BMC Pediatrics

RESEARCH ARTICLE Open Access

Probiotics for infantile colic: a systematic review

Jasim Anabrees[1*], Flavia Indrio[2], Bosco Paes[3] and Khalid AlFaleh[4]

Abstract

Background: Infantile colic is a common paediatric condition which causes significant parental distress. Increased intestinal coliform colonization in addition to alteration in Lactobacillus abundance and distribution may play an important role in its pathogenesis.
The objectives of this systematic review are to evaluate the efficacy of probiotic supplementation in the reduction of crying time and successful treatment of infantile colic.

Methods: Literature searches were conducted of MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials. Only randomized controlled trials enrolling term, healthy infants with colic were included. A meta-analysis of included trials was performed utilizing the Cochrane Collaboration methodology.

Results: Three trials that enrolled 220 breastfed infants met inclusion criteria, of which 209 infants were available for analysis. Two of the studies were assessed as good quality. *Lactobacillus reuteri (*strains-American Type Culture Collection Strain 55730 and DSM 17 938) was the only species utilized in the therapeutic intervention. Two of the trials were industry funded. Probiotic supplementation compared to simethicone or placebo significantly and progressively shortened crying times to 7 days reaching a plateau at three weeks post initiation of therapy [mean difference −56.03 minutes; 95% CI (−59.92, -52.15)]. Similarly, probiotics compared to placebo significantly increased the treatment success of infantile colic with a relative risk (RR) of 0.06; 95% CI (0.01, 0.25) and a number needed to treat of 2.

Conclusions: Although *L. reuteri* may be effective as a treatment strategy for crying in exclusively breastfed infants with colic, the evidence supporting probiotic use for the treatment of infant colic or crying in formula-fed infants remains unresolved. Results from larger rigorously designed studies will help draw more definitive conclusions.

Keywords: Infantile colic, Probiotics, Systematic review, Lactobacillus reuteri

Background

Infantile colic is a common problem in healthy thriving infants that is associated with excessive crying over a regular period during the day and is sustained for the first few months of life [1,2]. The condition has been historically described as irritable or compulsive crying or paroxysmal fussing with a multifactorial etiology [3]. Although it affects 5% -19% of young infants, [2,4,5] it remains a frustrating problem for parents and care givers because it is difficult to treat and may result in significant psychosocial consequences. A number of cross sectional studies report significant links between infantile colic and maternal depression and child abuse [6-11].

Despite forty years of research, the etiology of infantile colic remains elusive. The current literature suggests several causative mechanisms such as behavioral, food allergy and hypersensitivity, immaturity of gut function and dysmotility [12-14]. Of note, Shenassa et al. through a comprehensive review of 5 studies identified a possible link between maternal smoking and infantile colic which may be mediated through increased plasma and intestinal motilin levels [15]. Recently, the composition of intestinal microbiota has been addressed as an independent risk factor for infantile colic [16-18]. Studies indicate that inadequate lactobacilli in the first few months of life may affect intestinal fatty acid profile favoring the development of infantile colic [16,17]. Coliform bacteria have also been found more abundantly in colicky infants and it is speculated that altering the intestinal microbiota composition may positively influence the management of affected infants [19]. In practice, the only probiotic used for infantile

* Correspondence: jasim1800@yahoo.com
[1]Neonatal Care, Sulaiman Al Habib Medical Group, Arrayan Hospital, P.O. Box 272069, Riyadh 11352, Saudi Arabia
Full list of author information is available at the end of the article

colic is *Lactobacillus reuteri* (strains-American Type Culture Collection Strain 55730 or DSM 17 938). However, other Lactobacillus species such as *L.delbrueckii* subsp. *delbrueckii* DSM 20074 and *L. plantarum* MB 456 have proven inhibitory activity against gas-forming coliforms and may play a significant role in the management of infantile colic [20]. Similarly, Aloisio et al. evaluated four Bifidobacterium strains, namely, *B. breve* B632 (DSM 24706), B2274 (DSM 24707), B7840 (DSM 24708), and *B. longum* subsp. *longum* B1975 (DSM 24709), and found that they may be potentially useful for the treatment of infantile colic or as a preventive strategy for infantile bacterial-related diarrhea [21]. However, exploratory clinical trials investigating both the safety and efficacy of probiotics incorporating these species are yet to be conducted.

The objectives of this systematic review are to evaluate the efficacy of probiotic supplementation in the reduction of crying time and successful treatment of infantile colic.

