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A Probabilistic Transmission and Population Dynamic Model to Assess Tuberculosis Infection Risk

Chung-Min Liao,[1,*] Yi-Hsien Cheng,[1] Yi-Jun Lin,[1] Nan-Hung Hsieh,[1] Tang-Luen Huang,[1] Chia-Pin Chio,[1] Szu-Chieh Chen,[2,3] and Min-Pei Ling[4]

The purpose of this study was to examine tuberculosis (TB) population dynamics and to assess potential infection risk in Taiwan. A well-established mathematical model of TB transmission built on previous models was adopted to study the potential impact of TB transmission. A probabilistic risk model was also developed to estimate site-specific risks of developing disease soon after recent primary infection, exogenous reinfection, or through endogenous reactivation (latently infected TB) among Taiwan regions. Here, we showed that the proportion of endogenous reactivation (53–67%) was larger than that of exogenous reinfection (32–47%). Our simulations showed that as epidemic reaches a steady state, age distribution of cases would finally shift toward older age groups dominated by latently infected TB cases as a result of endogenous reactivation. A comparison of age-weighted TB incidence data with our model simulation output with 95% credible intervals revealed that the predictions were in an apparent agreement with observed data. The median value of overall basic reproduction number (R_0) in eastern Taiwan ranged from 1.65 to 1.72, whereas northern Taiwan had the lowest R_0 estimate of 1.50. We found that total TB incidences in eastern Taiwan had 25–27% probabilities of total proportion of infected population exceeding 90%, whereas there were 36–66% probabilities having exceeded 20% of total proportion of infected population attributed to latently infected TB. We suggested that our Taiwan-based analysis can be extended to the context of developing countries, where TB remains a substantial cause of elderly morbidity and mortality.

KEY WORDS: Population dynamics; probabilistic; risk; transmission; tuberculosis

1. INTRODUCTION

A recent World Health Organization report documented the diagnosis of nearly 10 million new cases of tuberculosis (TB) in 2007 with an estimated 1.3 million deaths from TB in the same year.[1] Therefore, TB remains a leading cause of death resulting in high morbidity and mortality worldwide, with an estimate of one-third of the world's population being infected with TB bacilli.[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 continuously grows.

TB infection is caused by inhalation of *Mycobacterium tuberculosis* bacilli in a droplet nucleus form with a diameter less than 5 μm.[2,3] All TB outbreaks have been associated with cough-generating

[1]Department of Bioenvironmental Systems Engineering, National Taiwan University, Taipei, Taiwan 10617, ROC.
[2]Department of Public Health, Chung Shan Medical University, Taichung, Taiwan 40201, ROC.
[3]Department of Family and Community Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan 40201, ROC.
[4]Department of Health Risk Management, China Medical University, Taichung, Taiwan, 40402, ROC.
[*]Address correspondence to Chung-Min Liao, Department of Bioenvironmental Systems Engineering, National Taiwan University, Taipei, Taiwan 10617, ROC; cmliao@ntu.edu.tw.

procedures,[4] and other medical examination and treatment such as bronchoscopy,[5] endotracheal intubation and suctioning,[6] open abscess irrigation,[7] and autopsy.[8] Emergence of strains resistant to multiple drugs has led to situations where treatment is no better than before the discovery of antibiotics.[9] Diagnosis of TB remains a major barrier to control of the disease because the standard method, the acid-fast smear using sputum, does not become positive until a few months after transmission occurs.[10] Culture-based techniques are more sensitive, but still take weeks to obtain results.[11]

Over 50% of global TB cases are found in southeastern Asia and the western Pacific. In Taiwan the incidence and mortality rate of TB infection are 62.0–74.6 (per 100,000 population) and 3.3–5.7 (per 100,000 population) from 2002 to 2008, respectively.[12] Hsueh *et al.*[13] found that aborigines and people living in mountainous regions had higher incidence rates of 290 and 256 per 100,000 population, respectively. Hsueh *et al.*[13] also implicated that high disease burden of TB and inadequate current control infrastructure and training for TB implementation, e.g., directly observed treatment shortcourse (DOTS) strategy, are posing a great impact on public health in Taiwan, leading to current challenges to TB control such as the increasing burden of patients with multidrug-resistant TB infection, the persistent high rate of mortality, and unsatisfactory compliance of treatment.

In recent decades, mathematical modeling of infectious diseases dynamics has grown substantially and been gaining certain momentum. Models could be used to address public concerns relating to an ever-expanding number of emerging diseases and to explore the importance of biological and ecological characteristics on disease transmission.[14,15] The most well-known susceptible-infectious-recovered (SIR) model is a potentially powerful tool for modeling transmission dynamics of diseases. The use of the SIR models in disease transmission dynamics should only increase in the future.

The simplest SIR model of TB epidemics came from Blower *et al.*[16] Blower *et al.*[16] developed a theoretical SIR-based age-implicit transmission model to investigate natural behavior of a TB epidemic, demonstrating that TB epidemics could be seen as a series of linked time-lagged subepidemics. In subsequent work, the model was expanded to include the population-level effects of chemoprophylaxis and treatment.[17] Their models, however, did not consider the contribution of exogenous reinfection to the overall disease incidence. Vynnycky and Fine[18] developed an age-structured deterministic TB transmission dynamic model to estimate the age-specific TB risks. The model had several unique aspects, one of which was its dynamic approach to estimate the reinfection contribution to age-specific TB incidence. Recently, Dye and Williams[19] modified the work of Blower *et al.*[17] and Vynnycky and Fine[18] to develop an age-dependent TB transmission model to describe how people acquire *M. tuberculosis* infection, move into the latent state, and progress to active disease.

The transmission and population dynamics of TB in Taiwan region are poorly understood. It is recognized that individual contribution of exogenous reinfection and endogenous reactivation plays an important role in the development of TB. To examine the TB population dynamics and potential risk of infection in the Taiwan epidemic, a well-established mathematical model of TB transmission built on previous TB models[16–20] was adopted to study the potential impact of TB transmission in the Taiwan region. A probabilistic risk model was also developed to estimate the site-specific risks of developing disease soon after recent primary infection, exogenous reinfection, or through endogenous reactivation among Taiwan regions.

