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A comparison of fluoroquinolones versus other antibiotics for treating enteric fever: meta-analysis

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ABSTRACT

Objectives To review evidence supporting use of fluoroquinolones as first line agents over other antibiotics for treating typhoid and paratyphoid fever (enteric fever).

Design Meta-analysis of randomised controlled trials.

Data sources Cochrane Infectious Diseases Group specialised register, CENTRAL (issue 4, 2007), Medline (1966-2007), Embase (1974-2007), LILACS (1982-2007), selected conferences, reference lists, and ongoing trial register (November 2007).

Review methods Trials comparing fluoroquinolones with chloramphenicol, cephalosporins, or azithromycin in culture-proven enteric fever were included. Two reviewers extracted data and assessed methodological quality. Odds ratios with 95% confidence intervals were estimated. Trials recruiting over 60% children were analysed separately from trials on adults. Primary outcomes studied were clinical failure, microbiological failure, and relapse.

Results Twenty trials were included. Trials were small and often of limited methodological quality. Only 10 trials concealed allocation and only three were blinded. In trials on adults, fluoroquinolones were not significantly different from chloramphenicol for clinical failure (594 participants) or microbiological failure (n=378), but reduced clinical relapse (odds ratio 0.14 (95% confidence interval 0.04 to 0.50), n=467, 6 trials). Azithromycin and fluoroquinolones were comparable (n=152, 2 trials). Compared with ceftriaxone, fluoroquinolones reduced clinical failure (0.08 (0.01 to 0.45), n=120, 3 trials) but not microbiological failure or relapse. Compared with cefixime, fluoroquinolones reduced clinical failure (0.05 (0.01 to 0.24), n=238, 2 trials) and relapse (0.18 (0.03 to 0.91), n=218, 2 trials). In trials on children infected with nalidixic acid resistant strains, older fluoroquinolones (ofloxacin) produced more clinical failures than azithromycin (2.67 (1.16 to 6.11), n=125, 1 trial), but there were no differences with newer fluoroquinolones (gatifloxacin, n=285, 1 trial). Fluoroquinolones and cefixime were not significantly different (n=82, 1 trial). **Conclusions** In adults, fluoroquinolones may be better than chloramphenicol for preventing clinical relapse. Data were limited for other comparisons, particularly for children.

INTRODUCTION

Enteric fever (typhoid or paratyphoid fever) caused by *Salmonella* serotype Typhi (*S*Typhi) or *Salmonella* serotype Paratyphi (*S* Paratyphi) remains endemic in many areas of the developing world, causing over 26 million infections and over 200 000 deaths annually.¹ The incidence is highest in south-central Asia and South East Asia (over 100/100 000 cases/year),¹ with the highest burden of disease in children aged 2-15 years.²⁻⁹ *S*Typhi represents the commonest cause of bacteraemia in this age group,^{4,6} and annual typhoid rates (confirmed by blood culture) in recent studies from India, Pakistan, and Indonesia range from 149 to as high as 573 cases per 100 000 children.⁹ Other regions contributing to global morbidity and mortality include Africa, Latin America, the Caribbean, and other parts of Asia.¹

Fluoroquinolones are recommended as first line therapy for children and adults infected with sensitive as well as multidrug resistant (resistant to all three first line inexpensive antibiotics, chloramphenicol, amoxicillin, and co-trimoxazole) *S*Typhi and Paratyphi.¹⁰ A summary¹¹ of randomised controlled trials of enteric fever concluded that fluoroquinolones had lower clinical failures and shorter fever clearance times compared with first line antibiotics and ceftriaxone and cefixime. However, few trials enrolled children,¹² and a meta-analysis was not conducted.

The recommendation to use fluoroquinolones as first line therapy for enteric fever, particularly in children, irrespective of sensitivity patterns—and without a thorough analysis and assessment of quality of evidence—has had profound public health implications for developing countries. These range from increasing costs of treatment to alarming rates of drug resistance. Strains of *S*Typhi and Paratyphi with reduced susceptibility to fluoroquinolones have rapidly emerged—most displaying resistance to nalidixic acid and associated with poor response to treatment.^{9,13-34} Even more alarming are reports of high level fluoroquinolone resistance.^{25,29,30,32,34-38} Although newer generation fluoroquinolones such as gatifloxacin are active against nalidixic acid resistant strains,^{39,40} it may only be a

matter of time before resistance to newer agents becomes widespread if indiscriminate and inappropriate use of fluoroquinolones for any febrile illness continues in endemic areas.⁴¹

However, although antimicrobial resistance patterns show wide regional variations,⁹ some reports suggest that multidrug resistant strains of *S*Typhi have declined from previously high figures,^{19 24 25 29 32 34 42-45} indicating

