Fluoroquinolones for treating tuberculosis (Review)

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[Intervention Review]

Fluoroquinolones for treating tuberculosis

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ABSTRACT

Background

Fluoroquinolones are sometimes used to treat multiple-drug-resistant and drug-sensitive tuberculosis. The effects of fluoroquinolones in tuberculosis regimens need to be assessed.

Objectives

To assess fluoroquinolones as additional or substitute components to antituberculous drug regimens for drug-sensitive and drug-resistant tuberculosis.

Search methods

In July 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 3), MEDLINE, EMBASE, LILACS, Science Citation Index, Database of Russian Publications, and *meta*Register of Controlled Trials. We also scanned reference lists of all identified studies and contacted researchers.

Selection criteria

Randomized controlled trials of antituberculous regimens containing fluoroquinolones in people diagnosed with bacteriologically positive (sputum smear or culture) pulmonary tuberculosis.

Data collection and analysis

Two authors independently applied inclusion criteria, assessed the risk of bias in the trials, and extracted data. We used risk ratio (RR) for dichotomous data, mean difference (MD) for continuous data (both with 95% confidence intervals (CI)), and the random-effects model if we detected heterogeneity and it was appropriate to combine data.

Main results

Eleven trials (1514 participants) met the inclusion criteria. No statistically significant difference was found in trials substituting ciprofloxacin, ofloxacin or moxifloxacin for first-line drugs in relation to cure (416 participants, 3 trials), treatment failure (388 participants, 3 trials), or clinical or radiological improvement (216 participants, 2 trials). Substituting ciprofloxacin into first-line regimens in drug-sensitive tuberculosis led to a higher incidence of relapse (RR 7.17, 95% CI 1.33 to 38.58; 384 participants, 3 trials) and longer time to sputum culture conversion (MD 0.50 months, 95% CI 0.18 to 0.82; 168 participants, 1 trial), although this was

confined to HIV-positive participants. Substituting for ethambutol in first-line regimens led to a higher incidence of total number of adverse events (RR 1.34, 95% CI 1.05 to 1.72; 492 participants, 2 trials). Adding or substituting levofloxacin to basic regimens in drug-resistant areas had no effect. A comparison of sparfloxacin versus ofloxacin added to regimens showed no statistically significant difference in cure (184 participants, 2 trials), treatment failure (149 participants, 2 trials), or the total number of adverse events (253 participants, 3 trials).

Authors' conclusions

Only ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin and moxifloxacin have been tested in randomized controlled trials for treating tuberculosis. We cannot recommend ciprofloxacin in treating tuberculosis. Trials of newer fluoroquinolones for treating tuberculosis are needed and are ongoing. No difference has been demonstrated between sparfloxacin and ofloxacin in drug-resistant tuberculosis.

PLAIN LANGUAGE SUMMARY

Substituting or adding fluoroquinolones to established first-line antituberculous drug regimens gives no additional benefit or risks

Fluoroquinolones have antituberculous activity, but are not one of the standard antituberculous medicines. Ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, and moxifloxacin have been tested in randomized controlled trials. Ciprofloxacin should not be used as a substitute drug in the standard antituberculous regimen as more people with drug-sensitive tuberculosis had relapses and it took longer for them to be cured. However, it was no different in terms of cure or number of adverse events. Sparfloxacin was no better than ofloxacin when added to antituberculous regimens in drug-resistant tuberculosis. Further trials are warranted.

BACKGROUND

Tuberculosis is caused by *Mycobacterium tuberculosis.* It may be fatal if untreated or treated inappropriately; it causes more adult deaths each year than any other single infectious disease (Kochi 1991). Pulmonary tuberculosis is the commonest clinical presentation of tuberculosis, and sputum-positive cases are the most important sources of infection in the community (Grzybowski 1975). Since 2005 the global tuberculosis epidemic has been on the threshold of decline, yet the global incidence of tuberculosis has been growing slowly, and much faster in sub-Saharan Africa, East Mediterranean and South-East Asia regions (WHO 2007a). There were an estimated 8.8 million people who became sick with the disease in 2005 and 1.6 million tuberculosis deaths (WHO 2007a).

Multiple-drug-resistant tuberculosis (MDR-TB), defined as in vitro resistance to at least isoniazid and rifampicin, is impairing the effectiveness of standard treatments and may contribute to increased mortality (Pablos-Mendez 2002). It is common in some countries and threatens tuberculosis control efforts (Table 1), especially the former Soviet Union, where, for example, the rates of MDR-TB among 'newly enrolled' and 'non-responding' cases in prisons were 24.6% and 92.1%, respectively (Portaels 1999). In Mariinsk in the Russian Federation, the high rates of MDR-TB have been associated with failure rates of 23% to 50% among sputum smear-positive cases receiving fully supervised short-course treatment with first-line drugs (Portaels 1999). In the USA, 3.5% of strains were resistant to isoniazid and rifampicin at the time of the outbreak of tuberculosis in early 1990s (Reichman 1996).

The risk factors for MDR-TB are previous treatment or relapse, originating from MDR-TB areas, a history of imprisonment, homelessness, and HIV infection. Tuberculosis is a leading cause of death among HIV-positive people. In Africa, HIV is the single most important factor determining the increased incidence of tuberculosis since 1990 (WHO 2007b).

Treatment options

Effective pharmacological treatment of tuberculosis been available since the 1940s. The efficacy of regimens containing rifampicin and isoniazid is well established for treatment and prevention, even in HIV-positive people (Woldehanna 2004; WHO 2003). Cure rates with rifampicin-containing regimens for six to nine months can approach 100%, provided the disease is sensitive to the drugs, there is no additional co-morbidity (especially HIV infection), and the patients adhere to treatment (STS/BMRC 1981; Anon 1983; Kohno 1992). Cure of drug-sensitive tuberculosis is defined

as sputum culture or smear negative, or both, at eight weeks and at the end of the treatment period. If the in vitro sensitivities are not known, then it is defined as at least two consecutive negative sputum smears or cultures with no subsequent positive sputum smears or cultures. For proven MDR-TB, it is defined as having a consistent negative sputum culture for the last 12 months of treatment with a minimum of three consecutive negative cultures taken at least 30 days apart.

The first-line (or essential) antituberculous drugs are the most active agents with proven clinical efficacy that form the core of initial standardized treatment regimens. These are isoniazid, rifampicin, pyrazinamide, and ethambutol (Blumberg 2003; WHO 2003; WHO 2006; WHO 2007c). Streptomycin, although used less commonly, is also a first-line drug on the World Health Organization's (WHO's) list of essential antituberculous drugs (WHO 2006; WHO 2007c). The WHO recommends second-line antituberculous drugs for those with MDR-TB or people intolerant of first-line drugs (WHO 2003; WHO 2006). The treatment of MDR-TB is difficult due to numerous adverse effects of second-line drugs and an expensive treatment regimen that usually lasts for around two years. Therefore, strategies for effective treatment and prevention of MDR-TB are urgently required. There is no single prescription for treating MDR-TB; appropriate use of second-line drug treatment is the key issue (Pablos-Mendez 2002; WHO 2006). It is difficult to estimate the performance of different antituberculous regimens in HIV-related tuberculosis (El-Sadr 2001). Recent research has highlighted the potential of including fluoroquinolones (sparfloxacin, ofloxacin, levofloxacin, moxifloxacin, and gatifloxacin) in treatment regimens for TB/MDR-TB (Telzak 1999; Wei 2000; Ginsburg 2003; WHO 2006). Guidelines suggest using fluoroquinolones as second-line drugs for treating drug-resistant tuberculosis or as a substitute for first-line drugs in cases of intolerance (Gillespie 1998; Blumberg 2003; WHO 2003; WHO 2006).

Fluoroquinolones

Fluoroquinolones are fluorine-containing nalidixic acid derivatives characterized by broad-spectrum antimicrobial activity. They have been included in antituberculous regimens (particularly for MDR-TB) since the late 1980s, but the role of fluoroquinolones in tuberculosis treatment still remains controversial. There are research data suggesting added efficacy of fluoroquinolones in managing MDR-TB when combined with well-established regimens (Huang 2000; WHO 2006), and there is evidence that levofloxacin and ofloxacin have a pivotal role in MDR-TB regimens (Yew 2000; Yew 2003). However, conflicting data have accumulated suggesting a lack of increased efficacy when fluoroquinolones are included in antituberculous regimens (Kohno 1992; Kennedy 1996; El-Sadr 1998; Burman 2006). One study suggested that substituting ofloxacin for ethambutol in an established first-line antituberculous regimen may make it possible to shorten tuberculosis chemotherapy from six months to five or even four months (TRC 2002), but this study contained no concurrent, recognized short-course chemotherapy as a control.

The favourable combination of pharmacodynamic and pharmacokinetic characteristics of fluoroquinolones (Ginsburg 2003) may give the following benefits when added to antituberculous regimens.

- Add to the bactericidal and sterilizing effect of the combination therapy by inhibiting DNA-gyrase and increasing penetration into the infection loci.
- Improve adherence to treatment due to the potentially better safety profile as compared with the first-line drugs and by allowing shorter courses of antituberculous treatment.

On the other hand, fluoroquinolones also have the potential to do harm.

- Increase liver and central nervous system (CNS) toxicity of antituberculous drugs (Yew 2001) and cause clinically significant drug interactions with antituberculous (Yew 2001), anti-HIV (Burman 1999), and other drugs, resulting in reduced efficacy and potential toxicity (WHO 2006).
- Cause additional adverse drug reactions, such as musculoskeletal damage, gastrointestinal problems (pseudomembranous colitis), cardiac arrhythmias, infections from fungi or bacteria, psychosis, and convulsions (Martindale 1996).
- Induce resistance in *M. tuberculosis* (Alangaden 1997; Jacobs 1999; Wang 2006), which may become cross-resistant to all the representatives of the fluoroquinolone class (Ginsburg 2003).

The problem of resistance to fluoroquinolones is further complicated by the broad indications of this class of antimicrobials in treatment of various lower respiratory tract and other infections. This may at least be partially responsible for the rising resistance rates among *M. tuberculosis* strains to fluoroquinolones (Ginsburg 2003). Retrospective studies have shown that empiric antituberculous treatment with fluoroquinolones or fluoroquinolone use for misdiagnosed pneumonia delayed diagnosis of tuberculosis in an endemic area and impaired outcomes (Yoon 2005; Wang 2006). *M. tuberculosis* isolates acquired ofloxacin resistance within one week (Wang 2006).

In the light of the above uncertainties, we have conducted a systematic review of trials of fluoroquinolones in people with tuberculosis. These drugs are likely to be used as substitutes for existing drugs or as an addition to current treatment regimens. This review examines the benefits and harms of their use with these two approaches.

OBJECTIVES

To assess fluoroquinolones as additional or substitute components to antituberculous drug regimens for drug-sensitive and drug-resistant tuberculosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

People diagnosed with bacteriologically positive (sputum smear or culture) pulmonary tuberculosis. Both drug-sensitive and drug-resistant tuberculosis are included.

Types of interventions

Intervention

Antituberculous regimens containing fluoroquinolones.

Control

Other antituberculous regimens (not containing fluoroquinolones, or containing different fluoroquinolone doses or other fluoroquinolones).

Types of outcome measures

Primary

- Cure. *For drug-sensitive tuberculosis (or where in vitro sensitivities are not known)*: sputum culture and/or smear negative at eight weeks and at the end of treatment period (at least two consecutive negative smears or cultures with no subsequent positive smears or cultures). *For participants with proven MDR-TB*: consistent negative sputum culture for the last 12 months of treatment with a minimum of three consecutive negative cultures taken at least 30 days apart.
- Treatment failure, defined as continued or recurrent positive sputum cultures after four months of treatment in participants in whom medication ingestion was assured. *For proven MDR-TB participants*: more than one positive culture in the last 12 months of treatment.

Secondary

- Relapse, defined as becoming sputum smear or culture positive within a year of being culture negative while receiving or having completed therapy; or signs of clinical or radiographic deterioration consistent with active tuberculosis.
- Time to cure, defined as a continuous outcome providing an estimate of time in weeks or months needed to achieve cure.
- Time to sputum culture or smear conversion, defined as a continuous outcome providing an estimate of time in weeks or months needed to achieve the first negative sputum culture.
- Clinical or radiological improvement at eight weeks and at the end of the treatment period.
- Death (from any cause, tuberculosis-related).

Adverse events and effects

- Serious adverse events, defined as fatal, life-threatening, requiring hospitalization, or change of treatment regimen.
- Adverse effects specifically associated with fluoroquinolones (eg tendon rupture).
- Total number of adverse events.

Search methods for identification of studies

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

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group's Specialized Register (July 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 3); MEDLINE (1966 to July 2007); EMBASE (1974 to July 2007); LILACS (1982 to July 2007); Science Citation Index (1940 to July 2007); and the Database of Russian Publications (1988 to July 2007). We also searched the *meta*Register of Controlled Trials (July 2007) using the following search terms: tuberculosis AND (fluoroquinolones OR moxiflacin OR ofloxacin OR gatifloxacin OR levofloxacin OR ciprofloxacin).

Conference proceedings

We searched the following conference proceedings for relevant abstracts: 4^{th} World Congress on TB, Washington, DC, USA, 3 to 5 June 2002 (published in *Tubercle*); International Union Against Tuberculosis Lung Disease (IUATLD) Annual Conference Proceedings (published in the *International Journal of Tuberculosis and Lung Disease* 1997 to 2007); American Thoracic Society Meetings Proceedings 2001 to 2007; and the British Society for Antimicrobial Therapy 2000 to 2007.

Researchers, organizations, and pharmaceutical companies

For the original review (Ziganshina 2005), we searched the current controlled trials website and contacted individual researchers working in the field, organizations (Centers for Disease Control and Prevention, the Clinical Trials Unit of the International Union against Tuberculosis and Lung Disease (IUATLD), and the UK Medical Research Council Clinical Trials Unit), and pharmaceutical companies (Bayer, Merck Sharp & Dohme, Hoechst Marion Roussel, and Aventis Pharma) for unpublished and ongoing trials.

Reference lists

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

Data collection and analysis

Selection of studies

We checked the citations and their abstracts to establish their relevance and obtained the full article if we agreed it was relevant and in cases of uncertainty. We independently applied the inclusion criteria using an eligibility form and resolved any disagreements by discussing them. Finally, where we were still unsure if the study should be included because further information was necessary, we allocated the study to the list of those awaiting assessment and then attempted to contact the study authors for clarification. We excluded studies that did not meet the inclusion criteria and gave the reason for exclusion in the 'Characteristics of excluded studies'.

Data extraction and management

We independently extracted data on trial methods, participants, interventions, and outcomes using a standardized data extraction form. We resolved any differences in the extracted data by referring to the original articles and through discussion. Where data were insufficient or missing we attempted to contact the trial authors for additional information.

For binary outcomes, we extracted the number of participants with the event in each group. For continuous outcomes, we used the arithmetic means and standard deviations for each group. If geometric means were used in the trial report, we would have extracted standard deviations on the log scale. Where possible, we extracted data to allow an intention-to-treat analysis (including all the participants in the groups to which they were originally randomly allocated). We calculated the percentage loss to follow up and presented it in the 'Characteristics of included studies' when the numbers randomized and the numbers analysed were inconsistent.

Assessment of risk of bias in included studies

We independently evaluated the risk of bias in the trials by classifying the generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear according to Jüni 2001, considering the inclusion of all randomized participants in the final analysis to be adequate if it was more than 90%, and stating whether the trial was open or who was blinded to the intervention. We presented the results of the risk of bias assessment in a table.

Data synthesis

We used Review Manager 5 to analyse the data, and grouped the trials to those that substituted or added fluoroquinolones to the basic antituberculous regimens. We used risk ratio (RR) as a measure of effect for binary outcomes, and mean difference (MD) for continuous data, and presented both with 95% confidence intervals (CI). We tested for homogeneity of effect sizes between the trials using the chi-squared test for heterogeneity. When heterogeneity was present ($P < 0.1$), and the number of trials permitted, we investigated it using HIV status (positive versus known HIV negative) in a subgroup analysis. Where we detected heterogeneity, and it was still appropriate to pool data, we used the random-effects model.

We were unable to use some methods described in the protocol because they were not possible with the available trials or because of variations in the outcome measures, but we intend to use these methods, described in Appendix 2, in future updates.

