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High risk of reinfection TB in hyperendemic settings: Reasons and remedies.

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It is known that in high TB incidence settings the rate of recurrent TB disease is much higher than the rate for first-time disease (1). Certainly many of these recurrent disease cases are due to relapse but the remaining cases are reinfection cases as confirmed by fingerprint comparison between the first episode and second episode. Indeed, it has been shown that, at least in one high incidence setting, the dominant cause of recurrent disease after the first year following cure is reinfection (2). In the same setting the rate of reinfection disease appears to be as high as four times the rate of first-time infection (primary) disease (3). High reinfection disease rates have also been reported from elsewhere (1).

It is not clear why the rate of reinfection disease can be elevated compared to the rate of primary disease. It may be speculated that people who have already experienced a primary disease episode have just been unfortunate in finding themselves in a high risk socioeconomic environment possibly involving their workplace, school, club or transport situation, where other infectious cases continue to be present (5, 6). Otherwise it could be that they are innately predisposed to progress to disease, possibly due to genetic risk factors (7, 8), lung damage caused by the previous episode, and perhaps smoking and drug abuse. It may be that a combination of these factors could be responsible. So a high rate of reinfection or a high rate of progress to disease or both could be responsible for the high rate of reinfection disease. The relative importance of these factors is the subject of much debate (9, 10) since direct observation of either of these rates is difficult.

To get some perspective on the magnitudes of the risk of reinfection and the rate of progress to disease required to manifest high rates of actual reinfection disease consider the following:
A cohort of 1000 patients has just successfully been treated for a primary TB disease episode and is shown to be cured. Suppose their (annual) risk of becoming reinfected is 0.80. This may seem impossibly high and it means that 400 of these patients will have been reinfected by the end of the first 6 months. Assuming the accepted rate of progress to disease is about 2.5 per hundred per year, during the course of the subsequent six months 400 x (2.5/100) x ½ = 5, i.e. 5 of the 1000 cured patients will have active TB disease by the end of the first year after cure. Of course more patients get reinfected during the second six month period and some of these will have joined the group of actively diseased patients by the end of that first year. But this number will certainly be less than the estimate of 5 found earlier. So a total of somewhere between 5 and 10 of the original 1000 patients will have active TB by the end of the first year. This means that the reinfection disease rate is about 0.75% which is of the same order as the reinfection disease rate after successful treatment estimated at 2.2 per 100 person-years in one particular high-incidence setting (3). Thus the intuitively impossibly high annual reinfection risk of 0.8 used in our calculation is actually quite realistic.

Estimating reinfection risk and progress to disease rate

We set about attempting to estimate the actual values of the risk of reinfection and the rate of progress to disease for the high-incidence community of Ravensmead

-Uitsig in Cape Town. A large database detailing the TB history of thousands of patients has been built up since about 1990. In particular for each patient the following dates are recorded:

1. Date of diagnosis of first disease episode,
2. Date of diagnosis of second disease episode for those patients experiencing a second disease episode.

Unfortunately fingerprint typing for both the first and the second disease episodes was not available for all the patients whose first episode had been cured (with bacteriological proof) - see Figure 1. It is reasonable to suppose that the cases where both episodes had been typed form a random sample of this larger population (i.e. genotyping information is missing completely at random). The patients with DNA fingerprints were representative for those without so that the cases where fingerprints were missing do not constitute a biased subset (3). We believe therefore that we may assume that fingerprints are missing in an entirely random way resulting from, for example, administrative error or loss of viability of specimens during transport from the clinics to the laboratories or just simple laboratory failures. So for those patients missing typing data, we assumed the same proportion p_{Diff} experienced reinfection disease as in the subgroup with typing data available for both episodes. Since we believed this to be a reasonable assumption we considered all cases with a cured first TB episode instead of only the subset with genotyping data available for both episodes. In this manner we obtained a larger subset to analyse. We noted that the proportion of the confirmed reinfection cases (where the first episode had been cured) compared to all recurrent cases (after cure) is $p_{Diff} = 0.57$ from 33/57 – see the last boxes in Figure 1. The risk of reinfection disease within a period of time t after cure of a first disease episode is then calculated as 0.57 times the risk of recurrent disease within a period of time t after cure of a first disease episode. By taking this approach we are able to use the date data from the much larger group of 943 patients (near the top of Figure 1).

