

STABILITY ANALYSIS OF MATHEMATICAL MODEL OF A RELAPSE TUBERCULOSIS INCORPORATING VACCINATION

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Abstract

A general SIQRM epidemic model with vaccination and relapse possibility is proposed for analysis in this work. The idea behind the proposed model is to check the effect of immunity obtained from vaccine or treatment, quarantine effect as well as waning effect of immunity on the transmission rate of Tuberculosis within a population that is subjected to proper education without restricted access. Some other infectious diseases in this category include measles and Ebola. Two equilibrium states of the proposed model are obtained as well as the effective reproduction number (R_{eff}). Stability analysis of the model at the Infection Free Equilibrium (I.F.E) state is established on the condition that $R_{eff} < 1$. Numerical simulation for the general SIQRM model was done using specific data for Tuberculosis disease and the result shows that proper education, vaccination and early diagnosis of an infectious individual for quarantining is an efficient way by which the spread of Tuberculosis can be reduced in the population while adequate medical attention yield better result for detected cases.

Keywords: Epidemic Model, Relapse, Immunity, Quarantine Effect, Simulation.

MSC2010:92B05

Introduction

General interest in infectious diseases and their control are fueled by discovery of new infectious disease, frequent re-appearance of plague and emergence of both preventive and therapeutic antibiotics to curb, manage and possibly eradicate the threat of such an infection [2]. Many fundamental concepts and principles to model disease transmission exist and have been built upon by several researchers to address specific infection dynamics. The most elementary of such models are the $S - I - R$; $S - I - S$; and $S - E - I - R$ with S as Susceptible, I as Infectious, R as Recovered and E as Exposed. In this work, a generalized $S - I - Q - R - M$ model is presented for analysis where S, I, R retain their meaning and Q denotes Quarantine and M denotes Immunity. Though, the generalized $S - I - Q - R - M$ model is scarcely used in literature, it however can be of immense importance in predicting the course of an infection as well as proffering effective and efficient ways by which an infection in this category can be treated and eliminated. Some of the infection

in this category includes Tuberculosis, Lassa Fever, Measles and Ebola. These infections requires high level of vigilance when they enter a population of susceptible individuals. The earlier these diseases are diagnosed from an individual, the better for the entire population if such an individual is quarantined. In this work, tuberculosis shall be used as a case study to show the effect of early detection, quarantine, vaccination and treatment of an infected individual on the overall epidemic of the disease within the host population. These diseases have high relapse rate if the infectious individual do not complete his dosage for treatment appropriately. Some basic definition of terms used in this work are discussed below.

Quarantine involves separation of people with restriction of access of susceptible individuals who were exposed to a contagious disease in order to check for infectiousness [9]. It is a measure that is always taken to prevent the spread of a highly infectious disease like tuberculosis and Ebola from spreading within a population. Quarantining an exposed/infected individual cannot be taken to mean stigmatization, it is just a necessary precaution taken to reduce the spread of such disease in the community.

Similarly, immunity to a disease is defined as the quality or state of the body system to resist a particular disease through the presence of multi-cellular organisms known as antibodies. Sometimes, immunity can be obtained through vaccination, treatment and personal hygiene. Vaccination offers temporary immunity which can sometimes last for a lifetime if contact with infection is minimized to susceptible population. However, obtaining a hundred percent vaccination of entire susceptible group is practically impossible due to several factors. Also, successful treatment and recovery from certain illness, like measles, offer some degree of immunity against its re-infection, thus, some therapeutic treatment to certain diseases offers immunity either temporal or permanent against such a disease.

Relapse is defined as the worsening of a clinical condition that had previously improved. This occur most times when an individual discontinued his treatment at the earliest possible time of recovery without completing his dosage [1]. Aside from non-adherence to drug prescription, another way by which relapse can occur is due to ineffectiveness of the drug being taken to cure the disease and some other biological factor. Relapse is different from re-infection because the latter has to come in contact with those infected before developing the symptoms of the infection while the former occur without any contact with infectious individual. For instance, standard treatment for active TB requires drug treatment with at least four dosages over six months period [6]. The case of re-infection of a treated illness without a second contact with the infective class is known as relapse. The dynamics of infection and re-infection differs from one illness to another. Thus, to obtain a general model, it is important to take cognizance of peculiarity of each diseases that may fall into the general category under consideration.

Tuberculosis is a contagious and infectious disease that is caused by *mycobacterium tuberculosis*. This disease has always been a major challenge to mankind since it was first discovered in the 1700s as the white plague. It has claimed lots of human lives and it is recorded as the top killer with close to 4000 mortality cases everyday [10]. Though, it is a preventable and curable disease, millions of people continue to fall ill with TB each year. It was reported that an estimated 10 million individuals got infected with TB in 2019, with 7.1 million having access to TB care while about five hundred thousand developed a drug-resistance TB illness [10]. Fors *et al.*, [6] developed and solved some TB models with some clinical characteristics that include immune system response and patient drug therapy adherence. In their work, they presented mathematical model for pharmacokinetics by using a single compartmental system with first order absorption and elimination of drugs in the plasma. Their study presented an integrated systems pharmacology model and simulation tool to support prediction of outcomes of different therapies for pulmonary tuberculosis infection. Mettle, Affi and Twumasi [11] modelled the dynamics of TB among high-burden district by using an *SEIR* epidemic model with demography. They also considered the effect of introducing treatment at the exposed stage on the overall transmission dynamics of the infection in the region considered. They

established that their model perform better in eight out of ten municipals considered in the region. Thus, in this work, a new generalized *SIQRM* model shall be used to consider the overall effect of quarantining an early detected TB carriers. Also, infant vaccination effect, effective treatment and waning of immunity from vaccination shall be considered on the overall effective reproduction number of TB under the *SIQRM* epidemic model.

MODEL FORMULATION

A non-linear deterministic model for the transmission dynamics of infectious diseases in the presence of immunity loss and relapse is built by dividing the total human population at time t , denoted by $N(t)$ into five disjoint epidemiological sub-populations, which are, Susceptible (S), Infected (I), Quarantine (Q), Recovered (R) and Partial Immunity (M). Thus, $N(t) = S(t) + I(t) + Q(t) + R(t) + M(t)$ Recruitment into susceptible compartment is assumed either through birth or immigration at the rate of π and immunity loss rate α , natural mortality occurs across all compartments at the rate μ , susceptible are vaccinated at the rate χ while they become infected with the force of infection which is given as $\lambda = \beta_1 I + \beta_2 Q$ where β_1, β_2 are the contact with infective and quarantined classes that are sufficient to bring about new infections. Infected class is treated and recovered at the rate ϵ , and the rate of progression to the quarantined class is γ . The induced death rate of infected class is δ_1 and re-infection rate is η . The quarantined class is reduced by natural mortality rate μ , induced death rate δ_2 and the recovery rate is ω_2 . Partial immunity compartment is increased at the rate of ω_1 as a result of immunity obtained from recovery. The flow diagram of the model is given in figure 1 below.

