# Evaluating strategies for tuberculosis to achieve the goals of WHO in China: a seasonal age-structured model study

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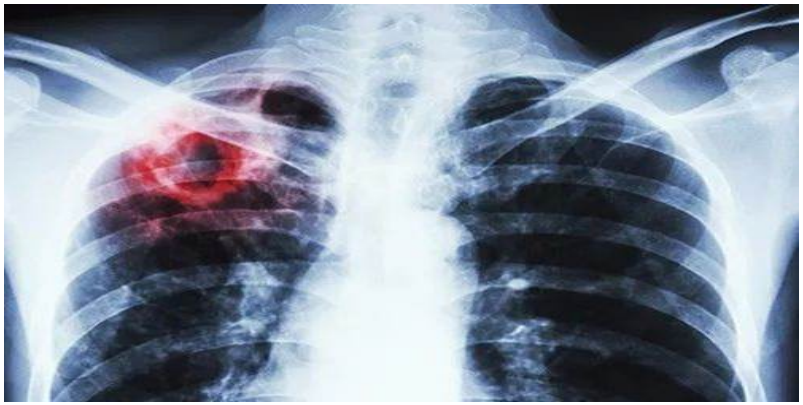
# Outline


1. Background
2. TB model
3. Fitting the model to the TB data of mainland China
4. Results
5. Conclusions and Discussion

# What is TB?



1. Tuberculosis (TB) is caused by bacteria (Mycobacterium tuberculosis) that most often affect the lungs. Tuberculosis (TB) is the worlds top infectious killer.
2. TB is spread from person to person through the air. When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected.
3. MDR-TB remains a public health crisis and a health security threat. Only about one in three people with drug resistant TB accessed treatment in 2020.

# Who is most at risk?

- Tuberculosis mostly affects adults in their most productive years. However, all age groups are at risk. Over 95% of cases and deaths are in developing countries.
- People who are infected with HIV are 18 times more likely to develop active TB (see TB and HIV section below). The risk of active TB is also greater in persons suffering from other conditions that impair the immune system. People with undernutrition are 3 times more at risk. Globally in 2020, there were 1.9 million new TB cases that were attributable to undernutrition.
- Alcohol use disorder and tobacco smoking increase the risk of TB disease by a factor of 3.3 and 1.6, respectively. In 2020, 0.74 million new TB cases worldwide were attributable to alcohol use disorder and 0.73 million were attributable to smoking.

# Global impact of TB

1. TB is one of the top 10 causes of death and the leading cause from a single infectious agent, which is higher than HIV/AIDS.
2. In 2019, there are about 10 million individuals suffering from TB in the world, within the range of 8.9-11 million, which is equivalent to an average of 130 individuals suffering from TB per 100,000 individuals, and the annual incidence rate is 5 to 500 per 100,000[1].

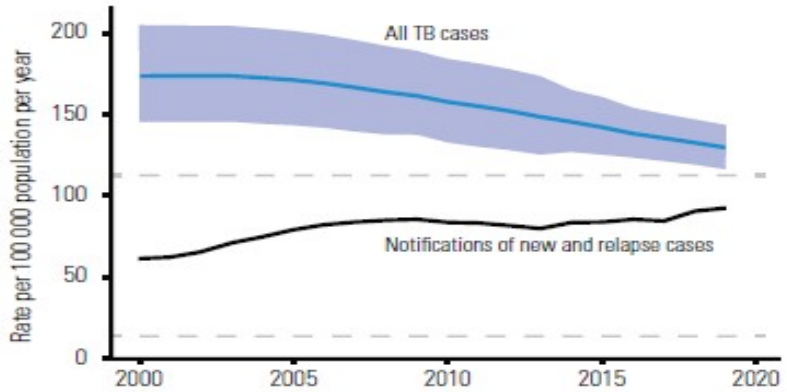



Figure: Global trend in the estimated TB incidence rate (blue), 2000-2019.

[1] World Health Organization, Global tuberculosis report 2020.

# Global Spread of TB

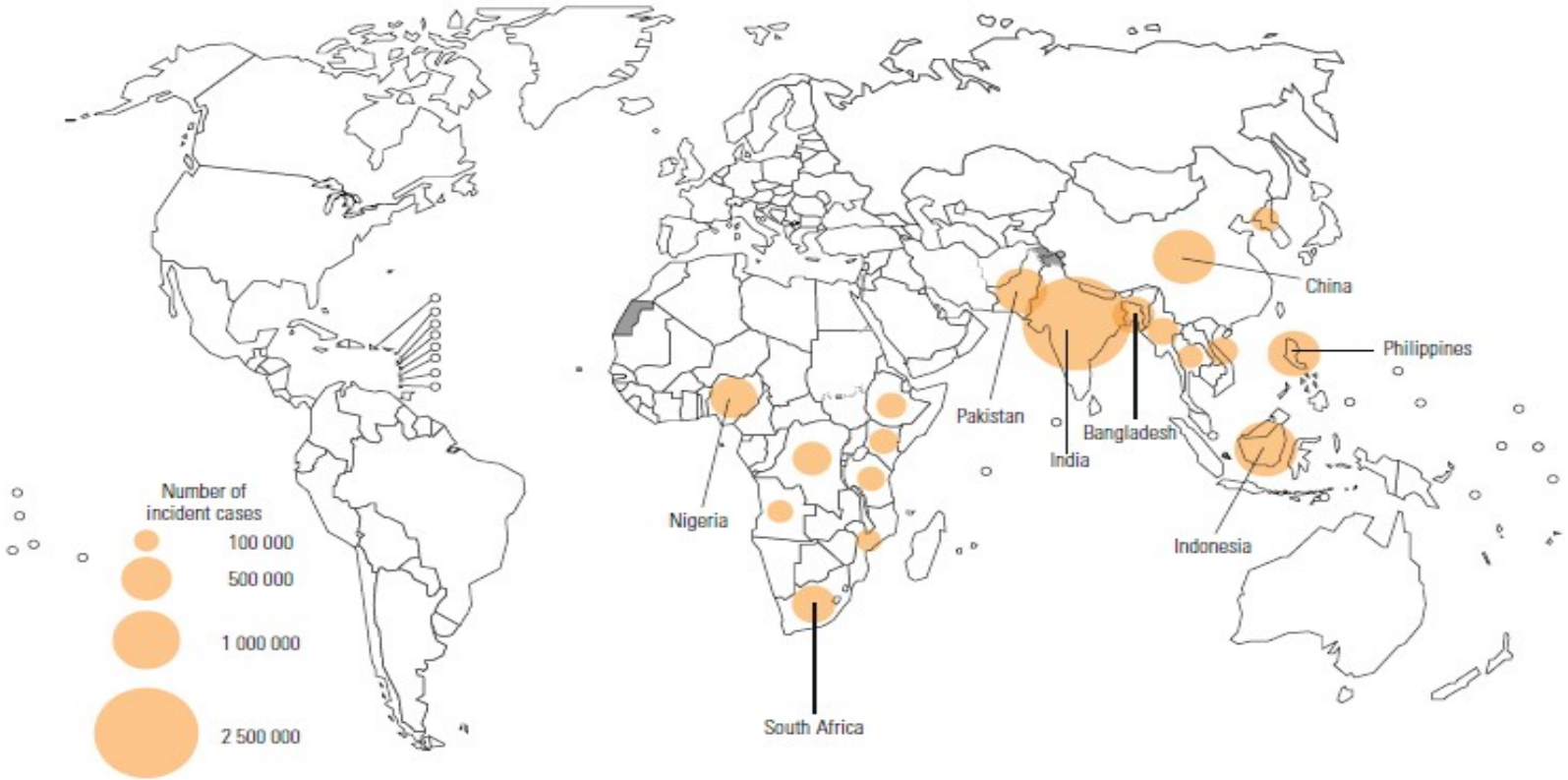



Figure: Countries that had at least 100,000 incident cases of TB in 2019.

India (26%), Indonesia (8.5%), China (8.4%), Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%), and South Africa (3.6%).

# Tuberculosis in China

- Tuberculosis is a serious public health problem in China.
- China has the world's third largest cases of tuberculosis, but progress in tuberculosis control was slow during the 1990s due to a malfunctioning health system.
- Detection of tuberculosis had stagnated at around 30% of the estimated total of new cases, and multidrug-resistant tuberculosis was a major problem.
- After the SARS epidemic was brought under control, the government increased its commitment and leadership to tackle public health problems and, among other efforts, increased public health funding, revised laws that concerned the control of infectious diseases, implemented the world's largest internet-based disease reporting system.

# The goals of WHO

Vision: Zero deaths, disease, and suffering due to tuberculosis

Goal: End the global tuberculosis epidemic

| | MILESTONES | | SDG* | END TB |
|---|---|---|---|---|
| | 2020 | 2025 | 2030 | 2035 |
| *Reduction in number of TB deaths* compared with 2015 (%) | 35% | 75% | 90% | 95% |
| *Reduction in TB incidence rate* compared with 2015 (%) | 20% | 50% | 80% | 90% |
| *TB-affected families facing catastrophic costs due to TB (%)* | 0% | 0% | 0% | 0% |

Ending the TB epidemic by 2030 is among the health targets of the United Nations Sustainable Development Goals (SDGs).)

# The goals of WHO

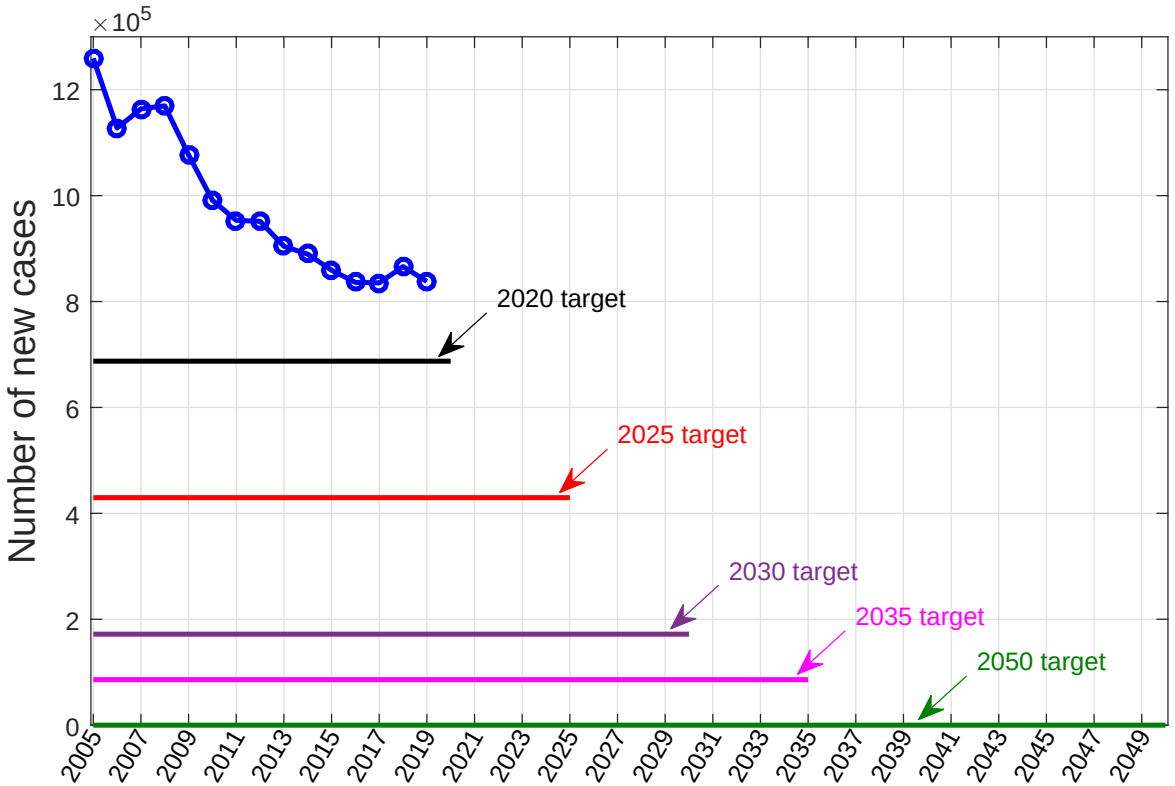



Figure: Number of new cases in China, 2005-2019.

