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Scenario Analysis for Programmatic Tuberculosis Control in Western Province, Papua New Guinea

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Tuberculosis (TB) and multidrug-resistant TB (MDR-TB) are major health problems in Western Province, Papua New Guinea. While comprehensive expansion of TB control programs is desirable, logistical challenges are considerable, and there is substantial uncertainty regarding the true disease burden. We parameterized our previously described mathematical model of *Mycobacterium tuberculosis* dynamics in Western Province, following an epidemiologic assessment. Five hypothetical scenarios representing alternative programmatic approaches during the period from 2013 to 2023 were developed with local staff. Bayesian uncertainty analyses were undertaken to explicitly acknowledge the uncertainty around key epidemiologic parameters, and an economic evaluation was performed. With continuation of existing programmatic strategies, overall TB incidence remained stable at 555 cases per 100,000 population per year (95% simulation interval (SI): 420, 807), but the proportion of incident cases attributable to MDR-TB increased from 16% to 35%. Comprehensive, provincewide strengthening of existing programs reduced incidence to 353 cases per 100,000 population per year (95% SI: 246, 558), with 46% being cases of MDR-TB, while incorporating programmatic management of MDR-TB into these programs reduced incidence to 233 cases per 100,000 population per year (95% SI: 198, 269) with 14% MDR-TB. Most economic costs were due to hospitalization during the intensive treatment phase. Broad scale-up of TB control activities in Western Province with incorporation of programmatic management of MDR-TB is vital if control is to be achieved. Community-based treatment approaches are important to reduce the associated economic costs.

Bayesian probability; models, biological; Papua New Guinea; tuberculosis; tuberculosis, multidrug-resistant

Abbreviations: BCG, Bacille Calmette-Guérin; DOTS, directly observed treatment, short-course; DS-TB, drug-susceptible tuberculosis; MDR-TB, multidrug-resistant tuberculosis; PMDT, programmatic management of multidrug-resistant tuberculosis; PNG, Papua New Guinea; TB, tuberculosis.

Tuberculosis (TB) is among the most significant health problems facing Papua New Guinea (PNG) today. The country presents a difficult environment for health programs, due to its mountainous terrain, low population density (15 persons/km^2), and limited human resource development (1). Even in this context, the discrepancy between TB-related health-care demands and programmatic capacity is particularly marked. This gap is highlighted by PNG's status as one of only 8 countries with more than 1,000 cases of TB annually but no capacity to perform in-country drug-susceptibility testing (2). Despite a history of sound health policy (3), the acknowledged seriousness of the TB epidemic in PNG (4), and past success in control of other infectious diseases (5), major challenges to effective control continue to exist (6) and the disease burden remains huge (7).

Since the 1970s and 1980s, health services in PNG have become increasingly decentralized to the provincial level (3). Western Province is geographically the largest and most sparsely populated province of PNG, with a population of 210,000 persons distributed across an area of approximately 100,000 km^2 (University of Papua New Guinea (Waigani, National Capital District, PNG), unpublished data, 2015). It is bordered to the west by the Indonesian province of Papua and to the south by a maritime border with Australia.

Recent World Health Organization statistics indicate that 1,130 new cases of multidrug-resistant tuberculosis (MDR-TB) occurred in PNG in 2012, though only 129 were confirmed (7). While reported national incidence rates for TB are moderately high, there is consistent emerging evidence to suggest that actual rates are considerably higher still (8, 9). While a national drug-resistance survey has not been conducted in PNG, subnational studies, reports, and notified cases imported to Australia suggest that MDR-TB is a substantial contributor to overall TB disease burden in PNG (9–13). Our previous epidemiologic assessment of TB in Western Province highlighted a number of the challenges involved in estimating the true burden of disease (9).

We were commissioned by the government of PNG to model programmatic interventions for TB control in Western Province in conjunction with Provincial TB control staff, in order to inform policy and better understand the potential impact of programmatic decisions on key indicators of disease burden. Considerations of particular importance in this context include whether the major expense and logistical challenges associated with rolling out provincewide programmatic management of MDR-TB is worthwhile, given the financial limitations in this resource-poor setting. In undertaking this modeling project, we also aimed to incorporate the many uncertainties inherent in the epidemiologic data relied upon for model inputs when interrogating such models.

