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MODELLING THE SPREAD OF TUBERCULOSIS, INCLUDING DRUG RESISTANCE AND HIV: A CASE STUDY IN PAPUA NEW GUINEA'S WESTERN PROVINCE

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Abstract

High tuberculosis (TB) prevalence in Papua New Guinea (PNG) is a serious public health concern. The epidemic in this region is exacerbated by the presence of drug-resistant TB strains as well as HIV infection. This presents a public health threat not only locally but also to Australia due to the high potential for cross-border transmission between PNG's Western Province and the Australian Torres Strait Islands. We present two mathematical models of TB in the Western Province: a simple model of the underlying TB dynamics, and a detailed model which accounts for the additional effects of HIV and drug resistance. The detailed model is used to make quantitative predictions about the impact of expanding the TB case detection rate under the Directly Observed Treatment, Short-course treatment regimen. This paper provides a framework for future investigation into the economic costs and public health benefits of potential TB interventions in this region, with the eventual aim of providing recommendations to guide policy makers in both PNG and Australia.

2000 *Mathematics subject classification*: primary 92D25; secondary 92C60, 92D30.

Keywords and phrases: tuberculosis, drug resistant, HIV, Papua New Guinea, mathematical model.

1. Introduction

Despite its ancient origins, tuberculosis (TB) remains a significant contributor to the global burden of infectious disease, with 9.27 million incident cases recorded in 2007 [42]. Additional challenges to tuberculosis control efforts in recent times have been presented by the emergence of HIV [12, 26] and drug-resistant strains of TB [48]. In certain regions, co-infection with HIV and the presence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains have led to higher TB mortality rates and increased the financial costs of the epidemic [41, 44].

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In Australia, TB prevalence has typically remained low, at about seven cases per 100 000 population over the past two decades. However in Papua New Guinea (PNG), Australia's nearest neighbour to the north, prevalence is much higher at 430 per 100 000 in 2007 [42]. Furthermore, PNG is experiencing a generalized HIV epidemic [29] and MDRTB strains have been identified in the Western Province [15], the region closest to Australian territory. The World Health Organisation (WHO) recommended course of treatment for TB is the Directly Observed Treatment, Short-course (DOTS) regimen. Access to DOTS in PNG is currently at a mere 14%, the lowest in the Western Pacific [45].

The Torres Strait Treaty between Australia and PNG allows passage by traditional inhabitants of the area between the Torres Strait and designated treaty villages in PNG's Western Province without possession of a visa [4]. A dramatic health gradient traverses this border due to superior access to adequate healthcare by Australians living in the Torres Strait Islands compared to their close neighbours in PNG. Freedom of movement in the treaty zone, with the incentive of access to higher-quality health services in the Torres Strait, has led to a highly porous border. Over 60 000 movements between the Western Province and the Torres Strait in both directions were recorded in 2008–09, 98% of them by PNG citizens [4]. As a result, infectious disease outbreaks in the Western Province pose a serious public health risk to the Torres Strait region and the nearby Australian mainland. Notably, 60 PNG nationals who presented to clinics in Australian territory between 2000 and 2006 had confirmed cases of TB; of these, 25% were MDRTB strains [15].

In this paper, a deterministic model of TB epidemiology is developed based on data from the PNG Western Province and, in the absence of information specific to this region, data from PNG as a whole or wider sources. The model differs from many recently published TB and TB/HIV co-infection models (for example, [1, 7, 8, 19, 27, 28, 30, 31]) in that it attempts to capture the interacting effects of drug resistance and HIV. We analyse the dynamics of TB transmission in PNG in order to predict and compare the effects of different epidemic intervention strategies. This paper lays the groundwork for future studies into PNG–Torres Strait cross-border transmission using a spatially differentiated model of the TB epidemic in this region.

2. Methods

2.1. Construction of a simple model We begin with a simple deterministic model based on that of Blower *et al.* [10] in order to capture the basic dynamics of the epidemic. HIV and drug-resistant TB strains are not included in this first model. Four classes of individuals are considered: susceptibles X, latently infected individuals L, and individuals with active tuberculosis, either infectious (pulmonary) T_I or noninfectious (extra-pulmonary) T_N. Table 1 gives a list of common acronyms and classes used throughout this paper. Individuals are born into the susceptible class at a rate b from the total population, $P = X + L + T_N + T_I$. Susceptibles contract TB by contact with infectious individuals at a rate proportional to the ratio

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TABLE 1. Glossary of abbreviations used throughout the paper.

AIDS	Acquired immune deficiency syndrome
DDTB	Deaths due to tuberculosis
DOTS	Directly Observed Treatment, Short course
DSTB	Drug-sensitive tuberculosis
HIV	Human immunodeficiency virus
LHS	Latin hypercube sampling
MDR	Multidrug resistant
PNG	Papua New Guinea
PRCC	Partial rank correlation coefficient
PYLTB	Person-years lived with tuberculosis
TB	Tuberculosis
TBC	Tuberculosis cases
WHO	World Health Organisation
XDR	Extensively drug resistant
L	Latent class
T_I	Infectious (pulmonary) class
T_N	Noninfectious (extra-pulmonary) class
X	Susceptible class

of infectious individuals to the total population, times an infecting constant β_N (where β_N is the product of the contact rates between individuals in the population and the probability of TB transmission per contact). Susceptible individuals who contract TB may move either directly into the active class ("fast" TB) with probability ϵ_N, or into the latent class ("slow" TB) with probability $1-\epsilon_N$. From the latent class, individuals progress to active TB at a rate v_N. Individuals contracting active TB move into either the infectious class with probability p_N or the noninfectious class with probability $1-p_N$. Tuberculous cases are cured (that is, infected individuals return to the susceptible class; see later for a discussion of this) at a rate c_{NI} for infectious cases or c_{NN} for noninfectious cases. Individuals may exit each class due to death at a rate μ_N for latent or susceptible individuals or μ_{NT} for those with active TB. These relationships are shown diagrammatically in Figure 1, and the corresponding mathematical description is given by the following set of equations:

$$\lambda = \beta_N \frac{T_I}{P},$$
$$\frac{dX}{dt} = bP + c_{NI}T_I + c_{NN}T_N - (\lambda + \mu_N)X,$$
$$\frac{dL}{dt} = (1-\epsilon_N)\lambda X - (v_N + \mu_N)L,$$

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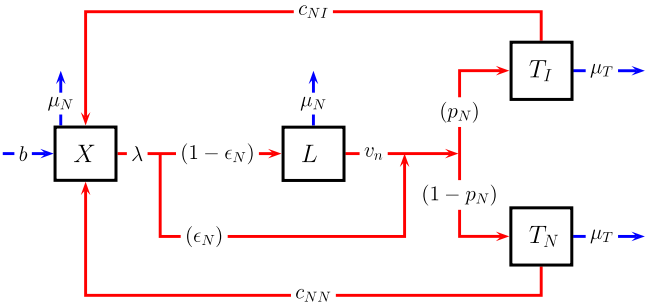

FIGURE 1. Flowchart showing movement between classes in the simple model. Arrow labels which are not bracketed indicate the rate at which individuals move from one class into the next, while those in brackets indicate probabilities multiplying the rates. Individuals are born into the susceptible class at a rate b from the total population ($P = X + L + T_I + T_N$).