Methods

Search strategy

Eligible studies were identified from OVID MEDLINE – National Library of Medicine [January 1966 to September 2012] using the following subject MeSH headings and text word terms: neonate(s), newborn(s), infant(s), probiotics, lactobacillus, bifidobacterium, colic; publication type was limited to controlled trials. No language restriction was applied. Other databases were also searched including: EMBASE (January 1980 to September 2012) the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, Issue 9, 2012). Additional citations were sought using references in articles retrieved from searches. Content experts were contacted to identify unpublished and ongoing studies.

Study selection

We included all randomized or quasi-randomized controlled trials that compared probiotics (any dose or composition) to placebo, control or other forms of treatment in healthy full term infants with infantile colic who were less than 4 months of age. All definitions of infantile colic were deemed acceptable. We considered articles in any language as long as there was an abstract in English indicating content.

Data extraction

Retrieved articles were assessed for eligibility, and two reviewers independently abstracted descriptive data on the subjects, type of intervention, infants allocated as control, outcomes and methodological quality of the articles. Discrepancies were resolved by discussion and consensus. Where data were incomplete, the principal investigator of the primary study was contacted for further information and clarification.

Methodological quality of the studies

Standard methods of the Cochrane Collaboration [22] were used to assess the methodological quality of included trials. For each trial, information was sought regarding the method of randomization, allocation concealment, blinding, and completeness of follow up and on reported outcomes of all infants enrolled in the trial. The methodological details of the studies were extracted from published data and by contacting the primary author where possible.

Data synthesis

The primary outcome was treatment success, defined as the percentage of children who achieved a reduction in the daily average crying time >50%. The secondary outcomes were duration of crying (minutes per day) and adverse events related to probiotic supplementation. For dichotomous outcomes, relative risk (RR) and its associated confidence interval were calculated. For continuous outcomes, treatment effect was expressed as mean difference and its calculated standard deviation. Meta-analysis of pooled data was performed using a fixed effects model with the assumption that L. *reuteri* DSM 17938 and L. *reuteri* ATCC 55730 are bioequivalent and the added recognition that the comparison groups were simethicone (one trial) or placebo (two trials). Review Manager (RevMan), Version 5.2 software was used for statistical analysis. A subgroup analysis was planned a priori to investigate the effect of probiotics in subjects with a positive family history of atopy, and additionally on different strains of probiotics utilized. Heterogeneity was defined as a significant test when the p value was < 0.1 and/or if similar differences were identified in treatment effects across studies. Tests for between-study heterogeneity (including the I^2 test) were performed.

Since included studies expressed their primary outcome (crying times) as median (range or interquartile range), in order to statistically pool the data and perform a meta-analysis, this outcome was converted into mean (standard deviation) as recommended by Hozo et al. [23].

Results

A total of 10 potentially relevant citations were obtained through our primary search strategy (Figure 1). Seven studies were excluded because the investigators used probiotic based formulae in non-colicky neonates, which undermined the primary objectives of the meta-analysis. Three trials met our inclusion criteria [24-26]. Although Szajewska et al. [26] planned an inclusion criterion of infants aged less than five months, the actual maximum age at enrolment was 81 days. Characteristics of the

