Sensitivity analysis of a model for tuberculosis

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Abstract: Tuberculosis (TB) is a growing problem worldwide, with an estimated third of the world's population currently infected. Of particular concern is the growing trend of dual epidemics of HIV and TB, with the associated multidrug-resistant TB (MDR-TB). Developed countries which had previously removed TB transmission from communities are being re-infected with the MDR-TB strains. In the USA, Centers for Disease Control & Prevention (2009) estimate that treatment of a single case of MDR-TB costs approximately USD$250,000, with a similar cost expected in Australia.

TB is a complicated disease with different rates of progression to, and different aspects of, the clinically active disease. Approximately 5–10% of those infected with TB develop 'fast' TB, and are expected to progress to clinically active TB within 2 years [Porco et al. 2001]. The remainder have 'slow' TB, and remain latently infected, with 5-10% progressing to clinically active TB in 20 years [Blower et al. 1995]. Those with clinically active TB are further divided into extra-pulmonary (non-infectious) and pulmonary (able to infect others). Note those in the 'pulmonary' category may also have extra-pulmonary TB, but the reverse is not true.

The control of TB spread is of paramount importance. The main intervention strategy adopted by the World Health Organisation (WHO) Stop TB program is the 'Directly Observed Treatment Short course' (DOTS) [World Health Organisation 2010]. Not all detection occurs under this program, but a significant amount of the treatment does, particularly for high burden countries. Therefore when considering interventions, we concentrate on the DOTS program, and do not consider other interventions here.

We develop a population level model for TB transmission, with a focus on incorporating the WHO's DOTS (Directly Observed Treatment Short-course) intervention program. The population is divided into 6 compartments, with 4 describing different stages of the disease (susceptible, latently infected, extra-pulmonary, and pulmonary), and 2 for the DOTS intervention program (detection and treatment).

This work has applications worldwide, but here we focus on the Torres Strait region where there is a high proportion of multidrug-resistant TB (MDR-TB). In particular, estimates suggest Papua New Guinea (PNG) may have the highest proportion of MDR-TB in the world [Gilpin et al. 2008], and the Torres Strait Islands could potentially act as a gateway for MDR-TB into mainland Australia.

A sensitivity analysis is important in terms of both data collection and refinement, and in the context of understanding and informing the control of TB. To perform the sensitivity analysis the model needs to be run many times with different parameter values. Latin hypercube sampling is used to efficiently cover the parameter space, in conjunction with partial rank correlation coefficient to determine which parameters most influence the disease dynamics.

The results show the most important parameter for TB in Papua New Guinea (PNG) is the rate of progression from latent to clinically active TB. Therefore, data refinement should concentrate on determining this rate as accurately as possible. The most important intervention parameter is the detection rate for the DOTS intervention program. This suggests an increase in DOTS coverage by even a small margin will result in a significant decrease in the incidence and prevalence of TB in PNG and other high burden countries.

Keywords: Tuberculosis, infectious disease, control, intervention, DOTS, sensitivity analysis

1 INTRODUCTION

Tuberculosis (TB) is a growing problem worldwide, especially with the emergence and high prevalence of multidrug-resistant strains. A third of the world population is estimated to be infected with TB, and the highest ever rates of multidrug-resistant TB were reported in 2010 [World Health Organisation 2010].

There has been some recent modelling work on TB transmission dynamics. Basu and Galvani (2008) and Rodrigues et al. (2007) have used models to consider drug-resistant TB, and Sharomi et al. (2008) and Roeger et al. (2009) have considered co-epidemics of HIV and TB. Baltussen et al. (2005), and Currie et al. (2005), consider both co-epidemics of HIV and TB, and drug-resistance through a failed treatment group, but do not explicitly consider a drug-resistant TB strain. Basu et al. (2009) also consider both co-epidemics of HIV and TB and drug-resistance, but their model focuses on a HIV intervention in Botswana. Thomas et al. (2010) consider the spread of TB in the Torres Strait region. Although they included both HIV and MDR-TB in their 'detailed' model, they do not include compartments to analyse intervention strategies. Therefore, a significant difference of this work is the inclusion of compartments to explicitly model interventions, such as the WHO recommended DOTS program. In particular, we perform a sensitivity analysis of the model to determine the most influential parameters. This is important in terms of both data collection and refinement, and in the context of control of TB.