METHODS

Model adaptation

We developed a mathematical model to simulate TB transmission in highly endemic areas of the Asia-Pacific region, such as PNG. The model has been presented in detail previously and consists of 10 compartments representing progression from susceptibility (either fully susceptible or partially immune) to latency (2 sequential latency compartments) to active disease (14). From here, patients may die, spontaneously recover, or be started on treatment, which may result in death, default with return to active disease, or recovery to partial immunity. All compartments representing *Mycobacterium tuberculosis* infection are duplicated for drug-susceptible TB (DS-TB) and MDR-TB. First-line treatment directed at DS-TB confers no benefit to patients with active MDR-TB (15), and DS-TB patients defaulting from first-line treatment regimens may undergo amplification of drug resistance to the level of MDR-TB. The model is intended to capture a number of components of disease dynamics in such regions, including: partial vaccine efficacy, declining risk of active disease with time from infection, reinfection during latency, and acquisition of drug resistance through de novo amplification (see Web Figure 1, Web Appendix 1, and Web Table 1, available at http://aje.oxfordjournals.org/).

Disease-specific parameter values are unchanged from those presented in the description of the base model, with the exception of the relative fitness of MDR-TB, as a high degree of uncertainty exists in relation to this parameter (16). Estimates and 95% simulation intervals for the local disease burden are based on an assessment of the regional epidemiology and program outcomes performed by one of the authors (E.S.M.) in 2012, also commissioned by the government of PNG (9), and are supplemented with reported national and provincial data where parameters are unavailable (Table 1).

An extension of the base model for this project was the inclusion of a mixing matrix (Web Appendix 2) to simulate mixing between districts of Western Province and with the neighboring Indonesian province of Papua. This matrix assumes liberal degrees of mixing, relative to verbal estimates obtained from local health workers. Of all TB transmission occurring in each district, 10% was assumed to result from index cases in each of the other 2 districts in the province, and 10% of transmission in North Fly District was assumed to occur from index cases in the Indonesian province of Papua (while the remainder (70% in North Fly, 80% in Middle Fly and South Fly) was assumed to result from transmission within the district).

Because TB incidence across PNG has consistently remained within the range of 300–350 cases per 100,000 population per year from 1990 to the present (2), the model was first allowed to reach equilibrium over a 163-year period from 1850 to 2013. Although total disease burden has remained relatively static, the situation regarding MDR-TB is more dynamic (17), as this strain has emerged over more recent decades since effective antibiotics became available. Despite this, until recently and over most of the period during which MDR-TB has emerged, effective treatment for MDR-TB strains has not been available. Given this situation, even with the incorporation of a significant fitness cost for the more resistant strain, MDR-TB dominates at model equilibrium (14). Therefore, we introduced MDR-TB into our model at a time consistent with our historical understanding of the emergence of MDR-TB in Western Province, adjusting both the timing of its emergence and its relative fitness along with other variable parameters to achieve the estimated proportion of incident strains attributable to MDR-TB in 2013.

Scenario development

We developed 5 potential intervention scenarios in consultation with staff of the Western Province office of the National Tuberculosis Program, advocates, and funding bodies. These scenarios are detailed in Web Table 2 and described in Table 2. We parameterized these proposed responses to our model structure to assess the effect of these responses over the period 2013–2023.

Scenario 1 simulates a continuation of the programmatic situation around the period 2011–2013. At this time, TB programs in the Province were primarily based on directly observed treatment, short-course (DOTS), with a pilot programmatic management of MDR-TB (PMDT) program being undertaken out of Daru, the capital of Western Province (18). Programmatic parameters, including treatment success rates, case detection rates, and availability of treatment for MDR-TB, were informed by our epidemiologic assessment with field visits undertaken across the Province in 2012 (9).

Scenario 2 consists of broad scale-up of DOTS-based programs, with additional PMDT throughout South Fly District, and pilot PMDT programs in the remaining 2 districts. Improved Bacille Calmette-Guérin (BCG) coverage is achieved

Table 1. Epidemiologic Values Used to Calculate Parameters for a Model of Tuberculosis Control in Western Province, Papua New Guinea

Epidemiologic Factor	Value	95% SI[a]	Source Reference(s)
Smear-positive pulmonary TB, %	40	25–55	51
Effective contact rate (β), per year infectious	25	5–45	—[b]
Calendar year of MDR-TB emergence	1980	1965–1995	—[c]
BCG coverage, %	65	45–85	52, 53
Case detection rate, %	70	50–90	2, 51
District default, % per 6-month treatment period[d]			
North Fly	15	5–25	9
Middle Fly	20	7–33	9
Fly	10	3–17	9
Relative fitness of MDR-TB (ratio)	0.7	0.4–1.0	16
% of cases with early progression	12.9		54
Duration of early latency, months	23		54
Late progression rate, % per year	0.375		55
Birth rate, no. of births per 1,000 population	29		1
Life expectancy, years	61.5		1
Average treatment duration, months			
DS-TB	6		26
MDR-TB	24[e]		26
Partial immunity multiplier	0.49		56
Untreated disease duration, years	3		57
Untreated case fatality, %			
Smear-positive TB	70		57
Smear-negative and extrapulmonary TB	20		57
Relative infectiousness (ratio)			
Smear-negative TB	0.24		58
Extrapulmonary TB	0		
Treated cases of DS-TB	0.02		59, 60
Treated cases of MDR-TB	0.18		59, 60
Relative mortality of treated cases (ratio)	0.5		61, 62
Amplification rate to MDR-TB,[f] %	3.5		63

Abbreviations: BCG, Bacille Calmette-Guérin; DS-TB, drug-susceptible tuberculosis; MDR-TB, multidrug-resistant tuberculosis; SI, simulation interval; TB, tuberculosis.

