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The Effectiveness of BCG Vaccination Using SEIR Mathematical Model of Tuberculosis Transmission

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Abstract: Tuberculosis (TB) is an airborne contagious disease that poses a threat to the human population around the world. In 2022, an estimated 10.6 million people fell ill with TB worldwide, making it the common cause of death globally. Although the implementation of the BCG vaccination program has started since a decade, the vaccine itself offers limited protection. As immunity wanes over time, re-infection will occur even in vaccinated individuals. This paper discussed the effectiveness of BCG vaccination to control the spread of the disease. The SEIR mathematical model of TB transmission is constructed by considering the re-infection of vaccinated individuals. A brief analysis on the existence and local stability of the equilibria is conducted along with the basic reproduction number. The results showed that the value of R_0 is 1.46 in the absence of vaccination, while $R_0 = 1.06$ when the vaccination rate is at $v = 0.55$. However, as $v \geq 0.63$, the value of R_0 is less than 1, indicating that the disease dies out. The numerical simulation proved the effectiveness of higher vaccination rates in order to eradicate the TB disease from the population. The study's findings can contribute to the advancement of public health policy to control the spread of the disease.

Keywords: BCG Vaccination, Stability Analysis, SEIR Model, Tuberculosis

1 Introduction

Tuberculosis (TB) is a curable disease but can be fatal without proper treatment. TB is a dangerous and infectious disease caused by the bacterium Mycobacterium Tuberculosis [1]. It can attack a lot of people regardless of age and gender. TB usually affects the lungs, but it can affect other parts of the body such as the brain, lymph nodes, bones, kidneys, and intestines [2]. Coughing, chest pain, shortness of breath, loss of appetite, weight loss, fever, cold, and fatigue are the common symptoms of TB disease. TB spreads through the air when people with lung TB cough, sneeze, or spit.

In Malaysia, BCG vaccination is given at birth to prevent TB disease. Albert Calmette and Camille Guerin were the first developers of the BCG vaccine, and it was first used in a newborn infant whose mother had TB in 1921 [3]. This vaccine is considered the world's most widely used vaccine in order to prevent tuberculosis ever since 1921 [3]. According to research, the BCG vaccine has an efficacy of roughly 75% in preventing some severe forms of TB in children, such as meningitis [4]. However, those who have been vaccinated with BCG still have the possibility of developing latent or active TB due to weaker immune systems.

Studies on tuberculosis using various mathematical models have existed for some time. Bahari et al. [5], Nasution et al. [6], and Widyaningsih et al. [7] used the SIR model to investigate the spread of tuberculosis in Kudus Regency and Indonesia, respectively. In addition, Nasution et al. [6] conducted

a study regarding the effect of BCG vaccination, while Widyaningsih et al. [7] examine the effect of vaccination by considering re-infection of the disease. Both findings revealed that vaccination will slow down the number of infected subpopulations, and the growth will keep declining when more people undergo vaccination. Ramli et al. [8] performed the Runge-Kutta method on the SEIR model to investigate the spread of tuberculosis in the presence of vaccination and treatment elements. Ramli et al. [8] expanded the SEIR model by dividing the susceptible sub-population and infected sub-population into two groups and performed Runge-Kutta to simulate the model. Ifati et al. [9] developed the Susceptible-Vaccinated-Exposed-Infected-Recovered (SVEIR) model by considering the relapse effect into account.

Many researchers have done their studies on TB transmission using the SEIR model. However, there was a lack of discussion on the effectiveness of the BCG vaccine in the presence of re-infection in previous studies. Therefore, this paper aimed to analyse the spread of TB transmission using the SEIR model. We want to demonstrate the spread of disease in the absence and presence of vaccination and to analyse the influence of vaccination rates on the susceptible, infected, and recovered populations. The study's findings will hopefully give a thorough understanding of TB to government agencies in order to control the spread of the disease. The following is the outline of this paper: Section 2 presents the formulation of the SEIR model and determination of both disease-free and endemic equilibrium points. Section 3 discusses the stability analysis result and the dynamical system of TB transmission when the vaccination rate parameter is varied. Section 4 highlights the conclusion and recommendations.

