Lactose avoidance for young children with acute diarrhoea (Review)

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[Intervention Review]

Lactose avoidance for young children with acute diarrhoea

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ABSTRACT

Background

Young children with acute diarrhoea, typically due to infectious gastroenteritis, may temporarily stop producing lactase, the intestinal enzyme that digests lactose. This means they may not digest lactose, the main sugar in milk, and this may worsen or prolong the diarrhoeal illness. However, there is uncertainty whether avoiding lactose-containing milk or milk products helps young children recover from acute diarrhoea more quickly.

Objectives

To assess if avoiding or reducing intake of lactose-containing milk or milk products shortens the duration and severity of illness in young children with acute diarrhoea. We also sought other indicators of morbidity and overall mortality.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (14 May 2013), Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library* (Issue 4, 2013), MEDLINE (1996 to 14 May 2013), EMBASE (1974 to 14 May 2013), and LILACS (1982 to 14 May 2013), and the reference lists of potentially relevant trials, key conference proceedings, and wrote to individuals and organizations in the field.

Selection criteria

Randomized or quasi-randomized controlled trials that assessed the effects of avoiding or reducing exposure to lactose in young children under five years with acute diarrhoea.

Data collection and analysis

We extracted data using the standard methods of the Cochrane Infectious Diseases Group, and two review authors independently evaluated trial quality and data extraction. Continuous outcomes were compared using mean difference (MD), and dichotomous outcomes using the risk ratio (RR). We presented all results with 95% confidence intervals (CI) and assessed the quality of evidence using the GRADE approach.

Main results

We included 33 trials enrolling 2973 children with acute diarrhoea. Twenty-nine trials were exclusively conducted on inpatients, all from high- or middle-income countries. Fifteen trials included children aged below 12 months, and 22 excluded children who were being breast-fed.

Compared to lactose-containing milk, milk products, or foodstuffs, lactose-free products may reduce the duration of diarrhoea by an average of about 18 hours (MD -17.77, 95% CI -25.32 to -10.21, 16 trials, 1467 participants, *low quality evidence*). Lactose-free products probably also reduce treatment failure (defined variously as continued or worsening diarrhoea or vomiting, the need for additional rehydration therapy, or continuing weight loss) by around a half (RR 0.52, 95% CI 0.39 to 0.68, 18 trials, 1470 participants, *moderate quality evidence*).

Diluted lactose-containing milk has not been shown to reduce the duration of diarrhoea compared to undiluted milk or milk products (five trials, 417 participants, *low quality evidence*), but may reduce the risk of treatment failure (RR 0.65, 95% CI 0.45 to 0.94, nine trials, 687 participants, *low quality evidence*).

Authors' conclusions

In young children with acute diarrhoea who are not predominantly breast-fed, change to a lactose-free diet may result in earlier resolution of acute diarrhoea and reduce treatment failure. Diluting lactose-containing formulas may also have some benefits but further trials are required to have confidence in this finding. There are no trials from low-income countries, where mortality for diarrhoea is high, and malnutrition is more common.

PLAIN LANGUAGE SUMMARY

The effect of removing or reducing lactose from milk in young children with acute diarrhoea

Acute diarrhoea, typically due to bacterial or viral infection, is a common childhood illness and, in low-income countries, remains an important cause of death. Over two million children under five years of age die each year in poorer countries because of acute diarrhoea. In richer countries, it does not usually cause death but it is a common reason for young children needing medical advice or hospital admission.

Young children with acute diarrhoea may temporarily be unable to digest lactose, the most common type of sugar in milk. Inability to digest and absorb lactose can make the diarrhoea worse and last longer. We looked for evidence that reducing children's lactose intake, either by feeding lactose-free milk or by diluting lactose-containing milk, shortens the duration of diarrhoea and prevents complications such as dehydration.

We looked for research up to 13 May 2013 and included 33 trials in our analyses. Twenty-two trials compared outcomes for children given a lactose-free feed with those for children given a lactose-containing feed and 11 trials compared outcomes for children fed a diluted milk feed with those for children given an undiluted milk feed.

We found evidence that feeds that do not contain lactose may reduce the duration of diarrhoea by an average of about 18 hours (*low quality evidence*). Lactose-free feeds probably lower the risk of children having prolonged or worsening diarrhoea (*moderate quality evidence*).

We did not find any evidence that diluted milk feeds reduce the duration of diarrhoea (*low quality evidence*) but these feeds may lower the risk of children having prolonged or worsening diarrhoea (*low quality evidence*).

The majority of trials excluded breast fed infants, and none were conducted in low-income countries where diarrhoea can cause death, so the review is relevant to infants and young children who are receiving formula or are weaned in high- and middle-income countries.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Lactose-free versus lactose-containing milk, milk products, or foodstuffs for young children with acute diarrhoea.

Patient or population: Young children with acute diarrhoea
Settings: Inpatient and outpatient
Intervention: Lactose-free milk, milk products, or foodstuffs
Control: Lactose-containing milk, milk products, or foodstuffs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Lactose-containing	Lactose-free			
Duration of diarrhoea (hours)	The mean duration of diarrhoea in the control groups ranged from **28.8 to 230 hours**	The mean duration in the intervention groups was **17.77 hours shorter** (25.32 to 10.21 shorter)	-	1467 (16 trials)	⊕⊕◯◯ **low**[1,2,3,4]
Treatment failure	**164 per 1000**	**85 per 1000** (64 to 112)	**RR 0.52** (0.39 to 0.68)	1470 (18 trials)	⊕⊕⊕◯ **moderate**[5,6,3,4]
Need for hospitalization	**63 per 1000**	**50 per 1000** (6 to 422)	**RR 0.79** (0.09 to 6.65)	83 (1 trials)	⊕◯◯◯ **very low**[7,8]

*The **assumed risk** is taken from the control group risk in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for serious risk of bias: Almost all trials were at high or unclear risk of bias for more than one of the risk of bias criteria, and only two studies were adequately blinded.

[2] Downgraded by 1 for serious inconsistency: A high level of heterogeneity between trials was found which could not be fully explained through subgroup analyses by age, setting, or income level of the country.

[3] No serious indirectness: The included trials were mainly conducted in inpatient settings, but came from a mix of high- and low-income countries. Subgroup analyses did not find any significant differences in estimate size based on age, setting, income level of the country, or differences in feed type apart from the lactose content.

[4] No serious imprecision: The result is a statistically significant effect in favour of lactose-free, with a narrow CI.

[5] Downgraded by 1 for serious risk of bias: Many of the trials were at high or unclear risk of selection, performance, and attrition bias. In a sensitivity analysis limited to the three trials at low risk of selection bias, no statistically significant effect was seen.

[6] No serious inconsistency: Statistical heterogeneity was low.

[7] Downgraded by 1 for serious indirectness: Only a single trial from a single setting evaluated this outcome.

[8] Downgraded by 2 for very serious imprecision: There were few participants and few events. The CIs were very wide for this outcome and the 95% CIs around the pooled effect estimate included both significant benefit and harm of intervention.

BACKGROUND

Description of the condition

Acute diarrhoea, most commonly due to infectious gastroenteritis, is common throughout the world. In high-income countries, acute diarrhoea is a common reason for primary care consultation and hospital referral. In the United Kingdom, up to one in six children each year see their general practitioner because of an episode of acute diarrhoea (Djuretic 1999). About 5% to 10% of hospital admissions of young children are for acute diarrhoeal illnesses (Armon 2001a; Malek 2006). In developing countries, infectious gastroenteritis is a common cause of morbidity and death in young children (Black 2010; Santosham 2010).

Transient deficiency of lactase, the enzyme present in the upper small intestine that digests lactose, may occur following acute diarrhoea (Sunshine 1964). Lactose is the most abundant sugar in animal milk, including human breast milk, and in adapted cow's milk formulas. If young children are unable to digest and absorb lactose because of lactase deficiency then continuing to ingest lactose-containing milk or milk products may worsen acute diarrhoea because of osmotic effects. This may exacerbate dehydration, malabsorption, malnutrition, and growth failure, and ultimately may contribute to child deaths in areas of the world where severe diarrhoeal illness is common.

Description of the intervention

Due to these potential adverse consequences of lactase deficiency, some practitioners advise reduced exposure of young children with acute diarrhoea to lactose-containing milk and milk products. As an alternative, children may be fed with lactose-free milk (for example, soy-based milk), milk with a reduced lactose content (for example, hydrolysed or lactase-treated cow's milk formula), or non-milk-based foodstuffs. Lactose exposure may also be reduced by diluting lactose-containing milk. However, lactose-free or lactose-reduced formula is not always available or affordable, especially in low-income settings. Feeding young children with diluted milk may reduce the intake of energy, protein, and other nutrients, and may have an adverse impact on illness recovery and growth, especially in infants for whom milk is the principal source of nutrients. If breastfeeding is interrupted because of a diarrhoeal illness then it may be difficult to re-establish after recovery, thus removing the advantages of breastfeeding for the mother and child.

Why it is important to do this review

Clinical guidelines based on literature evaluation and expert consensus offer conflicting advice regarding whether lactose avoidance should be advised for young children with acute diarrhoea (AAP 1996; Murphy 1998; Armon 2001b; AAP 2006; Dalby-Payne 2011). A systematic review published in 1994 found some evidence that lactose avoidance improved important clinical outcomes for young children with acute diarrhoea, especially for children who were severely dehydrated as a consequence of the acute diarrhoeal illness (Brown 1994). Several relevant randomized controlled trials (RCTs) have since been published. Furthermore, the review did not include any trials found by handsearching journals not covered by the electronic databases and did not attempt to find unpublished trials. There is a risk that important evidence may be missing because of publication bias.

OBJECTIVES

To assess the evidence that avoidance or reduction of intake of lactose-containing milk or milk products reduces the duration and severity of acute diarrhoea and associated mortality or morbidity in young children with acute diarrhoea.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomised controlled trials.

Types of participants

Children less than five years old with acute diarrhoea (liquid or semi-formed stools with increased frequency of defecation for less than seven days).

Types of interventions

1. Lactose-free versus lactose-containing (at least 2%) milk, milk products, or foodstuffs
2. Diluted (by at least 50%) versus undiluted lactose-containing milk, milk products, or foodstuffs (given for > 24 hours)

Types of outcome measures

Primary

1. Mortality
2. Duration of diarrhoea, defined as time to first normal stool (when subsequent stools were normal for a 24-hour period)

Secondary

1. Treatment failure (discontinuation of the intervention or withdrawal from the trial or change in nutritional management due to worsening diarrhoea or vomiting)
2. Need for hospitalization
3. Duration of hospital stay
4. Stool volume or frequency
5. Change in body weight

Search methods for identification of studies

We sought all relevant trials regardless of language or publication status (Lefebvre 2011).

Electronic searches

We searched the Cochrane Infectious Diseases Group Specialized Register (13 May 2013), Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library* (Issue 4, 2013), MEDLINE (1996 to 13 May 2013), EMBASE (1974 to 13 May 2013), and LILACS (1982 to 13 May 2013) using the search terms and strategy described in Table 1.

We searched ClinicalTrials.gov and Current Controlled Trials (last accessed on 14 May 2013) for completed or ongoing trials.

Searching other resources

We examined the reference lists of all potentially relevant trials and searched the abstracts from the annual meetings of the Pediatric Academic Societies (1993 to 2013), the European Society for Pediatric Research (1995 to 2012), and the UK Royal College of Paediatrics and Child Health (2000 to 2013). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contacting the authors, to fulfil the inclusion criteria.

We contacted individual researchers working in the field, organizations (including the World Health Organization (WHO), the Centers for Disease Control and Prevention, and the International Centre for Diarrhoeal Disease Research, Bangladesh), and pharmaceutical companies (Nestle, Wyeth, Cow & Gate, Milupa, and Boots Plc) for unpublished and ongoing trials.

Data collection and analysis

We used a data collection form to aid extraction of relevant information from each included trial. Stephen MacGillivray (SM) and William McGuire (WM) extracted the data separately. SM and WM resolved any disagreements by discussion or by consulting Tom Fahey (TF) until consensus was achieved. We contacted the investigators for further information if data from the trial reports were insufficient.

Selection of studies

SM and WM screened the title and abstract of all trials identified by the above search strategy and obtained the full articles for all potentially relevant trials. The two review authors re-assessed independently the full text of these reports using an eligibility form based on the inclusion criteria, excluded trials that did not meet all inclusion criteria, and stated the reasons in the 'Characteristics of excluded studies' table. SM and WM resolved any disagreements by discussion or by consulting TF until consensus was achieved. We scrutinized each of the papers to ensure that each trial was included only once.

Data extraction and management

SM and WM used a piloted data collection form to independently extract data from each trial. The two review authors compared data and resolved differences by discussion or by consulting TF until consensus was achieved. If data from the trial reports were insufficient, we attempted to contact the trial authors for information.

For each treatment arm, we extracted the number of randomized participants and the number of analysed participants for each outcome. For dichotomous outcomes, we recorded the number of participants experiencing the event in each group of the trial. As continuous data may be reported using arithmetic means, geometric means, or medians, we extracted information to allow us to calculate the arithmetic means and standard deviations, and information to calculate standard deviations on the log scale if the data were reported using geometric means, or extract medians and ranges to report in tables.

Assessment of risk of bias in included studies

SM and WM independently assessed the risk of bias for each trial using 'The Cochrane Collaboration's tool for assessing the risk of bias' and resolved differences of opinion through discussion (Higgins 2011). We followed the guidance to assess whether adequate steps were taken to reduce the risk of bias across six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias. We categorized our judgements as 'low risk of bias', 'high risk of bias', or 'unclear', and used this information to guide data interpretation.

Measures of treatment effect

We calculated risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CI). The number needed to treat for benefit (NNTB) or harm (NNTH) was determined for a statistically significant difference in the RD.

Dealing with missing data

We performed a complete case analysis.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2, and Chi^2 statistics. Heterogeneity was regarded as substantial where T^2 was greater than zero and either I^2 was greater than 50% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

If more than one trial was included in a meta-analysis, we examined the treatment effects of individual trials and the heterogeneity between trial results by inspecting the forest plots. We calculated the I^2 statistic for each analysis to quantify inconsistency across trials and described the percentage of variability in effect estimates that may be due to heterogeneity rather than sampling error. If substantial (I^2 > 50%) heterogeneity was detected, we explored the possible causes (for example, differences in study design, participants, interventions, or completeness of outcome assessments) in subgroup and sensitivity analyses.

Assessment of reporting biases

We looked for evidence of reporting bias (publication, local language, or small trial) by inspecting a funnel plot for asymmetry. If there was suspected asymmetry, we assessed this using a fixed-effect meta-regression model.

Data synthesis

We used the fixed-effect model for meta-analysis or a random-effects model where significant heterogeneity was present (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

When there was statistical heterogeneity (I^2 > 50%), we explored the possible causes and tried to explain it using subgroup analyses for:

- age (all participants < 12 months versus some participants ≥ 12 months)
- setting (inpatient versus outpatient)
- income level of country (low- or middle-income versus high-income)

We performed a post-hoc subgroup analysis to explore the differences in effect between trials in which the only difference between intervention and control groups were the presence or absence of lactose (for example, lactose-free cows milk formula versus lactose-containing cows milk formula), and trials where the intervention and control group also differed in regard to the type of foodstuff (for example, lactose-free soy milk formula versus lactose-containing cow's milk formula).

Sensitivity analysis

We carried out sensitivity analyses to explore how much of the variation between trials comparing lactose-free to lactose-containing milk, products, or foodstuffs was explained by risk of bias items. For each risk of bias domain, we performed a sensitivity analysis which included only trials at low risk of bias.

