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[Intervention Review]

Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

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ABSTRACT

Background

Preventing active tuberculosis (TB) from developing in people with latent tuberculosis infection (LTBI) is important for global TB control. Isoniazid (INH) for six to nine months has 60% to 90% protective efficacy, but the treatment period is long, liver toxicity is a problem, and completion rates outside trials are only around 50%. Rifampicin or rifamycin-combination treatments are shorter and may result in higher completion rates.

Objectives

To compare the effects of rifampicin monotherapy or rifamycin-combination therapy versus INH monotherapy for preventing active TB in HIV-negative people at risk of developing active TB.

Search methods

We searched the Cochrane Infectious Disease Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS; clinical trials registries; regional databases; conference proceedings; and references, without language restrictions to December 2012; and contacted experts for relevant published, unpublished and ongoing trials.

Selection criteria

Randomized controlled trials (RCTs) of HIV-negative adults and children at risk of active TB treated with rifampicin, or rifamycin-combination therapy with or without INH (any dose or duration), compared with INH for six to nine months.

Data collection and analysis

At least two authors independently screened and selected trials, assessed risk of bias, and extracted data. We sought clarifications from trial authors. We pooled relative risks (RRs) with their 95% confidence intervals (CIs), using a random-effects model if heterogeneity was significant. We assessed overall evidence quality using the GRADE approach.

Main results

Ten trials are included, enrolling 10,717 adults and children, mostly HIV-negative (2% HIV-positive), with a follow-up period ranging from two to five years.

Rifampicin (three/four months) vs. INH (six months)

Five trials published between 1992 to 2012 compared these regimens, and one small 1992 trial in adults with silicosis did not detect a difference in the occurrence of TB over five years of follow up (one trial, 312 participants; *very low quality evidence*). However, more people in these trials completed the shorter course (RR 1.19, 95% CI 1.01 to 1.30; five trials, 1768 participants; *moderate quality evidence*). Treatment-limiting adverse events were not significantly different (four trials, 1674 participants; *very low quality evidence*), but rifampicin caused less hepatotoxicity (RR 0.12, 95% CI 0.05 to 0.30; four trials, 1674 participants; *moderate quality evidence*).

Rifampicin plus INH (three months) vs. INH (six months)

The 1992 silicosis trial did not detect a difference between people receiving rifampicin plus INH compared to INH alone for occurrence of active TB (one trial, 328 participants; *very low quality evidence*). Adherence was similar in this and a 1998 trial in people without silicosis (two trials, 524 participants; *high quality evidence*). No difference was detected for treatment-limiting adverse events (two trials, 536 participants; *low quality evidence*), or hepatotoxicity (two trials, 536 participants; *low quality evidence*).

Rifampicin plus pyrazinamide (two months) vs. INH (six months)

Three small trials published in 1994, 2003, and 2005 compared these two regimens, and two reported a low occurrence of active TB, with no statistically significant differences between treatment regimens (two trials, 176 participants; *very low quality evidence*) though, apart from one child from the 1994 trial, these data on active TB were from the 2003 trial in adults with silicosis. Adherence with both regimens was low with no statistically significant differences (four trials, 700 participants; *very low quality evidence*). However, people receiving rifampicin plus pyrazinamide had more treatment-limiting adverse events (RR 3.61, 95% CI 1.82 to 7.19; two trials, 368 participants; *high quality evidence*), and hepatotoxicity (RR 4.59, 95% 2.14 to 9.85; three trials, 540 participants; *moderate quality evidence*).

Weekly, directly-observed rifapentine plus INH (three months) vs. daily, self-administered INH (nine months)

A large trial conducted from 2001 to 2008 among close contacts of TB in the USA, Canada, Brazil and Spain found directly observed weekly treatment to be non-inferior to nine months self-administered INH for the incidence of active TB (0.2% vs 0.4%, RR 0.44, 95% CI 0.18 to 1.07, one trial, 7731 participants; *moderate quality evidence*). The directly-observed, shorter regimen had higher treatment completion (82% vs 69%, RR 1.19, 95% CI 1.16 to 1.22, *moderate quality evidence),* and less hepatotoxicity (0.4% versus 2.4%; RR 0.16, 95% CI 0.10 to 0.27; *high quality evidence*), though treatment-limiting adverse events were more frequent (4.9% versus 3.7%; RR 1.32, 95% CI 1.07 to 1.64 *moderate quality evidence*)

Authors' conclusions

Trials to date of shortened prophylactic regimens using rifampicin alone have not demonstrated higher rates of active TB when compared to longer regimens with INH. Treatment completion is probably higher and adverse events may be fewer with shorter rifampicin regimens. Shortened regimens of rifampicin with INH may offer no advantage over longer INH regimens. Rifampicin combined with pyrazinamide is associated with more adverse events. A weekly regimen of rifapentine plus INH has higher completion rates, and less liver toxicity, though treatment discontinuation due to adverse events is probably more likely than with INH.

PLAIN LANGUAGE SUMMARY

Alternatives to isoniazid monotherapy for preventing active tuberculosis in HIV-negative persons

Tuberculosis (TB) is a disease that is caused by a bacterial infection that affects an estimated two billion people (about a third of the world's population). However, most people have dormant (latent) infections and only a small percentage of people infected with TB will develop an active disease. Preventing latent TB infection (LTBI) developing into active TB, through the use of drugs, is an important part of global TB control. Treatment with the drug isoniazid for six months is recommended, but the treatment period is long, it can cause liver damage, and only about half of the people who start this drug treatment complete it.

The authors of this review evaluated alternatives to isoniazid monotherapy in HIV-negative people with LTBI. They identified 10 randomized controlled trials that included 10,717 adults and children, who were mostly HIV-negative, with a follow-up period ranging from two to five years.

Rifampicin for three to four months may give quite similar results to isoniazid for six months in preventing TB, and may cause fewer side effects. As the treatment period with rifampicin is shorter, it may result in more people completing treatment. Two other drug combination treatments (rifampicin plus isoniazid, and rifampicin plus pyrazinamide) did not differ in preventing TB compared with isoniazid alone, but they resulted in more adverse events. A third combination of rifapentine plus isoniazid supervised weekly for three months was as effective in preventing TB as self-administered isoniazid for nine months, increased treatment completion, and caused less liver toxicity, though treatment-limiting adverse events were more frequent with the weekly rifapentine and isoniazid combination.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Rifampicin (3 to 4 months) compared to isoniazid (6 to 9 months) for preventing active TB in HIV-negative people

Patient or population: HIV-negative people at risk of TB infection[1]
Intervention: Rifampicin for 3 to 4 months
Comparison: Isoniazid for 6 to 9 months

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Isoniazid	Rifampicin				
Active TB Follow-up: 5 years	**150 per 1000**	**121 per 1000** (70 to 210)	**RR 0.81** (0.47 to 1.4)	332 (1 study)	◯◯◯◯ **very low**[2,3,4,5]	In the placebo arm of this four-arm trial (HKCS 1992), 36/159 (23%) developed active TB.
Adherence[6]	**690 per 1000**	**822 per 1000** (697 to 884)	**RR 1.19** (1.01 to 1.3)	1768 (5 studies)	⊕⊕⊕◯ **moderate**[2,7,8,9]	
Treatment-limiting adverse events	**93 per 1000**	**45 per 1000** (21 to 93)	**RR 0.48** (0.23 to 1)	1674 (4 studies)	◯◯◯◯ **very low**[10,11,12]	
Hepatotoxicity: [13] Grade 3 and 4 toxicity	**46 per 1000**	**7 per 1000** (3 to 16)	**RR 0.15** (0.07 to 0.4)	1774 (5 studies)	⊕⊕⊕◯ **moderate**[10]	Only one child allocated to rifampicin in Magdorf 1994 developed hepatotoxicity

*The basis for the **assumed risk** is the control group risk in single studies, and the median risk in the control group for pooled data. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The data in this table are mostly from four trials in adults (HKCS 1992; Menzies 2004; Menzies 2008; Chan 2012). In another trial in children (Magdorf 1994), data for comparative effectiveness could not be used for the outcomes of developing active TB (no cases detected in 100 children over two years of follow up), and treatment-limiting adverse events (not reported). The data for adherence and hepatotoxicity are from all five trials.

[2] No study limitations: None of the trials were judged as at high risk of bias. Not downgraded.

[3] No inconsistency: Single trial (HKCS 1992) in adults with silicosis. In Chan 2012 involving adult prisoners, active TB was not detected over five years of follow up, so comparable effectiveness could not be determined. Menzies 2004, and Menzies 2008 did not report this outcome. Not downgraded.

[4] Serious indirectness: This study was done over 20 years ago and only included adult men with silicosis from Hong Kong; the results are not easily generalised to other treatment groups or settings, and may not be applicable today. Downgraded by 1.

[5] Very serious imprecision: The 95% CI of the effect estimate includes appreciable benefit and harm with rifampicin. The study was underpowered to be able to confidently detect differences between the two regimens. Downgraded by 2.

[6] In Chan 2012, conducted in prisoners, treatment was directly observed (except when prisoners were on parole). Treatment in HKCS 1992; Menzies 2004 and Menzies 2008 were self-administered.

[7] Serious inconsistency: There was significant inconsistency in the pooled results from the five trials (I^2 = 82%), but the inconsistency was largely due to the lack of difference in adherence with the two regimens in the small trial in children (Magdorf 1994), compared to greater adherence with rifampicin over INH in the four trials in adults (test for subgroup differences P = 0.00008). There also was inconsistency in the pooled results of the four trials in adults (1^2 = 55%), but the trials differed in the magnitude of effect estimates and not in the direction of effects. Downgraded by 1.

[8] No serious indirectness: Definitions of adherence differed between the trials, and with current expectations none of the trials were conducted in high TB burden, low-income countries, where socioeconomic circumstances may differ from those in moderate to low TB burden, high-income countries. However, these factors may not affect the relative advantage of adherence to the shorter rifampicin regimen over the isoniazid regimen. Not downgraded.

[9] No serious imprecision: Though the upper and lower limits of the 95% CI of the pooled relative risk include possibly non-appreciable and appreciable benefits for adherence to rifampicin, the absolute increase in those adherent to rifampicin compared to INH (particularly in adults: 129 more people per 1000, 95% CI 68 to 203 more per 1000, adherent to rifampicin compared to isoniazid) is likely to represent an appreciable benefit for national TB control programmes, particularly in high TB burden countries. Not downgraded.

[10] Serious study limitations: Two of the four included trials (Menzies 2004; Menzies 2008) were judged at high risk of detection bias. Downgraded by 1.

[11] Serious inconsistency: The I^2 value (68%) indicated significant inter-trial variability in effect estimates. The heterogeneity was due to appreciably lower adverse events with rifampicin in Chan 2012, where prisoners were given interventions by DOT

and had higher adherence (78%), thereby exposing more people to INH, than in the other three trials where self-administered treatment resulted in lower adherence (62%) and treatment limiting adverse events did not differ significantly between both regiments. Downgraded by 1.

[12] Serious imprecision: The upper and lower limits of the 95% CI of the effect estimate include appreciable benefit and no difference in treatment-limiting adverse events with rifampicin compared to INH. Downgraded by 1.

[13]One trial (Chan 2012) randomized participants stratified for co-infection with HBV and HCV; HCV infection was an independent risk factor for developing hepatotoxicity. The other three trials did not report on co-infection with HBV or HCV.

BACKGROUND

Description of the condition

Tuberculosis (TB) continues to be a common cause of death worldwide. Between 8.5 to 9.2 million new cases of TB, and 1.1 to 1.6 million TB deaths were estimated to have occurred worldwide in 2010. Most of these new cases occurred in South-East Asia and the Western Pacific (59%), and in Africa (26%) (WHO 2011a). In 2011, there were an estimated 8.7 million new cases of TB, 13% of whom were co-infected with human immunodeficiency virus (HIV); 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals, of which 300,000 were in HIV-negative women (WHO 2012). Only 5.8 million of the new cases were notified, and 80% of the estimated 8.7 million cases were from the 22 countries with a high TB burden. China and India accounted for 40% and a further 24% were from Africa, which has the highest rates of cases and deaths per capita, and the highest number of people with TB and HIV co-infection (WHO 2012).

Latent TB

TB is caused by *Mycobacterium tuberculosis* (though the *M. tuberculosis* complex includes four other TB-causing mycobacteria: *M. bovis, M. africanum, M. canetti*, and *M. microti*). An estimated two billion people (about a third of the world's population) are infected with *M. tuberculosis*, but only 5% to 10% of them manifest clinically active TB disease (Lin 2010; WHO 2010a). In the remainder of those infected, immune responses completely eradicate the infection in ~10%; while the immune response only succeeds in containment of the infection in ~90%. Some *M. tuberculosis* bacilli evade the microbicidal mechanisms of immune cells and remain dormant and undetected, except by immunological tests, in granulomas in the lungs that are the immunological and physical barriers erected by the infected person's immune reaction to contain the infection (Barry 2009; Lin 2010; Ahmad 2011). This sub-clinical infection, with the potential for re-activation to develop active TB, is called latent TB infection (LTBI).

As opposed to active TB disease, people with LTBI are clinically asymptomatic, and have normal chest radiographs. The tuberculin skin test (TST) and interferon-gamma release assays (IGRA) are widely used to identify people with LTBI; however, both tests are associated with false positive and false negative results in different circumstances. While IGRAs have the potential to facilitate risk stratification of people with LTBI in low TB-transmission settings (Corbiere 2012), there is no gold standard test currently available for the diagnosis of LTBI in countries with a high TB burden, in immunocompromised individuals such as with those with HIV infection, and in young children; neither do these tests accurately predict progression to active TB disease, nor accurately monitor the response to preventive treatment (Pai 2008; Dyrhol-Riise, 2010; Cattamanchi 2011; Diel 2011; Machingaidze 2011; Pai 2011; Sester 2011; Rangaka 2012; Zwerling 2012).

Reactivation of LTBI

People with LTBI can develop active TB disease (reactivation of LTBI) when bacterial multiplication exceeds the immune responses mounted to control bacterial growth (Barry 2009; Lin 2010; Ahmad 2011; Zuniga 2012). The lifetime risk of developing active TB in people with LTBI is about 10%, and in about 50%, progression to active TB occurs within the first two years following *M. tuberculosis* infection (Frieden 2003). This risk of progression is much higher in certain high-risk groups including HIV-positive people, and in others on immunosuppression, or with diseases that suppress immunity. Also at moderately high risk are young children (below five years) who are close contacts of people with pulmonary TB, those with diabetes mellitus, silicosis, and with severe malnutrition (Jasmer 2002a; Barboza 2008; Lobue 2010). Incarcerated prisoners are also at risk of developing TB due to the high prevalence and incidence of TB among prisoners; overcrowding; and other factors that increase the spread of TB among prisoners, including those without HIV (TBCTA 2009). Health care workers, particularly those working in certain locations and roles, are also at higher risk of developing LTBI (and active TB), than the normal population (Pai 2005; Joshi 2006; Baussano 2011; Christopher 2011).

Description of the intervention

The risk of progression to active TB could be reduced by the treatment of people with LTBI. Although the same drugs are used for the treatment of active TB as are used for the treatment of LTBI, the principles of treatment of LTBI differ from that of active TB. People with active TB require treatment with a combination of drugs for a long duration and treatment with a single drug is not recommended to treat active TB due to the risk of developing resistance. The current internationally recommended regimen for the treatment of active TB is a combination of four drugs: isoniazid (INH), rifampicin, pyrazinamide, and ethambutol for the first two months; followed by two drugs: INH and rifampicin for the next four months (WHO 2007; WHO 2010b; CDC 2011; NICE 2011). In contrast, standard therapy for people with LTBI, with much lower mycobacterial loads, is a single drug (monotherapy) or a combination of two or more drugs (combination chemotherapy) for shorter durations (Jasmer 2002a).

INH prophylaxis in LTBI

Currently, INH monotherapy for six to nine months is recommended for the prevention of active TB in people at high risk of active TB (ATS/CDC 2003; WHO 2007; WHO 2010b; NICE 2011; WHO 2012). A Cochrane systematic review reported that

INH-monotherapy decreases the risk of active TB by about 60% (95% CI 42% to 69%) in HIV-negative people at high risk of active TB followed up for two years (Smieja 1999). While six- and 12-month courses of INH were associated with similar reductions in the risk of active TB, the risk of hepatotoxicity (liver damage) was marginally higher in people treated with INH for 12 months. Though all-cause mortality was not reduced, TB-related deaths were reduced by treatment with INH (Smieja 1999). Nine months of INH is considered optimal for chemoprophylaxis, and with good adherence, nine months of INH is 90% protective against active TB; though for practical considerations, many programmes recommend the shorter six-month course (Lobue 2010). The benefits of INH prophylaxis are most apparent in those with LTBI who are HIV-negative; the protective efficacy is greater in those who are HIV-positive when the TST is positive (WHO 2010b). However, the long treatment duration and the fear of liver damage (CDC 2010) result in fewer than 50% to 60% completing the prescribed course of INH treatment, particularly the nine-month course, outside of clinical trials (LoBue 2003; Marais 2006; Horsburgh 2009).

Alternative INH and non-INH monotherapy or combination chemotherapy regimens

The efficacy of monotherapy with other antituberculous drugs for a shorter duration, such as rifampicin (from the family of rifamycin compounds) for three to four months; or a combination of antituberculous drugs (rifampicin plus INH for three months, rifampicin plus pyrazinamide for two to three months) have been demonstrated against placebo (Akolo 2010), and compared to six to 12 months of INH (Ena 2005; Gao 2006) in systematic reviews and meta-analyses of studies done mostly in HIV-positive people. Many believe these shorter alternative regimens would enhance acceptance and adherence to treatment in people with LTBI (Cook 2006; Lardizabal 2006; van Zyl 2006; Lobue 2010).

Rifapentine

Another promising alternative in preventing active TB in those with LTBI is rifapentine, a cyclopentyl-substituted rifamycin that is as effective as rifampicin, but whose serum half-life is five times that of rifampicin, thus permitting weekly dosing. Intermittent rifapentine was effective and safe in the treatment of active TB, when combined with INH once weekly during the continuation phase of treatment in HIV-negative patients with active TB (Benator 2002; Bock 2002).

A Phase II randomized controlled trial (RCT) of weekly rifapentine 900 mg with INH 900 mg for three months versus daily rifampicin plus pyrazinamide for two months showed similar efficacy in preventing active TB in household contacts of people with pulmonary TB in Brazil, but had to be stopped early due to unanticipated liver toxicity in the rifampicin plus pyrazinamide arm (Schechter 2006).

Once weekly INH (900 mg) plus rifapentine (900 mg) for 12 weeks administered by directly-observed treatment (DOT) was equally effective in preventing TB over a median follow-up duration of approximately four years, as was twice-weekly, INH (900 mg) and rifampicin (600 mg) by DOT, and daily self-supervised INH (300 mg daily), taken for six months or for up to six years in trials of HIV-positive, TST-reactive participants from Brazil, Canada, Spain, and the US, aged ≥18 years who were not receiving antiretroviral treatment. Treatment completion was greater in the two rifamycin-containing regimens than the INH regimens. Grade 3 (severe) or Grade 4 (potentially life-threatening) adverse effects were more common in those randomized to INH for six years (Martinson 2011).

The efficacy of intermittent rifapentine plus INH prophylaxis has not been demonstrated in HIV-positive people with LTBI from high burden countries in Africa, in China, and in India. The effects of rifapentine compared to INH monotherapy in HIV-negative adults and children with LTBI are also uncertain.

Potential for adverse events with alternative regimens

Notwithstanding the potential advantage of enhanced adherence, the alternative drug regimens for the treatment of LTBI are also associated with a risk of adverse effects, including hepatotoxicity, peripheral neuropathy, hypersensitivity reactions, and increased uric acid levels (McElroy 2005; Andrade 2011). Among these, hepatotoxicity is the most common treatment-limiting adverse effect, and all three drugs commonly used for the treatment of LTBI - INH, rifampicin, and pyrazinamide - have the potential to cause hepatotoxicity. The earlier recommended combination of rifampicin plus pyrazinamide given daily or twice weekly for two months is not currently recommended in HIV-negative adults with LTBI due to empirical evidence (Gao 2006) and surveillance data, indicating high rates of severe liver injury with the combination (ATS/CDC 2003), although children and HIV-positive adults appear to tolerate this short-duration combination treatment better.

Concerns about drug resistance

Another concern, apart from hepatotoxicity, is the potential emergence of drug-resistant TB with INH monotherapy or combination short-course chemotherapy for LTBI.

The use of INH or rifampicin monotherapy for the treatment of LTBI could potentially promote the emergence of multiple-drug resistant TB (MDR-TB), defined as combined resistance to at least rifampicin and INH; and even extensively drug-resistant TB (XDR-TB), defined as MDR-TB strains additionally resistant to a fluoroquinolone and at least one of the second-line injectable agent such as kanamycin, amikacin, or capreomycin (WHO 2008).

In a systematic review of 13 studies including over 18,000 people treated with INH monotherapy and nearly 18,000 controls, the

pooled relative risk for the development of INH-resistant TB was not significantly increased (RR 1.45, 95% CI 0.85 to 2.47); and the risk was similar in studies of HIV-positive and HIV-negative people (Balcells 2006). However, many of the included studies were limited by the incomplete testing of isolates.

On the other hand, the use of combination chemotherapy for the treatment of LTBI could prevent, at least theoretically, the development of drug-resistant TB; but the risk of drug-resistant TB following treatment with regimens other than the conventional INH monotherapy is also currently unknown. Acquired rifamycin resistance has been documented in HIV-seropositive adults who fail or relapse after treatment with intermittent regimens combining INH with rifampicin, rifapentine, or rifabutin (CDC 2002); but the true extent of resistance, systematically ascertained from cohort studies or from RCTs, in HIV-negative people with LTBI is lacking. While contacts of people with INH-resistant TB can be effectively treated with rifampicin, there is currently insufficient evidence of moderate or high quality from RCTs on the optimal management of contacts of people with MDR-TB or XDR-TB (WHO 2011b; van der Werf 2012).

How the intervention might work

The potential advantages of alternative rifampicin-containing regimens over the standard six or nine months of INH prophylaxis in people with LTBI that need to be empirically demonstrated are:

1. increased acceptance and treatment completion rates in people with LTBI due to the shorter duration of treatment;
2. potentially reduced incidence of adverse events with non-INH containing regimens, particularly liver damage, leading to less need for intense monitoring and reduced costs associated with monitoring or in the management of adverse events;
3. equivalent efficacy as with six and nine months of INH;
4. possibly superior effectiveness, due to increased treatment completion rates compared to the six and nine month INH courses;
5. increased prescription of the alternative prophylactic regimens by physicians due to less perceived risks with treatment and more favourable risk/benefit assessments by physicians (and by people with LTBI);
6. reduced incidence of drug resistance due to increased treatment completion rates;
7. reduced resource costs and overall cost savings from the societal and payers' perspectives, in high and in low TB burden countries
8. reduction in deaths in people with LTBI

Why it is important to do this review

Since the risk of progression to active TB is far greater in HIV-positive than in HIV-negative people (Ahmad 2011; WHO 2011c), LTBI preventive treatment in HIV-negative people is less of a priority, particularly in resource-constrained settings. TB in people with HIV is more likely to be due to new infections (re-infection), particularly in high-transmission settings, rather than reactivation of LTBI (Houben 2011). Reactivation of LTBI is the major concern in HIV-negative people, and most of the active TB cases in low TB incidence countries, and in high TB incidence countries outside Africa such as China and India, arise from this pool of HIV-negative individuals with LTBI. In addition, in countries with a high TB incidence, the duration of protection with LTBI treatment may be reduced due to the increased incidence of re-infection, even in HIV-negative people (Nardell 2011).

An updated Cochrane Review concluded that while alternative regimens to INH for LTBI in HIV-positive people were as effective, they were less well tolerated (Akolo 2010). However, HIV-positive people differ from HIV-negative people in the frequency of co-morbid conditions (infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) and are often on concomitant medications that also increase the risk for adverse events, particularly liver toxicity (Gordin 2004). Current international guidelines (WHO 2010b; CDC 2011; NICE 2011) differ in their recommendations for LTBI preventive treatment in HIV-negative people. TB is common, and effective and well-tolerated preventive therapy is an important policy issue. A reliable summary across all relevant trials of alternative regimens with differing effect profiles compared to INH in HIV-negative people will help inform policies to control the global transmission of TB.

OBJECTIVES

To compare the effects of rifampicin monotherapy or rifamycin-combination therapy versus INH monotherapy for preventing active TB in HIV-negative people at risk of developing active TB.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs that randomized individuals or clusters of individuals. Quasi-RCTs (where allocation to intervention arms could be predicted) were excluded.

Types of participants

HIV-negative people at risk of developing active TB and without active TB at the time of enrolment.

While people with LTBI can be stratified by levels of risk of developing active TB (TBCTA 2009; Lobue 2010), we included all trials of HIV-negative people diagnosed to have LTBI, irrespective of risk stratification. We also included trials of children at risk for active TB (eg asymptomatic children of patients with pulmonary TB).

We excluded trials including primarily HIV-positive people.

Types of interventions

Intervention

Treatment with rifampicin or rifamycin-containing drug combinations (any dose or duration).

Control

INH monotherapy for six to 12 months.

Types of outcome measures

Primary

Rates of active TB.

Ideally this should have been based on mycobacterial diagnosis (smear or culture); histological diagnosis; or as a defined clinical syndrome with typical symptoms, consistent and independently assessed chest X-ray, and a documented response to anti-TB treatment (ATS 1990). We included data for active TB from trials that used a combination of clinical, mycobacterial, and radiological criteria even if the procedures used did not satisfy all ATS 1990 criteria. Where criteria used were not clear, we attempted to obtain information from trial authors, failing which we documented the criteria used, but did not exclude the trial.

Secondary

- TB-related deaths
- All-cause death
- Incidence of drug-resistant TB including MDR-TB and XDR-TB
- Adherence to treatment (as defined by the study authors)

Adverse events

- Serious adverse events (as defined by the study authors based on clinical as well as laboratory criteria)
- Drug-related deaths
- Hepatotoxicity (severity based on classifications such as those of Blumberg 2003, or as described in the trial report)
- Adverse events requiring treatment discontinuation
- Other adverse events (including skin rash, nausea or vomiting, diarrhoea, epigastric pain, fatigue or malaise, dizziness, headache, fever or chills, arthralgia, peripheral neuropathy, anorexia/weight loss, insomnia, pruritis, and dysmenorrhoea)

Search methods for identification of studies

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

Electronic searches

Databases

On 5 December 2012 we updated searches conducted in November 2008, January 2011, November 2011, and May 2012 of the Cochrane Infectious Diseases Group (CIDG) Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 11, 2012); MEDLINE; EMBASE; and LILACS using the terms detailed in Appendix 1. The search was conducted by Vittoria Lutje, the Trials Search Co-ordinator of the CIDG.

Additionally, in order to identify relevant trials from journals that may not be indexed in these databases, we searched the web-site of the Indian Medlars Center (IndMED; http://indmed.nic.in/) and the South Asian Database of Controlled Clinical Trials (http://www.cochrane-sadcct.org/) using 'tuberculosis' and 'isoniazid' as search terms.

Conference proceedings

We searched the following conference proceedings of the American Thoracic Society based on availability (http://www.thoracic.org/journals/pats/index.php):

- ATS International Conference, San Diego, May 2009
- ATS International Conference, New Orleans, May 2010
- ATS International Conference, Denver, Colorado, May 2011

We also searched the conferences proceedings of the International Union against Tuberculosis and Lung Disease (http://www.theunion.org/index.php/en/conferences):

- 1st Conference of The Union South-East Asia Region, New Delhi, India, September 2008
- 5th Conference of The Union Europe Region, Dubrovnik, Croatia, May 2009
- 13th Conference of The Union Latin American Region, San Salvador, El Salvador, March 2010
- 18th Union Conference for the African Region, Abuja, Nigeria, March 2011
- 3rd Conference of The Union Asia-Pacific Region, Hong Kong, China, July 2011

- 42nd Union World Conference on Lung Health, Lille, France, October 2011

Trials registries

We searched the *meta*Register of Controlled Trials (http://www.controlled-trials.com/mrct/) and the WHO International Trials Clinical Registry Platform's Search Portal (http://apps.who.int/trialsearch/) for ongoing or completed but unpublished trials.

Searching other resources

We contacted researchers in the field to identify additional studies that were eligible for inclusion. We also contacted relevant organizations, including the World Health Organization (WHO), the Prevention of Tuberculosis Trials Consortium (TBTC), and the Global Partnership to Stop TB, for unpublished and ongoing trials.

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

Data collection and analysis

Selection of studies

Three authors (SKS, TK, and AS) independently screened all citations and abstracts identified by the search strategy to identify potentially eligible studies. We obtained full text articles of potentially eligible studies. We assessed the articles for inclusion using a pre-designed eligibility form based on the inclusion criteria. We checked for multiple publications of the same data and selected one reference as the primary reference and listed the others as subsidiary references. We contacted the trial authors for clarification if eligibility was unclear. We resolved any differences in opinion with the fourth author (PT). We documented the reason for excluding studies. The fourth author (PT) independently checked the table of excluded studies to confirm the accuracy of the stated reasons for exclusion. We responded to peer referee and editorial suggestions on inclusion and exclusion of studies.

Data extraction and management

Two authors (SKS and TK) independently extracted data using a pre-tested data extraction sheet. For all included trials, we extracted information on the number of participants randomized and number for which outcomes were measured. We extracted the number of events and the number of participants in each treatment arm for dichotomous outcomes.

We resolved any discrepancies in the extracted data by discussion and, if required, referred to PT. PT independently checked all extracted data and extracted additional data. We attempted to contact the contact author or senior author for further details when data were not clear or not presented in the publication.

Assessment of risk of bias in included studies

Three authors (SKS, TK, and PT) independently assessed the risk of bias in the included trials. We attempted to contact the trial authors if details were missing or unclear in the publications. We resolved disagreements through consensus and in one instance by consulting an editor of the CIDG. We assessed each of the included trials for the risk of bias on six domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other biases. For each of these components, we assigned a judgement regarding the risk of bias as yes, no, or unclear (Higgins 2011). We recorded our judgements and justifications in risk of bias tables accompanying the characteristics of each included study and summarized the findings in a risk of bias summary figure.

Measures of treatment effect

TK and PT independently entered data and this was checked by all authors. We compared dichotomous outcomes using the risk ratio (RR) and we presented all results with their 95% confidence interval (CI) values.

Unit of analysis issues

If studies employ cluster randomizations (such as randomization by family, household, or institution), pooling of clustered data may pose problems if the reported analyses have not accounted for the clustering effect. Failing to account for intra-class correlation in clustered studies, leads to a unit of analysis error (Divine 1992) whereby P values are spuriously low and, CI values unduly narrow. When results had been adjusted for clustering, we attempted to extracted the point estimate and the 95% CI. If results had not adjusted for clustering, or were otherwise not usable, we attempted to account for clustering using methods described in the Cochrane Handbook, Chapter 16.3.4 and 16.3.5 (Higgins 2011b). When this was not possible (eg cluster sizes or number of clusters were not reported, loss of clusters were large, or the number of missing clusters were unknown), we extracted the data as for the individually randomized trials and used it in a sensitivity analysis.

Dealing with missing data

We attempted to obtain missing data from study authors. We conducted an intention-to-treat analysis in trials with no loss to follow-up and completed case analysis for trials with incomplete follow-up. We made no assumptions about those lost to follow-up but utilised this information in assessing risk of attrition bias due to incomplete outcome data reporting and in grading the overall quality of evidence for each outcome.

Assessment of heterogeneity

We assessed heterogeneity between the trials by examining forest plots for inconsistency in the direction or magnitude of the effect estimates, with non-overlapping CIs. We used the Chi^2 test for heterogeneity with a 10% level of significance to detect inconsistency in study results that exceeded chance, and the I^2 statistic to denote the percentage of inconsistency in results due to inter-trial variability that exceeded random error (Higgins 2003).

In general, we interpreted an I^2 value of 50% or greater to denote significant heterogeneity (Higgins 2003), though we acknowledged that this cut-off is arbitrary. We therefore interpreted I^2 values between 0% to 40% as possibly unimportant, 30% to 60% as possibly significant, 50% to 90% as possibly substantial, and 75% to 100% as possibly considerable; depending on whether the inconsistency in results were due to differences in the direction of effects estimates between trials, rather than due to differences in the magnitude of effect estimates favouring an intervention; as well as the strength of the evidence for heterogeneity from the P value for the Chi^2 test for heterogeneity (Deeks 2011).

Assessment of reporting biases

We would have evaluated the possibility of publication bias by the use of funnel plots, had there been 10 or more trials in a meta-analysis.

Data synthesis

We synthesised comparable data using the Mantel-Haenszel method to derive pooled, weighted risk ratios in fixed-effect meta-analyses. We used the random-effects model for data synthesis when heterogeneity was identified as significant (see above) and could not be explained by subgroup analyses (see below). If I^2 values revealed substantial inter-trial variability in effect estimates in excess of chance that were thought to be due to variations in clinical or methodological attributes, we suggested caution in interpreting the pooled estimates. Had substantial heterogeneity been unexplained, we would have presented the results of the trials in a forest plot, without summating their effect estimates.

Subgroup analysis and investigation of heterogeneity

When data were available, we explored potential sources of heterogeneity in the following subgroup analyses for the primary outcome measure: participant age (children < 18 years versus adults); presence of underlying systemic or pulmonary diseases (eg silicosis or chronic renal failure on haemodialysis); and treatment duration.

Sensitivity analysis

Where there were sufficient data, we undertook sensitivity analyses to investigate the robustness of the results to the exclusion of trials at high risk of bias.

Summarising and interpreting results

We used the GRADE approach to interpret findings (Schunemann 2008) and used GRADE Profiler (GRADE 2004) to import data from Review Manager (RevMan) to create 'Summary of findings' tables for each comparison included in this review. These tables provide information concerning the overall quality of the evidence from the trials, the magnitude of effect of the interventions examined, and the sum of available data on the primary outcome and selected secondary outcomes. The outcomes selected for inclusion in these tables that were rated important or critically important to clinical decision-making were: development of active TB; adherence; treatment-limiting adverse events; and hepatotoxicity. This summary was used to guide our conclusions and recommendations.

RESULTS

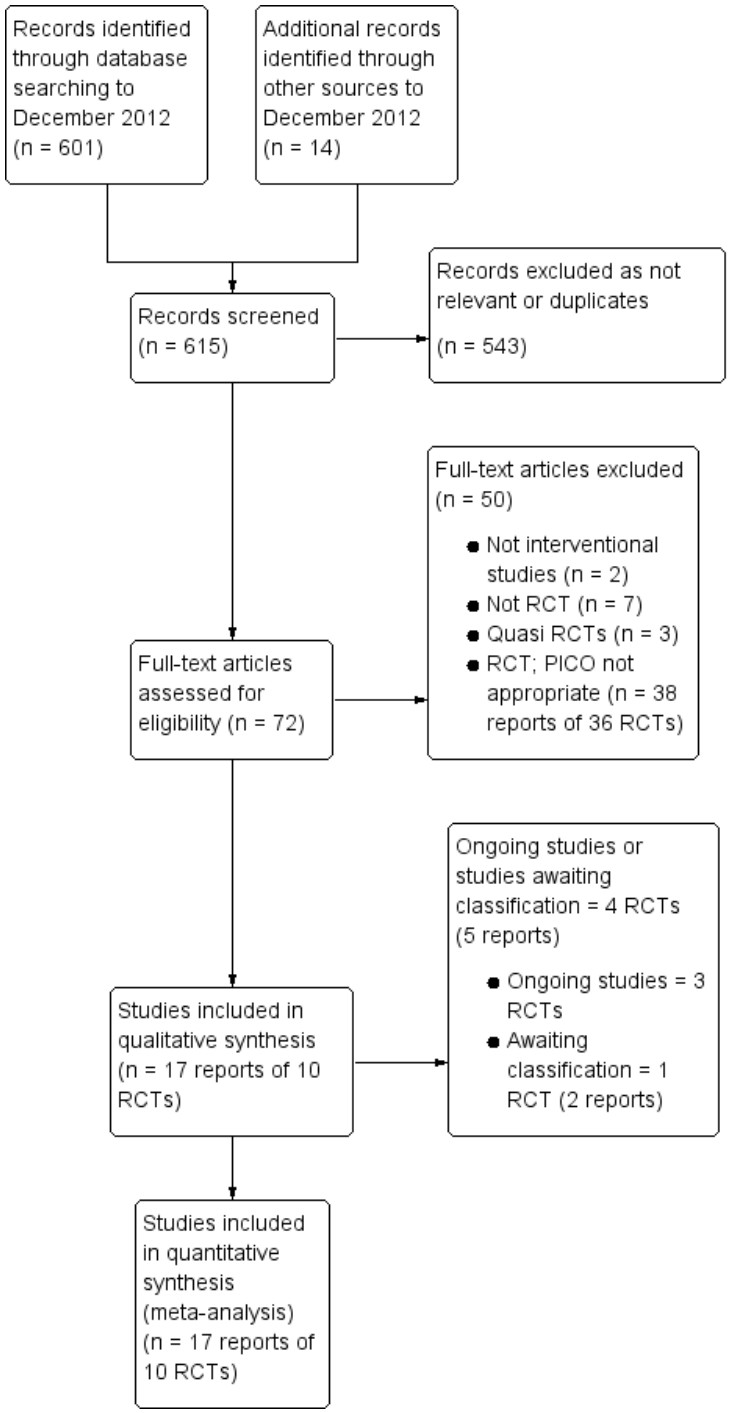
Description of studies

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

Results of the search

We retrieved 615 reports by our searches performed between November 2008 to December 2012. After we removed duplicates and excluded irrelevant reports, we identified 72 potentially relevant records and we obtained full text reports. We selected 10 RCTs for inclusion and we have shown the selection process in Figure 1.

Figure 1. Study flow diagram.



Included studies

The 10 RCTs (detailed in 17 reports) that met the inclusion criteria for this review are described in the Characteristics of included studies table. Salient features summarized below.

Participants, interventions, and comparisons

The 10 included trials randomized 10,717 participants to four sets of interventions. Eight trials randomized individuals, one trial (Tortajada 2005) randomized households (by index case), and one trial (Sterling 2011) randomized households as well as individuals.

1. Rifampicin monotherapy versus INH monotherapy

Five trials randomized 1781 participants to rifampicin (N = 891) given daily for three months (HKCS 1992) or for four months (Magdorf 1994; Menzies 2004; Menzies 2008; Chan 2012) versus INH monotherapy (N = 890) given daily for six months (HKCS 1992; Magdorf 1994; Chan 2012) or for nine months (Menzies 2004; Menzies 2008).

HKCS 1992 was a four-armed trial (rifampicin versus INH versus INH plus rifampicin versus placebo) conducted in 589 adult Chinese males with exposure to silica dust or with silicosis attending a special pneumoconiosis clinic in Hong Kong, who had no history of treatment for TB, and who had active TB ruled out by clinical assessment, three sputum smears and culture for *M. tuberculosis.* At inclusion, 94% of participants had a TST reaction of ≥ 10 mm. Participants were followed up for two to five years. Of the 159 people randomized to placebo only (data not used in quantitative synthesis in this review), 36 (23%) developed active TB over five years' follow-up; an indication of the high risk that those with silicosis and LTBI in this trial had of progression to TB.

Magdorf 1994 was a three-armed trial (rifampicin versus INH versus rifampicin plus pyrazinamide) conducted in Germany that randomized 150 boys and girls less than 18 years of age with a normal chest radiograph and who were TST convertors within the previous 24 months. Participants were followed up for two years.

Menzies 2004 randomized adult males and females with a positive TST who were referred for LTBI treatment by physicians to a university-associated respiratory clinic in Quebec, Canada, and who were not contacts of people with INH resistance, allergic to rifampicin, or taking drugs likely to interact with rifampicin. Of the 116 people randomized, 110 had a TST reaction of ≥ 10 mm. Participants were followed up until treatment completion (four months in the rifampicin arm and nine months in the INH arm).

Menzies 2008 included adult male and female participants from nine university affiliated hospitals in Brazil (1), Canada (7), Saudi Arabia (1), with similar inclusion and exclusion criteria, study design, aims, and duration of follow-up as in Menzies 2004. Of the 847 randomized participants, 804 had a TST reaction of ≥ 10 mm. Both these trial reports did not mention methods used to rule out those with active TB at inclusion.

Chan 2012 recruited consenting adult male prisoners in Taipei, Taiwan who were TST-positive and Quantiferon Gold Positive, and had no evidence of active TB, HIV infection, or liver disease. They were randomized to receive INH daily for six months or rifampicin daily for four months. The primary outcomes were safety and adherence as assessed at the end of treatment in each group. Patients were followed up for three years for efficacy and though data for this secondary outcome was not published in the trial report, Dr. Chan kindly provided us data on the development of active TB in those followed up.

The HIV status of participants were not reported in two trials (HKCS 1992; Magdorf 1994). In Menzies 2004 and Menzies 2008, randomization was stratified by the risk of developing active TB, with HIV infection considered a high risk factor; however, the former did not report the inclusion of any participant with HIV infection. Menzies 2008 enrolled six HIV-positive participants (1%) to rifampicin and seven (2%) to INH.

2. Rifampicin plus INH versus INH

Two trials randomized 536 people to receive a combination of rifampicin plus INH (N = 265) given daily for three months versus daily INH (N = 271) for six months (HKCS 1992) or for nine months (Martinez Alfaro 1998).

HKCS 1992 (described above) had one trial arm where 167 of the 589 randomized participants in this four-armed trial took rifampicin and INH daily for three months.

Martinez Alfaro 1998 was conducted at a general hospital in the Albacete province in Spain and randomized 196 people of all ages and both genders. The detailed inclusion and exclusion criteria are described in Characteristics of included studies The duration of follow-up was 19 ± 11 months in the INH plus rifampicin arm and 16 ± 10 months in the INH arm. Those randomized to INH were all adults.

3. Rifampicin plus pyrazinamide versus INH

Four trials (Magdorf 1994; Leung 2003; Sanchez-Arcilla 2004; Tortajada 2005) that randomized 661 participants evaluated rifampicin and pyrazinamide (N = 347) given daily for two months or to INH daily (N = 384) for six months.

Magdorf 1994 (described above) randomized 150 children who were TST convertors in the previous two years to three interven-

tions where 50 children in one arm were given rifampicin plus pyrazinamide daily for two months.

Leung 2003 recruited 77 Chinese adults (mostly males) with clinical and radiological evidence of silicosis attending the pneumoconiosis clinic of the department of health in Hong Kong, China, with a TST reaction of ≥ 10 mm. The report followed participants to treatment completion but the senior author of the report provided us with unpublished data on follow-up to five years.

Neither trial specified HIV-infection as an exclusion criterion, nor did they report if any participant was tested for HIV infection or were HIV-positive.

Sanchez-Arcilla 2004 randomized 172 homeless adult men and women recruited from government-run and charitable shelters in Madrid, Spain, with a TST reaction > 5 mm. Apart from a positive TST in all, 105 (61%) had at least one risk factor for LTBI. One participant in each arm was HIV-positive. The duration of follow-up was six months in the INH arm, and two months in those given rifampicin plus pyrazinamide.

Tortajada 2005 randomized 352 adults and children older than one year who were contacts of an infectious person with TB, was TST-positive, and met criteria for treatment of LTBI. None were HIV-positive. The trial was stopped prematurely after an interim evaluation due to unexpectedly high rates of liver toxicity. Duration of follow-up was unclear, and was likely to have to have been unequal for all participants due to the premature termination while recruitment had not been completed,

4. Rifapentine plus INH once a week (DOT) for three months versus daily INH daily (self administered) for nine months

Sterling 2011 is the primary publication of an ongoing trial, PREVENT-TB, (NCT00023452) that is due to be completed in 2013. This open-label, randomized, non-inferiority trial, compared three months of DOT once-weekly with rifapentine (900 mg) plus INH (900 mg) (combination-therapy group) with nine months of self-administered daily INH (300 mg) (INH-only group) in 7799 people at high risk for TB who fulfilled eligibility criteria (of 8053 initially randomized) from 26 centres in four countries: USA (21), Canada (3), Brazil (1), Spain (1). Children over two years of age were eligible but the proportions of children among those randomized was unclear. One hundred participants (2.7%) in the INH only arm and 105 (2.6%) in the combination arm were HIV-positive. The primary end point was confirmed TB, and the non-inferiority margin was 0.75%. Participants were followed up for 33 months after enrolment.

This trial used a combination of cluster and individual randomization; close contacts of the first eligible person in a household were randomized by household, and other high-risk participants who were not part of a household were randomized individually. The number of participants randomized in clusters were 1345 of 3986 (33.7%) in the combination-therapy arm and 1050 of 3745 (28%) in the INH-only arm.

Three trials (Sanchez-Arcilla 2004; Menzies 2008; Sterling 2011) did not report data separately for HIV- positive and HIV-negative participants, but we do not feel that the small proportions of HIV-positive individuals (2% in total) included in the three trials biased our analyses.

Outcomes

Five trials reported on the development of active TB (HKCS 1992; Magdorf 1994; Leung 2003; Tortajada 2005; Sterling 2011). Of these, Magdorf 1994 did not report the definition used for the diagnosis of active TB. HKCS 1992 followed up participants with silicosis with bacteriological and radiological evaluations for active TB over two to five years after completion of treatment. The other trial in people with silicosis (Leung 2003,) followed up participants for active TB with sputum and radiological examinations up to treatment completion, but we were provided unpublished data on the yearly evaluations for up to five years of follow-up (courtesy of Dr Leung). Tortajada 2005 did not provide criteria used for the diagnosis of active TB and had unequal ascertainment periods due to premature termination of the trial. The average duration of follow-up was also not reported in the trial. Sterling 2011 supplemented active follow-up of participants in US and Canada with passive follow-up of national US and Canadian TB databases. Chan 2012 provided unpublished data on follow-up by active case finding (clinical, X-ray; sputum culture) for three years. It was unclear if all trials used procedures that strictly adhered to ATS 1990 criteria

Of the remaining four trials, Martinez Alfaro 1998 evaluated efficacy by evaluating the diameter of induration produced by the TST following the course of treatment and at follow-up time points; we did not use this data in quantitative synthesis in this review. Efficacy was not a stated objective of Menzies 2004; Menzies 2008; and Sanchez-Arcilla 2004.

Of the secondary outcomes for this review some reported TB-related deaths and non-TB deaths, while Sterling 2011 provided data for all-cause deaths. HKCS 1992; Leung 2003; and Sterling 2011 reported the development of drug resistant TB including MDR-TB; none of the trials reported XDR-TB.

All the trials reported on adherence to treatment. All trials reported adverse events and serious adverse events, and treatment-limiting adverse events. The definitions used and methods to ascertain these outcomes differed and are described in Appendix 2.

Tortajada 2005 reported adjusted odds ratios and 95% CI that were adjusted for clustering, but we were not able to use these adjusted estimates since RRs were the effect measures used in this review. We were unable to use methods described in Chapter 16.3.4 and 16.3.5 of the Cochrane Handbook (Higgins 2011b) to extract reported data to adjust for clustering and compute adjusted RRs, since the number of clusters were not reported. Even if we had approximated this information from the data provided, the

number of missing clusters were also not known, due to the premature termination of the trial and the unequal follow-up periods of participants. Imputing data from cluster randomized trials in such circumstances are more prone to error than when data are missing in cluster randomized trials at random or are co-variate dependant (Ma 2011), We therefore extracted data as for individual RCTs. The outcomes of hepatotoxicity, and other adverse events are less likely to be significantly correlated within individuals in clusters, while a cluster effect is more likely for outcomes such as development of active TB and adherence. None of the included participants developed TB in this trial. For adherence, we assessed the impact on the pooled effect estimates in sensitivity analyses of the inclusion and exclusion of the adherence data from this trial that were not adjusted for a cluster effect.

Excluded studies

We excluded 50 reports pertaining to 47 studies. Two were not interventional studies; seven were not RCTs; and three were quasi-RCTs. Thirty-eight reports pertaining to 36 RCTs did not fulfil the inclusion criteria of our review (see Characteristics of excluded studies for further details).

Ongoing studies

The three ongoing trials aim to recruit over 6920 participants randomized to rifampicin given daily for four months versus INH for nine months and anticipate completing recruitment in 2013 (NCT01398618), 2014 (ISRCTN53253537), and 2016 (NCT00931736). Further details are provided under Characteristics of ongoing studies.

Studies awaiting classification

One RCT (White 2012) registered retrospectively (NCT00128206) was conducted among adult prisoners in San Francisco City and Country Jail diagnosed with LTBI at jail entry. The trial evaluated INH 900 mg DOT given twice weekly for nine months with daily rifampicin 600 mg. Of 364 randomized, only 29% (107) completed therapy (26% (47 of 184) of INH participants and 33% (60 of 180) of rifampicin participants. In addition to very high attrition and the non-standard administration of INH and rifampicin in this trial, compared to the other included trials of INH versus rifampicin there were discrepancies regarding primary and secondary outcomes, and the estimated sample size within the registration document and between the registration document and the trial publication. Drug toxicity, adherence, cost-effectiveness, reasons for non-completion, and efficacy are outcomes listed in the trials registration document, but data for cost effectiveness and efficacy are not available in the trial publication or in the results posted in the trials registry. In addition, 178 of those recruited were transferred or deported from prison (nearly 50%) and were classified as non-adherent, raising serious doubts as to the validity of the data on adherence. We shall decide on inclusion of the results of this trial in future updates of this review once clarifications are received from trial authors.

Risk of bias in included studies

The assessments regarding the risk of bias for all included studies are depicted in Figure 2; assessments for included trial are available in the "Risk of Bias" tables accompanying each study's characteristics and are summarised in Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

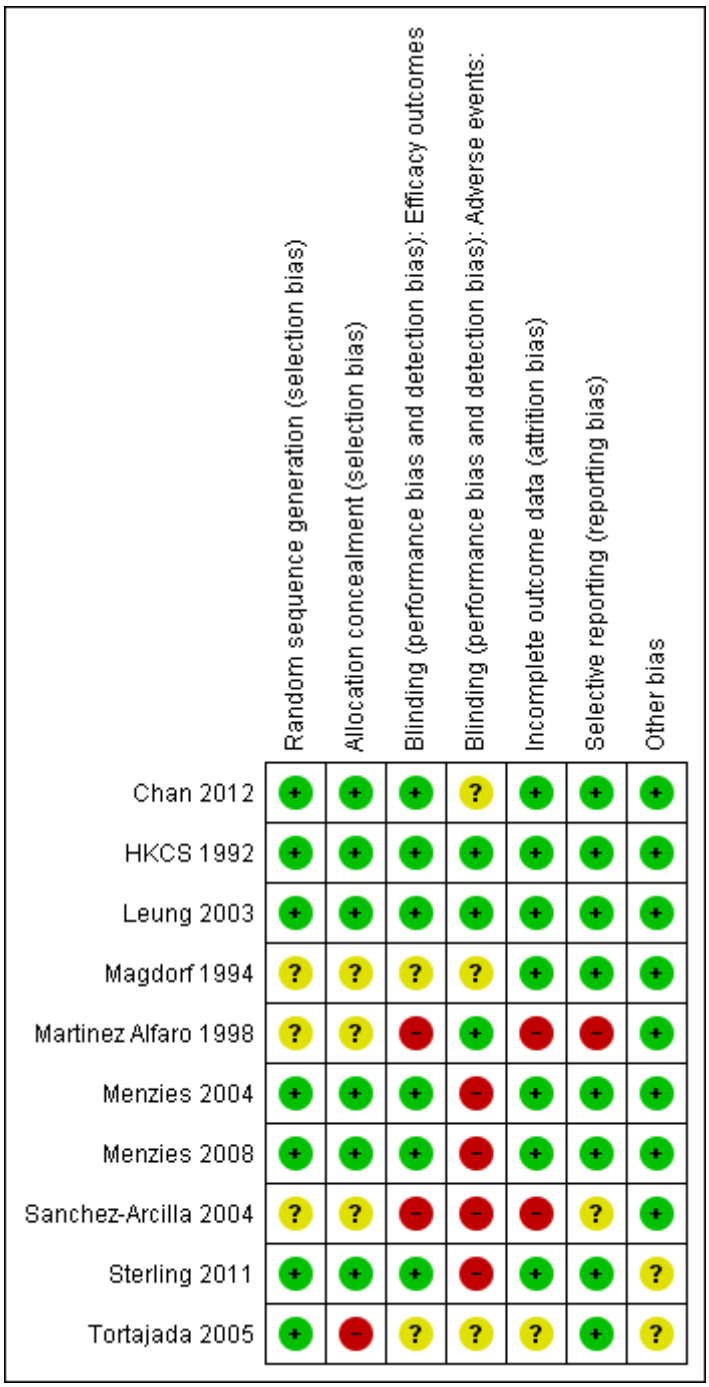
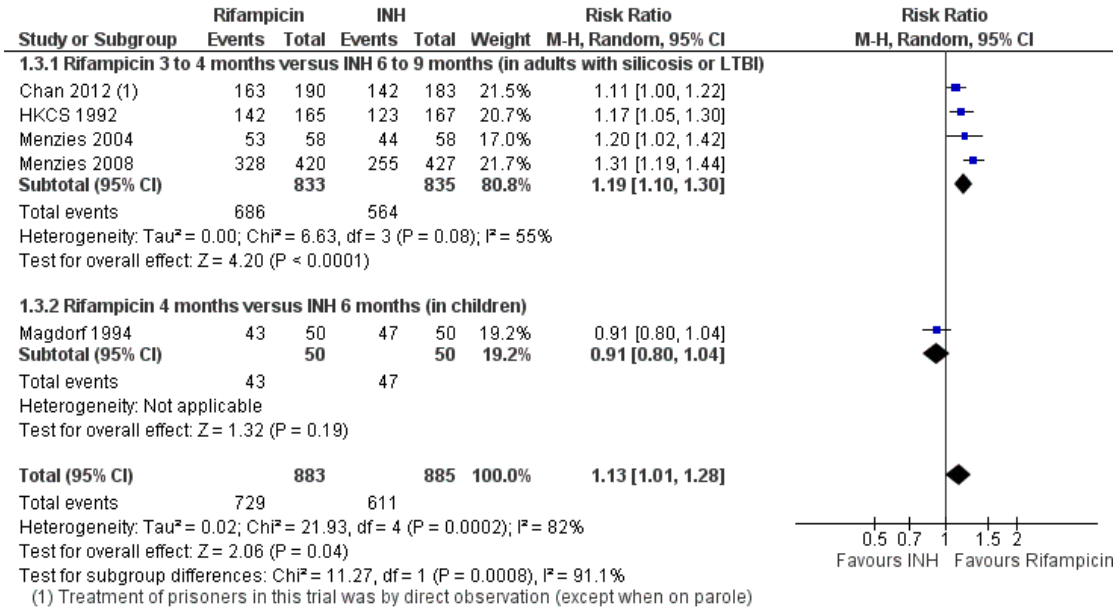


Figure 3. Forest plot of comparison: 1 Rifampicin versus INH, outcome: 1.3 Adherence.



Allocation

Six of the included studies were judged to be free of the risk of bias for sequence generation and allocation concealment (HKCS 1992; Leung 2003; Menzies 2004; Menzies 2008; Sterling 2011; Chan 2012). Tortajada 2005 was judged free of bias for sequence generation but at high risk of selection bias due to inadequate allocation concealment. Three trials (Magdorf 1994; Martinez Alfaro 1998; Sanchez-Arcilla 2004) provided inadequate details to assess adequacy of allocation concealment and were judged unclear with regard to the risk of selection bias.

Blinding

Efficacy outcomes: active TB, drug-resistant TB, and adherence

We judged seven of the included trials to be free of the risk of performance and detection bias with regard to efficacy outcomes. We judged one open-label trial (Martinez Alfaro 1998) as not free of the risk of bias with respect to self-reported adherence, and use of post-treatment TST diameter as a proxy indicator of active TB. The latter, apart from doubtful validity as an indicator of active TB after chemoprophylaxis, is at risk of bias due to knowledge of treatment allocation. Sanchez-Arcilla 2004 was also judged to be at high risk of detection bias for adherence due to selective supervision of only those with features of liver disease. Tortajada 2005 was judged unclear for detection bias.

Adverse events: hepatotoxicity, serious adverse events, and treatment-limiting adverse events

Three trials (Magdorf 1994; Chan 2012; and Tortajada 2005) were judged unclear. We judged four other open-labelled trials (Menzies 2004; Sanchez-Arcilla 2004; Menzies 2008; Sterling 2011) as at high risk of detection bias in ascertaining serious adverse events.

Incomplete outcome data

Martinez Alfaro 1998 did not report treatment allocation of the one participant who developed active TB. It is also unclear whether all patients were evaluated for active TB using standard clinical methods; the proxy measure reported was not used in this review. Sanchez-Arcilla 2004 was also judged at high risk of attrition bias

due to high differential drop-out rates in the two intervention arms. Tortajada 2005 was judged unclear for risk of attrition bias due to the premature termination due to hepatotoxicity and the resultant loss of an unknown number of clusters.

Selective reporting

Martinez Alfaro 1998 and Sanchez-Arcilla 2004 were judged as not free of the risk of reporting biases.

Other potential sources of bias

It was unclear whether the randomization procedures in Sterling 2011, which used a combination of cluster and individual randomization, led to biased efficacy estimates since analysis did not account for a cluster effect. However, a sensitivity analysis in the report that excluded those randomized in clusters did not alter effect estimates.

We judged Tortajada 2005 as unclear for other potential sources of bias due to the loss of clusters resulting from those that were not adjusted for clustering, and detail the methods used to deal with potential biases under outcomes in the description of Included studies. All the other trials appeared free of other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Rifampicin compared to isoniazid for preventing active TB in HIV-negative people; **Summary of findings 2** Rifampicin plus isoniazid compared to isoniazid for preventing active TB in HIV-negative people; **Summary of findings 3** Rifampicin plus pyrazinamide compared to isoniazid in preventing active TB in HIV-negative people; **Summary of findings 4** Rifapentine plus isoniazid weekly compared to isoniazid daily for preventing active TB in HIV-negative people at risk of TB infection

1. Rifampicin versus INH

Five trials provided data for this comparison. See Summary of findings for the main comparison for details of relative and absolute effects of the interventions linked to the overall quality of evidence for critically important and important outcomes.

Active TB

Three trials evaluated the development of TB but only one trial including adult Chinese men with silicosis and LTBI (HKCS 1992) reported that active TB developed over five years follow-up. The other two trials did not detect active TB over three years' follow-up in prisoners with LTBI (Chan 2012), or over two years' follow-up in children and adolescents at risk (Magdorf 1994). Rifampicin 600 mg/day given for three months did not differ significantly from INH 300 mg/day given for six months in proportions developing active TB (one trial, 332 participants, Analysis 1.1: subgroup 1.1.1). The cumulative percentage of active TB in those participants in this trial (HKCS 1992) evaluated over five years among those who completed their treatment without known interruption (rifampicin 142/165; INH 123/167) also did not differ significantly (rifampicin 10%, INH 14%).

One arm of the four-arm HKCS 1992 trial randomized 159 participants to matching placebo for rifampicin and INH (not included in the quantitative synthesis in this review). Of the 159 participants randomized to placebo 36 (23%) developed active TB, compared to 12% in the rifampicin arm and 15% in the INH arm.The cumulative percentage of those developing active TB over the five years among 133 participants on placebo who completed their treatment without interruption was 27%.

Drug resistance

The use of rifampicin in these trials was not reported to be associated with the emergence of rifampicin resistance, though only HKCS 1992 specifically reported on follow-up to monitor drug resistance. In this trial, two of 34 participants who developed active TB were found to be INH-resistant, and none were rifampicin-resistant (Analysis 1.2).

Adherence

In four trials comparing three to four months of rifampicin versus six to nine months of INH in adults (Chan 2012; HKCS 1992; Menzies 2004; Menzies 2008), those allocated to rifampicin were more likely to be adherent (RR 1.19, 95% CI 1.10 to 1.30; four trials, 1668 participants, Analysis 1.3: subgroup 1.3.1; Figure 3). There was a trend towards better compliance with rifampicin in the trials with INH given for nine months compared to INH given for six months but the results were not consistent (I^2 = 55%). In the trial with the least difference in adherence rates in the two arms (Chan 2012), treatment was by DOT in incarcerated prisoners, while in the remainder, treatment was self-administered.

Adherence did not significantly differ between rifampicin given for four months compared to INH given for six months in the small trial (Magdorf 1994) that recruited only children (one trial, 100 participants, Analysis 1.3; subgroup 1.3.2; Figure 3).

Safety

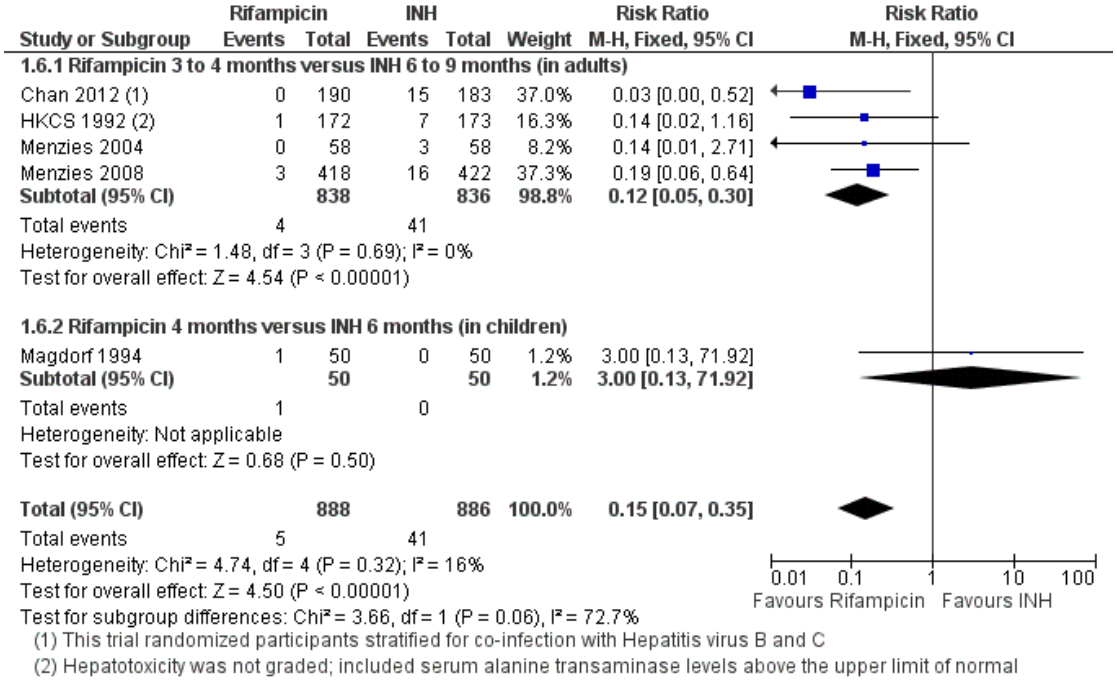
Rifampicin reduced the risk of*serious adverse event*s by 64% compared to INH in adults (RR 0.36, 95% CI 0.17 to 0.77; two trials, 956 participants, Analysis 1.4).

The point estimate for *treatment-limiting adverse events* from the four trials that provided data for this outcome also favoured rifampicin but the 95% CI did not rule out random error (RR 0.48, 95% CI 0.23 to 1.00; four trials, 1674 participants; Analysis 1.5).

The results were inconsistent (I^2 = 68%), due to one trial in incarcerated prisoners (Chan 2012), where adherence rates for INH by DOT was 78%, thereby exposing more people to the effects of INH, compared to 62% in the other three trials where INH was self-administered (HKCS 1992; Menzies 2004; Menzies 2008),. In the Chan 2012 trial, treatment with rifampicin was associated with an 82% reduction in the risk of treatment-limiting adverse events (worst estimate 50%, best estimate 94%) compared to INH given for six months (RR 0.18, 95% CI 0.06 to 0.50; one trial, 373 participants, Analysis 1.5). In this trial, about 20% of prisoners in each arm had HCV infection. In multivariate analysis, HCV infection and treatment with INH were independently associated with increased risk of drug discontinuation due to severe adverse events. Removing this trial reduced inconsistency in the results (I^2 = 18%), while effect estimates continued to non-significantly differ in the two intervention arms (RR 0.17, 95% CI 0.43 to 1.17; three trials, 1302 participants).

Rifampicin also consistently reduced the risk of *severe hepatotoxicity* by 88% in the four trials in adults (best estimate of relative risk reduction: 95%; worst estimate: 70% relative risk reduction) compared to INH (RR 0.12, 95% CI 0.05 to 0.30; four trials, 1674 participants, Analysis 1.6; Figure 4). The trial with the greatest relative risk reduction for hepatotoxicity was Chan 2012, where the higher frequency of HCV infection in those given INH for 6 months, is likely to have contributed to the differential risk of hepatotoxicity. Only one child on rifampicin was detected to have developed liver toxicity in Magdorf 1994 (one trial, 100 children, Analysis 1.6: subgroup 1.6.2),

Figure 4. Forest plot of comparison: 1 Rifampicin versus INH, outcome: 1.6 Hepatotoxicity.



No significant differences in event rates were reported for other adverse events including*gastrointestinal intolerance* (three trials, 1535 participants, Analysis 1.7), rash (two trials, 1213 participants, Analysis 1.8), *haematological adverse events* (one trial, 840 participants, Analysis 1.9), and for *any adverse event* (one trial, 322 participants, Analysis 1.10).

No data were reported on all cause mortality, deaths due to TB, or due to either drug.

2. Rifampicin plus INH versus INH alone

Two trials in adults evaluated the combination of rifampicin plus INH for three months versus INH given for six months (HKCS

1992) and for nine months (Martinez Alfaro 1998) (Summary of findings 2).

Active TB

Only one four-arm trial in silicosis patients reported this outcome (HKCS 1992). As with the comparison between rifampicin alone versus INH alone, the addition of INH 300 mg/day to rifampicin 600 mg/day for three months did not significantly reduce the risk of developing active TB when compared to INH 300 mg/ day given for six months (one trial, 328 participants, Analysis 2.1). However, analyses comparing the effects of INH plus rifampicin versus the placebo arm in the trial did reveal (as with rifampicin alone) significant reductions in the cumulative risk of active TB over five years of follow-up in 123/161 adults with silicosis who completed treatment with INH plus rifampicin with no known interruptions (16%) versus those who completed uninterrupted treatment with placebo (27%).

Drug resistance

Only HKCS 1992 reported data for this outcome and none of the adult men with silicosis given rifampicin plus INH or INH alone developed active TB with rifampicin-resistant mycobacteria. In the arm given rifampicin plus INH, two people had INH-resistant TB, while five of those given INH alone had INH-resistant TB. No instance of rifampicin resistance was detected (Analysis 2.2).

Adherence

In pooled data from HKCS 1992 and Martinez Alfaro 1998, adherence did not significantly differ in those given rifampicin plus INH for three months versus INH for six months or nine months (two trials, 524 participants, Analysis 2.3). Though there was a trend toward better adherence with rifampicin plus INH for three months in Martinez Alfaro 1998, where nine months of INH was used (Analysis 2.3: subgroup 2.3.2) the lower limit of the 95% CI included no difference and the test for subgroup differences did not exclude random error (P = 0.3).

Safety

INH added to rifampicin for three months did not significantly differ from INH given alone for six to nine months in the proportions developing *serious adverse events* (one trial, 196 participants, Analysis 2.4), *treatment-limiting adverse events* (two trials, 536 participants, Analysis 2.5); *hepatotoxicity* (two trials, 536 participants, Analysis 2.6); *gastrointestinal intolerance* (two trials, 510 participants, Analysis 2.7); or *any adverse event* (one trial, 314 participants, Analysis 2.8).
No *deaths* were reported in these trials.

3. Rifampicin plus pyrazinamide versus INH

Four trials (Leung 2003; Magdorf 1994; Sanchez-Arcilla 2004; Tortajada 2005) evaluated rifampicin plus pyrazinamide given for two months versus INH given for six months (Summary of findings 3).

Active TB

Three trials reported this outcome. Tortajada 2005 did not detect any participant with TB during this trial that was stopped early for harms; hence comparative efficacy could not evaluated. The proportions who developed active TB over two to five years' follow-up in adults with silicosis (Leung 2003) and in children (Magdorf 1994) did not significantly differ in those given rifampicin plus pyrazinamide compared to those given INH alone (two trials, 176 participants, Analysis 3.1).

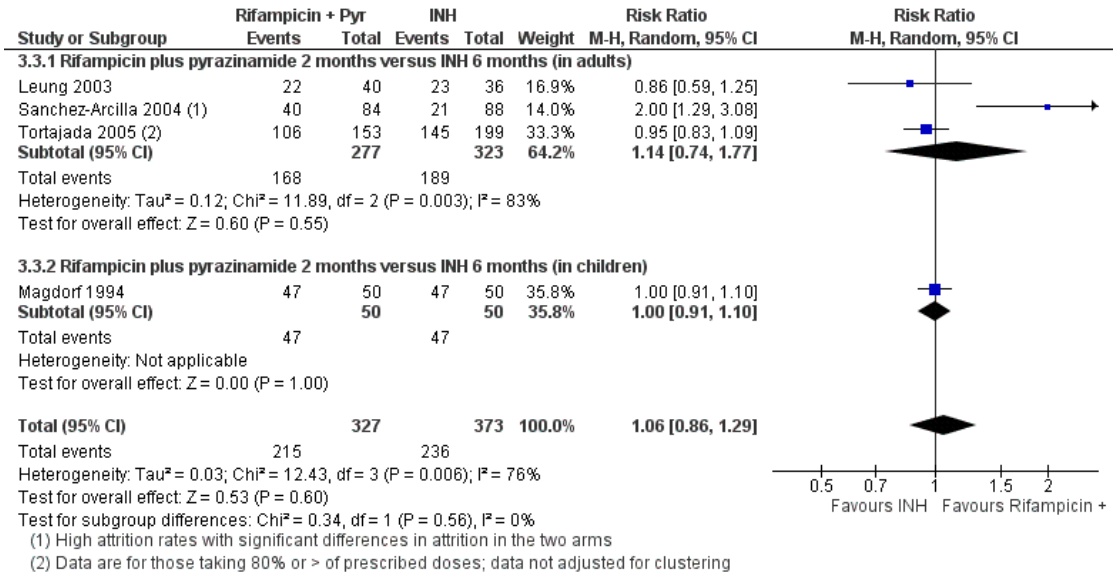
Drug resistance

One adult with silicosis in the INH arm of Leung 2003 developed active TB resistant to INH, while no other participant was detected to have TB resistant to rifampicin (Analysis 3.2).

Adherence

The pooled data from four trials did not reveal significant differences in adherence to rifampicin plus pyrazinamide or to INH (four trials, 700 participants, Analysis 3.3; Figure 5). Tests for subgroup differences between trials in adults and children were not statistically significant (P = 0.56), but the results of the trials in adults (Analysis 3.3: subgroup 3.3.1) were not consistent in the direction of effects (I^2 = 83%). In Sanchez-Arcilla 2004, adherence was significantly better with the shorter regimen of rifampicin plus pyrazinamide than with the longer INH regimen. This trial in homeless people had high attrition rates (36%) and the higher attrition in the longer INH arm (53%) than in the rifampicin plus pyrazinamide arm (18%), may explain the inconsistency in adherence rates in the three trials in adults. We have chosen to present pooled estimates but suggest that they be interpreted with caution due to substantial heterogeneity in the direction of effect estimates.

Figure 5. Forest plot of comparison: 3 Rifampicin plus pyrazinamide versus INH, outcome: 3.3 Adherence.



In sensitivity analysis, removal of the data for adherence from Sanchez-Arcilla 2004 from the pooled estimates resulted in consistent results (I^2 = 0%) and reduced imprecision (RR 0.98, 95% CI 0.0.90 to 1.06; four trials, 528 participants).

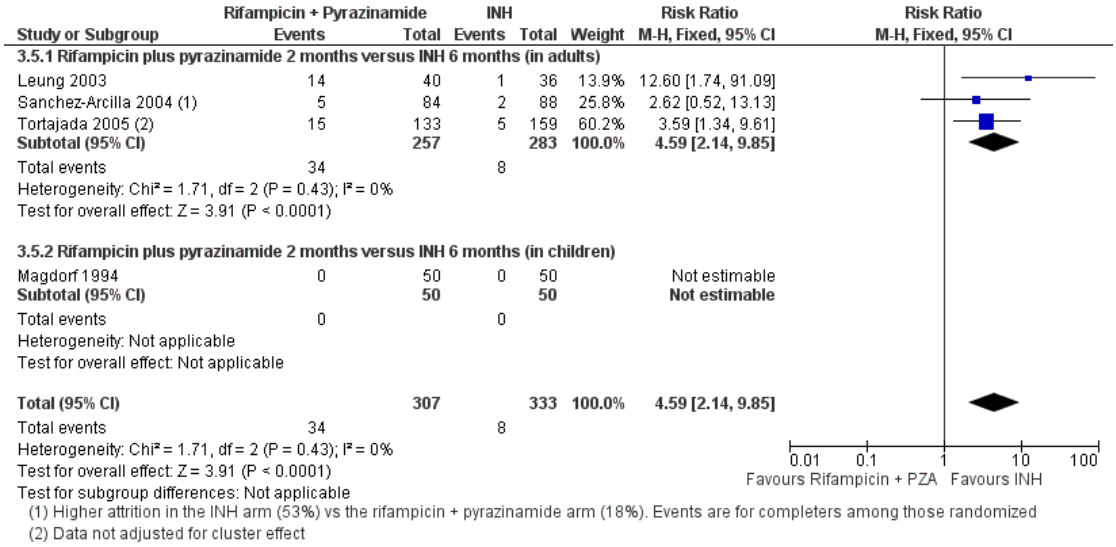
Safety

None of the included trials reported *serious adverse events*.

Treatment-limiting adverse events were significantly more frequent with rifampicin plus pyrazinamide than with INH (19% versus 5%; RR 3.61, 95% CI 1.82 to 7.19; two trials, 368 participants, Analysis 3.4).

Hepatotoxicity was not detected in Magdorf 1994 in 100 children randomized to rifampicin plus pyrazinamide or to INH, and comparative safety could not be evaluated. The three trials in adults reported hepatotoxicity significantly more frequently in those randomized to rifampicin plus pyrazinamide than to INH (11% versus 2%; RR 4.59, 95% CI 2.14 to 9.85; four trials, 540 participants, Analysis 3.5, Figure 6). This is likely to be an underestimate since in Sanchez-Arcilla 2004, hepatotoxicity was reported only for people who completed the trial among those randomized; and overall attrition was high (35%), with no data available about those lost to follow-up.

Figure 6. Forest plot of comparison: 3 Rifampicin plus pyrazinamide versus INH, outcome: 3.5 Hepatotoxicity.



At least one adverse event was reported significantly more frequently in Tortajada 2005 in people on rifampicin and pyrazinamide than in those on INH (RR 1.71, 95% CI 1.24 to 2.35; one trial, 292 participants; Analysis 3.6).

Gastrointestinal intolerance were significantly more frequent with the combination than with INH (RR 2.19, 95% CI 1.37 to 3.49; two trials, 368 participants; Analysis 3.7)

No significant differences were found between the two treatment arms for *rash* (one trial, 76 participants, Analysis 3.8), or *pruritis* (one trial, 76 participants, Analysis 3.9).

No*deaths* were reported in these trials.

4. Rifapentine plus INH once a week (DOT) for three months versus daily INH daily (self administered) for nine months

See Summary of findings 4 for details of relative and absolute effects of the interventions and the overall quality of evidence for critically important and important outcomes in Sterling 2011,

Active TB

This trial that was designed to demonstrate the non-inferiority of 12 doses of rifapentine plus INH DOT given weekly over three months compared to 270 doses of daily, self-administered INH over nine months. TB developed in seven of 3986 people (0.2%) in the combination treatment arm versus 15 of 3745 people (0.4%) in the INH arm over 33 months of follow-up after enrolment (one trial, 7731 participants, Analysis 4.1). Of those who took 100% of treatment doses, TB developed in five of 3376 subjects (0.1%) in the combination-therapy arm versus six of 2792 (0.2%) in the INH-only arm.

The combination-therapy was consistently non-inferior to the INH-only regimen in the primary analysis where the upper limit of the 95% CI of the difference was set at < 0.75%, and in sensitivity analysis when this was reduced to < 0.50%.

In this trial, close contacts of the first eligible person in a household were randomized by household, and other high-risk participants who were not part of a household were randomized individually. The risk of developing TB was similar when the results included only the first person randomized in a household, in sensitivity analysis done to adjust for the effects of clustering. The results were also similar after 24 months of follow-up after the last treatment. TB incidence rates did not differ disproportionately between the study sites in the US, Canada, Brazil, or Spain.

Mortality

Sterling 2011 reported no significant difference between interventions in all cause mortality (31/3986 (0.7%) versus 39/3745 (1%)) during therapy or within 60 days of treatment (one trial, 7731 participants, Analysis 4.2). None of these deaths were attributed to TB or to any of the study medications.

Drug resistance

One of the seven people who developed active TB (*M. bovis* on culture) in the combination treatment arm was HIV-positive with a CD4+ count of 271 per cubic mm at enrolment and completed treatment after many interruptions. The isolate was found to be rifapentine resistant. Of the 15 people in the INH alone arm who developed active TB, two had INH-resistant *M. tuberculosis* strains (Analysis 4.3).

Adherence

Adherence rates were significantly greater in those given the combination treatment by DOT (82%) compared to self-administered INH (69%) (RR 1.19, 95% CI 1.16 to 1.22; one trial, 7731 participants, Analysis 4.4).

Safety

The combination treatment was associated with significantly fewer *severe adverse events* (1.6%) than INH alone (2.8%) (RR 0.55, 95% CI 0.44 to 0.74; one trial, 7799 participants, Analysis 4.5). However, more people receiving the combination treatment had *treatment-limiting adverse events* that led to permanent discontinuation (4.9%) compared to those on INH alone (3.7%) (RR 1.32, 95% CI 1.07 to 1.64; one trial, 7731 participants, Analysis 4.6). The rifapentine combination was also associated with more frequent symptoms that were considered possible *hypersensitivity reactions* (3.8%) than with INH alone (0.5%) (RR 8.32, 95% CI 5.05 to 13.71; one trial, 7799 participants, Analysis 4.7). Six of the 152 people with possible hypersensitivity reactions had hypotensive episodes.

The combination resulted in significantly fewer instances of severe *hepatoxicity* (0.4%) than with INH given for nine months (2.7%) (RR 0.16, 95% CI 0.10 to 0.27; one trial, 7799 participants; Analysis 4.8).

The interventions did not significantly differ in producing a *rash* (one trial, 7799 participants, Analysis 4.9).

Of the 7799 subjects who received at least one dose of a study drug, 1062 (13.6%) had one adverse event, and 194 (2.5%) had more than one adverse event. Overall, there was a small but statistically significant excess in the proportions on INH alone (17.6%) who reported *any adverse event* than on the rifapentine plus INH combination (14.7%) (RR 0.84, 95% CI 0.76 to 0.93; one trial, 7799 participants, Analysis 4.10).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Rifampicin plus isoniazid (3 months) compared to isoniazid (6 to 9 months) for preventing active TB in HIV-negative people

Patient or population: HIV-negative people at risk of TB infection
Intervention: Rifampicin plus isoniazid for 3 months
Comparison: Isoniazid for 6 to 9 months

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	INH	Rifampicin plus INH				
Active TB Follow-up: 5 years	**150 per 1000**	**162 per 1000** (97 to 268)	**RR 1.08** (0.65 to 1.79)	328 (1 study)	⊕⊕◯◯ **very low**[1,2,3]	In the placebo arm of this four-arm trial (HKCS 1992), 36/159 (23%) developed active TB
Adherence	**758 per 1000**	**812 per 1000** (743 to 887)	**RR 1.07** (0.98 to 1.17)	524 (2 studies)	⊕⊕⊕◯ **high**[4,5,6]	
Treatment-limiting adverse events	**114 per 1000**	**133 per 1000** (85 to 208)	**RR 1.16** (0.74 to 1.82)	536 (2 studies)	⊕⊕◯◯ **low**[7,8,9]	
Hepatotoxicity	**55 per 1000**	**49 per 1000** (24 to 100)	**RR 0.88** (0.43 to 1.81)	536 (2 studies)	⊕⊕◯◯ **low**[7,8,9]	.

*The basis for the **assumed risk** is the control group risk in single studies and the median risk in the control group with pooled data. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No inconsistency: Single trial (HKCS 1992) in adults with silicosis. In another trial (Martinez Alfaro 1998), one participant from among 196 adults and children developed TB; however, the allocated treatment was not reported. Not downgraded.
[2] Serious indirectness: This trial, conducted in Hong Kong over 20 years ago, only included adult men with silicosis. The results are not easily generalised to other treatment groups or settings, and may not be applicable today. Downgraded by 1.
[3] Very serious imprecision: The wide 95% CI of the effect estimate includes appreciable benefit and harm with rifampicin. The study was underpowered to confidently detect differences between the two regimens. Downgraded by 2.
[4] No serious study limitation: Martinez Alfaro 1998 was considered to be at unclear risk detection bias, while HKCS 1992 was at low risk of bias; but the results of the two trials did not differ. Not downgraded.
[5] No serious indirectness: Both trials differed in their definitions of adherence and did not include people with LTBI from low income, resource-limited countries or settings with a high TB burden, where adherence rates might differ. However, this may not affect the differential advantage seen with the shorter rifampicin regimen, Not downgraded.
[6] No serious imprecision: The 95% CI of the pooled effect estimate included no effect but did not include appreciable benefit for INH or INH plus rifampicin. The sample size was adequate (total number of events exceeded 300). Not downgraded.
[7] No serious study limitations: Of the two studies, Martinez Alfaro 1998 was not blinded, but all participants were evaluated at protocol-specified time points for adverse events, minimising the risk of detection bias. Not downgraded.
[8] No serious indirectness: While the two trials were conducted in high-income countries, the occurrence of adverse events is unlikely to differ in other settings. Not downgraded.
[9] Very serious imprecision: The upper and lower limits of the 95% CI indicated appreciable benefit with both interventions and no significant difference between the two. The sample size was insufficient to detect significant differences with the interventions. Downgraded by 2.

Rifampicin plus pyrazinamide (2 months) compared to isoniazid (6 months) for preventing active TB in HIV-negative people

Patient or population: HIV-negative people at risk of TB infection[1]
Intervention: Rifampicin plus pyrazinamide for 2 months
Comparison: Isoniazid for 6 months

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Isoniazid	Rifampicin plus pyrazinamide				
Active TB: Follow-up: 2 to 5 years	**47 per 1000**	**61 per 1000** (20 to 192)	**RR 1.32** (0.42 to 4.13)	176 (2 studies)[2]	◯◯◯◯ **very low**[3,4,5]	
Adherence	**684 per 1000**	**725 per 1000** (588 to 882)	**RR 1.06** (0.86 to 1.29)	700 (4 studies)	◯◯◯◯ **very low** [6,7,8,9]	
Treatment-limiting adverse events	**53 per 1000**	**191 per 1000** (96 to 381)	**RR 3.61** (1.82 to 7.19)	368 (2 studies)	⊕⊕⊕⊕ **high**[10,11]	
Hepatotoxicity	**25 per 1000**	**115 per 1000** (54 to 246)	**RR 4.59** (2.14 to 9.85)	540 (3 studies)	⊕⊕⊕◯ **moderate**[12,13]	

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Data in this table are from four trials conducted in Hong-Kong (Leung 2003), Germany (Magdorf 1994), and Spain (Sanchez-Arcilla 2004; Tortajada 2005).

[2] Data for active TB were from Leung 2003 in adults with silicosis, and Magdorf 1994 in children. another trial (Tortajada 2005) had inadequate follow-up, as the trial was stopped early, and did not detect TB in 292 randomized adults, hence comparative efficacy between the two regimens could not be evaluated. Sanchez-Arcilla 2004 did not report this outcome among homeless men.

[3] No serious study limitations: Leung 2003 was free of the risk of bias, Magdorf 1994 was unclear for the risk of selection bias but.the results of both trials were similar. Not downgraded.

[4] Serious indirectness: The results for preventing TB from the two trials that contributed data may not generalize to other populations and settings. Downgraded by 1.

[5] Very serious imprecision: The upper and lower limits of the 95% CI included appreciable benefit with both interventions and no significant difference. The sample size was less than the optimal information size. Downgraded by 2.

[6] Serious study limitations: Magdorf 1994 was open-label but all children in both arms underwent evaluation for active TB at the same protocol specified time points, minimising the risk of ascertainment and detection bias.The other trials (Sanchez-Arcilla 2004; Tortajada 2005) were at high risk of bias and contributed nearly half of the weight to the pooled analysis. Downgraded by 1.

[7]Serious inconsistency: The 1^2 for the pooled estimate of the four trials was 76%, and was 83% in the subgroup trials in adults. This inconsistency was due to the differential attrition rates in Sanchez-Arcilla 2004. Downgraded by 1.

[8] No serious indirectness: The four trials included adults and children, adults with silicosis and homeless people, and though none were from low-income, high TB burden countries, this is unlikely to alter estimates of relative adherence to the two regimens. Not downgraded.

[9] Serious imprecision: The upper and lower limits of the 95% CI indicated appreciable benefit with isoniazid as well as no significant difference between the two interventions; however, the number of events was greater than 300 and the sample size exceeded the optimal information size. Downgraded by 1.

[10] Serious study limitations: Tortajada 2005 was at high risk of performance and detection bias and contributed 78% weight to the pooled results. Downgraded by 1.

[11] No serious indirectness: Leung 2003 included adults with silicosis and Tortajada 2005 included adults and children. The trials were not done in a low income or resource-limited country or setting. However, this is unlikely to affect the relative risk of treatment-limiting adverse events in these settings. Not downgraded.

[12] Very serious study limitations: Two of the three trials (Sanchez-Arcilla 2004; Tortajada 2005) were at high risk of performance and detection bias and contributed over 80% to the pooled effect estimates. Downgraded by 2.

[13] No serious indirectness: Leung 2003 included adults with silicosis. Tortajada 2005 included adults and children, and Sanchez-Arcilla 2004 was done in homeless people. Magdorf 1994 randomized 100 children but none developed hepatotoxicity, and hence this trial did not contribute data on comparative effects for this outcome. Though the trials were not done in a low-income or resource-limited country or setting, this is unlikely to significantly alter the relative risk of hepatotoxicity. Not downgraded.

Rifapentine plus isoniazid weekly for 3 months (12 doses) compared to isoniazid daily for 9 months (270 doses) for preventing active TB in HIV-negative people with LTBI

Patient or population: HIV-negative people at risk of TB infection[1]
Intervention: Rifapentine (900 mg) plus isoniazid (900 mg) weekly for 3 months (12 doses)
Comparison: Isoniazid (300 mg) daily for 9 months (270 doses)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Isoniazid	Rifapentine plus isoniazid				
Active TB Follow-up: 33 months after enrolment	**4 per 1000**	**2 per 1000** (1 to 4)	**RR 0.44** (0.18 to 1.07)	7731 (1 study)	⊕⊕⊕◯ **moderate** [2,3,4]	
Adherence	**690 per 1000**	**821 per 1000** (801 to 842)	**RR 1.19** (1.16 to 1.22)	7731 (1 study)	⊕⊕⊕◯ **moderate**[5,6]	
Treatment-limiting adverse events	**37 per 1000**	**49 per 1000** (40 to 61)	**RR 1.32** (1.07 to 1.64)	7731 (1 study)	⊕⊕⊕◯ **moderate**[7,8,9]	
Hepatotoxicity Follow-up: 5 months to 11 months	**27 per 1000**	**4 per 1000** (3 to 7)	**RR 0.16** (0.1 to 0.27)	7799 (1 study)	⊕⊕⊕⊕ **high**[7,10]	

*The basis for the **assumed risk** is the risk in the control group. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Multicentre, equivalence trial in adults and children (Sterling 2011) conducted in 26 centres in four countries: USA (21), Canada (3), Brazil (1), Spain (1)

[2] No study limitations: The trial used cluster randomization and individual randomization, and though the primary analysis did not adjust for clustering, a sensitivity analysis in the trial report excluding those randomized in clusters did not reveal differences in effect estimates. Not downgraded.

[3] Serious indirectness: Insufficient data is currently available regarding its efficacy in children. Downgraded by 1.

[4] No serious imprecision: This trial was a non-inferiority trial and the results met pre-stated non-inferiority margins. Not downgraded.

[5] Serious indirectness: The trial did not include participants from any low-income, high TB burden settings and it cannot be assumed that direct observation of 12 doses of the combination treatment over three months will be similar in high TB burden countries such as India and China that have difficulties implementing DOT even for those with active TB. Adherence with self-administered INH is also likely to differ in high TB burden countries. Downgraded by 1.

[6] No serious imprecision: The sample size and the number of events fulfilled the optimal information size and though the upper and lower limits of the 95% CI of the relative risk indicate non-appreciable benefits with the rifampicin combination, the 95% CI for the absolute increase in people adherent with the rifapentine combination indicates appreciable benefits are likely for adherence with the combination over INH. Not downgraded.

[7] No study limitations: This open label trial with direct observation of the combination treatment was at risk of detection bias since study personnel would have greater contact with participants in the combination arm compared to the self-administered INH arm. However, this would not apply to the detection of treatment- limiting adverse events (or hepatotoxicity). Not downgraded.

[8] No serious indirectness: The occurrence of treatment-limiting adverse events (and hepatotoxicity) is unlikely to differ in low income and high TB transmission settings. Although data for children are insufficient to draw firm conclusions, adverse events were not disproportionately reported for children in the trial. Not downgraded.

[9] Serious imprecision: The upper and lower limits of the 95% CI indicate appreciable benefit and non-appreciable benefit with the combination of rifapentine and INH.over INH and no statistically significant differences. Though events were few, the sample size was large Downgraded by 1.

[10] No serious imprecision: The upper and lower limits of the 95% CI indicate appreciable benefit with the rifapentine combination. The sample size and number of events fulfilled the requirements for the optimal information size. Not downgraded.

DISCUSSION

This review includes 10 trials that randomized 10,717 participants, mostly HIV-negative adults and children (2% HIV-positive), who were followed up for two to five years. INH was compared to rifampicin or to a rifamycin-containing regimen in four sets of comparisons.

Summary of main results

Rifampicin versus INH

Four months of rifampicin and the standard INH treatment of six or nine months may not differ in preventing progression to active TB in HIV-negative people with LTBI. Rifampicin probably increases adherence and treatment completion compared to INH in adults. It is uncertain if treatment-limiting adverse events are any different, but rifampicin probably results in significantly less hepatotoxicity in adults (0.2% to 1.5%) than INH (5%). No instances of rifampicin resistance were observed in 40 people who developed active TB while on rifampicin. However, more evidence for its efficacy in adults and in children, particularly from high TB burden countries, would be required before it is considered as an routine alternative to, or replacement for, standard INH prophylaxis in people with LTBI.

Rifampicin plus INH versus INH alone

No benefit in preventing progression to active TB, increasing adherence, or reducing the frequency of treatment-limiting adverse events and hepatotoxicity was detected when INH was added to rifampicin for three months compared to treatment with INH alone for six to nine months. This indicates that rifampicin plus INH combination treatment may not be a better alternative to INH alone (or rifampicin alone) for people with LTBI.

Rifampicin plus pyrazinamide versus INH

Rifampicin plus pyrazinamide for two months may not differ from INH for six months in preventing active TB in HIV-negative people with LTBI, or in treatment completion compared to INH in spite of the shorter treatment duration. This drug combination also probably increases the risk of hepatotoxicity in adults, and increases the incidence of treatment-limiting adverse events; These attributes are not consistent with those required of a public health intervention for preventing active TB in people with LTBI.

Rifapentine plus INH weekly for three months (DOT) versus daily INH for three months (self-administered)

Twelve doses of rifapentine plus INH administered weekly by DOT over three months is probably an effective and safer alternative to INH given for nine months in HIV-negative people at risk, though more data on the safety of the combination in adults (particularly the risk of hepatotoxicity in women), as well as in children are needed. One case of rifapentine resistance was observed in an HIV-positive individual who had low CD4 counts, though none were observed in HIV-negative people who developed active TB. The effects of this intermittent regimen in high TB burden countries in Africa, in China, and in India also need to be evaluated before its widespread use outside low TB burden countries can be envisaged.

Overall completeness and applicability of evidence

Completeness

We believe that we have identified all RCTs relevant to this review's objectives. The most important outcome when considering alternatives to INH is the development of active TB; yet, data for this outcome was reported only in three trial publications. Intermittent (twice weekly) rifampicin (600 mg) DOT in INH-resistant or intolerant cases, or when nine months of INH is not feasible; and rifabutin (300g) when rifampicin is contraindicated or not tolerated, are recommended by some guidelines (CDC 2000; NYC 2005). Another option proposed is self-administered INH plus rifapentine given daily for one month that was proven beneficial in the murine model (Zhang 2009), and postulated to be more cost effective than three months of weekly rifapentine plus INH, given by DOT or self-administered; and nine months of daily INH (Holland 2011). We did not find any RCTs comparing intermittent rifampicin, or rifabutin, or self-administered INH plus daily rifapentine, with standard INH prophylaxis in HIV-negative people with LTBI.

Applicability

While reactivation of LTBI can occur any time in a person's lifetime, the risk is the highest in the early years after infection, particularly in children. The duration of follow-up in the included trials ranged from two years in the trial in children to three to five years in the trials in adults. Since these trials were conducted in low to moderate TB transmission settings, and in largely HIV-negative populations, the risk of re-infection as opposed to reactivation is likely to have been low.

However, for the same reasons, the results from these trials may not yield the same effect estimates in high TB burden countries in Africa and Asia (particularly China and India) where re-infection rates would be higher and co-morbid conditions that impair effectiveness such as nutritional and micronutrient deficiencies, are higher. These trials were also conducted in high- and middle-income countries where health systems arrangements and the delivery of care, such as the availability of resources to provide DOT effectively, may differ from those in low-income countries where

treatment of active TB is a priority. There was also some variability in these trials regarding the diagnosis of LTBI, and the definitions used to diagnose active TB and in determining the incidence of hepatotoxicity. The data for children is from only one trial with a total sample size of 100. While the relative advantage in treatment completion and safety with the shorter rifampicin regimen over INH is likely to be seen even in low-income countries, these issues may limit the applicability of the evidence to resource-constrained countries with a high TB burden.

The trials included in the review excluded pregnant and lactating women, malnourished children, and children below two years of age, and this review does not provide evidence for the efficacy and safety of rifampicin in these vulnerable groups to inform clinical practice or policy. Similarly, data are insufficient to confirm or refute the efficacy and safety of rifapentine in young children below 12 years.

Ensuring adherence to shorter regimens for LTBI

Direct observation of short courses of rifampicin or 12 doses of weekly rifapentine plus INH is mandatory in order to ensure compliance with all doses, and is a factor that is critical to its efficacy. Several factors influence the acceptance of DOT in enhancing adherence and thereby cure in TB, including social and economic factors, the acceptance of the DOT provider, the location of treatment provision, the benefits provided, and the flexibility of the DOT service to individual needs (Noyes 2007; Volmink 2007). It is uncertain whether low-income, high TB burden countries can divert scarce resources from treating active TB to treating large numbers of asymptomatic people with LTBI.

Resource use and resource costs

Another factor that would influence the uptake of shorter rifampicin regimens over the standard nine months of INH in guidelines and policy is resource use and resource costs. While this review did not directly address economic outcomes, two of the trials in this review (Menzies 2008; Sterling 2011) provided additional information in supplementary reports on costs that would have a bearing on the uptake of these regimens in guidelines and in policy decisions.

A prospective examination of direct costs for scheduled and unscheduled visits from the perspective of the health care system in the high- and middle-income settings in the Menzies 2008 trial assumed the efficacy of rifampicin for four months and INH for nine months to be equivalent at 90% in the base case analysis, and sensitivity analyses to estimate the incremental cost-effectiveness ratio varied the efficacy of four months of rifampicin to as little as 60%. Four months of rifampicin was deemed to be cost saving while preventing more cases of TB reactivation, if its efficacy was 75% or greater. The difference in costs was primarily due to the greater number of scheduled clinic visits in the nine-month INH regimen, and also due to the greater number of unscheduled visits due to toxicity. All costs were in Canadian dollars in 2007, but rifampicin remained cost saving when costs where compared between centres in Canda and between centres in Canada and Brazil (Aspler 2010). Another decision analysis based on the same data concluded that four months of rifampicin was cost saving and more effective in preventing reactivation of TB at an efficacy threshold of 69% for rifampicin (Esfahani 2009). While other analyses have arrived at similar conclusions that four months of rifampicin is cost saving compared to nine months of INH (Holland 2009; Ziakas 2009), local cost variations for drugs and for monitoring, and variations in monitoring schedules, can alter these cost determinations. However, cost estimates based on actual efficacy estimates of the two regimens are currently unavailable, except from the limited data from one early trial in men with silicosis (HKCS 1992).

Rifapentine is more expensive than INH and the added costs incurred with direct observation of the combination suggest that rifapentine plus INH may not be cost effective. A formal cost-effectiveness analysis of Sterling 2011 is underway. However, a previous cost-effectiveness analysis using a computerized Markov model to estimate societal costs, concluded that rifapentine plus INH is cost saving for extremely high-risk patients and is cost-effective for lower-risk patients (Holland 2009). A subsequent re-analysis of cost-effectiveness also confirmed the cost-effectiveness of weekly rifapentine plus INH for three months versus nine months of INH (Holland 2011). However, the actual experience with this combination in real world settings outside a clinical trial, and careful monitoring for adverse events such as hypersensitivity reactions, hepatotoxicity, and other adverse events that may emerge when used widely in clinical practice, will inform decisions regarding cost-effectiveness of this intervention. Rifapentine is currently unavailable in many parts of the world, though the Centers for Disease Control (CDC) have recommended the use of the 12-dose weekly rifapentine and INH combination with DOT as an alternative regimen for treating LTBI (CDC 2011).

Drug resistance

Additional barriers to the uptake of four months of rifampicin in treating LTBI is the fear of inadvertent treatment of active TB leading to the development of rifampicin resistance (Stout 2010), or the emergence of rifampicin resistance if rifampicin were to be more widely used for treating LTBI. While the trials in this review did not reveal that anyone given rifampicin developed resistance, rifampicin resistance does occasionally occur in the context of LTBI prophylaxis particularly in immuno-compromised people (Ridzon 2005); thus, careful selection of people with LTBI for rifampicin prophylaxis would be necessary. Ensuring compliance would also be important if four months of rifampicin were to become standard treatment for LTBI, as interrupted courses of treatment would increase the potential for the emergence of widespread resistance to rifampicin. If this were to occur, then any potential cost savings with four months of rifampicin would be

rapidly offset by the costs of treating rifampicin resistance (Stout 2010).

However, given the growing prevalence of resistance to INH (WHO 2004), it is estimated that active case detection and treatment of LTBI with a non-INH regimen would lead to substantial health benefits (Khan 2002). The shorter duration of treatment with four months of rifampicin; comparable efficacy with INH; less frequent and less toxic adverse events with rifampicin; greater preference expressed among diverse populations for the shorter regimen; and their willingness to complete treatment even in the face of adverse events; greater feasibility to supervise the shorter course; and greater incremental cost-effectiveness (particularly in populations with high INH resistance) are potential reasons advanced to consider four months of rifampicin as standard treatment for LTBI prophylaxis (Reichman 2004).

Quality of the evidence

The assessments of the overall quality of the evidence were made using the GRADE approach (Schunemann 2008). The GRADE approach considers 'quality' to be a judgment of the extent to which we can be confident that the estimates of effect are correct. 'Quality' is graded for each pre-selected outcome on five domains. Evidence from randomized controlled studies is initially graded as high and downgraded by one or two levels on each domain after full consideration of: any limitations in the design of the studies, the directness (or applicability) of the evidence, the consistency and precision of the results, and the possibility of publication bias. This results in an assessment of the quality of a body of evidence as*high, moderate, low,* or*very low*. A GRADE quality level of *'high'* reflects confidence that the true effect lies close to that of the estimate of the effect for an outcome. A judgement of *'moderate'* quality indicates that the true effect is likely to be close to the estimate of the effect, but acknowledges the possibility that it is substantially different. *'Low'* and *'very low'* quality evidence limit our confidence in the effect estimate (Balshem 2011).

These judgements for pre-selected patient-important outcomes for each comparison in this review are presented in the 'Summary of findings' tables.

The evidence for the efficacy of shortened prophylactic regimens of rifampicin versus INH in LTBI was downgraded for indirectness since the results of the sole trial with useable data was conducted in adults with silicosis in Hong Kong over 20 years ago, and may not readily generalise to other settings today. We also downgraded the quality of evidence for imprecision, since the single trial that provided effect estimates was underpowered to rule out clinically important differences. We judged the resulting imprecision in the effect estimate, indicating appreciable benefit with both interventions, to be very serious and downgraded the evidence by two levels, following guidance in Guyatt 2011. The overall quality of the evidence for treatment limiting adverse events was also downgraded to *'very low'* due to serious study limitations, inconsistency and imprecision. Evidence graded as *'moderate'* quality for adherence and for hepatotoxicity suggests reasonable confidence in the estimates of better adherence and less frequent liver toxicity with rifampicin monotherapy compared to INH (Summary of findings for the main comparison).

The overall quality of evidence for all outcomes in the comparison of rifampicin plus INH versus INH alone was graded *'low'* to *'very low'* for similar reasons, except for adherence where *'high quality'* evidence indicates confidence in the estimates that adherence was not significantly different with the two treatment regimens (Summary of findings 2). The overall quality of the evidence indicating no significant difference with rifampicin plus pyrazinamide versus INH for preventing active TB and for adherence was graded *'low'* or *'very low';* but the evidence for safety outcomes was graded *'moderate* to *high quality'* (Summary of findings 3).

The evidence that a shortened course of weekly rifapentine plus INH is non-inferior to nine months of INH in preventing active TB was judged to be of *moderate quality;* the main factor limiting full confidence in this estimate was the uncertainty in generalising this result from settings with low to moderate TB incidence (North America, Europe and Brazil), to settings with higher TB incidence (Africa and Asia), and the limited data available to date regarding the effects of the weekly combination treatment in children (Summary of findings 4).

Potential biases in the review process

We used standard methods described in the Cochrane handbook for systematic reviews of interventions (Higgins 2011a), and complied with the Cochrane Collaboration's methodological standards for the conduct of new reviews of interventions (MECIR 2011).

Agreements and disagreements with other studies or reviews

Rifampicin versus INH

The results of Ziakas 2009, a meta-analysis of data from four studies (3336 participants), concluded that four months of treatment with rifampicin was associated with about half the non-completion rate of nine months of INH treatment and 12% the risk of hepatotoxicity. Although two of the included studies were retrospective comparisons, these results are in agreement with the results from our review.

Guidance for treatment of LTBI in the UK (NICE 2011) recommends either six months of INH or three months of rifampicin and INH for adults and children not known to have HIV infection. Four months of rifampicin finds no place as an alternative in these guidelines. NICE 2011 does recommend six months of rifampicin for contacts, aged 35 or younger, of people with INH-

resistant TB. In contrast, the rifampicin plus INH combination finds no place in the CDC guidelines, though four months of rifampicin does (CDC 2011).This review found that the liver toxicity of the combination of rifampicin plus INH was around 5% and similar to that seen with INH; and there was no advantage with the combination over INH alone in treatment completion rates. Rifampicin alone for four months has better adherence and less hepatotoxicity than INH, though there is insufficient high quality evidence regarding efficacy as yet.

Rifampicin plus INH versus INH

Four trials with 1601 participants comparing rifampicin plus INH to INH monotherapy were included in a systematic review (Akolo 2010). Among HIV-positive people, the efficacy of INH plus rifampicin was similar to that of INH monotherapy, while the treatment-limiting adverse events were significantly greater with the combination than with placebo, but not significantly different compared to INH. The effects of rifampicin plus INH on active TB and treatment-limiting adverse events among HIV-negative people in our review were similar to that observed among HIV-positive people in Akolo 2010. Another systematic review by Ena 2005 included trials comparing rifampicin plus INH with INH monotherapy irrespective of the HIV status of the participants. Ena 2005 included the two RCTs on HIV-negative people included in the present review, and three of the four RCTs included in Akolo 2010. The results in Ena 2005 on the effects of rifampicin plus INH on active TB and treatment-limiting adverse events were similar, compared to INH monotherapy, and were also concordant with the results of our review. However, the conclusions we draw with regard to its continued use for LTBI prophylaxis are based on the higher risk of hepatotoxicity with the combination that are similar to the risk with INH and greater than the risk with rifampicin alone.

Rifampicin plus pyrazinamide versus INH

The results of this review are in broad agreement with that of the systematic review and meta-analysis by Gao 2006 on the efficacy of rifampicin plus pyrazinamide for the prevention of active TB that included both HIV-negative as well as HIV-positive people. Notwithstanding differences in trial selection, the conclusions in Gao 2006 that rifampicin plus pyrazinamide was associated with a significantly higher risk of severe hepatotoxicity and severe adverse events among HIV-negative people, are in agreement with the conclusions in this review.

The Cochrane Review on the prevention of TB among HIV-positive people (Akolo 2010) reported that rifampicin plus pyrazinamide was similar in efficacy to INH monotherapy in preventing active TB (five trials including 3409 participants), with a 37% lower risk of treatment-limiting adverse events in the INH arms (five trials including 3409 participants). The effects of rifampicin plus pyrazinamide on active TB and treatment-limiting adverse events among HIV-negative people in our review are similar to that observed among HIV-positive people in Akolo 2010.

Weekly rifapentine plus INH

Based on the results of Sterling 2011 (and guided by the results of Schechter 2006 and Martinson 2011), rifapentine plus INH given as 12 weekly doses with DOT is now recommenced by the CDC as an alternative treatment regimen to standard INH in preventing active TB in otherwise healthy HIV-negative people above 12 years of age with LTBI, and in HIV-positive people who are not on antiretroviral agents (CDC 2011). The combination is also recommended for people who are less likely to complete a six or nine-month course of INH, where 12 supervised weekly doses may confer practical advantages, such as people in correctional facilities, in shelters, or recent immigrants who may have a high prevalence of LTBI infection. Expert opinion from the CDC panel recommends the use of the combination on a case by case basis for people not represented in the PREVENT-TB trial, including those with risk factors such as diabetes. The current CDC recommendations for children above two years and below 12 years continues to be nine months of INH, and is likely to remain so till the PREVENT-TB trial completes recruitment and reports the results in the remaining children.

No data from low-income, high TB burden countries are available for weekly rifapentine plus INH and this reduced our confidence in extrapolating the otherwise high quality evidence from this trial to settings where DOT may not be feasible, or practical, given resource constraints; and where reinfection rates are likely to be higher than in the low-transmission settings that Sterling 2011 was conducted in. The experience with rifapentine is limited and the potential for adverse events, hepatotoxicity, and the possibility of rifapentine resistance will require careful monitoring with more widespread use.

AUTHORS' CONCLUSIONS

Implications for practice

On current evidence shortened prophylactic regimens containing rifampicin or weekly, directly observed rifapentine plus INH appear no different to INH monotherapy given for six months to nine months for preventing active TB in people at risk. Rifampicin for four months and weekly directly-observed rifapentine plus INH for three months may have additional advantages of higher treatment completion and improved safety. However, the weekly rifapentine plus INH combination has not been evaluated against INH in low-income, high TB burden countries. Shorter regimens of rifampicin with INH may confer no additional benefits compared to longer INH treatment regimens. Rifampicin combined with pyrazinamide increases the risk of liver toxicity in adults.

Implications for research

A number of trials are ongoing that will provide data to clarify many of the issues raised in this review.

Three ongoing trials evaluating the efficacy of rifampicin (four months) compared to INH (nine months) in preventing active TB among adults and children with LTBI will provide data to add to the evidence from this review to inform guidance in countries on considering four months of rifampicin as an alternative to INH. NCT00931736 will include 5720 adults with LTBI from low-income, high TB transmission countries in Africa and Asia, and will also provide prospective data for estimating incremental cost-effectiveness of rifampicin over INH, based on actual efficacy estimates of the two regimens. NCT01398618 is being conducted in 300 adults in Taiwan. ISRCTN53253537 is recruiting 900 children with LTBI from high-income countries as well as high burden, low income countries in Africa and Asia. Efficacy, safety, tolerability, and the emergence of drug resistance are the outcomes sought and the results of this trial will add to the sparse data from the sole trial in this review of four months of rifampicin versus nine months of INH in children.

The rifapentine plus INH trial (PREVENT-TB; Sterling 2011) is ongoing (NCT00023452) and on completion will provide additional date on its efficacy, safety, and tolerability in approximately 454 additional young children to complement the currently insufficient evidence for children with this combination. An ongoing, open-label, three-armed, RCT in the US (NCT01582711) is examining 12 weekly doses of rifapentine 900 mg plus INH 900 mg DOT over three months versus self-administered rifapentine plus INH 12-dose regimen, or self-administered rifapentine plus INH 12 doses with weekly mobile phone short messaging system (SMS) reminders, in 1000 adults .

We did not find on-going trials evaluating adherence to preventive rifampicin-containing treatments for LTBI from low- and middle-income, high TB incidence countries. We also did not find any ongoing trials comparing intermittent rifampicin, or rifabutin, or self-administered INH plus daily rifapentine, with standard INH prophylaxis in HIV-negative people with LTBI.

In addition, pharmacovigilance for adverse events and resistance to rifamycins is also required as these regimens become more widely used. Further trials and implementation research exploring approaches for active case finding and to enhance adherence will help provide evidence to inform approaches to optimise TB control programmes.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Chan 2012

Methods	**Design:** Randomized, open label, two arm, parallel group, active controlled trial; stratified by HBV and HCV status **Period of study:** 2008 to 2010
Participants	**Number randomized:** 373 **Age:** > 18 years **Gender:** Males only **Inclusion criteria** 1. TST = or > 10 mm 2. Quantiferron Gold Test positive 3. HIV-negative 4. Provided written informed consent **Exclusion criteria** 1. Prison term < 6 months 2. Active TB disease (clinical exam, chest radiograph, sputum culture for *M. tuberculosis*) 3. Taking concomitant medications likely to cause drug interactions 4. Elevated glutamic pyruvate transaminase levels (=or > 3 times upper limit of normal - 40 U/L) 5. Elevated bilirubin levels (= or > 2 times upper limit of normal - 1.2 U/L) 6. Platlet count < 150000/mm^3
Interventions	**Intervention:** Rifampicin (10 mg/kg; up to 600 mg/day) for four months (N = 190) **Control:** INH (5 mg/kg, up to 300 mg/day) for six months (N = 183)
Outcomes	**Primary** 1. Adverse events leading to permanent discontinuation of treatment 2. Any cause leading to permanent discontinuation of treatment 3. Adherence 4. Dropouts 5. Mortality 6. Hepatotoxicity 7. Adverse events **Secondary** 1. Active TB (Active case finding; clinical, X-ray; sputum culture)
Notes	**Setting:** Prison for males **Country:** Taipei, Taiwan **Duration of follow-up:** Safety outcomes: End of treatment period in each arm (four months and six months); Efficacy outcome: three years **Funding:** Taiwan Centres for Disease Control (CDC) **Comments:**

	• At inclusion, 100% of patients had a TST ≥ 10 mm • DOT; adherence was defined as proportions completing treatment; also reported were proportions adherent but withdrawn due to adverse events • Unpublished information provided by Dr. Chan: Interventions were administered using DOT while in prison (nine in 4R and 15 in 6H arm paroled before completion were not given DOT). HBV positives: 13% in 6H arm; 15% in 4R arm; Anti-HCV positives: 21% 6H arm, 22% 4R arm • Data on proportions with active TB at three year follow-up were also provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The random allocation sequence within each stratum was generated using the random digit generator of Microsoft Excel 2003"
Allocation concealment (selection bias)	Low risk	Quote from protocol obtained through correspondence with first author: "Assignment will be placed in envelopes that will be numbered sequentially on the outside and stored in order in a box. An envelope in sequence will be taken on the baseline interview with the potential participant, along with consent forms and interview form. If the potential participant refuses or is found not to be eligible, the unopened envelope will be returned to the box, to be used in order for the next potential participant. The study nurse will obtain the number of this granted consent participant (given in the beginning of LTBI diagnosis) and this will be the participant's identification number for the clinical trial"
Blinding (performance bias and detection bias) Efficacy outcomes	Low risk	This study was open label in design and the duration of interventions differed. This is unlikely to introduce bias in assessing objective efficacy outcomes. Treatment was by DOT in both groups except for 25 participants on parole for part of the study. Unlikely to introduce bias in assessments of adherence
Blinding (performance bias and detection bias) Adverse events:	Unclear risk	The open label design and the differential time points for ascertaining hepatotoxicity could potentially introduce detection bias

Incomplete outcome data (attrition bias) All outcomes	Low risk	The published report did not report efficacy outcomes, but the trial authors provided these. Dropouts described and analysis was by intention to treat
Selective reporting (reporting bias)	Low risk	This trial was prospectively registered and all pre-stated outcomes were reported or provided by trial authors
Other bias	Low risk	No other sources of bias were detected.

HKCS 1992

Methods	**Design:** Randomized, double-blind, four-arm, parallel group, placebo-controlled (double dummy) trial **Period of study:** 1981 to 1987
Participants	**Number randomized:** 512 (in the three arms used in this review) **Age:** Less than 65 years **Gender:** Males only **Inclusion criteria** 1. History of exposure to silica dust and silicosis of any severity 2. No history of previous treatment for TB 3. Three sputum smears and culture negative for *M. tuberculosis* 4. No other evidence of active TB **Exclusion criteria** 1. Very poor general condition 2. Serious disease in addition to silicosis 3. Not expected to cooperate in drug adherence and follow-up
Interventions	**Interventions:** 1. Rifampicin 600 mg/day for 12 weeks, then placebo daily for 12 weeks (N = 172) 2. INH 300 mg/day plus rifampicin 600 mg/day for 12 weeks, then placebo daily for 12 weeks (N = 167) **Control:** 1. INH 300 mg/day daily for 24 weeks (N = 173) *Not used in quantitative synthesis in this review* Placebo daily for 24 weeks (N = 167)
Outcomes	1. Active TB by periodic active case detection for 2 to 5 years 2. Drug-resistant TB 3. Treatment completion without known interruption 4. Adverse events including hepatotoxicity and treatment-limiting adverse events
Notes	**Setting:** Special pneumoconiosis clinic of the Hong Kong Chest Service **Country:** Hong Kong, China **Duration of follow-up:** 2 to 5 years **Funding:** Unclear from report; Ciba-Geigy, Basel, Switzerland provided study drugs

	and matching placebos; some authors were employed by the British Medical Research Council **Comment:** • At inclusion, 94% of patients had a TST ≥ 10 mm. 36 of 159 (23%) patients in the placebo only arm developed active TB over five years follow-up • Active TB was diagnosed by serial sputum examinations (two specimens at weeks 12 and 24 and every 3 months from month nine to five years; serial chest X-rays (at 2, 6, 9, and 12 months; and every six months until five years) • Adherence was assessed by pill counts; data used in review are proportions completing treatment without interruption • Definition of hepatotoxicity was unclear; data on hepatotoxicity during months one to three and four to six were aggregated in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were allocated at random."
Allocation concealment (selection bias)	Low risk	"Each patient was allocated by entering his name in the next line of a register. This provided his study number and identified the specially packed box containing his supply of capsules and tablets for the study."
Blinding (performance bias and detection bias) Efficacy outcomes	Low risk	"The study was conducted double blind." Comment: Double-dummy design was employed where 12 weeks of placebo were added to the rifampicin and INH plus rifampicin arms after the first 12 weeks of active treatment to match the 24 weeks of INH treatment. Rifampicin placebo contained yellow and red iron oxide pigments
Blinding (performance bias and detection bias) Adverse events:	Low risk	"The study was conducted double blind." Comment: Double-dummy design was employed as described above. All participants were assessed for these adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	27 patients were withdrawn after randomization: 20 had bacteriological evidence of active TB; 2 were not considered to have silicosis by independent radiologist; 2 were admitted in error, 2 defaulted after first attendance; 1 died of unrelated causes during third month Withdrawals were completely accounted for and were similar in the intervention

HKCS 1992 (*Continued*)

		arms and was less than 10% overall
Selective reporting (reporting bias)	Low risk	Although the protocol or trial registration documents were not available, all pre-stated outcomes were reported, and covered all important outcomes expected from a trial of this nature
Other bias	Low risk	Patients were preselected for good adherence, and hence adherence rates reported in this trial may over estimate the adherence in real life. However, this may affect the external validity but not internal validity The true of effects of short course rifampicin and INH plus rifampicin on adherence could have been attenuated by the need to take an extra 12 weeks of placebo thereby obscuring the actual effects of a 12 week course. However, it is unclear to what extent this might have influenced the results of this trial; it also would affect external rather than internal validity

Leung 2003

Methods	**Design:** Randomized, two-arm, parallel group, open-label, active-controlled, trial **Period of study:** 1 October 2000 to 30 September 2002
Participants	**Number randomized:** 77 **Age:** Adults **Gender:** Mostly men **Inclusion criteria** 1. Patient with silicosis and radiographic profusion of small opacities of category ≥ 1 according to the Interntional Labour Office classification 2. TST ≥ 10 mm **Exclusion criteria** 1. Presence of active TB as evaluated by clinical assessment, at least two negative sputum smears and culture, and radiographic stability for six months 2. History of more than two months of treatment for TB 3. Intolerance to study medications in the past 4. Poor general condition 5. Gouty arthritis 6. Cirrhosis, symptomatic hepatitis, or liver dysfunction with alanine aminotransferase (ALT) more than 1.5 times the upper limit of normal (ULN)
Interventions	**Intervention:** 1. Rifampicin plus pyrazinamide (450 plus 1000 mg/day for those weighing less than 50 kg; 600 plus 1500 mg/day for those weighing ≥ 50 kg), daily for 2 months (N = 40) **Control:**

	1. INH, 5 mg/kg (maximum 300 mg/day), daily for 6 months (N = 37)
Outcomes	1. Active TB 2. Drug-resistant TB 3. Hepatotoxicity, treatment-limiting adverse events 4. Adherence
Notes	**Setting:** Pneumoconiosis Clinic of the Department of Health **Country:** Hong Kong, China **Duration of follow-up:** from published report up to treatment completion; unpublished follow-up data till 31 December 2005 (up to five years) was provided by study lead author Dr. Leung CC **Funding:** Not reported **Comment:** • Active TB was diagnosed by sputum examination for mycobacteria and chest radiography at 2, 6, and 12 months, and then yearly up to 10 years. Results not reported in the publication but were provided by the author • Adherence was assessed by a drug calender and pill counts and calculated as percentage of doses actually received of expected doses • The protocol was modified in December 2001 (after recruiting 34 patients in the INH 6 months arm and 38 patients in the rifampicin plus pyrazinamide 2 months arm) - habitual drinkers with intake for ≥ five days a week were excluded; dosage of pyrazinamide was reduced to 20 mg/kg/day rounded of to the nearest 250 mg lower than the calculated dose; liver functions were monitored every two weeks during the first two months instead of monthly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"subjects were randomised into two study arms by a random number table."
Allocation concealment (selection bias)	Low risk	Quote from correspondence with authors: "Patients were randomised by simple randomisation on 1:1 ratio on a sealed random sequence generated by a random number table" Comment: The review authors inferred that the "sealed random sequence" refers to the use of sealed envelopes to conceal allocation
Blinding (performance bias and detection bias) Efficacy outcomes	Low risk	Although not clearly stated in the report, this appears to be an open-label trial; intervention arms received different durations of treatment and had different outcome assessment time points. However, the time points for assessment for active TB were the

		same in both arms. Adherence was assessed in similar ways in both arms for the duration of treatment
Blinding (performance bias and detection bias) Adverse events:	Low risk	Comment: The frequency of liver function testing was changed following a mid-course protocol amendment due to a CDC alert on potential hepatotoxicity of the rifampicin plus pyrazinamide regimen. The protocol was modified after 14 months of 24 months trial so that habitual drinkers with intake for ≥ 5 days a week were excluded; dosage of pyrazinamide was reduced to 20 mg/kg/day; liver functions were monitored every two weeks during the first two months instead of monthly Quote from correspondence with author: "The dosage of pyrazinamide was reduced in December 2001 after recruiting 38 patients into the 2RZ arm and 34 patients into the 6H arm. Two more patients were recruited into the 2RZ arm and 3 more patients (including one case excluded post-randomisation because of discovery of previous treatment) were recruited into the 6H arm after that day" Comment: The actual impact of the protocol changes on the results is likely to have been minimal, since only five patients were enrolled in the trial after the protocol changes (two in rifampicin plus pyrazinamide arm and three in INH arm of which one was excluded)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient in the 6H arm was excluded after randomisation, as he later revealed a history of anti-TB treatment of more than two months. The baseline characteristics of the remaining 76 patients in the two study arms were comparable." Comment: Complete outcome data were available in the report for the remaining 76 patients. The exclusion of one participant is unlikely to introduce bias
Selective reporting (reporting bias)	Low risk	Although the protocol or trial registration documents were not available, all pre-stated outcomes were reported, and covered all important outcomes expected from a trial

Leung 2003 (*Continued*)

		of this nature
Other bias	Low risk	No additional biases were detected.

Magdorf 1994

Methods	**Design:** Randomized, open-label, three-arm, parallel group, active-controlled, trial **Period of study:** 1989
Participants	**Number randomized:** 150 **Age:** Children less than 18 years old **Gender:** Both genders **Inclusion criteria** 1. TST conversion within the past 24 months 2. Normal chest radiograph **Exclusion criteria** Not reported
Interventions	**Intervention:** 1. Rifampicin, 350 mg/m^2, daily for four months (N = 50) 2. Rifampicin, 350 mg/m^2, daily plus pyrazinamide, 30 mg/kg, daily for two months (N = 50) **Control:** 1. INH, 200 mg/m^2, daily for six months (N = 50)
Outcomes	1. Active TB (definition used not reported) 2. Adherence, based on self report, urine colour, prescription refill, and urinary testing for INH 3. Hepatotoxicity (definition not reported)
Notes	**Setting:** Unclear **Country:** Berlin, Germany **Duration of follow-up:** Two years **Funding:** Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"children were randomly allocated to these three regimens."
Allocation concealment (selection bias)	Unclear risk	No details were provided in the trial report.
Blinding (performance bias and detection bias) Efficacy outcomes	Unclear risk	This was an open-label trial but all participants in both arms underwent evaluations at protocol specified time points, and objective measures supplemented self-reports

Magdorf 1994 (*Continued*)

		on adherence, minimising the risk of bias. However, the definition used for diagnosing active TB was not described and it is unclear if this was systematically done
Blinding (performance bias and detection bias) Adverse events:	Unclear risk	In this open-label trial, it was unclear whether out of turn testing of liver functions was done at the physician's discretion, and if they were influenced by knowledge of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up.
Selective reporting (reporting bias)	Low risk	Although the protocol or trial registration documents were not available, all pre-stated outcomes were reported
Other bias	Low risk	No additional biases were detected.

Martinez Alfaro 1998

Methods	**Design:** Randomized, open-label, two-arm, parallel group, active-controlled trial **Period of study:** 1992 to 1996
Participants	**Number randomized:** 196 **Age:** All ages (however the INH arm had only adults) **Gender:** Both genders **Inclusion criteria** 1. Recent contact with a patient of active TB or radiological evidence of previous TB and TST ≥ 5 mm irrespective of age 2. TST converters 3. Injection drug abuse 4. Patients suffering from immunodepressive diseases such as diabetes mellitus, chronic renal insufficiency, neoplasias, silicosis, or those being treated with glucocorticoids, when TST ≥ 10 mm, irrespective of age 5. Patients without any risk factors but TST > 15 mm and aged under 35 **Exclusion criteria** 1. HIV infection 2. Pregnant or lactating women 3. Previous treatment or chemoprophylaxis for TB 4. Liver disease, ALT ≥ 2.5 times ULN 5. Any contraindication or allergy to study drugs
Interventions	**Intervention:** INH, 5 mg/kg (maximum 300 mg/day) plus rifampicin, 10 mg/kg (maximum 600 mg/day) for 3 months (N = 98) **Control:** INH, 5 mg/kg (maximum 300 mg/day) for 9 months (N = 98)

Outcomes	1. Compliance 2. Side effects *Outcome not used in quantitative synthesis* 3. Efficacy of treatment, as measured by diameter of TST following treatment (did not fulfil inclusion criteria)
Notes	**Setting:** Albacete General Hospital, Spain **Country:** Spain; Albacete province **Duration of follow-up:** 19 ± 11 months in INH plus rifampicin arm and 16 ± 10 months in the INH arm **Funding:** Partially funded by Fondo de Investigaciones Sanitarias de la Seguridad Social (FISS 94/0659) **Comments:** • Efficacy was not assessed in terms of prevention of active TB. One study patient developed active TB; however, the treatment allocation of this patient is not reported • Compliance assessed by clinic attendance and self-reported consumption of > 80% of doses • Key details were translated from Spanish and provided to us by the editorial group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from report: "comparative, randomised, and open study." Comment: No further details provided.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not mentioned.
Blinding (performance bias and detection bias) Efficacy outcomes	High risk	Adherence was assessed by clinic attendance and patient self reports in this open-label trial, and may have introduced detection bias
Blinding (performance bias and detection bias) Adverse events:	Low risk	Although the duration of follow-up differed in intervention arms, participants in both arms were evaluated at the same time points, Though this trial was not blinded, detecting serious and treatment-limiting adverse events were thought unlikely to have introduced bias
Incomplete outcome data (attrition bias) All outcomes	High risk	One study participant developed active TB; however, the allocated treatment is not reported. It is also unclear whether all patients were formally evaluated for active TB using standard measures

Martinez Alfaro 1998 (*Continued*)

Selective reporting (reporting bias)	High risk	The measure of efficacy as adopted in this trial was not considered a valid efficacy outcome. Efficacy data on active TB were not completely reported
Other bias	Low risk	No additional biases were detected.

Menzies 2004

Methods	**Design:** Randomized, two-arm, parallel group, open-label, active-controlled, trial **Period of study:** 21 January 2002 to 1 October 2002
Participants	**Number randomized:** 116 **Age:** ≥ 18 years **Gender:** both genders **Inclusion criteria** 1. Documented TST that met the criteria for a positive test by Canadian standards 2. Recommended treatment for LTBI by the treating physician **Exclusion criteria** 1. Contacts of INH-resistant cases 2. Patients allergic to rifampicin or those taking drugs interacting with rifampicin
Interventions	**Intervention:** Rifampicin, 10 mg/kg (maximum 600 mg/day) daily for 4 months (N = 58) **Control:** INH, 5 mg/kg (maximum 300 mg/day) daily for 9 months (N = 58)
Outcomes	1. Percentage of prescribed doses taken (monitored by medication event monitoring system); adherence more than 80% 2. Serious adverse events 3. Hepatotoxicity, defined as ALT more than 5 times ULN without symptoms or more than 3 times ULN with symptoms 4. Treatment-limiting adverse events *Outcomes not used for quantitative synthesis* Health care use and costs (included in evaluating applicability)
Notes	**Setting:** University-affiliated respiratory hospital **Country:** Quebec, Canada **Duration of follow-up:** 4 to 9 months **Funding:** Medical Research Council, Canada **Comment:** • 110 of 116 randomized subjects had TST ≥ 10 mm • The methods report that randomization was stratified based upon the risk of active TB, with HIV infection being considered a high risk factor. However, it is unclear whether any HIV- positive patient was enrolled in this study and to which arm. In another multicentric trial involving this research group (Menzies 2008), in one of the seven sites in Canada, and in two centres elsewhere, of 847 randomized, 13 participants had HIV infection, indicating a very low prevalence; it is unlikely that the

	proportion of HIV- positive in this trial was any different. • Active TB was not an outcome assessed in this trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from report: "Eligible patients who signed informed consent forms were randomised to 4 months of daily rifampicin (10 mg/kg, up to 600 mg/day) or 9 months of daily INH (5 mg/kg, up to 300 mg/day), using an Internet accessible computerized program that also verified eligibility. Randomization was stratified by risk of TB (high if patient was HIV-positive, had close contacts with active TB, or had fibronodular changes on chest X-ray; and low to moderate for all others), because compliance may be different in these risk groups." Comment: This suggests a central randomization process.
Allocation concealment (selection bias)	Low risk	No details were specifically provided but centralised randomization and the use of electronic pill dispensers to allocate interventions, indicates that allocation was likely to have been concealed
Blinding (performance bias and detection bias) Efficacy outcomes	Low risk	Comment: The duration of treatment differed in the two intervention arms in this open-label trial, however, efficacy outcomes assessed did not include active TB Quote from report: "The primary outcome was the percentage of prescribed doses taken, measured with an electronic device in the pill container cap, which recorded the date and time of bottle opening (medication event-monitoring system [MEMS] device)." Comment: This may not be an entirely accurate method of measuring adherence since it does not guarantee drug intake; however, it was thought unlikely to introduce bias in relative estimates of adherence in the two arms
Blinding (performance bias and detection bias)	High risk	After 1 month, liver functions were tested at the discretion of the treating physician

Menzies 2004 (*Continued*)

Adverse events:		who was not blinded to treatment allocation. This introduces the possibility of bias in the detection of hepatotoxicity
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized patients were accounted for.
Selective reporting (reporting bias)	Low risk	All stated outcomes were reported.
Other bias	Low risk	No additional biases were detected.

Menzies 2008

Methods	**Design:** Randomized, two-arm, parallel group, open-label, active-controlled, trial **Period of study:** 27 April 2004 to 31 January 2007 (the trial was stopped early at the recommendation of the data safety monitoring board after the third planned interim analysis)
Participants	**Number randomized:** 847 **Age:** ≥ 18 years **Gender:** both genders **Inclusion criteria** 1. Documented TST that met the criteria for a positive test by Canadian standards 2. Recommended treatment for LTBI by the treating physician **Exclusion criteria** 1. Contacts of INH or rifampicin-resistant cases 2. Patients allergic to INH or rifampicin or those taking drugs with clinically significant interaction
Interventions	**Intervention:** Rifampicin, 10 mg/kg (maximum 600 mg/day) daily for 4 months (N = 420) **Control:** INH, 5 mg/kg (maximum 300 mg/day) daily for 9 months (N = 427)
Outcomes	1. Grade 3 or 4 adverse events resulting in treatment discontinuation 2. On-time treatment completion defined as taking more than 80% of doses within 150 days for rifampicin and 301 days for INH taken; monitored by medication event monitoring system 3. Serious adverse events 4. Grade 3 or 4 hepatotoxicity defined as ALT more than 5 times the ULN without symptoms or more than 3 times with symptoms, and more than 10 times ULN, respectively 5. Treatment-limiting adverse events *Outcomes reported in supplementary publication but not used in quantitative synthesis in this review:* 7. Health care system costs

Notes	**Setting:** International multicentric trial involving nine university-affiliated hospitals **Country:** Brazil (1), Canada (7), Saudi Arabia (1) **Duration of follow-up:** 4 to 9 months **Funding:** Canadian Institutes of Health Research **Comment:** • 804 of 847 randomized subjects had TST ≥ 10 mm • HIV- positive patients were included in this trial. However, their numbers were small, and they were equal among the two arms: 7 (2%) of 427 in the INH arm and 6 (1%) of 420 participants in the rifampicin arm had HIV infection

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A Web-based programme verified eligibility and randomly assigned participants (by using a random-number generator), after they signed informed consent..(to interventions)....in blocks of varying size, stratified by centre. A team at the University of Sherbrooke, Sherbrooke, Quebec, Canada, prepared the web-based program and allocation sequence."
Allocation concealment (selection bias)	Low risk	The report (see above) indicates that centralised randomization was used and it is likely that the pill containers with electronic monitoring (see below) were serially numbered and linked to the randomization sequence
Blinding (performance bias and detection bias) Efficacy outcomes	Low risk	"Doses taken were measured with the Medical Event Monitoring System, an electronic device in the pill container cap that recorded the date and time of bottle opening." Comment: This may not be an entirely accurate method of measuring adherence since it does not guarantee drug intake; however, it will not introduce bias in relative estimates of adherence in the two arms
Blinding (performance bias and detection bias) Adverse events:	High risk	"The treating physician decided whether to discontinue, re-challenge with, or restart the study therapy, although the protocol specified that participants with grade 3 or 4 adverse events were not to be re-challenged. When all investigations were complete, and

		if therapy was permanently discontinued in response to the event, the patient's clinical course and results of investigations and re-challenge (if any) were made available to a 3-member independent review panel who were blinded to study drug." Comment: This particular outcome was independently adjudicated by a three member review panel blinded to treatment allocation; only those patients that permanently discontinued study drug were reviewed. However, treatment discontinuation was at the discretion of the treating physician who was not blinded "Between 16% and 24% of patients were missing laboratory assessments before treatment or during the first 2 months of treatment." Comment: This could potentially underestimate asymptomatic hepatotoxicity
Incomplete outcome data (attrition bias) All outcomes	Low risk	"In total, 1 patient taking rifampicin and 6 patients taking INH dropped out, and no information was available regarding their health status when they stopped therapy. In a worst case scenario, if all had developed grade 3 or 4 adverse events, the magnitude of the observed difference in these events would have increased, favouring rifampicin." Comment: In addition to the above, all randomized patients were accounted for in analysis of completion
Selective reporting (reporting bias)	Low risk	Although the trial protocol or trial registration documents were not available, all prestated outcomes were reported
Other bias	Low risk	The trial was stopped early for harms but this was done after the third interim analysis by the data safety monitoring board; the trial was not stopped early for apparent benefit

Sanchez-Arcilla 2004

Methods	**Design:** Randomized, two-arm, parallel group,open label, active controlled trial **Period of study:** Not stated
Participants	**Number randomized:** 172 **Age:** 18 years and above; Mean age 42.3 years; SD 12.8 years **Gender:** both genders; Males 116 (67%); Females 56 (33%) **Inclusion criteria** 1. Positive Mantoux test (TST; wheal equal to or more than 5 mm after 48 to 72 hours of intradermal injection of 0.1 ml intradermal (2 U RT-23) purified protein derivative on the surface of the forearm) **Exclusion criteria** 1. People allergic to any of the study drugs; those with severe liver disease; pregnancy; or age younger than 17 years
Interventions	**Intervention:** Rifampicin (600 mg / day for 2 months) plus pyrazinamide (20 mg /kg/day for 2 months) (N = 84) **Control:** INH prophylaxis (300 mg / day for 6 months) (N = 88)
Outcomes	1. Proportions initiating and completing treatment 2. Loss to follow-up 3. Intolerence to treatment 4. Hepatitis 5. Adverse effects
Notes	**Setting:** Homeless people in government-run and charitable shelters **Country:** Spain (Madrid) **Duration of follow-up:** 2 months and 6 months **Funding:** Not stated. Medication was provided free and the study was approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañón **Comments:** • All participants were indigent and 74 (43%) of participants were immigrants of whom 36 (21%) were illegal immigrants • One participant in each arm was HIV-positive. 105 (61%) had at least one risk factor for LTBI • All participants had a positive TST as defined by the study inclusion criteria; additionally, in suspected cases, chest X-rays, and sputum smears and cultures ruled out active pulmonary TB • Treatment was self-administered or supervised monthly or more frequently if symptoms or signs of toxicity appeared. If transaminase levels rose above 5 times without symptoms or more than 3 times over the baseline with symptoms of liver disease, treatment was withdrawn • This report in Spanish was translated using three separate web-based translation programmes that provided information sufficient to extract relevant data

Risk of bias

Bias	Authors' judgement	Support for judgement

Sanchez-Arcilla 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote from report, "prospective, randomised, controlled."
Allocation concealment (selection bias)	Unclear risk	Not stated; attempts to obtain additional details were unsuccessful
Blinding (performance bias and detection bias) Efficacy outcomes	High risk	The study did not measure efficacy, and was not blinded. Treatment was supervised if symptoms or signs of toxicity appeared; otherwise it was unsupervised, this is likely to increase the risk of bias in ascertaining adherence
Blinding (performance bias and detection bias) Adverse events:	High risk	The open-label design and direct supervision of people with signs of toxicity is likely to have introduced bias in ascertainment of adverse events
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 142 randomized, 30 (17%) did not initiate allocated interventions; 11 (12%) in those assigned to INH and 19 (23%) of those allocated to rifampicin and pyrazinamide. Overall 62 (36%) of those who initiated treatment were lost to follow-up and there were more losses in those randomized to the six month INH regimen 47 (53%) than to the combination regimen 15 (18%)
Selective reporting (reporting bias)	Unclear risk	No efficacy outcomes were reported; it is unclear if this was intended and not reported due to the high drop-out rate
Other bias	Low risk	No other biases were detected.

Sterling 2011

Methods	**Design:** Randomized, multicenter, two arm, parallel group, open label, phase III, active controlled, non-inferiority trial **Period of study:** June 2001 through February 2008
Participants	**Number randomized:** 8053 randomized; 322 subsequently found ineligible (mostly because source case had drug-resistant TB (50%) or negative cultures for *M. tuberculosis* (32%)). Number who received at least one dose of intervention: 7799 **Age**: > 2 years old **Gender**: Males or nonpregnant, non-nursing females. **Inclusion criteria:** 1. *Tuberculin (PPD) skin test reactors at high risk for developing TB but without*

	evidence of active TB. High-risk reactors are defined as:Household and other close contacts of people with culture-confirmed TB who are TST-positive as part of a contact investigation conducted within two years of the date of enrolment. Close contact is defined as > 4 hours in a shared airspace during a one-week period. Among close contacts, a positive TST is defined as > 5 mm induration after 5 TU of PPD placed intradermally using the Mantoux technique.TST converters--converting from a documented negative to positive TST within a two-year period. This is defined as people with a TST of > 10 mm within two years of a non-reactive test or people with an increase of > 10 mm within a two-year period. HIV-seropositive, TST positive (> 5 mm induration) people. People with > 2 cm^2 of pulmonary parenchymal fibrosis on chest X-ray, no prior history of TB treatment, > 5 mm induration on TST, and 3 sputum cultures negative for *M. tuberculosis* on final report. 2. *HIV-seropositive close contacts of people with culture-confirmed TB, regardless of TST status.* In addition, HIV-seropositive close contacts of people with culture-confirmed TB who have a documented history of completing an adequate course of treatment for active TB or LTBI, are also eligible. 3. *Willing to provide signed informed consent, or parental consent and participant assent.* **Exclusion criteria:** 1. Current confirmed culture-positive or clinical TB 2. Suspected TB (as defined by the site investigator) 3. TB resistant to INH or rifampicin in the source case 4. A history of treatment for > 14 consecutive days with a rifamycin or > 30 consecutive days with INH during the previous 2 years. 5. A documented history of a completing an adequate course of treatment for active TB or LTBI in a person who is HIV-seronegative. 6. History of sensitivity/intolerance to INH or rifamycins 7. Serum aminotransferase aspartate (AST, SGOT) > 5x upper limit of normal among people in whom AST is determined 8. Pregnant or nursing females 9. People currently receiving or planning to receive HIV-1 protease inhibitors or nonnucleoside reverse transcriptase inhibitors in the first 90 days after enrolment. 10. Weight < 10 kg
Interventions	**Intervention:** INH 900 mg once a week plus rifapentine 900 mg once a week for 3 months (DOT by health worker) (N = 3986) **Control:** INH 300 mg/day daily for 9 months (self-administered) (N = 3745) (INH dosing variations: 5 mg /kg body weight; rounded off to the nearest 50 to 100 mg; 300 mg maximum; INH 15 mg/kg (round up to nearest 50 or 100 mg; 900 mg max) once weekly x 12 doses if > 12 years old. INH 25 mg/kg (round up to nearest 50 or 100 mg; 900 mg max) if 2 to 11 years old Rifapentine dosing variations: 10 to 14 kg = 300 mg; > 14 to 25 kg = 450 mg; > 25 to 32 kg = 600 mg; > 32 to 50 kg = 750 mg; > 50 kg = 900 mg)
Outcomes	**Primary outcome:** 1. Culture-confirmed TB in subjects 18 years of age or older and culture-confirmed or clinical TB in children under the age of 18 years. **Secondary outcomes:**

	1. The development of culture-confirmed or probable TB combined (regardless of age) 2. Discontinuation of study drug permanently due to adverse drug reaction 3. Development of any grade 3 or 4 drug-related toxicity 4. Death due to any cause (grade 5 toxicity) 5. Discontinuation of therapy for any reason 6. Completion of the prescribed regimen *Outcomes stated (in protocol) but not reported* 1. Among participants concomitantly receiving methadone, the development of methadone withdrawal (defined as having more than 3 new symptoms for > 7 days: nausea and vomiting, abdominal cramps, body aches, restlessness, irritability, dilated pupils, tremors, involuntary twitching, lacrimation, rhinorrhoea, sneezing, yawning, excessive perspiration, goose flesh, or diarrhoea). 2. The development of culture-confirmed or probable TB (combined) among people who complete study-phase therapy. 3. The development of culture-confirmed or probable TB (combined) among HIV-positive people.
Notes	**Setting:** Academic and public institutions **Countries of recruitment:** 26 centres in four countries: USA (21), Canada (3), Brazil (1), Spain (1) **Duration of follow-up:** 33 months after enrolment **Funding:** TB Trials Consortium (funded by CDC) **Comments:** • 3584 people excluded after screening, of whom 1756 refused to participate • Close contacts were randomized by household, other high-risk participants were randomized individually (28% in the INH arm and 33.7% in the combination arm were randomized in clusters) • 5858 completed treatment as per protocol; 7731 (3745 INH, 3986 combination) included in modified intention to treat (MITT) analysis • 6883 (89%) of participants in the MITT sample were from USA or Canada; 43% were of Hispanic origin; 25% were black and 57% were white; 27% were self-reported current smokers, and around 50% reported alcohol use; 2.6% had HCV infection and 100 (2.7%) in INH only arm and 105 (2.6%) in the combination arm were HIV-positive • The initial objective of assessing clinical equivalence was re-stated in year four of the trial as an evaluation of non-inferiority for combination therapy with rifapentine plus INH, with an absolute non-inferiority margin (delta) of 0.75% • Per protocol was defined as participants who: 1) completed study drug phase within the targeted time period (11-12 doses of RPT/INH within 16 weeks or 240 doses of INH within 52 weeks) and who 2) were evaluated in person 33 months after enrolment • The modified ITT population excluded those who were found ineligible for the study after the enrolment • Further details of additional analyses are available in a published supplementary web-appendix. Further details of study design are available in the study protocol published online with the trial report • This study is ongoing but has stopped recruiting participants (NCT00023452) • Proportions of children in intervention arms not stated in published reports

	• Additional information provided in trial registration record for NCT00023452, "A sample size of 8,053 patients for the primary outcome was reached on February 15, 2008 (with expected follow-up completion time in 2010), leaving approximately 454 additional young children and 200 HIV- positive people to be enrolled to achieve the targets of 644 for each group. The additional data on tolerability in those subgroups will available for analysis in 2013"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from published supplementary protocol, "Each study site will have its own randomisation schedule, and randomisation will be stratified by study site and patient HIV status. Randomization will be blocked by site. Randomization schedules will be constructed of random blocks of 2, 4, or 6 patients. The above will ensure an approximate allocation ratio of 1:1 to each of the study regimens for both HIV-seronegative and HIV-seropositive patients" Comment: The review authors feel that central, stratified, block randomization, minimised selection bias
Allocation concealment (selection bias)	Low risk	Quote from published supplementary protocol, "Eligibility will be confirmed by a telephone call to the TBTC Data Center at CDC. Eligible patients will be randomized to either weekly RPT plus INH x 3 months (3RPT/INH) OR daily INH x 9 months (9INH) Comment: The review authors feel this ensured unpredictability in allocation to intervention arms
Blinding (performance bias and detection bias) Efficacy outcomes	Low risk	Quote from published supplementary protocol,"Adherence to study therapy, as determined by DOT records (3INH/RPT), pill count and interview (9INH). This will be documented on Form 3. Patients will bring their pill bottle to each monthly visit. If pill count and self-report disagree, pill count will supersede self-report. If the patient forgets to bring in pill bottle, information will be obtained by patient report." Comment: This was an open-label trial and the duration of treatment differed by six

		months in the intervention arms, however, standard procedures were employed in detecting active and drug resistant TB and the primary end-point was at 33 months after enrolment, ensuring that both arms had equal duration of observation for efficacy and compliance outcomes.The review authors feel these measures minimised the risk of performance and detection bias
Blinding (performance bias and detection bias) Adverse events:	High risk	In this open-label trial, participants in the once-weekly combination treatment arm were directly observed every week and the greater interaction with study personnel could account in part for the higher incidence of hypersensitivity reactions and adverse events noted with this new treatment combination as opposed to the self supervised INH participants who were seen only monthly. This risk of bias would not apply to the detection of hepatotoxicity
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 8053 participants randomized, 88% in the combination treatment arm and 86% in the INH arm completed 33 months of follow-up. However, the authors used a modified intention to treat analysis that included 96% of those randomized to each arm
Selective reporting (reporting bias)	Low risk	The study protocol and trials registration record reveal no evidence of selective reporting
Other bias	Unclear risk	Quote from supplementary protocol: "Among household close contacts, randomisation will occur by household. The first person in the household to enter the study will be randomised to one of the study arms, and all subsequent participants from the same household will receive the same regimen. All such participants must sign informed consent prior to randomisation of the first person in the household. Any household members subsequently identified who are eligible for the study will be randomised separately. All other participants will be randomised individually."

		Comment: 1050 (28%) of participants in the INH only arm and 1345 (33.7%) of participants in the combined arm were randomized in clusters (P < 0.05), the remainder were randomized individually; more people completed the trial in the combined group than the INH only arm and analyses did not account for clustering effect. However, a sensitivity analysis excluding those randomized in clusters did not reveal differences in effects

Tortajada 2005

Methods	**Design:** Cluster-randomized (by households), multi-centre, parallel group, open-label, active-controlled trial **Period of study:** 1 February 2001 to 28 February 2003 (stopped prematurely for increased incidence of hepatotoxicity)
Participants	**Number randomized:** 352 **Age:** > than 1 year old; (the trial recruited participants aged 1 year to > 35 years) **Gender:** both I**nclusion criteria:** 1. Individuals who were in contact with infectious PTB patients, and 2. Had a positive TST, and 3. Met any of the following criteria for treatment of LTBI: ○ recent TST conversion from negative to positive in individuals of any age; ○ any individual aged < 35 years in contact with a case of TB; ○ exposure for more than 6 h/day to patients with TB and positive sputum smear, independent of age; ○ immunosuppressed patients with daily exposure to a case of TB. **Exclusion criteria**: 1. Active TB, 2. Previous TB or LTBI treatment 3. Risk factors for HIV infection or HIV-seropositive 4. Renal or hepatic failure, 5. Chronic liver disease, or baseline liver enzyme levels .3 times the normal value 6. Concomitant use of other hepatotoxic drugs or drugs that might enhance the hepatic toxicity of study drugs 7. Current alcoholism 8. Pregnant women 9. Children < 1 year of age
Interventions	**Intervention:** 1. INH 5 mg/kg/d (max 300 mg/d) for 6 months (N = 199) **Control:** 1. Rifampicin 10 mg/kg/d (max 600 mg/d) plus Pyrazinamide* 25 mg/kg/d (max 2000 mg/d) for 2 months (N = 153) * The dose of pyrazinamide was reduced to 20 mg/kg/day after publication of the revised

	ATS/CDC recommendations in 2001
Outcomes	1. Active TB 2. Adherence (treatment completers- those who took 80% or > of prescribed medication) 3. Treatment-limiting adverse events 4. Hepatoxocicity 5. Nausea or vomiting 6. Patients with at least one adverse event *Outcomes reported but not used in this review* 1. Tolerance of treatment (scale of 1 to 10) 2. Daily adherence 3. Fatigue or malaise 4. Rash and/or pruritus
Notes	**Setting:** Nine public health care centres in four Spanish cities. **Countries of recruitment:** Spain **Duration of follow-up:** Unclear. Trial stopped prematurely due to higher than anticipated liver toxicity **Funding:** Supported by a National Funds for Health Research grant, FIS 00/0020-03, and a grant from SEPAR (Spanish Society of Pneumology). **Comments:** • Unequal numbers in each arm due to more contacts in the 6H arm • None of the participants were HIV-positive • TST positivity was an inclusion criterion; definition of TST positive used not stated • The number of clusters completing the trial ws unclear (the number of clusters recruited were not clear from the report, and the numbers completing were also not clearly stated, nor could they be reliably imputed)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was centralised and carried out using a computer programme."
Allocation concealment (selection bias)	High risk	"Each main investigator had an open list of randomisation provided by the coordinator of the study, and assigned participants to their group" Quote from correspondence with authors: "Yes, the investigation (sic) could know beforehand." Comment: An open list compromises the unpredictability of randomization sequence

Blinding (performance bias and detection bias) Efficacy outcomes	Unclear risk	This is an open-label trial; intervention arms received different durations of treatment and the frequency of scheduled clinic visits were different. However, adherence was assessed in similar ways in both arms for the duration of treatment. Method of ascertaining active TB was not stated; and since the trial was stopped early while recruitment was ongoing, participants would have had unequal periods of follow-up to detect the development of active TB
Blinding (performance bias and detection bias) Adverse events:	Unclear risk	Comment: Clinical evaluation for adverse effects was more frequent in the 2RZ arm (every 2 weeks) as compared to the 6H arm (monthly). However, laboratory testing for hepatotoxicity was performed in a similar way at 2, 4, 6, and 8 weeks in both arms. Additional testing was performed at 16 and 24 weeks in the 6H arm only. In addition, liver function tests were done on as needed basis in symptomatic patients Quote from report: "As it was not blinded, ascertainment bias may have influenced the evaluation of adherence, tolerance, and adverse effects." Comment: It is unclear whether this bias actually influenced the findings of this trial Quote from report: "The dosage of pyrazinamide was lowered to 20 mg/kg/d after publication of the revised ATS/CDC recommendations" (published on April 20, 2001) Comment: The actual impact of the protocol changes on the results is likely to have been minimal, since enrolment in the trial had started in February 1, 2001 only
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Forty contacts (20%) in the 6H arm and 20 (13%) in the 2RZ arm were lost to follow-up." Comment: Loss to follow-up was included as non-completion of treatment and the rate of loss to follow-up was comparable between the two arms. Since the analysis was by intention to treat, it is unlikely to have introduced bias. However, the number of missing clusters was not clear from the trial report

Tortajada 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	"The study was designed to evaluate the protection of 2RZ against active TB"; "During the study period, no case of active TB was diagnosed among the participants" Quotes from correspondence with authors: Question: "Were these patients followed-up after the enrolment was stopped in February 2003?" Answer: " No, they were not." Comment: Since the trial was stopped prematurely, periods of ascertainment for active TB would differ. However, this does not indicate selective reporting
Other bias	Unclear risk	The large number of losses to follow-up of individuals renders it difficult to assess the number of cluster randomized individuals remaining and hence difficult to estimate risk ratios adjusted for clustering to include with the results of the other two trials in meta-analysis using generic inverse variance techniques. Removal of the extracted data from the pooled results did not change the direction of effect but increased imprecision

ALT: Alanine transferase
HIV: Human Immunodeficiency Virus
INH: Isoniazid
TB: Tuberculosis
TST: Tuberculin Skin Test

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

Study	Reason for exclusion
Bailey 1974	Not RCT. Non-randomized comparison of INH versus no INH on hepatotoxicity in hospital employees with LTBI
Barnwell 1992	RCT: Intervention was additional health education and counselling to improve completion of INH prophylaxis
Batki 2002	RCT: Interventions were methadone and DOT to improve completion of INH prophylaxis in opioid-dependent patients with LTBI

(*Continued*)

Bridge 1967	Not a clinical trial: view point advocating roll out of INH treatment for LTBI in Michigan
Byrd 1977	RCT: INH versus placebo comparison of hepatotoxicity.
Catie 2001	Not an original study; a commentary on another RCT of post-treatment INH versus placebo for prevention of recurrent TB
Chaisson 2001	RCT: 3 × 2 factorial evaluation of twice-weekly DOT versus daily self-administration with peer counselling versus routine care, and monthly $ 10 stipend to improve adherence to INH prophylaxis in injection drug users with LTBI
Coly 2004	Not RCT: a study of factors associated with completion of LTBI treatment
Comstock 1967	Cluster RCT: comparison of INH versus placebo.
Comstock 1972	Not RCT; exploratory analysis of an RCT of INH versus placebo (Comstock 1967) and subsequent population roll out of INH for prevention of active TB among people with "untreated non-active TB"
Comstock 1974	RCT: Follow-up report on two RCTs of INH versus placebo.
Cowie 1996	RCT: comparison of rifampicin plus INH plus pyrazinamide for 3 months versus placebo for prevention of TB among South African gold miners with silicosis
Debre 1973	RCT: comparison of INH 5 months versus control in TST converters
Egsmose 1965	RCT: comparison of INH 12 months versus placebo among household contacts of open cases of pulmonary TB
Eule 1973	RCT: Treatment of active TB.
Eule 1973a	RCT: Treatment of active TB.
Felten 1989	RCT: comparison of INH versus placebo on the size of TST reaction in LTBI
Ferebee 1962	RCT: comparison of INH versus placebo among household contacts
Ferebee 1963	RCT: comparison of INH versus placebo in mental institutions
Ferebee 1968	RCT: Follow-up report on several United States Public Health Service sponsored RCTs comparing INH versus placebo
Fielding 2011	Protocol of a cluster RCT: compared routine INH prophylaxis targeted to those identified as at higher risk of TB (due to HIV infection or silicosis) against a "community-wide" approach in which INH prophylaxis is offered to all employees of gold mines
Frigati 2011	Not RCT: A cohort analysis within a placebo-controlled trial of INH compared with placebo in HIV-positive children
Gao 2006	Not RCT: meta-analysis of INH 6 - 12 months versus rifampicin plus pyrazinamide 2 to 3 months

(*Continued*)

Geijo 2007	RCT: comparison of INH 6 months versus INH plus rifampicin 3 months; but, included patients with primary TB and radiographic evidence of inactive TB
Geiter 1987	RCT: treatment of active pulmonary TB.
Glassroth 1977	RCT: comparison of cancer-related deaths between INH versus placebo groups of two United States Public Health Service sponsored RCTs
Graham 1996	Not RCT: cohort study of the effect of INH prophylaxis on risk of TB among injection drug users; 942 of 2960 patients were HIV-positive
Gupta 1993	RCT: comparison of no treatment versus INH 3 months versus INH plus rifampicin 1 month versus INH plus rifampicin 3 months versus INH plus rifampicin plus pyrazinamide 1 month; INH was given for 3 months only
Horwitz 1966	RCT: cluster RCT of INH versus placebo among adults in Greenland
Horwitz 1974	RCT: Another report on Horwitz 1966.
IUAT 1982	RCT: comparison of INH versus placebo.
Jasmer 2002b	Not RCT: Quasi-randomized comparison of INH 6 months versus rifampicin plus pyrazinamide 2 months; primary outcomes were adverse effects and treatment completion Quote from report: "Patients who met study criteria and agreed to participate were allocated in alternate weeks."
John 1994	RCT: comparison of INH 12 months versus placebo in dialysis and renal transplant patients
Krebs 1977	Not RCT: a review article.
Krebs 1979	RCT: comparison of INH versus placebo for the prevention of active TB among patients with fibrotic pulmonary lesions
Krebs 1980	RCT: comparison of INH versus placebo; Late results of Krebs 1979.
Lienhardt 2011	RCTin adults with newly diagnosed smear-positive pulmonary TB
Madhi 2011	RCT: INH versus placebo in HIV- positive children and HIV-negative children exposed to HIV during the perinatal period
Martinson 2011	RCT: participants were adults with HIV infection.
Moulton 2007	Not RCT: describes the design of a randomized evaluation of health services intervention to implement routine testing for LTBI and treatment with INH among HIV- positive patients in Brazil
Mount 1962	RCT: comparison of INH versus placebo for the prevention of TB among household contacts
Nazareth 1971	RCT: comparison of post-treatment INH versus placebo for the prevention of recurrent TB; two RCTs

(*Continued*)

Nunn 2011	RCT: Participants were people with newly diagnosed smear positive TB
Samandari 2011	RCT: participants were adults with HIV infection.
Schechter 2006	RCT: comparison of weekly INH plus rifapentine 12 weeks versus daily rifampicin plus pyrazinamide 8 weeks among household contacts of PTB
Spyridis 2007	NOt RCT: Quasi-randomized; two independent comparisons of INH 9 months versus INH plus rifampicin 4 months and INH plus rifampicin 4 months versus INH plus rifampicin 3 months. Outcomes were treatment completion, adverse events, and active TB Quote from report: "Patients were randomly assigned to 1 of 2 groups on the basis of their number in the clinic (odd or even)."
Veening 1968	RCT: comparison of INH versus placebo.

RCT: Randomized Controlled Trial
INH: Isoniazid

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

White 2012

Methods	**Design:** Randomized, parallel group, active controlled, open-label, trial **Period of study:** November 30, 2004 to September 24, 2007
Participants	**Number randomized:** 364 **Age:** Adults (age 18 years or older) **Gender:** Males = 339 (93%); Females = 25 (7%) **Inclusion criteria:** 1. San Francisco Jail inmates 2. Age 18 or older 3. Evidence of *M. tuberculosis* infection by positive TST (a documented reactive TST to 0.1 mL containing 5 Tuberculin Units) 4. Meet current national criteria for therapy for TB infection 5. Can provide informed consent **Exclusion criteria:** 1. History of treatment-limiting reaction to INH or rifamycins 2. Pregnancy or breast feeding 3. Active TB 4. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal 5. Bilirubin >2 times the upper limit of normal 6. Platelets <150 K/mm^3 7. Taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors (NNRTIs) 8. Unable to communicate in English or Spanish 9. Unable or unwilling to provide informed consent

	10. Not in the routine level of jail security for any reason (housed in "special security" areas) 11. Any condition that, in the best judgement of the investigator, would pose a risk to the subject during the study
Interventions	**Intervention:** 1. Rifampicin (600 mg) once daily (4-month regimen for a total of 120 doses that could be given over 6 months) (N = 180) **Control:** 1. INH (900 mg) administered twice weekly (9-month regimen for a total of 76 doses that could be given over 12 months) (N = 184)
Outcomes	**Primary outcomes*** 1. Drug toxicity (number of participants with laboratory test or clinical judgement resulting in the need to stop study medication over one year) **Secondary outcomes*** 1. Adherence 2. Cost-effectiveness 3. Reasons for completion or non-completion of therapy *From study protocol in the registration document (NCT00128206) first received by ClincalTrials.gov on 5 August 2005 (retrospectively registered). There are discrepancies within the registration document and between the registration document and the trial publication about primary and secondary outcomes
Notes	**Setting:** San Francisco City and County Jail **Country:** USA **Funding:** NIAID & NIH **Comments:** • Only 29% (107) of 364 randomized completed therapy (26% (47 of 184) of INH participants and 33% (60 of 180) of rifampicin participants (not significantly different) • INH was administered by direct observation in prison and by direct observation, incentives and case management outside prison and given twice weekly and not daily as is standard practice • INH could be given over 12 months. Any participant off treatment < 1 month in the first 3 months had the regimen extended by the number of missed doses. If off treatment for ≥ 1 month in the first 3 months, the regimen was restarted • If a participant missed a dose of rifampicin, medication was extended by the doses missed. Up to 2 weeks of missed doses could be added to the regimen; if a participant missed > 2 weeks, medication was restarted • The registration document states, "Follow-up will continue for each subject for five years after enrolment into the study", but no follow-up details beyond treatment completion is reported for those remaining in the study • Estimated sample size from registration document, " The study participants will include 972 San Francisco Jail inmates, 18 years and older, enrolled over a 28-month period, for a sample of 486 in each study group. Subjects, followed in jail and after release, will be followed to test three hypotheses: the null hypothesis of a difference in toxicity of rifampicin as compared to INH within a 95% confidence interval of (0.4 to 1.87) and no difference by study group in adherence and in cost-effectiveness". According to the published report, "Sample size was determined to be 360 based on the toxicity rates for INH and rifampicin (Menzies et al., 2004) while accounting for loss from deportation or transfer to prison (White et al., 2002)" • The registration record states, " Follow-up will continue for each subject for five years after enrolment into the study, to measure study endpoint (completion of care, taken off drugs for toxicity or loss to follow-up) and to measure subsequent treatment for LTBI or development of active TB by record review" • No efficacy outcomes or cost-effectiveness data are reported in the publication • The registration record states, " Initial enrolment estimates were not met, from lower TB rates, increased deportation rates and fewer Jail personnel for LTBI testing. The complexity of treatment in the jail led to technical

	problems in the analytic plan" • Overall, 30 (8%) were positive for HCV and 4 (1%) were positive for chronic HBV; it is unclear if any HIV-positive people were included • The first author has been contacted to clarify discrepancies and provide additional information on adherence and toxicity. A decision to include or exclude and subsequent action will be included in future updates of this review

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

ISRCTN53253537

Trial name or title	A randomized trial to compare completion and tolerability of 4 months rifampin (4 Rif) and 9 months INH (9 INH) in treatment of LTBI in children
Methods	Randomized, parallel group, open label, Phase III, active controlled trial
Participants	**Inclusion criteria:** 1. Children (age <18) with documented positive TST as defined below and prescribed 9INH for LTBI, for the indications below: Note: In the absence of a TST test, a positive QFT (or T-Spot) (according to manufacturers recommendations) (see screening, recruitment and randomisation procedures) is equivalent to a TST of 10 mm. 1.1. HIV positive (TST > 5 mm or QFT positive) 1.2. Age 5 or less (TST > 5 mm or QFT positive) 1.3. Other reason for immuno-compromised state - such as therapy for malignancy or post-transplant (TST > 5 mm or QFT positive) 1.4. Contact: with adult or adolescent with active contagious pulmonary TB TST > 5 mm or QFT positive) 1.5. Have both of the following factors if TST = 10 to 14mm or QFT positive or one factor if TST > 15mm : 1.5.1. Arrival in Canada, Australia, or Saudi Arabia in the past 2 years from countries with estimated annual incidence of active TB greater than 100 per 100,000 1.5.2. Body mass index (BMI) less than 10th percentile for their age 2. Interferon gamma release assays (IGRA's) are ex-vivo tests of immune response to TB antigens, that have been adopted in some centres as alternatives to the TST, although WHO has recently recommended IGRAs should not be used to replace the TST in low and middle-income countries 3. If an eligible child undergoes a commercially available IGRA (the QFT or T-Spot.TB), instead of a TST, and the result is positive, then they will be considered eligible 4. If both TST and IGRA are done, then the TST result will be used to determine eligibility 5. The TST may be negative for up to 8 weeks after primary infection, before adequate cell mediated immunity develops 6. Because of this, current practice is to begin LTBI treatment therapy immediately for children < 5 years old, even if TST negative 7. After 8 to 10 weeks the TST is repeated; LTBI therapy is continued if now TST positive, and stopped if still negative 8. Providers may continue therapy in very young, HIV-positive or malnourished children 9. We propose to enrol TST negative children aged < 5, if the treating physician prescribes LTBI therapy, because: 9.1. Primary endpoints are still relevant, and measurable in this group 9.2. Acceptability and completion in this subgroup are of particular interest 9.3. Children that have new primary TB are at particularly high risk to develop disease (this is the rationale

	for their treatment) 10. If the treating MD stops therapy because the TST is negative after 8 to 10 weeks, these children will be excluded from the analysis of treatment completion, but included in the incidence density analysis (person-time) of tolerability and safety **Exclusion criteria:** 1. Children who were contacts of TB cases known to be resistant to INH, RIF, or both (i.e. MDR) 2. Known HIV-positive individuals on antiretroviral agents whose efficacy would be substantially reduced by rifampin, unless therapy can safely be changed to agents not affected by rifampin 3. Pregnant women - rifampin and INH are considered safe in pregnancy, but therapy is usually deferred until 2 to 3 months post-partum to avoid fetal risk and the potential for increased hepatotoxicity immediately post partum 4. Children on any medication with clinically important drug interactions with INH or RIF, which their physician believes would make either arm contra-indicated. This includes women taking hormonal contraceptives who will not take alternative contraception 5. History of allergy/hypersensitivity to INH or to rifampin, rifabutin or rifapentine 6. Active TB. Children initially suspected to have active TB can be randomized once this has been excluded 7. Prior complete LTBI therapy or if children have taken > 1 week and are still taking the treatment. Children will be eligible if they took an incomplete LTBI therapy (less than 80% of recommended total dose) but > 6 months ago
Interventions	**Interventions:** Daily self-administered rifampin, 10 to 20 mg/kg/day for children (max = 600mg/day) for 4 months (4RIF) **Control:** The standard therapy will be daily self-administered INH,10 to 15 mg/kg/day for children (max = 300mg/day) for 9 months (9INH) As currently recommended vitamin B6 (pyridoxine) will be given with INH only to patients with risk factors for neuropathy - malnutrition, alcoholism, diabetes, or renal insufficiency or HIV positive For children, dosing for both INH and RIF will be age and weight dependent, with highest doses for infants, and lowest for adolescents
Outcomes	**Primary outcomes:** To compare the rates of premature discontinuation of study therapy because of adverse events of all grades judged probably related to 4RIF or 9INH, by the majority of an independent panel of 3 reviewers, blinded to study drug **Secondary outcomes:** 1. To compare the rates of study drug completion of all children randomized to 4RIF or 9INH. Completion will be defined as taking at least 80% of total planned doses within 23 weeks for 4RIF, or within 52 weeks for 9INH 2. To compare the rates of clinically diagnosed active TB as judged by an independent panel of paediatricians, up to 16 months post randomization in children who complete study therapy per protocol (efficacy) 3. To describe the occurrence of drug resistant microbiologically confirmed active TB among children randomized to the two arms, during 16 months post randomization
Starting date	01/08/2011
Contact information	Dr Dick Menzies, Montreal Chest Institute, Room K1.24, 3650 St. Urbain Street, Montreal, H2X 2P4, Canada. email: Dick.Menzies@mcgill.ca

ISRCTN53253537 (*Continued*)

Notes	Accessed: November 7, 2011 Acronym: P4v9 Status: Ongoing/Recruiting Target sample size: 900 Expected end date: 01/08/2014 Countries of recruitment: Australia, Benin, Canada, Ghana, Indonesia, Saudi Arabia Primary Sponsor: Canadian Institutes of Health Research (Canada), 160 Elgin Street, 9th Floor, 4809A, K1A0W9, Canada,Tel: +1 613 954 1968; email: info@cihr-irsc.gc.ca; web-site: http://www.cihr-irsc.gc.ca/e/193.html Registration Number: ISRCTN53253537

NCT00023452

Trial name or title	TBTC study 26: Effectiveness and tolerability of weekly rifapentine/INH for 3 months versus daily INH for 9 months for the treatment of LTBI
Methods	Randomized, open-label, active controlled, parallel group, phase III clinical trial
Participants	People of both genders aged 2 years or more **Inclusion criteria:** 1. Males or nonpregnant, non-nursing females > 2 years old. 2. Tuberculin (PPD) skin test reactors at high risk for developing TB but without evidence of active TB. High-risk reactors are defined as:Household and other close contacts of people with culture-confirmed TB who are TST-positive as part of a contact investigation conducted within two years of the date of enrolment. Close contact is defined as > 4 hours in a shared airspace during a one-week period. Among close contacts, a positive TST is defined as > 5 mm induration after 5 TU of PPD placed intradermally using the Mantoux technique.TST converters--converting from a documented negative to positive TST within a two-year period. This is defined as people with a TST of > 10 mm within two years of a non-reactive test or people with an increase of > 10 mm within a two-year period.HIV-seropositive, TST positive (> 5 mm induration) people. People with > 2 cm^2 of pulmonary parenchymal fibrosis on chest X-ray, no prior history of TB treatment, > 5 mm induration on TST, and 3 sputum cultures negative for *M. tuberculosis* on final report. 3. HIV-seropositive close contacts of people with culture-confirmed TB, regardless of TST status. In addition, HIV-seropositive close contacts of people with culture-confirmed TB who have a documented history of completing an adequate course of treatment for active TB or LTBI, are also eligible. 4. Willing to provide signed informed consent, or parental consent and participant assent. **Exclusion criteria:** 1. Current confirmed culture-positive or clinical TB 2. Suspected TB (as defined by the site investigator) 3. TB resistant to INH or rifampin in the source case 4. A history of treatment for > 14 consecutive days with a rifamycin or > 30 consecutive days with INH during the previous 2 years. 5. A documented history of a completing an adequate course of treatment for active TB or LTBI in a person who is HIV-seronegative. 6. History of sensitivity/intolerance to INH or rifamycins 7. Serum aminotransferase aspartate (AST, SGOT) > 5x upper limit of normal among people in whom AST is determined 8. Pregnant or nursing females 9. People currently receiving or planning to receive HIV-1 protease inhibitors or nonnucleoside reverse

NCT00023452 (*Continued*)

	transcriptase inhibitors in the first 90 days after enrolment. 10. Weight < 10 kg
Interventions	**Intervention:** INH 900 mg once a week plus rifapentine 900 mg once a week for 3 months (DOT) **Control:** INH 300 mg/day daily (self-administered)
Outcomes	**Primary outcomes:** 1. Culture-confirmed TB in people > 18 years old 2. Culture-confirmed or probable (clinical) TB in people < 18 years old **Secondary outcomes:** 1. Grade 3 or 4 drug-related toxicity 2. Death 3. Development of methadone withdrawal 4. Discontinuation of therapy for any reason 5. Completion of the prescribed regimen 6. Development of culture confirmed TB among HIV-positive patients 7. Development of resistance to study medications in isolates during LTBI study therapy 8. Discontinuation of study therapy due to adverse events
Starting date	June 2002
Contact information	Study Director: Elsa Villarino Sponsors: CDC; Department of Veterans Affairs Study Chair: Timothy Sterling; Vanderbilt University
Notes	First accessed November 7, 2011 Estimated study completion: December 2013 (December 2010-final data collection for primary outcomes) Status: "This study is ongoing, but not recruiting participants." Last updated October 7, 2011 Primary Sponsor: TB Trials Consortium (funded by CDC Division of Tuberculosis Elimination (DTBE) Atlanta, USA) Additional information provided, "A sample size of 8,053 patients for the primary outcome was reached on February 15, 2008 (with expected follow-up completion time in 2010), leaving approximately 454 additional young children and 200 HIV-positive people to be enrolled to achieve the targets of 644 for each group. The additional data on tolerability in those subgroups will available for analysis in 2013" Linked to: Sterling 2011 Registration Number: NCT00023452

NCT00931736

Trial name or title	A randomized clinical trial of 4 months of rifampin versus 9 months of INH for latent tuberculosis infection. Part 3 - effectiveness
Methods	Randomized, open-label, active controlled, parallel group, phase IV clinical trial

NCT00931736 (*Continued*)

Participants	Adults aged 18 years or more of both genders **Inclusion criteria:** • Documented positive TST (or in the absence of TST, a documented positive Quantiferon test) and prescribed nine months of INH for LTBI **Exclusion criteria:** • Patients who were contacts of TB cases known to be resistant to INH or rifampicin • Known HIV-positive individuals on antiretroviral agents whose efficacy would be substantially reduced by rifampin, unless therapy can safely be changed to agents not affected by rifampin • Pregnant women • Patients on any medication with clinically important drug interactions with INH rifampicin, which their physician believes would make either arm contraindicated • Patients with a history of allergy/hypersensitivity to INH or rifampicin, rifabutin or rifapentine • Patients with active TB • Patients who have already started LTBI therapy
Interventions	**Intervention:** Rifampicin, 600 mg/day for ≥ 50 kg, 450 mg/day for ≥ 36 kg and < 50 kg, 300 mg/day for < 30 kg, daily for four months **Control:** INH, 300 mg/day for ≥ 42 kg, 200 mg/day for < 42 kg, daily for nine months
Outcomes	**Primary outcome:** 1. Confirmed active TB over 28 months **Secondary outcome:** 1. Probable as well as confirmed active TB over 28 months 2. Grade 3 to 4 adverse events (judged by another blinded, independent three-member panel) 3. Occurrence of drug-resistant active TB 4. Costs - from the health system perspective
Starting date	August 2009
Contact information	Principal investigator: Dr Dick Menzies, Montreal Chest Institute; McGill University Health Centre; (514) 934-1934 ext 32129;email: dick.menzies@mcgill.ca Sponsors: McGill University; Canadian Institutes of Health Research
Notes	First accessed February 22, 2011 Last accessed: March 3, 2012 First Received on July 1, 2009; Last Updated on July 22, 2011 (no substantial changes to protocol) International multicentric trial involving eight countries (Australia, Benin, Brazil, Canada, Ghana, Indonesia, Republic of Korea, Saudi Arabia) and 11 centres Estimated completion: March 2016 (December 2013: final data collection date for primary outcome measure) Estimated enrolment: 5720 Status: "This study is currently recruiting participants" Comment: Proportion of HIV-positive participants is unknown Registration Number: NCT00931736

NCT01398618

Trial name or title	Comparing the efficacy of two preventive regimens for adult household contacts with latent tuberculosis infection
Methods	Randomized, parallel group, active controlled, open-label Phase III trial
Participants	**Inclusion Criteria:** 1. Household contact of patients with newly diagnosed, culture-confirmed pulmonary TB 2. Age > 18 3. TST-positive or QFT-positive 4. Haemoglobin > 8 g/dL 5. Neutrophil > 750 /uL 6. Total bilirubin < 2.5 mg/dL 7. Aspartic and alanine transaminases < 2 times of upper limit of normal 8. Willing to receive serology tests for HBV and HCV infection 9. No history of allergy to INH and rifampin 10. Not currently pregnant or breast-feeding **Exclusion Criteria:** 1. *M. tuberculosis* isolate of the index case were INH- or rifampin-resistant 2. Liver cirrhosis 3. Clinical or radiographic evidence of active TB 4. Active hepatitis 5. Currently receiving medication that have documented drug interaction with INH or rifampin 6. Life expectancy < three years
Interventions	**Intervention:** 600 mg rifampin daily for four months **Control:** 300 mg INH daily for nine months.
Outcomes	**Primary outcome:** Number of participants developing active TB (time frame: every six months for two years) **Secondary outcomes:** 1. Sensitivity and specificity of TST and QuantiFERON TB-Gold assay for the development of active pulmonary TB (time frame: every six months for two years) Sensitivity: No. of participants who were test-positive among all participants who developed active pulmonary TB Specificity: No. of participants who were test-negative among all participants who did not develop active pulmonary TB
Starting date	May 2011
Contact information	Wang, Jann-Yuan; Attending Physician, National Taiwan University Hospital, Taiwan (further contact details not provided)
Notes	Last date accessed March 3, 2012 Status: "This study is ongoing, but not recruiting participants" Target sample size: 300 Estimated date of completion: December 2013 Comment: Submitted July 1, 2011; Last update: July 19, 2011 (unclear if registered after recruitment com-

	menced) Comment: proportion of HIV-positive participants unclear Registration Number: NCT01398618

DATA AND ANALYSES

Comparison 1. Rifampicin versus INH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active TB	3	805	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.47, 1.40]
1.1 Rifampicin 3 months versus INH 6 months (in adults with silicosis): At 5 years	1	332	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.47, 1.40]
1.2 Rifampicin 4 months versus INH 6 months (in adult prisoners with LTBI): At 3 years	1	373	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Rifampicin 4 months versus INH 6 months (in children): At 2 years	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Drug-resistant TB	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.11, 2.26]
2.1 INH resistant TB: Rifampicin 3 months INH 6 months (in adults with silicosis)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.11, 2.26]
2.2 Rifampicin resistant TB: Rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adherence	5	1768	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.01, 1.28]
3.1 Rifampicin 3 to 4 months versus INH 6 to 9 months (in adults with silicosis or LTBI)	4	1668	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.10, 1.30]
3.2 Rifampicin 4 months versus INH 6 months (in children)	1	100	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.04]
4 Serious adverse events: (adults with LTBI)	2	956	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.17, 0.77]
5 Treatment-limiting adverse events	4	1674	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.23, 1.00]
5.1 Rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	345	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.54, 1.58]
5.2 Rifampicin 4 months versus INH 6 months (in adult prisoners with LTBI)	1	373	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.06, 0.50]
5.3 Rifampicin 4 months versus INH 9 months (in adults with LTBI)	2	956	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.23, 1.22]
6 Hepatotoxicity	5	1774	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.07, 0.35]
6.1 Rifampicin 3 to 4 months versus INH 6 to 9 months (in adults)	4	1674	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.05, 0.30]

6.2 Rifampicin 4 months versus INH 6 months (in children)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.92]
7 Gastrointestinal Intolerance	3	1535	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.73, 2.92]
7.1 Rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	322	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.74, 3.38]
7.2 Rifampicin 4 months versus INH 6 months (in adult prisoners with LTBI)	1	373	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.83]
7.3 Rifampicin 4 months versus INH 9 months (in adults with LTBI)	1	840	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [0.18, 21.76]
8 Rash	2	1213	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.21, 1.32]
8.1 Rifampicin 4 months versus INH 6 months (in adult prisoners with LTBI)	1	373	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.09, 2.60]
8.2 Rifampicin 4 months versus INH 9 months (in adults with LTBI)	1	840	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.19, 1.63]
9 Haematological adverse events (in adults with LTBI)	1	840	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.44]
10 Any adverse event (in adults with silicosis)	1	322	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.68, 1.43]

Comparison 2. Rifampicin plus INH versus INH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active TB: INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	328	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.65, 1.79]
2 Drug-resistant TB	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.08, 1.65]
2.1 INH resistant TB: INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.08, 1.65]
2.2 Rifampicin resistant TB: (INH plus rifampicin 3 months versus INH 6 months in adults with silicosis)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adherence	2	524	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.98, 1.17]
3.1 INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	328	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.91, 1.17]
3.2 INH plus rifampicin 3 months versus INH 9 months (in adults)	1	196	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.00, 1.27]

4 Serious adverse events: INH plus rifampicin 3 months versus INH 9 months (in adults)	1	196	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.30, 2.01]
5 Treatment-limiting adverse events	2	536	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.74, 1.82]
5.1 INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.67, 1.87]
5.2 INH plus rifampicin 3 months versus INH 9 months (in adults)	1	196	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.50, 3.32]
6 Hepatotoxicity	2	536	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.43, 1.81]
6.1 INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	340	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.30, 2.59]
6.2 INH plus rifampicin 3 months versus INH 9 months (in adults)	1	196	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.33, 2.32]
7 Gastrointestinal intolerance	2	510	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.80, 2.27]
7.1 INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	314	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.78, 3.55]
7.2 INH plus rifampicin 3 months versus INH 9 months (in adults)	1	196	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.52, 2.25]
8 Any adverse event: INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)	1	314	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.82, 1.65]

Comparison 3. Rifampicin plus pyrazinamide versus INH

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active TB	3	468	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.42, 4.13]
1.1 Rifampicin plus pyrazinamide 2 months versus INH 6 months (in adults)	2	368	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.33, 3.87]
1.2 Rifampicin plus pyrazinamide 2 months versus INH 6 months (in children)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.92]
2 Drug-resistant TB	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.37]
2.1 INH resistant TB: Rifampicin plus pyrazinamide 2 months versus INH 6 months (in adults with silicosis)	1	8	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.37]

2.2 Rifampicin resistant TB: Rifampicin plus pyrazinamide 2 months versus INH 6 months (in adults with silicosis)	1	8	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adherence	4	700	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.86, 1.29]
3.1 Rifampicin plus pyrazinamide 2 months versus INH 6 months (in adults)	3	600	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.74, 1.77]
3.2 Rifampicin plus pyrazinamide 2 months versus INH 6 months (in children)	1	100	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.91, 1.10]
4 Treatment-limiting adverse events (in adults)	2	368	Risk Ratio (M-H, Fixed, 95% CI)	3.61 [1.82, 7.19]
5 Hepatotoxicity	4	640	Risk Ratio (M-H, Fixed, 95% CI)	4.59 [2.14, 9.85]
5.1 Rifampicin plus pyrazinamide 2 months versus INH 6 months (in adults)	3	540	Risk Ratio (M-H, Fixed, 95% CI)	4.59 [2.14, 9.85]
5.2 Rifampicin plus pyrazinamide 2 months versus INH 6 months (in children)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 At least one adverse event (in adults)	1	292	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.24, 2.35]
7 Gastrointestinal Intolerance (in adults)	2	368	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [1.37, 3.49]
8 Rash (in adults)	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.8 [0.35, 9.25]
9 Pruritus (in adults)	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.83, 4.59]

Comparison 4. Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

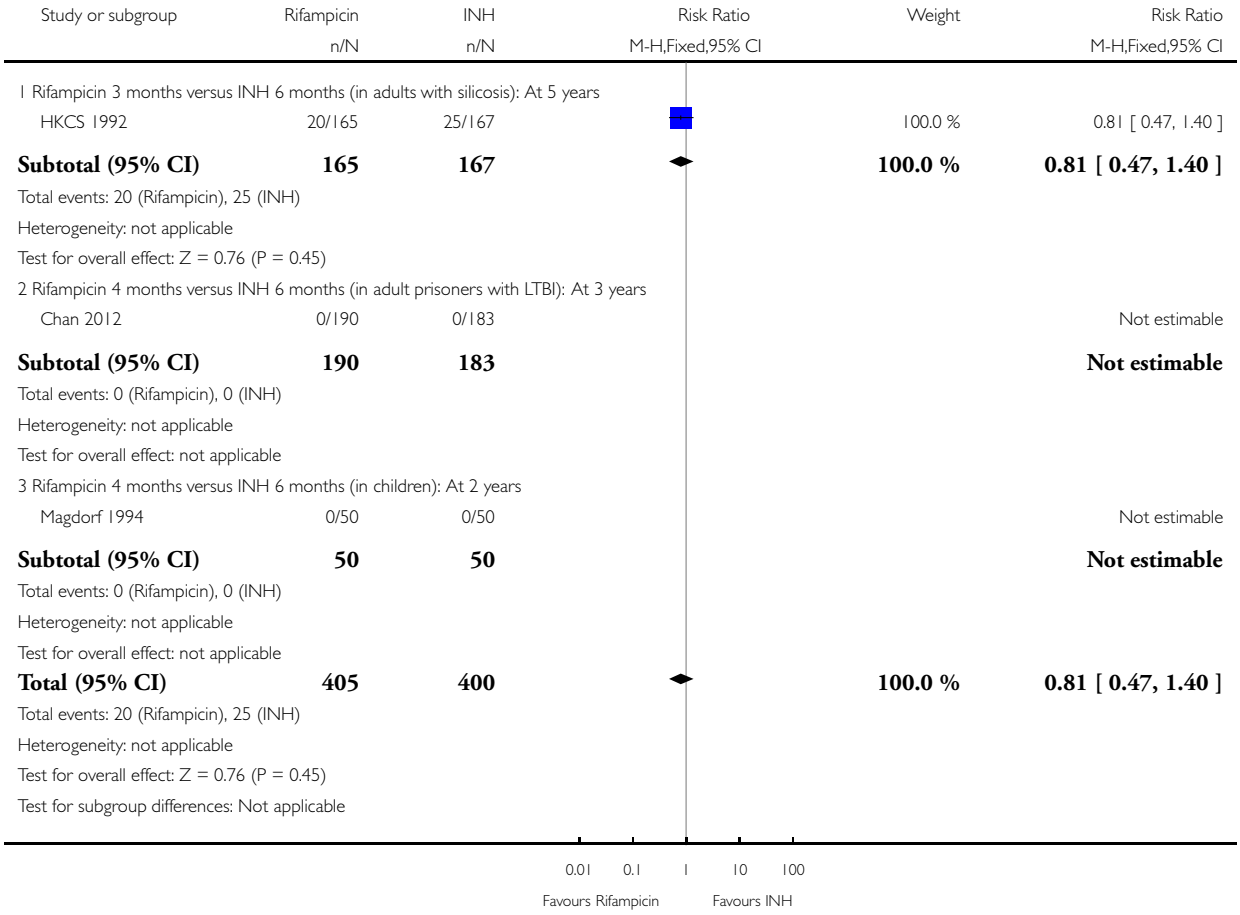
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Active TB	1	7731	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.18, 1.07]
2 All-cause mortality	1	7731	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.47, 1.19]
3 Drug-resistant TB	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 INH-resistant TB	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.02, 7.38]
3.2 Rifapentine-resistant	1	22	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.27, 131.34]
4 Adherence	1	7731	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.16, 1.22]
5 Serious adverse events	1	7799	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.40, 0.74]
6 Treatment-limiting adverse events	1	7731	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.07, 1.64]
7 Hypersensitivity	1	7799	Risk Ratio (M-H, Fixed, 95% CI)	8.32 [5.05, 13.71]
8 Hepatotoxicity	1	7799	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.10, 0.27]
9 Rash	1	7799	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.79, 2.39]
10 Any adverse event	1	7799	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.76, 0.93]

Analysis 1.1. Comparison 1 Rifampicin versus INH, Outcome 1 Active TB.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 1 Active TB

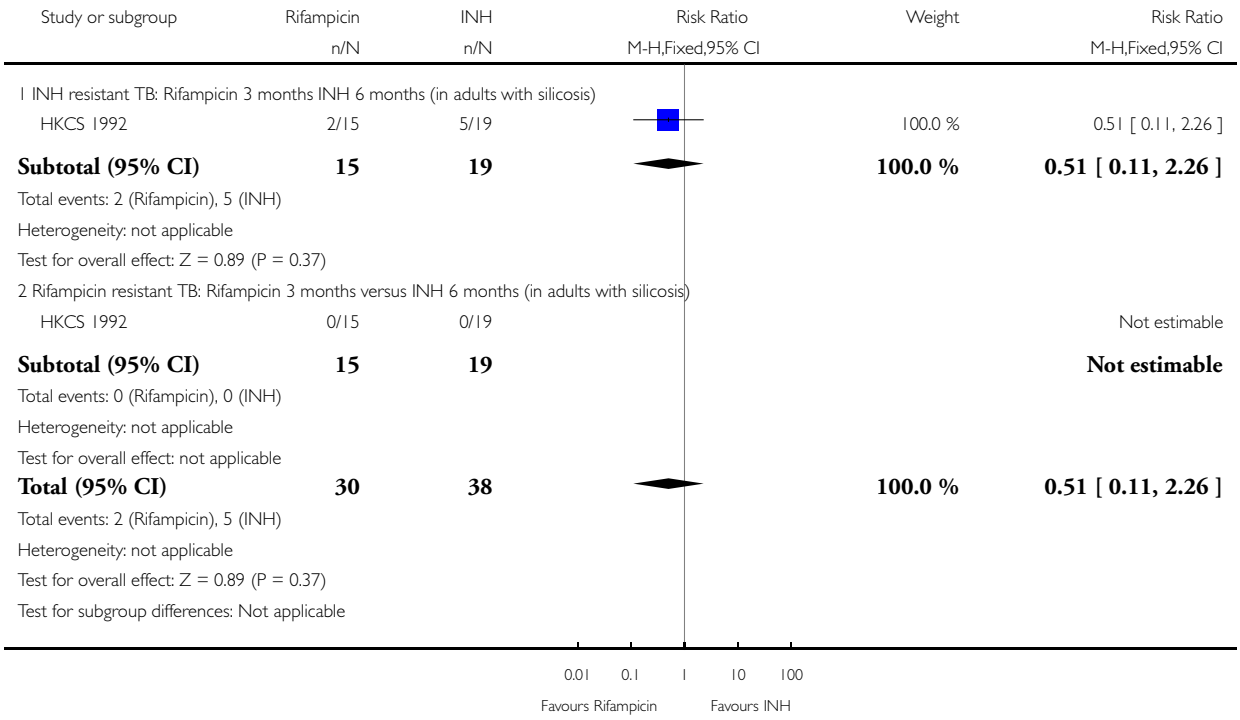


Analysis 1.2. Comparison 1 Rifampicin versus INH, Outcome 2 Drug-resistant TB.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 2 Drug-resistant TB

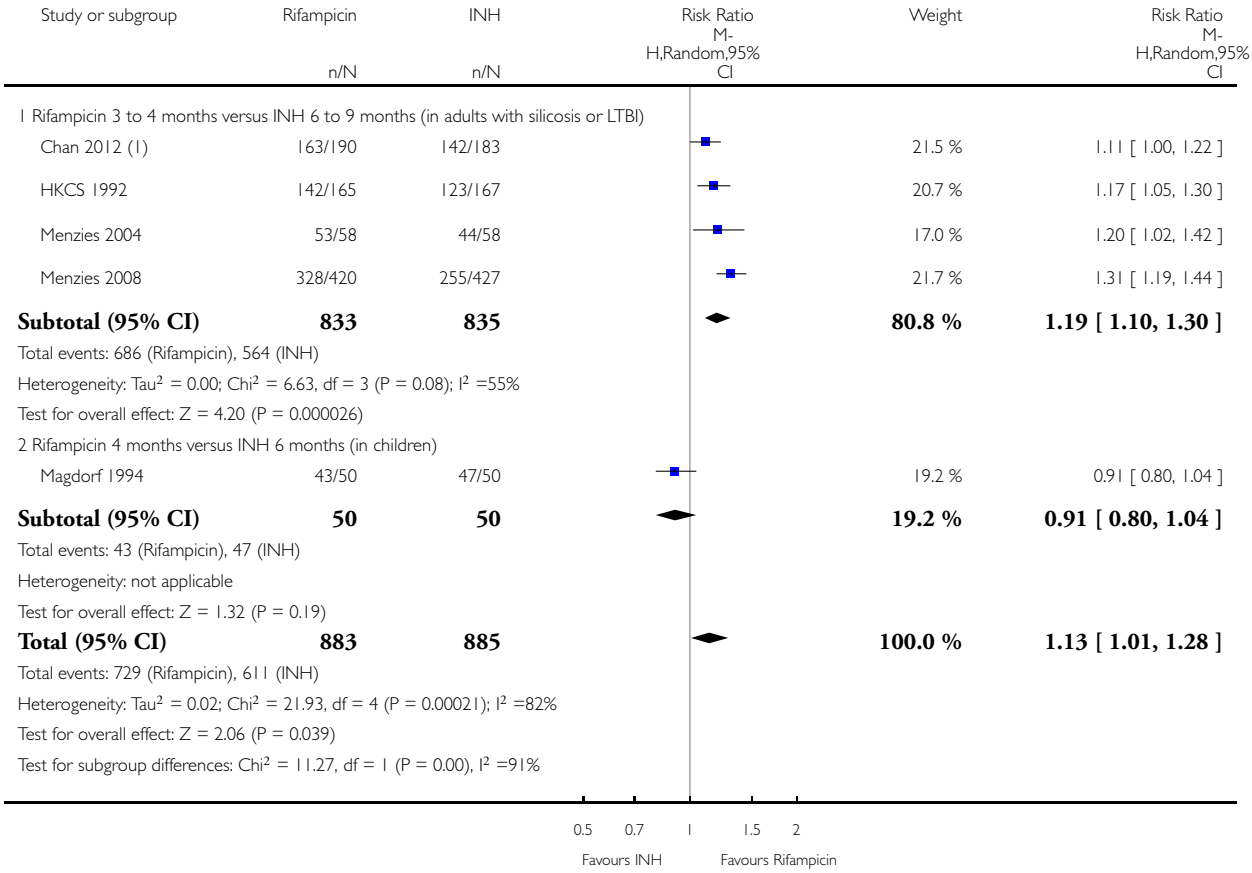


Analysis 1.3. Comparison 1 Rifampicin versus INH, Outcome 3 Adherence.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 3 Adherence



(1) Treatment of prisoners in this trial was by direct observation (except when on parole)

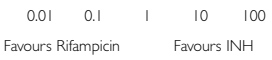
Analysis 1.4. Comparison 1 Rifampicin versus INH, Outcome 4 Serious adverse events: (adults with LTBI).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 4 Serious adverse events: (adults with LTBI)

Study or subgroup	Rifampicin n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Menzies 2004	2/58	8/58		32.1 %	0.25 [0.06, 1.13]
Menzies 2008	7/418	17/422		67.9 %	0.42 [0.17, 0.99]
Total (95% CI)	**476**	**480**		**100.0 %**	**0.36 [0.17, 0.77]**
Total events: 9 (Rifampicin), 25 (INH)					
Heterogeneity: Chi^2 = 0.33, df = 1 (P = 0.57); I^2 =0.0%					
Test for overall effect: Z = 2.65 (P = 0.0079)					
Test for subgroup differences: Not applicable					

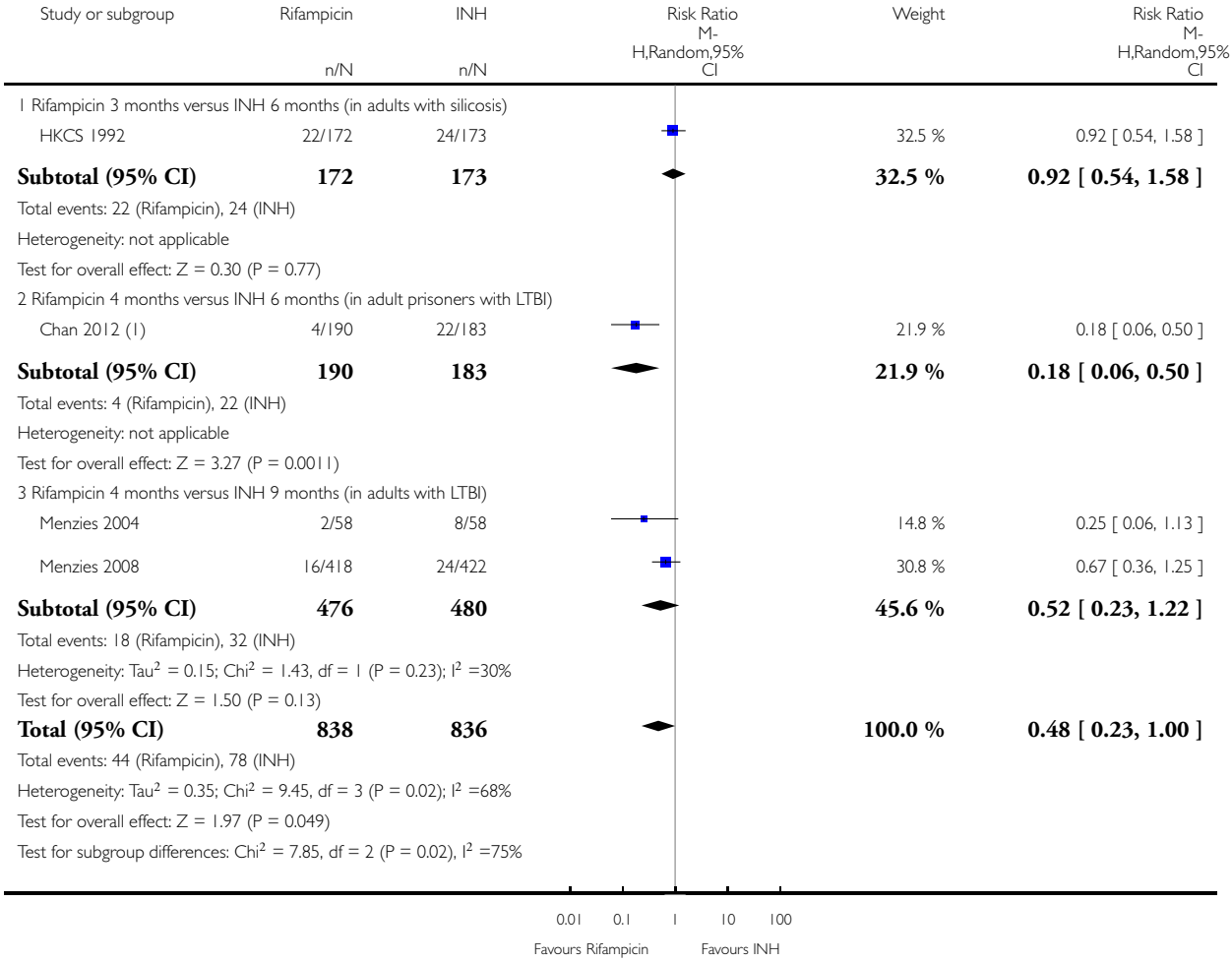


Analysis 1.5. Comparison 1 Rifampicin versus INH, Outcome 5 Treatment-limiting adverse events.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 5 Treatment-limiting adverse events



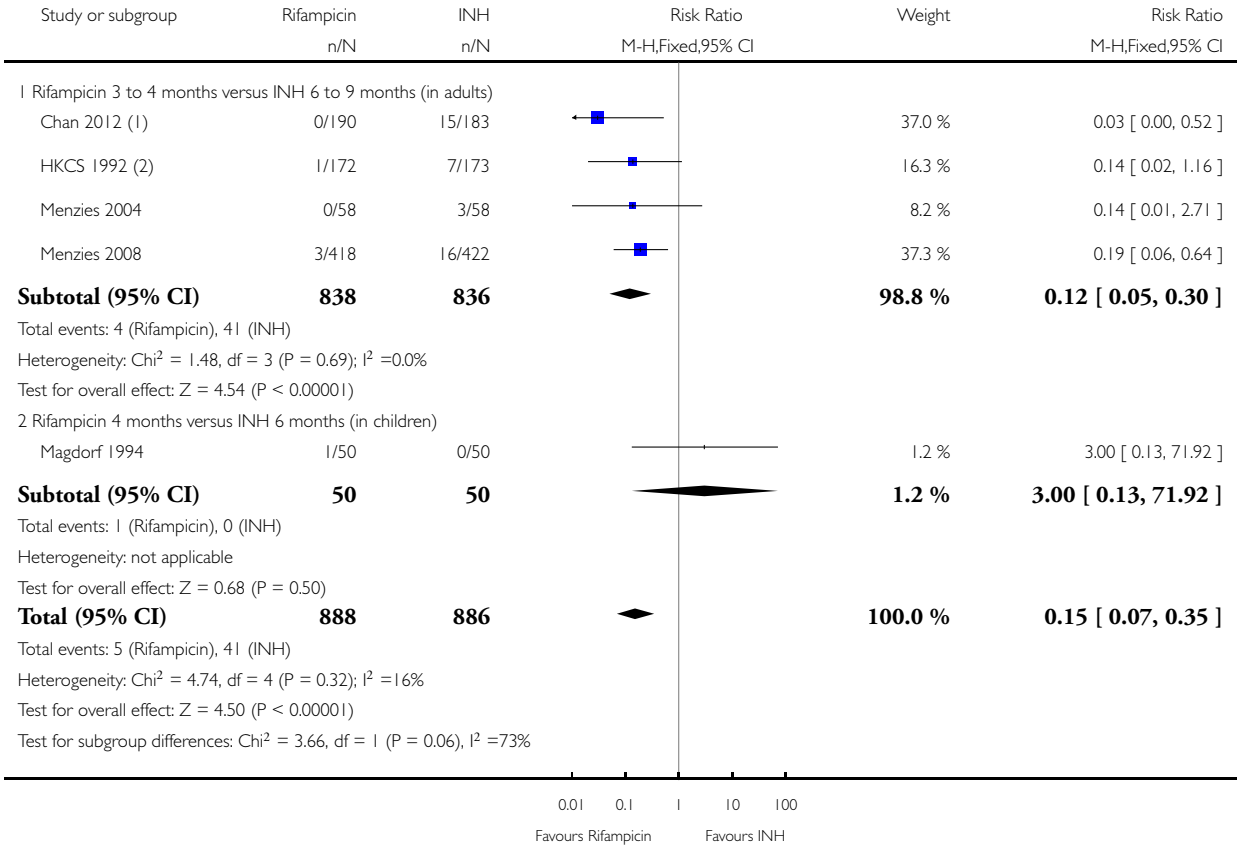
(1) 78% were adherent to INH due to directly observed treatment vs 62% in the three trials of self-administered treatment

Analysis 1.6. Comparison 1 Rifampicin versus INH, Outcome 6 Hepatotoxicity.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 6 Hepatotoxicity



(1) This trial randomized participants stratified for co-infection with Hepatitis virus B and C

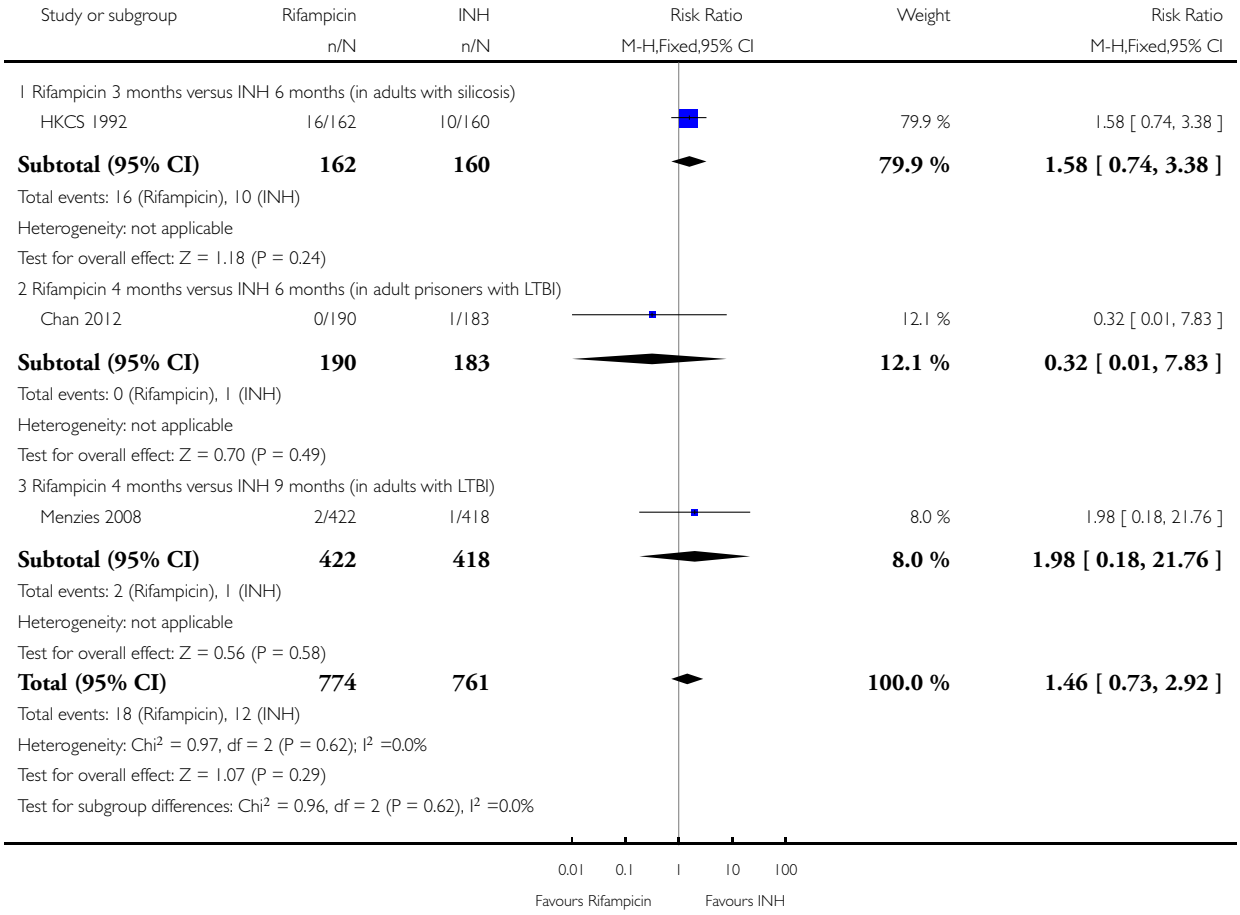
(2) Hepatotoxicity was not graded; included serum alanine transaminase levels above the upper limit of normal

Analysis 1.7. Comparison 1 Rifampicin versus INH, Outcome 7 Gastrointestinal Intolerance.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 7 Gastrointestinal Intolerance

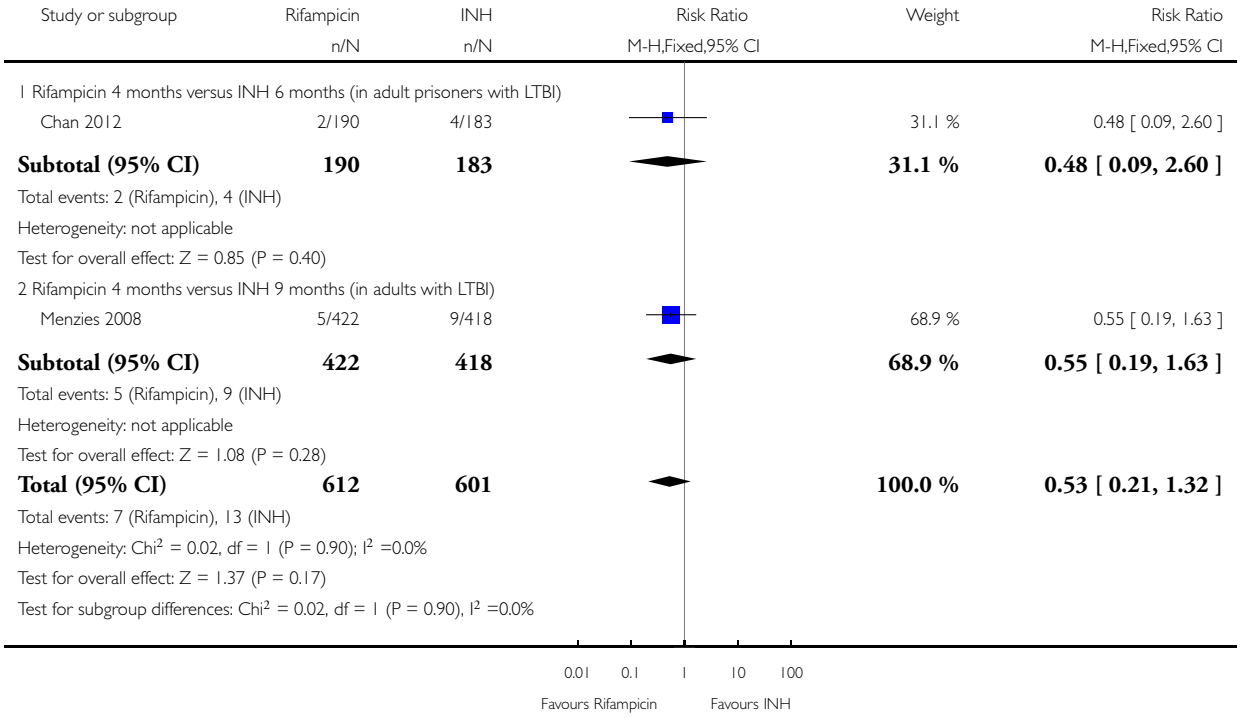


Analysis 1.8. Comparison 1 Rifampicin versus INH, Outcome 8 Rash.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 8 Rash



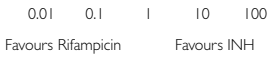
Analysis 1.9. Comparison 1 Rifampicin versus INH, Outcome 9 Haematological adverse events (in adults with LTBI).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 9 Haematological adverse events (in adults with LTBI)

Study or subgroup	Rifampicin n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Menzies 2008	1/422	2/418		100.0 %	0.50 [0.05, 5.44]
Total (95% CI)	**422**	**418**		**100.0 %**	**0.50 [0.05, 5.44]**
Total events: 1 (Rifampicin), 2 (INH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.57 (P = 0.57)					
Test for subgroup differences: Not applicable					



Analysis 1.10. Comparison 1 Rifampicin versus INH, Outcome 10 Any adverse event (in adults with silicosis).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 1 Rifampicin versus INH

Outcome: 10 Any adverse event (in adults with silicosis)

Study or subgroup	Rifampicin n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
HKCS 1992	42/162	42/160		100.0 %	0.99 [0.68, 1.43]
Total (95% CI)	**162**	**160**		**100.0 %**	**0.99 [0.68, 1.43]**
Total events: 42 (Rifampicin), 42 (INH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.07 (P = 0.95)					
Test for subgroup differences: Not applicable					

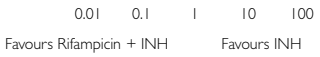
Analysis 2.1. Comparison 2 Rifampicin plus INH versus INH, Outcome 1 Active TB: INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 2 Rifampicin plus INH versus INH

Outcome: 1 Active TB: INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)

Study or subgroup	Rifampicin + INH n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
HKCS 1992	26/161	25/167		100.0 %	1.08 [0.65, 1.79]
Total (95% CI)	**161**	**167**		**100.0 %**	**1.08 [0.65, 1.79]**
Total events: 26 (Rifampicin + INH), 25 (INH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.29 (P = 0.77)					
Test for subgroup differences: Not applicable					

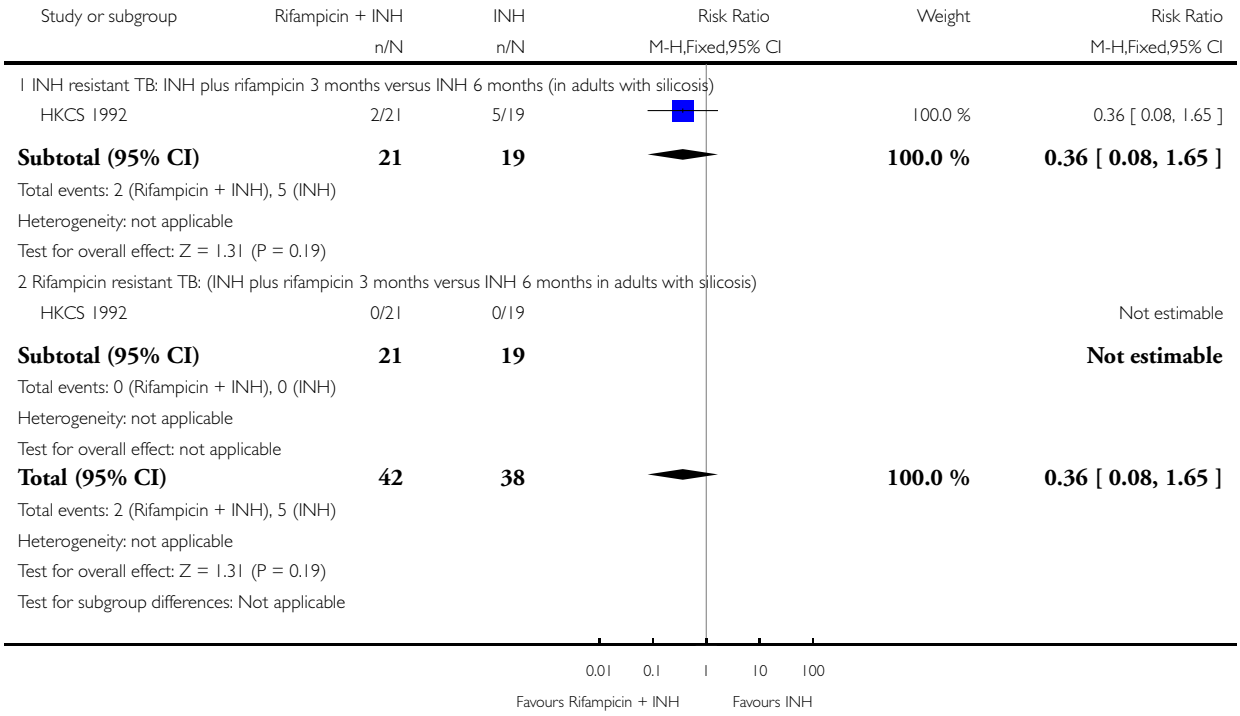


Analysis 2.2. Comparison 2 Rifampicin plus INH versus INH, Outcome 2 Drug-resistant TB.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 2 Rifampicin plus INH versus INH

Outcome: 2 Drug-resistant TB

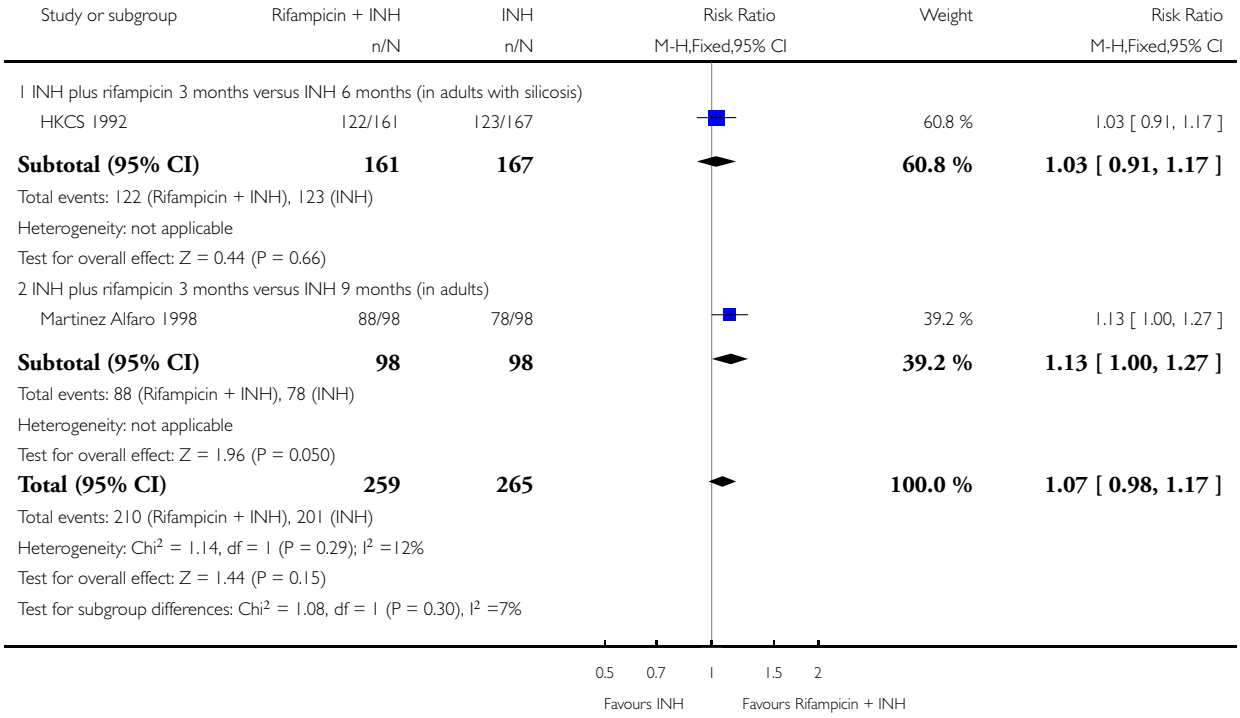


Analysis 2.3. Comparison 2 Rifampicin plus INH versus INH, Outcome 3 Adherence.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 2 Rifampicin plus INH versus INH

Outcome: 3 Adherence



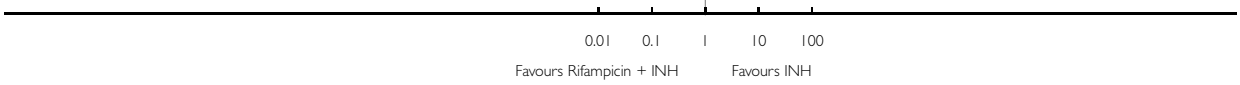
Analysis 2.4. Comparison 2 Rifampicin plus INH versus INH, Outcome 4 Serious adverse events: INH plus rifampicin 3 months versus INH 9 months (in adults).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 2 Rifampicin plus INH versus INH

Outcome: 4 Serious adverse events: INH plus rifampicin 3 months versus INH 9 months (in adults)

Study or subgroup	Rifampicin + INH n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Martinez Alfaro 1998	7/98	9/98		100.0 %	0.78 [0.30, 2.01]
Total (95% CI)	**98**	**98**		**100.0 %**	**0.78 [0.30, 2.01]**
Total events: 7 (Rifampicin + INH), 9 (INH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
Test for subgroup differences: Not applicable					

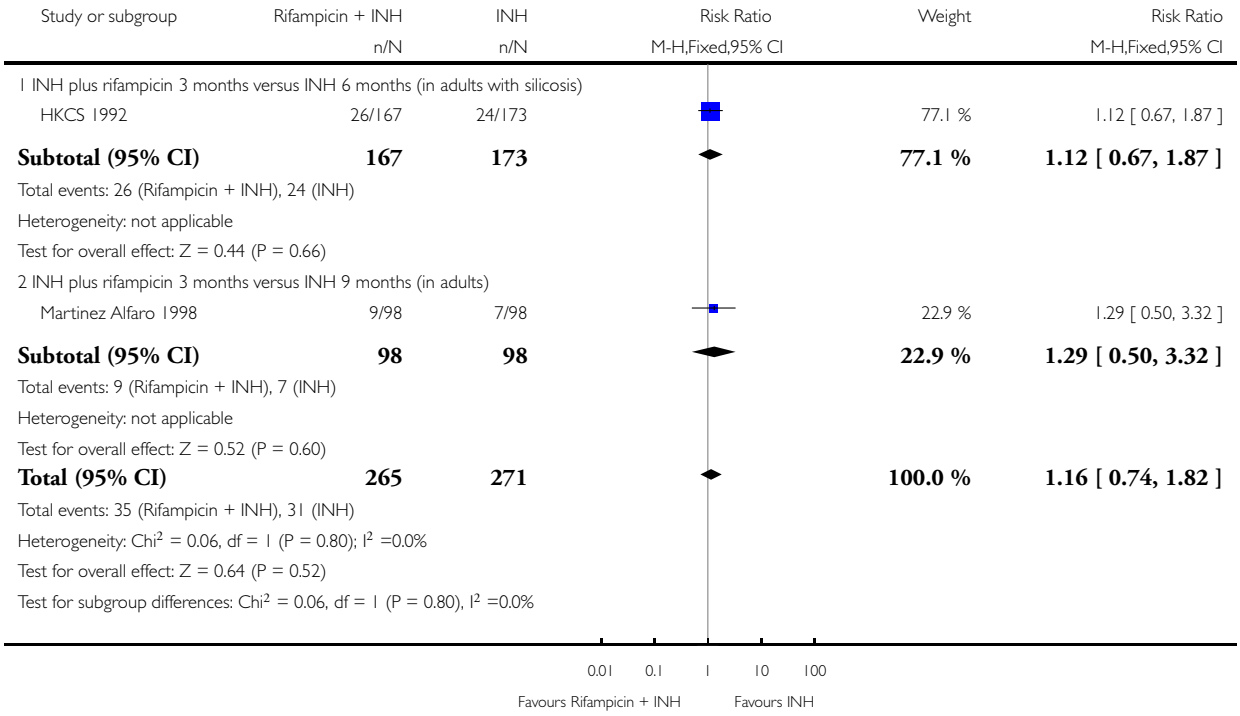


Analysis 2.5. Comparison 2 Rifampicin plus INH versus INH, Outcome 5 Treatment-limiting adverse events.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 2 Rifampicin plus INH versus INH

Outcome: 5 Treatment-limiting adverse events

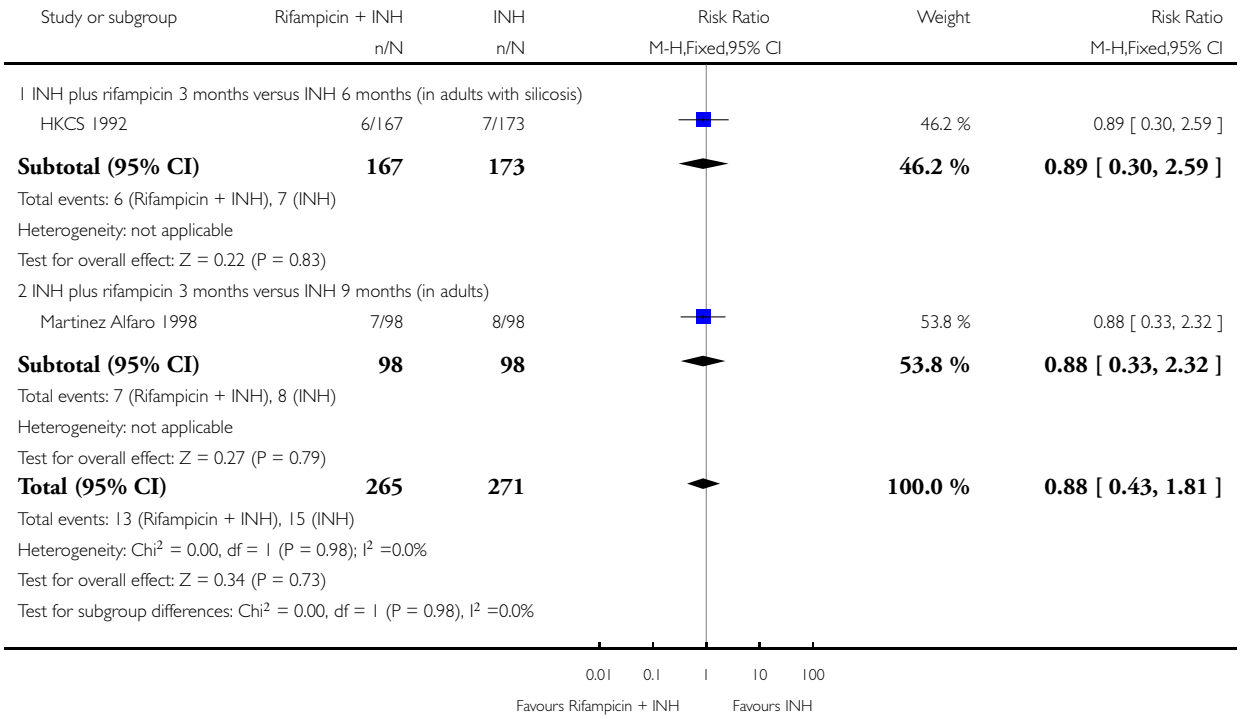


Analysis 2.6. Comparison 2 Rifampicin plus INH versus INH, Outcome 6 Hepatotoxicity.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 2 Rifampicin plus INH versus INH

Outcome: 6 Hepatotoxicity

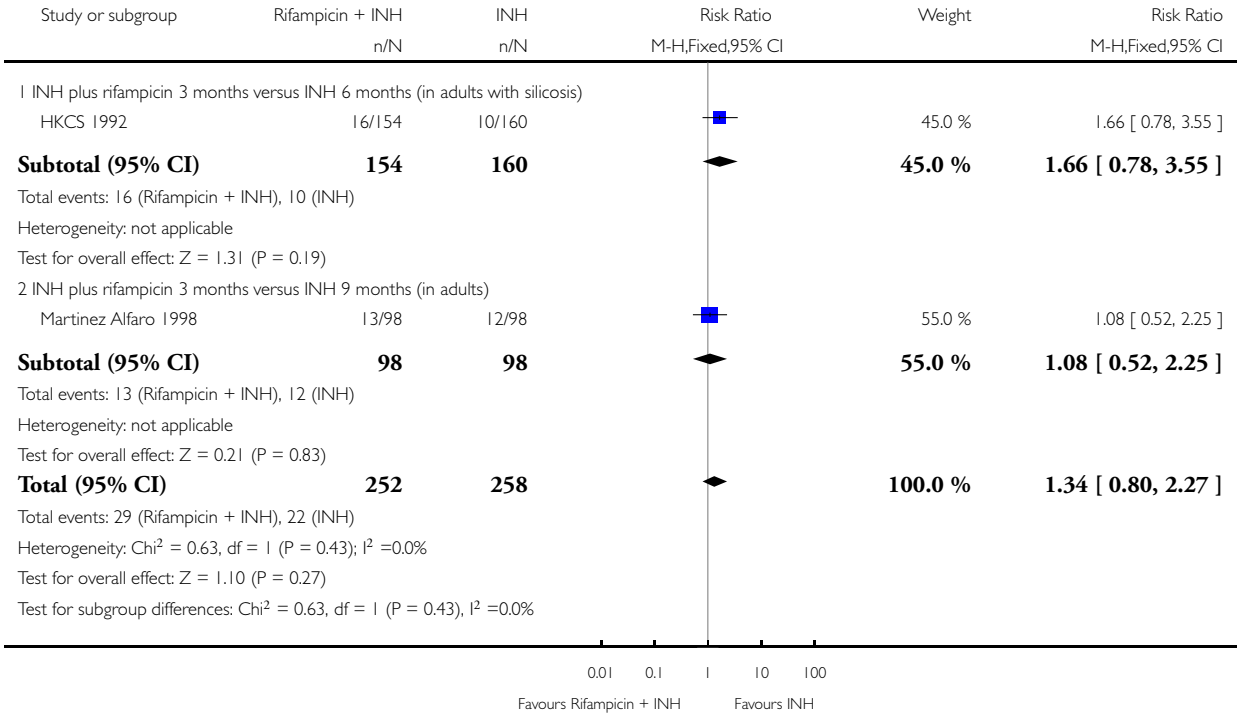


Analysis 2.7. Comparison 2 Rifampicin plus INH versus INH, Outcome 7 Gastrointestinal intolerance.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 2 Rifampicin plus INH versus INH

Outcome: 7 Gastrointestinal intolerance



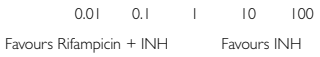
Analysis 2.8. Comparison 2 Rifampicin plus INH versus INH, Outcome 8 Any adverse event: INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 2 Rifampicin plus INH versus INH

Outcome: 8 Any adverse event: INH plus rifampicin 3 months versus INH 6 months (in adults with silicosis)

Study or subgroup	Rifampicin + INH n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
HKCS 1992	47/154	42/160		100.0 %	1.16 [0.82, 1.65]
Total (95% CI)	**154**	**160**		**100.0 %**	**1.16 [0.82, 1.65]**
Total events: 47 (Rifampicin + INH), 42 (INH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.84 (P = 0.40)					
Test for subgroup differences: Not applicable					

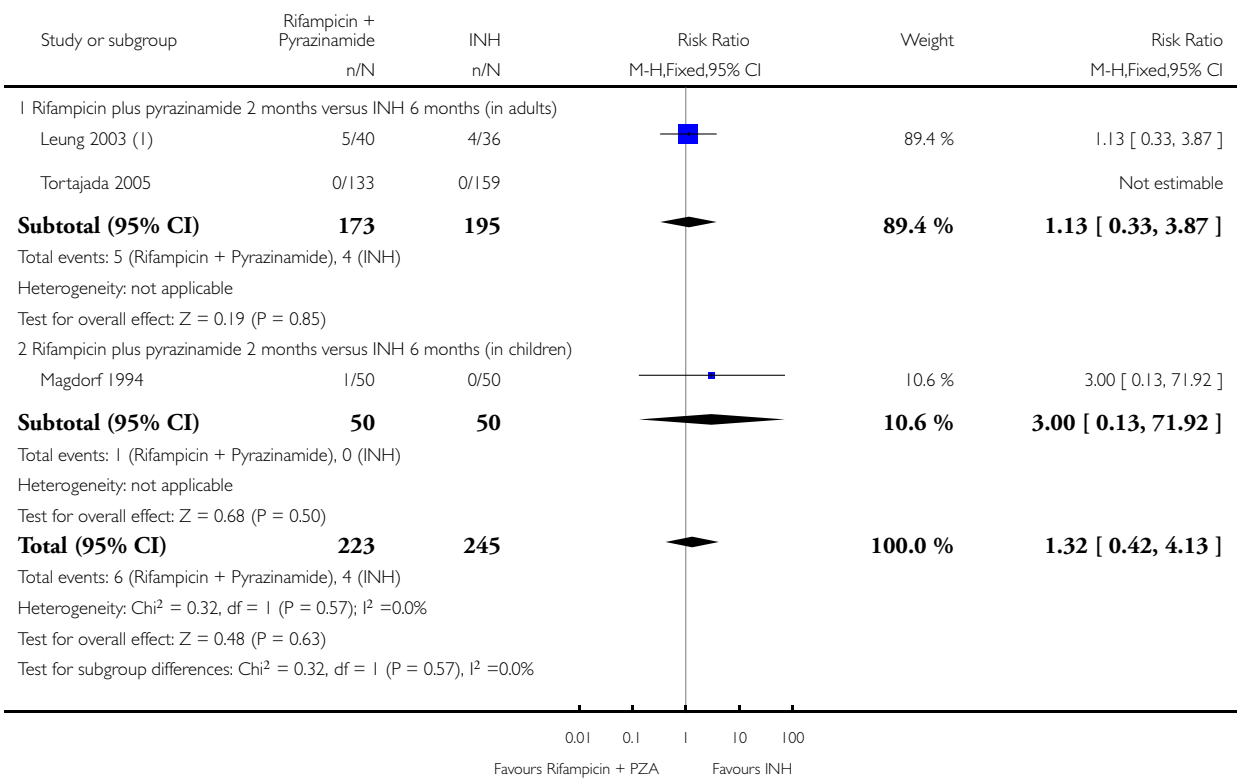


Analysis 3.1. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 1 Active TB.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 1 Active TB



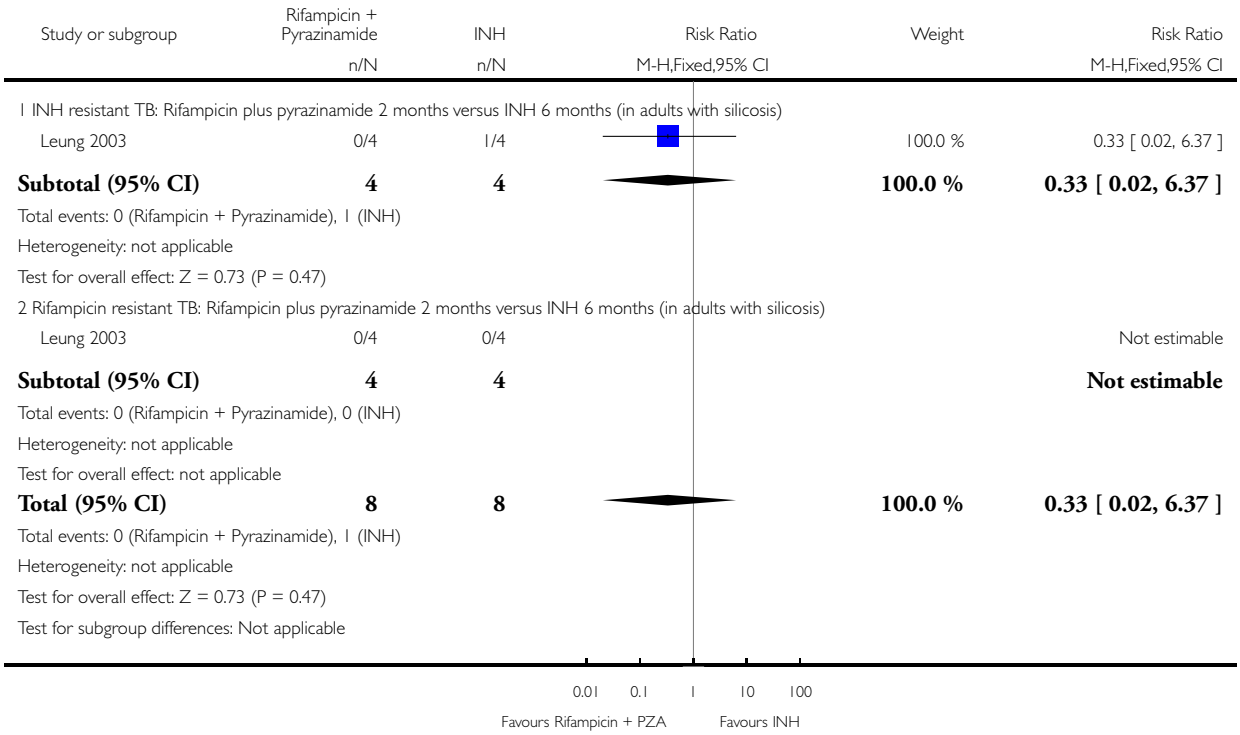
(1) Adults with silicosis

Analysis 3.2. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 2 Drug-resistant TB.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 2 Drug-resistant TB

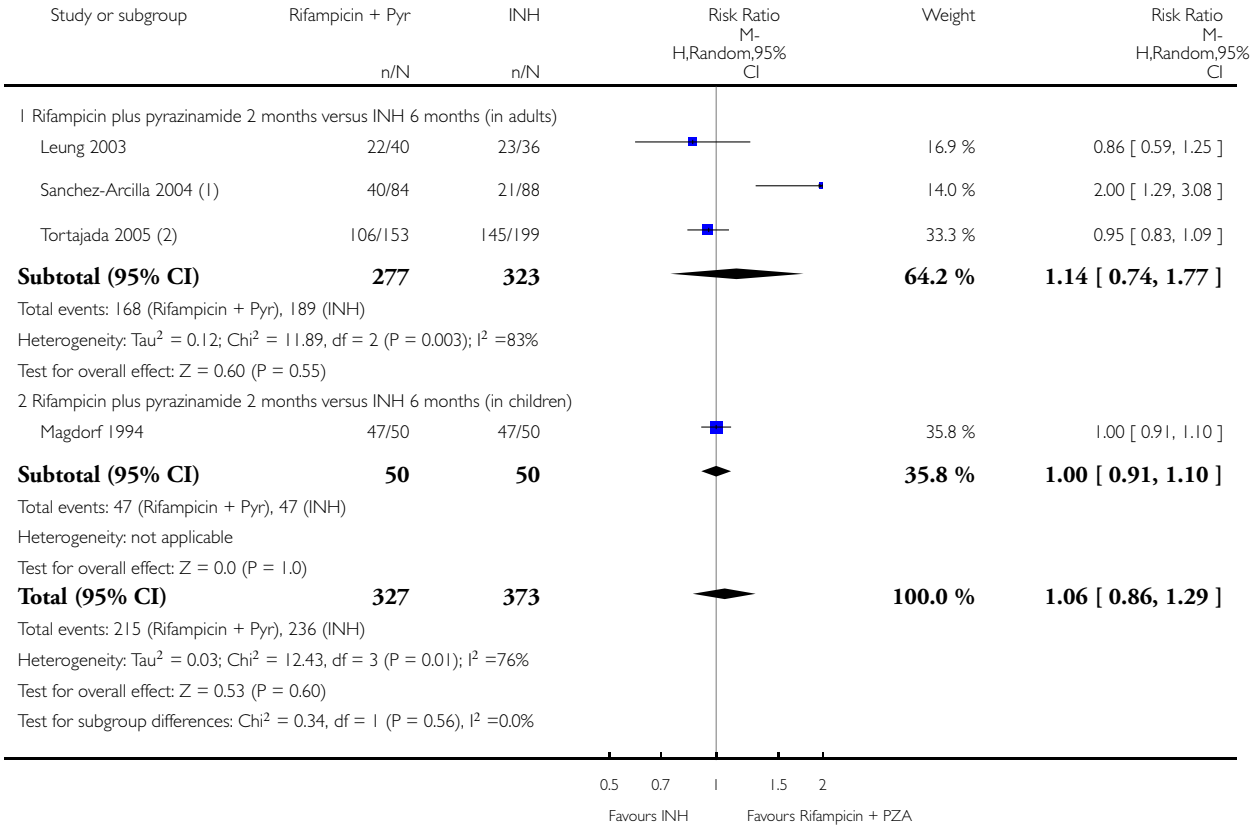


Analysis 3.3. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 3 Adherence.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 3 Adherence



(1) High attrition rates with significant differences in attrition in the two arms

(2) Data are for those taking 80% or > of prescribed doses; data not adjusted for clustering

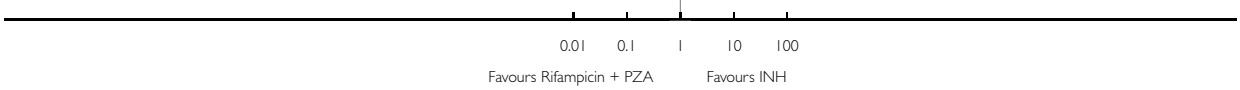
Analysis 3.4. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 4 Treatment-limiting adverse events (in adults).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 4 Treatment-limiting adverse events (in adults)

Study or subgroup	Rifampicin + Pyrazinamide n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Leung 2003	14/40	2/36		22.4 %	6.30 [1.54, 25.84]
Tortajada 2005	19/133	8/159		77.6 %	2.84 [1.28, 6.28]
Total (95% CI)	**173**	**195**		**100.0 %**	**3.61 [1.82, 7.19]**
Total events: 33 (Rifampicin + Pyrazinamide), 10 (INH)					
Heterogeneity: Chi^2 = 0.95, df = 1 (P = 0.33); I^2 =0.0%					
Test for overall effect: Z = 3.67 (P = 0.00025)					
Test for subgroup differences: Not applicable					

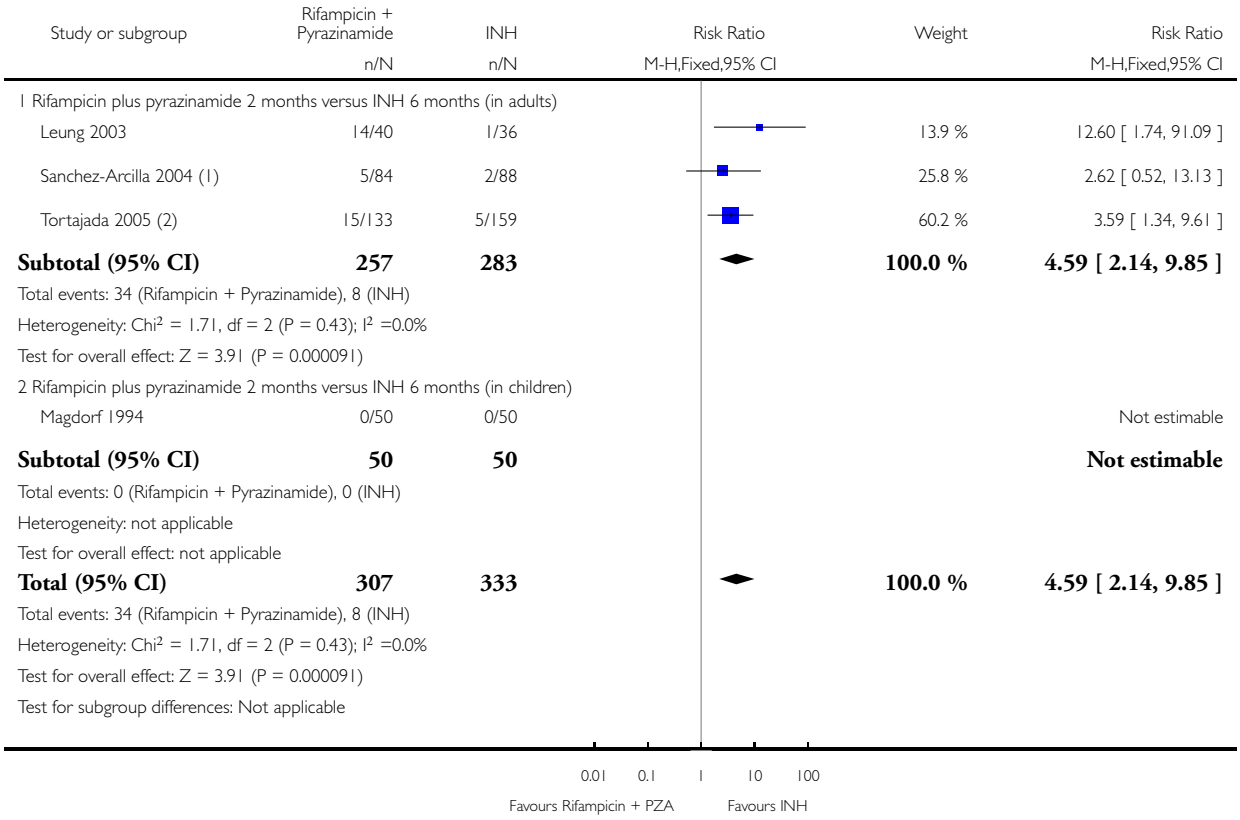


Analysis 3.5. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 5 Hepatotoxicity.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 5 Hepatotoxicity



(1) Higher attrition in the INH arm (53%) vs the rifampicin + pyrazinamide arm (18%). Events are for completers among those randomized

(2) Data not adjusted for cluster effect

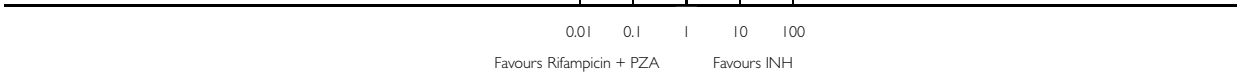
Analysis 3.6. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 6 At least one adverse event (in adults).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 6 At least one adverse event (in adults)

Study or subgroup	Rifampicin + Pyrazinamide n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tortajada 2005 (1)	60/133	42/159		100.0 %	1.71 [1.24, 2.35]
Total (95% CI)	**133**	**159**		**100.0 %**	**1.71 [1.24, 2.35]**
Total events: 60 (Rifampicin + Pyrazinamide), 42 (INH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.28 (P = 0.0010)					
Test for subgroup differences: Not applicable					



(1) Data not adjusted for cluster effect

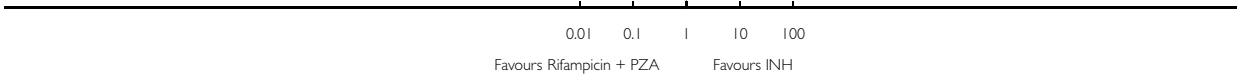
Analysis 3.7. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 7 Gastrointestinal Intolerance (in adults).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 7 Gastrointestinal Intolerance (in adults)

Study or subgroup	Rifampicin + Pyrazinamide n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Leung 2003 (1)	8/40	6/36		30.2 %	1.20 [0.46, 3.13]
Tortajada 2005 (2)	35/133	16/159		69.8 %	2.62 [1.52, 4.51]
Total (95% CI)	**173**	**195**		**100.0 %**	**2.19 [1.37, 3.49]**
Total events: 43 (Rifampicin + Pyrazinamide), 22 (INH)					
Heterogeneity: Chi^2 = 1.92, df = 1 (P = 0.17); I^2 =48%					
Test for overall effect: Z = 3.28 (P = 0.0010)					
Test for subgroup differences: Not applicable					



(1) Adults with silicosis

(2) Data not adjusted for cluster effect

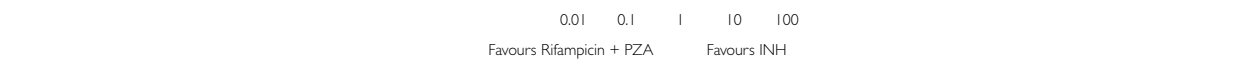
Analysis 3.8. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 8 Rash (in adults).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 8 Rash (in adults)

Study or subgroup	Rifampicin + Pyrazinamide n/N	INH n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Leung 2003	4/40	2/36		100.0 %	1.80 [0.35, 9.25]
Total (95% CI)	**40**	**36**		**100.0 %**	**1.80 [0.35, 9.25]**
Total events: 4 (Rifampicin + Pyrazinamide), 2 (INH)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					
Test for subgroup differences: Not applicable					

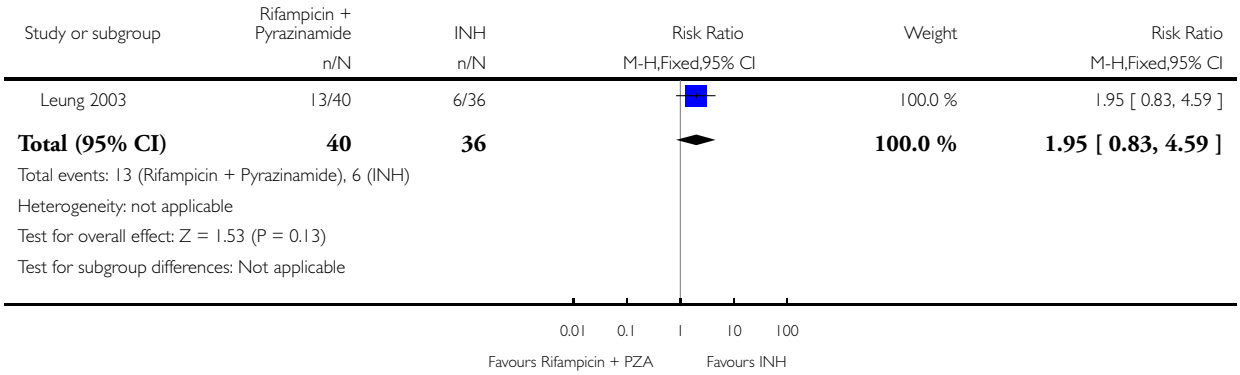


Analysis 3.9. Comparison 3 Rifampicin plus pyrazinamide versus INH, Outcome 9 Pruritus (in adults).

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 3 Rifampicin plus pyrazinamide versus INH

Outcome: 9 Pruritus (in adults)

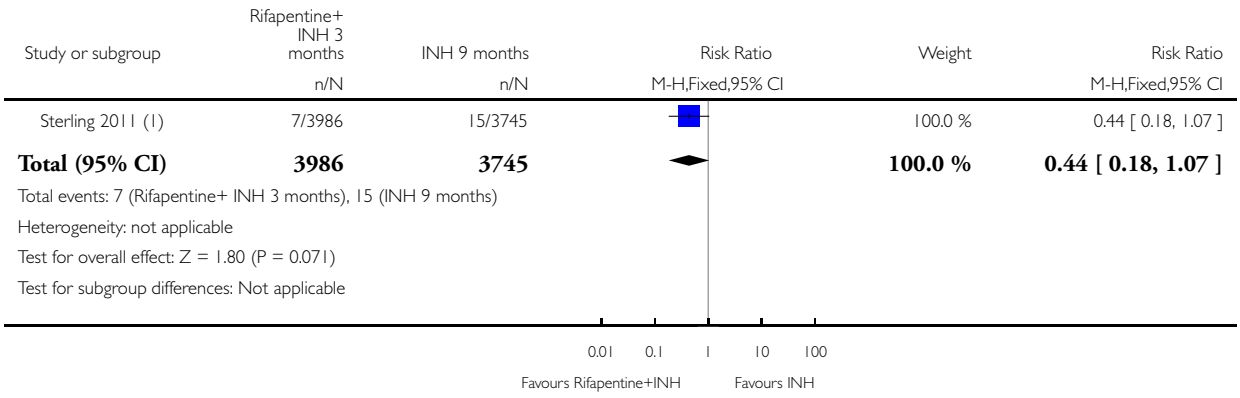


Analysis 4.1. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 1 Active TB.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 1 Active TB



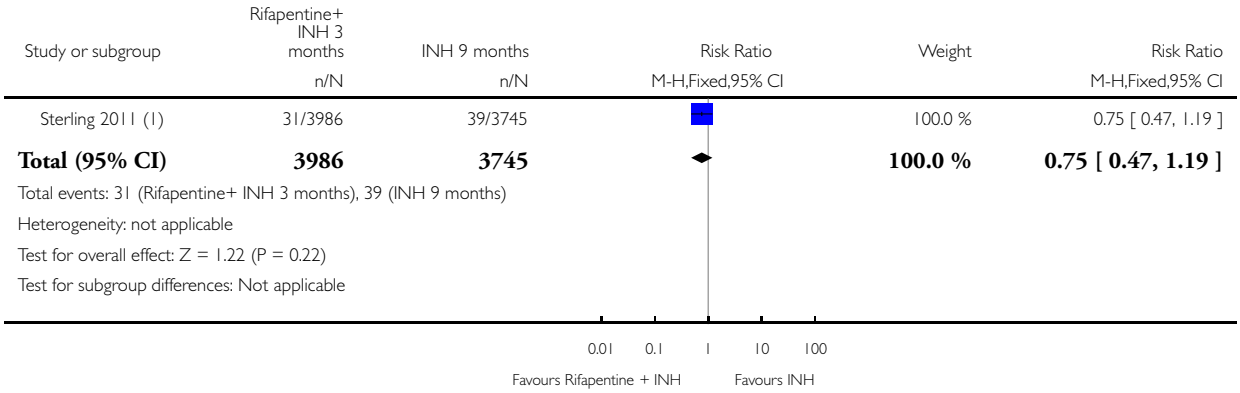
(1) Rifapentine + INH weekly (12 doses) vs INH daily (275 doses)

Analysis 4.2. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 2 All-cause mortality.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 2 All-cause mortality



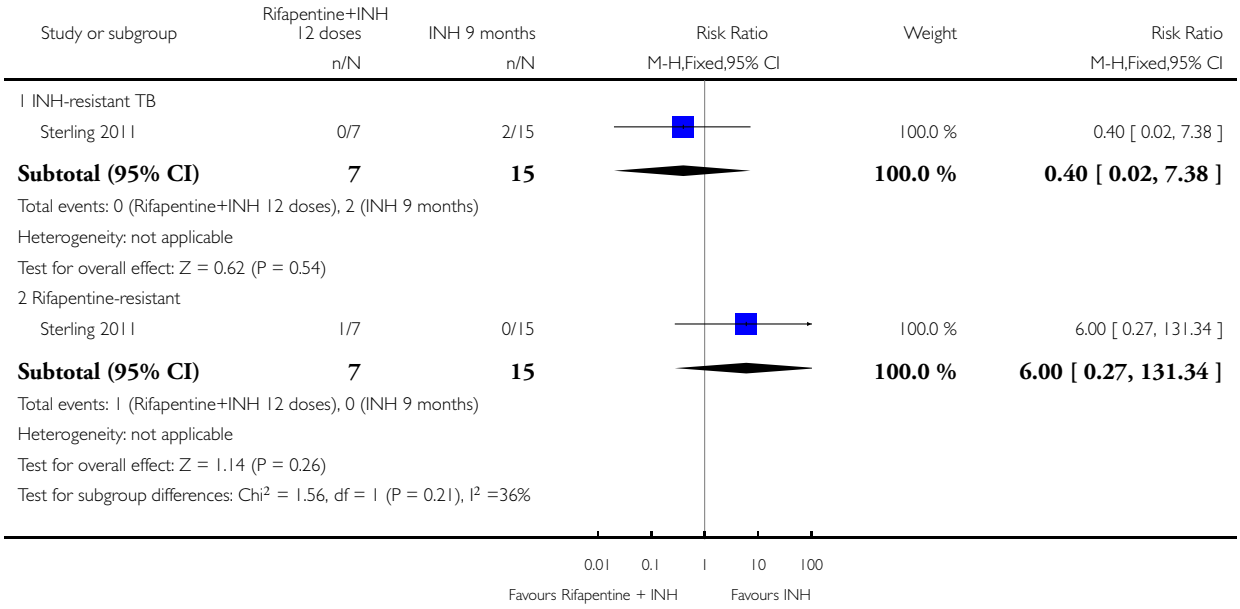
(1) Rifapentine + INH weekly (12 doses) vs INH daily (275 doses)

Analysis 4.3. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 3 Drug-resistant TB.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 3 Drug-resistant TB



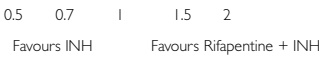
Analysis 4.4. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 4 Adherence.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 4 Adherence

Study or subgroup	Rifapentine+ INH 3 months n/N	INH 9 months n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sterling 2011 (1)	3273/3986	2585/3745		100.0 %	1.19 [1.16, 1.22]
Total (95% CI)	**3986**	**3745**		**100.0 %**	**1.19 [1.16, 1.22]**
Total events: 3273 (Rifapentine+ INH 3 months), 2585 (INH 9 months)					
Heterogeneity: not applicable					
Test for overall effect: Z = 13.14 (P < 0.00001)					
Test for subgroup differences: Not applicable					



(1) Rifapentine + INH weekly (12 doses) vs INH daily (275 doses)

Analysis 4.5. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 5 Serious adverse events.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 5 Serious adverse events

Study or subgroup	Rifapentine+ INH 3 months n/N	INH 9 months n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sterling 2011 (1)	64/4040	109/3759		100.0 %	0.55 [0.40, 0.74]
Total (95% CI)	**4040**	**3759**		**100.0 %**	**0.55 [0.40, 0.74]**
Total events: 64 (Rifapentine+ INH 3 months), 109 (INH 9 months)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.88 (P = 0.00010)					
Test for subgroup differences: Not applicable					

(1) Rifapentine + INH weekly (12 doses) vs INH daily (275 doses)

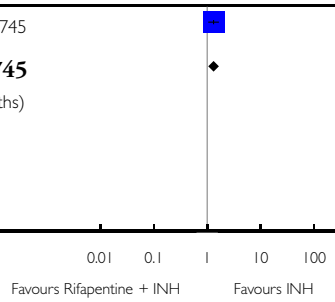
Analysis 4.6. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 6 Treatment-limiting adverse events.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 6 Treatment-limiting adverse events

Study or subgroup	Rifapentine+ INH 3 months n/N	INH 9 months n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sterling 2011 (1)	196/3986	139/3745		100.0 %	1.32 [1.07, 1.64]
Total (95% CI)	**3986**	**3745**		**100.0 %**	**1.32 [1.07, 1.64]**
Total events: 196 (Rifapentine+ INH 3 months), 139 (INH 9 months)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.59 (P = 0.0095)					
Test for subgroup differences: Not applicable					



(1) Rifapentine + INH weekly (12 doses) vs INH daily (275 doses)

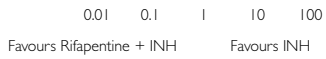
Analysis 4.7. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 7 Hypersensitivity.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 7 Hypersensitivity

Study or subgroup	Rifapentine+ INH 3 months n/N	INH 9 months n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sterling 2011 (1)	152/4040	17/3759		100.0 %	8.32 [5.05, 13.71]
Total (95% CI)	**4040**	**3759**		**100.0 %**	**8.32 [5.05, 13.71]**
Total events: 152 (Rifapentine+ INH 3 months), 17 (INH 9 months)					
Heterogeneity: not applicable					
Test for overall effect: Z = 8.32 (P < 0.00001)					
Test for subgroup differences: Not applicable					



(1) Rifapentine + INH weekly (12 doses) vs INH daily (275 doses)

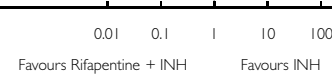
Analysis 4.8. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 8 Hepatotoxicity.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 8 Hepatotoxicity

Study or subgroup	Rifapentine+ INH 3 months n/N	INH 9 months n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sterling 2011 (1)	18/4040	103/3759		100.0 %	0.16 [0.10, 0.27]
Total (95% CI)	**4040**	**3759**		**100.0 %**	**0.16 [0.10, 0.27]**
Total events: 18 (Rifapentine+ INH 3 months), 103 (INH 9 months)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.14 (P < 0.00001)					
Test for subgroup differences: Not applicable					



(1) Rifapentine + INH weekly (12 doses) vs INH daily (275 doses). Excluding new cases of hepatitis A, B, or C

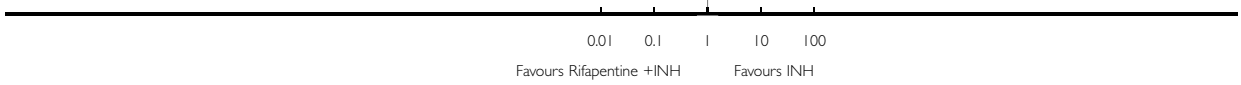
Analysis 4.9. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 9 Rash.

Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 9 Rash

Study or subgroup	Rifapentine+INH 12 doses n/N	INH 9 months n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sterling 2011	31/4040	21/3759		100.0 %	1.37 [0.79, 2.39]
Total (95% CI)	**4040**	**3759**		**100.0 %**	**1.37 [0.79, 2.39]**
Total events: 31 (Rifapentine+INH 12 doses), 21 (INH 9 months)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.13 (P = 0.26)					
Test for subgroup differences: Not applicable					



Analysis 4.10. Comparison 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months, Outcome 10 Any adverse event.

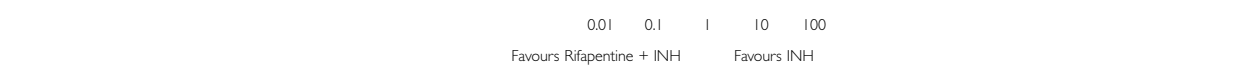
Review: Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB

Comparison: 4 Rifapentine plus INH weekly for 3 months versus INH daily for 9 months

Outcome: 10 Any adverse event

Study or subgroup	Rifapentine+INH 12 doses n/N	INH 9 months n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sterling 2011	595/4040	661/3759		100.0 %	0.84 [0.76, 0.93]
Total (95% CI)	**4040**	**3759**		**100.0 %**	**0.84 [0.76, 0.93]**

Total events: 595 (Rifapentine+INH 12 doses), 661 (INH 9 months)
Heterogeneity: not applicable
Test for overall effect: Z = 3.42 (P = 0.00062)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	tuberculosis	tuberculosis	tuberculosis	tuberculosis	tuberculosis
2	isoniazid	TUBERCULOSIS/DRUG THERAPY/PREVENTION AND CONTROL/THERAPY	TUBERCULOSIS/DRUG THERAPY/PREVENTION AND CONTROL/THERAPY	TUBERCULOSIS/DRUG THERAPY//THERAPY	isoniazid
3	1 AND 2	1 OR 2	1 OR 2	1 OR 2	1 AND 2
4	-	ISONIAZID/ THERAPEUTIC USE	ISONIAZID/ THERAPEUTIC USE	ISONIAZID	-
5	-	isoniazid	isoniazid	isoniazid	-

(*Continued*)

6	-	ANTITUBERCULAR AGENTS	ANTITUBERCULAR AGENTS	TUBERCULO-STATIC AGENT	-
7	-	4 OR 5 OR 6	4 OR 5 OR 6	4 OR 5 OR 6	-
8	-	3 AND 7	3 AND 7	3 AND 7	-
9	-	-	Limit 8 to Humans	Limit 8 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 (Lefebvre 2011); upper case: MeSH or EMTREE heading; lower case: free text term.

Appendix 2. Outcomes reported and definitions used in included studies

Study	Active TB[b]	TB related deaths	All cause deaths	Drug-resistant TB	Adherence	Serious adverse events	Drug-related deaths	Liver toxicity	Adverse events leading to treatment discontinuation	Other adverse events
Chan 2012[a]	Active case finding; clinical; X-ray; sputum culture	Not applicable	No deaths	Not applicable; not reported	Treatment was by direct observation; adherence defined as proportions completing treatment; also reported were proportions adherent but withdrawn due to adverse events	Modified criteria of the National Cancer Institute Common Terminology Criteria for Adverse Events: Graded hepatotoxicity; rash; gastrointestinal discomfort; drug interac-	Not applicable; no deaths	Grade 1: GPT[c] levels 1 to 3 times the ULN [d] Grade 2: GPT levels 3 to 5 times the ULN without symptoms Grade 3: GPT levels 3 to 10 times the ULN with hep-	Permanent discontinuation: any grade 3 to 4 AE [e] that did not resolve after temporary discontinuation for 2 weeks or recurred at 2 weeks after reinstitution of treatment after resolv-	Self-reported adverse events and physician evaluation

(*Continued*)

						tions		atitis-related symptoms or GPT levels 5 to 10 times the ULN without symptoms Grade 4: GPT levels > 10 times the ULN	ing	
HKCS 1992	Serial sputum examinations (two specimens at weeks 12 and 24, and every 3 months from month 9 to 5 years; serial chest X-rays (at 2, 6, 9, and 12 months; and every 6 months until 5 years)	Not applicable	One death due to lung cancer	Assessed by sputum culture and drug susceptibility to INH, rifampicin, and streptomycin. Results available for 65/83 (78%) of sputum positive cases of pulmonary TB (13 additional cases had extra-pulmonary TB	Assessed by pill counts; data used in review are proportions completing treatment without interruption	Not reported	Not applicable	Not graded: serum alanine transaminase levels above normal (28 IU/L *f*)	Not defined; decided by clinicians; reported are proportions where treatment was interrupted and was discontinued	Patient reports at assessment points
Leung 2003	Sputum examination for mycobacteria and	Not reported	No deaths	Sputum culture and drug sen-	Assessed through drug calendar and	Not reported	Not applicable	Serial liver functions monthly	Those with liver toxicity that	Patient reports. Skin, gastroin-

(*Continued*)

	chest radiography at months 2, 6, and 12, and then yearly up to 10 years. Results not reported but provided by author			sitivity	pill counts. Adherence calculated as percentage of doses actually received of expected doses			in first two months (later modified to once in two weeks) . Serum alanine transaminase > 5 times ULN or > 3 times ULN with symptoms of hepatitis on repeated testing	did not resolve after stopping treatment for at least two weeks or recurrence after resumption of treatment	testinal, joints, other
Magdorf 1994	Definition not described	Not reported	Not reported	Not reported	Self-reports; pill counts; urine testing for INH	Not defined or reported	Not reported	Not defined, but reported	Not defined or reported	Not reported
Martinez Alfaro 1998	Measured as a TFT induration after treatment. Not used in review	No deaths reported during trial	No deaths	Not reported	Clinic attendance and self-reported consumption of > 80% of doses	Not defined	Not reported	Serum GPT levels ≥ 5 times ULN	Not defined but reported	Milder liver dysfunction; gastrointestinal effects; others
Menzies 2004	Not assessed	No deaths reported during trial	No deaths reported	Not assessed	Electronic medication monitoring system; > 80% doses	Events leading to treatment discontinuation by treating physician	No deaths reported	Serum alanine transaminase ≥ 3 times ULN with symptoms of	Defined as serious adverse events in this trial	Subsumed under serious adverse events (nausea, vom-

(*Continued*)

					taken			hepatitis or ≥ 5 times ULN with no clinical symptoms		iting, fatigue, rash)
Menzies 2008	Not assessed	No deaths due to TB	One in INH arm	Not assessed	Electronic medication monitoring system; > 80% doses taken	National Cancer Institute Common Terminology Criteria for Adverse Events: Graded hepatotoxicity; rash; gastrointestinal discomfort; drug interactions	No drug related deaths	Grade 3: Liver aminotransferase levels 5 to 10 times ULN, or 3 to 10 times ULN with compatible symptoms Grade 4: > 10 ULN. Adjudicated by a 3 member panel	Grade 3 and 4 events and Grade 1 and 2 events that did not resolve on drug discontinuation or that recurred on resumption after resolution, as decided by physician	Grade 1 and 2 events; hematologic, gastrointestinal, rash, drug interaction
Sanchez-Arcilla 2004	Not assessed	Not reported	Not reported	Not assessed	Not defined. Treatment was self-administered or supervised monthly or more frequently if symptoms	Not separately defined	Not reported	Serum transaminase levels > 5 times ULN without symptoms, or > 3 times ULN with symptoms of	As for liver toxicity	Not defined; reported as other with no description of nature of event

(*Continued*)

					or signs of toxicity appeared			liver disease		
Sterling 2011	Active case finding; culture-confirmed (or clinical TB in children under the age of 18 years). Reviewed by an expert panel	No deaths	Reported	Sputum culture and drug susceptibility testing	DOT in combination arm and self-administered in INH arm. Adherent defined as consuming 11 of 12 combination doses within 16 weeks or 240 of 270 INH doses in 52 weeks	Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalisation or prolongation of an existing hospitalisation, a persistent or significant disability or incapacity, and a congenital anomaly or birth defect	No drug related deaths	Serum transaminase levels > 5 times ULN without symptoms, or > 3 times ULN with symptoms of liver disease	Common toxicity criteria version 2.0. Bethesda, MD: Cancer Therapy Evaluation Program; Any Grade 3 or 4 event	Common toxicity criteria
Tortajada 2005	Not stated; Trial stopped early for	No deaths	No deaths	Not described; no active TB	Pill counts and review of	Not defined; none reported	No drug related deaths	ALT/ AST values > 5 times	Not defined; decided by clin-	Self reported or detected by physi-

(*Continued*)

	harms			detected	calender annotations. Data used for adherence were those classified as treatment completers- those who took 80% or > of prescribed medication			ULN, (hepatotoxicity Grade 3)	icians; reported are treatment interruptions due to adverse events	cians

[a] Published and unpublished data;
[b] Glutamic pyruvic transaminase;
[c] Glutamyl transpeptidase;
[d] Upper limit of normal;
[e] Adverse event;
[f] Upper limit of normal

CONTRIBUTIONS OF AUTHORS

SKS conceived the review and wrote the protocol for this review. All authors helped draft the protocol. PT updated the background section of the protocol during review completion. SKS, TK, and AS screened studies for inclusion. PT checked excluded studies. SKS, TK, and PT assessed trials for risk of bias. TK and PT extracted and entered data. All authors checked entered data. TK wrote the draft of the review and drafted the summary of findings tables. PT revised the summary of findings tables and wrote the final version of the review. All authors contributed to revising the review in accordance with referees' comments and editorial suggestions, and approved the final version.

DECLARATIONS OF INTEREST

None of the authors declare financial or academic conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title of the review was changed from "Isoniazid mono-therapy versus other mono-therapies or combination chemotherapy for preventing active tuberculosis in HIV-negative persons" to "Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB)" to more accurately describe the focus of the review.

The background section was updated since the publication of the protocol to include more recent information relevant to understanding LTBI, and recent advances in the conceptual understanding of re-activation of LTBI. 'Risk of bias' tables and 'Summary of findings' tables were introduced as standard for Cochrane reviews after this protocol was published. We generated 'Risk of bias' for the included studies in this review using the methods described in Higgins 2011. We used GRADE profiler (GRADE 2004) and interpreted the evidence for each important and critically important outcome for the comparisons in the included trials using the GRADE approach (Schunemann 2008) to create 'Summary of findings' tables for each comparison. We selected outcomes to include in these tables though discussion, and before evaluating the search results.

We clarified in the methods section our approach to dealing with unit of analysis issues arising from cluster randomized trials that were not described in the protocol. These methods were based on advice provided in Higgins 2011b.

To respond to referees' comments, we restructured the background section to provide more clarity; made explicit that quasi-RCTs would be excluded under "Types of studies" and also provided additional information on the interpretation of I^2 values in the assessment of heterogeneity by following suggestions in Deeks 2011.

INDEX TERMS

Medical Subject Headings (MeSH)

*HIV Seronegativity; Antibiotics, Antitubercular [*therapeutic use]; Directly Observed Therapy; Drug Administration Schedule; Isoniazid [therapeutic use]; Latent Tuberculosis [*drug therapy]; Randomized Controlled Trials as Topic; Rifabutin [*therapeutic use]; Rifampin [*analogs & derivatives; *therapeutic use]; Tuberculosis, Pulmonary [*prevention & control]

MeSH check words

Adult; Child; Humans