Article

Probiotics to prevent infantile colic (Protocol)

Banks, Shel C, Thomas, Megan R, Gordon, Morris, Wallace, Chris and Akobeng, Anthony

Cochrane Library

Cochrane Database of Systematic Reviews

Probiotics to prevent infantile colic (Protocol)

Banks SSC, Thomas MR, Gordon M, Wallace C, Akobeng AK

Banks SSC, Thomas MR, Gordon M, Wallace C, Akobeng AK.
Probiotics to prevent infantile colic.
Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD012473.
DOI: 10.1002/14651858.CD012473.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Probiotics to prevent infantile colic

Shel SC Banks[1], Megan R Thomas[1], Morris Gordon[2,3], Chris Wallace[4], Anthony K Akobeng[5,6]

[1]Department of Child Health, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool, UK. [2]School of Medicine, University of Central Lancashire, Preston, UK. [3]Families Division, Blackpool Victoria Hospital, Blackpool, UK. [4]Postgraduate Department, Blackpool Victoria Hospital, Blackpool, UK. [5]Sidra Medical & Research Center, Doha, Qatar. [6]Weill Cornell Medical College, Doha, Qatar

Contact address: Morris Gordon, School of Medicine, University of Central Lancashire, Preston, UK. morris@betterprescribing.com, general@biyeeproperties.com.

Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.
Publication status and date: New, published in Issue 12, 2016.

Citation: Banks SSC, Thomas MR, Gordon M, Wallace C, Akobeng AK. Probiotics to prevent infantile colic. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No.: CD012473. DOI: 10.1002/14651858.CD012473.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

1. To assess the effectiveness and safety of prophylactic probiotics for preventing or reducing colic in infants.
2. To identify the likely effective probiotic strains for such an approach.

BACKGROUND

This protocol contains some technical terms, the definitions of which can be found in Appendix 1.

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).

Colic can affect up to 10% to 30% of infants worldwide (Clifford 2002; Rosen 2007), and although the prevalence of excessive crying varies according to the definition used, it most often peaks during the second month of life, with a prevalence of up to 12% (Lucassen 2001; Reijneveld 2001). 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). More recently, 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). Rome III diagnostic criteria for functional gastrointestinal disorders includes the following measures, in infants from birth to four months of age, for infantile colic: paroxysms of irritability; fussing or crying that starts and stops without obvious cause; episodes lasting three or more hours per day and occurring at least three days per week for at least three weeks; and no failure to thrive (Mostafa 2008). Colic is a symptom rather than a condition or diagnosis.

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 suffered colic (Romanello 2013). Therefore, all colicky infants should undergo a complete medical assessment in order to exclude underlying medical conditions that require investigation and treatment (Savino 2010a).

The etiopathogenesis of infantile colic remains undefined and is most likely multifactorial. 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 microorganisms; 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 proteins 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, a number of 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 (for example, 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 (Canabar 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 (Canabar 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 2013b).
    - Recent 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. A recent 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. Savino 2013a, however, 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 a Cochrane Review, Praveen 2014, have looked 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 breastmilk 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 prophylactically receiving probiotics 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 there is no 'one cause' of colic, and potential multifactorial 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 in recent years (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 the favourable growth or activity, or both, of one or more indigenous probiotic bacteria (Roberfroid 2007). Synbiotics are products containing both probiotics and prebiotics and are often used.

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 differ from those in healthy controls, it is proposed that supplying probiotic bacteria can redress this balance and provide a healthier intestinal microbiota landscape (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 benefit to the population with minimal risk.

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 colic symptoms in the infant, 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 and pain-relieving agents for the condition (Praveen 2014; Savino 2012, respectively).

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 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 reports 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 multicentric study; Pärtty 2013 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 preventative 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 the world over.

OBJECTIVES

1. To assess the effectiveness and safety of prophylactic probiotics for preventing or reducing colic in infants.

2. To identify the likely effective probiotic strains for such an approach.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs).

Types of participants

We will include newborn infants younger than one month of age without a diagnosis of infantile colic at recruitment, as defined by the study.

Types of interventions

We will include 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 is the effect of the intervention on infantile colic. We will not consider studies in which probiotics are given to infants for other purposes and in which colic or crying is not one of the main outcomes of interest. While, ideally, we are looking for comparisons of probiotic intervention versus no intervention, and probiotic intervention versus placebo, we will include studies comparing probiotic intervention with other interventions for separate analysis. In such a situation, we will only draw conclusions from these trials when there is evidence of the effectiveness of each intervention from other ('versus no treatment or placebo') trials.

Types of outcome measures

For all proposed outcomes, we will use final outcomes from the end of the trials, and we will record the timings of these outcomes as they may guide the subgroup analysis.

Primary outcomes

1. Reduction in the duration of crying (post-treatment versus baseline). Data may be continuous (for example, hours per day) or dichotomous (for example, reduction under a predefined threshold, as determined by the trial authors).

2. Adverse effects, including parental depression and mental illness, choking, bacterial infection, or apparent life-threatening events (dichotomous outcome).

Secondary outcomes

1. The number of responders in each group after treatment. We will define responders as those who experienced a decrease in the daily, average crying time of 50% from baseline (dichotomous outcome).

2. Reduction in frequency of crying episodes per 24 hours, where frequency is specified in the trials separately to the duration of the infant's crying (post-treatment versus baseline) (dichotomous outcome).

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

Search methods for identification of studies

We will identify relevant trials by searching the sources described below.

Electronic searches

We will search the following electronic databases and trial registers from inception onwards.

1. Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library, which includes the Cochrane Developmental, Psychosocial and Learning Problems Specialised Register.

