A DETERMINISTIC MODEL OF TUBERCULOSIS DYNAMICS

BY

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A THESIS SUBMITTED TO THE POST GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF MASTERS OF TECHNOLOGY (M.TECH) IN MATHEMATICS IN THE DEPARTMENT OF MATHS/COMPUTER SCIENCE,
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DECLARATION

I hereby declare that the thesis titled: "A DETERMINISTIC MODEL OF TUBERCULOSIS DYNAMICS" is my original work carried out under the supervision of Prof. N.I. Akinwande. It has never been presented elsewhere for the award of any degree, and that all works related to the field of study, before the present research have been duly acknowledged and referenced.

Ndaman Isah
Name of Student

02/08/2010
Signature and Date

CERTIFICATION

This thesis titled "A deterministic model of tuberculosis disease dynamics" by Ndamman Isah meets the regulations governing the award of the degree of Masters of Technology, Minna and I approved for its contribution to knowledge and literary presentation.

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ABSTRACT

This project proposes a deterministic mathematical model of the tuberculosis disease dynamics. The model population is partitioned into three distinct classes: the Susceptible, Exposed and the Infected. The dynamics of the three compartments was described by a system of ordinary differential equations. The equilibrium states of the system of equation are obtained and analyzed for stability. It is observed that the origin is stable when the birth rate (β) is less than the death rate (μ), while the condition for the stability or instability of the non-zero equilibrium state is obtained using the Bellman and Cookes condition for stability, Hypothetical values are used for the parameters to illustrate the inequality condition for stability.

CHAPTER ONE

INTRODUCTION

1.1 Background of the Study

Mathematical models are derivation of the mathematical relations which describe the features of the system under consideration. The method of analysis involving the use of equilibrium state and stability of the models are useful tools in the study of mathematical model of population dynamics according to Akinwande (1999).

Mathematical models have been used both analytically and numerically to give insight into the dynamics of many real life situations Benya (2005). Epidemiology is the study of diseases. Infectious diseases such as HIV/AIDS, tuberculosis, Lassa fever, SARS, Ebola, Rabies, Foot and Mouth disease e.t.c. cause millions of death yearly worldwide Fitzgibbon and laglais (2000).

Tuberculosis is one of the leading causes of death worldwide killing about two million people each year WHO (2009). It is estimated that about 1.7 billion people are infected worldwide WHO (2006).

The high incidence of tuberculosis in the developing countries is as a result of poverty and underdevelopment, which lead to overcrowding, malnutrition, lack of access to good health care services – which are contributory factors to the spread of the disease. The nature of population distribution is such that many people live in small areas, while others in larger areas have sparse concentration of people.

This uneven pattern of population distribution, which results into massive concentration of people in a limited area, is a major factor which has helped to sustain some diseases, especially the airborne diseases of which tuberculosis is one.

This work has been divided into five chapters. The first chapter is the introduction. The second chapter contains review of some literature related to this work. In chapter three we present the model equations, the equilibrium state and the characteristics equation are obtained. In chapter four we analyse the equilibrium state for stability and finally conclusion and recommendation are presented in chapter five.

1.2 Objectives of the Study

The objectives of this research work are:

1. To propose mathematical population model for tuberculosis disease pandemic.
2. To obtain and analyze the zero and non-zero equilibrium states for stability.
3. To draw conclusion from the result of the analysis relevant for the control and possible prevention of the diseases.

1.3 Significance of the Study

The threat of infectious disease is not only a major cause of death and misery to both human and animal populations but also it has the potential of major social and economic impact.

As human capital is part of resources of a nation, the study of population plays a vital role in the economic success of a nation especially where the health capacity of the population could be undermined.

Population studies are an aid to development planning both in the short and long term in areas such as labour, education, health, environmental preservation and social security to mention a few. Such studies provide

information and knowledge to government for effective policy formulation in order to achieve desired social and economic objectives.

1.4 Scope and Limitation of Study

In this work we present Susceptible – Exposed- Infected but Recovered (SEIR) model. This model is one strain (Drug-sensitive) with one form of latency and one class of active TB. In this model individuals can only move to the infected class from the latent class so there is only one progression rate, and there is recovery from latency and active class back to the susceptible class. The dynamics of tuberculosis between the compartments is presented in a system of ordinary differential equations. The zero and non-zero equilibrium states are obtained and analysed for stability. Hypothetical parameter values are then used to test the stability result for the non-zero equilibrium state.

1.5 Overview of Tuberculosis

1.5.1 Introduction

Tuberculosis (TB) is a chronic or acute bacterial infection that primarily attacks the lungs, but which may also affect the kidneys, bones, lymph nodes and brain. The disease is caused by mycobacterium tuberculosis, a rod-shaped bacterium.

The symptoms of tuberculosis include chest pain, cough, loss of appetite, weight loss, fever, chills, shortness of breadth and fatigue.

In 1993 Tuberculosis was declared a global emergency by the world health organisation (WHO), the first such designation ever made by that organisation. One individual becomes infected with Tuberculosis (TB) every second and 8 million people contract the disease every year according to WHO (2003).

It is also predicted by WHO that if left unchecked TB will kill 35 million people in the world over the next 20 years WHO (2003).

Tubercles found in mummified bodies, has shown that TB had been existing since at least the year 2000 BC WHO (2003). Writings of acient Babylonia, Egypt and China made references to TB. The term tuberculosis was derived from the Latin word tubercular and was first used in 1839. Tubercula means small lump, which refers to the small sear tissue of infected individuals. In the 19th century TB reappeared in Europe and United States on epidemic levels.

In the early 19th century, significant research into the causes and cure of TB began. The damage caused by TB was described in 900 autopsies by French physician Gaspard Bayle. A French army doctor J.A. Villenium showed that TB could be transmitted from humans to animals WHO(2003).

Due to lack of cure for TB an American physician Edward Trudeau who was affected by the disease twice (in 1873 and 1876) thought he was dying and traveled to Saranac lake in the Adirondack mountains of New York to spend his final days, eventually his symptoms disappeared and attributed the healing to the fresh air of the mountains. He built the first American Sanatorium in 1885. This later became a model for many sanatoriums that were used for TB treatment in the late 19th century and early 20th century. In 1930 United States had a total of 84,000 beds in 600 sanatoriums. Trudeau established the Trudeau Laboratory responsible for training most physicians versed in the treatment of TB, in the 50 years that followed.

Early in the 19th century, TB was thought to be a disease of morally superior individuals, but the epidemic continues to claim larger circle of people, often poor and the disadvantaged. In the absence of scientific knowledge, TB was attributed to a person's lifestyle.

The bacteria that cause TB was discovered by a German physician Robert Koch in 1882 WHO (2003). Koch demonstrated the presence of the bacteria and how it was transmitted, using simple but precise observations and experiments.

In 1924 the first TB vaccine (BCG) was produced at the Pasteur institute in Paris, by French bacteriologists, Albert Calmette and Canille Guerin working with a virulent strain of bovine (cow) tubercle bacillus with hope of protecting the world against TB. The vaccine was tested on a newborn child and it was successful. The beginning of modern antibiotic therapy for TB began in 1944 when an American microbiologist Selman Waksma isolated streptomycin from a fungus, streptomycin lavendulla.

Over the next 30 years there was a declining rate of disease incidence and mortality due to success of the drug therapy with these achievement public health officials believe TB could be conquered.

1.5.2 **Transmission and Infection**

TB is transmitted from person to person, usually by inhaling bacteria carried in the air droplets. When a person sick with TB coughs, sneezes or speaks some particles that carry two to three bacteria surrounded by a layer of moisture are released in the air. If another person inhales these particles the bacteria may lodge in that person's lungs and multiply. Other less common route of transmission is through the skin. Laboratory technicians who handle TB specimen can contract the disease through skin wounds. TB has also been

reported in people circumcised with unsterilized instrument and those who receive tattoos WHO (2003).

TB disease develops in two stages: Primary and Secondary stage.

1.5.2. (a) **Primary Tuberculosis**

At this stage the person is infected with TB bacteria, but often is not aware of it and does not manifest the symptoms of the disease. At this early stage primary TB is not contagious. Macrophages, immune cells that detect and destroy foreign matter, ingest the TB bacteria and carry them to the lymph nodes where they may be inhibited, destroyed, or they may multiply.

Active primary tuberculosis will develop if the bacteria multiply. If the bacteria are not destroyed but inhibited, the immune cells and the bacteria will form a mass known as granuloma or tubercle. The immune cells form a wall around the inactive bacteria. The TB bacteria remain walled off and inactive as long as the immune system remain strong. At this initial stage of TB, the bacteria may remain dormant in the body for many years, without the disease progressing.

