SENSITIVITY ANALYSES OF VACCINATION, TREATMENT AND DISEASE RELAPSE ON THE TRANSMISSION DYNAMICS OF TUBERCULOSIS

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Abstract

It is estimated that one-third of the world's population are infected with latent Tuberculosis (TB). This research presents an exhaustive deterministic model for the transmission and control dynamics of TB. This model incorporates significant parameters such as vaccination, treatment, disease relapse after recovery, vaccination wane, progression rate from latent to active TB, among others. The model was shown to possess a positive and bounded solution region. Furthermore, by employing the next generation matrix approach and the Lyapunov method respectively, it was obtained that there exists a locally stable disease-free equilibrium point for the model whenever the effective reproduction number, R_e, is less than unity and a unique globally stable endemic equilibrium point whenever $R_e > 1$. Sensitivity analysis of R_e was performed using the forward index sensitivity approach. Numerical simulation was performed on the model by implementing the fourth order Runge Kutta numerical computation method on MATLAB subroutine. Every parameter sensitive to R_e was varied and the effects of these parameters on the spread and eradication of TB was discussed.

INTRODUCTION

1. TB is an infectious disease caused by bacillus MTB. Pulmonary TB attacks the lungs while extra-pulmonary TB affect other body parts like the CNS, brain, spine, or kidneys of people with weak immune systems and children.
2. TB is the 10th leading cause of death worldwide since 2007 and the main cause of death from a single infectious agent, ranking above HIV/AIDS (Schlüter et al., 2021).
3. Treatment of TB via multiple antibiotics do not remove tubercle bacilli, the causative agent. Recovered individuals are classified as low-risk latent individuals who can get re-infected due to relapse

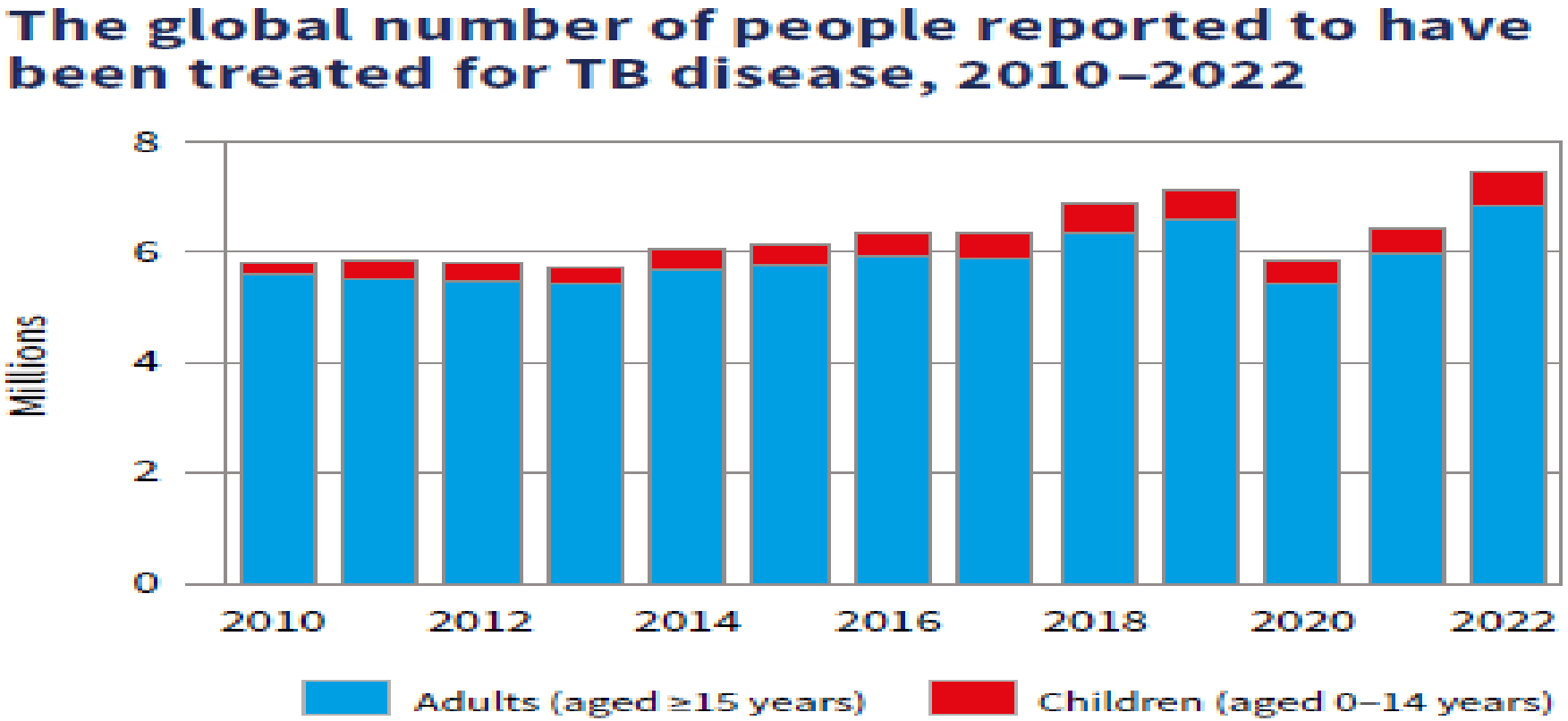


Figure: The Global Number of People treated for TB Disease, 2010–2022 (World Health Organization, 2023)

LITERATURE REVIEW

Abu-Raddad et al. (2009)

Made a prediction analysis of the incidence of TB on the WHO Southeast Asia region (which accounted, in 2006, for 35% of incident TB cases and 32% of the TB-related deaths worldwide) using an age-structured mathematical model with the consideration of efficacious treatment with drug regimens, effective vaccination and improved diagnostics as intervention strategies. It was estimated that in the absence of these strategies, about 101.7 million active TB cases and 17.9 million TB-related deaths were expected between 2015 and 2050. However, with these interventions, it is expected that 55.3 million cases of TB will be prevented and TB incidence will be lowered by 71% by 2050. However, the major reversals of progress in increasing the number of people newly diagnosed and treated with TB each year in 2020 and 2021, caused by COVID-19-related disruptions, resulted in a badly impacted progress towards global TB treatment targets (World Health Organization, 2023).

METHODOLOGY

The compartmental disease modeling approach. Each compartment of the model is made up of mutually exclusive time-dependent sub-population consisting of individuals with the same disease status. The total human population is classified into 5 mutually exclusive compartments.

