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Assessing the transmission risk of multidrug-resistant *Mycobacterium tuberculosis* epidemics in regions of Taiwan

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SUMMARY

Objective: The objective of this study was to link transmission dynamics with a probabilistic risk model to provide a mechanistically explicit assessment for estimating the multidrug-resistant tuberculosis (MDR TB) infection risk in regions of Taiwan.
Methods: A relative fitness (*RF*)-based MDR TB model was used to describe transmission, validated with disease data for the period 2006–2010. A dose–response model quantifying by basic reproduction number (R_0) and total proportion of infected population was constructed to estimate the site-specific MDR TB infection risk.
Results: We found that the incidence rate of MDR TB was highest in Hwalien County (4.91 per 100 000 population) in eastern Taiwan, with drug-sensitive and multidrug-resistant R_0 estimates of 0.89 (95% CI 0.23–2.17) and 0.38 (95% CI 0.05–1.30), respectively. The predictions were in apparent agreement with observed data in the 95% credible intervals. Our simulation showed that the incidence of MDR TB will be falling by 2013–2016. Our results indicated that the selected regions of Taiwan had only ~1% probability of exceeding 50% of the population with infection attributed to MDR TB.
Conclusions: Our study found that the ongoing control programs implemented in Taiwan may succeed in curing most patients with MDR TB and will reduce the TB incidence countrywide.

1. Introduction

A recent World Health Organization (WHO) report documented that approximately one-third of the human population is infected with *Mycobacterium tuberculosis*, with 8.8 million new cases and 1.1 million deaths in 2010, and that the bacterium is becoming increasingly resistant to antibiotic therapy.[1] Therefore, tuberculosis (TB) remains a leading cause of death and results in high morbidity and mortality worldwide.[1] On the basis of these statistics, TB is among the top 10 causes of death worldwide. Despite predictions of a decline in global incidence, the number of new cases continues to grow.

The emergence of strains resistant to multiple drugs has led to situations where treatment is no better than before the discovery of antibiotics.[2] The diagnosis of TB remains a major barrier to the control of the disease, because the standard method – the acid-fast smear using sputum – does not become positive until a few months after transmission has occurred.[3] Culture-based techniques are more sensitive, but still take weeks before providing results.[4]

Multidrug-resistant tuberculosis (MDR TB) has been documented in 114 countries and regions worldwide and has emerged as a global public health problem.[5] MDR TB is caused by strains resistant to at least isoniazid and rifampin, the two principal first-line drugs used in combination chemotherapy.[6] The treatment of MDR TB patients requires the use of second-line drugs for at least 24 months.[7] Thus, MDR TB is increasingly becoming a serious threat to TB control, and the recognition of extensively drug-resistant TB (XDR TB) has further highlighted this threat.[8]

Over 50% of global TB cases are found in Southeast Asia and the Western Pacific. In Taiwan, an estimated 149–164 new MDR TB cases emerged in the period 2007–2010.[9] Although MDR TB represents only 1.2% of total new TB cases in Taiwan, controlling MDR TB is challenging because it is difficult to diagnose and treat.

The simplest mathematical model for modeling MDR TB epidemics is that of Blower et al.[10] Over the past two decades, many expanded and sophisticated models have been used to predict the future burden of MDR TB.[2,11–15] In view of these models, it is recognized that the assumptions about the relative fitness (*RF*) of drug-resistant (DR) strains play a crucial role in describing drug resistance dynamics.[16,17] Moreover, accurate estimates of the underlying parameters such as detection rates and treatment success rates are of critical importance for predicting the spread of MDR TB.[2]

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The transmission and population dynamics of MDR TB in the regions of Taiwan are poorly understood. To examine the MDR TB population dynamics and potential risk of infection in the Taiwan epidemic, a well-established mathematical model of MDR TB transmission built on previous MDR TB models[2,11–15] was adopted to study the potential impact of MDR TB transmission. Although many excellent models for the transmission of MDR TB have been produced, an integrative, mechanistically explicit assessment on a regional scale for estimating the MDR TB infection risk is urgently needed.

Given the importance of this question with regard to a large percentage of MDR TB cases that have resulted from recent transmission, we sought to extend previously published models of MDR TB transmission dynamics to incorporate a disease risk model. Therefore, a probabilistic risk assessment model linked with the MDR TB transmission model was developed to estimate MDR TB infection risks and to assess the potential impact of control measures on the emergence of a new DR strain in the regions of Taiwan.

2. Materials and methods

2.1. Study data

Monthly data on the disease burden of TB in Taiwan were obtained from the Centers for Disease Control of Taiwan (Taiwan CDC) for the period 2005–2008 (http://www.cdc.gov.tw/). The incidence rate, morality rate, relapse proportion, reinfection proportion, and reactivation proportion were estimated based on Taiwan CDC TB data for each county (http://www.cdc.gov.tw/). In this study counties were geographically designated to four areas: northern, central, southern, and eastern regions. We found that the incidence rates were highest in Pingtung County in the southern region of Taiwan (108 per 100 000 population) and Hwalien (124 per 100 000 population) and Taitung (104 per 100 000 population) counties in the eastern region of Taiwan. Taipei City in the northern region of Taiwan had the lowest average incidence rate (50 per 100 000 population). Therefore, we used the TB epidemic data of Taipei City and Pingtung, Hwalien, and Taitung counties to investigate the MDR TB transmission dynamics and infection risk. Furthermore, the annual disease burden of MDR TB was adopted from the Taiwan Tuberculosis Control Report[18] and the Taiwan CDC national notifiable disease surveillance system[9] for each year during the period 2006–2010 to estimate the MDR TB incidence rates.

To model drug resistance dynamics, data on the *RF* of DR strains had to be determined. One of the methods to measure the *RF* of resistant strains is based on the results of genotype clustering studies, with a cluster defined as two or more cases having the same genetic fingerprint.[6] Based on the genotype clustering method, *RF* can be estimated by calculating the odds ratio as $RF = (C_R/N_R)/(C_S/N_S)$ where C_R, C_S, N_R, and N_S are the numbers of resistant (R) and sensitive (S) cases that appear singly (N) or in clusters (C).[6]

García-García et al.,[19] recently provided valuable data that can be used to estimate the *RF* of MDR TB that is resistant to isoniazid and rifampin. Briefly, García-García et al.[19] grouped TB patients with identical DNA fingerprints into clusters, with a cluster presumed to be epidemiologically linked. Twenty clusters were identified and investigated. They also excluded the possibility that resistance had been acquired since transmission by testing patients for drug susceptibility before treatment. Thus, a single cluster could only include sensitive or resistant strains.

