and more well-designed studies are required in this area.

## REFERENCES

- Hyman P, Milla P, Benninga M, et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006;130:1519–26.
- Reijneveld SA, van der Wal MF, Brugman E, et al. Infant crying and abuse. *Lancet* 2004;364:1340–2.
- Hunziker UA, Barr RG. Increased crying reduces infant crying: a randomized controlled trial. *Pediatrics* 1986;77:641–8.
- Barr RG, Kramer MS, Pless IB, et al. Feeding and temperament as a determinant of early infant crying/fussing behaviour. *Pediatrics* 1989;84:514–21.
- St James-Roberts I, Conroy S, Wilsher K. Clinical, developmental and social aspects of infant crying and colic. *Early Dev Parent* 1995;4:177–89.

6. Wessel M, Cobb J, Jackson E, et al. Paroxysmal fussing in infancy, sometimes called "colic". *Pediatrics* 1954;14:421–33.
7. Savino F, Castagno E, Bretto R, et al. A prospective 10-year study on children who had severe infantile colic. *Acta Paediatrica* 2005;94:129–32.
8. Canivet CA, Hagander BM, Jakobsson I, et al. Infantile colic: less common than previously estimated? *Acta Paediatrica* 1996;85:454–8.
9. Reijneveld SA, Brugman E, Hirasig RA. Excessive infant crying: the impact of varying definitions. *Pediatrics* 2001;108:893–7.
10. Rautava P, Heleneius H, Lehtonen L. Psychosocial predisposing factors for infantile colic. *BMJ* 1993;307:600–4.
11. Vandenplas Y, Abkari A, Bellaiche M, et al. Prevalence and health outcomes of functional gastrointestinal symptoms in infants from birth to 12 months of age. *J Pediatr Gastroenterol Nutr*. Post acceptance: August 21, 2015. Doi: 10.1097/MPG.0000000000000949.
12. Vik T, Grote V, Escribano J, et al. Infantile colic, prolonged crying and maternal postnatal depression. *Acta Paediatrica* 2009;98:1344–8.
13. St James-Roberts I, Conroy S, Wilsher K. Links between maternal care and persistent infant crying in the early months. *Child Care Health Dev* 1998;24:353–76.
14. Shenassa ED, Brown MJ. Maternal smoking and infantile gastrointestinal dysregulation: the case of colic. *Pediatrics* 2004;114:e497–505.
15. Chau K, Lau E, Greenberg S, et al. Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating Lactobacillus reuteri DSM 17938. *J Pediatr* 2015;166:74–8.
16. Mi GL, Zhao L, Qiao DD, et al. Effectiveness of Lactobacillus reuteri in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. *Antonie Van Leeuwenhoek* 2015;107:1547–53.
17. Savino F, Pelle E, Palumeri E, et al. Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. *Pediatrics* 2007;119:e124–30.
18. Savino F, Cordisco L, Tarasco V, et al. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. *Pediatrics* 2010;126:e526–33.
19. Sung V, Hiscock H, Tang MLK, et al. Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial. *BMJ* 2014;348:g2107.
20. Szajewska H, Gyrczuk E, Horvath A. Lactobacillus reuteri DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2013;162:257–62.
21. Caffarelli C, Baldi F, Bendandi B, et al. Cow's milk protein allergy in children: a practical guide. *Ital J Pediatr* 2010;36:5.
22. Fiocchi A, Brozek J, Schuneman H, et al. Diagnosis and rationale for action (DRACMA). *J Allergy Clin Immunol* 2010;126:57–161.
23. Duro D, Rising R, Cedillo M, et al. Association between infantile colic and carbohydrate malabsorption from fruit juices in infancy. *Pediatrics* 2002;109:797–805.
24. Morris S, St James-Roberts I, Sleep J, et al. Economic evaluation of strategies for managing crying and sleeping problems. *Arch Dis Child* 2001;84:15–9.
25. Brown M, Heine RG, Jordan B. Health and well-being in school-age children following persistent crying in infancy. *J Paediatr Child Health* 2009;45:254–62.
26. Iacovou M, Ralston R, Muir J, et al. Dietary management of infantile colic: a systematic review. *Matern Child Health J* 2012;16:1319–31.
27. Joanna Briggs Institute. The effectiveness of interventions for infant colic. *Austr Nurses J* 2008;14:31–3.
28. Sung V, Collett S, de Gooyer T, et al. Probiotics to prevent or treat excessive infant crying: systematic review and meta-analysis. *JAMA Pediatr* 2013;167:1150–7.
29. Lucassen P. Colic in infants. *BMJ Clin Evidence* 2010;2010:0309.
30. Garrison MM, Christakis DA. A systematic review of treatments for infant colic. *Pediatrics* 2000;106:184–90.
31. Savino F, Tarasco V. New treatments for infant colic. *Curr Opin Pediatr* 2010;22:791–7.
32. Cohen-Silver J, Ratnapalan S. Management of infantile colic: a review. *Clin Pediatr* 2009;48:14–7.
33. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. *J Paediatr Child Health* 2012;48:128–37.
34. Cowie J. Managing infant colic: a literature review. *Primary Health Care* 2013;23:16–21.
35. Savino F, Ceratto S, De Marco A, et al. Looking for new treatments of infantile colic. *Ital J Pediatr* 2014;40:53.
36. Urbanska M, Szajewska H. The efficacy of Lactobacillus reuteri DSM 17938 in infants and children: a review of the current evidence. *Eur J Pediatr* 2014;173:1327–37.
37. Sung V. Probiotic interventions in infantile colic. *Curr Opin Clin Nutr Metabol Care* 2015;18:307–11.
38. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
39. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
40. Higgins JPT, Green GS (editors). *Cochrane Handbook for Systematic Reviews of Interventions version 5.0.0 2008*.
41. Arkan D. Effectiveness of massage, sucrose solution, herbal tea or hydrolysed formula in the treatment of infantile colic. *J Clin Nurs* 2008;17:1754–61.
42. Alexandrovich I, Rakovitskaya O, Kolmo E, et al. The effect of fennel (Foeniculum vulgare) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. *Altern Ther Health Med* 2003;9:58–61.
43. Hill DJ, Roy N, Heine RG, et al. Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. *Pediatrics* 2005;116:E709–15.
44. Kianifar H, Ahanchian H, Grover Z, et al. Synbiotic in the management of infantile colic: a randomised controlled trial. *J Paediatr Child Health* 2014;50:808–15.
45. Savino F. A randomized double-blind placebo-controlled trial of a standardized extract of Matricariae recutita, Foeniculum vulgare and Melissa officinalis (COLIMIL<sup>®</sup>) in the treatment of breastfed colicky infants. *Phytother Res* 2005;19:335–40.
46. Sung V, Cabana MD, D'Amico F, et al. Lactobacillus reuteri DSM 17938 for managing infant colic: protocol for an individual participant data meta-analysis. *BMJ Open* 2014;4:2014–006475.
47. Weizman Z, Alkrinawi S, Goldfarb D, et al. Efficacy of herbal tea preparation in infantile colic. *J Pediatr* 1993;122:650–2.
48. Akcam M, Yilmaz A. Oral hypertonic glucose solution in the treatment of infantile colic. *Pediatr Int* 2006;48:125–7.
49. Alves JGB, de Brito R de CCM, Cavalcanti TS. Effectiveness of Mentha piperita in the Treatment of Infantile Colic: A Crossover Study. *eCAM* 2012;2012:981352.
50. Markestad T. Use of sucrose as a treatment for infant colic. *Arch Dis Childhood* 1997;76:356–8.
51. Metcalf TJ, Irons TG, Sher LD, et al. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics* 1994;94:29–34.
52. Kanabar D, Radhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *J Hum Nutr Diet* 2001;14:359–63.
53. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
54. Savino F. Focus on infantile colic. *Acta Paediatrica* 2007;96:1259–64.
55. Hill DJ, Hudson IL, Sheffield LJ, et al. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *J Allergy Clin Immunol* 1995;96:886–92.
56. Brody H, Miller FG. Lessons from recent research about the placebo effect—from art to science. *JAMA* 2011;306:2612–3.
57. Meissner K, Bingel U, Colloca L, et al. The placebo effect: advances from different methodological approaches. *J Neurosci* 2011;31:16117–24.
58. Partty A, Lehtonen L, Kalliomaki M, et al. Probiotic Lactobacillus rhamnosus GG therapy and microbiological programming in infantile colic: a randomized, controlled trial. *Pediatr Res* 2015;7:127.
59. Machtinger S, Moss R. Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody. *J Allergy Clin Immunol* 1986;77:341–7.