2. MEDLINE Ovid (from 1946).

3. MEDLINE In-Process & Other Non-Indexed Citations OvidSP (current issue).

4. MEDLINE Epub Ahead of Print Ovid (current issue).

5. Embase Ovid (from 1980).

6. CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; from 1937).

7. PsycINFO Ovid (from 1967).

8. Science Citation Index Expanded Web of Science (SCI; from 1970).

9. Social Sciences Citation Index Web of Science (SSCI; from 1970).

10. Conference Proceedings Citation Index - Science Web of Science (CPCI-S; from 1990).

11. Conference Proceedings Citation Index - Social Science & Humanities Web of Science (CPCI-SS&H; from 1990).

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

13. *Cochrane Database of Systematic Reviews* (CDSR; current issue) in the Cochrane Library.

14. Database of Abstracts of Reviews of Effects (DARE; current issue) in the Cochrane Library.
15. Epistemonikos (limited to systematic reviews; www.epistemonikos.org; all available years).
16. WorldCat (limited to theses; www.worldcat.org; all available years).
17. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; all available years).
18. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; apps.who.int/trialsearch; all available years).

We will search MEDLINE using the search strategy in Appendix 2, which uses the sensitivity maximising version of the Cochrane highly sensitive search strategy for identifying RCTs or quasi-RCTs, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We will adapt this strategy for other databases, without imposing any date or language restrictions. We will ensure the professional translation in full of studies published in languages other than English.

Searching other resources

Grey literature

We will handsearch 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 that are not yet published in full. There is some evidence that data from abstracts can be inconsistent with data in published articles (Pitkin 1999). Therefore, we will only include abstract publications if they present sufficient data on which to judge inclusion and assess quality. Where they do not present such data, we will attempt to contact authors for more information and meanwhile list them under 'Studies awaiting classification'.

Supplementary searching

We will inspect the references of all relevant studies and reviews and contact authors to request missing or incomplete data. In addition, we will run citation searches of included studies.

Personal contacts

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

Pharmaceutical companies

We will contact companies that produce probiotics and synbiotics, as well as 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 reviewers (MG and SSCB) will independently screen titles, abstracts, and full reports for eligibility against the inclusion criteria (see Criteria for considering studies for this review). Specifically, they will undertake the following tasks:

1. merge search results using reference management software and remove duplicate records of the same report;
2. examine titles then abstracts, and remove any records that do not meet the inclusion criteria;
3. retrieve the full texts of potentially relevant reports;
4. link together multiple reports of the same study;
5. examine full-text reports to determine whether studies meet the eligibility criteria;
6. correspond with investigators, when appropriate, to clarify study eligibility;
7. at all stages, note reasons for inclusion and exclusion of articles on a study flow spreadsheet, and resolve any disagreements through consensus;
8. make final decisions on study inclusion and resolve any discrepancies through a process of consensus; and
9. proceed to data collection.

We will record our selection process in a PRISMA diagram (Moher 2009).

Data extraction and management

We will develop data extraction forms a priori, as per the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will extract the following information.

1. 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).
2. Interventions and controls: number of groups, intervention(s) applied, frequency and duration of treatment, total number of treatments, and permitted cointerventions.

3. Methods: study design and duration, sequence generation, allocation concealment, blinding of outcome assessors, and evaluation of success of blinding.

4. Outcomes: outcomes assessed, definitions used, values of means and standard deviations (SDs) at baseline and at time points as defined by the study protocol (or change from baseline measures, if given).

5. Results: measures at the end of the 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.

6. 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 SSCB) will extract the data independently using the data extraction form. A third review author (MRT) will resolve any disagreements. We will collate data in the latest version of Review Manager (RevMan 2014).

Assessment of risk of bias in included studies

Two review authors (MG and SSCB) will independently evaluate each study for risk of bias using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* for the following domains (Deeks 2011; Higgins 2011b): 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 will judge each domain as being at 'low', 'high', or 'unclear' risk of bias. We will compare the judgments and discuss and resolve any inconsistencies in the assessments. A third review author (MRT) will resolve any persisting disagreements.

Sequence generation for randomisation

We will include only RCTs in the review. We will assess randomisation as being at low risk of bias if the procedure of randomisation sequence generation was explicitly described; examples include computer-generated random numbers, a random numbers table, or coin-tossing. If no description is given, we will contact the authors for further information, and if we fail to receive a response, we will assign a judgment of unclear risk of bias. We will consider studies that use non-randomised procedures (hospital number, date of birth) to have a high risk of bias.

Allocation concealment

We will assess 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; examples include centralised randomisation, numbered or coded containers, or sealed envelopes. Procedures that we will consider to have a high risk of bias include alternation or reference to case record numbers or dates of birth. We will also assign a judgement of high risk of bias to studies in which allocation concealment did not occur as intervention allocation may not have been in a random fashion and may have increased bias. We will contact the study authors if no description is given, and if we do not receive a response, we will assign a judgment of unclear risk of bias.

Blinding of parents and health professionals

In this context, the intervention is administered by parents, so in effect, we will consider them the target of the blinding procedures. Indeed, as the participants will be less than four months of age by the defined inclusion criteria, it is deemed that this item is not applicable to them. Furthermore, parents often act as outcome assessors. We will primarily assess 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.

Blinding of outcome assessment

For each included study, we will describe the methods used, if any, to blind the outcome assessors from knowledge of which intervention a participant received. We will judge studies to be at low risk of bias if they blinded the outcome assessors, or if we consider 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 will judge the study to be at high risk of bias because it is possible that the lack of blinding influenced the results. If no description is given, we will contact the study authors for more information, and if we do not receive a response, we will assign a judgment of unclear risk of bias. We will note the blinding of health professionals if reported.