Characteristics and methodological quality of trials included in meta-analysis

Study	Country and year of study (if stated)	Participants' age group, setting, culture site, and severity at enrollment*	No of participants (in fluoroquinolone group: other group)	Methodological quality of trials†	Drug regimens used‡
Fluoroquinolone versus chloramphenicol					
Quintero 1988 ⁶³ (conference abstract)	Mexico	Adult dosages, inpatients, blood culture, severity unknown§	26 (13:13)	Randomisation unclear, allocation concealment unclear, double blinded, follow-up adequate	Ciprofloxacin 750 mg orally 3 times a day. Chloramphenicol 750 mg orally 4 times a day. Duration not mentioned
Bran 1991 ⁶⁴ (conference abstract)	Guatemala	Adult dosages, inpatients, blood and/or bone marrow culture, severity unknown§	102 (51: 51)§	Randomisation unclear, allocation concealment unclear, double blinded, follow-up adequate	Ciprofloxacin 500 mg orally twice a day for 10 days. Chloramphenicol 750 mg orally every 6 hours for 14 days
Gottuzzo 1992 ⁶⁵	—	Adult inpatients, mainly blood culture, severity unknown§	98 (49:49)	Randomisation unclear, allocation concealment unclear, double blinded, follow-up adequate	Ciprofloxacin 500 mg orally every 12 hours for 10 days. Chloramphenicol 750 mg orally every 6 hours for 14 days
Morelli 1992 ⁶⁶	Italy 1985-90	Adult inpatients, blood culture, severity unknown	156([30:36:20:20]:30)¶	Randomisation adequate, allocation concealment unclear, unblinded, follow-up adequate	Ofloxacin 300 mg, pefloxacin 400 mg, ciprofloxacin 500 mg, enoxacin 300 mg (all orally every 8 hours for 15 days) Chloramphenicol 500 mg orally every 6 hours for 15 days
Yousaf 1992 ⁶⁷	Pakistan 1989-92	Adult inpatients, blood culture, severity unknown§	50 (25:25)	Randomisation unclear, allocation concealment unclear, unblinded, follow-up inadequate	Ofloxacin 200 mg orally twice a day for 14 days. Chloramphenicol 50 mg/kg/day orally, 30 mg/kg/day when afebrile, for 14 days
Abejar 1993 ⁶⁸	Philippines	Adult inpatients, blood culture, severity unknown	30 (15:15)	Randomisation unclear, allocation concealment unclear, unblinded, follow-up adequate	Fleroxacin 400 mg orally once a day for 10 days. Chloramphenicol 50 mg/kg/day orally in 3 divided doses every 8 hours for 14 days
Arnold 1993 ⁶⁹	Multicentre: South America, Indonesia, etc§	Adult inpatients, blood culture, no major complications	91 ([24:33]:34)	Randomisation unclear, allocation concealment unclear, unblinded, follow-up adequate	Fleroxacin 400 mg orally once a day for 7 days. Fleroxacin 400 mg orally once a day for 14 days. Chloramphenicol 50 mg/kg/day orally for 14 days
Cristiano 1995 ⁷⁰	Italy 1991-3	Adult inpatients, blood culture, all severe cases	60 (30:30)	Randomisation adequate, allocation concealment unclear, unblinded, follow-up adequate	Pefloxacin 1200 mg IV in 3 divided doses every 8 hours for 5 days then orally for 10 days. Chloramphenicol 2 g orally in 4 divided doses every 6 hours for 15 days
Gasem 2003 ⁷¹	Indonesia 1997	Adult inpatients, blood and/or bone marrow culture, no severe complications	55 (28:27)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up adequate	Ciprofloxacin 500 mg orally twice a day for 7 days. Chloramphenicol 500 mg orally four times a day for 14 days
Phongmany 2005 ^{72**}	Laos 2001-3	Adult inpatients, blood culture, uncomplicated	50 (27:23)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up adequate	Ofloxacin 15 mg/kg/day orally in 2 divided doses for 3 days. Chloramphenicol 50 mg/kg/day orally in 4 divided doses for 14 days
Fluoroquinolone versus ceftriaxone					
Wallace 1993 ⁷³	Bahrain	Adult inpatients, blood culture, severity unknown	42 (20:22)	Randomisation unclear, allocation concealment unclear, unblinded, follow-up adequate	Ciprofloxacin 500 mg orally twice a day for 7 days. Ceftriaxone 3 g/day IV for 7 days
Smith 1994 ^{74***}	Vietnam 1992-3	Adult inpatients, blood and/or bone marrow (n=44) stool (n=3) culture, uncomplicated	47 (22:25)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up inadequate	Ofloxacin 200 mg orally every 12 hours for 5 days. Ceftriaxone 3 g/day IV for 3 days
Tran 1994 ^{75**}	Vietnam 1992-3	Adult inpatients, blood culture, uncomplicated	31 (16:15)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up inadequate	Fleroxacin 400 mg orally once a day for 7 days. Ceftriaxone 2 g IV once daily for 5 days
Fluoroquinolone versus cefixime					
Yu, 1998 ⁷⁶ (in Chinese)	China	Adult inpatients, blood or bone marrow culture, severe cases included§	80 (40:40)	Randomisation unclear, allocation concealment unclear, unblinded, follow-up adequate	Levofloxacin 200 mg orally twice a day for 10 days. Cefixime 200 mg orally twice a day for 10 days
Cao 1999 ^{77**}	Vietnam 1995-6	Child (<15 years old) inpatients, blood culture, uncomplicated	82 (38:44)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up inadequate	Ofloxacin 10 mg/kg/day orally in 2 divided doses for 5 days. Cefixime 20 mg/kg/day orally in 2 divided doses for 7 days
Pandit 2007 ^{39**}	Nepal 2005	Adult and child (35.5% < 14 years) outpatients, blood culture, uncomplicated	158 (88:70)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up inadequate	Gatifloxacin 10 mg/kg/day orally once a day for 7 days. Cefixime 20 mg/kg/day orally in 2 divided doses for 7 days

Study	Country and year of study (if stated)	Participants' age group, setting, culture site, and severity at enrollment*	No of participants (in fluoroquinolone group: other group)	Methodological quality of trials†	Drug regimens used‡
Fluoroquinolone versus azithromycin					
Girgis 1999 ^{78**}	Egypt 1997-8	Adult inpatients, blood (n=62) stool (n=2) culture, uncomplicated	64 (28:36)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up adequate	Ciprofloxacin 500 mg orally twice a day for 7 days. Azithromycin 1 g orally once on day 1, then 500 mg once a day for 6 days (total of 7 days)
Chinh 2000 ^{79**}	Vietnam	Adult inpatients, blood culture, uncomplicated	88 (44:44)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up inadequate	Ofloxacin 200 mg orally twice a day (8 mg/kg/day) for 5 days. Azithromycin 1 g orally daily (20 mg/kg/day) for 5 days
Parry 2007 ^{80**}	Vietnam 1998-2002	Adult and child (87% <15 years) inpatients, blood and/or bone marrow culture, uncomplicated††	125 (63:62)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up inadequate	Ofloxacin 20 mg/kg/day orally in 2 divided doses for 7 days. Azithromycin 10 mg/kg/day orally once a day for 7 days
Dolecek 2008 ^{40**}	Vietnam (3 hospitals) 2004-5	Adult and child (73% <15 years) inpatients, blood and/or bone marrow culture, uncomplicated	285 (145:140)	Randomisation adequate, allocation concealment adequate, unblinded, follow-up adequate	Gatifloxacin 10 mg/kg/day orally once a day for 7 days. Azithromycin 20 mg/kg/day orally once a day for 7 days

*Severity of fever at enrollment was as defined by trial investigators.

