STABILITY ANALYSIS OF THE DISEASE-FREE EQUILIBRIUM STATE OF A MATHEMATICAL MODEL OF TUBERCULOSIS DYNAMICS

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Abstract
A mathematical model for the transmission dynamics and control of tuberculosis incorporating treatment at both latent and active classes was developed. The disease-free equilibrium state was analyzed for stability and the result shows that the state is globally stable when the basic reproduction number, R_0 *is less or equal to unity. Numerical simulation was used to verify the analytical result. It shows that the disease can be eradicated in 200 (years) if a high level of treatment is applied to both the active class and the latent class of the subpopulation.*

Keywords: Tuberculosis, disease-free equilibrium state, basic reproduction number, stability.

Introduction
Tuberculosis (TB) remains one of the world's deadliest communicable disease. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease, 360000 of whom were HIV positive. TB is slowly declining each year and it is estimated that 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment (WHO, 2014). An estimated 480000 and 590000 were the cases reported for incidence and prevalence of TB in Nigeria for 2014 respectively, while about 91000 died from the disease (WHO, 2015). The high incidence of tuberculosis in the developing countries is as a result of poverty and underdevelopment, which lead to overcrowding, malnutrition, lack of access to good health care services which are contributory factors to the spread of the disease. The nature of population distribution is such that many people live in small areas, while others in larger areas have sparse concentration of people. This uneven pattern of population distribution, which results into massive concentration of people in a limited area, is a major factor which has helped to sustain some diseases, especially the airborne diseases of which tuberculosis is one.

In order to find an efficient way to control an infection, it is of great important to establish its transmission dynamics. Mathematical modeling and analysis is central to disease epidemiology. Numerous mathematical models were developed to study a disease transmission, to evaluate the spread of epidemics, and more importantly, to understand the mechanisms of epidemics in order to prevent them or minimize the transmission of disease via behavior change, vaccination, treatment, quarantine and other measures. During the last three decades Egbetade *et al*. (2012), James *et al* (2012), Ibrahim *et al* (2013), okuonghae *et al* (2013), Bowong (2010) and Cagri *et al* (20013) have designed mathematical models to evaluate the effects of tuberculosis in different population settings. Considering the works of the aforementioned authors, a new mathematical model is developed incorporating treatment at both latent and active classes of the population.

Materials and Methods
Model Development

Dividing the total population into three (3) compartments of Susceptible, Latent and Active individuals we assumed that:

(a) There is homogeneous mixing of the population, where all people are equally likely to be infected by the active individuals in case of contact;
(b) There is constant recruitment rate into the susceptible class;
(c) New births are not infected at birth, i.e. the transmission is not vertical

The model variables and parameters are defined as follows:

$S(t)$ Susceptible individuals at time, t

$L(t)$ Latently infected individuals at time, t

$A(t)$ Active individuals at time, t

$N(t)$ Total population at time, t

Λ Recruitment rate

μ Natural death removal rate (or death due to other causes)

α Transmission probability per contact

τ_L Treatment rate of latently infected individuals

τ_A Treatment rate of active individuals

γ Progression rate from L class into A class due to lack of treatment or immunity

