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Mathematical Modelling of Multidrug-Resistant Tuberculosis with Vaccination

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Abstract Tuberculosis (TB) infectious disease caused by Mycobacterium tuberculosis (Mtb) remains a health threat to the community. In particular, TB infections that are resistant to drugs or commonly known as MDR-TB are still experiencing difficulties, especially in the treatment process. Currently, the development of a vaccine against latent TB is essential in combating the TB epidemic. In this paper, a mathematical model for MDR-TB is developed to estimate the impact of vaccination on future epidemiology. The equilibrium point and stability analysis of the model are also determined and performed, respectively. Furthermore, numerical simulations were carried out using MATLAB software based on the data that had been obtained to predict the development of MDR-TB associated vaccination and consider relevant suggestions in the future.

Keywords Numerical simulation; multidrug-resistant tuberculosis; stability; vaccination.

Mathematics Subject Classification 46N60, 92B99.

1 Introduction

Tuberculosis is amongst the 10 leading disease killers and refers to a single infectious agent caused by Mycobacterium tuberculosis (Mtb). Approximately, 10 million TB cases were reported in 2018 while multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) cases in the world have increased from 2017 report, was about 26088 cases. Most of the increase in global reports of TB cases since 2013 was explained by trends in India and Indonesia. In Indonesia, the TB cases have increased up to 70% from 2013 to 2018 with 116,000 were attributed to TB in 2018. Furthermore, the MDR/RR-TB case burden in Indonesia is estimated at $17,000 - 32,000$ compared to the previous year [1].

The high prevalence of tuberculosis in developing countries suggests that the current TB control strategy is less than optimal. Particularly, there is an increase in drug-resistant cases. Currently, the bacille Calmette-Gurin (BCG) vaccine is the only vaccine available to prevent tuberculosis but cases have shown that its effectiveness in adolescents and adults is unsure. Therefore, the development of new vaccines is an effective and indispensable strategy for TB control [2].

To determine the dynamics of TB disease spread, a mathematical modelling is required to represent the dynamics of transmission as a first step to analyze the spread and control of tuberculosis. Research on TB epidemic models has been widely conducted and is still ongoing. Research conducted by Nainggolan *et al.* [3] showed that vaccination can reduce the number of latent and infectious populations. Furthermore, Nkamba *et al.* [4] developed a dynamic model of TB and the results of their analysis indicated that vaccination was not sufficient to control TB but highlighted that an effective TB contact rate was the main key in the spread of TB. Mengistu and Witbooi [5] developed and analyzed a deterministic mathematical model for tuberculosis dynamics with vaccination and treatment for both classes at high risk of latent TB infection and active TB. The result concluded that an effective strategy for eliminating TB infection would be to reduce the transmission coefficient and increase treatment coverage for latent TB and active TB. The increase in cases, especially drug-resistant TB, suggests that current control strategies are less than optimal. Therefore, research to develop a dynamic model to predict the impact of multi-drug resistant TB is also underway ([6]–[9]). Research related to control programs was also conducted to reduce the incidence of MDR-TB [10].

Ronoh *et al.* [11] constructed a deterministic model assuming permanent incontinence and the results showed that MDR tuberculosis patients who failed treatment would still have MDR-TB in the population. Yu *et al.* [12] also analyzed the epidemic model of MDR-TB and revealed that the main key and spread of TB is to increase TB detection and to carry out active TB treatment appropriately so that it does not open the opportunity to develop into MDR-TB. Zefere and Mekonnen [13] formulated MDR-TB taking into account the vaccination class. The model performed sensitivity analyzes on baseline trial numbers showing that effective contact between susceptible or vaccinated individuals and infected individuals was the most influential parameter in MDR-TB dynamics.

