

Article

Age-Specific Mathematical Model for Tuberculosis Transmission Dynamics in South Korea

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Abstract: Korea has the highest burden of tuberculosis (TB) among Organization for Economic Co-operation and Development countries. Various strategies have been implemented to eradicate TB in Korea, and it is critical to evaluate previous TB management outcomes before framing future TB policies. Over the past few decades, the rapid increase in the aging population in Korea has substantially impacted the incidence of TB among the elderly. Thus, in this study, we aimed to develop a mathematical model for the assessment of TB management outcomes incorporating special features of TB transmission dynamics in Korea. First, we incorporate 2-age groups in our TB model because TB epidemics in Korea are different between the elderly and the non-elderly (<65 years vs. ≥65 years). Second, because the public-private mix has had a full-fledged impact since 2012, this study was divided into two periods (2001–2011 and 2012–2018). We developed a mathematical model of TB transmission dynamics with 2-age groups and age-specific model parameters were estimated based on actual TB epidemic data from 2001 to 2018. These parameters included transmission rates, relapse rates, and recovery rates. We conducted sensitivity analyses of various parameters, and investigated the impacts of these parameters on TB incidence. Our results demonstrate that the overall outcomes of both age-groups improved in the period of 2012–2018 compared with that in the period of 2001–2011. Age-specific interventions should be implemented to reduce the overall TB incidence. More intensive treatment efforts should be focused on the elderly, while the early detection and treatment rates for latent TB were the most significant factor to reduce TB incidence in both groups.

Keywords: TB mathematical model with two-age groups; transmission rate; treatment rate; early detection and treatment rate; relapse rate; the basic reproduction number; various interventions (public-private mix)



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1. Introduction

Tuberculosis (TB) is an infectious disease, one of the world's leading causes of death [1]. The World Health Organization (WHO) implemented the “Stop TB” strategy from 2006 to 2015 [2] and initiated the “End TB” strategy beginning in 2015 [3] with the goal of eliminating TB and related deaths worldwide by 2035. In particular, directly observed therapy (DOT) and public-private mix (PPM) are the most important key components for the two strategies to increase treatment coverage and success rates. In addition to DOT and PPM, WHO emphasized that proper baseline preparation to move the “End TB” strategy forward in the right direction and evaluation of the current epidemic situation are essential before rolling out key strategies [3]. In line with the WHO, Korea is also pursuing a mid- to long-term national tuberculosis project to achieve eradication of TB by 2035. The reported number of new TB cases in South Korea decreased by approximately 50% from 168 per 100,000 population in

1990 to 80 per 100,000 population in 2015. Nevertheless, the TB infection rate and TB death rate are higher than those of countries in the Organization for Economic Co-operation and Development [1].

The annual TB incidence in Korea has been on the decline since 2012 as a result of various policies, including PPM projects, consistent and comprehensive TB control strategies, and initiation of TB contact investigation (Figure 1). PPM, which began on a pilot scale in 2007 and was expanded to entire South Korea in 2011, is believed to be an essential component for controlling TB. The national PPM TB control project was launched in 2009. In 2012, there were approximately 120 hospitals and 200 TB special nurses. A similar level has been maintained ever since [4]. Treatment in the private sector has become more important in Korea. In 2001, the proportion of new patients reported from public health centers was 46.2%. In 2016, this number decreased to 7.8%, whereas the proportion of patients managed by private medical institutions increased to 92.2%. A government plan was established to intensify PPM to make the TB incidence zero as soon as possible. The government is reviewing an extension of the current monitoring period from 2 weeks to 8 months to increase the completion of treatment and the success rate. There is a need to assess the overall effectiveness of the PPM project before launching a new PPM plan in the future. Because full-fledged TB control by PPM has had an impact since 2012, it is necessary to compare the outcomes of 2001–2011 with those from 2012 to assess the effects of PPM on TB management.

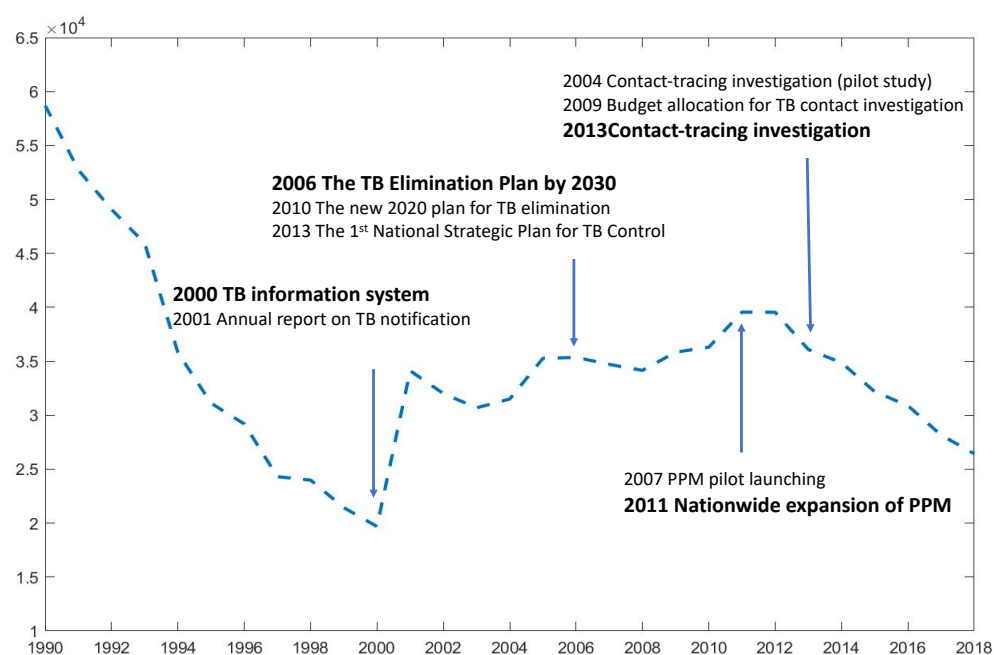


Figure 1. Annual TB incidence and various interventions at the national level are displayed from 1990 to 2018. Note that the annual incidence of TB was increased owing to a new TB surveillance system implemented by the Korean government in 2000. The PPM began on a pilot scale in 2007 and expanded to all of Korea in 2011.

It is challenging to measure epidemiological characteristics of TB transmission such as infection rates, recovery rates, and relapse rates owing to its long variable latency and complex interplays between hosts and environments. Moreover, many difficulties are involved in assessing the effectiveness of public health policies for TB, which have been implemented by the Korean government at a national level. Mathematical modeling can serve as a complementary tool to understand the complex dynamics of TB and evaluate the effectiveness of various TB prevention projects [5–7]. Studies have been conducted on TB transmission with age structures [8–13]. A TB mathematical model with three age groups that incorporated human immunodeficiency virus infections in South Africa was

developed [8]. The study investigated age-specific patterns in human immunodeficiency virus-negative TB notification rates in Cape Town in 2009. Another TB mathematical model with three age groups investigated the roles of the recovery rate and infection rates on TB cases in the elderly group in China [9]. Discrete network-based modeling of TB transmission was proposed in the United States using synthetic datasets [13]. This study predicted that household infection was more dominant than in other locations.

