Journal of the Nigerian Association of Mathematical Physics
Volume27, (*July, 2014*), pp 137 – 142

Some Global Properties of a Tuberculosis Mathematical Model Involving Case Detection And Waning Immunity

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Abstract

This work is concerned with providing an insight into some global behaviours of a tuberculosis mathematical model that included the effect of case detection and waning immunity acquired after previous treatment of the disease, using density dependent incidence. Using appropriately formulated Lyapunov functions, we show that the disease free equilibrium (DFE) of the model is globally asymptotically stable whenever a threshold quantity larger than the reproduction number is less than unity. It is suggested that this bound on the reproduction number was due to the presence of exogenous re-infection which further suggests the possibility of a backward bifurcation (whereby the DFE will co-exists with a stable endemic equilibrium) since the reproduction number will have to be less than the calculated threshold for the DFE to be globally stable. When the exogenous re-infection terms are removed and we assume that treatment confers long term immunity, the endemic equilibrium was shown to be globally asymptotically stable whenever it exists.

1.0 Introduction

Tuberculosis (TB), a highly infectious disease, has infected one third of the world's population, leading to between two and three million deaths each year [1]. For most individuals infected with TB, the immune system is able to control the causative agent, *Mycobacterium tuberculosis*, but not eliminate it. These individuals are not infectious and suffer no symptoms, although they usually test positive on a skin test. However, it is possible that after a latent period of years or decades, these individuals may become symptomatic and infectious. There is also a smaller fraction of individuals for whom the progression to active TB is much faster. This fast progression is particularly common forindividuals with a compromised immune system [2].

Several mathematical models for the transmission dynamics of tuberculosis have been formulated and analyzed, in some cases rigorously, depending on the concerns of the authors. Castillo-Chavez and Song [3] made a review of some of these models. The issue of case detection and the implementation of the direct observation therapy strategy (DOTS) was the aim of the study by Okuonghae and Aihie [4] while Okuonghae and Omosigho [5] investigated the effect of some key parameters that will help in improving the TB case detection rate. In Okuonghae [6], a novel mathematical model that takes into consideration heterogeneity in disease susceptibility and progression was formulated and rigorously analyzed, with results showing that a given fraction of those genetically susceptible to TB can form a threshold condition for controlling the spread of the disease in a population.

In most of the formulated models, characterizing the global properties of the systems equilibria using Lyapunov functions is still being investigated. This is because establishing global properties of a dynamical system is generally a nontrivial problem. The method of using Lyapunov functions provides sufficient conditions for the global stability of the disease equilibria; however it is usually not easy to find such a functional [7].

In this work, we will provide some global properties of a tuberculosis model that incorporates case detection and waning immunity acquire after previous treatment of the disease. The Lyapunov functions used in this paper to demonstrate the stability of the endemic equilibrium are of the same form as those used elsewhere [2, 7, 8] and in Okuonghae and Korobeinikov [9] to determine the global dynamics of SEIR, SEIS, and SIR models as well as mathematical models that are derivatives of the SEIR structures

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2.0 Model Formulation

Consider a population with population size $N(t)$ divided into the following epidemiological classes: Susceptible individuals, $S(t)$, Latent (exposed) individuals, $E(t)$, infectious individuals who are not detected, $I(t)$, infectious individuals who are detected, $J(t)$, and individuals who are treated and recover from tuberculosis, $T(t)$. Hence$N(t) = S(t) + E(t) + I(t) + J(t) + T(t)$.

Let us assume that Λ be the recruitment rate into the susceptible class, which could include immigrants and/or newborns that are uninfected. We further assume that μ is the per capita natural mortality rate for all individuals in the population. Let α_1 and α_2 be the transmission rates of the disease from the infectious individuals in the I and J classes, respectively, on the susceptible sub-population while γ_1 and γ_2 are the transmission rates of the disease from the infectious individuals in the I and J classes, respectively, on the treated sub-population. We assume that treatment induced a modification into the transmission process that allows for those treated to be less likely to becoming infected with the disease, so that $0 < \gamma_i \leq \alpha_i$, $\{i = 1,2\}$. In this formulation, we also assume that the population is homogeneously mixed, and all people are equally likely to be infected by the infectious individuals in a case of contact, and that transmission of the infection occurs with a bilinear incidence rate (which follows the law of mass action).