[a] Uncertainty ranges are presented for the first 9 parameters, which are varied throughout the baseline period according to the Metropolis algorithm described in the text (28).

[b] The main epidemiologic calibration parameter; it was allowed to vary over a broad range, along with other variable parameters, to achieve target incidence.

[c] Consistent with historical understanding of the emergence of MDR-TB in the Province.

[d] The ratio of these 3 variables to one another remains fixed, with the 3 variables being varied together under uncertainty analysis.

[e] For scenario 4, this parameter changes to 10 months from 2013 onwards. The value of 24 months applies to the baseline period and all other scenarios (scenarios 1, 2, 3, and 5) (27).

[f] Proportion of defaulting patients amplifying to MDR-TB.

through education and support of community health workers provided through basic management units, which thereby increases rates of neonatal BCG vaccination and supports catch-up vaccinations for children over the age of 1 year. Such strategies are consistent with evidence for the effectiveness of several provider-based interventions in improving vaccination coverage (19, 20). The expansion and improvement of DOTS-based care across the Province incorporates improved treatment adherence and reduction in loss to follow-up through increased use of human resources (21), improved record-keeping and staff training, and better reliability of the drug supply chain. Under this scenario, default rates per unit

Table 2. Hypothetical Scenarios Implemented in a Model of Tuberculosis Control in Western Province, Papua New Guinea, for the Period 2013–2023[a]

Scenario	DOTS-Based Care	Case Detection	Default Rates	BCG Coverage	PMDT		Average Duration of Treatment for MDR-TB, months
					South Fly District	North District and Middle Fly District	
1	Passive case-finding plus single GeneXpert (Cepheid Inc., Sunnyvale, California) instrument platform in South Fly District	Small increase (around 3%)	Unchanged from baseline	Unchanged from baseline	Pilot program for 80 patients	Nil	24
2	Major expansion	Missed cases reduced by 60%	Halved	Increased by 10%	Comprehensive	Pilot program for 40 patients in each district	24
3	Major expansion	Missed cases reduced by 60%	Halved	Increased by 10%	Comprehensive	Comprehensive	24
4	Major expansion	Missed cases reduced by 60%	Halved	Increased by 10%	Comprehensive	Comprehensive	10
5	Unchanged from baseline	Unchanged from baseline	Unchanged from baseline	Unchanged from baseline	Nil	Nil	24

Abbreviations: BCG, Bacille Calmette-Guérin; DOTS, directly observed treatment, short-course; MDR-TB, multidrug-resistant tuberculosis; PMDT, programmatic management of multidrug-resistant tuberculosis.

[a] Scenarios are described in full in Web Table 2.

time are halved from their baseline values. The case detection rate is improved through a combination of intensified case-finding strategies and improved knowledge of standard operating procedures for TB diagnosis and treatment commencement. Intensified case-finding is considered as symptom-based screening through health facilities of persons appearing for non-TB indications and similar screening of close contacts of persons diagnosed with active TB (22, 23). These strategies are predicted to improve the case detection rate from approximately 70% during the preintervention phase to percentages in the high 80s, which is comparable to the highest case detection rates reported for the World Health Organization's Western Pacific Region (e.g., China) (2).

Scenario 3 incorporates all of the interventions modeled in scenario 2, with the addition of provincewide PMDT. PMDT is considered as a comprehensive response to MDR-TB, incorporating GeneXpert (Cepheid Inc., Sunnyvale, California)-based diagnosis (24, 25) for all new and retreatment cases at basic management units and directly observed treatment according to the World Health Organization's guidelines for MDR-TB treatment (26), including inpatient management throughout the intensive phase of treatment with parenteral antibiotics. In settings where such programs are implemented, time to presentation and effective diagnosis are considered to be the primary drivers of delays to commencing treatment, while appropriate diagnosis through on-site molecular diagnostics is considered to result in identified patients' commencing appropriate treatment regimens where such resources are available.

