



THE EFFECTS OF IMMUNITY AND DRUG RESISTANCE ON THE TRANSMISSION DYNAMICS OF TUBERCULOSIS

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ABSTRACT

In this research, a Susceptible-Exposed-Infected-Recovered (SEIR) epidemiological model was modified to determine the effect of immunity and drug resistance on the transmission dynamics of tuberculosis. The equilibrium point was found and its stability was investigated. By analyzing the model, we found a threshold value R_0 , the basic reproduction number and the existence of the endemic point. The disease free equilibrium point of the model is locally stable (E_q^0) since basic reproduction number $R_0 < 1$ which was obtained from the numerical simulation of the model. The model has two non-negative equilibrium namely the disease free equilibrium (E_q^0) and endemic equilibrium point (EEP). The graphical solutions of the differential equations were developed using MATLAB as well as the computer simulation.

BACKGROUND OF THE STUDY

The sequencing of the genome for *M. tuberculosis*, completed in 1998 at the Sange Institute in Paris, must rank as one of the most important developments in the study of the history of tuberculosis. There are two principal reasons for this. First, it enabled scientists to confirm that human remains from prehistoric times, which were believed to show signs of tuberculosis disease on clinical grounds, could now be proved to have the tubercle bacillus present in the tissues. The DNA of the bacillus could be extracted from such specimens and provide positive identification. Secondly, the structure of the genomic sequence disproved an earlier hypothesis that humans had derived their disease from the animals they kept. For this to be true, the bacteria usually causing disease in animals, *M. bovis*, would have to have been the antecedent of the human tuberculosis bacterium, *M. tuberculosis*. Comparing the two bacterial genomes it is apparent that *M. tuberculosis* was, if anything, the antecedent of *M. bovis*, not the other way round. Therefore, it is possible that humans gave their disease to the animals. Further study is needed on this new genome driven hypothesis.

Tuberculosis is an airborne disease caused by *Mycobacterium tuberculosis* (MTB) bacteria. It is an ancient disease with evidence of its existence being found in relics from ancient Egypt, India and China. In the eighteenth century, Western Europe suffered terribly from this disease with prevalence as high as 900 deaths per 100,000. This was largely due

to poor ventilation, overcrowded housing, primitive sanitation and malnutrition among other risk factors that led to the epidemic (Daniel, 2006).

Today, this disease ranks as the second leading cause of morbidity and mortality in the world from a single infectious agent, after the human immunodeficiency virus (HIV). Interestingly, about one-third of the world's population is infected with MTB with approximately nine million people developing active tuberculosis and up to nearly two million people worldwide died from the disease every year.

Clearly, this reveals that the current investment in tuberculosis falls below the low and middle-income country's needs. (MTB) bacteria spread through inhaling droplets from the cough or sneeze of a person suffering from active tuberculosis. The bacteria enters the body causing an MTB infection affecting majorly the lungs but it can also affect any other part of the body including the urinary tract, brain, lymph nodes, bones, joints and the ear. Person(s) with lowered immunity such as those with HIV, diabetes, immune disorders, end-stage renal disease, those on drugs that suppress immunity, young children and pregnant women among others are at a higher risk of contracting the disease (Mandal, 2013).

Also people suffering from malnutrition due to lifestyle, drug abuse or poverty equally are at risk of contracting tuberculosis. Another category of people largely at risk of contracting tuberculosis are those who work closely or live close to a person with active tuberculosis and they could include health care workers, people living in crowded living spaces or confined places such as schools or prisons (Zaman, 2010). The intensity of transmission depends on factors related to the bacteria, the human host, the environment and migration. Non-climatic factors such as environmental development and urbanization, population movement and migration affect the severity and incidence of tuberculosis. When it comes to environment and urbanization, the incidence of tuberculosis is generally lower in prime urban areas than in rural areas as there is difficult accessing proper medical care in rural villages compared to urban areas. However, rapid urbanization of areas within or on the outskirts of urban centers is commonly done in an uncontrolled fashion without thought or planning. The settlers are mainly migrant workers from rural villages and they tend to settle mostly in poor, overcrowded houses commonly known as slums with hardly any proper sanitation and this in turn leads to increased exposure of the population to MTB hence a possibility of amplification of the disease to epidemic proportions through lack of effective treatment (Mandal, 2013).

Population movements have significant implications for tuberculosis transmission as migration introduces tuberculosis problem to the areas to which the migrants migrate to. Temporary migrant workers often bring the bacteria to lower prevalence areas and local transmission can be readily established (Semenza et al., 2010).

Tuberculosis is curable provided an early diagnosis is made and one follows the proper treatment regimen which could take six months up to two years for the active tuberculosis to clear (Trauer, Denholm and McBryde, 2014).

In 2015, there were an estimated 480, 000 new cases of multidrug-resistant TB (MDR-TB) and an additional 100, 000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment. India, China and the Russian Federation accounted for 45% of the combined 580, 000 cases (WHO, 2016).

AIM AND OBJECTIVES OF THE STUDY

The aim of this study is to model the effects of immunity and drug resistance on transmission dynamics of tuberculosis. Thus, the objectives are:

1. To derive the disease free equilibrium.
2. To obtain the basic reproduction number.
3. To carry out stability analysis on the model.
4. To solve the model equations numerically to show the effects of immunity and drug resistance on transmission dynamics of tuberculosis.

STATEMENT OF THE PROBLEM

There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015 (WHO, 2016). Andam, (2013) formulated a deterministic model for the transmission dynamics of tuberculosis. However, the model did not incorporate drug resistant to the first line of treatment of tuberculosis and immunity at susceptible class. We, therefore, intend to investigate the effects of immunity and drug resistance on transmission dynamics of tuberculosis.

RESEARCH QUESTIONS

1. How do we know the diseases is in free equilibrium state?
2. How long does it obtain the reproduction number?
3. How does it stability analysis on the model?
4. To know whether there is effect of immunity and drug resistance on transmission dynamic of tuberculosis.

SIGNIFICANCE OF THE STUDY

Considering the epidemics of tuberculosis and its attendant effects on population, the need to develop an effective control and management strategy cannot be over emphasized. Studying the effects of immunity and drug resistance on transmission dynamics of tuberculosis may yield interesting results that may usher in a new dimension in the control management by health service providers.

SCOPE OF THE STUDY

This research is only restricted to the use of mathematical modeling to investigate the effects of immunity and drug resistance on the transmission dynamics tuberculosis. A system of non-linear ordinary differential equations is formed and the trace method is used to study the stability of Disease Free Equilibrium Points of the model followed by numerical simulation only.

TB MODE OF TRANSMISSION

TB is an infectious disease which is spread from person-to-person through the air by droplet nuclei. Droplet nuclei are produced when person with pulmonary or laryngeal tuberculosis cough, sneeze, spit talk or sing. The size of the nuclei is estimated to be about 1-5 and normal air current can keep them airborne for a long time and spread them throughout a room or building until they are removed by natural or mechanical ventilation.

SIGNS AND SYMPTOMS OF TUBERCULOSIS

1. A bad cough that last three weeks or longer
2. Pain in the chest
3. Coughing up blood or sputum
4. Weakness or fatigue
5. Weight loss
6. No appetite

7. Fever
8. Sweating at night

TREATMENT OF TUBERCULOSIS

Antibiotics are used in the treatment of tuberculosis. Antibiotics treatment therapy is lengthy and one have to take them for 6 to 12 months to completely destroy the bacteria, the length of treatment and the type of drug that is needed is determined by age, overall health, result of susceptibility tests and whether one have TB infection or active TB.