As soon as the immune system becomes weakened the tubercle opens, releasing the bacteria and the infection may develop into secondary TB.

1.5.2 (b) **Secondary Tuberculosis**

At this secondary stage carriers of TB may infect others because the formerly dormant bacteria has multiplied and destroyed tissue in lungs, and has spread to the rest of the body via the blood stream resulting to a collection of fluid or air in the lungs which may be accompanied with cough of blood or phlegm through which other people can be infected.

1.5.3 **Diagnosis**

Two separate methods are used to diagonize TB. The tuberculin skin testing is a method of screening for exposure to TB infection. In this method a purified protein derived from the bacteria is injected into the skin. The skin area injected is inspected 48 to 72 hours later for lumps. A positive test means that TB infection has occurred. This method is not 100% accurate and does not always indicate the presence of active TB disease.

Identification of the bacteria in sputum (matter coughed up from the lungs) is a method used to establish the diagnosis of TB disease or other body fluids and tissues in addition to an abnormal chest x-ray and the presence of TB symptoms. Another test is required, once TB has been diagonised, so as to determine the most appropriate drugs for treating the particular strain of TB bacteria.

1.5.4 **Prevention and Treatment**

To reduce the spread of TB in public places, general preventive measures can be taken. Good ventilation system that lessens the chance of infection by dispersing the bacteria is also a preventive measure. Other preventive measures include ultraviolet lighting which reduces but does not eliminate the threat of infection by killing TB bacteria in confined spaces. Also vaccines, such as the Bacillus Calmette Guerin (BCG) vaccine, prepared from bacteria that have been weakened, are another preventive measure. This vaccine is most effective in preventing childhood cases of TB.

Drug therapy has become the cornerstone of treatment, with the advent of effective antibiotics for TB. Most drug therapies involve multiple drugs given for at least 6 months or even up to 9 or 12 months, because single drug treatment often causes bacteria resistance to drugs. The multiple drugs are a combination of antibiotics such as isoniazid, rifampcin, pyrazinamide and ethambutol. The entire gene sequence or genome of the bacteria were decoded successfully by scientist in 1998. This will likely create new methods for treatment and prevention of TB.

In order to ensure drug compliance WHO initiated the Directly Observed Treatment Short-course (DOTS) where health workers observed the patient

take their drugs as prescribed to avoid the development of multi-drug resistance – TB (MDR – TB) and extensively drug resistant TB (XDR-TB). The latter is resistant to first line and some second line drugs while the former is resistant to at least two first line drugs.

1.6 Mathematical Modeling

Mathematical modelling involves using variables and parameters to define the features of a system, in a formula or equations to represent any biological, physical or economic system.

Benyah (2005) defines mathematical modelling as "the process of creating a mathematical representation of some phenomenon in order to gain a better understanding of the phenomenon". Essentially, any real situation in physical and biological world whether natural or involving technology or human intervention, can be subjected to analysis by modeling if it can be described in quantitative terms.

Therefore, mathematical modelling is a powerful mathematical technique that allows a set of assumptions to be captured and be followed to their precise logical conclusion. It provides us with new hypothesis, suggests experiments and measures crucial parameters.

1.6.1 Types of Mathematical Model

The techniques used to construct the model and the degree of understanding/knowledge of the system to be modelled form the basis for distinguishing types of model when classified, according to Barnsley (2005)

Some are classified according to the type of variables involved. For instance

(a) Discrete or continuous according as the variables involved are discrete or continuous. Other types of model are

(b) Stochastic or deterministic according as chance factors are taken into account or not

(c) Dynamic or static according as time variations in the system are taken into account or not.

(d) Linear or non-linear according as the basic equations describing them are linear or non-linear

1.6.2 The Modelling Process

A thorough understanding of the underlying principles or factors of the system to be modelled, is a necessary condition for developing a mathematical model for a real life situation.

The modelling process requires the modeler to decide what factors are relevant to the problem and which factors could be de-emphasized.

In order to formulate a successful model Benya (2005) has outlined the following general approach in the formulation of a real life problem in mathematical terms:

(a) Identify the problem

(b) Identify the important variables and parameters

(c) Determine how the variables relate to each other stating the assumptions

(d) Develop the equations or inequalities that express the relationship between the variables.

(e) Analyze and solve the mathematical problem

(f) Interpret the result and relate it to real-life

A mathematical model of a system will often involve the variable time. In this case a solution of the model gives the state of the system i.e. the values of the dependent variable for appropriate values of t describes the system in the past, present or future.

1.6.3 Mathematical Model through Differential Equation

Mathematical modeling in terms of differential equation arises when the situation being modeled involved some continuous variable(s) varying with respect to some other continuous variables and we have some reasonable hypothesis about the rate of change of dependent variable with respect to independent variable.

When we have one dependent variable (say x) depending on one independent variable (say time t), we get a mathematical model in terms of ordinary differential equation.

1.7 Equilibrium State and Stability

1.7.1 Equilibrium State

An ordinary differential equation (ODE) is called an autonomous differential equation if the independent variable appears explicitly.

As an example, the first-order ODE below

$$\frac{dx}{dt} = f(x) \tag{1.1}$$

is an autonomous equation, since the right-hand side is independent of t explicitly.

The solution of the equation $f(x)=0$ are called the critical points of the autonomous ODE given in (1.1), referred to as equilibrium or steady state of the ODE. If the ODE has a constant solution $x(t)=c$, then $x=c$ is a critical point of (1.1) such a solution is called an equilibrium solution.

1.7.2 **Stability**

Stability in physics and engineering is the property which a body possesses such that once it is disturbed from a condition of equilibrium or steady motion; it will return to its original position or motion as a result of the action of the so-called restoring forces or torque.

Stability generally demands both restoring forces and damping factors in a moving or oscillating system. In an electrical or mechanical oscillating system, such as a servo mechanism if restoring forces are not properly timed and if damping is insufficient, these forces cannot fulfill their function rendering the system unstable and sending it out of control.

A solution $f(x)$ is said to be stable if any other solution of the equation that starts out sufficiently close to it when $x=0$ remains close to it for succeeding values of x if the difference approaches zero as x increases, the solution is

Perhaps, the following will give a better insight to the concept of equilibrium. From fig 1.2 below, if a ball is pushed down a hill, it may come to rest at positions A or C, but it is only by chance that the ball will be stationary exactly at B. The positions A and C are stable equilibra for the ball, whereas B is an unstable equilibrum. Suppose we place the ball carefully at point B, a gentle breeze or earth tremor will cause the ball to shift away from B. In contrast, positioning the ball at point A or C will result in the ball staying near the stable equilibrium, even on a gusty day.

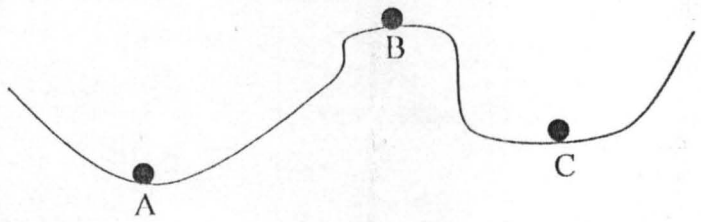

Fig 1.2: Stable and Unstable equilibrium of a ball on a hill..

Equilibrium is considered stable (for simplicity we will consider asymptotic stability only) if the system always returns to it after small disturbances, if the system moves away from equilibrium after small disturbances, then we say the equilibrium is unstable.

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

In this chapter we review some literatures that are related to the dynamics of tuberculosis (TB) disease pandemic.

Presently there exist thousands of research findings on TB disease dynamics. In most of the studies conducted on TB dynamics, the classical epidemic model has been used extensively to study the dynamics of the disease.

Usually such models show the movement between different compartments of the population.

Recent research efforts have been geared towards studying the heterogeneous factors in the population with a view to incorporating them into the model.

Below we present the efforts that have been made by researchers and their findings on various aspects of TB disease dynamics under the following subheadings.

- Transmission
- Infection
- Treatment

- Prevention
- HIV-TB co-infection

2.2 Transmission and Spread of Tuberculosis

Most early transmission models were deterministic but recent resurgence of tuberculosis (TB) in developed countries and increases in cases of casual contact and public transport suggested a model based on thorough understanding of the dynamics of the disease.