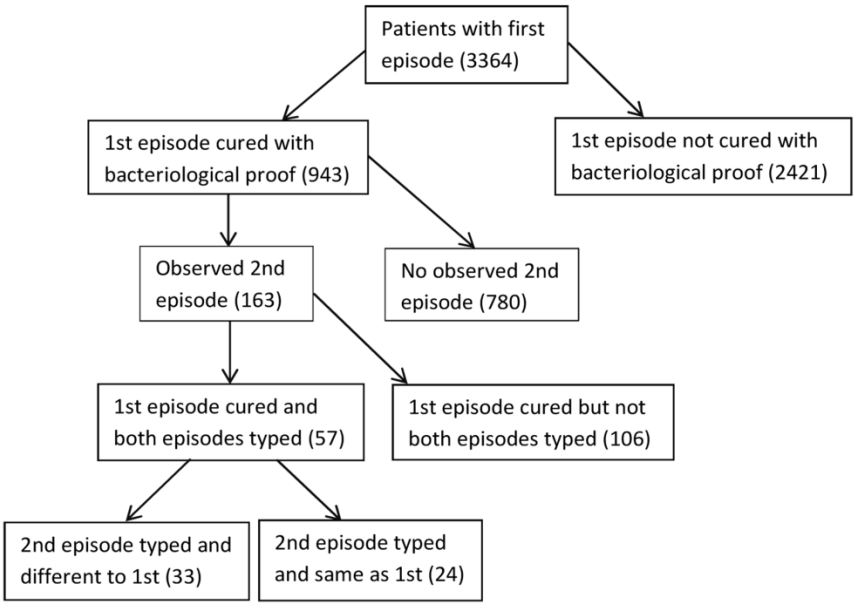

Figure 1. History of patients with a first episode of TB disease.

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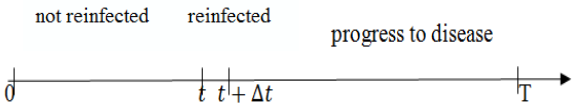
The task then is to use these dates and the inferred time from cure of first episode to the onset of the second disease episode to estimate the risk of reinfection and the rate of progress to disease after reinfection. This requires a far more subtle line of thought than the simplistic estimation used earlier. The following will provide some indication of how this analysis is conducted:

We let λ_1 and λ_2 denote the annual rate of reinfection and the annual rate of progression to active disease after reinfection, respectively.
The probability, D, of becoming reinfected and then progressing to disease within T years after cure of a previous infection is given by

$$D = \int_0^T e^{-\lambda_1 t}\,\lambda_1\left(1 - e^{-\lambda_2(T-t)}\right)dt \quad \ldots\ldots \quad (1)$$
$$= -e^{-\lambda_1 T} + \frac{\lambda_1}{\lambda_1-\lambda_2}[e^{-\lambda_1 T} - e^{-\lambda_2 T}] + 1$$
$$= \frac{1}{\lambda_1-\lambda_2}[\lambda_2 e^{-\lambda_1 T} - \lambda_1 e^{-\lambda_2 T}] + 1 \quad \ldots. \quad (2)$$

The integral in (1) arises from the following consideration:



Patients who become reinfected during the time interval from t to $t + \Delta t$ escaped reinfection prior to time t. The risk of that is $e^{-\lambda_1 t}$. The risk of reinfection during the period from t to $t + \Delta t$ is $\lambda_1 \Delta t$. The risk of progress to disease during the interval from t to T is $\left(1 - e^{-\lambda_2(T-t)}\right)$. By combining these risks and summing over all the Δt time intervals with $\Delta t \to 0$ we arrive at (1).
We proceed from equation (2) by calculating $\frac{dD}{dT} = \frac{-\lambda_1\lambda_2}{\lambda_1-\lambda_2}\left[e^{-\lambda_1 T} - e^{-\lambda_2 T}\right]$ and finding the second-order approximation (valid if $\lambda_i T \ll 1$ which will be the case for small T and λ_i):

$$\frac{dD}{dT} \sim \lambda_1\lambda_2 T\,[\,1 - \tfrac{1}{2}(\,\lambda_1 + \lambda_2)T\,] \ldots.. (3)$$

