Prediction of Different Interventions on the Burden of Drug-resistant Tuberculosis in China: a Dynamic Modeling Study

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Prediction of different interventions on the burden of drug-resistant tuberculosis in China: a dynamic modeling study

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Abstract

Background. Tuberculosis (TB) is one of the top ten causes of death worldwide. The World Health Organization adopted the “End TB Strategy”, whose goal is to end the global TB epidemic by 2035. However, achieving this goal will be difficult using current prevention and control measures.

Methods. A Susceptible-Exposed-Infectious-Recovered (SEIR) model that distinguishes drug-sensitive (DS) and drug-resistant (DR) TB in the entire Chinese population was established. Goodness-of-fit tests and sensitivity analyses were used to assess model performance. Predictive analysis was performed to assess the effect of different prevention and control strategies on DR-TB and achieving the goal of the End TB Strategy: 90% fewer cases of DR-TB by 2035.

Results. We used parameter fitting to determine the basic reproduction number of the model as R_0=0.6993. Chi-square test results indicated good model fits for the reported incidences of DS-TB (χ^2=0.144, P=1.000) and DR-TB (χ^2=0.076, P=1.000). The predictive analysis led to four major projections for the number of cases by 2035. First, if the transmission rate of DR-TB patients reaches 0 during the infectious period, there will be 208,754 fewer cases (failure to achieve to goal). Second, if the progression rate of latently infected people reaches 10%, there will be 255,075 fewer cases (92.2% lower than in 2015). Third, if the overall treatment and cure rate of patients with DS-TB improves to 100%, there will be 150,482 fewer cases (failure to achieve the goal). Fourth, if the cure rate of DR-TB increases to 40%, there will be 253,198 fewer cases (91.5% lower than in 2015).

Conclusions. We assessed several prevention and control measures for DR-TB. Interventions that target acquired DR and improvement of the cure rate of DS-TB have limited efficacy. However, interventions that target primary DR-TB, such as reducing the probability of transmission and the rate of disease progression in patients with DR-TB, have better efficacy. Improving treatment compliance and the cure rate of patients with DR-TB can also contribute to attaining the goal of the End TB Strategy.

Keywords: Tuberculosis; SEIR model; Drug-resistant TB; Basic reproductive number; End TB Strategy

Background

Tuberculosis (TB) is an ancient chronic infectious disease that is mostly transmitted *via* respiratory droplets. It is one of the top ten causes of death in the world and the second leading cause of death by a single pathogen, *Mycobacterium tuberculosis* (M.tb)[1]. According to the 2019 Global Tuberculosis Report, there were about 10 million new and recurrent TB cases worldwide during 2018, and the incidence rate was 130 per 100,000 people. A total of 1.45 million people died of TB worldwide during 2018, including 1.2 million people without AIDS and 0.25 million people with AIDS[1].

In 2014, the World Health Organization (WHO) proposed the "End TB Strategy", whose aim was to end the global TB epidemic by 2035[2]. More specifically, their

goals for 2035 were to reduce the absolute number of deaths from TB by 95%, reduce the incidence of TB by 90%, and eliminate catastrophic family expenditures due to TB compared with the 2015 baseline[2]. However, from a global perspective, most regions examined by the WHO and many high-burden TB countries will be unable to achieve the 2020 milestone of the End TB Strategy. Globally, the average annual decline in the incidence of TB was 1.6% between 2000 and 2018, and 2.0% between 2017 and 2018. Thus, the cumulative reduction between 2015 and 2018 was only 6.3%, significantly lower than the milestone of the End TB Strategy to reduce the incidence of TB by 20% between 2015 and 2020[1].

In addition, M.tb has evolved drug resistance due to spontaneous mutations and improper use of antimicrobial drugs. Multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB, which have developed due to bacterial resistance, have increased the difficulty of TB prevention and control[3]. The existing prevention and control methods therefore seem inadequate to achieve the goal of ending TB by 2035. Application of mathematical models to predict the potential impact of different interventions on TB may help to achieve the WHO goals.

In 1962, Waaler et al.[4] published the first model of TB dynamics, and this study clearly confirmed the utility of mathematical models in the study of TB transmission. The parameter estimation method in this model provided a reference for parameter fitting in subsequent models of TB dynamics. In 2015, Lin et al.[5] developed a TB model for China, and gave priority to interventions that may be implemented within the next 10 years, including improved referral of TB patients, introduction of new

treatments for drug-sensitive (DS) TB, and optimization of care for patients with MDR-TB. These researchers then used this model to explore changes in the TB burden under different scenarios or scenario combinations. Their results showed that it will be difficult reduce the incidence of TB by 50% and mortality by 75% by 2025.

