Recurrent tuberculosis in the pre-elimination era

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Summary

Recurrent tuberculosis (TB), defined as TB that reoccurs after a patient had been considered cured, constitutes a challenge to TB control. In TB low-burden countries, the underlying causes and consequences of recurrent TB are poorly understood. We conducted a literature review to summarize the evidence of recurrent TB in low-burden settings and to address current knowledge gaps. We included peer-reviewed publications on studies conducted in countries with an estimated TB incidence of less than 100 cases per 100,000 population. The Newcastle-Ottawa tool was used to assess study quality. The review yielded 44 manuscripts of which 39 were reports of observational studies and five of clinical trials. The median percentage of TB patients experiencing an episode of recurrent TB after treatment completion was 3.4% (IQR 1.6%-6.0%; range 0.4%-16.7%) in studies with a median follow-up of 7.8 years (IQR 5-12 years; range 2-33 years). The median percentage of recurrences that were attributable to endogenous reactivation (rather than exogenous reinfection) was 81% (IQR 73.1%-85.5%; range 49%-100%). Risk factors of recurrence in low-burden settings commonly identified included Human Immunodeficiency Virus infection, low socioeconomic status, foreign birth and infection with drug resistant TB. At present, the understanding of recurrence in low-burden settings is limited, in part due to substantial methodological differences between studies. Further research is required to delineate the mechanisms of TB recurrence, its health and clinical impacts as well as its implications for TB elimination efforts in low-burden countries.
In 2015, worldwide an estimated 10.4 million people developed tuberculosis (TB), and 1.8 million died from TB, including 0.4 million co-infected with the Human Immunodeficiency Virus (HIV) (1). Considerable progress has been made in global TB control over the past two decades. Significant advances in TB diagnosis, treatment and control have reduced global TB prevalence in 2015 by 42% and mortality by 47% relative to 1990 levels (1). The roll out of standard TB chemotherapy has averted an estimated 38.6 million deaths between 2000 and 2015 (1). An important outcome measure for global TB control is the percentage of treated TB patients who successfully complete their treatment, including those with bacteriological proof of cure and those who complete their treatment in the absence of either proof of bacteriological cure or of treatment failure. Global TB control efforts have resulted in an increase in the treatment success rate for new cases globally from 69% in 2000 to 84% 2005; between 2006 to 2014, rates have ranged between 83% and 87% (1).

Not all TB patients successfully treated for TB achieve long-term cure. Recurrent TB, defined as TB that reoccurs after a patient had been considered cured via standard TB treatment, therefore constitutes a challenge to TB control. Recurrent TB after successful treatment may be due to endogenous reactivation (relapse) or exogenous reinfection (2). According to World Health Organization (WHO) standard definitions, cases of recurrent TB are reported as ‘relapse’ cases (i.e. re-treatment cases after treatment success) without distinguishing true relapses from reinfection cases (3). In 2015, a total of 476,107 recurrent (‘relapse’) cases were notified, representing 7.7% of all notified new and relapse cases worldwide (4). Cases of recurrent TB often constitute a challenge to TB control programs due to the possibility of clinical sequelae related to the prior TB episode (5, 6), the risk of more extensive (7) and of drug-resistant disease (8) and more unfavourable treatment outcomes (9).

A new patient-centered approach which focuses on TB prevention and case finding among hard-to-reach populations and vulnerable (high-risk) groups is at the core of WHO’s new strategy for global TB elimination, called the End TB Strategy (10, 11). A closer focus on high-risk groups is especially important in TB low-burden countries where future TB elimination seems within reach (11). Whether people at risk of recurrent TB deserve consideration as one of the high-risk groups in low-burden countries is currently not known.
In this review, we aimed to summarise the current evidence of TB recurrence in countries and settings with a low burden of TB, including findings of relapse and reinfection as underlying mechanism of recurrence derived from molecular studies, and the determinants of recurrent TB risk. We discuss current knowledge gaps that should be addressed to improve understanding of the causes and consequences of recurrent TB at the individual level as well as the potential role of recurrence for TB control in the context of current TB elimination efforts in low-burden countries.

**Definitions and search strategy**

We conducted a systematic search of PubMed and Google Scholar databases using the keywords ‘relapse’, ‘recurrence’, ‘reinfection’, ‘re-infection’, ‘tuberculosis’ and ‘Mycobacterium tuberculosis’. References of identified manuscripts were screened for additional studies meeting the inclusion criteria. Search results were limited to manuscripts written in English and published in the past 30 years, i.e. between January 1st 1987 and May 1st 2017.

