Impact of population migration and seasonality on tuberculosis transmission: A multi-regional dynamic modeling and cost-effectiveness analysis in Jiangsu Province, China

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1 The basic reproduction number of model (1)

According to biological significance, all parameters in the model (1) are positive, and all variables in the equations are non-negative. The disease-free equilibrium of model (1) is given by

$$(S_1^0, C_1^0, 0, 0, 0, S_2^0, C_2^0, 0, 0, 0, S_3^0, C_3^0, 0, 0, 0, S_4^0, C_4^0, 0, 0, 0),$$

where,

$$S_1^0 = \frac{\Lambda_1}{\mu + \omega_{12} + \omega_{13} + \omega_{14}} \left(1 - q + \frac{\phi q}{\phi + \mu + \omega_{12} + \omega_{13} + \omega_{14}}\right),$$
$$C_1^0 = \frac{q\Lambda_1}{\phi + \mu + \omega_{12} + \omega_{13} + \omega_{14}},$$
$$S_2^0 = \frac{(\mu + \omega_{32})((1-q)\Lambda_2 + \phi C_2^0 + \omega_{12}S_1^0 + \omega_{42}S_4^0) + \omega_{32}((1-q)\Lambda_3 + \phi C_3^0 + \omega_{13}S_1^0 + \omega_{43}S_4^0)}{(\mu + \omega_{32})(\mu + \omega_{23}) - \omega_{23}\omega_{32}},$$
$$C_2^0 = \frac{(\phi + \mu + \omega_{32})(q\Lambda_2 + \omega_{12}C_1^0 + \omega_{42}C_4^0) + \omega_{32}(q\Lambda_3 + \omega_{13}C_1^0 + \omega_{43}C_4^0)}{(\phi + \mu + \omega_{32})(\phi + \mu + \omega_{23}) - \omega_{23}\omega_{32}},$$
$$S_3^0 = \frac{(\mu + \omega_{23})S_2^0 - \phi C_2^0 - ((1-q)\Lambda_2 + \omega_{12}S_1^0 + \omega_{42}S_4^0)}{\omega_{32}},$$
$$C_3^0 = \frac{(\phi + \mu + \omega_{23})C_2^0 - (q\Lambda_2 + \omega_{12}C_1^0 + \omega_{42}C_4^0)}{\omega_{32}},$$
$$S_4^0 = \frac{1}{\mu + \omega_{42} + \omega_{43}} \left((1-q)\,\Lambda_4 + \phi \frac{q\Lambda_4 + \omega_{14}C_1^0}{\phi + \mu + \omega_{42} + \omega_{43}} + \omega_{14}S_1^0\right),$$
$$C_4^0 = \frac{q\Lambda_4 + \omega_{14}C_1^0}{\phi + \mu + \omega_{42} + \omega_{43}}.$$

We define

$$\begin{aligned}
\bar{\beta}_0 =& \frac{1}{2Z}\int_0^{2Z} \left(a_0 + \left(1 + b_0 \sin\left(\frac{\pi t}{Z} + c_0\right)\right)\right) dt, \\
\bar{\beta}_1 =& \bar{\beta}_0 \exp(a_1 \times (\omega_{12} + \omega_{13} + \omega_{14})), \bar{\beta}_2 = \bar{\beta}_0 \exp(a_2 \times (\omega_{12} + \omega_{32} + \omega_{42} + \omega_{23})), \\
\bar{\beta}_3 =& \bar{\beta}_0 \exp(a_3 \times (\omega_{13} + \omega_{23} + \omega_{32} + \omega_{43})), \bar{\beta}_4 = \bar{\beta}_0 \exp(a_4 \times (\omega_{14} + \omega_{42} + \omega_{43})).
\end{aligned}$$

Since we took the average value of parameter $\beta_i,\ i = 1, 2, 3, 4$, the resulting quantity represents the average basic reproduction number. Following the next-generation matrix method [12], we can compute the average basic reproduction number, $\mathcal{R}_0$, we compute this average basic reproduction number, denoted as $\bar{\mathcal{R}_0}$. To apply this method, we first rewrite the 20 equations of system (1) in the form $\dot{x} = \mathscr{F} - \mathscr{V}$, where the state vector is defined as:

$$x = (S_1, C_1, L_1, I_1, T_1, S_2, C_2, L_2, I_2, T_2, S_3, C_3, L_3, I_3, T_3, S_4, C_4, L_4, I_4, T_4)^T \in \mathbb{R}^{20}.$$

For this purpose, we can decompose the right-hand side of model (1) into $\mathscr{F}-\mathscr{V}$, where the new infection terms $\mathscr{F}$ are given by:

$$\mathscr{F}=(0,0,f_{13},f_{14},0,0,0,f_{23},f_{24},0,0,0,f_{33},f_{34},0,0,0,f_{43},f_{44},0)^T,$$

where,

$$f_{i3}=\eta\frac{\overline{\beta}_iS_i(I_i+\rho T_i)}{N_i}+\frac{\theta\overline{\beta}_iC_i(I_i+\rho T_i)}{N_i}, f_{i4}=(1-\eta)\frac{\overline{\beta}_iS_i(I_i+\rho T_i)}{N_i}, i=1,\ 2,\ 3,\ 4.$$