It is difficult to achieve the goals of WHO in China if current mitigation strategies remain unchanged.

# Possible strategies

1. The improved vaccination can effectively prevent infection in susceptible individuals, and re-infection in latent individuals and recovered individuals to replace neonatal Bacille Calmette-Gurin (BCG).
2. The improved diagnostics can shorten the duration of infection and increase the probability of case detection before death from TB disease.
3. The improved treatment drugs can shorten the treatment time and reduce the relapse rate of the recovered individuals.

# Literature review on Modeling TB

- Castillo-Chavez C, Feng Z. To treat or not to treat: the case of tuberculosis. Journal of Mathematical Biology, 1997, 35: 629-656.
  The authors formulated one-strain and two-strain TB models to determine possible mechanisms that may allow for the survival and spread of naturally resistant strains of TB as well as antibiotic-generated resistant strains of TB.

- Castillo-Chavez C, Feng Z. Global stability of an age-structure model for TB and its applications to optimal vaccination strategies. Mathematical Biosciences, 1998, 151(2): 135-154.
  This article focuses on the study of an age-structure model for the disease transmission dynamics of tuberculosis in populations that are subjected to a vaccination program.

- Feng Z, Castillo-Chavez C, Capurro A F. A model for tuberculosis with exogenous reinfection. Theoretical Population Biology, 2000, 57(3): 235-247.
  The authors' results suggested that exogenous reinfection has a drastic effect on the qualitative dynamics of TB.

- Feng Z, Huang W, Castillo-Chavez C. On the role of variable latent periods in mathematical models for tuberculosis. Journal of Dynamics and Differential Equations, 2001, 13(2): 425-452.
  The qualitative behaviors of a system of ordinary differential equations and a system of differential-integral equations, which model the dynamics of disease transmission for tuberculosis, had been studied.

# Literature review on Modeling TB-Cntd

- B. Song, C. Castillo-Chavez, J. P. Aparicio. Tuberculosis models with fast and slow dynamics: the role of close and casual contacts. Mathematical Biosciences, 2002, 180(1-2): 187-205.
  Models that incorporate local and individual interactions are introduced in the context of the transmission dynamics of tuberculosis (TB).

- Y. Zhou, K. Khan, Z. Feng et al. Projection of tuberculosis incidence with increasing immigration trends. Journal of Theoretical Biology, 2008, 254(2): 215-228.
  The authors studied the impact of immigration latent TB cases on the overall TB incidence rate in the whole population.

- L. Liu, X-Q.Zhao, Y. Zhou. A tuberculosis model with seasonality. Bulletin of Mathematical Biology, 2010, 72(4): 931-952.
  The authors developed a compartmental model to describe TB seasonal incidence rate by incorporating periodic coefficients.

- J. Yang, X. Wang, X. Li, et al. Intrinsic transmission global dynamics of tuberculosis with age structure. International Journal of Biomathematics, 2011, 4(03): 329-346.
  The authors studied an age-structured epidemiological model for the disease transmission dynamics of TB.

- H. Cao, Y. Zhou, F. Brauer. Estimates of tuberculosis progression rate of children in China. Journal of Biological Dynamics, 2012, 6(2): 663-673.
  The authors studied a discrete mathematical model is formulated to describe tuberculosis (TB) progression from latent infection to active disease.

# Literature review on Modeling TB-Cntd

- Q. Hou, X. Sun, Y. Wang et al. Global properties of a general dynamic model for animal diseases: A case study of brucellosis and tuberculosis transmission. Journal of Mathematical Analysis and Applications, 2014, 414(1): 424-433.
  The authors proposed a new deterministic model which incorporates general incidences, various stages of infection and a general shedding rate of the pathogen to analyze the dynamics of these diseases.

- J. Zhang, Y. Li, X. Zhang. Mathematical modeling of tuberculosis data of China. Journal of Theoretical Biology, 2015, 365: 159-163.
  The authors proposed a mathematical model to fit tuberculosis data of China from January 2005 to December 2012 with the goodness of and obtain the optimal parameter values of the model.

- S. Liu, Y. Li, Y. Bi et al. Mixed vaccination strategy for the control of tuberculosis: A case study in China. Mathematical Biosciences and Engineering, 2017, 14(3): 695.
  ThE study presents a mathematical model of TB transmission considering BCG vaccination compartment to investigate the transmission dynamics nowadays.

- Y. Zhao, M. Li, S. Yuan. Analysis of transmission and control of tuberculosis in Mainland China from 2005C2016 was done based on the age-structure mathematical model. International Journal of Environmental Research and Public Health, 2017, 14(10): 1192.
  The authors proposed a susceptible-exposed-infectious-recovered (SEIR) epidemic model with age groupings, involving three categories: children, the middle-aged, and senior to investigate the role of age on the transmission of tuberculosis in Mainland China from 2005 to 2016.

# Literature review on Modeling TB-Cntd

- B. Ainseba , Z. Feng , M. Iannelli et al. Control strategies for TB epidemics. SIAM Journal on Applied Mathematics, 2017, 77(1): 82-107.
  A model for tuberculosis (TB) that includes immigration of susceptible and infected individuals was presented and analyzed.

- R. Xu, J. Yang, X. Tian et al. Global dynamics of a tuberculosis model with fast and slow progression and age-dependent latency and infection. Journal of Biological Dynamics, 2019, 13(1): 675-705.
  A mathematical model describing tuberculosis transmission with fast and slow progression and age-dependent latency and infection was investigated.

- Y. Cai, S. Zhao, Y Niu et al. Modelling the effects of the contaminated environments on tuberculosis in Jiangsu, China. Journal of Theoretical Biology, 2021, 508: 110453.
  The authors proposed a novel TB epidemic model accounting for the effects of the contaminated environments on TB transmission dynamics.

- Z.K. Guo, H. Xiang, H. F. Huo. Analysis of an age-structured tuberculosis model with treatment and relapse. Journal of Mathematical Biology, 2021, 82(5): 1-37.
  The authors formulated an age-structure TB model to study the effects of relapse and treatment on transmission dynamics of TB.

- M. Yao, Y. Zhang, W. Wang. Bifurcation analysis for an within-host Mycobacterium tuberculosis model. Discrete and Continuous Dynamical Systems-B, 2021, 26(4): 2299.
  In this paper, considering T cells can perform acceleration effect on their own recruitment, an in-host model of Mycobacterium tuberculosis was studied.
  ...

# Motivation

- The prevalence data on TB shows seasonal pattern. The reason is still unknown, but the higher infection rate in winter may be relevant to the increased periods spent in overcrowded, and poorly ventilated housing conditions, these phenomena are much more easily seen in winter.
- Highly infectious viruses and lack of vitamin D lead to immune deficiency, causes Mycobacterium TB to be reactivated in winter and spring.
- In addition, the diagnosis delay also has certain seasonal characteristics.
- In the model, we introduce the periodic transmission rate to characterize the seasonality of TB.
- Our goals are to calibrate the Mycobacterium TB transmission model based on age-stratified demographic and epidemiological data, and to evaluate the possibility of achieving the goals of WHO in China.

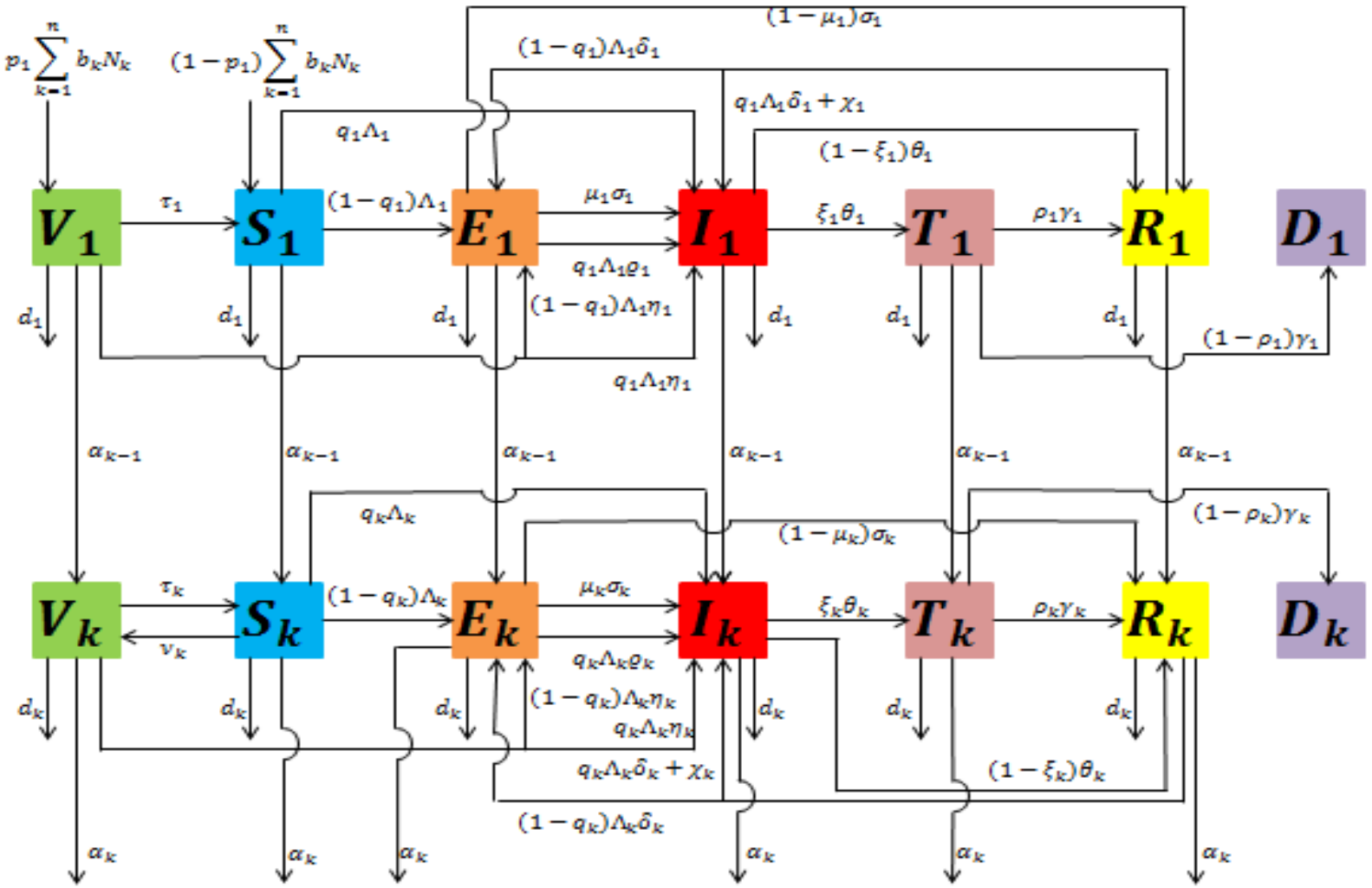
# Assumptions of the model

- A fraction of $p_1$ newborns are vaccinated.
- Susceptible individuals infected with Mycobacterium TB transfer to latent class and infected class at the rates $(1-q_k)\Lambda_k$ and $q_k\Lambda_k$, respectively.
- Latent individuals can become infected (recovered) class at the rate $\mu_k\sigma_k$ ( $(1-\mu_k)\sigma_k$),where $\sigma_k$ represents risk of reactivation.
- Latent individuals can also become infected class through 'fast progression' upon reinfection $(q_k\Lambda_k\varrho_k)$, where $\varrho_k \in (0,\ 1)$ represents that primary infection confers some degree of immunity.
- Infected individuals transfer to treated class and recovered class at the rates $(1-\xi_k)\theta_k$ and $\xi_k\theta_k$, respectively, where $\xi_k$ represents the proportion of infected class entering the treated class due to treatment and $1/\theta_k$ represents time delay during diagnosis of TB.