They found that the overall rate of resistance was 28.4%, with 10.8% having MDR TB. Based on genotype clustering analysis with multivariate risk factors associated with clustering, the odds ratio of MDR TB was estimated to be 0.16 (95% confidence interval (CI) 0.04–0.6). Based on this result, an optimal fitting technique was used to obtain a best-fitted distribution to capture the uncertainty. Their results indicated that drug resistance was a strong independent risk factor for treatment failure. They thus concluded that patients with DR TB had a dramatically increased probability of treatment failure and death.

2.2. Resistant TB transmission model

Previously developed DR TB transmission models[2,10,11,13,14] were adopted and modified to describe the population dynamics of MDR TB in Taiwan. The present model captures the five group dynamics of susceptible (S), latently infected with drug-sensitive (DS) TB (L_S), latently infected with MDR TB (L_R), DS infectious TB (T_S), and MDR infectious TB (T_R) and can be referred to as the two-strain TB model. The essential features of the present model are depicted in Figure 1.

Briefly, (1) susceptible individuals may be infected with either DS or MDR strains, (2) two types of TB are included – primary progressive TB (i.e., fast TB) and latently infected TB caused by endogenous reactivation or exogenous reinfection (i.e., slow TB), (3) a case may be spontaneously cured at a cure rate and move into the latent noninfection state, and (4) MDR TB may emerge when individuals are primary infected/reinfected with an MDR strain (i.e., primary resistance) or as a result of treatment failure (i.e., acquired resistance). Table 1 lists the system of ordinary differential equations with detailed explanations of the symbols for the two-strain TB model in Figure 1.

The expressions for the basic reproduction number (R_0),[14,20] quantifying the transmission potential of *M. tuberculosis* due to the subepidemic driven by DS TB (R_{0S}) and MDR TB (R_{0R}), are summarized in Table 1. R_0 is defined as the average number of successful secondary infection cases generated by a typical primary infected case in an entirely susceptible population.[21] When $R_0 > 1$ it implies that the epidemic is spreading within a population and the incidence is increasing, whereas $R_0 < 1$ means that the disease is dying out. An average R_0 of 1 means the disease is in endemic equilibrium within the population. R_0 essentially determines the rate of spread of an epidemic and how intensive a policy will need to be to control the epidemic.[22]

2.3. Probabilistic DS/MDR TB risk model

To develop a probabilistic DS/MDR TB risk model, a dose–response model describing the relationships of the transmission

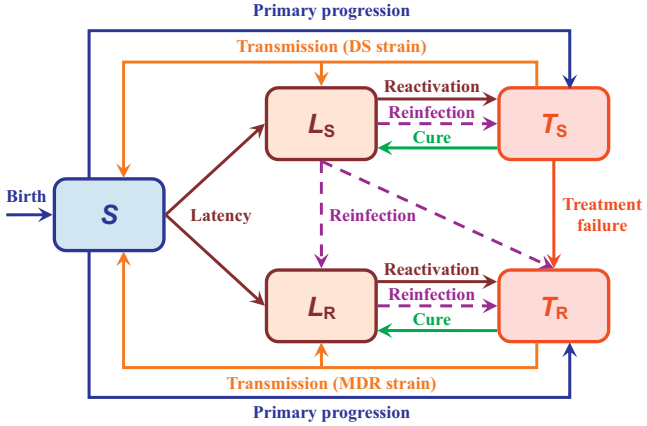

Figure 1. Drug-sensitive and drug-resistant two-strain TB model describing MDR TB population transmission dynamics in the present study.

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Table 1
Equations for the proposed two-strain TB model

Equation[a]		Meaning
Two-strain TB model[b]		
$\dot{S}(t) = \pi - (\beta_S T_S + \beta_R T_R + \mu)S$	(T1)	Susceptible individuals
$\dot{L}_S(t) = (1-p)\beta_S T_S S + c_S T_S - (\nu + p\sigma\beta_S T_S + \sigma\beta_R T_R + \mu)L_S$	(T2)	Latently infected individuals with DS TB
$\dot{L}_R(t) = (1-p)\beta_R T_R S + (1-p)\sigma\beta_R T_R L_S + c_R T_R - (\nu + p\sigma\beta_S T_S + p\sigma\beta_R T_R + \mu)L_R$	(T3)	Latently infected individuals with MDR TB
$\dot{T}_S(t) = p\beta_S T_S S + (\nu + p\sigma\beta_S T_S)L_S - (c_S + \mu + \mu_S + (1-c_S)c_F)T_S$	(T4)	DS infectious TB
$\dot{T}_R(t) = p\beta_R T_R S + p\sigma\beta_R T_R L_S + (\nu + p\sigma\beta_S T_S + p\sigma\beta_R T_R)L_R + (1-c_S)c_F T_S - (c_R + \mu + \mu_R)T_R$	(T5)	MDR infectious TB
Basic reproduction number		
$R_{0S} = \frac{\beta_S N p(\mu+\nu)}{(\mu+\nu)(\mu+\mu_S+c_S+(1-c_S)c_F)-c_S\nu}$	(T6)	Basic reproduction number of DS TB
$R_{0R} = \frac{\beta_R N p(\mu+\nu)}{(\mu+\nu)(\mu+\mu_R+c_R)-c_R\nu}$	(T7)	Basic reproduction number of MDR TB

TB, tuberculosis; DS, drug-sensitive; MDR, multidrug-resistant.
[a] Symbols: $\pi = N\delta$ is the recruitment rate (per person-year) where δ is the birth rate (per year) and N is the total population size; p is the probability of new infections that develop progressive primary active TB within 1 year; ν is the progression rate from latency to active TB (per year); μ is the background mortality rate (per year); μ_S is the DS TB caused mortality rate (per year); μ_R is the MDR TB caused mortality rate (per year); σ is the factor reducing the risk of infection as a result of acquired immunity to a previous infection with sensitive and resistant TB; c_S is the cure rate of active DS TB (per year); c_R is the cure rate of active MDR TB (per year); c_F is the proportion of DS TB treatment failure acquiring resistance; *ECR* is the effective contact rate (per year); β_S is the transmission rate for DS TB (per person per year); β_R is the transmission rate for MDR TB (per person per year).
[b] See Figure 1.

