Antimicrobial drugs for treating cholera (Review)

Leibovici-Weissman Y, Neuberger A, Bitterman R, Sinclair D, Salam MA, Paul M

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[Intervention Review]

Antimicrobial drugs for treating cholera

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ABSTRACT

Background

Cholera is an acute watery diarrhoea caused by infection with the bacterium *Vibrio cholerae,* which if severe can cause rapid dehydration and death. Effective management requires early diagnosis and rehydration using oral rehydration salts or intravenous fluids. In this review, we evaluate the additional benefits of treating cholera with antimicrobial drugs.

Objectives

To quantify the benefit of antimicrobial treatment for patients with cholera, and determine whether there are differences between classes of antimicrobials or dosing schedules.

Search methods

We searched the Cochrane Infectious Disease Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; African Index Medicus; LILACS; Science Citation Index; metaRegister of Controlled Trials; WHO International Clinical Trials Registry Platform; conference proceedings; and reference lists to March 2014.

Selection criteria

Randomized and quasi-randomized controlled clinical trials in adults and children with cholera that compared: 1) any antimicrobial treatment with placebo or no treatment; 2) different antimicrobials head-to-head; or 3) different dosing schedules or different durations of treatment with the same antimicrobial.

Data collection and analysis

Two reviewers independently applied inclusion and exclusion criteria, and extracted data from included trials. Diarrhoea duration and stool volume were defined as primary outcomes. We calculated mean difference (MD) or ratio of means (ROM) for continuous outcomes, with 95% confidence intervals (CI), and pooled data using a random-effects meta-analysis. The quality of evidence was assessed using the GRADE approach.

Main results

Thirty-nine trials were included in this review with 4623 participants.

Antimicrobials versus placebo or no treatment

Overall, antimicrobial therapy shortened the mean duration of diarrhoea by about a day and a half compared to placebo or no treatment (MD -36.77 hours, 95% CI -43.51 to -30.03, 19 trials, 1013 participants, *moderate quality evidence*). Antimicrobial therapy also reduced the total stool volume by 50% (ROM 0.5, 95% CI 0.45 to 0.56, 18 trials, 1042 participants, *moderate quality evidence*) and reduced the amount of rehydration fluids required by 40% (ROM 0.60, 95% CI 0.53 to 0.68, 11 trials, 1201 participants, *moderate quality evidence*). The mean duration of fecal excretion of vibrios was reduced by almost three days (MD 2.74 days, 95% CI -3.07 to -2.40, 12 trials, 740 participants, *moderate quality evidence).*

There was substantial heterogeneity in the size of these benefits, probably due to differences in the antibiotic used, the trial methods (particularly effective randomization), and the timing of outcome assessment. The benefits of antibiotics were seen both in trials recruiting only patients with severe dehydration and in those recruiting patients with mixed levels of dehydration.

Comparisons of antimicrobials

In head-to-head comparisons, there were no differences detected in diarrhoea duration or stool volume for tetracycline compared to doxycycline (three trials, 230 participants, *very low quality evidence*); or tetracycline compared to ciprofloxacin or norfloxacin (three trials, 259 participants, *moderate quality evidence*). In indirect comparisons with substantially more trials, tetracycline appeared to have larger benefits than doxycycline, norfloxacin and trimethoprim-sulfamethoxazole for the primary review outcomes.

Single dose azithromycin shortened the duration of diarrhoea by over a day compared to ciprofloxacin (MD -32.43, 95% CI -62.90 to -1.95, two trials, 375 participants, *moderate quality evidence*) and by half a day compared to erythromycin (MD -12.05, 95% CI -22.02 to -2.08, two trials, 179 participants, *moderate quality evidence*). It was not compared with tetracycline.

Authors' conclusions

In treating cholera, antimicrobials result in substantial improvements in clinical and microbiological outcomes, with similar effects observed in severely and non-severely ill patients. Azithromycin and tetracycline may have some advantages over other antibiotics.

PLAIN LANGUAGE SUMMARY

Antibiotics for treating cholera

Cochrane Collaboration researchers conducted a review of the effects of antibiotics for treating people with cholera. After searching for relevant trials, they included 39 randomized controlled trials enrolling 4623 people with cholera.

What is cholera and how might antibiotics work

Cholera is a form of severe watery diarrhoea, which spreads from person to person through food and water contaminated with the bacterium *Vibrio cholerae.* Cholera is common in places with poor water and sanitation, and sometimes causes large epidemics with thousands of people falling ill.

Cholera can cause severe dehydration and death, so the main treatment is to give fluids and salt either orally as oral rehydration salts, or by injection. By clearing the bacteria earlier than the patients own immune system, antibiotics could reduce the duration and severity of the illness, and reduce onward transmission to other people.

What the research says

Antibiotic treatment shortened the duration of diarrhoea by about one and a half days (the normal duration is between three and four days), and reduced the total amount of diarrhoea fluid by half. Consequently, the need for rehydration fluids was also reduced by almost half.

Antibiotic treatment also shortened the period of time where the patient remains contagious by reducing the duration of excretion of *Vibrio cholerae* in the diarrhoea.

The benefits of antibiotics were seen in trials recruiting only people with severe dehydration, and in those recruiting people with mixed levels of dehydration.

Tetracycline or azithromycin appear more effective than some of the other antibiotics tested, but the choice of which antibiotic to use will depend on local drug resistance.

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

Antimicrobial drugs versus placebo/no treatment for treating cholera

Patient or population: Adults and children with cholera diarrhoea
Intervention: Antimicrobial drugs
Comparison: Placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no treatment	Antimicrobial drugs				
Diarrhoea duration	The mean duration of diarrhoea in the control groups ranged from **29.3 to 127.2 hours**	The mean duration of diarrhoea in the intervention groups was **36.77 hours shorter** (43.51 to 30.03 hours shorter)		1013 (19 studies)	⊕⊕⊕◯ **moderate** [1,2,3,4]	
Stool volume	The median volume across control groups was 13.5 litres for adults and 368 ml/kg for children	The corresponding volume with antibiotics would be 7.3 litres for adults (6.1 to 7.6 L), and 184 mL/kg for children (166 to 206 mL/kg)	**ROM 0.50** (0.45 to 0.56)	1042 (18 studies)	⊕⊕⊕◯ **moderate**[1,2,3,4]	
Hydration fluid requirements	The median volume across control groups was 14 litres for adults and 374 mL/kg for children	The corresponding volume with antibiotics would be 8.4 litres for adults (7.4 to 9.5 L), and 224 mL/kg for children (198 to 254 mL/kg)	**ROM 0.60** (0.53 to 0.68)	1201 (11 studies)	⊕⊕⊕◯ **moderate**[1,2,3,4]	

Duration of pathogen secretion	The mean duration of pathogen secretion in the control groups ranged from **2.97 to 6.0 days**	The mean duration of pathogen secretion in the intervention groups was **2.74 days shorter** (3.07 to 2.40 days shorter)		740 (12 studies)	⊕⊕⊕○ **moderate**[5,2,3,4]	
Deaths	-	-	See comment	299 (7 studies)	-	No deaths occurred in these studies

*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; **ROM**: Ratio of means.

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

[1] Downgraded by 1 for risk of bias: in a sensitivity analysis restricted to the few trials at low risk of selection bias the effect size was smaller but remained statistically significant.
[2] No serious inconsistency: statistical heterogeneity was high, however this related to the size of the effect seen with different antibiotics. For meta-analysis within individual antibiotics statistical heterogeneity was low.
[3] No serious indirectness: although many of the trials are now old, and drug susceptibility patterns have changed, these results are likely to apply to treatment with antibiotics to which the current *V. cholerae* isolates are susceptible.
[4] No serious imprecision: both limits of the 95% CI represent statistically significant and clinically important effects.
[5] Downgraded by 1 for serious risk of bias: only one study was at low risk of selection bias.

BACKGROUND

Description of the condition

Cholera is an acute watery diarrhoea caused by the Gram-negative bacterium *Vibrio cholera*. There are many serogroups of *V. cholerae*, of which O1 and O139 cause disease in humans. *V. cholerae* lives in aquatic environments, where it can survive for years in a free living cycle (Alam 2007). It causes endemic disease in some countries and regions, but it has the potential to cause epidemics (affecting a large number of individuals within the population) and pandemics (occurring over a wide geographic area and affecting an exceptionally high proportion of the population). Children aged between two and 15 are at highest risk in endemic settings, while persons of all ages are affected during epidemics (Glass 1982; Sack 2004).

The incidence of cholera has been increasing globally since the beginning of the millennium, with a 24% increase in the number of cases reported for the years 2004 to 2008 as compared to the years 2000 to 2004 (WHO 2009a). However, the total of 190,130 cases reported in 2008 is considered to be a gross underestimate, because many endemic countries do not report cholera and this figure also excludes the estimated 500,000 to 700,000 cases labelled as acute watery diarrhoea that occur in some Asian and African countries (WHO 2009a). Today, the main affected regions worldwide are in Asia (Bangladesh, India, Thailand, Cambodia, and Vietnam) and many parts of Africa (including a recent outbreak described in Zimbabwe) (Chambers 2009; Mintz 2009; Sack 2004; WHO 2009b).More recently, the Haiti outbreak spread cholera to the neighbouring Dominican Republic, as well as to Cuba and Mexico (Ministry of Public Health and Population 2010; Moore 2014).

V. cholerae is transmitted to humans by the fecal-oral route, through ingestion of contaminated water or food (Zuckerman 2007). For example, one hypothesis suggests that *V. cholerae* was introduced into Haiti by infected Nepalese peacekeeping soldiers and that the epidemic spread of the organism was due to poor sanitation (Ceccarelli 2011; Frerichs 2012). The incubation period for cholera usually varies between eight to 72 hours, depending on the infectious dose and gastric acidity (WHO 2001). *V. cholerae* O1 and O139 both cause clinical disease by secreting an enterotoxin with a sub-unit structure comprising five B subunits and one A subunit (De 1959; Dutta 1959). The B subunits bind the toxin to a specific receptor (GM1 ganglioside) on the surface of the intestinal mucosal cells. The A subunit is then released into the cell where it activates adenylate cyclase, causing a net increase in cyclic adenosine monophosphate, which blocks the absorption of sodium by the villous cells. This leads to secretion of chloride by the crypt cells, followed by secretion of water, resulting in watery diarrhoea. In endemic settings, about 90% of cholera cases are defined as mild to moderate and are clinically impossible to distinguish from other acute watery diarrhoeas such as those caused by enterotoxigenic *Escherichia coli* (ETEC) and rotavirus. The remaining 10% of cases are labelled as severe cholera. Mortality from cholera depends on several factors, but is generally preventable. The overall case fatality reported by the World Health Organization (WHO) in 2008 was 2.7%, ranging from 0% to 14.3% in different countries (WHO 2009a). The reported mortality in Haiti has been as high as 4.6% in some areas, but later decreased to 1% or less throughout the country (Barzilay 2013).

Successful management of cholera depends on early diagnosis and prevention of dehydration, or prompt treatment of dehydration if it develops. Mild to moderate dehydration can be treated with Oral Rehydration Salts (ORS) solution, but severe dehydration usually requires intravenous (IV) fluids.

Description of the intervention

The intervention assessed in this review is the impact of antimicrobial treatment as an adjunct to rehydration therapy. In theory, antimicrobials will not have an immediate effect, because the toxin is already bound to intestinal cells. However, they should affect the duration of the disease by reducing further production of the toxin, either by inhibiting bacterial protein synthesis (tetracyclines, macrolides) and/or by promoting bacterial cell death.

Shortening the duration of viable pathogen excretion might also lead to reduced transmission of infection to others and reduced contamination of the environment.

The WHO recommends antimicrobial therapy only in the management of severe cases, ie those who need intravenous rehydration because of severe dehydration; patients who are lethargic or floppy, unconscious, or unable to drink ORS; or are children with an absence of tears and very slow return of skin pinch (WHO 2004). The current recommended treatment for adults is a single oral dose of doxycyline 300 mg or tetracycline 12.5 mg/kg six hourly for three days (WHO; Seas 1996). In children under eight years of age, co-trimoxazole, erythromycin or azithromycin are recommended (WHO).

The choice of antimicrobial agent is complicated by emerging resistance to antibiotics. Resistance to tetracycline emerged in 1979, followed by resistance to other antibiotic classes (Mhalu 1979). A 'creeping' increase in minimal inhibitory concentrations (MICs) to quinolones has been noted since the 1980s, mediated by chromosomal mutations. Tetracycline resistance, on the other hand, is plasmid mediated and thus MICs to tetracycline do not increase gradually. In endemic countries, most strains of *V. cholerae* are currently resistant to co-trimoxazole, with variable resistance to tetracyclines, macrolides and quinolones (Harris 2012). Thus, selection of antibiotic treatment should be directed by the results of antibiotic susceptibility testing of *V. cholerae* isolates at the onset of an outbreak.

Why it is important to do this review

Cholera epidemics continue to cause significant morbidity and mortality in many developing countries around the world. In October 2010, an epidemic of cholera started in Haiti and later spread to the neighbouring Dominican Republic. By October 2012, 604,635 cases and 7436 fatalities had been reported by the Haitian National Cholera Surveillance System (Barzilay 2013).

Many randomized, controlled clinical trials have been conducted to evaluate the efficacy of various antimicrobial agents for treating cholera. Based on the results of these trials, there is a general consensus that antimicrobial treatment shortens the duration of diarrhoea and reduces stool volume (Sack 2004; Seas 1996). However, no systematic review has previously summarized the evidence to quantify the benefit of antimicrobial treatment with regard to these outcomes.

With the latest epidemic of cholera in Haiti in mind, we believe that there is place for a systematic review that would help answer the following questions: to what extent do antimicrobials shorten the course of the clinical disease, reduce stool volume and the need for IV or oral hydration; whether certain antimicrobials or classes of antimicrobial are more effective than others at treating cholera; and what is the optimal treatment schedule.

OBJECTIVES

- To quantify the benefit of antimicrobial treatment for patients with cholera.
- To determine whether different antimicrobials have different effects.
- To determine whether different lengths of treatment or dosing of antimicrobials have different effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials or quasi-randomized studies (using alternation, date of birth, patient identification number, weekday).

Types of participants

Patients with diarrhoea caused by *V. cholerae* O1 or O139, regardless of their age and location of management (ie in-hospital or ambulatory). We included trials that recruited participants with undiagnosed diarrhoea (eg watery diarrhoea) when they presented a separate analysis of those patients with proven cholera. In this case, we only extracted data for proven cholera cases.

Types of interventions

- Any antimicrobial treatment versus placebo/no treatment.
- Any antimicrobial versus a different antimicrobial.
- Different dosing or durations of the same antimicrobials.

We excluded antibiotics that are not in current clinical use, such as streptomycin, paromomycin, formosulphathiazole, formosulphacetamide, and sulfaguanidine.

In our analyses, we did not include treatment arms in which over 90% of the *V. cholerae* isolates were resistant to the tested antimicrobial.

Types of outcome measures

Primary outcomes

- Duration of diarrhoea: from the time of initiation of the study drug until the end of diarrhoea as defined in the study.
- Stool volume: from the time of initiation of the study drug until end of diarrhoea as defined in the study.

Secondary outcomes

- All-cause deaths ('deaths' thereafter) during the acute disease stage (ie before resolution of diarrhoea).
- Duration of fecal excretion of the pathogen.
- Clinical failure: defined as persistence of watery stools beyond 48 hours of initiation of the study drug. When this outcome was reported at various time points, we chose the last time point reported.
- Bacteriological failure: defined as isolation of *V. cholerae* from stools beyond 48 hours of initiation of the study drug. When this outcome was reported at various time points, we chose the last time point reported.
- Hydration requirements: defined as the total volume of IV fluid administered. If not reported, we used data on the total volume of rehydration fluid administered, and when that was not reported, we used the total volume of ORS administered.

All outcome definitions, including the time points defining the outcome (such as schedule and frequency of monitoring), were recorded.

We intended to assess unscheduled use of IV rehydration, body weight change, development of severe hypokalaemia, severe hyponatraemia and resistance development, but these outcomes were not reported in most trials.

Search methods for identification of studies

A comprehensive search was conducted with the purpose of identifying all eligible trials regardless of language, year of publication, or status of publication (published in peer review journal, conference proceeding, thesis, or unpublished). The last search of all databases was conducted in November 2011 and the PubMed search was updated regularly until March 2014.

Electronic searches

We used the search strategy explained in Table 1. The search purposefully did not include terms related to the intervention because including the term 'antimicrobial' would prevent the identification of trials that provided only the name of the antimicrobial without using 'antimicrobial' as an Index or MeSH term. Listing all antimicrobial names was not possible since we were not aware of all types of antimicrobials that could have been assessed. In PubMed and EMBASE, search terms were used in combination with the search strategy for retrieving randomized controlled trials developed by The Cochrane Collaboration (Lefebvre 2011).

We searched the following databases for eligible trials: Cochrane Infectious Disease Group Specialized Register (CIDG SR); the Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; PubMed; EMBASE; African Index Medicus; LILACS; and the Science Citation Index (CSI).

We searched the following databases for unpublished or ongoing trials: metaRegister of Controlled Trials (mRCT) and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) for ongoing or unpublished trials.

Searching other resources

We attempted to contact key persons in agencies and organizations funding and conducting trials on the treatment of cholera via email, using our list of identified trials, and asked if they were aware of other unidentified trials. These persons and agencies included: Head of the Epidemic Control Preparedness Programme (ECPP) at the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B); Director of the National Institute of Cholera and Enteric Diseases (NICED), Kolkata, India; the All India Institute of Medical Sciences (AIIMS), Delhi, India; the US Naval Medical Research Unit (NAMRU), Jakarta, Indonesia; the Naval Medical Research Unit 3 (NAMRU-3), Cairo, Egypt; Epicentre, Paris, France; and the Institute Pasteur, Paris, France, and its network. We also attempted to contact people at the WHO.

References of all included trials were scanned.

We searched the proceedings of the following conferences: the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); and the Infectious Diseases Society of America (IDSA).

Data collection and analysis

Selection of studies

Two reviewers independently applied inclusion and exclusion criteria, and the search results were documented in an Excel spreadsheet. Disagreements were resolved by discussion; if they could not be resolved, we attempted to contact the authors of the trial to clarify questions on its eligibility. The trials' reports were scrutinized to ensure that multiple publications from the same trial were included only once. We recorded details of potentially relevant references that were excluded, along with the reason for their exclusion.

Data extraction and management

A data extraction form in Excel was developed, piloted and finalized. Two reviewers independently extracted the data from included trials into the form. Any disagreements on extracted data were resolved by discussion. If no consensus could be reached, the trial authors were contacted to clarify the issue. In the event of missing or incomplete data, we attempted to contact one or more of the trial's authors for clarification.

We extracted descriptive data on the trials, the patients and infection characteristics, including the *V. cholerae* serogroup and biotype, and resistance rates of the *V. cholerae* sp. isolates to the antimicrobials tested. For dichotomous data, we extracted the number of patients with event and the number of patients assessed. For continuous outcomes, we preferentially extracted means and standard deviations. If reported differently, we converted medians to means and calculated the variance according to the methods described by Hozo 2005. Standard errors and other dispersion measures were converted to standard deviations where possible (Higgins 2008). If not reported numerically, outcomes were extracted from graphs or figures presented in the publications (by counting pixels). Studies are named by first author (abbreviated), year of publication and trial location using the abbreviations listed in Table 2.

