A mathematical model of TB control with vaccination in an age-structured susceptible population

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Abstract. A new mathematical model for the transmission dynamics of tuberculosis (TB) with the intervention of vaccination in an age-structured susceptible population is designed and analyzed in this article. The model is constructed as an SEIR-based system of ten-dimensional ordinary differential equation. Each population is then further classified according to its age-class; children (<15 years old) and adult (15-65 years old). In the susceptible population, the classification goes even further by taking vaccination criteria into account. Mathematical analysis of the equilibrium points and its local stability is performed, both analytically and numerically, to help understand the possibility of the situation in the field for long-term behavior. We also show the form of the basic reproduction number as the spectral radius of the next-generation matrix. The basic reproduction number will become the threshold parameter to handle the existence of equilibrium points. Numerical simulations of the model are done for various scenarios to provide a better understanding of the analytical results. We can conclude that the vaccination strategy is successful in suppressing the spread of TB among the human population.

1. Introduction and model construction
Tuberculosis (TB) is a contagious disease caused by a bacillus –commonly Mycobacterium tuberculosis. The disease is transmitted by active TB patients through tiny droplets of liquid that comes out of the patient’s body when the patient speaks, coughs, or sneezes. The tiny droplets of liquid are then scattered in the air and inhaled by other individuals [1].

In some cases, TB infection can progress directly into active TB. However, in a large number of cases, TB infection initially enters a latent phase, in which the bacillus is made ‘asleep’ or inactive by the immune system of the infected individual. The development of TB infection into active TB is highly dependent on the immunity of the infected individual. Latent TB infection may progress to active TB if the infected individual experiences a decreased immunity, for example, due to HIV [1]. Such changes can occur at any time –from several months to several decades after the initial infection [2].

To end TB epidemiology, WHO recommends the use of Bacille Calmette-Guérin (BCG) vaccination as a prevention act against the disease. The BCG vaccine contains an attenuated Mycobacterium bovis [3]. BCG vaccine protection lasts up to 15 years since vaccination [4]. Although the efficacy of this vaccine continues to be controversial, until now, BCG vaccine is
still the only vaccine used to prevent TB disease. Its use is considered sufficient to counteract the chronic form of TB and suppress the actual death toll [5].

According to some researches, BCG vaccination administered at a younger age had a more significant impact than the vaccine given to individuals older than 15 years old [6]. The distinctive characteristics of TB disease in different age groups are not only seen in individual response to BCG vaccine. Children (1-15 years) were noted to have lower levels of morbidity and mortality rate than adults (15-65 years) [7]. Also, adults have a higher probability of transmitting the disease and entering the active TB phase immediately after the initial infection. The study of the interaction dynamics between age, immunity, and its effects on the evolution of pathogens is essential for the development of future vaccination strategies [8].

Many mathematical models have been constructed to investigate the dynamics of TB disease – be it models focusing on the process of relapse and reinfection [9, 10], immigration impacts [11], vaccinations [12, 13], as well as models that discuss the influence of the age class [14]. However, the model constructed by Yu, Mingtao, & Sanling (2017) [14] hadn’t distinguished the latent, infected, and recovered population according to its age groups – hence, the model was unable to explain the reinfection process.

Therefore, in this article, we construct a mathematical model that accommodates the vaccination process and age-group classification in TB transmission. To accommodate the latent phase contained in TB disease, this model adopts the SEIR epidemic model, in which each compartment is further divided by age-group. The susceptible subpopulations are then also divided according to the vaccination criteria. In this model, we assume that the vaccine efficacy in children is 100%; hence children who are currently under the protection of BCG vaccine cannot be infected with TB. We also assume that the vaccine efficacy in adults will decrease and that only adults can transmit TB. The transmission diagram of this model can be seen in Figure 1.

