Cochrane Library

Cochrane Database of Systematic Reviews

Parent training programmes for managing infantile colic (Protocol)

Thomas MR, Gordon M, Banks SSC, Wallace C

Thomas MR, Gordon M, Banks SSC, Wallace C.
Parent training programmes for managing infantile colic.
Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD012459.
DOI: 10.1002/14651858.CD012459.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Parent training programmes for managing infantile colic

Megan R Thomas[1], Morris Gordon[2,3], Shel SC Banks[1], Chris Wallace[4]

[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

Contact address: Morris Gordon, Families division, Blackpool Victoria Hospital, Whinney Heys Road, Blackpool, FY3 8NR, 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: Thomas MR, Gordon M, Banks SSC, Wallace C. Parent training programmes for managing infantile colic. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No.: CD012459. DOI: 10.1002/14651858.CD012459.

ABSTRACT

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

1. To evaluate the effectiveness and safety of parent training programmes for managing colic in infants under four months of age.
2. To identify the educational content and attributes of such published programmes.

BACKGROUND

Description of the condition

Infantile colic can be 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 2010a).

The prevalence of excessive crying varies according to the definition used, although, most often, it peaks during the second month of life with a prevalence of 1.5% to 11.9% (Reijneveld 2001). Traditionally, the definition of the condition was based on the rule of three, that is, unexplained episodes of paroxysmal 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. It refers to a clinical condition of fussing and crying for at least one week in an otherwise healthy infant (Hyman 2006). Rome III includes infantile colic, with diagnostic criteria including all of the following in infants from birth to four months of age: 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 and of itself.

The incidence of colic is estimated to be between 10% and 30% of infants born (Clifford 2002; Rosen 2007). Paroxysms of inconsolable crying are often accompanied by flushing of the face, meteorism (excessive flatulence in the intestinal tract with distention of the abdomen), drawing up of the legs, and flatulence (Savino 2010). Symptoms have historically typically started in the second week of life in both breast-fed and formula-fed infants and resolved 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 should not be encouraged (Savino 2007). However, about 5% of colicky crying infants do have a serious, underlying medical

problem (Freedman 2009; Savino 2005; Savino 2007), and there is evidence that older children presenting with migraine are more likely to have been babies who have suffered colic (Romanello 2013). Therefore, all colicky infants should undergo a complete medical assessment in order to exclude underlying medical conditions which require investigation and treatment (Savino 2010).

The etiopathogenesis of infantile colic as a symptom remains undefined and is most likely multifactorial. Despite the common nature of the condition, and the large amount of research investigating this area, there have been no breakthroughs in terms of the real mechanisms underlying infant colic.

It has been suggested that a number of behavioural factors (psychological and social) and biological components (food hypersensitivity, allergy, gut microflora, bloating from trapped gas and dysmotility) can contribute to its manifestation (Gupta 2007). These include the following.

First, lactose intolerance - due to a relative lactase deficiency - has been identified as a possible causative factor in infant colic. 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. 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 1998).

Second, the immunological model, which focuses on possible allergens, has been suggested as a cause of colic. A key allergen is cows' milk proteins in breast milk or infant formula. Intact proteins from the mother's diet can sometimes cross over into the breast milk and provoke an allergic response and symptoms of colic in her infants. Consequently, a low-allergen maternal diet, or hypoallergenic infant formula (Iacovou 2012), has been proposed as a form of treatment (Hill 2005; Schach 2002). The possibility that infantile colic could be related to allergens was first described by Shannon 1921. 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 of 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 the first therapeutic approach (Gupta 2007; Hall 2012 ; Savino 2010). Indeed, dietary changes, such as eliminating cows' milk proteins, 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, and colic associated with other gastrointestinal symptoms such as vomiting or diarrhoea) (Hill 1995; Hill 2005; Jakobsson 1983; Lucassen 2000; Savino 2014). However, UpToDate 2016 grades the introduction of hydrolysate formula for formula-fed infants or hypoallergenic diet for mothers of breast-fed infants as a "2C": "a very weak recommendation; other alternatives may be equally reasonable"; "benefits and risks may be finely balanced, or the benefits and risks may be uncertain" and "the evidence comes from observational studies, unsystematic clinical experience, or from randomised, controlled trials with serious flaws". A Cochrane review is underway to firm up the evidence (Savino 2014).

Third, there is growing evidence that the intestinal microbiota in colicky infants differ from those in non-colicky controls, since higher levels of anaerobic bacteria, such as coliform and *Escherichia coli*, microaerophilic bacteria, such as *Helicobacter pylori* (Ali 2012), and a lower concentration of *Lactobacilli* have been reported in infants with colic (Savino 2010). Human milk naturally contains these prebiotics; they are defined as indigestible oligosaccharides that 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 breast feeding on the development of colic in breast-fed infants (Clifford 2002), however, it is unclear if these studies compared exclusively breast-fed-from-birth infants with exclusively artificially-fed-from-birth infants, and so it is still not known whether any breastfeeding has some protective effect or whether any artificial feeding compromises the infant gut microbiome in some way. Evidence 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). Microbiota diversity is significantly lower in colicky infants and seems to decrease after birth rather than being that way from birth (de Weerth 2013). Evidence is building around the effectiveness of supplementing the infant's diet with probiotics to prevent colic and other symptoms (Oozeer 2013).

