1 **IJTLD State of the Art of the Series**

2 **Recurrent tuberculosis in the pre-elimination era**

3 Andrew Rosser MBBS[1,2]; Florian M. Marx MD[3], Manish Pareek PhD[1,2]

4 [1]Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

5 [2]Department of Infection and Tropical Medicine, University Hospitals of Leicester NHS Trust,

6 Leicester, UK

7 [3]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine

8 and Health Sciences, Stellenbosch University, Tygerberg Campus, Cape Town, South Africa

9 **Corresponding Author:** Dr Manish Pareek, Department of Infection, Immunity and

10 Inflammation, University of Leicester, University Road, Leicester, LE1 7RH

11 Email: mp426@le.ac.uk

12 **Word count:** summary 237; text 5119, references 78, tables 4; figures 1

13 **Running title:** Recurrent TB in the pre-elimination era

21 **Competing interests:** Dr Pareek reports an institutional grant (unrestricted) for project related to

22 blood-borne virus testing from Gilead Sciences outside the submitted work. All other authors

23 report no conflicts of interest.

24 **Contributions:** AR & FM acquired & interpreted the data & wrote the preliminary manuscript

25 draft; AR, FM & MP substantially revised it critically for intellectual content; all authors

26 approved the final version.

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.

Introduction

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

135 laboratory cross-contamination (14). Furthermore, lower resolution typing methods such

136 mycobacterial interspersed repetitive units variable number tandem repeat typing (MIRU-

137 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% (IQR4.7%-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

165   There is some but inconsistent evidence about an association between age and recurrent TB.

166   Crofts et al found that children between 0-14 years of age were at lower risk of recurrence

167   compared to 15-44 year-olds (hazard ratio (HR) 0.37 95%CI 0.22-0.62) (36); Golub et al

168   reported that those aged 40-49 years were at lower risk compared to those under 30 (HR 0.47

169   95%CI 0.25-0.89) (31); Kim et al showed that patients aged 65 years or older were at greater risk

170   than those under 45 years (odds ratio (OR) 1.88 95%CI 1.21-2.92) (51).

171   Male gender was a strong independent predictor of TB recurrence. Hung et al found that

172   males were twice as likely to experience recurrence (OR 2.23 95%CI 1.40-3.53) than females

173   and Millett et al found that males experienced up to four times higher risk (HR 4.3 95%CI 1.3-

174   14.6) (34, 47). The former suggested the observed association between male gender and

175   recurrence may be due to residual confounding of other risk factors more prevalent in men such

176   as smoking (47).

177   Low socioeconomic status was reported to be a significant risk factor for recurrence. In a

178   study conducted nation-wide in Taiwan, individuals earning less than New Taiwan (NT)$19200

179   (US$605) a month were found to be at elevated risk of recurrent TB (OR 2.99 95%CI 1.82-3.97)

180   compared to those earning NT$30,300 (US$954) or more a month (47). Other socio-economic

181   determinants including unemployment (OR 5.8; 95%CI 1.7-19.6; OR 1.94; 95%CI 1.02-3.67)

182   (39, 58), use of public transport (OR 2.02; 95%CI 1.06-3.84) (58) and inner city residence (HR

183   3.9; 95%CI 1.3-11.8) (40) were independently associated with recurrent TB.

184   Foreign country of birth and immigration were associated with TB recurrence across a range

185   of studies (34, 38, 48). Migrants to Spain were at elevated risk compared to the native population

186   (HR 3.2, 95%CI 1.2-9.0) (34). Among Mexican immigrants in the USA who experienced two

187   consecutive episodes of TB within 12 years of immigration reinfection was a more common

188   cause of recurrence than reactivation compared to native residents (OR 10.7; 95% CI, 1.7–86.3)

189   (48). Conversely, in a study conducted in California, individuals born in the USA were found to

190   be at greater risk of recurrence (HR 1.88 95%CI 1.34-2.63) than those elsewhere (38).

191   Certain ethnic groups were reported to be at elevated risk of recurrence. These included

192   indigenous groups vs. non-indigenous (OR 4.24; 95%CI 1.56-11.54) in Taiwan (43); South

193   Asians in the UK compared to the white population (HR 1.54; 95% CI 1.23-1.93) (36), and non-

194 Hispanic white ethnicity vs. non-white ethnicities in the USA (OR 3.0 95%CI 1.4-6.7 (33)

195 OR4.62 95%CI 1.28-16.68 (37)).

196 *Co-morbidities*

197 HIV type-1 infection was consistently associated with recurrence in low-burden settings (23, 36,

198 38, 40, 45, 51, 58). Pettit et al found that HIV infection was associated with recurrence due to

199 reinfection but not relapse (37). Another study could not confirm this result (46).The degree of

200 immunosuppression as measured by the peripheral CD4 lymphocyte count was inversely

201 associated with recurrence risk. Golub et al found that a CD4 count of between 200-349 cells

202 mm^{-3} measured during the initial TB diagnosis was associated with a lower risk of recurrence

203 compared to patients with counts of less than 200 cells mm^{-3} (HR 0.35; 95%CI 0.20-0.60) (31).

204 Similarly Pulido et al found a CD4 count of less than 100 cells mm^{-3} were at greater risk

205 compared to those with higher counts (relative hazard 3.4; 95%CI 1.1-11) (17)

206   The impact of antiretroviral therapy (ART) on TB recurrence was examined by Golub et al

207 who showed a lower likelihood of recurrence (HR 0.5 95%CI 0.28-0.89) (31) but this was only

208 one single study. The relationship between duration of the initial TB treatment episode and the

209 risk of recurrence in HIV positive patients was examined by two retrospective observational

210 cohort studies. Receiving more than 37 weeks of TB treatment was associated with a lower

211 recurrence risk (17, 23) compared to shorter durations although these studies predated the wide

212 use of ART. Similarly, Nahid et al showed the extension of the standard 6-month TB treatment

213 course was associated with a reduced risk of recurrence in a cohort where 47% of patients had

214 received no ART (HR 4.33 p=0.02) (29). This was consistent with a randomized controlled trial

215 conducted in high burden settings (59).

