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Oral rehydration salt solution for treating cholera: ≤ 270 mOsm/L solutions vs ≥ 310 mOsm/L solutions (Review)

Musekiwa A, Volmink J

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[Intervention Review]

Oral rehydration salt solution for treating cholera: ≤ 270 mOsm/L solutions vs ≥ 310 mOsm/L solutions

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ABSTRACT

Background

Oral rehydration solution (ORS) is used to treat the dehydration caused by diarrhoeal diseases, including cholera. ORS formulations with an osmolarity (a measure of solute concentration) of ≤ 270 mOsm/L (ORS ≤ 270) are safe and more effective than ORS formulations with an osmolarity of ≥ 310 mOsm/L (ORS ≥ 310) for treating non-cholera diarrhoea. As cholera causes rapid electrolyte loss, it is important to know if these benefits are similar for people suffering from cholera.

Objectives

To compare the safety and efficacy of ORS ≤270 with ORS ≥ 310 for treating dehydration due to cholera.

Search methods

We searched the Cochrane Infectious Disease Group Specialized Register (April 2011), CENTRAL (*The Cochrane Library* Issue 4, 2011), MEDLINE (1966 to April 2011), EMBASE (1974 to April 2011), and LILACS (1982 to April 2011). We also contacted organizations and searched reference lists.

Selection criteria

Randomized controlled trials comparing ORS ≤ 270 with ORS ≥ 310 for treating adults and children with acute diarrhoea due to cholera.

Data collection and analysis

Two reviewers independently applied eligibility criteria, assessed trial quality, and extracted data. We pooled dichotomous data using risk ratio (RR), pooled continuous data using mean difference (MD) or the standardized mean difference (SMD), and presented the results with 95% confidence intervals (CI).

Main results

For glucose-based ORS, seven trials (718 participants) met the inclusion criteria. Biochemical hyponatraemia (blood sodium levels < 130 mmol/L) was more common with ORS ≤ 270 (RR 1.67, CI 1.09 to 2.57; 465 participants, four trials), while a higher level of severe biochemical hyponatraemia (blood sodium levels < 125 mmol/L) in the same group was not significant (RR 1.58, CI 0.62 to 4.04; 465 participants, four trials). No instances of symptomatic hyponatraemia or death were noted in the trials that intended to record them. We found no statistically significant difference in the need for unscheduled intravenous infusion. Analyses separating children and adults showed no obvious trends.

Two trials also examined rice-based ORS. In the ORS ≤ 270 group, duration of diarrhoea was shorter (MD -11.42 hours, CI -13.80 to -9.04; 102 participants, two trials).

Authors' conclusions

In people with cholera, ORS ≤ 270 is associated with biochemical hyponatraemia when compared with ORS ≥ 310, but there are no differences in terms of other outcomes. Although this risk does not appear to be associated with any serious consequences, the total patient experience in existing trials is small. Under wider practice conditions, especially where patient monitoring is difficult, caution is warranted.

23 April 2019

No update planned

Research area no longer active

This is not a current research question.

PLAIN LANGUAGE SUMMARY

Oral rehydration salt solutions for treating cholera: lower salt content versus higher salt content solutions

Cholera is caused by pathogenic bacteria ingested with contaminated food or water and is commonly found where sanitation measures are poor. It causes severe diarrhoea and vomiting, which can lead to profound dehydration and potentially death. Oral rehydration solution (ORS) is an effective treatment for diarrhoea, and ORS with a salt concentration of ≤ 270 mOsm/L, which has a lower electrolyte content than the earlier ORS ≥ 310 mOsm/L, is safe and more effective in people with non-cholera diarrhoea. This review found that ORS ≤ 270 mOsm/L appears to be as effective as ORS ≥ 310 mOsm/L at rehydrating people with cholera, but may lead to low blood salt levels. More research is needed to better understand these potential safety issues.

Summary of findings for the main comparison. ORS ≤ 270 mOsm/L (glucose-based) compared to ORS ≥ 310 mOsm/L (glucose-based) for treating cholera

ORS ≤ 270 mOsm/L (glucose-based) compared to ORS ≥ 310 mOsm/L (glucose-based) for treating cholera

Patient or population: patients with cholera
Settings: resource-limited
Intervention: ORS ≤ 270 mOsm/L (glucose-based)
Comparison: ORS ≥ 310 mOsm/L (glucose-based)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ORS ≥ 310 mOsm/L (glucose-based)	ORS ≤ 270 mOsm/L (glucose-based)				
Death	See comment	See comment	Not estimable	121 (2 studies)	See comment	No deaths occurred in the two trials reporting mortality
Need for unscheduled intravenous infusion	**285 per 1000**	**245 per 1000** (188 to 319)	**RR 0.86** (0.66 to 1.12)	616 (5 studies)	⊕⊕⊕⊖ **moderate** [1]	
Symptomatic hyponatraemia	See comment	See comment	Not estimable	620 (5 studies)	See comment	No instances of symptomatic hyponatraemia were reported in the five trials reporting this outcome
Biochemical hyponatraemia (serum sodium < 130 mmol/L)	**121 per 1000**	**202 per 1000** (132 to 310)	**RR 1.67** (1.09 to 2.57)	465 (4 studies)	⊕⊕⊕⊖ **moderate** [2]	
Severe biochemical hyponatraemia (serum sodium < 125 mmol/L)	**26 per 1000**	**41 per 1000** (16 to 105)	**RR 1.58** (0.62 to 4.04)	465 (4 studies)	⊕⊕⊖⊖ **low** [1,2]	

Duration of diarrhoea (in hours)	The mean duration of diarrhoea (in hours) ranged across control groups from **38 to 79**	The mean duration of diarrhoea (in hours) in the intervention groups was **2.52 lower** (6.71 lower to 1.68 higher)		683 (6 studies)	⊕⊕⊕⊖ **moderate** [3]	
Stool output in first 24 hours after admission or randomization	The mean stool output in first 24 hours after admission or randomization ranged across control groups from **-0.76 to 0.05 standard deviations**	The mean stool output in first 24 hours after admission or randomization in the intervention groups was **0.13 standard deviations lower** (0.43 lower to 0.17 higher)		581 (4 studies)	⊕⊕⊕⊖ **moderate** [4]	SMD -0.13 (-0.43 to 0.17)

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. 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] Serious imprecision: wide 95% CI including both null effect (RR=1) and appreciable benefit (RR=0.75). Downgrade by 1.
[2] Serious study limitation: all four studies had unclear reporting of allocation concealment and blinding. Downgrade by 1.
[3] Serious inconsistency: statistical heterogeneity was high (I^2 = 76%, Chi^2 P = 0.0009). The reasons for this are unclear as heterogeneity persisted even after subgrouping children versus adults. Downgrade by 1.
[4] Serious inconsistency: statistical heterogeneity was high (I^2 = 63%. Chi^2 P = 0.04) due to one study (Faruque 1996) showing a significant treatment effect. Heterogeneity persisted even after subgrouping children versus adults. Downgrade by 1.

Summary of findings 2. ORS ≤ 270 mOsm/L (rice-based) compared to ORS ≥ 310 mOsm/L (glucose-based) for treating cholera

ORS ≤270 mOsm/L (rice-based) compared to ORS ≥ 310 mOsm/L (glucose-based) for treating cholera

Patient or population: patients with cholera
Settings: resource-limited
Intervention: ORS ≤ 270 mOsm/L (rice-based)
Comparison: ORS ≥ 310 mOsm/L (glucose-based)

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	ORS ≥310 mOsm/L (glucose-based)	**ORS ≤270 mOsm/L (rice-based)**				
Death	See comment	See comment	Not estimable	0 (0)	See comment	No trials reported this outcome
Need for unscheduled intravenous infusion	See comment	See comment	Not estimable	0 (0)	See comment	No trials reported this outcome
Symptomatic hyponatraemia	See comment	See comment	Not estimable	39 (1 study)	See comment	No instances of symptomatic hyponatraemia were reported in the one trial that assessed this outcome.
Severe biochemical hyponatraemia**(serum sodium < 125 mmol/L)**	**20 per 1000**	**7 per 1000** (0 to 162)	**RR 0.35** (0.02 to 8.1)	102 (2 studies)	⊕⊕⊖⊖ **low** [1]	
Biochemical hyponatraemia**(serum sodium < 130 mmol/L)**	**180 per 1000**	**119 per 1000** (47 to 304)	**RR 0.66** (0.26 to 1.69)	102 (2 studies)	⊕⊕⊖⊖ **low** [1]	
Duration of diarrhoea**(in hours)**	The mean duration of diarrhoea (in hours) ranged across control groups from **38 to 47 hours**	The mean duration of diarrhoea (in hours) in the intervention groups was **11.42 lower** (13.8 to 9.04 lower)		102 (2 studies)	⊕⊕⊖⊖ **low** [2,3]	
Stool output in first 24 hours after admission or randomization	See comment	See comment	Not estimable	0 (0)	See comment	No trials reported this outcome

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. 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 Very serious imprecision: the 95% CI is wide and the two trials are small. Downgrade by 2.
2 Serious inconsistency: statistical heterogeneity is high (I^2 = 90%, Chi^2 P = 0.001). Downgrade by 1.
3 Serious imprecision: the two trials are small. Downgrade by 1.

BACKGROUND

Description of the condition

Cholera is one of the most serious types of infectious diarrhoeal disease, inflicting severe social and economic hardship in outbreak areas (WHO 2001a). In 2007, the World Health Organization (WHO) noted an increase in the number of reported cholera cases and deaths, with an estimated 177,963 cases resulting in 4031 deaths across 53 countries, representing a 46% increase on the mean number of cases reported between 2002 and 2005 (WHO 2008). Due to under-reporting (in light of travel and trade-related sanction concerns) and other surveillance system limitations, reported cases are thought to represent only a fraction of actual cases (WHO 2008). Caused by ingesting food or water containing the bacterium *Vibrio cholerae*, cholera can spread rapidly among populations lacking access to safe water and adequate sanitation facilities. Upon infecting the small intestine, the bacteria produce a protein enterotoxin that induces the hypersecretion of water and electrolytes by the small intestinal mucosa. Symptoms of cholera include acute watery diarrhoea, vomiting, and severe dehydration, which can lead to death within 24 hours if left untreated (Sack 2004).

Description of the intervention

Oral rehydration solution (ORS) was developed in the late 1960s. It is an important intervention for reducing the morbidity and mortality associated with diarrhoeal disease, regardless of etiology (WHO 2000). ORS has been highly effective in reducing the high mortality rates experienced during cholera outbreaks, which often reached 50 per cent before the introduction of this treatment (Quotah 1999). Utilizing a simple and inexpensive solution of sodium and glucose, ORS enhances the absorption of sodium and fluid in the small intestine, even in cases of enterotoxic diarrhoea, where fluid loss is often substantial.

The former standard formulation of ORS consisted of 90 mmol/L of sodium, 20 mmol/L of potassium, 80 mmol/L of chloride, 10 mmol/L of citrate, and 111 mmol/L of glucose, with a total osmolarity of 311 mmol/L (ORS ≥ 310). Initially intended to replace sodium losses in adults with cholera, this formulation was previously recommended by the WHO and the United Nations Children's Fund (UNICEF) for treating all types of diarrhoea in children and adults (Rabbani 2000; WHO 2001b; WHO 2002). Even though the expanded use of this solution has saved millions of lives, its optimal composition remains an issue of debate (Duggan 2004; Guarino 2000; Nalin 2004).

