TUBERCULOSIS RECURRENTE: REVISIÓN SISTEMÁTICA Y META-ANÁLISIS DE TASAS DE INCIDENCIA Y DE PROPORCIONES DE RECAÍDAS Y REINFECCIONES.

RECURRENT TB: A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE INCIDENCE RATES AND THE PROPORTIONS OF RELAPSES AND REINFECTIONS

TRABAJO DE INVESTIGACIÓN PARA OPTAR POR EL TÍTULO PROFESIONAL DE MÉDICO CIRUJANO

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

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RESUMEN

Antecedente: La tuberculosis recurrente ocurre mediante dos mecanismos: reinfección o recaída, que pueden diferenciarse mediante técnicas de genotipificación. **Métodos:** Revisión sistemática y meta-análisis utilizando como base de datos MEDLINE, Lilacs/Scielo, y Cochrane, de estudios en inglés, francés y español publicados entre el 1 de enero de 1980 hasta el 30 de septiembre de 2020 y que evaluaron las recurrencias tras un tratamiento exitoso y/o diferenciaron recaídas de reinfecciones utilizando genotipificación Se utilizó un metanálisis de modelo de efectos aleatorios para estimar las tasas de incidencia y la proporción de recaídas y reinfecciones. Además, se realizó análisis de subgrupos. **Resultados:** La tasa de incidencia de tuberculosis recurrente agrupada fue 2.26 por 100 personas-año (95% IC 1.87-2.73; 145 estudios). La heterogeneidad fue alta (I^2=98%). La tasa de incidencia de tuberculosis recurrente incrementó de 1.47 (95% IC 0.87-2.46) a 4.10 (95% IC 2.67-6.28) por 100 personas-año entre estudios desarrollados en zonas de baja vs. alta incidencia de tuberculosis. La proporción de recaídas fue del 70% (95% IC 63-77%; I^2=85%; 48 estudios). La heterogeneidad estuvo determinada por la incidencia de TB, con una proporción de recaídas del 83% (95% IC 75-89%) vs 59% (95% IC 42-74%) en estudios de baja vs. alta incidencia, respectivamente. **Conclusión:** El riesgo de recurrencia es sustancial y la recaída es el mecanismo más frecuente de recurrencia. Sin embargo, con el aumento de incidencia de TB, la proporción de reinfecciones incrementa y el predominio de recaídas disminuye.

Palabras clave: Tuberculosis, Infección respiratoria, Epidemiología clínica

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 a MEDLINE, Lilacs/Scielo, and Cochrane search for studies in English, French, and Spanish published between January 1, 1980 and September 30, 2020 that assessed recurrences after 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 analysis 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 1.87-2.73; 145 studies). Heterogeneity was high (I^2=98%). Stratified pooled recurrence rates increased from 1.47 (95%CI 0.87-2.46) to 4.10 (95%CI 2.67-6.28) per 100 person-years for studies conducted in low vs. 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 63-77%; I^2=85%; 48 studies). Heterogeneity was determined by background TB incidence, as demonstrated by pooled proportions of 83% (95%CI 75-89%) vs 59% (95%CI 42-74%) relapse for studies from settings with low vs. 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 reinfection increases and the predominance of relapses among recurrences decreases.

Key words Tuberculosis, Clinical Epidemiology, Respiratory Infection

INTRODUCTION

The proportion of persons with tuberculosis (TB) that are successfully treated is a key indicator to monitor progress of the End TB Strategy.[1] The standardized 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 programs at least 85% of patients receiving it are successfully treated (cured or treatment completed) [5,6] in routine TB programs. After being cured, some persons 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 relapse from reinfection 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 investigate recurrent TB episodes. One review[7] found, without providing a pooled estimate, that the proportion of reinfection 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 thirteen 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, 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 relapses.