These three pathophysiological models indicate implicit treatment modalities, however, various therapeutic interventions have been used for infant colic that take a symptom-reduction, focused approach. These include pain relief (Savino 2002; Savino 2012); probiotic supplementation (Indiro 2014); complementary and alternative medicines and nutritional supplements such as fennel extract (Harb 2015) and chamomile (Perry 2011); sucrose and glucose solutions (Markestad 1997); and physical treatments such as manipulation (Dobson 2012; Olafdottir 2001), massage and reflexology (Huhtala 2000; Perry 2011). Although systematic reviews have failed to provide evidence of its efficacy in reducing colicky symptoms, by reducing trapped gas in the liquid of the

stomach, simethicone is still often used (Metcalf 1994). Various other physical treatments have been studied to reduce symptoms, including carrying (Barr 1991), which may affect baby in psychological or social ways, or address mechanical aspects such as crib vibration (Huhtala 2000); and acupuncture (Landgren 2010a; Landgren 2010b; Reinthal 2008; Skjeie 2013). Evidence of efficacy is not comprehensive (Garrison 2000).

Description of the intervention

An alternate approach that has been investigated is to focus on training, support and psychologically underpinned interventions for parents of infants with colic.

There is recognition of the role of parental anxiety in the reported incidence of colic and evidence that parental reassurance is successful in reducing reports of distress (Furlong 2012; Hiscock 2014; Taubman 1984; Taubman 1988; Wolfe 1994; Zwi 2011).

Guidance and informal education are often delivered by healthcare professionals to accompany any intervention for infantile colic so that parents and carers may better understand the potential aetiologies and pursue various management and treatment options (see, for example, Cook 2012). Parental behavioural modifications have often been suggested both for breast-fed and formula-fed infants, including advice to carry the infant (Barr 1991), not to carry the infant (McKenzie 1991), and to try to understand the infant's needs (Taubman 1984).

Whilst there have been some attempts to synthesise evidence-informed pathways for infantile colic that do include some parental resources, for example, NICE (National Institute for Health and Care Excellence) Clinical Knowledge Summaries, UpToDate Patient Information Tips/health professional information and Map of Medicine, it is well documented that the evidence base is poor and inconclusive. Indeed, NICE CKS 2014 states that their recommendations are pragmatic. There is currently no national or international consensus on best practice for such interventions.

How the intervention might work

Clearly such interventions do not address underlying pathology such as cows' milk protein allergy, gastro-oesophageal reflux, etc. However, there is a substantial infant population suffering from colic with no clear identifiable cause, who are known to have a natural history that will lead to symptom reduction by six months of age (Parkin 1993; St James-Roberts 1991). Parents have little firm idea of what will and what will not work (Oshikoya 2009), and so they try lots of potential solutions with variable results, which is extremely stressful for both baby and parents.

Many parent training programmes are focused on reassurance of the natural symptom reduction in time and explanation of some soothing strategies to reduce parental anxiety. This is believed to be important as parental anxiety can, in turn, reduce effectiveness of soothing strategies and increase the perceived impact of symptoms. Additionally, they seek to offer education on such soothing strategies or on understanding baby's potential needs in a manner that is consistent and in line with best practice to reduce conflicting messages, and offer a source of information that is not readily available to parents: baby often needs soothing or comfort rather than more feed, different feed, medicating, etc., and parents should be aware of the stress of a crying baby and seek to soothe themselves to avoid harming the child (Bryanton 2013; Chandran 2014; Levy 2015; Reijneveld 2001; Schmitt 1987). This combination of reassurance as to the natural history of symptom resolution, a consistent single set of messages regarding management advice, and explanation that a less anxious parent can reduce colic in the infant, will have two actions. First, it will ensure the infant gets the most appropriate soothing techniques in a consistent manner to reduce their symptoms. Second, it will reduce anxiety in parents, enhancing their satisfaction, quality of life and potentially improving their ability to deliver the soothing strategies.

Why it is important to do this review

There is no clarity as to the extent these components contribute to the overall efficacy of symptom reduction strategies or to parental anxiety levels. Some interventions have been ineffective such as the McRury 2010 study based on techniques found in a popular parenting book - *The Happiest Baby* - by Karp 2003. Given the clinical and methodological heterogeneity of studies on these interventions, the efficacy of these interventions in reducing infant colic remains inconclusive, at present.

Established studies and reports may now be outdated (e.g. Schmitt 1987; Taubman 1984), and more recent reported approaches are based on different approaches (e.g. Hiscock 2014 is based on an intervention described in Cook 2012; Keefe 2005), and so an up-to-date systematic review using Cochrane methodology is required.

It is also important to note that focus within the published body of work often seeks to assess 'whether' such training is effective (e.g. Hiscock 2014), and this can be considered of limited educational research value (Norcini 2011). This is important as, in this context, the intervention being considered is educational, and if this cannot be defined, it cannot be reliably and validly reproduced and disseminated in a systematic fashion. Therefore, equally relevant questions are 'how' it achieves this outcome, 'why' the teaching is effective and 'for whom and when' such training can be effective. A review and synthesis of the evidence must also address these items and, from an educational stance, identify a relevant theory from this evidence base (Haji 2013). This will support future professionals in understanding and delivering such an intervention in a reliable and reproducible manner. Even if such data are not explicit within primary studies, synthesis can highlight such outcomes, as has been increasingly shown in the field of health education (Gordon 2011; Gordon 2013).