216   Diabetes mellitus was consistently found to be independently associated with TB recurrence

217 (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

218 (47)) Only Lee et al. explored the degree to which blood sugar control (as measured through

219 glycated hemoglobin) affected recurrence risk. They found that patients with no measurement of

220 glycated hemoglobin were at higher risk of recurrence (OR 1.98; 95%CI 1.13-3.45) compared to

221 those with at least one measurement and suggested better glycaemic control through better

222 adherence to diabetes care and improved glucose monitoring (43) to explain their findings.

223   Chronic lung disease (CLD) was independently associated with TB recurrence as documented

224   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)

225   (47). Hung et al found this risk was independent of smoking status (47) whereas Pettit et al found

226   significant interaction between CLD and smoking (37).

227   Several life-style factors were found to be associated with recurrent TB. Patients who smoked

228   more than 20 cigarettes a day were more likely to experience TB recurrence than those smoking

229   less than 20 a day (OR 9.4; 95%CI 1.1-83.9) (39). A combined history of alcohol/injecting

230   drug/non-injecting drug use (HR 1.57; 99%CI 1.23-2.02)(51), alcoholism (OR 3.9; 95%CI 2.5-

231   6.1) (26) and intravenous drug use (HR 2.95; 95%CI 1.3-6.4) (34) were reported to be

232   independently associated with recurrent TB.

233   *Clinical / extent of disease*

234   Bodyweight measured at TB treatment initiation and failure to gain weight during TB

235   treatment were reported to be associated with TB recurrence. One study found that patients of

236   50-69kg were at lower risk than those under 50kg (OR 0.53; 95%CI 0.33-0.85) (43), whilst

237   another demonstrated that weight loss at the time of diagnosis of more than 10% (compared to

238   less than 10%) was associated with recurrent TB (OR 7.2; 95%CI 2.4-21.9) (39). Furthermore,

239   the failure to gain more than 5% of bodyweight within the first two months of TB treatment was

240   independently associated in both studies (27, 39).

241   The presence of pre-treatment pulmonary cavitation as assessed by chest x-ray was found to

242   be strongly associated with recurrence (OR 6.1 95%CI 2.2-16.9) (39). In two studies employing

243   genotyping, relapse was described as the underlying mechanism in this association (unadjusted

244   OR 3.2; 95%CI 1.4-7.5; OR 4.6 95%CI 1.1-26,9) (33, 35). Bilateral pulmonary involvement was

245   associated with recurrent TB in univariate analysis (OR 2.9; 95%CI 1.5-2.7). However, this

246   association did not remain after adjusting for other risk factors (OR 1.8; 95%CI 0.9-4.0).

247   *Treatment supervision/compliance*

248   Low compliance to the standard 6-month course of TB-treatment and irregular treatment

249   increases the risk of TB recurrence (60). Anaam et al. showed an association between failure to

250   take >80% of prescribed doses in the continuation phase of TB treatment (39) and the risk of

251   recurrence (OR 25.7 95%CI 2.2-297.9). The relationship between supervised (vs. self-

252   administered) therapy and the risk of recurrence was assessed by two studies. El-sahly et al

253 found supervised therapy was associated with a lower recurrence risk (OR 0.12; 95%CI 0.06-
254 0.23) (58) whereas Kim et al. did not find such association (51).

Bacillary risk factors

256   Infection with the Beijing strain was found to be associated with relapse (OR 15.8; 95%CI
257 1.3-192) in a study (33). This finding was limited to individuals of the Asian-Pacific Islander
258 race who were resident in the USA or Canada.

259   Few studies have investigated the effect of pre-treatment drug-resistance on TB recurrence
260 rates (61). Pyrazinamide mono-resistance, indicative of *Mycobacterium bovis* infection, was
261 found to be associated with TB recurrence (HR 2.93; 95%CI 1.19-7.19). Unexpectedly, isoniazid
262 mono-resistance was found to be associated with a reduced risk of recurrence in one study (HR
263 0.25; 95%CI 0.08-0.78) (38). The authors suggested this finding may be due to (intended)
264 intensified or extended TB treatment in patients with known mono-resistance.

265   Pre-treatment sputum smear-positive compared to smear-negative TB was found to be
266 associated with TB recurrence in two studies (HR 1.96; 95%CI 1.36-2.82) (HR 1.56; 99%CI
267 1.06-2.30) (38, 51). Furthermore, a lack of culture conversion after two months of TB treatment
268 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

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

Relapse and reinfection as underlying mechanisms of recurrent TB

277   Sixteen studies in this review used genotyping to define the burden of recurrent TB due to
278 relapse and reinfection. Of the different typing methods employed, IS6110 restriction fragment
279 length polymorphism (RFLP) typing and MIRU-VNTR were commonly used either alone or in
280 combination with spoligo-typing (see Table 3). Where strain-type DNA patterns of paired
281 isolates from both episodes were found to be identical by the genotyping method(s) used, this

282 was defined as a case of relapse. In 12 (75%) of studies, reinfection was defined by 1 or more
283 differences in DNA bands, in 3 (19%) studies by 2 or more differences, and in 1 study by 3 or
284 more differences.
285   Overall, the median percentage of recurrences due to endogenous re-activation (relapse) was
286 81.0% (IQR 73.1%-85.5%; range 49.0%-100%; 16 studies) (see Table 3) (19, 20, 22, 25, 28-30,
287 35, 37, 40, 45, 46, 48, 57, 58, 62). In a study conducted in Taiwan, reinfection was found to be
288 the underlying mechanism for 51% of recurrences (28).
289   Bang et al (35) reported that the majority of relapses occurred within the first four years,
290 whereas the risk of reinfection TB was constant throughout the 14 years of the study. Their
291 finding was consistent with those by Jasmer et al (25) who found that the relapse rate peaked in
292 the early period after treatment cessation with 69% of relapses within 6 months and 89% within
293 12 months (all HIV-negative individuals). Among HIV-positive individuals, 79% relapsed within
294 6 months. In both HIV-positive and -negative people, rates of reinfection TB did not appear to
295 vary over time.