Consequently, Aparacio et al (2000) developed a generalized household (cluster) model, which took close and casual contact into account. The household cluster comprise of social networks (family members, office mates, classmates, any person who have prolonged contact with an active case). The other cluster are those outside the social network. The basic reproductive number for the model is

$$R_0 = \frac{\beta n k}{\beta + \gamma + \mu + k} \tag{2.2.1}$$

where β is the transmission rate, n is size of cluster, μ natural mortality rate, γ is the total per-capita removal rate from the infected and k is the progression rate to active TB. It can be seen that R_0 depends nonlinearly on the parameter β

and linearly on the size n. The condition $R_0 > 1$ implies there exist endemic equilibrium and the disease persists.

It was found that the total number of secondary infections caused by casual contact is greater than those produced by contacts in active clusters. The reason being that the number of subpopulation living in the active cluster is smaller than the total population size.

Tuberculosis is transmitted to an uninfected person when an infected person pass the bacteria and the former inhales it therefore effort are being intensified to study the impact of TB in public transportation, as mass transportation plays a primary role in casually close contact Aparacio et al (2000)

Murphy et al (2002) investigated how mass public transport can influence the transmission of TB, because infectious people can move long distances and spread the disease far from their origin. Some simulations performed on the system reveal that the travel time, which the non-bus taking individuals spend in public transport contributes to the transmission of TB, because the low income group who often ride public transport near equilibrium, while the high income group who rarely ride public transport and have private cars are vulnerable to mycobacterium tuberculosis and spread it in their clusters.

called asymptotically stable. If a solution does not have either of these properties, it is called unstable.

1.7.3 Illustrative Examples

Equilibrium may be stable or unstable. For example, a pencil standing on its tip has unstable equilibrium. A picture on the wall always possesses stable equilibrium (fig 1.1)

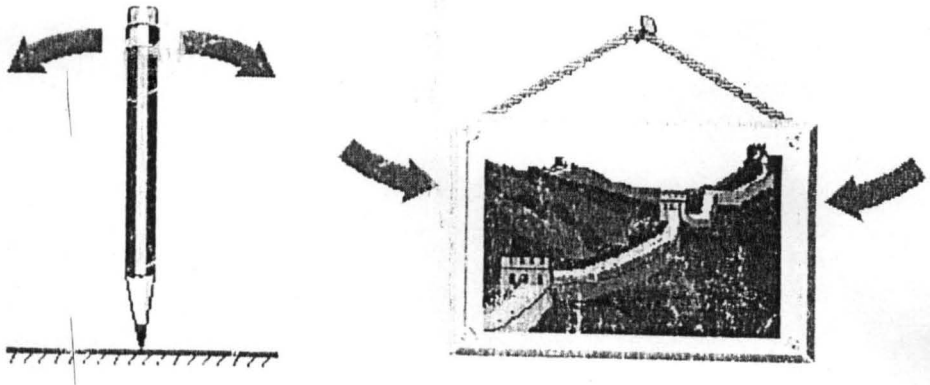

Fig 1.1: An Illustration of stable and unstable equilibrium of an object.

They went further to estimate the value of relevant parameters and found that on the average 100 people enter and leave the bus hourly and that one TB infection per 1000 traveler's was generated per hour of travel. They also found that about 30% of the new TB cases could be attributed to bus travel with the rate of transmission higher in poorly ventilated and crowded transportation system.

Research has also shown that genetic susceptibility affect endemic prevalence levels and alters the effect of treatment of tuberculosis patient. Genetic susceptibles are part of the susceptible subpopulation who can be infected with mycobacterium tuberculosis, as not all people are equally susceptible to TB Belamy (2000).

In 2002, Murphy et al (2002) presented a new model with two subpopulation to verify the effects of genetics factors on epidemic of TB, they found using numerical simulation that a small genetically susceptible subpopulation can drastically increase prevalence and incidence of TB in the general population. The result also show that if 30% is genetically susceptible, the prevalence of TB could double to 60%.

Tuberculosis is an air-borne contagious disease affecting about one third of the world population, out of which two third live in developing countries.

Spread of TB is rapid in areas with poor public health services and crowded living conditions. It is also spread in homeless shelters' prisons and areas where living conditions are disrupted by wars, famine and natural disasters.

These factors have been found to contribute to the spread of TB by many researchers. For instance, Semantimba et al (2005) formulated mathematical models with four compartment (SILT) to establish the conditions on the size of the area occupied by internally displaced peoples' camp (IDPCS) in Uganda. Both numerical and qualitative analysis of the model were performed and the effect of variation in the area size and recruitment rate on the different epidemiological states was investigated. They observe that a stable disease free equilibrium point exist provided that the characteristic area is greater than the product of the probability of survival from the latent stage to the infections stage $\left(\frac{k}{\mu+k+r_1}\right)$ and the number of latent infections produced by a typical infectious individual during his/her mean infection period $\left(\frac{\beta_1 CS+\beta_2 CT}{\mu+\delta+r_2}\right)$ where k is the rate of progression to active TB, r_1 is the recovery rate of latent class, μ is the natural death rate. β_1 and β_2 is the probability that a susceptible and treated individual respectively become infected per contact per unit time. μ is the natural death rate, while δ is the TB induced mortality rate, r_1 and r_2

recovery rate of latent and infected class respectively. S is the susceptible class, while T is the treated class. They found that for the existence of disease free equilibrium $A > \left(\frac{K}{\mu + K + r_1}\right)\left(\frac{\beta_1 CS + \beta_2 CT}{\mu + \delta + r_2}\right)$. In conclusion, the study recommends that the characteristic area per individual should be at least 0.25 square kilometers so as to minimize tuberculosis incidence.

This model differs from ours due to the creation of separate compartment for the treatment class. In our model treated individuals are returned to the susceptible class.

In a related research work by Koriko and Yusuf (2005) the dynamics of tuberculosis disease population was considered using the Susceptible – Infected - Recovered but Susceptible (SIRS) model, the infected class (I) is broken into those that will progress directly to active TB and those that will progress to Latent TB, this is different from our model where all individuals progresses into Latent class upon infection. The resulting model equations were solved numerically by simulations. It was found that the population dynamics depends more on the number of actively infected people in the population at the initial stage and on the disease incidence transmission rate at a given time.

2.3 Infection of Tuberculosis

Infection occurs when mycobacterium tuberculosis bacteria is lodged in the lung of a susceptible person from an infected person.

Due to the activity of immune cells in the lung, the person either becomes latently infected or actively infected. Researchers are now focusing their attention on the activities that occur within the lung that determines the type of infection.

A mathematical model of tuberculosis was formulated and used to evaluate strategy of targeting therapy to persons with recently acquired latent tuberculosis(TB) infection by Ziv et al (2001). The model was used to measure the effectiveness of therapy for early latent TB infection in reducing the prevalence of active TB. The model was able to show the kind of effective therapy for early latent tuberculosis infection that can eliminate active TB when combined with therapy for active TB.

The authors concluded that contact investigation where persons recently infected with mycobacterium tuberculosis (MTB) are identify and treated, can have a substantial effect on controlling TB epidemics.

Researchers at the Ohio State University Caldwell (2009) are using mathematical modeling to determine whether a change to the nature switching time would result in a more effective immune response.

Switching time refers to the changes that occur between the two immune response (the innate and the acquired), in fighting any invading pathogen. The innate immune response begins a fight against any pathogen; the acquired immune response follows with aim of attacking the specific pathogen causing the infection.

The model in this study simulates the entire activity in the immune response to TB paving the way of testing what the outcome would be if changes were made along the way for example if developing a drug can artificially inhibit or activate part of the process. A process that could determine what it would take to shorten the switching time and reduce the number of bacteria in the lung. The model calculates the average switching time to be about 50 days after TB invades the lung, this roughly coincides with clinical expectation that a skin test will be positive for TB between four and eight weeks after infection.

Furthermore, the model reveals that switching time of the immune response could be shortened and bacterial load reduced if interferon gamma (a cytokine

that participate in the conversion of one type of immune response to other) is introduced early during immune response.

They concluded that interferon gamma might be one component of a short approach to new TB therapies. According to Schlesinger a director in Ohio States centres for microbial interface biology "If we could shorten the treatment for TB that would be a very powerful means of breaking transmission cycles" Caldwell (2009).

It has been assumed for decades that secondary tuberculosis is caused by reactivation of endogenous infection rather than by a new exogenous infection.

However, studies have now showed that reinfection is caused by recurrence of tuberculosis after treatment (exogenous reinfection).