In this study, we consider a strategy to eradicate infectious tuberculosis, namely vaccination for latent TB individuals as in the model developed ([14], [15]). This is in line with the results of a study conducted by that treatment of latent TB infection (LTBI) will reduce the incidence of TB each year [16]. This research is expected to be scientific foundations needed for policymakers to control the spread of MDR-TB. This is in line with WHO which has launched a new strategy in realizing a healthy and TB-free world in 2018 "End TB Strategy". Besides, this research provides information to support the development of medical science, especially in the process of developing a TB vaccine that is currently being worked on [2]. In particular, this study can provide more additional information for local agencies in looking at the effect of vaccination on the dynamics of the spread of MDR-TB in the sub-district of the North Central Timor District, East Nusa Tenggara.

The current paper consists of several parts: The second part presents the dynamics of the MDR-TB model on the effects of vaccination, the third and fourth part are equilibrium and local stability, the fifth part is the numerical simulation and the conclusions are presented in the sixth section.

2 Epidemic Model

In this TB epidemic model, we assumed that drug-resistant infections are either caused by infection or as a result of irregular treatment or even no treatment at all. Furthermore, the human population was divided into five sub-populations namely vaccinated human V, exposed human E, infected human I_i, resistant infected human I_{mdr}, and recovered human R at the time t, respectively. Parameters used in this model were natural births at rate $\Lambda = n\nu$ recruitment of the population ν with the proportions n of which are vaccinated to protect them against tuberculosis infection. The vaccine will increase immunity so it is not easily exposed to Mtb. However, the vaccine given cannot provide complete immunity. Over time, the effectiveness of vaccines in humans decreases at rate $\beta V I_i$ with $\beta = \theta\beta_i$, the infection rate β_i, and vaccine effectiveness of $0 < \theta < 1$. Vaccination is also assumed in latent individuals at a rate ρE. Some latent individuals can develop the disease due to endogenous reactivation at rate ϵE. Some individuals in I_i received treatment at a rate ϑI_i while others experienced drug resistance (failed in treatment) at a rate of φI_i. Also, individuals in I_{mdr} underwent treatment at rate γI_{mdr}. In this compartmental model, there are natural human deaths with rate μ as well as deaths caused by infected TB and MDR-TB at rate $\eta_1 I_i$ and $\eta_2 I_{mdr}$, respectively.

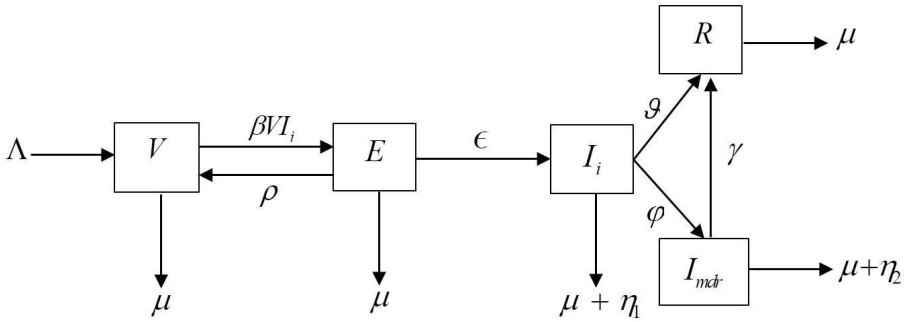

Figure 1: Schematic diagram for epidemic model of TB for vaccination in population.

The model is given by the following system of differential equations (1).

$$\begin{aligned}
\frac{dV}{dt} &= \Lambda + \rho E - (\beta I_i + \mu)V \\
\frac{dE}{dt} &= \beta V I_i - (\rho + \epsilon + \mu)E \\
\frac{dI_i}{dt} &= \epsilon E - (\vartheta + \varphi + \mu + \eta_1)I_i \\
\frac{dI_{mdr}}{dt} &= \varphi I_i - (\mu + \eta_2 + \gamma)I_{mdr} \\
\frac{dR}{dt} &= \vartheta I_i + \gamma I_{mdr} - \mu R
\end{aligned} \tag{1}$$