2. MATERIALS AND METHODS

2.1. Study Data

Monthly-based disease burden of TB data in Taiwan were obtained from reports of Centers for Disease Control of Taiwan (Taiwan CDC) for the period 2004–2008. The incidence rate, morality rate, and relapse proportion were calculated on the basis of Taiwan CDC TB data for each county, which were organized by geographical region.

To estimate the TB reinfection or reactivation proportions, we adopted a regression algorithm[21] of a linear regression model as: reinfection proportion $= -29.7 + 36.8 \times \log(\text{incidence rate})$ ($r^2 = 0.85$) to estimate the TB reinfection proportion from the incidence data. In this study, we selected three areas with the highest incidence together with one with the lowest incidence as the study sites for assessing the TB infection risk.

2.2. TB Transmission Model

A simple well-developed TB transmission model,[16,20] capturing five groups of dynamics of

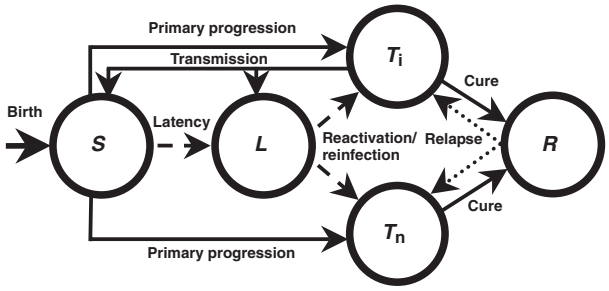

Fig. 1. Schematic of the susceptible-latently infected-tuberculosis-recovered (SLTR) model describing TB population transmission dynamics in this study.

susceptible (S), latently infected (L), infectious TB (T_i), noninfectious TB (T_n), and recovered (R) was adopted to investigate the population dynamics of TB in Taiwan and was referred to as the susceptible-latently infected-tuberculosis-recovered (SLTR) model. The essential features of the present model are depicted in Fig. 1.

In brief, (i) two certain types of TB were modeled: primary progressive TB (i.e., fast TB) and latently infected TB caused by endogenous reactivation or exogenous reinfection (i.e., slow TB), (ii) a case may be spontaneously cured at a cure rate and move into the recovered noninfection state R, and (iii) an individual in the recovered state may either relapse with equal probability into infectious or noninfectious TB or may never relapse and die of other causes at background mortality rate. Table I lists the system of ordinary differential equations with detailed symbol meanings corresponding to the model in Fig. 1 built based on past well-developed models.[16,20]

The expressions for basic reproduction number (R_0)[16] quantifying the transmission potential of *M. tuberculosis* due to the subepidemic driven by primary progression (R_0^{fast}), reactivation/reinfection (R_0^{slow}), and relapse (R_0^{relapse}) are summarized in Table I. The R_0 is defined as the average number of successful secondary infections cases generated by a typical primary infected case in an entirely susceptible population.[14] When $R_0 > 1$ it implies that the epidemic is spreading within a population and incidence is increasing, whereas $R_0 < 1$ means that the disease is dying out. An average R_0 of 1 means the disease is at 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]

Table I. Equations for TB Population Transmission Model[16]

Equation[a]		Meaning
SLTR Model[b]		
$\dot{S}(t) = \pi - (\lambda + \mu)S$	(T1)	Susceptible individuals
$\dot{L}(t) = (1-p)\lambda S - (v+\mu)L$	(T2)	Latently infected individuals
$\dot{T}_i(t) = pf\lambda S + qvL + \omega R - (\mu + \mu_T + c)T_i$	(T3)	Infectious TB cases
$\dot{T}_n(t) = p(1-f)\lambda S + (1-q)vL + \omega R - (\mu + \mu_T + c)T_n$	(T4)	Noninfectious TB cases
$\dot{R}(t) = cT_i + cT_n - (2\omega + \mu)R$	(T5)	Recovered TB cases
$N(t) = S(t) + L(t) + T_i(t) + T_n(t) + R(t)$	(T6)	Total population size
Basic Reproduction Number		
$R_0^{\text{total}} = R_0^{\text{fast}} + R_0^{\text{slow}} + R_0^{\text{relapse}}$	(T7)	Aggregate basic reproduction rate
$R_0^{\text{fast}} = (\frac{\beta\pi}{\mu})(\frac{1}{\mu+\mu_T+c})pf$	(T8)	The subepidemic driven by direct progression
$R_0^{\text{slow}} = (\frac{\beta\pi}{\mu})(\frac{1}{\mu+\mu_T+c})(\frac{q(1-p)v}{v+\mu})$	(T9)	The subepidemic driven by reactivation/reinfection
$R_0^{\text{relapse}} = (\frac{\beta\pi}{\mu})(\frac{1}{(\mu+\mu_T+c)((\mu+\mu_T+c)-((2\omega c)/(2\omega+\mu)))})$ $\bullet(p + \frac{(1-p)v}{v+\mu})(\frac{\omega c}{2\omega+\mu})$	(T10)	The subepidemic driven by relapse from recovered cases

[a]Symbol meaning: $\pi = N\delta$ is the recruitment rate (people per year) where δ is the birth rate (per year), $\lambda = T_i\beta$ is the force of infection (per year) where β is the transmission rate (per person per year), μ is the background mortality rate (per year), p is the probability of new infections that develop progressive primary active TB within one year, v is the progression rate from latency to active TB (per person per year), f is the probability of developing fast infectious TB, q is the probability of developing slow infectious TB, ω is the relapse rate to active TB for recovered TB cases (per person per year), μ_T is the TB caused mortality rate (per person per year), and c is the TB cure rate (per person per year).
[b]See Fig. 1.