Also, we assume that some of the treated individuals had a form of temporary immunity arising from the treatment received but this immunity waned over time and at the rate, σ, these individuals revert to susceptible status. Since exogenous re-infection plays a crucial role in TB dynamics [10, 11, 12], we include this phenomenon into the model and assume that β_1 and β_2 are the effective transmission rates for the latent class due to exogenous re-infection while k is the rate of progression of individuals in the latent state to the infectious classes.

We assume that ω is the fraction of infectious cases that are detected and treated (under a direct observation therapy strategy(DOTS) programme) while the remaining fraction $1 - \omega$ of the infectious cases are not detected for treatment (under the implementation of DOTS). Let $r_0$be the treatment rate of the latent cases while r_2 is the treatment rate of individuals in the detected class J. Further, we assume that infectious individuals in the undetected class, I, (other than natural mortality) either dies from the disease (at the rate d_1) or reverts to the latent state due to self-cure at the rate r_1 [13, 14, 15]. We assume that a fraction, q, of the treated persons fully recover while the remaning fraction ($p = 1 - q$) did not have full recovery and goes back to the latent class. Infectious individuals in the detected class die from the disease at the rated_2. We assume that the proportion of new infections that leads directly to infectious TB is very small so that we neglect fast progressions to infectious TB.

With these assumptions, we now have the following system of non-linear ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \alpha_1 SI - \alpha_2 SJ - \mu S + \sigma T, \\
\frac{dE}{dt} &= \alpha_1 SI + \alpha_2 SJ + \gamma_1 TI + \gamma_2 TJ + r_1 I + pr_2 J - (k + \beta_1 I + \beta_2 J + \mu + r_0)E, \\
\frac{dI}{dt} &= (1 - \omega)(k + \beta_1 I + \beta_2 J)E - (\mu + d_1 + r_1)I, \\
\frac{dJ}{dt} &= \omega(k + \beta_1 I + \beta_2 J)E - (\mu + d_2 + r_2)J, \\
\frac{dT}{dt} &= r_0 E + qr_2 J - \gamma_1 TI - \gamma_2 TJ - (\mu + \sigma)T. \qquad (1)
\end{aligned}$$

The model (1) above is similar to the one studied in Okuonghae and Korobeinikov [9]. However, the model (1) was not analysed as presented above; a modification of the model (1) led to system that was quantitatively and qualitatively analyzed in Okuonghae and Korobeinikov [9]. Also the model in [9] did not consider the effect of loss of immunity that allows a treated individual to revert to susceptible status (effect of σ).

3.0 Basic properties of mathematical model

Under the flow described by (1), the region $\mathcal{D} = \{(S, E, I, J, T) \in \mathbb{R}^5_{\geq 0}, S + E + I + J + T \leq \frac{\Lambda}{\mu}\}$ can be shown to be positively invariant. Further, each solution in $\mathbb{R}^5_{\geq 0}$ approaches $\mathcal{D}$ and hence our analysis is restricted to this region.
The rate of change of N is given by

$$\frac{dN}{dt} = \Lambda - \mu N - d_1 I - d_2 J. \qquad (2)$$

Thus whenever $N > \Lambda/\mu$, then $\frac{dN}{dt} < 0$. Hence since the right hand side of the equality (2) is bounded by $\Lambda - \mu N$, a standard comparison theorem [16] can be used to show that

$$N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t}). \qquad (3)$$

If $N(0) \leq \frac{\Lambda}{\mu}$, then $N(t) \leq \frac{\Lambda}{\mu}$. Thus $\mathcal{D}$is a positively invariant set under the flow described by (1) so that no solution path leaves through any boundary of $\mathcal{D}$. Hence it is sufficient to consider the dynamics of the model (1) in $\mathcal{D}$. In this region, the model can be considered as been epidemiologically and mathematically well-posed [17.]

