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Bifurcation Analysis of a Vaccination Model of Tuberculosis Infection

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Abstract: In this paper, we extend the model of Blower et al. [1] by incorporating certain infection terms such as vaccinated individuals, treatment rate, waning rate and efficacy rate. A bifurcation analysis is performed on the vaccination model by applying a bifurcation method based on the use of center manifold theory. We determine threshold values and derive sufficient conditions for both forward and backward bifurcations. Numerical simulations were carried out and bifurcation diagrams are presented as supporting evidences of our analytical results. The obtained results show the possibility of occurrence of forward and backward bifurcations even when the basic reproduction number is less than one so that it is now possible for the disease to exist. These results suggest the need for more study on the qualitative biological mechanisms responsible for backward bifurcation.

Keywords: Mathematical Models, Tuberculosis, Bifurcation, Vaccination, Center Manifold Theory, Stability

1. Introduction

In analysing disease transmission models, studies have shown the existence of forward and backward bifurcations in such models. In a forward bifurcation scenario, as R_0increases through one, a stable disease-free equilibrium loses its stability and a stable endemic equilibrium appears. The behaviour of the bifurcation curve is such that as we travel along it from the bifurcation point, the level of infection increases as R_0increases. Many epidemic models that exhibit forward bifurcation can be found in the literature [2]. The phenomenon of backward bifurcation is characterised by multiple endemic equilibria due to the decrease in R_0 as the level of infection increases. In other words, a stable disease-free equilibrium coexists with one or more stable endemic equilibria for $R_0 < 1$. This pattern has been noted in numerous models like multi-group models [3], immunity models [4], vaccination models [5], core group models [6] and treatment models [7].

Over the last decade, several papers have appeared dealing with a wide range of models that have the potential for exhibiting forward and backward bifurcations.

The model by Sharomi et al [8] studied the presence of backward bifurcation in some HIV vaccination models with standard incidence function. The authors noted that vaccine-induced backward bifurcation in some HIV models with standard incidence can be removed by using mass action incidence. As a result, the presence or absence of standard incidence may be crucial to the presence or absence of backward bifurcation in HIV vaccination models.

In [9], the existence of backward bifurcation in a discrete SIS model with vaccination was investigated. It was found that backward bifurcation may occur if the lumped parameter $R_{vac} = 1$. The disease can persist for $R_{vac} > 1$ and can be eradicated for $R_{vac} < 1$ if a forward bifurcation occurs at $R_{vac} > 1$. However, the disease may persist even when $R_{vac} < 1$ if a backward bifurcation occurs at $R_{vac} = 1$.

Greenhalgh and Griffiths [4] discussed the phenomenon of backward bifurcation in a three-stage model for Bovine Respiratory Syncytial Virus (BRSV) in cattle. It was shown that the 3-stage model undergoes backward bifurcation for small b, where b is the common per capital birth and death rate. Several bifurcation diagrams are obtained by fixing some of the parameter values for BRSV while varying the others.

The existence of backward bifurcation in the West Nile Virus (WNV) compartmental models has been investigated in [10]. In

their analysis, the authors found that it is the higher mortality rate of the host birds due to WNV infection that determines the occurrence of backward bifurcation.

Buonomo and Lacitignola [5] stressed the importance of a nonlinear incidence rate and an imperfect vaccine in the occurrence of backward bifurcation. A bifurcation analysis of the model shows the conditions ensuring the presence of either forward or backward bifurcation.

In [11], a deterministic model of TB without and with seasonality was developed. The objective of the authors was to study the presence of backward bifurcation in the model. They observed the existence of backward bifurcation when the basic reproduction number is less than unity. The authors concluded that the backward bifurcation scenario is caused by the re-infection of latently infected individuals with the TB disease.

Li and Cui [12] investigated the behaviour of a discrete-time SIS model with nonlinear incidence rate. The theoretical analysis and numerical simulations of the model demonstrated that the model exhibits a variety of dynamical behaviours such as backward bifurcation, hopf bifurcation, flip bifurcation and chaos.

2. Extension and Modification of Blower Model

In 1995, Blower et al proposed a model of TB infection dynamics consisting of three disease states namely susceptibles (S), latently infected (L) and infected (I). The model is given by the following set of 1st-order differential equations

$$S' = \pi - \beta IS - \mu S \tag{2.1}$$

$$L' = (1-\rho)\beta IS - (\mu + v)L \tag{2.2}$$

$$I' = \rho\beta IS + vL + (\mu + \mu_T)I \tag{2.3}$$

where

μ = natural death rate
π = recruitment rate of susceptible individuals
μ_T = death rate due to TB
v = rate of slow progression
ρ = rate of fast progression
β = transmission rate.