METHODS

Search strategy and selection criteria

The study protocol was prospectively registered in PROSPERO (number CRD42018077867). We included clinical trials, longitudinal studies, and studies using TB program databases that reported recurrent TB rates and/or the proportion of reinfection and relapse, published between January 1st, 1980 and September 30th, 2020, in English, French, and Spanish. We searched MEDLINE/PubMed, Cochrane, LILACS, and 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 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 program databases.

Duplicity of studies was identified using Covidence software, Veritas Health Innovation (available at www.covidence.org) or manually, e.g. 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 relapse and reinfection, our second outcome, we also included studies exploiting national or subnational TB program 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 relapse and reinfection. The nature of and rationale for modifying some items of the scale is detailed in 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 Appendix 3.

The meta-analysis of recurrent TB incidence was done with RStudio Version 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 (DL) 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 value < 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 World Health Organization[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 (6 or more month rifampicin, < 6 months of rifampicin and drug resistant TB regimens). Based on UNAIDS or government publications, background HIV prevalence, was dichotomized as low if <1% in the general population and high otherwise. For studies conducted before 1990, we categorized the country as low level unless it was recognized 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 by 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 value <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.

Pooled proportion of reinfection and relapse

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 reinfection and relapse 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 analysis we also used the variables specified above, except drug regimen (information not available for studies using TB program databases) and, additionally, the proportion of study patients with DNA fingerprinting results available for the first and recurrent TB episode (dichotomized with the upper tertile as cut-off), and the molecular method used. We calculated crude and adjusted odds ratios -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 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 program database. Sufficient data on patient follow-up was 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 Appendix 5.

Molecular techniques used to discriminate TB reinfection and relapse.

Of the studies reporting on reinfections and relapses, thirty used IS6110-restriction fragment length polymorphism analysis (IS6110 RFLP) to differentiate strains, 19 spoligotyping, 19 mycobacterial interspersed repetitive unit-variable number tandem repeat typing (MIRU-VNTR), two polymorphic GC-rich repetitive sequence genotyping (PGRS), one double repetitive element-polymerase chain reaction (DRE-PCR) and six whole genome sequencing (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 1.88 - 2.72). Heterogeneity was significant (I^2=98%). Figure 3 is the forest plot for this analysis. Details on the studies, including the follow-up information used to calculate person-years at risk, are shown in 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 Figures S1-S8. The funnel plot in 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 Table S3. Twenty four studies were of good quality, 84 fair and 37 poor quality.

Proportion of reinfection and relapse in recurrent TB episodes

For studies that differentiate between reinfection and relapse, the overall pooled proportion of relapses was 71% (95% CI 63-77%) and of reinfection 29% (95% CI 23-37%). Heterogeneity was high (I^2=79%) Figure 4 presents a forest plot of this analysis. Detailed data of the included studies are shown in Table S2.

Table 2 shows subgroup analyses of the proportion of relapse and reinfection 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 odds ratio 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 Figures S10-S17. The funnel plot for this outcome (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 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 as well as the reasons.

DISCUSSION

We found, across 145 studies, a pooled incidence rate of recurrent TB after successful treatment of 2.26 (95% CI 1.87 - 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 than the background rate, dramatically so in low and medium TB incidence settings. Relapses were the more common mechanism of recurrence across 48 studies, accounting for a pooled estimate of 70% (95%CI 63-77%) recurrent episodes. With increasing background TB incidence the proportion of reinfection 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 TB patients, 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 (0.98–11.90) 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 (1.2–2.7) and 4.5 (3.2–5.8) per 100 person-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 and 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 socio-economic 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 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 to 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 being recognized 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 one 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 persons at risk are closely followed up and higher recurrent TB incidence rates were found among clinical trials compared to 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 amongst 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 persons visiting high burden countries[19] and among people 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 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 the present review, with on average short durations of follow-up, 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 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 bacteriologically confirmed TB patients 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 program level and for research, should be scrutinized 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 sensitized to promptly seek care if symptoms reappear. Second, TB programs 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 programs to implement measures that enhance effective treatment of a first episode as amongst 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 bio-medical factors associated with relapse and socio-environmental ones associated with reinfection, so these can be addressed or guide care after cure. Romanowski et [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 programs 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.