# Assumptions of the model

- Treated individuals transfer to recovered class (deceased class) at the rate $\rho_k\gamma_k$ ( $(1-\rho_k)\gamma_k$).
- Recovered individuals are not totally immune to Mycobacterium TB infection, and transfer to latent class and infected class at the rates $(1-q_k)\Lambda_k\delta_k$ and $q_k\Lambda_k\delta_k$, respectively, where $\delta_k \in (0,\ 1)$ represents the level of immunity of recovered individuals.
- Vaccinated individuals transfer to latent class and infected class at the rates $(1-q_k)\Lambda_k\eta_k$ and $q_k\Lambda_k\eta_k$, respectively, where $\eta_k \in (0,\ 1)$ represents that the immunity generated by the vaccine has a protective effect on individuals.
- Relapse rate of recovered class is$\chi_k$, susceptible class is vaccinated at the rate $\nu_k$ $(2 \le k \le n)$, and the vaccine immunity lasts $\tau_k$ in age group $k$.

# The schematic diagram of the model



# Model formulation

$$
\begin{cases}
\dfrac{dS_1}{dt} = (1-p_1)(\alpha_1+d_1+u)e^{\mu t}P_1 + \tau_1 V_1 - (\Lambda_1(t)+d_1+\alpha_1)S_1, \\
\dfrac{dS_k}{dt} = \alpha_{k-1}S_{k-1} + \tau_k V_k - (\Lambda_k(t)+\nu_k+d_k+\alpha_k)S_k, & 2 \le k \le n, \\
\dfrac{dV_1}{dt} = p_1(\alpha_1+d_1+u)e^{\mu t}P_1 - (\eta_1\Lambda_1(t)+\tau_1+d_1+\alpha_1)V_1, \\
\dfrac{dV_k}{dt} = \alpha_{k-1}V_{k-1} + \nu_k S_k - (\eta_k\Lambda_k(t)+\tau_k+d_k+\alpha_k)V_k, & 2 \le k \le n, \\
\dfrac{dE_1}{dt} = (1-q_1)\Lambda_1(t)(S_1+\eta_1 V_1+\delta_1 R_1) - (q_1\Lambda_1(t)\varrho_1+\sigma_1+d_1+\alpha_1)E_1, \\
\dfrac{dE_k}{dt} = \alpha_{k-1}E_{k-1} + (1-q_k)\Lambda_k(t)(S_k+\eta_k V_k+\delta_k R_k) \\
\qquad - (q_k\Lambda_k(t)\varrho_k+\sigma_k+d_k+\alpha_k)E_k, & 2 \le k \le n, \\
\dfrac{dI_1}{dt} = q_1\Lambda_1(t)(S_1+\eta_1 V_1+\delta_1 R_1+\varrho_1 E_1) + \mu_1\sigma_1 E_1 + \chi_1 R_1 \\
\qquad - (\theta_1+d_1+\alpha_1)I_1, \\
\dfrac{dI_k}{dt} = \alpha_{k-1}I_{k-1} + q_k\Lambda_k(t)(S_k+\eta_k V_k+\delta_k R_k+\varrho_k E_k) + \mu_k\sigma_k E_k + \chi_k R_k \\
\qquad - (\theta_k+d_k+\alpha_k)I_k, & 2 \le k \le n, \\
\dfrac{dT_1}{dt} = \xi_1\theta_1 I_1 - (\gamma_1+d_1+\alpha_1)T_1, \\
\dfrac{dT_k}{dt} = \alpha_{k-1}T_{k-1} + \xi_k\theta_k I_k - (\gamma_k+d_k+\alpha_k)T_k, & 2 \le k \le n, \\
\dfrac{dR_1}{dt} = \rho_1\gamma_1 T_1 + (1-\mu_1)\sigma_1 E_1 + (1-\xi_1)\theta_1 I_1 - (\chi_1+\delta_1\Lambda_1(t)+d_1+\alpha_1)R_1, \\
\dfrac{dR_k}{dt} = \alpha_{k-1}R_{k-1} + \rho_k\gamma_k T_k + (1-\mu_k)\sigma_k E_k + (1-\xi_k)\theta_k I_k \\
\qquad - (\chi_k+\delta_k\Lambda_k(t)+d_k+\alpha_k)R_k, & 2 \le k \le n, \\
\dfrac{dD_1}{dt} = (1-\rho_1)\gamma_1 T_1, \\
\dfrac{dD_k}{dt} = (1-\rho_k)\gamma_k T_k, & 2 \le k \le n.
\end{cases}
$$

# The forces of infection

The forces of infection among individuals (susceptible, vaccinated, latent and recovered individuals) in age group $k$ are defined as

$$\Lambda_k(t) = \beta_k(t) \sum_{j=1}^{n} c_{kj} \frac{I_j + \omega_j T_j}{N_j}, \ 1 \leq k \leq n,$$

where $c_{kj}$ is the average number of contacts between individuals in age group $k$ and individuals in age group $j$, $\beta_k(t)$ is the probability of infection upon contacting an infectious person, and $\omega_j$ represents the coefficient that reduces the transmission rate due to treatment in age group $j$.

# Simplified TB model

We adopt the framework of Hethcote[2] and assume that the population has reached an equilibrium age distribution with exponential growth in the form $N_k(t) = \mathrm{e}^{ut} P_k$, where $u$ represents constant growth rate, and $P_k$ represents the size of the $k$-th age group at time 0, $P_k$ are constants satisfying

$$P_k = \frac{\alpha_{k-1} P_{k-1}}{\alpha_k + d_k + u}, \ k = 2, 3, \cdots, n.$$

The birth function can be expressed as

$$\sum_{k=1}^{n} b_k P_k = (\alpha_1 + d_1 + u) P_1.$$

[2]Hethcote HW (2000) The mathematics of infectious diseases. SIAM review 42(4):599-653

# Simplified TB model

Hence, the birth population per unit time is

$$\sum_{k=1}^{n} b_k N_k = \mathrm{e}^{ut} \sum_{k=1}^{n} b_k P_k = (\alpha_1 + d_1 + u)\mathrm{e}^{ut} P_1 = (\alpha_1 + d_1 + u) N_1,$$

where $P_1 = N_1(0)$.
Consider the fractions $s_k(t) = \frac{S_k(t)}{\mathrm{e}^{ut} P_k}$, $v_k(t) = \frac{V_k(t)}{\mathrm{e}^{ut} P_k}$, $e_k(t) = \frac{E_k(t)}{\mathrm{e}^{ut} P_k}$, $i_k(t) = \frac{I_k(t)}{\mathrm{e}^{ut} P_k}$, $f_k(t) = \frac{T_k(t)}{\mathrm{e}^{ut} P_k}$, $r_k(t) = \frac{R_k(t)}{\mathrm{e}^{ut} P_k}$, and let $a_{kj} = \frac{P_k}{P_j}$ denote the ratio of the age group $k$ and $j$. Then the system becomes

# Simplified TB model

$$
\begin{cases}
\frac{ds_1}{dt} = (1-p_1)(\alpha_1+d_1+u) + \tau_1 v_1 - (\lambda_1(t)+u+d_1+\alpha_1)s_1, \\
\frac{ds_k}{dt} = a_{(k-1)k}\alpha_{k-1}s_{k-1} + \tau_k v_k - (\lambda_k(t)+\nu_k+u+d_k+\alpha_k)s_k, & 2 \le k \le n, \\
\frac{dv_1}{dt} = p_1(\alpha_1+d_1+u) - (\eta_1\lambda_1(t)+\tau_1+u+d_1+\alpha_1)v_1, \\
\frac{dv_k}{dt} = a_{(k-1)k}\alpha_{k-1}v_{k-1} + \nu_k s_k - (\eta_k\lambda_k(t)+\tau_k+u+d_k+\alpha_k)v_k, & 2 \le k \le n, \\
\frac{de_1}{dt} = (1-q_1)\lambda_1(t)(s_1+\eta_1 v_1+\delta_1 r_1) - (q_1\lambda_1(t)\varrho_1+\sigma_1+u+d_1+\alpha_1)e_1, \\
\frac{de_k}{dt} = a_{(k-1)k}\alpha_{k-1}e_{k-1} + (1-q_k)\lambda_k(t)(s_k+\eta_k v_k+\delta_k r_k) \\
\qquad - (q_k\lambda_k(t)\varrho_k+\sigma_k+u+d_k+\alpha_k)e_k, & 2 \le k \le n, \\
\frac{di_1}{dt} = q_1\lambda_1(t)(s_1+\eta_1 v_1+\delta_1 r_1+\varrho_1 e_1) + \mu_1\sigma_1 e_1 + \chi_1 r_1 \\
\qquad - (\theta_1+u+d_1+\alpha_1)i_1, \\
\frac{di_k}{dt} = a_{(k-1)k}\alpha_{k-1}i_{k-1} + q_k\lambda_k(t)(s_k+\eta_k v_k+\delta_k r_k+\varrho_k e_k) + \mu_k\sigma_k e_k + \chi_k r_k \\
\qquad - (\theta_k+u+d_k+\alpha_k)i_k, & 2 \le k \le n, \\
\frac{df_1}{dt} = \xi_1\theta_1 i_1 - (\gamma_1+u+d_1+\alpha_1)f_1, \\
\frac{df_k}{dt} = a_{(k-1)k}\alpha_{k-1}f_{k-1} + \xi_k\theta_k i_k - (\gamma_k+u+d_k+\alpha_k)f_k, & 2 \le k \le n, \\
\frac{dr_1}{dt} = \rho_1\gamma_1 f_1 + (1-\mu_1)\sigma_1 e_1 + (1-\xi_1)\theta_1 i_1 - (\chi_1+\delta_1\lambda_1(t)+u+d_1+\alpha_1)r_1, \\
\frac{dr_k}{dt} = a_{(k-1)k}\alpha_{k-1}R_{k-1} + \rho_k\gamma_k f_k + (1-\mu_k)\sigma_k e_k + (1-\xi_k)\theta_k i_k \\
\qquad - (\chi_k+\delta_k\lambda_k(t)+u+d_k+\alpha_k)r_k, & 2 \le k \le n.
\end{cases}
$$

# Basic reproduction number

Let $C_{\mathcal{T}}$ be the ordered Banach space of all $\mathcal{T}$-periodic functions from $\mathbb{R}$ to $\mathbb{R}^{4n}$ with the maximum norm $\|\cdot\|$ and the positive cone $C_{\mathcal{T}}^{+} := \{\phi \in C_{\mathcal{T}} : \ \phi(t) \geq 0, \ \forall t \in \mathbb{R}\}$. According to the method in Wang and Zhao[3], we define a linear operator $L : \ C_{\mathcal{T}} \to C_{\mathcal{T}}$ as follows

$$(L\phi)(t) = \int_0^{\infty} Y(t, t-a)\mathcal{F}(t-a)\phi(t-a)da, \ \forall t \in \mathbb{R}, \ \phi \in C_T.$$

$L$ is called the next generation infection operator and the spectral radius of $L$ is defined as the basic reproduction number, $\mathcal{R}_0$. Therefore, $\mathcal{R}_0$ of the system can be expressed as follows

$$\mathcal{R}_0 := \rho(L).$$

[3]Wang W, Zhao XQ (2008) Threshold dynamics for compartmental epidemic models in periodic environments. Journal of Dynamics and Differential Equations 20(3):699-717.