2.3. Probabilistic TB Risk Model

To develop a probabilistic TB risk model, a dose-response model describing the relationships between transmission potential of *M. tuberculosis* (quantified by R_0) and 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 probability for each potentially infected contact. Theoretically, the total proportion of infected population during the epidemic (I) depends only on R_0, assuming a homogeneous and unstructured population,[14]

$$I = 1 - \exp(-R_0\, I). \tag{1}$$

Here we best fitted Equation (1) to the profile describing the relationship between I and R_0 based on Anderson and May[14] for R_0 ranging from 1 to 5 by using a nonlinear regression technique, resulting in a conditional probability of the infection given R_0 as:

$$P(I \mid R_0) \equiv 1 - \exp(1.63 - 1.66 R_0), \quad 1 < R_0 < 5, r^2 = 0.99. \tag{2}$$

TB infection risk can be calculated as the proportion of the population expected to be infected multiplied by the conditional probability of epidemic, given R_0. This results in a joint probability function or exceedance risk profile, which describes the probability of exceeding the R_0s of TB driven by primary progression, reactivation/reinfection, and relapse TB associated with infection proportion in a susceptible population. This can be expressed mathematically as:

$$R(I) = P(R_0) \times P(I \mid R_0), \tag{3}$$

where $R(I)$ is the cumulative distribution function describing the probabilistic infection risk of TB epidemic in a susceptible population at specific R_0 and $P(R_0)$ is the probability density function of R_0. Thus, 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 SLTR model (Table I, Eqs. (T1)–(T6)) can be parameterized based on available site-specific TB data provided by Taiwan CDC and otherwise based on data adopted from the literature. We used the model to project future site-specific TB incidence dynamics from 2005 to 2020 with 95% credible interval.

We validated the SLTR model by comparing predicted site-specific TB incidence with observed age-weighted TB incidence provided by Taiwan CDC from 2005 to 2008. To compare modeled and observed results, the best fit was evaluated using mean absolute percentage error (MAPE), computed from $\mathrm{MAPE} = \frac{1}{N}\sum_{n=1}^{N} \frac{|I_{o,n} - I_{s,n}|}{I_{o,n}} \times 100\%$, 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. Uncertainty Analyses and Simulation Scheme

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. A MC simulation was also performed with 10,000 iterations to generate 2.5 and 97.5 percentiles as the central 95th percentile range for all fitted models. Crystal Ball® software (Version 2000.2, Decisioneering, Inc., Denver, CO, USA) was employed to implement MC simulation. Model simulations were performed by using Berkeley Madonna 8.0.1 (Berkeley Madonna was developed by Robert Macey and George Oster of the University of California at Berkeley).

3. RESULTS

3.1. Quantitative Epidemiology of TB Data

Table II summarizes the estimates of TB incidence, mortality rate, relapse, reinfection, and reactivation proportion for major counties and cities situated in northern, central, southern, and eastern Taiwan, respectively, for the period 2004–2008. We found that the incidence rates were higher in Pingtung County in southern Taiwan (108 per 100,000 population) and Taitung (104 per 100,000 population) and Hwalien (124 per 100,000

Table II. Incidence, Mortality Rates, Relapse, Reinfection, and Reactivation Proportions of TB in Taiwan Region

Area/ County/City	Incidence Rate[a] Mean (*SD*)	TB Mortality Rate[b] Mean (*SD*)	Relapse Proportion[c] Mean (*SD*)	Reinfection Proportion[d] Mean (*SD*)	Reactivation Proportion[e] Mean (*SD*)
Taiwan	68 (5)	0.036 (0.013)	4.38 (0.11)	37.60 (0.90)	62.04 (0.51)
Northern Taiwan	57 (3)	0.032 (0.010)	3.77 (0.12)	34.97 (0.59)	65.03 (0.12)
Ilan County	78 (2)	0.031 (0.015)	5.04 (0.86)	39.59 (0.30)	60.41 (0.16)
Taipei City	50 (4)	0.033 (0.013)	2.70 (0.26)	32.69 (0.77)	67.31 (0.24)
Taipei County	60 (23)	0.028 (0.009)	4.23 (0.51)	35.88 (0.58)	64.12 (0.27)
Keelung City	80 (4)	0.025 (0.003)	4.01 (0.61)	40.24 (0.89)	59.76 (0.63)
Taoyuan County	57 (2)	0.033 (0.016)	4.13 (0.32)	34.84 (0.52)	65.16 (0.34)
Hsinchu County	53 (4)	0.034 (0.009)	2.75 (0.30)	33.74 (1.31)	66.26 (1.60)
Hsinchu City	48 (2)	0.041 (0.018)	1.30 (0.21)	32.09 (0.61)	67.91 (0.72)
Miaoli County	51 (8)	0.050 (0.023)	4.43 (0.23)	32.86 (2.61)	67.14 (2.19)
Central Taiwan	68 (4)	0.040 (0.015)	4.32 (0.20)	37.67 (1.05)	62.33 (0.43)
Taichung County	58 (4)	0.035 (0.023)	3.69 (0.44)	35.02 (1.12)	64.98 (0.81)
Taichung City	54 (2)	0.040 (0.019)	4.52 (0.30)	34.09 (0.56)	65.91 (0.47)
Changhwa County	73 (3)	0.057 (0.019)	3.87 (0.15)	38.85 (0.67)	61.15 (0.02)
Nantou County	86 (9)	0.034 (0.015)	5.64 (0.24)	41.38 (1.55)	58.62 (0.18)
Yunlin County	87 (10)	0.027 (0.005)	3.89 (0.53)	41.56 (1.82)	58.44 (1.09)
Chiayi County	74 (8)	0.036 (0.021)	4.90 (1.48)	39.06 (1.62)	60.94 (0.57)
Chiayi City	55 (5)	0.028 (0.010)	6.26 (1.23)	34.29 (1.49)	65.71 (1.76)
Southern Taiwan	83 (6)	0.038 (0.015)	4.67 (0.05)	40.88 (1.21)	59.12 (1.05)
Tainan County	74 (5)	0.031 (0.013)	4.07 (0.02)	39.04 (1.00)	60.96 (0.80)
Tainan City	55 (4)	0.029 (0.013)	6.08 (0.08)	34.33 (1.20)	65.67 (0.88)
Kaohsiung City	78 (5)	0.041 (0.015)	4.27 (0.26)	39.96 (1.09)	60.04 (1.17)
Kaohsiung County	96 (8)	0.034 (0.015)	5.11 (0.04)	43.18 (1.32)	56.82 (1.40)
Pingtung County	108 (10)	0.052 (0.021)	4.53 (0.09)	45.07 (1.44)	54.93 (1.20)
Eastern Taiwan	116 (10)	0.040 (0.019)	8.17 (0.54)	46.26 (1.32)	53.74 (0.67)
Taitung County	104 (10)	0.045 (0.026)	7.29 (1.61)	44.51 (1.49)	55.49 (1.10)
Hwalien County	124 (10)	0.037 (0.015)	8.68 (0.07)	47.35 (1.27)	52.65 (0.43)

