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Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

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Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever) (Review)

Thaver D, Zaidi AKM, Critchley JA, Azmatullah A, Madni SA, Bhutta ZA

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Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever) (Review)
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[Intervention Review]

Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

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ABSTRACT

Background

Fluoroquinolones are recommended as first-line therapy for typhoid and paratyphoid fever (enteric fever), but how they compare with other antibiotics and different fluoroquinolones is unclear.

Objectives

To evaluate fluoroquinolone antibiotics for treating enteric fever in children and adults compared with other antibiotics, different fluoroquinolones, and different durations of fluoroquinolone treatment.

Search strategy

In November 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 4), MEDLINE, EMBASE, LILACS, *m*RCT, conference proceedings, and reference lists.

Selection criteria

Randomized controlled trials of fluoroquinolones in people with blood or bone marrow culture-confirmed enteric fever.

Data collection and analysis

Two authors independently assessed the trials' methodological quality and extracted data. We calculated odds ratios (OR) for dichotomous data with 95% confidence intervals (CI). We analysed trials with greater than 60% children separately from trials of mostly adults.

Main results

Of 38 included trials, 22 had unclear allocation concealment and 34 did not use blinding. Four trials included exclusively children, seven had both adults and children, and three studied outpatients. ADULTS: Among primary outcomes (clinical failure, microbiological failure, and relapse), compared with chloramphenicol, fluoroquinolones were not statistically significantly different for clinical failure (594 participants) or microbiological failure (378 participants), but they reduced clinical relapse (OR 0.14, 95% CI 0.04 to 0.50; 467 participants, 6 trials). We detected no statistically significant difference versus co-trimoxazole (82 participants, 2 trials) or azithromycin

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(152 participants, 2 trials). Fluoroquinolones reduced clinical failure compared with ceftriaxone (OR 0.08, 95% CI 0.01 to 0.45; 120 participants, 3 trials), but not microbiological failure or relapse. Versus cefixime, fluoroquinolones reduced clinical failure (OR 0.05, 95% CI 0.01 to 0.24; 238 participants; 2 trials) and relapse (OR 0.18, 95% CI 0.03 to 0.91; 218 participants, 2 trials). CHILDREN: In children with high proportions of nalidixic acid-resistant strains, older fluoroquinolones increased clinical failures compared with azithromycin (OR 2.67, 95% CI 1.16 to 6.11; 125 participants, 1 trial), with no differences using newer fluoroquinolones (285 participants, 1 trial). Fluoroquinolones and cefixime were not statistically significantly different (82 participants, 1 trial). Trials comparing different durations of fluoroquinolone treatment were not statistically significantly different (889 participants, 9 trials). Norfloxacin had more clinical failures than other fluoroquinolones (417 participants, 5 trials).

Authors' conclusions

Trials were small and methodological quality varied. In adults, fluoroquinolones may be better for reducing clinical relapse rates compared to chloramphenicol. Data are limited for other comparisons, particularly in children.

PLAIN LANGUAGE SUMMARY

Not enough sound evidence for using fluoroquinolones in typhoid and paratyphoid fever compared with the standard antibiotics

The potentially fatal typhoid and paratyphoid fevers are caused by bacterial infection that begins in the small intestine (enteric fever). Transmission occurs through contaminated food and water, and there are areas where these diseases are endemic, such as Asia, Africa, and South and Central America. People often relapse or become carriers. Chloramphenicol has been the standard treatment, but the bacteria are becoming resistant. A new group of drugs, the fluoroquinolones, are being tried, but the review of trials found there were insufficient numbers of participants in the trials, which were also of varying quality, to be able to give recommendations with any degree of certainty, especially for children.

BACKGROUND

Definition

Enteric fever refers to either typhoid or paratyphoid fever. Typhoid fever is caused by *Salmonella enterica* serovar Typhi (*S.* Typhi), an enteric bacterium that colonizes only human hosts. Since humans are the only natural hosts of *S.* Typhi, direct or indirect contact with someone with typhoid fever or who is carrying *S.* Typhi (without symptoms) is essential for transmission of infection (Cleary 2000). Transmission most commonly occurs when susceptible individuals ingest food or water contaminated with faeces harbouring *S.* Typhi. Paratyphoid fever is considered a similar, but generally milder illness, and is caused by *S. enterica* serovar Paratyphi (*S.* Paratyphi) A, B, or C (Lee 2000). A recent report, however, suggests that the illness caused by *S.* Paratyphi A may be equal in severity to typhoid fever (Maskey 2006).

Epidemiology

Enteric fever — the majority of cases of which are caused by *S.* Typhi — continues to be a major health problem due to poor hygienic and sanitary conditions prevalent in low-income and middle-income countries. However, the pattern of enteric fever is changing in some endemic areas with an increase in the relative frequency of *S.* Paratyphi A isolated from patients with enteric fever (Chandel 2000; Ahmad 2002; Butt 2005; Ochiai 2005; Jesudason 2005; Woods 2006; Maskey 2008). Each year there are an estimated 16 million cases of enteric fever caused by *S.* Typhi and about 600,000 deaths (Ivanoff 1995). According to recent estimates the burden of typhoid for the year 2000 was 21 million cases (Crump 2004). Endemic regions comprise almost all of Asia (with South and South-East Asia considered areas of high incidence, ie over 100 cases per 100,000 population per year), Middle East, Africa, and South and Central America (Ivanoff 1995; Crump 2004). In population-based studies from endemic areas, the highest incidence has been reported in children between five and 10 years of age (Lin

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2000; Siddiqui 2006; Sur 2006) as well as in children under five years of age (Sinha 1999; Saha 2001; Saha 2003; Brooks 2005). In high-income countries, enteric fever has been virtually eliminated and most cases are those occurring in travellers returning from endemic areas. In the USA, 2445 cases of infections caused by *S.* Typhi were reported to the Centers for Disease Control and Prevention between 1985 and 1994, 72% of which were associated with international travel mainly to Mexico and the Indian subcontinent (Mermin 1998).

In endemic areas, most people are treated as outpatients, thus hospital-based data represent a subset of patients with a more severe illness who may consequently have a less favourable response to conventional therapy.

Pathogenesis

On ingestion, the salmonellae invade the intestinal epithelium, probably through the Peyer's patches (Cleary 2000). They then multiply in the lymphoid tissue, enter the mesenteric lymph nodes, and eventually reach the bloodstream. Once in the bloodstream, which is referred to as the 'primary blood stream invasion', the bacteria seed and multiply in several reticuloendothelial sites. The bacteria then spill over from these primarily infected sites back into the bloodstream, referred to as the 'secondary bloodstream invasion', and the patient begins to exhibit symptoms (Richens 2000). Infection then disseminates to several sites, most commonly the liver, spleen, bone marrow, gall bladder, and Peyer's patches (Lee 2000; Richens 2000). The ability of *S.* Typhi and *S.* Paratyphi to survive within macrophages is considered essential to the pathogenesis of enteric fever (Miller 2000).

Clinical features and diagnosis

The clinical features of enteric fever are non-specific and vary in different populations (Parry 2002). Common symptoms include fever, headache, and gastrointestinal complaints, such as diarrhoea or constipation, abdominal pain, nausea and vomiting, or loss of appetite (Lee 2000; Richens 2000). Some common findings on examination include liver enlargement, spleen enlargement, a coated tongue, and abdominal tenderness (Lee 2000; Richens 2000). The definitive diagnosis of enteric fever requires the isolation of *S.* Typhi or *S.* Paratyphi from blood, bone marrow, urine, bile, rose spots, and gastric or intestinal secretions. Blood cultures have a sensitivity of 60% to 80%, while bone marrow cultures have a greater sensitivity of 80% to 95% (Parry 2002).

Prognosis

About 10% of people infected with *S.* Typhi experience a relapse in the absence of treatment (Richens 2000). About 1% to 4% of people become long-term carriers (Lee 2000). Case-fatality rates range widely, from 1.6% in a hospital in Pakistan (Bhutta 1996) to as high as 44% in a subgroup of people with severe *S.* Typhi infection in Papua New Guinea (Richens 1995). The greater number of deaths observed in some low-income and middle-income countries could be due to delays in diagnosis, hospitalization, and commencement of effective treatment.

Treatment

Since its introduction in 1948, chloramphenicol has been widely used for treating enteric fever because of its wide availability and low cost. But chloramphenicol has some major disadvantages: it does not reduce the relapse rate (the rate of recurrence of infection with symptoms); it has no effect on the convalescent carrier or chronic carrier (a person who continues to excrete the organism in stool for one year after the illness); and it is not useful for treating multiple-drug-resistant (MDR) *S.* Typhi (Lee 2000).

MDR strains of *S.* Typhi, carrying plasmid-encoded resistance to all conventional first-line antibiotics (chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin), have become highly prevalent in several areas of the world since 1989. In the Indian subcontinent and China, the frequency of these MDR strains ranged from 50% to 80% of all *S.* Typhi isolates and reached 100% during outbreaks (Lee 2000). Effective treatment for people infected with MDR strains is critical because they have been observed to have a significantly higher incidence of complications than people infected with fully sensitive strains (Bhutta 1996). Many areas reported lower rates of MDR strains, and the re-emergence in some areas of strains fully susceptible to first-line antibiotics suggests that chloramphenicol could still be a valuable treatment option for enteric fever (Takkar 1995; Sood 1999; Wasfy 2002; Rodrigues 2003; Butt 2005; Walia 2005; Mohanty 2006). Conversely, recent studies have reported the emergence of MDR strains of *S.* Paratyphi A (Chandel 2000; Mahmood 2000; Butt 2005; Mohanty 2006).

The fluoroquinolones and other second-line antibiotics, such as third-generation cephalosporins (eg ceftriaxone and cefixime) and azithromycin (a macrolide antibiotic), are currently regarded as the antibiotics of choice for treating MDR strains.

The fluoroquinolones

The fluoroquinolones, such as ciprofloxacin, ofloxacin, fleroxacin, enoxacin, and pefloxacin, are a large family of anti-infective drugs synthesized around the quinolone core and that possess a broad antibacterial spectrum (Congeni 2002). The fluoroquinolones effectively penetrate macrophages and achieve high concentrations in bile (Miller 2000). Norfloxacin is the exception, because the World Health Organization (WHO) does not recommend it for

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treating enteric fever due to its low bioavailability (WHO 2003), which is 50% compared with 95% for ofloxacin (Hooper 2000). The fluoroquinolones are generally contraindicated for use in children under the age of 18 years, except for the treatment of certain infections, when no alternate agent is available (Gendrel 2003; Committee 2006). This contraindication is primarily due to concerns regarding their potential to cause arthropathy (joint disease), which has been clearly established in juvenile animal experiments (Simonin 1999). A review, however, reported that numerous studies evaluating ciprofloxacin use in children and adults have consistently failed to demonstrate cartilage damage (Congeni 2002). Arthralgia (joint pain) has been reported with fluoroquinolone use, but it occurs at a rate of less than 1.5% and appears to resolve entirely on discontinuation of the drug without leaving any evidence of long-term damage (Fish 2001).

The most common adverse effects associated with fluoroquinolones are gastrointestinal, such as nausea and diarrhoea, and central nervous system effects, such as headache, dizziness, and drowsiness (Fish 2001). Severe central nervous system events, such as psychosis and seizures are rare (Cross 2001). Other adverse effects include dermatologic reactions, hepatic enzyme elevation, hypersensitivity, nephrotoxicity, haematological reactions, tendonitis, and tendon rupture. Tendon rupture can occur with short-term use and small doses (Cross 2001). A potentially serious adverse effect is the prolongation of the QTc interval (Congeni 2002), which can lead to cardiac arrhythmias.

A summary of randomized controlled trials has shown that fluoroquinolones, when compared with ceftriaxone, cefixime, and first-line antibiotics, have lower clinical failure rates and lower fever clearance times in the treatment of enteric fever (Parry 2002). However, the review combined the data for both adults and children, and more importantly, the results for drug-sensitive and drug-resistant strains of *S.* Typhi and *S.* Paratyphi. The review also does not present findings of unpublished trials and may under represent non-English language trials, both of which are considered important components of a systematic review (Davies 1998).

The optimal duration of treatment for fluoroquinolones in enteric fever has yet to be clearly established. Although the recommended duration is 10 to 14 days, recent randomized controlled trials in Vietnam suggest that two-day and three-day courses may be sufficient to treat uncomplicated *S.* Typhi infections in children and adults (Tran 1995; Vinh 1996; Nguyen 1997). Such short-course therapy is favourable, as it will prove less costly, possibly less toxic, and will increase adherence to treatment.

However, a fact of great concern is the emergence of strains of *S.* Typhi and *S.* Paratyphi with reduced susceptibility to fluoroquinolones (Murdoch 1998; Threlfall 2001; Threlfall 2003; Rodrigues 2003; Karunanayake 2004; Slinger 2004; Butt 2005; Manchanda 2006; Mohanty 2006; Walia 2006; Chau 2007; Joshi 2007). This is demonstrated with the minimum inhibitory concentration (MIC) values for ciprofloxacin, which are higher (0.125 to 1 mg/L) compared with the usual values for fully susceptible strains (< 0.125 mg/L) (Parry 2004). Increasing numbers of treatment failures in infections caused by such strains are being reported, with short as well as long durations of fluoroquinolones (Brown 1994; Wain 1997; Asna 2003; Butt 2003; Rupali 2004; Slinger 2004; Manchanda 2006; Dimitrov 2007). These strains often display resistance to nalidixic acid (a first-generation quinolone) on routine disk diffusion susceptibility testing. Thus the presence of nalidixic acid resistance (NaR) among *S.* Typhi and *S.* Paratyphi can be used to identify strains with reduced susceptibility to fluoroquinolones (Wain 1997; Parry 2004), and is also the rationale for using NaR to denote reduced susceptibility to fluoroquinolones in this review. However, some strains with reduced susceptibility to fluoroquinolones do not exhibit NaR (Threlfall 2003; Cooke 2006), which suggests the need, in future, for direct determination and interpretation of fluoroquinolone MICs. More concerning are the emerging reports of isolates with absolute fluoroquinolone resistance (Harish 2004; Adachi 2005; Renuka 2005; Ahmed 2006; Mohanty 2006; Walia 2006; Joshi 2007). Newer generation fluoroquinolones, such as gatifloxacin, however, have been found to be active against NaR strains (Pandit 2007; Dolecek 2008).

OBJECTIVES

To evaluate fluoroquinolone antibiotics for treating enteric fever in children and adults compared with other antibiotics, different fluoroquinolones, and different durations of fluoroquinolone treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

People diagnosed with typhoid or paratyphoid fever based on microbiological confirmation from blood or bone marrow.

Types of interventions

Intervention

Fluoroquinolone antibiotic.

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Control

- Non-fluoroquinolone antibiotic (one or more).
- Different fluoroquinolone antibiotic.
- Different treatment duration of same fluoroquinolone antibiotic.

Types of outcome measures

Primary

- Clinical failure, defined as the presence of symptoms or the development of complications that necessitate change in antibiotic therapy or prolongation of existing therapy at the period specified by trial authors.
- Microbiological failure, defined as a positive culture from blood, bone marrow, or any sterile anatomic site at the period specified by trial authors.
- Relapse, defined as the recurrence of symptoms with a positive culture from blood or bone marrow or any sterile anatomic site, to the point of follow up defined by trial authors.

Secondary

- Fever clearance time, defined as the time in hours taken to defervesce from the start of the intervention or control drug with the definition of fever clearance as specified by trial authors.
- Length of hospital stay, defined as the time in days from entry into trial until discharge.
- Cost of therapy, defined as the total cost in US$ of the drug, drug delivery, and hospital stay.
- Convalescent faecal carriage, defined as a positive faecal culture detected at any time after the end of treatment up to one year of follow up.

Complications and adverse events (as defined by trial authors)

- Complications, defined as the appearance of complications during therapy such as abdominal (intestinal perforation, intestinal haemorrhage, hepatitis), cardiovascular (myocarditis, shock), neuropsychiatric (delirium, meningitis), respiratory (pneumonia, bronchitis), or haematological (anaemia, disseminated intravascular coagulation).
- Serious adverse events, defined as adverse events leading to death, requiring inpatient hospitalization or prolonged existing hospitalization, or life threatening, or resulting in persistent or significant disability or incapacity, such as joint disease, tendonitis and tendon rupture, prolongation of QTc interval, seizures, nephrotoxicity, haematological reactions, or severe dermatologic reactions.
- Other adverse events, such as nausea, diarrhoea, headache, dizziness, mild photosensitivity, hepatic enzyme elevations, and hypersensitivity reactions.

Search methods for identification of studies

Durrane Thaver worked with Vittoria Lutje (Information Retrieval Specialist, Cochrane Infectious Diseases Group) to attempt to identify all relevant trials regardless of language or publication status.

Databases

We searched the following databases using the search terms and strategy described in Table 4: Cochrane Infectious Diseases Group Specialized Register (November 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 4); MEDLINE (1966 to November 2007); EMBASE (1974 to November 2007); and LILACS (1982 to November 2007). We also searched the *meta*Register of Controlled Trials (*m*RCT) in November 2007 using the search term "(typhoid fever) NOT vaccine".

Table 4. Detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	typhoid fever	fluoroquinolone	QUINOLINES	QUINOLONE DERIVED ANTIINFECTIVE AGENT	typhoid
2	enteric fever	amifloxacin	QUINOLONES	fluoroquinolones	typhoid fever

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Table 4. Detailed search strategies (*Continued*)

3	paratyphoid fever	balofloxacin	ANTI-INFECTIVE AGENTS, QUINOLONE	amifloxacin	enteric fever
4	Salmonella typhi	cetefloxacin	ANTI-INFECTIVE AGENTS, FLUOROQUINOLONE	BALOFLOXACIN	Salmonella typhi
5	Salmonella paratyphi	ciprofloxacin	FLUOROQUINOLONES	balofloxacin	Salmonella paratyphi
6	-	clinafloxacin	fluoroquinolones	CETEFLOXACIN	-
7	-	enoxacin	amifloxacin	cetefloxacin	-
8	-	fleroxacin	balofloxacin	CIPROFLOXACIN	-
9	-	gatifloxacin	cetefloxacin	ciprofloxacin	-
10	-	gemifloxacin	CIPROFLOXACIN	CLINAFLOXACIN	-
11	-	grepafloxacin	ciprofloxacin	clinafloxacin	-
12	-	irloxacin	clinafloxacin	ENOXACIN	-
13	-	levofloxacin	ENOXACIN	enoxacin	-
14	-	lomefloxacin	enoxacin	FLEROXACIN	-
15	-	moxifloxacin	FLEROXACIN	fleroxacin	-
16	-	nordifloxacin	fleroxacin	GATIFLOXACIN	-
17	-	norfleroxacin	gatifloxacin	gatifloxacin	-
18	-	norfloxacin	gemifloxacin	GEMIFLOXACIN	-
19	-	ofloxacin	grepafloxacin	gemifloxacin	-
20	-	oxociprofloxacin	irloxacin	GREPAFLOXACIN	-
21	-	pefloxacin	levofloxacin	grepafloxacin	-
22	-	premafloxacin	lomefloxacin	IRLOXACIN	-
23	-	prulifloxacin	moxifloxacin	irloxacin	-
24	-	rufloxacin	nordifloxacin	LEVOFLOXACIN	-

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Table 4. Detailed search strategies (*Continued*)

25	-	sitafloxacin	norfleroxacin	levofloxacin	-
26	-	sparfloxacin	NORFLOXACIN	LOMEFLOXACIN	-
27	-	temafloxacin	norfloxacin	lomefloxacin	-
28	-	tosufloxacin	ofloxacin	MOXIFLOXACIN	-
29	-	trovafloxacin	oxociprofloxacin	moxifloxacin	-
30	-	1/29 - OR	PEFLOXACIN	NORDIFLOXACIN	-
31	-	typhoid fever	pefloxacin	nordifloxacin	-
32	-	enteric fever	premafloxacin	NORFLEROXACIN	-
33	-	paratyphoid fever	prulifloxacin	norfleroxacin	-
34	-	Salmonella typhi	rufloxacin	NORFLOXACIN	-
35	-	Salmonella paratyphi	sitafloxacin	norfloxacin	-
36	-	31/35 - OR	sparfloxacin	OFLOXACIN	-
37	-	30 and 36	temafloxacin	ofloxacin	-
38	-	-	tosufloxacin	OXO-CIPROFLOXACIN	-
39	-	-	trovafloxacin	oxociprofloxacin	-
40	-	-	1 - 39/OR	PEFLOXACIN	-
41	-	-	TYPHOID FEVER	pefloxacin	-
42	-	-	typhoid fever	PREMAFLOXACIN	-
43	-	-	enteric fever	premafloxacin	-
44	-	-	PARATYPHOID FEVER	PRULIFLOXACIN	-
45	-	-	paratyphoid fever	prulifloxacin	-
46	-	-	SALMONELLA TYPHI	RUFLOXACIN	-
47	-	-	Salmonella typhi	rufloxacin	-

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Table 4. Detailed search strategies (*Continued*)

48	-	-	SALMONELLA PARATYPHI	SITAFLOXACIN	-
49	-	-	Salmonella paratyphi	sitafloxacin	-
50	-	-	typhus	SPARFLOXACIN	-
51	-	-	41 - 50/OR	sparfloxacin	-
52	-	-	40 and 51	TEMAFLOXACIN	-
53	-	-	limit 52 to human	temafloxacin	-
54	-	-	-	tosufloxacin	-
55	-	-	-	1 - 54/OR	-
56	-	-	-	TYPHOID FEVER	-
57	-	-	-	typhoid fever	-
58	-	-	-	enteric fever	-
59	-	-	-	PARATYPHOID FEVER	-
60	-	-	-	paratyphoid fever	-
61	-	-	-	SALMONELLA TYPHI	-
62	-	-	-	Salmonella typhi	-
63	-	-	-	SALMONELLA PARATYPHI	-
64	-	-	-	Salmonella paratyphi	-
65	-	-	-	typhus	-
66	-	-	-	56 - 65/OR	-
67	-	-	-	55 and 66	-
68	-	-	-	limit 67 to human	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); upper case: MeSH or EMTREE heading; lower case: free text term.

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Conference proceedings

We searched the following conference proceedings for relevant abstracts: 5^{th} International Symposium on Typhoid Fever and other Salmonelloses, Karachi, Pakistan, 4 to 7 February 2002; 8^{th} Western Pacific Congress of Chemotherapy and Infectious Diseases, Perth, Australia, 1 to 5 December 2002; 43^{rd} Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 14 to 17 September 2003, Chicago, USA; *Final Programs* of the 44^{th} ICAAC, 30 October to 2 November 2004, in Washington D.C., USA; and the 45^{th} ICAAC, 16 to 19 December 2005, Washington D.C., USA.

Researchers

We contacted Dr Christopher Parry (in 2003) and Dr Jeremy Farrar and Dr Christiane Dolecek (in December 2007) for information on unpublished and ongoing trials.

Reference lists and review authors' personal collections

We also checked the reference lists of all retrieved trials and searched the review authors' personal literature collections for relevant trials.

Data collection and analysis

Selection of studies

Durrane Thaver and Asma Azmatullah screened the title, abstract, or keywords of each record identified with the search strategy, and retrieved the full text for potentially relevant trials and for records where the relevance was unclear. Durrane Thaver and Asma Azmatullah or Ali Madni independently applied the inclusion criteria to each potentially relevant trial to determine their eligibility. We resolved any disagreements through discussion with Anita Zaidi, or attempted to contact the trial authors if we still had doubts. We tabulated the excluded studies along with the reason for excluding them in the 'Characteristics of excluded studies'. We ensured that data from each trial was entered only once in our review.

Data extraction and management

Durrane Thaver and Asma Azmatullah or Ali Madni independently extracted data. For dichotomous outcomes, such as clinical failure, we extracted the total number of participants and number of participants that experienced the event. For continuous outcomes, such as fever clearance time, we extracted the total number of participants, arithmetic means, and standard deviations. If the standard deviation was not reported, we attempted to use the confidence interval or P value to derive it. We attempted to contact authors for means and standard deviations when they were not available. We also attempted to contact all trial authors to obtain additional data or when the data were not in the format we required. We compared the extracted data to identify errors. We resolved disagreements by consulting Anita Zaidi (or Zulfiqar Bhutta). Durrane Thaver and Asma Azmatullah entered data into Review Manager 4.2.

Assessment of risk of bias in included studies

Durrane Thaver and Asma Azmatullah or Ali Madni assessed the methodological quality of each included trial by assessing generation of allocation sequence, allocation concealment, blinding, and loss to follow up. We assessed generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear (Jüni 2001). We described blinding as double (trial uses a placebo or a double dummy technique such that neither the participant or care provider/assessor know which treatment is given), single (participant or care provider/assessor is aware of the treatment given), or open (all parties are aware of treatment), and considered it adequate if 90% or more of the randomized culture-positive participants were in the final analysis and inadequate if less than 90%. If the method was unclear, we attempted to contact the trial authors for clarification. We resolved disagreements through discussion and by consulting Anita Zaidi.

Data synthesis

We analysed data using Review Manager 4.2. We used the odds ratio (OR) for dichotomous data and the mean difference (MD) for continuous data, and presented each result with a 95% confidence interval (CI). We combined trials of different fluoroquinolones when evaluating treatment durations. We have not combined trials comparing: fluoroquinolones with different antibiotics (eg trials of fluoroquinolone versus chloramphenicol are not combined with trials of fluoroquinolone versus amoxicillin); adult participants with child participants; or drug-resistant *S.* Typhi and *S.* Paratyphi strains (NaR or MDR) with drug-sensitive *S.* Typhi and *S.* Paratyphi strains. We also analysed norfloxacin trials separate from the other fluoroquinolones because the WHO does not recommend this fluoroquinolone for treating enteric fever due to its low bioavailability (WHO 2003).

Stratification

We stratified the results according to the presence or absence of drug-resistant strains (MDR and NaR). We defined MDR as resistant to all three first-line antibiotics (chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin).

- *Fluoroquinolones versus first-line antibiotics*

(chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin) and norfloxacin versus chloramphenicol: Since the presence of MDR would affect the performance of first-line antibiotics, we stratified the trials into those that reported the absence of MDR strains, reported their presence, or did not report them or were unavailable. We also stratified the trials by the reported absence, presence, or not reporting of NaR strains, since this would affect the performance of the fluoroquinolone arm.

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Since the proportion of MDR strains would not differentially affect the performance of the second-line or the fluoroquinolone antibiotics, we did not stratify the results by MDR strains for the subsequent comparisons.

- *Fluoroquinolones versus second-line antibiotics* (azithromycin, ceftriaxone, cefixime) and norfloxacin versus ceftriaxone: We stratified these trials by the reported absence, presence, or not reporting or testing of NaR strains.
- *Norfloxacin versus other fluoroquinolones*: We did not stratify these by the NaR strains since both arms involved fluoroquinolones.
- *Different durations of fluoroquinolones*: Since the efficacy of different durations of fluoroquinolones would be affected by presence of NaR strains, we stratified these by NaR strains as described above.

However, in all above-mentioned analyses of NaR, in order to differentiate trials that had participants with NaR strains but involved newer fluoroquinolones which are not affected by NaR, we made a separate category ("NaR present, but newer fluoroquinolone"). Further analyses with varying proportions strains with reduced susceptibility to fluoroquinolones may be possible in future updates of the review.

We also conducted separate analyses for those trials that included mainly (more than 60%) children (defined as less than 16 years or as in text of trial) and those that included mainly adults; we classified all participants as adults if they were described as such by trial authors, regardless of the age of the youngest participant.

Intention-to-treat analyses

We were unable to conduct an intention-to-treat analysis on culture-positive cases since no further information was available for culture-positive participants who were lost to follow up. Instead, we conducted an available-case analysis, and we derived the per cent loss to follow up and tabulated the results (*see* Table 5).

Table 5. Assessment of risk of bias[a]

Comparison	Trial	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion of all randomized culture-positive participants in the final analysis
Fluoroquinolone vs chloramphenicol	Abejar 1993	Unclear	Unclear	Open	Adequate
	Arnold 1993	Unclear	Unclear	Open	Adequate
	Cristiano 1995	Adequate	Unclear	Open	Adequate
	Bran 1991	Unclear	Unclear	Double	Adequate

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Table 5. Assessment of risk of bias[a] *(Continued)*

	Gasem 2003	Adequate	Adequate	Open	Adequate
	Gottuzzo 1992	Unclear	Unclear	Double	Adequate
	Morelli 1992	Adequate	Unclear	Open	Adequate
	Phongmany 2005[b]	Adequate	Adequate	Open	Adequate
	Quintero 1988	Unclear	Unclear	Double	Adequate
	Yousaf 1992	Unclear	Unclear	Open	Inadequate
Fluoroquinolone vs ampicillin	Flores 1994	Unclear	Unclear	Open	Adequate
Fluoroquinolone vs co-trimoxazole	Hajji 1988[b]	Adequate	Adequate	Open	Adequate
	Limson 1989	Adequate	Unclear	Open	Adequate
Fluoroquinolone vs azithromycin	Dolecek 2008[b]	Adequate	Adequate	Open	Adequate
	Chinh 2000[b]	Adequate	Adequate	Open	Inadequate
	Girgis 1999[b]	Adequate	Adequate	Open	Adequate
	Parry 2007[b]	Adequate	Adequate	Open	Inadequate
Fluoroquinolone vs cefixime	Cao 1999[b]	Adequate	Adequate	Open	Inadequate
	Pandit 2007[b]	Adequate	Adequate	Open	Inadequate
	Yu 1998	Unclear	Unclear	Open	Adequate
Fluoroquinolone vs ceftriaxone	Tran 1994[b]	Adequate	Adequate	Open	Inadequate
	Smith 1994[b]	Adequate	Adequate	Open	Inadequate
	Wallace 1993	Unclear	Unclear	Open	Adequate
Norfloxacin vs chloramphenicol	Nalin 1987	Adequate	Unclear	Open	Adequate
	Sarma 1991[b]	Adequate	Unclear	Open	Adequate
Norfloxacin vs ceftriaxone	Huai 2000	Unclear	Unclear	Open	Adequate

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Table 5. Assessment of risk of bias[a] *(Continued)*

Norfloxacin vs other fluoroquinolones	Bai 1995	Unclear	Unclear	Open	Adequate
	Jia 1994	Unclear	Unclear	Double	Adequate
	Xiao 1991	Unclear	Unclear	Open	Adequate
	Yang 1991	Unclear	Unclear	Open	Adequate
Different durations of fluoroquinolones	Alam 1995	Unclear	Unclear	Open	Inadequate
	Duong 1995[b]	Adequate	Adequate	Open	Inadequate
	Kalo 1997	Unclear	Unclear	Open	Adequate
	Nguyen 1997[b]	Adequate	Adequate	Open	Inadequate
	Tran 1995[b]	Adequate	Adequate	Open	Inadequate
	Unal 1996	Unclear	Unclear	Open	Adequate
	Vinh 1996[b]	Adequate	Adequate	Open	Inadequate
	Vinh 2005[b]	Adequate	Adequate	Open	Adequate

[a] See 'Data collection and analysis' for the assessment methods, and the 'Characteristics of included studies' for the methods used in each trial.
[b] Trial author provided additional information.

Trials with more than two comparison groups

One trial compared a fluoroquinolone with two non-fluoroquinolone antibiotics (Yousaf 1992), and another trial compared a fluoroquinolone with a non-fluoroquinolone antibiotic (azithromycin) as well as a combination of both antibiotics (ofloxacin with azithromycin) (Parry 2007). We did not include the comparison of fluoroquinolone with combination of fluoroquinolone and non-fluoroquinolone. For Yousaf 1992 we separated the data into two meta-analyses: one comparing a fluoroquinolone with amoxicillin and the other with chloramphenicol.

When trials compared several different fluoroquinolones with a single non-fluoroquinolone antibiotic (Arnold 1993; Morelli 1992) or different fluoroquinolones against each other (Xiao 1991), we combined the groups treated with fluoroquinolones into a single fluoroquinolone group. For two trials, we only selected some groups; we included three groups out of the six for Morelli 1992 because they were common to other trials included in this review (Bai 1995; Jia 1994; Yang 1991), and only three of five groups for Xiao 1991 because each of the comparison groups had a sample size of less than 10. We intend to include the groups in future updates if more trials become available.

Heterogeneity

We checked for heterogeneity by visually inspecting the forest plots and by using the chi-squared test for homogeneity (using a 10% level of statistical significance). When we detected heterogeneity among studies and still considered it appropriate to pool the data, we used the random-effects model. We were unable to explore the following potential sources of heterogeneity using subgroup analyses because of the limited number of trials in each compari-

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son: drug dose; severe and/or complicated enteric fever (as defined by trialists) versus uncomplicated enteric fever; and different time points for outcome measurements.

Sensitivity analyses and publication bias

The small number of trials in each comparison also prevented us from performing a sensitivity analysis for each of the methodological quality factors for all comparisons except for fluoroquinolones compared to chloramphenicol. We assessed the presence of publication bias using a funnel plot only for primary outcomes which had more than five studies.

RESULTS

Description of studies

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

Trial selection

We assessed 70 trials for eligibility and included 38 (3279 participants) (*see* 'Characteristics of included studies') and excluded 25 (*see* 'Characteristics of excluded studies'). Among the remaining seven trials, which we assessed for eligibility, three were duplicate publications of the included studies (Hajji 1988; Arnold 1993; Jia 1994), two are ongoing (ISRCTN53258327; ISRCTN66534807; *see* 'Characteristics of ongoing studies'), and we were unable to retrieve two (Flores 1991; Soewandojo 1992; *see* 'Characteristics of studies awaiting classification').

Trial design and location

Eleven trials were conducted in Vietnam, six trials in China, two trials in each of the Philippines, Mexico, and Italy, and one trial in each of Albania, Bahrain, Bangladesh, Egypt, Guatemala, India, Indonesia, Laos, Morocco, Nepal, Pakistan, and Turkey. We could not determine the location of one trial (Gottuzzo 1992). Two were multicenter trials conducted in different countries (Nalin 1987; Arnold 1993).

Most trials were small and therefore lacked statistical power to detect differences between the treatment regimens. The smallest trial had 26 participants and the largest had 287 participants.

Participants

Most trials included only adults (minimum age for adults reported by trialists was $\geq$ 14 years), and only four trials exclusively included children (Vinh 1996; Cao 1999; Huai 2000; Vinh 2005). Seven trials included children and adults (Xiao 1991; Yang 1991; Alam 1995; Tran 1995; Pandit 2007; Parry 2007; Dolecek 2008), although 87%, 79%, and 73% of participants were children in three of these trials (Tran 1995; Parry 2007; Dolecek 2008) and were considered as trials on (mostly) children. Two of these, Alam 1995 and Pandit 2007, had 84% and 65% adults respectively, and were considered as a trial on (mostly) adults. Five trial reports did not mention the participants' age; however, four used adult dosages (Nalin 1987; Quintero 1988; Bran 1991; Jia 1994), and one used the keyword "adult" (Flores 1994).

All but three trials were conducted on inpatients; Alam 1995 was conducted on both inpatients and outpatients, and Tran 1995 was a community-based outpatient trial, while Pandit 2007 recruited outpatients presenting to the outpatient or emergency department of the study hospital.

Nineteen trials were conducted exclusively on participants with uncomplicated enteric fever or participants without major complications of enteric fever, and one included only participants with severe enteric fever (Cristiano 1995). (The terms "severe", "complicated", and "uncomplicated" were as defined by the trial authors.) The remaining trials either did not provide this information or included a combination.

Most trials used blood cultures or bone marrow cultures, or both, to confirm cases of enteric fever. Although three trials included stool culture-positive cases (Girgis 1999 (three cases); Hajji 1988 (nine cases); Smith 1994 (three cases)) and urine culture-positive cases (Hajji 1988 (one case)), we included them in the review since all three trials mainly included blood culture-positive cases. Five trials did not report the site of culture (Nalin 1987; Quintero 1988; Gottuzzo 1992; Yousaf 1992; Flores 1994), but based on information available, such as mention of follow up "blood cultures", we assumed that these trials included participants with predominantly blood culture-confirmed enteric fever.

Inclusion and exclusion criteria

Trialists tended to report outcomes only for culture-confirmed cases of enteric fever. Most trialists excluded culture-negative cases from detailed analysis, even if initially enrolled.

Interventions

Fluoroquinolones versus non-fluoroquinolone antibiotics

Twenty-three trials (1867 participants) compared fluoroquinolones with chloramphenicol (10 trials), amoxicillin or ampicillin (two trials), co-trimoxazole (two trials), azithromycin (four trials), ceftriaxone (three trials), or cefixime (three trials). Of these, two compared a newer fluoroquinolone (gatifloxacin) with azithromycin and cefixime respectively (Pandit 2007; Dolecek 2008).

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Norfloxacin trials

Three trials compared the fluoroquinolone norfloxacin with chloramphenicol (259 participants), one compared it with ceftriaxone (60 participants), and five trials (171 participants) compared it with pefloxacin, ofloxacin, and enoxacin.

Different durations of fluoroquinolone

Nine trials (889 participants) compared different fluoroquinolone treatment durations: 2 days with 3 days (three trials); 3 days with 5 days (two trials), 5 days with 7 days (one trial); 7 days with 10 days (one trial); 7 days with 14 days (one trial); and 10 days with 14 days (one trial).

Length of fluoroquinolone treatment

Most trials comparing fluoroquinolones (excluding norfloxacin) with a non-fluoroquinolone antibiotic treated the participants with the fluoroquinolone for seven (8 trials) or 10 days (6 trials) (range three to 15 days). Among trials comparing fluoroquinolones with first-line antibiotics (chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin), only three trials used a short-course fluoroquinolone regimen of three days (Phongmany 2005) or seven days (Arnold 1993; Gasem 2003). Among 10 trials that compared a fluoroquinolone with azithromycin (four trials), ceftriaxone (three trials), or cefixime (three trials), nine used a short-course fluoroquinolone regimen of five days (three trials) or seven days (six trials). All other trials used a long-course (greater than seven days) fluoroquinolone regimen.

Primary outcomes

We were able to extract data on all three primary outcomes - clinical failure, microbiological failure, and relapse - from 24 of the 38 trials, on any two primary outcomes from eight trials, and on any one primary outcome from six trials.

There were considerable variations regarding the time points at which outcomes were measured, particularly microbiological failure (such as day two, the end of treatment, and some days after treatment) and relapse (such as during therapy and up to two months of follow up). The precise descriptions also varied considerably; for example, some trialists defined "relapse" as the recurrence of similar signs and symptoms with confirmation by blood and/or bone marrow culture (sterile site, as defined in protocol), and others as confirmed by positive stool cultures (non-sterile site) only. Some trialists did not explicitly state how they confirmed relapse in their trial (*see* Table 3 'Definitions of outcomes').

Secondary outcomes

Twenty-eight trials reported mean fever clearance times, but six did not report the standard deviation or the information required to calculate a standard deviation. The 95% confidence intervals for the mean were reported in three trials (Chinh 2000; Vinh 2005; Parry 2007) from which we derived the standard deviation. Fever clearance times are usually skewed: several trials used non-parametric tests of statistical significance, and authors provided mean and standard deviation on request for four trials that reported a median fever clearance time in the original report (Cao 1999; Phongmany 2005; Pandit 2007; Dolecek 2008). The Student's *t* test was also used (it is unclear whether data were log transformed before conducting this test). Caution is required when interpreting the mean difference for fever clearance times, as there may be some skew, and the denominator in calculating mean fever clearance times was not clear in most trials. Since we could not ascertain whether trial authors had excluded "clinical failures" in their calculation of mean fever clearance times (or included the fever clearance time of participants who were switched over to another drug), the mean fever clearance times included in our meta-analyses could be biased.

We could extract data on the length of hospitalization from 12 trials, complications from 20 trials, serious adverse events from 28 trials, and other adverse events from 23 trials. Five trials reported laboratory adverse events distinct from clinical adverse events (Nalin 1987; Hajji 1988; Yang 1991; Abejar 1993; Smith 1994). We extracted these laboratory data but did not analyse them together with clinical adverse events to avoid the overlap of participants. Four trials reported the number of adverse events, and not the number of participants (Morelli 1992; Duong 1995; Girgis 1999; Chinh 2000). Only one author provided the cost of therapy as additional data (Girgis 1999).

Twenty-five trials measured convalescent faecal carriage, but we could not extract data from three trials because one included three participants who were not blood culture confirmed at enrolment (Arnold 1993), and two because the participants with positive stool cultures at follow up also had recurrence of symptoms and were reported as relapses (Wallace 1993; Unal 1996).

MDR and NaR strains

See Table 1.