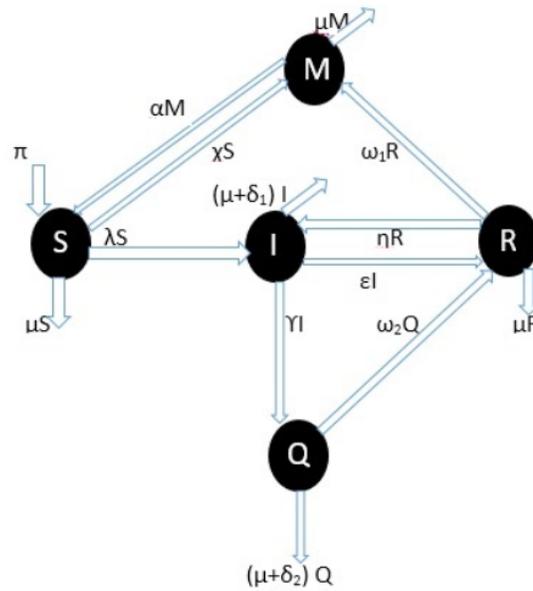


Figure 1: Pictorial representation of the Model

The above deterministic model is govern by the following non-linear system of ordinary differential equations:

$$\begin{aligned}
 \frac{dS}{dt} &= \pi + \alpha M - \lambda S - (\mu + \chi)S \\
 \frac{dI}{dt} &= \lambda S + \eta R - (\mu + \delta_1 + \gamma + \epsilon)I \\
 \frac{dQ}{dt} &= \gamma I - (\mu + \delta_2 + \omega_2)Q \\
 \frac{dR}{dt} &= \epsilon I + \omega_2 Q - (\mu + \eta + \omega_1)R \\
 \frac{dM}{dt} &= \omega_1 R + \chi S - (\mu + \alpha)M
 \end{aligned} \tag{0.1}$$

Where the force of infection λ is given as:

$$\lambda = \beta_1 I + \beta_2 Q \tag{0.2}$$

Basic Assumptions of the Model

The following assumptions are considered in constructing the model:

1. Recruitment is done only into the susceptible class.
2. The studied population is homogenous and varies with time.
3. Birth rate is greater than mortality rate.
4. The force of infection is expressed as $\lambda = \beta_1 I + \beta_2 Q$
5. Induced death rate at infected and quarantine classes are not equal.

Description of state variables, parameters value and their sources are given in table 1:

Table 1: Table of parameter value for the Model

| Symbol | Description | Value | Source |
|------------|------------------------------------|-------------------|---------|
| π | Recruitment rate | $\mu \times 10^5$ | [8] |
| χ | Vaccination rate | 0.3 | Assumed |
| α | Immunity loss | 0.5 | Assumed |
| μ | mortality rate | 0.02041 | [8] |
| γ | quarantined rate | 0.4 | Assumed |
| δ_1 | Induced death rate of I-class | 0.365 | [8] |
| δ_2 | Induced death rate of Q-class | 0.365 | [8] |
| η | Relapse or re-infection rate | 0.1 | [8] |
| ω_2 | Recovery rate of quarantined class | 1.5 | [8] |
| ω_1 | Recovery rate | 0.6 | Assumed |
| ϵ | Recovery rate | 0.75 | [8] |
| $S(t)$ | Susceptible per time | Varied | Assumed |
| $I(t)$ | Infected per time | Varied | Assumed |
| $Q(t)$ | Quarantine per time | Varied | Assumed |
| $R(t)$ | Recovered per time | Varied | Assumed |
| $M(t)$ | Immune class per time | Varied | Assumed |

Model Solution

Setting $c_1 = \mu + \chi$, $c_2 = \mu + \delta_1 + \gamma + \epsilon$, $c_3 = \mu + \delta_2 + \omega_2$, $c_4 = \eta + \mu + \omega_1$, $c_5 = \alpha + \mu$ for compactness of computation to obtain:

$$\begin{aligned}\frac{dS}{dt} &= \pi + \alpha M - \lambda S - c_1 S \\ \frac{dI}{dt} &= \lambda S + \eta R - c_2 I \\ \frac{dQ}{dt} &= \gamma I - c_3 Q \\ \frac{dR}{dt} &= \epsilon I + \omega_2 Q - c_4 R \\ \frac{dM}{dt} &= \omega_1 R + \chi S - c_5 M\end{aligned}\tag{0.3}$$

Theorem 1:

The set

$D = \left\{ (S, I, Q, R, M) \in \mathbb{R}_+^5 : N = S + I + Q + R + M \leq \frac{\pi}{\mu} \right\}$ is closed and positively invariant and attracting with respect to the system (1)

Proof:

From (1), setting

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dQ}{dt} + \frac{dR}{dt} + \frac{dM}{dt}$$

Such that

$$\begin{aligned}\frac{dN}{dt} &= \pi - \mu N - \delta_1 I - \delta_2 Q \\ \frac{dN}{dt} &\leq \pi - \mu N\end{aligned}$$

Solving the above with initial condition $N(0) = N_0$ to obtain

$$N(t) \leq \frac{\pi}{\mu} + \left(N_0 - \frac{\pi}{\mu} \right) e^{-\mu t}\tag{0.4}$$

It is obvious that $N(t)$ approaches $\frac{\pi}{\mu}$ as $t \rightarrow \infty$, thus, it follows that the system (1) is positively invariant and attracting in domain D . Therefore the model is mathematically and epidemiologically well-posed in D [4], and it is sufficient to consider solutions in D .

