Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever) (Review)

Effa EE, Bukirwa H

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 4
METHODS . . . 4
RESULTS . . . 7
Figure 1. . . . 13
Figure 2. . . . 15
Figure 3. . . . 16
Figure 4. . . . 16
Figure 5. . . . 17
DISCUSSION . . . 17
AUTHORS' CONCLUSIONS . . . 18
ACKNOWLEDGEMENTS . . . 19
REFERENCES . . . 19
CHARACTERISTICS OF STUDIES . . . 22
DATA AND ANALYSES . . . 29
Analysis 1.1. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 1 Clinical failure. . . . 30
Analysis 1.2. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 2 Microbiological failure. . 30
Analysis 1.3. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 3 Fever clearance time (hours). 31
Analysis 1.4. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 4 Adverse events (excluding serious adverse events). . . . 31
Analysis 2.1. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 1 Clinical failure. . . . 32
Analysis 2.2. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 2 Microbiological failure. . 32
Analysis 2.3. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 3 Relapse. . . . 33
Analysis 2.4. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 4 Fever clearance time (hours). 33
Analysis 2.5. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 5 Duration of hospital stay (days). 34
Analysis 2.6. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 6 Serious adverse events. . . 34
Analysis 3.1. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 1 Clinical failure. . . . 35
Analysis 3.2. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 2 Microbiological failure. . . 35
Analysis 3.3. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 3 Relapse. . . . 36
Analysis 3.4. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 4 Fever clearance time (hours). . 36
HISTORY . . . 36
CONTRIBUTIONS OF AUTHORS . . . 37
DECLARATIONS OF INTEREST . . . 37
SOURCES OF SUPPORT . . . 37
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 37
INDEX TERMS . . . 37

[Intervention Review]

Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Emmanuel E Effa[1], Hasifa Bukirwa[2]

[1]Internal Medicine, University of Calabar Teaching Hospital, Calabar, Nigeria. [2]Makerere University Medical School, Kampala, Uganda

Contact address: Emmanuel E Effa, Internal Medicine, University of Calabar Teaching Hospital, PMB 1278, Calabar, Cross River State, Nigeria. emmanueleffa@yahoo.com.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New, published in Issue 4, 2008.
Review content assessed as up-to-date: 31 July 2008.

Citation: Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD006083. DOI: 10.1002/14651858.CD006083.pub2.

ABSTRACT

Background

Enteric fever (typhoid and paratyphoid fever) is potentially fatal. Infection with drug-resistant strains of the causative organism *Salmonella enterica* serovar Typhi or Paratyphi increases morbidity and mortality. Azithromycin may have better outcomes in people with uncomplicated forms of the disease.

Objectives

To compare azithromycin with other antibiotics for treating uncomplicated enteric fever.

Search strategy

In August 2008, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2008, Issue 3), MEDLINE, EMBASE, LILACS, and *m*RCT. We also searched conference proceedings, reference lists, and contacted researchers and a pharmaceutical company.

Selection criteria

Randomized controlled trials comparing azithromycin with other antibiotics for treating children and adults with uncomplicated enteric fever confirmed by cultures of *S.* Typhi or Paratyphi in blood and/or stool.

Data collection and analysis

Both authors independently extracted data and assessed the risk of bias. Dichotomous data were presented and compared using the odds ratio, and continuous data were reported as arithmetic means with standard deviations and were combined using the mean difference (MD). Both were presented with 95% confidence intervals (CI).

Main results

Seven trials involving 773 participants met the inclusion criteria. The trials used adequate methods to generate the allocation sequence and conceal allocation, and were open label. Three trials exclusively included adults, two included children, and two included both adults and children; all were hospital inpatients. One trial evaluated azithromycin against chloramphenicol and did not demonstrate a difference for any outcome (77 participants, 1 trial). When compared with fluoroquinolones in four trials, azithromycin significantly reduced clinical failure (OR 0.48, 95% CI 0.26 to 0.89; 564 participants, 4 trials) and duration of hospital stay (MD -1.04 days, 95%

CI -1.73 to -0.34 days; 213 participants, 2 trials); all four trials included people with multiple-drug-resistant or nalidixic acid-resistant strains of *S.* Typhi or *S.* Paratyphi. We detected no statistically significant difference in the other outcomes. Compared with ceftriaxone, azithromycin significantly reduced relapse (OR 0.09, 95% CI 0.01 to 0.70; 132 participants, 2 trials) and not other outcome measures. Few adverse events were reported, and most were mild and self limiting.

Authors' conclusions

Azithromycin appears better than fluoroquinolone drugs in populations that included participants with drug-resistant strains. Azithromycin may perform better than ceftriaxone.

PLAIN LANGUAGE SUMMARY

Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Typhoid or paratyphoid fevers (known as enteric fever) are infectious diseases caused by *Salmonella* bacteria. There were over 25 million new cases worldwide in 2000. Infections are mostly in the middle- and low-income countries where sanitation and water supplies are poor. The diseases are common in the Indian subcontinent, South-East and Far East Asia, Africa, Central and South America, and the Mediterranean region. Enteric fever occurs mainly in young people between five and 19 years and in some areas it is common among children less than five years' old. The infection is usually transmitted by ingestion of food or water contaminated with faeces from people who have the infection. Symptoms include intermittent fever, severe headaches, abdominal discomfort, loss of appetite, malaise, vague abdominal tenderness, and enlarged liver and/or spleen. About 10% to 15% of people get complications, which include bleeding, shock, and inflammation of the pancreas, heart muscles, and the brain. For many years, antibiotics such as chloramphenicol, ampicillin, and cotrimoxazole were used for treating enteric fever. However, multiple-drug resistant strains of the bacteria have now emerged. Other antibiotics like the fluoroquinolones, cephalosporins, and azithromycin are used as well. This review of trials looked at azithromycin as a treatment for uncomplicated enteric fever. There were seven trials (from Egypt, Vietman, and India) involving 773 people, all treated in hospital. There was limited evidence showing azithromycin is effective for treating typhoid or paratyphoid fevers. This is especially important where there are multiple-drug resistant strains. Azithromycin was better than some of the other drugs used. However, care will need to be taken to prevent strains becoming resistant to azithromycin too. More large trials, preferably multicentred and involving outpatients in areas endemic for enteric fever, are needed.

BACKGROUND

Definition

Enteric fever (typhoid or paratyphoid fever) is a potentially fatal systemic infection. Typhoid fever is caused by *Salmonella enterica* serovar Typhi (*S.* Typhi) and paratyphoid fever is caused by *Salmonella enterica* serovar Paratyphi (*S.* Paratyphi) *A*, *B*, or *C*. These organisms cause disease specifically in humans. Paratyphoid fever is usually a less serious infection with milder symptoms and causes fewer deaths (Maskalyk 2003), although it may occasionally become complicated (Lang 1992; Rajagopal 2002).

Epidemiology

An estimated 21.6 million new cases of typhoid fever with about 216,510 deaths occurred globally in 2000. Paratyphoid fever caused about 5.4 million illnesses in the same year (Crump 2004). Most cases occur in the middle-income and low-income countries where sanitation is poor and water supply is inadequate (Lesser 2001). Endemic enteric fever is common in the Indian subcontinent, South-East and Far East Asia, Africa, Central and South America, and the Mediterranean region (Corales 2000). Incidence rates vary across areas; for instance, annual incidence rates of 198 per 100,000 have been reported in the Mekong valley region of Vietnam (Lin 2002) and 980 per 100,000 in Delhi, India (Sinha 1999). In the USA, most infections are linked to international

travel to countries where the disease is endemic; 356 cases were reported in 2003 (Hopkins 2005).

The peak incidence occurs in people between five and 19 years, and young adults (Bhan 2005). However, in some areas it is common among children less than five years' old (Sinha 1999). There are several risk factors for the infection such as extremes of age, sickle cell anaemia, a lack of acid in gastric juice (as seen in the elderly), and gastric surgery (Parry 1984; Corales 2000). The mortality rate is about 10% to 15% if untreated and is highest among children aged less than one year and the elderly (Butler 1991; Bhutta 1996).

Pathogenesis

The infection is usually transmitted by ingestion of food or water contaminated with faeces from people who have an acute infection, are convalescing, or are chronic carriers. A chronic carrier is defined as someone who excretes *S.* Typhi in stool or urine for more than one year (Bhan 2005). The severity of the infection is dependent on the initial infective dose, virulence of the organism, and the host immune response (Adams 1987). The organisms usually penetrate the intestinal lining from where they multiply in lymphoid tissues, are released into the blood stream, and then spread to various body organs, most commonly the liver, spleen, bone marrow, and gall bladder (Lesser 2001).

Clinical features

The clinical features of uncomplicated enteric fever include progressive intermittent fever, severe headaches, abdominal discomfort, cough, loss of appetite, malaise, vague abdominal tenderness, enlarged liver and/or spleen, and in the fair-skinned, rose-coloured spots on the chest and abdomen (Lesser 2001). Complications may include intestinal perforation that may require surgery, intestinal bleeding needing blood transfusion, shock, pancreatitis (inflammation of the pancreas), pneumonia, myocarditis (inflammation of the heart muscles), meningitis (inflammation of the covering of the brain), and psychosis (altered mental state). They occur in 10% to 15% of people and commonly in those people whose illness has lasted more than two weeks (Parry 2002), and usually require admission into hospital.

Diagnosis

The definitive diagnosis of enteric fever is the isolation of the organisms from blood or bone marrow. Cultures of bone marrow aspirate are reported to be positive in about 60% to 90% of patients, and organisms can be cultured even when patients have had antibiotics for some days (Vallenas 1985; Akoh 1991; Gasem 1995; Corales 2000). Stool, urine, intestinal secretions, rectal swabs, and skin snips of rose spots can also be cultured, but these have low yields. Serologic tests, like the agglutination reaction (Widal reaction), are not reliable because of false-positive results owing to cross-reaction with other *Salmonella* spp. and a sensitivity of only 70% (Maskalyk 2003). Newer methods of diagnosis such as the use of DNA probes and polymerase chain reaction to detect *S. T*yphi directly in blood are now available, but their use in endemic areas is limited (Parry 2002).

Treatment and drug resistance

For many decades, antibiotics such as chloramphenicol, ampicillin, and cotrimoxazole were used for treating enteric fever (Lesser 2001). The emergence of multiple-drug-resistant (MDR) *Salmonella* strains, which are resistant to chloramphenicol, ampicillin, and cotrimoxazole, has changed treatment options. MDR strains of *S.* Typhi have been reported from all parts of the world. In Quetta, Pakistan for instance 69% of *S.* Typhi isolated from blood was MDR (Mirza 1996), whereas in Vietnam 89.9% of isolates between 1998 and 2002 were MDR (Le 2004). Resistance was considerably lower in Tajikistan where 27% of isolates were MDR (Mermin 1999). A cluster of six cases with MDR typhoid has also been reported in South Africa (Coovadia 1992). In Nigeria and Kenya, MDR typhoid is reported as 61% (Akinyemi 2005) and 82.4% (Kariuki 2004) respectively. In 1995, 28% of all isolates of *S.* Typhi from humans in the USA were resistant to a wide range of drugs including ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracyclines (Ribot 2002). The incidence of MDR *S.* Typhi in the UK was reported as over 50% in 1999, up from 34% in 1995 and 1.5% six years earlier (Rowe 1997; Threlfall 2001). However, there are recent reports from Egypt and the Indian subcontinent of a fall in the proportion of MDR strains of *S.* Typhi (Wasfy 2002; Madhulika 2004; Lakshmi 2006).