Of the 38 included trials, only 13 trials reported the proportion of participants with NaR strains, among which it was absent in four trials (Hajji 1988; Smith 1994; Cao 1999; Phongmany 2005). The MICs of different fluoroquinolones reported in trials that did not report NaR strains ranged from < 0.016 to 8 mg/L, suggesting that some strains may have had reduced susceptibility to fluoroquinolones (reference ranges available in (CLSI 2006)), but precise numbers of such strains in each arm were not available.

One of the two trials comparing norfloxacin with chloramphenicol did not report the proportion of participants with MDR strains. Among 13 trials comparing other fluoroquinolones (excluding norfloxacin) with first-line antibiotics, MDR strains were present in one trial (Phongmany 2005) absent in eight trials, and four

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trials did not report on this (Gottuzzo 1992; Yousaf 1992; Arnold 1993; Flores 1994).

Risk of bias in included studies

See risk of bias summary in Table 5.

Generation of allocation sequence

Twenty-one trials used an adequate randomization method: eight used random-numbers lists or tables; and the rest were computer generated. Five of these trials used block randomization. The method used to generate the allocation sequence in the remaining 17 trials was unclear.

Allocation concealment

Sixteen trials used an adequate method (sealed envelopes) to conceal allocation. The method used in the remaining 22 trials was unclear.

Blinding

Four trials were described as "double blinded" and 34 trials were open; two trials did not mention use of placebo, but we assumed they were open (Flores 1994; Bai 1995).

Inclusion of all randomized culture-positive participants in the final analysis

We obtained the percentage of participants lost to follow up by dividing the number of culture-positive participants unaccounted for at follow up by the total number of culture-positive participants randomized. Thus 26 trials included an adequate (90% or more) number of participants in final analysis (or assumed to be adequate when there was no mention of losses to follow up), and 12 trials included an inadequate number (less than 90%).

Overall methodological quality

Only six open trials used adequate methods to generate the allocation sequence and conceal allocation, and had few or no losses at the final follow up for which data were reported (Hajji 1988; Girgis 1999; Gasem 2003; Phongmany 2005; Vinh 2005; Dolecek 2008). Ten other open trials used adequate methods of randomization and allocation concealment but did not have adequate follow up (Smith 1994; Tran 1994; Duong 1995; Tran 1995; Vinh 1996; Nguyen 1997; Cao 1999; Chinh 2000; Pandit 2007; Parry 2007).

Five open trials reported an adequate method of randomization and follow up (Nalin 1987; Limson 1989; Sarma 1991; Morelli 1992; Cristiano 1995). Four trials were double-blinded trials with adequate follow up (Quintero 1988; Bran 1991; Gottuzzo 1992; Jia 1994). Two open trials did not have any adequate quality measure (Yousaf 1992; Alam 1995), and the remaining 11 trials had only adequate follow up.

Effects of interventions

1. Fluoroquinolones versus first-line antibiotics (chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin)

1.1. Fluoroquinolones versus chloramphenicol

Ten trials made this comparison (Quintero 1988; Bran 1991; Gottuzzo 1992; Morelli 1992; Yousaf 1992; Abejar 1993; Arnold 1993; Cristiano 1995; Gasem 2003; Phongmany 2005). Three did not clarify the proportion of participants with MDR strains (Gottuzzo 1992; Yousaf 1992; Arnold 1993), and nine did not report NaR data, while this was absent in one trial (Phongmany 2005). One trial included five different fluoroquinolones – ofloxacin, pefloxacin, ciprofloxacin, enoxacin, and norfloxacin (Morelli 1992); we analysed the norfloxacin group separately, as explained above.

Clinical failure

We did not detect any statistically significant difference in clinical failure (Analysis 1.1, Figure 1) in trials that included participants without MDR strains (307 participants, 5 trials), participants with some MDR strains (50 participants, 1 trial), or an unknown proportion of participants with MDR strains (237 participants, 3 trials), or when we combined all subgroups (594 participants, 9 trials). In one included trial (Phongmany 2005), participants randomized to chloramphenicol when found infected with a chloramphenicol-resistant isolate were switched to the fluoroquinolone group and consequently did not experience clinical failure. These were restored to their originally randomized groups by the authors (with no clinical failures reported in chloramphenicol arm) (Phongmany 2005).

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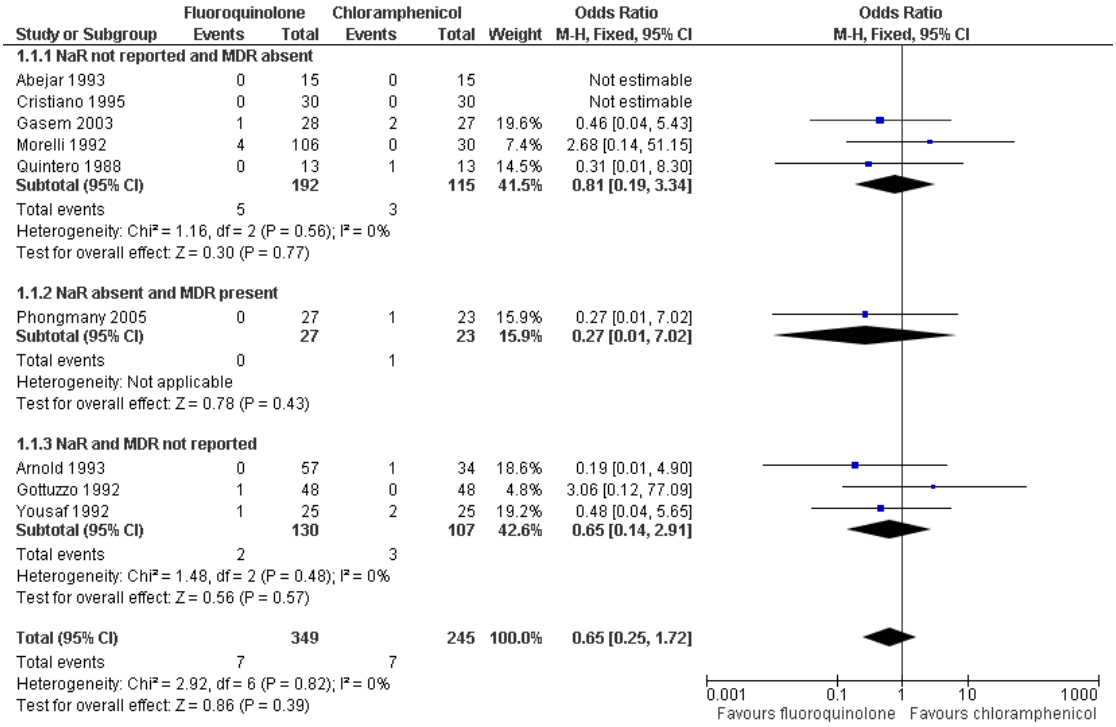
Figure 1. Fluoroquinolones vs chloramphenicol: clinical failure



We did not detect any statistically significant difference in clinical failure when we included only trials with adequate methodological quality (adequate methods of randomization and adequate allocation concealment, and no losses to follow up) (105 participants; Gasem 2003; Phongmany 2005; Analysis not shown).

Microbiological failure

We did not detect any statistically significant difference in the odds of microbiological failure in people without MDR strains (237 participants, 4 trials, Analysis 1.2). (Gasem 2003 performed both blood and bone marrow cultures for half of the participants at day three and for the other half of participants at day five of treatment to assess microbiological failure. We combined the blood culture results for both days, but we did not use bone marrow culture results as they were conducted on the same participants whose blood cultures were also taken.) In trials with an unknown proportion of participants with MDR strains (Analysis 1.2), the odds of microbiological failure were statistically significantly lower in the fluoroquinolone group (OR 0.24, 95% CI 0.06 to 0.96; 141 participants, 2 trials), but the results that favoured fluoroquinolones were of borderline statistical significance when we combined the two subgroups (OR 0.43, 95% CI 0.18 to 1.03; 378 participants, 6 trials).

We did not detect any statistically significant difference in microbiological failure when we included only trials with adequate methodological quality (adequate methods of randomization and adequate allocation concealment, and no losses to follow up) (45 participants, Gasem 2003, Analysis 1.2).

Relapse

In trials with no participants with MDR strains, the odds of relapse were reduced by 88%, which is statistically significant (OR 0.12, 95% CI 0.02 to 0.69; 281 participants, 4 trials, Analysis 1.3, Figure 2). However, we could not determine the precise definition or the site of culture to confirm a relapse in most of the trials (*see* Table 3), including Morelli 1992, which received the greatest weight in this meta-analysis. In the two trials with an unknown proportion of participants with MDR strains, we did not detect any statistically significant differences, but statistical power was very limited (186 participants, 2 trials, Analysis 1.3). The odds of relapse were reduced significantly when we combined both subgroups (OR 0.14, 95% CI 0.04 to 0.50; 467 participants, 6 trials, Analysis 1.3). When we excluded from the analysis those trials that did not clearly define relapse (Abejar 1993; Cristiano 1995),

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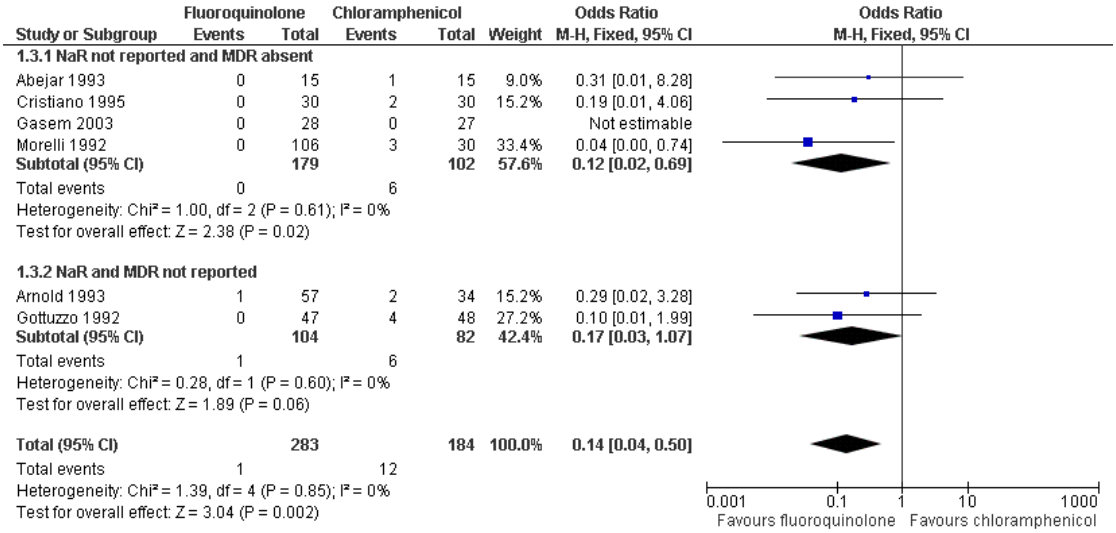
did not confirm relapse using cultures (Gasem 2003), or did not define relapse at all (Gottuzzo 1992; Morelli 1992), thus retaining only one trial (91 participants) with clearly blood culture-confirmed relapses (Arnold 1993) (sterile site-culture confirmed, as defined in the protocol), we did not find any difference between fluoroquinolones and chloramphenicol.

Figure 2. Fluoroquinolones vs chloramphenicol: relapse



The only trial with adequate methodological quality in this comparison did not report any relapses (55 participants, Gasem 2003, Analysis 1.3); however this was only reported during hospitalization, and longer follow up was not done.

Fever clearance time

The meta-analysis of two trials without participants with MDR strains tended to favour fluoroquinolones for fever clearance time, but the sample size was small so that the confidence intervals were very wide (MD -16.07 hours, 95% CI -35.03 to 2.88; 81 participants, Analysis 1.4). One trial (Phongmany 2005) with NaR absent and MDR present reported a statistically significantly lower mean fever clearance time in the fluoroquinolone group (MD -38.5 hours, 95% CI -59.90 to -17.10; 48 participants, Analysis 1.4). On combining both subgroups we detected a statistically significantly lower mean fever clearance time in the fluoroquinolone group (MD -25.93 hours, 95% CI -40.12 to -11.74; 129 participants, 3 trials, Analysis 1.4). Fever clearance time was slightly shorter in both Abejar 1993 and Cristiano 1995, but the trialists did not report standard deviations or precise results of tests of statistical significance, and we could not include them in the meta-analysis.

When we included only two above-mentioned trials with adequate methodological quality (Gasem 2003; Phongmany 2005), we detected a statistically significantly lower mean fever clearance time in the fluoroquinolone group (MD -27.56 hours, 95% CI -43.38 to -11.75; 103 participants, Analysis not shown).

Length of hospital stay

Three trials reported on the length of hospital stay (Analysis 1.5). One of them, Cristiano 1995, did not report the standard deviation (fluoroquinolone group: mean 5 days, range 3 to 8 days; chloramphenicol group: mean 5.53 days, range 2 to 8 days). We did not detect any statistically significant difference in the length of hospital stay in the other trial, Gasem 2003 (55 participants), which had no MDR and did not report NaR. One trial reported a statistically significantly lower mean length of hospital stay in the fluoroquinolone group (MD -5.90 days, 95% CI -7.42 to -4.38; 50 participants, Phongmany 2005). On combining both

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subgroups we detected a statistically significantly lower length of hospital stay in the fluoroquinolone group (MD -2.57 days, 95% CI -3.53 to -1.62; 105 participants, 2 trials). We detected statistically significant heterogeneity in the two trials; this could be due to differences in durations of fluoroquinolone treatment (15 days versus 3 days) in the two trials. We did not detect any statistically significant difference in the length of hospital stay when we used a random-effects model to combine the trials (105 participants, 2 trials, Analysis not shown). These were the only two trials that reported length of hospital stay, and both were of adequate methodological quality.

Convalescent faecal carriage

We found a statistically significant decrease in the odds of convalescent faecal carriage in the fluoroquinolone group in trials that did not have any participants with MDR strains (OR 0.17, 95% CI 0.04 to 0.70; 298 participants, 3 trials, Analysis 1.6). No trial of adequate methodological quality reported this outcome.

Complications and adverse events

We did not detect a statistically significant difference in the number of complications in two trials, both of adequate methodological quality, that reported these data (105 participants, Analysis 1.7). The complications included pneumonia, sepsis, myocarditis, gastrointestinal bleeding, and perforation (*see* Table 2). We did not detect a statistically significant difference in the number of non-serious adverse events, such as nausea, epigastric pain, skin rash, headache, and dizziness (245 participants, 5 trials, Analysis 1.8; *see* Table 6). We also did not detect any statistically significant differences in non-serious adverse events in the two trials with adequate methodological quality (105 participants, Analysis not shown; *see* Table 6). One trial mentioned selected serious adverse events, including one participant with severe rash in the ciprofloxacin group and one with severe leucopenia in the chloramphenicol group (Gottuzzo 1992; Table 7).

Table 6. Non-serious adverse events[a]

Comparison	Trial	No. of participants (in brackets except where specifically stated) with non-serious adverse events[b]		Laboratory adverse events[c]	
		Intervention	Control	Intervention	Control
Fluoroquinolone vs chloramphenicol	Abejar 1993	Fleroxacin: numbness in upper extremities (2)	Chloramphenicol: numbness in upper extremities (1)	Fleroxacin: increased creatinine (4)	Chloramphenicol: increased creatinine (4); increased blood urea nitrogen (2)

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Table 6. Non-serious adverse events[a] (*Continued*)

	Arnold 1993	Seborrheic dermatitis in 14-day fluoroquinolone group (1) Gastrointestinal complaints were most common, including nausea and vomiting; insomnia also reported; no. were not provided for culture-positive participants but reported together with culture-negative participants	Gastrointestinal complaints were most common, including nausea and vomiting; insomnia also reported; no. were not provided for culture-positive participants but reported together with culture-negative participants	Most frequent laboratory abnormalities included low neutrophil or total leukocyte count, low haemoglobin and haematocrit, but it does not say which event occurred in which arm and are reported together with culture-negative participants	
	Bran 1991	0	0	0	0
	Cristiano 1995	Pefloxacin: nausea (3); epigastric pain (3); transient rash (1)	Chloramphenicol: epigastric pain (5)	0	0
	Gasem 2003	Ciprofloxacin: 0	Chloramphenicol: rash (1)	Ciprofloxacin: 0	Chloramphenicol: mean decrease in haemoglobin levels (no. not stated)
	Gottuzzo 1992	Ciprofloxacin: not described	Chloramphenicol: leucopenia (10); others not described	Not described	Not described
	Morelli 1992	Events in 4 fluoroquinolone groups: epigastric pain (26); flushing (12); headache (8); dizziness (11); skin rash (4)	Events in chloramphenicol group: diarrhoea (3); epigastric pain (6); abdominal pain (4)	Not described	Not described
	Phongmany 2005	0	0	-	-
	Yousaf 1992	Ofloxacin: (3)	Chloramphenicol: (4)	Not described	Not described

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Table 6. Non-serious adverse events[a] (*Continued*)

Fluoroquinolone vs ampicillin or amoxicillin	Yousaf 1992	Ofloxacin: (3)	Amoxicillin: (11) (mostly diarrhoea, pruritis, rash)	Not described	Not described
Fluoroquinolone vs co-trimoxazole	Hajji 1988	Pefloxacin: photoxicity (1)	Co-trimoxazole: rash (1)	Pefloxacin: increased transaminase (2)	Co-trimoxazole: increased transaminases (1)
	Limson 1989	Ciprofloxacin: abdominal discomfort (4); dizziness (1)	Co-trimoxazole: nausea (5); pruritis (1)	0	0
Fluoroquinolone vs azithromycin	Dolecek 2008	Gatifloxacin: vomiting (1); diarrhoea (1)	Azithromycin: rash (1)	-	-
	Chinh 2000	No. events for ofloxacin: nausea (1); vomiting (3); abdominal pain (4)	No. events for azithromycin: nausea (5); vomiting (5); abdominal pain (4); rash (1)	Ofloxacin: increased mean levels of alanine and aspartate aminotransferase (all 44 participants)	Azithromycin: increased mean levels of alanine and aspartate aminotransferase (all 44 participants)
	Girgis 1999	Ciprofloxacin: nausea and vomiting (4); lightheadedness (2); dry mouth (4); loose stools (3); constipation (2)	Azithromycin: nausea and vomiting (6); lightheadedness (2); dry mouth (3); loose stools (3); constipation (2)	Ciprofloxacin: thrombocytosis (1); mild aspartate transaminase increase (3)	Azithromycin: thrombocytosis (4); mild aspartate transaminase increase (2)
	Parry 2007	Ofloxacin: joint discomfort which resolved (1); gastrointestinal side effects (no. not stated)	Azithromycin: joint discomfort which resolved (1); gastrointestinal side effects (no. not stated)	-	-
Fluoroquinolone vs cefixime	Cao 1999	No. events for ofloxacin: abdominal pain (4); diarrhoea (4); vomiting (1)	No. events for cefixime group: abdominal pain (1); diarrhoea (4); vomiting (1); rash (1)	Not described	Not described
	Pandit 2007	Gatifloxacin: nausea and vomiting (18). Among these, 2 with excessive vomiting re-	Cefixime: nausea and vomiting (1)	-	-

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Table 6. Non-serious adverse events[a] (*Continued*)

		quired intravenous antiemetics and fluids and observation in the hospital emergency room for up to 6 hours; 2 needed oral antiemetics			
	Yu 1998	Levofloxacin: 0	Cefixime: nausea and low appetite (2)	Levofloxacin: increased alanine aminotransferase (2)	Cefixime: increased alanine aminotransferase (1)
Fluoroquinolone vs ceftriaxone	Smith 1994	Ofloxacin: pruritis (1)	Ceftriaxone: skin rash (2)	Ofloxacin: mildly increased creatinine (1)	Ceftriaxone: 0
Norfloxacin vs chloramphenicol	Nalin 1987	Norfloxacin: clinical adverse events (6)	Chloramphenicol: clinical adverse events (7)	Norfloxacin: laboratory adverse events (10)	Chloramphenicol: laboratory adverse events (20)
	Sarma 1991	Norfloxacin: nausea (3); vomiting (3); headache (2)	Chloramphenicol: 0	Norfloxacin: 0	Chloramphenicol: decreased mean hematocrit (2), decreased white blood cell count (3), decreased platelet count (2)
Norfloxacin vs ceftriaxone	Huai 2000	Norfloxacin: nausea and vomiting (3)	Ceftriaxone: abdominal discomfort and nausea (1)	Not described	Not described
Norfloxacin vs other fluoroquinolones	Bai 1995	Enoxacin: rash (1)	Norfloxacin: abdominal discomfort (1)	Not described	Not described
	Jia 1994	Norfloxacin: 0	Pefloxacin: included nausea, vomiting, dizziness, measles like rash and abdominal discomfort (no. not stated)	Not described	Not described
	Morelli 1992	Norfloxacin: epigastric pain (6); flushing (4); dizziness (4)	No. events for ofloxacin: epigastric pain (4); flushing (4); headache (2)	Not described	Not described

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Table 6. Non-serious adverse events[a] (*Continued*)

			No. events for pefloxacin: rash (2); headache (6); epigastric pain (10) No. events for enoxacin: epigastric pain (3); flush (4); dizziness (7)		
	Xiao 1991	Norfloxacin: not described	Pefloxacin: nausea and anorexia (2); agitation and abnormal behaviour (1) Ofloxacin: nausea (2); measles like rash (3); salivation (1)	Not described	Not described
	Yang 1991	Ofloxacin: rash (1)	Norfloxacin: rash (1)	Norfloxacin: increased alanine aminotransferase (1)	-
Different durations of fluoroquinolones	Alam 1995	10-day: 4 participants had 11 events including malaise (1), dizziness (1), nausea (1), insomnia (1), rash (1), pruritis (1), lethargy (1), weakness (1), and headache (3)	14-day: 9 participants had 18 events including joint pain (1), malaise (3), abdominal pain (3), headache (1), dizziness (1), nausea (1), oral mucosal pain (2), insomnia (1), vomiting (1), vertigo (1), palpitations (1), and photosensitivity (1)	10-day: moderate eosinophilia (5)	14-day: moderate eosinophilia (3); increased serum creatinine (1)
	Duong 1995	3-day: insomnia (10)	No. events for 5-day: insomnia (17), nausea and vomiting (1)	Not described	Not described
	Kalo 1997	7-day: nausea, vomiting, or abdominal discomfort (4), but it does not say in which group	10-day: nausea, vomiting, or abdominal discomfort (4), but it does not say in which group	Not described	Not described
	Tran 1995	3-day (11): participants had insomnia, dizziness, epigastric	5-day (4): participants had insomnia, dizziness,	Not described	Not described

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Table 6. Non-serious adverse events[a] *(Continued)*

		pain, nausea, diarrhoea, headache and > 1 symptom; joint symptoms reported were not thought to be fluoroquinolone-induced Details were reported for culture-positive participants together with culture-negative participants	vomiting, rash; joint symptoms reported were not thought to be fluoroquinolone-induced Details were reported for culture-positive participants together with-culture negative participants		
	Unal 1996	5-day: nausea and vomiting (3)	7-day: nausea and vomiting (3)	5-day: 0	7-day: increase in transaminases (1)
	Vinh 1996	2-day: 0	3-day: urticaria (1)	Not described	Not described
	Vinh 2005	2-day: 0	3-day: 0	-	-

[a] Only trials reporting on non-serious adverse events are included.
[b] Zero (0) events only when specifically stated by trial author.
[c] Whenever this was reported separately.

Table 7. Serious adverse events[a]

Comparison	Trial*	No. participants (in brackets) with serious adverse events[b]	
		Intervention	Control
Fluoroquinolone vs chloramphenicol	Arnold 1993	Urinary retention (1), but it does not say in which group or if a culture-negative or culture-positive participant	
	Bran 1991	0	0
	Cristiano 1995	0	0
	Gasem 2003	0	0
	Gottuzzo 1992	Ciprofloxacin: severe rash (1); others not described	Chloramphenicol: severe leucopenia (1); others not described
	Phongmany 2005	0	0
	Quintero 1988	0	0

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Table 7. Serious adverse events[a] (*Continued*)

Fluoroquinolone vs ampicillin	Flores 1994	0	0
Fluoroquinolone vs co-trimoxazole	Hajji 1988	0	0
	Limson 1989	0	0
Fluoroquinolone vs azithromycin	Dolecek 2008	0	0
	Chinh 2000	0	0
	Girgis 1999	0	0
	Parry 2007	0	0
Fluoroquinolone vs cefixime	Pandit 2007	0	0
Fluoroquinolone vs ceftriaxone	Smith 1994	0	0
	Tran 1994	Fleroxacin: 0	Ceftriaxone: anaphylaxis (1)
Norfloxacin vs chloramphenicol	Nalin 1987	Nausea and vomiting "considered serious by the investigator": number with event unclear	0
	Sarma 1991	0	0
Norfloxacin vs other fluoroquinolones	Bai 1995	0	0
	Jia 1994	0	0
	Xiao 1991	Not described	Not described
	Yang 1991	0	0
Different durations of fluoroquinolones	Alam 1995	0	0
	Duong 1995	0	0
	Kalo 1997	0	0
	Nguyen 1997	0	0
	Tran 1995	0	0
	Unal 1996	0	0
	Vinh 1996	0	0
	Vinh 2005	0	0

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[a] Only trials reporting on serious adverse events are included.
[b] Zero (0) events only when specifically stated by trial author.

Funnel plot

We generated a funnel plot for clinical failure, microbiological failure, and relapse for the comparison of fluoroquinolone versus chloramphenicol, as there were more than five trials in these comparisons. No asymmetry was detected for the outcome clinical failure (Figure 3), while asymmetry was detected for microbiological failure (Figure 4) and relapse (Figure 5). However, the number of trials was very limited and well below the recommended number (10 trials) for meaningful interpretation.

Figure 3. Funnel plot to assess publication bias in outcome clinical failure for comparison of fluoroquinolones vs chloramphenicol

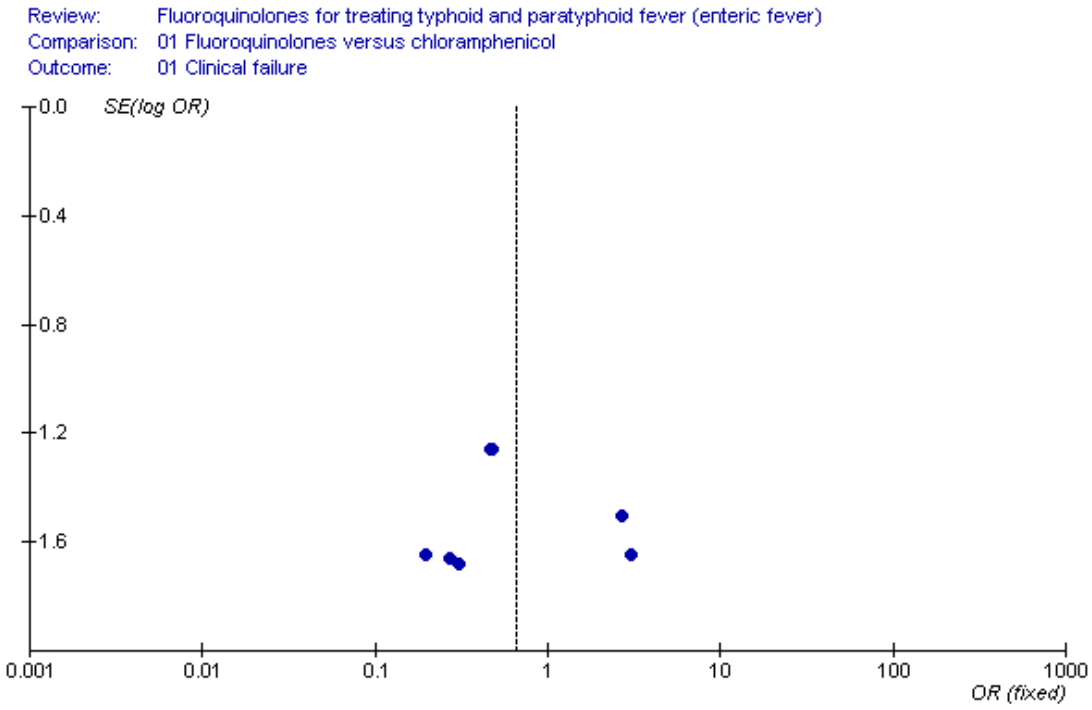

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Figure 4. Funnel plot to assess publication bias in outcome microbiological failure for comparison of fluoroquinolones vs chloramphenicol

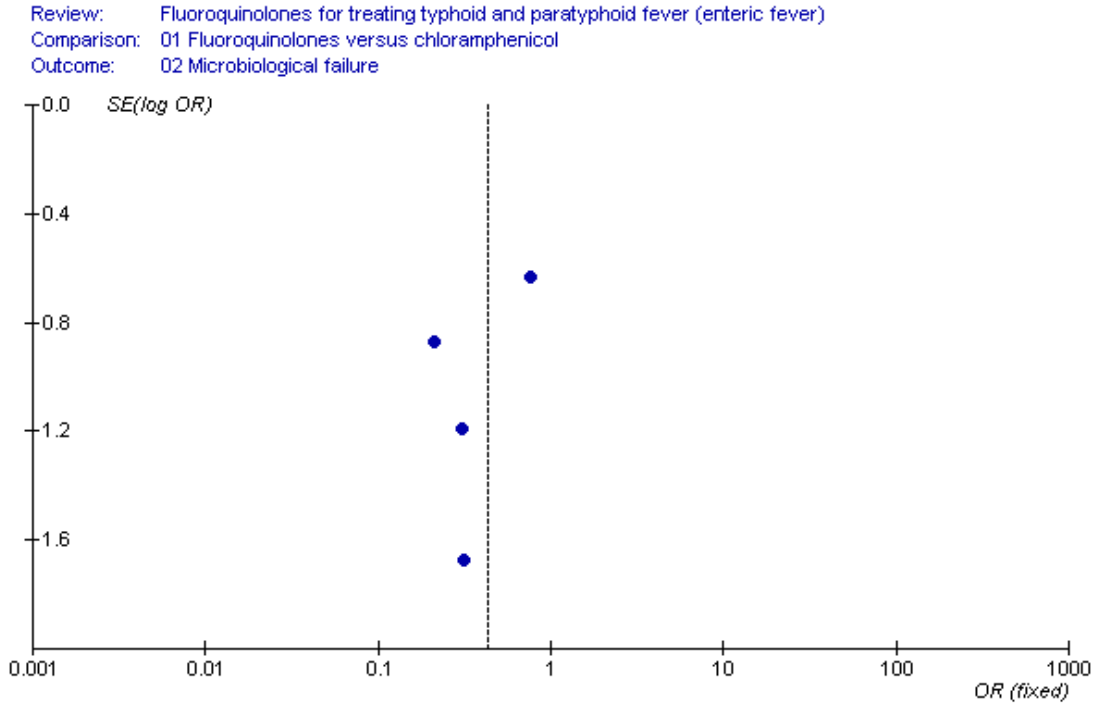

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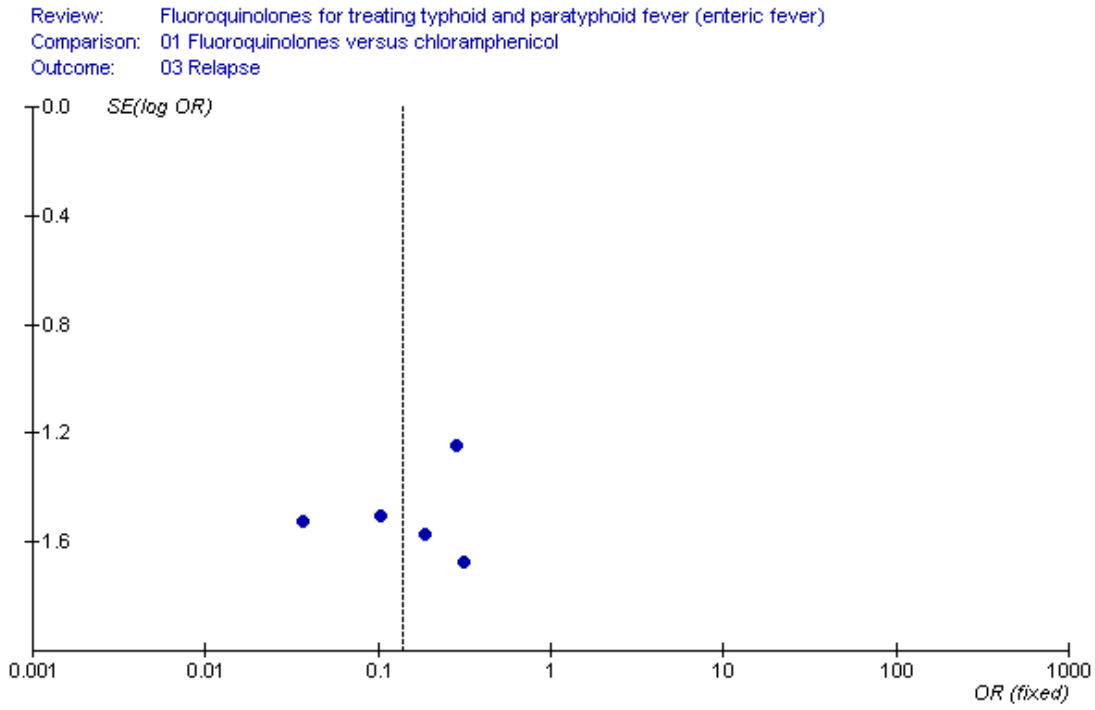
Figure 5. Funnel plot to assess publication bias in outcome relapse for comparison of fluoroquinolones vs chloramphenicol



1.2. Fluoroquinolones versus amoxicillin or ampicillin

Two trials, both with an unknown proportion of participants with MDR and NaR strains, compared a fluoroquinolone with amoxicillin (Yousaf 1992) or ampicillin (Flores 1994, only abstract available).

Clinical and microbiological failure, and adverse events

All results for measured outcomes were statistically significant in favour of the fluoroquinolones – clinical failure (OR 0.08, 95% CI 0.01 to 0.46; 90 participants, 2 trials, Analysis 2.1), microbiological failure (OR 0.10, 95% CI 0.02 to 0.58; 90 participants, 2 trials, Analysis 2.2), and non-serious adverse events, described as mostly diarrhoea and rashes (OR 0.17, 95% CI 0.04 to 0.73; 50 participants, 1 trial, Analysis 2.3 and Table 6) – but the numbers of participants were very small so that confidence intervals were very wide.

1.3. Fluoroquinolones versus co-trimoxazole

Hajji 1988 and Limson 1989 compared pefloxacin and ciprofloxacin respectively with co-trimoxazole. Neither trial included participants with MDR strains, and only Hajji 1988 specifically reported the absence of NaR strains in the participants.

Clinical and microbiological failure

There was a trend favouring fluoroquinolones over co-trimoxazole for clinical failure (82 participants, 2 trials, Analysis 3.1) and microbiological failure (82 participants, 2 trials, Analysis 3.2), but we did not find any statistically significant results for these outcomes, although statistical power was extremely low so that confidence intervals were very wide.

Fever clearance time

Only Hajji 1988 reported on fever clearance time, which was 104.88 hours (mean) for the fluoroquinolone group compared with 186.00 hours (mean) for the co-trimoxazole group (Student's *t* test; P value < 0.01; no standard deviation reported).

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Relapse and convalescent faecal carriers

Hajji 1988 reported no relapses or convalescent faecal carriers.

Adverse events

We did not detect any statistically significant differences in non-serious adverse events, such as rash, nausea, abdominal discomfort, and dizziness (82 participants, 2 trials, Analysis 3.3; *see* Table 6). Hajji 1988 reported no serious adverse events.

2. Fluoroquinolones versus second-line antibiotics (azithromycin, cefixime, and ceftriaxone)

2.1. Fluoroquinolones versus azithromycin: adults

Girgis 1999 and Chinh 2000 compared ofloxacin and ciprofloxacin, respectively, with azithromycin. Chinh 2000 reported that almost half of the participants were infected with NaR strains, while Girgis 1999 did not test for NaR. We observed a tendency for azithromycin to perform better than fluoroquinolones for all outcomes except fever clearance times, but the sample size was very small and confidence intervals were very wide. Thus we cannot exclude chance as an explanation for these findings.

Clinical and microbiological failure

We did not detect any statistically significant differences in clinical failure (152 participants, 2 trials, Analysis 4.1) or microbiological failure (152 participants, 2 trials, Analysis 4.2). Out of the six clinical failures in the fluoroquinolone arm in Chinh 2000, four were infected with NaR strains, which could possibly explain the trend favouring azithromycin for clinical failure.

Relapse

We did not detect any statistically significant differences in relapse (102 participants, 2 trials, Analysis 4.3).

Fever clearance time

We also did not find any statistically significant difference in fever clearance time (152 participants, 2 trials, Analysis 4.4). The higher proportion of NaR strains in Chinh 2000 could explain the heterogeneity observed between the two trials.

Length of hospital stay

We did not detect any statistically significant difference in the length of hospital stay (152 participants, Analysis 4.5).

Cost of therapy

We did not detect any statistically significant difference in the cost of therapy (mean US$ 28 (standard deviation (SD) 0) for fluoroquinolone group and mean US$ 35 (SD 0) for azithromycin group).

Convalescent faecal carriage

We detected a statistically significant increase in the odds of convalescent faecal carriage in the fluoroquinolone group (OR 21.33, 95% CI 1.18 to 386.00; 133 participants, 2 trials, Analysis 4.6), but the outcome was measured very early, at days two to three after the end of treatment, and the confidence interval is wide.

Complications and adverse events

We did not detect any statistically significant difference in complications (*see* Table 2 for details), as only one participant in each arm in Chinh 2000 had gastrointestinal bleeding (152 participants, 2 trials, Analysis 4.7). Non-serious adverse events included rashes and gastrointestinal symptoms, such as vomiting, abdominal pain, and diarrhoea or constipation, but the trialists did not report the number of participants with these events (Table 6); there were no serious adverse events.

2.2. Fluoroquinolones versus azithromycin: children

Two trials made this comparison: Parry 2007 had 98% NaR strains in the fluoroquinolone arm; and Dolecek 2008 had 96% NaR strains in the fluoroquinolone arm. However, the fluoroquinolone used in Dolecek 2008 was a new-generation fluoroquinolone, gatifloxacin, which is active against NaR strains; thus the two trial were not combined. In both trials more than 60% of participants were children.

Clinical and microbiological failure

Parry 2007: We found a statistically significant increase in odds of clinical failure with fluoroquinolone (OR 2.67, 95% CI1.16 to 6.11; 125 participants, 1 trial, Analysis 4.8). We did not detect any statistically significant difference in microbiological failure (125 participants, 1 trial, Analysis 4.9).

Dolecek 2008: We did not detect any statistically significant differences in clinical failure (285 participants, Analysis 4.8) or microbiological failure (285 participants, Analysis 4.9).

Relapse

Parry 2007: There were no relapses among participants seen at one month's follow up (114 participants followed from among 130 participants with culture-confirmed enteric fever, or less than 90% follow up at month for two included arms of the trial).

Dolecek 2008: We did not detect a statistically significant difference in relapse (264 participants, Analysis 4.10).

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Fever clearance time

Parry 2007: There was a statistically significant increase in fever clearance time (MD 57.60 hours, 95% CI 28.31 to 86.89; 125 participants, Analysis 4.11).
Dolecek 2008: We did not detect a statistically significant difference in fever clearance time (285 participants, Analysis 4.11).

Length of hospital stay

Parry 2007: There was a borderline statistically significant increase in the length of hospital stay in the fluoroquinolone group (MD 1.10 days, 95% CI 0.00 to 2.20; 125 participants, Analysis 4.12).
Dolecek 2008: We did not detect a statistically significant difference in length of hospital stay (285 participants, Analysis 4.12).

Convalescent faecal carriage

Parry 2007: We found a statistically significant increase convalescent faecal carriage in the fluoroquinolone group (OR 14.64, 95% CI 1.84 to 116.48; 124 participants, 1 trial, Analysis 4.13).
Dolecek 2008: We did not detect a statistically significant difference in convalescent faecal carriage (268 participants, Analysis 4.13).

Complications and adverse events

Parry 2007: We did not detect any statistically significant difference in complications, which included gastrointestinal bleeding (125 participants, Analysis 4.14; *see* Table 2). Non-serious adverse events such as gastrointestinal and temporary joint symptoms were reported (numbers for gastrointestinal symptoms not reported, *see* Table 6). No serious adverse events were reported.
Dolecek 2008: There was a statistically significant decrease in complications in the fluoroquinolone group (OR 0.05, 95% CI 0.00 to 0.94; 285 participants, Analysis 4.14). We did not detect any statistically significant differences in non-serious adverse events (285 participants, Analysis 4.15). There were no serious adverse events.