Based on previous models of TB dynamics, we focused on the prevention and control of DR-TB in China by establishment of a dynamic model, and then analyzed the short-term and long-term effects of different interventions on TB prevention and control. Our results will provide guidance for the development of future strategies that can prevent and control DR-TB in China and may allow attainment of the goals in the End TB Strategy.

Methods

Data Sources

National TB surveillance dataset

The number of TB cases in China from 2005 to 2018 were obtained from the official infectious disease report from the China Centre for Disease Control and Prevention (Table S1)[6]. Since 1996, all active TB cases were reported to the Chinese Centre for Disease Control and TB is classified as a class II mandatory notifiable disease.

Demographic data

Demographic information from 2005 to 2018 in China were from the National Bureau of Statistics [7], including the total population, birth rate, natural mortality

rate, and other parameters. All parameters were converted into corresponding time units before addition to the model.

TB Information Management System (TBIMS)

The TBIMS has data on TB cases diagnosed from 2008 to 2018, including gender, age, occupation, geographic region, registration classification, treatment outcome, drug resistance, and other factors. These data include date variables, such as the dates of initial symptoms and of the first diagnosis.

Literature review

TB infections develop slowly, with an incubation period, an infection period, and a treatment period that occur over a period of several years. Therefore, changes at the individual level have little effect on overall changes of model parameters at the population level. The determination of certain parameters in relevant studies of models of TB dynamics are consistent[8]. Thus, some of the parameters that were not available from the above three data sources were obtained from the relevant literature.

Model Description

We developed an extended Susceptible-Exposed-Infectious-Recovered (SEIR) 7-compartment model to evaluate the spread and incidence of DS- and DR-TB. Considering the epidemiological sources of DR-TB, there were two main modes of infection. First, patients who did not receive anti-TB treatment may become infected with DR M.tb for the first time. Second, acquired drug resistance may occur due to use of non-standard treatment during the post-onset treatment of patients who were previously infected by DS M.tb[9, 10]. Therefore, the whole population was divided

into seven compartments (Figure 1), based on the natural history of TB transmission. Specifically, the total population (N) was divided into four categories: susceptible to TB (S), latent infection (E), infected and infectious (I), and recovered (R), whose dynamics may be described as:

$$\frac{dS}{dt} = \pi - \mu S - \frac{\beta_s I_s}{N} S - \frac{\beta_r I_r}{N} S$$
$$\frac{dE_s}{dt} = \frac{\beta_s I_s}{N} S - vE_s - \mu E_s$$
$$\frac{dI_s}{dt} = vE_s + w_s R_s - [rc_s + (1-r)c]I_s - (\mu + \mu')I_s$$
$$\frac{dR_s}{dt} = rc_s I_s - (w_s + \mu)R_s \quad (1)$$
$$\frac{dE_r}{dt} = \frac{\beta_r I_r}{N} S - vE_r - \mu E_r$$
$$\frac{dI_r}{dt} = vE_r + w_r R_r + (1-r)cI_s - (c_r + \mu + \mu')I_r$$
$$\frac{dR_r}{dt} = c_r I_r - (w_r + \mu)R_r$$

Model Assumptions

a) The model assumed that all newborns were susceptible.

b) Birth, natural death, and death due to TB in the population were examined, so the model assumed these three parameters were fixed constants (to simplify calculations).

c) The official infectious disease report from the China CDC does not distinguish DS- and DR-TB, so information on this topic was from previous studies of DR-TB in China. The overall rate of DR-TB in China ranges from 24.6% to 37.8%[10], so the model assumed that the proportion of DR patients among all

new or recurrent TB patients was 30% each year.

Parameter Estimation and Model Fitting

Parameters were estimated by minimizing the sum of squares (MSS) using the fminsearch tool in MATLAB R2018a (version 9.4) [11, 12] using an unconstrained nonlinear minimization. Posterior parameter values were obtained when the results of fminsearch converged:

$$MSS = \sum \begin{pmatrix} log_2(1 + observed\ \ data\ \ per\ \ year) - \\ log_2(1 + fitting\ \ data\ \ per\ \ year) \end{pmatrix}^2 \quad (2)$$

To test the goodness of fit between the model and observed data, a Chi-Square test was used for the following two hypotheses: *(a)* null hypothesis H_0: modeled results I_s/I_r are equal to the observed number of TB cases (Table S1); *(b)* an alternative hypothesis H_1: modeled results are not equal to the observed number of TB cases.

