Recurrence in tuberculosis: relapse or reinfection?

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The importance of reinfection as a cause for recurrence of tuberculosis is unclear and has potential public-health implications. We systematically searched published material for studies using DNA fingerprinting to provide data on the issue. Very few studies were designed for that particular research objective and/or report on a sufficient number of observations. Differences in methods—eg, case-definitions—seriously hamper comparisons between studies. The proportion of recurrences due to reinfection ranged between 0% and 100%; however, this figure cannot be a useful indicator since the two causes of recurrence—relapse and reinfection—are essentially independent. Only one study provides an estimate of the incidence of recurrence due to reinfection, indicating its importance for HIV-infected patients in an environment with an unusually high tuberculosis incidence. We argue that apart from extreme situations like this one the problem of recurrence of tuberculosis due to reinfection has few implications for tuberculosis-control programmes.

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A recurrence of tuberculosis is a second episode of tuberculosis occurring after a first episode had been considered cured. The 2-year incidence of recurrence after treatment of pulmonary tuberculosis with rifampicin-containing regimens ranges from 0–27%.[1,2] The debate on whether a first episode of tuberculosis disease is due to endogenous reactivation of a previous infection, or to a more recent reinfection[3] applies, to some extent, to the second episode. Molecular techniques developed in the past 15 years have shown that some recurrences are due to reinfection by a different strain, rather than relapse with the same strain that had caused the first episode. The fact that a first episode of tuberculosis disease does not necessarily protect against a second episode caused by a different strain has implications for vaccine development.[4,5] The contribution of reinfection (versus relapse) to the overall burden of tuberculosis recurrence is still unclear and has potential public-health implications. In this article, the terms recurrence, relapse, and reinfection are defined as above (they are sometimes used with a different meaning in published material—eg, what we call recurrence in this review has long been, and sometimes still is, called relapse. We first review what is known on the mechanisms of recurrence due to reinfection, and relapse. We then examine their importance by a systematic review of the available studies using molecular techniques to differentiate them. We explore possible reasons for the wide disparity of results across studies, and finally discuss the public-health and operational implications of these findings.

Mechanisms and causes of recurrence

The risk of developing a second episode of tuberculosis after reinfection by *Mycobacterium tuberculosis* depends first on the risk of reinfection after a first episode (a function of what we have called here "background tuberculosis incidence") and, second, on the risk of this reinfection breaking down into a second tuberculosis episode. A study[2] has shown that HIV-infection, a major risk for an infection (or reinfection) breaking down into a first tuberculosis episode,[6] was also a major risk for a reinfection breaking down into a second episode.[2]

True relapse can only occur when tuberculosis bacilli persist after treatment despite apparent cure. In that sense, relapse and failure can be seen as different expressions (on a continuum) of the same problem: insufficient bacteriological cure of a first episode. The combined rate of failures and recurrences (in our terminology) was the standard indicator to judge the efficacy of the treatment regimens in the British Medical Research Council (BMRC) clinical trials, the major source of our current knowledge of tuberculosis treatment.[7]

Inadequate treatment, either regimen or treatment duration, is the main cause for true relapse. Rifampicin-containing regimens are associated with smaller recurrence rates than regimens without rifampicin of longer duration. Under routine conditions, adequate treatment regimens may not assure permanent cure because of poor compliance, or may become inadequate because of pre-existing drug resistance,[8,9] resulting in higher relapse (and failure) rates. The extent of the disease (as shown radiologically or bacteriologically) and/or residual radiological lesions have been seen to be associated with recurrence.[9–11] Silicosis,[12] advanced age,[10] and being male[13,14] have also occasionally been mentioned as risk factors. In the study mentioned earlier[2] HIV infection was not a risk factor for true relapse.