Annelis et al (1999) performs DNA finger printing with restriction fragment length polymorphism analysis on pairs of isolates of mycobacterium tuberculosis from 16 compliant patients who had been cured of pulmonary tuberculosis after treatment, but now reinfected. All the patients lived in endemic areas of South Africa. For the 12 of the 16 patients the restriction fragment – length polymorphism banding patterns for the isolates obtained were different from those for the isolates from the initial tuberculosis disease.

All the 15 patients tested for human immune deficiency virus were sero-negative. Therefore they conclude that exogenous reinfection might be the major cause of secondary tuberculosis after a previous cure in an area with high incidence of the disease.

A mathematical model for the time delay from initial Latent infection to active disease and infection transmission was proposed by Edwin and Shelley (1996).

Both the Activation delay function and time delay function were found. For the activation delay function $f_{i\theta}$, they consider the initially infected at time t_1 and define a time-delay function f_{ia} such that the probability that a surviving individual develops an active case in the time interval $(t_1+\tau)$and $(t_1+\tau+d\tau)$ is $f_{ia}d\tau$

The effective reproductive number for this model was found by using the effective incidence of new infections in the whole population which is $P(t)=P_0(t)X(t)$ and $R(t)=R_0(t)X(t)$. If $R(t)$ is equal to a constant R over many decades (even if R_0 and X vary slightly), the result is an exponential solution for the effective incidence

$$P(t)=P(0)\exp(+\Lambda t)$$

Where the constant Λ the fractional rate of change per year is related to the constant R by a ratio of integrals.

$$R = \frac{\int_0^{\infty} f(\tau) d\tau}{\int_0^{\infty} f(\tau) d\tau \exp(-\Lambda t)} \qquad (2.3.1)$$

Equation (2.3.1) shows that $R < 1$ when Λ is negative, $R > 1$ when Λ is positive and $R = 1$ for steady state of $\Lambda = 0$. Λ is the fractional rate of change. They used case rate tables in the United State, to calculate fractional rate of change per annum in the incidence of active TB. Estimates for the effective reproductive number were derived. The model predicted active case rates in various groups and compare them with published tables. It was observed from the comparison that the risk of activation decreases rapidly, then gradually, for the first 10 years after initial infection.

2.4 **Prevention of Tuberculosis**

Studies have shown that tuberculosis (TB) can be controlled. Some studies indicate the epidemiological class that can influence prevention of tuberculosis (TB) or its eradication.

Nucci et al (1997) evaluate the efficacy of TB control measures in hospitals to prevent nocosonmial (Hospital) transmission. The control measures employed in the hospitals are:-

i. Isolation of patients

ii. General ventilation

iii. Use of high efficiency particulate air (HEP) filters or ultra violent germicidal irradiation (UVG I)

iv. Adoption of appropriate respiratory protective (surgical) masks and particulates respirators such as HEP masks.

Using a room with a source of airborne infection and air disinfection devices as recommended above. The study shows that the only control measure that significantly reduces the infection rate is the administrative measure (isolation of patients) as the efficacy of other control measures decreases as the infectivity of the source case increases. The method was evaluated with a deterministic mathematical model for airborne contagion:

$$\frac{ds}{dt} = -\frac{P}{V}QS,$$

$$\frac{dQ}{dt} = -CQ + q, \ t \geq 0$$

with initial conditions $S(0) = S_0 > 0$

$$Q(0) = Q_0 \geq 0$$

Where Q is the ratio between the pulmonary ventilation P (assuming P=0.01m^3/min) and the volume V of the room. S is the susceptible class, C is the disinfection rate and q is the infection rate.

The model is solved to obtain

$$S(t,q,c) = S_0 \exp\left\{-\frac{pq}{v}.\frac{ct+e^{-ct}-1}{C^2}\right\} \qquad (2.4.1)$$

The rate of infection $(q)$is derived a posteriori when the number $\bar{s}$ of susceptible persons who were not infected is known. By solving $S(t,q,c)$= s with respect to q, with $\bar{s}$ given by (2.4.1) yields.

$$q = \frac{v}{p}.\frac{c^2}{ct+e^{-ct}-1}\log\frac{S_0}{\bar{s}}$$

Where $\bar{s}$ is the number of uninfected persons and S_0 the number of susceptible. The effect of Direct Observation Treatment Short-course (DOTS) programme initiated by WHO in preventing high prevalence levels of TB in the population have been presented in a paper by Phillip (2006).

Phillip formulated a mathematical model to forecast the impact of different scenarios for TB control measures of TB epidemic in the western pacific region. He develops initial condition for the model by first modeling a virgin

epidemic by simulating the introduction of a single infection case into a population of susceptible individuals, until equilibrium.

The model was used to generate an epidemic without introducing DOTS TB control measures (constrained) for 30 years, followed by a gradual introduction of DOTS progressing until the year 2005. The models shows decline in prevalence levels similar to the declines obtained from prevalence surveys conducted in the western pacific region and also exhibit the same trend with estimated prevalence trend published by WHO.

Having proved the efficacy of this method, a scenario for DOTS case detection rate and DOTS plus coverage for the period 2006-2010 were proposed to predict the impact of TB control on prevalence and mortality and also to predict the impact of DOTS plus on the MDR-TB.

The result obtain from the study shows that case detection rate should be increase to over 70% in order to attain the regional target of reducing prevalence and mortality by 50% compared to the levels of 2000. The result also indicates that implementation and expansion of DOTS plus programmes will have a long term impact on the proportion MDR-TB among prevalent TB cases.

Therefore, DOTS in combination with case detection can lower prevalence levels. DOTS is a strategy that focuses on treatment of active TB cases, a complementary approach is preventive treatment through contact tracing where recently infected (but not infectious) contacts of identified TB cases are placed on preventive therapy.

Juan et al (2006) presented a model which explores the effect of contact tracing on the prevalence level of TB. The analysis shows that treating a small fraction of the infected contacts effectively could significantly reduce the incidence of active TB.

2.5 Treatment of Tuberculosis

Tuberculosis was assumed to have been routed out in developed countries surprisingly it resurfaces in the late 1980's and since then it has been a subject for many studies. Treatment for tuberculosis is now based on Direct Observation Treatment Short-course (DOTS) as approved by WHO to avoid the emergence of resistance strain of the bacteria which is difficult to cure. Implementation of DOTS ensures that patients take their drugs in the presence of health care worker and complete their treatment.

In a study on the effect of DOTS in Nigeria Daniel and Andrei (2007) presented a mathematical model for tuberculosis and its dynamics under the implementation of DOTS in Nigeria.

The condition for the eradication of tuberculosis in Nigeria established by the model was based on the fraction of detected infectious individual under the DOTS treatment. Both numerical and qualitative analysis of the model were performed also the effect of the fraction of detected cases of active TB on the various epidemiological groups was investigated.

The qualitative analysis shows that there is a disease free equilibrium state and is globally asymptotically stable provided the fraction of detected cases exceeded a certain critical value. This means that the disease will be eradicated if this critical level of detection will be reached, implying that the basic requirement for the minimization of the incidence of TB is by increasing the detection rate. This assertion was also supported by the result of the numerical simulation.

In an attempt to study the effect of vaccination, treatment and population area size on the transmission dynamics of TB in a proportionate mixing population Umar (2007) propose a mathematical model that incorporates the density dependent dynamics of tuberculosis, the effect of treatment and vaccination.

The study reveals that if the population area size is large the density of the susceptible will be small and this will reduce the size of the basic reproduction number. Conversely, a small area will lead to high density of susceptible.

The equation

$$A > \left(\frac{1}{k_1 + m + \mu + \delta}\right)\left[C\beta_1 + C\beta_2 \frac{\sigma}{\mu}\right] \qquad (2.5.1)$$

describes the sizes of the area (A) required for stability of the disease free equilibrium. It was found that if A is greater than right hand side of (2.5.1) the density of the susceptible, $\left(\frac{\frac{\Delta}{\sigma} + \mu}{A}\right)$ will be small, thus reducing the size of the basic reproductive number (the number of individuals infected by an infected person during his infections period), conversely, if A is less than the right hand side of (2.5.1) the density of the susceptible will increase. Consequently, the basic reproductive number and infection generated by a single individual will be higher this effect could be eliminated with adequate vaccination and treatment as revealed by the study. The parameters β_1 is the transmission rate of an infected person not vaccinated, β_2 is the transmission rate of an infected person to a susceptible person not vaccinated, σ the rate at which susceptibles are vaccinated, m rate of removal of infectives, μ natural death rate, k_1

treatment rate of infectives and c per capita contact rate.. Hence they conclude that if the population has large area size and employ vaccination and treatment adequately, the disease can be eradicated completely from the population.