2 Materials and Methodology

In this section, we highlight the mathematical modelling formulation of tuberculosis in the presence of vaccination.

A SEIR Model Formulation

The mathematical model used is the SEIRS model adapted from Erinle-Ibrahim et al. [10]. In the paper, rate of re-infection is considered, but only treatment elements are being administered. By considering the situation where vaccinated individuals get re-infected with TB, we extend the paper by [10] by adding parameter v to the SEIR model in both susceptible and recovered compartments.

Figure 1 depicts the SEIR model compartment of susceptible, exposed, infected, and recovered populations. It is assumed that not all babies are given BCG injections. The first infected individual does not get infected immediately, and there is a possibility of re-infection.

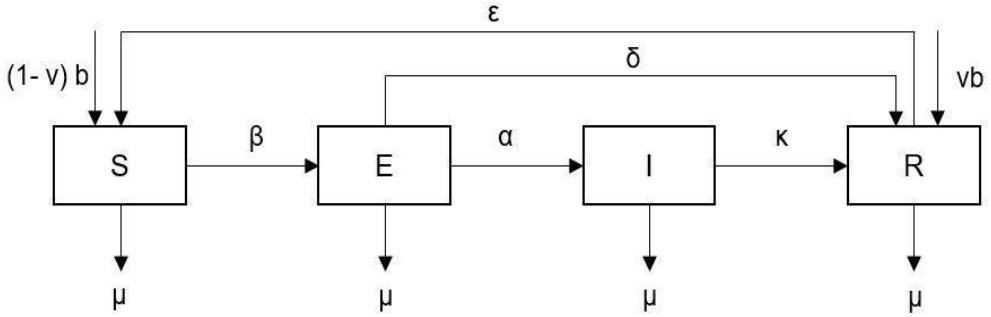


Figure 1: Compartment diagram of the spread of Tuberculosis model in the presence of vaccination.

All parameters are positive. β represents the infectious rate at which the susceptible become infected. The disease transmission by interactions between susceptible and infected populations is expressed as βSI . The rate of re-infection is given by ε and the disease progression rate from latent TB to active TB is given by α . κ and δ indicate the treatment rates of actively infected TB and

individuals with latent TB, respectively. The vaccination rate, v simply denotes the proportion of the population who received at least one dose of BCG vaccination. Lastly, the natural death rate is denoted by μ while the birth rate is defined by b .Considering these assumptions, the ordinary differential equations are expressed as follows:

$$\begin{aligned}
\frac{dS}{dt} &= (1-v)b-(\beta I+\mu)S+\varepsilon R \\
\frac{dE}{dt} &= \beta SI-(\delta+\mu+\alpha)E \\
\frac{dI}{dt} &= \alpha E-(\kappa+\mu)I \\
\frac{dR}{dt} &= vb+\kappa I+\delta E-(\varepsilon+\mu)R \\
N(t) &= S(t)+E(t)+I(t)+R(t)
\end{aligned} \tag{1}$$

where the initial conditions are as follows: $S(0)=S_0>0, E(0)=E_0>0, I(0)=I_0>0, R(0)=R_0>0$

B Basic Reproduction Number and Stability of Equilibria

The basic reproduction number, R_0 is derived by using the next generation matrix and represented by:

$$R_0=\frac{\beta b\alpha(\varepsilon+\mu-\mu v)}{\mu(\delta+\mu+\alpha)(\mu+\kappa)(\mu+\varepsilon)}$$

The value of R_0 depicts an average number of infected individuals that transfer to n number of susceptible individuals. If the value of $R_0>1$, the disease spreads rapidly and become endemic. Meanwhile, for $R_0<1$, the disease dies out. As for $R_0=1$, the disease stays in the population and remains constant from one infected individual to another susceptible individual.