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Table 1. Studies included in the review; recurrences and reinfections

Author, publication year	Country	Study design	Recurrences		
			Total (a)	With finger-print results (b)	Reinfection (% of b)
Hawken et al, 1993[18]	Kenya	Prospective cohort	11	3	1 (33)
Das et al, 1993[19]	Hong Kong	Retrospective analysis of samples from earlier RCT	NR	42	5 (12)
Godfrey-Faussett et al, 1994[20]	Kenya	Retrospective cohort	NR	5	1 (20)
Das et al, 1995[21]	India	Retrospective analysis of samples from earlier RCT	NR	13	3 (23)
Sahadevan et al, 1995[22]	India	Retrospective analysis of samples from earlier RCT	NR	29	9 (31)
el-Sadr et al, 1998[23]	USA	RCT in HIV-associated PTB	2	1	1 (100)
Vernon et al, 1999[24]	USA	RCT in HIV-associated PTB	8	7	0 (0)
Van Rie et al, 1999[25]	South Africa	Retrospective population-based, cohort (from laboratory database)	48	16	12 (75)
Johnson et al, 2000[13]	Uganda	Prospective cohort	13	4	0 (0)
Lourenco et al, 2000[26]	Brasil	Retrospective cohort (from laboratory database)	3	3	3 (100)
Caminero et al, 2001[27]	Gran Canaria	Retrospective, population-based cohort	11	8	6 (75)
Bandera et al, 2001[28]	Italy	Prospective, population-based cohort	NR	32	5 (16)
Sonnenberg et al, 2001[2]	South Africa	Prospective, population-based cohort (miners)	65	39	14 (36)

RCT=randomised controlled trial; PTB=pulmonary tuberculosis; NR=not reported.

Recurrence due to reinfection may be expected to be a more or less constant risk over time. By contrast, true relapse is more likely to occur soon after completion of treatment for the first episode (even if some true relapses can happen more than 15 years after the first tuberculosis episode[15]). In the BMRC trials, with up to 5 years' follow-up, most recurrences occurred in the first 6 months post-therapy.[7] Some have even proposed to define as "late failure" any recurrence in the first 6 months after end of treatment.[16]

Identification of the cause of recurrence requires the ability to differentiate the strains involved in the first and the second tuberculosis episode. To achieve this, recent genotyping methods rely on the high degree of polymorphism of some of the DNA insertion elements, or short repetitive sequences (IS), of *M tuberculosis*. The "fingerprint" pattern shows how a particular insertion element (eg, IS6110) is distributed through the genome. The most widely used fingerprinting technique (but not the only one) is the restriction fragment length polymorphism (RFLP).

Methods for the systematic literature review

The methods we used in our search of published articles are given in the Search strategy and selection criteria (see page 286). For comparability reasons, we included only patients in whom the site of disease included the lungs (with or without extrapulmonary involvement) during both initial and recurrent episodes. We extracted frequency measures, data on methods used (study design, case definitions), and risk factors for relapse (treatment regimen, drug-resistance patterns). We classified data according to HIV status, when available, and according to the estimated background incidence of tuberculosis (a proxy for risk of reinfection) in the study population. If no data were reported in the study itself in that respect, we used estimates provided by WHO for that country.[17]

Results

The search through electronic databases returned 391 hits. Most of them were epidemiological studies reporting on previously untreated patients or laboratory studies; eight met our inclusion criteria. Screening 188 articles reviewed for the study on the incidence of recurrence, and the bibliography of all articles meeting our inclusion criteria, allowed retrieval of five more studies. We did not exclude any study on the basis of a small sample size. The main characteristics and findings of the 13 studies are shown in table 1.

Treatment regimen used

Most studies report on recurrences after treatment of the first tuberculosis episode with rifampicin-containing regimen. The earlier studies[18–20] report on recurrences after treatment without rifampicin. Das et al[21] give no details on the regimens used.

Drug susceptibility of the causative strain of the first tuberculosis episode

Of 27 true relapses in the Italian study,[28] 15 happened after a first episode caused by a multidrug-resistant strain (MDR); only five initial strains had been fully sensitive. No resistance data are provided by Godfrey-Faussett et al,[20] Das et al,[21] Sahadevan et al,[22] Van Rie et al,[25] and Johnson et al.[13] In remaining studies, strains were seen to be "most" or all sensitive, with no mention of MDR.