Table: The Model's State Variables

Variables	Description
$S(t)$	Susceptible Population
$I_L(t)$	Latent TB Infected Population
$I_A(t)$	Active TB Infected Population
$R_T(t)$	TB Recovered Population
$V_T(t)$	TB Vaccinated Population

Parameters	Description
Λ	Recruitment rate into the susceptible population by birth or immigrat
μ	Natural death rate
δ_T	TB induced death rate
β_T	TB effectual contact/transmission rate
λ_T	Force of infection associated with TB
ν_T	TB vaccination rate
ω_T	Rate of loss of immunity for TB vaccinated class
θ_T	Rate of loss of immunity for TB recovered class
γ_T	Recovery rate via treatment for TB
ρ_1	Rate of progression from latent TB to active TB

The Tuberculosis Model

$$\frac{dS}{dt} = \Lambda - \nu_T S - \lambda_2 S + \omega_T V_T + \theta_T R_T - \mu S, \quad (1)$$

$$\frac{dI_L}{dt} = \lambda_2 S - \rho_1 I_L - \mu I_L, \quad (2)$$

$$\frac{dI_A}{dt} = \rho_1 I_L - \gamma_T I_A - (\delta_T + \mu) I_A, \quad (3)$$

$$\frac{dR_T}{dt} = \gamma_T I_A - \theta_T R_T - \mu R_T, \quad (4)$$

$$\frac{dV_T}{dt} = \nu_T S - \omega_T V_T - \mu V_T. \quad (5)$$

Satisfying the initial conditions;
$\{(S, I_L, I_A, R_T, V_T \in R_+^5 : S_0 \geq 0, I_{L0} \geq 0, I_{A0} \geq 0, R_{T0} \geq 0, V_{T0} \geq 0\}$.
The force of infection associated with TB is defined as: $\lambda_2 = \beta_T I_A$.

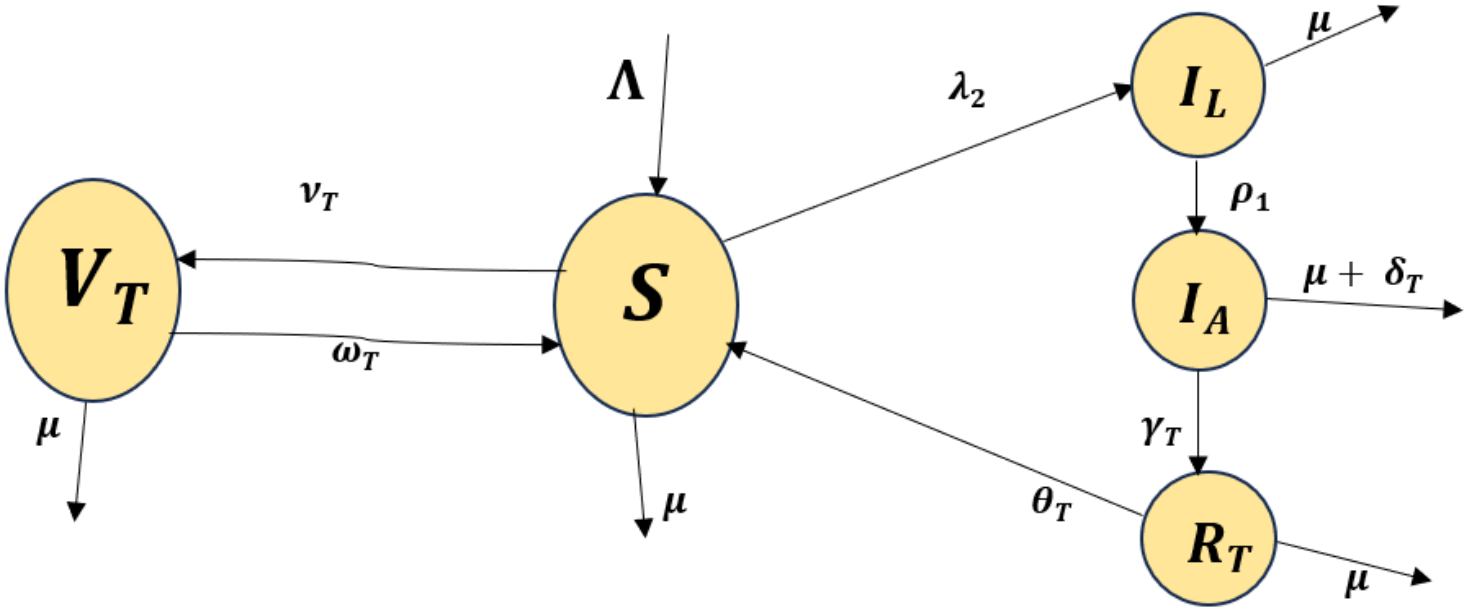


Figure: Flow Diagram for the Tuberculosis Model

Model Assumptions

1. Each population in the model is made up of individuals with homogeneous characteristic (disease status) and are thus mutually exclusive.
2. Only human to human mode of infection transmission is considered.
3. There exists an effective treatment measure for and individuals under treatment are religious with it;
4. The recovered population are not infectious.
5. There is no escape from the treatment centre until full recovery.
6. The latent period for all exposed individuals to TB is the same.
7. TB latent population do not receive treatment as they are asymptomatic and not infectious.
8. vaccination is given only to the susceptible population.
9. The recovered and vaccinated populations can experience a relapse and become re-infected with the disease.

Qualitative Properties of the Model

Boundedness of Solution

To obtain the invariant region of the model, the total human population is obtained as:

$$N(t) = S(t) + I_L(t) + I_A(t) + R_T(t) + V_T(t) \tag{6}$$

$$\begin{aligned} \frac{dN_T(t)}{dt} &= \Lambda - \mu N_T(t) - \delta_T I_A & (7)\\ &\leq \Lambda - \mu N(t) & (8) \end{aligned}$$

$$\ln(\Lambda - \mu N(t)) \geq -(\mu t + C)$$

$$\implies (\Lambda - \mu N(t)) \geq Ae^{-\mu t}$$

where $A = e^{-C}$ is a constant.