†Quality assessment as follows. Randomisation: adequate (methods such as computer generated random numbers or use of a random number table), inadequate (methods such as assignment based on day of presentation or alternation), unclear (method not described). Allocation concealment: adequate (methods such as use of sealed envelopes), inadequate (such as unsealed envelopes), unclear (no information provided). Blinding: single (either care provider/outcome assessor or participants were unaware of treatment), double (participants and care provider/outcome assessor were unaware of treatment), open (all parties were aware of treatment). Follow-up: adequate (≥90% of participants with culture confirmed infection followed up), inadequate (<90% of such participants followed up).

‡For trials that compared different fluoroquinolones (such as ofloxacin and ciprofloxacin) or different durations of fluoroquinolones (such as 7 and 14 days), we combined all fluoroquinolone groups for comparison with groups receiving the non-fluoroquinolone antibiotic.

§Some information not explicitly stated, but assumed based on information in trial.

¶The norfloxacin group was not included in this meta-analysis (see text for explanation).

**Author provided additional information.

††A third arm in this study, involving combination of treatments, was not included in this meta-analysis

that chloramphenicol could still be used in some endemic areas. On the other hand multidrug resistant strains of *S Paratyphi* may be emerging,^{24 29 46 47} which underscores the complexities of treatment and limited alternatives available.⁴⁸

This meta-analysis was undertaken to determine the strength of evidence supporting use of fluoroquinolones over chloramphenicol, ceftriaxone, cefixime, and azithromycin for treating enteric fever in children and adults.⁴⁹

METHODS

Search strategy and selection criteria

We searched the Cochrane Infectious Diseases Group's specialised register (November 2007), Cochrane central register of controlled trials (CENTRAL, issue 4, 2007), Medline (1966 to November 2007), Embase (1974 to November 2007), and LILACS (1982 to November 2007) using text words and medical subject headings (MeSH) "typhoid fever," "enteric fever," "paratyphoid fever," "*Salmonella Typhi*," "*Salmonella Paratyphi*" combined with the Cochrane Collaboration's search strategy.⁵⁰ A complete list of search terms used is available.⁴⁹ We identified relevant trials in all languages, searched selected conference proceedings, authors' files, reference lists, and the meta-Register of Controlled Trials (mRCT), and contacted experts for relevant ongoing or unpublished trials.⁴⁹

One reviewer screened titles and abstracts, and potentially relevant trials were further evaluated independently by two reviewers using pre-designed eligibility forms. Trials were included if they were

randomised and compared fluoroquinolone with another antibiotic in enteric fever confirmed with blood or bone marrow culture.

Data abstraction and methodological assessment

Two reviewers independently extracted data using piloted data extraction forms, compared data, and resolved disagreements. Primary outcomes (measured at time points described by investigators) were clinical failure (presence of symptoms or development of complications necessitating change in or prolongation of antibiotic therapy), microbiological failure (positive culture from blood, bone marrow, or any sterile anatomical site), and relapse (recurrence of symptoms with a positive culture from blood, bone marrow, or any sterile anatomical site). Secondary outcomes included fever clearance time (time taken in hours from the start of therapy to defervescence, as defined by authors), convalescent faecal carriage (positive faecal culture detected at any time after end of treatment up to one year of follow-up), cost of therapy, length of hospitalisation, complications, and adverse events.⁴⁹ We contacted study authors for additional data or to clarify data.

Two reviewers independently assessed methodological quality of trials based on the method of randomisation (generation of allocation sequence), allocation concealment, blinding, and follow-up of participants with culture-proven enteric fever (see table).^{49 51} We conducted an available case analysis and derived the proportion of participants lost to follow-up at final outcome.

Statistical analysis and stratifications

We conducted meta-analyses using Review Manager 5,⁵² with odds ratios for dichotomous data and mean differences for continuous data, presented with 95% confidence intervals. We used Mantel-Haenszel odds ratios since there were limited data and few trials.⁵³ Because the events are relatively rare, the estimated odds ratios can be considered similar to risk ratios.⁵³

We did not combine trials recruiting children (trials with >60% participants who were <16 years) with trials recruiting adults (≥ 16 years or “adults” as described by the investigators), since enteric fever differs in severity, clinical manifestations, and outcome in children and adults,⁵⁴⁻⁵⁷ and because of generic differences in drug pharmacokinetics and pharmacodynamics in children and adults. Adverse events from fluoroquinolones are still not clearly delineated in children.^{58,59} We stratified results by presence of multidrug resistant strains (for trials involving chloramphenicol) and nalidixic acid resistant strains (all trials). (All stratifications are presented elsewhere.⁴⁹) We generated a funnel plot to assess publication bias for comparisons with more than five trials. We assessed heterogeneity by visual inspection of graphs and χ^2 test for homogeneity (at 10% level of significance) and explained heterogeneity by exploring differences in drug doses or durations, severity of enteric fever (as defined by investigators), and time points of outcome measurement. We used a fixed effects model to pool data. When we found significant heterogeneity we used a random effects model if it was still considered appropriate to pool data.

RESULTS

Seventy potentially relevant trials were evaluated (fig 1 shows the numbers of studies evaluated at each stage).