In 2001, a Cochrane review changed the worldwide ORS formula for treating diarrhoea of all causes, reducing the total osmolarity to 245 mmol/L (ORS ≤ 270; Hahn 2002); this is currently regarded as the standard global formula.

How the intervention might work

Potential problems with the ORS ≥ 310 formulation are that it may not lower stool output or duration of diarrhoea, which reduces its acceptance in many communities (Rabbani 2000). Alternative formulations, including those that use lower electrolyte concentrations or replace glucose with complex carbohydrates such as rice powder, or both, have been introduced with the aim of reducing osmolarity in order to promote greater salt and water absorption in the small intestine.

Why it is important to do this review

ORS ≤ 270 was found to be just as safe and more effective than ORS ≥ 310 for treating diarrhoea in children (Hahn 2002). Acknowledging the benefits of ORS ≤ 270 solutions, including reduced stool output and duration of diarrhoea, WHO and UNICEF now recommend that countries use and manufacture formulations with a total osmolarity of 245 mmol/L (WHO 2001b). However, there are concerns about potential adverse effects of using ORS ≤ 270 solutions to treat people with cholera (Hahn 2002; Nalin 2004; WHO 2001b). Because cholera is associated with significant electrolyte loss, especially among children, the use of ORS with reduced sodium levels may place patients at a greater risk of developing biochemical hyponatraemia (blood sodium levels < 130 mmol/L) (Fuchs 2001). This can result in severe illness, including seizures, respiratory arrest, coma (symptomatic hyponatraemia), and even death. Especially in areas where cholera is endemic, practitioners require the best available evidence about the balance between the benefits and risks of different ORS formulations.

OBJECTIVES

To compare the safety and efficacy of ORS ≤ 270 and ORS ≥ 310 for treating dehydration due to cholera.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children with acute diarrhoea caused by *V. cholerae*, either confirmed (by stool microscopy or stool culture) or presumed.

Types of interventions

Intervention

ORS formulations with an osmolarity of ≤ 270 mOsm/L (total osmolarity of 250 mmol/L with reduced sodium).

Control

ORS formulations with an osmolarity of ≥ 310 mOsm/L (sodium 90 mmol/L, glucose 111 mmol/L, total osmolarity 311 mmol/L).

Types of outcome measures

Primary

Need for unscheduled intravenous infusion.

Symptomatic hyponatraemia as defined by trialists (symptoms include headache, lethargy, confusion, and seizures).

Secondary

Biochemical hyponatraemia as defined by trialists.
Duration of diarrhoea.
Stool output in first 24 hours after admission or randomization.
Vomiting during rehydration.
Death.

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).

Databases

We searched the following databases using the search terms and strategy described in Table 1.

- Cochrane Infectious Diseases Group's Specialized Register (April 2011).
- Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 4, 2011).
- MEDLINE (1966 to April 2011).
- EMBASE (1974 to April 2011).
- LILACS (1982 to April 2011).

Organizations

We provided individuals from the following key agencies and organizations with a list of the identified trials and asked for additional completed or ongoing trials: World Health Organization; Centre for Health and Population Research (ICDDR,B); Jawaharlal Nehru Medical College; National Institute of Cholera and Enteric Diseases, and the US Naval Medical Research Unit, Jakarta.

Reference lists

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

Data collection and analysis

Selection of studies

Two authors independently screened the results of the search to select potentially relevant studies and applied eligibility criteria using a pre-designed eligibility form based on the inclusion criteria. Corresponding full articles were retrieved and assessed using the eligibility criteria. Each of the articles was scrutinized to ensure that multiple publications from the same trial were included only once. Where there was ambiguity, we sought clarification from the trial authors and re-assessed the articles. We resolved any differences between the eligibility results through discussion. We excluded studies that did not meet the inclusion criteria and stated the reasons in the 'Characteristics of excluded studies'.

Data extraction and management

Using a specially designed data extraction form, two authors independently extracted information on methods, participants, interventions, and outcomes for each trial. One author entered the data into Review Manager 5 and this was independently checked by AM. We scrutinized data sources for multiple publications from the same data sets, referring to the original paper where there were any differences.

We extracted the number of participants randomized in each group and the numbers analyzed for each outcome. For dichotomous data, we extracted the number of events, and for continuous data we extracted the mean and standard deviation or information to estimate the standard deviation. We contacted the publication authors in the case of unclear or missing data. We resolved any differences through discussion.

Assessment of risk of bias in included studies

Two authors (JV and AM) independently assessed the risk of bias of the included studies using the latest Cochrane Collaboration tool for assessing the risk of bias. We followed the guidance to assess whether adequate steps were taken to reduce the risk of bias across six components: 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 'yes', 'no' or 'unclear', indicating a low, high or unclear risk of bias respectively. The results were summarized using the 'risk of bias summary' and the 'risk of bias graph', in addition to the risk of bias tables. When necessary, we contacted trial authors for clarification. We resolved any disagreements through discussion.

Measures of treatment effect

We pooled estimates of effect using risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data; and presented these results with 95% confidence intervals (CI). For continuous data that were expressed in different units, we calculated standardized mean difference (SMD).

Unit of analysis issues

Trials including more than two comparison groups were split and analyzed as individual pair-wise comparisons.

Dealing with missing data

If data from the trial reports were insufficient, unclear, or missing, we contacted the trial authors for additional information or clarification. We used the 'intention to treat' principle where there were no missing data. In the case of missing dichotomous data, we still used the 'intention to treat' principle but assumed that all the missing participants did not experience the event. For missing continuous data, we used the available case analysis.

Assessment of heterogeneity

We assessed heterogeneity by visually examining the forest plot to detect overlapping confidence intervals, and used the Chi^2 test with a 10% level of significance and the I^2 test statistic (Higgins 2003) with a value of 50% or more to identify substantial heterogeneity.

Assessment of reporting biases

We had planned to assess the likelihood of publication bias by examining the forest plot for asymmetry if we found sufficient trials (10 or more).

Data synthesis

We analyzed data for glucose-based and rice-based ORS ≤ 270 separately using Review Manager 5. In the absence of homogeneity of treatment effects, we used a random-effects model of meta-analysis.

Subgroup analysis and investigation of heterogeneity

We investigated clinical heterogeneity based on the age of participants by comparing children (< 11 years) with adults (> 11 years), as children may be particularly at risk of developing hyponatraemia.

Sensitivity analysis

We had planned to carry out a sensitivity analysis for risk of bias if we found sufficient trials, in order to investigate the robustness of the results to the quality components.

RESULTS

Description of studies

Trial selection

We identified 12 studies that appeared to meet our inclusion criteria. However, we excluded five of these studies because one did not evaluate people with cholera, two did not administer ORS ≤ 270 or ORS ≥ 310, one did not employ randomization, and one reported cholera and non-cholera data in aggregate only (see 'Characteristics of excluded studies'). We had previously noted two ongoing trials (*see* Bangladesh; India); these two trials have now been completed but we could not obtain their full text articles.

The seven randomized controlled trials included in the analysis were either small in size or only included a small subset of participants with cholera, producing a combined sample size of 797 participants. All trials were published in English-language biomedical journals. We have provided details of these trials in the 'Characteristics of included studies' and have summarized them below.

Participants and location

All trials, including one multicenter study trial (Choice 2001), were conducted in low-income countries: Bangladesh (Alam 1999; Choice 2001; Faruque 1996), Brazil (Choice 2001), India (Alam 1999; Alam 2000; Bhattacharya 1998; Choice 2001; Dutta 2000), Indonesia (Choice 2001; Pulungsih 2006), Peru (Choice 2001), and Vietnam (Choice 2001).

The majority of participants were adults (> 11 years), but three trials (151 participants) assessed children (< 11 years) with cholera (Alam 2000; Choice 2001; Dutta 2000). Five trials included only,or predominantly, male participants. All trial participants were suffering from a severe degree of dehydration.

Interventions

While all seven trials compared glucose-based ORS ≤ 270 and ORS ≥ 310, two trials also included an experimental rice-based ORS ≤ 270 trial arm (Bhattacharya 1998; Dutta 2000); the formulations are detailed in Table 2.

Before randomization, six trials administered intravenous rehydration solutions such as Ringer's lactate, Dhaka solution, or saline solution to correct severe dehydration (Alam 1999; Bhattacharya 1998; Choice 2001; Dutta 2000; Faruque 1996; Pulungsih 2006).

Six trials treated all participants with antibiotics (Alam 1999; Alam 2000; Bhattacharya 1998; Dutta 2000; Faruque 1996; Pulungsih 2006), while the seventh trial administered an antibiotic only when an intercurrent infection occurred (Choice 2001).

Four trials reported feeding (Alam 1999; Alam 2000; Choice 2001; Pulungsih 2006). Alam 1999 gave participants bread and bananas immediately after rehydration and standard meals three times daily thereafter. Children in Alam 2000 were fed curds and bread after they had begun rehydrating and breastfeeding was continued throughout. In Choice 2001, breastfeeding was also continued *ad libitum* and food appropriate to age was given to children during the maintenance phase. In Pulungsih 2006, noodles were offered immediately after rehydration and meals three times a day were given throughout. The three remaining trials did not report information on feeding.

Outcomes

The trials assessed the following pre-specified outcomes used in this review: need for unscheduled intravenous infusion; biochemical hyponatraemia; duration of diarrhoea; stool output in first 24 hours after admission or randomization; and vomiting during rehydration. Many of these indicators were measured at different time points (eg 24 hours after study inclusion, total study time). The trials also assessed other outcomes, which are described in the 'Characteristics of included studies'.

None of the trials assessed symptomatic hyponatraemia and death as pre-specified outcomes, although the incidence of clinical signs associated with hyponatraemia was either mentioned in the manuscript text or obtained through correspondence with the authors for five trials (Alam 1999; Choice 2001; Dutta 2000; Faruque 1996; Pulungsih 2006). Information on death was reported in the manuscript text of Bhattacharya 1998 and obtained by correspondence with the Choice 2001 trial authors.

We contacted the trial authors if the published reports did not include the outcomes assessed in this review; we received unpublished outcome data for Choice 2001 and Pulungsih 2006.

Risk of bias in included studies

The risk of bias in included studies are summarized in the 'risk of bias graph' (Figure 1) and the 'risk of bias summary' (Figure 2). Below we give a detailed explanation of the results.

Figure 1. Risk of bias graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

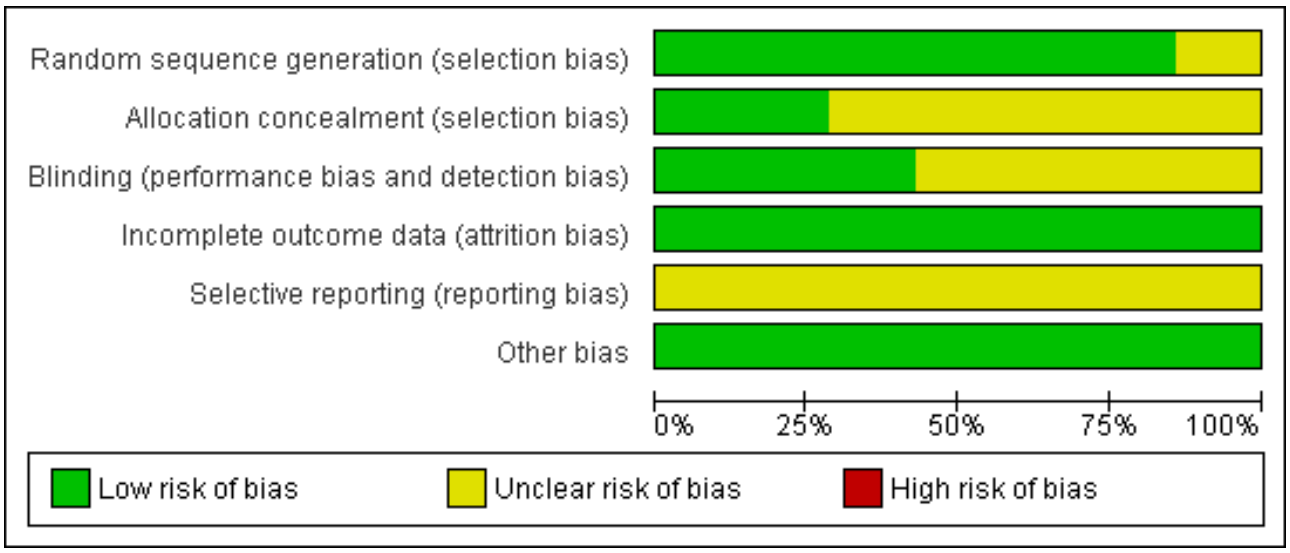

Figure 2. Risk of bias summary: review authors' judgements about each methodological quality item for each included study.