Model Equilibrium States

Solving the system of equations in (3) at stationary points to determine the equilibrium state of the model, it is observed that the model equations gives two independent solutions which are called the state of infection free (E_0) equilibrium or state of no infection and endemic (E_1) equilibrium state given respectively as:

$$E_0 = (S_0, I_0, Q_0, R_0, M_0) = \left(\frac{\pi c_5}{\mu(c_1 + \alpha)}, 0, 0, 0, \frac{\pi \chi}{\mu(c_1 + \alpha)} \right)\tag{0.5}$$

$E_1 = (S_1, I_1, Q_1, R_1, M_1)$ where

$$\begin{aligned}S_1 &= \frac{\eta \epsilon c_3 + \eta \gamma \omega_2 - c_2 c_3 c_4}{c_4(\gamma \beta_2 + c_3 \beta_1)} \\ I_1 &= -\frac{(\Pi \gamma \beta_2 c_4 c_5 + \Pi \beta_1 c_3 c_4 c_5 - \alpha \eta \gamma \chi \omega_2 - \alpha \eta \epsilon \chi c_3 + \alpha \chi c_2 c_3 c_4 + \eta \gamma c_1 c_5 \omega_2 + \eta \epsilon c_1 c_3 c_5 - c_1 c_2 c_3 c_4 c_5) c_3}{\alpha \gamma^2 \beta_2 \omega_1 \omega_2 + \alpha \gamma \epsilon \beta_2 c_3 \omega_1 + \alpha \gamma \beta_1 c_3 \omega_1 \omega_2 + \alpha \epsilon \beta_1 c_3^2 \omega_1 + \eta \gamma^2 \beta_2 c_5 \omega_2 + \eta \gamma \epsilon \beta_2 c_3 c_5 + \eta \gamma \beta_1 c_3 c_5 \omega_2 + \eta \epsilon \beta_1 c_3^2 c_5 - \gamma \beta_2 c_2 c_3 c_4 c_5 - \beta_1 c_2 c_3^2 c_4 c_5} \\ Q_1 &= -\frac{\gamma (\Pi \gamma \beta_2 c_4 c_5 + \Pi \beta_1 c_3 c_4 c_5 - \alpha \eta \gamma \chi \omega_2 - \alpha \eta \epsilon \chi c_3 + \alpha \chi c_2 c_3 c_4 + \eta \gamma c_1 c_5 \omega_2 + \eta \epsilon c_1 c_3 c_5 - c_1 c_2 c_3 c_4 c_5)}{\alpha \gamma^2 \beta_2 \omega_1 \omega_2 + \alpha \gamma \epsilon \beta_2 c_3 \omega_1 + \alpha \gamma \beta_1 c_3 \omega_1 \omega_2 + \alpha \epsilon \beta_1 c_3^2 \omega_1 + \eta \gamma^2 \beta_2 c_5 \omega_2 + \eta \gamma \epsilon \beta_2 c_3 c_5 + \eta \gamma \beta_1 c_3 c_5 \omega_2 + \eta \epsilon \beta_1 c_3^2 c_5 - \gamma \beta_2 c_2 c_3 c_4 c_5 - \beta_1 c_2 c_3^2 c_4 c_5} \\ R_1 &= -\frac{(\epsilon c_3 + \gamma \omega_2) (\Pi \gamma \beta_2 c_4 c_5 + \Pi \beta_1 c_3 c_4 c_5 - \alpha \eta \gamma \chi \omega_2 - \alpha \eta \epsilon \chi c_3 + \alpha \chi c_2 c_3 c_4 + \eta \gamma c_1 c_5 \omega_2 + \eta \epsilon c_1 c_3 c_5 - c_1 c_2 c_3 c_4 c_5)}{c_4 (\alpha \gamma^2 \beta_2 \omega_1 \omega_2 + \alpha \gamma \epsilon \beta_2 c_3 \omega_1 + \alpha \gamma \beta_1 c_3 \omega_1 \omega_2 + \alpha \epsilon \beta_1 c_3^2 \omega_1 + \eta \gamma^2 \beta_2 c_5 \omega_2 + \eta \gamma \epsilon \beta_2 c_3 c_5 + \eta \gamma \beta_1 c_3 c_5 \omega_2 + \eta \epsilon \beta_1 c_3^2 c_5 - \gamma \beta_2 c_2 c_3 c_4 c_5 - \beta_1 c_2 c_3^2 c_4 c_5)} \\ M_1 &= -\frac{1}{(\gamma \beta_2 + \beta_1 c_3) c_4 (\alpha \gamma \omega_1 \omega_2 + \alpha \epsilon c_3 \omega_1 + \eta \gamma c_5 \omega_2 + \eta \epsilon c_3 c_5 - c_2 c_3 c_4 c_5)} (\Pi \gamma^2 \beta_2 c_4 \omega_1 \omega_2 + \Pi \gamma \epsilon \beta_2 c_3 c_4 \omega_1 + \Pi \gamma \beta_1 c_3 c_4 \omega_1 \omega_2 + \\ &\quad \Pi \epsilon \beta_1 c_3^2 c_4 \omega_1 + \eta^2 \gamma^2 \chi \omega_2^2 + 2 \eta^2 \gamma \epsilon \chi c_3 \omega_2 + \eta^2 \epsilon^2 \chi c_3^2 + \eta \gamma^2 c_1 \omega_1 \omega_2^2 + 2 \eta \gamma \epsilon c_1 c_3 \omega_1^2 \omega_2 - 2 \eta \gamma \chi c_2 c_3 c_4 \omega_2 + \eta \epsilon^2 c_1 c_3^2 \omega_1 \\ &\quad - 2 \eta \epsilon \chi c_2 c_3^2 c_4 - \gamma c_1 c_2 c_3 c_4 \omega_1 \omega_2 - \epsilon c_1 c_2 c_3^2 c_4 \omega_1 + \chi c_2^2 c_3^2 c_4^2)\end{aligned}$$

Reproduction Number of the Model (R_{eff})

The two solutions of the model can better be understood with the help of effective reproduction number of the model (R_{eff}) which is defined as the number of new cases of the infection that arises from introduction of a single infective into the population of largely susceptible individuals. Some of the ways of calculating this R_{eff} is by the use of di-graph method, next generation matrix etc. The basic reproduction number of the model was calculated at the Infection Free equilibrium E_0 and obtained as:

$$R_{eff} = \frac{(\beta_1 c_3 + \beta_2 \gamma) S_0}{c_2 c_3} \quad (0.6)$$

Stability Analysis of the Model

Model (1) can exhibit behavioral change called bifurcation, at a point, the equilibrium may tend towards the infection free that is, no spread of disease, whereas at some other point, it may go to endemic state (break-out of the disease in the population). To interpret the mathematical model, there are different forms of analysis, which include but not limited to bifurcation analysis and stability analysis. This study consider the stability and bifurcation analysis of the model with reference to the effective reproduction number. It is important to note that the equilibrium point of a system is stable locally if all the associated eigenvalues of its variational matrix have negative real parts otherwise it is unstable at such a point. The following propositions and theorem shall be established to obtain the stability analysis of the model.

Proposition 1: $R_{eff} < 1$ implies non-existence of endemic equilibrium E_1 and $E_0 = E_1$ whenever $R_{eff} = 1$.