It is important to analyse the equilibria of the model (1) to see how the model will behave as time approaches infinity. Equilibria are obtained by setting the right side of each of the four differential equations (1) to zero. Assuming there is no TB disease, we obtained the disease-free equilibrium point as:

$$\Phi_0=(s_0,e_0,i_0,r_0)=\left(\frac{(\varepsilon+\mu-\mu v)b}{\mu(\varepsilon+\mu)},0,0,\frac{vb}{\varepsilon+\mu}\right)$$

Suppose the TB disease was present in the population and letting the right side of equation (1) to be zero, we obtained the endemic equilibrium point as:

$$\Phi_e=(s_e,e_e,i_e,r_e)$$

with

$$s_e=\frac{\mu^2(\mu+\alpha+\delta)(\mu+\kappa)(\varepsilon+\mu)}{b^2\beta\alpha(\varepsilon+\mu+\mu v)}$$

$$e_e=\frac{(\mu+\kappa)\left[(\varepsilon+\mu)(\mu\delta+\mu^2+\mu\alpha)-(1-v)b\beta\alpha\right]-bv\beta\alpha\varepsilon}{\alpha\left[\beta\varepsilon\left[\alpha\kappa+\delta(\kappa+\mu)\right]-\alpha(\varepsilon+\mu)(\beta\delta+\beta\mu+\beta\alpha)\right]}$$

$$i_e=\frac{(\varepsilon+\mu)\left[(\varepsilon+\mu)(\mu\delta+\mu^2+\mu\alpha)-(1-v)b\beta\alpha\right]-bv\beta\alpha\varepsilon}{\beta\varepsilon\left[\alpha\kappa+\delta(\kappa+\mu)\right]-\alpha(\varepsilon+\mu)(\beta\delta+\beta\mu+\beta\alpha)}$$

$$r_e=\left(\beta\cdot\frac{(\varepsilon+\mu)\left[(\varepsilon+\mu)(\mu\delta+\mu^2+\mu\alpha)-(1-v)b\beta\alpha\right]-bv\beta\alpha\varepsilon}{\beta\varepsilon\left[\alpha\kappa+\delta(\kappa+\mu)\right]-\alpha(\varepsilon+\mu)(\beta\delta+\beta\mu+\beta\alpha)}+\mu\right)\left(\frac{\mu(\delta+\mu+\alpha)(\kappa+\mu)(\varepsilon+\mu)}{\varepsilon\beta\alpha(\varepsilon+\mu+\mu v)}-\frac{(1-v)b}{\varepsilon}\right)$$

C Local stability of equilibria

Theorem 1 and Theorem 2 from [10] helps to determine the epidemiological state by using the basic reproduction number.

Theorem 1

1. If $R_0 < 1$, there exists free disease equilibrium point only
2. If $R_0 \geq 1$, there exists free disease equilibrium point and endemic equilibrium point.

Theorem 2

1. If $R_0 < 1$, free disease equilibrium point is asymptotically stable. As $t \to \infty$, the disease will be eradicated from the population.
2. If $R_0 \geq 1$, free disease equilibrium point is unstable
3. If $R_0 \geq 1$, endemic equilibrium point is asymptotically stable. The disease remains in the population as $t \to \infty$.

The calculation of basic reproduction number will determine under what condition the disease will reach an endemic or steady state. The value $R_0 < 1$ indicates that disease-free equilibrium is stable (LAS) and uninfected steady state is stable, thus the disease will die out from the population. The value $R_0 \geq 1$ indicates that disease-free equilibrium is not stable and endemic steady state is stable, resulting in the disease to spread in the population. The stability of these two equilibrium points is investigated using Jacobian matrix:

$$J_{seir} = \begin{bmatrix} -\beta i - \mu & 0 & -\beta s & \varepsilon \\ \beta i & -(\delta + \mu + \alpha) & \beta s & 0 \\ 0 & \alpha & -(\mu + \kappa) & 0 \\ 0 & \delta & \kappa & -(\mu + \varepsilon) \end{bmatrix} \tag{2}$$

The stability analysis is computed using Maple software, while MATLAB is used to simulate and analyse the dynamical system of tuberculosis transmission based on equation (1). The estimated values of parameters and initial conditions for SEIR model are given in Table 1 and Table 2, respectively. The initial values of S, E, I and R in Table 2 are taken from [14]. The vaccination rate, v denotes proportion of population who received at least one dose of BCG vaccination and is assumed to be between 0 and 1. The value $v = 0$ simply means that none from the population received BCG vaccination, while $v = 1$ means that all individuals in the population have received at least one dose of BCG vaccination.

