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ORIGINAL ARTICLE

What Does a Mathematical Model Tell About the Impact of Reinfection in Korean Tuberculosis Infection?

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Abstract
Objectives: According to the Korea Centers for Disease Control and Prevention, new active tuberculosis (TB) cases have increased since 2001. Some key factors explain and characterize the transmission dynamics of Korean TB infection, such as a higher ratio of latent individuals and a new reporting system implemented in 2001, among others.
Methods: We propose a mathematical TB model that includes exogenous reinfection to gain a better understanding of the recent trend for TB incidence. We divide the simulation time window into two periods, 1970–2000 and 2001–2012, according to the implementation date of a new TB detection system.
Results: Two sets of parameters, including the transmission rate, the latent period, the recovery rate, and the proportion of exogenous reinfection, are estimated using the least-squares method and calibrated to data on the incidence of active TB.
Conclusion: Among some key parameters in the model, the case finding effort turned out to be the most significant impacting component on the reduction in the active TB cases.

1. Introduction

Tuberculosis is a bacterial disease caused by the bacterium "Mycobacterium tuberculosis". Almost 10 million people are infected every year and two millions of them are killed by tuberculosis all over the world. Tuberculosis is a major cause of death for children, young adults and women of reproductive age, especially, in developing countries [1]. The Republic of Korea (hereafter "Korea") still has the highest infection rate and the highest mortality rate of TB infection among OECD countries in 2005 [2], even though it has been successful to have a dramatic reduction in the TB incidence last few decades. Annual new TB incidence rate is 87 people (per 100,000 people) that much higher than the OECD average of 17.7. Also, mortality induced by active TB cases is 10 people (per 100,000 people) that about five times higher than the average mortality rate 2.1. Recently, Korea Centers for

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Disease Control and Prevention reported new active-TB cases have increased particularly since 2001 [3]. One of main reasons for sudden increase of active-TB incidences is due to the start of a new tuberculosis surveillance system implemented by the Korean government in 2000. Moreover, there are other important factors for explaining of the current TB transmission dynamics such as increase of aged population, a still higher proportion of the latent individuals after the Korean War, a higher proportion of the retreated individuals and the emergence of multidrug-resistance TB [4].

It is extremely challenging to have a full understanding of the complex dynamics in any infectious disease. However, mathematical modeling, mathematical analysis and numerical simulations have been providing a complementary tool to understand the disease dynamics better [5]. There have been quite a number of researchers working on the mathematical modeling for TB [6−8]. Unlike the fast dynamics of influenza (a time scale is much faster than the one of TB), TB is a slow disease since it has a short and infectious period while having a long and variable latency period [9]. About a third of the world's population, or around 2 billion people, are the reservoir of the TB bacteria but most latently infected individuals do not become actively infectious (active TB). Around 10% of people infected with TB actually develop the disease within a five-year window while others do it after a long period of time (maybe not develop the disease at all for their entire life). On the other hand, infectious individuals remain for relatively shorter periods of time partially because of the antibiotic treatments.

This leads for us to take account of this long latent period as an important component in the TB progression model. The disease progression towards active TB can be accelerated with re-exposure to TB bacilli through repeated contacts with individuals with active TB resulting in exogenous reinfection which implies that latent individuals acquire a new infection from another infectious individual or endogenous infection, namely, reactivation of latent individuals [10−12]. In particular, the situation of the Republic of Korea such as a high latent ratio, exogenous reinfection should be a part of the model and it might play a key role in the Korean TB transmission. Recently, a Korean TB dynamical model has been developed including time-dependent coefficients and further optimal control theory has been employed to observe what would be more effective control measures to minimize the number of infected and exposed individuals [13]. In this manuscript, we modify this existing model by incorporating the exogeneous reinfection term from the work [12]. Parameter estimation for our new TB model is carried out using the least-square method to the TB incidence from two periods, 1970-2000 and 2001-2012. The model output and the TB incidence data are in a very good agreement. Based on the model and the parameters, sensitivity analysis is carried out in order to find out which parameters are key factors to reduce the active TB incidence.

2. Materials and methods

As studied in the earlier work, the standard SEIL compartmental model is taken as the base model for the TB transmission dynamics, which uses the Korean demographic parameters [13]. In addition, the exogeneous reinfection has been incorporated in the model (the mathematical model is given below).The new TB transmission model classifies individuals as the susceptible class (S), the exposed class(E), (or high-risk latent, that is, recently exposed but not yet infectious), the active-TB infectious class (I), and the low risk latent class or treated infected class (L).