Incomplete outcome data

Incomplete outcome data essentially include attrition, exclusions, and missing data.

We will assign a judgment of low risk of bias in the following instances:

1. if participants included in the analysis are exactly those who were randomised into the trial; missing outcome data are balanced in terms of numbers across intervention groups, with similar reasons for missing data across groups; or if there are no missing outcome data;

2. if for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not sufficient to have a clinically relevant impact on the intervention effect estimate;

3. if for continuous outcome data, the plausible effect size (standardised mean difference (SMD)) among missing outcomes

is not sufficient to have a clinically relevant impact on observed effect size; or

4. if missing data have been imputed using appropriate methods.

We will assign a judgment of high risk of bias in the following instances:

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

We will assign a judgment of unclear risk of bias in the following instances:

1. when there is insufficient reporting of attrition or exclusions, or both, to permit a judgment of low or high risk of bias;
2. when the study reported incomplete outcome data; or
3. when the trial did not clearly report the numbers randomised to intervention and control groups.

Selective outcome reporting

We will assess the reporting of outcomes as being at low risk of bias if the results of the trial report all of the study outcomes declared in the trial's methods section. We will also evaluate whether different reports of the study are available, including protocols, and examine them to ensure that there is no suggestion of selective outcome reporting. If no description is given, we will contact the authors for more information, and if we do not receive a response, we will assign a judgment of unclear risk of bias. If there is evidence of selective reporting (deviation from protocol, key planned outcomes not reported), we will assign a judgment of high risk of bias.

Other potential threats to validity

If the study is at risk of other sources of bias not captured by the above domains, we will assess it as being at high risk of bias, for instance, if the study was stopped early due to a data-dependent process, having a baseline imbalance between the group, or its sources of sponsorship or funding. We will assess the study as being at low risk of bias if it appears to be free from such threats to validity.

When the risk of bias is unclear from the published information, we will attempt to contact the study authors for clarification. If this is not forthcoming, we will assess these studies as being at unclear risk of bias.

Measures of treatment effect

Dichotomous data

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

Continuous data

If all studies use the same measurement scale, we will calculate mean differences (MD). When studies use different scales, we will calculate the SMD using Hedges' g. We will also report the 95% CI of the MD or SMD.

If necessary, we will calculate 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 SMD) are not directly available in the study publications.

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

If both continuous and dichotomous data are available for an outcome, we will include only the continuous outcome in the primary analysis. If some studies report an outcome as a dichotomous measure and others use a continuous measure of the same construct, we will convert the results for the former from the dichotomous measure to a SMD, provided that we can assume that the underlying continuous measure has approximately a normal or logistical distribution. (Otherwise, we will carry out two separate analyses.)

Unit of analysis issues

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 (that is, whether the number of observations matches the number of randomised 'units' (Deeks 2011)). It is unlikely that we will find cluster-randomised trials because such a design is uncommon in this field. However, if we do, we will use the intra-class 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 author to supply more data to allow calculation of an ICC estimate (Campbell 2000). It is only for those cluster trials that did not account for the cluster effects that we will use the ICC to calculate the effective sample size or the effective SD.

Studies with multiple treatment arms

In the primary analysis, we will combine results across all eligible intervention arms and compare them with the combined results across all eligible control arms (another intervention(s) or placebo), making single pairwise comparisons. Where such a strategy prevents investigation of potential sources of heterogeneity, we will analyse each type separately (against a common control group: placebo), but divide the sample size for common comparator arms proportionately across each comparison (Higgins 2011b). This simple approach allows the use of standard software (including RevMan 2014) and prevents the inappropriate double-counting of individuals.

Cross-over studies

In randomised, cross-over studies, individuals 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 (that is, to reduce the carry-over effect). A concern with the cross-over design is the risk of a carry-over effect (when the first treatment affects the second), which is of particular concern for this review given the nature of the interventions we are assessing. For this review, we will not include any data in cross-over studies after the first treatment period.

Dealing with missing data

Where data are missing, we will contact the corresponding authors of included studies to supply any unreported data.

For all outcomes in all studies, we will carry out analyses as far as possible on an intention-to-treat basis; that is, we will attempt to include all participants randomised to each group in the analyses, and we will analyse 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 will estimate SDs from other available data, such as standard errors, or we will impute them using the methods suggested in Higgins 2011b. We will conduct analyses based on participants completing the trial, in line with available case analysis; this will assume that missing data are at random. If there is a discrepancy between the number randomised and the number analysed in each treatment group, we will calculate and report the percentage lost to follow-up in each group.

When it is not possible to obtain missing data, we will record this in the data collection form, report it in the 'Risk of bias' table, and discuss the extent to which the missing data could alter the results and hence the conclusions of the review. For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by conducting sensitivity analyses (see Sensitivity analysis).

Assessment of heterogeneity

We will assess clinical heterogeneity by comparing the distribution of important participant characteristics between trials (for example, age) and trial characteristics (for example, randomisation, concealment, blinding of outcome assessment, losses to follow-up, treatment type, cointerventions).

We will employ a Chi^2 test of homogeneity, with a 10% level of significance, to determine the strength of evidence that heterogeneity is genuine. We will also present tau^2.

In addition, we will assess 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 will interpret the I^2 statistic as suggested in the latest version of Deeks 2011:

1. 0% to 40%: might not be important;
2. 30% to 60%: may represent moderate heterogeneity;
3. 50% to 90%: may represent substantial heterogeneity; and
4. 75% to 100%: suggests considerable heterogeneity.

Assessment of reporting biases

In order to minimise publication bias, we will attempt 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).

In addition, 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.