Theorem 2: The infection-free equilibrium (I.F.E) of system (3) is locally asymptotically stable whenever $R_{eff} < 1$ and unstable otherwise.

Proof: The Jacobian matrix of system (3) shall be used at the I.F.E. state to establish the above theorem. This is obtained by partially differentiating the five equations with the five state variables of the model and is given as:

$$J_{E_0} = \begin{bmatrix} -\lambda - c_1 & -\beta_1 S & -\beta_2 S & 0 & \alpha \\ \lambda & \beta_1 S - c_2 & \beta_2 S & \eta & 0 \\ 0 & \gamma & -c_3 & 0 & 0 \\ 0 & \varepsilon & \omega_2 & -c_4 & 0 \\ \chi & 0 & 0 & \omega_1 & -c_5 \end{bmatrix} \quad (0.7)$$

Evaluating J_{E_0} at the I.F.E and noting that $\lambda = \beta_1 I + \beta_2 Q$ to obtain;

$$J_{E_0} = \begin{bmatrix} -c_1 & -\beta_1 S_0 & -\beta_2 S_0 & 0 & \alpha \\ 0 & \beta_1 S_0 - c_2 & \beta_2 S_0 & \eta & 0 \\ 0 & \gamma & -c_3 & 0 & 0 \\ 0 & \varepsilon & \omega_2 & -c_4 & 0 \\ \chi & 0 & 0 & \omega_1 & -c_5 \end{bmatrix} \quad (0.8)$$

Definition 1: A square matrix \mathbf{J} is called a stable matrix (Hurwitz matrix) if all eigenvalues of \mathbf{J} have negative real part.

Thus, following definition 1, the I.F.E is locally asymptotically stable if the above matrix have negative eigenvalues. It is sufficient to use the Trace-Determinant approach to establish the I.F.E of the model. Thus, if the trace of the Jacobian matrix J_{E_0} is less than zero and its determinant is greater than zero, then all the eigenvalues are real and negative. Thus, obtaining the trace of the matrix above as:

$$Trace(J_{E_0}) = -(\beta_1 S_0 + c_1 + c_2 + c_3 + c_4 + c_5) \quad (0.9)$$

Which is obviously negative since all the parameters of the model are non-negative.

The determinant of the matrix is given as:

$$|J_{E_0}| = -\alpha \chi \gamma S_0 \beta_2 c_4 - \alpha \chi S_0 \beta_1 c_3 c_4 + \gamma S_0 \beta_2 c_1 c_4 c_5 + S_0 \beta_1 c_1 c_3 c_4 c_5 - \alpha \chi \epsilon \eta c_3 - \alpha \chi \eta \gamma \omega_2 + \alpha \chi c_2 c_3 c_4 + \epsilon \eta c_1 c_3 c_5 + \eta \gamma c_1 c_5 \omega_2 - c_1 c_2 c_3 c_4 c_5 \quad (0.10)$$

Re-arranging and simplifying to get

$$|J_{E_0}| = -\alpha \chi \gamma S_0 \beta_2 c_4 - \alpha \chi S_0 \beta_1 c_3 c_4 + \alpha \chi c_2 c_3 c_4 + \gamma S_0 \beta_2 c_1 c_4 c_5 + S_0 \beta_1 c_1 c_3 c_4 c_5 - c_1 c_2 c_3 c_4 c_5 + \epsilon \eta c_1 c_3 c_5 + \alpha \chi \epsilon \delta_2 \omega_1 + \alpha \chi \epsilon \omega_1 \omega_2 + \alpha \chi \eta \gamma \mu + \alpha \chi \eta \gamma \delta_2 + \alpha \chi \eta \gamma \omega_2 + \alpha \chi \eta \mu^2 + \alpha \chi \eta \mu \delta_1 + \alpha \chi \eta \mu \delta_2 + \alpha \chi \eta \mu \omega_2 + \alpha \chi \eta \delta_1 \delta_2 + \alpha \chi \eta \delta_1 \omega_2 + \alpha \chi \gamma \mu^2 + \alpha \chi \gamma \mu \delta_2 + \alpha \chi \gamma \mu \omega_1 + \alpha \chi \gamma \mu \omega_2 + \alpha \chi \gamma \delta_2 \omega_1 + \alpha \chi \gamma \omega_1 \omega_2 + \alpha \chi \mu^3 + \alpha \chi \mu^2 \delta_1 + \alpha \chi \mu^2 \delta_2 + \alpha \chi \mu^2 \omega_1 + \alpha \chi \mu^2 \omega_2 + \alpha \chi \mu \delta_1 \delta_2 + \alpha \chi \mu \delta_1 \omega_1 + \alpha \chi \mu \delta_1 \omega_2 + \alpha \chi \mu \delta_2 \omega_1 + \alpha \chi \mu \omega_1 \omega_2 + \alpha \chi \delta_1 \delta_2 \omega_1 + \alpha \chi \delta_1 \omega_1 \omega_2 + \alpha \eta \gamma \mu \omega_2 + \chi \eta \gamma \mu \omega_2 + \alpha \chi \epsilon \mu \delta_2 + \alpha \chi \epsilon \mu \omega_1 + \alpha \chi \epsilon \mu \omega_2 + \alpha \chi \epsilon \mu^2 + \eta \gamma \mu^2 \omega_2 \quad (0.11)$$

On further simplification, we obtain

$$|J_{E_0}| = -\alpha \chi c_2 c_3 c_4 \left(S_0 \left(\frac{\beta_2 \gamma + \beta_1 c_3}{c_2 c_3} \right) - 1 \right) + c_1 c_4 c_5 \left(1 - S_0 \left(\frac{\beta_2 \gamma + \beta_1 c_3}{c_2 c_3} \right) \right) + \alpha \chi \epsilon \mu \omega_1 + \alpha \chi \epsilon \mu \delta_2 + \alpha \chi \epsilon \delta_2 \omega_1 + \alpha \chi \epsilon \omega_1 \omega_2 + \alpha \chi \eta \gamma \mu + \alpha \chi \eta \gamma \delta_2 + \alpha \chi \eta \gamma \omega_2 + \alpha \chi \eta \mu^2 + \alpha \chi \eta \mu \delta_1 + \alpha \chi \eta \mu \delta_2 + \alpha \chi \eta \mu \omega_2 + \alpha \chi \eta \delta_1 \delta_2 + \alpha \chi \eta \delta_1 \omega_2 + \alpha \chi \gamma \mu^2 + \alpha \chi \gamma \mu \delta_2 + \alpha \chi \gamma \mu \omega_1 + \alpha \chi \gamma \mu \omega_2 + \alpha \chi \gamma \delta_2 \omega_1 + \alpha \chi \gamma \omega_1 \omega_2 + \alpha \chi \mu^3 + \alpha \chi \mu^2 \delta_1 + \alpha \chi \mu^2 \delta_2 + \alpha \chi \mu^2 \omega_1 + \alpha \chi \mu^2 \omega_2 + \alpha \chi \mu \delta_1 \delta_2 + \alpha \chi \mu \delta_1 \omega_1 + \alpha \chi \mu \delta_1 \omega_2 + \alpha \chi \mu \delta_2 \omega_1 + \alpha \chi \mu \omega_1 \omega_2 + \alpha \chi \delta_1 \delta_2 \omega_1 + \alpha \chi \delta_1 \omega_1 \omega_2 + \alpha \eta \gamma \mu \omega_2 + \chi \eta \gamma \mu \omega_2 + \alpha \chi \epsilon \mu \omega_2 + \alpha \chi \epsilon \mu^2 + \eta \gamma \mu^2 \omega_2 \quad (0.12)$$