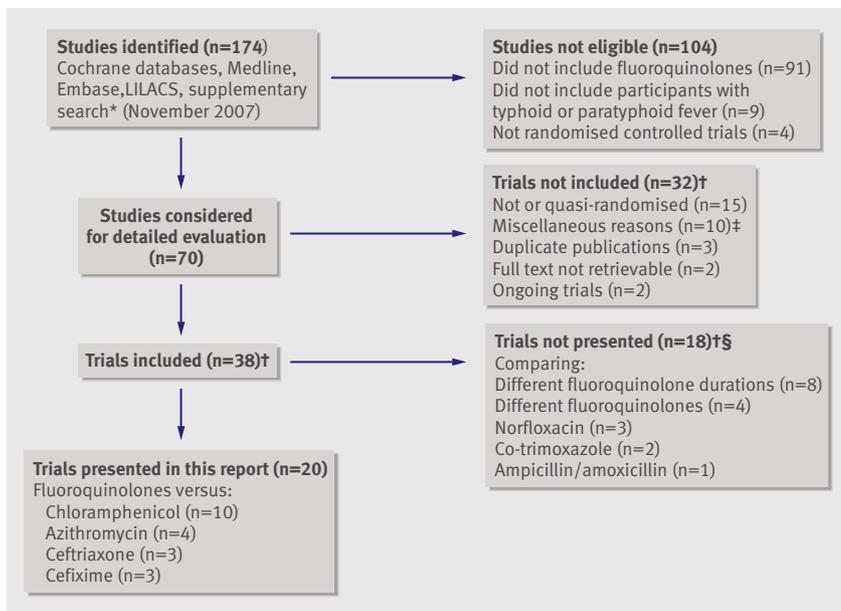


Fig 1 | Studies evaluated at each stage of the meta-analysis. (*Supplementary search includes: reference lists, authors' files, contacting experts, selected conference proceedings, on-going trial register. †See Cochrane review⁴⁹ for further details or analyses. ‡Includes sample size <5, comparing different formulations/routes of same fluoroquinolone, not enough information presented in published report. §Trials contributing to more than 1 category counted only once.)

Details of the excluded studies and the reasons for exclusion are available.⁴⁹ We excluded trials using norfloxacin⁶⁰⁻⁶² since this is not recommended for treating enteric fever because of its low oral bioavailability.¹⁰ We included 20 trials in the present analysis—fluoroquinolones were compared with chloramphenicol (10 trials),⁶³⁻⁷² ceftriaxone (three trials),⁷³⁻⁷⁵ cefixime (three trials),^{39,76,77} and azithromycin (four trials).^{40,78-80}

Study characteristics and methodological quality

The table details the trials' characteristics. Only three recruited children exclusively or predominantly.^{40,77,80} Sample sizes were small (ranging from 26⁶³ to 285⁴⁰). Duration of fluoroquinolone treatment ranged from three days⁷² to 15 days.^{66,70} Twelve trials had adequate methods of randomisation,^{39,40,66,70-72,74,75,77-80} 10 of which had adequate allocation concealment.^{39,40,71,72,74,75,77-80} Three were “double blinded.”⁶³⁻⁶⁵ Final follow-up of confirmed cases was adequate in 13.^{40,63-66,68-73,76,78} Definitions and time points of measurements for outcomes such as clinical and microbiological failure showed considerable variations.⁴⁹

Comparisons involving adults

Fluoroquinolone versus chloramphenicol

Three of the 10 included trials did not clarify the proportion of multidrug resistant strains.^{65,67,69} Multidrug resistant strains were absent in all other trials, except one.⁷² One trial had no isolates with nalidixic acid resistance⁷²—the others did not report this information.

The meta-analysis showed no significant differences between fluoroquinolones and chloramphenicol for clinical failure (odds ratio 0.65 (95% confidence interval 0.25 to 1.72), $n=594$, nine trials), but confidence intervals were wide (fig 2). The results were of borderline significance in favour of fluoroquinolones for microbiological failure (0.43 (0.18 to 1.03), $n=378$, six trials). The odds of clinical relapse were reduced significantly, by 86%, with fluoroquinolones (0.14 (0.04 to 0.50), $n=467$, six trials). Fluoroquinolone use was associated with a significantly lower mean fever clearance time (mean difference -25.93 hours (95% confidence interval -40.12 to -11.74), $n=129$, three trials) (see extra fig A on bmj.com) as well as convalescent faecal carriage (0.17 (0.04 to 0.70), $n=298$, three trials). There was significant heterogeneity ($P<0.00001$) between the two trials comparing length of hospitalisation, which could have been due to differences in fluoroquinolone treatment durations (3 days *v* 7 days). A random effects model showed no differences (-3.13 days (-8.52 to 2.26), $n=105$, two trials).

Sensitivity analysis (not shown)—When we restricted the analysis to trials of better methodological quality (that is, adequate methods of randomisation and allocation concealment) there was no change in results for clinical failure ($n=105$)^{71,72} or microbiological failure ($n=45$).⁷¹ For relapse, when we excluded trials which did not clearly define or did not confirm relapse using cultures, we retained only one trial