$$\mathscr{V}=\begin{pmatrix}
-(1-q)\Lambda_1+\frac{\overline{\beta}_1S_1(I_1+\rho T_1)}{N_1}+\mu S_1-\phi C_1+(\omega_{12}+\omega_{13}+\omega_{14})S_1\\
-q\Lambda_1-(1-\kappa)\gamma T_1+\frac{\theta\overline{\beta}_1C_1(I_1+\rho T_1)}{N_1}+(\phi+\mu)C_1+(\omega_{12}+\omega_{13}+\omega_{14})C_1\\
-(1-p)\delta I_1-\kappa\gamma T_1+(\alpha+\mu)L_1+(\omega_{12}+\omega_{13}+\omega_{14})L_1\\
-\alpha L_1+(\delta+\mu+d_a)I_1+(\omega_{12}+\omega_{13}+\omega_{14})I_1\\
-p\delta I_1+(\gamma+\mu+d_b)T_1+(\omega_{12}+\omega_{13}+\omega_{14})T_1\\
-(1-q)\Lambda_2+\frac{\overline{\beta}_2S_2(I_2+\rho T_2)}{N_2}+\mu S_2-\phi C_2-\omega_{12}S_1-\omega_{32}S_3-\omega_{42}S_4+\omega_{23}S_2\\
-q\Lambda_2-(1-\kappa)\gamma T_2+\frac{\theta\overline{\beta}_2C_2(I_2+\rho T_2)}{N_2}+(\phi+\mu)C_2-\omega_{12}C_1-\omega_{32}C_3-\omega_{42}C_4+\omega_{23}C_2,\\
-(1-p)\delta I_2-\kappa\gamma T_2+(\alpha+\mu)L_2-\omega_{12}L_1-\omega_{32}L_3-\omega_{42}L_4+\omega_{23}L_2,\\
-\alpha L_2+(\delta+\mu+d_a)I_2-\omega_{12}I_1-\omega_{32}I_3-\omega_{42}I_4+\omega_{23}I_2,\\
-p\delta I_2+(\gamma+\mu+d_b)T_2-\omega_{12}T_1-\omega_{32}T_3-\omega_{42}T_4+\omega_{23}T_2\\
-(1-q)\Lambda_3+\frac{\overline{\beta}_3S_3(I_3-\rho T_3)}{N_3}+\mu S_3-\phi C_3-\omega_{13}S_1-\omega_{23}S_2-\omega_{43}S_4+\omega_{32}S_3\\
-q\Lambda_3-(1-\kappa)\gamma T_3+\frac{\theta\overline{\beta}_3C_3(I_3+\rho T_3)}{N_3}+(\phi+\mu)C_3-\omega_{13}C_1-\omega_{23}C_2-\omega_{43}C_4+\omega_{32}C_3\\
-(1-p)\delta I_3-\kappa\gamma T_3+(\alpha+\mu)L_3-\omega_{13}L_1-\omega_{23}L_2-\omega_{43}L_4+\omega_{32}L_3\\
-\alpha L_3+(\delta+\mu+d_a)I_3-\omega_{13}I_1-\omega_{23}I_2-\omega_{43}I_4-\omega_{32}I_3\\
-p\delta I_3+(\gamma+\mu+d_b)T_3-\omega_{13}T_1-\omega_{23}T_2-\omega_{43}T_4-\omega_{32}T_3\\
-(1-q)\Lambda_4+\frac{\overline{\beta}_4S_4(I_4-\rho T_4)}{N_4}+\mu S_4-\phi C_4-\omega_{14}S_1+\omega_{42}S_4+\omega_{43}S_4\\
-q\Lambda_4-(1-\kappa)\gamma T_4+\frac{\theta\overline{\beta}_4C_4(I_4+\rho T_4)}{N_4}+(\phi+\mu)C_4-\omega_{14}C_1+\omega_{42}C_4+\omega_{43}C_4\\
-(1-p)\delta I_4-\kappa\gamma T_4+(\alpha+\mu)L_4-\omega_{14}L_1+\omega_{42}L_4+\omega_{43}L_4\\
-\alpha L_4+(\delta+\mu+d_a)I_4-\omega_{14}I_1+\omega_{42}I_4+\omega_{43}I_4\\
-p\delta I_4+(\gamma+\mu+d_b)T_4-\omega_{14}T_1+\omega_{42}T_4+\omega_{43}T_4
\end{pmatrix},$$

Since $\mathscr{F}$ and $\mathscr{V}$ are 20-dimensional column vectors, we calculate their Jacobian matrices $\mathbf{F}$ and $\mathbf{V}$ at the disease-free equilibrium. The average basic reproduction number $\bar{\mathcal{R}}_0$ is then determined as the spectral radius of $\mathbf{FV^{-1}}$. Due to the complexity of the analytical expression, we do not present the specific formula for $\bar{\mathcal{R}}_0$, but instead compute its numerical solution using Matlab.

2 Parameter estimation

2.1 Parameter range assumptions and sources

(1) Natural death rate (μ): It is assumed that the natural death of a person is an equally probable event. Therefore, the natural death rate is calculated as $\mu = 1/(77.51 \times 12)$, based on the life expectancy of 77.51 years in Jiangsu Province in 2015 [47].

(2) Hesitation period ($1/\delta$): A study from Shannxi showed that the delay time for TB patients decreased from 60 days in 2008 to 33 days in 2017 [4]. A national study reported average delay levels of 24 days (range: 0–404 days) for Eastern China, 42 days (0–730 days) for Central China, and 62 days (0–587 days) for Western China from 2005 to 2009 [52]. We assume the average hesitation period for symptomatic TB patients to decide on hospitalization is 1–2 months, yielding $\delta \in [0.5, 1]$.