We reviewed abstracts from the search. We included manuscripts of clinical trials and observational studies reporting data on the epidemiology, mechanisms and/or risk factors for recurrent TB if a definition of recurrent TB was stated. Studies were restricted to those that had been conducted in countries with an incidence of less than 100 TB cases per 100,000 population estimated by the WHO for the year that the reported study was started; Studies were excluded if (1) the definition of recurrent TB included events of TB after unknown or unfavorable treatment outcomes, and (2) if patients with TB recurrence were not compared to those with a single episode of TB.

We extracted data on sample size, TB recurrence definition, frequency measures, genotyping data and method, risk factors for recurrence and patient outcomes. We further extracted information about the methods used in the studies to determine treatment success and disease recurrence as well as the type of follow-up used. Risk factors were organized into categories of host, bacillary and those of drug resistant cohorts. Median and interquartile ranges (IQR) were calculated for the TB recurrence, relapse and reinfection rates. The proportion of recurrence due to endogenous reactivation (relapse, as opposed to exogenous reinfection) was recorded from studies with molecular strain-type information and an overall median value and IQR calculated.
The quality of all included studies was assessed by the Newcastle-Ottawa scale, a validated tool to appraise non-randomized and observational studies(12). The quality score was based upon three categories: (1) selection of the groups studied; (2) comparability; (3) assessment of exposure or outcome. Case-control and cohort studies awarded 7-8, 5-6, 4 and 0-3 were classified as very good, good, satisfactory or unsatisfactory respectively.

**Recurrence studies overview**

The search identified 71 papers, 44 (62%) of which met the inclusion criteria (see Figure 1). Of the latter, 39 (89%) were reports of observational studies and 5 (11%) of clinical trials. Of the 39 observational studies, 34 (87%) used passive follow-up of individuals to ascertain recurrent TB and 5 (13%) active follow-up. Eighteen (41%) studies were conducted in North America, 13 (30%) in Europe, 10 (23%) in Asia, 2 (4%) in South America and 1 (2%) in Australia. The median country-level TB incidence rate for studies included was 10.9 cases per 100,000 population (IQR 9.7-54; total range 1.5-96; 39 studies). Sixteen (36%) of the 44 studies included strain-type data to estimate frequencies of relapse and reinfection TB.

Based upon the Newcastle-Ottawa scale, 7(100%) case-control studies were of very good quality and of the cohort studies, 13(35%) were very good, 16(43%) good, 6(16%) satisfactory and 2(6%) unsatisfactory (see tables A3 and A4). Studies with unsatisfactory scores failed to describe the method of ascertainment of exposure, control for confounding and ensure adequacy of follow up.

Studies were heterogeneous in terms of the definitions used for recurrent TB (see Appendix Table A1). Thirteen (30%) defined treatment success of the first episode by bacteriological cure; nine (20%) identified the recurrent episode through active (rather than passive) follow-up; 21 (48%) required bacteriological confirmation to establish the recurrent episode.

Key study limitations included the use of isolated positive cultures to define recurrence (without controlling for false positive results, for example from cross contamination) (2). Passive rather than active follow-up was often used to detect recurrence cases, suggesting potential for under-detection of recurrence (13). The definitions of reinfection were based on differences in strain type patterns between episodes suggesting potential for misclassification of reinfection as relapse where population strain diversity is low or individuals are repeatedly infected from the same source case and of relapse as reinfection due to strain evolution, mixed infection or
laboratory cross-contamination (14). Furthermore, lower resolution typing methods such as mycobacterial interspersed repetitive units variable number tandem repeat typing (MIRU-VNTR) may incorrectly classify relapse as reinfection and vice versa (15).

**TB recurrence rates and timing**

The overall proportion of patients with TB recurrence was 3.4% (IQR 1.6%-6.0%; range 0.4%-16.7%; 42 studies) (see Tables 1&2) (16-57). For studies reporting on the average duration of patient follow-up, a median of 4.4% (IQR 1.9%-6.6%; range 0.4%-10%) of individuals experienced recurrence over a median follow-up period of 3 years (IQR 2.0-5.1 years; range 1.0-8.9 years; 21 studies). In studies employing active follow-up, 6.0% (IQR 4.7%-7.0%; range 0.8%-13.0%; 10 studies) of patients developed recurrence and in those using passive follow-up, the proportion was 2.9% (IQR 1.4%-5.2%; range 0.4%-16.7%; 34 studies).

Among the 12 studies providing total person-years of follow up, the median TB recurrence rate was 720 (IQR 473-2,024; range 71-3,780) per 100,000 person-years of follow-up. This was a median 31.5-fold (IQR 11.8-57.1; range 7.3-497.8) higher than the annual country-level TB incidence rate quoted in each study.