A REVIEW OF SOME RELATED LITERATURE

Epidemiology of Tuberculosis

Tuberculosis (TB) is one of the major public health threats, competing with the human immunodeficiency virus (HIV) as the cause of death due to infectious diseases worldwide. Although a declining trend in TB incidence, prevalence and mortality has been observed over the last decade, elimination of the disease at global level is still out of reach, and massive resource investment is still required. TB is a poverty-related disease that disproportionately affects the poorest; the most vulnerable and marginalized population groups wherever it occurs. Improving access to diagnosis and care, the basic requirements in the fight against TB, are particularly challenging in these persons. Besides, TB control cannot be carried out without setting up an effective surveillance system in order to define the course of the epidemic and assess the impact of control measures on the disease. Hence, TB national programs must devote significant resources to the disease-specific recording and reporting system. Routine surveillance systems represent the best method for drug resistance assessment and monitoring, though high-quality data can be generated only by the allocation of significant resources. The increasing number of detected multidrug-resistant forms is among the current most frightening issues, requiring a strong and comprehensive commitment in terms of funds allocation, research promotion and field implementation of new tools and protocols (WHO, 2014).

MATHEMATICAL MODELS ON TUBERCULOSIS

The first model for the transmission dynamics of tuberculosis was developed by Waaler, and Anderson (1962) who used a mathematical model to study the epidemiology of tuberculosis. With time other models have been developed to help prevent the risk of transmission of tuberculosis. Recent global reports of multidrug resistant and extensively drug-resistant tuberculosis have renewed concerns that antibiotic resistance may undermine progress in tuberculosis control (Young, Stark and Kirschner, 2008). Including MDR tuberculosis in mathematical models is relatively new and there are very few models with this aspect.

Mandal et al (2017), among the estimated 1 million cases of childhood (0-14 years) TB worldwide, about 75% occur in the 22 high burden countries only. Being one of the high burden countries for TB, almost 10% of total TB cases in India is Pediatric TB. Pediatric TB has traditionally received a lower priority compared to the adult form of the disease because it is considered non-infectious, difficult to diagnose, too few in number and the wrong assumption that effective control of adult TB along with BCG by itself could effectively control childhood TB. Fortunately, World Health Organization (WHO) and the Revised National Tuberculosis Control Program (RNTCP) in India have realized the importance of pediatric TB and included special considerations for the Pediatric TB. In the wake of the recent changes in the guidelines regarding diagnosis and management of TB by

the RNTCP and WHO, we would like to highlight the changes applicable especially for the pediatric population:

Three new goals in the management of TB have been adopted, viz.

- (a) relapse free cure;
- b) prevention of drug resistance and
- (c) break chain of transmission by rendering the patient non-infectious and decreasing the pool of infection.

Definition of presumptive pediatric TB is provided which includes children with persistent fever and cough, loss of weight (loss of 5% body weight as compared to highest weight recorded)/no weight gain in last 3 months and history of contact with infectious TB cases. Diagnosis of tuberculosis based only on X-ray to be called as 'Clinically diagnosed tuberculosis'. Classification based on drug resistance now also includes Mono-resistance (MR) and poly-drug resistance (PDR) TB apart from MDR (Multi-drug resistant) and XDR (Extensively-drug resistant) TB. MR is defined as resistance to one first-line anti-TB drug (ATD) only; while PDR refers to resistance to more than one first-line ATD, other than both INH and Rifampicin. Use of CBNAAT (Cartridge based nucleic acid amplification test) and Line probe assay for MTB (*Mycobacterium tuberculosis*) complex in pulmonary specimens for diagnosis of TBDR (Drug resistant)-TB in presumptive cases. Use of CBNAAT for the diagnosis of extrapulmonary TB (EPTB):

- (a) as an additional test to conventional smear microscopy, culture and cytology in fine-needle aspiration cytology (FNAC) specimens;
- (b) as an adjunctive test for tuberculous meningitis but
- (c) not be routinely used to diagnose pleural TB. Rapid drug susceptibility testing (DST) of at least Rifampicin is recommended at the time of TB diagnosis. In patients with Rifampicin-resistant or MDR- TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9-12 months may be used.

Agusto et al, (2015), used a deterministic model with isolation where they studied the transmission dynamics of three strains of mycobacterium tuberculosis (TB), namely; the drug sensitive, multi-drug-resistance (MDR) and extensively-drug-resistance (XDR) tuberculosis strains. Their result of the global sensitivity analysis indicated that the dominant parameters are the disease progression rate, the recovery rate, the infectivity parameter, the isolation rate, and the rate of cost to follow up and fraction of fast progression rates. They also found that an increase in isolation rate leads to a decrease in the total number of individuals who are cost to follow up.

James M. Traver et al (2014), they present a mathematical model to stimulate Tuberculosis (TB) transmission in highly endemic regions of the Asia-Pacific, where epidemiology does not appear to be primarily driven by HIV co-infection deterministic model captures many of the observed phenomena important to disease dynamics, including partial and temporary vaccine efficacy, declining risk of active disease following infection, the possibility of re-infection both during the infection latent period and after treatment, multi-drug resistant TB (MDR - TB) and resistance during treatment. They found that the model could not be calibrated to the estimated incidence ratio without allowing for re-infection during latency, and that even in the presence of a moderate fitness cost and a lower value of R_0 , MDR - TB becomes the dominant strain at equilibrium.

Mandal (2013), there is an emerging form of tuberculosis commonly known as multi-drug resistant (MDR) tuberculosis which is defined as tuberculosis resistant to both of the two most effective first line of antibiotic treatment of active tuberculosis i.e., isoniazid (INH) and rifampin (RIF), and it is harder and more expensive to treat. It is currently a major health concern to medical workers and researchers and one can get MDR tuberculosis by either spending time with an MDR patient or breathing in the MDR tuberculosis bacteria or those with active tuberculosis not following their prescribed treatment regimen or TB medicine not being readily available to them. MDR tuberculosis is much more difficult to treat and the mortality of persons with this form of tuberculosis is far much higher if the second line of antibiotic treatment is not effected promptly.

Kalu A. U et al, (2013), also presented an epidemiological model that tuberculosis can effectively be controlled or even be eradicated if effort is made to ensure that the total removal rate from both the latent and the infectious classes is always less than the product of total contraction and total breakdown of the susceptible class.

S.Mariam H. et al (2011), tuberculosis disease (TB) due to *Mycobacterium tuberculosis* infections caused an estimated 1.3 million deaths globally. When active TB is manifested the infection is normally treated with antibiotics, thereby providing an external pressure for the selection of antibiotic resistant bacilli. The risk of resistance development will be determined by a number of different factors, including the antibiotic selective pressure (set by the number, dosing and quality of the used drugs), any pre-existing resistances in the infecting clone, the immune status of the treated individuals and their compliance with the drug regime. In addition, since all resistance development in *M. tuberculosis* occurs via mutational changes in the chromosome, the bacterial population size and the bacterial mutation rate will also affect the probability by which resistant clones appear during treatment. Furthermore, the ability of a resistant clone to grow and rise in frequency in the treated individual is influenced by the effect of the resistance on bacterial fitness.

