Article

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[Intervention Review]

Probiotics to prevent infantile colic

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ABSTRACT

Background

Infantile colic is typically defined as full-force crying for at least three hours per day, on at least three days per week, for at least three weeks. Infantile colic affects a large number of infants and their families worldwide. Its symptoms are broad and general, and while not indicative of disease, may represent a serious underlying condition in a small percentage of infants who may need a medical assessment. Probiotics are live microorganisms that alter the microflora of the host and provide beneficial health effects. The most common probiotics used are of *Lactobacillus*, *Bifidobacterium* and *Streptococcus*. There is growing evidence to suggest that intestinal flora in colicky infants differ from those in healthy infants, and it is suggested that probiotics can redress this balance and provide a healthier intestinal microbiota landscape. The low cost and easy availability of probiotics makes them a potential prophylactic solution to reduce the incidence and prevalence of infantile colic.

Objectives

To evaluate the efficacy and safety of prophylactic probiotics in preventing or reducing severity of infantile colic.

Search methods

In January 2018 we searched CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, 10 other databases and two trials registers. In addition, we handsearched the abstracts of relevant meetings, searched reference lists, ran citation searches of included studies, and contacted authors and experts in the field, including the manufacturers of probiotics, to identify unpublished trials.

Selection criteria

Randomised control trials (RCTs) of newborn infants less than one month of age without the diagnosis of infantile colic at recruitment. We included any probiotic, alone or in combination with a prebiotic (also known as synbiotics), versus no intervention, another intervention(s) or placebo, where the focus of the study was the effect of the intervention on infantile colic.

Data collection and analysis

We used standard methodological procedures of Cochrane.

Main results

Our search yielded 3284 records, and of these, we selected 21 reports for full-text review. Six studies with 1886 participants met our inclusion criteria, comparing probiotics with placebo. Two studies examined *Lactobacillus reuteri DSM*, two examined multi-strain probiotics, one examined *Lactobacillus rhamnosus*, and one examined *Lactobacillus paracasei* and *Bifidobacterium animalis*. Two studies began probiotics during pregnancy and continued administering them to the baby after birth.

We considered the risk of bias for randomisation as low for all six trials; for allocation concealment as low in two studies and unclear in four others. All studies were blinded, and at low risk of attrition and reporting bias.

A random-effects meta-analysis of three studies (1148 participants) found no difference between the groups in relation to occurrence of new cases of colic: risk ratio (RR) 0.46, 95% confidence interval (CI) 0.18 to 1.19; low-certainty evidence; I^2 = 72%.

A random-effects meta-analysis of all six studies (1851 participants) found no difference between the groups in relation to serious adverse effects (RR 1.02, 95% CI 0.14 to 7.21; low-certainty evidence; I^2 not calculable (only four serious events for one comparison, two in each group: meconium plug obstruction, patent ductus arteriosus and neonatal hepatitis).

A random-effects meta-analysis of three studies (707 participants) found a mean difference (MD) of -32.57 minutes per day (95% CI -55.60 to -9.54; low-certainty evidence; I^2 = 93%) in crying time at study end in favour of probiotics.

A subgroup analysis of the most studied agent, *Lactobacillus reuteri*, showed a reduction of 44.26 minutes in daily crying with a random-effects model (95% CI -66.6 to -21.9; I^2 = 92%), in favour of probiotics.

Authors' conclusions

There is no clear evidence that probiotics are more effective than placebo at preventing infantile colic; however, daily crying time appeared to reduce with probiotic use compared to placebo. There were no clear differences in adverse effects.

We are limited in our ability to draw conclusions by the certainty of the evidence, which we assessed as being low across all three outcomes, meaning that we are not confident that these results would not change with the addition of further research.

PLAIN LANGUAGE SUMMARY

Probiotics to prevent infantile colic

What was the aim of this review?

The aim of this review was to investigate if probiotics given to healthy babies prevent infantile colic, and if they are safe.

Key messages

Although probiotics make little or no difference to the occurrence of infantile colic, they may reduce crying time and there were no safety concerns. We still require more research to work out if the onset of colic can be reduced.

What did the review study?

Infantile colic affects a large number of infants and their families worldwide. Infantile colic is a problem characterised by episodes of inconsolable crying lasting for longer than three hours per day, for more than three days a week, for at least three weeks.

Probiotics are live bacteria that, when ingested, can be beneficial for patients. Probiotics are cheap and readily available, and there is recent research investigating their use for this problem.

What were the main results of the review?

This review included six studies. The infants in the probiotics group were given different types of probiotics, and in different doses, and compared to infants who were given a placebo (dummy medicine).

The review found that, compared to placebo, probiotics made little or no difference to the occurrence of infantile colic, but appeared to reduce crying time. There was no difference in the reporting of side effects, with only four serious events reported in one large study, and these were clinically unlikely to be linked to the taking of either of the study products.

How up-to-date was this review?

We searched for studies that had been published up to January 2018.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Prophylactic probiotics compared to placebo for the prevention of infantile colic

Patient or population: infants without colic
Setting: outpatient
Intervention: prophylactic probiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with prophylactic probiotics				
Occurrence of new cases of colic Measured by: Wessel/ Rome III Criteria Follow-up: at study end	**Study population** **85 per 1000**	**39 per 1000** (15 to 101)	**RR 0.46** (0.18 to 1.19)	1148 (3 RCTs)	⊕⊕◯◯ **Low**[a]	-
Adverse effects Measured by: reporting Follow-up: during study period	**Study population** **2 per 1000**	**2 per 1000** (0 to 16)	**RR 1.02** (0.14 to 7.21)	1851 (6 RCTs)	⊕⊕◯◯ **Low**[b]	-
Duration of crying Measured in: minutes per day Follow-up: at study end	The mean crying time ranged across control groups from **60 minutes per day** to **88 minutes per day**	The mean crying time in the intervention group was **32.57 minutes per day lower** (55.60 minutes per day lower to 9.54 minutes per day lower)	-	707 (3 RCTs)	⊕⊕◯◯ **Low**[c]	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded two levels due to concerns regarding publication bias, imprecision and very serious inconsistency (substantial heterogeneity: I^2 = 72%).

[b] Downgraded two levels due to concerns regarding publication bias, general risk of bias and very serious imprecision (wide CI, which included appreciable harm; and low occurrence of events).

[c] Downgraded two levels due to concerns regarding publication bias, imprecision and very serious inconsistency (substantial heterogeneity: I^2 = 92%).

BACKGROUND

See Appendix 1 for definitions of some technical terms used in this review.

Description of the condition

Infantile colic is defined as periods of inconsolable, unexplained and incessant crying in a seemingly healthy infant that, quite understandably, leads to exhausted, frustrated and concerned parents seeking to comfort their child (Landgren 2011).

This condition appears to be more frequent in the first six weeks of life, occurring in 17% to 25% of newborns depending on geography and definitions employed, with prevalence often peaking at that point. It is important to note that without any intervention, colic symptoms are usually below the threshold of such diagnostic criteria by three months of age (Reijneveld 2001; Vandenplas 2015; Wolke 2017).

Traditionally, the definition of the condition was based on the rule of three; that is, unexplained episodes of crying for more than three hours per day for three days per week for at least three weeks (Wessel 1954). Since then, a new definition has been proposed, which refers to a clinical condition of fussing and crying for at least one week in an otherwise healthy infant (Hyman 2006). More recently, colic has been included under functional gastrointestinal disorders (Rome IV diagnostic criteria), and the definition has been expanded to include paroxysms of irritability and fussiness for at least one week in an infant who has no failure to thrive (Drossman 2016). This replaced the Rome III criteria from 2006 (Hyman 2006), which are still cited as many studies that are historical still refer to these criteria. The Rome III were actually more consistent with the previous Wessel (Wessel 1954) definition, explicitly stating that crying must be for three hours per day for three days per week for one week.

In colic, flushing of the face, meteorism (excessive flatulence in the intestinal tract with distention of the abdomen), drawing up of the legs, and flatulence often accompany the inconsolable crying (Savino 2010a). Symptoms typically start in the second week of life, in both breastfed and formula-fed infants, and usually resolve by three months of age (Lucas 1998). Generally speaking, these symptoms are not indicative of disease, and thus hospital admission for these infants is generally unnecessary, detrimental and not to be encouraged (Savino 2007a). However, about 5% of colicky, crying infants do have a serious, underlying medical problem (Freedman 2009; Savino 2005; Savino 2007a), and there is evidence that older children presenting with migraine are more likely to have been babies who had experienced colic (Romanello 2013). Therefore, parents and professionals ought to bear in mind that a medical assessment may be needed, to exclude underlying medical conditions in need of investigation and treatment (Savino 2010a).

The aetiopathogenesis of infantile colic remains undefined and is most likely multi-factorial. Despite the common nature of the condition, there is a general paucity of strong evidence in this area. It has been suggested that a number of behavioural factors (psychological and social) and biological components (food hypersensitivity or allergy, or both; gut micro-organisms; dysmotility) can contribute to its manifestation (Gupta 2007). These include the following.

- First, the immunological model, which focuses on possible allergens, has been suggested as a cause of colic.
    - A key allergen is cows' milk protein in infant formula or even mothers' milk. Intact proteins from a mother's diet can sometimes cross over into the breast milk, provoking an allergic response and symptoms of colic in her infant. Consequently, a low-allergen maternal diet or hypoallergenic infant formula have been proposed as a form of treatment (Hill 2005; Iacovou 2012; Schach 2002). Shannon 1921 first described the possibility of a relationship between infantile colic and allergens, and since then, several studies have evaluated the possible association between colic and food hypersensitivity (Heine 2013; Heine 2014; Hill 1995; Iacono 1991; Lothe 1982; Merras-Salmio 2013; Saps 2011).
    - The evidence shows that about 25% of infants with moderate or severe symptoms have cows' milk, protein-dependent colic (Axelsson 1986; Hill 2000; Lindberg 1999), which improves after some days on a hypoallergenic diet (Campbell 1989; Dupont 2010; Estep 2000; Iacono 1991; Iacono 2005; Jakobsson 1983; Jakobsson 2000; Lothe 1989; Savino 2001). For these infants, infantile colic could be the first manifestation of atopic disease, and for this reason, dietetic treatment should be one of the first therapeutic approaches (Gupta 2007; Hall 2012; Perry 2011; Savino 2010a). Indeed, dietary changes are particularly indicated in cases of suspected intolerance to cows' milk proteins (e.g. in infants with a positive family history; eczema or onset after the first month of life; or colic associated with other gastrointestinal symptoms, such as vomiting or diarrhoea) (Hill 1995; Hill 2005; Jakobsson 1983; Lucassen 2000; Savino 2014). Additionally, there is growing evidence that colic is 25% more prevalent in the babies of cigarette smokers and mothers who have used nicotine replacement in pregnancy and breastfeeding, suggesting that there is an intolerance of the nicotine itself (Milidou 2012), which manifests in symptoms of colic.
- Second, some studies have identified lactose intolerance - due to a relative lactase deficiency - as a possible causative factor in infant colic (Kanabar 2001). Carbohydrate malabsorption leads to the colonic fermentation of sugars and an increase in the levels of hydrogen gas (Infante 2011). The rapid production of hydrogen in the lower bowel distends the colon, sometimes causing pain, whereas the osmotic pressures generated by lactose and lactic acid in the colon cause an influx of water leading to further distension of the bowel (Kanabar 2001). Although

studies evaluating the degree of hydrogen in the breath of colicky infants have produced inconsistent results, increases in breath hydrogen levels have been reported (Hyams 1989; Miller 1990; Moore 1988).

- Third, there is growing evidence that the intestinal microbiota in colicky infants differ from those in healthy controls, since higher levels of anaerobic bacteria, such as coliform and *Escherichia coli*, and a lower concentration of *Lactobacilli* have been reported in infants with colic (Savino 2010a; Savino 2013a).
    - Evidence also shows that the microbiota of infants with colicky symptoms contain greater levels of aerobic bacteria, such as *Heliobacter pylori* (Ali 2012), and infants without colicky symptoms have more varied types of microbiota (de Weerth 2013). There is accumulating evidence that babies who are born by caesarean section have different intestinal microbiota (Grönlund 1999), and this and other factors affect infant gut colonisation. One review by Houghteling 2015 examined these factors and the mechanisms of disease that result from disrupted colonisation.
    - Human milk naturally contains prebiotics; they are defined as indigestible oligosaccharides, which could selectively enhance the proliferation of certain probiotic bacteria in the colon, especially *Bifidobacterium* species (Thomas 2010). Some studies have failed to find a protective effect of breastfeeding on the development of colic in breastfed infants (Clifford 2002). However, it is unclear whether these studies compared infants who were exclusively breastfed from birth with infants who were exclusively artificially fed from birth, so it is still not known whether breastfeeding has some protective effect or whether artificial feeding compromises the infant gut microbiome in some way. However, Savino 2013b demonstrated higher levels of coliforms in colicky infants who were not breastfed than in those who were breastfed or who were not colicky. Evidence also suggests that oligosaccharide prebiotics (a mixture of galacto-oligosaccharides and fructo-oligosaccharides) to encourage growth of the positive bacteria in the gut may be effective treatments for allergy and food intolerance in general (Arslanoglu 2012), and for crying in formula-fed infants with colic in particular (Savino 2006).

Many studies, such as Dupont 2010, Savino 2007b, Savino 2010b, and Szajewska 2013, and one Cochrane Review, Praveen 2014, have looked or are looking at the treatment or management of colicky symptoms and other functional gut disorders with probiotics and prebiotics. However, in these times of large-scale deviation from the biological norms of vaginal birth (NHS Maternity Statistics, England 2014-15), skin-to-skin contact after delivery and exclusive breast-milk feeding in the first weeks of life (NHS England Breastfeeding Initiation Q1 2015/16), it is easy to understand how an infant's microbiome may be altered from its intended formation by the absence of these events and the unintended gut colonisation of less favourable bacteria from the hospital, staff or feeding equipment. It is thought that the altered microbiota may be responsible for the colicky pain experienced by some infants, and that receiving probiotics prophylactically might protect the infant from that colicky pain ever occurring, by steering the trajectory of microbial gut colonisation nearer to that which was intended (Indrio 2014).

Of course, it is likely that colic has no single cause, and potential multi-factorial aetiologies may exist even in a single infant with colicky symptoms, while certainly existing in the colicky population.

Description of the intervention

The role of aberrant gut microbiota in infant colic has resulted in the increased study of the use of probiotics in this area (Braeggar 2011; Kukkonen 2008; Praveen 2014). Probiotics are live organisms with potential health benefits; they provide resilience to bacterial insult and threat to the host (Rijkers 2011).*Lactobacillus* and *Bifidobacterium* species are the organisms most commonly used as probiotics. Associated terms include 'prebiotics' and 'synbiotics'. Prebiotics are indigestible food ingredients that benefit the host by selectively stimulating favourable growth or activity, or both, of one or more indigenous probiotic bacteria (Roberfroid 2007), while synbiotics are products containing both probiotics and prebiotics and are often used. They can be delivered through tablets, capsules, suspensions or even as dry foods or granules. As the licensing arrangements for probiotic preparations vary from agent to agent and in different countries, there is a variety of specific dosing regimens and a range of different methods of accessing such agents.

There have been numerous studies around the effectiveness of supplementing the already symptomatic infant's diet with various probiotics and synbiotics to reduce the symptoms of colic, but these seem inconclusive when taken as a whole (Savino 2010b; Sung 2014; Szajewska 2013). However, evidence is building around the effectiveness of prophylactically supplementing the newborn infant with probiotics to prevent colic and other symptoms (Indrio 2014; Oozeer 2013). Additionally, evidence is accumulating on the safety of such an intervention (Savino 2010b).