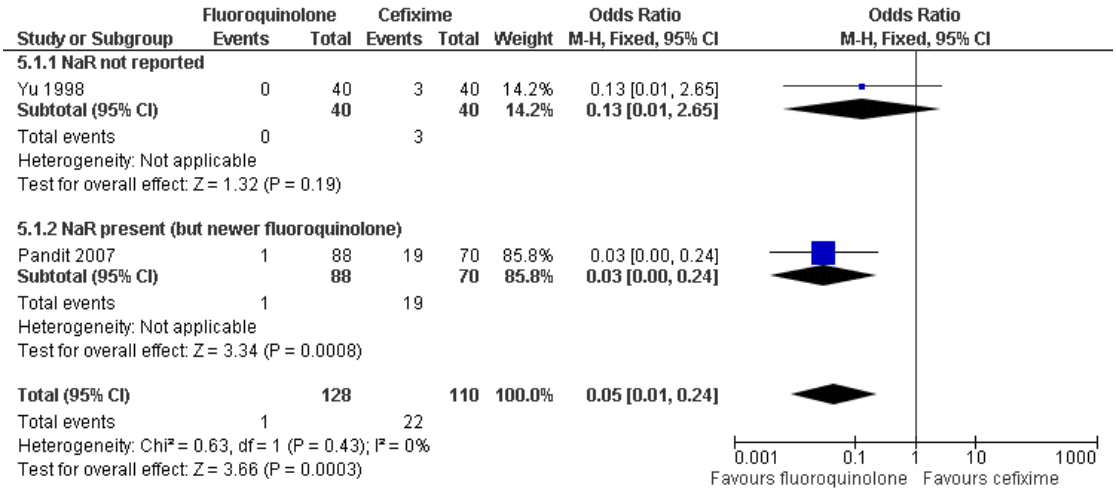
2.2. Fluoroquinolones versus cefixime: adults

Two trials of adults, or mostly adults (Yu 1998; Pandit 2007) compared a fluoroquinolone with cefixime. Although one trial (Pandit 2007) did have a high proportion of NaR strains, the newer fluoroquinolone used, gatifloxacin, is reported to be active against NaR strains; the other trial on adults (Yu 1998) did not provide any data for NaR strains. These two trials were combined in a meta-analysis. Pandit 2007 was an outpatient trial, where community medical auxiliaries conducted twice daily home-based assessments and provided directly observed treatment with study drugs; all participants were also seen at the hospital on day 10.

Clinical and microbiological failure

We detected a statistically significant decrease in odds of clinical failure in the fluoroquinolone group (OR 0.05, 95% CI 0.01 to 0.24; 238 participants, 2 trials, Analysis 5.1, Figure 6), and no statistically significant difference in microbiological failure (238 participants, Analysis 5.2).

Figure 6. Fluoroquinolones vs cefixime: clinical failure (adults or mostly adults)



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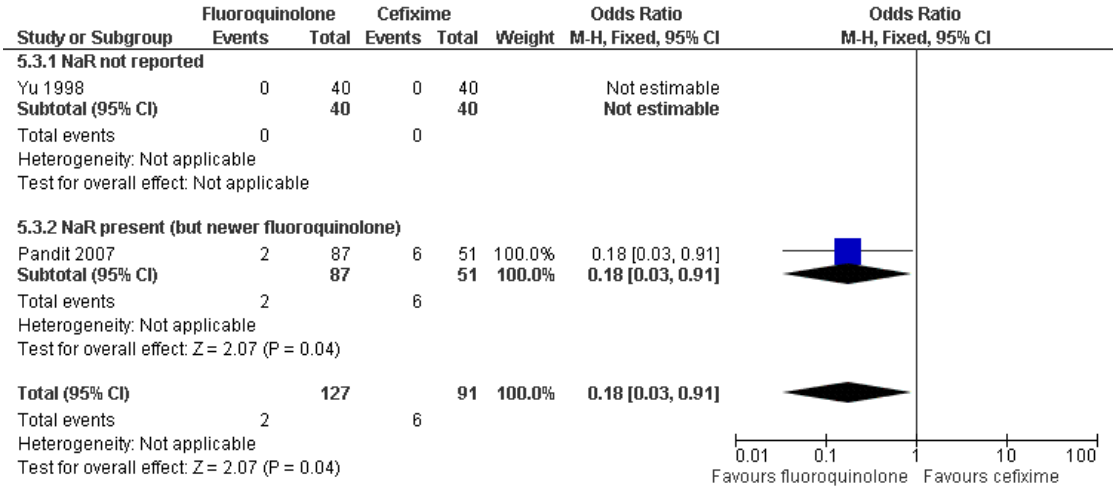
Relapse

There was a statistically significant reduction in relapse with the fluoroquinolone (OR 0.18, 95% CI 0.03 to 0.91; 218 participants, 2 trials, Analysis 5.3, Figure 7).

Figure 7. Fluoroquinolones vs cefixime: relapse (adults or mostly adults)



Fever clearance time

We detected a statistically significant reduction in fever clearance time with the fluoroquinolone (MD -41.69 hours, 95% CI -54.96 to -28.42; 238 participants, 2 trials, Analysis 5.4).

Cost of therapy

The estimated cost of treatment provided in one trial was US$ 1.2 for seven days of gatifloxacin and US$ 12 for seven days of cefixime (generic drugs manufactured in India) (Pandit 2007).

Convalescent faecal carriers

We did not find any statistically significant difference in convalescent faecal carriers (227 participants, 2 trials, Analysis 5.5).

Complications and adverse events

There was no statistically significant difference for complications, which included one death in the cefixime group (158 participants, 1 trial, Analysis 5.6; *see* Table 2), and no serious adverse events (158 participants, 1 trial).

We found statistically significant heterogeneity in trials comparing non-serious adverse events (Analysis 5.7). We did not find any statistically significant difference in the one included trial (80 participants), but we found a statistically significant increase in the odds of nausea and vomiting in the other trial (OR 17.74, 95% CI 2.30 to 136.58; 158 participants; *see* Table 6). The heterogeneity could be attributed to the different fluoroquinolones used in the two trials (the relatively newer, gatifloxacin and levofloxacin). We did not find any statistically significant difference in non-serious adverse events when we used a random-effects model to combine the trials (OR 3.30, 95% CI 0.11 to 97.30; 238 participants, 2 trials).

2.2. Fluoroquinolones versus cefixime: children

One trial, Cao 1999, compared a fluoroquinolone with cefixime in children; no NaR strains were reported. The results for all measured outcomes favoured fluoroquinolones, but the sample sizes were small and hence the confidence intervals were very wide.

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Clinical and microbiological failure

We did not detect any statistically significant difference in clinical failure (82 participants, Analysis 5.8) or microbiological failure (82 participants, Analysis 5.9).

Relapse

We did not detect any statistically significant difference in relapse (40 participants, Analysis 5.10).

Fever clearance time

There was a statistically significant reduction in fever clearance time in the fluoroquinolone group (MD -91.00 hours, 95% CI -115.89 to -66.11; 78 participants, Analysis 5.11).

Length of hospital stay

We found a statistically significant reduction in the length of hospital stay in the fluoroquinolone group (MD -3.00 days, 95% CI -4.53 to -1.47; 81 participants, Analysis 5.12).

Convalescent faecal carriers

No convalescent faecal carriers were reported.

Complications and adverse events

There was no statistically significant difference in complications (82 participants, Analysis 5.13), which included one death and one child with gastrointestinal bleeding in the fluoroquinolone arm, and one child requiring blood transfusion in the cefixime arm (*see* Table 2). Non-serious adverse events included gastrointestinal symptoms, such as abdominal pain (*see* Table 6), but the number of participants was not reported.

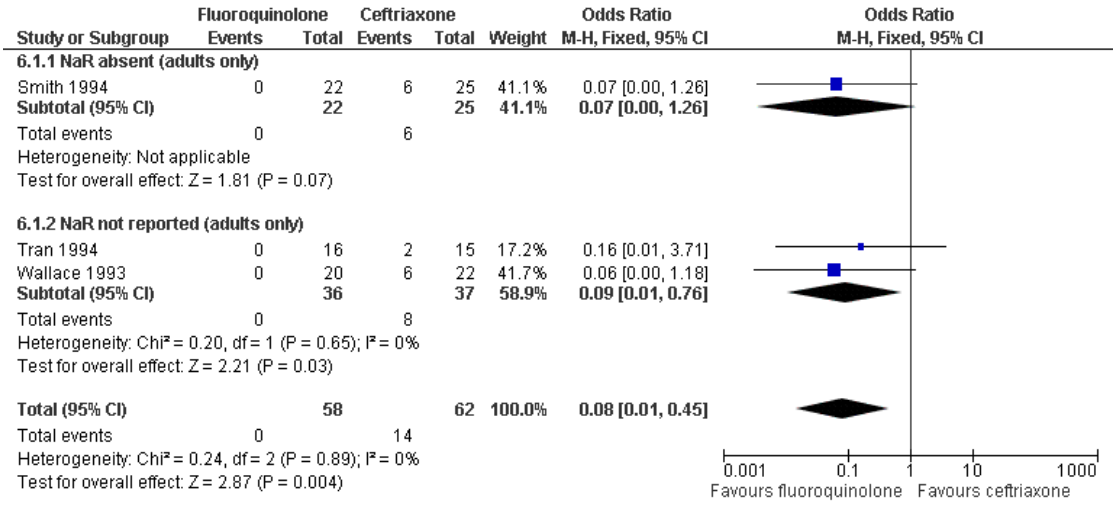
2.3. Fluoroquinolones versus ceftriaxone

Three trials compared a fluoroquinolone with ceftriaxone protocol (Wallace 1993; Smith 1994; Tran 1994). There were no NaR strains in Smith 1994, but this information was unavailable for Tran 1994 and Wallace 1993. The stratifications by NaR strains were not meaningful due to the limited number of trials in the comparison.

Clinical and microbiological failure

The odds of clinical failure were reduced by 92% in the fluoroquinolone group (OR 0.08, 95% CI 0.01 to 0.45; 120 participants, 3 trials, Analysis 6.1, Figure 8). We did not detect a statistically significant difference in the odds of microbiological failure (119 participants, 3 trials, Analysis 6.2), but sample sizes were small and confidence intervals were wide.

Figure 8. Fluoroquinolones vs ceftriaxone: clinical failure



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Relapse

We did not detect a statistically significant difference in the odds of relapse (81 participants, 3 trials, Analysis 6.3), but sample sizes were small and confidence intervals were wide.

Fever clearance time

Fever clearance times were statistically significantly lower in the fluoroquinolone group (MD -101.20 hours, 95% CI -129.21 to -73.19; 76 participants, 2 trials, Analysis 6.4). Tran 1994 excluded two clinical failures in the ceftriaxone group when calculating mean fever clearance time, which may result in an underestimate of the difference in this outcome.

Length of hospital stay

Smith 1994 reported the on length of hospital stay as a mean of nine days (range 6 to 13 days) in the ofloxacin group and a mean of 12 days (range 7 to 23 days) in the ceftriaxone group; standard deviation was not reported (P < 0.01).

Convalescent faecal carriage

We did not detect any significant difference for convalescent faecal carriage (81 participants, 3 trials, Analysis 6.5).

Complications and adverse events

There was no significant difference in the number of complications, including anaemia, jaundice (120 participants, 3 trials, Analysis 6.6; *see* Table 2), serious adverse events — one case of anaphylaxis in the ceftriaxone group (78 participants, 2 trials, Analysis 6.7; *see* Table 7), or non-serious adverse events, which included skin rash and pruritis (47 participants, 1 trial, Analysis 6.8; *see* Table 6); however, sample sizes were very small so confidence intervals were very wide.

3. Norfloxacin trials

We analysed norfloxacin trials separately from other fluoroquinolone trials because the WHO does not recommend this fluoroquinolone for treating enteric fever (WHO 2003).

3.1. Norfloxacin versus chloramphenicol

Only one of three trials reported the proportion of participants with NaR strains (all strains were resistant to norfloxacin) (Sarma 1991). MDR strains were present in Sarma 1991, not reported in Nalin 1987, and absent in Morelli 1992. In Sarma 1991 all eight MDR strains appeared in the norfloxacin group, and only 40 participants were randomized in all.

Clinical and microbiological failure

There was a statistically significant increase in the odds of clinical failure in the norfloxacin group among all trials (OR 5.80, 95% CI 1.87 to 17.98; 259 participants, Analysis 7.1); the one trial that did not report the proportion of MDR or NaR showed no statistically significant difference (169 participants, Nalin 1987).

We did not detect a statistically significant difference in the odds of microbiological failure (209 participants, 2 trials, Analysis 7.2).

Relapse

We did not detect a statistically significant difference in the odds of relapse (90 participants, 2 trials, Analysis 7.3).

Fever clearance time

For fever clearance time (Analysis 7.4), we observed marked heterogeneity between Sarma 1991 and Nalin 1987, which could be explained by the different definitions of fever clearance time used (*see* Table 3), thus we did not combine the trials. Sarma 1991, which also had some participants with MDR strains, showed that the fever clearance time was statistically significantly lower in the norfloxacin group (MD -36.00 hours, 95% CI -44.77 to -27.23; 40 participants), while Nalin 1987 showed that it was statistically significantly higher in the norfloxacin group (MD 38.40 hours, 95% CI 23.08 to 53.72; 169 participants).

Length of hospital stay

The length of hospital stay was uniform (14 days) in all participants included (Analysis 7.5).

Convalescent faecal carriage

We did not detect a statistically significant difference for convalescent faecal carriage (259 participants, 3 trials, Analysis 7.6).

Adverse events

We did not detect a statistically significant difference for non-serious adverse events, such as gastrointestinal symptoms (Table 6), in the norfloxacin group and decreased blood cell counts in the chloramphenicol group (209 participants, 2 trials, Analysis 7.7).

3.2. Norfloxacin versus ceftriaxone

One trial involving children, and which did not report the proportion of participants with NaR strains, made this comparison (Huai 2000).

Clinical failure

There was insufficient statistical power to detect a statistically significant difference in clinical failure between the two treatment groups (60 participants, Analysis 8.1).

Relapse

There was insufficient statistical power to detect a statistically significant difference in relapse between the two treatment groups (60 participants, Analysis 8.2).

Fever clearance time

The fever clearance time was statistically significantly higher in the norfloxacin group (MD 48 hours, 95% CI 30.82 to 65.18; 60 participants, Analysis 8.3).

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Adverse events

We did not find a statistically significant difference for non-serious adverse events, which were all gastrointestinal (60 participants, Analysis 8.4; *see* Table 6).

3.3. Norfloxacin versus other fluoroquinolones

Three trials compared norfloxacin with pefloxacin (three trials), ofloxacin (three trials, of which two did not state the proportion of children included in the trials (Xiao 1991; Yang 1991)), or enoxacin (two trials).

Clinical failure

The odds of clinical failure (Analysis 9.1) increased with norfloxacin compared with pefloxacin (OR 30.60, 95% CI 5.75 to 162.86; 200 participants, 3 trials), ofloxacin (OR 28.15, 95% CI 4.80 to 165.14; 123 participants, 3 trials), and enoxacin (OR 4.15, 95% CI 1.77 to 9.76; 142 participants, 2 trials).

Relapse

No relapses were reported for norfloxacin and pefloxacin or enoxacin, and we did not detect a statistically significant difference between ofloxacin and norfloxacin (106 participants, 2 trials, Analysis 9.2).

Fever clearance time

The fever clearance time (Analysis 9.3) was statistically significantly longer in the norfloxacin groups compared with the pefloxacin group (MD 18.83 hours, 95% CI 2.62 to 35.03; 144 participants, 2 trials) and enoxacin group (MD 60.00 hours, 95% CI 33.81 to 86.19; 102 participants, 1 trial). It was also longer compared with ofloxacin in Yang 1991 (MD 69.60 hours, 95% CI 42.03 to 97.17; 56 participants), but not in Xiao 1991 (MD -12.00 hours, 95% CI -40.58 to 16.58; 17 participants). However, the mean difference for Xiao 1991, which contributed data to the pefloxacin and ofloxacin comparisons, could have been underestimated because it was unclear whether the trialists had excluded clinical failures when calculating the mean fever clearance time.

Convalescent faecal carriage

We did not detect any statistically significant difference in convalescent faecal carriage (Analysis 9.4) between norfloxacin and pefloxacin (56 participants, 1 trial), ofloxacin (106 participants, 2 trials), and enoxacin (40 participants, 1 trial).

Adverse events

We did not detect a statistically significant difference in the number of non-serious adverse events (Analysis 9.5), mainly skin rashes (*see* Table 6), between norfloxacin and ofloxacin (56 participants, 1 trial) or enoxacin (102 participants, 1 trial).

4. Different fluoroquinolone durations

4.1. Fluoroquinolones for 2 days versus 3 days

One trial in adults (Nguyen 1997) and two in children (Vinh 1996; Vinh 2005) made this comparison. Although all three trials reported the percentage of participants with NaR strains — 2.5% (Vinh 2005), 5% (Nguyen 1997), and 13% (Vinh 1996) — we were unable to determine its impact on the results because there were so few trials.

Adults

We did not detect a statistically significant difference in clinical failure (100 participants, Analysis 10.1), relapse (50 participants, Analysis 10.3), fever clearance time (100 participants, Analysis 10.4), length of hospital stay (100 participants, Analysis 10.5), or complications (gastrointestinal bleeding, jaundice, and hypotension in the 3-day arm) (100 participants, Analysis 10.7; *see* Table 2). There were no microbiological failures or convalescent faecal carriers.

Children

We did not detect a statistically significant difference in clinical failure (296 participants, 2 trials, Analysis 10.1), microbiological failure (296 participants, 2 trials, Analysis 10.2), relapse (262 participants, 2 trials, Analysis 10.3), fever clearance time (296 participants, 2 trials, Analysis 10.4), length of hospital stay (296 participants, 2 trials, Analysis 10.5), convalescent faecal carriage (262 participants, 2 trials, Analysis 10.6), complications (gastrointestinal bleeding and delirium (296 participants, 2 trials, Analysis 10.7; *see* Table 2), or non-serious adverse events (urticaria in 3-day arm) (296 participants, Analysis 10.8; *see* Table 6). There were no serious adverse events.

4.2. Fluoroquinolones for 3 days versus 5 days

Two trials — one with over 70% children (Tran 1995) and one on adults (Duong 1995) — compared three days with five days of ofloxacin and fleroxacin, respectively. Duong 1995 did not perform NaR testing, while some participants in Tran 1995 had NaR strains, although the precise number of these participants was not available.

Adults

We did not detect a statistically significant difference in clinical failure (63 participants, Analysis 11.1), relapse (40 participants, Analysis 11.2), fever clearance time (663 participants, Analysis 11.3), or length of hospital stay (63 participants, Analysis 11.4). There were no microbiological failures, complications, or serious adverse events in either arm.

Children

We did not detect a statistically significant difference in relapse (154 participants, Analysis 11.2). Fever clearance time was statistically significantly lower in the three-day group (MD -12.00 hours, 95% CI -18.07 to -5.93; 195 participants, Analysis 11.3). There were no statistically significant differences in non-serious

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adverse events, such as insomnia, headache, nausea, vomiting and diarrhoea (228 participants, Analysis 11.5). There were no clinical failures, microbiological failures, convalescent faecal carriers, or serious adverse events in either arm.

4.3. Fluoroquinolones for 5 days versus 7 days

One trial, which did not report the proportion of participants with NaR strains, made this comparison (Unal 1996). There were no clinical failures in either arm, and we did not detect a statistically significant difference in microbiological failure (46 participants, Analysis 12.1), relapse (46 participants, Analysis 12.2), fever clearance time (46 participants, Analysis 12.3), or non-serious adverse events (46 participants, Analysis 12.4; *see* Table 6).

Fluoroquinolone for 7 days versus 10 or 14 days

We defined short-course treatment as seven or less days and long-course treatment as more than seven days. One trial compared perfloxacin for 7 days with 10 days (Kalo 1997), and a multicenter trial compared fleroxacin for 7 days with 14 days (Arnold 1993). Neither trial reported the proportion of participants with NaR strains. We did not detect a statistically significant difference in microbiological failure (87 participants, 2 trials, Analysis 13.1) or relapse (87 participants, 2 trials, Analysis 13.2). There were no clinical failures or convalescent faecal carriers.

Fluoroquinolones for 10 days versus 14 days

One trial, with seven per cent of the participants with NaR strains, made this comparison (Alam 1995). We did not detect a statistically significant difference in relapse (69 participants, Analysis 14.1), fever clearance time (69 participants, Analysis 14.2), or non-serious adverse events (gastrointestinal symptoms, headache and rashes in both arms, and one case of joint pain in the 14-day arm (69 participants, Analysis 14.3; *see* Table 6). There were no clinical or microbiological failures, or convalescent faecal carriers.

DISCUSSION

Even though in endemic areas enteric fever most commonly affects children, this review demonstrates the paucity of data from adequately designed randomized controlled trials in children.

Limitations in analysis and interpretation

The sample sizes in each trial, as well as the number of trials in each comparison, were very small. The pooled sample sizes were also very small, thus there was very little statistical power, and we cannot exclude chance as an explanation for results of many comparisons. The methodological quality and the quality of reporting of the trials were variable and sometimes poor. The method of allocation concealment was unclear in 22 trials, and the method of randomization was unclear in 17 of the 38 trials, meaning they were potentially open to selection bias. We could not perform meaningful sensitivity analyses excluding trials with poor methodological quality due to the small number of trials in each comparison, except for a limited number of comparisons of fluoroquinolones with chloramphenicol.

The small number of trials also precluded the meaningful use of a funnel plot (assessment of publication bias). In the funnel plots generated for primary outcomes for fluoroquinolones versus chloramphenicol, no asymmetry was found for clinical failure, but asymmetry was detected for microbiological failure and relapse. Although interpretation is extremely limited due to the limited number of trials, the asymmetry could indicate the failure to publish smaller trials that did not show any statistically significant difference between older drugs and fluoroquinolones (Stern 1997). However, we conducted a thorough search for trials and also identified an additional two ongoing trials, which we will include in a future update.

Another factor limiting these analyses and interpretation was the lack of explicit definitions of outcomes measured in some trials, especially for relapse, and wide variations in the times at which the outcomes were measured, particularly for microbiological failure and relapse. Some trials did not clearly report whether symptomatic relapse was confirmed by a positive blood culture. Resistance data were also not explicitly reported, particularly in older trials. Four of the 13 trials that compared fluoroquinolones with a first-line agent (chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin) did not report the proportion of participants with MDR strains, and only 13 of 38 trials reported NaR data.

Most of the trials did not explicitly report the number of participants included when measuring fever clearance time. The mean fever clearance times may also be skewed, which means some participants take longer times to clear fever due to a variety of reasons, and a meta-analysis of such arithmetic means may not be entirely accurate. The persistence of fever despite clearance of *S.* Typhi and *S.* Paratyphi from the bloodstream has been attributed to the continued production of pyrogenic cytokines (Islam 1988; Lasserre 1991; Bhutta 1994; Acharya 1995) and may also not be an adequate indicator of antibiotic efficacy.

We did not observe statistically significant heterogeneity in the included trials with the exception of those involving comparisons with norfloxacin and for selected secondary outcomes among some trials, such as in non-serious adverse events with use of a newer fluoroquinolone (gatifloxacin), and length of hospitalization for fluoroquinolones versus chloramphenicol. For the norfloxacin trials, we were unable to explain the observed heterogeneity due to the small number of trials, although the WHO does not recommend norfloxacin for treating enteric fever because of poor oral bioavailability (WHO 2003). Gatifloxacin is a relatively new drug; an ongoing trial of gatifloxacin in enteric fever was temporarily stopped due to safety concerns (ISRCTN53258327).

Applicability

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These meta-analyses included only blood or bone marrow culture-confirmed cases of enteric fever, whereas in most endemic areas, enteric fever is treated on the basis of clinical suspicion without confirmation by culture, owing to the absence of culture facilities. Most trials included adult inpatients. Inpatients represent the severe end of the spectrum of enteric fever. In endemic countries, up to 90% of cases of enteric fever are managed safely in the outpatient setting (Parry 2002). Also, children differ from adults with enteric fever in terms of disease presentation, severity, and complications (Butler 1991; Mahle 1993; Walia 2006). Another factor that may limit applicability in children is the relatively limited data regarding fluoroquinolone pharmacokinetics and adverse effects in this age group (Gendrel 2003; Committee 2006). Thus data obtained from adult inpatients have limited applicability to situations in many parts of the developing world where the vast majority of cases of enteric fever are in children and most of which are treated in the outpatient setting.

The use of fluoroquinolones as first-line antibiotics in such settings has resulted in gross overuse of these antibiotics and high levels of resistance to fluoroquinolone have emerged rapidly in *S.* Typhi and *S.* Paratyphi in countries where fluoroquinolones are used as first-line antibiotics (Biswal 1994; Brown 1994; Rowe 1995; Murdoch 1998; Chandel 2000; Chandel 2001; Threlfall 2001; Butt 2003; Threlfall 2003; Karunanayake 2004; Slinger 2004; Butt 2005; Manchanda 2006; Mohanty 2006; Walia 2006; Chau 2007; Joshi 2007).

Impact of resistance strains

The changing pattern of resistance, including rapidly rising resistance to fluoroquinolones, also affects the applicability of these results - particularly for older fluoroquinolones, such as ofloxacin. In one recent trial that included mainly children with a very high proportion of NaR strains, ofloxacin had significantly higher number of clinical failures (Parry 2007). We conducted sensitivity analyses to determine the impact of excluding trials with NaR or MDR strains, and those trials that did not report the proportion of participants with NaR or MDR strains. However, the analyses were mostly uninformative owing to lack of statistical power. Newer fluoroquinolones (such as gatifloxacin) are not affected by NaR strains (Pandit 2007; Dolecek 2008), and two trials with NaR strains but which used gatifloxacin were considered separately, where possible, from trials of older fluoroquinolones that reported NaR strains. More meaningful sensitivity analyses involving different proportions of strains with resistance to fluoroquinolones may be possible in future updates of this review.

Fluoroquinolones versus first-line antibiotics (chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin) in children

We are unable to draw conclusions about the use of fluoroquinolones compared to first-line drugs in children as we did not find any trials involving these comparisons.

Fluoroquinolones versus second-line drugs (azithromycin, ceftriaxone, and cefixime) in children

There were very limited data for these comparisons, and thus no firm conclusions can be made. One small, open trial with adequate methods of randomization and allocation concealment compared fluoroquinolone with cefixime (Cao 1999). The trial showed that fluoroquinolones were not significantly different from cefixime for all the primary outcomes studied (clinical failure, microbiological failure, and relapse), although confidence intervals were very wide. Fluoroquinolones were significantly better than cefixime in reducing fever clearance times.

An open trial published in 2007, which had adequate methods of randomization and allocation concealment, involved mostly children, and had a high proportion of NaR strains, found that ofloxacin administered for seven days had significantly higher clinical failure and fever clearance times compared with azithromycin (Parry 2007). Another trial, published in 2008 (Dolecek 2008), which also had adequate methodological quality, found no statistically significant differences between a newer fluoroquinolone (gatifloxacin) and azithromycin, although confidence intervals were very wide.

One trial that could not be included in this review compared ofloxacin and ceftriaxone in children (Kumar 2007). The only results presented were mean fever clearance times, which were significantly different in the ofloxacin group compared to the ceftriaxone group (4.97 vs 4.26 days, $P < 0.05$); other details, such as the number of participants in each group and number of strains with reduced susceptibility to fluoroquinolones, were not specified.

Fluoroquinolones versus first-line antibiotics (chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin) in adults

The sample sizes in these trials were very small and confidence intervals were very wide. Among 10 trials comparing fluoroquinolones with chloramphenicol, only two open trials reported using adequate methods of randomization and allocation concealment, and lost no participants during the short-term follow up (Gasem 2003; Phongmany 2005). We found fluoroquinolones to be better than chloramphenicol for reducing the odds of relapse. However, most trials were also of low methodological quality and did not explicitly report the definition, or the culture site used to confirm symptomatic relapse, or both. We did not find any significant difference between fluoroquinolones and chloramphenicol for relapses clearly confirmed by blood cultures, although this was based on only one trial with low statistical power and low methodological quality. We found fluoroquinolones to be better in reducing fever clearance time and duration of hospitalization including in trials of adequate methodological quality. Clinical failure and microbiological failure were comparable between the two groups although the confidence intervals were wide.

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We did not detect a statistically significant difference between fluoroquinolones and co-trimoxazole for any measured outcome in adults, but statistical power was very low and only one of the two open trials had adequate method of randomization, as well as allocation concealment and follow up (Hajji 1988). We found fluoroquinolones to be significantly better than amoxicillin or ampicillin for clinical and microbiological failure. However, neither of the two included trials reported the proportion of participants with MDR strains. One trial report was an abstract with limited information (Flores 1994), and the other was of low methodological quality (an open trial that had inadequate randomization and allocation concealment, and included less than 90% of the participants in the analysis) (Yousaf 1992). Thus both may have been open to selection bias, which may have operated in favour of the newer fluoroquinolones.

Fluoroquinolones versus second-line drugs (azithromycin, ceftriaxone, and cefixime) in adults

Fluoroquinolones were not significantly different from azithromycin for any primary outcome in inpatients. However, the confidence intervals were wide because only two small trials contributed data, although both used adequate methods of randomization and allocation concealment. The higher number of clinical failures observed in the fluoroquinolone group in one of these trials, Chinh 2000, could be due to a high proportion (> 50%) of participants infected with NaR strains.

Fluoroquinolones were associated with a significant and large reduction in the odds of clinical failure and fever clearance time compared with ceftriaxone, based on three small open trials involving inpatients (Wallace 1993; Smith 1994; Tran 1994). Two of these trials used an adequate method of randomization and allocation concealment (Smith 1994; Tran 1994). We did not find a statistically significant difference between the antibiotics for any other measured outcomes, although confidence intervals were wide, and we could not assess the impact of NaR strains on these results meaningfully.

We found results in favour of fluoroquinolones for clinical failure and relapse as well as fever clearance time from two trials comparing cefixime and a fluoroquinolone (Pandit 2007; Yu 1998), although one was of low methodological quality and did not report NaR strains. One of these trials used a newer fluoroquinolone active against NaR strains (Pandit 2007).

Comparison with past reviews

The results of this systematic review differ from those of an earlier summary of 57 randomized controlled trials of enteric fever, 10 of which compared a fluoroquinolone with a non-fluoroquinolone antibiotic (Parry 2002). Parry 2002, which did not use meta-analytic techniques, reported that clinical failures and fever clearance times with fluoroquinolone therapy were lower compared with first-line antibiotics, ceftriaxone, and cefixime. In our meta-analyses of 23 randomized controlled trials comparing fluoroquinolones with different antibiotics and which separated trials on children and adults, we found most trials to be of low methodological quality and lacking in statistical power, with wide confidence intervals. Hence, no conclusive evidence of superiority of fluoroquinolones over first-line antibiotics (chloramphenicol, co-trimoxazole, and ampicillin or amoxicillin) could be made for clinical failure. There is, however, better evidence to suggest that fever clearance times are lower with fluoroquinolones compared to chloramphenicol in adults. For comparisons of fluoroquinolones with ceftriaxone and cefixime, as mentioned above, we found clinical failures to be lower and fever clearance times also shorter with fluoroquinolones. However, these results are based on few trials, including some of low methodological quality, and mainly on data from adults.

Cost of therapy

In this review, we could not compare the cost of fluoroquinolone therapy in relation to other antibiotics because all but Girgis 1999 and Pandit 2007 did not report these data. In most low-income countries, fluoroquinolones are available at a much higher cost than first-line antibiotics; for example, in Pakistan, a 10-day course of ciprofloxacin costs approximately 1.5 times (local brand) to up to five times (international brand) that of a conventional 14-day course of chloramphenicol (retail prices of several brands in Karachi, Pakistan). The cost of a shorter (three-day) course of ciprofloxacin, however, ranges from less than half to 1.5 times greater than a 14-day chloramphenicol regimen; only one trial made this comparison (Phongmany 2005). Fluoroquinolones may be the least costly option for the treatment of MDR enteric fever compared with costs of azithromycin, cefixime, and ceftriaxone (retail prices of several brands in Karachi, Pakistan), but increasing numbers of clinical failures in trials with NaR strains with older fluoroquinolones (Chinh 2000; Parry 2007) suggest that this cost advantage of using older fluoroquinolones has been overwhelmed by declining efficacy in the face of rising resistance. Rising levels of resistance could in the near future also affect the efficacy of newer generation fluoroquinolones (Turner 2006).

Different fluoroquinolones

Among various fluoroquinolones, we found all three classes analysed (pefloxacin, ofloxacin, and enoxacin) to be significantly superior compared with norfloxacin for reducing clinical failure. These trials originated largely from China, and none specified the method of randomization, allocation concealment, blinding, or follow up, and thus we deemed them to be of low methodological quality.

Different durations of fluoroquinolone therapy

A large number of different durations were compared in several trials. The number of trials for each comparison was small, mostly with small sample sizes and hence lacking considerably in statistical power. Only two trials compared a short-course regimen (seven

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days or less) with a long-course regimen (more than seven days). Clinical failure, microbiological failure, and relapse rates were low in both arms, but the data were not sufficient to enable us to exclude chance as an explanation for these findings.

Adverse events

A serious adverse event was reported in three instances (anaphylaxis in ceftriaxone group, severe leucopenia in chloramphenicol group, and a rash in the ciprofloxacin group). Overall, few participants reported adverse events. These were mainly abdominal symptoms, such as nausea or vomiting, abdominal pain, or rashes; however, a trial involving a newer fluoroquinolone (gatifloxacin) reported a statistically significantly larger number of participants with nausea and vomiting when compared to the non-fluoroquinolone arm. Mild joint pain was reported in one case in a 14-day fluoroquinolone group. One child in each arm (fluoroquinolone and azithromycin arm) of a trial reported temporary joint discomfort. The maximum period of follow up was six months (two trials), thus most trials could not adequately address long-term adverse effects, particularly on growing joints.

AUTHORS' CONCLUSIONS

Implications for practice

A lack of data precludes firm conclusions to be made regarding superiority of fluoroquinolones over first-line antibiotics (chloramphenicol, ampicillin, amoxicillin), cefixime, or ceftriaxone in children. Data from one trial suggest that azithromycin may be better than ofloxacin (an older fluoroquinolone) in children infected with a high proportion of strains with reduced susceptibility to fluoroquinolones. We did not find any statistically significant differences in primary outcomes in one trial of azithromycin and gatifloxacin (a new-generation fluoroquinolone) in children.

In adult inpatients, data suggest that fluoroquinolones may be better than chloramphenicol for reducing clinical relapse. Limited data from adults suggest that fluoroquinolones may also be better than ceftriaxone for reducing clinical failure, and may be better than cefixime for reducing clinical failure and relapse. We did not find any statistically significant differences in primary comparisons of azithromycin and older fluoroquinolones in adults.

No conclusions could be made for superiority of any particular duration of fluoroquinolone therapy.

No conclusions can be made regarding adverse effects in children, owing to the short length of follow up in most of these trials, and few trials involving children.

Implications for research

Appropriate therapy for enteric fever remains a clinical and public health dilemma. High prevalence of resistance to first-line antibiotics (MDR strains) and rapid emergence of resistance to fluoroquinolones among *S.* Typhi and *S.* Paratyphi have added to the complexity of this issue in resource-constrained environments.

More evidence is required in the form of larger or multicentred well-designed and adequately powered trials of fluoroquinolones in children, particularly in outpatient settings with adequate follow up and monitoring of adverse events.

To prevent inappropriate use of fluoroquinolones in children with prolonged fever, a step-wise approach to determining the cause of such fever in children and appropriate guidelines for management must be developed and evaluated in outpatient settings in areas endemic for enteric fever. Close monitoring of resistance patterns as well as check on indiscriminate use of alternate agents is needed.

Combination therapy may also reduce the rate of development of resistance in *S.* Typhi and *S.* Paratyphi, and could also be evaluated further in trial settings. Newer fluoroquinolones, such as gatifloxacin, may have efficacy against NaR strains; however more evidence is needed, including an investigation in tolerance and safety profile.

Trialists must improve both the methodological quality of randomized controlled trials and explicitly document the methods they use to minimize selection and observeration bias, including the use of double blinding.

Trialists should also standardize definitions of primary outcomes and the time points at which these are measured, including quantification of strains with reduced susceptibility to fluoroquinolones and other study drugs (including proportion of isolates with high MICs for fluoroquinolones, and proportion of MDR and NaR strains for each study arm).