Derivation of Basic Reproductive Number (R_0)

The basic reproductive number (R_0) is the expected number of secondary cases produced in a completely susceptible population after introducing a typical infective individual[13]. In this study, R_0 for the period of 2005 to 2018 was determined using the method of van den Driessche and Watmough[14]. In particular, R_0 was divided into two parts:

$$R_0^s = \frac{\beta_s v}{(v+\mu)(c+\mu+\mu' - cr + c_s r)},\ R_0^r = \frac{\beta_r v}{(v+\mu)(c_r+\mu+\mu')}$$

$$R_0 = \sqrt{R_0^s \times R_0^r}$$

Predictive Analyses of Different Intervention Scenarios Targeting DR-TB

Well-fitted models were used to evaluate the effects of different TB prevention

and control measures. The intervention measures for DR-TB were strengthening management of DR patients, improving patient compliance, and screening for infection by latent DR-TB. The effects of these interventions were quantified as parameter changes, in which a changed parameter value was used to determine the short-term and long-term changes of the TB burden and attainment of the goals of the End TB Strategy.

Results

Model Fits

We obtained the parameters for birth rate, number of births, and natural mortality from demographic data[7], and calculated the parameters for the two TB cure rates based on patient registration information in the TBIMS. We obtained all other parameters from statistical fits using an MSS method (Table 1).

Then, we substituted the values of the fitted parameters into the model and calculated the number of DS-TB and DR-TB cases from 2005 to 2018. The results (Figure 2, Table 2) indicated the model provided a good approximation of the observed data. In particular, the goodness-of-fit (chi-square) test for the incidence of each type of TB had a *P* value of 1.000. Therefore, the model and the observed data had no statistically significant differences. This analysis also indicated that the basic reproductive numbers of DS-TB and DR-TB in China from 2005 to 2018 were 0.6342 and 0.7711, respectively. Therefore, the model predicted that the incidences of both types TB will gradually decline over time.

198

199

200 **Table 2. Chi-square test results of model fits for DS-TB and DR-TB.**

201

	χ^2	Degrees of freedom	P value
DS-TB	0.144	13	1.000
DR-TB	0.076	13	1.000

202

203 ***Sensitivity analysis***

204 Based on the formula for R_0, there is one basic reproductive number for DS-TB
205 and another basic reproductive number for DR-TB. We used these two values to
206 calculate the partial derivatives of the parameters that affect them. Without
207 considering the sensitivity analysis of natural mortality (μ) and TB mortality (μ'), the
208 results are:

209 $$\frac{\partial R_0^s}{\partial \beta_s} = \frac{v}{(v+\mu)(c+\mu+\mu' - cr + c_s r)}$$

210 $$\frac{\partial R_0^s}{\partial v} = \frac{\beta_s \mu}{(c+\mu+\mu' - cr + c_s r) \times (v+\mu)^2}$$

211 $$\frac{\partial R_0^s}{\partial c} = \frac{\beta_s v(r-1)}{(v+\mu) \times (c+\mu+\mu' - cr + c_s r)^2}$$

212 $$\frac{\partial R_0^s}{\partial c_s} = \frac{-\beta_s vr}{(v+\mu) \times (c+\mu+\mu' - cr + c_s r)^2}$$

213 $$\frac{\partial R_0^s}{\partial r} = \frac{-\beta_s v(c_s - c)}{(v+\mu) \times (c+\mu+\mu' - cr + c_s r)^2}$$

$$\begin{cases} \dfrac{\partial R_0^r}{\partial \beta_r} = \dfrac{v}{(v+\mu)(c_r+\mu+\mu')} \\ \dfrac{\partial R_0^r}{\partial v} = \dfrac{\beta_r \mu}{(c_r+\mu+\mu') \times (v+\mu)^2} \\ \dfrac{\partial R_0^r}{\partial c_r} = -\dfrac{\beta_r v}{(v+\mu) \times (c_r+\mu+\mu')^2} \end{cases}$$

We numerically simulated the parameters that affect the basic reproductive numbers of DS-TB and DR-TB, and these parameters ranged from 0% to 100% of the point estimates (Figure 3 and Figure 4).

Predictions of different interventions

We determined the effects of four interventions on the predicted number of DR-TB cases up to 2035.

Isolation and patient education (Figure 5A): Quarantine and educate patients with DR-TB to reduce their frequency of contact with other susceptible persons during the infectious period to reduce the transmission rate (β_r). This intervention reduced the β_r by 20%, 40%, 60%, 80%, and 100% relative to the initial value. The results showed that even the strongest intervention (i.e., no patients have contact with other susceptible groups during the infectious period) only led to 208,745 fewer cases of DR-TB by 2035 (failure to achieve 90% decrease).

