How host heterogeneity governs tuberculosis reinfection?

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Recurrent episodes of tuberculosis (TB) can be due to relapse of latent infection or exogenous reinfection, and discrimination is crucial for control planning. Molecular genotyping of \textit{Mycobacterium tuberculosis} isolates offers concrete opportunities to measure the relative contribution of reinfection in recurrent disease. Here, a mathematical model of TB transmission is fitted to data from 14 molecular epidemiology studies, enabling the estimation of relevant epidemiological parameters. Meta-analysis reveals that rates of reinfection after successful treatment are higher than rates of new TB, raising an important question about the underlying mechanism. We formulate two alternative mechanisms within our model framework: (i) infection increases susceptibility to reinfection or (ii) infection affects individuals differentially, thereby recruiting high-risk individuals to the group at risk for reinfection. The second mechanism is better supported by the fittings to the data, suggesting that reinfection rates are inflated through a population phenomenon that occurs in the presence of heterogeneity in individual risk of infection. As a result, rates of reinfection are higher when measured at the population level even though they might be lower at the individual level. Finally, differential host recruitment is modulated by transmission intensity, being less pronounced when incidence is high.

**Keywords:** tuberculosis epidemiology; transmission dynamics; partial immunity; reinfection

1. INTRODUCTION

Despite significant improvements in tuberculosis (TB) treatment over recent years, adequately treated patients are still at high risk of developing recurrent pulmonary disease (defined as an episode of TB following the cure of a previous episode). Recent estimates for the recurrence rate of TB across different regions point to an average of 2290 cases per 100 000 person-years at 12 months after treatment completion. In high-incidence regions, the average TB recurrence rate can reach 7850 per 100 000 person-years [1].

The contribution of exogenous reinfection with \textit{Mycobacterium tuberculosis} (\textit{Mtb}) versus that of endogenous reactivation (relapse) of latent \textit{Mtb} to the overall rate of recurrence of pulmonary disease is subject to controversies because these two mechanisms cannot be easily disentangled. Deciphering the weight of each of these mechanisms is of great importance for policy-making. Advances in DNA fingerprinting techniques allowed the genotyping of the \textit{Mtb}, causing different disease episodes [2]. These methods can reveal whether a new episode of disease is caused by infection with the same strain that caused a previous episode or a different one, enabling a classification into relapse or reinfection, respectively.

Longitudinal data from molecular epidemiological studies on TB reinfection have shown a positive correlation between the proportion of reinfection in recurrent cases and local incidence [3]. A long-term study, in an area of South Africa, with particularly high incidence, attributed the majority (77%) of recurrent TB cases to reinfection [4]. Moreover, the rate of TB reinfection was found to be four times higher than that of new TB, raising an important question about the underlying mechanism. Two possibilities have been proposed to explain these results: (i) infection increases susceptibility to reinfection or (ii) infection occurs at a higher rate in a high-risk subpopulation [5].

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review. The model postulates that some individuals are
world. The dataset was gathered by systematic literature
data relating TB incidence and reinfection proportion
mechanisms, and assess its capability to fit available
framework for TB transmission that encapsulates both
trated in figure 1). This process alone acts to inflate the
degree that is modulated by transmission intensity (illus-
over-represented in the treated subpopulation to a
affect individuals at higher risk, who will naturally be
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confers partial protection at the individual level. The rela-
ance incidence to disease is
parameters. For example, the rate of progression from pri-
this can be interpreted only in conjugation with other
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1/70 yr
12 yr
9
2, and
1,2, such that immunologi-
susceptibility and exposure [6–8]. Infection is more likely
to affect individuals at higher risk, who will naturally be
over-represented in the treated subpopulation to a
degree that is modulated by transmission intensity (illus-
trated in figure 1). This process alone acts to inflate the
rate of reinfection at the population level, even if infection
confers partial protection at the individual level. The rela-
tive susceptibility of individuals who have been previously
infected over those who are naive is represented by a
parameter \( \sigma \), the value of which will be estimated
by the fitting procedure.

2. METHODS
(a) Literature review
Through a systematic literature review, we aggregated
data on recurrent TB and its relationship with TB incidence.
Published epidemiological studies were located via PubMed
through searches on the following terms: tuberculosis,
recurrent, relapse, reinfection or re-infection. Studies were
included in the analysis if fulfilling the following criteria:
- study reports the number of recurrent TB cases, defined
positive culture after bacteriologically confirmed cure or
complete treatment following a first episode;
- study reports more than 10 recurrent TB cases;
- study discriminates between reinfection and relapse by
comparing \( M_{tb} \) DNA fingerprinting profiles of the initial
and recurrent episodes; and
- population-based study published up to March 2011.