potential of DS/DR *M. tuberculosis* quantifying by R_0 and the total proportion of infected population has to be constructed. Generally, the probability of infection for each susceptible person each day is based on the transmission probabilities for each potentially infected contact. According to Anderson and May,[21] in a homogeneous and unstructured population, the total proportion of infected population during the epidemic (I) depends only on R_0, and can theoretically be expressed as,

$$I = 1 - \exp(-R_0 I) \quad (1)$$

Equation 1 cannot be solved analytically. Thus, we solved Equation 1 numerically using a nonlinear regression model to best-fit the profile describing the relationship between I and R_0[21] for R_0 ranging from 1 to 5. Finally, I can be expressed as a function of R_0 only,

$$I(R_0) = 1 - \exp(1.63 - 1.66R_0),\ 1 < R_0 < 5,\ r^2 = 0.99 \quad (2)$$

Equation 2 can be seen as a conditional response distribution describing the dose–response relationship between I and R_0 and can be expressed as: $P(I|R_0)$. Thus, followed by Bayesian inference, the DS/DR TB infection risk (the posterior probability) can be calculated as the product of the probability distribution of R_0 (the prior probability) and the conditional response probability of the proportion of the population expected to be infected, given R_0 (the likelihood $P(I|R_0)$). This results in a joint probability distribution or a risk profile. This can be expressed mathematically as,

$$R(I) = P(R_0) \times P(I|R_0), \quad (3)$$

where $R(I)$ is the cumulative distribution function (cdf) describing the probabilistic infection risk of a TB epidemic in a susceptible population at specific R_0, and $P(R_0)$ is the probability density function (pdf) of R_0. The exceedance risk profile can be obtained by $1 - R(I)$. Each point on the exceedance risk curve represents both the probability that the total proportion will be infected and also the frequency with which that level of infection would be exceeded. The x-axis of the exceedance risk curve can be interpreted as a magnitude of effect (total proportion of infection), and the y-axis can be interpreted as the probability that an effect of at least that magnitude will occur.

2.4. Model parameterization and validation

The likely values of key parameters in the two-strain TB model (Table 1, equations T1–T5) can be parameterized based on available site-specific TB data provided by the Taiwan CDC, Department of Statistics, Ministry of the Interior, Taiwan,[23] and otherwise based on data adopted from the literature.[24–28] We used the model to project future site-specific TB incidence dynamics for 2006–2016 with the 95% credible interval.

We validated the two-strain TB model by comparing predicted site-specific MDR TB incidence with observed MDR TB incidence provided by the Taiwan CDC for 2006–2010. To compare modeled and observed results, the best fit was evaluated using the root mean squared error (RMSE), computed from RMSE = $\sqrt{\sum_{n=1}^{N}(I_{o,n} - I_{s,n})^2/N}$ where N denotes the number of observations, $I_{o,n}$ is the observed incidence, and $I_{s,n}$ is the simulation result corresponding to data point n.

2.5. Sensitivity and uncertainty analyses

A sensitivity analysis was performed to examine the influence of critical variables on the basic reproduction number. TableCurve 2D package (AISN Software Inc., Mapleton, OR, USA) and Statistica (version 9; Statsoft, Inc., Tulsa, OK, USA) were used to perform model fitting techniques and statistical analyses. A Monte Carlo (MC) technique was implemented to quantify the uncertainty and its impact on the estimation of expected risk. An MC simulation was also performed with 10 000 iterations to generate the 2.5 and 97.5 percentiles as the 95% CI for all fitted models. Crystal Ball software (Version 2000.2, Decisioneering, Inc., Denver, CO, USA) was employed to implement the MC simulation. Model simulations were performed using Berkeley Madonna 8.0.1 (Berkeley Madonna was developed by Robert Macey and George Oster of the University of California at Berkeley).

Figure 2 illustrates the overall computational algorithm of this study.

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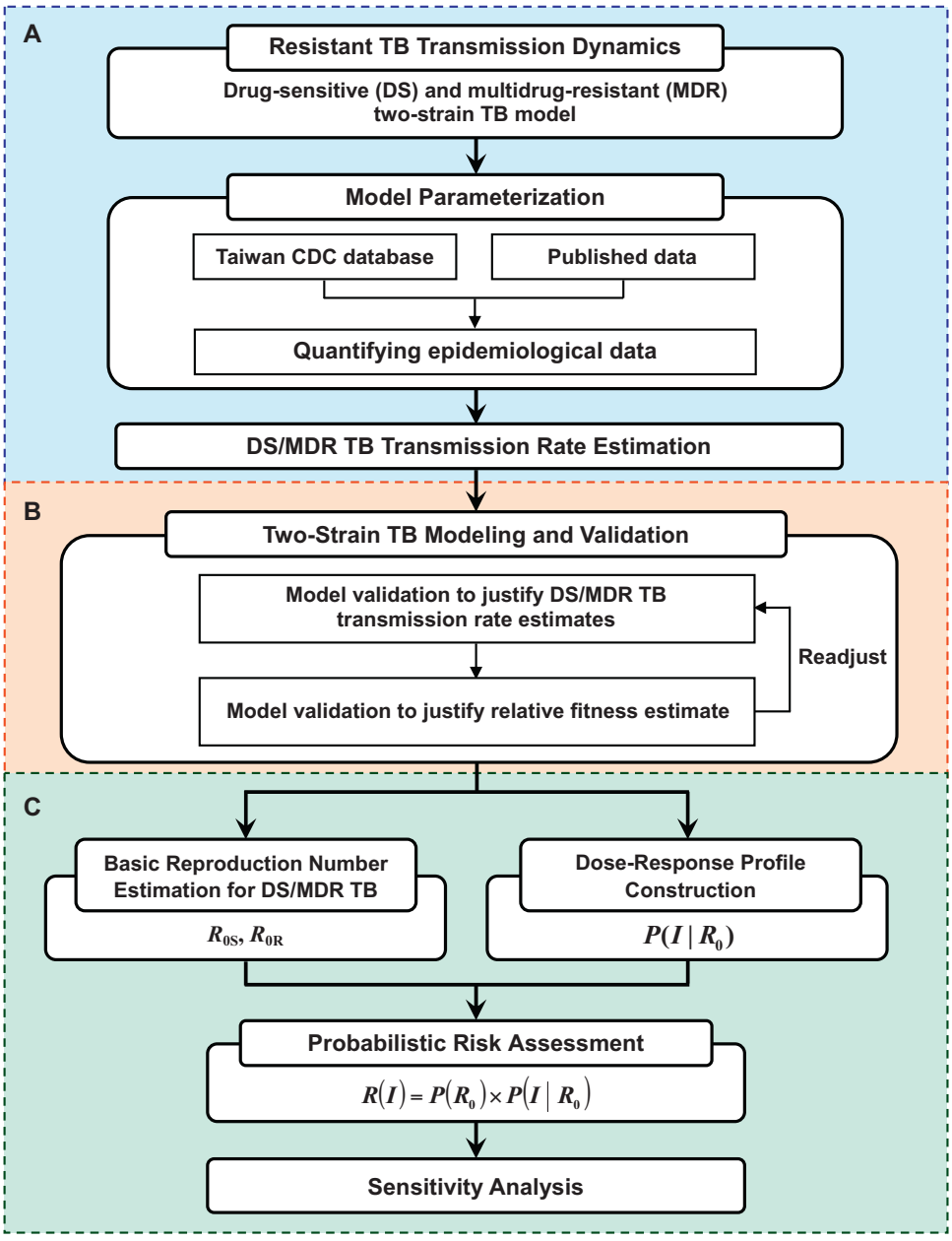