Screening for latent DR-TB infections (Figure 5B): Reduce the rate of disease progression (v) in patients with latent DR-TB infections. Because a large increase in the number of screenings for latent infection cannot be implemented rapidly, we assumed that the latent infection screening rate will increase steadily from 2021 to

2025. Thus, the following time-dependent piecewise function represents the value of the disease progression rate before and after intervention:

$$F(v_2) = \begin{cases} v_0, & t \le 192 \\ v_0 - \frac{xv_0}{60} \times (t - 120), & 192 < t \le 252 \\ (1-x)v_0, & t > 252 \end{cases}$$

The results showed that a reduction of the disease progression rate (v_2) to 10% of the initial value led to 255,075 fewer cases of drug-resistant TB by 2035 (92.2% decrease relative to the 2015 level).

Increasing the cure rate of DS-TB from standard treatment (Figure 5C): Increase the cure rate (c_s) of patients with DS-TB from the present value of 85% to 88%, 91%, 94%, 97% and 100%. The results showed that even if the cure rate of patients with DS-TB increased to 100%, this only led to 150,482 fewer cases of DR-TB cases by 2035 (failure to achieve 90% decrease)

Increasing the efficacy of treatment for DR-TB (Figure 5D): Increase the cure rate of DR-TB (c_r) from its current rate of 0.0493 steadily from 2021 to 2025. If a cure rate (c_0) of 0.075, 0.1, 0.2, 0.3, and 0.4 is achieved by 2025, the value of c_2 before and after the intervention can be expressed as a time-dependent piecewise function:

$$F(c_2) = \begin{cases} 0.0493, & t \le 192 \\ 0.0493 + \frac{c_0 - 0.0493}{60} \times (t - 192), & 192 < t \le 252 \\ c_0, & t > 252 \end{cases}$$

The results showed that when the disease cure rate (c_r) increases to 0.4, this led to 253,198 fewer cases of DR-TB by 2035 (91.5% decrease relative to the 2015 level).

Discussion

In this study, we established a dynamic model that describes the transmission of DS-TB and DR-TB. By use of parameter fitting, we first estimated the values of a series of parameters and demonstrated that they provided accurate estimations of the reported numbers of cases of DS and DR-TB in China from 2005 to 2018. The model equations and the calculations of the next-generation matrix led to an R_0 value of 0.6342 for DS-TB, an R_0 value of 0.7711 for DR-TB, and a compound R_0 value of TB transmission in the entire population of 0.6993. Because all these values are below 1.0, this indicates a gradual decline in the incidence of DS-TB and DR-TB in China over time.

Our model predictions identified the effects of four different interventions on the incidence of DR-TB. In particular, interventions that targeted the spread of primary DR-TB were significantly more effective than those that prevented or controlled the number of cases of acquired DR-TB. This is reflected by the higher efficacy of reducing the progression rate of DR-TB and increasing the cure rate of DR-TB. In other words, if the progression rate of latently infected people reaches 10%, there will be 255,075 fewer cases by 2035 (92.2% lower than in 2015). However, even if the proportion of patients cured of DS-TB is increases from the current 85% to the theoretical maximum of 100%, the goal of the End TB Strategy will not be reached by 2035. There are two major reasons for this result: *(a)* the current cure rate of DS-TB is already high, so further interventions will only have a small effect and *(b)* the incidence of DR-TB has become increasingly dominated by the spread of primary DR-TB during recent years. A previous study showed that the proportion of primary

drug resistance among DR-TB cases in Shanghai reached 82.5%[15]. Our predictions of the effects of different interventions are consistent with the presence of an increasing proportion of primary DR-TB in multiple studies[16]. In addition, our analysis of the effect of isolating and educating patients with DR-TB and reducing their frequency of contact with other susceptible persons during the infectious period indicated that this intervention did not achieve the goal of the End TB Strategy. This may be because very few people have latent infections of DR-TB, so there are also very few individuals who progress to active DR-TB.

We predicted the possible effects of several interventions on the incidence of DR-TB in China based on a dynamic model of DS-TB and DR-TB that provided accurate results from 2005 to 2018. Primary drug resistance, rather than acquired drug resistance, is increasingly the main source of DR-TB. Thus, we propose that preventing patients with active DR-TB from spreading this disease to susceptible people and screening and preventive treatment of patients with DR-TB will have the greatest effects on reducing the incidence of DR-TB in China.

Conclusions

This study established an SEIR model that distinguishes the transmission of DS-TB and DR-TB. Our modeling study used the next-generation matrix and then led to R_0 values of DS-TB, DR-TB, and a compound situation. However, we found that current interventions aren't achieving the goal of the End TB Strategy. Therefore, we assessed some prevention and control measures for DR-TB. The results provided by

our study may have some contributions to the achievement of the goal of the End of TB Strategy.

