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Smectite for acute infectious diarrhoea in children (Review)

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[Intervention Review]

Smectite for acute infectious diarrhoea in children

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ABSTRACT

Background

As mortality secondary to acute infectious diarrhoea has decreased worldwide, the focus shifts to adjuvant therapies to lessen the burden of disease. Smectite, a medicinal clay, could offer a complementary intervention to reduce the duration of diarrhoea.

Objectives

To assess the effects of smectite for treating acute infectious diarrhoea in children.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Pubmed), Embase (Ovid), LILACS, reference lists from studies and previous reviews, and conference abstracts, up to 27 June 2017.

Selection criteria

Randomized and quasi-randomized trials comparing smectite to a control group in children aged one month to 18 years old with acute infectious diarrhoea.

Data collection and analysis

Two review authors independently screened abstracts and the full texts for inclusion, extracted data, and assessed risk of bias. Our primary outcomes were duration of diarrhoea and clinical resolution at day 3. We summarized continuous outcomes using mean differences (MD) and dichotomous outcomes using risk ratios (RR), with 95% confidence intervals (CI). Where appropriate, we pooled data in meta-analyses and assessed heterogeneity. We explored publication bias using a funnel plot.

Main results

Eighteen trials with 2616 children met our inclusion criteria. Studies were conducted in both ambulatory and in-hospital settings, and in both high-income and low- or middle-income countries. Most studies included children with rotavirus infections, and half included breastfed children.

Smectite may reduce the duration of diarrhoea by approximately a day (MD -24.38 hours, 95% CI -30.91 to -17.85; 14 studies; 2209 children; low-certainty evidence); may increase clinical resolution at day 3 (risk ratio (RR) 2.10, 95% CI 1.30 to 3.39; 5 trials; 312 children; low-certainty evidence); and may reduce stool output (MD -11.37, 95% CI -21.94 to -0.79; 3 studies; 634 children; low-certainty evidence).

We are uncertain whether smectite reduces stool frequency, measured as depositions per day (MD -1.33, 95% CI -2.28 to -0.38; 3 studies; 954 children; very low-certainty evidence). There was no evidence of an effect on need for hospitalization (RR 0.93, 95% CI 0.75 to 1.15; 2 studies; 885 children; low-certainty evidence) and need for intravenous rehydration (RR 0.77, 95% CI 0.54 to 1.11; 1 study; 81 children; moderate-certainty evidence). The most frequently reported side effect was constipation, which did not differ between groups (RR 4.71, 95% CI 0.56 to 39.19; 2 studies; 128 children; low-certainty evidence). No deaths or serious adverse effects were reported.

Authors' conclusions

Based on low-certainty evidence, smectite used as an adjuvant to rehydration therapy may reduce the duration of diarrhoea in children with acute infectious diarrhoea by a day; may increase cure rate by day 3; and may reduce stool output, but has no effect on hospitalization rates or need for intravenous therapy.

2 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (27 Jun, 2017) were included

PLAIN LANGUAGE SUMMARY

Smectite for treating children with acute diarrhoea

What is the aim of this review?

The aim of this Cochrane Review was to find out if smectite (or diosmectite), a medicinal clay commonly prescribed to people who have diarrhoea in order to reduce their stool output, helps children with acute diarrhoea. We collected and analysed all relevant studies to answer this question and found 18 relevant studies.

Key messages

Giving smectite to children with acute diarrhoea may reduce its duration. However, more high-quality studies are still needed, including studies that assess different causes of diarrhoea and the economic effects of this treatment.

What was studied in the review?

Acute diarrhoea is one of the most common diseases in children. It is usually caused by a viral infection. The main aim of treatment is to maintain a good level of hydration. This is achieved with oral rehydration solutions, and few children need to be hospitalized or require intravenous rehydration. Still, even with proper hydration, having loose stools is a burden for both parents and patients.

Smectite may help by reducing inflammation in the gut; by acting as a barrier to reduce the penetration of toxins; or by increasing water absorption.

What are the main results?

We found 18 relevant studies with 2616 children that were conducted in both high-income and low- or middle-income countries. These studies compared children receiving smectite with children receiving routine care or a placebo (a pill or liquid that contains no medicine). Eight studies were funded by the manufacturer.

Smectite may reduce the duration of diarrhoea by one day (low-certainty evidence); may increase the number of children cured by day 3 (low-certainty evidence); and may slightly reduce the quantity of loose stools (low-certainty evidence).

We are uncertain whether smectite has an effect on how many stools children have (very low-certainty evidence). It may not have an effect on how many children need to be hospitalized (low-certainty evidence), and probably does not have an effect on how many children need intravenous rehydration (moderate-certainty evidence).

We found no reports of serious adverse effects. Minor adverse effects included constipation, vomiting, and bad taste, but these did not differ between groups.

How up-to-date is this review?

We searched for studies published up to 27 June 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Smectite compared to control for acute infectious diarrhoea in children

Smectite compared to control for acute infectious diarrhoea in children

Patient or population: acute infectious diarrhoea in children
Setting: hospital and outpatients
Intervention: smectite
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments (compared with control)
	Risk with control	Risk with smectite				
Duration of diarrhoea assessed with: clinical and parental assessment, measured in total hours Follow-up: mean 1 week	The mean duration of diarrhoea ranged from 32.6 to 118.92 hours	MD 24.38 hours fewer (30.91 fewer to 17.85 fewer)	-	2209 (14 RCTs)	⊕⊕⊖⊖ LOW[1,2]	Smectite may reduce the duration of diarrhoea
Clinical resolution at day 3 assessed with: clinical assessment by parents and clinicians Follow-up: mean 3 days	Study population		RR 2.10 (1.30 to 3.39)	312 (5 RCTs)	⊕⊕⊖⊖ LOW[3,4]	Smectite may increase the resolution of diarrhoea by the third day
	342 per 1000	718 per 1000 (445 to 1000)				
Stool frequency assessed with: clinical assessment as number of depositions per day Follow-up: mean 1 week	The mean stool frequency was 0 depositions per day	MD 1.33 depositions per day fewer (2.28 fewer to 0.38 fewer)	-	954 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[5,6,7]	We are uncertain whether or not smectite reduces stool frequency
Stool output assessed with: grams of stool output per kg of body weight in a 72-hour period Follow-up: mean 1 week	The mean stool output ranged from 90.7 to 118.8 g/kg	MD 11.37 g/kg fewer (21.94 fewer to 0.79 fewer)	-	634 (3 RCTs)	⊕⊕⊖⊖ LOW[7,8]	Smectite may decrease stool output
Need for hospitalization Follow-up: mean 1 week	Study population		RR 0.93 (0.75 to 1.15)	885 (2 RCTs)	⊕⊕⊖⊖ LOW[6,9]	Smectite may make little or no difference in the need for hospitalization
	85 per 1000	79 per 1000 (64 to 98)				

Need for intravenous access for rehydration Follow-up: mean 1 week	Study population		RR 0.77 (0.54 to 1.11)	81 (1 RCT)	⊕⊕⊕⊖ MODERATE[9]	Smectite probably makes little or no difference in the need for intravenoous access
	676 per 1000	520 per 1000 (365 to 750)				
Adverse events – constipation Follow-up: mean 1 week	Study population		RR 4.71 (0.56 to 39.19)	128 (2 RCTs)	⊕⊕⊖⊖ LOW[3,9]	Smectite may make little or no difference in the appeareance of adverse events
	0 per 1000	0 per 1000 (0 to 0)				
Death	-	-	-	-	-	There were no deaths in the included studies
Serious adverse events	-	-	-	-	-	There were no serious side effects in the included studies

*__The risk in the intervention group__ (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).

Abbreviations: CI: confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Four trials are quasi-randomized and without adequate blinding of participants.
[2]High heterogeneity (I^2 = 96%) among studies that may be explained by differences in age and definition of resolution, although the effect in all studies points in the same direction.
[3]Three studies have high risk of selection bias, including one that is quasi-randomized, and three did not perform adequate blinding of participants.
[4]High heterogeneity (I^2 = 81%), although the effect in all studies points in the same direction.
[5]High heterogeneity (I^2 = 97%), although all effects point in the same direction.
[6]Two of the three studies are classified as quasi-randomized with inadequate blinding of participants.
[7]A wide CI that does not exclude the threshold of appreciable clinical benefit.
[8]One quasi-randomized study was not pooled because the authors reported stool output as stool weight in total grams per day with an effect estimate favouring smectite (mean of 255.67 g in the smectite group versus 741.33 g in the control group) at day 3 of treatment.
[9]Wide CI that does not exclude an appreciable benefit or harm.

BACKGROUND

Description of the condition

Acute diarrhoea is defined as the passage of unusually loose or watery stools, usually at least three times in a 24-hour period, for less than 14 days (King 2003; WHO 2005; WHO/UNICEF 2013). Incidence of acute diarrhoea in children under five years of age is approximately two to three episodes per child per year (Walker 2013). The aetiology is usually infectious, and is usually transmitted by faecal-oral route, or by contaminated water or food. Although most cases of acute diarrhoea are self limited, the most common complication is dehydration where children are at higher risk compared to adults. The objective of treatment in many countries is to relieve symptoms and avoid complications. In low- and middle-income countries there are additional concerns to prevent dehydration and prevent the illness contributing to malnutrition. Therapeutic options for the latter objective include probiotics (Allen 2010), zinc (Lazzerini 2016), lactose-free formula (MacGillivray 2013), antibiotics, and antidiarrhoeal agents such as loperamide, racecadotril, and smectite.

Description of the intervention

Smectite is a medicinal clay commonly prescribed to reduce stool output in people with diarrhoea. A survey conducted in 29 European countries with a response rate of 34% found that 22% of physicians (9% in Western European countries and 41% in Eastern European countries) would give smectite as an adjuvant treatment to children with gastroenteritis (Szajewska 2000). In France, the use of smectite by private paediatricians may be as high as 84% (Uhlen 2004). Another survey, conducted in Prague, Czech Republic, found that 45.7% of children with acute diarrhoea received smectite (Kudlova 2010). A survey carried out in 20 hospitals in two Chinese provinces found that smectite was prescribed to 59.3% of adults with acute infectious diarrhoea (Hou 2013).

How the intervention might work

Dioctahedral smectite, or diosmectite, is a natural clay formed from sheets of aluminium and magnesium silicate. Its proposed mechanism of action differs from other antidiarrhoeal agents such as loperamide, which is an opioid-receptor agonist, and racecadotril, which acts as an enkephalinase inhibitor. Three possible mechanisms of action of smectite against diarrhoea have been proposed: an anti-inflammatory activity, alteration of the gut mucus barrier to reduce penetration of toxins, and adsorptive properties. These mechanisms have been replicated mainly in vitro and in animal models (Dupont 2009). In theory, these mechanisms would reduce stool output in children, thereby providing symptomatic relief and possibly preventing dehydration.

Why it is important to do this review

In many countries, symptomatic relief of diarrhoea is important to the public. Smectite is one such option for providing this relief. Two previous systematic reviews including 13 randomized controlled trials published between 1986 and 2013 provide evidence that smectite reduces the frequency and duration of diarrhoea in children (Das 2015; Szajewska 2006). The only reported adverse event was constipation. Since acute diarrhoea is usually a self limited illness, provided the person is properly hydrated, it is important to assess the efficacy and safety of adjuvant therapies such as smectite. With the publication of recent trials, there was a need to update the evidence on this topic.

OBJECTIVES

To assess the effects of smectite for treating acute infectious diarrhoea in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized trials comparing children with acute diarrhoea treated with smectite against a control group.

Types of participants

We included trials evaluating children, aged one month to 18 years old, with clinically defined diarrhoea of less than 14 days duration, presumed to be caused by an infectious agent. We excluded studies with other causes of diarrhoea, such as chronic or antibiotic-associated diarrhoea.

Types of interventions

We included trials assessing oral smectite against a control group, either placebo or no smectite. We did not exclude trials that administered other interventions, such as probiotics or zinc, provided that the intervention and control arms were treated identically.

Types of outcome measures

Primary outcomes

- Duration of diarrhoea, measured in hours.
- Clinical resolution at day 3 after starting treatment.