Assessment of risk of bias in included studies

Two reviewers independently assessed potential biases in included studies and extracted the data into the electronic table. We used a domain-based evaluation as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Reviewers were not blinded to trial authors, the publication status or other study characteristics. Each domain was assigned a low or high risk of bias, using the definitions provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). When there was insufficient information about the process, the domain was assigned an unclear risk of bias. The following domains were assessed for this review.

- **Sequence generation**
- **Allocation concealment**

- **Blinding of participants, personnel and outcome assessors:** we judged a priori that blinding will not affect the bacteriological outcomes or deaths, and thus did not attempt to explain results by this item.
- **Incomplete outcome data**: we assessed the number of exclusions and attrition for the primary outcomes. We classified studies as low risk of bias when all randomized patients were evaluated for a given outcome or up to 10% were missing without an explanation (Higgins 2008); we classified studies as unclear risk of bias when the number of randomized patients was unknown; all other studies were classified as high risk unless the reasons for attrition were provided and valid.
- **Selective outcome reporting:** we assessed this domain by comparing protocol-defined outcomes with those reported. When the protocol was unavailable, we compared outcome definitions in the methods with those reported in the results. When the study reported on the outcomes specified, it was classified as low risk; if outcomes were not defined in the protocol/methods or reported outcomes were not specified in the protocol/methods, the study was classified as high-risk; and when the outcome was poorly defined in the protocol/methods (e.g. no time point), we classified the study as unclear risk. We created a matrix of studies and outcomes (Higgins 2008).
- **Other biases:** early stop of the trial or one or more of its arms.

Disagreements regarding extracted data were resolved through discussion. If no consensus could be reached, we contacted the trial authors to clarify the issues. In the event of missing or incomplete data, we contacted one of the trial's authors and asked for the missing data.

Measures of treatment effect

For dichotomous data, we compared study groups using risk ratios (RRs). For continuous outcomes, we calculated absolute mean differences (MDs) when the units of analysis were uniform. For outcomes dependent on weight that were described in litres or mL/kg (for example, stool volume, hydration requirements), we computed the ratio of arithmetic means (ROM, Friedrich 2011; Friedrich 2012). All effect measures are reported with 95% confidence intervals (CIs).

Unit of analysis issues

When the same trial was included in a single meta-analysis more than once (because it had multiple intervention groups), we divided the number of events and participants in the placebo arm for dichotomous outcomes and we divided the number of participants for continuous outcomes (Higgins 2008).

Dealing with missing data

We tried to complement all missing data by correspondence with trial authors (via email). In case of missing data, we performed a complete case analysis for all outcomes and recorded the number of dropouts.

Assessment of heterogeneity

We visually inspected the forest plots before performing statistical tests. Heterogeneity in each meta-analysis was assessed using a Chi ^{2} test of heterogeneity, with a P value $\leq$ 0.10 used to indicate statistical significance, and using the I^2 test of inconsistency, with a value $\geq$ 50% indicating substantial inconsistency. The importance of the observed I^2 value was interpreted in terms of the magnitude and direction of the effects.

Assessment of reporting biases

In analyses that included more than 10 trials, we planned to construct funnel plots of effect estimates against study precision. Asymmetry was inspected visually to determine publication bias or other small study effects.

Data synthesis

We created an antimicrobial treatment network based on antimicrobial class, as previously described (Ioannidis 2009). We visually inspected the treatment network to identify missing comparisons. The following comparisons were conducted:

1. any antimicrobial versus placebo/no treatment, subcategorized by the antimicrobial;
2. direct comparisons between different antimicrobials or antimicrobial classes;
3. indirect comparisons between antimicrobials;
4. short versus longer duration of treatment with the same antimicrobial class, considering the effective antimicrobial treatment duration (related the duration of administration and the antibiotic's half-life);
5. low versus high doses of the same antimicrobial.

We pooled results without significant heterogeneity using the Mantel-Haenzel fixed-effect model. When significant heterogeneity was present and it was still appropriate to pool results, we used a random-effects model. For dichotomous outcomes with zero events reported in both arms of a trial, we conducted a meta-analysis of risk differences. ROMs were pooled using the inverse variance method on a log scale.

Indirect comparisons were performed using the methods described by Bucher 1997 and existing recommendations for reporting of indirect comparisons (Donegan 2010). Briefly, for continuous outcomes the mean difference for A versus B equalled : mean difference A versus placebo - mean difference B versus placebo; and variance C versus B equalled: variance A versus placebo + variance B versus placebo. For dichotomous outcomes, log (risk ratio of A

versus B) equalled: log(risk ratio of P (control) versus B (treatment)) - log(risk ratio of P (control) versus A (treatment)); and SE (log risk ratio A versus B) equalled: square root (standard error of the log risk ratio of P versus B + standard error of the log risk ratio of P versus A).

Analyses were performed using Review Manager 5 (Review Manager 5.0). Two authors working independently checked data entered into Review Manager 5.

Subgroup analysis and investigation of heterogeneity

We primarily investigated heterogeneity by sub-grouping all analyses by the type of antibiotic used. We then also examined the following subgroups.

- Age of participants: children or adults.
- *V. cholerae* serogroup: O1 versus O139. (If serogroup was not reported, we assumed that all *V. cholerae* strains in studies conducted before 1992 belonged to the O1 serogroup. Studies in which over 75% of all isolates were O1 were also included in the O1 subgroup.)
- Dehydration severity at baseline: trials recruiting only participants with severe dehydration vs those with variable inclusion (for clinical outcomes only).
- Timing of stool volume examination: separating studies in which continuous outcomes were monitored in exact time intervals of six or eight hours versus those with a vague time definition.

Sensitivity analysis

- We assessed the effect of allocation concealment on outcomes.
- We restricted the analysis to trials reporting means and standard deviations, excluding means that were estimated from medians.

Assessment of the quality of evidence

We assessed the quality of evidence across each outcome measure using the GRADE approach. The quality rating across trials has four levels: high, moderate, low, or very low. RCTs are initially categorized as high quality but can be downgraded after assessment of five criteria: risk of bias, consistency, directness, imprecision, and publication bias (Guyatt 2008). As part of the assessment of precision we performed sample size calculations for each outcome to determine if the trials or the meta-analysis were adequately powered to confidently detect or exclude clinically important effects (see Table 3; Table 4).

RESULTS

Description of studies

Results of the search

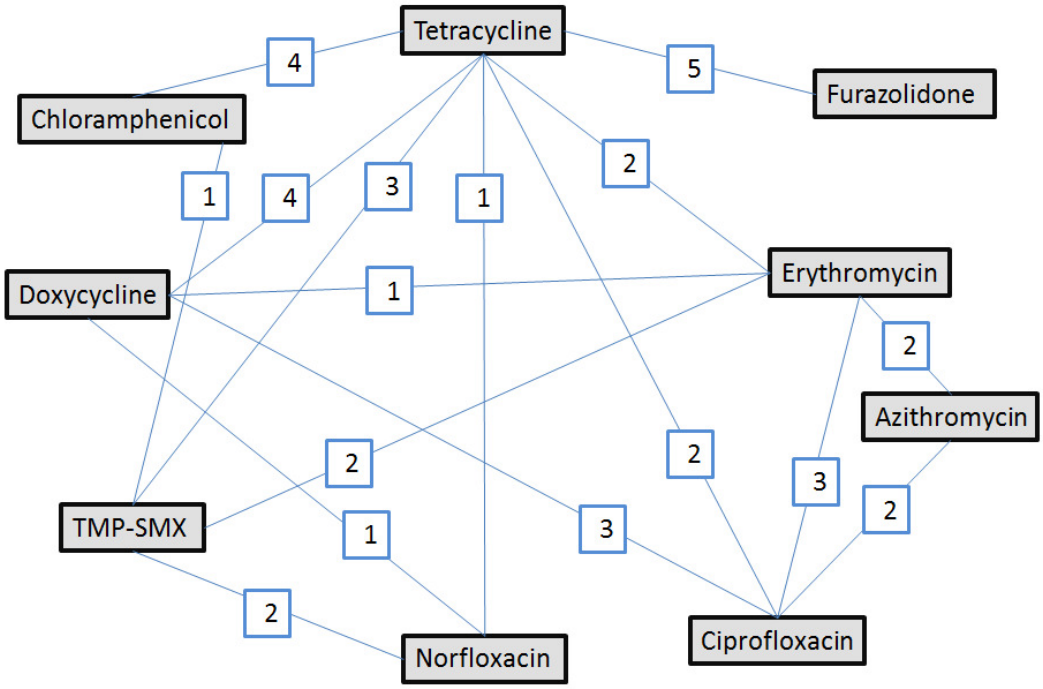
Our search yielded a large number of references: 65 were deemed relevant and the full text of 64 could be retrieved. Twenty-three studies were excluded for reasons specified in Characteristics of excluded studies. We were unable to obtain one article (Chatchai 1994) and three ongoing studies were identified (see the Characteristics of ongoing studies table).

Included studies

Thirty-nine different trials are included in this review, described in 41 publications. The trials were conducted between 1964 and 2007, and published between 1964 and 2010. The trials were predominantly conducted in Bangladesh, India and Pakistan (15, 10, and three trials, respectively), with additional trials in Thailand (2), Sri Lanka (1), Somalia (1), Nigeria (1), Ivory Coast (1), Peru (2), Turkey (1), Iran (1), and one multi-centre trial (Thailand, Indonesia, Ivory Coast, Mexico, Israel, and Italy).

Twelve trials were conducted during an epidemic of cholera and the remaining were conducted in endemic settings. Most trials were multi-armed: 16 trials included four or more study arms, rendering a large number of different comparisons. We created a treatment network showing the various comparisons and the number of trials examining each comparison (Figure 1). All the antimicrobials in Figure 1, except for azithromycin, were compared to placebo/no treatment (comparisons not shown in Figure 1).

Figure 1. An antimicrobial treatment network based on antimicrobial drug or class. This figure describes the different comparisons in all included studies which compared one antimicrobial vs another antimicrobial (comparisons vs. placebo/ no treatment not included).



Participant characteristics

A total of 4623 patients took part in the trials, with a median of 77 participants per trial (range 20 to 450). Nine of the trials included only children, 23 included only adults and the remaining seven included both. Seventeen trials excluded girls/ women, because of the difficulty separating stool from urine without a catheter, and seven further trials did not report on the sex of the study participants. The case definition in most trials specified a history of acute watery diarrhoea, lasting 24 hours or less. However, all trials included in their final analysis only patients with bacteriologically-proven cholera. Twenty-seven trials (70%) included some measure of severity in their case definition (eg low blood pressure, severe dehydration) and six trials excluded patients with severe cholera. Twenty-eight studies reported exclusion of patients who had received antimicrobial therapy prior to enrolment, two trials allowed inclusion of such patients, and the remaining did not refer to previous antimicrobial treatment.

Infection characteristics

The isolated *V. cholerae* strains belonged to serogroup O1 in 23 studies, serogroup O139 in three studies, and both serogroups in six studies, while the *V. cholerae* serogroup was not reported in the remaining studies. We assumed that the strains in studies conducted before 1992 (four studies) belonged to serogroup O1, as this was the year in which serogroup O139 first emerged [ICDDR,b 1993]. Identification of *V. cholerae* was made by culture in 12 studies (the earliest conducted in 1963 and the latest in 1996) and by dark field microscopy in 15 (the earliest published in 1971 and the latest conducted in 2002); the remaining publications did not describe the methods of laboratory confirmation.

Nineteen studies reported that all isolates were susceptible to the study drugs, while 13 studies did not report susceptibility data. The remaining seven studies reported various degrees of resistance to several different antimicrobials:

- Tetracycline resistance: Grados 1996 PER (7%); Khan 1995b BGD (100%); Rabbani 1989 BGD (13.3%); Roy 1998 BGD (24%)
- Cotrimoxazole: Kabir 1996 BGD (23%)

- Erythromycin: Bhattacharya 1990 IND (100%); Kabir 1996 BGD (23%)
- Furazolidone: Rabbani 1989 BGD (22.2%); Rabbani 1991 BGD (10%).

We excluded study arms with 100% resistance from the meta-analysis.

Excluded studies

Most excluded studies were non-randomized (see Characteristics of excluded studies). Two studies conducted by the same group were declared randomized, but the randomization methods were not described and differences between groups at baseline suggested a lack of adequate randomization (Mazumder 1974; Mazumdar 1977). We could not establish contact with the authors and these trials were excluded. We excluded a four-armed pseudo-randomized trial (using alternation) conducted in 1950, which assessed sulphaguanidine, formosulphathiazole, and formosulphacetamide against no treatment (Lahiri 1951). These antimicrobials are no longer used in humans and the mortality in this trial was higher in the antimicrobial arms (30 to 34%) than in the no treatment arm (18%). Finally, we excluded a trial conducted in 1964 in the Philippines (Uylangco 1965), which was a pseudo-randomized trial (using alternation) comparing sulphaguanidine versus no treatment.

Risk of bias in included studies

A visual summary of the risk of bias assessment can be seen in Figure 2 and Figure 3.

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

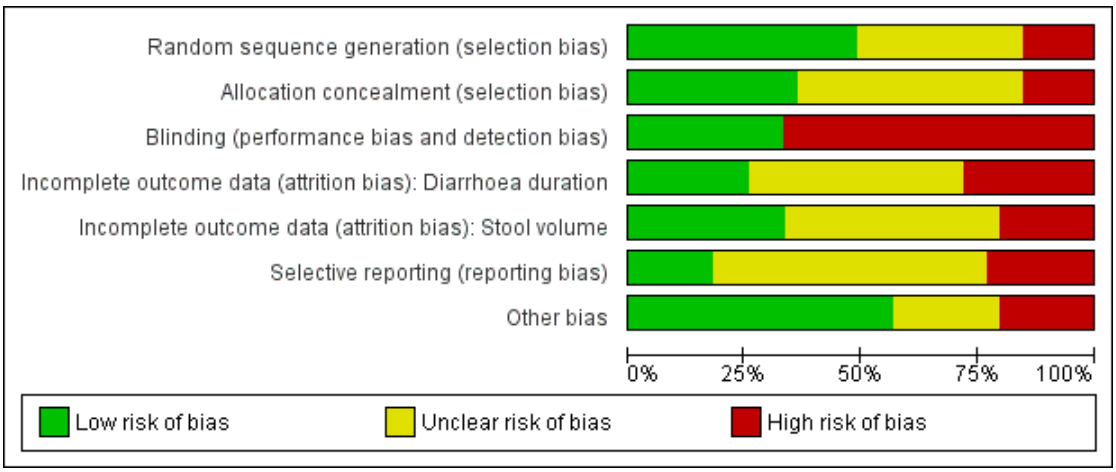
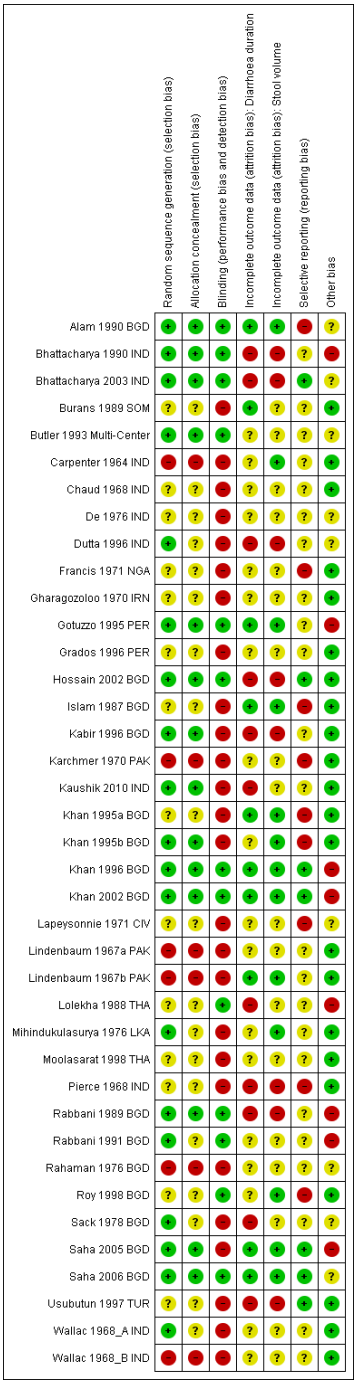


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Nineteen studies described an adequate method for generating a random allocation sequence. Five studies used alternate allocation based on the order of arrival at hospital and were considered to be at high risk of selection bias (Carpenter 1964 IND; Karchmer 1970 PAK; Lindenbaum 1967a PAK; Lindenbaum 1967b PAK; Rahaman 1976 BGD). The remaining trials did not describe their methods of randomization and so are at unclear risk.

Fourteen studies described an adequate method for concealing allocation and were judged to be at low risk of bias, and 20 studies did not describe allocation concealment and so are at unclear risk of bias.

Blinding

Sixteen trials were double blinded, while in two trials the outcome assessor alone was blinded. The remaining 21 trials were open-labelled.

Incomplete outcome data

We examined incomplete outcome data reporting for the two primary outcomes. Out of 30 trials reporting on diarrhoea duration, nine were classified as low risk, 11 as high risk and the remainder were classified as unclear risk of incomplete outcome because the number of randomized patients was not explicitly stated. Out of 29 trials reporting on stool volume, 13 were low risk, eight were high risk and the remainder were unclear.

Selective reporting

Study protocols were not available. The primary outcome was not defined in the methods section in eight (20.5%) of the publications. In most publications (26 out of 39, 66.7%), the primary outcomes were defined without specifying the time point for assessment, while the primary outcomes were fully defined in five publications. When primary outcomes were defined, 13 studies defined a single primary outcome, six studies defined more than one outcome and 12 studies included all outcomes as 'primary'. Primary and secondary outcomes defined in the methods were reported in the results quantitatively in all publications. The outcome matrix showed that out of the 39 included studies, the number of studies reporting review-defined outcomes were as follows:

- diarrhoea duration: 29
- volume of diarrhoea: 29
- deaths: 14
- duration of pathogen excretion: 16
- microbiological failure: 31
- clinical failure: 18
- volume of rehydration fluids (IV or orally): 24.

Other potential sources of bias

Eight trials were sponsored by a pharmaceutical company that manufactured one of the study drugs; another six received only the study drug from the company. Fourteen studies were under academic sponsorship, and the remaining 11 publications did not specify whether the trial was sponsored or not. Approval of an ethics committee was reported in 10 trials (24%) and informed consent was reported in 22 trials (54%).

Effects of interventions

See: **Summary of findings for the main comparison** Antimicrobial drugs versus placebo/no treatment for treating cholera; **Summary of findings 2** Azithromycin versus ciprofloxacin for treating cholera; **Summary of findings 3** Azithromycin versus erythromycin for treating cholera; **Summary of findings 4** Tetracycline versus doxycycline for treating cholera; **Summary of findings 5** Tetracycline versus quinolones for treating cholera; **Summary of findings 6** Doxycycline versus quinolones for treating cholera; **Summary of findings 7** Short compared to long duration of antimicrobials for treating cholera

Section 1. Antimicrobials versus placebo/ no treatment

A total of 23 trials included a comparison of antimicrobials versus placebo/no treatment, contributing to one or more of the outcomes detailed below. The last trial was completed in 1994.