This review sets out to consider the effectiveness of parent training programmes (when compared to other interventions), the safety of such programmes, and to identify the content and attributes underpinning such programmes.

OBJECTIVES

1. To evaluate the effectiveness and safety of parent training programmes for managing colic in infants under four months of age.

2. To identify the educational content and attributes of such published programmes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

Infants younger than four months of age who are already suffering from infantile colic as defined by the study, for example, Rome III (Mostafa 2008) or Wessel (Wessel 1954). Both breast-fed and formula-fed infants will be eligible.

Types of interventions

Any form of parental training programmes, alone or in combination, versus another intervention(s) or placebo. Examples of programme content may include:

1. normalisation material in any form;
2. soothing techniques; and
3. feeding management advice.

In the teaching forms of:

1. face-to-face courses;
2. online and e-learning;
3. printed materials;
4. home visits and coaching; and
5. remote support and counselling.

Types of outcome measures

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

Primary outcomes

1. A reduction in the duration of crying (post-treatment versus baseline). Data may be continuous (e.g. hours per day), or dichotomous (e.g. reduction under a predefined threshold, as determined by the trial authors).
2. Adverse effects, including parental depression and mental illness, choking, apparent life-threatening events (dichotomous outcome).

Secondary outcomes

1. The number of responders in each group after treatment: reduction in frequency of crying episodes per 24 hours (post-treatment versus baseline) (dichotomous outcome, as defined by the primary studies).
2. Parental or family quality of life, including measures of parental stress, anxiety or depression, as proposed by the primary studies and so no single scale may be possible (continuous outcome).
3. Infant sleep duration per 24 hours at seven, 14, and 21 days (post-treatment versus baseline) (continuous outcome).

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 Cochrane Developmental, Psychosocial and Learning Problems Specialised Register;
2. MEDLINE Ovid (1946 to date);
3. MEDLINE In-Process and Other Non-Indexed Citations Ovid (current issue);
4. MEDLINE Epub Ahead of Print Ovid (current issue);
5. Embase Ovid (1980 to date);
6. CINAHL Plus EBSCOhost (Cumulative Index to Nursing and Allied Health Literature; 1937 to date);
7. PsycINFO Ovid (1967 to date);
8. Science Citation Index - Expanded Web of Science (SCI; 1970 to date);

9. Social Sciences Citation Index Web of Science (SSCI; 1970 to date);
10. Conference Proceedings Citation Index - Science Web of Science (CPCI-S; 1990 to date);
11. Conference Proceedings Citation Index - Social Science and Humanities Web of Science (CPCI-SSH; 1990 to date);
12. LILACS (Latin American and Caribbean Health Science Information database; lilacs.bvsalud.org/en);
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; epistemonikos.org);
16. WorldCat (limited to theses; worldcat.org);
17. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov); and
18. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; apps.who.int/trialsearch).

We will search MEDLINE using the search strategy in Appendix 1, which uses the sensitivity maximizing version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2008). We will adapt this strategy for other databases. We will not impose any date or language restrictions. Studies published in languages other than English will be professionally translated in full.

Searching other resources

Grey literature

To assess more contemporaneous studies that have not yet been published in full, we will handsearch abstracts presented at relevant international meetings, including the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), published from 2010 onwards. 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 sufficient data are presented to judge inclusion and assess quality. Where such data are not presented, we will attempt to contact authors for more information, and meanwhile will place the studies in 'Awaiting classification'.

Reference searching

We will inspect the references of included studies for more trials. We will search the bibliographies of included studies to identify any other potentially relevant articles.

Personal contacts

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

Data collection and analysis

Selection of studies

Two review authors (Morris Gordon (MG) and Shel Banks (SB)) 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:

1. merge search results using reference management software and remove duplicate records of the same report;
2. examine titles and abstracts to remove irrelevant records;
3. retrieve full texts of potentially relevant reports;
4. link together multiple reports of the same study;
5. examine full-text reports for studies that 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 reports on a study flow spreadsheet, resolving any disagreements through consensus;
8. make final decisions on study inclusions 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 information described below.

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 (breast feeding, formula feeding), age at onset of colic, age at commencement of intervention, and evaluation of potential effect modifiers (e.g. age, gender).
2. Characeristics of intervention: content of training, pedagogical methods employed, context, resources and educator details, any theoretical underpinning described.
3. Interventions and controls: number of groups, intervention(s) applied, frequency and duration of treatment, total number of treatments, permitted cointerventions.

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

5. Outcomes: list of 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).

6. 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.

7. Other: references to other relevant studies, points to follow up with authors, comments from the authors, key conclusions from the study (by the authors), other comments from review authors.

Two review authors (MG and SB) will extract the data independently using the data extraction form. A third review author (Megan R Thomas (MRT)) will resolve any disagreements. We will collate data in the latest version of Review Manager 2014.