Abbreviations

Abbreviations	English full name
TB	Tuberculosis
Mtb	*Mycobacterium tuberculosis*
WHO	World Health Organization
MDR-TB	Multi-drug resistant tuberculosis
XDR-TB	Extensively drug-resistant tuberculosis
MSS	Minimum sum of square
DS-TB	Drug-sensitive tuberculosis
DR-TB	Drug-resistant tuberculosis

Declaration

Ethical approval and consent to participate

This study does not use any personal information and animals were not involved. Therefore, no ethical approval was necessary. In addition, all the authors consented to participate.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available in the official infectious disease report from the China Centre for Disease Control and Prevention, http://www.nhc.gov.cn/jkj/s2907/new_list.shtml, and the National

Bureau of Statistics, http://data.stats.gov.cn/tablequery.htm?code=AD03. The TB cases diagnosed data that support the findings of this study are available from the Chinese Center for Disease Control and Prevention but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Chinese Center for Disease Control and Prevention.

Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

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Author contributions

WY and WWB conceived and designed the study. XA, WZX, and WY carried out the data analyses and wrote the first draft manuscript. XA, WZX, and WWB revised the paper. All authors read and approved the final manuscript.

Acknowledgments

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Figure 1. Extended 7-compartment SEIR model of DS-TB and DR-TB. See Table 1 for definitions of all terms.

Figure 2. Model results (dashed lines) and observed cases (solid lines) of DS-TB and DR-TB in China from 2005 to 2018.

Figure 3. Numerical simulation of parameters affecting the basic reproductive number (R_0) of DS-TB.

Figure 4. Numerical simulation of parameters affecting the basic reproductive number (R_0) of DR-TB.

Figure 5. Predicted effects of four interventions for prevention and control of DR-TB. A, Reducing the transmission rate. B, Reducing the progression rate. C, Increasing the cure rate of DS-TB. D, Increasing the cure rate of DR-TB.

Table 1. Model parameters and corresponding R_0 values.

(Should be placed between line185-186)

Parameter	Description	Value	Source
β_s	DS-TB transmission rate	0.6356	Fitted/MSS
β_r	DR-TB transmission rate	0.3458	Fitted/MSS
v	Progression rate	7.99×10^{-5}	Fitted/MSS
w_s	DS-TB relapse rate	3.90×10^{-4}	Fitted/MSS
w_r	DR-TB relapse rate	1.96×10^{-4}	Fitted/MSS
c	DS-TB to DR-TB conversion rate	0.0376	Fitted/MSS
c_s	Cure rate of DS-TB	0.1299	TBIMS
c_r	Cure rate of DR-TB	0.0493	TBIMS
π	National monthly births	1,379,167	Fixed [17]
r	Proportion of DS-TB cured cases	0.85	Fixed [1]
μ	Monthly natural mortality rate	5.83×10^{-4}	Fixed [17]
μ'	Monthly mortality rate due to TB	4.17×10^{-3}	Fixed [1]
S(0)	Initial number of susceptible cases	721,500,000	Fixed [17]
Es(0)	Initial number of DS-TB exposed cases	404,950,000	Fixed[18]
Is(0)	Initial number of DS-TB cases	70,000	Fixed [19]
Rs(0)	Initial number of DS-TB recovered cases	0	Assumed
Er(0)	Initial number of DR-TB exposed cases	173,550,000	Fixed[18]
Ir(0)	Initial number of DR-TB cases	30,833	Fixed[19]
Rr(0)	Initial number of DR-TB recovered cases	0	Assumed

R_0^s	DS-TB basic reproductive number	0.6342	Calculated
R_0^r	DR-TB basic reproductive number	0.7711	Calculated
R_0	TB basic reproductive number	0.6993	Calculated

398

Figures

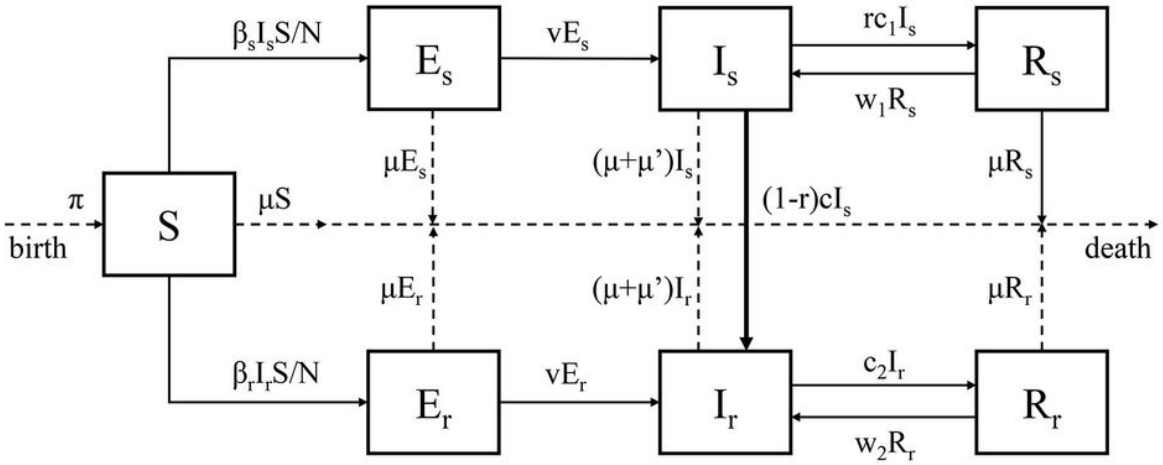

Figure 1

Extended 7-compartment SEIR model of DS-TB and DR-TB. See Table 1 for definitions of all terms.