Five studies focused on recurrence after treatment for multidrug-resistant (MDR) TB (see Table 2). The median proportion recurrence among MDR-TB patients was 6.5% (IQR 4.4%-8.5%; range 3.4-10) (52-56).

Data were not sufficient to meaningfully compare rates of recurrent TB among HIV positive and negative individuals.

Ten studies estimated the time to recurrence after completion of TB treatment, nine of which used passive and on active follow-up. The median time to recurrence was 1.4 years (IQR 1.1-2.8 years; range 0.6-5.8 years).

**Risk factors for TB recurrence**

Risk factors for recurrent TB were categorized into host and bacillary risk factors after non-MDR-TB treatment. We further report risk factors among individuals who completed an episode of MDR-TB treatment. Effect measures presented are adjusted for other risk factors unless otherwise specified.

**Host**
Socio-demographic

There is some but inconsistent evidence about an association between age and recurrent TB. Crofts et al found that children between 0-14 years of age were at lower risk of recurrence compared to 15-44 year-olds (hazard ratio (HR) 0.37 95%CI 0.22-0.62) (36); Golub et al reported that those aged 40-49 years were at lower risk compared to those under 30 (HR 0.47 95%CI 0.25-0.89) (31); Kim et al showed that patients aged 65 years or older were at greater risk than those under 45 years (odds ratio (OR) 1.88 95%CI 1.21-2.92) (51).

Male gender was a strong independent predictor of TB recurrence. Hung et al found that males were twice as likely to experience recurrence (OR 2.23 95%CI 1.40-3.53) than females and Millett et al found that males experienced up to four times higher risk (HR 4.3 95%CI 1.3-14.6) (34, 47). The former suggested the observed association between male gender and recurrence may be due to residual confounding of other risk factors more prevalent in men such as smoking (47).

Low socioeconomic status was reported to be a significant risk factor for recurrence. In a study conducted nation-wide in Taiwan, individuals earning less than New Taiwan (NT)$19200 (US$605) a month were found to be at elevated risk of recurrent TB (OR 2.99 95%CI 1.82-3.97) compared to those earning NT$30,300 (US$954) or more a month (47). Other socio-economic determinants including unemployment (OR 5.8; 95%CI 1.7-19.6; OR 1.94; 95%CI 1.02-3.67) (39, 58), use of public transport (OR 2.02; 95%CI 1.06-3.84) (58) and inner city residence (HR 3.9; 95%CI 1.3-11.8) (40) were independently associated with recurrent TB.

Foreign country of birth and immigration were associated with TB recurrence across a range of studies (34, 38, 48). Migrants to Spain were at elevated risk compared to the native population (HR 3.2, 95%CI 1.2-9.0) (34). Among Mexican immigrants in the USA who experienced two consecutive episodes of TB within 12 years of immigration reinfection was a more common cause of recurrence than reactivation compared to native residents (OR 10.7; 95% CI, 1.7–86.3) (48). Conversely, in a study conducted in California, individuals born in the USA were found to be at greater risk of recurrence (HR 1.88 95%CI 1.34-2.63) than those elsewhere (38).

Certain ethnic groups were reported to be at elevated risk of recurrence. These included indigenous groups vs. non-indigenous (OR 4.24; 95%CI 1.56-11.54) in Taiwan (43); South Asians in the UK compared to the white population (HR 1.54; 95% CI 1.23-1.93) (36), and non-
Hispanic white ethnicity vs. non-white ethnicities in the USA (OR 3.0 95%CI 1.4-6.7 (33) OR4.62 95%CI 1.28-16.68 (37)).

Co-morbidities

HIV type-1 infection was consistently associated with recurrence in low-burden settings (23, 36, 38, 40, 45, 51, 58). Pettit et al found that HIV infection was associated with recurrence due to reinfection but not relapse (37). Another study could not confirm this result (46). The degree of immunosuppression as measured by the peripheral CD4 lymphocyte count was inversely associated with recurrence risk. Golub et al found that a CD4 count of between 200-349 cells mm\(^{-3}\) measured during the initial TB diagnosis was associated with a lower risk of recurrence compared to patients with counts of less than 200 cells mm\(^{-3}\) (HR 0.35; 95%CI 0.20-0.60) (31). Similarly Pulido et al found a CD4 count of less than 100 cells mm\(^{-3}\) were at greater risk compared to those with higher counts (relative hazard 3.4; 95%CI 1.1-11) (17)

The impact of antiretroviral therapy (ART) on TB recurrence was examined by Golub et al who showed a lower likelihood of recurrence (HR 0.5 95%CI 0.28-0.89) (31) but this was only one single study. The relationship between duration of the initial TB treatment episode and the risk of recurrence in HIV positive patients was examined by two retrospective observational cohort studies. Receiving more than 37 weeks of TB treatment was associated with a lower recurrence risk (17, 23) compared to shorter durations although these studies predated the wide use of ART. Similarly, Nahid et al showed the extension of the standard 6-month TB treatment course was associated with a reduced risk of recurrence in a cohort where 47% of patients had received no ART (HR 4.33 p=0.02) (29). This was consistent with a randomized controlled trial conducted in high burden settings (59).