At $t = 0$, $N(0) = N_0 \geq 0$

$$\therefore (\Lambda - \mu N_0) \geq A$$

Thus, the feasible set of the solution of the model equations enter and remain in the region:

$$\Omega = \{(S, I_L, I_A, R_T, V_T) \in R_+^5 : N_T(t) \leq \frac{\Lambda}{\mu}\} \tag{9}$$

Positivity of the Solution

Theorem:
$\Omega_1 = \{(S, I_L, I_A, R_T, V_T) \in R_+^5 : (S_0 > 0, I_{L0} > 0, I_{A0} > 0, R_{T0} > 0, V_{T0} > 0)\}$, the solution of $\{(S, I_L, I_A, R_T, V_T)\}$ are non negative for $t \geq 0$.

$$EX : \frac{dS}{dt} = \Lambda - (\nu_C + \nu_T)S - \lambda_C S - \lambda_T S + \omega_C V_C + \omega_T V_T + \theta_C R_C + \theta_T R_T - \mu S$$

$$\geq -(\nu_C + \nu_T + \lambda_C + \lambda_T + \mu)S.$$

Thus,

$$\int \frac{dS}{S} \geq -\int (\nu_C + \nu_T + \lambda_C + \lambda_T + \mu)dt$$

$$\ln S(t) \geq -A(t) + C$$

$$S(t) \geq Be^{-A(t)},$$

where $A(t) = \int(\nu_C + \nu_T + \lambda_C + \lambda_T + \mu)dt$, C is a constant of integration.
At $t = 0, S_0 > 0$
$\therefore S(t = 0) = S_0 \geq B$

$$S(t) \geq S_0 e^{-A(t)} \tag{10}$$

$$\geq 0 \forall t \geq 0.$$

Equilibrium Points and Stability Analyses of the Models

Disease Free Equilibrium (DFE)

A DFE is a state in which a studied population remains in the absence of the disease(s). The DFE point was obtained by analyzing the models' parameters at the point where the population remains in the absence of the disease.

$$E_{T0} = (S^*, 0, 0, 0, V_T^*)$$

satisfying $I_L = I_A = R_T = 0$
The DFE point was obtained as:

$$E_{T0} = (\frac{\Lambda}{\mu}K, 0, 0, 0, \frac{\Lambda}{\mu}K^*) \tag{11}$$

where $K = \frac{(\mu+\omega_T)}{(\mu+\omega_T+\nu_T)}$
$S^* = \frac{\Lambda}{\mu}$ iff $K = 1$ and this $\implies \nu_T = 0$ and $V_T = 0$.

Local Stability Analyses of the DFE

The next-generation matrix approach defines R_0 as the spectral radius, the maximum of the absolute values of the eigenvalues, of the next generation matrix FV^{-1} of the system. If the effective reproduction number $R_e < 1$, then the DFE is locally asymptotically stable and unstable if $R_e > 1$.

$$F == \begin{pmatrix} 0 & \beta_T S^* & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} andV = \begin{pmatrix} (\rho_1 + \mu) & 0 & 0 \\ -\rho_1 & (\gamma_T + \delta_T + \mu) & 0 \\ 0 & -\gamma_T & (\theta_T + \mu) \end{pmatrix}$$

$$G = FV^{-1} = \begin{pmatrix} \frac{\beta_T S^* \rho_1}{(\delta_T+\gamma_T+\mu)(\mu+\rho_1)} & \frac{S\beta_T}{\delta_T+\gamma_T+\mu} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \lambda_T = [0, 0, \frac{\beta_T S^* \rho_1}{(\delta_T+\gamma_T+\mu)(\rho_1+\mu)}]$$

$$R_0^T = \frac{\beta_T S^* \rho_1}{(\delta_T+\gamma_T+\mu)(\rho_1+\mu)} \; R_e = R_0^T X = 0.0342992217681256$$

Global Stability Analyses of the DFE

We employed the generalized method of constructing Lyapunov functions given by Yusuf (2021). Define $V_T(t, S, I_L, I_A, R_T, V_T) = C_1 I_L + C_2 I_A; \quad C_1, C_2 > 0.$

$$\begin{aligned} \frac{dV_T}{dt} &= C_1 I_L' + C_2 I_A' \\ &= C_1(\beta_T I_A S - (\rho_1 + \mu) I_L) + C_2(\rho_1 I_L - (\gamma_T + \delta_T + \mu) I_A) \end{aligned}$$

$$= (C_1 \beta_T S - C_2(\gamma_T + \delta_T + \mu)) I_A + (C_2 \rho_1 - C_1(\rho_1 + \mu)) I_L \tag{12}$$

Substituting $C_1 = \frac{\rho_1}{\rho_1 + \mu}$ and $C_2 = 1$ in (12), we obtained;

$$V_T' = \left(\frac{\rho_1}{(\rho_1 + \mu)} \beta_T S - (\gamma_T + \delta_T + \mu)\right) I_A$$

$$< 0; \quad R_0^T < 1 \implies \frac{\rho_1}{(\rho_1 + \mu)} \beta_T S - (\gamma_T + \delta_T + \mu) < 0$$

$V_T' = 0$ iff $I_A = 0$. Therefore, the function V_T is strictly Lyapunov at the DFE point according to the LaSalle's invariance principle (La Salle, 1976) and hence E_0^T is globally asymptotically stable.

Endemic Equilibrium

The EEP for the model was obtained by solving for all state variables of each model, while equating there derivatives with respect to time to zero.
$E_T^* = (S^*, I_L^*, I_A^*, R_T^*, V_T^*)$, are positive state solutions of the models satisfying:
$\frac{dS}{dt} = \frac{dI_L}{dt} = \frac{dI_A}{dt} = \frac{dR_T}{dt} = \frac{dV_T}{dt} = 0$
$S^* = \frac{(\rho_1+\mu)(\gamma_T+\delta_T+\mu)}{\beta_T\rho_1} > 0,$
$V_T^* = \frac{\nu_T S^*}{(\omega_T+\mu)} = \frac{\nu_T(\rho_1+\mu)(\gamma_T+\delta_T+\mu)}{\beta_T\rho_1(\omega_T+\mu)} > 0,\ I_L^* = \frac{(\gamma_T+\delta_T+\mu)}{\rho_1} I_A^*$
$I_A^* = \frac{\Lambda - \frac{\mu S^*}{K}}{A}$
and $R_T^* = \frac{\gamma_T}{(\theta_T+\mu)} I_A^*$

The expressions for the state equations are positive provided $\Lambda - \frac{\mu S^*}{K} > 0$

$$\implies \frac{\Lambda K}{\mu S^*} = \frac{\frac{\Lambda}{\mu} K \beta_T \rho_1}{(\delta_T + \gamma_T + \mu)(\rho_1 + \mu)} > 1$$

There exists unique endemic equilibria for the models provided $R_0^T > 1$.