δ Tuberculosis induced death rate

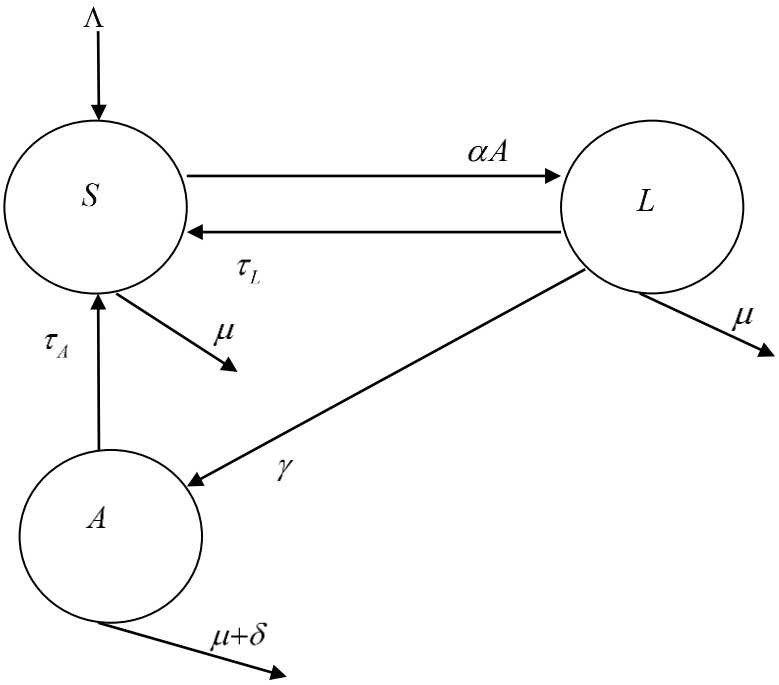

Figure 1: A schematic representation of the model

Schematic Diagram of Tuberculosis Transmission Dynamics

The susceptible subpopulation $S(t)$ is generated from constant recruitment of individuals at a rate Λ. They acquired infection via horizontal transfer from individuals in the active class (A) at a rate α and thus become latently infected. Individuals in the latent class recovered from the disease due to treatment at the rate τ_L and move back to the susceptible class or progresses to the active class at the rate γ. The active individual's can also recover from the disease due to treatment at the rate τ_A and move back to the susceptible class or die due to the disease at the rate δ. Natural death occurs in all classes
at a rate μ.

The proposed mathematical model of the dynamics is described by a system of ordinary differential equations given below from (3.1a) to (3.1c)

$$\frac{dS}{dt} = \Lambda - \alpha AS + \tau_L L + \tau_A A - \mu S$$

(3.1a)

$$\frac{dL}{dt} = \alpha AS - (\tau_L + \gamma + \mu)L \qquad (3.1b)$$

$$\frac{dA}{dt} = \gamma L - (\tau_I + \mu + \delta)A \qquad (3.1c)$$

Where

$$N = S + L + A \qquad (3.2)$$

From the model system (3.1), let

$$K_1 = (\tau_L + \gamma + \mu) \qquad (3.3)$$

$$K_2 = (\tau_A + \mu + \delta) \qquad (3.4)$$

.

Equations (3.1a) to (3.1c) becomes

$$\frac{dS}{dt} = \Lambda - \alpha AS + \tau_L L + \tau_A A - \mu S \qquad (3.5a)$$

$$\frac{dL}{dt} = \alpha AS - K_1 L \qquad (3.5b)$$

$$\frac{dA}{dt} = \gamma L - K_2 A \qquad (3.5c)$$

The total population size $N(t)$ can be determine by analysing (3.5a) to (3.5c) giving

$$\frac{dN}{dt} = \Lambda - \mu N - \delta A \qquad (3.6)$$

The model (3.1) is epidemiologically and mathematically well-posed in the domain,

$$\Omega = \left\{ \begin{pmatrix} S \\ L \\ A \end{pmatrix} \in R_+^3 \middle| \begin{matrix} S \geq 0, \\ L \geq 0, \\ A \geq 0, \\ S + L + A \leq N \end{matrix} \right\} \qquad (3.7)$$

This domain, Ω, is valid epidemiologically as the sub-populations $S, L,$ and A are all non-negative and have sums less than or equal the total population, N .

Existence of Equilibria, E^*

At equilibrium state the rate of change of each variable is equal to zero. i.e.

$$\frac{dS}{dt}=\frac{dL}{dt}=\frac{dA}{dt}=0 \tag{3.8}$$

Let

$$\begin{pmatrix} S \\ L \\ A \\ N \end{pmatrix}=\begin{pmatrix} S^* \\ L^* \\ A^* \\ N^* \end{pmatrix} \tag{3.9}$$

Thus, we have from system (3.5)

$$\Lambda-\alpha I^* S^*+\tau_L L^*+\tau_I I^*-\mu S^*=0 \quad \text{(3.10a)}$$

$$\alpha A^* S^*-K_1 L^*=0 \tag{3.10b}$$

$$\gamma L^*-K_2 A^*=0 \tag{3.10c}$$

From (3.10c), we have

$$A^*=\frac{\gamma L^*}{K_2} \tag{3.11}$$

Substituting (3.11) into (3.10b), gives

$$\frac{\alpha\gamma L^* S^*}{K_2}-K_1 L^*=0$$

i.e.