In previous studies, a mathematical model with reinfection was proposed and optimal treatment strategies were identified in Korea [14,15]. None of these previous works incorporated age-specific features in mathematical models of TB transmission dynamics in Korea. However, susceptibility to Mycobacterium is quite different in the elderly group [16,17], and the incidence among the elderly is rapidly increasing in South Korea. The proportion of elderly patients aged 65 years or older among newly reported TB cases was 19% (6547 of 34,123) in 2001 but increased to 42% (11,798 of 28,161) in 2017 (Table 1). The mortality rate of patients with TB is significantly high (82% of TB deaths) in the elderly in South Korea [18,19]. Considering these factors and the rapidly aging population of South Korea, an age-specific mathematical model is required to assess the epidemic of TB more precisely in Korea.

Table 1. Age-specific population size is shown [20]. Note that the elderly age group (≥ 65 years) is rapidly increasing while the number of newborn population is decreasing (λ_1).

	2001	2002	2003	2004	2005	2006	2007	2008	2009
Total	47,877,049	48,125,745	48,308,386	48,485,314	48,683,040	48,887,027	49,130,354	49,404,648	49,656,757
Group 1 (<65)	43,715,475	43,741,042	43,688,138	43,614,886	43,558,518	43,495,760	43,406,999	43,345,725	43,311,428
Group 2 (≥ 65)	4,161,574	4,384,703	4,620,248	4,870,428	5,124,522	5,391,267	5,723,355	6,058,923	6,345,329
λ_1	559,934	496,911	495,036	476,958	438,707	451,759	496,822	465,892	444,849
	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total	49,879,812	50,111,476	50,345,325	50,558,952	50,763,158	50,951,720	51,112,972	51,230,705	51,301,009
Group 1 (<65)	43,270,507	43,240,464	43,144,834	42,975,199	42,782,445	42,569,268	42,352,819	42,029,211	41,612,986
Group 2 (≥ 65)	6,609,305	6,871,012	7,200,491	7,583,753	7,980,713	8,382,452	8,760,153	9,201,494	9,688,023
λ_1	470,171	471,265	484,550	436,455	435,435	438,420	406,243	357,771	326,822

In this study, we developed a mathematical model for 1-group TB transmission dynamics and extended this model to an age-specific TB model with 2 age groups (<65 years vs. ≥ 65 years). Age-specific parameters were estimated based on actual TB incidence data in Korea from 2001 to 2018. These parameters included transmission rate, relapse rate, and treatment rate (or recovery rate). In particular, due to PPM had a full-fledged impact since 2012, the current study was divided into two periods (2001–2011 vs. 2012–2018). Therefore, these parameters were estimated before and after 2012 to assess how they were changed by various policies. Furthermore, we investigated the impacts of these parameters on TB incidence by performing sensitivity analyses.

2. Mathematical Models

2.1. Data and Sources

The annual reported number of TB cases in South Korea (2001–2018) were obtained from the Korean Center for Disease and Prevention Control (KCDC) [18–20]. To investigate age-specific analysis, we divided the total TB cases into 2 age groups. Group 1 included cases younger than 65 years old (<65 years), and group 2 included elderly cases (≥ 65 years). The total TB cases and TB cases in the 2 age groups from the year 2001 to the year 2018 are shown in Table 2. The yearly reported TB incidence among patients younger than 65 years decreased while the yearly reported TB incidence among those 65 years and older increased. Furthermore, the total population of South Korea and each population size of two-age groups are collected in Table 1. Note that the total population size of South Korea is slightly increasing; the elderly age group (≥ 65 years) is rapidly increasing while the number of newborn population is decreasing (λ_1).

The annual TB incidence and various interventions implemented at the national level are displayed in Figure 1. Note that there was a rapid increase in the annual TB incidence after 2000. This is mainly due to the initiation of a new TB surveillance system implemented by the Korean government in 2000. Moreover, the aging population combined with a higher proportion of the latent individuals after the Korean War was partial causes. Lastly, the proportion of relapsed individuals, and the emergence of multidrug-resistant (MDR)-TB was not negligible. The annual incidence of TB in Korea has been declining since 2012, probably as a result of various policies. We divided the total period into a 2-time window (2001 to 2011 and 2012 to 2018) to assess how the key parameters were changed during each period.

Table 2. Age-specific TB incidence is shown [18–20]; TB incidence among the elderly age group (≥ 65 years) is rapidly increasing.

	2001	2002	2003	2004	2005	2006	2007	2008	2009
Total	34,123	32,010	30,687	31,503	35,269	35,361	34,710	34,157	35,845
Group 1 (<65)	27,576	25,432	24,197	24,414	26,664	26,530	25,827	24,750	25,725
Group 2 (≥ 65)	6547	6578	6490	7089	8605	8831	8883	9407	10,120
	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total	36,305	39,557	39,545	36,089	34,869	32,181	30,982	28,161	26,433
Group 1 (<65)	25,573	27,698	26,747	23,932	22,658	20,243	18,654	16,363	14,404
Group 2 (≥ 65)	10,732	11,859	12,798	12,157	12,211	11,938	12,328	11,798	12,029

2.2. Mathematical Model for TB Transmission Dynamics

First, we considered a standard SEIR-model for TB transmission dynamics (with one-age group) as studied in previous studies [5–7,14]. The entire population was divided into four epidemiological compartments according to disease state: susceptible (S), latent (E), Infectious (I), and recovered (R). Denote that $S(t)$ is susceptible population size at time t and $E(t)$ is latent population size. Denote that $I(t)$ is population size of infectious individuals (active TB cases). Lastly, $R(t)$ represented recovered population size and $C(t)$ represented the number of cumulative active TB individuals. The total population size was defined as $N(t) = S(t) + E(t) + I(t) + R(t)$. Let us denote β be a transmission rate, and k be a progression rate from $E(t)$ to $I(t)$. α indicated early detection and treatment rates for latent TB, $E(t)$ to $R(t)$ (efforts of contact-tracing and treatment for latent individuals), and μ was the natural death rate. γ represented the recovery rate (from $I(t)$ to $R(t)$), whereas σ represented the relapse rate from $R(t)$ to $I(t)$. Note that the total population size $N(t)$ is given as $N(t) = S(t) + E(t) + I(t) + R(t)$. Hence, we have the following system of ordinary differential equations and see the diagram in Figure 2:

$$\begin{cases} \frac{dS}{dt} = \lambda - \beta S \frac{I}{N} - \mu S, \\ \frac{dE}{dt} = \beta S \frac{I}{N} - (\mu + k + \alpha) E, \\ \frac{dI}{dt} = kE - (\mu + \gamma) I + \sigma R, \\ \frac{dR}{dt} = \gamma I - \sigma R - \mu R + \alpha E. \end{cases} \quad (1)$$

More detailed descriptions of variables and parameters are listed in Tables 3 and 4. The basic reproduction number measures the average number of secondary infections by a primary infectious individual in a susceptible population [21]. We employ the next-generation method to compute the basic reproduction number as

$$\mathcal{R}_0 = \rho(FV^{-1}),$$

where ρ was defined as the spectral radius of the matrix FV^{-1} . Here, \mathcal{F} was the rate of appearance of new infections, and \mathcal{V} was the transfer of individuals out. Then, we found the Jacobian matrix of $\mathcal{F}(X)$ and $\mathcal{V}(X)$, where $X = (S, E, I, R)$. Denote $F = [\partial \mathcal{F}_i / \partial X_j]$ and $V = [\partial \mathcal{V}_i / \partial X_j]$ ($i, j = 1, 2, \dots, 4$) evaluated at the disease free equilibrium point $X^* = (N, 0, 0, 0)$. Then, the basic reproduction number, \mathcal{R}_0 (or the local reproduction number for the 1-group model) can be written as

$$\mathcal{R}_0 = \frac{\beta k}{(k + \mu)(\gamma + \mu + \alpha)}.$$

More details of the above derivations are given in the Appendix A.