(3) Hospitalization duration ($1/\gamma$): Due to the biological characteristics of Mycobacterium tuberculosis, TB treatment requires a course of at least 6–8 months, while multidrug-resistant tuberculosis necessitates 24 months [54]. Hence, hospitalized TB patients typically stay for 6–24 months, leading to $\gamma \in [0.0417,\ 0.1667]$.

(4) Treatment failure rate κ: The treatment completion rate for active tuberculosis patients in Jiangsu Province was 92.4% [15]. According to the 2018 Jiangsu Health and Family Planning Yearbook, the successful treatment rate reached 95% by 2017 [15]. Theoretically, the treatment failure ratio is 5%–7.6%. However, considering potential treatment abandonment, we doubled the failure range, resulting in $\kappa \in [5\%,\ 15.2\%]$.

(5) Hospitalization proportion p: A national study in 2010 found that 53.2% of 740 symptomatic tuberculosis patients did not seek medical care [50]. Thus, the proportion of patients who choose hospitalization $p \in [45\%,\ 55\%]$.

(6) BCG vaccine protection duration ($1/\phi$): BCG vaccine protection is generally believed to last 10–15 years (120–180 months) [58], so $\phi \in [0.0056,\ 0.0083]$.

(7) Vaccination ratio q: For newborns in Jiangsu Province, the BCG vaccination qualified rate is 99.78%, with an average protection rate of 85% [39]. The lower bound of the vaccination rate is estimated as $99.78\% \times 85\%$, yielding $q \in [0.8485,\ 1]$.

(8) Relapse proportion θ: A retrospective study in China showed that 5.3% (710/13,417) of successfully treated patients relapsed [44]. The proportion due to exogenous reinfection and endogenous reactivation is $\theta \in [0.01,\ 0.2]$.

(9) Incubation period ($1/\alpha$): The incubation period for active TB typically ranges from 3–9 months, rarely exceeding two years [1]. We assume the transition time from asymptomatic to symptomatic infection is 3–24 months, so $\alpha \in [0.0417,\ 0.3333]$.

(10) Seasonal period ($2Z$): Given population migration, TB incidence exhibits seasonal patterns. We assume a period of approximately one year [28], resulting in $2Z \in [6,\ 18]$.

(11) Transmission reduction factor (ρ): The range of the transmission reduction factor for treated individuals to susceptible or immune hosts is uncertain. We assume a broad range, $\rho \in [0.001,\ 1]$.

(12) Migration Rate (ω_{ij}): Since migration rates in this model are averaged and individual differences are not considered, we assume all individuals migrate. Under this homogeneous population assumption, the migration rate is relatively small. Although

not everyone migrates monthly, we model universal migration over extended periods, leading to $\omega_{ij} \in [0, 0.0001]$.

(13) Asymptomatic infection proportion (η). Susceptible individuals are assumed to be infected with the TB virus through a slow, asymptomatic process. The proportion of such infections is set to $\eta \in [0.1,\ 1]$.

(14) Periodic transmission rate parameters ($a_i,\ i = 0, 1, 2, 3, 4,\ b_0$ and c_0): The standard transmission rate β_i (for $i = 0, 1, 2, 3, 4$) typically ranges from 0.01 to 10. Accordingly, we define the ranges for parameters $a_i,\ i = 0, 1, 2, 3, 4,\ b_0$ and c_0 in the periodic transmission rate function.

(15) Disease-induced mortality rate: Given that disease-induced mortality is higher than natural mortality, we set a reasonable range for this parameter based on epidemiological data.

(16) Initial Susceptible Population ($S_i(0),\ i = 1, 2, 3$): Based on the number of permanent residents in Northern, Central, and Southern Jiangsu [48], we assign the value ranges for $S_i(0),\ i = 1, 2, 3$.

(17) Monthly birth rate ($\Lambda_i,\ i = 1, 2, 3, 4$): Using the number of newborn babies in Jiangsu in 2009 [47] and the distribution of permanent residents across Northern (38%), Central (20%), and Southern (42%) Jiangsu [48], we estimate the monthly newborn counts in each region. The ranges for $\Lambda_i,\ i = 1, 2, 3, 4$ are provided in Table 1.

(18) Initial hospitalized patients ($I_i(0),\ i = 1, 2, 3$): Based on the reported number of hospitalized TB patients in the three regions in January 2009, we set $I_1(0) = 1099$, $I_2(0) = 617$, and $I_3(0) = 799$;

(19) External population and initial conditions: We assume the population of out-of-province areas linked to TB epidemics in Jiangsu is approximately ten times that of Jiangsu itself. Thus, we assign values for $S_4(0)$ and $I_4(0)$. The initial values for the remaining 20 compartments are determined through reasonable inference.

2.2 Parameter estimation method and objective function

We will use the model (1) to simulate the reported monthly TB data of Jiangsu Province from January 2009 to December 2019, based on the province's population and TB epidemiological characteristics. Consequently, the 30 parameters in model (1) and 16 initial values are estimated using the global differential evolution and local sequential quadratic programming (DESQP) method implemented in DEDiscover (an optimization software). This method demonstrates superior optimization efficiency, particularly in convergence speed, compared to many other algorithms [34] and has been successfully applied in several previous studies [26, 31, 32, 55]. The objective function is selected as the Chi-square value [23, 24].