We extracted the data for the local incidence from the study
papers whenever possible. When no incidence was reported
in the study itself, we used the estimates for the year 2000
in the respective country, provided by the World Health
Organization [9]. The proportion of reinfection was defined
as the ratio between the number of patients with reinfection
and all recurrent TB cases. One study performed in
Cape Town also provided the ratio between the rate of
reinfection TB in successfully treated patients and the rate
of new cases of TB [4].

(b) Mathematical formulation
A mathematical model [10,11] is extended by enabling the
risk of infection to be heterogeneously distributed among
the population. The transmission model is replicated in two
subpopulations, indexed by \( i = 1,2 \), such that immunologi-
cally naive individuals in subpopulation 1 (low risk) are
subject to a per capita rate of infection \( (\lambda_i = \alpha_i \lambda) \), whereas
in subpopulation 2 (high risk) infection occurs at a higher
rate \( (\lambda_2 = \alpha_2 \lambda) \), where \( \alpha_1 < \alpha_2 \), and \( \gamma_1, \gamma_2 \) are the proportions
of the population in each risk group. Within each group, indi-
ciduals are classified—according to their infection history—
to susceptible (\( S_i \)), primary infection (\( P_i \)), latent (\( L_i \)),
active pulmonary tuberculosis (\( I_i \)) and recovered (\( R_i \)).
Latent and recovered individuals can be reininfected at a rate
that is proportional to the rate of first infection, with multi-
plicative factor \( \sigma \). The model is written as a system of
differential equations

\[
\begin{align*}
\frac{dS_i}{dt} &= \mu \gamma_i - (\lambda_i + \mu)S_i \\
\frac{dP_i}{dt} &= \lambda_i S_i + \sigma \lambda_i (L_i + R_i) - (\delta + \mu)P_i \\
\frac{dL_i}{dt} &= \delta P_i + \omega (L_i + R_i) - (\tau + \mu)L_i \\
\frac{dI_i}{dt} &= (1 - \phi) \delta P_i - (\sigma \lambda_i + \omega + \mu)L_i \\
\frac{dR_i}{dt} &= \tau I_i - (\sigma \lambda_i + \omega + \mu)R_i,
\end{align*}
\]

where \( \mu (=1/70 \text{ yr}^{-1}) \) is the birth and death rate, \( \phi (=0.05) \) is the proportion
of primary infections progressing to active pulmonary disease, and \( \tau (=2 \text{ yr}^{-1}) \) is the rate
at which infectious individuals are detected and treated.
An auxiliary parameter \( \delta (=12 \text{ yr}^{-1}) \) is included to represent
the rate of progression from primary infection, although
this can be interpreted only in conjunction with other
parameters. For example, the rate of progression from
primary infection to disease is \( \phi \delta (=0.6 \text{ yr}^{-1}) \). The value for
\( \mu \) is consistent with human populations with life expec-
tancy of 70 years, whereas \( \phi \) and \( \tau \) are consistent with the
medical literature [12]. The rate of relapse (\( \omega \)) is fixed
at the higher end of published estimates \( (\omega = 0.01 \text{ yr}^{-1}) \)
[13–17], with justification and sensitivity analysis provi-
ded in the electronic supplementary material. Parameters
referring to the reinfection factor (\( \sigma \)) and risk hetero-
genity are estimated in order to adjust the equilibrium
model solutions to the available data. By noting that \( \gamma_1 \)
and \( \gamma_2 \) are proportions, and thus \( \gamma_1 + \gamma_2 = 1 \), and by nor-
malizing the average risk factor such that \( \gamma_1 \alpha_1 + \gamma_2 \alpha_2 = 1 \),
heterogeneity is fully parametrized by the low-risk pa-
rameters, \( \gamma_1 (=\gamma) \) and \( \alpha_1 (=\alpha) \). The parameters are listed
in table 1.

(c) Measures of incidence
TB incidence (cases per 100 000 person-years) is calculated
from the equilibrium proportion of infectious individuals as

\[
Y = \left[ \phi \delta \sum_{i=1}^{2} P_i + \omega \sum_{i=1}^{2} (L_i + R_i) \right] \times 100 000 \\
= (\tau + \mu) \sum_{i=1}^{2} I_i \times 100 000.
\]
The treatment is the sum of... 

Table 1. Model parameters.