Data synthesis

When interventions are similar in terms of type of intervention, type of outcome assessed, and type of colic, we plan to group the studies and synthesise their results in a meta-analysis. We will present results for each combination of probiotic intervention, assessed outcome, and colic type, with the exception of those studies for which no data are observed. For instance, if two or more studies assessed the effects of prophylactic probiotic use in otherwise healthy children with colic and both measured daily crying, we

will perform a meta-analysis of the results. Because we assume that clinical heterogeneity is very likely to impact on our review results, given the wide breadth and types of interventions included, we will combine 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 will use these calculations to produce a pooled effect, which we will present in a forest plot. We will carry out statistical analysis using RevMan 2014. When data are insufficient, we will provide a narrative description of the results.

'Summary of findings' tables

We will assess the overall quality of evidence using the GRADE approach (Guyatt 2008). The GRADE approach appraises the quality 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-quality evidence, 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) will independently assess the overall quality of the evidence for each outcome after considering each of these factors and will grade them as follows:

1. high quality: further research is very unlikely to change confidence in the estimate of effect;
2. moderate quality: further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate;
3. low quality: further research is very likely to have an important impact on confidence in the estimate of effect, and is likely to change the estimate; or
4. very low quality: any estimate of effect is very uncertain.

We will use the outcomes below.

1. A reduction in the duration of crying (post-treatment versus baseline).
2. Adverse effects, including parental depression and mental illness, choking, bacterial infection, or apparent life-threatening events.
3. The number of responders in each group after treatment. We will define responders as those who experienced a decrease in the daily, average crying time such that they would no longer be defined as having infantile colic.
4. Reduction in frequency of crying episodes per 24 hours, where frequency is specified in the trials separately to the duration of the infant's crying (post-treatment versus baseline).
5. Infant sleep duration per 24 hours at seven, 14, and 21 days (post-treatment versus baseline) or where it is not grouped in this way in the individual trials, using a time window of between seven and 28 days.

Subgroup analysis and investigation of heterogeneity

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

1. mode of delivery of baby (vaginal versus caesarean section);
2. type of feeding (artificially fed versus breastfed);
3. short-term and long-term follow-up (fewer than four weeks versus four weeks or more of treatment);
4. preterm (pre-37 weeks and pre-33 weeks gestation) versus 'term' babies (born between 37 and 43 weeks gestation);
5. low-quality trials versus high-quality trials (allocation concealment versus lack of allocation concealment; blinding versus lack of blinding); and
6. type of probiotic (or combination of probiotic with prebiotic, also known as 'synbiotic').

These analyses will be exploratory as they involve non-experimental (cross study) comparisons and will involve primary outcomes. We will treat any conclusions with caution.

Sensitivity analysis

We will conduct sensitivity analyses to determine whether findings are sensitive to the following:

1. bias, by restricting the analyses to studies judged to be at low risk of bias for blinded assessment of the primary outcome;
2. imputed data, by calculating the treatment effect including and excluding the imputed data to assess whether this alters the outcome of the analysis;
3. dropouts and exclusions, by conducting worst-case versus best-case scenario analyses;
4. 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; and
5. the choice of meta-analysis model used, by comparing results from the fixed-effect model with those of the random-effects model.

While there may be heterogeneity in the interventions, as well as the comparisons, we consider that the consensus on definitions of symptoms for eligibility manages the risk of 'blurring' the results, but we remain vigilant, and if we perceive a risk while evaluating our findings, we may undertake a sensitivity analysis removing such trials to provide more definite findings.

ACKNOWLEDGEMENTS

We would like to acknowledge the editors for their helpful comments on earlier versions of this protocol, as well as the support from Cochrane Developmental, Psychosocial and Learning Problems.

REFERENCES

Additional references

Ali 2012

Ali AM. Helicobacter pylori and infantile colic. *Archives of Pediatrics & Adolescent Medicine* 2012;**166**(7):648–50. [DOI: 10.1001/archpediatrics.2011.1241; PUBMED: 22751879]

Arslanoglu 2012

Arslanoglu S, Moro GE, Boehm G, Wienz F, Stahl B, Bertino E. Early neutral prebiotic oligosaccharide supplementation reduces the incidence of some allergic manifestations in the first 5 years of life. *Journal of Biological Regulators and Homeostatic Agents* 2012;**26**(3 Suppl):49–59. [PUBMED: 23158515]

Axelsson 1986

Axelsson I, Jakobsson I, Lindberg T, Benediktsson B. Bovine beta-lactoglobulin in the human milk. A longitudinal study during the whole lactation period. *Acta Paediatrica Scandinavica* 1986;**75**(5):702–7. [PUBMED: 3564937]

Baldassarre 2010

Baldassarre ME, Laforgia N, Fanelli M, Laneve A, Grosso R, Lifschitz C. Lactobacillus GG improves recovery in infants with blood in the stools and presumptive allergic colitis compared with extensively hydrolyzed formula alone. *The Journal of Pediatrics* 2010;**156**(3):397–401. [DOI: 10.1016/j.jpeds.2009.09.012; PUBMED: 19880141]

Braeggar 2011

Braegger C, Chmielewska A, Decsi T, Kolacek S, Mihatsch W, Moreno L, et al. Supplementation of infant formula with probiotics and/or prebiotics: a systematic review and comment by the ESPGHAN committee on nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2011;**52**(2):238–50. [DOI: 10.1097/MPG.0b013e3181fb9e80; PUBMED: 21150647]

Campbell 1989

Campbell JP. Dietary treatment of infant colic: a double-blind study. *Journal of the Royal College of General Practitioners* 1989;**39**(318):11–4. [PUBMED: 2553940]