Diabetes mellitus was consistently found to be independently associated with TB recurrence (OR 11.15; 95%CI 2.5-50.7 (39); OR 1.96; 95%CI 1.22-3.15 (43); OR 1.51; 95%CI 1.02-2.13 (47)) Only Lee et al. explored the degree to which blood sugar control (as measured through glycated hemoglobin) affected recurrence risk. They found that patients with no measurement of glycated hemoglobin were at higher risk of recurrence (OR 1.98; 95%CI 1.13-3.45) compared to those with at least one measurement and suggested better glycaemic control through better adherence to diabetes care and improved glucose monitoring (43) to explain their findings.
Chronic lung disease (CLD) was independently associated with TB recurrence as documented by Pettit et al (OR 5.28; 95%CI 1.16-24.04) (37) and Hung et al (OR 1.59; 95%CI 1.08-2.36) (47). Hung et al found this risk was independent of smoking status (47) whereas Pettit et al found significant interaction between CLD and smoking (37).

Several life-style factors were found to be associated with recurrent TB. Patients who smoked more than 20 cigarettes a day were more likely to experience TB recurrence than those smoking less than 20 a day (OR 9.4; 95%CI 1.1-83.9) (39). A combined history of alcohol/injecting drug/non-injecting drug use (HR 1.57; 99%CI 1.23-2.02) (51), alcoholism (OR 3.9; 95%CI 2.5-6.1) (26) and intravenous drug use (HR 2.95; 95%CI 1.3-6.4) (34) were reported to be independently associated with recurrent TB.

Clinical / extent of disease

Bodyweight measured at TB treatment initiation and failure to gain weight during TB treatment were reported to be associated with TB recurrence. One study found that patients of 50-69kg were at lower risk than those under 50kg (OR 0.53; 95%CI 0.33-0.85) (43), whilst another demonstrated that weight loss at the time of diagnosis of more than 10% (compared to less than 10%) was associated with recurrent TB (OR 7.2; 95%CI 2.4-21.9) (39). Furthermore, the failure to gain more than 5% of bodyweight within the first two months of TB treatment was independently associated in both studies (27, 39).

The presence of pre-treatment pulmonary cavitation as assessed by chest x-ray was found to be strongly associated with recurrence (OR 6.1 95%CI 2.2-16.9) (39). In two studies employing genotyping, relapse was described as the underlying mechanism in this association (unadjusted OR 3.2; 95%CI 1.4-7.5; OR 4.6 95%CI 1.1-26.9) (33, 35). Bilateral pulmonary involvement was associated with recurrent TB in univariate analysis (OR 2.9; 95%CI 1.5-2.7). However, this association did not remain after adjusting for other risk factors (OR 1.8; 95%CI 0.9-4.0).

Treatment supervision/compliance

Low compliance to the standard 6-month course of TB-treatment and irregular treatment increases the risk of TB recurrence (60). Anaam et al. showed an association between failure to take >80% of prescribed doses in the continuation phase of TB treatment (39) and the risk of recurrence (OR 25.7 95%CI 2.2-297.9). The relationship between supervised (vs. self-administered) therapy and the risk of recurrence was assessed by two studies. El-sahly et al
found supervised therapy was associated with a lower recurrence risk (OR 0.12; 95%CI 0.06-0.23) (58) whereas Kim et al. did not find such association (51).

**Bacillary risk factors**

Infection with the Beijing strain was found to be associated with relapse (OR 15.8; 95%CI 1.3-192) in a study (33). This finding was limited to individuals of the Asian-Pacific Islander race who were resident in the USA or Canada.

Few studies have investigated the effect of pre-treatment drug-resistance on TB recurrence rates (61). Pyrazinamide mono-resistance, indicative of *Mycobacterium bovis* infection, was found to be associated with TB recurrence (HR 2.93; 95%CI 1.19-7.19). Unexpectedly, isoniazid mono-resistance was found to be associated with a reduced risk of recurrence in one study (HR 0.25; 95%CI 0.08-0.78) (38). The authors suggested this finding may be due to (intended) intensified or extended TB treatment in patients with known mono-resistance.

Pre-treatment sputum smear-positive compared to smear-negative TB was found to be associated with TB recurrence in two studies (HR 1.96; 95%CI 1.36-2.82) (HR 1.56; 99%CI 1.06-2.30) (38, 51). Furthermore, a lack of culture conversion after two months of TB treatment was found to be associated with recurrent TB (OR 2.4; 95%CI 1.2-4.9) (33).

