

The problem of TB reinfection – an opportunity

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Tuberculosis, mycobacterium tuberculosis (TB), is a bacterial disease notably infecting the lungs of its victims but possibly almost any other part of the body. Transmission occurs when bacterium-laden water droplets exhaled by an infectious person are breathed in by another person. Transmission may lead to active disease immediately or the infection could be contained by the immune system and remain in a latent state for many years, sometimes decades, possibly reactivating eventually when the victim's immune system weakens.

The incidence (number of new cases in the population per year) of TB found in various regions of the globe ranges from almost zero to more than 600 cases per 100 000 persons per year (Figure 1) (1). Incidence double this rate has also been reported for a few communities including some in South Africa (1). A significant contributing factor to these high incidence rates is undoubtedly the phenomenon of repeated infections leading to further disease episodes. Indeed, mixed infections involving different strains of TB in a large number of individuals of a population in a high incidence region have been reported (2-4) and the phenomenon of reinfection resulting in second

episodes of disease in patients has been documented (5). In a Dutch setting with a low tuberculosis incidence, approximately one in six new disease episodes among patients with previous tuberculosis infection or disease may be attributable to recent reinfection (6).

It is not known why some people experience more than one episode of TB disease but it is believed that various factors may play a role. For instance, a person experiencing a second episode of TB may simply be demonstrating that he/she has a higher susceptibility, either congenital or due to environmental conditions (7, 8). It is also possible that an episode of TB actually renders the patient more susceptible to infection or likely to become ill. All these issues have been surveyed by Verver et al (9). On the other hand, an effect that interferes with the actual cause-effect relationship is the possibility that a first episode of TB imparts some measure of immunity to further TB infections (2, 9, 10).

Reinfection is thus an important event with largely unknown reasons and consequences, for example, it can be speculated that multiple exposures may even trigger progression to disease. It would be reasonable

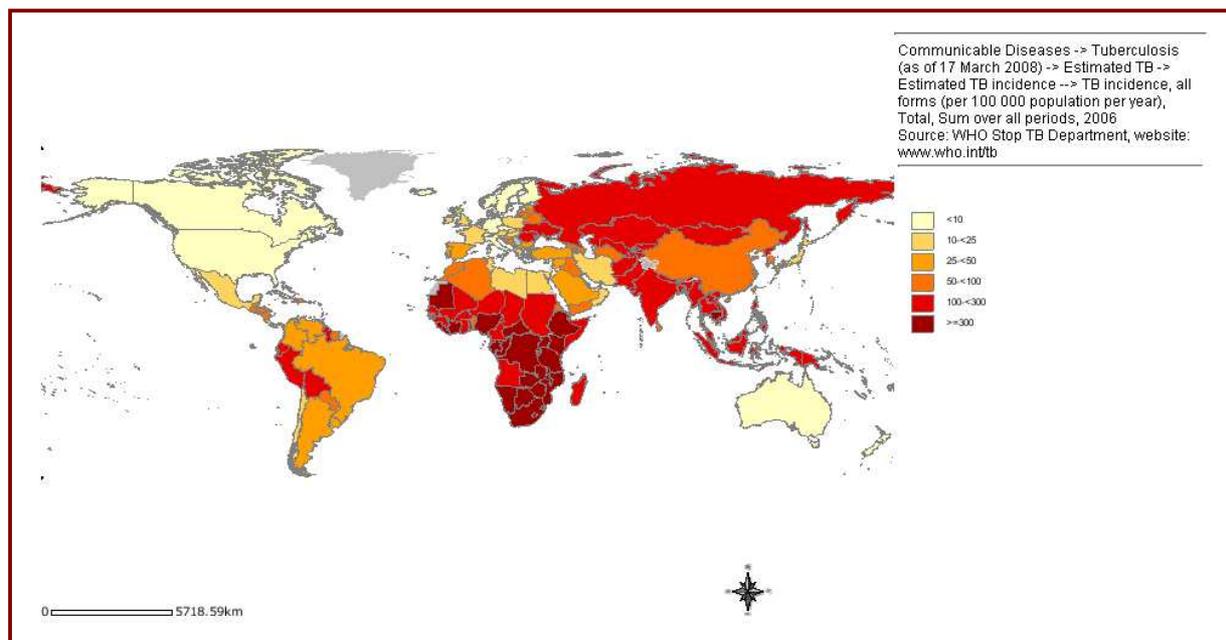


Figure 1: The global incidence of TB

to expect, however, that in communities where there is a high prevalence, the rate of reinfection will be correspondingly high, simply because of the higher risk of exposure. This higher rate of reinfection is indeed observed but the relationship to the incidence rate is not direct. Epidemiological studies suggest that the proportion of cases that can be attributed to reinfection is instead correlated with the logarithm of

natural higher rate of progression to disease can be reflected by a higher rate of progression generally. This does not, of course, yield an accurate indication when comparing data from different settings subject to large differences in HIV incidence. Deviations from model predictions could thus be anticipated in any community where there is a significant increased presence of HIV or sudden population change. Drug