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Abejar 1993

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	30 analysed[a]: 15 in fleroxacin group; 15 in chloramphenicol group Adult inpatients Inclusion criteria: clinical with blood culture positive Exclusion criteria: children and culture negative
Interventions	1. Fleroxacin (400 mg oral once daily for 10 days) 2. Chloramphenicol (50 mg/kg/day in 3 divided doses every 8 hours for 14 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time (no SD) 5. Other adverse events
Notes	Location: Philippines Date: not reported Severity of illness at entry: not reported

Alam 1995

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 64/72 (88.9%)
Participants	69 analysed[a]: 35 in 10-day group: 34 in 14-day group Adults (18 to 65 years) and 11 children (< 18 years) Both outpatients and inpatients (ciprofloxacin 10-day group had 20 outpatients and 14 inpatients, ciprofloxacin 14-day group had 21 outpatients and 14 inpatients) Inclusion criteria: blood or bone marrow culture positive for *S*. Typhi or *S*. Paratyphi Exclusion criteria: hypersensitivity to quinolones; severe renal disease; pregnant or lactating; patients < 18 years were randomized only if had MDR strain
Interventions	1. Ciprofloxacin (500 mg oral twice daily for 10 days) 2. Ciprofloxacin (500 mg oral twice daily for 14 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse

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Alam 1995 (*Continued*)

	4. Fever clearance time 5. Convalescent faecal carriage 6. Serious adverse events 7. Other adverse events
Notes	Location: Bangladesh Date: 1992-3 Severity of illness at entry: not reported

Arnold 1993

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	91 analysed[a]: 24 in the fluoroquinolone 7-day group; 33 in the fluoroquinolone 14-day group; 34 in the chloramphenicol group Adult inpatients aged 18 to 65 years Inclusion criteria: clinical Exclusion criteria: fever > 14 days; signs of typhoid fever > 21 days before enrolment; pregnant or lactating; hypersensitivity to chloramphenicol; nalidixic acid and its derivatives; history of cerebral disorders; severe concomitant disease; concomitant antimicrobial treatment
Interventions	1. Fleroxacin (400 mg oral once daily for 7 days) 2. Fleroxacin (400 mg oral once daily for 14 days) 3. Chloramphenicol (50 mg/kg/day oral for 14 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time (time to event) 5. Convalescent faecal carriage
Notes	Location: multicentre; country names not reported, but authors' affiliations were Brazil, Mexico, Korea, Indonesia, and Ivory Coast Date: not available Severity of illness at entry: major complications were excluded

Bai 1995

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%

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Bai 1995 (*Continued*)

Participants	102 analysed[a]: 52 in enoxacin group; 50 in norfloxacin group Adult inpatients aged 17 to 64 years Inclusion criteria: clinical with blood or bone marrow culture positive for *S.* Typhi Exclusion criteria: not mentioned
Interventions	1. Enoxacin (300 mg oral twice daily for 10 days or 3 to 5 days after afebrile) 2. Norfloxacin (200 mg oral 3 to 4 times a day for 14 days or 3 to 5 days after afebrile)
Outcomes	1. Clinical failure 2. Fever clearance time 3. Complications 4. Serious adverse events 5. Other adverse events
Notes	Location: China (Chinese language) Date: 1989-94 Severity of illness at entry: not reported

Bran 1991

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: double Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	102 analysed[a]: 51 in ciprofloxacin group; 51 in chloramphenicol group; only the total number of participants (102) was provided, but we assumed 51 in each group Age not mentioned (adult dosages used); most probably inpatients Inclusion criteria: blood and/or bone marrow culture positive for *S.* Typhi Exclusion criteria: not reported
Interventions	1. Ciprofloxacin (500 mg oral twice daily for 10 days) 2. Chloramphenicol (750 mg oral every 6 hours for 14 days)
Outcomes	1. Microbiological failure 2. Fever clearance time (no SD) 3. Convalescent faecal carriage 4. Serious adverse events 5. Other adverse events
Notes	Location: Guatemala Date: not reported Severity of illness at entry: not reported Conference abstract

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Cao 1999

Methods	Generation of allocation sequence: computer-generated Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 40/82 (49%)
Participants	82 analysed[a]: 38 in ofloxacin group; 44 in cefixime group Children inpatients aged < 15 years Inclusion criteria: fever and no obvious source of infection for > 7 days or < 7 days if family history of typhoid fever Exclusion criteria: severe disease; hypersensitivity to quinolones or third-generation cephalosporins; received either drug during this illness; or responded to ampicillin, chloramphenicol, or co-trimoxazole
Interventions	1. Ofloxacin (10 mg/kg/day oral in 2 divided doses for 5 days) 2. Cefixime (20 mg/kg/day oral in 2 divided doses for 7 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization 7. Convalescent faecal carriage 8. Serious adverse events 9. Other adverse events
Notes	Location: Vietnam Date: 1995-6 Severity of illness at entry: all uncomplicated Author provided further information

Chinh 2000

Methods	Generation of allocation sequence: computer-generated Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 38/91(42%)
Participants	88 analysed[a]: 44 in ofloxacin group; 44 in azithromycin group Adult inpatients aged ≥ 15 years Inclusion criteria: clinical with blood culture positive for *S.* Typhi or *S.* Paratyphi Exclusion criteria: severe or complicated disease; significant underlying disease; hypersensitivity to either trial drug; pregnant; history of treatment with fluoroquinolone or third-generation cephalosporins or macrolides within 1 week of admission
Interventions	1. Ofloxacin (200 mg oral twice daily for 5 days at 8 mg/kg/day) 2. Azithromycin (1 g oral daily for 5 days at 20 mg/kg/day)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse

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Chinh 2000 (*Continued*)

	4. Fever clearance time (mean and 95% confidence intervals; SD calculated by review author) 5. Complications 6. Length of hospitalization (mean and 95% confidence interval; SD calculated by review author) 7. Convalescent faecal carriage 8. Serious adverse events 9. Other adverse events (number of events stated)
Notes	Location: Vietnam Date: not available Severity of illness at entry: all uncomplicated Author provided further information

Cristiano 1995

Methods	Generation of allocation sequence: computer-generated Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	60 analysed[a]: 30 in pefloxacin group; 30 in chloramphenicol group Adult inpatients aged 17 to 64 years Inclusion criteria: severe culture-positive typhoid sepsis Exclusion criteria: received drug active against *S.* Typhi
Interventions	1. Pefloxacin (1200 mg intravenous in 3 divided doses every 8 hours for 5 days, then oral for 10 days) 2. Chloramphenicol (2 g oral in 4 divided doses every 6 hours for 15 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time (no SD) 5. Convalescent faecal carriage 6. Length of hospitalization (no SD) 7. Serious adverse events 8. Other adverse events
Notes	Location: Italy Date: 1991-3 Severity of illness at entry: all severe

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Dolecek 2008

Methods	Generation of allocation sequence: computer-generated, block randomization Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 268/288 (93%)
Participants	285 analysed[a]: 145 in gatifloxacin group; 140 in azithromycin group Adult and children inpatients aged 1 to 41 years (210/287 (73%) participants below the age of 15 years) Inclusion criteria: clinical or culture-positive enteric fever Exclusion criteria: no consent; pregnancy; age < 6 months; history of hypersensitivity to either of the trial drugs; any signs of severe typhoid fever or previous reported treatment with a fluoroquinolone antibiotics; a third-generation cephalosporin or macrolide antibiotic within 1 week before to hospital admission
Interventions	1. Gatifloxacin (10 mg/kg/day oral once daily for 7 days) 2. Azithromycin (20 mg/kg/day oral once daily for 7 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization 7. Convalescent faecal carriage 8. Serious adverse events 9. Other adverse events
Notes	Location: Vietnam (multi-centre, 3 hospitals) Date: 2004-5 Severity of illness at entry: all uncomplicated Received as an unpublished trial (with additional data), but reference updated to current citation upon publication

Duong 1995

Methods	Generation of allocation sequence: random-number table Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 40/63 (63%)
Participants	63 analysed[a]: 22 in 3-day group; 41 in 5-day group Adult inpatients aged 15 to 65 years Inclusion criteria: clinical Exclusion criteria: pregnant or lactating; hypersensitivity to nalidixic acid and derivatives; history of cerebral disorders; severe concomitant disease; complications of enteric fever; received any fluoroquinolone in previous week
Interventions	1. Fleroxacin (400 mg oral once daily for 3 days) 2. Fleroxacin (400 mg oral once daily for 5 days)
Outcomes	1. Clinical failure 2. Microbiological failure

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Duong 1995 (*Continued*)

	3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization 7. Serious adverse events 8. Other adverse events (number of events stated)
Notes	Location: Vietnam Date: 1993-4 Severity of illness at entry: all uncomplicated Author provided further information

Flores 1994

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	40 analysed[a]: 20 in ofloxacin group; 20 in ampicillin group Adults (abstract keyword); most probably inpatients Inclusion criteria: clinical with culture positive Exclusion criteria: not reported
Interventions	1. Ampicillin (1 g every 6 hours for 10 days) 2. Ofloxacin (400 mg every 12 hours for 10 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Serious adverse events
Notes	Location: Mexico Date: not reported Severity of illness at entry: not reported Abstract only

Gasem 2003

Methods	Generation of allocation sequence: random-number table Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	55 analysed[a]: 28 in ciprofloxacin group; 27 in chloramphenicol group Adult inpatients Inclusion criteria: clinical and $\geq$ 14 years Exclusion criteria: severe complications; treatment with chloramphenicol, ciprofloxacin, other fluoroquinolones before admission; history of allergy to chloramphenicol/quinolone; malaria or other infection; white blood cell count

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Gasem 2003 (*Continued*)

	< 2000/mL; pregnant or lactating
Interventions	1. Ciprofloxacin (500 mg twice daily for 7 days) 2. Chloramphenicol (500 mg oral 4 times a day for 14 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization 7. Serious adverse events 8. Other adverse events
Notes	Location: Indonesia Date: not reported Severity of illness at entry: none had severe complications on enrolment

Girgis 1999

Methods	Generation of allocation sequence: random-number list, block randomization Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	64 analysed[a]: 28 in ciprofloxacin group; 36 in azithromycin group Adult inpatients aged > 18 years Inclusion criteria: clinical Exclusion criteria: pregnant or lactating; allergy to ciprofloxacin or erythromycin/other macrolides; those with complications of typhoid fever; inability to swallow medications; significant underlying illness; treatment within past 4 days with an antibiotic with potential efficacy against *S*. Typhi
Interventions	1. Ciprofloxacin (500 mg oral twice daily for 7 days) 2. Azithromycin (1 g oral once daily for the first day followed by oral 500 mg once daily for total duration of 7 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization 7. Cost of treatment 8. Convalescent faecal carriage 9. Serious adverse events 10. Other adverse events (number of events stated)

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Girgis 1999 (*Continued*)

Notes	Location: Egypt Date: 1997-8 Severity of illness at entry: all uncomplicated Author provided further information

Gottuzzo 1992

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: double Inclusion of all randomized culture-positive participants in the final analysis: 95/98 (97%)
Participants	98 analysed[a]: 49 in ciprofloxacin group; 49 in chloramphenicol group Adult inpatients Inclusion criteria: clinical with culture positive for *S.* Typhi or *S.* Paratyphi
Interventions	1. Ciprofloxacin (500 mg oral every 12 hours for 10 days) 2. Chloramphenicol (750 mg oral every 6 hours for 14 days)
Outcomes	1. Clinical failure 2. Relapse
Notes	Location: not available Date: not available Severity of illness at entry: not reported

Hajji 1988

Methods	Generation of allocation sequence: random-number table Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	42 analysed[a]: 24 in pefloxacin group; 18 in co-trimoxazole group Adult inpatients aged > 16 years Inclusion criteria: clinical Exclusion criteria: not reported
Interventions	1. Pefloxacin (400 mg oral twice daily for 14 days) 2. Co-trimoxazole (160/800 mg oral twice daily for 14 days) 5 participants were given intravenous pefloxacin for mean 4.8 days; 4 were given intramuscular co-trimoxazole for mean 6 days
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time (no SD, non-exact P value)

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Hajji 1988 (*Continued*)

	5. Complications 6. Convalescent faecal carriage 7. Serious adverse events 8. Other adverse events
Notes	Location: Morocco Date: 1984-5 Severity of illness at entry: comatose or neurological disorders in 3 participants in pefloxacin group and 2 participants in co-trimoxazole group Author provided further information

Huai 2000

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	60 analysed[a]: 30 in norfloxacin group; 30 in ceftriaxone group Children inpatients Inclusion criteria: clinical with blood or bone marrow positive for *S.* Typhi Exclusion criteria: not mentioned
Interventions	1. Norfloxacin (10 to 20 mg/kg/day oral divided in 2 times per day until afebrile, no drug for 5 days, and administer again for 5 days) 2. Ceftriaxone (100 mg/kg/day intravenous until afebrile, no drug for 5 days, and administer again for 5 days)
Outcomes	1. Clinical failure 2. Relapse 3. Fever clearance time 4. Other adverse events
Notes	Location: China (Chinese language) Date: 1995-8 Severity of illness at entry: norfloxacin group had 7 participants with liver damage and 4 with myocardial damage; and ceftriaxone group had 8 participants with liver damage and 3 with myocardial damage

Jia 1994

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: double Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	130 analysed[a]: 63 in pefloxacin group; 67 in norfloxacin group Age not mentioned (adult dosages used); inpatients Inclusion criteria: clinical with culture positive blood or bone marrow for *S.* Typhi Exclusion criteria: not mentioned

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Jia 1994 (*Continued*)

Interventions	1. Pefloxacin (400 mg plus placebo oral twice daily for 10 to 14 days) 2. Norfloxacin (300 mg plus placebo oral 3 times a day for 10 to 14 days)
Outcomes	1. Clinical failure 2. Fever clearance time 3. Complications 4. Serious adverse events
Notes	Location: China (Chinese language) Date: 1991-2 Severity of illness at entry: not reported Both groups in Jia 1994 were the same as Weng 1996. Weng 1996 did not report use of placebo as Jia 1994 did. Weng 1996 also included other groups. Due to the ambiguity surrounding the use of placebo in the norfloxacin group, we decided to make Jia 1994 the primary reference because the methodology was clearer in this publication

Kalo 1997

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	30 analysed[a]: 15 in 7-day group; 15 in 10-day group Adult inpatients aged 16 to 42 years Inclusion criteria: blood-culture positive; ampicillin-resistant *S.* Typhi Exclusion criteria: received quinolones within 2 weeks before hospitalization
Interventions	1. Perfloxacin (400 mg oral twice daily for 7 days) 2. Perfloxacin (400 mg oral twice daily for 10 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Convalescent faecal carriage 5. Serious adverse events
Notes	Location: Albania Date: 1992-4 Severity of illness at entry: not reported

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Limson 1989

Methods	Generation of allocation sequence: random-number table Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	40 analysed[a]: 20 in ciprofloxacin group; 20 in co-trimoxazole group Adult inpatients aged 18 to 77 years Inclusion criteria: clinical Exclusion criteria: complications; drug allergy; renal impairment
Interventions	1. Ciprofloxacin (500 mg oral twice daily for 10 days) 2. Co-trimoxazole (160/800 mg oral twice daily for 14 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Serious adverse events 4. Other adverse events
Notes	Location: Philippines Date: not reported Severity of illness at entry: all uncomplicated

Morelli 1992

Methods	Generation of allocation sequence: computer-generated Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	156 analysed[a]: 30 each in ofloxacin and chloramphenicol groups; 36 in pefloxacin group; 20 each in ciprofloxacin, enoxacin, and norfloxacin groups Adult inpatients aged 16 to 60 years Inclusion criteria: blood culture positive for *S*. Typhi; high fever for not more than 5 days; toxic symptomatology Exclusion criteria: hypersensitivity or allergy to fluoroquinolone or antibiotic treatment
Interventions	1. Ofloxacin (300 mg oral every 8 hours for 15 days) 2. Pefloxacin (400 mg oral every 8 hours for 15 days) 3. Ciprofloxacin (500 mg oral every 8 hours for 15 days) 4. Enoxacin (300 mg oral every 8 hours for 15 days) 5. Norfloxacin (400 mg oral every 8 hours for 15 days) 6. Chloramphenicol (500 mg oral every 6 hours for 15 days)
Outcomes	1. Clinical failure 2. Relapse 3. Fever clearance time (no SD) 4. Convalescent faecal carriage 5. Other adverse events (number of events stated)

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Morelli 1992 (*Continued*)

Notes	Location: Italy Date: 1985-90 Severity of illness at entry: not reported We prepared different comparisons with these data: a combination of all 5 fluoroquinolone groups vs the chloramphenicol group; and norfloxacin vs ofloxacin, pefloxacin, and enoxacin

Nalin 1987

Methods	Generation of allocation sequence: randomized numbers Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	169 analysed[a]: 90 in norfloxacin group; 79 in chloramphenicol group Age not mentioned (adult dosages used); most probably inpatients Inclusion criteria: clinical Exclusion criteria: pregnant; prior antibiotic
Interventions	1. Chloramphenicol (500 mg every 4 to 6 hours for 14 days) 2. Norfloxacin (400 mg every 8 hours for 14 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Fever clearance time 4. Convalescent faecal carriage 5. Other adverse events
Notes	Location: multicentre in Chile, Guatemala, Mexico, and Peru Date: not reported Severity of illness at entry: all uncomplicated

Nguyen 1997

Methods	Generation of allocation sequence: block randomization Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 49/101 (49%)
Participants	100 analysed[a]: 47 in 2-day group; 53 in 3-day group Adult inpatients aged > 15 years Inclusion criteria: clinical Exclusion criteria: pregnant; severe disease requiring intensive care; known hypersensitivity to quinolones; received treatment with quinolones in the week before admission or responded to ampicillin, chloramphenicol, or co-trimoxazole
Interventions	1. Ofloxacin (15 mg/kg/day oral for 2 days) 2. Ofloxacin (10 mg/kg/day oral for 3 days)

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Nguyen 1997 (*Continued*)

Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization 7. Convalescent faecal carriage 8. Serious adverse events
Notes	Location: Vietnam Date: 1993-5 Severity of illness at entry: all uncomplicated Author provided further information

Pandit 2007

Methods	Generation of allocation sequence: computer-generated, block randomization Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 147/169 (87%)
Participants	158 analysed[a]: 88 in gatifloxacin group; 70 in cefixime group Adults and children outpatients aged 2.75 to 50 years (60/169 (35.5%) were children aged < 14 years) Inclusion criteria: clinical Exclusion criteria: not residing 2.5 km radius from hospital; age not between 2 to 65 years; not willing to give informed consent; not able to take oral medications; pregnant or lactating; history of seizures; not able to stay in city for treatment duration; known contraindication to cephalosporins or fluoroquinolones; complicated typhoid fever or received third-generation cephalosporins, fluoroquinolones, or macrolide in week before presentation to clinic
Interventions	1. Gatifloxacin (10 mg/kg/day in single dose oral for 7 days) 2. Cefixime (20 mg/kg/day in 2 divided doses oral for 7 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Convalescent faecal carriage 6. Complications 7. Serious adverse events 8 Other adverse events
Notes	Location: Nepal Date: 2005 Severity of illness at entry: all uncomplicated Author provided further information

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Parry 2007

Methods	Generation of allocation sequence: computer-generated Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 114/130 (88%)
Participants	125 analysed[a]: 63 in ofloxacin group; 62 in azithromycin group Adults and children inpatients 3 to 42 years (87% (163/187) were children < 15 years for all three arms) Inclusion criteria: clinical Exclusion criteria: severe or complicated disease; inability to swallow oral medications; history of significant underlying disease or hypersensitivity to either of trial drugs; pregnant or lactating; history of treatment with fluoroquinolones or expanded spectrum cephalosporins; macrolide within 1 week of hospital admission
Interventions	1. Ofloxacin (20 mg/kg/day in 2 divided doses oral for 7 days) 2. Azithromycin (10 mg/kg/day once a day oral for 7 days) Comparison not included in this review: 3. Ofloxacin-azithromycin (15 mg/kg/day in 2 divided doses oral ofloxacin for 7 days and 10 mg/kg/day once a day oral azithromycin for first 3 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time (mean and 95% confidence intervals; SD calculated by review author) 5. Complications 6. Length of hospitalization (mean and 95% confidence intervals; SD calculated by review author) 7. Convalescent faecal carriage 8. Serious adverse events 9. Other adverse events (numbers not stated)
Notes	Location: Vietnam Date: 1998-2002 Severity of illness at entry: all uncomplicated Author provided further information

Phongmany 2005

Methods	Generation of allocation sequence: random-number table, block randomization Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 48/50 (96%)
Participants	50 analysed[a]: 27 in ofloxacin group; 23 in chloramphenicol group Adult inpatients aged > 15 years Inclusion criteria: clinical or blood culture positive typhoid fever Exclusion criteria: age ≤15 years; pregnant; lactating; not able to take oral medication; not willing to give informed consent; not able to stay in hospital for the duration of treatment; known to have contraindications to chloramphenicol or ofloxacin; severe typhoid fever; or intractable vomiting

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Phongmany 2005 (*Continued*)

Interventions	1. Ofloxacin (15 mg/kg/day in 2 divided doses oral for 3 days) 2. Chloramphenicol (50 mg/kg/day oral in 4 divided doses for 14 days)
Outcomes	1. Clinical failure 2. Fever clearance time 3. Complications 4. Length of hospitalization 5. Serious adverse events 6. Other adverse events
Notes	Location: Laos Date: 2001-3 Severity of illness at entry: all uncomplicated Author provided further information

Quintero 1988

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: double Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	26 analysed[a]: 13 in ciprofloxacin group; 13 in chloramphenicol group Age not mentioned (adult dosages used); most probably inpatients Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	1. Ciprofloxacin (750 mg oral 3 times a day for unknown duration) 2. Chloramphenicol (750 mg oral 4 times a day for unknown duration)
Outcomes	1. Clinical failure 2. Fever clearance time 3. Serious adverse events
Notes	Location: Mexico Date: not reported Severity of illness at entry: not reported Conference abstract

Sarma 1991

Methods	Generation of allocation sequence: randomized numbers Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%

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Sarma 1991 (*Continued*)

Participants	40 analysed[a]: 20 participants in norfloxacin group; 20 participants in chloramphenicol group Adult inpatients aged 17 to 32 years Inclusion criteria: clinical with blood-culture positive for *S*. Typhi or *S*. Paratyphi Exclusion criteria: complications of typhoid fever; pregnancy; previous antibiotic; known allergy to norfloxacin or chloramphenicol
Interventions	1. Norfloxacin (400 mg oral every 12 hours for 7 days) 2. Chloramphenicol (60 mg/kg/day oral in 4 divided doses until afebrile then 40 mg/kg/day in 3 divided doses to complete 14 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization 7. Convalescent faecal carriage 8. Serious adverse events 9. Other adverse events
Notes	Location: India Date: 1990 Severity of illness at entry: all uncomplicated Author provided further information

Smith 1994

Methods	Generation of allocation sequence: computer-generated Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 50%
Participants	47 analysed[a]: 22 in ofloxacin group; 25 in ceftriaxone group Adult inpatients aged 15 to 63 years Inclusion criteria: clinical or culture positive for enteric fever Exclusion criteria: hypersensitivity to beta-lactam antibiotics or quinolones; previous treatment with broad-spectrum cephalosporins or quinolone within 1 week of hospital admission; those who responded to ampicillin, chloramphenicol, or co-trimoxazole
Interventions	1. Ofloxacin (200 mg oral every 12 hours for 5 days) 2. Ceftriaxone (3 g intravenous once a day for 3 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization (mean and range)

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Smith 1994 (*Continued*)

	7. Convalescent faecal carriage 8. Serious adverse events 9. Other adverse events
Notes	Location: Vietnam Date: 1992-3 Severity of illness at entry: all uncomplicated Author provided further information

Tran 1994

Methods	Generation of allocation sequence: computer-generated Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 15/31 (48.4%)
Participants	31 analysed[a]: 16 in fleroxacin group; 15 in ceftriaxone group Adult inpatients aged ≥ 16 years Inclusion criteria: clinical with a negative malaria blood film
Interventions	1. Fleroxacin (400 mg oral for 7 days) 2. Ceftriaxone (2 g intravenous for 5 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Convalescent faecal carriage 7. Serious adverse events
Notes	Location: Vietnam Date: 1992-3 Severity of illness at entry: all uncomplicated Author provided further information

Tran 1995

Methods	Generation of allocation sequence: computer-generated Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 50% (114/228)
Participants	228 analysed[a]: 118 in 3-day group; 110 in 5-day group Adults and children outpatients (180 culture positive were aged < 17 years) Inclusion criteria: clinical Exclusion criteria: unable to take oral medications due to vomiting; severe disease; shock; impaired consciousness; bleeding; peritonitis; pregnant; neonates; received a fluoroquinolone

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Tran 1995 (*Continued*)

Interventions	1. Ofloxacin (15 mg/kg/day oral for 3 days) 2. Ofloxacin (10 mg/kg/day oral for 5 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Convalescent faecal carriage 6. Serious adverse events 7. Other adverse events
Notes	Location: Vietnam Date: 1993-3 Severity of illness at entry: all uncomplicated Author provided further information

Unal 1996

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	46 analysed[a]: 22 in 5-day group; 24 in 7-day group Adult inpatients aged > 16 years Inclusion criteria: febrile disease; 1 or more blood and/or bone marrow culture positive for *Salmonella* species Exclusion criteria: age < 16 years; pregnant or lactating; jaundice; hepatic failure; antibiotics in the last 2 weeks
Interventions	1. Pefloxacin (400 mg oral twice daily for 5 days) 2. Pefloxacin (400 mg oral twice daily for 7 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Convalescent faecal carriage 6. Serious adverse events 7. Other adverse events
Notes	Location: Turkey Date: 1992-4 Severity of illness at entry: not reported

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Vinh 1996

Methods	Generation of allocation sequence: computer-generated Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 26/100 (26%)
Participants	100 analysed[a]: 53 in 2-day group; 47 in 3-day group Children inpatients aged 1 to 15 years Inclusion criteria: clinical or blood culture positive for *S.* Typhi Exclusion criteria: severe disease; complications, such as reduced level of consciousness, jaundice, shock, gastrointestinal bleed, clinical signs of intestinal perforation, prostate, and vomiting; unable to take oral medication; allergic to fluoroquinolones; received antibiotics that had efficacy against this organism
Interventions	1. Ofloxacin (15 mg/kg/day oral in 2 divided doses for 2 days) 2. Ofloxacin (15 mg/kg/day oral in 2 divided doses for 3 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Length of hospitalization 7. Convalescent faecal carriage 8. Serious adverse events 9. Other adverse events
Notes	Location: Vietnam Date: not reported Severity of illness at entry: all uncomplicated Author provided further information

Vinh 2005

Methods	Generation of allocation sequence: computer-generated Allocation concealment: sealed envelopes Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 196/202 (97%)
Participants	196 analysed[a]: 89 in ofloxacin 2-day group; 107 in ofloxacin 3-day group Children inpatients aged < 15 years Inclusion criteria: clinical Exclusion criteria: no informed consent from parent or guardian; previous treatment active against *S.* Typhi or *S.* Paratyphi (but those with no response to chloramphenicol, ampicillin, or co-trimoxazole were included); severe or complicated disease
Interventions	1. Ofloxacin (10 mg/kg/day oral in 2 divided doses for 2 days) 2. Ofloxacin (10 mg/kg/day oral in 2 divided doses for 3 days)

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Vinh 2005 (*Continued*)

Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time (mean and 95% confidence intervals; SD calculated by review author) 5. Complications 6. Length of hospitalization (mean and 95% confidence intervals; SD calculated by review author) 7. Convalescent faecal carriage 8. Serious adverse events 9. Other adverse events
Notes	Location: Vietnam Date: 1994-6 Severity of illness at entry: all uncomplicated Author provided further information

Wallace 1993

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 41/42 (97.6%)
Participants	42 analysed[a]: 20 in ciprofloxacin group; 22 in ceftriaxone group Adult inpatients Inclusion criteria: blood culture positive for *S.* Typhi Exclusion criteria: only positive Widal and/or a positive stool culture; age < 16 years; unable to take oral medications; possible proven pregnancy; and lack of fever at admission
Interventions	1. Ciprofloxacin (500 mg oral twice daily for 7 days) 2. Ceftriaxone (3 g/day intravenous for 7 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time (SD not reported) 5. Convalescent faecal carriage 6. Complications
Notes	Location: Bahrain Date: not reported Severity of illness at entry: not reported

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Xiao 1991

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	23 analysed[a]: 8 in norfloxacin group; 6 in pefloxacin group; and 9 in ofloxacin group Adult and children inpatients aged 11 to 62 years Inclusion criteria: clinical with blood or bone marrow culture positive for *S.* Typhi Exclusion criteria: not mentioned
Interventions	We evaluated 3 of the available 5 groups: 1. Norfloxacin (300 to 400 mg oral thrice a day for 14 days) 2. Pefloxacin (400 mg oral twice daily for 14 days) 3. Ofloxacin (300 mg oral twice daily for 14 days)
Outcomes	1. Clinical failure 2. Fever clearance time
Notes	Location: China (Chinese language) Date: not reported Severity of illness at entry: some participants had complications

Yang 1991

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	56 analysed[a]: 28 in ofloxacin group; 28 in norfloxacin group Inpatients; mean age 27 years (standard deviation 14 years) in ofloxacin group; mean 21 years (standard deviation 10 years) in norfloxacin group Inclusion criteria: clinical with blood culture positive for *S.* Typhi Exclusion criteria: not mentioned
Interventions	1. Ofloxacin (200 mg oral twice daily for 7 to 14 days) 2. Norfloxacin (300 to 400 mg oral 3 to 4 times a day for 10 to 24 days)
Outcomes	1. Clinical failure 2. Microbiological failure (definition incorrect, thus we did not enter data in this review) 3. Relapse 4. Fever clearance time 5. Convalescent faecal carriage 6. Serious adverse events 7. Other adverse events
Notes	Location: China (Chinese language) Date: 1989-91 Severity of illness at entry: not reported

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Yousaf 1992

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 75/85 (88.4%)
Participants	75 analysed[a]: 25 in ofloxacin group; 25 in chloramphenicol group; 25 in amoxicillin group Adult inpatients Inclusion criteria: culture positive Exclusion criteria: if received previous antibiotic therapy known to be effective against *S*. Typhi
Interventions	1. Ofloxacin (200 mg oral twice daily for 14 days) 2. Chloramphenicol (50 mg/kg/day, then 30 mg/kg/day when afebrile for 14 days) 3. Amoxicillin (4 to 6 g/day oral for 14 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Other adverse events
Notes	Location: Pakistan Date: 1989-92 Severity of illness at entry: not reported

Yu 1998

Methods	Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: open Inclusion of all randomized culture-positive participants in the final analysis: 100%
Participants	80 analysed[a]: 40 in levofloxacin group; 40 in cefixime group Adult aged 18 to 65 years; most probably inpatients Inclusion criteria: clinical with blood or bone marrow culture positive for *S*. Typhi or *S*. Paratyphi Exclusion criteria: not mentioned
Interventions	1. Levofloxacin (200 mg oral twice a day for 10 days) 2. Cefixime (200 mg oral twice a day for 10 days)
Outcomes	1. Clinical failure 2. Microbiological failure 3. Relapse 4. Fever clearance time 5. Complications 6. Convalescent faecal carriage 7. Other adverse events
Notes	Location: China (Chinese language) Date: not reported

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	Severity of illness at entry: included 'mild, common, and severe' types (1 'severe type' illness in levofloxacin group and 2 in cefixime group)

MDR: multiple-drug resistant; SD: standard deviation; *S.* Typhi/Paratyphi: *Salmonella enterica* serotype Typhi/Paratyphi.
[a] For details of number of participants enrolled, number randomized, and the number of participants with culture-confirmed enteric fever, *see* Table 1: Microbiology.

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

Agalar 1997	Not a randomized controlled trial because 1 group consisted of participants admitted in 1994 and the other group of participants admitted in 1995
Akhtar 1989	No mention of randomization
Akhtar 1992	Quasi-randomized controlled trial: participants were allocated alternatively to either ciprofloxacin group or chloramphenicol group, and resistance strains assigned to a third ciprofloxacin group; author provided this additional information
Bavdekar 1991	Interventions not randomly assigned
Bethell 1996	Children from the Vinh 1996 trial (which is included in this review) were entered into this pharmacokinetic study of oral vs intravenous ofloxacin
Chakravorty 1991	All treated with chloramphenicol; some switched over to another drug based on culture results
Chukwani 1998	2 fluoroquinolone drugs were given for different durations (7 days vs 14 days) in this randomized controlled trial
Daga 1994	Treatment assigned depending on treatment already taken, clinical course, and complications
Hou 1993	Randomized controlled trial comparing Chinese ofloxacin with Japanese ofloxacin
Jinlong 1998	Quasi-randomized controlled trial
Kumar 2007	Described as a randomized controlled parallel study of ofloxacin vs ceftriaxone in 93 children with multi-drug resistant typhoid fever proven by blood culture. The main outcome reported for both arms is mean fever clearance time; however the number of children in each arm is not available. We have contacted the author for additional information (December 2007) and will include this study if further information becomes available
Liberti 2000	No mention of randomization
Lu 1995	A total of 130 participants with any infectious disease were randomized into 2 groups (enoxacin and cefotaxime) ; there were only 2 participants with enteric fever in enoxacin group and 1 participant with enteric fever in cefotaxime group

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(*Continued*)

Nelwan 1995	Randomized controlled trial comparing 3 days with 6 days of ciprofloxacin that included 20 participants with serologically confirmed enteric fever (of a total of 59 participants randomized). We contacted the author (17 December 2003) to obtain additional data for blood culture confirmed cases and will include this in future updates should it become available
Peyramond 1986	Not a randomized controlled trial
Secmeer 1997	No randomization; allocation based on co-trimoxazole susceptibility
Singh 1993	No mention of randomization
Suhendro 2007	Compares 2 different formulations of ciprofloxacin; described as a prospective, open labelled, clinical trial, comparing safety and efficacy of extended-release ciprofloxacin 1000 mg once daily (Ciprofloxacin XR) and ciprofloxacin intermediate release 500 mg 2 times daily (Ciprofloxacin bid) in adults with typhoid fever
Takkar 1994	Not randomized
Tanphaichitra 1986	Randomized controlled trial of gonorrhoea; part of the report, but not part of the trial, were 8 participants with enteric fever that treated with ofloxacin
Uwaydah 1992	Compares 2 ciprofloxacin doses, not durations
Wain 1997	Study on *S.* Typhi isolates from blood cultures of participants included in 3 trials included in this review: Smith 1994; Vinh 1996; and Nguyen 1997
Zavala 1989	No mention of randomization
Zhang 1991	Randomized controlled trial including several infections; randomization not applied to the 63 typhoid participants treated with enoxacin
ZhongYang 1997	Randomized controlled trial comparing ofloxacin with norfloxacin for 14 days. It included 158 people with serologically confirmed enteric fever, out of a total of 429 people randomized. Microbiological failure, the only reported outcome for blood culture confirmed cases, was measured at different times for both arms (7 to 14 days for the ofloxacin group vs 7 days for the norfloxacin group). We contacted the author (July 2003) to obtain additional data for blood culture-confirmed cases and will include this in future updates should it become available

S. Typhi: *Salmonella enterica* serotype Typhi.

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

Flores 1991

Methods	NA
Participants	NA
Interventions	NA
Outcomes	NA
Notes	Unable to retrieve this study

Soewandojo 1992

Methods	NA
Participants	NA
Interventions	NA
Outcomes	NA
Notes	Unable to retrieve this study

NA: not available.

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

ISRCTN53258327

Trial name or title	"An open randomised study to assess the efficacy of gatifloxacin versus chloramphenicol for the treatment of uncomplicated typhoid fever in Kathmandu, Nepal"
Methods	"open randomised study"
Participants	Inclusion criteria: any patient with suspected uncomplicated enteric fever who gives consent Exclusion criteria: no consent, or pregnant
Interventions	1. Gatifloxacin 10 mg/kg/day once a day for 7 days 2. Chloramphenicol 75 mg/kg/day in 4 divided doses for 14 days
Outcomes	1. Failure of treatment, defined as occurrence of any 1 of: persistent fever at day 10 of treatment; failure to clear completely the admission symptoms at day 10; blood culture positive at day 10 of treatment; need for 'rescue' treatment with ceftriaxone; culture-confirmed relapse within 28 days of starting therapy; development on treatment of any complication (clinically significant bleeding, fall in the Glasgow Coma Score, perforation of the gastrointestinal tract, admission to hospital within 28 days of starting therapy)

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ISRCTN53258327 (*Continued*)

Starting date	1 May 2006 Anticipated end date: 30 June 2008
Contact information	Dr Buddha Basnyat (rishibas@wlink.com.np), Patan Hospital, Kathmandu, Nepal
Notes	Location: Nepal Registration number: ISRCTN53258327 Source of funding: The Wellcome Trust (UK) Note: trial was stopped temporarily in September 2006 after the reports of dysglycaemia associated with gatifloxacin, but it was resumed in December 2006 Percentage of children aged < 14 years in trial: around 45% of 703 enrolled participants

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	"randomised clinical 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; bodyweight > 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 previous week; pregnancy or breast-feeding; contraindications to ofloxacin or azithromycin; evidence for severe typhoid
Interventions	1. Ofloxacin 7.5 mg/kg every 12 hours for 3 days 2. Azithromycin 20 mg/kg every 24 hours for 3 days
Outcomes	1. Fever clearance time 2. Cure 3. Relapse 4. Faecal carriage
Starting date	1 May 2004 Anticipated end date: 31 December 2007
Contact information	Dr Paul Newton (paul@tropmedres.ac), Microbiology laboratory, Ministry of Health, Mahosot Hospital, Vientiane, Laos
Notes	Location: Laos Registration number: ISRCTN66534807 Source of funding: The Wellcome Trust (UK) Percentage of children in trial: none E-mail update by Dr Newton on 5 December 2007: on hold because of considerable decline in incidence of typhoid in Vientiane

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DATA AND ANALYSES

Comparison 1. Fluoroquinolones vs chloramphenicol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure	9	594	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.25, 1.72]
1.1 NaR not reported and MDR absent	5	307	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.19, 3.34]
1.2 NaR absent and MDR present	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.01, 7.02]
1.3 NaR and MDR not reported	3	237	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.14, 2.91]
2 Microbiological failure	6	378	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.18, 1.03]
2.1 NaR not reported and MDR absent	4	237	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.21, 2.12]
2.2 NaR and MDR not reported	2	141	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 0.96]
3 Relapse	6	467	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.04, 0.50]
3.1 NaR not reported and MDR absent	4	281	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.69]
3.2 NaR and MDR not reported	2	186	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.03, 1.07]
4 Fever clearance time	3	129	Mean Difference (IV, Fixed, 95% CI)	-25.93 [-40.12, -11.74]
4.1 NaR not reported and MDR absent	2	81	Mean Difference (IV, Fixed, 95% CI)	-16.07 [-35.03, 2.88]
4.2 NaR absent and MDR present	1	48	Mean Difference (IV, Fixed, 95% CI)	-38.5 [-59.90, -17.10]
5 Length of hospital stay	2	105	Mean Difference (IV, Fixed, 95% CI)	-2.57 [-3.53, -1.62]
5.1 NaR not reported and MDR absent	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.63, 0.83]
5.2 NaR absent and MDR present	1	50	Mean Difference (IV, Fixed, 95% CI)	-5.9 [-7.42, -4.38]
6 Convalescent faecal carriage (NaR not reported and MDR absent)	3	298	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.04, 0.70]
7 Complications	2	105	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.16, 3.05]
7.1 NaR not reported and MDR absent	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.18, 5.23]
7.2 NaR absent and MDR present	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.01, 7.02]
8 Adverse events (not serious)	5	245	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.46, 2.62]
8.1 NaR not reported and MDR absent	3	145	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.47, 3.73]
8.2 NaR not reported and MDR not reported	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.14, 3.59]

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8.3 NaR absent and MDR present	1	50	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 2. Fluoroquinolones vs amoxicillin (AMX) or ampicillin (AMP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure (MDR and NaR not reported)	2	90	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 0.46]
2 Microbiological failure (MDR and NaR not reported)	2	90	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.02, 0.58]
3 Adverse events (not serious) (MDR and NaR not reported)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Fluoroquinolones vs co-trimoxazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure (MDR absent)	2	82	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.01]
1.1 NaR absent	1	42	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 NaR not reported	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.01]
2 Microbiological failure (MDR absent)	2	82	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.01]
2.1 NaR absent	1	42	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 NaR not reported	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.01]
3 Adverse events (not serious) (MDR absent)	2	82	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.22, 2.69]
3.1 NaR absent	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.04, 12.67]
3.2 NaR not reported	1	40	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.19, 3.13]

Comparison 4. Fluoroquinolones vs azithromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure (in adults)	2	152	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.63, 17.43]
1.1 NaR present	1	88	Odds Ratio (M-H, Fixed, 95% CI)	3.32 [0.63, 17.43]
1.2 NaR not reported	1	64	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Microbiological failure (in adults)	2	152	Odds Ratio (M-H, Fixed, 95% CI)	2.05 [0.18, 23.44]
2.1 NaR present	1	88	Odds Ratio (M-H, Fixed, 95% CI)	2.05 [0.18, 23.44]
2.2 NaR not reported	1	64	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

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3 Relapse (in adults)	2	102	Odds Ratio (M-H, Fixed, 95% CI)	6.94 [0.31, 154.85]
3.1 NaR present	1	38	Odds Ratio (M-H, Fixed, 95% CI)	6.94 [0.31, 154.85]
3.2 NaR not reported	1	64	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Fever clearance time (in adults)	2	152	Mean Difference (IV, Fixed, 95% CI)	-8.95 [-20.09, 2.19]
4.1 NaR present	1	88	Mean Difference (IV, Fixed, 95% CI)	4.0 [-21.50, 29.50]
4.2 NaR not reported	1	64	Mean Difference (IV, Fixed, 95% CI)	-12.0 [-24.39, 0.39]
5 Length of hospital stay (days) (in adults)	2	152	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.32, 2.12]
5.1 NaR present	1	88	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.32, 2.12]
5.2 NaR not reported	1	64	Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Convalescent faecal carriage (in adults)	2	133	Odds Ratio (M-H, Fixed, 95% CI)	21.33 [1.18, 386.00]
6.1 NaR present	1	69	Odds Ratio (M-H, Fixed, 95% CI)	21.33 [1.18, 386.00]
6.2 NaR not reported	1	64	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Complications (in adults)	2	152	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.51]
7.1 NaR present	1	88	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.51]
7.2 NaR not reported	1	64	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Clinical failure (mostly children)	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 NaR present	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2 NaR present (but newer fluoroquinolone)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Microbiological failure (mostly children)	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 NaR present	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 NaR present (but newer fluoroquinolone)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Relapse (mostly children)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 NaR present (but newer fluoroquinolone)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
11 Fever clearance time (mostly children)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 NaR present	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
11.2 NaR present (but newer fluoroquinolone)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 Length of hospital stay (mostly children)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 NaR present	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.2 NaR present (but newer fluoroquinolone)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
13 Convalescent faecal carriage (mostly children)	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 NaR present	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
13.2 NaR present (but newer fluoroquinolone)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
14 Complications (mostly children)	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 NaR present	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
14.2 NaR present (but newer fluoroquinolone)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
15 Adverse events (not serious) (mostly children)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

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15.1 NaR present (but newer fluoroquinolone)	1	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 5. Fluoroquinolones vs cefixime

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure (adults or mostly adults)	2	238	Odds Ratio (M-H, Fixed, 95% CI)	0.05 [0.01, 0.24]
1.1 NaR not reported	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.65]
1.2 NaR present (but newer fluoroquinolone)	1	158	Odds Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.24]
2 Microbiological failure (adults or mostly adults)	2	238	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.23]
2.1 NaR not reported	1	80	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.92]
2.2 NaR present (but newer fluoroquinolone)	1	158	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.01, 6.53]
3 Relapse (adults or mostly adults)	2	218	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.03, 0.91]
3.1 NaR not reported	1	80	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 NaR present (but newer fluoroquinolone)	1	138	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.03, 0.91]
4 Fever clearance time (adults or mostly adults)	2	238	Mean Difference (IV, Fixed, 95% CI)	-41.69 [-54.96, -28.42]
4.1 NaR not reported	1	80	Mean Difference (IV, Fixed, 95% CI)	-36.0 [-51.29, -20.71]
4.2 NaR present (but newer fluoroquinolone)	1	158	Mean Difference (IV, Fixed, 95% CI)	-57.00 [-85.68, -32.32]
5 Convalescent faecal carriage (adults or mostly adults)	2	227	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.01, 6.50]
5.1 NaR not reported	1	80	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 NaR present (but newer fluoroquinolone)	1	147	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.01, 6.50]
6 Complications (adults or mostly adults)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 NaR present (but newer fluoroquinolone)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Adverse events (not serious) (adults or mostly adults)	2	238	Odds Ratio (M-H, Random, 95% CI)	3.30 [0.11, 97.30]
7.1 NaR not reported	1	80	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.10, 4.11]
7.2 NaR present (but newer fluoroquinolone)	1	158	Odds Ratio (M-H, Random, 95% CI)	17.74 [2.30, 136.58]
8 Clinical failure (children only)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 NaR absent	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Microbiological failure (children only)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 NaR absent	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Relapse (children only)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 NaR absent	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

