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Dynamic model of tuberculosis considering multi-drug resistance and their applications

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ABSTRACT

Infectious diseases have always been a problem that threatens people's health and tuberculosis is one of the major. With the development of medical scientific research, drug-resistant infectious diseases have become a more intractable threat because various drugs and antibiotics are widely used in the process of fighting against infectious diseases. In this paper, an improved dynamic model of infectious diseases considering population dynamics and drug resistance is established. The feasible region, equilibrium points and stability of the model are analyzed. Based on the existing data, this model can predict the development of the epidemic situation through numerical simulation, and put forward some relevant measures and suggestions.

1. Introduction

Nowadays, our fast-moving, interdependent and interconnected world offers countless new opportunities for the spread of infectious diseases. From a geographical point of view, the speed of today's infectious diseases is faster than any time in history. Among them, tuberculosis (TB) has been one of the major threats in the world, and is difficult to be controlled for its easy infection. While under this situation, drug-resistant TB began to appear and showed an upward trend. The main reason is that those patients with vulnerable touches of mycobacterium TB may develop multidrug resistance TB due to inadequate treatment courses, not take medicine with a doctor's instructions or inferior quality medicine in the treatment process (O'Brien, 1994). However, drug-resistant strains of TB variant caused by patient's forgetting to take medicine or terminating of treatment prior to the completion of a treatment cycle, may develop different levels of drug-resistance to those medications for treatment (Centers for Disease Control and Prevention (CDC), 2006; Migliori, De Iaco, Besozzi, Centis, & Cirillo, 2007). Drug-resistant TB has a higher mortality rate, among them, multi-drug resistant tuberculosis (MDR-TB) is more prominent, and has become another new serious problem (Lu, 2007).

According to the world health organization (WHO) global TB report in 2017, it is estimated that there will be 490,000 new cases of MDR-TB in 2016, in addition, 110,000 new patients who resistant to rifampicin meet the treatment conditions of multi drug resistance tuberculosis. India, China and the Russian federation together account for 47 per cent of the two (about 0.6 million cases). However, 600, 000 patients with MDR-TB in this study, only 129,000 (22 per cent) were enrolled for treatment.

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There is a gap between the incidence of drug-resistant TB and the number of received treatment cases, ten countries[1] accounted for 75 per cent, while India and China accounted for 39 per cent (Global tuberculosis repor, 2017).

Drug-resistant TB is a public health issue, which is serious and has attached deeply concern in many developing countries, as well as around the world, it also requires extending the period of treatment, and needs more expensive new drugs. The long-term threat of drug-resistant TB also reminds national health organizations around the world that they need to pay more attention to the research on their pathological mechanisms, infection laws and prevention as well as control measures. With the development of pharmacology, medicine and other research, e.g the study of genetics and bacteriology, there has been a certain degree of cognition of TB. However, due to the complexity of the anti-drug mechanism of TB, there is also no clear explanation for it (Wade et al., 2004). Different researchers in the world have tried to study TB through many factors such as population, behavior habits, ecological environment, social environment and so on. Souza WV et al. (Souza et al., 2007) studied the influence of population behavior. Fan YD et al. (Fan et al., 2008) analyzed the drug resistance under different age structures. Chan-yeung et al. (Chan-yeung et al., 2005) studied the drug resistance from the perspective of sociology.

Mathematical modeling is a very important tool to study epidemics, is also used to predict the spread of infectious diseases, and it enables public health policy makers to optimize the use of limited resources as well as to formulate policies effectively for specific populations. Waaler H et al. (Waaler, Geser, & Andersen, 1962) first proposed the mathematical model of TB in 1962. Brogger S (Brogger, 1967) proposed a non-complete linear infection rate in 1967 and perfected the model. Castillo-Chavez et al. (Castillo-Chavez & Feng, 1997) proposed the basic SEIR model for the spread of TB's study in 1997. Ronoh M et al. (Ronoh et al., 2016) extend the standard SEIRS epidemiology model of TB to include MDR-TB. Blower SM et al. (Blower, Small, & et. al, 1996) and Rodrigues P et al. (Rodrigues et al., 2004) increase the influence of drug-resistant factors respectively, and study the infection laws of drug-resistant TB. Liu YQ et al. (Liu & Sun, 2010) describe a novel model combines MDR-TB with undetected TB cases, and the basic reproduction number R_0 is calculated. Mishra BK et al. (Mishra & Srivastava, 2014) propose a mathematical model with an assumption for the transfer of proportion of susceptible population to the vaccination class is considered. Quarantine class is also considered in epidemic model for multidrug-resistant patients, and it is observed that it may play a vital role in controlling the disease. Trauer JM et al. (Trauer, Denholm, & McBryde, 2014) present a ten-compartment deterministic model captures many of the observed phenomena important to disease dynamics, including partial and temporary vaccine efficacy, declining risk of active disease following infection, the possibility of reinfection both during the infection latent period and after treatment, MDR-TB and de novo resistance during treatment. Agusto FB et al. (Agusto et al., 2015) present a deterministic model with isolation and lost to follow-up for the transmission dynamics of three strains of Mycobacterium TB. Kendall EA et al. (Kendall et al., 2017) developed a dynamic transmission model of multi-strain TB epidemics in hypothetical populations reflective of the epidemiological situations. Sharma A et al. (Sharma et al., 2017) calibrated a compartmental model to data from drug resistance surveys and WHO TB reports to forecast estimates of incident MDR and XDR TB and the percentage of incident MDR-TB caused by acquired drug resistance. Fofana MO et al. (Fofana et al., 2017) used a multistrain model of mycobacterium TB transmission in Southeast Asia to investigate how this practice might facilitate the emergence of extensive drug resistance, i.e., resistance to multiple core agents, and calibrated this model to regional TB and drug resistance data using an approximate Bayesian computational approach. Carvalho ARM et al. (Carvalho & Pinto, 2018) studied the impact of diabetes and MDR strains in a non-integer order model for TB infection in a community.

