**Title page**

**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 control programs is desirable, logistical challenges are considerable and there is substantial uncertainty regarding the true disease burden. We parameterised our previously described mathematical model to *M. tuberculosis* dynamics in Western Province, following an epidemiological assessment. Five scenarios representing alternative programmatic responses from 2013 to 2023 were developed with local staff. Bayesian uncertainty analyses were undertaken to explicitly acknowledge the uncertainty around key epidemiological parameters and an economic evaluation was performed. With continuation of existing programmatic strategies, overall incidence remained stable at 555 (420-807) per 100,000 per year, but the proportion of incident cases attributable to MDR-TB increased from 16% to 35%. Comprehensive, Province-wide strengthening of existing programs reduced incidence to 353 (246-558) with 46% MDR-TB, while incorporating programmatic management of MDR-TB into these programs reduced incidence to 233 (198-269) with 14% MDR-TB. Most economic costs were due to hospitalisation 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.

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

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 person/km2) and limited human resources development.(1) Even in this context, the discrepancy between tuberculosis related health care demands and programmatic capacity are particularly marked. This gap is highlighted by PNG’s status as one of only eight countries with more than 1000 cases of tuberculosis 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 and past success in control of other infectious diseases,(4) major challenges to effective control continue to exist (5) and the disease burden remains huge.(6)

Since around the 1970s and 1980s, health services in PNG have been increasingly decentralized to the provincial level.(3) Western Province is geographically the largest and most sparsely populated province of Papua New Guinea, with a population of 210,000 distributed across an area of approximately 100,000 km2. 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 estimate that 1,130 new MDR-TB cases occurred in 2012, although only 129 were confirmed.(6) While reported national incidence rates for tuberculosis are moderately high, there is consistent emerging evidence to suggest that actual rates are considerably higher still.(7, 8) While a national drug-resistance survey has not been conducted in PNG, sub-national studies, reports and notifications from imported cases to Australia suggest that MDR-TB is a substantial contributor to overall TB disease burden.(8-12) Our previous epidemiological assessment of TB in Western Province highlighted a number of the challenges in estimating the true burden of disease.(8)

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 Province-wide 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 epidemiological 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 regions of the Asia-Pacific, such as PNG. The model has been presented in detail previously and consists of ten compartments representing progression from susceptible (either fully susceptible or partially immune) through two sequential latency compartments to active disease.(13) From here, patients may die, spontaneously recover, or be commenced on treatment, which may result in death, default with return to active disease, or recovery to partial immunity. All compartments representing *M. tuberculosis* infection are duplicated for drug-susceptible (DS-TB) and MDR-TB. First line treatment directed at DS-TB confers no benefit to patients with active MDR-TB (14) and DS-TB patients defaulting from first-line regimens may undergo resistance amplification to 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. (Web Figure 1, Web Appendix 1 and Web Table 1)

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.(15) Estimates and uncertainty ranges for the local disease burden are based on an assessment of the regional epidemiology and program outcomes performed by one author in 2012 (ESM), also commissioned by the Government of Papua New Guinea,(8) and are supplemented with reported national and provincial data where parameters are unavailable. (Table 1)

An elaboration to 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 neighbouring 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 two districts of the province and 10% of transmission in the North Fly District was assumed to occur from index cases in the Indonesian province of Papua, (while the remainder [70% North Fly, 80% Middle and South Fly] was assumed to result from transmission within the district).

As TB incidence across PNG has remained consistently in the 300 to 350 per 100,000 per year range from 1990 to the present day,(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,(16) 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.(13) Therefore, we introduce MDR-TB into our model at a time consistent with our historical understanding of the emergence of MDR-TB in the 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**

Five potential intervention scenarios were developed in consultation with staff of the National Tuberculosis Program based in Western Province, advocates and funding bodies. These are presented in Web Table 2 and summarised in Table 2. We parameterised 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 directly observed treatment, short-course (DOTS)-based, with a pilot programmatic management of MDR-TB program being undertaken out of Daru, the capital of Western Province.(17) Programmatic parameters, including treatment success rates, case detection rates and treatment availability for MDR-TB are informed by our epidemiological assessment with field visits across the Province undertaken in 2012.(8)