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11 Fever clearance time (children only)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 NaR absent	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 Length of hospital stay (children only)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 NaR absent	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
13 Complications (children only)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 NaR absent	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 6. Fluoroquinolones vs ceftriaxone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure	3	120	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 0.45]
1.1 NaR absent (adults only)	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.26]
1.2 NaR not reported (adults only)	2	73	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.01, 0.76]
2 Microbiological failure	3	119	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.17]
2.1 NaR absent	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 9.37]
2.2 NaR not reported	2	72	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.01, 7.25]
3 Relapse	3	81	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.03, 3.47]
3.1 NaR absent (adults only)	1	23	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 9.07]
3.2 NaR not reported (adults only)	2	58	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 9.08]
4 Fever clearance time	2	76	Mean Difference (IV, Fixed, 95% CI)	-101.20 [-129.21, -73.19]
4.1 NaR absent (adults only)	1	47	Mean Difference (IV, Fixed, 95% CI)	-113.00 [-150.67, -79.33]
4.2 NaR not reported (adults only)	1	29	Mean Difference (IV, Fixed, 95% CI)	-79.0 [-124.24, -33.76]
5 Convalescent faecal carriage	3	81	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 9.08]
5.1 NaR absent	1	23	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 NaR not reported	2	58	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 9.08]
6 Complications	3	120	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.59]
6.1 NaR absent	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.59]
6.2 NaR not reported	2	73	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Serious adverse events	2	78	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 7.76]
7.1 NaR absent	1	47	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 NaR not reported	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 7.76]
8 Adverse events (not serious)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 NaR absent	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

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Comparison 7. Norfloxacin vs chloramphenicol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure	3	259	Odds Ratio (M-H, Fixed, 95% CI)	5.80 [1.87, 17.98]
1.1 MDR and NaR present	1	40	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 MDR absent and NaR not reported	1	50	Odds Ratio (M-H, Fixed, 95% CI)	41.48 [2.22, 774.60]
1.3 MDR and NaR not reported	1	169	Odds Ratio (M-H, Fixed, 95% CI)	2.81 [0.73, 10.79]
2 Microbiological failure	2	209	Odds Ratio (M-H, Fixed, 95% CI)	2.81 [0.73, 10.79]
2.1 MDR and NaR present	1	40	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 MDR and NaR not reported	1	169	Odds Ratio (M-H, Fixed, 95% CI)	2.81 [0.73, 10.79]
3 Relapse	2	90	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.92]
3.1 MDR and NaR present	1	40	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 MDR absent and NaR not reported	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.92]
4 Fever clearance time	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 MDR and NaR present	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 MDR and NaR not reported	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Length of hospital stay (MDR and NaR present)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Convalescent faecal carriage	3	259	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.29, 3.61]
6.1 MDR and NaR present	1	40	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 MDR absent and NaR not reported	1	50	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.23, 5.78]
6.3 MDR and NaR not reported	1	169	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.12, 6.36]
7 Adverse events (not serious)	2	209	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.40, 2.15]
7.1 MDR and NaR present	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.34, 4.46]
7.2 MDR and NaR not reported	1	169	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.24, 2.29]

Comparison 8. Norfloxacin vs ceftriaxone

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

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Comparison 9. Norfloxacin vs other fluoroquinolones (FQ)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Versus pefloxacin	3	200	Odds Ratio (M-H, Fixed, 95% CI)	30.60 [5.75, 162.86]
1.2 Versus ofloxacin	3	123	Odds Ratio (M-H, Fixed, 95% CI)	28.15 [4.80, 165.14]
1.3 Versus enoxacin	2	142	Odds Ratio (M-H, Fixed, 95% CI)	4.15 [1.77, 9.76]
2 Relapse	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Versus ofloxacin	2	106	Odds Ratio (M-H, Fixed, 95% CI)	2.08 [0.18, 24.31]
3 Fever clearance time	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Versus pefloxacin	2	144	Mean Difference (IV, Fixed, 95% CI)	18.83 [2.62, 35.03]
3.2 Versus ofloxacin	2	73	Mean Difference (IV, Fixed, 95% CI)	30.26 [10.42, 50.10]
3.3 Versus enoxacin	1	102	Mean Difference (IV, Fixed, 95% CI)	60.0 [33.81, 86.19]
4 Convalescent faecal carriage	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Versus pefloxacin	1	56	Odds Ratio (M-H, Fixed, 95% CI)	14.6 [0.71, 298.42]
4.2 Versus ofloxacin	2	106	Odds Ratio (M-H, Fixed, 95% CI)	3.90 [0.63, 24.30]
4.3 Versus enoxacin	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.24, 10.70]
5 Adverse events (not serious)	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Versus ofloxacin	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Versus enoxacin	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 10. Fluoroquinolones for 2 days vs 3 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure (NaR present)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Adults only	1	100	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.02, 1.47]
1.2 Children only	2	296	Odds Ratio (M-H, Fixed, 95% CI)	2.22 [0.81, 6.12]
2 Microbiological failure (NaR present)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Children only	2	296	Odds Ratio (M-H, Fixed, 95% CI)	1.96 [0.42, 9.05]
3 Relapse (NaR present)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Adults only	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.93]
3.2 Children only	2	262	Odds Ratio (M-H, Fixed, 95% CI)	2.61 [0.38, 18.03]
4 Fever clearance time (NaR present)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Adults only	1	100	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4.2 Children only	2	296	Mean Difference (IV, Fixed, 95% CI)	-8.55 [-20.10, 3.00]
5 Length of hospital stay (NaR present)	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Adults only	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.79, 0.39]
5.2 Children only	2	296	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.98, 0.09]
6 Convalescent faecal carriage (NaR present)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Children only	2	262	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.01, 7.75]
7 Complications (NaR present)	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

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7.1 Adults only	1	100	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.21]
7.2 Children only	2	296	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.21, 4.96]
8 Adverse events (not serious) (NaR present)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Children only	2	296	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.01, 7.28]

Comparison 11. Fluoroquinolones for 3 days vs 5 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical failure (NaR not reported)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Adults only	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Relapse	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Adults only (NaR not reported)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Children mostly (NaR present)	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Fever clearance time	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Adults only (NaR not reported)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3.2 Children mostly (NaR present)	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Length of hospital stay (NaR not reported)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Adults only	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Adverse events (not serious) (NaR present)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Children mostly	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 12. Fluoroquinolones for 5 days vs 7 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological failure (NaR not reported)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Relapse (NaR not reported)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Fever clearance time (NaR not reported)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Adverse events (not serious) (NaR not reported)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

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Comparison 13. Fluoroquinolones for 7 days vs 10 or 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Microbiological failure (NaR not reported)	2	87	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.08, 23.41]
2 Relapse (NaR not reported)	2	87	Odds Ratio (M-H, Fixed, 95% CI)	4.28 [0.17, 109.61]

Comparison 14. Fluoroquinolones for 10 days vs 14 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse (NaR present)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Fever clearance time (NaR present)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Adverse events (not serious) (NaR present)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

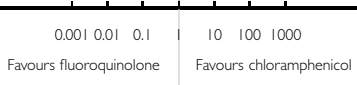
Analysis 1.1. Comparison 1 Fluoroquinolones vs chloramphenicol, Outcome 1 Clinical failure.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Fluoroquinolones vs chloramphenicol

Outcome: 1 Clinical failure

Study or subgroup	Fluoroquinolone n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR not reported and MDR absent				
Abejar 1993	0/15	0/15		0.0 [0.0, 0.0]
Cristiano 1995	0/30	0/30		0.0 [0.0, 0.0]
Gasem 2003	1/28	2/27		0.46 [0.04, 5.43]
Morelli 1992	4/106	0/30		2.68 [0.14, 51.15]
Quintero 1988	0/13	1/13		0.31 [0.01, 8.30]
Subtotal (95% CI)	**192**	**115**		**0.81 [0.19, 3.34]**
Total events: 5 (Fluoroquinolone), 3 (Chloramphenicol)				



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Study or subgroup	Fluoroquinolone n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 1.16, df = 2 (P = 0.56); I² =0.0%				
Test for overall effect: Z = 0.30 (P = 0.77)				
2 NaR absent and MDR present				
Phongmany 2005	0/27	1/23		0.27 [0.01, 7.02]
Subtotal (95% CI)	**27**	**23**		**0.27 [0.01, 7.02]**
Total events: 0 (Fluoroquinolone), 1 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.78 (P = 0.43)				
3 NaR and MDR not reported				
Arnold 1993	0/57	1/34		0.19 [0.01, 4.90]
Gottuzzo 1992	1/48	0/48		3.06 [0.12, 77.09]
Yousaf 1992	1/25	2/25		0.48 [0.04, 5.65]
Subtotal (95% CI)	**130**	**107**		**0.65 [0.14, 2.91]**
Total events: 2 (Fluoroquinolone), 3 (Chloramphenicol)				
Heterogeneity: Chi² = 1.48, df = 2 (P = 0.48); I² =0.0%				
Test for overall effect: Z = 0.56 (P = 0.57)				
Total (95% CI)	**349**	**245**		**0.65 [0.25, 1.72]**
Total events: 7 (Fluoroquinolone), 7 (Chloramphenicol)				
Heterogeneity: Chi² = 2.92, df = 6 (P = 0.82); I² =0.0%				
Test for overall effect: Z = 0.86 (P = 0.39)				

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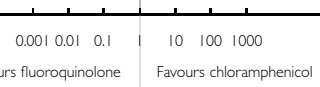
Analysis 1.2. Comparison 1 Fluoroquinolones vs chloramphenicol, Outcome 2 Microbiological failure.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Fluoroquinolones vs chloramphenicol

Outcome: 2 Microbiological failure

Study or subgroup	Fluoroquinolone n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR not reported and MDR absent				
Abejar 1993	0/15	1/15		0.31 [0.01, 8.28]
Bran 1991	0/51	0/51		0.0 [0.0, 0.0]
Cristiano 1995	0/30	0/30		0.0 [0.0, 0.0]
Gasem 2003	7/23	8/22		0.77 [0.22, 2.65]
Subtotal (95% CI)	**119**	**118**		**0.67 [0.21, 2.12]**
Total events: 7 (Fluoroquinolone), 9 (Chloramphenicol)				
Heterogeneity: Chi^2 = 0.25, df = 1 (P = 0.62); I^2 =0.0%				
Test for overall effect: Z = 0.67 (P = 0.50)				
2 NaR and MDR not reported				
Arnold 1993	2/57	5/34		0.21 [0.04, 1.15]
Yousaf 1992	1/25	3/25		0.31 [0.03, 3.16]
Subtotal (95% CI)	**82**	**59**		**0.24 [0.06, 0.96]**
Total events: 3 (Fluoroquinolone), 8 (Chloramphenicol)				
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%				
Test for overall effect: Z = 2.02 (P = 0.043)				
Total (95% CI)	**201**	**177**		**0.43 [0.18, 1.03]**
Total events: 10 (Fluoroquinolone), 17 (Chloramphenicol)				
Heterogeneity: Chi^2 = 1.62, df = 3 (P = 0.65); I^2 =0.0%				
Test for overall effect: Z = 1.90 (P = 0.058)				



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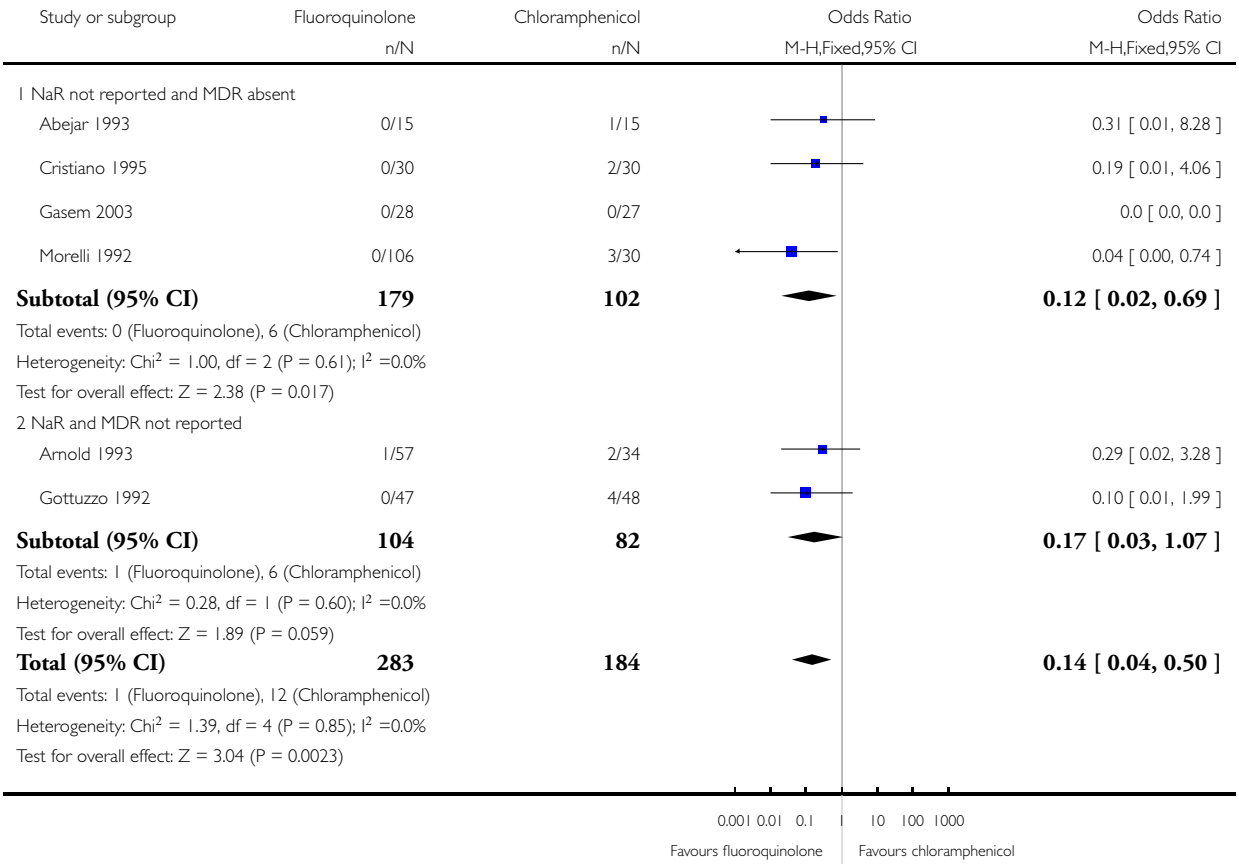
Analysis 1.3. Comparison 1 Fluoroquinolones vs chloramphenicol, Outcome 3 Relapse.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Fluoroquinolones vs chloramphenicol

Outcome: 3 Relapse



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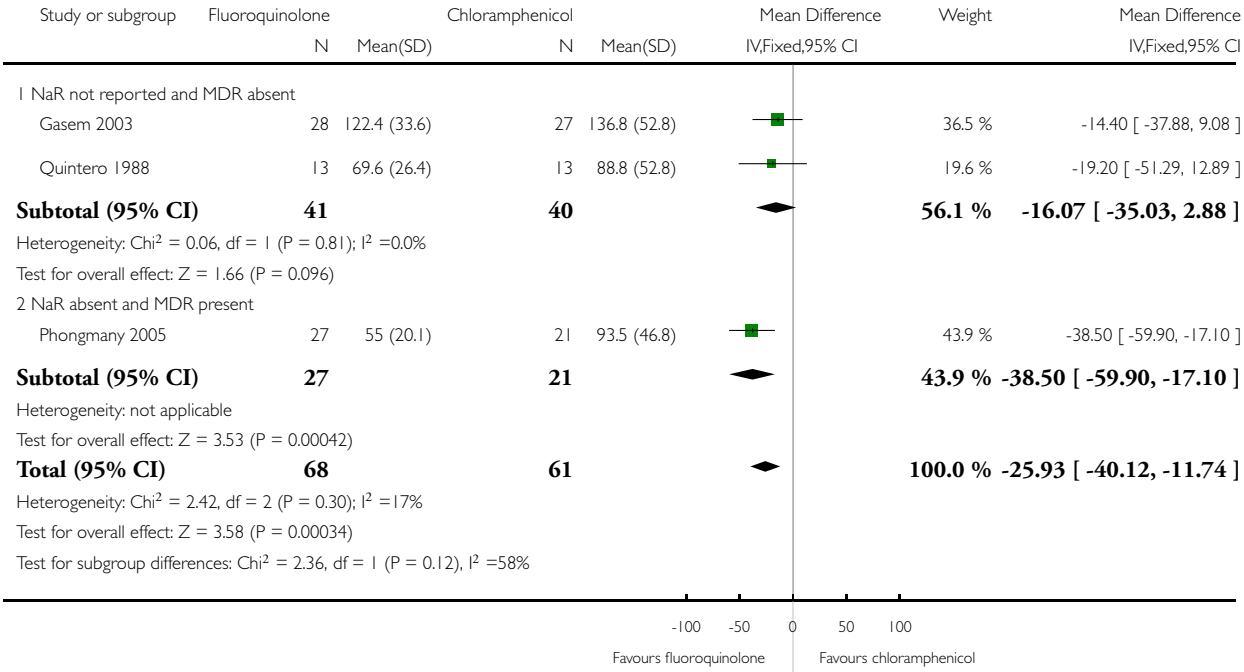
Analysis 1.4. Comparison 1 Fluoroquinolones vs chloramphenicol, Outcome 4 Fever clearance time.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Fluoroquinolones vs chloramphenicol

Outcome: 4 Fever clearance time



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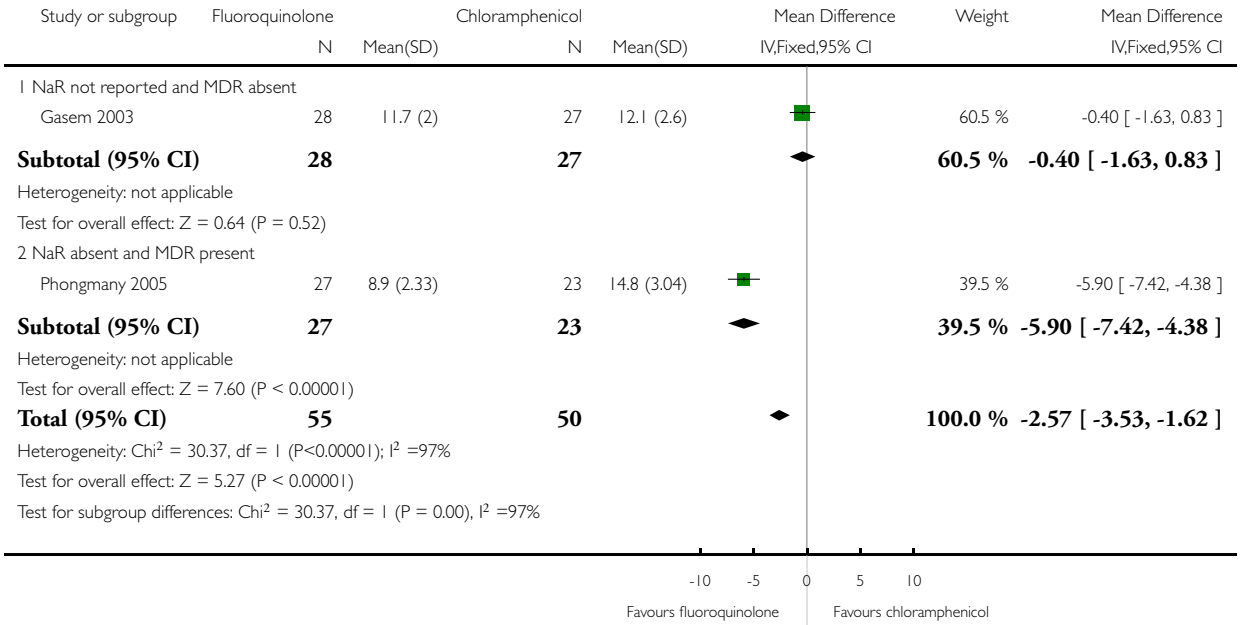
Analysis 1.5. Comparison 1 Fluoroquinolones vs chloramphenicol, Outcome 5 Length of hospital stay.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Fluoroquinolones vs chloramphenicol

Outcome: 5 Length of hospital stay



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Analysis 1.6. Comparison 1 Fluoroquinolones vs chloramphenicol, Outcome 6 Convalescent faecal carriage (NaR not reported and MDR absent).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Fluoroquinolones vs chloramphenicol

Outcome: 6 Convalescent faecal carriage (NaR not reported and MDR absent)

Study or subgroup	Fluoroquinolone n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bran 1991	0/51	1/51		14.8 %	0.33 [0.01, 8.21]
Cristiano 1995	0/30	2/30		24.4 %	0.19 [0.01, 4.06]
Morelli 1992	2/106	4/30		60.8 %	0.13 [0.02, 0.72]
Total (95% CI)	**187**	**111**		**100.0 %**	**0.17 [0.04, 0.70]**
Total events: 2 (Fluoroquinolone), 7 (Chloramphenicol)					
Heterogeneity: Chi^2 = 0.28, df = 2 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 2.45 (P = 0.014)					

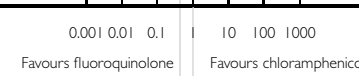
Analysis 1.7. Comparison 1 Fluoroquinolones vs chloramphenicol, Outcome 7 Complications.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Fluoroquinolones vs chloramphenicol

Outcome: 7 Complications

Study or subgroup	Fluoroquinolone n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 NaR not reported and MDR absent					
Gasem 2003	3/28	3/27		63.2 %	0.96 [0.18, 5.23]
Subtotal (95% CI)	**28**	**27**		**63.2 %**	**0.96 [0.18, 5.23]**
Total events: 3 (Fluoroquinolone), 3 (Chloramphenicol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
2 NaR absent and MDR present					
Phongmany 2005	0/27	1/23		36.8 %	0.27 [0.01, 7.02]
Subtotal (95% CI)	**27**	**23**		**36.8 %**	**0.27 [0.01, 7.02]**
Total events: 0 (Fluoroquinolone), 1 (Chloramphenicol)					



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Study or subgroup	Fluoroquinolone n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.78 (P = 0.43)					
Total (95% CI)	**55**	**50**		**100.0 %**	**0.71 [0.16, 3.05]**
Total events: 3 (Fluoroquinolone), 4 (Chloramphenicol)					
Heterogeneity: Chi^2 = 0.46, df = 1 (P = 0.50); I^2 =0.0%					
Test for overall effect: Z = 0.46 (P = 0.64)					

0.001 0.01 0.1 1 10 100 1000

Favours fluoroquinolone Favours chloramphenicol

Analysis 1.8. Comparison 1 Fluoroquinolones vs chloramphenicol, Outcome 8 Adverse events (not serious).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 1 Fluoroquinolones vs chloramphenicol

Outcome: 8 Adverse events (not serious)

Study or subgroup	Fluoroquinolone n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR not reported and MDR absent				
Abejar 1993	2/15	1/15		2.15 [0.17, 26.67]
Cristiano 1995	7/30	5/30		1.52 [0.42, 5.47]
Gasem 2003	0/28	1/27		0.31 [0.01, 7.95]
Subtotal (95% CI)	**73**	**72**		**1.32 [0.47, 3.73]**
Total events: 9 (Fluoroquinolone), 7 (Chloramphenicol)				
Heterogeneity: Chi^2 = 0.96, df = 2 (P = 0.62); I^2 =0.0%				
Test for overall effect: Z = 0.52 (P = 0.60)				
2 NaR not reported and MDR not reported				
Yousaf 1992	3/25	4/25		0.72 [0.14, 3.59]
Subtotal (95% CI)	**25**	**25**		**0.72 [0.14, 3.59]**
Total events: 3 (Fluoroquinolone), 4 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.41 (P = 0.68)				
3 NaR absent and MDR present				
Phongmany 2005	0/27	0/23		0.0 [0.0, 0.0]
Subtotal (95% CI)	**27**	**23**		**0.0 [0.0, 0.0]**
Total events: 0 (Fluoroquinolone), 0 (Chloramphenicol)				

0.001 0.01 0.1 1 10 100 1000

Favours fluoroquinolone Favours chloramphenicol

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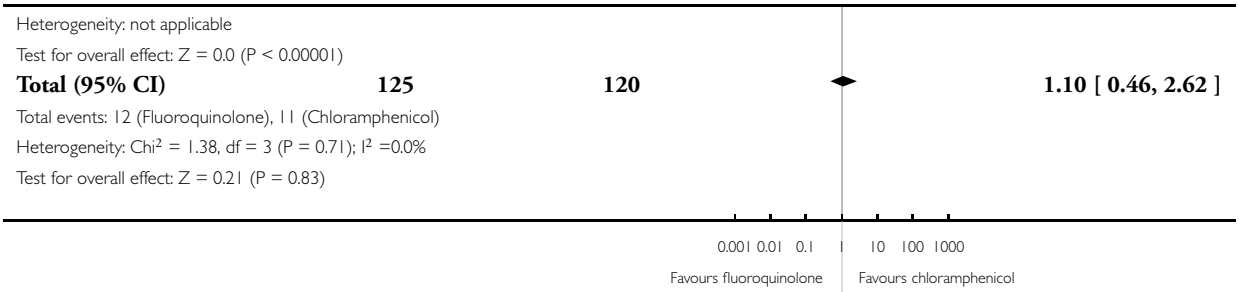
Study or subgroup	Fluoroquinolone n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**125**	**120**		**1.10 [0.46, 2.62]**
Total events: 12 (Fluoroquinolone), 11 (Chloramphenicol)				
Heterogeneity: Chi^2 = 1.38, df = 3 (P = 0.71); I^2 =0.0%				
Test for overall effect: Z = 0.21 (P = 0.83)				



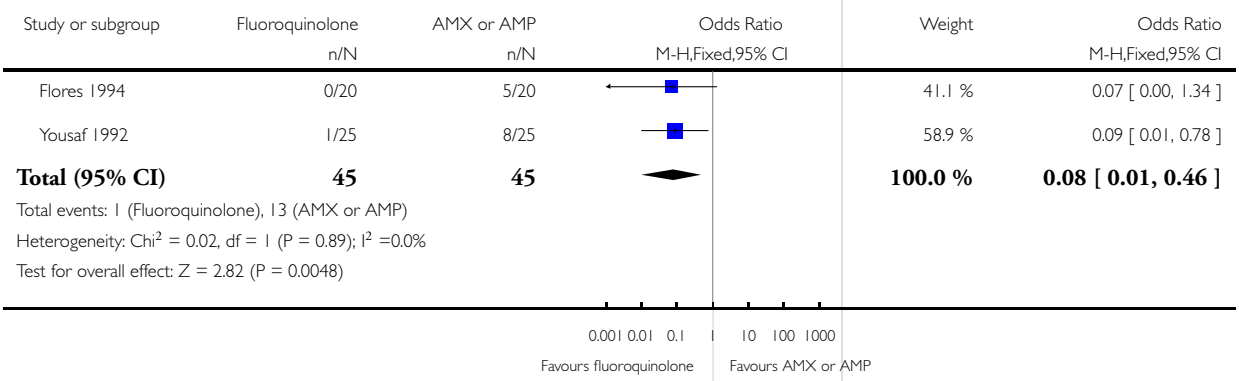
Analysis 2.1. Comparison 2 Fluoroquinolones vs amoxicillin (AMX) or ampicillin (AMP), Outcome 1 Clinical failure (MDR and NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Fluoroquinolones vs amoxicillin (AMX) or ampicillin (AMP)

Outcome: 1 Clinical failure (MDR and NaR not reported)

Study or subgroup	Fluoroquinolone n/N	AMX or AMP n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Flores 1994	0/20	5/20		41.1 %	0.07 [0.00, 1.34]
Yousaf 1992	1/25	8/25		58.9 %	0.09 [0.01, 0.78]
Total (95% CI)	**45**	**45**		**100.0 %**	**0.08 [0.01, 0.46]**
Total events: 1 (Fluoroquinolone), 13 (AMX or AMP)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 2.82 (P = 0.0048)					



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Analysis 2.2. Comparison 2 Fluoroquinolones vs amoxicillin (AMX) or ampicillin (AMP), Outcome 2 Microbiological failure (MDR and NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Fluoroquinolones vs amoxicillin (AMX) or ampicillin (AMP)

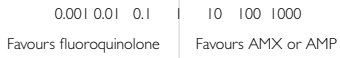
Outcome: 2 Microbiological failure (MDR and NaR not reported)

Study or subgroup	Fluoroquinolone n/N	AMX or AMP n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Flores 1994	0/20	3/20		30.8 %	0.12 [0.01, 2.53]
Yousaf 1992	1/25	8/25		69.2 %	0.09 [0.01, 0.78]
Total (95% CI)	**45**	**45**		**100.0 %**	**0.10 [0.02, 0.58]**

Total events: 1 (Fluoroquinolone), 11 (AMX or AMP)

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 2.57 (P = 0.010)



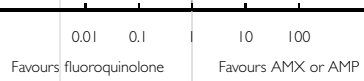
Analysis 2.3. Comparison 2 Fluoroquinolones vs amoxicillin (AMX) or ampicillin (AMP), Outcome 3 Adverse events (not serious) (MDR and NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 2 Fluoroquinolones vs amoxicillin (AMX) or ampicillin (AMP)

Outcome: 3 Adverse events (not serious) (MDR and NaR not reported)

Study or subgroup	Fluoroquinolone n/N	AMX or AMP n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Yousaf 1992	3/25	11/25		0.17 [0.04, 0.73]



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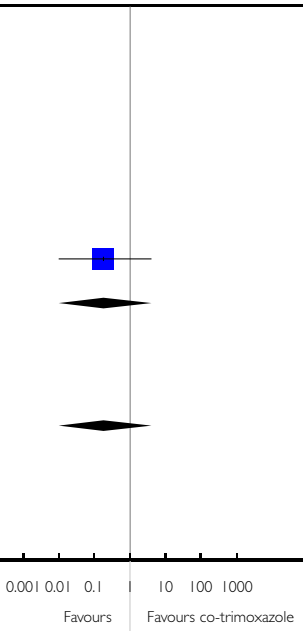
Analysis 3.1. Comparison 3 Fluoroquinolones vs co-trimoxazole, Outcome 1 Clinical failure (MDR absent).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Fluoroquinolones vs co-trimoxazole

Outcome: 1 Clinical failure (MDR absent)

Study or subgroup	Fluoroquinolone n/N	Co-trimoxazole n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR absent				
Hajji 1988	0/24	0/18		0.0 [0.0, 0.0]
Subtotal (95% CI)	**24**	**18**		**0.0 [0.0, 0.0]**
Total events: 0 (Fluoroquinolone), 0 (Co-trimoxazole)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 NaR not reported				
Limson 1989	0/20	2/20		0.18 [0.01, 4.01]
Subtotal (95% CI)	**20**	**20**		**0.18 [0.01, 4.01]**
Total events: 0 (Fluoroquinolone), 2 (Co-trimoxazole)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.08 (P = 0.28)				
Total (95% CI)	**44**	**38**		**0.18 [0.01, 4.01]**
Total events: 0 (Fluoroquinolone), 2 (Co-trimoxazole)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.08 (P = 0.28)				



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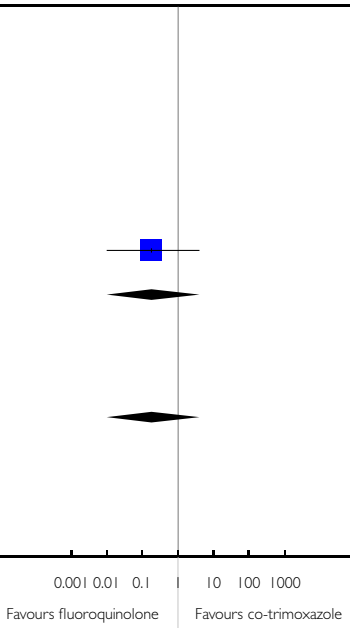
Analysis 3.2. Comparison 3 Fluoroquinolones vs co-trimoxazole, Outcome 2 Microbiological failure (MDR absent).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Fluoroquinolones vs co-trimoxazole

Outcome: 2 Microbiological failure (MDR absent)

Study or subgroup	Fluoroquinolone n/N	Co-trimoxazole n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR absent				
Hajji 1988	0/24	0/18		0.0 [0.0, 0.0]
Subtotal (95% CI)	**24**	**18**		**0.0 [0.0, 0.0]**
Total events: 0 (Fluoroquinolone), 0 (Co-trimoxazole)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 NaR not reported				
Limson 1989	0/20	2/20		0.18 [0.01, 4.01]
Subtotal (95% CI)	**20**	**20**		**0.18 [0.01, 4.01]**
Total events: 0 (Fluoroquinolone), 2 (Co-trimoxazole)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.08 (P = 0.28)				
Total (95% CI)	**44**	**38**		**0.18 [0.01, 4.01]**
Total events: 0 (Fluoroquinolone), 2 (Co-trimoxazole)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.08 (P = 0.28)				



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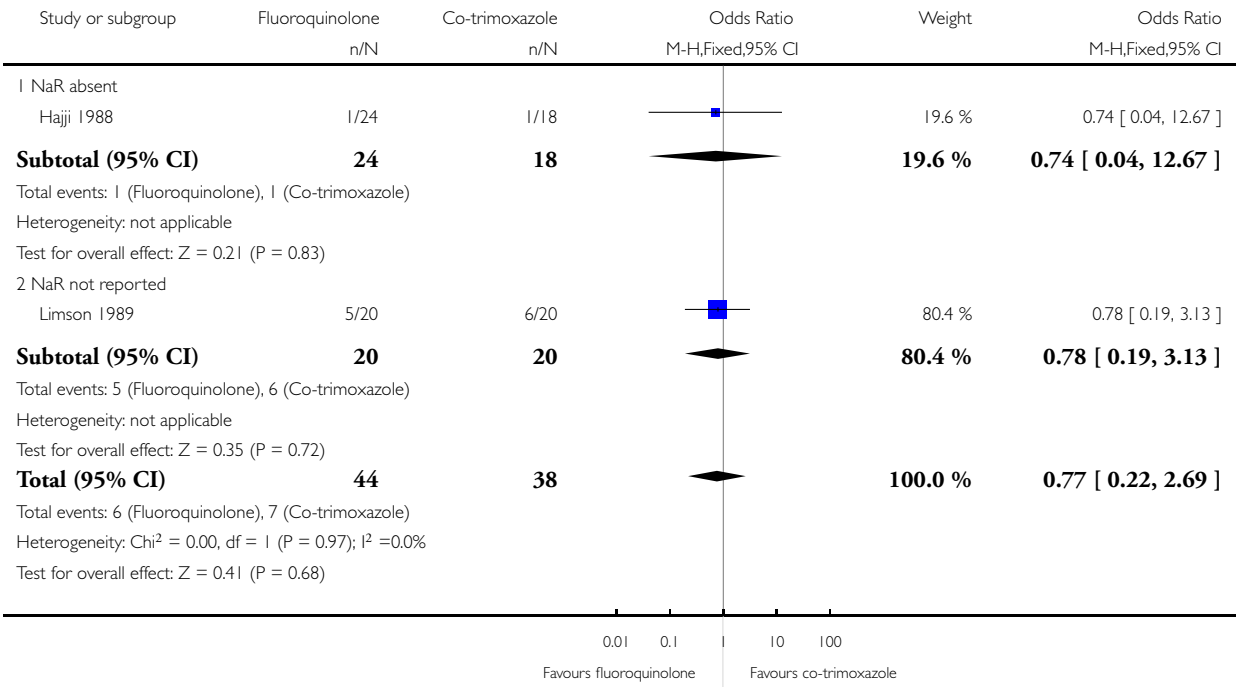
Analysis 3.3. Comparison 3 Fluoroquinolones vs co-trimoxazole, Outcome 3 Adverse events (not serious) (MDR absent).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 3 Fluoroquinolones vs co-trimoxazole

Outcome: 3 Adverse events (not serious) (MDR absent)



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Analysis 4.1. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 1 Clinical failure (in adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 1 Clinical failure (in adults)

Study or subgroup	Fluoroquinolone (FQ) n/N	Azithromycin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR present				
Chinh 2000	6/44	2/44		3.32 [0.63, 17.43]
Subtotal (95% CI)	**44**	**44**		**3.32 [0.63, 17.43]**
Total events: 6 (Fluoroquinolone (FQ)), 2 (Azithromycin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.42 (P = 0.16)				
2 NaR not reported				
Girgis 1999	0/28	0/36		0.0 [0.0, 0.0]
Subtotal (95% CI)	**28**	**36**		**0.0 [0.0, 0.0]**
Total events: 0 (Fluoroquinolone (FQ)), 0 (Azithromycin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**72**	**80**		**3.32 [0.63, 17.43]**
Total events: 6 (Fluoroquinolone (FQ)), 2 (Azithromycin)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.42 (P = 0.16)				

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Analysis 4.2. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 2 Microbiological failure (in adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 2 Microbiological failure (in adults)

Study or subgroup	Fluoroquinolone n/N	Azithromycin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR present				
Chinh 2000	2/44	1/44		2.05 [0.18, 23.44]
Subtotal (95% CI)	**44**	**44**		**2.05 [0.18, 23.44]**
Total events: 2 (Fluoroquinolone), 1 (Azithromycin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.58 (P = 0.56)				
2 NaR not reported				
Girgis 1999	0/28	0/36		0.0 [0.0, 0.0]
Subtotal (95% CI)	**28**	**36**		**0.0 [0.0, 0.0]**
Total events: 0 (Fluoroquinolone), 0 (Azithromycin)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**72**	**80**		**2.05 [0.18, 23.44]**
Total events: 2 (Fluoroquinolone), 1 (Azithromycin)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.58 (P = 0.56)				

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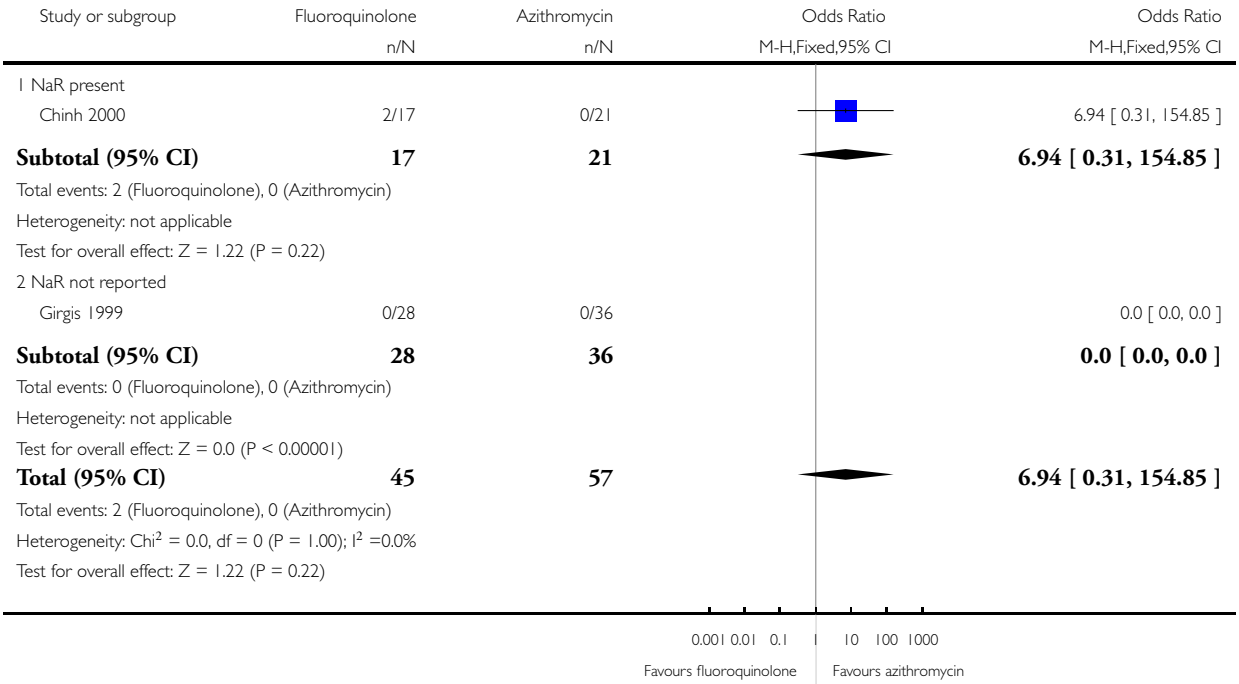
Analysis 4.3. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 3 Relapse (in adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 3 Relapse (in adults)