Clinical impact of recurrence

297   Few studies have examined the clinical outcome of recurrent TB patients in low-burden
298 settings. Mortality data were available in three studies (see Table 4). Kim et al (41) found that
299 mortality during TB treatment for recurrent TB was higher compared to first-time TB treatment
300 (11.8% vs. 8.7%).
301   Seventeen studies looked at the acquisition of any drug-resistance during a first treatment
302 episode. Two were excluded from analysis for failing to provide data for individual patients (see
303 Table 4). Overall the median level of drug resistant TB increased by 6.3% (IQR 0.7%-21.3%;
304 range 0.0%-27.4%) amongst patients with recurrent TB when compared to the level present in
305 primary TB episode. (19, 21-23, 25, 29, 35, 38, 45, 46, 49, 52, 54, 56, 57).

Discussion of review findings

307   This review shows that even in low-incidence countries, recurrent TB after successful TB
308 treatment is commonly observed, consistent with earlier findings by Panjabi et al. (63). We
309 found a median proportion of recurrent TB of 3.4% over a median duration of patient follow-up
310 of 7.8 years. Several studies identified in this review were able to directly compare rates of

311   recurrent TB to those of new TB, showing a median 31.5-fold higher rate of recurrent TB (17,

312   18, 25, 31, 34, 36, 40, 43, 47, 52, 55, 57). Our summary estimates are consistent with the

313   assumption that successfully treated patients are at several-fold higher risk of TB compared to

314   those never before treated for TB.

315   Molecular studies suggest that TB recurrence in low-incidence countries is due mainly to

316   endogenous reactivation (relapse, median: 81%) rather than reinfection. This finding corresponds

317   well with mathematical models suggesting that the extent to which reinfection contributes to

318   recurrent TB in different populations is a function of the background incidence of TB in that

319   population (28, 64). Although relapse was found to be more common than reinfection in low-

320   incidence countries, an exception to this rule may apply to risk groups and (sub-)populations

321   with a higher background incidence. For example, reinfection TB was found to be more common

322   than relapse among Mexican immigrants to the USA whose background TB incidence was

323   several-fold higher than among US born people (48, 65).

324   We note substantial variation in the estimates of recurrent TB after successful treatment

325   across the studies (total range of recurrent TB: 0.7% to 16.7%). Some of this variation is

326   explained by the heterogeneity of studies in terms of definitions for recurrent TB and the type

327   and duration of follow-up. For example, studies employing active follow-up reported higher rates

328   of recurrent TB compared to those relying on passive follow-up (i.e. self-presentation) of

329   individuals to diagnose recurrent TB. Additional variation may result from the different study

330   populations some of which may include more individuals at higher risk of recurrence than others.

331   Furthermore, differences in the quality of TB treatment and the supervision of patients during

332   their initial TB treatment episode as well as differences in the probability of becoming re-

333   infected (and thus of experiencing recurrent TB due to reinfection) may explain this variation.

334   Consistent with previous research (63), we document various risk factors for recurrent TB

335   among successfully treated patients in low-incidence countries. Similar to observations from

336   high-incidence countries (66, 67) we found HIV co-infection the most consistently noted risk

337   factor for recurrent TB in low-burden settings. Pettit et al (37) show that even in a low-incidence

338   setting an association between HIV and reinfection was present. Both, an increased susceptibility

339   to reinfection and lack of protective immunity leading to a high risk of disease progression

340   among people living with HIV seems to underlie this observation. Conversely, TB treatment

341   extension (17, 23) reduces the risk of recurrence among HIV infection, suggesting a role in

342   reactivation among HIV-infected people. Provision of ART appears to reduce future recurrence

343   risk (31) but more evidence is needed. Whether TB treatment extension should be considered,

344   and whether it can reduce recurrent TB even during ART is currently not known (68).

345   Other risk factors measured during or at the end of the first TB treatment episode were

346   identified, suggesting potential for interventions to identify individuals or groups of TB patients

347   at high risk of disease recurrence. These include low adherence during TB treatment,

348   comorbidities and potentially immunosuppressive conditions such as diabetes mellitus, lifestyle

349   factors, and bacillary factors. Some of these risk factors may underlie the associations between

350   socio-demographic factors and recurrent TB observed in several studies. For example,

351   associations between factors including gender, socioeconomic status, immigration and ethnic

352   background, and the adherence of patients to TB treatment have been described (69). Potential

353   predictors of recurrence identified include the change in pre-treatment bodyweight with TB

354   treatment (27, 39) and 2-month sputum culture positivity (33). Change in bodyweight with TB

355   treatment may be an attractive clinical marker to assess the risk of recurrent TB as it is easy to

356   implement and suitable even for low-resource settings, however it has not been rigorously

357   assessed. Lack of month-2 culture conversion is included TB treatment guidelines as a one

358   marker of risk of relapse after treatment completion (70) however it was shown to exhibit poor

359   specificity and sensitivity for predicting recurrence by one meta-analysis (71). More robust

360   clinical and biomarkers of treatment response to achieve a recurrence-free cure are required.

