Journal of Natural Sciences Research www.iiste.org
ISSN 2224-3186 (Paper) ISSN 2225-0921 (Online)
Vol.3, No.12, 2013

On Models of Tuberculosis with Exogenous Reinfection

Bwebum Cleofas Dang[1*], Samuel Musa[2], Abdulkareem Adamu[2], Moses Vandi Tumba[2], Wilson Adams W[2]
1. Department of Mathematics, University of Jos, PMB 2084, Jos-Nigeria.
2. Department of Mathematics, Modibo Adama University of Technology Yola, Adamawa Nigeria.
*Email: bwebumcd@yahoo.com, dangb@unijos.edu.ng

Abstract
A deterministic mathematical model by Feng et. al (2000) for the dynamics of tuberculosis with exogenous reinfection is modified. The old model and the modified model are studied qualitatively. The two models were analysed for existence and stability of disease-free states. It was found that a disease free state exists in each case, which is locally asymptotically stable, an indication that the disease is controllable. Numerical studies show that with treatment, the population of infected people is less in the modified model than the old model, this show that control of TB will be achieve faster with the modified model than with the old model.
Keywords: Locally asymptotically stable, Treatment, Disease-free-equilibrium, Tuberculosis

1.0 INTRODUCTION

Tuberculosis (TB) is a contagious disease that spreads through the air. When people with the disease cough, sneeze, talk, sing or spit, they propel the germs known as bacilli into the air. Only a small number of the bacilli need to be inhaled to cause an infection (WHO, 2009).

Tuberculosis is classified into active tuberculosis and inactive or latent tuberculosis. Active tuberculosis means the bacteria are active in the body which means the immune system is unable to stop these bacteria from causing illness. People with active tuberculosis in their lungs can transmit the bacteria, but if a person has latent TB, it means his body has been able to successfully fight the bacteria and stop them from causing illness. People who have latent tuberculosis do not feel sick, do not have symptoms and can not spread the disease. Latent people with HIV can easily become infectious. Left untreated, each person with infectious TB will spread the germs to about 10 to 15 people every year (CDC, 2010).

Progression toward active TB may accelerate with re-exposure to TB bacilli through repeated contacts with individuals with active TB. Hence we must not only look at TB infection as the progression from primary infection but also include the possibility of exogenous reinfection (i.e. acquiring a new infection from another infectious individual) (Styblo, 1991) and (Smith and Moss, 1994).

Tuberculosis spreads through the air; it is an airborne infectious disease that targets the world's most vulnerable people. In fact, 90% of all tuberculosis cases occur in the developing world. People with HIV/AIDS are especially susceptible to tuberculosis: a person is 20-37% more likely to develop tuberculosis if he or she is HIV positive. One third of the world's population is currently infected with the tuberculosis bacillus and new infections are occurring at a rate of one person per second (WHO, 2010).

According to CDC (2010), all health care settings need an infection-control programme designed to ensure prompt detection, airborne precaution and treatment of persons who have been suspected or confirmed to have TB disease. USAID is partnering with the government of some Nations on the prevention activities which include initiatives to prevent mother-to-child transmission and the prevention of sexual transmission of the HIV virus (abstinence and be faithful programs, condom: other prevention initiatives), (USAID, 2010).

TB disease can be treated by taking several drugs for six to nine months. There are about ten drugs currently approved by the U.S. food and drug administration (FDA) for the treatment of TB. The first line anti-TB agents that form the core of treatment regimens include: Isoniazid (INH), Rifampin (RIF), Ethambutol (EMB) and Pyrazinamide (PZA). Regimen for treating TB disease has initial phase of two months, followed by a choice of several options for the continuation phase of either four or seven months (total of six to nine months for treatment) (CDC, 2011).

The emergence of drug-resistant strains of M. Tuberculosis, and TB/HIV coinfection will likely cause a noticeable effect on TB treatment and control strategies (Kirschner, 1999), (Porco *et al.,* 2001) and (Floyd *et al.,* 2002).