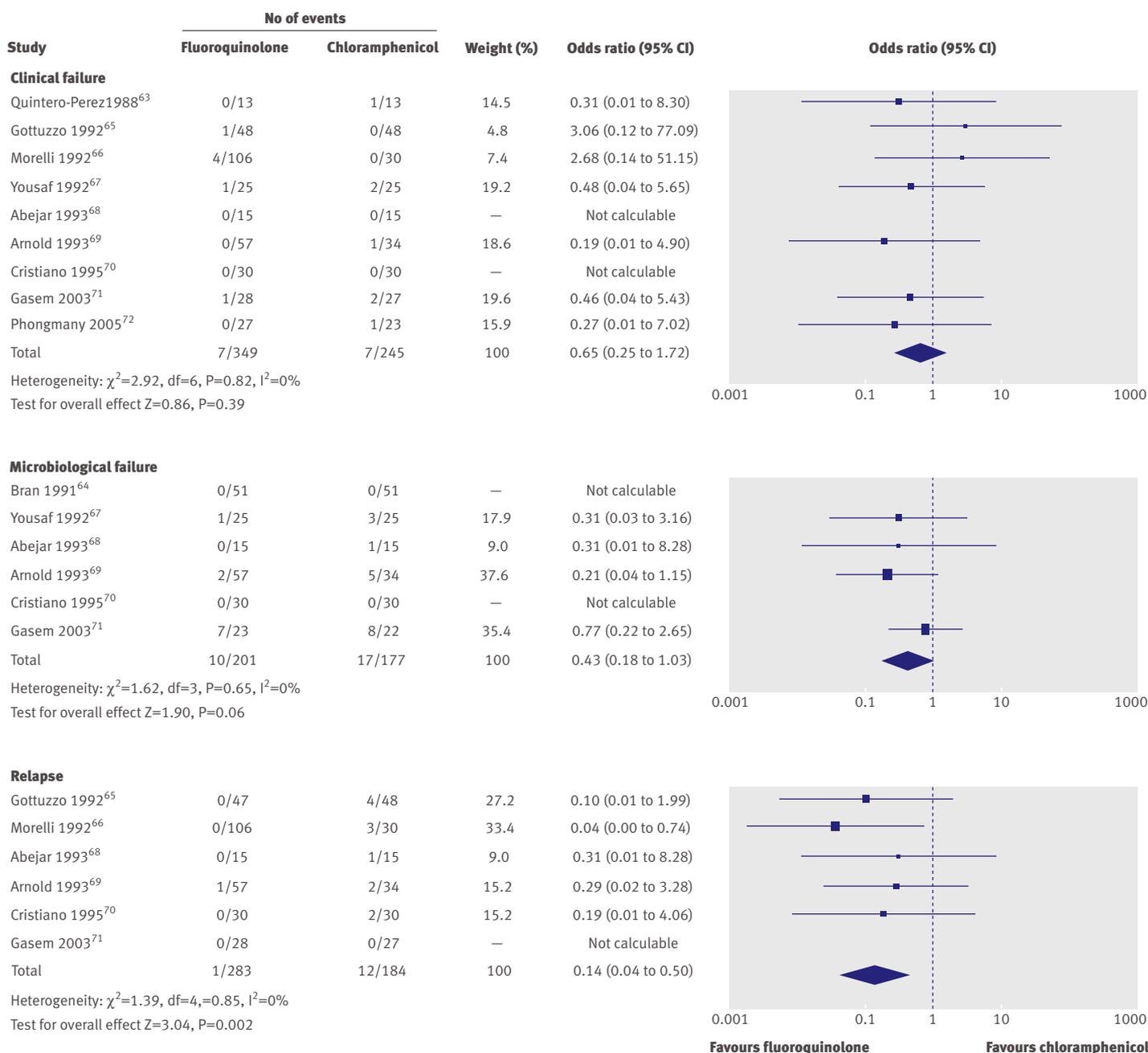


Fig 2 | Forest plots for trials of fluoroquinolones versus chloramphenicol for treating enteric fever in adult inpatients. Details of studies reporting proportion of multidrug resistant and nalidixic acid resistant strains are in text. See Cochrane review⁴⁹ for stratifications.

($n=91$)⁶⁹ with blood culture confirmed relapses and did not find any difference between fluoroquinolones and chloramphenicol, although confidence intervals were wide. The only methodologically adequate trial ($n=55$)⁷¹ did not report any clinical relapses during hospitalisation, without longer follow-up. Fever clearance times were significantly lower with fluoroquinolone use (-27.56 hours (-43.38 to -11.75), $n=103$).^{71 72} Both trials reporting length of hospital stay were of adequate methodological quality; there were no data for convalescent faecal carriage from these trials.

Funnel plots—The number of trials (4 to 7) in included funnel plots for outcomes clinical failure, microbiological failure, and relapse was well below the recommended number of trials (10) for meaningful interpretation. No asymmetry was detected for clinical failure, but some asymmetry was detected for microbiological failure and relapse.⁴⁹ (See extra fig B on bmj.com.)

Fluoroquinolone versus cefixime

One open trial conducted on mainly adult outpatients presenting to hospital had adequate methods of

