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Insights into Recurrent Tuberculosis: Relapse Versus Reinfection and Related Risk Factors

Kogieleum Naidoo and Navisha Dookie

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Abstract

Recurrent tuberculosis (TB) following successful treatment constitutes a significant challenge to TB control strategies. TB recurrence can be due to either reactivation of the same strain, i.e., relapse, or reinfection with a new strain. Recurrence due to reinfection has become an area of intense study due to its perceived significance in TB endemic settings with high rates of human immunodeficiency virus (HIV) coinfection. This review presents a descriptive analysis of recurrent TB disease and explores risk factors, immunopathogenesis, treatment, and preventative strategies. Currently available laboratory methods used to discriminate tuberculosis recurrence due to reinfection and relapse are discussed. We highlight risk factors for recurrence and strategies for early detection of TB recurrence. Enhanced treatment options such as intensified initial treatment, extension of treatment, and secondary preventative therapy for patients presenting with multiple risk factors are explored in this review. The potential value of identifying immunological correlates of risk and protection in recurrent TB is also briefly examined.

Keywords: recurrence, tuberculosis, relapse, reinfection, molecular typing

1. Introduction

Tuberculosis remains one of the most significant public health challenges globally, despite significant advances in tuberculosis (TB) control [1]. Approximately one-third of the world's population is estimated to harbor latent forms of the *Mycobacterium tuberculosis* (MTB) bacilli, creating a reservoir for future disease. The alarmingly high TB incidence and prevalence rates in countries that also have a high background prevalence of human immunodeficiency virus (HIV) have been persistent for more than a decade. The interplay between HIV infection and

TB has resulted in 10 times greater risk of TB reactivation from latent disease in coinfected individuals. In addition to the increased risk of TB reactivation disease, HIV coinfection has also been reported to substantially increase the rate of recurrent TB disease from reinfection due to the increased vulnerability of immune-compromised patients to TB infection [2, 3]. Recurrent TB disease occurs when patients who were previously treated for TB develop a new disease episode, due to either relapse (recurrence of the old infection) or reinfection (infection with a new strain) [4]. Recurrent TB disease is associated with poor treatment outcomes and higher mortality rates compared to primary TB infection [5]. Clinical, epidemiological, and/or microbiological data cannot be used to differentiate relapse and reinfection. Distinguishing between the two mechanisms requires evaluating the homology of the MTB strains isolated during the first and subsequent TB episode using molecular DNA fingerprinting technology [4].

In TB-endemic settings experiencing high rates of HIV coinfection, the rate of recurrent TB is significantly increased. Recurrence rates of up to 24.4% have been reported in HIV/TB-coinfected individuals, with most recurrences occurring within 2 years of successful treatment completion [5]. Prior to the development of DNA fingerprinting technology, primary TB disease was thought to impart some measure of immunity and subsequent TB infection was the result of reactivation of the strain from the original episode of infection [4]. However, with the advent of DNA fingerprinting techniques, numerous studies have explored the roles of relapse and reinfection in TB recurrence [6]. In countries with a high incidence of TB, reinfection has been reported as the main driver of recurrent TB, with molecular studies reporting up to 88% of TB recurrences due to reinfection in HIV-coinfected patients. In contrast, countries with a low TB incidence have reported TB relapse as the main cause of recurrent TB disease [7].

Current World Health Organization (WHO) guidelines use the term "relapse" to describe all TB recurrences during programmatic assessments. The term is largely generic and incorporates recurrence due to relapse or reinfection. The two mechanisms of TB recurrence exist as fundamentally independent forms of TB infection, have differing pathogenesis, and have different implications for patients and TB control programs [6, 7]. Relapse is associated with treatment failure and may be due to either clinical management complexities leading to subtherapeutic drug concentrations of key TB drugs due to drug–drug interactions or altered drug metabolism or from patient-related factors such as poor treatment adherence. Furthermore, relapse disease has been associated with an increased risk of acquiring drug-resistance in the infecting strain of MTB. Higher rates of TB relapse seen in HIV-infected patients may indicate the need for lengthier, more aggressive treatment to eliminate MTB infection compared to standard practice. High rates of reinfection are reflective of poor public health interventions that fail to reduce community transmission [3]. In the context of HIV coinfection, reinfection has been associated with failure to develop protective immunity after the first episode of TB resulting in this subset of patients bearing a higher susceptibility to reinfection with MTB [8]. The aim of the current review was to examine the disease burden due to recurrent TB disease and explore the risk factors, immunopathology, treatment, and prevention and the relative contribution of relapse versus reinfection to TB recurrence.

2. Epidemiology of recurrent TB

Population-based surveillance reports on the rates of recurrent TB following completion of anti-TB treatment are lacking. Recent estimates of recurrent TB across various regions indicate an average of 2290 cases/100000 person-years at 12 months following treatment completion. In high-incidence settings, this rate is as high as 7850 cases/100000 person-years [8]. An earlier report by Panjabi et al. analyzing 32 studies reported an overall recurrence rate of 3010 and 2290 per 100,000 person-years following 6 and 12 months of treatment, respectively, among controlled trials. They also reported that these rates were higher for observational studies compared to controlled trials. Rates were also reported to be higher in countries with high TB incidence [5]. Recurrence rates for specific regions have been emerging; many of which are demarcated as WHO high-burden countries. Glynn et al. reported a recurrence rate of 24.4 cases per 100 person-years in HIV-positive individuals and 4.7% per 100 person-years in their HIV-negative counterparts [9]. Charalambous et al. reported an overall recurrence rate of 7.89% per 100 person-years in the same setting among a mining population. The recurrence rate was higher in HIV-positive individuals at 8.86 cases per 100 person-years compared to 3.35 cases per 100 person-years in HIV-negative counterparts [10]. Narayanan et al. reported a recurrence rate of 14% among an HIV/TB-coinfected cohort of 306 patients from South India. Among the patients with recurrent TB, 88% of recurrent infections were due to reinfection [11]. Sun et al. reported a recurrence rate of 35 cases per 1000 person-years for patients with drug-sensitive TB and 65 cases per 1000 person-years among patients with drug-resistant TB [12]. Luzze et al. reported an overall recurrence rate of 8.4 cases per 100 person-years in a cohort from Uganda. The recurrence rate was also reported to be higher among HIV-positive individuals at 9.4 cases per 100 person-years compared to 6.7 cases per 100 person-years in HIV-negative counterparts [13]. Vree et al. reported a recurrence rate of 8.6% among a Vietnamese cohort of 244 patients [14]. Datiko et al. reported a recurrence rate of one case per 100 person-years (15 recurrent cases in 368 patients – 4.1%) among an Ethiopian cohort [15]. Moosazadeh et al. reported a recurrence incidence of 8.3% in Iran [16]. Crofts et al. reported the recurrence rate in England and Wales as 4.1 cases per 100 person-years; however, in HIV-positive individuals, this rate was reported as 7.6 cases per 100 person-years [17].

3. Definitions and terminology

Definitions of terms relating to recurrent TB disease that feature in this review are given below and some are illustrated in **Figure 1**.