Mathematical models of tuberculosis have been proposed and studied in order to gain better insight into the dynamics of the disease (see, Schinazi (2003); Castillo-Chavez and Feng (1997); Laura and Maria (1997); Singer and Krischner (2004); Shen *et al.,* (2006); Ssematimba *et al.* (2005); Hattaf *et al.* (2009); and Enagi (2011)).

Feng *et al.* (2000) looked at the effect of exogenous reinfection on the dynamics of TB. They found that the incorporation of exogenous reinfection into a model for the transmission dynamics of TB allows for the increase of the number of individuals that are at risk of becoming infectious. However, treated individuals in their model are assumed to move back to the exposed class instead of the susceptible class which means they are still infected. According to CDC (2011), TB disease can be treated successfully by taking medicine.

In this study, the model by Feng *et al.* (2000) is modified by assuming that treated individuals re-enter the

system as susceptible individuals. The existence and stability of the two models are investigated and analysed for stability.

2.0 MODEL FORMULATION

Here, we shall present the model developed by Feng et al. (2000) as well as the modified model

2.1 Parameters of the model

$S(t)$ = Susceptible individuals at time t
$E(t)$ = Exposed (infected but not infectious) individuals at time t
$I(t)$ = Infectious individuals at time t
$T(t)$ = Treated (effectively treated) individuals at time t
$N(t)$ = Total population at time t
Λ = Constant recruitment rate
β = Average number of susceptible individuals per contact per unit time
σ = Average number of treated individuals infected by one infectious individual per-contact per unit time: $0 \leq \sigma \leq 1$
c = Per-capita contact rate
μ = Per-capita natural death rate
k = Rate at which an individual leaves the latent class by becoming infectious
d = Per-capita disease induced death rate
r = Per-capita treatment rate
p = Level of reinfection

2.2 Flow Diagrams

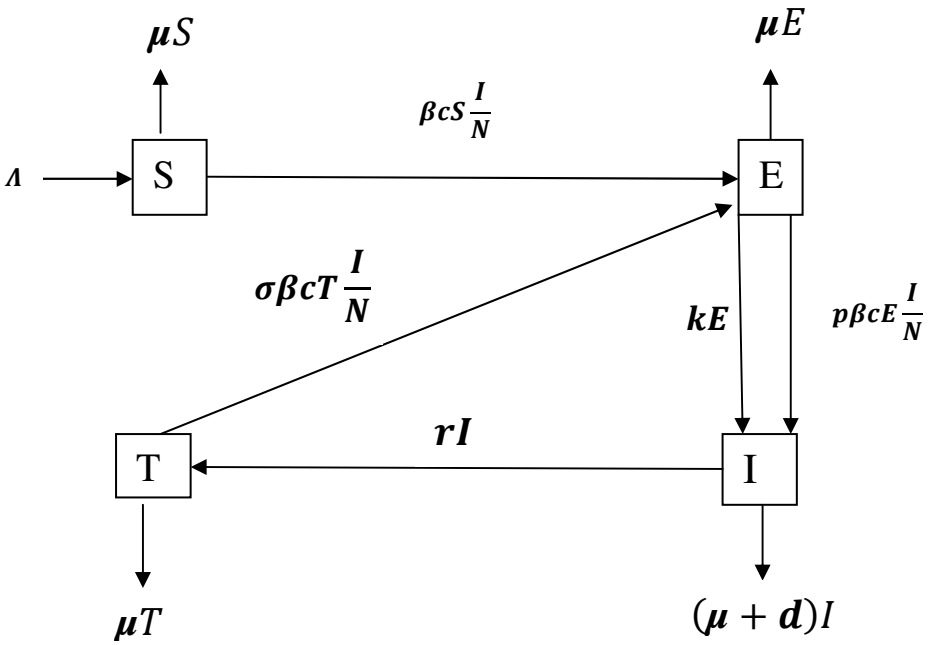

Figure 1: A Flow Diagram for the Transmission of TB (old model by Feng et al., (2000)).