Campbell 2000

Campbell M, Grimshaw J, Steen N. Sample size calculations for cluster randomised trials. Changing Professional Practice in Europe Group (EU BIOMED II Concerted Action). *Journal of Health Services Research & Policy* 2000;**5**(1):12–6. [PUBMED: 10787581]

Canabar 2001

Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *Journal of Human Nutrition and Dietetics* 2001;**14**(5):359–63. [PUBMED: 11906576]

Clifford 2002

Clifford TJ, Campbell MK, Speechley KN, Gorodzinsky F. Infant colic: empirical evidence of the absence of an association with source of early infant nutrition. *Archives of Pediatrics & Adolescent Medicine* 2002;**156**(11):1123–8. [PUBMED: 12413341]

de Weerth 2013

de Weerth C, Fuentes S, Puylaert P, de Vos WM. Intestinal microbiota of infants with colic: development and specific signatures. *Pediatrics* 2013;**131**(2):e550–8. [DOI: 10.1542/peds.2012-1449]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Deshpande 2010

Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. *Pediatrics* 2010;**125**(5):921–30. [DOI: 10.1542/peds.2009-1301]

Deshpande 2011

Deshpande GC, Rao SC, Keil AD, Patole SK. Evidence-based guidelines for use of probiotics in preterm neonates. *BMC Medicine* 2011;**9**:92. [DOI: 10.1186/1741-7015-9-92; PMC3163616]

Dupont 2010

Dupont C, Rivero M, Grillon C, Belaroussi N, Kalindjian A, Marin V. Alpha-lactalbumin-enriched and probiotic-supplemented infant formula in infants with colic: growth and gastrointestinal tolerance. *European Journal of Clinical Nutrition* 2010;**64**(7):765–7. [DOI: 10.1038/ejcn.2010.81; PUBMED: 20517331]

Estep 2000

Estep DC, Kulczycki A Jr. Treatment of infant colic with amino acid-based infant formula: a preliminary study. *Acta Paediatrica* 2000;**89**(1):22–7. [PUBMED: 10677052]

Freedman 2009

Freedman SB, Al-Harthy N, Thull-Freedman J. The crying infant: diagnostic testing and frequency of serious underlying disease. *Pediatrics* 2009;**123**(3):841–8. [DOI: 10.1542/peds.2008-0113; PUBMED: 19255012]

Garrison 2000

Garrison MM, Christakis DA. A systematic review of treatments for infant colic. *Pediatrics* 2000;**106**(1 Pt 2):184–90. [PUBMED: 10888690]

Gordon 2012

Gordon M, Harper V, Thomas AG, Akobeng A. Bowel preparation for paediatric colonoscopy. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD009976]

Grönlund 1999

Grönlund MM, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean

delivery. *Journal of Pediatric Gastroenterology and Nutrition* 1999;**28**(1):19–25. [PUBMED: 9890463]

Gupta 2007
Gupta SK. Update on infantile colic and management options. *Current Opinion in Investigational Drugs* 2007;**8**(11):921–6. [PUBMED: 17979025]

Guyatt 2008
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, GRADE Working Group, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924–6. [DOI: 10.1136/bmj.39489.470347.AD]

Hall 2012
Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. *Journal of Paediatrics and Child Health* 2012;**48**(2):128–37. [DOI: 10.1111/j.1440-1754.2011.02061.x; PUBMED: 21470331]

Heine 2013
Heine RG. Cow's-milk allergy and lactose malabsorption in infants with colic. *Journal of Paediatric Gastroenterology and Nutrition* 2013;**57**(Suppl 1):S25–7. [DOI: 10.1097/01.mpg.0000441930.13307.9b]

Heine 2014
Heine RG, Hill DJ, Hoskin CS. Infantile colic and food allergy. In: Metcalfe DD, Sampson HA, Simon RA, Lack G editor(s). *Food Allergy: Adverse Reactions to Foods and Food Additives*. 5th Edition. Chichester: John Wiley & Sons, 2014:171–81. [DOI: 10.1002/9781118744185.ch15]

Higgins 2011a
Higgins JPT, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b
Higgins JPT, Deeks JJ, Altman DG. Chapter 16: Special topics in statistics. In: Higgins JP, Green S, editor (s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hill 1995
Hill DJ, Hudson IL, Sheffield LJ, Shelton MJ, Menahem S, Hosking CS. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *Journal of Allergy and Clinical Immunology* 1995;**96**(6 Pt 1):886–92. [DOI: 10.1016/S0091-6749(95)70224-5; PUBMED: 8543745]

Hill 2000
Hill DJ, Hosking CS. Infantile colic and food hypersensitivity. *Journal of Pediatric Gastroenterology and Nutrition* 2000;**30 Suppl**(1):S67–76. [PUBMED: 10634302]

Hill 2005
Hill DJ, Roy N, Heine RG, Hosking CS, Francis DE, Brown J, et al. Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. *Pediatrics* 2005;**116**(5):e709–15. [DOI: 10.1542/peds.2005-0147; PUBMED: 16263986]

Houghteling 2015
Houghteling PD, Walker WA. Why is initial bacterial colonization of the intestine important to infants' and children's health?. *Journal of Paediatric Gastroenterology and Nutrition* 2015;**60**(3):294–307. [DOI: 10.1097/MPG.0000000000000597; PMC4340742; PUBMED: 25313849]

Hyams 1989
Hyams JS, Geertsma MA, Etienne NL, Treem WR. Colonic hydrogen production in infants with colic. *The Journal of Pediatrics* 1989;**115**(4):592–4. [PUBMED: 2795353]

Hyman 2006
Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastreoenterology* 2006;**130**(5):1519–26. [DOI: 10.1053/j.gastro.2005.11.065; PUBMED: 16678565]