Secondary outcomes

- Stool frequency, measured as number of depositions per day, on day 3 after starting treatment.
- Stool output, measured in g or mL/kg per day.
- Need for hospitalization.
- Need for intravenous access for rehydration.
- Death (from any cause or diarrhoea-related).
- Adverse events:
  - serious adverse events (life-threatening events).
  - other adverse events (for example, constipation, vomiting, among others).

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (27 June 2017); Cochrane Central Register of Controlled Trials (CENTRAL) (27 June 2017), published in the Cochrane Library (2017, Issue 5); MEDLINE (Pubmed; 1946 to

27 June 2017); Embase (Ovid; 1974 to 27 June 2017); and LILACS (Latin American and Caribbean Health Sciences Literature) (1982 to 27 June 2017). We also searched the metaRegister of Controlled Trials (mRCT) (27 June 2017) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (27 June 2017) using 'smectite' and 'diosmectite' as search terms (Appendix 1).

Searching other resources

Conference proceedings

We searched the following conference proceedings of the last two years (2014 to 2016) for relevant abstracts.

- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC).
- Infectious Diseases Society of America (IDSA) conferences.
- International Congress on Infectious Diseases (ICID) from the International Society for Infectious Diseases (ISID).

Researchers and organizations

We contacted researchers, authors of included trials, other experts in the field of infectious diseases, and pharmaceutical companies that manufacture smectite.

Reference lists

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Two review authors (GP and CC) independently screened the search results to identify potentially relevant trials and retrieved the full-text articles of these trials. GP and CC independently applied the inclusion criteria using an eligibility form, resolving any differences by discussing them with a third review author (VP or IF). We scrutinized the trial reports to ensure that multiple publications from the same trial were included only once. We listed the excluded studies and the reasons for their exclusion in the 'Characteristics of excluded studies' section. Finally, when we were unsure whether a trial should be included because further information was needed, we attempted to contact the trial authors for clarification and allocated the trial to the 'Studies awaiting classification' section. We have presented an adapted PRISMA flowchart showing study selection (Liberati 2009).

Data extraction and management

Two review authors (GP and CC) independently extracted prespecified characteristics of each trial using a standardized, piloted data extraction form. We attempted to contact trial authors in cases of unclear or missing data. We extracted the following data.

- The numbers of randomized and analysed participants in each treatment group for each outcome.
- The mean and standard deviation (SD) for each treatment group for continuous outcomes, and the number of participants with the event for each treatment group for dichotomous outcomes. If these values were not explicitly presented, we attempted to transform data where possible from available numbers such as 95% confidence intervals (CIs), standard errors, range or test statistics (that is, t, F, Z scores, P values, etc.). We obtained the SD from 95% CIs in one study according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We imputed SDs for studies that did not present any measure of data dispersion. We extracted information from figures in three trials that presented the results in this format and did not provide numerical values for measures of dispersion (Dupont 2009a; Dupont 2009b; Pociecha 1998a; Pociecha 1998b), using the Plot Digitizer open source software (Jelicic 2016). Two trials presented the information using median and 95% CI and provided a Kaplan-Meier curve with the data for both intervention and control group (Dupont 2009a; Dupont 2009b). We applied the Hozo and colleagues approach to calculate the best estimation of mean and SD (Hozo 2005).

Assessment of risk of bias in included studies

Two review authors (GP and CC) independently assessed the risk of bias of the included studies, resolving any disagreements by discussion with a third review author (VP or IF). We attempted to contact trial authors regarding unclear or unspecified information. We used the Cochrane 'Risk of bias' assessment tool, which includes the following domains (Higgins 2011).

- Sequence generation: describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
- Allocation concealment: describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
- Blinding (masking) of participants, personnel, and outcome assessors: describe all measures used, if any, to mask trial participants, personnel, and outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended masking was effective.
- Incomplete outcome data: describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition or exclusions where reported, and any re-inclusions in analyses performed by the review authors.
- Selective outcome reporting: state how the possibility of selective outcome reporting was examined by the review authors and what was found.
- Other sources of bias: state any important concerns about bias not addressed in the other domains in the tool.

We assessed the risk of bias for each component using 'yes', 'no', or 'unclear' to indicate a low, high, or unclear risk of bias, respectively. We have presented the 'Risk of bias' assessment in a 'Risk of bias' graph and the 'Risk of bias' tables.

Certainty of the evidence

We have presented the certainty of the evidence according to the GRADE approach. Two review authors (GP and CC) independently rated the certainty of the evidence for each outcome. Since we included randomized controlled trials, which are considered as high certainty, review authors could downgrade the body of

evidence depending on five criteria: limitations, inconsistency, indirectness, imprecision, and publication bias. Evidence could be upgraded if a large effect size was found, if there was a dose-response association, or if trial authors considered plausible confounding factors. We have presented a summary of the evidence in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome, and the rating of the overall certainty in effect estimates for each outcome. We used GRADEpro GDT to create the 'Summary of findings' table (GRADEpro GDT).

Measures of treatment effect

For continuous outcomes, we used mean differences (MD) as the measure of effect with 95% CIs. For outcomes with different measurements, for example stool output, which can be measured in grams or mL per kg, we used standardized mean differences (SMD). For dichotomous outcomes, we used risk ratios (RR) as the measure of effect with 95% CIs.

Unit of analysis issues

Given the condition under study and the trial participants, we did not expect to find cluster randomized controlled trials or cross-over trials. When we found trials with repeated measurements, we decided on a single time point (for example, diarrhoea resolution at day 3).

Dealing with missing data

When there were no missing data, we carried out analyses according to the intention-to-treat principle, that is all children were analysed according to the group to which they were initially randomized. If there were missing data, we attempted to contact trial authors to request any missing data. If the trial authors did not respond within four to eight weeks, we conducted the analyses based on only the available information.

Assessment of heterogeneity

We used forest plots to detect overlapping CIs, and applied the Chi^2 test with a P value < 0.10 to indicate statistical significance for heterogeneity. We investigated inconsistency with the I^2 statistic, considering a value from 0% to 40% as not important.

Assessment of reporting biases

We assessed reporting biases by examining asymmetry of funnel plots.

Data synthesis

One review author (GP) analysed the data using Review Manager 5 (RevMan 2014). When appropriate, we combined data by meta-analysis using a fixed-effect model. When we found inconsistency (I^2 statistic > 40%) or heterogeneity (Chi^2 test at a significant P value < 0.10), we combined the results using the random-effects model.

Subgroup analysis and investigation of heterogeneity

We expected to perform subgroup analysis based on age groups, given that severity of disease might be different among infants, children, and adolescents. Since the higher burden and mortality of acute diarrhoea is in infants (Walker 2013), we analysed subgroups under and over two years of age.

Sensitivity analysis

We performed sensitivity analyses regarding risk of bias to investigate the robustness of the results, that is restricting the analysis by taking into account trials at low versus high or unclear risk of bias, as specified in the Assessment of risk of bias in included studies section. We explored if the following markers affected the direction of results: randomization, allocation concealment, blinding, follow-up, and missing data. We also performed a sensitivity analysis excluding the trials that required estimations and figure extractions (Dupont 2009a; Dupont 2009b; Pociecha 1998a; Pociecha 1998b).

RESULTS

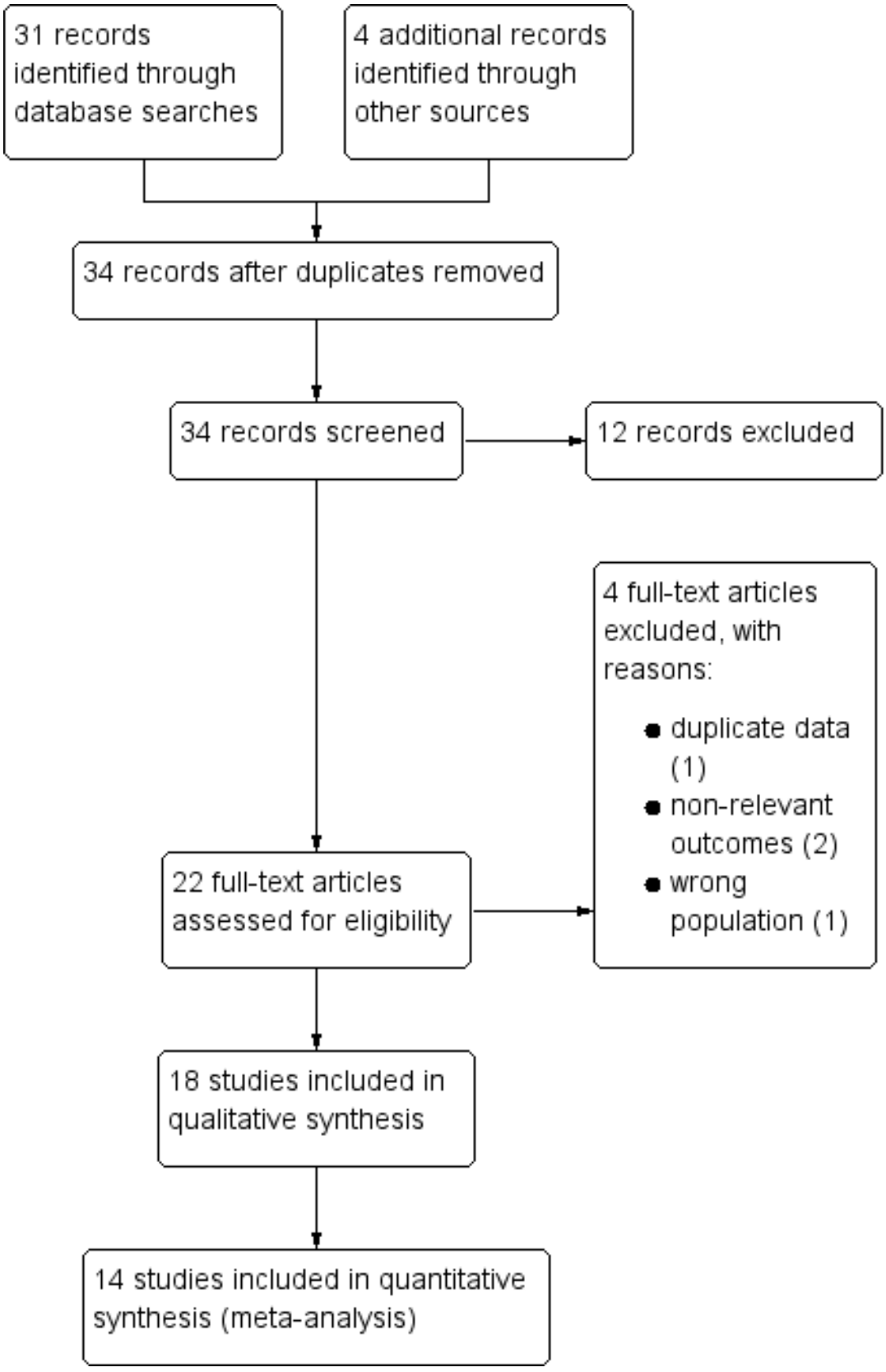
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

Our search strategy identified 34 potentially relevant studies, of which 22 studies were screened in full text. Eighteen studies met the inclusion criteria, and four were excluded (Dupont 1991; Dupont 1992; Karas 1996; Madkour 1994). The study flow diagram is shown in Figure 1. One reference included two studies (Dupont 2009a; Dupont 2009b). Another study is presented in the results as two separate studies because data were divided by age group (Pociecha 1998a; Pociecha 1998b).

Figure 1. Study flow diagram.



Included studies

Study location

Eleven studies were conducted in low- or middle-income countries: Peru, Malaysia, Egypt, Thailand, India, Pakistan, Indonesia, and China (Dupont 2009a; Dupont 2009b; Lachaux 1986; Lexomboon 1994; Madkour 1993; Mujawar 2012; Rehman 2013; Vivatvakin 1992; Wang 1995; Widiasa 2009; Zong 1997). Seven were conducted in high-income countries: France, Italy, Lithuania, and Poland (Gilbert 1991; Guarino 2001; Lachaux 1986; Milocco 1999; Narkeviciute 2002; Pieścik-Lech 2013; Pociecha 1998a; Pociecha 1998b). Most trials were conducted in hospitals, with two studies conducted in both hospital and an ambulatory setting (Madkour 1993; Wang 1995), three exclusively with outpatients (Guarino 2001; Lexomboon 1994; Mujawar 2012), and two that did not specify (Gilbert 1991; Zong 1997).