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta cS\frac{I}{N} - \mu S \\
\frac{dE}{dt} &= \beta cS\frac{I}{N} - p\beta cE\frac{I}{N} - (\mu + k + \alpha)E + \sigma\beta cL\frac{I}{N} \\
\frac{dI}{dt} &= p\beta cE\frac{I}{N} + kE - (\mu + \gamma + d)I \\
\frac{dL}{dt} &= \gamma I - \sigma\beta cL\frac{I}{N} - \mu L + \alpha E \\
N &= S + E + I + L
\end{aligned} \tag{1}$$

The birth and mortality rates per capita per unit of time are Λ and μ, respectively. βc is the transmission rate for the susceptible, exposed and low risk latent individuals with an infectious individual per contact per unit of time. It is assumed that it is less likely to get infected for the low risk latent individuals with a reduction constant, $0 \le \sigma \le 1$(5). k is the rate at which an individual leaves the latent class by becoming infectious. d is the per-capita disease-induced death rate and γ is the per-capita treatment rate. Individuals who do not progress from the class E to the class I are moving to the low risk latent class at the rate α, (e.g., taking the TB medications before occuring active TB or called "case finding effort"). The term $p\beta cE(I/N)$ models the exogenous reinfection rates with p representing the level of reinfection. A value of $0 < p < 1$ implies that reinfection is less likely than a new infection. Most developed countries have low incidence TB rate, therefore, the exogeneous reinfection can be ignored. As mentioned earlier, this is not the case of Korea, since Korea has a higher proportion of exposed or low risk latent individuals like developing countries. Hence, it is better to take account of exogeneous reinfection in the TB transmission model. Also, we assume a constant per-capita removal rate to focus exclusively on the role of exogenous reinfection then, the basic reproductive number R_0 for (1) can be obtained as follows:

Table 1. Definition of Parameter Values Used in Simulations. T1 = 1970−2000 yr and T2 = 2001−2011 yr

Parameter	Description	Value(T1)	Value(T2)	Reference
σ	Rate from L to I by contacting TB	0.9	0.9	[12]
k	Rate from E to I	0.005	0.005	[12]
d	Per-captiadeasease-induced death rate	0.0943	0.0943	[13]
$\alpha(t)$	Non-progress rate from E to I	0.06787	0.0352	Data fitted
p(t)	Level of reinfection	0.2958	0.2469	Data fitted
$\gamma(t)$	Treatment rate	0.81	1.5179	Data fitted
βc(t)	Number of new infectious	6.4737	18.673	Data fitted

$$R_0 = \left(\frac{\beta c}{\mu+\gamma+d}\right)\left(\frac{k}{\mu+k+\alpha}\right)$$

This dimensionless quantity is represented by the product $\beta c/(\mu + \gamma + d)$, that is, by the average population of infected people from one infectious individual during his or her infectious period and $k/(\mu+k+\alpha)$, the rate of the population, which survives the exposed period and go to the infectious class successfully. Therefore R_0 gives the number of secondary infectious cases produced by an infectious individual for a period of his or her infectious period in a population of susceptible individuals.

3. Results

The parameter estimation of the system (1) to the incidence data of active-TB cases in Korea from 1970 to 2011 is carried out. We first assume that $\mu(t)$ and $b(t)$ is time-dependent parameter for every year taken from [13]. The other parameters for σ, k, d are defined as constant taken from [12]. The rest of parameters are estimated through the least-square method: $\gamma(t)$ is an estimate of the treatment rate; $\beta c(t)$ is an estimate of the transmission rate; $\alpha(t)$ is an estimate of the case finding rate from E to I; $p(t)$ is an estimate of the level of reinfection.

For the parameter estimation procedure, the least-square method is used (built-in-function in Matlab). We split up the time interval [1970, 2011] into two intervals [1970, 2000], and [2001, 2011] due to the implementation of a new tuberculosis detection system in 2000. Now, we have estimations of $\gamma(t)$, $\beta c(t)$, $\alpha(t)$ and $p(t)$ for two distinct time windows, which are listed in Table 1. Figure 1 displays the actual data of active-TB incidence and its best fit or the model outputs from 1970 to 2011 yr. The active-TB incidence (shown as ∘) represents the number of new infectious individuals per each year compared with the model outputs, dashed and solid curves under two different sets of parameter values estimated in Table 1. The results demonstrate that our fitted TB model agrees well with the reported TB incidence data.