Second-line antibiotics like the fluoroquinolones (ciprofloxacin, ofloxacin, perfloxacin), third-generation cephalosporins (ceftriaxone, cefotaxime, cefixime), and azithromycin are often now used for treating MDR typhoid fever. (See Thaver 2008 for a Cochrane Review of fluoroquinolones for treating enteric fever.) Infections with isolates susceptible to nalidixic acid (prototype fluoroquinolone) respond extremely well to fluoroquinolones. Lately, there have been several reports of fluoroquinolone-resistant *S.* Typhi (Murdoch 1998; Asna 2003; Butt 2003). However, there are problems with identifying these strains. *S.* Typhi resistant to nalidixic acid may not respond to ciprofloxacin despite having minimum inhibitory concentration (MIC) values within current Clinical and Laboratory Standards Institute (CLSI) susceptibility range for ciprofloxacin (Wain 1997; Threlfall 1999; Ackers 2000). This means that in vitro susceptibility may not always translate to in vivo efficacy and that there is risk of treatment failures in those infected with such strains (Aarestrup 2003; Crump 2003). Nalidixic acid-resistant (NaR) isolates of *S.* Typhi and *S.* Paratyphi A are defined as susceptible by the microbiology laboratory using

the current CLSI breakpoints; however, they have reduced susceptibility to fluoroquinolones compared with wild-type strains and also respond less well to fluoroquinolone therapy. These are distinct from isolates of *S.* Typhi and Paratyphi A that are fully resistant to fluoroquinolones, for which treatment with fluoroquinolones will always lead to failure. Essentially there are three categories of susceptibilities to fluoroquinolones: fully susceptible (ie susceptible to nalidixic acid and ciprofloxacin); reduced susceptibility (ie NaR and susceptible to ciprofloxacin); and resistant (NaR and ciprofloxacin) (Rupali 2004; Parry 2006; Kownhar 2007).

Quinolone-resistant strains are reportedly also MDR (Parry 2002), and infection with resistant *S.* Typhi is associated with increased morbidity and mortality (Coovadia 1992). There are also reports from the Indian subcontinent of isolates that are fully resistant to fluoroquinolones and the extended spectrum cephalosporins *(* Renuka 2005*;* Mushtaq 2006*;* Joshi 2007). These reports further support the need for alternative antibiotics such as azithromycin for treating drug-resistant enteric fever.

Azithromycin

Azithromycin, a member of the macrolide group of antibiotics, has been used as an alternative drug for treating typhoid fever. It achieves low intravascular levels, has high intracellular tissue penetration, and a long elimination half life of 72 hours. These properties make for once-daily administration and reduction in the duration of therapy. The drug is rapidly absorbed from the gut and is well-tolerated when used orally (Carbon 1998; Chambers 2004). Adverse effects include allergic reactions, liver damage, nausea, diarrhoea, abdominal pains, rashes, and arrhythmias. In vitro studies have shown that it is more potent than traditional first-line drugs and other macrolides against *Salmonella* spp. with an average MIC of 8 μg/mL (range 4 to 16 μg/mL) (Metchock 1990; Butler 2001). There are no reports of resistance of *S.* Typhi to azithromycin, and recent studies have shown that it is effective both clinically and bacteriologically in treating enteric fever even in those caused by MDR strains (Tribble 1995; Girgis 1999). However, it is important to note that there are no currently accepted breakpoints and disc susceptibility zone interpretative criteria for azithromycin against *Salmonella* spp. Thus, it is difficult for laboratories to categorically state that a *S.* Typhi or *S.* Paratyphi isolate is susceptible or resistant to the drug.

This review therefore aims to assess available evidence on the efficacy and safety of azithromycin as an alternative drug in treating uncomplicated enteric fever.

OBJECTIVES

To compare azithromycin with other antibiotics for treating uncomplicated enteric fever.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Children or adults with uncomplicated enteric fever confirmed by culture of *S.* Typhi or *S.* Paratyphi in blood, stool, urine, or bone marrow aspirate. We define uncomplicated enteric fever as clinical diagnosis of typhoid or paratyphoid fever without overwhelming toxaemia, intestinal haemorrhage, intestinal perforation, shock, psychosis, or convulsions at the start of treatment.

Types of interventions

Intervention

Oral azithromycin.

Control

Other antibiotics such as chloramphenicol, ampicillin, amoxicillin, cotrimoxazole, ceftriaxone, and any fluoroquinolone.

Types of outcome measures

Primary

- Clinical failure, defined as persistent symptoms or development of complications requiring prolonged treatment or the addition or change of antimicrobial agent.
- Microbiological failure, defined as a positive culture from blood, bone marrow, or stool at the end of treatment as defined by trial authors.

Secondary

- Fever clearance time, defined as time in hours from start of trial or control drug until body temperature falls to values less than 38 °C and remains so for a period as specified by trial authors.
- Duration of hospital stay, defined as time in days from entry into trial until discharge.
- Relapse, defined as recurrence of symptoms in addition to a positive culture from blood, bone marrow, or stool within 30 days during the follow-up period.

Adverse events

- Serious adverse events, defined as those leading to death (eg intestinal perforation and haemorrhage), prolonged hospitalization (eg cholestatic jaundice), and disability.
- Adverse events requiring discontinuation of treatment (eg markedly elevated liver enzymes and impaired renal function).
- Other adverse events (eg nausea, vomiting, and diarrhoea).

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).

We searched the following databases using the search terms and strategy described in Table 1: Cochrane Infectious Diseases Group Specialized Register (August 2008); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2008, Issue 3); MEDLINE (1966 to August 2008); EMBASE (1974 to August 2008); and LILACS (1982 to August 2008). We also searched the *meta*Register of Controlled Trials (*m*RCT) in August 2008 using 'azithromycin' and 'typhoid' as search terms.

Table 1. Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	azithromycin	azithromycin	azithromycin	azithromycin	azithromycin
2	typhoid fever*	typhoid fever*	typhoid fever*	typhoid fever*	typhoid fever*
3	paratyphoid fever*	paratyphoid fever*	paratyphoid fever*	paratyphoid fever$	paratyphoid*
4	salmonell*	enteric fever	enteric fever	enteric fever	salmonell*
5	2 or 3 or 4	TYPHOID FEVER	TYPHOID FEVER	TYPHOID FEVER	2 or 3 or 4

Table 1. Detailed search strategies (*Continued*)

6	1 and 5	SALMONELL*	PARATYPHOID FEVER	salmonell$	1 and 5
7	-	2 or 3 or 4 or 5 or 6	salmonell*	2 or 3 or 4 or 5 or 6	-
8	-	1 and 7	2 or 3 or 4 or 5 or 6 or 7	1 and 7	-
9	-	-	1 and 8	Limit 8 to humans	-
10	-	-	Limit 9 to humans	-	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2008); upper case: MeSH or EMTREE heading; lower case: free text term.

We searched the conference proceedings of the 5th International Symposium on Typhoid Fever and other Salmonellosis, Karachi, Pakistan, 4 to 7 February 2002 for relevant abstracts. We contacted experts in the field, Drs Christopher Parry and Jeremy Farrar, for unpublished and/or ongoing trials. We also checked the reference lists of all studies identified by these methods.

Data collection and analysis

Selection of studies

Both authors independently screened results of literature search for potentially relevant trials. We retrieved full reports of the identified trials and independently determined if they met the inclusion criteria using a pre-tested eligibility form. We resolved contentious issues by discussion and, where necessary, by consulting a Cochrane Infectious Diseases Group (CIDG) Editor. We also attempted to contact authors for further information if trial eligibility was unclear. We listed all excluded studies along with the reasons for exclusion in the 'Characteristics of excluded studies'. We ensured that trials with multiple publications were included only once.

Data extraction and management

Both authors independently extracted data analysed as stated in the trial protocol using a pre-tested data extraction form. We extracted data for dichotomous outcomes, such as clinical failure and microbiological failure, by recording the total number of participants randomized, those that experienced these outcomes, and the number analysed. For continuous outcomes, such as fever clearance time and duration of hospital stay, we extracted the total number of participants analysed, arithmetic means, and standard deviation. Where standard deviations were not reported, we derived them using standard error of the mean. We also extracted data on reported adverse events. We contacted trial authors where the relevant details were not recorded or were unclear. Contentious issues were resolved by consensus or, when necessary, by consulting a CIDG Editor. The first author entered the data into Review Manager 5.

Assessment of risk of bias in included studies

Both authors independently assessed the risk of bias of eligible trials using a specially designed pre-tested form. We assessed generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Jüni 2001. We reported which parties (participant, care provider, or assessor) were blinded in each trial. We considered inclusion of all randomized culture-positive participants in the analysis to be adequate if 90% or more were included, inadequate if less than 90%, and unclear if this was not stated. We resolved disagreements through discussion or by consulting a CIDG Editor. We attempted to contact the trial authors where the method was either not stated or unclear.

Data synthesis

We analysed data using Review Manager 5. All results were presented with 95% confidence intervals (CI). Dichotomous data were presented and compared using the odds ratio. Continuous data, where arithmetic means and standard deviations (SD) were reported, were combined using the mean difference (MD). Where arithmetic means were reported for an outcome and the scale was naturally bound at zero, the ratio of the mean to standard deviation was used to check the assumption that the data were normally distributed. If we suspected the data were skewed (mean/SD < 2), then we did not combine the data in a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We assessed heterogeneity amongst the trials by inspecting the forest plot and using the chi-squared test (with P value < 0.1 representing heterogeneity) and the I^2 test (50% represents moderate level of heterogeneity). When we detected any heterogeneity among the trials for any outcome, we combined them using the random-effects model. We planned to do subgroup analyses for participant age (child versus adult), hospitalization (hospitalized or not), presence of multiple-drug resistance, and duration of treatment, but this was not possible as there were few trials with limited numbers of participants.

Sensitivity analysis

We could not conduct sensitivity analyses to explore the effect of the trials' risk of bias assessment, particularly allocation concealment, on the results. This was because there were few trials in each comparison. For the same reason publication bias could not be assessed using the funnel plot.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Trial selection

Eleven trials were identified and assessed for eligibility. Seven trials involving 773 participants met the inclusion criteria (Butler 1999; Girgis 1999; Chinh 2000; Frenck 2000; Frenck 2004; Parry 2007; Dolecek 2008); see details in the 'Characteristics of included studies'. Four were excluded (Wallace 1994; Tribble 1995; Chiu 1999; Li 2005); see details in the 'Characteristics of excluded studies'. One ongoing study was also identified and is described in the 'Characteristics of ongoing studies' (ISRCTN66534807).

Trial design and location

Three trials were conducted in Egypt (Girgis 1999; Frenck 2000; Frenck 2004), three in Vietnam (Chinh 2000; Parry 2007; Dolecek 2008), and one in India (Butler 1999). Both Butler 1999 and Dolecek 2008 were multicentred.

Participants

Three trials included only adults with the minimum reported age of 15 years (Butler 1999; Girgis 1999; Chinh 2000). Two trials were exclusively in children and adolescents with a minimum age of three years and a maximum of 17 years (Frenck 2000; Frenck 2004). Two trials had both children and adult participants with an age range of one to 42 years (Parry 2007; Dolecek 2008). All the trials were conducted on inpatients who had uncomplicated enteric fever and were found to have positive blood and/or stool cultures for *S.* Typhi or *S.* Paratyphi. All the trials had participants with MDR strains of *S.* Typhi. In two trials, Chinh 2000 and Dolecek 2008, over half of the participants were infected with MDR *S.* Typhi, while in another, Parry 2007, more than 80% of isolates were MDR. Nearly 100% had NaR *S.* Typhi in Parry 2007 and Dolecek 2008.