2 THE MODEL

Here we construct a relatively simple model for drug sensitive TB that ignores multidrug-resistant TB (MDR-TB) and HIV. Although these are important factors for TB, an understanding of the dynamics of TB is more straightforward with a simpler model. Future work will extend this model to include MDR-TB and then HIV to determine their importance by comparing the results to the baseline model presented in this article.

The model is a population level compartment model, where the population is divided into discrete compartments each representing a different stage of the disease. TB is a many-faceted disease, and hence the model is reasonably detailed to capture this complexity. Figure 1 depicts the compartment model for drug sensitive TB, based on previous work by Blower et al. (1995) and Thomas et al. (2010), though suitably altered to include aspects relevant to the explored DOTS (Directly Observed Treatment Short-course) intervention. The parameter descriptions and assumptions are presented in Table 1, Appendix A.

The population is divided into 6 compartments, 4 pertain to the disease (S, L, I, P), and 2 for the intervention (D & T). The 4 compartments for disease can be divided into three main groups:

1. those susceptible to TB (S),

2. those latently infected with TB (L), and

3. those with clinically active TB, namely extra-pulmonary (P) and the infectious pulmonary (I).

There are two different paths to having the clinically active disease: a proportion ϵ of recently infected individuals develop fast TB, whereas the rest, $1 - \epsilon$, have the slow latent infection. Note that ϵ is a probability, and not a rate. It is assumed that once someone is latently infected, they remain so until either death or they become clinically active. Progression from latent to active infection occurs with rate ν. Those with active TB are further divided into two groups. The proportion ρ are able to infect others, and have pulmonary infections (I); and the remainder, $1 - \rho$, are not able to infect others, and have extra-pulmonary infections (P). Once clinically active, it is possible for someone to spontaneously clear TB from their system, with rate ω. Those with clinically active TB have a higher death rate, μ_T, than the natural death rate of the susceptible and latently infected, μ_N.

The remaining population compartments are for the DOTS intervention program. The relevant DOTS treatment outcomes, as specified by the WHO (2009), are:

- cured (with probability c_I) – former patients from compartment 'I' who are no longer infectious.

- completed treatment (with rate ζ) – patients from compartment 'P' who have completed treatment.

- defaulted (with rate ψ) – patients with interrupted treatment for two consecutive months or more.
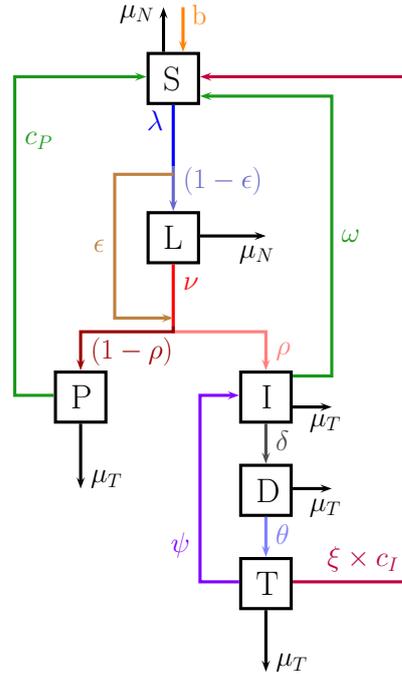
Figure 1. Population level compartment model. S=Susceptible, L=Latently infected, P=non-infectious clinically active TB, I=infectious clinically active TB, D=Detected but not yet treated, T=undergoing Treatment but still infectious. The parameters are described in Table 1 and the text.