![Transmission diagram of TB vaccination model with age-class.](image-url)
The system of ordinary differential equation governing the model is given by:

\[
\begin{align*}
\frac{dS_{1V}}{dt} &= A - (I_2 \beta_1 + d + m + \varphi) S_{1V}, \\
\frac{dS_{1V}}{dt} &= \varphi S_{1V} - (d + m) S_{1V}, \\
\frac{dS_{2V}}{dt} &= m S_{1V} + \phi S_{2V} - (I_2 \beta_2 + d) S_{2V}, \\
\frac{dS_{2V}}{dt} &= m S_{1V} - (\xi I_2 \beta_2 + d + \phi) S_{2V}, \\
\frac{dE_1}{dt} &= \beta_1 I_2 ((1 - p_1) S_{1V} + R_1) - (d + m + v) E_1, \\
\frac{dE_2}{dt} &= \beta_2 ((1 - p_2) (\xi I_2 S_{2V} + I_2 S_{2V}) + I_2 R_2) + m E_1 - (d + v) E_1, \\
\frac{dI_1}{dt} &= I_2 \beta_1 p_1 S_{1V} + \eta R_1 + v E_1 - (d + m + \mu + \gamma_1) I_1, \\
\frac{dI_2}{dt} &= \beta_2 (\xi I_2 p_2 S_{2V} + I_2 R_2) + m I_1 + \eta R_2 + v E_2 - (d + \mu + \gamma_2) I_2, \\
\frac{dR_1}{dt} &= I_1 \gamma_1 - (I_2 \beta_1 + d + \eta + m) R_1, \\
\frac{dR_2}{dt} &= m R_1 + I_2 \gamma_2 - (I_2 \beta_2 + d + \eta) R_2.
\end{align*}
\]

2. Model analysis

In this section, we analyze the existence of equilibrium points and basic reproduction number from system 1. System 1 has two equilibrium points, i.e., disease-free equilibrium (DFE) and endemic equilibrium (EE). The DFE point is given by:

\[
DFE = (S_{1V}^*, S_{1V}^*, S_{2V}^*, S_{2V}^*, E_1^*, E_2^*, I_1^*, I_2^*, R_1^*, R_2^*),
\]

where \( E_1^* = E_2^* = I_1^* = I_2^* = R_1^* = R_2^* = 0, S_{1V}^* = \frac{A}{d + m + \varphi}, S_{1V}^* = \frac{\varphi A}{(m + d)(d + \varphi)(d + \phi)}, S_{2V}^* = \frac{A m \varphi}{(m + d)(d + m + \varphi)(d + \phi)} \). In the disease-free state, the total population can be obtained by summing up the total healthy subpopulations, i.e., \( N = S_{1V}^* + S_{1V}^* + S_{2V}^* + S_{2V}^* = \frac{A}{d} \), which means that the total population in the disease-free state is neither affected by the age-group classification nor by the vaccination process. However, the proportion of each healthy subpopulations are indeed affected by the said factors.

The ratio of the un-vaccinated individuals to the vaccinated individuals is given by:

\[
\frac{S_{1V} + S_{2V}}{S_{1V} + S_{2V}} = \frac{d^3 + 2d^2m + d^2\phi + dm + 2dm\phi + m^2\phi + m\phi \varphi}{(d + \phi + m)\varphi}.
\]

By dismissing the age-group classification \((m = 0)\), we have

\[
\frac{S_{1V} + S_{2V}}{S_{1V} + S_{2V}} = \frac{d}{\varphi}.
\]

Vaccination is a recommended intervention to prevent the spread of TB. Therefore, the ratio of unvaccinated individuals to the vaccinated individuals is expected to be zero. Based on equation 2, it is seen that the ratio of the susceptible human who do not use vaccination and who use vaccination can tend to zero if the life expectancy of human increases or vaccination process increases.
The second equilibrium point is the one that describes a condition where all of the subpopulations in the system 1 is positive. The said point cannot be shown explicitly in this article. However, in the simplified case of system 1, i.e., when \((m = 0, p_1 = p_2 = p, \gamma_1 = \gamma_2 = \gamma, \beta_1 = \beta_2 = \beta)\), the EE point can be shown explicitly as a function of \(I\) in the following form:

\[ EE = (S_1^* = f_1(I), S_2^* = f_2(I), S_3^* = f_3(I), E^* = f_4(I), R^* = f_5(I), I^*) \]

