MODELING THE SPREAD OF TUBERCULOSIS IN CENTRAL REGION USING THE SUSCEPTIBLE-EXPOSED-INFECTED-SUSCEPTIBLE (SEIS) MATHEMATICAL MODEL

BY

SARKODIE ERIC

A THESIS SUBMITTED TO THE DEPARTMENT OF MATHEMATICS, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY,

IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF

MASTER OF SCIENCE IN INDUSTRIAL MATHEMATICS

DEPARTMENT OF MATHEMATICS

FACULTY OF DISTANCE LEARNING

COLLEGE OF SCIENCE

JUNE 2014

DECLARATION

I hereby declare that this submission is my own work towards the MSc. and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

Sarkodie Eric (PG6324611)	……	……..
(Student Name and ID)	Signature	Date

Certified by:

E. Osei-Frimpong (Dr.)	……	……..
(Supervisor)	Signature	Date

Certified by:

Prof. S. K. Amponsah	…….	…….
(Head of Department)	Signature	Date

ACKNOWLEDGEMENT

I wish to express my profound gratitude to the Omnipotent God for granting me the opportunity, strength, knowledge and wisdom to write this thesis.

I specially give thanks to my supervisor, Dr. E. Osei-Frimpong for always being there for me throughout the writing of this thesis. May God richly bless you for your advice, support and patience.

I would like to thank the Department of Mathematics, Kwame Nkrumah University of Science and Technology for a memorable part played in my education.

I highly appreciate the effort of Mr. Evans Nabare, Mr. James Baffoe, Mr. Richard Frimpong and Mr. Massadzi William for their friendly support and encouragement as well as suggestions offered me throughout the course.

I also owe a special debt of gratitude to Mr. Antwi-Adjei Cosmos, Mr. Albert A. Sey, Mrs. Mavis Agyeiwaa Yeboah, Ms. Lucy Emma Antwi-Boateng and Mr. Samuel Adoba for their inspiration and support in many ways.

I am also grateful to Mr. A. N. Wireko, Municipal Director of Agric. KEEA and Mr. Stephen N. Asante, Metropalitan Director of Agric. KMA for their encouragement and patience throughout the course.

Finally, I would like to thank my dearest brother, Mr. Anthony Baffoe, my mum, Ms. Naomi Badu and the entire family members for their effort in making me realize my dreams.

I appreciate the effort of all friends who encouraged me in one way or the other to achieve this dream. May God bless you all.

ABSTRACT

Tuberculosis (TB) is a growing problem worldwide, with an estimated one-third of the world's population currently infected.

In this thesis we modify the non-constant population SEIS model developed by Castillo-Chavez to a constant population model to predict the spread of tuberculosis in the Central Region of Ghana using data from the Central regional Health Directorate, Cape Coast.

We discuss the mathematics behind the model and various tools for judging effectiveness of policies and control methods.

The model has two equilibrium states namely, the disease – free and the endemic equilibrium points. The stability of each equilibrium point is discussed and the endemic equilibrium has been found to be stable while that of the disease-free was unstable. The basic reproduction number (R_o) was estimated to be 2. The disease was found to persist with $R_o > 1$ whenever the transmission rate was increased or the recovery rate reduced but turned to die out with $R_o < 1$, whenever the transmission rate was reduced or the recovery rate increased.

The results of our sensitivity analysis showed that the most sensitive parameter that controls the spread of tuberculosis in Central Region is the initial infection rate of the susceptible, σ. Decreasing the value of σ at the same rate as the other parameter values completely decreases the proportions of both the infective and the exposed more effectively than any parameter value.

From the analysis and discussions of the model, SEIS epidemiological model is a good model to study the spread of tuberculosis in Ghana.

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CHAPTER 1

INTRODUCTION

1.1 Background of the study

Mathematical models used for the spread of infectious disease are called dynamic epidemiological models because they describe change over time. They have a long history in epidemiology and have been used in a wide variety of diseases, including measles, influenza, rubella and chicken pox (Feng *et al.*, 2000). Most diseases studied using modeling techniques have age-specific transmission rates. They tend to have relatively short latent periods and relatively short contagious periods resulting in permanent immunity in the infected individual. A unique feature of tuberculosis is the ambiguity in the biological processes involved in disease transmission and activation. Transmission is further complicated by the inclusion of both biological and social factors. Hence, there have been relatively few attempts to use mathematical modeling to describe the behaviour of tuberculosis (TB).

Tuberculosis models are either deterministic or stochastic. The models operate by defining states for individuals within a population. Individuals are assigned to subpopulation groups based on characteristics such as 'infected with,' or 'immune to,' tuberculosis. Deterministic models have a finite number of states, and specify rules by which individuals move from one state to another through a series of differential equations. Stochastic models specify probabilities of movements between populations, and can therefore provide probabilities of particular model outcomes. Agent-based models also referred to as micro simulations and individual-based models represent a large set of individuals, each with their own independent, defined characteristics. Unlike compartmental models, agent-based models consider individuals as discrete entities. This information is updated at various time points, either stochastically (event driven models) or periodically (regular discrete models). The level of detail of such models is only limited by population size and computing power (Getz *et al.*, 2006).

By far the most common type used in the TB modeling literature, deterministic models are based on a series of classes, potentially including susceptible, infected and recovered, lending the name "SIR models."

Other possible classes include exposed, immune, and stages of disease. The movement from one class to another is defined by the modeler to reflect his/her understanding of tuberculosis epidemiology, and the questions to be tested by the model. For example, a TB model may be an SEIR model, or it may be an SEI model with no recovery.

In epidemiological models, R_o is defined as the basic reproduction number, which is the average number of secondary infections produced from one infected individual in a totally susceptible population. R_o is also referred to as the basic reproduction ratio or basic reproductive rate. In a deterministic model, R_o is a threshold quantity that must be greater than one for an infection to invade a new population and persist over time. However, because risk of infection may vary with many factors (e.g., age, vaccination, and nutritional status), the determination and interpretation of R_o depends on the susceptible population structure.

A dynamic model is, by definition, a simplification of reality. Every population exhibits heterogeneity; the degree of detail included in a model depends upon the goals of the modeler. In a deterministic model, a heterogeneous population can be split into a finite number of subpopulations, each of which is homogeneous. Then the epidemic dynamics are modeled deterministically with movement among subpopulations. However, placing an individual into one of a series of subpopulations is problematic, because group boundaries may not be mutually exclusive. Furthermore, many variations between individuals are better described by continuous rather than categorical variables. However, categorical approaches are often simpler to use mathematically than models including continuous variation, and model detail must be balanced against mathematical tractability (Getz *et al.,* 2006).

A second approach is described as an application of stochastic branching process theory where the R_o associated with each infectious case is allowed to vary. This approach is used to describe measles and smallpox (Getz *et al.* 2006), and it is demonstrated that assumptions of homogeneity oversimplify epidemic models of infectious disease such that estimates of R_o alone do not adequately describe disease dynamics. A failure to consider heterogeneity therefore may

seriously bias probability estimates of disease invasion or prevalence. A third approach is to create discrete-time stochastic simulation models based on individuals. This can be done in a network characterized by non-random associations between individuals (Achterberg, 2009).

Though complex, the process of creating a mathematical model forces the modeler to clarify disease assumptions and parameters; model results can provide qualitative and quantitative results including basic reproduction number and thresholds. They can be experimental tools for formulating and testing hypotheses, answering key questions, and estimating sensitivity to parameter changes (Achterberg, 2009).

1.2 Tuberculosis

Tuberculosis (TB) is an infectious disease that has plagued humans for many years. The organism that causes tuberculosis is known as the Mycobacterium tuberculosis.

Mycobacterium tuberculosis is a rod-shaped, slow-growing bacterium. Its cell wall has high acid content, which makes it hydrophobic, resistant to oral fluids.

Tuberculosis continues to kill millions of people yearly worldwide. In 1995, three (3) million people died from TB. More than 90% of TB cases occur in developing nations that have poor hygiene and health-care resources and high numbers of people infected with HIV (CDC, 2005).