3.1. Latent TB infection (LTBI)

LTBI is defined as a state of disease in which MTB persists within the host and is associated with damage that is evident at a cellular or tissue level but is not associated with the disease.
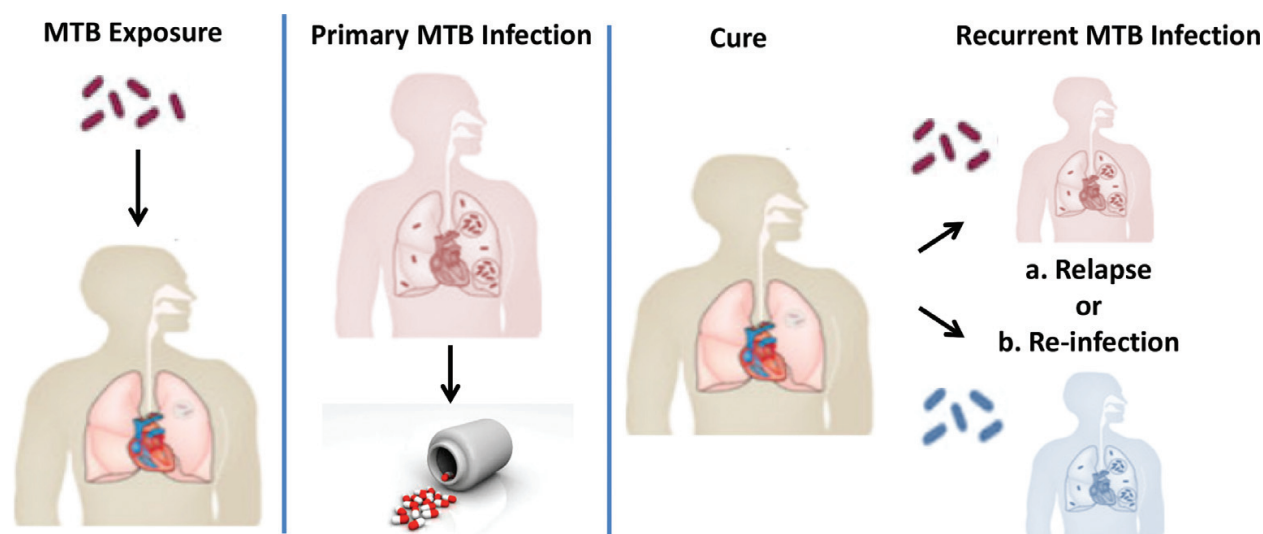
Figure 1. The continuum of *Mycobacterium tuberculosis* (MTB)–host interaction following MTB infection. Successful cure is achieved in ~95% of patients. In ~5% of patients, this cycle extends beyond successful treatment completion when the cycle of TB recurrence occurs either through (a) relapse of the original infection or (b) reinfection by new strain of MTB.

While this form of disease displays no clinical or radiological evidence of active disease, viable MTB bacilli are contained within tissues [18].

3.2. Primary TB disease

Primary TB is defined as disease occurring in a patient who has never been treated for TB or who has received less than 1 month of anti-TB treatment. In some instances, primary TB refers to the initial exposure of MTB; thereafter, the reactivation of TB disease following a period of clinical latency is referred to as postprimary or TB occurrence. In the current review, we refer to primary TB in accordance to the WHO definition [19].

3.3. Recurrent TB disease

Recurrent TB disease is defined as the diagnosis of a subsequent episode of TB following treatment completion or cure at the end of the most recent course of treatment. Recurrent TB disease occurs after the initial TB disease episode has been classified as clinically cured. According to WHO guidelines, cure is defined as smear and culture negative sputum samples from the last month of treatment and on at least one previous occasion [19].

3.4. TB relapse

Relapse disease is defined as a subsequent episode of TB disease due to the reactivation/ reemergence of the original infecting strain of MTB, determined by genotypic homogeneity assessment of primary and recurrent MTB strains [4]. Given that MTB strains are highly homogenous by nature, combined with high rates of transmission, classification of relapse infection is challenging [20].

3.5. TB reinfection

Reinfection is defined as a subsequent episode of TB disease due to the exogenous infection with an MTB strain that is distinct from the organism that caused the original infection [4]. A challenge regarding detection of reinfection is that in high TB-endemic settings, patients maybe exposed to be reinfected with a very similar strain that caused the primary infection, making differentiation between relapse disease and reinfection difficult.

4. Clinical presentation of recurrent TB

The symptoms of recurrent TB have been reported to vary in clinical and radiologic symptoms and are clinically indistinguishable from primary TB disease [21]. In general, TB symptoms are usually gradual in onset and duration and may vary from a few weeks to months. However, in young children and patients with HIV coinfection, a more acute onset of disease has been recorded. Typical symptoms such as fever, night sweats, and weight-loss occur among approximately 75, 45, and 55% of patients, respectively. The presence of a persistent nonremitting cough has been cited as the most common symptom, recorded in approximately 95% of patients with TB. Patients with cavitary lung disease, synonymous with recurrent TB disease, typically present with chronic cough, mostly accompanied by fever and/or the presence of night sweats and weight loss. The associated cough may be productive or nonproductive in nature. The sputum produced by patients maybe mucoid, mucopurulent, and bloodstained or may have severe hemoptysis. Other symptoms include chest pain and dyspnoea. Chest X-ray plays a critical role in diagnosis of sputum smear-negative patients [22]. **Figure 1** depicts the radiological progression of initial drug-susceptible TB (**Figure 2a**), followed by a recurrent TB episode (**Figure 2b**, diagnosis, and **Figure 2c**, end of treatment for recurrent TB). Typical chest radiograph findings include old fibrotic lesions, often cooccurring with other nonspecific features of tuberculosis such as lobar opacities, consolidation, fibrosis, and interstitial infiltrates. Severely immune-suppressed
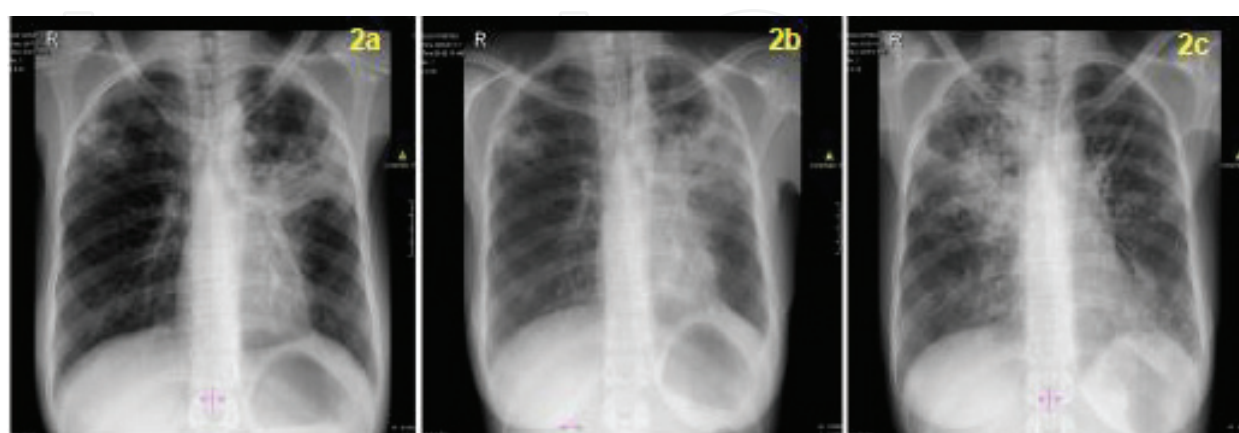

Figure 2. Chest X-rays of a patient with initial drug-sensitive TB, subsequently developed drug-resistant TB, depicting: (a) cavities and infiltrates in both lungs; (b) cavities and infiltrates on the right lung and fibrosis in the left lung; and (c) cavities, infiltrates, and patchy consolidation in right lung and consolidation in mid and lower zones of the left lung.

patients and young children are less likely to present with pathology on chest radiograph [22]. In the context of continuing disease due to poor adherence, recurrent TB is diagnosed by the clinical process, sputum smear microscopy, and chest radiograph [21]. Furthermore, the two mechanisms of recurrent TB are clinically indistinguishable and require specialized strain typing to differentiate between relapse and reinfection [4].

5. Methodology used to study recurrent TB

Discriminating TB reinfection from relapse through the study of the MTB genome using various laboratory methods is a key hallmark in the study of recurrent TB. DNA fingerprinting techniques are based on genomic variation, forming the basis of molecular epidemiological studies. The genome of the MTB complex is largely conserved with the presence of monomeric sequences repeated periodically, known as repetitive units. There are two types of repetitive units, namely, interspersed repeats (IR) and tandem repeats (TR). The former occur throughout the genome in the form of direct repeats and insertion sequences, while the latter are a series of head-to-tail direct uninterrupted repeats in the form of variable number tandem repeats (VNTR). The most common techniques used to distinguish between the two mechanisms of TB recurrence include *IS*6110-restriction fragment length polymorphism (*IS*6110-RFLP) analysis, mycobacterial interspersed repetitive-unit variable number of tandem repeats (MIRU-VNTR) typing, and spacer oligonucleotide genotyping (spoligotyping) [4, 23]. More recently, whole genome sequencing (WGS) has been used to compare strains representing different episodes of TB infection. One of the challenges associated with the former typing methods is the interpretation of similar isolates in the case of relapse disease. There is no standard for interpretation of changes in banding patterns when comparing specimens from different episodes of disease. It is suggested that identical bands or a difference of one band is good approximation for defining relapse. The use of WGS surmounts this issue by directly evaluating the number of single nucleotide polymorphism (SNP) differences between the disease episodes. There is still some uncertainty regarding the appropriate SNP cutoff value, which depends on the analysis platform and genome coverage. However, WGS is more robust as it excludes mixed infections and allows genomic associations with relapse and reinfection to be examined directly [8, 24, 25].