Allocation

Generation of allocation sequence

All trials were reported as randomized. Six trials employed permuted block randomization for generating the allocation sequence, which we judged as having a low risk of bias (Alam 1999; Bhattacharya 1998; Choice 2001; Dutta 2000; Faruque 1996; Pulungsih 2006); however, none of the trials explicitly mentioned how the sequence was generated. The remaining trial (Alam 2000) provided insufficient information to enable us to judge whether there was a high or low risk of bias.

Allocation concealment

Three trials did not describe methods used to conceal allocation and we judged them as having an unclear risk of bias (Alam 1999; Bhattacharya 1998; Dutta 2000). Two trials were judged as having a low risk of bias: one (Alam 2000) used identical packets that were given a number by a faculty colleague not involved in the study, and the other (Pulungsih 2006) used sachets that were centrally prepared and sequentially numbered according to a randomization code. The remaining two trials (Choice 2001; Faruque 1996) provided insufficient information to be able to judge them as having a low risk of bias and we therefore judged them as having an unclear risk of bias.

Blinding

Three trials reported that both participants and providers were blinded to treatment assignment (Alam 2000; Choice 2001; Pulungsih 2006) by stating that the trials were double-blind and that identical packets were used. These three were therefore judged as having a low risk of bias. Two trials (Alam 1999; Faruque 1996) reported that the trials were double blind but did not describe the blinding, and they were therefore judged as having an unclear risk of bias. Blinding methods were not described in the remaining two trials (Bhattacharya 1998;Dutta 2000), which were therefore judged as having an unclear risk of bias.

Incomplete outcome data

All seven trials were judged as having a low risk of bias since all randomized individuals were included in the final analysis of the seven trials. None of the seven trials had disproportionate numbers of losses to follow-up between the intervention and control arms. Numbers of losses to follow-up were very small in all seven trials.

Selective reporting

No study protocol was found for any of the seven trials and all were therefore judged as having an unclear risk of bias. There were no indications in the trial reports to suspect selective outcome reporting.

Other potential sources of bias

All seven trials were judged as having a low risk of bias as there was no reason to suggest any other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** ORS ≤ 270 mOsm/L (glucose-based) compared to ORS ≥ 310 mOsm/L (glucose-based) for treating cholera; **Summary of findings 2** ORS ≤ 270 mOsm/L (rice-based) compared to ORS ≥ 310 mOsm/L (glucose-based) for treating cholera

Comparison 1: ORS ≤ 270 (glucose-based) versus ORS ≥ 310 (glucose-based)

Of the seven trials (718 participants) that evaluated ORS ≤ 270 (glucose-based), three assessed only children (< 11 years; n = 132) and four evaluated only adults (> 11 years; n = 586).

Need for unscheduled intravenous fluid infusion:

There was a non-significant tendency towards fewer unscheduled intravenous infusions for those administered ORS ≤ 270 (glucose-based) (RR 0.86, CI 0.66 to 1.12; n = 616, five trials; Analysis 1.1).

Symptomatic hyponatraemia:

There was no symptomatic hyponatraemia detected in the five trials that assessed this outcome (Alam 1999; Choice 2001; Dutta 2000; Faruque 1996; Pulungsih 2006).

Biochemical hyponatraemia

Those receiving ORS ≤ 270 were almost 70% more likely to develop biochemical hyponatraemia (blood sodium levels < 130 mmol/L) (RR 1.67, CI 1.09 to 2.57; n = 465, four trials; Analysis 1.2).

Severe biochemical hyponatraemia

Although the point estimate for severe biochemical hyponatraemia (blood sodium levels < 125 mmol/L) was in the same direction as biochemical hyponatraemia, the result was statistically inconclusive (RR 1.58, CI 0.62 to 4.04; n = 465, four trials; Analysis 1.3).

Duration of diarrhoea

For children, we found no statistically significant difference in the duration of diarrhoea between the two groups (MD -2.75 hours, CI -9.79 to 4.29 hours, random effects model, n = 97, two trials, Analysis 1.4).

For adults, we detected substantial heterogeneity between the trials (Chi^2 = 16.05, df = 3, P = 0.001, I^2 = 81%, Analysis 1.4). Because of this heterogeneity, we report here the individual results for the four trials. We found a statistically significant difference in the duration of diarrhoea between the two formula groups in only one trial (Bhattacharya 1998) (MD -9.70 hours, CI -15.14 to -4.26 hours, Analysis 1.4). The difference was not statistically significant in the other three trials: Alam 1999 (MD 3.00 hours, CI -1.16 to 7.16 hours, Analysis 1.4); Faruque 1996 (MD -7.20 hours, CI -16.25 to 1.85 hours, Analysis 1.4); and Pulungsih 2006 (MD 1.00 hour, CI -3.18 to 5.18 hours, Analysis 1.4).

One study (Alam 2000) assessed children and reported the geometric means and standard deviations on a log scale, and so we could not pool it with other studies in a meta-analysis. The geometric mean, standard deviation and total for the ORS ≤ 270 group were 21.44, 1.32 and 19 respectively, and the corresponding values for the ORS ≥ 310 group were 19.97, 1.99 and 16 respectively. The mean difference was significant (MD 1.47, CI 0.33 to 2.61).

Stool output in first 24 hours after admission or randomization

We found no statistically significant difference in the stool output in the first 24 hours between the two formula groups (SMD -0.13, CI -0.43 to 0.17, random-effects model; n = 581, four trials; Analysis 1.5). Results from two studies (Faruque 1996; Pulungsih 2006) were skewed (mean/SD < 2) and therefore the results of the meta-analysis may not be reliable. We detected substantial statistical heterogeneity between the trials (Chi^2 = 8.16, df = 3, P 0.04; I^2 = 63%). The heterogeneity appears to be attributable either to the skewness detailed above or to the fact that the one trial demonstrating a statistically significant benefit in favour of the ORS ≤ 270 formula employed a formula with a lower sodium content than used in the other trials (Faruque 1996).

Vomiting during rehydration

The proportion of people that vomited during rehydration was similar in the two groups (RR 1.14, CI 0.92 to 1.40; n = 363, two trials; Analysis 1.6).

Death

No deaths were reported in the two trials that recorded mortality (Bhattacharya 1998; Choice 2001).

Exploring heterogeneity: children (< 11 years) versus adults (> 11 years)

Subgroup analyses assessing children and adults separately appeared to show differences in the direction of treatment effect

estimates for most outcomes. However, as the overall numbers of children were small and the confidence intervals tended to include both point estimates with some degree of overlap, it is difficult to determine whether these represent true differences. While the strength of treatment benefit for the outcome 'need for unscheduled intravenous infusion' appeared to be greater in children receiving ORS ≤ 270 (glucose-based) (RR 0.57, CI 0.29 to 1.11; n = 93, two trials; Analysis 1.1) than in adults (RR 0.93, CI 0.70 to 1.24; n = 523, three trials; Analysis 1.1) , the point estimate for children has a wider confidence interval and is not statistically significant at the predefined 5% level. Biochemical hyponatraemia may be more problematic for adults receiving the ORS ≤ 270 formula (RR 1.69, CI 1.06 to 2.69; n = 465, four trials; Analysis 1.2), yet this outcome for children was assessed in only one small trial with few events, resulting in a wider confidence interval and a lack of statistical significance (RR 1.58, CI 0.53 to 4.74; n = 39; Analysis 1.2). For the two diarrhoeal outcomes where statistically significant heterogeneity was evident, heterogeneity in adults persisted in the subgroup analysis.

Comparison 2: ORS ≤ 270 (rice-based) versus ORS ≥ 310 (glucose-based)

Two trials (102 participants) evaluated ORS ≤ 270 (rice-based).

Need for unscheduled intravenous fluid infusion

No information available.

Symptomatic hyponatraemia

No instances of symptomatic hyponatraemia were reported in the one trial that assessed this outcome (Dutta 2000).

Biochemical hyponatraemia

While the point estimates suggest a reduced risk of biochemical hyponatraemia (blood sodium levels < 130 mmol/L) for those receiving ORS ≤ 270 (rice-based), these findings are not statistically significant (RR 0.66, CI 0.26 to 1.69; n = 102, two trials; Analysis 2.1).

Severe hyponatraemia

Severe biochemical hyponatraemia (blood sodium levels < 125 mmol/L) was similar between the two groups; the confidence interval around the risk ratio is wide, reflecting the small number of events for this outcome (RR 0.35, CI 0.02 to 8.10; n = 102, two trials; Analysis 2.2).

Duration of diarrhoea

There was a statistically significant reduction in the duration of diarrhoea for those receiving the ORS ≤ 270 (rice-based) formula (MD -11.42 hours, CI -13.80 to -9.04; n = 102, two trials; Analysis 2.3).

Other outcomes

None of the trials evaluated or reported on the other outcomes of interest.

Exploring heterogeneity: children (< 11 years) versus adults (> 11 years)

One small trial was available for each subgroup for three outcomes of interest. For biochemical hyponatraemia, there was no statistically significant heterogeneity between the two subgroups (Chi^2 = 1.11, df = 1, P = 0.29; I^2=10%, Analysis 2.1). For severe biochemical hyponatraemia, there was no heterogeneity to be assessed as one of the trials had no events for both treatment arms and was therefore inestimable (Analysis 2.2). For duration of diarrhoea, there was considerable heterogeneity between the two subgroups (Chi^2 = 10.23, df = 1, P = 0.001; I^2=90%, Analysis 2.3).

DISCUSSION

Our review draws attention to the paucity of evidence on the effects of ORS ≤ 270 (glucose-based) compared with ORS ≥ 310 for treating people with cholera, with only seven trials evaluating 718 participants.

We intended to examine the safety of glucose-based ORS ≤ 270 for cholera by measuring the incidence of symptomatic hyponatraemia, as low blood sodium levels may be transient and therefore not necessarily result in serious illness. The 2001 WHO/UNICEF meeting of ORS formulation experts highlighted the importance of this outcome in people receiving treatment for cholera (WHO 2001b). An observational study found that the risk of symptoms associated with hyponatraemia in patients treated with ORS ≤ 270 was minimal and did not increase with the change in formulation (Alam 2006). As none of the trials found or explicitly evaluated symptomatic hyponatraemia, we could not assess this outcome. Instead, we measured the incidence of biochemical hyponatraemia. Asymptomatic hyponatraemia, while not providing a definitive marker for treatment failure, provides an important measure of potential risk for people with cholera.