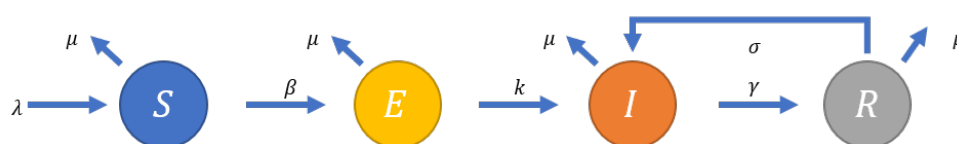


Figure 2. TB-transmission diagram for the 1-age group model (model (1)).

Table 3. Age-specific descriptions and initial values (in 2001) from [18,20].

Variable	Description	Initial Value
N_1, N_2	Total population size	43,715,475, 4,161,574
S_1, S_2	Susceptible class	26,602,668, 2,013,417
E_1, E_2	Exposed class	17,038,672, 2,141,610
I_1, I_2	Infected class	34,135, 6547
R_1, R_2	Treated class	40,000, 4000

Table 4. Age-specific baseline parameters and descriptions are obtained from [18–20,22].

Parameter	Description	Value	Source
λ_1	Recruitment of Group 1	See Table 1	[20]
λ_2	Recruitment rate from Group 1 to Group 2	1/65	[20]
μ_1, μ_2	Per-capita natural death rate	0.0005, 0.05	[20]
k_1, k_2	Progression rate from E to I	0.0015–0.0018, 0.00280–0.0038	[18]
α_1, α_2	Early detection and treatment rate for latent TB	0–0.18 for 2012–2018	Assumed
$c_{11}, c_{12}, c_{21}, c_{22}$	Contact rate	0.9208, 0.0792, 0.3515, 0.6485	[22]
β_1, β_2	Transmission rate	Estimated	-
σ_1, σ_2	Relapse rate	Estimated	-
γ_1, γ_2	Recovery rate	Estimated	-

We then extended the 1-group model (1) to 2-age group TB transmission model by incorporating age-specific parameters. Here, group 1 represents the age group younger than 65 years old, and group 2 includes the elderly group (≥ 65 years). Each compartment (SEIR) consists of 2-age groups: S_1, E_1, I_1, R_1 , and C_1 for Group 1, and S_2, E_2, I_2, R_2 , and C_2 for Group 2. $N_i(t) = S_i(t) + E_i(t) + I_i(t) + R_i(t)$ for $i = 1, 2$, and $N(t) = N_1(t) + N_2(t)$. For each age-group i , β_i was the transmission rate, and k_i was the progression rate from $E_i(t)$ to $I_i(t)$. $\alpha(t)$ indicated early detection and treatment rates for latent TB, $E_i(t)$ to $R_i(t)$ (here, $\alpha(t) = \alpha_1(t) = \alpha_2(t)$ is assumed), and μ_i was a natural death rate. γ_i represented the recovery rate (from $I_i(t)$ to $R_i(t)$), whereas σ_i represented the relapse rate from $R_i(t)$ to $I_i(t)$. The birth rate $\lambda_1(t)$ was used for $S_1(t)$ and we assumed that Group 1 moved to Group 2 (the elderly group) by the proportion of the elderly group, $\lambda_2(t)$ [20]. Each group members were mixing with a contact matrix $C = (C_{ij})$ for $i, j = 1, 2$ as the number of interactions or contact of age groups per unit time [22]. A TB transmission diagram of

the 2-group model is shown in Figure 3. The resulting 2-age group transmission model is described by the following system of differential equations:

$$\begin{cases} \frac{dS_1}{dt} = \lambda_1(t) - (\beta_1 c_{11} \frac{I_1}{N_1} + \beta_2 c_{12} \frac{I_2}{N_2}) S_1 - \mu_1(t) S_1 - \lambda_2(t) S_1, \\ \frac{dE_1}{dt} = (\beta_1 c_{11} \frac{I_1}{N_1} + \beta_2 c_{12} \frac{I_2}{N_2}) S_1 - (\mu_1(t) + k_1(t) + \alpha(t)) E_1 - \lambda_2(t) E_1, \\ \frac{dI_1}{dt} = k_1(t) E_1 - (\mu_1(t) + \gamma_1) I_1 + \sigma_1 R_1 - \lambda_2(t) I_1, \\ \frac{dR_1}{dt} = \gamma_1 I_1 - (\sigma_1 + \mu_1(t)) R_1 + \alpha(t) E_1 - \lambda_2(t) R_1, \end{cases} \quad (2)$$

$$\begin{cases} \frac{dS_2}{dt} = \lambda_2(t) S_1 - (\beta_1 c_{21} \frac{I_1}{N_1} + \beta_2 c_{22} \frac{I_2}{N_2}) S_2 - \mu_2(t) S_2, \\ \frac{dE_2}{dt} = \lambda_2(t) E_1 + (\beta_1 c_{21} \frac{I_1}{N_1} + \beta_2 c_{22} \frac{I_2}{N_2}) S_2 - (\mu_2(t) + k_2(t) + \alpha(t)) E_2, \\ \frac{dI_2}{dt} = \lambda_2(t) I_1 + k_2(t) E_2 - (\mu_2(t) + \gamma_2) I_2 + \sigma_2 R_2, \\ \frac{dR_2}{dt} = \lambda_2(t) R_1 + \gamma_2 I_2 - (\sigma_2 + \mu_2(t)) R_2 + \alpha(t) E_2, \end{cases} \quad (3)$$

More detailed descriptions of variables and parameters are listed in Tables 3 and 4. Similarly, we employed the next-generation method to compute the basic reproduction number for the 2-age group model (2) and (3) as

$$\mathcal{R}_0 = \rho(FV^{-1}),$$

where ρ was defined as the spectral radius of the matrix FV^{-1} . Here, let \mathcal{F} be the rate of new infections, and \mathcal{V} be the rate of individuals out. The Jacobian matrix of $\mathcal{F}(X)$ and $\mathcal{V}(X)$, where $X = (E_1, E_2, I_1, I_2)$ can be obtained as $F = [\partial \mathcal{F}_i / \partial X_j]$ and $V = [\partial \mathcal{V}_i / \partial X_j]$ ($i, j = 1, 2, \dots, 4$). They were evaluated at the disease free equilibrium point X^* . The details of the basic reproduction number (\mathcal{R}_0) are provided in the Appendix A.