$$L^*\left(\alpha\gamma S^*-K_1 K_2\right)=0$$

Thus

$$L^*=0 \tag{3.12}$$

or

$$\left(\alpha\gamma S^*-K_1 K_2\right)=0 \tag{3.13}$$

If (3.12) holds, then substituting it into (3.11) gives

$$A^*=0 \tag{3.14}$$

Substituting (3.12) and (3.14) into system (3.10a) gives

$$S^*=\frac{\Lambda}{\mu} \tag{3.15}$$

Thus, the disease-free equilibrium state of the model is given by

$$\left(S^*, L^*, A^*\right)=\left(\frac{\Lambda}{\mu}, 0, 0\right) \tag{3.16}$$

Similarly, if (3.13) holds, then

$$S^*=\frac{K_1 K_2}{\alpha\gamma} \tag{3.16}$$

Substituting (3.11) and (3.16) into system (3.10a) gives

$$\Lambda-K_1 L^*+\tau_L L^*+\frac{\tau_A \gamma L^*}{K_2}-\frac{\mu K_1 K_2}{\alpha\gamma}=0$$

i.e.

$$L^* = \frac{\left(\Lambda\alpha\gamma - \mu K_1 K_2\right)K_2}{\alpha\gamma\left(K_1K_2 - \tau_L K_2 - \tau_A\gamma\right)} \tag{3.17}$$

And substituting (3.17) into system (3.11) gives

$$A^* = \frac{\left(\Lambda\alpha\gamma - \mu K_1 K_2\right)}{\alpha\left(K_1K_2 - \tau_L K_2 - \tau_A\gamma\right)} \tag{3.18}$$

Thus, an endemic equilibrium state of the model is given by

$$\left(S^*, L^*, A^*\right) = \left(\frac{K_1K_2}{\alpha\gamma}, \frac{\left(\Lambda\alpha\gamma - \mu K_1 K_2\right)K_2}{\alpha\gamma\left(K_1K_2 - \tau_L K_2 - \tau_A\gamma\right)}, \frac{\left(\Lambda\alpha\gamma - \mu K_1 K_2\right)}{\alpha\left(K_1K_2 - \tau_L K_2 - \tau_A\gamma\right)}\right) \tag{3.19}$$

Basic Reproduction Number, R_0

Using the next generation operator technique described by Diekmann and Heesterbeek (2000) and subsequently analysed by Van den Driessche and Watmough (2002), we obtained the basic reproduction number, R_0 of the system model which is the spectral radius (ρ) of the next generation matrix, K.

i.e.

$R_C = \rho K$, where $K = FV^{-1}$

Let

$$E^0 = \left(S^0, L^0, A^0\right) \tag{3.20}$$

denote the disease-free equilibrium state, then

$$F = \begin{pmatrix} 0 & \alpha S^0 \\ 0 & 0 \end{pmatrix} \tag{3.21}$$

and

$$V = \begin{pmatrix} K_1 & 0 \\ -\gamma & K_2 \end{pmatrix} \tag{3.22}$$

Thus,

$$R_0 = \frac{\alpha\gamma\dfrac{\Lambda}{\mu}}{K_1K_2} \tag{3.23}$$

Local Stability Analysis of Disease-free Equilibrium State, E^0

We used the Jacobian stability approach to prove the local stability of the disease-free equilibrium state. Linearization of the system (3.10) at E^0, gives the Jacobian matrix

$$J\left(E^0\right) = \begin{pmatrix} -\mu & \tau_L & -\left(\alpha S^0 - \tau_A\right) \\ 0 & -K_1 & \alpha S^0 \\ 0 & \gamma & -K_2 \end{pmatrix} \tag{3.24}$$

We now make the following elementary row-transformation:

Add $\frac{\gamma}{K_1}$ times the second row to the third row.

$$J\left(E^0\right)=\begin{pmatrix} -\mu & \tau_L & -\left(\alpha S^0-\tau_A\right) \\ 0 & -K_1 & \alpha S^0 \\ 0 & 0 & -\left(\frac{K_1K_2-\gamma\alpha S^0}{K_1}\right) \end{pmatrix} \quad (3.25)$$

Thus, the eigenvalues are

$$\lambda_1=-\mu<0,\ \lambda_2=-K_1<0,$$

and

$$\lambda_3=-\left(\frac{K_1K_2-\gamma\alpha S^0}{K_1}\right)$$

now, for λ_3 to be negative, we must have

$$-\left(\frac{K_1K_2-\gamma\alpha S^0}{K_1}\right)<0$$

i.e

$$-K_1K_2+\gamma\alpha S^0<0$$

or

$$\frac{\alpha\gamma\frac{\Lambda}{\mu}}{K_1K_2}<1$$

Thus, $\lambda_3<0$ if $R_0<1$ implying all the eigenvalues have negative real parts, we therefore, established the following result.