3 Existence of Equilibrium Points

To reach the equilibrium point, each equation in the model (1) must satisfy

$$\frac{dV}{dt} = \frac{dE}{dt} = \frac{dI_i}{dt} = \frac{dI_{mdr}}{dt} = \frac{dR}{dt} = 0,$$

then model (1) becomes

$$\begin{aligned} \Lambda + \rho E - (\beta I_i + \mu)V &= 0 \\ \beta V I_i - (\rho + \epsilon + \mu)E &= 0 \\ \epsilon E - (\vartheta + \varphi + \mu + \eta_1)I_i &= 0 \\ \varphi I_i - (\mu + \eta_2 + \gamma)I_{mdr} &= 0 \\ \vartheta I_i + \gamma I_{mdr} - \mu R &= 0 \end{aligned} \tag{2}$$

for simplification, we let $c_0 = \rho + \epsilon + \mu$, $c_1 = \vartheta + \varphi + \mu + \eta_1$, and $c_2 = \mu + \eta_2 + \gamma$.

By performing calculations in model (2), we have two equilibrium points, namely disease-free and disease-endemic. The disease-free equilibrium for Mtb free state, e^0, can be written as follows

$$\left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right)$$

and the endemic equilibrium, e^*, can be written as follows:

$$\left(\frac{c_0 c_1}{\epsilon\beta}, \frac{\epsilon\beta\Lambda - \mu c_0 c_1}{\epsilon\beta(c_0 - \rho)}, \frac{\epsilon\beta\Lambda - \mu c_0 c_1}{\beta c_1(c_0 - \rho)}, \frac{\varphi(\epsilon\beta\Lambda - \mu c_0 c_1)}{\beta c_1 c_2(c_0 - \rho)}, \frac{1}{\mu}\frac{\epsilon\beta\Lambda - \mu c_0 c_1}{\beta c_1(c_0 - \rho)}(\vartheta + \frac{\varphi\gamma}{c_2})\right)$$

exists if only if $\frac{\epsilon\beta\Lambda}{\mu c_0 c_1} > 1$.

This condition is the basic reproduction number of this MDR-TB epidemic model. According to Ma and Li [17], the basic reproductive number, commonly denoted by R_0, is the average number of secondary infections produced by one infected individual in an entirely susceptible population. In other words, basic reproduction in an epidemic model could be written as

$$R_0 = \frac{\epsilon\beta\Lambda}{\mu c_0 c_1} \tag{3}$$

4 Local Stability Analysis

The behavior of the model (1) around the equilibrium point can be determined by linearizing the system using the Taylor series expansion around the equilibrium point. Using of calculations, a linearization of system (1) is obtained around the equilibrium point with the Jacobian matrix which is represented as follows.

$$Df(\bar{x}) = \begin{bmatrix} -\beta I_i \mu & \rho & -\beta V & 0 & 0 \\ \beta I_i \mu & -c_0 & \beta V & 0 & 0 \\ 0 & \epsilon & -c_1 & 0 & 0 \\ 0 & 0 & \varphi & -c_2 & 0 \\ 0 & 0 & \vartheta & \gamma & -\mu \end{bmatrix} \tag{4}$$

By Jacobian matrix (4) at disease-free equilibrium e^0, we have

$$Df(e^0) = \begin{bmatrix} -\mu & \rho & -\frac{\beta\Lambda}{\mu} \\ 0 & -c_0 & \frac{\beta\Lambda}{\mu} \\ 0 & \epsilon & -c_1 \end{bmatrix}$$

Theorem 1 *If $R_0 < 1$, then system (1) is locally asymptotically stable at disease-free equilibrium.*

Proof Based on the Jacobian matrix at e^0 and by means of calculations, the following characteristic equation is obtained

$$(-\lambda-\mu)^2(-\lambda-c_2)(\lambda^2+(c_0+c_1)\lambda+c_0c_1-\frac{\epsilon\beta\Lambda}{\mu})=0.$$

Therefore, the polynomial roots are the eigenvalues of the jacobian matrix obtained $\lambda_{1,2} = -\mu$,$\lambda_3 = -c_2$, and

$$\lambda_{4,5} = \frac{-(c_0+c_1) \pm \sqrt{(c_0+c_1)^2 - 4(c_0c_1 - \frac{\epsilon\beta\Lambda}{\mu})}}{2}.$$

These results indicate that all eigenvalues are negative with the condition $R_0 = \frac{\epsilon\beta\Lambda}{\mu c_0 c_1} < 1$. In other words, the system (1) is locally asymptotically stable at the disease-free equilibrium point.