Mathematical epidemiology has contributed a lot to the understanding of disease transmission processes and their control, but the specifics are still unknown. In the present work, we extend the standard SEIS mathematical model to take into account the MDR-TB. We assume that drug resistance can emerge by infection or as a consequence of treatment (not proper treated for various reasons). The feasible region, equilibrium points and stability of this model are analyzed, the numerical simulations are performed to predict the development of the epidemic situation.

2. Model and method

2.1. Model

The mechanism of the dynamical transfer of the disease through the total population is depicted in Fig. 1, where S is the susceptible, E_S is the exposed of general TB, E_r is the exposed of MDR-TB, I_S is the infected of general TB, I_r is the infected of MDR-TB.

Where b is natural birth rate. d is natural mortality. α is the death rate induced by disease. β is the coefficient indicating the rate at which new infections arise given contacts between susceptible and infectious individuals. γ is the cure rate of the infected humans. t_γ is the transformation rate from the infected with drug-sensitive strains to drug-resistant strains. All parameters are non-negative. Logistic model is employed to describe the population variation to time

$$\frac{dN}{dt} = (b-d)\left(1-\frac{N}{k}\right)N - \alpha(I_s + I_r) \tag{1}$$

[1] The treatment cap of drug-resistant TB cases in 10 countries from big to small is: India, China, Russian federation, Indonesia, Philippines, Pakistan, Nigeria, Ukraine, Myanmar and Uzbekistan.

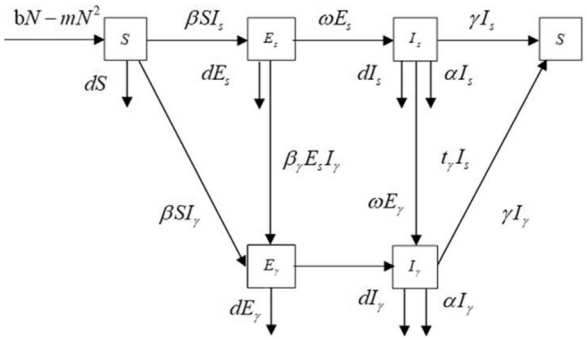

Fig. 1. The modified transfer diagram of the SEIS model.

Therefore, $bN - mN^2$ refers to the recruitment of susceptible individuals into the population by birth or by immigration, where $m = (b-\alpha)/k$, k is the environmental capacity.

According to the normal condition, we assume $b - d > 0$. It can be infer that when $N > k$, $\frac{dN}{dt} < 0$, then the final tread of entire trajectories of this equation are tend, enter or stay in$N = S + E_s + E_\gamma + I_s + I_\gamma \le k$. Therefore, the feasible region of this equation is

$$\Gamma = \left\{(S, E_s, E_\gamma, I_s, I_\gamma) \in R^5, 0 \le S, E_s, E_\gamma, I_s, I_\gamma \le k, 0 \le S + E_s + E_\gamma + I_s + I_\gamma \le k\right\}.$$

This model adopts bilinear incidence and follows system of ordinary differential equations

$$\begin{cases} \dfrac{dS}{dt} = bN - mN^2 - \beta SI_s - \beta SI_\gamma + \gamma I_s + \gamma I_\gamma - d \cdot S \\ \dfrac{dE_s}{dt} = \beta SI_s - \beta E_s I_\gamma - (\omega + d)E_s \\ \dfrac{dE_\gamma}{dt} = \beta SI_\gamma + \beta E_s I_\gamma - (\omega + d)E_\gamma \\ \dfrac{dI_s}{dt} = \omega E_s - (\gamma + \alpha + d + t_\gamma)I_s \\ \dfrac{dI_\gamma}{dt} = \omega E_\gamma + t_\gamma I_s - (\gamma + \alpha + d)I_\gamma \end{cases} \tag{2}$$