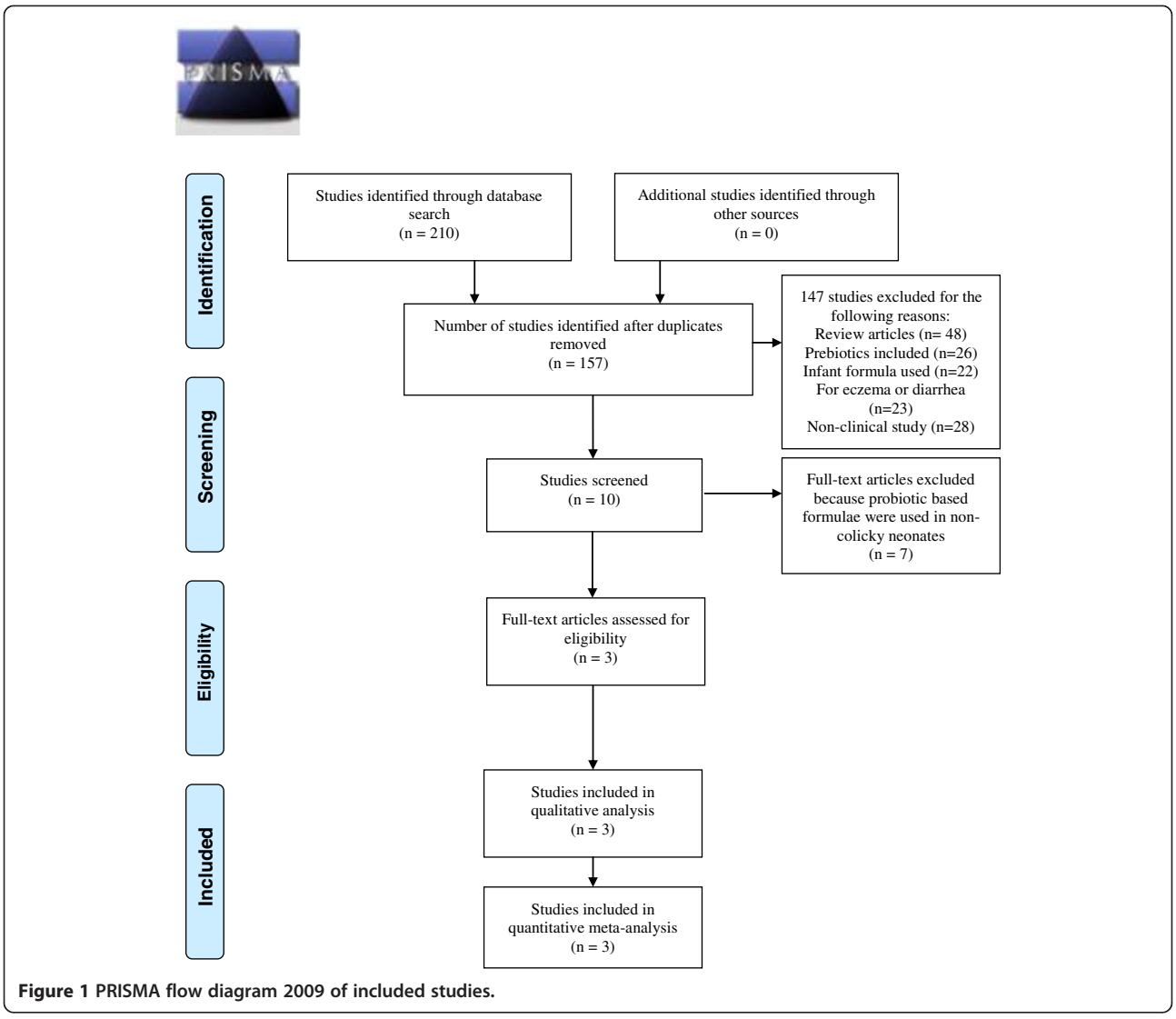

Figure 1 PRISMA flow diagram 2009 of included studies.

included trials are summarized in Table 1. Three ongoing trials are summarized in Table 2, but the data since incomplete were not included in this review.

Overall, 140 infants were exclusively breastfed [24,25] while Szajewska et al. additionally reported that 80 of the infants in their trial were exclusively or predominantly (>50%) breastfed [26]. In general, included trials had a low risk of bias (Table 3). A total of 209 healthy infants were enrolled across the three studies and most of the infants were exclusively breast fed. All of the clinical trials utilized the same probiotic species (*Lactobacillus reuteri; strains-American Type Culture Collection Strain 55730 or DSM 17 938*) with identical daily doses. One study evaluated the efficacy of probiotic supplementation against simethicone [24]. None of the included studies reported any adverse side effects of supplementation.

Effect of L. reuteri on crying time

The effect of L. reuteri on crying time was compared to simethicone or placebo. Data on crying time were reported by all three trials as a primary outcome and involved 209 infants. At seven days after initiation of treatment, infants in the probiotic group had a significantly shorter crying time. The crying time at 7 days was significant only in the fixed effects model, but was insignificant in the random effects model. However, the treatment effect was continuous and stabilized at three weeks following the initiation of therapy. Probiotics decreased crying times by almost one hour [mean difference –56.03 minutes; 95% CI (–59.92, -52.15)] (Figure 2). In order to reduce heterogeneity and the potential effect of simethicone, a sensitivity analysis on only the double-blind, placebo-controlled, trials [24,26] was conducted.

Table 1 Characteristics of trials included in the analysis

Study/year/reference	Description/study design	Birth weight and age at enrolment	Probiotic agent(s)	Dosage and duration	Control arm	Primary outcome
Savino/2007 [24]	April 2004 - May 2005. 90 exclusively breastfed infants with a diagnosis of infantile colic. Recruited in the Department of Pediatric and Adolescence Science (Regina Margherita Children Hospital, Turin, Italy) Open prospective randomized study.	Birth weight 2500-4000 g and aged 21–90 days	*L. reuteri* (American Type Culture Collection Strain 55730)	10^8 colony-forming units in 5 drops for 28 days	Simethicone	A reduction of average crying time to less than 3 hours a day on day 28.
Savino/2010 [25]	March 2008 and August 2009. 50 exclusively breastfed infants were recruited from general pediatricians and outpatients at the Department of Pediatrics, University of Turin (Regina Margherita Children Hospital) A Randomized, Double-Blind, Placebo-Controlled Trial	Birth weight 2500–4000 g and aged 2–16 weeks	*L. reuteri* DSM 17938	10^8 colony-forming units in 5 drops, once a day, 30 minutes before the feed in the morning, for 21 days	Placebo	A reduction of average crying time to less than 3 hours a day on day 21.
Szajewska/2013 [26]	January 2010 and December 2011. 80 exclusively or predominantly (>50%) breastfed infants Family primary care practice in Warsaw, Poland A Randomized, Double-Blind, Placebo-Controlled Trial	Full term infants aged <5 months	*L. reuteri* DSM 17938	10^8 colony-forming units in 5 drops, orally, once a day, for 21 days	Placebo	The percentage of children achieving a reduction in the daily average crying time more than 50% and the duration of crying at 7, 14, 21, and 28 days after randomization.