Table 2. Estimated incidence of recurrences due to reinfection, and relapse, per 100 person years (95% confidence intervals)[29]

Recurrences due to	HIV–	HIV+
Reinfection	0·35 (0·06–1·9)	11·0 (7·6–15·9)
Relapse	5·9 (3·9–9·0)	5·3 (3·1–9·0)

Duration of follow-up, and incidence of recurrence

Most studies had a median duration of follow-up between 15 and 30 months. Caminero et al,[27] Bandera et al,[28] and Lourenco et al[26] analysed data corresponding to 5 calendar years. Godfrey-Faussett et al[20] and Van Rie et al[25] give no data. Sonnenberg et al[2] are the only authors providing separate estimates of the incidence of recurrences due to reinfection, and to relapses (table 2).

Case-definition of recurrent tuberculosis: isolated positive cultures and timing

When only one positive culture is available to document an episode of tuberculosis, the probability of a false-positive diagnosis (resulting from laboratory contamination) is higher than when several positive specimens are available to support the diagnosis. Isolated positive cultures (IPC) were systematically excluded by Sahadevan et al[22] (15 pairs with at least one IPC excluded/44 pairs available) and by Das et al in India[21] (32/45), and in Hong Kong[19](42/84). They were included by Van Rie et al[25] (8/16) and Hawken et al[18] (3/3). Sonnenberg et al[2] excluded IPC as a diagnosis of recurrence (7/46 pairs), but not as a diagnosis of first tuberculosis episode (3/46). Other studies provide no data in that respect.

In terms of timing, recurrence was defined by Das et al in India[21] as a second episode of tuberculosis at least 3 months after the end of the first treatment; in Italy[28] this time interval was 6 months. In Gran Canaria,[27] recurrence was defined as a positive culture at least 12 months after the last positive culture of the first episode. For the remaining studies, recurrence could have happened at any time after the end of treatment for the first episode.

Table 3. Reinfection as the cause of recurrence, according to the estimated background tuberculosis incidence, and HIV status

Country of study	Reinfections among recurrences with fingerprinting results (%)		Odds ratio for recurrence due to reinfection HIV+/– (95% CI)
	HIV+	HIV-	
Low tuberculosis incidence (<50/100 000/year)			
Italy[28]	1/10 (10)	4/22 (18)	0·50 (0·02–6·40)*
Gran Canaria[27]	2/3 (67)	4/5 (80)	0·50 (0·01–34·8)*
USA[23]	1/1 (100)		
USA[24]	0/7 (0)		
High tuberculosis incidence (50–499/100 000/year)			
Kenya[18]	1/3 (33)		
Uganda[13]	0/3 (0)	0/1 (0)	
Hong Kong[19]		5/42 (12)†	
India[21]		3/13 (27)†	
India[22]		9/29 (31)†	
Brasil[26]	3/3 (100)		
Kenya[20]	1/5 (20)		
Very high tuberculosis incidence (>500/100 000/year)			
South Africa[25]		12/15 (80)	
South Africa (miners)[2]	13/21 (62)	1/18 (6)	27·63 (2·72–683)

*Calculated from the data extracted. †These studies made use of samples collected in the pre-HIV era; we assumed patients were HIV-negative.

Table 3 shows recurrences due to reinfection in relation to the HIV status of the patient, and to the background tuberculosis incidence (assumed to reflect the risk of reinfection).

Discussion

We are confident that our review did not miss any major study recorded in the databases searched, but these databases are notoriously biased towards articles published in the English language. We retrieved only few studies that attempted to quantify the contribution of reinfection to the problem of recurrence of tuberculosis. Fewer still were designed for that particular research objective and/or report on a number of observations such that the study results truly contribute to this research question. Widely different methods and settings precluded any attempt at a pooled analysis of the data.