We found that participants receiving ORS ≤ 270 were at greater risk of developing biochemical hyponatraemia (blood sodium levels < 130 mmol/L); however, the relatively few cases of severe biochemical hyponatraemia (blood sodium levels < 125 mmol/L) precludes firm conclusions regarding this outcome. These findings should, nevertheless, alert clinicians to the need for vigilance concerning the risk of hyponatraemia in non-trial settings.

For other outcomes, such as unscheduled intravenous infusion, stool output, vomiting, and duration of diarrhoea, there was little difference in effect between the two types of formulae. However, as most of the available trials are small with few events, they may have insufficient power to demonstrate important clinical differences even after pooling the results.

In separate analyses of two trials (102 participants) comparing ORS ≤ 270 (rice-based) with ORS ≥ 310 (glucose-based), we found no statistically significant differences except for the duration of diarrhoea, which was substantially shorter in the group receiving ORS ≤ 270 (rice-based). A similar finding was reported in a systematic review that compared rice-based ORS with glucose-based ORS ≥ 310 formulas in people with diarrhoea (Fontaine 1998).

Data available for assessing the safety and efficacy ORS ≤ 270 in children with cholera are also extremely limited, making it difficult to draw firm conclusions. Only one trial reported the risk of biochemical hyponatraemia in children (Dutta 2000) and it showed a trend favouring the ORS ≥ 310 formula, but this finding was not statistically significant.

WHO and UNICEF currently recommend formulations with a total osmolarity of 245 mmol/L for treating diarrhoea. It is not known, however, whether using ORS ≤ 270 is appropriate in cholera-endemic regions, where the balance between benefit and harm

can be tenuous. Logistically, having one ORS formula is easier. However, the increased risk of biochemical hyponatraemia in those receiving ORS ≤ 270 solutions is of concern. Even though there were no instances of symptomatic hyponatraemia or death, the total patient experience in the trials is very small and these effects cannot be ruled out under wider practice conditions. Moreover, careful monitoring of blood sodium levels may be difficult in areas where healthcare resources are limited, especially during complex emergencies and large epidemics. Further trials in both adults and children with cholera should be undertaken to clarify these issues.

Quality of evidence

The quality of evidence was assessed using the GRADE methodology. Overall the quality is moderate, meaning that further research is likely to have an important impact on our confidence in the estimate of effect, and may change the estimate. See Summary of findings for the main comparison and Summary of findings 2.

AUTHORS' CONCLUSIONS

Implications for practice

In people with cholera, ORS ≤ 270 results in more patients developing biochemical hyponatraemia, with no detectable benefits such as the need for unscheduled intravenous infusion, duration of diarrhoea, or stool volume, compared with the older ORS ≥ 310 formula. The increased risk of low blood sodium levels could have major implications in resource-constrained settings where clinicians may not have monitoring facilities and must rely on presumptive diagnosis. This review found no serious clinical consequences related to hyponatraemia in trial participants, but it is important to note that total patient experience in the existing trials is small.

WHO and UNICEF currently recommend an ORS ≤ 270 formulation for treating dehydration caused by all types of diarrhoea. While it may be easier to administer a single ORS formulation worldwide, the potential harms and limited evidence of improved efficacy for people with cholera should be kept in mind.

Implications for research

Further randomized controlled trials are needed to assess the balance between benefit and harm associated with the use of ORS ≤ 270 in people with cholera. These trials should be large enough to adequately assess important outcomes, including symptomatic hyponatraemia and death.

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India *{published data only (unpublished sought but not used)}*

Phase IV controlled trial to investigate further the impact of low osmolarity oral rehydration solution on the incidence and prevalence of hyponatraemia in diarrhoeic patients, especially those with cholera [Awaiting details].

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Alam 1999

Methods	Randomized controlled trial. Duration:1 year 10 months, from July 1995 to May 1997.
Participants	Number of participants: 300 randomized (168 men; 131 women). Inclusion criteria: adult men and women aged 15 to 55 years; history of acute watery diarrhoea for < 24 hours before admission; severe dehydration; stool positive for *Vibrio cholerae* under dark-field illumination; successful rehydration with intravenous infusion within 6 hours of admission. Exclusion criteria: suspected pregnancy; bloody diarrhoea; systemic infection requiring intravenous antibiotics; inability to rehydrate with intravenous infusion within 6 hours after admission.
Interventions	(1) ORS ≤ 270 (glucose-based).

Alam 1999 *(Continued)*

	(2) ORS ≥ 310 (glucose-based). See Additional Table 2 for the ORS compositions. Co-interventions: erythromycin (500 mg orally every 6 hours for 3 days). Food: bread, banana (immediately after rehydration), and standard meals (rice, fish, or meat, vegetables and lentils) 3 times daily. Water: given as desired, usually with meals.
Outcomes	(1) Need for unscheduled intravenous infusion.* (2) Duration of diarrhoea (after randomization, hours).* (3) Vomiting during rehydration during initial 24 hours.* (4) Stool weight (g/kg bodyweight) in first 24 hours after admission/randomization.* (5) Total stool weight, g/kg body weight. (6) Urine volume during initial 24 hours (ml/kg bodyweight). (7) Total urine volume (ml/kg body weight). (8) Initial 24 hours ORS intake (ml/kg body weight). (9) Total ORS intake (ml/kg body weight). (10) Initial 24 hours water intake (ml/kg body weight). (11) Total water intake (ml/kg body weight). (12) Biochemical hyponatraemia (< 130 mmol/L) 24 hours after admission.* (13) Biochemical hyponatraemia (< 125 mmol/L) 24 hours after admission.* (14) Biochemical hyponatraemia (< 120 mmol/L) 24 hours after admission.*
Notes	Location: Bangladesh. (Trial started at two sites, in Bangladesh and Indonesia, but it was discontinued at the latter due to inadequate participant supervision. No data from Indonesia included in the analysis.) Date: July 1995 to May 1997.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization list ... was prepared ... by use of permuted blocks of variable length."
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blind" but method not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Data collected on patients withdrawn from the study were included in the analysis up to the time of withdrawal." Loss to follow-up: Reduced 13/147 (8.8%) and Higher 16/153 (10.5%).
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	The study appears to be free of other bias.

Alam 2000

Methods	Randomized controlled trial. Duration: Unclear.
Participants	Number of participants: 179 randomized (cholera proved by culture in 35). Inclusion criteria: all children with acute diarrhoea (< four days duration) with dehydration that met one of the following: non-cholera diarrhoea, aged between three months and five years, children above three months with clinical suspicion of cholera. Exclusion criteria: children with clinical evidence of systemic infection; encephalopathy; electrolyte imbalance; convulsions; invasive diarrhoea.
Interventions	(1) ORS ≤ 270 (glucose-based). (2) ORS ≥ 310 (glucose-based). See Additional Table 2 for the ORS compositions. 75 ml/kg ORS in first 4 hours. Food: curds and banana feeds offered once hydration improved. Co-intervention: single dose of doxycycline (8 mg/kg) administered to all with clinical suspicion of cholera or stool positive for motiles (repeated if vomited within 0.5 hour of administration).
Outcomes	(1) Need for unscheduled intravenous infusion.* (2) Overall diarrhoea frequency (stool/4 hour). (3) Overall ORS consumed (L). (4) Overall diarrhoea duration.* (5) Weight gain. (6) Caloric intake (kcal/kg/day). (7) Serum sodium (meq/L). (8) Urine output (boys) (ml/kg/h). (9) Intravenous fluids (ml/kg).
Notes	Location: Diarrhea Training and Treatment Unit, Aligarh, India. Date: unclear.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized and serially given a number."
Allocation concealment (selection bias)	Low risk	"Since this was a double blind clinical trial, identical packets containing 5 sachets of the salts were randomized and serially given a number by a faculty colleague not involved in the study."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Since this was a double blind clinical trial, identical packets ...."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow up: ORS ≤ 270 1/19 (5.3%) and ORS ≥ 310 4/16 (25%). These percentages do not significantly differ.

Alam 2000 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	The study appears to be free of other bias.

Bhattacharya 1998

Methods	Randomized clinical trial. Duration: two years and eight months, from August 1993 to March 1996.
Participants	Number of participants: 123 randomized. Inclusion criteria: adult men; acute watery diarrhoea for < 24 hours; severe dehydration; severe cholera. Exclusion criteria: received antibiotics before hospitalization; received intravenous fluid before hospitalization; systemic illness.
Interventions	(1) ORS ≤ 270 (glucose-based). (2) ORS ≤ 270 (rice-based). (3) ORS ≥ 310 (glucose-based). See Additional Table 2 for the ORS compositions. Co-interventions: doxycycline (300 mg) as a single dose after correction of initial dehydration and when vomiting stops.
Outcomes	(1) Duration of diarrhoea (h).* (2) Total stool output (L). (3) Number (%) of participants with 24-hour serum sodium level of 125 to 130 mmol/L.* (4) Number (%) of participants with 24-hour serum sodium level of > 130 mmol/L.* (5) Total ORS intake (L). (6) Body weight increment (%). (7) Total fluid requirement (L).
Notes	Location: Infectious Diseases Hospital, Calcutta, India. Date: August 1993 to March 1996.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomly assigned" based on randomization chart and used permuted blocks of random numbers of block length 16.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding procedure described; rice-based and glucose based solutions likely to be different.
Incomplete outcome data (attrition bias)	Low risk	Results of all eligible patients reported. No loss to follow-up in both arms for both glucose and rice-based ORS.

Bhattacharya 1998 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	

Choice 2001

Methods	Randomized clinical trial. Duration: one year and eight months, from June 1995 to February 1997.
Participants	Number of participants: 675 randomized (58 with cholera). Inclusion criteria: male children aged one to 24 months; diarrhoea for < 72 hours (with passage of three or more watery stools in the 24 hours before admission); signs of some or severe dehydration. Exclusion criteria: bloody diarrhoea; clinical signs of systemic infection that required intravenous antibiotic therapy; severe malnutrition defined as admission weight for height < 65% of the National Center for Health Statistics standard (to account for rehydration); presence of obvious edema.
Interventions	(1) ORS ≤ 270 (glucose-based). (2) ORS ≥ 310 (glucose-based). See Additional Table 2 for the ORS compositions. Co-interventions: breastfeeding *ad libitum*; food appropriate for age during maintenance phase; water *ad libitum* during maintenance phase; antibiotics if developed intercurrent infections after enrolment.
Outcomes	(1) Stool output (g/kg) at 24 hours.* (2) Total stool output (g/kg). (3) ORS intake (ml/kg) at 24 hours. (4) Total ORS intake (ml/kg). (5) Vomiting in first 24 hours (%). (6) Vomitus 10 g/kg (%). (7) Unscheduled intravenous therapy in first 24 hours (%).* (8) Children with serum sodium at 24 hours (%): < 130 mmol/L; < 125 mmol/L.* (9) Duration of diarrhoea.*
Notes	Location (five centres): (1) Centre for Health and Population Research, Bangladesh (ICDDR,B). (2) Centro Pediatrico Professor Hosannah de Oliveira-Universidade Federal da Bahia, Salvador, Brazil. (3) All India Institute of Medical Sciences and Kasturba Hospital, New Delhi, India. (4) Hospital Nacional Cayetano Heredia, Lima, Peru. (5) Children's Hospital No. 1, Ho Chi Minh City, Vietnam. Date: June 1995 to February 1997.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization list ... were prepared ... using permuted blocks of variable length."
Allocation concealment (selection bias)	Unclear risk	"The randomization list and numbered ORS packets (...) were prepared at the WHO (Geneva, Switzerland)..."