The Jacobian matrix (4) at endemic equilibrium $e^\star$ is given by

$$Df(e^\star) = \begin{bmatrix} -\frac{\epsilon\beta\Lambda-\mu c_0c_1}{c_1(c_0-\rho)} - \mu & \rho & -\frac{c_0c_1}{\epsilon} \\ \frac{\epsilon\beta\Lambda-\mu c_0c_1}{c_1(c_0-\rho)} & -c_0 & \frac{c_0c_1}{\epsilon} \\ 0 & \epsilon & -c_1 \end{bmatrix}$$

Theorem 2 *If $R_0 > 1$, then system (1) is locally asymptotically stable at endemic equilibrium.*

Proof The equation for the characteristics of the Jacobian matrix is as follows

$$(-\lambda-\mu)(-\lambda-c_2)\left(\lambda^3+(x+\mu+c_0+c_1)\lambda^2+((x+\mu)(c_0+c_1)-\rho x)\lambda+xc_1(c_0-\rho)\right)=0,$$

where $x = \frac{\epsilon\beta\Lambda-\mu c_0c_1}{c_1(c_0-\rho)}$. It is clear that there are two negative eigenvalues, namely $\lambda_a = -\mu$, $\lambda_b = -c_2$. For other equations, the eigenvalues will be investigated using the Routh-Hurwitz Criteria. Note that $\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0$ where $A_1 = x+\mu+c_0+c_1$, $A_2 = (x+\mu)(c_0+c_1)-\rho x$, and $A_3 = xc_1(c_0-\rho$. Explain that $A_1, A_2, A_3 > 0$ with the condition $R_0 > 1$. Through calculations, we get $A_1A_2 - A_3 = (x+\mu)((c_1+\mu)(c_0+c_1)+(c_0+c_1-\rho)) + c_0(\mu(c_0+c_1)+x(c_0-\rho)) > 0$ if $R_0 > 1$. Based on the Routh-Hurwitz Criteria, all eigenvalues have a negative real part. Therefore, system (1) is locally asymptotically stable in endemic equilibrium provided $R_0 > 1$.

5 Numerical Simulation

Model simulation is provided to complete the analytical results obtained in the previous section. The parameter values used in this model simulation use parameter values from several works of literature and assumptions by considering the biological facts. The MDR-TB model simulation was carried out using MATLAB software. The parameter values for the MDR-TB epidemic model are presented in Table 1 below.

Table 1: Value of parameter for the epidemic model

Expressions	Symbols	Value	Source
Proportion for the born value to be vaccined	n	0.012-0.715	[12], [18]
The recruitment of the population	ν	10	[4]
Natural death	μ	0.019896	[11]
Contact rate of vaccined individuals make with infection individuals	β_i	3-5	[3], [13]
Proportion of innefficacy of vaccine individuals	θ	0.2	[4]
The rate of efficacy of vaccine individuals	ρ	0.5	[19]
Reactivation endogenous rate	ϵ	0.21	[11]
Death rate of TB disease	η_1	0.01	[11]
Death rate of MDR-TB	η_2	0.0575	[11]
Progression rate from the TB to MDR-TB	φ	0.470104	[11]
Successfully treatment rate in Active TB	ϑ	0.0575	[11]
Successfully treatment rate in MDR-TB	γ	0.1106456	[11]

For each simulation, we began with 100 vaccinated humans, 20 exposed humans, 1 active TB humans, 1 resistant humans and 1 recovered humans. We run simulations, in an interval of twenty years, to assess the effect of vaccine, contact, and treatment in basic reproduction number. Further, for proportion for natural birth was selected 0.012 [12] dan 0.715 [18], the recruitment of the population was selected 10 [4], inneffication and efficacy of vaccine were selected 0.2 [4] dan 0.5 [19], respectively. Also, transmission rate of vaccine individuals was selected 10.