The rate of progression from the clinically active but non-infectious (P) back to the susceptible compartment (S) is a combination of 'completed treatment' and the natural cure rate: $c_P = (\omega + \delta \xi \zeta)$, where δ and ξ are described below. The most important group for the transmission dynamics are those with pulmonary TB who are able to infect others. Therefore, compartment (I) progresses to compartments which describe the DOTS intervention program; compartments for those who have been detected (D), and those who are undergoing treatment but are still infectious (T). The detection rate, $\delta(t)$, is a time dependent function, staying at zero until the DOTS program begins in 1997 and increasing to the current value,

$$
\delta(t) = \begin{cases} 0 & t < 1997\,, \\ \dfrac{0.14}{\log(2007 - 1997)} \log(t - 1997) & 1997 \leq t < 2007\,, \\ 0.14 & t \geq 2007\,. \end{cases} \tag{1}
$$

It is assumed that everyone detected is treated, after a delay of $1/\theta$, unless they die first. It is also assumed that once someone defaults from treatment they are no longer 'detected'. That is, they return to the 'I' compartment. This follows from the assumption that all detected are treated, and that those undergoing treatment have either success or failure. Those who have failed treatment implicitly return to the treatment compartment (T) with rate $\xi(1 - c_I)$, where $1/\xi$ is the duration a person is infectious whilst undergoing treatment. Comparatively short average durations are expected for the populations in either the detection or treatment compartments (D & T), hence a natural cure rate was not included.

The governing system of equations is hence given by

$$
\begin{aligned}
\dot{S} &= bN + \omega I + c_P P + \xi c_I T - (\lambda + \mu_N)S\,, \\
\dot{L} &= (1 - \epsilon)\lambda S - (\nu + \mu_N)L\,, \\
\dot{I} &= \rho(\epsilon \lambda S + \nu L) + \psi T - (\omega + \delta + \mu_T)I\,, \\
\dot{P} &= (1 - \rho)(\epsilon \lambda S + \nu L) - (c_P + \mu_T)P\,, \\
\dot{D} &= \delta I - (\theta + \mu_T)D\,, \\
\dot{T} &= \theta D - (\psi + \xi c_I + \mu_T)T\,,
\end{aligned} \tag{2}
$$

where the over-dot denotes the derivative with respect to time, b is the birth rate of susceptibles into the population, $N = (S + L + I + P + D + T)$ is the total population, the force of infection $\lambda = \beta(I + D + T)/N$, and β is the transmission rate when a susceptible meets an infectious individual. Note the transmission rate is assumed to be equal for compartments I, D, & T, which is why 'T' is defined as those undergoing treatment *who are still infectious*. A full list of parameters and their definitions is given in Table 1, Appendix A.

Equations 2 are solved numerically using 'ode15s' in MATLAB [The MathWorks Inc 2010]. Therefore, parameter values must first be determined. Papua New Guinea (PNG) is used as a case study, as it is considered a high burden TB country, with an estimated average prevalence of 430/100,000 population, and incidence of 250/100,000 population in 2007 [World Health Organisation 2009]. In particular, there is believed to be a high prevalence of multidrug-resistant TB [World Health Organisation 2009, pg. 36]. This is of particular importance to Australia since due to treaty arrangements, the border between the Torres Strait Islands and the PNG Western Province is highly porous, with over 59,000 cross-border movements recorded in 2008–9 [Lumb et al. 2008]. The Torres Strait then potentially acts as a gateway for multidrug-resistant TB (MDR-TB) entry into mainland Australia. The parameter values, units, references and assumptions are presented in Table 1, Appendix A. The DOTS intervention program in PNG began in 1997 [World Health Organisation 2009], hence the detection rate, $\delta(t)$, becomes non-zero from then. The model was run with a single infectious case from '1800', until the epidemic stabilised. The transmission rate, β, was then chosen such that the incidence, prevalence, and death rate outputs matched the available data for PNG from the WHO (2009), as well as the total population in 2000. Other parameters were informed by the literature and the disease aetiology, as outlined in Table 1. The initial conditions for the sensitivity analysis were subsequently determined by the output of the '1800' run in the year equivalent to 1990. The sensitivity analysis was run from 1990 to 2032, as this allows the model to settle and covers the period of interest (1997-2032).

