

# *Azithromycin for treating uncomplicated typhoid and paratyphoid fever: An updated systematic review and meta-analysis.*

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**Background:** Typhoid and paratyphoid fevers are potentially fatal and common infections in low- and middle-income countries. Presently, there is rising resistance to a wide range of available antimicrobial agents. It is unclear whether azithromycin is efficacious and safe for uncomplicated enteric fever in adults and children.

**Methods:** We searched the following databases up to 5th November 2018: Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library), MEDLINE, EMBASE and LILACS, conference proceedings and reference lists of articles. We included randomized and quasi-randomized controlled trials comparing azithromycin with other antibiotics or a combination of antibiotics for treating children and adults with culture or rapid diagnostic test confirmed uncomplicated enteric fever. Effectiveness was compared using clinical failure, microbiological failure, adverse events, fever clearance time, relapse and duration of hospitalization. Two authors assessed trial eligibility, risk of bias and extracted data independently. We combined data in meta-analyses and used risk ratios (RR) and mean differences where appropriate (MD), presenting both measures with 95% confidence intervals (CI). We assessed the certainty of the evidence using the GRADE approach.

**Results:** We included twelve trials involving 1146 participants. Ten were in Asia while two were in North Africa. The duration of treatment ranged from five to seven days and included participants with drug resistant organisms. Except for blinding, the overall risk of bias of included studies was low. Azithromycin versus Chloramphenicol: Azithromycin appeared to be equivalent for all outcomes, but we are uncertain of this effect Azithromycin versus Fluoroquinolones:

Compared with the fluoroquinolone ofloxacin, azithromycin probably significantly reduced clinical failures by 55% (RR 0.45, 95% CI 0.25 to 0.80, 279 participants, 4 trials, *moderate certainty evidence*). It may reduce fever clearance time by about 9.5h even in populations with high prevalence of multi drug resistant (MDR) and nalidixic acid resistant (NaR) strains of *S. typhi* but we are uncertain of that effect. However, it appeared to be of similar efficacy for the other outcomes. Azithromycin appeared to result in little to no difference in efficacy for all outcomes when compared to ciprofloxacin and gatifloxacin. Azithromycin versus Ceftriaxone: Azithromycin probably results in a large reduction in the relapse rate by as much as 87% compared with ceftriaxone (RR 0.13 95% CI 0.03 to 0.56, 294 participants, 4 trials, *moderate certainty evidence*). It was similar in efficacy for the other outcomes.

**Combination therapies:** There were no differences in outcomes when azithromycin was compared with a combination of azithromycin plus ofloxacin or cefixime (*low certainty evidence*).

**Adverse events:** There were few reported adverse events of which most were gastrointestinal in nature and self-limiting.

**Conclusions:** Azithromycin probably results in fewer clinical failures and relapses in populations infected with drug resistant *S. typhi* and *paratyphi* but demonstrated no difference for the other outcomes. Adverse events are few and self-limiting.

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