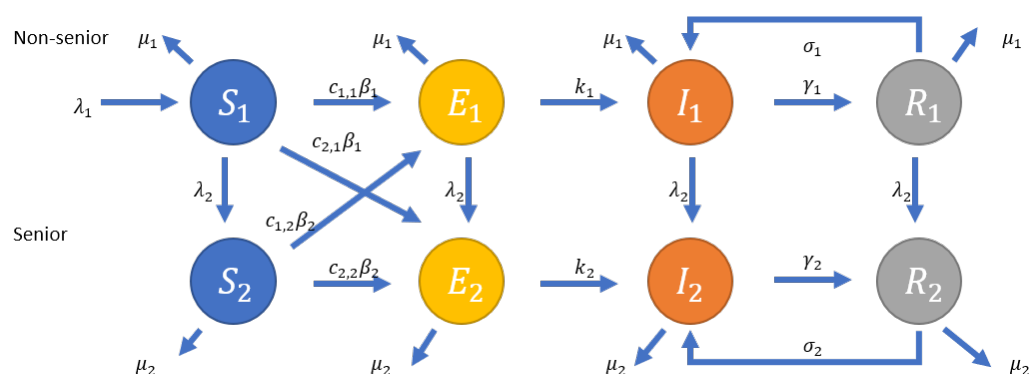


Figure 3. TB-transmission diagram for the 2-age group model (model (2) and (3)).

3. Numerical Results

3.1. Estimated Parameters

We estimated our model parameters using the annual TB incidence data listed in Table 2. We conducted 2 distinct time scenarios: a 1-time window from 2001 year to 2018 and 2-time window scenario of 2001 to 2011 and 2012 to 2018. To investigate the effectiveness of the extensive PPM interventions from the year 2012, we divided the time window into two parts: 2001 to 2011 and 2012 to 2018. We set the initial population size for each class (age-specific) as listed in Tables 1–4, the initial latent numbers of $E_{1,2}(t_0)$, the initial infectious individuals of $I_{1,2}(t_0)$, the initial recovered individuals ($R_{1,2}(t_0)$) were obtained from a previous study [18]. We assumed that the early detection and treatment rate for latent TB in both age groups were

the same $\alpha_1 = \alpha_2$, $\alpha_1 = \alpha_2 = 0$ for 2001–2011 and $\alpha_1 = \alpha_2 = 0 - 0.18$ during 2012–2018. Note that $\alpha_1 = \alpha_2 = 0 - 0.18$ is time-varying ranging from 0 to 0.18 (likewise for k_1 and k_2). It was assumed the treatment of latent TB started in 2012 and that the treatment rate in 2012 was 0% as a base year considering that screening and treatment of latent TB was first recommended in the 2011 TB guidelines. It is also assumed that the annual treatment rate increased by 3% points per year as the treatment completion rate of latent TB was reported to be about 20% in 2018 based on a policy evaluation interim report [23] and a research result for healthcare workers with latent TB in Korea [24].

We present the process of parameter estimation for the 2-group model because the process of parameter estimation for the 1-group model is more straightforward. A standard least-squares framework was employed to find a parameter set (θ) that minimized the least-squares error between the model outputs ($CI_{1,2}$ for each group $i = 1, 2$) and actual cumulative incidence TB data ($D_{1,2}$ for each group $i = 1, 2$). Note that $CI_{1,2}(t)$ is the solution of the differential equation of cumulative incidence for each age-group 1 and 2:

$$\frac{dCI_1}{dt} = k_1(t)E_1 + \sigma_1 R_1$$

$$\frac{dCI_2}{dt} = k_2(t)E_2 + \sigma_2 R_2$$

Here, θ included the transmission rate β_i , the recovery rate γ_i , and the relapse rate σ_i for each age group $i = 1, 2$. Furthermore, these parameters were divided into the time-window depending on the scenarios: 1-time window of 2001 to 2018 and 2-time window of 2001 to 2011 and 2012 to 2018.

The least-squares error $J(\theta)$ is defined as

$$J(\theta) = \sum_{j=1}^N \left((CI_1(t_j, y(t_j); \theta) - D_1(t_j))^2 + (CI_2(t_j, y(t_j); \theta) - D_2(t_j))^2 \right),$$

where θ represented a set of parameters, t_j time points, and $D_{1,2}$ cumulative incidence TB data for each age group $i = 1, 2$, respectively. The Nelder–Mead simplex method [25] was employed to minimize the total error in the least-squares sense using a direct search approach (MATLAB's built-in optimization function `fminsearch`). The optimal parameter values for the 1-group model and 2-group model are shown in Tables 5 and 6 for the 1- and 2-time windows, respectively. Based on these estimated parameters, we obtained the value of the basic reproduction number: $\mathcal{R}_0 = 0.1924$ in 2001–2011 and $\mathcal{R}_0 = 0.1515$ in 2012–2018.

Table 5. Parameter estimation for a 1-time window from 2001 to 2018. Age-specific transmission rates, relapse rate, and recovery rates were estimated according to TB incidence in South Korea.

		β : Transmission Rate	σ : Relapse Rate	γ : Recovery Rate
One-age group	2001–2018	1.4014	0.0003438	1.1338
Age < 65 years	2001–2018	1.6100	0.0001150	1.3434
Age \geq 65 years	2001–2018	1.2642	0.0003529	0.8585

Table 6. Parameter estimation for a 2-time window (2001 to 2011 and 2012 to 2018). Age-specific transmission rates, relapse rates, and recovery rates were estimated according to TB incidence in South Korea.

		β : Transmission Rate	σ : Relapse Rate	γ : Recovery Rate
One-age group	–2011	1.4524	0.0014410	1.1302
	2012–	1.2192	0.0004803	1.2754
Age <65 years	–2011	1.7249	0.0003150	1.1791
	2012–	1.2588	0.0000313	1.5050
Age \geq 65 years	–2011	1.3312	0.0010760	0.6625
	2012–	1.1986	0.0001055	0.7812

Figure 4 shows the red bars generated by the estimated parameters for the one-time window from 2001 to 2018. The leftmost panel shows the model output with annual TB data for the one-group model (1) while the middle and rightmost panels display the model output and yearly TB data of the two-group model (2) and (3). This compares TB Incidence data (blue bar) and the model output of one-age group (red bar). The TB incidence data and the model outputs in all panels were in good agreement.

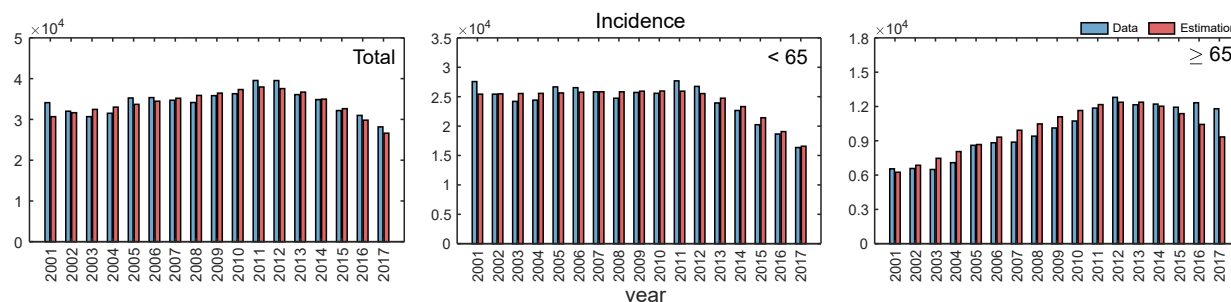


Figure 4. Model parameters were estimated in one period of 2001 to 2018. The leftmost panel showed TB Incidence data (blue bar) and the model output of the one-age group (red bar). Non-elderly TB incidence of the 2-age group is compared in the middle panel (blue for data and red for model output). Elderly TB incidence data (blue bar) and the model output of the 2-age group (red bar) are compared in the rightmost panel.