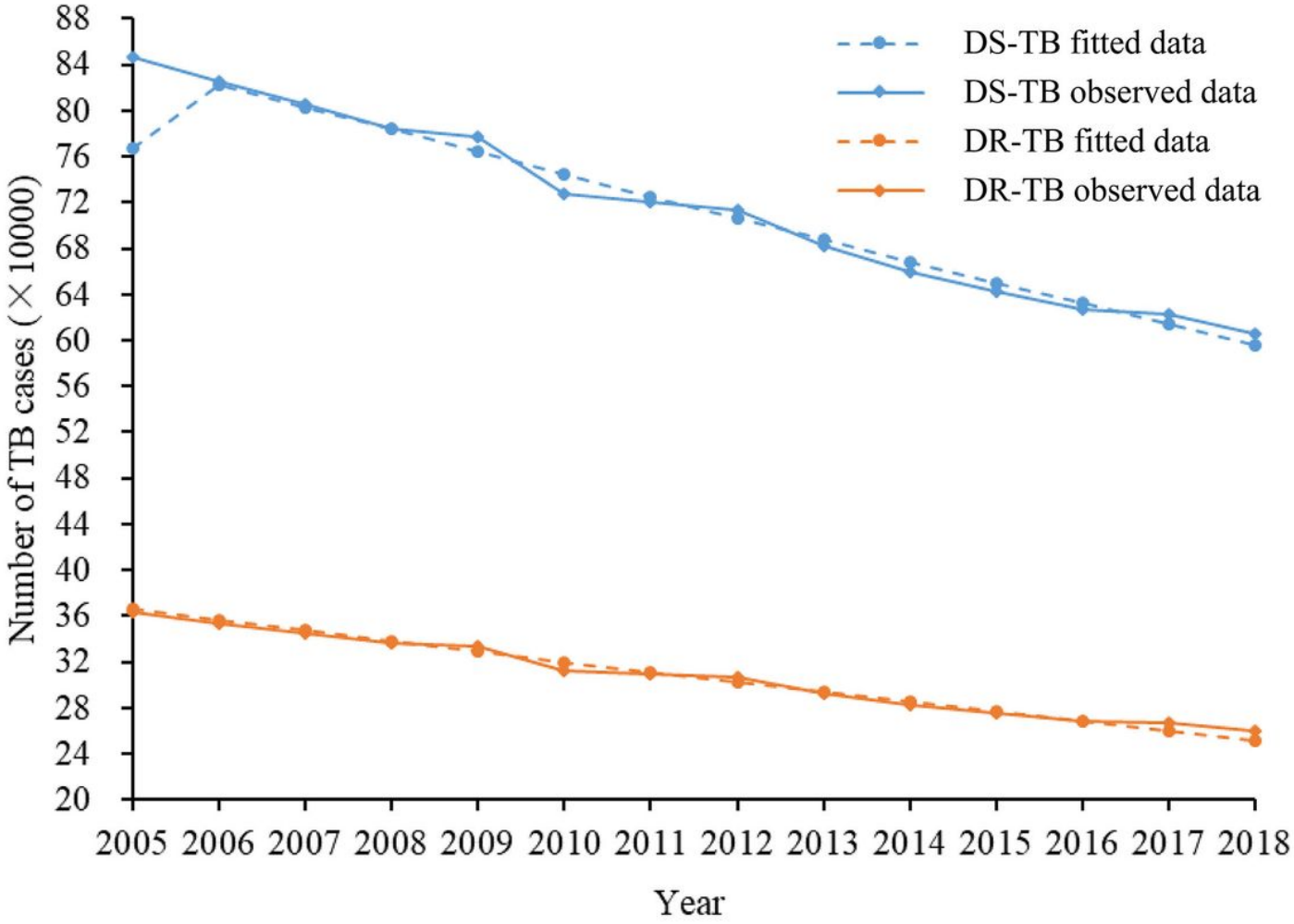

Figure 2

Model results (dashed lines) and observed cases (solid lines) of DS-TB and DR-TB in China from 2005 to 2018.

