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Antimicrobials for treating symptomatic non-typhoidal *Salmonella* infection (Review)

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[Intervention Review]

Antimicrobials for treating symptomatic non-typhoidal *Salmonella* infection

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ABSTRACT

Background

Non-typhoidal *Salmonella* (NTS) commonly causes diarrhoea, and is usually self-limiting, although sometimes people become ill with sepsis and dehydration. Routine antibiotic use for this infection could result in persistent colonization and the spread of resistant bacterial strains.

Objectives

To assess the efficacy and safety of giving antibiotics to people with NTS diarrhoea.

Search methods

We searched the Cochrane Infectious Diseases Group trials register (up to August 2012), the Cochrane Controlled Trials Register (CENTRAL) published in *The Cochrane Library (*up to Issue 8 2012); and MEDLINE, African Index Medicus, CINAHL, EMBASE, LILACS, and the Science Citation Index, all up to 6 August 2012. We also searched the *meta*Register of Controlled Trials *(m*RCT) for both completed and on going trials and reference lists of relevant articles.

Selection criteria

Randomized controlled trials (RCTs) comparing any antibiotic treatment for diarrhoea caused by NTS species with placebo or no antibiotic treatment. We selected trials that included people of all ages who were symptomatic for NTS infection. Examples of symptoms included fever, abdominal pain, vomiting and diarrhoea. We excluded trials where the outcomes were not reported separately for the NTS subgroup of patients. Two review authors independently applied eligibility criteria prior to study inclusion.

Data collection and analysis

Two review authors independently extracted data on pre-specified outcomes and independently assessed the risk of bias of included studies. The primary outcome was the presence of diarrhoea between two to four days after treatment. The quality of evidence was assessed using the GRADE methods.

Main results

Twelve trials involving 767 participants were included. No differences were detected between the antibiotic and placebo/no treatment arms for people with diarrhoea at two to four days after treatment (risk ratio (RR) 1.75, 95% confidence interval (CI) 0.42 to 7.21; one trial, 46 participants; very low quality evidence). No difference was detected for the presence of diarrhoea at five to seven days after treatment

(RR 0.83, 95% CI 0.62 to 1.12; two trials, 192 participants; very low quality evidence), clinical failure (RR 0.88, 95% CI 0.62 to 1.25; seven trials, 440 participants; very low quality evidence). The mean difference for diarrhoea was 0 days (95% CI -0.54 to 0.54; 202 participants, four studies; low quality evidence);for fever was 0.27 days (95% CI -0.11 to 0.65; 107 participants, two studies; very low quality evidence); and for duration of illness was 0 days (95% CI -0.68 to 0.68; 116 participants, two studies; very low quality evidence). Quinolone antibiotic treatment resulted in a significantly higher number of negative stool cultures for NTS during the first week of treatment (microbiological failure: RR 0.33, 95% CI 0.20 to 0.56; 166 participants, four trials).

Antibiotic treatment meant passage of the same *Salmonella* serovar one month after treatment was almost twice as likely (RR 1.96, 95% CI 1.29 to 2.98; 112 participants, three trials), which was statistically significant. Non-severe adverse drug reactions were more common among the patients who received antibiotic treatment.

Authors' conclusions

There is no evidence of benefit for antibiotics in NTS diarrhoea in otherwise healthy people. We are uncertain of the effects in very young people, very old people, and in people with severe and extraintestinal disease. A slightly higher number of adverse events were noted in people who received antibiotic treatment for NTS.

8 May 2019

No update planned

Other

Many trials of antibiotics in people with Salmonella have been conducted, which do not show an effect. Therefore, an update is not a current priority for the CIDG.

PLAIN LANGUAGE SUMMARY

Antibiotics for non-typhoidal *Salmonella* diarrhoea

Non-typhoidal *Salmonella* (NTS) can cause diarrhoea in people. In this review, we investigated the benefits and safety of antibiotics for treatment of NTS versus placebo or no antibiotic treatment. We found that in otherwise healthy people, treatment with antibiotics did not have any benefit over treatment with no antibiotics. Furthermore, treatment with antibiotics made it more likely that patients would continue to excrete the same organisms for up to one month after treatment. We are unable to comment on the use of antibiotics in very young people, very old people and people who are unable to fight off infection because the trials we identified did not include these patients.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Antibiotics versus placebo or no treatment for treating symptomatic NTS infection

Antibiotics versus placebo or no treatment for treating symptomatic NTS infection

Patient or population: patients symptomatic for NTS infection
Settings:
Intervention: Any antibiotic versus placebo or 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				
	Control	Antibiotics versus placebo or no treatment				
Duration of diarrhoea (days)	The mean duration of diarrhoea (days) ranged across control groups from **3 to 13 days**	The mean duration of diarrhoea (days) in the intervention groups was **0 higher** (0.54 lower to 0.54 higher)		202 (4 studies)	⊕⊕⊖⊖ **low**[1,2,3]	
Duration of fever (days)	The mean duration of fever (days) ranged across control groups from **1 to 2 days**	The mean duration of fever (days) in the intervention groups was **0.27 higher** (0.11 lower to 0.65 higher)		107 (2 studies)	⊕⊖⊖⊖ **very low**[1,4,5]	
Duration of illness (days)	The mean duration of illness (days) ranged across control groups from **3 to 19 days**	The mean duration of illness (days) in the intervention groups was **0 higher** (0.68 lower to 0.68 higher)		116 (2 studies)	⊕⊖⊖⊖ **very low**[1,5,6]	
Clinical treatment failure (Persistent or worsening symptoms at the end of treatment)	**230 per 1000**	**202 per 1000** (143 to 287)	**RR 0.88** (0.62 to 1.25)	440 (7 studies)	⊕⊖⊖⊖ **very low**[1,7,8]	
Presence of diarrhoea at 2-4 days	**77 per 1000**	**135 per 1000** (32 to 555)	**RR 1.75** (0.42 to 7.21)	46 (1 study)	⊕⊖⊖⊖ **very low**[1,5,9]	

Presence of diarrhoea at 5-7 days	**456 per 1000**	**378 per 1000** (282 to 510)	**RR 0.83** (0.62 to 1.12)	192 (2 studies)	⊕⊖⊖⊖ **very low**[1,5,10]

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

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

[1] Downgraded by one for risk of bias: allocation concealment was not adequately described in any of these studies.
[2] No serious indirectness: these four trials have tested standard doses of chloramphenicol, amoxicillin, ampicillin, ciprofloxacin, sulfadoxine-pyrimethamine, azithromycin, and cefixime. Most of the patients were children and severe cases have generally been excluded.
[3] Downgraded by one for imprecision: each of these antibiotics have only been tested in a single trial, and these trials are too small to confidently exclude the possibility of an effect.
[4] No serious indirectness: these two trials have tested four different antibiotics: ciprofloxacin, trimethaprim-sulfamethoxazole, azithromycin and cefixime. One trial was in adults and one in children.
[5] Downgraded by two for imprecision: each antibiotic was evaluated in a single small trial, with too few patients to confidently detect or exclude clinically important benefits or harms
[6] Downgraded by one for indirectness: one trial testing chloramphenicol is now over 50 years old. The remaining trial has only tested ciprofloxacin and trimethoprim-sulfamethoxazole.
[7] Dowgraded by one for inconsistency: one trial of norfloxacin did show a statistically significant benefit compared to placebo. However this result should be repeated before concluding that norfloxacin is beneficial.
[8] Downgraded by one for imprecision: these trials are individually small and tested different antibiotics. Even the cumulative sample size remains underpowered to confidently exclude benefits.
[9] Downgraded by one for indirectness: these two studies have only tested norfloxacin and fleroxacin. Clinically important benefit with alternative antibiotics cannot be excluded.
[10] Downgraded by one for indirectness: these two trials have only evaluated ampicillin and norfloxacin.

BACKGROUND

Description of the condition

Infection with *Salmonella* bacteria can cause typhoid fever in people if they are infected with *Salmonella enterica enterica*, serovar Typhi (*S.* Typhi) or *S. enterica enterica*, serovar Paratyphi (*S.* Paratyphi) A, B and C. Non-typhoidal *Salmonella* (NTS) disease is caused if the infectious agent is any of the NTS serovars, such as *S. enterica enterica*, serovar Enteritidis, or *S. enterica enterica*, serovar Typhimurium**.** This review focuses on NTS infection, which can present as either an invasive disease or as enterocolitis with diarrhoea. Another Cochrane Review studied treatments for typhoid fever (Effa 2011). This review examines the currently available body of evidence regarding antibiotic treatment of NTS infection. This review is an update of part of an earlier review which investigated the use of antibiotics for the treatment of both symptomatic and asymptomatic NTS infection (Sirinavin 2000).

Epidemiology

NTS infection is an important cause of food poisoning in most areas of the world. The disease is often under-reported as affected people can sometimes be asymptomatic and hence do not go to the hospital for treatment (Rabsch 2001). In the USA, an estimated 1.4 million people suffer from the disease annually, of which about 80,000 to 160,000 seek medical attention, approximately 16,000 are hospitalized and about 600 people die from the disease (Mead 1999). Invasive disease due to *Salmonella enterica enterica* serovar Typhi as well as NTS is common in children younger than five years old in developing countries, particularly in many places in sub-Saharan Africa (Graham 2002).

Animals are a major reservoir of NTS infection. The infection is mainly acquired by eating contaminated food, such as poultry, beef and eggs. However, it can also be transmitted by handling farm animals, like chickens. Infection can be passed transovarially from chickens to their eggs. Furthermore, bacteria can be spread by pets, including snakes. There has been a report of fatal *Salmonella* sepsis following platelet transfusion from an asymptomatic donor who acquired the infection from his pet boa constrictor (Jafari 2002). *Salmonella* bacteria can also be transmitted from person to person by the faecal-oral route, by direct contact with a contaminated person or fomites, medicines and rarely by aerosols (Mason 2000).

Although the findings of a prospective study in Africa highlighted the importance of person-to-person transmission in Kenya (Kariuki 2006), animal-to-human transmission is still recognised as being more important in accounting for the current epidemiological patterns of NTS.

Certain host factors, such as gastric acidity, can give some protection from NTS infection and infection usually requires large bacterial inocula. However, in people whose host defence mechanisms have been compromised, for example those on acid-suppressing drugs, patients with pernicious anaemia and infants, there is a higher risk of NTS infection. Notably, liquids which pass through the stomach quickly, or milk and cheese that raise the pH, enable smaller inocula to be infective.

Clinical Features

NTS infection can manifest in two distinct forms: either as an enterocolitis with diarrhoea or as an invasive disease, which can occur without diarrhoea. The latter form is particularly common in sub-Saharan Africa.

The syndrome of enterocolitis is more often present in developed countries and usually manifests with diarrhoea, abdominal pain and cramps, and sometimes fever. Symptoms usually start between six to 72 hours after exposure to the bacteria (but can sometimes be delayed for up a week) and tend to resolve within five to seven days (Hohmann 2001; MDH 2007). In general the incubation period depends on the immune system of the host and the bacterial inoculum size. Infection can cause acute severe diarrhoea or chronic and prolonged diarrhoea, which can result in the disturbance of fluid and electrolyte balances (Mason 2000). NTS infection can be severe, invasive and recurrent in patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), resulting in up to 47% mortality (Gordon 2002; Kankwatira 2004).

The infection can sometimes be invasive when it causes bacteraemia (bacteria in the bloodstream) or has extraintestinal manifestations (Chen 2007; Ispahani 2000). About 2% to 45% of people with diarrhoea may develop bacteraemia (bacteria in the bloodstream) with fever (Zapor 2005), while some may develop bacteraemia without diarrhoeal episodes (Boyle 2007). NTS can cause life-threatening infection in some individuals, especially those with HIV/AIDS. Recurrent *Salmonella* septicaemia is one of the conditions that defines the AIDS (Boyle 2007). Children with sickle cell anaemia are particularly at risk of NTS osteomyelitis.

Extraintestinal manifestations can result in complications, with various clinical focal syndromes affecting the meninges, bones, joints, adrenal gland, aorta, inner lining of the heart, the kidneys/urinary tract, and the lungs (Diez Dorado 2004; Zapor 2005). The risk factors for invasive disease in adults and children include immunosuppression of any cause, including HIV-positive status, malaria infection, severe anaemia, or malnutrition (Morpeth 2009). The development of extraintestinal focal infections is associated with higher mortality rates, more severe septic manifestations, longer hospital stays and a longer duration of antimicrobial therapy (Chen 2007).