Bhunu et al, (2008), presented a SEIR tuberculosis model which incorporated treatment of infectious individuals and chemoprophylaxis (treatment for the latently infected). The model assumed that the latently infected individuals develop active disease as a result of endogenous re-activation, exogenous re-infection and disease relapse. The study shows that treatment of infectious individuals is more effective in the first years of implementation as it cleared active TB immediately. As a result, chemoprophylaxis will do better in controlling the number of infectious due to reduced progression to active TB.

Cohen, and Murray (2004), modeled epidemics of multi- drug resistant tuberculosis of heterogeneous fitness. Their model suggested that the threat of multidrug resistance to tuberculosis control depends on relative fitness of MDR strains and this implied that the strains is considerably less than that of drug-sensitive strains and that the emergence of resistance would not jeopardize the success of tuberculosis control efforts. Their results implied that current epidemiological measures and short- term trends in the burden of MDR tuberculosis do not provide evidence that MDR tuberculosis strains can be contained in the absence of specific efforts to limit transmission from those with MDR disease.

Ziv et al, (2001), used an SEIR-model with fast and slow progression to numerically compare the effects of preventative treatment of those in the fast-progressing latent class with treatment of those with active, infectious disease. They concluded that contact tracing and preventative treatment compare quite favourably to treatment of those with the disease.

Dye et al, (1998), presented a model with explicit fast and slow progression from two latent classes. They studied drug-resistant TB alone, representing treatment failures as potential transmitters of drug-resistant TB. Using Monte Carlo methods to estimate the model's R_0 for drug-resistant TB, they argued that short-course chemotherapy can bring resistant strains under control, preventing drug-resistant TB from emerging, and that this can probably be done by meeting the WHO targets for case detection and cure.

METHODOLOGY

In this section, we will formulate the model with immunity and drug resistance effects on the transmission dynamics of tuberculosis.

EXISTING TUBERCULOSIS MODEL

We reviewed the existing model by Andam, (2013) in terms of assumptions, model description, model diagram, and model equations. This served as the framework for the model with immunity and drug resistant effect on the transmission dynamics of tuberculosis.

Model Assumptions

1. Age, sex, social status, race coupled with climatic conditions in the district does not affect the probability of an individual being infected.
2. The death rate of all individuals is balanced by a birth rate (birth and deaths occurs at equal rates).
3. He assumes that once an individual is infected, he or she becomes exposed to the environment before becoming infectious.

Description of the Model

In the model developed by Andam, (2013) the total population (N) is divided into four classes: Susceptible (S), Exposed (E), Infectious (I), and Recovered (R). The class of susceptible individuals S is increased by birth or immigration at a rate λ . It is decreased by infection due to contact with infected individuals at a rate β and diminished by natural death at a rate μ . The class of exposed individuals E is generated through contact with infected individuals and decreased by breakthrough into infected class I at a rate ϵ and diminished by natural death at a rate μ . The class of infected individuals I is generated by breakthrough of exposed individuals E , decreased by recovery from infection at a rate γ and diminished by natural death μ . This generates a class R of individuals who have complete protection against the disease and is diminished by natural death at a rate μ .

Model Diagram

Below is the model flow diagram of the dynamics of tuberculosis by Andam, (2013)

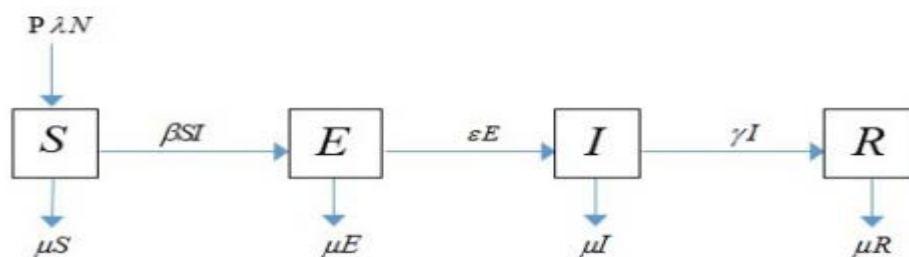


Figure 3.1: Existing Model Diagram by Andam, (2013).

Model Equations

Below is the system of first order non-linear ordinary differential equations formulated by Andam, (2013).

$$\frac{dS}{dt} = P\pi N - \beta SI - \mu S. \tag{1}$$

$$\frac{dE}{dt} = \beta SI - (\mu + \epsilon)E. \tag{2}$$

$$\frac{dE}{dt} = \varepsilon\beta - (\mu + \gamma)I. \tag{3}$$

$$\frac{dR}{dt} = \gamma I - \mu R. \tag{4}$$

Symbols	Description
N(t)	Total Population
S(t)	Number of Susceptible individuals at time t
E(t)	Number of Exposed individuals at time t
I(t)	Number of Infectious individuals at time t
R(t)	Number of Recovered individuals at time t
λ	Birth rate
β	Contact rate
μ	Death rate
ε	Infectious rate
γ	Recovery rate

Table 1.1: Parameters and variable description.

Reviewed Model

Below are the assumptions, description, diagram and model equations of the formulated modified model.

Assumptions of the with Immunity and Drug Resistance

The following assumptions were made:

1. Parameters and variables are considered non-negative.
2. Recruitment into the susceptible compartment is variable.
3. Transition into and out of any compartment is governed by a specified rate.
4. Natural death and death due to tuberculosis occurs at variable rate.
5. The members of the study population interact freely.

Description of the Model

The human population is categorized into six compartments such that at time $t \geq 0$ there are (S), susceptible humans, (M), immune infants, (E), exposed humans to tuberculosis, (I), infected humans with active tuberculosis, (R_{ES}), resistant humans to the first line of treatment, (R_H), recovered humans. Thus the size of the human population is given as $N = S + M + E + I + R_{ES} + R_H$. In our model, the recruitment into the susceptible human population is by birth $P\pi$. The size of the susceptible class is further increased by the immune infants in (M), partially immune humans in (R_H) after they lose their immunity at the rate η and ρ respectively. The susceptible class is decreased by natural death μ and exposed to MTB. The immune class (M) is increased by birth with immunity at a rate $(1-P)\pi$ and decreased by natural death μ . The exposed susceptible to MTB move to the

exposed classes (E) with the force of infection being β , resulting in an increase in the exposed class. Natural death μ and the proportion that move to the infected class (I) after developing active tuberculosis further decreased the exposed class. The infected class (I) is also reduced by natural death μ , disease induced death α , those who recover γ and also by those resistant to the first line of treatment σ . Thus, both the infected class (I) and the resistant class R_{ES} gain partial immunity at the rates γ and δ respectively thus moving to the recovered class (R) thus reducing their respective classes and also increasing the recovered class. The resistant class R_{ES} is also reduced by natural deaths μ and disease induced deaths α_1 while natural death μ and those who lose their partial immunity at the rate ρ reduce the recovered class.

Model Diagram

The flow diagram of the model with Immunity and Drug Resistance on the Transmission Dynamics of Tuberculosis is given in figure below.