RESULTS

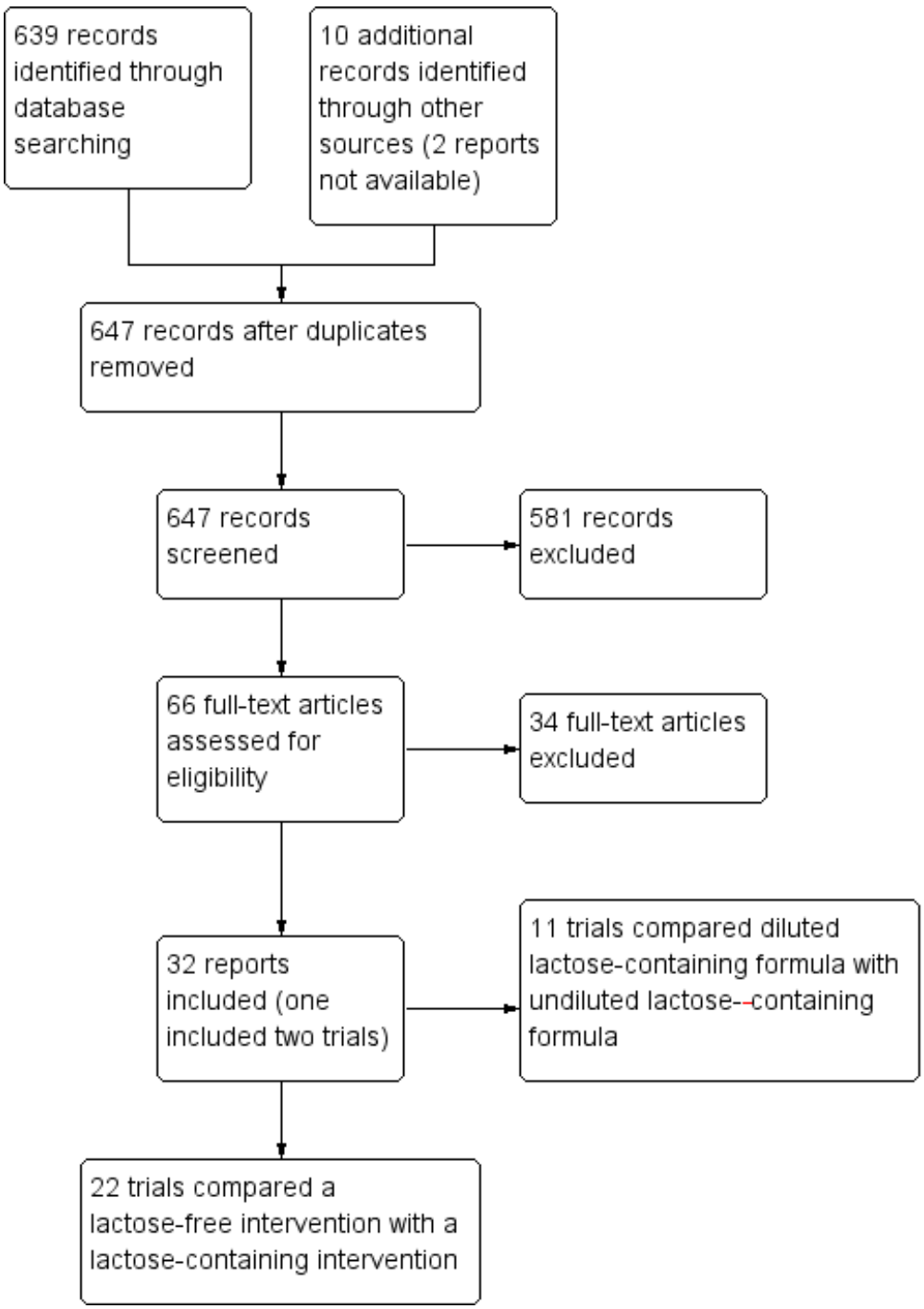
Description of studies

See the Characteristics of included studies and Characteristics of excluded studies sections.

Results of the search

We identified 647 records, of which we assessed 66 full-text articles for eligibility. Thirty-three trials, including 2973 participants, met all of our inclusion criteria; 22 trials compared a lactose-free intervention with a lactose-containing intervention, and 11 trials compared diluted lactose-containing formula with undiluted lactose-containing formula (Figure 1). One publication reported two trials (Conway 1989).

Figure 1. Study flow diagram.



We excluded 34 trials (Figure 1).

Another systematic review cites two reports of potentially relevant trials (Brown 1994). We were unable to obtain these reports, both based on "WHO/CDD supported studies", despite an extended search via the British Library (Chiriboga 1986; Madkour 1986). If the reports become available they may be included in an update of this review.

Included studies

Year of publication

Of the 33 included trials, two were published prior to 1980, 17 during the 1980s, and 14 in the 1990s or later (the most recent was published in 2012).

Trial location and setting

Fifteen trials were conducted in middle-income countries (Algeria, Brazil, China, Colombia, Egypt, Guatamala, India, Iran, Peru, South Africa, Thailand, and Venezuala), and 18 in high-income countries (Australia, Canada, Finland, Germany, Israel, Saudi Arabia, UK, and USA),and none in low-income countries.

Most trials were conducted in an inpatient setting, usually a specialist ward within a paediatric hospital. Two trials were conducted in both an inpatient and outpatient setting (Armitstead 1989; Allen 1994), and two trials were conducted in primary-care paediatric outpatient clinics (Groothuis 1986; Bhan 1988).

Participants

All included trials specified a participant upper age limit as an eligibility criterion, which varied from two months to 59 months. Fourteen trials limited inclusion to children aged below 12 months.

Initial level of dehydration

Six trials (five publications) included children with acute diarrhoea plus signs of mild dehydration (≤ 5%) (Bhan 1988; Armitstead 1989; Conway 1989; Lifshitz 1991; Prietsch 1999), eight trials included children with mild or moderate dehydration (5 to 10%) (Sutton 1968; Dagan 1984; Isolauri 1986; Brown 1991; Allen 1994; Wall 1994; Simakachorn 2004; Saneian 2012), and seven trials also included children with signs of severe dehydration (>10%) (Naidoo 1981; Dugdale 1982; Placzek 1984; Pichaipat 1986; Chew 1993; Lozano 1994; Fayad 1999). Eleven trials did not provide details about initial levels of dehydration.

In all trials, oral or intravenous rehydration therapy was available for use pre-randomization and during the intervention period.

Breast-feeding at trial entry

Twenty-two trials specifically excluded predominantly breast fed infants, and the remaining trials did not provide information on whether or not they were excluded.

Level of nutrition at trial entry

Eight trials excluded malnourished children (Ransome 1984; Conway 1989; Brown 1991; Romer 1991; Chew 1993; Allen 1994; Fayad 1999; Simakachorn 2004). Twenty-five trials did not provide information on whether or not malnourished children were eligible to participate.

Infectious causes of gastroenteritis

Most trials reported some data on the infectious aetiology of the diarrhoea. The most commonly identified (or reported) cause was rotavirus infection, but infections with *Escherichia coli* and other enteric bacilli were also reported. None of the trials included children diagnosed with cholera or severe dysentery.

Interventions

Twenty-two trials included a comparison of a lactose-free intervention with a lactose-containing intervention:

- Ten trials compared lactose-free cow's milk formula (most commonly a hydrolysed formula) with lactose-containing formula (Sutton 1968; Wolf 1989; Brown 1991; Lifshitz 1991; Clemente Yago 1993; Lozano 1994; Wall 1994; Simakachorn 2004; Xu 2009; Saneian 2012)
- Six trials compared soy-based (lactose-free) formula with lactose-containing cow's milk formula (Leake 1974; Naidoo 1981; Dagan 1984; Haffejee 1990; Allen 1994; Prietsch 1999)
- One publication reported a 3-arm trial: lactose-free cow's milk formula versus soy-based (lactose-free) formula versus lactose-containing cow's milk formula (Conway 1989)
- Two trials compared soy-based (lactose-free) formula with soy-based (lactose-containing) formula (Groothuis 1986; Fayad 1999)
- Two trials compared lactose-free mixed diet with lactose-containing milk formula (Bhan 1988; Romer 1991)
- One trial compared a mixed diet that included lactose-free formula with a mixed diet that included a lactose-containing formula (Isolauri 1986)

Eleven trials compared diluted lactose-containing formula with undiluted lactose-containing formula (Dugdale 1982; Haque 1983; Placzek 1984; Ransome 1984; Maudgal 1985; McDowell 1985; Pichaipat 1986; Armitstead 1989; Conway 1989; Touhami 1989; Chew 1993). In all trials, only the formula dilution differed

between groups. The intervention period ranged from 24 hours to 72 hours.

Outcomes

All trials except Maudgal 1985 reported duration of diarrhoea (typically defined as time from admission to excretion of the last liquid or semi-liquid stool) or treatment failure (typically defined as continued or worsening loose stools or vomiting, with ongoing weight loss or receipt of rehydration therapy) as primary outcomes. Other reported outcomes were change in body weight, stool volume or frequency after trial entry, need for hospital admission, and duration of hospital admission.

None of the trials aimed to assess the effect on mortality or specifically reported mortality as an outcome. Most trial reports commented that none of the participants died during the trial period but four reports did not comment on mortality rates (Leake 1974; Dagan 1984; Ransome 1984; Prietsch 1999).

Excluded studies

We excluded 34 trials following inspection of the full-text article (Characteristics of excluded studies). The most common reason for exclusion was that trial participants were suffering from chronic, persistent, or complicated diarrhoea.

Risk of bias in included studies

See: Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

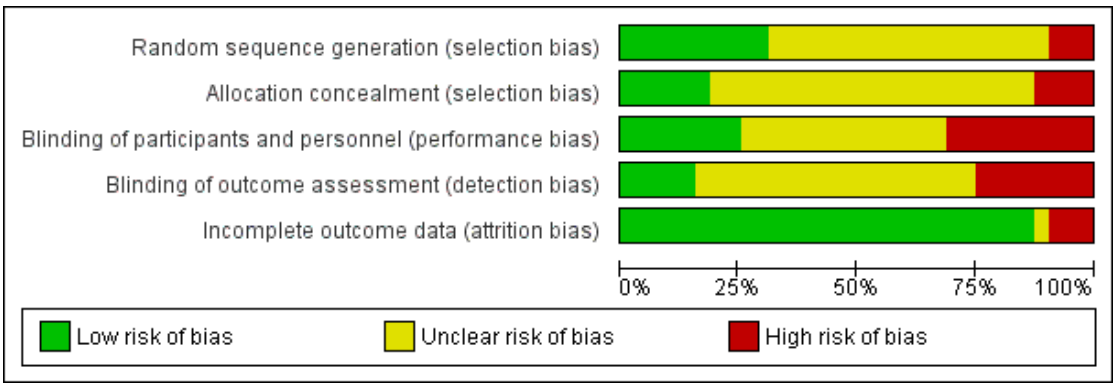
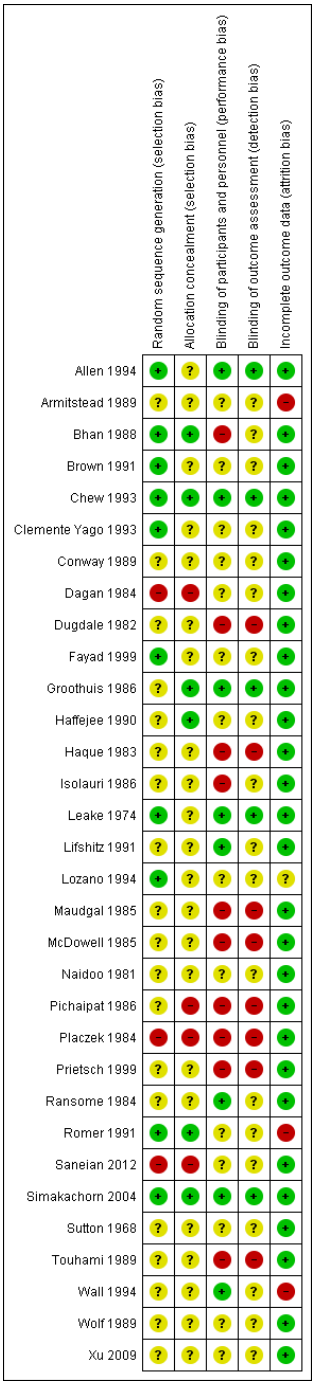


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



Allocation

Six trial reports described methods of allocation concealment consistent with low risk of selection bias (Groothuis 1986; Bhan 1988; Haffejee 1990; Romer 1991; Chew 1993; Simakachorn 2004). Most of the other trial reports did not describe the method of random sequence generation or allocation concealment and two trials were explicitly quasi-randomised and used alternate allocation (Dagan 1984; Saneian 2012).

Blinding

Five reports explicitly described methods that may have blinded parents, caregivers, clinicians, and investigators to the intervention (Leake 1974; Groothuis 1986; Chew 1993; Allen 1994; Simakachorn 2004). Eight trials did not blind participants, personnel or outcome assessment (Dugdale 1982; Haque 1983; Placzek 1984; Maudgal 1985; McDowell 1985; Pichaipat 1986; Touhami 1989; Prietsch 1999). We were not able to assess the risk of performance bias and detection bias in the other trials.

Incomplete outcome data

Only three trials had > 20% loss to follow-up (Armitstead 1989; Romer 1991; Wall 1994).

Selective reporting

We did not systematically explore selective reporting. One key aspect of selective reporting relates to whether authors report all the outcomes that they intended to measure, as stated in their protocol. In order to address this key aspect of selective reporting, we would have had to obtain the trial protocols. This was not possible as some of the trials were very old.

Effects of interventions

See: **Summary of findings for the main comparison** Lactose-free versus lactose-containing milk, milk products, or foodstuffs for young children with acute diarrhoea; **Summary of findings 2** Diluted (by at least 50%) versus undiluted lactose-containing milk, milk products, or foodstuffs for young children with acute diarrhoea

Comparison 1: Lactose-free versus lactose-containing milk, milk products, or foodstuffs

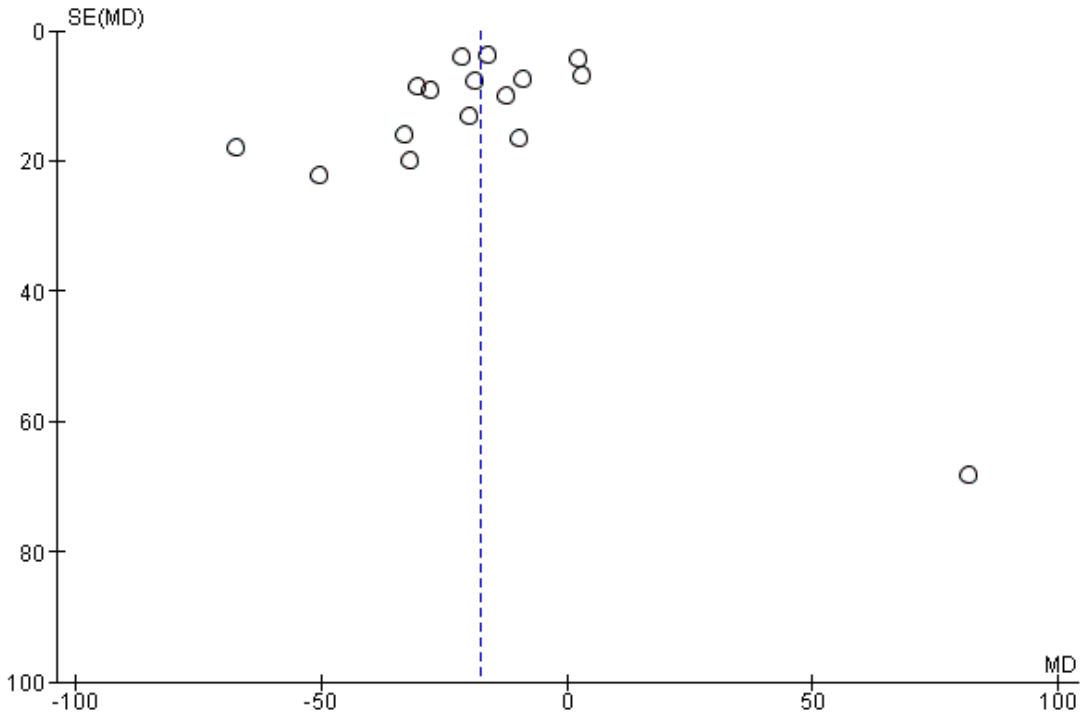
Mortality

Mortality was not reported as an outcome by any trials.

Duration of diarrhoea

Lactose-free milk, milk products, or foodstuffs were associated with a statistically significant reduction in the duration of diarrhoea of about 18 hours but with substantial heterogeneity in the size of this effect (MD -17.77 hours, 95% CI -25.32 to -10.21, random-effects model, I^2 = 67%, 16 trials, 1467 participants, Analysis 1.1) The funnel plot contained minor asymmetry raising the possibility of some publication bias (see Figure 4).

Figure 4. Funnel plot of comparison: 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs; outcome: 1.1 Duration of diarrhoea (hrs).



Subgroup analyses

Subgroup analyses by age (< 12 months versus ≥ 12 months), setting (inpatients versus outpatients), or income level of country (low- and middle-income versus high-income) did not adequately explain the observed heterogeneity (see Table 2).

However, a post-hoc subgroup analysis, restricted to the nine trials in which the only difference between feeds was the presence or absence of lactose, contained no statistical heterogeneity and found a statistically significant reduction in duration of diarrhoea of about 20 hours (MD -20.20 hours, 95% CI -24.71 to -15.69, I^2 = 0%, nine trials, 810 participants, Analysis 2.1). Statistical heterogeneity remained high in the subgroup of seven trials in which other differences between feeds existed (MD -14.38 hours, 95% CI -30.15 to 1.39, I^2= 74%, seven trials, 607 participants, Analysis 2.1).