Next, using the parameter values estimated through the least-square method, the model output is illustrated in Figure 2; the proportions of $S(t)/N(t)$, $E(t)/N(t)$, $I(t)/N(t)$, *and* $L(t)/N(t)$. The fraction of susceptible individuals is increased from aroud 0.36 to over 0.5 in a steady manner during the simulated time. The fraction of exposed individuals and the fraction of infectious individuals have been decreased significantly from 1970 until 2000 but they have been slightly increased after 2001.The fraction of latent individuals stays around 0.4 throughout the entire period of time. When we take a closer look at the fraction of active TB infected

$$\frac{dS}{dt} = b(t)N - \beta c(t)S\frac{I}{N} - \mu(t)S$$

$$\frac{dE}{dt} = \beta c(t)S\frac{I}{N} - p(t)\beta c(t)E\frac{I}{N} - (\mu(t)+k+\alpha(t))E + \sigma(t)\beta c(t)L\frac{I}{N}$$

$$\frac{dI}{dt} = p(t)\beta c(t)E\frac{I}{N} + kE - (\mu(t)+\gamma(t)+d)I$$

$$\frac{dL}{dt} = \gamma(t)I - \sigma(t)\beta c(t)L\frac{I}{N} - \mu(t)L + \alpha(t)E$$

$$\frac{dC}{dt} = p(t)\beta c(t)E\frac{I}{N} + kE$$

$$N = S + E + I + L$$

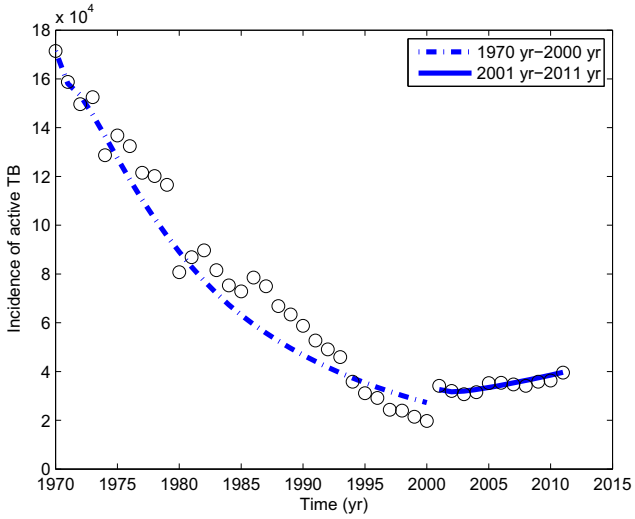

Figure 1. The reported incidence of active-TB (circle) and its best fit (dashed and solid curves), incidence are displayed.

individuals, the number of infectious individuals is expected to grow slowly since 2001.

Again, using the same parameter values that obtained above, we present some sensitivity analysis to find out which parameters are key factors to reduce the active TB incidence. Specifically, we focus on the treatment effort(γ), the case holding effort(σ) and the case finding effort(α) in the model equations (1) as noted in [14]. Numerical simulations are performed using three different values for each of these effort parameters. The effort γ denotes the effort of treatment of active TB infected individuals in I while σ denotes the effort of preventing low risk latent individuals from going back to the high risk or exposed class by forcing them to finish their treatment. Lastly, α denotes the effort of identifying exposed individuals so that they can be treated at their early stage and move to the low risk class. Here only the sensitivity analysis for the case finding effort is shown since this parameter is the most significant impact on the reduction of active TB cases.