where

\[
S_1^* = \frac{A}{I \beta + d + \varphi}, \\
S_2^* = \frac{\varphi A}{(\phi + d)(I \beta + d + \varphi)}, \\
S_3^* = \frac{\phi \varphi A}{(I \beta + d)(I \beta + d + \varphi)(\phi + d)}, \\
E^* = \frac{I \beta \epsilon}{(I \beta + d)(I \beta + d + \varphi)(d + v)(\phi + d)(I \beta + d + \eta)}, \\
R^* = \frac{\gamma I}{I \beta + d + \eta},
\]

and \(I^*\) as a solution of the fourth degree characteristic polynomial that has a general form as follows:

\[ I(A_0 + A_1 I + A_2 I^2 + A_3 I^3) = 0, \tag{3} \]

where

\[
A_0 = A\left(d^2 + d \phi + \phi \varphi)(d + v)(d + \eta) \beta - d(d + \varphi)(d + v)(d + \phi)(d^2 + d \eta + d \gamma + d \varphi + \eta \mu), \right. \\
A_1 = A(d + v)(2d^2 + d \eta + 2d \phi + \eta \phi + \phi \varphi) \beta^2 - (d + \phi)(3d^3 + 2d^2 \eta + 3d^2 \gamma + 3d \phi \mu + 3d \phi \nu + 2d \eta \mu \nu + d\eta \beta + d\eta \nu \phi + d\eta \beta + 2d \eta \nu \phi + \eta \mu \nu \phi) \beta, \\
A_2 = A(d + \phi)(d + v)(\beta^2 - (d + \phi)(3d^3 + 2d^2 \eta + 3d^2 \gamma + 3d \phi \mu + 3d \phi \nu + d \eta \mu \nu + d \eta \beta + d \eta \nu \phi + d \eta \beta + 2d \eta \nu \phi + \eta \mu \nu \phi) \beta^2, \\
A_3 = -\beta^3(d + \phi)(d^2 + d \gamma + d \mu + d \mu + d \nu + d \nu + \mu \nu + \eta \mu + \mu \nu \phi) \beta^2.
\]

Please note that this endemic equilibrium point will exist if there is at least one positive root from polynomial in equation 3, which lead us to condition

\[ I_1^* + I_2^* + I_3^* + I_4^* = -\frac{A_2}{A_3} \geq 0. \]

By choosing a parameter set, i.e., \(A = \frac{10000}{65}, d = \frac{1}{65}, \mu = 0.0025, \beta = 3.15 \times 10^{-4}, m = \frac{1}{10}, \nu = 6, \eta = 0.00341, \gamma = 0.25, \beta = \frac{1}{5}, p = 0.1, \phi = 0, \) such that we have \(-\frac{A_2}{A_3} = 110.06 \geq 0,\) the endemic equilibrium is given by \((S_1, S_2, S_3, E, I, R) = (2374.91, 28.95, 30.26, 63.41, 1536.36, 5716.47).\)

Next, we analyze the basic reproduction number \(R_0\) of system 1. Basic reproduction number is defined as the expected number of new cases caused by one initial infection in a
closed population during one infection period [15]. The $R_0$ of system 1 is given by the spectral radius of the spectral radius of the next-generation matrix of system 1. Please see [15] for further detail about how to construct $R_0$ using this approach. The basic reproduction number of system 1 is given by:

$$
R_0 = \frac{mv\beta_1 A (1 - p_1) \omega_2}{(d + v) (d + m + v) (d^2 + dq + 2 dm + d\mu + d\gamma_1 + \eta m + \eta \mu + m^2 + m\mu + m\gamma_1) \omega_1 + \frac{mv\beta_2 A (1 - p_2) (d\varphi \xi + d^2 + dm + d\phi + m\phi + \phi \varphi) \omega_1 + (d^2 + 2 dq + 2 dm + d\mu + d\gamma_1 + \eta m + \eta \mu + m^2 + m\mu + m\gamma_1) \omega_1}{(d + \eta) \beta_2 p_2 A m (d\varphi \xi + d^2 + dm + d\phi + m\phi + \phi \varphi) \omega_1} (4)
$$