The authors perform a qualitative analysis on the model and one of their main results is that the disease-free equilibrium (DFE) is globally asymptotically stable if $R_0 < 1$ while the endemic equilibrium is unstable when $R_0 > 1$. However, disease control measures such as vaccination and certain infection terms that play vital role in TB dynamics was not included in the system and consequently bifurcation analysis was not discussed. For this reason, we extend the model in [1] to include infection parameters such as vaccination (V), waning rate (q), treatment rate (s), proportion of recruitment due to immigration (γ), proportion of immigrants that are vaccinated (n) and efficacy rate of vaccine (f_1, f_2).

The proposed vaccination model is given by

$$S' = (1-\gamma)(1-n)\pi + sI - \beta IS - \mu S \tag{2.4}$$

$$V' = n(1-\gamma)\pi - qV - (1-f_1)\beta IV - \mu V \tag{2.5}$$

$$I' = \rho\beta IS + \rho(1-f_1)(1-f_2)\beta IV + (\mu + \mu_T + s)I \tag{2.6}$$

All the parameters are positive constants with the following interpretations S, V, I denotes the compartments of susceptible, vaccinated and infected individualsrespectively.

s denotes treatment rate
q denotes rate of waning of vaccine
γ denotes proportion of recruitment due to immigration
n denotes proportion of immigrants that are vaccinated
f_1 denotes efficacy rate of vaccine in protecting against initial infection
f_2 denotes efficacy rate of vaccine in slowing down progression to active TB

All other parameters are as defined in [1].

The vaccination model (2.4) - (2.6) shall be investigated for existence of forward and backward bifurcations. We derive conditions, in terms of the parameters of the model that ensure that either forward or backward bifurcation occurs. We apply bifurcation method introduced in [13] which is based on the use of center-manifold theory. In addition, we present a detailed numerical verification of the results obtained for both forward and backward bifurcations. Bifurcation diagrams are presented as supporting evidences of our analytical results.

3. Equilibrium Points and Local Stability

Model (2.4) - (2.6) has a disease-free equilibrium $A_0 = (S, V, I)$ given by

$$A_0 = \left(\frac{(1-\gamma)(1-n)\pi}{\mu} \quad \frac{n(1-\gamma)\pi}{\mu+q}, 0\right) \tag{3.1}$$

The endemic equilibrium point $A^* = (S^*, V^*, I^*)$ is such that

$$S^* = \frac{n\pi\rho(1-f_1)(1-f_2)(1-\gamma)}{q+(1-f_1)(\beta-\mu)(1-s\beta)} \tag{3.2}$$

$$V^* = \frac{n(1-\gamma)(1-s\beta)\pi}{q+(1-f_1)\beta-u} \tag{3.3}$$

$$I^* = \frac{n\pi\mu(1-f_1)(1-f_2)-(1-\gamma)(1-n)\pi}{(1-s\beta)(q+\beta-s-\mu)} \tag{3.4}$$

Using the technique developed in [14] for calculating R_0, the R_0 for the vaccination model (2.4) - (2.6) was calculated as

$$R_0 = \frac{\beta[(1-n)+q]\pi(1-f_1)(1-f_2)}{\mu(\mu+q)(\mu+s)} \tag{3.5}$$

Now, we focus on the disease-free equilibrium A_0 and investigate the occurrence of transcritical bifurcation at $R_0 = 1$.

The Jacobian matrix of (2.4) - (2.6) evaluated at the disease-free equilibrium A_0 is given by

$$J(A_0) = \begin{bmatrix} -\mu & 0 & s \\ 0 & -q-\mu & -(1-f_1)\beta \\ 0 & 0 & \mu+\mu_T+s \end{bmatrix} \tag{3.6}$$

so that the eigenvalues λ are real and given by $\lambda_1 = -\mu, \lambda_2 = -(\mu+q), \lambda_3 = \mu + \mu_T + s$ .At the bifurcation $R_0 = 1$, we have

$$R_0 = 1 \Leftrightarrow s = s^* = \frac{\beta[\mu(1-n)+q]\pi(1-f_1)(1-f_2)-\mu(\mu+q)}{\mu(\mu+q)} \quad (3.7)$$

It follows then that the disease-free equilibrium A_0 is locally stable when $s < s^*$ whereas it looses its stability when $s > s^*$.