$$\frac{dT_I}{dt} = p_N(\epsilon_N \lambda X + v_N L) - (c_{NI} + \mu_{NT})T_I,$$
$$\frac{dT_N}{dt} = (1 - p_N)(\epsilon_N \lambda X + v_N L) - (c_{NN} + \mu_{NT})T_N.$$

2.2. Construction of a detailed model In order to capture the relevant complexities of the PNG Western Province tuberculosis epidemic in recent times, the simple model was extended to include the effects of HIV infection and drug-resistant strains of TB. The general population was divided into HIV positive and HIV negative individuals. Of those with tuberculosis, drug-sensitive TB (DSTB) and multidrug-resistant TB (MDRTB) were considered, as well as infectious (pulmonary) and noninfectious (extra-pulmonary) TB. The HIV negative population was partitioned as follows: X_N, consisting of individuals susceptible to TB; L_N, individuals latently infected with drug-sensitive TB; T_{NI}, comprising infectious DSTB cases; T_{NN}, noninfectious DSTB cases; L_{NM}, individuals latently infected with MDRTB; T_{NMI}, those with infectious active MDRTB; T_{NMN}, noninfectious individuals with MDRTB. The same classes apply for HIV positive individuals, and are denoted by first subscript H instead of N.

Movement between classes in the HIV negative population when MDRTB is not considered operates identically as for the simple model, where all relevant parameters and classes have the subscript N. This pattern is mirrored for MDRTB, where the relevant classes and parameters have the additional subscript M. Following previous models of drug-resistant TB [6, 27], individuals may move from the active DSTB classes into the active MDRTB classes due to strain mutation after failed treatment at a rate γ. Individuals latently infected with DSTB may also become infected with MDRTB through primary transmission, in the same manner as for susceptible individuals. However, their probability of becoming infected is reduced by a factor of σ_N as a result of acquired immunity due to previous infection [27]. The patterns of movement for both DSTB and MDRTB are the same in the HIV positive group, where the subscript N is replaced by H, with the exception that individuals are assumed to be

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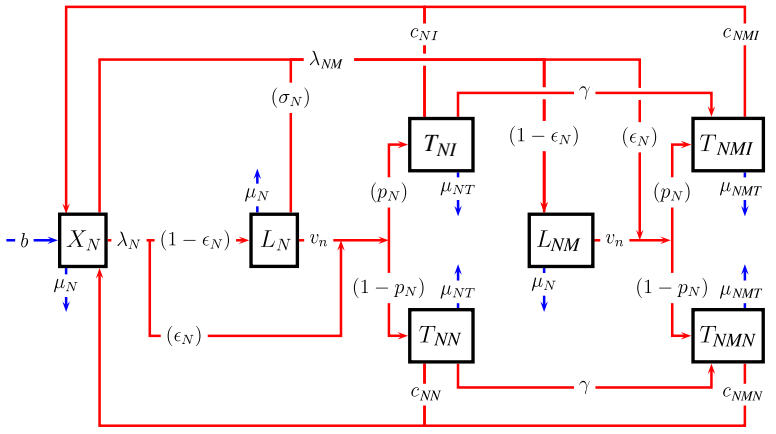

FIGURE 2. Flowchart showing movement between HIV negative classes in the detailed model. Nonbracketed labels on arrows indicate the rate at which individuals move from one class into the next, while those in brackets indicate probabilities multiplying the rates. Individuals are born into the HIV negative susceptible class at a rate b from the total population (the sum of all classes). Movement between HIV positive classes operates identically as for the HIV negative classes, where the first subscript N is replaced by the subscript H. Individuals may move from any HIV negative class into the equivalent HIV positive class at a rate λ_{HIV}.

born into the HIV negative class. Additionally, individuals may move from any HIV negative class into the corresponding HIV positive class with force of infection λ_{HIV}. These relationships are shown in Figure 2. The following sets of equations are used to construct the model.

The force of infection parameters are given by

$$\lambda_N = \beta_N \frac{T_{NI} + T_{HI}}{P_T},$$
$$\lambda_{NM} = \beta_{NM} \frac{T_{NMI} + T_{HMI}}{P_T},$$
$$\lambda_{HM} = \beta_{HM} \frac{T_{NMI} + T_{HMI}}{P_T},$$
$$\lambda_{\text{HIV}} = h \frac{P_H}{P_T},$$
$$\lambda_H = \beta_H \frac{T_{NI} + T_{HI}}{P_T},$$

where P_T is the total population, or the sum of all classes in the model.

The HIV negative population is governed by the following ODEs:

$$\frac{dX_N}{dt} = bP_T + c_{NI}T_{NI} + c_{NN}T_{NN} + c_{NMI}T_{NMI} + c_{NMN}T_{NMN} - (\mu_N + \lambda_N + \lambda_{NM} + \lambda_{\text{HIV}})X_N,$$

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$$\begin{aligned}
\frac{dL_N}{dt} &= (1-\epsilon_N)\lambda_N X_N - (\mu_N + \lambda_{\text{HIV}} + v_N + \sigma_N\lambda_{NM})L_N,\\
\frac{dL_{NM}}{dt} &= \lambda_{NM}(1-\epsilon_N)(X_N + \sigma_N L_N) - (\mu_N + v_N + \lambda_{\text{HIV}})L_{NM},\\
\frac{dT_{NI}}{dt} &= p_N(v_N L_N + \epsilon_N\lambda_N X_N) - (\mu_{NT} + c_{NI} + \gamma + \lambda_{\text{HIV}})T_{NI},\\
\frac{dT_{NN}}{dt} &= (1-p_N)(v_N L_N + \epsilon_N\lambda_N X_N) - (\mu_{NT} + c_{NN} + \gamma + \lambda_{\text{HIV}})T_{NN},\\
\frac{dT_{NMI}}{dt} &= p_N\{v_N L_{NM} + \epsilon_N\lambda_{NM}(X_N + \sigma_N L_N)\} + \gamma T_{NI}\\
&\quad - (\mu_{NMT} + c_{NMI} + \lambda_{\text{HIV}})T_{NMI},\\
\frac{dT_{NMN}}{dt} &= (1-p_N)\{v_N L_{NM} + \epsilon_N\lambda_{NM}(X_N + \sigma_N L_N)\} + \gamma T_{NN}\\
&\quad - (\mu_{NMT} + c_{NMN} + \lambda_{\text{HIV}})T_{NMN}.
\end{aligned}$$