Colic in all the trials was defined as crying episodes lasting ≥3 hours/day and occurring at least 3 days/week within 7 days prior to enrollment.

Table 2 The ongoing trials of probiotics and infant colic

No	Study	Inclusion and exclusion criteria	Primary outcome	Estimated enrollment	Arms
1	Effect of *L. rhamnosus* GG (LGG) on Infant Colic	Inclusion Criteria: Sixty healthy full-term colicky infants (gestational age 32–41 weeks) Exclusion Criteria: Chronic lung disease, Diarrhea (stools that take the shape of a container > 5x daily) Fever	Crying times of infants	60	Experimental: Nutramigen Lipil with Enflora Control: Nutramigen A + Hypoallergenic formula without lactobacilli
2	Control of Colic in Infants by Dietary Supplementation with the Probiotic *L. reuteri*	Inclusion Criteria: Infants aged between 14–60 days Breast fed, exclusively during length of trial Diagnosis of infantile colic according to Wessel's criteria Debut of colic symptoms 6 ± 1 days before randomization Gestational age between 37–42 weeks Apgar score higher than 7 at 5 minutes Mothers willing to follow a cow milk-free diet during the study period Written informed consent and stated availability throughout the study period Exclusion Criteria: Major chronic disease Gastrointestinal disease but controlled gastroesophageal reflux disease Administration of antibiotics the week before randomization Administration of probiotics the week before randomization Participation in other clinical trials	Reduction of daily average crying time to less than 3 hours from baseline	50	Experimental: *L. reuteri* Control: Not clear
3	Baby Biotics randomised controlled trial	Inclusion criteria Infant colic as defined by the modified Wessel's criteria Less than 3 months Greater than 36 weeks gestation at birth Birth weight of more than 2500 g. Exclusion criteria Failure to thrive Major medical problems Taking solids, antibiotics or *L. reuteri* and, if breastfeeding, mother taking *L. reuteri* at the time of study commencement; Cow's milk protein allergy Caregiver has insufficient English to understand informed consent and complete questionnaires.	Infant crying/fussing time (min/day)	160	Experimental: L. reuteri DSM 17938. Control: maltodextrose

Table 3 The quality and risk of bias in the trials included in the analysis

Study/year/ reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Savino/2007 [24]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Savino/2010 [25]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Szajewska/2013 [26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

The heterogeneity remained unaltered with a strikingly similar reduction in crying time at 21 days [mean difference −55.48 minutes; 95% CI (−59.46, -51.49)].

Effect of L. reuteri on overall response rate

The overall response rate of L. *reuteri* was compared to simethicone or placebo. Responders (or treatment success) was defined as the percentage of infants achieving a reduction in the daily average crying time of more than fifty percent. The response rate was reported in two of the trials at each assessment interval. Savino et al. reported the response rate at 28 days only [24]. A progressive, statistically significant response was noted starting at 7 days [25] after initiation of therapy (Figure 3). The effect was maximal at 21 days following the commencement of treatment, with a relative risk (RR) of 0.06; 95% CI (0.01, 0.25) and a number needed to treat (NNT) of 2. Of note, a similar progressive improvement was also evident in the control subjects; however, the positive effect was more pronounced in the probiotic group.

Effect with a history of atopy

The impact of atopy was documented in only one study [26]. A concomitant history of atopy did not alter the efficacy of probiotics in treated infants.

Discussion

We report the first systematic review of randomized trials addressing the efficacy of probiotics in infantile colic. A significant effect of *L. reuteri* supplementation (strains-American Type Culture Collection Strain 55730 and DSM 17 938) in shortening crying times and improvement in response rate was noted. This positive response was progressive with time and had its peak and plateau at three weeks after initiation of therapy. A similar positive effect was noted in the control group, which could be explained, by the natural history of infantile colic or a placebo effect [22,23]. However, the effect in the probiotic group was more pronounced. It is important to note that one of the strains (*L. reuteri* ATCC 55730) used in one of the included trials [24] was found to carry potentially transferable resistance traits for tetracycline and lincomycin in adults [27] and was replaced in subsequent studies by *L. reuteri* DSM 17938, a daughter strain that retained the original probiotic characteristics [28,29].