Primary analysis

Diarrhoea duration

On average, antimicrobials reduced the duration of diarrhoea by about one and a half days compared to placebo or no treatment (MD -36.77 hours, 95% CI -43.51 to -30.03, 18 trials, 1479 participants, Analysis 1.1). However, there were statistically significant subgroup differences in the magnitude of the effect (P < 0.00001). Tetracycline, the most studied antibiotic, shortened the duration of diarrhoea by almost two days (MD -47.38 hours, 95% CI -52.36 to -42.41, I^2 = 0%, 11 trials, 665 participants); doxycycline shortened the duration by just over one day (MD -25.44 hours, 95% CI -38.90 to -11.99, I^2 = 50%, three trials, 91 participants); and norfloxacin shortened the duration by less than half a day (MD -10.80 hours, 95% CI -14.13 to -7.48, I^2 = 0%, three trials, 123 participants).

Stool volume

Thirteen trials reported stool volume as total litres excreted, while four studies reported it as mL/kg body weight. The results were highly skewed in most trials.

Overall, the mean stool volume was 50% lower in those treated with antibiotics compared to placebo/no treatment (ROM 0.50, 95% CI 0.45 to 0.56, 17 trials, 1716 participants, Analysis 1.2). As with diarrhoea duration, there were statistically significant subgroup differences between antibiotics (P = 0.01). Tetracycline was again the most studied antibiotic and reduced stool volume by 56% (ROM 0.44, 95% CI 0.39 to 0.50, I^2 =0%, 12 trials, 771 participants). Large effects were also seen with norfloxacin (two trials), ciprofloxacin (one trial), doxycycline (three trials), chloramphenicol (three trials), furazolidone (five trials), and ampicillin (one trial).

Deaths

No deaths were reported in all trials, although only six trials explicitly stated that no deaths occurred (Analysis 1.3).

Clinical failure

Clinical failure was variably assessed between 48 to 96 hours after enrolment to the study or from starting to take the study drugs.

Overall, clinical failure was significantly lower with antimicrobial treatment (RR 0.21, 95% CI 0.13 to 0.34, 10 trials, 1023 patients, Analysis 1.4). Tetracycline reduced the risk of clinical failure by 90% (RR 0.10, 95% CI 0.05 to 0.22, I^2 = 46%, six trials, 431 participants), and statistically significant effects were also seen with fleroxacin (one trial), trimethoprim-sulfamethoxazole (TMP-SMX; two trials), chloramphenicol (two trials), and sulfometoxine (one trial).

Hydration requirements

Eight trials reported total hydration fluid requirement as litres, while three trials reported it as mL/kg body weight.

Overall, the total volume of hydration fluid required was 40% lower in patients given antibiotics (ROM 0.60, 95% CI 0.53 to 0.68, 11 trials, 1201 participants, Analysis 1.5). The effect was slightly greater than the pooled total with tetracycline (ROM 0.50, 95% CI 0.43 to 0.58, I^2 =19%, eight trials, 604 participants), and lower for doxycycline (ROM 0.76, 95% CI 0.57 to 1.02, I^2 = 37%, two trials, 66 participants) and norfloxacin (ROM 0.72, 95% CI 0.60 to 0.86, I^2 = 57%, two trials, 98 participants). Beneficial effects were also seen with chloramphenicol (two trials) and amoxicillin (one trial).

Pathogen excretion duration

The mean duration of pathogen excretion was significantly shorter in patients given antibiotics (MD -2.74 days, 95% CI -3.07 to -2.40, 11 trials, 1009 participants, Analysis 1.6). Tetracycline was the most studied antibiotic and reduced the duration of excretion by three days (MD -3.05 days, 95% CI -3.43 to -2.67, I^2 = 60%, 11 trials, 616 participants). Large beneficial effects were also seen with TMP-SMX (one trial), chloramphenicol (two trials), and furazolamide (three trials). All studies monitored stools for pathogen excretion daily.

Bacteriological failure

As for clinical failure, microbiological failure was variably assessed at 48 to 96 hours after enrolment to study or from start of the study drugs.

Overall, bacteriological failure was significantly lower with antimicrobial therapy (RR 0.25, 95% CI 0.16 to 0.39, 15 trials, 1147 patients, Analysis 1.7), but with significant subgroup differences (P < 0.00001) and significant heterogeneity within some subgroups. Considerable heterogeneity was present in the analysis of tetracycline, but all studies pointed in the same direction (RR 0.28, 95% CI 0.13 to 0.64, I^2 = 86%, seven trials, 320 participants), with large reductions seen in small trials of doxycycline (two trials), norfloxacin (three trials), fleroxacin (one trial), ciprofloxacin (one trial), and erythromycin (three trials).

Sensitivity analysis

Risk of bias

We evaluated the possible influence of poor study design on the observed effects of antimicrobial treatment by conducting a sensitivity analysis against the risk of selection bias. For duration of diarrhoea (Analysis 2.1), stool volume (Analysis 2.2), hydration requirements (Analysis 2.4), clinical failure (Analysis 2.3), and bacteriological failure (Analysis 2.6), the largest effects were observed in trials at high risk of selection bias and the smallest effects in trials at low risk of bias. Nevertheless, when the analysis was restricted to those to studies at low risk of bias, the benefits of antibiotics remained both statistically and clinically significant.

Conversion of medians to means

When excluding trials reporting results in medians (which we converted into means), the results remained almost identical to the main analysis (data not shown).

Time definition

For stool volume, the time interval for stool output assessment was eight hours in 16 studies, six hours in six studies, 24 hours or more in four studies, and not reported in 13 studies. Heterogeneity dropped significantly in the group of trials with exact time intervals

of eight hours (MD -42.21 hours, 95% CI -47.64 to -36.78, I^2 = 45%, nine trials, 1038 patients, Analysis 3.1).
For clinical and bacteriological failure, there were no significant differences in effects between trials assessing failure at 48, 72 or 96 hours (Analysis 3.2; Analysis 3.3).

Subgroup analysis

Age of participants

No statistically significant subgroup differences were seen (data not shown).

Cholera serogroups

No statistically significant subgroup differences were seen (data not shown).

Level of dehydration at baseline

The effect of antimicrobials was smaller in trials where all patients were severely dehydrated at baseline compared to studies with broader inclusion criteria (range 0 to 88% severely dehydrated) for duration of diarrhoea (test for subgroup differences P = 0.005, Analysis 4.1), stool volume (P = 0.07, Analysis 4.2), and hydration requirements (P = 0.04, Analysis 4.4). There were no subgroup differences for clinical failure (P = 0.77, Analysis 4.3).

Antimicrobial resistance

Restriction of the analysis of bacteriological failure to studies reporting that all cholera isolates were susceptible to the administered antimicrobials resulted in similar results to the overall analysis (RR of 0.13, 95% CI 0.06 to 0.27, Analysis 5.1).

Small study effects

The funnel plots for most outcomes in the comparison of antimicrobial versus placebo/no treatment did not show a small study effect; only in the clinical and microbiological failure analyses did small studies tend to show a larger effect, but these analyses included only a small proportion of existing studies.

Assessment of quality of evidence

This comparison is summarized in Summary of findings for the main comparison. The evidence for the large effect of antibiotics on the duration of diarrhoea, total stool volume, fluid requirement, and pathogen excretion duration was judged to be of moderate quality, meaning we have reasonable confidence in these results. We downgraded the quality of evidence from high to moderate because the effects appear to be exaggerated in trials at high risk of selection bias. We did not downgrade for inconsistency, as much of the observed heterogeneity was explained by differences between antibiotic classes and differences in the timing of outcome measurements. We also did not downgrade for indirectness despite many of the trials being old. We consider the observed effects applicable to effective antibiotics today.

Section 2. Comparison between different antimicrobials

Direct comparisons are addressed, followed by indirect comparisons where relevant. Funnel plots were not drawn for all head-to-head comparisons because of the paucity of trials in most comparisons.

Azithromycin versus ciprofloxacin

Two trials have directly compared single doses of azithromycin (effective duration of four days) and ciprofloxacin (effective duration of 12 hours) among children (Kaushik 2010 IND) and adults (Saha 2006 BGD).
Compared to ciprofloxacin, treatment with azithromycin reduced the mean duration of diarrhoea by over a day (MD -32.43 hours, 95% CI -62.90 to -1.95, two trials, 375 participants, Analysis 6.1), reduced stool volume by about two-thirds (ROM 0.35, 95% CI 0.28 to 0.44, one trial, 195 participants, Analysis 6.2), reduced hydration requirements by about a third (ROM 0.66, 95% CI 0.52 to 0.83, two trials, 375 participants, Analysis 6.3), and reduced bacteriological failure at 48 to 72 hours by over three-quarters (RR 0.23, 95% CI 0.16 to 0.34, two trials, 375 participants, Analysis 6.5).
This comparison is summarized in Summary of findings 2. The quality of the evidence for a reduction in diarrhoea duration was judged to be moderate. We downgraded the evidence because the trial that demonstrated the largest effect had baseline imbalances favouring azithromycin (Saha 2006 BGD). The effects on stool volume and bacteriological failure were further downgraded to low quality due to concerns about indirectness and inconsistency, respectively.

Azithromycin versus erythromycin

One trial directly compared single dose azithromycin (effective duration of four days) with three days of erythromycin (Khan 2002 BGD), and one trial compared a three-day regimen of both drugs (Bhattacharya 2003 IND).
Compared to erythromycin, azithromycin reduced the duration of diarrhoea by half a day (MD 12.05 hours, 95% CI -22.02 to -2.08, two trials, 179 participants, Analysis 7.1), and reduced the total stool volume by a third (ROM 0.69, 95% CI 0.56 to 0.85, two trials, 172 participants, Analysis 7.2). Hydration requirements were lower with azithromycin, but this did not reach statistical significance (two trials, 172 participants, Analysis 7.3), and no

differences were observed for clinical failure (Analysis 7.4) or bacteriological failure (Analysis 7.5).
This comparison is summarized in Summary of findings 3. The quality of evidence for the reduction in diarrhoea duration and stool volume was judged to be of moderate quality.

Tetracycline versus doxycycline

Three trials directly compared tetracycline with doxycycline. In two trials tetracycline was given four times daily for four days (De 1976 IND; Rahaman 1976 BGD), and in one trial tetracycline was given four times daily for two days (Alam 1990 BGD). All trials administered a total dose of 300 mg of doxycycline, spread over three days (Rahaman 1976 BGD), two days (De 1976 IND) or given as a single dose (Alam 1990 BGD).
Overall, no consistent clinically important differences were observed for diarrhoea duration, stool volume, or hydration requirements (three trials, 230 participants, Analysis 8.1; Analysis 8.2,Analysis 8.4), or for duration of pathogen excretion (two trials, 66 participants, Analysis 8.5). Only a few patients with bacteriological failure were reported, but this reached statistical significance in favour of tetracycline (RR 0.20, 95% CI 0.06 to 0.68, two trials, 198 participants, Analysis 8.6).
This comparison is summarized in Summary of findings 4. The evidence of no difference between antimicrobials was downgraded to low quality due to concerns about the risk of bias of the studies and their age, with the most recent study being 25 years old.
This direct evidence is in contrast to the indirect evidence comparing tetracycline (10 trials) and doxycycline (three trials) with placebo/no treatment. In this analysis, diarrhoea duration was almost a day shorter in the trials using tetracycline compared with the trials using doxycycline (MD 21.94 hours, 95% CI -36.29 to -7.59, Analysis 1.1), while the stool volume reduction was significantly higher with tetracycline (ROM 0.44, 95% CI 0.39 to 0.50) compared to doxycycline (ROM 0.64, 95% CI 0.51 to 0.81, Analysis 1.2, P = 0.004 for subgroup difference).

Tetracycline versus quinolones

Three trials compared tetracycline with quinolones. The three trials compared tetracycline 500 mg four times daily for three days with: ciprofloxacin 1 g single dose (Khan 1995a BGD); ciprofloxacin 250 mg once daily for three days (Gotuzzo 1995 PER); and norfloxacin 400 mg twice daily for three days (Moolasarat 1998 THA).
There were no statistically significant differences in the duration of diarrhoea (three trials, 259 participants, Analysis 9.1), stool volume (two trials, 234 participants, Analysis 9.2), clinical failure (one trial, 202 participants, Analysis 9.4), hydration requirements (two trials, 234 participants, Analysis 9.5), duration of pathogen excretion (one trial, 25 participants, Analysis 9.6), or bacteriological failure (two trials, 234 participants, Analysis 9.7).
This evidence of no difference was judged to be of low to moderate quality (see Summary of findings 5).
In indirect comparisons, tetracycline appeared to have a larger effect on diarrhoea duration than norfloxacin, compared to placebo/no treatment (P < 0.002 for subgroup difference, Analysis 1.1). Statsitically significant subgroup differences in favour of tetracycline were also seen for stool volume (P=0.004, Analysis 1.2) and hydration requirements (P=0.003, Analysis 1.5).

Tetracycline versus TMP-SMX

Three trials compared tetracycline (500 mg four times daily for three days) versus TMP-SMX (twice daily for three days) (Francis 1971 NGA; Gharagozoloo 1970 IRN; Grados 1996 PER).
Compared to TMP-SMX, diarrhoea duration was slightly shorter in those treated with tetracycline (MD -6.44 hours, 95% CI -10.93 to -1.96, two trials, 152 participants, Analysis 10.1); stool volume was not reported. Clinical failure was also lower with tetracycline (RR 0.56, 95% CI 0.34 to 0.92, two trials, 152 participants, Analysis 10.2). In one small trial, pathogen excretion was reduced by a day with tetracycline (MD -1.1 days, 95% CI -1.74 to -0.46, one trial, 45 participants, Analysis 10.3), but there was no difference in bacteriological failure across all three trials (three trials, 173 participants, Analysis 10.4).
In indirect comparisons, tetracycline was associated with a greater reduction in diarrhoea duration (MD -47.38 hours tetracycline vs -30.76 hours TMP-SMX, test for subgroup differences P=0.09, Analysis 1.1) and a greater reduction in clinical failure (RR 0.10 tetracycline vs 0.33 TMP-SMX, test for subgroup differences P = 0.02 , Analysis 1.4).

Tetracycline versus other antibiotics

Tetracycline has also been directly compared to: chloramphenicol (three trials); furazolidone (four trials); ampicillin (two trials); erythromycin (two trials); and sulphadoxine (two trials).
Tetracycline was more effective than chloramphenicol for all outcomes examined, without statistically significant differences (Analysis 11.1; Analysis 11.2; Analysis 11.4; Analysis 11.3), except for pathogen excretion duration where the difference of about one day was statistically significant (Analysis 11.5).
Tetracycline was also more effective than furazolidone for most outcomes examined, with these differences statistically significant for diarrhoea duration (mean difference -16.00 hours, 95% CI -31.26 to -0.74, Analysis 12.1), stool volume (Analysis 12.2), hydration requirements (Analysis 12.5), and clinical failure (Analysis 12.4). There was no difference in deaths (Analysis 12.3).
For the remaining comparisons (versus ampicillin, erythromycin and sulphadoxine), diarrhoea duration was not reported. Consistent clinical differences were not detected (data not shown), except for an advantage of tetracycline in hydration requirements in comparison to ampicillin or erythromycin (ROM 0.43, 95%

CI 0.25 to 0.73, Roy 1998 BGD) and in bacteriological failure in comparison to sulphadoxine (RR 0.14, 95% CI 0.02 to 0.96, Mihindukulasurya 1976 LKA).

Doxycycline versus quinolones

Four trials were included overall, with three of the trials having a similar treatment duration (single dose) (Dutta 1996 IND; Khan 1995a BGD; Khan 1996 BGD) and one trial having a longer duration (Usubutun 1997 TUR). Ciprofloxacin was examined in three trials and norfloxacin in one trial (Dutta 1996 IND).

There was no clinically or statistically significant difference in diarrhoea duration (Analysis 13.1), stool volume (Analysis 13.2) or deaths (Analysis 13.3). Hydration requirements were lower with quinolones, although there was only a small magnitude of effect based mostly on the results of a single trial (Analysis 13.4). Bacteriological failure occurred more frequently with doxycycline (RR 5.84, 95% CI 2.70 to 12.65, Analysis 13.5).

The quality of the evidence was rated low to moderate for the main outcomes (Summary of findings 6).

For indirect comparisons, no differences between doxycycline and quinolones were observed.

Erythromycin versus ciprofloxacin

Three trials compared erythromycin with ciprofloxacin (Khan 1995a BGD; Khan 1995b BGD; Saha 2005 BGD) and found no statistically significant differences (data not shown).

TMP-SMX versus other antibiotics

Two trials compared TMP-SMX with erythromycin (Burans 1989 SOM; Kabir 1996 BGD) and found no statistically significant differences (Analysis 14.1; Analysis 14.2; Analysis 14.3).

A single trial compared TMP-SMX with norfloxacin (Lolekha 1988 THA), but reported only diarrhoea duration; it found no significant difference between the drugs (data not shown).

Section 3. Short versus long duration of treatment (mean difference < 0 and risk ratio < 1 in favour of short duration)

Only the few trials (eight) comparing the same antimicrobial or antimicrobial class were included in this comparison. We divided the trials into subgroups according to the effective duration of treatment in the long treatment arm (24, 48, 72, or 96 hours). The duration of treatment in the short treatment arm was always shorter than 24 hours. This comparison is summarized in Summary of findings 7.

For clinical outcomes; one trial found that three days of norfloxacin (400 mg twice daily) was superior to a single dose (800 mg), but the remaining trials found no statistically significant benefits with longer durations; diarrhoea duration (seven trials, Analysis 15.1), stool volume (eight trials, Analysis 15.2), hydration requirements (six trials, Analysis 15.3), clinical failure (two trials, Analysis 15.5). In three trials comparing long and short durations of tetracycline, doxycycline and furazolidine respectively, there was a consistent reduction in the duration of pathogen excretion (MD 0.40 days, 95% CI 0.11 to 0.69, three trials, Analysis 15.4). There were also more bacteriological failures with shorter treatment (RR 1.53, 95% CI 1.01 to 2.32, Analysis 15.6), although the trials were generally at high risk of bias, and underpowered to detect these effects so provide only low quality evidence of this effect.

Section 4. Low versus high dose of treatment

The identified comparisons are detailed in Table 5. As antimicrobials and schedules were different, the studies could not be combined. No differences were detected in any trials for any comparisons, except for a comparison between single-dose doxycycline 200 mg versus 300 mg for adults (and 4 mg/kg versus 6 mg/kg for children). In this case, an advantage was found with the high dose for diarrhoea duration (two trials) and pathogen excretion duration (one trial, data not shown).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Azithromycin versus ciprofloxacin for treating cholera

Patient or population: Adults and children with cholera diarrhoea

Intervention: Azithromycin (single dose of 1 g or 20 mg/kg)
Comparison: Ciprofloxacin (single dose of 1 g or 20 mg/kg)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Ciprofloxacin	Azithromycin			
Diarrhoea duration	The mean duration of diarrhoea in the control groups ranged from **71.5 to 78 hours**	The mean duration of diarrhoea in the intervention groups was **32.43 hours shorter** (62.9 to 1.95 hours shorter)		375 (2 studies)	⊕⊕⊕◯ **moderate**[1,2,3,4]
Stool volume	The median volume across control groups was **322 mL/kg**	The corresponding volume with azithromycin would be **113 ml/kg** (90 to 142 mL/kg)	**ROM 0.35** (0.28 to 0.44)	195 (1 study)	⊕⊕◯◯ **low**[5,6,7]
Bacteriological failure	**492 per 1000**	**113 per 1000** (79 to 167 per 1000)	**RR 0.23** (0.16 to 0.34)	375 (2 studies)	⊕⊕◯◯ **low**[1,8,3,7]

*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; **ROM**: Ratio of means.