where

$$\omega_1 = (d + m + \varphi) (d^2 + dq + dm + d\gamma_2 + \eta \mu),$$

$$\omega_2 = 2d^3 + 4 d^2 \eta + 3 d^2 m + d^2 \mu + d^2 v + d^2 \gamma_1 + 2 d\eta^2 + 4 d\eta m + 2 d\eta \mu + 2 d\eta v + 2 d\eta \gamma_1 + dm^2 + dm\mu + dm\nu + dm\gamma_1 + \eta^2 m + \eta^2 \mu + \eta^2 v + \eta m^2 + \eta m\mu + \eta m\nu + \eta m\gamma_1 + \eta v\gamma_1.$$

In a simpler situation, where no age-class is implemented ($m = 0, p_1 = p_2 = p, \gamma_1 = \gamma_2 = \gamma, \beta_1 = \beta_2 = \beta$), the $R_0$ is simply given by:

$$R_0^* = \frac{(1 - p) (K_1 + K_2) v}{(v + d) (\gamma + d + \mu)} + \frac{p (K_1 + K_2)}{\gamma + d + \mu},$$

where $K_1 = \frac{\beta A}{d + \varphi}, K_2 = \frac{\beta \phi \varphi A}{d(d + \varphi)(\phi + \mu)}$.

To show how the $R_0$ determines the existence of endemic equilibrium point, we choose a set of parameter, i.e., $A = \frac{10000}{65}, d = \frac{1}{65}, \mu = 0.0025, \beta_1 = 2.75 \times 10^{-5}, \beta_2 = 3.15 \times 10^{-5}, m = \frac{1}{15}, v = 6, \eta = 0.00341, \gamma_1 = 0.496, \gamma_2 = 0.25, \phi = \frac{1}{15}, p_1 = 0.025, p_2 = 0.05, \varphi = 10^{-3}, \xi = 0.3,$ such that $R_0 = 1.20312 > 1$. From this set of parameter, the endemic equilibrium point is given by:

$$EE = (1575.858, 19.206, 3305.377, 14.707, 4.230, 20.327, 46.039, 530.024, 228.267, 4162.359).$$

3. Simulation of the autonomous system

The system 1 is simulated using the parameter values in Table 1 to illustrate the theoretical results contained in this article.

| Par     | Definition                  | Value     | Par     | Definition                  | Value     |
|---------|-----------------------------|-----------|---------|-----------------------------|-----------|
| $A$     | Birth rate                  | 10000/65  | $\alpha$| Vaccine efficacy            | 0.7 [17]  |
| $\varphi$| Vaccination rate            | 1         | $\xi$   | Vaccine failure ratio       | 0.3       |
| $m$     | Maturity rate               | 1/15      | $\nu$   | Transition rate             | 6 [14]    |
| $\beta_1$| Children infection rate     | 2.75 \times 10^{-5} [7] | $\gamma_1$| Children recovery rate      | 0.496 [16]|
| $\beta_2$| Adults infection rate       | 3.15 \times 10^{-5} [7] | $\gamma_2$| Adults recovery rate        | 0.25 [18] |
| $p_1$   | Children rapid infection ratio| 0.025 [8] | $\eta$   | Relapse rate                | 0.00341   |
| $p_2$   | Adults rapid infection ratio| 0.05 [16] | $d$      | Natural death rate          | 1/65      |
| $\phi$  | Vaccine effect reduction rate| 1/15 [4]   | $\mu$   | Disease-induced death rate  | 0.0025 [20]|

Table 1: Model parameters.
The first simulation is given in Figure 2 to see how $R_0$ change respect to the change of other parameters in model 1. Sensitivity analysis of the basic reproduction number ($R_0$) in equation 4 is performed on the parameters that affect vaccine performance, i.e., vaccination rate ($\phi$), vaccine effect reduction rate ($\varphi$), and vaccine failure ratio ($\xi$).