Participants

Most studies included infants aged one to 24 months. One study did not include infants (Mujawar 2012), and one did not report age (Wang 1995). Nine studies included children aged two to 12 years old. No trials included adolescents. Two trials included only males (Dupont 2009a; Dupont 2009b). One report divided its results into two age groups: less than 12 months and 13 to 36 months (Pociecha 1998a; Pociecha 1998b).

Two studies included exclusively breastfed infants (Dupont 2009a; Dupont 2009b), and seven studies included children who were breastfed (Lexomboon 1994; Osman 1992; Pieścik-Lech 2013; Pociecha 1998a; Pociecha 1998b; Rehman 2013; Vivatvakin 1992; Widiasa 2009). One study excluded breastfed infants (Narkeviciute 2002). Thirteen trials reported rotavirus as the most frequent gastroenteritis aetiology. No studies included dysentery or bloody diarrhoea or children with cholera. One study included children with moderate malnutrition (Widiasa 2009), while the other studies excluded children with any degree of malnutrition.

Most trials defined diarrhoea as three or more loose stools, but the duration varied among studies: four defined it as less than two days (Guarino 2001; Lexomboon 1994; Mujawar 2012; Widiasa 2009); six as less than three days (Dupont 2009a; Dupont 2009b; Narkeviciute 2002; Pociecha 1998a; Pociecha 1998b; Rehman 2013; Vivatvakin 1992); one as less than four days (Lachaux 1986); five as less than five days (Madkour 1993; Milocco 1999; Pieścik-Lech 2013; Wang 1995; Zong 1997); one as less than seven days (Osman 1992); and one referred to it as "recent" (Gilbert 1991).

Interventions

Doses of smectite varied between 1 g and 6 g per dose, and frequency of administration varied from once daily to every six hours. Most trials used 1.5 g per dose in infants less one year and 3 g in older infants or children. Two trials administered 3 g twice a day for three days, and then once a day in infants less than one year, and double the dose in older children (Dupont 2009a; Dupont 2009b). Five trials gave 1.5 g of smectite twice a day to infants less than one year, with double the dose for older children (Gilbert 1991; Guarino 2001; Milocco 1999; Pociecha 1998a; Pociecha 1998b; Wang 1995). Two studies gave a loading dose of 3 g (Lexomboon 1994; Narkeviciute 2002). Two trials administered smectite every eight hours (Mujawar 2012; Rehman 2013), and one study gave it every six hours (Madkour 1993). Two trials gave smectite every eight hours to children weighing less than 10 kg, and every six hours to children above 10 kg (Osman 1992; Vivatvakin 1992). Two studies gave *Lactobacillus rhamnosus* GG to both the intervention and the control group (Pieścik-Lech 2013; Pociecha 1998a; Pociecha 1998b). Two studies did not report the dose (Widiasa 2009; Zong 1997).

The duration of treatment also differed among studies. Four studies gave smectite until recovery (Dupont 2009a; Dupont 2009b; Narkeviciute 2002; Pieścik-Lech 2013); two administered the treatment for three days (Madkour 1993; Milocco 1999); five for five days (Mujawar 2012; Osman 1992; Rehman 2013; Vivatvakin 1992; Widiasa 2009); and one for six days (Pociecha 1998a; Pociecha 1998b). The remaining studies did not specify the duration of treatment.

Outcomes

Primary outcomes

Fifteen studies reported the duration of diarrhoea (Dupont 2009a; Dupont 2009b; Gilbert 1991; Guarino 2001; Lachaux 1986; Madkour 1993; Milocco 1999; Mujawar 2012; Narkeviciute 2002; Pieścik-Lech 2013; Pociecha 1998a; Pociecha 1998b; Rehman 2013; Vivatvakin 1992; Widiasa 2009; Zong 1997), but the outcome was defined differently. Six trials defined it as time to the last loose stool (Guarino 2001; Madkour 1993; Narkeviciute 2002; Pieścik-Lech 2013; Vivatvakin 1992; Widiasa 2009); three as time to first formed stool (Dupont 2009a; Lachaux 1986; Rehman 2013); one as time to first soft or formed stool (Dupont 2009b); three as time to normalization of stools (Gilbert 1991; Mujawar 2012; Pociecha 1998a; Pociecha 1998b); and two did not provide a clear definition (Milocco 1999; Zong 1997).

Five trials reported clinical resolution of diarrhoea at day 3 (Lachaux 1986; Lexomboon 1994; Madkour 1993; Osman 1992; Vivatvakin 1992).

Secondary outcomes

Four studies reported stool frequency: three as number of depositions per day (Guarino 2001; Madkour 1993; Osman 1992), and one as the total number of stools during follow-up (Milocco 1999). Three trials reported stool output as grams per kilogram of child's weight at 72 hours (Dupont 2009a; Dupont 2009b), and one in grams per day (Osman 1992). Two studies reported need for hospitalization (Guarino 2001; Pieścik-Lech 2013). One study reported need for intravenous access for rehydration (Pieścik-Lech 2013). No studies reported deaths.

Risk of bias in included studies

See: Characteristics of included studies; Figure 2; Figure 3 for the risk of bias in included studies.

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

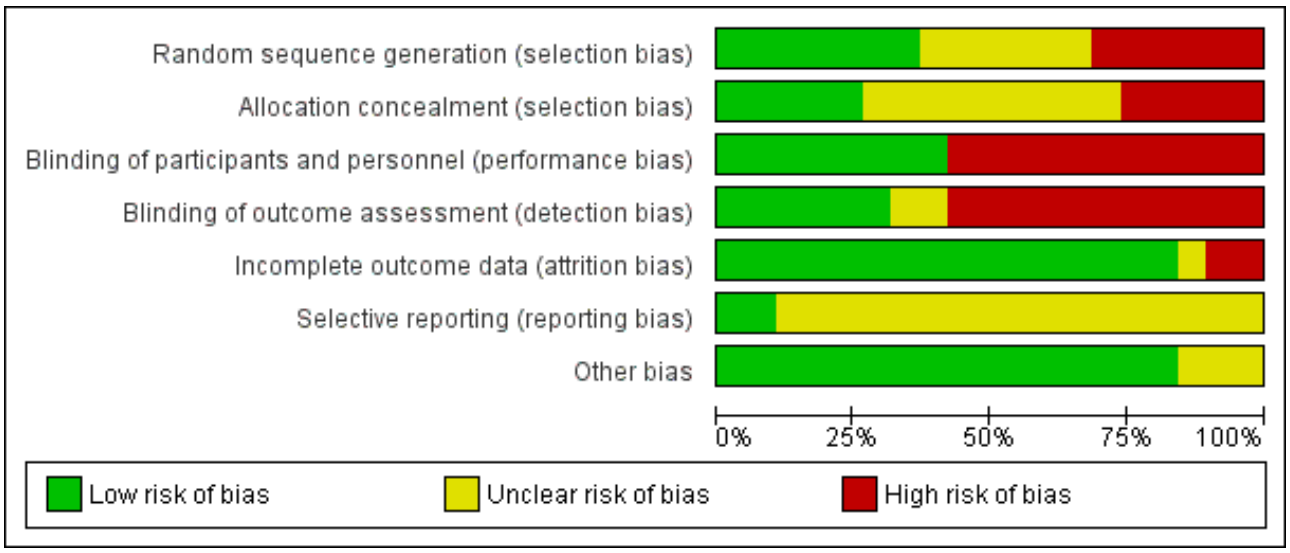
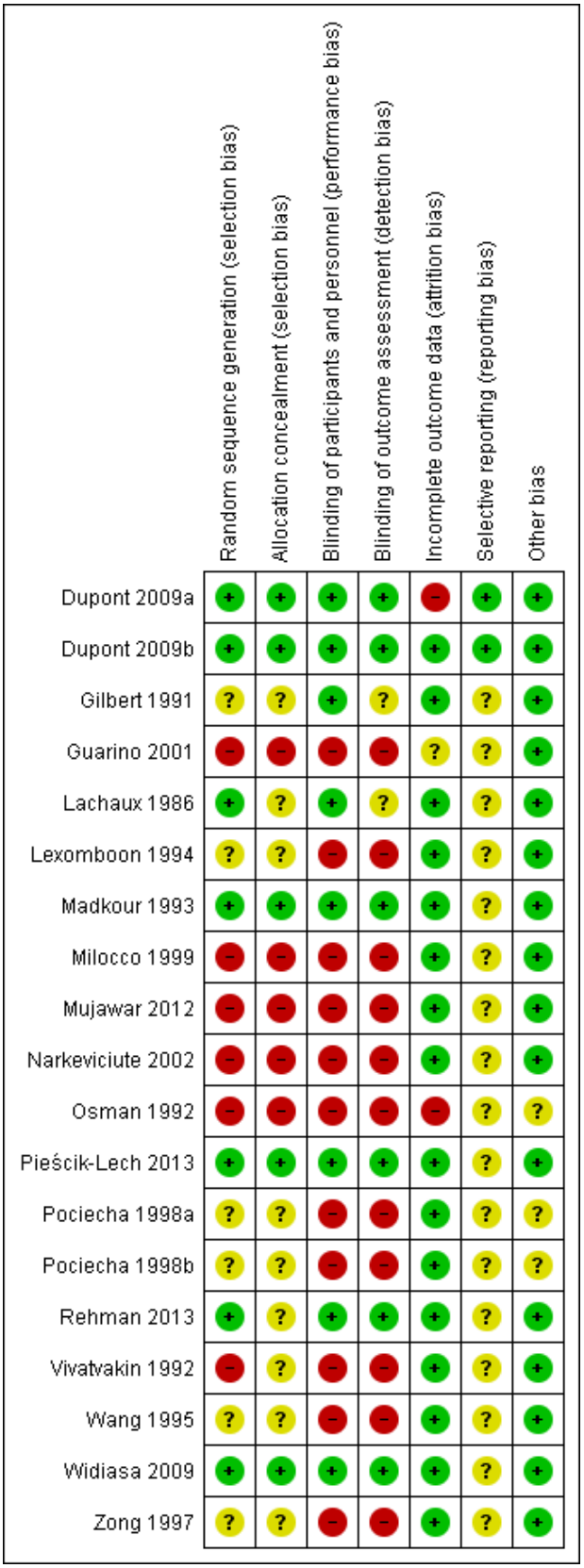


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Seven studies had an adequate description of randomization method (Dupont 2009a; Dupont 2009b; Lachaux 1986; Madkour 1993; Pieścik-Lech 2013; Rehman 2013; Widiasa 2009). In five trials the information about random allocation was unclear (Gilbert 1991; Lexomboon 1994; Pociecha 1998a; Pociecha 1998b; Wang 1995; Zong 1997). Five studies were quasi-randomized trials in which children were allocated alternately, by birthday or serial number (Guarino 2001; Milocco 1999; Mujawar 2012; Narkeviciute 2002; Osman 1992). We suspected selection bias in one study as groups differed in the aetiology of diarrhoea, and the method of randomization was not described (Vivatvakin 1992).

Five studies adequately described allocation concealment (Dupont 2009a; Dupont 2009b; Madkour 1993; Pieścik-Lech 2013; Widiasa 2009). We considered all quasi-randomized trials as having high risk of bias regarding allocation concealment.

Blinding

Eight trials were reported as double-blind and used a placebo as control (Dupont 2009a; Dupont 2009b; Gilbert 1991; Lachaux 1986; Madkour 1993; Pieścik-Lech 2013; Rehman 2013; Widiasa 2009). The remaining trials were not blinded (Guarino 2001; Lexomboon 1994; Milocco 1999; Mujawar 2012; Narkeviciute 2002; Osman 1992; Pociecha 1998a; Pociecha 1998b; Vivatvakin 1992; Wang 1995; Zong 1997).

Incomplete outcome data

Fourteen trials had appropriate follow-up and analysis of more than 90% of participants. Two included less than 90% in the analysis (Dupont 2009a; Osman 1992). In one trial information was insufficient to permit judgement (Guarino 2001).

Selective reporting

Two trials had a registered protocol (Dupont 2009a; Dupont 2009b).