Inclusion and exclusion criteria

All included trials reported well-defined inclusion and exclusion criteria. Criteria for enrolment were clinical but positive blood/or stool culture for *S.* Typhi or *S.* Paratyphi required for inclusion in the study. All trials excluded pregnant and lactating women, and those with serious underlying diseases, previous antibiotic treatment, severe illness, and history of allergy to any of the study drugs.

Interventions

Trials compared azithromycin with ceftriaxone (Frenck 2000; Frenck 2004), ciprofloxacin (Girgis 1999), ofloxacin (Chinh 2000; Parry 2007), gatifloxacin (Dolecek 2008), and chloramphenicol (Butler 1999). No trials compared azithromycin with other first-line antibiotics such as ampicillin and cotrimoxazole.

All seven trials used a short-course azithromycin regimen (five to seven days). Two trials treated participants for five days (Chinh 2000; Frenck 2004), whereas the other five trials used a seven-day regimen (Butler 1999; Girgis 1999; Frenck 2000; Parry 2007; Dolecek 2008).

Outcome measures

Primary outcomes

Definitions and time points at which primary outcomes were measured varied. Some trials considered response as 'clinical cure' or

'microbiological cure'. In two trials, microbiological failure was not explicitly defined (Butler 1999; Frenck 2000) and, in two other trials, the definition of fever clearance was unclear (Frenck 2000; Frenck 2004); see details in Table 2. We were able to extract data on both primary outcomes (clinical failure and microbiological failure) from all seven trials.

Table 2. Definitions of outcome measures

Comparison	Trial	Clinical failure	Microbiological failure	Relapse	Fever clearance time
Azithromycin vs chloramphenicol	Butler 1999	Lack of improvement or worsening of signs and symptoms or need to change antibiotic therapy	Not defined	Clinical: return of fever after day 14 Bacteriological recurrence: blood culture positive for *S.* Typhi or *S.* Paratyphi on day 21 or 35 days after start of therapy	Not defined
Azithromycin vs fluoroquinolones	Girgis 1999	Lack of resolution of symptoms by day 7 or development of a major complication of typhoid fever after 5 days of therapy	Blood culture positive for *S.* Typhi or *S.* Paratyphi on day 4 or 10	Recurrence of fever with signs and symptoms of typhoid fever within 4 weeks of therapy completion along with isolation of organism in culture	First day on which maximum temperature < 38.0 °C with maintenance of temperature at this level for at least 48 hours
	Chinh 2000	Persistence of fever and symptoms for > 5 days after end of treatment or development of severe complications during treatment, requiring a change in therapy	Isolation of *S.* Typhi or serovar *S.* Paratyphi A from blood or a sterile site after completion of treatment	Recurrence of symptoms and signs suggestive of enteric fever after the participant had been discharged as well from the hospital	Time from start of treatment until the body temperature fell < 37.5 °C and remained at < 37.5 °C for 48 hours
	Parry 2007	Persistence of fever and at least 1 other typhoid related symptom for > 7 days after start of treatment, or development of complications during treatment requiring change in therapy	Isolation of *S.* Typhi or Paratyphi from blood or sterile site after completion of treatment	Recurrence of symptoms and signs suggestive of enteric fever within the 4-week period after participant discharged from hospital plus blood culture positive for *S.* Typhi or *S.* Paratyphi	Time from start of treatment until body temperature 37.5 °C and remained so for 48 hours
	Dolecek 2008	Persistence of fever and symptoms 2 days	Positive blood culture on day 7 to 9 after	Occurrence of symptoms and signs of ty-	Time from the start of the antibiotic treat-

Table 2. Definitions of outcome measures (*Continued*)

		after end of treatment, ie on day 10 or need for re-treatment due to insufficient treatment response as judged by the treating physician	start of treatment	phoid fever within 1 month after completion of treatment	ment to when the axillary temperature first fell ≤ 37.5 ºC and remained there for at least 48 hours
Azithromycin vs ceftriaxone	Frenck 2000	Persistence of > 1 typhoid-related symptom or sign present at study entry, or development of a typhoid-related complication after at least 4 days of therapy	Not defined	Recurrence of fever with symptoms of typhoid fever within 4 weeks of completion of therapy along with isolation of *S.* Typhi or *S.* Paratyphi from blood	Not defined
	Frenck 2004	Persistence of > 2 typhoid-related symptoms or signs present at study entry or as development of a typhoid-related complication	Blood culture positive for *S.* Typhi on day 8	Recurrence of fever and clinical features of typhoid within 30 days of completing therapy, along with isolation of *S.* Typhi from the blood	Not defined

S. Paratyphi: *Salmonella enterica* serovar Paratyphi; *S.* Typhi: *Salmonella enterica* serovar Typhi.

Secondary outcomes

We were able to extract data on all three secondary outcomes (fever clearance time, relapse, and duration of hospital stay) from only two trials (Chinh 2000; Parry 2007). Apart from Frenck 2000 and Frenck 2004, the other three trials did not include data on duration of hospital stay.

We could extract data on adverse events (both clinical and laboratory) from four trials (Girgis 1999; Chinh 2000; Frenck 2004; Dolecek 2008). One trial only reported laboratory-based adverse events (Frenck 2000), while one reported only clinical adverse events (Butler 1999).

MDR and NaR strains

All seven trials reported the proportion of participants with MDR strains. One trial did not specify the proportion in either study arm (Butler 1999), and only three trials indicated the proportion of participants with NaR strains in either study arm study (Chinh 2000; Parry 2007; Dolecek 2008,). Overall, between 1.5% and 85% of participants were infected with MDR strains especially of *S.* Typhi; see Table 3 for details.

Table 3. Participants with MDR and NaR strains

Comparison	Trial	Participants	Culture positive (site)	S. Typhi/ Paratyphi	Number (%) with MDR	Number (%) with NaR	Notes
Azithromycin vs chloramphenicol	Butler 1999	109 enrolled and randomized	92 (blood)	82/10 azithromycin 38/4 chloramphenicol 29/6 15 participants excluded for various reasons	10 (11%)	Not stated	-
Azithromycin vs fluoroquinolone	Chinh 2000	97 enrolled and randomized	88 (blood)	86/2 not stated	68 (77.2%) Azithromycin: 33 Fluoroquinolone 35	46 (52%) Azithromycin: 25 Fluoroquinolon: 21	1 isolate was not available for sensitivity testing
	Girgis 1999	123 enrolled and randomized	52 (blood); 2 (stool); 10 (both blood and stool)	34/2 azithromycin 26/2 ciprofloxacin	21 (33%) Azithromycin: 6 Fluoroquinolone: 15	Not stated	-
	Parry 2007	241 enrolled and random-	199 (blood or bone marrow)	198/1 62/0 azithro-	165 (83%) Azithromycin:	172 (86%) Azithromycin	This study had 3 arms

Table 3. Participants with MDR and NaR strains (*Continued*)

		ized		mycin 63/0 ofloxacin 62/1 ofloxacin-azithromycin	53 Fluoro-quinolone: 57	55 (89%) Fluoro-quinolone 62 (98%)	
	Dolecek 2008	358 enrolled and randomized	288 (blood or bone marrow)	144/1 gatifloxacin 138/4 azithromycin	153 (58%) Gatifloxacin: 87 (63.5%) Azithromycin: 66 (52.3%)	254 (96.5%) Gatifloxacin:132 (96.3%) Azithromycin:121 (96%)	Only 263 isolates had antibiotic susceptibility testing
Azithromycin vs ceftriaxone	Frenck 2000	108 enrolled and randomized	64 (blood)	64/0	11 (17.2%)	Not stated	-
	Frenck 2004	128 enrolled and randomized	65 (blood); 13 (stool)	64/0	1 (1.5%)	Not stated	-

MDR: multiple-drug resistant; NaR: nalidixic acid resistant.

Risk of bias in included studies

See Table 4 for a summary of the risk of bias assessment.

Table 4. Risk of bias assessment

Comparison	Trial	Allocation sequence generation	Allocation concealment	Blinding	Randomized participants in the analysis
Azithromycin vs chloramphenicol	Butler 1999	Adequate	Adequate	Open	Inadequate
Azithromycin vs ofloxacin	Chinh 2000	Adequate	Adequate	Open	Adequate
Azithromycin vs gatifloxacin	Dolecek 2008	Adequate	Adequate	Open	Adequate
Azithromycin vs ciprofloxacin	Girgis 1999	Adequate	Adequate	Open	Adequate

Table 4. Risk of bias assessment (*Continued*)

Azithromycin vs ofloxacin	Parry 2007	Adequate	Adequate	Open	Adequate
Azithromycin vs ceftriaxone	Frenck 2000	Adequate	Adequate	Open	Adequate
Azithromycin vs ceftriaxone	Frenck 2004	Adequate	Adequate	Open	Adequate

Generation of allocation sequence

All seven included trials used an adequate method to generate the allocation sequence: random-number list (Frenck 2000; Girgis 1999); table of random numbers (Butler 1999); random-number generator (Frenck 2004); and computer-generated randomization list (Chinh 2000; Parry 2007; Dolecek 2008).

Allocation concealment

All included trials used an adequate method to conceal allocation (sealed envelopes).

Blinding

Six trials were described as open for participants and physicians/caregivers (Butler 1999; Girgis 1999; Chinh 2000; Frenck 2000; Frenck 2004; Parry 2007). Dolecek 2008 was described simply as open label. One trial specifically stated that outcome assessors were not blinded (Butler 1999), while we obtained similar information from the trialists of two other trials (Chinh 2000; Parry 2007). The blinding of outcome assessors was unclear in three trials (Girgis 1999; Frenck 2000; Frenck 2004).

Inclusion of all culture-positive participants in final analysis

In all seven trials, only culture-positive participants were considered evaluable. Six trials included 90% or more of culture-positive participants in the final analysis, while Butler 1999 included 84%.

Intention-to-treat analyses

In all but Dolecek 2008 the trialists' analyses of the results were not by intention to treat as they excluded culture-negative participants. The analyses were both as pre-specified in the protocol (per protocol) and by intention to treat in Dolecek 2008; we used the per protocol data in this review.

Effects of interventions

1. Azithromycin versus chloramphenicol

Clinical and microbiological failure

One trial with 77 participants, including 11% with MDR *S.* Typhi, made this comparison (Butler 1999). There was a tendency for azithromycin to have lower odds of clinical failure, but the results were not statistically significant (77 participants, Analysis 1.1). There was also no statistically significant difference in the odds of microbiological failure in both groups (77 participants, Analysis 1.2).

Relapse

No relapses were reported.

Fever clearance time

Fever clearance time was shorter in the azithromycin group (mean 98.4 hours) compared to the chloramphenicol group (mean 103.2 hours), but the results were not statistically significant (77 participants, Analysis 1.3).

Duration of hospital stay

No data were reported for duration of hospital stay.

Adverse events

No data were reported for serious adverse events (Table 5). Five other adverse events were reported in the azithromycin group (Table 6), two were gastrointestinal (no details for the other three). No other adverse events were reported for the chloramphenicol group (77 participants, Figure 1, Analysis 1.4).