How the intervention might work

Given the growing evidence that the intestinal microbiota in colicky infants differs from those in healthy controls, it is proposed that supplying probiotic bacteria can redress this balance and provide a healthier intestinal microbiota landscape. This is required for normal gut transit and it is postulated will reduce the functional symptoms associated within colic (Savino 2010a; Savino 2013a; Savino 2013b). As the evidence base suggests, common factors impact this colonisation process, such as birth by caesarean

section (Grönlund 1999), and it is proposed that offering probiotics prophylactically to all as a form of primary prevention could offer significant benefits to the population with minimal risks.

Why it is important to do this review

As previously stated in Praveen 2014 and above, infantile colic is a common disorder with a stressful effect on both the infant and parent/carer; however, the pathogenesis of colic is poorly understood and involves a range of risk factors. Some of the most commonly prescribed treatments for infant colic have been found to be no more effective than placebo (Garrison 2000; Lucassen 2000; Savino 2012). It has been increasingly thought that gut microbiota play an important role in the pathogenesis of colic (Savino 2007b), and probiotic supplementation has been suggested as a treatment for symptoms of colic in infants, although observational studies and clinical trials have provided mixed reports on whether this is beneficial (Savino 2010a; Sung 2012; Sung 2014). Two Cochrane Reviews are currently underway examining the effects of probiotics for infantile colic (Praveen 2014) and pain-relieving agents for the condition (Savino 2012).

Considering the impact of the condition and the increasing scope of oral probiotics in the field of neonatology (necrotising enterocolitis) and paediatrics (allergic enteritis) (Baldassarre 2010; Deshpande 2010; Deshpande 2011), as well as the relatively low cost and easy availability of probiotics, we believe it is important to evaluate the current evidence on probiotics as a type of prophylactic therapy to prevent the onset of infant colic, in terms of both effectiveness and safety, using the rigorous methodology of a Cochrane Review.

Increasingly, work is being undertaken to assess and describe microbiota in the days, weeks and months after the infant's birth; for example, de Weerth 2013 reported the evolution of changes in microbiota that match the course of infant colic resolving over three months. This illustrates why it may be more effective to give probiotics prophylactically, early in life, to prevent colic rather than using them to try to treat it after it has occurred.

New, large-scale studies have come to light in this area of postnatal probiotics, including Indrio 2014, which enrolled 589 infants in a multi-centric study; Pärtty 2013a with almost 100 preterm participants; and Kukkonen 2008, which included over 1000 infants. It is thus timely to revisit this area and assess the potential use of probiotics as a preventive measure for colic, which, if proven effective, could reduce or eliminate infant and parent/carer stress in the early weeks and months of a baby's life.

OBJECTIVES

To evaluate the efficacy and safety of prophylactic probiotics in preventing or reducing severity of infantile colic.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cluster and crossover trials.

Types of participants

Newborn infants younger than one month of age without a diagnosis of infantile colic at recruitment, as defined by the study. Gestational age range from 32 weeks to term.

Types of interventions

Any probiotic, alone or in combination with a prebiotic (also known as synbiotics), versus no intervention, another intervention(s) or placebo, and where the study considered the effect on the onset of infantile colic. We considered any dosing regimen or frequency of intervention. The intervention was given to pregnant women (prior to delivery at any time), lactating mothers (while breastfeeding in the study) and newborn infants (as defined above).

Types of outcome measures

For all proposed outcomes, we used final outcomes from the end of the trials, and recorded the timings of these outcomes as we planned to perform subgroup analyses if we found sufficient studies (this was not the case).

Primary outcomes

- Occurrence of new cases of colic at study end, as defined by the Wessel criteria.
- Adverse effects, including parental depression and mental illness, choking, bacterial infection or apparent life-threatening/serious events (dichotomous outcome).

Secondary outcomes

- Duration of crying (post-treatment versus baseline). Data could have been continuous (e.g. hours per day) or dichotomous (e.g. reduction under a predefined threshold, as determined by the study authors).
- Number of responders in each group after treatment. We defined responders as those who experienced a decrease in the daily, mean crying time of 50% from baseline (dichotomous outcome).
- Frequency of crying episodes per 24 hours, where frequency was specified in trials separately to duration of infant's crying (post-treatment versus baseline) (dichotomous outcome).

- Crying time at completion in each group in minutes per day.
- Infant sleep duration per 24 hours at seven, 14 and 21 days (post-treatment versus baseline) (continuous outcome), or, where it was not grouped in this way in individual trials, using a time window of between seven and 28 days.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases and trial registers in June 2016 and January 2018. There were no date or language restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 12) in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register.
- MEDLINE Ovid (1946 to January week 3 2018).
- MEDLINE In-Process & Other Non-Indexed Citations Ovid (searched 30 January 2018).
- MEDLINE Epub Ahead of Print Ovid (searched 30 January 2018).
- Embase Ovid (1974 to 29 January 2018).
- CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 to 30 January 2018).
- PsycINFO Ovid (1967 to January week 4 2018).
- Science Citation Index - Expanded Web of Science (SCI-Expanded; 1970 to 28 January 2018).
- Social Sciences Citation Index Web of Science (SSCI; 1970 to 28 January 2018).
- Conference Proceedings Citation Index - Science Web of Science (CPCI-S; 1990 to 28 January 2018).
- Conference Proceedings Citation Index - Social Science & Humanities Web of Science (CPCI-SS&H; 1990 to 28 January 2018).
- LILACS (Latin American and Caribbean Health Science Information Database; lilacs.bvsalud.org/en; searched 30 January 2018).
- *Cochrane Database of Systematic Reviews* (CDSR; 2018, Issue 1) part of the Cochrane Library (searched 30 January 2018).
- Database of Abstracts of Reviews of Effects (DARE; 2015, Issue 2. Final Issue) part of the Cochrane Library (searched 3 June 2016).
- Epistemonikos (limited to systematic reviews; www.epistemonikos.org; all available years).
- WorldCat (limited to theses; www.worldcat.org; searched 30 January 2018).
- ClinicalTrials.gov (www.clinicaltrials.gov; searched 30 January 2018).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; apps.who.int/trialsearch; searched 30 January 2018).

The search strategies for each source are reported in Appendix 2.

Searching other resources

Grey literature

We handsearched abstracts presented at relevant international meetings, including the European Society for Paediatric Gastroenterology Haematology and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), published from their earliest availability (2010) until the most recent meeting (2015), with the aim of finding relevant studies not yet published in full. There is some evidence that data from abstracts can be inconsistent with data in published articles (Pitkin 1999). The studies that we did find either did not meet our inclusion criteria (Criteria for considering studies for this review), or were not sufficiently detailed for us to assess eligibility. Therefore, because we had determined that we would only include abstract publications if they presented sufficient data on which to judge inclusion and assess quality, we have not included any studies found in such a way.

Supplementary searching

We inspected the references of all relevant studies and reviews for any potentially relevant studies that we may have missed, and contacted the authors of included studies to request any missing or incomplete data (with the exception of a prepublication copy of the now published Baldassarre 2016 study, no responses were received). In addition, we ran citation searches of included studies.

Personal contacts

We contacted leaders in the field to try to identify other published and unpublished studies.

Pharmaceutical companies

We contacted the companies that produce probiotics and synbiotics, as well as the companies that produce medication and formula preparations, as per the Background section, to search for any other relevant ongoing and unpublished studies.

Data collection and analysis

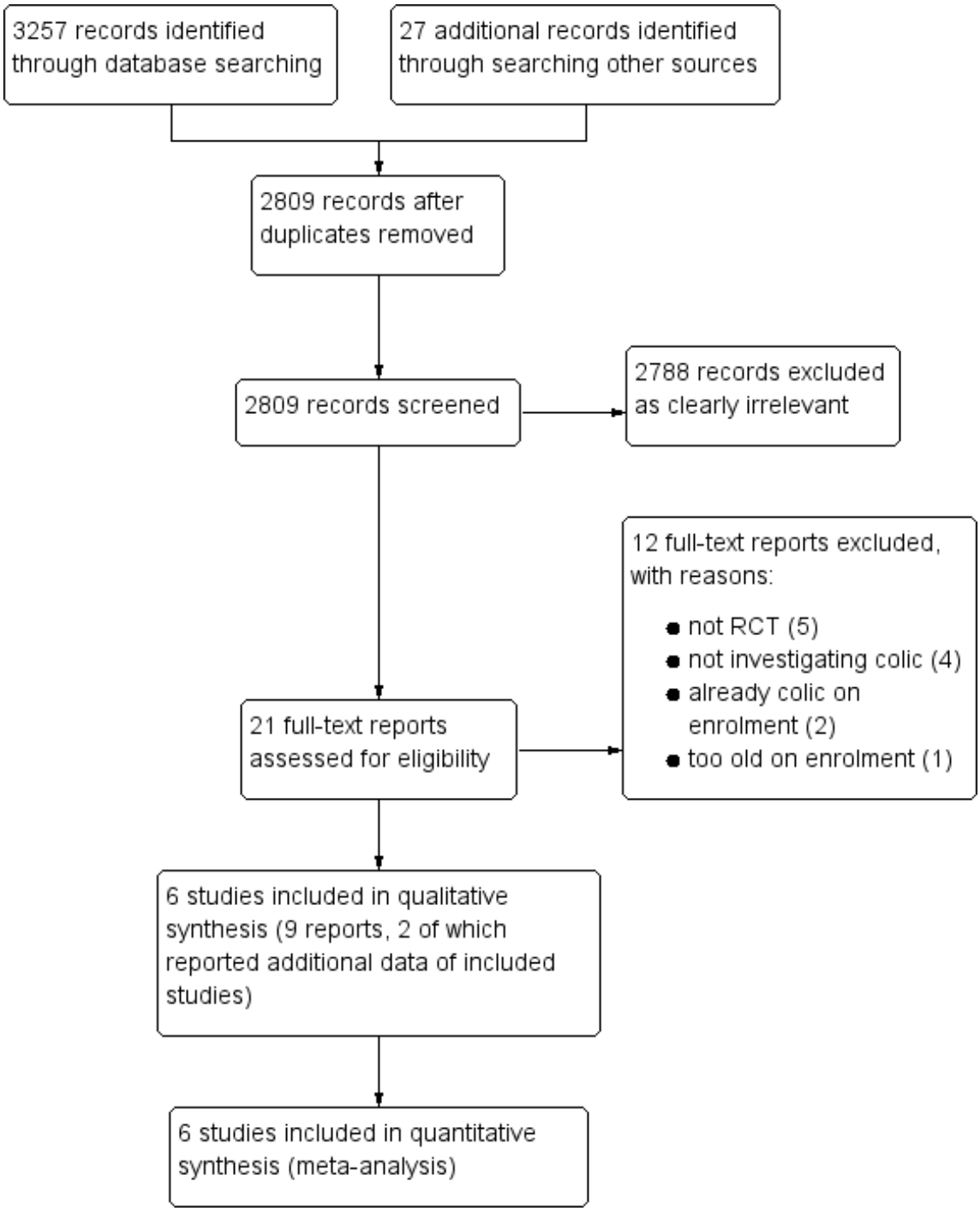
Selection of studies

Having collated references and removed duplicates, two review authors (MG and SSCB) independently screened titles, abstracts and full reports for eligibility against the inclusion criteria (see Criteria for considering studies for this review). Specifically, they undertook the following tasks.

- Merged search results using reference management software and removed duplicate records of the same report.
- Examined titles then abstracts, and removed any records that did not meet the inclusion criteria.
- Retrieved the full texts of potentially relevant reports.
- Linked together multiple reports of the same study.
- Examined full-text reports to determine whether studies met the eligibility criteria.
- Corresponded with investigators, when appropriate, to clarify study eligibility.
- At all stages, noted reasons for inclusion and exclusion on a study-flow spreadsheet, and resolved any disagreements through consensus.
- Made final decisions on study inclusion, resolving any discrepancies by discussion until a consensus was reached and involving a third review author (GT) if needed.
- Proceeded to data collection.

Our selection process has been included in a PRISMA diagram (Moher 2009). See Figure 1.

Figure 1. Study flow diagram. RCT: randomised controlled trial.



Data extraction and management

We developed a data extraction form a priori, as per the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and piloted the form on the first two RCTs to ensure it was fit for purpose. We extracted the following information.

- Characteristics of participants: source of participants, inclusion and exclusion criteria, total number at baseline, total number at completion, setting, definition of colic applied, diagnostic criteria applied, type of feeding (breastfeeding, formula feeding), age at onset of colic, age at commencement of intervention and evaluation of potential effect modifiers (e.g. age, gender).
- Interventions and controls: number of groups, intervention(s) applied, frequency and duration of treatment, total number of treatments and permitted cointerventions.
- Methods: study design and duration, sequence generation, allocation concealment, blinding of outcome assessors and evaluation of success of blinding.
- Outcomes: outcomes assessed, definitions used, values of means and standard deviations (SD) at baseline and at time points as defined by the study protocol (or change from baseline measures, if given).
- Results: measures at end of protocol, follow-up data (including means and SDs, standard errors or confidence intervals (CI) for continuous data, and summary tables for dichotomous data), withdrawals and losses to follow-up.
- Other: references to other relevant studies, points to follow-up with the study authors, comments from the study authors, key conclusions from the study (by the study authors) and other comments from the review authors.

Two review authors (MG and GT) independently extracted the data using the data extraction form. A third review author (MRT) resolved any disagreements. We collated the data in the latest version of Review Manager 5 (RevMan 5) (Review Manager 2014).

Assessment of risk of bias in included studies

Two review authors (MG and SSCB) independently evaluated each study for risk of bias, using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011; Higgins 2011b), and set out in Appendix 3, for the following domains: sequence generation; allocation concealment; blinding of parents and health professionals; blinding of outcome assessment; incomplete outcome data; selective outcome reporting and other potential threats to validity. We judged each domain as being at low, high or unclear risk of bias. We compared the judgements and discussed and resolved any inconsistencies in the assessments. A third review author (MRT) was available to resolve any persisting disagreements.

Measures of treatment effect

Dichotomous data

We presented dichotomous data as risk ratios (RR), since the effects of the RR are readily understood (Walter 2000). We reported all RRs with their associated 95% CIs and probability values (when possible).

Continuous data

When all studies use the same measurement scale, we calculated mean differences (MD) and presented these with 95% CI. For methods to handle studies that use different measurement scales, see protocol, Banks 2016, and Table 1.

When necessary, we calculated effect estimates from P values, t statistics, analysis of variance (ANOVA) tables or other statistics, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), but only in situations when the raw data (MD or standardised mean difference (SMD)) were not directly available in the study publications.

For this analysis, we used, according to need, either change scores or final values without combining them.

If both continuous and dichotomous data were available for an outcome, we included only the continuous outcome in the primary analysis.

Unit of analysis issues

Cluster-randomised studies

We did not encounter any cluster-randomised trials. See protocol, Banks 2016, and Table 1 for methods to handle such studies in future updates of this review.

Studies with multiple treatment arms

In the primary analysis, we combined results across all eligible intervention arms and compared them with the combined results across all eligible control arms (another intervention(s) or placebo), and made single, pair-wise comparisons. Where such a strategy prevented investigation of potential sources of heterogeneity, we analysed each type separately (against a common control group: placebo), but divided the sample size for common comparator arms proportionately across each comparison (Higgins 2011b).

This simple approach allowed the use of standard software (including Review Manager 2014) and prevented the inappropriate double counting of participants.

Cross-over studies

In randomised cross-over studies, participants receive each intervention sequentially, in a random order. Cross-over studies usually contain a washout period, which is a stage after the first treatment but before the second treatment, where time is given for the active effects of the first treatment to wear off before the new treatment begins in order to reduce the carry-over effect (where the first treatment affects the second). The risk of a carry-over effect is a concern in cross-over studies and especially for this review given the nature of the interventions we assessed. For this review, we only included data from the first treatment period from cross-over studies.