Effects of interventions

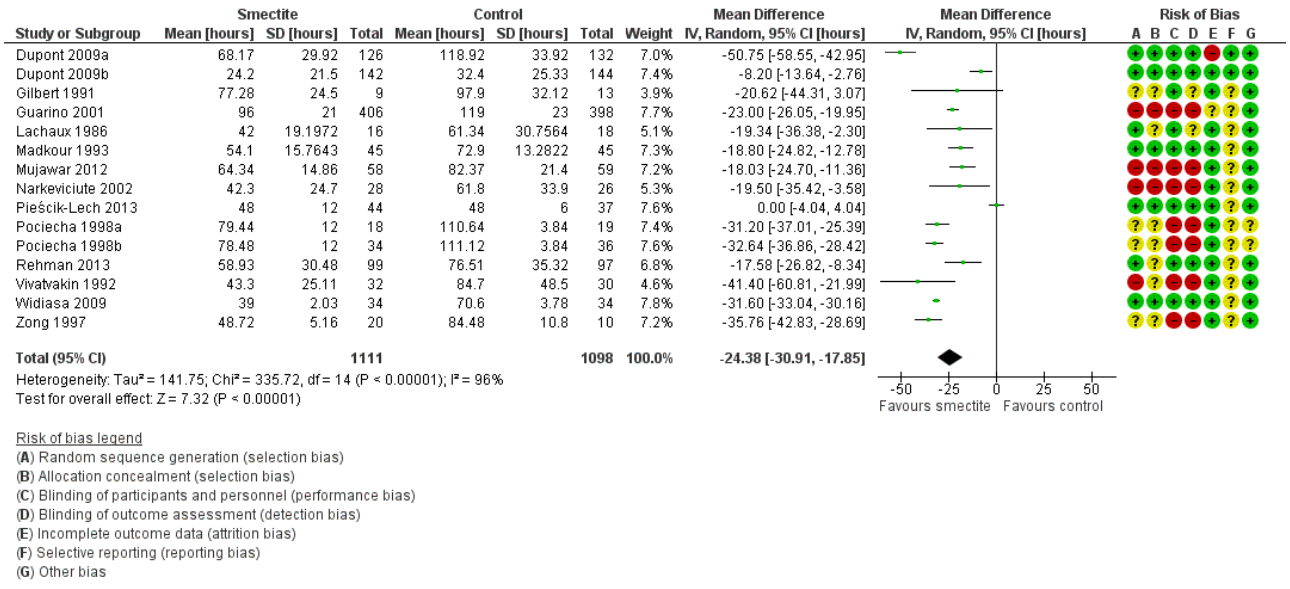
See: **Summary of findings for the main comparison** Smectite compared to control for acute infectious diarrhoea in children

Primary outcomes

1.1 Duration of diarrhoea

Overall, duration of diarrhoea was reduced by approximately 24 hours (mean difference (MD) -24.38, 95% confidence interval (CI) -30.91 to -17.85; 14 trials; 2209 children, Analysis 1.1; low-certainty evidence). There was significant heterogeneity (I^2 = 96%). This high inconsistency was due to differences in effect size of the benefit, not because of opposing directions of effects (Figure 4).

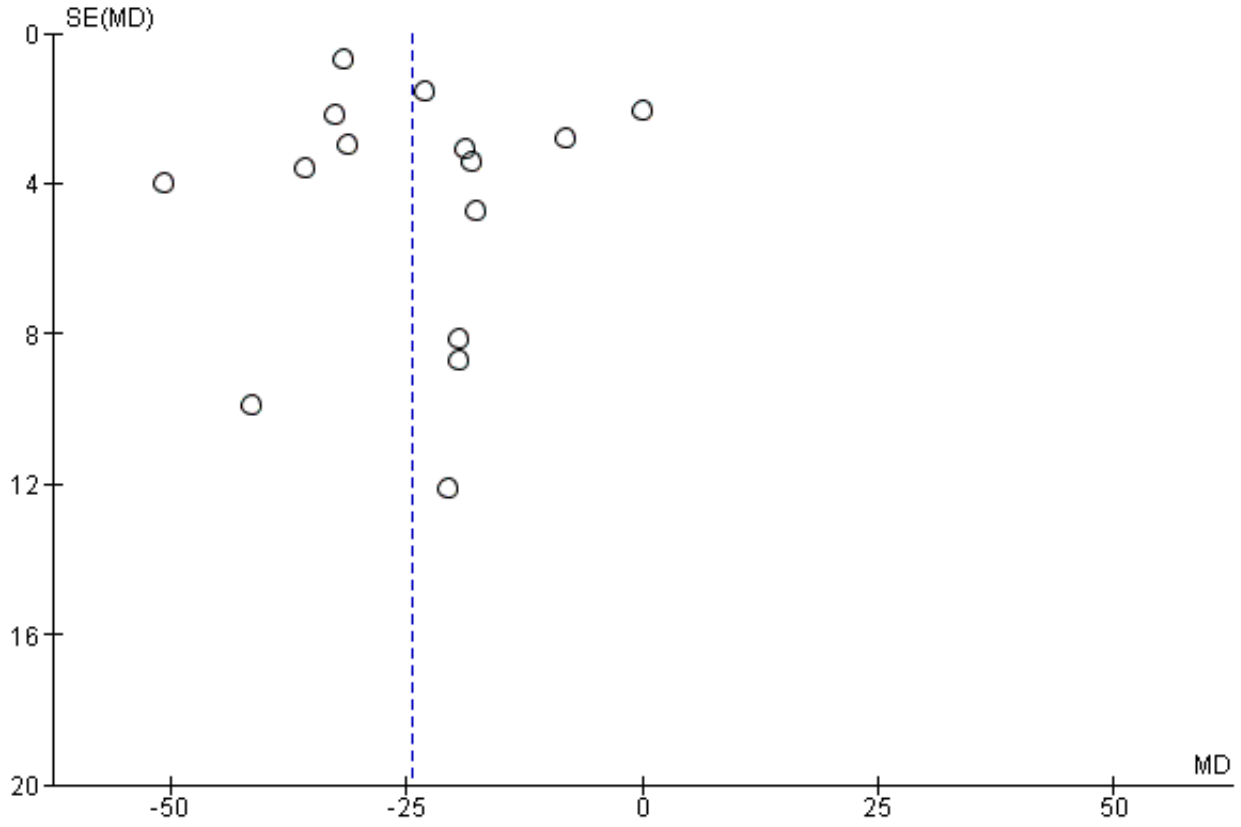
Figure 4. Forest plot of comparison: 1 Diarrhoea primary outcomes, outcome: 1.1 Mean duration of diarrhoea (hours).



A sensitivity analysis exploring the effect of randomization, allocation concealment, blinding, and follow-up did not change the result of the meta-analysis significantly. Sensitivity analysis excluding the trials that required estimations and figure extractions did not significantly change the result of the meta-analysis (MD -22.07, 95% CI -30.38 to -13.76) (Dupont 2009a; Dupont 2009b; Pociecha 1998a; Pociecha 1998b).

On visual inspection, the funnel plot was roughly symmetric, with most studies centred together at the top, probably reflecting spuriously small standard deviations of the continuous outcome that is skewed (Figure 5).

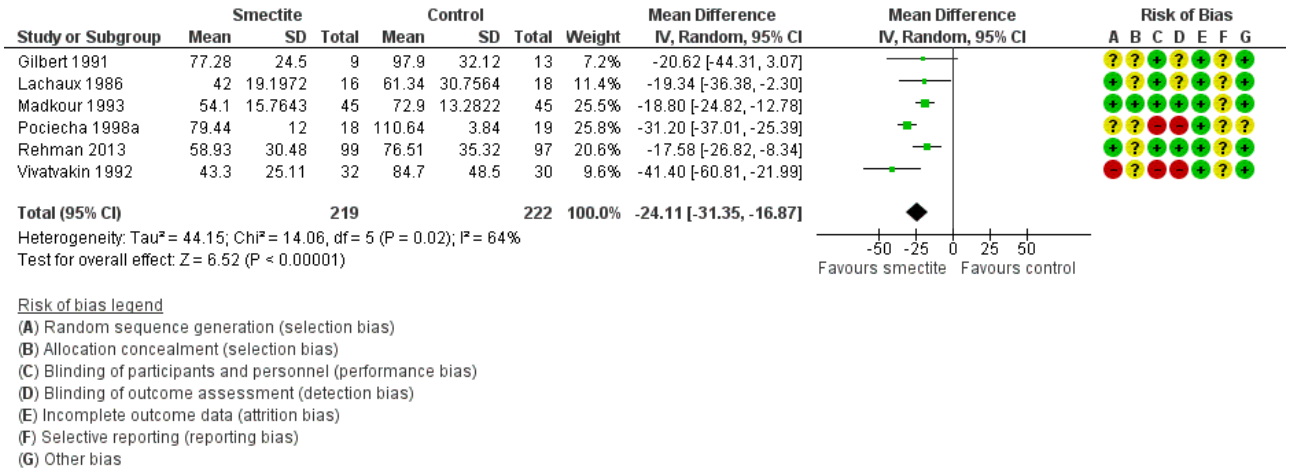
Figure 5. Funnel plot of comparison: 1 Diarrhoea primary outcomes, outcome: 1.1 Mean duration of diarrhoea (hours).



1.2 Duration of diarrhoea, infants less than two years

Five studies included only infants younger than two years (Gilbert 1991; Lachaux 1986; Madkour 1993; Rehman 2013; Vivatvakin 1992). One study reported results for infants less than 12 months (Pociecha 1998a). Smectite reduced the duration of diarrhoea by 24 hours (MD -24.11, 95% CI -31.35 to -16.87; 441 infants; Analysis 1.2). Other studies included both infants and children, but they did not provide enough information to be able to perform a subgroup analysis according to age (Figure 6).

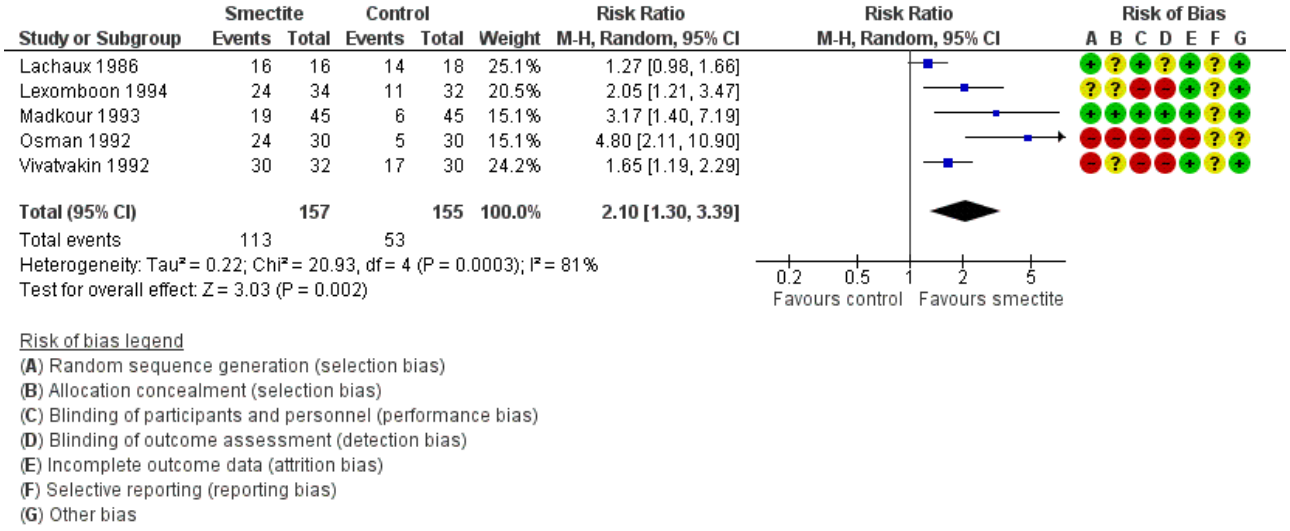
Figure 6. Forest plot of comparison: 1 Diarrhoea primary outcomes, outcome: 1.2 Mean duration of diarrhoea, studies including only infants < 2 years.



1.3 Clinical resolution at day 3 after starting treatment

Smectite increased the rate of clinical resolution at day 3 (risk ratio (RR) 2.10, 95% CI 1.30 to 3.39; 5 trials; 312 children; Analysis 1.3; low-certainty evidence) (Figure 7). After performing a sensitivity analysis excluding trials with high risk of bias (Osman 1992; Vivatvakin 1992), the pooled effect was not significant (RR 1.90, 95% CI 0.96 to 3.77; 3 trials; 190 children).