Scenario 2 consists of broad scale-up of DOTS-based programs, with additional programmatic management of MDR-TB (PMDT) throughout South Fly District, and pilot PMDT programs in the remaining two districts. Improved Bacille Calmette-Guérin (BCG) coverage is achieved 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 aged over one. Such strategies are consistent with evidence for the effectiveness of several provider-based interventions in improving vaccination coverage.(18, 19) The expansion and improvement of DOTS-based care across the Province incorporates improved treatment adherence and reduction in loss to follow-up through increased human resources,(20) improved record keeping and staff training and better reliability of the drug supply chain. Under this Scenario, default rates per unit 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 individuals presenting for non-TB indications and similar screening of close contacts of cases diagnosed with active TB.(21, 22) These strategies are predicted to improve the case detection rate from around 70% during the pre-intervention phase to percentages in the high 80s, which are comparable to the highest case detection rates reported in the Western Pacific Region (e.g. China).(2)

Scenario 3 incorporates all the interventions modeled in Scenario 2, but with the addition of Province-wide PMDT. PMDT is considered as a comprehensive response to MDR-TB, incorporating GeneXpert® (Cepheid, Sunnyvale, CA)-based diagnosis (23, 24) for all new and re-treatment cases at basic management units and directly-observed treatment according to the World Health Organization’s guidelines for MDR-TB treatment,(25) 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 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 ten months.(26) As 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 than in Scenarios 1 to 3. However, as 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 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 beta probability density function with shape parameters of α=2 and β=2, centred 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 based on our epidemiological assessment. These were 600 (standard deviation 50) per 100,000 per year for incidence and 20% (standard deviation 7.5%) for the proportion of incidence attributable to MDR-TB. A Metropolis algorithm 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 multiplied by the product of the probability of each of the two model outputs considered, based on the fixed probability distributions described for each of these variables. The resulting likelihood of each parameter set is compared to the likelihood of the previous parameter set and 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 five 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 epidemiological modelling described above and PNG’s costed Country Strategic Plan for TB (applicable to the period 2011-2015). The focus of this analysis was to consider the additional programmatic costs incurred by Scenarios 2-5 by comparison to Scenario 1, considering total costs of medication supply, total costs of hospitalisation 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 exchange rate of 2.15K (PNG Kina) to US$1, 25% procurement costs, 10% insurance costs, a 2011 per night hospitalisation cost of 190K (27, 28) and no discounting over time. Although children were not explicitly distinguished by the model, we assume 20% of cases are paediatric and a mean paediatric weight of 40kg 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,(29) supplemented with international prices for gatifloxacin and clofazamine in Scenario 4 and for BCG.(30) Duration of hospitalisation was assumed to be two months for standard MDR-TB treatment, consistent with national guidelines, and was assumed to be two weeks for DS-TB and five months for MDR-TB treatment in Scenario 4. Program costs listed are the costs of additional programmatic requirements for Scenarios 2-4 by comparison to 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 so are not presented with uncertainty ranges. Composition of regimens, medication unit costs, total daily regimen costs and fixed programmatic costs are presented in Web Tables 3 to 6. Economic outputs based on the same epidemiological results, but three alternative economic assumptions are presented in Web Table 7.

**RESULTS**

**Scenario analysis**

Results of the five 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 result 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 Province-wide 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 Province-wide 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 Province-wide 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 ten months under Scenario 4 is modest. This is attributable to the detection rate 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 ten 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 Province-wide 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.

A univariable sensitivity analysis was performed in our previous publication which considered the model’s general characteristics.(13) This analysis found that the model outputs were most highly sensitive to detection rates and comparatively insensitive to default and BCG vaccination rates.