5.1. *IS*6110 RFLP typing

*IS*6110 RFLP is a well-validated method used extensively for MTB typing. This method relies upon the IS*6110* insertion element as a genetic marker was long recognized as the gold standard for studying the molecular epidemiology of MTB [26, 27]. The *IS*6110 insertion element has proven stable *in vitro* and *in vivo* with low transpositional frequency and is present in up to 25 copies in MTB. Strain identification using this method relies on variation in both the number and location of *IS*6110 elements in the MTB genome. The restriction endonuclease *Pvu*II cleaves the IS*6110* element once by recognizing a particular palindromic sequence. The result is thousands of DNA fragments of different lengths that are then separated according to size by gel electrophoresis. Notably, different molecular weight fragments arise because of the

varying distances between insertion sequences, which create a specific banding pattern characteristic of that isolate. Dendograms are constructed to graphically represent the similarity coefficients between isolates, allowing them to be clustered into groups based on banding patterns. Visual inspection can then be used to decide which isolates among these groups are identical or differ by only one or two bands. The IS*6110* method has been standardized enabling comparison of fingerprints globally. Thus, IS*6110* RFLP genotyping can provide a comparison of the strains involved at the initial and recurrent TB episodes by comparing the fingerprint patterns. MTB isolates with identical *IS*6110 DNA fingerprints or slight variations in banding patterns identify relapse of a prior infection, while distinct fingerprints identify reinfection with a new strain of MTB [26–28]. Challenges of utilizing this typing technique includes lower discriminatory power in isolates with low copy numbers of the *IS*6110 element, usually less than six copies of the element, the high level of expertise required for the technique and analysis, and poor reproducibility of the technique. Furthermore, strains displaying identical *IS*6110 banding patterns have been reported to display unique genetic identities in the presence of a secondary technique [4].

5.2. MIRU-VNTR typing

MIRU-VNTR typing is a PCR-based technique followed by detection by capillary electrophoresis, which characterizes both the number and sizes of variable tandem repeats in 12 or more loci. The repeat number is highly variable in many loci and is therefore termed "variable number tandem repeat" loci. They consist of small repetitive sequences of 40- to 100-bp and are unique in nature. They are scattered in 41 locations in the genome of MTB and are present mainly in the intergenic regions. The principle of this method is PCR amplification of 12- to 24-VNTR loci using primers complementary to the flanking regions, followed by gel electrophoresis. The size of the PCR amplicon reflects the tandem repeat unit, which is then converted into a numerical code to get a digital format in which each digit represents the number of copies present at that locus. This method utilizes variations in repetitive sequences, which are not under selective pressure and evolve relatively rapidly making it an ideal tool for molecular epidemiological studies. The discriminatory power of MIRU-VNTR is proportional to the number of loci included. MIRU-VNTR typing using a standardized set of 24 loci is now the international standard and is currently employed in European countries and globally. This method is rapid, reproducible, and cheaper than RFLP typing. Historically, this method was widely used in its 12-loci format that had a lower discriminatory power compared to IS*6110* RFLP [4, 23].

5.3. Spoligotyping

Spoligotyping is a hybridization assay that detects variability in genomic direct repeat (DR) locus of the MTB complex. The DR region of MTB consists of multiple copies of a conserved 36 bp sequence region (the DRs), which are separated by multiple unique spacer sequences. This method involves PCR amplification of the entire DR locus using primers that are complementary to the flanking spacer sequences, followed by hybridization to a membrane with 43 spacer oligonucleotides. The resulting bands produce a dark band in the presence of a spacer or no band if a spacer is absent. The pattern is converted into a 43 digit binary code

and subsequently converted into a 15 digit octal code. This code is unique and represents a specific banding pattern. This is a simple, high-throughput method that is cost-effective. It is, however, less discriminatory than RFLP typing. This method is ideal as a first-line screening tool, to be followed by other typing methods if needed [4, 23].

5.4. Whole genome sequencing

WGS analysis has been widely applied to the field of molecular epidemiology in the last decade. WGS plays a significant role in examining outbreaks and identifying transmission events where strains are genetically indistinguishable by conventional methods. WGS-based genotyping offers the optimal resolution of MTB complex isolates and holds the advantage of generating additional data, such as drug resistance [25]. Byrant et al. recently demonstrated the higher discriminatory power of WGS compared to MIRU-VNTR to differentiate relapse from reinfection. The decreasing cost of this platform, coupled with advances in genomics, makes WGS the most desirable single analysis tool for identification, prediction of drug resistance, and epidemiological typing. WGS also has a significant role in detecting MTB mixed strain infections. This method is set to become the gold standard for typing in the near future [24].

6. Relapse and reinfection

Published studies also vary in reported rates of TB disease due to reinfection from as low as <3–>60%. An earlier review by Lambert et al. failed to show a consistent trend when reporting whether TB recurrence is due to relapse versus reinfection [6]. Unsurprisingly, recurrence due to TB reinfection has been reported to be the main mechanism of recurrent TB disease in geographical regions with a high burden of TB disease; however, high rates of reinfection have also been reported from low- and moderate-incidence settings. Conversely, a poor association between reinfection and recurrent TB disease in high-burden settings has also been reported. This highlights that a consistent trend in recurrent TB disease is lacking [8, 10, 11, 24, 29–59]. Studies indicate that relapse generally occurs within a year following treatment, while reinfection predominates after the first year following treatment [8, 52]. In the context of HIV coinfection, there is a 2.4 times higher hazard ratio for recurrent TB disease, in comparison to HIV-uninfected individuals. HIV coinfection and antiretroviral treatment have been associated with an increased risk of recurrent TB due to reinfection [41, 47]. In a 13-year study conducted in Cape Town, South Africa, TB relapse rate peaked at 3.93% (95% confidence interval [CI], 2.35–5.96%) per annum 0.35 (95% CI, 0.15–0.45) years after treatment completion, whereas reinfection tuberculosis rate peaked at 1.58% (95% CI, 0.94–2.46%) per annum 1.20 (95% CI, 0.55–1.70) years after completion [52]. Reports of higher rates of TB reinfection may occur inadvertently likely due to laboratory contamination resulting in incorrect classification, mislabeling of isolates, mixed strain infections, varying clinical and radiological profile of patients, and length of follow-up. Varying lengths in the follow-up period make it difficult to make comparisons between studies. **Table 1** details published studies distinguishing reinfection from relapse in their reporting recurrent TB disease.

Author, publication year	Country	Study design	Number of patients analyzed	Recurrences (Total)	With fingerprinting results[a]	Reinfection (% of a)	Strain typing method	HIV status	Comment
Hawken et al. (1993)[c] [29]	Kenya	Prospective cohort	196	11	3	1 (33)	NA	HIV infected and uninfected	Increased recurrence rate (34-fold higher) in HIV-infected group compared to HIV-uninfected counterparts. Thiacetazone-containing regimen was used for treatment. Study not powered to determine the relative contribution of relapse or reinfection to TB recurrence.
Das et al. (1993)[c] [30]	Hong Kong	Retrospective analysis RCT	NA	Not reported	42	5 (12)	IS986-RFLP and phage typing	Not reported	Monthly sputum cultures were analyzed over a two-year period. Only 5 patients showed distinct differences in serial isolates. Detection of possible mixed infection, given the heterogeneity detected among serial samples. No HIV data or risk factors reported.
Godfrey-Faussett et al. (1994)[c] [31]	Kenya	Retrospective cohort	NA	Not reported	5	1 (20)	NA	HIV infected and uninfected	Study not powered to determine the relative contribution of relapse or reinfection to TB recurrence. No risk factors reported.
Das et al. (1995)[c] [32]	India	Retrospective analysis RCT	NA	30	13	3 (23)	IS6110-RFLP	Not reported	The main objective of the study was to determine the utility of IS6110-RFLP to distinguish between relapse and reinfection in recurrent TB.
Sahadevan et al. (1995)[c] [33]	India	Retrospective analysis RCT	52	44	29	9 (31)	IS6110-RFLP	Not reported	The main objective of the study was to modify the IS6110-RFLP assay using a direct repeat probe to increase its ability to distinguish between relapse and reinfection in recurrent TB.
El-Sadr et al. (1998)[c] [34]	USA	RCT	NA	2	1	1 (100)	NA	HIV infected	The main aim of the study was to determine the efficacy of levofloxacin