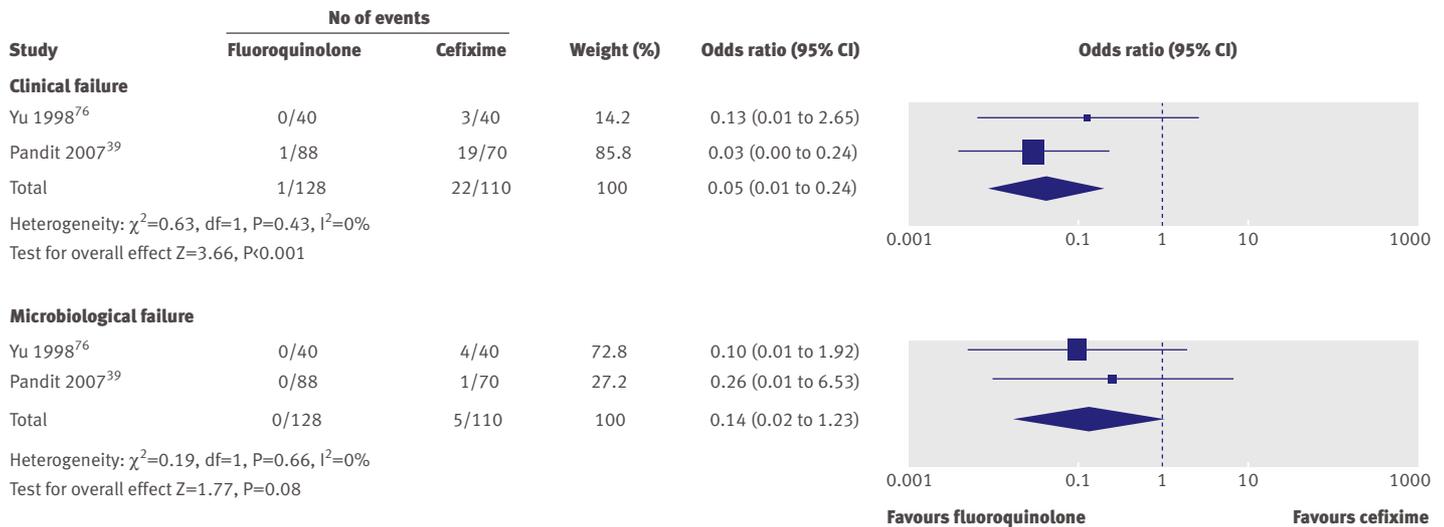


Fig 3 | Forest plots for trials of fluoroquinolones versus cefixime for treating enteric fever in adult outpatients and inpatients. There were no relapses in either arm in Yu et al 1998.⁷⁶ Pandit et al 2007³⁹ reported 2/87 v 6/51 relapses (odds ratio 0.18 (95% confidence interval 0.03 to 0.91)). Details of studies reporting proportion of nalidixic acid resistant strains are in text.

randomisation and allocation concealment but inadequate follow-up.³⁹ Community medical auxiliaries conducted home based assessments twice daily and provided directly observed treatment with study drugs; all participants were also seen at the hospital on day 10.³⁹ Although nalidixic acid resistance was present, the newer generation fluoroquinolone used (gatifloxacin) is unaffected by nalidixic acid resistance.³⁹ The other trial on adult inpatients had unclear methodology, and resistance data were not extractable.⁷⁶ The meta-analysis showed a significant reduction in clinical failure (odds ratio 0.05 (95% confidence interval 0.01 to 0.24), $n=238$) as well as relapse in the fluoroquinolone group (0.18 (0.03 to 0.91), $n=218$) (fig 3). No differences were detected for microbiological failure (0.14 (0.02 to 1.23), $n=238$), but the confidence interval was wide. There was a significant reduction in fever clearance time with fluoroquinolones (mean difference -41.69 hours (-54.96 to -28.42), $n=238$) (see extra fig A). There were no differences in convalescent faecal carriers (0.26 (0.01 to 6.50), $n=227$).

Fluoroquinolones versus ceftriaxone

All three trials recruiting adult inpatients were open.⁷³⁻⁷⁵ Two had adequate methods of randomisation and allocation concealment but inadequate follow-up.^{74,75} Nalidixic acid resistant strains were absent in one⁷⁴ and were not reported in the others. The meta-analysis showed a significantly lower odds of clinical failure with fluoroquinolones (0.08 (0.01 to 0.45), $n=120$), but there was no difference in microbiological failure (0.32 (0.03 to 3.17), $n=119$) or relapse (0.34 (0.03 to 3.47), $n=81$), although confidence intervals were wide (fig 4). Fever clearance time was significantly lower with fluoroquinolones (-101.20 hours (-129.21 to -73.19), $n=76$) (see extra fig A). There were no differences in convalescent faecal carriage (0.35 (0.01 to 9.08) $n=81$).

Fluoroquinolones versus azithromycin

Both open trials recruiting adult inpatients, had adequate methods of randomisation and allocation concealment.^{78,79} One had adequate follow-up.⁷⁸ There was a high proportion of nalidixic acid resistant strains in one (52%),⁷⁹ but this information was not reported in the other trial. There were no significant differences in clinical failure (3.32 (0.63 to 17.43), $n=152$), microbiological failure (2.05 (0.18 to 23.44), $n=152$), or relapse (6.94 (0.31 to 154.85), $n=102$), although the confidence intervals were wide and comparisons lacking in statistical power (see extra fig C on bmj.com). There were no significant differences in fever clearance times (-8.95 hours (-20.09 to 2.19), $n=152$) (extra fig A) or length of hospital stay (-0.90 days (-0.32 to 2.12), $n=152$). There was a significant increase in convalescent faecal carriage with fluoroquinolone use (21.33 (1.18 to 386), $n=133$; this was measured early on days 2-3 after end of treatment).⁷⁹

Comparisons involving children

Fluoroquinolone versus cefixime

We found only one open trial recruiting hospitalised children, with adequate methods of randomisation and allocation concealment but inadequate follow-up.⁷⁷ No child was infected by a nalidixic acid resistant strain. Reduction in clinical failure was of borderline significance in favour of fluoroquinolones (0.12 (0.01 to 1.02), $n=82$). There were no significant differences in microbiological failure (0.22 (0.01 to 4.74), $n=82$) or relapse (0.32 (0.01 to 8.26), $n=40$). Although a trend favouring fluoroquinolone can be seen, the confidence intervals were wide. There was a significant reduction in fever clearance time (-91.00 hours (-115.89 to -66.11), $n=78$) and length of hospital stay with fluoroquinolones (-3 days (-4.53 to -1.47 days), $n=81$). No convalescent faecal carriers were reported.

Fluoroquinolones versus azithromycin

Both open trials on mostly paediatric inpatients, with adequate methods of randomisation and allocation concealment, had uniformly high proportions of nalidixic acid resistant strains (98%⁸⁰ and 96%⁴⁰ in fluoroquinolone arms). One trial used gatifloxacin,⁴⁰ which is active against nalidixic acid resistant strains; we therefore did not combine these trials in a meta-analysis. With ofloxacin there was a significant increase in clinical failure (2.67 (1.16 to 6.11), n=125), no significant differences in microbiological failure (0.98 (0.13 to 7.21), n=125), and no relapses at one month follow-up (<90% participants followed).⁸⁰ Ofloxacin use significantly increased fever clearance time (57.60 hours (28.31 to 86.89), n=125) and convalescent faecal carriage (14.64 (1.84 to 116.48), n=124) and a borderline increase in length of hospitalisation (1.10 days (0.00 to 2.20), n=125). In the trial of gatifloxacin versus azithromycin (n=285) there were no significant differences in clinical or microbiological failure (0.96 (0.30 to 3.06) and 0.64 (0.11 to 3.88)), relapse (6.64 (0.34 to 129.74), n=264), fever clearance time (0.73 hours (-12.97 to 14.43)), length of hospital stay (0.19 days (-0.49 to 0.87)), or convalescent faecal carriage (2.89 (0.12 to 71.58), n=268), although confidence intervals were wide.⁴⁰