Dealing with missing data

Where data were missing, we contacted the corresponding authors of included studies requesting them to supply any unreported data; details are given in the Characteristics of included studies table.
For all outcomes in all studies, we carried out analyses as far as possible on an intention-to-treat basis; that is, we attempted to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated regardless of whether or not they received the allocated intervention.
For missing continuous data, we estimated SD from other available data, such as standard errors, or we imputed them using the methods suggested in Higgins 2011b. We conducted analyses based on participants completing the trial, in line with available-case analysis; this assumed that missing data were at random. If there was a discrepancy between the number randomised and the number analysed in each treatment group, we calculated and reported the percentage lost to follow-up in each group.
When it was not possible to obtain missing data, we recorded this on the data collection form, reported it in the 'Risk of bias' table, and discussed the extent to which the missing data could alter the results and hence the conclusions of the review. For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by conducting sensitivity analyses (Banks 2016), but as there were few studies in our analysis, this was not possible. See Table 1.

Assessment of heterogeneity

We assessed clinical heterogeneity by comparing the distribution of important participant characteristics between trials (e.g. age) and trial characteristics (e.g. randomisation, concealment, blinding of outcome assessment, losses to follow-up, treatment type, cointerventions).
We employed a Chi^2 test of homogeneity, with a 10% level of significance, to determine the strength of evidence that heterogeneity was genuine.
In addition, we assessed statistical heterogeneity by examining the I^2 statistic (Deeks 2011), a quantity that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error. We interpreted the I^2 statistic as suggested in Deeks 2011:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity and
- 75% to 100%: suggests considerable heterogeneity.

Assessment of reporting biases

To minimise publication bias, we attempted to obtain the results of any unpublished studies, in order to compare the results extracted from published journal reports with the results obtained from other sources (including correspondences).
We were unable to assess reporting biases using funnel plots due to the small number of included studies. See Banks 2016, and Table 1.

Data synthesis

When interventions were similar in terms of type of intervention, type of outcome assessed and type of colic, we grouped the studies and synthesised their results in a meta-analysis. We presented results for each combination of probiotic intervention, assessed outcome and colic type, with the exception of those studies for which there were no data. For instance, when two or more studies assessed the effects of prophylactic probiotic use in otherwise healthy infants with colic and both measured daily crying, we performed a meta-analysis of the results. Because we assumed that clinical heterogeneity was very likely to impact on our results, given the wide breadth and types of interventions included, we combined the studies using a random-effects model, regardless of statistical evidence of heterogeneity of effect sizes, calculating individual treatment effects and assigning weight using inverse variance. We used these calculations to produce a pooled effect, which we presented in a forest plot. We carried out statistical analysis using RevMan 5 (Review Manager 2014). When data were insufficient, we provided a narrative description of the results.

'Summary of findings' tables

We assessed the overall certainty of the evidence using the GRADE approach (Guyatt 2008). The GRADE approach appraises the certainty of a body of evidence based on the extent to which one can be confident that an estimate of effect, or association, reflects

the item being assessed. RCTs start as high-certainty but may be downgraded due to risk of bias (methodological quality), indirectness of evidence, unexplained heterogeneity, imprecision (sparse data) and publication bias. Two review authors (SB and MG) independently assessed the overall certainty of the evidence for each outcome after considering each of these factors and graded them as follows.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We reported our ratings for the outcomes listed below in Summary of findings for the main comparison, which we constructed using GRADEpro GDT (GRADEpro GDT).

- Occurrence of new cases of colic at study end.
- Adverse effects, including parental depression and mental illness, choking, bacterial infection or apparent life-threatening events/serious events (dichotomous outcome) during study period.
- Duration of crying at study end.

Subgroup analysis and investigation of heterogeneity

Large numbers of subgroup analyses may lead to misleading conclusions (Oxman 1992; Yusuf 1991). We conducted the following subgroup analyses, when possible.

- Type of feeding (artificially fed babies versus breastfed babies).
- Preterm babies (pre-37 weeks' and pre-33 weeks' gestation) versus term babies (born between 37 and 43 weeks' gestation).
- Antenatal starting of probiotics for pregnant women with continuation postnatally versus postnatal probiotics (see Differences between protocol and review).
- Type of probiotic (or combination of probiotic with prebiotic, also known as 'synbiotic').

Due to the heterogeneity of primary study designs and reported outcomes, such analysis were limited, with data not reported to explore many of these outcomes.
We were unable to conduct our other, preplanned subgroup analyses (Banks 2016), due to a lack of data. See Table 1.

Sensitivity analysis

We conducted a sensitivity analysis to determine whether findings were sensitive to the choice of meta-analysis model used, by comparing results from the fixed-effect model with those of the random-effects model. We were unable to conduct our other, preplanned sensitivity analyses (Banks 2016), due to a lack of data. See Table 1.

RESULTS

Description of studies

Results of the search

Our Electronic searches, conducted up to January 2018, retrieved 3257 records. We identified a further 27 records by searching references. After removing duplicates, we screened the titles and abstracts of the remaining 2809 records for eligibility, discarding those that were clearly irrelevant. We selected 21 records for full-text review (See Figure 1). Of these, we excluded 12 studies (see Characteristics of excluded studies) and included six studies (see Characteristics of included studies table). We found no studies awaiting classification or ongoing studies.

Included studies

Study design

This review included nine reports describing six RCTs (Baldassarre 2014; Indrio 2008; Indrio 2014; Kukkonen 2008; Pärtty 2013a; Vlieger 2009).

Participants

The studies included 1886 participants. Participants were pregnant women, breastfeeding mothers or newborn babies, depending on study design.

Interventions

In two studies pregnant women began the intervention at 36 weeks' gestation and continued until birth (Baldassarre 2014; Kukkonen 2008). In one of these two studies, Baldassarre 2014, the mothers, who were all breastfeeding, continued taking the probiotic or placebo for four weeks after the baby was born; in the other study, Kukkonen 2008, the infants were then given the intervention probiotic or placebo. In one study, Pärtty 2013a, preterm infants of gestational age 32 (+ 0) to 36 (+ 6) weeks began the intervention on day one of life. In three studies, formula-fed infants

began the intervention either from birth (Indrio 2014), or within the first week of life (Indrio 2008; Vlieger 2009).
The duration of the interventions varied from 30 days (Indrio 2008) to six months (Kukkonen 2008).
Two studies used a synbiotic instead of just probiotic (Kukkonen 2008; Vlieger 2009).

Control/comparisons

All studies used placebo as the control. No studies employed a no intervention group or other interventions.

Outcomes

The specific outcomes selected for the various studies ranged from breast milk analysis to infant stool analysis, infections to regurgitation, and from GP visits, hospital admissions and days of work lost, to our main search outcome of crying or colicky symptoms. Colic was defined in a number of ways, including using Rome III (Hyman 2006) criteria (Baldassarre 2014; Indrio 2008; Indrio 2014), and the Wessel (Wessel 1954) criteria (Kukkonen 2008; Pärtty 2013a). One study used incidence of colic as an outcome measure, but authors were not specific about how this was assessed (Vlieger 2009).

Funding

Four of the studies were funded by industry (Indrio 2008; Indrio 2014; Pärtty 2013a; Vlieger 2009). In two studies, industry supplied the interventional product but had no other involvement in the study (Indrio 2008; Indrio 2014), and in two studies industry funded the authors' salary (Pärtty 2013a; Vlieger 2009). See Characteristics of included studies table for further information.

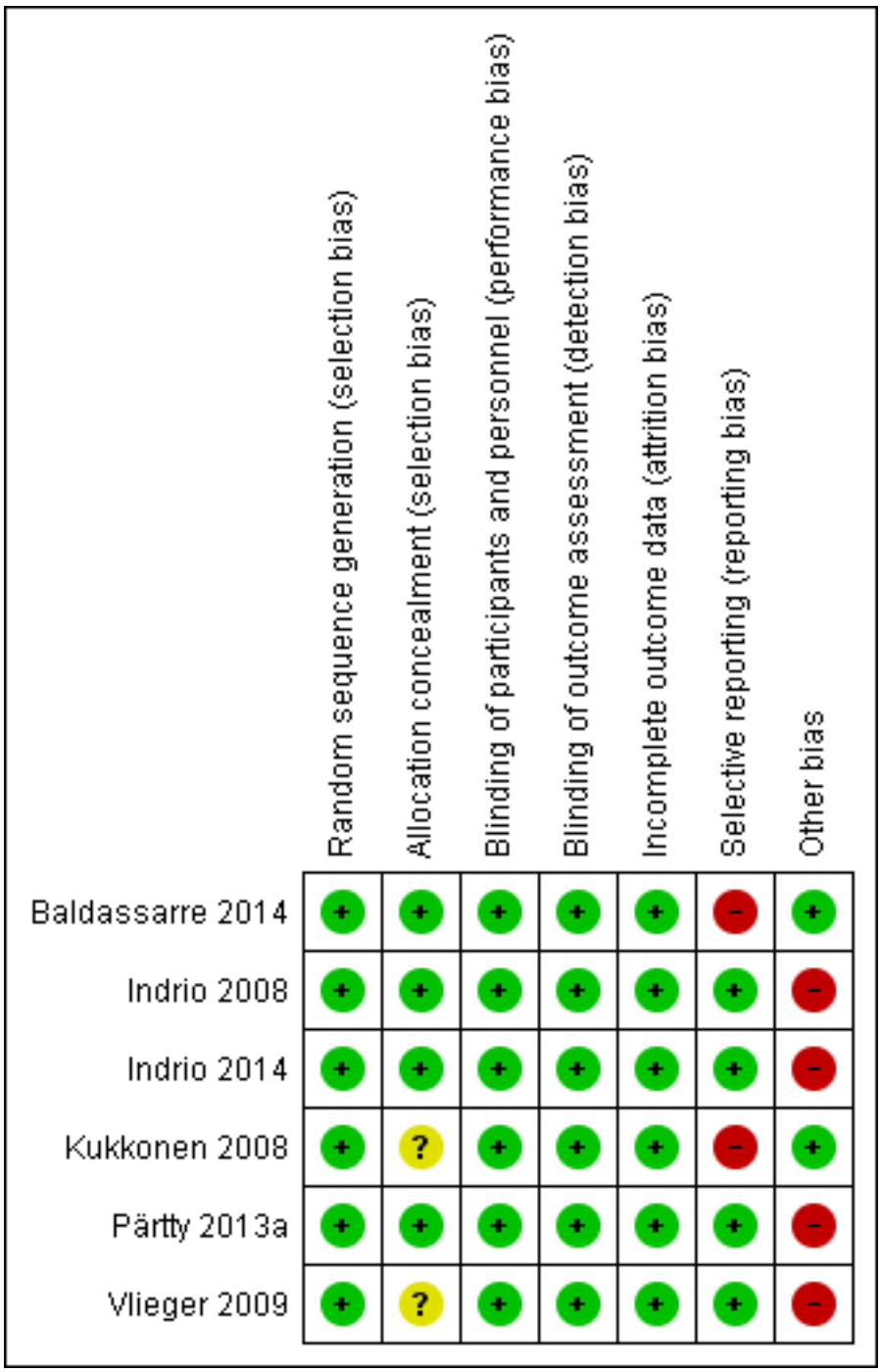
Excluded studies

We excluded 12 studies (from 12 reports). Five studies were not RCTs (Di Mauro 2013; Mommaerts 2011; Olivares 2011; Pärtty 2013b; Wade 2001); four studies did not investigate colic (Cekola 2015; Garofoli 2014; Hoy-Schulz 2016; Savino 2015); two studies did not administer probiotics prophylactically (Simone 2014; Szajewska 2013); and one study started the intervention in infants from four months of age, so was not prophylactic by our definition (Weizman 2006). See the Characteristics of excluded studies table.

Risk of bias in included studies

The results of our 'Risk of bias' assessment for the included studies is summarised in Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Five studies described an adequate method of random allocation of participants to intervention groups (Indrio 2008; Indrio 2014; Kukkonen 2008; Pärtty 2013a; Vlieger 2009), so we rated these studies at low risk of bias on this domain. For one study, Baldassarre 2014, this was unclear, but reported as adequate in the full manuscript (Baldassarre 2016), so we rated this study at low risk of bias.

Allocation concealment

We considered allocation concealment to be described adequately in one study, which we rated at low risk of bias on this domain (Pärtty 2013a). Additionally, the lead authors of three studies responded to a request for further information and confirmed adequate allocation concealment, so we rated these studies at low risk of bias (Baldassarre 2014; Indrio 2008; Indrio 2014). The remaining two studies either did not describe or mention allocation concealment, so we considered those studies at unclear risk of bias on this domain (Kukkonen 2008; Vlieger 2009).

Blinding

We rated five studies at low risk of performance bias and detection bias because they described adequate methods for blinding (Indrio 2008; Indrio 2014; Kukkonen 2008; Pärtty 2013a; Vlieger 2009). We also rated the remaining study by Baldassarre 2014 at low risk of performance and detection bias as we were able to confirm adequate blinding from the full, published manuscript (Baldassarre 2016).

Incomplete outcome data

We judged all six studies at low risk of attrition bias because dropouts were either balanced across treatment groups, with similar reasons for withdrawal, or there were few dropouts (Baldassarre 2014; Indrio 2008; Indrio 2014; Kukkonen 2008; Pärtty 2013a; Vlieger 2009).

Selective reporting

We judged four studies at low risk of reporting bias because they discussed the key declared outcomes from their methods, including adverse outcomes and these matched those reported in trial registration records or protocols (Indrio 2008; Indrio 2014; Pärtty 2013a; Vlieger 2009). Two studies did not state the outcome of investigating colic in the trial registration record and were at high risk of reporting bias (Baldassarre 2014; Kukkonen 2008)

Other potential sources of bias

Because of the nature of the evidence contained within these studies, and the claims for one product or intervention over another in such a vulnerable population, we considered any involvement by the companies supplying or manufacturing the intervention product in the conduct of the studies or the writing up of results, to trigger a rating of high risk of other bias. Two studies declared no financial involvement with industry, whether by provision of experimental product or by direct financial support for the work, and so we rated them at low risk of other bias (Baldassarre 2014; Kukkonen 2008). The remaining four studies stated that they were supported by the manufacturers of the intervention, or received support from the manufacturers, or both, and so we rated them at high risk of other bias (Indrio 2008; Indrio 2014; Pärtty 2013a; Vlieger 2009). We contacted the authors to confirm that there was no such involvement and thereby downgraded the judgement, but received no responses to our requests. None of the studies appeared to have any other potential sources of bias other than industry funding.

Effects of interventions

See: **Summary of findings for the main comparison** Prophylactic probiotics compared to placebo for the prevention of infantile colic

See Characteristics of included studies table.

All six included studies compared probiotics to placebo. No studies employed a no intervention group or another intervention. Below, we presented the results of the main analyses for this comparison by outcome, followed by the results of key subgroup analyses based on participants and interventions. For the purposes of readability, we reported the results of sensitivity analyses using the fixed-effect model directly after the results of analyses using the random-effects model.

We summarised the evidence for 'occurrence of new cases of colic', 'adverse effects' and 'crying time' in Summary of findings for the main comparison. We downgraded our certainty in the evidence from all analyses to low, due to concerns with imprecision, substantial unexplained statistical heterogeneity and low event numbers within adverse effects. It is worth noting that for all these analyses, we downgraded the certainty of the evidence due to concerns with publication bias. This was based on other reviews cited in the field on infantile colic that included negative trials. We felt that with the small number of individually positive studies in this review, there was a pervasive risk, hence leading to this judgement.

Probiotics versus placebo

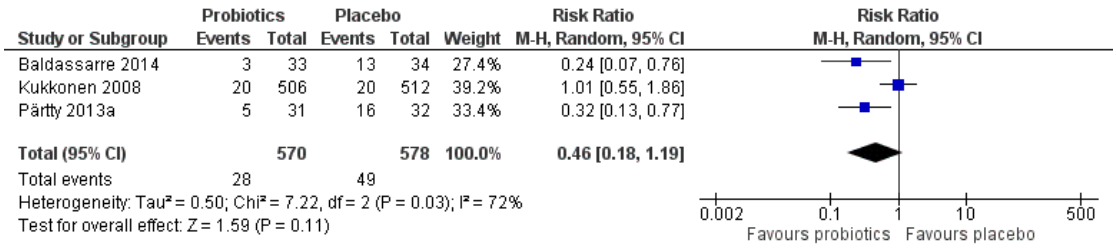
All six included studies compared probiotics to placebo (Baldassarre 2014; Indrio 2008; Indrio 2014; Kukkonen 2008; Pärtty 2013a; Vlieger 2009). Two studies used probiotics with prebiotics, so-called synbiotics (Kukkonen 2008; Vlieger 2009).