**Risk factors in multidrug- and extensively drug-resistant TB cohorts**

Few studies examined risk factors for TB recurrence amongst patients with MDR-TB and extensively drug-resistant (XDR-) TB in low-burden settings. Among successfully treated MDR-TB patients, pre-XDR and XDR resistance profiles (HR 7.3 95%CI 1.2-44) (52), pre-treatment pulmonary cavitation as seen on chest x-ray (HR 10.2; 95%CI 1.2-89) (52) and previous TB treatment (HR 4.28; 95%CI 1.16-4.00) were reported to be associated with the risk of TB recurrence (53).

**Relapse and reinfection as underlying mechanisms of recurrent TB**

Sixteen studies in this review used genotyping to define the burden of recurrent TB due to relapse and reinfection. Of the different typing methods employed, IS6110 restriction fragment length polymorphism (RFLP) typing and MIRU-VNTR were commonly used either alone or in combination with spoligo-typing (see Table 3). Where strain-type DNA patterns of paired isolates from both episodes were found to be identical by the genotyping method(s) used, this
was defined as a case of relapse. In 12 (75%) of studies, reinfection was defined by 1 or more differences in DNA bands, in 3 (19%) studies by 2 or more differences, and in 1 study by 3 or more differences.

Overall, the median percentage of recurrences due to endogenous re-activation (relapse) was 81.0% (IQR 73.1%-85.5%; range 49.0%-100%; 16 studies) (see Table 3) (19, 20, 22, 25, 28-30, 35, 37, 40, 45, 46, 48, 57, 58, 62). In a study conducted in Taiwan, reinfection was found to be the underlying mechanism for 51% of recurrences (28).

Bang et al (35) reported that the majority of relapses occurred within the first four years, whereas the risk of reinfection TB was constant throughout the 14 years of the study. Their finding was consistent with those by Jasmer et al (25) who found that the relapse rate peaked in the early period after treatment cessation with 69% of relapses within 6 months and 89% within 12 months (all HIV-negative individuals). Among HIV-positive individuals, 79% relapsed within 6 months. In both HIV-positive and -negative people, rates of reinfection TB did not appear to vary over time.

**Clinical impact of recurrence**

Few studies have examined the clinical outcome of recurrent TB patients in low-burden settings. Mortality data were available in three studies (see Table 4). Kim et al (41) found that mortality during TB treatment for recurrent TB was higher compared to first-time TB treatment (11.8% vs. 8.7%).

Seventeen studies looked at the acquisition of any drug-resistance during a first treatment episode. Two were excluded from analysis for failing to provide data for individual patients (see Table 4). Overall the median level of drug resistant TB increased by 6.3% (IQR 0.7%-21.3%; range 0.0%-27.4%) amongst patients with recurrent TB when compared to the level present in primary TB episode. (19, 21-23, 25, 29, 35, 38, 45, 46, 49, 52, 54, 56, 57).

**Discussion of review findings**

This review shows that even in low-incidence countries, recurrent TB after successful TB treatment is commonly observed, consistent with earlier findings by Panjabi et al. (63). We found a median proportion of recurrent TB of 3.4% over a median duration of patient follow-up of 7.8 years. Several studies identified in this review were able to directly compare rates of
recurrent TB to those of new TB, showing a median 31.5-fold higher rate of recurrent TB (17, 18, 25, 31, 34, 36, 40, 43, 47, 52, 55, 57). Our summary estimates are consistent with the assumption that successfully treated patients are at several-fold higher risk of TB compared to those never before treated for TB.

Molecular studies suggest that TB recurrence in low-incidence countries is due mainly to endogenous reactivation (relapse, median: 81%) rather than reinfection. This finding corresponds well with mathematical models suggesting that the extent to which reinfection contributes to recurrent TB in different populations is a function of the background incidence of TB in that population (28, 64). Although relapse was found to be more common than reinfection in low-incidence countries, an exception to this rule may apply to risk groups and (sub-)populations with a higher background incidence. For example, reinfection TB was found to be more common than relapse among Mexican immigrants to the USA whose background TB incidence was several-fold higher than among US born people (48, 65).

We note substantial variation in the estimates of recurrent TB after successful treatment across the studies (total range of recurrent TB: 0.7% to 16.7%). Some of this variation is explained by the heterogeneity of studies in terms of definitions for recurrent TB and the type and duration of follow-up. For example, studies employing active follow-up reported higher rates of recurrent TB compared to those relying on passive follow-up (i.e. self-presentation) of individuals to diagnose recurrent TB. Additional variation may result from the different study populations some of which may include more individuals at higher risk of recurrence than others. Furthermore, differences in the quality of TB treatment and the supervision of patients during their initial TB treatment episode as well as differences in the probability of becoming re-infected (and thus of experiencing recurrent TB due to reinfection) may explain this variation.