RESULTS

Description of studies

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

Trial selection

We identified 42 potentially relevant articles of which 12 (reporting on 11 different trials) met our inclusion criteria (*see* 'Characteristics of included studies'). Two studies are awaiting assessment for inclusion in the review because we are attempting to obtain the data that were originally presented at a conference and remain unpublished (Abdullah 1997; Abdullah 1998). We have detailed the reasons for excluding the remaining 28 studies in the 'Characteristics of excluded studies'. There are eight ongoing studies (*see* 'Characteristics of ongoing studies').

Participants

The 11 trials included 1514 participants with a range of 20 to over 300 per trial. The participants were aged 13 years or older (mean age 39.54 years), and in one trial, Saigal 2001, ranged between eight and 63 years. Sixty-seven per cent were male with a range of 45% to 81% across trials.

Three trials included only individuals who had bacteriologically proven MDR-TB (Huang 2000; Sun 2000; Ji 2001), one trial involved only drug-sensitive participants (Kennedy 1996), and three trials included both drug-resistant and drug-sensitive individuals as one group (El-Sadr 1998; Lu 2000; Burman 2006). The remaining trials did not report on drug sensitivity.

Four trials included both HIV-positive and HIV-negative participants as one group (Kennedy 1993; Kennedy 1996; El-Sadr 1998; Burman 2006), although one also stratified the analysis by HIV status (Kennedy 1996). Four trials involved participants presumed to be HIV-negative according to local endemicity, reference data, and exclusion criteria (Mohanty 1993; Huang 2000; Lu 2000; Sun 2000). The remaining three trials did not report on HIV status.

Location and follow up

Trials were conducted in China (four trials), Japan (one trial), Tanzania (three trials), North America and Africa (one trial), and the USA (one trial). The mean duration of follow up ranged from eight weeks to 21 months.

Interventions

1. Fluoroquinolone (ciprofloxacin, ofloxacin, or moxifloxacin) substituted into regimen

Six trials compared ciprofloxacin, ofloxacin, or moxifloxacin substituted for first-line antituberculous drugs (rifampicin, ethambutol, or pyrazinamide plus ethambutol) in combination therapy with an established antituberculous drug regimen (Kohno 1992; Kennedy 1993; Mohanty 1993; Kennedy 1996; Saigal 2001; Burman 2006).

2. Fluoroquinolone (levofloxacin) added to regimen

One trial compared levofloxacin added to an established antituberculous regimen with that regimen (El-Sadr 1998).

3. Comparison of fluoroquinolones (levofloxacin versus ofloxacin) substituted into regimen

One trial compared levofloxacin with ofloxacin, each substituting for rifampicin in antituberculous first-line and second-line regimens (Lu 2000).

4. Comparison of fluoroquinolones (sparfloxacin versus ofloxacin) added to regimens

Three trials compared sparfloxacin with ofloxacin when they were each added to various isoniazid and rifampicin-containing antituberculous regimens (Huang 2000; Sun 2000; Ji 2001).

The trials used different daily oral doses of levofloxacin (300 mg or 500 mg) and ofloxacin (200 mg, 600 mg, or 800 mg (16 mg/kg)) but the same doses of sparfloxacin (400 mg) and ciprofloxacin (750 mg) for both the initiation and continuation phases. Burman 2006 used 400 mg of moxifloxacin for the initiation phase. The treatment doses of standard antituberculous drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, prothionamide, thioacetazone, and streptomycin) varied among the trials. All of the included trials ensured the adherence of participants by administering the drugs under direct observation with special nursing facilities in outpatient settings or in hospital settings.

Outcomes

None of the trials reported on all eight outcome measures chosen for this review. The reported outcomes included cure (seven trials), treatment failure (five trials), relapse (three trials), time to sputum culture or smear conversion (two trials), clinical or radiological improvement (seven trials), death (one trial), serious adverse events (four trials), and total adverse events (five trials). None of the trials reported on time to cure or fluoroquinolone-specific adverse effects.

Risk of bias in included studies

See Table 2 for details of individual trials.

The methods used to generate the allocation sequence and to conceal allocation were adequate in one trial (Kennedy 1996), adequate only for the allocation sequence in three trials (El-Sadr 1998; Lu 2000; Saigal 2001), and unclear in the other trials. One trial blinded the providers, participants, and radiograph assessor (Mohanty 1993), two trials blinded the assessors (El-Sadr 1998; Kennedy 1996), and one trial blinded the participants (Lu 2000). Two trials used no blinding (Kennedy 1993; Saigal 2001), and blinding in the remaining five trials was unclear (one was described as "open"). All but Mohanty 1993 and Burman 2006 included more than 90% of the randomized participants in the final analysis (three had no losses to follow up), which we considered adequate.

Effects of interventions

1. Fluoroquinolone substituted into regimen (6 trials)

Five trials used one of the two older fluoroquinolones ciprofloxacin or ofloxacin (Kohno 1992; Mohanty 1993; Kennedy 1993;

Kennedy 1996; Saigal 2001), and one trial used moxifloxacin in the initiation phase (Burman 2006). Saigal 2001 trial looked at the safety of ofloxacin substituting for rifampicin in participants with chronic liver disease.

1.1. Cure (sputum culture conversion at 8 weeks)

Fluoroquinolone substitution did not have an effect on cure (416 participants, 3 trials, Analysis 1.1). The heterogeneity observed in the original version of the review (Ziganshina 2005) and tentatively attributed to the differences in drug substitutions (ciprofloxacin for ethambutol plus pyrazinamide in Kennedy 1996 and for rifampicin in Mohanty 1993) and differences in the basic antituberculous regimen, including streptomycin in the Mohanty 1993, disappeared with the addition of the results of the Burman 2006 trial (moxifloxacin for ethambutol).

1.2. Treatment failure at 12 months

We found no statistically significant difference between the regimens (388 participants, 3 trials, Analysis 1.2).

1.3. Relapse

Substituting with ciprofloxacin or ofloxacin was associated with a higher incidence of relapse (RR 7.17, 95% CI 1.33 to 38.58; 384 participants, 3 trials, Analysis 1.3). Kennedy 1996, which substituted ciprofloxacin for pyrazinamide plus ethambutol in participants with drug-sensitive tuberculosis, stratified the results according to HIV status. The risk ratio was not statistically significantly different for HIV-positive or HIV-negative participants (Analysis 1.4).

1.4. Time to sputum culture conversion

Overall, time to sputum culture conversion was longer in the substitution group in Kennedy 1996 (MD 0.50 months, 95% CI 0.18 to 0.82; 168 participants, 1 trial, Analysis 1.5).
We assessed the influence of HIV status on this outcome with the limited data stratified by HIV-status, as provided by the trial authors. The trial compared substitution with ciprofloxacin for pyrazinamide plus ethambutol in drug-sensitive areas and in participants with fully sensitive tuberculosis. For HIV-positive participants the mean difference was 1.20 months (95% CI 0.67 to 1.73; 55 participants, 1 trial, Analysis 1.6) and for HIV-negative participants it was 0.20 months (95% CI -0.10 to 0.50; 101 participants, 1 trial, Analysis 1.6).

1.5. Clinical or radiological improvement at 8 weeks

The trials did not demonstrate a statistically significant difference between the groups (216 participants, 2 trials, Analysis 1.7). We could explain the statistically significant heterogeneity by the different drugs used in the substitution, the difference in the basic antituberculous regimens (Mohanty 1993 used streptomycin), or by the loss of more than 10% of the participants to follow up in Kohno 1992.

1.6. Serious adverse events

We found no demonstrable difference in the number of serious adverse events (743 participants, 5 trials, Analysis 1.8). The events included nausea and vomiting, severe anaemia, conjunctivitis, pruritic rash, convulsions including one HIV-positive participant in the ciprofloxacin group in Kennedy 1993 who subsequently died, and hepatotoxicity in four participants with chronic liver disease that manifested with nausea, anorexia, malaise, and jaundice (Saigal 2001; rifampicin group). One participant died in the moxifloxacin group in Burman 2006; the authors attributed the death to pulmonary embolism unrelated to antituberculous treatment.

1.7. Total number of adverse events

We calculated the total number of adverse events in Burman 2006 by summing up the numbers of the listed adverse events for each group; we excluded death, hospitalization, and selected symptoms (any grade) from this calculation to avoid double summation of the same event. Overall we did not detect a statistically significant difference between the groups, or heterogeneity (712 participants, 4 trials, Analysis 1.9). These adverse events included fever, rash, gastrointestinal disturbance, hepatotoxicity, arthralgia, vision change, giddiness, and serious adverse events. We subgrouped the results by fluoroquinolone substitutions for ethambutol and found that they – moxifloxacin in Burman 2006 and ofloxacin in Kohno 1992 – resulted in a greater number of adverse events (RR 1.34, 95% CI 1.05 to 1.72; 492 participants, 2 trials, Analysis 1.10).

2. Fluoroquinolone added to regimen

El-Sadr 1998 compared levofloxacin (a newer fluoroquinolone) added to and compared with the standard combination of isoniazid, rifampicin, pyrazinamide, and ethambutol for two months of the induction phase in participants suspected to have HIV in drug-resistant areas. This trial, with 174 participants, provided data for six of the review outcomes. It did not demonstrate a difference in terms of cure (sputum culture conversion at eight weeks (Analysis 2.1), treatment failure at 12 months (Analysis 2.2), clinical or radiological improvement at eight weeks (Analysis 2.3), death from any cause (Analysis 2.4), tuberculosis-related death (Analysis 2.5), or serious adverse events (Analysis 2.6).

3. Comparison of fluoroquinolones (levofloxacin versus ofloxacin) substituted into regimen

Lu 2000, which included 144 participants with presumed MDR-TB, compared levofloxacin with ofloxacin, each substituting for rifampicin in both phases of antituberculous treatment as well as in the retreatment regimen for presumed drug-resistant tuberculosis. The basic regimen included isoniazid, ethambutol, pyrazinamide, and thioacetazone given daily. The trial did not detect a statistically significant difference in cure (sputum culture conversion within two to three weeks,Analysis 3.1), treatment failure at 12 months (Analysis 3.2), clinical or radiological improvement at eight weeks (Analysis 3.3), or the total number of adverse events (Analysis 3.4).

4. Comparison of fluoroquinolones (sparfloxacin versus ofloxacin) added to regimens

The three trials that compared newer fluoroquinolones with older fluoroquinolones were all conducted in China and published in and after the year 2000 (Huang 2000; Sun 2000; Ji 2001). They compared sparfloxacin and ofloxacin added to basic regimens (containing isoniazid and rifampicin) in participants with proven or presumed MDR-TB.

4.1. Cure (sputum culture conversion within 2 to 3 weeks)

The trials showed quite different results, with higher cure rates with sparfloxacin in Huang 2000 but little difference in numbers cured in Sun 2000 (184 participants, 2 trials, Analysis 4.1). The reason for the difference may be due to the difference in the basic drug regimens.

4.2. Treatment failure at 12 months

We detected no statistically significant difference, although there were fewer failures in the sparfloxacin group (149 participants, 2 trials, Analysis 4.2).

4.3. Clinical or radiological improvement at 8 weeks

We found no statistically significant difference between the sparfloxacin and ofloxacin groups (333 participants, 3 trials, Analysis 4.3).

4.4. Total number of adverse events

We found no statistically significant difference in the total number of adverse events (253 participants, 3 trials, Analysis 4.4).

DISCUSSION

Despite inherent difficulties around methodology, drug regimens, and implementation in comparisons of fluoroquinolones for treating tuberculosis (Ginsburg 2003), methodologically sound randomized controlled trials are beginning to emerge. Current treatment guidelines have been formulated by expert opinion, and those on fluoroquinolone use have been guided by experimental and retrospective clinical studies (WHO 2006). We undertook this systematic review to provide quantified information and chose clinical outcome measures relevant to the overall healthcare burden of tuberculosis and avoided surrogate measures, such as early bactericidal activity (EBA).

Ten small trials and one large trial of moxifloxacin in the initiation phase (Burman 2006) with 1514 participants met the inclusion criteria. Only two of the trials were of high quality with adequate generation of allocation sequence and allocation concealment (Kennedy 1996; El-Sadr 1998). Most of the trials were conducted in low-income and middle-income countries, which means the results of this review are likely to be applicable to the situations where the burden of tuberculosis is high and new revised treatment strategies are most needed.

Fluoroquinolones in drug-sensitive tuberculosis

The results provide clear evidence for the lack of equivalence in terms of relapse and time to sputum culture conversion when older fluoroquinolones (ciprofloxacin or ofloxacin) are substituted into and compared with first-line antituberculous regimens (rifampicin, ethambutol, or pyrazinamide plus ethambutol). These results are consistent with a note to the Editor of *Chest* of stressing that ciprofloxacin is not a component of first-line treatment of tuberculosis (O'Brien 1994). They also agree with the results of the trials that explored early bactericidal activity in the first two days of ciprofloxacin treatment and showed less activity of ciprofloxacin compared with rifampicin and isoniazid (Sirgel 1997; Sirgel 2000). At the same time we did not find evidence for a difference in cure rate (sputum culture conversion at eight weeks), clinical or radiological improvement, or the number of serious adverse events.

Fluoroquinolones in drug-resistant tuberculosis

Although retrospective clinical studies have shown effectiveness of fluoroquinolones (levofloxacin and ofloxacin) in MDR-TB (Yew 2000; Yew 2003; Chan 2004), the one randomized controlled trial in this review that evaluated a fluoroquinolone (levofloxacin) added to a first-line regimen in areas with drug resistance found no statistically significant difference in outcomes when compared with a standard antituberculous combination (El-Sadr 1998). This was a small trial, and more prospective randomized controlled trials that compare levofloxacin, ofloxacin, and other newer fluo-

roquinolones with second-line antituberculous drugs for treating MDR-TB are essential.

All other trials in drug-resistant tuberculosis compared different fluoroquinolones substituted into or added to regimens. One trial compared levofloxacin and ofloxacin substituted for rifampicin (Lu 2000). It included participants undergoing treatment or re-treatment for drug-resistant or drug-sensitive tuberculosis and did not provide evidence for superiority in effect of levofloxacin over ofloxacin. Three trials compared sparfloxacin with ofloxacin added to regimens containing isoniazid and rifampicin in participants with proven or presumed MDR-TB. Overall there was no statistically significant difference in terms of cure and reduced treatment failure rate in the two trials reporting on these outcomes.

Levofloxacin, sparfloxacin, and moxifloxacin are new fluoroquinolones characterized by more favourable pharmacodynamic and pharmacokinetic profiles in terms of lower minimum inhibitory concentrations (MICs) against *M. tuberculosis* and a better value for the area under the inhibitory concentration time curve over 24 hours (AUC24/MIC) than ciprofloxacin and ofloxacin. These pharmacological advantages might be translated into improved clinical outcomes, but further trials need to investigate this.

HIV co-infection

HIV increases the risk of rapid progression of tuberculosis (Daley 1992; Shafer 1995), and tuberculosis is the most common cause of death in HIV-positive adults in low-income and middle-income countries (Corbett 2003). Only one trial stratified data by HIV status (Kennedy 1996). It tested ciprofloxacin substituted into first-line regimens for drug-sensitive tuberculosis and reported that the time to sputum culture conversion was longer in HIV-positive participants. There is an urgent need to determine the most appropriate antituberculous regimens for HIV-positive people and for further trials to explore the role of fluoroquinolones in these regimens.

Adverse events and effects

None of the trials reported on fluoroquinolone-specific adverse effects, such as tendon rupture, but they did report the number of adverse events, including those considered serious enough to discontinue or change treatment. The fluoroquinolones did not increase the incidence of serious adverse events. Substitutions for ethambutol in first-line basic regimens with ofloxacin or moxifloxacin resulted in higher total numbers of adverse events. When newer fluoroquinolones were compared with older ones, there seemed to be a favourable trend in favour of the newer drugs.

AUTHORS' CONCLUSIONS

Implications for practice

Five fluoroquinolones – ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, and moxifloxacin – have been tested in randomized controlled trials for treating tuberculosis. In drug-sensitive tuberculosis, ciprofloxacin increased the relapse rate and time to cure when substituted into first-line regimens, but it showed no difference in terms of number of participants cured at the end of the treatment and number of adverse events. We cannot recommend it as an equivalent first-line drug substitute. No randomized controlled trials have looked at substituting newer fluoroquinolones for second-line drugs in drug-resistant tuberculosis. No difference has been demonstrated between sparfloxacin and ofloxacin in drug-resistant tuberculosis.