The HIV positive population is governed by the following ODEs:

$$\begin{aligned}
\frac{dX_H}{dt} &= \lambda_{\text{HIV}}X_N + c_{HI}T_{HI} + c_{HN}T_{HN} + c_{HMI}T_{HMI} + c_{HMN}T_{HMN}\\
&\quad - (\mu_H + \lambda_H + \lambda_{HM})X_H,\\
\frac{dL_H}{dt} &= \lambda_{\text{HIV}}L_N + (1-\epsilon_H)\lambda_H X_H - (\mu_H + v_H + \sigma_H\lambda_{HM})L_H,\\
\frac{dL_{HM}}{dt} &= \lambda_{\text{HIV}}L_{NM} + \lambda_{HM}(1-\epsilon_H)(X_H + \sigma_H L_H) - (\mu_H + v_H)L_{HM},\\
\frac{dT_{HI}}{dt} &= \lambda_{\text{HIV}}T_{NI} + p_H(v_H L_H + \epsilon_H\lambda_H X_H) - (\mu_{HT} + c_{HI} + \gamma)T_{HI},\\
\frac{dT_{HN}}{dt} &= \lambda_{\text{HIV}}T_{NN} + (1-p_H)(v_H L_H + \epsilon_H\lambda_H X_H) - (\mu_{HT} + c_{HN} + \gamma)T_{HN},\\
\frac{dT_{HMI}}{dt} &= \lambda_{\text{HIV}}T_{NMI} + p_H\{v_H L_{HM} + \epsilon_H\lambda_{HM}(X_H + \sigma_H L_H)\} + \gamma T_{HI}\\
&\quad - (\mu_{HMT} + c_{HMI})T_{HMI},\\
\frac{dT_{HMN}}{dt} &= \lambda_{\text{HIV}}T_{NMN} + (1-p_H)\{v_H L_{HM} + \epsilon_H\lambda_{HM}(X_H + \sigma_H L_H)\} + \gamma T_{HN}\\
&\quad - (\mu_{HMT} + c_{HMN})T_{HMN}.
\end{aligned}$$

2.3. Numerical simulation and parameter estimates Numerical simulations of both the simple and detailed models were performed in MATLAB. The model presented in the previous section is applicable to any region where DSTB, MDRTB and HIV coexist in the population. Here we consider a case study of TB spread in the Western Province of PNG and make parameter estimates to reflect the current situation there.

The parameter values were taken from a review of the available literature. Data specific to the Western Province were used where available; otherwise, PNG-wide

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data were used. In the absence of information specific to PNG, wider sources were considered. The remaining parameters for which "estimate" is quoted as a source were obtained by fitting the model to epidemiological data from PNG. Data on prevalence of TB in PNG, population size in the Western Province, and prevalence of HIV in PNG were obtained from sources [3, 23, 38] respectively. Where possible, upper and lower bounds for the parameter estimates were determined. Table 2 gives the parameter values which were used in numerical simulation of the simple and detailed models, as well as a description of the parameter, the source of the value and any relevant comments.

2.4. Analysis of intervention strategies Further MATLAB simulations were undertaken in order to demonstrate the capacity of the detailed model to evaluate and compare future TB interventions. An examination of one likely intervention strategy was carried out, namely expanding the availability to Western Province residents of the WHO-recommended DOTS program. A full discussion of other possible interventions and their implementation is given elsewhere [5].

In order to model the effects of improved access to DOTS, the model was simulated from 2007 to 2020. We chose fixed initial values in the year 2007 for each outcome variable based on the results of the numerical simulation described in the previous section. The year 2007 was chosen as this is the last year for which accurate data exist on TB prevalence rates in PNG [38].

Three different DOTS detection rates were investigated. Firstly, the DOTS detection rate was kept stable at its current level of 15% ($d = 0.15$) throughout the simulation. This represents the baseline scenario for which the DOTS detection rate was taken from a recent WHO estimate for PNG [45] (see Table 2). The process was then repeated with the interventions introduced in 2010: once with the DOTS detection rate increased to 50% ($d = 0.5$), and again with the detection rate at 100% ($d = 1.0$).

Following the method of Murray and Salomon [21], the total number of deaths due to TB (DDTB) and TB cases (TBC) expected to accumulate over the decade from 2010 to 2020 were then calculated for each of the DOTS detection rates modelled. We also calculated the number of person-years lived with TB (PYLTB) over the same time period. The public health benefits gained by increasing DOTS detection were then quantified by subtracting the intervention scenario results from the baseline results.

2.5. Uncertainty and sensitivity analysis Uncertainty was evaluated using Latin hypercube sampling (LHS), following the method given in [9, 24]. LHS is a technique used when there is uncertainty in a model's input parameters. The parameters are repeatedly sampled from suitable probability distributions in such a way that the parameter space is evenly covered. The model is then simulated repeatedly using the randomly sampled parameter sets. LHS ensures high sampling efficiency and hence requires fewer runs of the model in order to obtain consistent results compared to basic random sampling [9].

For our analysis, triangular probability distributions were created for each parameter using the minimum, maximum and mode given in Table 2. Where no mode

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TABLE 2. Parameter values used in the detailed and simple models. Parameter values are discussed further in Section 3.3.

Parameter	Description	Value			Notes and references
		Min	Mode	Max	
b	Natural birth rate		0.0317		[35]
μ_N	Natural death rate	0.0072		0.008	[35]
μ_H	HIV positive, TB negative death rate	0.027	0.028	0.029	Number of AIDS deaths over the total number of HIV positive people in PNG in 2007 [34] plus the natural death rate μ_N.
μ_{NT}	HIV negative, TB positive death rate	0.05	0.10	0.15	[43]
μ_{HT}	HIV positive, TB positive death rate	0.11	0.25	0.43	[43]
μ_{NMT}	MDRTB positive, HIV negative death rate	0.6		0.85	[32]
μ_{HMT}	MDRTB positive, HIV positive death rate	0.72		0.89	[33]
ϵ_N	Proportion of HIV negative people progressing to active TB within 1 year of infection		0.05		Estimate: 5–10% of those infected with TB progress to active TB within 2 years [25].
ϵ_H	Proportion of HIV positive people progressing to active TB within 1 year of infection	0.1	0.3	0.5	Estimate
p_N	Proportion of HIV negative people developing infectious TB	0.57	0.7	0.88	Mean value taken from [47]. Values taken from two other studies ([1, 42] respectively) were used as proxy for upper and lower bounds.
p_H	Proportion of HIV positive people developing infectious TB	0.87	0.92	0.97	Calculated using an odds ratio compared to the HIV negative population given in [47].
v_N	Rate of progression to active TB in HIV negative people		0.001		Estimate
v_H	Rate of progression to active TB in HIV positive people		0.006		Estimate, noting that HIV positive people are 5–7 times more likely to develop TB than HIV negative people [28].
d	DOTS detection rate		0.15		Annual new smear-positive notifications under DOTS divided by estimated annual new smear-positive incidence, 2007 [45].
n	Proportion of cases detected under DOTS that went on to treatment through DOTS		0.91		Data from 2007 [45].
s	Likelihood of treatment success		0.59		Percentage of new smear-positive cases treated under DOTS successfully cured in 2007 [45].
c_{NI}, c_{NN}	HIV negative TB cure rate		0.09		Calculated as $d \times n \times s$ after introduction of DOTS in 1997 [39]; prior to this, natural cure rate of 0.04 estimated. Due to a lack of information, cure rates for infectious and noninfectious cases have been assumed to be equal.
c_{HI}, c_{HN}	HIV positive TB cure rate		0.025		Estimate
c_{NMI}, c_{NMN}	HIV negative MDRTB positive cure rate		0.054		Estimate: [20] gives 53.7%, which is nearly as high as the likelihood for drug-susceptible TB in PNG, hence c_{NMI} and c_{NMN} here are much lower than in [20].