Figure 2. Schematic representation of the principal algorithms and approach methodology used in this study.

3. Results

3.1. Population dynamics of DS/MDR TB

Table 2 summarizes the estimates of the MDR TB incidence rate for Hwalien, Taitung, and Pingtung counties and Taipei City in the period 2006–2010. We found that the incidence rate of MDR TB was highest in Hwalien County (4.91 per 100 000 population). Taipei City had the lowest average MDR TB incidence rate of 0.43 per 100 000 population.

The results of the model parameterization are listed in Table 3. Published data[19] were optimal-fitted to obtain the likelihood distribution of *RF* by MC simulation. This resulted in a normal (N) distribution of *RF* with a mean of 0.32 and standard deviation (SD) of 0.14 (Table 3). We incorporated the estimated probability distributions of the model parameter with site-specific initial population sizes (Table 3) into the two-strain TB model (Table 1, equations T1–T5) to project future site-specific population dynamics of MDR TB incidence for 2006–2016 (Figures 3 and 4).

Figure 3A–D demonstrates the comparison of the MDR TB incidence rates between predictions adjusted by β_S and β_R estimates of the 25th, 50th, and 75th percentiles. The results indicated that the predictions with the 50th percentile were consistent with the observed data in Taipei City (Figure 3A), whereas for Pingtung and Taitung Counties, the predictions with the 25th percentile were in a good agreement with the observations (Figure 3C and D) for the period 2007–2010. However, the observed MDR TB incidence in Hwalien County showed a decreasing trend of predictions that was fairly consistent with the 50th percentile data points (Figure 3B). Thus, we modeled based on the justified β_S estimate of the 25th percentile for Pingtung and Taitung counties and the 50th percentile for Hwalien County and Taipei City, varying with different *RF* values to further validate the model against the justified *RF* estimate (Figure 4).

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Table 2
MDR TB incidence rates (per 100 000 population) during 2006–2010[a]

Sites	2006	2007	2008	2009	2010	Average[b]
Hwalien County	8.66	4.63	2.14	4.99	4.12	4.91 ± 2.37
Taitung County	5.85	2.94	1.87	1.29	2.16	2.82 ± 1.79
Pingtung County	1.33	1.26	0.99	0.57	0.68	0.97 ± 0.34
Taipei City	0.62	0.36	0.46	0.38	0.35	0.43 ± 0.11

MDR TB, multidrug-resistant tuberculosis.
[a] Incidence rate (per 100 000 population): annual region confirmed MDR TB cases/total regional population number. Adopted from the Taiwan tuberculosis control report[18] and Taiwan CDC national notifiable disease surveillance system.[9]
[b] Mean ± standard deviation.

Figure 4A–D shows the comparison of the MDR TB incidence data with our *RF*-adjusted model simulation outcomes with 95% credible intervals, indicating that the predictions were in apparent agreement with the observed data during the period 2007–2010. The model was also extended to project the MDR TB incidence rate for the period 2011–2016. Despite the simplicity of the model, we found a fair quantitative agreement between model predictions and observed data (the average RMSE ranging from 0.11 to 1.58, comparable to the data average standard deviation of 0.11–2.37). Our model had the lowest RMSE values for the predictions with the 75th (RMSE = 1.10), 50th (RMSE = 0.50), 50th (RMSE = 0.16), and 50th percentiles (RMSE = 0.05) in Hwalien, Taitung, and Pingtung counties and Taipei City, respectively, indicating that all RMSE values are less than the standard deviation of the observed data (Figure 4 and Table 2). Overall, the model captures the transmission and population dynamics of MDR TB in high TB incidence areas in Taiwan for the period 2007–2010.

3.2. DS/MDR TB infection risk estimates

To estimate the probability of DS/MDR TB infection risk, the transmission potential quantified by basic reproduction number (R_{0S} and R_{0R}) had to be determined. The site-specific R_{0S} and R_{0R} due to a subepidemic driven by primary progression, reactivation/reinfection, and cure were calculated based on equations listed in Table 1 (equations T6 and T7) (Figure 5). The MC simulation result showed that the optimized log-normal distribution was the most suitable fitted model for R_{0S} and R_{0R}. We found that, for instance, in the highest TB epidemic area of Hwalien County, the R_{0S} and R_{0R} estimates were 0.89 (95% CI 0.23–2.17) and 0.38 (95% CI 0.05–1.30), respectively, whereas R_{0S} and R_{0R} values were estimated to be 0.94 (95% CI 0.24–2.28) and 0.38 (95% CI 0.05–1.33), respectively, in Taitung County. The R_{0S} and R_{0R} estimates in Pingtung County were 0.85 (95% CI 0.21–2.08) and 0.34 (95% CI 0.04–1.13), respectively, whereas Taipei City had the lowest values with R_{0S} and R_{0R} estimates of 0.84 (95% CI 0.21–2.00) and 0.30 (95% CI 0.04–0.97), respectively.