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 persons years (95% confidence intervals)	Crude incidence rate ratio (95% confidence intervals)	p-value	Adjusted incidence rate ratio (95% confidence intervals)	p-value
By background TB incidence level		23.20			<0.001		0.009
Low (< 30 cases per 100,000)	25		1.47 (0.89; 2.45)	Ref		Ref	
Moderate (31-100 cases per 100,000)	47		1.63 (1.22; 2.18)	1.09 (0.65; 1.83)		1.15 (0.71; 0.86)	
Medium (101-300 cases per 100,000)	59		2.87 (2.22; 3.71)	1.95 (1.20; 3.18)		1.87 (1.16; 3.02)	
High (> 300 cases per 100,000)	14		4.10 (2.67; 6.28)	2.75 (1.43; 5.27)		2.28 (1.20; 4.34)	
Background HIV prevalence		17.42			<0.001		0.094
Low level (<1%)	101		1.79 (1.43; 2.26)	Ref		Ref	
High level	44		3.64 (2.82; 4.68)	1.99 (1.38; 2.87)		1.34 (0.94; 1.98)	
TB drug regimen		1.35			0.053		0.019
6 or more months of rifampicin	98		2.17 (1.75; 2.70)	Ref		Ref	
Less than 6 months of rifampicin	20		3.67 (2.28; 5.90)	1.69 (1.00; 2.86)		1.61 (1.05; 2.47)	
Drug resistant TB regimens	27		1.48 (0.76; 2.87)	0.75 (0.43; 1.29)		0.73 (0.45; 1.19)	
Study design		7.87			0.029		
Clinical trials	43		3.17 (2.41; 4.16)	1.55 (1.05; 2.31)			
Observational studies	102		1.98 (1.58; 2.48)	Ref			
Sample size		14.12			0.059		0.054

	0-153	37		2.81 (1.76; 4.49)	1.86 (1.08; 3.21)		2.08 (1.25; 3.44)	
	154-335	36		2.53 (1.87; 3.44)	1.58 (0.98; 2.53)		1.53 (0.99; 2.35)	
	336-668	36		2.67 (1.90; 3.76)	1.70 (1.07; 2.70)		1.40 (0.93; 2.12)	
	>668	36		1.57 (1.13; 2.18)	Ref		Ref	
Planned follow-up (years)			2.97			0.019		.0110
	< 1 year	24		4.01 (2.51; 6.40)	Ref		Ref	
	1-2 years	60		2.36 (1.79; 3.11)	0.58 (0.33; 1.02)		0.55 (0.34; 0.89)	
	> 2 years	61		1.82 (1.37; 2.42)	0.46 (0.26; 0.79)		0.49 (0.31; 0.79)	
Type of follow-up			0			0.457		
	Passive	40		1.77 (1.21; 2.61)	Ref			
	Active	94		2.49 (1.97; 3.15)	1.39 (0.91; 2.14)			
Quality of the study			0			0.478		
	Good quality	24		1.91 (1.31; 2.78)	Ref			
	Fair quality	84		2.21 (1.71; 4.85)	1.18 (0.71; 1.98)			
	Poor quality	37		2.78 (2.01; 3.86)	1.45 (0.79; 2.64)			