In 2008, the World Health Organization (WHO) estimated that one-third of the global population was infected with TB bacteria.

Mycobacterium tuberculosis scanning electron micrograph is shown in the figure below

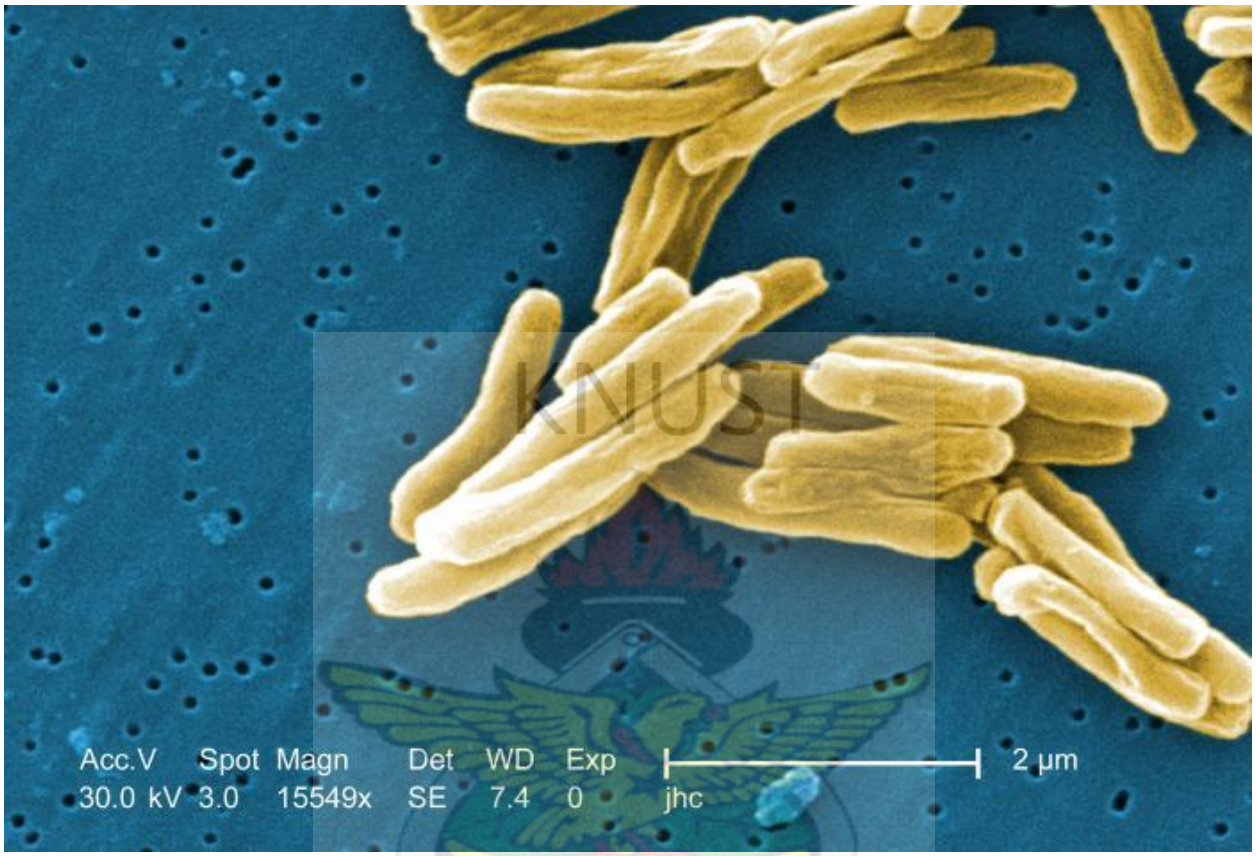

Figure 1.1: Mycobacterium tuberculosis scanning electron micrograph

1.2.1 Causes and Symptoms of Tuberculosis

All cases of TB are passed from person to person via droplets. When someone with TB infection coughs, sneezes, or talks, tiny droplets of saliva or mucus are expelled into the air, which can be inhaled by another person.

Once infectious particles reach the alveoli (small saclike structures in the air spaces in the lungs), another cell, called the macrophage, engulfs the TB bacteria.

Then the bacteria are transmitted to the lymphatic system and bloodstream and spread to other organs occurs.

The bacteria further multiply in organs that have high oxygen pressures, such as the upper lobes of the lungs, the kidneys, bone marrow, and meninges -- the membrane-like coverings of the brain and spinal cord.

When the bacteria cause clinically detectable disease, you have TB.

Only about 10% of people infected with M. tuberculosis ever develop tuberculosis disease.

People who have inhaled the TB bacteria, but in whom the disease is controlled, are referred to as infected. Their immune system has walled off the organism in an inflammatory focus known as a granuloma. They have no symptoms, frequently have a positive skin test for TB, yet cannot transmit the disease to others. This is referred to as latent tuberculosis infection or LTBI.

Risk factors for TB infection include the following: HIV infection, low socioeconomic status, alcoholism homelessness, crowded living conditions, diseases that weaken the immune system, migration from a country with a high number of cases and health-care workers.

The symptoms of tuberculosis do not become evident in most cases, unless the disease has advanced. The common symptoms of tuberculosis include cough for a prolonged duration that is more than three weeks, unexplained or intended weight loss, fatigue, general feeling of tiredness, fever, sweating at night, chills and loss of appetite. Having these signs and symptoms does not mean that you have tuberculosis. There are many other diseases which have the same symptoms. So you need to undergo various tests, so that you are sure that you have tuberculosis. Signs and symptoms of active tuberculosis may also vary depending on the organ that is affected. Most of the times, the lungs of the patients are affected. Symptoms of tuberculosis of the lungs include cough for three or more weeks, blood in cough, chest pain or pain while breathing or coughing. Tuberculosis can also affect organs apart from the lungs. The other organs that are affected by tuberculosis include lymph nodes, genitourinary nodes, bone and joint sites, lining covering the outside of the gastrointestinal tract (Centre for Disease Control and Prevention, 2007).

1.2.2 Testing for TB Infection

There are two kinds of tests that are used to determine if a person has been infected with TB bacteria: the tuberculin skin test and TB blood tests.

A positive TB skin test or TB blood test only tells that a person has been infected with TB bacteria. It does not tell whether the person has latent TB infection (LTBI) or has progressed to TB disease. Other tests, such as a chest x-ray and a sample of sputum, are needed to see whether the person has TB disease.

1.2.2.1 Tuberculin skin test

The TB skin test (also called the Mantoux tuberculin skin test) is performed by injecting a small amount of fluid (called tuberculin) into the skin in the lower part of the arm. A person given the tuberculin skin test must return within 48 to 72 hours to have a trained health care worker look for a reaction on the arm. The health care worker will look for a raised, hard area or swelling, and if present, measure its size using a ruler. Redness by itself is not considered part of the reaction.

The skin test result depends on the size of the raised, hard area or swelling. It also depends on the person's risk of being infected with TB bacteria and the progression to TB disease if infected.

1.2.2.2 TB Blood Tests

TB blood tests (also called interferon-gamma release assays or IGRAs) measure how the immune system reacts to the bacteria that cause TB. An IGRA measures how strong a person's immune system reacts to TB bacteria by testing the person's blood in a laboratory

(Centre for Disease Control and Prevention, 2007).

1.2.3 How to Cure Tuberculosis

The tuberculosis cure usually involves taking antibiotics for 6 to 12 months. Tuberculosis continues to kill about 2 to 3 million people every year. Treatment of tuberculosis requires the use of special tuberculosis medications. All these medicines produce serious side effects. To cure tuberculosis, the patients have to take several antibiotics. The tuberculosis bacteria should respond to at least three of them every day for up to two years. However, even with this treatment, there is a possibility that some patients might die. Between 4 and 6 out of every 10 patients die during the treatment of tuberculosis (Centre for Disease Control and Prevention, 2007).