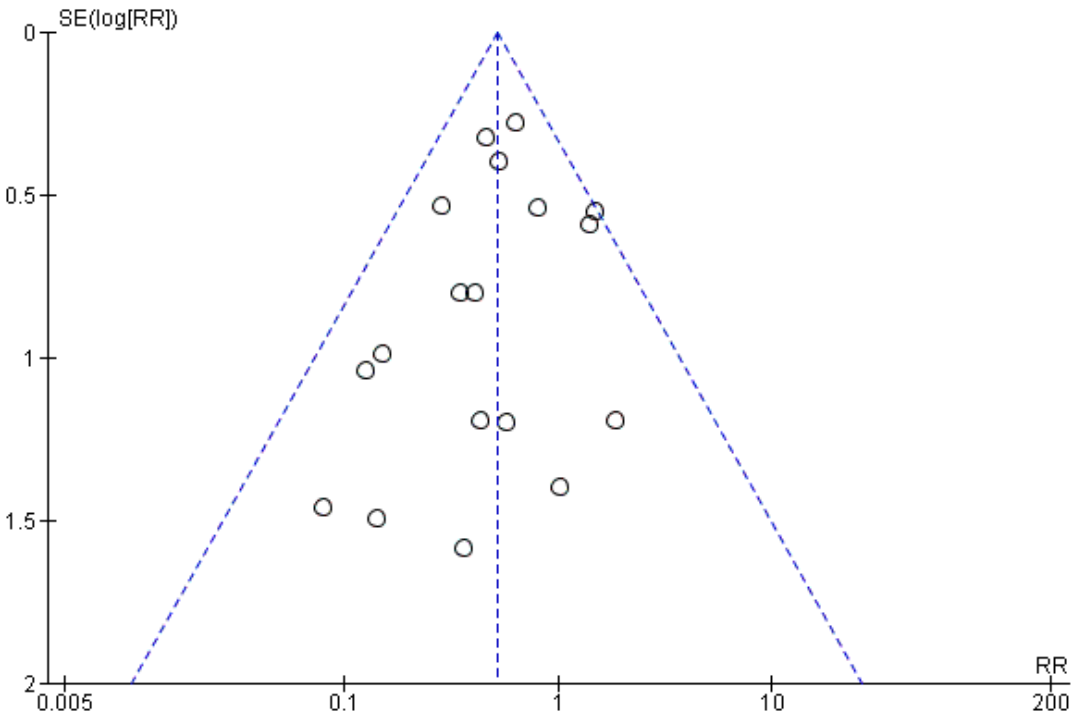
Sensitivity analyses

We conducted a series of sensitivity analysis restricting the analysis to trials at low risk of bias for the individual risk of bias criteria, and the result remained statistically significant in favour of lactose-free products throughout (see Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5).

Treatment failure

Lactose-free milk, milk products, or foodstuffs were associated with a reduction in the risk of treatment failure of around 50% without statistical heterogeneity between trials (RR 0.52, 95% CI 0.39 to 0.68), fixed-effect model, I^2 = 0%, 18 trials, 1470 participants, Analysis 1.2). The funnel plot again appeared somewhat asymmetrical but the regression test was not statistically significant (Figure 5). Overall, lactose-free products resulted in eight fewer treatment failures per 100 children treated (RD -0.08, 95% CI -0.11 to -0.05), with a NNTB of 12 (95% CI 9 to 20).

Figure 5. Funnel plot of comparison: 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs; outcome: 1.2 Treatment failure.



Subgroup analyses

Subgroup analyses by age (< 12 months versus ≥ 12 months), setting (inpatients versus outpatients), income level of country (low- and middle-income versus high-income), and other differences in feed types (in addition to presence or absence of lactose) did not introduce heterogeneity or detect any subgroup differences (Analysis 2.2; see Table 3).

Sensitivity analyses

All of the sensitivity analyses of trials with low risk of bias across domains found effect sizes similar to the primary analyses. None contained substantial statistical heterogeneity (Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10).

Need for hospitalization

Only one trial reported the need for community-based trial participants to be admitted to hospital due to worsening diarrhoea (Groothuis 1986), and did not detect a statistically significant difference (RR 0.79, 95% CI 0.09 to 6.65, one trial, 83 participants, Analysis 1.3) .

Duration of hospital stay

There was no statistically significant difference in the number of days spent in hospital across the five trials which report this outcome (MD -0.31 days, 95% CI -0.83 to 0.21, five trials, 246 participants, fixed-effect model, I^2 = 0%, Analysis 1.4).

Stool volume or frequency

Three trials reported data on stool volume up to 24 hours (Brown 1991; Romer 1991; Simakachorn 2004), without statistically significantly differences (MD -9.23 g/kg/day, 95% CI -32.61 to 14.14, three trials,194 participants, Analysis 1.5). None of the trial reported stool frequency.

Change in body weight

Two trials reported data on mean percentage weight gain from admission until discharge or recovery (Fayad 1999; Romer 1991), without statistically significant differences between groups (MD -0.25, 95% CI -0.92 to 0.42, two trials, 228 participants, Analysis 1.6)

Comparison 2: Diluted (by at least 50%) versus undiluted lactose-containing milk, milk products, or foodstuffs

Mortality

No trials reported mortality as an outcome.

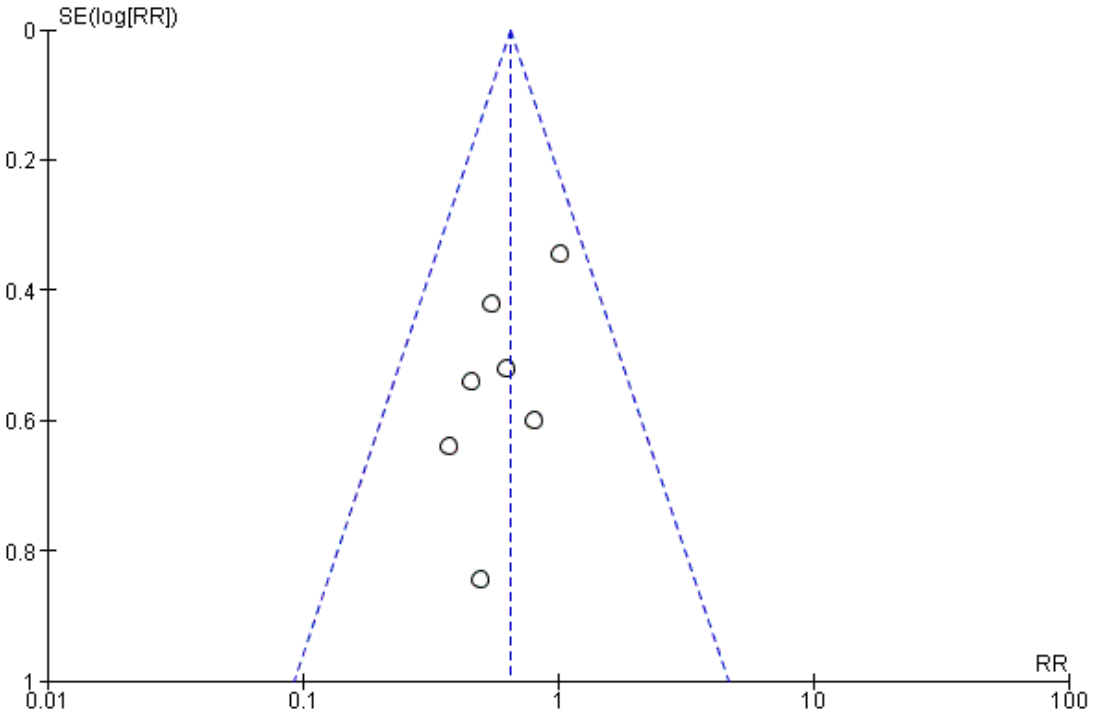
Duration of diarrhoea

No statistically significant differences in mean duration of diarrhoea were reported (MD -2.01 hours, 95% CI -9.71 to 5.68, five trials, 471 participants, Analysis 4.1).

Treatment failure

Diluted milk was associated with a statistically significant reduction in the risk of treatment failure of about a third (RR 0.65, 95% CI 0.45 to 0.94, fixed-effects model, I^2 = 0%), nine trials, 687 participants, Analysis 4.2). The funnel plot contained some asymmetry raising the possibility that some publication bias may be influencing this result (see Figure 6). Overall, diluted products resulted in six fewer treatment failures per 100 children treated (RD -0.06, 95% CI -0.11 to -0.01), with a NNTB of 17 (95% CI 9 to 100).

Figure 6. Funnel plot of comparison: 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs; outcome: 4.2 Treatment failure.



Need for hospitalization

This was not reported by any included trials.

Duration of hospital stay

Diluted milk products were not associated with a statistically significant difference in hospital stay (MD -0.17 days, 95% CI -0.50 to 0.16, nine trials, 804 participants, Analysis 4.3).

Stool volume or frequency

Two trials reported mean stool volume in the first 24 hours after admission with no statistically significant differences between groups (two trials, 212 participants, see Analysis 4.4). We did not perform a meta-analysis because of inconsistency in the reporting of the data.

Four trials reported the mean number of stools per day and again there were no statistically significant differences between groups (MD -0.21 stools/day, 95% CI -0.99 to 0.57, four trials, 417 participants, Analysis 4.5).

Change in body weight

Two trials reported mean percentage weight gain from admission until discharge or recovery (Armitstead 1989; Chew 1993), without statistically significantly differences between groups (MD -0.75%, 95% CI -1.81 to 0.32, two trials, 187 participants, Analysis 4.6).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs for young children with acute diarrhoea.

Patient or population: Young children with acute diarrhoea
Settings: Inpatient and outpatient
Intervention: Diluted lactose-containing milk, milk products, or foodstuffs
Control: Undiluted lactose-containing milk, milk products, or foodstuffs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Undiluted	Diluted			
Duration of diarrhoea (hours)	The mean duration of diarrhoea in the control groups ranged from **47 to 92 hours**	The mean duration of diarrhoea in the intervention groups was **2.01 hours shorter** (9.71 lower to 5.68 higher)	-	471 (5 trials)	⊕⊕◯◯ **low**[1,2,3,4]
Treatment failure	**173 per 1000**	**112 per 1000** (78 to 163)	**RR 0.65** (0.45 to 0.94)	687 (9 trials)	⊕⊕◯◯ **low**[1,2,3,5]
Need for hospitalization	-	-	-	(0 trials)	-

*The **assumed risk** is taken from the control group risk in the meta-analysis. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for serious risk of bias: Only one of these trials adequately described a method of allocation concealment to be considered at low risk of selection bias, and only two conducted any form of blinding.

[2] No serious inconsistency: Statistical heterogeneity was low.

[3] No serious indirectness: These trials were from a mix of high-, middle-, and low-income settings, and included children up to three years of age. All were conducted in inpatient settings.

[4] Downgraded by 1 for serious imprecision: The 95% CIs around the pooled effect estimate included both significant benefit and harm of intervention.

[5] Downgraded by 1 for serious imprecision: The result was statistically significant, but the meta-analysis remained underpowered to have full confidence in this effect.

DISCUSSION

Summary of main results

We included 33 trials (from 32 reports), enrolling 2973 children. Trials varied regarding the age of participants, the income of the country where the trial took place, and the types of interventions. Most participants were inpatients rather than outpatients.

None of the included trials reported mortality as an outcome.

Compared to lactose-containing milk, milk products, or foodstuffs, lactose-free products may reduce the duration of diarrhoea by about18 hours (MD -17.77, 95% CI -25.32 to -10.21, 16 trials, 1467 participants, *low quality evidence*). Lactose-free products probably also reduce the risk of treatment failure (typically defined as continued or worsening diarrhoea or vomiting, the need for additional rehydration therapy, or on-going weight loss) by around a half (RR 0.52, 95% CI 0.39 to 0.68), 18 trials, 1470 participants, *moderate quality evidence*).

Diluted lactose-containing milk has not been shown to reduce the duration of diarrhoea compared to undiluted milk or milk products (MD -2.01 hours, 95% CI -9.71 to 5.68, five trials, 471 participants, *low quality evidence*), but may reduce the risk of treatment failure by around a third (RR 0.65, 95% CI 0.45 to 0.94, nine trials, 687 participants, *low quality evidence*).

Overall completeness and applicability of evidence

The included trials come from a variety of inpatient settings in high-, middle-, and low-income countries. Notably, only one trial was conducted in sub-Saharan Africa.

Mortality, one of our primary outcomes given the high mortality from acute diarrhoea in low- and middle-income countries, was not reported by any of the trials. This is probably due to most trials limiting inclusion to clinically stable infants, and excluding those at higher risk of death (those severely dehydrated or malnourished).

Also, most trials specifically excluded breast-fed infants from participation, and consequently the findings of this review cannot be applied to this group. A consensus view prevails that any disadvantage related to continued lactose exposure from breastfeeding during diarrhoeal illness is likely to be outweighed by the immunological, anti-infective and nutritional benefits of breast milk. In addition, there are concerns that interruption of breastfeeding during an acute diarrhoeal illness may lead to cessation of breastfeeding completely, so it is generally not advised.

Most trials were conducted in secondary or referral healthcare settings, predominantly hospital inpatient wards, and may not be directly applicable to the community or primary care settings where most diarrhoea is treated. However, in general the level of illness severity of most participants in these trials was similar to that of children who could be safely cared for at home. Most trials did not recruit severely malnourished or dehydrated infants or children. The available trial data, however, do not provide adequate evidence to evaluate any effect of the interventions on the need for consequent hospital admission.

Most trials reported that rotavirus infection was the most commonly identified cause of acute diarrhoea in trial participants. Given plans to implement a rotavirus vaccination programme in many countries over the next few years, the infectious epidemiology of acute diarrhoea is likely to change. It is uncertain how applicable the evidence from this review will be when rotavirus is no longer the commonest infectious agent, especially since rotavirus infection may be more strongly associated with transient lactase deficiency than other, particularly bacterial, causes of infectious gastroenteritis (Saavedra 1989).

Quality of the evidence

We assessed the quality of the evidence using the GRADE approach and presented the basis for the judgements in two summary of findings tables (Summary of findings for the main comparison; Summary of findings 2).

The evidence that lactose-free milk or milk products reduces the duration of diarrhoea is of low quality, meaning we can have only limited confidence in this result. The evidence was downgraded due to the high level of heterogeneity in the magnitude of the observed effect that was not adequately explained by pre-specified subgroup analyses and because many of the included trials were at unclear or high risk of bias. However, we also noted that the result remained statistically significant in sensitivity analyses where only the trials at low risk of bias were included. The funnel plot contained some minor asymmetry but this was not considered substantial enough to downgrade for risk of publication bias. The evidence for a reduction in treatment failure is of moderate quality, meaning we can have reasonable confidence in this result.

Of note, a post-hoc subgroup analysis suggested that the unexplained heterogeneity may be due to differences in the types of interventions. In some trials, the comparisons differed not only regarding lactose content of the formula but also in other aspects of the diet. Mostly, these were comparisons of soy-based with cow's milk-based formulas. Some trials also compared mixed diets (cereals, rice, vegetable oils) with or without milk, milk products, or foodstuffs. A subgroup analysis restricted to those trials which compared the same formula, with or without lactose, found a reduction in diarrhoea duration of around 20 hours with no statistical heterogeneity.

Evidence for the effect of diluted lactose-containing products on diarrhoea duration was of low quality due to concerns about the risk of bias of the included trials (with only one trial taking adequate steps to reduce the risk of selection bias, and only two trials conducting any blinding), and imprecision of the result with very wide CIs. The evidence for a reduction in treatment failure was

of moderate quality, again downgraded due to concerns about the risk of bias of the included trials.

Potential biases in the review process

The main concern with the review process is the possibility that the findings are subject to publication and other reporting biases, including better availability of numerical data for inclusion in meta-analyses from trials which reported statistically significant or clinically important effects (Hopewell 2009). We attempted to minimize this threat by searching the proceedings of the major international conferences to identify trial reports that are not (or not yet) published in full form in academic journals. We cannot be sure that other trials have been undertaken but not reported, thus the concern remains that such trials are less likely than published trials to have detected statistically significant or clinically important effects.

We were not able to obtain the full text of two reports that were cited in a previous systematic review (Brown 1994), despite seeking them via the British Library international search facility (Chiriboga 1986; Madkour 1986). In the previous review, these reports were described as RCTs of diluted versus undiluted milk for young children with acute diarrhoea. Neither found a statistically significant effect on the duration of diarrhoea. If we obtain these articles, we will assess them for eligibility for inclusion in an update of this review.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence indicates that for young children who are predominantly bottle-fed or weaned, a change to a lactose-free diet probably results in earlier resolution of acute diarrhoea. Applicability of these findings to community-settings is uncertain as most participants in the included trials were inpatients. Alternatively, diluting lactose-containing formulas may have some benefits but further trials are necessary to have confidence in this finding.