4. Bifurcation Analysis

We will make use of Theorem A in [13] for the bifurcation analysis of the model system (2.4) - (2.6). The theorem prescribes the role of the coefficients a and b of the normal form representing the system dynamics on the center manifold in decending the direction of the transcritical bifurcation occurring at $\phi = 0$. More precisely, if $a < 0$and $b > 0$, then the bifurcation is forward, if $a > 0$ and $b > 0$, then the bifurcation is backward.

Let us consider a general system of ODE's with a parameter ϕ:

$$x = f(x, \phi), f: R^n \times R \to R^n, f \in C^2(R^n \times R) \quad (B1)$$

Without loss of generality, we assume that $x = 0$ is an equilibrium for $(B1)$

Theorem 1[13]

Assume

(I) $A = D_x f(0,0)$ is the linearization matrix of system (B1) around the equilibrium $x = 0$ with ϕ evaluated at 0. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;

(II) Matrix A has a (nonnegative) right eigenvector w and a left eigenvector v corresponding to the zero eigenvalues.

(III) Let f_k denotes the k^{th} component of f and

$$a = \sum_{k,v,j=1}^{n} v_k, w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), b = \sum_{k,i=1}^{n} v_k, w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0), \quad (4.1)$$

Then the local dynamics of system $(B1)$ around $x = 0$ are totally determined by $a$and b.

(i) $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1, x = 0$ is locally asymptotically stable and there exists a positive unstable equilibrium $0 < \phi \ll 1, x = 0$ is unstable and there exists a negative and locally asymptotically stable equilibrium;

(ii) $a < 0, b < 0$. When $\phi < 0$, with $|\phi| \ll 1, x = 0$ is unstable; when $0 < \phi \ll 1, x = 0$ is locally asymptotically stable and there exists a positive unstable equilibrium;

(iii) $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1, x = 0$ is unstable and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1, x = 0$ is stable and a positive unstable equilibrium appears;

(iv) $a < 0, b > 0$ When ϕ changes from negative to positive, x=0 changes its stability from stable to unstable.

Correspondingly, a negative unstable equilibrium becomes positive and locally asymptotically stable.

Now, we investigate the nature of the bifurcation involving the disease-free equilibrium A_0 at $R_0 = 1$. We apply Theorem 1 to show that model system (2.4) - (2.6) may exhibit a backward bifurcation when $s = s^*$.

We now consider the Jacobian matrix $J(A_0, s^*)$ written as

$$J(A_0, s^*) = \begin{bmatrix} -\mu & 0 & \frac{\beta[\mu(1-n)+q](1-f_1)(1-f_2)-\mu}{\mu(\mu+q)} \\ 0 & -q-\mu & -(1-f_1)\beta \\ -\mu & 0 & \left[\frac{\beta[\mu(1-n)+q](1-f_1)(1-f_2)-\mu_T}{\mu(\mu+q)}\right] \end{bmatrix} \quad (4.2)$$

Here, the eigenvalues of the above matrix are given by:

$$\lambda_1 = -\mu;\ \lambda_2 = -\mu - q;\ \lambda_3 = 0.$$

Thus, $\lambda_3 = 0$ is a simple zero eigenvalue and the other eigenvalues are real and negative. Hence, when $R_0 = 1$ (or equivalently $s = s^*$), the DFE A_0 is a nonhyperbolic equilibrium and the assumption (B1) of Theorem A is thus verified.

We denote by $w = (w_1, w_2, w_3)^T$ a right eigenvector associated with the zero eigenvalue $\lambda_3 = 0$.Then, it follows that

$$\left.\begin{aligned} -\mu w_1 + \left[\frac{\beta[\mu(1-n)+q](1-f_1)(1-f_2)}{\mu(\mu+q)} - \mu\right] w_3 = 0 \\ (-q-\mu)w_2 - (1-f_1)\beta w_3 = 0 \\ \left[\frac{\beta[\mu(1-n)+q](1-f_1)(1-f_2)}{\mu(\mu+q)} + \mu_T\right] w_3 = 0 \end{aligned}\right\} \quad (4.3)$$

Solving eqn (4.3) for w_1, w_2, w_3, we obtain

$$w = \left(-q-\mu, \frac{(1-f_1)\beta\mu^2(\mu+q)}{\beta[\mu(1-n)+q](1-f_1)(1-f_2)-\mu(\mu+q)}, 1\right)^T \quad (4.4)$$