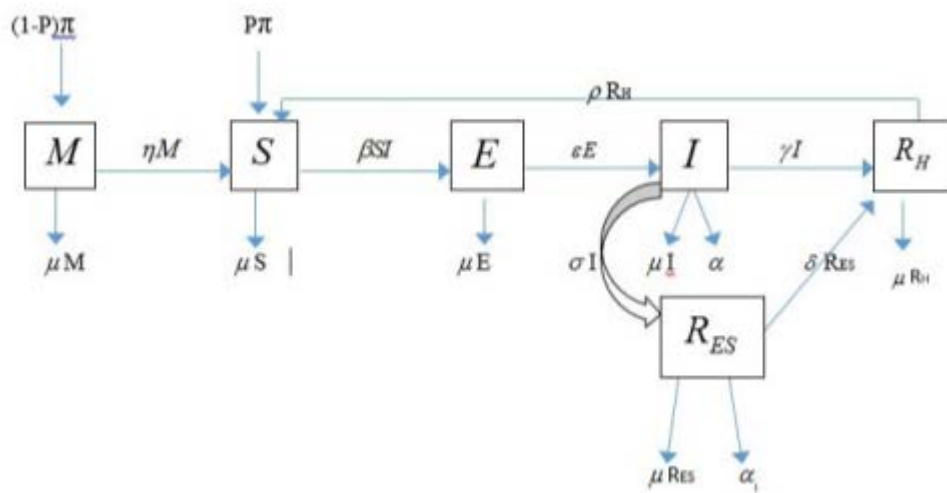


Figure 3.2: Model with immunity and drug resistance effect on the transmission.

3.3.4 Model Equations

$$\frac{dM}{dt} = (1 - P)\mu - (\mu + n)M. \tag{5}$$

$$\frac{dS}{dt} = P\pi + nM - \beta SI - \mu S p. \tag{6}$$

$$\frac{dE}{dt} = \beta SI - (\mu + \epsilon)E. \tag{7}$$

$$\frac{dI}{dt} = \epsilon E - (\mu + \alpha + \gamma + \sigma)I. \tag{8}$$

$$\frac{dR_H}{dt} = \gamma I - (\mu + \alpha_1 + \delta)R_{ES}. \tag{9}$$

Where $S(0) = S_0, V(0) = V_0, E(0) = E_0, I(0) = I_0, R_{ES}(0) = R_{ES0}, R_H(0) = R_{H0}$.
 Note that $N = S + M + E + I + R_{ES} + R_H$.

Symbols	Description
M(t)	Number of immune infants at time t
R _H (t)	Number of Recovered humans from both active and MDR tuberculosis at time t
R _{ES} (t)	Number of Resistant humans to first line of treatment at time t
I(t)	Number of Infectious individuals at time t
Pπ	Birth rate without immunity
(1-P)π	Birth rate with immunity
H	Rate at which immune infants become susceptible
A	Disease induced death rate due to active tuberculosis
α ₁	Disease induced death rate due to MDR tuberculosis
Δ	Recovery rate of infected humans from MDR tuberculosis
Σ	Rate at which infected humans become resistance to first line of treatment
P	Rate at which infected humans become susceptible

Table 1.2: Additional parameters and variables.

Method of Model Analysis

Various methods are considered in this section to carry out the analysis which are as follows:

Existence and Uniqueness

Theorem 1

Let D denote the region $|t - t_0| \leq \alpha$ and $|x - x_0| \leq b$, where $x = (x_1, x_2, x_3 \dots x_n)$ and $x_0 = (x_{0,1}, x_{0,2}, x_{0,3} \dots x_{0,n})$. Suppose that $f(t, x)$ satisfies Lipchiz condition $|f(t, x_1) - f(t, x_2)| \leq K|x_1 - x_2|$ where the pair (t, x_1) and (t, x_2) belongs to D and K is a positive constant. Thus consider the following lemma.

Lemma 1

Let $x_1 = M, x_2 = S, x_3 = E, x_4 = I, x_5 = R_{ES}, x_6 = R_H$ and f_1, f_2, f_3, f_4, f_5 and f_6 be the respective equations in system (5) - (9) and let $\lambda = \beta x_2 x_4$. The goal is to show that $\frac{df_i}{dx_j}, i, j = 1, 2, 3, 4, 5, 6$ are continuous and bounded in D. Now

$$f_1 = (1-P)\pi - (\mu + \eta)x_1$$

$$\left| \frac{df_1}{dx_1} \right| = |-\mu - \eta| < \infty; \left| \frac{df_1}{dx_2} \right| = \left| \frac{df_1}{dx_3} \right| = \left| \frac{df_1}{dx_4} \right| = \left| \frac{df_1}{dx_5} \right| = \left| \frac{df_1}{dx_6} \right| = 0 < \infty$$

Similarly, going on in same manner for f_2, f_3, f_4, f_5 and f_6 of model (5 - 9) above, we see that their partial derivatives exists for all equations and are continuous and bounded. Hence the system (5 - 9) has a unique solution.

3.4.2 Positivity of the solution

Lemma 2

Let the initial solution set $\{M(0) > 0, S(0) > 0, E(0) > 0, I(0) > 0, R_{ES}(0) > 0, R_H(0) > 0\} \in \mathbb{R}^6_+$, then the solution set $\{M(t), S(t), E(t), I(t), R_{ES}(t), R_H(t)\}$ is positive for all time $t > 0$.

Proof

Let the force of infection be $\lambda = \beta SI$. Consider the first equation (i.e. equation (5))

$$\frac{dM}{dt} = (1 - P)\pi - (\mu + n)M.$$

$$\geq -(\mu + n)M.$$

$$M(t) = M(0)\exp^{-\int(\mu+n)dt} > 0$$

Also for the second equation (i.e. equation (3.6))

$$\frac{dS}{dt} = P\pi + nM - \beta SI - \mu S + pR_H.$$

$$\geq -(\beta I + \mu)S.$$

$$S(t) = S(0)\exp^{-\int(\beta I + \mu)dt} > 0.$$

Going in same manner for the third, fourth, fifth and sixth equation, we found that $E(t) > 0$, $I(t) > 0$, $R_{ES}(t) > 0$, $R_H(t) > 0$ respectively. Hence the solution set is positive for all time $t > 0$.

Invariant Set

If a solution of a differential equation or a system of differential equations start on a given space, surface, or curve and remains within it for all time t , then the set is said to be invariant. Hence a positively invariant set will have solutions that are positive for all time. Now, let $N = S + M + E + I + R_{ES} + R_H$ be the total population at any time t . Therefore,

$$\begin{aligned} \frac{dN}{dt} &= \frac{dM}{dt} + \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR_{ES}}{dt} + \frac{dR_H}{dt} \\ &= \pi - P\pi - \mu M - \eta M + P\pi + \eta M - \beta SI - \mu S + pR_H + \beta SI - \mu E - \varepsilon E + \varepsilon E - \mu I \\ &\quad - \alpha I - \gamma I - \sigma I - \mu R_{ES} - \alpha_1 R_{ES} - \delta R_{ES} + \gamma I - \mu R_H - pR_H + \delta R_{ES}. \\ \frac{dN}{dt} &= \pi - \alpha I - \alpha_1 R_{ES} - \mu(M + S + E + I + R_{ES} + R_H) \\ &= \pi - \alpha I - \alpha_1 R_{ES} - \mu N. \\ \frac{dN}{dt} &= \pi - \mu N. \end{aligned}$$