Author, publication year	Country	Study design	Number of patients analyzed	Recurrences (Total)	With fingerprinting results[a]	Reinfection (% of a)	Strain typing method	HIV status	Comment
								and uninfected	to the standard treatment regimen for drug-susceptible TB. The addition of levofloxacin resulted in low relapse rates, thus small sample size.
Vernon et al. (1999)[c] [35]	USA	RCT	71	8	7	0 (0)	IS6110-RFLP	HIV infected	This was an early study aimed at assessing the a once-weekly regimen of isoniazid and rifapentine with twice-weekly isoniazid and rifampin in the continuation phase of treatment for pulmonary TB in HIV-infected and -uninfected patients. The current report assessed only the HIV-infected cohort. Relapse TB was associated with an increase in rifamycin resistance.
Van Rie et al. (1999)[c] [36]	South Africa	Retrospective analysis-lab database	698	48	16	12 (75)	IS6110-RFLP	HIV uninfected	High-TB endemic setting. All patients in the cohort were reported to be HIV-uninfected. Reinfection was reported to occur within 7 to 8 months of previous cure. Reinfection in a high-endemic area in HIV-uninfected patients, probably due to the increased risk of developing recurrent TB after primary infection.
Johnson et al. (2000)[c] [37]	Uganda	Prospective cohort	291	17	4	0 (0)	IS6110-RFLP	HIV infected and uninfected	The main aim of the study was to assess the efficacy of an unsupervised, rifampicin-containing regiment for drug-susceptible TB in HIV-infected adults. No cases of reinfection. Relapse is probably an indication of the new regimen failing

Author, publication year	Country	Study design	Number of patients analyzed	Recurrences (Total)	With fingerprinting results[a]	Reinfection (% of a)	Strain typing method	HIV status	Comment
									or poor adherence in the current study.
Lourenco et al. (2000)[c] [38]	Brazil	Retrospective cohort	32	12	12	3 (25)	DRE-PCR and IS6110-RFLP	HIV infected	The study aimed to assess the relative contribution of relapse and reinfection in HIV-coinfected patients with recurrent TB. Study was not powered to assess the contribution of HIV. Among the three patients with reinfection, all were unique strains.
Caminero et al. (2001)[c] [39]	Gran Canaria Island	Retrospective population based-cohort	92	23	18	8 (44)	IS6110-RFLP	HIV infected and uninfected	The study setting has a moderate incidence of tuberculosis. Reinfection was attributed to TB recurrence in both HIV-infected and -uninfected patients. A dominant strain was reported for reinfection and relapse. Relapse was associated with increased drug resistance.
Bandera et al. (2001)[c] [40]	Italy	Prospective population based-cohort	2127	32	32	5 (16)	IS6110-RFLP	HIV infected and uninfected	Low TB incidence setting. Two of the five cases of reinfection were associated with drug resistance during recurrent TB episode, and three cases represented dominant strains circulating in the setting. Higher risk of relapse was described for HIV-infected and MDR-TB patients.
Sonnenberg et al. (2001)[c] [41]	South Africa	Prospective population based-cohort miners	65	65	39	14 (36)	IS6110-RFLP	HIV infected and uninfected	Thirteen of the fourteen recurrences occurred within 6 months of follow-up were attributed to relapse. HIV coinfection was cited as a strong risk factor for recurrence due to reinfection. Residual cavitation was also attributed to recurrent disease.

Author, publication year	Country	Study design	Number of patients analyzed	Recurrences (Total)	With fingerprinting results[a]	Reinfection (% of a)	Strain typing method	HIV status	Comment
Gracia de Viedma et al. (2002) [42]	Spain	Retrospective population based-cohort	2567	172	43	14 (33)	DRE-PCR; spoligotyping	HIV infected and uninfected	Low TB incidence and low exposure MTB, relapse was the main cause of recurrence. Patients displayed poor anti-TB treatment adherence. No association with HIV.
Fitzpatrick et al. (2002) [43]	Uganda	Retrospective population based-cohort	1100	40	40	9 (23)	Not reported	HIV infected and uninfected	Low HIV incidence setting, main cause of recurrence was relapse. Three of the four HIV-infected patients were reinfected with MTB. The remaining patient was sputum smear negative.
Lan et al. (2002) [44]	Vietnam	Retrospective population based-cohort	2901	168	39	0 (0)	IS6110-RFLP	Not reported	Primary MDR-TB was cited as a risk factor for relapse, associated with the Beijing strain. However, the study was not powered to detect risk factors related to relapse.
El Sahly et al. (2003) [45]	USA	Retrospective population based-cohort	Not reported	100	38	8 (21)	IS6110-RFLP and spoligotyping	HIV infected and uninfected	Low TB incidence setting. Relapse was the main driver of recurrence, with increased in drug resistance in the recurrent episode of TB. Only two of the eight patients with reinfection were HIV infected.
Jasmer et al. (2004) [46]	Canada, USA	RCT	1244	79	75	3 (4)	IS6110-RFLP	HIV infected and uninfected	High levels of reinfection despite Canada and USA having low TB incidence.
Verver et al. (2005) [47]	South Africa	RCT	447	61	31	24 (77)	IS6110-RFLP	HIV infected included	Recurrence following successful treatment as per definition of this review. Reinfection not stratified by HIV status.
Scaaf et al. (2005) [48]	South Africa	Prospective cohort	87	9	4	1 (25)	IS6110-RFLP	HIV infected	Pediatric population. Reinfection described in one patient; analysis of episode 1 and 3 of TB. Two further

Author, publication year	Country	Study design	Number of patients analyzed	Recurrences (Total)	With fingerprinting results[a]	Reinfection (% of a)	Strain typing method	HIV status	Comment
									cases of reinfection defined by epidemiologic data and DST.
Shen et al. (2006) [49]	China	Retrospective population based-cohort	202	54	52	32 (62)	IS6110-RFLP; MIRU-VNTR	Not reported	Data on HIV status not available; however, low HIV incidence setting (0.6 cases/100,000 person-years). No time interval defined between end of treatment and new episode of TB.
Cacho et al. (2007) [50]	Spain	Retrospective population based-cohort	645	20	8	1 (13)	IS6110-RFLP; MIRU-VNTR	HIV infected and uninfected	Patient with TB reinfection was HIV negative. Relapse was attributed to recurrent TB in this setting. No differences in risk factors reported for relapse and reinfection.
Charalambous et al. (2008) [10]	South Africa	Mining population	609	57	16	11 (69)	IS6110-RFLP	HIV infected and uninfected	Among the HIV-positive group, 10 of the 14 recurrences were due to reinfection. However, only two pairs available in the negative group. One case of reinfection and one case of relapse.
Narayanan et al. (2009) [11]	India	Prospective population based-cohort	Not reported	74	48	44 (92)	IS6110-RFLP; MIRU-VNTR; spoligotyping	HIV infected and uninfected	Reinfection was cited as the main cause of recurrence in HIV-infected patients (88%), while relapse was the main cause of recurrence in HIV-uninfected counterparts (91%).
Bang et al. (2009) [51]	Denmark	Retrospective population based-cohort	4154	73	73	19 (26)	IS6110-RFLP	Not reported	The risk of TB recurrence by reinfection increased with time. No data available for risk factors contributing to recurrence.
Marx et al. (2010) [52]	South Africa	Retrospective population based-cohort	309	203	130	66 (51)	IS6110-RFLP	HIV infected and uninfected	Relapse and reinfection not stratified by HIV status. Relapse occurred early after treatment completion, while reinfection occurred ≥1 year of treatment completion.