Table 1: Parameter values used in SEIR model

Parameter	Description	Value	Source
b	Birth rate	0.3	[11]
μ	Natural death rate	0.25	[11]
β	Infectious rate	6.55	[8]
α	Disease progression rate from latent TB to active TB	0.023	[12]
δ	Treatment rate for individuals with latent TB	0.153	[12]
κ	Treatment rate of actively infected TB	0.04123	[13]
ε	Rate of re-infection	0.25	[11]
v	Vaccination rate	(0-1)	Assumed

Table 2: Initial values in SEIR model

Variable	Value	Sources
S(0)	0.64239	[14]
E(0)	0.35588	[14]
I(0)	0.00097	[14]
R(0)	0.00076	[14]

3 Results and Discussion

A Stability analysis

This section discusses the result of stability analysis and the basic reproduction number of the SEIR model in further details. First, we analyse the dynamic of the model for $v = 0$ or without vaccination to project the peak of the outbreak that may happen in the near future. Maple software was used to calculate the value of R_0 using the data in Table 1 and Table 2. In the absence of vaccination, we got the value of $R_0 = 1.46$ while in the presence of vaccination with $v = 0.55$, the value of $R_0 = 1.06$. It can be observed that vaccination helps to reduce the transmission of TB in the population. Moreover, as the value of $v \geq 0.63$, the value of R_0 was less than 1 that indicates the disease will be eradicated from the population. The result is in agreement with previous studies done by [6,9,11,12]. Therefore, it is possible to conclude that the higher vaccination rates, the disease is less likely to spread and decreases the number of people exposed to the disease.

Next, the stability analysis was conducted for both disease-free and endemic equilibrium points. In order to determine the eigenvalues, the equilibrium points were substituted in the Jacobian matrix (2). The stability analysis results are summarised in Table 3, Table 4 and Table 5.

Table 3: Stability analysis result for SEIR model without vaccination $(v = 0)$

Equilibrium point: $\Phi = (s, e, i, r)$	**Eigenvalues**	**Stability result**
$\Phi_0 = (1.2, 0, 0, 0)$	$\lambda_1 = -0.5000$ $\lambda_2 = -0.2500$ $\lambda_3 = -0.7891$ $\lambda_4 = 0.0719$	Unstable
$\Phi_e = (0.0846, 0.276, 0.0214, 0.0846)$	$\lambda_1 = -0.2500$ $\lambda_2 = -0.0703$ $\lambda_3 = -0.5411$ $\lambda_4 = -0.7459$	Stable

Table 4: Stability analysis result for SEIR model with vaccination $(v = 0.55)$

Equilibrium point: $\Phi = (s, e, i, r)$	**Eigenvalues**	**Stability result**
$\Omega_0 = (0.87, 0, 0, 0.33)$	$\lambda_1 = -0.5000$ $\lambda_2 = -0.2500$ $\lambda_3 = -0.7269$ $\lambda_4 = 0.0096$	Unstable
$\Omega_e = (0.8235, 0.0334, 0.0026, 0.3404)$	$\lambda_1 = -0.0096$ $\lambda_2 = -0.2500$ $\lambda_3 = -0.5050$ $\lambda_4 = -0.7199$	Stable