<table>
<thead>
<tr>
<th>symbol</th>
<th>definition</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>birth and death rate</td>
<td>1/70 yr$^{-1}$</td>
</tr>
<tr>
<td>$\phi$</td>
<td>proportion progressing from primary infection to disease</td>
<td>0.05</td>
</tr>
<tr>
<td>$\delta$</td>
<td>rate of progression from primary infection</td>
<td>12 yr$^{-1}$</td>
</tr>
<tr>
<td>$\tau$</td>
<td>rate at which infectious individuals are detected and treated</td>
<td>2 yr$^{-1}$</td>
</tr>
<tr>
<td>$\omega$</td>
<td>rate of endogenous reactivation</td>
<td>0.01 yr$^{-1}$</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>reinfection factor</td>
<td>estimated</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>proportion low-risk group</td>
<td>estimated</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>low-risk factor</td>
<td>estimated</td>
</tr>
</tbody>
</table>

Following the criteria used in the data collection, we classify a recurrent TB case as an individual who enters the infectious class after having gone through the recovered class. This combines two pathways: relapse while in the recovered class, $Y_{\text{relapse}}$, and exogenous reactivation with progression to active disease, $Y_{\text{reinfection}}$ (direct or following a latent period). We derive these quantities formally from equation (2.1). The instantaneous rate of relapse after successful treatment is the sum of $R_i \rightarrow I_i$ transitions

$$Y_{\text{relapse}} = \omega \sum_{i=1}^{\infty} R_i,$$  

while the instantaneous rate of reinfection after successful treatment is the sum of $R_i \rightarrow P_i(L_i \rightarrow P_i) n \rightarrow I_i$ and $R_i \rightarrow P_i(L_i \rightarrow P_i) n \rightarrow L_i \rightarrow I_i$ transitions for any number ($n$) of iterations of the cycle $P_i \rightarrow L_i \rightarrow P_i$, derived as

$$Y_{\text{reinfection}} = \sum_{i=1}^{\infty} \left\{ \sigma \lambda R_i \left( \frac{\phi \delta}{\delta + \mu} + \frac{(1 - \phi) \delta \omega}{(\delta + \mu)(\omega + \mu + \sigma \lambda)} \right) \times \left( \frac{\sigma \lambda (1 - \phi) \delta}{(\delta + \mu)(\omega + \mu + \sigma \lambda)} \right)^n \right\} = \sum_{i=1}^{\infty} \left\{ \sigma \lambda R_i \left( \frac{\phi \delta}{\delta + \mu} + \frac{(1 - \phi) \delta \omega}{(\delta + \mu)(\omega + \mu + \sigma \lambda)} \right) \times \frac{(\delta + \mu)(\omega + \mu + \sigma \lambda)}{(\delta + \mu)(\omega + \mu + \sigma \lambda)} \right\}. $$

Hence, the proportion of reinfection over all recurrent TB after successful treatment is

$$p = \frac{Y_{\text{reinfection}}}{Y_{\text{relapse}} + Y_{\text{reinfection}}}. $$

The rate of new TB is given by

$$Y_{\text{new}} = \sum_{i=1}^{\infty} \lambda_S \left( \frac{\phi \delta}{\delta + \mu} + \frac{(1 - \phi) \delta \omega}{(\delta + \mu)(\omega + \mu + \sigma \lambda)} \right) \times \left( \frac{\delta + \mu}{(\delta + \mu)(\omega + \mu + \sigma \lambda)} \right).$$

Finally, for comparison with the Cape Town study [4], we define $\kappa$ as the ratio of the rate of reinfection TB among successfully treated patients over the rate of new TB cases among those who have never had a TB episode, formally calculated as

$$\kappa = \frac{Y_{\text{reinfection}}/(R_1 + R_2)}{Y_{\text{new}}/(\delta_1 + \delta_2)}. $$

(d) Meta-analysis

We perform a meta-analysis of the relationship between the proportion of reinfection in recurrent TB ($p$) and the incidence of TB ($Y$) by fitting the model described in equation (2.1) to the dataset collected by the systematic literature review. By taking the incidence rate as an independent variable of a nonlinear regression, we estimate the set of model parameters that best describe the observed trends in the proportion of TB reinfection. First, we have considered a model where the host population is homogeneous with respect to risk of infection, and proceeded to assess whether heterogeneity would significantly improve the ability of the model to fit to the data. A Gaussian–Newton algorithm was implemented to fit the model output to the data according to the least-squares criterion. We used an F-test and a log-likelihood test to assess whether the heterogeneous model provides a significantly better fit to the data.