Figure 3 presents the proportions of $S(t)/N(t)$, $E(t)/N(t)$, $I(t)/N(t)$, *and* $L(t)/N(t)$ using three different values of α to illustrate the impact of the case finding on the transient dynamics of TB after 2011 up to 2030. The corresponding results are plotted in red dotted curve, blue solid curve and black dashed curve using $\alpha = 0.0252$ and $\alpha = 0.0352$ (the baseline value from the estimation as given in Table 1) and $\alpha = 0.0752$, respectively. As shown in Figure 3, the proportion of active-TB incidences $I(t)/N(t)$ will be as twice as the one in 2011 year when $\alpha = 0.0352$ (or even more so with $\alpha = 0.0252$). When we put more effort on this case finding rate as $\alpha = 0.0752$, the

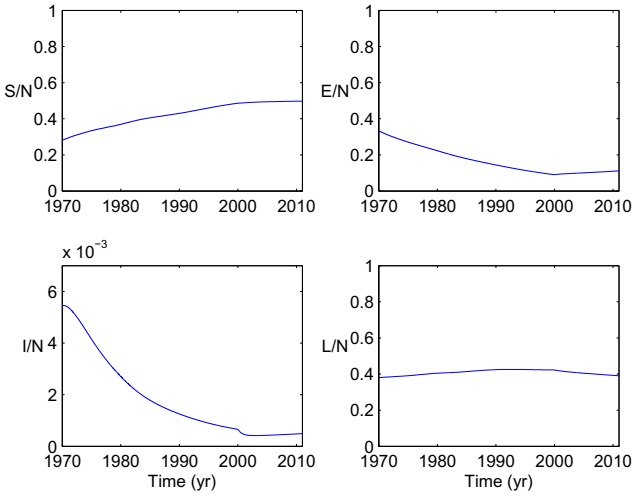

Figure 2. The proportions of S(t)/N(t), E(t)/N(t), I(t)/N(t) and L(t)/N(t) are plotted.

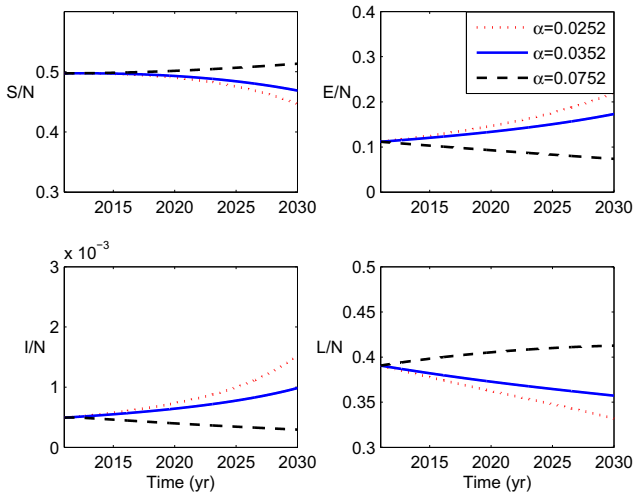

Figure 3. The fractions of state variables, S(t)/N(t), E(t)/N(t), I(t)/N(t) and L(t)/N(t), are plotted.

proportion of active-TB incidences $I(t)/N(t)$ will be almost half around 2030 year. The results of sensitivity analysis for the other two cases, the treatment efforts and the case holding effort, are similar as the ones of the case finding effortof course, not as significant as the case finding case but some impact to a certain extent.

This is consistent with the results for the basic reproductive number given earlier. Because the case holding control has no influence on basic reproductive number, the treatment effort and the case finding effort have influences on the basic reproductive number in a not simple way. More rigorous mathematical analysis will be needed for clarifying the impact of these efforts on the dynamics in terms of the basic reproduction number.

4. Discussion

Mathematical modeling in infectious diseases has played an important role to give us some insights on which counter measures would be more effective for reducing the negative impact of active-TB incidence. In this manuscript, we have modified a mathematical model for the TB dynamics in order to look into the role of exogeneous reinfection and moreover, in order to understand the recent increase in active-TB incidences in Korea. The importance of exogenous reinfections is still under debate. There have been some evidences, which support endogenous tuberculosis may be the main cause of tuberculosis while other using the same epidemiological data, has also shown the importance of exogenous reinfection in the USA. In the Netherlands, the contribution of endogenous and exogenous reinfection to the total disease load was studied [12 and references are therein]. We would like to take more rigorous study to investigate these contributions in the Korean TB transmission in the near future. The proposed model output for the active-TB incidence shows a good agreement with the observed data. Among some key parameters in the model, the case finding effort turned out to be the most significant impacting component on the reduction in the active TB cases. However, our results show that concentrating on treatment alone or case finding alone will not dramatic affect the reduction in the active TB incidences. Therefore, taking two or more of the key parameters at the same time will go a long way in reducing the burden of the active TB. More systematic sensitivity analysis and extensive mathematical analysis should be and will be carried out in our future research.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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