Primary outcomes

Occurrence of new cases of colic

We conducted a random-effects meta-analysis of three studies with 1148 participants (Baldassarre 2014; Kukkonen 2008; Pärtty 2013a), and found no significant difference between the two groups in relation to the occurrence of new cases of colic (RR 0.46, 95% CI 0.18 to 1.19; Analysis 1.1; Figure 3; low-certainty evidence, downgraded twice due to concerns with publication bias, imprecision and very serious inconsistency; Summary of findings for the main comparison). In a sensitivity analysis using the fixed-effect model, we found a significant difference in favour of probiotics (RR 0.58, 95% CI 0.38 to 0.90; Analysis 1.2). This inconsistency between the two models suggests statistical heterogeneity, and is consistent with the I^2 statistic, which was high at 72%. We were unable to investigate the causes of this heterogeneity further, as originally planned (Banks 2016), due to the limited reported data.

Figure 3. Forest plot of comparison: 1 Probiotic preparation versus placebo, outcome: 1.1 Occurrence of new cases of colic: random-effects model.



Adverse effects

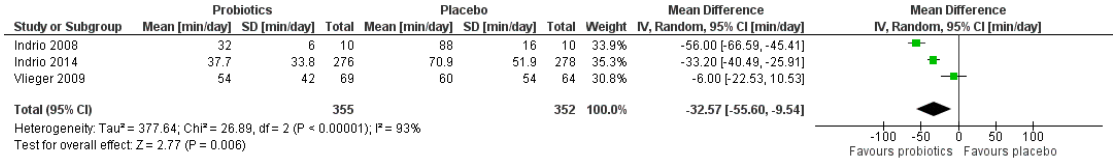
We conducted a meta-analysis of all six studies (Baldassarre 2014; Indrio 2008; Indrio 2014; Kukkonen 2008; Pärtty 2013a; Vlieger 2009), and found no difference between the groups in relation to serious adverse effects (RR 1.02, 95% CI 0.14 to 7.21; 1851 participants; Analysis 1.3; low-certainty evidence, downgraded twice due to concerns with publication bias, general risk of bias and very serious inconsistency; Summary of findings for the main comparison). It is worth noting that there were just four events reported across all six studies, all in the same study with two in each condition. These were meconium plug obstruction, patent ductus arteriosus and neonatal hepatitis. This prevented calculation of the I^2 statistic. This same study reported all minor events that occurred, with similar rates of neonatal morbidity (probiotic versus prebiotic: jaundice: 11 versus 6 events; hypoglycaemia: 14 versus 11 events; infection 11 versus 24 events; oxygen supplementation: 11 versus 18 events). These were all appropriate background rates for such events in a normal neonatal population and also unlikely related to either study arm.

Secondary outcomes

Duration of crying

We conducted a random-effects meta-analysis of three studies with 707 participants (Indrio 2008; Indrio 2014; Vlieger 2009), and found a difference between the two groups in favour of probiotics, for crying time (MD -32.57 minutes per day, 95% CI -55.60 to -9.54; Analysis 1.4; Figure 4; low-certainty evidence, downgraded twice due to concerns with publication bias, imprecision and very serious inconsistency; Summary of findings for the main comparison). We found similar results when using a fixed-effect model in a sensitivity analysis (MD -32.57, 95% CI -55.6 to -9.54; Analysis 1.5). The I^2 statistic for both analyses was 93%, with a significant Chi^2 result, suggesting considerable statistical heterogeneity for which we subsequently downgraded the certainty of the evidence in the GRADE analysis.

Figure 4. Forest plot of comparison: 1 Probiotic preparation versus placebo, outcome: 1.4 Crying time: random-effects model (minutes/day).



Single study results

Kukkonen 2008 compared a mixture of four probiotic species *(Lactobacillus rhamnosus GG,* LC705, *Bifidobacterium vreve Bb99*, *Propionibactterium freudenreichii* ssp *shermanii*) with placebo and found no significant difference between the groups in relation to infantile colic, defined as excessive crying in both groups.

Pärtty 2013a compared placebo with *Galacto-oligosaccharide* and with *Lactobacillus rhamnosus GG*, and found fewer excessive criers in both intervention groups compared with the placebo group (P = 0.02). Only one other study used *Lactobacillus rhamnosus*, but it was mixed with other probiotics (Kukkonen 2008).

Vlieger 2009 compared prebiotic formula (containing *Lactobacillus paracasei, Paracasei* and*Bifidobacterium animalis, Lactis*) with the same formula without probiotics and found no difference between the groups in relation to crying time. Infants who were not going to be breastfed were started on this milk within one week of birth and continued to receive it for three months. This study was designed to determine whether probiotic intervention was safe. It found no difference between the prebiotic and placebo groups in relation to mean crying time (1.8 hours per day) at three months of age.

Baldassarre 2016 (an additional report of Baldassarre 2014) compared multi-strain probiotics (*Lactobacillus paracasei*, *Plantarum*, *Acidophilus*,*Delbruieckii subsp. bulgaricus*,*Bifidobacterium longum*,*Breve*,*Infantis*,*Streptococcus thermophiles*) with placebo and found that colic was less frequent in the probiotic group compared to the placebo group (P = 0.007).

No studies reported data on our other secondary outcomes: duration of crying; number of responders; frequency of crying episodes per 24 hours; infant sleep duration per 24 hours.

Subgroup analyses

There was much heterogeneity in the included studies, primarily in relation to the species of probiotic given and the age of infants who received it. Subgroup consideration is shown below, highlighting the relevant meta-analysis where there was scope to complete this. It is worth noting that, given the small number of studies included in the review, these analyses were comprised of only a few studies or, in some cases, a single study. Given the clinical heterogeneity, this is a necessary set of analyses, but must be interpreted with caution.

Type of feeding

Two studies looked at the effects of probiotics for artificially fed or breastfed babies (or both) (Indrio 2014; Pärtty 2013a). We were unable to conduct a meta-analysis due to the different outcome measures reported between these studies. Indrio 2008 compared 10 artificially fed babies receiving probiotics with 10 artificially fed babies receiving placebo. Crying time in preterm infants fed formula and supplemented with placebo was recorded as 88 (SD 16) minutes per day, compared to 32 (SD 6) minutes per day in formula-fed infants supplemented with probiotics, giving a reduction of 56 (SD 16) minutes per day or 71.8%. Pärtty 2013a used mixed probiotics (31 infants) and placebo (32 infants) groups made up of breastfeeding babies, mixed-fed babies and artificially fed babies. This study rated babies as excessive criers if their total crying time exceeded three hours per day, causing clinical concern but without medical causes during the study visits in months one and two (modified Wessel criteria: Wessel 1954), resolving by six months of age. Babies who did not meet this criterion were labelled "contented". Just 22% of babies in the probiotic group were categorised as excessive criers compared with 56% of babies in the placebo group. The paper did not record crying time and the study author did not respond to our requests for more information.

Preterm versus term babies

Two studies looked at the effects of probiotics for preterm babies (gestational age from 32 (+ 0) weeks to 36 (+ 6) weeks) for 30 days (Indrio 2008) and 60 days (Pärtty 2013a). Indrio 2008 chose to supplement the babies with *Lactobacillus reuteri* (1×10^8 colony-forming unit (CFU) per day), and Pärtty 2013a with *Lactobacillus rhamnosus* (1×10^9 CFU per day from birth to day 30, and twice per day from days 31 to 60). Both studies recruited at birth. Indrio 2008 entered the babies into the study between days one and three of life whereas Pärtty 2013a entered babies into the study between days three and five of life. Data were not presented in a consistent format for these studies to facilitate meta-analysis.

Two studies looked at the effects of probiotics on term babies (Indrio 2014; Kukkonen 2008). We were unable to conduct a meta-analysis of the results from these studies because of the heterogeneity of both the population and the intervention. Indrio 2014 looked at healthy infants given probiotics within the first week of life and for 90 days. Kukkonen 2008 looked at infants at increased risk of allergy who were supplemented with probiotics from birth, after the mother had been given probiotics from 36 weeks' gestation until birth. Duration of crying time for participants in Indrio 2014 was 38 minutes per day in the probiotic group versus 71 minutes per day in the placebo group at study end. Kukkonen 2008 claimed no difference in rates of infantile colic, defined as four or more hours of crying per day on at least three days per week, between the probiotic and placebo groups (4% occurrence in each group). They also defined another outcome based on a definition of a 'less-frequent crying group' (once or twice per week), which was 10% in both probiotic intervention and placebo participants on completion. Kukkonen 2008 was set up to look at long-term safety and impact on infection, rather than intestinal comfort, whereas Indrio 2014 was looking for a preventive measure for constipation, colic and intestinal discomfort.

An analysis of two studies with 687 term infants (Indrio 2014; Vlieger 2009), comparing probiotics and placebo, found no difference between the groups (MD -20.65 minutes per day, 95% CI -47.23 to 5.92; Analysis 1.6; moderate-certainty evidence, downgraded once due to serious inconsistency concerns).

Antenatal starting of probiotics for pregnant women with continuation postnatally versus postnatal probiotics

Two studies with 1085 participants included probiotic supplements given to pregnant women from 36 weeks' gestation as the first part of the intervention (Baldassarre 2014; Kukkonen 2008). Baldassarre 2014 described colic as being more frequent in the placebo group than in the probiotic group (RR 4; Chi^2 = 7.2). A logistic regression analysis showed the only factor with significant impact on colic was the mothers' probiotic consumption. The results of Kukkonen 2008 showed no significant difference between the groups in relation to infantile colic, defined as excessive crying in both groups. We conducted a random-effects meta-analysis for our primary outcome, occurrence of colic, and found no difference between groups (RR 0.54, 95% CI 0.13 to 2.20; Analysis 1.7). Data were not available to allow subgroup analysis for our other outcomes.

Type of probiotic

We found two studies with 574 participants comparing one specific probiotic, *Lactobacillus reuteri,* to placebo (Indrio 2008; Indrio 2014). We conducted a random-effects meta-analysis and found a significant reduction in crying time in favour of the probiotic group (MD -44.26 minutes per day, 95% CI -66.60 to -21.93; 574 participants; Analysis 1.8; Figure 5; moderate-certainty evidence, downgraded once due to serious inconsistency). We found similar results when we used a fixed-effect model in a sensitivity analysis (MD -40.53 minutes per day, 95% CI -46.53 to -34.52; Analysis 1.9; Figure 6). However, both studies looked at different patient groups: Indrio 2008 included preterm infants and Indrio 2014 included term infants.

Figure 5. Forest plot of comparison: 1 Probiotic preparation versus placebo, outcome: 1.7 Mean crying time at study end: random-effects model.

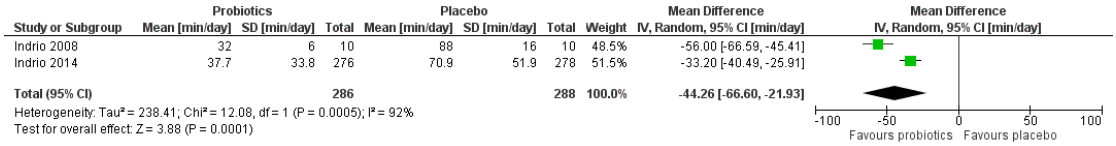
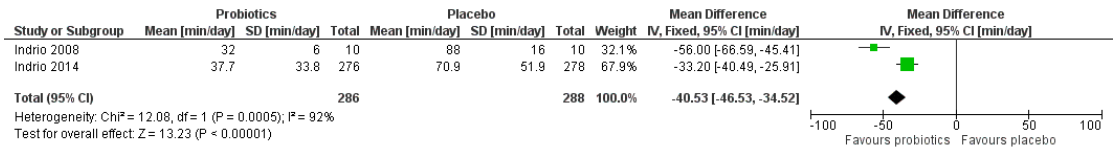


Figure 6. Forest plot of comparison: 1 Probiotic preparation versus placebo, outcome: 1.8 Mean crying time at study end: fixed-effect model.



DISCUSSION

Summary of main results

The prophylactic use of probiotics in the prevention of infantile colic has been increasingly studied, with four of the six studies (838 participants) included in this review published within the last four years. Below, we summarised our findings.

- One meta-analysis of only three studies (1148 infants) that investigated the primary outcome of 'occurrence of new cases of colic' found no difference between the groups, despite their being 40% less cases of infantile colic in the probiotic group (low-certainty evidence, downgraded two levels for very serious inconsistency).
- The primary outcome of 'serious adverse effects' was reassuringly low, although this was limited to the time period in which the probiotics were administered, and only one study reported minor events (low-certainty evidence, downgraded two levels due to very serious imprecision).
- One meta-analysis of three studies (702 infants) found a reduction in the secondary outcome of 'crying time at completion in each group' (low-certainty evidence, downgraded two levels due to very serious inconsistency), as did a subgroup analysis for the specific strain of *Lactobacillus reuteri* in two studies (574 infants).

Overall completeness and applicability of evidence

The completeness and applicability of the evidence was hampered by several issues. There was significant clinical heterogeneity. As with other reviews of probiotics, the range of species used as a probiotic raised a clinical problem in terms of applying the evidence in practice. Additionally, the study population varied across the studies, including both preterm and term infants, breastfeeding and bottle feeding and studies that started prior to delivery and postdelivery, with some administering the probiotic only to the mother before and after birth (breastfeeding infants) and some to the mother before birth and the infant directly after birth.

The lack of reporting the primary outcome of the occurrence of colic was a major issue with the completeness of the evidence. As these studies were focused on the prophylactic use of probiotics to prevent colic, not reporting the onset of colic using established diagnostic criteria were a significant issue that, although clearly widespread, prevented the use of the results. Reassuringly, five of the six studies defined colic similarly using Rome III or Wessel criteria (although not necessarily reporting data on this outcome); however, one study did not clarify the definition (this study did not give data for this outcome either, so this did not impact analysis). This may become a greater concern in the future as Rome IV signals a significant shift in diagnostic criteria (see below).

Another issue to consider was the time point at which the crying outcome was measured, which varied from 30 days to 90 days. This heterogeneity further limited the clinical relevance and validity of the result, which was further compounded by the paucity of evidence from low- and middle-income countries. Given the accepted issues in the field with the self-limiting nature of colic and subjective problems with its assessment, this may represent a lack of need for such research in these areas, but nevertheless limits the ability to apply such findings in those settings. Altogether, these issues limit the overall strength and utility of the results.

The final issue was the reporting of safety. While most studies commented about the absence of serious adverse effects, only one gave details on these and minor adverse effects in a manner that allowed consideration of the significance of these findings to the evidence base. It is vital to have detailed information in this area.

Quality of the evidence

We thoroughly reviewed the studies for results, and assessed their risks of bias. We considered the evidence at relatively low risk of bias. A note of caution in the interpretation of these results was that four of the six included studies received financial support from industry, including milk manufacturers or the makers of the probiotic used. This was the one area correspondingly noted to show high risk of bias in the assessment as the review authors judged that without full justification and explanation regarding the nature of such funding, a significant risk existed. Further independent studies would be helpful.

The issue regarding the choice of outcomes, discussed above under Overall completeness and applicability of evidence, was also key to the certainty of the evidence. This led to the GRADE certainty of evidence being impacted by a lack of evidence on this appropriate primary outcome.