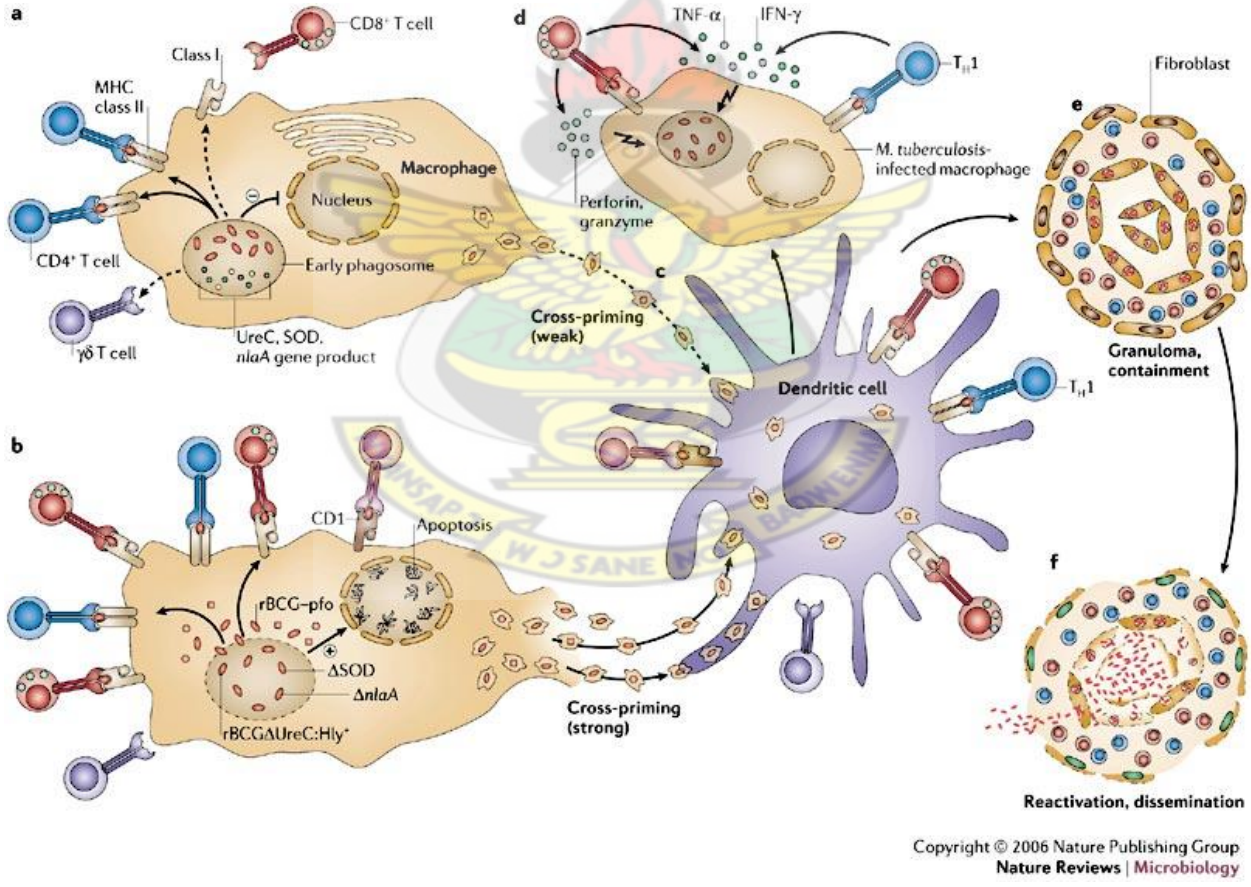

Figure 1.2: The immune response to Mycobacterium tuberculosis infection or vaccination with BCG or recombinant modified BCG.

There are chances that a patient suffering from tuberculosis can be completely cured today. But the patient has to understand the disease and co-operate fully in the treatment program. Both latent and active tuberculosis can be treated with antibiotics. Latent tuberculosis can be treated with only one antibiotic; active tuberculosis is treated with several antibiotics at one time. Active tuberculosis has to be treated really well, and patients will have to start treatment by admitting themselves in the hospital so that they will not spread the disease, as tuberculosis is highly contagious (Centre for Disease Control and Prevention, 2007).

1.2.3.1 Bacille Calmette-Geurin(BCG) Vaccine

The BCG vaccine is a vaccine that was developed to prevent tuberculosis (TB) disease. It is often given to newly born individuals, where there is a high prevalence of TB. This is done in order to prevent childhood tuberculosis, meningitis, and miliary disease. The vaccine is a live vaccine, derived from a strain *of Mycobacterium bovis*. It was first administered to humans in 1921(CDC,2008).

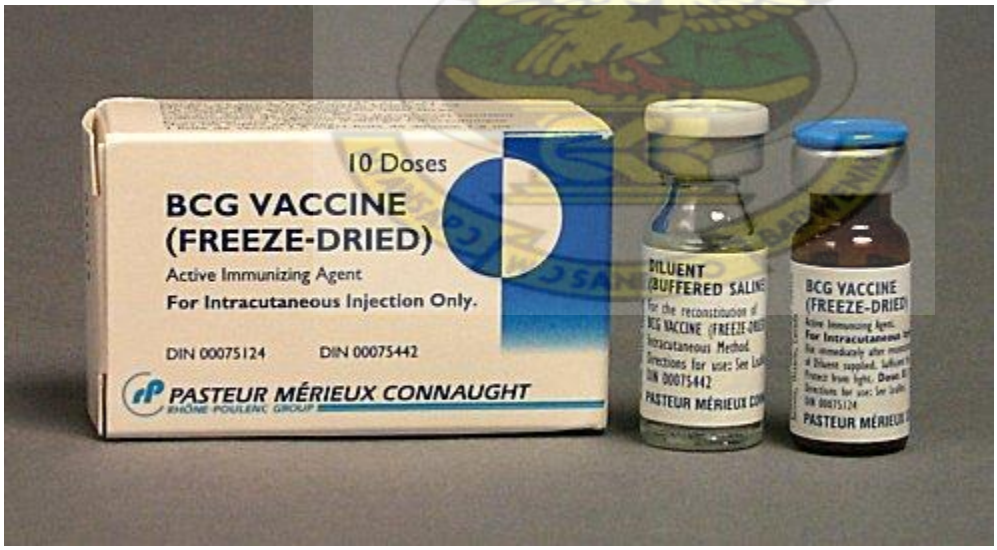

Figure 1.3 BCG Vaccine

1.3 Problem Statement

Tuberculosis, an ancient disease that has caused more suffering and death than any other infectious disease continues to be a major public health problem in Ghana (CDC, 2007). Over forty-six thousand (46,000) new cases of TB are annually estimated by the World Health Organization (W.H.O.) in Ghana. According to the latest W.H.O. data published in April 2011, death as a result of TB infection in Ghana reached 11,738 or 6.25% of total deaths. Also, TB occupies sixth position of the top twenty causes of death in Ghana. The epidemiology of TB in Ghana has therefore become imperative, needing research and effort to help control the spread and eradicate this disease (CDC, 2005).

1.4 Objectives of the Study

The main objectives of the study are:

- To formulate a modified constant population SEIS model for tuberculosis in Central Region
- To determine the spread of the disease in Central Region
- To perform the stability analysis of the equilibrium states of the SEIS model

1.5 Methodology

An SEIS model would be formulated and it is one of the models used to describe the epidemiology of infectious diseases. This computes the amount of Susceptible, Exposed and Infected individuals in a locality. In this model, recovered individuals do not acquire immunity as in some models, but rather become susceptible to the disease again. The model equation would be solved and analysed by the deterministic approach. Simulation will be done using MatLab and sensitivity analysis will then be carried out on the parameter values to determine their effect on the spread of the disease.