In an attempt to further understand the molecular biology of the NTS strains responsible for invasive disease in sub-Saharan Africa, multilocus sequence analysis of certain strains of *S.* Typhimurium from patients in Kenya and Malawi was performed. A dominant genotype, ST 313, was identified which is responsible for many cases of the invasive disease. ST 313 isolates harbour genome signatures that differentiate them from *S.* Typhimurium causing gastroenteritis in other regions of the world. These include a novel repertoire of prophage elements and evidence of genome degradation (Kingsley 2009). In Africa, ST 313 infection presents as a separate clinical entity with generalized sepsis and focal infection due to its adaptability to the human host.

Some people may have infection caused by NTS without showing any symptoms of the disease while excreting the organism in their stool (asymptomatic carriers) (Jertborn 1990). In certain cases following recovery from symptoms of the disease, individuals continue to excrete NTS bacteria in their stools (convalescent carriers) (Buchwald 1984). These carrier states can be for a short period of time. However, excretion of the organism may be prolonged especially in children aged less than five years old and

can persist for more than a year (chronic carriers) (Buchwald 1984; Mason 2000). A carrier is considered cured from the first day of three consecutive negative stool cultures (ie when the *Salmonella* is absent in the stool), and this may be difficult to achieve with antibiotic treatment (Carlstedt 1990).

Diagnosis

Salmonellosis is diagnosed by isolating *Salmonella* bacteria from the stool, blood (if associated with bacteraemia and extraintestinal infection) (Kankwatira 2004), or, less commonly, urine (if there is a focal infection of the urinary tract) (Diez Dorado 2004; Vallenas 1985). *Salmonella* bacteria can also be isolated from bone marrow aspirates. The bacterial concentration in bone marrow can sometimes be as much as 10 times that in peripheral blood. In patients who have received antibiotic treatment, the bacteria may still be found in the bone marrow even when it may no longer be present in the blood when cultured.

Description of the intervention

Antimicrobial agents are either natural or synthetic substances which can kill or inhibit the growth of microbial organisms. They are generally described based on their mechanism of action which may determine if a particular antibiotic may be clinically useful for the treatment of an infection.

How the intervention might work

There are several reasons why clinicians have concerns regarding the use of antibiotics to treat NTS infection. Antibiotic use may not result in rapid control of symptoms or stop the excretion of the bacteria in stools. Instead it may lengthen the time period that bacteria are excreted in the stools, thereby increasing the risk of infecting other people (Lin 2003). Concerns about the development of antibiotic resistance have limited their use for NTS treatment (Hakanen 2006; Molbak 2002; Panhotra 2004; Rowe 1997) and infection with multiple-drug resistant strains of NTS has been noted to result in higher mortality and morbidity rates.

There have been several reports regarding the emergence of antibiotic resistant strains of NTS, particularly following the increased and more widespread use of antibiotics for treatment of NTS infection in livestock. The number of cases appears to be increasing (Frost 1996; Hakanen 2006; Molbak 2002).

Notably, some people continue to carry S*almonella* bacteria even after the antibiotics have treated the symptoms. For example, the previous version of this Cochrane Review showed that antibiotic treatment may result in more negative stool cultures especially during the first week of treatment, with more positive stool cultures after the third week of treatment due to relapse of infection (Sirinavin 2000). Also, there are risks of adverse drug reactions to these antibiotics, such as skin rash with ampicillin, leucopenia with co-trimoxazole, and urticaria, severe headache, nausea, epigastric pain, and dizziness with fluoroquinolones (Reese 1991). There are also concerns regarding the use of quinolones in young children because of the risk of tendonitis (Yee 2002).

Why it is important to do this review

This review is an update of certain aspects of a previous Cochrane Review, which investigated the use of antibiotics for treating *Salmonella* gut infections in both symptomatic and asymptomatic people (Sirinavin 2000). Since the review, the use of new antibiotics, such as fluoroquinolones for adults and third-generation cephalosporins for children, has become more widespread and new trials have been conducted using these drug interventions. In this review, we have focused our investigation on NTS symptomatic patients only. We have updated the review methods to reflect recent methodological changes and we searched for new trials taking into account these changes.

OBJECTIVES

To evaluate the efficacy and safety of antimicrobial agents for treating NTS infection.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs).

Types of participants

People with culture-proven NTS infection (excluding *S.* Typhi and *S.* Paratyphi A, B and C).

We also included studies that investigated diarrhoea in general and analysed patients with culture-proven NTS patients as a subgroup.

Studies evaluating only asymptomatic patients were excluded.

Types of interventions

Intervention

Oral or parenteral antibiotic (at any dose and for any duration of treatment).

Control

Placebo or no treatment.

Types of outcome measures

Primary

- Presence of diarrhoea at two to four days afer randomization.

Secondary

- Duration of diarrhoea.
- Presence of diarrhoea at five to seven days.
- Clinical failure (defined as worsening or persistent symptoms at the end of the treatment regime).
- Presence of fever at two to four days (from commencement of treatment/randomization).
- Duration of fever (from randomization).
- Duration of illness.
- Presence of life-threatening extraintestinal focal infection (meningitis, septic arthritis, pneumonia, osteomyelitis, bacteraemia, pyelonephritis).
- All cause death.
- Microbiological failure (defined as culture-proven *Salmonella* infection at the end of the treatment regime).
- Faecal carriage of the same *Salmonella* serovar one month after the end of antibiotic treatment.

Adverse Events

- Other adverse events.

Search methods for identification of studies

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

Electronic searches

Databases

We searched the following databases using the search terms detailed in Table 1: Cochrane Infectious Disease Group Specialized Register (up to August 2012); Cochrane Central Register of Controlled Trials (CENTRAL) published in *The Cochrane Library* (Issue 8 2012); MEDLINE (from 1966 to 6 August 2012); African Index Medicus (accessed on 14 August 2012), CINAHL (from 1981 to 6 August 2012), EMBASE (from 1980 to 6 August 2012); LILACS (from 1982 to 6 August 2012); and the Science Citation Index (from 1970 to 6 August 2012). We also searched the *meta*Register of Controlled Trials (*m*RCT) on 6 August 2012 for both completed and ongoing trials (Table 2) and the reference lists of relevant articles.

Searching other resources

Organizations and pharmaceutical companies

To help identify unpublished and ongoing trials, we contacted the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC) and the pharmaceutical companies Pfizer and GlaxoSmithKline. We also searched the WHO Clinical Trials platform for relevant ongoing trials.

Conference proceedings

We searched the following conference proceedings for relevant abstracts: the International Symposium on Typhoid Fever and Other Salmonellosis (from 2000 to 2010) and the International Symposium on Invasive Salmonelloses (from 2000 to 2008).

Reference lists

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

Data collection and analysis

Selection of studies

Two authors (IO, CO) independently screened the results (titles and abstracts) of the literature search for potentially relevant trials. We retrieved full text articles of the potentially relevant trials and independently determined whether they met the review inclusion criteria using a pre-tested eligibility form. For each step of the review, we resolved contentious issues through discussion. We consulted an editor from the Cochrane Infectious Disease Group where necessary. We also attempted to contact trial authors for further information where trial eligibility was unclear. We have listed all excluded studies along with the reason for exclusion (see Characteristics of excluded studies). We ensured that trials with multiple publications were included only once.

Data extraction and management

Two authors (IO, CO) independently extracted data using a pre-tested data extraction form. One author (CO) entered the data into Review Manager 5 while a second author (IO) cross-checked the data for completeness and accuracy. We extracted data concerning the number of participants randomized and the number of participants analyzed in each group for each reported outcome. For dichotomous outcomes we extracted data concerning the total number of participants randomized, the number of participants experiencing the events and number of participants in each treatment group. For continuous outcomes, we extracted the number of participants for each treatment arm, arithmetic means and standard deviations. Where we encountered data with skewed distribution, we extracted geometric means and standard deviations on the log scale where geometric means were reported, or medians and ranges if medians were reported. For rate and count outcomes (such as participants with outcomes that occurred more than once over the period of trial), we extracted the number of events or episodes experienced in each trial arm and person-time over which the events were experienced for each group. We extracted hazard ratios and standard deviations for time-to-event outcomes (such as the development of life-threatening extraintestinal focal infection). We extracted data on reported adverse events. We contacted the trial authors where the relevant details were not recorded or were unclear. We resolved any disagreements regarding data extraction through discussion and by asking the third review author to attempt data extraction. If necessary, we also sought assistance from an editor with the Cochrane Infectious Diseases Group.

Assessment of risk of bias in included studies

Two review authors (IO, CO) assessed the risk of bias independently according to the specifications of the latest edition of the Cochrane Handbook (Higgins 2011). We independently assessed the risk of bias within each included study in relation to the following five domains:sequence generation, allocation concealment, blinding, handling of incomplete outcome data and selective outcome reporting by using the ratings of 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias).

Details of specific assessments are as outlined in the Cochrane Handbook (Higgins 2011).

Measures of treatment effect

Continuous data

We analysed continuous data if means and standard deviations were available. Where mean differences were provided, we extracted and utilized these values for the analysis irrespective of whether mean and standard deviation values were provided as we were interested in post-intervention values. We re-calculated the standard deviation values in instances where the standard error was reported. Also, we extracted data from studies that reported adequately on skewed continuous data as medians rather than means. Where appropriate, we have reported these data separately.

Binary data

We analysed binary outcomes by calculating the risk ratio (RR) with 95% confidence interval (CI).

Dealing with missing data

When necessary, we attempted to contact the study author(s) to supply any unreported data (eg group means and standard deviations (SDs), details of dropouts, and details of interventions received by the control group). If a study reported outcomes for participants that completed the trial only or for participants who followed the protocol only, we contacted authors to provide additional information to facilitate intention-to-treat analyses. In instances where this was not possible we performed a complete case analysis.

Assessment of heterogeneity

We assessed statistical heterogeneity by examining the I^2 statistic (Higgins 2011), which describes approximately the proportion of total variation that is due to variation between studies. In addition, we employed the Chi^2 test of homogeneity at 10% level of statistical significance to determine the strength of evidence against the hypothesis that all studies come from the same population. An I^2 statistic value of between 0% and 40% may not be significant; of between 30% to 60% may represent moderate heterogeneity; of between 50% to 90% may represent statistical heterogeneity; and between 75% and 100% may indicate considerable heterogeneity. We also inspected forest plots, as poor overlap may be due to significant heterogeneity.

Assessment of reporting biases

We had planned that if there are more than 10 trials in a comparison, we will prepare funnel plots (estimated treatment effects against their standard error) to explore publication bias. Asymmetry could be due to publication bias, but can also be due to a relationship between trial size and effect size. As we did not identify at least 10 trials for any comparison, we did not prepare funnel plots to explore publication bias.

Data synthesis

We conducted meta-analyses for trials with similar characteristics. We aimed to carry out an intention-to-treat analysis but we carried out a complete-case analysis where there was loss to follow-up. We used the fixed-effect model and presented all our results with 95% CI.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses to assess the benefit of antibiotic treatment. Subgroups were as follows: participant age (infants < 1 year versus elderly > 60 years); route of drug administration (oral versus parenteral); hospitalization (hospitalized versus not hospitalized); and type of antibiotic (fluoroquinolone versus other antibiotics). Where there was sufficient data, we conducted subgroup analyses to investigate the effect of the antibiotic on the absence of diarrhoea at two days and at four days post treatment.

We planned to assess important clinical heterogeneity by comparing the distribution of important clinical (study participants, study setting, type of intervention and co-intervention) and methodological (randomization, allocation concealment, blinding of outcome assessment, losses to follow up) heterogeneity factors. However this was not possible due to insufficient data.

Also, we could not perform most of the planned subgroup analyses because of insufficient data.

Sensitivity analysis

We conducted sensitivity analyses to explore the effect of the methodological quality of the trials and to ascertain whether studies with a high risk of bias overestimated the effect of treatment.

RESULTS

Description of studies

Results of the search

Our search for this review (Table 1) retrieved 70 potentially relevant records after duplicate records were removed. This search was last updated on the 6 August 2012 with no new relevant additions. We found one ongoing trial that met our eligibility criteria (Tsai 2012) .