Implications for research

If further trials are judged necessary, these should include assessment of acceptability of the interventions and of the cost-benefits. Uncertainty exists particularly regarding the effects of lactose-avoidance strategies in:

1. contributing to reductions in mortality in young children with acute severe diarrhoea complicated by malnutrition in low-income settings, and

2. hospital admission or repeat consultation in community (outpatient or primary care or pharmacist-led) settings, or as parent-led interventions.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Allen 1994

Methods	RCT
Participants	Formula-fed infants (2 months to 12 months) with acute non-bloody diarrhoea < 7 days duration, with mild or moderate dehydration Exclusion criteria: Being breast-fed, intolerant to trial formulae, malnourished infants (height or weight below 3rd percentile)
Interventions	1. Soy-based formula (Isomil®): N = 39 2. Lactose-containing formula (SMA®): N = 34
Outcomes	Duration of diarrhoea (until last abnormal stool when subsequent stools were normal for 24 hr period) Treatment failure Weight gain Formula intake Duration of hospital admission (inpatients only) Follow-up period: 14 days
Notes	Setting: Tertiary care hospital, Toronta, Canada. Included hospitalized (N = 13) and non-hospitalized (N = 20) infants Infants were initially rehydrated using an oral electrolyte solution or intravenous dextrose sodium solution Stool pathogens: Rotavirus (14%); adenovirus (3%): *Salmonella* spp. (3%); not identified (80%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Infants were consecutively assigned...according to a table of random numbers."
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"In order to maintain blinding the bottles containing formula were coded and given to parents without informing them of the content"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurses performed telephone assessment of outcomes. "Investigators and study participants were kept blinded to the study formula received, even after treatment failure"

Allen 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for all outcomes were available for 73 of 76 enrolled infants (three infants were removed from the trial within one day of enrolment because of non-compliance)

Armitstead 1989

Methods	RCT
Participants	Formula-fed infants (< 9 months) with acute diarrhoea or vomiting or both < 7 days, with mild dehydration Exclusion criteria: Breast fed babies, babies previously treated for acute diarrhoea elsewhere, and babies with chronic diarrhoea, cow's milk protein intolerance, or drug induced diarrhoea
Interventions	1. Whey hydrolysate, low lactose-free formula (Alfare®): N = 24 2. Diluted standard (usual) formula (¼ strength for 24 hrs, ½ strength for 24 hrs, ¾ strength for 24 hrs, then full strength): N = 22 3. Full strength formula: N = 22 COMPARISON 1. Group 1 versus Group 3 COMPARISON 2. Group 2 versus Group 3
Outcomes	Stool frequency Percentage change in weight Duration of hospital stay (inpatients) Relapse Refusal of feeding Follow-up period: 14 days
Notes	Setting: Tertiary care hospital, London, UK. Included hospitalized (57%) and non-hospitalized (outpatient) (43%) infants Infants were rehydrated using an oral electrolyte solution for 24 hrs prior to trial entry Stool pathogens: Viral (34%); bacterial (16%); not identified (50%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.

Armitstead 1989 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	High risk	Outcome data were not reported for 22 of 68 (32%) enrolled infants (Six of 24 infants allocated to Group 1 refused the whey hydrolysate formula)

Bhan 1988

Methods	RCT
Participants	Children (3 months to 24 months) with acute diarrhoea < 7 days, with mild dehydration Exclusion criteria: Prior antibiotic therapy; milk elimination during concurrent illness; concurrent non-gastrointestinal infections; blood in stools; clinical signs of moderate to severe dehydration
Interventions	1. Non-milk based (lactose-free) locally prepared formula (rice, lentil, sugar, and coconut oil): N = 30 2. Cow's milk formula (Lactogen full protein, Nestle: lactose 4.6 g/100 mL, with 2.5 g/100 mL sugar added): N = 30
Outcomes	Duration of diarrhoea Treatment failure (worsening diarrhoea leading to change of nutritional management) Weight gain Energy intake Follow-up period: "until recovery" (patients reviewed at home)
Notes	Location: Community-care (outpatient) facility, New Delhi, India. Infants were initially rehydrated using an oral rehydration solution (50 mL/kg) and mothers were advised to continue oral rehydration therapy at home (10mL/kg for each liquid stool passed) Stool pathogens: Rotavirus (28%); bacterial, mainly *E. coli* (42%): not identified (30%) .

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was achieved using permutation blocks of fixed length"
Allocation concealment (selection bias)	Low risk	Allocation concealment was achieved "with the help of sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details given in trial report but unlikely that they were blinded

Bhan 1988 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three participants with treatment failure were excluded from the final analyses

Brown 1991

Methods	RCT
Participants	Boys* (3 months to 24 months) with acute diarrhoea < 4 days. (*Only male to facilitate separation of urine and stool for microbiological analyses) Exclusion criteria: Prior antibiotic therapy; severe systemic infections; receiving > two breast feeds per day; another episode of diarrhoea < two weeks previously; "poor nutritional status"; presence of oedema
Interventions	1. Lactase treated (low lactose) 95% hydrolysed milk: N = 30 2. Cow's milk formula: N = 28
Outcomes	Duration of diarrhoea (time after admission until excretion of the last liquid or semi-liquid stool not followed by another liquid or semi-liquid stool within 24 hrs) Treatment failure defined as: a) Recurrent dehydration if after successful initial rehydration clinical evidence of > 5% dehydration or electrolyte disorders b) Severe diarrhoea if faecal excretion was greater > 350 g/kg/day for one day or > 250 g/kg/day for two consecutive days c) Severe prolonged diarrhoea if faecal output was still > 100 g/kg/day during the sixth day of treatment Follow-up period: 6 days
Notes	Setting: Inpatient specialist hospital clinic, Lima, Peru. This trial include two further groups (data not included in this review): 3. Wheat noodles and 95% lactose-hydrolysed milk: N = 29 4. Wheat noodles and diluted (50%) cow's milk formula: N = 29 (not included in diluted versus not diluted comparison because of wheat noodle co-intervention) Stool pathogens: Rotavirus (22%); bacterial, mainly *E. coli* (62%); mixed (32%); not identified (25%).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were assigned "using a fixed-interval, blocked randomization procedure."
Allocation concealment (selection bias)	Unclear risk	No details given as to how this was achieved.

Brown 1991 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double-masked" study but no details given. "Clinical personnel responsible for patient management were unaware of treatment assignments."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One (of 59) participant was withdrawn within two days and not included in the final analyses

Chew 1993

Methods	RCT
Participants	Boys (< 6 months) with acute diarrhoea < 120 hrs, without clinical signs of severe dehydration Exclusion criteria: Breast-fed, severe malnutrition, systemic infections, or other diseases requiring additional treatments
Interventions	1. Full strength milk formula: N = 80 2. Diluted milk formula (½ strength for 24 hrs, ¾ strength for 24 hrs, then full strength) : N = 79
Outcomes	Duration of diarrhoea Treatment failure Total stool output Number of stools (over 5 days)* Weight gain by discharge Follow-up period: 5 days *(reported number of stools divided by 5 to give daily mean number)
Notes	Setting: Hospital inpatients, Guatemala and Brazil. Oral rehydration solution and plain water could be given according to WHO recommendations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"One randomization list per centre was established...with random permuted blocks of variable length (6 to 12 subjects per block)."
Allocation concealment (selection bias)	Low risk	"Master randomization lists were then placed in sealed serially numbered envelopes."

Chew 1993 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The different formulae, which were similar in appearance, were administered through opaque feeding bottles."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Staff and investigators did not know which formula was being given."
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 participants (10%) did not complete the trial and were not included in the final analyses, mainly (N = 14) because they had severe infection requiring antibiotic treatment

Clemente Yago 1993

Methods	RCT
Participants	Formula-fed infants (1 to 12 months) with acute diarrhoea < 7 days duration Exclusion criteria: None stated.
Interventions	1. Cow's milk (lactose-containing) formula: N = 32 2. Lactose-free formula: N = 28
Outcomes	Duration of diarrhoea Treatment failure Weight change Stool volume Follow-up period: not stated
Notes	Setting: Hospital (inpatients); Hospital Severo Ochoa, Madrid, Spain Stool pathogens: Not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated using a random numbers table
Allocation concealment (selection bias)	Unclear risk	No allocation concealment described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding described.

Clemente Yago 1993 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome assessment.

Conway 1989

Methods	RCT
Participants	Formula-fed infants (6 weeks to 12 months) with acute gastroenteritis < 14 days duration, with mild or moderate dehydration Exclusion criteria: Malnourished infants
Interventions	1. Standard cow's milk formula graded re-feeding (24 hrs oral rehydration solution; 24 hrs ½ strength; 24 hrs ¾ strength formula): N = 50 2. Lactose-free cow's milk from time of admission until 2 days after stools returned to normal: N = 50 3. Standard cow's milk formula: N = 50 4. Lactose-free soy-based formula: N = 50 COMPARISON 1. Group 2 + 4 versus Group 3 Subgroup comparison "of trials in which only difference between feeds was the presence or absence of lactose": Group 2 versus Group 3 COMPARISON 2. Group1 versus Group 3.
Outcomes	Weight change Duration of diarrhoea Duration of hospitalization Treatment failure (continued or increased severity of diarrhoea with weight loss, or deteriorating fluid-electrolyte imbalance, or both) Follow-up period: Until hospital discharge
Notes	Location: Seacroft Hospital, Leeds, UK. Dehydrated infants were given oral rehydration solution or intravenous fluids Stool pathogens: Rotavirus (23%); bacterial, mainly *Salmonella* spp., *E. coli* (12%); not identified (65%).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.

Conway 1989 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All trial participants were available for analysis.

Dagan 1984

Methods	Quasi-RCT
Participants	Infants (1 month to 12 months) with acute diarrhoea < 7 days duration which resulted in weight loss, with mild, moderate, or severe dehydration Exclusion criteria: None stated.
Interventions	1. Full strength cow's milk formula (with 5% glucose added): N = 35 2. Soy-based formula (Hyprovit®): N = 40
Outcomes	Duration of diarrhoea Changes in body weight Length of hospital stay Number of days requiring intravenous fluids Treatment failure (persistence of dehydration or vomiting and diarrhoea) Follow-up period: Until hospital discharge
Notes	Setting: Hospital inpatients, Israel. Infants in one general paediatric service given one intervention and infants in a second service given other intervention Oral and intravenous rehydration therapies available. Stool pathogens (only bacteria reported): *E. coli* (40%); *Shigella* spp. (5%); not detected (55%).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quasi-randomized.
Allocation concealment (selection bias)	High risk	Quasi-randomized.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.

Dagan 1984 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All trial participants were available for analysis.

Dugdale 1982

Methods	RCT
Participants	Children (6 months to 59 months) with acute gastroenteritis < 7 days, without "other major illness" Exclusion criteria: Not stated.
Interventions	1. Diluted milk (½ strength for 24 hrs, then full strength): N = 32 2. Full strength milk: N = 28
Outcomes	Treatment failure Weight change (in first 24 hrs only) Duration of hospital admission Follow-up period: Not stated, but included post-discharge assessment
Notes	Setting: Inpatient service at Mater Children's Hospital, Brisbane, Australia Oral and intravenous rehydration therapies available. Stool pathogens: Not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Children aged > 5 years recruited were not included in any analyses

Fayad 1999

Methods	RCT
Participants	Formula-fed boys (3 months to 18 months) with acute watery diarrhoea < 7 days, without blood visible in the stool. Most (99%) of participants were mildly or moderately dehydrated Exclusion criteria: Breast-fed, severe malnutrition, systemic infections, or other diseases requiring additional treatments
Interventions	1. Soy-based formula with lactose (69 g/L): N = 100 2. Soy-based formula with sucrose: N = 100
Outcomes	Duration of diarrhoea Treatment failure Weight gain Stool output Follow-up period: Until cessation of diarrhoea or hospital discharge, whichever came sooner
Notes	Setting: Inpatient service at Cairo University Children's Hospital, Egypt Oral and intravenous rehydration therapies available. Stool pathogens: Not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomization list was established at Wyeth Nutritionals International with random permuted blocks of variable lengths. "
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 (of 200) enrolled participants were withdrawn and excluded before beginning the treatment phase; eight participants because dehydration could not be corrected, and eight because diarrhoea stopped during the rehydration phase. An intention-to-treat analysis could not be performed

Groothuis 1986

Methods	RCT
Participants	Formula-fed infants (< 12 months) with acute diarrhoea < 7 days, without evidence of dehydration Exclusion criteria: Breast-fed, receiving antibiotics.
Interventions	1. Soy-based formula with lactose: N = 20 2. Soy-based formula with sucrose: N = 22 3. Soy-based formula with polycose: N = 20 4. Soy-based formula with polycose-sucrose: N = 21
Outcomes	Stool output Weight gain Hospitalization Follow-up period: Two weeks.
Notes	Location: Outpatient clinic, Colorado, USA. All infants were fed with clear liquids for 24 hrs, half strength formula for an additional 24 hrs, and full strength trial formula on the third day Parents were asked to limit feeding of solids for the intervention period Five infants ware admitted to hospital: one for suspected sepsis, and the remaining four had developed more diarrhoea and had become dehydrated Stool pathogens: Rotavirus (24%); bacterial (7%); not identified (69%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Low risk	"...opaque packaging units that were coded by the hospital pharmacists"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Interventions were "pre-measured in identical opaque packaging units that were coded by the hospital pharmacists, who retained the random coded table until completion of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Interventions were "pre-measured in identical opaque packaging units that were coded by the hospital pharmacists, who retained the random coded table until completion of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants lost to follow-up but no intention-to treat analysis performed

Haffejee 1990

Methods	RCT
Participants	Formula fed children (< 28 months) with acute diarrhoea < 7 days, without evidence of dehydration Exclusion criteria: Breast-fed. Receipt of oral rehydration therapy, antibiotics, or antidiarrhoeal preparations during the 5 days prior to admission; or any dietary modification, restriction of lactose intake, or withholding of food during this period; patients unable to tolerate oral feeds and those (mainly older children) who were receiving formula feeds before onset of diarrhoea
Interventions	1. Cow's milk formula: N = 124 2. Lactose-free soy-based formula N = 77
Outcomes	Duration of diarrhoea Follow-up period: 14 days
Notes	Location: Hospital inpatient ward, Durban, South Africa. Oral and intravenous rehydration therapies available. Stool pathogens (only rotavirus reported): Rotavirus (56%).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Low risk	"Randomization was achieved by opening a sealed envelope containing a previously determined feeding schedule"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Duration of diarrhoea not reported for 6 withdrawn participants: two infants died in acute stage (one in each group), and four infants developed chronic (> 14 days) diarrhoea (three in cow's milk group and one in soy group)

Haque 1983

Methods	RCT
Participants	Children (1 to 24 months) with acute diarrhoea and mild, moderate, or severe dehydration Exclusion criteria: None stated.
Interventions	Clear fluids for 6 to 24 hrs then either: 1. Diluted milk formula (¼ strength for 24 hrs, ½ strength for 24 hrs, then full strength) : N = 52 2. Full strength milk formula: N = 46 (Third group allocated to immediate milk feeding without clear fluids, not included in this analysis)
Outcomes	Duration of diarrhoea Changes in body weight Length of hospital stay Follow-up period: Until hospital discharge
Notes	Setting: Inpatient (hospital), Saudi Arabia. Oral and intravenous rehydration therapies available. Stool pathogens: Not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.

Isolauri 1986

Methods	RCT
Participants	Children (6 to 34 months) with acute diarrhoea. Exclusion criteria: None stated.
Interventions	1. Mixed diet with milk and milk products eliminated: N = 27 2. Mixed diet with usual milk and milk products retained: N = 38
Outcomes	Duration of diarrhoea and vomiting Duration of hospital admission Weight gain Recurrence of diarrhoea within one month Follow-up period: Up to one month
Notes	Setting: Hospital inpatient ward, Finland. All children in both groups received ordinary mixed diet appropriate for age Stool pathogens (only rotavirus reported): Rotavirus (71%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Parents were aware of the type of diet".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.