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

[1] Downgraded by one for serious risk of bias: the study showing the largest effects had baseline imbalances which would favour azithromycin and was sponsored by a pharmaceutical company. The second trial was open label.

[2] No serious inconsistency: statistical heterogeneity was high (I^2 = 97%), but both studies found effects in favour of azithromycin and the heterogeneity was in the size of this effect.

[3] No serious indirectness: one study was in children in India, one study was in adults in Bangladesh.

[4] No serious imprecision: both studies found effects that were statistically significant and clinically important.

[5] Downgraded by one for serious risk of bias: this single study had baseline imbalances which would favour azithromycin and was sponsored by a pharmaceutical company.

[6] Downgraded by one for serious indirectness: only a single trial on adults in India assessed this outcome.

[7] No serious imprecision: both limits of the 95% confidence intervals imply clinically important benefits.

[8] Downgraded by one for serious inconsistency: a large effect was seen in the trial from India at high risk of bias; in the second trial, very few episodes of treatment failure were recorded, with both drugs performing well.

Azithromycin versus erythromycin for treating cholera

Patient or population: Adults and children with cholera diarrhoea
Intervention: Azithromycin (20 mg/kg single dose, one trial; 10 mg/kg once daily for three days, one trial)
Comparison: Erythromycin (12.5 mg/kg four times daily for three days, both trials)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Erythromycin	Azithromycin			
Diarrhoea duration	The mean duration of diarrhoea in the control groups ranged from **33.5 to 42.0 hours**	The mean duration of diarrhoea in the intervention groups was **12.05 hours shorter** (22.02 to 2.08 hours shorter)		179 (2 studies)	⊕⊕⊕◯ **moderate**[1,2,3,4]
Stool volume	The median volume across control groups was **3.1 litres in adults or 186 mL/kg in children**	The corresponding volume with azithromycin would be **2.1 litres in adults** (1.7 to 2.6 litres), or **128 mL/kg in children** (104 to 158 mL/kg)	**ROM 0.69** (0.56 to 0.85)	172 (2 studies)	⊕⊕⊕◯ **moderate**[1,3,4,5]
Bacteriological failure	**126 per 1000**	**197 per 1000** (101 to 381 per 1000)	**RR 1.56** (0.80 to 3.02)	179 (2 studies)	⊕⊕◯◯ **low**[1,3,6]

*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; **ROM**: Ratio of means.

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

[1] Downgraded by one for serious risk of bias: one study had high loss to follow-up > 25% in both groups, and one was sponsored by the drug manufacturer.

[2] No serious inconsistency: statistical heterogeneity was high (I^2 = 70%), but both studies found effects in favour of azithromycin and the heterogeneity was only in the size of this effect.

[3] No serious indirectness: both studies were in children, with one study from India and one from Bangladesh.

[4] No serious imprecision: both trials found statistically significant effects.

[5] No serious inconsistency: statistical heterogeneity was low.

[6] Downgraded by one for serious imprecision: the 95% CI is wide and includes important differences between drugs.

Tetracycline versus doxycycline for treating cholera

Patient or population: Adults and children with cholera diarrhoea
Intervention: Tetracycline (four times daily for two to four days)
Comparison: Doxycycline (300 mg total dose given over one to three days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Doxycycline	Tetracycline			
Diarrhoea duration	The mean duration of diarrhoea in the control groups ranged from **15 to 32 hours**	The mean duration of diarrhoea in the intervention groups was **2.01 hours shorter** (8.21 hours shorter to 4.19 hours longer)		230 (3 studies)	⊕⊕⊕◯ **moderate**[1,2,3,4]
Stool volume	The median volume across control groups was**3 litres**	The corresponding volume with tetracycline would be **2.9 litres** (2.5 to 3.4 litres)	**ROM 0.97** (0.83 to 1.14)	336 (3 studies)	⊕⊕⊕◯ **moderate**[1,2,3,4]
Bacteriological failure	**153 per 1000**	**31 per 1000** (9 to 104 per 1000)	**RR 0.2** (0.06 to 0.68)	198 (2 studies)	⊕⊕⊕◯ **moderate**[5,6]

*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; **ROM**: Ratio of means.

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] No serious risk of bias: one trial was at low risk of selection bias and this study found no effect consistent with the other two trials.
[2] Downgraded by one for serious inconsistency: statistical heterogeneity is high ($I^2 = 66\%$), with one trial showing a benefit of six hours and two showing no effect.
[3] No serious indirectness: the studies were conducted in children and adults in India and Bangladesh. Of note is that tetracycline was only given for two days in two of these trials.
[4] No serious imprecision: the 95% CI probably excludes clinically important effects.
[5] No serious risk of bias: one study was at low risk of selection bias and one was at unclear risk.
[6] Downgraded by one for serious imprecision: the number of events is very low and underpowered to have confidence in this result.

Tetracycline versus quinolones for treating cholera

Patient or population: Adults and children with cholera diarrhoea
Intervention: Tetracycline (500 mg four times daily for three days)
Comparison: Quinolone (Ciprofloxacin 1 g single dose or 250 mg once daily for three days, or norfloxacin 400 mg twice daily for three days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Quinolone	Tetracycline			
Diarrhoea duration	The mean duration of diarrhoea in the control groups ranged from **30 to 51 hours**	The mean duration of diarrhoea in the intervention groups was **0.91 hours shorter** (4.53 hours shorter to 2.72 hours longer)		259 (3 studies)	⊕⊕⊕◯ **moderate**[1,2,3,4]
Stool volume	The median volume across control groups was **215 mL/kg**	The corresponding volume with tetracycline would be **187 ml/kg** (161 to 219 mL/kg)	**ROM 0.87** (0.75 to 1.02)	236 (2 studies)	⊕⊕◯◯ **low**[1,2,5]
Bacteriological failure	**9 per 1000**	**9 per 1000** (1 to 59 per 1000)	**RR 0.99** (0.14 to 6.82)	234 (2 studies)	⊕⊕◯◯ **low**[1,2,6]

*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; **ROM**: Ratio of means.

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

[1] Downgraded by one for serious risk of bias: only one trial was at low risk of selection bias; this study found no significant effect consistent with the other two trials.
[2] No serious inconsistency: statistical heterogeneity is low (I^2 = 0%).
[3] No serious indirectness: the studies were conducted in children and adults in Bangladesh, Peru and Thailand. The most recent trial was conducted in 1996.
[4] No serious imprecision: the 95% CI probably excludes clinically important effects.
[5] Downgraded by one for serious imprecision: the 95% CI includes both clinically important effects and no difference.
[6] Downgraded by one for serious imprecision: the number of events is very low and underpowered to have confidence in this result.

Doxycycline versus quinolones for treating cholera

Patient or population: Adults and children with cholera diarrhoea
Intervention: Doxycycline (300 mg single dose or 100 mg twice daily for three days)
Comparison: Quinolones (Ciprofloxacin 1 g single dose or norfloxacin 800 mg single dose or norfloxacin 400 mg BD for three days)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Quinolones	Doxycycline			
Diarrhoea duration	The mean duration of diarrhoea in the control groups ranged from **35 to 60 hours**	The mean diarrhoea duration in the intervention groups was **4.64 hours longer** (2.14 hours shorter to 11.42 hours longer)		126 (3 studies)	⊕⊕◯◯ **low**[1,2,3,4]
Stool volume	The median volume across control groups was **148 mL/kg**	The corresponding volume with doxycycline would be **149 mL/kg** (121 to 185 mL/kg)	**ROM 1.01** (0.82 to 1.25)	435 (4 studies)	⊕⊕◯◯ **low**[5,3,6]
Bacteriological failure	**32 per 1000**	**188 per 1000** (87 to 408 per 1000)	**RR 5.84** (2.7 to 12.65)	386 (4 studies)	⊕⊕◯◯ **low**[5,3,6]

*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; **ROM**: Ratio of means.

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

[1] Downgraded by one for serious risk of bias: none of the trials concealed allocation adequately enough to be at low risk of selection bias.
[2] No serious inconsistency: statistical heterogeneity is low ($I^2 = 31\%$).
[3] No serious indirectness: the studies were conducted in children and adults in Bangladesh, Turkey and India. The most recent trial was conducted in 1994.
[4] Downgraded by one for serious imprecision: all three trials are small and the overall 95% CI includes a mean difference of almost half a day.
[5] Downgraded by one for serious risk of bias: only one of the trials concealed allocation adequately enough to be at low risk of selection bias.
[6] Downgraded by one for serious imprecision: the 95% CI includes clinically important benefits and harms.

Short compared to Long duration of antimicrobials for cholera

Patient or population: Adults and children with cholera diarrhoea
Intervention: Short duration of treatment
Comparison: Long duration of treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Long duration	Short duration			
Diarrhoea duration	-	-	**MD 0.34** (-4.65 to 5.32)	431 (7 studies)	⊕⊕◯◯ **low**[1,2]
Stool Volume	-	-	**ROM 1.05** (0.94 to 1.18)	496 (8 studies)	⊕⊕◯◯ **low**[1,2]
Bacteriological failure	**93 per 1000**	**142 per 1000** (94 to 216)	**RR 1.53** (1.01 to 2.32)	672 (9 studies)	⊕⊕◯◯ **low**[1,3]

*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; **ROM**: Ratio of means.

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

[1] Downgraded by one for serious risk of bias: Only one trial adequately described a method of allocation concealment to prevent the risk of selection bias.

[2] Downgraded by one for serious inconsistency: Statistically significant benefits were seen in one trial comparing Norfloxacin 400 mg twice daily for three days with 800 mg once only. Other comparisons did not find statistically significant differences.

[3] Downgraded by 1 for serious imprecision: The number of events in these trials was very low and the trials were underpowered to detect differences. Although the meta-analysis result is statistically significant, the 95% CI is wide and includes clinically important effects and unimportant effects.

DISCUSSION

Summary of main results

Overall, antimicrobial therapy shortened the mean duration of diarrhoea by about a day and a half compared to placebo or no treatment (*moderate quality evidence*). It also reduced the total stool volume by 50% (*moderate quality evidence*) and reduced the amount of rehydration fluids required by 40% (*moderate quality evidence*). In addition, antimicrobial therapy reduced the mean duration of fecal excretion of vibrios by almost three days (*moderate quality evidence*). In the presence of adequate supportive care, no deaths were reported in all trials.

There was significant heterogeneity in the magnitude of these benefits, however, attributed to the effect of three main variables. These variables are: 1) allocation concealment, with trials at low risk of selection bias having smaller effects; 2) time point for outcome assessment, with trials with longer intervals between assessments demonstrating greater effects; and 3) the type of antimicrobial, with tetracycline appearing to have larger biological effects than other antibiotics.

The analysis of different antimicrobials included many comparisons (Figure 3).Tetracycline was the antibiotic most commonly compared to placebo/no treatment, and in indirect comparisons appeared to have larger effects compared to placebo than other antibiotics. However, in head-to-head comparisons tetracycline did not demonstrate significant benefits on either diarrhoea duration or stool volume compared to doxycycline (*low quality evidence*), or ciprofloxacin or norfloxacin (*moderate quality evidence*). Azithromycin has not been compared directly to placebo or tetracycline. However, single dose azithromycin shortened the duration of diarrhoea by over a day compared to ciprofloxacin (*moderate quality evidence*) and by half a day compared to erythromycin (*moderate quality evidence*). Quinolones in general were not more effective than other antibiotics.

When evaluating duration of treatment, long duration (> 24 hours) reduced the duration of pathogen secretion, and reduced rates of bacteriological failure (*low quality evidence*), but for clinical outcomes short and long treatment duration did not differ significantly.

Overall completeness and applicability of evidence

The above benefits of antibiotics should be considered valid when treating people infected with *V. cholera* strains that are susceptible to the antibiotics used, as was the case in these primary studies. The majority of included trials are now over 20 years old, and bacterial susceptibility is dynamic and may increase or decrease over time dependant on factors such as antibiotic consumption and the emergence of new serotypes. Therefore, some of the included antibiotics may not currently be relevant, due to resistance, but may become relevant again in the future if reversal of resistance occurs, as has been described for tetracycline (Faruque 2007). In the ongoing outbreak in Mexico for example, the *V. cholera* strain has reduced susceptibility to quinolones and is resistant to TMP-SMX, but is susceptible to tetracycline and chloramphenicol (WHO 2013).

Currently, the WHO recommends antimicrobial treatment only for patients with severe dehydration (WHO 2004), and most trials (70%) included in our review mandated some measure of severity at baseline. However, the percentage of patients with severe dehydration at baseline (when reported) ranged between 0% and 100%, and our sub-group analysis at the trial level found similar or larger effects in those trials recruiting patients with a mixed severity of dehydration. This suggests that the benefits of antibiotics extends to patients without severe dehydration.

Stratifying analyses by age revealed no differences in effects between children and adults. However, only a few trials included just children and thus the current evidence applies mostly to adults. The trials included mostly male participants for technical reasons (stool collection). Although the evidence resulting from these trials directly applies to male patients, we cannot think of any biological reason why antimicrobial therapy should have different effects in males and females.

The effect of antimicrobial treatment on resistance development was not assessed in these studies. In any case, randomized controlled trials are probably not the optimal platform to examine resistance development in cholera.

Quality of the evidence

Risk of bias relating to allocation concealment affected the magnitude of effect in comparisons between antimicrobials and placebo/no treatment, with the benefits of antimicrobials exaggerated in trials at high risk for bias. We downgraded the quality of evidence for this comparison based on limitations in the designs for these trials. However, a highly significant benefit was observed in the subgroup of trials at low risk for bias regarding allocation concealment for all outcomes, thus our GRADE classifications were conservative. We did not conduct sensitivity analyses for other methodological limitations of the studies, such as blinding, because the objectively-assessed outcomes included in our review are relatively resistant to bias once the patient is allocated to one of the study arms (Wood 2008).

Potential biases in the review process

Many trials did not report *V. cholerae* susceptibility to the antibiotics being tested. Where reported, resistance rates were low; in rare cases, where *V. cholerae* isolates were resistant to the tested

antibiotic, we excluded this arm. Our assumption is that, at the time of the trial, resistance to the tested antibiotics was low.

The outcomes of stool volume and requirements for rehydration fluids were reported in different units of measurement in the studies included in our review: either total amount in litres or in mL/kg bodyweight. Although the latter is the more appropriate way of presenting these outcomes, only few trials reported weight-adjusted results. For both outcomes, the distribution of data was skewed. Meta-analysis of the (log) ratio of means (or imputed means) served us well in overcoming some of the problems of summarizing non-normally distributed continuous data. It has been shown empirically that ratio of means meta-analysis produces treatment effects similar to difference-based methods (Friedrich 2011). While these results should be viewed with caution, we believe they are more informative than merely describing the outcomes of individual trials.

We performed several indirect comparisons to complement direct randomized comparisons, which were usually based on few trials. Indirect comparisons are non-randomized and compare antibiotics used in different settings and circumstances, and thus should be viewed with caution.

Agreements and disagreements with other studies or reviews

It is generally agreed that antimicrobial therapy helps shorten the duration of disease and should thus be used. In their review, Sack 2004 estimated that a one to three day course of antimicrobials shortens recovery time from four to five days to two to three days. Ours is the first systematic review to provide absolute figures for this and other outcomes. This quantification can assist health officials in policy decisions and help develop transmission models for cholera epidemics, such as the ones proposed for the epidemic in Haiti (Andrews 2011; Tuite 2011).

Tetracycline and azithromycin appear to have advantages over other antibiotics and a possible explanation for this could be their mechanism of action. Both of these antimicrobials inhibit protein synthesis and so may directly inhibit the synthesis of the protein enterotoxin responsible for cholera symptoms.

AUTHORS' CONCLUSIONS

Implications for practice

The current evidence supports the use of antibiotics to reduce the duration and severity of cholera, and to reduce the duration of pathogen excretion. The benefits shown in this review are relevant to the treatment of individual patients, but they may also extend to other patients by curtailing pathogen excretion and so interrupting transmission during epidemics.

While patients with severe dehydration are most at risk of death, the benefits of antibiotics probably extend to those with less severe degrees of dehydration. Treatment of these groups during epidemics may also help to ease pressure on health services and decrease transmission.

The choice of antibiotic will depend on the drug susceptibility of the epidemic strain, but the evidence supports the use of tetracycline or azithromycin when isolates are susceptible to these antibiotics.

Implications for research

Trials assessing the efficacy of antimicrobial treatment among cholera patients with mild or no dehydration are needed. These and other studies (randomized or observational) should attempt to examine the effects of antimicrobial treatment on the spread of cholera and on outbreak containment. Since resistance of *V. cholerae* to antimicrobials is an issue of great importance and rising concern, future trials should monitor and report on resistance development in persisting isolates and on baseline resistance profiles throughout the duration of the trial. In this review, we have shown the effect of bias in randomized controlled trials on results. Future trials should adhere to low-risk allocation concealment methods for randomization and include women as well as men.

A trial comparing azithromycin with tetracycline, both given for the same effective duration (eg single dose azithromycin versus three to four days of tetracycline) would be interesting, since azithromycin has so far only been compared with erythromycin and ciprofloxacin given for shorter durations.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Alam 1990 BGD

Methods	Randomized controlled trial. Follow up duration: until faecal cultures were negative for two consecutive days
Participants	Location: Dhaka, Bangaladesh. Years: 1986 to 1987. Participants: age > 15 yrs; 40% females. Number of participants: 261 randomized, 246 evaluated. Cholera serogroup: O1 (biotype: El-tor, classical). Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: 500 mg four times per day for 2 days. PO Doxycycline: 300 mg single dose. PO Doxycycline: 200 mg single dose. Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in hours (defined as: duration of diarrhoea from entry to study until 8 hours have passed since last watery stool) Stool volume in mL/kg body weight (defined as: volume of diarrhoea from entry to study until last watery stool) Bacteriological failure (defined as: number of patients with *V. cholerae* in stool on day 3 of study).
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, glucose ORS.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Number code kept in WHO headquarters in Geneva (thus assumed code is random)
Allocation concealment (selection bias)	Low risk	Sealed numbered envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	Only 15 out of 261 patients were not evaluated, reasons were not specified

Alam 1990 BGD (*Continued*)

Incomplete outcome data (attrition bias) Stool volume	Low risk	Only 15 out of 261 patients were not evaluated, reasons were not specified
Selective reporting (reporting bias)	High risk	Study outcomes were not specified at all in the methods section
Other bias	Unclear risk	Study sponsor: academic. Drugs provided by Pfizer.