We now consider the left eigenvector $v = (v_1, v_2, v_3)^T$ satisfying $v.w = 0$:

$$\left.\begin{aligned} -\mu v_1 = 0 \\ (-q-\mu)v_2 = 0 \\ -(1-f_1)\beta v_2 - \frac{[v_3\mu(\mu+q)]\mu_T + v_2(1-f_1)(1-f_2)}{\mu(\mu+q)} + \mu_T = 0 \end{aligned}\right\} \quad (4.5)$$

By solving (4.5), we have$v_1 = v_2 = 0$ and with $v_3 = 1$, the left eigenvector $v$is thus given by

$$v = (0, 0, 1)^T \quad (4.6)$$

We now compute the coefficient a and b defined in Theorem A.Taking into account system (2.4) - (2.6) and

considering only the nonzero components of the left eigenvector v, then from (4.1) we have

$$a = v_3 w_1^2 \frac{\partial^2 f_3}{\partial S^2}(A_0, s^*) + 2v_3 w_1 w_2 \frac{\partial^2 f_3}{\partial S \partial V}(A_0, s^*) + 2v_3 w_1 w_3 \frac{\partial^2 f_3}{\partial S \partial I}(A_0, s^*) + v_3 w_2^2 \frac{\partial^2 f_3}{\partial V^2}(A_0, s^*) + 2v_3 w_2 w_3 \frac{\partial^2 f_3}{\partial S \partial I}(A_0, s^*) + v_3 w_3^2 \frac{\partial^2 f_3}{\partial I^2}(A_0, s^*) \quad (4.7)$$

and

$$b = v_3 w_1 \frac{\partial^2 f_3}{\partial S \partial s}(A_0, s^*) + v_3 w_2 \frac{\partial^2 f_3}{\partial S \partial s}(A_0, s^*) + v_3 w_3 \frac{\partial^2 f_3}{\partial I \partial s}(A_0, s^*) \quad (4.8)$$

where

$$\left.\begin{aligned} f_1 &= (1-\gamma)(1-n)\pi + sI - \beta IS - \mu S \\ f_2 &= n(1-\gamma)\pi - qV - (1-f_1)\beta IV - \mu S \\ f_3 &= \rho\beta IS + \rho(1-f_1)(1-f_2)\beta IV + (\mu + \mu_T + s)I \end{aligned}\right\} \quad (4.9)$$

By substituting (4.4), (4.6) and (4.9) into (4.7)-(4.8), we get

$$a = -2\rho\beta(\mu + q)a_0, b = \frac{\beta[\mu(1-n)+q]\pi(1-f_1)(1-f_2)}{\mu(\mu+q)} \quad (4.10)$$

where

$$a_0 = \frac{1-\mu(1-f_1)^2(1-f_2)^2\beta\mu^2}{\beta[(1-n)+q](1-f_1)(1-f_2)-\mu(\mu+q)} \quad (4.11)$$

Since the coefficient b is always positive, it is the sign of the coefficient a and consequently the sign of the quantity a_0 which determines the local dynamics of the disease around the disease-free equilibrium for $R_0 = 1$. For our vaccination model to exhibit a forward bifurcation, $b > 0$ and a_0 (as defined in (4.11) must be positive so that condition $a < 0$ will be satisfied. In the backward bifurcation situation, the sign of a_0 must be negative for the quantity $a > 0$. For numerical verification of the results in (4.10) and (4.11), we consider the following parameter values for both forward and backward bifurcations.

Forward bifurcation

Parameter values are chosen as follows:

$\beta = 0.00006, q = 0.0013, f_1 = f_2 = 0.05, n = 0.3, \pi = 0.001\ \mu = 0.01$.Using these numerical values, $a_0 = 8.884 \times 10^3$ which is greater than zero. Hence, $a > 0$. We calculate $b = 6.977 \times 10^{-1} > 0$.As a consequence, system (2.4) – (2.6) exhibits a forward bifurcation.

Backward bifurcation

To verify the condition $a > 0, b > 0$ required for backward bifurcation, the following parameter values are considered: $\mu = 0.01, f_1 = f_2 = 0.01, q = 0.004, n = 0.2, \pi = 0.003, \beta = 0.03$.Then, using (4.10) and (4.11), $b = 7.561 \times 10^{-1} > 0, a_0 = -62.035 < 0$ and consequently $a > 0$ in view of (4.10).

Next, we investigate the role specifically played by treatment (s), transmission (β), waning (q) and efficacy (f_1, f_2) parameters in the occurrence of forward or backward bifurcation. To achieve this, we present bifurcation diagrams in figures 1-2.