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TABLE 2. Continued ...

c_{HMI}, c_{HMN}	HIV positive MDRTB positive cure rate	0.006	Estimate
α	Proportion of drug-sensitive TB treatment failure acquiring multi-drug resistance	0.05	Estimate
γ	Rate of progression from active drug-sensitive TB to active MDRTB as a result of failed treatment	0.02	Calculated as $\alpha \times (1 - s)$. Prior to DOTS introduction in 1997, assumed to be zero.
σ_N	Factor reducing risk of infection by a new strain of TB due to acquired immunity from infection by another strain in HIV negative cases	0.25	[27]
σ_H	Factor reducing risk of infection by a new strain of TB due to acquired immunity from infection by another strain in HIV positive cases	0.5	Estimate
β_N	TB transmission coefficient in HIV negative people	5.7	Estimate
β_{NM}	MDRTB transmission coefficient in HIV negative people	5.7	Assumed to be the same as β_N.
β_H	TB transmission coefficient in HIV positive people	11.4	Estimate
β_{HM}	MDRTB transmission coefficient in HIV positive people	17.1	Estimate
h	HIV transmission coefficient	0.065	Estimate: [16] cites a higher value of 0.315, see discussion for further details.

is given in the table, a value equidistant from the minimum and maximum was used. When no upper and lower bounds were found, the variable was assigned uncertainty of 5% in both directions.

Each parameter was randomly sampled from its distribution and the model was run three times as described above, using the baseline scenario and each intervention scenario. From the results, the numbers of DDTB, TBC and PYLTB averted due to each intervention were calculated. This was repeated 5000 times, producing an empirical probability distribution for each of the outcome variables from which mean values and 95% confidence intervals could be determined.

A sensitivity analysis using the results of the LHS process was conducted in order to qualitatively assess the responsiveness of outcomes from the intervention analysis to a given input parameter. This process allowed identification of the crucial parameters to which the results were most sensitive, providing direction for future improvement in the accuracy and precision of model output.

The partial rank correlation coefficient (PRCC) is a measure of the degree of monotonicity between two parameters which adjusts for the effects of other variables in the system [9]. A PRCC can therefore be used to assess the sensitivity of a model to variation in one of its input parameters whilst adjusting for the effects of uncertainty in the other parameters. For this model, PRCCs were calculated for each input parameter

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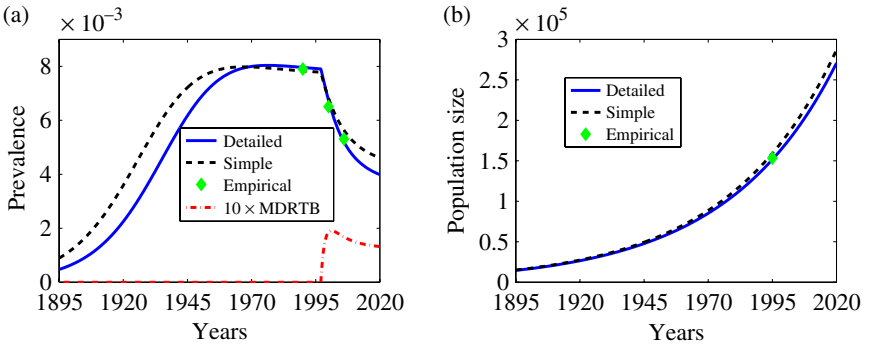

FIGURE 3. Numerical simulation of the detailed and simple models using the mode parameter values given in Table 2. Where no mode is given, a number approximately equidistant from the upper and lower bounds was chosen. Plot (a) shows the total TB prevalence given by the detailed and simple models, and 10 times the prevalence of MDRTB given by the detailed model. Plot (b) shows the size of the total population from both models. In each instance, the simulated values are plotted together with empirical data from sources [23, 38], shown as the diamonds.

against the three output variables used to compare the effects of intervention strategies (DDTB, TBC and PYLTB between 2010 and 2020). We also calculated P-values for testing the hypothesis of no partial correlation against the alternative of a nonzero partial correlation.

3. Results

3.1. Numerical simulation of TB in the Western Province Graphical results from MATLAB simulations of both the detailed and simple models using the parameter values given in Table 2 are shown in Figure 3. The prevalence of TB and population size for the detailed and simple models from 1895 to 2020 are shown. The data used to fit the models and obtain parameter estimates are also shown in Figure 3. These results are for the baseline DOTS detection rate of 15%.

The results shown are broadly similar to those obtained by other simple TB models (for example, [1, 10]). One notable difference in this model is the dramatic shift in rates of change, particularly in the prevalence of TB, from 1997 onwards. This occurs because the cure rates c_{NI} and c_{NN} increase from 0.04 to 0.09 per person per year with the introduction of DOTS in the same year [39]. This was also chosen as the year in which MDRTB first arises due to strain mutation under the selective pressure of DOTS.

The results from the simple and detailed models in Figure 3 are qualitatively similar but differ in the detail. TB prevalence for the simple model progresses slightly more rapidly than for the detailed model and peaks approximately two decades earlier. From about 1980 onwards, outputs from the two models continue to follow similar paths. However, after the introduction of DOTS in 1997 the TB prevalence for the simple model declines slightly less rapidly than for the detailed model, such that TB

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TABLE 3. The number of new TB cases (TBC), deaths due to TB (DDTB) and years lived with TB (PYLTB) that could be averted over the the decade from 2010 to 2020 in PNG's Western Province when the TB detection rate under DOTS is increased relative to the current level of 15%. Mean values (95% confidence intervals) from 5000 runs of the model are shown.

TB detection rate under DOTS		TBC averted	DDTB averted	PYLTB averted
50%	Number	773 (528, 1017)	601 (530, 673)	5026 (3590, 6462)
	Percent	28 (24, 32)	44 (42, 46)	46 (43, 49)
100%	Number	1174 (818, 1531)	907 (794, 1020)	7513 (5512, 9514)
	Percent	43 (37, 48)	66 (64, 68)	69 (66, 73)

prevalence predicted by the detailed model is approximately 13% lower than for the simple model by 2020. Differences in population size for both models are very small throughout the simulations, although the population grows slightly more rapidly as simulated by the simple model.

In the detailed model, the HIV prevalence rate was modelled with very little variation over time, increasing from near 1% in 1990 to near 1.1% in 2010. This was considered to be appropriate given the lack of data representing HIV prevalence and rates of change in PNG's Western Province. The only source identified which gave a Western Province-specific value reported an HIV prevalence of 1.05% to 1.2% [3]. Both of these values came from voluntary testing studies and are hence subject to the error typically associated with nonrandom samples. However, for the purposes of this study we elected to use reported prevalence data in preference to estimation due to lack of quantitative and qualitative information to provide a basis for the latter approach.

3.2. Intervention strategies The numbers of new TB cases, deaths due to TB and person-years lived with TB expected to occur in the Western Province over the decade from 2010 to 2020 were calculated for each level of DOTS coverage. The numbers of new cases, deaths and person-years lived with TB averted under each improved level of DOTS coverage compared to the baseline scenario (no change in coverage) were determined as a measure of the success of that strategy. The results are given in Table 3.