Our systematic review included currently available, high quality studies. However; our overall conclusion is compromised by the small number of enrolled infants despite the common prevalence of infantile colic, and the heterogeneity of included studies that assessed crying time. This heterogeneity can be explained by the clear imbalance of both groups at baseline, in the study reported by Savino et al. [25]. The probiotic group started with significantly longer crying times that quickly moved to a profoundly positive benefit after 7 days of treatment. Most of the included subjects were exclusively breast fed which limits the generalizability of the findings to formula fed infants. However, the incidence of colic in breast and bottle fed infants is similar [30] because the pathogenesis of the disorder is likely multifactorial and the use of probiotics may be influential in the treatment of colic by altering faecal microbiota and gut inflammation irrespective of feeding patterns [16-19,31].

The earlier trial by Savino et al. [24] involved the use of simethicone in the placebo arm. This may have decreased the magnitude of the effect of probiotics unless the effect of simethicone was not indifferent to placebo. The sensitivity analyses confirmed that the inclusion of the simethicone treated patients in this study did not significantly impact heterogeneity or the crying time at 21 days. One well recognized limitation of all studies on infant colic is the need for a more objective way of measuring duration of crying rather than relying on the parents' compliance to establish this outcome. Computer recordings of crying episodes comprise a more concrete form of assessment and should be considered for future studies. Two of the included trials were supported by the manufacturer of the probiotic strain under study, which raises the possibility of bias. However, the likelihood is small since the trials were fully investigator-initiated and data controlled with transparent disclosure of potential conflicts of interest by the respective authors [32,33].

Recently few studies have addressed the role of changing intestinal microbiota in the pathogenesis of colic. Colicky infants were found to have increased colonization by coliforms especially E.coli and decreased and altered colonization