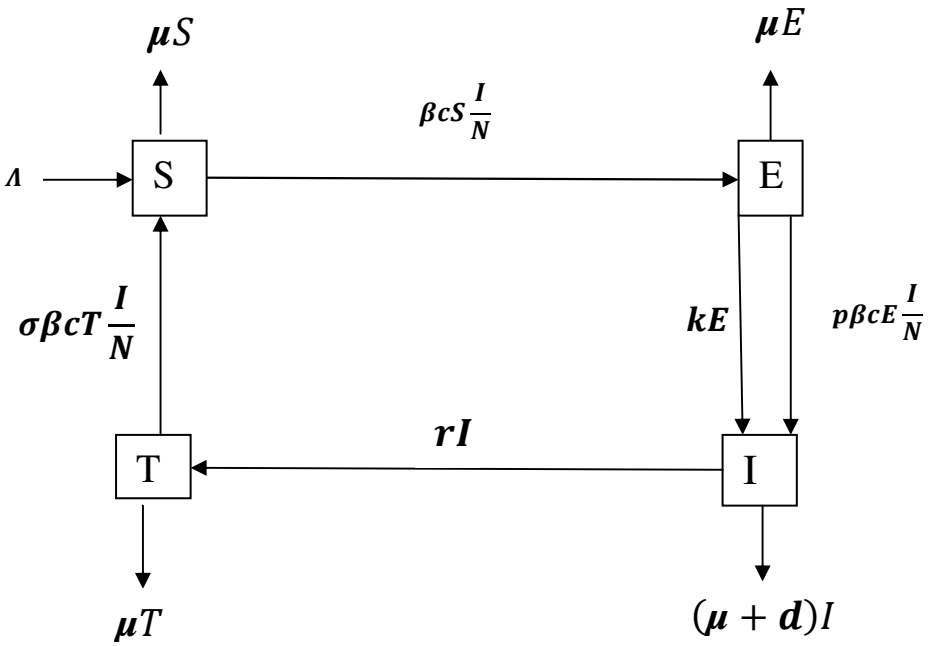

Figure 2: A Flow Diagram for the Transmission of TB (Modified model)

2.3 Model Equations

Here we present the model formulated by Feng *et al.* (2000) and the modified model using the flow diagram in figure 1 and figure 2, respectively. The host population is divided into the four epidemiological classes, namely: susceptible $S(t)$, exposed (infected but not infectious) $E(t)$, infectious $I(t)$ and treated (removed) $T(t)$. It is assume that an individual can be infected only through contacts with infectious individuals in both models.

The model equations by Feng *et al.* (2000) are given below

$$\frac{dS}{dt} = \Lambda - \beta cS\frac{I}{N} - \mu S \quad (2.3.1)$$

$$\frac{dE}{dt} = \beta cS\frac{I}{N} - p\beta cE\frac{I}{N} - (\mu + k)E + \sigma\beta cT\frac{I}{N} \quad (2.3.2)$$

$$\frac{dI}{dt} = p\beta cE\frac{I}{N} + kE - (\mu + r + d)I \quad (2.3.3)$$

$$\frac{dT}{dt} = rI - \sigma\beta cT\frac{I}{N} - \mu T \quad (2.3.4)$$

$$N = S + E + I + T \quad (2.3.5)$$

In the modified model, it is assumed that treatment is effective, so that all treated individuals re-enter the system as susceptible people. The new scenario as depicted in the flow diagram (figure 2) above. Thus, we have the following modified model.

$$\frac{dS}{dt} = \Lambda - \beta cS\frac{I}{N} - \mu S + \sigma\beta cT\frac{I}{N} \quad (2.3.6)$$

$$\frac{dE}{dt} = \beta cS\frac{I}{N} - p\beta cE\frac{I}{N} - (\mu + k)E \quad (2.3.7)$$

$$\frac{dI}{dt} = p\beta cE\frac{I}{N} + kE - (\mu + r + d)I \quad (2.3.8)$$

$$\frac{dT}{dt} = rI - \sigma\beta cT\frac{I}{N} - \mu T \quad (2.3.9)$$

3.0 Existence of Disease-Free Equilibrium States

To find the existence of disease-free equilibrium states of the system, the left hand sides of (2.3.1)-(2.3.4) are equated to zero and the resulting system solved simultaneously.