$$\begin{aligned} |J_{E_0}| &= -\alpha \chi c_2 c_3 c_4 (R_{eff} - 1) + c_1 c_4 c_5 (1 - R_{eff}) + \alpha \chi \epsilon \mu \omega_1 + \alpha \chi \epsilon \mu \delta_2 + \alpha \chi \epsilon \delta_2 \omega_1 + \alpha \chi \epsilon \omega_1 \omega_2 + \\ &\alpha \chi \eta \gamma \mu + \alpha \chi \eta \gamma \delta_2 + \alpha \chi \eta \gamma \omega_2 + \alpha \chi \eta \mu^2 + \alpha \chi \eta \mu \delta_1 + \alpha \chi \eta \mu \delta_2 + \alpha \chi \eta \mu \omega_2 + \alpha \chi \eta \delta_1 \delta_2 + \alpha \chi \eta \delta_1 \omega_2 + \\ \Rightarrow &\alpha \chi \gamma \mu^2 + \alpha \chi \gamma \mu \delta_2 + \alpha \chi \gamma \mu \omega_1 + \alpha \chi \gamma \mu \omega_2 + \alpha \chi \gamma \delta_2 \omega_1 + \alpha \chi \gamma \omega_1 \omega_2 + \alpha \chi \mu^3 + \alpha \chi \mu^2 \delta_1 + \alpha \chi \mu^2 \delta_2 + \\ &\alpha \chi \mu^2 \omega_2 + \alpha \chi \mu \delta_1 \delta_2 + \alpha \chi \mu \delta_1 \omega_1 + \alpha \chi \mu \delta_1 \omega_2 + \alpha \chi \mu \delta_2 \omega_1 + \alpha \chi \mu \omega_1 \omega_2 + \alpha \chi \delta_1 \delta_2 \omega_1 + \alpha \chi \delta_1 \omega_1 \omega_2 + \\ &\alpha \eta \gamma \mu \omega_2 + \chi \eta \gamma \mu \omega_2 + \alpha \chi \epsilon \mu \omega_2 + \alpha \chi \epsilon \mu^2 + \eta \gamma \mu^2 \omega_2 + \alpha \chi \mu^2 \omega_1 \end{aligned} \quad (0.13)$$

Which is strictly positive whenever $R_{eff} < 1$. Thus, the I.F.E is locally asymptotically stable whenever $R_{eff} < 1$ and unstable otherwise.

Global Stability Analysis of the Model at Infection Free Equilibrium

We adopt Castillo-Chavez *et al.*, [12] to obtain the global stability analysis of the new generalized *SIQR*M tuberculosis model. Suppose:

$$\begin{aligned} \frac{dX}{dt} &= F(X, Z) \\ \frac{dZ}{dt} &= G(X, Z), \quad G(X, 0) = 0 \end{aligned} \quad (0.14)$$

where both $X \in \mathfrak{R}^m$ and $Z \in \mathfrak{R}^n$ and their components denote the number of uninfected and infected individuals respectively and $E_0 = (x^*, 0)$ is the infection free equilibrium point. Then, the fixed point $E_0 = (x^*, 0)$ is a globally asymptotic stable (g.a.s.) equilibrium of the system (3) provided that $R_{eff} < 1$ (l.a.s.) and that assumptions (H1) and (H2) below are satisfied:

(H1) For $\frac{dX}{dt} = F(X, 0)$, X^* is globally asymptotically stable (g.a.s.)

(H2) $G(X, Z) = AZ - \hat{G}(X, Z)$, $\hat{G}(X, Z) \geq 0$ for $(X, Z) \in \Omega$

where $A = D_z G(X^*, 0)$ is an M -matrix (the off diagonal elements of A are non-negative) and 0 is the region where the model makes biological sense.

Theorem 3: The equilibrium point $E_0 = (W^*, 0)$ of system (3) is Globally Asymptotically Stable provided that $R_{eff} < 1$ and unstable if otherwise.

Proof: It is sufficient to establish the two criteria from Castillo-Chavez *et al.*, (2002) to establish the globally asymptotically stable (g.a.s.) equilibrium for the system (3). Splitting system of equations (3) into:

$$\begin{aligned} X &= (S, R, M), \quad Z = (I, Q) \\ \frac{dX}{dt} &= F(X, Z) = \begin{pmatrix} \pi + \alpha M - \lambda S - c_1 S \\ \epsilon I + \omega_2 Q - c_4 R \\ \omega_1 R + \chi S - c_5 M \end{pmatrix} \\ F(X, 0) &= \begin{pmatrix} \pi + \alpha M - c_1 S \\ 0 \\ \chi S - c_5 M \end{pmatrix} \end{aligned} \quad (0.15)$$

Solving the resulting equation in (15) at equilibrium to obtain

$$F(X, 0) = E_0 = (S_0, R_0, M_0) = \left(\frac{\pi c_5}{\mu(c_1 + \alpha)}, 0, \frac{\pi \chi}{\mu(c_1 + \alpha)} \right)$$

Also, from (15),

$$\begin{aligned} \frac{dS}{dt} &= \pi + \alpha M - c_1 S \\ \Rightarrow \frac{dS}{dt} &\leq \pi - c_1 S \\ \therefore S(t) &\leq \frac{\pi}{\mu} + \left(S(0) - \frac{\pi}{\mu} \right) e^{-\mu t} \end{aligned} \quad (0.16)$$