Figure 7. Forest plot of comparison: 1 Diarrhoea primary outcomes, outcome: 1.3 Clinical resolution at day 3 after starting treatment.

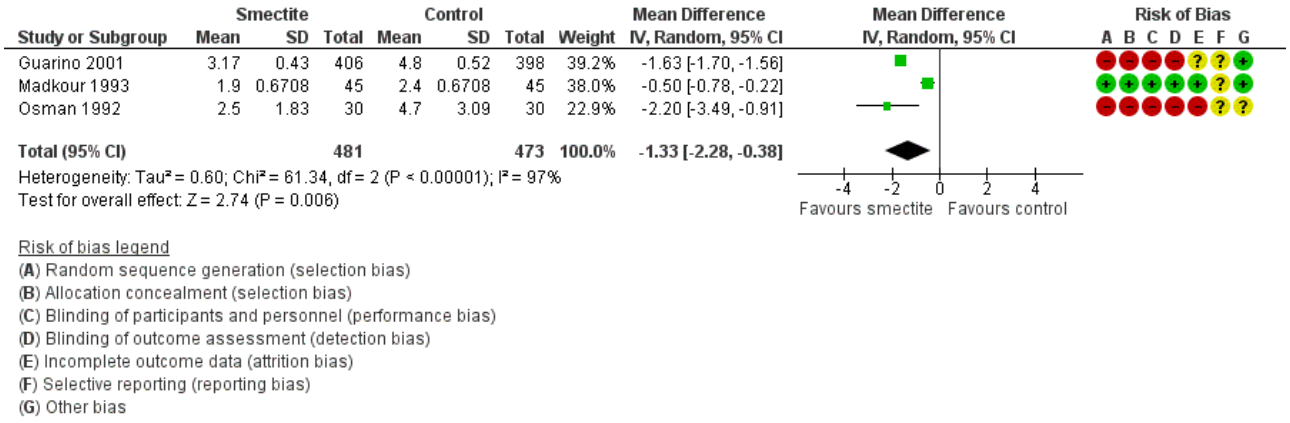


Secondary outcomes

2.1 Stool frequency

Three studies measured stool frequency as number of depositions per day, all of them reporting data on day 3 (Guarino 2001; Madkour 1993; Osman 1992). Smectite reduced stool frequency by one (MD -1.33, 95% CI -2.28 to -0.38; 3 trials; 954 children; Analysis 2.1; very low-certainty evidence) (Figure 8). One study measured stool frequency as total number of depositions during follow-up; the mean number of depositions was 10 in both groups (Milocco 1999).

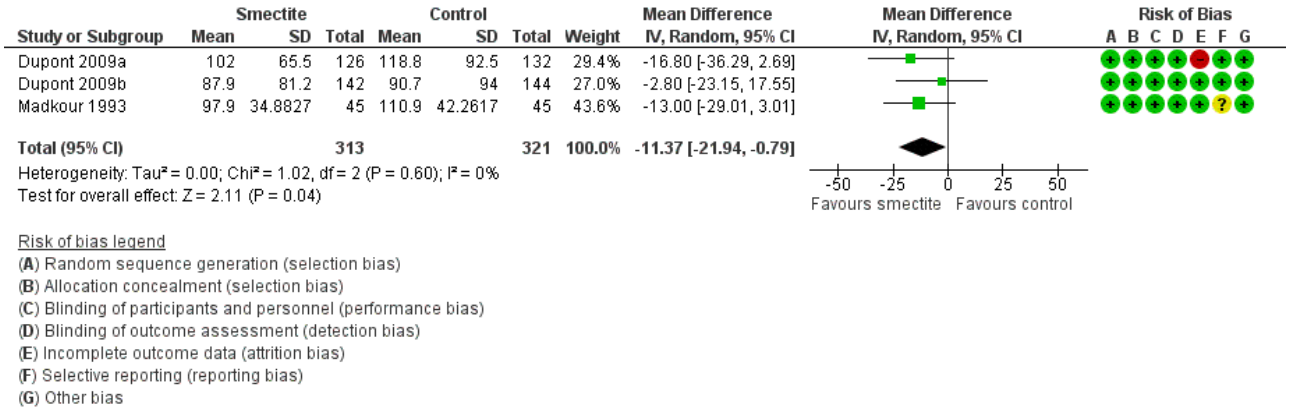
Figure 8. Forest plot of comparison: 2 Diarrhoea secondary outcomes, outcome: 2.1 Stool frequency, measured as number of depositions per day, on day 3 after starting treatment.



2.2 Stool output

Four studies evaluated stool output. Three studies reported cumulative stool output at 72 hours (Dupont 2009a; Dupont 2009b; Madkour 1993). Smectite reduced stool output by 11 g/kg (MD -11.37, 95% CI -21.94 to -0.79; 3 trials; 634 children; Analysis 2.2; low-certainty evidence) (Figure 9). Another study was not pooled because the authors reported stool output as stool weight in total grams per day with an effect estimate favouring smectite (mean of 255.67 g in the smectite group versus 741.33 g in the control group) at day 3 of treatment (Osman 1992).

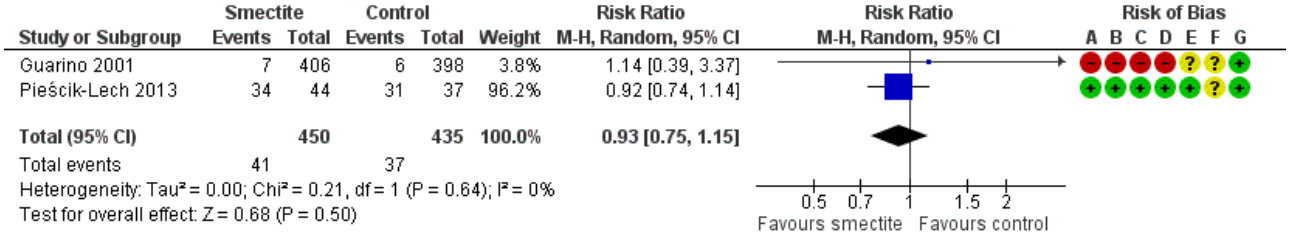
Figure 9. Forest plot of comparison: 2 Diarrhoea secondary outcomes, outcome: 2.2 Stool output, measured in g/kg at 72 hours.



2.3 Need for hospitalization

Two studies reported data on need for hospitalization. There was no evidence of benefit using smectite (RR 0.93, 95% CI 0.75 to 1.15; 2 trials; 885 children; Analysis 2.3; low-certainty evidence) (Figure 10).

Figure 10. Forest plot of comparison: 2 Diarrhoea secondary outcomes, outcome: 2.3 Need for hospitalization.



2.4 Need for intravenous access for rehydration

There was no evidence of an effect on need for intravenous rehydration (RR 0.77, 95% CI 0.54 to 1.11; 1 trial; 81 children; Analysis 2.4; moderate-certainty evidence).

2.5 Death (from any cause or diarrhoea-related)

No deaths were reported in any of the included trials.

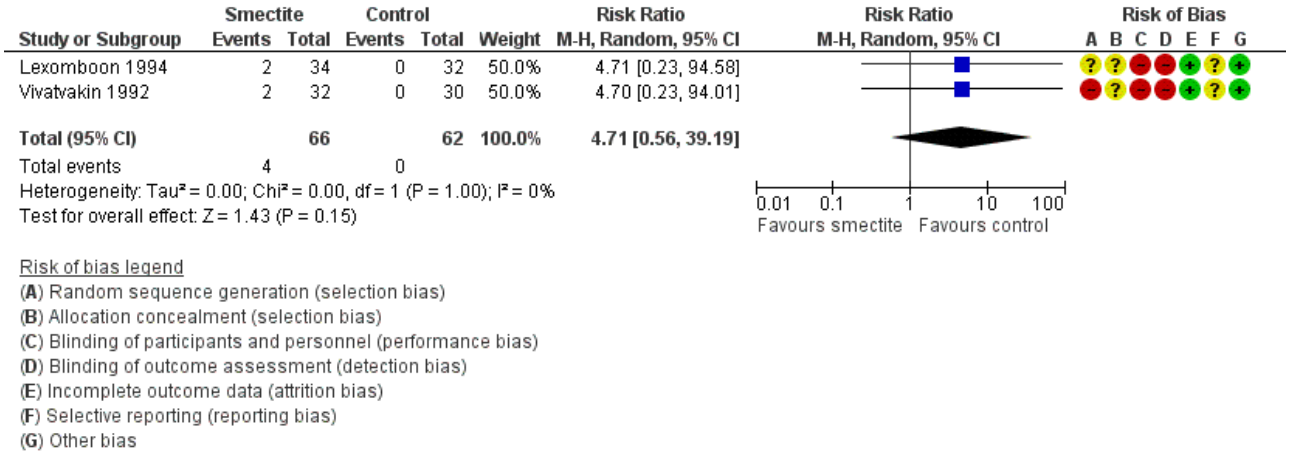
2.6 Serious adverse events (life-threatening events)

There were no reports of serious adverse events.

2.7 Other adverse events (constipation, vomiting)

The most commonly reported adverse effect was constipation. However, the risk of constipation using smectite was very uncertain due to imprecision, with very few events and wide confidence intervals (RR 4.71, 95% CI 0.56 to 39.19; 2 trials; 128 children; Analysis 2.5; low-certainty evidence) (Figure 11). There were also no differences between groups regarding vomiting or fever. Another minor adverse event mentioned in trials was bad taste, but there were no specific numbers for the intervention and control groups.

Figure 11. Forest plot of comparison: 2 Diarrhoea secondary outcomes, outcome: 2.5 Constipation.



DISCUSSION

Summary of main results

We identified 18 studies that compared smectite to a control group. Overall, smectite reduced the duration of diarrhoea by approximately a day, increased clinical resolution by day 3, and had a modest benefit on stool frequency and output. This evidence of benefit persisted after a sensitivity analysis accounting for randomization method, even though five trials were quasi-randomized. Eight trials reported the inclusion of breastfed infants.

There was no evidence of an effect on the need for hospitalization or intravenous rehydration, deaths, or serious side effects.

Overall completeness and applicability of evidence

Studies were conducted in diverse settings in both high-income and low- or middle-income countries, and including both ambulatory and hospital patients. Aetiology also varied, with most trials including a large proportion of children with rotavirus. Most studies excluded children with malnutrition. Most of the studies were funded by the industry. Although external funding and commercial interests are well recognized as a potential source of bias in clinical trials, most investigators provided reasonable information that shows that the manufacturers had no, or a very limited, active role in the design and conduct of the studies.

Quality of the evidence

We assessed the certainty of the evidence using the GRADE system, which is displayed in 'Summary of findings' table 1 (Summary of findings for the main comparison). Overall, the certainty of the body of evidence ranged from very low to moderate. For our primary outcomes, the certainty of evidence was low mainly due to concerns of risk of bias and inconsistency of the results. Regarding risk of bias, we included four quasi-randomized trials, and another four trials did not clearly describe the randomization process. Also, seven trials were not blinded.

The high heterogeneity observed may be due to differences in the definition of the condition, the age of participants, and the different aetiologies. In one study, Pieścik-Lech 2013, another explanation for heterogeneity could be that both the intervention and the control group received a probiotic, but the other study that added a probiotic as a co-intervention did not contribute to such inconsistency (Pociecha 1998a; Pociecha 1998b). The high inconsistency observed was mainly due to differences in effect size of the benefit and not because of opposing directions of effects.

Potential biases in the review process

We made every attempt to limit biases during the review process by ensuring a comprehensive search for potentially eligible studies. We believe that the authors' independent assessments of eligibility of studies for inclusion and data extraction have minimized the potential for additional bias beyond that detailed in the 'Risk of bias' tables in the Characteristics of included studies and in the funnel plot.