Bhattacharya 1990 IND

Methods	Randomized controlled trial. Follow up duration: not specified, probably while in hospital
Participants	Location: Kolkata, India. Years: not specified. Participants: age > 18 yrs. No females participated. Number of participants: 78 randomized, 37 evaluated. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Norfloxacin: 400 mg twice per day for 5 days. PO TMP-SMX: (Trimetoprim: 160 mg; Sulfamethoxazol: 800 mg) twice per day for 5 days PO Placebo: 1 Tab. twice per day for 5 days. Resistance to intervention: 100% resistance to TMP-SMX, 0% resistance to Norfloxacin
Outcomes	Diarrhoea duration in hours (definition not specified). Total stool volume in litres (definition not specified in study) Deaths (definition not specified in study, probably while in hospital) Bacteriological failure (defined as: number of patients with *V. cholerae* in stool on day 3 of study).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS according to WHO recommendations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.

Bhattacharya 1990 IND (*Continued*)

Allocation concealment (selection bias)	Low risk	Identical pills coded according to a code that was opened after completion of the study
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	Approximately 50% of the patients in each group were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	High risk	Approximately 50% of the patients in each group were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	High risk	Study sponsor: academic, Ranbaxy Laboratories Ltd.

Bhattacharya 2003 IND

Methods	Randomized controlled trial. Follow up duration: not specified, probably while in hospital
Participants	Location: Kolkata, India. Years: 2000 to 2002. Participants: children. No females participated. Number of participants: 80 randomized, 56 evaluated. Cholera serogroup: O1, O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Azithromycin: 10 mg/kg once per day for 3 days; PO placebo matching Erythromycin PO Erythromycin: 12.5 mg/kg four times per day for 3 days; PO placebo matching Azithromycin Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in hours (definition not specified). Total stool volume in litres (definition not specified in study) Deaths (full recovery stated for all study participants). Bacteriological failure (all patients stopped secreting vibrios in stool within first day of treatment)
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS according to WHO recommenda-

Bhattacharya 2003 IND (*Continued*)

	tions	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table (using block randomizations of various block lengths)
Allocation concealment (selection bias)	Low risk	Sealed numbered envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind.
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	11 out of 40 in the azithromycin group and 13 out of 40 in the erythromycin group were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	High risk	11 out of 40 in the azithromycin group and 13 out of 40 in the erythromycin group were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Low risk	Study outcomes were clearly specified and reported.
Other bias	Unclear risk	Sponsor not stated.

Burans 1989 SOM

Methods	Randomized controlled trial. Follow up duration: not specified, while in hospital.
Participants	Location: Mogadishu, Somalia. Years: not specified. Participants: children and adults. Female participation not specified Number of participants: 47 randomized, 47 evaluated. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Erythromycin: adults 800 mg; children 20 mg/kg twice per day until discharge PO TMP-SMX: (adults: Trimetoprim 160 mg, Sulfametoxazol 800 mg; children: Trimetoprim 4 mg/kg; Sulfametoxazol 20 mg/kg) twice per day until discharge PO Dextrose (as placebo): twice per day until discharge. Resistance to intervention: 2% resistance to TMP-SMX, 0% resistance to Erythromycin

Burans 1989 SOM (*Continued*)

Outcomes	Diarrhoea duration in days (definition not specified). Bacteriological failure (no. of patients with stool free of vibrios after 24, 48, and 72 hours)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Placebo was used, but it was cherry flavoured.
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	All patients randomized to each group were evaluated.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Low risk	Study sponsor: academic.

Butler 1993 Multi-Center

Methods	Randomized controlled trial. Follow up duration: 5 days.
Participants	Location: multicenter (Thailand, Indonesia, Ivory coast, Mexico, Israel, Italy) Years: 1987 to 1989. Participants: adults. Female participation not specified. Number of participants: 508 randomized, 46 evaluated. Cholera serogroup: not specified. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: yes.
Interventions	PO Fleroxacin: 400 mg once per day for 3 days. PO Fleroxacin: 400 mg single dose; PO placebo once per day for the next two days PO Placebo: once per day for 3 days.

Butler 1993 Multi-Center (*Continued)*

	Resistance to intervention: no resistance.
Outcomes	Clinical failure (defined as: continuation of diarrhoea over 48 hours since beginning of treatment) Bacteriological failure (defined as: stool culture positive for *V. cholerae* on day 3 of study) .
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers generated by a computer.
Allocation concealment (selection bias)	Low risk	Number code was not revealed to investigators until the study ended
Blinding (performance bias and detection bias) All outcomes	Low risk	Doubel blind. All patients received identical looking pills, in the same amount
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Unclear risk	Study sponsor: manufacturer of Fleroxacin.

Carpenter 1964 IND

Methods	Quasi-randomized controlled trial. Follow up duration: at least 7 days.
Participants	Location: Kolkata, India. Years: 1963. Participants: adults. No females participated. Number of participants: 20 randomized, 20 evaluated. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: not specified. Exclusion due to severity of symptoms: no.

Carpenter 1964 IND (*Continued*)

Interventions	IV Tetracycline: 100 mg four times per day for the first day. PO Tetracycline: 500 mg four times per day for 3 days No treatment. Resistance to intervention: not specified.
Outcomes	Total stool volume in litres (definition not specified in study) Deaths (defined as number of deaths during follow up, information obtained from correspondence with the author) Pathogen secretion duration in days (defined as number of days with a positive culture for *V. cholerae*). Clinical failure (defined as number of patients with stool volume > 3450 mL/day after 72 hours of treatment) Bacteriological failure (defined as: stool culture positive for *V. cholerae* after 48 and 72 hours of treatment).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, water, barley water

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	The first patient to arrive received no antibiotics and the second received Tetracycline
Allocation concealment (selection bias)	High risk	Patients received treatment according to time of arrival at the hospital
Blinding (performance bias and detection bias) All outcomes	High risk	Control arm received no treatment.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Stool volume	Low risk	All randomized patients were evaluated.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Low risk	Study sponsor: academic.

Chaud 1968 IND

Methods	Randomized controlled trial. Follow up duration: while in hospital, average of 7 days.
Participants	Location: Kolkata, India. Years: not specified. Participants: adults. No females participated. Number of participants: 72 randomized, 72 evaluated. Stool positive for *V. cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: not specified. Exclusion due to severity of symptoms: no.
Interventions	PO Forazolidone: 100 mg four times per day for 3 days. PO Forazolidone: 400 mg once per day for 3 days. PO Tetracycline: 250 mg four times per day for 3 days. Resistance to intervention: not specified.
Outcomes	Deaths (full recovery stated for all study participants). Bacteriological failure (defined as: vibrios in stool after 48 hours from beginning of treatment) Bacteriological relapse (defined as: positive rectal swab after a negative one)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Low risk	Study sponsor: academic.

De 1976 IND

Methods	Randomized controlled trial. Follow up duration: not specified, probably while in hospital
Participants	Location: Kolkata, India. Years: 1975. Participants: children and adults. No females participated. Number of participants: number randomized not specified, 76 evaluated Cholera serogroup: not specified. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Doxycycline: adults 200 mg single dose first day, 100 mg single dose second day; children 4 mg/kg single dose first day, 2 mg/kg single dose second day PO Doxycycline: adults 200 mg single dose; children 4 mg/kg single dose PO Doxycycline: adults 300 mg single dose; children 6 mg/kg single dose PO Tetracycline: adults 500 mg four times per day; children 250 mg four times per day for 2 days Resistance to intervention: not specified.
Outcomes	Diarrhoea duration in hours (defined as: time until the appearance of semisolid stools) Total fluid output in litres (definition not specified in study) Deaths (during follow up). Pathogen secretion duration in hours (definition not specified in study) Bacteriological failure (defined as: vibrios in stool after 48 hours from beginning of treatment)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, plain water.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Number of patients randomized was not specified.

De 1976 IND (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Unclear risk	Study sponsor: academic, WHO, Pfizer supplied the Doxycycline

Dutta 1996 IND

Methods	Randomized controlled trial. Follow up duration: 5 days.
Participants	Location: Kolkata, India. Years: 1993 to 1994. Participants: adults. No females participated. Number of participants: 160 randomized, 111 evaluated. Cholera serogroup: O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Doxycycline: 300 mg single dose. PO Norfloxacin: 400 mg twice per day for 3 days. PO Norfloxacin: 800 mg single dose. No treatment. Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in hours (defined as: time until passage of last unformed stool) Total fluid output in litres (definition not specified in study) Deaths (during follow up). Bacteriological failure (defined as: continued excretion of *V. cholerae* O139 in stool at day 3).
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS according to WHO recommendations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts. Outcome assessor was blinded

Dutta 1996 IND (*Continued*)

Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	11 to 14 patients out of 40 in each group were not evaluated for the outcome, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	High risk	11 to 14 patients out of 40 in each group were not evaluated for the outcome, reasons were not specified
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Unclear risk	Study sponsor: academic.

Francis 1971 NGA

Methods	Randomized controlled trial. Follow up duration: 23 days.
Participants	Location: Ibadan, Nigeria. Years: not specified. Participants: age > 10 years. Female participation not specified Number of participants: number randomized not specified, 65 evaluated. Stool positive for *V. cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Fanasil: 2 g single dose. Followed by PO Dextrose (as placebo) twice per day for 3 days PO Tetracyclime: 500 mg four times per day for 3 days. PO TMP-SMX: (Trimetoprim 160 mg, Sulfametoxazol 900 mg) bid for 3 days PO Dextrose (as placebo) bid for 3 days. Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in days (defined as: number of days until the patients ceased to pass more than 2 stools per day) Pathogen secretion duration in days (definition not specified in study) Clinical failure (defined as: more than 2 stools per day on day 2 or 3 of the study) Bacteriological failure (defined as: continued excretion of *V. cholerae* in stool at day 2 or 3 of study).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, ORS type not specified Early stop: Placebo and Fanasil arms were stopped early.
Risk of bias	

Francis 1971 NGA (*Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding broken, two arms were stopped early.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	High risk	Study outcomes were not specified at all in the methods section
Other bias	Low risk	Study sponsor: academic.

Gharagozoloo 1970 IRN

Methods	Randomized controlled trial. Follow up duration: until faecal cultures were negative for three consecutive days
Participants	Location: Teheran, Iran. Years: not specified. Participants: children and adults. Female participation not specified Number of participants: number randomized not specified, 42 evaluated Cholera serogroup: O1. Exclusion due to previous use of antibiotics: not specified. Exclusion due to severity of symptoms: not specified.
Interventions	PO Chloramphenicol: 12.5 mg/kg (maximal dose 500 mg) four times per day for a minimum of 3 days (or until stool culture negative) PO Tetracycline: 10 mg/kg (maximal dose 500 mg) four times per day for a minimum of 3 days (or until stool culture negative) PO TMP-SMX: (Trimetoprim 5 mg/kg maximal dose 195 mg, Sulfametoxazol 25 mg/kg maximal dose 800 mg) bid for a minimum of 3 days (or until stool culture negative) PO Dextrose (as placebo): twice per day for a minimum of 3 days (or until stool culture negative) Resistance to intervention: not specified.
Outcomes	Bacteriological failure (defined as: stool positive for *V. cholerae* after day 2 of study). Bacteriological relapse (defined as: re-appearance of *V. cholerae* in stool after initial eradication).

Gharagozoloo 1970 IRN (*Continued*)

Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, ORS type not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Low risk	Study sponsor: academic.

Gotuzzo 1995 PER

Methods	Randomized controlled trial. Follow up duration: 4 days.
Participants	Location: Lima, Peru. Years: 1992 to 1993. Participants: adults aged 18 to 65 years; 35% females. Number of participants: 214 randomized, 202 evaluated. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Ciprofloxacin: 250 mg once per day for 3 days. PO placebo matching Tetracycline PO Tetracycline: 500 mg four times per day for 3 days. PO placebo matching Ciprofloxacin Resistance to intervention: no resistance.

Gotuzzo 1995 PER (*Continued*)

Outcomes	Diarrhoea duration in hours (defined as: time from initial administration of study drug to the last liquid stool passed) Stool volume in mL/kg (definition not specified in study). Clinical failure (defined as: diarrhoea on day 2 or 3 of study) Bacteriological failure (defined as: stool positive for *V. cholerae* after day 3 of study).
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS according to the WHO recommendations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random table with fixed blocks of ten.
Allocation concealment (selection bias)	Low risk	Envelopes labelled only with study number.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	Only 7 out of 107 in the ciprofloxacin group and 5 out of 107 in the tetracycline group were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	Low risk	Only 7 out of 107 in the ciprofloxacin group and 5 out of 107 in the tetracycline group were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	High risk	Study sponsor: Bayer.

Grados 1996 PER

Methods	Randomized controlled trial. Follow up duration: 5 days.
Participants	Location: Lima, Peru. Years: 1993. Participants: age > 15 years; 32% females. Number of participants: number randomized not specified, 107 evaluated. Stool positive

Grados 1996 PER (*Continued*)

	for *V. cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO TMP-SMX: (Trimetoprim 160 mg, Sulfametoxazol 800 mg) twice per day for 3 days PO Tetracycline: 500 mg four times per day for 3 days. Resistance to intervention: 7% resistance to tetracycline.
Outcomes	Diarrhoea duration in hours (defined as: time from initial administration of study drug until stool output < 400 mL/hour) Clinical failure (defined as: diarrhoea output above 400 mL/hour until discharged) Bacteriological failure (defined as: stool positive for *V. cholerae* 48 hours after completing treatment).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS type not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Number of patients randomized was not specified.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Low risk	Study sponsor: academic.

Hossain 2002 BGD

Methods	Randomized controlled trial. Follow up duration: until faecal cultures were negative for two consecutive days
Participants	Location: Dhaka, Bangladesh. Years: 1993. Participants: adults. No females participated. Number of participants: 50 randomized, 43 evaluated. Stool positive for *V. cholerae* required for inclusion. Cholera serogroup: O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: 500 mg four times per day for 3 days. PO placebo: four times per day for 3 days. Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in hours (defined as: time from initial administration of study drug until the end of the last 8-hour period when a liquid stool has been passed) Stool volume in mL/kg (defined as: volume of stool in the 72 hours following the first administration of study drug) Pathogen secretion duration in days (definition not specified in study) Clinical failure (defined as: continuation of diarrhoea after 72 hours from initiation of study drug) Bacteriological failure (defined as: *V. cholerae* in stool after 72 hours from initiation of study drug). Clinical relapse (defined as: initial resolution of diarrhoea followed by passage of liquid stool anytime during the study) Bacteriological relapse (defined as: a positive culture following a negative stool sample that was obtained 72 hours after initiation of study drug)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, rice-based ORS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated number list.
Allocation concealment (selection bias)	Low risk	Randomization list kept with a researcher not involved in the study, pharmacist supplied drug by number
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.

Hossain 2002 BGD (*Continued*)

Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	4 out of 25 patients in the tetracycline group and 3 out of 25 in the placebo group were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	High risk	4 out of 25 patients in the tetracycline group and 3 out of 25 in the placebo group were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Low risk	Study outcomes were clearly specified and reported.
Other bias	Low risk	Study sponsor: academic.

Islam 1987 BGD

Methods	Randomized controlled trial. Follow up duration: not specified.
Participants	Location: Dhaka, Bangladesh. Years: not specified. Participants: adults; 46% females. Number of participants: 125 randomized, 118 evaluated. Stool positive for *V. cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: 1 g single dose. PO Tetracycline: 2 g single dose. PO Tetracycline: 500 mg four times per day for 1 day. No treatment. Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in hours (defined as: time until the end of the last 8 hour period in which liquid stool was passed) Stool volume in mL/kg (definition not specified in study). Pathogen secretion duration in days (definition not specified in study) Bacteriological failure (defined as: *V. cholerae* in stool after 48 or 72 hours). Clinical relapse (defined as: the return of liquid stool after passing solid stool) Bacteriological relapse (defined as: a patient who became bacteriologically negative for at least two consecutive days and was subsequently positive for *V. cholerae*).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS type not specified

Islam 1987 BGD (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	Notes drawn from an envelope, not stated whether sealed and opaque
Blinding (performance bias and detection bias) All outcomes	High risk	Control arm was given no treatment.
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	Only 5 out of 50 in the SD1 group and 2 out of 25 in the SD2 group were not evaluated, all patients in the tetracycline and control group were evaluated. Reasons for inclusion were not specified
Incomplete outcome data (attrition bias) Stool volume	Low risk	Only 5 out of 50 in the SD1 group and 2 out of 25 in the SD2 group were not evaluated, all patients in the tetracycline and control group were evaluated. Reasons for inclusion were not specified
Selective reporting (reporting bias)	High risk	Study outcomes were not specified at all in the methods section
Other bias	Low risk	Study sponsor: academic.

Kabir 1996 BGD

Methods	Randomized controlled trial. Follow up duration: 5 days minimum.
Participants	Location: Dhaka, Bangladesh. Years: 1991 to 1992. Participants: children aged 1 to 8 years. No females participated Number of participants: 54 randomized, 48 evaluated. Stool positive for *V. cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Erythromycin: 12.5 mg/kg four times per day for 5 days. PO TMP-SMX: (Trimetoprim 5 mg/kg, Sulfametoxazol 25 mg/kg) twice per day for 5 days

Kabir 1996 BGD (*Continued*)

	No treatment. Resistance to intervention: 23% resistance to Erythromycin and TMP-SMX
Outcomes	Diarrhoea duration in hours (defined as: time until the end of the last 8 hour period in which liquid stool was passed) Stool volume in mL/kg (definition not specified in study). Clinical failure (defined as: duration of diarrhoea which exceeded 72 hours) Bacteriological failure (defined as: *V. cholerae* in stool after day 3 of study).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, rice-based ORS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing the treatment code.
Blinding (performance bias and detection bias) All outcomes	High risk	Control arm was given no treatment.
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	6 out of 54 patients randomized were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	High risk	6 out of 54 patients randomized were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Low risk	Study sponsor: academic.

Karchmer 1970 PAK

Methods	Quasi-randomized controlled trial. Follow up duration: 14 days.
Participants	Location: Dacca, Pakistan. Years: 1966. Participants: children; 51% females. Number of participants: number randomized not specified, 78 evaluated Cholera serogroup: O1. Exclusion due to previous use of antibiotics: not specified.

Karchmer 1970 PAK (*Continued*)

	Exclusion due to severity of symptoms: not specified.
Interventions	PO Furazolidone: 1.25 mg/kg four times per day for 7 days. PO Tetracycline: 2.5 mg/kg four times per day for 7 days. PO Tetracycline: 7.75 to 15.25 mg/kg four times per day for 7 days No treatment. Resistance to intervention: not specified.
Outcomes	Diarrhoea duration in 8 hour periods (defined as: time until the end of the last 8 hour period in which liquid stool was passed) Stool volume in litres (definition not specified in study). Pathogen secretion duration in days (definition not specified in study)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration only.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	According to day of admission.
Allocation concealment (selection bias)	High risk	Treatment allocated by day of week.
Blinding (performance bias and detection bias) All outcomes	High risk	Control arm was given no treatment.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Number of patients randomized was not specified.
Selective reporting (reporting bias)	High risk	Study outcomes were not specified at all in the methods section
Other bias	Low risk	Study sponsor: academic.

