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Article *in* Asian Research Journal of Mathematics · January 2019

DOI: 10.9734/ARJOM/2019/45821

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12(1): 1-12, 2019; Article no.ARJOM.45821
ISSN: 2456-477X

Attempt to Model Tuberculosis with the Effects of Both Treatment and Case Detection

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ARJOM/2019/45821
Editor(s):
(1) Dr. William Chin, Professor, DePaul University, Chicago, USA.
Reviewers:
(1) Shaibu Osman, Catholic University of Eastern Africa, Kenya.
(2) Tony Spiteri Staines, University of Malta, Malta.
Complete Peer review History: http://www.sdiarticle3.com/review-history/45821

Original Research Article

Received: 17 October 2018
Accepted: 07 January 2019
Published: 21 January 2019

Abstract

Tuberculosis (TB) is an infectious disease that usually affect the lungs. It is caused by bacteria and spread through the air. Due to the high rate of spread and later leads to death due to TB, this led to formulation of a model in order to enlighten the public and health department at large of its effects. A non-linear mathematical model (NLMM) of TB with the effect of case discovery and treatment was formulated and analyzed. The population under study was divided into four compartments namely susceptible (S), exposed (E), infected(I) and recovered (R). S individuals move to E class or once they come into contact with an infected person and this is usually based on immunity level of an individual. This is incorporated through progression rate which could be quick or slow. The basic reproduction number (R_o) and an equilibrium of the model were computed. It was found out that the disease-free equilibrium of the model is locally asymptotically stable when $R_o < 1$. The model exhibits backward bifurcation (BB) under certain constraints on parameters, which results to existence of multiple endemic equilibrium for $R_o < 1$. This tells that an accurate estimation of parameters and the level of curb measures are required to lower the infection prevalence of TB regions where it is common and just not enough to get rid of the disease

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from the population. R_o needs to be highly reduced to confirm the global stability of the disease free-equilibrium. Numerical simulations (NS) was done using MATLAB software to graphically illustrate the effect of case discovery, detection and treatment of TB infection. It was found that the rise in the rate of case detection shifts the BB diagram towards right which led in the rise of the threshold value of R_o. It was also shown that the equilibrium level of infective population reduces when infective population is subjected to treatment. NS were carried out to support the analytic results. This project intends to help the heath sector and Kenyans at large to seek tests and treatment earlier so as to minimize the death rate.

Keywords: Mycobacterium tuberculosis; basic reproduction number; mathematical model; case detection; stability and simulation.

1 Introduction

Tuberculosis (TB) is an infectious disease that usually affect the lungs. It is caused by bacteria and spread through the air. The prevalence of TB worldwide has been declining due to control measures (strategies) and Vaccination [1,2]. However, there is a renewed research that is sparked by the reappearance of new infection of TB with high burden of infection in regions of Southeast Asia [1]. According WHO [3], TB is one of the major common cause of death in developing countries from infectious diseases e.g. HIV/ AIDS. This disease is treatable and curable, although more than 1.5 million deaths are reported each year. The recent report also indicates that it is impossible to have total eradication of the disease because it is hard to develop an effective vaccine, expensive, time consuming during diagnostic process and long period of time the infected person is subjected on treatment [3,4]. According to Athithan and Ghosh [5] a lot of TB infected individuals are not aware of their infection and they easily transmit disease once they come in contact susceptible individual. Sometime the patient may fail to complete the dose when undermedication and go back to work and this often cause new TB infection to people surrounding them. However, Humphrey [4] in his research point out that case discovery, detection and proper treatment are crucial in curbing the transmission of TB.