Lipsitch and Levin (1998) use mathematical models of mycobacterium population dynamics under antimicrobial treatment to investigate the impact of non-compliance, heterogeneity and other factors on the success of treatment.

The ascent of drug resistance in treated hosts with non-compliance and/ or protected compartment of bacteria where only one drug is active was generated by prediction with the model. The simulation takes into account random mutation and growth rate of bacteria in the protected compartment.

The model prediction shows that relative rates of killing are important than mutation rates in determining the order in which resistance mutants ascend. The prediction of the model in combination with data about drug resistance patterns, reveal that non-compliance and not heterogeneity is the cause of treatment failure.

2.6 HIV TB Co-Epidemics

A co-epidemic occurs when the spread of one infections disease stimulates the spread of another infection.

HIV and TB exhibit unique symbiosis despite biological differences their relationship is synergistic as the presence of one exacerbates the other. HIV infected individuals are particularly susceptible to acquiring TB infection WHO (2006). An HIV infected individual with latent TB is 50 times more likely to develop active TB in a given year than an HIV uninfected individual WHO (2006).

Elisa et al (2008) develop two covariant of a co-epidemic model of the two diseases. The stability criteria for the disease free equilibrium and the quasi-disease free equilibria (define as the existence of one disease along with the complete eradication of the other) were determined.

They presented an illustrative numerical analysis of the HIV-TB co-epidemics in India which was used to explore the effects of hypothetical prevention and treatment scenarios.

The numerical analysis shows that exclusively treating HIV or TB may reduce the target epidemic but the other epidemic will subsequently exacerbate. The analysis also suggest a coordinated treatment effect that include highly active antiretroviral therapy for HIV, latent TB prophylaxis and active TB treatment as necessary in slowing down the HIV – TB co-epidemic.

Simple mathematical model was developed by Bermejo and Richard (2005) to study the impact of HIV epidemic on TB incidence in developing countries, using figures from published reports to estimate the rise of TB incidence as the HIV epidemic expands. The expected increase in TB incidence and the percentage of TB cases that will be HIV positive are plotted against the HIV prevalence.

The study shows that if appropriate action is not taken, TB incidence in developing countries will double as the prevalence of HIV infection reaches 13 per hundred adult.

Oluwaseun et al. (2008) presented a paper on a deterministic model on the synergistic interaction between HIV and mycobacterium tuberculosis. The model was simulated to evaluate impact of different treatment strategies. They found that HIV only treatment strategy saves more cases of the mixed infection than the TB – only strategy.

Also for low treatment rates the mixed only strategy saves the least number of cases (of HIV, TB and the mixed infection) when compared to other strategies.

The researchers then conclude that if resources are limited, then directing such resources to treating one of the diseases is more beneficial in reducing new cases of the mixed infection than targeting the mixed infection only diseases.

CHAPTER THREE

MATERIALS AND METHOD

3.1 Introduction

The transmission dynamics of tuberculosis comprises of the following stages. It begins when an infectious person propels TB germs into the air through speaking, talking, sneezing or spiting and is inhaled by a susceptible person.

The bacteria may lodge in the person's lung and multiply. If the immune system in the lung is able to fight the bacteria and render it inactive (walled off) the person will develop latent TB which is not infectious and does not harm the host.

The person may remain with latent TB for as long as possible unless cured by treatment with antibiotics. If the bacteria later become active due to breakdown of the immune system the person will degenerate to active TB, at this stage he is symptomatic and infectious and can be cured if treated otherwise the person may die from the infection. The person when cured becomes susceptible as he is likely to be re-infected on contact with an infected person.

In this chapter, we develop a deterministic model of the dynamics of TB disease infection. The population P(t) is divided into three compartments. The Susceptible class $S(t)$, the Exposed class $E(t)$, and the infected class $I(t)$.

$$P(t) = S(t) + E(t) + I(t).$$

The Susceptible class are those members of the population that are not infected with tuberculosis, but are likely to contact TB when exposed to infected person, the Exposed class $E(t)$ are those members of the population who have been infected, but are asymptomatic and cannot infect others. The infected class $I(t)$ are members of the population that have been infected, symptomatic and can infect other during contact.

Here, we describe the dynamics of tuberculosis using a system of ordinary differential equations; we obtain the zero and non-zero equilibrium states and obtain the characteristics equation.

3.2 Basic Assumptions

At time t, the following movements occur between the compartments

(i) Members of the Susceptible class $S(t)$ move into the exposed class $E(t)$ due to infection at the rate α.

(ii) Members of the Exposed class $E(t)$ move into Infected class $I(t)$ due to lack of treatment or break down of immunity at the rate γ.

(iii) Members of the Exposed class $E(t)$ move back into the Susceptible class $S(t)$ due to treatment at the rate r_1.

(iv) Members of the Infected class $I(t)$ move into the Susceptible class $S(t)$ due to treatment/recovery at the rate r_2.

(v) New births are not infected at birth hence they belong to the susceptible population.

(vi) Birth rate (β) and death rate (μ) are uniform for the population. The infected class has an additional death burden δ due to infection.

3.3 The Model Equations

$P(t)$ = Total population

$$P(t) = S(t) + E(t) + I(t) \tag{3.1}$$

$$\frac{dS(t)}{dt} = \beta[S(t) + E(t) + I(t)] - [\alpha I(t)+\mu]S(t)+r_1E(t)+r_2I(t) \tag{3.2}$$

$$\frac{dE(t)}{dt} = \alpha I(t)\, S(t) - (\mu + \gamma + r_1)\, E(t) \tag{3.3}$$

$$\frac{dI(t)}{dt} = \gamma E(t) - (\mu + \delta + r_2)\, I(t) \tag{3.4}$$

The diagram below shows the dynamics between the compartments:

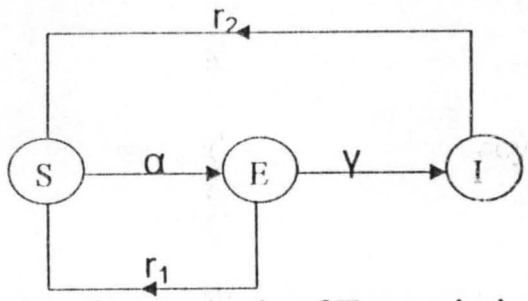

Fig 3.1: A flow diagram for the mode of Transmission of tuberculosis

The parameters are defined as follows:

α = The rate of contracting TB due to interaction of *S(t)* and *I(t)*

β = natural birth rate for the population *P(t)*

μ = natural death rate for the population *P(t)*

γ = progression rate from Exposed class *E(t)* into Infected class *I(t)* due to lack of treatment/immunity.

δ = death rate due to TB infection in the Infected class *I(t)*

3.4 The Equilibrium States of the Model

Let $S(t) = x$, $E(t) = y$, $I(t) = z$ (3.6)

At equilibrium we have that:

$$\beta(x + y + z) - (\alpha z + \mu)x + r_1 y + r_2 z = 0$$

$$(\beta - \mu - \alpha z)x + (\beta + r_1)y + (\beta + r_2)z = 0 \quad (3.7)$$

$$\alpha z x - (\mu + \gamma + r_1)y = 0 \quad (3.8)$$

$$\gamma y - (\mu + \delta + r_2)z = 0 \quad (3.9)$$

From (3.9) we have that:

$$z = \frac{\gamma y}{\mu + \delta + r_2} \quad (3.10)$$

Substituting for z into (3.8) gives

$$\frac{\alpha\gamma xy}{\mu+\delta+r_2}-(\mu+\gamma+r_1)y=0$$

i.e. $$\left[\frac{\alpha\gamma x}{\mu+\delta+r_2}-(\mu+\gamma+r_1)\right]y=0 \qquad (3.11)$$

So either $y=0$ or (3.12)

$$\frac{\alpha\gamma x}{\mu+\delta+r_2}-(\mu+\gamma+r_1)=0$$

i.e. $$x=\frac{(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma} \qquad (3.13)$$

From (3.12) when $y=0$ and substituting $y=0$ into (3.10) we obtain $z=0$

When $y=0, z=0$ in (3.7) we have that $x=0$.

Hence $(x,y,z) = (0,0,0)$ is an equilibrium state.