Author, publication year	Country	Study design	Number of patients analyzed	Recurrences (Total)	With fingerprinting results[a]	Reinfection (% of a)	Strain typing method	HIV status	Comment
Crampin et al. (2010) [53]	Malawi	Long-term cohort	584	53	39	13 (33)	IS6110-RFLP	HIV infected and uninfected	Reinfection was cited as the main cause of recurrence in HIV-infected patients (52%), while relapse was the main cause of recurrence in HIV-uninfected counterparts (93.7%).
Vargese et al. (2012) [54]	Saudi Arabia	Retrospective population-based cohort	Not reported	223	223	39 (17)	MIRU-VNTR	Not reported	14% of reinfection cases were associated with resistance to ≥1 first-line drug.
Bryant et al. (2013) [24]	Malaysia, South Africa, and Thailand	Sub-study of RCT	Not reported	50	36	3 (9)	MIRU-VNTR and WGS	HIV infected and uninfected	Main objective of the substudy was to determine the role of WGS to distinguish relapse from reinfection.
Guerra-Assuno et al. (2014) [8]	Malawi	Prospective population-based cohort	1471	139	75	20 (26)	IS6110-RFLP and WGS	HIV infected and uninfected	Reinfection was most common in HIV-infected patients. Relapse was associated with an increased prevalence of isoniazid resistance.
Interrante et al. (2015) [55]	USA	Population-based cohort	3039	136	136	20 (15)	IS6110-RFLP; MIRU-VNTR	HIV infected and uninfected	18 of the 136 cases of recurrence TB were HIV infected. Of these, four cases were attributed to reinfection.
Schiroli et al. (2015) [56]	Italy	Prospective cohort study	4682	83	83	19 (23)	IS6110-RFLP; MIRU-VNTR	HIV infected and uninfected	No causal association with HIV status. Increased drug resistance in patients with recurrent TB.
Korhonen et al. (2016) [57]	Finland	Population-based cohort	8299	48	21	3 (14)	WGS based spoligotyping	HIV infected and uninfected	Low rate of HIV coinfection in cohort (1/21). The difference in the number of SNPs in relapse isolates was reported to be 0–6. In the presence of dominant strain types, reinfection cannot be ruled out. In one case of relapse, the difference in the number of SNPs was reported to be 38 over a 2-year period.

Author, publication year	Country	Study design	Number of patients analyzed	Recurrences (Total)	With fingerprinting results[a]	Reinfection (% of a)	Strain typing method	HIV status	Comment
Shen et al. (2017) [58]	China	Retrospective population-based cohort	13,417	710	141	59 (42)	IS6110-RFLP; MIRU-VNTR	Not reported	Low HIV prevalence in the study setting. Patients with cavitation, diabetes, and initial drug resistance were at high risk for recurrent TB. Reinfection contributed to a significant number of cases.
Whitney et al. (2017) [59]	Southern Africa	Substudy of RCT	Not reported	51	35	3 (9)	MIRU-VNTR and WGS	Not reported	Main objective of the substudy was to determine the role of WGS to distinguish relapse from reinfection. The difference in the number of SNPs in relapse isolates was reported to be 0–5.

[a]Total number of recurrent TB episodes within the cohort.

[b]Percentage of recurrent TB episodes caused by reinfection (calculated from a).

[c]Adapted from the systematic review by Lambert et al. [6]

Abbreviations: DRE-PCR, double repetitive element-polymerase chain reaction; DST, drug susceptibility profile; MDR-TB, multidrug resistant-tuberculosis; MIRU-VNTR, mycobacterial interspersed repetitive unit-variable number tandem repeats; MTB, *Mycobacterium tuberculosis*; RCT, randomized controlled trial; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism.

Table 1. Studies conducted on recurrent tuberculosis infections, distinguishing the contribution reinfection versus relapse.

7. Risk factors for recurrent TB

Trinh et al. outlined risk factors for TB recurrence in three categories: (i) treatment response associated with relapse, (ii) individual vulnerability associated with both relapse and reinfection, and (iii) repeat exposure associated with reinfection. Risk factors contributing to each of these categories are detailed below and outlined in **Table 2** (adapted from Trinh et al. [3]).

7.1. Treatment response: relapse

7.1.1. Treatment regimen, adherence, and drug resistance

Incomplete bacteriologic cure, which is usually caused by irregular medication intake, is the most common cause of relapse. Inadequate treatment regimens, poor treatment adherence, and unrecognized drug resistance have been cited as risk factors for relapse TB infection. Regimens with low bactericidal potency, inadequate treatment duration, inappropriate drug choice, and undetected drug resistance all contribute to treatment failure and relapse disease. The use of standardized regimens in the absence of full drug susceptibility testing contributes to inadequate regimen choice and further impacts on the development of drug resistance and relapse [3, 6, 60]. Earlier studies reporting on the association between inadequate treatment regimen and risk for recurrent TB cited the use of thiacetazone-containing regimens. Thiacetazone is an antitubercular drug that was used widely in combination with isoniazid for the treatment of TB. This agent has since been replaced by the widespread use of standardized

TB recurrence risk		
Treatment response: relapse	**Individual vulnerability: relapse or reinfection**	**Repeat exposure: reinfection**
1. Treatment regimen • Inadequate treatment • Undetected drug resistance 2. Treatment adherence • Poor compliance • Drug shortage 3. Drug PK/PD* and pharmacogenomic determinants • Poor drug penetration • Variable PK values • Genetic mutations that alter drug metabolizing enzymes	1. Individual Vulnerability • HIV infection (CD4 count) • Previous TB disease and residual lung damage • Greater area of lung tissue involved • Positive sputum culture at 2 months of treatment • Diabetes Mellitus • Extremes of Age • Vulnerable groups and social risk factors • Infection with strains that have an increased propensity for drug resistance 2. Reduced local defenses • Cigarette smoking • Air pollution • Silicoses • Chronic lung disease	1. Epidemic control • High TB prevalence 2. Infection control • Clinics/hospitals/ prisons • Public transport • Places of socialization 3. TB contacts • Household contacts • Social or work contacts • Overcrowding or poor living conditions

*PK = pharmacokinetics; PD = pharmacodynamics.

Table 2. Risk factors for TB recurrence, adapted from Trinh et al. [3].

regimens containing rifampicin [21, 61]. Poor treatment adherence has also been reported to drive the development of drug resistance and thus relapse. Poor adherence to anti-TB treatment is associated with increased treatment duration, complex multidrug regimens, as well as social risk factors. Other issues linked to regimen choice and adherence include substandard drug quality and drug stock outs, and these are associated with poorly resourced, high TB-endemic countries [3]. Recurrent TB is also associated with an increased risk of developing drug resistance. Studies have reported an increase in acquired rifamycin-resistant TB in patients that received rifamycin-based directly observed therapy. In both studies, the key risk factor for rifamycin-resistance acquisition was HIV coinfection with advanced immunosuppression. In a cohort of 93 relapse patients with no prior evidence of MDR-TB, Chiang et al. reported that the prevalence of overall drug resistance was 33.3% and the prevalence of MDR-TB in the relapse patients was 12.9% [62]. Similarly, Sun et al. reported higher rate of TB recurrence in MDR-TB patients. In a cohort of 100 MDR and 150 non-MDR TB patients, recurrence rates of 65/1000 and 35/1000 person-years, respectively, were reported. The increased prevalence of drug resistance in relapse patients is exacerbated by the inefficacy of standardized retreatment regimens and underscores the need for increased MDR-TB case detection for retreatment patients [12].

7.1.2. Drug pharmacodynamics (PD) and pharmacokinetics (PK)

Host-specific factors such as PD, PK, and pharmacogenomics impact on the response to anti-TB treatment. Current anti-TB treatment dosing is based on the patient's body weight [63]. Drug concentrations and pharmacokinetics vary among patients, resulting in adverse reactions due to toxicity as well as suboptimal drug concentrations that impact on the development of drug resistance and relapse. Plasma concentrations of HIV and anti-TB drugs have been reported to display wide interindividual variability associated with genetic mutations in the respective drug-metabolizing enzymes or transporter proteins [64–66].