Iacono 1991
Iacono G, Carroccio A, Montalto G, Cavataio F, Bragion E, Lorello D, et al. Severe infantile colic and food intolerance: a long-term prospective study. *Journal of Pediatric Gastroenterology and Nutrition* 1991;**12**(3):332–5. [PUBMED: 2072224]

Iacono 2005
Iacono G, Merolla R, D'Amico D, Bonci E, Cavataio F, Di Prima L, et al. Gastrointestinal symptoms in infancy: a population-based prospective study. *Digestive and Liver Disease* 2005;**37**(6):432–8. [DOI: 10.1016/j.dld.2005.01.009; PUBMED: 15893282]

Iacovou 2012
Iacovou M, Ralston RA, Muir J, Walker KZ, Truby H. Dietary management of infantile colic: a systematic review. *Maternal and Child Health Journal* 2012;**16**(6):1319–31. [DOI: 10.1007/s10995-011-0842-5; PUBMED: 21710185]

Indrio 2014
Indrio F, Di Mauro A, Riezzo G, Civardi E, Intini C, Corvaglia L, et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial. *JAMA Pediatrics* 2014;**168**(3):228–33. [DOI: 10.1001/jamapediatrics.2013.4367; PUBMED: 24424513]

Infante 2011
Infante D, Segarra O, Luyer BL. Dietary treatment of colic caused by excess gas in infants: biochemical evidence. *World Journal of Gastroenterology* 2011;**17**(16):2104–8. [DOI: 10.3748/wjg.v17.i16.2104; PMC3084395; PUBMED: 21547129]

Jakobsson 1983
Jakobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind crossover study. *Pediatrics* 1983;**71**(2):268–71.

Jakobsson 2000
Jakobsson I, Lothe L, Ley D, Borschel MW. Effectiveness of casein hydrolysate feedings in infants with colic. *Acta Paediatrica* 2000;**89**(1):18–21. [PUBMED: 10677051]

Kukkonen 2008
Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. *Pediatrics* 2008;**122**(1):8–12. [DOI: 10.1542/peds.2007-1192; PUBMED: 18595980]

Landgren 2011
Landgren K, Hallström I. Parents' experience of living with a baby with infantile colic - a phenomenological hermeneutic study. *Scandinavian Journal of Caring Sciences* 2011;**25**(2):317-24. [DOI: 10.1111/j.1471-6712.2010.00829.x; PUBMED: 20723153]

Lederberg 2001
Lederberg J, McCray AT. 'Ome Sweet 'Omics-a genealogical treasury of words. www.the-scientist.com/?articles.view/articleNo/13313/title/-Ome-Sweet--Omics---A-Genealogical-Treasury-of-Words/ (accessed 7 December 2016).

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lindberg 1999
Lindberg T. Infantile colic and small intestinal function: a nutritional problem?. *Acta Paediatrica* 1999;**88**(430):58–60.

Lothe 1982
Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics* 1982;**70**(1):7–10. [PUBMED: 7088636]

Lothe 1989
Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics* 1989;**83**(2):262–6. [PUBMED: 2913556]

Lucas 1998
Lucas A, St James-Roberts I. Crying, fussing and colic behaviour in breast- and bottle-fed infants. *Early Human Development* 1998;**53**(1):9–18. [PUBMED: 10193923]

Lucassen 2000
Lucassen PL, Assendelft WJ, Gubbels JW, Van Eijk JT, Douwes AC. Infantile colic: crying time reduction with a whey hydrolysate: a double-blind, randomized, placebo-controlled trial. *Pediatrics* 2000;**106**(6):1349–54. [PUBMED: 11099588]

Lucassen 2001
Lucassen PL, Assendelft WJ, van Eijk JT, Gubbels JW, Douwes AC, van Geldrop WJ. Systematic review of the occurrence of infantile colic in the community. *Archives of Disease in Childhood* 2001;**84**(5):398–403. [DOI: 10.1136/adc.84.5.398]

Merras-Salmio 2013
Merras-Salmio L, Pelkonen AS, Kolho KL, Kuitunen M, Mäkelä MJ. Cow's milk-associated gastronintestinal symptoms evaluated using the double-blind, placebo-controlled food challenge. *Journal of Paediatric Gastroenterology and Nutrition* 2013;**57**(3):281–6. [DOI: 10.1097/MPG.0b013e3182993fe0; PUBMED: 23974059]

Milidou 2012
Milidou I, Henriksen TB, Jensen MS, Olsen J, Søndergaard C. Nicotine replacement therapy during pregnancy and infantile colic in the offspring. *Pediatrics* 2012;**129**(3):e652–8. [DOI: 10.1542/peds.2011-2281]

Miller 1990
Miller JJ, Brand JC, McVeagh P. Breath hydrogen excretion in infants with colic. *Archives of Disease in Childhood* 1990;**65**(2):248. [PMC1792219]

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of Internal Medicine* 2009;**151**(4):264–9. [PUBMED: 19622511]

Moore 1988
Moore DJ, Robb TA, Davidson GP. Breath hydrogen response to milk containing lactose in colicky and noncolicky infants. *The Journal of Pediatrics* 1988;**113**(6):979–84. [PUBMED: 3193321]

Mostafa 2008
Mostafa R. Rome III: The functional gastrointestinal disorders, third edition, 2006. *World Journal of Gastroenterology* 2008;**14**(13):2124–25. [DOI: 10.3748/wjg.14.2124; PMC2701540]

Naidoo 2011
Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD007443.pub2]

NHS England Breastfeeding Initiation Q1 2015/16
NHS England Statistical Release Breastfeeding Initiation & Breastfeeding Prevalence 6-8 weeks Quarter 1 2015/16. https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2014/03/Breastfeeding-1516Q11.pdf September 2015:4.