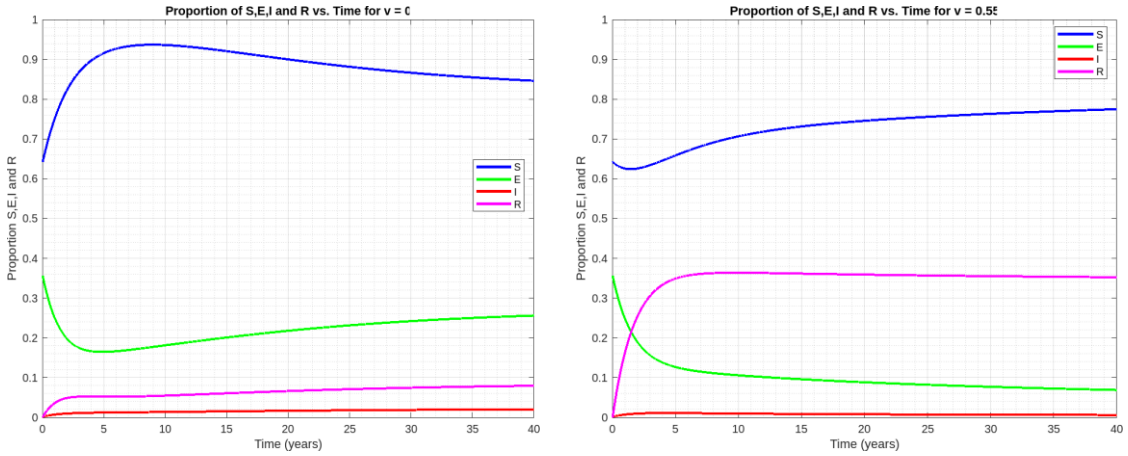
Table 5: Stability analysis result for SEIR model with vaccination $(v = 0.63)$

Equilibrium point: $\Phi = (s, e, i, r)$	**Eigenvalues**	**Stability result**
$K_0 = (0.822, 0, 0, 0.378)$	$\lambda_1 = -0.5000$ $\lambda_2 = -0.2500$ $\lambda_3 = -0.7169$ $\lambda_4 = -0.0003$	**Stable**

Based on Table 3, Table 4 and Table 5, the SEIR model represents two equilibrium points with corresponding eigenvalues. The eigenvalues for disease-free equilibrium, Φ_0 and Ω_0 have at least one positive sign, which leads to unstable pattern. On the other hand, all eigenvalues for endemic equilibrium points, Φ_e and Ω_e were negative, resulting in a stable pattern. Based on Theorem 2, we managed to prove the stability of disease-free and endemic equilibrium points as unstable and stable, respectively, as the value of $R_0 \geq 1$. However, as can be seen in Table 5, the eigenvalues were all negative for disease-free equilibrium point. This concludes that K_0 was only stable on disease-free state. Since R_0 for $v \geq 0.63$ was less than 1, it satisfies Theorem 1 and Theorem 2 that indicates the existence of disease-free equilibrium point only.

B TB Transmission in the Absence and Presence of Vaccination

Figure 2 shows the dynamics of compartment populations over time.



(a) (b)

Figure 2: The SEIR model simulation in the (a) absence and (b) presence of vaccination.

In Figure 2(a), we observed that the susceptible population increased drastically and reached the peak in 8 years before decreasing gradually and reaching 0.85 by the end of stimulated time. In contrast, the susceptible population in Figure 2(b) decreases slightly from 0.64239 to 0.625501 and remains increasing for the rest of the years. This situation arises due to incorporating vaccination among newborn infants and the effectiveness of vaccination given during the re-infection phase.

Meanwhile, the exposed population in Figure 2(a) decreases in the first 4 years to 0.17 before slightly increasing till the rest of the years. This situation contradicts the exposed population in Figure 2(b), where the curve shows a declining pattern throughout the time.

Figure 2(a) shows that the infected population increased greatly from 0.00097 to 0.0117683 in the first 5 years and steadily increased for the next 35 years. On the contrary, Figure 2(b) shows that the infected population increased from 0.00097 to 0.0105112 in the first 5 years before decreasing at a slow

pace for the next 35 years. This implies that the vaccination programme for the newborn infants and the treatment given to actively infected TB individuals contribute to the decreasing rate of the infected population.

Lastly, the recovered population in Figure 2(a) can be seen increased at a slow pace from 0.00076 to nearly 0.08 for over 40 years. Conversely, the recovered population in Figure 2(b) increased greatly from 0.00076 to 0.34893 in the first 5 years and remained constant for the remaining years. This is the result of those with latent TB getting treated and those with infectious TB receiving adequate treatment and vaccination.