So now if we plot the graph (Figure 2), obtained from the data, which shows how the risk of reinfection disease varies over time, then we can correlate gradients to this graph at various times to the predictions of equation (3). In this way the values of λ_1 and λ_2 can be estimated (Figure 3).

It should be noted that in the analysis of our data individuals who experienced recurrence after the cure of their first episode, were censored at the time of recurrence (meaning that they were only considered to be at risk of reinfection until that time and only contributed to the analysis until that time), while those who did not experience relapse or reinfection (as far as we know) prior to the 10th of October 2005 (the date of the last clinic visit in the data set) were censored at this date. This type of censoring is called right censoring.

No information regarding, for example, migration or death was available after treatment ended for a patient. It was therefore necessary to make the assumption that if an individual did not return to the clinic, they survived recurrent TB disease as well as death. This assumption will most likely result in an underestimate of the rate of reinfection. The survival analysis was performed using the R programming language and built-in functions of an R package called 'survival'. These functions correctly account for right censoring.

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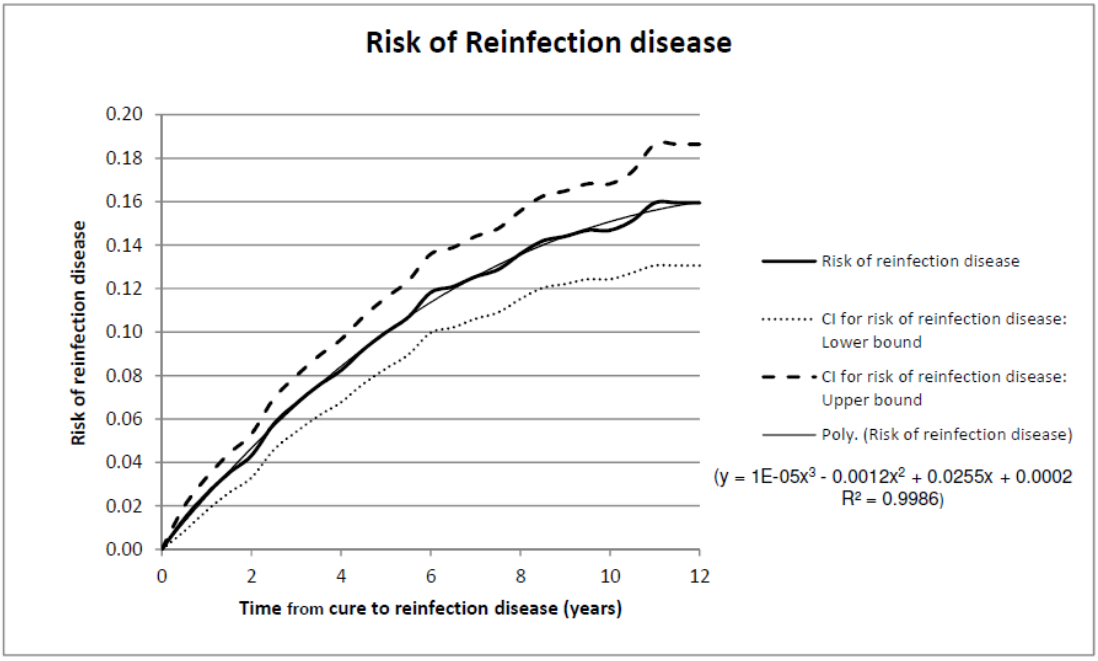

Figure 2. Risk of patient experiencing a reinfection TB disease episode T years after cure of a primary episode.