When $y\neq 0$, x is given by (3.13) substituting for z and x as given by (3.10) and (3.13) respectively into equation (3.7) we obtain:

$$\left[\beta-\mu-\alpha\left(\frac{\gamma y}{\mu+\delta+r_2}\right)\right]\left[\frac{(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma}\right]+(\beta+r_1)y$$

$$+(\beta+r_2)\left(\frac{\gamma y}{\mu+\delta+r_2}\right)=0 \qquad (3.14)$$

$$\beta\left(\frac{(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma}\right)-\mu\left(\frac{(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma}\right)-\alpha\left[\frac{\gamma y}{\mu+\delta+r_2}\right]$$

$$\left(\frac{(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma}\right)+(\beta+r_1)y+(\beta+r_2)\left(\frac{\gamma y}{\mu+\delta+r_2}\right)=0$$

$$\frac{\beta(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma}-\mu\frac{(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma}-\frac{(\alpha\gamma y)(\mu+\gamma+r_1)}{(\mu+\delta+r_2)}$$

$$\frac{(\mu+\delta+r_2)}{\alpha\gamma}+\frac{(\beta+r_1)y}{1}+\frac{(\beta+r_2)\gamma y}{\mu+\delta+r_2}=0$$

$$\frac{\beta(\mu+\gamma+r_1)(\mu+\delta+r_2)^2-\mu(\mu+\gamma+r_1)(\mu+\delta+r_2)^2-(\alpha\gamma y)(\mu+\gamma+r_1)(\mu+\delta+r_2)+\alpha\gamma(\mu+\delta+r_2)(\beta+r_1)y+\alpha\gamma^2y(\beta+r_2)}{\alpha\gamma(\mu+\delta+r_2)}=0$$

$$\beta(\mu+\gamma+r_1)(\mu+\delta+r_2)^2-\mu(\mu+\gamma+r_1)(\mu+\delta+r_2)^2-(\alpha\gamma y)(\mu+\gamma+r_1)$$

$$(\mu+\delta+r_2)+\alpha\gamma(\mu+\delta+r_2)(\beta+r_1)y+\alpha\gamma^2y(\beta+r_2)=0$$

i.e. $$\alpha\gamma y(\mu+\delta+r_2)(\beta+r_1)+\alpha\gamma^2y(\beta+r_2)-(\alpha\gamma y)(\mu+\gamma+r_1)(\mu+\delta+r_2)=$$

$$\mu(\mu+\gamma+r_1)(\mu+\delta+r_2)^2-\beta(\mu+\gamma+r_1)(\mu+\delta+r_2)^2$$

$$y\left[\alpha\gamma(\mu+\delta+r_2)(\beta+r_1)+\alpha\gamma^2(\beta+r_2)-(\alpha\gamma)(\mu+\gamma+r_1)(\mu+\delta+r_2)\right]=$$

$$\left[\mu(\mu+\gamma+r_1)(\mu+\delta+r_2)^2-\beta(\mu+\gamma+r_1)(\mu+\delta+r_2)^2\right]$$

$$y=\frac{\mu(\mu+\gamma+r_1)(\mu+\delta+r_2)^2-\beta(\mu+\gamma+r_1)(\mu+\delta+r_2)^2}{\alpha\gamma(\mu+\delta+r_2)(\beta+r_1)+\alpha\gamma^2(\beta+r_2)-(\alpha\gamma)(\mu+\gamma+r_1)(\mu+\delta+r_2)}$$

$$y=\frac{(\mu+\delta+r_2)^2[\mu(\mu+\gamma+r_1)-\beta(\mu+\gamma+r_1)]}{\alpha\gamma[(\mu+\delta+r_2)(\beta+r_1)+\gamma(\beta+r_2)-(\mu+\gamma+r_1)(\mu+\delta+r_2)]} \qquad (3.15)$$

Substituting (3.15) into 3.10 we have that:

$$z = \frac{\gamma(\mu+\delta+r_2)^2[\mu(\mu+\gamma+r_1)-\beta(\mu+\gamma+r_1)]}{\alpha\gamma[(\mu+\delta+r_2)(\beta+r_1)+\gamma(\beta+r_2)-(\mu+\gamma+r_1)(\mu+\delta+r_2)]}{\mu+\delta+r_2}$$

$$z = \frac{(\mu+\delta+r_2)[\mu(\mu+\gamma+r_1)-\beta(\mu+\gamma+r_1)]}{\alpha[(\mu+\delta+r_2)(\beta+r_1)+\gamma(\beta+r_2)-(\mu+\gamma+r_1)(\mu+\delta+r_2)]} \qquad (3.16)$$

The equilibrium states are:

(a) The Zero equilibrium state is given by:

$(x, y, z) = (0,0,0)$ and

(b) The non-zero equilibrium states are:

$$x = \frac{(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma}$$

$$y = \frac{(\mu+\delta+r_2)^2[\mu(\mu+\gamma+r_1)-\beta(\mu+\gamma+r_1)]}{\alpha\gamma[(\mu+\delta+r_2)(\beta+r_1)+\gamma(\beta+r_2)-(\mu+\gamma+r_1)(\mu+\delta+r_2)]}$$

$$z = \frac{(\mu+\delta+r_2)[\mu(\mu+\gamma+r_1)-\beta(\mu+\gamma+r_1)]}{\alpha[(\mu+\delta+r_2)(\beta+r_1)+\gamma(\beta+r_2)-(\mu+\gamma+r_1)(\mu+\delta+r_2)]}$$

To obtain the characteristic equation we obtain the Jacobin determinant of the system equations which is given by:

$$\begin{vmatrix} \beta-\mu-\alpha z-\lambda & \beta+r_1 & \beta+r_2-\alpha x \\ \alpha z & -(\mu+\gamma+r_1)-\lambda & \alpha x \\ 0 & \gamma & -(\mu+\delta+r_2)-\lambda \end{vmatrix} = 0$$

and the characteristic equation is then given by

$$(\beta-\mu-\alpha z-\lambda)[\gamma\alpha x-(\mu+\gamma+r_1+\lambda)(\mu+\delta+r_2+\lambda)]+(\beta+r_1)[\alpha z(\mu+\delta+r_2+\lambda)]$$
$$+[(\beta+r_2-\alpha x)(\gamma\alpha z)]=0$$

$$(\beta-\mu-\alpha z-\lambda)(\gamma\alpha x)-(\beta-\mu-\alpha z-\lambda)(\mu+\gamma+r_1+\lambda)(\mu+\delta+r_2+\lambda)$$
$$+(\beta\alpha z+r_1\alpha z)(\mu+\delta+r_2+\lambda)+(\beta+r_2-\alpha x)(\gamma\alpha z)=0 \qquad (3.17)$$

CHAPTER FOUR

RESULTS

4.1 Stability of Zero Equilibrium State

At Zero Equilibrium state $(x, y, z) = (0,0,0)$. The characteristic equation (3.17) takes the form:

$$(\beta - \mu - \lambda)[(\mu + \gamma + r_1 + \lambda)(\mu + \delta + r_2 + \lambda)] = 0 \tag{4.1}$$

i.e $(\beta - \mu - \lambda)(\mu + \gamma + r_1 + \lambda)(\mu + \delta + r_2 + \lambda) = 0$

i.e either $(\beta - \mu - \lambda) = 0$ or $(\mu + \gamma + r_1 + \lambda) = 0$ or $(\mu + \delta + r_2 + \lambda) = 0$

hence,

$(\beta - \mu - \lambda) = 0$

$$\Rightarrow \quad \lambda_1 = (\beta - \mu) \tag{4.2}$$

Also, if we consider,

$(\mu + \gamma + r_1 + \lambda) = 0$

We have:

$$\lambda_2 = -(\mu + \gamma + r_1) \tag{4.3}$$

Similarly,

$(\mu + \delta + r_2 + \lambda) = 0$

$$\Rightarrow \quad \lambda_3 = -(\mu + \delta + r_2) \tag{4.4}$$

From (4.3) and (4.4) $\lambda_2<0$ and $\lambda_3<0$ respectively. $\lambda_1<0$ if $\beta<\mu$, $\lambda_1>0$ if $\beta>\mu$. So the zero equilibrium state is stable if $\beta<\mu$ and unstable if otherwise.