7.2. Individual vulnerability: relapse and reinfection

7.2.1. Individual vulnerability

7.2.1.1. HIV infection

HIV coinfection has been reported to increase the rate of recurrent TB disease, especially in high TB-endemic settings where TB recurrence rates of up to 24.4% have been reported. A cohort study in Malawi showed that the rates of tuberculosis relapse were similar between HIV-positive and -negative individuals [53]. Similar results were found in a study of South African mineworkers [41]. In contrast, several studies have reported a nearly three-fold higher incidence of recurrent TB among HIV-positive individuals as compared to their negative counterparts. In a review of 32 studies, Panjabi et al. reported excessive rates of recurrent TB following the completion of treatment using standardized regimens. Among the controlled trials included in the review, the overall recurrence rates (per 100,000 person-years) were 3010 (95% confidence interval 2230–3970) and 2290 (95% confidence interval 1730–2940), respectively, at 6 and 12 months following treatment completion. Recurrence rates were reported to

be higher for observational studies compared to controlled trials in countries with higher TB incidence rates. In the studies reviewed, recurrence rates were found to be higher among HIV-infected (6.7, 95% confidence interval 5.9–7.6) compared to HIV-uninfected (3.3 95% confidence interval 2.8–3.9) individuals. In the HIV-infected group, recurrent TB was associated with low initial CD4 T-cell count and anti-TB treatment less than 37 weeks of duration. While the association of low initial CD4+ T-cell count and TB recurrence was unclear in this review, the authors reported that small sample sizes lacked sufficient power to detect differences in recurrence rates between patients with high and low CD4+ T-cell counts [5]. An earlier study by Pulido et al. was the only study in the analysis that reported a statistically significant relationship in a multivariate analysis. A complimentary explanation is that patients with severe immunosuppression secondary to HIV die from other causes before TB recurs. Studies also reported that anti-TB treatment for less than 37 weeks was the most influential predictor of TB recurrence. The risk of TB recurrence in patients with low CD4+ T-cell counts was four times higher than that in patients with higher CD4+ T-cell counts. This also highlights that the six-month standard treatment regimen may be suboptimal at preventing recurrent TB in patients with low initial CD4+ T-cell counts [67]. Chaisson et al. reported similar findings in their review of two studies, which compared the rates of recurrent TB among HIV-infected and HIV-uninfected individuals [7]. In an Indian cohort, Narayanan et al. reported higher rates of recurrent TB in HIV-infected individuals compared with the HIV-uninfected group (14% versus 9%). In addition, recurrence due to reinfection was reported in 88% of the HIV-infected group and 9% of the HIV-uninfected group (p < 0.05). Among the recurrent isolates, patients from the HIV-infected group were associated with more clustering of strains and increased drug resistance [11].

7.2.1.2. Previous TB disease and residual lung damage

The severity of lung disease indicated by the presence of cavities and, in particular, residual cavities is a significant risk factor for recurrent TB disease. Lung cavities persisting at the end of treatment has been reported as a dominant correlate of recurrent disease in many studies [5]. Sonnenberg et al., in a study of South African mineworkers, found that residual cavitation was a risk factor for tuberculosis relapse [41]. The association between residual cavitation and recurrent disease has been attributed to poor penetration of anti-TB drugs into the cavity walls surrounding fibrotic tissue. It has also been postulated that MTB strains, like other nontuberculous mycobacteria, may have increased propensity for the infection of previously damaged tissue. The relationship between residual lung cavitation with recurrent TB disease warrants further investigation. Future studies should be aimed to assess the number and size of cavities present before and at the end of recurrent TB disease [5].

7.2.1.3. Greater area of lung tissue involved in infection

Several studies have reported that the extent of lung tissue involved in disease was a predictor of recurrent TB disease. However, no standard measure was applied to establish the amount of lung tissue involved in disease, and thus measures of lung area varied between studies [5]. Mallory et al. divided lung tissue into three areas, recording the number of zones with lesions. The authors report a dose–response association between the number of lung zones with

fibrosis and the likelihood of recurrence to strongly suggestive of a relationship [68]. Tam et al. scored lung involvement by combining the total area of lung tissue with lesions [69].

7.2.1.4. Positive sputum culture at 2 months of treatment

Numerous studies reflect evidence in support of a positive sputum bacteriologic status during anti-TB treatment and recurrent TB disease. These findings suggest that a positive sputum culture at 2 months of treatment is predictive of recurrence. This association has been attributed to an inadequate response to the intensive phase of anti-TB treatment [5]. Horne et al. conducted a systematic review and meta-analysis to assess the accuracy of positive sputum smear or culture for predicting treatment failure or relapse in pulmonary TB. The authors demonstrated that both sputum smear and culture during tuberculosis treatment have low sensitivity and modest specificity for predicting failure and relapse. Although the study represented a diverse group of patients, the individual studies had similar performance characteristics [70]. Gillepsie et al. reiterated the poor predictability of culture conversion for long-term outcomes. While two-month culture conversion is associated with relapse-free cure, this correlation is not strong enough to reliably predict outcomes for individual patients or definitively guide the selection of regimen in drug development [71].

7.2.1.5. Diabetes mellitus

Diabetes mellitus (DM) is recognized as a risk factor for the reactivation of TB infection and relapse infection following the completion of treatment. Diabetics have been reported to have three times higher risk of developing pulmonary TB compared to nondiabetics [72, 73]. Numerous studies have reported that DM coinfection adversely affects TB treatment outcomes, which included treatment failure, death, and relapse. In addition to the interaction between DM and TB, the high reported prevalence of DM in MDR-TB is alarming, with approximately 10–23% of MDR-TB patients having DM. A proposed hypothesis for this association is that altered immunity accompanied with DM has an effect on MDR-TB transmission, as with other immunodeficiency disease. A recent systematic review aimed to quantitatively evaluate the propensity for patients with DM and TB to cluster according to the genotype of the infected MTB strain. While the meta-analysis failed to show an association between TB transmission patterns in DM patients, among the 4076 patients analyzed, 13% had DM with 27% of these patient isolates displaying clustering. Further work is needed to address this phenomenon. These factors highlight the need for continual monitoring of DM patients who complete treatment for incident TB and possible use of secondary isoniazid prophylaxis treatment. In addition, comanagement for DM-TB patients will be significant in reducing relapse in these patients [74].

7.2.1.6. Extremes of age

Young adults (15–44 years) have been reported to have the highest risk for recurrent disease [75]. Children under 15 years and adults over 65 years have a lower risk compared to young adults. Age is linked to default on treatment; however, no particular age has been singled out in association with recurrence [21]. It is postulated that children have lower bacterial load as well as increased supervision and attention to care, indicated by higher rates of treatment

completion. There are limited data available on recurrence in children. Scaaf et al. reported 11 recurrences of TB disease in a cohort of 87 children. Of the eighty-seven children described in the study, nine had a second episode of TB, and two of which had a third episode of confirmed TB. Full epidemiological profiling could not be conducted, as clinical isolates representing the first episode of TB were not available for five of the cases [48].

7.2.1.7. Vulnerable groups and social risk factors

Vulnerable groups with increased susceptibility to TB infection and recurrent TB include HIV-coinfected patients, children, health care workers (HCWs), prisoners, homeless persons, drug users, and close contacts of TB patients. HIV coinfection, discussed above, is associated with high rates of recurrent TB. Children contribute a significant proportion of the TB disease burden and suffer severe tuberculosis-related morbidity and mortality, particularly in endemic areas. HCWs are placed at a higher risk for the acquisition of nosocomially acquired TB. Risk factors include poor or malfunctioning infection control measures and poor utilization of personal protective equipment. There is also a significant risk of secondary hospital outbreaks related to undetected and untreated TB. Prisoners, homeless persons, and drug users are at higher risk for TB and recurrent infections as they represent underserved populations. These populations are also more likely to be coinfected with HIV and are more difficult to manage and treat adherently. Imprisonment has been recognized as a significant risk factor for TB transmission. Household contacts of TB patients have been reported to be at high risk for developing TB, including drug-resistant TB. Preventative therapy remains the most significant tool to reduce the risk of TB infection among high-risk individuals [3, 79].

7.2.1.8. Infection with certain strain types

Infection with strains of the Beijing genotype has been associated with unfavorable TB outcomes. The Beijing genotype has gained particular attention due to reports on its association with drug-resistant TB in outbreaks and population-based studies [3]. Huyen et al. demonstrated that the Beijing genotype was associated with an increased rate of relapse in Vietnam. Among a cohort of 1068 patients that were followed up for 18 months, 23 cases of relapse occurred, linked to this genotype [83]. Nguyen et al. reported similar findings for the same settings. However, this strain type has been reported to account for 40% of TB cases in Vietnam, and this may represent high transmission rates rather than the success of the strain [84].

