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Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins (Review)

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[Intervention Review]

Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins

Rebecca Kuehn[1], Nicole Stoesser[2], David Eyre[3], Thomas C Darton[4], Buddha Basnyat[2,5], Christopher Martin Parry[1,2]

[1]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. [2]Nuffield Department of Medicine, University of Oxford, Oxford, UK. [3]Big Data Institute, Nuffield Department of Population Health, University of Oxford, Oxford, UK. [4]Department of Infection, Immunity and Cardiovascular Disease, The University of Sheffield, Sheffield, UK. [5]Oxford Clinical Research Unit/Patan Academy of Health Science, Nepal International Clinic, Kathmandu, Nepal

Contact: Christopher Martin Parry, christopher.parry@lstmed.ac.uk.

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ABSTRACT

Background

Typhoid and paratyphoid (enteric fever) are febrile bacterial illnesses common in many low- and middle-income countries. The World Health Organization (WHO) currently recommends treatment with azithromycin, ciprofloxacin, or ceftriaxone due to widespread resistance to older, first-line antimicrobials. Resistance patterns vary in different locations and are changing over time. Fluoroquinolone resistance in South Asia often precludes the use of ciprofloxacin. Extensively drug-resistant strains of enteric fever have emerged in Pakistan. In some areas of the world, susceptibility to old first-line antimicrobials, such as chloramphenicol, has re-appeared. A Cochrane Review of the use of fluoroquinolones and azithromycin in the treatment of enteric fever has previously been undertaken, but the use of cephalosporins has not been systematically investigated and the optimal choice of drug and duration of treatment are uncertain.

Objectives

To evaluate the effectiveness of cephalosporins for treating enteric fever in children and adults compared to other antimicrobials.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, Embase, LILACS, the WHO ICTRP and ClinicalTrials.gov up to 24 November 2021. We also searched reference lists of included trials, contacted researchers working in the field, and contacted relevant organizations.

Selection criteria

We included randomized controlled trials (RCTs) in adults and children with enteric fever that compared a cephalosporin to another antimicrobial, a different cephalosporin, or a different treatment duration of the intervention cephalosporin. Enteric fever was diagnosed on the basis of blood culture, bone marrow culture, or molecular tests.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were clinical failure, microbiological failure and relapse. Our secondary outcomes were time to defervescence, duration of hospital admission, convalescent faecal carriage, and adverse effects. We used the GRADE approach to assess certainty of evidence for each outcome.

Main results

We included 27 RCTs with 2231 total participants published between 1986 and 2016 across Africa, Asia, Europe, the Middle East and the Caribbean, with comparisons between cephalosporins and other antimicrobials used for the treatment of enteric fever in children and adults. The main comparisons are between antimicrobials in most common clinical use, namely cephalosporins compared to a fluoroquinolone and cephalosporins compared to azithromycin.

Cephalosporin (cefixime) versus fluoroquinolones

Clinical failure, microbiological failure and relapse may be increased in patients treated with cefixime compared to fluoroquinolones in three small trials published over 14 years ago: clinical failure (risk ratio (RR) 13.39, 95% confidence interval (CI) 3.24 to 55.39; 2 trials, 240 participants; low-certainty evidence); microbiological failure (RR 4.07, 95% CI 0.46 to 36.41; 2 trials, 240 participants; low-certainty evidence); relapse (RR 4.45, 95% CI 1.11 to 17.84; 2 trials, 220 participants; low-certainty evidence). Time to defervescence in participants treated with cefixime may be longer compared to participants treated with fluoroquinolones (mean difference (MD) 1.74 days, 95% CI 0.50 to 2.98, 3 trials, 425 participants; low-certainty evidence).

Cephalosporin (ceftriaxone) versus azithromycin

Ceftriaxone may result in a decrease in clinical failure compared to azithromycin, and it is unclear whether ceftriaxone has an effect on microbiological failure compared to azithromycin in two small trials published over 18 years ago and in one more recent trial, all conducted in participants under 18 years of age: clinical failure (RR 0.42, 95% CI 0.11 to 1.57; 3 trials, 196 participants; low-certainty evidence); microbiological failure (RR 1.95, 95% CI 0.36 to 10.64, 3 trials, 196 participants; very low-certainty evidence). It is unclear whether ceftriaxone increases or decreases relapse compared to azithromycin (RR 10.05, 95% CI 1.93 to 52.38; 3 trials, 185 participants; very low-certainty evidence). Time to defervescence in participants treated with ceftriaxone may be shorter compared to participants treated with azithromycin (mean difference of −0.52 days, 95% CI −0.91 to −0.12; 3 trials, 196 participants; low-certainty evidence).

Cephalosporin (ceftriaxone) versus fluoroquinolones

It is unclear whether ceftriaxone has an effect on clinical failure, microbiological failure, relapse, and time to defervescence compared to fluoroquinolones in three trials published over 28 years ago and two more recent trials: clinical failure (RR 3.77, 95% CI 0.72 to 19.81; 4 trials, 359 participants; very low-certainty evidence); microbiological failure (RR 1.65, 95% CI 0.40 to 6.83; 3 trials, 316 participants; very low-certainty evidence); relapse (RR 0.95, 95% CI 0.31 to 2.92; 3 trials, 297 participants; very low-certainty evidence) and time to defervescence (MD 2.73 days, 95% CI −0.37 to 5.84; 3 trials, 285 participants; very low-certainty evidence). It is unclear whether ceftriaxone decreases convalescent faecal carriage compared to the fluoroquinolone gatifloxacin (RR 0.18, 95% CI 0.01 to 3.72; 1 trial, 73 participants; very low-certainty evidence) and length of hospital stay may be longer in participants treated with ceftriaxone compared to participants treated with the fluoroquinolone ofloxacin (mean of 12 days (range 7 to 23 days) in the ceftriaxone group compared to a mean of 9 days (range 6 to 13 days) in the ofloxacin group; 1 trial, 47 participants; low-certainty evidence).

Authors' conclusions

Based on very low- to low-certainty evidence, ceftriaxone is an effective treatment for adults and children with enteric fever, with few adverse effects. Trials suggest that there may be no difference in the performance of ceftriaxone compared with azithromycin, fluoroquinolones, or chloramphenicol. Cefixime can also be used for treatment of enteric fever but may not perform as well as fluoroquinolones.

We are unable to draw firm general conclusions on comparative contemporary effectiveness given that most trials were small and conducted over 20 years previously. Clinicians need to take into account current, local resistance patterns in addition to route of administration when choosing an antimicrobial.

PLAIN LANGUAGE SUMMARY

Cephalosporin antibiotics for the treatment of enteric fever (typhoid fever)

Key messages

• There may be no difference in the performance of ceftriaxone (a type of cephalosporin) compared with azithromycin, fluoroquinolones, or chloramphenicol (other antimicrobial medicines) for adults and children with enteric fever (typhoid fever).

• Cefixime (another type of cephalosporin) can also be used for treatment of enteric fever in adults and children but may not be as effective as fluoroquinolones.

• Policymakers and clinicians need to consider local antibiotic resistance patterns when considering treatment options for enteric fever.

What is enteric fever?

Enteric fever is a common term for two similar illnesses known individually as typhoid fever and paratyphoid fever. These illnesses only occur in people and are caused by bacteria known as *Salmonellatyphi* and *Salmonella paratyphi* A, B or C. These illnesses are most common in low- and middle-income countries where water and sanitation may be inadequate. Enteric fever typically causes fever and headache with diarrhoea, constipation, abdominal pain, nausea and vomiting, or loss of appetite. If left untreated, some people can develop serious complications and may die.

What are cephalosporins and how might they work?

The cephalosporins are a large family of antimicrobial medicines, which are commonly used to treat a variety of infectious diseases. Individual cephalosporins (such as cefixime and ceftriaxone) vary in the specific bacteria they can treat, how they are given - by mouth (orally) or injected (intravenously) - and when they were developed. Some cephalosporins can treat *Salmonellatyphi* and *Salmonella paratyphi* A, B, or C, the bacteria causing enteric (typhoid) fever.

In the past, enteric fever responded extremely well to other types of antimicrobial medicines, such as chloramphenicol. However, bacterial resistance to multiple antimicrobial medicines has become a major public health problem in many areas, especially Asia and Africa. Specific cephalosporins are now often used to treat enteric fever due to evolving drug resistance to other antimicrobials.

What did we want to find out?

We wanted to discover whether cephalosporins are better or worse in treating adults and children with enteric fever compared to other commonly given antimicrobials such as fluoroquinolones and azithromycin. To discover this, we wanted to know if treatment with cephalosporins would lead to persisting symptoms of disease (clinical failure), persisting *Salmonellatyphi* and *Salmonella paratyphi* A, B, or C bacteria in blood (microbiological failure), or return of symptoms or *Salmonellatyphi* and *Salmonella paratyphi* A, B, or C in the blood (relapse).

We also wanted to know how long cephalosporins take to reduce fever, if they reduce the length of time a patient needs to stay in hospital, whether patients' faeces (stool) would still carry the bacteria and thus remain infectious, and whether they cause any unwanted effects in patients.

What did we do?

We searched for studies that compared the treatment of a cephalosporin antimicrobial to another type of antimicrobial, or compared the treatment of a cephalosporin antimicrobial to another different cephalosporin antimicrobial, in adults or children who had enteric fever diagnosed through a laboratory test, such as blood culture.

What did we find?

We identified 27 studies involving 2231 adults and children from Africa, Asia, Europe, the Middle East, and the Caribbean that compared cephalosporin antimicrobial treatment in enteric fever with other antimicrobials.

Ceftriaxone was found to be an effective treatment for enteric fever, with few unwanted effects, and was similar to azithromycin, fluoroquinolones and chloramphenicol in its ability to treat enteric fever.

Cefixime can also be used to treat enteric fever but may not perform as well when compared to fluoroquinolone antimicrobials.

These findings only apply if the bacteria causing the enteric fever infection is vulnerable to the antimicrobial given to treat the infection; that is, the bacteria is not resistant to the antimicrobial.

What are the limitations of the evidence?

We have low confidence in our estimates, for these findings because of the low number of patients in the included studies. Also, in most included studies patients and doctors knew which antimicrobial the patient was receiving, which could have biased the results.

How up to date is this evidence?

These results are current up to 24 November 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Cefixime versus fluoroquinolones for treating enteric fever

Population: adults and children with enteric fever

Setting: inpatients and outpatients; Nepal, Pakistan, Vietnam (July 1995 to September 2005)

Intervention: oral cefixime

Comparator: oral fluoroquinolones (ciprofloxacin, ofloxacin, gatifloxacin)

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk*	Comparative risk				
	Fluoroquinolone	Cefixime				
Clinical failure	2 per 100	21 per 100 (5 to 88)	**RR 13.39** (3.24 to 55.39)	240 (2 trials)	Low[a]	Cefixime may result in an increase in clinical failure
Microbiological failure	0 in 126[b]	3 in 114[c]	**RR 4.07** (0.46 to 36.41)	240 (2 trials)	Low[d]	Cefixime may result in an increase in microbiological failure
Relapse	2 per 100	7 per 100 (2 to 29)	**RR 4.45** (1.11 to 17.84)	220 (2 trials)	Low[d]	Cefixime may result in an increase in relapse
Time to defervescence	The mean time to defervescence across fluoroquinolone groups ranged from **2.5 to 4.38 days**	The mean time to defervescence in the cefixime group was**1.74 days longer** (0.5 days longer to 2.98 days longer)	**MD 1.74** (0.50 to 2.98)	425 (3 trials)	Low[e]	Cefixime may increase the time to defervescence
Duration of hospital stay	-	-	-	-	-	No trials reported duration of hospital stay
Convalescent faecal carriage	No events reported in the fluoroquinolone group	No events reported in the cephalosporin group	Analysis not possible[f]	-	-	No trials reported any cases of persistent convalescent faecal carriage

Serious adverse events	No events reported in the fluoroquinolone group	No events reported in the cephalosporin group	Analysis not possible[f]	-	-	No trials reported any cases of serious adverse events

*The **assumed risk** is from the median control group risk across trials. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Footnotes
[a]Downgraded one level due to serious risk of bias and one level for serious imprecision due to few participants and very wide CIs.
[b]Number as reported in the trials.
[c]Number as reported in the trials. It was not possible to calculate the corresponding risk using the RR due to zero risk in the control group.
[d]Downgraded one level due to serious risk of bias and one level for serious imprecision due to few participants and wide CIs.
[e]Downgraded one level due to serious risk of bias and one level for inconsistency due to statistical heterogeneity.
[f]Analysis not possible due to zero events in control and intervention groups.

Summary of findings 2. Ceftriaxone versus azithromycin for treating enteric fever

Population: children under 18 years of age with enteric fever

Setting: inpatient; Egypt and India

Intervention: parenteral ceftriaxone

Comparator: oral azithromycin

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk*	Comparative risk				
	Azithromycin	Ceftriaxone				
Clinical failure	7 per 100	3 per 100 (1 to 11)	**RR 0.42** (0.11 to 1.57)	196 (3 trials)	Low[a]	Ceftriaxone may result in a decrease in clinical failure

Microbiological failure	1 per 100	2 per 100 (0 to 11)	**RR 1.95** (0.36 to 10.64)	196 (3 trials)	Very low[b]	There may be no difference in microbiological failure in participants treated with ceftriaxone compared to azithromycin, but the evidence is very uncertain
Relapse	0 in 89[c]	15 in 96[d]	**RR 10.05**[e] (1.93 to 52.38)	185 (3 trials)	Very low[f]	Ceftriaxone may result in an increase in relapse compared to azithromycin, but the evidence is very uncertain
Time to defervescence	The mean time to defervescence across azithromycin groups ranged from **4.1 to 5.5 days**.	The mean time to defervescence in the cefixime group was **0.52 days fewer** (0.91 days fewer to 0.12 days fewer)	**MD −0.52** (−0.91 to −0.12)	196 (3 trials)	Low[a]	Ceftriaxone may result in a shorter time to defervescence compared to azithromycin
Duration of hospital stay	-	-	-	-	-	No trials reported duration of hospital stay
Convalescent faecal carriage	No events in the azithromycin group	No events in the ceftriaxone group	Analysis not possible[g]	-	-	No trials reported any cases of persistent convalescent faecal carriage
Serious adverse events	No events in the azithromycin group	No events in the ceftriaxone group	Analysis not possible[g]	-	-	No trials reported any serious adverse events

*The **assumed risk** is from the median control group risk across trials. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **MD:** mean difference

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GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

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Footnotes
[a]Downgraded one level due to serious risk of bias and one level for serious imprecision due to low participant numbers.
[b]Downgraded one level due to serious risk of bias and two levels for serious imprecision due to low participant numbers and low number of events.
[c]Numbers as reported in the trial.
[d]Numbers as reported in the trial. It was not possible to calculate the corresponding risk using the RR due to zero risk in the control group.
[e]It was possible to calculate RR as continuity correction of 0.5 was applied.

[f]Downgraded one level due to serious risk of bias and two levels for serious imprecision due to low number of events, low participant numbers, and wide CIs.
[g]Analysis not possible due to zero events in the intervention and control groups.

Summary of findings 3. Ceftriaxone versus fluoroquinolones for treating enteric fever

Population: adults and children with enteric fever

Setting: inpatient and outpatient; India, Nepal, Vietnam, (1992 to 2014)

Intervention: parenteral ceftriaxone

Comparator:oral fluoroquinolone

Outcomes	**Illustrative comparative risks (95% CI)**		**Relative effect (95% CI)**	**Number of participants** (trials)	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk*	**Comparative risk**				
	Fluoroquinolone	**Ceftriaxone**				
Clinical failure	10 per 100	38 per 100 (7 to 100)	**RR 3.77** (0.72 to 19.81)	359 (4 trials)	Very low[a]	The evidence is very uncertain about the effect of ceftriaxone on clinical failure
Microbiological failure	1 per 100	2 per 100 (1 to 9)	**RR 1.65** (0.40 to 6.83)	316 (3 trials)	Very low[b]	There may be no difference in microbiological failure in participants treated with ceftriaxone compared to fluoroquinolone, but the evidence is very uncertain
Relapse	3 per 100	3 per 100 (1 to 10)	**RR 0.95** (0.31 to 2.92)	297 (3 trials)	Very low[c]	There may be no difference in relapse in participants treated with ceftriaxone compared to fluoroquinolone, but the evidence is very uncertain
Time to defervescence	The mean time to defervescence across fluoroquinolone groups ranged from **3.38 to 4 days**	The mean time to defervescence in the ceftriaxone group was **2.73days longer** (0.37 days shorter to 5.84 days longer)	**MD 2.73** (−0.37 to 5.84)	285 (3 trials)	Very low[d]	The evidence is very uncertain about the effect of ceftriaxone on the time to defervescence
Duration of hospital stay	The mean duration of hospital stay in the fluoroquinolone (ofloxacin) group was	The mean duration of hospital stay in the ceftriaxone group was **12 days** (range 7 to 23 days).	Analysis not possible[e]	47 (1 trial)	Low[f]	Ceftriaxone may result in a shorter duration of hospital stay

	9 days (range 6 to 13 days).					
Convalescent faecal carriage	2 in 35[g]	0 in 38[g]	**RR 0.18** (0.01 to 3.72)	73 (1 trial)	Very low[c]	Ceftriaxone may result in a decrease in convalescent faecal carriage rate, but the evidence is very uncertain
Serious adverse events	No events in the fluoroquinolone group	No events in the cephalosporin group	Analysis not possible[h]	-	-	No serious adverse events were reported

*The **assumed risk** is from the median control group risk across trials. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Footnotes
[a]Downgraded one level for serious risk of bias, one level for serious inconsistency due to moderate statistical heterogeneity and two levels for serious imprecision due to low participant numbers, low number of events and wide CIs.
[b]Downgraded one level for serious risk of bias and two levels for serious imprecision due to low participant numbers, wide CIs and low number of events.
[c]Downgraded one level for serious risk of bias and two levels for serious imprecision due to low participant numbers and low number of events.
[d]Downgraded one level for serious risk of bias, one level for inconsistency due to high statistical heterogeneity and one level for serious imprecision due to low participant numbers.
[e]Analysis not possible due unavailable data on standard deviation and 95% CIs.
[f]Downgraded one level for serious risk of bias and one level for serious imprecision due to data arising from one trial with low participant numbers.
[g] Numbers as reported in the trial.
[h]Analysis not possible due to no events in the intervention or control groups.

BACKGROUND

Enteric fever, also referred to as typhoid fever, is a systemic infection caused by either *Salmonella enterica* serovar *typhi* (*S typhi*; typhoid fever) or *Salmonella enterica* serovar *paratyphi* (*S paratyphi*) A, B, or C (paratyphoid fever), and results in a bacteraemic febrile illness specific to humans. The bacteria are transmitted between humans via the faecal-oral route, usually through contaminated food and water. It is most common in regions with inadequate water and sanitation infrastructure. The highest burden of disease occurs in South Asia and in sub-Saharan Africa in children five to nine years of age (Stanaway 2019). Enteric fever is difficult to diagnose in endemic settings, leading to a high rate of misdiagnosis; cases of typhoid fever may thus be over- or underestimated. Frequent use of antimicrobials for febrile illnesses, including suspected enteric fever, contributes to the emergence of antimicrobial resistance through frequent empirical use of antimicrobials for febrile illnesses. Increasing antimicrobial resistance in both *S typhi* or *S paratyphi* A, B, or C, is now a serious public health concern. Lack of timely antimicrobial treatment can lead to life-threatening complications. Therapeutic options are sparse due to increasing antimicrobial resistance. Antimicrobial options for multiple-drug-resistant strains include cefixime (an oral cephalosporin), azithromycin (an oral macrolide), fluoroquinolones, and ceftriaxone (a parenteral cephalosporin).

Description of the condition

Epidemiology

In 2017 the global number of cases of typhoid and paratyphoid fever was estimated to be 14.3 million, with *Styphi* causing 76.3% of cases, in the Global Burden of Disease trial (Stanaway 2019). This overall represented a decline from previous estimates ranging between 11.9 million to 27.1 million cases per year (Antillón 2017; Buckle 2012; Crump 2004; Kim 2017; Mogasale 2014). Global deaths from typhoid and paratyphoid fever were estimated at approximately 135,900 (76,900 to 218,900) in 2017, and higher in typhoid compared to paratyphoid cases (Stanaway 2019). Regions with the highest estimated burden of disease are South Asia, Southeast Asia, and sub-Saharan Africa (Garrett 2022; Marks 2017; Meiring 2021). In some areas estimates are limited by lack of data, most notably from Oceania and Latin America. Cases occur in high-income countries in returned travellers from endemic countries or in those in close contact with people recently returned from endemic countries, and occasionally food-borne outbreaks occur. Overall, typhoid and paratyphoid fevers were responsible for 9.8 million (5.6 to 15.8) disability-adjusted life-years (DALYs) in 2017, 67.0% (61.6 to 72.4) occurring amongst children younger than 15 years of age (Stanaway 2019).