# Basic reproduction number

In order to calculate the basic reproduction number, $\mathcal{R}_0$, according to the Theorem 2.1 in Wang and Zhao, we introduce the linear $\mathcal{T}$-periodic system as follows

$$\frac{\mathrm{d}\omega}{\mathrm{d}t} = \Big[ -\mathcal{V}(t) + \frac{\mathcal{F}(t)}{\lambda}\Big]\omega,\ t \in \mathbb{R}, \tag{1}$$

where parameter $\lambda \in (0, \infty)$. Let the evolution operator of System on $\mathbb{R}^{4n}$ be $W(t, s, \lambda),\ t \geq s,\ s \in \mathbb{R}$. It is clear that $\Phi_{\mathcal{F}-\mathcal{V}}(t) = W(t, 0, 1),\ t \geq 0$ can be obtained. Hence, we derive

$$\Phi_{\frac{\mathcal{F}}{\lambda}-\mathcal{V}}(t) = W(t, 0, \lambda),\ t \geq 0.$$

# Basic reproduction number

## Lemma

*(Referring to Theorem 2.1 in Wang and Zhao.) The following statements are valid:*

*(1) If* $\rho(W(\mathcal{T},0,\lambda))=1$ *has a positive solution* $\lambda_0$*, then* $\lambda_0$ *is an eigenvalue of* $L$*, and hence* $\mathcal{R}_0>0$*.*

*(2) If* $\mathcal{R}_0>0$*, then* $\lambda=\mathcal{R}_0$ *is the unique solution of* $\rho(W(\mathcal{T},0,\lambda))=1$*.*

*(3)* $\mathcal{R}_0=0$ *if and only if* $\rho(W(\mathcal{T},0,\lambda))<1$ *for all* $\lambda>0$*.*

## Lemma

*(see Theorem 2.2 in Wang and Zhao. The following statements are valid:*

*(1)* $\mathcal{R}_0=1$ *if and only if* $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\mathcal{T}))=1$*.*

*(2)* $\mathcal{R}_0>1$ *if and only if* $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\mathcal{T}))>1$*.*

*(3)* $\mathcal{R}_0<1$ *if and only if* $\rho(\Phi_{\mathcal{F}-\mathcal{V}}(\mathcal{T}))<1$*.*

# Extinction of the disease

We assume that $\varrho_k = 0,\ \delta_k = 0,\ 1 \leq k \leq n$, and we introduce the following theorem.

## Theorem

*The disease-free periodic solution $\mathcal{P}_0$ of System is globally asymptotic stable if $\mathcal{R}_0 < 1$, and is unstable if $\mathcal{R}_0 > 1$.*

# Uniform persistence of the disease

We assume that $\varrho_k = 0,\ \delta_k = 0,\ 1 \le k \le n$, and we introduce the following theorem.

## Theorem

*If the basic reproduction number $\mathcal{R}_0 > 1$, then there is a positive constant $\varepsilon > 0$ such that when*

$$\left\|(\mathbf{S}_0, \mathbf{V}_0, \mathbf{E}_0, \mathbf{I}_0, \mathbf{F}_0, \mathbf{R}_0) - \mathcal{P}_0\right\| \le \varepsilon$$

*for any $(\mathbf{S}_0, \mathbf{V}_0, \mathbf{E}_0, \mathbf{I}_0, \mathbf{F}_0, \mathbf{R}_0) \in X_0$, we have*

$$\limsup_{m\to\infty} d\big(F^m(\mathbf{S}_0, \mathbf{V}_0, \mathbf{E}_0, \mathbf{I}_0, \mathbf{F}_0, \mathbf{R}_0), \mathcal{P}_0\big) \ge \varepsilon,$$

*where $d(x, y)$ represents the distance between $x$ and $y$.*

# Uniform persistence of the disease

## Theorem

*If the basic reproduction number* $\mathcal{R}_0 > 1$, *then there exists a* $\varsigma > 0$ *such that the solution* $(\mathbf{S}(t), \mathbf{V}(t), \mathbf{E}(t), \mathbf{I}(t), \mathbf{F}(t), \mathbf{R}(t))$ *of the system with initial value condition* $(\mathbf{S}_0, \mathbf{V}_0, \mathbf{E}_0, \mathbf{I}_0, \mathbf{F}_0, \mathbf{R}_0) \in X_0$ *satisfies*

$$\liminf_{t\to\infty} e_k(t) \geq \varsigma,\ \liminf_{t\to\infty} i_k(t) \geq \varsigma,\ \liminf_{t\to\infty} f_k(t) \geq \varsigma,\ \liminf_{t\to\infty} r_k(t) \geq \varsigma,\ (1 \leq k \leq n)$$

*and system admits at least one positive periodic solution.*

# Even if $\mathcal{R}_0 < 1$, the epidemic may take off

## Remark

*Since exogenous reinfection and reinfection of recovered individuals, that is,* $\varrho_k \neq 0$, $\delta_k \neq 0$, $1 \leq k \leq n$, *we known that* $\mathcal{R}_0$ *is not a threshold parameter between the persistence and extinction of the disease*[a]. *This implies that even if* $\mathcal{R}_0 < 1$, *the epidemic may take off. We verify the above conclusions through numerical simulations.*

[a] Bhunu C, Garira W, Mukandavire Z, Zimba M (2008) Tuberculosis transmission model with chemoprophylaxis and treatment. Bulletin of Mathematical Biology 70(4):1163-1191.

# The dynamics with different values of $\mathcal{R}_0$

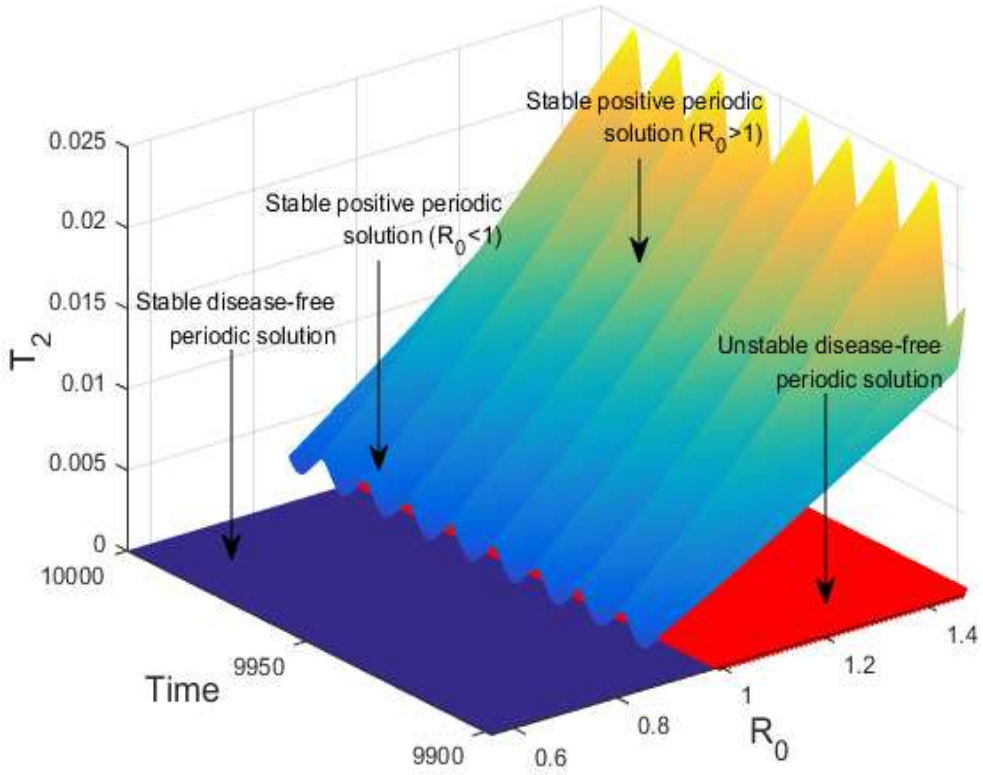



Figure: The existence of periodic solutions.

1. When $\mathcal{R}_0 < 1$, the system has at least one stable positive periodic solution and one stable disease-free periodic solution.

2. When $\mathcal{R}_0 > 1$, the system has at least one stable positive periodic solution and one unstable disease-free periodic solution.