Consistent with previous research (63), we document various risk factors for recurrent TB among successfully treated patients in low-incidence countries. Similar to observations from high-incidence countries (66, 67) we found HIV co-infection the most consistently noted risk factor for recurrent TB in low-burden settings. Pettit et al (37) show that even in a low-incidence setting an association between HIV and reinfection was present. Both, an increased susceptibility to reinfection and lack of protective immunity leading to a high risk of disease progression among people living with HIV seems to underlie this observation. Conversely, TB treatment extension (17, 23) reduces the risk of recurrence among HIV infection, suggesting a role in
reactivation among HIV-infected people. Provision of ART appears to reduce future recurrence risk (31) but more evidence is needed. Whether TB treatment extension should be considered, and whether it can reduce recurrent TB even during ART is currently not known (68).

Other risk factors measured during or at the end of the first TB treatment episode were identified, suggesting potential for interventions to identify individuals or groups of TB patients at high risk of disease recurrence. These include low adherence during TB treatment, comorbidities and potentially immunosuppressive conditions such as diabetes mellitus, lifestyle factors, and bacillary factors. Some of these risk factors may underlie the associations between socio-demographic factors and recurrent TB observed in several studies. For example, associations between factors including gender, socioeconomic status, immigration and ethnic background, and the adherence of patients to TB treatment have been described (69). Potential predictors of recurrence identified include the change in pre-treatment bodyweight with TB treatment (27, 39) and 2-month sputum culture positivity (33). Change in bodyweight with TB treatment may be an attractive clinical marker to assess the risk of recurrent TB as it is easy to implement and suitable even for low-resource settings, however it has not been rigorously assessed. Lack of month-2 culture conversion is included TB treatment guidelines as a one marker of risk of relapse after treatment completion (70) however it was shown to exhibit poor specificity and sensitivity for predicting recurrence by one meta-analysis (71). More robust clinical and biomarkers of treatment response to achieve a recurrence-free cure are required.

The clinical impact of recurrence has been addressed by some authors. It appears recurrence is associated with infection with increasingly drug-resistant strains. However, what drives resistance in patients after successful treatment has not been established. There was limited information on clinical outcomes of patients with recurrence with only one study (51) showing a small increase in mortality among those with recurrent disease in comparison to those without a previous episode of TB.

Our review was limited by the substantial heterogeneity in the methodology employed across studies. For example, studies differed in their length of patient follow-up limiting the formulation of summary measures of TB recurrence. Due to the low number of studies, we were unable to analyze trends of recurrent TB in subpopulations and particular geographic areas. Finally, this review did not include studies published in languages other than English which may have
excluded additional information on the epidemiology of recurrent TB, its mechanisms and risk factors.

**Moving towards TB elimination in low-incidence settings – how important is recurrent TB?**

In low-incidence countries and settings, the vast majority of TB is found among people without a history of previous disease. The relative contribution of recurrent disease to TB incidence thus appears to be relatively low (36-38, 40). Nevertheless, recurrent TB deserves consideration in the context of TB elimination.

As low-incidence countries and settings are expected to move towards TB elimination in the forthcoming years, targeting control measures to groups at high TB risk will be essential for progress (11). Even in low-incidence settings, individuals previously cured from TB may experience more than a 10-fold higher risk of TB compared to individuals never before treated (34). They may thus count among the TB high-risk groups suitable for control measures, even though part of their excess TB risk may be explained by an overlap with other known TB risk factors commonly found in this group such as HIV infection, diabetes, smoking, alcohol and substance abuse (30, 34, 36, 43, 51).

Although relatively rare in the general population, recurrence might contribute more substantially to the TB burden in certain subgroups with a higher risk of the disease. For example, a high risk of recurrent TB among migrants has been reported (34, 38, 48). A large cohort study among Filipino immigrants to the United States found that one-third of individuals who developed TB after immigration had presented at entry with radiological findings consistent with previously active TB (72) consistent with the possibility that recurrence of TB (rather than reactivation of latent TB infection alone) might have contributed to the disease burden in this group. Furthermore, with decreasing incidence of TB in the general population, recurrent TB due to re-activation of old TB lesions in the elderly population (73, 74) is expected to become a more important cause of TB. The excess risk of TB associated with a past history of TB should therefore be considered when tailoring target TB control measures to high-risk groups such as immigrants or the elderly, in order to achieve TB elimination.