![Image](a)\hspace{1cm}(b)\hspace{1cm}(c)

Figure 2: Basic reproduction number ($R_0$) sensitivity analysis curve refers to (a) vaccination rate, (b) vaccine effect reduction rate, and (c) vaccine failure ratio. The y-axis is the $R_0$.

From Figure 2, we can see that $R_0$ has a negative correlation with $\varphi$ and a positive correlation both with $\phi$ and $\xi$. It can be seen that enlarging $\varphi$ will reduce $R_0$. In the other hand, enlarging $\phi$ or $\xi$ will increase $R_0$. This results next will be illustrate in how the change of $\varphi$ and $\phi$ impact the dynamic of model 1.

From the autonomous simulation with the variation of $\varphi$ value in Figure 3(a), we can see that:

- Although there is indeed a vaccination process in the population, the total population in $S_2$ eventually decreases. That is because the vaccinated adults will lose its vaccine effect, 15 years after the vaccination. For the same reason, the total population in $S_2U$ eventually increases.

- The dynamics in the infected subpopulations ($E_1, E_2, I_1, I_2, R_1$ dan $R_2$) apparently more affected by other factors, e.g., transition rate ($v$) and recovery rate ($\gamma$). The variation of $\varphi$ value does not seem to affect the said subpopulations significantly. However, the total individuals in each subpopulation seem slightly greater when the vaccination rate is lower.

Aside from the distinctive vaccination rate used in the simulation, in Figure 3(b), we can see that the total healthy population tends to increase while the total infected population tends to decrease. When $\varphi = 10$, the total population keeps changing until it reaches $DFE = (15, 1860, 6614, 1511, 0, 0, 0, 0, 0)$ and when $\varphi = 0.05$, the total population keeps changing until it reaches $EE = (1093, 666, 4237, 522, 2, 12, 19, 39, 297, 983)$.

In Figure 4(a), we can see that the significant changes only happen on the susceptible adults subpopulations. This is because the process of vaccine effect reduction only happens on the said subpopulations. Observe that the increase of total individual in $S_2$, and the decrease of the total individual in $S_2U$, is slightly slower when the vaccine offers protection for as long as 20 years than when the vaccine protection only lasts for ten years. Also, the shorter vaccine protection period
results in more infected and recovered adults. It can also be calculated that when $\phi = 1/20$, the system 1 tends to approach $DFE = (142, 1733, 6358, 1767, 0, 0, 0, 0, 0, 0)$ as $t \to \infty$, while when $\phi = 1/10$, it tends to approach $EE = (142, 1728, 5669, 989, 1, 5, 119, 5, 1326)$ as $t \to \infty$. 

Figure 3: (a) The dynamics of each compartment in model 1 and (b) the dynamics of total healthy ($S_{1U} + S_{1V} + S_{2U} + S_{2V}$) and infected ($E_1 + E_2 + I_1 + I_2 + R_1 + R_2$) population, with $\varphi = 10$ for $R_0 = 0.99846$ (blue), $\varphi = 0.05$ for $R_0 = 1.12655$ (red), and $t \in [0, 20]$ years.

Figure 4: (a) The dynamics of each compartment in model 1 and (b) the dynamics of total healthy ($S_{1U} + S_{1V} + S_{2U} + S_{2V}$) and infected ($E_1 + E_2 + I_1 + I_2 + R_1 + R_2$) population, with $\varphi = 1/20$ for $R_0 = 0.97713$ (blue), $\varphi = 1/10$ for $R_0 = 1.05281$ (red), and $t \in [0, 20]$ years.
4. Conclusion
In this article, a mathematical model of the spread of TB disease involving the age-classes in susceptible compartments has been developed. The model has two equilibrium points, i.e., the disease-free equilibrium and the endemic equilibrium point. The basic reproduction number ($R_0$) has been constructed using the next-generation matrix approaches. From the analytical study on the system, we know that other than administering vaccination, TB transmission can be reduced by increasing life expectancy. However, the autonomous simulation shows that the best way to reduce TB transmission is by working on its performance, involving its vaccination rate, vaccine protection period, and vaccine efficacy.

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