Other outcomes

Complications—There were significantly lower complications with gatifloxacin compared with azithromycin (0.05 (0.00 to 0.94), n=285).⁴⁰ No differences were found in other trials of fluoroquinolones with chloramphenicol,^{71 72} ceftriaxone,⁷³⁻⁷⁵ cefixime,^{39 77} or azithromycin.⁷⁸⁻⁸⁰

Adverse events—There were no differences in non-serious adverse events with azithromycin,⁴⁰ chloramphenicol,^{67 68 70-72} or ceftriaxone.⁷⁴ The meta-analysis of trials comparing fluoroquinolone and cefixime showed significant heterogeneity, and was combined using a random effects model (3.30 (0.11 to 97.30), n=238). There were no differences in serious adverse events with ceftriaxone.^{74 75} Other trials either reported no complications or adverse events in either arm, or reported events without actual numbers of participants experiencing these events.⁴⁹

DISCUSSION

Main findings and limitations

Even though enteric fever most commonly affects children in areas where it is endemic, this review shows the paucity of evidence supporting the use of fluoroquinolones in this age group from adequately designed randomised controlled trials. Adult inpatients are the group most studied, although they form only a small

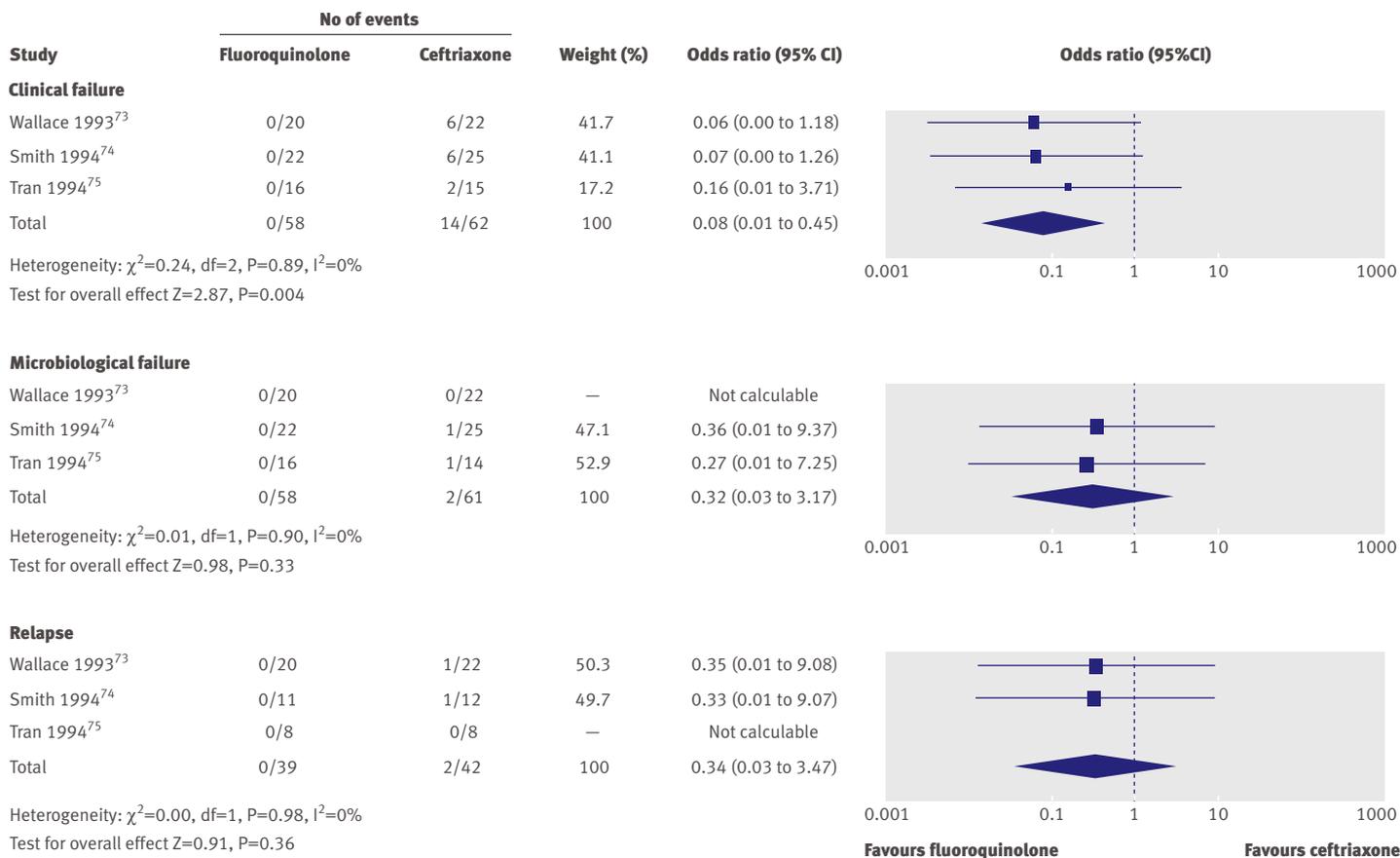


Fig 4 | Forest plots for trials of fluoroquinolones versus ceftriaxone for treating enteric fever in adult inpatients. Details of studies reporting proportion of nalidixic acid resistant strains are in text. See Cochrane review⁴⁹ for stratifications.

proportion of overall typhoid burden. Even in this subgroup, most trials were small with limited statistical power and serious methodological limitations.

