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A Note on the Global Stability of Equilibria of a Tuberculosis Mathematical Model with Re-treatment

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Abstract

The spread of tuberculosis is studied through a mathematical model that includes re-treatment of previously failed treatments. For the model, Lyapunov functions are used to show that when the basic reproduction number is less than or equal to one, the disease-free equilibrium is globally asymptotically stable. In a special case where disease-induced death is insignificant and where treatments (and re-treatments) were successful, when the associated reproduction number is greater than one, the endemic equilibrium is globally asymptotically stable.

1.0 Introduction

Tuberculosis (TB) has continued to be a health challenge to millions world over, a third of the world's population is infected and about two to three million deaths are recorded each year, especially in developing countries [1]. TB is caused by the bacteria agent, *Mycobacterium tuberculosis*. Individuals infected are initially not infectious and suffer no symptoms even when they test positive on a skin test. In about 10% of all cases, infected individuals progresses from the latent period (which could last several years or decades) to the infectious, symptomatic stage of the disease[1,2].

A global control strategy adopted by the WHO to help reduce the number of active TB cases as well as promote proper treatment of patients with tuberculosis is the Direct Observation Therapy Strategy (DOTS). Non-adherence to treatment of TB results in resurgence of resistance strains, making it even more difficult to cure. DOTS have evolved into a strategy that makes it compulsory for patients to complete their treatment. The DOTS program uses a nurse or surrogate who delivers and supervises the patients taking all the doses of their drugs rather than relying on the patients to take the drugs on their own [3].

In Okuonghae [4], a mathematical model was presented that investigate the effect of re-treatment (after a previous treatment failed) on the dynamics of the disease in a population. The model includes treatment strategies that employs both DOTS and non-DOTS methods. While the work includes global analysis for the disease-free equilibrium (DFE) for the sub-models carved out of the main model (as well as include local stability analysis of the endemic equilibrium), the work in Okuonghae [4] did not consider the global properties of the DFE of the complete model and any global study of the endemic equilibrium, even for special cases.

In this work, the global dynamics of the complete model in Okuonghae [4] (the DFE and a special case of the endemic equilibrium) are resolved through the use of Lyapunov functions. Establishing global properties of a dynamical system is generally not a trivial problem. The most successful approach to the problem is the direct Lyapunov method [5]. However, the method requires an auxiliary function with specific properties, a Lyapunov function, which is not easy to find [6].

The Lyapunov function used in this paper to demonstrate the stability of theendemic equilibria(in the special case) is of the Goh-Volterra type as those used in Gumel [7] and Melesse and Gumel [8]. A similar Lyapunov function was used in Goh [9] and Takeuchi [10] to study Lotka-Volterra systems for predator-prey interactions.

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2.0 DOTS Model with Re-treatment

Consider a population with population size $N(t)$ divided into subpopulations based on epidemiological status; individuals are classified as susceptible, $S(t)$;latent (exposed), $E(t)$; infectious, $I(t)$;first treatment $T_1(t)$; re-treated, $T_2(t)$.

Let Λ be the recruitment rate into the susceptible class, which could include immigrants and/or newborns that are uninfected and assume that μ is the per capita natural mortality rate for all individuals in the population. Let β_1 and β_2 be the transmission rates of the disease amongst the susceptible and treated individuals, respectively. 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 $0 \le \beta_2 \le \beta_1$.Assume that the rate at which latent individuals progress to the active TB case is k or gets treated at the rate r_0. Also, let q be the fraction of active cases treated under DOTS while n_1 is the fraction of these that were successfully treated while $\boldsymbol{p = 1 - q}$is the fraction of active cases treated under non-DOTS program while n_2 is the fraction of these that were successfully treated. Assume further that r_1 is the treatment rate for the infectious individuals, $\boldsymbol{m}$is the fraction of the retreated cases that were successful and d be the disease-induced death rate. In this formulation, we assumed that exogenous re-infection is negligible and most infections in the population do not progress quickly to the infectious stage (hence the need to neglect fast progression in the dynamics).

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

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 SI/N - \mu S, \\
\frac{dE}{dt} &= (\beta_1 S + \beta_2(T_1+T_2))I/N - (k+\mu+r_0)E + (1-m)(1-n_1)qr_1 I \\
&\quad + (1-n_2)pr_1 I, \\
\frac{dI}{dt} &= kE - (d+\mu+r_1)I, \\
\frac{dT_1}{dt} &= r_0 E + n_1 qr_1 I + n_2 pr_1 I - \mu T_1 - \beta_2 T_1 I/N, \\
\frac{dT_2}{dt} &= m(1-n_1)qr_1 I - \mu T_2 - \beta_2 T_2 I/N,
\end{aligned} \qquad (1)$$

where $0 \le n_1 \le 1, 0 \le n_2 \le 1, 0 \le m \le 1, p = 1-q, and\ N = S+E+I+T_1+T_2$.