Types of Studies

Twenty trials met our initial inclusion criteria but we excluded eight of these studies because patients with diarrhoea of different infectious aetiologies were randomized and the data for the *Salmonella* subgroup was not reported in a manner that would be of use to our review (Bessudo 1972; Dryden 1996; Lolekha 1988; Noguerado 1995; Pichler 1986; Pichler 1987; Robins-Browne 1983; Taylor 2006). We therefore included 12 studies in our review, which reported information regarding 767 patients with NTS.

Types of Patients

We included one study that involved both children (aged 12 years) and adults (Wistrom 1992). Five studies (n = 323) included adolescents and adults (Butler 1993; Goodman 1990; Neil 1991; Pitkajarvi 1996; Sanchez 1993) and five studies (n = 284) included infants aged over 6 weeks and children (Chiu 1999; Garcia de Olarte 1974; Kazemi 1973; Macdonald 1954; Nelson 1980). One study (n = 168) included all ages (Joint Project ASID 1970). Almost all studies excluded pregnant patients and those with underlying diseases, previous antibiotic treatment, severe illness and history of allergy to the group of study drug. One study included malnourished children (Garcia de Olarte 1974).

Eleven studies involved sporadic cases of patients presenting for treatment of either acute diarrhoea or travellers' diarrhoea. One study reported an outbreak in hospital personnel in the USA (Neil 1991). Randomization was conducted on diarrhoeal patients prior to culture results being available in eight studies (Butler 1993; Garcia de Olarte 1974; Goodman 1990; Kazemi 1973; Neil 1991; Nelson 1980; Sanchez 1993; Wistrom 1992). All studies included symptomatic patients, but two also included asymptomatic patients (Neil 1991; Pitkajarvi 1996). For assessment of microbiological failure, we used data that combined both symptomatic and asymptomatic patients as the distribution of asymptomatic patients was similar in both the treatment and control groups.

Duration of diarrhoea preceding entry to the study varied between the included studies, however the duration was similar between control and experimental groups in each study. In eleven studies, the history was short (< 7 days). One study had a range of between 1 to 34 days (Nelson 1980). One study did not specifically state the

duration (Joint Project ASID 1970). Garcia de Olarte 1974 included patients who were less than and more than seven days with the diarrhoea. In one study, patients were randomized on the ninth day following onset of symptoms (Neil 1991).

Studies were from Europe and Scandinavia (four studies), North America (four studies), Australia (one study) Taiwan (one study). There were two international multicentre studies: one included Italy, Thailand, Indonesia, Ivory coast, Mexico and Israel and the second included Asia, South America and Italy. There was one study from Colombia.

Exact *Salmonella* serovars were not reported in all of the studies. The outbreak assessed in Neil 1991 was caused by *S. java*. About 90% of culture positive cases were caused by *S. enteritidis* in one study (Pitkajarvi 1996), and by *S. typhimurium* in another (Macdonald 1954). In two studies in infants and children (Kazemi 1973, Nelson 1980), *S. typhimurium* was the cause in 31% and 53% of the patients, respectively.

Types of Intervention

Ten different drugs were investigated including: norfloxacin (two studies, Pitkajarvi 1996; Wistrom 1992), cotrimoxazole (three studies Goodman 1990; Sanchez 1993; Kazemi 1973), ampicillin (three studies Garcia de Olarte 1974; Kazemi 1973; Nelson 1980), ciprofloxacin (three studies Goodman 1990; Neil 1991; Sanchez 1993), neomycin (one study Joint Project ASID 1970), chloramphenicol (one study Macdonald 1954), amoxycillin (one study Nelson 1980), azithromycin (one study Chiu 1999), cefixime (one study Chiu 1999) and fleroxacin (one study Butler 1993). Nine studies included a placebo comparison, and three studies included a comparison against no treatment. Dose schedules, route of administration and duration varied across trials (see Characteristics of included studies).

Duration of treatment varied between three to 14 days. One study included single dose treatment (fleroxacin) (Butler 1993), but all the rest of the studies included multiple dose treatment. Seven trials had treatment regimens that lasted for five days (Chiu 1999; Garcia de Olarte 1974; Goodman 1990; Joint Project ASID 1970; Nelson 1980; Sanchez 1993; Wistrom 1992). One trial lasted for three days (Butler 1993), three trials had regimens that lasted between 10 to 14 days (chloramphenicol, norfloxacin, or ciprofloxacin; Macdonald 1954; Neil 1991; Pitkajarvi 1996), and one trial lasted for seven days (Kazemi 1973).

In all the included trials, most of the *Salmonella* strains were sensitive to the study drugs. One study reported on *Salmonella* strains resistant to ampicillin, which was the drug used in the study. This resistance was reported in three patients treated with ampicillin but not enough data was provided to enable comparison with the placebo group.

Outcome Assessment

The period of follow-up varied between six months and five days. In two studies (Butler 1993; Garcia de Olarte 1974), follow-up was less than 14 days and was 14 days in two studies (Goodman 1990; Macdonald 1954). Length of follow-up was between five to eight weeks in five studies (Chiu 1999; Neil 1991; Nelson 1980; Sanchez 1993; Joint Project ASID 1970), three months in one study (Wistrom 1992) and six months in two studies (Kazemi 1973; Pitkajarvi 1996). However, in the longer periods of follow-up the number of evaluable patients dropped considerably.

Differences between the studies in the present review and the previous version

This review includes only RCTs that have investigated the use of antibiotics for the treatment of symptomatic NTS infection. We have excluded quasi-RCTs and trials that have investigated the use of antibiotics in the treatment of asymptomatic infection. These trials were included in the earlier version of the review (Sirinavin 2000).

Risk of bias in included studies

Risk of bias in the included studies is presented in Figure 1 and Figure 2.

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

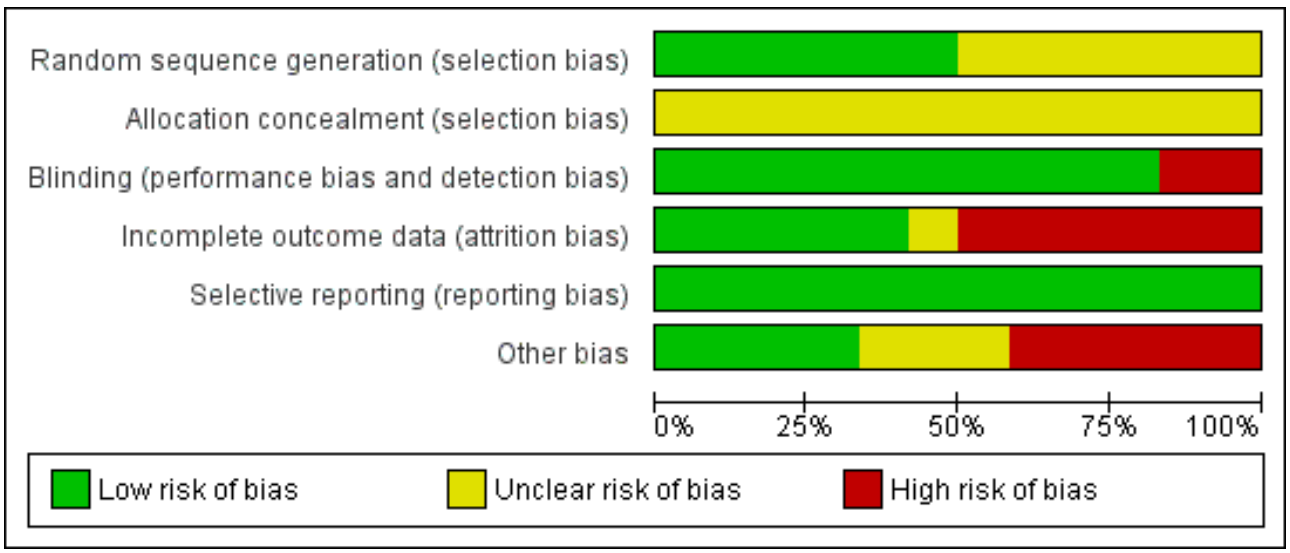


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

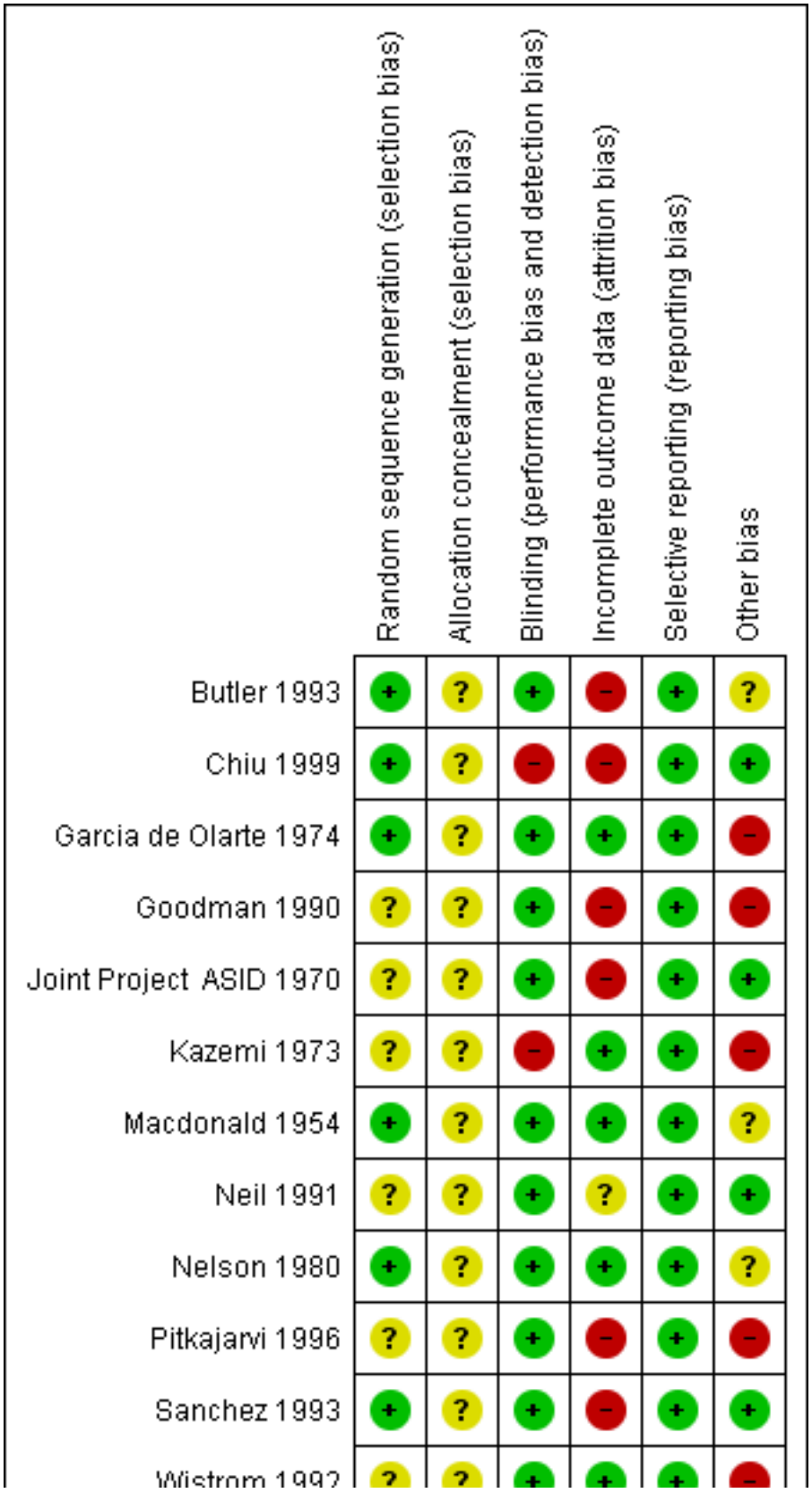
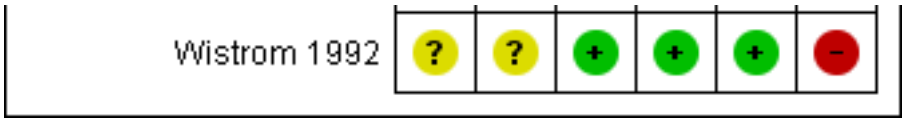


Figure 2. (Continued)



Allocation

Generation of allocation sequence was reported and judged to be adequate in six studies (Butler 1993; Chiu 1999; Garcia de Olarte 1974; Macdonald 1954; Nelson 1980; Sanchez 1993). It was not reported and judged to be unclear in six studies(Goodman 1990; Joint Project ASID 1970; Kazemi 1973; Neil 1991; Pitkajarvi 1996; Wistrom 1992).