We did not find any trial comparing fluoroquinolones with chloramphenicol in children, and so cannot make recommendations specific to this age group. In trials comparing fluoroquinolones and chloramphenicol in adults data were insufficient to detect significant differences in clinical or microbiological failure. Any true treatment difference, if one existed, was obscured by wide confidence intervals, and the role of chance cannot be excluded as an explanation for these findings. Microbiological failure, measured at varying time points, was based on blood cultures, although one reviewed trial⁷¹ also reported bone marrow culture results for ciprofloxacin compared with chloramphenicol (67% *v* 100% positive cultures on day 5, $P=0.04$). Although this difference was significant, it was smaller than anticipated since penetration of ciprofloxacin intracellularly was expected to eradicate a much higher proportion of *STyphi*.⁷¹ Data suggest that fluoroquinolones were better than chloramphenicol for reducing clinical relapse, but most investigators did not define relapse explicitly and data are lacking for relapse confirmed by culture. The wide confidence intervals produced when we restricted our analyses to trials of adequate methodological quality underscore the limited evidence available. As well as a lack of explicit definitions for measured outcomes and variations in times at which these were measured, resistance data (multidrug resistant and nalidixic acid resistant) were not explicitly reported, particularly in older trials.

While data were limited for comparisons of fluoroquinolones and cefixime in children, unblinded comparisons involving adults suggest that fluoroquinolones are better than cefixime for reducing clinical failure and relapse and better than ceftriaxone for reducing clinical failure. The lack of methodological rigour—failure to conceal allocation by some and failure to use blinding in all—suggests that these results may have been influenced by selection bias and observer bias and may overestimate the benefit of fluoroquinolones compared with older antibiotics.⁵¹ There were too few trials to ascertain presence of publication bias using funnel plots. However, some asymmetry observed for microbiological failure and relapse for trials involving chloramphenicol suggests the possibility of publication bias or failure to publish smaller studies showing non-significant results.⁸¹

Our results thus differ from those of a previous review, a summary of randomised controlled trials of enteric fever,¹¹ which found fluoroquinolones to be superior to chloramphenicol, ceftriaxone, and cefixime for clinical failure and fever clearance times. Although our data suggest that fluoroquinolones had significantly lower fever clearance times compared with chloramphenicol, cefixime, and ceftriaxone, the analyses of fever clearance times must be interpreted with caution. Mean fever clearance times often follow a skewed distribution—although most patients clear fever quickly, some take much longer times—so meta-analyses conducted using arithmetic means may

not be accurate. The persistence of fever in some patients despite apparent clearance of *STyphi* and *S Paratyphi* from the bloodstream has been attributed to the continued production of pyrogenic cytokines.⁸²⁻⁸⁵ This suggests that time taken to clear fever may not be an adequate measure of antibiotic efficacy, and consequently may not be an appropriate end point in typhoid therapy trials. Some investigators also did not specify whether clinical failures were excluded or included in calculations of mean fever clearance time.

Cost considerations

We could not compare the costs of fluoroquinolone and other antibiotics because of lack of data from trials. Although fluoroquinolones may be the least costly alternative for multidrug resistant enteric fever, this cost advantage has diminished with increasing numbers of strains resistant to older fluoroquinolones such as ciprofloxacin and ofloxacin.^{9 13-38} Newer fluoroquinolones such as gatifloxacin are effective against nalidixic acid resistant strains,³⁹ but more evidence of efficacy compared with other antibiotics, tolerance, and safety is required,³⁹ as well as close monitoring of resistance patterns and check on indiscriminate use. For children, one trial found that ofloxacin performed poorly compared with azithromycin in patients infected with nalidixic acid resistant strains,⁸⁰ while data for azithromycin versus gatifloxacin are limited.⁴⁰

Applicability

Our results may be applicable only to hospitalised adults with culture confirmed enteric fever—since most of the trials enrolled such patients. Hospitalised patients represent the more severe end of the spectrum of enteric fever, and adults differ from children in disease presentation, severity, and complications.⁵⁴⁻⁵⁷ In developing regions most patients with typhoid fever are children—often managed as outpatients without confirmation by culture.¹¹ Indeed, rates of hospitalisation of primary care patients for culture confirmed enteric fever have been under 1% with algorithm-based early recognition and management (Z A Bhutta et al, unpublished data). The widespread empiric use of fluoroquinolones is also not generally recommended in children because of the potential risk of arthropathy.^{58,59}

Future directions and policy implications

Appropriate treatment for enteric fever is a clinical and public health challenge, with rising levels of drug resistance and limited evidence for use of newer agents, particularly for children. Large, well designed, and methodologically rigorous trials are needed to compare fluoroquinolones with first line antibiotics in community or outpatient settings, reflecting practice in low income countries, with accurate reporting of resistance data. Long term follow-up and monitoring of adverse effects are also required. Investigators must standardise definitions and time points of measurements of

WHAT IS ALREADY KNOWN ON THIS TOPIC

Fluoroquinolones have been recommended as first line therapy for adults and children with enteric (typhoid and paratyphoid) fever

However, evidence supporting their use has not been thoroughly analysed, and resistance to these agents has spread alarmingly

WHAT THIS STUDY ADDS

There is limited evidence from methodologically rigorous, unbiased trials of fluoroquinolones in enteric fever, particularly in children

outcomes, particularly those of subjective nature, such as clinical failure. The identification of strains with reduced susceptibility to fluoroquinolones which do not exhibit nalidixic acid resistance^{20,27} indicates the need for reporting and interpretation of fluoroquinolone minimum inhibitory concentrations. In addition to objective studies of treatment efficacy and cost effectiveness, we need evaluations of algorithmic approaches to diagnosis and management of prolonged fever in children in regions where typhoid is endemic.⁸⁶ Such protocols will guide antibiotic use and may curb rising resistance. Surveillance systems for monitoring burden of disease and resistance patterns are required.⁸⁷

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