Measuring the importance of relapse versus reinfection: a conceptual framework

Study results usually are compared using the proportion of reinfection accounting for the total recurrences. On that basis, heterogeneity between studies is striking. For HIV-negative patients, for instance, reinfections account for 18–80%[27,28] of recurrences in low-tuberculosis-incidence countries, and from 6–80%[2,25] in a very-high-tuberculosis-incidence setting (South Africa). Small sample sizes (resulting in unstable estimations) can partly explain this wide range. But it is also conceptually wrong to compare proportions, because reinfection and relapse are actually two essentially independent causes leading to an identical clinical outcome. (They may not be completely independent because some host factors might predispose both to recurrence due to reinfection and to relapse). In one of the most quoted studies on the subject, Das et al[19] report that 12% of recurrences were due to reinfection and 88% to relapse, but these recurrences were after treatment of the initial tuberculosis episode with regimens that have since been abandoned precisely because of their high relapse rate.[30] In the Italian study,[28] most relapses occurred in patients whose first episode was caused by an MDR strain—a disease unlikely to be fully cured by a standard 6-month treatment regimen. The difference between the proportion of recurrences due to reinfections in the Italian study (16%) and in Gran Canaria (75%)[27]—where all relapses occurred in patients with a fully sensitive first tuberculosis episode—could simply indicate that there were many more relapses in the Italian study. These studies tell us nothing of what we really want to know, that is the incidence of reinfections (under different tuberculosis background incidences). Only Sonnenberg and collegues'[2] study provides such estimates.

Potential for bias in study results

Differences in methods can also contribute, to varying degrees, to the heterogeneity of the study results. How recurrence was defined is of major importance. Because failure and early relapse are actually a continuum, some studies defined recurrence as an episode occurring at least 3 months, or 6 months, after cure of the first episode,

making such results barely comparable with studies counting recurrences since the day the first treatment ended. Apart from timing, the bacteriological definition of recurrence is also important. In the BMRC trials, half of the IPC were seen to be the result of laboratory cross contamination; IPC were not associated with clinical recurrence later in the course of follow-up.[31] In our review, IPC accounted for half, or more, of the samples in some studies; some authors have included them, others not. Cross-contamination can of course vary from one laboratory to another, but the potential for bias (overestimation of the role of reinfection) is high in these studies that included IPC.

The risk of bias due to chance reinfection by the same strain is small, given the heterogeneity of strains circulating in the community.[2,27,28,32] Studies with different length of follow-up are hard to compare (as opposed to relapse, risk of recurrence due to reinfection is likely to be more or less constant over time). IS6110 RFLP, which has been used in most of the studies covered by this review, is considered to be the most reliable fingerprinting technique because of its stability, high discriminatory power, and reproducibility[33]—unless many strains contain few or no IS6110 copies. In Sahadevan and colleagues' study[22] 40% of the strains had few or no IS3110 copies—another method was used. It does not seem that the RFLP methods used in the studies reviewed could have been the source of a major bias.

Risk factors for recurrence due to reinfection

Only one study[2] had sufficient power to show an association between HIV and risk of reinfection; despite large confidence intervals the association is strong (perhaps surprisingly there was only one case of reinfection among HIV-negative patients). This is an elegant demonstration of what had been suspected for a long time, and is plausible given our knowledge on the increased risk of breakdown to disease after tuberculosis infection in the HIV population.

Our review could not confirm the expected association between the risk of recurrence due to reinfection, and the "background tuberculosis incidence". Apart from the major biases discussed above, one reason could be that our measure of background tuberculosis incidence is probably a poor proxy of the real risk of reinfection experienced by the individual patients, because this figure (especially in low-tuberculosis-incidence countries) pools together the higher risk of a small population, and the lower risk of a large population. For instance, Bandera et al[28] report that the annual incidence of tuberculosis per 100 000 is roughly 14·4 for native Italians, and 109 for immigrants. That study reported an association between risk of recurrence due to reinfection, and being an immigrant.

Practical implications of these findings

The discussion below extends beyond the results of the studies reviewed, and expresses the opinion of the authors.