Prevention

Disease burden can be reduced by provision of adequate water and sanitation infrastructure and through typhoid vaccination. The World Health Organization (WHO) has approved three typhoid vaccines which, until recently, have not been part of national routine immunization programmes. Several countries are now introducing the typhoid Vi conjugate vaccine following evidence from recent randomized controlled trials (RCTs; Patel 2021; Qadri 2021; Shakya 2021). There are no paratyphoid fever vaccines (WHO 2019).

Clinical

Infection is caused by consumption of food or water contaminated with *S typhi* or *S paratyphi* during preparation where insufficient food hygiene and handwashing facilities are practised (Crump 2019). Contamination occurs when bacteria are shed in the faeces of individuals who are acutely unwell, convalescing or are chronic carriers (Bhan 2005). Risk of transmission is increased by lack of access to clean drinking water, insufficient food hygiene practices and poor sanitation including inadequate handwashing. The severity of the infection depends on the initial infective dose, the virulence of the organism, the host's co-morbidities and immune response (Tsolis 1999). The bacteria usually penetrate the intestinal mucosa and proliferate in the underlying lymphoid tissue, from where they disseminate via the lymphatic system or are released into the bloodstream, or both, resulting in spread to other organs. The organs most commonly affected include the liver, spleen, bone marrow and gall bladder (Parry 2002; Raffatellu 2008).

The clinical features of enteric fever typically include progressive intermittent fever, headache, abdominal discomfort, anorexia, hepatomegaly and splenomegaly (Bhan 2005; Walia 2006). It is not possible to distinguish between typhoid and paratyphoid fever on the basis of clinical symptoms. Complications of enteric fever occur in 10% to 15% of cases, are more frequent in patients whose illness has lasted over two weeks, and can affect multiple organ systems (Bhan 2005; Parry 2002). Intestinal perforation and haemorrhage, shock, pancreatitis, cholecystitis, pneumonia, myocarditis and encephalopathy are possible (Bhan 2005).

Between 1% to 5% of patients develop chronic carriage of salmonellae following infection (defined as excretion of bacteria in faeces or urine for more than 12 months; Ferreccio 1988). Chronic carriage occurs more frequently in women, and in patients with gallstones or other biliary tract abnormalities (Levine 1982). Biliary carriage has been associated with an increased risk of cancer, particularly of the biliary system (Caygill 1994).

Diagnosis

Typhoid and paratyphoid fever present a challenge to diagnose clinically, especially in children, as symptoms overlap with other causes of fever. The optimum method to confirm diagnosis is through blood or bone marrow culture, which can take days for a result, and are often not easily available in low-resource, endemic regions (Baker 2010). A negative blood culture does not exclude the diagnosis. Culture of faeces, urine or bile can be undertaken, however a positive result may indicate chronic carriage rather than acute infection (Wain 1998).

Bacterial culture facilitates antimicrobial susceptibility testing which is helpful in guiding the appropriate antibiotic therapy. Disc diffusion and minimal inhibitory concentration (MIC) breakpoints incorporate an 'intermediate' or decreased ciprofloxacin susceptibility (DCS) category as well as a resistant category (CLSI 2021). Older options for detecting the intermediate category include a test for nalidixic acid susceptibility or perfloxacin susceptibility: nalidixic acid-resistant (NaR) or perfloxacin-resistant organisms have intermediate susceptibility to ciprofloxacin (CLSI 2021; Crump 2003). It is important to note that the possibility of an 'intermediate' or DCS category was not appreciated when fluoroquinolones were first evaluated in RCTs and so was not determined in the isolates in these early trials. Susceptibility breakpoints for azithromycin have been proposed based on MIC distributions and limited clinical data (CLSI 2021; Sjolund-Karlsson 2011).

The benefit of serological tests for the diagnosis of enteric fever is limited by the persistence of positive results following from previous infection. Newer diagnostic tests using enzyme-linked immunosorbent assay (ELISA), immunochromatographic platforms and nucleic acid amplification are in development, but none have proven to be sensitive and specific enough to be widely adopted in routine clinical diagnostics (Neupane 2021; Parry 2002). Further, serological tests, such as the Widal test and commercial rapid diagnostic tests, are not confirmatory in the acute phase of illness. The Widal test lacks sensitivity and specificity, and the moderate sensitivity and specificity of available rapid diagnostic tests (such as Typhidot-M, TUBEX, and Test-it typhoid tests) does not support their use as a replacement for blood culture for diagnosing enteric fever (Levine 1982; Parry 1999; Wijedoru 2017).

Prognosis

Stanaway 2019 estimated a mean all-age global case fatality of 0.95% (0.54 to 1.53) in 2017, consistent with expert opinion of case fatality being approximately 1% with treatment (Buckle 2012; Crump 2004). Higher case fatality estimates were seen in children and older adults, and in lower-income countries (Stanaway 2019). Typhoid fever has a low mortality when it is recognized early and treated with effective antimicrobials; delays in treatment, ineffective antimicrobial treatment, or lack of quality medical care leads to a significant increase in complications and case-fatality rate (Wain 2015).

Treatment

Antimicrobial monotherapy is usually used to treat enteric fever, but the optimal choice of drug and duration of therapy depend on locally prevalent antimicrobial resistance patterns. Common resistance patterns include combined plasmid resistance to the older antimicrobials (chloramphenicol, amoxycillin and trimethoprim-sulphamethoxazole - multidrug resistance), intermediate susceptibility or resistance (non-susceptibility) to fluoroquinolones and to azithromycin, usually mediated by target site gene mutations, and resistance to ceftriaxone and cefixime caused by extended spectrum beta lactamase genes. The occurrence of different resistance patterns has varied and continues to evolve by location and over time. In a recent systematic review of trials published between 1990 and 2018, resistance was widespread and has increased for all antimicrobials in all regions, except for a decline of multiple-drug-resistant (MDR) *S typhi* in South Asia between 1990 and 2018 (Browne 2020). Global resistance patterns are characterized by data gaps, incomplete reporting, and problems with quality assurance.

Combination antimicrobial therapy is a potential treatment option. Combinations such as ceftriaxone/ciprofloxacin, have been commonly used in the USA (Crump 2008), a small comparative trial of monotherapy versus combination therapy in Nepal included ceftriaxone/azithromycin and cefixime/azithromycin combinations (Zmora 2018), and combination therapy is currently being evaluated in an ongoing multi-centre RCT (NCT04349826). The benefits of combination antimicrobial combination therapy have not been conclusively proven.

Current recommendations for the duration of antimicrobial treatment include 5 to 10 days for oral treatment with a fluoroquinolone or azithromycin, and 7 to 14 days for cephalosporins. Intravenous treatment with carbapenems are often used when ceftriaxone resistance occurs in patients with severe disease. Duration of antimicrobial therapy aims to continue treatment for two to three days post defervescence (Nabarro 2022). Choice of drug is influenced by disease severity, drug availability, availability of facilities to administer intravenous medication, and local resistance patterns.

Description of the intervention

Cephalosporins are beta-lactam compounds in which the beta-lactam ring has been fused to a 6-membered dihydrothiazine ring, forming the cephem nucleus. Although historically they have been divided into generations, depending on their antibacterial spectrum of activity, it is now considered more helpful to consider the individual characteristics and spectrum of activity for each cephalosporin (Bazan 2011; Kalman 1990).

Cephalosporins inhibit cell wall synthesis by binding to penicillin-binding proteins, and are bactericidal. They have time-dependent killing activity, which requires levels that are continuously above the MIC of the pathogen being treated. Dosing frequency is variable, but some cephalosporins such as ceftriaxone have a distinct advantage in having a half-life sufficiently long to be given once daily (Kalman 1990).

Most cephalosporins distribute well into the extracellular fluid of most tissues, and some cephalosporins also sufficiently penetrate into cerebrospinal fluid and can be used in the treatment of central nervous system infections. Penetration of cephalosporins into the intracellular compartment is poor. Elimination is mostly through the renal system, although significant biliary excretion is a feature of some cephalosporins, such as ceftriaxone and cefoperazone. They are generally well-tolerated, although some patients may display hypersensitivity; hepatic dysfunction and interstitial nephritis (Kalman 1990).

Certain cephalosporins, historically referred to as extended-spectrum cephalosporins or third- and fourth-generation cephalosporins, typically have activity against salmonellae and can be used in the management of enteric fever. A number of cephalosporin-beta lactamase-inhibitor combination drugs (for example, ceftazidime-avibactam; ceftolazone-tazobactam) have recently become available and may become valuable for the treatment of extended-spectrum beta-lactamase-producing salmonellae. They have yet to be evaluated for enteric fever in clinical trials.

How the intervention might work

Effective treatment of enteric fever is hampered by the development of multiple-drug resistance to first-line agents (amoxicillin/ampicillin, cotrimoxazole and chloramphenicol) worldwide in the late 1980s and 1990s (Karkey 2018; Rowe 1997). This has led to the use of fluoroquinolones (ciprofloxacin, ofloxacin, fleroxacin, perfloxacin, and gatifloxacin). However, since the late 1990s, intermediate and full fluoroquinolone resistance has emerged, especially in South Asia (Karkey 2018). In fluoroquinolone-resistant isolates, treatment with an extended-spectrum cephalosporin, including ceftriaxone (intramuscular or intravenous) and cefixime (oral), or treatment with azithromycin (an oral macrolide), is often the treatment of choice (Basnyat 2007; Basnyat 2010).

Why it is important to do this review

Effective antimicrobials are required to treat enteric fever and to reduce disease transmission in the context of ongoing and emerging antimicrobial resistance patterns in different parts of the world (Browne 2020).

Sporadic cases of *S typhi* resistant to first-line agents, fluoroquinolones and third-generation cephalosporins have now originated in Iraq, Bangladesh, India, and Pakistan (Ahmed 2012; Gul 2017; Kleine 2017; Munir 2016; Pfeifer 2009). Subsequently, the large-scale emergence of temporally clustered cases of extensively drug-resistant (XDR) *S typhi* strains, (resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins), with a large number of resistance determinants, were reported in Pakistan (Klemm 2018). The only active treatments for XDR strains documented in Pakistan are oral azithromycin and intravenous carbapenems (Chatham-Stephens 2019; Qureshi 2020). Intravenous treatment with carbapenems is not available or affordable for most patients in countries where enteric fever is endemic, and recently azithromycin-resistant cases of *S typhi* have been reported in Bangladesh, Pakistan, and Nepal (Duy 2020; Hooda 2019; Iqbal 2020). Azithromycin resistance has not yet been reported in XDR organisms. The potential spread of XDR and azithromycin-resistant *S typhi* strains is thus a major clinical concern, and it is of importance to have more than one therapeutic option to treat this disease.

Ceftriaxone and cefixime are currently widely used in the management of enteric fever (Nabarro 2022; WHO 2021). The safety profile of cephalosporins is considered to be good in children, whereas enough concern exists in relation to the safety profile of fluoroquinolones in paediatric medicine for them to remain unapproved for the treatment of enteric fever by the US Food and Drug Administration (FDA). Developing a more comprehensive understanding of how these drugs can be best used in the treatment of enteric fever will have an impact on the cost of treatment, the improvement of clinical outcomes and the provision of baseline data for the development of future clinical trials.

Cochrane Reviews of the use of fluoroquinolones and azithromycin in the treatment of typhoid have previously been undertaken (Effa 2011), but the use of broad-spectrum beta-lactams such as ceftriaxone and cefixime in the era of *S typhi* and *S paratyphi* resistance has not been systematically investigated to date.

OBJECTIVES

To evaluate the effectiveness of cephalosporins for treating enteric fever in children and adults compared to other antimicrobials.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs)

Types of participants

Adults and children diagnosed with typhoid or paratyphoid fever on the basis of blood culture, bone marrow culture or molecular tests.

Types of interventions

Intervention

Treatment with a cephalosporin antimicrobial of any dose or duration.

Cephalosporins considered in this review are shown in Table 1.

Control

- Other antimicrobials, including:
  - fluoroquinolones
  - azithromycin
  - aztreonam
  - chloramphenicol
- Different cephalosporins
- Different treatment durations of the intervention cephalosporin

Types of outcome measures

Primary outcomes

- Clinical failure: defined as the presence of symptoms or development of complications that necessitate a change in antimicrobial therapy or prolongation of existing therapy at the time period specified by trial authors; or, death related to the disease within the trial time period as opposed to an adverse event arising from any therapy administered.
- Microbiological failure: defined as a positive culture from blood, bone marrow or any sterile anatomical site during the period specified by the trial authors.
- Relapse: defined as the recurrence of symptoms with a positive culture from blood, bone marrow or any sterile anatomical site to the point of follow-up defined by the trial author.

Secondary outcomes

- Time to defervescence: defined as the time in days taken to defervesce from the start of the intervention or control drug with the definition of fever clearance as defined by the trial authors.
- Length of hospital stay: defined as the time in days from trial entry until discharge from hospital
- 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.

Adverse events

We sought any adverse events or effects reported. Serious adverse events are defined as any untoward events occurring in the trial time period that result in death, are life-threatening, require patient hospitalization or prolongation of existing hospitalization, or result in persistent or significant disability/incapacity or require intervention to prevent permanent impairment or damage. We also sought events requiring the discontinuation of treatment.

Search methods for identification of studies

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

Electronic searches

Databases

We searched the following electronic databases using the search terms and strategies described in Appendix 1:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 10), published in the Cochrane Library, searched 24 November 2021;
- MEDLINE Ovid (1946 to 23 November 2021);
- Embase Ovid (1996 to 2021, Week 46, searched 24 November 2021); and
- LILACS (BIREME) 1982 to 23 November 2021, searched 24 November 2021.

We also searched ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP).

Searching other resources

Conference proceedings

We handsearched abstracts from the following annual meetings: International Symposium on Typhoid Fever and Other Salmonelloses; the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); the Infectious Diseases Society of America (IDSA); the Western Pacific Congress on Chemotherapy and Infectious Diseases; the European Congress of Clinical Microbiology and Infectious Diseases; and the American Society of Tropical Medicine and Hygiene.

Researchers

We contacted researchers in the field to identify additional trials that may be eligible for inclusion.

Reference lists

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

Data collection and analysis

Selection of studies

Two review authors independently screened the title, abstract, and keywords of each record identified from the searches; Nicole Stoesser (NS) and David Eyre (DE) screened the search results obtained in February 2013; Thomas Darton (TD) and Christopher Parry (CP) screened the search results obtained in April 2017; and Rebecca Kuehn (RK) and CP screened the search results obtained in November 2021. We retrieved the full-text articles of all potentially relevant trials and all trials where the relevance was unclear from screening.

Two review authors independently applied the inclusion criteria to each of the full-text articles obtained following screening; NS and DE for the February 2013 searches; TD and CP for the April 2017 searches; and RK and CP for the November 2021 searches.

We resolved any disagreements through discussion between review authors. If there were further doubts, we attempted to contact the trial authors for further information. We have listed the excluded trials and reasons for exclusion in the Characteristics of excluded studies section. We entered the data from each eligible trial only once.

Data extraction and management

Two review authors (NS and DE) independently extracted data from trials identified in the February 2013 searches using a standardized, pre-tested data extraction form incorporating information about the trial population, intervention used (type of drug, means of administration, duration of treatment) and outcomes (side effects, success of treatment). TD and CP completed the same data extraction process for trials identified in the April 2017 search and CP and RK completed the same data extraction process for trials identified in the November 2021 search.

For dichotomous outcomes, we extracted data concerning clinical failure, the total number of participants randomized, the number of participants analysed and the total number of participants who experienced that event.

For continuous outcomes, we extracted data concerning time to defervescence, the total number of participants, arithmetic means, and standard deviations. If trials did not report the standard deviation, we used the confidence interval (CI) to calculate it.

We contacted trial authors for additional data when they were unavailable or not in the format required to undertake the analyses.

We compared extracted data between review authors to identify errors. Any conflicts were resolved by discussion with CP or BB.

Two review authors (NS and RK) entered data into the Review Manager file (RevMan Web 2022), and DE and CP verified data entry was correct.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each included trial: NS and DE for the 2013 search, TD and CP for the April 2017 search, and RK and CP for the 2021 search, using the Cochrane risk of bias tool, RoB 1 (Higgins 2011). We used the tool to assess whether adequate steps were taken to reduce the risk of bias across six domains: sequence generation, allocation concealment, blinding (of participants, personnel and outcome assessors), incomplete outcome data (follow-up was considered adequate if 90% or more of the randomized culture-positive participants were in the final analysis and inadequate if this figure was less than 90%), selective outcome reporting and other sources of bias. We categorized judgements as either 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear'. We compared entries and resolved disagreements by discussion between review authors.

We summarized the risk of bias judgements in tables.

Measures of treatment effect

We presented and compared dichotomous data using risk ratios (RR), and continuous data using mean difference (MD).

All results are presented with the corresponding 95% CI.

Unit of analysis issues

For trials where more than two different antimicrobials were compared to each other, we separated data for each different antimicrobial so each antimicrobial was compared to a different antimicrobial as an individual pairwise comparison.

We undertook a count of adverse and serious adverse events by participant, associated with the antimicrobial administered.

We did not identify any cluster-RCTs for inclusion in this review.

Dealing with missing data

We planned to apply intention-to-treat (ITT) principles to data extraction, but data were insufficient.

We assessed trials for high loss of participants to follow-up, or a lack of balance between groups, and we used evaluable participants only.

Assessment of heterogeneity

We assessed for heterogeneity by visually inspecting the forest plots, by comparing the heterogeneity statistic, Q, with the Chi^2 distribution, and reported the amount of heterogeneity using the I^2 statistic (Deeks 2022; Higgins 2003).

Statistical heterogeneity was declared if the P value was less than 0.1 for the Chi^2 statistic, or if the I^2 statistic was equal to or greater than 40% (40% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity; Deeks 2022).

Assessment of reporting biases

We planned to assess the presence of publication bias by looking for funnel plot asymmetry if there were 10 or more trials available for analysis of each primary outcome, but this was not possible due to the low number of trials.

Data synthesis

We analysed data using RevMan Web 2022.

We analysed data using pairwise comparisons. We compared each cephalosporin with each comparator antimicrobial class and subgrouped by the specific antimicrobial.

The data are organized into the following comparisons:

- cefixime versus fluoroquinolones
- ceftriaxone versus azithromycin
- ceftriaxone versus fluoroquinolones
- ceftriaxone versus cefixime
- ceftriaxone versus chloramphenicol
- cefixime versus chloramphenicol
- cefixime versus cefpodoxime
- cefoperazone versus chloramphenicol
- cefixime versus aztreonam
- ceftriaxone versus aztreonam
- duration of ceftriaxone

If clinical and methodological characteristics of individual trials were sufficiently homogeneous, we pooled the data in meta-analyses. When there were no concerns of clinical or statistical heterogeneity we used the fixed-effect model in meta-analyses. Where clinical or statistical heterogeneity was detected, and we still considered it appropriate to pool the data, we used the random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by conducting subgroup analyses according to age (paediatric populations 0 to 16 years and adults over 17 years), hospitalization status, presence of MDR/NaR/intermediate ciprofloxacin susceptibility and duration of treatment. We tried to make contact with the trial authors if these distinctions were unclear from the data.

These planned subgroup analyses were not possible due to the limited number of trials in each comparison.

Sensitivity analysis

We planned to assess the robustness of the data by performing a sensitivity analysis for each of the risk of bias assessment factors, but were again unable to do this due to the low number of trials.

Summary of findings and assessment of the certainty of the evidence

We presented the main results of the review in summary of findings tables, including a rating of the certainty of evidence based on the GRADE approach. We followed current GRADE guidance as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2022).

We rated each outcome as described by Balshem 2011 as either:

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect.
- Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

We created separate summary of findings tables for the comparisons of cephalosporins with antimicrobials that are in common use for the treatment of enteric fever and with chloramphenicol:

- cefixime versus fluoroquinolones
- ceftriaxone versus azithromycin
- ceftriaxone versus fluoroquinolones

The summary of findings tables included all primary and secondary outcomes that the included trials reported.