Figure 2-3 presents the simulation results for initial conditions based on existing data with $n = 0.012$, so $R_0 < 1$. In Figure 2, we can see that there is always vaccinated in the population while the infected TB disappears. Thus the trajectories converge to the free state equilibrium point. This means that disease disappears in the host population as shown in Theorem 1. The second graph in Figure 3, is given a trajectory graph when $n = 0.715$ so that $R_0 > 1$. From this figure, we can see that TB disease, the infected TB (latent, active TB, and MDR-TB) will remain in a stable population. This means that the endemic equilibrium point is locally stable according to Theorem 2.

The following is given a numerical simulation to see the interaction between several parameters and the basic reproduction number of the model. The parameters in question are the parameters contained in the reproduction number itself, i.e. Λ, β, ρ, ϑ, and γ.

Figure 4 shows that disease will persist in the population provided the recruitment rate of susceptible individuals is vaccinated and the infection rate increases.

Figure 5 indicates that the greater the effect of vaccination in individuals with exposed TB and the rate of vaccination for recruitment, the epidemic will not occur in the population. However, the opposite occurs epidemics when the vaccination rate for latent TB is low.

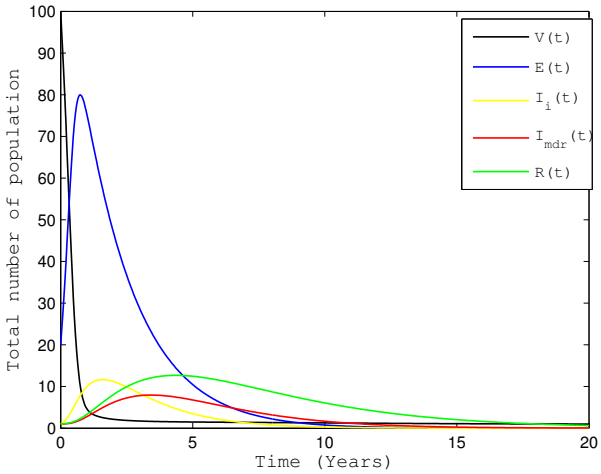

Figure 2: The trajectories of epidemic model (1) showing the locally stability of the disease free equilibrium ($R_0 < 1$).

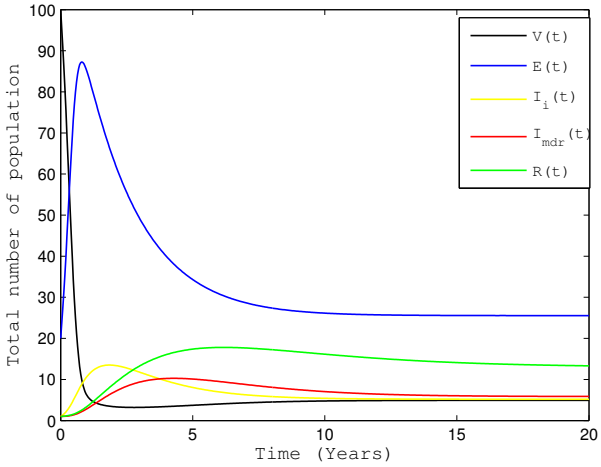

Figure 3: The trajectories of epidemic model (1) showing the locally stability of the endemic equilibrium ($R_0 > 1$).