TB death occur mostly in less and middle-income countries. Mycobacterium TB has been known to be causative agent that normally causes spread and growth of TB in human [1,5]. This bacteria agent often targets the lungs, but it can strike any other parts of the body organs such as spines, kidney and brain. This disease normally cause death when not properly treated. If the examination of TB (especially respiratory TB) is delayed, postponed or the patient subjected to poor/ inadequate treatment of cases with latent TB usually result to high infection prevalence of this disease in endemic [4,5]. Naresh and Pandey [1] pointed out that human beings are the natural reservoir of tuberculosis that spreads from person to person by direct contact (inhaling tubercle bacilli, that are emitted during sneezing, talking or coughing, etc.) by individuals that are infected with TB. In addition, approximately 8-10 million new case of infection of TB occur every year and this figure is growing steadily with the advent of HIV infection [6,7]. The main cause of increase of new infection in developing countries is because of rural migration to city slums, poverty, poor living conditions and food security. However, it is also reported that approximately 8 million people develop active tuberculosis every year where each of which can infect approximately 10-15 people in one year just by breathing [1,7,8]. Overall, the mortality rate from Tuberculosis is about 8%, less than 1% in the young cases and over 30% in the elderly cases according to Naresh and Pandey [1].

Mathematical model (MM) is one of the best and appropriate tools for better understanding of the transmission dynamics of infectious diseases well as control and preventive measures [9-14], including Malaria-TB co-infection, HIV-TB co-infection and co-infection of TB and parasitic disease. For instance, Naresh and Pandey [1] modeled cumulative effect of ecological factors in the habitat on the spread of TB. Naresh and Tripathi [7] studied the co-infection of TB and HIV through modelling in a variable size population. Feng et al. [10] developed a two strain Tuberculosis model and examined the effects of variable periods of latency on the disease transmission dynamics

The recent study also show that low drug efficacy values usually result in extension of treatment period [5]. The findings from Magombedze's model shows that administration of the recommended first three drug regimens usually heal TB infection. It was also found out that TB also spread indirectly by bacterial agent that are emitted by infected individual in the habitat apart from direct contact with infective in the population [5,9].

In MM, we translate our beliefs about how the world functions into the language of mathematics. A model is a quantified simplification of the complex reality. The construction of a model involves the formulation of a hypothesis about the nature of the relationships that exists between the various relevant factors. Its quality depends on the accuracy of its underlying assumptions. Though Tuberculosis is curable death are being reported at a very high rate [3].

The very first epidemiological model was formulated by Daniel Bernoulli in 1760 in order to evaluate the impact of variation on human life expectancy. However, deterministic epidemiology modelling seems to have started in the 20^{th}century when it was formulated and analyzed a discrete time model on measles in 1906, followed by Ross [15] with his work on malaria in 1911.

Li et al. [16] studied the global dynamics of a SEIR model with varying total population size. The model assumes that the local density of the total population is a constant though the total population size may vary with time. They used the homogeneity of the vector field of the model to analyze the derived system of the fractions (S, E, I, R)in determining the behavior of the population sizes (S, E, I, R) and the total population. The global stability is proved by employing the theory of monotone dynamical systems together with a stability criterion for periodic orbits of multidimensional autonomous systems due to Li and Muldowney [16].

In 2006 Magombedze and Mwenje came up with a mathematical model of chemotherapy of human Tuberculosis infection which showed that TB is leads to high infection rate in endemic areas [9].

In 2008 Okhuangahe and Aihie [17] theoretically analyses a case discovery, detection and direct observation therapy strategy in Nigeria. Later in 2010 Bowong et al. [18] with a mathematical model with two differential infectivity. Their result was rejected due to biasness and lack of efficiency.

Although many models have been developed for TB infection most of them have concentrated on transmission dynamics strategies. In this study, we developed a mathematical model (MM) for effects of case discovery and treatment of TB.

Based on the factors in the habitat for spread of TB [1,5,15], the model was formulated by taking into account two major variable that is human and bacteria population. The result obtained using the model were analyzed, discussed and concluded that due bacteria in the environment, an equilibrium level of the infected individuals increases. In addition, the general TB model with two differential infectivity were discussed plus the global properties. The case of discovery, treatment and its effectiveness has been discussed [5,9,18,16]. In the development of the model, compartment model was considered in this case where the population understudy is divided into subclasses S, E, I_1, I_2 and R where $R$is the latent class that arises as result of treatment failure. A standard incidence was considered and it indicated that the system exhibit BB that makes the total elimination of TB very difficult. We therefore, formulated MM as in [1,5] by putting into consideration a simple mass action type incidence. This led to division of population into four subclasses, S, E, I and R making this model a bit much simple and exhibiting all complexities discussed.