361   The clinical impact of recurrence has been addressed by some authors. It appears recurrence is

362   associated with infection with increasingly drug-resistant strains. However, what drives

363   resistance in patients after successful treatment has not been established. There was limited

364   information on clinical outcomes of patients with recurrence with only one study (51) showing a

365   small increase in mortality among those with recurrent disease in comparison to those without a

366   previous episode of TB.

367   Our review was limited by the substantial heterogeneity in the methodology employed across

368   studies. For example, studies differed in their length of patient follow-up limiting the formulation

369   of summary measures of TB recurrence. Due to the low number of studies, we were unable to

370   analyze trends of recurrent TB in subpopulations and particular geographic areas. Finally, this

371   review did not include studies published in languages other than English which may have

372 excluded additional information on the epidemiology of recurrent TB, its mechanisms and risk
373 factors.

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

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

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

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

400 Finally, drug-resistant TB is expected to represent an important barrier to TB elimination in
401 low-incidence countries and settings (11). Observed high rates of disease recurrence among

402 people cured from drug-resistant TB (52, 75, 76) and, vice-versa, elevated rates of drug-resistant

403 disease among recurrent TB patients (58) suggest that recurrent TB may play an important role

404 when tackling the burden (and transmission) of drug-resistant TB in order to achieve elimination.

405 The relative ease with which people at risk of recurrent TB may be identifiable from previous

406 treatment records might make them attractive for additional control measures. However, the

407 costs of such targeted interventions should be carefully weighed against their benefits in low-

408 incidence populations. Whether reducing recurrent TB (and associated transmission) in the

409 general population or in specific high-risk groups such as immigrants or individuals cured from

410 drug-resistant TB could form part of an enhanced TB control strategy to support TB elimination

411 is currently not known and should be evaluated in the future.

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

413 Various studies have been conducted in low-burden countries to improve our understanding of

414 recurrent TB, its frequency, underlying mechanisms and risk factors. Future studies of the

415 epidemiology of recurrent TB should seek to improve comparability, for example by developing

416 and applying consensus definitions of recurrence and standardizing the reporting of the

417 frequency and timing of recurrent TB with total length of follow up provided in person-years.

418 While studies to date have focused on establishing risk factors for recurrence and

419 distinguishing relapse from reinfection, future research is needed to better understand the

420 biological, microbiological and pathophysiological mechanisms of disease recurrence. Basic

421 science directed towards understanding these mechanisms may highlight novel therapeutic

422 approaches and potential biomarkers predicting the probability of definite cure vs. disease re-

423 activation and reinfection TB.

424 Although individuals risk factors of recurrence have been identified, to date, little is known

425 about suitable strategies to effectively prevent recurrence among high-risk individuals. Research

426 is needed to understand the benefits of individualized and intensified TB treatment towards

427 achieving long-term cure. This may entail research on the effect of adjuvant therapies to reduce

428 lung destruction and inflammation (77), the modification of other individual risk factors (78),

429 and the possibility of extending the duration of TB treatment for certain groups of patients at

430 high risk of recurrence (38).

431   More research is also needed to better understand the long-term consequences of recurrent TB

432   to individuals and health-care systems. There is currently a lack of knowledge about the clinical,

433   social and socio-economic consequences that TB and recurrent TB imposes on patients, their

434   families, and the health-care system. At the health-care level, more information is also needed to

435   understand the extent to which recurrent TB contributes to the overall TB burden in different

436   populations. Particularly in populations where drug-resistant and MDR-TB is highly prevalent,

437   the role of TB recurrence towards the acquisition and transmission of drug-resistance, and in

438   reverse, the role of drug-resistance towards increasing recurrent TB, should be investigated.

439   Finally, former TB patients should be re-considered as an important high-risk group for TB

440   control. As low-burden countries will scale up control efforts among high-risk groups in order to

441   reach TB elimination in the future, implementation research and mathematical modeling could

442   help determine the circumstances under which interventions targeted at former TB patients, such

443   as increased efforts to prevent or early detect TB recurrence, may be a cost-effective element of

444   comprehensive TB elimination strategies in low-burden countries and beyond.

References

1.	WHO. Global Tuberculosis Report 2016. World Heatlh Organisation, 2016.

2.	Lambert ML, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Van der Stuyft P. Recurrence in tuberculosis: relapse or reinfection? The Lancet Infectious diseases. 2003;3(5):282-7.

3.	Definitions and reporting framework for tuberculosis - 2013 revision (updated December 2014).2014. Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf.

4.	Global tuberculosis database. Available from: http://www.who.int/tb/data/en/.

5.	Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. Respiration; international review of thoracic diseases. 2013;86(1):76-85.

6.	Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. Thorax. 2000;55(1):32-8.

7.	Steininger WJ, Howard WL. A study of re-treatment cases vs original treatment cases of pulmonary tuberculosis. Diseases of the chest. 1959;35(5):480-93.

8.	Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(4):382-90.

9.	Marx FM, Dunbar R, Hesseling AC, Enarson DA, Fielding K, Beyers N. Increased risk of default among previously treated tuberculosis cases in the Western Cape Province, South Africa. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012;16(8):1059-65.

10.	The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organisation; 2013.

11.	Lonnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. The European respiratory journal. 2015;45(4):928-52.

12.	Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [18th of October 2017]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

13.	Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: systematic review. BMJ (Clinical research ed). 2008;336(7642):484-7.

14.	Glynn JR, Yates MD, Crampin AC, Ngwira BM, Mwaungulu FD, Black GF, et al. DNA fingerprint changes in tuberculosis: reinfection, evolution, or laboratory error? The Journal of infectious diseases. 2004;190(6):1158-66.

15.	Bryant JM, Harris SR, Parkhill J, Dawson R, Diacon AH, van Helden P, et al. Whole-genome sequencing to establish relapse or re-infection with Mycobacterium tuberculosis: a retrospective observational study. The Lancet Respiratory medicine. 2013;1(10):786-92.