The results of our GRADE analysis revealed low-certainty evidence for the two primary outcomes, occurrence of colic, downgraded twice due to unexplained statistical heterogeneity, and adverse effects, downgraded twice due to wide CI and low event numbers. The evidence for the secondary outcome of crying time was also low due to substantial statistical heterogeneity.

The final issue of note was the time to follow-up. Similar to other reviews on colic, there was a range of times to measuring outcomes, from one month to three months. This could limit the generalisability or at least predictions of prognosis from this evidence.

Potential biases in the review process

We conducted comprehensive searches, including extensive searches of the grey literature, to identify all relevant studies. However, it was apparent that some included studies did not clearly describe themselves as aiming to prevent colic, even though they reported this outcome within the text. As this became apparent in screening, while we were very cautious, it is possible that some trials may have been missed.

To avoid bias, two review authors (MG, SSCB) independently evaluated study eligibility, extracted data and assessed risk of bias; on two occasions, we resolved initial disagreements about inclusion or exclusion with another member of the team (GTO), in line with our protocol (Banks 2016). One of the excluded trials was completed by a previous collaborator of this team (Savino 2015). However, he had no involvement in the current review.

There were no other potential biases.

Agreements and disagreements with other studies or reviews

We found no previous systematic review investigating the prophylactic use of probiotics for infantile colic.

There are outstanding reviews for the treatment of colic, Praveen 2014, and pain-relieving agents for colic, Savino 2012, both of which are still at protocol stage within Cochrane.

One systematic review using the high-quality network meta-analysis method investigated one of the preparations studied in this review (*Lactobacillus reuteri*) and also found reductions in crying time when treating colic (Gutiérrez-Castrellón 2017).

AUTHORS' CONCLUSIONS

Implications for practice

There is limited evidence that prophylactic probiotics are more effective in preventing infantile colic than placebo or no intervention. There is some evidence that they may reduce key outcomes, such as crying time and evidence demonstrating a lack of adverse effects. The overall certainty of the evidence and strength of these conclusions is extremely limited due to sparse data, heterogeneity and risk of bias in the studies. Given this current synthesis, it is not possible to advise a change in practice. While the evidence is limited, it is important to note that these agents are available directly to families without physician involvement in many countries. Therefore, these findings may be important to discuss with families, to allow appropriate interpretation.

Implications for research

Given the concept above regarding the wide availability of many of these agents direct to families, there is an urgent need to recognise the increasing interest in this area and respond with appropriate research that can truly inform and guide evidence-based practice.

Future studies need to use the full range of outcome measures relevant to, and presented in, this synthesis of the existing evidence consistently. Studies investigating the potential to reduce the onset of new infantile colic should always report this as one of their outcomes and be clear on the definition used to allow appropriate comparison with previous studies. It may be prudent to report the definition of colic using more than one diagnostic system to resolve this concern.

Reporting of all adverse effects, those needing withdrawal, serious adverse effects and particularly long-term safety follow-up are vital to meaningfully move the evidence base forward.

Future studies focusing on specific patient groups, such as infants with known aberrant gut flora, and specific probiotic strains are also needed. Wider research investigating predictive factors for the onset of colic would allow targeted prophylactic use.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Baldassarre 2014

Methods	**Study design:** double-blind, placebo-controlled, randomised trial **Unit:** Obstetrics and Gynecology Unit, Department of Biomedical and Human Oncological Science (DIMO), University of Bari **Location:** Bari, Italy **Setting:** outpatient
Participants	**Sample size:** 67 mothers/term neonate pairs **Number of dropouts/withdrawals:** 1 pair **Age:** mothers = 33 years (mean); neonates = 39 weeks' gestational age **Inclusion criteria:** healthy, pregnant women at low obstetric risk **Exclusion criteria:** pre-existing clinical conditions such as diabetes; hypertension; autoimmune disease; asthma; allergies; renal or hepatic diseases; viral, bacterial or protozoan infection; anaemia; twin pregnancies; pregnancy disease and preterm deliveries; smoking more than 10 cigarettes/day; use of other probiotics during the study protocol
Interventions	**Intervention (n = 33: 30 breastfed and 3 mix fed):** high concentration, multi-strain probiotic supplement, in packets. 900 billion viable lyophilised bacteria of 4 different strains of lactobacilli (*L paracasei* DSM 24733, *L plantarium* DSM 24730,*L acidophilus* DSM 24735 and *L delbrueckii* subsp*bulgaricus* DSM 24734), 3 strains of bifidobacteria (*B longum* DSM 24736, *BB breve* DSM 24732 and *B infantis* DSM 24737) and 1 strain of *Streptococcus thermophilus* DSM 24731 **Control (n = 34: 29 breastfed and 5 mix fed; of which, 1 lost to follow-up):** corn starch **Duration of intervention:** from 36 weeks' gestation to 4 weeks postnatally
Outcomes	**Primary outcomes:** analysis of breast milk for cytokine patterns, secretory IgA in breast milk and stools, faecal lactoferrin **Secondary outcomes:** safety, anthropometric data and gastrointestinal events (regurgitation, bowel movements and colic symptoms following Rome III criteria in the neonatal or toddler period) **Timings of measurements:** within 72 hours after delivery and at day 30
Notes	**Study start date:** April 2011 **Study end date:** December 2013 **Declared DOI:** none **Perceived DOI:** none **Funding source:** publication costs covered by NOPAIN Onlus Italian Association for Pain Disease Treatment **Comment:** the paper itself did not include all of this information, but the author was able to supply further information in the form of a draft and now published report (Baldassarre 2016). **Clinical trials record:** NCT01367470

Risk of bias

Baldassarre 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "randomisation performed using a computer generated allocation sequence."
Allocation concealment (selection bias)	Low risk	**Comment:** specifically mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** all participants, as well as scientific and medical personnel dedicated to the study and distributing the study agents or assessing the samples and analyses were blinded to group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** all participants accounted for; 1 infant in the placebo group was lost to follow-up
Selective reporting (reporting bias)	High risk	**Comment:** colic was not stated to be an outcome measure in the clinical trials registry record for this study, yet it was reported in the paper
Other bias	Low risk	**Comment:** none noted

Indrio 2008

Methods	**Study design:** double-blind, randomised study **Unit:** Neonatology section of the Department of Pediatrics at the University of Bari **Location:** Bari, Italy **Setting:** inpatient and outpatient
Participants	**Sample size:** 30 neonates **Number of dropouts/withdrawals:** 0 **Age:** range 3-5 days **Inclusion criteria:** healthy, appropriate-for-gestational age, preterm infants, with normal APGAR scores **Exclusion criteria:** respiratory distress, congenital malformation, inborn errors of metabolism, or confirmed sepsis or infection
Interventions	**Intervention (n = 10 formula fed):** 5 drops/day of *L reuteri* at a dose of 1×10^8 CFU/day **Control (n = 20: 10 = exclusively breastfed (non-participants) and 10 = formula fed):** placebo **Duration of intervention:** 30 days

Indrio 2008 (*Continued*)

Outcomes	**Primary outcomes:** number of episodes per day of regurgitation, vomiting and inconsolable crying; and the number of evacuations per day **Secondary outcomes:** assessment of gastric electrical activity, gastric emptying **Timings of measurements:** day 4 and day 35 after birth
Notes	**Study start date:** January 2006 **Study end date:** September 2006 **Declared DOI:** none **Perceived DOI:** none **Funding source:** supported by BioGaia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "were randomly assigned to IG [intervention group] or CG [control group]."
Allocation concealment (selection bias)	Low risk	**Comment:** not mentioned. We contacted the study author, through the interventional agent supplier, who confirmed central allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** none noted
Selective reporting (reporting bias)	Low risk	**Comment:** none noted
Other bias	High risk	**Comment:** supported by BioGaia, who make the product.

Indrio 2014

Methods	**Study design:** prospective, multi-centre, double-blind, placebo-controlled, randomised clinical trial **Unit:** 9 paediatric units **Location:** Italy **Setting:** outpatients
Participants	**Sample size:** 554 neonates **Number of dropouts/withdrawals:** 86 (38 = intervention; 48 = control) **Age:** 39 weeks' gestational age **Inclusion criteria:** gestational age > 37 to < 41 weeks, age < 1 weeks on entry into the study, birth weight adequate for gestational age, APGAR score > 10 at 10 minutes, no congenital disorders or clinical or physical alterations at clinical examination, and no antibiotic or probiotic administration before inclusion **Exclusion criteria:** those not meeting the above inclusion criteria
Interventions	**Intervention (n = 238):** 5 drops/day of *L reuteri* DSM 17938 at dose of 1×10^8 CFU/day, suspended in oil in a bottle with a dropper cap, given to neonates every day for 90 days **Control (n = 230):** identical formulation of oils supplied in an identical bottle **Duration of intervention:** 90 days
Outcomes	**Primary outcomes:** reduction of daily crying time, regurgitation and constipation during the first 3 months of life **Secondary outcomes:** cost-benefit analysis of the probiotic supplementation with number of primary paediatrician visits; feeding changes; hospitalisations; access to a paediatric emergency department; loss of parental working days; and use of simethicone, cimetropium bromide and natural or herbal products to control gastrointestinal symptoms **Timings of measurements:** 3 months
Notes	**Study start date:** September 2010 **Study end date:** October 2012 **Declared DOI:** none **Perceived DOI:** none **Funding source:** supported by BioGaia, who make the product used in the study **Clinical trials record:** NCT01235884

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote:** "an independent statistician generated the random allocation sequence."
Allocation concealment (selection bias)	Low risk	**Comment:** not mentioned. We contacted the study author, through the interventional agent supplier, who confirmed central allocation concealment

Indrio 2014 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Quote:** "the study personnel, health care workers, and parents were masked to the study group allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Quote:** "Parents and investigators were masked to the intervention."
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** none noted
Selective reporting (reporting bias)	Low risk	**Comment:** none noted
Other bias	High risk	**Comment:** supported by BioGaia who make the product.

Kukkonen 2008

Methods	**Study design:** randomised, placebo-controlled, double-blind trial **Unit:** none specified **Location:** Helsinki, Finland **Setting:** outpatient
Participants	**Sample size:** 1018 infants **Number of dropouts/withdrawals:** not reported but 939 completed the 6-month follow-up and 925 completed the 2-year follow-up **Age:** not reported **Inclusion criteria:** pregnant women carrying children at increased risk of allergy recruited from antenatal clinics **Exclusion criteria:** < 37 weeks' gestational age, twin baby, major malformation
Interventions	**Intervention (n = 468):** pregnant women from 36 weeks took capsules containing a mixture of *Lactobacillus rhamnosus GG and LC705, Bifidobacterium breve* Bb99 and *Propiobibacterium freudenreichii* ssp *shermanii* JS ($8\text{-}9 \times 10^9$ CFUs in each capsule). For 6 months after birth, the infants received 1 opened capsule of the same probiotics and 0.8 g of galacto-oligosaccharides in liquid form daily **Control (n = 471):** placebo **Duration of intervention:** 4 weeks before delivery and 6 months after birth
Outcomes	**Primary outcomes:** neonatal morbidity, infantile colic and defecation, feeding-related behaviours (vomiting, constipation, excessive crying and abdominal discomfort) **Secondary outcomes:** anthropometric measurement, infection, antibiotics and other disease **Timings of measurements:** 3, 6, 12 and 24 months
Notes	**Study start date:** November 2000 **Study end date:** March 2003 **Declared DOI:** none

Kukkonen 2008 (*Continued*)

	Perceived DOI: none **Funding source:** Helsinki University Central Hospital Research Funds and Valio **Clinical trials record:** NCT00298337

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** randomised, double-blind, placebo-controlled study with 2 parallel groups and computer-generated block randomisation at 35 weeks' gestation
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned. We contacted the study author but received no response
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** none noted
Selective reporting (reporting bias)	High risk	**Comment:** while the manuscript mentioned a primary outcome of colic, it was not explicitly stated in the trial registration record
Other bias	Low risk	**Comment:** none noted

Pärtty 2013a

Methods	**Study design:** randomised, double-blind, placebo-controlled trial **Unit:** Department of Pediatrics, Turku University Hospital **Location:** Turku, Finland **Setting:** inpatient and outpatient
Participants	**Sample size:** 94 preterm infants **Number of dropouts/withdrawals:** 26 (28%) at 12 months of age **Age:** 34.6 weeks (range 32-36 weeks) gestational age **Inclusion criteria:** gestational age between 32 (+ 0) and 36 (+ 6) weeks, birth weight > 1500 g, and absence of any congenital defects in the gastrointestinal system or defects preventing enteral nutrition **Exclusion criteria:** infants not meeting the above inclusion criteria

Pärtty 2013a (*Continued*)

Interventions	**Intervention (n = 62):** prebiotic mixture (n = 31) of polydextrose and galacto-oligosaccharides 1:1; 600 mg/day in 1 dose from day 1 to day 30 and 600 mg twice daily from day 31 to day 60. Probiotics (n = 31) *Lactobacillus rhamnosus* GG (ATCC 53103) 1 × 10^9 CFU/day in 1 dose from day 1 to day 30 and 1 × 10^9 CFU twice daily from day 31 to day 60 **Control (n = 32):** microcrystalline cellulose and dextrose anhydrate **Duration of intervention:** 2 months
Outcomes	**Primary outcomes:** frequency of crying, frequency of stools, consistency of stools **Secondary outcomes:** analysis of gut microbiota **Timings of measurements:** 1, 2, 4, 6 and 12 months of age
Notes	**Study start date:** June 2008 **Study end date:** May 2011 **Declared DOI:** Mead Johnson provided part of 1 authors' salary **Perceived DOI:** none **Funding source:** Mead Johnson **Clinical trials record:** NCT00167700

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	**Quote:** "computerised block randomisation"
Allocation concealment (selection bias)	Low risk	**Comment:** specifically mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** specifically mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** specifically mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** none noted
Selective reporting (reporting bias)	Low risk	**Comment:** colic and adverse effects specifically mentioned in both the trial registration record and the manuscript
Other bias	High risk	**Comment:** paid for by a specialist infant milk manufacturer (Mead Johnson) who provided the products and part of the salary of 1 of the authors

Vlieger 2009

Methods	**Study design:** randomised controlled trial **Unit:** 5 antenatal clinics in central part of the Netherlands **Location:** Netherlands **Setting:** outpatient
Participants	**Sample size:** 159 neonates **Number of dropout/withdrawals:** 33 dropouts (16 = intervention; 17 = control) **Age:** 40.1 weeks' gestational age = intervention, 39.9 weeks' gestational age = control **Inclusion criteria:** pregnant mothers who intended to bottle feed their infant from birth onwards and mothers who stopped breastfeeding within the first week after birth, infant had to be born at ≥ 37 weeks' gestation and had to be aged < 7days at time of enrolment **Exclusion criteria:** use of antibiotics in the first week, congenital illnesses or malformations that could affect normal growth and insufficient knowledge of the Dutch language
Interventions	**Intervention (n = 69):** standard formula supplemented with 1×10^7 CFU *B animalis* ssp *lactis/g (*also known as *Bifidobacterium* Bb-12) deposited under American Type Culture Collection (ATCC) number 27536 and 1×10^7 CFU *L paracasei* ssp *paracasei/g* (*L casei C*RL-431, ATCC 55544) **Control (n = 64):** standard, milk-based powder products supplemented with 0.24 g of prebiotic galacto-oligosaccharides **Duration of intervention:** 3 months
Outcomes	**Primary outcomes:** safety and tolerance of formula containing probiotics, differences in growth parameters at 3 months of age **Secondary outcomes:** differences in growth parameters at 6 months of age, crying and sleeping, stool characteristics, infant use of antibiotics, visits to general practitioner, periods with signs of upper respiratory tract infections and gastrointestinal infections, vomiting diarrhoea, constipation, colic, and rash or eczema **Timings of measurements:** 1, 2, 3 and 6 months of age
Notes	**Study start date:** November 2004 **Study end date:** January 2007 **Declared DOI:** 2 of the authors are employed by the sponsor, all other authors have no conflict of interest **Perceived DOI:** none **Funding source:** Friesland Foods and 2 of the authors were employed by the sponsor **Clinical trials record:** ISRCTN78225533

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Comment:** computer-generated random number generator for concealment.
Allocation concealment (selection bias)	Unclear risk	**Comment:** not mentioned

Vlieger 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	**Comment:** did not specifically state but was implied.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	**Comment:** did not specifically state but was implied.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Comment:** none noted
Selective reporting (reporting bias)	Low risk	**Comment:** none noted
Other bias	High risk	**Comment:** funded by a formula manufacturing company; 2 authors worked for the company

APGAR: appearance, pulse, grimace, activity, respiration; CFU: colony-forming unit; DOI: declaration of interest(s); IgA: immunoglobulin A; n: number of participants.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cekola 2015	Study did not investigate prevention of colic.
Di Mauro 2013	Conference abstract that did not describe an RCT.
Garofoli 2014	Study of regurgitation not crying.
Hoy-Schulz 2016	Not study of colic, and started at 4 weeks.
Mommaerts 2011	Review.
Olivares 2011	Conference poster abstract looking at safety of probiotics used prophylactically
Pärtty 2013b	Research article, not an RCT.
Savino 2015	Study not examining colic.
Simone 2014	Not prophylactic.
Szajewska 2013	Not prophylactic.