Figure 5 displays the red bars generated by the estimated parameters for the 2-time window from 2001 to 2011 and from 2012 to 2018. The leftmost panel presents the TB incidence data (blue bar) and the model output of the 1-age group (red bar), and the middle and rightmost panels show age-specific TB incidence data (blue bar) and the model output of the 2-age group (red bar). In addition, TB incidence data and the model outputs in both panels are in good agreement.

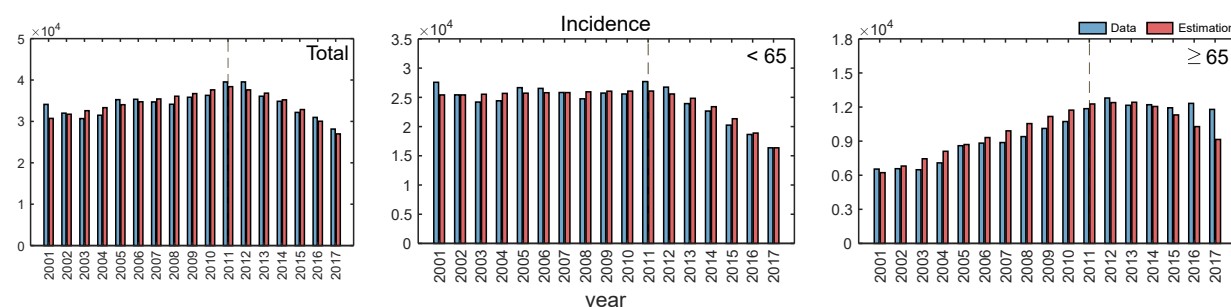


Figure 5. Model parameters were estimated in the 2-time window of 2001 to 2011 and 2012–2018. The leftmost panel showed TB Incidence data (blue bar) and the model output of the one-age group (red bar). Non-elderly TB incidence of the 2-age group is compared in the middle panel (blue for data and red for model output). Elderly TB incidence data (blue bar) and the model output of the 2-age group (red bar) are compared in the rightmost panel.

As shown in both results of Figures 4 and 5, the total number of TB cases steadily increased up to the year 2011 and started decreasing from 2012 to 2018. However, the number of age-specific TB cases in Group 1 (non-elderly group) remained at the same level up to the year 2011 and started decreasing rapidly from 2011 to 2018 (middle panel of Figure 5). On the other hand, the number of TB cases in Group 2 (elderly group) steadily increased from 2001 to 2011 and slightly decreased from 2012 to 2018. Hence, the total number of TB cases decreased since 2012 owing to a significant reduction in the number of TB cases in Group 1 (see the rightmost panel of Figure 5).

3.2. Sensitivity Analysis

We carried out sensitivity analysis to explore the impacts of input parameter values on the variation of the model outputs. A value function of $V(\theta)$ was computed to measure the level of sensitivity of each parameter in both models (1- and 2-group models). For example, the following function $V(\theta)$ can be obtained for the one-group model:

$$V(\theta) = \max_{0 \leq k \leq M} \left| \frac{CI(t_f, y(t_f); \theta_k) - CI(t_f, y(t_f); \theta_0)}{CI(t_f, y(t_f); \theta_0)} \right| \quad (4)$$

where $CI(t)$ is the solution of the differential equation of cumulative incidence

$$\frac{dCI}{dt} = \beta S \frac{I}{N}$$

with t_f (the final time), and θ_0 was the estimated parameters (Tables 5 and 6).

This can be extended to the 2-group model as shown below:

$$V_1(\theta) = \max_{0 \leq k \leq M} \left| \frac{CI_1(t_f, y(t_f); \theta_k) - CI_1(t_f, y(t_f); \theta_0)}{CI_1(t_f, y(t_f); \theta_0)} \right|,$$

$$V_2(\theta) = \max_{0 \leq k \leq M} \left| \frac{CI_2(t_f, y(t_f); \theta_k) - CI_2(t_f, y(t_f); \theta_0)}{CI_2(t_f, y(t_f); \theta_0)} \right|$$

where $CI_i(t)$ is the solution of the differential equation of cumulative incidence for each age group $i = 1, 2$ with t_f (the final time), and θ_0 is the estimated parameters given in Tables 5 and 6. We employed a global sensitivity method developed in a previous study [26]; this method used the variance decomposition approach. First, we varied input parameters, therefore, this caused variations in the model output. Next, we computed the variance of the model output. Then, a partial variance was calculated by partitioning of model output variance to determine what fraction of the model output variance was caused by the variation of each model parameter input. Let us denote CI as a cumulative incidence of the 1-group model, and CI_1, CI_2 as the age-specific cumulative incidence of the 2-age group model.

Figure 6 shows the sensitivity analysis for the 2-age group model on the 2-window time 2001 to 2011 and 2012 to 2018. The value of the Equation (4) was computed and is displayed on the y-axis as varying model parameters. The left panel of Figure 6 displays the sensitivity analysis of the three parameters (β, γ, σ) in 2001–2011 while the results are shown for the four parameters ($\beta, \gamma, \sigma, \alpha$) in 2012–2018. The model output CI_1 (cumulative incidence for the age group < 65) was more sensitive to most parameters in the both periods except γ_2 in 2001–2011 and α_2 in 2012–2018. The model output CI_2 (cumulative incidence for the age group > 65) was more sensitive to the recovery rate γ_2 in 2001–2011 and the early detection and treatment rate for latent TB, α_2 in the period from 2012 to 2018. Furthermore, the right panel of Figure 6 shows the sensitivity analysis of the contact rate parameters (only two parameters C_{11}, C_{22} were varied since $C_{11} + C_{12} = 1$ and $C_{21} + C_{22} = 1$). This shows that the both model outputs CI_1 and CI_2 were not significantly sensitive to the contact rates.

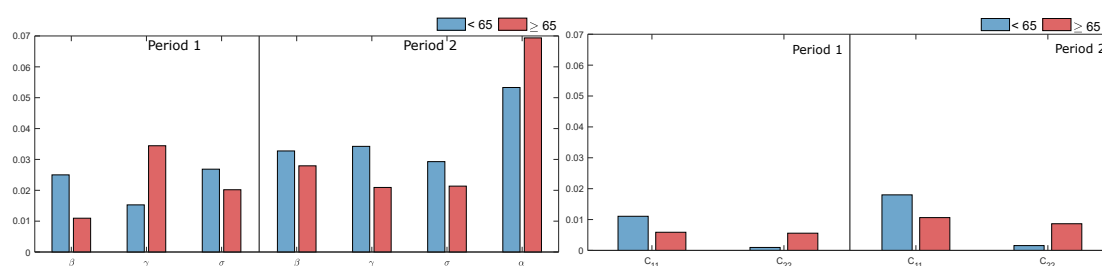


Figure 6. Sensitivity analysis for the 2-age group model was performed for the 2-window period: 2001 to 2011 and 2012 to 2018. In the left panel, transmission rates β_2^2 and the early diagnostic rate, α_2^2 in Group 2 (≥ 65 years) for the period from 2012 to 2018 year were most significant. The right panel showed the results of the contact rates, which were less significant.