Assessment of risk of bias in included studies

Two review authors (MG and SB) will independently evaluate each study for risk of bias using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011; Higgins 2011b) 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 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. We will complete a 'Risk of bias' table for each included study and present the 'Risk of bias' summary graphically.

Sequence generation

We will include only RCTs or quasi-RCTs in this review. We will assess randomisation as being at low risk of bias if the procedure of sequence generation was explicitly described to confirm it was random; 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 to be at 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 centralized randomisation, numbered or coded containers, or sealed envelopes. Procedures considered to have a high risk of bias include alternation or reference to case record numbers or dates of birth. We will also assign a high risk of bias if allocation concealment did not occur, as intervention allocations could have been foreseen and thus introduced potential bias. If no description is given, we will contact the study authors and if no response is received, 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 and so, in effect, they will be considered 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 as to which intervention they, on behalf of the infant, received.

Blinding of outcome assessment

We will describe, for each included study, 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 were blinded or if we consider that the lack of blinding could not have affected the results. If blinding was not done, or not possible due to the nature of 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 if:

1. participants included in the analysis are exactly those who were randomised into the trial, if 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. 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. for continuous outcome data, the plausible effect size (standardized mean differences (SMD)) among missing outcomes is not sufficient to have a clinically relevant impact on observed effect size; or

4. missing data have been imputed using appropriate methods.

We will assign a judgment of high risk of bias when:

1. 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. for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is sufficient to induce clinically relevant bias in the intervention effect estimate;

3. 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. an 'as-treated' analysis is carried out in cases where there is substantial departure of the intervention received from that assigned at randomisation;

5. there is a potentially inappropriate application of simple imputation; or

6. the dropout rate is reported as higher than 20%, since there is evidence that dropout rates higher than 20% are likely to increase bias in treatment estimates (Unnebrink 2001; Wright 2003).

We will assign a judgment of unclear risk of bias when:

1. there is insufficient reporting of attrition or exclusions, or both, to permit a judgment of low or high risk of bias;

2. the study reported incomplete outcome data; or

3. the numbers randomised to intervention and control groups are not clearly reported.

Selective outcome reporting

We will assess the reporting of outcomes as being at low risk of bias if all the study outcomes declared in the methods section have been reported in the results. We will also evaluate whether different reports of the study are available, including protocols, and examine them to ensure there is no suggestion of selective outcome reporting. If no description is given, we will contact the authors for more information and if no response is received, we will assign a judgment of unclear risk of bias. If there is evidence of selective reporting (such as a significant departure from the protocol or key outcomes that were due to be investigated are 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, we will assess it as being at high risk of bias. For instance, if it was stopped early due to a data-dependent process, having a baseline imbalance between the groups, or 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 published information, we will attempt to contact 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 dichotomous data with their associated 95% CI and probabilities of control and treatment groups (where possible).

Continuous data

If all studies use the same measurement scale, we will calculate mean differences (MD) for change scores. Where studies use different scales, we will calculate the SMD using Hedges' (adjusted)*g*. If necessary, we will calculate effect estimates from P values, t-statistic, analysis of variance (ANOVA) tables, or other statistics as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

For this analysis we will use, according to need, either change scores or final values, without combining them: we will not combine these two different indices in meta-analysis and will only meta-analyse homogeneous data sets.

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 the underlying continuous measure has approximately a normal or logistic distribution (otherwise we will carry out two separate analyses).

Unit of analysis issues

Cluster-randomised trials

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 'units' that were randomised (Deeks 2011)). It is unlikely that we will find cluster-randomised trials because this design is uncommon in this field. However, if we do, 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). When the ICC cannot be used, we will use values available in the published literature as an

external source, when available, as well as contacting the author to supply more data to allow an estimate of the ICC to be calculated (Campbell 2000).

Studies with multiple treatment arms

In the primary analysis, we will combine results across all eligible intervention arms (parent training programmes, i.e. courses or written materials), 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 programme 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 Review Manager 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, and this is of particular concern given the educational nature of the interventions being assessed. For this review, we will not include any data in cross-over studies after the first treatment period.

Qualitative analysis

For qualitative outcomes, we will avoid making a priori hypotheses and conclusions, in keeping with a grounded theory approach. Following collection and processing, two review authors (MG and SB) will code the data using Nvivo 2015. An initial thematic index will be developed, with the addition of emerging thematic categories according to interpretation of the content of the data. The analysis will proceed through three stages consisting of open, axial and selective coding, with constant comparison taking place throughout each phase. Each stage will provide categories that could be used to explore the themes of the data and build an interpretation that can address the overarching research questions. To clarify, as per the section on Types of outcome measures above, studies that are qualitative reports of parent training programmes, with no quantitative assessment, will not be included. Rather, extraction and synthesis of qualitative data of the intervention itself will be performed.

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 statistics (missing SDs), 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 make no assumptions about loss to follow-up for continuous data, and we will base analyses on those participants completing the trial. 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. Where 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 (e.g. age) and trial characteristics (e.g. randomisation, concealment, blinding of outcome assessment, losses to follow-up, treatment type, cointerventions). 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; or
4. 75% to 100%: suggests considerable heterogeneity.

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 report Tau^2.