Implications for research

New trials looking at the effects and safety of fluoroquinolones that stratify results by drug resistance and HIV status are urgently needed. New trials evaluating the effects of fluoroquinolones substituted for second-line antituberculous drugs in drug-resistant tuberculosis are warranted. Further new trials comparing different dose regimens of fluoroquinolones substituted into or added to established antituberculous schedules could help in developing the optimal recommendations in treating tuberculosis. Future trials should include analyses of correlations between microbiological data, such as early bactericidal activity (EBA), and clinical outcomes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Burman 2006

Methods	Multicentre randomized controlled trial Generation of allocation sequence: randomized in a factorial design; continent and pulmonary cavitation are stratification factors Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the final analysis: 59/336 (17.6%) excluded from final analysis Mean duration of follow up: 8 weeks
Participants	Number: 336 randomized; 277 evaluated Inclusion criteria: aged 18 years or older with suspected pulmonary tuberculosis and acid-fast bacilli in an expectorated sputum sample Exclusion criteria: history of > 7 days of a fluoroquinolone antibiotic or tuberculosis treatment within the previous 6 months; pregnancy or breastfeeding; initial sputum cultures negative for *Mycobacterium tuberculosis* or resistance to rifampicin, fluoroquinolones, or pyrazinamide (patients whose isolates were resistant to isoniazid were included)
Interventions	Fluoroquinolone (moxifloxacin) substituted into regimen (replacing ethambutol) for 2 months (8 weeks), initial 2 weeks of daily therapy 1. Moxifloxacin (400 mg daily) orally plus basic regimen (5 days a week or thrice a week for both dosing regimens) for 2 months 2. Ethambutol (0.8 g - 40 to 55 kg; 1.2 g - 56 to 75 kg; 1.6 g - 76 to 90 kg) daily orally 5 days a week OR (1.2 g - 40 to 55 kg; 2 g - 56 to 75 kg; 2.4g - 76 to 90 kg) thrice weekly for 2 months plus basic regimen Basic regimen: Isoniazid (300 mg), rifampicin (450 mg if ≤ 45 kg; 600 mg if > 45 kg), and pyrazinamide (1 g - 40 to 55 kg; 1.5 g - 56 to 75 kg; 2 g - 76 to 90 kg) given orally 5 days a week for 2 months; or Isoniazid (15 mg/kg, max dose 900 mg), rifampicin (450 mg if ≤ 45 kg; 600 mg if > 45 kg), and pyrazinamide (1.5 g - 40 to 55 kg; 2.5 g - 56 to 75 kg; 3 g - 76 to 90 kg) given thrice weekly orally for 2 months
Outcomes	1. Cure (sputum culture negative at 8 weeks) 2. Adverse events 3. Serious adverse events 4. Total number of adverse events (calculated by review authors by summing up reported adverse events)
Notes	Location: Canada, South Africa, Uganda, USA Human immunodeficiency virus (HIV) status: HIV-positive participants (30/169 randomized - study group, 30/167 randomized - control group) Drug-resistance status: isoniazid resistance (15/169 randomized - study group, 10/167 randomized - control group) ; 11 participants with resistance to rifampicin, fluoroquinolone or pyrazinamide - excluded from analysis

El-Sadr 1998

Methods	Multicentre randomized controlled trial Generation of allocation sequence: centrally randomized with stratified permuted block randomization; the research unit is a stratification factor Allocation concealment: unclear Blinding: assessors only Inclusion of all randomized participants in the final analysis: adequate for 8 weeks; 39% lost to follow up in continuation phase Mean duration of follow up: 12 months
Participants	Number: 174 randomized; 101 evaluated Inclusion criteria: suspected human immunodeficiency virus (HIV) and pulmonary tuberculosis; age > 18 years in resistant areas or > 13 years in other areas; aspartate aminotransferase (AST) $\leq$ 10 times upper limit; serum bilirubin < 2.5 times upper limit; serum creatinine $\leq$ 3 times upper limit or creatinine clearance rate $\geq$ 50 mL/min Exclusion criteria: history of multiple-drug-resistant tuberculosis (MDR-TB) or close contact with an MDR-TB patient; > 3 weeks continuous antituberculous treatment immediately prior to enrolment; > 12 weeks antituberculous therapy in the past 2 years; pregnancy; exclusively extrapulmonary tuberculosis
Interventions	Fluoroquinolone (levofloxacin) added to regimen 1. Levofloxacin plus standard regimen 500 mg levofloxacin daily for 2 weeks (induction phase); then 750 mg levofloxacin thrice weekly for 6 weeks; then standard regimen only (continuation phase) 2. Standard regimen Induction phase (2 weeks daily): isoniazid (300 mg), vitamin B6 (50 mg), rifampicin (450 to 600 mg; < 50 to > 50 kg), pyrazinamide (1.5 to 2.0 g; < 50 to > 50 kg), ethambutol (20 mg/kg; rounded to the nearest 400 mg) 6 weeks (thrice weekly): isoniazid (600 to 900 mg; < 50 to > 50 kg), vitamin B6 (50 mg), rifampicin (600 mg), pyrazinamide (2.0 to 2.5 g; < 50 to > 50 kg), ethambutol (30 mg/kg; rounded to the nearest 400 mg) Continuation phase lasting 6 or 9 months (18 or 31 weeks of total therapy) (twice weekly): isoniazid (600 to 900 mg; < 50 to > 50 kg), vitamin B6 (50 mg), rifampicin (600 mg)
Outcomes	1. Cure (sputum culture negative at 8 weeks and at the end of treatment period; at least 2 consecutive negative cultures with no subsequent positive cultures) 2. Treatment failure (sputum smear positive at 8 weeks) 3. Death (from any cause) 4. Death (tuberculosis-related) 5. Clinical or radiological improvement 6. Serious adverse events
Notes	Location: USA HIV status: suspected HIV-positive participants (separate data not provided) Drug-resistance status: resistant areas

Huang 2000

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the final analysis: no losses Mean duration of follow up: 12 months
Participants	Number: 104 randomized and evaluated Inclusion criteria: multiple-drug-resistant tuberculosis (MDR-TB) patients with positive sputum smear after 1 year conventional antituberculous treatment; sputum culture showing growth of mycobacterium with multiple resistance to at least 2 of streptomycin, isoniazid, rifampicin, pyrazinamide, or ethambutol; no history of allergy to fluoroquinolone; age 16 to 75 years Exclusion criteria: heart, liver or kidney dysfunction, and diabetes
Interventions	Comparison of different fluoroquinolones (sparfloxacin versus ofloxacin) added to regimen 1. Sparfloxacin (0.2 twice daily) plus standard regimen 2. Ofloxacin (0.3 twice daily) plus standard regimen Standard regimen: isoniazid (0.3 g), rifampicin (0.45 g), ethambutol (0.75 g), pyrazinamide (1.5 g), streptomycin (0.75 g intramuscularly)
Outcomes	1. Sputum smear or culture conversion 2. Clinical or radiological improvement 3. Total number of adverse events
Notes	Location: China Human immunodeficiency virus (HIV) status: presumed HIV negative Drug-resistance status: MDR-TB

Ji 2001

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the final analysis: no losses to follow up Mean duration of follow up: 12 months
Participants	Number: 69 randomized (2 new cases; 67 retreatment cases); 69 evaluated Inclusion criteria: multiple-drug-resistant tuberculosis (MDR-TB); sputum-positive (not reported if culture or smear) inpatients; age 18 to 70 years; new and retreatment cases Exclusion criteria: not reported
Interventions	Comparison of different fluoroquinolones (sparfloxacin versus ofloxacin) added to regimen 1. Sparfloxacin (200 mg/day orally for 2 months) plus standard regimen 2. Ofloxacin (200 mg/day orally for 2 months) plus standard regimen Standard regimen: isoniazid (0.3 g), pyrazinamide (1.5 g)

Ji 2001 (*Continued*)

Outcomes	1. Treatment failure 2. Clinical or radiological improvement and sputum conversion 3. Total number of adverse events
Notes	Location: China Human immunodeficiency virus (HIV) status: not reported Drug-resistance status: MDR-TB

Kennedy 1993

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: none Inclusion of all randomized participants in the final analysis: 95.6% included in analysis; 7 (4.4%) excluded Mean duration of follow up: 6 months
Participants	Number: 160 randomized; 153 evaluated Inclusion criteria: "presented with pulmonary TB"; new cases; age > 18 years Exclusion criteria: severe renal, hepatic, or cardiovascular disease
Interventions	Fluoroquinolone (ciprofloxacin) substituted into regimen (replacing pyrazinamide and ethambutol) 1. Ciprofloxacin (750 mg; for the first 4 months) plus basic regimen 2. Pyrazinamide (25 mg/kg; daily for the first 4 months) and ethambutol (15 mg/kg; daily for the first 2 months) plus basic regimen Basic regimen (daily orally for 6 months): isoniazid (300 mg) and rifampicin (600 mg)
Outcomes	1. Treatment failure 2. Serious adverse events 3. Adverse events 4. Total number of adverse events
Notes	Location: Tanzania Human immunodeficiency virus (HIV) status: 37% to 40% HIV-positive Drug-resistance status: presumed sensitive

Kennedy 1996

Methods	Randomized controlled trial Generation of allocation sequence: centrally randomized by computer generated allocation sequence in block size of 10 patients Allocation concealment: sealed, opaque envelopes Blinding: only assessors Inclusion of all randomized participants in the final analysis: 6 (9%) lost to follow up Mean duration of follow up: 12 months (6 months after cessation of the 6 months' therapy)
Participants	Number: 200 randomized Inclusion criteria: acid-fast bacilli present in the sputum on direct fluorescent microscopy Exclusion criteria: history of treatment of tuberculosis or other exposures to any of the study drugs; sputum cultures positive for mycobacteria other than Mycobacterium tuberculosis; isolates of *M. tuberculosis* resistant to any of the study drugs; severe renal, hepatic, or cardiovascular disease; pregnancy or lactation; history of adverse reaction to any of the study drugs; epilepsy, concomitant treatment with theophylline; severe tuberculosis unlikely to survive
Interventions	Fluoroquinolone (ciprofloxacin) substituted into regimen (replacing pyrazinamide and ethambutol) 1. Ciprofloxacin (750 mg; for the first 4 months) plus basic regimen 2. Pyrazinamide (25 mg/kg; daily for the first 4 months) and ethambutol (15 mg/kg; daily for the first 2 months) plus basic regimen Basic regimen (daily for 6 months): isoniazid (300 mg) and rifampicin (600 mg)
Outcomes	1. Treatment failure (clinical at 12 months) 2. Relapse (sputum culture-proven relapse during a 6-month follow-up period after the completion of the 6 months' treatment regimen) 3. Sputum smear conversion (time (months) to first negative results) 4. Sputum culture conversion (time (months) to first negative results) 5. Sputum culture negative at 4 weeks 6. Sputum culture negative at 8 weeks 7. Number of weeks sputum culture negative by the end of trial (8 weeks)
Notes	Location: Tanzania Human immunodeficiency virus (HIV) status: data stratified by HIV status Drug-resistance status: fully drug-sensitive tuberculosis A preliminary report on 20 participants with 8 weeks of follow up (no losses) that provided information on outcomes (5), (6), and (7) was published in 1993

Kohno 1992

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the final analysis: 32 (20% 25%) lost to follow up Mean duration of follow up: 12 months
Participants	Number: 156 randomized; 124 evaluated Inclusion criteria: inpatients previously untreated; sputum smear-positive or culture-positive pulmonary tuberculosis, age > 15 years (range 15 to 81 years)

Kohno 1992 (*Continued*)

	Exclusion criteria: not reported
Interventions	Fluoroquinolone (ofloxacin) substituted into regimen (replacing ethambutol) 1. Ofloxacin (600 mg for the initial 2 months; 300 mg for the following 7 months) plus basic regimen 2. Ethambutol (1 g) plus basic regimen Basic regimen (orally, daily for 9 months): isoniazid (300 mg), rifampicin (600 mg)
Outcomes	1. Relapse (12 months after cessation of therapy) 2. Radiological improvement
Notes	Location: Nagasaki, Japan Human immunodeficiency virus (HIV) and drug-resistance status: not reported

Lu 2000

Methods	Randomized controlled trial Generation of allocation sequence: random-number table Allocation concealment: unclear Blinding: participants blinded; unclear if providers and assessors blinded Inclusion of all randomized participants in the final analysis: 6/144 (4.167%) lost to follow up Mean duration of follow up: 6 months
Participants	Number: 144 randomized; 138 evaluated Inclusion criteria: sputum smear positive and x-ray confirmed pulmonary tuberculosis, including newly diagnosed (antituberculous treatment $\leq$ 1 month) or retreatment pulmonary tuberculosis (treatment failure, or after completion of routine chemotherapy with rifampicin or ethambutol for < 6 months, or pyrazinamide < 3 months; or patients relapsed, but never use of fluoroquinolone-resistant and fluoroquinolone-sensitive cases); age 15 to 70 years; body weight > 40 kg Exclusion criteria: pregnancy; severe heart, liver, or kidney diseases; other severe complications
Interventions	Comparison of different fluoroquinolones (levofloxacin versus ofloxacin) added to regimen 1. Intervention group: isoniazid (0.3 g), ethambutol (0.75 to 1 g), pyrazinamide (1.5 g), thioacetazone (0.6 g), levofloxacin (0.3 g) 2. Control group: isoniazid (0.3 g), ethambutol (0.75 to 1 g), pyrazinamide (1.5 g), thioacetazone (0.6 g), ofloxacin (0.6 g)
Outcomes	1. Cure (sputum smear conversion for 2 consecutive months) 2. Radiological improvement 3. Total number of adverse events
Notes	Location: China Human immunodeficiency virus (HIV) status: presumed HIV negative Drug-resistance status: multiple-drug-resistant tuberculosis (MDR-TB) (presumed 38/73)

Mohanty 1993

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: providers, participants, and radiograph assessors blinded Inclusion of all randomized participants in the final analysis: 25/60 (42%) lost to follow up Mean duration of follow up: 6 months of therapy, and 12 months after cessation of therapy
Participants	Number: 60 randomized; 53 evaluated at 2 months, and 35 at 6 months Inclusion criteria: age > 15 years (age range 15 to > 45 years (9 participants)), sputum smear positive; not previously taken > 3 weeks antituberculous therapy; willing to stay in hospital for initial 2 months' intensive phase of treatment Exclusion criteria: diabetes; human immunodeficiency virus (HIV) infection; hypertension; other concomitant diseases; pregnant women
Interventions	Fluoroquinolone (ciprofloxacin) substituted into regimen (replacing rifampicin) 1. Ciprofloxacin (750 mg orally daily for 6 months) plus basic regimen 2. Rifampicin (450 mg orally daily for 6 months) plus basic regimen Basic regimen: streptomycin (0.75 g intramuscularly) and pyrazinamide (1.5 g orally) daily for 2 months; isoniazid (400 mg orally daily) for 6 months
Outcomes	1. Sputum smear conversion at 2 and 6 months 2. Treatment failure 3. Relapse 4. Radiological improvement at 2 and 6 months 5. Serious adverse events requiring change of treatment regimen
Notes	Location: India HIV status: all participants HIV-negative Drug-resistance status: no data

Saigal 2001

Methods	Randomized controlled trial Generation of allocation sequence: random-number table Allocation concealment: unclear Blinding: none Inclusion of all randomized participants in the final analysis: no losses Mean duration of follow up: 12 months
Participants	Number: 31 randomized and evaluated Inclusion criteria: histological evidence of caseating granulomas; sputum positive for acid-fast bacilli; sputum-culture positive for Mycobacterium tuberculosis; positive polymerase chain reaction (PCR) for *M. tuberculosis* in tissues; chronic liver disease informed written consent Exclusion criteria: serum bilirubin > 5 mg/dL; baseline alanine aminotransferase/aspartate aminotransferase (ALT/AST) ALT/AST > 200 international units/L (IU/L); serum creatinine > 2.5 mg/dL; increase in ALT/AST > 2-fold baseline levels over 1 week before starting the antituberculous drugs

Saigal 2001 (*Continued*)