Figure 1. Azithromycin (AZM) vs chloramphenicol (CM): Adverse events (excluding serious adverse events)

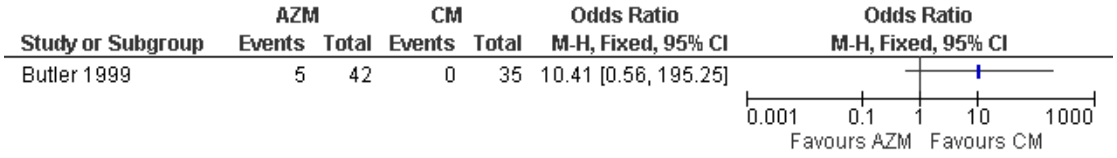


Table 5. Serious adverse events

Comparison	Trial	Intervention	Control
Azithromycin vs chloramphenicol	Butler 1999	None	None
Azithromycin vs fluoroquinolone	Chinh 2000	None	None
	Dolecek 2008	None	None
	Girgis 1999	None	None
	Parry 2007	None	None
Azithromycin vs ceftriaxone	Frenck 2000	None	None
	Frenck 2004	None	None

Table 6. Other adverse events

Comparison	Trial	Clinical adverse events[a]		Laboratory adverse events[a]	
		Intervention	Control	Intervention	Control
Azithromycin vs chloramphenicol	Butler 1999	Azithromycin: 5 gastrointestinal (2) others not stated	None	Not described	Not described
Azithromycin vs fluoroquinolone	Chinh 2000	Azithromycin: Gastrointestinal bleeding (1); nausea (5); vom-	Ofloxacin Gastrointestinal bleeding; nausea (1); vomiting (3); abdom-	Azithromycin: mild elevation in mean transaminase levels	Ofloxacin: mild elevation in mean transaminase levels

Table 6. Other adverse events (*Continued*)

		iting (5); abdominal pain (4); skin rash (1)	inal pain (4); skin rash (0)		
	Girgis 1999	Azithromycin: nausea or vomiting (6); lightheadedness (2); dry throat or mouth (3); loose stools (3); constipation (2)	Ciprofloxacin: nausea or vomiting (4); lightheadedness (2); dry throat or mouth (4); loose stools (3); constipation (2)	Azithromycin: thrombocytosis (4); mild increase in aspartate amino transaminase levels (2)	Ciprofloxacin: thrombocytosis (1); mild increases in aspartate transaminases levels (3)
	Parry 2007	Azithromycin: joint discomfort (1)	Ofloxacin: joint discomfort	Azithromycin: none	Ofloxacin: none
	Dolecek 2008	Azithromycin: Gastrointestinal bleeding (4) Liver dysfunction (2) Maculopapular rash (1) Pneumonia (2)	Gatifloxacin: vomiting (1); diarrhoea (1)	Azithromycin: mild elevations in median transaminase levels	Gatifloxacin: mild elevations in median transaminase levels
Azithromycin vs ceftriaxone	Frenck 2000	Azithromycin: gastrointestinal symptoms most commonly vomiting	Ceftriaxone: gastrointestinal symptom less; pains at injection site (6)	Azithromycin: mild elevation in alanine aminotransferase (1) and aspartate transaminases (2); thrombocytosis (4)	Ceftriaxone: mild elevations in alanine transaminase (1) and aspartate transaminase (4), thrombocytosis (3)
	Frenck 2004	Azithromycin: vomiting (11); diarrhoea (10); nausea (5); abdominal pain (3); anorexia (3); cough (3)	Ceftriaxone: vomiting (7); diarrhoea (15); nausea (7); abdominal pain (5); anorexia (6); cough (2)	Azithromycin: mild increases in aspartate transaminase levels (2) and alanine transaminase levels (2); thrombocytosis (7)	Ceftriaxone: mild increases in aspartate transaminase levels (2) and alanine transaminase levels (5); thrombocytosis (7)

[a] Number of participants with adverse event.

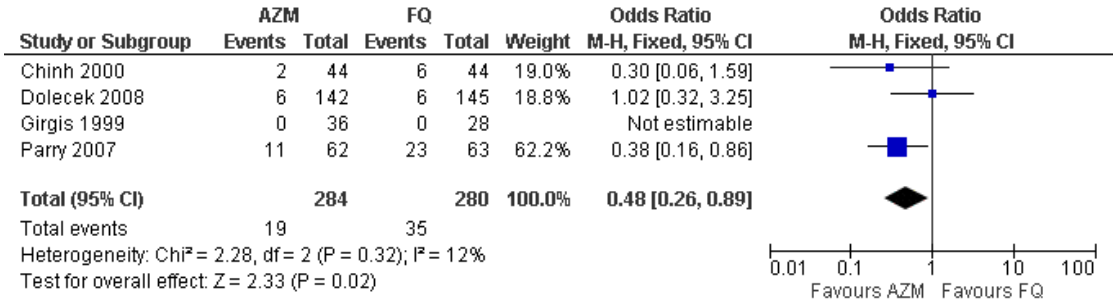
2. Azithromycin versus fluoroquinolones

Four trials involving 564 participants compared azithromycin with ciprofloxacin (Girgis 1999, 64 participants), ofloxacin (Chinh 2000, 88 participants and Parry 2007, 125 participants), and gatifloxacin (Dolecek 2008, 287 participants). The trials had varying proportions of participants with MDR and NaR strains. In Girgis 1999, a third of participants were infected with MDR strains, with 16.6% of participants in the azithromycin group and 53.6% in the ciprofloxacin group. Over half (77%) of participants in Chinh 2000 had MDR strains of *S.* Typhi: 48.5% were in the azithromycin group and 51.5% were in the ofloxacin group. Also, 46 (52%) participants were infected with NaR strains, 25 in the azithromycin group and 21 in the fluoroquinolone group. Of the participants in Parry 2007, 85% and 89% of those in the azithromycin group were infected with MDR and NaR strains, respectively, compared to 90% and 98% respectively in the ofloxacin group. In Dolecek 2008, 58% of the isolates were reported as MDR (87 in the gatifloxacin arm and 66 in the azithromycin), while 96% were NaR (132 in the gatifloxcin arm and 121 in the azithromycin arm).

Clinical and microbiological failure

There were fewer clinical failures with azithromycin (OR 0.48, 95% CI 0.26 to 0.89; 564 participants, 4 trials, Figure 2, Analysis 2.1). There were no statistically significant differences in microbiological failure (564 participants, 4 trials, Analysis 2.2) and relapse (491 participants, 4 trials, Analysis 2.3).

Figure 2. Azithromycin (AZM) vs fluoroquinolones (FQ): Clinical failure



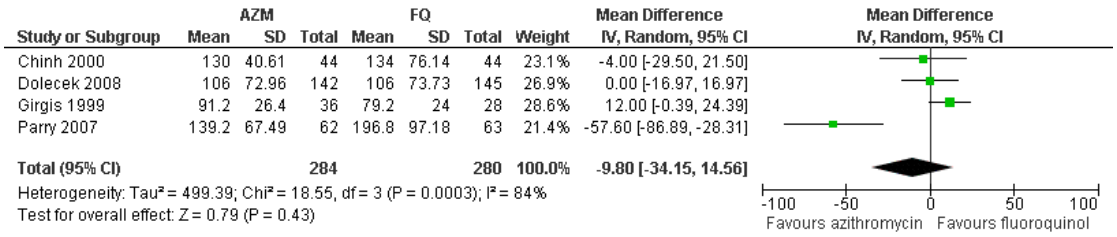
Relapse

There were no statistically significant differences in relapse (491 participants, 4 trials, Analysis 2.3).

Fever clearance time

There was marked heterogeneity for fever clearance time with no significant difference between the interventions when analysed using the random-effects model (564 participants, 4 trials, Figure 3, Analysis 2.4). The heterogeneity may be explained by differences in the definition of fever clearance time and the different fluoroquinolones used in the four trials.

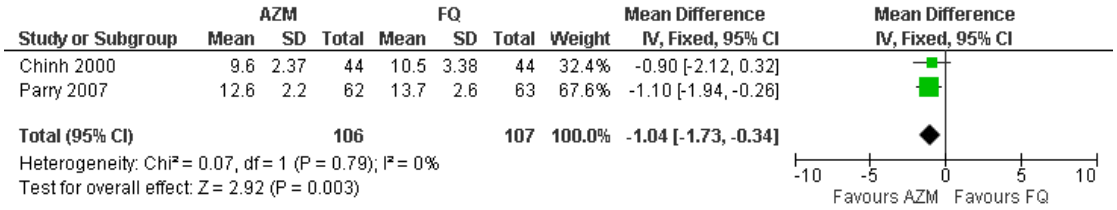
Figure 3. Azithromycin (AZM) vs fluoroquinolones (FQ): Fever clearance time (h)



Duration of hospital stay

Two trials reported on the duration of hospital stay (Chinh 2000; Parry 2007), which was significantly shorter in the azithromycin group (MD -1.04 days, 95% CI -1.73 to -0.34 days; 213 participants, 2 trials, Figure 4, Analysis 2.5).

Figure 4. Azithromycin (AZM) vs fluoroquinolones (FQ): Duration of hospital stay (days)



Adverse events

There were no serious adverse events reported in any of the trials (see Table 5). Adverse events that lead to discontinuation of the trial drugs included gastrointestinal bleeding in four participants and maculopapular rash in a participant. Both events were in the azithromycin arm of Dolecek 2008. There was a single event of gastrointestinal bleeding in each arm of Chinh 2000, but the trial drugs were not discontinued (Table 6).

Other common clinical adverse events reported in both arms of all included trials were nausea, vomiting, abdominal pains and skin rash. In Dolecek 2008, two participants in the azithromycin arm developed features of liver dysfunction and another two had pneumonia. One participant in each of the azithromycin and ofloxacin groups reported joint discomfort in Parry 2007. Laboratory-based adverse events were thrombocytosis and elevated aspartate amino transaminases, but these were not different between treatment groups.

3. Azithromycin versus ceftriaxone

Two trials involving 132 children made this comparison (Frenck 2000; Frenck 2004). About 17% of participants had *S.* Typhi MDR strains in Frenck 2000, whereas Frenck 2004 reported only one participant with MDR strains.

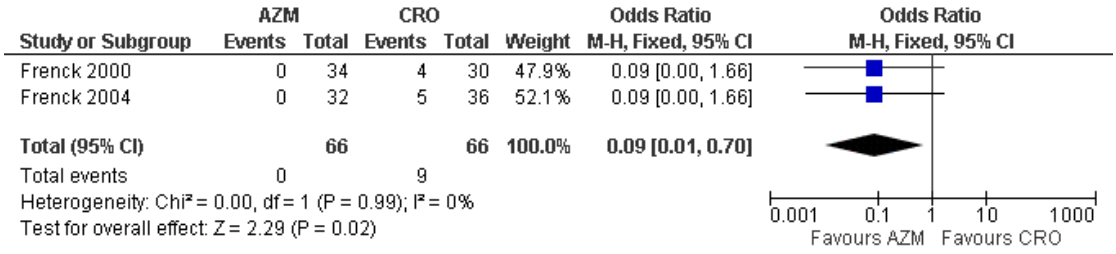
Clinical and microbiological failure

There was no statistically significant difference between the two groups in the odds of clinical failure (132 participants, 2 trials, Analysis 3.1) and microbiological failure (132 participants, 2 trials, Analysis 3.2).

Relapse

The odds of relapse were reduced by 91% in the azithromycin group and this was statistically significant, but the number analysed is small and the confidence intervals wide (OR 0.09, 95% CI 0.01 to 0.70; 132 participants, 2 trials, Figure 5, Analysis 3.3).