Obviously, as;

$$t \rightarrow \infty, \quad S(t) \rightarrow \frac{\pi}{\mu} \quad (0.17)$$

Similarly, solving for M from (15) to obtain $M(t) \leq ke^{-c_5 t}$ which approaches a constant value as $t \rightarrow \infty$. Thus, condition H1 is satisfied. Now,

$$G(X, Z) = \begin{bmatrix} \lambda S + \eta R - c_2 I \\ \gamma I - c_3 Q \end{bmatrix} = \begin{bmatrix} (\beta_1 I + \beta_2 Q)S + \eta R - c_2 I \\ \gamma I - c_3 Q \end{bmatrix} \quad (0.18)$$

Put $A = D_z G(X^*, 0)$ (the Jacobian matrix of the infected compartment at the infection free equilibrium state),

$$\begin{aligned} A &= \begin{bmatrix} \beta_1 S_0 - c_2 & \beta_2 S_0 \\ \gamma & -c_3 \end{bmatrix} \\ AZ &= \begin{bmatrix} \beta_1 S_0 - c_2 & \beta_2 S_0 \\ \gamma & -c_3 \end{bmatrix} \begin{bmatrix} I \\ Q \end{bmatrix} \\ &= \begin{bmatrix} (\beta_1 S_0 - c_2)I + \beta_2 S_0 Q \\ \gamma I - c_3 Q \end{bmatrix} \end{aligned} \quad (0.19)$$

From $H1$, $S_0 \rightarrow \frac{\pi}{\mu} = N$

$$\begin{aligned} AZ &= \begin{bmatrix} \beta_1 NI - c_2 I + \beta_2 NQ \\ \gamma I - c_3 Q \end{bmatrix} \\ \hat{G}(X, Z) &= AZ - G(X, Z) \\ \hat{G}(X, Z) &= \begin{bmatrix} \beta_1 NI - c_2 I + \beta_2 NQ \\ \gamma I - c_3 Q \end{bmatrix} - \begin{bmatrix} (\beta_1 I + \beta_2 Q)S + \eta R - c_2 I \\ \gamma I - c_3 Q \end{bmatrix} \end{aligned} \quad (0.20)$$

At infection free equilibrium, $R_0 = 0$. Using this for further simplification, we have;

$$\begin{aligned} \hat{G}(X, Z) &= \begin{bmatrix} (\beta_1 I + \beta_2 Q)(N - S) \\ 0 \end{bmatrix} \\ &= \begin{bmatrix} (\beta_1 I + \beta_2 Q)N \left(1 - \frac{S}{N}\right) \\ 0 \end{bmatrix} \geq 0 \end{aligned} \quad (0.21)$$

Since $0 \leq S \leq N$, it is clear that $\hat{G}(X, Z) \geq 0$. And since E_0 is G.A.S. equilibrium of $\frac{dX}{dt}$ from $H1$, it follows that E_0 is Globally Asymptotically Stable (G.A.S)

Bifurcation Analysis of the Model

The stability analysis of an equilibrium point determines whether a system remain near the equilibrium point when subjected to slight adjustment (or perturbation). Thus, the solution of an epidemic models are considered reasonable when small perturbation does not lead to large variation. In this section, we shall be considering the bifurcation analysis of the *SIQRM* tuberculosis model at infection free equilibrium by using centre manifold theory as applied by Mukandavire *et al.*, 2009 [7]. For easy representation, let $S = x_1$, $I = x_2$, $Q = x_3$, $R = x_4$ and $M = x_5$, then system (3) becomes:

$$\begin{aligned} f_1 &= \frac{dx_1}{dt} = \pi + \alpha x_5 - \lambda x_1 - c_1 x_1 \\ f_2 &= \frac{dx_2}{dt} = \lambda x_1 + \eta x_4 - c_2 x_2 \\ f_3 &= \frac{dx_3}{dt} = \gamma x_2 - c_3 x_3 \\ f_4 &= \frac{dx_4}{dt} = \epsilon x_2 + \omega_2 x_3 - c_4 x_4 \\ f_5 &= \frac{dx_5}{dt} = \omega_1 x_4 + \chi x_1 - c_5 x_5 \end{aligned} \quad (0.22)$$

Using (6) and (17), the bifurcation parameter is chosen at $R_{eff} = 1$ as:

$$\beta = \beta^* = \frac{c_2 c_3 \mu}{\pi (\beta_1 c_3 + \beta_2 \gamma)}$$

The matrix (8) has a right eigenvector denoted by $U = (u_1, u_2, u_3, u_4, u_5)^T$ as follows:

$$J_{Right} = \begin{pmatrix} -c_1 & \frac{-\beta_1^* \pi}{\mu} & \frac{-\beta_2^* \pi}{\mu} & 0 & \alpha \\ 0 & \frac{\beta_1^* \pi}{\mu} - c_2 & \frac{\beta_2^* \pi}{\mu} & \eta & 0 \\ 0 & \gamma & -c_3 & 0 & 0 \\ 0 & \epsilon & \omega_2 & -c_4 & 0 \\ \chi & 0 & 0 & \omega_1 & -c_5 \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \end{pmatrix} = 0 \quad (0.23)$$

Solving (23) to get,

$$\begin{aligned} u_2 > 0 \quad (free), \quad u_3 &= \frac{\gamma u_2}{c_3}, \quad u_4 = \left(\frac{\epsilon c_3 + \omega_2 \gamma}{c_3 c_4} \right) u_2 \\ u_1 &= \frac{c_4 c_5 (c_3 \beta_1^* \pi + \beta_2^* \pi \gamma) - \mu \omega_1 \alpha (\epsilon c_3 + \omega_2 \gamma)}{\mu c_3 c_4} \\ u_5 &= \frac{\chi c_4 c_5 (c_3 \beta_1^* \pi + \beta_2^* \pi \gamma) + (1 - \alpha) \mu \omega_1 (\epsilon c_3 + \omega_2 \gamma)}{\mu c_3 c_4} \end{aligned} \quad (0.24)$$