3 SENSITIVITY ANALYSIS

Essential to any mathematical model of disease progression is a sensitivity analysis to ascertain which parameters dominate the results. Latin Hypercube Sampling is used to efficiently cover the parameter space, in conjunction with Partial Rank Correlation Coefficient (PRCC) multivariate analysis to determine the dominant parameters, as previously done by Sanchez and Blower (1997), Marino et al. (2008), *inter alios*. A PRCC rank close to magnitude 1 indicates a dominant parameter, while the least important parameter rank coefficients are near zero. The PRCC analysis requires a monotonically increasing function, hence the cumulative number with clinically active TB $(P + I + D + T)$ is used.

The parameter values are used from the PNG case study, though several are excluded from the sensitivity analysis as they are not of interest for our study: the birth rate, b; the natural death rate, μ_N. The total population, N, was also excluded. Hence there are 12 parameters of interest (noting c_P is calculated using other parameters). In keeping with previous work [Thomas et al. 2010] and others, triangular distributions are assumed for all parameters, with a range of $\pm 50\%$ the value presented in Table 1, Appendix A. To explore the stability of the results to the width of the distribution, ranges from $\pm 10\%$ to $\pm 90\%$ were also explored, and the results were qualitatively the same, with relatively small quantitative differences in the rank. 2000 samples were generated using the Latin Hypercube.

Figure 2 depicts the result of the sensitivity analysis, where parameters with low sensitivity, PRCC value $\leq |0.1|$, have been excluded. The latent period for TB is long (20 years on average), and so the number of individuals in the 'L' compartment accumulates and provides a large reservoir for new active cases. As a result, the rate those latently infected become clinically active, ν, is of more importance to the TB dynamics than the transmission rate, β. Therefore, data refinement should concentrate on determining the rate ν as accurately as possible. The latently infected reservoir also explains why the proportion with fast TB, ϵ, becomes less important as the epidemic progresses. The inclusion of the disease parameters ω and ρ is understandable, as the number of people and period of time the clinically active and infectious are able to infect others are obviously important factors. The only intervention parameter with a magnitude > 0.1 is the detection rate, $\delta(t)$. Within the intervention parameters, the rate of detection being the most important makes sense, as we assume all those detected are treated. The DOTS intervention program commenced in PNG in 1997 [World Health Organisation 2009] and hence $\delta(t)$ starts becoming important around this time.
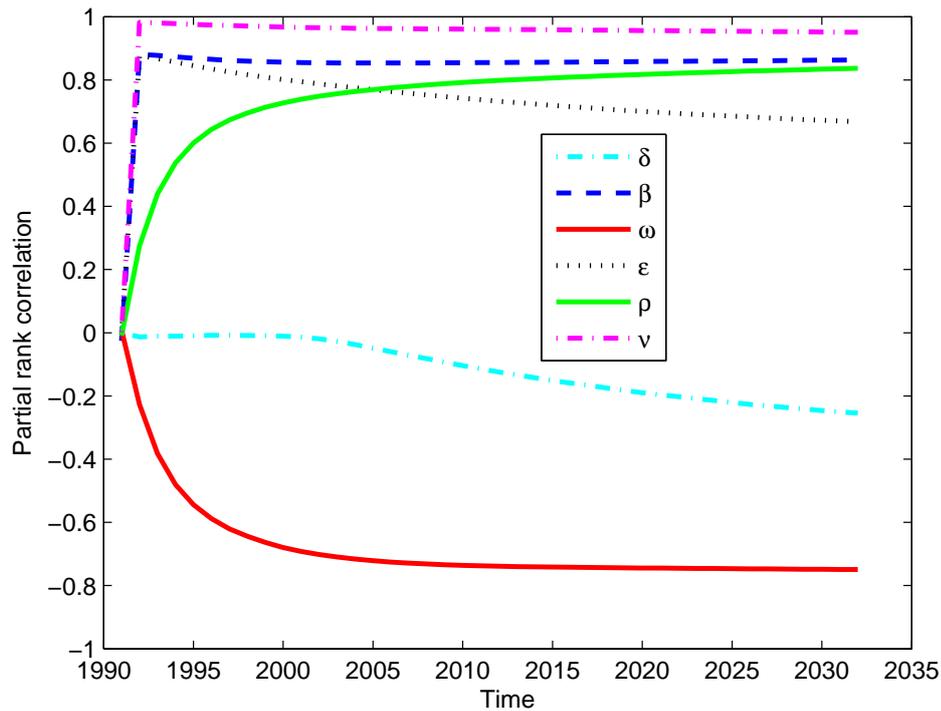
Figure 2. Sensitivity analysis of the model, comparing the relative monotonicity of the cumulative number with active TB (I+P+D+T) with various parameters. Only dominant parameters with a magnitude > 0.1 are shown.