2.3 Statistics and error analysis

To evaluate the statistical significance of the fitting results between the model and the actual data, we introduce two important indicators: the root mean square percentage error (RMSPE) and the mean absolute percentage error (MAPE). The statistical definitions of RMSPE and MAPE are as follows:

Table 1 The value, standard error and confidence interval of the parameters.

Name	Value	Standard deviation	Confidence interval	p-Value
$\delta \in [0.5, 1]$	0.5886	0.093	[0.4058, 0.7715]	8.19×10^{-10}
$\eta \in [0.1,\ 0.9]$	0.2076	0.0779	[0.0543, 0.3609]	0.0081
$\gamma \in [0.0417,\ 0.1667]$	0.048	0.0187	[0.0112, 0.0847]	0.0107
$\kappa \in [0.05,\ 0.152]$	0.1363	0.0373	[0.0629, 0.2097]	3.00×10^{-4}
$p \in [0.45,\ 0.55]$	0.522	0.084	[0.3568, 0.6872]	1.60×10^{-9}
$\phi \in [0.0056,\ 0.0083]$	0.0077	0.0018	[0.0042, 0.0112]	2.13×10^{-5}
$q \in [0.8485,\ 1]$	0.976	0.071	[0.8363, 1.1157]	4.23×10^{-34}
$\rho \in [0.001,\ 1]$	0.0553	0.0319	[0, 0.1182]	0.084
$\theta \in [0.15,\ 0.2]$	0.1562	0.048	[0.0619, 0.2506]	0.0012
$\omega_{12} \in [0, 0.0001]$	1.7407×10^{-9}	1.1882×10^{-4}	$[0,\ 2.3369 \times 10^{-4}]$	1.0000
$\omega_{13} \in [0, 0.0001]$	3.6855×10^{-5}	1.1801×10^{-4}	$[0,\ 2.6895 \times 10^{-4}]$	0.7550
$\omega_{14} \in [0, 0.0001]$	7.7700×10^{-9}	3.3623×10^{-5}	$[0,\ 6.6135 \times 10^{-5}]$	0.9998
$\omega_{23} \in [0, 0.0001]$	0.0001	4.5986×10^{-4}	[0, 0.0010]	0.8280
$\omega_{32} \in [0, 0.0001]$	3.3230×10^{-9}	1.3925×10^{-4}	$[0,\ 2.7387 \times 10^{-4}]$	1.0000
$\omega_{42} \in [0, 0.0001]$	1.0090×10^{-5}	3.7003×10^{-5}	$[0,\ 8.2864 \times 10^{-5}]$	0.7852
$\omega_{43} \in [0, 0.0001]$	4.5245×10^{-9}	3.3362×10^{-5}	$[0,\ 6.5618 \times 10^{-5}]$	0.9999
$\Lambda_1 \in [100,\ 2.60 \times 10^4]$	160.4447	2.5412	[155.445, 165.4445]	2.51×10^{-182}
$\Lambda_2 \in [100,\ 1.31 \times 10^4]$	103.1313	2.2355	[98.7332, 107.5294]	3.44×10^{-143}
$\Lambda_3 \in [100,\ 2.35 \times 10^4]$	327.9504	4.5777	[318.9441, 336.9568]	1.11×10^{-198}
$\Lambda_4 \in [200,\ 1.24 \times 10^6]$	2120	9.3371	[2100, 2140]	0
$\alpha \in [0.0417,\ 0.3333]$	0.058	0.0092	[0.0399, 0.0761]	1.00×10^{-9}
$Z \in [3,\ 9]$	6.1034	0.0187	[6.0667, 6.1402]	0
$a_0 \in [0.01,\ 10]$	0.0941	0.0398	[0.0158, 0.1725]	0.0186
$a_1 \in [0,\ 10]$	7.5885	0.4629	[6.6779, 8.4991]	3.02×10^{-44}
$a_2 \in [0,\ 10]$	1.8819	0.2672	[1.3562, 2.4076]	1.16×10^{-11}
$a_3 \in [0,\ 10]$	4.9542	0.4916	[3.987, 5.9213]	6.41×10^{-21}
$a_4 \in [0,\ 10]$	6.8961	1.81×10^{-5}	[6.8961, 6.8961]	0
$b_0 \in [-1,\ 1]$	0.5429	0.0018	[0.5393, 0.5465]	0
$c_0 \in [0,\ 1]$	0.0037	0.0081	[0, 0.0196]	0.6464
$d_a \in [0.01,\ 0.1]$	0.0579	0.0459	[0, 0.1482]	0.208
$d_b \in [0.01,\ 0.1]$	0.0906	0.0341	[0.0234, 0.1577]	0.0084

$$\text{MAPE} = \left(\frac{1}{n} \sum_{t=1}^{n} \left| \frac{I(t)^* - I(t)}{I(t)^*} \right| \right) \times 100\%, \tag{2.1}$$

$$\text{RMSPE} = \sqrt{\frac{\sum\limits_{t=1}^{n} \left[(I(t)^* - I(t))/I(t)^* \right]^2}{n-1}} \times 100\%, \tag{2.2}$$

where $I(t)^*$ represents the clinical case data and the model-fitted number of infected persons at time t, respectively. Here, n denotes the number of data points

Table 2 The value, standard error and confidence interval of the initial condition.