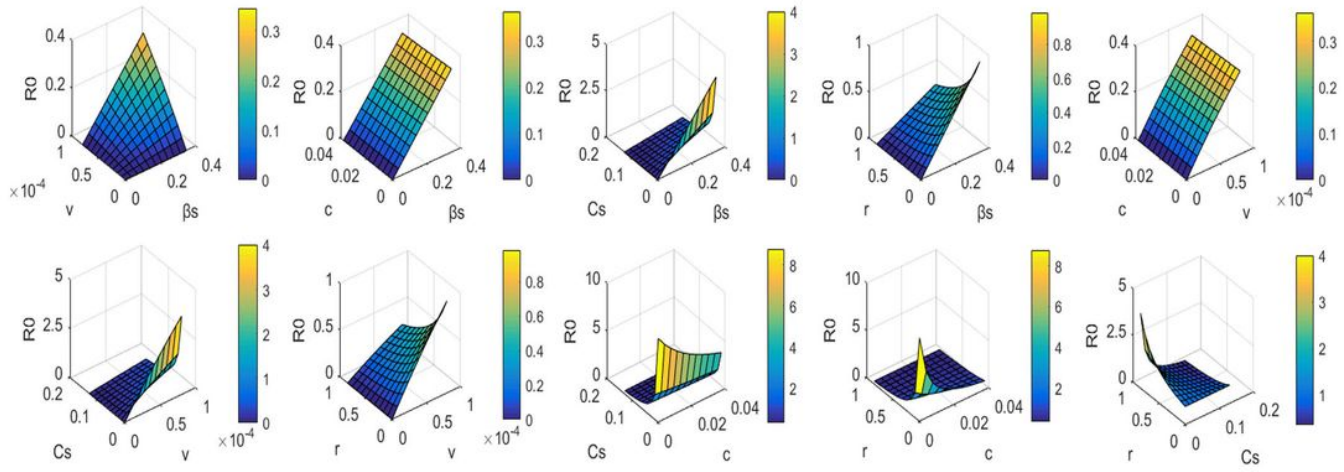

Figure 3

Numerical simulation of parameters affecting the basic reproductive number (R0) of DS-TB.

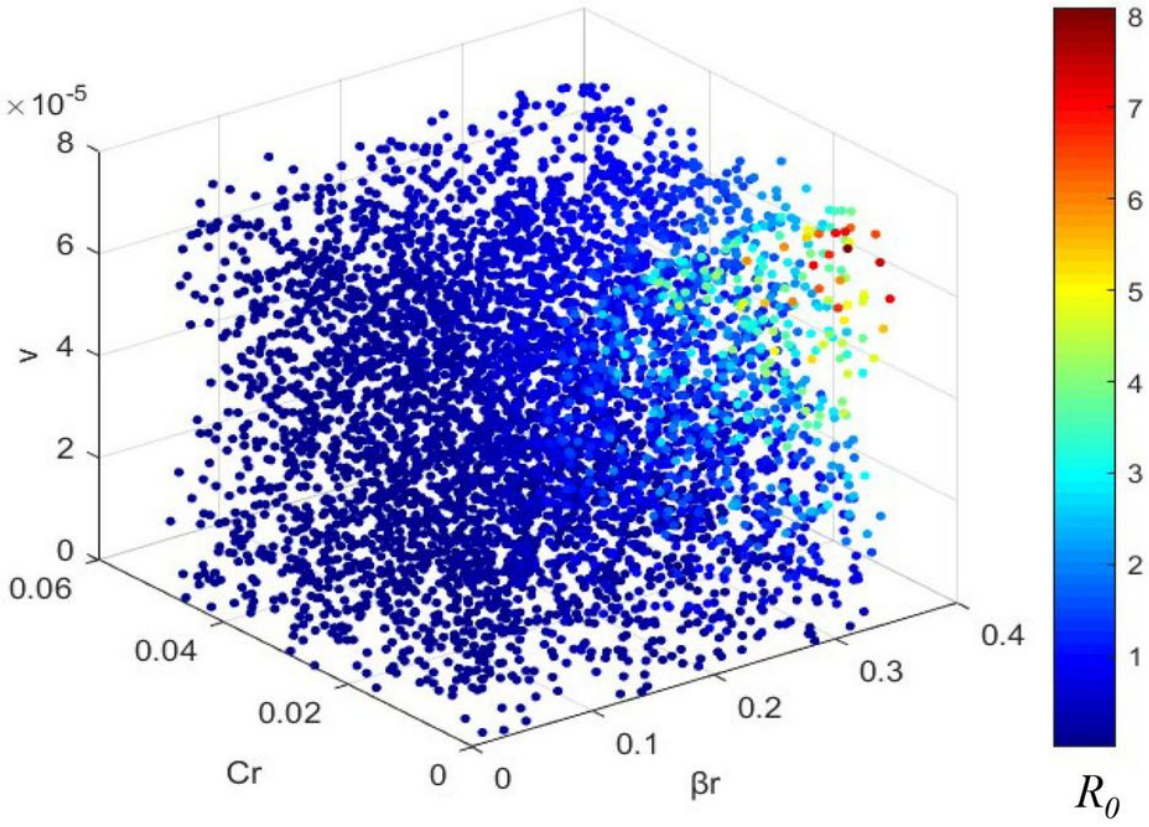

Figure 4

Numerical simulation of parameters affecting the basic reproductive number (R0) of DR-TB.