# Data collection and analysis

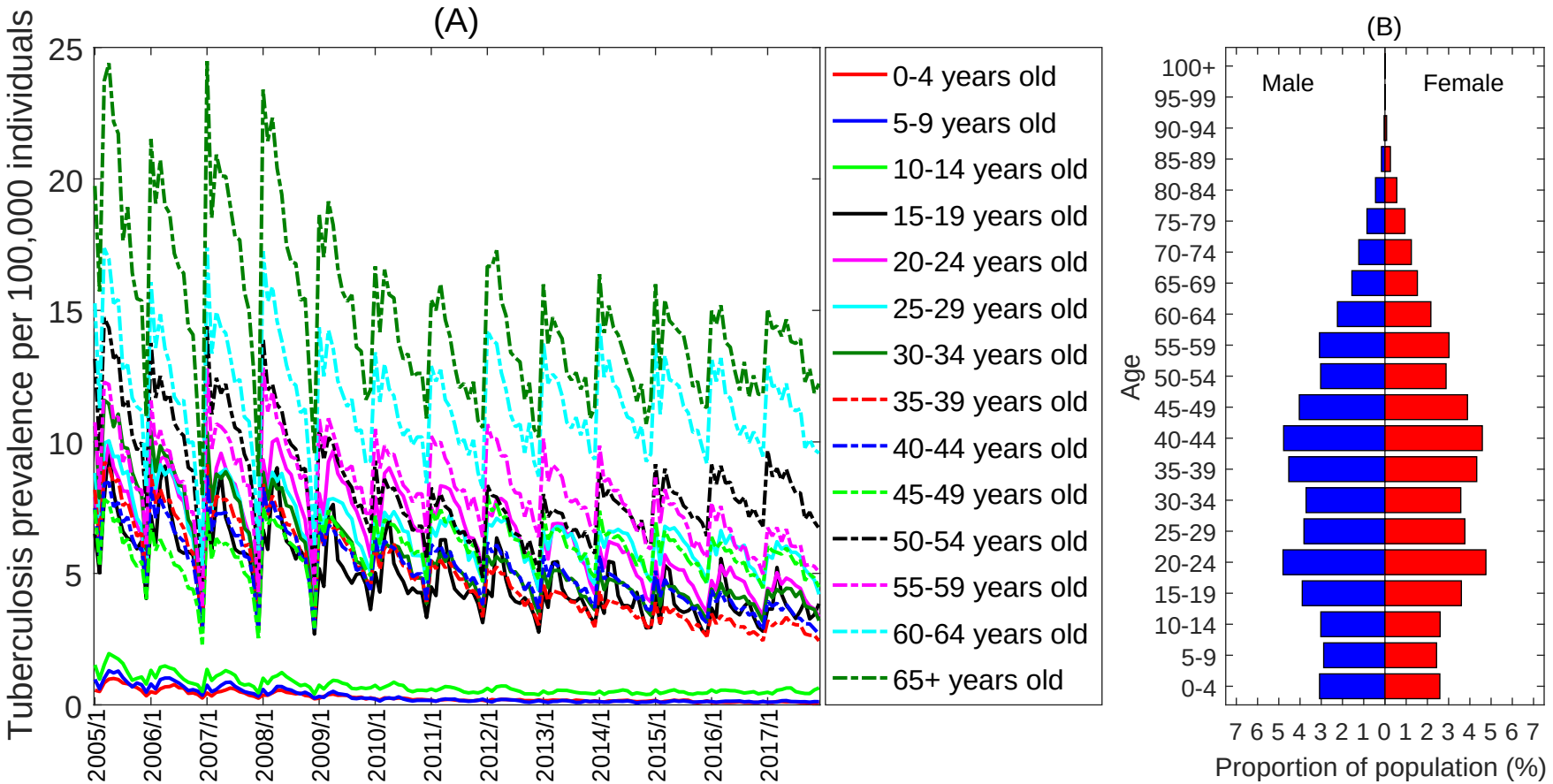


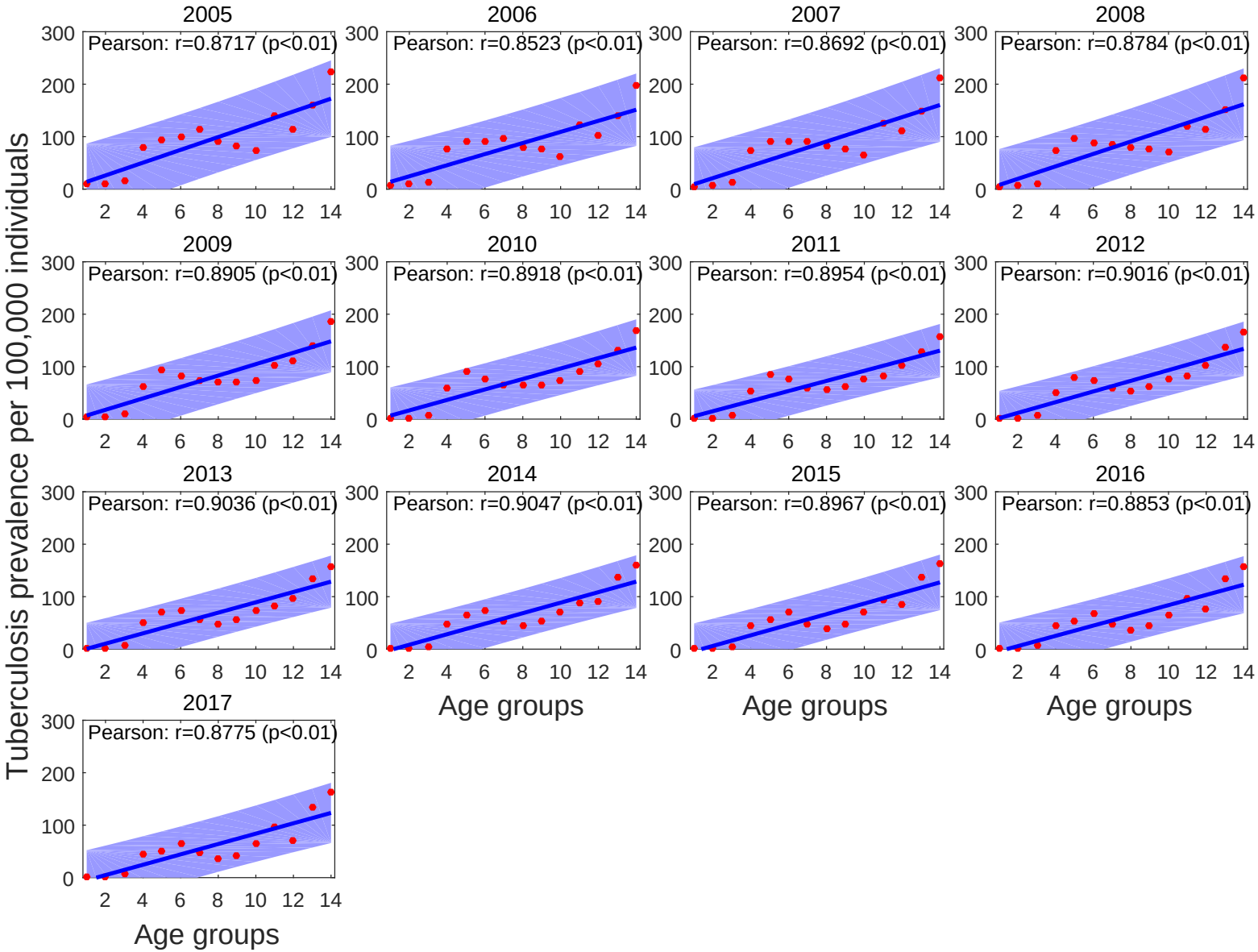

Figure: (A) TB prevalence per 100,000 individuals. (B) The population pyramids by age and gender in China.

# Data collection and analysis

**Table:** Distribution of monthly TB prevalence per 100,000 individuals in mainland China from January 2005 to December 2017. Q1 represents 25th percentile, Q3 represents 75th percentile.

| Age group | Mean±SD | Min | Q1 | Median | Q3 | Max |
|---|---|---|---|---|---|---|
| 0-4 | 0.2851±0.2069 | 0.0736 | 0.1437 | 0.1899 | 0.3823 | 1.0040 |
| 5-9 | 0.3288±0.2876 | 0.0729 | 0.1292 | 0.1714 | 0.4809 | 1.3029 |
| 10-14 | 0.7130±0.3242 | 0.3850 | 0.4845 | 0.5817 | 0.8180 | 1.9499 |
| 15-19 | 4.8932±1.5238 | 2.6848 | 3.7416 | 4.4346 | 5.8425 | 9.8901 |
| 20-24 | 6.5233±1.7891 | 3.1442 | 4.9817 | 6.4877 | 7.9775 | 10.1162 |
| 25-29 | 6.5874±1.3739 | 3.2667 | 5.6593 | 6.5625 | 7.3056 | 10.0414 |
| 30-34 | 5.7410±2.0181 | 3.0830 | 4.2417 | 5.0779 | 6.8463 | 11.5837 |
| 35-39 | 4.9694±1.7879 | 2.4363 | 3.3583 | 4.6634 | 6.2546 | 9.2314 |
| 40-44 | 5.2128±1.3936 | 2.6938 | 4.0760 | 5.0763 | 6.1453 | 8.7398 |
| 45-49 | 5.9061±0.9827 | 2.2969 | 5.3437 | 5.9281 | 6.5457 | 7.9757 |
| 50-54 | 8.4524±2.1371 | 4.6131 | 7.0249 | 7.9349 | 9.5958 | 14.7280 |
| 55-59 | 8.1967±1.8172 | 3.7646 | 6.7916 | 8.1814 | 9.5053 | 12.8277 |
| 60-64 | 11.6263±2.0954 | 5.2955 | 10.2514 | 11.4184 | 12.9065 | 17.3916 |
| 65+ | 14.8427±3.2316 | 7.9119 | 12.4234 | 14.2146 | 16.5781 | 24.4819 |
| All age groups | 84.2783±19.2311 | 43.5115 | 70.7735 | 80.7513 | 95.2204 | 138.6615 |

# Data analysis



# Data collection and analysis

1. Pearson's correlation analysis showed that the prevalence of TB per 100,000 individuals was highly positively correlated with the age of individuals infected with TB from 2005 to 2017.
2. The correlation coefficient between the prevalence of TB per 100,000 individuals and the age of individuals infected with TB was greater than 0.85 ($p < 0.01$) from 2005 to 2017, which indicates that older people are more likely to be infected by Mycobacterium TB.

# Contact matrices ($c_{ij}$)

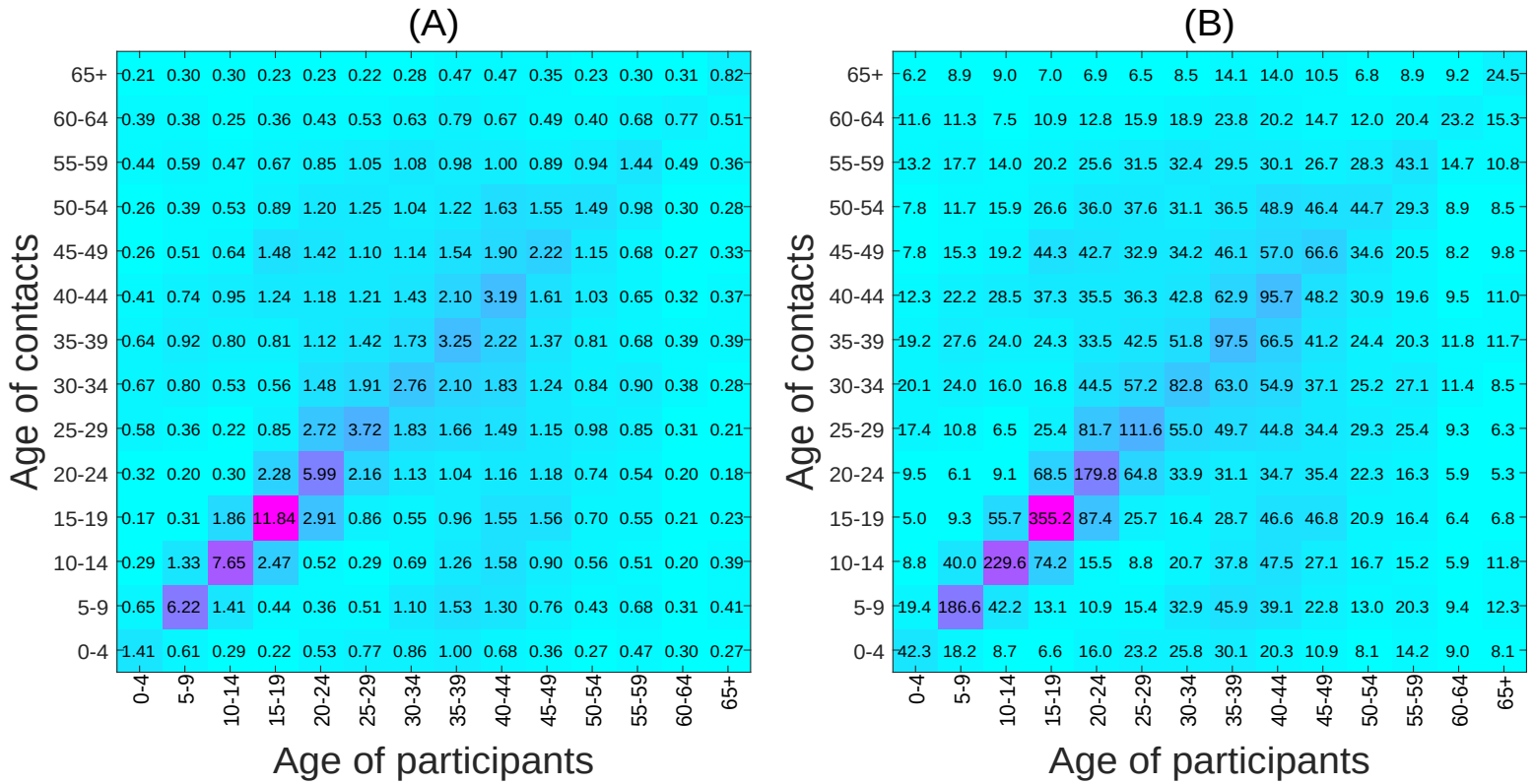
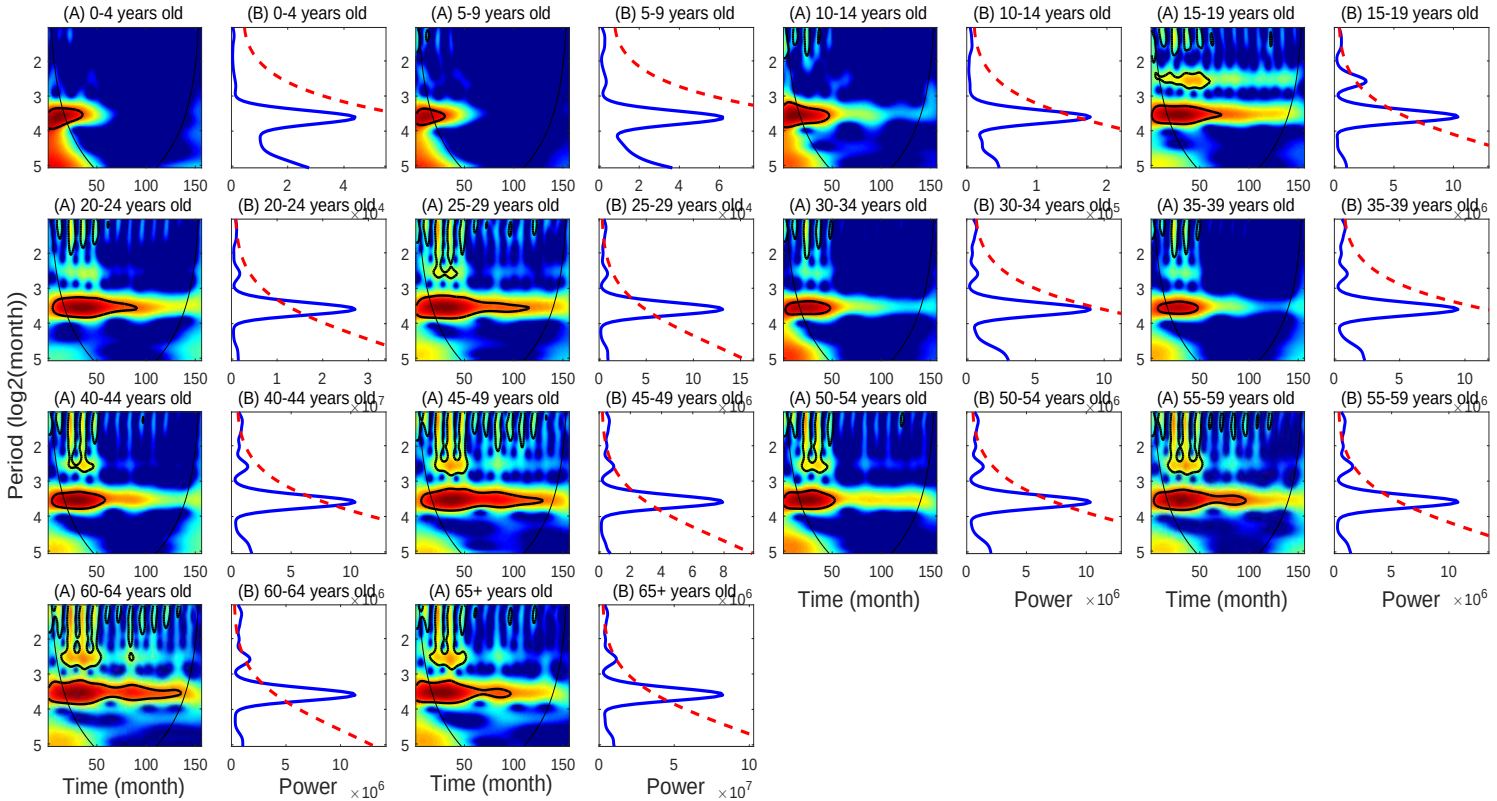