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Analysis 4.4. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 4 Fever clearance time (in adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 4 Fever clearance time (in adults)

Study or subgroup	Fluoroquinolone N	Mean(SD)	Azithromycin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 NaR present							
Chinh 2000	44	134 (76.14)	44	130 (40.61)		19.1 %	4.00 [-21.50, 29.50]
Subtotal (95% CI)	**44**		**44**			**19.1 %**	**4.00 [-21.50, 29.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							
2 NaR not reported							
Girgis 1999	28	79.2 (24)	36	91.2 (26.4)		80.9 %	-12.00 [-24.39, 0.39]
Subtotal (95% CI)	**28**		**36**			**80.9 %**	**-12.00 [-24.39, 0.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.90 (P = 0.058)							
Total (95% CI)	**72**		**80**			**100.0 %**	**-8.95 [-20.09, 2.19]**
Heterogeneity: Chi^2 = 1.22, df = 1 (P = 0.27); I^2 =18%							
Test for overall effect: Z = 1.57 (P = 0.12)							
Test for subgroup differences: Chi^2 = 1.22, df = 1 (P = 0.27), I^2 =18%							

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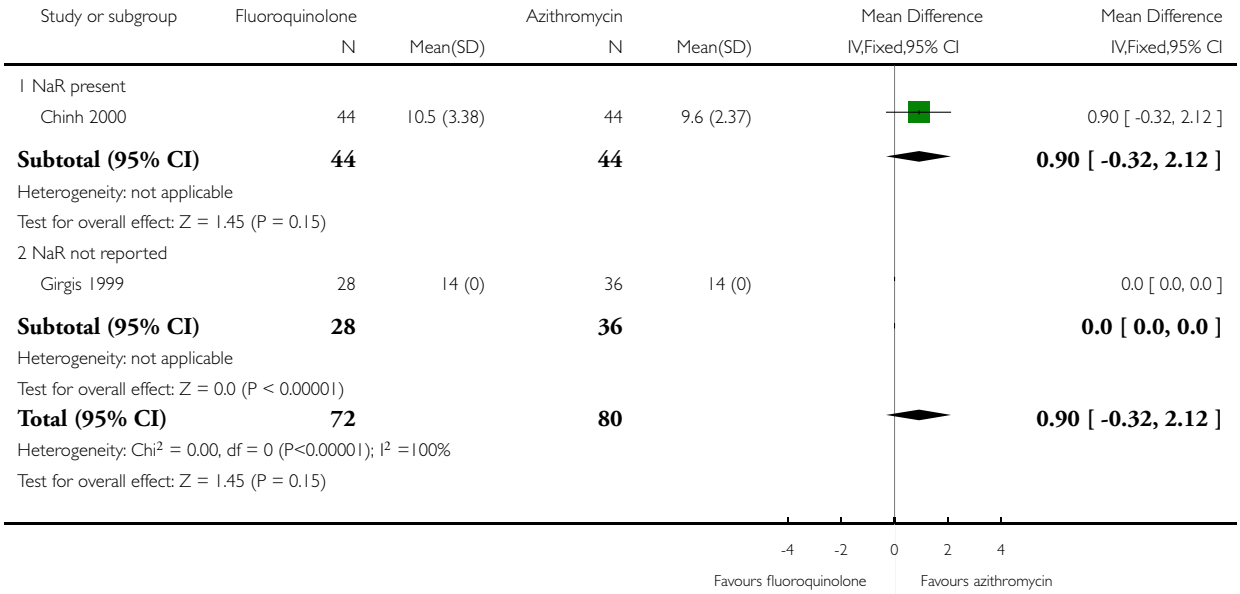
Analysis 4.5. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 5 Length of hospital stay (days) (in adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 5 Length of hospital stay (days) (in adults)



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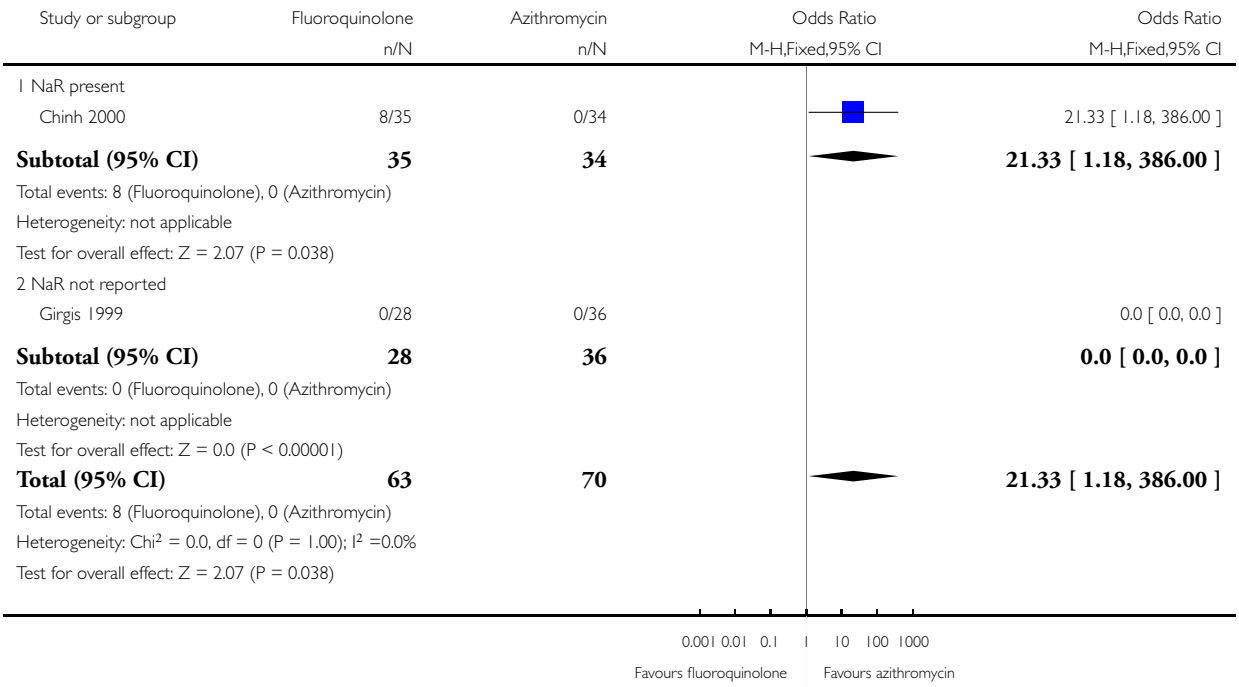
Analysis 4.6. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 6 Convalescent faecal carriage (in adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 6 Convalescent faecal carriage (in adults)



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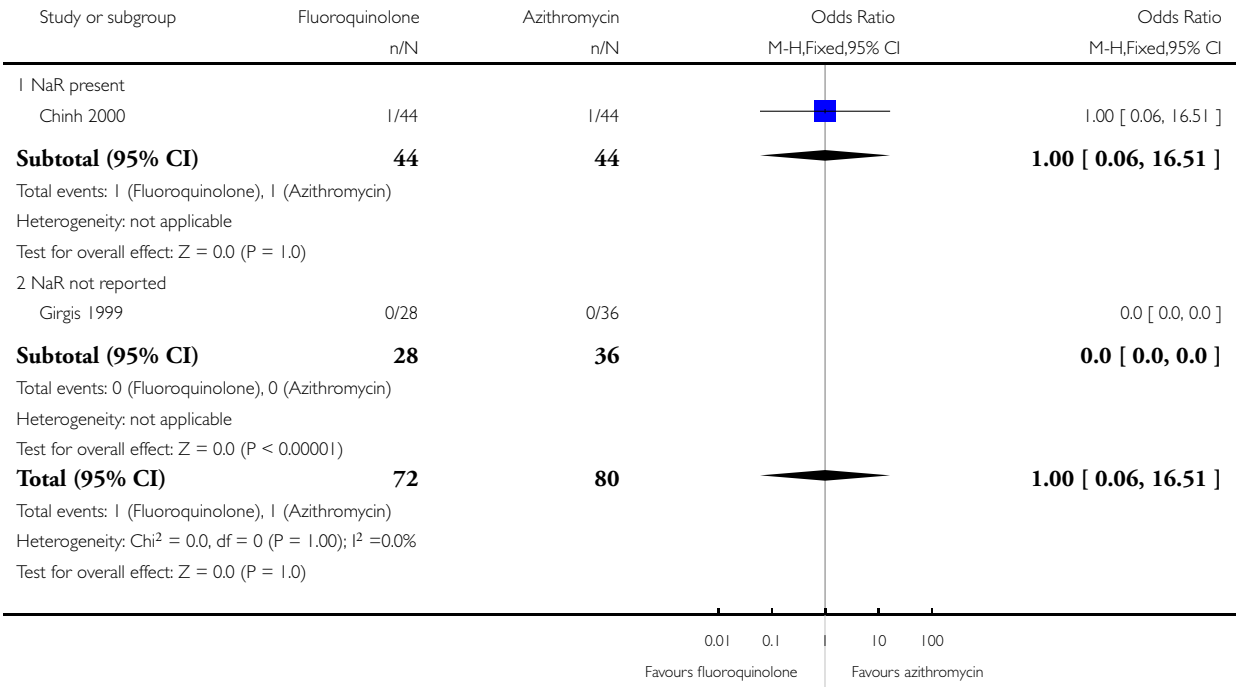
Analysis 4.7. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 7 Complications (in adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 7 Complications (in adults)

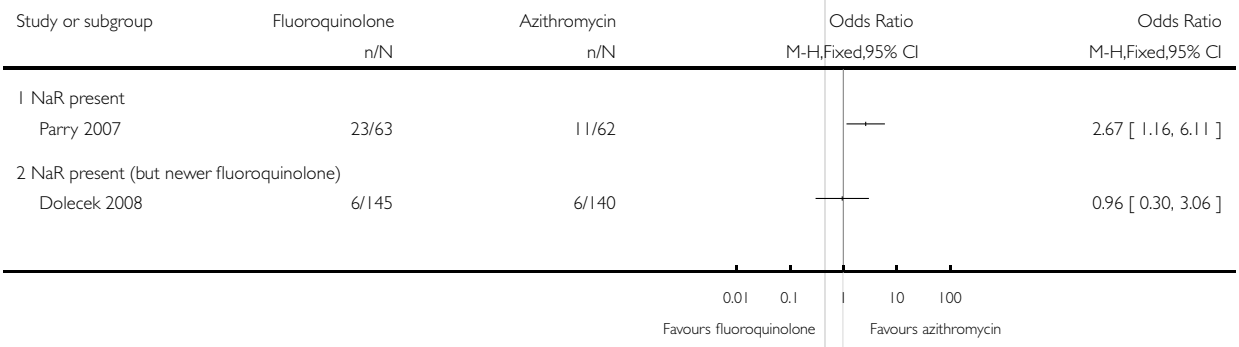


Analysis 4.8. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 8 Clinical failure (mostly children).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 8 Clinical failure (mostly children)



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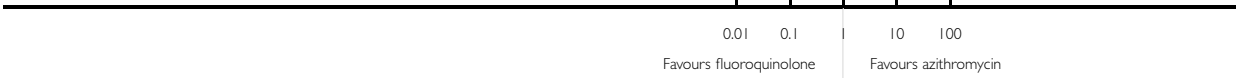
Analysis 4.9. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 9 Microbiological failure (mostly children).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 9 Microbiological failure (mostly children)

Study or subgroup	Fluoroquinolone n/N	Azithromycin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR present				
Parry 2007	2/63	2/62		0.98 [0.13, 7.21]
2 NaR present (but newer fluoroquinolone)				
Dolecek 2008	2/145	3/140		0.64 [0.11, 3.88]



Analysis 4.10. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 10 Relapse (mostly children).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 10 Relapse (mostly children)

Study or subgroup	Fluoroquinolone n/N	Azithromycin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR present (but newer fluoroquinolone)				
Dolecek 2008	3/137	0/127		6.64 [0.34, 129.74]

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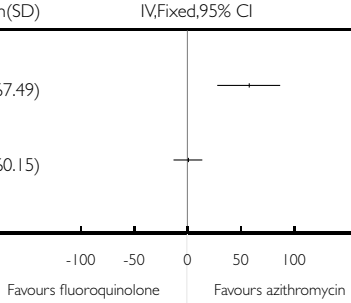
Analysis 4.11. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 11 Fever clearance time (mostly children).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 11 Fever clearance time (mostly children)

Study or subgroup	Fluoroquinolone N	Mean(SD)	Azithromycin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 NaR present						
Parry 2007	63	196.8 (97.18)	62	139.2 (67.49)		57.60 [28.31, 86.89]
2 NaR present (but newer fluoroquinolone)						
Dolecek 2008	145	115.97 (57.78)	140	115.24 (60.15)		0.73 [-12.97, 14.43]



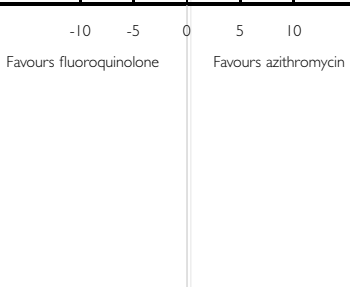
Analysis 4.12. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 12 Length of hospital stay (mostly children).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 12 Length of hospital stay (mostly children)

Study or subgroup	Fluoroquinolone N	Mean(SD)	Azithromycin N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 NaR present						
Parry 2007	63	13.7 (3.85)	62	12.6 (2.21)		1.10 [0.00, 2.20]
2 NaR present (but newer fluoroquinolone)						
Dolecek 2008	145	13.85 (2.79)	140	13.66 (3.04)		0.19 [-0.49, 0.87]



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Analysis 4.13. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 13 Convalescent faecal carriage (mostly children).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 13 Convalescent faecal carriage (mostly children)

Study or subgroup	Fluoroquinolone n/N	Azithromycin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR present				
Parry 2007	12/62	1/62		14.64 [1.84, 116.48]
2 NaR present (but newer fluoroquinolone)				
Dolecek 2008	1/137	0/131		2.89 [0.12, 71.58]

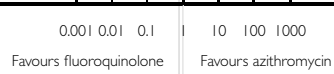
Analysis 4.14. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 14 Complications (mostly children).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 14 Complications (mostly children)

Study or subgroup	Fluoroquinolone n/N	Azithromycin n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR present				
Parry 2007	0/63	2/62		0.19 [0.01, 4.05]
2 NaR present (but newer fluoroquinolone)				
Dolecek 2008	0/145	8/140		0.05 [0.00, 0.94]



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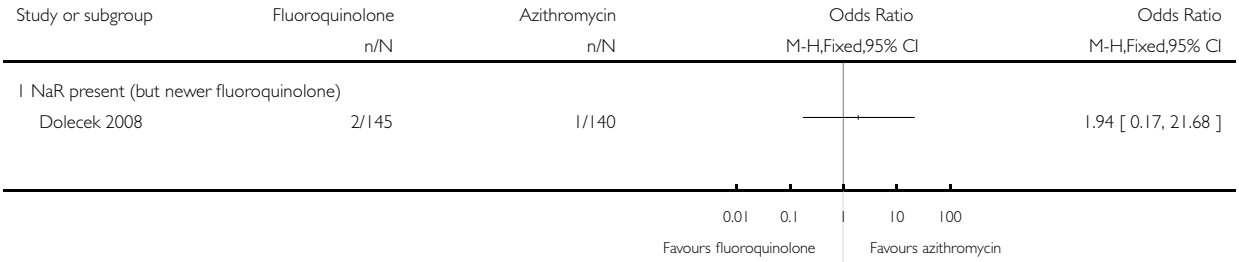
Analysis 4.15. Comparison 4 Fluoroquinolones vs azithromycin, Outcome 15 Adverse events (not serious) (mostly children).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 4 Fluoroquinolones vs azithromycin

Outcome: 15 Adverse events (not serious) (mostly children)

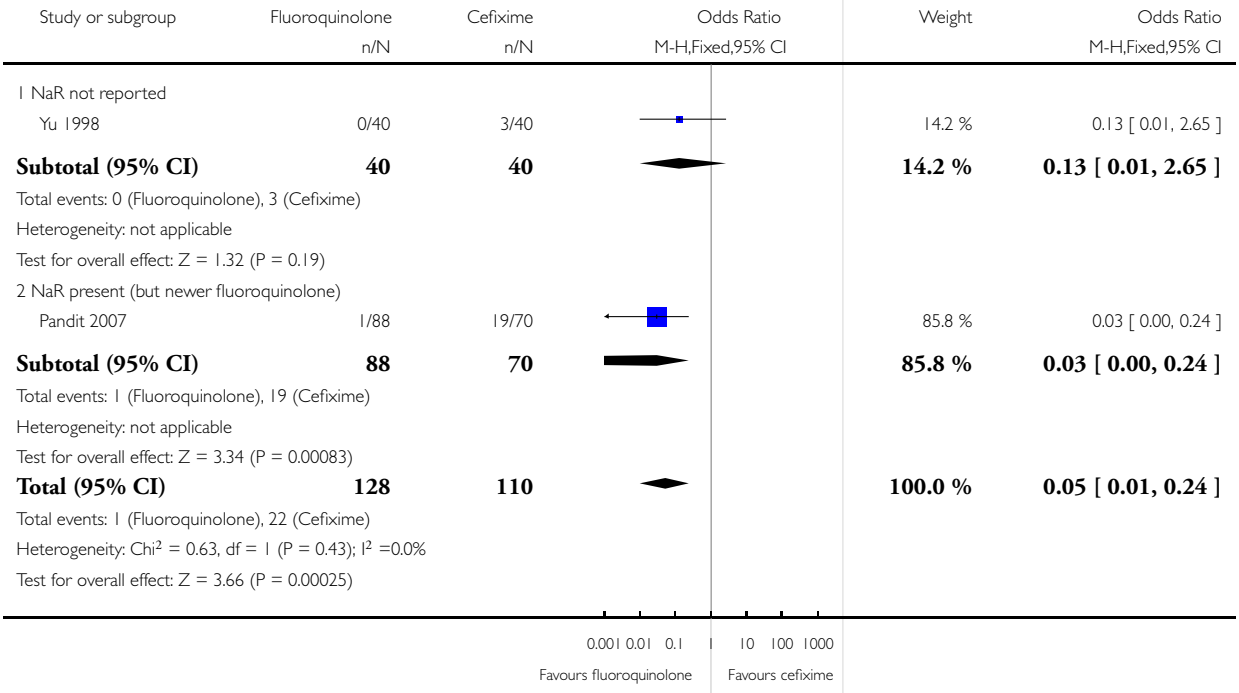


Analysis 5.1. Comparison 5 Fluoroquinolones vs cefixime, Outcome 1 Clinical failure (adults or mostly adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 1 Clinical failure (adults or mostly adults)



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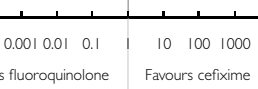
Analysis 5.2. Comparison 5 Fluoroquinolones vs cefixime, Outcome 2 Microbiological failure (adults or mostly adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 2 Microbiological failure (adults or mostly adults)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 NaR not reported					
Yu 1998	0/40	4/40		72.8 %	0.10 [0.01, 1.92]
Subtotal (95% CI)	**40**	**40**		**72.8 %**	**0.10 [0.01, 1.92]**
Total events: 0 (Fluoroquinolone), 4 (Cefixime)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
2 NaR present (but newer fluoroquinolone)					
Pandit 2007	0/88	1/70		27.2 %	0.26 [0.01, 6.53]
Subtotal (95% CI)	**88**	**70**		**27.2 %**	**0.26 [0.01, 6.53]**
Total events: 0 (Fluoroquinolone), 1 (Cefixime)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.82 (P = 0.41)					
Total (95% CI)	**128**	**110**		**100.0 %**	**0.14 [0.02, 1.23]**
Total events: 0 (Fluoroquinolone), 5 (Cefixime)					
Heterogeneity: Chi^2 = 0.19, df = 1 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 1.77 (P = 0.076)					



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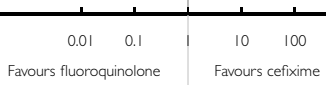
Analysis 5.3. Comparison 5 Fluoroquinolones vs cefixime, Outcome 3 Relapse (adults or mostly adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 3 Relapse (adults or mostly adults)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR not reported				
Yu 1998	0/40	0/40		0.0 [0.0, 0.0]
Subtotal (95% CI)	**40**	**40**		**0.0 [0.0, 0.0]**
Total events: 0 (Fluoroquinolone), 0 (Cefixime)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 NaR present (but newer fluoroquinolone)				
Pandit 2007	2/87	6/51		0.18 [0.03, 0.91]
Subtotal (95% CI)	**87**	**51**		**0.18 [0.03, 0.91]**
Total events: 2 (Fluoroquinolone), 6 (Cefixime)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.07 (P = 0.038)				
Total (95% CI)	**127**	**91**		**0.18 [0.03, 0.91]**
Total events: 2 (Fluoroquinolone), 6 (Cefixime)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 2.07 (P = 0.038)				



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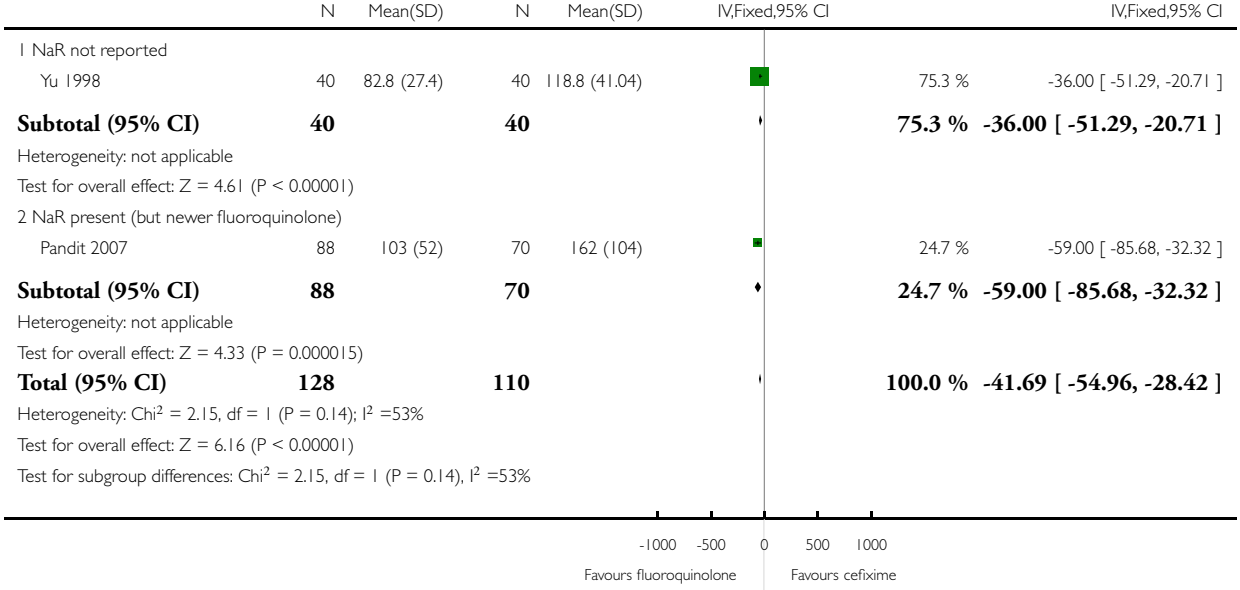
Analysis 5.4. Comparison 5 Fluoroquinolones vs cefixime, Outcome 4 Fever clearance time (adults or mostly adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 4 Fever clearance time (adults or mostly adults)

Study or subgroup	Fluoroquinolone N	Mean(SD)	Cefixime N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 NaR not reported							
Yu 1998	40	82.8 (27.4)	40	118.8 (41.04)		75.3 %	-36.00 [-51.29, -20.71]
Subtotal (95% CI)	**40**		**40**			**75.3 %**	**-36.00 [-51.29, -20.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.61 (P < 0.00001)							
2 NaR present (but newer fluoroquinolone)							
Pandit 2007	88	103 (52)	70	162 (104)		24.7 %	-59.00 [-85.68, -32.32]
Subtotal (95% CI)	**88**		**70**			**24.7 %**	**-59.00 [-85.68, -32.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.33 (P = 0.000015)							
Total (95% CI)	**128**		**110**			**100.0 %**	**-41.69 [-54.96, -28.42]**
Heterogeneity: Chi^2 = 2.15, df = 1 (P = 0.14); I^2 =53%							
Test for overall effect: Z = 6.16 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.15, df = 1 (P = 0.14), I^2 =53%							



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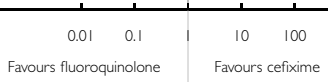
Analysis 5.5. Comparison 5 Fluoroquinolones vs cefixime, Outcome 5 Convalescent faecal carriage (adults or mostly adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 5 Convalescent faecal carriage (adults or mostly adults)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR not reported				
Yu 1998	0/40	0/40		0.0 [0.0, 0.0]
Subtotal (95% CI)	**40**	**40**		**0.0 [0.0, 0.0]**
Total events: 0 (Fluoroquinolone), 0 (Cefixime)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 NaR present (but newer fluoroquinolone)				
Pandit 2007	0/82	1/65		0.26 [0.01, 6.50]
Subtotal (95% CI)	**82**	**65**		**0.26 [0.01, 6.50]**
Total events: 0 (Fluoroquinolone), 1 (Cefixime)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.82 (P = 0.41)				
Total (95% CI)	**122**	**105**		**0.26 [0.01, 6.50]**
Total events: 0 (Fluoroquinolone), 1 (Cefixime)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.82 (P = 0.41)				



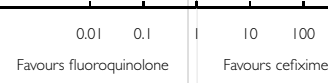
Analysis 5.6. Comparison 5 Fluoroquinolones vs cefixime, Outcome 6 Complications (adults or mostly adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 6 Complications (adults or mostly adults)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR present (but newer fluoroquinolone)				
Pandit 2007	0/88	1/70		0.26 [0.01, 6.53]



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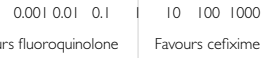
Analysis 5.7. Comparison 5 Fluoroquinolones vs cefixime, Outcome 7 Adverse events (not serious) (adults or mostly adults).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 7 Adverse events (not serious) (adults or mostly adults)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 NaR not reported					
Yu 1998	2/40	3/40		50.8 %	0.65 [0.10, 4.11]
Subtotal (95% CI)	**40**	**40**		**50.8 %**	**0.65 [0.10, 4.11]**
Total events: 2 (Fluoroquinolone), 3 (Cefixime)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.65)					
2 NaR present (but newer fluoroquinolone)					
Pandit 2007	18/88	1/70		49.2 %	17.74 [2.30, 136.58]
Subtotal (95% CI)	**88**	**70**		**49.2 %**	**17.74 [2.30, 136.58]**
Total events: 18 (Fluoroquinolone), 1 (Cefixime)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.76 (P = 0.0057)					
Total (95% CI)	**128**	**110**		**100.0 %**	**3.30 [0.11, 97.30]**
Total events: 20 (Fluoroquinolone), 4 (Cefixime)					
Heterogeneity: Tau^2 = 4.98; Chi^2 = 6.05, df = 1 (P = 0.01); I^2 =83%					
Test for overall effect: Z = 0.69 (P = 0.49)					



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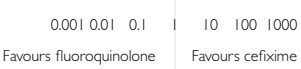
Analysis 5.8. Comparison 5 Fluoroquinolones vs cefixime, Outcome 8 Clinical failure (children only).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 8 Clinical failure (children only)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR absent				
Cao 1999	1/38	8/44		0.12 [0.01, 1.02]



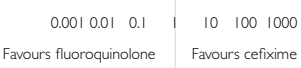
Analysis 5.9. Comparison 5 Fluoroquinolones vs cefixime, Outcome 9 Microbiological failure (children only).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 9 Microbiological failure (children only)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR absent				
Cao 1999	0/38	2/44		0.22 [0.01, 4.74]



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Analysis 5.10. Comparison 5 Fluoroquinolones vs cefixime, Outcome 10 Relapse (children only).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 10 Relapse (children only)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR absent				
Cao 1999	0/20	1/20		0.32 [0.01, 8.26]

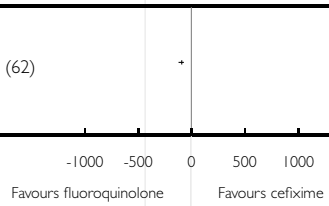
Analysis 5.11. Comparison 5 Fluoroquinolones vs cefixime, Outcome 11 Fever clearance time (children only).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 11 Fever clearance time (children only)

Study or subgroup	Fluoroquinolone N	Mean(SD)	Cefixime N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 NaR absent						
Cao 1999	37	119 (50)	41	210 (62)		-91.00 [-115.89, -66.11]



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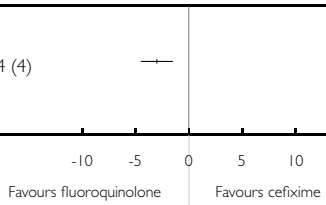
Analysis 5.12. Comparison 5 Fluoroquinolones vs cefixime, Outcome 12 Length of hospital stay (children only).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 12 Length of hospital stay (children only)

Study or subgroup	Fluoroquinolone N	Mean(SD)	Cefixime N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 NaR absent						
Cao 1999	37	11 (3)	44	14 (4)		-3.00 [-4.53, -1.47]



Analysis 5.13. Comparison 5 Fluoroquinolones vs cefixime, Outcome 13 Complications (children only).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 5 Fluoroquinolones vs cefixime

Outcome: 13 Complications (children only)

Study or subgroup	Fluoroquinolone n/N	Cefixime n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR absent				
Cao 1999	2/38	1/44		2.39 [0.21, 27.43]

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Analysis 6.1. Comparison 6 Fluoroquinolones vs ceftriaxone, Outcome 1 Clinical failure.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 6 Fluoroquinolones vs ceftriaxone

Outcome: 1 Clinical failure

Study or subgroup	Fluoroquinolone n/N	Ceftriaxone n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 NaR absent (adults only)					
Smith 1994	0/22	6/25		41.1 %	0.07 [0.00, 1.26]
Subtotal (95% CI)	**22**	**25**		**41.1 %**	**0.07 [0.00, 1.26]**
Total events: 0 (Fluoroquinolone), 6 (Ceftriaxone)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.071)					
2 NaR not reported (adults only)					
Tran 1994	0/16	2/15		17.2 %	0.16 [0.01, 3.71]
Wallace 1993	0/20	6/22		41.7 %	0.06 [0.00, 1.18]
Subtotal (95% CI)	**36**	**37**		**58.9 %**	**0.09 [0.01, 0.76]**
Total events: 0 (Fluoroquinolone), 8 (Ceftriaxone)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.21 (P = 0.027)					
Total (95% CI)	**58**	**62**		**100.0 %**	**0.08 [0.01, 0.45]**
Total events: 0 (Fluoroquinolone), 14 (Ceftriaxone)					
Heterogeneity: Chi^2 = 0.24, df = 2 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 2.87 (P = 0.0042)					

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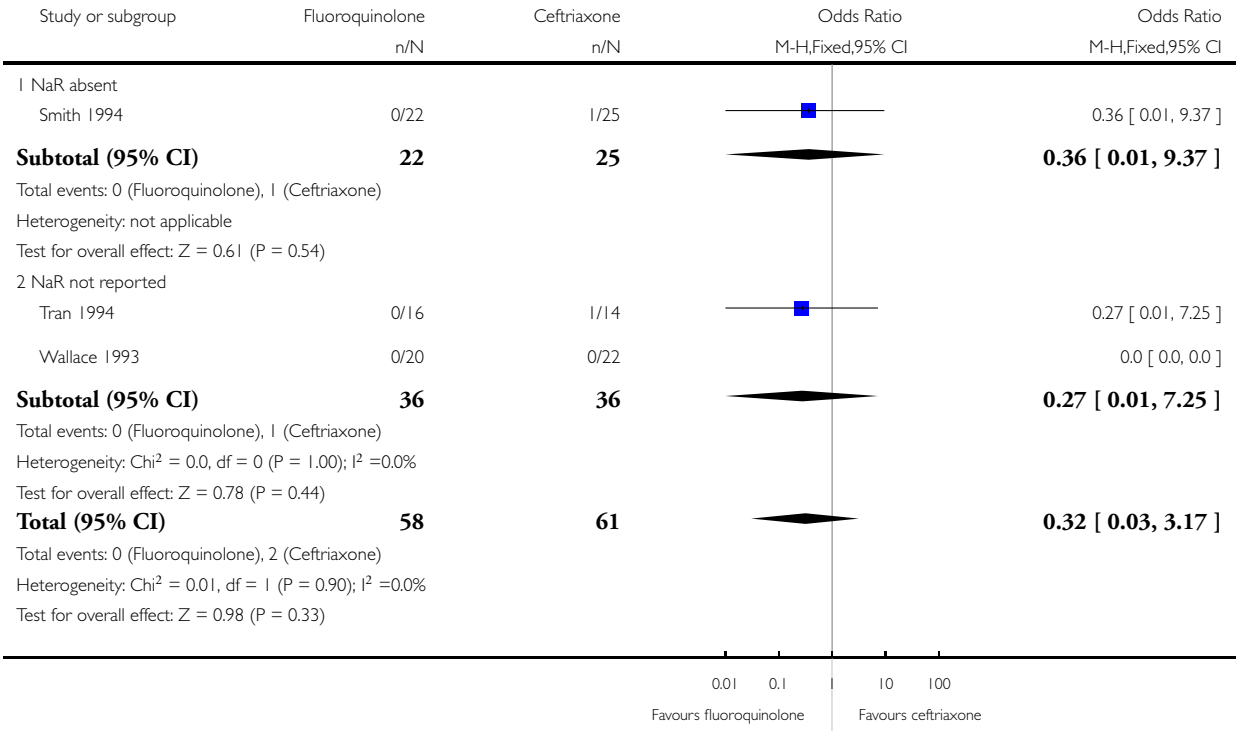
Analysis 6.2. Comparison 6 Fluoroquinolones vs ceftriaxone, Outcome 2 Microbiological failure.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 6 Fluoroquinolones vs ceftriaxone

Outcome: 2 Microbiological failure



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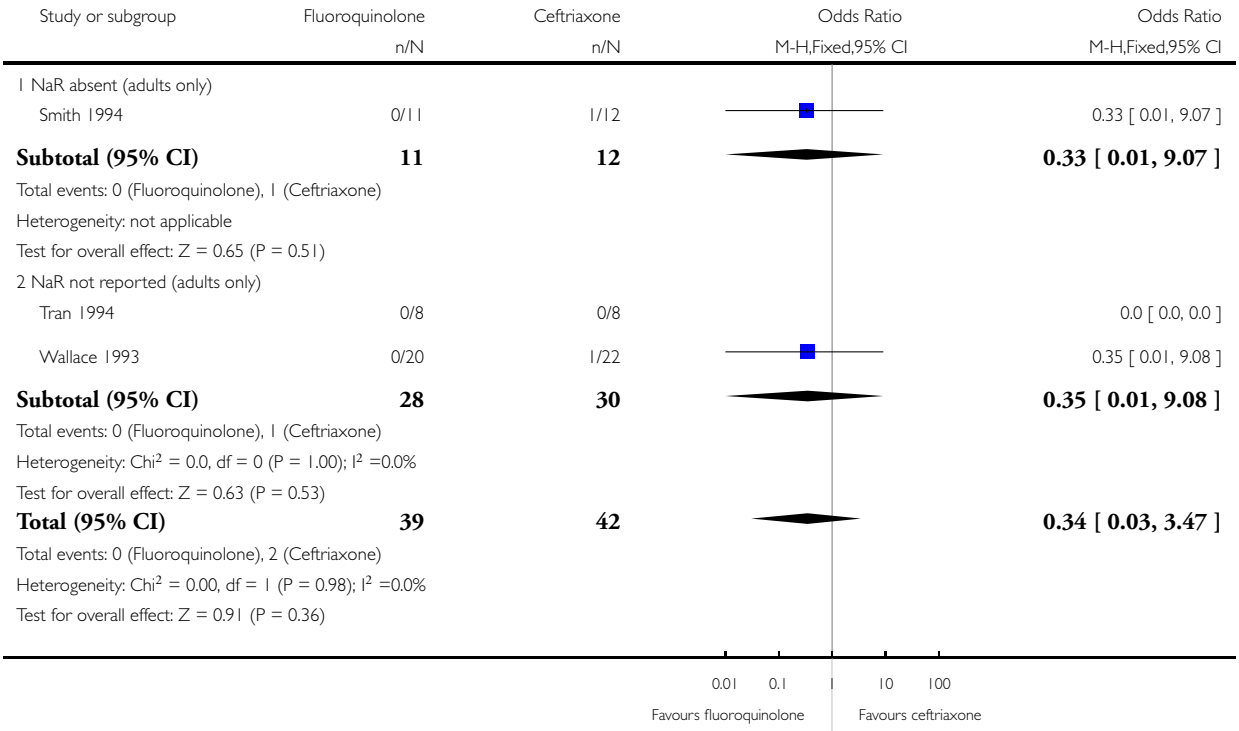
Analysis 6.3. Comparison 6 Fluoroquinolones vs ceftriaxone, Outcome 3 Relapse.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 6 Fluoroquinolones vs ceftriaxone

Outcome: 3 Relapse



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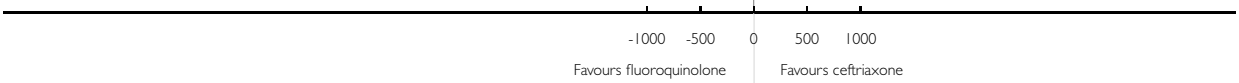
Analysis 6.4. Comparison 6 Fluoroquinolones vs ceftriaxone, Outcome 4 Fever clearance time.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 6 Fluoroquinolones vs ceftriaxone

Outcome: 4 Fever clearance time

Study or subgroup	Fluoroquinolone N	Mean(SD)	Ceftriaxone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 NaR absent (adults only)							
Smith 1994	22	81 (25)	25	196 (87)		61.7 %	-115.00 [-150.67, -79.33]
Subtotal (95% CI)	**22**		**25**			**61.7 %**	**-115.00 [-150.67, -79.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.32 (P < 0.00001)							
2 NaR not reported (adults only)							
Tran 1994	16	81 (40)	13	160 (75)		38.3 %	-79.00 [-124.24, -33.76]
Subtotal (95% CI)	**16**		**13**			**38.3 %**	**-79.00 [-124.24, -33.76]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.42 (P = 0.00062)							
Total (95% CI)	**38**		**38**			**100.0 %**	**-101.20 [-129.21, -73.19]**
Heterogeneity: Chi^2 = 1.50, df = 1 (P = 0.22); I^2 =33%							
Test for overall effect: Z = 7.08 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.50, df = 1 (P = 0.22), I^2 =33%							