Thus for the model by Feng et al (2000), we have

$$0 = \Lambda - \beta cS\frac{I}{N} - \mu S \quad (3.0.1)$$

$$0 = \beta cS\frac{I}{N} - p\beta cE\frac{I}{N} - (\mu + k)E + \sigma\beta cT\frac{I}{N} \quad (3.0.2)$$

$$0 = p\beta cE\frac{I}{N} + kE - (\mu + r + d)I \quad (3.0.3)$$

$$0 = rI - \sigma\beta cT\frac{I}{N} - \mu T \quad (3.0.4)$$

But at the disease free equilibrium state, $E = 0, I = 0, T = 0$. Substituting these in equation (3.0.1)-(3.0.4) and

solving simultaneously gives
$(S^*, E^*, I^*, T^*) = \left(\frac{\Lambda}{\mu}, 0,0,0\right)$.
Hence we have proved the following theorem

Theorem 3.1

Given the system of equations in (2.3.1)-(2.3.4),
the disease-free equilibrium state of the model exists and is given by $\left(\frac{\Lambda}{\mu}, 0,0,0, \right)$.

3.2 Stability of the Disease Free Equilibrium Point

The disease-free equilibrium point, $\Psi = \left(\frac{\Lambda}{\mu}, 0,0,0, \right)$ is stable if the eigenvalues of the Jacobian matrix evaluated at Ψ have negative real parts (Roussel, 2005).
The Jacobian matrix at the disease free equilibrium state Ψ is giving by

$$J_\Psi = \begin{pmatrix} -\mu & 0 & -\beta c & 0 \\ 0 & -(\mu + k) & \beta c & 0 \\ 0 & k & -(\mu + r + d) & 0 \\ 0 & 0 & r & -\mu \end{pmatrix}$$

To get the eigenvalues, we obtain the characteristics equation of the Jacobian matrix
Thus,
$|J_\Psi - \lambda I| = 0$
Evaluating the characteristic equation above for λ we have
$\lambda_1 = -\mu$
and, $\lambda_2 = -\mu$
The other two roots are obtained from solving the quadratic equation
$\lambda^2 + \big((\mu + k) + (\mu + r + d)\big)\boldsymbol{\lambda} + (\mu + k)(\mu + r + d) - k\beta c = 0$
Hence,

$$\lambda = \frac{-(\boldsymbol{2\mu+k+r+d}) \pm \sqrt{(\boldsymbol{2\mu+k+r+d})^{\boldsymbol{2}} - \boldsymbol{4}\big((\mu+k)(\mu+r+d) - k\beta c\big)}}{2}$$

Let $Q = \boldsymbol{2\mu + k + r + d}$, $Q_1 = (\mu + k)(\mu + r + d) - k\beta c$

then $\lambda_3 = \frac{-Q}{2} + \frac{\sqrt{Q^2 - 4Q_1}}{2}$

and $\lambda_4 = \frac{-Q}{2} - \frac{\sqrt{Q^2 - 4Q_1}}{2}$

If $Q_1 > 0$, then

$\lambda_3 < \frac{-Q}{2} + \frac{\sqrt{Q^2}}{2} = \frac{-Q}{2} + \frac{Q}{2} = 0$ and

$\lambda_4 < \frac{-Q}{2} - \frac{\sqrt{Q^2}}{2} = \frac{-Q}{2} - \frac{Q}{2} = -Q$

Therefore,
$\lambda_3 < 0$ and $\lambda_4 < 0$
Thus establishing that
$\lambda_1 < 0, \lambda_2 < 0, \lambda_3 < 0, \lambda_4 < 0$
Hence, the proof of the following theorem,

Theorem 3.3

Given $k, r, d, \beta, c, \mu > 0$,
if $\beta c < \frac{(\mu+k)(\mu+r+d)}{k}$
then the disease-free equilibrium state of the system (2.3.1) – (2.3.4) is locally asymptotically stable.