Figure 6A demonstrates the conditional dose–response profile of $P(I|R_0)$ based on Equation 2. Given the site-specific R_{0S} and R_{0R} distributions (Figure 5) and conditional dose–response relationship $P(I|R_0)$ (Figure 6A), the site-specific exceedance risk probability of DS/MDR TB infection can then be estimated by Equation 3 (Figure 6B and C). We found that the total DS TB incidences in

Table 3
Probability distributions (N = normal, LN = log-normal) of parameter values and initial population sizes used in the two-strain TB model, and basic reproduction number (R_0) estimations[a]

	Probability distribution			
	Hwalien County	Taitung County	Pingtung County	Taipei City
Model parameter				
p[b]	N (0.08, 0.03)			
ν (per year)[c]	N (0.00392, 0.0007)			
μ (per year)[d]	LN (0.031, 2.05)	LN (0.031, 2.05)	LN (0.030, 2.11)	LN (0.027, 2.00)
μ_S (per year)[e]	N (0.037, 0.015)	N (0.040, 0.019)	N (0.052, 0.021)	N (0.033, 0.013)
μ_R (per year)[f]	N (0.30, 0.05)			
c_S (per year)[e]	N (0.64, 0.07)	N (0.61, 0.08)	N (0.68, 0.09)	N (0.72, 0.01)
c_R (per year)[f]	LN (0.10, 2.68)	LN (0.08, 2.83)	LN (0.18, 1.89)	LN (0.28, 1.41)
c_F[e]	N (0.034, 0.018)	N (0.024, 0.022)	N (0.017, 0.007)	N (0.016, 0.005)
ECR (per year)[c]	LN (7.40, 1.33)			
N (person)[d]	N (345 297, 2748)	N (236 156, 3174)	N (893 289, 5625)	N (2 625 962, 8435)
π (per person year)	2960	2228	7284	21217
RF[g]	N (0.32, 0.14)			
σ[h]	0.25			
β_S (per person per year)[i]	LN (2.14×10^{-5}, 1.33)	LN (3.13×10^{-5}, 1.33)	LN (8.28×10^{-6}, 1.33)	LN (2.82×10^{-6}, 1.33)
β_R (per person per year)[j]	LN (6.11×10^{-6}, 1.91)	LN (8.93×10^{-6}, 1.91)	LN (2.36×10^{-6}, 1.91)	LN (8.03×10^{-7}, 1.91)
Initial population size[k]				
N	346 301	237 450	893 529	2 624 309
S	344 338	236 153	888 554	2 612 793
L_S	1262	865	3241	9561
L_R	13	9	33	97
T_S	659	409	1690	1843
T_R	30	14	12	16

TB, tuberculosis.
[a] See Table 1 for symbol meanings.
[b] Estimated as 0.04 (0.015–0.14) for <15 years old and 0.14 (0.08–0.25) for >15 years old.[24]
[c] *ECR* (effective contact rate) and ν are estimated based on Blower et al.[25]
[d] Estimated based on data from the Department of Statistics, Ministry of the Interior, Taiwan (http://www.moi.gov.tw/stat/index.aspx).[23]
[e] Estimated based on Taiwan CDC data (http://www.cdc.gov.tw/).
[f] Estimated based on Dye and Espinal.[26]
[g] *RF* is the relative fitness estimated based on García-García et al.[19]
[h] Adopted from Rodrigues et al.[14]
[i] $\beta_S = ECR/N$, where N is the total population size.[27]
[j] $\beta_R = RF \times \beta_S$.[11,13,14]
[k] The initial population sizes in 2006 of N, T_S, and T_R are adopted from the Taiwan Tuberculosis Control Report.[18] $S = N - L_S - L_R - T_S - T_R$. $L_S = 0.004 \times 0.92 \times 0.99 \times N$, and $L_R = 0.004 \times 0.92 \times 0.01 \times N$, where 0.004 is adopted from Yeh et al.,[28] $0.92 = (1 - 0.08)$,[24] and the proportions of infections that develop L_S (0.99) and L_R (0.01) are assumed.

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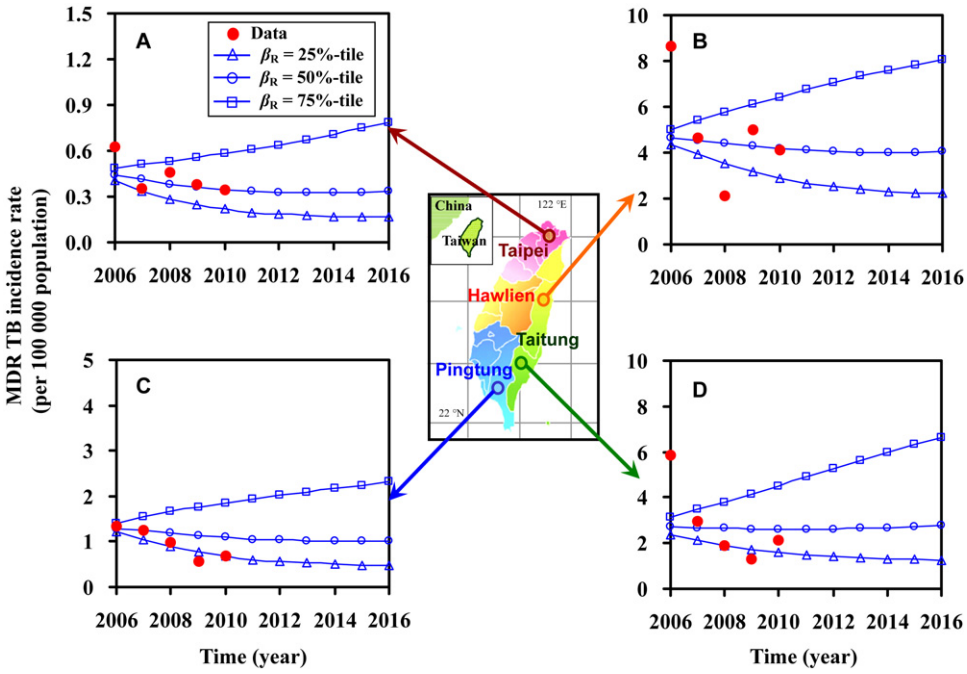

Figure 3. Modeling incidence rates (per 100 000 population) of MDR TB varying with different β_R estimates of 25th, 50th, and 75th percentiles during 2006–2016 by two-strain TB model and the comparison of incidence rates between predictions with β_S- and β_R-adjusted model simulation outcomes and observed data during 2006–2010 in (A) Taipei City, (B) Hwalien County, (C) Pingtung County, and (D) Taitung County.