Integrating this by variable separable method we have

$$\begin{aligned} \int \frac{dN}{\pi - \mu N} &= \int dt \\ -\frac{1}{\mu} &= \ln(\pi - \mu N) + \ln C = t \\ \ln(\pi - \mu) - \mu \ln C &= -\mu t \\ \ln(\pi - \mu N) - \ln C^\mu &= -\mu t \\ \ln(\pi - \mu N) &= -\mu t + \ln C^\mu \\ \mu - \mu N &= \exp^{-\mu t + \ln C^\mu} \\ \pi - \mu N &= N_0 \exp^{-\mu t}; \text{ where } N_0 = C^\mu \\ \mu N &= \pi - N_0 \exp^{-\mu t} \\ N &= \frac{1}{\mu} (\pi - N_0 \exp^{-\mu t}) \end{aligned}$$

Where N_0 is the initial population at time $t = 0$, thus as $t \rightarrow \infty$, we have $N = \frac{\pi}{\mu}$ Now, at any time (t) , the total population

$$N(t) \leq \frac{\pi}{\mu}$$

and therefore, if we let Ω to represent the invariant set, then

$$\Omega = \left\{ (M + S + E + I + R_{ES} + R_H) \in R_+^6 : N = \frac{\pi}{\mu} \right\}$$

Equilibrium States

The equilibrium state for the model is obtained by setting the model equations to zero.

$$i. e \frac{dM}{dt} = \frac{dS}{dt} = \frac{dE}{dt} = \frac{dI}{dt} \frac{dR_{ES}}{dt} = \frac{dR_H}{dt} = 0$$

Disease Free Equilibrium (Eq⁰)

The disease free equilibrium point of a system represent the state at which there are no infections in the whole population. Now, considering the two compartments $\frac{dM}{dt}$ and $\frac{dS}{dt}$.

$$\frac{dM}{dt} = (1 - P)\pi - (\mu + \eta)M.$$

$$(1 - P)\pi - (\mu + \eta)m = 0.$$

$$M^0 = \frac{(1 - \eta)\pi}{\mu + \eta}.$$

$$\frac{dS}{dt} = P\pi + \eta M - \beta SI - \mu S + pR_H = 0.$$

$$P\pi + \eta M - \beta SI - \mu S + pR_H = 0.$$

$$S^0 = \frac{P\pi(\mu + \eta) + (1 - P)\eta\pi}{\mu(\mu + \eta)}$$

$$E^0 = I^0 = R_{ES}^0 = 0.$$

Therefore, the disease free equilibrium state for the model is

$$Eq^0(M^0, S^0, E^0, I^0, R_{ES}^0, R_H^0) = \left(\frac{(1-P)\pi}{\mu+\eta}, \frac{P\pi(\mu+\eta)+(1-P)\eta\pi}{\mu(\mu+\eta)}, 0, 0, 0, 0 \right).$$

Basic Reproduction Number

The reproduction number R_0 is defined as the average number of secondary cases of infection generated by one primary case in a whole susceptible population. The basic reproduction number is used to predict whether the epidemic will spread or die out.

In this model, I will adopt the method of the next generation on the equations (5-9) in the form of matrices F and V.

Let:

F_i be the rate of approach of the new infection in a compartment.

V_i be the transfer of individuals out of compartment by another means.

X_0 be the disease-free equilibrium (Eq⁰).

The basic reproduction number is (R_0) is obtained by setting;

$R_0 = \rho(FV^{-1})$; where $F = \left[\frac{\partial F_i(x_0)}{\partial x_j} \right]$ and $V = \left[\frac{\partial V_i(x_0)}{\partial x_j} \right]$ for $i \geq 1$ for the number of compartments and $1 \leq j \leq m$ for the infected compartments only.

$\rho(FV^{-1})$ denotes the spectral radius of the matrix F and V are $m \times m$ matrices, where m is the number of infected classes (Diekmann, & Heesterbeek, 2000). Considering the infected compartments;

$$\left. \begin{aligned} \frac{dE}{dt} &= \beta SI - (\mu + \varepsilon)E \\ \frac{dI}{dt} &= \varepsilon E - (\mu + \alpha + \gamma + \sigma)I \end{aligned} \right\} \quad (10)$$

The system (10) can be represented in a matrix form as follows;

$$\begin{pmatrix} \frac{dE}{dt} \\ \frac{dI}{dt} \end{pmatrix} = \begin{pmatrix} 0 & \beta S \\ 0 & 0 \end{pmatrix} \begin{pmatrix} E \\ I \end{pmatrix} - \begin{pmatrix} \mu + \varepsilon & 0 \\ -\varepsilon & \mu + \alpha + \gamma + \sigma \end{pmatrix} \begin{pmatrix} E \\ I \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & \beta S \\ 0 & 0 \end{pmatrix} = \begin{pmatrix} 0 & \beta \frac{P\pi(\mu + \eta) + (1 - P)\eta\pi}{\mu(\mu + \eta)} \\ 0 & 0 \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & \beta \frac{P\pi(\mu + \eta) + (1 - P)\eta\pi}{\mu(\mu + \eta)} \\ 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \mu + \varepsilon & 0 \\ -\varepsilon & \mu + \alpha + \gamma + \sigma \end{pmatrix}$$

To find

$$V^{-1} = \frac{1}{|V|} AdjV.$$

$$|V| = \begin{vmatrix} \mu + \varepsilon & 0 \\ -\varepsilon & \mu + \alpha + \gamma + \sigma \end{vmatrix}$$

$$|V| = (\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma)$$

and

$$AdjV = \begin{pmatrix} \mu + \alpha + \gamma + \sigma & 0 \\ \varepsilon & \mu + \varepsilon \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu + \varepsilon} & 0 \\ \frac{\varepsilon}{(\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma)} & \frac{1}{\mu + \alpha + \gamma + \sigma} \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} 0 & \beta \frac{P\pi(\mu + \eta) + (1 - P)\eta\pi}{\mu(\mu + \eta)} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\mu + \varepsilon} & 0 \\ \frac{\varepsilon}{(\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma)} & \frac{1}{\mu + \alpha + \gamma + \sigma} \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} \frac{\beta\varepsilon[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \varepsilon)(\mu + \eta)(\mu + \alpha + \gamma + \sigma)} & \frac{\beta[P\pi + (1 - P)\eta\pi]}{\mu(\mu + \alpha + \gamma + \sigma)(\mu + \eta)} \\ 0 & 0 \end{pmatrix}$$

$$\rho(FV^{-1}) = \begin{vmatrix} \frac{\beta\varepsilon[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \varepsilon)(\mu + \eta)(\mu + \alpha + \gamma + \sigma)} - \lambda & \frac{\beta[P\pi + (1 - P)\eta\pi]}{\mu(\mu + \alpha + \gamma + \sigma)(\mu + \eta)} \\ 0 & 0 - \lambda \end{vmatrix} = 0$$

$$\left(\frac{\beta\varepsilon[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \varepsilon)(\mu + \eta)(\mu + \alpha + \gamma + \sigma)} - \lambda \right) (-\lambda) = 0$$

$$\lambda_1 = 0$$

and

$$\frac{\beta\varepsilon[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \varepsilon)(\mu + \eta)(\mu + \alpha + \gamma + \sigma)} - \lambda = 0$$

$$\lambda_2 = \frac{\beta\varepsilon[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \varepsilon)(\mu + \eta)(\mu + \alpha + \gamma + \sigma)}$$

$$\rho(FV^{-1}) = \frac{\beta\varepsilon[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \varepsilon)(\mu + \eta)(\mu + \alpha + \gamma + \sigma)}$$

$$R_0 = \frac{\beta\varepsilon[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \varepsilon)(\mu + \eta)(\mu + \alpha + \gamma + \sigma)}$$

The disease free equilibrium point of model (5 - 9) is locally stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Local Stability Analysis of the Disease Free Equilibrium of the Model

To check for the local stability of the disease free equilibrium of the model, we use trace method.