1.6 Justification

Although there have been researches on Tuberculosis in Ghana, there has not been any Mathematical modeling of Tuberculosis using the SEIS model. A combination of this thesis and other models of TB will pave a broader way for us to overcome the problem of TB in this country. Tuberculosis is a retrogressing factor in the country's development. Death as a result of Tuberculosis hampers the country's productivity and hence a threat to socio-economic development. This thesis will therefore be of paramount importance by helping in the control of Tuberculosis in Ghana.

1.7 Organization of the Thesis

The thesis is made up of five (5) main chapters. Chapter one being the introduction of the thesis comprises of the background of TB, problem statement, objectives, methodology and organization. Related researches done by others would be reviewed in chapter two. Chapter 2 will also include some Mathematical definitions and theorems related to the model under study. Chapter three would be about Mathematical model formulation. The analysis and results are presented in chapter four. Chapter five is about conclusion and recommendations for further studies.

CHAPTER 2

REVIEW OF FUNDAMENTALS

This chapter looks into the review of related works on tuberculosis using the SEIS and other deterministic models. Besides, some definitions and theorems related to the study will be considered.

The first mathematical model of TB was presented by Waaler *et al*. (1962). Following this, there were several numerical studies, primarily focusing on cost-effectiveness of different interventions (Brogger, 1967; Revelle *et al*., 1969). Revelle *et al*. (1969) used a model with one progression rate and various latent classes representing different treatment and control strategies, and argued that vaccination was cost-effective in countries with high TB burdens. Waaler continued his work in Waaler (1968a), Waaler (1968b), Waaler and Piot (1969), Waaler (1970) and Waaler and Piot (1970). After the 1970's little work on models of tuberculosis appeared in the literature until the mid-1990's.

2.1 THE SEIS MODEL FOR TUBERCULOSIS

Feng *et al.* (1999) studied differential equations and differential-integral equations that describe the dynamics of disease transmission for tuberculosis (TB). The main interest was to study these models to understand the long-time behaviour of the dynamics of disease transmission, thus, whether the disease would die out eventually or would persist. They looked at the effects of variable periods of latency on the dynamics of TB by considering an SEIS model with individuals moving back to the susceptible (S) class from both the Exposed (E) and the Infectious (I) classes due to treatment. The findings of their studies revealed that the addition of an arbitrarily distributed latency period to the basic TB model does not alter the qualitative dynamics of TB, the disease either dies out or remains endemic regardless of the shape of the incubation/latent period distribution.

Rui Xu (2012) investigated an SEIS epidemiological model with a saturation incidence rate and a time delay representing the latent period of the disease. By means of Lyapunov functional, LaSalle's invariance principle and comparison arguments, it was shown that the global dynamics is completely determined by the basic reproduction number. It is proven that the basic reproduction number is a global threshold parameter in the sense that if it is less than unity, the disease-free equilibrium is globally asymptotically stable and therefore the disease dies out; whereas if it is greater than unity, there is a unique endemic equilibrium which is globally asymptotically stable and thus the disease becomes endemic in the population. Numerical simulations were carried out to illustrate the main results.

Fan *et al*. (2001) presented a mathematical model on the global dynamics of an SEIS epidemiological model that incorporates constant recruitment, exponential natural death as well as the disease related death, so that the population size might vary in time. They established that the basic reproductive number (R_o) is a sharp threshold parameter and completely determines the global dynamics of their model. Besides, they again established that if $R_o \leq 1$, the disease free equilibrium is globally stable and the disease always dies out and if $R_o > 1$, a unique endemic equilibrium is globally stable so that the disease persists at the endemic equilibrium if it is initially present.

Heterogeneity is experienced in every population in a variety of forms. A number of models have tried to clearly model such heterogeneous characteristics. Though the root causes of heterogeneity differ between models, the methodological formulations are similar. These models exhibit a framework that can be reduced to comparable general models of TB transmission dynamics. However, these models give room for a number of explicit assumptions, and allow for the study of a wider range of aspects of TB. Two articles (Murphy *et al.* 2002 & 2003) are discussed in detail as examples of the inclusion of heterogeneity in a deterministic model.

Murphy *et al.* (2002) developed a TB model on the effects of heterogeneity in demographically distinct populations. In a deterministic model, the overall population was split into six subpopulations: for each group of 'uninfected with TB,' 'latently infected,' or 'actively infected,' there existed a group that was genetically neutral and a group that was genetically susceptible (rates of TB acquisition and progression are higher compared to the genetically neutral group) toward TB. Though the authors interpret their model in terms of underlying genetic

susceptibility, the results are equally applicable to any environmental or behaviour condition that creates variable susceptibility to TB. There is a constant birth rate, and death rates are dependent on disease status. Active TB individuals only die from constant disease rate. All births enter into uninfected categories (either genetically susceptible or neutral). Individuals move from uninfected categories to latently infected or actively infected. Latently infected individuals move to actively infected. Individuals can leave any population by death, and those in the actively infected population have a given disease-related death rate. The results indicate that in a population with a high level of genetic susceptibility, TB prevalence is only slightly affected by changes in transmission. Conversely, in a population with a small genetically susceptible subpopulation, transmission rates are more important. The determination of R_o for a heterogeneous population is done here using numerical simulations. Their model had several unique biological assumptions and they include the following: 1) Latently infected individuals cannot be re-infected by active TB individuals; 2) there exists an annual reactivation rate for latently infected individuals; and 3) the contact rates are non-linear. In 2003, Murphy *et al.* did further work on their model by considering how the presence of a genetically susceptible subpopulation alters the effects of TB treatment at both latent and active stages. It is assumed that treatment doesn't guarantee immunity, but instead it moves individuals from actively infected to latently infected. Treatment of latently infected individuals reduces their reactivation rate. Results indicate that exclusive treatment of latently infected individuals alone is not as effective as treatment of actively infected individuals alone. Treatment strategies of latently infected individuals show that low chemotherapy levels have almost no effect on reducing prevalence regardless of the genetic susceptibility level.

2.2 THE EFFECT OF HIV ON TUBERCULOSIS INFECTION

In a deterministic model and numerical analysis, West and Thompson (1997) investigated the magnitude and duration of the effect that increasing HIV may have on TB. Similarly focused, Porco *et al.* (2001) use a discrete event model simulation to predict the potential impact of HIV on the probability and severity of TB outbreaks.

However, while West and Thompson model individuals as having TB stages nested within each stage of HIV, the stochastic model of Porco *et al.* is based on four main populations: uninfected

individuals; those infected only with HIV; those infected only with TB; and those dually infected. HIV-positive individuals are further subdivided by stage of infection—the nesting order is reversed from that used by West and Thompson (1997).

Using available parameter estimates, West and Thompson conclude that the background rate of TB infection, interaction between subpopulations of HIV stages, and the increase in TB susceptibility for HIV-positive individuals will have strong effects on future TB incidence in the United States. The model results of Porco *et al.* (2001) indicate that at moderate to low TB treatment rates, a moderate HIV epidemic can double the size of TB outbreaks compared to when HIV is not present. However, when the treatment rate of TB is very high, the amplification effect of HIV can be significantly reduced. Simulation results agree with molecular epidemiological data in that the incidence rate of TB is comprised of multiple small and a few large outbreaks. However, these large outbreaks may occur as a result of chance and not necessarily due to increased strain fitness. Based on their results, the authors advocate for both TB and HIV treatment as a means to control TB outbreaks; the presence of HIV does not negate the value of TB therapeutics in developing nations.

To explicitly consider HIV and TB combined control efforts, Currie *et al.* (2003) compare TB chemotherapy with three strategies for prevention, two of which focus directly on HIV treatment, in a deterministic model. The model includes TB reinfection and treatment failure. They find that even where HIV prevalence is high, treating active TB is the most effective way to minimize the number of TB cases over the next 10 years. Treatment of only latent TB is comparatively ineffective over all time scales. Reducing HIV is relatively ineffective over 10 years, but much more effective over 20 years.