Figure 4 shows that the rates of TB prevalence in the Western Province are predicted to decline rapidly following the introduction of improved access to the DOTS program. Shown is the total prevalence which includes diagnosed and undiagnosed cases. When DOTS coverage is increased to 100%, prevalence declines to 0.1% by 2015, and appears to level off thereafter. However, when DOTS coverage is increased to only 50%, prevalence reduces to just above 0.2% by 2015 but continues to decline. The model also predicts that 775 cases with 95% confidence interval (530, 1015), 600 (530, 675) deaths and 5025 (3590, 6640) person-years lived with TB could be averted over the next 10 years if DOTS coverage were increased to 50%. If coverage were increased to 100%, 1175 (820, 1530) cases, 910 (795, 1020) deaths and 7515

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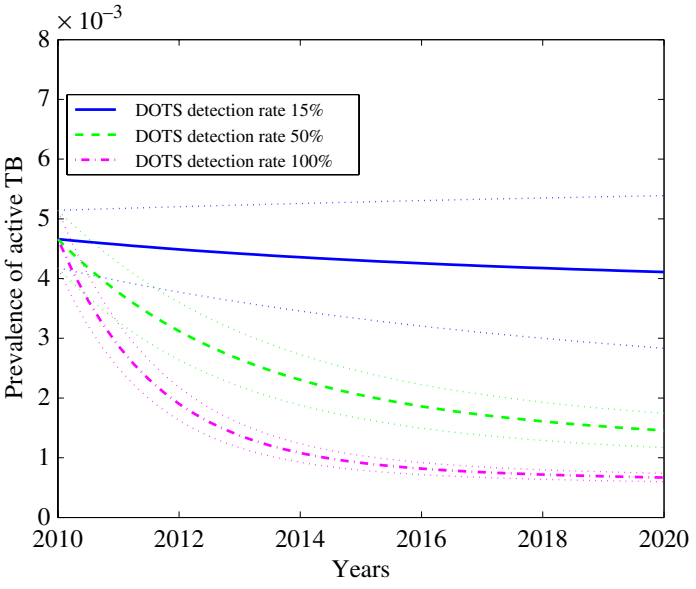

FIGURE 4. Numerical simulation of the detailed model from 2010 to 2020 when different DOTS detection rates are applied, showing the mean and 95% confidence intervals from 5000 runs of the model. The model parameter values from Table 2 were used. Where no mode is given, a value equidistant from the upper and lower bounds was used. Values for which no upper or lower bounds are given were assigned 5% uncertainty in both directions.

(5510, 9515) person-years lived with TB could be averted in the same period. As expected, increasing coverage to 100% is more beneficial than increasing to 50%, but the latter will still produce significant reductions in morbidity and mortality.

3.3. Sensitivity analysis The results of the sensitivity analysis are shown in Table 4. Those values found to have statistically significant PRCC (significance level 0.001) from a test with null hypothesis PRCC = 0 are indicated by an asterisk. The following input parameters had statistically significant PRCCs whose magnitudes were greater than 0.2 for all three outcome variables: μ_{NT}, ϵ_N, p_N, υ_N, c_{NI} and β_N. In addition to these, b, μ_{NMT}, c_{NN}, c_H, υ_H, ϵ_H, β_H, h and γ had PRCC values for one or more outcome variables that were statistically significant but whose magnitudes were less than 0.2. The effect of these latter parameters on the model outputs tested was therefore minor.

The HIV negative, TB positive death rate (μ_{NT}) and the proportion of HIV negative people developing infectious TB (p_N) had PRCCs of particularly large magnitude ($\geq$0.90) for all three model outputs, and uncertainty in these variables therefore had the greatest impact on variability in the results. In addition, the proportion of HIV negative people progressing to active TB (ϵ_N), the HIV negative transmission rate (β_N) and the rate of progression from latent to active TB in HIV negative people (υ_N)

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TABLE 4. Partial rank correlation coefficients (PRCC) of each of the input parameters in the detailed model compared to the output variable given by the cumulative number of new TB cases (TBC), deaths due to TB (DDTB) and person-years lived with TB (PYLTB) between 2010 and 2020. An asterisk denotes statistically significant values (significance level 0.001).

Variable	PRCC			Variable	PRCC		
	TBC	DDTB	PYLTB		TBC	DDTB	PYLTB
b	0.13*	0.11*	0.11*	c_{NI}	−0.28*	−0.42*	−0.45*
μ_N	−0.04	−0.02	−0.03	c_{NMI}	−0.03	−0.02	−0.03
μ_H	−0.01	0.00	0.00	c_{NN}	−0.03	−0.10*	−0.15*
μ_{NT}	−0.96*	0.96*	−0.99*	c_{NMN}	0.00	−0.03	0.00
μ_{NMT}	−0.08	−0.10*	−0.16*	c_{HI}	0.00	−0.01	0.00
μ_{HT}	−0.02	0.01	−0.03	c_{HMI}	−0.01	−0.01	0.00
μ_{HMT}	0.00	−0.01	0.00	c_{HN}	−0.01	0.02	−0.01
ϵ_N	0.66*	0.63*	0.64*	c_{HMN}	0.01	0.03	0.01
ϵ_H	0.05*	0.00	0.00	β_N	0.67*	0.60*	0.65*
p_N	0.95*	0.90*	0.91*	β_{NM}	0.03	0.03	0.00
p_H	0.00	0.03	0.01	β_H	0.02	0.01	0.00
v_N	0.61*	0.54*	0.58*	β_{HM}	0.00	−0.01	−0.01
v_H	0.06*	0.09*	0.03	h	0.04	0.05*	−0.01
σ_N	0.02	0.01	0.01	γ	0.04	0.10*	−0.10*
σ_H	−0.04	0.00	−0.03				

had PRCCs of high magnitude ($\geq$0.50) with all outcome variables. The HIV negative cure rate (c_{NI}) had PRCCs of moderate magnitude, between 0.27 and 0.46, with all outputs.

Most of the parameters with statistically significant PRCCs had positive PRCC values, indicating that an increase in the parameter leads to an increase in the outcome of interest. The exceptions included the cure rates c_{NI} and c_{NN}, which had negative PRCCs for all three outcome variables. The death rate μ_{NT} had negative PRCCs for DDTB and PYLTB but a positive value for TBC, while μ_{NMT} had negative PRCCs with all three outputs. Finally, the rate of strain mutation after treatment failure, γ, had a negative PRCC with the number of person-years lived with TB.

4. Discussion

4.1. Model construction The similarity between the simulations of the detailed and simple models shown in Figure 3 demonstrates that the alterations made to the simple model to construct the detailed model did not have a dramatic effect on the modelled TB prevalence. The low PRCCs of HIV- and MDRTB-related parameters with the outcome variables tested show that changes in, for example, MDRTB or HIV/TB co-infected cure rates or infection rates will have little effect on the wider TB epidemic. However, MDRTB patients are significantly more costly due to the higher price of second-line drugs, longer duration of treatment, higher mortality and higher

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hospitalization rates [17]. Co-infection of TB with HIV is more costly and lengthy to treat, with lower success rates than TB in HIV negative patients [14]. Furthermore, at most times evaluated the detailed model predicted a lower TB prevalence than the simple model (see Figure 3); a likely explanation is that HIV and MDRTB lead to a greater number of TB deaths. This is supported by the observed slower population growth for the detailed model, suggesting a higher overall death rate due to the presence of HIV and MDRTB. This is most noticeable after the appearance of MDRTB in 1997, after which TB prevalence for the detailed model declined more rapidly than for the simple model. In light of the significant additional morbidity and mortality caused by drug resistance and HIV infection, it is still necessary and important to consider their impacts when comparing the costs and benefits of TB control strategies. Moreover, previous models which included both drug resistance and HIV highlighted the need for interventions targeted to drug-resistant strains, especially in settings with high HIV prevalence [6–8].