2 Model Formulation and Description

Since other models developed were rejected due to biasness and lack of efficiency [1,5,8], to achieve the objective of the study we formulated a mathematical model based on a system of Ordinary Differential Equation for effects case discovery and treatment of TB.

The whole population under study is divided into four different classes i.e. S class, E class, TBinfected (I) class and Rclass ($S \to E \to I \to R$) and discussed both treatment and case detection making it unbiased and effective following closely discussion made by Athithan and Ghosh [5].
The total population (N) under study is given by

$$N_t = S_t + E_t + I_t + R_t \tag{1}$$

Where $S_t, E_t,\ I_t$ and $R_t$is the fractions of the S individuals, the E individuals, the TB infectious individuals and the R (treated) individuals in the population, respectively at time t. Assuming N is varying and homogeneously mixed for instance all people have an equal chance of being infected by the infected individuals with TB in a case of a direct contact. Also, it is assumed that a proportionΨ of I individuals are identified with TB so they are under medication. So, transmission of TB due to this detected TB patients will be less compared to those infected individuals who are not identified with TB. Since immunity level of individuals any given population varies, so it is assumed that a proportion$0 < \phi < 1$ of the individuals with new infection develops TB fast and directly joins infected class whereas $1-\phi$small part of individuals with new infection moves to E class first and then gradually moves to I class. Moreover, if E individuals come intocontact with I individuals, they become infected with TB (infectious). In addition, also E individuals become infected after some time if not treated if there is disease progression. This is illustrated in the transfer diagram of the model described in Fig. 1.

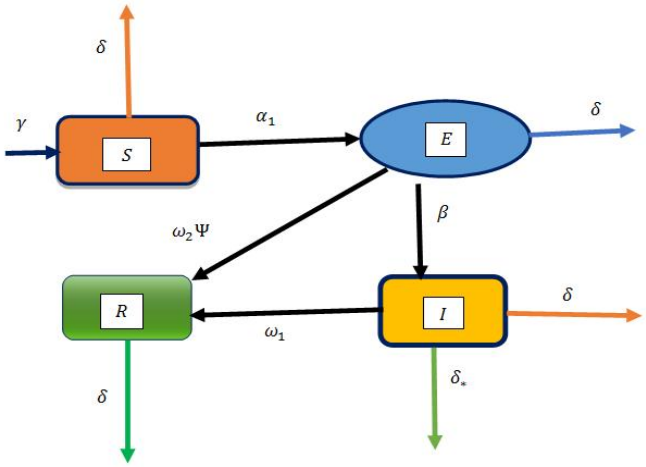

Fig. 1. TB compartmental model

The mathematical model was formulated as follows, keeping the compartmental model above in mind and by putting into consideration simple mass action interaction:

$$\begin{aligned}
S_t^{'} &= \gamma - \delta S - [\alpha_1\Psi + \alpha_2(1-\Psi)]IS \\
E_t^{'} &= (1-\phi)[\alpha_1\Psi + \alpha_2(1-\Psi)]IS - \beta EI - (\delta + \omega_1 + \theta)E \\
I_t^{'} &= \phi[\alpha_1\Psi + \alpha_2(1-\Psi)]IS + \beta EI - (\delta + \delta_* + \omega_2\Psi)I + \theta E \\
R_t^{'} &= \omega_1 E + \omega_2\Psi I - \delta R
\end{aligned} \tag{2}$$

The model (1) is simplified further as follows:

$$\begin{aligned}
S_t^{'} &= \gamma - \delta S - m_0 IS \\
E_t^{'} &= [(1-\phi)m_0 S - \beta E]I - m_1 E \\
I_t^{'} &= [\phi m_0 S + \beta E - m_2]I + \theta E \\
R_t^{'} &= \omega_1 E + \omega_2\Psi I + \theta E
\end{aligned} \tag{3}$$