Though Porco *et al.* (2001) state that TB therapeutics are not ineffective in the presence of HIV, Getz *et al.* (2006) further explore this relationship, and preliminary model results indicate that a 2 month TB treatment compared to a 6 month treatment regime may offer important benefits that appear to be reduced when HIV prevalence is high. The model is currently being used to investigate scenarios with increased treatment compliance, reduced relapse after treatment and enhanced case detection.

Including treatment and progression dynamics of both HIV and TB introduces a high level of

complexity into a model, which is compounded by high levels of uncertainty in parameter values characterizing both TB and HIV (Getz *et al.* 2006). To attempt to resolve this uncertainty, Raimundo *et al.* (2003) use empirical data from a closed environment to try to better estimate transmission coefficients for both HIV and TB in a deterministic model. The threshold between absence of infection and endemic basins are analyzed. The interaction between TB and HIV is considered with data from women incarcerated in the Female Penitentiary of Sao Paulo State, Brazil. Homogeneous mixing among all individuals is assumed, there is no recovery, and reinfection (and/or reactivation) exists. Model results indicate that TB can, to some extent, be preventative for HIV infection when HIV incidence and prevalence are low (and assuming segregation for AIDS patients). On the other hand, the presence of HIV, even when low, increases rates of TB and speeds progression to active disease. In combination with the results of Getz *et al.* (2006), it is clear that the combination of HIV and TB in a population will increase transmission of each, and limit the treatment of both.

2.3 SOME STUDIES ON TUBERCULOSIS USING DETERMINISTIC MODELS EITHER THAN THE SEIS MODEL

Castillo-Chavez and Feng (1996) formulated one-strain and two-strain TB models to determine possible mechanisms that may allow for the survival and spread of naturally resistant strains of TB as well as antibiotic-generated resistant strains of TB. Analysis of their models showed that non-antibiotic co-existence is possible but rare for naturally resistant strains while co-existence is almost the rule for strains that result from the lack of compliance with antibiotic treatment by TB infected individuals.

Blower *et al*. (1997) present time-dependent uncertainty and sensitivity analyses in order to quantitatively understand the transmission dynamics of tuberculosis epidemics in the absence of treatment. The time-dependent uncertainty analysis enabled them to evaluate the variability in the epidemiological outcome variables of the model during the progression of a tuberculosis epidemic. Calculated values for the disease incidence, disease prevalence, and mortality rates

were approximately consistent with historical data. The time-dependent sensitivity analysis revealed that only a few of the model's input parameters significantly affected the severity of a tuberculosis epidemic; these parameters were the disease reactivation rate, the fraction of infected individuals who develop tuberculosis soon after infection, the number of individuals that an infectious individual infects per year, the disease death rate, and the population recruitment rate. Their analysis demonstrated that it is possible to improve the understanding of the behaviour of tuberculosis epidemics by applying time dependent uncertainty and sensitivity analysis to a transmission model.

Deterministic model of tuberculosis without and with seasonality was designed and analyzed into its transmission dynamics by Bowong and Kurths (2011). They first presented and analyzed a tuberculosis model without seasonality, which incorporates the essential biological and epidemiological features of the disease. The model was shown to exhibit the phenomenon of backward bifurcation, where a stable disease-free equilibrium coexists with one or more stable endemic equilibriums when the associated basic reproduction number is less than unity. Then, the extension of their TB model by incorporating seasonality was developed and the basic reproduction ratio defined. Parameter values of the model were estimated according to demographic and epidemiological data in Cameroon.

The simulation results were in good accordance with the seasonal variation of the reported cases of active TB in Cameroon.

E. Salpeter and R. Salpeter also formulated a Mathematical model for TB. The authors used epidemiologic data on tuberculosis to construct a model for the time delay from initial latent infection to active disease, when infection transmission occurs. They used case rate tables in the United States to calculate the fractional rate of change per annum (A) in the Incidence of active tuberculosis. They then derived estimates for the effective reproductive number (R) and the cumulative transmission, defined as the number of people whom one infected person will infect in his or her lifetime and over many multiple successive transmissions, respectively. For A of -4 percent per year, the average US condition from 1930 to 1995, they estimated the reproductive number to be about 0.55 and the cumulative transmission to be about 1.2. The estimated rate of the new latent infections in the United States is 80, 000 per year, the estimated prevalence of latent infections is 5 percent, and the number of transmissions of infections per active case is 3.5.

From the model, the authors predicted active case rates in various age groups and compared them with published tables. The comparison suggests that the risk of activation decreases rapidly, then gradually, for the first 10 years after initial infection; the risk is relatively constant from 10 to 40 years and may decrease again after 40 years. The authors also discussed how this model could be used to help make decisions about tuberculosis control measures in the population.

An SIS model for bacterial infectious diseases, like tuberculosis, typhoid,etc., caused by direct contact of susceptibles with infectives as well as by bacteria was proposed and analyzed by M. Ghosh et al (2005). Here the demography of the human population was constant immigration and the cumulative rate of the environmental discharges was a function of total human population. Further their model was extended to the model for socially structured population (rich and poor) where poor people worked as service provider in the houses of rich people but did not settle in the habitat of rich people. It was assumed that bacteria population did not survive in the clean environment of rich people and only affected the population in the degraded environment of the poor class. The stability of the equilibriums was studied by using the theory of differential equation and computer simulation. It was concluded that the spread of the infectious disease increased when the growth of bacteria caused by conducive environmental discharge due to human sources increased. Also the spread of the infectious disease in rich class increased due to the interaction with service providers, who were living in relatively poor environmental condition, suggesting the need to keep our environment clean all around.

Achterberg (2001) used the deterministic mode to study demographic non-stability and environmental change over time. To do so, vaccination, population growth, overall well-being, and exposure are modeled as functions of both contact rate and infectivity per exposure. Though interpreted as environmental and behavioural change, mathematically this construction is similar to the way in which Murphy *et al.* (2002 & 2003) carried out their study on heterogeneity.

Several TB models aim to investigate optimal treatment strategies. Lietman and Blower (2000) study pre- and post-exposure vaccines, using models with fast and slow progressors, and vaccines parametrized by their “take”, “degree” and “duration”, permitting various mechanisms by which these programs may be less than 100% effective. They find that even if a vaccine is only moderately effective, it may reduce TB epidemics if coverage is high. A strategy of

continuous vaccination of newborns after a single mass vaccination of susceptibles appears to perform best. However the vaccines simulated are theoretical and estimates of the efficacy of the existing vaccine Bacille Calmette-Gu´erin (BCG) are highly variable (Colditz *et al*., 1994, 1995). In Ziv *et al*. (2001) the authors use 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 conclude that contact tracing and preventative treatment compare quite favorably to treatment of those with disease.

2.4 **Differential Equation**

Definition: An equation containing the derivatives of one or more dependent variables, with respect to one or more independent variables, is said to be a differential equation. An example of a differential equation is shown below;

$$a\frac{d^2x}{dt^2} + b\frac{dx}{dt} + cx = d \qquad (2.01)$$

where x is the variable and t is its derivative.

Differential equations play a prominent role in engineering, physics, economics, and other disciplines. Differential equations arise in many areas of science and technology, especially whenever a deterministic relation involving some continuously varying quantities and their rate of change in space or time is known. This is illustrated in classical mechanics, where the motion of a body is described by its position and velocity as the time value varies. Newton's laws allow one (given the position, velocity, acceleration and various forces acting on the body) to express these variables dynamically as a differential equation for the unknown position of the body as a function of time. In some cases, this differential equation may be solved explicitly.

An example of modeling a real world problem using differential equations is the determination of the velocity of a ball falling through the air, considering only gravity and air resistance. The ball's acceleration towards the ground is the acceleration due to gravity minus the deceleration

due to air resistance. Gravity is considered constant, and air resistance may be modeled as proportional to the ball's velocity. This means that the ball's acceleration, which is a derivative of its velocity, depends on the velocity (and the velocity depends on time). Finding the velocity as a function of time involves solving a differential equation (Wikipedia, Differential Equations).