NHS Maternity Statistics, England 2014-15
Hospital Episode Statistics NHS Maternity Statistics - England, 2014-15. Health and Social Care Information Centre http://content.digital.nhs.uk/catalogue/PUB19127/nhs-mate-eng-2014-15-summ-repo-rep.pdf Jan 2016:12.

Oozeer 2013
Oozeer R, van Limpt K, Ludwig T, Ben Amor K, Martin R, Wind RD, et al. Intestinal microbiology in early

life: specific prebiotics can have similar functionalities as human-milk oligosaccharides. *The American Journal of Clinical Nutrition* 2013;**98**(2):561S–71S. [DOI: 10.3945/ajcn.112.038893]

Oxman 1992
Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. *Annals of Internal Medicine* 1992;**116**(1):78–84. [PUBMED: 1530753]

Perry 2011
Perry R, Hunt K, Ernst E. Nutritional supplements and other complementary medicines for infantile colic: a systematic review. *Pediatrics* 2011;**127**(4):720–33. [DOI: 10.1542/peds.2010-2098; PUBMED: 21444591]

Pitkin 1999
Pitkin RM, Branagan MA, Burmeister LF. Accuracy of data in abstracts of published research articles. *JAMA* 1999;**281**(12):1110–1. [PUBMED: 10188662]

Praveen 2014
Praveen V, Praveen S, Deshpande G, Patole SK. Oral probiotics for infantile colic. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD010986]

Pärtty 2013
Pärtty A, Luoto R, Kalliomäki M, Salminen S, Isolauri E. Effects of early prebiotic and probiotic supplementation on development of gut microbiota and fussing and crying in preterm infants: a randomized, double-blind, placebo-controlled trial. *The Journal of Pediatrics* 2013;**163**(5):1272–7.e2. [DOI: 10.1016/j.jpeds.2013.05.035; PUBMED: 23915796]

Reijneveld 2001
Reijneveld SA, Brugman E, Hirasing RA. Excessive infant crying: the impact of varying definitions. *Pediatrics* 2001;**108**(4):893–7. [PUBMED: 11581441]

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rijkers 2011
Rijkers GT, de Vos WM, Brummer RJ, Morelli L, Corthier G, Marteau P. Health benefits and health claims of probiotics: bridging science and marketing. *British Journal of Nutrition* 2011;**106**(9):1291–6. [DOI: 10.1017/S000711451100287X; PUBMED: 21861940]

Roberfroid 2007
Roberfroid M. Prebiotics: the concept revisited. *Journal of Nutrition* 2007;**137**(3 Suppl 2):830S–7S. [PUBMED: 17311983]

Romanello 2013
Romanello S, Spiri D, Marcuzzi E, Zanin A, Boizeau P, Riviere S, et al. Association between childhood migraine and history of infantile colic. *JAMA* 2013;**309**(15):1607–12. [DOI: 10.1001/jama.2013.747; PUBMED: 23592105]

Rosen 2007
Rosen LD, Bukutu C, Le C, Shamseer L, Vohra S. Complementary, holistic, and integrative medicine: colic. *Pediatrics in Review* 2007;**28**(10):381–5. [DOI: 10.1542/pir.28-10-381]

Saps 2011
Saps M, Lu P, Bonilla S. Cow's-milk allergy is a risk factor for the development of FGIDs in children. *Journal of Paediatric Gastroenerology and Nutrition* 2011;**52**(2):166–9. [DOI: 10.1097/MPG.0b013e3181e85b55; PUBMED: 20975580]

Savino 2001
Savino F, Cresi F, Silvestro L, Oggero R. Use of an amino-acid formula in the treatment of colicky breastfed infants. *Acta Paediatrica* 2001;**90**(3):359–60. [PUBMED: 11332183]

Savino 2005
Savino F, Castagno E, Bretto R, Brondello C, Palumeri E, Oggero R. A prospective 10-year study on children who had severe infantile colic. *Acta Paediatrica Supplement* 2005;**94**(449):129–32. [DOI: 10.1080/08035320510043691; PUBMED: 16214780]

Savino 2006
Savino F, Palumeri E, Castagno E, Cresi F, Dalmasso P, Cavallo F, et al. Reduction of crying episodes owing to infantile colic: a randomized controlled study on the efficacy of a new infant formula. *European Journal of Clinical Nutrition* 2006;**60**(11):1304–10. [DOI: 10.1038/sj.ejcn.1602457; PUBMED: 16736065]

Savino 2007a
Savino F. Focus on infantile colic. *Acta Paediatrica* 2007;**96**(9):1259–64. [DOI: 10.1111/j.1651-2227.2007.00428.x; PUBMED: 17718777]

Savino 2007b
Savino F, Pelle E, Palumeri E, Oggero R, Miniero R. Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. *Pediatrics* 2007;**119**(1):e124–30. [DOI: 10.1542/peds.2006-1222]

Savino 2010a
Savino F, Tarasco V. New treatments for infant colic. *Current Opinion in Pediatrics* 2010;**22**(6):791–7. [DOI: 10.1097/MOP.0b013e32833fac24; PUBMED: 20859207]

Savino 2010b
Savino F, Cordisco L, Tarasco V, Palumeri E, Calabrese R, Oggero R, et al. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. *Pediatrics* 2010;**126**(3):e526–33. [DOI: 10.1542/peds.2010-0433; PUBMED: 20713478]

Savino 2012
Savino F, Tarasco V, Lingua C, Moja L, Ricceri F. Pain-relieving agents for infant colic. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD009999]

Savino 2013a
Savino F, Ceratto S, Opramolla A, Locatelli E, Tarasco V, Amaretti A, et al. Coliforms and infant colic: fish analysis of fecal samples of breastfed and formula fed infants. *Journal of Paediatric Gastroenterology and Nutrition* 2013;**56**(2):472.