Stability of the EEP

We defined an appropriate Lyapunov function for the TB model at E_T^* as:

$$L_T(S, I_L, I_A, R_C.V_C) = \frac{1}{2}[(S-S^*)+(I_L-I_L^*)+(I_A-I_A^*)+(R_T-R_T^*)+(V_T-V_T^*)]^2 \tag{13}$$

$$\frac{dL_t}{dt} = (N_T - N_T^*) \times \frac{dN_T}{dt}.$$

$$= (N_T - (\frac{\Lambda}{\mu R_0^T} + I_A^* B_C)) \times (\Lambda - \mu N_T - \delta_T I_A)$$

$$\leq (N_T - \frac{\Lambda}{\mu})(\Lambda - \mu N_T)$$

$$\leq -\frac{(\Lambda - \mu N_T)^2}{\mu} \leq 0 \tag{14}$$

Since $I_A > 0$ and $R_0^T > 1$ at E_T^*.
Therefore, for $R_0^T > 1$, the endemic equilibrium point E_T^* exists and the function L_T is strictly Lyapunov function. This implies that E_T^* is globally asymptotically stable.

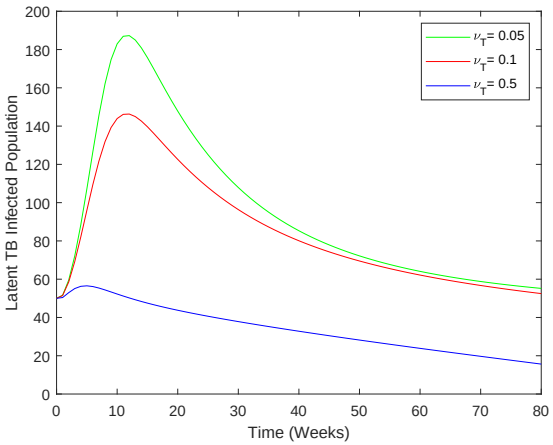
Sensitivity Analyses

This analysis helps to determine the exact impact of each parameter contained in R_e. The normalized forward sensitivity index of R_e with respect to a parameter p: $\Gamma_p^{R_e} = \frac{\partial R_e}{R_e} \div \frac{\partial p}{p}$

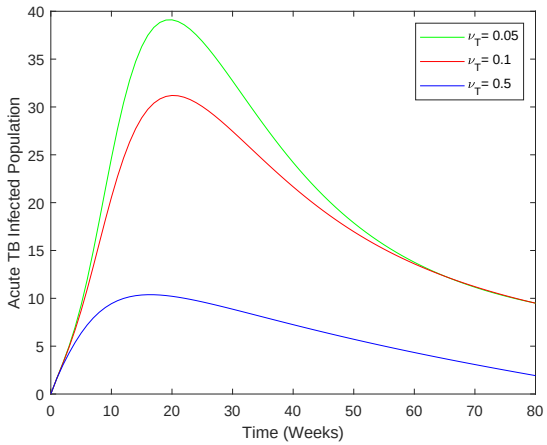
Table: Sensitivity Indices for the Basic Reproduction Numbers

Parameters	**Signs**	**Values**
Λ	+	1
β_T	+	1
ρ_1	+	0.0038064
ω_T	+	0.8297130
ν_T	-	0.9882296
γ_T	-	0.7628824
δ_T	-	0.2365526
μ	-	0.8458547