Scenario 4 modifies scenario 3 to describe outcomes with similar programmatic scale-up but use of a short-course treatment regimen recently found to result in excellent treatment outcomes when implemented in Bangladesh and considered to have an average duration of 10 months (27). Because default rates are assumed to relate primarily to local programmatic conditions, the default rate per unit time remains the same as for other regimens, resulting in a considerably higher treatment success rate for MDR-TB than in scenarios 1–3. However, because scenarios 3 and 4 assume universal treatment availability for diagnosed patients, the rate of treatment commencement remains unchanged.

Lastly, scenario 5 describes withdrawal of external support with reversion to the programmatic situation that existed prior to 2011–2013. Under this scenario, all model parameters remain unchanged, but the pilot PMDT program being undertaken in South Fly District is lost.

Uncertainty analysis

Prior probability distributions for each parameter included in our uncertainty analysis in 2013 were formed with a β probability density function with shape parameters of $\alpha = 2$ and $\beta = 2$, centered around the baseline estimate, with ranges as presented in Table 1. Normally distributed likelihood functions for the model outputs of total incidence in 2013 and proportion of incidence attributable to MDR-TB in 2013 were defined on the basis of our epidemiologic assessment. These were 600 cases (standard deviation, 50) per 100,000 population per year for incidence, and the proportion of incidence attributable to MDR-TB was 20% (standard deviation,

7.5%). A Metropolis algorithm (28) was used to estimate the joint posterior probability distribution of both the model parameters and the projected future epidemic curves. The joint posterior probability is calculated as the product of the prior probability of each input parameter and the probability of each of the 2 model outputs considered, based on the fixed probability distributions described for each of these variables. The resulting likelihood of each parameter set is compared with the likelihood of the previous parameter set, and the new set of parameter values is accepted if the likelihood of the new set is greater than that of the previous set. If the likelihood of the new parameter set is less than that of the previous set, the probability of its acceptance is set equal to the likelihood of the new set divided by the previous set, and rejected otherwise. Each accepted parameter set is then used to estimate outcomes for each of the 5 scenarios from 2013 to 2023, and each parameter is then independently varied to generate the next parameter set for consideration until 10,000 model runs have been accepted and applied to each scenario.

Economic analysis

An economic analysis was performed based on the disease rates produced from the epidemiologic modeling described above and PNG's costed Country Strategic Plan for TB (applicable to the period 2011–2015) (29). The focus of this analysis was to consider the additional programmatic costs incurred by scenarios 2–5 in comparison with scenario 1, considering total costs of medication supply, total costs of hospitalization, and the additional costs associated with programmatic scale-up. This was supplemented by estimates from other sources where required, as not all intervention costs fall within the remit of Provincial TB activities. Economic assumptions consisted of an inflation rate of 6% per annum, a 2011 currency exchange rate of 2.15K (PNG Kina) to US$1, 25% procurement costs, 10% insurance costs, a 2011 hospitalization cost of 190K (US$88.37) per night (30, 31), and no discounting over time. Although children were not explicitly distinguished by the model, we assumed that 20% of cases were pediatric and assumed a mean pediatric weight of 40 kg for economic calculations. DS-TB prices were based on daily fixed-dose combination treatment, and MDR-TB treatment regimens were taken from the PNG Country Guidelines for PMDT (32), supplemented with international prices for gatifloxacin and clofazamine in scenario 4 and for BCG (33). Duration of hospitalization was assumed to be 2 months for standard MDR-TB treatment, consistent with national guidelines, and was assumed to be 2 weeks for DS-TB and 5 months for MDR-TB treatment in scenario 4. Program costs listed are the costs of additional programmatic requirements for scenarios 2–4 in comparison with scenario 1. These include equipment for basic management units, community outreach visits, staff salaries and incentives, infrastructural development, reporting costs, and communication costs and are fixed for each scenario (and thus are not presented with 95% simulation intervals). The compositions of regimens, medication unit costs, total daily regimen costs, and fixed programmatic costs are presented in Web Tables 3–6. Economic outputs based on the same epidemiologic results but 3 alternative economic assumptions are presented in Web Table 7.

RESULTS

Scenario analysis

Results from the 5 scenario analyses are presented in Figure 1 and Table 3. Under scenario 1, the introduction of a GeneXpert and pilot MDR-TB treatment program in Daru results in a slight overall reduction in disease burden, with a particularly marked improvement in South Fly. However, the modestly expanded management of MDR-TB fails to control disease attributable to this strain, with a progressively greater proportion of disease incidence resulting from the resistant strain.

Under scenario 2, a moderate improvement in overall disease burden is observed, due to the provincewide expansion and improvement of TB control activities. However, despite the introduction of PMDT in South Fly, MDR-TB comprises a markedly greater proportion of incident cases, partly due to reductions in DS-TB incidence. Improvements are seen in the provincewide TB-specific mortality rate, although this is offset as the proportion of disease attributable to MDR-TB increases.