3.4 Existence of Disease-Free Equilibrium State of the Modified Model

Setting the left hand side of the model (2.3.6)-(2.3.9) to zero gives

$$0 = \Lambda - \beta c S\frac{I}{N} - \mu S + \sigma\beta c T\frac{I}{N} \quad (3.4.1)$$

$$0 = \beta c S\frac{I}{N} - p\beta c E\frac{I}{N} - (\mu + k)E \quad (3.4.2)$$

$$0 = p\beta c E\frac{I}{N} + kE - (\mu + r + d)I \quad (3.4.3)$$

$$0 = rI - \sigma\beta c T\frac{I}{N} - \mu T \quad (3.4.4)$$

At the disease-free equilibrium state, $E = 0, I = 0, T = 0$
Therefore substituting these in equations (3.4.1)-(3.4.4) and solving simultaneously we get $(S^*, E^*, I^*, T^*) = \left(\frac{\Lambda}{\mu}, 0,0,0\right)$

Hence we have proof the following theorem

Theorem 3.5

Given the system of equations in (2.3.6)-(2.3.9),

the disease-free equilibrium state of the model exists and it is giving by $\Psi = \left(\frac{\Lambda}{\mu}, 0,0,0, \right)$.

3.6 Stability of the Disease Free Equilibrium State

The disease-free equilibrium state, $\Psi = \left(\frac{\Lambda}{\mu}, 0,0,0, \right)$ is stable if all the eigenvalues of the Jacobian matrix evaluated at that state have negative real parts (Roussel, 2005).

Therefore the Jacobian matrix at the disease free equilibrium state Ψ is giving by

$$J_\Psi = \begin{pmatrix} -\mu & 0 & -\beta c & 0 \\ 0 & -(\mu+k) & \beta c & 0 \\ 0 & k & -(\mu+r+d) & 0 \\ 0 & 0 & r & -\mu \end{pmatrix}$$

The above matrix is equal to the previous one, and so has same eigen values at the same equilibrium state.

Theorem 3.7

Given $k, r, d, \beta, c, \mu > 0$,

if $\beta c < \frac{(\mu+k)(\mu+r+d)}{k}$

then the disease-free equilibrium state of the system (2.3.6)-(2.3.9) is locally asymptotically stable.

4.0 Numerical Experiment

4.1 Numerical Scheme

Using the method developed by Gumel *et al.* (2002) a semi-implicit finite difference method, our numerical scheme is developed. The scheme is developed by approximating the time derivative by its first order forward difference approximation given as

$$\frac{ds(t)}{dt} = \frac{s(t+h)-s(t)}{h} + o(h^2) \text{ as } t \to 0 \qquad (4.1.1)$$

where $h > 0$ is an increment in t (the step length)

Discretizing the interval $t \geq t_0 = 0$ at points $t_n = nl$ $(n = 1, 2, \ldots.)$, the solution at the grid point correspond to s_n is $s(t_n)$. The solution of an approximating numerical method will be denoted by S_n. A first order numerical method for solving S in the general model based on approximating the time derivative by (2.4.1) and making appropriate approximations for the right-hand-side terms, is (for the old model by (Feng *et al.*, 2000).

$$\frac{S_{n+1}-S_n}{h} = \Lambda - \mu S_{n+1} - \beta c S_{n+1} \frac{I_n}{S_n+E_n+I_n+T_n} \qquad (4.1.2)$$

$$\frac{E_{n+1}-E_n}{h} = \beta c S_{n+1} \frac{I_n}{S_n+E_n+I_n+T_n} - p\beta c E_{n+1} \frac{I_n}{S_n+E_n+I_n+T_n} - (\mu+k)E_{n+1} + \sigma\beta c T_n \frac{I_n}{S_n+E_n+I_n+T_n} \qquad (4.1.3)$$

$$\frac{I_{n+1}-I_n}{h} = p\beta c E_{n+1} \frac{I_{n+1}}{S_n+E_n+I_n+T_n} + kE_{n+1} - (\mu+r+d)I_{n+1} \qquad (4.1.4)$$

$$\frac{T_{n+1}-T_n}{h} = rI_{n+1} - \sigma\beta c T_{n+1} \frac{I_{n+1}}{S_n+E_n+I_n+T_n} - \mu T_{n+1} \qquad (4.1.5)$$

$$N_n = S_n + E_n + I_n + T_n \qquad (4.1.6)$$

Rearranging the method (4.1.2)- (4.1.5) above we have

$$S_{n+1} = \frac{(S_n+h\Lambda)(S_n+E_n+I_n+T_n)}{(S_n+E_n+I_n+T_n)(1+h\mu)+h\beta c I_n}$$