Differential equations are mathematically studied from several different perspectives, mostly concerned with their solutions, the set of functions that satisfy the equation. Only the simplest differential equations admit solutions given by explicit formulas; however, some properties of solutions of a given differential equation may be determined without finding their exact form. If a self-contained formula for the solution is not available, the solution may be numerically approximated using computers. The theory of dynamical systems puts emphasis on qualitative analysis of systems described by differential equations, while many numerical methods have been developed to determine solutions with a given degree of accuracy (Abbott and Neill, 2003).

2.4.1 Types of differential equations

2.4.1.1 Ordinary differential equation

Definition: An ordinary differential equation (ODE) is a differential equation in which the unknown function (also known as the dependent variable) is a function of a single independent variable. That is,

$$F(x,y,y',\ldots\ldots,y^{(n)}) = 0 \qquad (2.02)$$

where y is a function of $xy' = \frac{dy}{dx}$ is the first derivative with respect to x and $y^{(n)} = d^n y/dx^n$ is the nth derivative with respect to x.

In the simplest form, the unknown function is a real or complex valued function, but more generally, it may be vector-valued or matrix-valued. This corresponds to considering a system of ordinary differential equations for a single function.

Ordinary differential equations are further classified according to the order of the highest derivative of the dependent variable with respect to the independent variable appearing in the

equation. The most important cases for applications are first-order and second-order differential equations.

2.4.1.2 Partial differential equation

Definition: A partial differential equation (PDE) is a differential equation in which the unknown function is a function of multiple independent variables and the equation involves its partial derivatives. Generally, it is represented as shown below;

$$F\ (D^k u(x),\ D^{k-1} u(x), \ldots\ldots, Du(x), u(x), x) = 0 \qquad (2.03)$$

$x \in \Omega$ where $u: \Omega \rightarrow R$ is the unknown.

The order is defined similarly to the case of ordinary differential equations, but further classification into elliptic, hyperbolic, and parabolic equations, especially for second-order linear equations, is of utmost importance. Some partial differential equations do not fall into any of these categories over the whole domain of the independent variables and they are said to be of mixed type (Blanchard *et al*. 2006).

2.4.2 Linear and non-linear differential equations

Both ordinary and partial differential equations are broadly classified as linear and nonlinear.

Definition: A differential equation is linear if the unknown function and its derivatives appear to the power 1. When the unknown function and its derivatives appear to the power either than 1, then the differential equation is described as nonlinear. Examples of linear and nonlinear differential equations are shown in equations (2.04) and (2.05).

$$\frac{dy}{dt} = t^2 y + \cos t \qquad (2.04)$$

$$\frac{d^2 y}{dx^2} = 2x \left(\frac{dy}{dx}\right)^2 \qquad (2.05)$$

The characteristic property of linear equations is that their solutions form an affine subspace of an appropriate function space, which results in much more developed theory of linear differential equations. Homogeneous linear differential equations are also such that the sum of any set of solutions or multiples of solutions is also a solution. The coefficients of the unknown function and its derivatives in a linear differential equation are allowed to be functions of the independent variable or variables and if these coefficients are constants then one speaks of a constant coefficient linear differential equation.

There are very few methods of solving nonlinear differential equations exactly; those that are known typically depend on the equation having particular symmetries. Nonlinear differential equations can exhibit very complicated behaviour over extended time intervals, characteristic of chaos. Even the fundamental questions of existence, uniqueness, and extend ability of solutions for nonlinear differential equations, and well-posedness of initial and boundary value problems for nonlinear PDEs are hard problems and their resolution in special cases is considered to be a significant advance in the mathematical theory.

Linear differential equations frequently appear as approximations to nonlinear equations. These approximations are only valid under restricted conditions. For example, the harmonic oscillator equation is an approximation to the nonlinear pendulum equation that is valid for small amplitude oscillations (Zwillinger, 1997).

2.5 Description of some Deterministic Models

When dealing with large populations, as in the case of tuberculosis, deterministic mathematical models are used. In a deterministic model, individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of the epidemic. Letters such as M, S, E, I, and R are often used to represent different stages.

The transition rates from one class to another are mathematically expressed as derivatives, hence the model is formulated using differential equations. While building such models, it must be assumed that the population size in a compartment is differentiable with respect to time and that

the epidemic process is deterministic. In other words, the changes in population of a compartment can be calculated using only the history used to develop the model (Brauer & Castillo-Chavez, 2001).

Some deterministic models have been discussed below.

2.5.1 SI(S) Models

The SI(S)model is a two-state deterministic model which assumes that a person can be in one of only two states, either susceptible(S) or infectious(I). These states are often called compartments, and the corresponding models are called compartment models. Not all diseases are accurately described by a model with only two states, but a two-state model is useful in describing some classes of micro parasitic infections to which individuals never acquire a long lasting immunity. Certain RNA viruses such as rhinoviruses and coronaviruses (the common cold) mutate so rapidly that individuals recently recovered from a cold will still be susceptible to other strains of the same virus circulating in a population. In a simple model for this process, individuals never enter a recovered state, but rather alternate between being susceptible and being infectious.

In an SI model (or any standard compartment model), individuals move from the Susceptible state (S) to the Infectious state (I) by mixing or interacting with infectious individuals. If almost the entire population is Susceptible, then the rate of change in the number of Infectious people (Δ I) must be proportional to the transmission rate:

$$\Delta I \alpha \beta I \tag{2.06}$$

where β, is the transmission rate. This expression is, of course, incorrect for large numbers of infectious people because the total population is not always entirely susceptible to infection. Once there are no susceptible people left to infect, there can be no new infections. The correct expression is given by:

$$\Delta I \alpha \frac{\beta}{p} SI \tag{2.07}$$

where the total population P = (S+I), and S/P is the fraction of the population Susceptible to infection. The proportionality expression (2.07) is an interaction product that represents the interaction between infectious people and susceptible people as a simple product. This interaction product, determines the new incidence of infection (McKendrick, 1925).

The Reproductive Number of an SI(S) model

Whether or not a disease will spread throughout a population is determined by the Basic Reproductive Number,R_o. For an SIS model, R_o is the product of the infectious period and the transmission rate.

When $R_o > 1.0$, the disease is infectious. When $R_o < 1$, the disease will die out. By implementing interventions that lower the transmission rate, public health officials can reduce the basic reproductive rate of a disease.

2.5.2 SIR(S) Models

The SI(S) model contains the important interaction product,

$$\frac{\beta}{p} SI \qquad (2.08)$$

which describes how infectious people transmit an infection to susceptible people. However, notall infectious disease is well described by only two states. More generally, after exposure to micro parasitic infection, individuals who recover from a disease will enter a third state where they are immune to subsequent infection. This Recovered State, R, appears in the SIR(S) compartment models.

For infections that confer lifelong immunity in the recovered state, an SIR model is appropriate. Typical examples for which an SIR model is used include measles and mumps. In cases

involving seasonal flu, immunity is not lifelong and may decrease over time. Immunity loss can reflect a decrease in an individual's immune response, or a genetic drift in the circulating strain of virus that diminishes the effectiveness of the acquired immunity. In either case, an SIRS model represents the rate at which people in a Recovered state return to a susceptible state at a rate α, the immunity loss rate. The equations that define an SIR or SIRS model are shown in equations (2.09).

$$\Delta S = -\beta(\frac{s}{p})I + \alpha R + \mu(P - S)$$

$$\Delta I = \beta(\frac{s}{p})I - \gamma I - \mu I \qquad (2.09)$$

$$\Delta R = \gamma I - \alpha R - \mu R$$

In an SIR(S) model, the disease parameters include the total population, the transmission rate, the recovery rate, and the initial number of infectious people. It also includes the initial Recovered population, the number of people who are initially immune. Assume this number is initially set to zero and, as before, the birth rate and death rates are also taken to be zero. Below these constants, the number of people in each of the states, S, I, and R is a function of time. At t=1 (day), the population in S is simply the total population – the number initially infectious. The new incidence is calculated from these two numbers, using Equation 2. From this term and the other terms in Equation 2, the number of people in the S, I, and R states is computed at each successive time step. Assume, for example, that the immunity loss rate is set near zero (α = 0.01). Since initially almost the entire population is susceptible, an epidemic wave results. Over long periods of time, the model still goes to a fixed point with a very low level of endemic infection. However, if the immunity loss rate had been set to zero (lifelong immunity), the infectious disease would have gone extinct since this is a closed compartment model.