C Impact of varying vaccination rate, v in Susceptible, Infected and Recovered populations

This section presents the numerical simulation by varying vaccination rates, v to understand the dynamics of system (1). The vaccination rate denotes proportion of individual who have received at least one dose of vaccine.

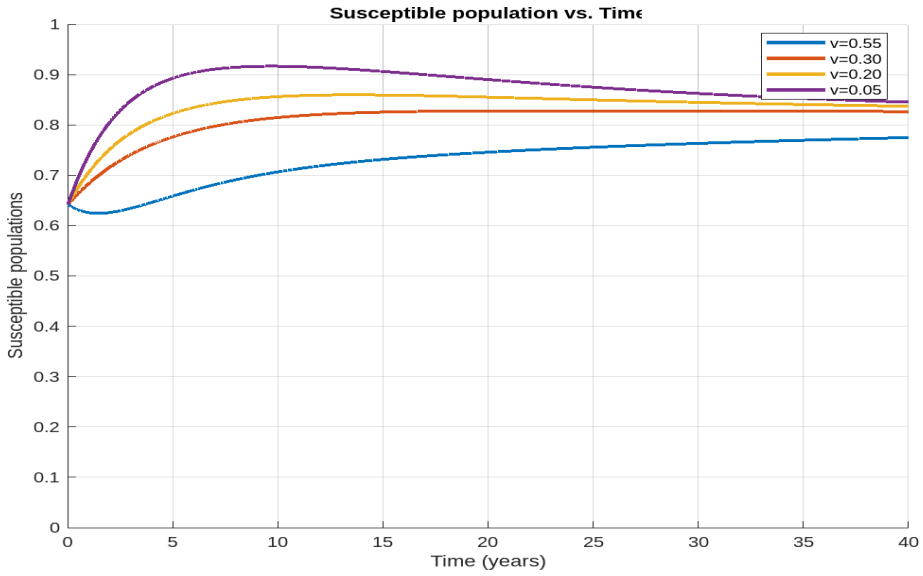


Figure 3: The influence of vaccination rates, v on susceptible population.

Figure 3 shows the impacts of vaccination rates on the susceptible population. The vaccination rates were steadily increased from $v = 0.05$ to $v = 0.20$ to $v = 0.30$ and $v = 0.55$. The effect on the susceptible population was examined and the susceptible population was found to decrease from approximately 0.85 to 0.84 to 0.83 to 0.77. We can see that the number of susceptible populations decreased as vaccination rates increased. This shows that more vaccinated newborns were moved to the recovered population. The slight increasing pattern at the beginning of the graphs was due to the relapsed individuals who moved from recovered population to susceptible population.

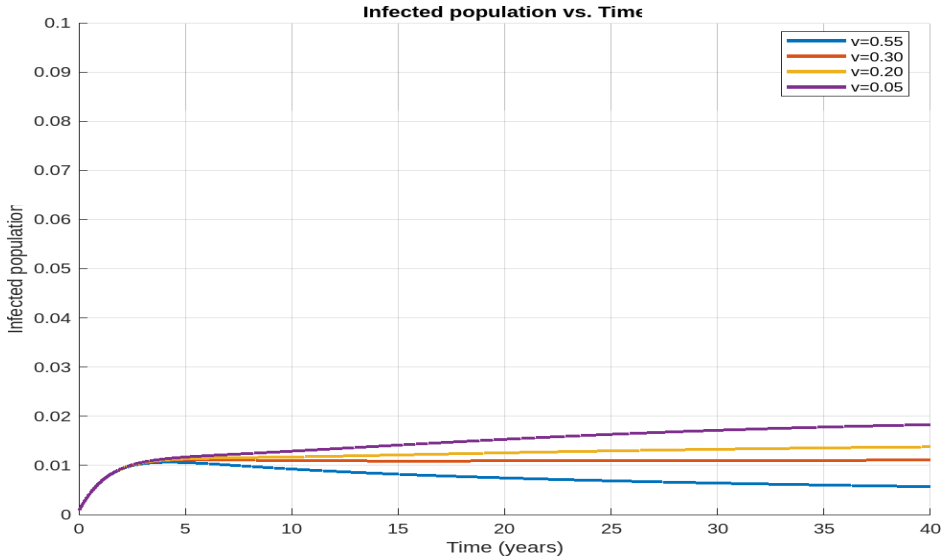


Figure 4: The influence of vaccination rates, v on infected population.