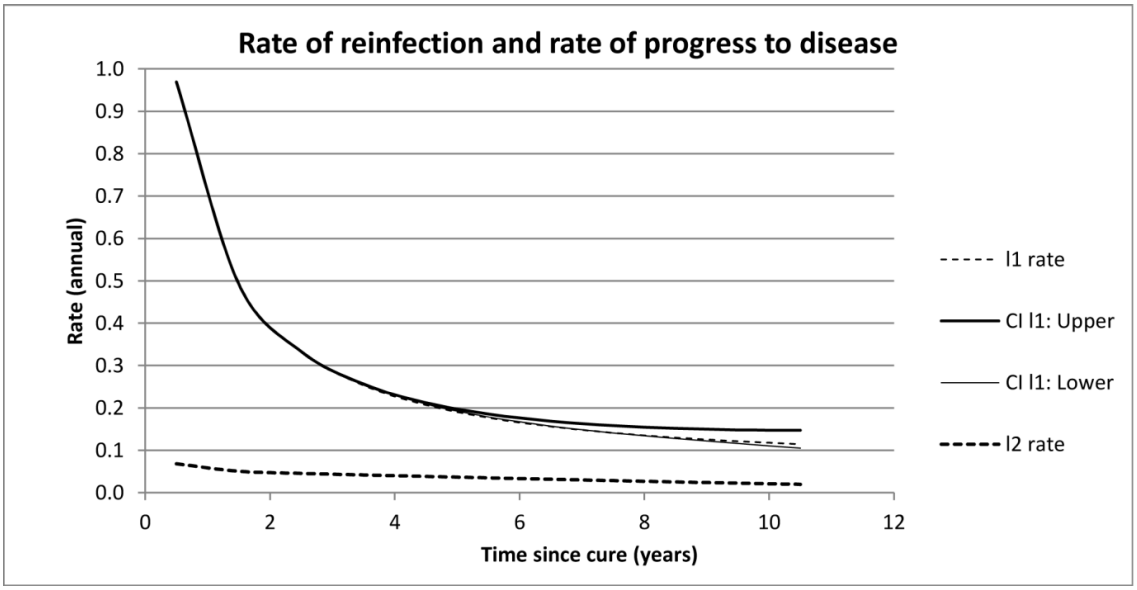

Figure 3. λ_1, the annual risk of reinfection, is estimated by the graph labelled l1, while λ_2, the rate of progress to disease, is estimated by the graph labelled l2. Note however, that after about the end of the first year the graph over-estimates the risk of reinfection.

From Figure 3 it is seen that immediately after cure of a primary disease episode (i.e. about six months after diagnosis and commencement of treatment) a patient is at very high risk of reinfection, but this risk diminishes very quickly. The graph estimating the risk of reinfection follows the trend $r = 0.6228\ x^{-0.746}$ and an integration over the initial six months after completion of treatment shows that about 40% of the patients will have become reinfected. Compare this with the earlier hypothetical crude estimate. The proportion rises to about 66% by the end of a further six months. Unfortunately this graph over-estimates the risk of reinfection beyond the first year after cure and should not be used for that purpose.

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Figure 3 also shows that the rate of progress to disease is initially about double that typical for the general population, but this rate also decreases over time.

It has been established elsewhere that in hyperendemic settings reinfection is the major cause of recurrent TB disease. We found in the present study pertaining to the specific settings identified that it can be expected that approximately 57% of patients who were cured of a first episode and who experienced a recurrent episode, experienced reinfection as opposed to relapse.

These reinfection cases constitute a significant proportion (at least 10%) of all cases where the first episode had been cured. Moreover we also note that 43% of the patients who were cured with proof had a second episode with the same strain as the first. For the purposes of our analysis we conservatively regarded these as relapse cases but it is quite likely that such patients had been reinfected by commonly circulating strains or even by the (untreated) people responsible for infecting them the first time. In fact, we have previously found an association of specific Mtb strains with humans with a particular HLA type (11), and this could also explain why, in a hyperendemic setting with a number of strains present in the environment, the strain infecting the host the second time is often the same as the first, as this strain is the best "fit" for that host. Since reinfection with the same strain was an exclusion criterion here, the estimated rate of reinfection leading to disease is an underestimate.