$$E_{n+1} = \frac{E_n(S_n+E_n+I_n+T_n)+h\beta c S_{n+1} I_n + h\sigma\beta c T_n I_n}{(S_n+E_n+I_n+T_n)\big(1+h(\mu+k)\big)+hp\beta c I_n}$$

$$I_{n+1} = \frac{(S_n+E_n+I_n+T_n)(I_n+hkE_{n+1})}{(S_n+E_n+I_n+T_n)\big(1+h(\mu+r+d)\big)-ph\beta c E_{n+1}}$$

$$T_{n+1} = \frac{(S_n+E_n+I_n+T_n)(hrI_{n+1}+T_n)}{(S_n+E_n+I_n+T_n)(1+\mu h)+h\sigma\beta c I_{n+1}}$$

And for the modified model we have

$$\frac{S_{n+1}-S_n}{h} = \Lambda - \mu S_{n+1} - \beta c S_{n+1} \frac{I_n}{S_n+E_n+I_n+T_n} + \sigma\beta c T_n \frac{I_n}{S_n+E_n+I_n+T_n} \qquad (4.1.7)$$

$$\frac{E_{n+1}-E_n}{h} = \beta c S_{n+1} \frac{I_n}{S_n+E_n+I_n+T_n} + p\beta c E_{n+1} \frac{I_n}{S_n+E_n+I_n+T_n} - (\mu+k)E_{n+1} \qquad (4.1.8)$$

$$\frac{I_{n+1}-I_n}{h} = p\beta c E_{n+1} \frac{I_{n+1}}{S_n+E_n+I_n+T_n} + kE_{n+1} - (\mu+r+d)I_{n+1} \qquad (4.1.9)$$

$$\frac{T_{n+1}-T_n}{h} = rI_{n+1} - \sigma\beta c T_{n+1} \frac{I_{n+1}}{S_n+E_n+I_n+T_n} - \mu T_{n+1} \qquad (4.1.10)$$

Rearranging the method (4.1.7)-(4.1.10) above we have

$$S_{n+1} = \frac{(S_n+h\Lambda)(S_n+E_n+I_n+T_n)+h\sigma\beta c T_n I_n}{(S_n+E_n+I_n+T_n)(1+h\mu)+h\beta c I_n}$$

$$E_{n+1} = \frac{E_n(S_n+E_n+I_n+T_n)+h\beta cS_{n+1}I_n}{(S_n+E_n+I_n+T_n)(1+h(\mu+k))+hp\beta cI_n}$$

$$I_{n+1} = \frac{(S_n+E_n+I_n+T_n)(I_n+hkE_{n+1})}{(S_n+E_n+I_n+T_n)(1+h(\mu+r+d))-ph\beta cE_{n+1}}$$

$$T_{n+1} = \frac{(S_n+E_n+I_n+T_n)(hrI_{n+1}+T_n)}{(S_n+E_n+I_n+T_n)(1+\mu h)+h\sigma\beta cI_{n+1}}$$

Solutions of the models are obtained using computer program (Visual Basic 6.0) and the parameter values in table 4.2 below

4.2 Table of parameter values

Parameter \ Expt	1	2	3	4	5
$S(0)$	13250	13250	13250	13250	13250
$E(0)$	0	10500	10500	10500	13250
$I(0)$	0	1000	1000	1000	1000
$T(0)$	0	250	250	250	250
$N(0)$	13250	25000	25000	25000	25000
Λ	417	417	417	417	417
β	0	80	80	80	80
σ	0	0.9	0.9	0.9	0.9
c	0	0.1	0.1	0.1	0.1
μ	0.0167	0.0167	0.0167	0.0167	0.0167
k	0	0.005	0.005	0.005	0.005
d	0	0.1	0.1	0.1	0.1
r	0	0	1	2	3
p	0.4	0.4	0.4	0.4	0.4

4.3 Results of Numerical Experiments

4.3.1 Experiment One

This experiment is carried out in the absence of infection for which all the terms that lead to infection is zero, the only parameters which are not zero include: the initial susceptible population, constant recruitment rate and natural death rate. The result displayed in figure 5.1 shows that there is no infectious population for both models, which is true because no member of the population is infected.