This model does not accurately represent the timing of the appearance of HIV. The first case of HIV in PNG was recorded in 1987 [40], but HIV was introduced at the start of this model for simplicity. It was found that introducing HIV at a later stage in the model led either to prevalence rates that were much lower than expected or to unrealistic exponential growth of both the HIV and TB epidemics. A likely reason for this is that the latent stage of HIV infection (HIV positive without symptoms of AIDS) has not been included. A detailed analysis of HIV dynamics in PNG would be severely restricted by a lack of available data and was considered to be beyond the scope of this study. A model which resulted in almost constant HIV prevalence was therefore preferable to expanding the model to account for further complexities of the HIV epidemic. Similarly, the PNG TB epidemic is likely to have existed for several hundred years more than is depicted in this model. As such, for the purposes of accurately modelling the epidemic in PNG in order to analyse intervention strategies, this model is only valid from 1990 onwards.

Unlike many mathematical models of infectious disease, a recovered class was not included in this model; instead, cured individuals move directly back into the susceptible class. This assumes that rates of infection are approximately the same for recovered and susceptible individuals [36]. This assumption may be inaccurate in light of data from some recent studies. For example, Nahid *et al.* [22] recorded relapse rates in HIV infected and HIV negative patients that were evidently higher than the usual infection rate, and a WHO surveillance report [46] indicates higher rates of MDRTB in relapse cases than in new cases. Furthermore, Rodrigues *et al.* [27] report model outcomes that are significantly different from models where reinfection was not considered. Unfortunately no data are available on reinfection rates for the Western Province of PNG, and so reinfection rates were taken to be the same as initial infection rates [36] to avoid increasing uncertainty in model output due to the inclusion of additional parameters of which there is no knowledge. One can consider that the effect of relapse cases can be absorbed by the transmission coefficient as an overall average, given that this is the data that are fitted to.

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In preference to including a DSTB/MDRTB co-infected class in the model, it has been assumed that in mixed DSTB/MDRTB cases, active infection will develop only from the resistant strain. This is justified by the selective advantage of drug-resistant strains under treatment, and represents a worst-case scenario in terms of public health and economic costs [27]. Basu *et al.* [6] similarly avoid defining co-infected classes by including a "risk of infection" parameter for each strain. However, in contrast to the approach used in this model, Basu *et al.* assume that risk of infection decreases with increasing drug resistance due to fitness trade-offs. Rodrigues *et al.* [27] present an alternative model with the addition of a DSTB/MDRTB co-infected class. However, current knowledge about the conditions under which competing strains will be expressed as active TB is incomplete. In the case of PNG's Western Province, no existing data differentiate between primary infection with MDRTB, co-infected cases and strain mutation; the impact of co-infection on the TB epidemic in this region cannot therefore be determined. As such, we have adopted the simpler and more conservative approach in this model. Further studies on modes of transmission of drug-resistance in PNG may elucidate this issue.

4.2. Parameter estimates Since we were not able to find sufficient data on transmission coefficients beyond the simplest HIV negative, drug-susceptible case, these values were chosen to reflect the increased likelihood of HIV positive people contracting TB due to their immune-deficient state. Evidence also suggests that HIV positive individuals have an enhanced probability of contracting MDRTB [13]: as such, β_{HM} has been chosen to be larger than β_M by a greater amount than β_H is larger than β_N. However, a recent review of the link between HIV infection and MDRTB states that MDRTB infection does not take hold more readily than drug-susceptible TB in HIV sufferers [37]. The assumption used in this model may therefore need to be re-examined in future investigations when more data are available.

The transmission coefficient for the HIV epidemic used in this model ($h = 0.065$) was much smaller than the value calculated in a study by Hyman *et al.* ($h = 0.315$ [16]). Hyman *et al.* assumed a contact rate of five partners per year and a probability of transmission per partner of 0.063; however, the population under study was a small, high-risk sub-population, and thus has higher contact rates than the general population. Using the probability of transmission calculated by Hyman *et al.*, the transmission coefficient used in this model corresponds to a contact rate of just over one partner per year. This is likely to be more accurate as applied to this model, particularly since we have not differentiated between sexually active and inactive individuals.

4.3. Intervention analysis: sensitivity and uncertainty The sensitivity analysis showed quantitatively which input parameters had the greatest impact on variability in the model output. The two most important parameters as determined by this analysis were the TB positive death rate, μ_{NT}, and the proportion of HIV negative people developing infectious TB, p_N. Increasing p_N led to greater numbers of deaths, cases and person-years lived with TB between 2010 and 2020. It is therefore clear that reducing the number of infectious cases would be substantially beneficial for TB

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control efforts. A higher death rate leads to more deaths but fewer cases and fewer person-years lived with TB. However, the latter points are not necessarily indicative of improved public health outcomes given that these reductions are due to TB sufferers dying more rapidly and with greater probability.

In order to reduce uncertainty in the model outputs, values for both these parameters could be improved upon by the emergence of new empirical data. Better estimation of μ_{NT} requires more stringent testing and monitoring of cases in the Western Province. The uncertainty range for p_N could be reduced by clearer delineation between data on incidence of extra-pulmonary TB only and incidence of patients with both pulmonary and extra-pulmonary TB. Existing data sources do not always clearly differentiate between these two situations, making it difficult to infer the proportion of TB sufferers who are infectious.

Other parameters revealed to be important by the PRCC analysis included the proportion of HIV negative people progressing to active TB (ϵ_N), the HIV negative transmission rate (β_N) and the rate of progression from latent to active TB in HIV negative people (υ_N). Increases in each of these values led to increases in all three outcome variables, as demonstrated by their positive PRCCs. The large magnitude of their PRCC values across all three outcomes also indicates that interventions targeting these parameters (that is, reducing transmission rates or rates of progression) could be substantially and broadly effective in TB control.

Unlike μ_{NT} and p_N, achieving a higher degree of accuracy for ϵ_N, υ_N and β_N is not a simple matter of better data collection and may not be feasible. Specifically, information on prevalence of latent infection and duration of the latent period is limited due to the symptomless nature of this stage of the disease. As a result, values for the likelihood of TB transmission when two individuals come into contact, a quantity which is required for estimation of the transmission coefficient β_N, would be cumbersome to estimate. Similarly, rates of progression from latent to active TB would be difficult to obtain, as the time at which a given individual was first infected is generally unknown.

A more practical approach is to estimate these values by fitting the model to historical trends in TB transmission, as was done for several of the parameters used in this model. However, once again this approach is hampered by the lack of data concerning prevalence of latent disease. Furthermore, the accuracy of this study is limited by the unavailability of data specific to the Western Province; although PNG-wide prevalence rates may be used as proxy, the Western Province epidemic is likely to be more severe due to higher MDRTB rates [15] and inadequate healthcare provision in this region [2]. Aligning the model precisely with PNG-wide TB rates would therefore be likely to lead to underestimates of the values of β_N, υ_N and ϵ_N.