Figure 5. Azithromycin (AZM) vs ceftriaxone (CRO): Relapse



Fever clearance time

Fever clearance time was less in the ceftriaxone arm, but the difference was not statistically significant (132 participants, 2 trials, Analysis 3.4).

Duration of hospital stay

Neither trial reported on duration of hospitalization.

Adverse events

There were no reported serious adverse events (Table 5). Both trials reported gastrointestinal symptoms as common with vomiting commonest in the azithromycin group in Frenck 2000. Pain at the injection site was reported in six participants in the ceftriaxone group. Other adverse events included mild increases in aspartate and alanine transaminases, and thrombocytosis in both groups.

DISCUSSION

Seven trials met our inclusion criteria and all were conducted in low- and middle-income countries. These areas have a high burden of the disease and present greater opportunities for disease transmission, including transmission of antibiotic-resistant *S. enterica* strains. Enteric fever caused by MDR and NaR strains is a significant public health problem as it appears to be responsible for outbreaks of epidemics in these areas (Parry 2004).

The methodological quality of all seven included trials was generally high. For instance, all trials used adequate methods to gener-

ate the allocation sequence and conceal allocation. The trials included adults, children, or both, and all participants were given a definitive diagnosis through the isolation of *S.* Typhi or *S.* Paratyphi from blood and/or stools. The choice of microbiologic cultures over serologic diagnosis may be because the clinical manifestation of the disease may be atypical in children and adults, and a distinction from other febrile illnesses is difficult to make in some adults (Ferreccio 1984; Dutta 2001; Bhan 2005). However, serologic diagnosis with the Widal or other serological tests is widely used in endemic areas as facilities for microbiologic cultures are lacking (House 2001). Few trials reported the proportion of participants infected with MDR or NaR strains. Only three of the trials indicated the proportion of NaR strains in the trial arms (Chinh 2000; Parry 2007; Dolecek 2008), although reports of such strains date back over a decade ago and are found in virtually all continents. The proportion of participants with NaR strains is particularly important for the comparison with fluoroquinolones because such strains may exhibit reduced susceptibility to fluoroquinolones. Chinh 2000, Parry 2007, and Dolecek 2008 were three of the four trials comparing azithromycin with fluoroquinolones, and both involved a high proportion of NaR infections. However, the NaR infections did not significantly affect the outcomes for both intervention drugs.

The included trials compared azithromycin with chloramphenicol (Butler 1999), fluoroquinolones (ciprofloxacin (Girgis 1999), ofloxacin (Chinh 2000; Parry 2007), and gatifloxacin (Dolecek 2008)), and ceftriaxone (Frenck 2000; Frenck 2004). Another Cochrane Review has synthesized the evidence for all fluoroquinolones for treating enteric fever (Thaver 2008). Overall, because of the small number of trials eligible for this review, pooled sample size, and wide confidence intervals for each comparison, we are not able to make firm conclusions as to the benefit of azithromycin over the other drugs. However, we have identified an ongoing trial and expect that future updates of this review will include more data and allow for further analyses (eg subgroup analysis and publication bias).

The findings of this review may not be widely generalizable for several reasons. Azithromycin was compared to few alternatives when other drugs have potential; for example, there are reports of a re-emergence of strains that are fully sensitive to first-generation antibiotics in Asia (Sood 1999; Gogia 2006). The reporting by the trials of the proportion of participants with NaR strains was poor. The response of NaR strains to antibiotics is extremely variable. Nalidixic acid-sensitive strains of *S.* Typhi and Paratyphi may not necessarily be susceptible to other fluoroquinolones. The trials all used a short-course regimen (five to seven days), which suggests a need to reduce costs and encourage adherence to treatment while ensuring effectiveness; indeed short courses have been associated with higher relapse rates in some studies of ceftriaxone (Smith 1994; Bhutta 2000). Also, all trial participants were admitted to hospital, while over 90% of people in endemic areas are treated as outpatients (Parry 2002; Bhan 2005). Two trials used ceftriaxone - this has to be administered parenterally, which means that patients have to be admitted into hospital, a practice that will increase the overall cost of treatment of the disease.

All seven trials reported on adverse events. Most adverse events were gastrointestinal in nature, and they were few and mild. Gastrointestinal bleeding occurred in one participant in each of the azithromycin and fluoroquinolone arms in Chinh 2000, and in four participants in the azithromycin arm in Dolecek 2008. Laboratory abnormalities like elevation in liver enzymes and platelet counts (thrombocytosis) were also few. Four trials compared azithromycin with fluoroquinolones, and there has been concern about the use of fluoroquinolones in children based on reports that they cause joint damage in growing beagle dogs (Burkhardt 1990; Stahlmann 2000). However, no bone, joint, or tendon abnormalities have been shown as a result of the long-term use of fluoroquinolones in other clinical conditions like cystic fibrosis and short-term use in the treatment of typhoid fever in those infected with MDR *S.* Typhi (Schaad 1995; Doherty 2000). No such adverse events were reported in the two trials comparing azithromycin with a fluoroquinolone in children and adults (Parry 2007; Dolecek 2008).

AUTHORS' CONCLUSIONS

Implications for practice

There is limited evidence on the superiority of azithromycin over first-line antibiotics, fluoroquinolones, and cephalosporins even when used in people infected with MDR or NaR strains of *S.* Typhi or *S.* Paratyphi, or both. Available evidence shows that azithromycin appears to be as good as the other comparator drugs for most outcomes and appears to be better than fluoroquinolones in terms of reducing clinical failure and duration of hospital stay, and ceftriaxone in terms of reducing relapse. Considering the potential of development of resistance to any new antibiotic introduced, azithromycin should be used guardedly to prevent the emergence of strains resistant to the drug.

Implications for research

Large trials, preferably multicentred and involving outpatients in areas endemic for enteric fever should be undertaken. Also, more trials comparing azithromycin with first-line antibiotics (eg chloramphenicol, cotrimoxazole, and amoxicillin) should be undertaken as these are cheaper and have fewer reported adverse events. Furthermore, trialists should indicate clearly the proportions of participants infected with MDR and/or NaR strains of *S.* Typhi. Harmonization of the definition of outcome measures should also be done in addition to longer periods of follow up to assess long term risk of adverse events and the use of azithromycin in preventing chronic carriage of the organism. Finally, more effort should be put at standardizing use of serological tests for the rapid di-

agnosis of enteric fever as facilities for microbiologic isolation of the organisms are expensive and, as a result, largely unavailable in endemic areas.

ACKNOWLEDGEMENTS

Emmanuel Effa was awarded a Reviews for Africa Programme Fellowship (www.mrc.ac.za/cochrane/rap.htm), funded by a grant from the Nuffield Commonwealth programme, through The Nuffield Foundation. This review was developed during the Reviews for Africa Programme organized by the South African Cochrane Centre, June 2006. This document is an output from a project funded by the UK Department for International Development (DFID) for the benefit of developing countries. The views expressed are not necessarily those of DFID.

We acknowledge Professor Martin Meremikwu for guidance in developing the protocol and the review, members of staff of South African Cochrane Centre for guidance in the preparation of the protocol and development of the review, and Professor Paul Garner and Dr Harriet MacLehose (CIDG Co-ordinating Editor and Assistant Editor, respectively) for help and guidance in preparing the protocol and writing the review.

REFERENCES

References to studies included in this review

Butler 1999 *{published data only}*
Butler T, Sridhar CB, Daga MK, Pathak K, Pandit RB, Khakhria R, et al.Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. *Journal of Antimicrobial Chemotherapy* 1999;**44**(2):243–50.

Chinh 2000 *{published and unpublished data}*
Chinh NT, Parry CM, Ly NT, Ha HD, Thong MX, Diep TS, et al.A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. *Antimicrobial Agents and Chemotherapy* 2000; **44**(7):1855–9.

Dolecek 2008 *{published data only}*
Dolecek C, La TTP, Rang NN, Phuong LT, Tuan PQ, DU DC, et al.A multi-center randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid and paratyphoid fever in children and adults in Vietnam. *PLoS ONE* 2008;**3**(5):e2188.

Frenck 2000 *{published data only}*
Frenck RW Jr, Nakhla I, Sultan Y, Bassily SB, Girgis YF, David J, et al.Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clinical Infectious Diseases* 2000;**31**(5):1134–8.

Frenck 2004 *{published data only}*
Frenck RW Jr, Mansour A, Nakhla I, Sultan Y, Putnam S, Wierzba T, et al.Short-course azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents. *Clinical Infectious Diseases* 2004;**38**(7):951–7.

Girgis 1999 *{published data only}*
Girgis NI, Butler T, Frenck RW, Sultan Y, Brown FM, Tribble D, et al.Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. *Antimicrobial Agents And Chemotherapy* 1999;**43**(6):1441–4.

Parry 2007 *{published data only}*
Parry CM, Ho VA, Phuong le T, Bay PV, Lanh MN, Tung le T, et al.Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. *Antimicrobial Agents Chemotherapy* 2007;**51**(3):819–25.

References to studies excluded from this review

Chiu 1999 *{published data only}*
Chiu CH, Lin TY, Ou JT. A clinical trial comparing oral azithromycin, cefixime and no antibiotics in the treatment of acute uncomplicated salmonella enteritis in children. *Journal of Paediatric Child Health* 1999;**35**(4):372–4.

Li 2005 *{published data only}*
Li D. Therapeutic effect of azithromycin in children with typhoid. *Chinese Journal of Contemporary Pediatrics* 2005;**7**(1):57–8.

Tribble 1995 *{published data only}*
Tribble D, Girgis N, Habib N, Butler T. Efficacy of azithromycin for typhoid fever. *Clinical Infectious Diseases* 1995;**21**(4):1045–6.

Wallace 1994 *{published data only}*
Wallace MR, Yousif AA, Habib NF, Tribble DR. Azithromycin and typhoid. *The Lancet* 1994;**343**(8911):1497–8.

References to ongoing studies

ISRCTN66534807 *{published data only}*
ISRCTN66534807. A randomised clinical trial of azithromycin versus ofloxacin in the treatment of adults with uncomplicated fever at Mahosot Hospital, Vientiane, Lao PDR. www.controlled-trials.com/ISRCTN66534807 (accessed 23 May 2006).

Additional references

Aarestrup 2003
Aarestrup FM, Wiuff C, Molbak K, Threlfall EJ. Is it time to change fluoroquinolone breakpoints for Salmonella spp.?. *Antimicrobial Agents Chemotherapy* 2003;**47**(2):827–9.

Ackers 2000
Ackers ML, Puhr ND, Tauxe RV, Mintz ED. Laboratory-based surveillance of Salmonella serotype Typhi infections in the United States: antimicrobial resistance on the rise. *JAMA* 2000;**283**(20): 2668–73.

Adams 1987
Adams EB. Typhoid and paratyphoid fevers. In: Weatherall DJ, Ledingham JG, Warrell DA editor(s). *Oxford Textbook of Medicine*. 2nd Edition. Oxford: Oxford University Press, 1987:183–5.

Akinyemi 2005
Akinyemi KO, Smith SI, Oyefolu AOB, Coker AO. Multidrug resistance in Salmonella enterica serovar typhi isolated from patients with typhoid fever complications in Lagos, Nigeria. *Public Health* 2005;**119**(4):321–7.

Akoh 1991
Akoh J. Relative sensitivity of blood and bone marrow cultures in typhoid fever. *Tropical Doctor* 1991;**21**(4):174–6.