Explanations for the high rate of reinfection after cure

Our study revealed that patients cured of a first disease episode were at great risk of becoming reinfected during the initial months after cure. Initially the annual reinfection rate is about 0.85 (earlier we gave a very simple explanation of why this is actually a perfectly reasonable value for the reinfection rate), but the rate drops off very rapidly during the subsequent two to three years and continues to drop so that by about ten years since cure the rate has a value typical of that for the population generally. It may be hypothesised that these patients continued in a high risk environment after cure, but such high risk conditions diminish over time for them as, for example, they move to different employment or the infectious people to whom they had been exposed become cured themselves. But we also know that human genetic susceptibility plays a significant role in determining which of the latently or newly infected hosts progress to active disease (12), and we may expect these hosts to have repeated episodes of disease in a hyperendemic area. We hypothesize that different allelic frequencies in genes that are crucial at a number of stages in the immune defence against Mtb will impact the host resistance to this infection and its progression.

Within an admixed population such as that investigated here, there will be a wide variety of susceptibility alleles, some derived from different ancestral input (13-15) and others representing normal variation in any population (16-19). Resistance to TB may encompass resistance to infection, or resistance to progression of disease, and our linkage studies in this community show that two separate loci are involved (20), and we postulated that patients who maintain a zero measure for skin test positivity, are inherently resistant. This cohort would by definition not have the first episode of TB, and would therefore not be included in the present study. Those who are most susceptible will succumb rapidly again after the first infection, while as time passes and this susceptible cohort is "removed" from the pool of patients

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recovering from TB, the apparent rate of reinfection will go down. This mechanism is supported by other studies (21, 22), as fitting the data better than the hypothesis that infection increases susceptibility to reinfection.

However, we need to consider another possible explanation for the high rate of reinfection shortly after cure, namely, that the patient's immune system remains compromised for a significant period after bacterial cure, as a result of the disease episode. Cytokine levels and networks may remain disrupted due to their slow recovery after an episode of TB. In patients cured of an episode of TB, the levels of IFN-γ immunoreactivity remain suppressed at the end of therapy (23) and for at least 12 months after the start of therapy (24). IFN-γ is important in the TH1-type cytokine response, and while a depressed level of IFN-γ activity may point to genetic susceptibility in some patients, the levels at 18 months have recovered to control levels, indicating the time dependence of the effect (24). The ratios of other cytokine such as TNF-α/IL-10 were significantly increased in TB patients before, during, and also at the end of treatment compared to those of control subjects (23). Pathogenic mycobacteria can subvert the autophagy/apoptotic pathways, and a number of signalling cascades, and the extent and duration of these effects is not known.

The delicate balance between the survival of the pathogen and the success of the host defence system could be tipped in favour of disease success in the months after an infection, for a combination of all the above reasons (25) and this, in combination with the genetic susceptibility previously discussed, manifests as an early increase in disease after cure.

The first episode of TB has already served to identify those infected persons that are likely to progress to disease, and the public health benefit of monitoring this subset of the population for a short period to prevent the even smaller subset which may be the most genetically susceptible and is at increased risk of a second episode of disease, seems well worth the effort. Recently it was announced (26) that a blood test had been discovered that can predict more than a year ahead whether someone is likely to progress to active TB disease.

Whether such monitoring should be implemented and for how long such monitoring should continue would be best determined by a cost-benefit analysis compared to other types of control measures.

This study does not provide definitive answers as to why the rate of actual reinfection soon after cure is so high. However, should monitoring take place, it is likely that the reason a patient has become reinfected so quickly could become evident. This in itself could suggest more efficient measures.

A full account of this work is given in: Uys P, Brand H, Warren R, van der Spuy G, Hoal EG, van Helden PD. The risk of tuberculosis reinfection soon after cure of a first disease episode is extremely high in a hyperendemic community. PlosOne. 2015;10(12):e0144487.

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