(*Continued*)

Wade 2001	Review of other studies, in *Clinical Evidence*.
Weizman 2006	Not from birth (from 4 months).

RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Probiotic preparation versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Occurrence of new cases of colic: random-effects model	3	1148	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.18, 1.19]
2 Occurrence of new cases of colic: sensitivity analysis with fixed-effect model	3	1148	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.38, 0.90]
3 Serious adverse effects	6		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Duration of crying random-effects model	3	707	Mean Difference (IV, Random, 95% CI)	-32.57 [-55.60, -9.54]
5 Duration of crying: sensitivity analysis with fixed-effect model	3	707	Mean Difference (IV, Random, 95% CI)	-32.57 [-55.60, -9.54]
6 Duration of crying: subgroup analysis with term babies only	2	687	Mean Difference (IV, Random, 95% CI)	-20.65 [-47.23, 5.92]
7 Occurrence of colic: subgroup analysis with pregnant women	2	1085	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.13, 2.20]
8 Mean duration of crying at study end: random-effects model, subgroup L Reuteri	2	574	Mean Difference (IV, Random, 95% CI)	-44.26 [-66.60, -21.93]
9 Mean duration of crying at study end: sensitivity analysis with fixed-effect model	2	574	Mean Difference (IV, Fixed, 95% CI)	-40.53 [-46.53, -34.52]

Analysis 1.1. Comparison 1 Probiotic preparation versus placebo, Outcome 1 Occurrence of new cases of colic: random-effects model.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

Outcome: 1 Occurrence of new cases of colic: random-effects model

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Baldassarre 2014	3/33	13/34		27.4 %	0.24 [0.07, 0.76]
Kukkonen 2008	20/506	20/512		39.2 %	1.01 [0.55, 1.86]
Pärtty 2013a	5/31	16/32		33.4 %	0.32 [0.13, 0.77]
Total (95% CI)	**570**	**578**		**100.0 %**	**0.46 [0.18, 1.19]**
Total events: 28 (Probiotics), 49 (Placebo)					
Heterogeneity: Tau^2 = 0.50; Chi^2 = 7.22, df = 2 (P = 0.03); I^2 =72%					
Test for overall effect: Z = 1.59 (P = 0.11)					
Test for subgroup differences: Not applicable					

Analysis 1.2. Comparison 1 Probiotic preparation versus placebo, Outcome 2 Occurrence of new cases of colic: sensitivity analysis with fixed-effect model.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

Outcome: 2 Occurrence of new cases of colic: sensitivity analysis with fixed-effect model

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baldassarre 2014	3/33	13/34		26.4 %	0.24 [0.07, 0.76]
Kukkonen 2008	20/506	20/512		41.0 %	1.01 [0.55, 1.86]
Pärtty 2013a	5/31	16/32		32.5 %	0.32 [0.13, 0.77]
Total (95% CI)	**570**	**578**		**100.0 %**	**0.58 [0.38, 0.90]**
Total events: 28 (Probiotics), 49 (Placebo)					
Heterogeneity: Chi^2 = 7.22, df = 2 (P = 0.03); I^2 =72%					
Test for overall effect: Z = 2.42 (P = 0.016)					
Test for subgroup differences: Not applicable					

Analysis 1.3. Comparison 1 Probiotic preparation versus placebo, Outcome 3 Serious adverse effects.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

Outcome: 3 Serious adverse effects

Study or subgroup	Probiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Baldassarre 2014	0/33	0/34		Not estimable
Indrio 2008	0/10	0/10		Not estimable
Indrio 2014	0/276	0/278		Not estimable
Kukkonen 2008	2/502	2/512		1.02 [0.14, 7.21]
Pärtty 2013a	0/31	0/32		Not estimable
Vlieger 2009	0/69	0/64		Not estimable

Analysis 1.4. Comparison 1 Probiotic preparation versus placebo, Outcome 4 Duration of crying random-effects model.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

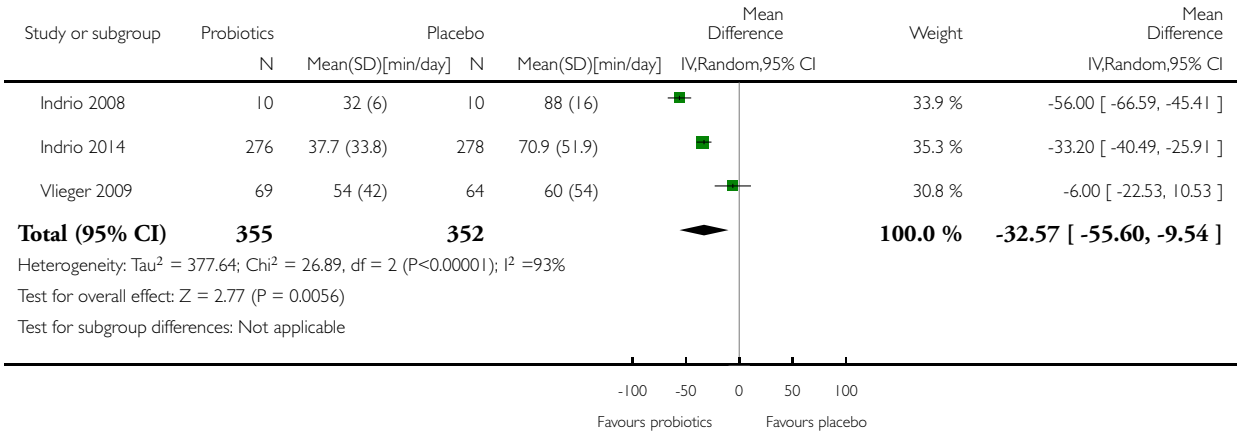
Outcome: 4 Duration of crying random-effects model

Study or subgroup	Probiotics N	Mean(SD)[min/day]	Placebo N	Mean(SD)[min/day]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Indrio 2008	10	32 (6)	10	88 (16)		33.9 %	-56.00 [-66.59, -45.41]
Indrio 2014	276	37.7 (33.8)	278	70.9 (51.9)		35.3 %	-33.20 [-40.49, -25.91]
Vlieger 2009	69	54 (42)	64	60 (54)		30.8 %	-6.00 [-22.53, 10.53]
Total (95% CI)	**355**		**352**			**100.0 %**	**-32.57 [-55.60, -9.54]**

Heterogeneity: Tau^2 = 377.64; Chi^2 = 26.89, df = 2 (P<0.00001); I^2 =93%

Test for overall effect: Z = 2.77 (P = 0.0056)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Probiotic preparation versus placebo, Outcome 5 Duration of crying: sensitivity analysis with fixed-effect model.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

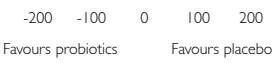
Outcome: 5 Duration of crying: sensitivity analysis with fixed-effect model

Study or subgroup	Probiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Indrio 2008	10	32 (6)	10	88 (16)		33.9 %	-56.00 [-66.59, -45.41]
Indrio 2014	276	37.7 (33.8)	278	70.9 (51.9)		35.3 %	-33.20 [-40.49, -25.91]
Vlieger 2009	69	54 (42)	64	60 (54)		30.8 %	-6.00 [-22.53, 10.53]
Total (95% CI)	**355**		**352**			**100.0 %**	**-32.57 [-55.60, -9.54]**

Heterogeneity: $Tau^2 = 377.64$; $Chi^2 = 26.89$, df = 2 (P<0.00001); $I^2 = 93\%$

Test for overall effect: Z = 2.77 (P = 0.0056)

Test for subgroup differences: Not applicable

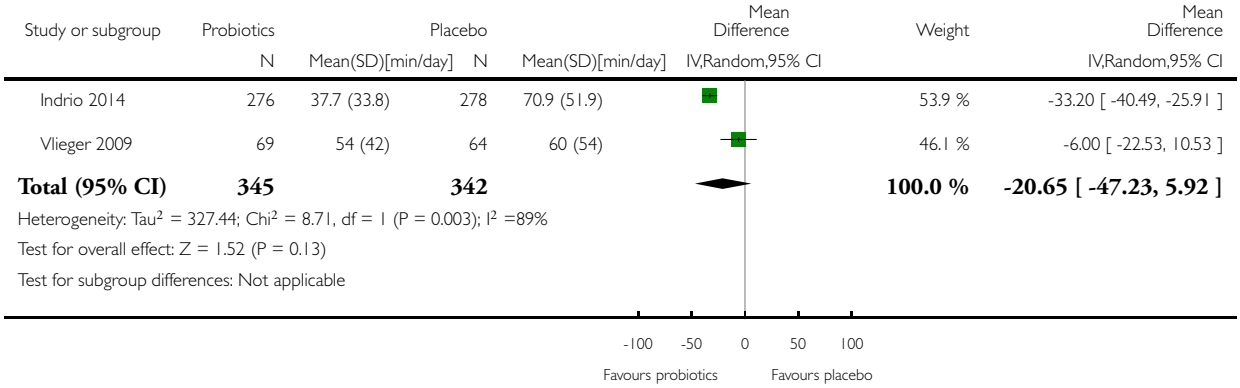


Analysis 1.6. Comparison 1 Probiotic preparation versus placebo, Outcome 6 Duration of crying: subgroup analysis with term babies only.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

Outcome: 6 Duration of crying: subgroup analysis with term babies only

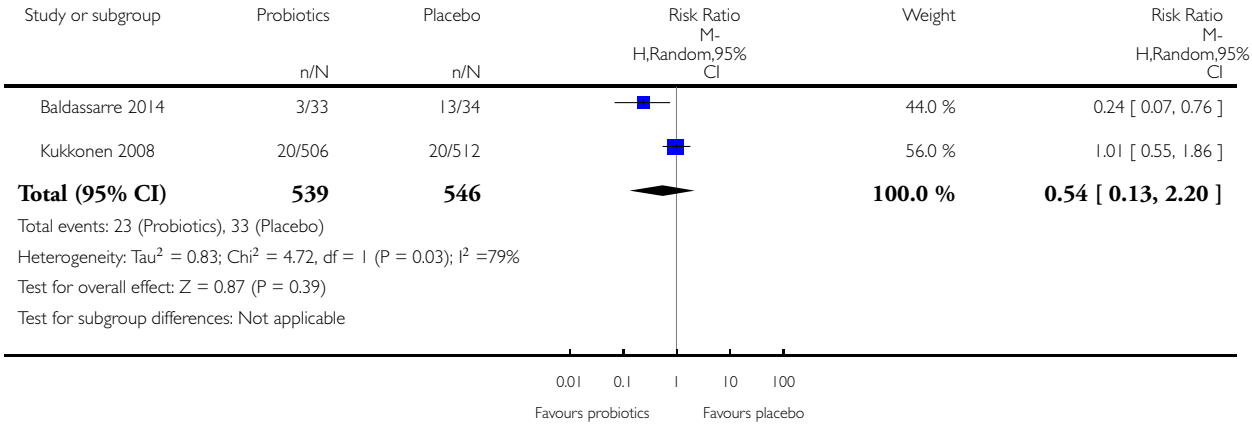


Analysis 1.7. Comparison 1 Probiotic preparation versus placebo, Outcome 7 Occurrence of colic: subgroup analysis with pregnant women.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

Outcome: 7 Occurrence of colic: subgroup analysis with pregnant women



Analysis 1.8. Comparison 1 Probiotic preparation versus placebo, Outcome 8 Mean duration of crying at study end: random-effects model, subgroup L Reuteri.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

Outcome: 8 Mean duration of crying at study end: random-effects model, subgroup L Reuteri

Study or subgroup	Probiotics N	Mean(SD)[min/day]	Placebo N	Mean(SD)[min/day]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Indrio 2008	10	32 (6)	10	88 (16)		48.5 %	-56.00 [-66.59, -45.41]
Indrio 2014	276	37.7 (33.8)	278	70.9 (51.9)		51.5 %	-33.20 [-40.49, -25.91]
Total (95% CI)	**286**		**288**			**100.0 %**	**-44.26 [-66.60, -21.93]**

Heterogeneity: $Tau^2 = 238.41$; $Chi^2 = 12.08$, df = 1 (P = 0.00051); $I^2 = 92\%$

Test for overall effect: Z = 3.88 (P = 0.00010)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Probiotic preparation versus placebo, Outcome 9 Mean duration of crying at study end: sensitivity analysis with fixed-effect model.

Review: Probiotics to prevent infantile colic

Comparison: 1 Probiotic preparation versus placebo

Outcome: 9 Mean duration of crying at study end: sensitivity analysis with fixed-effect model

Study or subgroup	Probiotics N	Mean(SD)[min/day]	Placebo N	Mean(SD)[min/day]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Indrio 2008	10	32 (6)	10	88 (16)		32.1 %	-56.00 [-66.59, -45.41]
Indrio 2014	276	37.7 (33.8)	278	70.9 (51.9)		67.9 %	-33.20 [-40.49, -25.91]
Total (95% CI)	**286**		**288**			**100.0 %**	**-40.53 [-46.53, -34.52]**

Heterogeneity: Chi² = 12.08, df = 1 (P = 0.00051); I² =92%

Test for overall effect: Z = 13.23 (P < 0.00001)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Unused methods

Method	Approach
Measurement of treatment effects	**Continuous data** When studies use different scales, we will calculate the standardised mean difference (SMD) using Hedges' g, and present it with 95% confidence intervals If some studies report an outcome as a dichotomous measure and others used a continuous measure of the same construct, we will convert the results for the former, the dichotomous measure, to a SMD
Cluster-randomised studies	For each included study, we will determine whether the unit of analysis is appropriate for the unit of randomisation and the design of that study (i.e. whether the number of observations match the number of randomised 'units' (Deeks 2011)). The presence of cluster-randomised trials is unlikely because such a design is uncommon in this field. However, if we encounter such trials, we will use the intraclass correlation coefficient (ICC) to convert trials to their effective sample size before incorporating them into the meta-analysis, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). If the ICC is not available, we will use values from the published literature as an external source, when available, as well as contacting the study authors and re-

Table 1. Unused methods (*Continued*)

	questing them to supply more data to allow calculation of an ICC estimate (Campbell 2000). We will only use the ICC to calculate the effective sample size or the effective SD for those cluster-randomised trials that do not account for the cluster effects. We will label such studies with a C
Assessment of reporting bias	If there are more than 10 studies grouped in a comparison, we will evaluate whether reporting biases are present by using funnel plots to investigate any relationship between effect estimates and study size or precision, or both, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). Due to the small number of studies expected, no formal test for plot asymmetry is planned
Subgroup analysis and investigation of heterogeneity	• Mode of delivery of baby (vaginal vs caesarean section). • Short-term and long-term follow-up (< 4 weeks vs ≥ 4 weeks of treatment). • Low-quality trials vs high-quality trials (allocation concealment vs lack of allocation concealment; blinding vs lack of blinding).
Sensitivity analysis	We will conduct sensitivity analyses to determine whether findings are sensitive to the following: • bias, by restricting the analyses to studies judged to be at low risk of bias for blinded assessment of the primary outcome; • imputed data, by calculating the treatment effect including and excluding the imputed data to assess whether this alters the outcome of the analysis; • dropouts and exclusions, by conducting worst-case vs best-case scenario analyses; • the definition of colic used, by conducting analyses on studies using the stringent Wessel definition of infant colic (Wessel 1954), the more recent definition given by Hyman 2006, and a non-recognised definition.