Finally, increases in the infectious cure rate (c_{NI}) had a significant impact on reducing numbers of all three outcomes, as expected. Although upper and lower bounds for this value were not given, its accuracy is likely to be high as the relevant data were recorded under the WHO's DOTS program. As expected, c_{NI} was far more important than the noninfectious cure rate (c_{NN}). This is because curing infectious

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cases decreases the number of new infections arising, whereas reducing the number of noninfectious cases has no effect on this figure.

The sensitivity analysis also demonstrated the qualitative impact of either increasing or decreasing the input parameters: a negative PRCC indicates an inverse relationship. This helped us to identify the parameters for which more accurate estimates would be most helpful in reducing output uncertainty and to understand the role of these parameters in the TB epidemic. In general, the signs of the statistically significant PRCCs were as expected and could be explained in biological terms. For example, increasing the rate of progression from latent to active disease (v_N or v_H) led to more TBC, DDTB and PYLTB due to a greater number of people progressing to active disease before death from other causes. Conversely, increasing the TB death rate (μ_{NT}) led to more DDTB, but fewer TBC and PYLTB since those who developed active TB died more quickly, decreasing the average duration of infection.

However, one unexpected result was the negative PRCC between the MDRTB positive, HIV negative death rate (μ_{NMT}) and the number of DDTB, although this PRCC was of relatively low magnitude. A possible explanation is that individuals developing active MDRTB died so rapidly that they prevented further TB infections to the extent of also reducing the number of TB deaths. This suggests that in this model, the large majority of MDRTB cases died before they could be cured. Further investigation is needed in order to confirm or reject this hypothesis and to determine whether this result reflects the dynamics of a true TB epidemic or an inaccuracy in our model.

Finally, it is worth noting that a high degree of accuracy in the predictions of the model may not be necessary in order to achieve the long-term aims of this study. When attempting to identify the optimal approach to control of the Western Province/Torres Strait TB epidemic, it is sufficient to demonstrate that one strategy outperforms all others for all plausible values of input parameters. In that sense, precise projections of TB incidence and deaths are not required. However, when economic outcomes are accounted for, this is dependent on the interplay of cost and benefit. That is, if one strategy is determined to be both the lowest cost and the most successful approach to reducing disease burden over the entire parameter space and the relevant time period, then no further investigation is needed. In the event that no single option fulfils both roles, more precise predictions of incidence and TB-related deaths and the associated costs of each candidate intervention must be sought in order to optimize the reduction of disease burden with the financial resources available. A preliminary cost–benefit analysis would therefore aid in determining the necessity of refining parameter estimates in order to increase the model's accuracy.

5. Conclusion

This paper demonstrates the application of a general TB model to a specific region with unique characteristics in Papua New Guinea's Western Province. This provides the framework for future investigation into cost-benefit optimization of intervention

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strategies for TB in the Western Province and the Australian Torres Strait Islands. A detailed model accounting for the impact of MDRTB and HIV infection has been constructed and will be used for quantitative prediction of the effects of various intervention strategies in this region. Sensitivity analyses of the detailed model have revealed aspects of the model which could be improved in future studies. Further, preliminary investigation using the detailed model into the number of deaths, new TB cases and person-years lived with TB that might be avoided by increasing the case detection rate under DOTS has laid the groundwork for assessment of more detailed control recommendations.

Throughout this paper, various estimates of parameters have been used. Many of these estimates are still relatively uncertain and further research is needed to narrow the ranges of the parameters, particularly the ones indicated as important by the sensitivity analysis. Although the results are generally robust to ranges of parameters, there are particular parameter combinations that may change the results considerably. For example, if the death rate of HIV positive, TB positive people was substantially higher than HIV negative, TB positive people, then a general increase in HIV prevalence could lead to a reduction in TB incidence due to the increased death rate of HIV positive people. Care is needed when assessing the outcomes of the model that these types of outlying parameter ranges are not overly influencing the results.

As well as assessing the impact of increasing the DOTS programme coverage, other interventions that could be assessed using this model include those based around the use of new drugs and diagnostic tools targeting both drug-sensitive and drug-resistant tuberculosis. Recent studies suggest that drugs such as moxifloxacin and gatifloxacin may shorten duration of treatment and be effective against resistant strains [18], and that rapid assays for fluroquinolone resistance have the potential to greatly reduce drug susceptibility testing time [11]. Modelling the impact of such interventions at a population level is essential for future tuberculosis policy. Equally, changes in population risk profiles, such as increased rates of HIV and changes in cross-border population movements which impact on transmission patterns, can be accounted for using this model.

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References

[1] J. P. Aparcio and C. Castillo-Chavez, "Mathematical modelling of tuberculosis epidemics", *Math. Biosci. Eng.* **6** (2009) 209–237.

[2] Australian Agency for International Development, "Senate Foreign Affairs, Defence and Trade Committee inquiry into matters relating to the Torres Strait region", 2009.