Choice 2001 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	"Double blind." "The 2 ORS preparations were similar in appearance and packaged in identical polyethylene bags."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One child was randomized for a second period of diarrhoea ..., the data from his second episode were not included in the final analysis." "A total of 125 children were withdrawn from the study before cessation of diarrhoea;...Data collected on all such children up to the time of withdrawal were included in the analysis." No loss to follow up reported.
Selective reporting (reporting bias)	Unclear risk	Study protocol not available.
Other bias	Low risk	The study appears to be free of other bias.

Dutta 2000

Methods	Randomized clinical trial. Duration: two years and nine months, from August 1995 to May 1998.
Participants	Number of participants: 58 randomized. Inclusion criteria: male children aged two to 10 years; stool positive for *Vibrio cholerae*; acute watery diarrhoea < 24 hours duration; signs of severe dehydration (sunken eyes, very dry mouth and tongue, absence of tears, loss of skin elasticity, diminished urine output). Exclusion criteria: antibiotic use; received intravenous fluid; systemic illness.
Interventions	(1) ORS ≤ 270 (glucose-based). (2) ORS ≤ 270(rice-based). (3) ORS ≥ 310 (glucose-based). See Additional Table 2 for the ORS compositions. Co-interventions: tetracycline tablet (50 mg/kg/day of body weight in four divided doses for three days after correction of initial dehydration).
Outcomes	(1) Incidence of symptomatic hyponatraemia.* (2) Total stool output (L). (3) Total ORS intake (L). (4) Body weight (kg). (5) Serum sodium level (mmol/L). (6) Serum sodium level < 125 mmol/L.* (7) Serum sodium level 125 to 130 mmol/L.* (8) Duration of diarrhoea.*
Notes	Location: Infectious Diseases Hospital, Calcutta, India. Date: August 1995 to May 1998.
Risk of bias	

Dutta 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment allocation was random, according to a random number chart prepared using permuted blocks of random numbers of block length 9."
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported in both arms for glucose and rice-based ORS.
Selective reporting (reporting bias)	Unclear risk	Study protocol not available.
Other bias	Low risk	The study appears to be free of other sources of bias.

Faruque 1996

Methods	Randomized clinical trial. Duration: six months, during the second half of 1994.
Participants	Inclusion criteria: males aged 15 to 49 presenting severe cholera-like diarrhoea of < 24 hours duration; severe dehydration requiring intravenous therapy (patients with clinical signs of dehydration who had postural hypotension with a feeble or imperceptible radial pulse and systolic blood pressure of less than 90 mmHg); dark-field positive for *Vibrio cholerae*. Exclusion criteria: no concurrent illness or recognized chronic disease; recent history of antibiotic use.
Interventions	(1) ORS ≤ 270 (glucose-based). (2) ORS ≥ 310 (glucose-based). See Additional Table 2 for the ORS compositions. Co-interventions: intravenous therapy to correct dehydration over a period of three to four hours; saline solution (sodium 133, chloride 98, potassium 13, acetate 48 mmol/L); erythromycin (500 mg, six hourly); additional intravenous therapy (rapidly administered) for patients who went into negative fluid balance and where clinical signs of dehydration reappeared (saline solution consisting of sodium 133, chloride 98, potassium 13, acetate 48 mmol/L).
Outcomes	(1) Need for unscheduled intravenous infusion.* (2) Stool volume in first 24 hours after admission/randomization (ml/kg).* (3) Duration of diarrhoea (hours).* (4) Vomiting during rehydration (0 to 24 hours and 24 to 48 hours).* (5) Stool output (ml/kg) 24 to 48 hours. (6) Stool output (ml/kg) 0 to 48 hours. (7) ORS intake (ml/kg) 0 to 24 hours. (8) ORS intake (ml/kg) 24 to 48 hours. (9) ORS intake (ml/kg) 0 to 48 hours. (10) Urine output (ml/kg) 0 to 24 hours. (11) Urine output (ml/kg) 24 to 48 hours. (12) Urine output (ml/kg) 0 to 48 hours.

Faruque 1996 *(Continued)*

	(13) Serum sodium (mmol/L) at 24 hours and 48 hours. (14) Serum potassium (mmol/L) at 24 hours and 48 hours. (15) Serum chloride (mmol/L) at 24 hours and 48 hours. (16) Serum total carbon dioxide at 24 hours and 48 hours. (17) Number of patients with a 24-hour serum sodium of < 125 mmol/L, 125 to 130 mmol/L, and > 130 mmol/L.*
Notes	Location: International Centre for Diarrhoel Disease Research, Bangladesh (ICDDR,B). Date: second half of 1994.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization done in blocks."
Allocation concealment (selection bias)	Unclear risk	"serially numbered boxes of ORS packets prepared by hospital pharmacy."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double blind" but method not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results of all eligible patients reported. No loss to follow-up in both arms.
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	

Pulungsih 2006

Methods	Randomized clinical trial. Duration: one year, from January 1994 to January 1995.
Participants	Number of participants: 160 randomized. Inclusion criteria: Patients aged 12 to 60 with acute watery diarrhoea for less than 24 hours prior to admission; clinical signs of severe dehydration according to WHO guidelines; stool output less than 5 g/kg/h during initial intravenous infusion; no visible blood in stool. Exclusion criteria: Pregnant women; patients with systemic infections or other diseases requiring specific additional treatment.
Interventions	(1) ORS ≤ 270 (glucose-based). (2) ORS ≥ 310 (glucose-based). See Additional Table 2 for the ORS compositions.
Outcomes	(1) Patients requiring additional intravenous fluid infusion (%).* (2) Stool output in first 24 hours after admission/randomization (ml).* (3) Total stool output (ml).

Pulungsih 2006 *(Continued)*

	(4) Duration of diarrhoea after randomization (h).* (5) Volume of vomiting 24 hours after randomization (ml). (6) Total volume of vomiting (ml). (7) Urine output 24 hours after randomization (ml). (8) Total urine output (ml). (9) ORS intake 24 hours after randomization (ml). (10) Total ORS intake (ml). (11) Symptomatic hyponatraemia (12) Asymptomatic hyponatraemia (13) Serum potassium concentrations (14) Asymptomatic hypokalaemia (serum potassium <3 mEq/ml)
Notes	Location: Prf. Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia. Date: January 1994 to January 1995.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization list" with "random permuted blocks of variable length" used.
Allocation concealment (selection bias)	Low risk	Sachets centrally prepared; sequentially numbered and correspond to the randomization code.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double blind" reduced osmolarity and standard ORS solutions identical in appearance; sachets identical in appearance.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All eligible patients included in the analysis as randomized. No loss to follow-up in both arms.
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	

Allocation concealment: A = adequate; B = unclear (see 'Methods of the review'); ORS: oral rehydration solution; *outcomes assessed in this review.

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

Study	Reason for exclusion
Bhan 1995	Participants did not have cholera.
Dutta 2001	Included participants with cholera and non-cholera diarrhoea. Results reported in aggregate; we have requested the disaggregated data.
Gutman 1969	Participants were not administered either ORS ≤ 270 or ORS ≥ 310.
Mahalanabis 1974	Participants were not administered either ORS ≤ 270 or ORS ≥ 310.
Nalin 1968	Non-randomized trial. Participants were not administered ORS ≤ 270.

ORS: oral rehydration solution.

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

Bangladesh

Trial name or title	To investigate further the impact of low osmolarity ORS on the incidence and prevalence of hyponatraemia in diarrhoeic patients, especially those with cholera (Study ID: NCT00672308).
Methods	Randomized controlled trial.
Participants	Not known.
Interventions	(1) ORS ≤ 270. (2) ORS ≥ 310.
Outcomes	Not known.
Starting date	Not known.
Contact information	Centre for Health and Population Research, (ICDDR,B).
Notes	Location: Dhaka, Bangladesh. Awaiting details. Study ID: NCT00672308.

India

Trial name or title	Phase IV controlled trial to investigate further the impact of low osmolarity ORS on the incidence and prevalence of hyponatraemia in diarrhoeic patients, especially those with cholera (Study ID: NCT00490932).
Methods	Surveillance study.
Participants	About 20,000 patients (adults and children) with diarrhoea (non-cholera and cholera).
Interventions	(1) ORS ≤ 270. (2) ORS ≥ 310.
Outcomes	Not known.
Starting date	Not known.
Contact information	Awaiting details.
Notes	Location: Calcutta, India. Awaiting details. Study ID: NCT00490932.