Theorem 1: The disease-free equilibrium state, E^0 of the model is locally asymptotically stable (LAS) if $R_0<1$.

Global stability of disease-free equilibrium point, E^0

The epidemiological implication of theorem 1 is that tuberculosis can be eliminated (control) from the population when $R_0<1$, if the initial size of the sub-populations of the model are in the basin of attraction of the E^0.

In order to ensure that tuberculosis is independent of the initial size of the sub-populations of the model, it is necessary to show that the E^0 is globally-asymptotically stable (GAS). One common approach in studying the global asymptotic stability of the DFE is to construct an appropriate Lyapunov function.

Theorem 3: The disease- free equilibrium E^0 of the model is globally asymptotically stable (GAS) in Ω if $R_0\le1$.

Proof: Consider the Lyapunov function:

$$f=\gamma L+K_1A \quad (2.26)$$

Its derivatives along the solutions of the model equations is

$$f' = \gamma L' + K_1 A' \qquad (2.27)$$
$$= \gamma\left(\alpha AS - K_1 L\right) + K_1\left(\gamma L - K_2 A\right)$$
$$= \alpha\gamma AS - K_1 K_2 A$$
$$= AK_1 K_2\left(\frac{\alpha\gamma S}{K_1 K_2} - 1\right)$$

Now, since $S \le S^0$, we have

$$f' \le K_1 K_2 A\left(\frac{\alpha\gamma S^0}{K_1 K_2} - 1\right)$$

i.e.

$$f' \le K_1 K_2 A\left(R_0 - 1\right)$$

When $R_0 \le 1$, $f' \le 0$; the equality $f' = 0$ holds when $R_0 = 1$ and $A = 0$. Thus $A = 0$ is the largest invariant subsets in the set $f' = 0$. Thus, according to the asymptotical stability theorem of Lyapunov-LaSalle theorem E^0 is overall globally asymptotically stable in $\Re_+^3$ and hence, the result is proved**.**

Numerical Simulation

Our numerical results were obtained and confirmed using different levels of treatment. At high levels of treatments (fig.1) the disease reduce drastically and vanishes at two hundred (200) years from the active class, while in the latent class the population of infective declines gradually and vanishes after 300 years. We examine treatment at low levels (fig.2) and the result show that the disease cannot be wipe out in the latent class but can be eradicated from the active class at about 270 years. Further, the impact of treatment leads to increase in population of the susceptibles (fig. 3).

The values of the parameters were obtained using data from Nigeria's central intelligence agency, on the population of Nigeria (177,155,754), life expectancy (52.64 years), birth rate 38.03/1000 population and natural death 13.16/1000 (CIA, 2014); other parameter values are from literature. The model parameters and their values are presented in Table 1

Table 1: Model Parameter and Values

Parameter	Description	Estimated value	Reference
Λ	Recruitment rate	9000	Estimated
S(t)	Susceptible class	162,000000	Estimated
L(t)	Latently infected	10,000000	Estimated
A(t)	Actively infected	5000000	Estimate

N(t)	Total Nigeria population	177000000	CIA
τ_L	Treatment for latent class	$0 < \tau_L < 1$	Estimate
τ_A	Treatment for active class	$0 < \tau_A < 1$	Estimate
μ	Natural death rate	0.01316	CIA
γ	Progression from latent to active class	0.000256	Cagri et al
δ	TB induced death rate	0.139	Cagri et al
α	Contact rate	0.0002	Estimate