Lemma 2

The disease free equilibrium point (Eq^0) is locally asymptotically stable if the trace $\text{Tr}(J Eq^0) < 0$ and the determinant $\text{Det}(J Eq^0) > 0$ where $J Eq^0$ is the Jacobian matrix of the disease free equilibrium.

Proof

Recall system (5 - 9)

$$\begin{aligned}
 f_1 &= (1 - P)\pi - (\mu + \eta)M. \\
 f_2 &= P\pi + \eta M - \beta SI - \mu S + \rho R_H. \\
 f_3 &= \beta SI - (\mu + \varepsilon)E. \\
 f_4 &= \varepsilon E - (\mu + \alpha + \gamma + \sigma)I. \\
 f_5 &= \sigma I - (\mu + \alpha_1 + \delta)R_{ES}. \\
 f_6 &= \gamma I - (\mu + \rho)R_H + \delta R_{ES}.
 \end{aligned}$$

The Jacobian matrix of the system of equations is given as;

$$\begin{pmatrix}
 -(\mu + \eta) & 0 & 0 & 0 & 0 & 0 \\
 \eta & -(\beta I + \mu) & 0 & -\beta S & 0 & \rho \\
 0 & \beta I & -(\mu - \varepsilon) & \beta S & 0 & 0 \\
 0 & 0 & \varepsilon & -(\mu + \alpha + \gamma + \sigma) & 0 & 0 \\
 0 & 0 & 0 & \sigma & -(\mu + \alpha_1 + \delta) & 0 \\
 0 & 0 & 0 & \gamma & \delta & -(\mu + \rho)
 \end{pmatrix}$$

At disease free equilibrium (Eq^0) the component is given as

$$(Eq^0) = (M^0, S^0, E^0, I^0, R_{ES}^0, R_H^0) = \left(\frac{(1-P)\pi}{\pi + \eta}, \frac{P\pi(\mu + \eta) + (1-P)\eta\pi}{\mu(\mu + \eta)}, 0, 0, 0, 0 \right)$$

There Jacobian matrix of the becomes;

$$\begin{aligned}
 (JEq^0) &= \begin{pmatrix}
 0 & 0 & 0 & 0 & 0 & 0 \\
 -(\mu + \eta) & 0 & 0 & -\beta \frac{[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \eta)} & 0 & \rho \\
 \eta & -\mu & 0 & 0 & 0 & 0 \\
 0 & 0 & -(\mu + \varepsilon) & \beta \frac{P\pi(\mu + \eta) + (1 - P)\eta\pi}{\mu(\mu + \eta)} & 0 & 0 \\
 0 & 0 & \varepsilon & -(\mu + \alpha + \gamma + \sigma) & 0 & 0 \\
 0 & 0 & 0 & \sigma & -(\mu + \alpha_1 + \delta) & 0 \\
 0 & 0 & 0 & \gamma & \delta & -(\mu + \rho)
 \end{pmatrix} \\
 (JEq^0) &= \begin{pmatrix}
 -\beta & 0 & 0 & 0 & 0 & 0 \\
 \eta & -\mu & 0 & -D & 0 & \rho \\
 0 & 0 & -C & D & 0 & 0 \\
 0 & 0 & \varepsilon & -E & 0 & 0 \\
 0 & 0 & 0 & \sigma & -F & 0 \\
 0 & 0 & 0 & \gamma & \delta & -G
 \end{pmatrix}
 \end{aligned}$$

Where $B = (\mu + \eta)$, $C = (\mu + \varepsilon)$, $D = \beta \frac{[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \eta)}$, $E = (\mu + \alpha + \gamma + \sigma)$, $F = (\mu + \alpha_1 + \delta)$ and $G = (\mu + \rho)$.

Now, the trace is determine as;

$$-(B + \mu + C + E + F + G) < 0.$$

and

$$\begin{aligned}
 Det(JEq^0) &= -B \begin{vmatrix} -\mu & 0 & -D & 0 & \rho \\ 0 & -C & D & 0 & 0 \\ 0 & \varepsilon & -E & 0 & 0 \\ 0 & 0 & \sigma & -F & 0 \\ 0 & 0 & \gamma & \delta & -G \end{vmatrix} \\
 &= -B(-\mu \begin{vmatrix} -C & D & 0 & 0 \\ \varepsilon & -E & 0 & 0 \\ 0 & \sigma & -F & 0 \\ 0 & \gamma & \delta & -G \end{vmatrix} - D \begin{vmatrix} 0 & -C & 0 & 0 \\ 0 & \varepsilon & 0 & 0 \\ 0 & 0 & -F & 0 \\ 0 & 0 & \delta & -G \end{vmatrix} + \rho \begin{vmatrix} 0 & -C & D & 0 \\ 0 & \varepsilon & -E & 0 \\ 0 & 0 & \sigma & -F \\ 0 & 0 & \gamma & \delta \end{vmatrix}) \\
 &= -B \left[-\mu \left(-C \begin{vmatrix} -E & 0 & 0 \\ \sigma & -F & 0 \\ \gamma & \delta & -G \end{vmatrix} - D \begin{vmatrix} \varepsilon & 0 & 0 \\ 0 & -F & 0 \\ 0 & \delta & -G \end{vmatrix} \right) - D(C \begin{vmatrix} 0 & 0 & 0 \\ 0 & -F & 0 \\ 0 & \delta & -G \end{vmatrix}) \right. \\
 &\quad \left. + \rho(C \begin{vmatrix} 0 & - & 0 \\ 0 & \sigma & -F \\ 0 & \gamma & \delta \end{vmatrix} + D \begin{vmatrix} 0 & \varepsilon & 0 \\ 0 & 0 & -F \\ 0 & 0 & \delta \end{vmatrix}) \right] \\
 &= -B \left[-\mu \left(-C \begin{vmatrix} -E & -F & 0 \\ \delta & -G \end{vmatrix} - D \begin{vmatrix} \varepsilon & -F & 0 \\ \delta & -G \end{vmatrix} \right) - D(C \begin{vmatrix} -F & 0 \\ \delta & -G \end{vmatrix}) \right. \\
 &\quad \left. + \rho(C \begin{vmatrix} E & -F \\ 0 & \delta \end{vmatrix}) + D \begin{vmatrix} -\varepsilon & -F \\ 0 & \delta \end{vmatrix} \right] \\
 &= -B[-\mu(-C)(-E)(FG) - D(\varepsilon)(FG) - D(C(0)(FG) + \rho(C(E)(0) + D(-\varepsilon)(0)))] \\
 &= -B(-\mu C E F G + \mu \varepsilon D F G - 0 + 0 + 0) \\
 &= -B(-\mu C E F G + \mu \varepsilon D F G) \\
 &= \mu B C E F G - \mu \varepsilon B D F G.
 \end{aligned}$$