**Economics**

For Scenario 3, under the hospitalisation assumptions described above, a large proportion of the Province’s 200-300 total inpatient beds are taken up with 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, hospitalisation 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 hospitalisation 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, Province-wide 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 the disease in the Province will remain uncontrolled and 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, and 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 modelling literature regarding a number of key parameters,(31) particularly the relative fitness of MDR-TB,(15) 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 uncertainty ranges 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.(32)

Currently in Western Province, an established PMDT program is available only in the capital, Daru, and our modelling suggests that this program will not adequately control this strain across the Province. Even when comprehensive, Province-wide management of DS-TB is provided in combination with expanded PMDT in South Fly, satisfactory control of MDR-TB is not achieved. However, when Province-wide 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 previously described,(13) 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, and is consistent with observations from the Province.(9) 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 centralised management units with experience in MDR-TB treatment, including accurate diagnostics, capacity for monitoring and prolonged hospitalisation, and so are often highly resource-intensive. In our modelling, the majority of costs are due to hospitalisation 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 hospitalisation would consume the large majority of inpatient facilities across the Province. Therefore, alternative models, particularly those providing decentralised, community-based PMDT after brief hospitalisation should also be explored and may provide additional benefits, including reduced treatment default.(33)

Our Scenarios describe a range of possible responses, ranging from inaction, through to highly ambitious multifactorial interventions. Despite the challenges faced in delivering effective programmatic TB control in this setting,(34) 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,(35) and to facilitate advocacy for more ambitious programs.(36, 37) 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 the programmatic response,(38, 39) and past modelling studies have demonstrated the importance of TB control in the Province for transmission of infection to Australian communities.(40) Moreover, the Burnet Institute is increasingly involved in providing support to TB control in the Province,(41) with its approach informed by the results of this modelling. Elsewhere in the world, modelling of cross-border transmission at the intersection of low and high burden regions has demonstrated that improved control in high burden setting can be cost-saving for the low burden country.(42)

Although 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 observed.(26) Although international randomised controlled trials of this approach are ongoing,(43) a growing international consensus is actively seeking to move ahead with expansion of this regimen for PMDT.(44, 45) Local considerations must be incorporated in any proposed new approach, 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 therapy. We found a relatively modest epidemiological impact of changing to this regimen, although this is largely due to our assumption that treatment of MDR-TB is limited by case detection, rather than treatment availability. Moreover, due to 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 hospitalisation period for this regimen were reduced to two months (as in the third section of Web Table 7), this regimen becomes cost saving in terms of hospitalisation, with hospitalisation costs of 52,500K in addition to the savings on drug costs.

We present an economic analysis informed by the principles of the Methods for Economic Evaluation Project,(46) focusing on costs associated with programmatic scale-up and resource consumption of each Scenario. Comparator Scenarios include both a business-as-usual projection, as well as a projection of disease burden in the absence of external funding support to the Province, while the major patient subgroups considered are 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 be considered, other recent modelling of DOTS-expansion in South Fly have found such interventions to be among the “best buys” for health in developing countries.(47) Our analysis aims to consider all health system costs accrued through programmatic scale up, but does 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 and a reduction in inpatient stay under short course MDR-TB regimens to two months. This arbitrary alternative nightly bed cost was considered as this unit cost contributed 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 to shift treatment towards a community model and reductions in bed costs could be in reducing overall costs.

Our modelling predicts that the high burden of TB and the large contribution of MDR-TB to incidence in Western Province are unlikely to improve with current, DOTS-based programmatic responses. Only Province-wide 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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This article contains supporting information.