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

Study subgroup	Number of studies	R^2	Proportion of reinfections % (95% confidence intervals)	Proportion of relapses % (95% confidence intervals)	Crude odds ratio for reinfections	p-value	Adjusted odds ratio for reinfections	p-value
By background TB incidence level		25.48				0.009		0.034
Low (< 30 cases per 100,000)	16		17 (11; 25)	84 (77; 90)	Ref	-	Ref	
Moderate (31-100 cases per 100,000)	7		39 (25; 55)	61 (45; 75)	3.19 (1.21; 8.41)	-	3.64 (1.31; 10.10)	
Medium (101-300 cases per 100,000)	17		35 (23; 50)	65 (50; 77)	2.81 (1.30; 6.09)	-	2.76 (1.18; 6.45)	
High (> 300 cases per 100,000)	8		41 (26; 58)	59 (42; 74)	3.54 (1.50; 8.38)	-	6.90 (2.06; 23.14)	
By background HIV prevalence		2.58				0.586		0.847
Low level (<1%)	26		28 (22; 44)	73 (64; 81)	Ref	-	Ref	
High level	22		32 (20; 38)	64 (51; 75)	1.21 (0.61; 2.40)	-	0.89 (0.39; 2.04)	
Study design		7.87				0.385		0.217
Cohort study	26		32 (23; 43)	68 (57; 77)	Ref		Ref	
Program database review	17		29 (20; 40)	71 (60; 80)	0.86 (0.43; 1.72)	-	1.51 (0.76; 3.02)	
Clinical trial	5		16 (04; 49)	84 (51; 97)	0.39 (0.11; 1.48)	-	0.39 (0.11; 1.40)	
Study sample size		7.48				0.434		0.246
<9	14		42 (26; 60)	58 (40; 74)	1.52 (0.57; 4.06)		2.01 (0.69; 5.85)	
9-16	11		25 (18; 33)	75 (67; 82)	0.74 (0.13; 1.85)		1.20 (0.48; 3.01)	

17-48	11		25 (13; 43)	76 (57; 87)	0.69 (0.29; 1.62)		0.86 (0.35; 2.11)	
>48	12		31 (18; 48)	69 (52; 82)	Ref		Ref	
Follow-up (years)		1.24				0.579		
<2 years	12		25 (12; 46)	75 (54: 88)	Ref			
≥ 2 years	36		31 (24-39)	69 (61; 77)	1.26 (0.55; 2.89)			
By molecular method		5.67				0.625		0.751
RFLP	21		27 (18; 39)	72 (53; 85)	Ref		Ref	
Spoligotyping	2		37 (23; 53)	63 (47; 77)	2.09 (0.35;		2.33 (0.42; 13.02)	
MIRU VNTR	18		27 (18; 39)	73 (61; 82)	0.98 (0.47; 2.03)		1.42 (0.67; 3.02)	
Whole genome sequencing	6		36 (18; 60)	64 (40; 62)	1.50 (0.49; 4.54)		1.39 (0.48; 3.98)	
By DNA fingerprinting		2.51				0.522		
≤ 88 %	15		26 (16; 39)	74 (61; 84)	1.27 (0.60; 2.68)			
>88 %	33		31 (23; 40)	69 (60; 77)	Ref			
Quality of the study		1.37				0.990		0.545
Good	7		29 (16; 48)	71 (84; 53)	Ref		Ref	
Fair	22		29 (20; 40)	71 (80; 59)	0.97 (0.34; 2.78)		0.56 (0.21; 1.50)	
Poor	19		30 (20; 4)	70 (81, 57)	1.04 (0.36; 3.01)		0.59 (0.21; 1.62)	

Table 3 GRADE evidence profile

№ of studies	**Certainty assessment**						**Effect**			**Certainty**	**Importance**
	Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of events**	**№ of individuals**	**Measure (95% CI)**		
Recurrent TB incidence rate per 100 person-years											
145	observational studies	serious [a]	serious [b]	not serious	not serious	none	6548	153565	2.26 per 100 person-years (1.87 - 2.73)	⊕⊕◯◯ LOW	IMPORTANT
Proportion of reinfections											
48	observational studies	serious[c]	serious [d]	not serious	not serious	none	523	1533	30% (23 - 37)	⊕⊕◯◯ LOW	IMPORTANT

Explanations

a. 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 table S3 for details).

b. 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.

c. 7 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 RFLP) for differentiating relapses and reinfections (see table S4 for details).

d. Heterogeneity was high (I^2=79%) 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.

Competing interests None declared

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Patient consent Not required

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