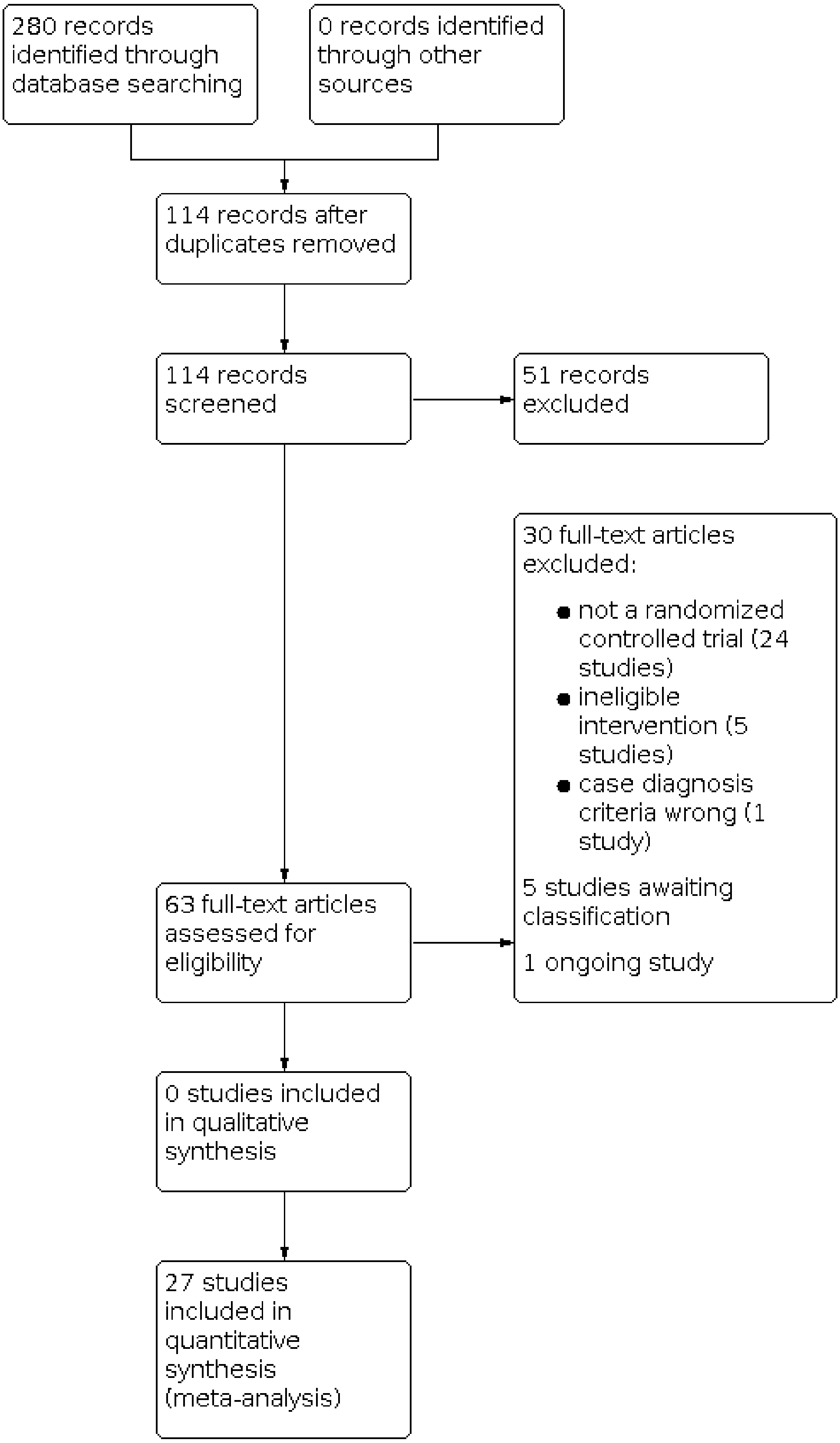
RESULTS

Description of studies

Results of the search

We assessed the full texts of 63 trials for eligibility following separate searches conducted in February 2013, April 2017, and November 2021. We included 27 trials and excluded 30. The trial selection process following PRISMA guidelines is available in Figure 1. Five trials are awaiting classification - one of these is only published as an abstract with insufficient detail to classify it (Studies awaiting classification). We identified one ongoing trial (Ongoing studies).

Figure 1.


280 records identified through database searching
0 records identified through other sources
114 records after duplicates removed
114 records screened
51 records excluded
30 full-text articles excluded:
not a randomized controlled trial (24 studies)
ineligible intervention (5 studies)
case diagnosis criteria wrong (1 study)
5 studies awaiting classification
1 ongoing study
63 full-text articles assessed for eligibility
0 studies included in qualitative synthesis
27 studies included in quantitative synthesis (meta-analysis)

Included studies

The 27 trials included 2231 participants. Most trials were small and lacked statistical power to detect differences between the treatment regimens. The smallest trial had 25 participants and the largest had 382 participants.

Fifteen trials reported drug susceptibility patterns, with data on MDR strains in 13 trials and NaR in one trial. See Characteristics of included studies for further details of reported microbiology and susceptibility data.

Trial setting

The trials were conducted in Bahrain (1), Bangladesh (3), Egypt (4), Haiti (1), India (2), Italy (1), Nepal (4), Pakistan (5), the Philippines (1), South Africa (1), Turkey (1), and Vietnam (3).

Trials were published between 1986 and 2016.

Most trials were conducted in an inpatient setting; three trials were conducted on outpatients (Arjyal 2016; Pandit 2007; Rizvi 2007).

Participants

Eleven trials (666 participants) were exclusively in children under 16 years old (Bhutta 1994; Bhutta 2000; Cao 1999; Girgis 1995; Kumar 2007; Memon 1997; Moosa 1989; Pape 1986; Rabbani 1998; Shakur 2007; Tatli 2003); two trials (176 participants) included participants up to the age of 17 years (Frenck 2000; Frenck 2004); and one trial (54 participants) included participants up to the age of 18 years (Nair 2017). Four trials (177 participants) were exclusively in adults over 15 years old (Butler 1993; Lasserre 1991; Smith 1994; Wallace 1993). Nine trials (1158 participants) included children and adults (Acharya 1995; Arjyal 2016; Girgis 1990; Islam 1988; Islam 1993; Morelli 1988; Pandit 2007; Rizvi 2007; Tran 1994).

Most trials were conducted on patients with uncomplicated typhoid fever at trial entry with only a few including patients with severe or complicated disease at the time of trial entry.

Most trials recruited patients on the basis of blood culture or bone marrow cultures or both. Most trials only reported outcomes for the culture-positive patients and few reported on the basis of intention to treat, including patients who were randomized but were culture-negative.

Interventions

Fifteen trials compared ceftriaxone with an antimicrobial from an alternative class: azithromycin (3 trials), ciprofloxacin (1 trial), fleroxacin (1 trial), ofloxacin (1 trial), gatifloxacin (1 trial), chloramphenicol (7 trials), aztreonam (1 trial). All trials comparing ceftriaxone with azithromycin were conducted in participants under 18 years old.

Nine trials compared cefixime with an antimicrobial from an alternative class: ciprofloxacin (1 trial), ofloxacin (2 trials), gatifloxacin (1 trial), chloramphenicol (3 trials), aztreonam (1 trial), and cefpodoxime (1 trial). No trials compared cefixime with azithromycin.

Two trials compared ceftriaxone with cefixime.

Two trials compared cefoperazone with chloramphenicol.

No trials directly compared different dosages of cephalosporins. One trial directly compared a longer and shorter duration of ceftriaxone.

Outcomes

Most trials reported our primary outcomes: clinical failure (26 trials); microbiological failure (21 trials) and relapse (21 trials).

The definition of outcomes varied between trials; some did not define outcomes at all. The time period at which outcomes were assessed also varied considerably between trials, for example, some trials defined time to defervescence as the first documented 'normal' body temperature and other trials as an axillary temperature of less than 37.5 °C for at least 48 hours. In some trials it was not clear whether the adverse events recorded were considered due to the antimicrobial received or the disease process itself. Further details are presented in Characteristics of included studies section.

We received data from one author group to calculate the mean time to defervescence in the comparison of cefixime versus fluoroquinolones (Pandit 2007).

Excluded studies

Of the 30 excluded trials, we excluded 24 because they were not randomized, or it was unclear if they were randomized. For further details see Characteristics of excluded studies section.

Risk of bias in included studies

See summary of risk of bias assessment in Figure 2 and Figure 3.

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

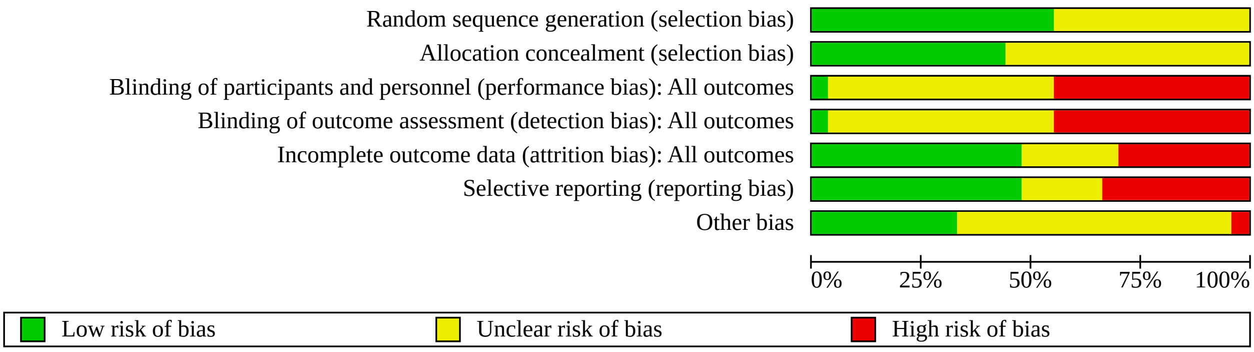


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial

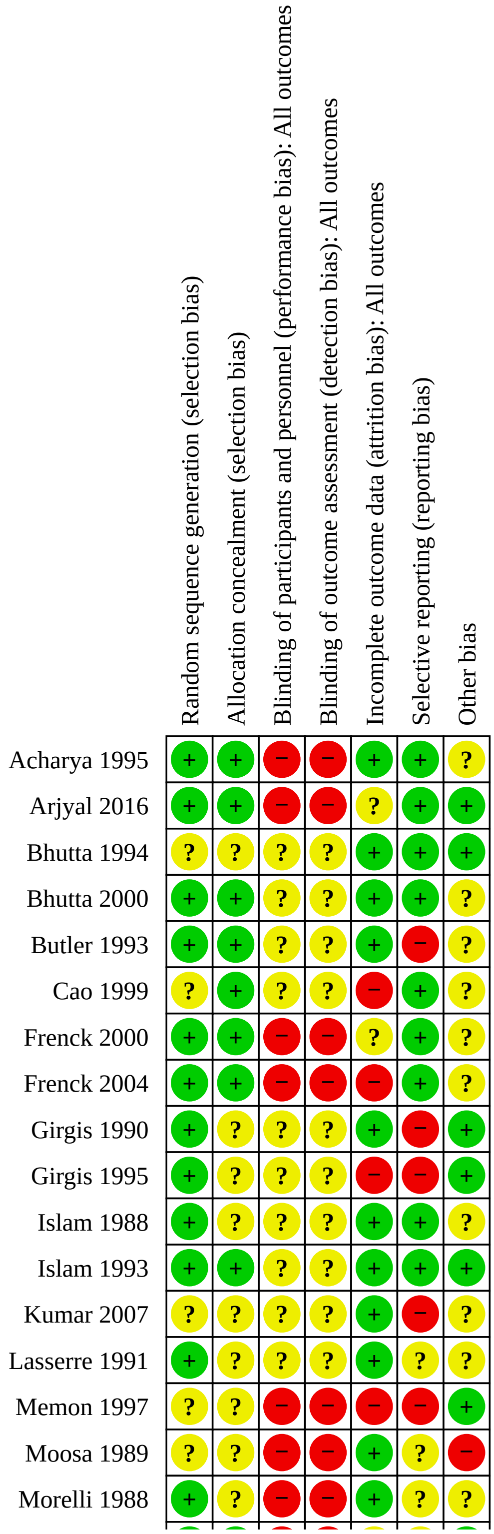
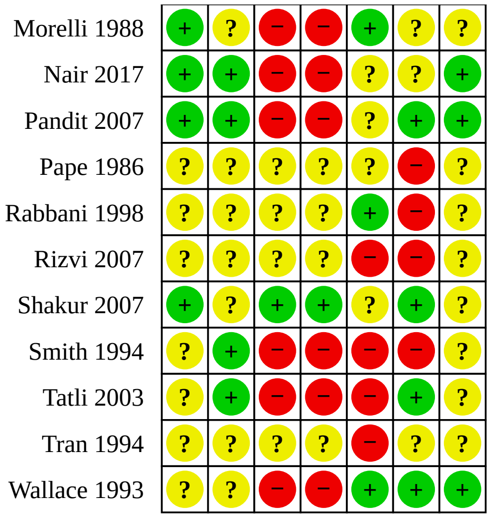


Figure 3. (Continued)



Allocation

We judged random sequence generation to be at low risk of bias in 15 trials that used computer-generated random allocation methods or randomized number tables. Twelve trials did not report details concerning how they randomized participants, leading to the judgement of an unclear risk of bias.

We judged the method used to generate the allocation sequence to be satisfactory, leading to a judgement of a low risk of bias in 12 trials, all of which used a sealed envelope method of allocation concealment. The risk of allocation bias was unclear in 15 trials due to lack of reporting on the method used, if any.

Blinding

One trial was double-blinded, which we assessed as low risk of bias, 12 trials were open and we judged them to be at high risk of bias, and 14 trials did not give any details on the presence or absence of blinding and we judged the risk of bias to be unclear.

Incomplete outcome data

Outcome data were incomplete in eight trials and we judged them to be at high risk of bias. Six trials did not clearly report details on outcome data, leading a judgement of unclear risk of bias, and we judged 13 trials to be low risk of bias due to all participant data accounted for at follow-up.

Selective reporting

We judged 13 trials to be at low risk of reporting bias as they reported data for all stipulated outcomes. We judged nine trials to be at high risk of bias as they did not report data for at least one prespecified outcome. We judged five trials to be at unclear risk of bias as they did not clearly report data on prespecified outcomes.

Other potential sources of bias

One trial reported that a pharmaceutical company had supplied the intervention antimicrobial and provided "assistance" with the trial, so we judged it to be at high risk of other bias.

We judged 17 trials to be at unclear risk of bias due either to the trials receiving antimicrobial donations or funding, or both, from pharmaceutical companies without further information regarding the involvement of the pharmaceutical company in the trial, or not reporting conflicts of interest. We judged nine trials to be at low risk of bias as all authors declared no conflict of interest and we did not identify any other sources of bias.

Effects of interventions

See: **Summary of findings 1** Cefixime versus fluoroquinolones for treating enteric fever; **Summary of findings 2** Ceftriaxone versus azithromycin for treating enteric fever; **Summary of findings 3** Ceftriaxone versus fluoroquinolones for treating enteric fever

Comparisons 1 to 3 relate to questions pertaining to common, currently used antimicrobial treatments for enteric fever and correspond to Summary of findings 1, Summary of findings 2, and Summary of findings 3. Comparison 4 compares cefixime with ceftriaxone.

Comparisons 5 to 7 concern cephalosporins compared with chloramphenicol. These comparisons may be relevant in regions of the world where chloramphenicol susceptibility has recovered.

Comparison 8 compares cefixime with cefpodoxime, comparison 9 compares cefixime with aztreonam and comparison 10 compares ceftriaxone with aztreonam. These comparisons may be relevant in regions where these drugs are in use.

Comparison 11 concerns the question pertaining to the duration of treatment of enteric fever with ceftriaxone.

1. Cefixime versus fluoroquinolones

Three trials published more than 14 years ago provided comparisons between cefixime and a fluoroquinolone in adults and children. One trial compared cefixime with ciprofloxacin (Rizvi 2007); two with ofloxacin (Cao 1999; Rizvi 2007); and one with gatifloxacin (Pandit 2007). Two of the three trials reported that the bacterial isolates were susceptible to the trial antimicrobials (Cao 1999; Pandit 2007).

Clinical failure

Clinical failure was higher in participants treated with cefixime compared with participants treated with a fluoroquinolone (28/114 (25%) participants treated with cefixime compared to 2/126 (1.6%) participants with fluoroquinolones; RR 13.39, 95% CI 3.24 to 55.39; 2 trials, 240 participants; low-certainty evidence; Analysis 1.1). One trial, which compared participants treated with cefixime with participants treated with ciprofloxacin and participants treated with ofloxacin reported no cases of clinical failure in either the intervention group or control groups (Rizvi 2007).

Microbiological failure

Microbiological failure was reported in 3 of 114 (2.6%) participants treated with cefixime compared with zero cases in 126 participants treated with fluoroquinolones (RR 4.07, 95% CI 0.46 to 36.41; 2 trials, 240 participants; low-certainty evidence; Analysis 1.2). One trial, which compared participants treated with cefixime to participants treated with ciprofloxacin and participants treated with ofloxacin reported no cases of microbiological failure in either the intervention group or control groups (Rizvi 2007).

Relapse

Relapse was higher in participants in the cefixime group compared to participants in the fluoroquinolone group (RR 4.45, 95% CI 1.11 to 17.84; two trials, 220 participants; low-certainty evidence; Analysis 1.3).

Time to defervescence

Time to defervescence was longer in participants treated with cefixime compared to participants treated with fluoroquinolones (MD 1.74 days, 95% CI 0.50 to 2.98; 3 trials, 425 participants; low-certainty evidence; Analysis 1.4). The mean time to defervescence in participants treated with ceftriaxone was 4.26 days compared to a mean time of 4.97 days in participants treated with ofloxacin in one trial; we were unable to calculate the mean difference in time to defervescence in this trial due to unreported ranges and SDs (Kumar 2007).

Convalescent faecal carriage

No persistent convalescent faecal carriage was detected in the one trial that reported this outcome (130/158 stool cultures were obtained from participants at six months' follow-up. We were unable to separate data by intervention and control group (Pandit 2007).

Length of hospital stay

No trials reported length of hospital stay.

Adverse events

In one trial a participant in the ofloxacin group died unexpectedly on the second day of treatment; a post-mortem clinical diagnosis of myocarditis was made (Cao 1999). It is unknown whether this was due to the drug or the disease process. In a further trial, a participant in the cefixime group died (Pandit 2007). Treatment with cefixime had started on day 14 of illness. Severe thrombocytopenia and gastrointestinal bleeding developed on day 6 of treatment, progressing to an acute respiratory distress syndrome with disseminated intravascular coagulation from which the participant did not recover. This deterioration was considered to be due to progression of the disease. No other serious adverse events were reported.

Excessive vomiting requiring intravenous fluids and antiemetics was noted in 2/92 participants and nausea in 23/92 participants receiving gatifloxacin compared to zero cases for both symptoms in the cefixime group (Pandit 2007). A skin rash requiring an oral antihistamine was noted in 1/77 participants in the cefixime group (Pandit 2007).

2. Ceftriaxone versus azithromycin

Two older trials and one more recent trial compared ceftriaxone and azithromycin (Frenck 2000; Frenck 2004; Nair 2017). The trial participants were all under 18 years of age. Two of the three trials reported that the bacterial isolates were susceptible to the trial antimicrobials (Frenck 2000; Frenck 2004).

Clinical failure

Clinical failure was reported in 3/100 (3%) of participants treated with ceftriaxone compared to 7/96 (7.3%) treated with azithromycin (RR 0.42, 95% CI 0.11 to 1.57; 3 trials, 196 participants; low-certainty evidence; Analysis 2.1).

Microbiological failure

Microbiological failure was reported in 3/100 (3%) of participants in the ceftriaxone group compared to 1/96 (1%) of participants in the azithromycin group (RR 1.95, 95% CI 0.36 to 10.64; 3 trials, 196 participants; very low-certainty evidence; Analysis 2.2).

Relapse

Relapse was reported in 15 of 96 participants in the ceftriaxone group compared to zero cases in 89 participants in the azithromycin group (RR 10.05, 95% CI 1.93 to 52.38; 3 trials, 185 participants; very low-certainty evidence; Analysis 2.3).

Time to defervescence

Time to defervescence was shorter in participants treated with ceftriaxone compared to participants treated with chloramphenicol (MD −0.52 days, 95% CI −0.91 to −0.12; 3 trials, 196 participants; low-certainty evidence; Analysis 2.4).

Convalescent faecal carriage

Convalescent faecal carriage of *Salmonella* was not detected in any participant on day 10 following treatment in either intervention or control group in one trial (Frenck 2000). Two trials reported that no participants were found to have *S typhi* in stool culture at one month follow-up (Frenck 2004; Nair 2017).

Length of hospital stay

No trials reported length of hospital stay.

Adverse events

No serious adverse outcomes were reported.