Figure: (A) The daily average number of contacts per person in the participant age group[4]. (B) The monthly average number of contacts per person in the participant age group.

[4] Prem K, Cook AR, Jit M (2017) Projecting social contact matrices in 152 countries using contact surveys and demographic data. PLOS Computational Biology 13(9):e1005697

# Fitting the seasonal fluctuation of TB ($\beta_k(t)$)




(A) The wavelet spectrum analysis of monthly new TB cases. High power values are colored in red , orange,yellow: intermediate, cyan and blue: low. The black line is the 95% confidence level. (B) The average wavelet spectrum (blue ) and 95% confidence contour (red).

# Parameter estimation for $\beta_k(t)$

We choose $\beta_k(t)$ as the periodic function for each age group as follows

$$\beta_k(t) = \hat{\beta}_k \left(1 + \bar{\beta}_k \sin\left(\frac{2\pi t}{12} + \phi_k\right)\right),\ 1 \le k \le 14,$$

where $\hat{\beta}_k$ is called the baseline level of transmission, $\bar{\beta}_k$ is known as the amplitude of seasonal variation or simply the strength of seasonality[5], $\phi_k$ indicates the phase of the $\mathcal{T}$-periodic function.

[5]Cintron-Arias A, Banks HT, Capaldi A, Lloyd AL (2009) A sensitivity matrix based methodology for inverse problem formulation. Journal of Inverse and Ill-posed Problems 17(6):1-20.

# Parameter estimation

Next, we use the MCMC method[6] to fit the system for 800000 iterations with a burn-in of 750000 iterations. We estimate the unknown parameters and initial conditions for System, using the monthly number of new TB cases in mainland China. The unknown parameters and initial values set is

$$\hat{\chi} = (\hat{\chi}_1, \cdots, \hat{\chi}_k, \cdots, \hat{\chi}_n),$$

where

$$\hat{\chi}_k = \begin{cases} \big(\hat{\beta}_k, \bar{\beta}_k, \phi_k, \delta_k, \varrho_k, \theta_k, \sigma_k, \chi_k, I_k(0), R_k(0), V_k(0)\big), & 1 \le k \le 2, \\ \big(\hat{\beta}_k, \bar{\beta}_k, \phi_k, \delta_k, \varrho_k, \theta_k, \sigma_k, \chi_k, I_k(0), R_k(0)\big), & 3 \le k \le 14. \end{cases}$$

[6] Haario H, Laine M, Mira A, Saksman E (2006) DRAM: Efficient adaptive MCMC. Statistics and Computing 16(4):339-354.

# Parameter estimation-Cntd

Let $\hat{C}_k(t, \hat{\chi}), (1 \leq k \leq 14)$ represent the cumulative number of TB cases, then the cumulative infection cases of the $k$-th age group can be expressed as follows

$$\frac{\mathrm{d}\hat{C}_k(t, \hat{\chi})}{\mathrm{d}t} = \xi_k \theta_k I_k, \ (1 \leq k \leq n).$$

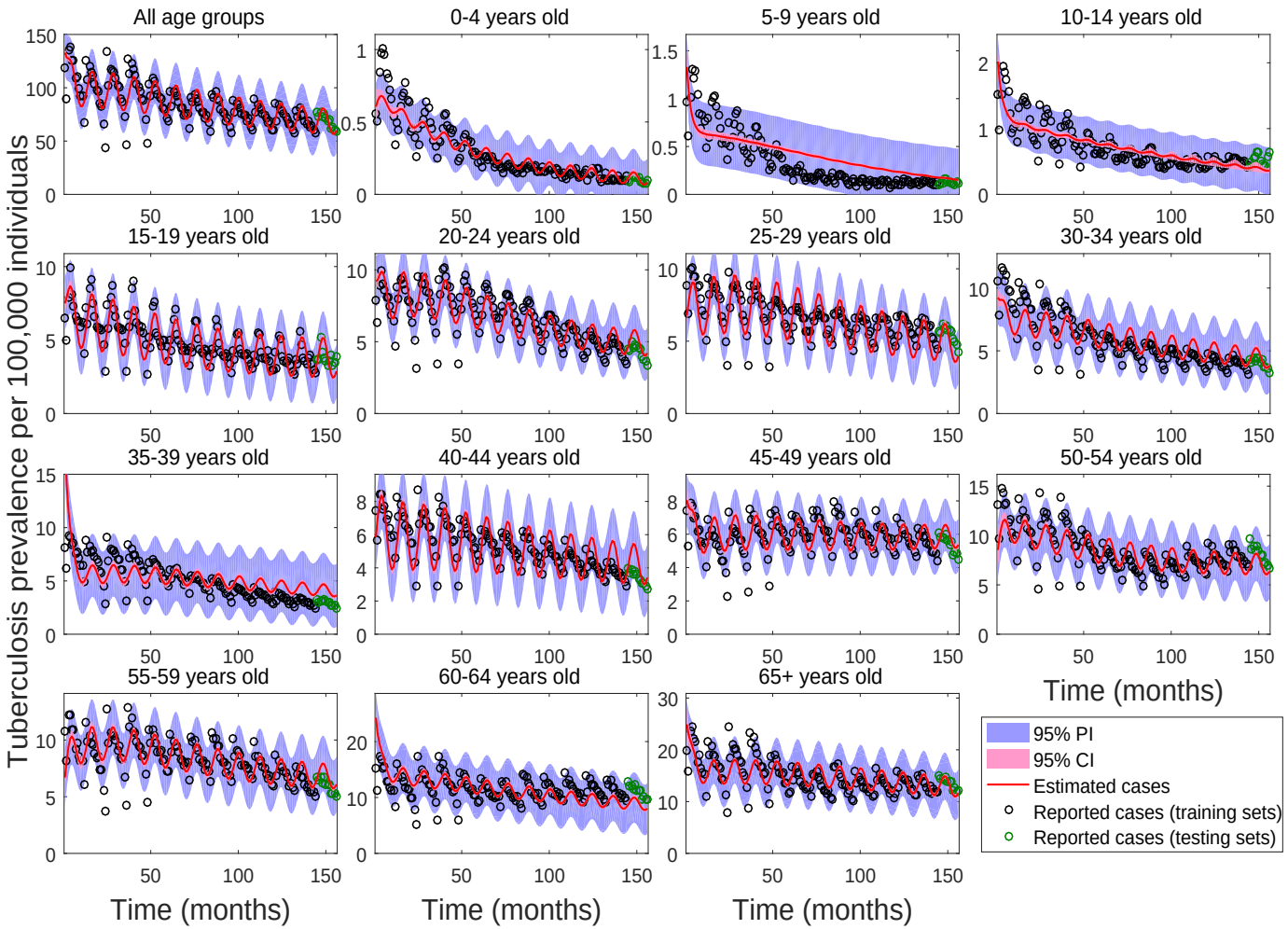
The number of new TB cases of the $k$-th age group can be expressed as follows

$$\hat{P}_k(t, \hat{\chi}) = \xi_k \theta_k I_k, \ (1 \leq k \leq n),$$

where $\hat{P}_k$ represents the number of new TB cases of the $k$-th age group, the time step is month in the simulations.

# Curve fitting for different groups

We randomly select 10% of the last 50,000 samples as the final distribution of parameters.



# Curve fitting for different years

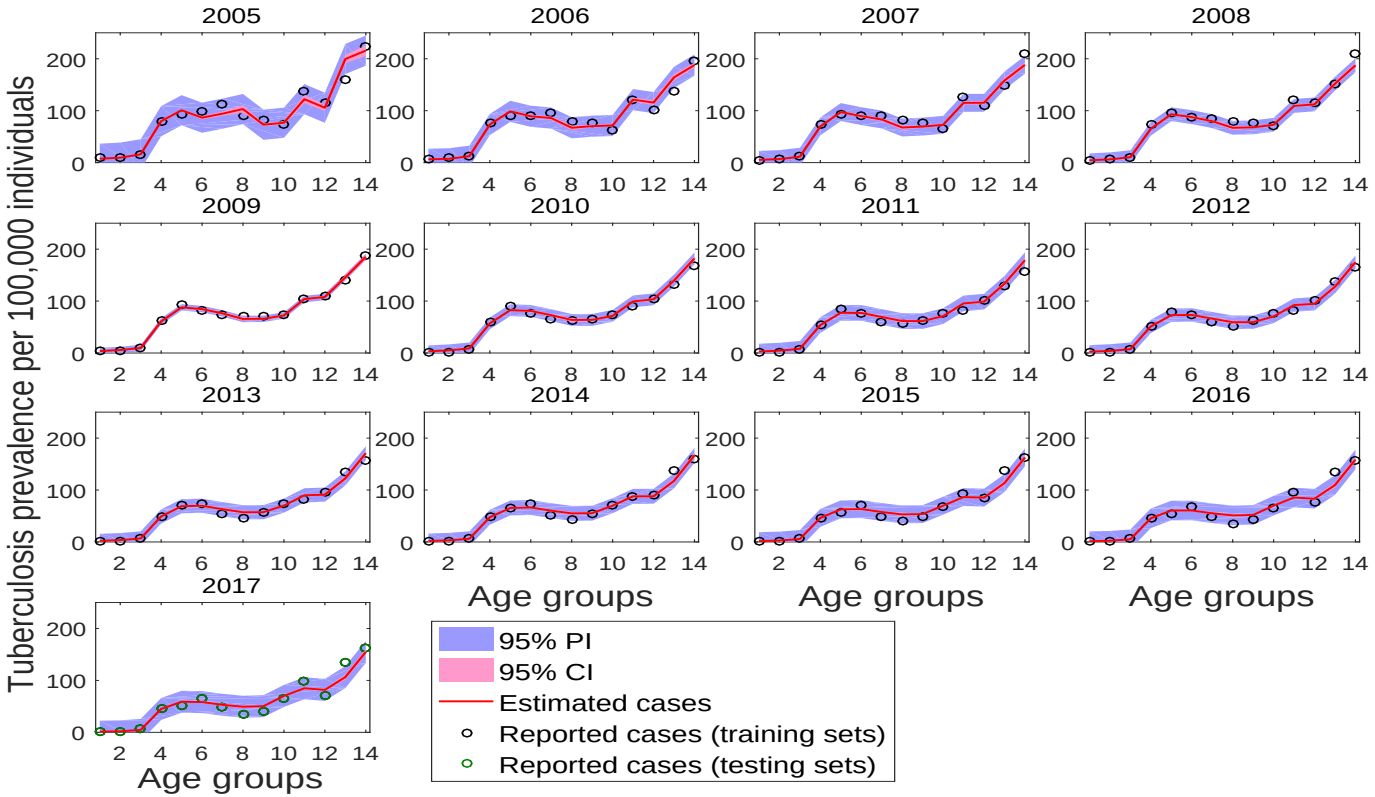



Figure: The fitting results of TB prevalence per 100,000 individuals varying with age groups. The solid red line represents the simulated curve of the system. Black circles represent training data, and green circles represent testing data. The 95% confidence and prediction intervals are shown in light red and light blue, respectively.