Kaushik 2010 IND

Methods	Randomized controlled trial. Follow up duration: 7 days.
Participants	Location: Delhi, India. Years: 2006 to 2007. Participants: Children aged 2 to 12 years; 43% female. Number of participants: 407 randomized, 180 evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: not specified. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: yes.
Interventions	PO Azithromycin: 20 mg/kg single dose. PO Ciprofloxacin: 20 mg/kg single dose. Resistance to intervention: 0.6% resistance to Ciprofloxacin. Resistance to Azithromycin not specified
Outcomes	Diarrhoea duration hours (defined as: time from entry to study until resolution of diarrhoea) Pathogen secretion duration in hours (definition not specified in study) Clinical failure (defined as: continuation of diarrhoea after 72 hours from the beginning of therapy) Bacteriological failure (defined as: *V. cholerae* in stool on day 3 of the study). Clinical relapse (defined as: cessation of diarrhoea for one day or longer, followed by the return of diarrhoea) Bacteriological relapse (defined as: positive stool culture following a negative one)
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS (type unspecified)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Identical sealed envelopes, opened only after enrolment.
Blinding (performance bias and detection bias) All outcomes	High risk	Different pills, both given single dose
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	114 out of 205 in the azithromycin group and 113 out of 202 in the ciprofloxacin group were not evaluated, reasons were not specified

Kaushik 2010 IND (*Continued*)

Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Low risk	No sponsor.

Khan 1995a BGD

Methods	Randomized controlled trial. Follow up duration: 3 days.
Participants	Location: Dhaka, Bangladesh. Years: not specified. Participants: adults. No females participated. Number of participants: 64 randomized, 63 evaluated. Cholera serogroup: O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: 500 mg four times per day for 3 days. PO Erythromycin: 500 mg four times per day for 3 days. PO Ciprofloxacin: 1 g single dose. PO Doxycycline: 300 mg single dose. Resistance to intervention: not specified.
Outcomes	Diarrhoea duration in hours (defined as: time from administration of study drug until the end of the last 8 hour period in which liquid stool was passed) Stool volume in mL/kg (definition not specified in study).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS type not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts.

Khan 1995a BGD (*Continued*)

Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	All patients, with the exception of 1 out of 16 in the erythromycin group, were evaluated
Incomplete outcome data (attrition bias) Stool volume	Low risk	All patients, with the exception of 1 out of 16 in the erythromycin group, were evaluated
Selective reporting (reporting bias)	High risk	Study outcomes were not specified at all in the methods section
Other bias	Low risk	Study sponsor: academic.

Khan 1995b BGD

Methods	Randomized controlled trial. Follow up duration: 3 to 5 days.
Participants	Location: Dhaka, Bangladesh. Years: 1992. Participants: adults. No females participated. Number of participants: 75 randomized, 72 evaluated. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Ciproflixacin: 500 mg twice per day for 3 days. PO Erythromycin: 500 mg four times per day for 3 days. PO Nalidixic acid: 500 mg four times per day for 3 days. PO Pivmecillinam: 400 mg four times per day for 3 days. PO Tetracycline: 500 mg four times per day for 3 days. Resistance to intervention: 75% resistance to Tetracycline in all arms; 100% resistance to Tetracycline in the Tetracycline arm
Outcomes	Stool volume in mL/kg (definition not specified in study). Clinical failure (defined as: continuation of diarrhoea after 72 hours of treatment) Bacteriological failure (defined as: *V. cholerae* in stool after day 2 or 3 of study).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS type not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomized method with a block size of 10.

Khan 1995b BGD (*Continued*)

Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Stool volume	Low risk	All patients, with the exception of 3 out of 15 in the tetracycline group, were evaluated
Selective reporting (reporting bias)	High risk	Study outcomes were not specified at all in the methods section
Other bias	Low risk	Study sponsor: academic.

Khan 1996 BGD

Methods	Randomized controlled trial. Follow up duration: 12 days.
Participants	Location: Dhaka and rural Matlab district, Bangladesh. Years: 1993 to 1995. Participants: adults. No females participated. Number of participants: 272 randomized, 260 evaluated. Cholera serogroup: O1, O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	O1 group: PO Ciproflixacin: 1 g single dose. PO placebo matching Doxycycline PO Doxycycline: 300 mg single dose. PO placebo matching Ciproflixacin O139 group: PO Ciproflixacin: 1 g single dose. PO placebo matching Doxycycline PO Doxycycline: 300 mg single dose. PO placebo matching Ciproflixacin Resistance to intervention: one O1 strain isolated which was resistant to Doxycycline
Outcomes	Stool volume in mL/kg (definition not specified in study). Clinical failure (defined as: continuation of diarrhoea after 48 or 72 hours of treatment) Bacteriological failure (defined as: *V. cholerae* in stool after day 2 or 3 of study).
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS type not specified
Risk of bias	

Khan 1996 BGD (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated list, randomization blocks of 10.
Allocation concealment (selection bias)	Low risk	Patients were consecutively assigned numbers, perilously allocated to treatment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	Only 12 out of 272 were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	Low risk	Only 12 out of 272 were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Low risk	Study outcomes were clearly specified and reported.
Other bias	High risk	Study sponsor: academic, Bayer, Pfizer supplied drugs.

Khan 2002 BGD

Methods	Randomized controlled trial. Follow up duration: 12 days.
Participants	Location: Dhaka and rural Matlab district, Bangladesh. Years: 1999. Participants: children aged 1 to 15 years. No females participated Number of participants: 128 randomized, 123 evaluated. Cholera serogroup: O1, O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Azithromycin: 20 mg/kg (maximal individual dose: 1 g) single dose. PO placebo matching Erithromycin PO Erithromycin: 12.5 mg/kg (maximal individual dose: 500 mg) four times per day PO placebo matching Azithromycin Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in hours (defined as: interval between administration of study drug to the end of the last 6 hours period in which patient passed a watery stool) Stool volume in mL/kg (definition not specified in study). Clinical failure (defined as: continuation of diarrhoea after 48 or 72 hours of treatment) Bacteriological failure (defined as: *V. cholerae* in stool after day 2 of study).

Khan 2002 BGD (*Continued*)

	Clinical relapse (defined as: re-appearance of diarrhoea after discharge) Bacteriological relapse (defined as: positive culture on day 7 after discharge)
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS type not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list using a block randomization method with a block size of four, stratified by site
Allocation concealment (selection bias)	Low risk	Patients were consecutively assigned a study number and provided study treatment that had been randomly pre-assigned to that number. List kept centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills. Outcome assessor also blinded
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	Only 2 out of 65 in the azithromycin group and 3 out of 63 in the erythromycin group were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	Low risk	Only 2 out of 65 in the azithromycin group and 3 out of 63 in the erythromycin group were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Low risk	Study outcomes were clearly specified and reported.
Other bias	High risk	Study sponsor: academic, Pfizer.

Lapeysonnie 1971 CIV

Methods	Randomized controlled trial. Follow up duration: 8 days.
Participants	Location: Godoume, Cote d'Ivoire. Years: 1970. Participants: children and adults. Female participation not specified Number of participants: number randomized not specified, 37 evaluated

Lapeysonnie 1971 CIV (*Continued*)

	Cholera serogroup: O1. Exclusion due to previous use of antibiotics: not specified. Exclusion due to severity of symptoms: no.
Interventions	PO Sulfometoxine: dose according to age, adult dose 2 g single dose PO Pyridoxine as placebo: dose according to age single dose. Resistance to intervention: not stated.
Outcomes	Clinical failure (defined as: no definitive disappearance of diarrhoea on day 3 or 5 of study)
Notes	Ethics committee involved: not specified. Consent requested and given from study participants: not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	High risk	Stated as double blind, but patients received different pills in different amounts
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	High risk	Study reported on different outcomes in the results than previously specified in the methods
Other bias	Unclear risk	Ethics committee involved: not specified. Consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, ORS type not specified

Lindenbaum 1967a PAK

Methods	Quasi-randomized controlled trial. Follow up duration: until stools were negative for *V. cholerae* for 3 consecutive days.
Participants	Location: Dacca, Pakistan. Years: 1964 to 1966. Participants: adults; 34% females. Number of participants: number randomized not specified, 313 evaluated. Stool positive for *V.cholerae* required for inclusion. Cholera serogroup: Not specified (probably O1). Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: 250, 500 or 750 mg four times per day for 2, 3 or 4 days PO Chloramphenicol: 250, 500 or 750 mg four times per day for 2 or 3 days PO Streptomycin: 1 g four times per day for 2 or 3 days. PO Paromomycin: 250 or 500 mg four times per day for 2 or 3 days No treatment. Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in 8 hour periods (defined as: time until the end of the last 8 hour period in which liquid stool was passed) Stool volume in litres (definition not specified in study). Deaths during study (definition not specified in study). Pathogen secretion duration in days (definition not specified in study) Clinical failure (defined as: diarrhoea that lasted more than 4 days in treated patients) Clinical relapse (defined as: passing formed stool and subsequently passing watery stool enough to require resumption of IV hydration) Bacteriological relapse (defined as: stool negative for at least one day and than positive again)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration only. Early stop: Streptomycin and Paromomycin arms were stopped early

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomization according to day of admission.
Allocation concealment (selection bias)	High risk	Treatment allocation according to day of admission.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts and durations

Lindenbaum 1967a PAK (*Continued*)

Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Number of patients randomized was not specified.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Low risk	No sponsor.

Lindenbaum 1967b PAK

Methods	Quasi-randomized controlled trial. Follow up duration: until stools were negative for *V. cholerae* for 3 consecutive days.
Participants	Location: Dacca, Pakistan. Years: 1964 to 1966. Participants: children aged 6 weeks to 10 years; 46% females Number of participants: 243 randomized, 238 evaluated. Stool positive for *V.cholerae* required for inclusion. Cholera serogroup: Not specified (probably O1). Exclusion due to previous use of antibiotics: not specified. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: 125 or 250 mg four times per day for 2, 3 or 4 days PO Chloramphenicol: 125, 250 or 500 mg four times per day for 2 or 3 days PO Streptomycin: 500 mg four times per day for 2 or 3 days. PO Paromomycin: 125 or 250 mg four times per day for 2 or 3 days No treatment. Resistance to intervention: not specified.
Outcomes	Diarrhoea duration in 8 hour periods (defined as: time until the end of the last 8 hour period in which liquid stool was passed) Stool volume in litres (definition not specified in study). Pathogen secretion duration in days (definition not specified in study) Clinical failure (defined as: diarrhoea that lasted more than 4 days in treated patients) Clinical relapse (defined as: passing formed stool and subsequently passing watery stool enough to require resumption of IV hydration) Bacteriological relapse (defined as: stool negative for at least 1 day and then positive again)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration only. Early stop: Streptomycin and Paromomycin arms were stopped early
Risk of bias	

Lindenbaum 1967b PAK (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomization according to day of admission.
Allocation concealment (selection bias)	High risk	Treatment allocation according to day of admission.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts and durations
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	Only 5 out of 243 were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	Low risk	Only 5 out of 243 were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Low risk	No sponsor.

Lolekha 1988 THA

Methods	Randomized controlled trial. Follow up duration: 10 to 15 days.
Participants	Location: Nohnburi, Thailand. Years: 1986 to 1987. Participants: adults; 51% females. Number of participants: 450 randomized, 47 evaluated. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: no. Exclusion due to severity of symptoms: yes.
Interventions	PO Norfloxacine: 400 mg twice per day for 3 days. PO TMP-SMX: (Trimetoprim 160 mg, Sulfametoxazol 800 mg) twice per day for 3 days PO placebo: twice per day for 3 days. Resistance to intervention: 2% resistance to TMP-SMX.
Outcomes	Duration of diarrhoea in hours (defined as: time from start of treatment until disappearance of watery stools and no more than 3 stools per day) Bacteriological failure (defined as: positive stool culture on day 4 of study)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS type not specified

Lolekha 1988 THA (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	Only a few of the patients randomized (14 to18 out of 150 in each group) were evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	High risk	Study sponsor: academic, Astra Alab.

Mihindukulasurya 1976 LKA

Methods	Randomized controlled trial. Follow up duration: 5 days minimum.
Participants	Location: Angoda, Sri Lanka. Years: not specified. Participants: adults; 45% females. Number of participants: 20 randomized and evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: not specified (most probably O1). Exclusion due to previous use of antibiotics: no. Exclusion due to severity of symptoms: no.
Interventions	PO Sulphadoxine: 2 g single dose. PO Tetracycline: 500 mg four times per day for 3 days. Resistance to intervention: no resistance.
Outcomes	Stool volume in litres (definition not specified in study). Bacteriological failure (defined as: *V. cholerae* in stool on day 2 or 3 of study).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified

Mihindukulasurya 1976 LKA (*Continued*)

	Type of hydration used in study: IV hydration, ORS type not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts. Outcome assessor was blinded
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Stool volume	Low risk	All patients randomized were evaluated.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Low risk	No sponsor.

Moolasarat 1998 THA

Methods	Randomized controlled trial. Follow up duration: not specified.
Participants	Location: Bangkok, Thailand. Years: 1994 to 1996. Participants: children and adults; 48% females. Number of participants: number randomized not specified, 25 evaluated Cholera serogroup: O1, O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: yes.
Interventions	PO Tetracycline: adults 500 mg; children 12.5 mg/kg four times per day for 3 days PO Norfloxacine: adults 400 mg; children 7.5 mg/kg twice per day for 3 days Resistance to intervention: no resistance.
Outcomes	Duration of diarrhoea (definition not specified in study). Deaths (during study). Pathogen secretion duration in days (definition not specified in study)

Moolasarat 1998 THA (*Continued*)

Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, ORS type not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different pills in different amounts.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Time point for outcome assessment not defined.
Other bias	Low risk	No sponsor.

Pierce 1968 IND

Methods	Randomized controlled trial. Follow up duration: not specified.
Participants	Location: Kolkata, India. Years: 1967. Participants: adults. No females participated. Number of participants: 65 randomized, 49 evaluated. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: adults 500 mg four times per day for 2 days PO Furazolidone: 200 mg four times per day for 3 days. PO Furazolidone: 400 mg once per day for 3 days. No treatment. Resistance to intervention: no resistance.

Pierce 1968 IND (*Continued*)

Outcomes	Duration of diarrhoea (defined as: time from entry to study until the last passage of any liquid stool). Stool volume in mL/kg (definition not specified in study). Deaths (during study). Pathogen secretion duration in hours (defined as: time from entry until the last positive stool culture was obtained) Clinical relapse (defined as: recurrence of diarrhoea after termination of therapy) Bacteriological relapse (defined as: positive culture after 3 days with negative cultures)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, water, green coconut water

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Control arm was given no treatment
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	Number of patients randomized to each group was not specified. Data was evaluated for only 49 patients out of a total of 65 patients participating
Incomplete outcome data (attrition bias) Stool volume	High risk	Number of patients randomized to each group was not specified. Data was evaluated for only 49 patients out of a total of 65 patients participating
Selective reporting (reporting bias)	High risk	Study outcomes were not specified at all in the methods section
Other bias	Low risk	Study sponsor: academic.

Rabbani 1989 BGD

Methods	Randomized controlled trial. Follow up duration: 7 days minimum.
Participants	Location: Dhaka, Bangladesh. Years: not specified. Participants: adults. Female participation not specified. Number of participants: 114 randomized, 87 evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: not specified. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: yes.
Interventions	PO Tetracycline: 1 g single dose. PO Furazolidone: 400 mg single dose. PO placebo: 2 tabs single dose. Resistance to intervention: 13% resistance to Tetracycline; 22% resistance to Furazolidone
Outcomes	Diarrhoea duration hours (defined as: time until the end of the last 8 hour period in which liquid stool was passed) Stool volume in litres (definition not specified in study). Clinical failure (defined as: continuation of diarrhoea on day 4 or after) Bacteriological failure (defined as: positive stool cultures 48 or 96 hours after treatment) Clinical relapse (defined as: cure on day 4 with subsequent relapse) Bacteriological relapse (defined as: stool positive for *V cholerae* on day 6).
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, water.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Low risk	Assuming the table was code: bottles containing the drugs numerically coded, code kept in New York and opened only after the study had been completed
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	27 out of 114 were not evaluated, reasons were not specified

Rabbani 1989 BGD (*Continued*)

Incomplete outcome data (attrition bias) Stool volume	High risk	27 out of 114 were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	High risk	Study sponsor: Norwich Eaton Pharmaceuticals.

Rabbani 1991 BGD

Methods	Randomized controlled trial. Follow up duration: not specified.
Participants	Location: Dhaka, Bangladesh. Years: 1985 to 1987. Participants: children aged 1 month to 14 years; 28% females Number of participants: number randomized not specified, 106 evaluated. Stool positive for *V.cholerae* required for inclusion. Cholera serogroup: not specified. Exclusion due to previous use of antibiotics: not specified. Exclusion due to severity of symptoms: yes.
Interventions	PO Furazolidone: 7 mg/kg single dose. PO Furazolidone: 1.75 mg/kg four times per day for 3 days. PO placebo: single dose. PO placebo: four times per day for 3 days. Resistance to intervention: 12% resistance to Furazolidone on the single dose arm; no resistance to Furazolidone on the multiple dose arm
Outcomes	Diarrhoea duration hours (defined as: time until the end of the last 8 hour period in which liquid stool was passed) Stool volume in litres (definition not specified in study). Pathogen secretion duration in days (definition not specified in study) Clinical failure (defined as: continuation of diarrhoea beyond 72 hours from the start of treatment) Bacteriological failure (defined as: stool cultures positive for *V. cholerae* on days 2, 3 or 4 after the start of treatment).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, water.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rabbani 1991 BGD (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated list of random numbers.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Number of patients randomized was not specified.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	High risk	Study sponsor: Norwich-Eaton Pharmaceuticals, Inc.

Rahaman 1976 BGD

Methods	Quasi-randomized controlled trial. Follow up duration: not specified.
Participants	Location: Dhaka, Bangladesh. Years: 1974 to 1975. Participants: children and adults. Female participation not specified Number of participants: number randomized not specified, 51 evaluated Cholera serogroup: not specified. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Doxycycline: adults 100 mg; children 2 mg/kg twice per day on the first day, once per day on the next 3 days PO Tetracycline: 5 mg/kg four times per day for 4 days. PO placebo: administration manner not specified. Resistance to intervention
Outcomes	Diarrhoea duration hours (definition not specified in study) Stool volume in litres (definition not specified in study). Deaths (during study). Pathogen secretion duration in days (definition not specified in study)
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, ORS type not specified

Rahaman 1976 BGD (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Cards pre-arranged consecutively.
Allocation concealment (selection bias)	High risk	Cards pre-arranged consecutively; codes held in sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Placebo was used only to match Doxycycline, not Tetracycline
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Number of patients randomized was not specified.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Unclear risk	Study sponsor: academic, Pfizer supplied placebo.

Roy 1998 BGD

Methods	Randomized controlled trial. Follow up duration: 4 days.
Participants	Location: Dhaka, Bangladesh. Years: not specified. Participants: children aged 1 to 5 years. Female participation not specified Number of participants: 184 randomized and evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Erythromycin: 12.5 mg/kg four times per day for 3 days. PO Ampicillin: 12.5 mg/kg four times per day for 3 days. PO Tetracycline: 6.5 mg/kg four times per day for 3 days. PO placebo: four times per day for 3 days. Resistance to intervention: 1% resistance to Ampicillin; 2% resistance to Erythromycin; and 24% resistance to Tetracycline

Roy 1998 BGD (*Continued*)

Outcomes	Stool volume in litres (definition not specified in study). Bacteriological failure (defined as: stool cultures positive for *V. cholerae* 48 hours after the start of treatment).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, rice-based ORS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Outcome not reported.
Incomplete outcome data (attrition bias) Stool volume	Low risk	All patients randomized were evaluated.
Selective reporting (reporting bias)	High risk	Study outcomes were not specified at all in the methods section
Other bias	Low risk	Study sponsor: academic.