Two trials reported that transient vomiting occurred more frequently in participants treated with azithromycin than those treated with ceftriaxone (Frenck 2000; Frenck 2004). One trial reported that 6/30 participants experienced pain at the site of ceftriaxone injection up to 24 hours later (Frenck 2000). Two trials reported non-severe asymptomatic thrombocytosis in a few participants in both treatment groups (Frenck 2000; Frenck 2004). One trial reported diarrhoea in 10/32 (3.2%) participants treated with azithromycin compared to 15/36 (5.4%) participants treated with ceftriaxone (Frenck 2004). One trial reported vomiting and diarrhoea in a few participants in each treatment group; this may have been due to the disease or the drug (Nair 2017).

3. Ceftriaxone versus fluoroquinolones

Three older trials and two more recent trials compared ceftriaxone with fluoroquinolones in adults and children: one compared with ciprofloxacin (Wallace 1993); one with fleroxacin (Tran 1994); two with ofloxacin (Kumar 2007; Smith 1994); and one with gatifloxacin (Arjyal 2016). The three older trials reported that all bacterial isolates were susceptible to the trial antibiotics (Smith 1994; Tran 1994; Wallace 1993). In the two more recent trials, resistance was reported in 2/93 (2.2%) bacterial isolates to ceftriaxone and 7/93 (7.5%) bacterial isolates to ofloxacin (Kumar 2007), and resistance to gatifloxacin in 14/112 (12%) bacterial isolates but no resistance to ceftriaxone (Arjyal 2016).

Two trials used a maximum dose of 2 g of ceftriaxone daily (Arjyal 2016; Tran 1994), and two trials used a maximum dose of 2.5 g daily (Smith 1994; Wallace 1993). In one trial including children only, the maximum dose of ceftriaxone was not reported; dose information given was 100 mg per day (Kumar 2007).

Clinical failure

Three trials conducted over 20 years earlier reported clinical failure in 15/62 (24.2%) participants treated with ceftriaxone compared to 0/58 (0%) participants treated with a fluoroquinolone (Smith 1994; Tran 1994; Wallace 1993); a more recent trial (Arjyal 2016), reported 19/119 (16.0%) participants with clinical failure in the ceftriaxone group compared with 18/120 (15.0%) participants in the fluoroquinolone group (RR 3.77, 95% CI 0.72 to 19.81; 4 trials, 359 participants; very low-certainty evidence; Analysis 3.1). One trial reported no cases of clinical failure in participants receiving ceftriaxone and no cases in participants receiving ofloxacin (Kumar 2007). No clear relationship was seen on analysis according to ceftriaxone dose (2 g daily compared to more than 2 g daily).

Microbiological failure

Microbiological failure was not significantly different in participants in the ceftriaxone group compared to participants in the fluoroquinolone group (RR 1.65, 95% CI 0.40 to 6.83; 3 trials, 316 participants; very low-certainty evidence; Analysis 3.2). No clear relationship was seen on analysis according to ceftriaxone dose (2 g daily compared to more than 2 g daily).

Relapse

Relapse was not significantly different in participants in the ceftriaxone group compared to participants in the fluoroquinolone group (RR 0.95, 95% CI 0.31 to 2.92; 3 trials, 297 participants; very low-certainty evidence; Analysis 3.3). One trial reported that no participant in either the ceftriaxone or ofloxacin group experienced clinical relapse with fever (Kumar 2007). No clear relationship was seen on analysis according to ceftriaxone dose (2 g daily compared to more than 2 g daily).

Time to defervescence

Average time to defervescence was 2.73 days longer in participants treated with ceftriaxone compared to participants treated with fluoroquinolones, but the analysis was underpowered and we are uncertain if this is a true difference (MD 2.73 days, 95% CI −0.37 to 5.84; 3 trials, 285 participants; very low-certainty evidence; Analysis 3.4). No clear relationship was seen on analysis according to ceftriaxone dose (2 g daily compared to more than 2 g daily). We were unable to calculate the mean time to defervescence calculated in one trial due to missing data on standard deviation (Kumar 2007).

Convalescent faecal carriage

Convalescent faecal carriage was not detected in 0/38 (0%) participants treated with ceftriaxone compared to detection in 2/35 (5.7%) participants treated with gatifloxacin (RR 0.18, 95% CI 0.01 to 3.72; 1 trial, 73 participants; very low-certainty evidence; Analysis 3.5).

Length of hospital stay

The mean length of hospital stay was longer in participants treated with ceftriaxone compared to participants treated with ofloxacin. However, there was overlap in the ranges between treatment groups (mean of 12 days (range 7 to 23 days) in the ceftriaxone group compared to a mean of 9 days (range 6 to 13 days) in the ofloxacin group; 1 trial, 47 participants; low-certainty evidence, Smith 1994). We were unable to calculate the mean difference due to unknown standard deviations in each group.

Adverse events

One trial reported a 'probable' anaphylactic reaction in 1 of 15 participants in the ceftriaxone group (Tran 1994). One trial reported a mild skin rash in 2 of 25 participants in the ceftriaxone group and pruritis in 1 of 22 participants in the ofloxacin group (Smith 1994). One trial reported complications of hepatitis (9/62 participants), intestinal bleeding (3/62 participants) and pleural effusion (1/62 participants); it was not stated which treatment was received by participants experiencing these complications or whether they were considered due to the drug or the disease process (Kumar 2007).

4. Ceftriaxone versus cefixime

Two older trials compared ceftriaxone with cefixime (Bhutta 1994; Girgis 1995). The trial participants were all under 18 years of age. The trials reported that all bacterial isolates were susceptible to the trial antimicrobials.

Clinical failure

Clinical failure was reported in 3/68 (4.4%) participants treated with ceftriaxone compared to 3/75 (4.0%) treated with cefixime (RR 1.00, 95% CI 0.22 to 4.49; 143 participants; 2 trials; Analysis 4.1).

Microbiological failure

Microbiological failure was reported in 2/68 (2.9%) of participants in the ceftriaxone group compared to 1/75 (1%) of participants in the cefixime group (RR 2.00, 95% CI 0.19 to 20.67; 2 trials, 143 participants; Analysis 4.2).

Relapse

Relapse was reported in 5/68 (7.4%) participants in the ceftriaxone group compared to 4/75 participants in the cefixime group (RR 1.36, 95% CI 0.37 to 4.98; 2 trials, 143 participants; Analysis 4.3).

Time to defervescence

Time to defervescence was shorter in participants treated with ceftriaxone compared to participants treated with chloramphenicol (MD −1.48 days, 95% CI −2.13 to −0.83; 2 trials, 143 participants; Analysis 4.1).

Convalescent faecal carriage

Neither trial reported convalescent faecal carriage of *Salmonella*.

Length of hospital stay

Neither trial reported length of hospital stay.

Adverse events

No serious adverse outcomes were reported.

5. Ceftriaxone versus chloramphenicol

Eight trials conducted between 1988 and 2003 compared ceftriaxone and chloramphenicol (Acharya 1995; Butler 1993; Girgis 1990; Islam 1988; Islam 1993; Lasserre 1991; Moosa 1989; Tatli 2003). The trial participants include adults and children. Seven of the eight trials reported that the bacterial isolates were susceptible to the trial antimicrobials.

Clinical failure

Clinical failure was reported in 15/202 (7.4%) of participants treated with ceftriaxone compared to 10/185 (5.4%) treated with chloramphenicol (RR 1.43, 95% CI 0.68 to 3.00; 7 trials, 387 participants; Analysis 5.1).

Microbiological failure

There were no microbiological failures in participants in either group (Analysis 5.2).

Relapse

Relapse was reported in 5/189 (2.6%) of participants treated with ceftriaxone compared to 13/176 (7.4%) participants in the chloramphenicol group (RR 0.45, 95% CI 0.20 to 1.04; 7 trials, 365 participants; Analysis 5.3).

Time to defervescence

Time to defervescence was shorter in participants treated with ceftriaxone compared to participants treated with chloramphenicol (MD −2.54 days, 95% CI −3.13 to −1.95; 55 participants, 1 trial; Analysis 5.4).

Convalescent faecal carriage

Convalescent faecal carriage was detected in two participants treated with ceftriaxone compared to none treated with chloramphenicol (RR 3.20, 95% CI 0.34 to 29.94; 2 trials, 118 participants; Analysis 5.5).

Length of hospital stay

No trials reported length of hospital stay.

Adverse events

In one trial, one participant died with pneumonia and hypotension among the 32 participants in the ceftriaxone group; one death due to pneumonia and one intestinal perforation was reported in the 31 participants in the chloramphenicol group (Islam 1988).

Several trials reported decreases in the haemoglobin concentration, white cell and platelet count in the participants during treatment with chloramphenicol that were greater than in those treated with ceftriaxone (Acharya 1995; Butler 1993; Islam 1993). Chloramphenicol was discontinued because of increasing leucopenia or thrombocytopenia, or both in 3/23 (13.0%) participants in Acharya 1995; and 2/14 (14.3%) participants in Butler 1993.

One participant in each of two trials developed a skin rash that disappeared after discontinuation of ceftriaxone (Islam 1993; Lasserre 1991)

6. Cefixime versus chloramphenicol

Three trials conducted between 1997 and 2007 compared cefixime and chloramphenicol (Memon 1997; Rabbani 1998; Rizvi 2007). The trial participants include adults and children. One trial observed resistance to chloramphenicol in 66/85 (78%) bacterial isolates (Memon 1997). The other two trials did not clearly present the levels of in vitro resistance to chloramphenicol.

Clinical failure

Clinical failure was reported in 4/107 (3.7%) participants treated with cefixime compared to 51/108 (47.2%) treated with chloramphenicol (RR 0.09, 95% CI 0.04 to 0.23; 3 trials, 215 participants; Analysis 6.1).

Microbiological failure

One trial reported microbiological failures, with no failures in the participants treated with cefixime but 9/44 (20.4%) failures in those treated with chloramphenicol (RR 0.05. 95% CI 0.00 to 0.84; 1 trial, 90 participants; Analysis 6.2).

Relapse

No trials reported relapse.

Time to defervescence

Time to defervescence was shorter in participants treated with cefixime compared to participants treated with chloramphenicol (mean difference of −2.50 days, 95% CI −3.23 to −1.77; 1 trial, 90 participants; Analysis 6.3).

Convalescent faecal carriage

No trials reported convalescent faecal carriage.

Length of hospital stay

No trials reported length of hospital stay.

Adverse events

There were no severe adverse events.

In the 41 participants in the cefixime group in one trial, abdominal distension was reported in two participants, urticaria in one participant, and epistaxis with thrombocytopenia in one participant (Memon 1997). In a further trial, nausea and vomiting was reported in 3/46 participants (Rizvi 2007).

Side effects attributed to chloramphenicol in one trial were abdominal distension in 3/44 participants and diarrhoea in 1/44 participants (Memon 1997). In a further trial, nausea and vomiting was reported in 4/44 participants and anaemia in 2/44 participants (Rizvi 2007).

7. Cefoperazone versus chloramphenicol

Two trials compared cefoperazone with chloramphenicol (Morelli 1988; Pape 1986). One trial was conducted in adolescents and adults in Italy (Morelli 1988), and the other trial was conducted in children in Haiti (Pape 1986).

Clinical failure

Clinical failure was reported in 2/40 (5%) participants treated with cefoperazone compared to 3/41 (7.3%) participants treated with chloramphenicol (RR 0.74, 95% CI 0.10 to 5.36; 2 trials, 81 participants; Analysis 7.1).

Microbiological failure

One trial reported no cases of microbiological failure in either treatment group at the end of treatment (Morelli 1988). One trial did not report the number of participants in each treatment group who experienced microbiological failure (Pape 1986).

Relapse

Relapse was reported in 2/27 (7.4%) participants treated with cefoperazone compared to 4/28 (14.3%) participants in the chloramphenicol group (RR 0.52, 95% CI 0.10 to 2.60; 1 trial, 55 participants; Analysis 7.2).

One trial reported no cases of relapse in either treatment group (Pape 1986).

Time to defervescence

Time to defervescence was shorter in participants treated with cefoperazone compared to chloramphenicol (MD −2.3 days, 95% CI −2.89 to −1.71; 1 trial, 21 participants; Analysis 7.3).

We were unable to calculate the mean time to defervescence in one trial due to missing data on standard deviation (Morelli 1988).

Convalescent faecal carriage

Convalescent faecal carriage was detected in one participant treated with cefoperazone compared to four participants treated with chloramphenicol (RR 0.25, 95% CI 0.03 to 2.10; 1 trial, 56 participants; Analysis 7.4).

One trial reported no cases of positive stool culture in either treatment group six weeks after completion of treatment in one trial (Pape 1986).

Length of hospital stay

Neither trial reported length of hospital stay.

Adverse events

In one trial there were three deaths out of 13 participants in the chloramphenicol group and one death out of 12 participants in the cefoperazone group; the trial authors reported the causes of death to be gastrointestinal bleeding and perforation (2 participants), hypotension and severe diarrhoea (1 participant) and presumed myocarditis with arrhythmias (1 participant; Pape 1986). The trial authors reported that all patients in the trial had an abnormal state of consciousness on trial enrolment, and that three participants out of 13 in the chloramphenicol group and one participant out of 12 in the cefoperazone group were additionally noted to be in shock on trial enrolment (Pape 1986).

In one trial, one participant experienced nausea and reflux in the chloramphenicol group (Morelli 1988).

8. Cefixime versus cefpodoxime

One small trial of 40 participants conducted in Bangladesh compared cefixime with cefpodoxime (Shakur 2007). All participants were children.

Clinical failure

Clinical failure was reported in 1/19 (5.3%) participants treated with cefixime compared to 1/21 (4.8%) participants treated with cefpodoxime (RR 1.11, 95% CI 0.07 to 16.47; 1 trial, 40 participants; Analysis 8.1).

Microbiological failure

No cases of microbiological failure were reported in either group (1 trial, 40 participants).

Relapse

No cases of relapse were reported in either group at three months of follow-up (1 trial, 40 participants).

Time to defervescence

Time to defervescence was shorter in participants treated with cefixime compared to cefpodoxime (MD −0.6 days, 95% CI −2.03 to 0.83; 1 trial, 40 participants; Analysis 8.2).

Convalescent faecal carriage

Convalescent faecal carriage was not reported.

Length of hospital stay

Length of hospital stay was not reported.

Adverse events

No serious adverse outcomes were reported. One participant in the cefixime group developed mild, self-limiting diarrhoea; one participant in the cefpodoxime group developed a mild, self-limiting maculopapular rash (Shakur 2007).

9. Cefixime versus aztreonam

One small trial conducted in participants less than 16 years of age in Egypt compared cefixime with aztreonam (Girgis 1995).

Clinical failure

No cases of clinical failure were reported in any participant in either treatment group at four weeks of follow-up (1 trial, 81 participants).

Microbiological failure

No cases of microbiological failure were reported in either treatment group at four weeks of follow-up (1 trial, 81 participants).

Relapse

Relapse was reported in 3/50 (6%) participants treated with cefixime compared to 2/31 (6.5%) participants in the aztreonam group (RR 0.93, 95% CI 0.16 to 5.26; 1 trial, 81 participants; Analysis 9.1).

Time to defervescence

Time to defervescence was shorter in participants treated with aztreonam compared to cefixime (MD 0.2 days, 95% CI −0.42 to 0.82; 81 participants; 1 trial; Analysis 9.2).

Convalescent faecal carriage

No cases of positive stool culture were reported in either treatment group at four weeks of follow-up (1 trial, 81 participants).

Length of hospital stay

We were unable to differentiate data concerning length of hospital stay from data concerning duration of participant illness.

Adverse events

No serious adverse events were reported. trial authors reported that mild reactions including nausea, vomiting and abdominal pain were observed in some participants in both treatment groups.

10. Ceftriaxone versus aztreonam

One small trial conducted in participants less than 16 years of age in Egypt compared ceftriaxone with aztreonam (Girgis 1995).

Clinical failure

No cases of clinical failure were reported in any participant in either treatment group at four weeks of follow-up (1 trial, 74 participants).

Microbiological failure

No cases of microbiological failure were reported in either treatment group at four weeks of follow-up (1 trial, 74 participants).

Relapse

Relapse was reported in 2/43 (4.7%) participants treated with ceftriaxone compared to 2/31 (6.5%) participants in the aztreonam group (RR 0.72, 95% CI 0.11 to 4.84; 1 trial, 74 participants; Analysis 10.1).

Time to defervescence

Time to defervescence was shorter in participants treated with ceftriaxone compared to aztreonam (MD −1.4 days, 95% CI −2.44 to −0.36; 1 trial, 74 participants; Analysis 10.2).

Convalescent faecal carriage

No cases of positive stool culture were reported in either treatment group at four weeks of follow-up (1 trial, 74 participants).

Length of hospital stay

We were unable to differentiate data concerning length of hospital from data concerning duration of participant illness.

Adverse events

No serious adverse events were reported. trial authors reported that mild reactions including nausea, vomiting and abdominal pain were observed in some participants in both treatment groups.

11. Duration of treatment with third-generation cephalosporins

One small trial published over 20 years ago directly compared duration of therapy of ceftriaxone (Bhutta 2000). This is the only drug with a direct comparison on treatment length.

Clinical failure

Clinical failure was reported in 2/29 (6.9%) participants treated with a seven-day course of ceftriaxone compared with 1/28 (3.6%) participants treated with a 14-day course of ceftriaxone (RR 1.93, 95% CI 0.19 to 20.12; 1 trial, 57 participants; Analysis 11.1).

Relapse

Relapse was reported in 4/29 (13.8%) participants treated with a seven-day course of ceftriaxone compared with zero cases in 28 participants treated with a 14-day course of ceftriaxone (RR 8.70, 95% CI 0.49 to 154.49; 1 trial, 57 participants; Analysis 11.2).

Time to defervescence

Time to defervescence was reduced in the 14-day course of ceftriaxone group compared to the group treated with seven days of ceftriaxone (MD 0.20 days, 95% CI −1.46 to 1.86; 1 trial, 57 participants; Analysis 11.3).

DISCUSSION

Antimicrobials in common use for the treatment of enteric fever are cefixime, ceftriaxone, azithromycin, and the fluoroquinolones. Resistance to all these antimicrobial classes has emerged in the last 10 years.

Summary of main results

This Cochrane Review included 27 trials with 2231 participants investigating cephalosporins compared to other antimicrobials for the treatment of enteric fever in adults and children. The main findings of this review regarding ceftriaxone and cefixime compared to other first-line antimicrobials used most commonly for the treatment of enteric fever are summarized in Summary of findings 1 (cefixime versus fluoroquinolones), Summary of findings 2 (ceftriaxone versus azithromycin), and Summary of findings 3 (ceftriaxone versus fluoroquinolones). The number of trials per outcome was low, 19 of 27 included trials were conducted over 20 years ago and many lacked statistical power to detect differences between the treatment regimens. The certainty of evidence is low to very low across all outcomes.

Clinical failure, microbiological failure and relapse may be slightly increased in patients treated with cefixime compared to fluoroquinolones (low-certainty evidence). Of note, one quarter of participants treated with cefixime were clinical failures.

It is very uncertain whether clinical failure is increased in patients treated with ceftriaxone compared to fluoroquinolones (very low-certainty evidence). There may be no difference in microbiological failure and relapse in participants treated with ceftriaxone compared to fluoroquinolones (low-certainty evidence).

Ceftriaxone may result in a decrease in clinical failure and an increase in microbiological failure compared to azithromycin in patients under 18 years of age (low-certainty evidence). Relapse may be slightly decreased in patients treated with ceftriaxone compared to treatment with fluoroquinolones (low-certainty evidence), and may be increased in patients < 18 years of age treated with ceftriaxone compared to azithromycin (low-certainty evidence). Ceftriaxone may result in a decrease in convalescent faecal carriage compared to fluoroquinolones (low-certainty evidence).

There may be no difference in clinical failure, microbiological failure and relapse in participants under 18 years of age treated with ceftriaxone compared to cefixime (low-certainty evidence). In addition, there may be no difference in clinical failure, microbiological failure and relapse in participants treated with ceftriaxone compared to chloramphenicol (low-certainty evidence).

Clinical failure and microbiological failure may be decreased in patients treated with cefixime compared to chloramphenicol (low-certainty evidence) although this result may be confounded by high levels of resistance to chloramphenicol in at least one trial.