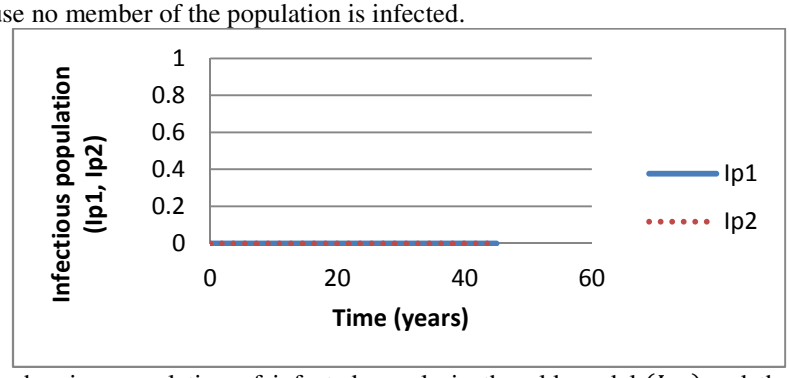

Figure 5.1: Graph showing population of infected people in the old model (Ip_1) and that in the new model (Ip_2).

4.3.2 Experiment Two

In this experiment, the dynamics of the disease with treatment rate $r = 0$ is considered and the result (figure 5.2) shows that the infectious population of both the old and the modified model will grow above the initial infectious population and then begin to decline.

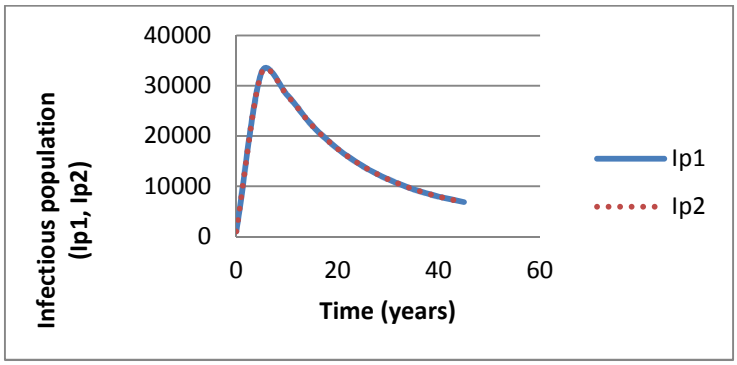

Figure 5.2: Graph showing the population of infected people with treatment rate $r = 0$, other parameter values are on table 4.2

4.3.3 Experiment Three

In this experiment, the dynamics of the disease under a treatment rate of $r = 1$ is considered, there is a sharp increase in the infectious population for both model above the initial infectious population (figure 3.3.1). The infectious population of the old model grow higher than the infectious population of the modified model, and then a gradual decline in the two populations is noticed.

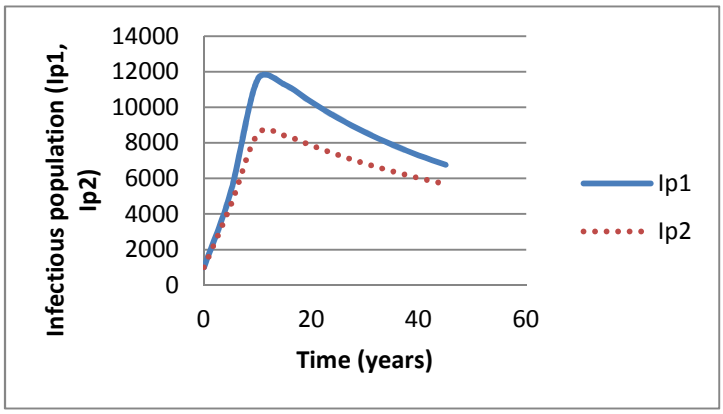

Figure 5.3: Graph showing the population of infected people with treatment rate $r = 1$, other parameter values are on table 4.2

4.3.4 Experiment Four

Here the dynamics of the disease under the treatment rate of $r = 2$ are considered. The result shows that there is no increase in the population of the infectious class in both models as it is seen in figure 3.4.1, rather there is a sharp decline in the infectious population of both the old and modified model under study, but the infectious population of the old model grow higher than the modified model.