Once data have been extracted, clinical and methodological heterogeneity will be judged by discussion between authors (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

In order to minimize 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 correspondence).

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).

Data synthesis

Where interventions are similar in type of parental training programme and type of outcome assessed, we plan to group the studies and synthesize their results in a meta-analysis. We will present results for each combination of parental training programme, assessed outcome and colic type, with the exception of those studies for which no data are observed. For instance, if two or more studies assess the effects of a parental training programme for parents of otherwise healthy children with colic and both measure the 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 evidence of statistical heterogeneity. We will calculate all overall effects using inverse variance methods. We will carry out statistical analysis using Review Manager 2014. Where data are insufficient to allow meta-analysis or qualitative analysis, we will provide a narrative synthesis and descriptive summary of the study outcomes.

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. However, we remain vigilant and if a risk is perceived upon evaluation of our findings, a sensitivity analysis removing such trials to provide more definite findings may be required.

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:

1. type of feeding (bottle-fed versus breast-fed);
2. short-term and long-term follow-up (four weeks or less versus more than four weeks of treatment);
3. type of parental training (face-to-face versus distance or written materials); and
4. crying time in consideration with infant's age.

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

Sensitivity analysis

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

1. trials with low levels of potential bias versus trials with high levels of potential bias;
2. missing information or missing results (using 20% attrition as 'high risk' of bias, see above);
3. 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-recognized definition; and
4. the choice of model used, by comparing results from the random-effects model, which we are using, with those from the fixed-effects model.

Presentation of main results

We will assess the overall quality of evidence using the GRADE approach (Guyatt 2008). We will present the results of our assessment in a 'Summary of findings' table, per comparison, created using GRADEpro GDT software (GRADEpro GDT 2014). The comparisons used will be those outlined in the studies, and so may be another intervention(s) or placebo. Our table will include information on the type of participants, the interventions and comparisons used in each case, and the outcomes and their measurements for each study, as well as the setting and the length of follow-up. 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. Intention-to-treat data would be of better quality than per protocol results. Two review authors (SB and MG) will independently assess and agree the overall quality of the evidence for each outcome after considering each of these factors, and will grade them as:

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 include any rationale for the downgrading of the quality of the evidence in the footnotes of the table

We will take the assumed risk from the median of the risk in the control groups amongst included studies. We will use the following outcomes:

1. a reduction in the duration of crying (post-treatment versus baseline);
2. adverse effects, including parental depression and mental illness, choking, apparent life-threatening events;

3. the number of responders in each group after treatment: reduction in frequency of crying episodes per 24 hours (post-treatment versus baseline);

4. parental or family quality of life, including measures of parental stress, anxiety or depression, as proposed by the primary studies and so no single scale may be possible; and

5. infant sleep duration per 24 hours at seven, 14, and 21 days (post-treatment versus baseline).

ACKNOWLEDGEMENTS

We would like to acknowledge the editor for their helpful comments on earlier versions of this protocol, and 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, Weinz 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 Homeostatic Agents* 2012;**26**(3 Suppl):49–59. [PUBMED: 23158515]

Axelsson 1986

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

Barr 1991

Barr RG, McMullan SJ, Spiess H, Leduc DG, Yaremko J, Barfield R, et al. Carrying as colic "therapy": a randomized controlled trial. *Pediatrics* 1991;**87**(5):623–30. [PUBMED: 2020506]

Bryanton 2013

Bryanton J, Beck CT, Montelpare W. Postnatal parental education for optimizing infant general health and parent-infant relationships. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: 10.1002/14651858.CD004068.pub4; PUBMED: 24284872]

Campbell 1989

Campbell JP. Dietary treatment of infant colic: a double-blind study. *British Journal of General Practice* 1989;**39**(318):11–4. [PMC1711543; 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]

Chandran 2014

Chandran A, Zhu J, Paul IM, Kjerulff KH. Infant colic in relation to maternal social support, partner involvement in caring for newborn, and happiness of the mother partner relationship. *Journal of Pediatric Gastroenterology and Nutrition* 2014;**59**(2 Suppl):S51. [journals.lww.com/jpgn/Documents/NASPGHAN%202014%20abstracts.pdf]

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]

Cook 2012

Cook F, Bayer J, Le HND, Mensah F, Cann W, Hiscock H. Baby Business: a randomised controlled trial of a universal parenting program that aims to prevent early infant sleep and cry problems and associated parental depression. *BMC Pediatrics* 2012;**12**(13):1–10. [DOI: 10.1186/1471-2431-12-13]

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; PUBMED: 23319531]

Deeks 2011

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 9: Analysing data and undertaking meta-analyses. 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.