Sack 1978 BGD

Methods	Randomized controlled trial. Follow up duration: until stools were negative for *V. cholerae* for 2 consecutive days.
Participants	Location: Dhaka, Bangladesh. Years: not specified. Participants: children and adults. No females participated. Number of participants: 74 randomized, 65 evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.

Sack 1978 BGD (*Continued*)

Interventions	PO Doxycycline: adults 200 mg; children 4 mg/kg single dose. PO Doxycycline: adults 100 mg; children 2 mg/kg twice per day on the first day, once per day on the next 3 days Resistance to intervention: not specified.
Outcomes	Stool weight in mg/kg (definition not specified in study).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, water.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Predetermined list of random numbers.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Patients received different amounts of pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	9 out of 74 patients randomized were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Outcome not reported.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Unclear risk	Study sponsor: academic. Pfizer Laboratory measured serum levels

Saha 2005 BGD

Methods	Randomized controlled trial. Follow up duration: 6 weeks.
Participants	Location: Dhaka and rural Matlab district, Bangladesh. Years: 2001 to 2002. Participants: children aged 2 to 15 years. Female participation not specified Number of participants: 180 randomized, 162 evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: O1, O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.

Interventions	PO Ciprofloxacin: 20 mg/kg (maximal dose 750 mg) single dose PO Erythromycin: 12.5 mg/kg (maximal dose 500 mg) four times per day for 3 days Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration in hours (defined as: time from the administration of study drug until the end of the last 6 hour period without diarrhoea) Stool volume in litres (definition not specified in study). Clinical failure (defined as: continuation of diarrhoea after 48 hours from the administration of study drug) Bacteriological failure (defined as: stool cultures positive for *V. cholerae* after day 2 of study).
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, rice-based ORS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list prepared by individuals not otherwise involved in the study with a block size of eight
Allocation concealment (selection bias)	Low risk	Sealed boxes opened after a patient had been enrolled in the study and assigned a study number
Blinding (performance bias and detection bias) All outcomes	High risk	Patients in different arms received different amounts of medication
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	Only 12 out of 90 patients in the ciprofloxacin group and 6 out of 90 in the erythromycin group were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	Low risk	Only 12 out of 90 patients in the ciprofloxacin group and 6 out of 90 in the erythromycin group were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Low risk	Study outcomes were clearly specified and reported.
Other bias	High risk	Study sponsor: academic, Bayer AG.

Saha 2006 BGD

Methods	Randomized controlled trial. Follow up duration: 12 to 15 days.
Participants	Location: Dhaka, Bangladesh. Years: 2002 to 2004. Participants: adults. No females participated. Number of participants: 198 randomized, 195 evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: O1, O139. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Azithromycin: 1 g single dose; PO placebo matching Ciprofloxacin PO Ciprofloxacin: 1 g single dose; PO placebo matching Azithromycin Resistance to intervention: no resistance.
Outcomes	Diarrhoea duration hours (defined as: time from administration of study drug until the end of the last 6 hours period without diarrhoea) Stool volume in mL/kg (definition not specified in study). Clinical failure (defined as: continuation of diarrhoea after 48 hours from administration of study drug) Bacteriological failure (defined as: stool cultures positive for *V. cholerae* after 48 hours from administration of study drug).
Notes	Ethics committee involved: yes. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, rice-based ORS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomizations with a block of six done by an independent researcher who was not involved in the study
Allocation concealment (selection bias)	Low risk	Drugs and placebo were put in identical bottles with sequential numbers according to the randomized list
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical looking pills.
Incomplete outcome data (attrition bias) Diarrhoea duration	Low risk	Only 2 out of 99 in the azithromycin group and 1 out of 99 in the ciprofloxacin group were not evaluated, the reasons were not specified

Saha 2006 BGD (*Continued*)

Incomplete outcome data (attrition bias) Stool volume	Low risk	Only 2 out of 99 in the azithromycin group and 1 out of 99 in the ciprofloxacin group were not evaluated, the reasons were not specified
Selective reporting (reporting bias)	Low risk	Study outcomes were clearly specified and reported.
Other bias	Unclear risk	Study sponsor: academic, Pfizer supplied Azithromycin.

Usubutun 1997 TUR

Methods	Randomized controlled trial. Follow up duration: not specified.
Participants	Location: Ankara, Turkey. Years: 1994. Participants: adults; 32% females. Number of participants: 90 randomized, 74 evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: not specified. Exclusion due to severity of symptoms: no.
Interventions	PO Ciprofloxacin: 1 g single dose. PO Ciprofloxacin: 500 mg twice per day for 1 day. PO Doxycycline: 100 mg twice per day for 3 days. No treatment. Resistance to intervention: no resistance to Ciprofloxacin; resistance to Doxycycline not specified
Outcomes	Diarrhoea duration in days (defined as: time until day of study when patient did not pass watery stool for 8 hours) Stool volume in mL/kg (definition not specified in study). Bacteriological failure (defined as: *V. cholerae* in stool after study day 4). Clinical relapse (defined as: re-appearance of watery stool after a remission of 8 hours) Bacteriological relapse (defined as: re-appearance of *V. cholerae* in stool after two negative stool exams).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: yes. Type of hydration used in study: IV hydration, ORS type not specified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Usubutun 1997 TUR (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Control arm was given no treatment.
Incomplete outcome data (attrition bias) Diarrhoea duration	High risk	A relatively large number of patients in each group (and a total of 16 out of 90) were not evaluated, reasons were not specified
Incomplete outcome data (attrition bias) Stool volume	High risk	A relatively large number of patients in each group (and a total of 16 out of 90) were not evaluated, reasons were not specified
Selective reporting (reporting bias)	Low risk	Study outcomes were clearly specified and reported.
Other bias	Low risk	No sponsor.

Wallac 1968˙A IND

Methods	Randomized controlled trial. Follow up duration: 7 days minimum.
Participants	Location: Kolkata, India. Years: 1965 to 1966. Participants: adults. No females participated. Number of participants: number randomized not specified, 33 evaluated. Stool positive for *V .cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: 500 mg four times per day for 2 days. PO Tetracycline: 250 mg four times per day for 3 days. No treatment. Resistance to intervention: not specified.
Outcomes	Diarrhoea duration in hours (definition not specified in study) Stool volume in litres (definition not specified in study). Deaths (during study). Pathogen excretion duration in days (definition not specified in study) Clinical relapse (definition not specified in study). Bacteriological relapse (definition not specified in study).

Wallac 1968˙A IND (*Continued*)

Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, green coconut water

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Previously randomized schedule.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	Control arm was given no treatment.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Number of patients randomized was not specified.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Low risk	Study sponsor: academic.

Wallac 1968˙B IND

Methods	Randomized controlled trial. Follow up duration: 7 days minimum.
Participants	Location: Kolkata, India. Years: 1965 to 1966. Participants: adults. No females participated. Number of participants: number randomized not specified, 33 evaluated. Stool positive for *V.cholerae* required for inclusion. Cholera serogroup: O1. Exclusion due to previous use of antibiotics: yes. Exclusion due to severity of symptoms: no.
Interventions	PO Tetracycline: 2 g once per day for 2 days. PO Chloramphenicol: 500 mg four times per day for 3 days. PO Sulfaguanidine: 500 mg every four hours for 2 days; 2 g three times per day for 5 days No treatment. Resistance to intervention: not specified.

Wallac 1968˙B IND (*Continued*)

Outcomes	Diarrhoea duration in hours (definition not specified in study) Stool volume in litres (definition not specified in study). Deaths (during study). Pathogen excretion duration in days (definition not specified in study) Clinical relapse (definition not specified in study). Bacteriological relapse (definition not specified in study).
Notes	Ethics committee involved: not specified. consent requested and given from study participants: not specified Type of hydration used in study: IV hydration, green coconut water

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Treatment given alternately.
Allocation concealment (selection bias)	High risk	Treatment given alternately.
Blinding (performance bias and detection bias) All outcomes	High risk	Control arm was given no treatment.
Incomplete outcome data (attrition bias) Diarrhoea duration	Unclear risk	Number of patients randomized was not specified.
Incomplete outcome data (attrition bias) Stool volume	Unclear risk	Number of patients randomized was not specified.
Selective reporting (reporting bias)	Unclear risk	Primary outcomes were not specified.
Other bias	Low risk	No sponsor.

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

Study	Reason for exclusion
Cash 1973	Patients were not randomly assigned to treatment groups.
Chatterjee 1953	The article is not a controlled trial, and does not concern antimicrobial therapy
Gotuzzo 1994	An open, non-comparative trial.

(*Continued*)

Greenough 1964	Patients were not randomly assigned to treatment groups.
Kobari 1967	Patients were not randomly assigned to treatment groups.
Kobari 1967a	Patients were not randomly assigned to treatment groups.
Lahiri 1951	The antimicrobial treatment used is unknown and is not used in practice. The supportive care described was inadequate
Mazumdar 1977	Previous work by the same author raises questions regarding the quality of randomizations and risk of bias
Mazumder 1974	Patients were poorly matched in baseline, which raises questions regarding the quality of randomizations and risk for bias
Okuda 2007	The trial described was an in vitro experiment.
Pastore 1977	Patients were not randomly assigned to treatment groups.
Rabbani 1986	The publication is a review, not a trial.
Rabbani 1996	The publication is a review, not a trial.
Sagara 1994	Not all study arms contain cholera patients.
Seal 1954	Patients were not randomly assigned to treatment groups.
Seijo 1996	Patients were not randomly assigned to treatment groups.
Uylangco 1965	The antimicrobial treatment is no longer used in practice.
Uylangco 1966	Patients were not randomly assigned to treatment groups.
Uylangco 1967	Patients were not randomly assigned to treatment groups.
Uylangco 1978	Patients were not randomly assigned to treatment groups.
Uylangco 1984	Patients were not randomly assigned to treatment groups.
Wallace 1968	The publication is an editorial letter, not a trial.
Woodward 1969	Patients were not randomly assigned to treatment groups.

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

Chatchai 1994

Methods	Unknown
Participants	Unknown
Interventions	Doxycycline 300 mg, single dose Tetracyline 500 mg four times per day
Outcomes	Unknown
Notes	This reference came up in the search conducted in *The Cochrane Library*: http://www.mrw.interscience.wiley.com/cochrane/clcentral/articles/179/CN-00617179/frame.html There are no UK holdings for the journal. This publication was requested as a World Wide Search by Caroline Hercod in December 2009; the search is still ongoing

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

Khan˙Ongoing

Trial name or title	Randomized, Double Blind, Controlled Clinical Trial to Evaluate the Efficacy of Multiple-Dose Ciprofloxacin With Single Dose Azithromycin Therapy for Adults With Cholera Due to Multiply Resistant Strains of V. Cholerae O1 or O13
Methods	Interventional trial Allocation: randomized Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double blind (subject, investigator) Primary purpose: treatment
Participants	18 to 60 year old males, duration of diarrhoea not exceeding 24 hours
Interventions	Ciprofloxacin, twice per day for 3 days, dose not specified. Azithromycin, 1 g Azithromycin single dose.
Outcomes	Primary Outcome Measures: • To determine whether clinical success of therapy in the two treatment regimens are comparable. [Time Frame: 48 hours] Secondary Outcome Measures: • Compare the rates of bacteriological success. • Compare the diarrhoea duration. • Compare stool volume of patients. • Measure stool concentrations of the two drugs and compare them with MICs of *V. cholerae*. • Record and compare adverse events. [Time Frame: 48 hours]

Khan · Ongoing (*Continued*)

Starting date	July 2007
Contact information	Wasif A Khan, MBBS, MS (880-2) 8860523-32 ext 2348, wakhan@icddrb.org
Notes	Contact with Dr. Khan regarding this trial was established on February 2010, at which point he was in the process of data handling and could not share information

Saha · Ongoing

Trial name or title	Randomized, Open, Parallel Group Clinical Trial to Compare the Efficacy and Safety of a Single Dose of Ciprofloxacin Oral Suspension 20 Mg/Kg With a 3-Day Course of Erythromycin Oral Suspension Administered in a Dose of 12.5 Mg/Kg Every 6 Hours (12 Doses) in the Treatment of Children,With Clinically Severe Cholera Due to *V. cholerae* O1 or O139.
Methods	Interventional trial Allocation: randomized Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: treatment
Participants	Age: 2 to 15 years. Gender: male. Duration of illness: < 24 hours. Written informed consent for participation in the study from either of the parents, or guardian, and oral assent from children aged 8 years
Interventions	Ciprofloxacin Oral Suspension, 20 mg/kg, single dose. Erythromycin Oral Suspension, 12.5 mg/kg four times per day, for 3 days
Outcomes	Primary Outcome Measures: • Rates of clinical success Secondary Outcome Measures: • Rates of bacteriologic success at test of cure visit. • Duration of diarrhoea. • Rates of clinical relapse. • Rates of bacteriologic relapse. • Duration of faecal excretion of *V. cholerae* O1 or *V. cholerae* O139. • Measurements of six-hourly volume of watery stool will be done for the period in which patients are hospitalized. • Proportion of patients requiring unscheduled intravenous fluids. • Frequency of vomiting and its volume. • Frequency of stool per day. • Frequency of vomit per day. • Safety. • PK-assessment of serum and stool.
Starting date	May 2001

Saha˙Ongoing (*Continued*)

Contact information	Debasish Saha, MBBS,MS, International Centre for Diarrhoeal Disease Research, Bangladesh, dsaha@icddrb.org
Notes	An attempt to contact the author was made on February 2010.

Saha˙Ongoing˙B

Trial name or title	Randomized, Double-Blind, Controlled Clinical Trial to Compare Efficacy of a Single Dose of Azithromycin Versus a Single Dose of Ciprofloxacin in the Treatment of Adults With Clinically Severe Cholera Due to *V. cholerae* O1 or O139
Methods	Interventional trial Allocation: randomized Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double blind Primary Purpose: treatment
Participants	18 to 60 year old males, duration of diarrhoea not exceeding 24 hours
Interventions	Azithromycin, single dose. Ciprofloxacin, single dose.
Outcomes	Primary Outcome Measures: • Clinical success. • Bacteriological success. Secondary Outcome Measures: • Rates of clinical and bacteriologic relapse. • Duration of diarrhoea in hours, and duration of faecal excretion of *V. cholerae* O1 or O139 in days. • Volume of watery/liquid stool for each 6 and 24 hour of the study, and also the total amount of watery/liquid stools during the study period. • Frequency of vomiting and the amount of vomitus, and proportion of patients with vomiting on each study day. • Intake of oral and intravenous fluids for each 24 hour as well as the entire duration of the study. • Proportion of patients with resolution of diarrhoea on each study day. • Proportion of patients with a positive culture for infecting *V. cholerae* O1 or O139 on each study day.
Starting date	December 2002
Contact information	Debasish Saha, MBBS,MS, International Centre for Diarrhoeal Disease Research, Bangladesh, dsaha@icddrb.org
Notes	An attempt to contact the author was made on February 2010.

DATA AND ANALYSES

Comparison 1. Antimicrobial versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	18	1479	Mean Difference (IV, Random, 95% CI)	-36.77 [-43.51, -30.03]
1.1 Norfloxacin	3	123	Mean Difference (IV, Random, 95% CI)	-10.80 [-14.13, -7.48]
1.2 Ciprofloxacin	1	48	Mean Difference (IV, Random, 95% CI)	-43.37 [-57.48, -29.27]
1.3 Tetracycline	11	665	Mean Difference (IV, Random, 95% CI)	-47.38 [-52.36, -42.41]
1.4 Doxycycline	3	91	Mean Difference (IV, Random, 95% CI)	-25.44 [-38.90, -11.99]
1.5 Erythromycin	2	46	Mean Difference (IV, Random, 95% CI)	-33.73 [-56.53, -10.92]
1.6 TMP-SMX	4	100	Mean Difference (IV, Random, 95% CI)	-30.76 [-49.33, -12.18]
1.7 Chloramphenicol	3	196	Mean Difference (IV, Random, 95% CI)	-37.17 [-50.14, -24.20]
1.8 Furazolidone	4	210	Mean Difference (IV, Random, 95% CI)	-34.12 [-49.52, -18.72]
2 Stool Volume	17	1536	Ratio of means (Random, 95% CI)	0.50 [0.45, 0.56]
2.1 Norfloxacin	2	98	Ratio of means (Random, 95% CI)	0.61 [0.51, 0.74]
2.2 Ciprofloxacin	1	48	Ratio of means (Random, 95% CI)	0.42 [0.22, 0.82]
2.3 Tetracycline	12	720	Ratio of means (Random, 95% CI)	0.44 [0.39, 0.50]
2.4 Doxycycline	3	91	Ratio of means (Random, 95% CI)	0.64 [0.51, 0.81]
2.5 Erythromycin	2	84	Ratio of means (Random, 95% CI)	0.81 [0.48, 1.35]
2.6 TMP-SMX	1	26	Ratio of means (Random, 95% CI)	0.89 [0.46, 1.70]
2.7 Chloramphenicol	3	196	Ratio of means (Random, 95% CI)	0.54 [0.32, 0.90]
2.8 Furazolidone	4	210	Ratio of means (Random, 95% CI)	0.49 [0.33, 0.74]
2.9 Ampicillin	1	63	Ratio of means (Random, 95% CI)	0.57 [0.42, 0.79]
3 Deaths	6	299	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.05, 0.05]
3.1 Norfloxacin	2	98	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
3.2 Tetracycline	4	103	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.08, 0.08]
3.3 Doxycycline	2	65	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.11, 0.11]
3.4 Furazolidone	1	33	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.16, 0.16]
4 Clinical failure	10	1023	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.13, 0.34]
4.1 Fleroxacin	1	145	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.24, 0.62]
4.2 Tetracycline	6	431	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.05, 0.22]
4.3 Erythromycin	1	22	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.20, 1.10]
4.4 TMP-SMX	2	55	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.17, 0.66]
4.5 Chloramphenicol	2	185	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.05, 0.40]
4.6 Furazolidone	2	148	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.23, 1.54]
4.7 Sulfometoxine	1	37	Risk Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.40]
5 Hydration requirements	11	1201	Ratio of means (Random, 95% CI)	0.60 [0.53, 0.68]
5.1 Norfloxacin	2	98	Ratio of means (Random, 95% CI)	0.72 [0.60, 0.86]