Where $B = (\mu + \eta)$, $C = (\mu + \varepsilon)$, $D = \beta \frac{[P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \eta)}$, $E = (\mu + \alpha + \gamma + \sigma)$, $F = (\mu + \alpha_1 + \delta)$ and $G = (\mu + \rho)$.

$$\begin{aligned}
 Det(JFq^0) &= \mu(\mu + \eta)(\mu + \varepsilon)(\mu + \rho)(\mu + \alpha_1 + \delta)(\mu + \alpha + \gamma + \sigma) \\
 &\quad - \mu \varepsilon \left[\frac{\beta [P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \eta)} \right] (\mu + \alpha_1 + \delta)(\mu + \rho)(\mu + \eta) \\
 &= \mu(\mu + \eta)(\mu + \varepsilon)(\mu + \alpha_1 + \delta)(\mu + \alpha + \gamma + \sigma) \\
 &\quad \left[1 - \frac{\beta [P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \eta)(\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma)} \right] \\
 &= \mu B C E F G \left(1 - \frac{\beta [P\pi(\mu + \eta) + (1 - P)\eta\pi]}{\mu(\mu + \eta)(\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma)} \right) \\
 Det(JEq^0) &= \mu B C E F G (1 - R_0)
 \end{aligned}$$

Thus, the $Det(JEq^0)$ will only be greater than zero if $R_0 < 1$. Hence if it's so, the disease free equilibrium point (Eq^0) is locally asymptotically stable.

Endemic Point

Setting (5 – 9) to zero we have

$$M^* = \frac{(1 - p)\pi}{\mu + \eta} = \frac{(1 - p)\pi}{K_1}$$

$$S^* = \frac{p\pi K_1 + \eta\pi(1-p) + pAR_H^*}{(\beta I^8 + \mu)K_1}$$

$$E^* = \frac{\beta S^* I^*}{K_2}, I^* = \frac{\varepsilon E^*}{K_3} \rightarrow \quad (11)$$

$$R_{ES}^* = \frac{\sigma I^*}{K_4}, R_H^* = \frac{\gamma I^* + \delta R_{ES}^*}{R_5}$$

Where $K_1 = (\mu + \eta), R_2 = \mu + \varepsilon, K_3 = \mu + d + \gamma + \sigma, K_4 = \mu + \alpha_1 + \delta, K_5 = \mu + \rho$.

From (11) $E^* = \frac{I^* K_3}{\varepsilon}$.

$$\Rightarrow \frac{I^* K_3}{\varepsilon} = \frac{\beta S^* I^*}{K_2} \Rightarrow S^* = \frac{K_2 K_3}{\beta \varepsilon}$$

$$\frac{K_2 K_3}{\beta \varepsilon} = \frac{\frac{p\pi k_1 + \eta\pi(1-p)}{K_1} + \frac{pK_1(\gamma K_4 + \delta\sigma)I^*}{K_1 K_4 K_5}}{(\beta I^* + \mu)K_1}$$

$$\Rightarrow I^* = \frac{p\pi\beta\varepsilon K_1 K_4 K_5 + \beta\varepsilon\eta\pi(1-p)K_4 K_5 - K_1 K_2 K_3 K_4 K_5 \mu}{K_1 K_2 K_3 K_4 K_5 \beta - pK_1 \beta \varepsilon (\gamma K_4 - \delta\sigma)}$$

$K^* = K_3 \frac{K_6}{K_7}$ where $K_6 = \rho\pi\beta K_1 K_4 K_5 + \beta\varepsilon\eta\pi(1-p)K_4 K_5 - K_1 K_2 K_3 K_4 \mu$.

$$K_7 = K_1 K_2 K_3 K_4 K_5 \beta - pK_1 \beta \varepsilon (\gamma K_4 - \delta\sigma)$$

$$R_{ES}^* = \frac{\sigma K_3 K_6}{K_4 K_7}$$

$$R_H^* = \frac{(\gamma K_4 + \delta\sigma)K_6}{K_4 K_5 K_7} = \frac{K_6(\gamma K_4 + \delta\sigma)}{K_4 K_5 K_7}$$

$$S^* = \frac{K_2 K_3}{\beta \varepsilon}$$

$$M^* = \frac{(1-p)\pi}{K_1}$$

$$E^* = \frac{K_2 K_3 K_6}{\varepsilon K_7} I^* = \frac{K_6}{K_7}$$

$$\text{From } I^* = \frac{K_6}{K_7}$$

Since the force of infection $\lambda^* = \beta I^* S^*$ then

$$\lambda^* = \beta I^* S^* = \left\{ \frac{K_1 K_2 K_3 K_4 K_5 \mu (R_0 - 1)}{K_1 K_2 K_3 K_4 K_5 \beta - pK_1 \beta (\gamma K_4 + \delta\sigma)} \right\}$$

Lemma 3:

The endemic Equilibrium point (EEP) exist and is unique and is locally asymptotically stable if and only if $R_0 > 1$. (By Descartes Rule of signs).

RESULT AND DISCUSSION

Numerical Simulation

The numerical simulation of the model was carried out using MATLAB. The estimated parameter values used in the simulation of this model are presented in table 2.1. Since the parameter values are known, then we can solve our system of differential equations (5 - 9), since the model uses six separate differential equations one must use a numerical solver to plot the solution.

This is easier with MATLAB. We used the parameter values (Table 2.1) in MATLAB and plot the graph. The numerical simulation result is displayed in figure 1.1.

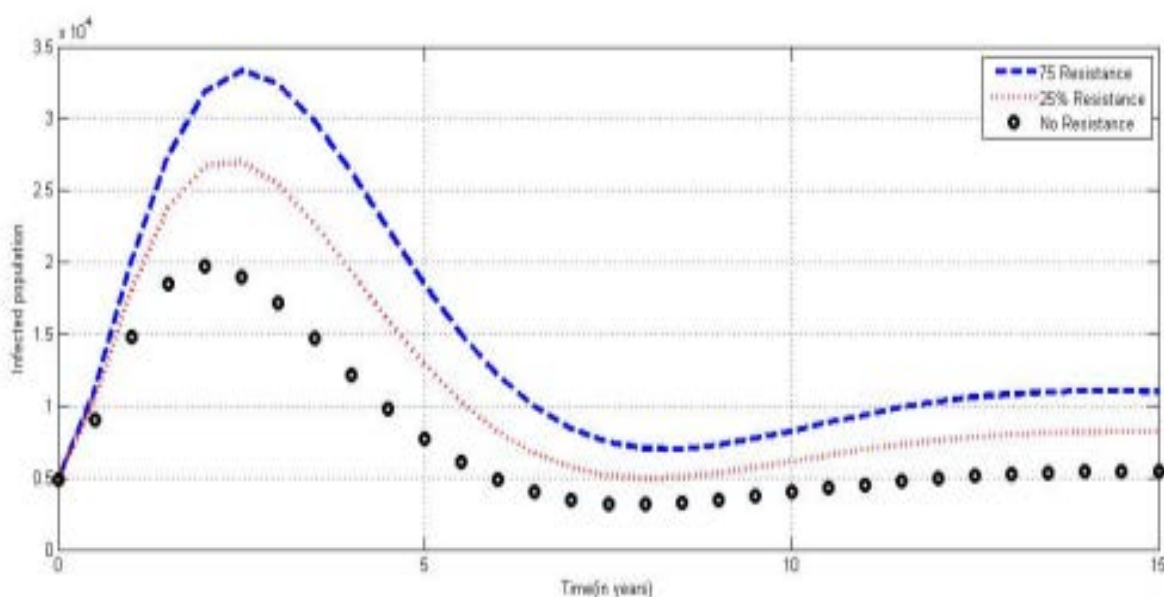


Figure 1.1: Numerical Simulation of Infected Individual against time.