Finally, drug-resistant TB is expected to represent an important barrier to TB elimination in low-incidence countries and settings (11). Observed high rates of disease recurrence among
people cured from drug-resistant TB (52, 75, 76) and, vice-versa, elevated rates of drug-resistant disease among recurrent TB patients (58) suggest that recurrent TB may play an important role when tackling the burden (and transmission) of drug-resistant TB in order to achieve elimination. 

The relative ease with which people at risk of recurrent TB may be identifiable from previous treatment records might make them attractive for additional control measures. However, the costs of such targeted interventions should be carefully weighed against their benefits in low-incidence populations. Whether reducing recurrent TB (and associated transmission) in the general population or in specific high-risk groups such as immigrants or individuals cured from drug-resistant TB could form part of an enhanced TB control strategy to support TB elimination is currently not known and should be evaluated in the future.

**Recurrent TB in low-incidence countries: priorities for future research**

Various studies have been conducted in low-burden countries to improve our understanding of recurrent TB, its frequency, underlying mechanisms and risk factors. Future studies of the epidemiology of recurrent TB should seek to improve comparability, for example by developing and applying consensus definitions of recurrence and standardizing the reporting of the frequency and timing of recurrent TB with total length of follow up provided in person-years.

While studies to date have focused on establishing risk factors for recurrence and distinguishing relapse from reinfection, future research is needed to better understand the biological, microbiological and pathophysiological mechanisms of disease recurrence. Basic science directed towards understanding these mechanisms may highlight novel therapeutic approaches and potential biomarkers predicting the probability of definite cure vs. disease re-activation and reinfection TB.

Although individuals risk factors of recurrence have been identified, to date, little is known about suitable strategies to effectively prevent recurrence among high-risk individuals. Research is needed to understand the benefits of individualized and intensified TB treatment towards achieving long-term cure. This may entail research on the effect of adjuvant therapies to reduce lung destruction and inflammation (77), the modification of other individual risk factors (78), and the possibility of extending the duration of TB treatment for certain groups of patients at high risk of recurrence (38).
More research is also needed to better understand the long-term consequences of recurrent TB to individuals and health-care systems. There is currently a lack of knowledge about the clinical, social and socio-economic consequences that TB and recurrent TB imposes on patients, their families, and the health-care system. At the health-care level, more information is also needed to understand the extent to which recurrent TB contributes to the overall TB burden in different populations. Particularly in populations where drug-resistant and MDR-TB is highly prevalent, the role of TB recurrence towards the acquisition and transmission of drug-resistance, and in reverse, the role of drug-resistance towards increasing recurrent TB, should be investigated. Finally, former TB patients should be re-considered as an important high-risk group for TB control. As low-burden countries will scale up control efforts among high-risk groups in order to reach TB elimination in the future, implementation research and mathematical modeling could help determine the circumstances under which interventions targeted at former TB patients, such as increased efforts to prevent or early detect TB recurrence, may be a cost-effective element of comprehensive TB elimination strategies in low-burden countries and beyond.
References


63. Panjabi R, Comstock GW, Golub JE. Recurrent tuberculosis and its risk factors: adequately treated patients are still at high risk. The international journal of tuberculosis and lung
627 disease: the official journal of the International Union against Tuberculosis and Lung Disease.
629
630 64. Uys PW, van Helden PD, Hargrove JW. Tuberculosis reinfection rate as a proportion of
631 total infection rate correlates with the logarithm of the incidence rate: a mathematical model.
633
634 65. Schmit KM, Wansaula Z, Pratt R, Price SF, Langer AJ. Tuberculosis - United States,
636
638 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South
640
641 67. Crampin AC, Mwaungulu JN, Mwaungulu FD, Mwafulirwa DT, Munthali K, Floyd S, et
642 al. Recurrent TB: relapse or reinfection? The effect of HIV in a general population cohort in
644
646 updated systematic review and meta-analysis on the treatment of active tuberculosis in patients
648
650 to tuberculosis treatment: a systematic review of qualitative research. PLoS medicine.
652
654 American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases
656 Clinical infectious diseases: an official publication of the Infectious Diseases Society of
658
660 monitoring during tuberculosis treatment for predicting outcome: systematic review and meta-
662
664 tuberculosis reactivation risk in United States immigrants. American journal of respiratory and
666
667 73. Hauer B, Brodhun B, Altmann D, Fiebig L, Loddenkemper R, Haas W. Tuberculosis in
668 the elderly in Germany. The European respiratory journal. 2011;38(2):467-70.
669
670 74. Salinas Garrido I, Taberner Huguet E, Garrós Garay J, Gil Alaña P, Ciruelos Ayuso E,
671 Lopez Aranaga I, et al. Thoracic tuberculosis (TB) in 75 to 100 year-old patients. European
672 Respiratory Journal. 2016;48(suppl 60).
673
675 Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance.
677
679 of patients with multidrug resistant tuberculosis four years after standardized first-line drug
681
682 77. Ong CW, Elkington PT, Friedland JS. Tuberculosis, pulmonary cavitation, and matrix
683 metalloproteinases. American journal of respiratory and critical care medicine. 2014;190(1):9-
684 18.
Table 1: Studies conducted in low-burden settings included in the review (excluding MDR-TB specific studies)