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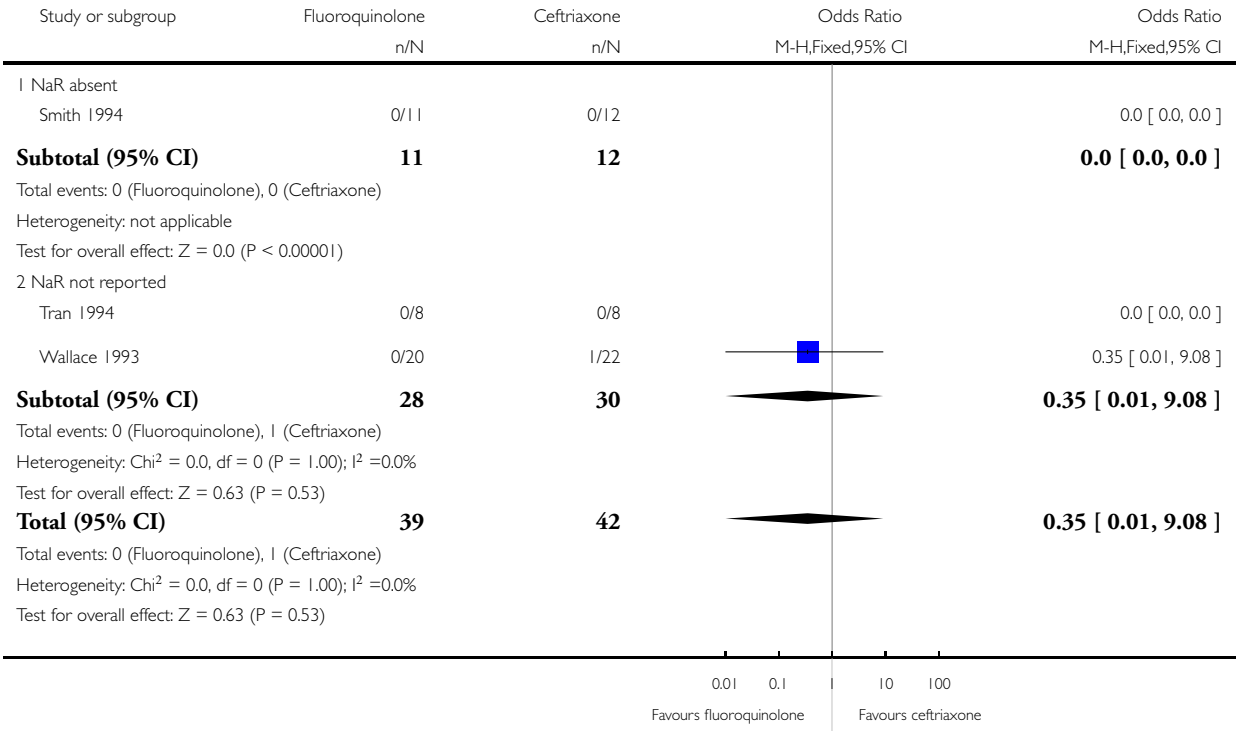
Analysis 6.5. Comparison 6 Fluoroquinolones vs ceftriaxone, Outcome 5 Convalescent faecal carriage.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 6 Fluoroquinolones vs ceftriaxone

Outcome: 5 Convalescent faecal carriage



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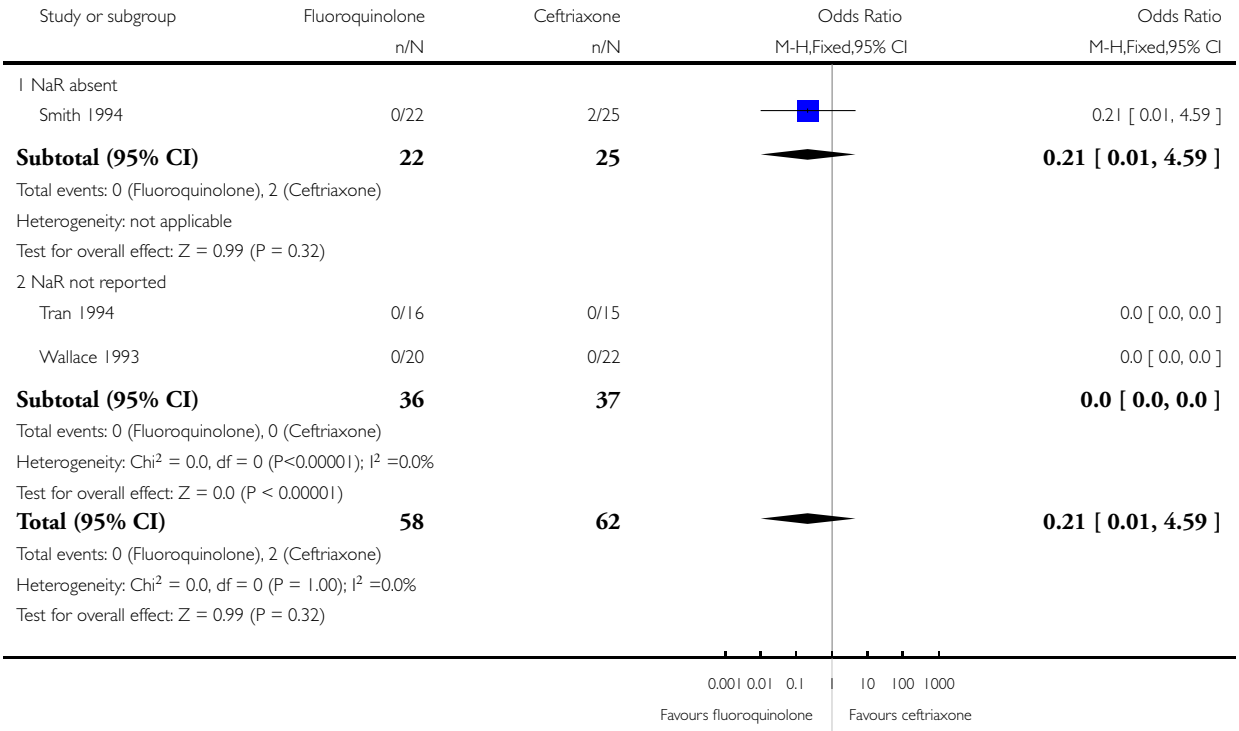
Analysis 6.6. Comparison 6 Fluoroquinolones vs ceftriaxone, Outcome 6 Complications.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 6 Fluoroquinolones vs ceftriaxone

Outcome: 6 Complications



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Analysis 6.7. Comparison 6 Fluoroquinolones vs ceftriaxone, Outcome 7 Serious adverse events.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 6 Fluoroquinolones vs ceftriaxone

Outcome: 7 Serious adverse events

Study or subgroup	Fluoroquinolone n/N	Ceftriaxone n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR absent				
Smith 1994	0/22	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**22**	**25**		**0.0 [0.0, 0.0]**
Total events: 0 (Fluoroquinolone), 0 (Ceftriaxone)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 NaR not reported				
Tran 1994	0/16	1/15		0.29 [0.01, 7.76]
Subtotal (95% CI)	**16**	**15**		**0.29 [0.01, 7.76]**
Total events: 0 (Fluoroquinolone), 1 (Ceftriaxone)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.73 (P = 0.46)				
Total (95% CI)	**38**	**40**		**0.29 [0.01, 7.76]**
Total events: 0 (Fluoroquinolone), 1 (Ceftriaxone)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 0.73 (P = 0.46)				

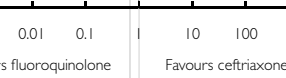
Analysis 6.8. Comparison 6 Fluoroquinolones vs ceftriaxone, Outcome 8 Adverse events (not serious).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 6 Fluoroquinolones vs ceftriaxone

Outcome: 8 Adverse events (not serious)

Study or subgroup	Fluoroquinolone n/N	Ceftriaxone n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 NaR absent				
Smith 1994	1/22	2/25		0.55 [0.05, 6.49]



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Analysis 7.1. Comparison 7 Norfloxacin vs chloramphenicol, Outcome 1 Clinical failure.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 7 Norfloxacin vs chloramphenicol

Outcome: 1 Clinical failure

Study or subgroup	Norfloxacin n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 MDR and NaR present				
Sarma 1991	0/20	0/20		0.0 [0.0, 0.0]
Subtotal (95% CI)	**20**	**20**		**0.0 [0.0, 0.0]**
Total events: 0 (Norfloxacin), 0 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 MDR absent and NaR not reported				
Morelli 1992	8/20	0/30		41.48 [2.22, 774.60]
Subtotal (95% CI)	**20**	**30**		**41.48 [2.22, 774.60]**
Total events: 8 (Norfloxacin), 0 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 2.49 (P = 0.013)				
3 MDR and NaR not reported				
Nalin 1987	9/90	3/79		2.81 [0.73, 10.79]
Subtotal (95% CI)	**90**	**79**		**2.81 [0.73, 10.79]**
Total events: 9 (Norfloxacin), 3 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.51 (P = 0.13)				
Total (95% CI)	**130**	**129**		**5.80 [1.87, 17.98]**
Total events: 17 (Norfloxacin), 3 (Chloramphenicol)				
Heterogeneity: Chi^2 = 2.85, df = 1 (P = 0.09); I^2 =65%				
Test for overall effect: Z = 3.04 (P = 0.0023)				

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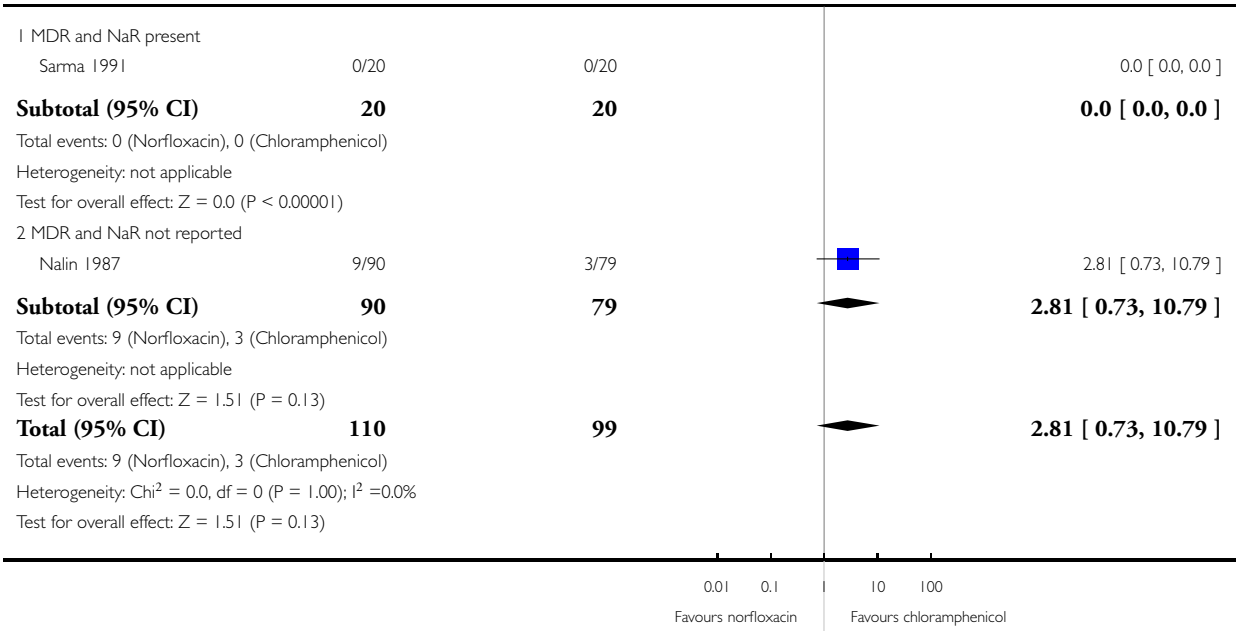
Analysis 7.2. Comparison 7 Norfloxacin vs chloramphenicol, Outcome 2 Microbiological failure.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 7 Norfloxacin vs chloramphenicol

Outcome: 2 Microbiological failure

Study or subgroup	Norfloxacin n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 MDR and NaR present				
Sarma 1991	0/20	0/20		0.0 [0.0, 0.0]
Subtotal (95% CI)	**20**	**20**		**0.0 [0.0, 0.0]**
Total events: 0 (Norfloxacin), 0 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 MDR and NaR not reported				
Nalin 1987	9/90	3/79		2.81 [0.73, 10.79]
Subtotal (95% CI)	**90**	**79**		**2.81 [0.73, 10.79]**
Total events: 9 (Norfloxacin), 3 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.51 (P = 0.13)				
Total (95% CI)	**110**	**99**		**2.81 [0.73, 10.79]**
Total events: 9 (Norfloxacin), 3 (Chloramphenicol)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.51 (P = 0.13)				



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Analysis 7.3. Comparison 7 Norfloxacin vs chloramphenicol, Outcome 3 Relapse.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 7 Norfloxacin vs chloramphenicol

Outcome: 3 Relapse

Study or subgroup	Norfloxacin n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 MDR and NaR present				
Sarma 1991	0/20	0/20		0.0 [0.0, 0.0]
Subtotal (95% CI)	**20**	**20**		**0.0 [0.0, 0.0]**
Total events: 0 (Norfloxacin), 0 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 MDR absent and NaR not reported				
Morelli 1992	0/20	3/30		0.19 [0.01, 3.92]
Subtotal (95% CI)	**20**	**30**		**0.19 [0.01, 3.92]**
Total events: 0 (Norfloxacin), 3 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.07 (P = 0.28)				
Total (95% CI)	**40**	**50**		**0.19 [0.01, 3.92]**
Total events: 0 (Norfloxacin), 3 (Chloramphenicol)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.07 (P = 0.28)				

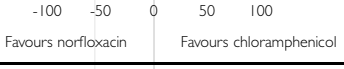
Analysis 7.4. Comparison 7 Norfloxacin vs chloramphenicol, Outcome 4 Fever clearance time.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 7 Norfloxacin vs chloramphenicol

Outcome: 4 Fever clearance time

Study or subgroup	Norfloxacin N	Mean(SD)	Chloramphenicol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 MDR and NaR present						
Sarma 1991	20	88 (12)	20	124 (16)		-36.00 [-44.77, -27.23]
2 MDR and NaR not reported						
Nalin 1987	90	160.8 (60)	79	122.4 (40.8)		38.40 [23.08, 53.72]



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Analysis 7.5. Comparison 7 Norfloxacin vs chloramphenicol, Outcome 5 Length of hospital stay (MDR and NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 7 Norfloxacin vs chloramphenicol

Outcome: 5 Length of hospital stay (MDR and NaR present)

Study or subgroup	Norfloxacin N	Mean(SD)	Chloramphenicol N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Sarma 1991	20	14 (0)	20	14 (0)		0.0 [0.0, 0.0]

Analysis 7.6. Comparison 7 Norfloxacin vs chloramphenicol, Outcome 6 Convalescent faecal carriage.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 7 Norfloxacin vs chloramphenicol

Outcome: 6 Convalescent faecal carriage

Study or subgroup	Norfloxacin n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 MDR and NaR present				
Sarma 1991	0/20	0/20		0.0 [0.0, 0.0]
Subtotal (95% CI)	**20**	**20**		**0.0 [0.0, 0.0]**
Total events: 0 (Norfloxacin), 0 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 MDR absent and NaR not reported				
Morelli 1992	3/20	4/30		1.15 [0.23, 5.78]
Subtotal (95% CI)	**20**	**30**		**1.15 [0.23, 5.78]**
Total events: 3 (Norfloxacin), 4 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.17 (P = 0.87)				

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Study or subgroup	Norfloxacin n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
3 MDR and NaR not reported				
Nalin 1987	2/90	2/79		0.88 [0.12, 6.36]
Subtotal (95% CI)	**90**	**79**		**0.88 [0.12, 6.36]**
Total events: 2 (Norfloxacin), 2 (Chloramphenicol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.13 (P = 0.90)				
Total (95% CI)	**130**	**129**		**1.03 [0.29, 3.61]**
Total events: 5 (Norfloxacin), 6 (Chloramphenicol)				
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%				
Test for overall effect: Z = 0.04 (P = 0.96)				

0.1 0.2 0.5 1 2 5 10

Favours norfloxacin Favours chloramphenicol

Analysis 7.7. Comparison 7 Norfloxacin vs chloramphenicol, Outcome 7 Adverse events (not serious).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 7 Norfloxacin vs chloramphenicol

Outcome: 7 Adverse events (not serious)

Study or subgroup	Norfloxacin n/N	Chloramphenicol n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 MDR and NaR present					
Sarma 1991	8/20	7/20		37.6 %	1.24 [0.34, 4.46]
Subtotal (95% CI)	**20**	**20**		**37.6 %**	**1.24 [0.34, 4.46]**
Total events: 8 (Norfloxacin), 7 (Chloramphenicol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 MDR and NaR not reported					
Nalin 1987	6/90	7/79		62.4 %	0.73 [0.24, 2.29]
Subtotal (95% CI)	**90**	**79**		**62.4 %**	**0.73 [0.24, 2.29]**
Total events: 6 (Norfloxacin), 7 (Chloramphenicol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.59)					
Total (95% CI)	**110**	**99**		**100.0 %**	**0.92 [0.40, 2.15]**
Total events: 14 (Norfloxacin), 14 (Chloramphenicol)					
Heterogeneity: Chi^2 = 0.36, df = 1 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					

0.1 0.2 0.5 1 2 5 10

Favours norfloxacin Favours chloramphenicol

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Analysis 8.1. Comparison 8 Norfloxacin vs ceftriaxone, Outcome 1 Clinical failure (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 8 Norfloxacin vs ceftriaxone

Outcome: 1 Clinical failure (NaR not reported)

Study or subgroup	Norfloxacin n/N	Ceftriaxone n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Huai 2000	6/30	2/30		3.50 [0.65, 18.98]

Analysis 8.2. Comparison 8 Norfloxacin vs ceftriaxone, Outcome 2 Relapse (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 8 Norfloxacin vs ceftriaxone

Outcome: 2 Relapse (NaR not reported)

Study or subgroup	Norfloxacin n/N	Ceftriaxone n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Huai 2000	2/30	0/30		5.35 [0.25, 116.31]

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Analysis 8.3. Comparison 8 Norfloxacin vs ceftriaxone, Outcome 3 Fever clearance time (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 8 Norfloxacin vs ceftriaxone

Outcome: 3 Fever clearance time (NaR not reported)

Study or subgroup	Norfloxacin N	Mean(SD)	Ceftriaxone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Huai 2000	30	134.4 (38.4)	30	86.4 (28.8)		48.00 [30.82, 65.18]

Analysis 8.4. Comparison 8 Norfloxacin vs ceftriaxone, Outcome 4 Adverse events (not serious) (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 8 Norfloxacin vs ceftriaxone

Outcome: 4 Adverse events (not serious) (NaR not reported)

Study or subgroup	Norfloxacin n/N	Ceftriaxone n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Huai 2000	3/30	1/30		3.22 [0.32, 32.89]

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Analysis 9.1. Comparison 9 Norfloxacin vs other fluoroquinolones (FQ), Outcome 1 Clinical failure.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 9 Norfloxacin vs other fluoroquinolones (FQ)

Outcome: 1 Clinical failure

Study or subgroup	Norfloxacin n/N	Other FQ n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Versus pefloxacin					
Jia 1994	13/67	0/63		45.2 %	31.46 [1.83, 541.56]
Morelli 1992	8/20	0/36		23.6 %	49.64 [2.67, 923.71]
Xiao 1991	6/8	1/6		31.3 %	15.00 [1.03, 218.30]
Subtotal (95% CI)	**95**	**105**		**100.0 %**	**30.60 [5.75, 162.86]**
Total events: 27 (Norfloxacin), 1 (Other FQ)					
Heterogeneity: Chi^2 = 0.38, df = 2 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 4.01 (P = 0.000061)					
2 Versus ofloxacin					
Morelli 1992	8/20	0/30		30.9 %	41.48 [2.22, 774.60]
Xiao 1991	6/8	0/9		16.9 %	49.40 [2.02, 1207.15]
Yang 1991	5/28	0/28		52.1 %	13.34 [0.70, 253.89]
Subtotal (95% CI)	**56**	**67**		**100.0 %**	**28.15 [4.80, 165.14]**
Total events: 19 (Norfloxacin), 0 (Other FQ)					
Heterogeneity: Chi^2 = 0.43, df = 2 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 3.70 (P = 0.00022)					
3 Versus enoxacin					
Bai 1995	18/50	5/52		56.7 %	5.29 [1.78, 15.69]
Morelli 1992	8/20	4/20		43.3 %	2.67 [0.65, 10.97]
Subtotal (95% CI)	**70**	**72**		**100.0 %**	**4.15 [1.77, 9.76]**
Total events: 26 (Norfloxacin), 9 (Other FQ)					
Heterogeneity: Chi^2 = 0.57, df = 1 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 3.26 (P = 0.0011)					

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Analysis 9.2. Comparison 9 Norfloxacin vs other fluoroquinolones (FQ), Outcome 2 Relapse.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 9 Norfloxacin vs other fluoroquinolones (FQ)

Outcome: 2 Relapse

Study or subgroup	Norfloxacin n/N	Other FQ n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Versus ofloxacin				
Morelli 1992	0/20	0/30		0.0 [0.0, 0.0]
Yang 1991	2/28	1/28		2.08 [0.18, 24.31]

Analysis 9.3. Comparison 9 Norfloxacin vs other fluoroquinolones (FQ), Outcome 3 Fever clearance time.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 9 Norfloxacin vs other fluoroquinolones (FQ)

Outcome: 3 Fever clearance time

Study or subgroup	Norfloxacin N	Mean(SD)	Other FQ N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Versus pefloxacin							
Jia 1994	67	124.56 (78.48)	63	99.84 (26.4)		66.4 %	24.72 [4.83, 44.61]
Xiao 1991	8	163.2 (26.4)	6	156 (26.4)		33.6 %	7.20 [-20.74, 35.14]
Subtotal (95% CI)	**75**		**69**			**100.0 %**	**18.83 [2.62, 35.03]**
Heterogeneity: Chi^2 = 1.00, df = 1 (P = 0.32); I^2 =0%							
Test for overall effect: Z = 2.28 (P = 0.023)							
2 Versus ofloxacin							
Xiao 1991	8	163.2 (26.4)	9	175.2 (33.6)		48.2 %	-12.00 [-40.58, 16.58]
Yang 1991	28	175.2 (69.6)	28	105.6 (26.4)		51.8 %	69.60 [42.03, 97.17]
Subtotal (95% CI)	**36**		**37**			**100.0 %**	**30.26 [10.42, 50.10]**
Heterogeneity: Chi^2 = 16.22, df = 1 (P = 0.00006); I^2 =94%							
Test for overall effect: Z = 2.99 (P = 0.0028)							
3 Versus enoxacin							
Bai 1995	50	240 (72)	52	180 (62.4)		100.0 %	60.00 [33.81, 86.19]

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Study or subgroup	Norfloxacin N	Mean(SD)	Other FQ N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**50**		**52**			**100.0 %**	**60.00 [33.81, 86.19]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.49 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 6.87, df = 2 (P = 0.03), I^2 =71%							

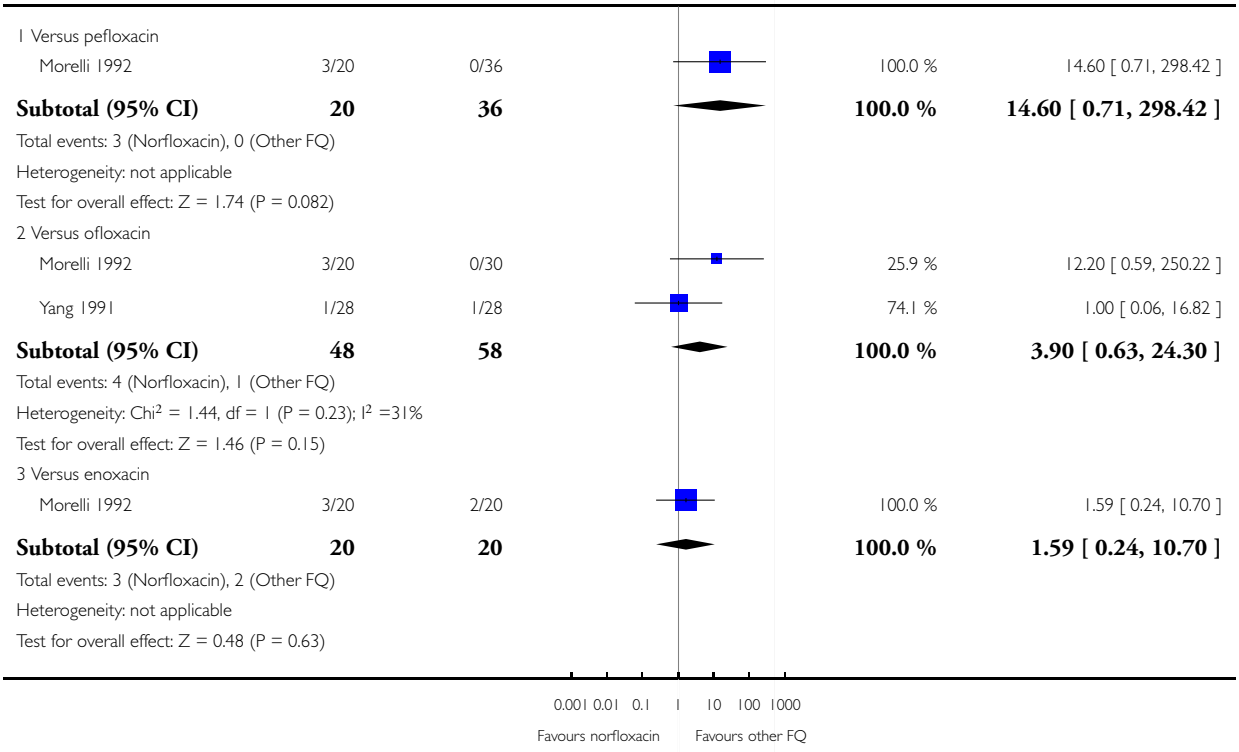
Analysis 9.4. Comparison 9 Norfloxacin vs other fluoroquinolones (FQ), Outcome 4 Convalescent faecal carriage.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 9 Norfloxacin vs other fluoroquinolones (FQ)

Outcome: 4 Convalescent faecal carriage

Study or subgroup	Norfloxacin n/N	Other FQ n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Versus pefloxacin					
Morelli 1992	3/20	0/36		100.0 %	14.60 [0.71, 298.42]
Subtotal (95% CI)	**20**	**36**		**100.0 %**	**14.60 [0.71, 298.42]**
Total events: 3 (Norfloxacin), 0 (Other FQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.74 (P = 0.082)					
2 Versus ofloxacin					
Morelli 1992	3/20	0/30		25.9 %	12.20 [0.59, 250.22]
Yang 1991	1/28	1/28		74.1 %	1.00 [0.06, 16.82]
Subtotal (95% CI)	**48**	**58**		**100.0 %**	**3.90 [0.63, 24.30]**
Total events: 4 (Norfloxacin), 1 (Other FQ)					
Heterogeneity: Chi^2 = 1.44, df = 1 (P = 0.23); I^2 =31%					
Test for overall effect: Z = 1.46 (P = 0.15)					
3 Versus enoxacin					
Morelli 1992	3/20	2/20		100.0 %	1.59 [0.24, 10.70]
Subtotal (95% CI)	**20**	**20**		**100.0 %**	**1.59 [0.24, 10.70]**
Total events: 3 (Norfloxacin), 2 (Other FQ)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					



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Analysis 9.5. Comparison 9 Norfloxacin vs other fluoroquinolones (FQ), Outcome 5 Adverse events (not serious).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 9 Norfloxacin vs other fluoroquinolones (FQ)

Outcome: 5 Adverse events (not serious)

Study or subgroup	Norfloxacin n/N	Other FQ n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Versus ofloxacin				
Yang 1991	1/28	1/28		1.00 [0.06, 16.82]
2 Versus enoxacin				
Bai 1995	1/50	1/52		1.04 [0.06, 17.11]

Analysis 10.1. Comparison 10 Fluoroquinolones for 2 days vs 3 days, Outcome 1 Clinical failure (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 10 Fluoroquinolones for 2 days vs 3 days

Outcome: 1 Clinical failure (NaR present)

Study or subgroup	2 days n/N	3 days n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Adults only					
Nguyen 1997	1/47	6/53		100.0 %	0.17 [0.02, 1.47]
Subtotal (95% CI)	**47**	**53**		**100.0 %**	**0.17 [0.02, 1.47]**
Total events: 1 (2 days), 6 (3 days)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
2 Children only					
Vinh 1996	6/53	2/47		35.7 %	2.87 [0.55, 14.98]
Vinh 2005	6/89	4/107		64.3 %	1.86 [0.51, 6.81]
Subtotal (95% CI)	**142**	**154**		**100.0 %**	**2.22 [0.81, 6.12]**
Total events: 12 (2 days), 6 (3 days)					
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 1.54 (P = 0.12)					

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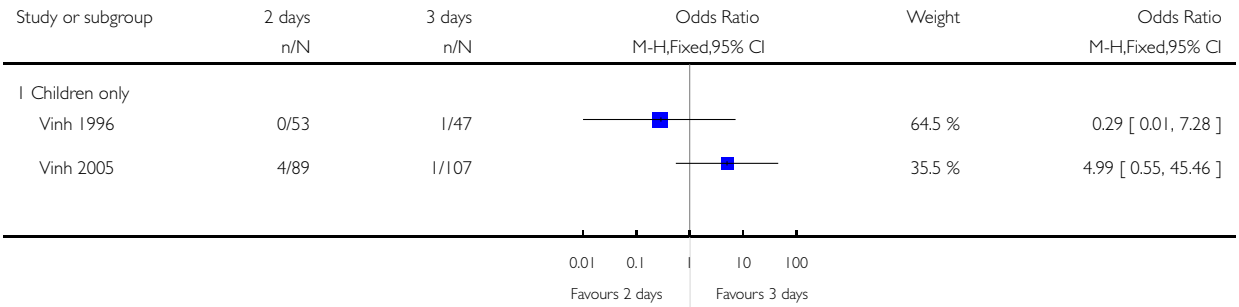
Analysis 10.2. Comparison 10 Fluoroquinolones for 2 days vs 3 days, Outcome 2 Microbiological failure (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 10 Fluoroquinolones for 2 days vs 3 days

Outcome: 2 Microbiological failure (NaR present)



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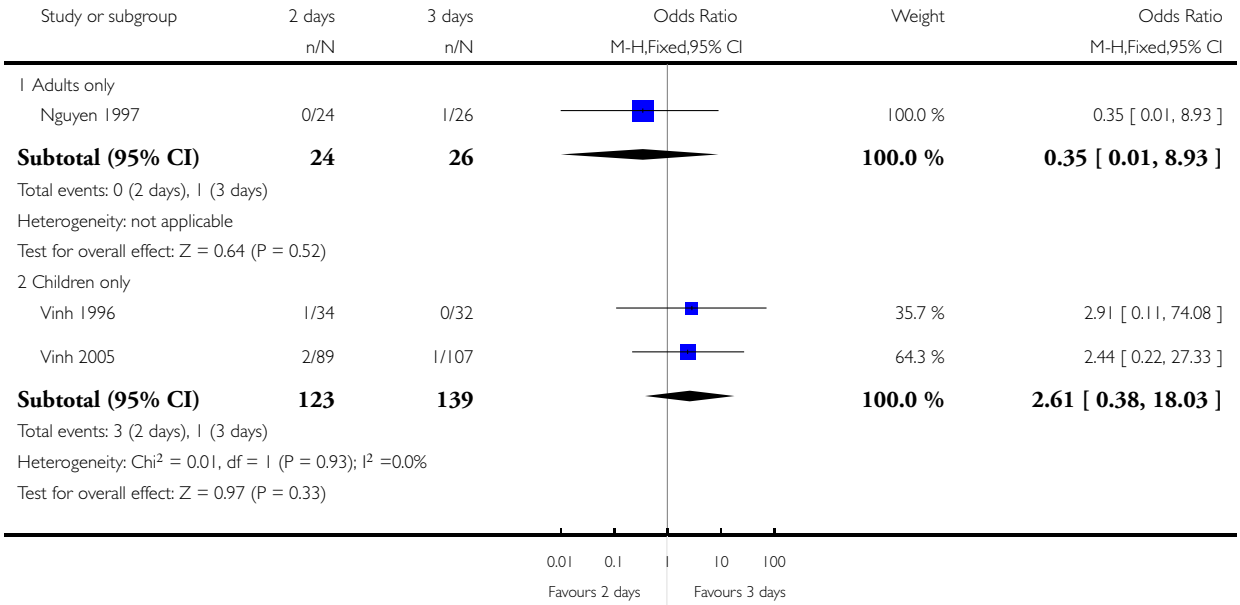
Analysis 10.3. Comparison 10 Fluoroquinolones for 2 days vs 3 days, Outcome 3 Relapse (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 10 Fluoroquinolones for 2 days vs 3 days

Outcome: 3 Relapse (NaR present)



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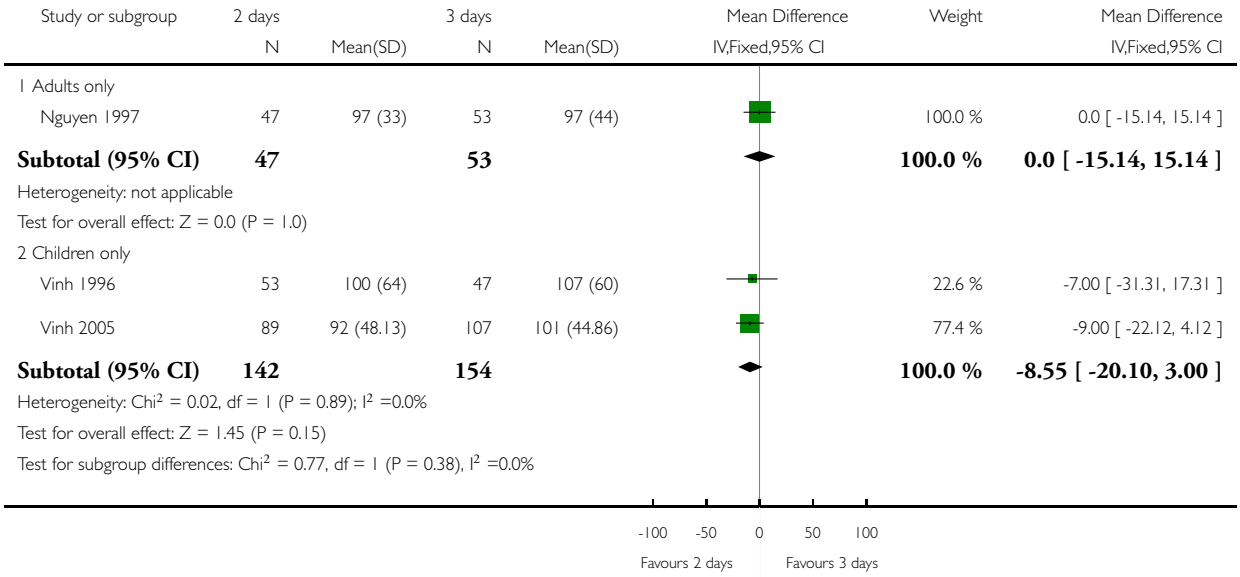
Analysis 10.4. Comparison 10 Fluoroquinolones for 2 days vs 3 days, Outcome 4 Fever clearance time (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 10 Fluoroquinolones for 2 days vs 3 days

Outcome: 4 Fever clearance time (NaR present)



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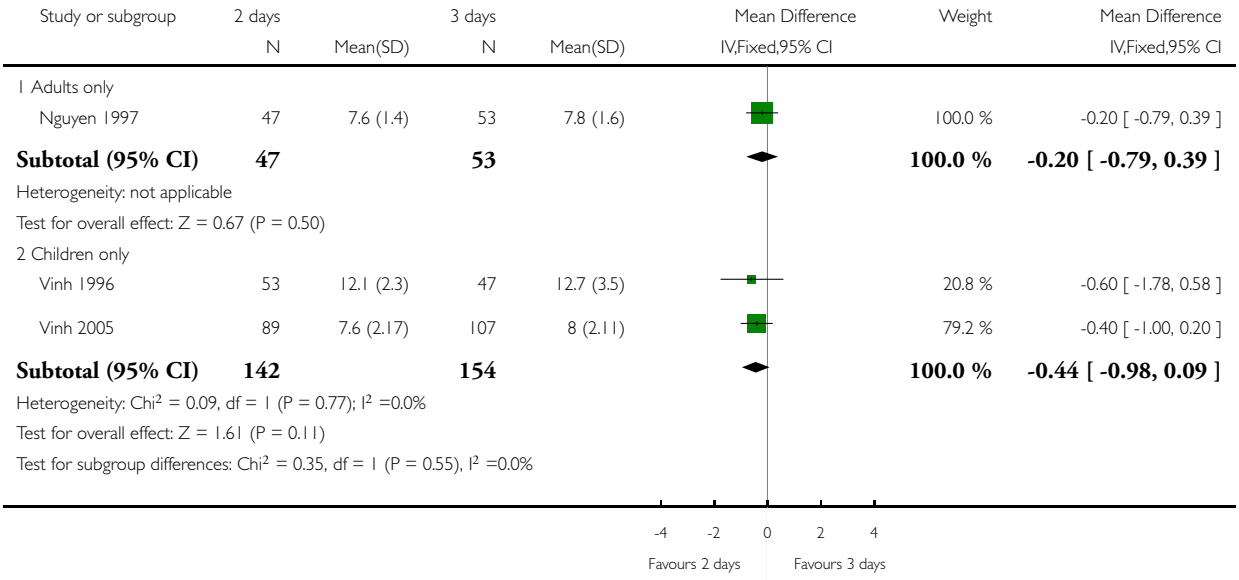
Analysis 10.5. Comparison 10 Fluoroquinolones for 2 days vs 3 days, Outcome 5 Length of hospital stay (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 10 Fluoroquinolones for 2 days vs 3 days

Outcome: 5 Length of hospital stay (NaR present)

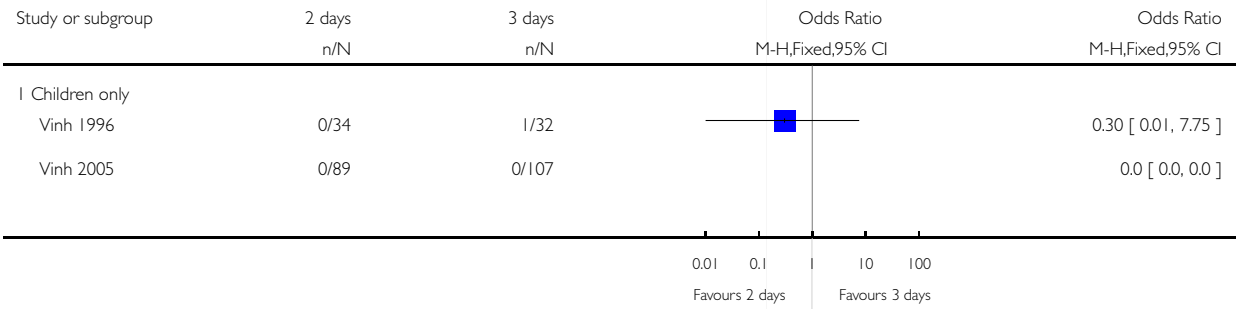


Analysis 10.6. Comparison 10 Fluoroquinolones for 2 days vs 3 days, Outcome 6 Convalescent faecal carriage (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 10 Fluoroquinolones for 2 days vs 3 days

Outcome: 6 Convalescent faecal carriage (NaR present)



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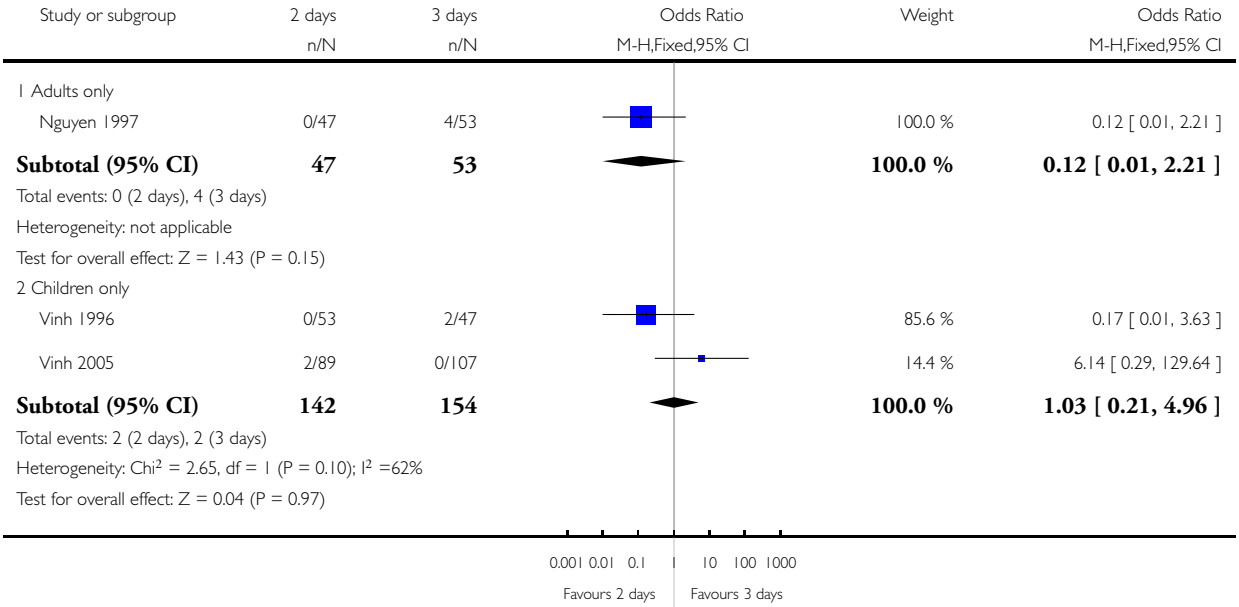
Analysis 10.7. Comparison 10 Fluoroquinolones for 2 days vs 3 days, Outcome 7 Complications (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 10 Fluoroquinolones for 2 days vs 3 days

Outcome: 7 Complications (NaR present)

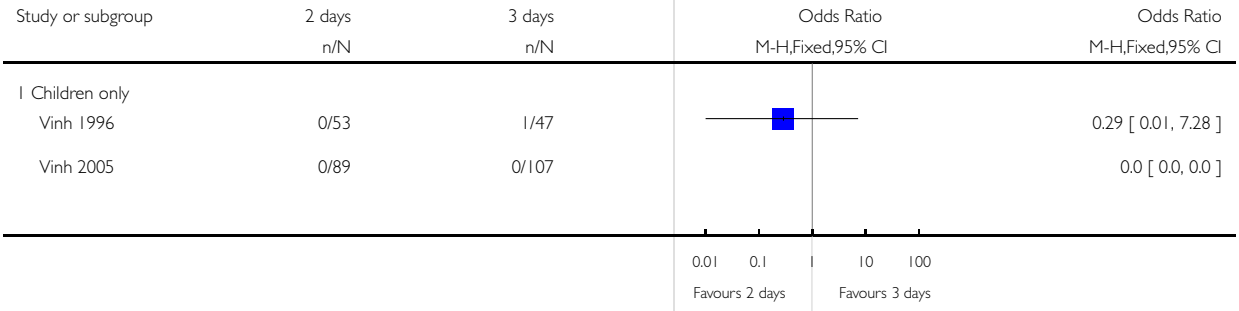


Analysis 10.8. Comparison 10 Fluoroquinolones for 2 days vs 3 days, Outcome 8 Adverse events (not serious) (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 10 Fluoroquinolones for 2 days vs 3 days

Outcome: 8 Adverse events (not serious) (NaR present)



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Analysis 11.1. Comparison 11 Fluoroquinolones for 3 days vs 5 days, Outcome 1 Clinical failure (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 11 Fluoroquinolones for 3 days vs 5 days

Outcome: 1 Clinical failure (NaR not reported)

Study or subgroup	3 days n/N	5 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Adults only				
Duong 1995	0/22	1/41		0.60 [0.02, 15.35]

Analysis 11.2. Comparison 11 Fluoroquinolones for 3 days vs 5 days, Outcome 2 Relapse.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 11 Fluoroquinolones for 3 days vs 5 days

Outcome: 2 Relapse

Study or subgroup	3 days n/N	5 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Adults only (NaR not reported)				
Duong 1995	0/14	1/26		0.59 [0.02, 15.35]
2 Children mostly (NaR present)				
Tran 1995	0/79	1/75		0.31 [0.01, 7.79]

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Analysis 11.3. Comparison 11 Fluoroquinolones for 3 days vs 5 days, Outcome 3 Fever clearance time.