Dobson 2012

Dobson D, Lucassen PL, Miller JJ, Vlieger AM, Prescott P, Lewith G. Manipulative therapies for infantile colic. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD004796.pub2; PUBMED: 23235617]

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]

Furlong 2012
Furlong M, McGilloway S, Bywater T, Hutchings J, Smith SM, Donnelly M. Behavioural and cognitive-behavioural group-based parenting programmes for early-onset conduct problems in children aged 3 to 12 years. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD008225.pub2; PUBMED: 22336837]

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

Gordon 2011
Gordon M, Findley R. Educational interventions to improve handover in health care: a systematic review. *Medical Education* 2011;**45**(11):1081–9. [DOI: 10.1111/j.1365-2923.2011.04049.x; PUBMED: 21933243]

Gordon 2012
Gordon M, Harper V, Thomas AG, Akobeng AK. Bowel Preparation for Paediatric Colonoscopy. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD009976]

Gordon 2013
Gordon M. Non-technical skills training to enhance patient safety. *Clinical Teacher* 2013;**10**(3):170–5. [DOI: 10.1111/j.1743-498X.2012.00640.x; PUBMED: 23656679]

GRADEpro GDT 2014 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 30 December 2015. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

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, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendation. *BMJ* 2008;**336**(7650):924–6. [DOI: 10.1136/bmj.39489.470347.AD; PMC2335261; PUBMED: 18436948]

Haji 2013
Haji F, Morin MP, Parker K. Rethinking programme evaluation in health professions education: beyond 'did it work?'. *Medical Education* 2013;**47**(4):342–51. [DOI: 10.1111/medu.12091; PUBMED: 23488754]

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]

Harb 2015
Harb T, Matsuyama M, David M, Hill RJ. Infant colic - what works: a systematic review of interventions for breast-fed infants. Journal of Pediatric Gastroenterology and Nutrition 2016; Vol. 62, issue 5:668–86. [DOI: 10.1097/MPG.0000000000001075; PUBMED: 26655941]

Heine 2013
Heine RG. Cow's-milk allergy and lactose malabsorption in infants with colic. *Journal of Pediatric Gastroenterology and Nutrition* 2013;**57**(Supplement 1):25–7. [DOI: 10.1097/01.mpg.0000441930.13307.9b]

Heine 2014
Heine RG, Hill DJ. 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 (UK): John Wiley & Sons Ltd, 2014:171–81.

Higgins 2011a
Higgins JP, Deeks JJ, editor(s). 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 JP, Deeks JJ, Altman DG, editor(s). 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. [PUBMED: 8543745]

Hill 2000
Hill DJ, Hosking CS. Infantile colic and food hypersensitivity. *Journal of Pediatric Gastroenterology and Nutrition* 2000;**30**(1 Suppl):67–76. [DOI: 10.1097/00005176-200001001-00011; 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]

Hiscock 2014
Hiscock H, Cook F, Bayer J, Le HND, Mensah F, Cann W, et al. Preventing early infant sleep and crying problems and postnatal depression: a randomized trial. *Pediatrics* 2014;**133**(2):e346–54. [DOI: 10.1542/peds.2013-1886; PUBMED: 24394682]

Huhtala 2000
Huhtala V, Lehtonen L, Heinonen R, Korvenranta H. Infant massage compared with crib vibrator in the treatment of colicky infants. *Peditatrics* 2000;**105**(6):e84. [PUBMED: 10835097]

Hyams 1989
Hyams JS, Geertsma MA, Etienne NL, Treem WR. Colonic hydrogen production in infants with colic. *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]

Indiro 2014
Indiro 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. [PUBMED: 6823433]

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]

Karp 2003
Karp H. *The Happiest Baby on the Block*. New York: Bantam Dell, 2003.

Keefe 2005
Keefe MR, Barbosa GA, Froese-Fretz A, Kotzer AM, Lobo M. An intervention program for families with irritable infants. *MCN, The American Journal of Maternal/Child Nursing* 2005;**30**(4):230–6. [PUBMED: 16000966]

Landgren 2010a
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]

Landgren 2010b
Landgren K, Kvorning N, Hallström I. Acupuncture reduces crying in infants with infantile colic: a randomised, controlled, blind clinical study. *Acupuncture in Medicine* 2010;**28**(4):174-9. [DOI: 10.1136/aim.2010.002394; PMC3002757; PUBMED: 20959312]

Lefebvre 2008
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.

Levy 2015
Levy RL, van Tilburg MA, Langer S, Romano J, Mancl LA, Feld SI. Parent-only intervention reduces symptoms and disability in abdominal pain patients. *Gastroenterology* 2016;**150**(4 Suppl 1):S100. [DOI: 10.1016/S0016-5085(16)30444-9]

Lindberg 1999
Lindberg T. Infantile colic and small intestinal function: a nutritional problem?. *Acta Paediatrica. Supplement* 1999;**88**(430):58–60. [PUBMED: 10569224]

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]

Map of Medicine

Map of Medicine: infantile colic. app.mapofmedicine.com/mom/1/page.html?department-id=6&specialty-id=1031&pathway-id=3225&page-id=7947&history=clear (accessed 30 December 2015).