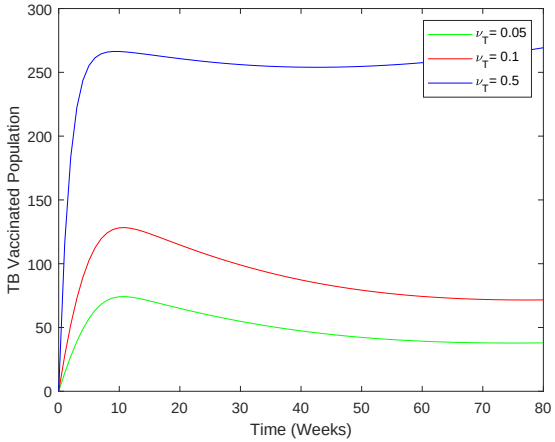
Numerical Simulation of the Model



(a) Latent profile

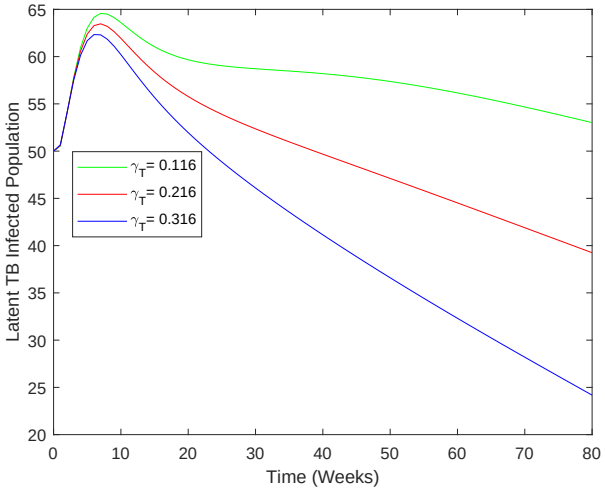


(b) Infected Profile

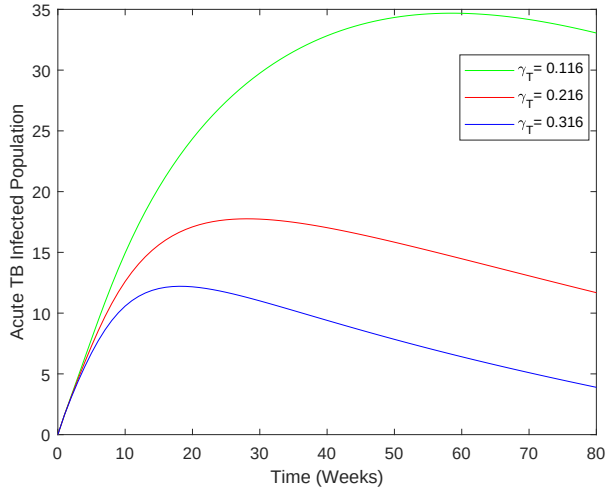


(c) Vaccinated Profile

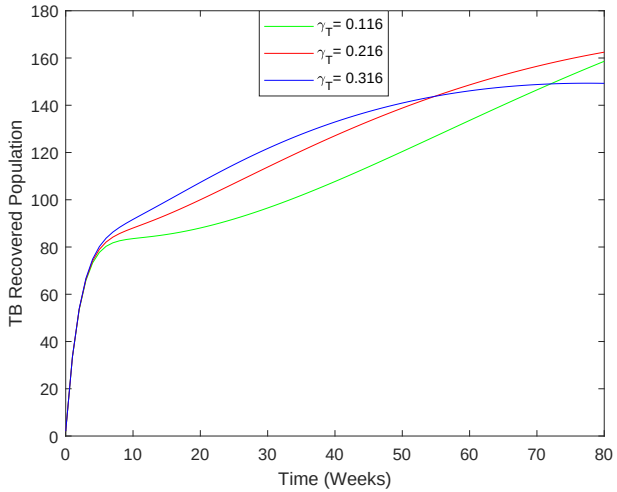
Figure: Effects of Vaccination



(a) Latent profile

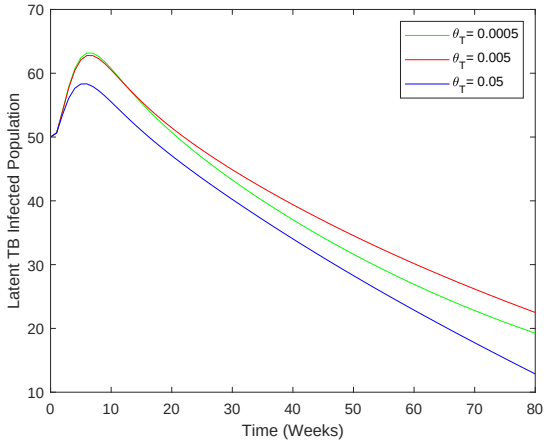


(b) Infected Profile

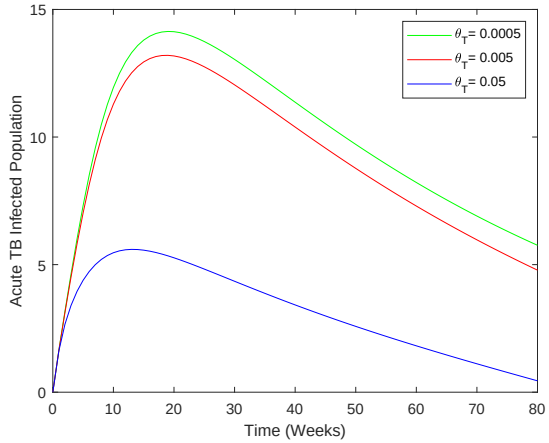


(c) Recovered Profile

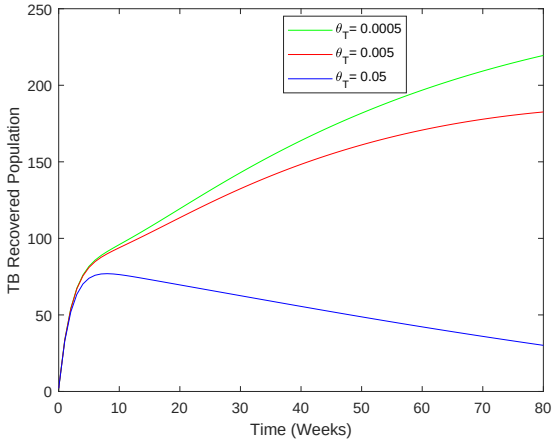
Figure: Effects of Treatment



(a) Latent profile

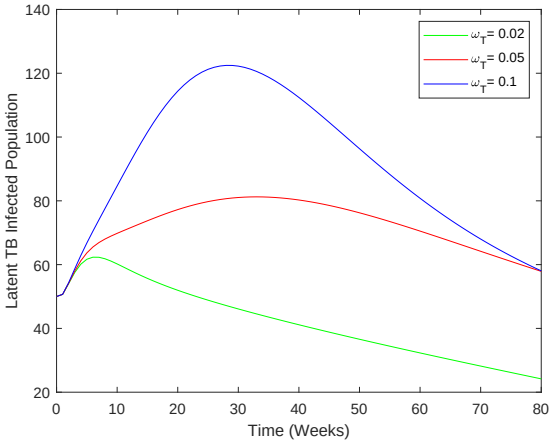


(b) Infected Profile