No studies explicitly reported concealment of allocation.

Blinding

With regard to blinding, 10 studies were described as double blinded and also gave matching placebo to the control arm (Butler 1993; Garcia de Olarte 1974; Goodman 1990; Joint Project ASID 1970; Macdonald 1954; Neil 1991; Nelson 1980; Pitkajarvi 1996; Sanchez 1993; Wistrom 1992). Two studies were not blinded (Kazemi 1973; Chiu 1999) and we therefore judged these as having a high risk of bias.

Incomplete outcome data

Six studies (Butler 1993; Chiu 1999; Goodman 1990; Joint Project ASID 1970; Pitkajarvi 1996; Sanchez 1993) did not account for incomplete outcome data.

Five studies (Garcia de Olarte 1974; Kazemi 1973; Macdonald 1954; Nelson 1980; Wistrom 1992) did account for incomplete outcome data. We judged Neil 1991 as unclear with regard to incomplete outcome because we were unable to assess how the trialists dealt with incomplete outcome data.

Selective reporting

Regarding selective outcome reporting, we did not have the trial protocol for the included studies and could not determine whether the authors had reported them selectively or not. However, we had no reason to believe they were selectively reported and we have judged this factor as low risk in all studies.

Other potential sources of bias

Six studies (Garcia de Olarte 1974; Goodman 1990; Kazemi 1973; Neil 1991; Pitkajarvi 1996; Wistrom 1992) were funded by drug companies and the authors have not made any statements regarding the extent of involvement of these companies in the design, conduct, analysis and reporting of the trials. In four studies (Butler 1993; Joint Project ASID 1970; Macdonald 1954; Nelson 1980) we do not have information regarding the source of funding. One study (Chiu 1999) was funded by the National Health Research Council and one study (Sanchez 1993) was funded by the hospital's Department of Medicine. We judged as unclear those studies that did not provide information regarding the source of funding and we judged as low risk those studies that were funded by neutral bodies such as research institutes and hospital departments.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotics versus placebo or no treatment for treating symptomatic NTS infection

Primary outcome

Presence of diarrhoea at two to four days

One small study reported this (RR 1.75, 95% CI 0.42 to 7.21; n = 46; Analysis 1.1; Butler 1993).

Secondary outcomes

Duration of diarrhoea

This was reported in nine trials, but only four studies provided a measure of variance (Chiu 1999; Macdonald 1954; Nelson 1980; Sanchez 1993). A fixed-effect meta-analysis using the generic inverse variance method yielded a mean difference of -0.00 days (95% CI -0.54 to 0.54), thus not detecting any impact of antibiotics on duration of diarrhoea (Analysis 1.2). However, two of the studies (Chiu 1999; Nelson 1980) in this meta-analysis had skewed data. This finding appears to be consistent across some of the other studies listed in Table 3.

Presence of diarrhoea at five to seven days

Clinical assessment at 5 to 7 days post treatment was reported in two trials with data that we could use (Garcia de Olarte 1974; Wistrom 1992); no effect of antibiotics was demonstrated (RR 0.83, 95% CI 0.62 to 1.12; Analysis 1.3).

Clinical failure

We defined this as worsening or persistent symptoms at the end of treatment, and we were able to assess this in seven trials (Butler 1993; Chiu 1999;Garcia de Olarte 1974; Macdonald 1954; Nelson 1980; Sanchez 1993). No effect was detected overall (RR 0.88, 95 % CI 0.62 to 1.25; Analysis 1.4).

In studies by Sanchez 1993 and Chiu 1999 no clinical relapses were observed.

In the study by Pitkajarvi 1996, one of the patients was reported to have diarrhoea at day 10 when the treatment regimen had ended. We judged this patient to have encountered treatment failure but the trialists did not give specific information as to the group to which this patient belonged.

Presence of fever at two to four days

No studies defined and reported this outcome in a way that would enable us to extract it as a separate outcome for further analysis.

Duration of fever

Chiu 1999 and Sanchez 1993 reported on this outcome and we performed a meta-analysis to examine the overall effects

of antibiotics on this outcome. There were differences in study characteristics in terms of their patient population and antibiotic intervention, which gave a mean difference of 0.27 days (95% CI -0.11 to 0.65; Analysis 1.5) and showed no difference that could be attributed to antibiotics . However, this result was generated with skewed data. This finding is consistent across the other studies that we could not combine. We have listed them in Table 4.

Duration of illness

We were able to analyse the results for this outcome from two studies (Macdonald 1954; Sanchez 1993), which demonstrated no difference in duration of illness between the groups that could be accounted for by antibiotics (Mean difference -0.00 days, 95% CI -0.68 to 0.68; Analysis 1.6).

This finding was also found to be consistent with the other studies we could not perform meta-analysis on (Table 5).

This outcome was reported by Joint Project ASID 1970 in the form of a graph and we attempted to extract this data from the graph. However we encountered two problems: firstly, the total percentage of patients reported in the graph did not add up to a 100% so it is possible that not all the patients were included in that analysis, and secondly, the standard deviation was not reported and could not be calculated.

Presence of life-threatening extraintestinal focal infection

There was no information on this outcome in any of the included studies. This may be partially because all existing studies excluded the types of patients in which this complication could have been more likely.

All-cause death

Garcia de Olarte 1974 reported 12 deaths among the patients in their trial, two of which occurred in patients culture proven for *Salmonella.* However, the trialists did not mention the group to which they were randomized.

Butler 1993 reported three deaths and these were not in the *Salmonella* subgroup of patients.

Bacteriological outcomes

Salmonella cultures were conducted at varying periods in the included studies after the start of treatment. Many studies excluded from follow-up patients that had become culture negative (based on two to three consecutive negative cultures) so they could not detect patients who relapsed. Also, some studies had high dropout rates.

Microbiological failure

We defined this as culture-proven*Salmonella* infection at the end of therapy. We were able to extract data on this outcome from eight trials (Butler 1993; Garcia de Olarte 1974; Goodman 1990; Joint Project ASID 1970; Kazemi 1973; Macdonald 1954; Neil 1991; Pitkajarvi 1996) to enable meta-analysis to be performed. We conducted an a-priori subgroup analysis to investigate the differential impact of quinolone antibiotics versus placebo or no treatment compared to other antibiotics versus placebo or no treatment. Quinolone antibiotics appeared better at preventing microbiological failure when compared to placebo or no treatment (RR 0.33, 95 % CI 0.2 to 0.56; Analysis 1.7).There was no difference between antibiotic and no treatment with regard to microbiological failure with other antibiotics. We excluded the Wistrom 1992 study from the quinolone subgroup because outcome assessment in this study occurred much later after treatment and the results increased the inherent heterogeneity in the comparison. It showed no advantage over treatment with quinolones. The study with the largest weighting in the non-quinolone subgroup (Joint Project ASID 1970) used neomycin which is a non-absorbable antibiotic.

Other included studies in this review did not contribute data to this meta-analysis because they reported this outcome without stratifying according to which organism was cultured for the respective patients in their trials or reported only in qualitative terms.

Faecal carriage of the same Salmonella serovar one month after treatment

We were only able to extract data on this outcome from studies that assessed and reported this outcome for the subgroup of patients of interest in the review (Chiu 1999; Neil 1991; Wistrom 1992). In the study by Wistrom 1992, we extracted data from a graph that reported 39% of placebo patients versus 79% of the norfloxacin patients as being culture positive at 28 to 30 days post treatment. We translated this to 35 out of 45 patients in the antibiotic arm versus 14 out of 37 patients in the placebo arm.

We performed a meta-analysis on these three studies. This showed that antibiotic administration causes a higher incidence of carriage of the same *Salmonella* serovar at one month post treatment, with 41 of 62 events in the antibiotic group compared to 17 of 50 events in the placebo group (RR 1.96, 95 % CI 1.29 to 2.98; Analysis 1.8).

Nelson 1980 reported bacteriologic relapse in four patients in each of the two antibiotic arms and no relapse in the placebo arm. The relapses reported occurred between day 4 and day 52 post intervention. The difference between antibiotic arms and placebo arm was statistically significant (P = 0.003).

Other studies that assessed this outcome at different times also showed findings that appear consistent with the result of our meta-analysis above (Kazemi 1973; Nelson 1980; Pitkajarvi 1996; Sanchez 1993) and this is summarized in Table 6.

Adverse events

We defined serious adverse events as those leading to death, disability or prolonged hospitalization. We were also interested in adverse events that may have required stopping of treatment, for example gross derangements of biochemical markers of toxicity from baseline, and other adverse events that may have been noted during the course of the treatment trials. Not all of the studies reported adverse events. Some studies reported adverse events as overall events in all diarrhoeal patients randomized to comparative groups (Chiu 1999; Garcia de Olarte 1974; Goodman 1990; Joint Project ASID 1970; Macdonald 1954). Again, the individual studies looked at different antibiotic drug classes and different durations and routes of treatment. We decided not to perform a meta-analysis of the data from these trials regarding adverse events but instead perform a narrative synthesis of the reported events with respect to the antibiotic drug class in line with our a priori subgroup analysis.

Quinolone antibiotics

Ciprofloxacin:

Sanchez 1993 reported that 11 patients had slightly raised levels of liver transaminase and one had slight leukopenia. The differences in incidence were not statistically significant between drug and placebo groups. Neil 1991 reported an increase in diarrhoea in five of the eight patients randomized to ciprofloxacin as against one of the eight patients who received placebo. A case of vomiting and two cases of nausea were noted in the ciprofloxacin group. However, all were judged as minor events.

Fleroxacin:

Butler 1993 reported adverse events in 33 patients but there was no significant difference between the groups (antibiotic versus placebo). The most commonly reported symptoms were headache, dizziness, epigastric pain, stomach discomfort and anorexia. No changes were made to therapy.

Norfloxacin:

Pitkajarvi 1996 reported that one patient in the norfloxacin group had nausea that led to discontinuation of treatment on day six of the trial. Wistrom 1992 reported adverse events in 16 and 13 patients in the norfloxacin and placebo groups, respectively. Headache or other central nervous system symptoms were the most common complaint in both groups, reported by 10 and eight patients in the norfloxacin and placebo groups, respectively. Three patients had a severe headache, one in the norfloxacin group and two in the placebo group. One patient reported a severe stomach pain in the placebo group. These adverse events caused a discontinuation of treatment.

Other antibiotics

Kazemi 1973 reported vomiting and generalized maculopapular rash in three and two patients respectively who received sulphamethoxazole trimethoprim. No patient had his drug discontinued.

Nelson 1980 reported candida skin rash in four infants and children after treatment with ampicillin and in one of the children treated with amoxicillin. There was a report of eosinophilia in two ampicillin treated patients and one each in the amoxicillin and placebo groups. Slight elevations of transaminase enzymes were also noted in two placebo patients and one amoxicillin patient. An elevation of blood urea nitrogen was also noted in one of the amoxicillin patients.

DISCUSSION

Summary of main results

The results of this systematic review suggest that antibiotics may not be of clinical benefit for the treatment of NTS diarrhoea. We were unable to demonstrate any statistically significant effect of antibiotic treatment on any of our clinical outcomes of intervention efficacy. Antibiotic administration appeared to increase the risk of microbiological relapse and fecal carriage at follow-up in patients who were treated compared to those who were either not treated or treated with placebo. Although no serious adverse events were reported among the patients in our included studies, a slightly higher number of other adverse events were associated with the use of antibiotics as compared with placebo or no treatment. Although most of the authors did not report statistically significant differences between the antibiotic and placebo groups, the observed adverse events are of enough clinical significance to discourage antibiotic use, particularly when its use is of questionable benefit.

These findings are of importance both from clinical and public health perspectives. Routine antibiotic administration for the treatment of NTS diarrhoea could potentially worsen disease transmission in the community as many of the treated patients could go on to excrete pathogens for longer periods than they normally would if they were not treated with antibiotics. This would have some impact on the incidence of acute bacterial diarrhoeal episodes. There is also the potential for the spread of resistant strains with the use of unnecessary antibiotics. The question regarding the appropriateness or otherwise of antibiotic administration with regard to NTS diarrhoea is one that has been controversial with respect to the findings that have been made in studies that have attempted to answer this question.