The system (1) has a disease-free equilibrium (DFE), given by

$$\xi_0 = (S^0, E^0, I^0, J^0, T^0) = (\frac{\Lambda}{\mu}, 0,0,0,0)$$

Using the next generation operator method [18] on (1), we can calculate the effective reproduction number. Using the notations in van den Driessche and Watmough [18], the matrices F and V, for the new infection terms and the remaining transfer terms, respectively, are given by

$$\text{F} = \begin{pmatrix} 0 & \alpha_1\frac{\Lambda}{\mu} & \alpha_2\frac{\Lambda}{\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \text{and V} = \begin{pmatrix} a & -r_1 & -pr_2 \\ -(1-\omega)k & b & 0 \\ -\omega k & 0 & c \end{pmatrix}$$

Where $a = k + \mu + r_0,\ b = \mu + d_1 + r_1,\ c = \mu + d_2 + r_2$.

Hence the effective reproduction number (obtained from the spectral radius of the matrix FV^{-1}) is given by

$$\mathcal{R}_T = \frac{\Lambda}{\mu}\frac{k[c(1-\omega)\alpha_1 + b\omega\alpha_2]}{[kp\omega br_2 + \big((\mu + d_1)a + (k\omega + \mu + r_0)r_1\big)c]}$$

The threshold quantity $\mathcal{R}_T$represents the average number of secondary cases generated by a typical infected individual in a susceptible population in the presence of treatment.

The following result follows from Theorem 2 in [18].

Lemma 1. The DFE of the model (1) is locally asymptotically stable if $\mathcal{R}_T < 1$, and unstable if $\mathcal{R}_T > 1$.

The epidemiological implication of Lemma 1 is that when $\mathcal{R}_T$ is less than unity, a small influx of infected individuals into the community would not generate large outbreaks, and the disease dies out in time.

4.0 Global stability of ξ_0 when $\mathcal{R}_T \leq 1$.

We claim the following:

Theorem 1. The DFE of the model (1) is globally asymptotically stable whenever $\mathcal{R}_T < \mathcal{R}_x < 1$ where

$$\mathcal{R}_x = \boldsymbol{max}\{\frac{\alpha_1\Lambda}{\mu(\mu + d_1)}, \frac{\alpha_2\Lambda}{\mu(\mu + d_2)}\}$$

Proof: Consider the Lyapunov function

$$U(S, E, I, J, T) = S - S^0 \ln S + E + I + J + T.$$

Recalling that $p + q = 1$, the Lyapunov derivative becomes

$$\frac{dU}{dt} = \frac{dS}{dt} - \frac{S^0}{S}\frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dJ}{dt} + \frac{dT}{dt}$$

Substituting the right hand side of the derivatives in the model (1), the Lyapunov derivative then becomes

$$\begin{aligned} \frac{dU}{dt} &= \Lambda - \alpha_1 SI - \alpha_2 SJ - \mu S + \sigma T - \frac{S^0}{S}(\Lambda - \alpha_1 SI - \alpha_2 SJ - \mu S + \sigma T) \\ &+ \alpha_1 SI + \alpha_2 SJ + \gamma_1 TI + \gamma_2 TJ + r_1 I + pr_2 J - (k + \beta_1 I + \beta_2 J + \mu + r_0)E \\ &+ (1-\omega)(k + \beta_1 I + \beta_2 J)E - (\mu + d_1 + r_1)I + \omega(k + \beta_1 I + \beta_2 J)E - (\mu + d_2 + r_2)J \\ &+ r_0 E + qr_2 J - \gamma_1 TI - \gamma_2 TJ - (\mu + \sigma)T. \end{aligned}$$

After several calculations, we then have that

$$\frac{dU}{dt} = \Lambda\left(2 - \frac{S^0}{S} - \frac{S}{S^0}\right) - \sigma T\frac{S^0}{S} - \mu E - \mu T + \left(\frac{\alpha_1\Lambda}{\mu(\mu + d_1)} - 1\right)I + \left(\frac{\alpha_2\Lambda}{\mu(\mu + d_2)} - 1\right)J\ .$$

Since the arithmetic mean is greater than or equal to the geometric mean, the function $2 - \frac{S^0}{S} - \frac{S}{S^0}$ is negative. Hence we see that

$$\frac{dU}{dt} < 0$$

if $\chi_1 = \frac{\alpha_1\Lambda}{\mu(\mu + d_1)} < 1$**and** $\chi_2 = \frac{\alpha_2\Lambda}{\mu(\mu + d_2)} < 1$.