2.2. Reproduction number R_0

Let $x = (S, E_s, E_\gamma, I_s, I_\gamma)^T$, divided x into 2 parts, $x_1 = (S, E_s, I_s)^T$, x_2=$(S, E_r, I_r)^T$. The infected compartments are E and I, giving $m = 2$. Following the method of next generation matrix by P.van den Driessche and Watmough (van den DriesscheJames, 2005), we derive the reproduction number of TB (R_1) and MDR TB (R_2), respectively.

$$f_1 = \begin{bmatrix} \beta SI_s \\ 0 \\ 0 \end{bmatrix}, \quad v_1 = \begin{bmatrix} \beta E_s I_\gamma + (w + d)E_s \\ (\gamma + \alpha + d + t_\gamma)I_\gamma - \omega E_s \\ -bN + mN^2 + \beta SI_\gamma - \gamma I_s - \gamma I_\gamma + dS \end{bmatrix}.$$

It's easy to get

$$F_1{}' = \begin{bmatrix} 0 & \beta S_0 \\ 0 & 0 \end{bmatrix}, \quad V_1{}' = \begin{bmatrix} \omega + d & 0 \\ -\omega & \gamma + \alpha + d + t_\gamma \end{bmatrix},$$

$$F_1{}' V_1{}'^{-} = \begin{bmatrix} \dfrac{\beta S_0 \omega}{(\omega + d)(\gamma + \alpha + d + t_\gamma)} & \dfrac{\beta S_0}{\gamma + \alpha + d + t_\gamma} \\ 0 & 0 \end{bmatrix}.$$

Therefore,

$$R_1 = \rho\left(F_1{}' V_1{}'^{-}\right) = \frac{\beta\omega S_0}{(\omega + d)(\gamma + \alpha + d + t_\gamma)} \tag{3}$$

Similarly,

$$f_2 = \begin{bmatrix} \beta S I_\gamma + \beta E_s I_\gamma \\ 0 \\ 0 \end{bmatrix}, \quad v_2 = \begin{bmatrix} (w + d)E_\gamma \\ (\gamma + \alpha + d)I_\gamma - \omega E_\gamma - t_\gamma I_s \\ -bN + mN^2 + \beta S I_\gamma - \gamma I_s - \gamma I_\gamma + dS \end{bmatrix}.$$

Then,

$$F_2{}' = \begin{bmatrix} 0 & \beta S_0 \\ 0 & 0 \end{bmatrix}, \quad V_2{}' = \begin{bmatrix} \omega + d & 0 \\ -\omega & \gamma + \alpha + d \end{bmatrix},$$

$$F_2{}' V_2{}'^{-} = \begin{bmatrix} \dfrac{\beta S_0 \omega}{(\omega + d)(\gamma + \alpha + d)} & \dfrac{\beta S_0}{\gamma + \alpha + d} \\ 0 & 0 \end{bmatrix}.$$

Therefore,

$$R_2 = \rho\left(F_2{}' V_2{}'^{-}\right) = \frac{\beta\omega S_0}{(\omega + d)(\gamma + \alpha + d)} \tag{4}$$

Then, the basic reproduction number

$$R_0 = \max\{R_1, R_2\} = \max\left\{\frac{\beta\omega S_0}{(\omega + d)(\gamma + \alpha + d + t_\gamma)}, \frac{\beta\omega S_0}{(\omega + d)(\gamma + \alpha + d)}\right\} \tag{5}$$

Because $t_\gamma > 0$, then

$$R_0 = \max\{R_1, R_2\} = R_2 = \frac{\beta\omega S_0}{(\omega + d)(\gamma + \alpha + d)} \tag{6}$$

Though the MDR-TB population is much less than the TB (5% or so), it's the MDR-TB basic reproduction number R_2 that determines whether TB can invade the population.

2.3. Stability analysis

Put $N = S + E_s + E_\gamma + I_s + I_\gamma$ into Eq. (2), we get

$$\begin{cases} \dfrac{dN}{dt} = (b - d)N - mN^2 - \alpha(I_s + I_\gamma) \\ \dfrac{dE_s}{dt} = \beta(N - E_s - E_\gamma - I_s - I_\gamma)I_s - \beta E_s I_\gamma - (\omega + d)E_s \\ \dfrac{dE_\gamma}{dt} = \beta(N - E_s - E_\gamma - I_s - I_\gamma)I_\gamma + \beta E_s I_\gamma - (\omega + d)E_\gamma \\ \dfrac{dI_s}{dt} = \omega E_s - (\gamma + \alpha + d + t_\gamma)I_s \\ \dfrac{dI_\gamma}{dt} = \omega E_\gamma + t_\gamma I_s - (\gamma + \alpha + d)I_\gamma \end{cases} \tag{7}$$