[a]Incidence rate (per 100,000 population; 2004–2008): Annual regional confirmed TB case/total regional population number. Adopted from Taiwan CDC database.
[b]TB mortality rate (per person per year; 2004–2008): Annual regionally TB induced mortality/annual regional incidence. Adopted from Taiwan CDC database.
[c]Relapse proportion (2006–2007): (Annual regionally relapsed cases/total regionally notification cases) × 100%. Adopted from Taiwan CDC database and Taiwan tuberculosis control report.[32]
[d]Reinfection proportion (2004–2008) = $-29.7 + 36.8 \times \log(\text{incidence rate})$.[21]
[e]Reactivation proportion (2004–2008) = 100% − reinfection proportion.

population) Counties in eastern Taiwan. Taipei City of northern Taiwan, however, had the lowest average incidence and mortality rate with an incidence rate of 50 per 100,000 population. Therefore, we used TB epidemic data of Taipei City, Pingtung, Hwalien, and Taitung Counties to investigate the TB infection risks.

Figs. 2A–D demonstrates the time series dynamics of TB incidences in the selected four study sites during 2004–2008. Despite annual variation in incidence, there was little variability in the distribution of confirmed cases among age groups from 2004 to 2008 (Fig. 2E). More than 90% of cases were found in adults aged 25–64 and older, with the largest fraction of cases among > 64-year olds (Fig. 2E).

Overall, in Taiwan the average TB incidence rate, mortality rate, and relapse proportion were estimated to be 68 per 100,000 population, 0.036 per person per year for the period 2004–2008, and 4.38% for the period 2006–2007, respectively (Table II). The highest TB incidence rate was found in eastern Taiwan (116 per 100,000 population) with the estimated mortality rate and relapse proportion of 0.040 per person per year and 8.17%,

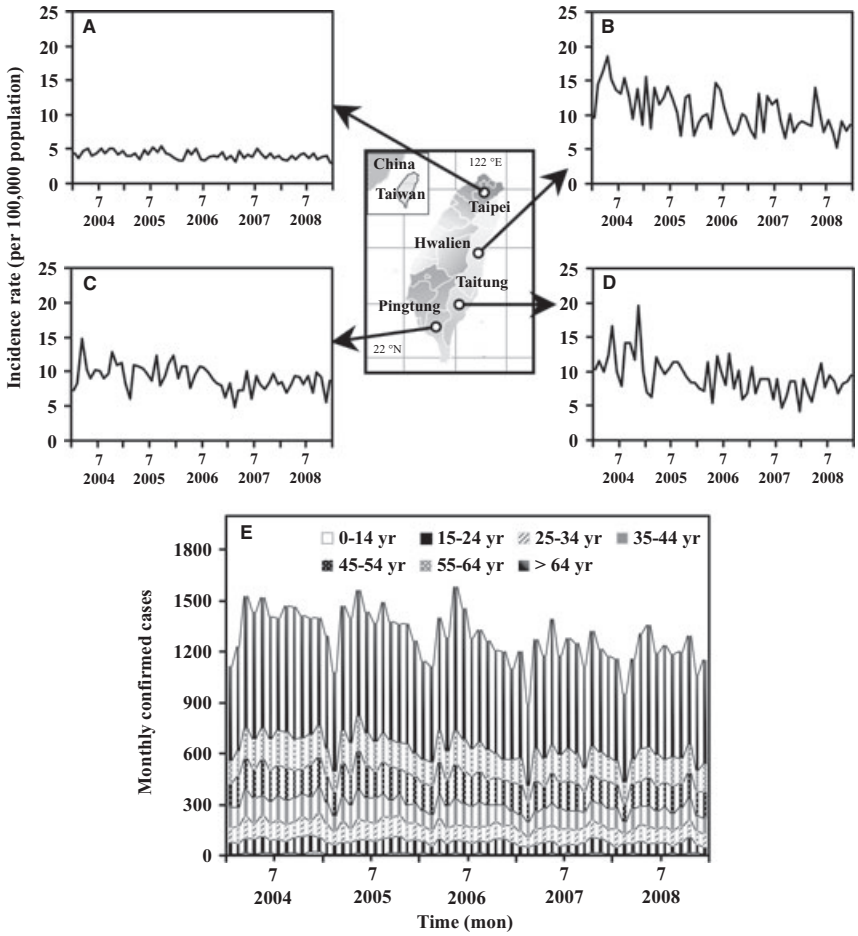

Fig. 2. Monthly-based TB incidence rate (per 100,000 population) time series dynamics during 2004–2008 in (A) Taipei City, (B) Hwalien County, (C) Pingtung County, and (D) Taitung County. (E) Monthly-based age-weighted confirmed TB incidence time series dynamics during 2004–2008 in Taiwan.

respectively (Table II). Eastern Taiwan had the largest proportion of TB relapse cases (8.17%) in which Hwalien County gave 8.68% relapse proportion (Table II).

Our result indicated that the average reinfection proportions of TB in southern and eastern Taiwan were estimated to be 41–46% during 2004–2008, whereas northern Taiwan had a relative lower proportion of 35% (Table II). The proportion of reinfection (47.35%) in Hwalien County was close to that of reactivation (52.65%; Table II). Generally, the average proportion of endogenous reactivation (53–67%) was larger than that of exogenous reinfection (32–47%) based on the regression model of Wang *et al.*[21] in Taiwan during 2004–2008 (Table II).

3.2. Population Dynamics of TB

The results of model parameterization are listed in Table III. We incorporated the estimated probability distributions of model parameter with site-specific initial population sizes (Table III) into the SLTR model (Table I, Eqs. (T1)–(T6)) to project future site-specific population dynamics of TB incidence from 2005 to 2020 (Fig. 3). Simulation results indicated that fast TB incidence declined (Figs. 3A, C, E, and G) and relapse TB incidence (Figs. 3B, D, F, and H) increased over time.