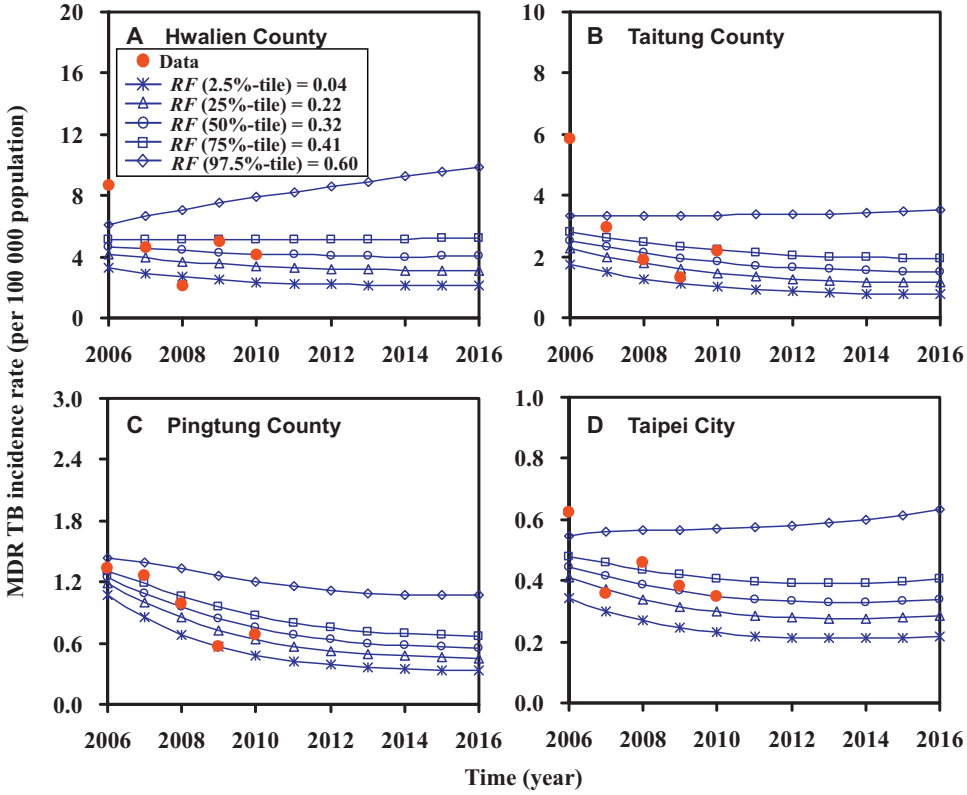

Figure 4. Incidence rates (per 100 000 population) of MDR TB estimates based on the justified β_S estimate varying with different *RF* values for 2006–2016 and the comparison of the incidence data with *RF*-adjusted model simulation outcomes with 95% credible intervals during 2006–2010 in (A) Hwalien County, (B) Taitung County, (C) Pingtung County, and (D) Taipei City.

Hwalien, Taitung, and Pingtung counties and Taipei City had respective probabilities of nearly 13%, 16%, 11%, and 9.7% for the total proportion of infected population exceeding 50%, whereas there were 18–27% probabilities of having exceeded 20% of the total proportion of infected population (Figure 6B). Our results also indicated that the selected four regions had only ~1% probability of exceeding 50% of the population with infection attributed to MDR TB (Figure 6C).

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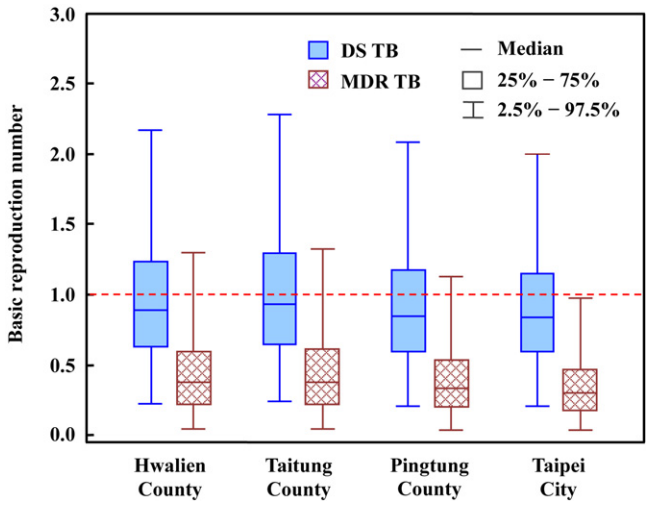

Figure 5. Box and whisker plot illustrating the basic reproduction number of DS TB (R_{0S}) and MDR TB (R_{0R}) in Hwalien, Taitung, and Pingtung counties and Taipei City.

3.3. Sensitivity analysis

Our sensitivity analysis indicated that an increase in R_{0R} was attributed mainly to: (1) relative fitness (*RF*), (2) the probability of new infections that develop progressive primary active TB within 1 year (p), and (3) the transmission rate for DS TB (β_S) (Table 4). However, an increase in the cure rate of active MDR TB (c_R) can decrease R_{0R} moderately.

In our four selected study areas, the most important input variables for R_{0R} appeared to be *RF* and p, which contributed to 40.51–44.35% and 30.63–32.70% of output variances, respectively (Table 4). Thus our results indicate that *RF* is the key parameter in shaping R_{0R}. Therefore, the rate of spread of an MDR TB epidemic could be controlled by reducing *RF*.

4. Discussion

4.1. Population dynamics of DR TB

Although it is recognized that exogenous reinfection plays an important role in DR TB epidemics,[12,13,29] several mathematical models to predict the future spread of DR TB have not taken it into consideration.[2,10,11] There are a few DR TB models that have considered reinfection,[12,13,29] but the implementations have varied significantly. Blower and Chou[29] and Dye and Williams[12] incorporated reinfection at a reduced rate by partial immunity applying to latently infected individuals only.