60. Jakobsson I, Lindberg T, Benediktsson B, et al. Dietary bovine beta-lactoglobulin is transferred to human milk. *Acta Paediatr Scand* 1985;74:342–5.
61. Fukushima Y, Kawata Y, Onda T, et al. Consumption of cow milk and egg by lactating women and the presence of b-lactoglobulin and ovalbumin in breast milk. *Am J Clin Nutr* 1997;65:30–5.
62. Miller JJ, McVeagh P, Fleet GH, et al. Effect of yeast lactase enzyme on “colic” in infants fed human milk. *J Pediatr* 1990;117:261–3.
63. Madhok V, Fahey T. N-of-1 trials: an opportunity to tailor treatment in individual patients. *Br J Gen Pract* 2005;55:171–2.
64. Mills EJ, Chan AW, Wu P, et al. Design, analysis, and presentation of crossover trials. *Trials* 2009;10:27.

### Thomas Phaer on Good Breast Milk

Thomas Phaer (1510–1560), called by some the “Father of English Pediatrics,” in 1546 published, in English, a text entitled *The Regiment of Lyfe* in which he described the nature of wholesome breast milk and how to increase the yield of it. The passage is reproduced below exactly as written followed by a more liberal rendition with modern spellings.

The mylke is good that is whyte and sweete and when y droppe it on your nayle and do move your finger neyther fleteth abrod at every stering nor will hange faste upon your naile when ye turne it downward, but the whyche is between bothe is beste.<sup>1</sup> Sometime it chaunceth that the milke waseth, so that ye nource can not have sufficient to susteine the child, for which I will declare remedies. . . appropriate to ye encreasing the mylke in the breste. Pasneppe rootes and fenelle roots sodden in broth of chickens and afterward eaten with a little fresche butter maketh encrease of mylke within the brestes. Another. The powder of earth wormes dried and drunken in the broth of a neates tonge is a singular experiment for ye same intent.<sup>2</sup>

1. This is the original breast milk nail test described by Soranus of Ephesus (fl. 98–138) in *Gynecologia*.

2. Good breast milk is white and sweet and a drop placed on your nail will neither immediately roll off, nor cling excessively. Sometimes it happens that breast milk dries up and the nurse has insufficient milk to sustain the child, for which I offer remedies to increase the milk. Parsnip and fennel cooked in chicken broth and eaten with a little fresh butter increases milk in the breasts. Also, powdered desiccated earthworms cooked in cow (*neates*) tongue broth yields the same intent.

—Submitted by Angel Rafael Colón