3.3. Impacts of Key Parameters on Incidence

We investigated the impacts of some essential model parameters on incidence for the 1-age and 2-age group models. In Section 3.1, estimated parameters of both models (1-age group and 2-age groups) were given in Tables 5 and 6. Here, we explain the details of estimated parameters of the 1-age group and the 2-age group in the 1-time window (2001–2018) in Table 5. The transmission rate of the 1-age group was $\beta = 1.4014$, the relapse rate was $\sigma = 0.0003438$ and the recovery rate was $\gamma = 1.1338$. For the 2-group model, the transmission rates were $\beta = 1.61$ for Group 1 and $\beta = 1.2642$ for Group 2. The relapse rates for $\sigma = 0.000115$ for Group 1 and $\sigma = 0.0003529$ for Group 2. The recovery rates were $\gamma = 1.3434$ for Group 1 and $\gamma = 0.8585$ for Group 2.

Next, we presented estimated parameters of the 1-age group in the 2-time window in Table 6. The transmission rate of the 1-age group, $\beta = 1.4524$ from the first period (2001–2011) was decreased to $\beta = 1.2192$ in the second period (2012–2018). Similarly, the relapse rate was reduced from $\sigma = 0.0014410$ to $\sigma = 0.0004803$, whereas the recovery rate was slightly increased from $\gamma = 1.1302$ to $\gamma = 1.2754$. We presented estimated parameters of the 2-age group in the 2-time window. The transmission rate of Group 1 from the first period (2001–2011) $\beta = 1.7249$ was decreased to $\beta = 1.2588$ in the second period (2012–2018). Similarly, the relapse rate of Group 1 was reduced from $\sigma = 0.0003150$ to $\sigma = 0.0000313$, whereas the recovery rate was increased from $\gamma = 1.1791$ to $\gamma = 1.5050$. Lastly, the transmission rate of Group 2 from the first period $\beta = 1.3312$ was decreased to $\beta = 1.1986$ in the second period (2012–2018). Similarly, the relapse rate of Group 2 was reduced from $\sigma = 0.001076$ to $\sigma = 0.0001055$, whereas the recovery rate was increased from $\gamma = 0.6625$ to $\gamma = 0.7812$. Overall, both the transmission rates and the relapse rates were decreased in both age groups. In addition, the recovery rates were increased in both age groups during the second period (2011–2018).

We explored the impacts of the following four parameters on age-specific incidence for the 2-time window scenario: transmission rates, β and relapse rate, σ , recovery rates, γ , and early detection and treatment rate for latent TB, α . These four parameter values were re-scaled from the baseline parameter values, from 1 to 5 times larger. Other parameter values were fixed as the baseline values as shown in Table 4. Figure 7 displays the results of the 2-group TB transmission model; the top panel shows the impacts of the four key parameters on incidence for the 2-age group model. Note that the impact of the transmission rate (β) and early detection and treatment rate for latent TB, (α) were most significant in both groups. Furthermore, we carried out a short-term prediction of TB dynamics beyond 2018. The bottom panel of Figure 7 illustrates short-term prediction results from 2019 to 2022 for the 2-age group TB model under the 4-parameter values. This means that the prediction results are obtained by solving the model Equations (2) and (3) using the same parameter values of the second period 2012–2018 given in Table 6. Red and orange triangles represent an age-specific short-term prediction of the year 2019–2022 with variances (in rose-colored shades). Similarly, the impact of early detection and treatment rate for latent TB (α) in the prediction results was most significant in both Groups 1 and 2 in the rightmost panel (wider rose-colored shade, i.e., larger variance). Our results indicated that various interventions (PPM) combined with the active implementation of the early detection and treatment rate

for latent TB in all age groups might reach the goal of “End TB” strategy sooner than we expected.

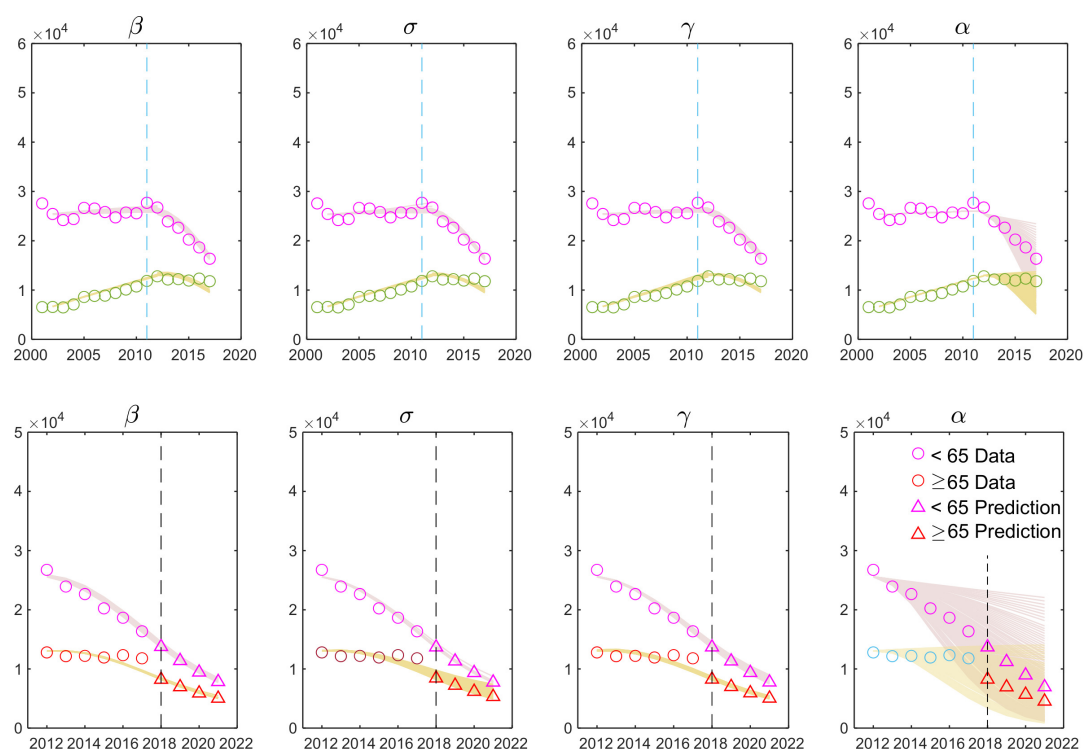


Figure 7. The top panel shows the impacts of the 4 estimated parameter values given in Table 6. Note that the impact of the transmission rate (β) and the early detection effort (α) was significant in both Groups 1 and 2. The bottom panel shows short-term predictions for 2019–2022 under the same parameter values estimated for the period 2012–2018. Note that maintaining various policies will decrease TB incidence in both age-groups.

Lastly, the impacts of various interventions on the TB incidence in the second time window were displayed in Figure 8. The green bar indicated the results obtained using the same parameter values of the first period (2001–2011), which was extended on the second period (2012–2018) in all three panels. The blue bar represented TB incidence data while the red bar represented the model output using the estimated parameters as given Tables 5 and 6. The leftmost panel presents the TB incidence data (blue bar) and the model output of the 1-age group (red bar), whereas the middle and rightmost panels illustrate age-specific TB incidence data (blue bar) and the model output of the 2-age group (the red bar denoted by Estimated 2 represented the results using parameters estimated during the second period, 2012–2018). Clearly, the annual TB cases (green bar) steadily increased from 2012 to 2018 regardless of the 1-age group or the 2-age group models. This implied that the estimated parameter values in the second period (2012–2018) confirmed that various interventions including PPM were effective (compare the results of the red and green bars). In fact, the green bar increased more in the rightmost panel (elderly TB cases), whereas the green bar decreased slightly in the middle panel (non-elderly TB cases). This underscored that more intensive treatments should be focused in the elderly population.