Where

$m_0 = [\alpha_1\Psi + \alpha_2(1-\Psi)]$
$m_1 = \delta + \omega_2 + \theta,$
$m_2 = \delta + \delta_* + \omega_2\Psi$

The following are parameters used in the compartmental model in Fig. 1 above:

Variable	Definition
γ	The immigration rate of susceptible individuals
δ	The rate at which natural death occurs
δ_*	The rate at which individual die due to infection with TB
Ψ	Case detection / discovery rate
α_1	Rate of transmission of TB
α_2	Rate of transmission of TB (undetermined)
β	Contact rate between exposed and infected class
θ	Rate of progression from exposed to infected class
$\omega_1 \& \omega_2$	The rate at which individuals infected recover from TB due to treatment

Fig. 2. Tables showing parameters and their definition

The model was formulated and depicted as shown above based on the assumption that every patient recovers from diseases since in this study, we could not have a perfect situation.

2.1 Equilibrium analysis

The disease- free equilibrium (DFE) at time $t = 0$ is given as

$$E_0 = (S_0, E_0, I_0, R_0) = \left[\frac{\gamma}{\delta}, 0,0,0\right]$$

The next generation operator method is used to compute disease-free equilibrium E_0 as shown below.

$$W = \begin{pmatrix} 0 & (1-\phi)m_0S_0 \\ 0 & \phi m_0 S_0 \end{pmatrix} \quad \text{and} \quad T = \begin{pmatrix} m_1 & 0 \\ -\theta & m_2 \end{pmatrix}$$

Where W is the matrix that represent new infection terms in the model and T is the matrix with the remaining transfer terms that represent transmission rate of TB [5].

We therefore compute WT^{-1} as

$$WT^{-1} = \begin{pmatrix} \frac{\theta(1-\phi)m_0S_0}{m_1m_2} & \frac{(1-\phi)m_0S_0}{m_2} \\ \frac{\theta\phi m_0 S^0}{m_1m_2} & \frac{\phi m_0 S_0}{m_2} \end{pmatrix}$$

But since $S_0 = \frac{\gamma}{\delta}$ our new matrix becomes

$$\begin{pmatrix} \frac{\theta(1-\phi)m_0\gamma}{\delta m_1m_2} & \frac{(1-\phi)m_0\gamma}{\delta m_2} \\ \frac{\theta\phi m_0\gamma}{\delta m_1m_2} & \frac{\phi m_0\gamma}{\delta m_2} \end{pmatrix}$$

This can further be simplified as

$$\Longrightarrow WT^{-1} = \frac{m_0\phi\gamma}{\delta m_2}\begin{pmatrix} \frac{\theta\left[\frac{1}{\phi}-1\right]}{m_1} & \frac{1}{\phi}-1 \\ \frac{\theta}{m_1} & 1 \end{pmatrix}$$

Hence,R_0 which is the spectral radius of the matrix $WT^{-1}$is given by

$$R_0 = \frac{\gamma m_0[(1-\phi)\theta+\phi m_1]}{m_1 m_2} \tag{4}$$

Theorem 1 *The DFE, E_0 of the model (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*
The TB model can be understood clearly based on the threshold value basic reproduction number (R_0). Therefore, theorem 1 depicts that TB can be eradicated from the community when R_0 is less than a unity if the original sizes of the sub-populations of the model are in the basin of attraction of E_0 [1,5,19,20]. Naresh and Pandey [1] also established that it is locally asymptotically stable if and only if when $R_0 < 1$ then there is exists DFE although the DFE may not be globally asymptotically stable even ifR_0 is less than a unity. However, it is possible for$R_0$to be less than a unity and leads to a possibility of having BB (bi-stability) when a stable endemic equilibrium point (EEP) may co-exist with the DFE. Therefore, to determine the conditions for the existence of the EEP for the model (2), represented by $E_1 = (S^*, E^*, I^*, R^*)$then the equations in (3) are solved in terms of the infection at steady state(I^*), that must satisfy the following polynomial,

$$h(I^*) = C_1(I^*)^2 + C_2 I^* + C_3 = 0$$

Where

$$C_1 = \beta m_0 m_2$$
$$C_2 = \beta(\delta m_2 - m_0\gamma) + m_0 m_1 m_2$$
$$C_3 = \delta m_1 m_2 - m_0\gamma\{\theta(1-\phi) - \phi m_1\}$$