Table 4
Probabilistic sensitivity analysis for the basic reproduction number of MDR TB (R_{0R})

Input parameter[a]	Contribution (%)			
	Hwalien County	Taitung County	Pingtung County	Taipei City
RF	41.20%	40.51%	41.81%	44.35%
p	30.67%	31.98%	30.63%	32.70%
β_S	14.59%	14.07%	51.68%	15.45%
ν	0.00%	0.02%	0.02%	0.02%
N	0.00%	0.01%	0.00%	0.00%
μ	−1.18%	−0.80%	−1.34%	−1.34%
μ_R	−3.19%	−2.32%	−2.05%	−1.58%
c_R	−9.16%	−10.29%	−8.47%	−4.57%

MDR TB, multidrug-resistant tuberculosis.
[a] See Tables 1 and 2 for symbol meanings.

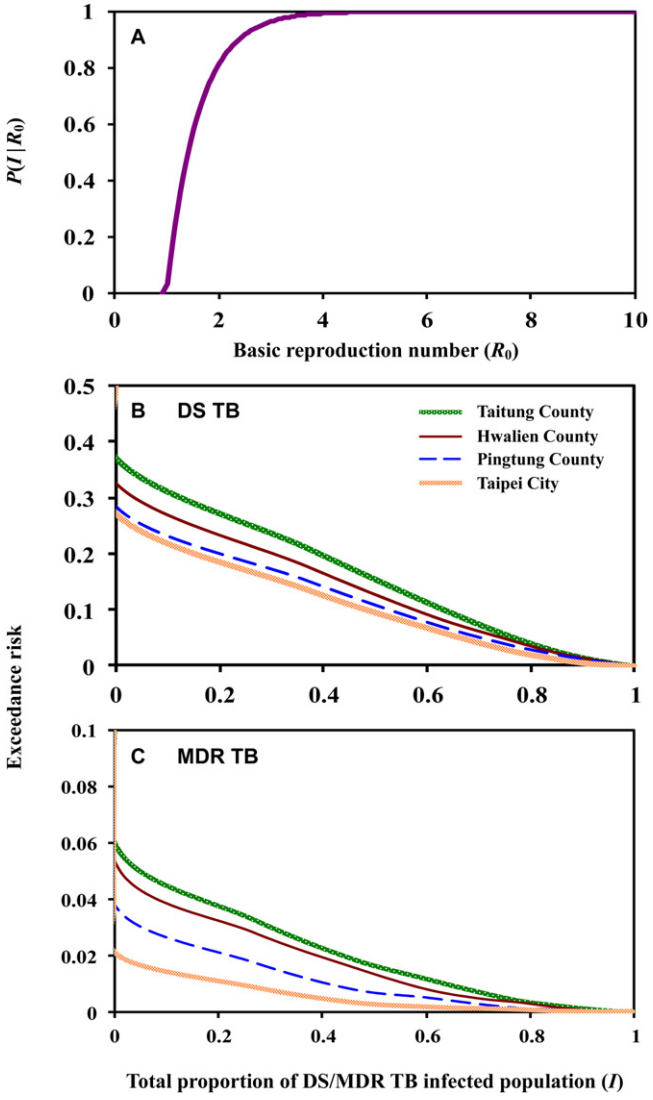

Figure 6. (A) Dose–response profile representing the estimate of the total proportion of TB-infected population, $P(I)$, based on R_0 estimated from Equation 2. Exceedance risks of the total proportions of TB infections estimated for (B) DS TB and (C) MDR TB in Hwalien, Taitung, and Pingtung counties and Taipei City.

Cohen and Murray[13] considered that latent and recovered individuals have partial immunity against reinfection and have identical susceptibilities to reinfection. Furthermore, several epidemiological studies have demonstrated that DR and MDR strains have heterogeneity in fitness.[6,16,17] Most models have indicated that *RF* is the most important parameter influencing the disease burden of DR and MDR TB. However, these did not directly estimate the impact of heterogeneity of *RF* for DR strains on transmission dynamics, especially for MDR strains.[10–12,14] A few studies have allowed for variation in *RF* of MDR strains to model the emergence of an MDR TB epidemic.[13,29]

We constructed a two-strain TB model based on the past well-developed DR TB transmission models that have incorporated reinfection, emergence of multidrug resistance during therapy, heterogeneity of *RF* of MDR strains, and competition between DS and MDR strains to describe the transmission and population dynamics of MDR TB in Taiwan.

Practically, our present model captures the transmission and population dynamics of MDR TB in high TB incidence areas of Taiwan for the period 2007–2010. Our study found that the incidence rate of MDR TB was highest in eastern Taiwan (4.91 per

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100 000 population) compared to the lowest average incidence of 0.43 per 100 000 population in northern Taiwan. Several studies have indicated that MDR TB is a major problem in the aboriginal population in eastern Taiwan.[30–32] However, the observed MDR TB incidence at our four study sites showed a decreasing trend due to improvements in TB control measures in Taiwan, in particular the implementation of the MDR TB program (Multi-Drug Resistant TB Medicare System) in 2007. Given the high frequency of MDR TB in eastern Taiwan, our simulation showed that the incidence of MDR TB will be falling by 2013–2016. Our results also indicated that there was only a ~1% probability of exceeding 50% of the population with infection attributed to MDR TB. Therefore, the annual decline in the incidence of MDR TB in Taiwan can be expected with good TB control programs.

Our results also showed that the basic reproduction number of MDR strains (R_{0R}) was lower than that of non-MDR strains (R_{0S}), indicating that the *RF* of MDR strains is less than 1. If we maintained this situation, the number of MDR strains could be decreased to the lower numbers generated by mutation. Our findings also implicitly provide information that the ongoing control programs implemented in Taiwan may succeed in curing most patients with MDR TB and reduce the TB incidence countrywide.

However, TB is a very complex disease and, in addition to host–pathogen parameters, one has to consider several socio-economic factors for modeling population dynamics of TB or DR TB.[3,15,33,34] Socio-economic factors such as the paucity of medical service resources, information barriers, financial difficulties, and the inconvenience of transportation could result in less effective TB control among aborigines in eastern Taiwan.[31]

It is also important to consider the immune system that is affected by co-infections, past therapeutic history, and age.[35] Recently, evidence has also indicated a strong association between smoking and TB. den Boon et al.[36] reported that more than 80% of current smokers or ex-smokers were positive for the TB skin test as compared to less than 3% of nonsmokers. Aborigines in the eastern Taiwan region are subpopulations with high smoking frequencies. We thus anticipate that future studies may include some of these parameters in the analysis to forecast the reduction in the incidence of TB or MDR TB.