16.	Ormerod LP, Prescott RJ. Inter-relations between relapses, drug regimens and compliance with treatment in tuberculosis. Respiratory medicine. 1991;85(3):239-42.

17.	Pulido F, Pena JM, Rubio R, Moreno S, Gonzalez J, Guijarro C, et al. Relapse of tuberculosis after treatment in human immunodeficiency virus-infected patients. Archives of internal medicine. 1997;157(2):227-32.

490   18.   el-Sadr WM, Perlman DC, Matts JP, Nelson ET, Cohn DL, Salomon N, et al. Evaluation
491   of an intensive intermittent-induction regimen and duration of short-course treatment for human
492   immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for
493   Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG). Clin Infect
494   Dis. 1998;26(5):1148-58.
495   19.   Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin
496   monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine
497   and isoniazid. Tuberculosis Trials Consortium. Lancet. 1999;353(9167):1843-7.
498   20.   Sudre P, Pfyffer GE, Bodmer T, Prod'hom G, Furrer H, Bassetti S, et al. Molecular
499   epidemiology of tuberculosis among HIV-infected persons in Switzerland: a countrywide 9-year
500   cohort study. Swiss HIV Cohort Study. Infection. 1999;27(6):323-30.
501   21.   Sterling TR, Alwood K, Gachuhi R, Coggin W, Blazes D, Bishai WR, et al. Relapse rates
502   after short-course (6-month) treatment of tuberculosis in HIV-infected and uninfected persons.
503   AIDS (London, England). 1999;13(14):1899-904.
504   22.   Bandera A, Gori A, Catozzi L, Degli Esposti A, Marchetti G, Molteni C, et al. Molecular
505   epidemiology study of exogenous reinfection in an area with a low incidence of tuberculosis.
506   Journal of clinical microbiology. 2001;39(6):2213-8.
507   23.   Driver CR, Munsiff SS, Li J, Kundamal N, Osahan SS. Relapse in persons treated for
508   drug-susceptible tuberculosis in a population with high coinfection with human
509   immunodeficiency virus in New York City. Clin Infect Dis. 2001;33(10):1762-9.
510   24.   Nettles RE, Mazo D, Alwood K, Gachuhi R, Maltas G, Wendel K, et al. Risk factors for
511   relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a
512   comparison by HIV serostatus and rifamycin use. Clin Infect Dis. 2004;38(5):731-6.
513   25.   Jasmer RM, Bozeman L, Schwartzman K, Cave MD, Saukkonen JJ, Metchock B, et al.
514   Recurrent tuberculosis in the United States and Canada: relapse or reinfection? American journal
515   of respiratory and critical care medicine. 2004;170(12):1360-6.
516   26.   Selassie AW, Pozsik C, Wilson D, Ferguson PL. Why pulmonary tuberculosis recurs: a
517   population-based epidemiological study. Annals of epidemiology. 2005;15(7):519-25.
518   27.   Khan A, Sterling TR, Reves R, Vernon A, Horsburgh CR. Lack of weight gain and
519   relapse risk in a large tuberculosis treatment trial. American journal of respiratory and critical
520   care medicine. 2006;174(3):344-8.
521   28.   Wang JY, Lee LN, Lai HC, Hsu HL, Liaw YS, Hsueh PR, et al. Prediction of the
522   tuberculosis reinfection proportion from the local incidence. The Journal of infectious diseases.
523   2007;196(2):281-8.
524   29.   Nahid P, Gonzalez LC, Rudoy I, de Jong BC, Unger A, Kawamura LM, et al. Treatment
525   outcomes of patients with HIV and tuberculosis. American journal of respiratory and critical care
526   medicine. 2007;175(11):1199-206.
527   30.   Cacho J, Perez Meixeira A, Cano I, Soria T, Ramos Martos A, Sanchez Concheiro M, et
528   al. Recurrent tuberculosis from 1992 to 2004 in a metropolitan area. The European respiratory
529   journal. 2007;30(2):333-7.
530   31.   Golub JE, Durovni B, King BS, Cavalacante SC, Pacheco AG, Moulton LH, et al.
531   Recurrent tuberculosis in HIV-infected patients in Rio de Janeiro, Brazil. AIDS (London,
532   England). 2008;22(18):2527-33.
533   32.   Faustini A, Hall AJ, Mantovani J, Sangalli M, Perucci CA. Treatment outcomes and
534   relapses of pulmonary tuberculosis in Lazio, Italy, 1999-2001: a six-year follow-up study.