Reinfection can be a cause of recurrence of tuberculosis after cure both in low-incidence and high-incidence countries; in HIV-positive as well as in HIV-negative patients. Should this be taken into account when assessing the efficacy of new treatment regimens for tuberculosis, as it is often heard? A randomised controlled trial will still be able to compare the efficacy of different treatment regimens by ensuring that the incidence of reinfection is similar in each arm of the trial. However, where the risk of (disease following) reinfection is very high, and the sample size small, the problem of recurrence due to reinfection could be a challenge to the power of the study. The incidence of true relapses will be overestimated in both arms.

The public-health implications of reinfection as a possible cause of recurrence depend on how important is the problem, as compared with other problems met by tuberculosis control in various environments. So, how important is it? The cornerstone of tuberculosis control is the early detection and cure of the contagious patients to decrease transmission, but at a global level WHO estimates that only 27% of all incident cases of smear-positive pulmonary tuberculosis are being treated within its directly observed treatment, short course (DOTS) strategy:[17] many patients are not detected, and those detected are often poorly treated and not cured. In most of the studies reviewed here, relapses (which are, for the most part, due to inadequate treatment, with or without drug resistance) cause more cases of recurrence than reinfection (even among South African miners, where risk of reinfection is high); for those studies that provide data in this respect, default to treatment, failure, and/or multidrug resistance seem to be more important threats to tuberculosis control than recurrences.[25,27,28] If most smear-positive tuberculosis cases probably receive no proper treatment at all, should the minority of treated cases that experience a recurrence due to reinfection be a major concern? If anything, this review on the causes of tuberculosis recurrence leads us to stress the need for improved performance of the main tuberculosis control strategy: detecting early, and curing patients with tuberculosis. With an effective treatment there will be fewer relapses (together with fewer failures, and less drug resistance), and in the long term, fewer recurrences due to reinfection, since the control strategy effectively reduces tuberculosis transmission.

But recurrences due to reinfection are definitely a serious problem for HIV-infected South African miners. In such a situation, combining an unusual high risk of reinfection, high HIV-prevalence, and an apparently well-organised tuberculosis control programme, the authors make a convincing case for considering post-treatment prophylaxis in HIV-infected patients as a public-health strategy.[2] A randomised controlled trial has shown some benefit of isoniazid prophylaxis after tuberculosis treatment for HIV-infected patients in Haiti.[34] Operational feasibility and long-term benefits of such a strategy remain to be studied.

What should the clinician faced with a case of tuberculosis recurrence, make from all of this? Recurrences due to relapse and to reinfection are clinically indistinguishable; the issue of importance for clinical decision-making is drug-susceptibility of the strain. Susceptibility testing would be routine in more developed countries; in resource-poor countries, standardised second-line regimen are recommended for second episodes of tuberculosis.

Search strategy and selection criteria

Data for this review were identified by searches of Medline and Cab Health. Search terms (free text) were "tuberculosis" and "DNA-fingerprinting". We also looked at articles screened for the purpose of another systematic literature review on the incidence of tuberculosis recurrence; finally we scrutinised the bibliography of the relevant articles retrieved that way. There were no language restrictions. The following inclusion criteria were used: studies published up to July 2002, reporting on recurrence (or relapse) after cure of a first episode of tuberculosis, with results of DNA fingerprinting available for both episodes; study patients selected as part of a cohort study (prospective or retrospective), as opposed to anecdotal reporting with no information on how cases were selected; and details on site of disease available for both episodes.