Leake 1974

Methods	RCT
Participants	Formula-fed infants (1 week to 8 months) with acute severe diarrhoea < 7 days duration Exclusion criteria: None stated. Lost to follow-up: 1 (from group 2 due to severe intolerance to soy and milk formulas)
Interventions	1. Soy-based (lactose-free) formula (Isomil®): N = 11 2. Cow's milk formula: N = 11

Leake 1974 (*Continued*)

Outcomes	Treatment failure (> 5 watery stools per day for 3 consecutive days) Follow-up period: Not stated.
Notes	Setting: Hospital inpatient department, California, USA. Oral rehydration therapy was available when required prior to randomization to feed Stool pathogens: Not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"the patient was assigned to one of two groups by a table of random numbers."
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All formulas were kept in coded sterile bottles. The formula codes were broken at the end of the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All formulas were kept in coded sterile bottles. The formula codes were broken at the end of the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was lost to follow-up but not accounted for in analysis

Lifshitz 1991

Methods	RCT
Participants	Formula-fed boys (< 12 months) with acute severe diarrhoea < 7 days, and clinical signs of > 5% dehydration Exclusion criteria: Systemic infections treated with antibiotics. Breast fed in the month before admission
Interventions	1. Diluted (2/3) cow's milk: N = 10 2. Cow's milk formula (Nanon®): N = 10 3. Lactose-free milk formula (Portagen®): N = 10 4. Lactose-free milk formula (Pregestimil®): N = 10 5. Lactose-free milk formula (Prosobee®): N = 10 COMPARISON 1. Group 1 + 2 versus Group 3 + 4 + 5 (COMPARISON 2. Not eligible since Group 1 dilution < 50%)
Outcomes	Recovery by 72 hrs Volume of diarrhoea Need for oral or intravenous rehydration Treatment failure

Lifshitz 1991 (*Continued*)

	Follow-up period: 72 hrs.
Notes	Setting: Hospital metabolic inpatient unit, San Paulo, Brazil Stool pathogens: *E. coli* (50%); "others" (14%); not detected (36%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The physicians in charge of the patients were unaware of feeding selection given throughout the study."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up assessment.

Lozano 1994

Methods	RCT
Participants	Children (1 to 24 months) with acute diarrhoea < 7 days, and evidence of dehydration Exclusion criteria: Receiving > 50% of daily milk as breast milk, not receiving lactose or milk formula prior to illness, antibiotic therapy < 48 hrs prior to admission, chronic malabsorption syndrome
Interventions	1. Lactose-free formula (AL-110®): N = 29 2. Cow's milk (lactose-containing) formula (NAN1® or NAN2®): N = 28
Outcomes	Duration of diarrhoea Weight change Treatment failure Follow-up period: Until discharge
Notes	Setting: Hospital (inpatients), Bogota, Colombia. Stool pathogens: (only rotavirus reported): Rotavirus (44%).

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"allocated to intervention or control group...using block randomization"
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details given in trial report.

Maudgal 1985

Methods	RCT
Participants	Children (mean age 1 year) with "mild" gastroenteritis.
Interventions	1. "Graduated" re-feeding with milk or cow's milk formula: ¼ strength for 24 hrs, ½ strength for further 24 hrs, then full strength: N = 86 2. Immediate re-feeding with full strength milk or cow's milk formula: N = 89
Outcomes	Duration of hospital admission Stool frequency (until 96 hrs) Weight change (until 96 hrs) Follow-up period: Not stated, presumed until discharge.
Notes	Setting: Hospital (inpatients) ward, St. George's Hospital, London, UK Stool pathogens: Rotavirus (about 30%); others not specified or not detected Note: Duration of diarrhoea reported in Brown 1994; unclear where these data came from, so not included in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.

Maudgal 1985 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data not reported for 6 (of 181) recruited children.

McDowell 1985

Methods	RCT
Participants	Children (3 months to 18 months) with acute diarrhoea (gastroenteritis) < 5 days, with any severity of dehydration Exclusion criteria: Need for intravenous rehydration.
Interventions	1. Immediate full-strength cow's milk formula: N = 47 2. Diluted formula: ¼ strength for 12 hrs; ½ strength for 12 hrs; ¾ strength for 12 hrs; then full strength: N = 46
Outcomes	Treatment failure Duration of hospital admission Follow-up period: Until discharge
Notes	Setting: Hospital (inpatient) ward, Countess of Chester Hospital, Chester, UK Oral rehydration therapy was available when required prior to randomization to feed Stool pathogens: Pathogens detected in 50% (mix of rotavirus, adenovirus, *E. coli*, *Salmonella* spp. and *Giardia lamblia*).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.

Naidoo 1981

Methods	RCT
Participants	Infants (< 12 months) with severe diarrhoea < 48 hrs, and evidence of dehydration Exclusion criteria: None stated. All infants were dehydrated on admission and most had electrolyte imbalance requiring I/V fluid therapy
Interventions	1. Lactose-free soy-based formula (Isomil®): N = 56 2. Standard (lactose-containing) cow's milk formula: N = 56
Outcomes	Treatment failure (infant required another period of fasting or intravenous fluid, or > 5 watery stools/day for 3 consecutive days) Number of stools/day Readmission to hospital Follow-up period: Not stated
Notes	Setting: Hospital (inpatient), Durban, South Africa. Stool pathogens: Not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given in trial report - only states that child was: "assigned at random"
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.

Pichaipat 1986

Methods	RCT
Participants	Infants (< 12 months) with acute liquid or watery diarrhoea < 5 days, and evidence of dehydration Exclusion criteria: None stated. Infants were dehydrated on admission and most had electrolyte imbalance requiring intravenous fluid therapy

Pichaipat 1986 (*Continued*)

Interventions	Diluted formula (50%), for 24 hrs: N = 20 Full strength formula: N = 20
Outcomes	Treatment failure Stool frequency (48 hrs) Duration of hospitalization Follow-up period: Not stated
Notes	Ratchasima Hospital (in patients), Maharaj Nakhon, Thailand. Stool pathogens: Rotavirus (about 50%); one case of *Vibrio parahaemolyticus*, one case of *E. coli* infection.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	High risk	Cards selected ("pulled out") that indicated diluted or full strength formula
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.

Placzek 1984

Methods	Quasi-RCT
Participants	Children (< 18 months) with acute gastroenteritis < 5 days, and > 5% dehydration Exclusion criteria: Breast fed, "not thriving".
Interventions	1. "Graduated" re-feeding with milk or cow's milk formula: ¼ strength for 24 hrs, ½ strength for 24 hrs, ¾ strength for 24 hrs, then full strength: N = 25 2. Immediate re-feeding with full strength cow's milk formula: N = 23
Outcomes	Treatment failure (1/25 versus 7/23) Stool frequency on day 3 Weight change (until 96 hrs) Duration of hospital stay

Placzek 1984 (*Continued*)

	Oral or intravenous rehydration therapy was given as required Follow-up period: Until discharge
Notes	Setting: Hospital (inpatient) ward, Queen Elizabeth Hospital for Children, London, UK Stool pathogens: Rotavirus (about 30%); other enterovirus (about 20%); *E. coli* (about 10%); mixed (6%); not detected (44%).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate allocation.
Allocation concealment (selection bias)	High risk	Alternate allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up.

Prietsch 1999

Methods	RCT
Participants	Infants (1 month to 12 months) with acute diarrhoea < 7 days duration and evidence of dehydration Exclusion criteria: Breast fed, chronic diarrhoea, neurological disturbances, immune deficiencies, or uncontrollable vomiting
Interventions	1. Soy-based formula (lactose-free): N = 44 2. Lactose-containing cow's milk formula: N = 45
Outcomes	Duration of diarrhoea Treatment failure Follow-up period: Not stated
Notes	Setting: Inpatient facility, Brazil. Stool pathogens: Rotavirus (10%); "parasites" (5%); bacterial (16%); not identified (69%)

Risk of bias

Prietsch 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned to two groups - no further information.
Allocation concealment (selection bias)	Unclear risk	No information.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.

Ransome 1984

Methods	RCT
Participants	Children (3 months to 36 months) with acute gastroenteritis requiring intravenous therapy Exclusion criteria: Severe malnutrition (marasmus or kwashiorkor), and absence of lactose in the stools
Interventions	1. Full strength cow's milk formula: N = 37 2. "Graduated" cow's milk formula: ½ strength for 24 hrs, 2/3 strength for further 48 hrs, then full strength on fourth day: N = 37
Outcomes	Duration of diarrhoea Treatment failure (withdrawn due to lactose malabsorption) Follow-up period: Not stated.
Notes	Setting: Hospital (inpatient) ward, Johannesburg, South Africa Stool pathogens: Not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.

Ransome 1984 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The milk room attendant was the only person who knew the formulation of the two milks until the trial was over"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Duration of diarrhoea not reported for children with "treatment failure" (18%)

Romer 1991

Methods	RCT
Participants	Boys (3 months to 14 months) with acute diarrhoea < 4 days, with signs of dehydration, Exclusion criteria: Shock, severe malnutrition, underlying disease, breast-fed (> 2 breast milk feeds daily), treated with antibiotics during the previous 2 weeks
Interventions	1. Lactose-free mixed diet (soup based on chicken, plantain, and coconut oil): N = 36 2. Diet with cow's milk at normal concentration for age (8.8% for 3-6 months; 13.5% for over 6 months): N = 37
Outcomes	Duration of diarrhoea Weight change Treatment failure Follow-up period: Until discharge
Notes	Setting: Hospital (inpatient) facility, Caracas, Venezuela. WHO oral rehydration solution (WHO-ORS) available for both groups on admission Stool pathogens: (only rotavirus reported): Rotavirus (44%).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...the study was carried out by blocked randomization".
Allocation concealment (selection bias)	Low risk	"An envelope corresponding to each patient was only opened when he was given WHO-ORS"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.

Romer 1991 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	High risk	17 of 76 participants (22%) were excluded and not included in any analyses

Saneian 2012

Methods	Quasi-RCT
Participants	Formula-fed children (1 month to 24 months) with acute non-bloody diarrhoea, < 14 days Exclusion criteria: Bloody stools, major systemic illness, severe malnutrition (weight for age <60% or weight for height <70%), severe dehydration requiring intravenous infusion, severe vomiting, or history of antibiotic therapy
Interventions	1. Lactose-free formula: N = 37 2. Lactose-containing formula: N = 37 (No further description of formula reported)
Outcomes	Duration of diarrhoea (only defined as "time to diarrhoea relief") Weight change Follow-up period: 7 days
Notes	Setting: Outpatient facility; University Hospitals in Isfahan, Iran (community-based intervention). Oral rehydration therapy administered at first assessment for dehydrated children Stool pathogens: Not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate allocation.
Allocation concealment (selection bias)	High risk	Alternate allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.

Incomplete outcome data (attrition bias) All outcomes	Low risk	Three participants (all controls) were lost to follow-up.

Simakachorn 2004

Methods	RCT
Participants	Formula fed boys (3 months to 24 months) with acute watery diarrhoea < 7 days, with mild or moderate dehydration Exclusion criteria: Children with mucous bloody stools, major systemic illness, or severe malnutrition
Interventions	1. Lactose-free formula (Dumex®): N = 40 2. Lactose-containing formula (Dumex®): N = 40
Outcomes	Duration of diarrhoea Treatment failure Weight change Follow-up period: 7 days
Notes	Setting: Hospital (inpatient) facility: Maharat Nakhon Ratchasima Hospital, Thailand Oral rehydration fluids administered as required during first 4 hrs of admission Stool pathogens: Rotavirus (53%); bacterial "entero-pathogens" (19%); not identified (28%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation [was in] blocks of four".
Allocation concealment (selection bias)	Low risk	"[randomisation blocks contained] 2 lactose-free and 2 lactose containing...numerically coded"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"[intervention] could not be distinguished from [comparator]"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as "double blind". Not explicitly stated if assessors were also blind to treatment assignment but given that the intervention could not be distinguished and codes were applied it is highly likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	"no participants were lost to follow-up".

Sutton 1968

Methods	RCT
Participants	Children (< 24 months) hospitalized with acute gastroenteritis, < 73 days Exclusion criteria: Chronic disease, received antibiotics < 48 hrs before trial entry
Interventions	1. Lactose-free formula (glucose 6.4%): N = 48 2. Lactose-containing formula (lactose 6.4%): N = 49 Both formulae were given in increased concentrations over first few days to full strength
Outcomes	Duration of diarrhoea Treatment failure (defined as persisting profuse diarrhoea after a second fast) Number of stools per day Follow-up period: Until discharge
Notes	Setting: Hospital (inpatient), Ontario, Canada. Stool pathogens: Not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given in trial report.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up.

Touhami 1989

Methods	RCT
Participants	"Well nourished and weaned" infants (< 9 months) with acute diarrhoea Exclusion criteria: Breast-fed.
Interventions	1. Full strength cow's milk formula: N = 40 2. "Graduated" cow's milk formula: ½ strength for 24 hrs, then full strength: N = 40

Touhami 1989 (*Continued*)

Outcomes	Duration of diarrhoea Treatment failure Oral rehydration therapy given as required on admission prior to randomization Follow-up period: Until discharge
Notes	Setting: l'Unité de Recherche "Mère-Enfant", Institut des Sciences Médicale Oran, Algeria

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	86% follow-up: 5 infants in each group withdrawn by parents, and 1 infant in intervention group withdrawn because of a "complication"

Wall 1994

Methods	RCT
Participants	Children (< 24 months) with acute gastroenteritis, < 5 days, with or without vomiting Exclusion criteria: Extra-intestinal infection.
Interventions	1. Lactose-free corn syrup-based milk formula (O-LAC®): N = 29 2. Low lactose (95% hydrolysed) milk formula (De-Lact®): N = 29 3. Standard 100% lactose-containing cow's milk formula (Enfalac®): N = 33 COMPARISON 1. Group 1 + 2 versus Group 3 Subgroup comparison "of trials in which only difference between feeds was the presence or absence of lactose": Group 2 versus Group 3
Outcomes	Duration of diarrhoea (reported as median/range) Treatment failure (continued or increased severity of diarrhoea with weight loss or deteriorating fluid and electrolyte balance) Weight change Follow-up period: 48 hrs

Wall 1994 (*Continued*)

Notes	Setting: Hospital (inpatient) wards, Brisbane and Adelaide, Australia Prior to randomization, dehydrated infants received oral or Iintravenouse fluids Stool pathogens: Rotavirus (38%); adenovirus (3%); *E. coli* (3%); *Salmonella* spp. (2%) ; *G. lamblia* (1%); not identified (53%).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given in trial report.
Allocation concealment (selection bias)	Unclear risk	No details given in trial report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The formulae were supplied and packaged so as to blind care-givers and investigators"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given in trial report.
Incomplete outcome data (attrition bias) All outcomes	High risk	21 of 91 participants (23%) dropped out and were not accounted for in any analyses

Wolf 1989

Methods	RCT
Participants	Formula-fed infants (< 60 days) admitted to hospital with acute diarrhoea Exclusion criteria: None stated
Interventions	1. Lactose-containing formula: N = 14 2. Lactose-free (hydrolysed) formula (Alfare): N = 14
Outcomes	Treatment failure Weight gain Follow-up period: Not stated
Notes	Setting: University Children's Hospital, Ulm, Germany. Stool pathogens: Not reported.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomized. No further details.

Wolf 1989 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	None described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	None described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	None described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 of 28 (18%) participants were lost to follow-up.

Xu 2009

Methods	RCT
Participants	Formula-fed infants (< 12 months) with acute diarrhoea. Exclusion criteria: None stated
Interventions	1. Lactose-containing cow's milk formula: N = 63 2. Lactose-free cow's milk formula: N = 63
Outcomes	Duration of diarrhoea Treatment failure Follow-up period: Not stated
Notes	Inpatients and outpatients departments, Children's Hospital of Fudan University, Shanghai, China Stool pathogens: Not identified.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	None described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as "double blind".

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data for six infants (three in each group) withdrawn because of formula intolerance (parental request) or worsening vomiting were not reported for "duration of diarrhoea" (but were included in "treatment failure")

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

Study	Reason for exclusion
Agustina 2007	Both control and intervention groups received formulas with low levels of lactose
Alarcon 1991	Comparison of lactose-free milk with very low lactose-containing milk (1.5% lactose)
Binns 2007	Both control and intervention groups contained the same level of lactose
Brand 1977	Included children both with and without diarrhoea.
Brunster 1990	Not a RCT or quasi-RCT.
Dagan 1980	Reports findings from a study already included (Dagan 1984).
Dewit 1987	Participants had chronic (not acute) diarrhoea.
Donovan 1987	Participants had chronic (not acute) diarrhoea.
Eichenberger 1984	Some participants had sub-acute diarrhoea.
Ferrari 1987	Neither formula contains sufficient lactose.
Fox 1990	Comparison of full strength cow's milk with rapid regrade (within 24 hrs) to full strength cow's milk
Herrera-Anaya 1987	Participants had chronic (not acute) diarrhoea.
Hoghton 1996	Study of immediate modified feeding with no group receiving any lactose-containing milk or food
Hohenauer 1983	No lactose-containing intervention.
Ibanez 1986	Unclear if study is a comparison between lactose-containing and lactose-free feeds
Kukuruzovic 2002	Comparison of lactose-free formula with a formula containing only a trace of lactose (Alfare)
Loredo-Adala 1984	Unclear as to the content of lactose in either the control or intervention group
Mahalanabis 1993	No lactose-containing intervention.

