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*Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD004530.  
DOI: [10.1002/14651858.CD004530.pub4](https://doi.org/10.1002/14651858.CD004530.pub4).

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[Intervention Review]

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

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**Editorial group:** Cochrane Infectious Diseases Group.

**Publication status and date:** Unchanged, published in Issue 5, 2019.

**Citation:** Effa EE, Lassi ZS, Critchley JA, Garner P, Sinclair D, Olliaro PL, Bhutta ZA. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD004530. DOI: [10.1002/14651858.CD004530.pub4](https://doi.org/10.1002/14651858.CD004530.pub4).

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## ABSTRACT

### Background

Typhoid and paratyphoid are febrile illnesses, due to a bacterial infection, which remain common in many low- and middle-income countries. The World Health Organization (WHO) currently recommends the fluoroquinolone antibiotics in areas with known resistance to the older first-line antibiotics.

### Objectives

To evaluate fluoroquinolone antibiotics for treating children and adults with enteric fever.

### Search methods

We searched The Cochrane Infectious Disease Group Specialized Register (February 2011); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2011, Issue 2); MEDLINE (1966 to February 2011); EMBASE (1974 to February 2011); and LILACS (1982 to February 2011). We also searched the *metaRegister* of Controlled Trials (*mRCT*) in February 2011.

### Selection criteria

Randomized controlled trials examining fluoroquinolone antibiotics, in people with blood, stool or bone marrow culture-confirmed enteric fever.

### Data collection and analysis

Two authors independently assessed the trial's methodological quality and extracted data. We calculated risk ratios (RR) for dichotomous data and mean difference for continuous data with 95% confidence intervals (CI).

Comparative effectiveness has been interpreted in the context of; length of treatment, dose, year of study, known levels of antibiotic resistance, or proxy measures of resistance such as the failure rate in the comparator arm.

### Main results

Twenty-six studies, involving 3033 patients, are included in this review.

### *Fluoroquinolones versus older antibiotics (chloramphenicol, co-trimoxazole, amoxicillin and ampicillin)*

In one study from Pakistan in 2003-04, high clinical failure rates were seen with both chloramphenicol and co-trimoxazole, although resistance was not confirmed microbiologically. A seven-day course of either ciprofloxacin or ofloxacin were found to be superior. Older studies of these comparisons failed to show a difference (six trials, 361 participants).

In small studies conducted almost two decades ago, the fluoroquinolones were demonstrated to have fewer clinical failures than ampicillin and amoxicillin (two trials, 90 participants, RR 0.11, 95% CI 0.02 to 0.57).

### *Fluoroquinolones versus current second-line options (ceftriaxone, cefalexin, and azithromycin)*

The two studies comparing a seven day course of oral fluoroquinolones with three days of intravenous ceftriaxone were too small to detect important differences between antibiotics should they exist (two trials, 89 participants).

In Pakistan in 2003-04, no clinical or microbiological failures were seen with seven days of either ciprofloxacin, ofloxacin or cefixime (one trial, 139 participants). In Nepal in 2005, gatifloxacin reduced clinical failure and relapse compared to cefixime, despite a high prevalence of NaR in the study population (one trial, 158 participants, RR 0.04, 95% CI 0.01 to 0.31).

Compared to a seven day course of azithromycin, a seven day course of ofloxacin had a higher rate of clinical failures in populations with both multi-drug resistance (MDR) and nalidixic acid resistance (NaR) enteric fever in Vietnam in 1998-2002 (two trials, 213 participants, RR 2.20, 95% CI 1.23 to 3.94). However, a more recent study from Vietnam in 2004-05, detected no difference between gatifloxacin and azithromycin with both drugs performing well (one trial, 287 participants).

### **Authors' conclusions**

Generally, fluoroquinolones performed well in treating typhoid, and maybe superior to alternatives in some settings. However, we were unable to draw firm general conclusions on comparative contemporary effectiveness given that resistance changes over time, and many studies were small. Policy makers and clinicians need to consider local resistance patterns in choosing a fluoroquinolone or alternative.

There is some evidence that the newest fluoroquinolone, gatifloxacin, remains effective in some regions where resistance to older fluoroquinolones has developed. However, the different fluoroquinolones have not been compared directly in trials in these settings.

8 May 2019

No update planned

Other

An updated search (5 Sep, 2016) identified 4 studies for inclusion ('Studies awaiting classification' section: Ali 2011; Arjyal 2016; Chandey 2012; Koirala 2013). In an external analysis for the WHO, inclusion of these 4 studies did not change the 2011 published version's results. The WHO used these results in 2017 (unpublished report for the WHO SAGE Typhoid Working Group, 2017).

## **PLAIN LANGUAGE SUMMARY**

### **Fluoroquinolones for treating enteric fever**

**Researchers in The Cochrane Collaboration conducted a review of the effect of fluoroquinolone antibiotics in people enteric fever. After searching for relevant studies, they identified 26 studies involving 3033 patients. Their findings are summarized below.**

#### **What is enteric fever and how might fluoroquinolones work?**

Enteric fever is a common term for two similar clinical illnesses known individually as typhoid fever and paratyphoid fever. These 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. In left untreated some people can develop serious complications and can be fatal.

The fluoroquinolones are a large family of antibiotic drugs, which are commonly used for a variety of infectious diseases. In the past, enteric fever responded extremely well to fluoroquinolones, but drug resistance has become a major public health problem in many areas especially Asia.

#### **What the research says**

Effect of using fluoroquinolones:

Generally, fluoroquinolones are effective in typhoid.

Policy makers and clinicians will need to consider local antibiotic resistance when considering treatment options for enteric fever.

One relatively new fluoroquinolone, gatifloxacin, seems to remain effective in some regions where resistance to older fluoroquinolones has developed.