The endemic equilibrium in terms of $I_*$is given by

$$S^* = \frac{\gamma}{\delta + m_0 I^*}, \quad E^* = \frac{(1-\phi)m_0 I^* S^*}{\beta I^* + m_1}, \quad R^* = \frac{v_1 E^* + v_2 \Psi I^*}{d}$$

The following cases to be considered (depending on the signs of C_2 and C_1since C_1,is positive) to study the number of positive roots of $h(I^*) = 0$

$$J(E_0) = \begin{bmatrix} -\delta & 0 & \frac{-m_0\gamma}{\delta} & 0 \\ 0 & -m_1 & \frac{(1-\phi)m_0\gamma}{\delta} & 0 \\ 0 & \theta & \frac{\phi m_0\gamma}{\delta} - m_2 & 0 \\ 0 & \omega_1 & \omega_2\Psi & -\delta \end{bmatrix}$$

Consider the case when $R_0 = 1$. Suppose that$\phi = \phi^*$is chosen as a bifurcation parameter. Solving for $\phi$from $R_0 = 1$gives

$$\phi = \phi^* = \frac{\theta\gamma m_0 + \delta m_1 m_2}{\gamma m_0(m_1 - \theta)}$$

Using the following theorem from one will be able to determine whether or not the system (6) exhibits BB at R_0= 1.

2.2 Global stability analysis

Here, we closely follow the discussion of Athithan and Ghosh [5] on global stability of the differential equation. It is important to see that is impossible for the model to undergo backward bifurcation (BB) if β= 0. This study indicates that for BB to occur then there is need for exogenous reinfection [1,5,21].

Theorem 2: *The DFEof model* (3) *without exogenous reinfection (i.e. when* β= 0*) is globally asymptotically stable if* $R_0 < 1$

Proof:

By use of the comparison theorem to prove the global stability of the DFE, the equations for the infected compartments in model (3) is re-written as

$$\begin{pmatrix} E_t' \\ I_t' \end{pmatrix} = (W - T)\begin{pmatrix} V \\ E \end{pmatrix} - \begin{pmatrix} (1-\phi)m_0 I[S_0 - S] \\ \phi m_0 I[S_0 - S] \end{pmatrix}$$

where *W*and Tare as defined above in section 2.2.1. Since $S \leq S_0 = \frac{\gamma}{\delta}$for all $t > 0$, it follows that

$$\begin{pmatrix} E^* \\ I^* \end{pmatrix} \leq (W - T)\begin{pmatrix} E \\ I \end{pmatrix}$$

Since all the Eigen values of the matrix $W - T$have negative real parts [14] then model 3 is stable whenever $R_0 < 1$.So, $(E, I) \to (0,0)$ as $t \to \infty$. By the comparison theorem, it follows that $(E, I) \to (0,0)$ and $S \to \frac{\gamma}{\delta} t \to \infty$. Then $(S, E, I, R) \to E_0$ as $t \to \infty$ So, E_0 is globally asymptotically stable for $R_0 < 1$ when $\beta = 0$

2.3 Local stability analysis based on Endemic Equilibrium Point (EEP)

Theorem 3

The EEP of model (3) *is locally asymptotically stable when*$\tau_2, \tau_1 > 0$ *where* τ_1, τ_2 *and* τ_0*, are stated in the proof of the theorem.*

Proof

The EEP has the corresponding variation matrix V given by

$$V = \begin{pmatrix} x_{11} & 0 & x_{13} \\ x_{21} & x_{22} & x_{23} \\ x_{31} & x_{32} & x_{33} \end{pmatrix}$$