Notably, the actual number of patients in the included studies and subsequent meta-analysis were few and when taken alone, may not be enough to detect a statistically and clinically meaningful difference. However, the direction of effect was fairly consistent across the studies in the review.

Overall completeness and applicability of evidence

The studies we included in this review were mostly those that studied patients with acute bacterial diarrhoea, and we extracted data from the NTS subgroup. The studies did not assess the impact of antibiotics on severe diarrhoeal illness caused by *Salmonella*, as severe illness was an exclusion criteria in almost all of the studies. One of our included studies evaluated malnourished children, but no studies evaluated other immunocompromised people (people with AIDS, or other immunocompromising conditions). In one of the trials, immunocompromised people were specifically excluded. We therefore cannot answer the question as to the benefit or otherwise of antibiotic intervention in this group of patients. We could also not answer the question as to the benefit or otherwise of antibiotic administration in very young or very old people as most of the studies did not include these patients at all. In studies where they were included the numbers were very few and outcome assessments were not reported separately. We were therefore unable to perform a subgroup analysis on this category of patients.

One of the potential risks of intestinal salmonellosis in young infants is extraintestinal infection. No study reported on this outcome and this review is unable to provide information as regards the effects of antibiotics on this outcome in children. There was no study of the effect of a fluoroquinolone in infants and young children, partly because of safety concerns stemming from the observed effects on cartilage in animals.

A major concern regarding treatment with fluoroquinolones, and indeed all antibiotics, is the risk of emergence of resistance and outbreaks of infections due to resistant organisms, which could potentially cause serious extraintestinal infections in high risk groups.

Notably, we may have missed studies that assessed people with diarrhoea that included patients with *Salmonella* but did not refer

to this group of patients in its title/abstract or MESH etc, but only in the full text or tables.

Quality of the evidence

Our review utilized evidence from RCTs. Some of the data that we have included in the meta-analysis are skewed and so our overall effect estimates must be interpreted with caution. Using the GRADE process to evaluate the quality of evidence from the trials, most of the evidence is very low quality.

Potential biases in the review process

We faced challenges in our data extraction, and assessment of the intervention effect on our pre-specified outcomes as a result of the generally poor quality of reporting of some of the outcomes in the trials, particularly with regard to the consistent reporting of continuous outcomes. Also, the included trials and some of the excluded trials could have contributed more to the review if the authors had performed subgroup analysis with respect to the isolated pathogens after stool culture. This would help to better elucidate the pattern of antimicrobial drug efficacy in the treatment of bacterial diarrhoea.

Agreements and disagreements with other studies or reviews

Two studies (Carlstedt 1990; Hatalin 1972), which were included in the previous version of the review (Sirinavin 2000), did not meet our inclusion criteria mainly because of methodological issues and because they did not include patients who were symptomatic for NTS gastroenteritis. The present review has utilized data from a new study that was not included in the earlier review (Chiu 1999).

This review is still affected by some of the methodological issues in the included trials in the earlier version of the review. However, the results of our review is in agreement with the previous review.

Only one new trial is now available that was not available at the time of the 1999 review. None of the identified trials have investigated invasive NTS disease. This highlights the need for more research into other aspects of NTS infection.

AUTHORS' CONCLUSIONS

Implications for practice

We are unable to demonstrate a positive clinical effect of antibiotic therapy on the treatment of NTS diarrhoea in people with non-severe diarrhoea. Adverse drug reactions, although minimal, do occur with antibiotic treatment. Antibiotic administration, therefore, should not be routinely recommended. For patients with some underlying immunosuppressive disorder, or in patients who are very young or very old, current data are insufficient to make a conclusive statement as regards appropriate management.

Antibiotic therapy appears to result in early negative stool cultures, but higher rates of relapse afterwards.

Implications for research

We are unable to comment on the effects of antibiotic therapy on NTS intestinal infection in the high-risk groups for extraintestinal invasion (infants, elderly and immuno-compromised patients) and on severe diarrhoea. There is a need for further randomized, placebo controlled trials in these patients. These trials would have to be adequately powered to enable the detection of clinically meaningful effects and multicentre collaboration may be beneficial.

New antibiotics with potential for therapeutic usefulness in treatment of symptomatic *Salmonella* infection need to be investigated in the context of RCTs. One of the identified but excluded trials evaluated the use of rifaximin but could not be included in the review because the number of NTS patients was very small and included with other patients.

These trials can proceed to study all patients with bacterial diarrhoea but would perform subgroup analysis by the isolated pathogen. These trials need to include enough patients to be able to have statistical power and also need to study the patients long enough (for at least 8 to 10 weeks) to enable a clearer picture to be obtained as regards microbiological failure and detection of the same *Salmonella* serovar 1 to 2 months after treatment. Also these studies would need to continue to examine the stool cultures even after they become initially culture negative as this would enable it detect patients who relapse after treatment.

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CHARACTERISTICS OF STUDIES

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

Butler 1993

Methods	Multicentre RCT in six countries between July 1987 and September 1989. Oral or written informed consent was obtained prior to entry into the study.
Participants	Adults with acute diarrhoea. Excluded if had previously taken antibiotics, unwell, or with other gut pathogen. 508 randomized; 46 culture positive for NTS included.
Interventions	1: Oral fleroxacin 400 mg single dose 2: Oral fleroxacin 400 mg daily for three days 3. Placebo 110 patients were randomized to the placebo and single dose arms and 112 patients randomized to the multiple dose arm. 176 randomized patients were excluded.
Outcomes	Stool cultures were done on day 3 and 5 after start of treatment. Outcomes of interest were: time to cessation of diarrhoea, mean number of loose stools per day, number of stool cultures negative for initial pathogens on day 3 and 5 after start of therapy. Reported adverse events. Blood and urine adverse events - renal and hepatic function tests, and crystalluria.
Notes	No specific serotype was indicated. Countries: Italy, Thailand, Ivory Coast, Indonesia, Mexico and Israel. Ethical approval was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment regimens were randomized from computer generated numbers.
Allocation concealment (selection bias)	Unclear risk	We do not know how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators were blinded. Placebo tablets were used.
Incomplete outcome data (attrition bias)	High risk	Patients with incomplete outcomes were excluded from the analysis.

Butler 1993 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Although we do not have the trial protocol, we do not believe the outcomes were selectively reported.
Other bias	Unclear risk	Funding: no statement was made.

Chiu 1999

Methods	RCT conducted between August 1995 and March 1996. No information regarding the source of ethical approval.
Participants	42 patients were randomized. Patients were included in the trial if they were aged over 6 months and presented with blood or mucoid diarrhoea with or without fever, and had a positive stool culture. Excluded if they had a toxic appearance, were vomiting, had abdominal distension, had taken antibiotics in the past 72 hours, and had a negative stool culture.
Interventions	This was a three arm trial: 1: 10mg/kg per day of oral azithromycin once daily 2: Cefixime 10 mg/kg per day of oral cefixime in two divided doses Control: No antibiotic. Treatment was administered for 5 days. 14 patients were randomized to each arm.
Outcomes	This trial assessed number of days of fever and diarrhoea.
Notes	Done in Taiwan. Funded by the National Health Research Institute, Department of Health, National Science Council. There was resistance to azithromycin in two cases treated with cefixime. No specific serotype of *Salmonella* was referred to in the study.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation sequence was generated by computer randomization.
Allocation concealment (selection bias)	Unclear risk	No information was supplied regarding concealment.
Blinding (performance bias and detection bias) All outcomes	High risk	Patient and clinician were not blinded, no information regarding blinding of outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	High risk	The patients who were lost to follow-up were excluded from analysis.

Chiu 1999 *(Continued)*

Selective reporting (reporting bias)	Low risk	Although we do not have the trial protocol, there was no evidence of selective reporting.
Other bias	Low risk	No suggestion of other sources of bias.

Garcia de Olarte 1974

Methods	Double blind RCT conducted between January 1970 and January 1972. At inclusion, patients had both a stool sample and a rectal swab collected, rectal swabs for culture were collected daily and after 10 days every 3 days.
Participants	282 children were randomized. 110 children in this trial were culture positive for *Salmonella*. Children were excluded from the trial if they had other illnesses requiring antibiotics, if they were under 6 weeks of age, and had a history of allergy to penicillin or its derivatives.
Interventions	Intervention: ampicillin 100 mg/kg in equally divided doses every six hours. Control: matching placebo. Intervention was administered intramuscularly in the first year of the trial and orally in the second. Intervention was administered for 5 days. Among the *Salmonella* culture positive children, 57 were randomized to antibiotic and 53 randomized to placebo.
Outcomes	Outcomes assessed in this trial include: number of patients excreting pathogens for more than or equal to 48 hours, number of days till culture negative, number of patients excreting pathogens after 5 days of therapy, number of days till diarrhoea improved, number of days to cessation of diarrhoea, number of days till patients were afebrile, number of patients with diarrhoea for more than 5 days. Incidence of bacteriologic relapse and all cause mortality were also assessed.
Notes	Two patients in this trial had positive culture for *S.* Typhi, but outcomes are not reported separately for them. 45 different serotypes of *Salmonella* were identified among the 280 patients who excreted *Salmonella*. *S. enteritidis* ser London, *S. enteritidis* ser Muenchen, *S. enteritidis* ser Typhimurium were the most frequently isolated serotypes. Conducted in Colombia. Ethical approval was received from the Human Experimentation Committee in Dallas, USA and the Concejo Normativo in Medellin, Colombia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation sequence was generated by random number table.
Allocation concealment (selection bias)	Unclear risk	No information as to how allocation was concealed in trial report.
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial report describes the investigators and participants as blinded. There was use of a matching placebo, and dosing frequency was similar.

Garcia de Olarte 1974 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Patients appear to have been analysed as per intention to treat although the trial report does not specifically say so.
Selective reporting (reporting bias)	Low risk	Although we do not have the trial protocol, there is no reason to believe trial was selectively reported.
Other bias	High risk	The study was funded by a drug company grant - from the International Division of Bristol Myers Company. The trial report does not say whether they played any role in study design, analysis and reporting.

Goodman 1990

Methods	Double blind, placebo controlled RCT, conducted between June 1985 and September 1987. Follow-up was for 14 days. Stool samples were collected at each visit for microbiological assessment.
Participants	Patients were included if they were 18 years or more and had an acute diarrhoeal illness lasting 7 days or less. Patients were excluded if they were pregnant, had a history of allergy to nalidixic acid, trimethoprim or sulphamethoxazole, had received antibiotics within the preceding two weeks had a history of significant renal or hepatic dysfunction, were using cathartics or could not give consent. This trial randomized 202 patients in total and had 15 *Salmonella* patients whose ages ranged between 20 and 46 years. Among these 15 patients, 2 were randomized to ciprofloxacin, 4 to sulphamethoxazole trimethoprim, and 7 to placebo. None of the participants were immunosuppressed.
Interventions	1: Ciprofloxacin 500 mg. 2: Trimethoprim-Sulphamethoxazole 160-800 mg. Control: Placebo. Treatment was administered twice daily for 5 days.
Outcomes	Clinical outcomes: cure, improvement, relapse, and failure. Microbiological failure, adverse events.
Notes	The reporting of adverse events was not separate for the *Salmonella* subgroup of patients. There are a few inconsistencies in the report regarding number of patients with *Salmonella*. Table 2 lists 13 *Salmonella* patients, but elsewhere the text refers to 15.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information as to how the sequence was generated.
Allocation concealment (selection bias)	Unclear risk	No information as to how the allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial report describes the study as blinded, and there was use of matching placebo.

Goodman 1990 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	The trial report has not specified use of intention to treat. Patients with incomplete outcome data were excluded from the analysis.
Selective reporting (reporting bias)	Low risk	Although the trial protocol is not available to us, we have no reason to suspect the trial was selectively reported.
Other bias	High risk	Funded by a grant from Miles Pharmaceutical Co, New Haven CT, USA. The trial report has not made any statement as regards their involvement with the design, conduct, analysis and reporting of the trial.