Interventions	Fluoroquinolone (ofloxacin) and pyrazinamide substituted into regimen (replacing rifampicin) 1. Ofloxacin (400 mg orally) and pyrazinamide (World Health Organization (WHO) dose of 25 mg/kg for initial 2 months) daily for 12 months plus basic regimen 2. Rifampicin (WHO dose of 10 mg/kg orally) daily for 12 months plus basic regimen Basic regimen: (orally, daily for 12 months): isoniazid (WHO dose of 5 mg/kg), ethambutol (WHO dose of 15 mg/kg daily; for the initial 2 months)
Outcomes	1. Serious adverse events (hepatotoxicity requiring interruption and change of treatment)
Notes	Location: India Human immunodeficiency virus (HIV) and drug-resistance status: no data

Sun 2000

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of all randomized participants in the final analysis: no losses Mean duration of follow up: 9 months
Participants	Number: 80 randomized and evaluated Inclusion criteria: multiple-drug-resistant tuberculosis (MDR-TB) with isoniazid and rifampicin resistance; sputum culture positive after 1 year of treatment with streptomycin, isoniazid, rifampicin, pyrazinamide, and ethambutol; advanced pulmonary inflammatory or cavity enlarged; no prior fluoroquinolone treatment; adults (mean age 45.5±5.5 years; range 20 to 71 years) Exclusion criteria: heart, liver, or kidney dysfunction; diabetes
Interventions	Comparison of different fluoroquinolones (sparfloxacin versus ofloxacin) added to regimen 1. Sparfloxacin (0.1 g) 4 times daily plus basic regimen 2. Ofloxacin (0.2 g thrice daily) plus basic regimen Basic regimen: isoniazid (0.2 g), rifampicin (0.15 g), and protionamide (0.2 g thrice daily) for 6 months
Outcomes	1. Sputum smear or culture conversion 2. Clinical or radiological improvement 3. Total number of adverse events
Notes	Location: China Human immunodeficiency virus (HIV) status: presumed HIV negative Drug-resistance status: all proven MDR-TB

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

Study	Reason for exclusion
Andries 2005	Experimental animal study, plus a small section in healthy human volunteers (tolerability); not a trial report
Anonymous 1997	No randomization or control group
Chambers 1998	The outcome, early bactericidal activity, not in review
Chen 2003	No randomization, and the intervention was a combination of levofloxacin plus capreomycin
Chukanov 2006	Mixed intervention of ciprofloxacin, ofloxacin, or levofloxacin plus kanamycin or amikacin added to the basic regimen in study group versus streptomycin added to the basic regimen in control group
Estebanez 1992	Exclusively urogenital tuberculosis
Gosling 2003	The outcome, early bactericidal activity, not in review
Grishin 1998	No randomization; cohort study
Johnson 2006	The outcome, early bactericidal activity, not in review
Kawahara 1992	No randomization
Kumar 2004	Study in healthy volunteers, not a trial report, in which the outcome was uric acid concentration in urine samples excreted over 0 to 8 h
Marra 2005	Retrospective safety study; not a trial report
O'Brien 1994	Communication to the Editor of Chest; not a trial report
Pletz 2004	The outcome, early bactericidal activity, not in review
Sirgel 1997	The outcome, early bactericidal activity, not in review
Sirgel 2000	The outcome, early bactericidal activity, not in review
Sokolova 1998	No randomization; cohort study
Suo 1996	No randomization; not a controlled study
TRC 2002	No control arm, that is, a group treated without the studied fluoroquinolone (ofloxacin), a different fluoroquinolone, or different dose
Valerio 2003	No randomization and outcomes not reported

(*Continued*)

Venter 2006	The outcome, indices of adrenocortical function, not in review; none of the included outcomes reported, too small (20 participants)
Wang 2006	Retrospective study; not a trial report
Yoon 2005	Retrospective case-control study; not a trial report
Zhang 1997	The efficacy of bronchofibrescope and catheter intervention with ofloxacin and amikacin studied in comparison with traditional chemotherapy
Zhang 2006	The efficacy of rifabutin versus rifapentine containing antituberculous regimens studied, both regimens included levofloxacin; study question not in review
Zhao 2003	No randomization
Zheng 2004	Mixed intervention of levofloxacin plus pasiniazide plus *Mycobacterium vaccae*
Zhu 2006	The efficacy of rifabutin versus rifapentine containing antituberculous regimens studied, both regimens included levofloxacin; study question not in review

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

Abdullah 1997

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Abdullah 1998

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

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

ISRCTN07062956

Trial name or title	A randomised comparison of ciprofloxacin, levofloxacin and gatifloxacin for the treatment of adults with tuberculous meningitis
Methods	-
Participants	Inclusion criteria: aged > 14 years; clinical diagnosis of tuberculous meningitis Exclusion criteria: aged < 15 years; pregnant or breastfeeding; patients in whom the physician believes fluoroquinolones are contraindicated (eg previous adverse reaction); consent of either patient or their relatives not obtained
Interventions	1. Conventional 4-drug antituberculous chemotherapy (ATC) (comprising of isoniazid, rifampicin, pyrazinamide, and ethambutol) 2. Conventional 4-drug ATC plus ciprofloxacin 3. Conventional 4-drug ATC plus levofloxacin 4. Conventional 4-drug ATC plus gatifloxacin
Outcomes	1. Clinical: a. fever clearance, coma clearance, date of discharge, death at 2 months, disability or death at 9 months b. Cerebrospinal fluid pressure, lactate, white cell count, protein, and glucose 2. Microbiological: a. time to cerebrospinal fluid sterility b. time to negative amplified tuberculous meningitis direct test (Mycobacterium Tuberculosis Direct [MTD] test: Gen-probe, California)
Starting date	1 April 2003
Contact information	Dr Guy Thwaites (guy.thwaites@btinternet.com), Oxford University Clinical Research Unit, Vietnam
Notes	Location: Vietnam Registration number: ISRCTN07062956 Source of funding: The Wellcome Trust (UK)

ISRCTN13670619

Trial name or title	A comparative study of the bactericidal and sterilizing activity of three fluoroquinolones: gatifloxacin, moxifloxacin and ofloxacin substituted for ethambutol in the 2 month initial phase of the standard anti-tuberculosis treatment regimen also containing rifampicin, isoniazid and pyrazinamide (South Africa)
Methods	-
Participants	Inclusion criteria: male/female of 18 to 65 years; weight 38 to 80 kg; recently microscopically diagnosed pulmonary tuberculosis; findings in medical history and physical examination not exceeding grade 2; voluntarily signed informed consent; confirmed negative pregnancy test at the screening visit; willing to use effective contraceptive methods during treatment; normal lab values not exceeding grade 2, except haemoglobin < 6. 5 g/dL and potassium < 3.0 mEq/L (> grade 1); consent for a pre-screening biological test to exclude possible multi-drug-resistant tuberculosis (MDR-TB) and negative MDR-TB screen test will be a check if pre-screening biological test is done

ISRCTN13670619 (*Continued*)

	Exclusion criteria: history of tuberculosis within the last 3 years; concomitant infection requiring additional anti-infectious treatment (especially anti-retroviral medication (ARV)); human immunodeficiency virus (HIV)-infected patients at World Health Organization stage 4; diabetes mellitus or non-insulin dependent diabetes mellitus requiring treatment; drug and alcohol abuse; history of drug hypersensitivity and/or active allergic disease; impaired renal, hepatic or gastric function that may interfere with drug absorption, distribution, metabolism, or elimination
Interventions	1. Standard antituberculous treatment (isoniazid, rifampicin, pyrazinamide, and ethambutol) 2. Isoniazid, rifampicin, pyrazinamide, and gatifloxacin 3. Isoniazid, rifampicin, pyrazinamide, and ofloxacin 4. Isoniazid, rifampicin, pyrazinamide, and moxifloxacin
Outcomes	Bactericidal and sterilizing activity
Starting date	25 November 2004
Contact information	Dr T Kanyok (kanyokt@who.int), UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), Switzerland
Notes	Location: South Africa Registration number: ISRCTN13670619 Sources of funding: UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR)

ISRCTN44153044

Trial name or title	An international multicentre controlled clinical trial to evaluate high dose RIFApentine and a QUINolone in the treatment of pulmonary tuberculosis
Methods	-
Participants	Inclusion criteria: newly diagnosed pulmonary tuberculosis; 2 sputum specimens positive for tubercle bacilli on direct smear microscopy; either no previous antituberculous chemotherapy, or < 2 weeks of previous chemotherapy; aged 18 years and over; firm home address that is readily accessible for visiting and be intending to remain there during the entire treatment and follow-up period; willing to agree to participate in the study and to give a sample of blood for HIV testing Exclusion criteria: any condition (except HIV infection) that may prove fatal during the study period; tuberculous meningitis; pre-existing nontuberculous disease likely to prejudice the response to, or assessment of, treatment (eg insulin-dependent diabetes, liver or kidney disease, blood disorders, peripheral neuritis); female and known to be pregnant or breastfeeding; suffering from a condition likely to lead to unco-operative behaviour such as psychiatric illness or alcoholism; contraindications to any medications in the study regimens; requires anti-retroviral treatment (ART) at diagnosis; history of prolonged QTc syndrome or current or planned therapy with quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, or terfenadine during the intensive phase of antituberculous therapy; haemoglobin < 7g/L; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper range; creatinine clearance < 30 mL/min; history of seizures; HIV positive with a CD4 count < 200/mm^3; weight < 35 kg

ISRCTN44153044 (*Continued*)

Interventions	1. 2 months of daily ethambutol (E), moxifloxacin (M), rifampicin (R), and pyrazinamide (Z) followed by 2 months of twice weekly moxifloxacin and rifapentine (2EMRZ/2P2M2). 2. 2 months of daily ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by 4 months of once weekly moxifloxacin and rifapentine (2EMRZ/4P1M1) 3. 2 months of daily ethambutol (E), isoniazid (H), rifampicin (R), and pyrazinamide (Z) followed by 4 months of daily isoniazid and rifampicin (2EHRZ/4HR)
Outcomes	1. Combined rate of failure at the end of treatment and relapse, measured at 18 months 2. Presence of rifamycin monoresistance (RMR) in relapse cultures of HIV-infected patients, measured at 5, 6, 7, 8, 9, 10, 11, 12, 15, 18 months on the 4-month arm and 7, 8, 9, 10, 11, 12, 15, 18 months on the 6-month arm, plus at any unscheduled visit 3. Occurrence of serious adverse events at any time during chemotherapy, recorded as they present themselves throughout the course of the trial 4. Sputum culture results at 2 months after the initiation of chemotherapy, measured at all visits 5. Rate of completion of chemotherapy according to the protocol, measured at all visits 6. Number of observed doses of chemotherapy ingested, measured at all visits 7. Any adverse events, recorded as they present themselves throughout the course of the trial
Starting date	31 July 2007
Contact information	Dr Amina Jindani (ajindani@sgul.ac.uk), Centre for Infection Department of Cellular and Molecular Medicine St. George's University of London, UK
Notes	Location: South Africa, Mozambique, Zimbabwe, Zambia Registration number: ISRCTN44153044 Source of funding: European and Developing Countries Clinical Trials Partnership (EDCTP) (The Netherlands)

ISRCTN85595810

Trial name or title	Controlled comparison of two moxifloxacin containing treatment shortening regimens in pulmonary tuberculosis
Methods	-
Participants	Inclusion criteria: signed written consent or witnessed oral consent in the case of illiteracy, before undertaking any trial related activity; 2 sputum specimens positive for tubercle bacilli on direct smear microscopy at the local laboratory; no previous antituberculous chemotherapy; aged 18 years and over; firm home address that is readily accessible for visiting and willingness to inform the study team of any change of address during the treatment and follow-up period; agreement to participate in the study and to give a sample of blood for human immunodeficiency virus (HIV) testing; laboratory parameters performed up to 14 days before enrolment; serum aspartate aminotransferase (AST) activity < 3 times the upper limit of normal (ULN); serum total bilirubin level < 2.5 times ULN; creatinine clearance level > 30 mL/min; haemoglobin level of at least 7.0 g/dL; platelet count of at least 50 x 10^9 cells/L; serum potassium > 3.5 mmol/L; negative pregnancy test (women of childbearing potential); pre-menopausal women must be using a barrier form of contraception or be surgically sterilized or have an intra-uterine contraceptive device in place Exclusion criteria: unable to take oral medication; previously enrolled in this study; received any investiga-

ISRCTN85595810 (*Continued*)

	tional drug in the past 3 months; received an antibiotic active against *Mycobacterium tuberculosis* in the last 14 days (fluoroquinolones, macrolides, standard antituberculous drugs); any condition that may prove fatal during the first two months of the study period; tuberculous meningitis or other forms of severe tuberculosis with high risk of a poor outcome; pre-existing non-tuberculosis disease likely to prejudice the response to, or assessment of, treatment (eg insulin-dependent diabetes, liver or kidney disease, blood disorders, peripheral neuritis, chronic diarrhoeal disease); pregnant or breast feeding; suffering from a condition likely to lead to unco-operative behaviour (eg psychiatric illness or alcoholism); contraindications to any medications in the study regimens; known to have congenital or sporadic syndromes of QTc prolongation or receiving concomitant medication reported to increase the QTc interval (eg amiodarone, sotalol, disopyramide, quinidine, procainamide, terfenadine); end stage liver failure (class Child-Pugh C); uncorrected hypokalaemia; weight < 35 kg; known allergy to any fluoroquinolone antibiotic or history of tendinopathy associated with quinolones; HIV infection with CD4 count < 250 x 10^9/L; patients already receiving anti-retroviral therapy; patients whose initial isolate is shown to be multiple drug resistant
Interventions	1. 8 weeks of chemotherapy with ethambutol, isoniazid, rifampicin, and pyrazinamide plus the moxifloxacin placebo, followed by 9 weeks of isoniazid and rifampicin plus the moxifloxacin placebo, followed by 9 weeks of isoniazid and rifampicin only 2. 8 weeks of chemotherapy with moxifloxacin, isoniazid, rifampicin, and pyrazinamide plus the ethambutol placebo, followed by 9 weeks of moxifloxacin, isoniazid and rifampicin, followed by 9 weeks of the isoniazid placebo and the rifampicin placebo 3. 8 weeks of chemotherapy with ethambutol, moxifloxacin, rifampicin, and pyrazinamide plus the isoniazid placebo, followed by 9 weeks of moxifloxacin and rifampicin plus the isoniazid placebo, followed by 9 weeks of the isoniazid placebo and the rifampicin placebo Dosages dependent on patient weight category (all drugs taken orally): 1. Moxifloxacin: 400 mg 2. Rifampicin: ≤ 45 kg - 450 mg; > 45 kg - 600 mg 3. Isoniazid: 300 mg 4. Pyrazinamide: < 40 kg - 25 mg/kg rounded to nearest 500 mg; 40 to 55 kg - 1000 mg; 55 to 75 kg - 1500 mg; > 75 kg - 2000 mg 5. Ethambutol: < 40 kg - 15 mg/kg rounded to nearest 100 mg; 40 to 55 kg - 800 mg; 55 to 75 kg - 1200 mg; > 75 kg - 1600 mg
Outcomes	1. Combined failure of bacteriological cure and relapse within 1 year of completion of therapy 2. Proportion of patients with grade 3 or 4 adverse events according to the World Health Organization grade 3. Proportion of participants culture negative at 8 weeks 4. Time to culture negative sputum 5. Speed of decline of sputum viable count
Starting date	1 June 2007
Contact information	Prof Stephen Gillespie, Centre for Medical Microbiology, Royal Free and University College Medical School, UK
Notes	Location: Kenya, South Africa, Tanzania, Zambia Registration number: ISRCTN85595810 Sources of funding: European and Developing Countries Clinical Trials Partnership (EDCTP) (The Netherlands); TB Alliance (USA); Bayer HealthCare Pharmaceuticals (USA); Sanofi-Aventis (France)