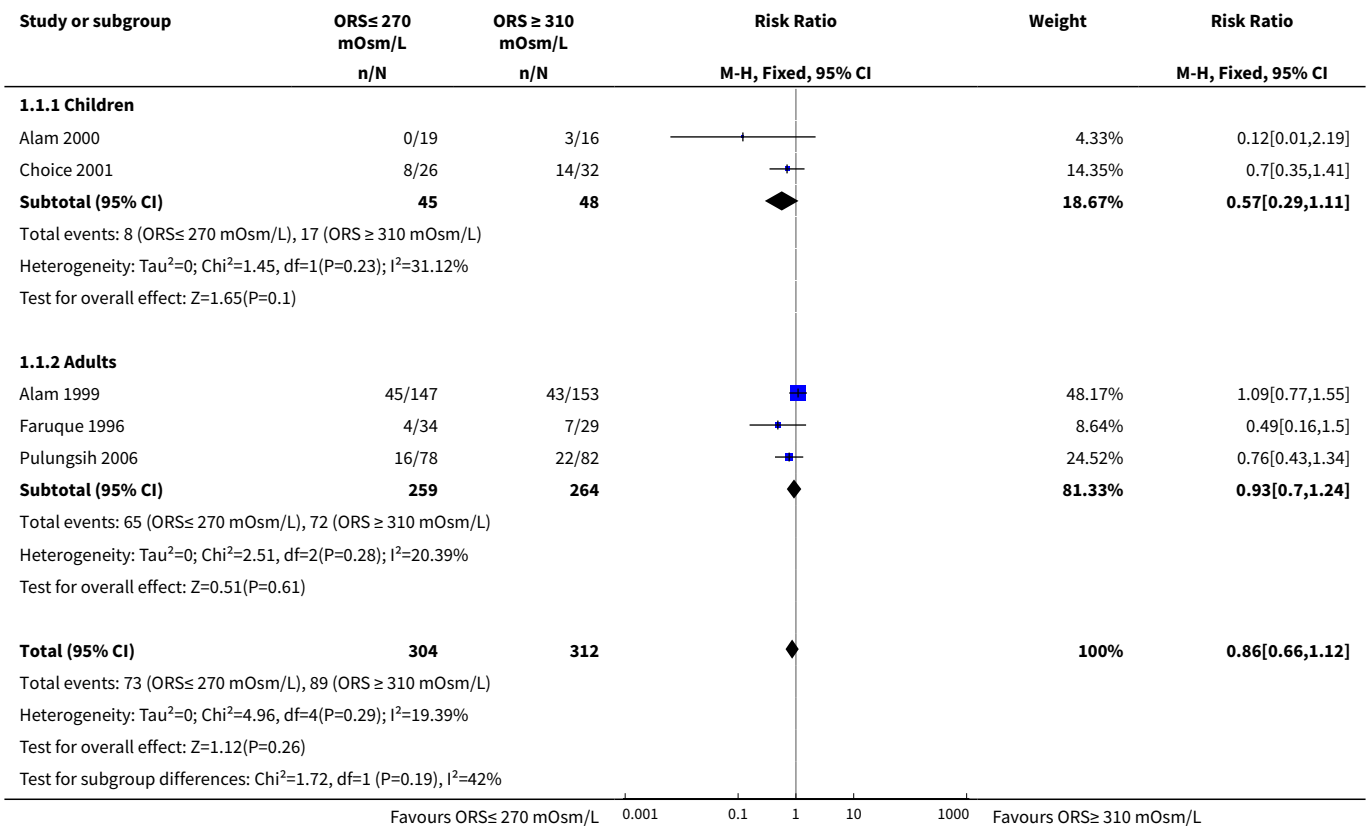
ORS: oral rehydration solution

DATA AND ANALYSES

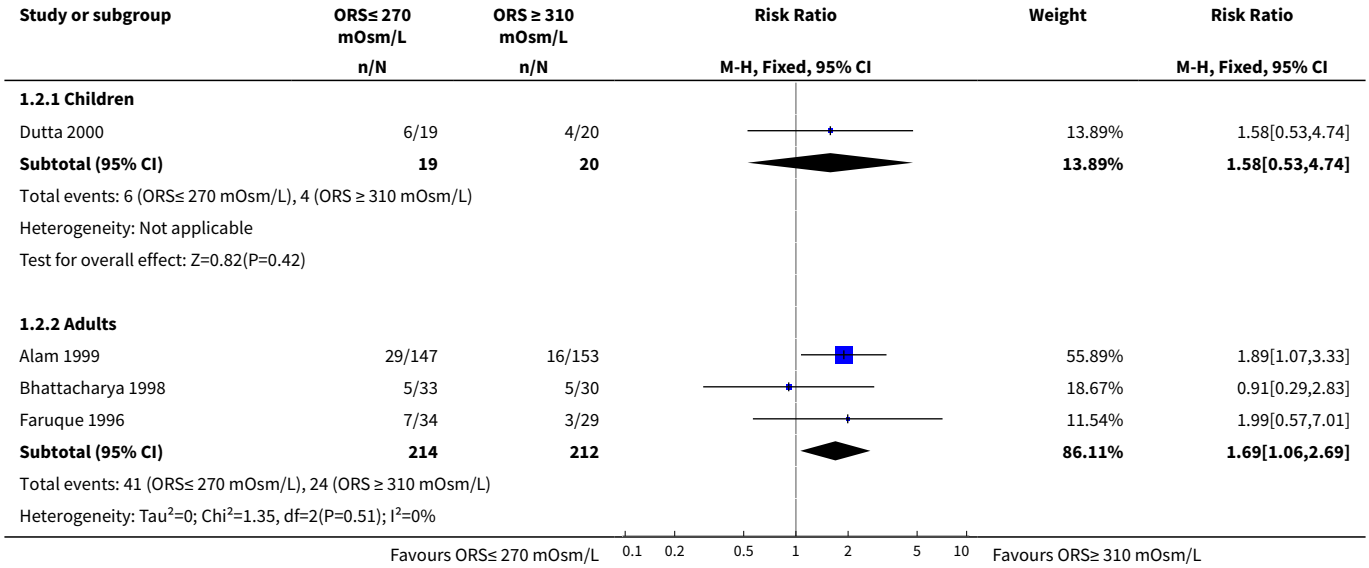
Comparison 1. Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (glucose-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based)

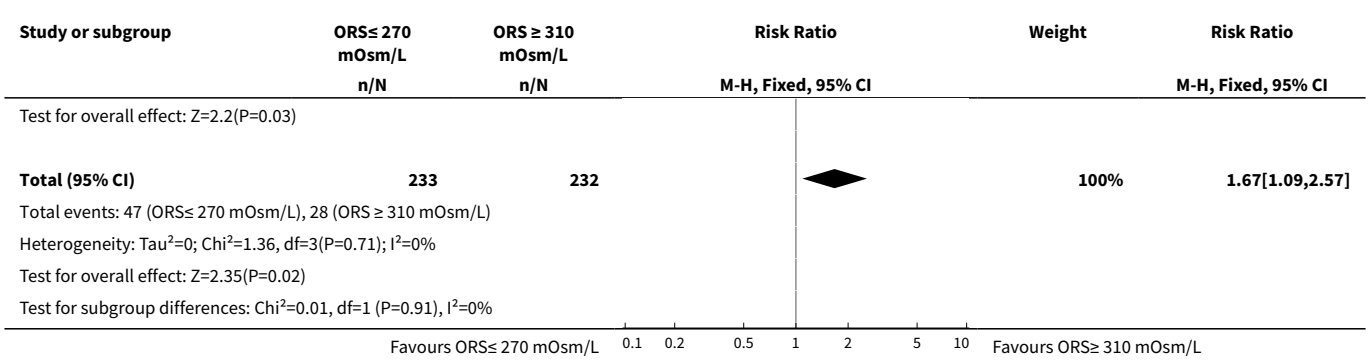
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Need for unscheduled intravenous infusion	5	616	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.66, 1.12]
1.1 Children	2	93	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.29, 1.11]
1.2 Adults	3	523	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.70, 1.24]
2 Biochemical hyponatraemia (serum sodium < 130 mmol/L)	4	465	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.09, 2.57]
2.1 Children	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.53, 4.74]
2.2 Adults	3	426	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.06, 2.69]
3 Severe biochemical hyponatraemia (serum sodium < 125 mmol/L)	4	465	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.62, 4.04]
3.1 Children	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 8.10]
3.2 Adults	3	426	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [0.68, 5.31]
4 Duration of diarrhoea	6	683	Mean Difference (IV, Random, 95% CI)	-2.52 [-6.71, 1.68]
4.1 Children	2	97	Mean Difference (IV, Random, 95% CI)	-2.75 [-9.79, 4.29]
4.2 Adults	4	586	Mean Difference (IV, Random, 95% CI)	-2.72 [-8.83, 3.39]
5 Stool output in first 24 hours after admission or randomization	4	581	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.43, 0.17]
5.1 Children	1	58	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.49, 0.55]
5.2 Adults	3	523	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.57, 0.20]
6 Vomiting during rehydration	2	363	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.92, 1.40]
6.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	2	363	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.92, 1.40]

Analysis 1.1. Comparison 1 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (glucose-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 1 Need for unscheduled intravenous infusion.

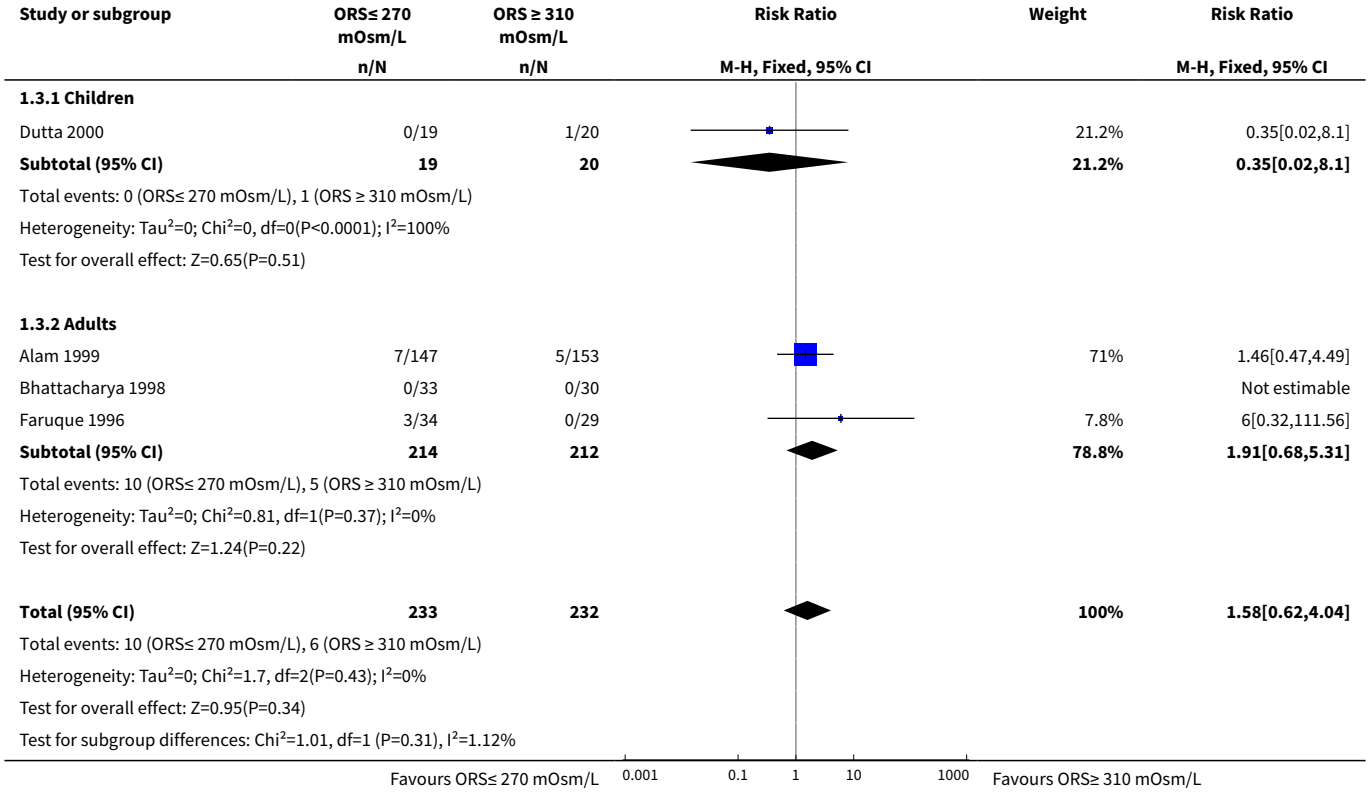


Analysis 1.2. Comparison 1 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (glucose-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 2 Biochemical hyponatraemia (serum sodium < 130 mmol/L).