4.2. Infection risk estimates of DS/MDR TB

Our results on R_0 estimates showed that R_{0S} was larger than R_{0R} at the four study sites. The persistence of both DS and DR TB (i.e., coexistence) occurs if $R_{0S} > 1$ and $R_{0S} > R_{0R}$. Under these conditions, the coexistence can even occur when $R_{0R} < 1$.[6,11] We also found that the incidence of DS TB in Hwalien, Taitung, and Pingtung counties and Taipei City had respective probabilities of nearly 13%, 16%, 11%, and 9.7% of the total proportion of infected population exceeding 50%, whereas there was only ~1% probability of having exceeded 50% of the population with infection attributed to MDR TB.

Although it appears unlikely that MDR TB will result in an emergence, the case reproduction numbers of DS TB are alarming from a conservative point of view. As long as patients carry sensitive strains, there will always be some relative MDR TB cases, due to MDR TB arising from treatment failure, mutation at some constant frequency, and the occasional transmission of MDR strains. However, in the worst case scenario, when the basic reproduction number of DR strains exceeds that of DS strains, resistant cases can out-compete sensitive cases and all patients will eventually carry resistant strains.

4.3. Limitations and implications

A key weakness of this approach is that in many cases the true uncertainty around key parameter values may not be captured adequately. It is difficult, if not impossible, to assess the validity of either the individual adjustment parameters or the final estimate, because, to our knowledge, well-established standard values for comparison do not exist. Our sensitivity analysis shows that *RF* is the key parameter influencing the basic reproduction number of MDR TB (R_{0R}). Several studies on the population dynamics of DR TB have shown *RF* to be a key determinant in assessing the future burden of DR TB[11] and MDR TB.[12,13,26] In the present study, the most unknown important parameter is *RF* of MDR strains as compared with DS strains.

We found a wide range of molecular epidemiological *RF* of MDR strain estimates.[6,16] The *RF* estimates for MDR TB ranged from an almost 10-fold higher fitness compared to DS strains in Russia, to a nearly 10-fold lower fitness in Mexico. The possible reasons for this high variability in *RF* of MDR strains are differences in study design and setting, differences in sample size, and different methodologies.[16] Although, there is a wide range of *RF*, several researchers[12,13,26] have used low *RF* for mathematical modeling of MDR TB. Dye and Williams[12] used a parameter value for *RF* of MDR strains ranging from 0.7 to 1.0. Dye and Espinal[26] modified their *RF* estimates for MDR strains to uniform distribution between 0.04 and 0.6 based on a TB cluster study.[19] Cohen and Murray[13] assumed that the 'unfit' MDR strains had a low fitness (0.3) relative to the DS strain, whereas the 'fit' MDR strain had *RF* ranging from 0.8 to 1.2.

García-García et al.[19] recently provided valuable data from a molecular epidemiology study in Mexico that can be used to estimate *RF* of MDR TB. The MDR TB incidence rate in Mexico in 2008 was estimated to be 0.6 (95% CI 0.3–0.9) per 100 000 population.[37] The average MDR TB incidence rate for Taiwan during 2007–2010 (0.7 per 100 000 population) provided by the Taiwan CDC was similar to that of Mexico. Thus, we estimated *RF* for MDR strains with a normal (N) distribution of a mean 0.32 and a standard deviation 0.14 based on García-García et al.[19] Epidemiological studies in Taiwan have demonstrated that MDR TB is attributed to acquired resistance rather than primary resistance.[30,38] Burgos et al.[39] estimated the relative secondary-case ratio of MDR TB to DS TB, indicating that there were no secondary cases associated with MDR strains. All of the above results indicate that MDR strains may have lower transmissibility than DS strains. Thus, MDR strains may have a low *RF* value.

The proposed two-strain TB model only implicitly accounts for the patterns of mixing among infectious cases and their contacts, and the risks of TB among those infected are constant through time. Styblo[40] assumed an average duration of infectiousness of 2 years, suggesting that on average each smear-positive case contacted 10 individuals per year. A more recent study carried out in the Netherlands found that the number of individuals contacted by each TB case had changed over time, declining from nearly 22 individuals contacted in 1900 to nearly 10 individuals contacted in 1950.[41] In a recent meta-analysis, Trunz et al.[42] used the available data from 11 countries and estimated the contact rate from the ratio of annual risk of infection/prevalence. There was a wide range of contact rates ranging from 3.1 to 13.2. Based on Blower et al.,[25] our estimated effective contact rate (*ECR*) of 7.40 (95% CI 4.20–13.23) is similar to that of Styblo,[40] Vynnycky and Fine,[41] and Trunz et al.[42]

In addition to *RF* and *ECR*, model parameters such as the cure rate of DS (c_S) and MDR TB (c_R) and treatment failure acquiring resistance (c_F) have also been proposed as important epidemiological factors.[11–13,26] The design of effective treatment programs will need to take into account both the magnitude of the *RF* and its future evolution via compensatory mutation.[2]

The practical implications of this study might be used for risk management. First, the quality of the local data allowed us a rare opportunity to generate data-driven models for MDR TB

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transmission dynamics. Dynamic models rooted in local data are important for providing clear recommendations for control strategies. Second, a theoretical understanding will improve our ability to interpret data variability. With limited information on site-specific parameters, numerical simulations can be undertaken for randomly selected parameter values in an attempt to discern typical behaviors. Models of the type described in this paper have largely been explored through simulation in terms of their predictive power. More data are needed to validate the model predictions.

In conclusion, the MDR TB transmission model incorporated with the quantitative risk assessment together with time trends in DS and DR TB cases in Taiwan can be used to predict the MDR TB infection risk potential. We suggest that an annual decline in MDR TB incidence in Taiwan can be anticipated from ongoing control programs. The models, data on trends in DS/DR TB cases, and model simulations used in this study can be applied to assess the efficacy of potential control strategies on the emergence of a new DR strain.

Conflict of interest: No conflict of interest to declare.

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