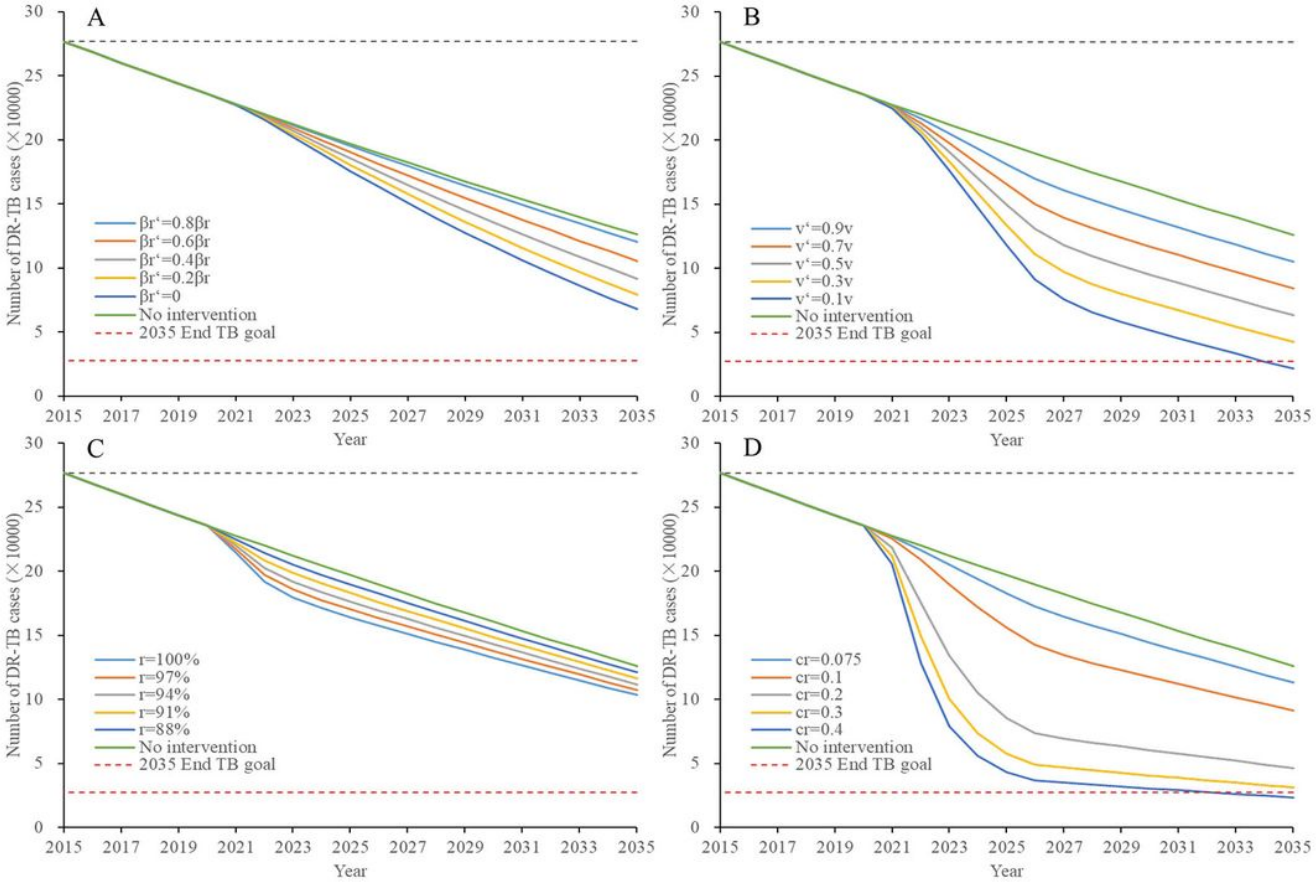

Figure 5

Predicted effects of four interventions for prevention and control of DR-TB. A, Reducing the transmission rate. B, Reducing the progression rate. C, Increasing the cure rate of DS-TB. D, Increasing the cure rate of DR-TB.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile.xlsx