(*Continued*)

Margolis 1990	Compared patients assigned to any treatment diet (some lactose-containing some non-lactose) with those who continued to receive their usual diet
McClean 1990	Only compares a dilute lactose intervention with either a very low lactose-containing intervention or a lactose-free intervention
Mitchell 1977	Participants both with and without diarrhoea were included.
Ooi 1989	Compared graduated feeding with cow's milk versus immediate full feeding with soy-based formula
Palma 1997	Not comparing lactose against non-lactose.
Rajah 1988	Participants had prolonged (not acute) diarrhoea.
Rees 1979	Compared continuing on full-strength milk with taking clear fluids until the diarrhoea settled before full-strength milk was reintroduced either immediately, or gradually in quarter-strength steps
Rothman 1980	Participants suffered from kwashiorkor and not necessarily diarrhoea
Sagaro 1991	Participants suffered from persistent diarrhoea.
Schmidt 1990	Not a RCT and all participants did not have acute diarrhoea.
Silveira 1989	Participants had prolonged (not acute) diarrhoea.
Sperotto 1998	Not a RCT.
Suthutvoravut 1983	Participants had prolonged (not acute) diarrhoea.
Ubaldo 1998	Not described as randomized.
Wehba 1989	Comparison of lactose-free milk with very low lactose-containing milk
Wemmer 1977	Unclear if participants had acute diarrhoea. Unclear about lactose content in intervention and comparison group

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chiriboga 1986

Methods	Information not available.
Participants	Information not available.
Interventions	Information not available.

Chiriboga 1986 (*Continued*)

Outcomes	Information not available.
Notes	Cited in Brown 1994. Article not available from British Library.

Madkour 1986

Methods	Information not available.
Participants	Information not available.
Interventions	Information not available.
Outcomes	Information not available.
Notes	Cited in Brown 1994. Article not available from the British Library.

DATA AND ANALYSES

Comparison 1. Lactose-free versus lactose-containing milk, milk products, or foodstuffs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of diarrhoea (hours)	16	1467	Mean Difference (IV, Random, 95% CI)	-17.77 [-25.32, -10.21]
2 Treatment failure	18	1470	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.39, 0.68]
3 Need for hospitalization	1	83	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.09, 6.65]
4 Duration of hospital stay (days)	5	246	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.83, 0.21]
5 Stool volume (g/kg body weight/day)	3	194	Mean Difference (IV, Random, 95% CI)	-9.23 [-32.61, 14.14]
6 Weight change (at discharge or recovery)	2	228	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.92, 0.42]

Comparison 2. Subgroup analyses (other differences in feed type): Lactose-free versus lactose-containing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of diarrhoea (feed type)	16	1417	Mean Difference (IV, Random, 95% CI)	-17.94 [-25.61, -10.26]
1.1 Only difference between trial groups is presence or absence of lactose	9	810	Mean Difference (IV, Random, 95% CI)	-20.20 [-24.71, -15.69]
1.2 Treatment groups differ in types of feed as well as presence or absence of lactose	7	607	Mean Difference (IV, Random, 95% CI)	-14.38 [-30.15, 1.39]
2 Treatment failure (feed type)	18	1391	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.40, 0.69]
2.1 Only difference between trial groups is presence or absence of lactose	11	894	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.42, 0.85]
2.2 Treatment groups differ in types of feed as well as presence or absence of lactose	7	497	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.28, 0.66]

Comparison 3. Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of diarrhoea (sequence generation)	8	605	Mean Difference (IV, Fixed, 95% CI)	-17.85 [-23.87, -11.82]
2 Duration of diarrhoea (allocation concealment)	4	385	Mean Difference (IV, Random, 95% CI)	-16.89 [-31.43, -2.36]
3 Duration of diarrhoea (blinding of participants and personnel)	3	273	Mean Difference (IV, Random, 95% CI)	-31.53 [-46.25, -16.82]
4 Duration of diarrhoea (blinding of outcome assessment)	3	273	Mean Difference (IV, Random, 95% CI)	-31.53 [-46.25, -16.82]
5 Duration of diarrhoea (complete outcome assessment)	13	1164	Mean Difference (IV, Random, 95% CI)	-17.75 [-26.62, -8.89]
6 Treatment failure (sequence generation)	9	657	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.37, 0.84]
7 Treatment failure (allocation concealment)	3	207	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.16, 1.41]
8 Treatment failure (blinding of participants and personnel)	5	305	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.36, 0.81]
9 Treatment failure (blinding of outcome assessment)	3	174	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.28, 0.79]
10 Treatment failure (complete outcome assessment)	14	1116	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.37, 0.72]

Comparison 4. Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of diarrhoea (hrs)	5	471	Mean Difference (IV, Fixed, 95% CI)	-2.01 [-9.71, 5.68]
2 Treatment failure	9	687	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.45, 0.94]
3 Duration of hospital stay (days)	9	804	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.50, 0.16]
4 Stool volume (g/kg/day or g/day)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Number of stools per day	4	417	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.99, 0.57]
6 Weight change (at discharge or recovery)	2	187	Mean Difference (IV, Fixed, 95% CI)	-0.75 [-1.81, 0.32]

Analysis 1.1. Comparison 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs, Outcome 1 Duration of diarrhoea (hours).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs

Outcome: 1 Duration of diarrhoea (hours)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose-containing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Sutton 1968	48	70.6 (27.7)	49	101 (52.5)		7.6 %	-30.40 [-47.06, -13.74]
Dagan 1984	40	83.52 (32.64)	35	150.72 (101.76)		3.3 %	-67.20 [-102.40, -32.00]
Isolauri 1986	27	31.2 (16.8)	38	28.8 (19.2)		10.4 %	2.40 [-6.40, 11.20]
Bhan 1988	28	264 (240)	26	182.4 (259.2)		0.3 %	81.60 [-51.92, 215.12]
Conway 1989	100	49 (47.6)	50	68 (43.6)		8.1 %	-19.00 [-34.27, -3.73]
Haffejee 1990	75	61.4 (43.5)	120	70.5 (60.3)		8.3 %	-9.10 [-23.71, 5.51]
Romer 1991	30	55.59 (48.86)	26	75.53 (49.61)		5.0 %	-19.94 [-45.81, 5.93]
Brown 1991	30	119 (63)	28	151 (86)		2.9 %	-32.00 [-71.02, 7.02]
Clemente Yago 1993	28	105.6 (74.4)	32	115.2 (50.4)		3.7 %	-9.60 [-42.22, 23.02]
Allen 1994	39	108 (86.4)	34	158.4 (100.8)		2.4 %	-50.40 [-93.80, -7.00]
Lozano 1994	28	41.9 (32)	24	54.5 (40)		6.6 %	-12.60 [-32.51, 7.31]
Fayad 1999	86	23 (21)	86	39 (28)		10.9 %	-16.00 [-23.40, -8.60]
Prietsch 1999	44	81.36 (31.92)	45	78.48 (34.8)		8.6 %	2.88 [-10.99, 16.75]
Simakachorn 2004	40	64.2 (39.9)	40	92 (42.3)		7.2 %	-27.80 [-45.82, -9.78]
Xu 2009	60	197 (90)	60	230 (86)		3.9 %	-33.00 [-64.50, -1.50]
Saneian 2012	37	40.8 (16.8)	34	62.4 (16.8)		10.7 %	-21.60 [-29.42, -13.78]
Total (95% CI)	**740**		**727**			**100.0 %**	**-17.77 [-25.32, -10.21]**

Heterogeneity: $Tau^2 = 122.46$; $Chi^2 = 45.59$, df = 15 (P = 0.00006); $I^2 = 67\%$

Test for overall effect: Z = 4.61 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs, Outcome 2 Treatment failure.

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs

Outcome: 2 Treatment failure

Study or subgroup	Lactose free n/N	Lactose containing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Allen 1994	13/39	18/34		15.8 %	0.63 [0.36, 1.09]
Bhan 1988	2/28	1/26		0.9 %	1.86 [0.18, 19.29]
Brown 1991	6/30	4/28		3.4 %	1.40 [0.44, 4.45]
Clemente Yago 1993	1/28	2/32		1.5 %	0.57 [0.05, 5.97]
Conway 1989	12/100	4/50		4.4 %	1.50 [0.51, 4.41]
Dagan 1984	0/40	5/35		4.8 %	0.08 [0.00, 1.39]
Fayad 1999	2/90	6/94		4.8 %	0.35 [0.07, 1.68]
Leake 1974	1/11	6/10		5.2 %	0.15 [0.02, 1.05]
Lifshitz 1991	9/30	13/20		12.8 %	0.46 [0.24, 0.87]
Lozano 1994	1/29	2/25		1.8 %	0.43 [0.04, 4.48]
Naidoo 1981	4/56	14/56		11.5 %	0.29 [0.10, 0.81]
Prietsch 1999	1/44	1/45		0.8 %	1.02 [0.07, 15.85]
Romer 1991	2/36	5/37		4.1 %	0.41 [0.09, 1.98]
Simakachorn 2004	0/40	3/40		2.9 %	0.14 [0.01, 2.68]
Sutton 1968	1/48	8/49		6.5 %	0.13 [0.02, 0.98]
Wall 1994	7/58	5/33		5.2 %	0.80 [0.27, 2.31]
Wolf 1989	0/11	1/12		1.2 %	0.36 [0.02, 8.04]
Xu 2009	8/63	15/63		12.3 %	0.53 [0.24, 1.17]
Total (95% CI)	**781**	**689**		**100.0 %**	**0.52 [0.39, 0.68]**

Total events: 70 (Lactose free), 113 (Lactose containing)

Heterogeneity: Chi^2 = 16.63, df = 17 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 4.78 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs, Outcome 3 Need for hospitalization.

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs

Outcome: 3 Need for hospitalization

Study or subgroup	Lactose-free n/N	Lactose-containing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Groothuis 1986	1/20	4/63		100.0 %	0.79 [0.09, 6.65]
Total (95% CI)	**20**	**63**		**100.0 %**	**0.79 [0.09, 6.65]**

Total events: 1 (Lactose-free), 4 (Lactose-containing)

Heterogeneity: not applicable

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs, Outcome 4 Duration of hospital stay (days).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs

Outcome: 4 Duration of hospital stay (days)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose-containing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Allen 1994	7	1.6 (0.98)	6	2.7 (1.4)		15.2 %	-1.10 [-2.43, 0.23]
Armitstead 1989	8	3.5 (1.55)	10	3.6 (2.24)		8.8 %	-0.10 [-1.86, 1.66]
Conway 1989	50	7.1 (3.6)	25	6.9 (2.2)		15.5 %	0.20 [-1.12, 1.52]
Dagan 1984	40	10.5 (4.62)	35	12.8 (9.76)		2.2 %	-2.30 [-5.84, 1.24]
Isolauri 1986	27	2.9 (1.2)	38	3.1 (1.6)		58.3 %	-0.20 [-0.88, 0.48]
Total (95% CI)	**132**		**114**			**100.0 %**	**-0.31 [-0.83, 0.21]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.29$, df = 4 (P = 0.51); $I^2 = 0.0\%$

Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs, Outcome 5 Stool volume (g/kg body weight/day).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs

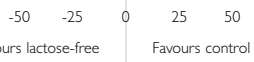
Outcome: 5 Stool volume (g/kg body weight/day)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose-containing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Brown 1991	30	66 (44)	28	56 (39)		40.1 %	10.00 [-11.37, 31.37]
Romer 1991	30	114.88 (66.22)	26	147.18 (104.78)		17.7 %	-32.30 [-79.03, 14.43]
Simakachorn 2004	40	38.87 (38.51)	40	56.7 (50.49)		42.2 %	-17.83 [-37.51, 1.85]
Total (95% CI)	**100**		**94**			**100.0 %**	**-9.23 [-32.61, 14.14]**

Heterogeneity: Tau^2 = 235.90; Chi^2 = 4.72, df = 2 (P = 0.09); I^2 =58%

Test for overall effect: Z = 0.77 (P = 0.44)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs, Outcome 6 Weight change (at discharge or recovery).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 1 Lactose-free versus lactose-containing milk, milk products, or foodstuffs

Outcome: 6 Weight change (at discharge or recovery)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose-containing N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Fayad 1999	86	4.2 (2.3)	86	4.3 (2.5)		86.5 %	-0.10 [-0.82, 0.62]
Romer 1991	30	2.19 (3.01)	26	3.39 (3.82)		13.5 %	-1.20 [-3.02, 0.62]
Total (95% CI)	**116**		**112**			**100.0 %**	**-0.25 [-0.92, 0.42]**

Heterogeneity: Chi² = 1.21, df = 1 (P = 0.27); I² =18%

Test for overall effect: Z = 0.73 (P = 0.47)

Test for subgroup differences: Not applicable

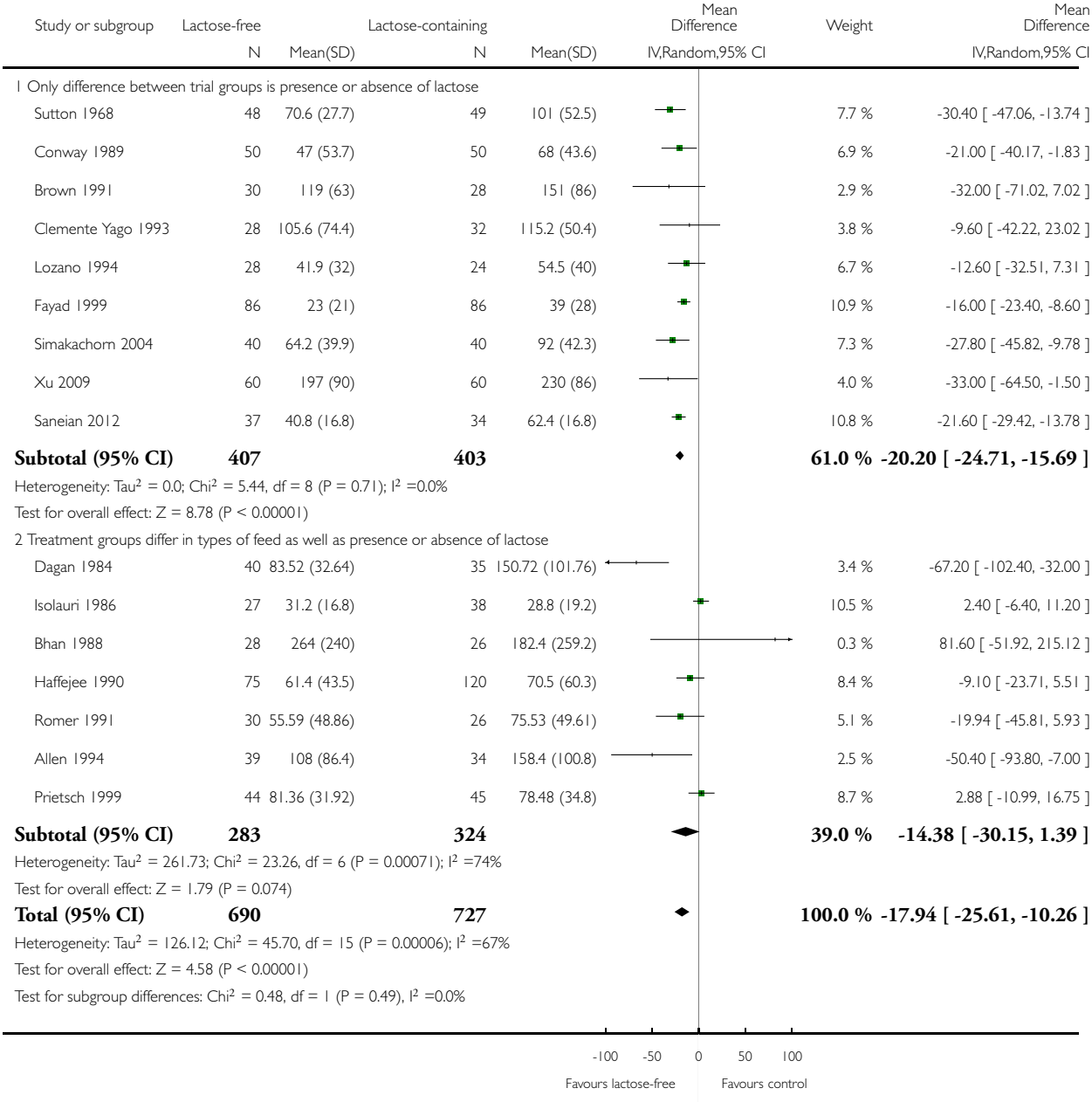
Analysis 2.1. Comparison 2 Subgroup analyses (other differences in feed type): Lactose-free versus lactose-containing, Outcome 1 Duration of diarrhoea (feed type).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 2 Subgroup analyses (other differences in feed type): Lactose-free versus lactose-containing