Markestad 1997

Markestad T. Use of sucrose as a treatment for infant colic. *Archives of Disease in Childhood* 1997;**76**(4):356–8. [DOI: 10.1136/adc.76.4.356]

McKenzie 1991

McKenzie S. Troublesome crying in infants: effect of advice to reduce stimulation. *Archives of Disease in Childhood* 1991; **66**(12):1416–20. [PMC1793390; PUBMED: 1776889]

McRury 2010

McRury JM, Zolotor AJ. A randomized, controlled trial of a behavioral intervention to reduce crying among infants. *Journal of the American Board of Family Medicine* 2010; **23**(3):315–22. [DOI: 10.3122/jabfm.2010.03.090142; PUBMED: 20453177]

Merras-Salmio 2013

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

Metcalf 1994

Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics* 1994;**94**(1):29–34. [PUBMED: 8008533]

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; PUBMED: 2317079]

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 1998

Moore DJ, Robb TA, Davidson GP. Breath hydrogen response to milk containing lactose in colicky and noncolicky infants. *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):2124–5. [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]

NICE CKS 2014

NICE Clinical Knowledge Summary. Colic - infantile. cks.nice.org.uk/colic-infantile (accessed 30 December 2015).

Norcini 2011

Norcini J, Anderson B, Bollela V, Burch V, Costa MJ, Duvivier R, et al. Criteria for good assessment: consensus statement and recommendations from the Ottawa 2010 Conference. *Medical Teacher* 2011;**33**(3):206–14. [DOI: 10.3109/0142159X.2011.551559; PUBMED: 21345060]

Nvivo 2015 [Computer program]

QSR International Pty Ltd. Nvivo 11 for Windows. Version 11. Doncaster, Australia: QSR International Pty Ltd, 2015.

Olafdottir 2001

Olafdottir E, Forshei S, Fluge G, Markestad T. Randomised controlled trial of infantile colic treated with chiropractic spinal manipulation. *Archives of Disease in Childhood* 2001; **84**(2):138–41. [PMC1718650; PUBMED: 11159288]

Oozeer 2013

Oozeer R, van Limpt K, Ludwig T, Amor KB, Martin R, Wind RD, et al. Intestinal microbiology in early life: specific prebiotics can have similar functionalities as human-milk oligosaccharides. *American Journal of Clinical Nutrition* 2013;**98**(2):561S–71S. [DOI: 10.3945/ajcn.112.038893; PUBMED: 23824728]

Oshikoya 2009

Oshikoya KA, Senbanjo IO, Njokanma OF. Self-medication for infants with colic in Lagos, Nigeria. *BMC Pediatrics* 2009;**9**(9):1–8. [DOI: 10.1186/1471-2431-9-9; PMC2645392; PUBMED: 19193235]

Oxman 1992

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

Parkin 1993

Parkin PC, Schwartz CJ, Manuel BA. Randomized controlled trial of three interventions in the management of persistent crying of infancy. *Pediatrics* 1993;**92**(2):197–201. [PUBMED: 8337017]

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]

Reijneveld 2001

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

Reinthal 2008
Reinthal M, Andersson S, Gustafsson M, Plos K, Lund I, Lundeberg T, et al. Effects of minimal acupuncture in children with infantile colic - a prospective, quasi-randomised single blind controlled trial. *Acupuncture in Medicine* 2008;**26**(3):171–82. [PUBMED: 18818563]

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

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. *Pediatrics in Review* 2007;**28**(10):381–5. [DOI: 10.1542/pir.28-10-381; PUBMED: 17908860]

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 Pediatric Gastroentrology 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 2002
Savino F, Brondello C, Cresi F, Oggero R, Silvestro L. Cimetropium bromide in the treatment of crisis in infantile colic. *Journal of Pediatric Gastroenterology and Nutrition* 2002;**34**(4):417–9. [PUBMED: 11930101]

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 2007
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 2010
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 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 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; PUBMED: 11845737]

Schmitt 1987
Schmitt BD. Seven deadly sins of childhood: advising parents about difficult developmental phases. *Child Abuse & Neglect* 1987;**11**(3):421–32. [PUBMED: 3479226]

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.

Skjeie 2013
Skjeie H, Skonnord T, Fetveit A, Brekke M. Acupuncture for infantile colic: a blinding-validated, randomized controlled multicentre trial in general practice. *Scandinavian Journal of Primary Health Care* 2013;**31**(4):190–6. [DOI: 10.3109/02813432.2013.862915; DOI: PMC3860294]

St James-Roberts 1991
St James-Roberts I, Halil T. Infant crying patterns in the first year: normal community and clinical findings. *Journal of Child Psychology and Psychiatry and Allied Disciplines* 1991;**32**(6):951–68. [PUBMED: 1744198]

Sterne 2011
Sterne JAC, Egger M, Moher D, editor(s). 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.

Taubman 1984
Taubman B. Clinical trial of the treatment of colic by modification of parent-infant interaction. *Pediatrics* 1984; **74**(6):998–1003. [PUBMED: 6390331]

Taubman 1988
Taubman B. Parental counseling compared with elimination of cow's milk or soy milk protein for the treatment of infant colic syndrome: a randomized trial. *Pediatrics* 1988;**81**(6): 756–61. [PUBMED: 3285312]

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]

Unnebrink 2001
Unnebrink K, Windeler J. Intention-to-treat: methods for dealing with missing values in clinical trials of progressively deteriorating diseases. *Statistics in Medicine* 2001;**20**(24): 3931–46. [PUBMED: 11782044]

UpToDate 2016
Turner TL, Palamountain S. Infantile colic: management and outcome. www.uptodate.com/contents/infantile-colic-management-and-outcome (accessed 30 December 2015).