4.2 Stability of the Non-zero Equilibrium State

At non-zero equilibrium state

$$x = \frac{(\mu+\gamma+r_1)(\mu+\delta+r_2)}{\alpha\gamma}$$

$$y = \frac{(\mu+\delta+r_2)^2[\mu(\mu+\gamma+r_1)-\beta(\mu+\gamma+r_1)]}{\alpha\gamma[(\mu+\delta+r_2)(\beta+r_1)+\gamma(\beta+r_2)-(\mu+\gamma+r_1)(\mu+\delta+r_2)]}$$

$$z = \frac{(\mu+\delta+r_2)[\mu(\mu+\gamma+r_1)-\beta(\mu+\gamma+r_1)]}{\alpha[(\mu+\delta+r_2)(\beta+r_1)+\gamma(\beta+r_2)-(\mu+\gamma+r_1)(\mu+\delta+r_2)]}$$

As applied in Bellman and Cooke (1963), the result of Bellman and Cooke theorem states that

Theorem

Let $\Delta(z) = p(z,e^z)$ where p(z,w) is a polynomial with principal term. Suppose $\Delta(iy)$, $y \in I$, is separated into its real and imaginary parts,

$\Delta(iy)=F(y) + iG(y)$. If all zeros of $\Delta(z)$ have negatives real parts, then the zeros of F(y) and G(y) are real, simple, alternate and

$$F(0)G'(0)-F'(0)G(0) > 0 \qquad (4.5)$$

For $y \in I$, conversely, all zeros of $\Delta(z)$ will be in the left half-plane provided that either of the following conditions is satisfied:

(i) All the zeros of F(y) and G(y) are real simple; and alternate and inequality (A) is satisfied for at least one y.

(ii) All the zeros of F(y) are real and, for each zero, Relation (A) is satisfied.

(iii) All the zeros of G(y) are real and, for each zero, Relation (A) is satisfied.

(iv) All the zeros of G(y) are real and, for each zero,

The inequality (4.5) is applied to the characteristic equation (3.17). We consider (3.17) in the form

$$H(\lambda) = 0$$

And obtain from (3.17)

$$H(\lambda) = (\beta - \alpha z - \mu - \lambda)(\gamma \alpha x) - (\beta - \alpha z - \mu - \lambda)(\mu + \gamma + r_1)(\mu + \delta + r_2 + \lambda) + (\beta \alpha z + r_1 \alpha z)(\mu + \delta + r_2 + \lambda) + (\gamma \alpha z)(\beta - \alpha x + r_2) \quad (4.6)$$

setting $\lambda = iw$ we get

$$H(iw) = F(w) + iG(w) \quad (4.7)$$

Where $F(w)$ and $G(w)$ are the real and imaginary parts of $H(iw)$.

substituting $\lambda = iw$ into (4.6) we obtain:

$$iw) = (\beta - \alpha z - \mu - iw)(\gamma\alpha x) - (\beta - \alpha z - \mu - iw)(\mu + \gamma + r_1 + iw)(\mu + \delta + r_2 + iw)$$
$$+ (\beta\alpha z + r_1\alpha z)(\mu + \delta + r_2 + iw) + (\gamma\alpha z)(\beta - \alpha x + r_2)$$
$$= (\beta - \alpha z - \mu - iw)\gamma\alpha x - [(\beta - \alpha z - \mu) - iw][(\mu + \gamma + r_1) + iw][(\mu + \delta + r_2) + iw]$$
$$+ (\beta\alpha z + r_1\alpha z)[(\mu + \delta + r_2) + iw] + (\gamma\alpha z)(\beta - \alpha x + r_2)$$
$$= (\beta - \alpha z - \mu)(\gamma\alpha x) - iw(\gamma\alpha x) - [(\beta - \alpha z - \mu)(\mu + \gamma + r_1) + w^2 - iw(\mu + \gamma + r_1)$$
$$+ iw(\beta - \alpha z - \mu)][(\mu + \delta + r_2) + iw] + \beta\alpha z[(\mu + \delta + r_2) + iw]$$
$$+ r_1\alpha z[(\mu + \delta + r_2) + iw] + \gamma\alpha z(\beta - \alpha x + r_2)$$
$$= (\beta - \alpha z - \mu)(\gamma\alpha x) - iw(\gamma\alpha x) - [(\beta - \alpha z - \mu)(\mu + \gamma + r_1) + w^2](\mu + \delta + r_2)$$
$$[-iw(\mu + \gamma + r_1) + iw(\beta - \alpha z - \mu)](\mu + \delta + r_2) - iw[(\beta - \alpha z - \mu)$$
$$(\mu + \gamma + r_1) + w^2] + w^2(\mu + \gamma + r_1) - w^2(\beta - \alpha z - \mu) +$$
$$\beta\alpha z(\mu + \delta + r_2) + iw(\beta\alpha z) + (r_1\alpha z)(\mu + \delta + r_2) + iw(r_1\alpha z) + \gamma\alpha z(\beta - \alpha x + r_2)$$
$$= (\beta - \alpha z - \mu)(\gamma\alpha x) - iw(\gamma\alpha x) - (\beta - \alpha z - \mu)(\mu + \gamma + r_1)(\mu + \delta + r_2) + w^2(\mu + \delta + r_2)$$
$$- iw(\mu + \delta + r_2)(\mu + \gamma + r_1) + iw(\mu + \delta + r_2)(\beta - \alpha z - \mu) - iw(\beta - \alpha z - \mu)$$
$$(\mu + \gamma + r_1) - iw^3 + w^2(\mu + \gamma + r_1) - w^2(\beta - \alpha z - \mu) + \beta\alpha z(\mu + \delta + r_2)$$
$$+ iw(\beta\alpha z) + r_1\alpha z(\mu + \delta + r_2) + iw(r_1\alpha z) + \gamma\alpha z(\beta - \alpha x + r_2)$$

we obtain F(w) and G(w) of equation (4.7) from (4.8) as follows

$$F(w) = (\beta - \alpha z - \mu)(\gamma\alpha x) - (\beta - \alpha z - \mu)(\mu + \gamma + r_1)(\mu + \delta + r_2) + w^2(\mu + \delta + r_2)$$
$$+ w^2(\mu + \gamma + r_1) - w^2(\beta - \alpha z - \mu) + \beta\alpha z(\mu + \delta + r_2) + r_1\alpha z(\mu + \delta + r_2)$$
$$+ \gamma\alpha z(\beta - \alpha x + r_2)$$
$$G(w) = w(\beta - \alpha z - \mu)(\mu + \delta + r_2) - w(\gamma\alpha x) - w(\mu + \delta + r_2)(\mu + \gamma + r_1) - w(\beta - \alpha z - \mu)$$
$$(\mu + \gamma + r_1) - w^3 + w(\beta\alpha z) + w(r_1\alpha z)$$

$$F'(w) = 2w(\mu + \delta + r_2) + 2w(\mu + \gamma + r_1) - 2w(\beta - \alpha z - \mu)$$

$$G'(w) = (\beta\alpha z) + (r_1\alpha z) - (\gamma\alpha x) - (\mu + \delta + r_2)(\mu + \gamma + r_1) - (\mu + \gamma + r_1)(\beta - \alpha z - \mu) - 3w^2$$

Setting $w = 0$

$$F(0) = (\beta - \alpha z - \mu)(\gamma\alpha x) - (\beta - \alpha z - \mu)(\mu + \gamma + r_1)(\mu + \delta + r_2) + (\beta\alpha z)(\mu + \delta + r_2) + (r_1\alpha z)(\mu + \delta + r_2) + (\gamma\alpha z)(\beta - \alpha x + r_2) \quad (4.9)$$

$$F'(0) = 0 \quad (4.10)$$

$$G'(0) = (\beta\alpha z) + (r_1\alpha z) - (\gamma\alpha x) - (\mu + \delta + r_2)(\mu + \gamma + r_1) - (\beta - \alpha z - \mu)(\mu + \gamma + r_1) \quad (4.11)$$

$$G(0) = 0 \quad (4.12)$$

We have from the Bellman and Cooke's theorem (**Bellman and Cooke (1963)**) that:

The condition Re $\lambda < 0$; is given by the inequality:

$$F(0)G'(0) - F'(0)G(0) > 0 \quad (4.13)$$

The equation (4.13) is the stability condition for the non zero equilibrium.