Similarly, the left eigenvector $V = (v_1, v_2, v_3, v_4, v_5)$ is obtained from the solution of:

$$J_{Left} = \begin{pmatrix} v_1 & v_2 & v_3 & v_4 & v_5 \end{pmatrix} \begin{pmatrix} -c_1 & -\beta_1^* \pi & -\beta_2^* \pi & 0 & \alpha \\ 0 & \frac{\beta_1^* \pi}{\mu} - c_2 & \frac{\beta_2^* \pi}{\mu} & \eta & 0 \\ 0 & \gamma & -c_3 & 0 & 0 \\ 0 & \epsilon & \omega_2 & -c_4 & 0 \\ \chi & 0 & 0 & \omega_1 & -c_5 \end{pmatrix} = 0 \quad (0.25)$$

as:

$$\begin{aligned} v_1 > 0 \quad free, \quad v_5 &= \frac{c_1 v_1}{\chi}, \quad v_2 = \left(\frac{c_5 y_6 + \gamma y_8}{c_5 y_5 + \gamma y_7} \right) v_1 \\ v_4 &= \frac{1}{c_4} \left(\frac{\eta (c_5 y_6 + \gamma y_8)}{c_5 y_5 + \gamma y_7} + \frac{\omega_1 c_1 v_1}{\chi} \right) v_1 \\ v_3 &= \frac{1}{\gamma} \left[y_6 + y_5 \left(\frac{c_5 y_6 + \gamma y_8}{c_5 y_5 + \gamma y_7} \right) \right] v_1 \end{aligned} \quad (0.26)$$

where $y_5 = \frac{\beta_1^* \pi}{\mu} - c_2 + \frac{\eta \epsilon}{c_4}$, $y_6 = \frac{\beta_1^* \pi}{\mu} + \frac{\epsilon \omega_1 c_1}{c_4 \chi}$, $y_7 = \frac{\beta_2^* \pi}{\mu} + \frac{\omega_2 \eta}{c_4}$ and $y_8 = \frac{\beta_2^* \pi}{\mu} + \frac{\omega_1 c_1}{c_4 \chi}$. According to Centre Manifold Theory (CMT), as applied by Mukandavire *et al.*, (2009), the dynamics of equilibrium of system (3) depend solely on a and b given as:

$$\begin{aligned} a &= \sum_{k,i,j=1}^n v_k u_i u_j \frac{\partial g_k(0,0)}{\partial x_i \partial x_j} \\ b &= \sum_{k,i,j=1}^n v_k u_i \frac{\partial g_k(0,0)}{\partial x_i \partial \phi} \end{aligned} \quad (0.27)$$

The non-zero second order partial derivative of (3) at I.F.E is given in equation (28) below:

$$\begin{aligned} \frac{\partial^2 f_1}{\partial x_1 \partial x_2} &= \frac{\partial^2 f_1}{\partial x_2 \partial x_1} = -\beta_1; & \frac{\partial^2 f_1}{\partial x_2 \partial \beta_1} &= \frac{\partial^2 f_1}{\partial \beta_1 \partial x_2} = -\frac{\pi}{\mu} \\ \frac{\partial^2 f_1}{\partial x_1 \partial x_3} &= \frac{\partial^2 f_1}{\partial x_3 \partial x_1} = -\beta_2; & \frac{\partial^2 f_1}{\partial x_3 \partial \beta_2} &= \frac{\partial^2 f_1}{\partial \beta_2 \partial x_3} = -\frac{\pi}{\mu} \\ \frac{\partial^2 f_2}{\partial x_1 \partial x_2} &= \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \beta_1; & \frac{\partial^2 f_2}{\partial x_2 \partial \beta_1} &= \frac{\partial^2 f_2}{\partial \beta_1 \partial x_2} = \frac{\pi}{\mu} \\ \frac{\partial^2 f_2}{\partial x_1 \partial x_3} &= \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \beta_2; & \frac{\partial^2 f_2}{\partial x_3 \partial \beta_2} &= \frac{\partial^2 f_2}{\partial \beta_2 \partial x_3} = \frac{\pi}{\mu} \end{aligned} \quad (0.28)$$

Substituting (24), (26) and (28) into (27) with further simplification to obtain:

$$\begin{aligned} a &= \frac{-2v_1 u_2^2 \gamma \beta^* [\pi c_4 (c_5 \beta_1 + \gamma \beta_2 \chi) + \omega_1 c_1 (c_5 + \gamma \mu)]}{\chi \mu c_3 c_4} < 0 \\ b &= \frac{v_1 u_2 \pi}{\mu} > 0 \end{aligned} \quad (0.29)$$

Whenever $a < 0$ and $b > 0$, by CMT, ϕ changes from negative to positive, the equilibrium point 0 changes its stability from stable to unstable. Correspondingly, a negative unstable equilibrium becomes positive and locally asymptotically stable. Hence, the model exhibits forward bifurcation when $R_{eff} = 1$. The implication of bifurcation is that the classical requirement of having the basic reproduction number less than unity, although necessary, is no longer sufficient to curtail the spread of the disease within the host community.

Numerical simulation and discussion

The *SIQRM* model developed for analysis in this work is an entirely new model for tuberculosis disease. Thus, the numerical analysis of the result obtained was presented in this section using secondary data obtained from literature. Different initial values for all the state variables are used to obtain the graphs while the values of the parameters used are as stated in Table 1. The initial populations were chosen so that the total population $N(t) = S(t) + I(t) + Q(t) + R(t) + M(t) = 6000$. The population for each curve are chosen as follows:

Curve 1: $S(t) = 5000$, $I(t) = 200$, $Q(t) = 100$, $R(t) = 200$ and $M(t) = 500$ while curve 2 has 3500, 1200, 400, 300 and 600 respectively, curve 3: 3000, 1000, 500, 600 and 900 respectively and curve 4 has 4500, 300, 200, 300 and 700 respectively. The graph for each compartment is plotted and the result were given below:

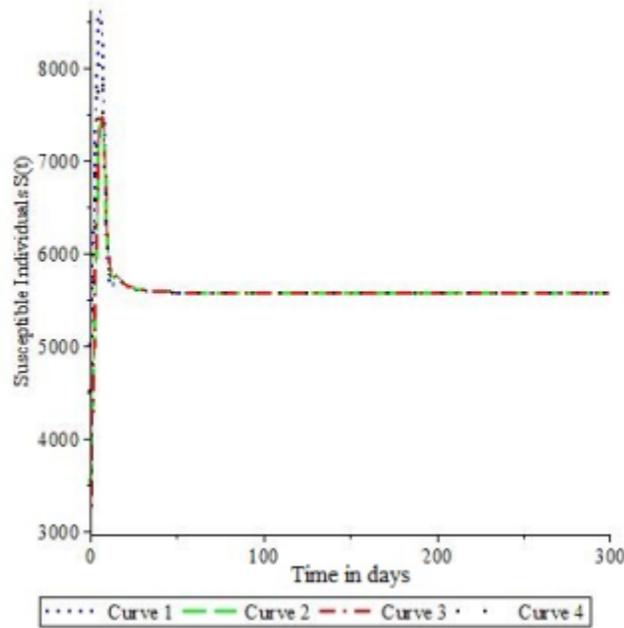


Figure 2: Change in S-compartment

The above figure 2 showed the rate of change in compartment S-population as time increases. The population first increase, then it decreases until it reached the equilibrium point.