APPENDICES

Appendix 1. Definition of terms

Term	Definition
Coliforms	Coliform bacteria are an indicator of sanitary quality of foods and water. They ferment lactose with the production of acid and gas. Coliforms can be found in the aquatic environment, in soil and on vegetation; they are universally present in large numbers in the faeces of warm-blooded animals. While coliforms themselves are not normally causes of serious illness, they are easy to culture, and their presence is used to indicate that other pathogenic organisms of faecal origin may be present. Such pathogens include disease-causing bacteria, viruses or protozoa and many multicellular parasites. Coliform procedures may be performed in aerobic or anaerobic conditions
Dysmotility	A condition in which muscles of the digestive system become impaired and changes in the speed, strength or co-ordination in the digestive organs occurs. In the normal small intestine, liquefied food and secretions, including digestive enzymes are pushed onwards by waves of muscular contraction
Enteritis	Inflammation of the intestine, especially the small intestine, usually accompanied by diarrhoea
Microbiome	The micro-organisms in a particular environment (including the body or a part of the body)
Microbiota	**Quote:** "the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space" (Lederberg 2001).
Necrotising enterocolitis	A medical condition primarily seen in premature infants where portions of the bowel undergo necrosis (tissue death). It occurs postnatally and is one of the most common causes of morbidity in premature infants
Oligosaccharides	A saccharide polymer (complex carbohydrate) containing a small number of simple sugars, which are not digestible by humans, and instead function as prebiotics to support the growth of certain types of bacteria in the gut
Paroxysms	A sudden recurrence or intensification of symptoms such as a spasm or seizure. Also called paroxysmal attacks

Appendix 2. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library

Searched 3 June 2016 (276 records)
Searched 30 January 2018 (95 records)
#1[mh Colic]
#2colic*
#3((stomach or abdominal or abdomen*) near/3 (spasm* or pain* or cramp*))
#4((gastric or gastro*) near/3 (spasm* or pain* or cramp*))
#5[mh Crying]
#6(cry or crying or cries)
#7{or #1-#6}

#8[mh infant]
#9(baby or babies or infant* or child* or newborn* or neonat*)
#10{or #8-#9}
#11[mh "Dietary Supplements"]
#12[mh "Complementary Therapies"]
#13[mh "Gastrointestinal Agents"]
#14[mh probiotics]
#15(probiotic* or synbiotic*)
#16[mh lactobacillaceae]
#17lactobac*ill*
#18[mh Bifidobacterium]
#19Bifidobacter*
#20Bifidus*
#21[mh Saccharomyces]
#22Saccharomyc*
#23[mh Streptococcus]
#24streptococc*
#25(Biogaia or Culturelle or Enflora* or Florastor or ((Gerber* or Nestle*) near/2 (Goodstart or Good Start)) or Nutramigen or VSL*3)
#26{or #11-#25}
#27#7 and #10 and #26 in Trials

MEDLINE Ovid

Searched 2 June 2016 (182 records)
Searched 30 January 2018 (71 records)
1 colic/
2 colic$.tw.
3 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).tw.
4 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).tw.
5 crying/
6 (cry or crying or cries).tw.
7 or/1-6
8 Dietary Supplements/
9 Complementary Therapies/
10 Gastrointestinal Agents/
11 probiotics/
12 (probiotic$ or synbiotic$).tw.
13 exp lactobacillaceae/
14 lactobac?ill$.tw.
15 exp Bifidobacterium/
16 Bifidobacter$.tw.
17 Bifidus$.tw.
18 exp Saccharomyces/
19 Saccharomyces$.tw.
20 Streptococcus/
21 streptococc$.tw.
22 (Biogaia or Culturelle or Enflora$ or Florastor or ((Gerber$ or Nestle$) adj2 (Goodstart or Good Start)) or Nutramigen or VSL?3).tw.
23 or/8-22
24 exp infant/
25 (baby or babies or infant$ or child$ or newborn$ or neonat$).tw.
26 24 or 25
27 randomized controlled trial.pt.

28 controlled clinical trial.pt.
29 randomi#ed.ab.
30 placebo$.ab.
31 drug therapy.fs.
32 randomly.ab.
33 trial.ab.
34 groups.ab.
35 or/27-34
36 exp animals/ not humans.sh.
37 35 not 36
38 7 and 23 and 26 and 37

MEDLINE In-Process & Other Non-Indexed Citations Ovid

Searched 2 June 2016 (44 records)
Searched 30 January 2018 (45 records)
1 colic$.tw,kw.
2 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).tw,kw.
3 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).tw,kw.
4 (cry or crying or cries).tw,kw.
5 or/1-4
6 (probiotic$ or synbiotic$).tw,kw.
7 lactobac?ill$.tw,kw.
8 Bifidobacter$.tw,kw.
9 Bifidus$.tw,kw.
10 Saccharomyces$.tw,kw.
11 streptococc$.tw,kw.
12 (Biogaia or Culturelle or Enflora$ or Florastor or ((Gerber$ or Nestle$) adj2 (Goodstart or Good Start)) or Nutramigen or VSL?3).tw,kw.
13 or/6-12
14 5 and 13
15 (baby or babies or infant$ or child$ or newborn$ or neonat$).tw,kw.
16 14 and 15

MEDLINE Epub Ahead of Print Ovid

Searched 2 June 2016 (2 records)
Searched 30 January 2018 (3 records)
1 colic$.tw,kw.
2 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).tw,kw.
3 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).tw,kw.
4 (cry or crying or cries).tw,kw.
5 or/1-4
6 (probiotic$ or synbiotic$).tw,kw.
7 lactobac?ill$.tw,kw.
8 Bifidobacter$.tw,kw.
9 Bifidus$.tw,kw.
10 Saccharomyces$.tw,kw.
11 streptococc$.tw,kw.
12 (Biogaia or Culturelle or Enflora$ or Florastor or ((Gerber$ or Nestle$) adj2 (Goodstart or Good Start)) or Nutramigen or VSL?3).tw,kw.
13 or/6-12
14 5 and 13

15 (baby or babies or infant$ or child$ or newborn$ or neonat$).tw,kw.
16 14 and 15

Embase Ovid

Searched 2 June 2016 (1817 records)
Searched 30 January 2018 (81 records)
1 colic/
2 crying/
3 colic$.tw.
4 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).tw.
5 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).tw.
6 (cry or crying or cries).tw.
7 or/1-6
8 exp infant/
9 (baby or babies or infant$ or child$ or newborn$ or neonat$).tw.
10 8 or 9
11 7 and 10
12 Infantile colic/
13 11 or 12
14 diet supplementation/
15 alternative medicine/
16 gastrointestinal agent/
17 probiotic agent/
18 synbiotic agent/
19 (probiotic$ or synbiotic$).tw.
20 exp Lactobacillaceae/
21 lactobac?ill$.tw.
22 exp Bifidobacterium/
23 Bifidobacter$.tw.
24 exp Saccharomyces/
25 Saccharomyces$.tw.
26 exp Streptococcus/
27 streptococc$.tw.
28 (Biogaia or Culturelle or Enflora$ or Florastor or ((Gerber$ or Nestle$) adj2 (Goodstart or Good Start)) or Nutramigen or VSL?3).tw.
29 or/14-28
30 Randomized controlled trial/
31 controlled clinical trial/
32 Single blind procedure/
33 Double blind procedure/
34 triple blind procedure/
35 Crossover procedure/
36 (crossover or cross-over).tw.
37 ((singl$ or doubl$ or tripl$ or trebl$) adj1 (blind$ or mask$)).tw.
38 Placebo/
39 placebo.tw.
40 prospective.tw.
41 factorial$.tw.
42 random$.tw.
43 assign$.ab.
44 allocat$.tw.
45 volunteer$.ab.

46 or/30-45
47 13 and 29 and 46

CINAHL EBSCOhost (Cumulative Index to Nursing and Allied Health Literature)

Searched 2 June 2016 (152 records)
Searched 30 January 2018 (62 records)
S1 (MH "Infant Colic")
S2 (MH "Colic")
S3 TI(colic*) OR AB(colic*)
S4 TI((stomach or abdominal or abdomen*) N3 (spasm* or pain* or cramp*)) or AB((stomach or abdominal or abdomen*) N3 (spasm* or pain* or cramp*))
S5 TI((gastric or gastro*) N3 (spasm* or pain* or cramp*)) or AB((gastric or gastro*) N3 (spasm* or pain* or cramp*))
S6 (MH "Crying")
S7 TI(cry or crying or cries) OR AB(cry or crying or cries)
S8 S2 OR S3 OR S4 OR S5 OR S6 OR S7
S9 (MH "Infant+")
S10 TI(baby or babies or infant* or child* or newborn* or neonat*) or AB(baby or babies or infant* or child* or newborn* or neonat*)
S11 S9 OR S10
S12 S8 AND S11
S13 S1 OR S12
S14 (MH "Dietary Supplements")
S15 (MH "Alternative Therapies")
S16 (MH "Gastrointestinal Agents")
S17 (MH "Probiotics")
S18 (probiotic* or synbiotic*)
S19 (MH "Lactobacillus")
S20 lactobac#ill*
S21 (MH "Bifidobacterium")
S22 Bifidobacter*
S23 Bifidus*
S24 Saccharomyces*
S25 (MH "Streptococcus")
S26 streptococc*
S27 (Biogaia or Culturelle or Enflora* or Florastor or ((Gerber* or Nestle*) N2 (Goodstart or Good Start)) or Nutramigen or VSL?3)
S28 S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27
S29 S13 AND S28

PsycINFO Ovid

Searched 2 June 2016 (13 records)
Searched 30 January 2018 (2 records)
1 Crying/
2 colic$.tw.
3 ((stomach or abdominal or abdomen$) adj3 (spasm$ or pain$ or cramp$)).tw.
4 ((gastric or gastro$) adj3 (spasm$ or pain$ or cramp$)).tw.
5 (cry or crying or cries).tw.
6 or/1-5
7 (infancy 2 23 mo or neonatal birth 1 mo).ag.
8 (baby or babies or infan$ or child$ or neonat$ or newborn$).tw.
9 7 or 8
10 6 and 9
11 dietary supplements/

12 Alternative Medicine/
13 probiotic$.mp.
14 synbiotic$.mp.
15 lactobac?ill$.mp.
16 Bifidobacter$.mp.
17 Bifidus$.mp.
18 Saccharomyces$.mp.
19 streptococc$.mp.
20 (Biogaia or Culturelle or Enflora$ or Florastor or ((Gerber$ or Nestle$) adj2 (Goodstart or Good Start)) or Nutramigen or VSL?3).mp.
21 or/11-20
22 10 and 21

Science Citation Index - Expanded Web of Science (SCI-Expanded)

Searched 3 June 2016 (35 records)
Searched 30 January 2018 (138 records)
# 12 #10 AND #5
Indexes=SCI Timespan=2016-2018
# 11 #10 AND #5
Indexes=SCI Timespan=All years
# 10 #9 OR #8 OR #7 OR #6
Indexes=SCI Timespan=All years
# 9 Ts=(probiotic* or synbiotic*)
Indexes=SCI Timespan=All years
# 8 TS= (Gerber* or Goodstart or "Good Start")
Indexes=SCI Timespan=All years
# 7 TS= (Biogaia or Culturelle or Enflora* or Florastor or Nutramigen or VSL*3)
Indexes=SCI Timespan=All years
# 6 TS =(Bifidobacter* or Bifidus* or lactobac*ill* or Saccharomyces* or streptococc*)
Indexes=SCI Timespan=All years
# 5 (#1 or #2 or #3) and #4
Indexes=SCI Timespan=All years
# 4 TS=(infant* or baby or babies or newborn* or neonat*)
Indexes=SCI Timespan=All years
# 3 TS=((stomach or abdominal or abdomen*) Near/3 (spasm* or pain* or cramp*))
Indexes=SCI T Timespan=All years
# 2 TS= ((gastric or gastro*) Near/3 (spasm* or pain* or cramp*))
Indexes=SCI Timespan=All years
# 1 TS=(colic* or cry or cries or crying)
Indexes=SCI Timespan=1970-2016

Social Sciences Citation Index Web of Science (SSCI)

Searched 03 June 2016 (2 records)
Searched 30 January 2018 (1 record)
# 12 #10 AND #5
Indexes=SSCI Timespan=2016-2018
# 11 #10 AND #5
Indexes=SSCI Timespan=All years
# 10 #9 OR #8 OR #7 OR #6
Indexes=SSCI Timespan=All years
# 9 Ts=(probiotic* or synbiotic*)

Indexes=SSCI Timespan=All years
# 8 TS= (Gerber* or Goodstart or "Good Start")
Indexes=SSCI Timespan=All years
# 7 TS= (Biogaia or Culturelle or Enflora* or Florastor or Nutramigen or VSL*3)
Indexes=SSCI Timespan=All years
# 6 TS =(Bifidobacter* or Bifidus* or lactobac*ill* or Saccharomyces* or streptococc*)
Indexes=SSCI Timespan=All years
# 5 (#1 or #2 or #3) and #4
Indexes=SSCI Timespan=All years
# 4 TS=(infant* or baby or babies or newborn* or neonat*)
Indexes=SSCI Timespan=All years
# 3 TS=((stomach or abdominal or abdomen*) Near/3 (spasm* or pain* or cramp*))
Indexes=SSCI Timespan=All years
# 2 TS= ((gastric or gastro*) Near/3 (spasm* or pain* or cramp*))
Indexes=SSCI Timespan=All years
# 1 TS=(colic* or cry or cries or crying)
Indexes=SSCI Timespan=All years

Conference Proceedings Citation Index - Science (CPCI-S) and Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SS&H); Web of Science

Searched 03 June 2016 (7 records)
Searched 30 January 2018 (7 records)
# 12 #10 AND #5
Indexes=CPCI-S, CPCI-SSH Timespan=2016-2018
# 11 #10 AND #5
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 10 #9 OR #8 OR #7 OR #6
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 9 Ts=(probiotic* or synbiotic*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years.
#8 TS= (Gerber* or Goodstart or "Good Start")
Indexes=CPCI-S, CPCI-SSH Timespan=All years
#7 TS=(Biogaia or Culturelle or Enflora* or Florastor or Nutramigen or VSL*3)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 6 TS =(Bifidobacter* or Bifidus* or lactobac*ill* or Saccharomyces* or streptococc*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 5 (#1 or #2 or #3) and #4
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 4 TS=(infant* or baby or babies or newborn* or neonat*)
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 3 TS=((stomach or abdominal or abdomen*) Near/3 (spasm* or pain* or cramp*))
Indexes=CPCI-S, CPCI-SSH Timespan=All years
# 2 TS= ((gastric or gastro*) Near/3 (spasm* or pain* or cramp*))
Indexes=CPCI-S, CPCI-SSH Timesp.an=All years
# 1 TS=(colic* or cry or cries or crying)
Indexes=CPCI-S, CPCI-SSH Timespan=All years

LILACS (Latin American and Caribbean Health Science Information Database; lilacs.bvsalud.org/en)

Searched 6 June 2016 (7 records)
Searched 30 January 2018 (1 record)