7.2.2. Reduced local defenses

7.2.2.1. Tobacco smoking

A systematic review by Lin et al. demonstrated that tobacco smoke is consistently associated with increased risk of TB infection. In comparison to nonsmokers, smoking increases the risk of developing active TB and mortality. Smoking has been reported to affect baseline severity, bacteriologic response, treatment outcome, and relapse in TB. Smoking has also been reported to alter the lung immune responses to MTB, contributing to a higher susceptibility to individual TB infection. Chronic exposure to tobacco and air pollutants impairs the normal clearance of secretions on the bronchial mucosal surface and may allow MTB to evade the early host immune defenses. Smoke also inhibits the activity of alveolar macrophages by reducing the phagocytic

ability of the cells. Lower levels of pro-inflammatory cytokines have also been reported for smokers [76]. Leung et al. evaluated the impact of smoking on TB outcomes by monitoring 16,435 patients receiving anti-TB treatment at chest clinics in Hong Kong. Overall, 16.7% of negative treatment outcomes were attributed to smokers, with the key contributor being default and death in smokers. Among 13,349 patients who were successfully treated for TB, 426 cases of relapse were detected. They reported a clear gradient (hazard ratios of 1.00, 1.33, and 1.63) of relapse risk from nonsmokers to previous smokers and current smokers, with an overall population attributable risk of 19.4% (current smokers: 12.2%; previous smokers: 7.2%) [77].

7.2.2.2. Air pollution

In addition to tobacco smoke, environmental exposures have been associated with an increased risk for developing TB. Air quality, which is impacted by atmospheric pollution and carbon monoxide, has been reported to induce bacillary reactivation and to increase the incidence of TB [76]. De Castro Fernandes et al. reported that air pollution was directly related to TB incidence in Brazil. Other studies conducted in the US and Russia also reported a link between the concentration of smoke, suspended particulate matter, and TB in relation to carbon dioxide and nitric oxide levels. Air pollution generated by traffic in Taiwan, linked to sulfur dioxide, ozone, and carbon monoxide, was linked to culture-confirmed TB. Similarly, a study conducted in South Korea revealed that exposure to sulfur dioxide increased the risk of TB by 7%. Indoor air pollution, resulting from the use of solid fuels for cooking, has been recognized as a risk factor for TB disease. The role of these factors in recurrent TB requires further study [78].

7.2.2.3. Chronic lung disease

Chronic lung diseases, including chronic obstructive pulmonary disease (COPD), asthma, and interstitial lung diseases such as silicosis, have been recognized as risk factors for the development of tuberculosis. Studies have demonstrated that 25–30% of silicosis patients develop TB with a relative risk for TB of 2.8 in silicosis patients when compared to the general population. However, there are limited data on the role of chronic lung disease in recurrent TB [79]. Pettit et al. reported an increased risk of TB recurrence with chronic lung disease (OR 5.28, 95% CI 1.16–2404, P = 0.03). However, a major limitation of the study was the low recurrence rate in the cohort, as the study was conducted in a low TB-incidence setting. Conversely, reports now suggest that a history of TB may lead to chronic lung disease, particularly COPD and bronchiectasis [80]. A recent systematic review by Byrne et al. reported a strong and consistent positive association between a history of TB and the presence of chronic respiratory diseases, including COPD and bronchiectasis. This suggests that the development of chronic lung disease following TB increases the risk of recurrent TB infection. In addition, tobacco smoking is an attributable risk factor for the development of COPD and thus may be a link in the development of TB and recurrent TB [80].

7.3. Repeat exposure: reinfection

7.3.1. Epidemic control, infection control, and close TB contacts

On a public health level, recurrent tuberculosis accounts for a considerable proportion of TB cases in weak TB control programs and contributes to ongoing transmission of infection to

close contacts in the home environment, community, and health care facilities. In high-incidence settings, recurrence has been attributed mainly to reinfection, with up to 75% of cases being attributed to reinfection. Reinfection represents a constant risk over time in patients with a history of TB. High reinfection rates have important implications for TB control strategies and underscore the need to reduce transmission in the community and the urgent need for rapid diagnosis and treatment of TB [3, 7, 8]. Coupled with comorbidities such HIV and diabetes that result in reduced immunity, such populations become more susceptible to infection and reinfection [5, 74]. Recent studies have indicated that transmission events are most likely to occur with the community and not within the household. A recent report on an XDR-TB cohort in South Africa demonstrated that 19% of patients that were discharged were linked to secondary case of TB [81]. Shah et al. reported that XDR-TB in the KwaZulu-Natal province of South Africa was linked to transmission of disease as opposed to inadequate drug treatment for MDR-TB. The authors demonstrated person-to-person and hospital-based epidemiological links [82]. Taken together, these studies highlight that epidemic control requires an increased focus on interrupting transmission and the need to establish community-based containment strategies, including voluntary long-term community stay facilities and palliative care in tuberculosis-endemic settings [81, 82].

8. Immunopathogenesis of recurrent TB

MTB has evolved with the human host over decades and has successfully evaded natural immune defenses, progressing to a stage of relative dormancy. Successful control of the TB epidemic would be best achieved with an effective preventative vaccine; however, the incomplete understanding of natural correlates of protection that an effective vaccine should emulate has hampered vaccine development. The continuum of the host-pathogen interaction following MTB infection to TB disease extends across the innate immune, adaptive immune, and quiescent and active replicating phases of infection. In approximately 5% of patients, this cycle extends beyond successful treatment completion when the cycle of TB recurrence may occur. In this subset of patients, persistence of MTB results in relapse, whereas in others, reinfection with MTB results in subsequent disease. Biomarkers indicative of the spectrum of TB disease have been described; however, there are limited reports on biomarkers of recurrent TB [85]. The matter of whether or not the first episode of TB imparts some measure of immunity has not been explicitly established but is assumed to have an impact [86].

Thobakgale et al. conducted a study in a cohort of HIV-coinfected patients with a history of previous successful TB treatment, which aimed to identify innate immune correlates associated with TB recurrence. Production of interleukin-1 (IL-1) beta by innate immune cells following ex-vivo stimulation with Toll-like receptor (TLR) and Bacillus Calmette-Guérin (BCG) stimulants correlated with differential TB recurrence outcomes. Elevated IL-1 beta production by monocytes following TLR stimulation was protective against TB recurrence. In contrast, production of IL-1 beta by monocytes and myeloid dendritic cells following stimulation with BCG was associated with an increased risk for recurrent TB. These findings highlight significant differences in the host immune response to TB and require validation in larger cohort of patients [87]. Sivro et al. studied the role of plasma cytokine correlates of TB recurrence in a

cohort of HIV-coinfected patients with a history of previous successful TB treatment. The study reported higher levels of plasma levels of interleukin-6 (IL-6), IL-1 beta, and soluble IL-1 receptor antagonist were associated with increased risk of TB recurrence, while plasma interferon beta levels decreased the risk of TB recurrence. These findings highlight that the markers of systemic inflammation, which are also involved in the rapid progression of HIV, predict TB recurrence in HIV-coinfected patients [88].

Gene expression profiling of ex-vivo whole blood specimens has demonstrated transcriptomic changes in patients with recurrent TB as compared to healthy counterparts, including significant changes in gene expression during successful treatment. Mistry et al. identified a gene signature that identified a set of genes in patients with recurrent TB that clearly distinguished this group from patients who remained cured [89]. Cliff et al. reported on the expression of 668 genes in patients who experience recurrent TB in comparison to those who remained cured, with the differences lasting up to 4 weeks following TB diagnosis. The upregulated genes were involved in cytotoxic cell-mediated killing. These findings suggest that patients who subsequently relapse exhibit altered immune responses, including robust cytolytic responses to MTB *in vitro* at diagnosis, compared to patients who achieved cure [90]. Thompson et al. reported on several clinically significant host-blood RNA signatures that predicted TB treatment outcomes, stratifying patients according to their risk of treatment failure. The signature correlated with pulmonary inflammatory states measured by PET-CT scanning and can complement current sputum-based testing methods for a rapid and accurate alternate testing method [91].

De Steenwinkel et al. reported on the differences between primary and recurrent TB in relation to changes in mycobacterial load in infected organs, immunopathology, and plasma cytokine levels using a murine model. In comparison to primary TB, recurrent TB was associated with lower mycobacterial load in the lung, spleen, and liver. Significantly lower levels of tumor necrosis factor-alpha, interferon-alpha, IL-6, MIG/CXCL9, IP-10/CXCL10, and lL-17 were observed for recurrent TB. In addition, memory Th-1 cells were locally and systemically expanded and congregated in the lung during recurrent TB, promoting efficient control of MTB growth [92].