Requirements for future studies on the cause of recurrence after tuberculosis treatment

This area of research is relatively new. The few studies covered by this review have paved the way, but only studies with a rigorous methodology, like Sonnenberg's,[2] could significantly add knowledge to the issue. By definition, these studies should be longitudinal (prospective, or retrospective). Complete outcomes of the first tuberculosis treatment (cure? failure? default?) and the risk factors for true relapse (details of treatment regimen, compliance, drug resistance if available) during this first episode should be reported. Follow-up should be at least 2 years, if possible, and incidence of recurrence (both causes) calculated using survival methods. The bacteriological case definitions used for the diagnosis of the first and second episode of tuberculosis should be precisely reported. If IPC are included, they should be linked to clinical data and quality-control mechanisms used to monitor cross-contamination in the laboratory reported (RFLP can sometimes be used for that purpose: if the IPC comes from a patient with no clinical symptoms, and the strain is seen to be similar to those of other samples processed the same day in the same laboratory, it will be concluded that it is rather due to cross-contamination). Recording recurrences from the first day after the patient had been considered cured would avoid semantic problems and allow computation of recurrence rates under various time-defined definitions. A high sample size will be needed.

A different type of design has been used to study the cause of tuberculosis recurrence,[15] based on traditional molecular epidemiology methods (tuberculosis episodes with strains found in a cluster are attributed to recent transmission, those with isolated strains to "endogenous reactivation"[35]). The main advantage is that this method does not require the availability of the strain that caused the first episode. A major limitation is that it can only identify the cause of recurrences occurring many years after the first episode; incidences cannot be calculated.

Conclusions

Only one study in our review[2] has reliably compared the incidence rates of recurrence due to reinfection and relapses with a methodology that allows conclusions to be drawn on the increased risk for reinfection (not relapse) among HIV-positive patients in an environment with extremely high-background-tuberculosis incidence.

As our present knowledge basically stems from one study, it would make sense to replicate it, particularly in high-tuberculosis-incidence countries, and among HIV-positive patients. Such studies would be long and expensive. On the other hand, we believe that the problem of recurrence due to reinfection is likely to be of practical importance only for tuberculosis programmes adequately meeting their priorities in terms of cure rate and coverage, and in situations where risk of reinfection is very high. Few places in the world would meet these criteria.

Conflicts of interest

None declared.

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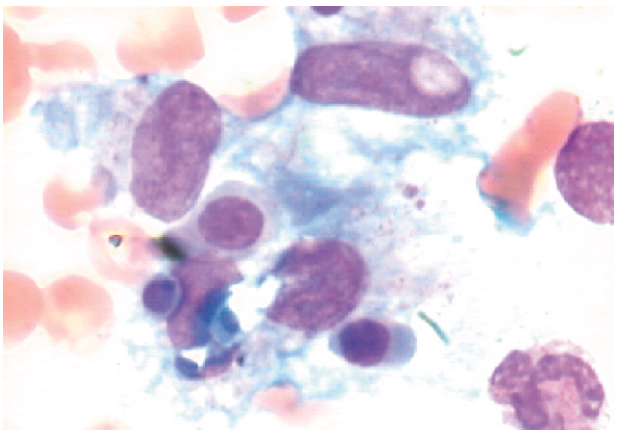
Clinical picture

Haemophagocytic syndrome following pseudomonas septicaemia



A 6-month-old boy was admitted with a 3-week history of fever, pallor, abdominal distension, and purulent otorrhoea. Family history was unremarkable. Physical examination showed a fever of 39°C and moderate hepatosplenomegaly. Laboratory results showed pancytopenia (white blood cell count 2500/μL, haemoglobin 6·2 mg/dL, haematocrit 20%, platelet count 38 000/ μL), hypertriglyceridaemia (380 mg/dL), hypofibrinogenaemia (48 mg/dL), hyponatraemia (122 meq/L), hypoproteinaemia (4·2 g/dL), and increased erythrocyte sedimentation rate (80 mm/h); all indicative of haemophagocytic syndrome. The bone-marrow aspiration, showing phagocyted erythrocytes, platelets, and leucocytes by benign histiocytes (figure), confirmed the diagnosis of haemophagocytic syndrome. *Pseudomonas aeruginosa* was grown both in the blood and ear leakage specimen cultures. Despite broad-spectrum antibiotics and supportive therapy, the patient died on the 7th day of admission. Hemophagocytic syndrome should be considered as an underlying disorder in children who present pancytopenia. It can occur as a familial haemophagocytic syndrome but is more commonly associated with an infection.

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