Agreements and disagreements with other studies or reviews

Our findings agree with those of previous systematic reviews (Das 2015; Szajewska 2006). Due to the differences in time of publication, our review includes more trials than the review by Szajewska 2006, and assesses the certainty of the evidence based on the GRADE approach. The review by Das 2015 included 13 out of the 18 studies that were included in this review. Szajewska 2006 reported a reduction of 22.7 hours in the duration of diarrhoea, while Das 2015 reported 22.39 hours. Szajewska 2006 and Das 2015 also report significant results for cure rate at day 3. While Das 2015 reported clinical resolution at day 5 and 7, we considered day 3 to be more clinically relevant.

AUTHORS' CONCLUSIONS

Implications for practice

Smectite reduces the duration of symptoms of infectious diarrhoea by a day, and at least 17 hours, and increases clinical resolution at day 3. The effect on stool frequency and output is modest. Although smectite did not have an effect on other relevant outcomes such as the need for intravenous therapy or hospitalization, fewer hours of diarrhoea may be considered clinically significant in different settings and contexts, taking into account that most cases of infectious diarrhoea are self limited and resolve within three to five days with adequate hydration and medical care.

Implications for research

Further research with a focus on adequate randomization and blinding is needed. Future studies may explore the causes of heterogeneity in the effect of smectite, its possible benefit in vulnerable populations such as children under two years of age or with malnutrition, and its effect on certain specific aetiologies such as rotavirus or dysentery producing bacteria. Economic analyses will also provide information to guide practice in different countries or settings.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

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

Dupont 2009a

Methods	Randomized controlled trial Length of follow-up: not stated
Participants	Number: 300 enrolled children Inclusion criteria: inpatients; well-nourished male infants and children aged 1 to 36 months with watery diarrhoea < 3 days duration, with 3 watery stools per day and at least 1 watery stool in the past 24 hours; mild-to-moderate dehydration Exclusion criteria: severe dehydration or malnutrition, bloody diarrhoea, fever 39 °C or higher, previous medications Breastfeeding: exclusively breastfed infants were excluded
Interventions	Intervention group: diosmectite. Dosage 3 g twice a day for 3 days, then 3 g daily for infants younger than 12 months. Double the dose for older children Control: placebo
Outcomes	Duration of diarrhoea (until first formed stool) Stool output in g/kg in the first 72 hrs
Notes	Location: Peru Setting: urban Cause of diarrhoea: rotavirus 22%. Other aetiologies not specified. Source of funding: industry Registration number: NCT00352716

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomized in sequential ascending order by a statistician

Dupont 2009a *(Continued)*

Allocation concealment (selection bias)	Low risk	Sponsor-assigned biostatistician prepared a list of treatment allocation codes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was identical to diosmectite in size, weight, colour, smell, taste, and appearance, and was inert. Blinding seems appropriate.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blind review of data by outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	40 children (13%) were non-adherent, and the rest analysed as per protocol.
Selective reporting (reporting bias)	Low risk	None detected. Registered trial
Other bias	Low risk	No other biases detected.

Dupont 2009b

Methods	Randomized controlled trial Length of follow-up: not stated
Participants	Number: 302 enrolled children Inclusion criteria: inpatients; well-nourished male infants and children aged 1 to 36 months with watery diarrhoea < 3 days duration, with 3 watery stools per day and at least 1 watery stool in the past 24 hours; mild-to-moderate dehydration Exclusion criteria: severe dehydration or malnutrition, bloody diarrhoea, fever 39 °C or higher, previous medications Breastfeeding: exclusively breastfed infants were excluded
Interventions	Intervention group: diosmectite. Dosage 3 g twice a day for 3 days, then 3 g daily for infants younger than 12 months. Double the dose for older children Control: placebo
Outcomes	Duration of diarrhoea (until first soft or formed stool) Stool output in g/kg in the first 72 hrs
Notes	Location: Malaysia Setting: urban Cause of diarrhoea: rotavirus 12%. Other aetiologies not specified. Source of funding: industry Registration number: NCT00352989

Risk of bias

Dupont 2009b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomized in sequential ascending order by a statistician
Allocation concealment (selection bias)	Low risk	Sponsor-assigned biostatistician prepared a list of treatment allocation codes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo was identical to diosmectite in size, weight, colour, smell, taste, and appearance, and was inert. Blinding seems appropriate.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blind review of data by outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 children (5%) were non-adherent, and the rest analysed as per protocol.
Selective reporting (reporting bias)	Low risk	None detected. Registered trial
Other bias	Low risk	No other biases detected.

Gilbert 1991

Methods	Randomized controlled trial Length of follow-up: not stated
Participants	Number: 56 enrolled children Inclusion criteria: inpatients; children aged 2 to 24 months with moderate-to-severe acute diarrhoea Exclusion criteria: malnutrition Breastfeeding: not specified
Interventions	Intervention group: diosmectite. Dosage 1.5 g twice a day for infants younger than 12 months. Double the dose for older children Control: placebo Another control group received loperamide 0.11 mg/kg every 8 hours.
Outcomes	Duration of diarrhoea (time to normalization of stools) Stool frequency on day 5
Notes	Location: France Setting: urban Cause of diarrhoea: rotavirus 18%, *Staphylococcus aureus* 3%, *Escherichia coli* 3%, *Campylobacter* spp. 3%, *Candida* spp. 1%

Gilbert 1991 *(Continued)*

	Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomized but no method described.
Allocation concealment (selection bias)	Unclear risk	No method described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of placebo; probably adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per-protocol analysis. 4 children (7%) excluded and not analysed.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Guarino 2001

Methods	Quasi-randomized controlled trial Length of follow-up: not stated
Participants	Number: 804 enrolled children Inclusion criteria: outpatients; well-nourished children aged 3 to 60 months with acute diarrhoea of mild-to-moderate severity < 2 days duration, with 3 watery stools per day Exclusion criteria: malnutrition, chronic diseases, previous medications Breastfeeding: not specified
Interventions	Intervention group: diosmectite. Dosage 1.5 g twice a day for infants younger than 12 months. Double the dose for older children Control: no medication
Outcomes	Duration of diarrhoea (from first to the last liquid–loose stool output preceding the return of normal stools) Diarrhoea at day 7 Vomiting Fever

Guarino 2001 *(Continued)*

	Hospitalization rate
Notes	Location: Italy Setting: urban Cause of diarrhoea: rotavirus 4%, not specified bacterial aetiology 1% Source of funding: industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized. Participants selected in sequential one-to-one basis.
Allocation concealment (selection bias)	High risk	Not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Lachaux 1986

Methods	Randomized controlled trial Length of follow-up: not stated
Participants	Number: 36 enrolled infants Inclusion criteria: inpatients; infants aged 2 to 24 months with acute watery diarrhoea < 4 days duration, with mild-to-moderate dehydration Exclusion criteria: previous medications, concomitant illness Breastfeeding: not stated
Interventions	Intervention group: diosmectite. Dosage 3 g per day to infants < 1 year, 6 g per day to infants > 1 year. Duration not stated. Control: placebo

Lachaux 1986 *(Continued)*

Outcomes	Duration of diarrhoea (from first drug administration to last liquid stool before a formed one) Clinical resolution at day 3 and 5 Adverse events
Notes	Location: France Setting: urban Cause of diarrhoea: rotavirus 77% Source of funding: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stated as "drawing lots"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of placebo; probably adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Use of placebo; probably adequate blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 loss per group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Lexomboon 1994

Methods	Randomized controlled trial Length of follow-up: 5 days
Participants	Number: 66 enrolled children Inclusion criteria: outpatients; well-nourished children aged 1 to 24 months with acute diarrhoea < 2 days duration, with 3 watery stools within 24 hours Exclusion criteria: severe dehydration, dysentery, fever higher than 38.5 °C, previous medications Breastfeeding: included
Interventions	Intervention group: diosmectite. Dosage: loading dose of 3 g, then 1.5 g twice a day

Lexomboon 1994 *(Continued)*

	Control: no medication
Outcomes	Diarrhoea at day 3 and 5 Tolerability
Notes	Location: Thailand Setting: urban Cause of diarrhoea: rotavirus 27%, *Campylobacter jejuni* 8%, enteropathogenic *Escherichia coli* 5%, *Salmonella* spp. 6%, *Shigella* spp. 3%, *Plesiomonas shigelloides* 2% Source of funding: industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomized. No method described.
Allocation concealment (selection bias)	Unclear risk	No method described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Madkour 1993

Methods	Randomized controlled trial Length of follow-up: until recovery from diarrhoea
Participants	Number: 90 enrolled children Inclusion criteria: inpatients; well-nourished male children aged 3 to 24 months with watery diarrhoea < 5 days duration, with dehydration of any severity Exclusion criteria: prolonged diarrhoea, malnutrition, major illnesses Breastfeeding: not specified

Madkour 1993 *(Continued)*

Interventions	Intervention group: diosmectite. Dosage 1.5 g, 4 times daily for 3 days Control group: placebo
Outcomes	Duration of diarrhoea (from enrolment to last liquid stool) Frequency of diarrhoea Duration of vomiting Feeding pattern
Notes	Location: Egypt Setting: urban Cause of diarrhoea: rotavirus 16%. Other aetiologies not specified. Source of funding: WHO and industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization by Diarrheal Disease Control Programme of the WHO
Allocation concealment (selection bias)	Low risk	Numerically coded envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Use of placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Milocco 1999

Methods	Quasi-randomized controlled trial Length of follow-up: not stated
Participants	Number: 35 enrolled children Inclusion criteria: inpatients; children aged 0 to 60 months with watery diarrhoea < 5 days duration

Milocco 1999 *(Continued)*

	Exclusion criteria: not stated Breastfeeding: not specified
Interventions	Intervention group: diosmectite. Dosage 1.5 g twice a day for infants younger than 12 months. Double the dose for older children Control: no medication
Outcomes	Number of stools at 48 hrs Duration of diarrhoea (not clearly defined) Fever, vomiting, weight loss
Notes	Location: Italy Setting: urban Cause of diarrhoea: rotavirus 23%, *Salmonella* spp. 11%, *Cryptosporidium* 6% Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants selected "alternatively"; not truly random.
Allocation concealment (selection bias)	High risk	Not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 losses to follow-up in intervention group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Mujawar 2012

Methods	Quasi-randomized controlled trial Length of follow-up: not stated
Participants	Number: 117 enrolled children

Mujawar 2012 *(Continued)*

	Inclusion criteria: outpatients; well-nourished children aged 24 to 60 months with watery diarrhoea < 2 days duration; mild-to-moderate dehydration Exclusion criteria: bloody diarrhoea, chronic illness, previous medications Breastfeeding: not specified
Interventions	Intervention group: diosmectite. Dosage 1.5 g thrice a day for 5 days Control group: no medication
Outcomes	Duration of diarrhoea (until normal stool consistency) Complications: severe dehydration, severe dysentery, respiratory infection, and anaemia
Notes	Location: India Setting: urban Cause of diarrhoea: not specified Source of funding: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not truly random; participants selected by serial number.
Allocation concealment (selection bias)	High risk	Not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis. 8 children (7%) were lost to follow-up and were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Narkeviciute 2002

Methods	Quasi-randomized controlled trial Length of follow-up: not stated
Participants	Number: 54 enrolled children

Narkeviciute 2002 *(Continued)*

	Inclusion criteria: inpatients; well-nourished infants and children aged 6 to 48 months with watery diarrhoea < 3 days duration, with 3 watery stools per day; mild-to-moderate dehydration Exclusion criteria: severe dehydration, malnutrition, chronic or concomitant illness Breastfeeding: excluded
Interventions	Intervention group: diosmectite. Dosage: loading dose of 3 g; 1.5 g, 3 times a day for children < 10 kg, 4 times a day for > 10 kg Control: no medication
Outcomes	Duration of diarrhoea (time to last watery/semiliquid stool) Length of stay
Notes	Location: Lithuania Setting: urban Cause of diarrhoea: rotavirus 70%, enteropathogenic *Escherichia coli* 4%, *Campylobacter* spp. 8% Source of funding: industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not truly random; participants selected by birthday.
Allocation concealment (selection bias)	High risk	Not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Osman 1992

Methods	Quasi-randomized controlled trial Length of follow-up: 5 days

Osman 1992 *(Continued)*

Participants	Number: 71 infants and children Inclusion criteria: inpatients; infants and children (no age limit specified, mean age of 13 months) with acute watery diarrhoea < 7 days duration, with mild-to-moderate dehydration Exclusion criteria: systemic illness; previous use of antibiotics or antidiarrhoeal agents; malnutrition Breastfeeding: included
Interventions	Intervention group: diosmectite. Dosage 1.5 g every 8 hours to infants < 10 kg, 1.6 g every 6 hours to infants > 10 kg for a maximum of 5 days Control: no medication
Outcomes	Clinical resolution (return of stools to previous formed consistency and average number of frequency) Stool output (g/kg) Stool frequency
Notes	Location: Egypt Setting: urban Cause of diarrhoea: rotavirus 43%, bacterial (not specified) 23% Source of funding: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not truly random; participants selected alternately.
Allocation concealment (selection bias)	High risk	Not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol analysis with 4 exlusions in intervention group (12%) and 7 losses in control group (19%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Unclear risk	No other biases detected.