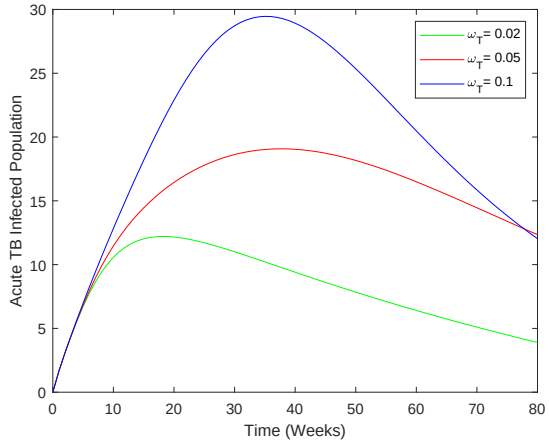


(c) Recovered Profile

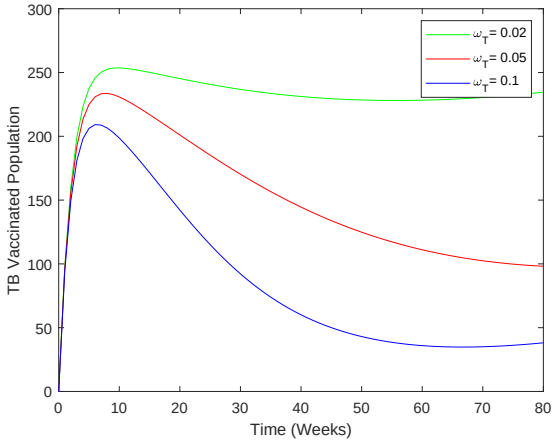
Figure: Effects of Disease Relapse



(a) Latent profile



(b) Infected Profile



(c) Vaccinated Profile

Figure: Effects of Loss of Immunity after Vaccination

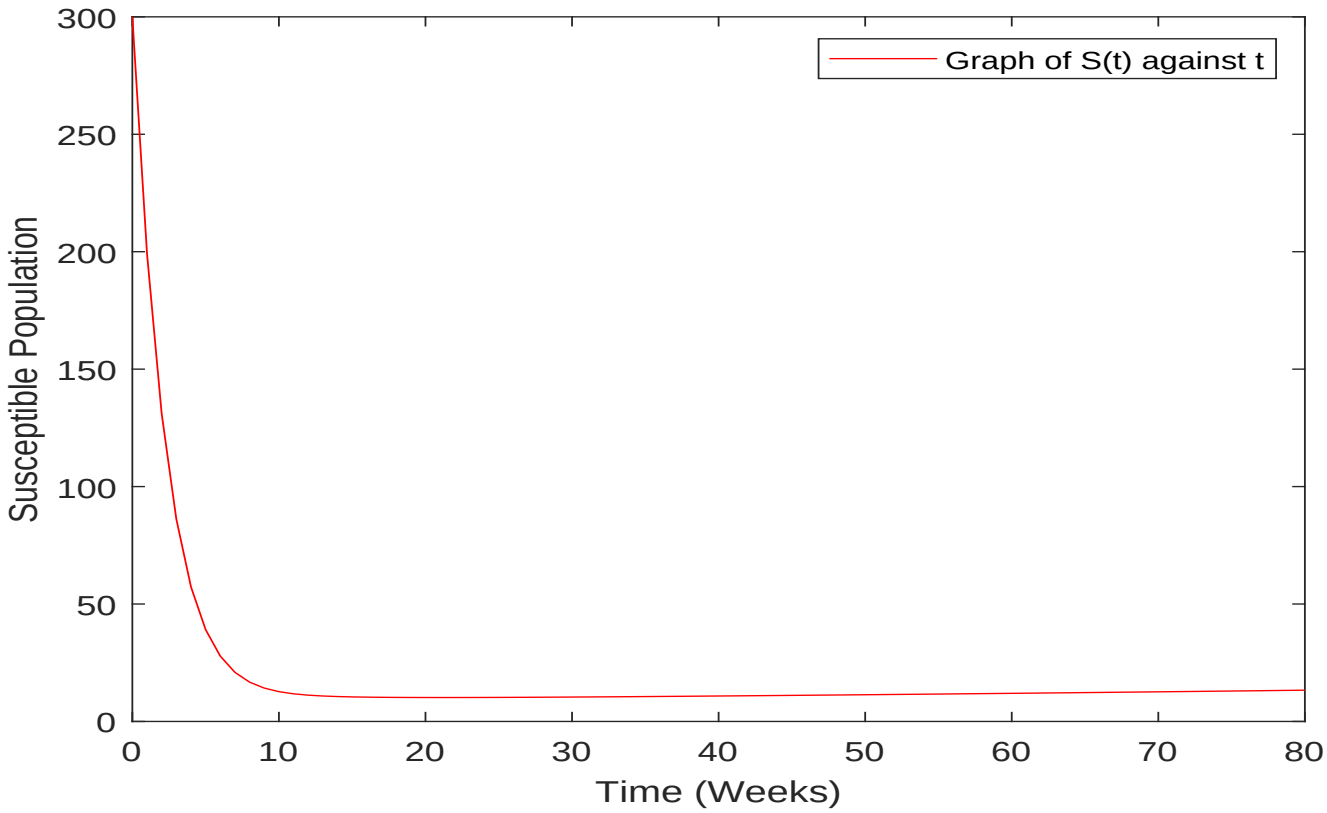


Figure: Susceptible TB Population against Time

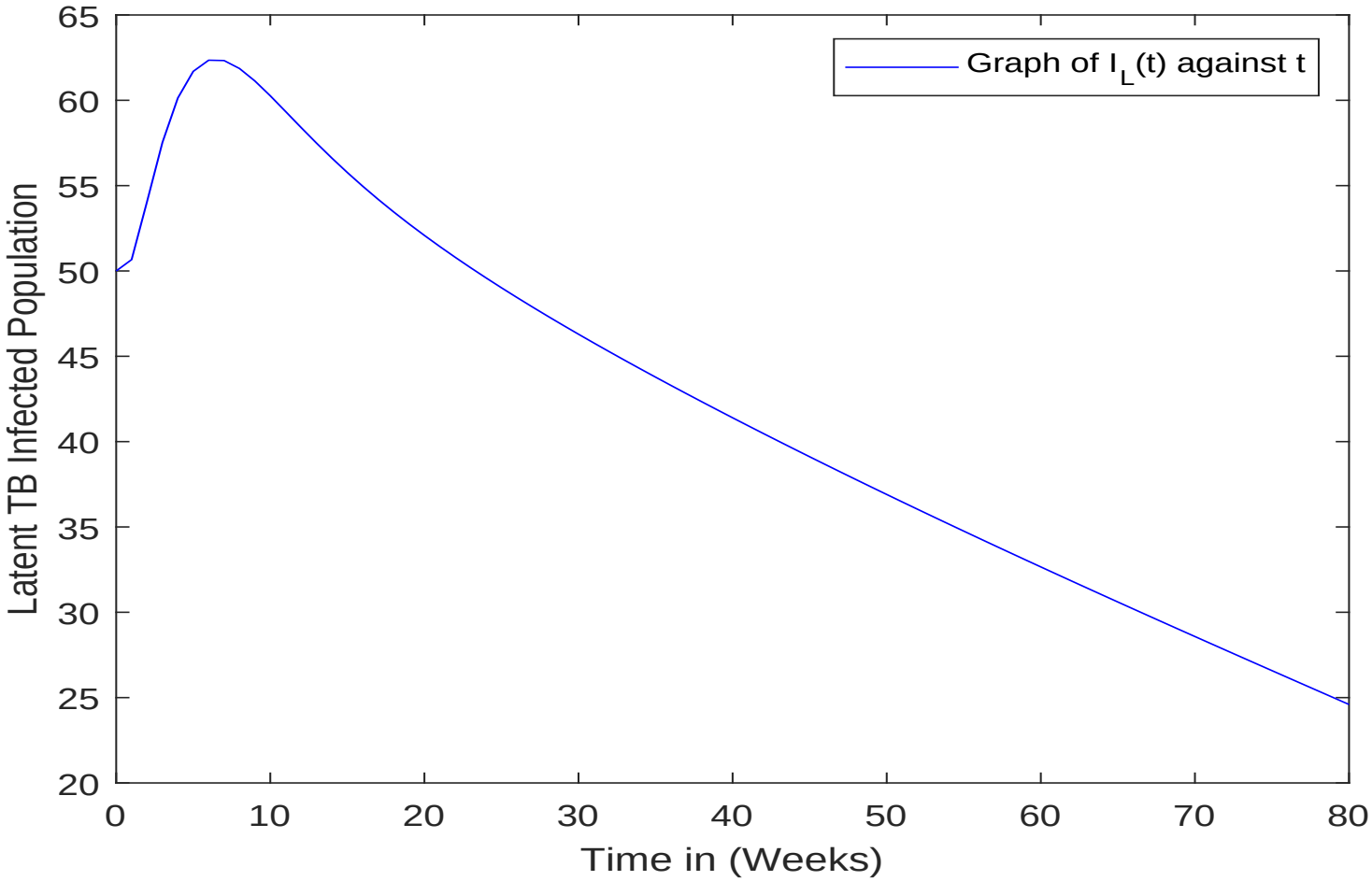


Figure: Latent TB Infected Population against Time

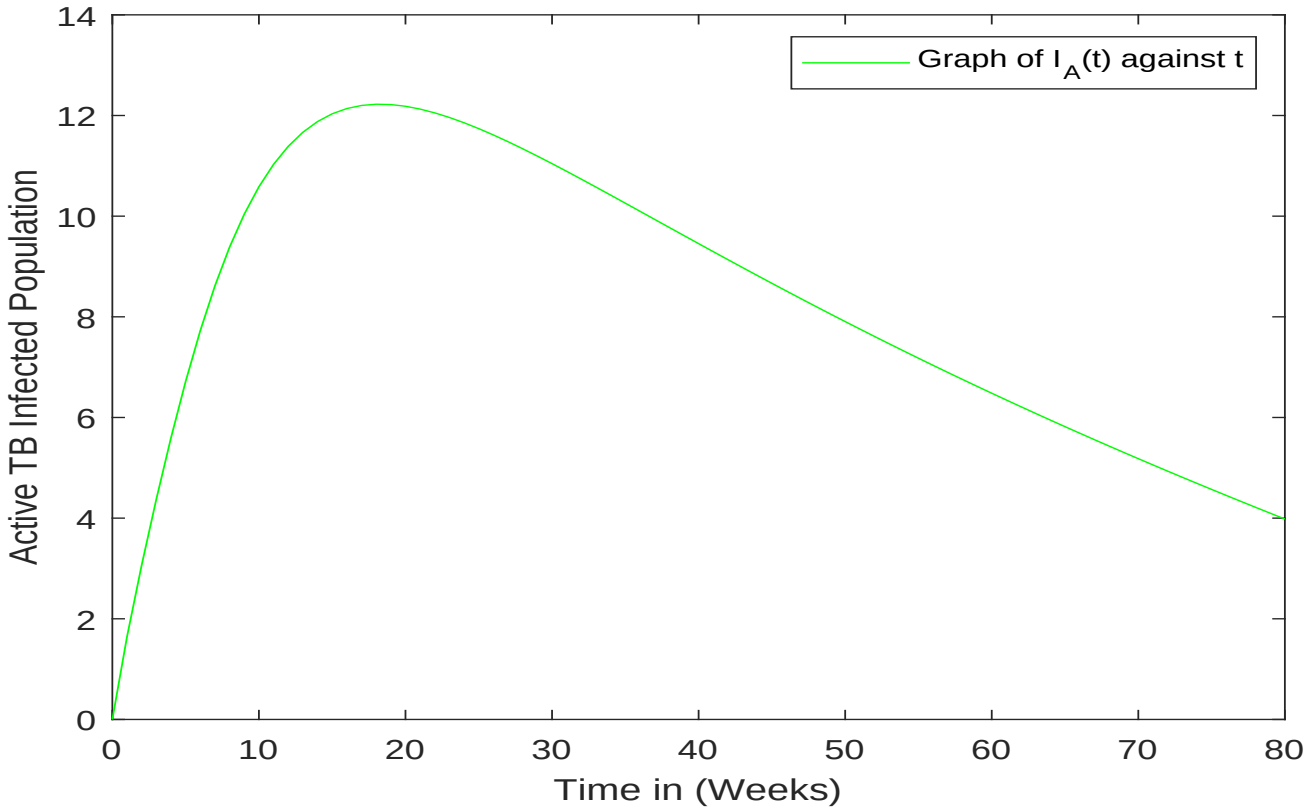


Figure: Active TB Infected Population against Time

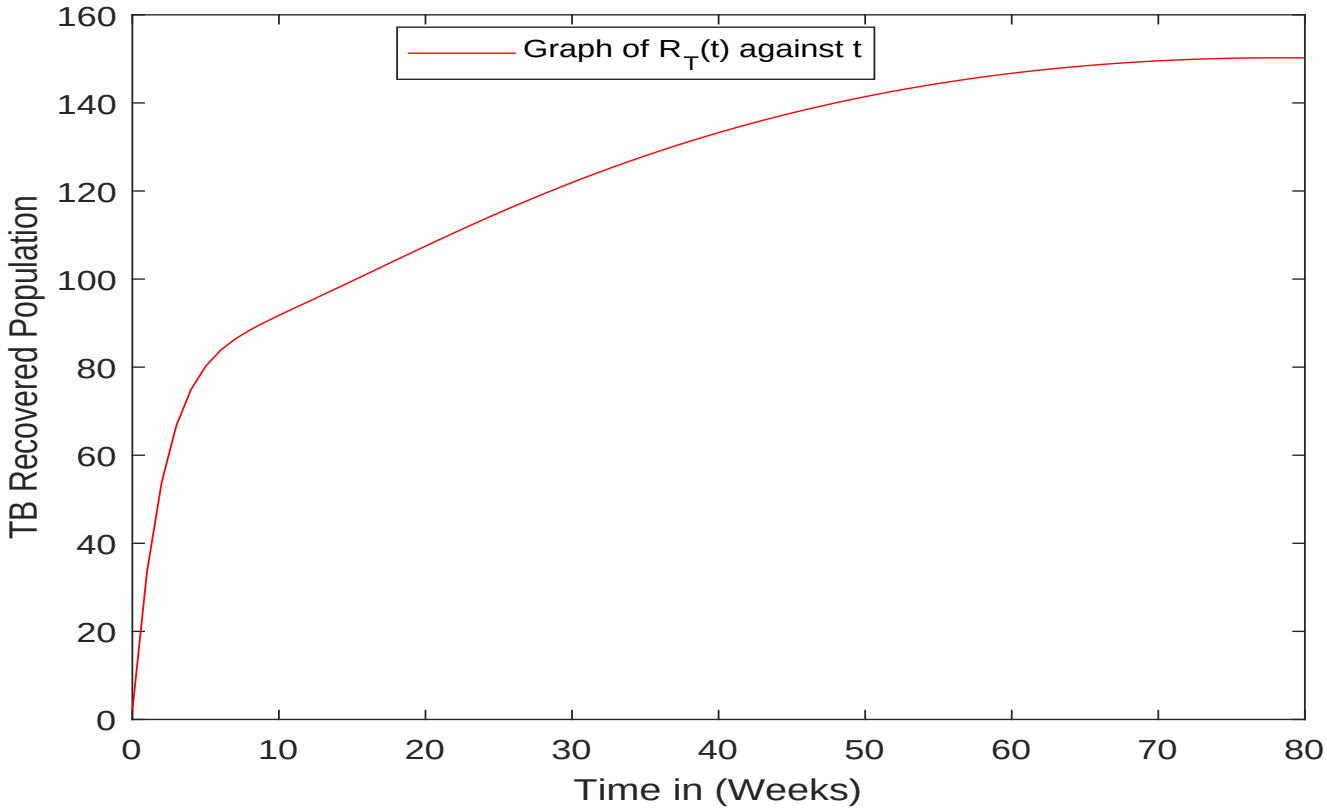


Figure: TB Recovered Population against Time