Joint Project ASID 1970

Methods	Double blind, placebo controlled RCT. Trialists attempted to follow up the patients for up to 6 weeks.
Participants	239 patients were randomized, but analysis was only possible for 168 patients. Age: 0 to > 65 years.
Interventions	Intervention: Oral neomycin 50 mg/kg body weight daily in divided doses. Control: Placebo. Treatment lasted for 5 days. Among the 168 that were analysed, 78 were randomized to antibiotic and 90 to placebo.
Outcomes	The duration of clinical illness and the incidence of negative stool cultures, incidence of relapse.
Notes	We attempted to extract outcome measures in this trial from the graphs, but have not used it in a meta-analysis because of concerns that not all the patients in the trial are accounted for and lack of information as to the reasons for the exclusions. The trialists referred to non-invasive *Salmonella* and specifically excluded the typhoidal*Salmonella*. No specific serotypes of NTS were mentioned.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No statement was made as to how allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	No statement was made as to allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial describes the outcome assessors as blinded, and there was use of placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	Trialists excluded all the patients who did not complete the trial from the analysis. They did not do and did not report an intention to treat analysis.
Selective reporting (reporting bias)	Low risk	Although we do not have the trial protocol, we have no reason to believe the outcomes were selectively reported.
Other bias	Low risk	Nothing to suggest other bias.

Kazemi 1973

Methods	RCT.
Participants	36 children with *Salmonella* gastroenteritis aged between 10 months and 15 years were randomized. None of the patients was immunosuppressed. Patients were included if they had a history of fever and diarrhoea lasting more than 3 days, mucus or blood in diarrhoeal stools and if they had NTS proven by culture. Exclusion criteria - received antibiotics within the preceding 5 days, renal or hepatic disease, blood dyscrasia and*Salmonella* bacteraemia. Participants were followed up for 6 months.
Interventions	1: Sulphamethoxazole-trimethoprim (100 mg/20 mg per 24 hours) given orally in 4 divided doses. 2 : Ampicillin (100 mg per kg/day). CONTROL: No treatment. Treatment was administered for 7 days. 14 children were randomized to intervention arm 1, 10 to intervention arm 2, 12 to control arm.
Outcomes	Outcomes of interest included duration of diarrhoea, duration of fever, duration of illness, duration of hospitalization, microbiological failure, adverse events (generalized maculopapular rash and vomiting), convalescent fecal carriage of *Salmonella*.
Notes	Conducted in Canada. 6 patients were lost to follow up and these were excluded from the analysis. The *Salmonella* serotypes in the study were *Salmonella* Typhimurium (19), *Salmonella* Heidelberg (2), *Salmonella* Blockley (5), *Salmonella* Montevideo (1), *Salmonella* Newport (5), *Salmonella* Infantis (1), *Salmonella* Enteritidis (1), *Salmonella* Java (1) and *Salmonella* Thompson (1).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trialists describe the trial as randomized but do not say how the sequence was generated.
Allocation concealment (selection bias)	Unclear risk	The trialists do not state how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	The trial had an arm where participants were not treated. There is no statement as to whether outcome assessors were blinded to the treatment patients received in the two treatment arms and the fact that the patients in the control arm were not treated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trialists accounted for all the patients excluded from analysis although they did not do an intention to treat analysis.
Selective reporting (reporting bias)	Low risk	We are not able to verify the protocol but do not have any reason to believe that there was selective outcome reporting.
Other bias	High risk	The study was supported by a grant from a pharmaceutical company, Hoffman La Roche Ltd. The trialists have not made any statement regarding the extent of their involvement in the design, conduct, analysis and reporting of the trial.

Macdonald 1954

Methods	RCT conducted between November 1951 and March 1953.
Participants	51 children was randomized. Children included were less than 2 years of age, presented with diarrhoea, and had a positive culture for NTS without any coexisting parenteral infection. Enteritis was less than one week in duration. Exclusion criteria - anorexia and severe dehydration.
Interventions	Intervention: Oral chloramphenicol 120 mg/kg 6-8 hourly for 10 days. Control: No specific treatment. 25 children were randomized to antibiotic and 26 to no treatment.
Outcomes	This trial evaluated duration of illness, clinical and microbiological failure, and duration of diarrhoea.
Notes	The isolated *Salmonellae* were *Salmonella* Typhimurium (48), *Salmonella* Adelaide (2), *Salmonella* Derby (1). No information was provided regarding the source of ethical approval.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation sequence was generated by a table of random numbers and allocation was done on the basis of odds and evens.
Allocation concealment (selection bias)	Unclear risk	The trial report does not provide information regarding allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Outcome assessors were blind as to which arm a patient belonged.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial is not reported as intention to treat but all patients were accounted for in the analysis.
Selective reporting (reporting bias)	Low risk	Although we do not have the trial protocol, we have no reason to believe outcomes were selectively reported.
Other bias	Unclear risk	No information provided as regards the source of funding for the trial.

Neil 1991

Methods	Placebo controlled, double blind RCT.
Participants	15 patients were randomized in this trial. Trial commenced on day 9 after disease outbreak. To be eligible for inclusion: acute onset of abdominal pain or diarrhoea with at least one of fever, headache, nausea or vomiting, informed consent. All participants had a positive stool culture for *S. java.* Pregnant women and people receiving previous antibiotic therapy were excluded.
Interventions	Intervention: Oral ciprofloxacin 750 mg twice daily. Control: Matching placebo. Treatment was administered for 14 days.

Neil 1991 *(Continued)*

	8 patients were randomized to the intervention arm and 7 patients to the control arm.
Outcomes	The outcomes assessed in this trial included: duration of stool culture positivity, incidence of adverse events, incidence of relapse after treatment.
Notes	The strain of *Salmonella* in the study was *Salmonella* java. Ethical clearance from Brown University, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial report does not state how allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Trial report does not state how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial was described as blinded and there was use of matching placebo.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	We are unable to assess how the trialists dealt with incomplete outcome data. They do not say they did an intention to treat analysis.
Selective reporting (reporting bias)	Low risk	Although we do not have the protocol, we have no reason to believe trial was selectively reported.
Other bias	Low risk	The study was funded by a drug company, Miles Pharmaceuticals although this was retrospective.

Nelson 1980

Methods	RCT.
Participants	45 children were randomized in this trial. Children in this trial had uncomplicated *Salmonella* gastroenteritis (no extraintestinal infection, no high fever, no toxic appearance suggesting bacteraemia). Children were excluded if there was a history of adverse reactions to penicillins, if there was another focus of infection like otitis media, pneumonia, and if the child was aged less than 6 weeks of age.
Interventions	1: Ampicillin. 2: Amoxicillin. Control: Matching placebo. Treatment was administered for 5 days.
Outcomes	This trial assessed the number of days to first negative culture, incidence of bacteriologic relapse and number of days until last positive culture, number of days to clinical improvement, number of days to cessation of diarrhoea, and incidence of relapse.

Nelson 1980 *(Continued)*

Notes	Conducted in USA. 1 of the patients in this trial was positive for *S.* paratyphi B which is not the subject of this review. The isolated *Salmonella* were categorized by serogroup as follows: *Salmonella* Typhimurium (14), *Salmonella* Heidelberg (7), *Salmonella* Agona (2), *Salmonella* Newport (1) *Salmonella* Manhattan (1) *Salmonella* Rubislaw (7), *Salmonella* Oranienburg (1), *Salmonella* Anatum (1), *Salmonella* Mississippi (1), *Salmonella* Infantis (1), *Salmonella* Javiana (1). No information as regards the source of ethical approval.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number lists. Separate lists were used for randomization of patients less than and more than 1 year of age.
Allocation concealment (selection bias)	Unclear risk	No information could be extracted regarding allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial is described as double blind, and matching placebo was used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Trial appears to have conducted an intention to treat analysis, as all randomized patients are in the analysis except for one randomized patient who was excluded from analysis and this was because of a false inclusion as he did not have a positive stool culture at the point of randomization even though he had 5 days earlier.
Selective reporting (reporting bias)	Low risk	Although we do not have the trial protocol, we have no reason to believe trial was selectively reported.
Other bias	Unclear risk	No information regarding funding.

Pitkajarvi 1996

Methods	RCT. Conducted between October 1989 and May 1992.
Participants	100 patients were randomized (47 to intervention and 45 to control group). 8 patients were lost to follow up. Inclusion criteria - age between 18 and 60 years of age, acute gastroenteritis, bacteriologically verified *S almonella* in their stool in the 4 days prior to the study. Exclusion criteria - pregnancy or lactation, hypersensitivity to quinolones, additional antibacterial treatment during the 14 days preceding the trial entry, proven or suspected gall bladder disease or gall stones, impaired kidney function, severe illness or nausea, known HIV infection, or were handling perishable food.
Interventions	Intervention: Oral norfloxacin 400 mg twice daily. Control: Matching placebo. Treatment lasted for 10 days.
Outcomes	Clinical outcomes were assessed in terms of the time to disappearance of clinical symptoms (loose stools, abdominal cramps, vomiting and fever). Bacteriological efficacy was assessed in terms of elimination, persistence (growth of original pathogen without previous post treatment elimination), relapse

Pitkajarvi 1996 *(Continued)*

	(growth of original pathogen after previous post treatment elimination) and reinfection (growth of a new pathogen post-treatment). Incidence of adverse events was also assessed.
Notes	As regards the *Salmonella* serotypes, the trialists confirmed that all the patients has *Salmonella* infection and only excluded *Salmonella* Typhi. Patients were followed up for 6 months. Ethical clearance from City of Tampere, Finland.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information as to how the allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	No information as to how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial is described as double blind, placebo controlled.
Incomplete outcome data (attrition bias) All outcomes	High risk	Trialists have excluded patients who were lost to follow up from the analysis. They have not done an intention to treat analysis.
Selective reporting (reporting bias)	Low risk	Although we do not have the protocol, nothing in the trial report suggests selective outcome reporting.
Other bias	High risk	Funding was provided by Astra Arcus AB Sodertalje, Sweden. Trial report has not stated their extent of involvement with design, conduct analysis and reporting of the trial.

Sanchez 1993

Methods	RCT. conducted between June 1988 and September 1990. Patients were followed up for 42 days. Patients gave written informed consent.
Participants	78 patients were randomized, but outcomes were analysed for 65 patients. Inclusion criteria - age > 14 years old, diarrhoea < 48 hours and an axillary temperature of more than or equal to 37.5 degrees celsius. Exclusion criteria - pregnancy, >50 years of age, chronic renal insufficiency, Diabetes Mellitus, Cirrhosis, of the liver, neoplasia, immunodeficiency, gastrectomy, antibacterial drug ingestion during the 72 hours prior to admission, had severe gastroenteritis, or had a negative stool culture or a positive culture with an organism other than *Salmonella*.
Interventions	1: Oral ciprofloxacin 500 mg twice daily. 2: Oral trimethoprim-sulphamethoxazole (160/800) mg twice daily. Control: Matching placebo. Treatment was administered for 5 days. 23 patients were randomized to intervention arm 1, 26 to intervention arm 2 and 16 to the control arm.
Outcomes	Duration of clinical symptoms, excretion of *Salmonella* in stool, incidence of adverse events (liver enzymes).

Sanchez 1993 *(Continued)*

Notes	The serotypes in this study were *Salmonella* Typhimurium in 4 cases and *Salmonella* Enteritidis in the rest. Approved by the ethical committees of the respective hospitals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was generated by computer random number programme.
Allocation concealment (selection bias)	Unclear risk	No information is provided regarding allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial used identical drug and placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	Trialists excluded patients from analysis if they were lost to follow up, if the protocol was violated, if they withdrew consent, or were unable to tolerate the study drug (vomiting). Patients were also excluded from analysis because they had incomplete outcome data as a result of their not being evaluated clinically on days 3 and 4 of treatment.
Selective reporting (reporting bias)	Low risk	Although we do not have the trial protocol, we have no reason to believe trial was selectively reported.
Other bias	Low risk	Funding was provided by the Department of Medicine of the Hospital de Mutua de Terrassa.