Where the elements in the matrix above are defined as follows

$$x_{11} = -(\delta + m_0 I^*),\ x_{13} = -m_0 s^*$$

$$x_{21} = (1-\phi)m_0 I^*, x_{22} = -(\beta I^* + m_1), x_{23} = (1-\phi)m_0 S^* - \beta E^*$$

$$x_{31} = \phi m_0 I^*, x_{32} = \beta I^* + \theta, x_{33} = \phi m_0 I^* + \beta E^* - m_2$$

The Eigen values are determined from V as $|V - \lambda I| = 0$. This result to a characteristic polynomial corresponding to above matrix given as $\lambda^3 + \tau_2\lambda^2 + \tau_1\lambda + \tau_0 = 0$ (2.4.1)

and the solutions to this Equation (2.4.1) is eigen values (λ)

Where the coefficient,

$$\tau_0 = -[x_{11}(x_{22}x_{33} - x_{23}x_{32}) - x_{13}(x_{21}x_{32} - x_{31}x_{22})]$$

$$\tau_2 = -(x_{11} + x_{22} + x_{33})$$

$$\tau_1 = [(x_{22}x_{33} - x_{23}x_{32}) + (x_{11}x_{33} - x_{31}x_{33})] + x_{11}x_{22}$$

From recent studies [1,5], we established that the endemic EEP will be locally asymptotically stable by using Routh-Hurwitz criteria if the following conditions are made and satisfied.

(i) The coefficient τ_2 should be greater zero.
(ii) All the coefficient in Equation 2.4.1 should be expressed as

$$\begin{vmatrix} \tau_2 & \tau_0 \\ 1 & \tau_1 \end{vmatrix}.$$

Since $\tau_2 > 0$therefore, the EEP is locally asymptotically stable if the other inequality $\tau_1 > 0$is satisfied.

3 Numerical Simulation Analysis

The model (3) was simulated using various set of parameters based on Athithan and Ghosh [5] values and assumptions.

$$\gamma = 18, \delta = 0.075, \alpha 1 = 0.001, \ \alpha 2 = 0.003, \ \phi = 0.235, \quad \Psi = 0.57,$$
$$\beta = 0.005, \omega_1 = 0.08, \quad \omega_2 = 0.08, \quad \delta_* = 0.032, \quad \theta = 0.0001.$$

These set of parameters resulted into two endemic equilibria as given below

$E_1 = (187.997, 29.986, 11.003, 38.097)$ and $E_2 = (128.002, 30.496, 34.988, 55.010)$ The disease-free equilibrium point was found to be $E_0 = (239,0,0,0)$.

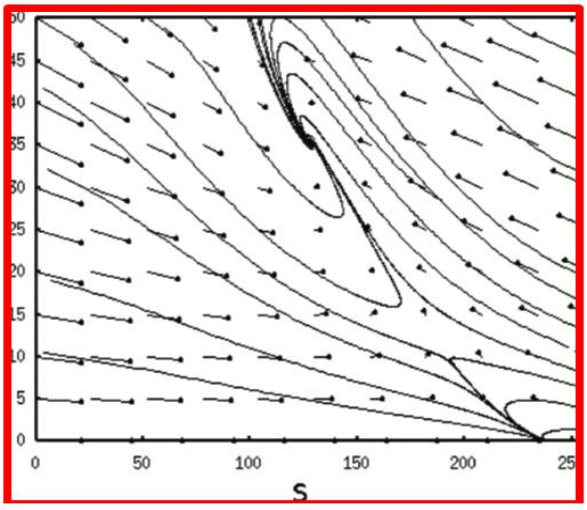

Fig. 3. S-I phase plane showing the bi-stability

This fact is illustrated by S-I phase plane in Fig. 3, where the equilibrium point E_1 is unstable but $E_0$and $E_2$are locally asymptotically stable. Fig.4 is obtained by putting into consideration the fast progression rate of TBϕas the bifurcation parameter. The horizontal axis is labelled with the value of R_0 corresponding to this bifurcation parameter ϕ