But from (4.10) and (4.12) we have $F'(0) = 0$ and $G(0) = 0$

Hence equation (4.13) becomes

$$F(0)G'(0) > 0 \quad (4.14)$$

Let $J = F(0)G'(0)$ (4.15)

Then non-zero state will be stable when J>O. The stability condition (4.14) is tested with hypothetical parameter values and the results obtained are shown in table (4.1) below:

Table 4:1 Numerical Simulation for the Stability Analysis of Non-zero equilibrium state using hypothetical parameter values with Ms Excel

ß	μ	α	Ϋ	δ	r_1	r_2	F(0)	G'(0)	J	Remark
0.02	0.015	0.001	0.15	0.01	0.1	0.01	-0.0000000055893	-0.0198713	0.0000000055893	stable
0.02	0.015	0.002	0.15	0.01	0.15	0.02	-0.0000000091203	-0.0299166	0.0000000091203	stable
0.02	0.015	0.003	0.15	0.01	0.2	0.03	-0.0000000114074	-0.0419610	0.0000000114074	stable
0.02	0.015	0.004	0.15	0.01	0.25	0.04	-0.0000000128059	-0.0560044	0.0000000128059	stable
0.02	0.015	0.005	0.15	0.01	0.3	0.05	-0.0000000134798	-0.0720468	0.0000000134798	stable
0.02	0.015	0.006	0.15	0.01	0.35	0.06	-0.0000000135124	-0.0900882	0.0000000135124	stable
0.02	0.015	0.007	0.15	0.01	0.4	0.07	-0.0000000129493	-0.1101286	0.0000000129493	stable
0.02	0.015	0.008	0.15	0.01	0.45	0.08	-0.0000000118173	-0.1321680	0.0000000118173	stable
0.02	0.015	0.009	0.15	0.01	0.5	0.09	-0.0000000101325	-0.1562064	0.0000000101325	stable
0.02	0.015	0.01	0.15	0.01	0.55	0.1	-0.0000000079051	-0.1822437	0.0000000079051	stable

CHAPTER FIVE

DISCUSSION OF RESULT, CONCLUSION AND RECOMMENDATION

5.1 Discussion of Result and Conclusion

We observe from (4.2) that the zero equilibrium state is a state of population extinction, will be stable if the birth rate is unusually less than the death rate. However since the eigenvalues are not all negative we conclude that the zero equilibrium is unstable. We observe from Table (4.2) that when the recovery rate for the latent class (r_1), the recovery rate for the active class (r_2)and the rate of infection of TB (α) are varied from low values to high values J remains positive for both low and high values since the values are greater than zero we conclude that the non-zero equilibrium is stable, the stability of non-zero equilibrium implies that treatment of TB at both latent and Active stage is an effective treatment strategy that could lead to the control and possibly the eradication of the disease hence the population is sustainable.

5.2 Recommendations

Tuberculosis is an airborne disease and therefore prevention and control of tuberculosis could be achieved if the following measures are adopted.

1. Avoid and prevent over crowding in homes, rooms and dwellings

2. Prevent or control exposure to infected animals such as cattle, birds, dogs, cats and infected persons.
3. Keep the immune system healthy by avoiding drugs and alcohols as they suppress the immune system.
4. Ensure good, adequate hygiene measures.
5. Adequate ventilation system should be provided in rooms and public shelters.
6. Preventive vaccines such as the Bacillus Calmette Guerin (BCG) should be administered to particularly children.
7. It is important for individuals to cover their mouth with handkerchief when they sneeze or cough in public places.
8. The town planning authorities should ensure that adequate spaces are provided between houses during allocation of plots.
9. All immigrants should be screened for tuberculosis.
10. In health-care settings, high efficiency particulate air (HEPA) filters should be provided in rooms where TB patients are kept.
11. Health-care workers should be provided with respiratory protective devices.
12. Healthcare workers should be given periodic training and education on care of patients with TB.

13. All health-care centres involve in TB treatment should adopt the Direct Observation Treatment Short-course (DOTS) strategy for treatment of patients.

14. Government should create awareness and sensitize the public on transmission and spread of TB.

15. Government should embark on contact tracing for newly infected individuals, so that they can be placed on anti-TB therapy immediately.

16. The model investigates the stability or otherwise of a single-strain (drug sensitive-type of TB only), the model can be extended to investigate two-strain TB (the drug sensitive and non-drug sensitive) for stability or instability.

REFERENCES

Akinwande, N.I. (1999), "The characteristic Equation of a Non-Liner Age structured population model", Trieste Italy international centre for theoretical physics preprint IC/99/53.

Annelis V.R., Robin W, Maddeine R, Thomas C.V, Robert P.G, Donald A.E, Nulda B and Paul D.V (1999): Exogenous re-infection as a cause of recurrent TB after curative treatment *New Journal of Medicine 341:174-1179*

Aparicio, J.P., Caapurri A.F., Castillo Chavez C. (2000): Transmission and Dynamics of Tuberculosis on generalized household *Journal of Theoretical Biology. 206:327-347.*

Associate Degree Nursing program, (2009) Primary/Secondary/Tertiary Prevention in TB, Unpublished Lecture Notes, Mt. San Antonio College.

Bansley, M. (2005): Models and Modeling, Environmental Modeling Files and Directories, University of Wales, Swansea.

Belamy R.L. (200): Identifying genetic susceptibility factors for tuberculosis infection in Africans: a combined approach using candidate gene study and genome-wide screen, *China Science 245-250.*

Bellman R. and Cooke K.C. (1963): Differential difference equations, London. Academic Press.

Benya F., (2005). Introduction to Mathematics modeling, paper Presented at the 7th regional conference on modeling simulation and optimization, Cape Coast, Ghana.

Bermejo A and Richard E. (2005): Mathematical Model on Impact of HIV Epidemic on RB in developing countries, New York. Ellis Horwood Limited,

Caldwell E. (2009): Fighting TB might be a Matter of Flipping a Switch in Immune Response, Psychology and Psychiatry: News Report, Ohio State University Researchers.

Daniel O. and Andrei K. (2007): Dynamics of Tuberculosis: The Effect of Directly Observed Treatment Short-course in Nigeria, *Mathematical Model of Natural Phenomenon. Vol. 2, No. 1; 101-113.*

Edwin E.S and Shelly R.S (1996): Mathematical model for the epidemiology of TB, with estimates of the reproductive number and

infection-delay function, *America Journal of Epidemiology vol. 142, No. 4.*

Elisa F.L, Naween K.V. and Margeret L.B., (2008): controlling co-epidemics: analysis of HIV and TB infection dynamics, Unpublished PhD Dissertation School of management, Yale University, new Haven.

Fitzgibbon W.E and Langlais M. (2000): Mathematical Model for the Spread of Infectious Disease, Unpublished Master Thesis University of Houston, Texas.

Jaun P.A abs Julio C.H (2006): Preventive Treatment of Tuberculosis through Contact Tracing, *American Mathematical Society. 410:17.*

Koriko O.K and Yusuf T.T (2008): Mathematical Model to Simulate TB Disease Population Dynamics, America Journal of Applied Science.

Lipsitch M. and Levin B.R. (1998): Population dynamics of TB treatment: Mathematical model of the roles of non-compliance and bacterial heterogeneity in the evolution of drug resistance *International Journal of Tuberculosis and Lung disease. 2 (3): 187-199.*

Microsoft Corporation (2003): Overview of tuberculosis, Encarta Dictionary, U.S.A

Microsoft Corporation (2003): Treatment and infection, Encarta Dictionary, U.S.A

Murphy B.M, Singer B.H. and et al (2002): Comparing epidemic tuberculosis in demographically distinct heterogeneous population, *Mathematical Biologic/sciences 180:161-185.*

Nucci C.M and Laura G. (1997): Using a mathematical model to evaluate the efficacy of TB control measures, *National Institute for Infection diseases. 3, No. 3.*

Oluwaseun S., Chandra N.P and Abba B.G. (2008): Mathematical Analysis of the transmission of dynamics of HIV/TB co-infection in the present of treatment, *Mathematical Bioscience and Engineering: 5, No. 1, 145-174.*

Phillipe G. (2006): Mathematical Modeling of the TB epidemic in the western pacific region. WHO/WRPO Report, Manila.

Sowumi, C.O.A. (2000): Stability of steady state and boundedness of a two sex population model, Non linear Analysis, 39:693-709.

Samamtimba, J.Y.T Mungisha A. and Luboobi L.S (2005): Mathematical model for the dynamics of TB in density-dependent population: the

case study if internally displaced peoples camp (IDPC) in Uganda, *Journal of Mathematical and Statistics.*

Umar, M.A (2007): Effect of Vaccination, Treatment and Population Area Size on the Transmission Dynamics of Tuberculosis in a Proportion Mixing Population, *Journal of Applied Science. 2(2): 150-155.*

World Health organization (2006) frequently asked questions about HIV and TB, WHO Report, Geneva Switzerland.

World Health Organization (WHO) (2009): Anti-retroviral therapy (ART) WHO Report Geneva, Switzerland.

Ziv E, Daly C.L and Blower S.M (2001): Early therapy of latent tuberculosis infection, *America Journal Epidemiology 153 (4,15): 381-385 (5).*