Under scenarios 3 and 4, expansion of TB control activities across the province, incorporating provincewide PMDT, results in improvements in disease burden that are notably greater than those described in scenario 2, with particular improvements in mortality rates. The additional reduction in disease burden due to shortening of the regimen to 10 months under scenario 4 is modest. This is attributable to the detection rate's being the limiting factor in patients commencing treatment, such that the reduction in treatment duration does not increase the number of patients starting treatment per unit time.

Under scenario 5, disease burden increases slightly over the 10-year period, with MDR-TB contributing a steadily greater proportion of incident cases and outcomes marginally worse than under scenario 1.

Uncertainty

Posterior distributions of the parameter values in relation to their respective priors are presented in Web Figures 2 and 3. The degree of uncertainty in estimates of outcomes is greater with respect to the proportion of disease attributable to MDR-TB than for total incidence and TB-specific mortality for the Province. This is largely attributable to the considerable uncertainty around both the relative fitness of this strain and its current and historical burden in the Province. Despite this, the large majority of model runs show an increase in proportionate incidence of MDR-TB in the absence of provincewide PMDT.

Despite the extensive mixing assumed between populations and the dilution of programmatic effects through TB importation from Indonesia to North Fly, district-level outcomes are not strongly influenced by surrounding areas.

We previously performed a univariable sensitivity analysis that considered the model's general characteristics (14). This analysis found that the model outputs were most highly sensitive to detection rates and comparatively insensitive to default and BCG vaccination rates.