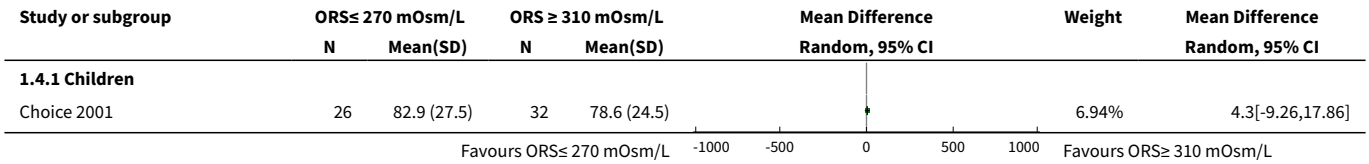


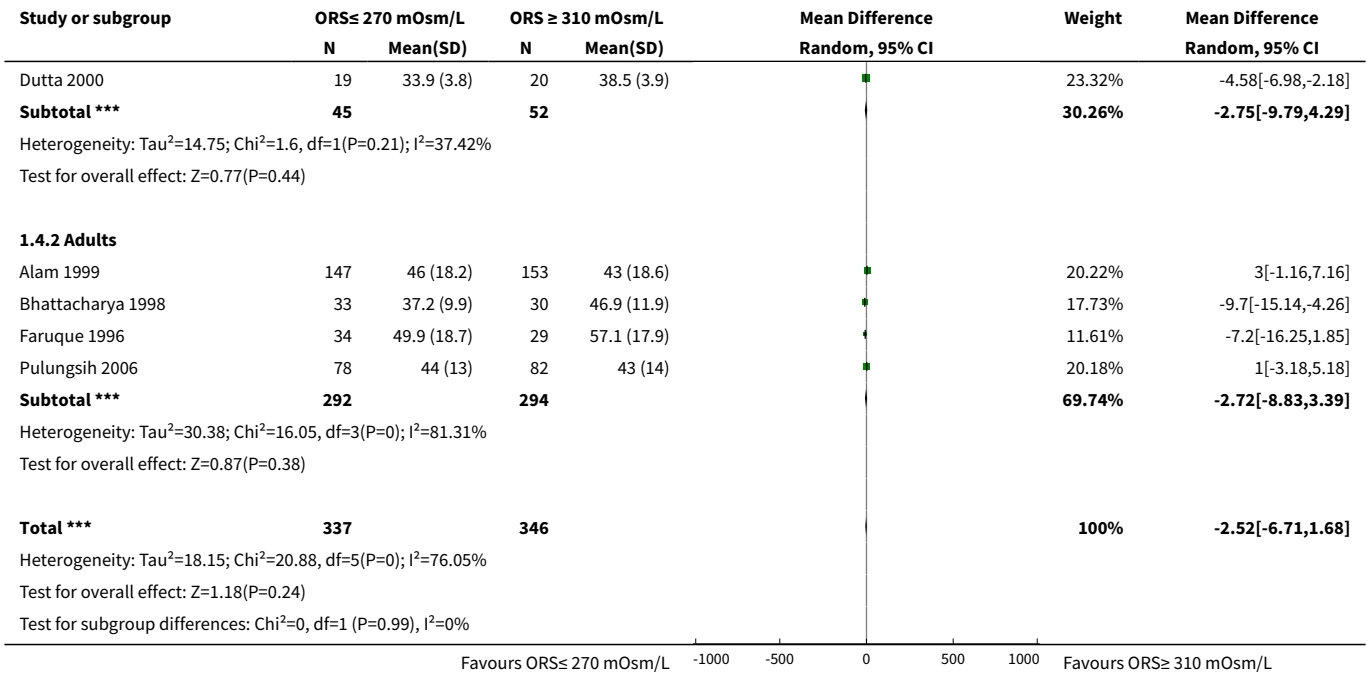


Analysis 1.3. Comparison 1 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (glucose-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 3 Severe biochemical hyponatraemia (serum sodium < 125 mmol/L).

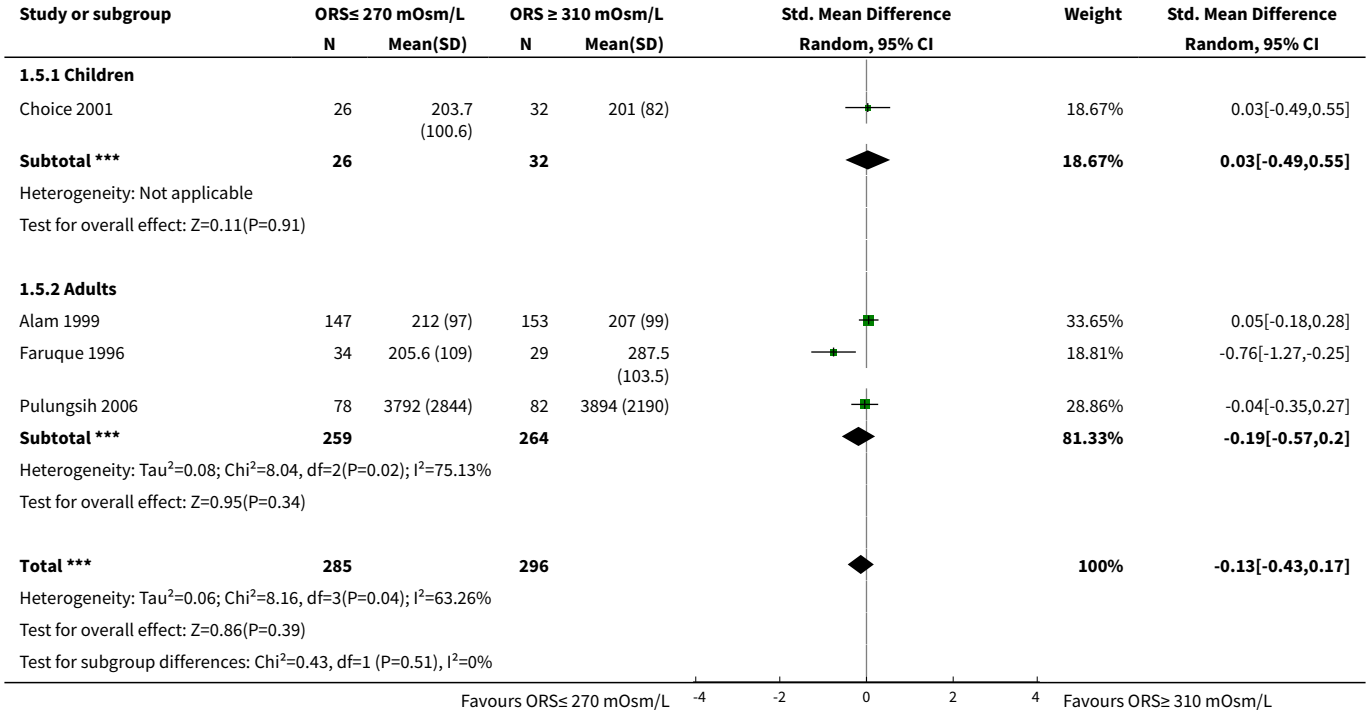


Analysis 1.4. Comparison 1 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (glucose-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 4 Duration of diarrhoea.

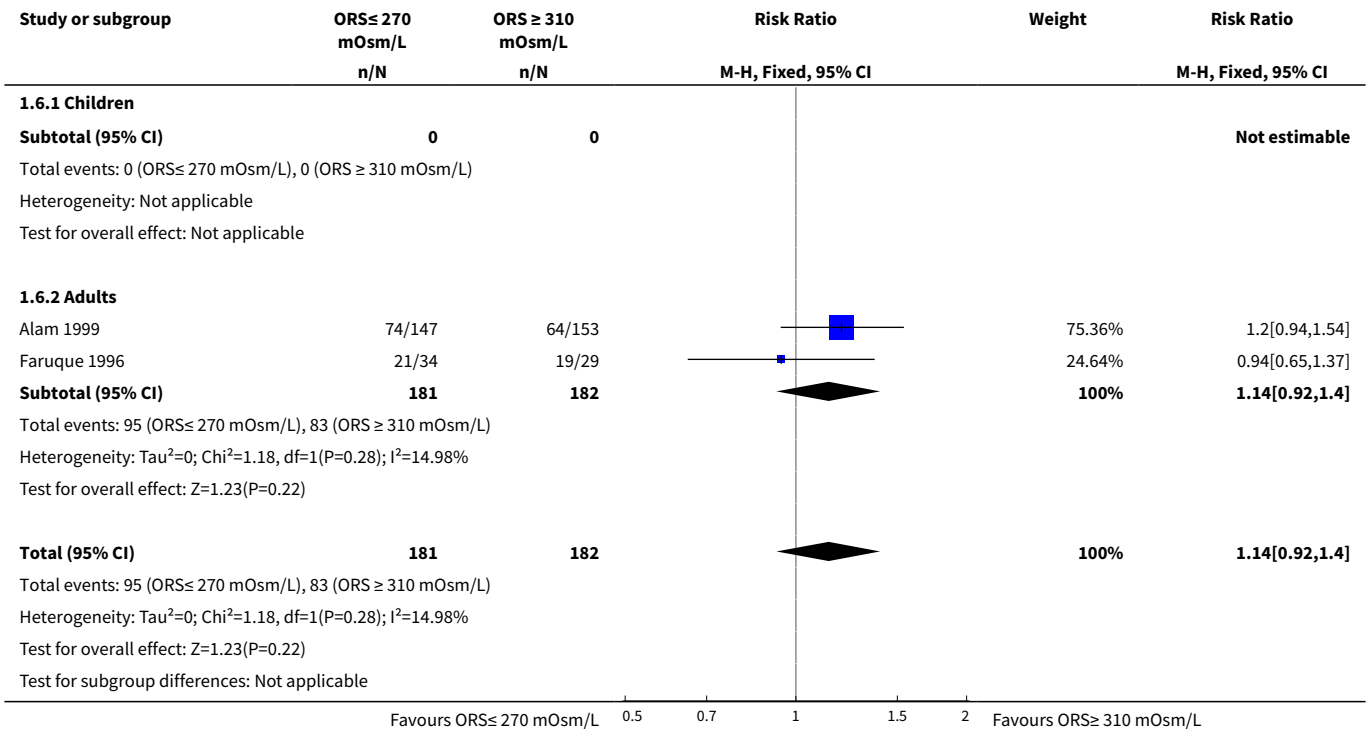




Analysis 1.5. Comparison 1 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (glucose-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 5 Stool output in first 24 hours after admission or randomization.



Analysis 1.6. Comparison 1 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (glucose-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 6 Vomiting during rehydration.



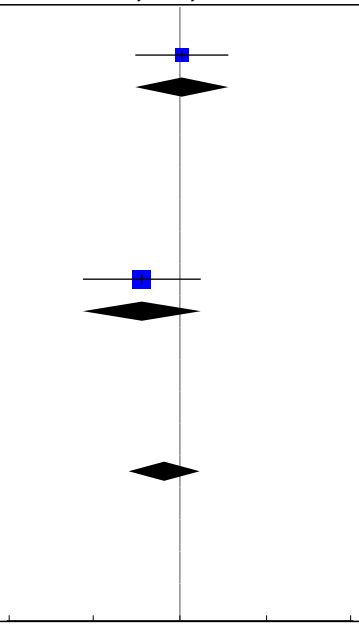
Comparison 2. Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (rice-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Biochemical hyponatraemia (serum sodium < 130 mmol/L)	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.26, 1.69]
1.1 Children	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.31, 3.62]
1.2 Adults	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.08, 1.74]
2 Severe biochemical hyponatraemia (serum sodium < 125 mmol/L)	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 8.10]
2.1 Children	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 8.10]
2.2 Adults	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Duration of diarrhoea	2	102	Mean Difference (IV, Fixed, 95% CI)	-11.42 [-13.80, -9.04]
3.1 Children	1	39	Mean Difference (IV, Fixed, 95% CI)	-9.13 [-11.89, -6.37]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.2 Adults	1	63	Mean Difference (IV, Fixed, 95% CI)	-18.0 [-22.68, -13.32]

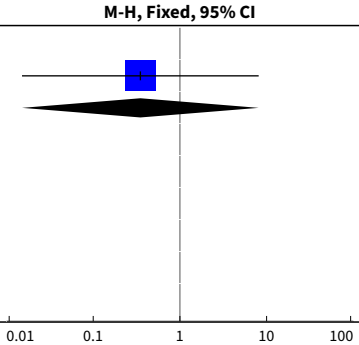
Analysis 2.1. Comparison 2 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (rice-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 1 Biochemical hyponatraemia (serum sodium < 130 mmol/L).