(tw:((colic* OR crying OR cries OR cry) AND (baby OR babies OR infant* OR neonat* OR newborn*))) AND (tw:((probiotic* OR synbiotic* OR bifidobacter* OR bifidus* OR lactobac* OR saccharomyces* OR streptococc* OR biogaia OR culturelle OR enflora* OR florastor OR nutramigen OR vsl* OR gerber* OR goodstart OR "Good Start"))) AND (instance:"regional") AND (db: ("LILACS"))

Cochrane Database of Systematic Reviews (CDSR) part of the Cochrane Library

Searched 3 June 2016 (7 records)
Searched 30 January 2018 (5 records)
#1[mh Colic]
#2(colic*):ti,ab
#3[mh Crying]
#4(cry or crying or cries):ti,ab
#5{or #1-#4}
#6[mh infant]
#7(baby or babies or infant* or child* or newborn* or neonat*):ti,ab
#8{or #6-#7}
#9#5 and #8
#10[mh "Dietary Supplements"]
#11[mh "Complementary Therapies"]
#12[mh "Gastrointestinal Agents"]
#13[mh probiotics]
#14(probiotic* or synbiotic*):ti,ab
#15[mh lactobacillaceae]
#16(lactobac*ill*):ti,ab
#17[mh Bifidobacterium]
#18(Bifidobacter*):ti,ab
#19(Bifidus*):ti,ab
#20[mh Saccharomyces]
#21(Saccharomyc*):ti,ab
#22[mh Streptococcus]
#23(streptococc*):ti,ab
#24(Biogaia or Culturelle or Enflora* or Florastor or ((Gerber* or Nestle*) near/2 (Goodstart or Good Start)) or Nutramigen or VSL*3)
#25{or #10-#24}
#26#9 and #25 in Cochrane Reviews (Reviews and Protocols)
#27 #9 and #25 in Cochrane Reviews Published online June 2016 - January 2018 (Reviews and Protocols)

Database of Abstracts of Reviews of Effects (DARE) part of the Cochrane Library

Searched 3 June 2016 (5 records)
#1[mh Colic]
#2(colic*):ti,ab
#3[mh Crying]
#4(cry or crying or cries):ti,ab
#5{or #1-#4}
#6[mh infant]
#7(baby or babies or infant* or child* or newborn* or neonat*):ti,ab
#8{or #6-#7}
#9#5 and #8
#10[mh "Dietary Supplements"]
#11[mh "Complementary Therapies"]
#12[mh "Gastrointestinal Agents"]
#13[mh probiotics]

#14(probiotic* or synbiotic*):ti,ab
#15[mh lactobacillaceae]
#16(lactobac*ill*):ti,ab
#17[mh Bifidobacterium]
#18(Bifidobacter*):ti,ab
#19(Bifidus*):ti,ab
#20[mh Saccharomyces]
#21(Saccharomyc*):ti,ab
#22[mh Streptococcus]
#23(streptococc*):ti,ab
#24(Biogaia or Culturelle or Enflora* or Florastor or ((Gerber* or Nestle*) near/2 (Goodstart or Good Start)) or Nutramigen or VSL*3)
#25{or #10-#24}
#26#9 and #25 in Other Reviews

Epistemonikos (www.epistemonikos.org)

Searched 6 June 2016. Limited to systematic reviews (26 records)
Searched 30 January 2018. Limited to systematic reviews added since 6 June 2016 (3 records)
(title:((title:(probiotic* OR synbiotic* OR Bifidobacter* OR Bifidus* OR lactobac*ill* OR Saccharomyces* OR streptococc*) OR abstract:(probiotic* OR synbiotic* Bifidobacter* OR Bifidus* OR lactobac*ill* OR Saccharomyces* OR streptococc*))) OR abstract:((title:(probiotic* OR synbiotic* Bifidobacter* OR Bifidus* OR lactobac*ill* OR Saccharomyces* OR streptococc*) OR abstract:(probiotic* OR synbiotic* Bifidobacter* OR Bifidus* OR lactobac*ill* OR Saccharomyces* OR streptococc*)))) AND (title:(infant* OR baby OR babies OR newborn* OR neonat*) OR abstract:(infant* OR baby OR babies OR newborn* OR neonat*)) AND (title:(cry OR cries OR fussing OR colic OR stomach OR abdom* OR gastric OR gastro* OR cramp* OR spasm* OR pain*) OR abstract:(cry OR cries OR fussing OR colic OR stomach OR abdom* OR gastric OR gastro* OR cramp* OR spasm* OR pain*)

WorldCat (www.worldcat.org/)

Searched 6 June 2016. Limited to dissertations and theses (4 records)
Searched 30 January 2018. Limited to dissertations and theses 2016-2018 (0 records)
kw:(colic* OR crying OR cries OR cry) AND KW:(baby OR babies OR infant* OR neonat* OR newborn*) AND KW:(probiotic* OR synbiotic* OR bifidobacter* OR bifidus* OR lactobac* OR saccharomyces* OR streptococc* OR biogaia OR culturelle OR enflora* OR florastor OR nutramigen OR vsl* OR gerber* OR goodstart OR "Good Start")

ClinicalTrials.gov (www.clinicaltrials.gov/ct2/home)

Searched 6 June 2016 (95 records)
Searched 30 January 2018. Limited to: First posted after 6 June 2016 (11 records)
ADVANCED SEARCH Biogaia OR Culturelle OR Enflora* OR Florastor OR Nutramigen OR VSL* OR Gerber* OR Goodstart OR "Good Start" | Child
OR
BASIC SEARCH (colic OR crying) AND (probiotics OR synbiotics)

WHO ICTRP (apps.who.int/trialsearch/Default.aspx)

Searched 6 June 2016 (44 records)
Searched 30 January 2018. Limited to: Received from 06 June 2016 (14 records)
Basic search
probiotics and colic OR probiotics AND crying OR synbiotics and colic OR synbiotics AND crying
Advanced search
Intervention: Biogaia OR Culturelle OR Enflora* OR Florastor OR Nutramigen OR VSL* OR Gerber* OR Goodstart OR "Good Start"
Search for: clinical trials in children

Recruitment status: All

Appendix 3. Criteria for assigning 'Risk of bias' judgements

Sequence generation for randomisation

We only included RCTs in this review. We assessed randomisation as being at low risk of bias where the procedure of randomisation sequence generation was explicitly described (e.g. computer-generated random numbers, random numbers table or coin-tossing). Where there was no description, we contacted the authors for further information, assigning a rating of unclear risk of bias when we received no response. We would have considered studies that use non-randomised procedures (hospital number, date of birth) to have a high risk of bias; however, this was not the case for any of the studies.

Allocation concealment

We assessed concealment of treatment allocation as being at low risk of bias if the procedure was explicitly described and adequate efforts were made to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment (e.g. centralised randomisation, numbered or coded containers or sealed envelopes). Procedures that we would have considered to have a high risk of bias included alternation or reference to case record numbers or dates of birth, although there were no mention of these methods being used in any of our included studies. Where there was no description of the method of allocation concealment, we contacted the study authors, assigning a judgement of unclear risk of bias when we received no response.

Blinding of parents and health professionals

In this context, the intervention was administered by parents, so, in effect, we considered them the target of the blinding procedures. Indeed, as the participants were under four months of age by the defined inclusion criteria (Criteria for considering studies for this review), it was deemed that this item was not applicable to them. Furthermore, parents often acted as outcome assessors. We primarily assessed the risk of bias associated with the blinding of parents of participants based on the likelihood that such blinding was sufficient to ensure that parents had no knowledge of which intervention the infant received. If the study was open label, we assigned a judgement of high risk of bias. If the study was reported with detail as blinded, we assigned a judgement of low risk of bias. If it was unclear, we contacted the study authors, assigning a rating of unclear risk of bias when no response was received.

Blinding of outcome assessment

For each included study, we described the methods used, if any, to blind the outcome assessors from knowledge of which intervention a participant received. We judged studies at low risk of bias if they blinded the outcome assessors, or where we considered that the lack of blinding could not have affected the results. If blinding was not done or was not possible because of the nature of the intervention, we judged the study at high risk of bias because it is possible that the lack of blinding influenced the results. If there was no description, we contacted the study authors for more information, and if there was no response, we assigned a judgement of unclear risk of bias. The blinding of health professionals was noted, if reported.

Incomplete outcome data

Incomplete outcome data essentially included attrition, exclusions and missing data.
We assigned a judgement of low risk of bias if:

- participants included in the analysis were exactly those who were randomised into the trial; missing outcome data were balanced in terms of numbers across intervention groups, with similar reasons for missing data across groups or if there were no missing outcome data;
- for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not sufficient to have a clinically relevant impact on the intervention effect estimate;
- for continuous outcome data, the plausible effect size (SMD) among missing outcomes was not sufficient to have a clinically relevant impact on the observed effect size; or
- missing data were imputed using appropriate methods.

We assigned a judgement of high risk of bias when:

- reasons for missing outcome data were likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups;
- for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was sufficient to induce clinically relevant bias in the intervention effect estimate;
- for continuous outcome data, the plausible effect size (SMD) among missing outcomes was sufficient to induce clinically relevant bias in the observed effect size;
- an 'as-treated' analysis was carried out in cases where there was a substantial departure of the intervention received from that assigned at randomisation; or
- there was a potentially inappropriate application of simple imputation.

We assigned a judgement of unclear risk of bias when:

- there was insufficient reporting of attrition or exclusions, or both, to permit a judgement of low or high risk of bias;
- the study reported incomplete outcome data; or
- the trial did not clearly report the numbers randomised to intervention and control groups.

Selective outcome reporting

We assessed the reporting of outcomes as being at low risk of bias if the results of the trial reported all of the study outcomes declared in the trial's methods section. We also evaluated whether different reports of the study were available, including protocols, and examined them to ensure that there was no suggestion of selective outcome reporting. If there was no description, we contacted the authors for more information, and if we did not receive a response, we assigned a judgement of unclear risk of bias. When there was evidence of selective reporting (deviation from protocol, key planned outcomes not reported), we assigned a judgement of high risk of bias.

Other potential threats to validity

When the study was at risk of other sources of bias not captured by the above domains, we assessed it at high risk of bias; for instance, if the study was stopped early due to a data-dependent process, had a baseline imbalance between the groups or its sources of sponsorship or funding. We assessed the study at low risk of bias if it appeared to be free from such threats to validity. When the risk of bias was unclear from the published information, we attempted to contact the study authors for clarification. When this was not forthcoming, we assessed these studies as being at unclear risk of bias.

CONTRIBUTIONS OF AUTHORS

TGO: contributed to data extraction, 'Risk of bias' assessment, analysis and full write-up of the review.

MG: conceived the project; cosearched, screened and reviewed full-text reports; extracted data; judged the risk of bias and certainty of the evidence; analysed the data; and cowrote the manuscript.

SSCB: cosearched, screened and reviewed full-text reports; extracted data; judged the risk of bias and certainty of the evidence; analysed the data; and cowrote the manuscript.

MRT: is the named correspondent. MRT reviewed the final protocol and review, and contributed to the text and analysis.

AA: reviewed the final protocol and review, and contributed to the text and analysis.

DECLARATIONS OF INTEREST

TGO: none.

MG is employed by Blackpool Victoria Hospital (NHS) and declares that he received some financial support from the Trust to employ a Research Assistant; however, they had no involvement in the planning or execution of this review. MG has received travel grants from 2016 to 2019 from Ferring and BioGaia to attend scientific meetings and these companies produce treatments for colic that may be tested in this study. MG declares that these companies had no involvement in the planning, design or conceptual planning of this study. MG has received travel grants from Tillotts Pharma and Synergy Pharmaceuticals to attend meetings to present the results of previous works. They have had no input or involvement in any aspect of the review process during this or previous systematic reviews carried out by MG, such as *Bowel preparation for paediatric colonoscopy* (Gordon 2012) and *Probiotics for maintenance of remission in ulcerative colitis* (Naidoo 2011).

SSCB is being paid as a Research Assistant for this review from Blackpool Teaching Hospitals NHS Foundation Trust*. SSCB is Chair of the Local Infant Feeding Information Board (LIFIB), which produces evidence-based information on infant feeding topics for health professionals. SSCB is a self-employed Infant Feeding Information Specialist and provides expertise in infant feeding, writing briefing papers and newsletters, etc., and delivering workshops across the northwest of England. This is for the LIFIB and the Sudden Unexpected Death of a Child Prevention Team in Lancashire. Money from Lancashire County Council, via The Breastfeeding Network, funds the latter, and work related to this is paid for by the hour. SSCB is self-employed as an International Board Certified Lactation Consultant in private practice. SSCB is a Committee Member of the main Lactation Consultants of Great Britain (LCGB) Committee and Chair of the Communications Team. She is also Chair of the committee for the Breastfeeding Festival, which puts on one × two-day event each year to celebrate breastfeeding and provide interesting and educational speaker sessions on infant feeding. All of these positions are unfunded and voluntary but travel expenses are paid. SSCB declares that she was a Lay Member on the National Institute for Health and Care Excellence (NICE) Guideline Committee on Faltering Growth in Infants and Children from 2015 to 2017 for which she was paid an honorarium by NICE. She also declares that she is a trustee of the UK Association of Milk Banking; an unfunded position with travel expenses up to twice a year, and sometimes accommodation at conferences to run stalls etc. are paid. SSCB declares that neither she personally nor any of the entities that she represents take funding of any kind from any commercial interests in infant feeding or early years, and that she works completely within the professional code of ethics as an International Board Certified Lactation Consultant.

MRT has been part of an advisory board for Roche related to a study for people with Down's syndrome about improving cognition. MRT was reimbursed for her travel costs, and her Trust received fees for her time. MRT confirms that she has not received any fees from any other commercial sources from 2015 to 2018.

AA: none.

*Disclaimer: MRT, MG, TGO are members of staff of the Blackpool Victoria Hospital. The authors alone are responsible for the views expressed herein; they do not necessarily represent the decisions, policy or views of the NHS or Department of Health.

SOURCES OF SUPPORT

Internal sources

- Blackpool Teaching Hospitals NHS Foundation Trust, UK.

Blackpool Teaching Hospitals is the employer of three review authors: MG and MT are employed in the medical team for the hospital, and SB was employed by the hospital as a Research Assistant for 12 months.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Changes to authorship: Chris Wallace, who contributed to the development of the protocol (Banks 2016), was replaced by Teck Ong.

- Objectives. We modified the 'Objectives' to make it more concise.

- Types of studies. For added clarity, we specified that cluster and cross-over trials were eligible for inclusion.

- Types of interventions. In the protocol, Banks 2016, we stated that in order to be included in the review a study would have to focus on the effect of the intervention on infantile colic. Before completing the screening, and after discussion within the author group, we decided that we would include studies where the infants were asymptomatic and the study considered the onset of colic, even if it was not the main focus of the study. Given that the prophylactic use of these drugs in almost all trials considered a number of outcomes, we felt this was reasonable.

- Primary outcomes. The primary outcome measure 'reduction in the duration of crying' in the published protocol (Banks 2016), was, in fact, not appropriate. As by definition all babies included in studies at baseline did not have infantile colic, reduction in crying is not an appropriate primary outcome and was subsequently replaced, prior to data extraction, with the primary outcome 'occurrence of new cases of colic at study end, as defined by the Wessel criteria'.

- Secondary outcomes. We reworded the outcomes of 'reduction in the duration of crying' and 'reduction in frequency of crying episodes per 24 hours', to the following more neutral formulations, to reflect the fact that we are assessing the variable rather than a deterioration in the variable: 'duration of crying' and 'frequency of crying episodes per 24 hours'.

- 'Summary of findings' tables. We updated the GRADE criteria in line with current guidance, to refer to 'certainty', instead of 'quality' (high certainty, moderate certainty, low certainty and very low certainty).

- Subgroup analysis and investigation of heterogeneity. It became clear that there were a number of included papers that started administering treatments to pregnant women and continuing this in some form postnatally. This was not a form of study that was expected and therefore a further subgroup analysis was added to explore the impact of this particular approach.