# Goodness of curve fitting

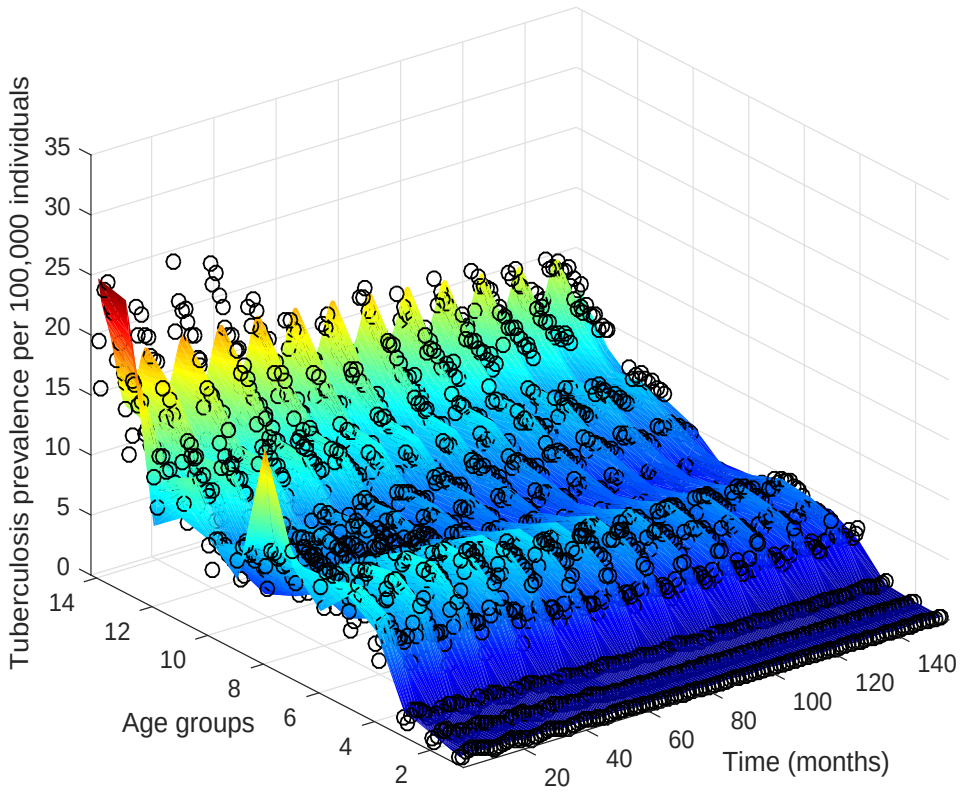
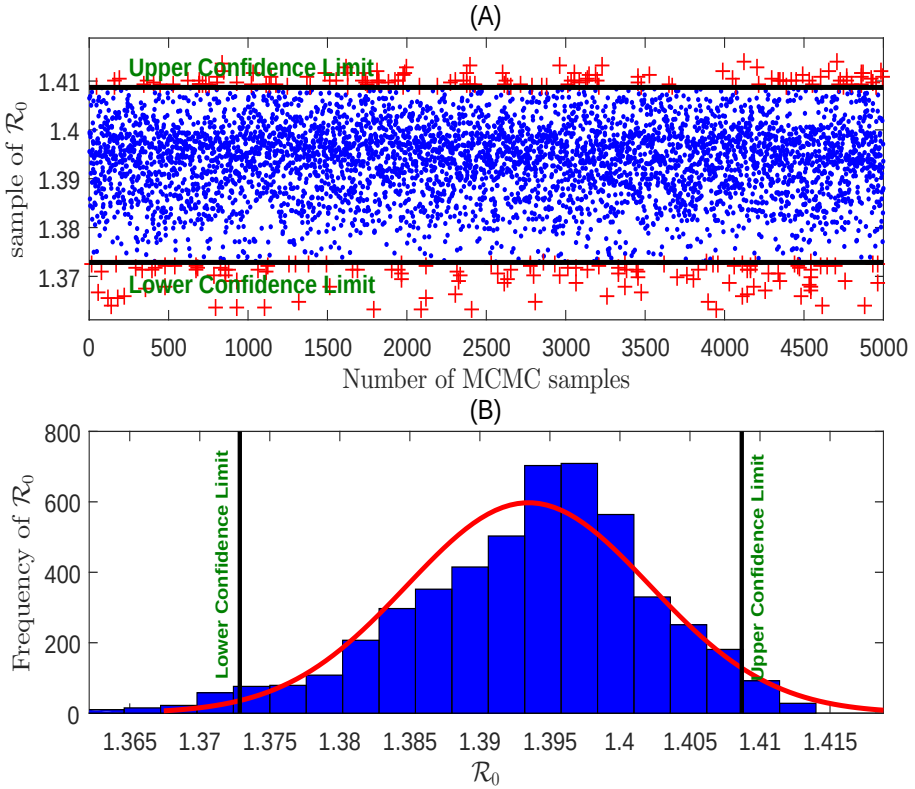



Figure: 3-D graph of the fitting results of monthly TB prevalence per 100,000 individuals from January, 2005 to December, 2017.

# Basic reproduction number




The basic reproduction number, $\mathcal{R}_0$, is estimated to be 1.3935 (95%CI : (1.3729, 1.4087)). Since $\mathcal{R}_0 > 1$, the system is uniformly persistent, which indicates that TB will not go extinct in the future without additional control measures.

# Sensitivity analysis

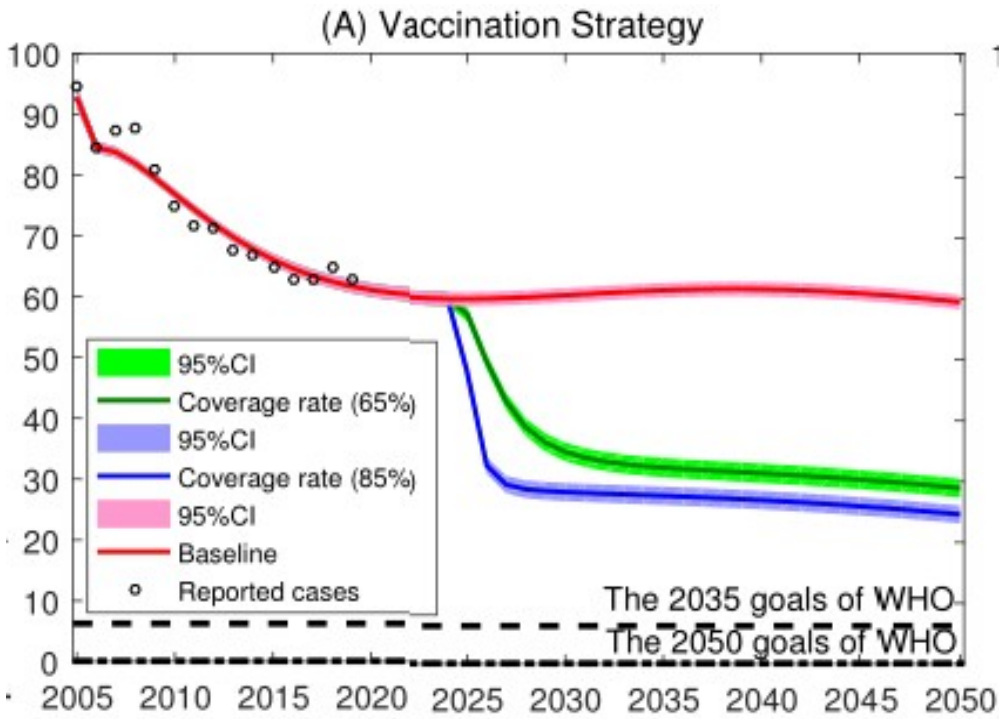
**Table:** The PRCCs of the parameters with respect to the new cases in 2017.

| Parameters | PRCC | $p$-value | Parameters | PRCC | $p$-value |
|---|---|---|---|---|---|
| $\theta_k(1 \leq k \leq 14)$ | -0.6258 | $p < 0.01$ | $\nu_3$ | -0.2328 | $p < 0.01$ |
| $\sigma_k(1 \leq k \leq 3)$ | 0.05428 | $p = 0.01544$ | $\nu_4$ | -0.6337 | $p < 0.01$ |
| $\sigma_k(4 \leq k \leq 11)$ | 0.6828 | $p < 0.01$ | $\nu_5$ | -0.7569 | $p < 0.01$ |
| $\sigma_k(12 \leq k \leq 13)$ | 0.8540 | $p < 0.01$ | $\nu_6$ | -0.6285 | $p < 0.01$ |
| $\sigma_k(k = 14)$ | 0.5283 | $p < 0.01$ | $\nu_7$ | -0.5623 | $p < 0.01$ |
| $\chi_k(1 \leq k \leq 3)$ | 0.1118 | $p < 0.01$ | $\nu_8$ | -0.6748 | $p < 0.01$ |
| $\chi_k(4 \leq k \leq 11)$ | 0.8098 | $p < 0.01$ | $\nu_9$ | -0.6995 | $p < 0.01$ |
| $\chi_k(12 \leq k \leq 13)$ | 0.8740 | $p < 0.01$ | $\nu_{10}$ | -0.6317 | $p < 0.01$ |
| $\chi_k(k = 14)$ | 0.8205 | $p < 0.01$ | $\nu_{11}$ | -0.5642 | $p < 0.01$ |
| | | | $\nu_{12}$ | -0.5188 | $p < 0.01$ |
| | | | $\nu_{13}$ | -0.4984 | $p < 0.01$ |
| | | | $\nu_{14}$ | -0.7533 | $p < 0.01$ |

# Sensitivity analysis

1. The relapse rate of recovered individuals over 15 years old (i.e. $\chi_k$ $(4 \leq k \leq 14)$) is highly positively correlated with the total number of new cases, the relapse rate of recovered individuals under 15 years old (i.e. $\chi_k$ $(1 \leq k \leq 3)$) is not correlated with the total number of new cases.
2. The risk of reactivation in latently infected individuals (i.e. $\sigma_k$ $(4 \leq k \leq 14)$) over 15 years old is higher than that in latently infected individuals (i.e. $\sigma_k$ $(1 \leq k \leq 3)$) under 15 years old.
3. The diagnosis rate of TB (i.e. $\theta_k$ $(1 \leq k \leq 14)$) is highly negatively correlated with the total number of new cases.
4. The vaccination rate for susceptible individuals (i.e. $\nu_k$ $(4 \leq k \leq 14)$) over 15 years old is highly negatively correlated with the total number of new cases. In particular, the vaccination rates of susceptible individuals over 65 and between 20 and 24 have the strongest correlation with the total number of new cases.