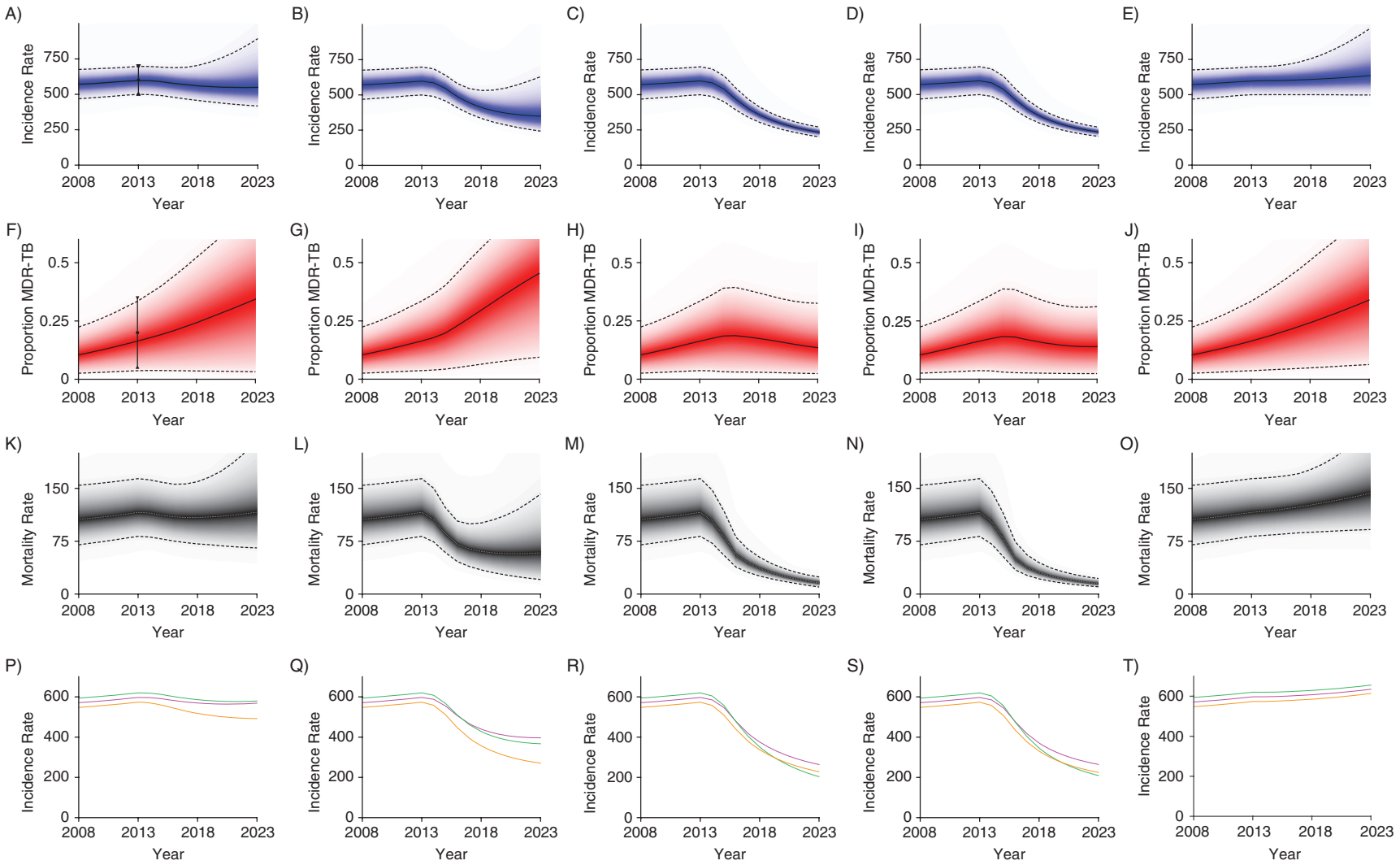

Figure 1. Burden of tuberculosis (TB) in Western Province, Papua New Guinea, under 5 modeled scenarios of programmatic interventions for TB control, with 95% simulation intervals (dashed lines). Columns of panels represent (from left to right) scenarios 1–5: scenario 1, panels A, F, K, and P; scenario 2, panels B, G, L, and Q; scenario 3, panels C, H, M, and R; scenario 4, panels D, I, N, and S; and scenario 5, panels E, J, O, and T. Rows of panels show (from top to bottom) incidence (panels A–E), proportion of incidence attributable to multidrug-resistant TB (panels F–J), disease-specific mortality rate (panels K–O), and incidence rate by district (panels P–T). We performed 10,000 model runs, with Bayesian variation to baseline parameters as described in the Methods section of the text. For each accepted parameter set, outputs were generated for the intervention period (2013–2023) for each scenario. For panels A–O, lower dashed lines indicate the 2.5th percentile of model runs, the solid line (or dotted white line, for mortality) indicates the 50th percentile of model runs, upper dashed lines indicate the 97.5th percentile of model runs, and shading is proportional to the density of model outputs. Vertical bars with central dots indicate the 95% simulation intervals of outputs. In the lower row of panels, the 50th percentile of model runs is presented for each district (magenta, North Fly; green, Middle Fly; orange, South Fly).

Table 3. Outcomes From a Model of Tuberculosis Control in Western Province, Papua New Guinea, in 2023 or During the Intervention Period (2013–2023)[a]

TB Outcome	Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
	Median	95% SI	Median	95% SI	Median	95% SI	Median	95% SI	Median	95% SI
Incidence, per 100,000 population per year										
Total	555	420, 807	353	246, 558	233	198, 269	233	200, 268	638	496, 883
DS-TB	355	243, 476	189	140, 243	199	155, 246	199	156, 246	409	281, 550
MDR-TB[b]	195	13, 531	164	24, 401	32	6, 71	33	6, 69	223	33, 560
Total incidence by district, per 100,000 population per year										
North Fly	574	436, 829	402	270, 658	263	224, 308	264	224, 307	637	496, 882
Middle Fly	585	444, 842	373	234, 639	204	166, 241	209	178, 242	658	515, 904
South Fly	496	370, 740	270	222, 350	227	193, 260	223	190, 256	617	476, 861
Total prevalence, per 100,000 population	931	601, 1,518	517	233, 998	207	150, 277	171	130, 218	1,122	793, 1,676
Mortality rate, per 100,000 population per year	117	67, 197	61	23, 123	16	10, 24	15	9, 22	143	93, 219
% of population latently infected	54	48, 60	49	44, 54	46	41, 50	46	41, 50	56	50, 62
Cumulative no. of incident cases, thousands	11.7	9.5, 15.0	9.1	7.4, 11.8	7.9	6.7, 9.2	7.9	6.7, 9.1	12.6	10.3, 15.9
Cumulative no. of deaths, thousands	2.3	1.6, 3.3	1.5	0.9, 2.2	1.0	0.7, 1.3	0.9	0.6, 1.2	2.6	1.9, 3.6
No. of treatment commencements, thousands										
DS-TB	7.7	5.9, 9.8	5.9	4.5, 7.4	6.0	4.6, 7.4	6.0	4.6, 7.4	7.4	5.7, 9.7
MDR-TB	400	400, 400	590	115, 1,275	964	271, 2,125	1,262	298, 2,588	0	0, 0
Treatment time, thousand patient-months										
DS-TB	3.5	2.7, 4.4	3.8	2.9, 4.7	4.0	3.1, 4.8	4.0	3.2, 4.9	3.4	2.6, 4.3
MDR-TB	2.9	2.4, 3.4	6.2	1.3, 13.1	2.1	0.5, 4.4	11.0	2.8, 21.7	0	0, 0
Maximum no. of hospital beds required	37	29, 45	56	36, 79	80	46, 139	156	68, 307	29	22, 36
DS-TB drug regimen costs, thousand ₭[c]	0.55	0.42, 0.68	0.55	0.42, 0.68	0.56	0.43, 0.69	0.56	0.43, 0.70	0.54	0.41, 0.68
MDR-TB drug regimen costs, million ₭	1.4	1.1, 1.6	2.5	0.5, 5.2	7.8	1.6, 16.2	3.9	0.8, 8.2	0	0, 0
Hospitalization costs, million ₭	34.1	26.1, 43.0	36.6	22.6, 55.0	56.5	27.3, 96.4	83.5	32.4, 155.6	27.8	21.0, 36.9
Program costs,[d] thousand ₭	0		1,915		2,065		2,065		0	
Total costs, million ₭	36.5	28.3, 45.3	41.5	25.8, 61.6	67.1	31.7, 113.3	90.9	36.4, 162.6	29.1	22.2, 36.6