5.2 Tetracycline	8	604	Ratio of means (Random, 95% CI)	0.50 [0.43, 0.58]
5.3 Doxycycline	2	66	Ratio of means (Random, 95% CI)	0.76 [0.57, 1.02]
5.4 Erythromycin	2	84	Ratio of means (Random, 95% CI)	0.68 [0.38, 1.21]
5.5 TMP-SMX	1	26	Ratio of means (Random, 95% CI)	0.87 [0.35, 2.17]
5.6 Chloramphenicol	2	185	Ratio of means (Random, 95% CI)	0.55 [0.34, 0.87]
5.7 Furazolidone	2	75	Ratio of means (Random, 95% CI)	0.85 [0.60, 1.21]
5.8 Ampicillin	1	63	Ratio of means (Random, 95% CI)	0.44 [0.22, 0.88]
6 Pathogen excretion duration	11	1009	Mean Difference (IV, Random, 95% CI)	-2.74 [-3.07, -2.40]
6.1 Tetracycline	10	616	Mean Difference (IV, Random, 95% CI)	-3.05 [-3.43, -2.67]
6.2 TMP-SMX	1	29	Mean Difference (IV, Random, 95% CI)	-3.20 [-4.93, -1.47]
6.3 Chloramphenicol	3	196	Mean Difference (IV, Random, 95% CI)	-2.43 [-3.03, -1.82]
6.4 Furazolidone	3	168	Mean Difference (IV, Random, 95% CI)	-2.04 [-2.71, -1.37]
7 Bacteriological failure	15	1147	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.16, 0.39]
7.1 Norfloxacin	3	142	Risk Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.11]
7.2 Fleroxacin	1	145	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.32]
7.3 Ciprofloxacin	1	48	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.03, 0.26]
7.4 Tetracycline	7	320	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.13, 0.64]
7.5 Doxycycline	2	64	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.30]
7.6 Erythromycin	3	108	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.09, 0.33]
7.7 TMP-SMX	4	94	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.13, 1.05]
7.8 Chloramphenicol	1	15	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.38, 1.41]
7.9 Furazolidone	2	148	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.25, 2.08]
7.10 Ampicillin	1	63	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.57, 0.99]

Comparison 2. Sensitivity analysis: Antimicrobial versus placebo/no treatment by allocation concealment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	18	1479	Mean Difference (IV, Random, 95% CI)	-36.77 [-43.51, -30.03]
1.1 Low risk	4	203	Mean Difference (IV, Random, 95% CI)	-25.41 [-40.82, -10.01]
1.2 Unclear	9	638	Mean Difference (IV, Random, 95% CI)	-34.26 [-40.32, -28.20]
1.3 High risk	5	638	Mean Difference (IV, Random, 95% CI)	-45.01 [-51.01, -39.01]
2 Stool Volume	17	1536	Ratio of means (Random, 95% CI)	0.50 [0.45, 0.56]
2.1 Low risk	4	207	Ratio of means (Random, 95% CI)	0.68 [0.47, 0.99]
2.2 Unclear	8	700	Ratio of means (Random, 95% CI)	0.51 [0.46, 0.58]
2.3 High risk	6	629	Ratio of means (Random, 95% CI)	0.42 [0.36, 0.49]
3 Clinical failure	10	1023	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.13, 0.34]
3.1 Low risk	4	323	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.26, 0.63]
3.2 Unclear	3	196	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.09, 0.55]
3.3 High risk	3	504	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.04, 0.17]
4 Hydration requirements	11	1201	Ratio of means (Random, 95% CI)	0.60 [0.53, 0.68]
4.1 Low risk	4	203	Ratio of means (Random, 95% CI)	0.71 [0.57, 0.89]
4.2 Unclear	4	463	Ratio of means (Random, 95% CI)	0.59 [0.49, 0.71]
4.3 High risk	3	535	Ratio of means (Random, 95% CI)	0.50 [0.43, 0.58]
5 Pathogen excretion duration	11	1009	Mean Difference (IV, Random, 95% CI)	-2.74 [-3.07, -2.40]

5.1 Low risk	1	43	Mean Difference (IV, Random, 95% CI)	-3.5 [-3.83, -3.17]
5.2 Unclear	5	359	Mean Difference (IV, Random, 95% CI)	-2.26 [-2.69, -1.83]
5.3 High risk	5	607	Mean Difference (IV, Random, 95% CI)	-3.07 [-3.43, -2.71]
6 Bacteriological failure	15	1147	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.16, 0.39]
6.1 Low risk	4	215	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.14, 0.88]
6.2 Unclear	10	912	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.13, 0.39]
6.3 High risk	1	20	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.72]

Comparison 3. Sensitivity analysis: Antimicrobial versus placebo/no treatment by time outcome definitions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration by outcome definitions	18	1479	Mean Difference (IV, Random, 95% CI)	-36.77 [-43.51, -30.03]
1.1 Vague time definitions	9	441	Mean Difference (IV, Random, 95% CI)	-28.51 [-36.65, -20.38]
1.2 8 hours periods	9	1038	Mean Difference (IV, Random, 95% CI)	-42.21 [-47.64, -36.78]
2 Clinical failure at 48/72/96 hours	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 48 hours	2	198	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.20, 0.70]
2.2 72 hours	6	307	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.27, 0.51]
2.3 96 hours	4	608	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.04, 0.37]
3 Bacteriological failure 48/72/96 sub totals only	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 48 hours	10	747	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.19, 0.54]
3.2 72 hours	7	474	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.11, 0.37]
3.3 96 hours	4	313	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.14, 0.74]

Comparison 4. Antimicrobial versus placebo/no treatment subgrouped by severity of dehydration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	18	1479	Mean Difference (IV, Random, 95% CI)	-36.77 [-43.51, -30.03]
1.1 100% severe dehydration	6	296	Mean Difference (IV, Random, 95% CI)	-26.24 [-35.66, -16.82]
1.2 Others	12	1183	Mean Difference (IV, Random, 95% CI)	-41.31 [-45.99, -36.62]
2 Stool Volume	17	1575	Ratio of means (Random, 95% CI)	0.50 [0.45, 0.56]
2.1 100% severe dehydration	6	263	Ratio of means (Random, 95% CI)	0.58 [0.50, 0.66]
2.2 Others	11	1312	Ratio of means (Random, 95% CI)	0.48 [0.42, 0.56]
3 Clinical failure	10	1023	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.13, 0.34]
3.1 100% severe dehydration	2	73	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.04, 0.68]
3.2 Others	8	950	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.13, 0.37]

4 Hydration requirements	11	1201	Ratio of means (Random, 95% CI)	0.60 [0.53, 0.68]
4.1 100% severe dehydration	3	186	Ratio of means (Random, 95% CI)	0.73 [0.65, 0.83]
4.2 Others	8	1015	Ratio of means (Random, 95% CI)	0.55 [0.47, 0.64]

Comparison 5. Antimicrobial vs. placebo/no treatment subgrouped by antimicrobial resistance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bacteriological failure arms with no resistance only	9	611	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.06, 0.27]
1.1 Norfloxacin	3	142	Risk Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.11]
1.2 Fleroxacin	1	145	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.32]
1.3 Ciprofloxacin	1	48	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.03, 0.26]
1.4 Tetracycline	3	185	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.09, 0.62]
1.5 Doxycycline	1	38	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.03, 0.41]
1.6 Erythromycin	1	24	Risk Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.44]
1.7 TMP-SMX	1	29	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.27, 2.38]

Comparison 6. Azithromycin versus ciprofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	2	375	Mean Difference (IV, Random, 95% CI)	-32.43 [-62.90, -1.95]
2 Stool Volume	1	195	Ratio of means (Random, 95% CI)	0.35 [0.28, 0.44]
3 Hydration requirements	2	362	Ratio of means (Random, 95% CI)	0.66 [0.52, 0.83]
4 Clinical failure	2	375	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.23, 0.44]
5 Bacteriological failure	2	375	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.16, 0.34]

Comparison 7. Azithromycin versus erythromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	2	179	Mean Difference (IV, Random, 95% CI)	-12.05 [-22.02, -2.08]
2 Stool Volume	2	172	Ratio of means (Random, 95% CI)	0.69 [0.56, 0.85]
3 Hydration requirements	2	179	Ratio of means (Random, 95% CI)	0.77 [0.56, 1.05]
4 Clinical failure	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5 Bacteriological failure	2	179	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.80, 3.02]

Comparison 8. Tetracycline versus doxycycline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	3	230	Mean Difference (IV, Random, 95% CI)	-2.01 [-8.21, 4.19]
2 Stool Volume	3	230	Ratio of means (Random, 95% CI)	0.97 [0.83, 1.14]
3 Deaths	2	66	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.08, 0.08]
4 Hydration requirements	3	230	Ratio of means (Random, 95% CI)	0.91 [0.78, 1.06]
5 Pathogen excretion duration	2	66	Mean Difference (IV, Random, 95% CI)	-0.46 [-1.03, 0.11]
6 Bacteriological failure	2	198	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.68]

Comparison 9. Tetracycline versus quinolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	3	259	Mean Difference (IV, Random, 95% CI)	-0.91 [-4.53, 2.72]
2 Stool Volume	2	234	Ratio of means (Random, 95% CI)	0.87 [0.75, 1.02]
3 Deaths	1	25	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.14, 0.14]
4 Clinical failure	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.33, 1.38]
5 Hydration requirements	2	234	Ratio of means (Random, 95% CI)	0.98 [0.90, 1.07]
6 Pathogen excretion duration	1	25	Mean Difference (IV, Random, 95% CI)	0.05 [-0.42, 0.52]
7 Bacteriological failure	2	234	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.14, 6.82]

Comparison 10. Tetracycline versus TMP-SMX

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	2	152	Mean Difference (IV, Random, 95% CI)	-6.44 [-10.93, -1.96]
2 Clinical failure	2	152	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.34, 0.92]
3 Pathogen excretion duration	1	45	Mean Difference (IV, Random, 95% CI)	-1.10 [-1.74, -0.46]
4 Bacteriological failure	3	173	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.71, 2.02]

Comparison 11. Tetracycline versus chloramphenicol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	3	356	Mean Difference (IV, Random, 95% CI)	-11.49 [-25.93, 2.96]
2 Stool Volume	3	356	Ratio of means (Random, 95% CI)	0.72 [0.50, 1.04]
3 Clinical failure	2	340	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.13, 1.04]
4 Hydration requirements	2	340	Ratio of means (Random, 95% CI)	0.81 [0.53, 1.24]
5 Pathogen excretion duration	3	356	Mean Difference (IV, Random, 95% CI)	-0.96 [-1.48, -0.44]

Comparison 12. Tetracycline versus furazolidone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	3	121	Mean Difference (IV, Random, 95% CI)	-14.00 [-31.26, -0.74]
2 Stool Volume	3	120	Ratio of means (Random, 95% CI)	0.63 [0.48, 0.83]
3 Deaths	2	73	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
4 Clinical failure	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.08, 0.79]
5 Hydration requirements	2	82	Ratio of means (Random, 95% CI)	0.63 [0.46, 0.87]
6 Pathogen excretion duration	2	64	Mean Difference (IV, Random, 95% CI)	-0.89 [-1.98, 0.20]
7 Bacteriological failure	2	105	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.45, 1.08]

Comparison 13. Doxycycline versus quinolones

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	3	126	Mean Difference (IV, Random, 95% CI)	4.64 [-2.14, 11.42]
2 Stool Volume	4	435	Ratio of means (Random, 95% CI)	1.01 [0.82, 1.25]
3 Deaths	1	54	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
4 Hydration requirements	2	87	Ratio of means (Random, 95% CI)	1.18 [1.02, 1.35]
5 Bacteriological failure	4	386	Risk Ratio (M-H, Fixed, 95% CI)	5.84 [2.70, 12.65]

Comparison 14. TMP-SMX versus erythromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	2	68	Mean Difference (IV, Random, 95% CI)	5.39 [-7.82, 18.60]
2 Clinical failure	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.14, 1.76]
3 Bacteriological failure	2	68	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.16, 0.12]

Comparison 15. Short versus long duration of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Diarrhoea duration	7	431	Mean Difference (IV, Random, 95% CI)	0.34 [-4.65, 5.32]
1.1 Long duration 24 hours	2	88	Mean Difference (IV, Random, 95% CI)	-5.30 [-24.64, 14. 04]
1.2 Long duration 48 hours	2	204	Mean Difference (IV, Random, 95% CI)	1.01 [-2.26, 4.27]
1.3 Long duration 72 hours	2	85	Mean Difference (IV, Random, 95% CI)	3.63 [-16.16, 23.43]
1.4 Long duration 96 hours	1	54	Mean Difference (IV, Random, 95% CI)	6.60 [0.84, 12.36]
2 Stool Volume	8	486	Ratio of means (Random, 95% CI)	1.05 [0.94, 1.18]
2.1 Long duration 24 hours	2	88	Ratio of means (Random, 95% CI)	0.98 [0.72, 1.33]
2.2 Long duration 48 hours	2	204	Ratio of means (Random, 95% CI)	0.99 [0.83, 1.17]
2.3 Long duration 72 hours	2	85	Ratio of means (Random, 95% CI)	1.03 [0.76, 1.39]
2.4 Long duration 96 hours	2	109	Ratio of means (Random, 95% CI)	1.15 [0.82, 1.61]
3 Hydration requirements	6	403	Ratio of means (Random, 95% CI)	1.10 [0.99, 1.22]
3.1 Long duration 24 hours	1	48	Ratio of means (Random, 95% CI)	1.01 [0.66, 1.55]
3.2 Long duration 48 hours	2	204	Ratio of means (Random, 95% CI)	1.08 [0.91, 1.28]
3.3 Long duration 72 hours	1	32	Ratio of means (Random, 95% CI)	0.86 [0.27, 2.76]
3.4 Long duration 96 hours	2	119	Ratio of means (Random, 95% CI)	1.07 [0.83, 1.38]
4 Pathogen excretion duration	3	141	Mean Difference (IV, Random, 95% CI)	0.40 [0.11, 0.69]
4.1 Long duration 24 hours	1	48	Mean Difference (IV, Random, 95% CI)	0.90 [-0.21, 2.01]
4.2 Long duration 48 hours	1	40	Mean Difference (IV, Random, 95% CI)	0.25 [0.03, 0.47]
4.3 Long duration 72 hours	1	53	Mean Difference (IV, Random, 95% CI)	0.59 [0.16, 1.01]
5 Clinical failure	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Long duration 72 hours	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Long duration 96 hours	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Bacteriological failure	9	672	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.01, 2.32]
6.1 Long duration 24 hours	1	48	Risk Ratio (M-H, Fixed, 95% CI)	7.58 [0.41, 139.32]
6.2 Long duration 48 hours	2	286	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.87, 3.45]
6.3 Long duration 72 hours	3	125	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.58, 2.17]
6.4 Long duration 96 hours	3	213	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.61, 3.90]

ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR	CENTRAL	PUbMed[a]	EMBASE[a]	LILACS	AIM	SCI
1	Cholera	Cholera	"Cholera"[MeSH]	Cholera	Cholera$	Cholera	Cholera
2	Cholerae	Cholerae	Cholera	Cholerae	random$	Cholerae	Cholerae
3	1 or 2	1 or 2	Cholerae	1 or 2	aleator$	1 or 2	1 or 2
			1 or 2 or 3		1 and (2 or 3)		

[a] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2011).

Table 2. Trial location abbreviations

Abbreviation	Country
BGD	Bangaladesh
CIV	Cote d'Ivoire
IND	India
IRN	Iran
LKA	Sri Lanka
NGA	Nigeria
PAK	Pakistan
PER	Peru
SOM	Somalia
THA	Thailand
TUR	Turkey

Table 3. Optimal Information Size Calculations: Continuous outcomes

Outcome	Hypothesis	Power	α error	Mean in control group	Mean in intervention group	Standard deviation	Total sample size required
Diarrhoea duration	Superiority	80%	5%	30[1]	15	10	14
				30[1]	22	10	50
				130[1]	65	40	12
				130[1]	98	40	50
Duration of pathogen excretion	Superiority	80%	5%	3[2]	1.5	1	20
				3[2]	2.25	1	76
				6[2]	3	2	20
				6[2]	4.5	2	76

Calculations performed with http://www.sealedenvelope.com.

[1] The mean duration of diarrhoea in the control groups ranged from 29.3 to 127.2 hours (Analysis 1.1).

[2] The mean hydration requirements in the control groups ranged from 2.97 to 6 days (Analysis 1.6).

Table 4. Optimal Information Size Calculations: Dichotomous outcomes

Outcome	Hypothesis	Power	α error	Proportion in control group	Proportion intervention group	Total sample size required
Clinical failure	Superiority	80%	5%	60%[1]	30%[3]	80
				60%	45%[4]	342
				12%[2]	6%[3]	708
				12%	9%[4]	3272
Bacteriological failure	Superiority	80%	5%	75%	37.5%[3]	48
				75%	56.25%[4]	194
				20%	10%[3]	394
				20%	15%[4]	1806

Calculations performed with http://www.sealedenvelope.com.

[1] The overall proportion of clinical failures in people randomized to placebo or no treatment was 61% (Analysis 1.4).

[2] The overall proportion of clinical failures in people randomized to antibiotics was approximately was 12% (Analysis 1.4).

[3] Based on a RR of 0.5.

[4] Based on a RR of 0.75.

[5] The overall proportion of bacteriological failures in people randomized to placebo or no treatment was 74% (Analysis 1.7).
[6] The overall proportion of bacteriological failures in people randomized to antibiotics was approximately was 20% (Analysis 1.7).

Table 5. Dose comparison

Study	Antimicrobial	Low dose	High dose	Duration	Population
Pierce 1968 IND	furazolidone	200 mg	400 mg	72 hours	Adults
Alam 1990 BGD	doxycycline	200 mg	300 mg	Single dose	Adults
De 1976 IND	doxycycline	Adults: 200 mg; Children: 4 mg/kg	Adults: 300 mg; Children: 6 mg/kg	Single dose	Adults and children
Karchmer 1970 PAK	tetracycline	10 mg/kg/day in 4 doses	31-62 mg/kg/day in 4 doses	7 days	Children
Islam 1987 BGD	tetracycline	1 g	2 g	Single dose	Adults

CONTRIBUTIONS OF AUTHORS

YLK conducted the preliminary search. YLK and MP selected the studies for the review and extracted the data. AN and RB assisted in risk of bias assessment and the second revision. MAS was consulted where problems arose. YLK performed all necessary calculations for conversion of data and entered data into Review Manager 5. YLK and MP performed the data analysis. YLK and MP wrote the first draft of the review and all authors revised and wrote the final review.

DECLARATIONS OF INTEREST

None declared. Prof. Mohammed Abdus Salam is an author of some of the trials included in our review.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Methods of pooling outcomes dependent on weight were changed from standardized mean differences (SMDs) to ratio of means. SMDs had no clinical meaning and could not be translated into a clinically meaningful outcome because of the varying standard deviations reported in the trials. The SMD analysis also abolished the heterogeneity that was apparent when looking at the results of the individual trials.

- We decided to exclude antimicrobials that are not currently in clinical use for treating cholera.

- With regards to data analysis, in order to include all patients in trials with multiple study arms, we acted as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). For dichotomous results, we divided the number of events and participants in the placebo arm, and for continuous results we divided the number of participants and used mean and standard deviation as is. This was done instead of using the antimicrobial 'hierarchy' first designed in the protocol for this review, which allowed the inclusion of only one study arm versus, placebo from these trials.

- We added subgroup analyses based on timing definitions for monitoring and severity of dehydration at baseline. We omitted sensitivity analyses regarding intention to treat in the outcome of clinical failure.

- We changed the time definitions for the outcomes of clinical failure and bacteriological failure.

- We did not include the outcomes of clinical and bacteriological relapse in our review. The reason for this decision was that relapse could occur only in patients that had been cured (for example, patients who never stopped purging could never relapse). This definition caused a bias against the arms receiving antimicrobial treatment, which seemed to experience relapse more than the placebo/no treatment arms.