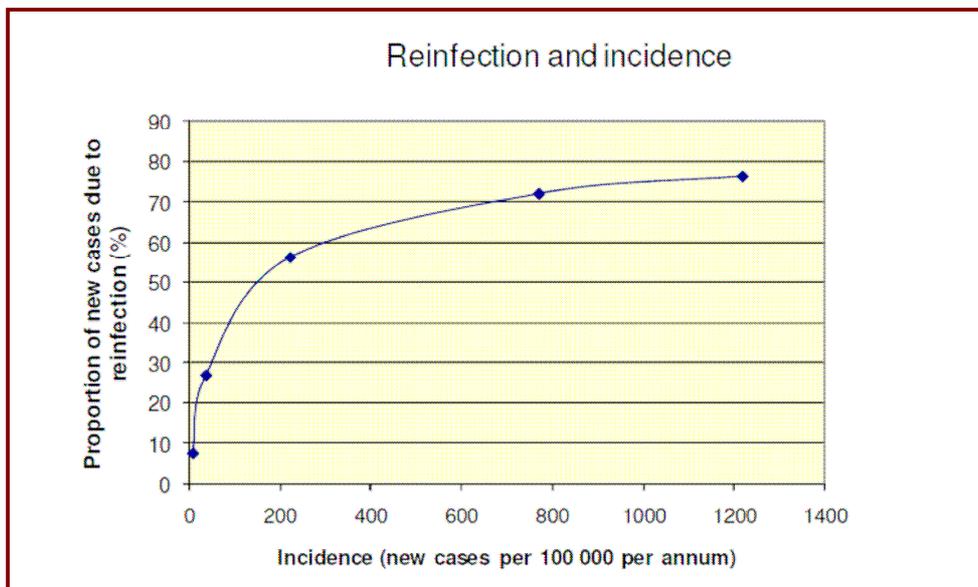


Figure 2: Simulation of actual data. The very high proportion of new cases due to reinfection when incidence is high is noteworthy

the incidence (11). By way of illustration, this indicates that a doubling in the rate of incidence, i.e. a 100% increase, correlates with an increase in the reinfection rate by an amount of only 69% (Figure 2).

The influence of incidence on the reinfection rate thus appears to be a fundamental issue (11, 12) but this specific relationship is unexpected. We investigated this further by constructing a Markov model that simulates the epidemiology of a TB endemic in a hypothetical region (13). In order to accomplish this it was necessary to make a number of assumptions described as follows:

The Markov model paradigm assumes that the population size is constant, but we regard this to be a reasonable assumption given a short period estimation. Immigration and emigration must therefore also be excluded. However, these restrictions can be relaxed to a certain extent without seriously undermining the deductions made from this model. Our model was intended to assist in investigating reported data (11). Unfortunately the HIV statuses of the patients involved in that study were not reported. For internal consistency across different incidence rates within our model we elected to exclude HIV considerations. However, assuming a constant proportion of HIV positive cases among the TB infected cases, their

resistant TB as a separate or specific entity is not considered in the model, which we do not think is a serious shortcoming because the incidence of drug resistant TB is relatively low compared to susceptible TB and the basic principles are the same. Drug resistant TB can be regarded as a component of the TB epidemic.

Our theoretical investigation revealed that the phenomenon of repeated infection is driven by the condition that the risk of a second, disease-causing infection for a person who has recovered from an episode of disease is about 7 (± 4) times greater than the risk of a first-time infection that leads to disease (13). This estimate is in close agreement with actual minimum estimates based on data from a high TB incidence community (9), where the risk of developing a second episode of TB after infection was estimated to be 4-7 times higher than a first episode.

Two possible explanations for this higher risk are an innate higher susceptibility of genetic origin and environmental and socio-economic conditions specific to the patient. But whatever the reasons, it is evident that, because of their highly elevated risk, recovered TB cases need follow-up monitoring and this is particularly so in communities where the incidence of TB is high (Figure 2).

In view of this elevated risk, we suggest that TB cases require regular follow-up, and that this should be more intense for the first 3 years after an episode, but that even thereafter, follow-up is indicated. The logistics of such follow-up protocols could be relatively easy to implement and the strategy would make a considerable contribution to reducing the incidence of TB. The cost-benefit analysis indicates a major enhancement of TB control programmes at minimal additional cost.

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