NCT00144417

Trial name or title	TBTC Study 28: Evaluation of a moxifloxacin-based, isoniazid-sparing regimen for tuberculosis treatment
Methods	-
Participants	Inclusion criteria: suspected pulmonary tuberculosis with acid-fast bacilli in a stained smear of expectorated or induced sputum. Patients whose sputum cultures do not grow *M. tuberculosis* and those having an *M. tuberculosis* isolate resistant to (one or more) isoniazid, rifampin, fluoroquinolones, will be discontinued from the study, but followed for 14 days to detect late toxicities from study therapy. Patients having extra-pulmonary manifestations of tuberculosis, in addition to smear-positive pulmonary disease, are eligible for enrolment. Sputum must be expectorated or induced; smear results from respiratory secretions obtained by bronchoalveolar lavage or bronchial wash may not be used for assessment of study eligibility; willingness to have HIV testing performed, if HIV serostatus is not known or if the last documented negative HIV test was more than 6 months before enrolment. HIV testing does not need to be repeated if there is written documentation of a positive test (positive ELISA and Western Blot or a plasma HIV-RNA level > 5000 copies/mL) at any time in the past; 7 or fewer days of multidrug therapy for tuberculosis disease in the 6 months preceding enrolment; 7 or fewer days of fluoroquinolone therapy in the 3 months preceding enrolment; age > 18 years; Karnofsky score of at least 60 (requires occasional assistance but is able to care for most of his/her needs); signed informed consent; women with child-bearing potential must agree to practice an adequate (barrier) method of birth control or to abstain from heterosexual intercourse during study therapy; serum amino aspartate transferase (AST) activity $\leq$ 3 times upper limit of normal; serum total bilirubin level $\leq$ 2.5 times upper limit of normal; serum creatinine level $\leq$ 2 times upper limit of normal; complete blood count with hemoglobin level of at least 7.0 g/dL; complete blood count with platelet count of at least 50,000/mm ^{3} ; serum potassium > 3.5 meq/L; negative pregnancy test (women of childbearing potential) Exclusion criteria: breastfeeding; known intolerance to any of the study drugs; known allergy to any fluoroquinolone antibiotic; concomitant disorders or conditions for which moxifloxacin (MXF), isoniazid (INH) , rifampin (RIF), pyrazinamide (PZA), or ethambutol (EMB) are contraindicated (including severe hepatic damage, acute liver disease of any cause, and acute uncontrolled gouty arthritis); current or planned therapy during the intensive phase of therapy using drugs having unacceptable interactions with rifampin (rifabutin can be substituted for rifampin during the continuation phase of therapy); current or planned antiretroviral therapy during intensive phase of therapy; history of prolonged QT syndrome or current or planned therapy with quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, or terfenadine during the intensive phase of therapy; pulmonary silicosis; central nervous system tuberculosis
Interventions	1. Moxifloxacin (with rifampin, pyrazinamide, and ethambutol) 2. Isoniazid (with rifampin, pyrazinamide, and ethambutol)
Outcomes	1. Culture-conversion rate at the end of the intensive phase of therapy 2. Safety and tolerability 3. Time to culture-conversion using data from 2-, 4-, 6-, and 8-week cultures 4. Proportion of patients with any Grade 3 or 4 adverse reactions 5. Adverse events and 2-month culture conversion rates among HIV-infected patients vs. HIV-uninfected patients 6. Rates of treatment failure 7. Delayed toxicity attributable to moxifloxacin (toxicity that becomes evident after the 8 weeks of moxifloxacin therapy)
Starting date	February 2006
Contact information	Richard E Chaisson (Study Chair), Johns Hopkins University, USA

NCT00144417 (*Continued*)

Notes	Location: Brazil, Canada (Manitoba, Quebec), South Africa, Spain, Uganda, USA (Arkansas, California, Colorado, Washington DC, Georgia, Illinois, Maryland, Massachusetts, New Jersey, New York, North Carolina, Tennessee, Texas, Washington) Registration number: NCT00144417 Sponsors and collaborators: Centers for Disease Control and Prevention; Global Alliance for TB Drug Development; Bayer

NCT00216385

Trial name or title	A controlled trial of a 4-month quinolone-containing regimen for the treatment of pulmonary tuberculosis
Methods	-
Participants	Inclusion criteria: male or female; aged 18 to 65 years; currently suffering from recently diagnosed microscopically proven pulmonary tuberculosis and providing informed consent for inclusion in the study Exclusion criteria: history of tuberculosis treatment within the last 3 years; history of diabetes mellitus or noninsulin dependent diabetes mellitus requiring treatment; concomitant infection requiring additional anti-infective treatment (especially anti-retroviral therapy); HIV- infected patients with WHO stage 3 infection - except those presenting with only the "loss of weight>10% body weight" criterion - and all HIV infected patients at WHO stage 4
Interventions	1. 4-month gatifloxacin-containing antituberculous regimen 2. Standard antituberculous regimen
Outcomes	1. Percentage of relapses by 24 months following treatment cure 2. Percentage of adverse events 3. Time to relapse 4. Percentage of smear and culture conversion at 8 weeks 5. Percentage of patient cured at the end 6. of treatment 7. Time to a composite "unsatisfactory" endpoint 8. Distribution of type and grading of adverse events
Starting date	January 2005
Contact information	Christian Lienhardt (Study Director), Institut de Recherche pour le Developpement, France
Notes	Location: Benin, Guinea, Kenya, Senegal, South Africa Registration number: NCT00216385 Sponsors and collaborators: Institut de Recherche pour le Developpement; World Health Organization; European Commission

NCT00396084

Trial name or title	Randomized, open label, multiple dose Phase I study of the early bactericidal activity of linezolid, gatifloxacin, levofloxacin, and moxifloxacin in HIV-non-infected adults with Initial episodes of sputum smear-positive pulmonary tuberculosis (DMID 01-553)
Methods	-
Participants	Inclusion criteria: adults, male or female, aged 18 to 65 years; women with child-bearing potential (not surgically sterilized or postmenopausal for < 1 year) must be using or agree to use an adequate method of birth control (condom: intravaginal spermicide (foams, jellies, sponge) and diaphragm: cervical cap or intrauterine device) during study drug treatment; newly diagnosed sputum smear-positive pulmonary tuberculosis as confirmed by sputum AFB smear and chest x-ray findings consistent with pulmonary tuberculosis; willing and able to provide informed consent; reasonably normal hemoglobin (≥ 8 gm/dL), renal function (serum creatinine < 2 mg/dL), hepatic function (serum AST < 1.5 times the upper limit of normal for the testing laboratory and total bilirubin < 1.3 mg/dL), and random blood glucose < 150 mg/dL Exclusion criteria: HIV infection; weight < 75% of ideal body weight; presence of significant hemoptysis; patients who cough up frank blood (more than blood streaked sputum); pregnant or breastfeeding women and those who are not practicing birth control; significant respiratory impairment (respiratory rate > 35/min); clinical suspicion of dissemated tuberculosis or tuberculosis meningitis; presence of serious underlying medical illness (eg such as liver failure, renal failure, diabetes mellitus, chronic alcoholism, decompensated heart failure, haematologic malignancy) or patients receiving myelosuppressive chemotherapy; patients receiving any of monoamine oxidase inhibitors (phenelzine, tranylcypromine), adrenergic/serotonergic agonists such as pseudoephedrine and phenylpropanolamine (frequently found in cold and cough remedies), tricyclic antidepressants (amitriptyline, nortriptyline, protriptyline, doxepin, amoxapine, etc), antipsychotics (eg chlorpromazine and buspirone), serotonin re-uptake inhibitors (fluoxetine, paroxetine, sertaline, etc), buproprion, agents known to prolong the QTc interval [erythromycin, clarithromycin, astemizole, type Ia (quinidine, procainamide, disopyramide) and III (amiodarone, sotalol) anti-arrhythmics, carbamazepine, insulin, sulfonylureas, and meperidine; presence of QTc prolongation (> 450 msec) on baseline EKG; allergy or contraindication to use of study drugs; treatment with antituberculous medications or other antibiotics with known activity against Mycobacterium tuberculosis during the preceding 6 months; inability to provide informed consent; total white blood cell count < 3000/mm^3; platelet count < 150,000/mm^3; patients with suspected drug-resistant tuberculosis (eg contact to source patient with drug-resistant tuberculosis, patients who have relapsed after previous treatment for tuberculosis); patients likely, in the opinion of the local investigator, to be unable to comply with the requirements of the study protocol
Interventions	Participants will be randomized to receive gatifloxacin, levofloxacin, moxifloxacin, or isoniazid (control), and after these arms are enrolled, they will be randomized to receive either linezolid (600 mg once daily) or linezolid (600 mg twice daily) or isoniazid (control). After the initial treatment, all participants will receive 6 months of standard antituberculous treatment outside of the hospital
Outcomes	1. Early bactericidal activity 2. Extended early bactericidal activity 3. Safety evaluations including clinical examination, complete blood counts, and serum total bilirubin, aspartate aminotransferase, and creatinine, and urinalysis will be followed to monitor for drug toxicity
Starting date	February 2004
Contact information	John Johnson (jlj@po.cwru.edu)

NCT00396084 (*Continued*)

Notes	Location: University of Espírito Santo, Vitória, Brazil Registration number: NCT00396084 Sponsors: National Institute of Allergy and Infectious Diseases (NIAID)

DATA AND ANALYSES

Comparison 1. Fluoroquinolone substituted into regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure (sputum culture conversion) at 8 weeks	3	416	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.17]
1.1 Ciprofloxacin vs rifampicin	1	60	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.88, 1.32]
1.2 Ciprofloxacin vs ethambutol plus pyrazinamide	1	20	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.42, 1.09]
1.3 Moxifloxacin vs ethambutol	1	336	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.83, 1.19]
2 Treatment failure at 12 months	3	388	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.71, 6.42]
2.1 Ciprofloxacin vs rifampicin	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 70.83]
2.2 Ciprofloxacin vs ethambutol plus pyrazinamide	2	328	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.63, 6.58]
3 Relapse	3	384	Risk Ratio (M-H, Fixed, 95% CI)	7.17 [1.33, 38.58]
3.1 Ciprofloxacin vs ethambutol plus pyrazinamide	1	168	Risk Ratio (M-H, Fixed, 95% CI)	15.72 [0.91, 270.96]
3.2 Ciprofloxacin vs rifampicin	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.33, 27.23]
3.3 Ofloxacin vs ethambutol	1	156	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Relapse: by HIV status	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 HIV-positive participants: ciprofloxacin vs ethambutol plus pyrazinamide	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 HIV-negative participants: ciprofloxacin vs ethambutol plus pyrazinamide	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Time to sputum culture conversion (months)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Ciprofloxacin vs ethambutol plus pyrazinamide	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6 Time to sputum culture conversion (months): by HIV status	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 HIV-positive participants: ciprofloxacin vs ethambutol plus pyrazinamide	1		Mean Difference (IV, Random, 95% CI)	Not estimable
6.2 HIV-negative participants: ciprofloxacin vs ethambutol plus pyrazinamide	1		Mean Difference (IV, Random, 95% CI)	Not estimable
7 Clinical or radiological improvement at 8 weeks	2	216	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.49, 1.59]

7.1 Ciprofloxacin vs rifampicin	1	60	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.88, 1.32]
7.2 Ofloxacin vs ethambutol	1	156	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.44, 1.08]
8 Serious adverse events	5	743	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.56, 1.72]
8.1 Ciprofloxacin vs rifampicin	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 15.26]
8.2 Ofloxacin vs ethambutol	1	156	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.47, 3.57]
8.3 Ciprofloxacin vs ethambutol plus pyrazinamide	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.20, 4.69]
8.4 Ofloxacin vs rifampicin	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.79]
8.5 Moxifloxacin vs ethambutol	1	336	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.50, 3.05]
9 Total number of adverse events	4	712	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.96, 1.43]
9.1 Ciprofloxacin vs rifampicin	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.22, 4.56]
9.2 Ciprofloxacin vs ethambutol plus pyrazinamide	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.60, 1.24]
9.3 Ofloxacin vs ethambutol	1	156	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.70, 5.44]
9.4 Moxifloxacin vs ethambutol	1	336	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.00, 1.66]
10 Total number of adverse events, substitutions for ethambutol	2	492	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.05, 1.72]

Comparison 2. Fluoroquinolone added to regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure (sputum culture conversion) at 8 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Levofloxacin vs no levofloxacin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Treatment failure at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Levofloxacin vs no levofloxacin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Clinical or radiological improvement at 8 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Levofloxacin vs no levofloxacin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Death from any cause	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Levofloxacin vs no levofloxacin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Tuberculosis-related death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Levofloxacin vs no levofloxacin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Levofloxacin vs no levofloxacin	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 3. Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure (sputum culture conversion) within 2 to 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Treatment failure at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Clinical or radiological improvement at 8 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Total number of adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens

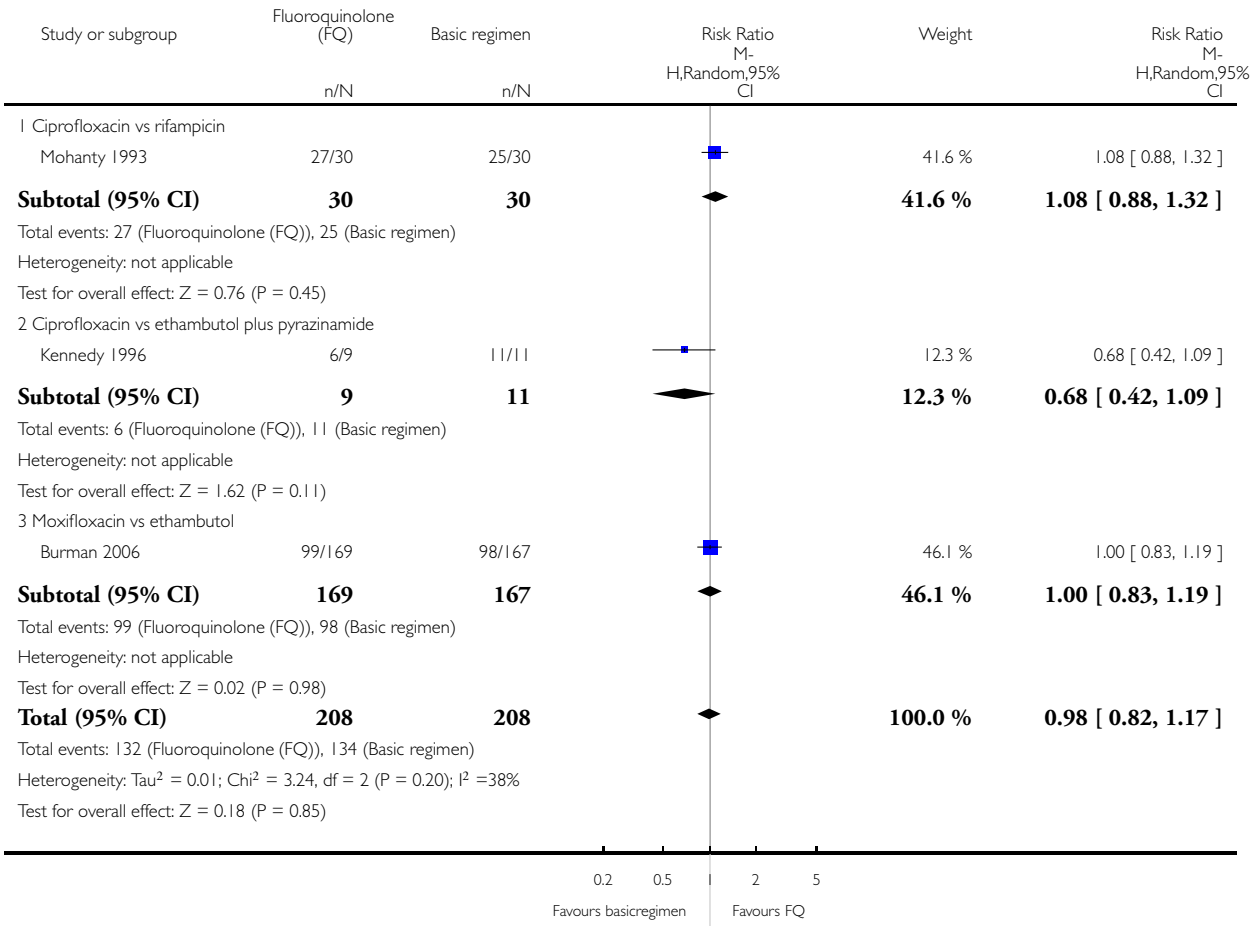
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure (sputum culture conversion within 2 to 3 weeks)	2	184	Risk Ratio (M-H, Random, 95% CI)	2.10 [0.77, 5.71]
2 Treatment failure at 12 months	2	149	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.26, 1.47]
3 Clinical or radiological improvement at 8 weeks	3	333	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.92, 1.24]
4 Total number of adverse events	3	253	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.59, 1.64]