Asna 2003
Asna SM, Haq JA, Rahman MM. Nalidixic acid-resistant Salmonella enterica serovar Typhi with decreased susceptibility to ciprofloxacin caused treatment failure: a report from Bangladesh. *Japanese Journal of Infectious Diseases* 2003;**56**(1):32–3.

Bhan 2005
Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. *Lancet* 2005;**366**(9487):749–62.

Bhutta 1996
Bhutta ZA. Impact of age and drug resistance on mortality in typhoid fever. *Archives of Diseases in Childhood* 1996;**75**(3):214–7.

Bhutta 2000
Bhutta ZA, Khan IA, Shadmani M. Failure of short-course ceftriaxone chemotherapy for multidrug-resistant typhoid fever in children: a randomized controlled trial in Pakistan. *Antimicrobial Agents and Chemotherapy* 2000;**44**(2):450–2.

Burkhardt 1990
Burkhardt JE, Hill MA, Carlton WW, Kesterson JW. Histologic and histochemical changes in articular cartilages of immature beagle dogs dosed with difloxacin, a fluoroquinolone. *Veterinary Pathology* 1990;**27**(3):162–70.

Butler 1991
Butler T, Islam A, Kabir I, Jones PK. Patterns of morbidity and mortality in typhoid fever dependent on age and gender: a review of 552 hospitalized patients with diarrhea. *Review of Infectious Diseases* 1991;**13**(1):85–90.

Butler 2001
Butler T, Frenck RW, Johnson RB, Khakhria R. In vitro effects of azithromycin on Salmonella typhi: early inhibition by concentrations less than the MIC and reduction of MIC by alkaline pH and small inocula. *Journal of Antimicrobial Chemotherapy* 2001; **47**(4):455–8.

Butt 2003
Butt T, Ahmad RN, Mahmood A, Zaidi S. Ciprofloxacin treatment failure in typhoid fever case, Pakistan. *Emerging Infectious Diseases* 2003;**9**(12):1621–2.

Carbon 1998
Carbon C. Pharmacodynamics of macrolides, azalides, and streptogramins: effect on extracellular pathogens. *Clinical Infectious Diseases* 1998;**27**(1):28–32.

Chambers 2004
Chambers HF. Chloramphenicol, tetracyclines, macrolides, clindamycin, and streptogramins. In: Katzung BG editor(s). *Basic and Clinical Pharmacology*. 9th Edition. Boston: McGraw Hill, 2004:754–63.

Coovadia 1992
Coovadia YM, Gathiram V, Bhamjee A, Garratt RM, Mlisana K, Pillay N, et al.An outbreak of multiresistant Salmonella typhi in South Africa. *Quarterly Journal of Medicine* 1992;**82**(298):91–100.

Corales 2000
Corales R. Typhoid fever. www.Emedicine.com/med/topic2331/ .html (accessed 20 August 2004).

Crump 2003
Crump JA, Barrett TJ, Nelson JT, Angulo FJ. Reevaluating fluoroquinolone breakpoints for Salmonella enterica serotype Typhi and for non-Typhi salmonellae. *Clinical Infectious Diseases* 2003;**37** (1):75–81.

Crump 2004
Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bulletin of the World Health Organization* 2004;**82**(5):346–53.

Doherty 2000
Doherty CP, Saha Sk, Cutting WA. Typhoid fever, ciprofloxacin and growth in young children. *Annals of Tropical Paediatrics* 2000; **20**(4):297–303.

Dutta 2001
Dutta TK, Beeresha, Ghotekar LH. Atypical manifestations of typhoid fever. *Journal of Postgraduate Medicine* 2001;**47**(4):248–51.

Ferreccio 1984

Ferreccio C, Levine MM, Manterola A, Rodriguez G, Rivara I, Prenzel I, et al.Benign bacteremia caused by Salmonella typhi and paratyphi in children younger than two years. *Journal of Pediatrics* 1984;**104**(6):899–901.

Gasem 1995

Gasem MH, Dolmans WM, Isbandrio BB, Wahyono H, Keuter M, Djokomoeljanto R. Culture of Salmonella typhi and Salmonella paratyphi from blood and bone marrow in the suspected typhoid fever. *Tropical and Geographical Medicine* 1995;**47**(4):164–7.

Gogia 2006

Gogia A, Agarwal PK, Khosla P, Jain S, Jain KP. Quinolone-resistant typhoid fever. *Indian Journal Medical Sciences* 2006;**60**(9):389–90.

Hopkins 2005

Hopkins RS, Jajosky RA, Hall PA, Adams DA, Connor FJ, Sharp P, et al.Centers for Disease Control and Prevention (CDC). Summary of notifiable diseases--United States, 2003. *MMWR* 2005;**52**(54): 1–85.

House 2001

House D, Wain J, Ho VA, Diep TS, Chinh NT, Bay PV, et al.Serology of typhoid fever in an area of endemicity and it's relevance to diagnosis. *Journal of Clinical Microbiology* 2001;**39**(3): 1002–7.

Joshi 2007

Joshi S, Amarnath SK. Fluoroquinolone resistance in Salmonella typhi and S. paratyphi A in Bangalore, India. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2007;**101**(3):308–10.

Jüni 2001

Jüni P, Altman DG, Egger M. Systematic reviews in healthcare: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323** (7303):42–6.

Kariuki 2004

Kariuki S, Revathi G, Muyodi J, Mwituria J, Munyalo A, Mirza S, et al.Characterization of multidrug-resistant typhoid outbreaks in Kenya. *Journal of Clinical Microbiology* 2004;**42**(4):1477–82.

Kownhar 2007

Kownhar H, Shankar EM, Rajan R, Rao UA. Emergence of nalidixic acid-resistant Salmonella enterica serovar Typhi resistant to ciprofloxacin in India. *Journal of Medical Microbiology* 2007;**56** (1):136–7.

Lakshmi 2006

Lakshmi V, Ashok R, Susmita J, Shailaja VV. Changing trends in the antibiograms of Salmonella isolates at a tertiary care hospital in Hyderabad. *Indian Journal of Medical Microbiology* 2006;**24**(1): 45–8.

Lang 1992

Lang R, Maayan MC, Lidor C, Savin H, Kolman S, Lishner M. Salmonella paratyphi C osteomyelitis: report of two separate episodes 17 years apart. *Scandinavian Journal of Infectious Diseases* 1992;**24**(6):793–6.

Le 2004

Le TA, Lejay-Collin M, Grimont PAD, Hoang TL, Nguyen TV, Grimont F, et al.Endemic, epidemic clone of Salmonella enterica serovar typhi harboring a single multidrug-resistant plasmid in Vietnam between 1995 and 2002. *Journal of Clinical Microbiology* 2004;**42**(7):3094–9.

Lefebvre 2008

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (updated February 2008). The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Lesser 2001

Lesser CF, Miller SI. Salmonellosis. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL editor(s). *Harrison's Principles of Internal Medicine*. 15th Edition. Vol. **1**, New York: McGraw-Hill, 2001:971–3.

Lin 2002

Lin FY, Vo AH, Phan VB, Nguyen TT, Bryla D, Tran CT, et al.The epidemiology of typhoid fever in the Dong Thap province, Mekong Delta region of Vietnam. *American Journal of Tropical Medicine and Hygiene* 2000;**62**(5):644–8.

Madhulika 2004

Madhulika U, Harish BN, Parija SC. Current pattern in antimicrobial susceptibility of Salmonella Typhi isolates in Pondicherry. *Indian Journal of Medical Research* 2004;**120**(2): 111–4.

Maskalyk 2003

Maskalyk J. Typhoid fever. *Canadian Medical Association Journal* 2003;**169**(2):132.

Mermin 1999

Mermin JH, Villar R, Carpenter J, Roberts L, Samaridden A, Gasanova L, et al.A massive epidemic of multidrug-resistant typhoid fever in Tajikistan associated with consumption of municipal water. *Journal of Infectious Diseases* 1999;**179**(6):1416–22.

Metchock 1990

Metchock B. In-vitro activity of azithromycin compared with other macrolides and oral antibiotics against Salmonella typhi. *Journal of Antimicrobial Chemotherapy* 1990;**25 Suppl A**:29–31.

Mirza 1996

Mirza SH, Beeching NJ, Hart CA. Multi-drug resistant typhoid: a global problem. *Journal of Medical Microbiology* 1996;**44**(5):317–9.

Murdoch 1998

Murdoch DA, Banatvaia N, Bone A, Shoismatulloev BI, Ward LR, Threlfall EJ. Epidemic ciprofloxacin-resistant Salmonella typhi in Tajikistan. *Lancet* 1998;**351**(9099):339.

Mushtaq 2006

Mushtaq MA. What after ciprofloxacin and ceftriaxone in the treatment of Salmonella Typhi?. *Pakistan Journal of Medical Sciences* 2006;**22**(1):51–4.

Parry 1984

Parry EHO. Typhoid fever. In: Parry EHO editor(s). *Principles of Medicine in Africa*. 2nd Edition. Oxford: Oxford University Press, 1984:268–76.

Parry 2002

Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *New England Journal of Medicine* 2002;**347**(22):1770–82.

Parry 2004
Parry CM. The Treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Viet Nam. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2004;**98**(7):413–22.

Parry 2006
Parry CM, Karunanayake L, Coulter JBS, Beeching NJ. Test for quinolone resistance in typhoid fever. *BMJ* 2006;**333**(7561):260–1.

Rajagopal 2002
Rajagopal A, Ramasamy R, Mahendran G, Thomas M. Hepatic abscess complicating paratyphoid infection. *Tropical Gastroenterology* 2002;**23**(4):181–2.

Renuka 2005
Renuka K, Sood S, Das BK, Kapil A. High-level ciprofloxacin resistance in Salmonella enterica serotype typhi in India. *Journal of Medical Microbiology* 2005;**54 pt 10**:999–1000.

Review Manager 5
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Ribot 2002
Ribot EM, Wierzba RK, Angulo FJ, Barrett TJ. Salmonella enterica serotype Typhimurium DT104 isolated from humans, United States 1985, 1990, and 1995. *Emerging Infectious Diseases* 2002;**8**(4):387–91.

Rowe 1997
Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant Salmonella typhi: a worldwide epidemic. *Clinical Infectious Diseases* 1997;**24 Suppl 1**:106–9.

Rupali 2004
Rupali P, Abraham OC, Jesudason MV, John TJ, Zachariah A, Sivaram S, et al.Treatment failure in typhoid fever with ciprofloxacin susceptible Salmonella enterica Serotype Typhi. *Diagnostic Micribiology and Infectious Disease* 2004;**49**(1):1–3.

Schaad 1995
Schaad UB, abdus Salam M, Aujard Y, Dagan R, Green SD, Peltola H, et al.Use of fluoroquinolones in pediatrics: consensus report of an International Society of Chemotherapy commission. *Pediatric Infectious Disease Journal* 1995;**14**(1):1–9.

Sinha 1999
Sinha A, Sazawal AK, Kumar R, Sood S, Reddaiah VP, Singh B, et al.Typhoid fever in children aged less than 5 years. *Lancet* 1999;**354**(9180):734–7.

Smith 1994
Smith MD, Duong NM, Hoa NT, Wain J, Ha HD, Diep TS, et al.Comparison of ofloxacin and ceftriaxone for short course treatment of enteric fever. *Antimicrobial Agents Chemotherapy* 1994;**38**(8):1716–20.