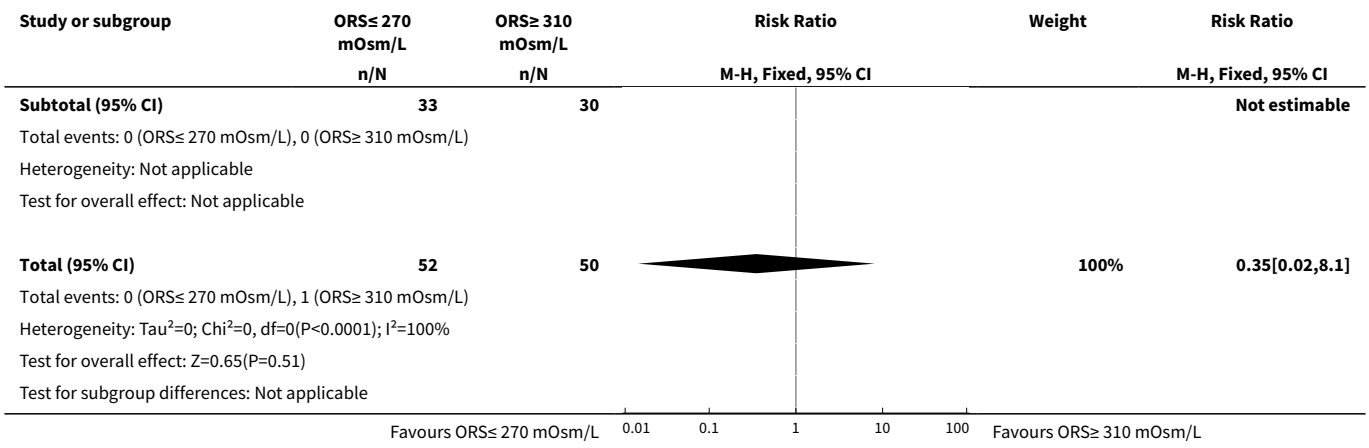
Study or subgroup	ORS≤ 270 mOsm/L n/N	ORS≥ 310 mOsm/L n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Children					
Dutta 2000	4/19	4/20		42.66%	1.05[0.31,3.62]
Subtotal (95% CI)	**19**	**20**		**42.66%**	**1.05[0.31,3.62]**
Total events: 4 (ORS≤ 270 mOsm/L), 4 (ORS≥ 310 mOsm/L)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.08(P=0.94)					
2.1.2 Adults					
Bhattacharya 1998	2/33	5/30		57.34%	0.36[0.08,1.74]
Subtotal (95% CI)	**33**	**30**		**57.34%**	**0.36[0.08,1.74]**
Total events: 2 (ORS≤ 270 mOsm/L), 5 (ORS≥ 310 mOsm/L)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.27(P=0.2)					
Total (95% CI)	**52**	**50**		**100%**	**0.66[0.26,1.69]**
Total events: 6 (ORS≤ 270 mOsm/L), 9 (ORS≥ 310 mOsm/L)					
Heterogeneity: Tau^2=0; Chi^2=1.11, df=1(P=0.29); I^2=9.79%					
Test for overall effect: Z=0.87(P=0.38)					
Test for subgroup differences: Chi^2=1.09, df=1 (P=0.3), I^2=8.5%					



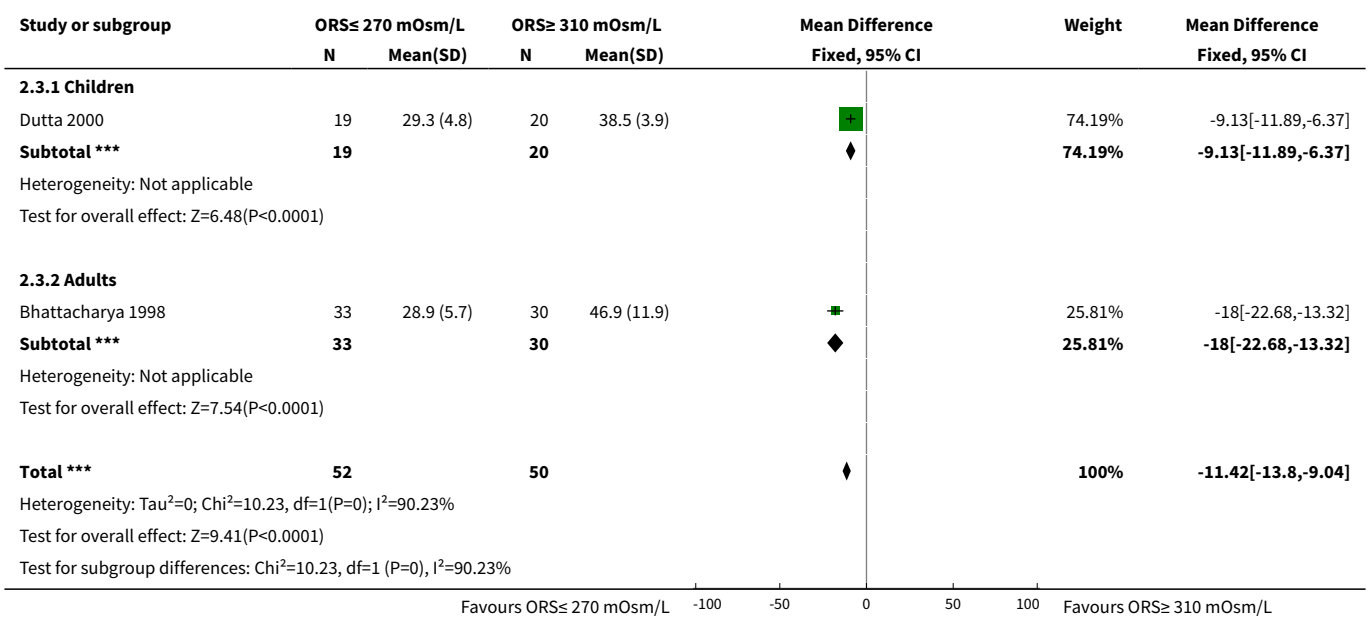
Analysis 2.2. Comparison 2 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (rice-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 2 Severe biochemical hyponatraemia (serum sodium < 125 mmol/L).

Study or subgroup	ORS≤ 270 mOsm/L n/N	ORS≥ 310 mOsm/L n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Children					
Dutta 2000	0/19	1/20		100%	0.35[0.02,8.1]
Subtotal (95% CI)	**19**	**20**		**100%**	**0.35[0.02,8.1]**
Total events: 0 (ORS≤ 270 mOsm/L), 1 (ORS≥ 310 mOsm/L)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.65(P=0.51)					
2.2.2 Adults					
Bhattacharya 1998	0/33	0/30			Not estimable





Analysis 2.3. Comparison 2 Oral rehydration solution (ORS) formulations ≤ 270 mOsm/L (rice-based) versus ORS formulations ≥ 310 mOsm/L (glucose-based), Outcome 3 Duration of diarrhoea.



ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR*	CENTRAL**	MEDLINE**	EMBASE**	LILACS**
1	cholera	cholera	CHOLERA	CHOLERA	cholera
2	rehydration solutions	oral rehydration solution	cholera	cholera	oral rehydration

Table 1. Detailed search strategies *(Continued)*

3	fluid therapy	fluid therapy	1 or 2	1 or 2	hypotonic
4	hypotonic	hypotonic solution	REHYDRATION SOLUTIONS	FLUID THERAPY	reduced osmolarity
5	ORS	ORS	FLUID THERAPY	HYPOTONIC SOLUTION	2 or 3 or 4
6	--	2 or 3 or 4 or 5	HYPOTONIC SOLUTIONS	ORAL REHYDRATION THERAPY	1 and 5
7	--	1 and 6	OSMOLAR CONCENTRATION	ORAL REHYDRATION SOLUTION	--
8	--	--	oral rehydration solution	oral rehydration solution	--
9	--	--	ORS	ORS	--
10	--	--	osmolar*	OSMOLARITY	--
11	--	--	osmolality	HYPEROSMOLARITY	--
12	--	--	reduced osmolarity	osmolar$	--
13	--	--	hypo-osmolar	osmolality	--
14	--	--	4-13/OR	reduced ADJ osmolarity	--
15	--	--	3 and 14	Hypo ADJ osmolar$	--
16	--	--	Limit 15 to human	4-15/OR	--
17	--	--	--	3 and 16	--
18	--	--	--	Limit 17 to human	--
	*Cochrane Infectious Diseases Group Specialized Register	**Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Alderson 2004); Upper case: MeSH or EMTREE heading; Lower case: free text term			

Table 2. Composition of oral rehydration solutions used in the trials

ORS type	Trials	Sodium[a]	Potassium[a]	Chloride[a]	Citrate[a]	Glucose[a]	Rice powder[b]	Total osmolarity[a]
ORS ≥ 310 (glucose-based)	All trials	90	20	80	10	111	--	311
ORS ≤ 270 (glucose-based)	Dutta 2001	60	20	50	10	84	--	224
"	Faruque 1996	67	20	66	7	89	--	249
"	Bhattacharya 1998 Dutta 2000	70	20	80	8	90	--	268
"	Alam 1999 Choice 2001 Pulungsih 2006	75	20	65	10	75	--	245
ORS ≤ 270 (rice-based)	Bhattacharya 1998 Dutta 2000	70	20	80	8	--	50	178

ORS: oral rehydration solution; [a]mmol/L; [b]g

WHAT'S NEW

Date	Event	Description
8 November 2011	New citation required but conclusions have not changed	The review has a new author team and has some data errors corrected.
30 May 2011	New search has been performed	Title changed to 'Oral rehydration salt solution for treating cholera: ≤ 270 mOsm/L solutions vs ≥ 310 mOsm/L solutions'. Changes to secondary outcomes measures, detailed in section 'Differences between protocol and review'. Several apparent errors in data extraction from previous version were corrected.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 4, 2004

Date	Event	Description
2 March 2009	New search has been performed	Corrected stool volume SMD for Alam 2000, as pointed out in Peter Gotzsche's query (Sept 2006)
21 February 2009	New citation required and conclusions have changed	Substantive amendment
21 February 2009	New search has been performed	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Colleen Murphy (CM) initiated the review and developed the eligibility and data extraction forms, with Seokyung Hahn (SH) and Jimmy Volmink (JV) providing input. CM and JV selected the trials for inclusion in the initial version of the review. CM, JV and Alfred Musekiwa (AM) extracted the data and assessed trial quality, and CM contacted authors for additional information for the first published version of the review. CM and AM entered the data and conducted the analysis. CM wrote the first draft of the review, with all reviewers contributing to the final text and analysis. AM responded to editor's comments and drafted this review update in line with RevMan 5.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- South African Medical Research Council, South Africa.
- Stellenbosch University, South Africa.
- Wits Reproductive Health and HIV Institute (WRHI), South Africa.

External sources

- Department for International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title has been changed to 'Oral rehydration solution for treating cholera: ORS ≤ 270 mOsm/L solutions vs ORS ≥ 310 mOsm/L solutions'. The secondary outcome stool volume was changed to stool output to accommodate some stool weight measurements as reported by other trials.

We had planned the following analyses but they were not appropriate for the data available: (1) analysis of geometric means and standard deviation using log normal approximation; (2) analysis of time-to-event or censored data, when available, to estimate the log hazards ratio and its variance within each trial, using methods proposed by Parmar 1998; (3) examination of funnel plots for asymmetry indicative of publication bias; and (4) sensitivity analysis to determine the degree to which the results were influenced by the adequacy of allocation concealment.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholera [*complications]; Dehydration [*therapy]; Diarrhea [*complications]; Glucose; Hyponatremia [*etiology]; Osmolar Concentration; Randomized Controlled Trials as Topic; Rehydration Solutions [adverse effects] [chemistry] [*therapeutic use]

MeSH check words

Adult; Child; Humans