Analysis 1.1. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 1 Cure (sputum culture conversion) at 8 weeks.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 1 Cure (sputum culture conversion) at 8 weeks

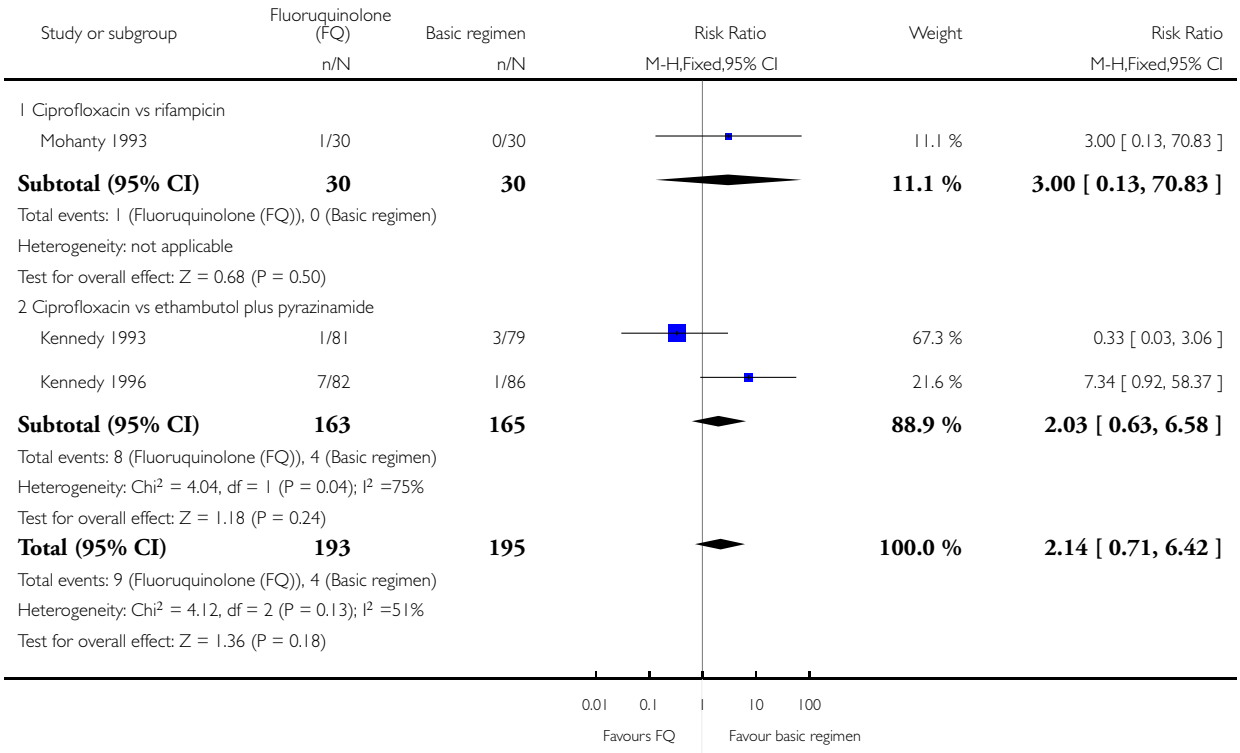


Analysis 1.2. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 2 Treatment failure at 12 months.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 2 Treatment failure at 12 months

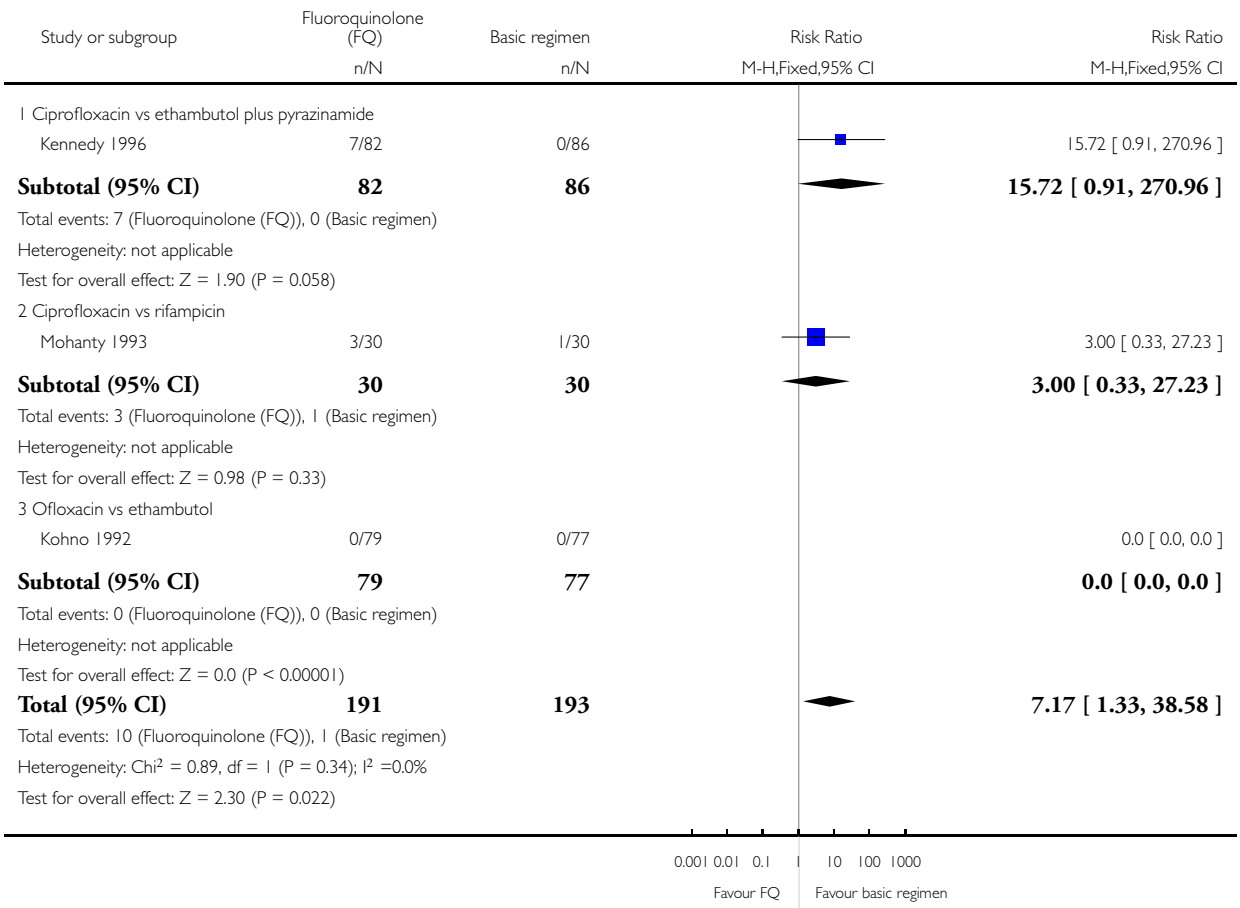


Analysis 1.3. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 3 Relapse.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 3 Relapse

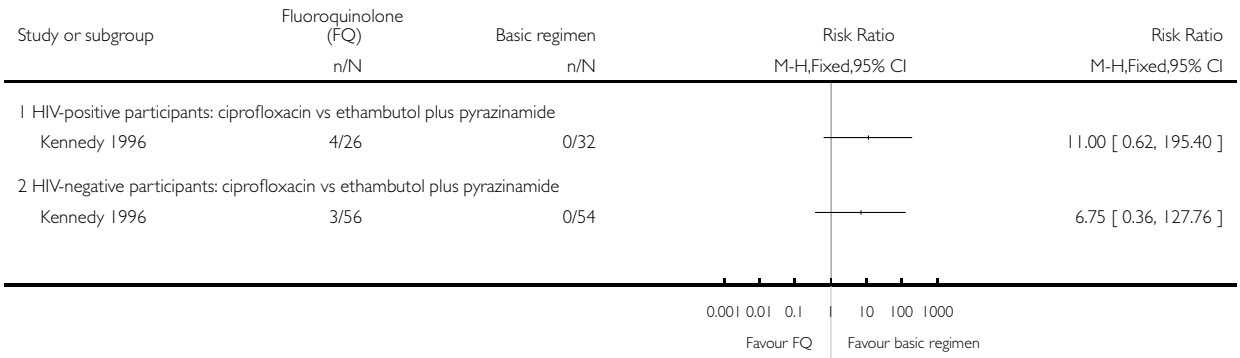


Analysis 1.4. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 4 Relapse: by HIV status.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 4 Relapse: by HIV status

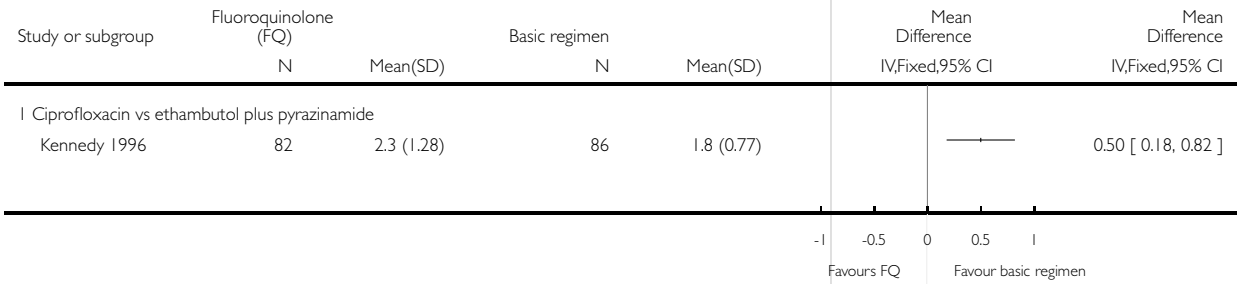


Analysis 1.5. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 5 Time to sputum culture conversion (months).

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 5 Time to sputum culture conversion (months)



Analysis 1.6. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 6 Time to sputum culture conversion (months): by HIV status.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 6 Time to sputum culture conversion (months): by HIV status

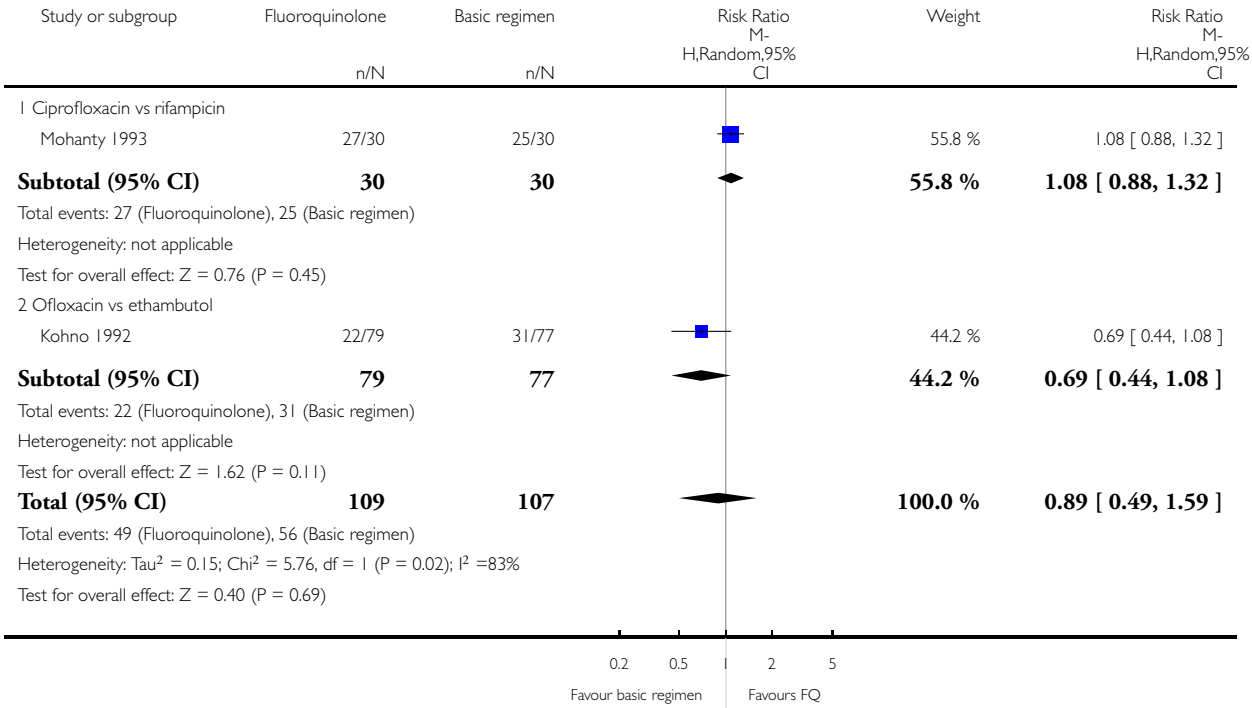
Study or subgroup	Fluoroquinolone (FQ) N	Mean(SD)	Basic regimen N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 HIV-positive participants: ciprofloxacin vs ethambutol plus pyrazinamide						
Kennedy 1996	25	2.9 (1.28)	30	1.7 (0.51)		1.20 [0.67, 1.73]
2 HIV-negative participants: ciprofloxacin vs ethambutol plus pyrazinamide						
Kennedy 1996	50	2 (0.77)	51	1.8 (0.77)		0.20 [-0.10, 0.50]

Analysis 1.7. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 7 Clinical or radiological improvement at 8 weeks.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 7 Clinical or radiological improvement at 8 weeks

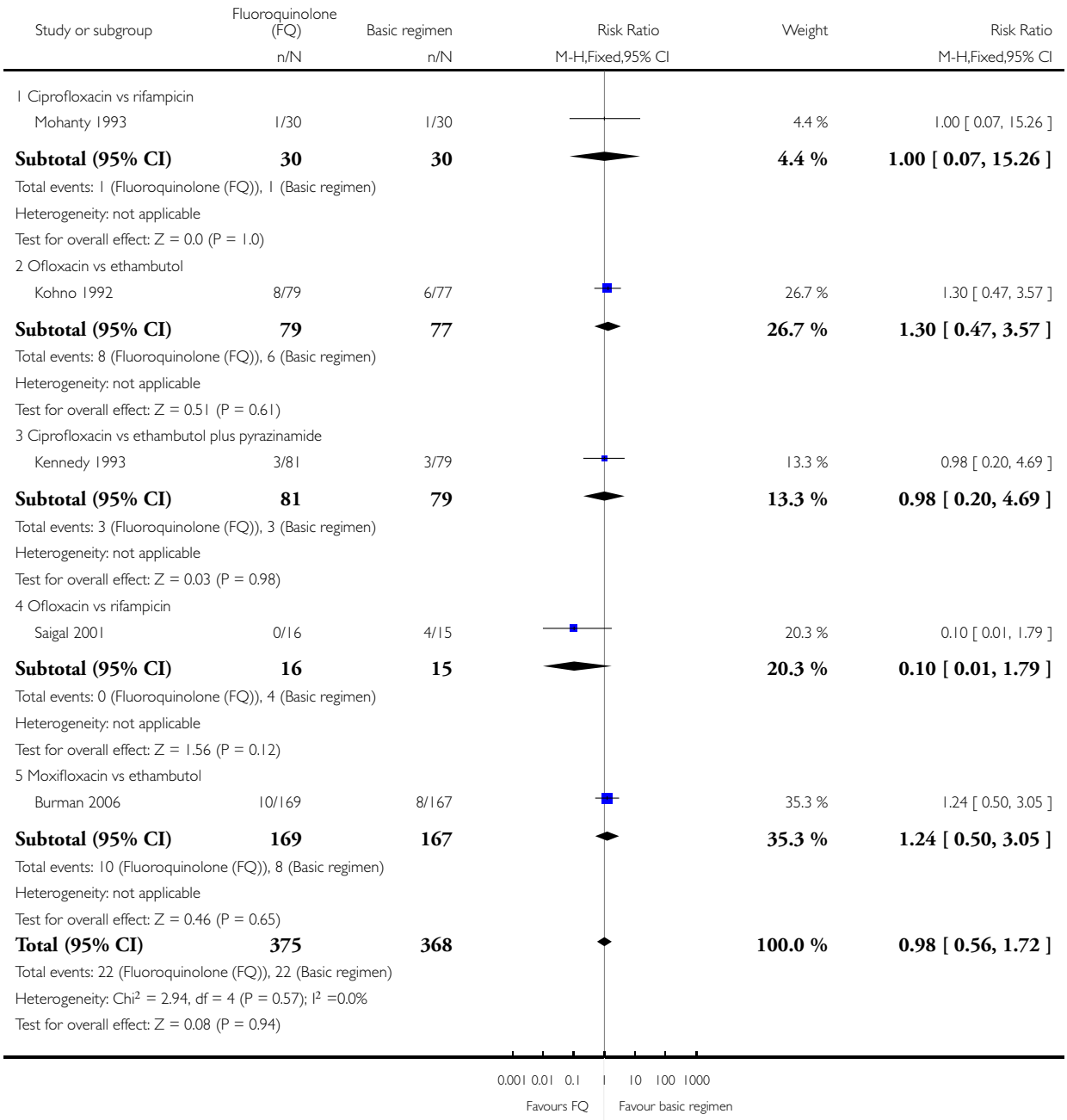


Analysis 1.8. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 8 Serious adverse events.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 8 Serious adverse events