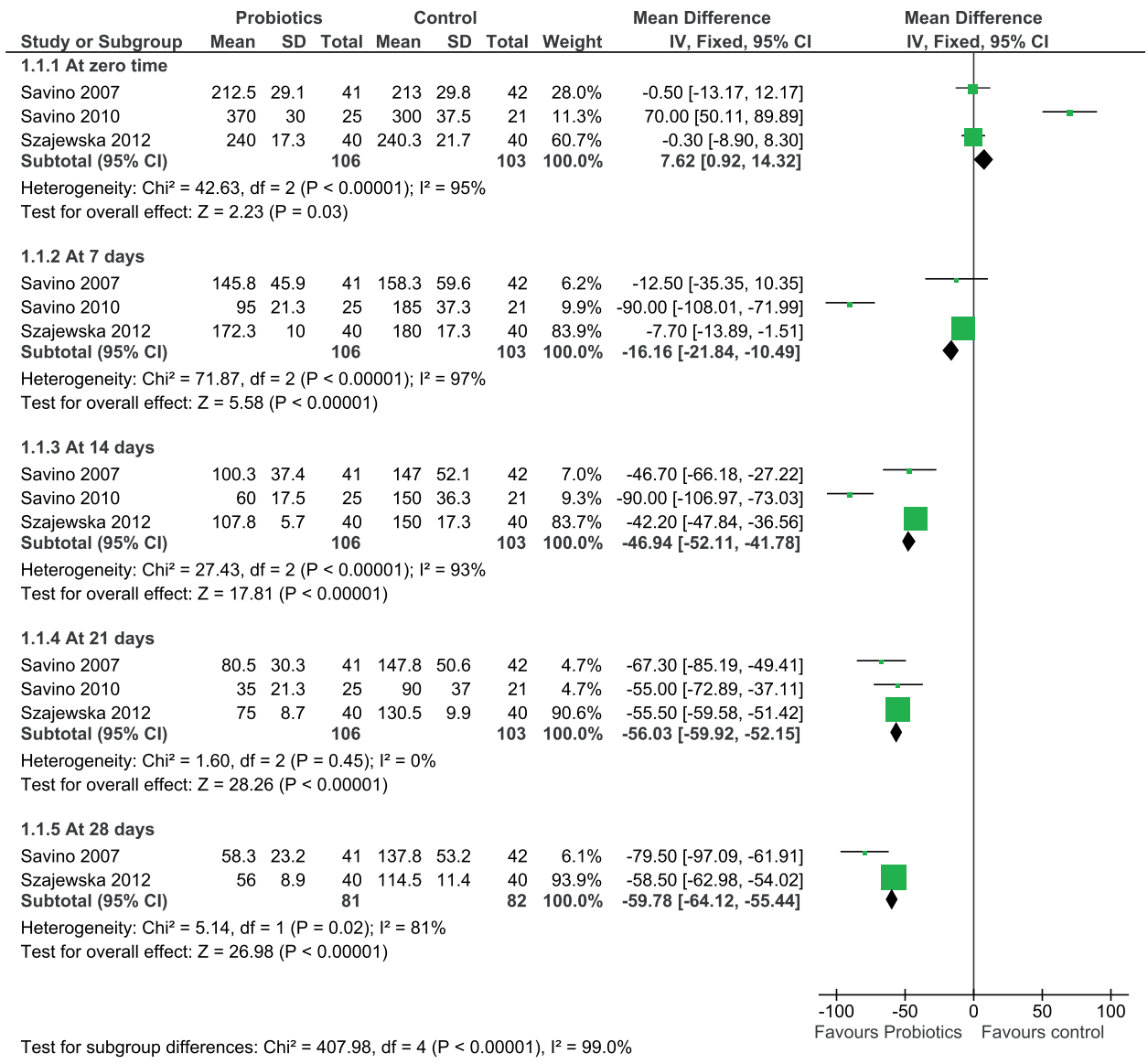

Figure 2 Forest plot of L. *reuteri* ATCC 55730 and L. *reuteri* DSM 17938 versus control effect in decreasing mean crying times (min) over 28 days.

patterns by lactobacillus species [17-19]. Furthermore, *L. reuteri* also exerts an antimicrobial effect against enteric pathogens which may induce an immunologic response [34-36]. Immune modulation could also play a role in the efficacy of probiotics in infantile colic as it may represent the first sign of food hypersensitivity [37]. Since probiotic supplementation appears to require time to exert an effect in colicky infants, it would be interesting to evaluate its efficacy as a prophylactic treatment after birth. It's unclear whether a similar or cumulative effect would be observed if other formulations of probiotic bacteria are utilized either alone or in combination with the same strains of *L. reuteri.*

Conclusions

Our review supports the beneficial effects of probiotic supplementation in infantile colic in predominantly breast fed infants. *L. reuteri (strains-American Type Culture Collection Strain 55730 and DSM 17 938)* significantly decreased the rate (minutes/day) of crying and no short term safety concerns were identified. However, all three included studies demonstrate a positive outcome which may be a reflection of the relatively small, combined, sample size that overshadows the true effect which may be realized in a single, large-scale, multicenter, randomized trial. More independent studies are still

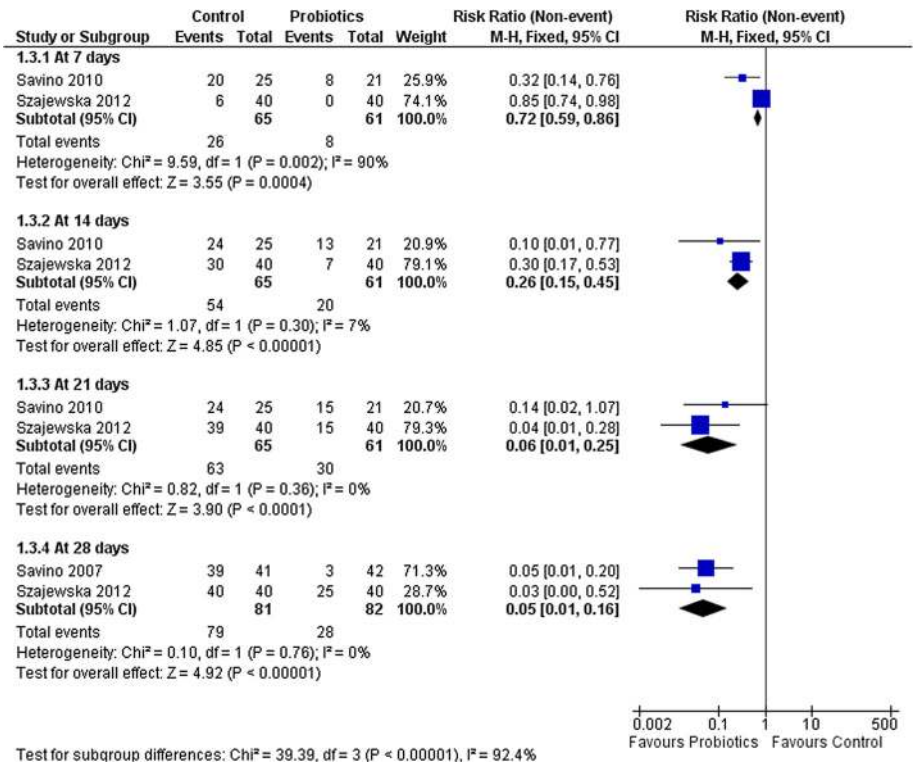

Figure 3 Forest plot of L. *reuteri* ATCC 55730 and L. *reuteri* DSM 17938 versus control effect in improving infantile colic treatment success rate over 28 days.

required in diverse ethnic populations, especially in formula fed infants, [38] prior to adopting a change in practice.