535   International journal of infectious diseases : IJID : official publication of the International
536   Society for Infectious Diseases. 2008;12(6):611-21.
537   33.   Burman WJ, Bliven EE, Cowan L, Bozeman L, Nahid P, Diem L, et al. Relapse
538   associated with active disease caused by Beijing strain of Mycobacterium tuberculosis. Emerging
539   infectious diseases. 2009;15(7):1061-7.
540   34.   Millet JP, Orcau A, de Olalla PG, Casals M, Rius C, Cayla JA. Tuberculosis recurrence
541   and its associated risk factors among successfully treated patients. Journal of epidemiology and
542   community health. 2009;63(10):799-804.
543   35.   Bang D, Andersen AB, Thomsen VO, Lillebaek T. Recurrent tuberculosis in Denmark:
544   relapse vs. re-infection. The international journal of tuberculosis and lung disease : the official
545   journal of the International Union against Tuberculosis and Lung Disease. 2010;14(4):447-53.
546   36.   Crofts JP, Andrews NJ, Barker RD, Delpech V, Abubakar I. Risk factors for recurrent
547   tuberculosis in England and Wales, 1998-2005. Thorax. 2010;65(4):310-4.
548   37.   Pettit AC, Kaltenbach LA, Maruri F, Cummins J, Smith TR, Warkentin JV, et al. Chronic
549   lung disease and HIV infection are risk factors for recurrent tuberculosis in a low-incidence
550   setting. The international journal of tuberculosis and lung disease : the official journal of the
551   International Union against Tuberculosis and Lung Disease. 2011;15(7):906-11.
552   38.   Pascopella L, Deriemer K, Watt JP, Flood JM. When tuberculosis comes back: who
553   develops recurrent tuberculosis in california? PloS one. 2011;6(11):e26541.
554   39.   Anaam MS, Ibrahim MI, Al Serouri AW, Bassili A, Aldobhani A. A nested case-control
555   study on relapse predictors among tuberculosis patients treated in Yemen's NTCP. Public health
556   action. 2012;2(4):168-73.
557   40.   Millet JP, Shaw E, Orcau A, Casals M, Miro JM, Cayla JA. Tuberculosis recurrence after
558   completion treatment in a European city: reinfection or relapse? PloS one. 2013;8(6):e64898.
559   41.   Kim L, Moonan PK, Yelk Woodruff RS, Kammerer JS, Haddad MB. Epidemiology of
560   recurrent tuberculosis in the United States, 1993-2010. The international journal of tuberculosis
561   and lung disease : the official journal of the International Union against Tuberculosis and Lung
562   Disease. 2013;17(3):357-60.
563   42.   Choi H, Lee M, Chen RY, Kim Y, Yoon S, Joh JS, et al. Predictors of pulmonary
564   tuberculosis treatment outcomes in South Korea: a prospective cohort study, 2005-2012. BMC
565   infectious diseases. 2014;14:360.
566   43.   Lee PH, Lin HC, Huang AS, Wei SH, Lai MS, Lin HH. Diabetes and risk of tuberculosis
567   relapse: nationwide nested case-control study. PloS one. 2014;9(3):e92623.
568   44.   Jo KW, Yoo JW, Hong Y, Lee JS, Lee SD, Kim WS, et al. Risk factors for 1-year relapse
569   of pulmonary tuberculosis treated with a 6-month daily regimen. Respiratory medicine.
570   2014;108(4):654-9.
571   45.   Unis G, Ribeiro A, Esteves L, Spies F, Picon P, Costa E, et al. Tuberculosis recurrence in
572   a high incidence setting for HIV and tuberculosis in Brazil. BMC infectious diseases.
573   2014;14(1):548.
574   46.   Schiroli C, Carugati M, Zanini F, Bandera A, Di Nardo Stuppino S, Monge E, et al.
575   Exogenous reinfection of tuberculosis in a low-burden area. Infection. 2015;43(6):647-53.
576   47.   Hung CL, Chien JY, Ou CY. Associated factors for tuberculosis recurrence in Taiwan: a
577   nationwide nested case-control study from 1998 to 2010. PloS one. 2015;10(5):e0124822.
578   48.   Interrante JD, Haddad MB, Kim L, Gandhi NR. Exogenous Reinfection as a Cause of
579   Late Recurrent Tuberculosis in the United States. Annals of the American Thoracic Society.
580   2015;12(11):1619-26.