4 CONCLUSIONS

The sensitivity analysis shows that 5 of the 6 most important parameters pertain to the disease itself, and these are not easily influenced by interventions. However amongst the intervention parameters, the detection rate, δ, has a reasonably important influence on the cumulative number of people with clinically active TB. In PNG, the current DOTS detection rate is at a mere 14%. The more remote regions, such as in the Western Province, are likely to have an even lower detection rate. Increasing $\delta(t)$ to the WHO target of 70% case detection may not be viable given the small, isolated communities in the regional areas of PNG, but the sensitivity analysis suggests that increases smaller than the target will still have a significant impact in reducing (negative correlation) both the incidence and prevalence of TB.

The model presented here is a relatively simple population level compartment model. Future work will extend this to include a metapopulation, to explore the cross-border transmission dynamics of TB in the PNG-Torres Strait Island region. Further extensions will consider multidrug-resistant TB and the co-epidemic of HIV, to determine the simplest possible realistic model of TB for transmission from high to low burden regions.

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A PARAMETER DESCRIPTIONS

Table 1. Table of parameter values and assumptions. Values given for Papua New Guinea (PNG).

Parameter	Description	Value	Units	Source(s)	Notes and assumptions
b	Natural birth rate	0.0317	/year	UNPD (2008)	
μ_N	Natural death rate	0.0159	/year	UNPD (2008)	Inverse of lifespan, averaged over female and male.
μ_T	TB positive death rate	0.0165	/year	WHO (2009)	Calculated as μ_N+ TB induced death rate.
ϵ	Proportion progress to active TB within one year of infection	0.0375	None	Porco et al. (2001)	Estimate, noting 5–10% infected with TB progress to active TB within 2 years.
ρ	Proportion developing infectious TB	0.7	None	Yang et al. (2004)	
ν	Rate of progression to active TB	0.0039	/year	Blower et al. (1995)	Midpoint of reference values: 7.8% in 20 years.
ω	Natural cure rate of active TB	0.3168	/year	Tiemersma et al. (2011)	Equal for the 'I' & 'P' compartments.
β	TB transmission co-efficient	6.8	/year	N/A	Estimates. Assuming equal transmission from I, D, & T.
$\delta(t)$	Case detection rate under DOTS (pulmonary cases)	Eq. (1)	/year	WHO (2009) Table 33, pg. 69	Time (t) dependent function starting at zero and logarithmically increasing to 0.14 in 2007.
$1/\theta$	Delay between detection and treatment	4	Weeks	Bassili et al. (2008)	Conservative as Western Province of PNG isolated.
$1/\xi$	Duration person infectious whilst undergoing treatment	5.5	Weeks	Fortún et al. (2007)	NOT the 6 months required for treatment as not infectious that long.
c_I	Proportion of treated infectious cases successfully cured	0.59	None	WHO (2009) Table 35, pg. 72	
ψ	Default rate from treatment	0.21	/year	WHO (2009)	
ζ	Completion rate of treatment from 'P'	0.15	/year	WHO (2009) Table 35	
$c_P(t)$	Rate of progression from 'P' to 'S'	$\omega + \delta(t)\,\xi\,\zeta$	/year	N/A	Time (t) dependent, since it's function of $\delta(t)$.
N	Total population	46,407	People	UNPD (2008)	South Fly district of PNG only in 2000.