3. RESULTS

We conducted a systematic literature review and found 14 molecular epidemiological studies reporting the proportion of reinfection in recurrent TB across communities presenting a wide range of endemic levels [3,4,18–29]. Table 2 summarizes the data collected.
Figure 2 shows the output of the homogeneous and heterogeneous versions of equation (2.1) that best fit the dataset, whereas the estimated parameters are listed in table 3. The figure shows the proportion of reinfection TB in recurrent cases ($p$) versus TB incidence ($Y$) at equilibrium. The model shows a markedly nonlinear relationship between the proportion of reinfection and local incidence, which was not captured by previous studies [3]. The ratio ($\kappa$) of the rate of reinfection TB over the rate of new TB predicted by the model is plotted in figure 3, where it can be confronted with the measure obtained for Cape Town [4]. Curves are generated by the best-fitting models identified in figure 2: homogeneous host population (dotted) and heterogeneous host population (dashed).

Table 3. Estimated parameter values.

<table>
<thead>
<tr>
<th>parameter</th>
<th>heterogeneous model</th>
<th>homogeneous model</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma$</td>
<td>0.98 [0.95, 1.00]$^a$</td>
<td>n.a.</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.15 [0.00, 0.56]$^a$</td>
<td>n.a.</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0.51 [0.00, 2.37]$^a$</td>
<td>3.87 [1.61, 7.79]$^a$</td>
</tr>
<tr>
<td>residual sum of squares</td>
<td>0.30</td>
<td>0.74</td>
</tr>
<tr>
<td>standard error estimate</td>
<td>0.16</td>
<td>0.24</td>
</tr>
<tr>
<td>$F$-test</td>
<td>8.12 (0.007)$^b$</td>
<td>n.a.</td>
</tr>
<tr>
<td>log-likelihood test</td>
<td>12.70 (0.002)$^b$</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

$^a$Mode [95% CI]. $^b$Score ($p$-value).

to show that heterogeneity enables a significantly better fit to the data (table 3). The best scenario provided by this analysis estimates the heterogeneity parameters as $\gamma = 0.98$ and $\alpha = 0.15$, suggesting that the risk of infection is about 40 times higher than average in the 2 per cent subpopulation at highest risk. Although these are necessarily crude approximations that enabled the model to simultaneously fit a vast spectrum of epidemiological scenarios, they can serve as a basis for further resolution in a region-specific manner. The estimated reinfection factor ($\sigma = 0.51$) indicates that previous infection has a protective effect, contrary to a model proposed previously [30].

4. DISCUSSION

We propose a minimal model for TB transmission to describe the relative contributions of reinfection and relapse to recurrent TB across a range of transmission intensities. A nonlinear relation between the proportion of reinfection and the local incidence is derived by fitting this mechanistic model to the dataset resulting from a systematic literature review. By accounting for heterogeneity in the risk of infection, we obtain significantly better model fittings to epidemiological data. This trend is in agreement with current understanding of TB transmission, especially in regions of low to moderate transmission, where TB is confined to particular risk groups with sporadic small outbreaks in the general population [31,32], and has been previously noted in theoretical studies [33]. Infection acts upon this variation and predominantly recruits those individuals at higher risk to the recovered category, thus inflating the rate of reinfection (as illustrated in figure 1). As a result,
population measures of reinfection rates in relation to first infection (k) are higher than the reinfection factor at the individual level, s.

The model predicts that, under heterogeneity, regions of low to moderate transmission support relatively higher k than regions of high transmission. This is again owing to the way differential recruitment acts upon individuals at higher risk. For highly endemic regions, transmission intensity tends to homogenize the distributions of both susceptible and recovered individuals, making differential recruitment less pronounced [34]. Cape Town is the only study reporting the information required to estimate this ratio. Similar studies providing this data for other regions would be very valuable to confirm the validity and increase the accuracy of the results reported here.

The parameter estimation procedure (provided in the electronic supplementary material) supports higher relapse rates than those previously stated for European countries [14,15], whereas recent studies in African [13] and Asian [16,17] regions suggest values that are compatible with those considered here. This may be due to higher prevalence of co-infection with HIV in those settings or simply reflect regional differences in nutrition, smoking patterns, environmental conditions, population structure or the natural history of TB [16,17,35,36]. Despite these acknowledged differences, we have opted for constancy across regions in model parameters, with the exception of acknowledged differences, we have opted for constancy across regions in model parameters, with the exception of

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