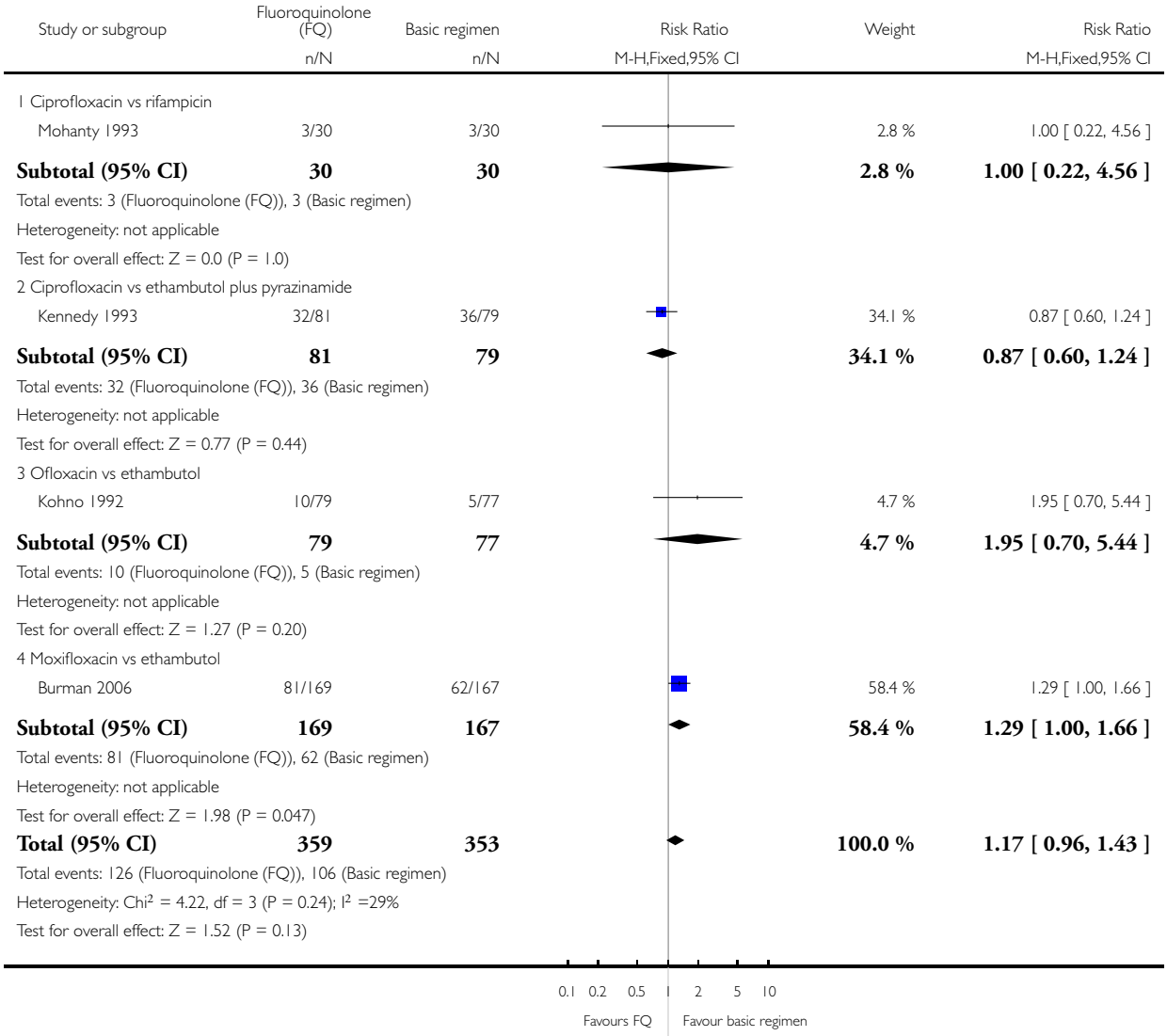


Analysis 1.9. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 9 Total number of adverse events.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 9 Total number of adverse events



Analysis 1.10. Comparison 1 Fluoroquinolone substituted into regimen, Outcome 10 Total number of adverse events, substitutions for ethambutol.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 1 Fluoroquinolone substituted into regimen

Outcome: 10 Total number of adverse events, substitutions for ethambutol

Study or subgroup	Fluoroquinolones n/N	Ethambutol n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burman 2006	81/169	62/167		92.5 %	1.29 [1.00, 1.66]
Kohno 1992	10/79	5/77		7.5 %	1.95 [0.70, 5.44]
Total (95% CI)	**248**	**244**		**100.0 %**	**1.34 [1.05, 1.72]**

Total events: 91 (Fluoroquinolones), 67 (Ethambutol)

Heterogeneity: $Chi^2 = 0.60$, df = 1 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 2.32 (P = 0.020)

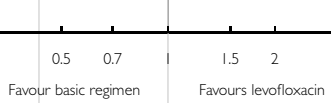
Analysis 2.1. Comparison 2 Fluoroquinolone added to regimen, Outcome 1 Cure (sputum culture conversion) at 8 weeks.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 2 Fluoroquinolone added to regimen

Outcome: 1 Cure (sputum culture conversion) at 8 weeks

Study or subgroup	Levofloxacin n/N	Basic regimen n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Levofloxacin vs no levofloxacin				
El-Sadr 1998	46/87	36/87		1.28 [0.93, 1.76]

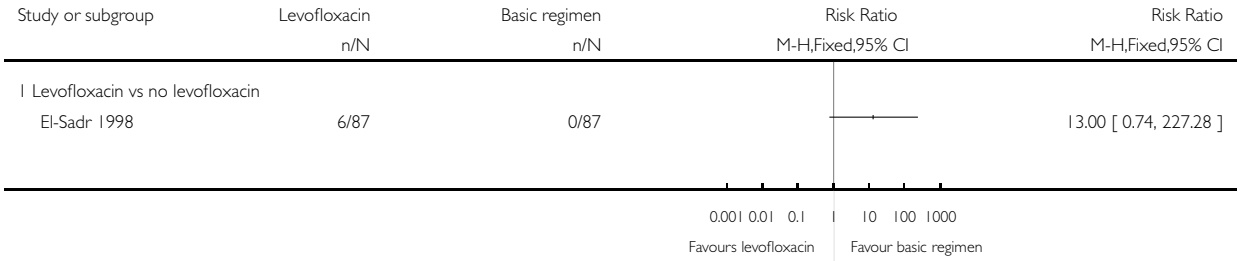


Analysis 2.2. Comparison 2 Fluoroquinolone added to regimen, Outcome 2 Treatment failure at 12 months.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 2 Fluoroquinolone added to regimen

Outcome: 2 Treatment failure at 12 months

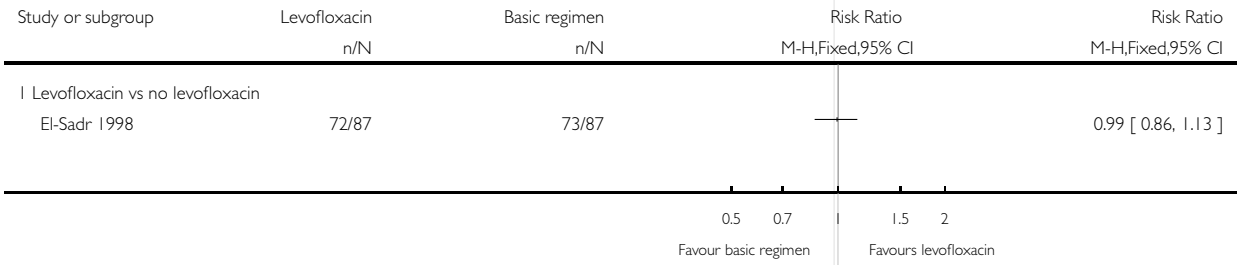


Analysis 2.3. Comparison 2 Fluoroquinolone added to regimen, Outcome 3 Clinical or radiological improvement at 8 weeks.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 2 Fluoroquinolone added to regimen

Outcome: 3 Clinical or radiological improvement at 8 weeks

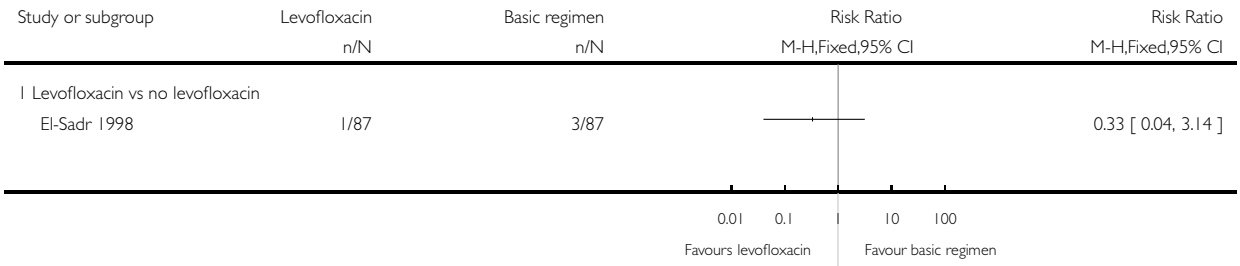


Analysis 2.4. Comparison 2 Fluoroquinolone added to regimen, Outcome 4 Death from any cause.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 2 Fluoroquinolone added to regimen

Outcome: 4 Death from any cause

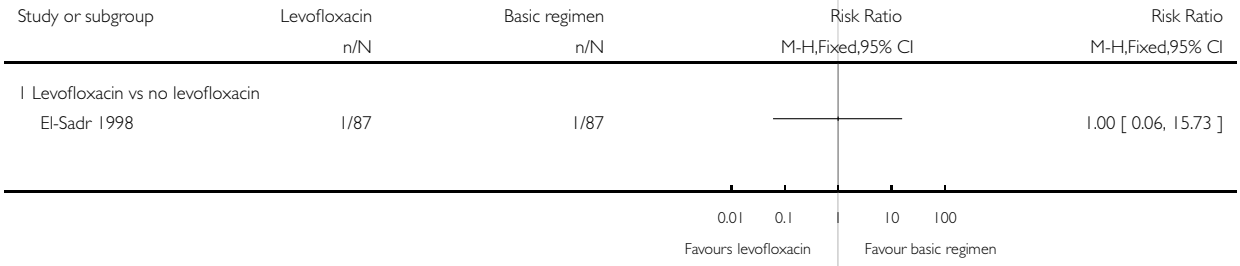


Analysis 2.5. Comparison 2 Fluoroquinolone added to regimen, Outcome 5 Tuberculosis-related death.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 2 Fluoroquinolone added to regimen

Outcome: 5 Tuberculosis-related death

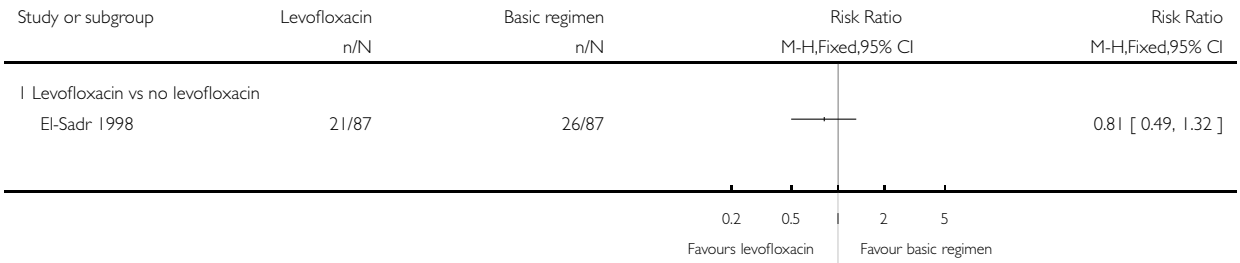


Analysis 2.6. Comparison 2 Fluoroquinolone added to regimen, Outcome 6 Serious adverse events.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 2 Fluoroquinolone added to regimen

Outcome: 6 Serious adverse events

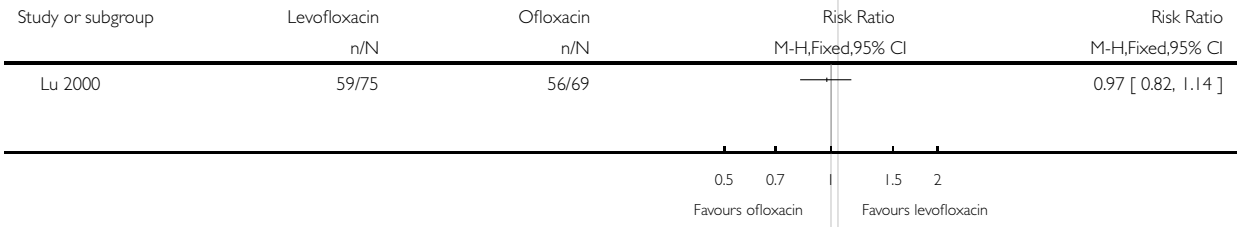


Analysis 3.1. Comparison 3 Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen, Outcome 1 Cure (sputum culture conversion) within 2 to 3 weeks.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 3 Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen

Outcome: 1 Cure (sputum culture conversion) within 2 to 3 weeks



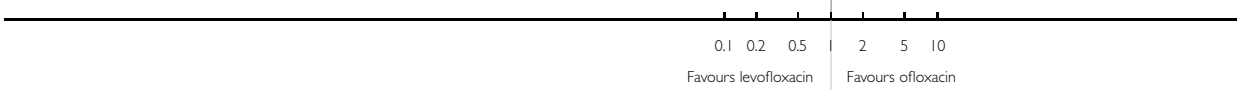
Analysis 3.2. Comparison 3 Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen, Outcome 2 Treatment failure at 12 months.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 3 Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen

Outcome: 2 Treatment failure at 12 months

Study or subgroup	Levofloxacin n/N	Ofloxacin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Lu 2000	3/75	2/69		1.38 [0.24, 8.01]



Analysis 3.3. Comparison 3 Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen, Outcome 3 Clinical or radiological improvement at 8 weeks.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 3 Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen

Outcome: 3 Clinical or radiological improvement at 8 weeks

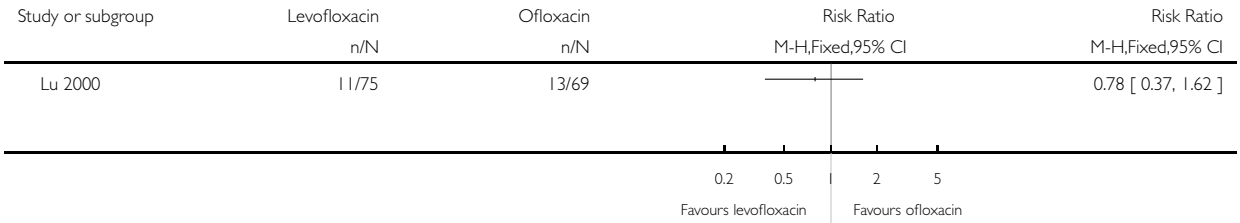
Study or subgroup	Levofloxacin n/N	Ofloxacin n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Lu 2000	43/75	35/69		1.13 [0.83, 1.53]

Analysis 3.4. Comparison 3 Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen, Outcome 4 Total number of adverse events.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 3 Comparison of fluoroquinolones (levofloxacin vs ofloxacin) substituted into regimen

Outcome: 4 Total number of adverse events

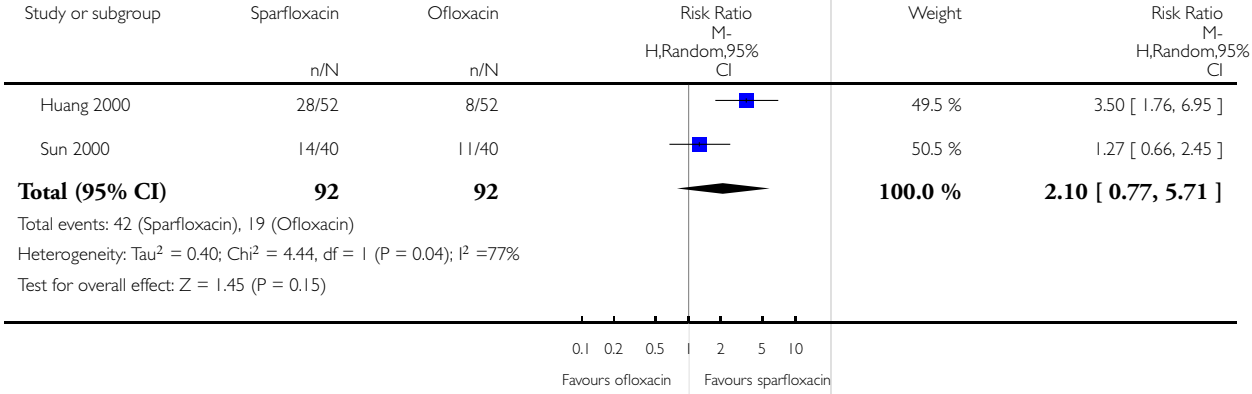


Analysis 4.1. Comparison 4 Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens, Outcome 1 Cure (sputum culture conversion within 2 to 3 weeks).