Sood 1999
Sood S, Kapil A, Das B, Jain Y, Kabra SK. Re-emergence of chloramphenicol-sensitive Salmonella typhi. *Lancet* 1999;**353**(9160):1241–2.

Stahlmann 2000
Stahlmann R, Kühner S, Shakibaei M, Schwabe R, Flores J, Evander SA. Chondrotoxicity of ciprofloxacin in immature beagle dogs: immunohistochemistry, electron microscopy and drug plasma levels. *Archives of Toxicology* 2000;**73**(10-11):564–72.

Thaver 2008
Thaver D, Zaidi AKM, Critchley JA, Azmatullah A, Madni SA, Bhutta ZA. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004530.pub2]

Threlfall 1999
Threlfall EJ, Ward LR, Skinner JA, Smith HR, Lacey S. Ciprofloxacin-resistant Salmonella typhi and treatment failure. *Lancet* 1999;**353**(9164):1590–1.

Threlfall 2001
Threlfall EJ, Ward LR. Decreased susceptibility to ciprofloxacin in Salmonella enterica serotype typhi, United Kingdom. *Emerging Infectious Diseases* 2001;**7**(3):448–50.

Vallenas 1985
Vallenas C, Hernandez H, Kay B, Black R, Gotuzzo E. Efficacy of bone marrow, blood, stool and duodenal contents for bacteriologic confirmation of typhoid fever in children. *Pediatric Infectious Disease* 1985;**4**(5):496–8.

Wain 1997
Wain J, Hoa NT, Chinh NT, Vinh H, Everett MJ, Diep TS, et al.Quinolone-resistant Salmonella typhi in Viet Nam: molecular basis of resistance and clinical response to treatment. *Clinical Infectious Diseases* 1997;**25**(6):1404–10.

Wasfy 2002
Wasfy MO, Frenck R, Ismail TF, Mansour H, Malone JL, Mahoney FJ. Trends of multiple-drug resistance among Salmonella serotype Typhi isolates during a 14-year period in Egypt. *Clincal Infectious Diseases* 2002;**35**:1265–8.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Butler 1999

Methods	Generation of allocation sequence: table of random numbers Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture positive participants in final analysis: 77/92 (84%)
Participants	Number enrolled and randomized: 109 Number culture positive: 92 Adults aged ≥ 18 years; 26.3 years was mean age for azithromycin group and 28.5 years was mean age for chloramphenicol group Inclusion criteria: fever of 38.5 °C or history of fever for 4 to 15 days; abdominal tenderness; hepatomegaly; splenomegaly; rose spots Exclusion criteria: pregnancy and lactation; allergies to chloramphenicol, erythromycin, or other macrolide antibiotics; complications; prior treatment with antimicrobials within 7 days
Interventions	1. Azithromycin: oral capsules at 500 mg once daily for 7 days 2. Chloramphenicol: oral at 2 to 3 g in 4 divided doses for 14 days
Outcomes	1. Clinical failure 2. Bacteriological eradication 3. Relapse 4. Adverse events Not included in this review 1. Clinical cure 2. Clinical improvement
Notes	Location: India Date: not stated MDR *S.* Typhi: 10 (11%)

Chinh 2000

Methods	Generation of allocation sequence: computer-generated randomization list Allocation concealment: serially numbered sealed envelopes Blinding: open Inclusion of all randomized culture positive participants in the final analysis: 100%
Participants	Number enrolled and randomized: 97 Number culture positive: 88 Adult inpatients aged ≥ 15 years with a mean age of 26.6 years in the azithromycin group and 24.7 years in the ofloxacin group Inclusion criteria: clinical features of enteric fever; blood-culture positive with serovar Typhi or serovar Paratyphi A Exclusion criteria: severe or complicated disease; history of significant underlying disease; history of hypersensitivity to either of the trial drug; pregnancy; previous treatment with quinolone; third-generation cephalosporin or macrolide

Chinh 2000 (*Continued*)

	within 1 week of hospital admission
Interventions	1. Azithromycin: oral 1 g daily for 5 days 2. Ofloxacin: oral 200 mg twice daily for 5 days
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Duration of hospitalization 6. Adverse events
Notes	Location: Vietnam Date: not stated MDR *S.* Typhi: azithromycin group 33 (77%); ofloxacin group 35 (80%)

Dolecek 2008

Methods	Generation of allocation sequence: computer-generated block randomization Allocation concealment: sequentially numbered, folded opaque, sealed envelopes Blinding: open label Inclusion of all randomized culture positive participants in the final analysis: > 90%
Participants	Number enrolled and randomized: 358 Number culture positive: 287 Inclusion criteria: clinically suspected or culture-confirmed uncomplicated typhoid Exclusion criteria: age < 6 months; history of significant underlying disease; history of hypersensitivity to either of the trial drugs; pregnancy; previous treatment with quinolone third-generation cephalosporin or macrolide within 1 week of hospital admission
Interventions	1. Azithromycin: tablet or suspension 20 mg/kg/day once daily for 7 days 2. Gatifloxacin: oral 10 mg/kg/day once daily for 7 days
Outcomes	1. Fever clearance time 2. Clinical failure 3. Microbiological failure 4. Relapse 5. Faecal carriage
Notes	Location: Vietnam Date: 2006 Registration number: ISRCTN67946944 MDR strains: 58% NaR strains: 96%

Frenck 2000

Methods	Generation of allocation sequence: block randomization using random-number list Allocation concealment: sequentially numbered sealed envelopes Blinding: open label Inclusion of all randomized culture positive participants in the final analysis: 100%
Participants	Number enrolled and randomized: 108 Number culture positive: 64 Children aged 3 to 17 years with the mean age for the azithromycin group being 9.7 years and for the ceftriaxone group 10.1 years Inclusion criteria: documented fever with temperature ≥ 38.5 °C plus a history of fever for at least 4 days plus any 2 of abdominal tenderness, hepatomegaly, splenomegaly, and rose spots Exclusion criteria: allergy to ceftriaxone/macrolides; major complications; significant underlying illness; treatment with *S.* Typhi susceptible antibiotics in the past 4 days; pregnancy or lactation
Interventions	1. Azithromycin: oral suspension at 20 mg/kg/day with a maximum of 500 mg/day given daily for 7 days; 34 participants 2. Ceftriaxone: intramuscular injection at 75 mg/kg/day with a maximum of 2.5 g/day given daily for 7 days; 30 participants
Outcomes	1. Clinical failure 2. Microbiological cure 3. Fever clearance 4. Relapse 5. Adverse events
Notes	Location: Egypt Date: not reported MDR *S.* Typhi: azithromycin group 5 (18%); ceftriaxone group 6 (20%)

Frenck 2004

Methods	Generation of allocation sequence: block randomization using random-number generator Allocation concealment: sequentially numbered sealed envelopes Blinding: open Inclusion of all randomized participants in the final analysis: 100%
Participants	Number enrolled and randomized: 128 Number analysed (culture positive): 68 Children and adolescent inpatients with mean age of azithromycin group being 11.8 years and ceftriaxone group being 10.8 years Inclusion criteria: documented fever (rectal temperature > 38.0 °C or oral temperature > 37.5 °C) and > 2 of abdominal tenderness, hepatomegaly, splenomegaly, and/or a coated tongue Exclusion criteria: allergy to both ceftriaxone and macrolides; major complications; significant underlying illness; treatment in the past 4 days with antibiotic effective against *S.* Typhi; inability to swallow oral medication
Interventions	1. Azithromycin: oral suspension at 20 mg/kg/day with a maximum dose of 1000 mg/day for 5 days; 32 participants 2. Ceftriaxone: intravenous at 75 mg/kg/day with a maximum dose of 2.5 g/day for 5 days; 36 participants

Frenck 2004 (*Continued*)

Outcomes	1. Clinical failure 2. Microbiological failure 3. Clinical relapse 4. Duration of fever 5. Adverse events
Notes	Location: Egypt Date: not reported MDR *S.* Typhi: 1 participant

Girgis 1999

Methods	Generation of allocation sequence: block randomization based on a random-number list Allocation concealment: sealed envelopes Blinding: participants and providers were blinded; blinding of outcome assessors unclear Inclusion of all randomized culture positive participants in the final analysis: 100%
Participants	Number enrolled and randomized: 123 Number analysed (culture positive): 64 Adult inpatients > 18 years Inclusion criteria: fever $\geq$ 38.5 °C plus a history of fever for at least 4 days in addition to 2 or more of abdominal tenderness, hepatomegaly, splenomegaly, and rose spots Exclusion criteria: pregnancy or lactation; allergy to ciprofloxacin or erythromycin (or other macrolides); complication of typhoid fever; inability to swallow oral medication; significant underlying illness; and treatment within the past 4 days with an antibiotic potentially effective against *S.* Typhi
Interventions	1. Azithromycin: oral 1 g for the first day then oral 500 mg daily for 7 days; 36 participants 2. Ciprofloxacin: oral 500 mg twice daily for 7 days; 28 participants
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Adverse events
Notes	Location: Egypt Date: not stated MDR: azithromycin group 6 (16.6%); ciprofloxacin group 15 (53.6%)

Parry 2007

Methods	Generation of allocation sequence: computer-generated randomization list Allocation concealment: serially numbered sealed envelopes Inclusion of all randomized participants in final analysis: 100%

Parry 2007 (*Continued*)

Participants	Number enrolled and randomized: 241 Number analysed (culture positive): 199 Children and adults with clinical features of enteric fever Inclusion criteria: documented fever for at least 4 days plus at least 1 of abdominal pain/tenderness, diarrhoea or constipation, hepatomegaly, splenomegaly, and/or rose spots Exclusion criteria: evidence of severe or complicated disease; inability to swallow oral medications; history of significant underlying disease or of hypersensitivity to either of trial drugs; pregnancy or lactation; history of treatment with a fluoroquinolone or third-generation cephalosporin or macrolide within 1 week of hospital admission
Interventions	1. Azithromycin: tablet or suspension 10 mg/kg/day once daily for 7 days 2. Ofloxacin: oral 20 mg/kg/day twice daily for 7 days
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Duration of hospitalization 6. Adverse events
Notes	Location of trial: Vietnam Date: not stated MDR strains: azithromycin group 53 (85%); ofloxacin group 57 (90%) NaR strains: azithromycin group 55 (89%); ofloxacin group 62 (98%)

MDR: multiple-drug resistant; NaR: nalidixic acid resistant.