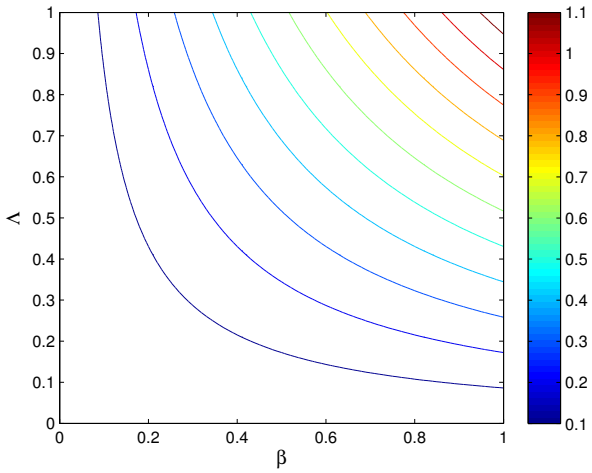

Figure 4: The interaction of Λ and β with R_0.

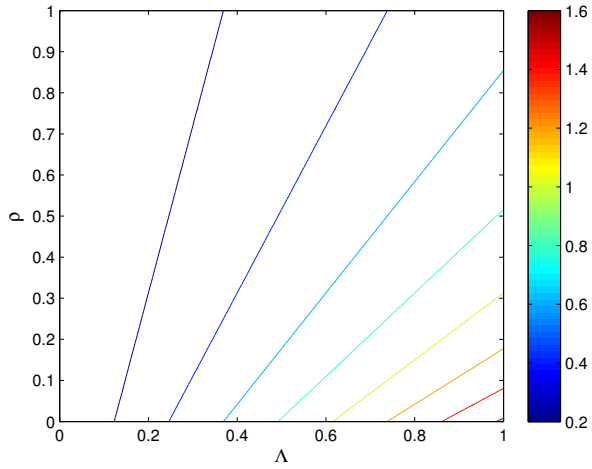

Figure 5: The interaction of Λ and ρ with R_0.

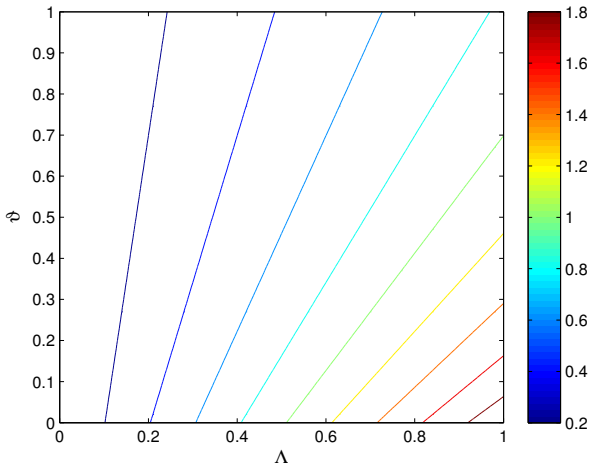

Figure 6: The interaction of Λ and ϑ with R_0.

Figure 6 reveals that the disease can be overcome regardless of the large number of susceptible individuals vaccinated if the successful treatment rate in individuals with TB disease increases.

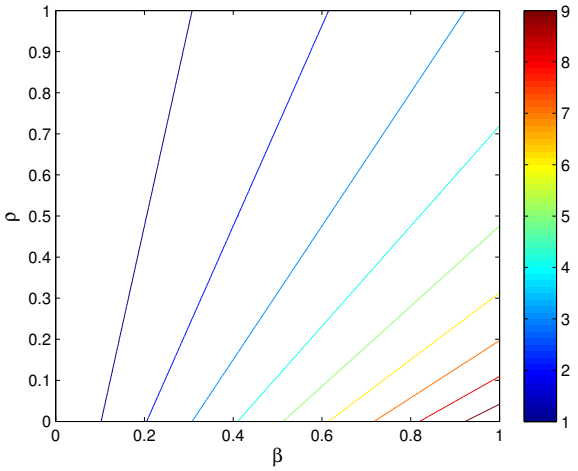

Figure 7: The interaction of β and ρ with R_0.