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<th>Recurrence incidence rate (10^5 PYs)</th>
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</table>

*per 100,000 population; national TB incidence rates were taken from the start of each study †HIV positive cohort; Δ recurrence proportion for clinical trial control and intervention group given ‡data unavailable, range quoted for 1992-2005 from paper. Abbreviations: PYs – person years;
Table 2: MDR-TB specific studies conducted in low-burden settings included in the review

<table>
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<tr>
<th>Author</th>
<th>Country</th>
<th>TB Incidence*</th>
<th>Cohort size</th>
<th>Recurrences</th>
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<th>Duration (years)</th>
<th>Recurrence incidence rate ($10^5$ PYs)</th>
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<td>(56)</td>
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<td>3.4</td>
<td>4.8</td>
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Summary estimate: 6.5% (IQR 4.4%-8.5%; range 3.4-10)

* per 100,000 population; national TB incidence rates were taken from the start of each study.
Table 3. TB relapse and reinfection in low-burden settings

<table>
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<th>Total TB cases¶</th>
<th>Total recurrences</th>
<th>Paired strain typed isolates⁞</th>
<th>Relapse (%)</th>
<th>Reinfection (%)</th>
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<td>8 (100)</td>
<td>0 (0)</td>
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<td>IS6110 RFLP</td>
<td>267</td>
<td>11</td>
<td>11 9 (82)</td>
<td>18</td>
<td>(20)</td>
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<td>IS6110 RFLP; Spoligotyping</td>
<td>2127</td>
<td>32</td>
<td>32 84</td>
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<td>Netherlands</td>
<td>12.2</td>
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<td>Δ</td>
<td>183</td>
<td>183 84</td>
<td>16</td>
<td>(62)</td>
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</tr>
<tr>
<td>El-Sahly</td>
<td>USA</td>
<td>8.5</td>
<td>IS6110 RFLP; Spoligotyping</td>
<td>Δ</td>
<td>186</td>
<td>41 69-76‡</td>
<td>24-31‡</td>
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<td>IS6110 RFLP and others (see paper)</td>
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<td>136</td>
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<td>4682</td>
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<td>83 77</td>
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Summary estimate (relapse): 81% (IQR 73%-85%; range 49%-100%)

*per 100,000 population; national TB incidence rates were taken from the start of each study. ¶the number of successfully treated TB cases included in each study
⁞the number of cases for which paired strain-type DNA information was available; Δ–the total number of successfully treated patients was not stated. † data unavailable, range quoted for 1992-2005 from paper. ‡ In this study two cohorts of patients were analyzed separately and the data is provided for each.

Abbreviations: RFLP – restriction fragment length polymorphism; MIRU-VNTR – mycobacterial interspaced repeat unit – variable number tandem repeat;
Table 4. The clinical impact of TB recurrence in low-burden settings

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<td>Primary episode (n)</td>
<td>Recurrence (n)</td>
</tr>
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<td>19% (64)</td>
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<tr>
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<td>(22)</td>
</tr>
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<td>13% (24)†</td>
<td>4% (25)†</td>
<td>(28)</td>
</tr>
<tr>
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<td>25% (4)</td>
<td>(57)</td>
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</tr>
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</tr>
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<tr>
<td>Pascopella</td>
<td>8.8% (147)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>El-sahly‡</td>
<td>‘Group A’: 9.7%; ‘Group B’: 13.1% †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avery</td>
<td>0% (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chen</td>
<td>17% (6)</td>
<td>0% (6)</td>
<td></td>
</tr>
<tr>
<td>Sterling</td>
<td>20% (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avendano</td>
<td>25% (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driver</td>
<td>27% (95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vernon</td>
<td>50% (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>0% (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary estimate % increase resistance (all studies): 6.3% (IQR 0.7%-21.3%; range 0.0%-27.4%)

† Data detailing changes in the phenotypic resistance profile for isolates from individual patients was not provided and thus these patients were not included in the analysis. The figures shown describe the change in prevalence of drug resistant isolates between the first and recurrence episode. ‡ In this study two cohorts of patients were analyzed separately and the data is provided for each. ¶ Chi squared test for the difference in mortality p<0.001