Ceftriaxone and cefixime and all comparator antimicrobials were generally well tolerated. One death in a child receiving oxfloxacin (a fluoroquinolone) was reported in one trial (Cao 1999); it is unknown whether this death was due to the drug or the disease process. An adult receiving cefixime died in a further trial (Pandit 2007), with the death considered to be due to progression of the disease process. Two participants died, one in each arm of a trial comparing ceftriaxone and chloramphenicol, probably due to the disease process (Islam 1988). In a further trial in Haiti, in which all recruited children had severe typhoid fever with altered consciousness, there were three deaths out of 13 participants in the chloramphenicol group and one death out of 12 participants in the cefoperazone group; the trial authors reported the causes of death to be gastrointestinal bleeding and perforation (2 participants), hypotension and severe diarrhoea (1 participant) and presumed myocarditis with arrhythmias (1 participant; Pape 1986). A 'probable' anaphylactic reaction in one participant receiving ceftriaxone was reported in one trial (Tran 1994). Chloramphenicol was discontinued because of increasing leucopenia or thrombocytopenia, or both, in five participants in two trials (Acharya 1995; Butler 1993).

The optimal antimicrobial, dose and duration of therapy, cannot be determined from these review findings. One trial directly compared different doses of ceftriaxone however no conclusion can be drawn as the trial was underpowered (Bhutta 2000).

No trials comparing ceftriaxone with azithromycin were conducted in participants over 18 years old and no included trials directly compared cefixime with azithromycin.

Overall completeness and applicability of evidence

In general, participants with typhoid fever responded to cephalosporin treatment provided that the isolate was susceptible to the antimicrobial used. But we were unable to draw any definite conclusions on the presence or absence of important differences between cephalosporins and other antimicrobials in the treatment of enteric fever. There are too few trials within each comparison, and the trials themselves are underpowered. Data are especially lacking concerning the outcome of convalescent faecal carriage and duration of hospital stay across all antimicrobial comparisons. Some included trials are over two decades old, and took place when trial methodology was not as developed as in contemporary trials, although they were performed at a time when *S typhi* and *S paratyphi* isolates were still susceptible to older antimicrobials, allowing the efficacy assessment of older antimicrobials. In addition, antimicrobial susceptibility data were incompletely reported in some trials.

For contemporary treatment decisions, local resistance patterns need to be carefully considered. The threat of further spread of XDR strains highlights the importance of the implementation of antimicrobial stewardship policies in endemic areas.

There are no included trials comparing cefixime with azithromycin; we identified one trial during screening that compared cefixime with azithromycin, however there was disparity in the reported duration of treatment with azithromycin received by participants. Unfortunately, we did not receive a response from the trial authors requesting clarification on this discrepancy, and we excluded this trial (Amin 2021).

Certainty of the evidence

The certainty of evidence for the main comparisons' outcomes presented in the summary of findings tables were low (see Summary of findings 1) or ranged between very low and low (see Summary of findings 2; Summary of findings 3). There was a lack of standardization across outcomes and the quality of reporting was inconsistent.

We downgraded all outcomes by one level for serious risk of bias. Only one trial out of 28 was blinded. Details of the risk of bias assessments are reported in the Assessment of risk of bias in included studies section.

A significant limitation for the certainty of evidence was the low number of participants, events, or both leading to wide CIs and low certainty in the estimated effects. We downgraded almost all outcomes by one or two levels for imprecision.

We did not downgrade any outcomes for indirectness. In all cases, the effect estimates were based on comparisons of interest, on the population of interest, and on outcomes of interest (where reported). We did not assess publication bias due to the low number of trials within comparisons.

Potential biases in the review process

The search methods were thorough and included searching the proceedings of international typhoid conferences. However, it is possible that we did not capture randomized clinical trials conducted in China or Latin America due to language barriers.

No included trials directly compared cefixime with azithromycin; we approached the authors of one trial undertaking this comparison for clarification of data, however this approach was not successful (Amin 2021).

Agreements and disagreements with other studies or reviews

A Cochrane Review including the comparisons of fluoroquinolones to cefixime, fluoroquinolones to ceftriaxone, and cefixime to azithromycin has been published (Effa 2011); our review findings are in agreement.

AUTHORS' CONCLUSIONS

Implications for practice

Ceftriaxone can effectively treat enteric fever in adults and children with few adverse effects, and may be superior to alternatives in some settings. The evidence for the efficacy of cefixime in randomized controlled trials (RCTs) is limited. We were unable to draw firm general conclusions on comparative contemporary effectiveness in the context of antimicrobial resistance differing by geographical location and over time, and many trials were small. Clinicians need to take into account current, local resistance patterns when choosing an antimicrobial.

Implications for research

In light of the importance of the need for effective antimicrobials to treat enteric fever in a context of increasing antimicrobial resistance, we need multi-centred, adequately powered trials testing new antimicrobials or new combinations of antimicrobials, with robust methods and analytical design. Data reporting should be stratified by bacterial antimicrobial resistance and vaccination status, where possible.

Future research may be guided by the results of the one identified, ongoing RCT in South Asia, which is examining the benefit of adding cefixime to azithromycin compared with azithromycin alone in uncomplicated, clinically suspected enteric fever in a planned sample size of 1500 participants (Ongoing studies).

Definitions of outcomes and their measurement (development of a core outcome set) should also be standardized to make more effective comparisons and adaptability across regions.

Research and development of low-cost, sensitive and specific diagnostic tests for typhoid fever would improve diagnostic accuracy and decrease the use of unnecessary or incorrect antibiotic treatment, impacting antimicrobial resistance compromising treatment in many areas of the world.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Acharya 1995

Study characteristics	
Methods	Trial design: randomized Time period/duration of trial: unclear Duration of follow-up: 21 days

Participants	Setting: hospital emergency/out-patient departments
	Location: Kathmandu, Nepal
	Age: adults and children (15 and 8 in each treatment group, respectively). Mean age (± SD) was 18.1 (± 4.8) in ceftriaxone group, 19.4 (± 6.2) in chloramphenicol group
	Gender: male = 39, female = 7
	Health status of participants: not recorded
	Inclusion criteria:
	• fever > 38.5 °C for > 4 days and
	• one or more of the following:
	  ○ abdominal pain/tenderness
	  ○ splenomegaly
	  ○ rose spots
	  ○ relative bradycardia;
	• blood culture also had to be positive for *S typhi* or *S paratyphi*
	Exclusion criteria:
	• antimicrobial therapy for ≥ 2 days in the week before clinical presentation that had led to clinical improvement;
	• severe/complicated presentations including hypotension, pneumonia, rectal bleeding, altered consciousness, suspected intestinal perforation

Interventions	• Chloramphenicol, adults and children: oral, 60 mg/kg/day 4 times/day until defervescence; dose subsequently reduced to 40 mg/kg/day to complete a 14-day regimen • Ceftriaxone, adults: IV, given over 30 min, 2 g once/day for 3 days

Acharya 1995 *(Continued)*

	Ceftriaxone, children: IV, given over 30 min, 50 mg/kg once/day for 3 days. Children > 40 kg in weight were dosed as for adults
Outcomes	• Clinical cure: resolution of fever, clinical symptoms and signs; no need for re-treatment; no relapse during trial period • Bacteriological cure: blood culture negative at end of treatment • Relapse: return of fever with isolation of *S typhi/paratyphi* within 2 months of starting therapy • Treatment failure: persistence of fever with no other cause, or persistent bacteraemia • Adverse events: adverse drug reactions such as urticaria/rash, phlebitis, nausea and vomiting were monitored daily until discharge from hospital • Faecal carriage: culture on day 21 after start of treatment • Haematologic measurements (haemoglobin, white cell count and platelets) days 4 and 15 after start of treatment
Organism type and antimicrobial susceptibility	*S typhi* = 38 (16 in ceftriaxone group, 22 in chloramphenicol group); *S paratyphi A* = 8 (7 in ceftriaxone group, 1 in chloramphenicol group) Drug resistance: 1 isolate in ceftriaxone group resistant to chloramphenicol; MDR numbers not reported
Notes	Not possible to separate adult from paediatric data Sponsor: research supported by a grant from F. Hoffman LaRoche and company (Roche pharmaceuticals), manufacturers of ceftriaxone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Serially numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open design
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up as per protocol
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Unclear risk	Research supported by a grant from F. Hoffman LaRoche and company (Roche pharmaceuticals), manufacturers of ceftriaxone

Arjyal 2016

Study characteristics	
Methods	Trial design: randomized Time period/duration of trial: 18 September 2011-14 July 2014 Duration of follow-up: 6 months
Participants	Setting: presenting to the outpatient or emergency department of Patan Hospital or the Civil Hospital Location: Lalitpur, Nepal Age: 2-45 years; median age 20 (IQR 14-23.5 years) in ceftriaxone group 19 (IQR 15-23 years) in gatifloxacin group Gender: male = 180, female = 59 Health status of participants: not recorded Inclusion criteria: • body temperature at least 38.0 °C for ≥ 4 days • no focus of infection as assessed by physical examination and laboratory tests • ability to give written, informed consent (from parent or guardian if patient < 18 years) Exclusion criteria: • pregnancy • diabetes mellitus • signs of severe typhoid (e.g., obtundation, shock, clinical jaundice, active gastrointestinal bleeding) • history of hypersensitivity to either of the trial drugs, or had been given a fluoroquinolone, a third-generation cephalosporin, or macrolide within the previous week. • Patients who had received chloramphenicol, amoxycillin, or co-trimoxazole within the previous week if the treating clinician reported a clinical response
Interventions	• Gatifloxacin 10 mg/kg/day, oral, 7 days • Ceftriaxone 60 mg/kg/day to 2 g/day if 2-13 years old, IV, 7 days OR ceftriaxone 2 g/day if ≥ 14 years, IV, 7 days
Outcomes	Primary endpoint was a composite of treatment failure as ≥ 1 of: • prolonged fever clearance time > 7 days after treatment initiation (fever clearance time defined as the time from the first dose of the trial drug until the temperature fell to ≤ 37.5 °C and remained there for at least 2 days) • need for rescue treatment as judged by treating physician • positive blood culture on day 8 of treatment (microbiological failure) • culture-confirmed or syndromic enteric fever relapse within 28 days of treatment initiation • development of enteric fever-related complications (e.g. clinically significant bleed, fall in GCS, GI perforation, admission to hospital within 28 days of treatment initiation) Secondary endpoints were: • fever clearance time • time to relapse until day 28 or at any time during follow-up • confirmed and syndromic relapse at day 28 • faecal carriage of *S typhi* or *S paratyphi* at 1 month, 3 months, or 6 months after randomization assessed in culture-positive participants only
Organism type and antimicrobial susceptibility	*S typhi* = 81 (43 in gatifloxacin group and 38 in ceftriaxone group); *S paratyphi* = 35 (19 in gatifloxacin group and 16 in ceftriaxone group). 14 of the 81 *S typhi* isolates were resistant to gatifloxacin (MIC > 1 µg/mL). None of the isolates were resistant to ceftriaxone.

Arjyal 2016 *(Continued)*

Notes	725 patients were screened for the trial, with 246 enrolled and randomized. 479 were ineligible, because of being in receipt of antibiotics in the week before trial entry (n = 178), refusal of consent (n = 163), outside the age criteria (n = 53), could not arrange to be followed up (n = 64), pregnant or lactating (n = 6), or other reasons (n = 15). 7 patients were excluded after randomization because of refusing IV medication (n = 3), an alternative diagnosis was confirmed (n = 3), and dropped out before a single dose (n = 1) leaving 239 participants analysed by ITT. 120 participants assigned to receive gatifloxacin, and 62 of these were culture-positive; 119 were assigned to receive ceftriaxone and 54 of these were culture-positive. The trial was designed to randomly assign 300 patients to treatment. The trial was halted prematurely on clinical grounds following the recommendation of the Data and Safety Monitoring Board following the appearance of gatifloxacin-resistant strains and resulting treatment failures.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized in blocks of 100 from a computer generated randomization list, by an investigator not involved in patient recruitment or assessment."
Allocation concealment (selection bias)	Low risk	"The randomization sequence and block size was concealed from the physicians allocating treatment and managing the patients, prior to patient enrollment. Treatment allocations were kept in sealed opaque envelopes, which were opened only on enrollment of the patient to the trial after all inclusion and exclusion criteria had been checked."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 participants dropped out of the trial
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Low risk	No conflicts of interest reported; trial sponsor and funder had no involvement in trial design, process, analyses, or write-up

Bhutta 1994

Study characteristics

Methods	Trial design: randomized Time period/duration of trial: June 1991-May 1992 Duration of follow-up: 12 weeks after cessation of therapy
Participants	Setting: hospital paediatric services Location: Karachi, Pakistan

Bhutta 1994 *(Continued)*

	Age: children 6 months-13 years of age. Mean age (+/- SD) was 8.4 (+/- 3.1) in ceftriaxone group, 6.6 (+/- 3.5) in cefixime group Gender: male = 31, female = 19 Health status of participants: not recorded Inclusion criteria: • suspected MDR-typhoid, with clinical features suggestive of typhoid and no response to treatment with oral chloramphenicol, amoxicillin or co-trimoxazole for at least 7 days and/or history of close contact with an MDR-culture-positive case Exclusion criteria: • vomiting, abdominal distension, ileus, or preceding ceftriaxone or cefixime therapy in the preceding week
Interventions	• Ceftriaxone: IV, 60 mg/kg/day once daily for 14 days • Cefixime: oral, 5 mg/kg/day twice daily for 14 days
Outcomes	• Treatment failure: persistent pyrexia (≥ 38.5 °C for ≥ 24 h) and toxicity after 10 days of therapy • Time to fever clearance (defervescence): temperature of ≤ 37.5 °C after 48 h of therapy • Relapse: recurrence of clinical features of illness and a positive blood culture within 8 weeks of cessation of therapy • Microbiological failure: not strictly defined, but mentioned as an outcome • Typhoid morbidity score: defined as 0-2 on the basis of fever, sensorium, hepatomegaly, presence of diarrhoea and vomiting, abdominal pain, abdominal examination • Times to loss of irritability, abdominal pain, regression of splenomegaly • Adverse events: monitored during the course of therapy - clinical and laboratory values (not specified)
Organism type and antimicrobial susceptibility	*S typhi* only. 50/59 children had MDR-typhoid following susceptibility testing.
Notes	80 children with suspected MDR admitted; typhoid confirmed on blood/bone marrow cultures in 59 cases, 9 of which were fully susceptible. Only MDR cases completed protocol and included in outcome analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details on randomization process given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias)	Low risk	All participants followed up as per protocol

Bhutta 1994 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Low risk	No other obvious reasons for bias identified

Bhutta 2000

Study characteristics	
Methods	Trial design: randomized Time period/duration of trial: unclear Duration of follow-up: unclear
Participants	Setting: hospital paediatric services Location: Karachi, Pakistan Age: all children Mean age (+/- SD) was 7.1 (+/- 3.7) in short-course (7 days) ceftriaxone group, 5.6 (+/- 33.4) in conventional (14 days) ceftriaxone group Gender: male = 32, female = 25 Health status of participants: not recorded Inclusion criteria: • proven MDR typhoid Exclusion criteria: • none listed
Interventions	• Ceftriaxone: IV, 65 mg/kg/day once daily for 7 days • Ceftriaxone: IV, 65 mg/kg/day once daily for 14 days
Outcomes	• Clinical failure: persistence of fever along with a < 2-point reduction in typhoid morbidity score by day 7 of therapy • Time to defervescence: not defined, but results given as an outcome measure • Relapse: recurrence of fever along with a positive blood culture for *S typhi* with a similar antibiogram to the original infecting strain within 8 weeks of the completion of therapy • Bacteriological failure: persistence of *S typhi* in cultures obtained at day 3 or after • Typhoid morbidity score - admission, day 3, day 7: score of 0-2 given based on fever, mental state, liver size, diarrhoea, vomiting, abdominal pain and abdominal examination result • Time to return of appetite: measured in days • Adverse events: not specified
Organism type and antimicrobial susceptibility	MDR-*S typhi*
Notes	118 consecutive children admitted; alternative diagnosis established in 87 and non-MDR *S typhi* in 19. 5 children were treated with amoxicillin on the basis of a Widal test, but were culture-negative.

Bhutta 2000 *(Continued)*

	Sponsor: research was supported by an unrestricted grant from Roche pharmaceuticals, the manufacturers of ceftriaxone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization used
Allocation concealment (selection bias)	Low risk	Sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up as per protocol
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Unclear risk	Research was supported by an unrestricted grant from Roche pharmaceuticals, the manufacturers of ceftriaxone

Butler 1993

Study characteristics

Methods	Trial design: randomized Time period/duration of trial: unclear Duration of follow-up: unclear
Participants	Setting: hospital services Location: Kathmandu, Nepal Age: adults ≥ 18 years of age Mean age (+/- SD) was 23.4 (+/- 5.9) in ceftriaxone group, 24.2 (+/- 7.6) in chloramphenicol group Gender: male = 28, female = 1 Health status of participants: not recorded Inclusion criteria: • age • ≥ 4 days of preceding fever and

Butler 1993 *(Continued)*

	• ≥ 2 of the following features:
	  ◦ temperature ≥ 38 °C
	  ◦ diarrhoea
	  ◦ splenomegaly
	  ◦ hepatomegaly
	  ◦ rose spots
	
	Exclusion criteria:
	
	• effective antimicrobial therapy in the preceding 2 weeks
	• allergy to chloramphenicol or cephalosporins
	• presence of complicated disease (shock, coma, rectal bleeding, suspected intestinal perforation listed)

Interventions	• Ceftriaxone: IV, 2 g administered over 30 min once daily for 3 consecutive days • Chloramphenicol: oral, 50 mg/kg/day divided into 4 doses for 14 days
Outcomes	• Clinical cure: afebrile without a major complication (perforation or bleeding), without the need to change antibiotic therapy and no relapse after discharge • Time to defervescence: the first day the oral temperature fell to < 38 °C for at least 48 h • Relapse: return of symptoms with isolation of *S typhi* or *S paratyphi A* in the blood within 2 months after the start of therapy • Bacteriological cure: negative blood culture on days 4 and 15 after start of therapy • Faecal carriage: faecal cultures performed on days 0, 7, 15 and 21 after start of therapy • Cytokine measurements: IL-6, gamma interferon, TNF-R concentrations in plasma measured before therapy commenced, on day 4 of therapy and on day 15 of therapy • Adverse events: not prespecified, discussed as part of results
Organism type and antimicrobial susceptibility	*S typhi* = 23; *S paratyphi A* = 6. 29 isolates susceptible to ceftriaxone, 28 isolates susceptible to chloramphenicol
Notes	Only data from blood/faecal culture-positive participants included in the analysis Sponsor: the research was supported by a grant from Hoffman-La Roche pharmaceuticals, who manufactured ceftriaxone.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table used
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given

Butler 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up as per protocol
Selective reporting (reporting bias)	High risk	The prespecified outcome of time to defervescence was not reported
Other bias	Unclear risk	The research was supported by a grant from Hoffman-La Roche pharmaceuticals, who manufactured ceftriaxone

Cao 1999

Study characteristics	
Methods	Trial design: randomized Time period/duration of trial: July 1995-April 1996 Duration of follow-up: 28 days after completion of treatment
Participants	Setting: hospital paediatric ward Location: Dong Nai, Vietnam 82 participants Age: children ≤ 15 years of age Mean age was 6.9 years (SD 3.3. years) Gender: reported as "equal" Health status of participants: not recorded Inclusion criteria: • age • ≥ 7 days of preceding fever without contact history • typhoid contact history • Widal O antibody titre of ≥ 100 Exclusion criteria: • severe disease requiring intensive care • hypersensitivity to third-generation cephalosporins or quinolones • pre-treatment with third-generation cephalosporin or quinolone during this illness • pre-treatment and clinical response with chloramphenicol, ampicillin, first-/second-generation cephalosporins, co-trimoxazole
Interventions	• Ofloxacin: oral, 10 mg/kg/day in 2 divided doses for 5 days • Cefixime: oral, 20 mg/kg/day in 2 divided doses for 7 days
Outcomes	• Clinical cure: resolution of symptoms and fever, and no evidence of relapse

Cao 1999 *(Continued)*

	• Clinical failure: deterioration in clinical condition or a failure of resolution of symptoms requiring further treatment • Microbiological failure: blood culture positive for *S typhi* after completion of treatment • Relapse: symptoms suggestive of typhoid fever with a blood culture positive for *S typhi* during the 28 days after discharge • Fever clearance time: time from onset of treatment until fever ≤ 37.5 °C for at least 24 h • Day at which child able to eat and walk • Adverse events: not prespecified, discussed as part of response to treatment • Faecal culture: 28 days after treatment (3 cultures taken)
Organism type and antimicrobial susceptibility	Resistance to ampicillin, chloramphenicol, co-trimoxazole and tetracycline in 70 isolates; no resistance to nalidixic acid or trial drugs detected
Notes	Analysis limited to culture-confirmed cases of infection. 138 participants with clinically suspected typhoid fever; 82 had blood cultures positive for *S typhi*. Sponsor: Roussel-Uclaf pharmaceuticals donated the ofloxacin tablets used in the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not specified
Allocation concealment (selection bias)	Low risk	Serially numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	High risk	1 participant in cefixime group lost to follow-up early (microbiological failure). At 28 days, only 40 participants were available for assessment (exact breakdown unclear)
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Unclear risk	Roussel-Uclaf pharmaceuticals donated the ofloxacin tablets used in the trial.