581   49.   Avery K, Abbara A, Ghani R, Davidson RN. Recurrent tuberculosis at a large
582   tuberculosis centre in the UK. The Journal of infection. 2015;70(4):427-9.
583   50.   Li F, Song CY, Zhao F, Liang ML, Liu ZM, Guo XY, et al. Follow-up Study of
584   Retreatment TB Patients with Sputum Smear and/or Culture Positive Two Years after They were
585   Declared Cured with First-line Anti-TB Drugs in Shandong Province. Biomedical and
586   environmental sciences : BES. 2015;28(2):152-6.
587   51.   Kim L, Moonan PK, Heilig CM, Yelk Woodruff RS, Kammerer JS, Haddad MB. Factors
588   associated with recurrent tuberculosis more than 12 months after treatment completion. The
589   international journal of tuberculosis and lung disease : the official journal of the International
590   Union against Tuberculosis and Lung Disease. 2016;20(1):49-56.
591   52.   Chen MY, Lo YC, Chen WC, Wang KF, Chan PC. Recurrence after Successful
592   Treatment of Multidrug-Resistant Tuberculosis in Taiwan. PLoS one. 2017;12(1):e0170980.
593   53.   Blondal K, Viiklepp P, Guethmundsson LJ, Altraja A. Predictors of recurrence of
594   multidrug-resistant and extensively drug-resistant tuberculosis. The international journal of
595   tuberculosis and lung disease : the official journal of the International Union against
596   Tuberculosis and Lung Disease. 2012;16(9):1228-33.
597   54.   Lee J, Lim HJ, Cho YJ, Park YS, Lee SM, Yang SC, et al. Recurrence after successful
598   treatment among patients with multidrug-resistant tuberculosis. The international journal of
599   tuberculosis and lung disease : the official journal of the International Union against
600   Tuberculosis and Lung Disease. 2011;15(10):1331-3.
601   55.   Chiang CY, Enarson DA, Yu MC, Bai KJ, Huang RM, Hsu CJ, et al. Outcome of
602   pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study. The European respiratory
603   journal. 2006;28(5):980-5.
604   56.   Avendano M, Goldstein RS. Multidrug-resistant tuberculosis: long term follow-up of 40
605   non-HIV-infected patients. Canadian respiratory journal : journal of the Canadian Thoracic
606   Society. 2000;7(5):383-9.
607   57.   Dobler CC, Crawford AB, Jelfs PJ, Gilbert GL, Marks GB. Recurrence of tuberculosis in
608   a low-incidence setting. The European respiratory journal. 2009;33(1):160-7.
609   58.   El Sahly HM, Wright JA, Soini H, Bui TT, Williams-Bouyer N, Escalante P, et al.
610   Recurrent tuberculosis in Houston, Texas: a population-based study. The international journal of
611   tuberculosis and lung disease : the official journal of the International Union against
612   Tuberculosis and Lung Disease. 2004;8(3):333-40.
613   59.   Perriens JH, St Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, et al. Pulmonary
614   tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12
615   months. The New England journal of medicine. 1995;332(12):779-84.
616   60.   Menzies D, Benedetti A, Paydar A, Martin I, Royce S, Pai M, et al. Effect of duration and
617   intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-
618   analysis. PLoS medicine. 2009;6(9):e1000146.
619   61.   Sun Y, Harley D, Vally H, Sleigh A. Impact of Multidrug Resistance on Tuberculosis
620   Recurrence and Long-Term Outcome in China. PLoS one. 2017;12(1):e0168865.
621   62.   de Boer AS, Borgdorff MW, Vynnycky E, Sebek MM, van Soolingen D. Exogenous re-
622   infection as a cause of recurrent tuberculosis in a low-incidence area. The international journal of
623   tuberculosis and lung disease : the official journal of the International Union against
624   Tuberculosis and Lung Disease. 2003;7(2):145-52.
625   63.   Panjabi R, Comstock GW, Golub JE. Recurrent tuberculosis and its risk factors:
626   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.
628 2007;11(8):828-37.
629 64.   Uys PW, van Helden PD, Hargrove JW. Tuberculosis reinfection rate as a proportion of
630 total infection rate correlates with the logarithm of the incidence rate: a mathematical model.
631 Journal of the Royal Society, Interface / the Royal Society. 2009;6(30):11-5.
632 65.   Schmit KM, Wansaula Z, Pratt R, Price SF, Langer AJ. Tuberculosis - United States,
633 2016. MMWR Morbidity and mortality weekly report. 2017;66(11):289-94.
634 66.   Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1
635 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South
636 African mineworkers. Lancet. 2001;358(9294):1687-93.
637 67.   Crampin AC, Mwaungulu JN, Mwaungulu FD, Mwafulirwa DT, Munthali K, Floyd S, et
638 al. Recurrent TB: relapse or reinfection? The effect of HIV in a general population cohort in
639 Malawi. AIDS (London, England). 2010;24(3):417-26.
640 68.   Ahmad Khan F, Minion J, Al-Motairi A, Benedetti A, Harries AD, Menzies D. An
641 updated systematic review and meta-analysis on the treatment of active tuberculosis in patients
642 with HIV infection. Clin Infect Dis. 2012;55(8):1154-63.
643 69.   Munro SA, Lewin SA, Smith HJ, Engel ME, Fretheim A, Volmink J. Patient adherence
644 to tuberculosis treatment: a systematic review of qualitative research. PLoS medicine.
645 2007;4(7):e238.
646 70.   Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official
647 American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases
648 Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis.
649 Clinical infectious diseases : an official publication of the Infectious Diseases Society of
650 America. 2016;63(7):e147-e95.
651 71.   Horne DJ, Royce SE, Gooze L, Narita M, Hopewell PC, Nahid P, et al. Sputum
652 monitoring during tuberculosis treatment for predicting outcome: systematic review and meta-
653 analysis. The Lancet Infectious diseases. 2010;10(6):387-94.
654 72.   Walter ND, Painter J, Parker M, Lowenthal P, Flood J, Fu Y, et al. Persistent latent
655 tuberculosis reactivation risk in United States immigrants. American journal of respiratory and
656 critical care medicine. 2014;189(1):88-95.
657 73.   Hauer B, Brodhun B, Altmann D, Fiebig L, Loddenkemper R, Haas W. Tuberculosis in
658 the elderly in Germany. The European respiratory journal. 2011;38(2):467-70.
659 74.   Salinas Garrido I, Tabernero Huguet E, Garrós Garay J, Gil Alaña P, Ciruelos Ayuso E,
660 Lopez Aranaga I, et al. Thoracic tuberculosis (TB) in 75 to 100 year-old patients. European
661 Respiratory Journal. 2016;48(suppl 60).
662 75.   Cox H, Kebede Y, Allamuratova S, Ismailov G, Davletmuratova Z, Byrnes G, et al.
663 Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance.
664 PLoS medicine. 2006;3(10):e384.
665 76.   He GX, Xie YG, Wang LX, Borgdorff MW, van der Werf MJ, Fan JH, et al. Follow-up
666 of patients with multidrug resistant tuberculosis four years after standardized first-line drug
667 treatment. PloS one. 2010;5(5):e10799.
668 77.   Ong CW, Elkington PT, Friedland JS. Tuberculosis, pulmonary cavitation, and matrix
669 metalloproteinases. American journal of respiratory and critical care medicine. 2014;190(1):9-
670 18.

671   78.   Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B, van de Vijver S, Panduru NM, et al.
672   Clinical management of concurrent diabetes and tuberculosis and the implications for patient
673   services. The lancet Diabetes & endocrinology. 2014;2(9):740-53.