Wistrom 1992

Methods	Multicentre RCT conducted between September 1989 - April 1991.
Participants	82 patients in this trial had stool culture positive for *Salmonella*. This study randomized 598 patients. Patients were included if they had a history of diarrhoea lasting up to 5 days, fever, vomiting and abdominal cramps in the past 24 hours. Exclusion criteria were pregnancy, nursing, quinolone hypersensitivity, antibiotic treatment within the three preceding weeks, suspected renal failure, concomitant treatment with drugs known to interact with norfloxacin, non infectious diarrhoea, suspected *Clostridium difficile* infection, food poisoning, severe vomiting or suspected septicaemia, HIV infection and previous inclusion in the study. Patients had to be over 12 years of age.
Interventions	Intervention - 400 mg of norfloxacin twice daily taken orally. Control - matching placebo. Treatment was administered for 5 days. 45 patients were randomized to the intervention arm and 37 to the control arm.
Outcomes	Clinical outcomes - cure (< or = 1 loose stool per 24 hours without additional symptoms), improvement (two loose stools per 24 hours without additional symptoms or one loose stool per 24 hours with accompanying symptoms) or failure. Recurrence was defined as return to inclusion criteria within 7 days after the last treatment dose. Early treatment failure was defined as discontinued treatment after 7 or fewer doses and appropriate antibiotic treatment due to diarrhoeal disease.

Wistrom 1992 *(Continued)*

	Bacteriologic outcomes were elimination, persistence (identification of the same pathogen before and after treatment at the first follow up), relapse (bacteriologic recurrence with the initial pathogen) or re-infection (clinical recurrence with a new pathogen). Median time to cure was incorporated into duration of illness.
Notes	The isolated organisms were *Salmonella* Enteritidis (38), *Salmonella* Typhimurium(20), other *Salmonella* species(24). Conducted in Sweden.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial does not mention how the sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Trial does not mention how allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial is described as double blind and used a matching placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the patients randomized were subsequently accounted for in the analysis.
Selective reporting (reporting bias)	Low risk	Although we do not have the trial protocol, we have no reason to believe trial was selectively reported.
Other bias	High risk	Funding was from Astra Arcus AB, Sodertalje, Sweden. No statement as regards their role in the design, conduct, analysis, and reporting of the trial.

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

Study	Reason for exclusion
Bessudo 1972	This trial investigated rifampicin and no treatment. They gave their intervention group the antibiotic and the control group was untreated. However they report that they gave 3 of the patients in the control group another antibiotic which they do not name and they reported everything together. Secondly they report that of the patients in their intervention group, some of them had been treated with another antibiotic which they do not name just prior to the trial. Thirdly we are unable to extract any data of relevance to the review because of the nature of reporting.
Carlstedt 1990	This was a quasi RCT.
Dryden 1996	This study did not report separate outcome assessment for the NTS patients.
Ericsson 1983	This study investigated a drug, bicozamycin, no longer utilized in medical practice.
Hatalin 1972	This was a quasi RCT.
Lolekha 1988	This study did not report separate outcome assessment for the NTS patients in the study.

Study	Reason for exclusion
Mattila 1993	This study did not report its data clearly enough to permit meaningful interpretation and inclusion in meta-analysis.
Mensa 1989	The study was not actually randomized.
Noguerado 1995	This study did not report separate outcome assessment for the NTS patients.
Pichler 1986	This study did not report separate outcome assessment for the NTS patients
Pichler 1987	This study did not report separate outcome assessment for the NTS patients.
Robins-Browne 1983	This study did not report separate outcome assessment for the NTS patients.
Sirinavin 2003	This was a RCT, but it evaluated asymptomatic patients.
Svenungsson 1990	This trial investigated asymptomatic patients.
Taylor 2006	This study did not report a separate outcome assessment for the NTS patients.
Wolfsdorf 1973	This trial had only one patient who had*Salmonella* but the patient became culture positive after treatment and was not ab initio.

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

Tsai 2012

Trial name or title	The Role of Short-course Ceftriaxone Therapy in the Treatment of Severe Nontyphoidal Salmonella Enterocolitis.
Methods	Randomized Controlled Trial
Participants	Children aged between 3 months and 18 years with suspected severe Salmonella enterocolitis - defined as those with a high fever (core body temperature more than 38.5) persisting for longer than 48 hours - diarrhoea with mucous and bloody-tinged stool. EXCLUSION CRITERIA - Children with a toxic appearance, severe vomiting and abdominal distension - suggestive of sepsis or toxic megacolon, those with an increased risk of invasive NTS diseases - immunosuppressive illnesses - had taken antibiotics during the 7 days before the visit will be excluded
Interventions	Ceftriaxone
Outcomes	To evaluate if short-course of ceftriaxone therapy could shorten the clinical courses of severe NTS enterocolitis in children and the excretion of Salmonella in faeces.
Starting date	August 2010

Tsai 2012 *(Continued)*

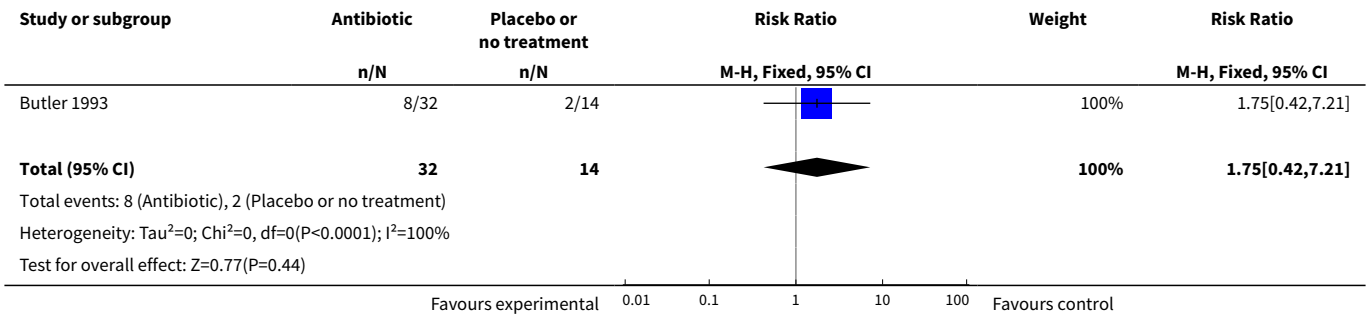
Contact information	**Ming_Han Tsai, MD,** **tel: 886-2-24313131 ext.: 2626** Chang Gung Memorial Hospital Taoyuan 333 drtsai1208@gmail.com
Notes	NCT01278017

DATA AND ANALYSES

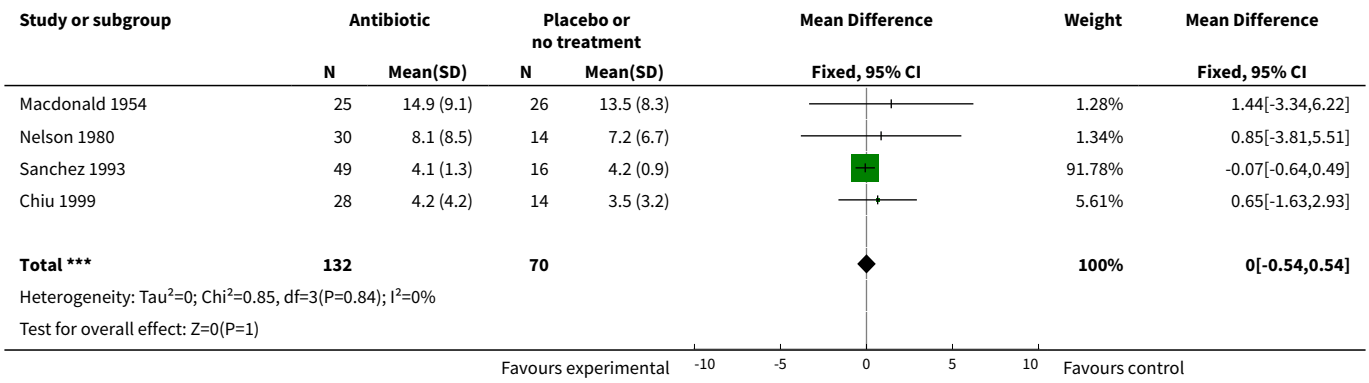
Comparison 1. Antibiotics versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Presence of diarrhoea at 2 to 4 days	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.42, 7.21]
2 Duration of diarrhoea	4	202	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.54, 0.54]
3 Presence of diarrhoea at 5 to 7 days	2	192	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.12]
4 Clinical failure	7	440	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.62, 1.25]
5 Duration of fever	2	107	Mean Difference (IV, Fixed, 95% CI)	0.27 [-0.11, 0.65]
6 Duration of illness	2	116	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.68, 0.68]
7 Microbiological failure	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Quinolones versus placebo	4	166	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.20, 0.56]
7.2 Other antibiotics versus placebo	4	362	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.83, 1.11]
8 Fecal carriage of the same *Salmonella* serovar after 1 month following the end of antibiotic treatment	3	112	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.29, 2.98]

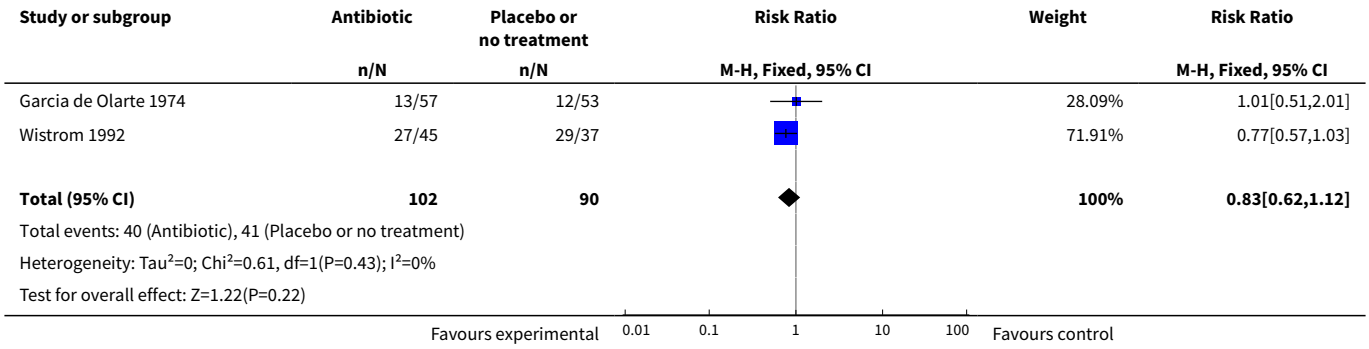
Analysis 1.1. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 1 Presence of diarrhoea at 2 to 4 days.



Analysis 1.2. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 2 Duration of diarrhoea.

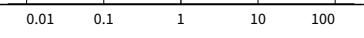


Analysis 1.3. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 3 Presence of diarrhoea at 5 to 7 days.



Analysis 1.4. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 4 Clinical failure.

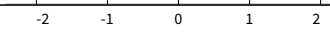
Study or subgroup	Antibiotic n/N	Placebo or no treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Macdonald 1954	3/25	2/26		4.44%	1.56[0.28,8.56]
Garcia de Olarte 1974	13/57	12/53		28.14%	1.01[0.51,2.01]
Nelson 1980	4/30	0/14		1.52%	4.35[0.25,75.74]
Wistrom 1992	17/45	24/37		59.6%	0.58[0.37,0.91]
Butler 1993	8/32	2/14		6.3%	1.75[0.42,7.21]
Sanchez 1993	0/49	0/16			Not estimable
Chiu 1999	0/28	0/14			Not estimable
Total (95% CI)	**266**	**174**		**100%**	**0.88[0.62,1.25]**
Total events: 45 (Antibiotic), 40 (Placebo or no treatment)					
Heterogeneity: Tau^2=0; Chi^2=5.98, df=4(P=0.2); I^2=33.13%					
Test for overall effect: Z=0.73(P=0.46)					



Favours experimental — Favours control

Analysis 1.5. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 5 Duration of fever.