UpToDate Patient Information Tips
UpToDate. Tips for reducing colic. www.uptodate.com/contents/image?imageKey=PI/69458&topicKey=PI%2F15897&utdPopup=true (accessed 30 December 2015).

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]

Wolfe 1994
Wolfe D, Gray P, Meyer R. Excessive infant crying: a controlled study of mothers helping mothers. *Pediatrics* 1994;**94**(3):322–32. [PUBMED: 8065857]

Wright 2003
Wright CC, Sim J. Intention-to-treat approach to data from randomized controlled trials: a sensitivity analysis. *Journal of Clinical Epidemiology* 2003;**56**(9):833–42. [PUBMED: 14505767]

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]

Zwi 2011
Zwi M, Jones, H, Thorgaard C, York A, Dennis JA. Parent training interventions for Attention Deficit Hyperactivity Disorder (ADHD) in children aged 5 to 18 years. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD003018.pub3; PUBMED: 22161373]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. 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$)).tw.
5 crying/
6 (cry or crying or cries).tw.
7 or/1-6
8 exp Infant/
9 (baby or babies or infant$ or child$ or newborn$ or neonat$).tw.
10 or/8-9
11 7 and 10
12 exp Parents/
13 Parenting/
14 exp Parent-Child Relations/
15 family relations/
16 exp maternal behavior/
17 maternal deprivation/
18 paternal behavior/

19 paternal deprivation/
20 (parent$ or mother$ or father$ or maternal$ or paternal$ or famil$).tw.
21 or/12-20
22 Health Education/
23 education/
24 teaching/
25 (class$ or coach$ or counsel$ or curricul$ or educat$ or group$ or intervention$ or learn$ or package$ or program$ or support$ or teach$ or train$).tw.
26 or/22-25
27 21 and 26
28 exp Parents/ed [Education]
29 ((home$ or nurse$ or famil$ or mother$ or parent$ or father$) adj2 visit$).tw.
30 or/27-29
31 11 and 30
32 randomized controlled trial.pt.
33 controlled clinical trial.pt.
34 randomi#ed.ab.
35 placebo$.ab.
36 drug therapy.fs.
37 randomly.ab.
38 trial.ab.
39 groups.ab.
40 or/32-39
41 exp animals/ not humans.sh.
42 40 not 41
43 31 and 42

CONTRIBUTIONS OF AUTHORS

Shel Banks and Morris Gordon wrote the protocol. Megan R Thomas reviewed the protocol and is lead author. Chris Wallace reviewed the protocol. Morris Gordon has overall responsibility for managing the review.

DECLARATIONS OF INTEREST

Megan R Thomas - none known.

Morris Gordon (MG) - has received travel grants in the last three years from Ferring Pharmaceuticals and Biogaia to attend scientific meetings to present the results of previous and ongoing Cochrane systematic reviews on probiotics amongst other therapies. These companies have had no involvement in this or any other research or synthesis project by MG in terms of conception, planning, design, carrying out or writing up works. They have had no editorial input or control in this or any other previous works by MG. MG has received travel grants from Ferring Pharmaceuticals, Vifor Pharma, Danone/Nutricia, Abbott and Tillots Pharma AG to attend meetings to present 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. MG declares that whilst Ferring and Biogaia produce products that can be used for colic, from the author team's scope of the literature they do not expect these to be used in any of the trials in this review. MG also declares that Danone/Nutricia produce formulas that may be competing treatments for colic in this review, but Abbott, Tillots and Vifor have no products of interest. MG has had involvement as an author on Cochrane reviews, including 'Bowel preparation for paediatric colonoscopy' (Gordon 2012) and 'Probiotics for maintenance of remission in ulcerative colitis' (Naidoo 2011). MG is a Paediatrician with an interest in gastroenterology. This involves seeing patients referred with infantile colic and managing them in line with current accepted evidence-based practice.

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) - providing syntheses of evidence-based information on infant feeding topics for health professionals. SSCB works as a Consultant for LIFIB and the Sudden Unexpected Death of a Child Prevention Team. Until March 2016, this post was funded by money from the local authority via Breastfeeding Network and SSCB was paid by the hour. SSCB also works as an Internationally Board Certified Lactation Consultant in private practice. SSCB declares that neither she personally nor any of the entities 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 Internationally Board Certified Lactation Consultant.

Chris Wallace (CW) - was involved in a review looking at probiotics as a 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 for travel and accommodation from the Young Investigators Award (YIA) to attend the meeting. Chris has been an author on a Cochrane review entitled probiotics for chronic constipation in childhood, and as a member of ESPGHAN, he applied for a young investigator award to present findings at the annual meeting in 2016. ESPGHAN had no involvement in the project.

SOURCES OF SUPPORT

Internal sources

- Blackpool Teaching Hospitals NHS Foundation Trust, UK.

Blackpool Teaching Hospitals is the employer of all four review authors: Morris Gordon and Megan R Thomas are employed in the medical team for the hospital, Chris Wallace is employed as a Foundation Year 2 Doctor and Shel SC Banks is employed as a Project Manager in infant feeding, with a 12-month sabbatical as Research Assistant to complete this review.
The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of Blackpool Teaching Hospitals NHS Foundation Trust.

External sources

- None, Other.