674

675

Table 1: Studies conducted in low-burden settings included in the review (excluding MDR-TB specific studies)

Author	Country	TB Incidence*	Cohort size	Recurrences	%	Duration (yrs)	Recurrence incidence rate (10^5 PYs)	Ref
Ormerod	UK	10.5	873	27	3.1	9		(16)
Pulido[†]	Spain	38.5	189	15	7.9	9	2700	(17)
El-Sadr	USA	9.7	101	2	2.0[Δ]	5	1042	(18)
Vernon	USA	8.5	61	8	9.7-16.7[Δ]	4		(19)
Sudre[†]	Switzerland	1.5	267	11	4.1	9		(20)
Sterling[†]	USA	9.7	174	10	5.7	5		(21)
Bandera	Italy	9.5	2127	32	1.5	5		(22)
Driver	USA	9.7	4571	123	2.7	7.5		(23)
Nettles	USA	9.7	407	14	3.8	9		(24)
Jasmer	USA / Canada	8.5 / 6.7	1244	79	6.4	7	3780	(25)
Selassie	USA	18.1	15464	452	2.9	33		(26)
Khan	USA	8.5	857	67	7.1	2		(27)
Wang	Taiwan	68.2	2071	61	2.9	6		(28)
Nahid[†]	USA	10.3	558	16	2.9	12		(29)
Cacho	Spain	40	645	8	1.2	15		(30)
Golub	Brazil	54	1080	96	8.9	4.3	2800	(31)
Faustini	Italy	7.7	360	20	5.5	7		(32)
Burman	USA/ Canada	8.5 / 6.7	1004	61	6.3	10		(33)
Millett	Spain	21	681	29	4.3	11	530	(34)
Dobler	Australia	5.9	5723	26	0.5	13	70.7	(57)
Bang	Denmark	6.9-10.5[‡]	4154	73	1.8	13.5		(35)
Crofts	England and Wales	10.9	53214	588	1.1	8	410	(36)
Pettit	USA	5.8	1431	20	1.4	7		(37)
Pascopella	USA	9.7	23517	148	0.6	15		(38)
Anaam	Yemen	66	774	44	5.7	2.7		(39)
Millett	Spain	27	971	13	1.3	7	341	(40)
Kim	USA	9.7	302140	15407	5.1	18		(41)
Choi	Korea	96	392	17	4.3	8		(42)
Lee	Taiwan	67	21939	305	1.4	5	488	(43)
Jo	Korea	50	317	6	1.9	11		(44)
Unis	Brazil	54	1449	203	14	7		(45)
Schiroli	Italy	9.5	4682	83	1.7	15		(46)
Hung	Taiwan	66	4041	152	3.8	13	734	(47)
Interrante	USA	9.7	312589	3039	1.0	19		(48)
Avery	UK	11.2	3515	14	0.4	12		(49)
Li	China	86	1134	189	16.7	5		(50)
Kim	USA	9.7	142221	1714	1.2	13		(51)

*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

Author	Country	TB Incidence[*]	Cohort size	Recurrences	(%)	Duration (years)	Recurrence incidence rate (10^5 PYs)	Ref
Avendaño	Canada	8.2	40	4	10	2.8		(56)
Chiang	Taiwan	41	153	10	6.5	6	2024	(55)
Lee	Korea	80	90	4	4.4	5		(54)
Blondal	Estonia	58	129	11	8.5	7.4		(53)
Chen	Taiwan	63	295	10	3.4	4.8	720	(52)
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

Author	Country	TB Incidence[*]	Typing Method	Total TB cases¶	Total recurrences	Paired strain typed isolates⫶	Relapse (%)	Reinfection (%)	Ref
Vernon	USA	8.5	IS6110 RFLP	61	8	8	8 (100)	0 (0)	(19)
Sudre	Switzerland	1.5	IS6110 RFLP	267	11	11	9 (82)	18	(20)
Bandera	Italy	9.5	IS6110 RFLP; Spoligotyping	2127	32	32	84	16	(22)
De Boer	Netherlands	12.2	IS6110 RFLP	Δ	183	183	84	16	(62)
El-Sahly	USA	8.5	IS6110 RFLP; Spoligotyping	Δ	186	41	69-76‡	24-31‡	(58)
Jasmer	USA / Canada	8.5; 6,7	IS6110 RFLP and others (see paper)	1244	79	75	96	4	(25)
Cacho	Spain	40	IS6110 RFLP; 15-locus MIRU-VNTR	645	8	8	87	13	(30)
Wang	Taiwan	68.2	Spoligotyping; 12-locus MIRU VNTR	2071	61	49	49	51	(28)
Nahid	USA	10.3	IS6110 RFLP	558	9	9	100	0	(29)
Dobler	Australia	5.9	IS6110 RFLP and others (see paper)	5723	26	15	73	27	(57)
Bang	Denmark	6.9-10.5†	IS6110 RFLP	4154	73	73	74	26	(35)
Pettit	USA	5.8	IS6110 RFLP and others (see paper)	1431	20	15	80	20	(37)
Millett	Spain	27	IS6110 RFLP and others (see paper)	971	13	6	50	50	(40)
Unis	Brazil	54	Spoligotyping; 24-locus MIRU VNTR	1449	203	13	69	21	(45)
Interrante	USA	9.7	IS6110 RFLP and others (see paper)	312589	136	136	85	15	(48)
Schiroli	Italy	9.5	Spoligotyping; 12-locus MIRU VNTR	4682	83	83	77	23	(46)
						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

Author	Mortality (n)		Resistance increase in recurrence isolate			Reference
	Recurrence	Primary episode	Recurrence (n)	Relapse (n)	Reinfection (n)	
Kim	11.8% (12631) ¶	8.7% (252524)				(41)
Schiroli				19% (64)	35% (20)	(46)
Bandera				0% (27)	40% (5)	(22)
Wang				13% (24)†	4% (25)†	(28)
Dobler				18% (11)	25% (4)	(57)
Bang	5.5% (73)			7% (54)	0% (19)	(35)
Jasmer				1.4% (72)	0% (3)	(25)
Unis				0% (9)	0% (4)	(45)
Nahid			6.3% (16)			(29)
Pascopella			8.8% (147)			(38)
El-sahly‡			'Group A': 9.7%; 'Group B': 13.1% †			(58)
Avery			0% (9)			(49)
Chen	17% (6)		0% (6)			(52)
Sterling			20% (10)			(21)
Avendano			25% (4)			(56)
Driver			27% (95)			(23)
Vernon			50% (8)			(19)
Lee			0% (1)			(54)
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