Name	Value	Standard deviation	Confidence interval	p-Value
$S_1(0) \in [0.05,\ 3] \times 10^7$	1.12×10^4	20.8453	$[1.12,\ 1.13] \times 10^4$	0
$S_2(0) \in [0.01,\ 2] \times 10^7$	8.84×10^3	24.1572	$[8.80,\ 8.89] \times 10^3$	0
$S_3(0) \in [0.05,\ 3] \times 10^7$	1.52×10^4	24.501	$[1.51,\ 1.52] \times 10^4$	0
$S_4(0) \in [0.002,\ 8] \times 10^8$	5.25×10^5	104.364	$[5.25,\ 5.25] \times 10^5$	0
$C_1(0) \in [0.1,\ 6] \times 10^4$	3.37×10^4	26.5617	$[3.36,\ 3.37] \times 10^4$	0
$C_2(0) \in [0.25,\ 3] \times 10^4$	1.82×10^4	28.2114	$[1.81,\ 1.82] \times 10^4$	0
$C_3(0) \in [0.1,\ 6] \times 10^4$	2.21×10^4	34.0526	$[2.21,\ 2.22] \times 10^4$	0
$C_4(0) \in [0.01,\ 1] \times 10^5$	9.50×10^4	56.6372	$[9.48,\ 9.51] \times 10^4$	0
$L_1(0) \in [0.1,\ 6] \times 10^4$	1.41×10^4	18.1132	$[1.41,\ 1.42] \times 10^4$	0
$L_2(0) \in [0.25,\ 3] \times 10^4$	5.68×10^3	11.4761	$[5.66,\ 5.70] \times 10^3$	0
$L_3(0) \in [0.1,\ 6] \times 10^4$	7.89×10^3	23.2891	$[7.85,\ 7.94] \times 10^3$	0
$L_4(0) \in [0.1,\ 6] \times 10^4$	3.37×10^4	31.269	$[3.37,\ 3.38] \times 10^4$	0
$T_1(0) \in [10,\ 1100]$	947.4652	6.1108	[935.4426, 959.4878]	2.17×10^{-302}
$T_2(0) \in [10,\ 617]$	366.0843	4.7602	[356.719, 375.4496]	5.71×10^{-208}
$T_3(0) \in [10,\ 800]$	708.7387	6.978	[695.01, 722.4674]	5.58×10^{-245}
$T_4(0) \in [50,\ 3000]$	1.97×10^3	1.4736	$[1.97,\ 1.97] \times 10^3$	0

Table 3 The criteria of $MAPE$ and $RMSPE$.

$MAPE$ and $RMSPE$	Forecasting power
$< 10\%$	Highly accurate forecasting
10-20%	Good forecasting
20-50%	Reasonable forecasting
$> 50\%$	Inaccurate forecasting

simulated. Table 3 presents the criteria for evaluating goodness of fit using MAPE and RMSPE [21]. When we apply model (1) to fit the tuberculosis patient data in Jiangsu Province, the results show MAPE= 8.15% and RMSPE= 12.05%. These values indicate that model (1) and its parameters have significant statistical validity, demonstrating its feasibility for analyzing the prevalence of tuberculosis in Jiangsu Province.

3 Effects of different prevention and control intensities

3.1 The influence of migration rate

Population flow is not a smooth process, particularly during the Spring Festival when it exhibits a geometric increase. Several outbreaks in China, including SARS and COVID-19 [24], have been linked to rapid population movement. Similarly, diseases such as HFMD [22, 29] and influenza often peak during Spring Festival and other holidays, also correlating with population flow. To assess the impact on tuberculosis transmission during these periods, we simulate increased migration rates by assuming: a fivefold increase in migration frequency (both intra- and inter-provincial), a tenfold increase in monthly migrants, and a fourfold reduction in migration intervals (the overall impact is 200 times). These changes are collectively reflected in mobility parameters $\omega_{13}, \omega_{23}, \omega_{42}$ to evaluate the effect of intensified human mobility on outbreaks.

In Central Jiangsu (seeing Figure 3 (b)), migration rate demonstrates a bidirectional effect on TB cases, indicating that population movement plays a complex role in TB transmission and highlighting the importance of migration rate as a sensitive research parameter. The increased migration rate significantly impacts TB transmission, as supported by existing studies [3, 10, 11, 14, 33, 35, 37, 49]. Conversely, our model shows that reduced mobility has minimal effect, consistent with Coffee's findings [9]. This occurs because further mobility reductions do not substantially alter transmission rates ($\beta_i, i = 1, 2, 3, 4$), and public attention primarily focuses on the risks posed by increased mobility during holidays.

The green curve ($\omega_{43} \times 200$) in Figure 3 (b) demonstrates that increased migration rate (ω_{43}) can elevate TB patient numbers. The blue dotted line (all) in Figure 3 (b), representing the overall fitting of migration rates from North (ω_{13}), Central (ω_{23}), and Outside (ω_{43}) Jiangsu to South Jiangsu, shows a fluctuating upward trend.

In the related study of Southern Jiangsu, we set the intensity coefficient of population migration's impact on TB transmission rates across regions as a key parameter. We can attribute the increasing effect of frequent crowd flows during holidays to mobility intensity, with simulation results shown in Figure 3 (c). As shown in the figure, the curves of this intensity coefficient for all three regions demonstrate dynamic correlations with fluctuations in TB case numbers. The yellow curve ($a_3 \times 500$) and purple dotted line ($a_2 \times 500$) in Figure 3 (c) partially overlap, exhibiting relatively smooth overall fluctuations. This indicates that increasing the influence intensity coefficient in northern and central Jiangsu has a certain impact on the number of infected individuals.