Parameters	Value
N	1000
Π	5000
μ	0.9
P	0.04
B	0.05
E	0.06
Γ	0.65
A	0.6
Δ	0.3
α_1	0.04
H	0.088
Σ	0, 0.25, 0.75

Table 2.1: Estimation of Parameter and Constant

The graph of figure (1.1) represent three cases from table (2.1), the first case when $\sigma = 0$ that is the initial state, second case when $\sigma = 0.25$ and the third case when $\sigma = 0.75$. We can see that there was less number of infected population when there is no resistance and infection is increased as we increases the resistance from 25% to 75% with respect to time.

DISCUSSION

From the numerical simulation of the condition in figure (4.1) above, it shows that there was less number of infected population when there is no resistance and infection is

increased as we increases the resistance from 25% to 75%. This was achieved by first choosing $\sigma = 0$ simulation gives $R_0 = 0.865116 < 1$, secondly when $\sigma = 0.25$ simulation gives $R_0 = 0.907885 < 1$ and lastly when $\sigma = 0.75 < 1$ simulation gives $R_0 = 0.751353 < 1$ showing that the disease free equilibrium point (Eq^0) of the model is locally stable in all the three (3) different values of σ . Since the basic reproduction number $R_0 < 1$, it implies that the disease will gradually die out in the population when there are no resistance and the disease will increase when there is resistance to first line of treatment.

SUMMARY

This research was designed to model, analyzed and to study the effect of immunity and drug resistance on the transmission dynamics of tuberculosis using MSEIR model. The disease free equilibrium was obtained Eq^0 , the basic reproduction number was obtained (R_0), stability analysis of the model was obtained, the existence of the endemic point and also numerical simulation of the model was done using MATLAB software with estimate values from table (2.1) using different values of sigma (σ) as in figure 1.1 above which shows that there was less number of infected population when there is no resistance and infection is increased as we increase the resistance from 25% to 75% which was also achieved by changing the value of sigma from 0 to 0.25 and then to 0.75. The result shows that there is less number of infected population when there is no resistance to first line of treatment in the population.

CONCLUSION

Mathematical model is a useful technique for solving real life situations; a deterministic model to study the effect of immunity and drug resistance on the transmission dynamics of tuberculosis was modeled and analyzed in order to see the effect of resistance to first line of treatment in a population. The analysis and numerical simulation of the model reveal that the disease free equilibrium (Eq^0) is locally stable since $R_0 < 1$, which implies that TB disease will be gradually eliminated from the population. The numerical simulation of the model was carried out using MATLAB.

RECOMMENDATION

In line with this research findings the following recommendations are made;

1. Encourage the use of mathematical models to model real life problems, which simplifies problems in the society.
2. The government should integrate TB programmes into other existing health services such as outreach, maternal and child welfare programmes among others in order to increase its awareness.
3. The government should intensify the education on TB in schools, community gathering, worship centers etc., to sensitize the individuals in the communities of its existence, free access to medical care and treatment duration.
4. TB patients who migrate must be given referral to the clinics in such areas for continuation of treatment.
5. Further research work is also recommended in order to help develop other suitable models to help public health professionals to adopt other strategies to control and eradicate the disease.

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APPENDIX

```
function vprime = tbmodel(t,y)
vprime = zeros(6,1);
pi = 5000;
rho = 0.56;
beta = 0.05
varepsilon = 0.06;
gamma = 0.65;
alpha = 0.6;
delta = 0.3;
alpha1 = 0.04;
% immunity and resistance parameters
```

eta = 0.088;

sigma = 0; % Variables y(1) = M; y(2) = S; y(3) = E; y(4) = I; y(5) = R_{ES} ; y(6) = R_H ;

yprime(1) = (1-p)*pi-(mu+eta)*y(1);

yprime(2) = p*pi+eta*y(1)-beta*y(2)*y(4)-rho*y(6)-mu*y(1);

yprime(3) = beta*y(2)*y(4)-(mu+varepsilon)*y(3);

yprime(4) = varepsilon*y(3)-(mu+alpha+gamma+sigma)*y(4);

yprime(5) = sigma*y(4)-(mu+alpha1+delta)*y(5);

yprime(6) = gamma*y(4)-(mu+rho)*y(6)+delta*y(5);

function vprime = tbmodel(t,y)

vprime = zeros(6,1);

p_i = 5000; rho = 0.56;

beta = 0.05

varepsilon = 0.06;

gamma = 0.65;

alpha = 0.6;

delta = 0.3;

alpha1 = 0.04;

% immunity and resistance parameters

eta = 0.088;

sigma = 0.25;

% Variables y(1) = M; y(2) = S; y(3) = E; y(4) = I; y(5) = R_{ES} ; y(6) = R_H;

yprime(1) = (1-p)*pi-(mu+eta)*y(1);

yprime(2) = p*pi+eta*y(1)-beta*y(2)*y(4)-rho*y(6) mu*y(1);

yprime(3) = beta*y(2)*y(4)-(mu+varepsilon)*y(3);

yprime(4) = varepsilon*y(3)-(mu+alpha+gamma+sigma)*y(4);

yprime(5) = sigma*y(4)-(mu+alpha1+delta)*y(5);

yprime(6) = gamma*y(4)-(mu+rho)*y(6)+delta*y(5);

function vprime = tbmodel(t,y)

vprime = zeros(6,1);

p_i = 5000; rho = 0.56;

beta = 0.05

varepsilon = 0.06;

gamma = 0.65;

alpha = 0.6;

delta = 0.3;

alpha1 = 0.04;

% immunity and resistance parameters

eta = 0.088;

sigma = 0.75;

% Variables y(1) = M; y(2) = S; y(3) = E; y(4) = I; y(5) = R_{ES} ; y(6) = R_H ;

yprime(1) = (1-p)*pi-(mu+eta)*y(1);

yprime(2) = p*pi+eta*y(1)-beta*y(2)*y(4)-rho*y(6) mu*y(1);

yprime(3) = beta*y(2)*y(4)-(mu+varepsilon)*y(3);

yprime(4) = varepsilon*y(3)-(mu+alpha+gamma+sigma)*y(4);

yprime(5) = sigma*y(4)-(mu+alpha1+delta)*y(5);

yprime(6) = gamma*y(4)-(mu+rho)*y(6)+delta*y(5);

```
y0 = [102520, 12126, 2122, 4844, 1928, 6298];  
tspan = [0:0.5:15];  
[T, Y ] = ode45('tbmodel', tspan, y0);  
[P, Q] = ode45('tbmodel25imm', tspan, y0);  
[R, S] = ode45('tbmodel75imm', tspan, y0);  
plot(T,Y(:,4),'-')  
hold on  
plot(P,Q(:,4),'k')  
hold on  
plot(R,S(:,4),'o')  
xlabel('Time(in years)')  
ylabel('Infected population')  
legend('No Resistance', '25% Resistance', '75% Resistance')
```

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