[3] Australian Doctors International, "Pre-program assessment for health in Western Province—a report prepared for the PNG Sustainable Development Program Limited", 2007.
[4] Australian Government Department of Immigration and Citizenship, "Submission to the Senate inquiry into matters relating to the Torres Strait region", 2009, http://www.aph.gov.au/Senate/committee/fadt_ctte/torresstrait/submissions.htm.
[5] H. Barrington, "Tuberculosis control strategies for the Torres Strait region, with a focus on multi-drug resistant tuberculosis", Internal Report, National Centre for Epidemiology and Population Health, Australian National University, January 2010.
[6] S. Basu, J. Andrews, E. Poolman, N. Gandhi, N. Shah, A. Moll, P. Moodley, A. Galvani and G. Friedland, "Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study", *Lancet* **370** (2007) 1500–1506.
[7] S. Basu and A. Galvani, "The transmission and control of XDR TB in South Africa: an operations research and mathematical modelling approach", *Epidemiol. Infect.* **136** (2008) 1585–1598.
[8] S. Basu, D. Maru, E. Poolman and A. Galvani, "Primary and secondary tuberculosis preventive treatment in HIV clinics: simulating alternative strategies", *Int. J. Tuberc. Lung Dis.* **13** (2009) 652–658.
[9] S. M. Blower and H. Dowlatabadi, "Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example", *Int. Stat. Rev.* **62** (1994) 229–243.
[10] S. M. Blower, A. R. McLean, T. C. Porco, P. M. Small, P. C. Hopewell, M. A. Sanchez and A. R. Moss, "The intrinsic transmission dynamics of tuberculosis epidemics", *Nat. Med.* **1** (1995) 815–821.
[11] K. C. Chang, W. W. Yew and R. C. Y. Chan, "Rapid assays for fluoroquinolone resistance in mycobacterium tuberculosis: a systematic review and meta-analysis", *J. Antimicrob. Chemoth.* **65** (2010) 1551–1561.
[12] E. L. Corbett, C. J. Watt, N. Walker, D. Maher, B. G. Williams, M. C. Raviglione and C. Dye, "The growing burden of tuberculosis: global trends and interactions with the HIV epidemic", *Arch. Intern. Med.* **163** (2003) 1009–1021.
[13] V. Coronado *et al.*, "Transmission of multidrug-resistant *mycobacterium tuberculosis* among persons with Human Immunodeficiency Virus in an urban hospital: epidemiological and restriction fragment length polymorphism analysis", *J. Infect. Dis.* **168** (1993) 1052–1055.
[14] C. S. M. Currie, K. Floyd, B. G. Williams and C. Dye, "Cost, affordability and cost-effectiveness of strategies to control tuberculosis in countries with high HIV prevalence", *BMC Public Health* **5** (2005) 130.
[15] C. M. Gilpin, G. Simpson, S. Vincent, T. P. O'Brien, T. A. Knight, M. Globan, C. Coulter and A. Konstantinos, "Evidence of primary transmission of multidrug-resistant tuberculosis in the Western Province of Papua New Guinea", *Med. J. Australia* **188** (2008) 148–152.
[16] J. M. Hyman, J. Li and E. A. Stanley, "The differential infectivity and staged progression models for the transmission of HIV", *Math. Biosci.* **155** (1998) 77–109.
[17] Y. Kang, Y.-J. Choi, Y.-J. Cho, S. M. Lee, C.-G. Yoo, Y. W. Kim, S. K. Han, Y.-S. Shim and J.-J. Yim, "Cost of treatment for multidrug-resistant tuberculosis in South Korea", *Respirology* **11**(6) (2006) 793–798.
[18] U. Lalloo and A. Ambaram, "New antituberculous drugs in development", *Curr. HIV/AIDS Rep.* **7** (2010) 143–151.
[19] L. Liu, X. Zhao and Y. Zhou, "A tuberculosis model with seasonality", *Bull. Math. Biol.* **72** (2010) 931–952.
[20] G. B. Migliori *et al.*, "Clinical and operational value of the extensively drug-resistant tuberculosis definition", *Eur. Respir. J.* **30** (2007) 623–626.
[21] C. Murray and J. Salomon, "Modeling the impact of global tuberculosis control strategies", *Proc. Natl. Acad. Sci. USA* **95** (1998) 13881–13886.
[22] P. Nahid, L. C. Gonzalez, I. Rudoy, B. C. de Jong, A. Unger, M. Kawamura, D. H. Osmond, P. C. Hopewell and C. L. Daley, "Treatment outcomes of patients with HIV and tuberculosis", *Am. J. Respir. Crit. Care Med.* **175** (2007) 1199–1206.
[23] Papua New Guinea Statistics Office, "Papua New Guinea 2000 Census", 2000.

[24] T. C. Porco and S. M. Blower, "Quantifying the intrinsic transmission dynamics of tuberculosis", *Theor. Popul. Biol.* **54** (1998) 117–132.
[25] T. C. Porco, P. M. Small and S. M. Blower, "Amplification dynamics: predicting the effect of HIV on tuberculosis outbreaks", *J. Acq. Immun. Def. Synd.* **28** (2001) 437–444.
[26] M. C. Raviglione, D. E. Snider and A. Kochi, "Global epidemiology of tuberculosis: morbidity and morality of a worldwide epidemic", *J. Am. Med. Assoc.* **273** (1995) 220–226.
[27] P. Rodrigues, M. Gabriela, M. Gomes and C. Rebelo, "Drug resistance in tuberculosis—a reinfection model", *Theor. Popul. Biol.* **71** (2007) 196–212.
[28] L.-I. W. Roeger, Z. Feng and C. Castillo-Chavez, "Modeling TB and HIV co-infections", *Math. Biosci. Eng.* **6** (2009) 815–837.
[29] C. E. Ryan, J. Gare, S. M. Crowe, K. Wilson, J. C. Reeder and R. B. Oelrichs, "The heterosexual HIV type 1 epidemic in Papua New Guinea is dominated by subtype C", *AIDS Res. Hum. Retrov.* **7** (2007) 941–944.
[30] M. Sánchez, J. Lloyd-Smith, B. Williams, T. Porco, S. Ryan, M. Borgdorff, J. Mansoer, C. Dye and W. Getz, "Incongruent HIV and tuberculosis co-dynamics in Kenya: interacting epidemics monitor each other", *Epidemics* **1** (2009) 14–20.
[31] O. Sharomi, C. Podder and A. Gumel, "Mathematical analysis of the transmission dynamics of HIV/TB coinfection in the presence of treatment", *Math. Biosci. Eng.* **5** (2008) 145–174.
[32] S. Shenoi, S. Heysell, A. Moll and G. Friedland, "Multidrug-resistant and extensively drug-resistant tuberculosis: consequences for the global HIV community", *Curr. Opin. Infect. Dis.* **22** (2009) 11–17.
[33] E. E. Telzak, K. D. Chirgwin, E. T. Nelson, J. P. Matts, K. A. Sepkowitz, C. A. Benson, D. C. Perlman and W. M. El-Sadr, "Predictors for multidrug-resistant tuberculosis among HIV infected patients and response to specific drug regimens", *Int. J. Tuberc. Lung Dis.* **3** (1999) 337–343.
[34] UNAIDS: the Joint United Nations Programme on HIV/AIDS, "2008 report on the global AIDS epidemic, Annex I: HIV and AIDS estimates and data 2007 and 2001", 2008.
[35] United Nations Population Division, "World population prospects: the 2008 revision population database", 2008.
[36] E. Vynnycky and P. E. M. Fine, "Lifetime risks, incubation period, and serial interval of tuberculosis", *Am. J. Epidemiol.* **152** (2000) 247–263.
[37] C. Wells, J. Cegielski, L. Nelson, K. Lserson, T. Holtz, A. Finlay and K. Castro, "HIV infection and multidrug-resistant tuberculosis—the perfect storm", *J. Infect. Dis.* **196** (2007) S87–S107.
[38] World Health Organisation, "World Health Organisation Statistical Information System".
[39] World Health Organisation, "Tuberculosis control in the WHO Western Pacific Region—2003 report", 2003.
[40] World Health Organisation, "Papua New Guinea: summary country profile for HIV/AIDS treatment scale-up", December 2005, http://www.who.int/hiv/HIVCP_PNG.pdf.
[41] World Health Organisation, "Financing M/XDR-TB control and care", in: *Key bottlenecks in M/XDR-TB control and patient care* (2009).
[42] World Health Organisation, "Global tuberculosis control—epidemiology, strategy, financing", Technical Report, World Health Organization, 2009.
[43] World Health Organisation, "TB Country Profile: Papua New Guinea", 2009.
[44] World Health Organisation, "TB/HIV Facts 2009", 2009.
[45] World Health Organisation, "Tuberculosis control in the Western Pacific Region", 2009.
[46] World Health Organisation, "Multidrug-resistant and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response", 2010.
[47] Z. Yang, Y. Kong, F. Wilson, B. Foxman, A. H. Fowler, C. F. Marrs, M. D. Cave and J. H. Bates, "Identification of risk factors for extrapulmonary tuberculosis", *Clin. Infect. Dis.* **38** (2004) 199–205.
[48] M. Zignol, M. S. Hosseini, C. Lambregts-van Weezenbeek, P. Nunn, C. J. Watt, B. G. Williams and C. Dye, "Global incidence of multidrug-resistant tuberculosis", *J. Infect. Dis.* **194** (2006) 479–485.