Savino 2013b
Savino F, Juncker A, Opramolla A, Tarasco V, Ceratto S, Bonde I, et al. Metagenomic analysis of fecal samples from healthy and colicky infants. *Journal of Paediatric Gastroenterology and Nutrition* 2013;**56**(2):154.

Savino 2014
Savino F, Tarasco V, Sorrenti M, Lingua C, Moja L, Gordon M, et al. Dietary modifications for infantile colic. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD011029]

Schach 2002
Schach B, Haight M. Colic and food allergy in the breastfed infant: is it possible for an exclusively breastfed infant to suffer from food allergy?. *Journal of Human Lactation* 2002; **18**(1):50–2. [DOI: 10.1177/089033440201800108]

Shannon 1921
Shannon WR. Colic in breast-fed infants as a result of sensitization to foods in the mother's diet. *Archives Paediatrica* 1921;**38**:756–61.

Sterne 2011
Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor (s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Sung 2012
Sung V, Hiscock H, Tang M, Mensah F, Heine RG, Stock A, et al. Probiotics to improve outcomes of colic in the community: protocol for the Baby Biotics randomised controlled trial. *BMC Pediatrics* 2012;**12**:135. [DOI: 10.1186/1471-2431-12-135; PMC3508922; PUBMED: 22928654]

Sung 2014
Sung V, Hiscock H, Tang ML, Mensah FK, Nation ML, Satzke C, et al. Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial. *BMJ* 2014;**348**:g2107. [DOI: 10.1136/bmj.g2107]

Szajewska 2013
Szajewska H, Gyrczuk E, Horvath A. Lactobacillus reuteri DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo-controlled trial. *The Journal of Pediatrics* 2013;**162**(2): 257–62. [DOI: 10.1016/j.jpeds.2012.08.004; PUBMED: 22981952]

Thomas 2010
Thomas DW, Greer FR, American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section on Gastroenterology, Hepatology, Nutrition. Probiotics and prebiotics in pediatrics. *Pediatrics* 2010;**126** (6):1217–31. [DOI: 10.1542/peds.2010-2548; PUBMED: 21115585]

Walter 2000
Walter SD. Choice of effect measure for epidemiological data. *Journal of Clinical Epidemiology* 2000;**53**(9):931–9. [PUBMED: 11004419]

Wessel 1954
Wessel MA, Cobb JC, Jackson EB, Harris GS Jr, Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics* 1954;**14**(5):421–35. [PUBMED: 13214956]

Yusuf 1991
Yusuf S, Wittes J, Probstfield K, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;**266**(1):93–8. [PUBMED: 2046134]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Definition of terms

Term	Definition
Paroxysms	A sudden recurrence or intensification of symptoms such as a spasm or seizure. Also called paroxysmal attacks
Dysmotility	A condition in which muscles of the digestive system become impaired and changes in the speed, strength or coordination 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
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
Microbiota	"the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space." (Lederberg 2001)
Microbiome	The microorganisms in a particular environment (including the body or a part of the body)
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
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
Enteritis	Inflammation of the intestine, especially the small intestine, usually accompanied by diarrhoea

Appendix 2. MEDLINE search strategy

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$).mp.
13 exp lactobacillaceae/
14 lactobac?ill$.mp.
15 exp Bifidobacterium/

16 Bifidobacter$.mp.
17 Bifidus$.mp.
18 exp Saccharomyces/
19 Saccharomyces$.mp.
20 Streptococcus/
21 streptococc$.mp.
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$).tw.
26 24 or 25
27 randomised controlled trial.pt.
28 controlled clinical trial.pt.
29 randomi#ed.ab.
30 placebo$.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

CONTRIBUTIONS OF AUTHORS

MG is the named correspondent; SB is the lead author. SB and MG wrote the protocol; MT and CW reviewed the draft protocol. MG has overall responsibility for managing the review.

DECLARATIONS OF INTEREST

- Shel SC Banks (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 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.

- Megan R Thomas (MRT) has been part of an advisory board for Roche related to a study for individuals with Down 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 in the past three years.

- Morris Gordon (MG) has received travel grants in the last three years from Ferring and BioGaia to attend scientific meetings and produce treatments for colic that may be tested for inferiority in this study. MG has received travel grants from Abbott Nutrition; Warner Chilcott; Norgine Pharmaceuticals; Ferring Pharmaceuticals; BioGaia; Tillotts; Clinova; Vifor; Nutricia; Danone; and Laboratorios Casen Fleet 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 and Probiotics for maintenance of remission in ulcerative colitis (Gordon 2012; Naidoo 2011, respectively). MG is a

Paediatrician with an interest in gastroenterology, which involves seeing patients referred with infantile colic and managing in line with current, accepted, evidence-based practice.

- Chris Wallace (CW) was involved in a review looking at probiotics as treatment for chronic constipation, which was accepted for poster presentation at the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Annual Meeting. CW received funding from the Young Investigator Award (YIA) for travel and accommodation to attend the meeting.

- Anthony K Akobeng: nothing to declare.

SOURCES OF SUPPORT

Internal sources

- Blackpool Teaching Hospitals NHS Foundation Trust, UK.

Blackpool Teaching Hospitals is the employer of three reviewers: MG and MT are employed in the medical team for the hospital, and SB is employed by the hospital as a research assistant.

External sources

- No sources of support supplied