The behaviour of the system (1) was studied in Okuonghae [4], but the global stability of the disease-free and endemic equilibria was not treated; we resolve them here.

Let us set $\beta_1 = \beta_2 = \beta$ whereby the susceptible and the treated have an equal transmission amongst them.

Using the next generation matrix approach [11], the basic reproduction number for system (1) is

$$R_0 = \frac{k\beta}{(d+\mu+r_1)(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)}.$$

The threshold quantity R_0 represents the average number of secondary cases generated by a typical infected individual in a susceptible population in the presence of treatment.

Under the flow described by (1), the region $\mathcal{A} = \{(S,E,I,T_1,T_2) \in \mathbb{R}^5_{\ge 0}, S+E+I+T_1+T_2 \le \frac{\Lambda}{\mu}\}$is positively invariant.

For $R_0 \le 1$, the only equilibrium is the disease-free equilibrium (DFE) $Q_0 = (\Lambda/\mu, 0, 0, 0, 0)$ in $\mathcal{A}$. For $R_0 > 1$, Q_0 is present as is an additional equilibrium $Q^* = (S^*, E^*, I^*, T_1^*, T_2^*)$ in $\mathcal{A}$ with $S^*, E^*, I^*, T_1^*, T_2^* > 0$. Any solution which has an initial condition in $\mathbb{R}^5_{\ge 0}$for which $E^* + I^* + T_1^* + T_2^*$is positive immediately moves into the interior of the positive orthant. On the other hand, if the initial condition in $\mathbb{R}^5_{\ge 0}$satisfies $E^* = I^* = T_1^* = T_2^* = 0$, then the solution limits to Q_0

3.0 Global stability of Q_0 for $R_0 \le 1$

We claim the following:

Theorem 1. ***The disease free equilibrium*** Q_0***, of the model (1), is globally asymptotically stable on*** $\mathbb{R}^5_{\ge 0}$ ***if*** $R_0 \le 1$.

Proof: Consider the linear Lyapunov function

$$U = kE + (k+\mu+r_0)I$$

Differentiating U with respect to time (where dot indicates differentiation with respect to time) gives,

$$\begin{aligned}\dot{U} &= k\dot{E} + (k+\mu+r_0)\dot{I} \\ &= k\beta(S+T_1+T_2)I/N - [(d+\mu+r_1)(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)]I.\end{aligned}$$

Since $\frac{(S+T_1+T_2)}{N} \le 1$ in $\mathcal{A}$, we then have that

$$\begin{aligned}\dot{U} &\le k\beta I - [(d+\mu+r_1)(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)]I \\ &= [(d+\mu+r_1)(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)]I \times \\ &\quad \left[\frac{k\beta}{(d+\mu+r_1)(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)} - 1\right] \\ &= [(d+\mu+r_1)(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)]I(R_0 - 1)\end{aligned}$$

Clearly $\dot{U} \le 0$ when $R_0 \le 1$ with equality only at Q_0 i.e. when $I = 0$. Hence by the LaSalle's Invariance Principle [12], $\big(E(t), I(t), T_1(t), T_2(t)\big) \to (0,0,0,0)$ as $t \to \infty$.

So the limit set of each solution is contained in the largest invariant set for which $I = 0$, this being the singleton $\{Q_0\}$.

4.0 Global Stability of Q^* For Special Case.

Consider the model (1) with $d = 0,\ \beta_2 = 0, m = n_2 = 1$. In this special case, we assume that the population has a small proportion of disease-induced deaths and that treatments (and re-treatments of failed treatments) are successful with the treated classes now removed from the transmission process by reason of, say, awareness or some form of 'isolation'.

Now we observe that with $d = 0$, $N \to \frac{\Lambda}{\mu}$ as $t \to \infty$. Let $N = \frac{\Lambda}{\mu}$ and $\tilde{\beta} = \frac{\beta\mu}{\Lambda}$ so that the force of infection now becomes

This then reduces model (1) to $\lambda = \tilde{\beta}IS$

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - \tilde{\beta}SI - \mu S, \\ \frac{dE}{dt} &= \tilde{\beta}SI - (k+\mu+r_0)E \\ \frac{dI}{dt} &= kE - (\mu+r_1)I, \\ \frac{dT_1}{dt} &= r_0E + n_1qr_1I + pr_1I - \mu T_1 \\ \frac{dT_2}{dt} &= (1-n_1)qr_1I - \mu T_2\end{aligned} \qquad (2)$$

and the associated reproduction number now becomes

$$R_{0d} = \frac{k\beta}{(\mu+r_1)(k+\mu+r_0)}.$$

Further, let

$$\mathcal{A}_0 = \{(S,E,I,T_1,T_2) \in \mathcal{A}: E = I = T_1 = T_2 = 0\}.$$

We claim the following:

Theorem 2. ***The endemic equilibrium of the model (2) is globally asymptotically stable in $\mathcal{A}\backslash\mathcal{A}_0$ whenever $S^*, E^*, I^*, T_1^*, T_2^* > 0$ (which holds when $R_{0d} > 1$) and $d = 0,\ \beta_2 = 0, m = n_2 = 1$.***

Proof: Consider the following non-linear Lyapunov function of the Goh-Volterra type

$$V = S - S^* - S^* \ln\frac{S}{S^*} + E - E^* - E^* \ln\frac{E}{E^*} + \frac{\tilde{\beta}S^*}{\mu+r_1}\left(I - I^* - I^* \ln\frac{I}{I^*}\right).$$

Taking the derivative of V with respect to time (where dot represents differentiating with respect to time), we have

$$\dot{V} = \dot{S} - \frac{S^*}{S}\dot{S} + \dot{E} - \frac{E^*}{E}\dot{E} + \frac{\tilde{\beta}S^*}{\mu+r_1}\left(\dot{I} - \frac{I^*}{I}\dot{I}\right).$$

Substituting the expressions for the derivatives in (2) into the derivative of the Lyapunov function, we now have

$$\dot{V} = \Lambda - \tilde{\beta}SI - \mu S - \frac{S^*}{S}[\Lambda - \tilde{\beta}SI - \mu S] + \tilde{\beta}SI - (k+\mu+r_0)E - \frac{E^*}{E}[\tilde{\beta}SI - (k+\mu+r_0)E] \quad (3)$$
$$+ \frac{\tilde{\beta}S^*}{\mu+r_1}[kE - (\mu+r_1)I] - \frac{\tilde{\beta}S^*}{\mu+r_1}\frac{I^*}{I}[kE - (\mu+r_1)I].$$

Observe from (2) that, at steady state,

$$\Lambda = \tilde{\beta}S^*I^* + \mu S^*, \quad (k+\mu+r_0) = \frac{\tilde{\beta}S^*I^*}{E^*}, \quad (\mu+r_1) = \frac{kE^*}{I^*} \quad (4)$$

Substituting the expressions in (4) into (3), and after several algebraic manipulations, we have

$$\dot{V} = \mu S^*\left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) + 3\tilde{\beta}S^*I^* - \tilde{\beta}\frac{(S^*)^2}{S}I^* - \tilde{\beta}SI\frac{E^*}{E} - \tilde{\beta}S^*\frac{(I^*)^2}{I}\frac{E}{E^*}$$
$$= \mu S^*\left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) + \tilde{\beta}S^*I^*\left(3 - \frac{S^*}{S} - \frac{SIE^*}{S^*I^*E} - \frac{I^*E}{IE^*}\right)$$

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

$$\left(2 - \frac{S}{S^*} - \frac{S^*}{S}\right) \le 0, \quad \left(3 - \frac{S^*}{S} - \frac{SIE^*}{S^*I^*E} - \frac{I^*E}{IE^*}\right) \le 0.$$

Thus $\dot{V} \le 0$ for $S^*, E^*, I^*, T_1^*, T_2^* > 0$ (which holds when $R_{0d} > 1$). Hence V is a Lyapunov function in $\mathcal{A}$ and it follows by the LaSalle's Invariance Principle [12], that every solution to the equations of the model (2), and initial conditions in $\mathcal{A}\backslash\mathcal{A}_0$ approaches the associated endemic equilibrium Q^*, of the model as $t \to \infty$.

5.0 Conclusion

The global stability of the disease-free equilibrium and a special case of the endemic equilibrium for system (1) has now been resolved. If $R_0 \le 1$, then each solution limits to the disease-free equilibrium; the disease dies out of the population. If $R_{0d} > 1$, then there is a unique endemic equilibrium (for the special case where disease-induced death is insignificant) which is globally asymptotically stable among all states for which the disease is present; if disease is present in the population, then it will persist.

The use of Lyapunov functions in proving the global stability of dynamical systems is generally not a trivial exercise. We leave it as future work to examine the global stability of the endemic equilibrium for the complete system (1); applying the technique outlined above to deal with mathematical models with frequency dependent incidence (as used in model (1)) is generally challenging.

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