**ABBREVIATIONS**

BCG, Bacille Calmette-Guérin

DOTS, directly-observed treatment, short-course

DS-TB, drug susceptible tuberculosis

MCH, maternal and child health

MDR-TB, multidrug-resistant tuberculosis

PMDT, programmatic management of multidrug-resistant tuberculosis

PNG, Papua New Guinea

TB, tuberculosis

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**Table 1. Epidemiological values used to calculate model parameters in Western Province, Papua New Guinea.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Epidemiological value** | **Value** | **Uncertainty range**a | **Source** |
| Smear-positive pulmonary, % | 40 | (25 – 55) | (48) |
| Effective contact rate (β), per year infectious | 25 | (5 – 45) | b |
| MDR-TB emergence, calendar year | 1980 | (1965 – 1995) | c |
| BCG coverage, % | 65 | (45 – 85) | (49, 50) |
| Case detection rate, % | 70 | (50 – 90) | (2, 48) |
| Default North Fly, % per 6-month treatment periodd | 15 | (5 – 25) | (8) |
| Default Middle Fly, % per 6-month treatment periodd | 20 | (7 – 33) | (8) |
| Default South Fly, % per 6-month treatment periodd | 10 | (3 – 17) | (8) |
| Relative fitness MDR-TB | 0.7 | (0.4 – 1.0) | (15) |
| Early progression proportion, % | 12.9 |  | (51) |
| Time in early latency, months | 23 |  | (51) |
| Late progression rate, % per year | 0.375 |  | (52) |
| Birth rate, per thousand population | 29 |  | (1) |
| Life expectancy, years | 61.5 |  | (1) |
| Average treatment duration DS-TB, months | 6 |  | (25) |
| Average treatment duration MDR-TB, months | 24e |  | (25) |
| Partial immunity multiplier | 0.49 |  | (53) |
| Untreated disease duration, years | 3 |  | (54) |
| Untreated case fatality, smear-positive TB, % | 70 |  | (54) |
| Untreated case fatality, smear-negative and extrapulmonary TB, % | 20 |  | (54) |
| Relative infectiousness of smear-negative TB | 0.24 |  | (55) |
| Relative infectiousness of extrapulmonary TB | 0 |  |  |
| Relative infectiousness of treated cases DS-TB | 0.02 |  | (56, 57) |
| Relative infectiousness of treated cases MDR-TB | 0.18 |  | (56, 57) |
| Relative mortality of treated cases | 0.5 |  | (58, 59) |
| Amplification rate to MDR-TB, % | 3.5 |  | (60) |
| MDR-TB, multidrug resistant tuberculosis; DS-TB, drug susceptible tuberculosis.  aUncertainty ranges are presented for the first nine parameters, which are varied throughout the baseline period according to the Metropolis algorithm described.  bThe main epidemiological calibration parameter. Allowed to vary over broad range along with other variable parameters to achieve target incidence.  cConsistent with historical understanding of emergence of MDR-TB in the Province.  dThe ratio of these three variables to one another remains fixed, with the three variables varied together under uncertainty analysis.  eFor 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 (1, 2, 3 and 5).(26) | | | |

**Table 2. Summary of scenarios implemented for Western Province, Papua New Guinea from 2013 to 2023.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **DOTS-based care** | **Case detection** | **Default rates** | **BCG coverage** | **PMDT in South Fly** | **PMDT in North and Middle Fly** | **Average treatment duration for MDR-TB** |
| **Scenario 1** | Passive case finding plus single GeneXpert in South Fly | Small increase (around 3%) | Unchanged from baseline | Unchanged from baseline | Pilot program for 80 patients | Nil | 24 months |
| **Scenario 2** | Major expansion | Missed cases reduced by 60% | Halved | Increased by 10% | Comprehensive | Pilot program for 40 patients in each district | 24 months |
| **Scenario 3** | Major expansion | Missed cases reduced by 60% | Halved | Increased by 10% | Comprehensive | Comprehensive | 24 months |
| **Scenario 4** | Major expansion | Missed cases reduced by 60% | Halved | Increased by 10% | Comprehensive | Comprehensive | 10 months |
| **Scenario 5** | Unchanged from baseline | Unchanged from baseline | Unchanged from baseline | Unchanged from baseline | Nil | Nil | 24 months |

Scenarios are described in full in Web Table 2. BCG, Bacille Calmette-Guérin; DOTS, directly observed treatment, short-course; MDR-TB, multidrug-resistant tuberculosis; PMDT, programmatic management of drug-resistant tuberculosis.