Now define$\boldsymbol{\mathcal{R}_x = max\{\chi_1, \chi_2\}}$.Since each of χ_1 and χ_2 are not exactly $\mathcal{R}_T$ and are a bit larger than$\mathcal{R}_T$, then we conclude that

$$\frac{dU}{dt} < 0$$

whenever$\boldsymbol{\mathcal{R}_T < \mathcal{R}_x < 1}$**,** with $\frac{dU}{dt} = 0$ only at the DFE where $E = I = J = T = 0$.
It follows from the LaSalle's Invariance Principle [19], that
$\big(E(t), I(t), J(t), T(t)\big) \to (0,0,0,0)$ as $t \to \infty$.

We observe that $\mathcal{R}_T$ is bounded above by the max of χ_1 and χ_2. Hence we conjecture that the global stability of the DFE is restricted by these parametersdue to the presence of exogenous re-infection and the effect of σ (the parameter that captures waning immunity acquired from previous treatment).
Now consider the model (1) whereβ_1 and β_2 are set to zero to exclude the effect of exogenous re-infection. Also we set $\sigma = 0$ and assume long term immunity to re-infection after previous treatment ($\gamma_1 = \gamma_2 = 0$).
This then reduces the model (1) to

$$\frac{dS}{dt} = \Lambda - \alpha_1 SI - \alpha_2 SJ - \mu S,$$
$$\frac{dE}{dt} = \alpha_1 SI + \alpha_2 SJ + r_1 I + pr_2 J - (k + \mu + r_0)E,$$
$$\frac{dI}{dt} = (1-\omega)kE - (\mu + d_1 + r_1)I,$$
$$\frac{dJ}{dt} = \omega kE - (\mu + d_2 + r_2)J,$$

$$\frac{dT}{dt} = r_0 E + qr_2 J - \mu T. \qquad (4)$$

The model (4) can be considered in the region $\mathcal{B} = \{(S,E,I,J,T) \in \mathbb{R}^5_{\geq 0}, S + E + I + J + T \leq \frac{\Lambda}{\mu}\}$and we can show that this region is positively invariant using the approach demonstrated for the region discussed above. It is easy to show (using a suitably chosen Lyapunov function) that the DFE of the modified model (4) is globally asymptotically stable in $\mathcal{B}$whenever the associated reproduction number is less than 1.

We now show that the endemic equilibrium of the model (4) is globally asymptotically stable in $\mathcal{B}$ whenever it exists. Of course the classic condition for the existence of the endemic equilibrium is that the associated reproduction number should be greater than unity and it is easy to show that the endemic equilibrium of the model (4) exists and is unique when the reproduction number is greater than unity.
We now claim the following:

Theorem 2. The endemic equilibrium of the system (4) is globally asymptotically stable.
Proof: Let the endemic equilibrium be written as

$$\xi_1 = (S^*, E^*, I^*, J^*, T^*)$$

where at least one of the infected classes is not zero.
Now consider the non-linear Lyapunov function

$$\mathcal{V}(S,E,I,J) = S - S^* \ln S + E - E^* \ln E + a(I - I^* \ln I) + b(J - J^* \ln J)$$

where $a = \frac{\alpha_1 S^* I^* + r_1 I^*}{(\mu + d_1 + r_1)I^*}$ and $b = \frac{\alpha_2 S^* J^* + qr_2 J^*}{(\mu + d_2 + r_2)J^*}$.
Taking the derivative of $\mathcal{V}$ with respect to time, we have

$$\frac{d\mathcal{V}}{dt} = \frac{dS}{dt}\left(1 - \frac{S^*}{S}\right) + \frac{dE}{dt}\left(1 - \frac{E^*}{E}\right) + a\frac{dI}{dt}\left(1 - \frac{I^*}{I}\right) + b\frac{dJ}{dt}\left(1 - \frac{J^*}{J}\right)$$