The results reveal that for all study sites, slow TB will predominate in a stable epidemic. Furthermore, based on the fact that more than 90% of cases were found in adults aged 25–64 and older, the simulation results also indicate that as the epidemic reaches a steady state, the age distribution of cases will finally shift toward the older age groups dominated by slow TB cases as a result of endogenous reactivation (Figs. 2E and 3). Thus, we proposed that most cases among teenagers and younger adults were estimated to be attributable to recent primary (fast) progression. Generally, the relapse TB incidences were

Table III. Probability Distributions (N = normal, LN = lognormal) of Parameter Values and Initial Population Size Used in the SLTR Model (see Table I for the symbol meanings)

	Probability Distribution			
	Hwalien County	Taitung County	Pingtung County	Taipei City
Model parameter				
ECR[a] (per year)	LN (7.43, 1.50)			
p[b]	N (0.08, 0.03)			
q[c]	N (0.78, 0.11)			
ν[c] (per person per year)	N (0.00392, 0.0007)			
f[d]	N (0.68, 0.07)			
δ[e] (per year)	N (0.0085,0.0005)	N (0.0093,0.0003)	N (0.0081,0.0007)	N (0.0081, 0.0002)
μ[e] (per year)	LN (0.031, 2.05)	LN (0.031, 2.05)	LN (0.030, 2.11)	LN (0.027, 2.00)
μ_T[d] (per person per year)	N (0.037, 0.015)	N (0.040, 0.019)	N (0.052, 0.021)	N (0.033, 0.013)
c[d] (per person per year)	N (0.61, 0.05)	N (0.56, 0.02)	N (0.57, 0.05)	N (0.68, 0.07)
ω[d] (per person per year)	N (0.0027, 0.00003)	N (0.0023, 0.00005)	N (0.00135, 0.00003)	N (0.00073, 0.00007)
β[f] (per person per year)	2.1×10^{-5} ($9.7\times10^{-6} - 4.8\times10^{-5}$)	3.1×10^{-5} ($1.4\times10^{-5} - 6.9\times10^{-5}$)	8.3×10^{-6} ($3.8\times10^{-6} - 1.8\times10^{-5}$)	2.8×10^{-6} ($1.3\times10^{-6} - 6.3\times10^{-6}$)
π[g] (person per year)	2,960	2,228	7,284	21,217
Population size				
N[h]	348,223	239,658	899,249	2,619,424
S	340,311	233,860	879,751	2,566,680
L[i]	6,616	4,553	17,085	49,769
T_i	473	240	647	524
T_n	332	558	890	1,247
R	491	447	876	1,204

[a] ECR = effective contact rate estimated based on Blower *et al.*[16]
[b] Estimated by 0.04 (0.015–0.14) for < 15 years old and 0.14 (0.08–0.25) for > 15 years old.[29]
[c] Adopted from Blower *et al.*[16]
[d] Estimated based on Taiwan CDC data.
[e] Estimated based on data from Department of Statistics, Ministry of the Interior, Taiwan.
[f] $\beta = ECR/N$ (mean with 95% CI).[33]
[g] $\pi = N\delta$.[33]
[h] The initial population sizes in 2005 of N, S, T_i, T_n, and R are adopted from Taiwan Tuberculosis Control Report[34] where $S = N - L - T_i - T_n - R$.
[i] $L = 0.02 \times 0.95 \times N$ where $0.02 = (0.01 + 0.03)/2$[35] and 0.95 is adopted from Oxlade *et al.*[36]

all below 5 per 100,000 population during simulation time course (Figs. 3B, D, F, and H).

Figs. 4A–D demonstrates the comparison of the age-weighted TB incidence data with our model simulation output with 95% credible intervals, indicating that the predictions are in an apparent agreement with the observed data. The model was able to match TB incidence in adults aged 15–54 year-olds from 2005 to 2008. Despite the simplicity of the model, we found a fair quantitative agreement between model predictions and local data (Fig. 4E). Overall, the model captures the transmission and population dynamics of TB among 15–54-year-olds in high TB incidence areas in Taiwan during 2005–2008.

3.3. TB Infection Risk Estimates

To estimate the probability of TB infection risk, the transmission potential quantified by R_0) had to be determined. The site-specific R_0 due to subepidemic driven by primary progression (fast), reactivation/reinfection (slow), and relapse were calculated based on equations listed in Table I (Eqs. (T7)–(T10)) (Fig. 5). The MC simulation result showed that the optimized log-normal distribution was the most suitable fitted model for R_0. We found that, for instance, in the highest TB epidemic area of Hwalien County, the R_0^{total} value was estimated to be 1.65 (central 95th percentile range: 0.45–6.45), whereas R_0^{fast} and R_0^{slow}estimates were 0.56 (0.13–1.64) and 0.86 (0.15–3.86), respectively. The median R_0^{total}estimates in Taitung and Pingtung Counties were 1.72 and 1.65, respectively, whereas Taipei City had the lowest R_0 values with R_0^{total} estimates of 1.50 (0.45–4.98).

Fig. 6A presents the dose-response profile showing the estimate for the total proportion of TB infected population (I) that depended only on R_0 based