Figure 4 shows the effect of vaccination rates on infected population. The vaccination rates considered were $v = 0.05$, $v = 0.20$, $v = 0.30$ and $v = 0.55$. The number of infected populations were 0.0185, 0.015,0.011 and 0.005, respectively. It can be seen that the number of infected individuals decreased as vaccination rates increased. This implies that vaccination is the most effective strategy to slow down the spread of TB disease along with the treatment received by the latent TB and active TB individuals.

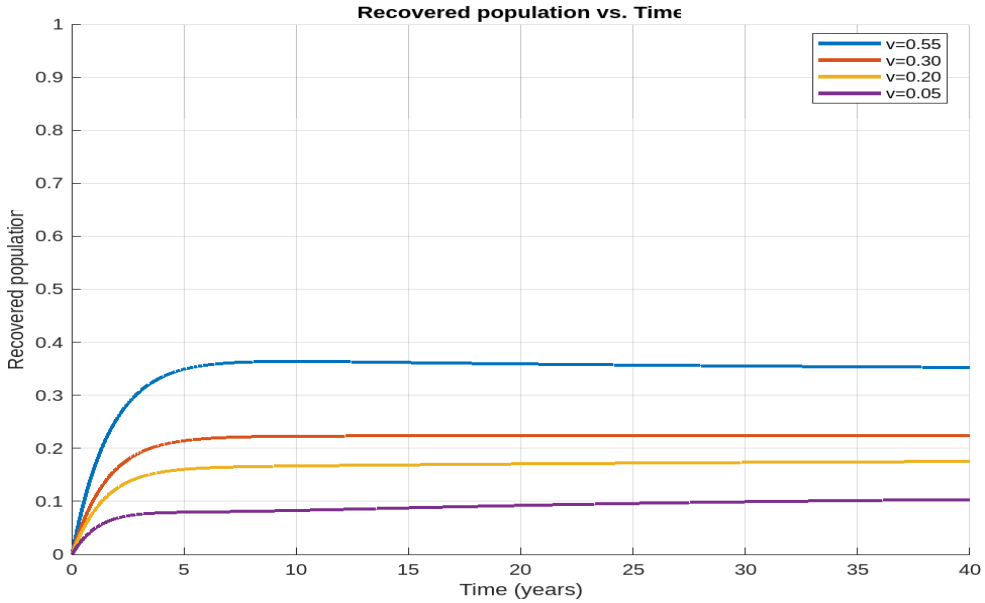


Figure 5: The influence of vaccination rates, v on recovered population.

Figure 5 shows the effect of vaccination rates on recovered population. The vaccination rates were steadily increasing from $v = 0.05$ to $v = 0.20$ to $v = 0.30$ and $v = 0.55$. The implication is that the recovered population increased from 0.1 to 0.18 to 0.22 and further to 0.36, respectively. Based on the simulation, the number of recovered populations rose as vaccination rates increased. This concludes that vaccinated newborn infants, the treated latent, and active TB patients contributed to the increase of recovered population.

4 Conclusion and Recommendations

In this paper, the SEIR model was employed to analyse the TB transmission. The stability analysis for both disease-free and endemic equilibrium points were presented and analysed. For the case of re-infection, the implementation of treatment [10] and vaccine reduced the number of latent and active TB patients. The presence of both elements leads to a decrease of susceptible population and hence, reducing the number of infected populations. In summary, our analysis has revealed that high vaccination rate and ongoing proper treatment would prevent the TB disease from perpetuating in the state. We suggest the enhancement of case detection of TB for high-risk group living in Malaysia or immigrants. We also suggest the mathematical models that are based on age-structured and non-age structured like SQIRD (Susceptible-Quarantine-Infected-Recovered-Death) model for more detailed analysis on TB or other contagious diseases.

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