Review: Fluoroquinolones for treating tuberculosis

Comparison: 4 Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens

Outcome: 1 Cure (sputum culture conversion within 2 to 3 weeks)

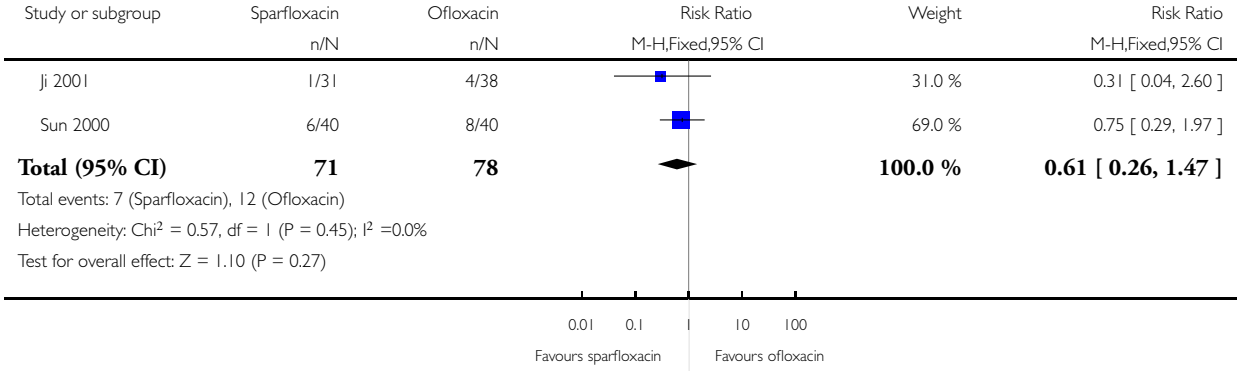


Analysis 4.2. Comparison 4 Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens, Outcome 2 Treatment failure at 12 months.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 4 Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens

Outcome: 2 Treatment failure at 12 months

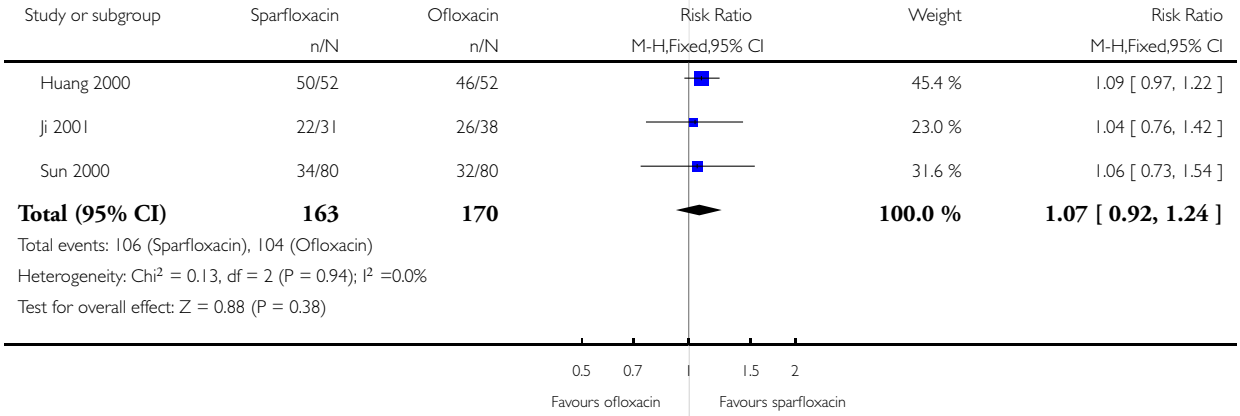


Analysis 4.3. Comparison 4 Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens, Outcome 3 Clinical or radiological improvement at 8 weeks.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 4 Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens

Outcome: 3 Clinical or radiological improvement at 8 weeks

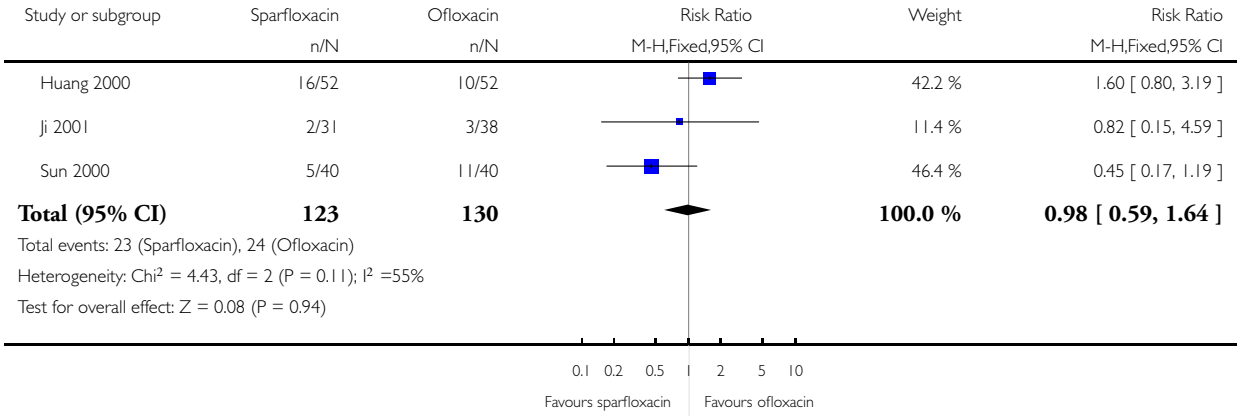


Analysis 4.4. Comparison 4 Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens, Outcome 4 Total number of adverse events.

Review: Fluoroquinolones for treating tuberculosis

Comparison: 4 Comparison of fluoroquinolones (sparfloxacin vs ofloxacin) added to regimens

Outcome: 4 Total number of adverse events



ADDITIONAL TABLES

Table 1. Highest multiple-drug-resistant tuberculosis (MDR-TB) rates in 1998[a]

Location	New case	Previously treated case
Estonia	14.1	18.1
Henan Province, China	10.8	15.1
Latvia	9.0	12.0
Ivanovo Oblast, Russian Federation	9.0	12.3
Tomsk Oblast, Russian Federation	6.5	13.7

[a] Source: Loddenkemper 2002.

Table 2. Risk of bias assessment

Trial	Allocation sequence generation	Allocation concealment	Blinding	Inclusion[a]
Burman 2006	Unclear	Unclear	Unclear	Inadequate

Table 2. Risk of bias assessment (*Continued*)

El-Sadr 1998	Adequate	Unclear	Assessors only	Adequate for 8 weeks Inadequate for continuation phase (39% lost)
Huang 2000	Unclear	Unclear	Unclear	Adequate
Ji 2001	Unclear	Unclear	Unclear	Adequate
Kennedy 1993	Unclear	Unclear	None	Adequate
Kennedy 1996	Adequate	Adequate	Assessors only	Adequate
Kohno 1992	Unclear	Unclear	Unclear	Inadequate
Lu 2000	Adequate	Unclear	Participants: yes Providers and assessors: unclear	Adequate
Mohanty 1993	Unclear	Unclear	Providers, participants, and radiograph assessors: yes	Inadequate
Saigal 2001	Adequate	Unclear	None	Adequate
Sun 2000	Unclear	Unclear	Unclear	Adequate

[a] Inclusion of all randomized participants in the final analysis.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]	SCI[b]	Russian database
1	tuberculosis	TUBERCULOSIS	TUBERCULOSIS	TUBERCULOSIS	tuberculosis	tuberculosis	tuberculosis
2	fluoroquinolones	tuberculosis	tuberculosis	tuberculosis	fluoroquinolones	fluoroquinolones	quinolones

(*Continued*)

3	-	fluoro-quinolone	1 or 2	1 or 2	ciprofloxacin	ciprofloxacin	fluoro-quinolones
4	-	amifloxacin	QUINO-LINES	QUINOLINE DERIVED ANTIINFEC-TIVE AGENTS	enoxacin	enoxacin	ciprofloxacin
5	-	balofloxacin	QUINOLONES	fluoro-quinolones	fleroxacin	fleroxacin	clinafloxacin
6	-	cetefloxacin	ANTI-IN-FECTIVE AGENTS, QUINOLONE	amifloxacin	norfloxacin	norfloxacin	enoxacin
7	-	ciprofloxacin	FLUORO-QUINOLONES	balofloxacin	pefloxacin	pefloxacin	fleroxacin
8	-	clinafloxacin	amifloxacin	CETE-FLOXACIN	2-7/or	2-7/or	gatifloxacin
9	-	enoxacin	balofloxacin	cetefloxacin	1 and 8	1 and 8	gemifloxacin
10	-	fleroxacin	cetefloxacin	CIPROFLO-XACIN	-	-	grepafloxacin
11	-	gatifloxacin	CIPROFLO-XACIN	ciprofloxacin	-	-	levofloxacin
12	-	gemifloxacin	ciprofloxacin	CLI-NAFLOXACIN	-	-	lomefloxacin
13	-	grepafloxacin	clinafloxacin	clinafloxacin	-	-	moxifloxacin
14	-	irloxacin	ENOXACIN	ENOXACIN	-	-	norfleroxacin
15	-	levofloxacin	enoxacin	enoxacin	-	-	norfloxacin
16	-	lomefloxacin	FLEROX-ACIN	FLEROX-ACIN	-	-	ofloxacin
17	-	moxifloxacin	fleroxacin	fleroxacin	-	-	pefloxacin
18	-	nordifloxacin	gatifloxacin	GATI-FLOXACIN	-	-	premafloxacin
19	-	norfleroxacin	gemifloxacin	gatifloxacin	-	-	rufloxacin

(*Continued*)

20	-	norfloxacin	grepafloxacin	GEMI-FLOXACIN	-	-	sparfloxacin
21	-	ofloxacin	irloxacin	gemifloxacin	-	-	temafloxacin
22	-	oxo-ciprofloxacin	levofloxacin	GREPAFLOXA(	-	-	trovafloxacin
23	-	pefloxacin	lomefloxacin	grepafloxacin	-	-	-
24	-	premafloxacin	moxifloxacin	IRLOXACIN	-	-	-
25	-	prulifloxacin	nordifloxacin	irloxacin	-	-	-
26	-	rufloxacin	norfleroxacin	LEV-OFLOXACIN	-	-	-
27	-	sitafloxacin	NOR-FLOXACIN	levofloxacin	-	-	-
28	-	sparfloxacin	norfloxacin	LOME-FLOXACIN	-	-	-
29	-	temafloxacin	ofloxacin	lomefloxacin	-	-	-
30	-	tosufloxacin	oxo-ciprofloxacin	MOXI-FLOXACIN	-	-	-
31	-	trovafloxacin	PE-FLOXACIN	moxifloxacin	-	-	-
32	-	2-31/OR	pefloxacin	NORDI-FLOXACIN	-	-	-
33	-	1 and 32	premafloxacin	nordifloxacin	-	-	-
34	-	-	prulifloxacin	NOR-FLEROX-ACIN	-	-	-
35	-	-	rufloxacin	norfleroxacin	-	-	-
36	-	-	sitafloxacin	NOR-FLOXACIN	-	-	-
37	-	-	sparfloxacin	norfloxacin	-	-	-
38	-	-	temafloxacin	OFLOXACIN	-	-	-

(*Continued*)

39	-	-	tosufloxacin	ofloxacin	-	-	-
40	-	-	trovafloxacin	OXO-CIPROFLOXAC	-	-	-
41	-	-	4-40/or	oxo-ciprofloxacin	-	-	-
42	-	-	3 and 41	PE-FLOXACIN	-	-	-
43	-	-	limit 42 to human	pefloxacin	-	-	-
44	-	-	-	PRE-MAFLOXACIN	-	-	-
45	-	-	-	premafloxacin	-	-	-
46	-	-	-	PRULIFLOXAC	-	-	-
47	-	-	-	prulifloxacin	-	-	-
48	-	-	-	RU-FLOXACIN	-	-	-
49	-	-	-	rufloxacin	-	-	-
50	-	-	-	SITAFLOXACII	-	-	-
51	-	-	-	sitafloxacin	-	-	-
52	-	-	-	SPARFLOXACI	-	-	-
53	-	-	-	sparfloxacin	-	-	-
54	-	-	-	TEMAFLOXAC	-	-	-
55	-	-	-	temafloxacin	-	-	-
56	-	-	-	tosufloxacin	-	-	-
57	-	-	-	4-56/or	-	-	-
58	-	-	-	3 and 57	-	-	-

(*Continued*)

59	-	-	-	limit 58 to human	-	-	-

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

Appendix 2. Methods for future updates

Method	Details
Continuous data	If continuous data are reported with geometric means, we will combine the findings on a log scale and report them on the original one, and, where appropriate, calculate a summary statistic for each outcome
Stratifying trials	We will stratify the trials by the route of drug administration, oral or intravenous
Heterogeneity	We will investigate heterogeneity using presence of drug resistance (between trials: areas with drug resistance versus those without; within trials where drug resistance is common: participants with confirmed multiple-drug-resistant tuberculosis (MDR-TB) versus those without), fluoroquinolone dose, age (< versus ≥ 15 years), and length of treatment
Sensitivity analysis	We will investigate the effect of methodological quality using a sensitivity analysis
Funnel plots	We will use funnel plots to examine asymmetry, which may be caused by publication bias or heterogeneity

WHAT'S NEW

Last assessed as up-to-date: 13 October 2007.

Date	Event	Description
18 August 2008	Amended	Converted to new review format with minor editing.

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 3, 2005

Date	Event	Description
13 November 2007	New citation required but conclusions have not changed	2008, Issue 1: We updated the search and included one new trial. Alexander Vizel stepped down as a co-author

CONTRIBUTIONS OF AUTHORS

Lilia Ziganshina and Bertie Squire were authors of the original review and were jointly involved in this update.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Kazan State Medical Academy, Not specified.
- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2005, Issue 3 (first review version): We did not search SIGLE because we searched for conference proceedings using alternative sources. We added “sputum smear positive” to the definition of the relapse outcome, and added “total number of adverse events” to the list of outcome measures.

INDEX TERMS

Medical Subject Headings (MeSH)

Antitubercular Agents [*therapeutic use]; Ciprofloxacin [therapeutic use]; Fluoroquinolones [*therapeutic use]; Ofloxacin [therapeutic use]; Randomized Controlled Trials as Topic; Tuberculosis, Multidrug-Resistant [*drug therapy]; Tuberculosis, Pulmonary [*drug therapy]

MeSH check words

Humans