Frenck 2000

Study characteristics

Methods	Trial design: randomized Time period/duration of trial: unclear Duration of follow-up: 4 weeks

Frenck 2000 *(Continued)*

Participants	Setting: hospital
	
	Location: Cairo, Egypt
	
	Age: all children 4-17 years of age
	
	Mean age (+/- SD) was 9.8 (+/- 2.8 years) overall; in ceftriaxone group, 10.1 (range: 5-14) in azithromycin group
	
	Gender: male = 53, female = 55
	
	Health status of participants: some underlying illnesses part of exclusion criteria
	
	Inclusion criteria:
	
	• age
	• documented fever ≥ 38.5 °C
	• history of fever for at least 4 days +
	• at least 2 of the following:
	  ◦ abdominal tenderness
	  ◦ hepatomegaly
	  ◦ splenomegaly
	  ◦ rose spots
	
	Exclusion criteria:
	
	• allergy to ceftriaxone, erythromycin or other macrolides
	• major complications of typhoid fever (e.g. pneumonia, intestinal haemorrhage or perforation, shock, coma)
	• inability to swallow oral medications
	• significant underlying illness (e.g. heart disease, asthma requiring chronic medications, immunodeficiencies),
	• treatment within the last 4 days with either trial medication, or chloramphenicol, co-trimoxazole, or ampicillin
	• possible pregnancy/lactation

Interventions	• Ceftriaxone: IM with 1% lidocaine, 75 mg/kg/day once daily (maximum dose 2.5 g) for 7 days • Azithromycin: oral suspension, 10 mg/kg/day once daily (maximum dose 500 mg/day) for 7 days
Outcomes	• Clinical cure: resolution of all typhoid-related symptoms or signs by the end of 7 days of therapy • Clinical failure: persistence ≥ 1 typhoid-related symptoms or signs present at trial entry, or as development of a typhoid-related complication after at least 4 days of therapy • Microbiological cure: sterile blood culture on days 4 and 10 of therapy • Relapse: recurrence of fever with signs or symptoms of typhoid fever within 4 weeks of completion of therapy along with isolation of *S typhi* or *S paratyphi* from blood culture • Fever clearance time: rectal temperature not > 38.4 °C during any 24-h period • Mean laboratory values on day 10 of treatment - full blood count, liver and renal function tests • Blood culture results day 4 and 10 • Faecal culture result day 10 • Adverse events: structured questionnaire administered daily during hospitalization to monitor symptoms (including fever, headache, rash, abdominal pain, constipation, diarrhoea and/or anorexia and other possible adverse events)
Organism type and antimicrobial susceptibility	All *S typhi*; 6 MDR-*S typhi* in ceftriaxone and 5 MDR-*S typhi* in azithromycin group
Notes	108 individuals enrolled and randomized; data evaluated for only 64 children (34 in azithromycin and 30 in ceftriaxone groups) who were positive for *S typhi* on blood culture.

Frenck 2000 *(Continued)*

	Sponsor: financial support from Pfizer Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization from random list of numbers
Allocation concealment (selection bias)	Low risk	Serially numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 azithromycin recipients and 2 ceftriaxone recipients lost to follow-up after hospital discharge
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Unclear risk	Financial support from Pfizer Pharmaceuticals

Frenck 2004

Study characteristics

Methods	Trial design: randomized Time period/duration of trial: unclear Duration of follow-up: 4 weeks
Participants	Setting: hospital Location: Cairo, Egypt Age: all children 3-17 years of age Mean age: 10.8 (+/- 3.35) in ceftriaxone group, 11.8 (+/- 3.6) in azithromycin group Gender: male = 39, female = 29 Health status of participants: "significant underlying illness" part of exclusion criteria Inclusion criteria: • age • documented fever (rectal temperature ≥ 38.0 °C/oral temperature ≥ 37.5 °C and • at least 2 of the following: ○ abdominal tenderness

Frenck 2004 *(Continued)*

	◦ hepatomegaly ◦ splenomegaly ◦ a coated tongue Exclusion criteria: • allergy to ceftriaxone or macrolides • major typhoid fever-associated complications • inability to swallow oral medication • significant underlying illness • treatment within the last 4 days with an antibiotic that may be effective against *S typhi* • possible pregnancy/lactation
Interventions	• Ceftriaxone: IV, 75 mg/kg/day once daily (maximum dose 2.5 g) for 5 days • Azithromycin: oral suspension, 20 mg/kg/day once daily (maximum dose 1000 mg/day) for 5 days
Outcomes	• Clinical cure: resolution of all typhoid-related symptoms or signs by the end of 7 days of therapy • Clinical failure: persistence of ≥ 2 typhoid-related symptoms or signs present at trial entry, or as development of a typhoid-related complication • Clinical improvement: defined as partial resolution of illness • Microbiological failure: presence of an *S typhi*-positive blood culture on day 8 of the trial • Microbiological cure: sterile blood culture on day 8 of therapy (3 days after discontinuation of antibiotic therapy) • Persistent bacteraemia: defined as *S typhi* in blood culture on day 3 after initiating antibiotic therapy • Clinical relapse: recurrence of fever and clinical features of typhoid within 30 days of completion of therapy along with isolation of *S typhi* from blood culture • Duration of fever: fever defined as rectal temperature > 38 °C or oral temperature > 37.5 °C, absence for clearance not defined, reported as mean number of days • Blood culture positive: blood culture positive for *S typhi* on day 3/day 8 of the trial • Faecal culture positive: faecal culture positive for *S typhi* on day 8/day 30 of the trial • Mean laboratory values on day 10 of treatment: full blood count, liver and renal function tests • Adverse events: serious - not defined; minor - listed in results as vomiting, diarrhoea, nausea, abdominal pain, anorexia and cough
Organism type and antimicrobial susceptibility	*S typhi* - all participants; *S paratyphi* not included. 1 isolate was MDR; no isolate resistant to ceftriaxone
Notes	128 enrolled; 68 had *S typhi* isolated from blood or stool culture and constituted the trial group Sponsor: financial support from Pfizer pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation for blocks of 8 participants
Allocation concealment (selection bias)	Low risk	Serially numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial

Frenck 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	High risk	11/68 (16.2%) participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Unclear risk	Financial support from Pfizer pharmaceuticals

Girgis 1990

Study characteristics	
Methods	Trial design: randomized Time period/duration of trial: 1987-1989 Duration of follow-up: 4 weeks
Participants	Setting: hospital Location: Cairo, Egypt Age: adults and children. Mean age (+/- SD) was 13.65 (+/- 7.22) overall Gender: male = 31, female = 24 Health status of participants: not recorded Inclusion criteria: • signs and symptoms suggestive of acute enteric fever
Interventions	• Ceftriaxone: IM, dissolved in 2% lidocaine 60-80 mg/kg/day (maximum of 4 g) once daily for 5-7 days • Chloramphenicol: oral, 50-80 mg/kg/day in 4 divided doses for 12-14 days
Outcomes	• Clinical cure: resolution of fever, clinical symptoms and signs; no need for re-treatment; no relapse during trial period • Bacteriological cure: blood, urine and stool culture negative at end of treatment • Relapse: return of fever with isolation of *S typhi*/*S paratyphi* during 4-week follow-up period • Treatment failure: persistence of fever with no other cause, or persistent bacteraemia • Time to fever clearance: number of days until disappearance of fever, afebrile defined as 37.5 °C • Adverse events: not pre-defined, listed as mild (diarrhoea, abdominal pain, injection site pain) • Laboratory analyses: Widal test, full blood count, glucose, renal function test and liver function tests • Time to resolution of specific symptoms and signs: headache, mental changes, abdominal pain, splenomegaly, hepatomegaly
Organism type and antimicrobial susceptibility	*S typhi* in 25 participants on ceftriaxone, and 27 participants on chloramphenicol. *S paratyphi* in 3 participants on chloramphenicol All isolates susceptible to ceftriaxone and chloramphenicol

Girgis 1990 *(Continued)*

Notes	74 initially randomized; only those with *S typhi*/*S paratyphi* in blood cultures were included in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data reported for all stipulated outcome measures
Selective reporting (reporting bias)	High risk	Duration of hospitalization prespecified as an outcome, however no specific values reported
Other bias	Low risk	No obvious conflicts of interest

Girgis 1995

Study characteristics

Methods	Trial design: randomized Time period/duration of trial: unclear, before 1995 Duration of follow-up: 4 weeks
Participants	Setting: hospital Location: Cairo, Egypt Age: children < 16 years. Mean age (+/- SD) was 10.34 (+/- 2.89) in cefixime group, 10.05 (+/- 3.48) in ceftriaxone group, 9.03 (+/- 9.1) in the aztreonam group Gender: male = 67, female = 57 Health status of participants: not recorded Inclusion criteria: • signs and symptoms suggestive of acute enteric fever without complications of disease
Interventions	• Cefixime: oral, 15-20 mg/kg/day in 2 doses for a minimum of 14 days • Ceftriaxone: IM in gluteal region, 50-70 mg/kg/day (maximum of 4 g) once daily for 5 days

Girgis 1995 *(Continued)*

	• Aztreonam: IM in gluteal region, 50-70 mg/kg/dose (maximum of 8 g) every 8 h for 3 days Antibiotics continued beyond period specified until 2 afebrile days were observed
Outcomes	• Clinical cure: definition not specified • Bacteriologic eradication: not specified, but blood, urine and stool cultures taken before therapy, at end of day 3 of therapy, and 2 and 4 weeks post-therapy • Time to defervescence: days until disappearance of fever (afebrile defined as fever < 37.5 °C) • Length of hospital stay: not defined • Mean laboratory values on day 10 of treatment - full blood count, liver and renal function tests before treatment, end of therapy and 2 and 4 weeks post-therapy • Cost analysis of therapy: calculated according to the method specified in Kerr 1992 • Adverse events: not predefined, "side reactions" and adverse events discussed as part of results
Organism type and antimicrobial susceptibility	All MDR-*S typhi* (resistant to chloramphenicol, ampicillin and co-trimoxazole by disk diffusion)
Notes	165 children enrolled and randomized, but only analysed those 124 participants with MDR-*S typhi* who completed 4 weeks of follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated" list for randomization
Allocation concealment (selection bias)	Unclear risk	No mention of methods
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	High risk	Some loss to follow-up - exact numbers not clearly reported
Selective reporting (reporting bias)	High risk	Length of hospital stay prespecified as an outcome measure but no clear data were reported Data for culture results at various time points were not reported
Other bias	Low risk	No obvious conflicts of interest reported

Islam 1988

Study characteristics

Methods	Trial design: randomized

Islam 1988 *(Continued)*

	Time period/duration of trial: June 1984-December 1985 Duration of follow-up: 1 week from date of discharge
Participants	Setting: International Centre for Diarrhoeal Disease Research Location: Dhaka, Bangladesh Age: all individuals 6 months-60 years of age (29 adults, 34 children < 16 years of age). Mean age (+/- SD) was 14.6 (+/- 7.4) in chloramphenicol group and 14.7 (+/- 8.2) in ceftriaxone group Gender: male = 45, female = 18 Health status of participants: not recorded Inclusion criteria: • age • fever for ≥ 4 days • diarrhoea (at least 3 liquid stools in the preceding 24 h) • abdominal pain or tenderness • O agglutinin titre for *S typhi* ≥ 80 Exclusion criteria: • history of effective antimicrobial therapy within 1 week before hospitalization • known allergy to penicillin or cephalosporin • other complications (including GI haemorrhage or perforation, or jaundice)
Interventions	• Ceftriaxone: IV over 30 min, 3 or 4 g for adults and 75 mg/kg/day for children once daily for 7 days • Chloramphenicol: oral or IV, 60 mg/kg/day in 4 doses until defervescence, then 40 mg/kg/day in 4 divided doses to complete 14 days of therapy
Outcomes	• Clinical cure: if survived, became afebrile without a major complication (perforation, bleeding), did not require treatment for typhoid fever and did not relapse before discharge • Bacteriologic eradication: blood cultures negative at end of therapy • Time to defervescence: first afebrile day the participant's rectal temperature dropped to ≤ 37.8 and remained there for > 48 h • Relapse: return of symptoms and *S typhi* in blood cultures within 2 months after the start of therapy • Length of hospital stay: not assessed • Haematologic responses on day 7 and 14 after start of treatment • End of diarrhoea: defined as day the last liquid stool was passed • Drug concentrations on treatment: measured using high-performance liquid chromatography on days 3 and 7 of treatment • Cultures: blood cultures day 3 and 14; faecal culture days 7 and 14 • Adverse events: monitored for urticaria, rashes, nausea, vomiting and phlebitis during therapy; specific complications reported included pneumoniae, peritonitis and intestinal perforation
Organism type and antimicrobial susceptibility	All *S typhi*, no MDR
Notes	Only those with blood or stool cultures positive for *S typhi* were studied. Sponsor: research supported by a grant from Hoffmann-La Roche, manufacturers of ceftriaxone

Risk of bias

Bias	Authors' judgement	Support for judgement

Islam 1988 *(Continued)*

Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Unclear risk	Research supported by a grant from Hoffmann-La Roche, manufacturers of ceftriaxone

Islam 1993

Study characteristics	
Methods	Trial design: randomized Time period/duration of trial: 1986-1987 Duration of follow-up: 1 week from date of discharge
Participants	Setting: International Centre for Diarrhoeal Disease Research Location: Dhaka, Bangladesh Age: all individuals 6 months-60 years of age. Mean age was 18 years (3.5-35 years) in ceftriaxone group, and 18 years (2-35 years) in the chloramphenicol group Gender: male = 32, female = 27 Health status of participants: not recorded Inclusion criteria: • age • fever for ≥ 4 days • diarrhoea (at least 3 liquid stools in the preceding 24 h) • abdominal pain or tenderness • O agglutinin titre for *S typhi* ≥ 80 Exclusion criteria: • history of recent antimicrobial therapy • known allergy to penicillin or cephalosporin

Islam 1993 *(Continued)*

	• other complications (including gastrointestinal haemorrhage or perforation, or jaundice
Interventions	• Ceftriaxone: IV over 30 min, 4 g for adults (> 14 years) and 75 mg/kg/day for children once daily for 5 days • Chloramphenicol: oral or IV, 60 mg/kg/day in 4 doses until defervescence, then 40 mg/kg/day in 4 divided doses to complete 14 days of therapy
Outcomes	• Clinical cure: if survived, became afebrile (temp ≤ 37.8 by day 7 of treatment) without a major complication (perforation, bleeding), did not require treatment for typhoid fever and did not relapse before discharge • Bacteriologic eradication: blood cultures negative at end of therapy • Time to defervescence: first afebrile day the patient's rectal temperature dropped to ≤ 37.8 and remained there for > 48 h • Relapse: return of symptoms after treatment was completed and *S typhi* in blood/stool cultures within 2 weeks of start of therapy • Cultures: blood culture on days 3 and 14 of treatment; faecal culture on days 5, 14 of treatment and 1 week after hospital discharge • Haematologic responses on day 5 and 14 after start of treatment • End of diarrhoea: day the last liquid stool was passed • Drug concentrations on treatment • Adverse events: not prespecified, reported as found. Pneumonia and urinary tract infection reported on specifically.
Organism type and antimicrobial susceptibility	All *S typhi*
Notes	Only those with blood and/or stool cultures positive for *S typhi* were studied.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up described
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Low risk	No obvious conflicts of interest

Kumar 2007

Study characteristics	
Methods	Trial design: prospective, randomized, controlled, parallel trial Time period/duration of trial: May 2002-April 2004 Duration of follow-up: 3 months
Participants	Setting: Department of Paediatrics, Batra Hospital and Medical Research Centre Location: New Delhi, India Age: 0-12 years Gender: male = 40, female = 22 Health status of participants: not recorded Inclusion criteria: • clinical presentation of typhoid fever without localising signs and a positive blood culture for *S typhi* • informed consent Exclusion criteria: • effective antibiotic therapy 1 week prior to admission • known allergy to penicillin/chloramphenicol/quinolones/cephalosporins • immunization with typhoid vaccine
Interventions	All given chloramphenicol (75 mg/kg/day) by oral or IV route until culture results known • Ofloxacin: 20 mg/kg/day; number of doses/route of administration/duration not specified • Ceftriaxone: 100 mg/kg/day; number of doses/route of administration/duration not specified
Outcomes	• Clinical cure: no deterioration and response to treatment within 7-10 days of starting specific therapy • Time to defervescence: time interval from starting an appropriate antimicrobial chemotherapy until the documentation of normal body temperature • Relapse: defined as fever or complications in 3 months of follow-up • Complications: unclear whether these were considered outcomes of treatment or specific complications of underlying infection
Organism type and antimicrobial susceptibility	All MDR *S typhi*
Notes	99 blood-culture-proven *S typhi* cases, 62 of which were MDR *S typhi*. Only MDR *S typhi* cases considered for randomization

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given

Kumar 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	No breakdown of complication/adverse events data for treatment groups
Other bias	Unclear risk	Conflicts of interest not reported

Lasserre 1991

Study characteristics	
Methods	Trial design: RCT Time period/duration of trial: July 1985-May 1987 Duration of follow-up: minimum of 21 days after the end of treatment
Participants	Setting: San Lazaro Hospital Location: Manila, Philipines Age: "Adult" patients Gender: male = 31, female = 28 Health status of participants: not recorded Inclusion criteria: • clinical signs and symptoms compatible with uncomplicated typhoid fever (absence of intestinal bleeding, perforation or pneumonia) • blood culture positive for *S typhi* or *S paratyphiA* or *B* Exclusion criteria: • none specified (specifically mention that prior antibiotic treatment and severe disease were not reasons for exclusion)
Interventions	• Ceftriaxone: IV over 10-15 min, 3 g/day once daily for 3 days • Ceftriaxone: IV over 10-15 min, 4 g/day once daily for 3 days • Chloramphenicol: orally, 3 g/day in 4 divided doses for first 2 days and then 2 g/day for 12 days
Outcomes	• Clinical cure: disappearance of clinical signs of typhoid fever, absence of complications such as bleeding or perforation and negative blood, urine and stool cultures at the end of treatment • Time to defervescence: axillary temperature < 37.5 °C for at least 48 h • Relapse: reappearance of fever and a positive blood culture within 3 weeks after completing antibiotic therapy • Culture: blood and urine cultures days 3, 4, 8 and 15 of treatment. Faecal cultures on 3 consecutive days at end of treatment and days 8, 15 in ceftriaxone group; days 3, 4 and 8 of treatment and 3 consecutive days at end of treatment in chloramphenicol group • Disappearance of toxic signs was defined by 2 of the following: restoration of appetite, regression of fatigue and cessation of headache • "Standard" laboratory blood and urine tests at end of treatment • Reinfection: reappearance of typhoid after 3 weeks • Adverse events: not prespecified, discussed as part of results section

Lasserre 1991 *(Continued)*

Organism type and antimicrobial susceptibility	*S typhi* = 55 (MDR *S typhi* = 0), *S paratyphi* = 6. All strains susceptible to ceftriaxone and chloramphenicol
Notes	Antibiotic treatment started at the time the blood culture was positive - trial authors note this was usually around the third or 4th day of hospitalization Excluded 2 participants in group 1 - 1 had only 2 days of follow-up after treatment, and 1 because of a skin rash and switch in therapy to chloramphenicol Sponsor: ceftriaxone provided by Hoffman-La Roche pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computerised randomisation list"
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up of 1 case. This lost case was excluded from the analysis.
Selective reporting (reporting bias)	Unclear risk	"Standard laboratory blood and urine tests were performed just before antibiotic treatment and the day following its termination". No further details on this testing were reported.
Other bias	Unclear risk	Ceftriaxone provided by Hoffman-La Roche pharmaceuticals

Memon 1997

Study characteristics

Methods	Trial design: prospective, RCT Time period/duration of trial: November 1993-October 1994 Duration of follow-up: 2 weeks after the completion of antibiotic therapy
Participants	Setting: Department of Paediatrics, Civil Hospital and Lyari General Hospital Location: Karachi, Pakistan Age: all patients < 15 years of age Gender: male = 59, female = 26 Health status of participants: not recorded Inclusion criteria: • probable clinical diagnosis of enteric fever (fever > 5 days, nausea, vomiting, hepatomegaly, splenomegaly, hepatic tenderness)