9. Treatment of recurrent TB

Current WHO guidelines advocate the use of the standard six-month TB treatment regimen for all new and retreatment drug-susceptible TB cases. This regimen comprises a two-month intensive treatment of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by a four-month continuation phase of isoniazid and rifampicin. They further recommend the use of rapid molecular-based drug susceptibility testing (DST) to guide regimen choice for all retreatment TB patients. However, in settings where rapid DSTs are not available, empiric treatment is advised based on the following recommendations. Patients with a high likelihood of MDR-TB should be initiated on an empiric MDR-TB regimen using clinical discretion or if the patients have relapsed or defaulted on treatment after a second or subsequent course of treatment. The second recommendation is a retreatment regimen of 2 months of isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin, followed by 1 month of isoniazid, rifampicin, pyrazinamide, and ethambutol and finally 5 months of isoniazid, rifampicin, and ethambutol [93].

It is well recognized by many that a stratified medicine approach would be a desirable approach for the retreatment of TB. However, the challenge associated with a stratified medicine approach is in identifying groups that are eligible for a longer treatment regimen [94, 95]. There are many identifiable risk factors associated with recurrence, such as a baseline cavitation and month-two smear status that may indicate the need for increasing treatment duration. However, the recent REMoxTB and RIFQUIN studies, which evaluated new regimens aimed at shortening treatment duration for drug-susceptible TB, reported a relapse risk of 2.8 and 3.2%, respectively, with an 18-month follow-up period [96]. Among the factors attributed to poor success of the new regimens in the REMoxTB study, it was suggested that baseline cavitation modified the differences between the results. In contrast, 91% (n = 386) of the patients on the standard 6-month regimen with baseline cavitation had a favorable outcome at the end of the follow-up period [71]. A systematic review by Menzies et al. related to treatment outcomes of rifampicin-containing regimens of various durations showed only a modest benefit in regimens given for nine or more months in comparison to the standard six-month treatment. Thus, the benefit of a stratified treatment approach remains debatable [97].

In the context of recurrence due to relapse or reinfection disease, a different treatment approach is required. In the case of reinfection, this can be considered as a new primary infection, and thus, standard regimens may be effective. In contrast, relapse is associated with an increased risk of drug resistance due to the persistence of the original infecting strain under suboptimal treatment. Collectively, all the factors mentioned here underscore the significance an individualized treatment approach guided by DST [92, 93].

10. Preventative therapy for recurrent TB

Active TB disease has been shown to be preventable by the use of primary preventative therapy (pPT), which aims to prevent the first episode of TB in individuals in whom active TB has been excluded. The average preventative effect of pPT in HIV-uninfected individuals is a 60% reduction in the incidence of recurrent TB, while in HIV-infected individuals, the average effect is a 30% reduction in recurrent TB [98, 99]. A potential approach to prevent recurrent TB is secondary preventative therapy (sPT), by continuing the use of anti-TB therapy following completion of treatment for TB. sPT aims to reduce the incidence of recurrent TB in TB patients who have completed treatment for their most recent episode of TB [100]. The World Health Organization (WHO) recommends the use of isoniazid preventative therapy (IPT) in patients with HIV infection.

The TEMPRANO (trial of early antiretrovirals and isoniazid preventative therapy in Africa) study demonstrated that the use of 6 months of IPT combined with early antiretroviral therapy reduced the risk of severe HIV-related comorbidities by 44% and all-cause mortality by 33% [101]. Kabali et al. reported reduced mortality in tuberculin skin test (TST)-positive patients with CD4+ T-cell counts >200 cells/mm^3 in a Tanzanian cohort [102]. Charalambous et al. demonstrated a 49% reduction in mortality that remained significant even in patients who had a past history of TB. However, in high-burden countries and in TST-positive patients, a 36-month course of IPT has been recommended. The 36-month IPT course demonstrated a 74%

reduced risk of active TB and 68% reduction in mortality compared to the 6-month course [103]. The REMEMBER (reducing early mortality and early morbidity by empirical tuberculosis treatment regimens) study aimed to assess whether empirical TB treatment will reduce early mortality compared with IPT in patients with advanced HIV disease initiating antiretroviral therapy. Overall, empirical TB therapy did not reduce early mortality compared to IPT. However, the low mortality rate in the study underscores the need for TB screening and IPT in patients with HIV [104].

In their review of four studies, Bruin et al. reported the effect of sPT for the prevention of recurrent TB in HIV-infected individuals and the context in which the preventative approach may be applied. All four studies reported that sPT decreased incidence of recurrent TB in comparison to nontreatment groups. Relative reductions varied from 55.0 to 82.1%. However, only one of the four studies reported a significant effect on overall survival [100]. Perriens et al. described the use of isoniazid (INH) and rifampicin (RIF) twice weekly for an additional 6 months in comparison to a placebo. Patients receiving sPT were reported to be significantly less likely to develop recurrent TB compared to the placebo group (relative risk 0.21, p < 0.01) [105]. Haller et al. assessed the effectiveness of INH and sulphadoxine-pyrimethamine as sPT. The relative rate for the incidence of recurrent TB in patients receiving additional treatment (n = 134) and those not (n = 129) was 0.30 (95% confidence interval: 0.09–0.94) [106]. Fitzgerald et al. assessed the use of INH for an additional year following the completion of initial treatment compared to a placebo group. The intervention significantly reduced the incidence of recurrent TB from 7.8 per 100 person-years to 1.4 per 100 person-years (relative risk 0.18, confidence interval: 0.04–0.83) [107]. Churchyard et al. assessed the effect of INH in combination with cotrimoxazole versus cotrimoxazole only or no intervention in HIV-infected gold miners in South Africa. The rate ration for the development of recurrent TB in comparing the groups with INH and the group without INH was 0.45 (95% confidence interval: 0.26–0.78) [108]. As with pPT, the ideal duration and drug choice remain unclear. In all four studies, the duration of treatment varied from 6 to 24 months. The duration of effectiveness of sPT could not be assessed due to the short follow-up periods of the studies. None of the studies included made a distinction between relapse and reinfection as the mechanism of recurrent TB. Furthermore, Haller et al. and Fitzgerald et al. diagnosed recurrent TB by clinical assessment only, which could indicate overestimation of recurrent TB [106, 107].

11. Conclusion and future perspectives

Recurrent TB poses a major threat to TB control programs, especially given the persistent vulnerability of HIV-infected patients to tuberculosis, and the higher propensity of recurrent disease being due to resistant MTB strains. In the absence of large-scale population-based surveillance reports, the overall rate of recurrent TB following completion of treatment is significantly underestimated. Current estimates are based on a combination of randomized controlled trials and observational studies, with reliability estimates of the former limited by study follow-up time, and the latter prominently demonstrating higher rates of recurrence. Under clinical trial conditions, adherence rates are better; treatment facilities are more accessible and incorporate adequate follow-up after treatment, leading to improved treatment

outcomes and lower rates of recurrence. In contrast, observational studies reflect the operating environment of most high-burden TB facilities.

Distinguishing between relapse and reinfection is of paramount importance in addressing the burden of recurrent TB disease. High rates of relapse demand renewed interventions to improve individual patient care while high rates of reinfection demand improved infection and epidemic control measures. Urgent attention is required to address challenges of adherence, such as social and health care worker support systems and step-down management facilities. With the heightened risk or recurrent TB in HIV, TB screening should be conducted at all ART follow-up visits, and TB preventative therapy should be implemented in all HIV-positive patients completing TB treatment. Enhanced infection control strategies should be implemented in clinical and community settings to reduce ongoing transmission of TB. There has been considerable disparity in the studies reporting on the role of relapse versus reinfection. Further large-scale studies are required to address the role of relapse and reinfection as well as the role of mixed infections in recurrent TB.

This review highlights well-established principles in TB control. TB recurrence rates are grossly underestimated and are highest in those with extensive pulmonary disease and cavitary disease and in those with comorbidities such as HIV infection and diabetes. Active case findings among these patients within 12 months of completing treatment would enable early detection of TB recurrence. Enhanced treatment options, such as intensified initial treatment, extension of treatment, and secondary preventative therapy for patients presenting with multiple risk factors will prevent recurrent TB infection. Understanding the immunological correlates that offer protection against recurrent TB will also play a role in host-directed therapy and reducing recurrent TB.

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