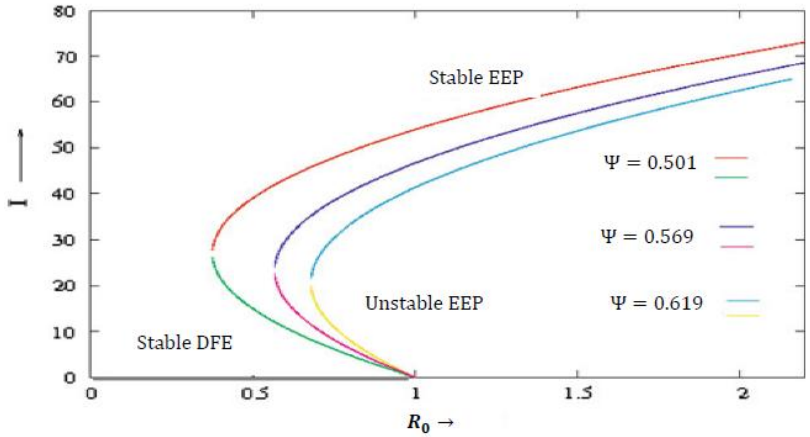

Fig. 4. BB plot of I

From this Fig. 4 it is observed that when R_0 is between 0 to R_0^c, then the DFE is stable and for $R_0^c < R_0 < 1$ there exists bi-stability where either the DFE is stable (or) the EEP is stable. However, in order to clearly see the effect of discovery rate Ψ then then bifurcation diagram is drawn for different values of Ψ .Therefore, this Fig. 4 gives clear picture of bifurcation diagram where it shows the case detection that plays an important role in the transmission dynamics of TB. It can also be observed that when the case detection rate is increased the bifurcation diagram shifts towards right making theR_{0^c}value to increase. This implies that if Ψ is large enough then BB will not exist. Therefore, in this situation $R_0$is less than a unity will be sufficient to eradicate the disease from the community. However, when the probability of detection is increased this usually result in reduction of reproduction number and this causes the number of new infections; the critical detection level to correspond $R_0 = 1$.

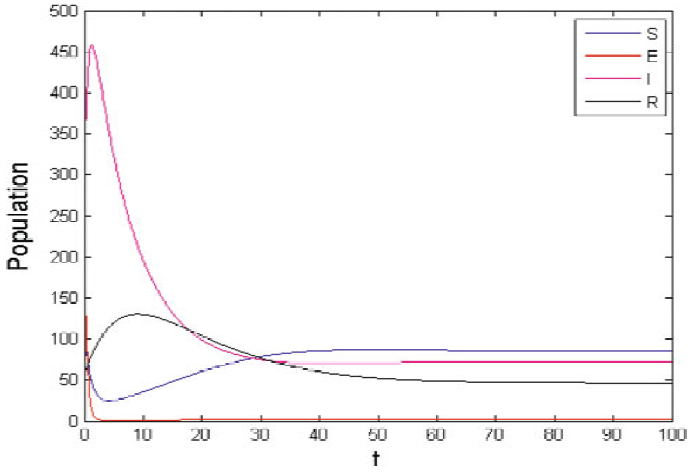

Fig. 5. Variation of S, E, I, R with time for $R_0 > 1$

From Fig. 5, it is observed that there is still existence of the diseases since not all people have recovered from TB. This evidenced by the basic reproduction number which is greater than 1. This value is 2.63 computed using set of parameters in section 3.0 [22].

Fig. 6 below demonstrates the stability of DFE using the of parameters in section 3.0. It is observed that the DFE exist and stable since the basic reproduction number computed is less than a unity ($R_0 = 0.785$). Again, BB is not exhibited as case detection rate is quite high.