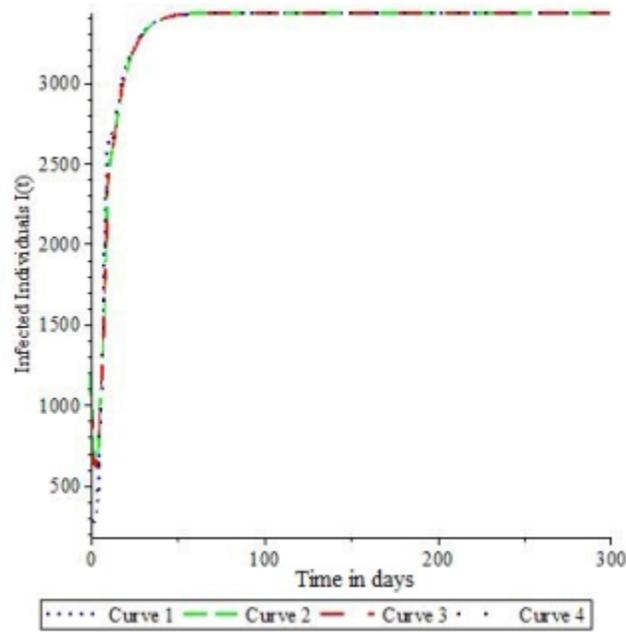


Figure 3: Change in I-compartment

The introduction of an infected individual alters the dynamics of any population as long as the reproduction number of the disease is greater than unity. This is obvious from the figure 3 as I-compartment increases in population until an equilibrium position is obtained.

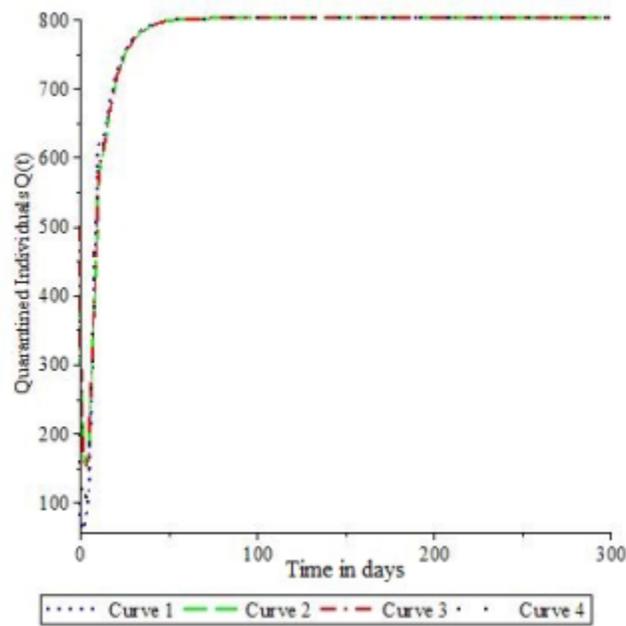


Figure 4: Change in Q-compartment

The more cases of infection reported, the more the removal of people exposed, which is the reason while figure 4 has an upward trend until the equilibrium is reached.

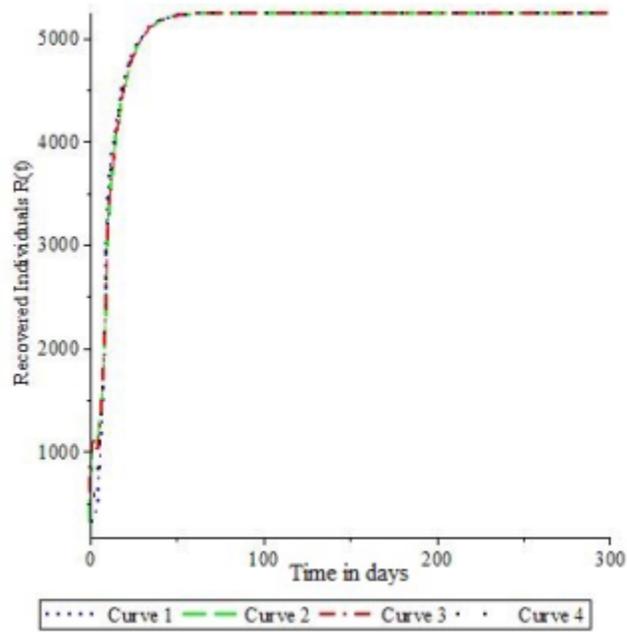


Figure 5: Change in R-compartment

Recovered individuals increases due to presence of effective treatment until the equilibrium point is attained as can be seen in the figure 5 above.

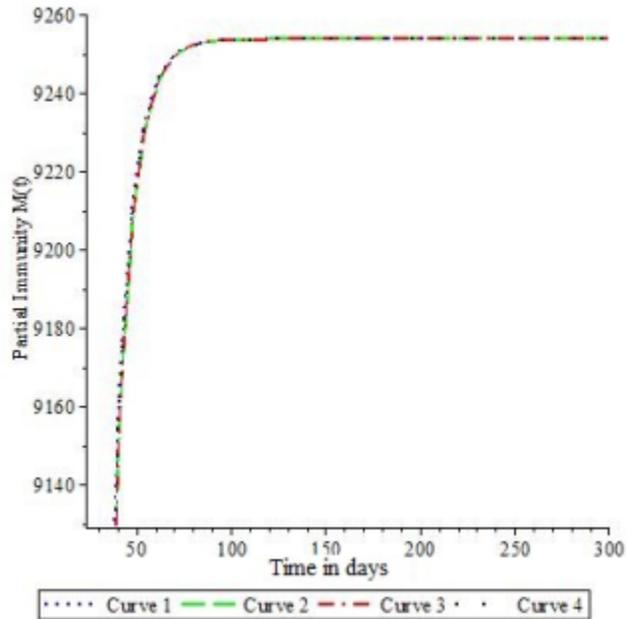


Figure 6: Change in M-compartment

The number of immune individuals increases with time due to immunity obtained from vaccine as well as partial immunity obtained from effective treatment of the disease.

Conclusion

A five-compartmental deterministic mathematical model for the transmission of infectious disease in the presence of vaccination, immunity loss and relapse is formulated and analyzed at the disease free equilibrium state. The model reproduction number was obtained and used to establish the local stability analysis of the model at DFE. Simulation was done and the findings of the study include:

1. Two equilibria states exist for the model which are the disease free and endemic equilibria points
2. Whenever the reproduction number of the disease is less than unity, the disease cannot spread within the community.
3. In the presence of effective treatment, the number of individual with immunity increases due to boost in the anti-bodies.
4. Quarantine can only be effective if people are well sensitized about the sign and symptoms of the infection, else the infection will continue to rise within the host community.

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