The Recovered State, R, in an SIR(S) model is sometimes called the Removed state. This alternate name is appropriate as recovered individuals are immune in the model and therefore "removed" from the interaction term that leads to new incidence of infectious individuals (Equation 1a). If the immunity loss rate is non-zero, then Removed individuals become susceptible at a rate α. If we include a mortality rate m in each compartment, for an SIR(S) model, the basic Reproductive Number**,** R_o**,** is given by:

$$R_o = \frac{\beta}{\gamma + \mu} \qquad (2.010)$$

(Kermack and McKendrick , 1932).

2.5.3 SEIR(S) Models

Many infectious diseases are also characterized by an incubation period between exposure to the pathogen and the development of clinical symptoms. If the exposed individual is not infectious during this incubation period (e.g., not shedding virus), it is important to model the incubation time explicitly. Note that there is a difference between an incubation time and a period of latency. A virus may or may not be dormant when an individual is in an exposed state. It is important to model the Exposed (E) state explicitly when there is a delay between the time at which an individual is infected and the time at which that individual becomes infectious. In this case an SEIR(S) model is appropriate. Smallpox, for example, has an incubation period of 7-14 days.

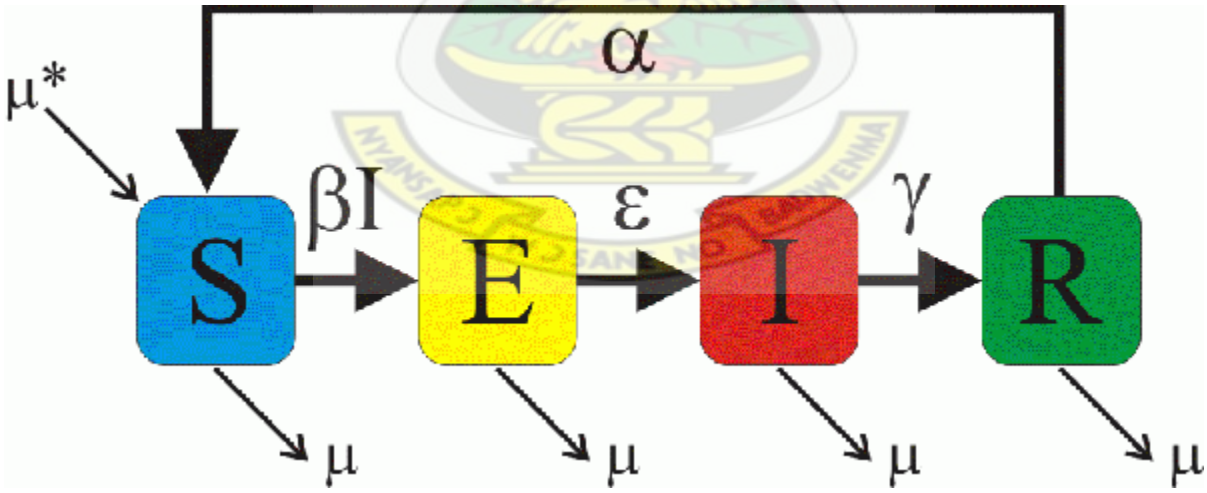

Figure 2.1: An SEIR(S) compartment model.

The rate parameters are the same as for an SIR(S) model with the addition of an incubation rate e which reflects the time between exposure (infection) and becoming infectious.

The Exposed State

As shown in Figure 2.1, the SEIR model has four compartments or states, and therefore four equations are required to parameterize it. The infectious process is the same as for SI and SIR except that infected individuals first enter the exposed state where they begin an incubation time. Equation (2.07) then becomes:

$$\Delta E \; \alpha \; \beta(\frac{S}{P})I \tag{2.011}$$

Exposed individual transition from the E state to the I state at a rate ε, which reflects the incubation rate of the disease.

SEIR(S) Rate Equations

The rate equations for the SEIR model are shown in equations (2.07) below:

$$\Delta S = -\beta(\frac{S}{P})I + \alpha R + \mu(P - S)$$

$$\Delta E = \beta(\frac{S}{P})I - \varepsilon E - \mu E \tag{2.012}$$

$$\Delta I = \varepsilon E - \gamma I - \mu I$$

$$\Delta R = \gamma I - \alpha R - \mu R$$

The four states defined by the SEIR model by no means reflect the totality of compartmental models in epidemiology. In many cases, the population itself is segmented. The reproductive rate of a disease, the incubation rate, recovery rate, and mortality can all vary based on socio-economic factors, gender, age, and infrastructure (health care, sanitation, water quality). For many studies, the population itself is divided based on these or other factors that affect the

transition rates from one state (compartment) to the next. For instance, studies involving finite birth and death rates may account for the maternal immunity conferred on new born infants; this transient immune state can be added to any of the models describe above. Models of sexually transmitted diseases (STDs) distinguish between males and females, partitioning an SI model into the states Sm, Sf, Im, If. Even more complex models include multi-serotype models for Flaviviridae viruses such as Dengue Fever. In Dengue Fever, previous infection by one strain of Dengue Fever can lead to more severe infection (and a greater viral load) in newly infected individuals. Multi-serotype models have been developed that account for historical infection in populations where several serotypes of the virus are circulating (Porter, 1978).

2.5.4 The SEIS Model

The SEIS model takes into consideration the exposed or latent period of the disease, giving an additional compartment, E(t).

$$S \rightarrow E \rightarrow I \rightarrow S$$

In this model an infection does not leave a long lasting immunity thus individuals that have recovered return to being susceptible again, moving back into the S(t) compartment. The following differential equations describe this model:

$$\frac{dS}{dT} = B - \beta SI - \mu S + \gamma I$$

$$\frac{dE}{dT} = \beta SI - (\varepsilon + \mu)E \qquad (2.013)$$

$$\frac{dI}{dT} = \varepsilon E - (\gamma + \mu)I$$

2.6 Linear and Nonlinear Models

Another important concept in modeling is linearity. A linear model uses parameters that are constant and do not vary throughout a simulation. This means that we can enter one fixed value for the parameter at the beginning of the simulation and it will remain the same throughout.

A non-linear model introduces dependent parameters that are allowed to vary throughout the course of a simulation run, and its use becomes necessary where interdependencies between parameters cannot be considered insignificant. The choice between using a linear and a non-linear model is dependent upon how significantly the values of any of the parameters involved vary in relation to any of the other parameters.

In a linear model, all the parameters are independent of any of the others. In a real device, however, parameters are always dependent upon other parameters to some degree, but in many cases if the dependency is so small it can be ignored. For example, the density of any solid material is dependent upon its temperature, but the variation is generally so small over normal temperature ranges that it can be ignored, and the material density is usually modeled as a linear, constant parameter. Where possible, it is always best to use a linear model, as it is simpler and faster running than a non-linear model (Blanchard *et al.* 2002).

To model a non-linear parameter, we must update the simulation material parameters at each iteration step of the simulation. Although modeling parameters as non-linear in a simulation gives a more accurate representation, it increases simulation run time significantly.

2.7 Equilibrium States

Equilibrium is a state of a system which does not change. If the dynamics of a system is described by a differential equation (or a system of differential equations), then equilibriums can be estimated by setting a derivative (all derivatives) to zero.

Equilibrium may be stable or unstable. Equilibrium is considered stable if the system always returns to it after small disturbances. If the system moves away from the equilibrium after small disturbances, then the equilibrium is unstable.