Substituting the expressions for the derivatives in (4) into the derivative of the Lyapunov function, we have

$$\frac{d\mathcal{V}}{dt} = (\Lambda - \alpha_1 SI - \alpha_2 SJ - \mu S)\left(1 - \frac{S^*}{S}\right) + (\alpha_1 SI + \alpha_2 SJ + r_1 I + pr_2 J - (k + \mu + r_0)E)\left(1 - \frac{E^*}{E}\right)$$
$$+a[(1-\omega)kE - (\mu + d_1 + r_1)I]\left(1 - \tfrac{I^*}{I}\right) + b[\omega kE - (\mu + d_2 + r_2)J]\left(1 - \tfrac{J^*}{J}\right). \qquad (5)$$

From the model (4), at steady state, we can see that,

$$\Lambda = \alpha_1 S^* I^* + \alpha_2 S^* J^* + \mu S^*,$$
$$\alpha_1 S^* I^* + \alpha_2 S^* J^* + r_1 I^* + pr_2 J^* = (k + \mu + r_0)E^*,$$
$$(1-\omega)kE^* = (\mu + d_1 + r_1)I^*,$$
$$\omega kE^* = (\mu + d_2 + r_2)J^*. \qquad (6)$$

Substituting the expressions in (6) into (5), and after several tedious calculations, we now have

$$\frac{d\mathcal{V}}{dt} = \mu S^*\left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) + \alpha_1 S^* I^*\left(3 - \frac{SIE^*}{S^*I^*E} - \frac{S^*}{S} - \frac{I^*E}{IE^*}\right) + \alpha_2 S^* J^*\left(3 - \frac{SJE^*}{S^*J^*E} - \frac{S^*}{S} - \frac{J^*E}{JE^*}\right) + r_1 I^*\left(2 - \frac{IE^*}{I^*E} - \frac{I^*E}{IE^*}\right)$$
$$+ qr_2 J^*\left(2 - \frac{JE^*}{J^*E} - \frac{J^*E}{JE^*}\right).$$

Finally, since the arithmetic mean exceeds the geometric mean, the following inequalities hold:

$$\left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) \leq 0, \left(3 - \frac{SIE^*}{S^*I^*E} - \frac{S^*}{S} - \frac{I^*E}{IE^*}\right) \leq 0, \left(3 - \frac{SJE^*}{S^*J^*E} - \frac{S^*}{S} - \frac{J^*E}{JE^*}\right) \leq 0,$$
$$\left(2 - \frac{IE^*}{I^*E} - \frac{I^*E}{IE^*}\right) \leq 0, \left(2 - \frac{JE^*}{J^*E} - \frac{J^*E}{JE^*}\right) \leq 0.$$

Thus $\frac{d\mathcal{V}}{dt} \leq 0$ for $S, E, I, J, T > 0$. The equality $\frac{d\mathcal{V}}{dt} = 0$ holds only on the plane $S = S^*, \frac{I}{I^*} = \frac{J}{J^*} = \frac{E}{E^*}$.

5.0 Conclusion

This work examines some global properties of a tuberculosis mathematical model that considers the effect of case detection and waning immunity on the dynamics of TB. It was observed from the analysis that the DFE is globally asymptotically stable, in the presence of exogenous re-infection and waning immunity after previous treatment, only when the associated reproduction number is less than a larger threshold quantity that was less than one. Hence the effective reproduction number was bounded above by that quantity. Therefore having the reproduction number to be less than one is therefore no longer sufficient in driving the epidemic to zero; the effective reproduction number has to be strictly less than the threshold quantity bounding it.

Exogenous re-infection plays a role in hampering the use of the reproduction number for TB control, especially with disease elimination in mind. This is especially so as it induces the phenomenon of backward bifurcation whereby the DFE co-exists with another stable endemic equilibrium when the associated reproduction number is less than unity. We observe that when the exogenous re-infection terms are set to zero and long term immunity was assumed, it is then possible to demonstrate that the DFE of the modified mathematical model will be globally asymptotically stable whenever the associated reproduction number is less than unity while the endemic equilibrium was shown to be globally asymptotically stable whenever it exists and the associated reproduction number is greater than unity.

A more theoretical result to further demonstrate the effect of exogenous re-infection on the dynamics of TB with regards to inducing a backward bifurcation can be shown using the Center Manifold Theorem [3, 20]. However we have shown from this work that having the associated reproduction number bounded by a threshold quantity less than unity could suggests the effect of certain key parameters on the global behaviour of the DFE and such parameters could cause the system to undergo a backward bifurcation.

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