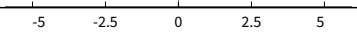
Study or subgroup	Antibiotic N	Antibiotic Mean(SD)	Placebo or no treatment N	Placebo or no treatment Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Sanchez 1993	49	2.1 (0.8)	16	1.9 (0.7)		85.19%	0.21[-0.2,0.62]
Chiu 1999	28	1.8 (2)	14	1.2 (1.3)		14.81%	0.6[-0.39,1.59]
Total ***	**77**		**30**			**100%**	**0.27[-0.11,0.65]**
Heterogeneity: Tau^2=0; Chi^2=0.5, df=1(P=0.48); I^2=0%							
Test for overall effect: Z=1.37(P=0.17)							



Favours experimental — Favours control

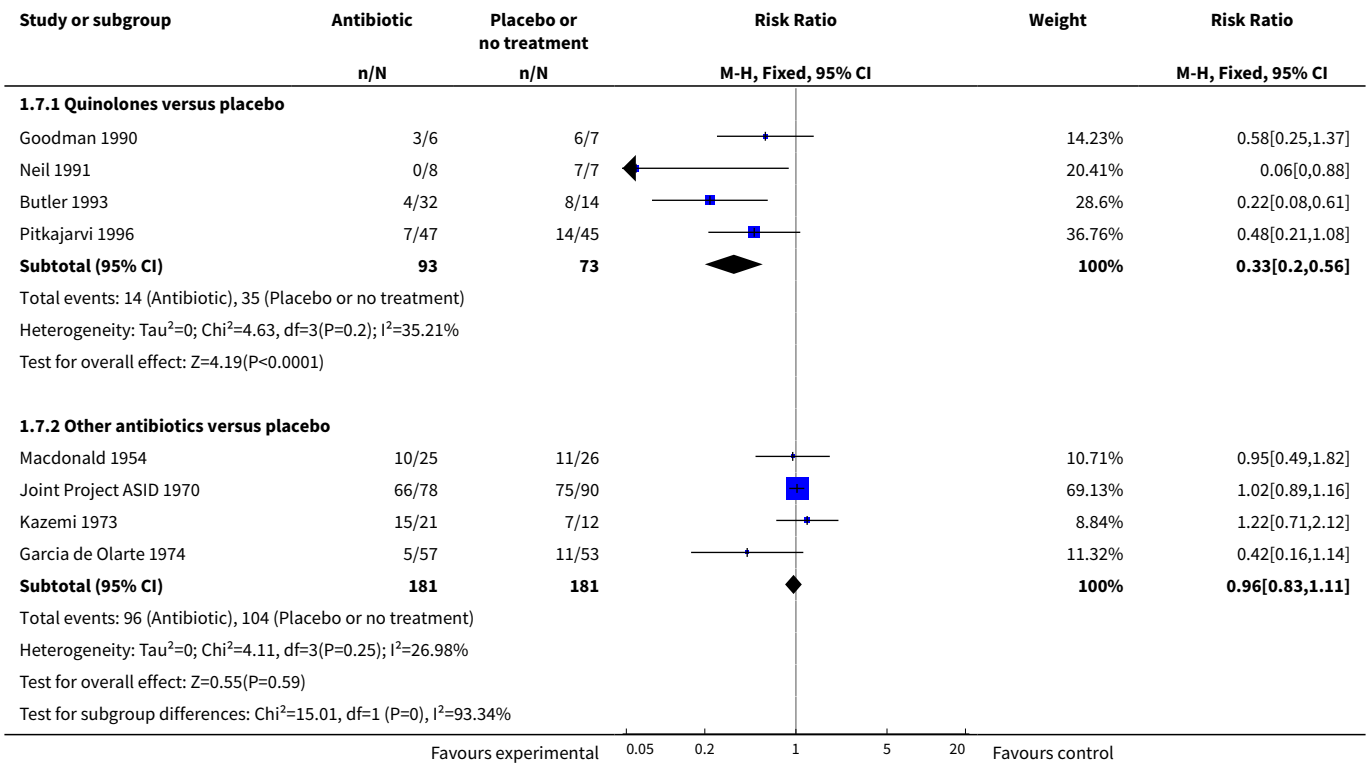
Analysis 1.6. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 6 Duration of illness.

Study or subgroup	Antibiotic N	Antibiotic Mean(SD)	Placebo or no treatment N	Placebo or no treatment Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Macdonald 1954	25	19.5 (9.2)	26	19 (9.1)		1.83%	0.56[-4.48,5.6]
Sanchez 1993	49	3.7 (1.3)	16	3.7 (1.2)		98.17%	-0.01[-0.7,0.67]
Total ***	**74**		**42**			**100%**	**-0[-0.68,0.68]**
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%							
Test for overall effect: Z=0.01(P=0.99)							

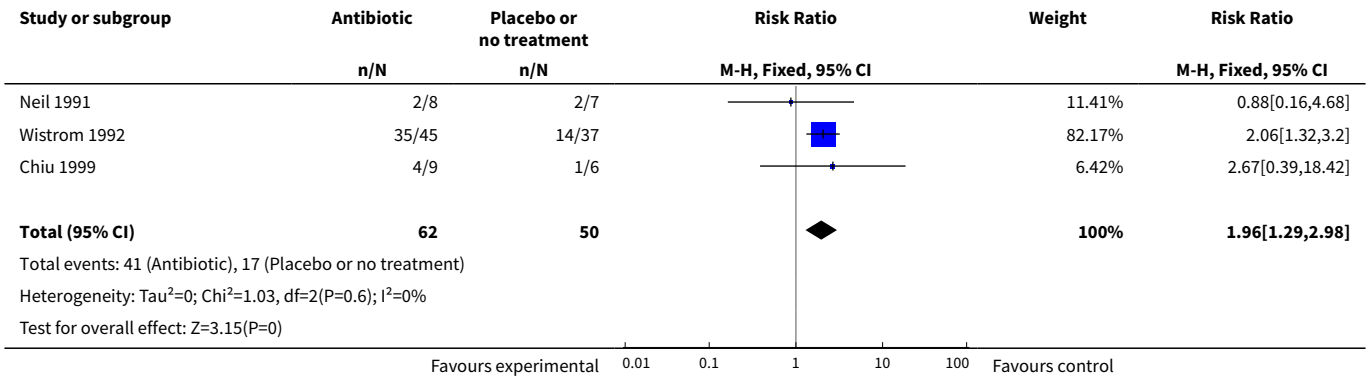


Favours experimental — Favours control

Analysis 1.7. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 7 Microbiological failure.



Analysis 1.8. Comparison 1 Antibiotics versus placebo or no treatment, Outcome 8 Fecal carriage of the same *Salmonella* serovar after 1 month following the end of antibiotic treatment.



ADDITIONAL TABLES

Table 1. Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]	SCI

Table 1. Detailed search strategies *(Continued)*

1	Salmonell* NOT typhoid*	Salmonell* NOT typhoid*	Salmonell* NOT typhoid*	Salmonell$	Salmonell$ NOT typhoid$	Salmonell* NOT typhoid*
2	antibiotic*	SALMONELLA INFECTIONS	SALMONELLA INFECTIONS	SALMONELLOSIS	antibiotic$	antibiotic*
3	antimicrobial*	1 or 2	1 or 2	1 or 2	antimicrobial$	antimicrobial*
4	treat*	ANTI-BACTERIAL AGENTS	ANTI-BACTERIAL AGENTS	ANTIBIOTIC-AGENT	treat$	treat*
5	therap*	antibiotic*	antibiotic*	antibiotic$	therap$	therap*
6	2 or 3 or 4 or 5	ANTI-INFECTIVE AGENTS	ANTI-INFECTIVE AGENTS	ANTIINFECTIVE- AGENT	2 or 3 or 4 or 5	2 or 3 or 4 or 5
7	1 and 6	ampicillin*	ampicillin*	ampicillin$	1 and 6	1 and 6
8	—	amoxicillin*	amoxicillin*	amoxicillin$	—	randomized controlled trial*
9	—	cotrimoxazole	cotrimoxazole	cotrimoxazole	—	randomised controlled trial*
10	—	chloramphenicol	chloramphenicol	chloramphenicol	—	controlled clinical trial*
11	—	fluoroquinolone*	fluoroquinolone*	fluoroquinolone$	—	double blind*
12	—	quinolone*	quinolone*	quinolone$	—	single blind*
13	—	ofloxacin	ofloxacin	ofloxacin	—	placebo*
14	—	norfloxacin	norfloxacin	norfloxacin	—	8-13/or
15	—	ciprofloxacin	ciprofloxacin	ciprofloxacin	—	7 and 14
16	—	fleroxacin	fleroxacin	fleroxacin	—	—
17	—	cephalosporin*	cephalosporin*	cephalosporin$	—	—
18	—	ceftriaxone	ceftriaxone	ceftriaxone	—	—
19	—	cefotaxime	cefotaxime	cefotaxime	—	—
20	—	cefixime	cefixime	cefixime	—	—
21	—	4-20/or	4-20/or	4-20/or	—	—

Table 1. Detailed search strategies *(Continued)*

22	—	—	Limit 21 to Human	Limit 21 to Humans	—	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2011); upper case: MeSH or EMTREE heading; lower case; free text term.

Table 2. Search strategy for the *meta*Register of Controlled Trials

'(diarrhoea AND Salmonell*) NOT (typhi OR paratyphi)'

Table 3. Duration of Diarrhoea

Study ID	Intervention	Effect estimate (mean in days)	Is Difference Significant	Number of patients
Garcia de Olarte 1974	Ampicillin	5.2 in ampicillin arm versus 4.2 in placebo arm (effect measure reported - mean in days)	No	110
Kazemi 1973	Co trimoxazole & ampicillin	2.8 (range of 1 to 5) in the co trimoxazole group 3.1 (range of 1 to 7) in the ampicillin group 3 (range of 1 to 10) in the untreated group		36

Table 4. Duration of Fever

Study ID	Intervention	Effect estimate (mean in days)	Is difference significant?	Number of patients
Kazemi 1973	Co-Trimoxazole & ampicillin	3.2 (range 2-7) in the sulphamethoxazole-trimethoprim group 1.6 (range 1-2) in the ampicillin group 2.6 (range 1-7) in the no treatment group		36
Garcia de Olarte 1974	Ampicillin	0.8 in ampicillin arm vs 1.0 in placebo arm	No	110

Table 5. Duration of Illness

Study ID	Intervention	Effect estimate (mean in days)	Is difference significant?
Kazemi 1973	Ampicillin & co trimoxazole	3.8 (range 2 to 7) in the sulphamethoxazole-trimethoprim group	No

Table 5. Duration of Illness *(Continued)*

		2.6 (range 1 to 7) in the ampicillin group 4 (range 1 to 6) in the no treatment group	
Nelson 1980	Ampicillin & amoxicillin	20.4 in the ampicillin group 17.6 in the amoxicillin group 16.5 in the placebo group	No
Wistrom 1992	Norfloxacin	Median days of treatment 5 days in norfloxacin group 7 days in placebo group.	No (P > 0.2)

Table 6. Fecal carriage of same*Salmonella* serovar 1 month after treatment

Study ID	Intervention	Effect estimate	Is difference significant?
Pitkajarvi 1996	Norfloxacin	21% of patients relapsed in antibiotic arm, 16% relapsed in placebo arm	No
Nelson 1980	Ampicillin and amoxicillin	Relapse in 4 patients in both antibiotic arms. None in placebo	Yes (P = 0.003)
Sanchez 1993	Ciprofloxacin and co trimoxazole	3/45 antibiotic patients (2 in the ciprofloxacin group, and 1 in the trimethoprim sulphamethoxazole group) relapsed versus 1/12 placebo patients at 3 weeks 2/41 antibiotic patients relapsed versus 1/15 placebo patients at 6 weeks	No
Kazemi 1973	Co trimoxazole and ampicillin	No patients had positive cultures at 8 weeks. One co-trimoxazole patient was positive at 6 months.	No

WHAT'S NEW

Date	Event	Description
5 October 2012	New citation required but conclusions have not changed	This is a major update of a published review (Sirinavin 2000), including revised methods, a revised title, and a new author team.
5 October 2012	New search has been performed	New searches, new methods, and new author team have been incorporated.

CONTRIBUTIONS OF AUTHORS

Drs Ifeanyi Onwuezobe, Phillip Oshun and Chibuzo Odigwe wrote the protocol, applied inclusion criteria, assessed methodological quality, analysed the data and wrote the review.

DECLARATIONS OF INTEREST

We declare that we have no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria.
- Institute of Tropical Disease Research & Prevention, University of Calabar Teaching Hospital, Calabar, Nigeria.

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  Aubrey Sheiham Public Health & Primary Care Scholarship

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods section has been revised as we allowed inclusion of studies that recruited patients with unspecified diarrhoea or gastroenteritis and extracted and analysed the data for the subgroup of patients with documented Salmonellosis.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Diarrhea [*drug therapy] [microbiology]; Gastroenteritis [drug therapy]; Gastrointestinal Diseases [drug therapy]; Randomized Controlled Trials as Topic; Salmonella Infections [*drug therapy]; Salmonella paratyphi A; Salmonella typhi

MeSH check words

Adult; Child; Child, Preschool; Humans; Infant