3.2 Control strategies for tuberculosis transmission in Jiangsu Province

Based on the BCG vaccine coverage and tuberculosis (TB) prevention and control efforts in Jiangsu Province, it is evident that the epidemic continues to outbreaks annually. Consequently, effectively reducing the TB epidemic level remains a significant challenge [56]. According to the sensitivity analysis results, the most influential parameters on the epidemic situation were identified as p, θ, α, ρ, δ, and certain migration rates. We examined northern, central, and southern Jiangsu Province as examples to study the effect of parameters in the sensitivity model on the number of patients, respectively (see Figure 3 (a), (b), (c)).

The five parameters represent key levers for TB control: (1) increasing treatment uptake (p) through public health campaigns; (2) accelerating treatment initiation (δ) by improving healthcare access and diagnostics; (3) shortening the infectious period (α) via early detection and intervention; (4) minimizing reinfection/reactivation risks

(θ) through post-treatment monitoring; and (5) reducing transmission during treatment (ρ) by ensuring effective infection control. Together, they emphasize rapid diagnosis, effective treatment, and sustained follow-up to curb.

4 Cost-effectiveness analysis

Based on the actual treatment and control costs of tuberculosis in Jiangsu Province, we provide a detailed breakdown of expenditures on tuberculosis prevention and treatment from five aspects: protective measures, screening, treatment, primary healthcare, and controlling dissemination costs.

4.1 The cost of tuberculosis prevention, control and treatment

4.1.1 Protective measure

The BCG vaccine is more effective in reducing the risk of tuberculous meningitis and miliary tuberculosis in children. Therefore, it should be administered to newborns as soon as possible after birth to prevent tuberculosis [17]. For the i-th area, the cost of BCG vaccination is calculated as follows:

$$C_{pre}(i) = \int_0^T e^{-rt} q \Lambda_i C_{BCG} dt, i = 1, 2, 3,$$

where $r = 0.03$ is the health discount rate, C_{BCG} represents the unit cost of a single BCG vaccine (see Table 4).

4.1.2 Screening

The symptoms of tuberculosis (TB) are similar to those of some common respiratory diseases, and some patients are asymptomatic in the early stages, often being detected during health screenings. Performing tuberculin tests (PPD tests) on susceptible individuals, followed by chest imaging and sputum smears to detect Mycobacterium tuberculosis in those at risk or in the latent stage, can more accurately diagnose active TB cases, enabling timely treatment, reducing TB transmission, and lowering patient mortality [13, 19, 20]. For the i-th area, the screening cost is calculated as:

$$C_{screen}(i) = \int_0^T e^{-rt} \left\{ M C_{PPD} + N \left(C_{CT} + C_{TSE} \right) \right\} dt.$$

where, $M = q\Lambda_i + \phi C_i + (1-k) r T_i + z_i w_{ij} (S_i + C_i)$ and $N = (1-\eta)\frac{\beta_i S_i (I_i + \rho T_i)}{N_i} + \alpha L_i$, for $i = 1, 2, 3$. Here, C_{PPD}, C_{CT}, and C_{TSE} represent the costs per PPD test, chest imaging, and sputum smear for detecting Mycobacterium tuberculosis (see Table 4), respectively. We assume a strong PPD-positive result indicates active TB, and $z_i, i = 1, 2, 3$ denotes the proportion of people working outside the home. Since the TB prevalence among the mobile population in Jiangsu Province is significantly higher than that among the household population, and the current census shows that the mobile population primarily consists of workers [18, 51], TB screening is particularly important for outgoing workers.

4.1.3 Treatment

The tuberculosis (TB) treatment program consists of two phases: intensive and consolidation [38]. The initial treatment for pulmonary TB is divided into a 2-month intensive phase and a 4-month consolidation phase. The intensive phase uses four drugs: isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E), while the consolidation phase uses two drugs: isoniazid (H) and rifampicin (R). For patients requiring retreatment, a drug susceptibility test should be conducted first [20, 42]. Those who are sensitive should receive a 2-month intensive phase and 6-month consolidation phase. The intensive phase uses five drugs (H, R, Z, E, and streptomycin (S)), and the consolidation phase uses three drugs (H, R, and E) [6, 8].

For drug-resistant patients, a drug-resistant retreatment regimen is used, consisting of a 4-month intensive phase and 5-month consolidation phase. The intensive phase uses seven drugs: amikacin (Am), moxifloxacin (Mfx), propylthioisonicotinic acid hydrazide (Pto), high-dose isoniazid (H), clofazimine (Cfz), pyrazinamide (Z), and ethambutol (E). The consolidation phase uses four drugs: moxifloxacin (Mfx), clofazimine (Cfz), pyrazinamide (Z), and ethambutol (E) [7, 8, 45]. For the i-th area, the treatment cost is calculated as:

$$C_{test}(i) = \int_0^T e^{-rt} \left[p\delta I_i C_{IT} + AC_{DST} + AB\delta I_i p C_{DRR} + A(1-B)\delta p I_i C_{TS}\right] dt, i = 1, 2, 3.$$

Here, C_{IT} represents the cost per patient in the initial treatment phase, C_{DST} is the cost per drug susceptibility test, C_{DRR} is the cost per drug-resistant patient in the retreatment phase, and C_{TS} is the cost per sensitive patient in the retreatment phase. We assume A is the proportion of patients not cured in the initial treatment phase, and B is the proportion of drug-resistant patients in the retreatment phase (see Table 4) [53].