Abbreviations: DS-TB, drug-susceptible tuberculosis; ₭, Kina; MDR-TB, multidrug-resistant tuberculosis; SI, simulation interval.

[a] All values represent the 50th percentile for the scenario outcomes, with accompanying 95% SIs (2.5th percentile, 97.5th percentile). Disease burden outcomes are the provincewide rates observed on January 1, 2023. Cumulative cases, deaths, treatment commencements, months under treatment, drug regimen costs, and hospitalization costs are the cumulative values for the period January 1, 2013–December 31, 2022. "Maximum no. of hospital beds required" specifies the highest number of patients simultaneously requiring inpatient treatment at any point in time during the intervention period.

[b] Absolute incidence, as opposed to proportion presented in output figures.

[c] We assumed a 2011 currency exchange rate of 2.15₭ to US$1.

[d] Program costs are fixed costs for program scale-up that are unaffected by disease burden and thus are not presented with 95% SIs.

Economics

For scenario 3, under the hospitalization assumptions described above, a large proportion of the Province's 200–300 total inpatient beds are taken up by TB patients in their intensive phase of treatment, while under scenario 4, the bed capacity of the Province could be overwhelmed. Moreover, for all scenarios described, hospitalization costs contribute the large majority of the overall costs, while for all scenarios that incorporate treatment of MDR-TB (1–4), most drug costs arise from treatment of this strain. As expected, the alternative economic analyses (Web Table 7) demonstrate that these hospitalization costs are markedly and proportionately reduced by modifying the bed-night unit cost or the duration of inpatient treatment during the intensive phase.

DISCUSSION

Our study highlights the importance of comprehensive, provincewide programmatic improvements to TB control in Western Province, PNG. Without such broad-scale approaches, further increases in the overall disease burden are anticipated, and the problem of drug resistance is likely to escalate. If further programmatic development does not occur, especially in relation to expansion of PMDT, it is likely that TB will remain uncontrolled in the Province and that the proportion of disease attributable to MDR-TB will increase. We previously undertook an assessment of the TB burden in Western Province to gain an improved understanding of disease dynamics (9), and we subsequently worked with a range of professionals involved in coordinating, funding, and providing TB services across Western Province to develop a realistic set of scenarios representing possible responses to TB control in the Province.

Despite our background research, significant uncertainty as to the true disease burden in the Province persists. Regions of the world with high TB burden are often also those for which the data on the epidemic are the poorest. This is the case for Western Province, where incidence, MDR-TB burden, proportion of cases infectious, BCG coverage, case detection rate, default rate, and timing of MDR-TB emergence are all uncertain. Moreover, there is uncertainty in the modeling literature regarding a number of key parameters (34), particularly the relative fitness of MDR-TB (16), which makes estimation of the likely contribution of this strain to disease burden more difficult. Therefore, we present an approach to explicitly quantifying the degree of uncertainty inherent in our estimates for the outcomes considered. Our model outputs show particularly wide 95% simulation intervals in relation to the proportional incidence of MDR-TB, which is attributable to the uncertainty regarding the relative fitness of this strain and the wide uncertainty as to the proportionate burden of MDR-TB, due to the absence of a comprehensive drug-resistance survey (35).

Currently in Western Province, an established PMDT program is available only in the capital, Daru, and our modeling suggests that this program will not adequately control this strain across the Province. Even when comprehensive, provincewide management of DS-TB is provided in combination with expanded PMDT in South Fly, satisfactory control of MDR-TB is not achieved. However, when provincewide PMDT is scaled up under scenarios 3 and 4, the reduction in disease burden due to DS-TB is achieved alongside reductions in MDR-TB burden. As we previously described (14), this is due to the observation that once MDR-TB constitutes a significant proportion of incident cases, the majority of new cases occur through community transmission. This is also consistent with the observation of unique genetic profiles in strains of MDR-TB isolated from patients originating from Western Province (10). Therefore, our results reinforce that prevention of resistance amplification through adequate treatment of DS-TB would be insufficient to prevent the continued emergence of MDR-TB.