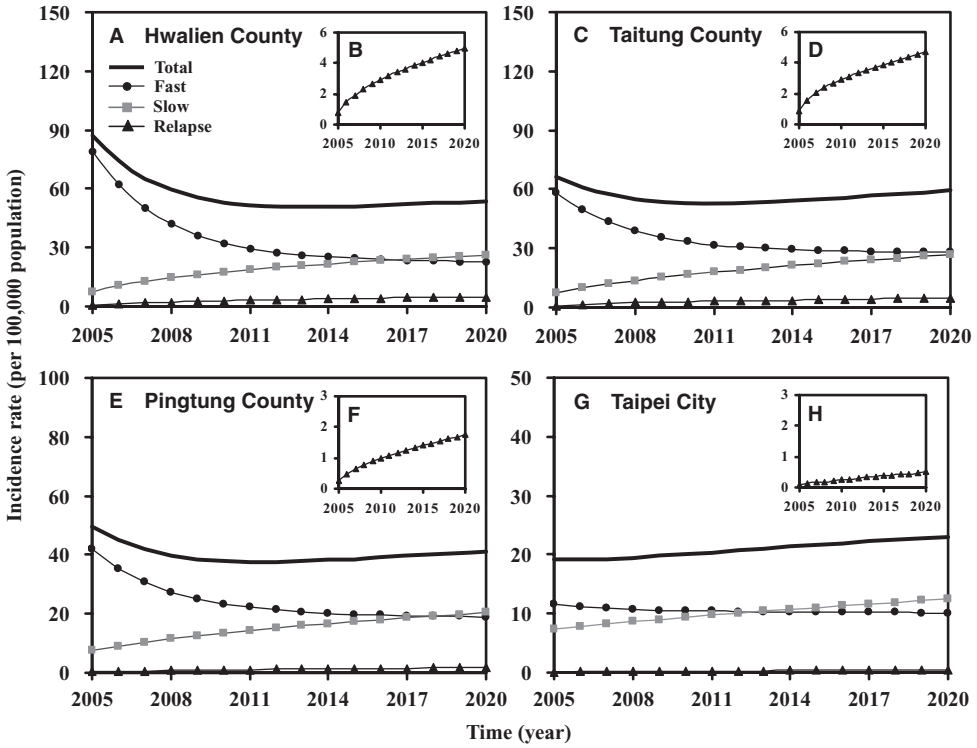

Fig. 3. Incidence rates (per 100,000 population) estimates based on SLTR model for total (fast + slow + relapse), fast, slow, and relapse TB populations during 2005–2020 in (A) Hwalien County, (C) Taitung County, (E) Pingtung County, and (G) Taipei City, respectively. Inserts (B, D, F, and H) show the enhanced time-courses of TB incidence rate.

on Equation (2). Given the site-specific R_0 distributions (Fig. 5) and dose-response relationship $P(I \mid R_0)$ (Fig. 6A), the site-specific exceedance risk probability of TB infection can then be estimated following Equation (3) (Figs. 6B–E). We found that total TB incidences (fast + slow + relapse) in Hwalien, Taitung, and Pingtung Counties, respectively, had nearly 24.5%, 27.1%, and 25.2% probabilities of total proportion of infected population exceeding 90%, whereas there were 63–66% probabilities having exceeded 20% of total proportion of infected population (Fig. 6). Our results also indicate that Hwalien and Taitung Counties had a nearly 24–26% probability of having exceeded 50% of population infected attributed to slow TB.

3.4. Sensitivity Analysis

Table IV shows the critical variables in the probabilistic sensitivity analysis for R_0. An increase in any one of the following three parameters corresponds with an increase of R_0^{total}: (i) the transmission rate (β), (ii) the probability of new infections that develop progressive primary active TB within one year (p), and (iii) the progression rate from latency to active TB (ν). However, an increase in any of the remaining three parameters corresponds to a decrease of R_0^{total}: (i) the background mortality rate (μ), (ii) the TB cure rate (c), and (iii) the TB caused mortality rate (μ_{T}). In our four selected study areas, the

Table IV. Probabilistic Sensitivity Analysis for Basic Reproduction Number

	Contribution (%)			
Input Parameter	Hwalien County	Taitung County	Pingtung County	Taipei City
β	39.87%	37.62%	37.03%	42.82%
p	3.95%	5.03%	4.97%	4.24%
q	0.98%	1.16%	1.56%	1.23%
ν	1.59%	1.71%	2.01%	2.57%
f	0.18%	0.25%	0.30%	0.67%
μ	−52.21%	−53.44%	−52.38%	−45.61%
μ_{T}	−0.19%	−0.51%	−0.23%	−0.02%
c	−1.03%	−0.27%	−1.50%	−2.81%
ω	0.01%	0.01%	0.02%	0.02%

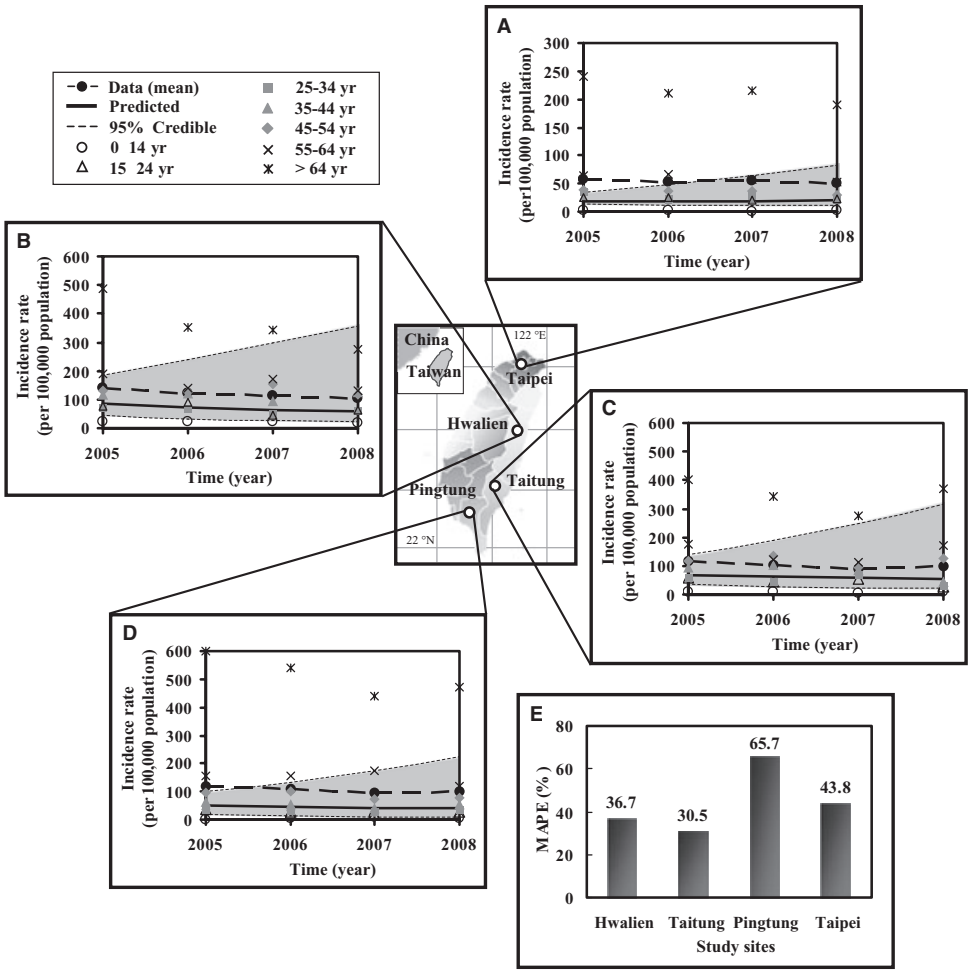

Fig. 4. Comparisons of incidence rates (per 100,000 population) between predictions by SLTR model with 95% credible intervals and age-specific data during 2005–2008 in (A) Taipei City, (B) Hwalien County, (C) Taitung County, and (D) Pingtung County. (E) Mean absolute percentage error (MAPE) estimates between predictions and observed mean data in Hwalien, Taitung, and Pingtung Counties, and Taipei City.

most important input variables for R_0 appeared to be transmission rate (β) and background mortality rate (μ), which contributes to 37.03–42.82% and 45.61–53.44% of output variances, respectively (Table IV). Our results indicate that β is the key parameter for influence on R_0. Therefore, the rate of spread of a TB epidemic could be controlled by reducing β.