**Table 3. Outcomes by modelled in Western Province, Papua New Guinea at 2023 or over the intervention period (2013 to 2023).**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Scenario 1** | | **Scenario 2** | | **Scenario 3** | | **Scenario 4** | | **Scenario 5** | |
|  | **Median** | **Range** | **Median** | **Range** | **Median** | **Range** | **Median** | **Range** | **Median** | **Range** |
| Total incidence, per 100,000 per year | 555 | (420-807) | 353 | (246-558) | 233 | (198-269) | 233 | (200-268) | 638 | (496-883) |
| DS-TB incidence, per 100,000 per year | 355 | (243-476) | 189 | (140-243) | 199 | (155-246) | 199 | (156-246) | 409 | (281-550) |
| MDR-TB incidence,a per 100,000 per year | 195 | (13-531) | 164 | (24-401) | 32 | (6-71) | 33 | (6-69) | 223 | (33-560) |
| North Fly total incidence, per 100,000 per year | 574 | (436-829) | 402 | (270-658) | 263 | (224-308) | 264 | (224-307) | 637 | (496-882) |
| Middle Fly total incidence, per 100,000 per year | 585 | (444-842) | 373 | (234-639) | 204 | (166-241) | 209 | (178-242) | 658 | (515-904) |
| South Fly total incidence, per 100,000 per year | 496 | (370-740) | 270 | (222-350) | 227 | (193-260) | 223 | (190-256) | 617 | (476-861) |
| Total prevalence, per 100,000 | 931 | (601-1518) | 517 | (233-998) | 207 | (150-277) | 171 | (130-218) | 1122 | (793-1676) |
| Mortality rate, per 100,000 per year | 117 | (67-197) | 61 | (23-123) | 16 | (10-24) | 15 | (9-22) | 143 | (93-219) |
| Proportion latently infected, % | 54 | (48-60) | 49 | (44-54) | 46 | (41-50) | 46 | (41-50) | 56 | (50-62) |
| Cumulative 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 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) |
| DS-TB treatment commencements, thousands | 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 treatment commencements | 400 | (400-400) | 590 | (115-1275) | 964 | (271-2125) | 1262 | (298-2588) | 0 | (0-0) |
| DS-TB treatment time, thousand patient months | 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 treatment time, thousand patient months | 2.9 | (2.4-3.4) | 6.2 | (1.3-13.1) | 2.1 | (0.5-4.4) | 1.1 | (2.8-21.7) | 0 | (0-0) |
| Maximum hospital beds required | 37 | (29-45) | 56 | (36-79) | 80 | (46-139) | 156 | (68-307) | 29 | (22-36) |
| DS-TB drug regimen costs, thousand Kina | 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 Kina | 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) |
| Hospitalisation costs, million Kina | 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,b thousand Kina | 0 |  | 1915 |  | 2065 |  | 2065 |  | 0 |  |
| Total costs, million Kina | 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) |
| All values are 50th centile of scenario outcomes (2.5th centile – 97.5th centile). Disease burden outcomes are the Province-wide rates observed on 1st January 2023. Cumulative cases, deaths, treatment commencements, months under treatment, drug regimen costs and hospitalisation costs are the cumulative values over the period 1st January 2013 to 31st December 2022. Maximum hospital beds required specifies the highest number of patients simultaneously requiring inpatient treatment at any point in time during the intervention period.  DS-TB, drug-susceptible tuberculosis; MDR-TB, multidrug-resistant tuberculosis.  aAbsolute incidence, as opposed to proportion presented in output figures.  bProgram costs are fixed costs for program scale-up that are unaffected by disease burden and so are not presented with uncertainty ranges. | | | | | | | | | | |

**Figure title and legend**

**Figure 1.** TB burden under the five modelled scenarios, with uncertainty ranges.

Columns of panels represent Scenarios 1 to 5 from left to right, that is 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; Scenario 5, panels E, J, O and T. Rows of panels from top to bottom are incidence (panels A, B, C, D and E), proportion of incidence attributable to MDR-TB (panels F, G, H, I and J), disease-specific mortality rate (panels K, L, M, N and O) and incidence rate by district (P, Q, R, S and T). 10,000 model runs were performed, with Bayesian variation to baseline parameters as described. For each accepted parameter set, outputs are generated for the intervention period (2013-2023) for each scenario. For panels A to O, lower dashed lines indicate the 2.5th centile of model runs, solid line (or dotted white line for mortality) indicates the 50th centile of model runs, upper dashed lines 97.5th centile of model runs and shading is proportional to density of model outputs. Vertical bars with central dots indicate uncertainty ranges of outputs. For lower row of panels, the 50th centile of model runs for each district is presented; districts are magenta, North Fly; green, Middle Fly; orange, South Fly.