We obtain the equilibrium points for the system of Eq. (7) by equating each of the equations to 0 as shown below, that is $\frac{d}{dt} = 0$, then

$$\begin{cases} (b-d)N - mN^2 - \alpha(I_s + I_\gamma) = 0 \\ \beta(N - E_s - E_\gamma - I_s - I_\gamma)I_s - \beta E_s I_\gamma - (\omega + d)E_s = 0 \\ \beta(N - E_s - E_\gamma - I_s - I_\gamma)I_\gamma + \beta E_s I_\gamma - (\omega + d)E_\gamma = 0 \\ \omega E_s - (\gamma + \alpha + d + t_\gamma)I_s = 0 \\ \omega E_\gamma + t_\gamma I_s - (\gamma + \alpha + d)I_\gamma = 0 \end{cases} \tag{8}$$

The solution of this equation set is the equilibrium point of the system. It is easy to obtain the two equilibrium points of the equation, they are $x_{00} = (0,0,0,0,0)^T$ and $x_{01} = (S_0,0,0,0,0)^T$, where S_0 is the total population N, and $S_0 \leq k$.

The parameters derived from the fifth Chinese TB sample survey in 2010 (Wang et al., 2012) and WHO's official statistics on Chinese TB cases from 2010 (World Health Organization, 2011) are shown in Table 1.

The cure rate γ and the infection rate are determined by TB detection rate f,

$$\beta = \frac{6 \times (1-f)}{S} \tag{9}$$

$$\gamma = c^* f \tag{10}$$

where β means if an infected person is not isolated, it will infect 6 susceptible people in one year.

2.3.1. Stability of equilibrium

According to the model parameters in Table 1, the two equilibrium points of this model are $x_{00} = (0,0,0,0,0)^T$ and $x_{01} = (3.6 \times 10^9, 0, 0, 0, 0)^T$.

In this paper, the local stability of the equilibrium point depended on the eigen values of Jacobi matrix, which is obtained by linearizing the nonlinear system of the original model at the equilibrium point. If all the real part of eigen values are negative, the solution of this system converges, hence the equilibrium point is locally stable. If the eigen values are zeros, there may be bifurcation phenomenon, which will be further discussed later.

Here, we discuss x_{00} first, the Jacobi matrix at point x_{00} is

$$\begin{pmatrix} b-d & 0 & 0 & -\alpha & -\alpha \\ 0 & -\omega - d & 0 & 0 & 0 \\ 0 & 0 & -\omega - d & 0 & 0 \\ 0 & \omega & 0 & -\gamma - \alpha - d - t_\gamma & 0 \\ 0 & 0 & \omega & t_\gamma & -\gamma - \alpha - d \end{pmatrix}.$$

Then, the corresponding eigen values are

$$[\lambda_{001}, \lambda_{002}, \lambda_{003}, \lambda_{004}, \lambda_{005}] = [b-d, -\omega - d, -\omega - d, -\gamma - \alpha - d - t_\gamma, -\gamma - \alpha - d] \tag{11}$$

All the parameters except λ_{00} are negative, the original equation set is locally asymptotically stable at x_{00} only in the case of $\lambda_{00} < 0$, that is $b - d < 0$ which is not accordant with reality.

Put the parameters of Table 1 into Eq. (11), then

$$[\lambda_{001}, \lambda_{002}, \lambda_{003}, \lambda_{004}, \lambda_{005}] = [0.005, -0.187, -0.187, -0.9248, -0.8748].$$

Because $\lambda_{001} = 0.005 > 0$, the model is unstable at point x_{00} under this parameter.

Discuss point x_{01} similarly, the Jacobi matrix at point x_{01} is

Table 1
Model parameters and values.

Parameter	Description	Value
α	Death rate induced by disease	0.05
b	Natural birth rate	0.012
d	Natural mortality	0.007
t_γ	Transformation rate from the TB to MDR-TB	0.05
f	TB detection rate	0.87
ω	Removal rate of the exposed to the infected	0.18
c	Successfully cure rate	0.94
k	Environmental capacity	3.6×10^9 (Zhou & He, 1999)

$$\begin{pmatrix} d-b & 0 & 0 & -\alpha & -\alpha \\ 0 & -\omega-d & 0 & \beta k & 0 \\ 0 & 0 & -\omega-d & 0 & \beta k \\ 0 & \omega & 0 & -\gamma-\alpha-d-t_\gamma & 0 \\ 0 & 0 & \omega & t_\gamma & -\gamma-\alpha-d \end{pmatrix}.$$