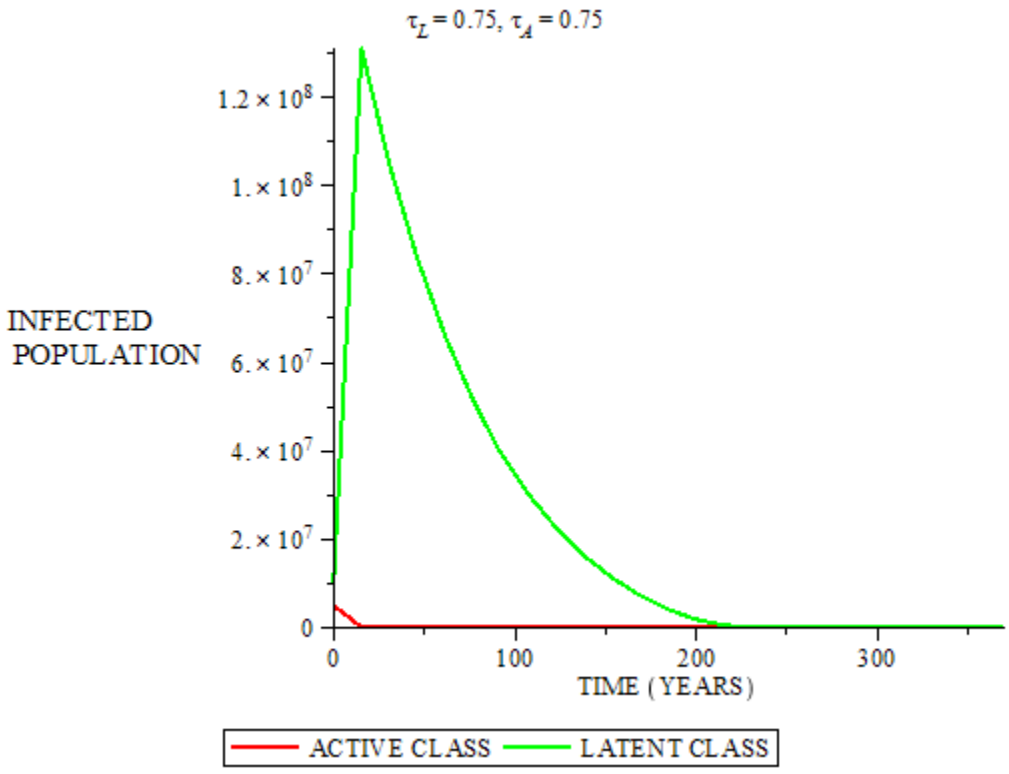

Figure 1: Shows the effect of high level treatment on the active and latent class