Memon 1997 *(Continued)*

	• ability to take oral medications Exclusion criteria: • antibiotic use in the preceding 72 h • allergy to trial antibiotics • previous documentation of resistance to trial antibiotics • concomitant infection (e.g. TB, UTI, malaria, other liver disease)
Interventions	• Cefixime: route of administration unspecified, 10 mg/kg/day to 12 mg/kg/day in 2 divided doses for 2 weeks • Chloramphenicol: route of administration unspecified, 100 mg/kg/day in 4 divided doses for 2 weeks
Outcomes	• Clinical cure: failure of antibiotic therapy defined as persistence of fever and/or clinically toxic appearance even after 7 days of antibiotic therapy; participants then switched to other treatment group • Time to defervescence: defervescence defined as body temperature < 38 °C for 24 h without use of anti-pyretics • Relapse: not defined, reported as part of the results • Laboratory parameters: tests taken not prespecified, reported on only in discussion: "None of the patients had elevated liver enzymes at the end of therapy" • Cost of therapy: calculated as cost of antibiotic given to each participant according to the manufacturer's suggested retail price • Adverse events: not prespecified, reported as part of results
Organism type and antimicrobial susceptibility	Exact breakdown unclear, but 66/85 isolates were MDR *Salmonella* species. Only 11 strains susceptible to chloramphenicol, amoxicillin and cotrimoxazole. Unclear what proportion of participants with chloramphenicol-resistant isolates were being treated in the chloramphenicol arm
Notes	242 evaluated as probable cases; 140 had no microbiologic confirmation or had other exclusion criteria. 17 participants with culture-proved enteric fever did not complete trial in accordance with protocol or were lost to follow-up. 85 completed trial and evaluated. Those that failed in each group were then treated with the other antibiotic being evaluated, or ceftriaxone as third-line treatment (n = 2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	High risk	17/85 (20%) participants did not complete trial as per protocol or were lost to follow-up

Memon 1997 *(Continued)*

Selective reporting (reporting bias)	High risk	At least half of outcomes not prespecified or reported on
Other bias	Low risk	No conflicts of interest reported

Moosa 1989

Study characteristics	
Methods	Trial design: prospective, randomized, open Time period/duration of trial: unclear, before June 1989 Duration of follow-up: unclear, at least 6 weeks after initial eradication
Participants	Setting: admitted to children's ward at King Edward VII Hospital Location: Durban, South Africa Age: not defined - "children" Gender: male = 6, female = 23 Health status of participants: not recorded Inclusion criteria: • bacteriologically confirmed typhoid fever Exclusion criteria: • no organisms grown from pretherapy cultures • on concomitant antibiotics • severe disease (e.g. shock) or complications or severe renal impairment • known hypersensitivity to penicillins or cephalosporins
Interventions	• Ceftriaxone: IM with 1% lidocaine, approximately 80 mg/kg/day for 5 days • Chloramphenicol: oral, 50 mg/kg/day in 4 divided doses for 3 weeks
Outcomes	• Clinical cure: fever subsided at 5 days and no clinical/bacteriological evidence of infection for 6 weeks • Bacteriologic eradication: not defined • Time to defervescence: time in days until absence of fever (defined as temperature > 37.5 °C) • Relapse: cultures (blood, urine or faeces) positive within 6 weeks after initial eradication with or without return of clinical symptoms • Clinical improvement: condition improved, blood culture negative by day 3 but fever persisted for > 5 days) • Treatment failure: signs and symptoms of infection remained unchanged or worsened or if cultures not negative by day 7 • Laboratory parameters: full blood count, liver enzymes, urea and electrolytes checked on admission and at least once a week • Cultures: blood culture on admission, days 3 and 7 as a minimum; urine and faecal culture on admission and after completion of therapy • Adverse events: not prespecified, discussed as part of results

Moosa 1989 *(Continued)*

Organism type and antimicrobial susceptibility	*S typhi* = 59 (MDR *S typhi* = not specified), *S paratyphi* = none
Notes	1 participant in trial did not have a positive blood culture (urine and faeces were positive on day 15) Blood cultures also positive with other organisms in 4 participants, including *Salmonella enteritidis* and *Shigella* species. Sponsor: Roche products supplied ceftriaxone and provided "assistance" with the trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Data on laboratory tests (blood count, urea etc.) were not reported
Other bias	High risk	Pharmaceutical company Roche supplied ceftriaxone and provided "assistance" with the trial

Morelli 1988

Study characteristics

Methods	Trial design: randomized, open Time period/duration of trial: January 1985-November 1985 Duration of follow-up: 8 weeks after treatment
Participants	Setting: hospital, Ospedale per Malatie Inffetive Location: Naples, Italy Age: all (mean age 25.9, range: 12-45) Gender: male = 36, female = 20 Health status of participants: not recorded Inclusion criteria: • blood culture positive for *S typhi*,

Morelli 1988 *(Continued)*

	• "toxic symptomatology" • fever > 39 °C Exclusion criteria: • clinical or laboratory findings suggestive of other infections • known or suspected hypersensitivity to cephalosporins • any other antibiotic treatment
Interventions	• Cefoperazone: IV, 2 g in 100 mL of saline every 8 h for adults and 100 mg/kg/day for children; duration unspecified • Chloramphenicol: oral, 500 mg every 6 h for adults, 50 mg/kg/day for children; duration unspecified
Outcomes	No prespecified outcomes Blood cultures and faecal cultures taken at start and end of treatment
Organism type and antimicrobial susceptibility	*S typhi* = 56. Details only on MICs for cefoperazone and chloramphenicol (2 isolates in chloramphenicol treatment group were resistant to cefoperazone)
Notes	Cure, relapse, culture positivity and defervescence time reported on in results, but not defined.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerized list
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up reported
Selective reporting (reporting bias)	Unclear risk	No prespecified outcomes given
Other bias	Unclear risk	Conflicts of interest not reported

Nair 2017

Study characteristics	
Methods	Trial design: randomized, open Time period/duration of trial: not stated Duration of follow-up: 30 days after enrolment

Participants	Setting: presenting to Department of Paediatrics, Army College of Medical Sciences, New Delhi, India and admitted to paediatric ward
	Location: New Delhi, India
	Age: 3 to 18 years
	Gender: male = 28, female = 36
	Health status of participants: not recorded
	Inclusion criteria:
	• patients with documented fever (a rectal temperature > 38.0 °C or an oral temperature > 37.5 °C) of > 4 days and
	• having > any 2 of the following symptoms or signs:
	  ◦ splenomegaly
	  ◦ hepatomegaly
	  ◦ abdominal tenderness
	  ◦ a coated tongue.
	• Ability for parent/guardian to give written informed consent.
	• Only patients with blood and/or stool cultures positive for *S typhi* were evaluated
	Exclusion criteria:
	• patients who had inability to swallow oral medications
	• having major typhoid complications like pneumonia, shock, coma, intestinal haemorrhage, perforation
	• significant underlying illness
	• patients who had received antibiotics that were effective against *S typhi* in the past 4 days
	• allergic to either ceftriaxone or azithromycin

Interventions	• Ceftriaxone: IV, 75 mg/kg/day once daily (maximum dose 2.5 g) for 7 days • Azithromycin: oral, 20 mg/kg/day once daily (maximum dose 1000 mg/day) for 7 days
Outcomes	Primary outcome • Clinical success - response defined as becoming afebrile within 7 days of starting treatment Secondary outcomes • Fever clearance time • Microbiological cure (negative blood culture) by day 7 and day 30 • Relapse: fever with recurrent typhoid-related symptoms within 1 month of completing treatment in a patient who had been successfully treated with or without a positive blood culture. Excluded individuals given prolonged or rescue treatment • Cultures: faecal samples taken at 7 and 30 days • Adverse events: not prespecified, listed in the results
Organism type and antimicrobial susceptibility	64 participants with *S typhi* isolated from blood cultures. In 6 also cultured from faeces. No information concerning antimicrobial susceptibility pattern
Notes	124 clinical cases of suspected enteric fever, with 64 enrolled and randomized. 58 were ineligible, with an alternative diagnosis within 48 h of admission. 2 participants had taken a fluoroquinolone before admission to hospital. 34 participants assigned to receive ceftriaxone, and 30 assigned to azithromycin

Nair 2017 *(Continued)*

	Participants with positive pre-treatment culture analyses were analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment assignments were determined by block randomization based on a random number list."
Allocation concealment (selection bias)	Low risk	"These were sealed in envelopes by a medical professional uninvolved in the treatment trial. At the time of enrolment, the investigator unsealed the envelope to determine which treatment the subject would receive."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants did not return for post-treatment follow-up evaluation
Selective reporting (reporting bias)	Unclear risk	Stipulated outcome measures not clearly articulated
Other bias	Low risk	No conflicts of interest reported

Pandit 2007

Study characteristics

Methods	Trial design: randomized, open Time period/duration of trial: 5 June 2005-8 September 2005 Duration of follow-up: 6 months after enrolment
Participants	Setting: presenting to the outpatient or emergency department of Patan Hospital Location: Lalitpur, Nepal Age: 2-65 years; median age 17 (range: 2-64 years) Gender: male = 247, female = 135 Health status of participants: not recorded Inclusion criteria: • clinically diagnosed enteric fever • residence within 2.5 km of the hospital • ability to take oral medications • no pregnancy/lactation • no history of seizures • ability to stay in the city for the duration of the treatment • no contraindications to quinolones or cephalosporins • ability to give written informed consent Exclusion criteria:

Pandit 2007 *(Continued)*

	• signs of complicated typhoid defined as the presence of jaundice, gastrointestinal bleeding, peritonism, shock, encephalopathy, convulsions, myocarditis or arrhythmia at the time of enrolment • receipt of a third-generation cephalosporin, fluoroquinolone or macrolide in the week prior to presentation at the clinic
Interventions	• Cefixime: oral, 20 mg/kg/day in 2 divided doses for 7 days • Gatifloxacin: oral, 10 mg/kg/day as a single dose for 7 days
Outcomes	Primary outcome • Fever clearance time - time to first drop in oral temperature ≤ 37.5 °C and remaining as such for 48 h Secondary outcomes • Acute treatment failure: severe complications, persistence of fever > 38 °C, persistence of symptoms for > 7 days after start of therapy, requirement for additional or rescue treatment • Overall treatment failure: acute treatment failure + relapse + death • Relapse: fever with a positive blood culture within 1 month of completing treatment in a patient who had been successfully treated. Excluded individuals given prolonged or rescue treatment • Cultures: faecal samples taken at end of 1st, 3rd and 6th month • Adverse events: not prespecified, listed in the results
Organism type and antimicrobial susceptibility	No breakdown of results by organism/susceptibility
Notes	482 clinical cases of enteric fever, with 390 enrolled and randomized. 92 were ineligible, with the commonest reason being receipt of antibiotics in the week before trial entry (n = 49). 187 participants assigned to receive cefixime, and 77 of these were culture-positive; 203 were assigned to gatifloxacin and 92 of these were culture-positive Both ITT (all 390 randomized participants) and positive pre-treatment culture analyses (defined as the per protocol participants, with positive pre-treatment culture results). We requested and received data from the trial authors to calculate the mean time to defervescence.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly assigned patients (1:1) without stratification to either treatment. The randomisation was computer-generated computer with blocks of 4 or six (with equal probabality) by a clinical trials pharmacist."
Allocation concealment (selection bias)	Low risk	"We concealed treatment allocations inside opaque sealed envelopes, which were numbered sequentially to correspond to patient enrollment numbers. Envelopes were kept in a locked drawer and were opened in strict numerical order by a trial clinician (who had previously screened the patients and obtained consent)."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias)	High risk	Open trial

Pandit 2007 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11/382 (2.9%) participants dropped out of trial
Selective reporting (reporting bias)	Low risk	Data reported for all stipulated outcome measures
Other bias	Low risk	No conflicts of interest reported; trial sponsor and funder had no involvement in trial design, process, analyses, or write-up

Pape 1986

Study characteristics	
Methods	Trial design: randomized, unblinded Time period/duration of trial: before May 1985 Duration of follow-up: at least 6 weeks after therapy started

Participants	Setting: Pediatric Service of University Hospital of Haiti
	Location: Port-Au-Prince, Haiti
	Age: children, mean age 8.6 years (2-15 years)
	Gender: male = 10, female = 15
	Health status of participants: not recorded
	Inclusion criteria:
	• all patients with a clinical diagnosis of probable typhoid fever
	   ○ "toxic condition"
	   ○ fever > 39 °C
	• no signs or symptoms suggesting other infections
	Exclusion criteria:
	• appearance of terminal illness
	• known or suspected allergy/intolerance to cephalosporins
	• requirement of concomitant antibiotics for other infections
	• isolation of bacteria other than *S typhi* from blood cultures
	• cultures negative for *S typhi*

Interventions	• Cefoperazone: IV or IM, 100 mg/kg/day in 2 divided doses, then reduced to 50 mg/kg/day when the temperature was < 38 °C and the patient was able to tolerate oral feeding, 14 days • Chloramphenicol: IV or oral, 100 mg/kg/day in 4 divided doses, then reduced to 50 mg/kg/day when the temperature was < 38 °C and the patient was able to tolerate oral feeding, 14 days
Outcomes	• Efficacy of antimicrobial regimens judged by clinical response to treatment - not strictly defined, but based on fever defervescence and time to sterile blood cultures after initiation of therapy • Microbiological failure: not strictly defined; implicitly described as blood culture negative at 2 weeks • Relapse: not defined, but measured. Just used "clinical or bacterologic relapse" • Time to defervescence: defined in results section as maximum daily rectal temperature < 38 °C for a 24-h period • Culture: blood culture at days 2 and 14 after start of therapy; faecal culture on days 2, 14 and at 6 weeks after initiation of therapy • Time to blood culture-negative in days • Adverse events: not prespecified, described in results

Pape 1986 *(Continued)*

Organism type and antimicrobial susceptibility	*S typhi* = 25 (MDR *S typhi* = 0), *S paratyphi* = 0
Notes	5 patients excluded on criteria: 1 died 3 h after hospitalization, 2 had bacteraemia caused by other Enterobacteriaceae and 2 patients had negative sets of cultures. 3 participants given dexamethasone. These participants and participants who died were excluded from the outcomes analysis. Sponsor: trial supported by Pfizer international

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants died
Selective reporting (reporting bias)	High risk	It was unclear whether time to a negative blood culture result could be adequately assessed given the specified sampling method in the protocol
Other bias	Unclear risk	Trial supported by grant from Pfizer international

Rabbani 1998

Study characteristics

Methods	Trial design: randomized Time period/duration of trial: August 1994-February 1995 Duration of follow-up: 4 weeks after completion of treatment
Participants	Setting: Department of Paediatric Medicine, Nishtar Hospital Location: Multan, Pakistan Age: children < 15 years of age; mean age 6.2 years (range: 2-12 years) Gender: male = 31, female = 9 Health status of participants: not recorded Inclusion criteria: • typhoid fever confirmed by isolation of *S typhi* from blood or bone marrow culture Exclusion criteria: • concurrent infections

Rabbani 1998 *(Continued)*

	• unconsciousness • culture-negative participants
Interventions	• Cefixime: oral, 10 mg/kg/day in 2 divided doses, for 14 days • Chloramphenicol: oral, 50 mg/kg/day in 4 divided doses, for 14 days
Outcomes	• Non-response to therapy: defined as persistent pyrexia (not defined) after 7 days of appropriate therapy • Time to defervescence - not strictly defined, measured in days after start of treatment • Adverse events: "side-effects" monitored
Organism type and antimicrobial susceptibility	*S typhi* = (MDR *S typhi* = not measured), *S paratyphi* = 0. All isolates susceptible to cefixime, 37 isolates susceptible to chloramphenicol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	Reporting of outcomes that were not prespecified, including "cure rate"
Other bias	Unclear risk	Unclear whether participants with chloramphenicol-resistant isolates were being 'treated' in the chloramphenicol arm

Rizvi 2007

Study characteristics

Methods	Trial design: randomized Time period/duration of trial: January 2003 to January 2004 Duration of follow-up: 28 days
Participants	Setting: outpatient department of the Social Security Hospital Location: Karachi, Pakistan Age: > 12 years of age; mean age 31.7 years (SD +/-8.2 years)

Rizvi 2007 *(Continued)*

	Gender: male = 112, female = 115 Health status of participants: 16 had diabetes mellitus, 15 hypertension, 9 bronchial asthma, 1 sickle cell anaemia Inclusion criteria: • clinical and bacteriological diagnosis of enteric fever, either on positive blood or stool culture, or by positive Typhi-Dot test Exclusion criteria: • infection with other organisms • pregnancy • known hypersensitivity to trial medications
Interventions	• Cefixime: oral, 200 mg twice daily for 7 days • Ciprofloxacin: oral, 500 mg twice daily for 7 days • Ofloxacin: oral, 200 mg twice daily for 7 days • Chloramphenicol: oral, 750 mg 4 times/day for 14 days • Co-trimoxazole: oral, 960 mg twice daily for 14 days
Outcomes	• Clinical cure: reduction of maximum daily temperature equal to or < 37 °C and /or disappearance of clinical signs and symptoms at the end of treatment with no clinical evidence of infection during further follow-up • Clinical improvement: all clinical signs and symptoms subsiding significantly within 7 and 14 days, respectively, but with incomplete resolution of clinical evidence of infection • Clinical relapse: reappearance of signs and symptoms after initial disappearance for at least 48 h • Clinical failure: no significant clinical response to therapy • Not assessable: a clinical judgement of cure, improvement or failure could not be made for various reasons such as no follow-up evaluation tests performed, an underlying condition, or premature termination of the treatment • Bacteriological cure: blood/faecal cultures negative for *S typhi*/*S paratyphi* by day 7 of treatment and remained negative for up to 3 weeks after treatment • Bacteriologial failure: persistence of *S typhi*/*S paratyphi* on day 7 or 14 or recurrence of the initial pathogen at the end of treatment • Bacteriological relapse: elimination of pathogen within 7 or 14 days, but reappearance in blood/stool within 3 weeks after the end of treatment • Culture: blood and faeces at days 0, 3, 5, 7, 14 and 28 • Time to defervescence: not prespecified, but measured in days • Adverse events: not prespecified, but recorded in results
Organism type and antimicrobial susceptibility	*S typhi* = 208 (MDR *S typhi* =), *S paratyphi* = 18
Notes	All participants missing > 1 day of therapy were excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given

Rizvi 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	High risk	Numbers lost to follow-up were not specified
Selective reporting (reporting bias)	High risk	Data not reported for all stipulated outcome measures
Other bias	Unclear risk	Breakdown of data unclear in tables

Shakur 2007

Study characteristics	
Methods	Trial design: randomized, double blind Time period/duration of trial: March 2003-June 2004 Duration of follow-up:
Participants	Setting: Dhaka Shishu (Children) Hospital, Sher-e-Bangla Nagar Location: Dhaka, Bangladesh Age: 6 months-12 years Gender: male = 22, female = 18 Health status of participants: not recorded Inclusion criteria: • clinical features consistent with typhoid fever Exclusion criteria: • participants taking antibiotics for the preceding 72 h • suspected complicated typhoid fever-like abdominal distension, ileus, toxic encephalopathy
Interventions	• Cefpodoxime: oral, 16 mg/kg/day divided every 12 h for 10 days • Cefixime: oral, 20 mg/kg/day divided every 12 h for 10 days
Outcomes	• Clinical cure: complete resolution of all presenting symptoms and signs after 10 days of therapy • Bacteriological cure: elimination of all originally isolated pathogens • Time to defervescence: defervescence defined as a temperature below 37.5 °C for at least 48 h without anti-pyretics • Cost of antibiotic administered according to manufacturers' suggested retail price • Adverse events: not prespecified, recorded as part of results
Organism type and antimicrobial susceptibility	No specific details given, assumed all *S typhi*
Notes	140 initially assessed, 44 randomized, 40 completed trial Sponsor: trial funding provided by Aristopharma

Shakur 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomization technique was done using a computer program
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Medicines were supplied in bottles that were similar in size, shape and colour and without commercial labels
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Attending physicians unaware of treatment being given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4/40 (10%) participants lost to follow-up
Selective reporting (reporting bias)	Low risk	Data for all stipulated outcome measures reported
Other bias	Unclear risk	Trial funding provided by Aristopharma