The corresponding eigen values are given by

$$\begin{aligned}
\lambda_{011} &= d-b \\
\lambda_{012} &= -d-\frac{1}{2}\omega-\frac{1}{2}\gamma-\frac{1}{2}\alpha+\frac{1}{2}\left(\omega^2-2\gamma\omega-2\alpha\omega+\gamma^2+2\gamma\alpha+\alpha^2+4\beta\omega k\right)^{\frac{1}{2}} \\
\lambda_{013} &= -d-\frac{1}{2}\omega-\frac{1}{2}\gamma-\frac{1}{2}\alpha-\frac{1}{2}\left(\omega^2-2\gamma\omega-2\alpha\omega+\gamma^2+2\gamma\alpha+\alpha^2+4\beta\omega k\right)^{\frac{1}{2}} \\
\lambda_{014} &= -d-\frac{1}{2}\omega-\frac{1}{2}\gamma-\frac{1}{2}\alpha-\frac{1}{2}t_\gamma+\frac{1}{2}\begin{pmatrix} {t_\gamma}^2+\omega^2-2\gamma\omega-2\alpha\omega+\gamma^2+2\gamma\alpha+ \\ 2\gamma t_\gamma+\alpha^2+2\alpha t_\gamma+4\beta\omega k \end{pmatrix}^{\frac{1}{2}} \\
\lambda_{015} &= -d-\frac{1}{2}\omega-\frac{1}{2}\gamma-\frac{1}{2}\alpha-\frac{1}{2}t_\gamma-\frac{1}{2}\begin{pmatrix} {t_\gamma}^2+\omega^2-2\gamma\omega-2\alpha\omega+\gamma^2+2\gamma\alpha+ \\ 2\gamma t_\gamma+\alpha^2+2\alpha t_\gamma+4\beta\omega k \end{pmatrix}^{\frac{1}{2}}
\end{aligned} \tag{12}$$

Obviously, λ_{011}, λ_{013}, and $\lambda_{015}<0$. We find $\lambda_{012}<0$ as long as $\frac{\beta\omega k}{(\gamma+\alpha+d)(\omega+d)}<1$, and $\lambda_{014}<0$ as long as $\frac{\beta\omega k}{(\omega+d)(\gamma+\alpha+d+t_r)}<0$. Noticed $R_1=\frac{\beta\omega k}{(\omega+d)(\gamma+\alpha+d+t_r)}$and $R_2=\frac{\beta\omega k}{(\gamma+\alpha+d)(\omega+d)}$ respectively, then the equation set is locally asymptotically stable at point x_{01} when $R_1<0$ and $R_2<0$.

Put the parameters of Table .1 into the Jacobi matrix, then obtain the Jacobi matrix of original equation set at point x_{01}

$$\begin{bmatrix} -0.005 & 0 & 0 & -0.05 & -0.05 \\ 0 & -0.187 & 0 & 1.2217 & 0 \\ 0 & 0 & -0.187 & 0 & 1.2217 \\ 0 & 0.18 & 0 & -0.9248 & 0 \\ 0 & 0 & 0.18 & 0.05 & -0.8748 \end{bmatrix} \tag{13}$$

And get the eigen values

$$[\lambda_{011},\ \lambda_{012},\ \lambda_{013},\ \lambda_{014},\ \lambda_{015}]=[-0.005,\ -1.1526,\ -1.1124\ ,\ 0.0408,\ 0.0506] \tag{14}$$

Because$\lambda_{012},\ \lambda_{014}>0$, this model is unstable at point x_{01} under these parameters.

2.3.2. Stability of endemic equilibrium

There may exist other endemic equilibriums of this equation set in feasible region. By solving the equation set as follows

$$\begin{cases} (b-d)N-mN^2-\alpha(I_s+I_\gamma)=0 \\ \beta(N-E_s-E_\gamma-I_s-I_\gamma)I_s-\beta E_s I_\gamma-(\omega+d)E_s=0 \\ \beta(N-E_s-E_\gamma-I_s-I_\gamma)I_\gamma+\beta E_s I_\gamma-(\omega+d)E_\gamma=0 \\ \omega E_s-(\gamma+\alpha+d+t_\gamma)I_s=0 \\ \omega E_\gamma+t_\gamma I_s-(\gamma+\alpha+d)I_\gamma=0 \end{cases} \tag{15}$$

It can be found that there is another endemic equilibrium within the feasible region

$$x_{02}=\left(2.0267\times10^9,\ 0, 4.305\times10^8,\ 0\ , 8.86\times10^7\right)^T \tag{16}$$