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

Chiu 1999	Randomized controlled trial comparing azithromycin, cefixime, and no antibiotics in uncomplicated non-typhoid *Salmonella enteritis*
Li 2005	Included participants with complicated typhoid fever and used intravenous azithromycin
Tribble 1995	Non-comparative and non-randomized trial
Wallace 1994	Report of 4 cases in which all treated with azithromycin and switched to another drug when there was no improvement

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

ISRCTN66534807

Trial name or title	"A randomised clinical trial of Azithromycin versus Ofloxacin in the treatment of adults with uncomplicated typhoid fever at Mahosot Hospital, Vientiane, Lao People's Democratic Republic (PDR)"
Methods	Randomized controlled trial
Participants	Inclusion criteria: adult (> 15 years) non-pregnant patients with suspected or blood culture proven typhoid; fever > 37.5 °C; informed written consent to the study; able to stay in hospital for 7 days; able to take oral medication; body weight > 40 kg; likely to be able to complete 6 months' follow up; none of the exclusion criteria Exclusion criteria: known hypersensitivity to ofloxacin or azithromycin; administration of chloramphenicol, co-trimoxazole, ampicillin, azithromycin, or a fluoroquinolone during the previous week; pregnancy or breastfeeding; contradictions to ofloxacin or azithromycin; evidence for severe typhoid
Interventions	1. Azithromycin: oral for 3 days 2. Ofloxacin: oral for 3 days
Outcomes	1. Fever clearance 2. Cure rate 3. Relapse rate 4. *S.* Typhi stool carriage rate
Starting date	1 May 2004 Anticipated end date: 31 December 2006
Contact information	Dr Paul Newton (paul@tropmedres.ac), Ministry of Health Microbiology Laboratory, Mahosot Hospital, Vientiane, Laos
Notes	Location: Laos Registration number: ISRCTN66534807 Source of funding: The Wellcome Trust (UK)

DATA AND ANALYSES

Comparison 1. Azithromycin (AZM) vs chloramphenicol (CM)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Microbiological failure	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Fever clearance time (hours)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Adverse events (excluding serious adverse events)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure	4	564	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.26, 0.89]
2 Microbiological failure	4	564	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.32, 3.19]
3 Relapse	4	491	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 1.08]
4 Fever clearance time (hours)	4	564	Mean Difference (IV, Random, 95% CI)	-9.80 [-34.15, 14.56]
5 Duration of hospital stay (days)	2	213	Mean Difference (IV, Fixed, 95% CI)	-1.04 [-1.73, -0.34]
6 Serious adverse events	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Azithromycin (AZM) vs ceftriaxone (CRO)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure	2	132	Odds Ratio (M-H, Fixed, 95% CI)	2.58 [0.48, 13.87]
2 Microbiological failure	2	132	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.07, 4.62]
3 Relapse	2	132	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 0.70]
4 Fever clearance time (hours)	2	132	Mean Difference (IV, Fixed, 95% CI)	9.12 [-1.11, 19.36]

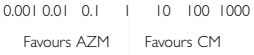
Analysis 1.1. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 1 Clinical failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Azithromycin (AZM) vs chloramphenicol (CM)

Outcome: 1 Clinical failure

Study or subgroup	AZM n/N	CM n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Butler 1999	0/42	2/35		0.16 [0.01, 3.40]



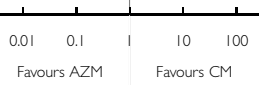
Analysis 1.2. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 2 Microbiological failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Azithromycin (AZM) vs chloramphenicol (CM)

Outcome: 2 Microbiological failure

Study or subgroup	AZM n/N	CM n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Butler 1999	0/42	1/35		0.27 [0.01, 6.85]



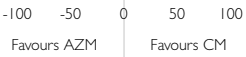
Analysis 1.3. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 3 Fever clearance time (hours).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Azithromycin (AZM) vs chloramphenicol (CM)

Outcome: 3 Fever clearance time (hours)

Study or subgroup	AZM N	Mean(SD)	CM N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Butler 1999	42	98.4 (57.6)	35	103.2 (74.4)		-4.80 [-34.98, 25.38]



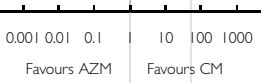
Analysis 1.4. Comparison 1 Azithromycin (AZM) vs chloramphenicol (CM), Outcome 4 Adverse events (excluding serious adverse events).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Azithromycin (AZM) vs chloramphenicol (CM)

Outcome: 4 Adverse events (excluding serious adverse events)

Study or subgroup	AZM n/N	CM n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Butler 1999	5/42	0/35		10.41 [0.56, 195.25]



Analysis 2.1. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 1 Clinical failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 1 Clinical failure

Study or subgroup	AZM n/N	FQ n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Chinh 2000	2/44	6/44		0.30 [0.06, 1.59]
Dolecek 2008	6/142	6/145		1.02 [0.32, 3.25]
Girgis 1999	0/36	0/28		0.0 [0.0, 0.0]
Parry 2007	11/62	23/63		0.38 [0.16, 0.86]
Total (95% CI)	**284**	**280**		**0.48 [0.26, 0.89]**

Total events: 19 (AZM), 35 (FQ)

Heterogeneity: Chi² = 2.28, df = 2 (P = 0.32); I² =12%

Test for overall effect: Z = 2.33 (P = 0.020)

Analysis 2.2. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 2 Microbiological failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 2 Microbiological failure

Study or subgroup	AZM n/N	FQ n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Chinh 2000	1/44	2/44		0.49 [0.04, 5.59]
Dolecek 2008	3/142	2/145		1.54 [0.25, 9.38]
Girgis 1999	0/36	0/28		0.0 [0.0, 0.0]
Parry 2007	2/62	2/63		1.02 [0.14, 7.45]
Total (95% CI)	**284**	**280**		**1.01 [0.32, 3.19]**

Total events: 6 (AZM), 6 (FQ)

Heterogeneity: Chi² = 0.55, df = 2 (P = 0.76); I² =0.0%

Test for overall effect: Z = 0.02 (P = 0.98)

Analysis 2.3. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 3 Relapse.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 3 Relapse

Study or subgroup	AZM n/N	FQ n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Chinh 2000	0/21	2/17		0.14 [0.01, 3.22]
Dolecek 2008	0/127	4/137		0.12 [0.01, 2.18]
Girgis 1999	0/36	0/28		0.0 [0.0, 0.0]
Parry 2007	0/62	0/63		0.0 [0.0, 0.0]
Total (95% CI)	**246**	**245**		**0.13 [0.01, 1.08]**

Total events: 0 (AZM), 6 (FQ)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%

Test for overall effect: Z = 1.89 (P = 0.059)

Analysis 2.4. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 4 Fever clearance time (hours).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

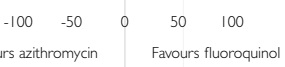
Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 4 Fever clearance time (hours)

Study or subgroup	AZM N	Mean(SD)	FQ N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chinh 2000	44	130 (40.61)	44	134 (76.14)		23.1 %	-4.00 [-29.50, 21.50]
Dolecek 2008	142	106 (72.96)	145	106 (73.73)		26.9 %	0.0 [-16.97, 16.97]
Girgis 1999	36	91.2 (26.4)	28	79.2 (24)		28.6 %	12.00 [-0.39, 24.39]
Parry 2007	62	139.2 (67.49)	63	196.8 (97.18)		21.4 %	-57.60 [-86.89, -28.31]
Total (95% CI)	**284**		**280**			**100.0 %**	**-9.80 [-34.15, 14.56]**

Heterogeneity: Tau^2 = 499.39; Chi^2 = 18.55, df = 3 (P = 0.00034); I^2 =84%

Test for overall effect: Z = 0.79 (P = 0.43)



Analysis 2.5. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 5 Duration of hospital stay (days).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 5 Duration of hospital stay (days)

Study or subgroup	AZM N	Mean(SD)	FQ N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Chinh 2000	44	9.6 (2.37)	44	10.5 (3.38)		32.4 %	-0.90 [-2.12, 0.32]
Parry 2007	62	12.6 (2.2)	63	13.7 (2.6)		67.6 %	-1.10 [-1.94, -0.26]
Total (95% CI)	**106**		**107**			**100.0 %**	**-1.04 [-1.73, -0.34]**

Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%

Test for overall effect: Z = 2.92 (P = 0.0035)

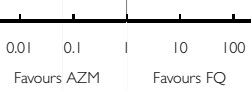
Analysis 2.6. Comparison 2 Azithromycin (AZM) vs fluoroquinolones (FQ), Outcome 6 Serious adverse events.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Azithromycin (AZM) vs fluoroquinolones (FQ)

Outcome: 6 Serious adverse events

Study or subgroup	AZM n/N	FQ n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Chinh 2000	1/44	1/44		1.00 [0.06, 16.51]
Dolecek 2008	4/142	2/145		2.07 [0.37, 11.50]
Parry 2007	2/62	0/63		5.25 [0.25, 111.56]



Analysis 3.1. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 1 Clinical failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Azithromycin (AZM) vs ceftriaxone (CRO)

Outcome: 1 Clinical failure

Study or subgroup	AZM n/N	CRO n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Frenck 2000	3/34	1/30		52.3 %	2.81 [0.28, 28.53]
Frenck 2004	2/32	1/36		47.7 %	2.33 [0.20, 27.03]
Total (95% CI)	**66**	**66**		**100.0 %**	**2.58 [0.48, 13.87]**

Total events: 5 (AZM), 2 (CRO)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%

Test for overall effect: Z = 1.10 (P = 0.27)

Analysis 3.2. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 2 Microbiological failure.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Azithromycin (AZM) vs ceftriaxone (CRO)

Outcome: 2 Microbiological failure

Study or subgroup	AZM n/N	CRO n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Frenck 2000	1/34	1/30		42.5 %	0.88 [0.05, 14.69]
Frenck 2004	0/32	1/36		57.5 %	0.36 [0.01, 9.26]
Total (95% CI)	**66**	**66**		**100.0 %**	**0.58 [0.07, 4.62]**

Total events: 1 (AZM), 2 (CRO)

Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%

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

Analysis 3.3. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 3 Relapse.

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Azithromycin (AZM) vs ceftriaxone (CRO)

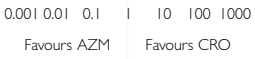
Outcome: 3 Relapse

Study or subgroup	AZM n/N	CRO n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Frenck 2000	0/34	4/30		47.9 %	0.09 [0.00, 1.66]
Frenck 2004	0/32	5/36		52.1 %	0.09 [0.00, 1.66]
Total (95% CI)	**66**	**66**		**100.0 %**	**0.09 [0.01, 0.70]**

Total events: 0 (AZM), 9 (CRO)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%

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



Analysis 3.4. Comparison 3 Azithromycin (AZM) vs ceftriaxone (CRO), Outcome 4 Fever clearance time (hours).

Review: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever)

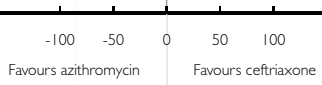
Comparison: 3 Azithromycin (AZM) vs ceftriaxone (CRO)

Outcome: 4 Fever clearance time (hours)

Study or subgroup	AZM N	Mean(SD)	CRO N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Frenck 2000	34	98.4 (24.4)	30	93.6 (24)		74.3 %	4.80 [-7.08, 16.68]
Frenck 2004	32	108 (45.6)	36	86.4 (38.4)		25.7 %	21.60 [1.43, 41.77]
Total (95% CI)	**66**		**66**			**100.0 %**	**9.12 [-1.11, 19.36]**

Heterogeneity: Chi^2 = 1.98, df = 1 (P = 0.16); I^2 =49%

Test for overall effect: Z = 1.75 (P = 0.081)



HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 4, 2008

CONTRIBUTIONS OF AUTHORS

Emmanuel Effa wrote the protocol, assisted in conducting the literature search, extracted data, and wrote the review. Hasifa Bukirwa co-extracted data and provided guidance, editorial support, and mentoring.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Calabar Teaching Hospital, Nigeria.
- Effective Health Care Alliance Programme (EHCAP), Nigeria.

External sources

- Reviews for Africa Programme Fellowship, South Africa.
- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We attempted to search according to the methods outlined in the protocol; we were unable to retrieve some conference proceedings or obtain information on studies from some organizations and pharmaceutical companies contacted. Data were extracted as specified in the trial protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Anti-Bacterial Agents [*therapeutic use]; Azithromycin [*therapeutic use]; Paratyphoid Fever [*drug therapy]; Randomized Controlled Trials as Topic; Typhoid Fever [*drug therapy]

MeSH check words

Adult; Child; Humans