Pieścik-Lech 2013

Methods	Randomized controlled trial Length of follow-up: 7 days
Participants	Number: 88 enrolled children Inclusion criteria: inpatients/outpatients; well-nourished infants and children aged 4 to 60 months with watery diarrhoea < 5 days duration, with 3 watery stools per day Exclusion criteria: recent history of diarrhoea, chronic diseases Breastfeeding: included
Interventions	Intervention group: diosmectite, dose 3 g once daily until diarrhoea stopped, plus *Lactobacillus* GG, dose of 6 x 10^9 colony forming units, once daily for 7 days Control group: placebo plus *Lactobacillus* GG
Outcomes	Duration of diarrhoea (time from randomization until the last watery stool, or at least 12 h with no stool) Stool frequency Consistency of stools Need for antibiotic therapy Diarrhoea recurrence Need for hospitalization Need for intravenous rehydration therapy
Notes	Location: Poland Setting: urban Cause of diarrhoea: rotavirus 60%, adenovirus 5%, *Salmonella* spp. 5%, *Staphylococcus aureus* 3%, enteropathogenic *Escherichia coli* 1% Source of funding: Medical University of Warsaw

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization
Allocation concealment (selection bias)	Low risk	Randomization prepared by independent investigator.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Use of placebo

Pieścik-Lech 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Per-protocol analysis with 7 losses in control group (8%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Pociecha 1998a

Methods	Randomized controlled trial Length of follow-up: 28 days
Participants	Number: 56 enrolled infants Inclusion criteria: inpatients; well-nourished infants ≤ 12 months with watery diarrhoea of rotaviral aetiology < 3 days duration, with moderate dehydration Exclusion criteria: chronic diseases, aetiologies other than rotavirus Breastfeeding: included
Interventions	Intervention group: diosmectite, dose 1.5 g twice daily for 6 days, plus *Lactobacillus* GG in "age dependent dose" Control group: *Lactobacillus* GG A third group received polyvinylpolypyrrolidone plus *Lactobacillus* GG.
Outcomes	Duration of intravenous rehydration Duration of fever and vomiting Duration of diarrhoea (time to normalization of consistency of the stool or a day without stool) Need of hospitalization after discharge
Notes	Location: Poland Setting: urban Cause of diarrhoea: rotavirus 100% Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomized. No method described.
Allocation concealment (selection bias)	Unclear risk	No method described.

Pociecha 1998a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Unclear risk	No other biases detected.

Pociecha 1998b

Methods	Randomized controlled trial Length of follow-up: 28 days
Participants	Number: 105 enrolled infants Inclusion criteria: inpatients; well-nourished infants > 12 months with watery diarrhoea of rotaviral aetiology < 3 days duration, with moderate dehydration Exclusion criteria: chronic diseases, aetiologies other than rotavirus Breastfeeding: included
Interventions	Intervention group: diosmectite, dose 3 g twice daily for 6 days, plus *Lactobacillus* GG in "age dependent dose" Control group: *Lactobacillus* GG A third group received polyvinylpolypyrrolidone plus *Lactobacillus* GG.
Outcomes	Duration of intravenous rehydration Duration of fever and vomiting Duration of diarrhoea (time to normalization of consistency of the stool or a day without stool) Need of hospitalization after discharge
Notes	Location: Poland Setting: urban Cause of diarrhoea: rotavirus 100% Source of funding: not stated
Risk of bias	

Pociecha 1998b *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomized. No method described.
Allocation concealment (selection bias)	Unclear risk	No method described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Unclear risk	No other biases detected.

Rehman 2013

Methods	Randomized controlled trial Length of follow-up: 6 days
Participants	Number: 206 enrolled children Inclusion criteria: inpatients; well-nourished infants and children aged 6 to 24 months with watery diarrhoea < 3 days duration, with 3 watery stools per day and at least 1 in the past 24 hours; mild-to-severe dehydration Exclusion criteria: bloody diarrhoea, medications, malnutrition, systemic infection Breastfeeding: included
Interventions	Intervention group: diosmectite, dose 1 g in infants < 12 months and 1.5 g in older children, every 8 hours, plus zinc (dose not specified) for 5 days Control group: placebo plus zinc
Outcomes	Duration of diarrhoea (until first stool of pre-diarrhoeal consistency)
Notes	Location: Pakistan Setting: urban Cause of diarrhoea: not specified Source of funding: not specified

Rehman 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by lottery
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement. Mentions only "lottery method".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Use of placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per-protocol analysis. 10 losses to follow-up (5%), 4 in intervention group, 6 in control group
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Vivatvakin 1992

Methods	Randomized controlled trial Length of follow-up: 5 days
Participants	Number: 62 enrolled children Inclusion criteria: inpatients; infants/children aged 1 to 24 months with acute secretory diarrhoea < 3 days duration, with 3 watery stools per day Exclusion criteria: severe dehydration, third-degree malnutrition, other medications, chronic illnesses Breastfeeding: included
Interventions	Intervention group: diosmectite. Dosage 1.5 g, every 12 hrs for infants < 3 kg; every 8 hrs for infants 4 to 10 kg; every 6 hrs for children 11 to 15 kg, for a maximum of 5 days Control: no medication
Outcomes	Duration of diarrhoea (from first intervention dose until last liquid stool) Number of stools Change in weight Oral liquid intake
Notes	Location: Thailand

Vivatvakin 1992 *(Continued)*

	Setting: urban Cause of diarrhoea: rotavirus in 3% of children in intervention group, 19% in control group. Stool cultures were reported positive for *Salmonella* and *Aeromonas* spp. in 7% and 9% of children in the control and study group, respectively, but numbers of each bacterial aetiology per group were not stated. Source of funding: industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Stated as randomized, but no method of randomization described. Selection bias is suspected as groups were different in the aetiology of diarrhoea.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases were detected.

Wang 1995

Methods	Randomized controlled trial Length of follow-up: not stated
Participants	Number: 55 enrolled children Inclusion criteria: acute diarrhoea < 5 days duration. No age limit or other inclusion criteria stated. Exclusion criteria: not stated Breastfeeding: not stated
Interventions	Intervention group: diosmectite. Dosage 3 g per day in infants < 1 year old, 6 g per day in > 1 year Control: Bismuth complex. Dosage 5 mL, 3 times per day
Outcomes	Clinical resolution at day 5
Notes	Location: China

Wang 1995 *(Continued)*

	Setting: not clear Cause of diarrhoea: not reported Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No method of randomization described.
Allocation concealment (selection bias)	Unclear risk	No method described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Widiasa 2009

Methods	Randomized controlled trial Length of follow-up: until recovery
Participants	Number: 68 enrolled infants Inclusion criteria: inpatients; infants aged 6 to 12 months with watery diarrhoea < 2 days duration, with 3 watery stools per day and mild-to-moderate dehydration Exclusion criteria: severe malnutrition, bloody diarrhoea, severe disease Breastfeeding: included
Interventions	Intervention group: diosmectite. Dose not specified. Control group: placebo
Outcomes	Duration of diarrhoea (time until normal consistency and frequency)
Notes	Location: Indonesia Setting: urban

Widiasa 2009 *(Continued)*

	Cause of diarrhoea: not specified
	Source of funding: industry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization
Allocation concealment (selection bias)	Low risk	Coded, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Use of placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

Zong 1997

Methods	Randomized controlled trial
	Length of follow-up: not stated
Participants	Number: 45 enrolled children
	Inclusion criteria: infants and children aged 2 to 30 months with watery diarrhoea of < 5 days duration
	Exclusion criteria: not specified
	Breastfeeding: not reported
Interventions	Intervention group: diosmectite. Dose not specified.
	Control: lactein tablet. Dose not specified.
	A third group received diosmectite and antibiotics.
Outcomes	Duration of diarrhoea (not clearly defined)
Notes	Location: China
	Setting: unclear

Zong 1997 *(Continued)*

	Cause of diarrhoea: rotavirus 100% Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No method of randomization described.
Allocation concealment (selection bias)	Unclear risk	No method described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement. No protocol registered.
Other bias	Low risk	No other biases detected.

WHO: World Health Organization

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

Study	Reason for exclusion
Dupont 1991	Wrong outcome: permeability to mannitol and lactulose
Dupont 1992	Wrong outcome: permeability to mannitol and lactulose
Karas 1996	Wrong population: neonates
Madkour 1994	Duplicate

DATA AND ANALYSES

Comparison 1. Diarrhoea primary outcomes

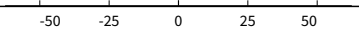
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean duration of diarrhoea	15	2209	Mean Difference (IV, Random, 95% CI)	-24.38 [-30.91, -17.85]
2 Mean duration of diarrhoea, studies including only infants < 2 years	6	441	Mean Difference (IV, Random, 95% CI)	-24.11 [-31.35, -16.87]
3 Clinical resolution at day 3 after starting treatment	5	312	Risk Ratio (M-H, Random, 95% CI)	2.10 [1.30, 3.39]

Analysis 1.1. Comparison 1 Diarrhoea primary outcomes, Outcome 1 Mean duration of diarrhoea.

Study or subgroup	Smectite N	Smectite Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Dupont 2009a	126	68.2 (29.9)	132	118.9 (33.9)		7.05%	-50.75[-58.55,-42.95]
Dupont 2009b	142	24.2 (21.5)	144	32.4 (25.3)		7.43%	-8.2[-13.64,-2.76]
Gilbert 1991	9	77.3 (24.5)	13	97.9 (32.1)		3.86%	-20.62[-44.31,3.07]
Guarino 2001	406	96 (21)	398	119 (23)		7.7%	-23[-26.05,-19.95]
Lachaux 1986	16	42 (19.2)	18	61.3 (30.8)		5.11%	-19.34[-36.38,-2.3]
Madkour 1993	45	54.1 (15.8)	45	72.9 (13.3)		7.34%	-18.8[-24.82,-12.78]
Mujawar 2012	58	64.3 (14.9)	59	82.4 (21.4)		7.24%	-18.03[-24.7,-11.36]
Narkeviciute 2002	28	42.3 (24.7)	26	61.8 (33.9)		5.34%	-19.5[-35.42,-3.58]
Pieścik-Lech 2013	44	48 (12)	37	48 (6)		7.6%	0[-4.04,4.04]
Pociecha 1998a	18	79.4 (12)	19	110.6 (3.8)		7.37%	-31.2[-37.01,-25.39]
Pociecha 1998b	34	78.5 (12)	36	111.1 (3.8)		7.58%	-32.64[-36.86,-28.42]
Rehman 2013	99	58.9 (30.5)	97	76.5 (35.3)		6.77%	-17.58[-26.82,-8.34]
Vivatvakin 1992	32	43.3 (25.1)	30	84.7 (48.5)		4.63%	-41.4[-60.81,-21.99]
Widiasa 2009	34	39 (2)	34	70.6 (3.8)		7.8%	-31.6[-33.04,-30.16]
Zong 1997	20	48.7 (5.2)	10	84.5 (10.8)		7.17%	-35.76[-42.83,-28.69]
Total ***	**1111**		**1098**			**100%**	**-24.38[-30.91,-17.85]**

Heterogeneity: Tau^2=141.75; Chi^2=335.72, df=14(P<0.0001); I^2=95.83%

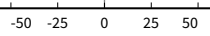
Test for overall effect: Z=7.32(P<0.0001)



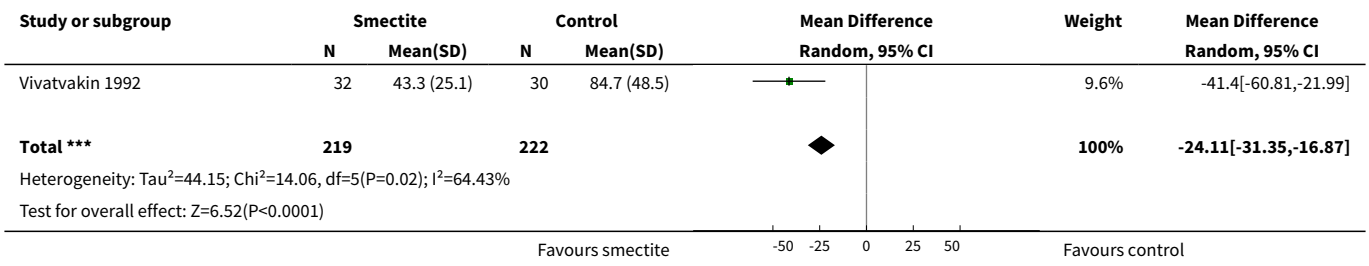
Favours smectite — Favours control

Analysis 1.2. Comparison 1 Diarrhoea primary outcomes, Outcome 2 Mean duration of diarrhoea, studies including only infants < 2 years.