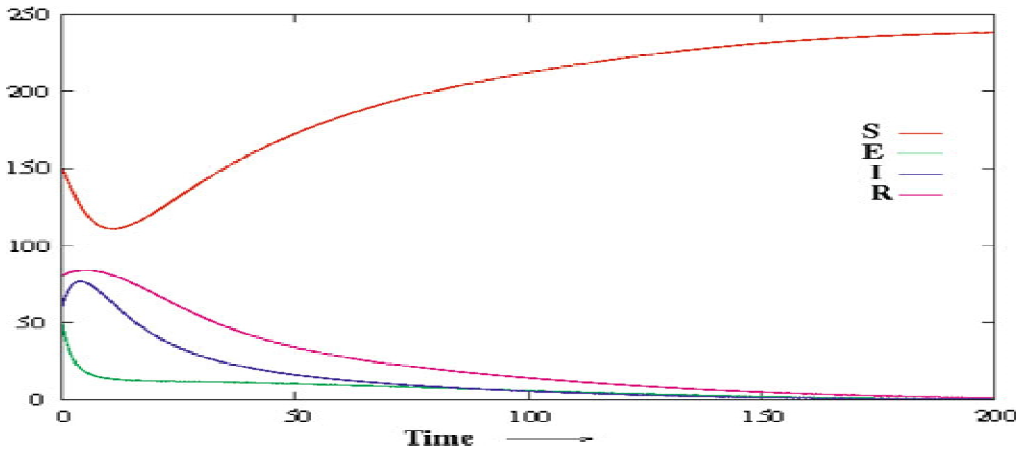

Fig. 6. Variation of S, E, I, R with time for $R_0 < 1$

From this Fig. 6 it is also observed that increase in treatment rate also result increase number of susceptible individuals while recovery, infected and exposed individuals declines due to existence of DFE.

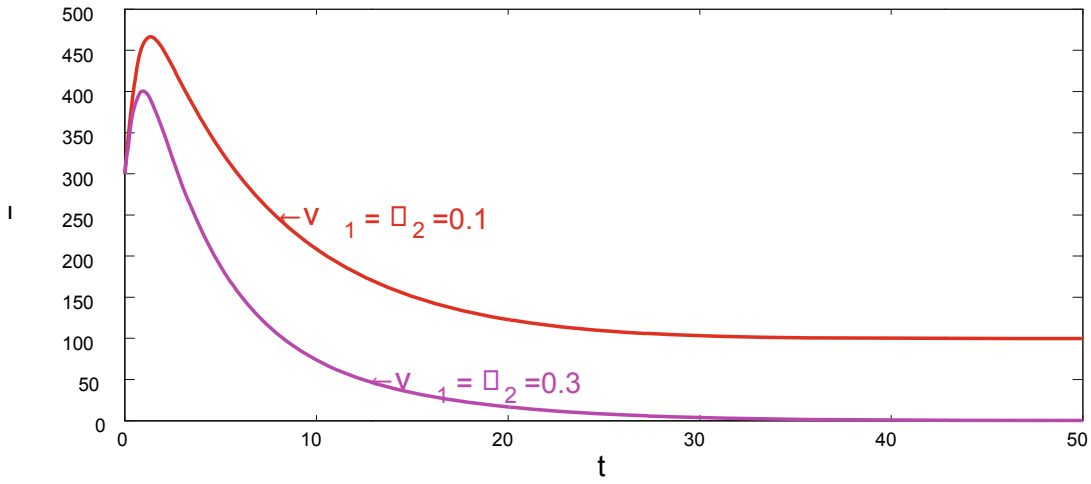

Fig. 7. Variation of infected individuals under study with time for different rates of treatment

Fig. 7 shows the effect of rate of treatment applied to infected individuals with TB. It is noticed that when the rate of treatment is increased the infective population decreases and this suggest that the disease can beeradicated from the population. However, this also implies that disease-free equilibrium becomes stable with the increase in the rates of treatment since R_0decreases.

4 Conclusion

The study indicated that the model undergoes the phenomenon of BB, when the associated. $R_0 < 1$. These results are very crucial as they govern the eradication and persistence of the TB in any given habitat. The model gives a concise image of the impact of treatment and its relationship with the effect of case discovery / detection on the dynamics of TB. Moreover, this study also indicated that the prospects of curbing the spread of TB is best if only the treatment strategy and techniques applied can be maintained and case detection/ discovery importantly improved upon.

Acknowledgement

This project would have not been possible without the dedicated and insightful guidance of a number of people. Thank you all and may God bless you.

Competing Interests

Authors have declared that no competing interests exist.

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