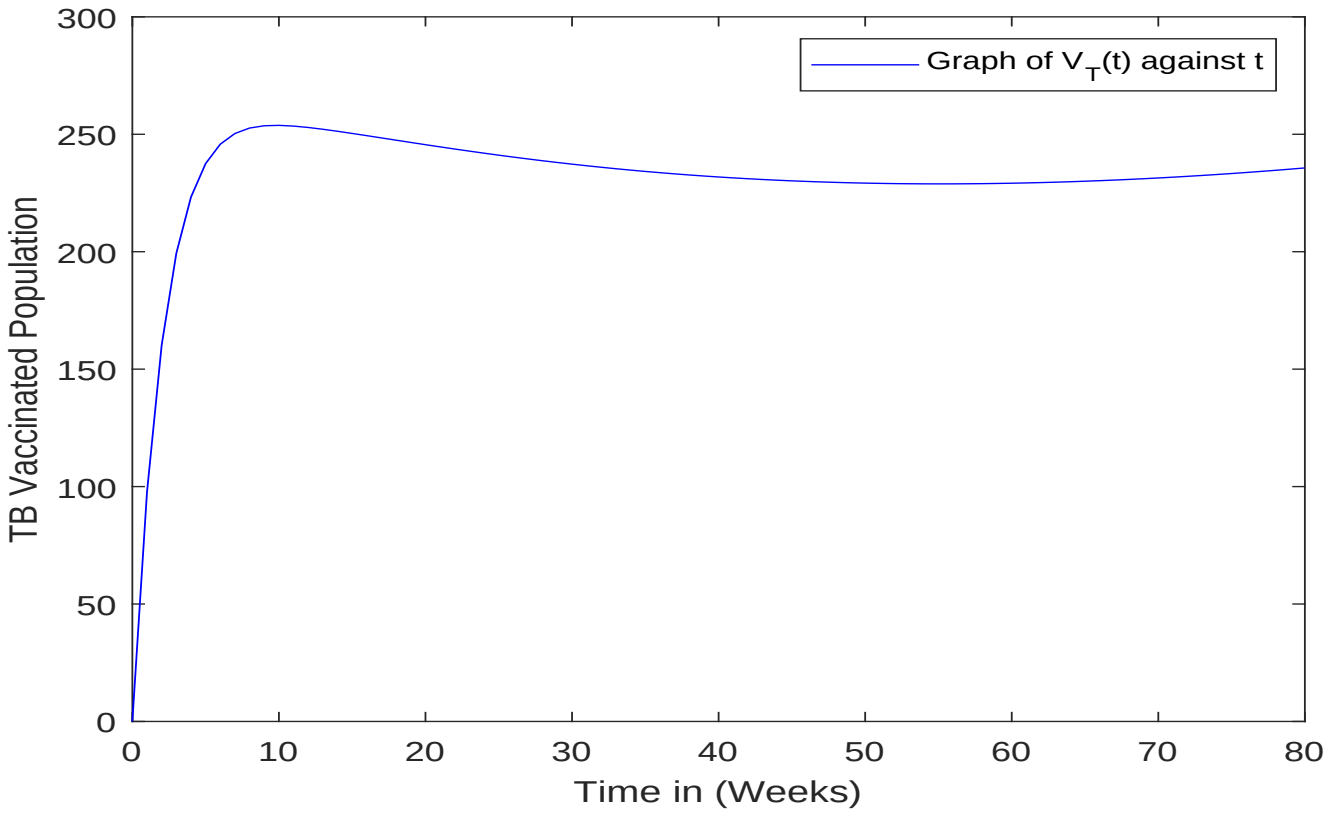


Figure: TB Vaccinated Population against Time

Conclusion and Recommendations

1. Establish the effectiveness of mathematical modeling in predicting future trends and possible controls for infectious disease in general and TB in particular.
2. Presents a very comprehensive and robust model for Tuberculosis.
3. Results of the stability analyses shows a stable DFE for TB suggesting that the diseases can be well managed if necessary implementations are made.
4. A stable endemic equilibruim point exists but do not co-exists with the DFE.
5. Sensitivity analyses show that recruitment and contact/transmission rates are the most sensitive parameter to increase the spread of the diseases while vaccination and treatment rates are the most sensitive to decrease the spread.
6. The simulation results show that the infected population approaches zero but didn't converge on zero; hence the need for an OCP is necessary to obtain a control solution.
7. We recommend awareness on efficacy of vaccinations for Tuberculosis.
8. We highly advise point of care diagnosis for quick, easily accessible and accurate diagnosis followed by treatment.


Thank You For
Listening

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