Such programs, as currently conceived, generally require centralized management units with experience in MDR-TB treatment, including accurate diagnostics, capacity for monitoring, and prolonged hospitalization, and so are often highly resource-intensive. In our modeling, the majority of costs are due to hospitalization of patients with MDR-TB during the intensive phase of their treatment. While this is in keeping with current PNG national guidelines, the need for such extensive hospitalization would consume the large majority of inpatient facilities across the Province. Therefore, alternative models, particularly those providing decentralized, community-based PMDT after brief hospitalization, should also be explored and might provide additional benefits, including reduced treatment default (36).

Our scenarios describe a range of possible responses, ranging from inaction to highly ambitious multifactorial interventions. Despite the challenges faced in delivering effective programmatic TB control in this setting (37), we believe it is important to consider such responses. This is because significant impacts from simple public health interventions have previously been demonstrated in resource-limited settings when implemented at a community level (38), and because it will facilitate advocacy for more ambitious programs (39, 40). Operational research to identify the most pragmatic and cost-effective interventions for TB control in Western Province is essential as the Australian Government moves from a model of clinical care at the border towards comprehensive support for a programmatic response (41, 42), and past modeling studies have demonstrated the importance of TB control in the Province for transmission of infection to Australian communities (43). Moreover, the Burnet Institute (Melbourne, Victoria, Australia) is increasingly involved in providing support for TB control in the Province (44), with its approach being informed by the results of this modeling. Elsewhere in the world, modeling of cross-border transmission at the intersection of low- and high-burden regions has demonstrated that improved control in high-burden settings can be cost-saving for the low-burden country (45).

Although they are not currently recommended by the World Health Organization or PNG's National Tuberculosis Program, short-course or "Bangladesh protocol" MDR-TB regimens have been shown to be effective in several settings, with marked improvements in completion and cure rates being observed (27). Although international randomized controlled trials of this approach are ongoing (46), a growing international consensus is actively seeking to move ahead with expansion of this regimen for PMDT (47, 48). Local considerations must be incorporated into any proposed new approach, and it must be particularly informed by prevailing

drug resistance patterns. PNG may be a suitable location for introduction of such short-course regimens, particularly given the high default rates observed with existing approaches to TB therapy. We found a relatively modest epidemiologic impact of changing to this regimen, although this was largely due to our assumption that treatment of MDR-TB is limited by case detection rather than treatment availability. Moreover, because of our highly conservative assumption that the entire intensive phase of treatment of this regimen would be provided on an inpatient basis, the regimen is not cost-saving. If the hospitalization period for this regimen were reduced to 2 months (as in the third section of Web Table 7), this regimen would become cost-saving in terms of hospitalization, with hospitalization costs of 52,500K (US$24,418.60), in addition to the savings on drug costs.

In this paper, we have presented an economic analysis informed by the principles of the Methods for Economic Evaluation Project (49), focusing on costs associated with programmatic scale-up and resource consumption in each scenario. Comparator scenarios included both a business-as-usual projection and a projection of disease burden in the absence of provision of external funding support to the Province, while the major patient subgroups considered were those with DS-TB and MDR-TB strains. Although cost-effectiveness and cost-benefit analyses were not undertaken due to the number of disease-related or health-related endpoints considered, other recent modeling of DOTS expansion in South Fly District has found such interventions to be among the "best buys" for health in developing countries (50). Our analysis aimed to consider all health-system costs accrued through programmatic scale-up, but it did not consider non-health-system costs or opportunity costs to patients. While the results presented in Table 3 do not incorporate a discounting rate according to our terms of reference, we include results of alternative analyses employing a 3% rate of discounting of both cost and health outcomes, an arbitrary alternative nightly inpatient bed cost of 100K (US$46.51), and a reduction in the length of inpatient stay under short-course MDR-TB regimens to 2 months. This arbitrary alternative nightly bed cost was considered because bed cost was a large component of total costs but was highly uncertain, as it is likely to differ according to the relative contribution of the health system and the patients' families to inpatient care. The alternative economic analyses highlight how effective measures designed to shift treatment towards a community model and reductions in bed costs could be in reducing overall costs.

Our modeling predicts that the high burden of TB and the large contribution of MDR-TB to TB incidence in Western Province are unlikely to improve with current, DOTS-based programmatic responses. Only provincewide scale-up of existing programs in combination with comprehensive PMDT will control the epidemic without an exacerbation of the drug-resistance problem.

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