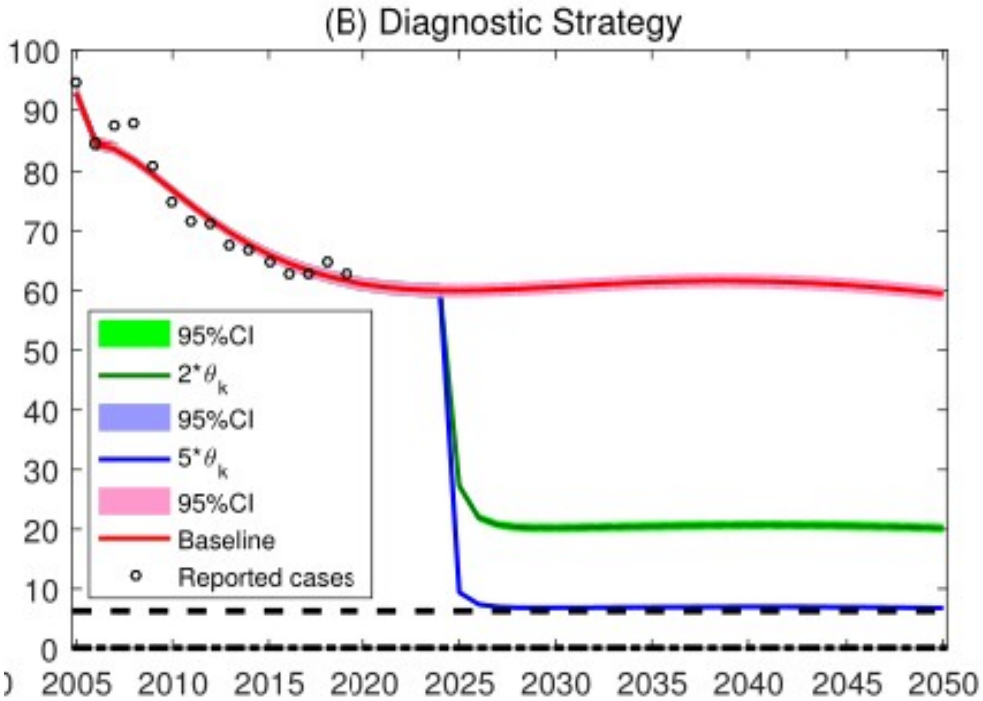
# Vaccination strategy




1. We predict that increasing the percentage of vaccinated susceptible individuals to 65% and 85% can reduce the TB prevalence per 100,000 individuals by 47.44% and 54.98% by 2035, respectively.

2. We further predict that increasing the percentage of vaccinated susceptible individuals to 65% and 85% can reduce the TB prevalence per 100,000 individuals by 51.40% and 58.66% by 2050, respectively.

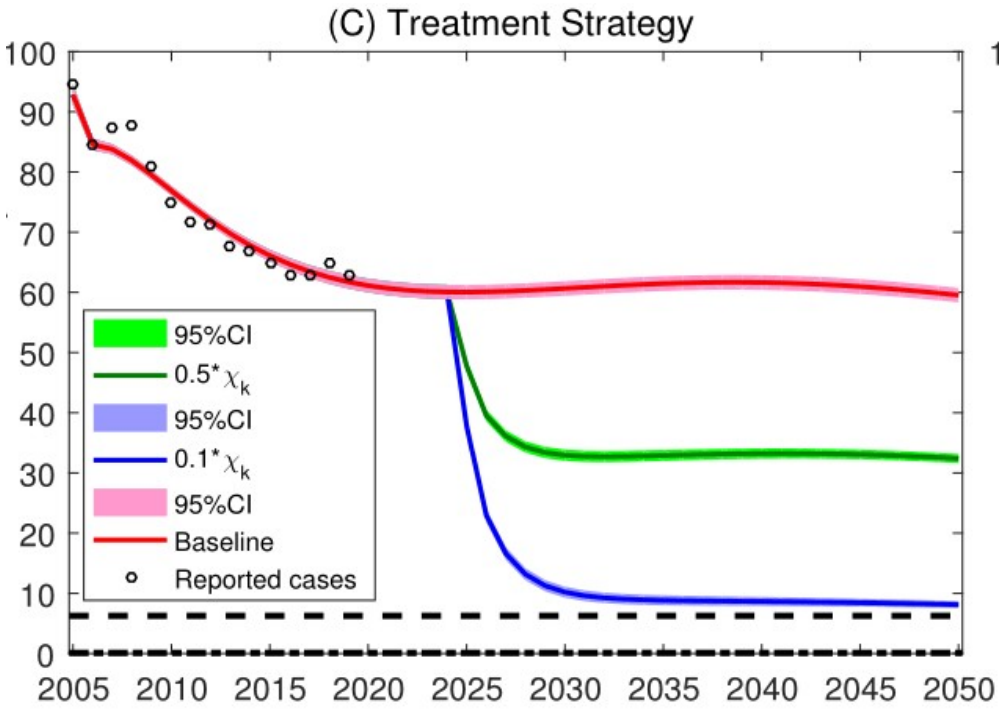
# Diagnosis strategy




1. We predict that decreasing the delayed diagnosis time of infected individuals to its 1/2 and 1/5 can reduce the TB prevalence per 100,000 individuals by 66.63% and 88.74% by 2035, respectively .

2. Decreasing the delayed diagnosis time of infected individuals to its 1/2 and 1/5 can reduce the TB prevalence by 66.09% and 88.59% by 2050, respectively.

# Treatment strategy




1. We predict that decreasing the relapse rate of recovered individuals by half or 90% can reduce the TB prevalence per 100,000 individuals by 46.45% and 85.61% by 2035, respectively.

2. We further predict that changing the relapse rate of recovered individuals by half or 90% can reduce the TB prevalence per 100,000 individuals by 45.55% and 86.33% by 2050, respectively.

# Combination of multiple intervention strategies

We simulate the follows eight scenarios:

Scenario A: Vaccine coverage is 85%, Diagnosis rate is $5\theta_k$, Relapse rate is $0.1\chi_k$;

Scenario B:Vaccine coverage is 85%, Diagnosis rate is $5\theta_k$, Relapse rate is $0.5\chi_k$;

Scenario C: Vaccine coverage is 85%, Diagnosis rate is $2\theta_k$, Relapse rate is $0.1\chi_k$;

Scenario D: Vaccine coverage is 85%, Diagnosis rate is $2\theta_k$, Relapse rate is $0.5\chi_k$;

Scenario E: Vaccine coverage is 65%, Diagnosis rate is $5\theta_k$, Relapse rate is $0.1\chi_k$;

Scenario F: Vaccine coverage is 65%, Diagnosis rate is $5\theta_k$, Relapse rate is $0.5\chi_k$;

Scenario G: Vaccine coverage is 65%, Diagnosis rate is $2\theta_k$, Relapse rate is $0.1\chi_k$;

Scenario H: Vaccine coverage is 65%, Diagnosis rate is $2\theta_k$, Relapse rate is $0.5\chi_k$.

# Combination of multiple intervention strategies

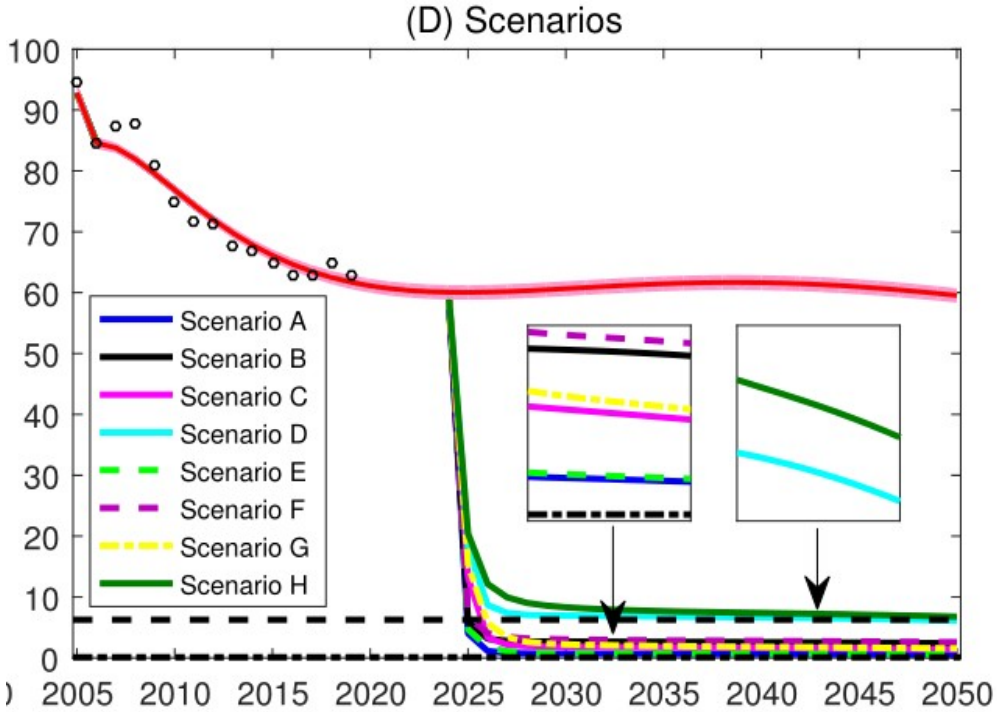



**Table:** The combination of vaccination strategy, diagnostic strategy, and treatment strategy.

| Scenario | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| TBP (2035) | 0.67 | 2.64 | 1.74 | 6.81 | 0.73 | 2.88 | 1.96 | 7.69 |
| Decline rate (2035) | 98.91% | 95.71% | 97.17% | 88.92% | 98.81% | 95.32% | 96.81% | 87.50% |
| TBP (2050) | 0.55 | 2.40 | 1.42 | 6.13 | 0.59 | 2.59 | 1.56 | 6.78 |
| Decline rate (2050) | 99.07% | 95.96% | 97.62% | 89.70% | 99.01% | 95.65% | 97.38% | 88.61% |

TBP: TB prevalence per 100,000 individuals.

# Conclusions and Discussion

1. Age structure and seasonal transmission rate are incorporated into a non-autonomous differential equation model to study the dynamic properties of the model.
2. The TB prevalence per 100,000 individuals was highly positively correlated with the age of infected individuals from 2005 to 2017 (Pearson correlation coefficients: $>0.85$, $p<0.01$).
3. The basic reproduction number, $\mathcal{R}_0$, is estimated to be 1.3935 ($95\%CI : (1.3729, 1.4087)$), which indicates that the TB is uniformly persistent.
4. The system has at least one positive periodic solution.
5. The vaccination rate of susceptible individuals over 15 years old and the diagnosis rate of TB are highly negatively correlated with the total number of new TB cases.

# Conclusions and Discussion-Cntd

6. The relapse of recovered individuals over 15 years old is highly positively correlated with the total number of new TB cases.
7. When scenario A (i.e. coverage rate 85%, diagnosis rate $5\theta_k$, relapse rate $0.1\chi_k$) is selected, the TB prevalence per 100,000 individuals can be reduced by 98.91% and 99.07% in 2035 and 2050, respectively.
8. The goals of WHO in 2050 cannot be achieved because of reinfection in latent and recovered populations if current strategies do not change. The elimination of TB requires additional strategies, such as large-scale vaccination for latent and recovered individuals.
9. There are still some limitations. Heterogeneities among individuals and behavior change were not taken into account in the model.

# Mathematical Biology research group

Faculty

Students

# Welcome to Harbin Engineering University


*Thank you for your attention!*