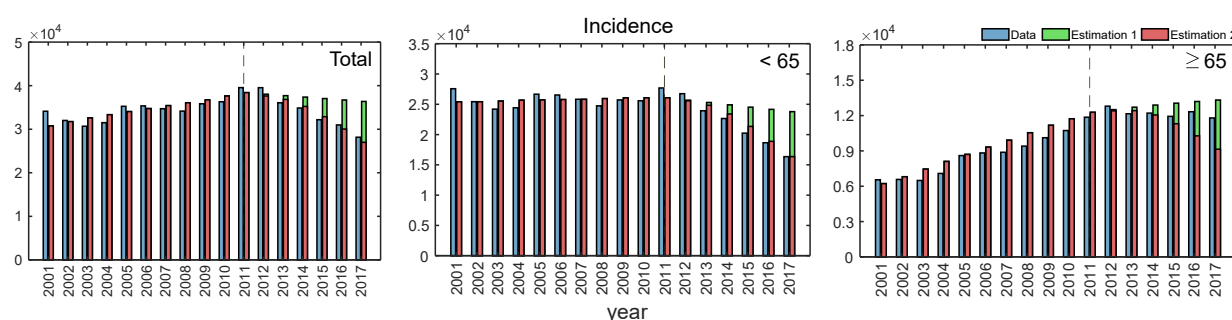


Figure 8. The green bar indicates the results obtained using the same parameter values of the first period (2001–2011), which was extended to the second period (2012–2018) in all three panels. The leftmost panel showed TB incidence data (blue bar) and the model output of the one-age group (red bar). Non-elderly TB incidence of the 2-age group is compared in the middle panel (blue for data and red for model output). Elderly TB incidence data (blue bar) and the model output of the 2-age group (red bar) are compared in the rightmost panel. The green bar increased more in the rightmost panel (elderly TB cases) and decreased slightly in the middle panel (non-elderly TB cases).

4. Discussion

In this study, we developed a mathematical model of the current TB transmission dynamics from 2001 to 2018. The population was divided by the following four epidemiological statuses: susceptible (S), exposed (E), infectious (I), and recovered (R). Some key parameters were estimated based on the epidemiological data for the entire population in South Korea. These parameters included transmission rates, β and relapse rate, σ , recovery rates, γ , and early detection and treatment rate for latent TB, α . Since TB case of the elderly population increase, we have refined the each epidemiological status into 2-age groups (elderly ≥ 65 and non-elderly < 65). Furthermore, due to the nationwide expansion of PPM, the period also was divided into 2001–2011 and 2012–2018 in order to investigate the effectiveness of PPM from 2012 to 2018.

We conducted age-specific and time-specific parameter estimation of the 1-age group and 2-age group models based on the actual TB data. TB incidence (or reported cases) was the outcome of complex interactions between various interventions and TB transmission dynamics. Because there were too many hidden factors, it was very challenging to separate them effectively in our model. Thus, we selected the most critical factors and investigated the impacts of such interventions implicitly on the transmission rates, β and relapse rate, σ , and recovery rates, γ . There was one clear factor that we could model explicitly: an early detection/treatment effort (α) is included as a separate parameter in our model.

The total number of TB cases decreased since 2012 due to a significant reduction in the number of TB cases among the non-elderly. However, the number of new TB cases in the elderly group is increasing mainly due to the aging trend in South Korea. The number of new TB cases in the elderly increased 1.84 times from 6547 in 2011 to 12,029 in 2018 (Table 2), but the elderly population increased 2.33 times from 4,161,574 (8.7% of the total population) to 9,688,023 (18.9% of the total population) during the same period (Table 1). Infectivity of infectious TB patients varied by age [16,17,27], and as the aging population is rapidly progressing in Korea, this study aimed to evaluate key parameters on TB transmission dynamics according to age group. Under our 2-age group model, the transmission rate was lower than that of the non-elderly group (< 65), which may be less exposed to the vicious cycle of moving and transferring because the elderly population has less contact with the public than younger people [27]. However, given that the relapse and treatment success rates were poorer than those in the non-elderly population, TB treatment for the elderly needs to focus more on strategies to improve the relapse and treatment success rates. Since these results are hidden in the 1-age group model, the 2-age group model may help establish TB treatment priorities by age group.

This study estimated key parameters on transmission and treatment outcome to assess how they affected TB incidence before and after 2012. The results of this study showed that all the key parameters improved during the second period (2012–2018, Period 2) compared

with that during the first period (2001–2011, Period 1). This implies that the nationwide anti-TB policies such as PPM, National Strategic Plan for TB Control, and Contact-tracing Investigation since the late 2000s have been effective in reducing TB transmission and improving treatment outcomes. Under the 1- and 2-group models, we achieved consistent results. The transmission rates and relapse rates were decreased in both age groups and the recovery rates were increased in both age groups during Period 2. These results highlight that the nationwide PPM projects and other policies were successful in reducing the transmission and relapse rates and in increasing the recovery rates (or the treatment rates). However, the results about transmission rates should be interpreted carefully considering the slow progression of TB in our models. Since it can take months to decades to become infectious TB from latent TB [28,29], the current outcomes of transmission are the results of gradual activation of latent TB in the past. Therefore, the results of Period 2 are also a combination of the results of many interventions that have been implemented during and before Period 1, and interventions implemented in Period 2 are expected to affect future transmission rates. There were some differences in the estimated parameters between the results of the 1-group TB model and the 2-group TB model. Therefore, we need to conduct further extensive investigation on how to interpret the results of the 1- and 2-group models.

The results of this study showed that the decreased TB incidence in Period 2 could be related to the decreased transmission rate. In addition, the decrease can be linked to an increase in treatment completion rate and treatment success rate. Based on the annual report on the notified TB in Korea, the treatment success rate increased to 83.1% (range, 81.6–84.5%) in Period 2 from 78.7% (range, 74.3–82.3%) in Period 1 [18,30]. Subsequently, the increased treatment success could lead to the decrease in the probability of infection and relapse. Thus, far, few studies have been published on the TB relapse rate in South Korea. One nested case-control study observed 12,183 TB patients and found that 0.9% of patients relapsed during the follow-up [31]. Another retrospective review study on patients with MDR-TB patients reported that the 39-month relapse rate was 4.4%, which converted to a relapse rate of approximately 1.4% over 1 year [32]. The relapse rate assessed in this study was much lower than the previously reported results because the population in this study included patients with latent TB. Therefore, it should be noted more on the decreasing trend of relapse rates in this study. Treatment adherence and completion also affect relapse and continuous attention should be paid to increase compliance and the completion rate of TB treatment [33]. Along with the PPM project and other interventions, health authorities have been trying to change the paradigm of future TB management policies from treatment to prevention before an outbreak; The Korea Disease Control and Prevention Agency has recommended diagnosis and treatment of latent TB as an independent chapter in the 2011 TB treatment guidelines, the TB prevention Act was amended in 2016 to oblige community workers in congregated settings to undergo latent TB tests and treatments, and screening and treatment was first recommended for healthcare workers in the 2017 TB treatment guidelines [19,34]. In the present study, we evaluated that early detection and treatment for latent TB in the high-risk group (>65 years) would be most effective to reduce the incidence of active TB in Korea. Therefore, it is necessary to set up and strengthen more careful management policies regarding latent TB elimination and treatment in the future.