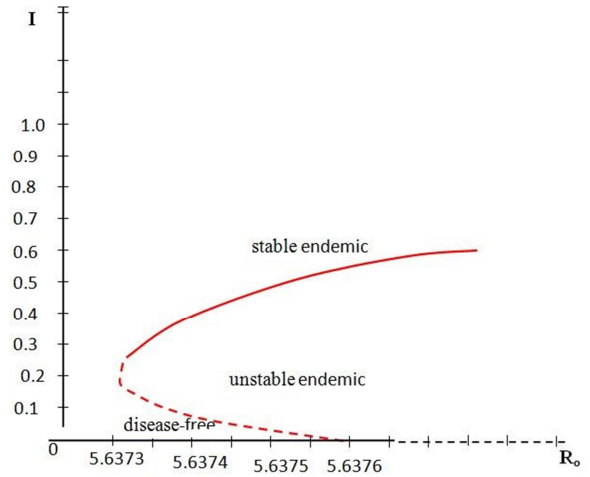

Fig. 1. *Bifurcation diagram in the plane (R_0, I) for the case $s = 0.24$.*

The bifurcation parameter.is the basic reproduction numberR_0. The solid lines denote stability while the dashed lines denoteinstability. The numerical values for other parameters are as follows:

$$\mu = 0.01, n = 0.006, q = 0.5, \pi = 0.009, f_1 = f_2 = 0.03, \beta = 1.5.$$

Using these values, $R_0 = 5.6376$ $and\ s^* = 0.19$. Hence, $s > s^*$ and the model undergoes a backward bifurcation.

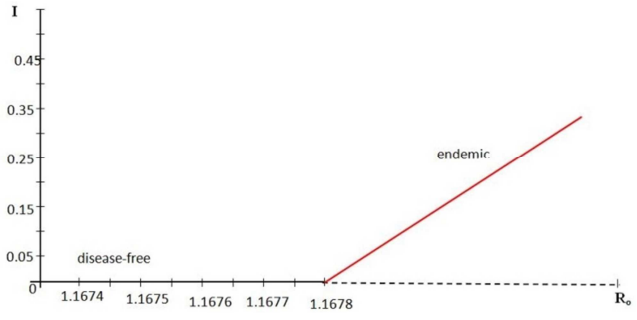

Fig. 2. *Bifurcation diagram in the plane (R_0, I).*

The solid lines denote stability while the dashed linesdenoteinstability. Parameter values are $\mu = 0.01, n = 0.001, q = 0.039, \pi = 0.009, f_1 = f_2 = 0.6, \beta = 0.05, s = 0.07$.system (2.4)- (2.6) exhibits a forward bifurcation. The bifurcation value is $R_0 = 1.1678$.

5. Results and Discussions

We have performed a bifurcation analysis on our vaccination model described in (2.4) - (2.6) by applying the bifurcation method which is based on the use of center manifold theory. Conditions ensuring the occurrence of forward or backward bifurcations are derived. For forward bifurcation, the criterion $a < 0$ and $b > 0$ is required where a and b are both given by conditions (4.10) - (4.11). In the case of backward bifurcation scenario, the condition $a > 0$, $b > 0$ must be satisfied. The two qualitative conditions are numerically verified using realistic parameter values of the model. The obtained results validated the bifurcation conditions.

In addition, numerical simulations show that the existence of a certain kind of bifurcation critically depends on the interplay among the four biological parameters explicitly included in the model. These are treatment (s), waning (q), transmission (β) and efficacy (f_1, f_2) parameters. If the therapeutic treatment (s) is above a certain threshold value $s^* with$ a high transmission rate, a mediocre efficacy rate and a waning rate $q > 0$, the model exhibits a backward bifurcation. Figure 1 depicts this situation. Our analysis further reveals that if transmission parameter β is sufficiently small, treatment rate lies below a certain threshold and an intermediate vaccine efficacy the bifurcation is forward. The bifurcation diagram describing this situation is shown in figure 2.

6. Conclusion

One of the major undertakings of modeling is to explore the backward bifurcations in the model. This is because in a backward bifurcation, disease elimination is no longer feasible for $R_0 < 1$. Since the phenomenon of backward bifurcation is possible in our proposed model, we perform bifurcation analysis, where we determine threshold values and obtain conditions for both forward and backward bifurcations. Some numerical simulations were performed to verify our analytical results. From the results, the transmission rate must be sufficiently small, treatment rate must lie below a certain threshold value and an intermediate vaccine efficacy in order to have a forward bifurcation. A backward bifurcation requires a high transmission rate, a mediocre vaccine efficacy and a treatment rate which must lie above a certain threshold value.

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