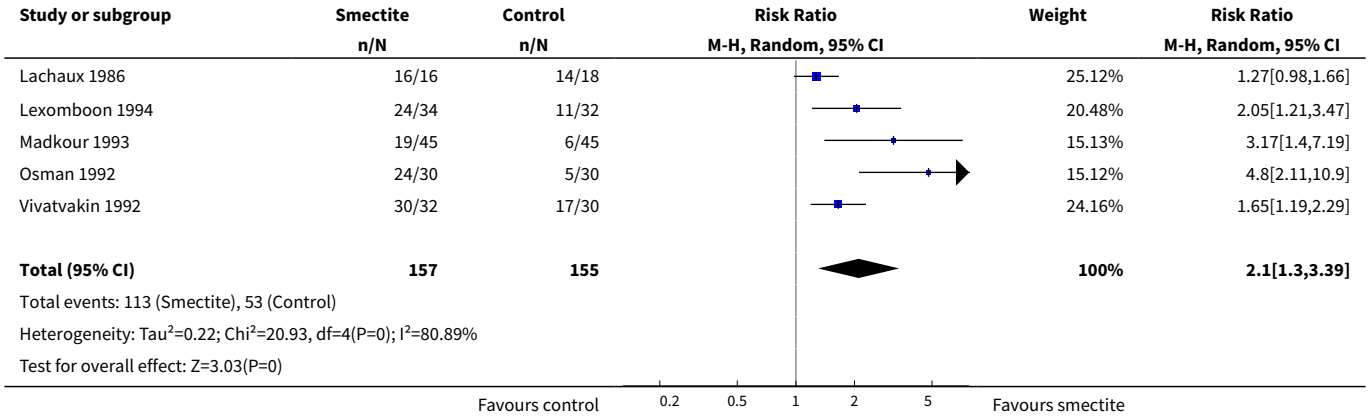
Study or subgroup	Smectite N	Smectite Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Gilbert 1991	9	77.3 (24.5)	13	97.9 (32.1)		7.18%	-20.62[-44.31,3.07]
Lachaux 1986	16	42 (19.2)	18	61.3 (30.8)		11.4%	-19.34[-36.38,-2.3]
Madkour 1993	45	54.1 (15.8)	45	72.9 (13.3)		25.47%	-18.8[-24.82,-12.78]
Pociecha 1998a	18	79.4 (12)	19	110.6 (3.8)		25.79%	-31.2[-37.01,-25.39]
Rehman 2013	99	58.9 (30.5)	97	76.5 (35.3)		20.56%	-17.58[-26.82,-8.34]



Favours smectite — Favours control



Analysis 1.3. Comparison 1 Diarrhoea primary outcomes, Outcome 3 Clinical resolution at day 3 after starting treatment.

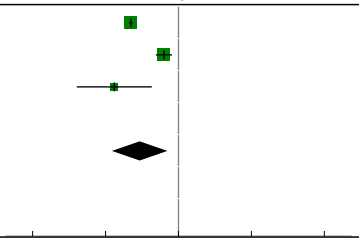


Comparison 2. Diarrhoea secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stool frequency, measured as number of depositions per day, on day 3 after starting treatment	3	954	Mean Difference (IV, Random, 95% CI)	-1.33 [-2.28, -0.38]
2 Stool output, measured in g or mL/kg per day	3	634	Mean Difference (IV, Random, 95% CI)	-11.37 [-21.94, -0.79]
3 Need for hospitalization	2	885	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.15]
4 Need for intravenous access for rehydration	1	81	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.54, 1.11]
5 Constipation	2	128	Risk Ratio (M-H, Random, 95% CI)	4.71 [0.56, 39.19]

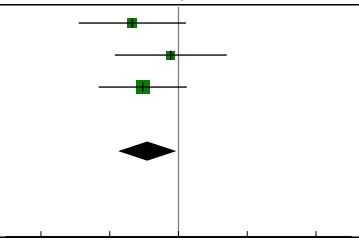
Analysis 2.1. Comparison 2 Diarrhoea secondary outcomes, Outcome 1 Stool frequency, measured as number of depositions per day, on day 3 after starting treatment.

Study or subgroup	Smectite N	Smectite Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Guarino 2001	406	3.2 (0.4)	398	4.8 (0.5)		39.17%	-1.63[-1.7,-1.56]
Madkour 1993	45	1.9 (0.7)	45	2.4 (0.7)		37.98%	-0.5[-0.78,-0.22]
Osman 1992	30	2.5 (1.8)	30	4.7 (3.1)		22.85%	-2.2[-3.49,-0.91]
Total ***	**481**		**473**			**100%**	**-1.33[-2.28,-0.38]**
Heterogeneity: Tau²=0.6; Chi²=61.34, df=2(P<0.0001); I²=96.74%							
Test for overall effect: Z=2.74(P=0.01)							



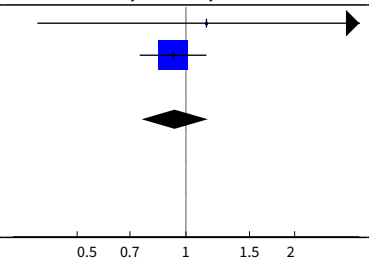
Analysis 2.2. Comparison 2 Diarrhoea secondary outcomes, Outcome 2 Stool output, measured in g or mL/kg per day.

Study or subgroup	Smectite N	Smectite Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Dupont 2009a	126	102 (65.5)	132	118.8 (92.5)		29.42%	-16.8[-36.29,2.69]
Dupont 2009b	142	87.9 (81.2)	144	90.7 (94)		26.99%	-2.8[-23.15,17.55]
Madkour 1993	45	97.9 (34.9)	45	110.9 (42.3)		43.59%	-13[-29.01,3.01]
Total ***	**313**		**321**			**100%**	**-11.37[-21.94,-0.79]**
Heterogeneity: Tau²=0; Chi²=1.02, df=2(P=0.6); I²=0%							
Test for overall effect: Z=2.11(P=0.04)							



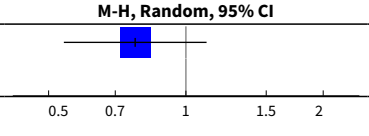
Analysis 2.3. Comparison 2 Diarrhoea secondary outcomes, Outcome 3 Need for hospitalization.

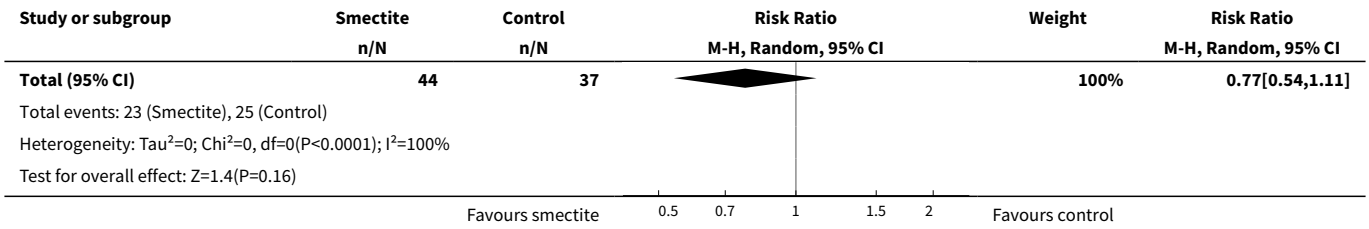
Study or subgroup	Smectite n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Guarino 2001	7/406	6/398		3.77%	1.14[0.39,3.37]
Pieścik-Lech 2013	34/44	31/37		96.23%	0.92[0.74,1.14]
Total (95% CI)	**450**	**435**		**100%**	**0.93[0.75,1.15]**
Total events: 41 (Smectite), 37 (Control)					
Heterogeneity: Tau²=0; Chi²=0.21, df=1(P=0.64); I²=0%					
Test for overall effect: Z=0.68(P=0.5)					



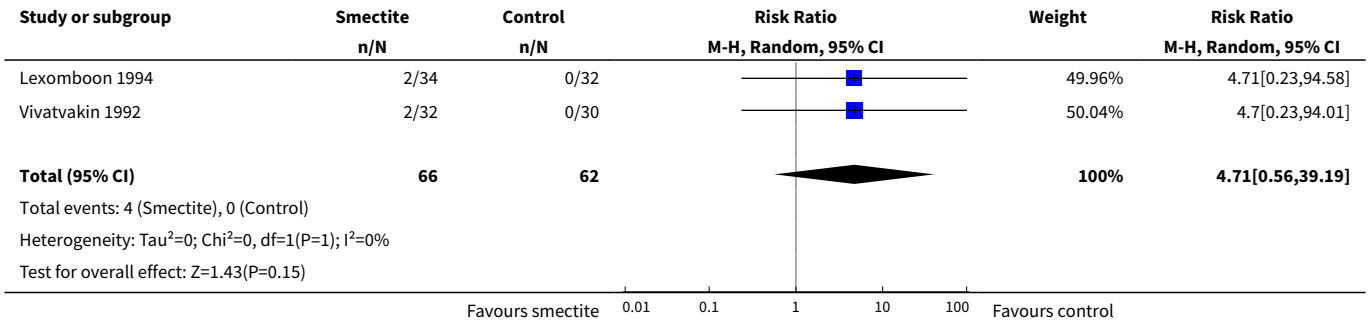
Analysis 2.4. Comparison 2 Diarrhoea secondary outcomes, Outcome 4 Need for intravenous access for rehydration.

Study or subgroup	Smectite n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pieścik-Lech 2013	23/44	25/37		100%	0.77[0.54,1.11]





Analysis 2.5. Comparison 2 Diarrhoea secondary outcomes, Outcome 5 Constipation.



APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[b]
1	smectite	Smectite [Supplementary concept]	Smectite [Supplementary concept]	Smectite ti, ab	smectite
2	dios-mectite	smectite* ti, ab	smectite* ti, ab	Diosmectite ti, ab	dios-mectite
3	1 or 2	Diosmectite ti, ab	Diosmectite ti, ab	1 or 2	1 or 2
4	–	"smecta"[Supplementary Concept]	"smecta"[Supplementary Concept]	Limit 3 to hu-man	-
5	-	1 or 2 or 3 or 4	1 or 2 or 3 or 4	-	-
6	-	Limit 5 to humans	Limit 5 to humans	-	-

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]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.

CONTRIBUTIONS OF AUTHORS

Giordano Pérez-Gaxiola and Carlos Cuello-García prepared the protocol and manuscript. Ivan D Florez checked the protocol and manuscript, and provided advice. Víctor Pérez-Pico checked the protocol and provided advice as an infectious diseases specialist.

DECLARATIONS OF INTEREST

Giordano Pérez-Gaxiola, Carlos A Cuello-García, Ivan D Florez, Víctor M Pérez-Pico: we certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of this Cochrane Review (for example, employment, consultancy, stock ownership, honoraria, or expert testimony).

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added Ivan D Florez as an author.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Antidiarrheals [*therapeutic use]; Diarrhea [*therapy] [virology]; Randomized Controlled Trials as Topic; Rotavirus Infections [*complications]; Silicates [*therapeutic use]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant