Original research

Recurrent TB: a systematic review and meta-analysis of the incidence rates and the proportions of relapses and reinfections

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ABSTRACT

Background A recurrent tuberculosis (TB) episode results from exogenous reinfection or relapse after cure. The use of genotyping allows the distinction between both.

Methods We did a systematic review and meta-analysis, using four databases to search for studies in English, French and Spanish published between 1 January 1980 and 30 September 2020 that assessed recurrences after TB treatment success and/or differentiated relapses from reinfections using genotyping. We calculated person years of follow-up and performed random-effects model meta-analysis for estimating pooled recurrent TB incidence rates and proportions of relapses and reinfections. We performed subgroup analyses by clinical–epidemiological factors and by methodological study characteristics.

Findings The pooled recurrent TB incidence rate was 2.26 per 100 person years at risk (95% CI 1.87 to 2.73; 145 studies). Heterogeneity was high (I^2=98%). Stratified pooled recurrence rates increased from 1.47 (95% CI 0.87 to 2.46) to 4.10 (95% CI 2.67 to 6.28) per 100 person years for studies conducted in low versus high TB incidence settings. Background HIV prevalence, treatment drug regimen, sample size and duration of follow-up contributed too. The pooled proportion of relapses was 70% (95% CI 63% to 77%; I^2=85%; 48 studies). Heterogeneity was determined by background TB incidence, as demonstrated by pooled proportions of 83% (95% CI 75% to 89%) versus 59% (95% CI 42% to 74%) relapse for studies from settings with low versus high TB incidence, respectively.

Interpretation The risk of recurrent TB is substantial and relapse is consistently the most frequent form of recurrence. Notwithstanding, with increasing background TB incidence the proportion of reinfections increases and the predominance of relapses among recurrences decreases.

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Key messages

What is the key question?
- What is the incidence of recurrent TB and the proportions of relapses and reinfections?

What is the bottom line?
- The risk of recurrent TB is substantial and relapse is consistently the most frequent form of recurrence, yet, as background incidence increases, the proportion of reinfections also increases and the predominance of relapses among recurrences decreases.

Why read on?
- Understanding of the frequency of recurrent TB, relapses and reinfections will help to implement better post treatment follow-up and to reduce TB burden.

INTRODUCTION

The proportion of people with TB that are successfully treated is a key indicator to monitor progress of the End TB Strategy.[1] The standardised four-drug regimen for drug susceptible pulmonary TB has shown favourable outcome at the end of treatment in over 92% of cases in clinical trials[2–4] and in TB programmes at least 85% of patients receiving it are successfully treated (cured or treatment completed).[5 6] After being cured, some individuals can develop a recurrent episode of TB, as a result of an endogenous reactivation of the first infection or of an exogenous new infection.[7–9] Historically,[9] it was not possible to differentiate relapses from reinfections in recurrent episodes because they are clinical indistinguishable. Moreover, reinfection was considered to be rare.[10] The advent of molecular techniques using DNA markers[8] permits comparison of the genotype of strains isolated in the first and recurrent TB episode. Episodes sharing the same strain are classified as relapses while those with two different strains are classified as reinfections.

The incidence of recurrent TB and the proportion of reinfections and relapses can guide TB control. Furthermore, these relative frequencies depend on the background transmission rate besides the effectiveness of treatment. While relapses generally predominate, studies conducted in high TB incidence populations usually identify a larger proportion of cases due to reinfection than studies in countries where the burden of TB disease is lower.[10–12] Notwithstanding, a higher than expected incidence of relapse calls for an evaluation of the efficacy of the first-episode treatment regimen.[13] On the other hand, if reinfection rates are higher than expected, reducing the risk of transmission is fundamental.

Two systematic reviews published in 2003 investigated recurrent TB episodes. One review[7] found, without providing a pooled estimate, that the proportion of reinfections ranged between 0% and 100%. The other[13] analysed the influence of HIV-status and rifampin-based treatment on recurrence and found a recurrent TB rate of 1.9 cases per 100 person years among HIV negative and 4.5 per 100 person years among HIV-positive individuals and recurrence rates that increased with decreasing duration of therapy. A 2007 systematic review[14] pooled recurrent TB rates across 10 controlled trials and found a rate of 2.3 per 100 person years at 12 months after treatment completion. In the 13 years that passed since this last review was published, the scientific literature on recurrences has boomed alongside the markedly increased use of genotyping methods. This raises not only the need to review anew the phenomenon of TB recurrences but offers also the opportunity to more comprehensively look into the difference between relapses and reinfections because new genotyping techniques, including whole-genome sequencing (WGS), allow enhanced resolution to differentiate between *Mycobacterium tuberculosis* strains.[8 15] We conducted a systematic review of the literature published in the last four decades to assess the recurrent TB incidence rate and the proportion of recurrent TB cases due to reinfection and relapse.

METHODS

Search strategy and selection criteria

We included clinical trials, longitudinal studies and studies using TB programme databases that reported recurrent TB rates and/or the proportion of reinfections and relapses, published between 1 January 1980 and 30 September 2020, in English, French and Spanish. We searched Medline/PubMed, Cochrane, Literatura Latinoamericana y del Caribe en Ciencias de la Salud (LILACS) and Scientific Electronic Library Online (SciELO). Literature search strategies for Medline/PubMed used medical subject headings (MeSH) and text words related to TB recurrence. For all databases, key search terms included variations on the concept "tuberculosis AND (recurrence OR reinfection OR relapse OR reactivation)". The search strategy is fully described in online supplemental appendix 1. We also reviewed references of included articles. In addition to studies using epidemiological designs, we included peer-reviewed studies reporting data from TB programme databases.

Duplicity of studies was identified using Covidence software, Veritas Health Innovation (available at www.covidence.org) or manually, for example, when the titles were in two different languages. When two studies reported on the same group of subjects but used different molecular techniques, the study whose technique had the best discriminatory power was included. When two studies analysed recurrent episodes in the same population over the same time period, full texts were reviewed and the study with less restricted exclusion criteria was withheld in order to capture more recurrences.

Titles and abstracts of retrieved studies were screened independently by two authors (VV and SR) to identify studies that met the inclusion criteria. Disagreements were resolved through discussion with a third author (LO). If abstracts were not available or did not provide sufficient information to decide on eligibility, the study was included in the full-text review. Our inclusion criteria were studies reporting on recurrent TB defined as a new diagnosis of TB after a successfully treated TB episode. Studies had to define treatment success as cured (bacteriologically negative at month 5) or treatment completion. All TB regimens were included. For recurrent TB incidence, our first outcome, we selected studies that followed up successfully treated patients to detect recurrences. For proportions of relapses and reinfections, our second outcome, we also included studies exploiting national or subnational TB programme databases, which do not report follow-up data for all patients.

Data extraction and analysis

The two primary reviewers (VV and SR) extracted data independently into a Google Form prepared for the study that had been tested on five randomly selected studies. Discrepancies in data extraction were resolved through discussion with a senior researcher (LO). Data extracted included study characteristics, number of TB cases who successfully completed treatment, type of follow-up (active, where patients are sought after to determine the presence or absence of a recurrent TB episode vs passive or routine TB register based, where patients self-present at health facilities), duration of follow-up in years, number of recurrent episodes, number of relapses and reinfections, test used to diagnose a recurrent TB episode, and molecular techniques used. We assessed the risk of bias using a modified Newcastle Ottawa Scale[16] for both outcomes. We adapted this tool for all studies, regardless of study design, to evaluate the risk of bias in their estimations of the incidence of recurrences, as well as of the proportions of relapses and reinfections. The nature of and rationale for modifying some items of the scale is detailed in online supplemental appendix 2.

Pooled recurrent TB incidence

The recurrent TB incidence rate was calculated by dividing the number of recurrent TB episodes by the total person years at risk. The person years at risk contributed by the patients with a successfully treated first TB episode was extracted as reported by the study or, depending on the reported data, calculated as detailed in online supplemental appendix 3.

The meta-analysis of recurrent TB incidence was done with RStudio V.1.1.463 using the meta package and the command metarate. Rates were expressed as recurrences per 100 person years. We used a DerSimonian-Laird random effects model for meta-analysis in view of the heterogeneity between studies. We tested for heterogeneity by using the I^2 statistic with $p<0.05$ as threshold. Results were displayed in forest plots. We evaluated the risk of publication bias by assessing symmetry in a funnel plot and performing Egger's test.

We performed subgroup analyses of the recurrent TB rate pooled by clinical–epidemiological factors related to study setting and by methodological study characteristics. Background TB incidence was based on the country-level TB incidence per 100 000 population provided by the WHO[17] for the year of study or at midterm in case of follow-up >1 year. Before 2000, estimated incidence is not available and we used the case notification rate provided by WHO. We classified countries' incidence as low if <30 per 100 000 population, moderate if between 30 and 100, medium if between 100 and 300 and high if >300. Regarding type of follow-up, clinical trials were considered to have 'active follow-up' unless otherwise specified, and observational studies were classified based on the follow-up description in the methods. Type of treatment regimen, took into account the most used regimen in the study (if more than one) and was classified in three subgroups (six or more month rifampicin, <6 months of rifampicin and drug resistant TB regimens). Based on UNAIDS or government publications, background HIV prevalence, was dichotomised as low if <1% in the general population and high otherwise. For studies conducted before 1990, we

categorised the country as low level unless it was recognised as contributing early to HIV epidemic.

We explored reasons for heterogeneity by estimating stratified incidence rate ratios of recurrent TB. First, we used univariate meta-regression with the variables listed above and obtained R^2 statistics, which reflect the proportion of between-studies variance explained by each variable. Subsequently, we performed multivariate meta-regression. We included in an initial model all covariates with $p<0.2$ in the univariate analysis, as well as potential confounding variables that were statistically non-significant. Using backward stepwise selection, we eliminated non-significant ($p>0.05$ in likelihood ratio test) and non-confounding variables from the model.

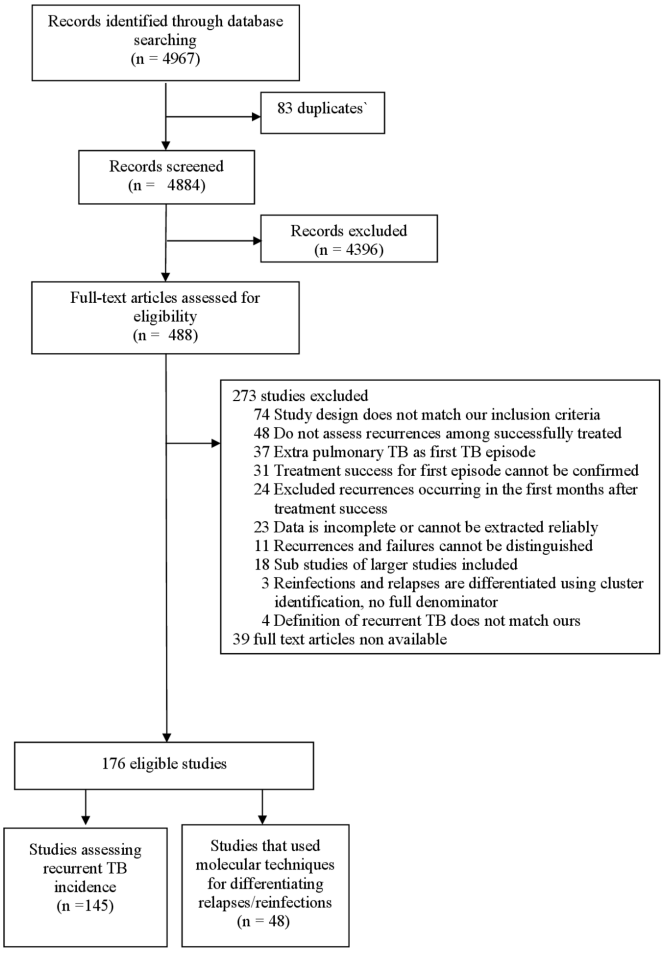

Figure 1 Flowchart of study selection.

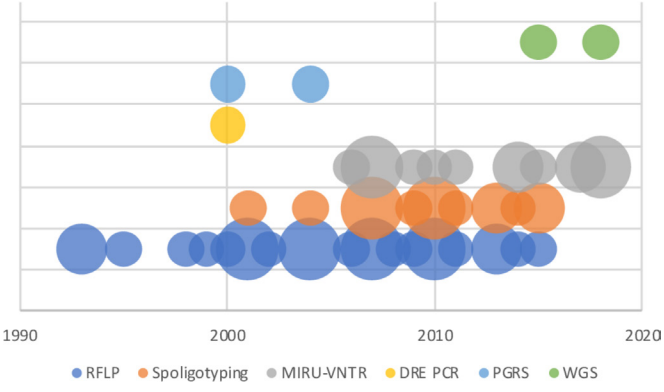

Figure 2 Frequency of use of molecular techniques to discriminate tuberculosis reinfections and relapses, 1990-2020. Size of the circle is proportional to the number of studies. DRE-PCR, double repetitive element-PCR; PGRS, polymorphic GC-rich repetitive sequence genotyping; RFLP, restriction fragment length polymorphism; WGS, whole-genome sequencing.

Pooled proportions of reinfections and relapses

We describe the frequency of use over time of molecular technique to differentiate relapses from reinfections in the included studies. To calculate the proportions of reinfections and relapses, we divided the number of reinfections and relapses by the number of recurrent TB episodes with DNA fingerprinting results. Meta-analysis was performed as described above. In subgroup analyses, we also used the variables specified above, except drug regimen (information not available for studies using TB programme databases) and, additionally, the proportion of study patients with DNA fingerprinting results available for the first and recurrent TB episode (dichotomised with the upper tertile as cut-off), and the molecular method used. We calculated crude and adjusted ORs for reinfection in the different study subgroups and used meta-regression to assess heterogeneity. We followed the multivariate modelling strategy described above.

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in our study. The PRISMA checklist can be found in online supplemental appendix 4. We evaluated the certainty of evidence of our results using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[18]

RESULTS

The search yielded 4884 articles. The selection process in shown in figure 1. We identified 488 articles for retrieving the full text. Thirty-nine full-text articles were not available and 273 were excluded. A total of 176 studies met the inclusion criteria. There were 111 cohort studies, 48 clinical trials and 17 studies using a TB programme database. Sufficient data on patient follow-up were available in 145 studies, which were included in the meta-analysis of recurrent TB incidence rate. Fourty-eight studies could be included in the meta-analysis of the proportion of reinfections and relapses, of which 24 were also included in the former analysis. The characteristics of all studies are outlined in the online supplemental appendix 5.

Molecular techniques used to discriminate TB reinfection and relapse

Of the studies reporting on reinfections and relapses, 30 used IS6110-restriction fragment length polymorphism analysis (IS6110 RFLP) to differentiate strains, 19 spoligotyping, 19 mycobacterial interspersed repetitive unit-variable number tandem repeat typing, two polymorphic GC-rich repetitive sequence genotyping, one double repetitive element-PCR and six WGS. IS6110-RFLP was the only method used before 2000. Twenty-one studies used more than one method; the most frequent combination was IS6110-RFLP with spoligotyping. Figure 2 shows the use of novel molecular techniques over time.

Recurrent TB incidence rate

The pooled estimate of the recurrent TB incidence across 145 studies was 2.26 per 100 person years at risk (95% CI 1.87 to 2.73). Heterogeneity was significant ($I^2=98\%$). Figure 3 shows the forest plot for this analysis. Details on the studies, including the follow-up information used to calculate person years at risk,

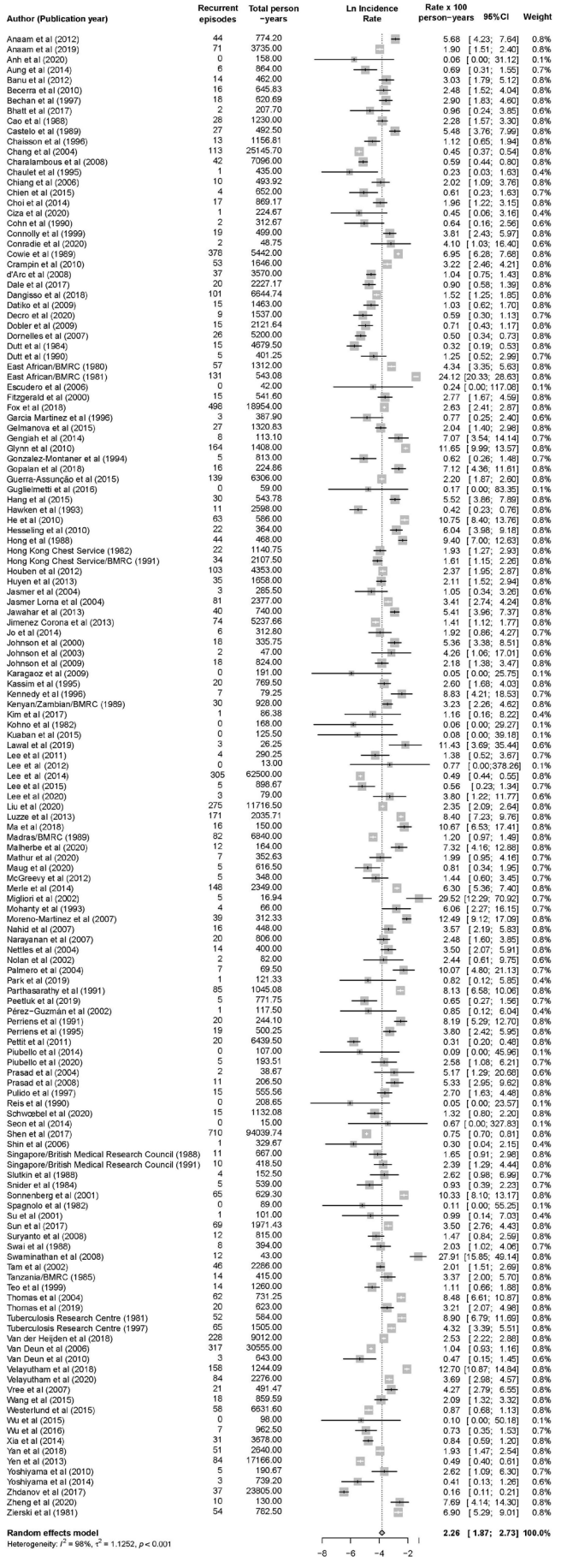

Figure 3 Forest plot of the recurrent tuberculosis incidence rate.

are shown in online supplemental table S2). The mean follow-up after successful treatment was 2.3 years.

In univariate stratified analysis, background TB incidence, background HIV prevalence, sample size and study design were important sources of heterogeneity (table 1). Recurrence rates were an order of 10, 15, 25 and over 50 times higher than background rates in high, median, moderate and low TB incidence settings, respectively. After adjusting, we found that the rate of recurrent TB in studies conducted in high incidence settings was more than twice higher than the rate in studies from low background TB incidence, and that studies with less than 6 months of rifampicin treatment had almost twice the recurrent TB incidence rate found in studies with 6 or more months of rifampicin therapy.

Forest plots for each subgroup analysis are shown in online supplemental figures 1–8. The funnel plot in online supplemental figure S9 shows mild asymmetry, pointing at a possible publication bias, but Egger's test is not significant (p=0.79).Quality assessment for studies included in this outcome is presented on online supplemental table S3. Twenty-four studies were of good quality, 84 fair and 37 poor quality.

Proportion of reinfections and relapses in recurrent TB episodes

For studies that differentiate between reinfections and relapses, the overall pooled proportion of relapses was 70% (95% CI 63% to 77%) and of reinfection 30% (95% CI 23% to 37%). Heterogeneity was high (I^2=85%) Figure 4 presents a forest plot of this analysis. Detailed data of the included studies are shown in online supplemental table S2.

Table 2 shows subgroup analyses of the proportion of relapses and reinfections and meta-regression results. When we assessed potential sources of heterogeneity, we found background TB incidence to significantly and substantially contribute, while study design and quality, sample size, background HIV prevalence and molecular method used had a moderate influence. In multivariate analysis, only background TB incidence had a statistically significant—positive and strong—effect on the OR for reinfections, but HIV prevalence, study design, molecular method used, sample size and study quality, all acted as confounders.

Subgroup analysis forest plots are shown in online supplemental figures S10–S17. The funnel plot for this outcome (online supplemental figure S18) is not asymmetric and Egger's test is not significant (p=0.06). Quality assessment for studies included in this outcome is presented in online supplemental table S4. Seven studies were graded good quality, 22 fair and 19 poor quality.

Extrapolating the pooled proportion of reinfections and relapses from the studies included in this analysis to the pooled recurrent TB rate estimated from the studies included in the corresponding analysis yields a rate of relapses of 1.60 per 100 person years and a rate of reinfection of 0.68 per 100 person years.

We evaluate the results using the GRADE approach and reported the evidence profile table (table 3), indicating that certainty is low for both outcomes and the reasons for it.

DISCUSSION

We found, across 145 studies, a pooled incidence rate of recurrent TB after successful treatment of 2.26 (95% CI 1.87 to 2.73) per 100 person years for a mean follow-up of 2.3 years. The recurrent TB incidence rate increased as the background TB incidence increased and was systematically manifold higher

Table 1 Univariate subgroup analysis and multivariate meta-regression of the incidence rate of TB recurrence

Study subgroup	N	R^2	TB recurrence incidence rate per 100 person years (95% CIs)	Crude incidence rate ratio (95% CIs)	P value	Adjusted incidence rate ratio (95% CIs)	P value
By background TB incidence level		23.20			<0.001		0.009
Low (<30 cases per 100 000)	25		1.47 (0.89 to 2.45)	Ref		Ref	
Moderate (31–100 cases per 100 000)	47		1.63 (1.22 to 2.18)	1.09 (0.65 to 1.83)		1.15 (0.71 to 0.86)	
Medium (101–300 cases per 100 000)	59		2.87 (2.22 to 3.71)	1.95 (1.20 to 3.18)		1.87 (1.16 to 3.02)	
High (>300 cases per 100 000)	14		4.10 (2.67 to 6.28)	2.75 (1.43 to 5.27)		2.28 (1.20 to 4.34)	
Background HIV prevalence		17.42			<0.001		0.094
Low level (<1%)	101		1.79 (1.43 to 2.26)	Ref		Ref	
High level	44		3.64 (2.82 to 4.68)	1.99 (1.38 to 2.87)		1.34 (0.94 to 1.98)	
TB drug regimen		1.35			0.053		0.019
6 or more months of rifampicin	98		2.17 (1.75 to 2.70)	Ref		Ref	
Less than 6 months of rifampicin	20		3.67 (2.28 to 5.90)	1.69 (1.00 to 2.86)		1.61 (1.05 to 2.47)	
Drug-resistant TB regimens	27		1.48 (0.76 to 2.87)	0.75 (0.43 to 1.29)		0.73 (0.45 to 1.19)	
Study design		7.87			0.029		
Clinical trials	43		3.17 (2.41 to 4.16)	1.55 (1.05 to 2.31)			
Observational studies	102		1.98 (1.58 to 2.48)	Ref			
Sample size		14.12			0.059		0.054
0–153	37		2.81 (1.76 to 4.49)	1.86 (1.08 to 3.21)		2.08 (1.25 to 3.44)	
154–335	36		2.53 (1.87 to 3.44)	1.58 (0.98 to 2.53)		1.53 (0.99 to 2.35)	
336–668	36		2.67 (1.90 to 3.76)	1.70 (1.07 to 2.70)		1.40 (0.93 to 2.12)	
>668	36		1.57 (1.13 to 2.18)	Ref		Ref	
Planned follow-up		2.97			0.019		0.0110
<1 year	24		4.01 (2.51 to 6.40)	Ref		Ref	
1–2 years	60		2.36 (1.79 to 3.11)	0.58 (0.33 to 1.02)		0.55 (0.34 to 0.89)	
>2 years	61		1.82 (1.37 to 2.42)	0.46 (0.26 to 0.79)		0.49 (0.31 to 0.79)	
Type of follow-up		0			0.457		
Passive	40		1.77 (1.21 to 2.61)	Ref			
Active	94		2.49 (1.97 to 3.15)	1.39 (0.91 to 2.14)			
Quality of the study		0			0.478		
Good quality	24		1.91 (1.31 to 2.78)	Ref			
Fair quality	84		2.21 (1.71 to 2.85)	1.18 (0.71 to 1.98)			
Poor quality	37		2.78 (2.01 to 3.86)	1.45 (0.79 to 2.64)			

than the background rate, dramatically so in low and medium TB incidence settings. Relapses were the most common mechanism of recurrence across 48 studies, accounting for a pooled estimate of 70% (95%CI 63% to 77%) recurrent episodes. With increasing background TB incidence, the proportion of reinfections increased and the predominance of relapses among recurrences decreased.

Our pooled estimate of recurrent TB incidence rate is in line with two previous systematic reviews. In 2007, Panjabi *et al*,[14] excluding studies in HIV-positive-cured patients with TB, reported across 14 observational studies and 18 clinical trials a median recurrence rate for the 12 months after completing standard treatment regimens of 2.58 (0.98 to 11.90) per 100 person years. In 2003, Korenromp *et al*[13] found across 47 prospective studies reporting TB recurrences after cure and a recurrent rate of 1.9 (1.2 to 2.7) and 4.5 (3.2 to 5.8) per 100 person to years among HIV-negative and HIV-positive patients, respectively.

Recurrent TB is determined by a wide array of factors. We could extract from the included studies information on several of them. Clinical–epidemiological ones, background TB incidence, HIV prevalence and treatment regimens contribute to the heterogeneity of the pooled recurrent TB incidence rate. Methodological factors such as study sample size and planned follow-up duration also play an important role. Factors we had no information on may be an additional source of heterogeneity, adherence to treatment for instance, for relapse, or socioeconomic status related overcrowding for reinfection. This may in itself explain the mild asymmetry observed in the funnel plot, but despite 12/145 reviewed articles reporting zero events, we cannot completely exclude publication bias from unpublished small studies finding no recurrences.

Our study confirms the intuitive notion that the recurrent TB and background TB incidence are correlated, which has previously been reported. Korenromp *et al*[13] also found that recurrent

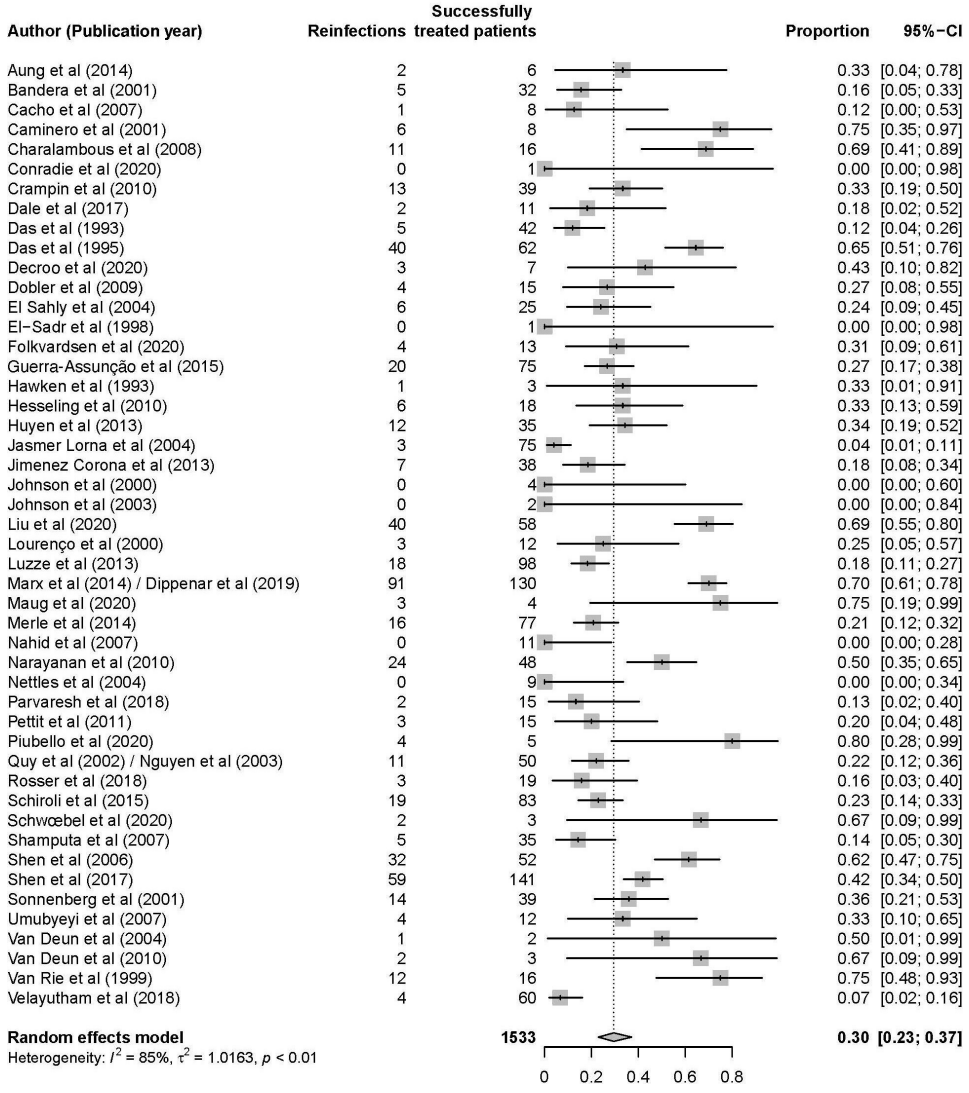

Figure 4 Forest plot of the proportion of reinfections among recurrent tuberculosis episodes.

TB rates increased with 0.14 per 100 person years for every increase in background TB incidence of 100 per 100 000 person years. Panjabi *et al*[14] reported a median recurrent TB rate of 7.85 compared with 1.78 per 100 person years in high (>100 cases per 100 000) versus low incidence settings. Furthermore, our results point at higher recurrent TB rates in high HIV prevalence settings which is also consistent with the earlier reviews.[13] HIV infection has been recognised as a strong risk factor for recurrence due to immunosuppression or continuous exposure to health services.

It is also not surprising that recurrent TB rates were higher in studies with planned follow-up below 1 year. However, type of follow-up nor study design were significantly associated with recurrences in multivariate analysis possibly for lack of power. Notwithstanding, recurrent TB can be better identified if populations at risk are closely followed up and higher recurrent TB incidence rates were found among clinical trials compared with observational studies.[14] Studies using TB programme databases can miss recurrent TB episodes if only patients attending the same health facilities or entered in the same information system are counted.

We identified relapses as the most common mechanism of recurrence, also in line with previous reviews,[7 13] but found quite some heterogeneity among studies. Background TB incidence was the most important source. Other factors such as background HIV prevalence, study design and quality, sample size and molecular methods used confounded, but were not independent significant determinants of heterogeneity. However, it cannot be excluded that this may be partially due to meta-regression having relatively limited power and the small number of studies included for this outcome. Still, the funnel plot for this outcome did not show asymmetry by visual inspection and Egger's test was not significant.

The proportion of reinfections increased with background TB incidence, which is most likely the result of continuous exposure to a more infectious environment after treatment completion. Akin to this, an increased relative frequency of reinfection has been reported in low incidence settings among people visiting high burden countries[19] and in frequent contact with health facilities.[20]

Length of follow-up has also been found to determine the reinfections ratio.[21] The risk of relapse decreases over time and they occur predominantly in the first year after treatment completion, while late recurrences tend to be reinfections. Therefore, short follow-up periods spuriously increases this ratio. We see an extreme example of it in two contrasting studies from India and

Table 2 Univariate subgroup analysis of proportion of relapses and reinfections and multivariate meta-regression of the OR for reinfection

Study subgroup	Number of studies	R^2	Proportion of reinfections % (95% CIs)	Proportion of relapses % (95% CIs)	Crude OR for reinfections	P value	Adjusted OR for reinfections	P value
By background TB incidence level		25.48				0.009		0.034
Low (<30 cases per 100 000)	16		17 (11 to 25)	84 (77 to 90)	Ref	–	Ref	
Moderate (31–100 cases per 100 000)	7		39 (25 to 55)	61 (45 to 75)	3.19 (1.21 to 8.41)	–	3.64 (1.31 to 10.10)	
Medium (101–300 cases per 100 000)	17		35 (23 to 50)	65 (50 to 77)	2.81 (1.30 to 6.09)	–	2.76 (1.18 to 6.45)	
High (>300 cases per 100 000)	8		41 (26 to 58)	59 (42 to 74)	3.54 (1.50 to 8.38)	–	6.90 (2.06 to 23.14)	
By background HIV prevalence		2.58				0.586		0.847
Low level (<1%)	26		28 (20 to 38)	73 (64 to 81)	Ref	–	Ref	
High level	22		32 (22 to 44)	64 (51 to 75)	1.21 (0.61 to 2.40)	–	0.89 (0.39 to 2.04)	
Study design		7.87				0.385		0.217
Cohort study	26		32 (23 to 43)	68 (57 to 77)	Ref		Ref	
Programme database review	17		29 (20 to 40)	71 (60 to 80)	0.86 (0.43 to 1.72)	–	1.51 (0.76 to 3.02)	
Clinical trial	5		16 (04 to 49)	84 (51 to 97)	0.39 (0.11 to 1.48)	–	0.39 (0.11 to 1.40)	
Study sample size		7.48				0.434		0.246
<9	14		42 (26 to 60)	58 (40 to 74)	1.52 (0.57 to 4.06)		2.01 (0.69 to 5.85)	
9–16	11		25 (19 to 33)	75 (67 to 82)	0.74 (0.13 to 1.85)		1.20 (0.48 to 3.01)	
17–48	11		25 (13 to 43)	76 (57 to 87)	0.69 (0.29 to 1.62)		0.86 (0.35 to 2.11)	
>48	12		31 (18 to 48)	69 (52 to 82)	Ref		Ref	
Follow-up		1.24				0.579		
<2 years	12		25 (12 to 46)	75 (54 to 88)	Ref			
≥2 years	36		31 (24 to 39)	69 (61 to 77)	1.26 (0.55 to 2.89)			
By molecular method		5.67				0.625		0.751
RFLP	21		27 (18 to 39)	72 (53 to 85)	Ref		Ref	
Spoligotyping	2		37 (23 to 53)	63 (47 to 77)	2.09 (0.35 to 12.46)		2.33 (0.42 to 13.02)	
MIRU VNTR	18		27 (18 to 39)	73 (61 to 82)	0.98 (0.47 to 2.03)		1.42 (0.67 to 3.02)	
Whole-genome sequencing	6		37 (18 to 60)	64 (40 to 62)	1.50 (0.49 to 4.54)		1.39 (0.48 to 3.98)	
By DNA fingerprinting		2.51				0.522		
≤88%	15		26 (16 to 39)	74 (61 to 84)	1.27 (0.60 to 2.68)			
>88%	33		31 (23 to 40)	69 (60 to 77)	Ref			
Quality of the study		1.37				0.990		0.545
Good	7		29 (16 to 48)	71 (84 to 53)	Ref		Ref	
Fair	22		29 (20 to 40)	71 (80 to 59)	0.97 (0.34 to 2.78)		0.56 (0.21 to 1.50)	
Poor	19		30 (20 to 43)	70 (81 to 57)	1.04 (0.36 to 3.01)		0.59 (0.21 to 1.62)	

MIRU-VNTR, mycobacterial interspersed repetitive unit-variable number tandem repeat typing; RFLP, restriction fragment length polymorphism.

South Africa. Velayutham *et al*[22] identified 97% relapses in the first year after treatment completion, while Marx *et al*[21] found 51% reinfections up to 13 years after treatment. In our review, stratified analysis showed only a discrete difference in pooled relapse proportion between studies with up to 2 years and 2 or more years of intended follow-up.

Our review has several limitations. Differences between definitions of recurrent TB were frequent and few studies reported

Table 3 Grading of Recommendations, Assessment, Development and Evaluation evidence profile

	Certainty assessment						Effect				
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of events	No of individuals	Measure (95% CI)	Certainty	Importance
Recurrent TB incidence rate per 100 person years											
145	Observational studies	Serious*	Serious†	Not serious	Not serious	None	6548	153565	2.26 per 100 person years (1.87 to 2.73)	⊕⊕◯◯ Low	Important
Proportion of reinfections											
48	Observational studies	Serious‡	Serious§	Not serious	Not serious	None	523	1533	30% (23 to 37)	⊕⊕◯◯ Low	Important

*Using the modified Newcastle Ottawa Scale, 24 studies were graded good quality, 84 fair quality and 37 poor quality. Lesser quality grading was mainly due to selection of a non-representative study population, clinical–radiological diagnosis of recurrent TB, short duration of follow-up and high proportion of lost to follow-up (see online supplemental table S3 for details).
†Heterogeneity was high (I^2=98%) and caused by differences in background incidence of TB and HIV prevalence, TB drug regimen used, study sample size and planned duration of follow-up.
‡Seven studies were graded good quality, 22 fair quality and 19 poor quality. The main reasons for lesser quality grading were non-representative study population, no bacteriological confirmation of cure and use of only one not highly discriminatory method (spoligotyping or restriction fragment length polymorphism) for differentiating relapses and reinfections (see online supplemental table S4 for details).
§Heterogeneity was high (I^2=85%) and strongly related to background TB incidence level. Possible other sources were study sample size, study design and quality, HIV prevalence level and molecular method used for genotyping.

death after treatment. The former could entail random misclassification, the latter, if due to TB recurrence, could result in underestimated recurrence rates. Furthermore, most studies did not report laboratory quality standards assessment, while recurrences diagnosed on isolated positive cultures caused by cross contamination will lead to overestimated reinfection frequencies. We could also not sort out the presence of mixed infections, which alter the interpretation of genotyping. Besides, recent literature[8] has described the possibility of reinfection with the same strain, which is more frequent with small numbers circulating, and leads to misclassification as relapse. Finally, since WHO recommended implementing Xpert in 2010, more patients with bacteriologically confirmed TB are diagnosed and treated. However, cure could become difficult to verify in these patients. Also, augmented use of more sensitive diagnostic techniques will lead to increased detection of recurrent TB. On the other hand, for recurrences diagnosed with molecular assays, differentiation between relapse and reinfection will be virtually excluded. These various possible effects, at programme level and for research, should be scrutinised as empirical evidence for them becomes available.

Our results have implications for clinical management and public health strategies. First of all, patients who have successfully completed TB treatment should be made aware that the risk of developing a subsequent episode is higher than the risk of suffering a first one, and be sensitised to promptly seek care if symptoms reappear. Second, TB programmes could routinely monitor the full continuum of TB care[23–25] and follow-up treated patients for a period of one or more years for timely detecting recurrent episodes and preventing long-term mortality.[26] However, the best strategies to ensure that all patients are actively followed up beyond treatment completion are yet to be determined, but could be designed studying patients' pathways after cure.[27] Third, our study clarifies the relative contributions of relapse and reinfection. It demonstrates relapses are the predominant form of recurrences in all settings, which should prompt TB programmes to implement measures that enhance effective treatment of a first episode as among others assure strict adherence and provide universal drug susceptibility testing to ensure adequate drug regimens.

To make follow-up for recurrence more practical, future studies could identify biomedical factors associated with relapse and socioenvironmental ones associated with reinfection, so these can be addressed or guide care after cure. Romanowski *et al*[28] already found that despite poor predictive ability, cavitary disease and 2-month smear positivity could be used as markers for higher risk of relapse. If risk factors for reinfection would be identified, they should likewise condition post-treatment follow-up, particularly in high TB incidence settings, which endure a higher proportion of reinfections. Modelling studies could further explore the potential impact on TB control of such improved detection of TB recurrences.

Falling prices of molecular technologies permit more widespread implementation of genotyping. Regardless of background incidence, TB control programmes should be encouraged to monitor the relative contributions of relapse and reinfection towards TB recurrence. This will permit to gain deeper understanding of the local dynamics of this health problem, to plan for, balance and adjust efforts at curbing its occurrence, and to improve individual patient long-term outcomes.

Contributors LO, CS and VV conceived the presented idea, initiated the project and were responsible for the design of the protocol. SR and VV did the review, data extraction, synthesis of results and quality assessment of studies. PVdS, LO, SR and VV contributed to the analysis of the results. All authors discussed the results and contributed to the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Universidad Peruana Cayetano Heredia Ethics Committee (FWA00000525) waived ethical approval.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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Supplementary material

Title: Recurrent tuberculosis: a systematic review and meta-analysis of the incidence rates and the proportions of relapse and reinfection

Vega V (1), Rodríguez S (1), Van der Stuyft P (2), Seas C (1,3), Otero L (1,3).

Appendix 1 Search strategy

Search strategy PUBMED

((((((((((("tuberculosis"[MeSH Terms]) OR "tuberculosis"[Title/Abstract])) AND ((((("recurrence"[MeSH Terms]) OR recurren*[Tite/Abstract])) OR ((((reinfection*[Title/Abstract]) OR relapse*[Title/Abstract])) OR "reactivation*"[Title/Abstract])))))) NOT (((""addresses""[Publication Type] OR ""autobiography""[Publication Type] OR ""bibliography""[Publication Type] OR ""book illustrations""[Publication Type] OR ""case reports""[Publication Type] OR ""comment""[Publication Type] OR ""dictionary""[Publication Type] OR ""directory""[Publication Type] OR ""editorial""[Publication Type] OR ""electronic supplementary materials""[Publication Type] OR ""ephemera""[Publication Type] OR ""expression of concern""[Publication Type] OR ""festschrift""[Publication Type] OR ""government publications""[Publication Type] OR ""guideline""[Publication Type] OR ""interactive tutorial""[Publication Type] OR ""interview""[Publication Type] OR ""lectures""[Publication Type] OR ""legal cases""[Publication Type] OR ""legislation""[Publication Type] OR ""letter""[Publication Type] OR ""news""[Publication Type] OR ""newspaper article""[Publication Type] OR ""patient education handout""[Publication Type] OR ""periodical index""[Publication Type] OR ""personal narratives""[Publication Type] OR ""pictorial works""[Publication Type] OR ""popular works""[Publication Type] OR ""portraits""[Publication Type] OR ""practice guideline""[Publication Type] OR ""technical report""[Publication Type] OR OR ""video audio media""[Publication Type] OR ""webcasts""[Publication Type])))))) NOT

Animals[Mesh:noexp])

Filters: Publication date from 1980/01/01; English; Spanish; French

Cochrane Library

"tuberculosis":ti,ab,kw AND "recurrence":ti,ab,kw or "relapse":ti,ab,kw or "reinfection":ti,ab,kw or "reactivation":ti,ab,kw

Filters: Publication date from 1980/01/01

Scielo

(ti:(tuberculosis) OR ab:(tuberculosis)) AND ((ti:(recurren$)or ab:(recurren$)) OR (ti:(reinfección)or ab:(reinfección)) OR (ab:(recaída) OR ti:(recaída)) OR (ti:(reactivación)or ab:(reactivación))

Lilacs

(tw:((tw:((tw:("tuberculosis")) AND (tw:(reinfección)) OR (tw:(recurren*)) OR (tw:(reactivación)) OR (tw:(recaída)) AND (db:("LILACS")))))) NOT (type_of_study:("case_reports")) AND (instance:"regional") AND (la:("es" OR "en"))

Appendix 2: Modified New Castle Ottawa Scale for risk of bias

First outcome: Incidence rate of recurrent TB

	Original scale	Modified scale	Rationale for changes
Selection			
1	Representativeness of the exposed cohort A. Truly representative **(one star)** B. Somewhat representative **(one star)** C. Selected group D. No description of the derivation of the cohort	Representativeness of the **successfully treated** TB patient population A. Truly representative General population **(one star)** B. Somewhat representative Population at probable higher risk of TB (ex. low socio-economic status, miners) **(one star)** C. Selected group (ex. only diabetic or HIV positive patients) D. No description of the derivation of the cohort	Our study question - the rate of recurrent TB- requires a representative population of persons who were successfully treated (either completing TB treatment or cured) and are at risk of relapse or reinfection. Selected populations are those at higher risk of reinfection or relapse, than the general population.
2	Selection of the non-exposed cohort A. Drawn from the same community as the exposed cohort (**one star**) B. Drawn from a different source C. No description of the derivation of the non-exposed cohort	Not applicable as our research question does not include a comparison group.	
3	Ascertainment of exposure A. Secure record (e.g., surgical record) (**one star**) B. Structured interview (**one star**) C. Written self-report D. No description E. Other	Ascertainment of cure A. Confirmed record of cure (smear negative at month 5) **(one star)** B. Confirmed record of treatment completion (the full regimen was completed) C. Unclear record of cure or treatment completion	We consider as “exposure”, “to be at risk of TB after a TB episode that has been cured or successfully treated”. We downgrade the quality for “successfully treated” as patients in this category may not have been cured, and subsequent active TB may actually be a late treatment failure, not a true relapse.

4	Demonstration that outcome of interest was not present at start of study A. Yes (**one star**) B. No	Redundant with item 3; not included	
Comparability			
1	A. Comparability of cohorts on the basis of the design or analysis controlled for confounders B. The study controls for age, sex and marital status (**one star**) C. Study controls for other factors (list) (**one star**) D. Cohorts are not comparable on the basis of the design or analysis controlled for confounders	Not applicable; not included	
Outcome			
1	Assessment of outcome A. Independent blind assessment (**one star**) B. Record linkage (**one star**) C. Self-report D. No description E. Other	Assessment of recurrent episodes A. The recurrent TB episode was defined in the methods as bacteriologically confirmed (**one star)** B. The recurrent TB episode was defined in the methods as bacteriological confirmed or clinical-radiological diagnosis C. The recurrent TB episode was self-reported D. No description	When the recurrent TB episode is bacteriologically confirmed, we can be confident the disease is active TB. Clinical radiological TB diagnoses are less accurate given possible post-TB lung conditions or physicians' inclination to re diagnose TB in case of recurrent chest symptoms
2	Was follow-up long enough for outcomes to occur A. Yes (**one star**) B. No Indicate the median duration of follow-up and a brief rationale for the assessment above:_____	Was follow-up long enough for outcomes to occur A. Yes ≥ 2 years (**one star**) B. No, < 2 years	We propose two years as the cutoff considering it covers the high risk period for relapse and allows sufficient time for reinfections to occur.

3	Adequacy of follow-up of cohorts A. Complete follow-up- all subject accounted for (**one star**) B. Subjects lost to follow-up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (**one star**) C. Follow-up rate less than 80% and no description of those lost D. No statement	No change for this item.	
Scale			
	Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain	Good quality: 2 stars in selection domain AND 3 in outcome domain Fair quality: 1 star in selection domain OR 2 in outcome domain Poor quality: If 0 stars in selection domain OR 0-1 in outcome domain	We adapted the scale in line with the modifications.

Second outcome: Proportion of reinfections and relapses

	Original scale	Modified scale	Rationale for changes
Selection			
1	Representativeness of the exposed cohort A. Truly representative (**one star**) B. Somewhat representative (**one star**) C. Selected group D. No description of the derivation of the cohort	Representativeness of the **successfully treated** TB patient population A. Truly representative: General population **(one star)** B. Somewhat representative: Population at probable higher risk of TB (ex. By socio-economical status, miners) **(one star)** C. Selected group (ex. only diabetic, HIV) D. No description of the derivation of the cohort	Same as for the first outcome.
2	Selection of the non-exposed cohort A. Drawn from the same community as the exposed cohort (**one star**) B. Drawn from a different source C. No description of the derivation of the non-exposed cohort	Not applicable; not included	
3	Ascertainment of exposure A. Secure record (e.g., surgical record) (**one star**) B. Structured interview (**one star**) C. Written self-report D. No description E. Other	Ascertainment of cure A. Confirmed record of cure (smear negative at month 5) **(one star)** B. Confirmed record of treatment completion (the full regimen was completed) C. Unclear record of cure or treatment completion	Same as for the first outcome
4	Demonstration that outcome of interest was not present at start of study A. Yes (**one star**)	Redundant; not included	

	B. No		
Comparability			
1	Comparability of cohorts on the basis of the design or analysis controlled for confounders A. The study controls for age, sex and marital status (**one star**) B. Study controls for other factors (list) (**one star**) C. Cohorts are not comparable on the basis of the design or analysis controlled for confounders	Not applicable; not included	
Outcome			
1	Assessment of outcome A. Independent blind assessment (**one star**) B. Record linkage (**one star**) Self report C. No description D. Other	Assessment of outcome A. The study use high discriminatory genotyping methods (WGS or MIRU - VNTR) (**one star**) B. The study combines more than 1 method for differentiating relapses and reinfections (**one star**) C. The study uses only one not high discriminatory method for differentiating relapses and reinfections (spoligotyping or RFLP)	The type of test used to discriminate reinfections from relapses is a key item for this outcome. Studies using high discriminatory methods will be less biased. However, the combination of tests can also provide high discriminatory power.

2	Was follow-up long enough for outcomes to occur? A. Yes (**one star**) B. No Indicate the median duration of follow-up and a brief rationale for the assessment above:_____	Was follow-up long enough for outcomes to occur? A. Yes ≥ 2 years (**one star**) B. No, < 2 years	Same as for the first outcome.
3	Adequacy of follow-up of cohorts A. Complete follow-up- all subject accounted for (**one star**) B. Subjects lost to follow-up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (**one star**) C. Follow-up rate less than 80% and no description of those lost D. No statement	% availability of DNA fingerprinting for classifying recurrent episodes as relapse or reinfection A. >88% (**one star**) B. ≤88%	We considered completeness of availability of DNA fingerprinting to be a key item for estimates of proportion of reinfections and relapses to be accurate. We established the cut-off point to separate the upper from the 2 lower tertiles of % fingerprinting availability.
Score			
	Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain	Good quality: 2 stars in selection AND 3 in outcome Fair quality: 1 star in selection OR 2 in outcome Poor quality: 0 stars in selection OR 0-1 in outcome	Same as for the first outcome.

Appendix 3 Calculation of person-years at risk of recurrent TB

Formula	**Data available**	**Total person-years at risk** of recurrent TB
F1	If incidence rate or Person-Years at risk available	Extracted as reported
F2	If mean follow-up duration for all patients was provided	$\#Successfully\ treated\ patients\ x\ Mean\ follow\ up\ duration\ (years)$
F3	if the mean follow up time is provided only for the patients not lost	$(\#Patients\ not\ lost\ x\ Mean\ follow\ up\ duration\ (years)) + 0.5\ (Planned\ follow\ up\ duration(years)\ x\ \#Patients\ lost$
F4	If mean time to recurrence was provided:	$(\#Recurrent\ patients\ x\ Mean\ time\ to\ recurrence(years)) + 0.5\ (Planned\ follow\ up\ duration(years)\ x\ \#Patients\ lost) + (Planned\ follow\ up\ duration(years)\ x\ \#\ Patients\ without\ recurrence)$
F5	If all the above was not possible	$(\#Patients\ successfully\ treated - 0.5\ x\ (\#Patients\ with\ recurrence + \#Patients\ lost))\ x(Planned\ follow\ up\ duration(years)$

Appendix 4 PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3

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Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4-5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5-6 Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment	6-7 Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2 Table 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies.	Figure
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-8

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17a

Appendix 5 Characteristics of included studies.

Authors	Study setting	Study population	Type of follow-up	Treatment regimen *	TB treatment delivery
Clinical trials					
Aung et al (2012)	Bangladesh	General population	Passive	(2-3)HRZE/$4H_3R_3$	Health facility DOTS
Balasubramaniam et al (1990)	Madras, India	General population	Active	3SRHZ, 3SRHZ/2HZ, 3SHZ/2HZ	Health facility DOTS
Castelo et al (1989)	Sao Paulo, Brazil	General population	Active	2HRZ then, randomly allocated to: 4HR or $4H_3R_2$	Self administered treatment
Chaulet et al (1995)	Algeria	General population	Active	Group S: 2HRZ 4HRZ Group C: 6HRZ	Health facility DOTS
Cohn et al (1990)	Denver, US	General population	Not specified	2HRZS/6HR	Health facility DOTS
Conradie et al (2020)	South Africa	XDR-TB	Non specified	(26weeks) BdqPtoLzd	Health facility DOTS
East African/BMRC (1980)	East Africa and Zambia	General population	Active	For 6 or 8 months 2SHRZ/TH, 1SHRZ/TH, 1SHRZ/S2H2Z2 2SHR/TH-t	Health facility DOTS
East African/BMRC (1981)	East Africa and Zambia	General population	Active	2SHRZ/(9w)HRZ, 2SHRZ/(9w)HR, 2SHRZ/(9w)HZ, 2SHRZ/(9w)H,SHRZ/(9w)H	Health facility DOTS
East and Central African/BMRC (1986)	Kenia, Zambia, Tanzania, Uganda	General population	Active	2SHRZ/4HR - 2SHRZ/4HZ - 2SHRZ/4H - 2SHRZ/6H	Health facility DOTS
El-Sadr et al (1998)	New York, US	HIV-1 infected patients	Active	Induction :2HRZE o 2HRZELfx Continuation: 4HR or 7HR	Health facility DOTS
Fitzgerald et al (2000)	Port au Prince, Haiti	General population	Passive	6 month therapy Initiation phase: HRZ and continuation phase (H_2R_2).	Not specified
Gengiah et al (2014)	South Africa	HIV-1 infected patients	Not specified	2HRZE4/HR in FDC	Health facility DOTS
Gonzalez-Montaner et al (1994)	Argentina, Brazil and Thailand	General population	Not specified	2HRZE/2HR Rifampicin or rifabutin	Health facility DOTS
Gopalan et al (2018)	Chennai, Vellore, and Madurai, south India	HIV-1 infected patients	Active	(1) $2EHRZ_7/4HR_7$; (2) $2EHRZ_7/4HR_3$; and (3) $2EHRZ_3/4HR_3$	Self administered treatment / DOTS
Hong et al (1988)	Seoul, Korea	retreatment	Active	(1) 12RE (2) $12R_3E_3$ (3) $3R_3E_3Z_3/9R_3E_3Z_3S_3$ (4)$3H_3R_3Pto_3/9R_3E_3$	Health facility DOTS
Hong Kong Chest Service (1982)	Hong Kong	General population	Active	6HRSZE3 / 6HRSZ3 / 6HRSE3 / 6HRZE3 / 6HRZE7	Health facility DOTS

Hong Kong Chest Service/BMRC (1991)	Hong Kong	General population	Not specified	2HRSZ/2HRS/2HR , 4HSZ/2HR, 4HRSZ/2HRZ , 6HRZ. Later part of intake, combined vs separate formulation.	Health facility DOTS
Jasmer Lorna et al (2004)	United States and Canada	General population	Active	Rifampin based treament for 6 months	Not specified
Jawahar et al (2013)	Chennai and Madurai, South India	General population	Active	2 $G_3H_3R_3Z_3$ / 2 $G_3H_3R_3$ 2 $M_3H_3R_3Z_3$ / 2 $M_3H_3R_3$ 2 $E_3H_3R_3Z_3$ /4 H_3R_3	Health facility DOTS
Johnson et al (2000)	Kampala Uganda	General population	Active	2HREZ/6HR	Not supervised ambulatory treatment
Johnson et al (2003)	Kampala Uganda	General population	Active	2HRZE/4HR + Interleukin-2	Not specified
Johnson et al (2009)	Kampala, Uganda, Vitória, Brazil; Makati City, Philippines.	General population	Active	2HRZE/2HR - 2HRZE/4HR	Health facility DOTS
Kennedy et al (1996)	Kilimanjaro, Tanzania	General population	Active	4HRCiprofloxacin/2HR 2HRZE/2HRZ/2HR	Health facility DOTS
Kenyan/Zambian/BMRC (1989)	Kenia-Zambia	General population	Not specified	2SHRZ/4TH + Levamisole	Self administered treatment / DOTS
Kohno et al (1992)	Nagasaki	General population	Active	9 months of daily ofloxacin (2 possible doses) or E plusR and H.	Health facility DOTS
Lee et al (2012)	Seoul, South Korea	XDR	Active	Linezolid therapy that started immediately or after 2 months, at a dose of 600 mg per day, without a change in their background regimen.	Health facility DOTS
Madras/BMRC (1989)	Hong Kong	Smear negative	Not specified	Culture positive: 4SHRZ or $4S_3H_3R_3Z_3$ or $6S_3H_3R_3Z_3$. Cultures negative 3SHRZ or $3S_3H_3R_3Z_3$ or $4S_3H_3R_3Z_3$.	Health facility DOTS
Maug et al (2020)	Bangladesh	Smear positive	Active	2EHRZ/4HR y dosis doble Rifampin 2EHRZ/4HR	Health facility DOTS
Merle et al (2014)	Cotonou, Benin; Conakry, Guinea; Nairobi, Kenya; Dakar, Senegal; Durban, South Africa.	General population	Active	Control: 2HRZE 4HR Experimental: 2HRZG 2HRG	Not specified
Mohanty et al (1993)	India	General population	Not specified	2SHRZ/4HR , 2SHZCipro/4HCipro	Not specified
Narayanan et al (2007)	Chennai, India	General population	Active	2HRZE3/6HE	Self administered treatment / DOTS

Parthasarathy et al (1991)	Madras and Bangalore, India	General population	Active	R3: 3HRZS R5: 3HRZS/$5S_2H_2Z_2$ R6: 3HZS/$5S_2H_2Z_2$	Health facility DOTS
Perriens et al (1995)	Kinshasa, DRC	General population	Passive	2HRZ4HR In some HIV positive, the treatment was extended	Not specified
Singapore/BMRC (1981)	Singapore, Chinese, Malay and Indian	General population	Active	2SHRZ/2 or 4 HRZ or 2SHRZ/2 or 4 HR	Health facility DOTS
Singapore/BMRC (1988)	Singapore	General population	Active	(1) 2SHRZ/$4H_3R_3$ (2) 1SHRZ/$5H_3R_3$ (3) 2HRZ/$4H_3R_3$	Health facility DOTS
Singapore/BMRC (1991)	Singapore	General population	Active	Initial phase: (1) 2SHRZ (2) 1SHRZ (3) 2HRZ Continuation phase: 6HR3	Health facility DOTS
Snider et al (1984)	Poland	General population	Not specified	(1) 2HRZ/4H2R2 (2) 2HRZS/4H2R2	Health facility DOTS
Somner et al (1990)	Britain	General population	Not specified	1) 2HRSE/(4-10)HR 2) 2HRSE/(7-16)HR	Not specified
Su et al (2001)	Taipei, Taiwan	General population	Active	(1) 2Rifater+E/Rifinah+E (2) 2HRZE/4HR	Self administered treatment
Swai et al (1988)	Kenya	Isoniazid resistant TB patients	Active	2SZRE/4RE or 2SZRE/7RE	Community DOTS
Tam et al (2002)	Hong Kong	General population	Not specified	2HRZS/HR_3 2HRZS/HRp_1 2HRZS/HRp_1.2/3	Health facility DOTS
Tanzania/BMRC (1985)	Africa	General population	Active	2 SHRZ/4TH /// 2SHRZ/4H	Health facility DOTS
Teo et al (1999)	Singapore	General population	Active	2SHRZ/4H(3)R(3) /// 1SHRZ/5H(3)R(3) /// 2HRZ/4H(3)R(3)	Health facility DOTS
Tuberculosis Research Centre (1981)	Madras, India	General population	Passive	2 weeks EHS plus → EH or E_2H_2 or E_1H_2 or E_1H_1	
Tuberculosis Research Centre (1997)	Madurai, South India	General population	Not specified	(1) 2HRZE/6EH (2) 2$E_2H_2R_2Z_2$/4EHR (3) 2$H_2R_2Z_2$/4H_2R_2	Self administered treatment / DOTS
Velayutham et al (2020)	Chennai, Madurai and Vellore in South India.	General population	Non specified	3MfxHRZE / 2MfxHRZE/2Mfx3H3R3 / 2HRZE/4HR	Health facility DOTS
Wu et al (2015)	Taiwan	General population	Active	The FDC group received Rifaters and E for the first two months, followed by Rifinahs (H + R) and E for an additional four months or longer. Theseparate formulation (SF) group received 2HRZE4HRE.	Health facility DOTS

Yan et al (2018)	China	Retreatment patients	Active	2HREZS/ 6HRE - 5MxfPARfbEZ	Health facility DOTS
Zierski et al (1981)	Poland	General population	Not specified	Regimen A (6 HRE) Regimen B (2 HRElHR) Regimen C (2 HRE/lHRE) Regimen D (2 HRE/lHRE)	Not specified
Observational prospective studies					
Anaam et al (2012)	Yemen	General population	Passive	4HRZE/6HE	Health facility DOTS
Anaam et al (2019)	Yemen	General population	Active	2HRZE/6HR	DOTS Comunitario
Anh et al (2020)	Vietnam	MDR	Active	(4-6)LfxKmCfzPtoEHZ/5LfxCfzEZ	Not specified
Aung et al (2014)	Bangladesh	MDR	Active	FX, E, Z, and clofazimine throughout, supplemented during the minimum 4-month intensive phase by kanamicin, prothionamide, and H.	Health facility DOTS
Banda et al (2000)	Southern Region of Malawi	Smear negative	Active	2ERHZ/6EH	Health facility DOTS
Becerra et al (2010)	Lima, Peru	MDR TB patients	Active	MDR-TB regimen	Health facility DOTS
Bechan et al (1997)	Durban, South Africa	General population	Not specified	(26weeks) H2R2Z2S2	Health facility DOTS
Cao et al (1988)	China	General population	Active	2H3R3Z3S3/4H3R3, 2H3R3Z3E3S3/6H3R3E3	Health facility DOTS
Chaisson et al (1996)	Cité Soleil, Haiti	General population	Pasive	(8weeks)HRZE/(18weeks)HR	Health facility DOTS
Chang et al (2004)	Hong Kong	General population	Pasive	2HRZ/4HR 2RZE/4RE	Health facility DOTS
Charalambous et al (2008)	Free State Province, South Africa	South African gold miners	Active	Rifampin based short-course chemotherapy regimen(not specified)	Facility based DOTS
Chien et al (2014)	Taiwan	Isoniazid resistant TB patients	Passive	2HRZE/4HR	Health facility DOTS
Choi et al (2014)	South Korea	General population	Active	Not specified. 9-month treatment for susceptible TB, indivual regimen for resistant patients.	Not specified
Connolly et al (1999)	KwaZulu-Natal, South Africa	General population	Passive and Active	HRZE given in hospital (median 17 days), followed by 2H2R2Z2E2 to 6H2R2	Health facility DOTS and community based DOTS
Cowie et al (1989)	South Africa	Gold miners	active	Variable. Rifampin based regimens	Health facility DOTS

Crampin et al (2010)	Karonga, Malawi	General population	Active	Smear-positive patients: Prior to 1997: 2SHRZ/6TH. 1997-2001: 2SHRZ/6EH After 2001: 2SHRZ/6SH. Smear-negative patients: Prior to 1997: 1SHT/11TH. 1997-2001: 1SHE/11EH. After 2001: 2HRZ/6EH	Not specified
d'Arc et al (2008)	Recife, Brazil	General population	Passive	2HRZ/4HR	Not specified
Dutt et al (1984)	Arkansas, US	General population	Active	1HR/8H3R2	Self administered treatment /DOTS
Dutt et al (1990)	Arkansas, US	General population	Pasive	1HR(Rifamate)/5HR	Self administered treatment /DOTS
Escudero et al (2006)	Hospital La Fuenfría, Madrid, Spain	MDR	Active	Empirical treatment based on prior treatment. One parenteral drug plus at least three oral drugs. "The parenteral drug was used during the first 6 months, as follows: 5 days a week for 2 months, 3 days a week for the next 2 months and 2 days a week for the last 2 months. Definitive therapeutic regimens were determined according to the DST results. The planned treatment duration was 18 months, or 12 months of continual negative cultures after the first two negative cultures."	Not specified
Fox et al (2018)	Vietnam	General population	Mixed	2HRZE/4HR	Health facility DOTS
Garcia Martinez et al (1996)	North-western region of Leon-Chinandega, Nicaragua	General population	Active	2SRHZ/ 6TH (157 patients) 2STH/10TH (90 patients)	Health facility DOTS
Guerra-Assunção et al (2015)	Karonga, Malawi	General population	Active	1996-2001 New smear-positive patients: 2SHRZ/6HE. New smear-negative patients:1SEH/11HE 2001-2007: 2HRZE/6HE After 2007: 2HRZE/4HR	Not specified
Hang et al (2015)	Hanoi, Vietnam	General population		2S(E)HRZ/6HE	Health facility DOTS
Hawken et al (1993)	Nairobi, Kenya	HIV-1 infected patients	Active	1TSH11TH 1TSH11TH + Another antituberculosis drug. 1HRZS 1HRZ 4TH	Not specified
Hesseling et al (2010)	Western Cape Province, South Africa	Non HIV-infected patients	Active	2RHZE/4HR	Facility based DOTS

				*The intensive phase was prolonged to 3 months if smear conversion had not occurred at 2 months	
Houben et al (2012)	Karonga, Malawi	HIV-patients	Active	Smear positive before 1997: 2SHRZ/6TH From 2001: 2EHRZ/6EH Smear negative before 1997: 1SHT/11TH From 2001: 1SHE/11HE Since 2007: 2HRZE/4HR	Not specified
Huyen et al (2013)	Mekong River Delta, Vietnam	General population	Active	2HRSZ/6HE	Not specified
Jasmer et al (2004)	San Francisco, US	General population	Passive	6 months of standard therapy	Health facility DOTS / Self administered treatment
Jimenez Corona et al (2013)	Orizaba, Veracruz, Mexico	General population	Active	1995 and 1998 New cases: 2HRZ/4HR Retreatment cases: 2HRZ/4HR plus E or S. After 1998 New cases: 2HRZE/4HR Retreatment cases: 2HRZES(/1HRZE/5HRE.RZE/5HRE.	Community based DOTS
Karagaoz et al (2009)	Istambul, Turkey	MDR	Not specified	"Second-line drugs, occasionally, an aminoglycoside (amikacin, capreomycin), a quinolone derivative (ofloxacin, ciprofloxacin), prothionamide and cycloserine were used in treatment of MDR- TB patients and some of the first line drugs, such as Z and E, thought to be susceptible, were included in the new regimen. If quinolone derivatives and prothionamide had already been used in previous regimen, drugs such as clofazimine, para-aminosalycylic acid (PAS), T, amoxicillin-clavulanic acid and capreomycin were included in the regimen."	Health facility DOTS
Kassim et al (1995)	Abidjan, Nigeria	General population	Active	2HRZ4HR	Self administered treatment
Kuaban et al (2015)	Cameroon	MDR	Active	4KmPtoCfzHEZ/8HKm	Health facility DOTS
Lawal et al (2019)	South africa	General population	Active	Standard regimen	Not specified
Lee et al (2014)	Taiwan	Diabetes	Passive	Standard regimen	Health facility DOTS
Lee et al (2020)	Seoul, South Korea	Cavitary tuberculosis	Active	2HRZE/4HRor 2HRZE/ 7HR	Not specified

Malherbe et al (2020)	Cape Town, South Africa	General population	Active	Standard regimen	Not specified
Mathur et al (2020)	Hyderabad, Telangana, India	Smear positive pulmonary TB patients	Active	Standard regimen	Not specified
McGreevy et al (2012)	Post-au-Prince, Haiti	HIV-1 infected recurrent TB patients		2HRZES/1HRZE/5HRE	Not specified
Miles et al (1984)	Nong Samet, Cambodia	Refugees	Active	2HRSZ/4HR	Health facility DOTS
Narayanan et al (2010)	Chennai and Madurai, India	HIV-infected patients	Active	HIV-infected patients received 2H3R3Z3E3/4-7R3H3. Some HIV-negative patients were treated with the same regimen of 2HRZE/4R3H3 whereas, others, received a regimen containing 3HRZOfloxacin/1 or 2 H3R3	Facility based DOTS
Nolan et al (2002)	Seatle, US	isoniazid-resistant tuberculosis	Pasive	6HREZ	Self administered treatment / DOTS
Palmero et al (2004)	Buenos Aires, Argentina	MDR	Active	Individual regimens: E, Z, S and/or second line drugs	Self administered treatment / DOTS
Pandey et al (2020)	India	General population	Active	2HRZE/4HR	Health facility DOTS
Peetluk et al (2019)	Brazil	General population	Active	2HRZE/4HR	Health facility DOTS
Perez-Guzman et al (2002)	Mexico	Drug resistant	Active	Treatment according DST rsults	Self administered treatment
Perriens et al (1991)	DRC		Pasive	2HST/10TS	Not specified
Pettit et al (2011)	Tennesee, US	General population	Passive	"National and international guidelines for treatment of drug-susceptible TB recommend a 6-month rifamycin-based regimen. In USA treatment is extended to 9 months in patients with cavitary pulmonary TB and a positive sputum culture after 2 months or silico tuberculosis."	Facility based DOTS
Piubello et al (2014)	Niamey, Niger.	MDR	Active	4GfxCfzEZKmPtoH/8GfxCfzEZ	Health facility DOTS
Prasad et al (2004)	Uttar Padresh, India	MDR	Active	Kanamycin (initial 4-6 months), ethionamide, H, PAS and cycloserine for a minimum period of two years.	Health facility DOTS

Prasad et al (2008)	India	General population	Active	Cat I, Cat II, Cat III	Health facility DOTS
Pulido et al (1997)	Madrid, Spain	HIV-patients	Passive	Regimen that include H a R for 6 or more months supplemented with Z,E,S or combination for the first 2 months.	Not specified
Reis et al (1990)	Brazil	Pediatric population	Active	6HR	Not specified
Schwœbel et al (2020)	Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Niger and Rwanda.	General population	Active	4-6Knm,Cfz,Mfx,HZPto/5MfxZCfz	Health facility DOTS
Shen et al (2017)	Shanghai, China	General population	Passive	Standard regimen	Not specified
Sonnenberg et al (2001)	Gauteng, South Province, South Africa	South African mineworkers	Active	At least 6 months of 2HRZE/4HR.	Health facility DOTS
Spagnolo et al (1982)	US	General population	Not specified	2HRE/7HR	Self administered treatment
Suryanto et al (2008)	South Sulawesi Province, Republic of Indonesia	General population	Active	2HRZE/3H3R3 4FDC (225 mg INH, 450 mg RMP, 1200 mg PZA and 825 mg EMB.) was used and 2FDC (450 mg INH and 450 mg RMP)	Health facility DOTS
Swaminathan et al (2008)	Tambaram, Chennai	HIV-patients	Active	2EHRZ3/4RH3	DOTS comunity
Thomas et al (2005)	Tamil Nadu, India	General population	Active	2H3R3Z3E3/4H3R3	Health facility DOTS
Thomas et al (2019)	Chennai and Pune, India	General population	Active	(1) daily (daily in both intensive and continuation phases)—2EHRZ7/4HR7; (2) part-daily (daily intensive phase and intermittent continuation phase)— 2EHRZ7 /4HR3 ; and (3) intermittent (thrice weekly throughout)—2EHRZ3/4HR3	Health facility DOTS
Van Deun et al (2004)	Bangladesh, India	MDR-TB infected patients	Passive	New cases received 2HRZE/6HT. Retreatment cases received 2SEHRZ/1EHRZ/5EHR.	Health facility DOTS
Van Deun et al (2010)	Bangladesh	MDR	Active	"All regimens were based on a fluoroquinolone (ofloxacin or, in regimen 6, gatifloxacin), kanamycin, and prothionamide as the core drugs, supplemented by other potentially active	Health facility DOTS

				companion drugs (first-line drugs and clofazimine)."	
Velayutham et al (2018)	Tamil Nadu, Karnataka, Delhi, Maharashtra, Madhya Pradesh and Kerala, India	General population	Active	(2 H3R3Z3E3 / 4H3R3)	Health facility DOTS
Vree et al (2007)	Northern Vietnam	General population	Active	The standard treatment regimen for new patients consists of daily 2SHRZ/6HE).	Health facility DOTS
Westerlund et al (2015)	Lima, Peru	General population	Active	Standard regimen	Not specified
Yoshiyama et al (2010)	Khatmandu Valley, Nepal	Retreatment patients	Active	2HRZSE/1HRZE/5HRE	Health facility DOTS
Zheng et al (2020)	China	General population		Standard regimen	Health facility DOTS
Observational retrospective studies					
Banu et al (2012)	Chennai, India	General population	Active	(2 H3R3Z3E3 / 4H3R3)	Health facility DOTS
Chiang et al (2006)	Taipei, Taiwan	MDR TB patients	Active	Individualized MDR TB 1	Self administered treatment
Ciza et al (2020)	Burundi	Rifampicine resistance	Pasive	(4-5)KmMfxPtoCfHZE/5MfxCfzZE	Health facility DOTS
Dale et al (2017)	Victoria, Australia	General population	Passive	6-month standard regimen	Self administered treatment
Dangisso et al (2018)	Dale and Yirgalem, Ethiopia	Smear positive	Active	Standard regimen	Not specified
Datiko et al (2009)	Dale and Wonsho, Sidama, Ethiopia	General population	Active	Standard regimen	Health facility DOTS
Decro et al (2020)	Bangladesh	RR TB patients	Passive	2KmCfxGfxEHPZ / 5 GfxEZCfz (Gfx and H in high dose regimen)	Not specified
Gelmanova et al (2015)	Tomsk, Russian Federation	MDR TB patients	Passive	All patients were treated with regimens that included second-line drugs, fluoroquinolones and parenteral agents (not specified)	Not specified
Glynn et al (2010)	Gauteng, South Africa	Miners	Passive	2HRZE 4HR 2HRZES, 1HRZE, and 5HRE	Health facility DOTS
Guglielmetti et al (2016)	Bligny, Pitié Salpêtrière and Bichat Hospitals, France	MDR	Passive	According to patient include bedaquiline	Not specified
He et al (2010)	Heilongjiang, China	MDR	Passive	Second line treatment	Health facility DOTS

Jo et al (2014)	Seoul, South Korea	General population	Passive	2HRZE/4HRE	Self administered treatment
Kim et al (2017)	South Korea	General population	Not specified	Culture positive: 4SHRZ or 4S3H3R3Z3 or 6S3H3R3Z3 . Cultures negative 3SHRZ or 3S3H3R3Z3 or 4S3H3R3Z3.	Health facility DOTS
Lee et al (2011)	Seoul, South Korea	MDR TB patients	Not specified	Drug resistant TB regimen	Not specified
Lee et al (2015)	Seoul, South Korea	H resistant TB patients	Passive	Drug resistant TB regimen	Not specified
Liu et al (2020)	Beijing	General population	Pasive	WHO recommendation	Health facility DOTS
Luzze et al (2013)	Kampala, Uganda	General population	Active	94%: 2HRZE/4-6RZ 2HRZE/6EZ	Not specified
Ma et al (2018)	Beijing Chest Hospital, , Shenyang Chest Hospital	Diabetes Mellitus 2	Passive	2HREZS/6HRE	Not specified
Marx et al (2014) / Dippenar et al (2019)	Cape Town, South Africa	General population	Active	Standard first-line treatment	Facility based DOTS
Migliori et al (2002)	Ivanovo Oblast, Russsian Federation	MDR TB patients	Passive	Cat-I, Cat-II, Cat-III	Not specified
Moosazadeh et al (2015)	Iran	General population	Passive	Standard regimen	Not specified
Moreno-Martinez et al (2007)	Región Soconusco, Chiapas, México	General population	Passive	Not specified	Not specified
Nahid et al (2007)	San Francisco, US	HIV-1 infected patients	Passive	Rifamyicin based 6 month regimen. 32 patients on ARV took rifabutin	Facility based DOTS
Nettles et al (2004)	Baltimore, US	General population	Passive	" Al patients were treated with 15 daily doses of 4-drug therapy (H, R or rifabutin, Z, and E in standard doses. Patients subsequently received twice-weekly- 4-drug therapy for 6 weeks, followed by a course of twice-weekly I and R or rifabutin".	Facility based DOTS
Ormerod et al (2002)	Blackburn, Hyndburn and Ribble Valley districts, UK	General population	Passive	2RHZ(E)/4RH	Not specified
Park et al (2019)	South Korea	Rheumatological disease patients		2HRZE/4HR	Not specified
Picon et al (2007)	Rio Grande do Sul, Porto Alegre, Brazil	General population	Passive	2HRZ/4HR Other regimens used, R always included.	Self administered treatment

Piubello et al (2020)	Niamey, Maradi and Zinder; Niger	RR/MDR patients	Active	MDR TB regimen	Health facility DOTS
Seon et al (2014)	Republic of Korea	General population	Active	2HRZE/7HRE	Not specified
Shin et al (2006)	Peru	MDR	Mixed	"Regimens generally included at least 5 drugs to which the infecting isolate was susceptible, and treatment duration was 18–24 months."	Not specified
Slutkin et al (1988)	San Francisco	General population	Passive	Treatment regimen was 3HRE/6HR.	Health facility DOTS
Sun et al (2017)	Henan Province, China	General population	Active	2HRZE4HR Retreatment: 2HRZE/6HRE	Health facility DOTS
Van der Heijden et al (2018)	Durban, South Africa	General population	Passive	New drug-susceptible TB patients received 2HREZ/4HR.	Not specified
Van Deun et al (2006)	Bangladesh	General population	Passive	2EHRZ/6HT control 3EHRZ/6HT extension group	Not specified
Vieira et al (2017)	Carapicuiba, Sao Paulo Brazil	General population	Passive	Standard treatment	Health facility DOTS
Wang et al (2015)	Taiwan	HIV-patients	Active	2HRZE/6HR	Health facility DOTS
Wu et al (2015)	Changning, Shanghai, China	General population	Passive	2HRZE(S)/4HR	Not specified
Xia et al (2014)	Beijing, China	General population	Passive	2H3R3Z3E3/4H3R3 or 2HRZE/4HR	Health facility DOTS
Yen et al (2014)	Taipe, Taiwan	General population	Passive	WHO recommended treatment	Health facility DOTS
Yoshiyama et al (2014)	Fukujuji Hospital, Japan	MDR TB patients	Passive	E, Z, Cm (until 1995) or aminoglycoside, fluoroquinolone (Ofx in 1990s and Gfx or Lfx in the 2000s), Eto, Cs, an PAS. The minimum duration of treatment was 2 years	Not specified
Zhdanov et al (2017)	Israel	General population	Passive	Standard treatment	Health facility DOTS
TB program databases					
Bandera et al (2001)	Lombardy region, Milan, Italy	General population	Passive	6 months of combination therapy (not specified)	Not specified
Cacho et al (2007)	Madrid, Spain	General population	Passive	2HRZ/4HZ or 2HRZE / 4HR	Not specified
Caminero et al (2001)	Gran Canaria, Spain	General population	Active	2HRZ/4HR	Facility based DOTS
Das et al (1995)	Madras India	General population	Unknown	Not specified	Not specified

Das et al (1993)	Madras India	General population	Unknown	Not specified	Not specified
Dobler et al (2009)	New South Wales, Australia	General population	Passive	Drug-sensitive TB: 2HRZE/4HR MDR TB: Second line TB drugs for 1 or 2 years	Facility based DOTS
ElSahly et al (2004)	Houston and Harris County, Texas, US	General population	Active	Not specified	Community based DOTS
Folkvardsen et al (2020)	Denmark	Patients infected with DKC2 strain	Not specified	Not specified	Not specified
Lourenco et al (2000)	Rio de Janeiro, Brasil	HIV-infected patients	Passive	2HRZE/7HR	Not specified
Parvaresh et al (2018)	New South Wales	General population	Passive	Not specified	Health facility DOTS
Quy et al (2002) / Lan et al (2003)	Ho Chi Min, Vietnam	General population	Not specified	2SRHZ/6HE	Facility based DOTS
Rosser et al (2018)	Lecistershire and Rutland, UK	General population	Not specified	2EHRZ3/4RH3	Not specified
Schiroli et al (2015)	Lombardy region, Milan, Italy	General population	Passive	Not specified	Not specified
Shamputa et al (2007)	Bangladesh	General population	Passive	New smear-positive cases received a daily Category I: 2HRZE/6HT. Retreatment patients were treated with Category II: 2SHREZ/1HREZ/5H3R3E3	Not specified
Shen et al (2006)	Shanghai, China	General population	Active	Not specified	Community DOTS
Umubyeyi et al (2007)	Rwanda	General population	Active	New smear-positive cases received standard Category I regimen, consisting of 2HRZE/4H3R3. Retreatment patients with at least one month of a drug intake were treated with Category II 2HRZES/1ZE/5H3R3E3	Not specified
VanRie et al (1999)	Cape Town, South Africa	General population	Passive	New cases were treated with H, ryfampin, and Z for 6 to 8 months, while retreatment patients received a four-drugs regimen.	Health facility DOTS

*The number before the acronym represents the number of months. The subscript represents the weekly dose, if none, it is taken daily, H=isoniazid, R=rifampicin, Z=pyrazinamide, E=Ethambutol, S=Streptomycin, TH=Thiacetazone, Bdq=Bedaquiline, Pto=pretomonid Lnz=linezolid, Mfx=Moxifloxacin, Cfz=clofazimine, Km=kanamycin, Ofx=ofloxacin, Lfx=levofloxacin, Cs=cycloserine, Eto=ethionamide, Gfx=Gatifloxacin, PAS =*p-aminosalicylic acid*

Appendix 6. Individual data of included studies

Table S1 Individual outcomes of cohort studies and clinical trials included in the review and calculation of person-years of follow up

	Extracted by study											Calculated			WHO estimates
Author	Nº of patients successfully treated (denominator)	Nº of TB recurrent episodes (numerator)	Death	Moved	Other	Loss to follow up	Total censored	Planned follow-up (years, unless specified)	Person years of follow up	Mean follow-up (years)	Mean time to recurrence (years)	Total person yearsears calculated	Recurrent TB incidence calculated (per 100 pyear)	Formula used *	Background incidence per 100,000 pop
Clinical trials															
Castelo et al (1989)	506	27	-	-	-	-	0	1	-	-	-	4923	5.48	F5	62.3
Chaulet et al (1995)	228	1	-	-	-	21	21	2	-	2.00	-	435	0.23	F3	49.0
Cohn et al (1990)	108	2	7	-	-	-	7	3	-	-	2.58	313	0.64	F4	9.2
East African/BMRC (1980)	737	57	45	-	15	45	105	2	-	-	-	1312	4.34	F5	103.1
East African/BMRC (1981)	551	131	6	-	3	31	40	1.2	-	-	-	543	24.12	F5	212.0
Fitzgerald et al (2000)	274	15	-	-	-	-	0	-	542	-	-	542	2.77	F1	123.9
Gengiah et al (2014)	51.00	8	-	8	-	-	-	-	113	-	1.75	113	7.07	F1	820.0
Gonzalez-Montaner et al (1994)	467	5	-	-	-	116	116	2	-	-	-	813	0.62	F5	39.9/48.2/82.3
Gopalan et al (2018)	241	16	-	-	-	14.00	14	1	225	-	-	225	7.12	F1	234.0
Hong et al (1988)	352	44	-	-	-	192	192	2	-	-	-	468	9.40	F5	254.7
Hong Kong Chest Service (1982)	792	22	18	-	3	20	41	1.5	-	-	-	1141	1.93	F5	150.3
Hong Kong Chest Service/BMRC (1991)	888	34	11	12	6	27	56	2.5	-	-	-	2108	1.61	F5	145.4
Jasmer Lorna et al (2004)	1229	81	-	-	-	-	0	2	-	-	-	2377	3.41	F5	6.7
Jawahar et al (2013)	380	40	-	-	-	-	0	2	-	-	-	720	5.56	F5	279.0
Johnson et al (2000)	225	18					87	2	335			335	5.36	F5	117.0
Johnson et al (2009)	388	18	4			2	6	2	-	-	5.00	824	0.35	F4	274.0
Johnson et al (2003)	95	2	-	-	-	-	0	6	-	-	-	564	2.18	F5	248.0
Kennedy et al (1996)	168	7	2	10			12	0.5	-	-	-	79	8.83	F5	95.7

Kenyan/Zambian/BMRC (1989)	502	30	3	-	1	42	46	2	-	-	-	928	3.23	F5	128.5
Kohno et al (1992)	92	0	-	-	-	16	16	2	-	-	-	168	0.00	F5	46.3
Lee et al (2012)	13	0	-	-	-	-	0	1	-	-	-	13	0.00	F5	94.0
Madras/BMRC (1989)	1620	82	19	76	2	21	118	4.5	-	-	-	6840	1.20	F5	150.2
Merle et al (2014)	1356	148	37	-	20	172	229	2.0	-	-	-	2335	6.34	F5	820.0
Mohanty et al (1993)	35	4	-	-	-	-	0	24	-	-	-	792	6.06	F5	120.0
Narayanan et al (2007)	413	20	-	-	-	-	0	2	-	-	-	806	2.48	F1	289.0
Parthasarathy et al (1991)	688	85	7	22	4	-	33	24 months after treatment start	-	-	-	1046	8.13	F5	152.2
Perriens et al (1995)	420	19	37	-	-	117	154	1.5	-	-	-	501	3.80	F5	91
Singapore/BMRC (1988)	350	11	13	2	3	4	22	2	-	-	-	667	1.65	F5	72.1
Singapore/BMRC (1991)	287	10	5	1	-	-	6	1.5	-	-	-	419	2.39	F5	98.5
Snider et al (1984)	272	5	-	-	-	-	0	2	-	-	-	539	0.93	F5	61
Su et al (2001)	51	1	-	-	-	-	0	2	-	-	-	101	0.99	F5	33.7
Swai et al (1988)	224	8	7	-	-	39	46	2	-	-	-	394	2.03	F5	33.00
Tam et al (2002)	534	46	6	-	-	-	6	4.5	-	-	-	2286	2.01	F5	109.3
Tanzania/BMRC (1985)	224	14	2	-	-	17	19	2	-	-	-	415	3.37	F5	62
Teo et al (1999)	271	14	14	-	-	10	24	5	-	-	-	1260	1.11	F5	76.3
Tuberculosis Research Centre (1981)	172	52	-	-	-	-	0	4	-	-	-	584	8.90	F5	300.0
Tuberculosis Research Centre (1997)	787	65	1	-	-	3	4	2	-	-	-	1505	4.32	F5	117.6
Wu et al (2015)	98	0	-	-	-		0	1	-	-	-	98	0.00	F5	82.0
Yan et al (2018)	661	51	-	-	-	215	215	5	-	-	-	2640	1.93	F5	73.0
Zierski et al (1981)	363	54	13	-	-	33	46	2.5	-	-	-	783	6.90	F5	451.0
Conradie et al (2020)	100	2	1		1	1	3	0.5				48.75	4.10	F5	146.00
Maug et al (2020)	638	5				38	38	1				616.50	0.81	F5	221.00
Velayutham et al (2020)	1180	84					0	2				2276.00	3.69	F5	234.00
Cohort studies															
Anaam et al (2012)	814	44	16	-	-	24	40	1	-	-	0.55	774	5.68	F5	25
Aung et al (2014)	435	6	-	-	-	-	0	2	-	-	-	864	0.69	F3	221
Banu et al (2012)	238	14	-	-	-	-	0	2	-	-	-	462	3.03	F4	234
Becerra et al (2010)	442	16	85	-	-	40	125	2.0	646		0.53	646	2.48	F5	183.00
Bechan et al (1997)	348	18		33	-	-	33	-		1.75	1.03	621	2.90	F5	212.7
Cao et al (1988)	649	28	39	1	-	-	40	2	-	-	-	1230	2.28	F1	29.5
Chaisson et al (1996)	341	13	-	-	-	-	0	3.5	-	-	-	1157	1.12	F1	145.1
Chang et al (2004)	12183	113	-	-	-	-	-	2.0	-	-	8.90	25146	0.45	F5	36.4
Charalambous et al (2008)	609	42	-	-	-	-	0	31 -Mar-2002	7096	1.02	-	7096	0.59	F1	585.00

Chiang et al (2006)	153	10	-	-	-	-	0	6	493	-	-	494	2.02	F5	8.70
Chien et al (2014)	328	4	-	-	-	-	-	2	-	-	-	652	0.61	F5	85.00
Choi et al (2014)	289	17	20	-	-	11	31	3.3	-	0.83	-	869	1.96	F5	88
Connolly et al (1999)	403	19	58	78	-	-	136	-	499	1.20	-	499	3.81	F5	323
Cowie et al (1989)	2776	378	-	-	-	-	0	3	5442	-	-	5442	6.95	F5	175.4
Crampin et al (2010)	584	53	-	-	-	-	0	10.8	1646	-	-	1646	3.22	F5	392.00
d'Arc et al (2008)	754	37	43	-	-	-	43	5.0	-	-	-	3570	1.04	F4	104
Dale et al (2017)	3885	20	-	-	-	-	0	31/Dec/ 2014	-	5.70	2.66	2227	0.90	F5	6.5
Dangisso et al (2018)	1688	101	-	-	-	-	0	-	-	-	-	6645	1.52	F5	310
Datiko et al (2009)	368	15	-	-	-	-	0	-	1463	3.87	-	1463	1.03	F5	168
Dobler et al (2009)	3731	15	-	-	-	-	0	31/Dec/ 2006	-	5.70	1.42	2122	0.71	F5	6.3
Picon et al (2007)	610	26	-	-	-	-	0	-	-	7.70	-	5200	0.50	F5	45
Dutt et al (1984)	751	15	105	45	-	-	150	7	-		-	4680	0.32	F5	11.8
Dutt et al (1990)	211	5	34	6	-	-	40	2	401	3.75	-	401	1.25	F5	11.8
Escudero et al (2006)	21	0	-	-	-	-	0	2	-	-	-	42	0.00	F5	23
Fox et al (2018)	9825	498	198	-	-	-	198	2	-	-	-	18954	2.63	F1	133
Garcia Martinez et al (1996)	204	3	5	-	-	10	15	17-32 months	388	-	2.05	388	0.77	F5	84.00
Gelmanova et al (2015)	399	27	30	20	41	15	106	6	1320	3.53	-	1321	2.04	F5	80.2
Glynn et al (2010)	646	164	-	-	-	-	0	31-Dec- 2004	1408	-	-	1408	11.65	F5	245.4
Guerra-Assunção et al (2015)	1471	139	-	-	-	64	64	-	6306	-	-	6306	2.20	F5	153
Guglielmetti et al (2016)	36	0	-	-	-	13	13	2	-	-	-	59	0.00	F5	9
Hang et al (2015)	413	30	-	-	-	10	10	1.3	-	1.33	0.38	544	5.52	F5	164.00
Hawken et al (1993)	196	11	12	-	19	-	31	-	2598	1.25	8.00	2598	0.42	F5	72.3
He et al (2010)	194	63	12	56	7	20	95	4	-	4.00	-	586	10.75	F5	94
Hesseling et al (2010)	211	22	5	10	-	21	36	2.0	-	-	-	364	6.04	F5	841
Houben et al (2012)	1133	103	309	-	-	105	414	30-Jun-2011	4353	-	-	4353	2.37	F5	75
Huyen et al (2013)	1073	35	20	-	-	5	25	1.5	1658	1.53	-	1658	2.11	F5	172
Jasmer et al (2004)	305	3	-	-	-	36	36	1	-	-	-	286	1.05	F5	5.7
Jimenez Corona et al (2013)	1019	74	-	-	-	-	0		-	5.14	-	5238	1.41	F5	21
Jo et al (2014)	317	6	-	-	-	-	0	1	-	-	0.30	313	1.92	F5	85
Karagaoz et al (2009)	102	0	-	-	-	13	13	2	-	1.60	-	191	0.00	F5	33
Kassim et al (1995)	523	20	-	-	-		0	1.5	-	-	-	770	2.60	F3	216
Kim et al (2017)	A: 30 B: 56	1	-	-	-	-	-	-	-	A: 1.08 B: 0.96	1.48	86.38	1.16	F4	92

Kuaban et al (2015)	134	0	-	-	-	17	17	1	-	-	-	126	0.00	F5	271
Lawal et al (2019)	53	3	-	-	-		0	0.5	-	-	0.42	26	11.43	F5	567
Lee et al (2011)	90	4	-	-	-		0	2	-	3.23	1.10	290	1.38	F1	77.00
Lee et al (2014)	21939	305	-	-	-	-	-	31-Dec- 2010	-	3.00	1.40	62500	0.49	F1	89.00
Lee et al (2015)	133	5	-	-	-	-	0	-	-	0.53		71	7.05	F5	88
Luzze et al (2013)	1701	171	-	-	-	-	0	-	-	1.24	0.54	2036	8.40	F1	400
Ma et al (2018)	58	16	-	-	-	0	0	3	-	-	-	150	10.67	F5	64
McGreevy et al (2012)	120	5	8	-	-	5	13	3	-	4.50	1.42	348	1.44	F5	238.00
Migliori et al (2002)	21	5	-	-	-	-	0	-	-	0.54	0.86	17	29.52	F5	89
Moreno-Martinez et al (2007)	310	39	-	-	-	-	0	-	312	1.17	-	312	12.49	F5	21.00
Nahid et al (2007)	558	16	53	26		128	207	1	4489	-	-	4489	0.36	F5	8.70
Nettles et al (2004)	407	14	-	-	-	-	0	1	-	-	-	400	3.50	F5	8.70
Nolan et al (2002)	42	2	-	-	-	-	0	2	-	-	-	82	2.44	F4	8.6
Palmero et al (2004)	73	7	-	-	-	-	0	1	-	-	-	70	10.07	F5	34.6
Park et al (2017)	51	8	-	8	-	-	8	-	113		1.75	113	7.07	F5	820
Perez-Guzman et al (2002)	31	1	3	-	-	11	14	5	-	-	-	118	0.85	F5	18.3
Perriens et al (1991)	332	20	-	-	-	49	49	1	244	0.75 / 0.89	-	244	8.19	F5	300.00
Pettit et al (2011)	1431	20	-	-	-	-	0	1	-	4.50	1.14	6440	0.31	F5	5.1
Piubello et al (2014)	58	0	5	4	-	-	9	2	-	-	-	107	0.00	F5	118
Prasad et al (2004)	29	2	-	-	-	4	4	31-Apr- 2004	-	1.33	-	39	5.33	F5	285
Prasad et al (2008)	212	11	-	-	-	-	0	1	-	-	-	207	5.17	F5	285.00
Pulido et al (1997)	189	15	-	-	-	-	0	-	-	2.63	-	556	2.70	F1	17.5
Reis et al (1990)	117.00	0	-	-	-	-	0	4.5	-	1.78	-	209	0.00	F5	69.50
Seon et al (2014)	12	0	-	-	-	-	0	2	-	1.25	-	15	0.00	F5	88
Shen et al (2017)	13417	710	-	-	-	-	0	1	-	-	1.30	94040	0.76	F5	89
Shin et al (2006)	86	1	2	0	0	0	2	4 years after treatment start	-	3.83	-	330	0.30	F5	183
Slutkin et al (1988)	197	4	4	11	54	16	85	1	-	-	-	153	2.62	F5	9.3
Sonnenberg et al (2001)	326	65	-	-	-	-	0	31-Dec- 1998	629	2.09	-	629	10.33	F5	216
Spagnolo et al (1982)	49	0	4	-	-	5	9	2	-	-	-	89	0.00	F5	10.9
Sun et al (2017)	234	69	-	-	-	-	0	9	-	-	5.7	1971	3.50	F5	71.10
Suryanto et al (2008)	344	12	29	-	-	143	172	-	815		4.30	815	1.47	F5	363.00
Swaminathan et al (2008)	31	12	7	-	-	-	7	2	-	-	-	43	27.91	F5	289
Thomas et al (2005)	534	62	8	16	-	7	31	1.5	-	-	-	732	8.48	F5	289.00
Thomas et al (2019)	455	20	21	-	-	40	61	2	623	1.50	-	623	3.21	F5	211
Van der Heijden et al (2018)	3004	228	-	-	-	-	0	31-Dec-2013	-	3.00	-	9012	2.53	F5	963

Van Deun et al (2006)	15436	317	-	-	-	-	0	2	-	-	-	30555	1.04	F5	221.00
Van Deun et al (2010)	335	3	12	12	-	0	24	2	-	-	-	643	0.47	F3	221
Velayutham et al (2018)	1210	158	-	-	-	102	102	1	-	-	-	1244	12.70	F4	211
Vree et al (2007)	304.00	21	19	17	10	14	60	-	-	1.62	0.67	492	4.27	F5	27.90
Wang et al (2015)	508	18	-	-	-	-	0	2	860	-	-	860	2.09	F5	65.00
Westerlund et al (2015)	710	58	-	-	-	67	67	10	-	7.70	-	6632	0.87	F1	122
Wu et al (2015)	196	7	-	-	-	-	0	5	-	-	-	963	0.73	F1	27.90
Xia et al (2014)	935	31	-	-	-	-	-	4.0	-	-	-	3678	0.84	F5	67.00
Yen et al (2014)	5567	84	914	-	-	-	914	6	17166	-	-	17166	0.49	F1	86.00
Yoshiyama et al (2010)	170	5	3	31	-	15	49	1.	-	-	-	191	2.62	F5	163.00
Yoshiyama et al (2014)	168	3	4	-	-	-	4	-	-	4.40	1.10	739	0.41	F5	36.00
Zhdanov et al (2017)	3515	37	-	-	-	-	0	31/Dec/ 2011	23805	-	2.60	23805	0.16	F5	7.60
Anaam et al (2019)	814	71	28			35	63	5				3735.00	1.90	F5	48.00
Anh et al (2020)	79	0					0	2				158.00	0.00	F5	188.00
Ciza et al (2020)	209	1					0	2		1.07	0.5	224.68	0.45	F4	111.00
Decro et al (2020)	773	9						2				1537.00	0.59	F5	221.00
Lee et al (2020)	60	3					0	1		1.32	3.14	79.00	3.80	F4	146.00
Liu et al (2020)	4043	275					0	3				11716.50	2.35	F5	67.00
Malherbe et al (2020)	88	12				NO	0	2				164.00	7.32	F5	147.00
Mathur et al (2020)	187	7	15				15	2			1.09	352.63	1.99	F4	204.00
Park et al (2019)	35	1	1				1	2		3.47		121.33	0.82	F2	99.00
Peetluk et al (2019)	517	5					0	1.5				771.75	0.65	F5	43.00
Piubello et al (2020)	211	5	7			20	27	1			0.20	193.51	2.58	F4	105.00
Schwœbel et al (2020)	823	15	51			205	256	2		1.32	0.69	1132.08	1.33	F3	183.78
Zheng et al (2020)	35	10	4			2	6	5			2	130.00	7.69	F4	70.00
Bhatt et al (2017)	93	2										207.70	0.96	F1	244.00

*Formulas detailed in Appendix 3

Table S2: Proportion of relapses and reinfections in cohort studies, clinical trials and TB program database studies

Author	Genotyping molecular technique *	Recurrences	Recurrences with fingerprint results N (%)	Relapse N (%)	Reinfection N (%)	Background incidence per 100,000 pop**	Follow up period in years	HIV-prevalence
Clinical trials								
Conradie et al (2020)	WGS	2	1 (50)	1 (100)	0 (0)	146	0.49	19.3
El-Sadr et al (1998)	RFLP	2	1 (50)	1(100)	0	9.2	> 2	0.4
Jasmer Lorna et al (2004)	RFLP, Polymorphic guanine-cytosine–rich sequence–based RFLP analysis	81	75 (93)	72 (96)	3 (4)	6.7	2	0.4
Maug et al (2020)	Spoligotyping, MIRU VNTR, Deeplex MycTB	5	4 (80)	1 (25)	3 (75)	221	1	<1
Merle et al (2014)	MIRU VNTR	148	77 (52)	61 (79)	16 (21)	820	2	>1
Cohort studies								
Aung et al (2014)	Spoligotyping, MIRU VNTR	6	6 (100)	4(66)	2(33)	221	>2	<0.5
Charalambous et al (2008)	RFLP	42	16 (38)	5 (31)	11 (67)	585	1.02	14.65
Crampin et al (2010)	RFLP, Spoligotyping	53	39 (74)	26 (67)	13 (33)	392	10.75	14
Dale et al (2017)	MIRU VNTR	20	11 (55)	9 (82)	2 (18)	6.5	5.7	0.1
Decroo et al (2020)	Spoligotyping, MIRU VNTR, SNP genotyping	8	7 (87)	4 (57)	3 (43)	228	1.5	0.3
Guerra-Assunção et al (2015)	RFLP, Spoligotyping, WGS	139	75 (54)	55 (73)	20 (27)	397	2	14
Hawken et al (1993)	RFLP	11	3 (27)	2 (67)	1 (33)	72.3	1.25	5.5
Hesseling et al (2010)	RFLP	22	18 (82)	12 (67)	6 (33)	841	2	12.7
Huyen et al (2013)	Spoligotyping	35	35 (100)	23 (66)	12 (34)	172	1.5	0.4
Jimenez Corona et al (2013)	RFLP, Spoligotyping	74	38 (51)	31 (82)	7 (18)	21	5.14	0.3
Johnson et al (2000)	RFLP	4	4 (100)	0	4 (100)	117	2	9.5
Johnson et al (2003)	RFLP	2	2 (100)	0	2 (100)	248	6	9.5
Liu et al (2020)	MIRU VNTR	275	58 (21)	18 (31)	40 (69)	67.00	3	<0.1
Luzze et al (2013)	RFLP	171	98 (57)	80 (82)	18 (18)	400	1.24	6.5
Marx et al (2014) / Dippenar et al (2019)	RFLP. / WGS	203	130(64)	39(30)	91(70)	746	>2	14

Nahid et al (2007)	RFLP	16	11 (69)	11 (100)	0 (0)	8.7	1	0.4
Narayanan et al (2010)	RFLP, Spoligotyping, MIRU VNTR	74	48(65)	24(50)	24(50)	285	>2	0.1
Nettles et al (2004)	RFLP	14	9 (64)	9 (100)	0 (0)	7.9	1	0.4
Pettit et al (2011)	RFLP, Spoligotyping, MIRU VNTR	20	15 (75)	12 (80)	3 (20)	5.1	1	0.4
Piubello et al (2020)	No specified	5	5 (100)	1 (20)	4 (80)	105	0.92	0.3
Schwœbel et al (2020)	WGS, Spoligotyping	15	3 (20)	1 (33)	2 (66)	183	2	1.1
Shen et al (2017)	MIRU VNTR	710	141 (20)	82 (58)	59 (42)	89	1	0.1
Sonnenberg et al (2001)	RFLP	65	39 (60)	25 (64)	14 (36)	216	2.09	7.1
Van Deun et al (2004)	RFLP	2	2 (100)	1 (50)	1 (50)	52.9	2	<1
Van Deun et al (2010)	Spoligotyping	3	3 (100)	1 (33)	2 (66)	221	2	<0.5
Velayutham et al (2018)	MIRU VNTR	123	60 (48)	56 (93)	4 (7)	211	1	<0.5
TB program databases								
Bandera et al (2001)	RFLP, Spoligotyping	32	32 (60)	27 (84)	5 (16)	17.5	5	0.2
Cacho et al (2007)	RFLP, Spoligotyping, MIRU VNTR	8	8 (100)	7 (88)	1 (13)	25.7	6	0.4
Caminero et al (2001)	RFLP	11	8 (73)	2 (25)	6 (75)	22	5	0.4
Das et al (1993)	RFLP	42	42 (100)	37 (88)	5 (12)	109.3	2	0.2
Das et al (1995)	RFLP	62	62 (100)	22 (35)	40 (65)	130.7	3	0.2
Dobler et al (2009)	RFLP, Spoligotyping, MIRU VNTR	15	15 (100)	11 (73)	4 (27)	6.3	12	0.1
El Sahly et al (2004)	RFLP, Spoligotyping, genotyping method Not specified	100	25 (25)	19 (76)	6 (24)	2.9	5	0.4
Folkvardsen et al (2020)	WGS	32	13	9	4	8.3	22	0.1
Lourenço et al (2000)	RFLP, Polymorphic guanine-cytosine–rich sequence–based RFLP analysis , DRE-PCR	12	12 (100)	9 (75)	3 (25)	55.9	4	0.3
Parvaresh et al (2018)	MIRU VNTR, WGS	18	15(83)	13(87)	2(13)	6.3	6	0.1
Quy et al (2002) / Lan et al (2003)	RFLP	168	50 (30)	39 (78)	11 (22)	68	2	0.2
Rosser et al (2018)	MIRU VNTR	82	19(23)	16(84)	3(16)	13	20	0.16
Schiroli et al (2015)	Spoligotyping, MIRU VNTR	83	83 (100)	64 (77)	19 (23)	8.6	15	0.3

Shamputa et al (2007)	RFLP, Spoligotyping, MIRU VNTR	35	35 (100)	30 (86)	5 (14)	221	7	<1
Shen et al (2006)	RFLP, MIRU VNTR	202	52 (26)	20 (39)	32 (62)	102	5	0.1
Umubyeyi et al (2007)	Spoligotyping, MIRU VNTR	13	13 (100)	8 (62)	4 (31)	92	3	3.9
Van Rie et al (1999)	RFLP	48	16 (33)	4 (25)	12 (75)	1000	6	15.9

*RFLP= IS6110-restriction fragment length polymorphism, MIRU VNTR= mycobacterial interspersed repetitive unit-variable number tandem repeat typing; WGS: Whole Genome Sequencing

**Estimated incidence of tuberculosis for all cases as estimated the World Health Organization and reported in the Global Tuberculosis Database[16]

Appendix 7 Quality Assessment

Table S3 Recurrent TB incidence rate: Quality Assessment according to the modified NewCastle Ottawa Scale

Title	Selection		Outcome			Score		Overall qualiy Rating
	Representativeness of the population	Ascertainment of exposure	Assessment of outcome	Length of follow up	Adequacy of follow-up of cohorts	Selection	Outcome	
Anaam et al (2012)	A	B	A	B	B	1	1	POOR
Anaam et al (2019)	A	A	B	A	B	2	2	FAIR
Anh et al (2020)	C	B	B	A	A	0	2	POOR
Aung et al (2014)	C	B	A	A	A	0	2	POOR
Banu et al (2012)	A	A	A	A	A	2	3	GOOD
Becerra et al (2010)	C	A	A	A	B	1	2	FAIR
Bechan et al (1997)	A	A	A	B	A	2	2	FAIR
Bhatt et al (2017)	B	B	A	A	A	1	2	FAIR
Cao et al (1988)	A	A	A	A	A	2	3	GOOD
Castelo et al (1989)	A	B	A	B	D	1	0	POOR
Chaisson et al (1996)	A	A	A	A	A	2	3	GOOD
Chang et al (2004)	A	A	B	A	A	2	2	FAIR
Charalambous et al (2008)	B	A	B	A	A	2	2	FAIR
Chaulet et al (1995)	A	A	A	A	B	2	3	GOOD
Chiang et al (2006)	C	A	A	A	A	1	2	FAIR
Chien et al (2014)	C	B	A	A	A	0	2	POOR
Choi et al (2014)	A	A	A	A	B	2	3	GOOD
Ciza et al (2020)	C	A	A	A	A	1	2	FAIR
Cohn et al (1990)	A	B	A	A	D	1	1	POOR
Connolly et al (1999)	A	A	A	B	A	2	2	FAIR

Conradie et al (2020)	C	A	A	B	B	1	1	POOR
Cowie et al (1989)	B	A	B	A	A	2	2	FAIR
Crampin et al (2010)	A	A	B	A	A	2	2	FAIR
d'Arc et al (2008)	A	B	A	A	A	1	2	FAIR
Dale et al (2017)	A	B	A	B	A	1	1	POOR
Dangisso et al (2018)	B	B	A	A	A	1	2	FAIR
Datiko et al (2009)	A	A	A	A	A	2	3	GOOD
Decro et al (2020)	C	B	A	A	A	0	2	POOR
Dobler et al (2009)	A	B	A	B	A	1	1	POOR
Dornelles et al (2007)	A	A	A	A	A	2	3	GOOD
Dutt et al (1984)	A	A	A	A	A	2	3	GOOD
Dutt et al (1990)	A	A	A	A	A	2	3	GOOD
East African/BMRC (1980)	A	A	B	A	B	2	2	FAIR
East African/BMRC (1981)	A	A	A	B	B	2	2	FAIR
Escudero et al (2006)	C	A	A	A	A	1	2	FAIR
Fitzgerald et al (2000)	A	A	B	A	A	2	2	FAIR
Fox et al (2018)	A	B	A	A	A	1	2	FAIR
Garcia Martinez et al (1996)	A	A	A	A	B	2	3	GOOD
Gelmanova et al (2015)	C	B	A	A	B	0	2	POOR
Gengiah et al (2014)	C	B	A	A	A	0	2	POOR
Glynn et al (2010)	B	B	B	A	A	1	2	FAIR
Gonzalez-Montaner et al (1994)	A	A	A	A	C	2	2	FAIR
Gopalan et al (2018)	C	A	A	B	B	1	1	POOR
Guerra-Assunção et al (2015)	A	B	A	A	B	1	2	FAIR
Guglielmetti et al (2016)	C	B	A	A	C	0	1	POOR

Hang et al (2015)	A	A	A	B	B	2	2	FAIR
Hawken et al (1993)	C	A	A	A	A	1	2	FAIR
He et al (2010)	C	B	A	A	B	0	2	POOR
Hesseling et al (2010)	B	B	A	A	B	1	2	FAIR
Hong et al (1988)	C	A	A	A	C	1	1	POOR
Hong Kong Chest Service (1982)	A	A	A	B	B	2	2	FAIR
Hong Kong Chest Service/BMRC (1991)	A	A	A	A	B	2	3	GOOD
Houben et al (2012)	C	B	A	A	B	0	2	POOR
Huyen et al (2013)	A	A	A	B	B	2	2	FAIR
Jasmer et al (2004)	A	B	A	B	B	1	1	POOR
Jasmer Lorna et al (2004)	A	B	A	A	A	1	2	FAIR
Jawahar et al (2013)	A	A	B	A	A	2	2	FAIR
Jimenez Corona et al (2013)	A	B	A	A	A	1	2	FAIR
Jo et al (2014)	A	B	B	B	A	1	1	POOR
Johnson et al (2000)	A	A	A	A	A	2	3	GOOD
Johnson et al (2003)	A	B	A	B	A	1	1	POOR
Johnson et al (2009)	A	B	B	A	B	1	2	FAIR
Karagaoz et al (2009)	C	A	A	A	B	1	2	FAIR
Kassim et al (1995)	B	A	A	B	A	2	2	FAIR
Kennedy et al (1996)	A	B	B	B	A	1	1	POOR
Kenyan/Zambian/BMRC (1989)	A	A	A	A	B	2	3	GOOD
Kim et al (2017)	A	B	A	B	D	1	0	POOR
Kohno et al (1992)	A	A	A	A	B	2	3	GOOD
Kuaban et al (2015)	C	B	A	B	B	0	1	POOR

Lawal et al (2019	A	B	A	B	A	1	1	POOR
Lee et al (2011)	C	B	B	A	A	0	2	POOR
Lee et al (2012)	C	A	A	A	A	1	2	FAIR
Lee et al (2014)	C	B	A	B	A	0	1	POOR
Lee et al (2015)	C	B	A	B	A	0	1	POOR
Lee et al (2020)	C	B	A	B	A	0	1	POOR
Liu et al (2020)	A	A	B	A	A	2	2	FAIR
Luzze et al (2013)	B	A	A	B	A	2	2	FAIR
Ma et al (2018)	C	B	A	A	A	0	2	POOR
Madras/BMRC (1989)	C	B	A	A	B	0	2	POOR
Malherbe et al (2020)	A	A	A	A	D	2	2	FAIR
Mathur et al (2020)	A	A	B	A	A	2	2	FAIR
Maug et al (2020)	A	B	A	B	B	1	1	POOR
McGreevy et al (2012)	C	B	A	A	B	0	2	POOR
Merle et al (2014)	A	A	A	A	B	2	3	GOOD
Migliori et al (2002)	C	A	B	B	A	1	1	POOR
Mohanty et al (1993)	A	A	A	A	A	2	3	GOOD
Moreno-Martinez et al (2007)	A	A	A	B	A	2	2	FAIR
Nahid et al (2007)	C	A	A	A	C	1	1	POOR
narayanan et al (2007) trial	A	A	A	A	A	2	3	GOOD
Nettles et al (2004)	A	A	A	B	A	2	2	FAIR
Nolan et al (2002)	C	C	B	A	D	0	1	POOR
Palmero et al (2004)	C	A	A	B	A	1	1	POOR
Park et al (2019)	C	B	B	A	A	0	2	POOR
Parthasarathy et al (1991)	A	A	A	B	A	2	2	FAIR

Peetluk et al (2019)	A	B	B	B	A	1	1	POOR
Perez-Guzman et al (2002)	C	A	A	A	C	1	1	POOR
Perriens et al (1991)	A	A	A	B	B	2	2	FAIR
Perriens et al (1995)	A	A	A	B	C	2	1	POOR
Pettit et al (2011)	A	A	A	A	A	2	3	GOOD
Piubello et al (2014)	C	B	A	A	A	0	2	POOR
Piubello et al (2020)	C	B	A	B	B	0	1	POOR
Prasad et al (2004)	C	A	A	B	B	1	1	POOR
Prasad et al (2008)	A	B	A	B	A	1	1	POOR
Pulido et al (1997)	C	A	A	A	A	1	2	FAIR
Reis et al (1990)	C	A	A	A	A	1	2	FAIR
Schwœbel et al (2020)	C	B	A	A	C	0	1	POOR
Seon et al (2014)	B	B	A	A	A	1	2	FAIR
Shen et al (2017)	A	B	A	A	A	1	2	FAIR
Shin et al (2006)	C	B	A	A	A	0	2	POOR
Singapore/BMRC (1988)	A	A	B	A	B	2	2	FAIR
Singapore/BMRC (1991)	A	A	A	B	A	2	2	FAIR
Slutkin et al (1988)	A	B	A	B	B	1	1	POOR
Snider et al (1984)	A	A	A	A	D	2	2	FAIR
Sonnenberg et al (2001)	C	A	A	A	A	1	2	FAIR
Spagnolo et al (1982)	A	B	A	A	B	1	2	FAIR
Su et al (2001)	A	B	B	A	D	1	1	POOR
Sun et al (2017)	C	B	A	A	A	0	2	POOR
Suryanto et al (2008)	A	A	A	A	C	2	2	FAIR
Swai et al (1988)	C	A	A	A	B	1	2	FAIR

Swaminathan et al (2008)	C	A	B	A	A	1	2	FAIR
Tam et al (2002)	A	C	A	A	B	1	2	FAIR
Tanzania/BMRC (1985)	A	A	A	A	B	2	3	GOOD
Teo et al (1999)	A	B	A	A	B	1	2	FAIR
Thomas et al (2005)	A	A	A	B	B	2	2	FAIR
Thomas et al (2019)	A	A	B	A	B	2	2	FAIR
Tuberculosis Research Centre (1981)	A	A	A	A	A	2	3	GOOD
Tuberculosis Research Centre (1997)	A	A	A	A	B	2	3	GOOD
Van der Heijden et al (2018)	A	A	A	A	A	2	3	GOOD
Van Deun et al (2006)	A	B	A	A	A	1	2	FAIR
Van Deun et al (2010)	C	B	A	A	A	0	2	POOR
Velayutham et al (2018)	A	A	A	B	B	2	2	FAIR
Velayutham et al (2020)	A	A	B	A	A	2	2	FAIR
Vree et al (2007)	A	B	A	B	B	1	1	POOR
Wang et al (2015)	C	B	A	A	A	0	2	POOR
Westerlund et al (2015)	A	A	A	A	B	2	3	GOOD
Wu et al (2016)	A	B	A	B	A	1	1	POOR
Wu et al (2015)	A	B	A	A	A	1	2	FAIR
Xia et al (2014)	A	B	B	A	A	1	2	FAIR
Yan et al (2018)	C	B	B	A	C	0	1	POOR
Yen et al (2014)	A	B	B	A	A	1	2	FAIR
Yoshiyama et al (2010)	C	A	A	B	B	1	1	POOR
Yoshiyama et al (2014)	C	A	A	A	A	1	2	FAIR

Zhdanov et al (2017)	A	B	A	A	A	1	2	FAIR
Zheng et al (2020)	A	B	B	A	B	1	2	FAIR
Zierski et al (1981)	A	A	A	A	B	2	3	GOOD

*Each item received a maximum of one star according scale shown in Appendix 07. Score quality rating based on total number of stars received: Good quality: 2 in selection domain AND 3 in outcome domain. Fair quality: 1 star in selection domain OR 2 stars in outcome domain. Poor quality: If 0 stars in selection criteria OR 0-1 stars in outcome criteria

Table S4: Proportion of relapses and reinfections: Quality Assessment according to the modified NewCastle Ottawa Scale

Title	Selection	Outcome	Selection	Outcome	Selection	Scores		Overall Qualiy Rating
	Representativeness of population	Ascertainment of exposure	Assessment of outcome	Length of follow up	Lost to genotyping	Selection	Outcome	
Aung et al (2014)	C	B	A	A	A	0	3	POOR
Bandera et al (2001)	A	A	B	A	A	2	3	GOOD
Cacho et al (2007)	B	A	A	A	A	2	3	GOOD
Caminero et al (2001)	A	A	C	A	B	2	1	POOR
Charalambous et al (2008)	B	A	C	B	B	2	0	POOR
Conradie et al (2020)	C	A	A	B	B	1	1	POOR
Crampin et al (2010)	A	A	B	A	B	2	2	FAIR
Dale et al (2017)	A	B	A	A	B	1	2	FAIR
Das et al (1993)	C	A	C	A	A	1	2	FAIR
Das et al (1995)	B	A	C	A	A	2	2	FAIR
Decro et al (2020)	C	B	A	B	B	0	1	POOR
Dobler et al (2009)	A	B	A	A	A	1	3	FAIR
El Sahly et al (2004)	B	A	B	A	B	2	2	FAIR
El-Sadr et al (1998)	B	B	C	A	B	1	1	POOR
Folkvardsen et al (2020)	B	A	A	A	B	2	2	FAIR
Guerra-Assunção et al (2015)	A	B	A	A	B	1	2	FAIR
Hawken et al (1993)	C	A	C	B	B	1	0	POOR
Hesseling et al (2010)	B	B	C	A	B	1	1	POOR
Huyen et al (2013)	A	A	C	B	A	2	1	POOR
Jasmer Lorna et al (2004)	A	B	A	A	A	1	3	FAIR

Jimenez Corona et al (2013)	A	B	B	A	B	1	2	FAIR
Johnson et al (2000)	A	A	C	A	B	2	1	POOR
Johnson et al (2003)	A	B	C	A	A	1	2	FAIR
Liu et al (2020)	A	A	A	A	B	2	2	FAIR
Lourenço et al (2000)	C	B	B	A	A	0	3	POOR
Luzze et al (2013)	A	A	C	B	B	2	0	POOR
Marx et al (2014) / Dippenar et al (2019)	B	A	A	A	B	2	2	FAIR
Maug et al (2020)	A	B	A	B	B	1	1	POOR
Merle et al (2014)	A	A	A	A	B	2	2	FAIR
Nahid et al (2007)	C	A	C	B	B	1	0	POOR
Narayanan et al (2010)	A	A	A	A	B	2	2	FAIR
Nettles et al (2004)	A	A	C	B	B	2	0	POOR
Parvaresh et al (2018)	B	A	A	A	B	2	2	FAIR
Pettit et al (2011)	A	A	A	B	B	2	1	POOR
Piubello et al (2020)	C	B	D	B	A	0	1	POOR
Quy et al (2002) / Nguyen et al (2003)	B	A	C	A	B	2	1	POOR
Rosser et al (2018)	B	A	A	A	B	2	2	FAIR
Schiroli et al (2015)	A	A	A	A	A	2	3	GOOD
Schwœbel et al (2020)	C	B	A	A	B	0	2	POOR
Shamputa et al (2007)	A	B	A	A	A	1	3	FAIR
Shen et al (2006)	A	B	A	A	B	1	2	FAIR
Shen et al (2017)	A	B	A	A	B	1	2	FAIR
Sonnenberg et al (2001)	C	A	C	A	B	1	1	POOR
Umubyeyi et al (2007)	A	A	A	A	A	2	3	GOOD

Van Deun et al (2004)	B	B	C	A	A	1	2	FAIR
Van Deun et al (2010)	C	B	C	A	A	0	2	POOR
VanRie et al (1999)	A	B	C	A	B	1	1	POOR
Velayutham et al (2018)	A	A	A	B	B	2	1	POOR

*Each item received a maximum of one star according scale shown in Appendix 07. Score quality rating based on total number of stars received: Good quality: 2 in selection AND 3 in outcome. Fair quality: 1 star in selection OR 2 stars in outcome. Poor quality: 0 stars in selection OR 0-1 stars in outcome

Appendix 8 Supplementary figures

Figure S1 Recurrent TB incidence rate by background TB incidence level

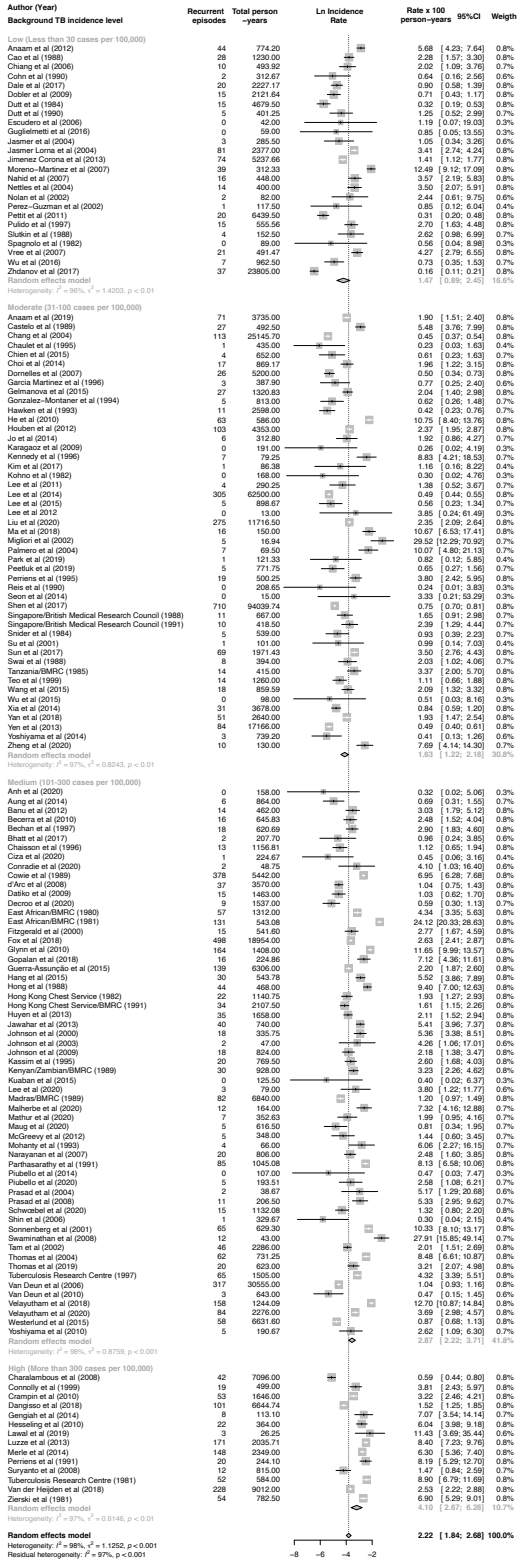


Figure S2 Recurrent TB incidence rate by type of follow up

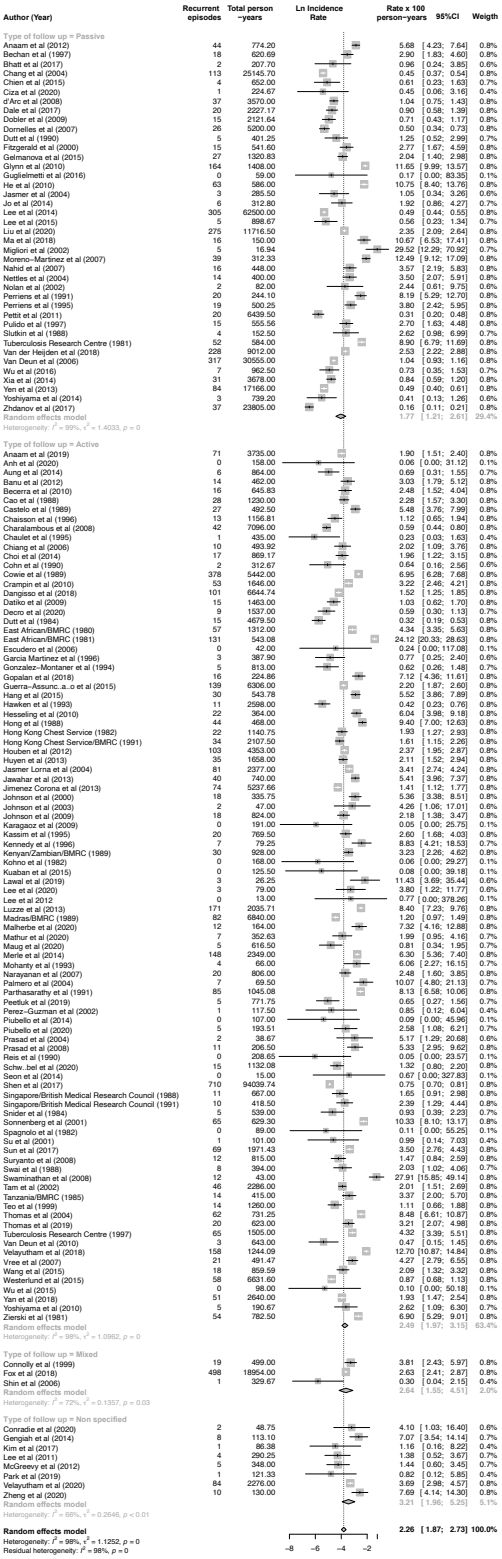


Figure S3 Forest plot of the recurrent TB incidence rate by study design

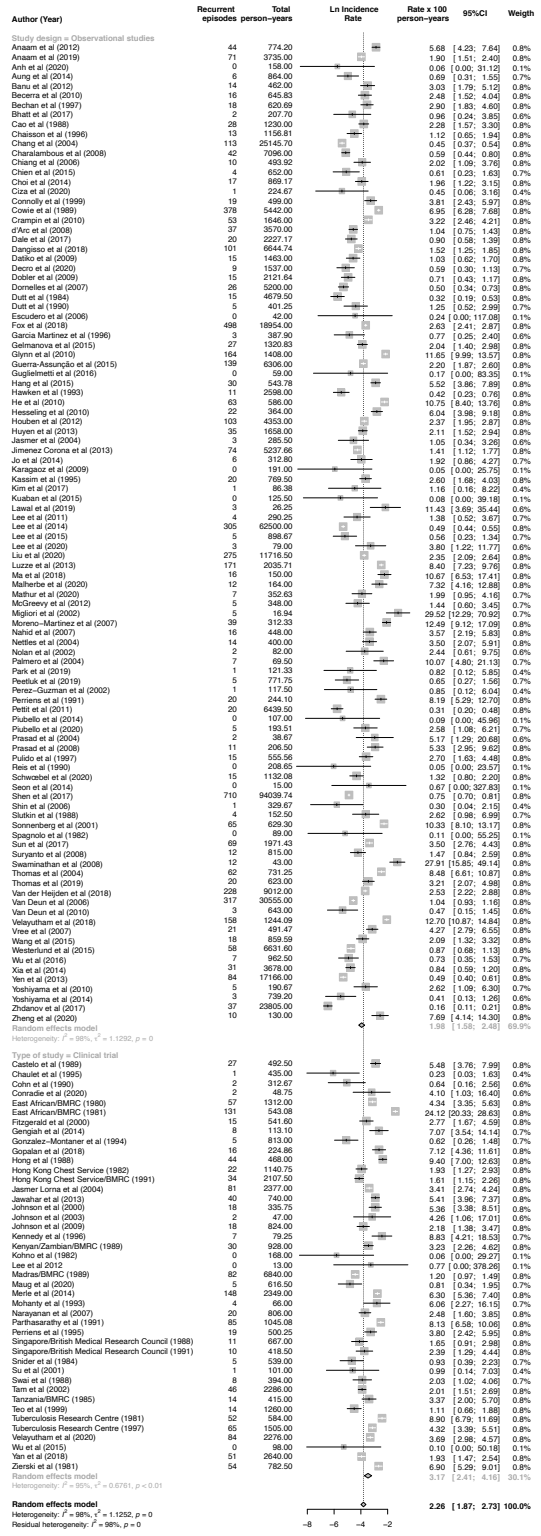


Figure S4 Forest plot of the recurrent TB incidence rate by TB drug regimen

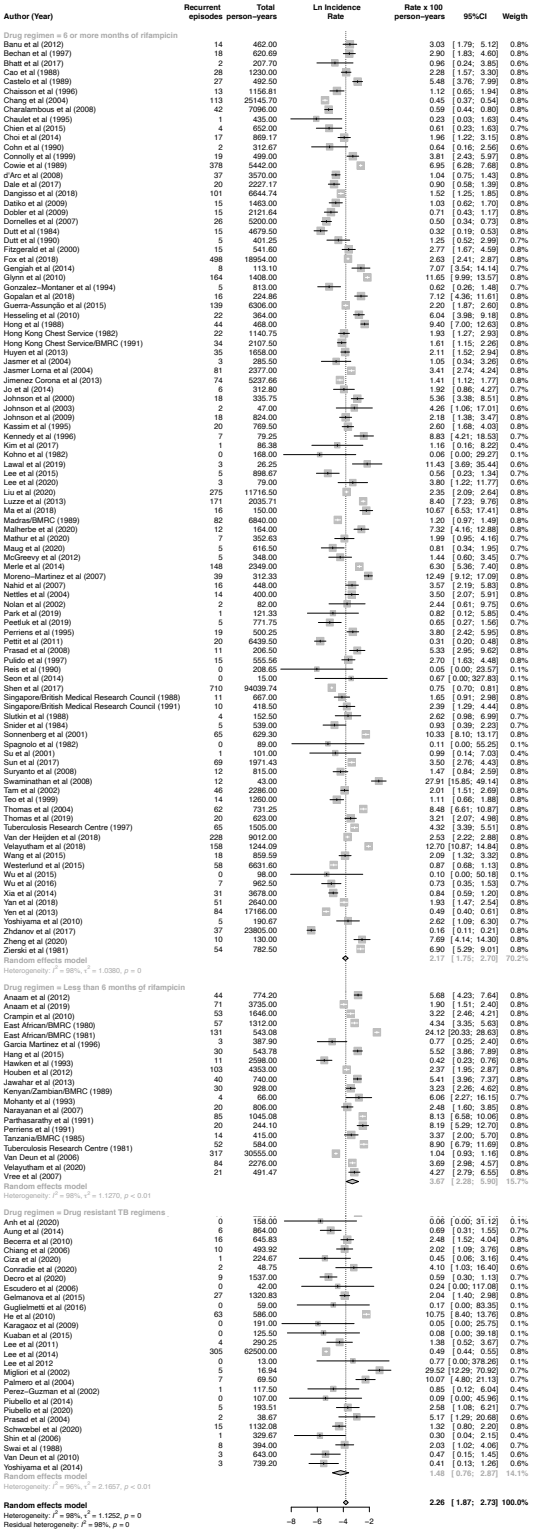


Figure S5 Forest plot of the recurrent TB incidence rate by background HIV prevalence level

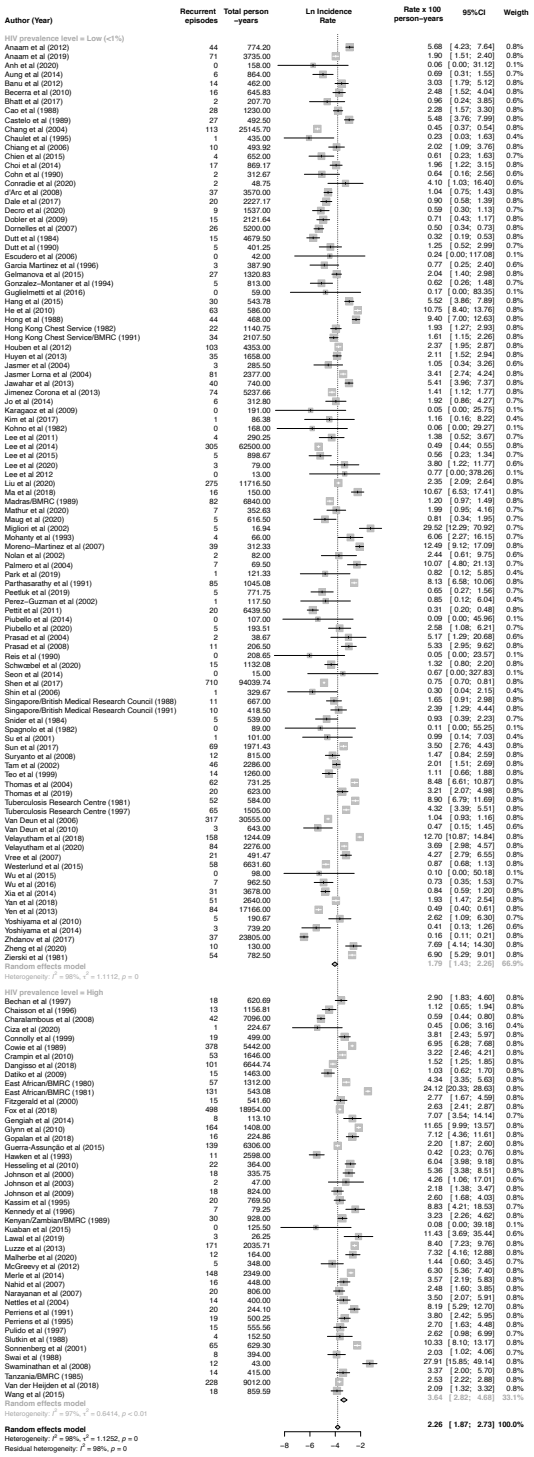


Figure S6 Forest plot of the recurrent TB incidence rate by study sample size

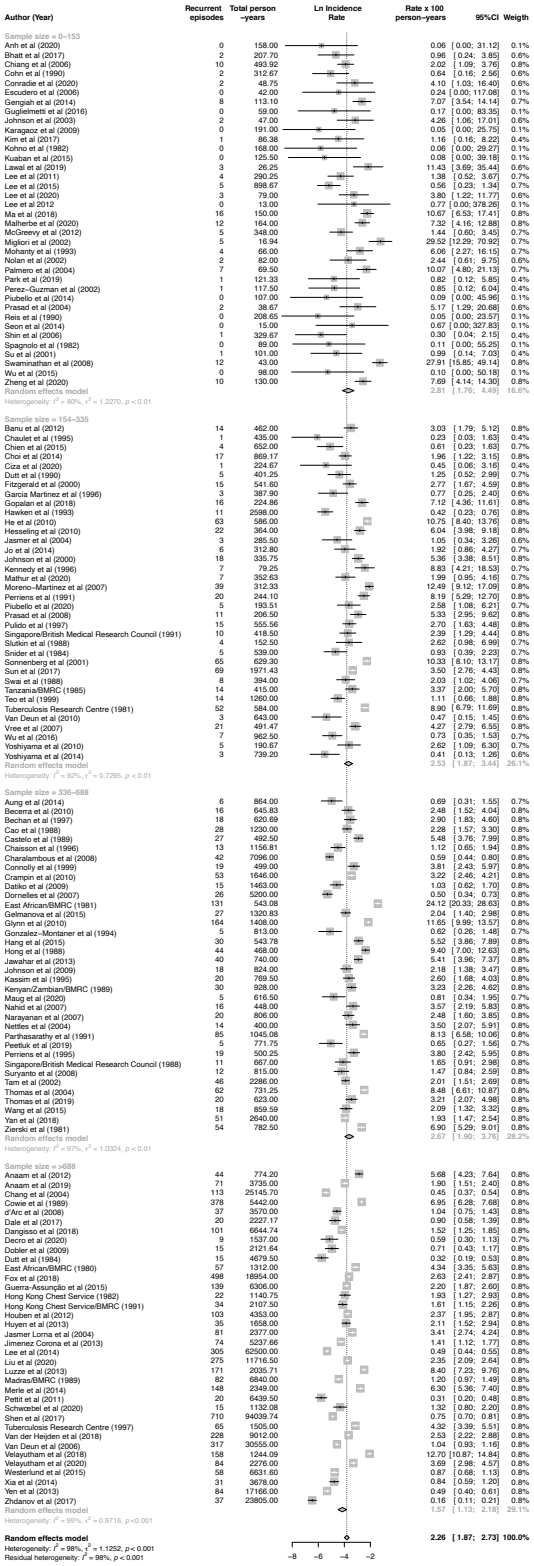


Figure S7 Forest plot of the recurrent TB incidence rate by study quality

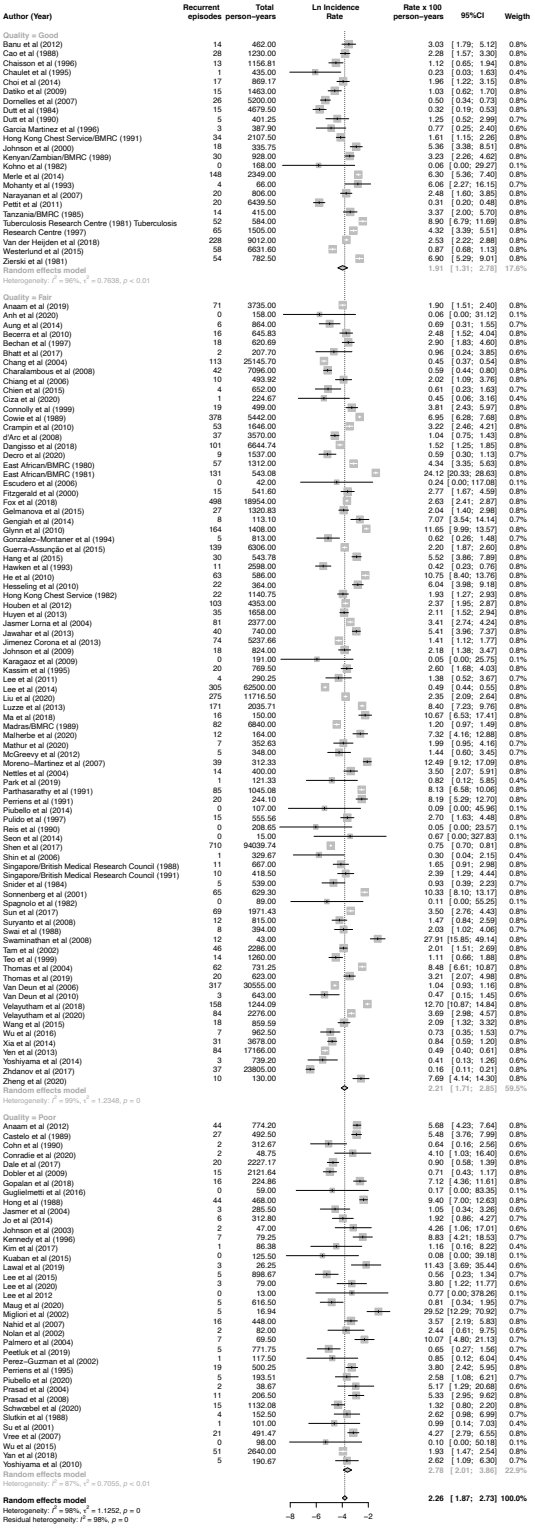


Figure S8 Forest plot of the recurrent TB incidence rate by planned follow-up time

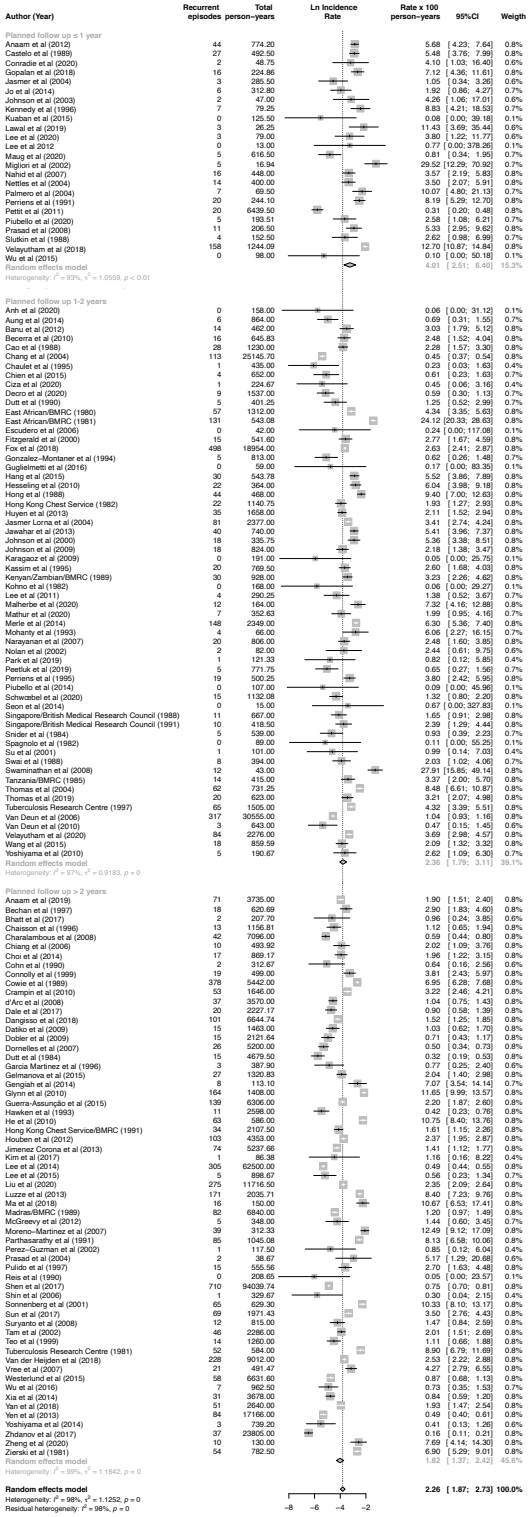


Figure S9 Funnel plot Recurrent TB incidence rate

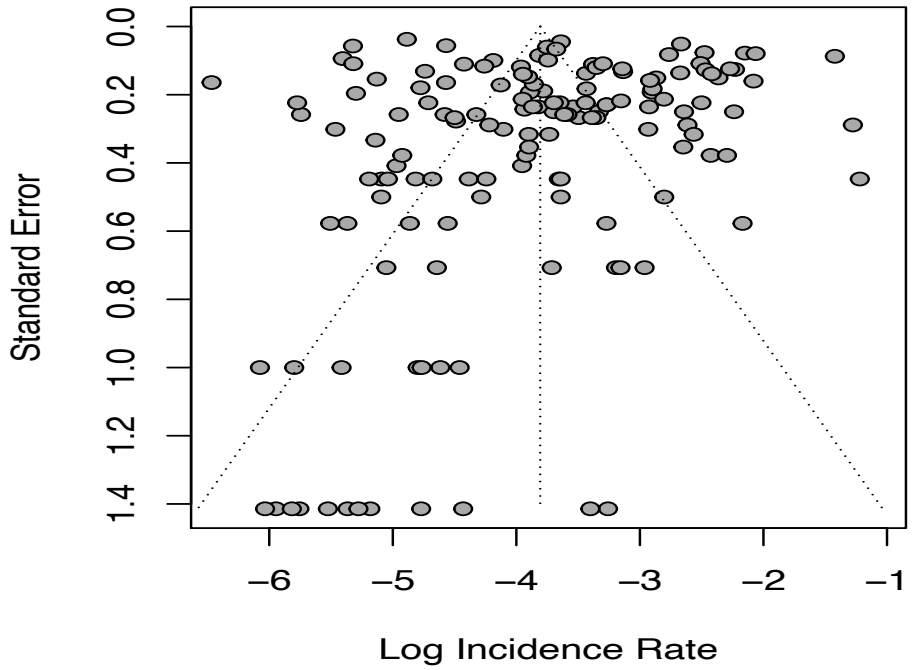


Figure S10 Forest plot of the proportion of reinfections among recurrent TB episodes by background TB incidence

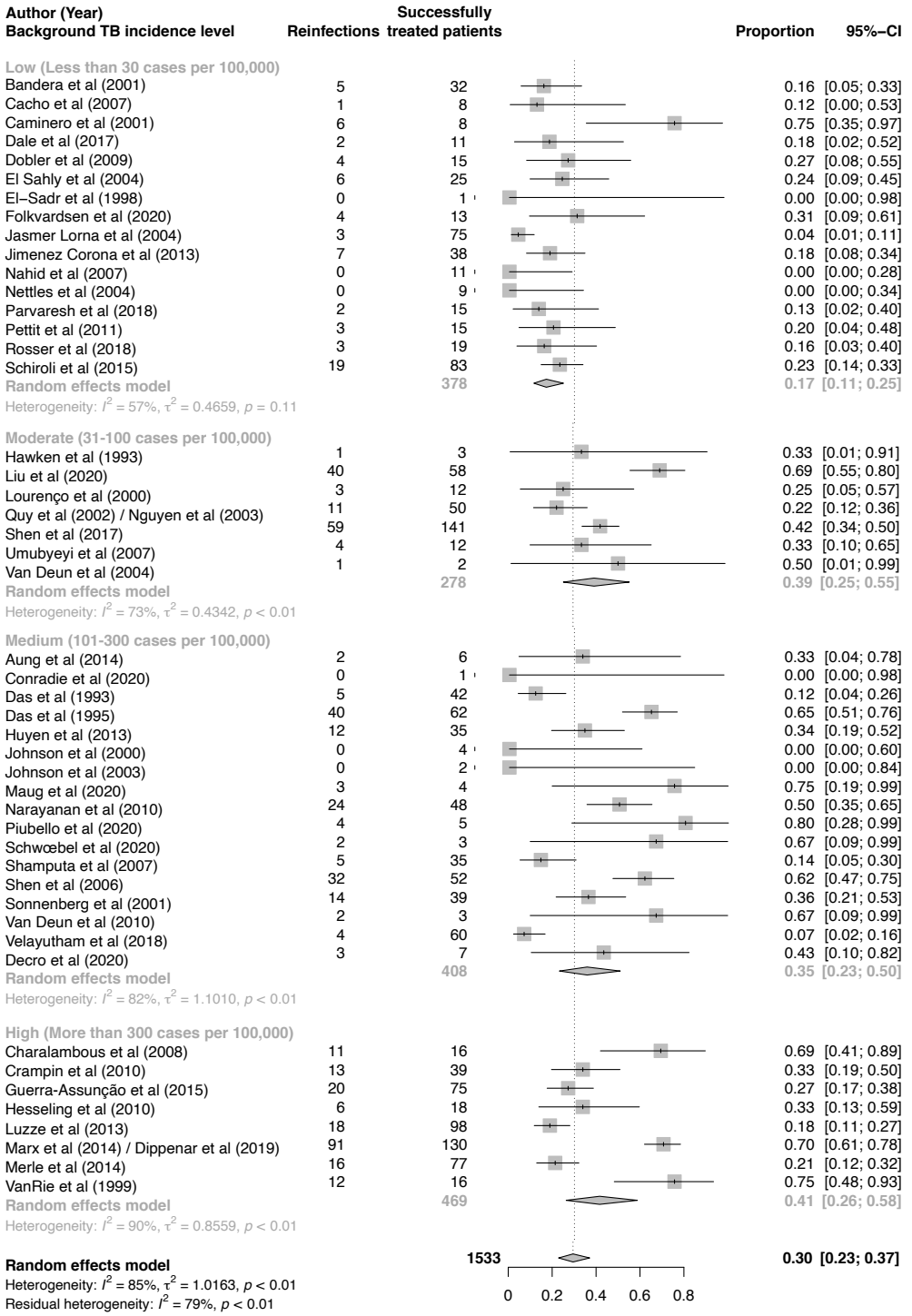


Figure S11 Forest plot of the proportion of reinfections among recurrent TB episodes by background HIV prevalence level

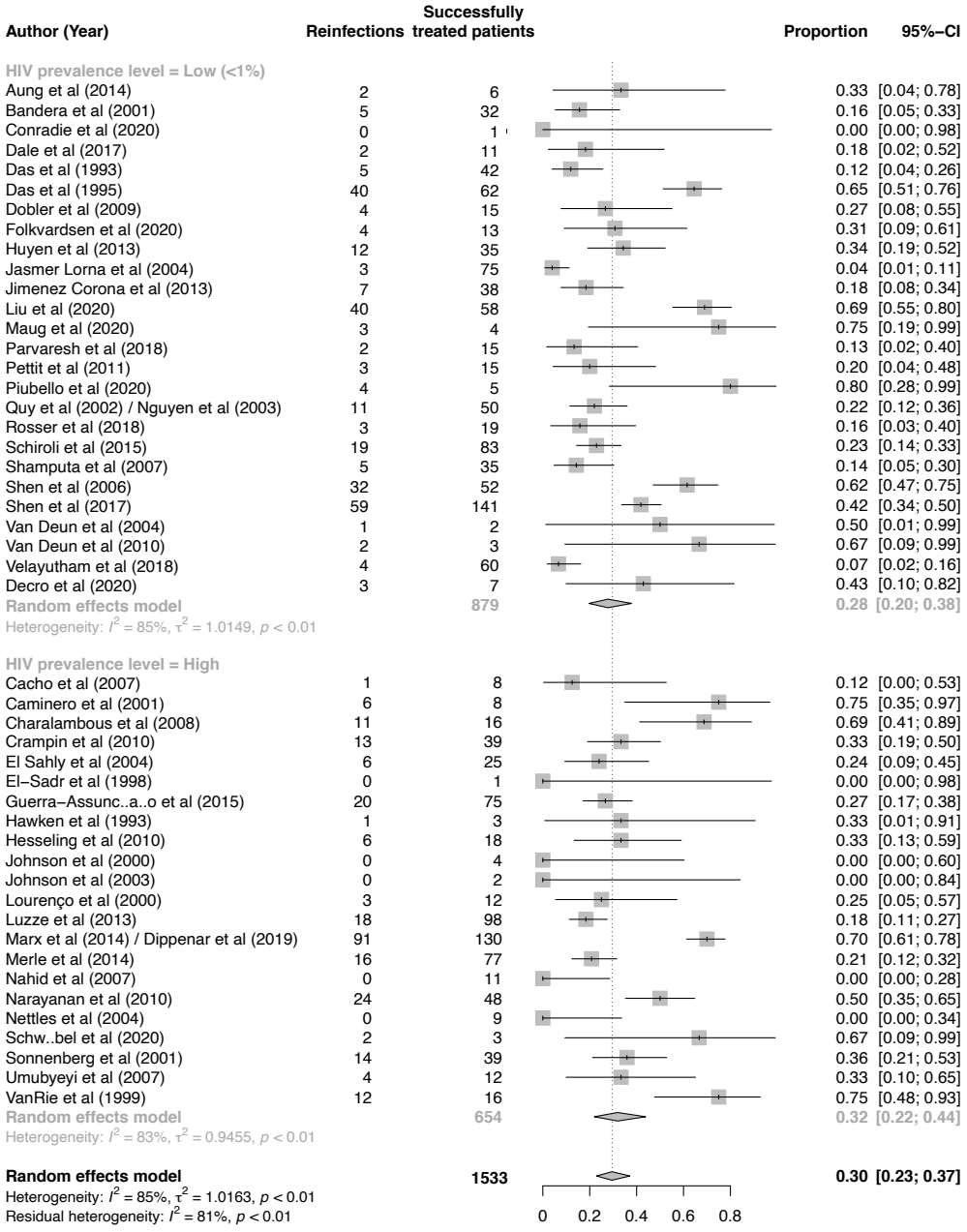


Figure S12 Forest plot of the proportion of reinfections among recurrent TB episodes by study design

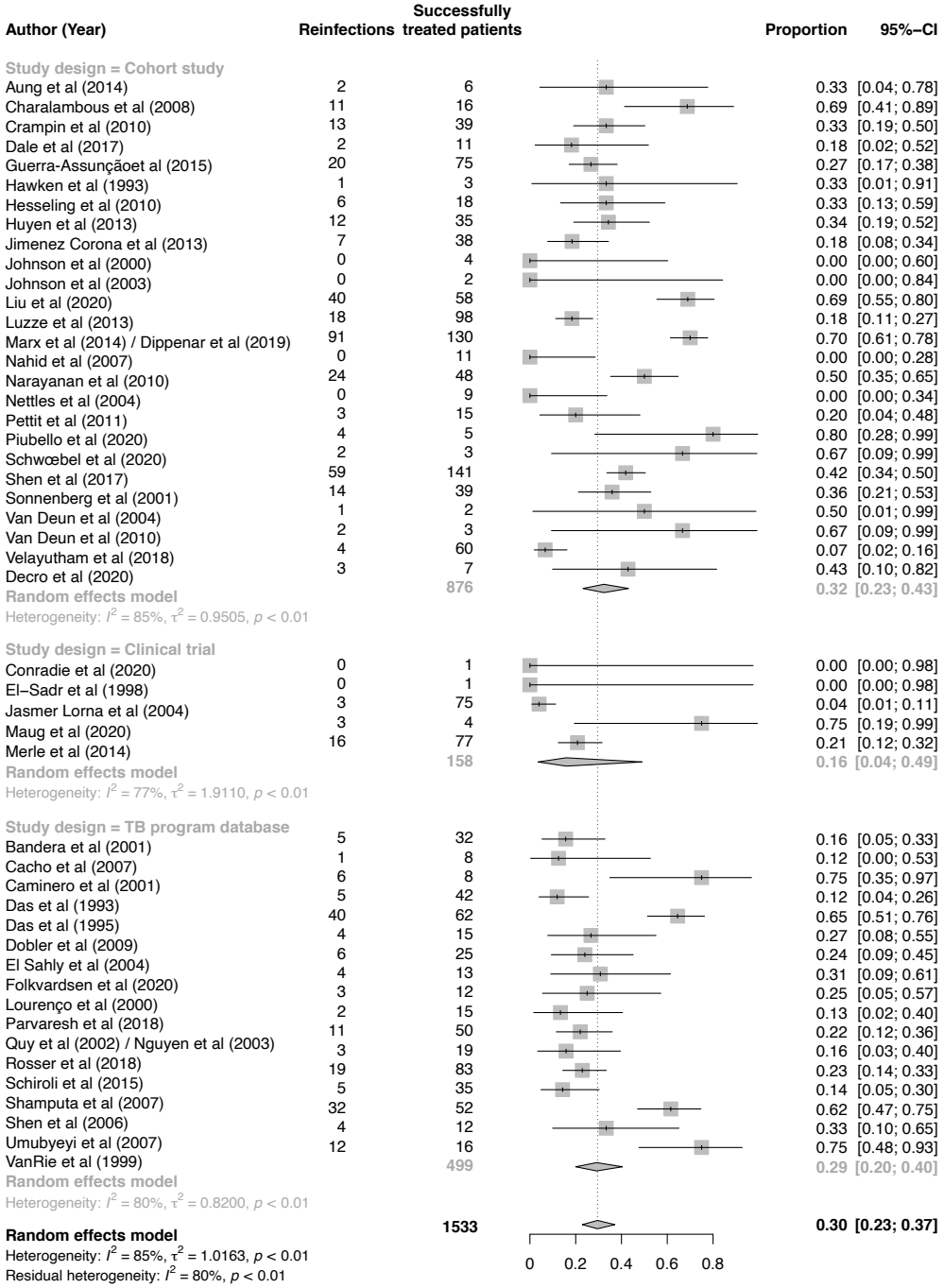


Figure S13 Forest plot of the proportion of reinfections among recurrent TB episodes by length of follow-up/observation period

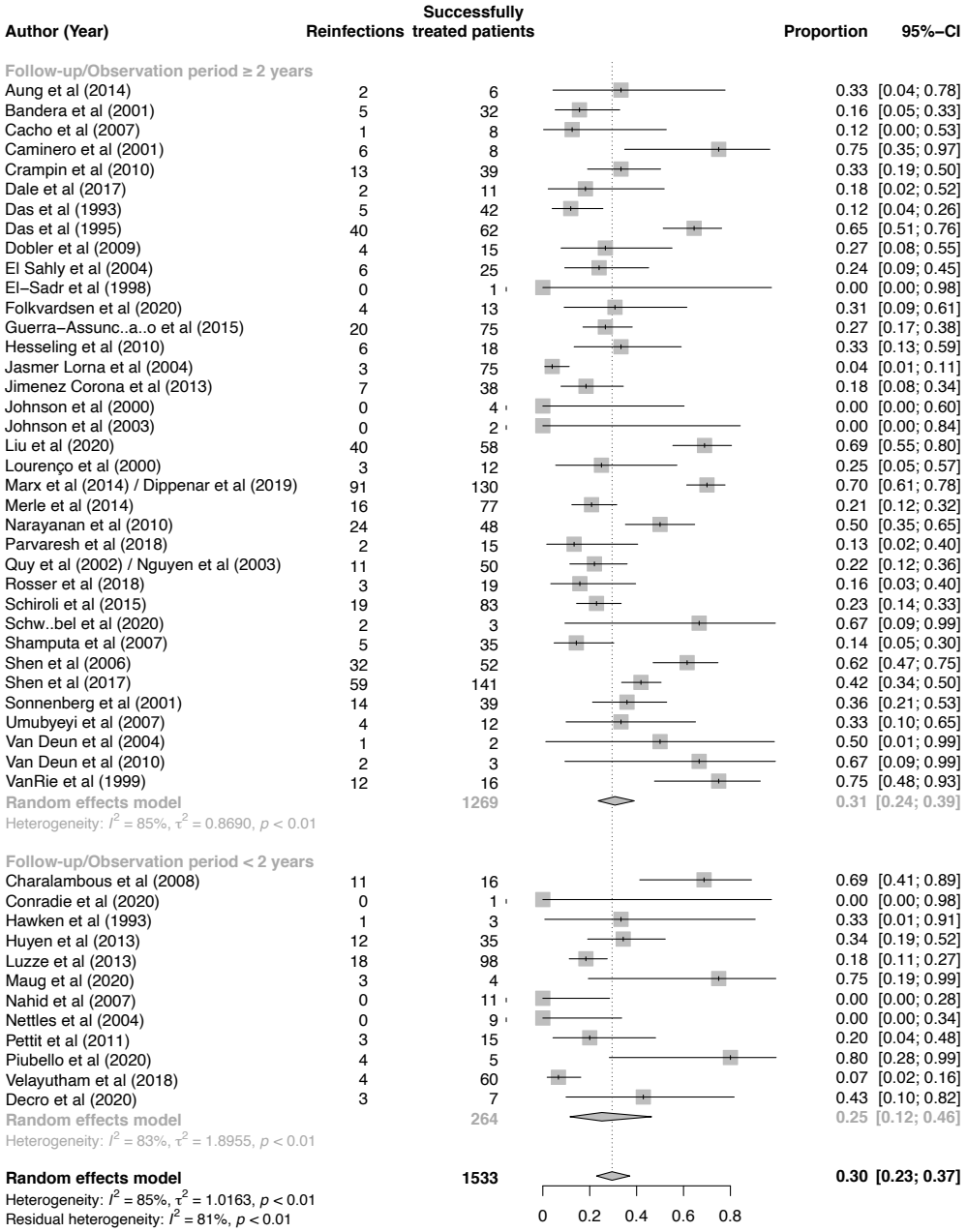


Figure S14 Forest plot of the proportion of reinfections among recurrent TB episodes by the proportion of episodes with DNA fingerprinting availability

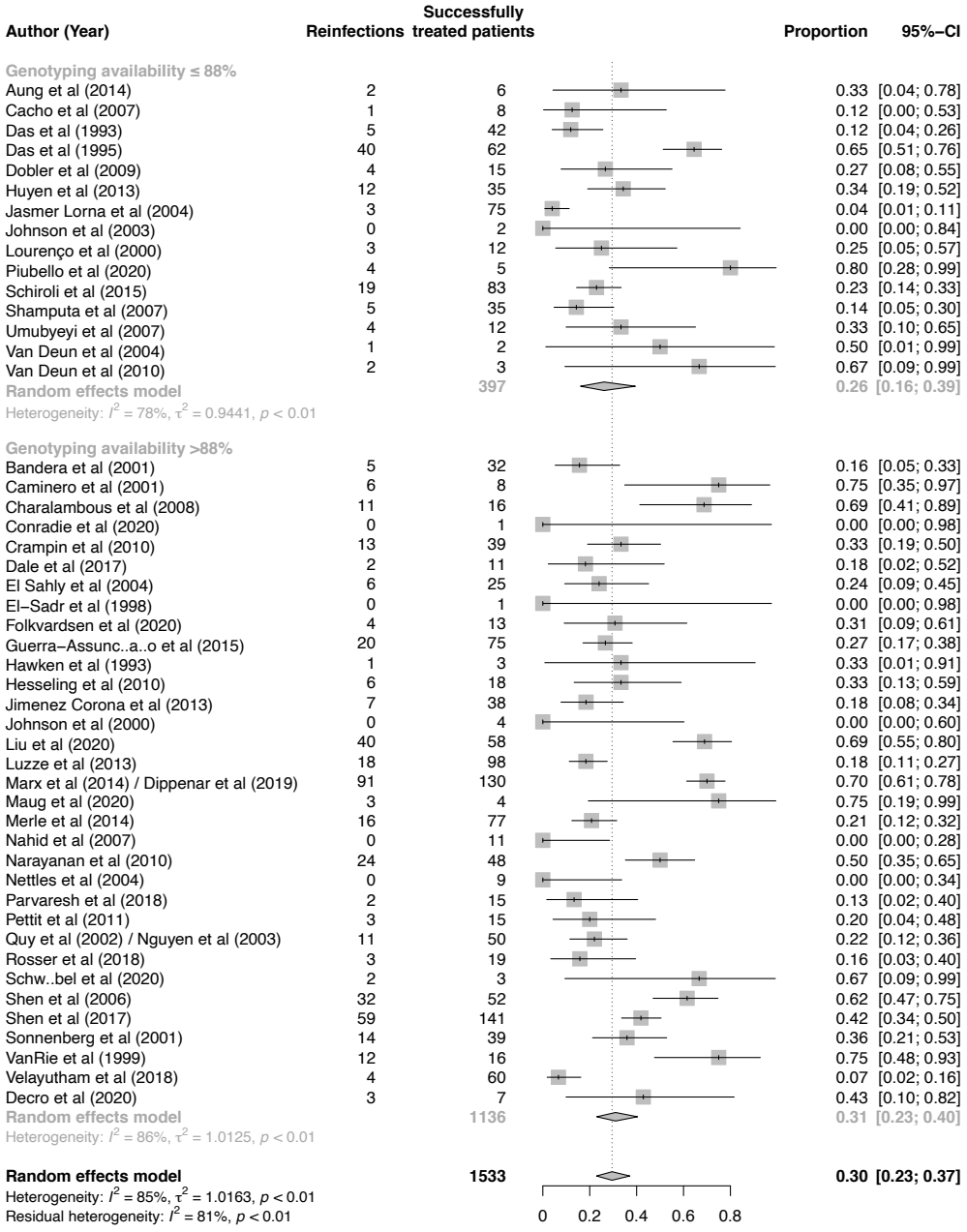


Figure S15 Forest plot of the proportion of reinfections among recurrent TB episodes by molecular method used

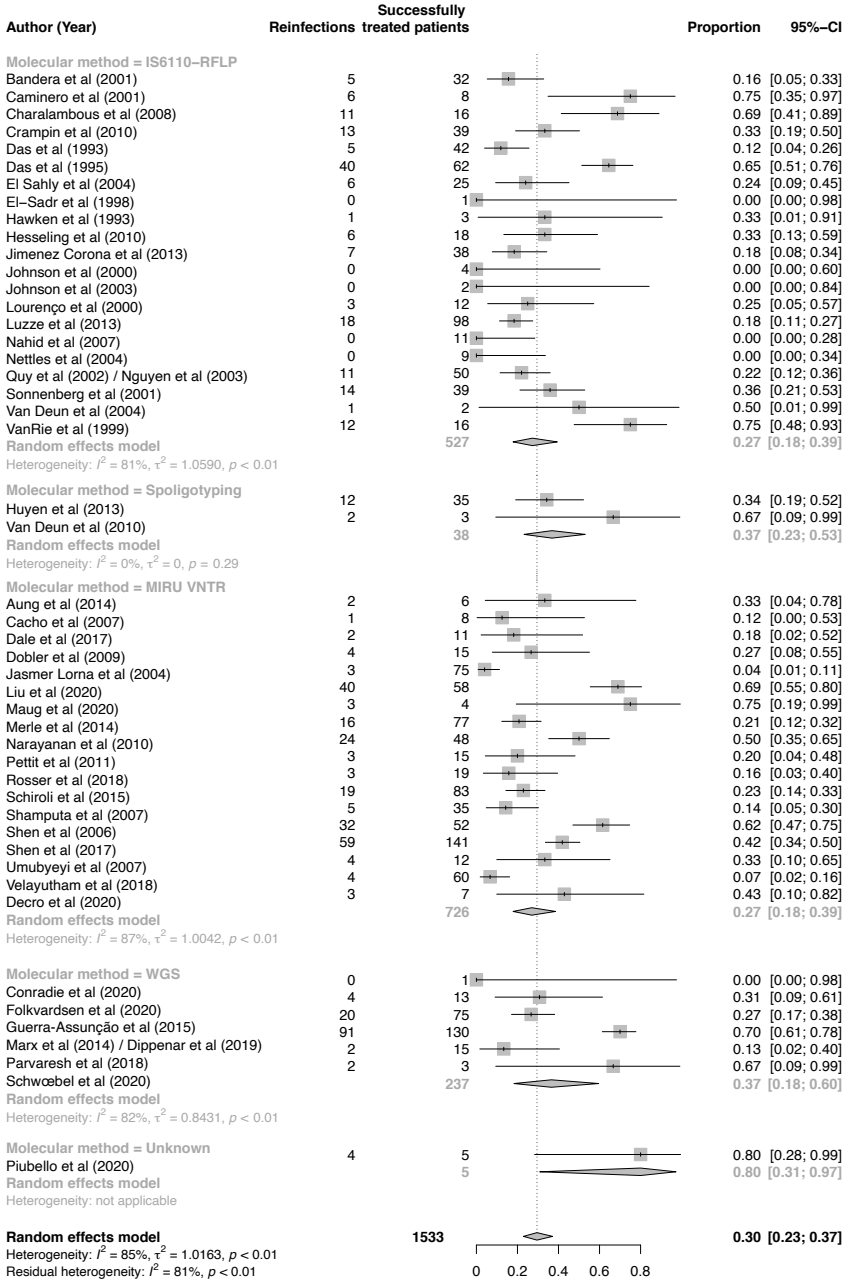


Figure S16 Forest plot of the proportion of reinfections among recurrent TB episodes by study sample size

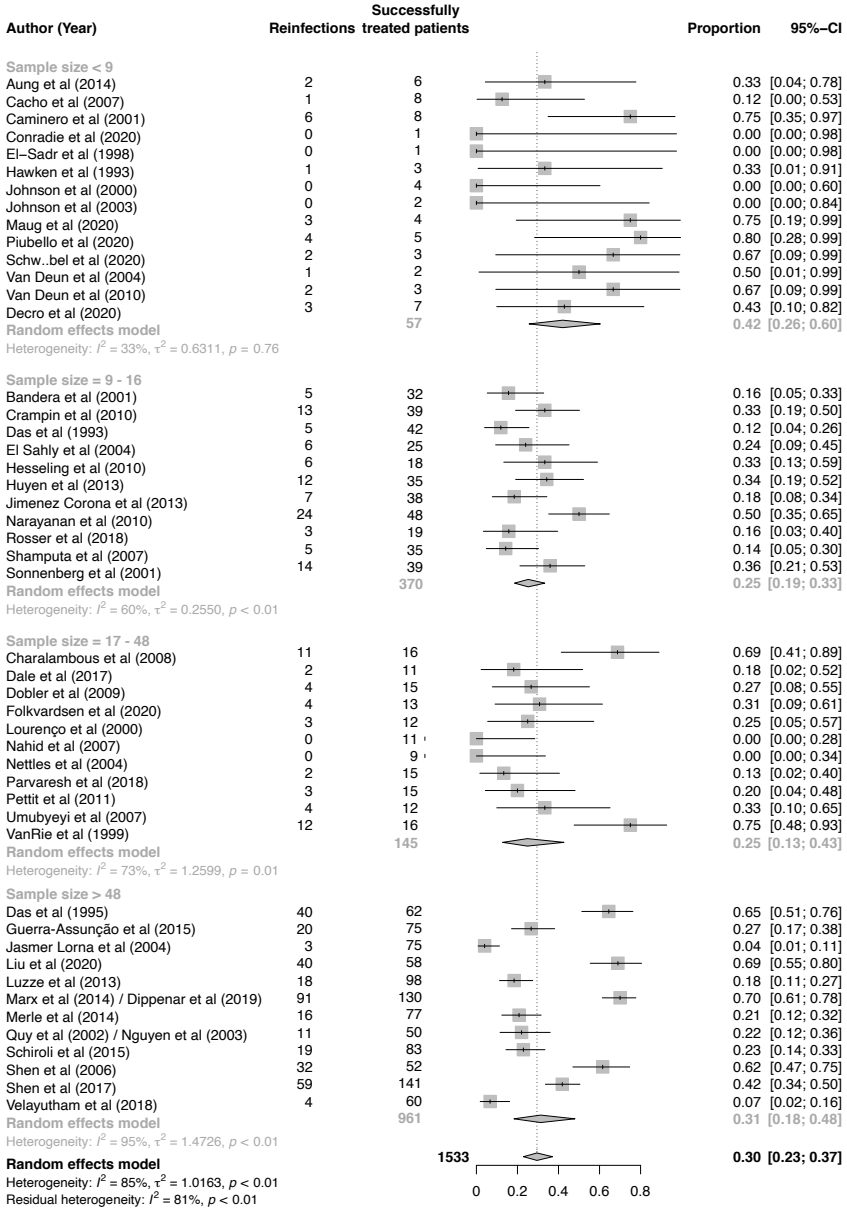


Figure S17 Forest plot of the proportion of reinfections among recurrent TB episodes by study quality

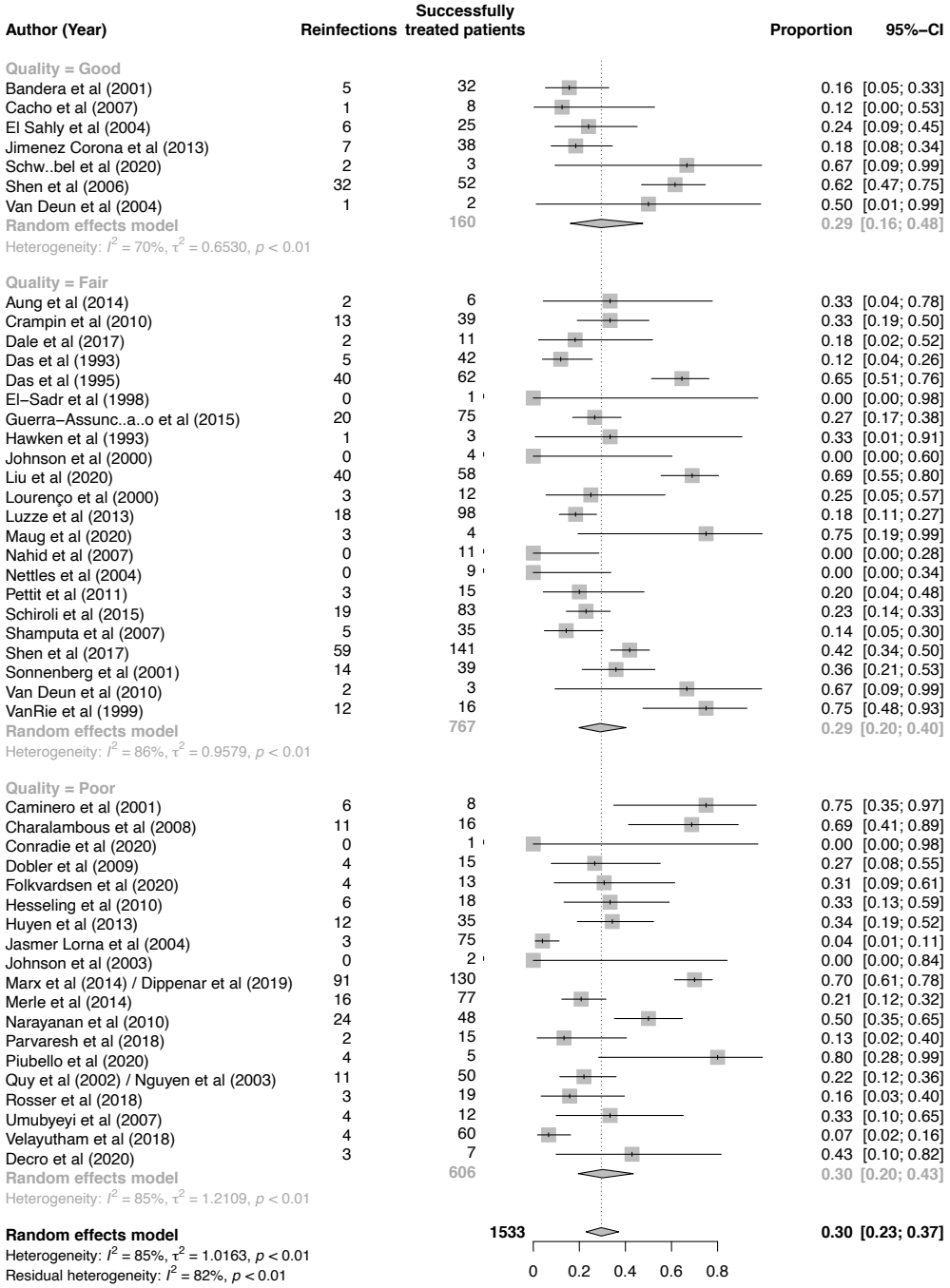
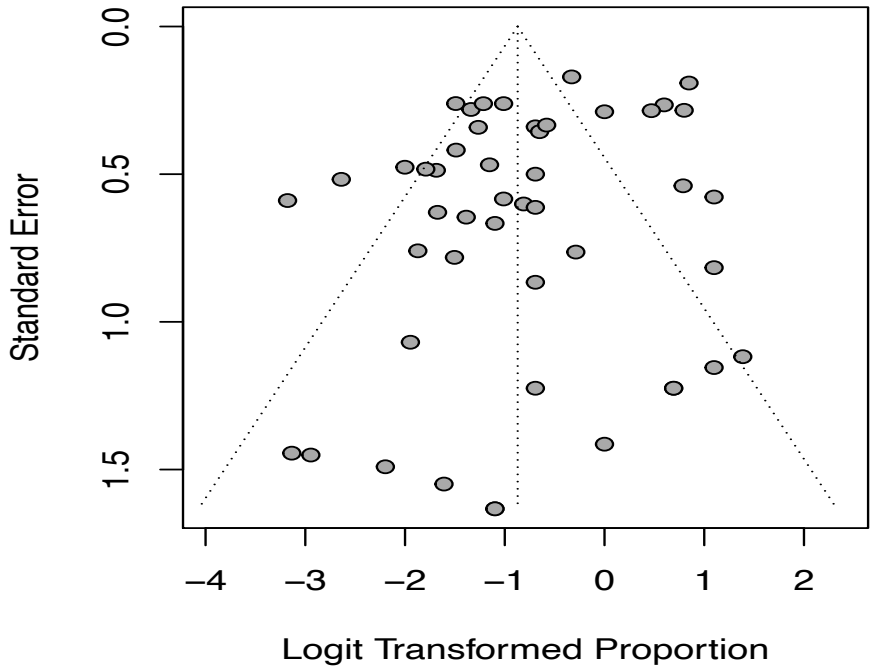


Figure S18 Funnel plot Proportion of reinfections



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