Outcome: 1 Duration of diarrhoea (feed type)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose-containing N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Only difference between trial groups is presence or absence of lactose							
Sutton 1968	48	70.6 (27.7)	49	101 (52.5)		7.7 %	-30.40 [-47.06, -13.74]
Conway 1989	50	47 (53.7)	50	68 (43.6)		6.9 %	-21.00 [-40.17, -1.83]
Brown 1991	30	119 (63)	28	151 (86)		2.9 %	-32.00 [-71.02, 7.02]
Clemente Yago 1993	28	105.6 (74.4)	32	115.2 (50.4)		3.8 %	-9.60 [-42.22, 23.02]
Lozano 1994	28	41.9 (32)	24	54.5 (40)		6.7 %	-12.60 [-32.51, 7.31]
Fayad 1999	86	23 (21)	86	39 (28)		10.9 %	-16.00 [-23.40, -8.60]
Simakachorn 2004	40	64.2 (39.9)	40	92 (42.3)		7.3 %	-27.80 [-45.82, -9.78]
Xu 2009	60	197 (90)	60	230 (86)		4.0 %	-33.00 [-64.50, -1.50]
Saneian 2012	37	40.8 (16.8)	34	62.4 (16.8)		10.8 %	-21.60 [-29.42, -13.78]
Subtotal (95% CI)	**407**		**403**			**61.0 %**	**-20.20 [-24.71, -15.69]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.44$, df = 8 (P = 0.71); $I^2 = 0.0\%$							
Test for overall effect: Z = 8.78 (P < 0.00001)							
2 Treatment groups differ in types of feed as well as presence or absence of lactose							
Dagan 1984	40	83.52 (32.64)	35	150.72 (101.76)		3.4 %	-67.20 [-102.40, -32.00]
Isolauri 1986	27	31.2 (16.8)	38	28.8 (19.2)		10.5 %	2.40 [-6.40, 11.20]
Bhan 1988	28	264 (240)	26	182.4 (259.2)		0.3 %	81.60 [-51.92, 215.12]
Haffejee 1990	75	61.4 (43.5)	120	70.5 (60.3)		8.4 %	-9.10 [-23.71, 5.51]
Romer 1991	30	55.59 (48.86)	26	75.53 (49.61)		5.1 %	-19.94 [-45.81, 5.93]
Allen 1994	39	108 (86.4)	34	158.4 (100.8)		2.5 %	-50.40 [-93.80, -7.00]
Prietsch 1999	44	81.36 (31.92)	45	78.48 (34.8)		8.7 %	2.88 [-10.99, 16.75]
Subtotal (95% CI)	**283**		**324**			**39.0 %**	**-14.38 [-30.15, 1.39]**
Heterogeneity: $Tau^2 = 261.73$; $Chi^2 = 23.26$, df = 6 (P = 0.00071); $I^2 = 74\%$							
Test for overall effect: Z = 1.79 (P = 0.074)							
Total (95% CI)	**690**		**727**			**100.0 %**	**-17.94 [-25.61, -10.26]**
Heterogeneity: $Tau^2 = 126.12$; $Chi^2 = 45.70$, df = 15 (P = 0.00006); $I^2 = 67\%$							
Test for overall effect: Z = 4.58 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.48$, df = 1 (P = 0.49), $I^2 = 0.0\%$							

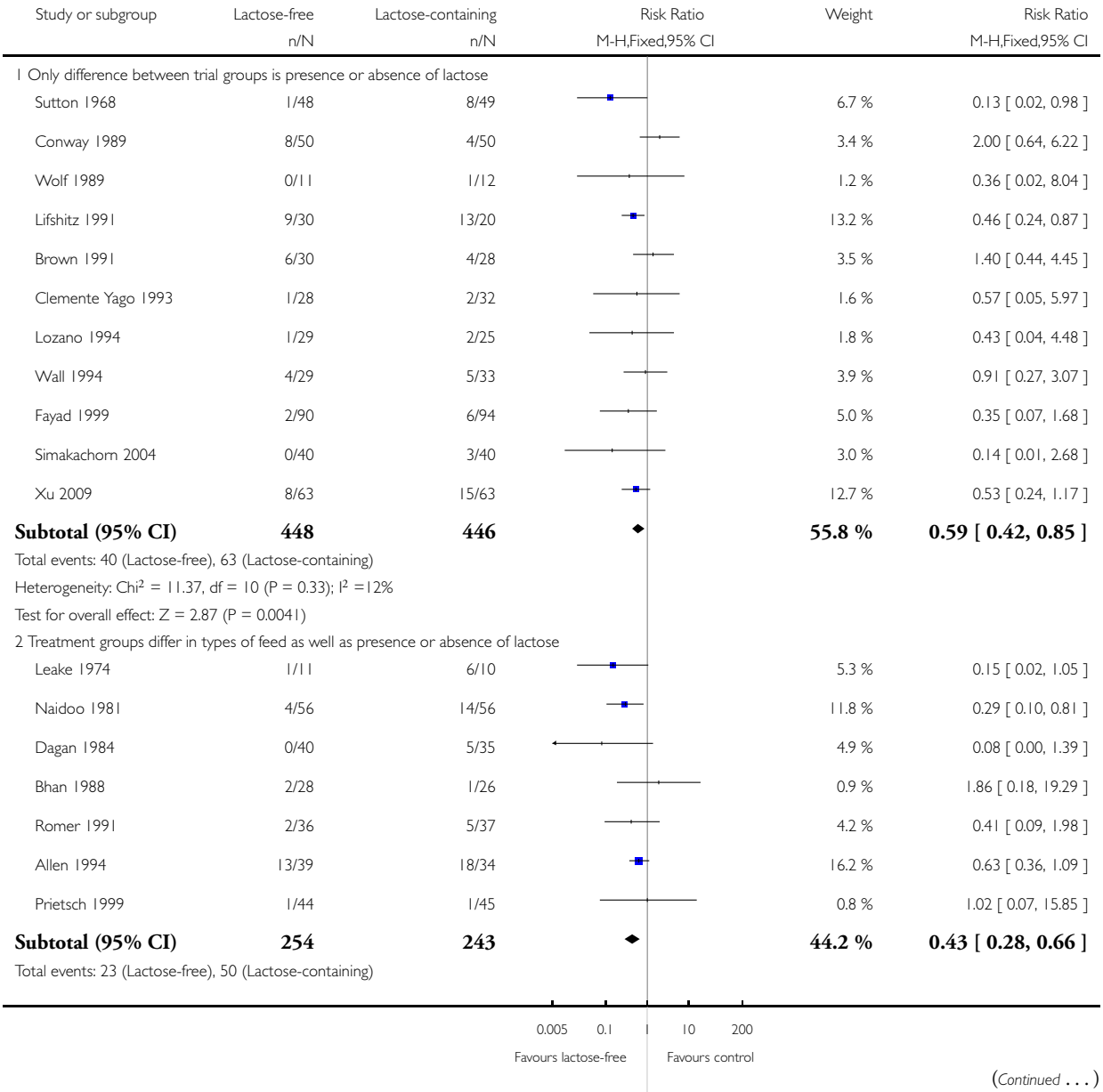


Analysis 2.2. Comparison 2 Subgroup analyses (other differences in feed type): Lactose-free versus lactose-containing, Outcome 2 Treatment failure (feed type).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 2 Subgroup analyses (other differences in feed type): Lactose-free versus lactose-containing

Outcome: 2 Treatment failure (feed type)



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Study or subgroup	Lactose-free n/N	Lactose-containing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 6.80, df = 6 (P = 0.34); I² =12%					
Test for overall effect: Z = 3.84 (P = 0.00012)					
Total (95% CI)	**702**	**689**	◆	**100.0 %**	**0.52 [0.40, 0.69]**
Total events: 63 (Lactose-free), 113 (Lactose-containing)					
Heterogeneity: Chi² = 18.46, df = 17 (P = 0.36); I² =8%					
Test for overall effect: Z = 4.66 (P < 0.00001)					
Test for subgroup differences: Chi² = 1.29, df = 1 (P = 0.26), I² =23%					

Analysis 3.1. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 1 Duration of diarrhoea (sequence generation).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 1 Duration of diarrhoea (sequence generation)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bhan 1988	28	264 (240)	26	182.4 (259.2)		0.2 %	81.60 [-51.92, 215.12]
Brown 1991	30	119 (63)	28	151 (86)		2.4 %	-32.00 [-71.02, 7.02]
Romer 1991	30	55.59 (48.86)	26	75.53 (49.61)		5.4 %	-19.94 [-45.81, 5.93]
Clemente Yago 1993	28	105.6 (74.4)	32	115.2 (50.4)		3.4 %	-9.60 [-42.22, 23.02]
Allen 1994	39	108 (86.4)	34	158.4 (100.8)		1.9 %	-50.40 [-93.80, -7.00]
Lozano 1994	28	41.9 (32)	24	54.5 (40)		9.2 %	-12.60 [-32.51, 7.31]
Fayad 1999	86	23 (21)	86	39 (28)		66.3 %	-16.00 [-23.40, -8.60]
Simakachorn 2004	40	64.2 (39.9)	40	92 (42.3)		11.2 %	-27.80 [-45.82, -9.78]
Total (95% CI)	**309**		**296**		◆	**100.0 %**	**-17.85 [-23.87, -11.82]**
Heterogeneity: Chi² = 6.75, df = 7 (P = 0.46); I² =0.0%							
Test for overall effect: Z = 5.81 (P < 0.00001)							
Test for subgroup differences: Not applicable							

Analysis 3.2. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 2 Duration of diarrhoea (allocation concealment).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 2 Duration of diarrhoea (allocation concealment)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bhan 1988	28	264 (240)	26	182.4 (259.2)		1.2 %	81.60 [-51.92, 215.12]
Haffejee 1990	75	61.4 (43.5)	120	70.5 (60.3)		42.2 %	-9.10 [-23.71, 5.51]
Romer 1991	30	55.59 (48.86)	26	75.53 (49.61)		22.1 %	-19.94 [-45.81, 5.93]
Simakachorn 2004	40	64.2 (39.9)	40	92 (42.3)		34.5 %	-27.80 [-45.82, -9.78]
Total (95% CI)	**173**		**212**			**100.0 %**	**-16.89 [-31.43, -2.36]**

Heterogeneity: $Tau^2 = 74.80$; $Chi^2 = 4.64$, df = 3 (P = 0.20); $I^2 = 35\%$

Test for overall effect: Z = 2.28 (P = 0.023)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 3 Duration of diarrhoea (blinding of participants and personnel).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 3 Duration of diarrhoea (blinding of participants and personnel)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Allen 1994	39	108 (86.4)	34	158.4 (100.8)		11.5 %	-50.40 [-93.80, -7.00]
Simakachorn 2004	40	64.2 (39.9)	40	92 (42.3)		66.7 %	-27.80 [-45.82, -9.78]
Xu 2009	60	197 (90)	60	230 (86)		21.8 %	-33.00 [-64.50, -1.50]
Total (95% CI)	**139**		**134**			**100.0 %**	**-31.53 [-46.25, -16.82]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.90$, df = 2 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 4.20 (P = 0.000027)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 4 Duration of diarrhoea (blinding of outcome assessment).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 4 Duration of diarrhoea (blinding of outcome assessment)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Allen 1994	39	108 (86.4)	34	158.4 (100.8)		11.5 %	-50.40 [-93.80, -7.00]
Simakachorn 2004	40	64.2 (39.9)	40	92 (42.3)		66.7 %	-27.80 [-45.82, -9.78]
Xu 2009	60	197 (90)	60	230 (86)		21.8 %	-33.00 [-64.50, -1.50]
Total (95% CI)	**139**		**134**			**100.0 %**	**-31.53 [-46.25, -16.82]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.90$, df = 2 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 4.20 (P = 0.000027)

Test for subgroup differences: Not applicable

Analysis 3.5. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 5 Duration of diarrhoea (complete outcome assessment).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 5 Duration of diarrhoea (complete outcome assessment)

Study or subgroup	Lactose-free N	Mean(SD)	Lactose N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Sutton 1968	48	70.6 (27.7)	49	101 (52.5)		9.3 %	-30.40 [-47.06, -13.74]
Dagan 1984	40	83.52 (32.64)	35	150.72 (101.76)		4.4 %	-67.20 [-102.40, -32.00]
Isolauri 1986	27	31.2 (16.8)	38	28.8 (19.2)		12.2 %	2.40 [-6.40, 11.20]
Bhan 1988	28	264 (240)	26	182.4 (259.2)		0.4 %	81.60 [-51.92, 215.12]
Conway 1989	50	47 (53.7)	25	68 (43.6)		7.3 %	-21.00 [-43.66, 1.66]
Haffejee 1990	75	61.4 (43.5)	120	70.5 (60.3)		10.1 %	-9.10 [-23.71, 5.51]
Brown 1991	30	119 (63)	28	151 (86)		3.8 %	-32.00 [-71.02, 7.02]
Clemente Yago 1993	28	105.6 (74.4)	32	115.2 (50.4)		4.8 %	-9.60 [-42.22, 23.02]
Allen 1994	39	108 (86.4)	34	158.4 (100.8)		3.2 %	-50.40 [-93.80, -7.00]
Fayad 1999	86	23 (21)	86	39 (28)		12.7 %	-16.00 [-23.40, -8.60]
Prietsch 1999	44	81.36 (31.92)	45	78.48 (34.8)		10.4 %	2.88 [-10.99, 16.75]
Simakachorn 2004	40	64.2 (39.9)	40	92 (42.3)		8.8 %	-27.80 [-45.82, -9.78]
Saneian 2012	37	40.8 (16.8)	34	62.4 (16.8)		12.6 %	-21.60 [-29.42, -13.78]
Total (95% CI)	**572**		**592**			**100.0 %**	**-17.75 [-26.62, -8.89]**

Heterogeneity: Tau^2 = 146.83; Chi^2 = 44.03, df = 12 (P = 0.00002); I^2 =73%

Test for overall effect: Z = 3.93 (P = 0.000086)

Test for subgroup differences: Not applicable

Analysis 3.6. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 6 Treatment failure (sequence generation).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 6 Treatment failure (sequence generation)

Study or subgroup	Lactose-free n/N	Lactose-containing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Leake 1974	1/11	6/10		12.8 %	0.15 [0.02, 1.05]
Bhan 1988	2/28	1/26		2.1 %	1.86 [0.18, 19.29]
Romer 1991	2/36	5/37		10.1 %	0.41 [0.09, 1.98]
Brown 1991	6/30	4/28		8.4 %	1.40 [0.44, 4.45]
Clemente Yago 1993	1/28	2/32		3.8 %	0.57 [0.05, 5.97]
Allen 1994	13/39	18/34		39.2 %	0.63 [0.36, 1.09]
Lozano 1994	1/29	2/25		4.4 %	0.43 [0.04, 4.48]
Fayad 1999	2/90	6/94		12.0 %	0.35 [0.07, 1.68]
Simakachorn 2004	0/40	3/40		7.1 %	0.14 [0.01, 2.68]
Total (95% CI)	**331**	**326**		**100.0 %**	**0.56 [0.37, 0.84]**

Total events: 28 (Lactose-free), 47 (Lactose-containing)

Heterogeneity: $Chi^2 = 6.75$, df = 8 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 2.78 (P = 0.0054)

Test for subgroup differences: Not applicable

Analysis 3.7. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 7 Treatment failure (allocation concealment).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 7 Treatment failure (allocation concealment)

Study or subgroup	Lactose-free n/N	Lactose-containing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bhan 1988	2/28	1/26		11.0 %	1.86 [0.18, 19.29]
Romer 1991	2/36	5/37		52.1 %	0.41 [0.09, 1.98]
Simakachorn 2004	0/40	3/40		37.0 %	0.14 [0.01, 2.68]
Total (95% CI)	**104**	**103**		**100.0 %**	**0.47 [0.16, 1.41]**

Total events: 4 (Lactose-free), 9 (Lactose-containing)

Heterogeneity: $Chi^2 = 1.99$, df = 2 (P = 0.37); $I^2 = 0.0\%$

Test for overall effect: Z = 1.35 (P = 0.18)