Abbreviations

CI: Confidence interval; NNT: Number needed to treat; RR: Relative risk.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JA: Conceptualized the study design, protocol development, inclusion selection, quality assessment and statistical analysis, and drafted the initial manuscript. FI: Was involved in the study conception and design, oversaw the protocol development and data interpretation and participated in the manuscript preparation. BP: Critically reviewed and amended the manuscript and circulated the final version for approval and submission. KA: Played a major role in the study conception, design, protocol development, inclusion selection, quality assessment and statistical analysis and worked collaboratively on the draft of the initial manuscript. All authors read and approved the final manuscript.

Acknowledgments

We extend our sincere appreciation to the Deanship of Scientific Research at King Saud University for funding this project through the Research Group project # RGB-VPP-248.

Funding source

This study was funded by King Saud University.

Author details

[1]Neonatal Care, Sulaiman Al Habib Medical Group, Arrayan Hospital, P.O. Box 272069, Riyadh 11352, Saudi Arabia. [2]Department of Pediatrics, University of Bari, Bari, Italy. [3]Department of Pediatrics (Neonatal Division), McMaster University, Hamilton, Ontario, Canada. [4]Department of Pediatrics, King Saud University, Riyadh, Saudi Arabia.

Received: 11 May 2013 Accepted: 14 November 2013
Published: 15 November 2013

References

1. Illingworth RS: **Infantile colic revisited.** *Arch Dis Child* 1985, **60:**981–985.
2. Lucassen PL, Assendelft WJ, van Eijk JT, *et al*: **Systematic review of the occurrence of infantile colic in the community.** *Arch Dis Child* 2001, **84:**398–403.
3. Wessel MA, Cobb JC, Jackson EB, Harris GS Jr, Detwiler AC: **Paroxysmal fussing in infancy, sometimes called colic.** *Pediatrics* 1954, **14:**421–435.
4. Castro-Rodríguez JA, Stern DA, Halonen M, *et al*: **Relation between infantile colic and asthma/atopy: a prospective study in an unselected population.** *Pediatrics* 2001, **108:**878–882.
5. Gelfand AA, Thomas KC, Goadsby PJ: **Before the headache: infant colic as an early life expression of migraine.** *Neurology* 2012, **79:**1392–1396.
6. Vik T, Grote V, Escribano J, European Childhood Obesity Trial Study Group, *et al*: **Infantile colic, prolonged crying and maternal postnatal depression.** *Acta Paediatr* 2009, **98:**1344–1348.
7. Akman I, Kuscu K, Ozdemir N, *et al*: **Mothers' postpartum psychological adjustment and infantile colic.** *Arch Dis Child* 2006, **91:**417–419.
8. Dennis CL, Ross L: **Relationships among infant sleep patterns, maternal fatigue, and development of depressive symptomatology.** *Birth* 2005, **32:**187–193.
9. Miller AR, Barr RG, Eaton WO: **Crying and motor behavior of six-week-old infants and postpartum maternal mood.** *Pediatrics* 1993, **92:**551–558.