4. DISCUSSION

4.1. Population Dynamics of TB Transmission in Taiwan

Our study found that Hawlien (124 per 100,000 population) and Taitung (104 per 100,000 population) Counties situated in eastern Taiwan had the highest TB incidences among Taiwan regions during 2004–2008. Generally, more than 90% of TB cases were found in adults aged 25–64 and older, with the largest fraction among > 64-year olds. We also found that the proportion of endogenous reactivation (53–67%) was larger than that of exogenous reinfection (32–47%) during 2004–2008. This result indicated that there was a trend of an increasing proportion of TB among the elderly. The plausible reason may be that with the falling of birth rate and increasing of longevity, the aging of populations is rising in Taiwan.

Our simulations showed that as the epidemic reaches a steady state, the epidemic would finally be dominated by slow TB cases as a result of endogenous reactivation. The simulated epidemic is similar to that of Blower *et al.*,[16] Vynnycky and Fine,[18]

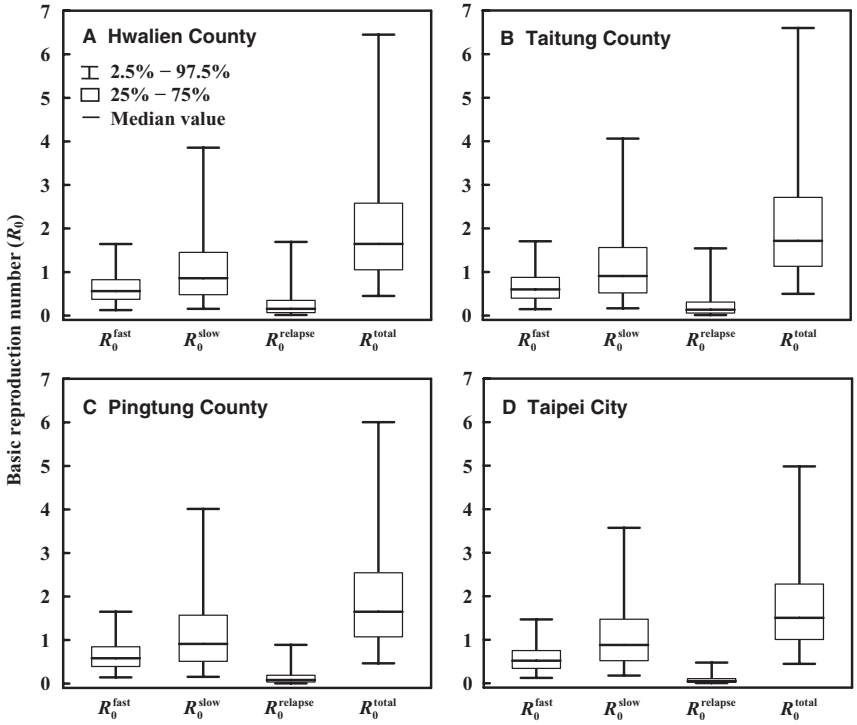

Fig. 5. Basic reproduction number (R_0) simulated by SLTR model with central 95th percentile range for fast, slow, relapse, and total (fast + slow + relapse) TB populations, respectively, in (A) Hwalien County, (B) Taitung County, (C) Pingtung County, and (D) Taipei City.

and Dye and Williams.[19] Most notifications in the older groups were estimated to be a result of endogenous reactivation, whereas among the teenagers and younger adults, they were estimated to be attributable to recent primary progression.[23,24] Thus, the dominated endogenous reactivation may probably occur at older age groups while the primary progression may occur among teenagers and younger adults.

Our simulations also showed that the incidences of total TB decrease slowly and decrease substantially for fast TB, whereas for slow TB of latent infections, the incidence arises (Fig. 3). The decline of fast TB in Taiwan might be attributed to universal Bacillus Calmette-Guérin vaccination and the improvement of TB control measures in Taiwan, in particular, the implementation of DOTS since 2006.[13] The reason for the "slowdown" in incidence rate of total TB is due in part to a growing proportion of TB cases from the slow reactivation of long-standing latent infections.[19,25,26] However, the reasons for the incidence of slow TB increase may be explained as: (i) more than 90% of cases were found in adults aged 25–64 and older, with the largest fraction of cases among > 64-year olds (Fig. 2E), (ii) latently infected individuals develop disease slowly through endogenous reactivation and therefore it will often occur in elderly, (iii) the falling of birth rate and increasing of longevity result in the aging of populations in Taiwan (the average life expectancy is approximately 80 years), and (iv) our SLTR model could not evaluate the impact of control strategy for targeting therapy to persons with latent TB infection.

4.2. TB Infection Risk Estimates

The median values of overall R_0 (R_0^{total}) in Hwalien, Taitung, and Pingtung Counties were estimated to be 1.65, 1.72, and 1.65, respectively, whereas Taipei City had the lowest R_0^{total} estimate of 1.50. We also found that Hwalien and Taitung Counties had a nearly 24–26% probability of having exceeded 50% of infected population attributed to slow TB. A relatively high TB risk was found among elderly based on our reanalyzed CDC data and that could explain the slowing decline of TB in Taiwan.