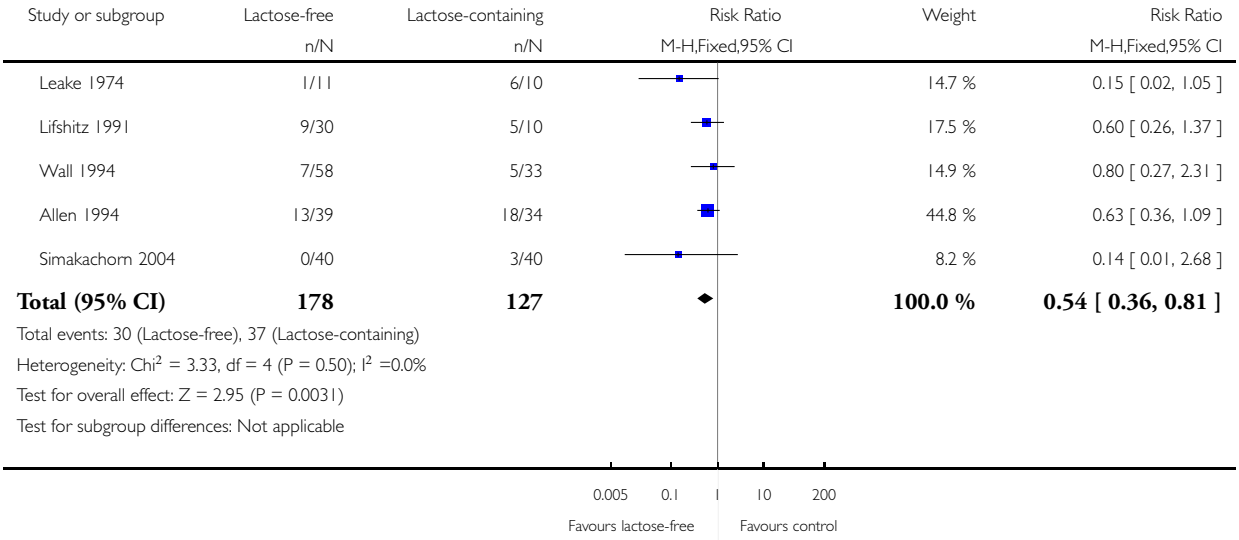
Test for subgroup differences: Not applicable

Analysis 3.8. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 8 Treatment failure (blinding of participants and personnel).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 8 Treatment failure (blinding of participants and personnel)



Analysis 3.9. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 9 Treatment failure (blinding of outcome assessment).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 9 Treatment failure (blinding of outcome assessment)

Study or subgroup	Lactose-free n/N	Lactose-containing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Leake 1974	1/11	6/10		21.7 %	0.15 [0.02, 1.05]
Allen 1994	13/39	18/34		66.3 %	0.63 [0.36, 1.09]
Simakachorn 2004	0/40	3/40		12.1 %	0.14 [0.01, 2.68]
Total (95% CI)	**90**	**84**		**100.0 %**	**0.47 [0.28, 0.79]**

Total events: 14 (Lactose-free), 27 (Lactose-containing)

Heterogeneity: Chi^2 = 3.08, df = 2 (P = 0.21); I^2 =35%

Test for overall effect: Z = 2.86 (P = 0.0042)

Test for subgroup differences: Not applicable

Analysis 3.10. Comparison 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing, Outcome 10 Treatment failure (complete outcome assessment).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 3 Sensitivity analyses (low risk of bias): Lactose-free versus lactose-containing

Outcome: 10 Treatment failure (complete outcome assessment)

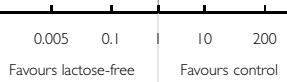
Study or subgroup	Lactose-free n/N	Lactose-containing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sutton 1968	1/48	8/49		9.3 %	0.13 [0.02, 0.98]
Leake 1974	1/11	6/10		7.4 %	0.15 [0.02, 1.05]
Naidoo 1981	4/56	14/56		16.5 %	0.29 [0.10, 0.81]
Dagan 1984	0/40	5/35		6.9 %	0.08 [0.00, 1.39]
Bhan 1988	2/28	1/26		1.2 %	1.86 [0.18, 19.29]
Wolf 1989	0/11	1/12		1.7 %	0.36 [0.02, 8.04]
Conway 1989	12/100	4/50		6.3 %	1.50 [0.51, 4.41]
Brown 1991	6/30	4/28		4.9 %	1.40 [0.44, 4.45]
Lifshitz 1991	9/30	5/10		8.8 %	0.60 [0.26, 1.37]
Clemente Yago 1993	1/28	2/32		2.2 %	0.57 [0.05, 5.97]
Allen 1994	13/39	18/34		22.6 %	0.63 [0.36, 1.09]
Prietsch 1999	1/44	1/45		1.2 %	1.02 [0.07, 15.85]
Fayad 1999	2/90	6/94		6.9 %	0.35 [0.07, 1.68]
Simakachorn 2004	0/40	3/40		4.1 %	0.14 [0.01, 2.68]
Total (95% CI)	**595**	**521**		**100.0 %**	**0.52 [0.37, 0.72]**

Total events: 52 (Lactose-free), 78 (Lactose-containing)

Heterogeneity: Chi^2 = 15.87, df = 13 (P = 0.26); I^2 =18%

Test for overall effect: Z = 3.98 (P = 0.000070)

Test for subgroup differences: Not applicable



Analysis 4.1. Comparison 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs, Outcome 1 Duration of diarrhoea (hrs).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs

Outcome: 1 Duration of diarrhoea (hrs)

Study or subgroup	Diluted		Undiluted		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Haque 1983	52	72 (33.6)	46	72 (31)		36.2 %	0.0 [-12.79, 12.79]
Ransome 1984	32	59.04 (47.52)	29	62.88 (45.24)		10.9 %	-3.84 [-27.12, 19.44]
Touhami 1989	34	39 (40.8)	35	47 (53.2)		11.9 %	-8.00 [-30.33, 14.33]
Conway 1989	50	64 (53.7)	50	68 (43.6)		16.1 %	-4.00 [-23.17, 15.17]
Chew 1993	71	92 (44)	72	92 (50)		24.9 %	0.0 [-15.43, 15.43]
Total (95% CI)	**239**		**232**			**100.0 %**	**-2.01 [-9.71, 5.68]**

Heterogeneity: Chi^2 = 0.50, df = 4 (P = 0.97); I^2 =0.0%

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable

Analysis 4.2. Comparison 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs, Outcome 2 Treatment failure.

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs

Outcome: 2 Treatment failure

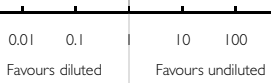
Study or subgroup	Diluted n/N	Undiluted n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Dugdale 1982	3/32	7/28		0.38 [0.11, 1.31]
Ransome 1984	5/37	8/37		0.63 [0.23, 1.73]
Placzek 1984	4/25	8/23		0.46 [0.16, 1.33]
McDowell 1985	7/46	13/47		0.55 [0.24, 1.25]
Pichaipat 1986	0/20	0/20		0.0 [0.0, 0.0]
Touhami 1989	0/35	0/34		0.0 [0.0, 0.0]
Conway 1989	2/50	4/50		0.50 [0.10, 2.61]
Armitstead 1989	4/22	5/22		0.80 [0.25, 2.59]
Chew 1993	14/79	14/80		1.01 [0.52, 1.98]
Total (95% CI)	**346**	**341**		**0.65 [0.45, 0.94]**

Total events: 39 (Diluted), 59 (Undiluted)

Heterogeneity: $Chi^2 = 3.20$, df = 6 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 2.29 (P = 0.022)

Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs, Outcome 3 Duration of hospital stay (days).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs

Outcome: 3 Duration of hospital stay (days)

Study or subgroup	Diluted		Undiluted		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Armitstead 1989	17	4 (0.53)	14	3.6 (2.2)		0.40 [-0.78, 1.58]
Chew 1993	79	3.8 (1.8)	80	3.8 (2.1)		0.0 [-0.61, 0.61]
Conway 1989	50	6.9 (3.2)	50	6.9 (2.2)		0.0 [-1.08, 1.08]
Dugdale 1982	31	5.4 (0)	28	4.7 (0)		0.0 [0.0, 0.0]
Haque 1983	52	3.1 (1.4)	48	3.6 (1.2)		-0.50 [-1.01, 0.01]
Maudgal 1985	86	3.6 (0)	89	2.9 (0)		0.0 [0.0, 0.0]
McDowell 1985	45	4.4 (0)	47	3.8 (0)		0.0 [0.0, 0.0]
Pichaipat 1986	20	4.2 (1.8)	20	4.1 (1.4)		0.10 [-0.90, 1.10]
Placzek 1984	25	7.6 (0)	23	7.2 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**405**		**399**			**-0.17 [-0.50, 0.16]**

Heterogeneity: Chi^2 = 3.18, df = 4 (P = 0.53); I^2 =0.0%

Test for overall effect: Z = 1.00 (P = 0.32)

Test for subgroup differences: Not applicable

Analysis 4.4. Comparison 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs, Outcome 4 Stool volume (g/kg/day or g/day).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs

Outcome: 4 Stool volume (g/kg/day or g/day)

Study or subgroup	Diluted N	Mean(SD)	Undiluted N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Chew 1993	71	338 (354)	72	335 (268)		3.00 [-100.02, 106.02]
Touhami 1989	34	381 (292)	35	407 (278)		-26.00 [-160.60, 108.60]

Analysis 4.5. Comparison 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs, Outcome 5 Number of stools per day.

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs

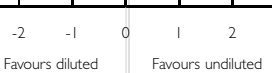
Outcome: 5 Number of stools per day

Study or subgroup	Diluted N	Mean(SD)	Undiluted N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Dugdale 1982	31	3.4 (0)	28	3.6 (0)		0.0 [0.0, 0.0]
Maudgal 1985	86	3.4 (2.8)	89	4.1 (3.8)		-0.70 [-1.69, 0.29]
Pichaipat 1986	20	5.6 (3.4)	20	5 (3.6)		0.60 [-1.57, 2.77]
Chew 1993	71	7.8 (5.2)	72	7.2 (4.4)		0.60 [-0.98, 2.18]
Total (95% CI)	**208**		**209**			**-0.21 [-0.99, 0.57]**

Heterogeneity: Chi^2 = 2.49, df = 2 (P = 0.29); I^2 =20%

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable

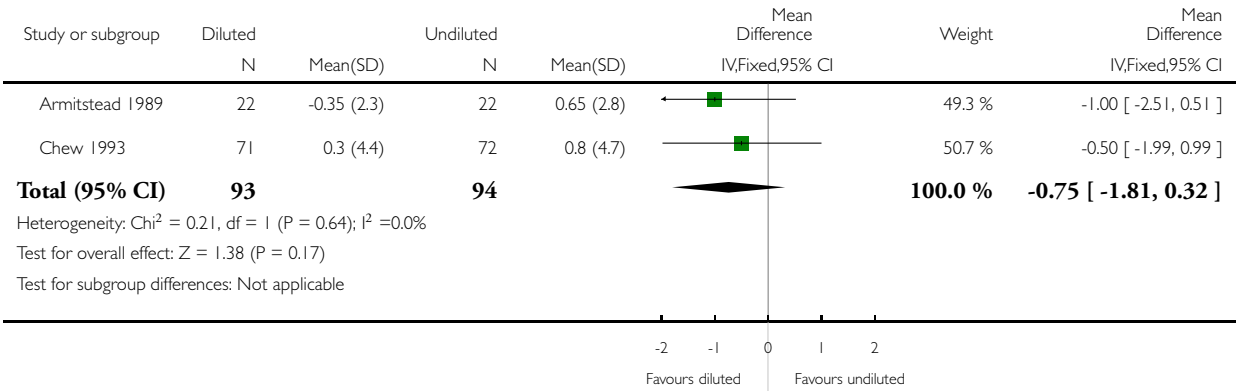


Analysis 4.6. Comparison 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs, Outcome 6 Weight change (at discharge or recovery).

Review: Lactose avoidance for young children with acute diarrhoea

Comparison: 4 Diluted versus undiluted lactose-containing milk, milk products, or foodstuffs

Outcome: 6 Weight change (at discharge or recovery)



ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR*	CENTRAL	MEDLINE**	EMBASE**	LILACS**
1	diarrhea	diarrhea	diarrhea	diarrhea	diarrhea
2	gastroenteritis	gastroenteritis	diarrhoea	DIARRHEA	lactose
3	lactose	1 or 2	DIARRHEA, INFANTILE	gastroenteritis	soy
4	milk	lactose intolerance	gastroenteritis	1 or 2 or 3	infant formula
5	formula	LACTOSE INTOLERANCE	1 or 2 or 3 or 4	lactose intolerance	2 or 3 or 4

Table 1. Detailed search strategies (*Continued*)

6	soya	milk	lactose intolerance	LACTOSE-INTOLERANCE	1 and 5
7	1 or 2	soy	LACTOSE INTOLERANCE	soy	--
8	3 or 4 or 5 or 6	formula	SOY MILK	soya	--
9	7 and 8	4 or 5 or 6 or 7 or 8	MILK SUBSTITUTES	ARTIFICIAL MILK	--
10	--	3 and 9	INFANT FORMULA	milk substitute	--
11	--	--	6 or 7 or 8 or 9 or 10	infant formula	--
12	--	--	5 and 11	5 or 6 or 7 or 8 or 9 or 10 or 11	--
13	--	--	--	4 and 12	--

* Cochrane Infectious Diseases Group Specialized Register.
** Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2011) ; Upper case: MeSH or EMTREE heading; Lower case: free text term.

Table 2. Subgroup analyses of duration of diarrhoea (lactose-free versus lactose-containing)

Duration of diarrhoea	Trials (participants)	MD (95% CI) hours (random-effects)	Tau²	Chi² (df)	I²
1. Age					
All participants 12 months of age or less	6 (567)	-25.23 (-45.01, -5.45)	404.88	19.00 (5) P = 0.002	74%
Some of participants older than 12 months	10 (900)	-16.08 (-24.21, -7.94)	90.19	26.57 (9) P = 0.0001	66%
2. Setting					
Inpatient	14 (1342)	-17.94 (-26.28, -9.59)	139.73	39.82 (13) P = 0.0001	67%
Outpatient	2 (143)	7.59 (-83.51, 98.69)	2996.57	2.29 (1) P = 0.13	56%
3. Income level					

Table 2. Subgroup analyses of duration of diarrhoea (lactose-free versus lactose-containing) (*Continued*)

Low- or middle-income country	10 (947)	-15.77 (-22.64, -8.90)	42.09	15.59 (9) P = 0.08	42%
High-income country	6 (520)	-24.88 (-44.18, -5.57)	417.61	28.14 (5) P < 0.0001	82%

df = degrees of freedom

Table 3. Subgroup analyses of treatment failure (lactose-free versus lactose-containing)

Treatment failure	Trials (participants)	RR (95% CI) (fixed-effect)	Chi² (df)	I²
1. Age				
All participants 12 months of age or less	10 (779)	0.51 (0.37, 0.69)	9.15 (9) P = 0.0001	0%
Some of participants older than 12 months	10 (900)	-16.08 (-24.21, -7.94)	7.37 (7) P = 0.02	5%
2. Setting				
Inpatient	17 (1416)	0.50 (0.38, 0.66)	15.63 (16) P = 0.00001	0%
Outpatient	1 (54)	-	-	-
3. Income level				
Low- or middle-income country	10 (880)	0.50 (0.34, 0.72)	6.69 (9) P = 0.0001	0%
High-income country	8 (590)	0.54 (0.36, 0.80)	9.64 (7) P = 0.002	27%

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 10, 2013

Date	Event	Description
15 April 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

SM, WM, and TF developed the protocol. SM coordinated the primary search and screening. SM and WM assessed reports for inclusions, assessed trial quality, and extracted data. TF contributed to discussions to resolve any disagreements. SM and WM undertook data analyses and drafted the review. All authors contributed to the final review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Dundee, UK.
- Hull York Medical School and NIHR Centre for Reviews and Dissemination, University of York, UK.

External sources

- Tenovus Scotland, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not perform the planned subgroup analysis of trials that included participants who were moderately or severely malnourished because this participant characteristic was not consistently reported or described (in standard way). Instead, we undertook subgroup analyses by income level of country (low- or middle-income versus high-income countries).

An additional post-hoc subgroup analysis (suggested by external referee, not stated in the protocol) was conducted, which was identified clearly as a post-hoc analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Dairy Products [*adverse effects]; Diarrhea, Infantile [*prevention & control]; Lactose [administration & dosage; *adverse effects]; Milk [*chemistry]; Randomized Controlled Trials as Topic

MeSH check words

Animals; Humans; Infant