10. Miller-Loncar C, Bigsby R, High P, *et al*: **Infant colic and feeding difficulties.** *Arch Dis Child* 2004, **89:**908–912.
11. Smart J, Hiscock H: **Early infant crying and sleeping problems: a pilot study of impact on parental well-being and parent-endorsed strategies for management.** *J Paediatr Child Health* 2007, **43:**284–290.
12. Miller AR, Barr RG: **Infantile colic. Is it a gut issue?** *Pediatr Clin North Am* 1991, **38:**1407–1423.
13. Treem WR: **Infant colic. A pediatric gastroenterologist's perspective.** *Pediatr Clin North Am* 1994, **41:**1121–1138.
14. Lucassen PL, Assendelft WJ, Gubbels JW, *et al*: **Effectiveness of treatments for infantile colic: systematic review.** *BMJ* 1998, **316:**1563–1569.
15. Shenassa ED, Brown MJ: **Maternal smoking and infantile gastrointestinal dysregulation: the case of colic.** *Pediatrics* 2004, **114:**e497–e505.
16. Lehtonen L, Korvenranta H, Eerola E: **Intestinal microflora in colicky and noncolicky infants: bacterial cultures and gas–liquid chromatography.** *J Pediatr Gastroenterol Nutr* 1994, **19:**310–314.
17. Savino F, Cresi F, Pautasso S, *et al*: **Intestinal microflora in breastfed colicky and non-colicky infants.** *Acta Paediatr* 2004, **93:**825–829.
18. Savino F, Bailo E, Oggero R, *et al*: **Bacterial counts of intestinal Lactobacillus species in infants with colic.** *Pediatr Allergy Immunol* 2005, **16:**72–75.
19. Savino F, Cordisco L, Tarasco V, *et al*: **Molecular identification of coliform bacteria from colicky breastfed infants.** *Acta Paediatr* 2009, **98:**1582–1588.
20. Savino F, Cordisco L, Tarasco V, *et al*: **Antagonistic effect of Lactobacillus strains against gas-producing coliforms isolated from colicky infants.** *BMC Microbiol* 2011, **11:**157. Doi: 10.1186/1471-2180-11-157.
21. Aloisio I, Santini C, Biavati B, *et al*: **Characterization of Bifidobacterium spp. strains for the treatment of enteric disorders in newborns.** *Appl Microbiol Biotechnol* 2012, **96:**1561–1576.
22. Higgins JPT, Green S (Eds): *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*, The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org.
23. Hozo SP, Djulbegovic B, Hozo I: **Estimating the mean and variance from the median, range, and the size of a sample.** *BMC Med Res Methodol* 2005, **5:**13.
24. Savino F, Pelle E, Palumeri E, *et al*: **Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study.** *Pediatrics* 2007, **119:**e124–e130.
25. Savino F, Cordisco L, Tarasco V, *et al*: **Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial.** *Pediatrics* 2010, **126:**e526–e533.
26. Szajewska H, Gyrczuk E, Horvath A: **Lactobacillus reuteri DSM 17938 for the Management of Infantile Colic in Breastfed Infants: A Randomized, Double-Blind, Placebo-Controlled Trial.** *J Pediatr* 2013, **162:**257–262.
27. Egervärn M, Danielsen M, Roos S, Lindmark H, Lindgren S: **Antibiotic susceptibility profiles of Lactobacillus reuteri and Lactobacillus fermentum.** *J Food Prot* 2007, **70:**412–418.
28. Savino F, Tarasco V: **New treatments for infant colic.** *Curr Opin Pediatr* 2010, **22:**791–797.
29. Rosander A, Connolly E, Roos S: **Removal of antibiotic resistance gene-carrying plasmids from Lactobacillus reuteri ATCC 55730 and characterization of the resulting daughter strain, L. reuteri DSM 17938.** *Appl Environ Microbiol* 2008, **74:**6032–6040.
30. Lucas A, St J-RI: **Crying, fussing and colic behaviour in breast- and bottle-fed infants.** *Early Hum Dev* 1998, **53:**9–18.
31. Rhoads JM, Fatheree NY, Norori J, *et al*: **Altered fecal microflora and increased fecal calprotectin in infants with colic.** *J Pediatr* 2009, **155:**823–828. e1.
32. Ross JS, Gross CP, Krumholz HM: **Promoting transparency in pharmaceutical industry-sponsored research.** *Am J Public Health* 2012, **102:**72–80.
33. Dunn AG, Gallego B, Coiera E: **Industry influenced evidence production in collaborative research communities: a network analysis.** *J Clin Epidemiol* 2012, **65:**535–543.
34. Spinler JK, Taweechotipatr M, Rognerud CL, *et al*: **Human-derived probiotic Lactobacillus reuteri demonstrate antimicrobial activities targeting diverse enteric bacterial pathogens.** *Anaerobe* 2008, **14:**166–171.
35. Lin YP, Thibodeaux CH, Pena JA, *et al*: **Probiotic Lactobacillus reuteri suppress proinflammatory cytokines via c-Jun.** *Inflamm Bowel Dis* 2008, **14:**1068–1083.
36. Liu Y, Fatheree NY, Mangalat N, *et al*: **Human-derived probiotics Lactobacillus reuteri strains differentially reduce intestinal inflammation.** *Am J Physiol Gastrointest Liver Physiol* 2010, **299:**G1087–G1096.
37. Smits H, Engering A, van der Kleij D, *et al*: **Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin.** *J Allergy Clin Immunol* 2005, **115:**1260–1267.
38. Sung V, Hiscock H, Tang M, *et al*: **Probiotics to improve outcomes of colic in the community: Protocol for the Baby Biotics randomised controlled trial.** *BMC Pediatr* 2012, **12:**135. Doi: 10.1186/1471-2431-12-135.

doi:10.1186/1471-2431-13-186
Cite this article as: Anabrees *et al.*: Probiotics for infantile colic: a systematic review. *BMC Pediatrics* 2013 **13**:186.