4.1.4 Primary health care

In the TB prevention and control system, the cost of primary healthcare encompasses several supportive inputs for patients. As one of the pilot counties under the national "Care and Action" program, Haimen District, Nantong City, Jiangsu Province, has developed the "Haimen District Tuberculosis Care and Action Pilot Program Implementation Rules" aligned with local conditions. Patients who adhere to medication schedules and attend regular checkups receive transportation and nutritional allowances upon completing treatment.

We define the food and transportation allowance for compliant patients as C_{cost} [46]. Additionally, the program provides enhanced support for vulnerable groups, including low-income individuals, those facing financial hardship due to illness, and multidrug-resistant TB (MDR-TB) patients. Subsidies are granted to both ordinary TB and MDR-TB patients, denoted as C_{PT} and C_{NY}, respectively [46]. Furthermore, to promote health education, psychological support, and nutritional assistance, the program includes nutritional supplements for hospitalized patients at risk, with the proportion of at-risk patients represented by F and the corresponding nutritional supplement cost as C_F [46].

The total primary healthcare cost for the i-th area is then calculated as follows:

$$C_{HC}(i) = \int_0^t e^{-rt} \left[C_{cost} (1-p) \delta I_i + C_{PT} (1-B) \delta I_i + C_{NY} B \delta I_i + C_F F p \delta I_i \right] dt, i = 1, 2, 3.$$

4.1.5 Controlling dissemination

Infectious tuberculosis (TB) is primarily transmitted through the air. When TB patients cough, sneeze, or speak, they release Mycobacterium tuberculosis bacilli into the air. Individuals who inhale this contaminated air are at risk of infection [36]. To effectively control the spread of TB, strict disinfection protocols are required for individuals in close contact with patients (e.g., doctors, nurses), related medical equipment, and the hospital room environment, all of which contribute to the costs associated with controlling disease dissemination.

Let D represent the proportion of patients classified as severely ill. To meet infection control requirements, severely ill patients are isolated in individual rooms, while those with milder symptoms are accommodated four to a room. Consequently, the total number of required wards for the i-th area can be calculated as: $\frac{p\delta I_i(1-D)}{4} + P\delta I_i D, i = 1, 2, 3.$

Let C_{JJ} denote the cost per use of rapid hand sanitizer [16]. and C_{KZ} represent the cost per mask [5].

(1) Doctor protection cost:

Assume a doctor enters each room once daily and wears a mask throughout the visit. The doctor is required to disinfect their hands with a rapid hand sanitizer both before entering and after leaving the room. Accordingly, the cost for protecting doctors from infection in the i-th area is given by:

$$C_{YS}(i) = \int_0^t e^{-rt} \left[2C_{JJ} \left(\frac{p\delta I_i (1-D)}{4} + P\delta I_i D \right) + C_{KZ} \right] dt, i = 1, 2, 3.$$

(2) Nurse protection cost:

Assume a nurse enters each ward E times per day and wears a mask continuously throughout their shift. The nurse must also disinfect their hands before and after each entry and exit from the room. Therefore, the nurse protection cost for the i-th area is:

$$C_{HS}(i) = \int_0^t e^{-rt} \left[2EC_{JJ} + 4C_{KZ} \right] dt, i = 1, 2, 3.$$

(3) Medical equipment disinfection cost:

Let C_{BF} denote the disinfection cost per room for medical equipment [16]. Assume each room is equipped with an individual stethoscope and sphygmomanometer. These items must be cleaned and disinfected before and after each use with 75% alcohol and medical cotton balls. The total cost for disinfecting medical equipment in the i-th area is

$$C_{QX}(i) = \int_0^t e^{-rt} C_{BF} \left(\frac{p\delta I_i (1-D)}{4} + P\delta I_i D \right) dt, i = 1, 2, 3.$$

(4) Room management cost [40]:

(a)Air-exchange system cost: Rooms for TB patients are equipped with an air-exchange system. The system operates for 1 hour continuously after being activated every 4 hours. Assuming the system's power rating is 3 kW, and neglecting maintenance and depreciation costs, the electricity cost is calculated based on the average general industrial price of approximately 0.8 yuan/kWh. The operating cost of the air-exchange system for the i-th area is:

$$C_{HF}(i) = \int_0^t 14.4 e^{-rt} \left(\frac{p\delta I_i (1-D)}{4} + P\delta I_i D \right) dt, i = 1, 2, 3.$$

(b) Ultraviolet disinfection cost: The air in patient rooms and office areas is disinfected using UV circulating air sterilizers, while corridor air is disinfected via UV lamp irradiation. Due to the minimal energy consumption (daily cost below 1 RMB), this component is omitted from the cost analysis.