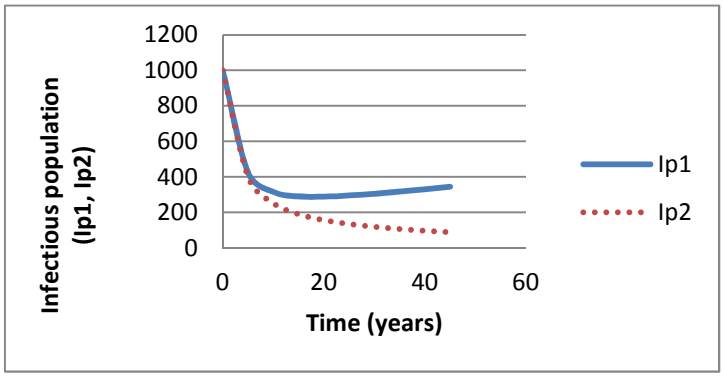

Figure 3.4.1: Graph showing the population of infected people with treatment rate $r = 2$, other parameter values are on table 4.2

4.3.5 Experiment Five

When the dynamics of the disease is considered under a treatment rate of $r = 3$, the result as displayed in figure 5.12.1 shows that there is a sharp decline in the infectious population of both models within a period of about 5

years and then it stabilises at a very low population. Difference between the infectious population of the modified model and the old model is not significant in this experiment as it was seen on figure 3.5.1.

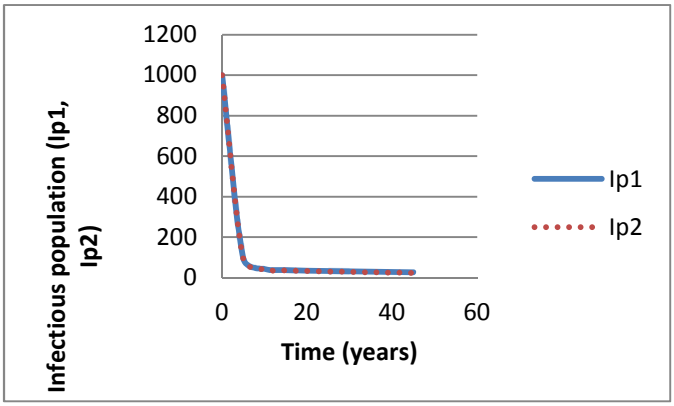

Figure 3.5.1: Graph showing the population of infected people with treatment rate $r = 3$, other parameter values are on table 4.2

5.0 Discussion of Results

The result from experiment one shows that in the absence of infection, there will be no individuals in the infectious class for both models, which is true because no one is infected and so we expect that there should be no infectious individual for both the modified and the old model.

In experiments two and three where treatment rate is $r = 0$ and $r = 1$ respectively, the result shows that with such treatment rate, eradication is not possible which means the net transmission rate of the disease will not reduce and hence there will be no stability in the disease free equilibrium state.

The results in experiment four and five show that with treatment rate of $r = 2$ and $r = 3$ respectively, eradication is possible provided the treatment rate is not less than two. Nevertheless, the infectious population of the modified model decline much faster than the old model when the treatment is $r = 2$. This means that using the old model by Feng et al. (2000), resources will be wasted since it gives a wrong estimate of infectious individuals.

The result stated in theorem 3.3 and 3.7 revealed that tuberculosis with exogenous reinfection is controllable since from our studies, both models are stable for a specified stability condition which is to keep the net transmission rate very low this means that the treatment rate need to be intensify in other to achieve such stability. Therefore parameter values for experiment four and five agree with the condition in theorem 3.3 and 3.7, in that as treatment increase, we achieve stability and hence control of the disease.

5.1 Conclusion

The population of infected people in the new model is same as that on the old model in the absence of treatment. However, with treatment in place, the population of infected people in the new model is less than that in the old model therefor control of infection is achieved faster with the new model than with old model.

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