Smith 1994

Study characteristics

Methods	Trial design: randomized, open Time period/duration of trial: December 1992-June 1993 Duration of follow-up: 4-6 weeks following end of treatment
Participants	Setting: Centre for Tropical Diseases, Cho Quan Hospital; Infectious diseases referral centre for southern Vietnam Location: Ho Chi Minh City, Vietnam Age: adults, ≥15 years Gender: male = 29, female = 18 Health status of participants: not recorded Inclusion criteria: • clinically suspected or culture-confirmed enteric fever Exclusion criteria: • known hypersensitivity to beta-lactam antibiotics or quinolone compounds • previous treatment with a broad-spectrum cephalosporin or quinolone compound within 1 week of hospital admission • ampicillin, chloramphenicol, or trimethoprim-sulfamethoxazole treatment with clinical response within 1 week of hospital admission
Interventions	• Ceftriaxone: IV, 3 g (approximately 60 mg/kg) once daily for 3 days • Ofloxacin: oral, 200 mg every 12 h for 5 days

Smith 1994 *(Continued)*

Outcomes	• Acute treatment failure was defined as continuing symptoms and fever for at least 7 days after starting the treatment regimen. A patient defined as cured if all symptoms improved, fever cleared, and there was no evidence of relapse. • Microbiological failure: not defined; assumed culture-negative at day 8 • Relapse: not defined in methods, assumed culture-negative at day 8 and then positive on follow-up; plasmid analysis and ribotyping of strains to confirm relapse • Time to defervescence: defervescence was defined as a temperature of < 37.5 °C for at least 48 h • Length of hospital stay: mean and range • Culture: blood on days 4, 6, 8 for first 25 participants and 2, 3, 8 for next 35 participants; faeces and urine on day 8 • Laboratory parameters: full blood count and biochemistry tests at day 8 • Adverse events: not prespecified, but discussed in the results
Organism type and antimicrobial susceptibility	*S typhi* = 41 (MDR *S typhi* = 26), *S paratyphi* = 6
Notes	60 participants entered into the trial, 47 participants were culture-positive. Relapse versus re-infection reassessed by plasmid analysis (gel electrophoresis of whole plasmids and restriction endonuclease fragments) and ribotyping. Sponsor: ceftriaxone and ciprofloxacin provided by Roche pharmaceuticals and Russel-UCLAF respectively.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Low risk	Individual sealed envelopes opened at time of randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss of follow-up in 50% of participants
Selective reporting (reporting bias)	High risk	Data on laboratory parameters day 8 not reported
Other bias	Unclear risk	Ceftriaxone and ciprofloxacin provided by Roche pharmaceuticals and Russel-UCLAF respectively

Tatli 2003

Study characteristics

Tatli 2003 *(Continued)*

Methods	Trial design: randomized Time period/duration of trial: September 1998-July 2001 Duration of follow-up: 28 days
Participants	Setting: Harran University Research Hospital, and the Children's Hospital Location: Sanliurfa, Turkey Age: < 16 years of age Gender: male = 41, female = 31 Health status of participants: not recorded Inclusion criteria: • suspected typhoid fever, defined as no other obvious source of infection and high-grade fever (≥ 39 °C) persisting for > 5 days Exclusion criteria: • negative blood cultures • history of antimicrobial therapy in previous 10 days
Interventions	• Ceftriaxone: IV, 75 mg/kg per day (maximally 2 g/day) in 2 divided doses until the axillary temperature remained below 37.5°C for at least 24 h, then additional 5 days of therapy at the same dose • Chloramphenicol: 75 mg/kg per days (maximally 2 g/day) in 4 divided doses for 14 days
Outcomes	• Clinical cure: absence of fever on 7th day of therapy; clinical signs and symptoms resolved and the patient remained well during follow-up • Microbiological failure: blood culture positive for *S typhi* after completion of therapy • Relapse: high fever (≥ 38.5 °C) and blood culture positive for *S typhi* during the 28 days after discharge • Defervescence time: time from the onset of treatment until the fever was 37.5 °C or below for at least 24 h • Convalescent faecal carriage: not defined, but assessed • Adverse events: not prespecified, but clinical and biochemical side effects of treatment assessed in results
Organism type and antimicrobial susceptibility	*S typhi* = 72 (MDR *S typhi* = 0), *S paratyphi* = 0
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial

Tatli 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	6 participants in ceftriaxone group and 8 in the chloramphenicol group not assessed because of "communication failure"
Selective reporting (reporting bias)	Low risk	Data reported on all stipulated outcomes
Other bias	Unclear risk	Potential conflicts of interest not commented on

Tran 1994

Study characteristics

Methods	Trial design: randomized Time period/duration of trial: 1992-1993 Duration of follow-up: 28 days after treatment
Participants	Setting: Cho Quan Hospital Location: Ho Chi Minh City, Vietnam Age: all patients (mean age: 24 years (SD 7 years) in fleroxacin group; 29 (SD 15) in ceftriaxone group) Gender: male = 22, female = 9 Health status of participants: not recorded Inclusion criteria: • axillary temperature > 37.5 °C for > 7 days • 'toxic' appearance • negative malaria blood film Exclusion criteria: • not specified
Interventions	• Ceftriaxone: IV, 2 g once daily for 5 days • Fleroxacin: oral, 400 mg in a single dose daily for 7 days
Outcomes	• Clinical cure: reduction of maximum daily axillary temperature to < 37.5 °C and complete disappearance of all other signs and symptoms within 14 days with no clinical evidence of infection during further follow-up • Microbiological failure: microbiological cure defined as initial pathogen eliminated from blood, bone marrow and stool within 14 days, all cultures remaining negative for at least 21 days • Time to defervescence: defervescence defined as axillary temperature < 37.5 °C • Laboratory parameters: blood, renal and hepatological tests before and after treatment • Culture: blood days 0, 3 and end of treatment; faeces day 0 and end of treatment • Adverse events: not prespecified, but assessed as part of the results
Organism type and antimicrobial susceptibility	*S typhi* = 27 (MDR *S typhi* = 12), *S paratyphi A* = 4
Notes	46 patients with a clinical diagnosis randomized; 31 patients had the diagnosis confirmed on culture Sponsor: funded by the Roche Asian Research Foundation

Risk of bias

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

Tran 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up of 15/31 (48.4%) participants
Selective reporting (reporting bias)	Unclear risk	Data reported on all stipulated outcomes
Other bias	Unclear risk	Funded by the Roche Asian Research Foundation

Wallace 1993

Study characteristics	
Methods	Trial design: randomized Time period/duration of trial: unclear, before 1993 Duration of follow-up: 2 months
Participants	Setting: unclear Location: unclear Age: 42 adult participants > 16 years (mean age: 28.2 years in ceftriaxone group, 26.8 years in ciprofloxacin group) Gender: no details given Health status of participants: not recorded Inclusion criteria: • blood culture positive • acute *S typhi* infection Exclusion criteria: • inability to take oral medication • possible or proven pregnancy • lack of fever at time of admission
Interventions	• Ceftriaxone: IV, 3 g once daily for 7 days • Ciprofloxacin: oral, 500 mg twice daily for 7 days
Outcomes	• Clinical cure: clinical failure defined as fever > 38 °C after 7 days of therapy or who deteriorated clinically after 5 full days of therapy; cure if patient afebrile and asymptomatic on or before day 7 and did not require additional therapy during 2 months of follow-up

Wallace 1993 *(Continued)*

	• Relapse: readmission for typhoid within 2 months of discharge with a positive blood or stool culture for *S typhi* with the same antibiogram as previous • Convalescent faecal carriage: not defined, but stool culture positivity assessed at 28 days post-enrolment
Organism type and antimicrobial susceptibility	*S typhi* = 42 (MDR *S typhi* = 22), *S paratyphi* = 0
Notes	The trial was terminated when the clinicians involved in the trial felt that it was no longer ethical to randomize patients to receive ceftriaxone, given the higher cost, need for IV access and perceived lower efficacy of this regimen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Data reported on all stipulated outcome measures
Other bias	Low risk	No potential conflicts of interest reported

GCS: Glasgow Coma Scale; **GI:** gastrointestinal; **IM:** intramuscular(ly) **IQR:** interquartile range; **IL-6:** interleukin 6; **ITT:** intention-to-treat; **IV:** intravenous(ly); **MDR:** multiple-drug resistance; **MIC:** minimal inhibitory concentration; **RCT:** randomized controlled trial; **SD:** standard deviation; ***S typhi*:***Salmonella typhi*; ***S paratyphi:*** *Salmonella paratyphi*; **TB:** tuberculosis; **TNF-R:** tumour necrosis factor receptor; **UTI:** urinary tract infection

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

Study	Reason for exclusion
Arjyal 2011	No cephalosporin as an intervention
Begue 1998	Not a RCT
Begum 2014	Not a RCT
De Carvalho 1982	Not a RCT

Study	Reason for exclusion
Ebright 1983	Not a RCT
Farid 1987	Not a RCT
Gnassingbe 2010	Not a RCT
Jiangli 1995	Not a RCT
Khichi 2001	No cephalosporin as an intervention
Lan 1986	Not a RCT
Medina 2000	Not a RCT
Meloni 1988	Not a RCT
Morelli 1992	No cephalosporin as an intervention
Nagaraj 2016	Not a RCT
Naveed 2016	Participants diagnosed on clinical criteria with no blood cultures performed
Nelson 1967	Not a RCT
Park 1985	Not a RCT
Raoult 1984	Not a RCT
Rolston 1992	Not a RCT
Singh 1993	No cephalosporin as an intervention
Sirinavin 2003	Not a RCT
Soe 1987	Not a RCT
Thaver 2009	Not a RCT
Ti 1985	Not a RCT
Trivedi 2012	Not a RCT
Uwaydah 1976	Not a RCT
Uwaydah 1984	Not a RCT
Vinh 2005	No cephalosporin as an intervention
Yi 1995	Not a RCT
Zmora 2018	Not a RCT

RCT: randomized controlled trial

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

Amin 2021

Methods	Trial design: randomized Time period/duration of trial: January 2017- December 2017 Duration of follow-up: 6 months from discharge
Participants	62 participants Setting: "Medicine ward of Dhaka Medical College Hospital (DMCH) and an outdoor setting in private practice in Dhaka metropolitan city, Mymensingh and Sylhet town." Bangladesh Age: > 15 years and < 65 years Gender: Health status of participants: Inclusion criteria: • clinically suspected and • culture-confirmed uncomplicated typhoid fever Exclusion criteria: • pregnancy • age < 15 years and > 65 years • history of hypersensitivity to either of the trial drugs • any signs of severe typhoid fever (shock, deep jaundice, encephalopathy, convulsions, bleeding, suspicion or evidence of gut perforation, neurological features, etc) • previously reported treatment with fluoroquinolone antibiotics or, a third-generation cephalosporin or macrolide antibiotics within 1 week prior to hospital admission • patient on active management for Ischaemic heart disease, chronic bronchial asthma and COPD • significant underlying illness (affecting the bone marrow, kidneys, liver, heart, lungs, or nervous system) • known allergy to the experimental drug
Interventions	Intervention: • cefixime 16 mg/kg/day for 14 days Comparators: • Azithromycin 20 mg/kg. Dose frequency and duration of treatment reported differently throughout the trial • Ciprofloxacin 20 mg/kg/day for 14 days
Outcomes	• Clinical cure • Time to defervescence • Complications • Microbiological failure • Relapse
Notes	Dose of azithryomycin reported differently throughout the trial

Hamidullah 2019

Methods	Trial design: participants assigned to a treatment group by lottery method Setting: Department of Paediatrics, Hayatabad Medical Complex, Peshawar, Pakistan Time period/duration of trial: November 2015-May 2016 Duration of follow-up: not specified
Participants	140 participants Gender: 81 male; 59 female Age: 2 years-12 years old Inclusion criteria: • not clearly reported Exclusion criteria: • not clearly reported
Interventions	• Intervention: ceftriaxone IV 75 mg/kg/day (maximum dose, 2.5 g/day) twice daily for 10 days • Comparator: azithromycin 10 mg/kg/day (maximum dose, 500 mg/day) once daily for 7 days
Outcomes	• Time to defervescence • Clinical failure • Complications
Notes	

Huai 2000

Methods	Unable to access trial
Participants	Unable to access trial
Interventions	Unable to access trial
Outcomes	Unable to access trial
Notes	

Thapaet 2019

Methods	Trial design: unclear if randomized. "Patients were enrolled into two treatment groups." Setting: Nepal, Patan Hospital Time period/duration of trial: not specified Duration of follow-up: not specified
Participants	250 participants Age: 4 to 65 years old

Thapaet 2019 *(Continued)*

	Inclusion criteria: • fever 38 °C for at least 4 days • able to take oral medication • able to consent • able to attend follow-up visits and contactable via telephone Exclusion criteria: • fever for > 10 days • diabetes mellitus • pregnancy • severe infection • jaundice • active gastrointestinal bleeding • shock • hypersensitivity to drugs • patient requiring IV treatment
Interventions	Intervention: • ceftriaxone. Dose and route of administration not clearly reported Comparator: • azithromycin. Dose not clearly reported
Outcomes	• Fever clearance time • Clinical failure • Microbiological failure
Notes	

Welch 1986

Methods	Trial design: randomized Time period/duration of trial: not specified Duration of follow-up: 30 days after discharge
Participants	Setting; Paula Jaraquemada Hospital Location: Santiago, Chile Age: hospitalized children - age not specified Gender: no details Health status of participants: not recorded Inclusion criteria: bacteriologically confirmed enteric fever (blood or bone marrow culture) Exclusion criteria: none specified
Interventions	 • Ceftriaxone: 80 mg/kg once daily, IV, 6 days

Welch 1986 *(Continued)*

	• Chloramphenicol: approximately 50 mg/kg/day in 3-4 doses, oral, 14 days
Outcomes	• Clinical cure: not defined but reported • Microbiological failure: not defined but reported • Relapse: not defined but reported • Convalescent faecal carriage: stool cultures taken 30 days after discharge • Adverse events: not prespecified, assessed as part of results
Notes	Conference abstract/presentation only (Welch E. Ceftriaxone versus chloramphenicol in children suffering from typhoid or paratyphoid fever. Paper presented at Ixth International Congress of Infectious and Parasitic Diseases, Munich, July 1986)

COPD: chronic obstructive pulmonary disease

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

NCT04349826

Study name	Azithromycin and cefixime combination versus azithromycin alone for the out-patient treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia; a randomized controlled trial
Methods	Allocation: randomized Intervention model: parallel assignment Masking: quadruple (participant, care provider, investigator, outcomes assessor) Masking description: double blind Primary purpose: treatment Estimated enrolment: 1500 Estimated trial completion date: August 2023
Participants	Ages: 2 years to 65 years Gender: all Inclusion criteria: • history of fever at presentation for ≥ 72 h and a documented fever (≥ 37.5 °C (axillary) or ≥ 38 °C (oral)) • age ≥ 2 years (and ≥ 10 kg) to 65 years • no clear focus of infection on initial clinical evaluation • malaria rapid diagnostic test (RDT) negative; dengue nonstructural protein (NS) 1 RDT negative; scrub typhus RDT negative; C-reactive protein (CRP) rapid test ≥10 mg/L • able to take oral treatment • able to attend for follow-up and can be contacted by telephone • 2ritten fully informed consent to participate in the trial including assent for children in addition to parental/legal guardian consent. Exclusion criteria:

NCT04349826 *(Continued)*

	• history of fever for > 14 days • pregnant or positive pregnancy test or breastfeeding • presence of clinical symptoms or signs indicating a focal infection such as pneumonia; urinary infection, meningitis, eschar • obtundation, haemodynamic shock, visible jaundice, gastrointestinal bleeding or any signs of severe disease that may require immediate hospitalization • being treated for TB or HIV or severe acute malnutrition • patients with cardiac disease • patient requiring IV antibiotics for any reason • previous history of hypersensitivity to any of the treatment options • either of the trial drugs are contraindicated for any reason (e.g. drug interactions) • has received azithromycin or cefixime in the last 5 days • receiving another antimicrobial and responding clinically to the treatment as judged by the attending clinician.
Interventions	Active comparator: azithromycin + cefixime • Azithromycin 20 mg/kg/day oral dose once daily (maximum 1 g/day) and cefixime 20 to 30 mg/kg/day oral dose in 2 divided doses (maximum 400 mg twice a day) for 7 days Placebo comparator: azithromycin + placebo • Azithromycin 20 mg/kg/day oral dose once daily (max 1 g/day) for 7 days and cefixime-matched placebo for 7 days
Outcomes	Primary outcomes • Treatment failure Secondary outcomes • Fever clearance time (FCT) in participants in each treatment arm • Time from onset of treatment to treatment failure • Time from symptom onset to treatment failure • Adverse event • Faecal carriage of *S typhi* or *S paratyphi* • Cost-effectiveness of treatment
Starting date	Recruitment commenced in May 2021 - recruitment ongoing
Contact information	clinicaltrials.gov/ct2/show/NCT04349826
Notes	Sponsor: Oxford University Clinical Research Unit, Vietnam

ADDITIONAL TABLES

Table 1. Cephalosporins considered in this review

Cephalosporins
Cefcapene
Cefdaloxime

Table 1. Cephalosporins considered in this review *(Continued)*

Cefdinir
Cefditoren
Cefetamet
Cefixime
Cefmenoxime
Cefodizime
Cefoperazone
Cefotaxime
Cefpimizole
Cefclidine
Cefepime
Cefluprenam
Cefoselis
Cefpodoxime
Ceftazidime
Cefteram
Ceftibuten
Ceftizoxime
Ceftriaxone
Cefozopran
Cefpirome

HISTORY

Protocol first published: Issue 3, 2013

CONTRIBUTIONS OF AUTHORS

Nicole Stoesser and David Eyre authored the review protocol, with input from Christopher Parry and Buddha Basnyat (Stoesser 2013).

Nicole Stoesser and David Eyre screened the search results, extracted data, and completed the risk of bias assessments for trials found in the search in February 2013. Rebecca Kuehn, Christopher Parry, and Thomas Darton screened the search results and extracted data for trials found in the April 2017 and November 2021 search.

All authors contributed to examining the data, writing the review, and approved the final version prior to publication.

DECLARATIONS OF INTEREST

RK is a Cochrane Infectious Diseases Group Research Associate, and was not involved in the editorial process. She has no known conflicts of interest.

NS has no known conflicts of interest.

DE has received grants from the NIHR, Gilead Sciences, and the Robertson Foundation, and has no known conflicts of interest.

TD is a previous contributor to WHO Guidance for the Surveillance of Vaccine Preventable Diseases (typhoid), and has no known conflicts of interest.

BB is a co-author on two trials included in this review (Arjyal 2016; Pandit 2007).

CP is a co-author on the following trial included in this review (Cao 1999).

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

  Cochrane Infectious Diseases Group

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- Foreign, Commonwealth, and Development Office (FCDO), UK

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- Wellcome Trust, UK

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- Department for Health and Social Care/Department for International Developement/Global Challenges Research Fund/Medical Research Council/Wellcome Trust, UK

  BB and CP are supported by the Joint Global Health Trials Scheme (MR/TOO5033/1) awarded to the University of Oxford

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original protocol, Stoesser 2013, we had planned the intervention to be cephalosporins historically referred to as "third or fourth generation." In this review, the intervention was changed to a cephalosporin antimicrobial of any dose or duration to reflect the move away from the concept of "generations" of cephalosporins since the publication of the original protocol. We amended the title accordingly.

We had planned to stratify results by antimicrobial resistance type for all trials where these data are available (MDR: NaR or DCS, or both). This analysis was not possible due to data not reported or data unable to be separated by resistance type. We have described the details of trials that reported on the presence of antimicrobial resistance in the Characteristics of included studies section.

In the original protocol, Stoesser 2013, we had not specified the approach that would be taken to reporting the summary of findings and assessment of the certainty of the evidence. We have now reported this approach in the Methods section under 'Summary of findings and assessment of the certainty of the evidence.'

In the original protocol, Stoesser 2013, the objectives included identifying optimal antimicrobial agents and doses. This was not feasible with the data, and we have simplified the objectives by removing this objective.

The author list has changed since the publication of original protocol in 2013, to reflect the contribution and involvement of each author in the production of the final review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; *Anti-Infective Agents [therapeutic use]; Azithromycin [adverse effects]; Cefixime [therapeutic use]; Ceftriaxone [therapeutic use]; Cephalosporins [therapeutic use]; Chloramphenicol [therapeutic use]; Ciprofloxacin [therapeutic use]; Fluoroquinolones [therapeutic use]; Monobactams [therapeutic use]; Ofloxacin [therapeutic use]; Pakistan; *Paratyphoid Fever [drug therapy]; Recurrence; *Typhoid Fever [drug therapy]

MeSH check words

Adolescent; Adult; Child; Humans