(c) Sanitation tools disinfection cost: recorded C_{HL} represent the cost of disinfecting sanitation tools per room [16]. Given the specific infection control requirements for TB, rooms must be disinfected daily using chlorine-based disinfectant for items such as bedside tables, cloths, and mops. Assuming the use of standard chlorine disinfectant priced at 1.5 yuan per 500 ml, a total of 3 liters of disinfectant solution is required for mopping the floor twice and wiping the bedside table once. The cost for disinfecting sanitation tools in the i-th area is:

$$C_{TD}(i) = \int_0^t e^{-rt} C_{HL} \left(\frac{p\delta I_i (1-D)}{4} + P\delta I_i D \right) dt, i = 1, 2, 3.$$

(d) Domestic waste (taking Suzhou City as an example): The cost of a small bucket is denoted as C_{XT}. Each tuberculosis patient requires a dedicated small bucket for sputum treatment, which contains chlorine disinfectant. Statistical analysis shows that the waste generated by tuberculosis patients accounts for 61.8% of all infectious waste. According to historical data [27], the total infectious waste in Suzhou is estimated to be 6,242.86 tons, with a treatment cost of RMB 3.6 per kilogram, resulting in an annual domestic waste treatment cost of RMB 22.475 million. The cost of treating this domestic waste (including sputum containers) in the i-th area is given by the following formula:

$$C_{SH}(i) = \int_0^t e^{-rt} \left(C_{XT} P\delta I_i + 22,475,000 \right) dt, i = 1, 2, 3.$$

4.2 Disability adjusted life years (DALYs)

We define DALYs (Disability-Adjusted Life Years) and ICER (Incremental Cost-Effectiveness Ratio) as key metrics for assessing the cost-effectiveness of tuberculosis

Table 4 Parameter definitions and values.

Parameter	Description	Value	Source
C_{BCG}	BCG vaccine cost	24.4	[17]
C_{PPD}	Tuberculin skin test cost	75	[19]
C_{CT}	Chest imaging cost	72.5	[20]
C_{TSE}	Sputum smear microscopy cost	30	[20]
z_1	Migrant workers from Northern Jiangsu	21.78%	[48]
z_2	Migrant workers from Central Jiangsu	14.08%	[48]
z_3	Migrant workers from Southern Jiangsu	0.38%	[48]
C_{IT}	Initial TB treatment cost	292.95	[38] [16]
C_{DST}	Drug susceptibility test cost	610	[20]
C_{DRR}	Drug-resistant TB treatment cost	23967.6	[38] [16]
C_{TS}	Retreatment cost (drug-susceptible)	663.288	[53]
A	Treatment failure rate (initial)	87.5%	Assumed
B	Drug resistance rate (retreatment)	57.1%	[53]
C_{cost}	Patient transport and meals cost	380	[46]
C_{PT}	Non drug-resistant patient subsidy	500	[46]
C_{NY}	Drug-resistant patient subsidy	2000	[46]
F	Nutritional risk prevalence	61.8%	[27]
C_F	Nutritional subsidy	500	[46]
D	Severe TB patient proportion	61.8%	[27]
C_{JJ}	Hand sanitizer cost	0.2	[5]
C_{KZ}	Medical mask cost	3	[16]
C_{BF}	Equipment disinfection cost	3	[37]
C_{HL}	Cleaning tool disinfection cost	9	[5]
C_{XT}	Sputum container cost	1.6	[5]
E	Daily nurse visits	25	Assumed

(TB). DALYs measures the overall health burden caused by the disease and is calculated using the formula:

$$DALY = YLL + YLD,$$

where YLL (Years of Life Lost) = Ns×Le (Ns = number of deaths, Le = standardized life expectancy at age of death), and YLD (Years Lived with Disability) = I×DW×Ld (I = number of illness events, DW = disability weight, Ld = average duration of disability) [41, 43].

(1) Number of deaths: The number of deaths due to the target disease or intervention in the study population. Based on actual tuberculosis mortality data from Jiangsu Province (2009–2019), the total number of deaths over the following 20 years was estimated using the formula $d_a I_i + d_b T_i, i = 1, 2, 3$.

(2) Standard life expectancy: According to Jiangsu Province Bureau of Statistics data, the per capita life expectancy in Jiangsu Province was 77.51 years in 2015 [47].

(3) Number of illnesses: The number of cases caused by the target disease in the study population, stratified by disability severity (e.g., mild, moderate, severe).

(4) Disability weight: A measure reflecting the impact of different health states on quality of life, ranging from 0 (full health) to 1 (death).

(5) Duration of disability: The time from illness onset to recovery, death, or study endpoint.

Through analysis of TB patient data, it was determined that among TB-infected individuals receiving treatment: The disability weight for drug-intolerant patients was 0.132, with a treatment duration of 7 months ($A \times 6 + (1\text{-}A) \times 14 = 7$); The disability weight for drug-resistant patients was 0.333, with a treatment duration of 15 months; The disability weight for active TB patients was 0.333 [46], with active periods of 9 months for drug-intolerant patients and 17 months for drug-resistant patients.

The YLD was calculated by combining patient numbers with these parameters:

$$\frac{dI_i}{dt} \times 0.333 \times (9 + 17) + (1 - AB)\frac{dT_i}{dt} \times 0.132 \times 7 + AB\frac{dT_i}{dt} \times 0.333 \times 15, i = 1, 2, 3,$$

where specific values for parameters A and B are provided in Table 4.

4.3 Incremental cost effectiveness ratio (ICER)

The Incremental Cost-Effectiveness Ratio (ICER) measures the change in cost and health benefits between two intervention strategies. It is crucial to specify both the cost and the corresponding change in DALYs for different intervention strategies. The ICER is calculated using the following formula:

$$ICER = \frac{Costs_{Intervention} - Costs_{Statusquo}}{DALYs_{Intervention} - DALYs_{Statusquo}},$$

where, $Costs = C_{pre} + C_{screen} + C_{test} + C_{HC} + C_{KZ}$ and $C_{KZ} = C_{YS} + C_{HS} + C_{QX} + C_{HF} + C_{TD} + C_{SH}$.

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