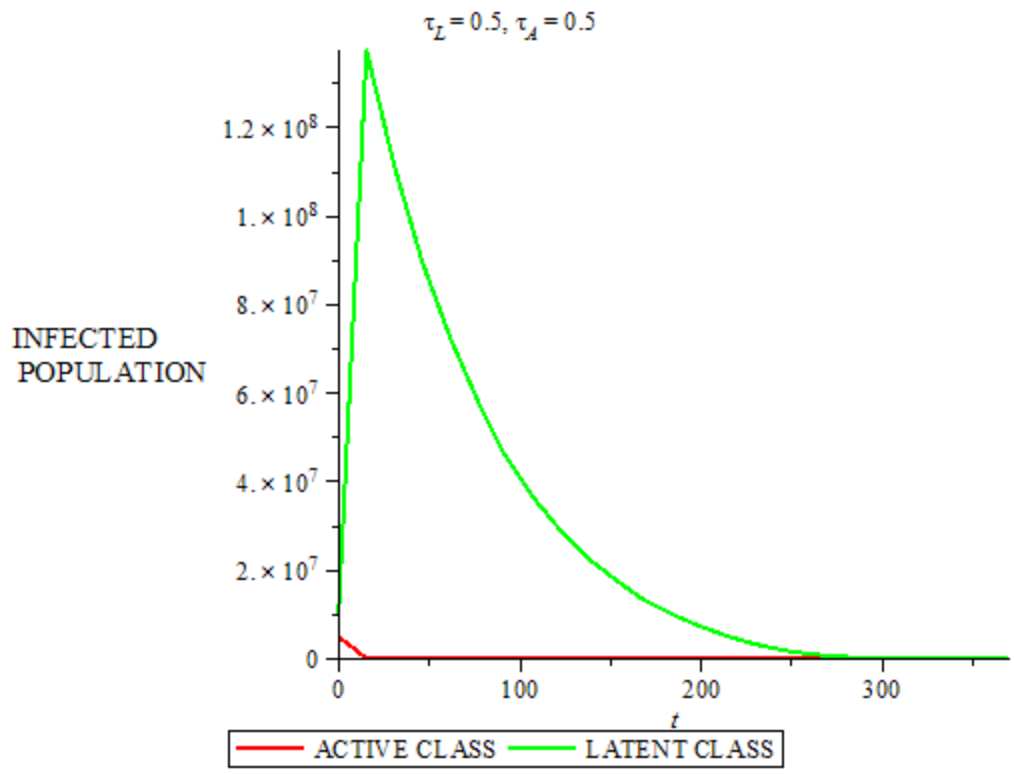

Figure 2: Shows the effect of low level of treatment on both Active and Latent class

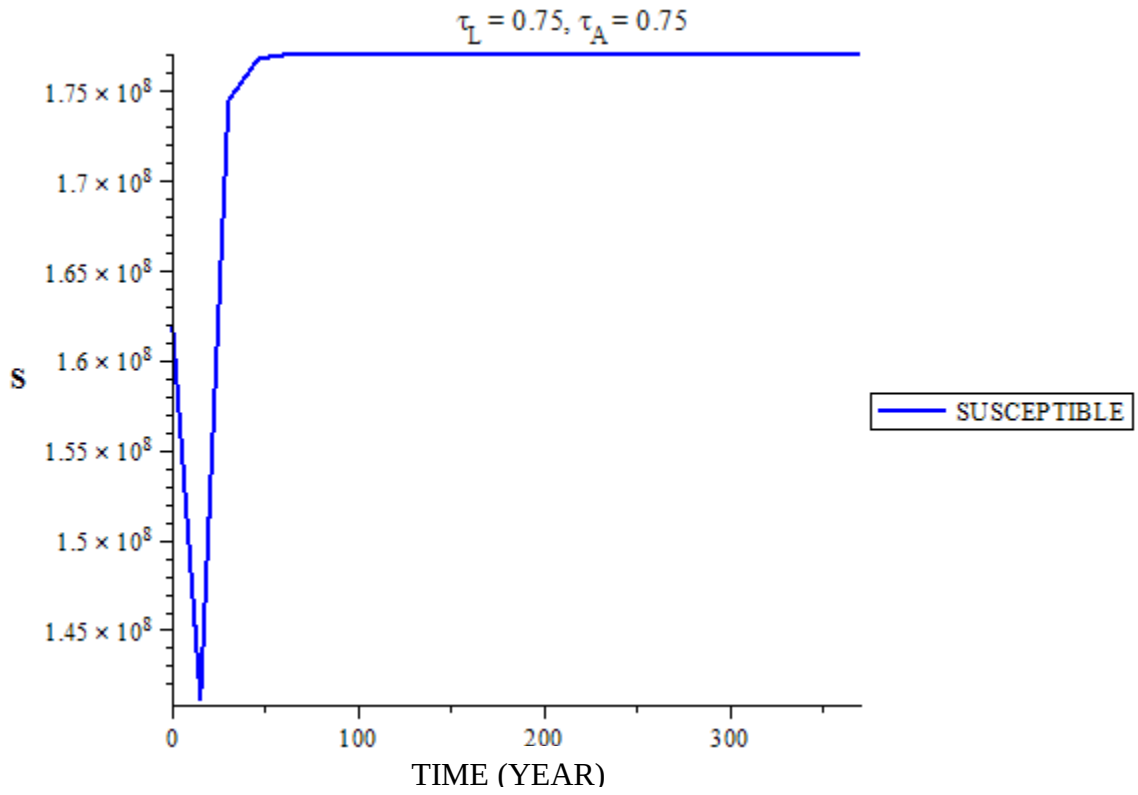

Figure 3: Shows the effect of treatment of active and latent class on susceptible class

Conclusion

A mathematical model of the dynamics and control of tuberculosis was developed and analysed for stability. The existences of disease-free and endemic equilibria states were obtained. The basic reproduction number R_0 was computed. The analysis revealed that for $R_0 \leq 1$, the disease-free equilibrium is globally asymptotically stable so that the disease always dies out. If $R_0 > 1$ the disease free equilibrium point is unstable and the endemic equilibrium emerges. Thus, $R_0 \leq 1$ when the effective contact rate (α) is very small and the treatment rates of latent individual (τ_L), and infectious individuals (τ_A) are high.

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