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 11 Fluoroquinolones for 3 days vs 5 days

Outcome: 3 Fever clearance time

Study or subgroup	3 days N	Mean(SD)	5 days N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults only (NaR not reported)						
Duong 1995	22	89 (31)	41	82 (36)		7.00 [-10.01, 24.01]
2 Children mostly (NaR present)						
Tran 1995	103	60 (21.6)	92	72 (21.6)		-12.00 [-18.07, -5.93]

Analysis 11.4. Comparison 11 Fluoroquinolones for 3 days vs 5 days, Outcome 4 Length of hospital stay (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 11 Fluoroquinolones for 3 days vs 5 days

Outcome: 4 Length of hospital stay (NaR not reported)

Study or subgroup	3 days N	Mean(SD)	5 days N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Adults only						
Duong 1995	22	7.5 (0.15)	41	7.47 (0.14)		0.03 [-0.05, 0.11]

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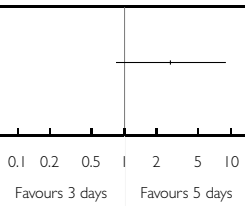
Analysis 11.5. Comparison 11 Fluoroquinolones for 3 days vs 5 days, Outcome 5 Adverse events (not serious) (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 11 Fluoroquinolones for 3 days vs 5 days

Outcome: 5 Adverse events (not serious) (NaR present)

Study or subgroup	3 days n/N	5 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Children mostly				
Tran 1995	11/118	4/110		2.72 [0.84, 8.83]



Analysis 12.1. Comparison 12 Fluoroquinolones for 5 days vs 7 days, Outcome 1 Microbiological failure (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 12 Fluoroquinolones for 5 days vs 7 days

Outcome: 1 Microbiological failure (NaR not reported)

Study or subgroup	5 days n/N	7 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Unal 1996	1/22	0/24		3.42 [0.13, 88.40]

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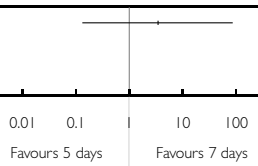
Analysis 12.2. Comparison 12 Fluoroquinolones for 5 days vs 7 days, Outcome 2 Relapse (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 12 Fluoroquinolones for 5 days vs 7 days

Outcome: 2 Relapse (NaR not reported)

Study or subgroup	5 days n/N	7 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Unal 1996	1/22	0/24		3.42 [0.13, 88.40]



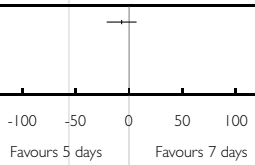
Analysis 12.3. Comparison 12 Fluoroquinolones for 5 days vs 7 days, Outcome 3 Fever clearance time (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 12 Fluoroquinolones for 5 days vs 7 days

Outcome: 3 Fever clearance time (NaR not reported)

Study or subgroup	5 days N	Mean(SD)	7 days N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Unal 1996	22	74.4 (24)	24	81.6 (24)		-7.20 [-21.08, 6.68]



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Analysis 12.4. Comparison 12 Fluoroquinolones for 5 days vs 7 days, Outcome 4 Adverse events (not serious) (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 12 Fluoroquinolones for 5 days vs 7 days

Outcome: 4 Adverse events (not serious) (NaR not reported)

Study or subgroup	5 days n/N	7 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Unal 1996	3/22	4/24		0.79 [0.16, 4.00]

Analysis 13.1. Comparison 13 Fluoroquinolones for 7 days vs 10 or 14 days, Outcome 1 Microbiological failure (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 13 Fluoroquinolones for 7 days vs 10 or 14 days

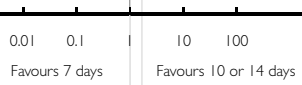
Outcome: 1 Microbiological failure (NaR not reported)

Study or subgroup	7 days n/N	10 or 14 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Arnold 1993	1/24	1/33		1.39 [0.08, 23.41]
Kalo 1997	0/15	0/15		0.0 [0.0, 0.0]
Total (95% CI)	**39**	**48**		**1.39 [0.08, 23.41]**

Total events: 1 (7 days), 1 (10 or 14 days)

Heterogeneity: $Chi^2 = 0.0$, $df = 0$ ($P = 1.00$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.23$ ($P = 0.82$)



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Analysis 13.2. Comparison 13 Fluoroquinolones for 7 days vs 10 or 14 days, Outcome 2 Relapse (NaR not reported).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 13 Fluoroquinolones for 7 days vs 10 or 14 days

Outcome: 2 Relapse (NaR not reported)

Study or subgroup	7 days n/N	10 or 14 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Arnold 1993	1/24	0/33		4.28 [0.17, 109.61]
Kalo 1997	0/15	0/15		0.0 [0.0, 0.0]
Total (95% CI)	**39**	**48**		**4.28 [0.17, 109.61]**

Total events: 1 (7 days), 0 (10 or 14 days)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.88 (P = 0.38)

Favours 7 days Favours 10 or 14 days

Analysis 14.1. Comparison 14 Fluoroquinolones for 10 days vs 14 days, Outcome 1 Relapse (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 14 Fluoroquinolones for 10 days vs 14 days

Outcome: 1 Relapse (NaR present)

Study or subgroup	10 days n/N	14 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Alam 1995	0/35	2/34		0.18 [0.01, 3.96]

Favours 10 days Favours 14 days

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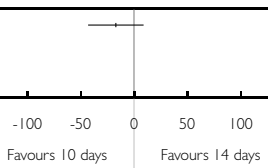
Analysis 14.2. Comparison 14 Fluoroquinolones for 10 days vs 14 days, Outcome 2 Fever clearance time (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 14 Fluoroquinolones for 10 days vs 14 days

Outcome: 2 Fever clearance time (NaR present)

Study or subgroup	10 days N	Mean(SD)	14 days N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Alam 1995	35	100.8 (45.6)	34	117.6 (62.4)		-16.80 [-42.65, 9.05]



Analysis 14.3. Comparison 14 Fluoroquinolones for 10 days vs 14 days, Outcome 3 Adverse events (not serious) (NaR present).

Review: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever)

Comparison: 14 Fluoroquinolones for 10 days vs 14 days

Outcome: 3 Adverse events (not serious) (NaR present)

Study or subgroup	10 days n/N	14 days n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Alam 1995	4/35	9/34		0.36 [0.10, 1.30]

WHAT'S NEW

Last assessed as up-to-date: 1 April 2008.

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2 April 2008	New search has been performed	**New trials:** Five new trials added for the following comparisons: fluoroquinolone vs chloramphenicol (adults, 1 trial); fluoroquinolone vs cefixime (mostly adults, 1 trial); fluoroquinolone vs azithromycin (mostly children, 2 trials); and fluoroquinolone 2 days vs 3 days (children, 1 trial). Two ongoing trials identified and referenced. Two trials were screened for eligibility and excluded (Kumar 2007; Suhendro 2007). **Tables and figures:** Updated Table 1 (Microbiology) to include "Multidrug resistance (MDR) defined as", and added minimum inhibitory concentrations (MICs) of fluoroquinolones where nalidixic acid resistance was not stated. (See 'Background' for explanation). Added funnel plots for the fluoroquinolones vs chloramphenicol comparison: Analysis 1.1 (clinical failure), Analysis 1.2 (microbiological failure), and Analysis 1.3 (relapse). **Methods:** Durrane Thaver and Asma Azmatullah selected the studies from the updated search results, and extracted data and assessed the methodological quality for the new included trials. **Minor corrections:** Analysis 6.6 (Complications: NaR not reported) and Table 2 (Complications): for Wallace 1993 for ceftriaxone group, changed from 1 to 0 (this was described as a 'persistent' complication, and appears to not have developed during treatment). Analysis 7.4 (Mean fever clearance time: MDR and NaR not reported): for Nalin 1987 (norfloxacin vs chloramphenicol) changed 167.5 hours to corrected value of 160.8 hours for norfloxacin group. Analysis 11.2 (Relapse), Analysis 11.3 (Fever clearance time), and Analysis 11.5 (Adverse events: not serious): for Tran 1995 changed from children only to children mostly, as stated in text of review. Table 3 (Definitions of outcomes): For Abejar 1993, moved statement ("blood culture positive at Day 23?") from under "relapse" to "microbiological failure" (resolved disagreement after consensus). Table 1 (Microbiology): Revision of MDR status for Xiao 1991 and Huai 2000, and included additional information for resistance data for Yu 1998. Table 2 (Complications): for Gottuzzo 1992, moved "gastrointestinal bleed, others not stated" to correct column.
2 April 2008	New citation required but conclusions have not changed	**New author:** Asma Azmatullah joined the author team. **Main changes to the results because of the new trials:** For adults, fluoroquinolones had statistically significantly lower fever clearance times compared with chloramphenicol, and also had statistically significantly lower clinical failure and relapse rates compared with cefixime. **Conclusions:** Our conclusions are unchanged, that is,

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(*Continued*)

		"data are limited, particularly for children".

Table 1. Microbiology

Comparison	Trial	Participants	Culture positive (site)	*S. Typhi/ Paratyphi*	Number (%)[a] with MDR	MDR defined as[b]	Number (%*)[a] NaR[c]	Notes on resistance
Fluoroquinolone vs chloramphenicol	Abejar 1993	Not stated	30 (blood)	30/0 Fluoroquinolone: 15 Chloramphenicol: 15	0	Not stated No resistance to chloramphenicol in chloramphenicol group	Not stated	-
	Arnold 1993	184 enrolled and randomized	91 (blood)	85/6 Fluoroquinolone 7-day: 23/1 Fluoroquinolone 14-day: 30/3 Chloramphenicol: 32/2	Not stated	Not stated	Not stated	-
	Bran 1991	102 randomized	102 (blood and/or bone marrow)	102/0	0	Not stated No resistance to chloramphenicol in either group	Not stated	-
	Cristiano 1995	60 enrolled and randomized	60 (blood)	60/0 Fluoroquinolone: 30 Chloramphenicol: 30	0	Not stated No resistance to chloramphenicol, ampicillin, or cotrimoxazole	Not stated MIC range of pefloxacin was < 0.016 to 0.5	-
	Gasem 2003	100 enrolled and randomized	55 (blood and/or bone marrow)	50/5	0	Not stated No resistance to	Not stated MIC range of ciproflo-	-

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Table 1. Microbiology (*Continued*)

						chloramphenicol 12.8% resistant to ampicillin or co-trimoxazole	xacin was < 1	
	Gottuzzo 1992	Not stated	98 (not stated)	Not stated	Not stated	Not stated	Not stated	-
	Morelli 1992	156 enrolled and randomized	156 (blood)	156/0	0	Not stated MIC range for chloramphenicol was 0.5 to 4 mg/L	Not stated MIC ranges were: ofloxacin 0.03 to 0.25; pefloxacin 0.06 to 0.5; ciprofloxacin 0.016 to 0.063; enoxacin 0.25; norfloxacin 0.063 to 0.25	-
	Phongmany 2005	107 enrolled and randomized	50 (blood)	50/0 Fluoroquinolone: 27 Chloramphenicol: 23	3/50 (6%) Fluoroquinolone: 1/27 Chloramphenicol: 2/23	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	0	Chloramphenicol resistance: 4/50 Fluoroquinolone: 1/27 Chloramphenicol: 3/23[d] Ampicillin: 5/50 Fluoroquinolone: 2/27 Chloramphenicol: 3/23 Co-trimoxazole: 4/50

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Table 1. Microbiology (*Continued*)

								Fluoro-quinolone: 1/27 Chloram-phenicol: 3/23
	Quintero 1988	Not stated	26 (not stated)	26/0 Fluoro-quinolone: 13 Chloram-phenicol: 13	0	Not stated No resistance to chloram-phenicol	Not stated	-
	Yousaf 1992	85 enrolled and randomized	85 (not stated)	Not stated	Not stated	Not stated	Not stated	-
Fluoro-quinolone vs ampicillin	Flores 1994	Not stated	40 (not stated)	40/0 Fluoro-quinolone: 20 Ampicillin: 20	Not stated	Not stated	Not stated	-
Fluoro-quinolone vs co-trimoxazole	Hajji 1988	77 enrolled and randomized	42 (blood and/or stool)	28/4 (from blood culture)	0	Not stated 1 isolate re-sistant to co-trimox-azole was in pefloxacin group	0	-
	Limson 1989	53 enrolled and randomized	40 (blood)	28/12 Fluoro-quinolone: 15/5 Co-trimoxa-zole: 13/7	0	Not stated No resis-tance to co-trimoxazole 16 were re-sistant to chloram-phenicol	Not stated	-
Fluoro-quinolone vs azithromy-cin	Dolecek 2008	358 enrolled and randomized	288 (blood or bone marrow)	282/5 Fluoro-quinolone: 144/1 Azithromy-cin: 138/4	153 (58%) of 263 *S.* Ty-phi Fluoro-quinolone: 87/137 Azithromy-	Resistant to all 3 (chlo-rampheni-col, ampi-cillin, co-tri-moxazole)	253 (96%) of 263 *S.* Ty-phi Fluoro-quinolone: 132/137 Azithromy-	All 5 *S.* Paratyphi were suscep-tible

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Table 1. Microbiology (*Continued*)

					cin: 66/126		cin: 121/126	
	Chinh 2000	97 enrolled and randomized	91 (blood)	86/2	68 (78%) of 87 Fluoroquinolone: 35 Azithromycin: 33	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	46 (52.3%; of 87 strains evaluated) Fluoroquinolone: 21 Azithromycin: 25	-
	Girgis 1999	123 enrolled and randomized	64 (62 by blood, 2 by stool)	60/4 Fluoroquinolone: 34/2 Azithromycin: 26/2	21/64 (33%) Fluoroquinolone: 15 Azithromycin: 6	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	Not stated	-
	Parry 2007	160 enrolled and randomized (excluding fluoroquinolone with azithromycin combination arm)	130 (blood and/or bone marrow)	125/0 Fluoroquinolone: 63/0 Azithromycin: 62/0	110/125 (88%) Fluoroquinolone: 57/63 Azithromycin: 53/62	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	117/125 (94%) Fluoroquinolone: 62/63 Azithromycin: 55/62	-
Fluoroquinolone vs cefixime	Cao 1999	138 enrolled and randomized	82 (blood)	82/0 Fluoroquinolone: 38 Cefixime: 44	70 (85%) *S.* Typhi: 32 *S.* Paratyphi: 38	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole) and tetracycline	0	-
	Pandit 2007	390 enrolled and randomized	169 (blood)	119/50 Fluoroquinolone: 65/27 Cefixime: 54/23	0	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	136/163 (83%) Fluoroquinolone: 71/89 Cefixime: 65/74	-

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Table 1. Microbiology (*Continued*)

	Yu 1998	80 randomized	80 (blood or bone marrow)	40/40 Fluoroquinolone: 21/19 Cefixime: 19/21	Not stated Individual drug resistance was reported, but reported together with isolates involved in another trial	Not stated	Not stated MIC for levofloxacin was ≤0.03 to 1 mg/L, but reported together with isolates involved in another trial	3/98 strains resistant to cefixime, but unclear which arm these were in and also were not separated from isolates involved in another trial
Fluoroquinolone vs ceftriaxone	Smith 1994	60 enrolled and randomized	47 (44 by blood and/or bone marrow, 3 by stool)	41/6 Fluoroquinolone: 21/1 Ceftriaxone: 20/5	26 (55%) Fluoroquinolone: 14 Ceftriaxone: 12	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole) and tetracycline	0	-
	Tran 1994	46 enrolled and randomized	31 (blood)	27/4 Fluoroquinolone: 14/2 Ceftriaxone: 13/2	12 (38%)	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	Not stated MIC for fleroxacin was mostly 0.06 (additional information from trial author)	-
	Wallace 1993	43 enrolled and 42 randomized	42 (blood)	42/0 Fluoroquinolone: 20 Ceftriaxone: 22	22 (52%) Fluoroquinolone: 11 Ceftriaxone: 11	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	Not stated	-
Norfloxacin vs chloramphenicol	Nalin 1987	184 enrolled and randomized	169 (not stated)	169/0 Fluoroquinolone: 90 Chloramphenicol: 79	Not stated	Not stated 1 isolate with 'intermediate susceptibility' in norfloxacin group	Not stated	-

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Table 1. Microbiology (*Continued*)

	Sarma 1991	40 enrolled and randomized	40 (blood and/or bone marrow)	38/2	8 (20%)	Not stated	4 (10%) (all reported as resistant to norfloxacin)	-
Norfloxacin vs ceftriaxone	Huai 2000	196 enrolled, but only 60 cases resistant to ampicillin, co-trimoxazole, or chloramphenicol were randomized	60 (56 by blood, 4 by bone marrow)	60/0 Fluoroquinolone: 30 Ceftriaxone: 30	Not stated	Not stated All described as resistant to ampicillin, chloramphenicol, or co-trimoxazole	Not stated	-
Fluoroquinolone vs another fluoroquinolone	Bai 1995	102 randomized	102 (blood or bone marrow)	102/0 Norfloxacin: 50 Enoxacin: 52	Not stated	Not stated	Not stated	-
	Jia 1994	130 randomized	130 (blood or bone marrow)	130/0 Norfloxacin: 67 Pefloxacin: 63	Not stated	Not stated	Not stated	-
	Xiao 1991	40 randomized (5 groups)	37 (blood or bone marrow) (6 groups)	37/0	Not stated	Not stated. All resistant to chloramphenicol; 1 resistant to norfloxacin; 4 resistant to pefloxacin	Not stated For 30 isolates tested, MIC range for ciprofloxacin was 0.03 to 1; norfloxacin < 0.03 to 2; ofloxacin 0.03 to 8; pefloxacin 0.03 to 2	-
	Yang 1991	56 randomized	56 (blood)	56/0 Norfloxacin: 28 Ofloxacin: 28	Not stated	Not stated Resistance to chloramphenicol in 18/27, ampicillin in	Not stated Resistance to norfloxacin: 3 (in ofloxacin group)	-

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Table 1. Microbiology (*Continued*)

						24/28, and co-trimoxazole in 25/26 isolates tested from ofloxacin group		
Different durations of fluoroquinolone	Alam 1995	76 enrolled and randomized	72 (blood or bone marrow)	61/8 Fluoroquinolone 10-day: 30/5 Fluoroquinolone 14-day: 31/3	36/69 (52%) Fluoroquinolone 10-day: 18 Fluoroquinolone 14-day: 18	Resistance to all drugs used conventionally against *S.* Typhi and *S.* Paratyphi	5/69 (7%) Fluoroquinolone 10-day: 2 Fluoroquinolone 14-day: 3 (derived from data presented for MIC for ciprofloxacin)	-
	Duong 1995	95 enrolled and randomized	63 (blood or bone marrow)	62/1 Fluoroquinolone 5-day: 40/1 Fluoroquinolone 3-day: 22/0	Around 80% [trialist's estimate]	Not available	Not stated	-
	Kalo 1997	30 (ampicillin-resistant) enrolled and randomized	30 (blood)	30/0	12/30 (40%)	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	Not stated	-
	Nguyen 1997	107 enrolled and randomized	101 (blood)	95/5 Fluoroquinolone 2-day: 43/4 Fluoroquinolone 3-day: 52/1	75/95 (79%) Fluoroquinolone 2-day: 35 Fluoroquinolone 3-day: 40	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole) and tetracycline	5/95 (5%) Fluoroquinolone 2-day: 1 Fluoroquinolone 3-day: 4	-
	Tran 1995	438 enrolled, 425	228 (blood)	207/19 (2 other	189 Fluoro-	Resistant to standard an-	Few NaR strains	-

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Table 1. Microbiology (*Continued*)

		randomized		Salmonella)	quinolone 3-day: 98 Fluoro-quinolone 5-day: 91	tibiotics	present, number not stated	
	Unal 1996	46 randomized	46 (blood and/or bone marrow)	19/27 Fluoro-quinolone 5-day: 8/14 Fluoro-quinolone 7-day: 11/13	6/46 (13%) Fluoro-quinolone 5-day: 3 Fluoro-quinolone 7-day: 3	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	Not stated MIC for pefloxacin was 0.06 to 1	-
	Vinh 1996	108 enrolled and randomized	100 (blood)	100/0 Fluoro-quinolone 2-day: 53 Fluoro-quinolone 3-day: 47	84 Fluoro-quinolone 2-day: 46 Fluoro-quinolone 3-day: 38	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole) and tetracycline	13 (13%) Fluoro-quinolone 2-day: 6 Fluoro-quinolone 3-day: 7	-
	Vinh 2005	235 enrolled and randomized	202 (blood)	196/0 Fluoro-quinolone 2-day: 89 Fluoro-quinolone 3-day: 107	176/196 (90%) Fluoro-quinolone 2-day: 82/89 Fluoro-quinolone 3-day: 94/107	Resistant to all 3 (chloramphenicol, ampicillin, co-trimoxazole)	4/161 (2.5%) Fluoro-quinolone 2-day: 1/72 Fluoro-quinolone 3-day: 3/89	-

MDR: multiple-drug-resistant strain; MIC: minimum inhibitory concentration; NaR: nalidixic acid-resistant strain.
[a] Calculation: number with MDR or NaR divided by number culture positive.
[b] As stated or implied in text of report.
[c] Or MIC of fluoroquinolone if available (all ranges in mg/L).
[d] These participants were switched to fluoroquinolone when organisms were found resistant to assigned drug.

Table 2. Complications[a]

Comparison	Trial	No. of participants (in brackets) with complications[b]	
		Intervention	Control

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Table 2. Complications[a] (*Continued*)

Fluoroquinolone vs chloramphenicol	Arnold 1993	Gastrointestinal haemorrhage, gastrointestinal perforation, and pneumonia occurred, but report does not say in which group, and trial combined both culture-negative and culture-positive participants	
	Gasem 2003	Ciprofloxacin: pneumonia (3)	Chloramphenicol: sepsis, myocarditis, pneumonia (1); gastrointestinal bleed (1); pneumonia (1)
	Gottuzzo 1992	Ciprofloxacin: gastrointestinal bleed (1); others not described	Not described
	Phongmany 2005	Ofloxacin: 0	Chloramphenicol: gastrointestinal bleed and perforation (1)
Fluoroquinolone vs co-trimoxazole	Hajji 1988	0	0
Fluoroquinolone vs azithromycin	Dolecek 2008	Gatifloxacin: 0	Azithromycin: liver dysfunction (2); pneumonia (2); gastrointestinal bleed (4)
	Chinh 2000	Ofloxacin: gastrointestinal bleed (1)	Azithromycin: gastrointestinal bleed (1)
	Girgis 1999	0	0
	Parry 2007	Ofloxacin: 0	Azithromycin: gastrointestinal bleed (2)
Fluoroquinolone vs cefixime	Cao 1999	Ofloxacin: death (1); small gastrointestinal bleed (1)	Cefixime: required blood transfusion (1)
	Pandit 2007	Gatifloxacin: 0	Cefixime: death with gastrointestinal bleed; thrombocytopenia; disseminated intravascular coagulation (1)
	Yu 1998	0	0
Fluoroquinolone vs ceftriaxone	Smith 1994	Ofloxacin: 0	Ceftriaxone: anaemia (1); jaundice and anaemia (1)
	Tran 1994	0	0
	Wallace 1993	0	0
Norfloxacin vs chloramphenicol	Nalin 1987	Norfloxacin: gastrointestinal bleed (number unclear)	Chloramphenicol: 0
	Sarma 1991	0	0

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Table 2. Complications[a] (*Continued*)

Norfloxacin vs other fluoroquinolones	Bai 1995	0	0
	Jia 1994	0	0
	Xiao 1991	Gastrointestinal bleeds (2) and encephalopathy (1): unclear which group they occurred in	Gastrointestinal bleeds (2) and encephalopathy (1): unclear which group they occurred in
	Yang 1991	Not described	Not described
Different durations of fluoroquinolones	Duong 1995	0	0
	Nguyen 1997	2-day: 0	3-day: gastrointestinal bleed (2); jaundice (1); hypotension (1)
	Vinh 1996	2-day: 0	3-day: delirium (1); gastrointestinal bleed (1)
	Vinh 2005	2-day: gastrointestinal bleed (2)	3-day: 0

[a] Only trials reporting on complications are included.
[b] Zero (0) events only when specifically stated by trial author.

Table 3. Definitions of outcomes[a]

Comparison	Trial	Clinical failure	Microbiological failure	Relapse	Fever clearance time	Stool culture taken
Fluoroquinolones vs chloramphenicol	Abejar 1993	Not defined	Not defined (positive day 23 blood culture?)	Not defined	Outcome not reported	Outcome not reported
	Arnold 1993	Cure or improvement in 7 days	Non-eradication of original pathogen from blood samples between days 2 and 9 of treatment	Reappearance of signs and symptoms within 3 weeks after the end of treatment accompanied by reappearance of pathogen in blood	Outcome not reported	32 to 60 days; results unclear
	Bran 1991	Not defined	Not defined	Outcome not reported	Not defined	2 months after treatment

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Table 3. Definitions of outcomes[a] (*Continued*)

	Cristiano 1995	Not defined	Blood culture positive at end of treatment (at 15 days)	Within 30 days after end of treatment (the 2 relapses were blood culture negative and were stool culture positive before relapse)	Not defined	30 days
	Gasem 2003	Not afebrile within 7 days of treatment	Blood culture positive at days 3 and 5	Reappearance of fever after defervescence during hospitalization (under 14 days)	Defined as first day that temperature fell < 37.5 °C and remained under for ≥ 48 hours	Outcome not reported
	Gottuzzo 1992	"One participant who developed a gastrointestinal bleed in first 36 hours of treatment was considered a failure"	Outcome not reported	Not defined	Outcome not reported	Outcome not reported
	Morelli 1992	Persistence of fever	Outcome not reported	Not defined	Not defined	3 weeks
	Phongmany 2005	Continuation of symptoms and tympanic temperature > 38 °C for > 10 days after start of treatment or continuation of symptoms and high tympanic temperature > 39 °C at 7 days after start of treatment or development of signs of severe disease	Outcome not reported	Outcome not reported	Time from onset of treatment to first recording of a tympanic temperature < 38 °C (~ 37.5 °C axillary) which remained < 38 °C for 48 hours ('Fever Clearance Time 38')	Outcome not reported
	Quintero 1988	"persistent fever"	Outcome not reported	Outcome not reported	Not defined	Outcome not reported

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Table 3. Definitions of outcomes[a] (*Continued*)

	Yousaf 1992	Persistence or reappearance of all presenting signs and symptoms or increase in severity of at least 1 sign or symptom or both	Persistence of baseline pathogen at day 14	Outcome not reported	Outcome not reported	Outcome not reported
Fluoroquinolone vs ampicillin	Flores 1994	At end of treatment	At end of treatment	Outcome not reported	Outcome not reported	Outcome not reported
Fluoroquinolone vs cotrimoxazole	Hajji 1988	Fever and presence of clinical symptoms and positive cultures	Positive cultures at days 4, 15, and 30	Reappearance of fever, clinical symptoms, and/or bacteraemia at days 4, 15, and 30	Time for rectal temperature to be sustained ≤ 37.5 °C for ≥ 2 days	30 days
	Limson 1989	Persistent fever or no improvement in symptoms after 5 days of therapy	Positive cultures during and after therapy	Outcome not reported	Outcome not reported	Outcome not reported
Fluoroquinolone vs azithromycin	Dolecek 2008	Persistence of fever and symptoms 2 days after the end of treatment, ie on day 10	Positive blood culture on day 7 to 9 after the start of treatment	Symptoms and signs suggestive of typhoid fever within 1 month after completion of treatment (only culture positive data extracted)	Time from start of antibiotic treatment to when the axillary temperature first fell ≤ 37. 5 °C and remained there for at least 48 hours	Follow ups at 1, 3, and 6 months; participants who attended at least 2 consecutive follow-up visits were evaluated
	Chinh 2000	Persistence of fever and symptoms for > 5 days after the end of treatment or development of severe complications (severe gastrointestinal bleed, intestinal perforation, visi-	Isolation of *S.* Typhi/*S.* Paratyphi from blood or other sterile site after completion of treatment	Recurrence of signs and symptoms suggestive of enteric fever after discharge at 4 to 6 weeks of follow up	Time from start of treatment until body temperature fell < 37.5 °C and remained at ≤ 37.5 °C for 48 hours	Days 2 to 3 after end of treatment

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Table 3. Definitions of outcomes[a] (*Continued*)

		ble jaundice, myocardi- tis, renal failure, shock, coma) during treatment requiring change in treatment				
	Girgis 1999	Lack of resolution of symptoms by day 7 or development of major complications of typhoid fever after 5 days of therapy	Blood culture positive for *S.* Typhi/*S.* Paratyphi on day 10	Recurrence of fever with signs/symptoms of typhoid fever in 4 weeks of therapy completion and culture positive	First day on which maximum temperature ≤ 38 °C and at this level for ≥ 48 hours	1 month
	Parry 2007	Presence of fever and at least 1 other typhoid related symptom for > 7 days after start of treatment or development of severe complications (severe gastrointestinal bleeding, perforation, visible jaundice, myocarditis, pneumonia, renal failure, shock, or altered consciousness level, during treatment requiring change in therapy	Isolation of *S.* Typhi or *S.* Paratyphi from blood or sterile site after completion of treatment	Recurrence of symptoms or signs suggestive of enteric fever within 4-week period after patient had been discharged well from hospital accompanied by positive blood culture for *S.* Typhi or *S.* Paratyphi	Time from start of treatment until body temperature reached ≤ 37.5 °C and remained at this for 48 hours	After end of initial 7-day treatment and before hospital discharge (with isolate having the same susceptibility pattern as original isolate)
Fluoroquinolone vs cefixime	Cao 1999	Deterioration in clinical condition or failure of resolution of symptoms requiring further treatment	Blood culture positive for *S.* Typhi after completion of treatment	Symptoms suggestive of typhoid fever with a positive blood or bone marrow culture up to 4 weeks after discharge[b]	Time from onset of treatment until fever was 37.5 °C or below for at least 24 hours	1 month mostly, few seen after a longer period

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Table 3. Definitions of outcomes[a] (*Continued*)

	Pandit 2007	Any severe complication, persistence of fever (> 38 °C), persistence of symptoms for > 7 days after start of treatment, requiring additional or rescue treatment	Blood culture positive on day 10	Fever with blood culture positive within a month of completing treatment (patients given rescue treatment or prolonged treatment were excluded)	Time to 1st drop in oral temperature ≤ 37.5 °C remaining ≤ 37.5 °C for 48 hours	1 month
	Yu 1998	"inefficient" (categories included in assessment of clinical effectiveness were "cure, effective, improved and inefficient")	Eradicated (bacteria elimination rate)	Carrying bacteria at 3 months follow up	Not defined	Not defined
Fluoroquinolone vs ceftriaxone	Smith 1994	Acute treatment failure as continuing symptoms and fever for at least 7 days after starting the treatment regimen	Blood culture positive at day 8	Recurrence of fever and symptoms in the period up to 6 weeks after discharge with a positive blood or bone marrow culture[b]	Time to defervescence to < 37.5 °C for at least 48 hours	4 to 6 weeks
	Tran 1994	No reduction of maximum daily temperature to < 37.5 °C nor complete disappearance of all other signs and symptoms within 14 days and with clinical evidence of infection during further follow up	Blood, bone marrow, or stool culture within 14 days, and all culture negative for at least 21 days	Return of fever and symptoms up to 4 weeks after discharge with a blood or bone marrow culture positive[b]	Time until fever reached < 37.5 °C	1 month
	Wallace 1993	Fever > 38 °C after 7 days of therapy or who deteriorated clini-	Blood culture positive at day 3	Readmission for typhoid within 2 months of discharge with stool	Not defined	Days 1, 7, and 28; results unclear

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Table 3. Definitions of outcomes[a] (*Continued*)

		cally after 5 full days		or blood culture positive for *S.* Typhi of the same antibiogram (1 relapse had both stool and blood culture positive)		
Norfloxacin vs chloramphenicol	Nalin 1987	Not defined	Not defined	Outcome not reported	First day at which temperature < 37.5 °C	Not defined
	Sarma 1991	Persistence of all signs and symptoms of infection	Positive blood culture at 7 days	Recurrence of illness within 14 days of completion of treatment	Disappearance of fever after therapy and maintenance of normal temperature with clinical cure and blood sterilization	56 days
Norfloxacin vs ceftriaxone	Huai 2000	Fever after 7 days of treatment, positive bacteria, existence of symptoms and complications	Outcome not reported	Relapse after 1 month of follow up	Not defined	Outcome not reported
Norfloxacin vs another fluoroquinolone	Bai 1995	No effect or deteriorated after 3 days of treatment	Outcome not reported	Outcome not reported	Restoration of normal temperature	Outcome not reported
	Jia 1994	No effect or deteriorated	Outcome not reported	Outcome not reported	Restoration of normal temperature	Outcome not reported
	Xiao 1991	Temperature not decreased or even increased, clinical symptoms were improved or deteriorated after 1 week of treatment	Outcome not reported	Outcome not reported	Not defined	Outcome not reported

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Table 3. Definitions of outcomes[a] (*Continued*)

	Yang 1991	Temperature not decreased after 8 or more days treatment or changed to other treatment	Temperature back to normal but bacteria culture positive from faeces	Temperature back to normal after treatment but after 2 to 4 weeks fever started again and blood cultures positive and *S.* Typhi isolated	Not defined	At "convalescence"
Different durations of fluoroquinolones	Alam 1995	Lack of improvement or deterioration in clinical condition during treatment	Growth of *S.* Typhi or *S.* Paratyphi in blood in first follow up (day 3)	Recurrence of febrile illness with growth of *S.* Typhi or *S.* Paratyphi in blood culture after initial cure	Time to return of oral temperature to ≤ 37.5 °C after initiation of therapy and remained so for at least 48 hours	Second follow up (at 2 months)
	Duong 1995	No improvement or reappearance of signs and symptoms at least 48 hours after end of treatment	Blood or bone marrow culture positive 48 hours after last dose of fleroxacin	Blood culture positive within 1 month follow up	Not defined	Outcome not reported
	Kalo 1997	Fever at day 5	Blood culture positive at day 4	Relapse during hospitalization and 2 month follow up	Outcome not reported	Days 7 to 12
	Nguyen 1997	Continuing fever and symptoms for 7 days after the start of treatment or deterioration in clinical condition before 7 days that warranted further treatment	Blood or bone marrow culture positive after end of treatment before discharge	Recurrent fever and symptoms with bone marrow or blood culture positive mostly up to 6 weeks after discharge[b]	Time at which fever fell below 37.5 °C for at least 24 hours	Usually 6 weeks (occasionally up to 12 weeks)
	Tran 1995	Persistent fever and symptoms for > 7 days after start	Blood or bone marrow culture positive after end of treatment	Symptoms since study with positive blood culture	Not defined	1 month

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Table 3. Definitions of outcomes[a] (*Continued*)

		of treatment				
	Unal 1996	Continued or worsening symptoms after 7 days of therapy	Failure to eradicate organism	Similar signs and symptoms after apparently being cured for a month (the participant had a positive stool culture)	Time for temperature to be below 37.5 °C for at least 48 hours	1 month; results unclear
	Vinh 1996	Continued fever and symptoms for > 7 days after treatment	Positive blood culture or bone marrow culture for *S.* Typhi taken > 48 hours after the last dose of treatment	Recurrence of fever and symptoms with positive blood or bone marrow culture up to 6 weeks (26 participants followed up to 12 weeks) after discharge[b]	Time from start of treatment until axillary temperature fell below 37.5 °C and remained below this level for > 48 hours	4 to 6 weeks (for 66 participants); and at 3 months (for 26 participants)
	Vinh 2005	Fever and symptoms persisting for ≥ 7 days after start of therapy, or development of severe or complicated disease	Blood culture positive for same organism between 7 to 28 days after completion of therapy	Recurrence of typhoid fever symptoms usually with positive blood culture after hospital discharge until 28 days post discharge (only data for blood culture-confirmed relapse extracted)	Period from start of treatment until temperature remained at or below 37.5 °C for at least 48 hours	Immediately after treatment

S. Typhi/*S.* Paratyphi: *Salmonella enterica* serovar Typhi/Paratyphi.
[a] All definitions as stated or implied by trial authors.
[b] With an organism with the same sensitivity pattern, ribotype, and plasmid profile as the original isolate.

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HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 2, 2005

CONTRIBUTIONS OF AUTHORS

Durrane Thaver conducted the literature search, extracted and entered data, analysed results, and wrote the review. Asma Azmatullah co-extracted and double-entered data, and assisted in literature search, data analysis and writing the review (for this update). Ali Madni co-extracted data (for Thaver 2005). Anita Zaidi was consulted to resolve disagreements. Anita Zaidi, Julia Critchley, and Zulfiqar Bhutta provided technical input and edited the manuscript.

DECLARATIONS OF INTEREST

None known. Professor ZA Bhutta has been involved in typhoid therapy trials in children, none of which involved fluoroquinolones.

SOURCES OF SUPPORT

Internal sources

- The Aga Khan University Hospital, Pakistan.

External sources

- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title from 'Fluoroquinolones for treating enteric fever' and added "any sterile anatomic site" to the definition of the "relapse" primary outcome.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects; *therapeutic use]; Fluoroquinolones [adverse effects; *therapeutic use]; Norfloxacin [therapeutic use]; Paratyphoid Fever [*drug therapy]; Randomized Controlled Trials as Topic; Treatment Outcome; Typhoid Fever [*drug therapy]

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MeSH check words

Adult; Child; Humans

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