The Jacobi matrix of the equation set at point x_{02} is

$$J=\begin{bmatrix} J_{11} & J_{12} & J_{13} & J_{14} & J_{15} \\ J_{21} & J_{22} & J_{23} & J_{24} & J_{25} \\ J_{31} & J_{32} & J_{33} & J_{34} & J_{35} \\ J_{41} & J_{42} & J_{43} & J_{44} & J_{45} \\ J_{51} & J_{52} & J_{53} & J_{54} & J_{55} \end{bmatrix} \tag{17}$$

where,

$$\begin{aligned} J_{11} &= b-d-7043452464m \\ J_{14} &= J_{15}=-\alpha \\ J_{22} &= J_{33}=-9205043\beta-(\omega+d) \\ J_{24} &= 1364949290\beta \\ J_{31} &= 9205043\beta \\ J_{34} &= -9205043\beta \\ J_{35} &= 1355744247\beta \\ J_{42} &= J_{53}=\omega \\ J_{44} &= -\gamma-\alpha-d-t_{\gamma} \\ J_{55} &= -\gamma-\alpha-d \\ J_{54} &= t_{\gamma} \end{aligned}$$

The rest values are zero.

By substituting the parameters of Table 1, we can obtain the Jacobi matrix of this model at point x_{02}

$$J=\begin{bmatrix} -6.2972\times10^{-4} & 0 & 0 & -0.05 & -0.05 \\ 0 & -0.24041 & 0 & 0.90875 & 0 \\ 0.055 & 0 & -0.24041 & -0.05341 & 0.85534 \\ 0 & 0.18 & 0 & -0.9248 & 0 \\ 0 & 0 & 0.18 & 0.05 & -0.8748 \end{bmatrix} \tag{18}$$

The eigen values are given by

$$[\lambda_{021},\ \lambda_{022},\ \lambda_{023},\ \lambda_{024},\ \lambda_{025}]=[-0.0122,\ -0.0411,\ -1.0626\ ,\ -0.0528,\ -1.1124] \tag{19}$$

According to the stability theory: when the eigen values are all negative ($\mathrm{Re}\lambda_i<0,\ \mathrm{Im}\lambda_i=0$), the node is stable. Therefore, x_{02} is stable, namely, the model is locally asymptotically stable at the endemic equilibrium point x_{02} under the parameters of Table 1.

3. Numerical simulation

According to the data of the fifth Chinese TB sample survey in 2010 and WHO's official statistics on Chinese TB cases in 2010 (Wang et al., 2012; World Health Organization, 2011), the initial values for numerical simulation of the MDR-TB dynamics model are shown in Table 2.

3.1. TB development trend in future 20 years

Based on these data of Table 2, we studied TB development in China in 20 years since 2010. Fig. 2 is the simulation of TB and MDR TB infective number, red line and blue line represent general TB and MDR-TB respectively, while black line is the total cases of general TB and MDR-TB. It showed the number of infected of general TB has a downward trend, while the number of infected of XDR-TB is always rise in the later 20 years, which proves that MDR-TB's control and prevention should

Table 2
Initial parameters values for numerical simulation.

Parameter	Description	Value
N	Size of human population	1.34×10^9
S	The susceptible	1.334×10^9
E	The total exposed (E_s+E_r)	5×10^6
I	The total infected (I_s+I_r)	1.06×10^6
E_s	The exposed of general TB	4.74×10^6
E_r	The exposed of MDR-TB	3×10^5
I_s	The infected of general TB	1×10^6
I_r	The infected of MDR-TB	6×10^4

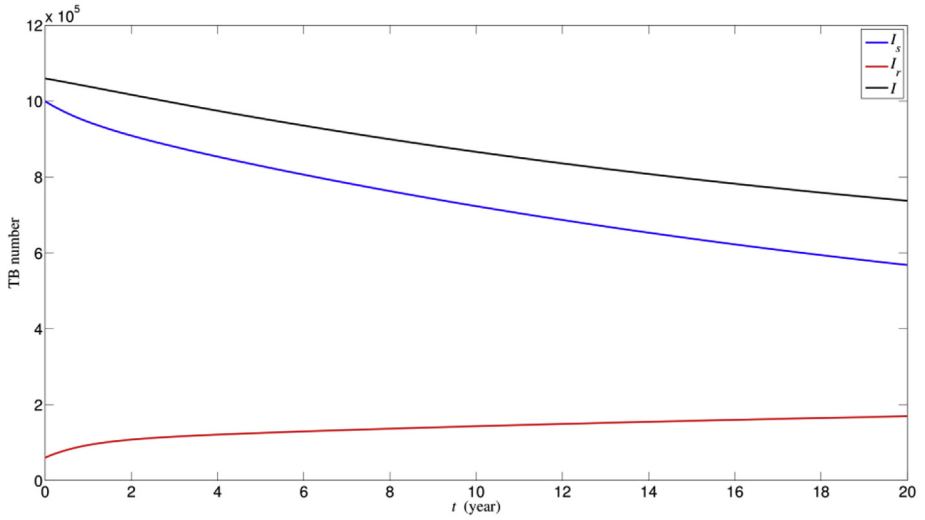

Fig. 2. Simulation of TB cases in 20 years.

be more prominent. Beyond that, the increase in the number of infected of MDR-TB will lead to more exposed and even new infected, the demand for drugs to cure these infected is larger and more time-consuming. In all respects, there are more difficulties in subsequent control and prevention of TB, therefore, it is more important to do it now.