Our results also found that the risk of TB infection is still relatively high in Taipei City, indicating that the total TB risk of 42% probability had exceeded 50% of infected population. This reason may be due to Taipei City being a high-density urban area having high contact rate between or within the susceptible compared with rural areas. Yet, compared with rural areas, a higher proportion of people living

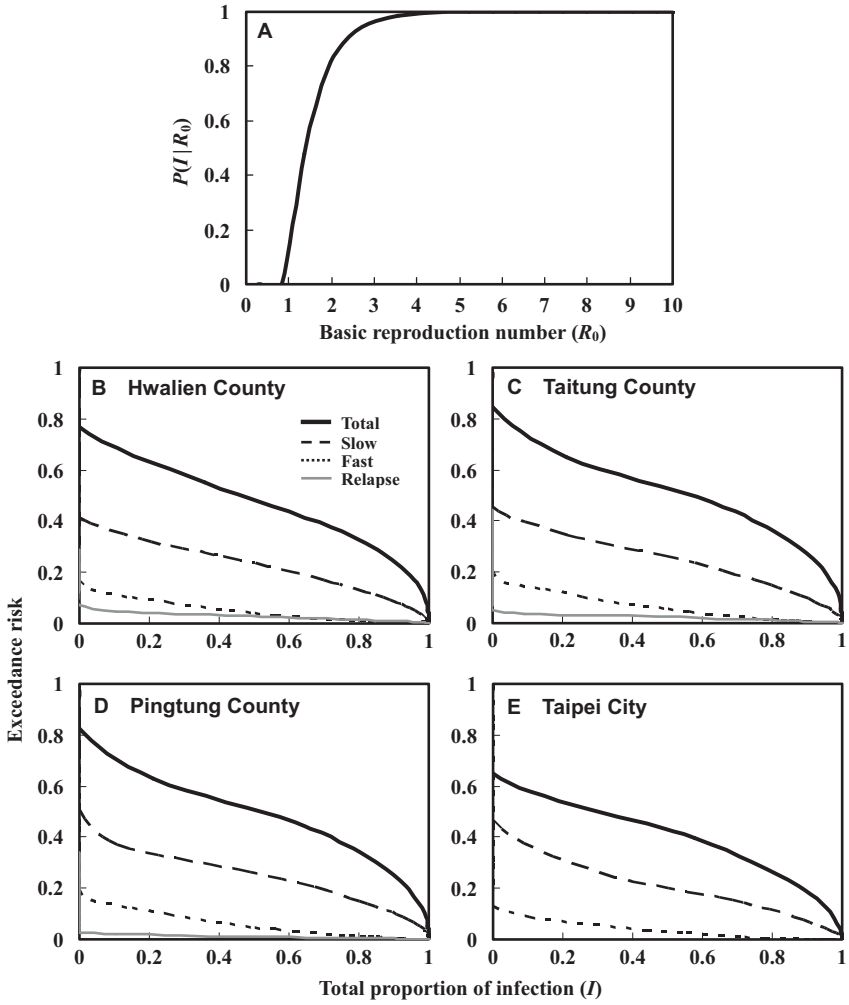

Fig. 6. (A) Dose-response profile representing the estimate of the total proportion of TB infected population, P(I), based on R_0 estimated from Equation (2). Exceedance risks of total proportions of TB infections estimation for total (fast + slow + relapse), slow, fast, and relapse TB populations, respectively in (B) Hwalien County, (C) Taitung County, (D) Pingtung County, and (E) Taipei City.

in Taipei are wealthy and have better access to health services.

TB infection seems to persist even in relatively small populations, possibly through recurring infections in adults. If individuals experiencing their first infection are the primary drivers of endemics, then demographic changes will have a strong influence on endemic dynamics. Therefore, differences in population demographics and epidemiology of TB diseases, and, potentially, vaccine effectiveness, would need to be carefully considered when predicting the TB transmission dynamics in local regions. Moreover, the factors such as numbers of alcoholics,[13] smokers,[27] and diabetics[13] can also be incorporated into the TB models to improve the predictability and they could have important dynamic consequences, which are worth exploring in future research.

4.3. Limitations and Implications

Although our model predicted apparently the region-specific TB dynamics and estimated the TB infection risk, further refinement of the model may be necessary. In this study, data gaps are the major limitation of the model, resulting in the predictions possibly being underestimated. The proposed TB transmission model had only implicitly accounted for the patterns of mixing among infectious cases and their contacts, and the risk of TB among those infected are constant through time. Blower *et al.*[16] estimated the effective contact rate (*ECR*) to be a triangular distribution with lower, mode, and upper values of 3, 7, and 13, respectively. Styblo[28] assumed an average duration of infectiousness of two years; this implied that on average each smear-positive case contacts 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, declined from about 22 individuals contacted in 1900 to about 10 individuals contacted in 1950.[29] The reasons for the decline in the *ECR* are several, such as that average size of each household has decreased over time, increasing segregation of infectious cases to sanatoria, or reducing the probability of a contact becoming infected with *M. tuberculosis* given a certain exposure through improved hygiene or nutrition. The proposed model captured the transmission and population dynamics of TB among 15–54-year-olds in high TB incidence areas; however, the most pronounced discrepancy between model and data occurred in the 0–14 and > 64-year age groups. To resolve this question, the TB transmission model needs to be extended to explore the interplay between survival, fertility, and the risk of TB with age with sufficient data availability.[20,30] Thus, we suggest that age-structured contact pattern is one of the critical elements for understanding the epidemiology of TB and can more accurately interpret TB epidemiological data.

Realistic age structure shows certain impact on the TB transmission model.[18,30] However, age- and gender-specific parameter values in the SLTR model are not easily to be parameterized in Taiwan due to data limitation. To compensate these predicaments, we may adopt published data related to age-specific risks of developing active TB together with our study results to improve model predictability. For instance, we can adjust the parameters such as the probability of new infections that develop progressive primary active TB within one year (p), the progression rate from latency to active TB (ν), and taking into account the probability of smear conversion from noninfectious to infectious TB.[31] To account for these factors will require better data, and structural and quantitative adjustments to the standard TB model.[20]

The practical implications of our results might be initiated for risk management. First, the quality of the local data allows us a rare opportunity to generate data-driven models for TB transmission dynamics in the Taiwan region. 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. We tested this idea through epidemiological modeling studies together with basic disease data. Models of the type described in this article were largely explored through simulation in terms of their predictive power. More data are needed to validate the model predictions. Finally, we can extend our Taiwan-based analysis to the context of developing countries, where *M. tuberculosis* remains a substantial cause of elderly morbidity and mortality.

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