This study has some limitations. First, our model can be improved by refining the exposed class (the fast and slow progression rates from exposed to infectious TB), as reported in [28]. In addition, more precise data (such as relapse rates and fast and slow progression rates from E to I) would be helpful to draw more meaningful insights from the basic reproduction number. In general, most active TB cases arise from latent TB, with only a minor fraction (approximately 10%) undergoing fast progression from primary exposure to active TB [29], and the risk of active TB from latent TB increases with co-infection of HIV [35,36] but prevalence of HIV co-infection in South Korea is very low. Considering these factors and the lack of Korean data currently available to distinguish fast and slow progression of TB, this study focused on the age-specific TB dynamic model. We would like to develop a model incorporating fast and slow progression in our future

research. Second, the role of the relapse rate, the basic reproduction, or the contact rate should be further investigated. In TB dynamics, it is very challenging to measure these parameters accurately because of various complex factors such as long latent periods, variable population sizes, transmission rates, which are changing in time along with living conditions, social behaviors, and environmental changes. Therefore, it is difficult to elucidate the role of the relapse rate, the basic reproduction number, or the contact rate in our current study. Further investigation should be carefully carried out in future research. Third, this study did not separately assume parameters for MDR-TB, including extensively drug-resistant TB (XDR-TB), which accounted for approximately 3.4% of new TB cases. The parameters in this study were estimated in patients with TB, including those with MDR-TB, and the estimated parameters and outcomes in this study reflected the effects of MDR-TB and XDR-TB in a weighted manner. Lastly, this study assumed that approximately one-third of the total population was LTBI and that direct treatment for LTBI has been increasing very slowly since 2012. To complement the uncertainty of this limitation, various sensitivity analyses were conducted. It should be considered that the results of this study may vary depending on the LTBI ratio and the direct treatment rate from LTBI to recovery.

In conclusion, this study presents an age-specific TB dynamic model, and key parameters on TB transmission were estimated using the model to evaluate the treatment outcomes of TB in South Korea. The evaluation results showed the same tendency as previous reports, indicating that this study can be used as a supplement to the evaluation and treatment strategy for future TB management in South Korea.

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Appendix A

The Basic Reproduction Number \mathcal{R}_0

We employed the method developed in a previous study to compute the basic reproductive number [21]. First, the basic reproductive number of the 1-group model (1) was computed as follows; let \mathcal{F} denote the rate of new infections while the net transition rates out of the corresponding compartment were denoted by \mathcal{V} . \mathcal{F} and \mathcal{V} are a function of $X = (S, E, I, R)$ and we take the derivative of both \mathcal{F} and \mathcal{V} with respect to X , then we obtain $F = [\partial \mathcal{F}_i / \partial X_j]$ and $V = [\partial \mathcal{V}_i / \partial X_j] (i, j = 1, 2, \dots, 4)$. Next, we evaluate them at the disease-free equilibrium point $X^* = (N, 0, 0, 0)$. Finally, the spectral radius ρ of matrix FV^{-1} gives the basic reproductive number, where

$$F = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix}, V = \begin{pmatrix} \mu + k & 0 \\ -k & \mu + \gamma + \alpha \end{pmatrix} \quad (\text{A1})$$

$$FV^{-1} = \begin{pmatrix} \frac{\beta+k}{(k+\mu)(\mu+\gamma+\alpha)} & \frac{\beta}{\mu+\gamma+\alpha} \\ 0 & 0 \end{pmatrix}$$

$$\mathcal{R}_0 = \frac{\beta k}{(\mu+k)(\mu+\gamma+\alpha)}$$

Similarly, we computed the basic reproductive number of the 2-age group model (2) as follows; Let $X = (E_1, I_1, E_2, I_2)^T$ and we let \mathcal{F} denote the rate of new infections in the four components class, thus $\mathcal{F}(X)$ denoted all the new infections. The net transition rates out of the corresponding compartment were denoted by $\mathcal{V}(X)$. We defined 2 matrices $F = (\frac{\partial \mathcal{F}}{\partial X_i}(X^*))$ and $V = (\frac{\partial \mathcal{V}}{\partial X_i}(X^*))$ evaluated at the disease-free equilibrium, X^* . The spectral radius ρ of matrix FV^{-1} gives the basic reproductive number.

$$F = \begin{pmatrix} 0 & 0 & \beta_1 c_{11} & \beta_1 c_{12} \\ 0 & 0 & \beta_2 c_{21} & \beta_2 c_{22} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad (A2)$$

$$V = \begin{pmatrix} \mu_1 + k_1 + \alpha + \lambda_2 & 0 & 0 & 0 \\ -\lambda_2 & \mu_2 + k_2 + \alpha & 0 & 0 \\ -k_1 & 0 & \mu_1 + \gamma_1 + \lambda_2 & 0 \\ 0 & -k_2 & -\lambda_2 & \mu_2 + \gamma_2 \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} \frac{\beta_1 c_{11} k_1}{f_1 f_3} + \frac{\beta_2 c_{12} \lambda_2 (f_2 k_1 + f_3 k_2)}{f_1 f_2 f_3 f_4} & \frac{\beta_2 c_{12} k_2}{f_2 f_4} & \frac{\beta_1 c_{11} f_4 + \beta_2 c_{12} \lambda_2}{f_3 f_4} & \frac{\beta_2 c_{12}}{f_4} \\ \frac{\beta_1 c_{21} k_1}{f_1 f_3} + \frac{\beta_2 c_{22} \lambda_2 (f_2 k_1 + f_3 k_2)}{f_1 f_2 f_3 f_4} & \frac{\beta_2 c_{22} k_2}{f_2 f_4} & \frac{\beta_1 c_{21} f_4 + \beta_2 c_{22} \lambda_2}{f_3 f_4} & \frac{\beta_2 c_{22}}{f_4} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$\mathcal{R}_0 = \frac{\sqrt{S} + \beta_1 c_{11} f_2 f_4 k_1 + \beta_2 c_{22} f_1 f_3 k_2 + \beta_2 c_{12} f_2 k_1 \lambda_2 + \beta_2 c_{12} f_3 k_2 \lambda_2}{(2f_1 f_2 f_3 f_4)}$$

$$S = (((\beta_1 c_{11} k_1 f_2 f_4 + \beta_2 c_{22} k_2 f_1 f_3) + (\beta_2 c_{12} k_1 \lambda_2 f_2 + \beta_2 c_{12} k_2 \lambda_2 f_3))^2 - 4\beta_1 \beta_2 f_1 f_2 f_3 f_4 k_1 k_2 (c_{11} c_{22} - c_{12} c_{21}))$$

where

$$\begin{aligned} f_1 &= \mu_1 + k_1 + \alpha + \lambda_2 \\ f_2 &= \mu_2 + k_2 + \alpha \\ f_3 &= \mu_1 + \gamma_1 + \lambda_2 \\ f_4 &= \mu_2 + \gamma_2 \end{aligned}$$

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