The second column in Table 3 is the statistics of TB cases recorded in WHO's official database for the next 8 years since 2010 World Health Organization, 2012; World Health Organization, 2013; World Health Organization, 2014; World Health Organization, 2015; World Health Organization, 2016; World Health Organization, 2017.

. Based on the estimate TB detection rate (87%), the real TB cases derived from WHO TB report are shown in the third column in Table 3. The trend of the total number of TB cases in 8 years is simulated and compared with the data derived from WHO TB report in Fig. 3.

3.2. Impact of parameters' variation on numerical simulation

The establishment of dynamics model of MDR-TB infection aims at predicting the future outbreaks as well as helping in exploring the best possible preventions and control strategies through numerical simulation, therefore, putting forward some suggestions. In this paper, we consider the effect of detection rate (f), transformation rate (t_γ) and successfully cure rate (c) on model numerical simulation.

f will affect β and γ by Eqs. (9) and (10). Fig. 4 showed TB and MDR-TB's development under different f. It showed f greatly affect the development of TB and MDR-TB. Fig. 5 showed the TB and MDR-TB's development under different t_γ. It showed t_γ also affect the development of MDR-TB. Successfully cure rate coefficient's effect is also studied in Fig. 6 which showed it is less than those of f and t_γ.

4. Discussion

From the simulation results (Fig. 4), it is easy to find that the increase of f will lead to a significant decline in population of the infected in 20 years. It is also showed that t_r greatly affect the development of MDR-TB. MDR-TB results from either primary infection with resistant bacteria or may develop in the course of a patient's treatment. Though t_r is only 5%, it account for over 70% of the MDR-TB cases after 20 years. Drug resistance arises due to the improper use of antibiotics in chemotherapy

Table 3
Number of TB cases in China from 2010 to 2017, by WHO.

year	TB case notifications	The derived real TB case
2017	7.73×10^5	8.89×10^5
2016	7.84×10^5	9.01×10^5
2015	8.04×10^5	9.24×10^5
2014	8.26×10^5	9.49×10^5
2013	8.55×10^5	9.83×10^5
2012	9.01×10^5	1.04×10^6
2011	9.12×10^5	1.05×10^6
2010	9.23×10^5	1.06×10^6

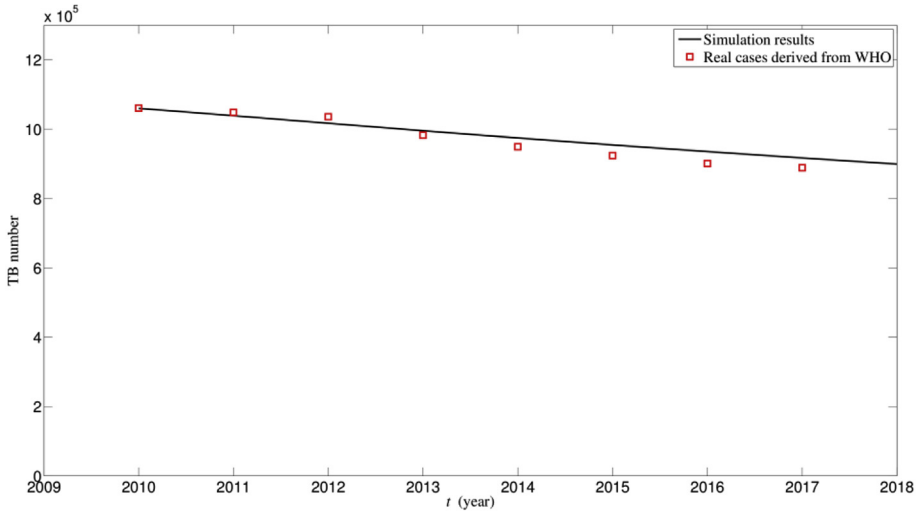

Fig. 3. TB cases from 2010 to 2017.