Figure 7 presents that for an increased transmission rate, the disease remains in the population even though the vaccine administration in latent TB individuals is increased.

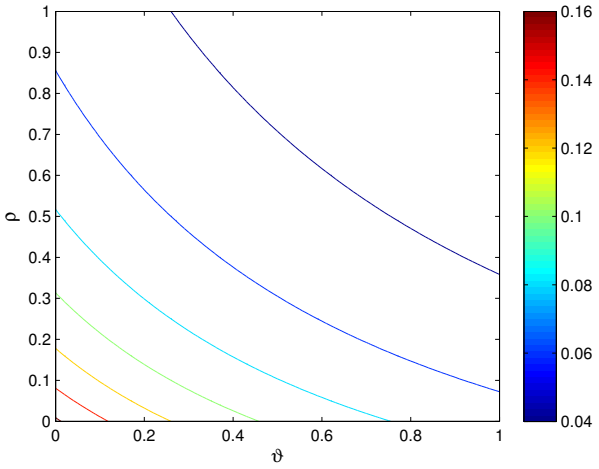

Figure 8: The interaction of ρ and ϑ with R_0.

Figure 8 indicates that in the population there will be no epidemic if the rate of vaccine administration in latent TB individuals and the rate of treatment in active TB individuals is carried out optimally.

Figure 9 shows that for an increased infection rate of susceptible individuals, the disease will remain in the population even though the level of treatment in TB disease individuals is optimized.

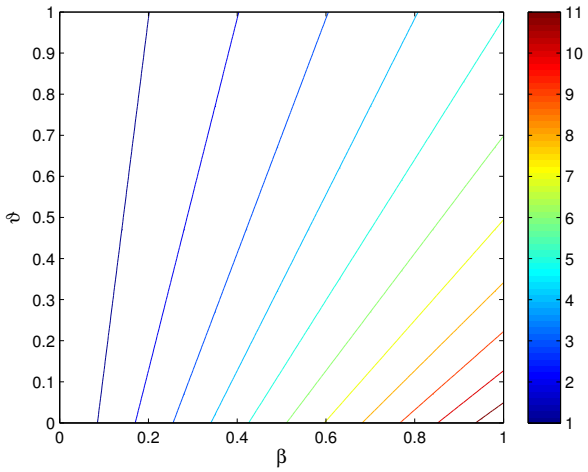

Figure 9: The interaction of β and ϑ with R_0.

6 Conclusion

Based on the analysis, we found the basic reproduction number is less than one, the disease will disappear from the population, otherwise if it is more than one then an epidemic will occur. The numerical simulation results indicate that the contact rate, vaccination rate both in vaccinated susceptible and latent TB, and successful treatment in TB disease play an important role in the dynamics of TB transmission. An increase in the contact rate of vaccinated individuals who are infected will have an impact on the occurrence of an epidemic even if the administration of vaccines in latent individuals only or treatment in active TB individuals alone will be enlarged. Furthermore, the simulation also obtained four alternatives to eradicate TB disease in the population. It appears that vaccination for latent TB and treatment for TB disease simultaneously is the right combination to control TB disease to prevent epidemics (Figure 8). This is in line with the results of research by Mengistu and Witbooi [5]. In addition, vaccination in latent individuals will be able to limit progression to active TB and with prompt and appropriate treatment for active TB (complete cure) will cut that individual into MDR-TB individuals. Therefore, this study is in accordance with current research on vaccine development in latent TB [2].

For future work, it is necessary to carry out sensitivity analysis on the basic reproduction model in particular and the individual with TB to see the most influential parameters in the spread of MDR-TB. Also, the formation of the next model, to include vulnerable individuals (who are not vaccinated) by considering the fact that not all new borns are vaccinated with BCG (parents' awareness of vaccinating their children, especially in areas where the importance of health is still low). And importantly, the model with vaccination must be distinguishable by age and the correct dose as expressed by Harris *et al.* [20].

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