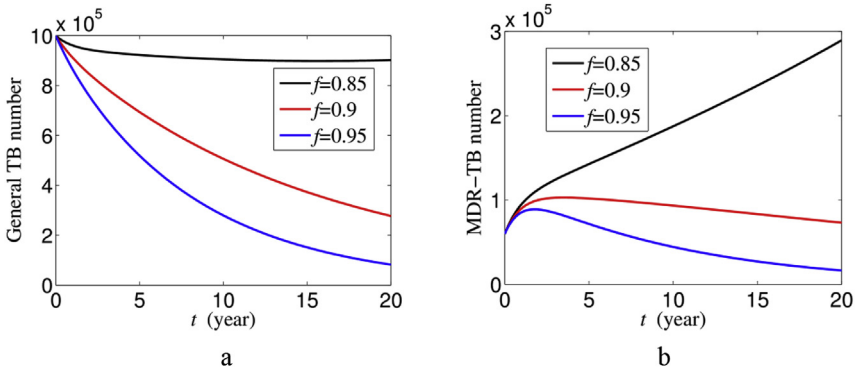

Fig. 4. TB and MDR-TB's development under different f.

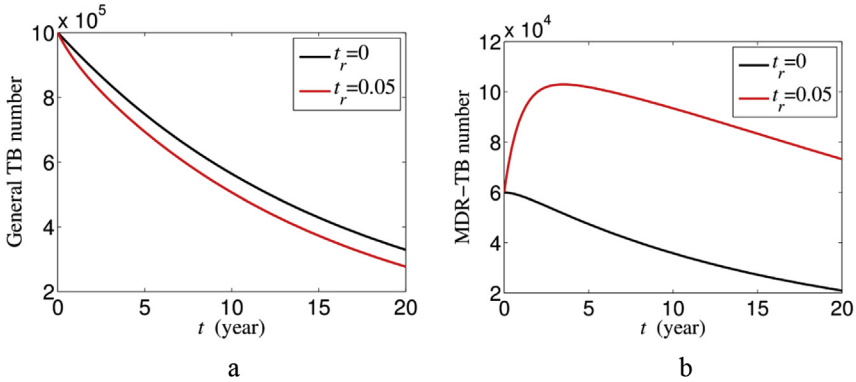

Fig. 5. TB and MDR-TB's development under different t_γ.

of drug-susceptible TB patients. This improper use is a result of a number of actions, including administration of improper treatment regimens by health-care workers and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with poor TB control programs, therefore, The WHO-recommended treatment strategy for detection and cure of TB is “Directly Observed Treatment, Short-course" (DOTS) which may prevents the development of MDR-TB by ensuring the full course of treatment is followed (World Health Organization, 2018-05).

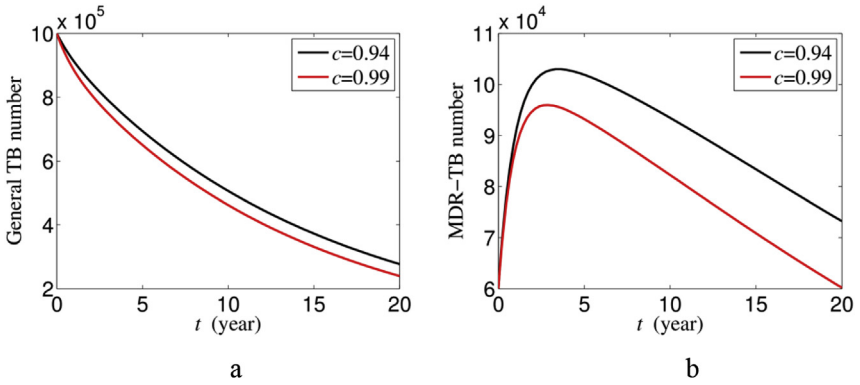

Fig. 6. TB and MDR-TB's development under different *c*.

DOTS can also increase cure rates up to 95 percent. Obviously, increasing cure rates will help decrease TB cases, but the decrease rate by cure rate is far less than that by detection rate. To a certain extent, the increase in cure rate is far more difficult than that in detection rate, therefore, improving the detection rate f is a primary task in the process of TB's prevention and control.

5. Conclusion

In the present work, the numerical simulations are performed to predict the development of the epidemic situation. We assume that drug resistance can emerge by infection or as a consequence of treatment (not proper treated for various reasons). In this paper, we extend the standard SEIS mathematical model to take into account the MDR-TB. The feasible region, stability of two equilibriums as well as an endemic equilibrium of this model are analyzed. It is found that the first equilibrium is unstable under the assumption, while the second equilibrium is locally asymptotically stable only at the condition of $R_1 < 0$ and $R_2 < 0$. With parameters derived from WHO's calculation of Chinese TB statistics, we found the equilibrium is unstable, while the endemic equilibrium is stable.

We carried on numerical simulation and analyze the impact of models' parameters on TB development. The simulation results proved that the key to better prevent and control the spread and develop of TB is to improve the detection rate f, and the conversion rate from TB to MDR TB contribute most of the MDR TB cases.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Human and animal rights

This article does not contain any studies with human participants or animals performed by any of the authors.

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