The notion of stability can be applied to other types of attractors (limit cycle, chaos), however, the general definition is more complex than for equilibriums. Stability is probably the most important notion in science because it refers to what we call "reality". Everything should be stable to be observable. For example, in quantum mechanics, energy levels are those that are stable because unstable levels cannot be observed.

In this study, our equilibrium states will be a analyzed using the Routh-hurwitz stability criterion.

2.8 Routh-Hurwitz stability criterion

Routh-hurwitz stability criterion is a method that can be used to establish the stability of a system without solving its characteristic equation.
(Hurwitz, 1964).

Consider the characteristic equation

$$a_0\lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \ldots + a_{n-1}\lambda + a_n = 0 \qquad (2.014)$$

describing the dynamic system. Note that the necessary condition for the stability is satisfied if all the coefficients ai > 0. Therefore, we assume that the coefficient a0 > 0. We write the so-called Hurwitz matrix. It is composed as follows. The main diagonal of the matrix contains elements a_1, a_2, ..., a_n. The first column contains numbers with odd indices a_1, a_3, a_5, ... In each row, the index of each following number (counting from left to right) is 1 less than the index of its predecessor. All other coefficients a_i with indices greater than n or less than 0 are replaced by zeros. The result is a matrix shown below:

$$\begin{bmatrix} a_1 & a_0 & 0 & 0 & 0 & 0 & \vdots & 0 \\ a_3 & a_2 & a_1 & a_0 & 0 & 0 & \vdots & 0 \\ a_5 & a_4 & a_3 & a_2 & a_1 & a_0 & \vdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \vdots & \cdots \\ 0 & 0 & 0 & 0 & 0 & 0 & \vdots & a_n \end{bmatrix} \qquad (2.015)$$

The principal diagonal minors Δ_i of the Hurwitz matrix are given by the formulas

$$\Delta_1 = a_1, \quad \Delta_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix}, \Delta_3 = \begin{vmatrix} a_1 & a_0 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{vmatrix}, \Delta_n = \begin{vmatrix} a_1 & a_0 & 0 & \vdots & 0 \\ a_3 & a_2 & a_1 & \vdots & 0 \\ a_5 & a_4 & a_3 & \vdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & 0 & \vdots & a_n \end{vmatrix}$$

We now formulate the Routh-Hurwitz stability criterion : The roots of the characteristic equation have negative real parts if and only if all the principal diagonal minors of the Hurwitz matrix are positive provided that $a_0 > 0$: $\Delta_1 > 0, \Delta_2 > 0, ..., \Delta_n > 0$. Since $\Delta_n = a_n \Delta_{n-1}$, the last inequality can be written as $a_n > 0$.

For the most common systems of the 2nd, 3rd and 4th order, we obtain the following stability criteria:

<u>For a second order system</u>, the condition of the stability is given by

$$a_0 > 0, \quad \Delta_1 = a_1 > 0, \quad \Delta_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix} = a_1 a_2 > 0$$

Or

$$a_0 > 0, \quad a_1 > 0, \quad a_2 > 0,$$

that is, all coefficients of the quadratic characteristic equation must be positive. In other words, for a system of 2nd order, the necessary condition of the stability is also the sufficient one. We emphasize that we consider here the asymptotic stability of the zero solution.

For a 3rd order system, the stability criterion is defined by the inequalities

$$a_0 > 0, \quad \Delta_1 = a_1 > 0, \quad \Delta_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix} = a_1 a_2 - a_0 a_3 > 0, \quad \Delta_3 = a_3 > 0$$

Or

$$a_0 > 0, \quad a_1 > 0, \quad a_2 > 0, \quad a_3 > 0, \quad a_1 a_2 - a_0 a_3 > 0.$$

Similarly, for a 4th order system, we obtain the following set of inequalities:

$$a_0 > 0, \quad \Delta_1 = a_1 > 0, \quad \Delta_2 = \begin{vmatrix} a_1 & a_0 \\ a_3 & a_2 \end{vmatrix} = a_1 a_2 - a_0 a_3 > 0,$$

$$\Delta_3 = \begin{vmatrix} a_1 & a_0 & 0 \\ a_3 & a_2 & a_1 \\ 0 & a_4 & a_3 \end{vmatrix} = a_1 a_2 a_3 - a_1^2 a_4 - a_0 a_3^2 > 0 \qquad (2.016)$$

or

$$a_i > 0 \ (i = 0,..., 4), \quad a_1 a_2 - a_0 a_3 > 0, \quad a_1 a_2 a_3 - a_1^2 a_4 - a_0 a_3^2 > 0.$$

If all the n − 1 principal minors of the Hurwitz matrix are positive and the *n*th order minor is zero: $\Delta_n = 0$, the system is at the boundary of stability. Since , then there are two options: The coefficient (s, e, i) to (s^*, e^*, i^*). = 0. This corresponds to the case when one of the roots of the characteristic equation is zero. The system is on the boundary of a periodic stability.

The determinant $\Delta_{n-1} = 0$. In this case, there are two complex conjugate imaginary roots. The

system is on the boundary of the oscillatory stability. The Routh-Hurwitz stability criterion belongs to the family of algebraic criteria. It can be conveniently used to analyze the stability of low order systems. The computational complexity grows significantly with the increase of the order. In such cases, it may be preferable to use other criteria such as the Lienard-Shipart theorem or the Nyquist frequency criterion (Routh, 1877).

2.9 Uncertainty and Sensitivity analysis in modeling

Uncertainty in model predictions can arise from many sources including

- Conceptualization of disease, either the disease is too complex or too simple.
- Inaccuracies/ uncertainty in input data
- Use of inappropriate data/ inappropriate interpretation of data
- User error

Impact of the uncertainty from some of these sources can be quantitatively assessed through sensitivity analysis which involves specifying a potential range over which the parameter is thought to vary.

Sensitivity analysis methods can either be deterministic or stochastic (Drummond,2005).

. Main types of sensitivity analysis used:

(1) One way sensitivity analysis

(2) Multi way sensitivity analysis

(3) Scenario analysis

(4) Threshold analysis

(5) Probabilistic sensitivity analysis

(Oxlade, 2011).

One way sensitivity analysis

Estimates for each parameter are varied one at a time to investigate the impact on study results.

Multi way sensitivity analysis

This recognizes that more than one parameter is uncertain and that each could vary within its specified range. Better approach, but with many parameters there can be an infinite number of combinations to consider

Scenario analysis

A series of scenarios are constructed representing a subset of the potential multi-way analysis.

Threshold analysis

Critical values of a parameter central to decision are identified. Aanalyst determines threshold and then assess which combination of parameters cause the threshold to be exceeded. All of these approaches are deterministic.

Probabilistic sensitivity analysis (PSA):

Probabilistic sensitivity analysis is often called Monte Carlo simulation and incorporates stochastic element into analysis.

PSA is important when you do not want an "average" result. It provides a sense of uncertainty in predictions and requires defining ranges/distributions for parameters.

Can run the model repeatedly (1000's of times) and each time it will select input parameter values from set distributions can build up a distribution of outcomes and see range/uncertainty.

2.9.1 Limitations of Sensitivity Analysis

- Variation of uncertain parameters one at a time ignores possible interaction between parameters.
- The analyst has discretion as to which variables and what alternative values are included in sensitivity analysis.
- Interpretation is arbitrary as there are no guidelines/standards as to what degree of variation in results is acceptable evidence that the analysis is robust (Oxlade,2011).

CHAPTER 3

THE MODEL

3.1 Introduction

Tuberculosis models are either deterministic or stochastic. The models operate by defining states for individuals within a population essentially assigning individuals to subpopulation groups based on characteristics such as 'infected with,' or 'immune to,' tuberculosis.

Deterministic models have a finite number of states, and specify rules by which individuals move from one state to another through a series of differential equations.

In this chapter, we are going to formulate our SEIS model based on the deterministic approach and develop expressions for the equilibrium points. Expressions which will be used to test for the stability of these steady states will also be developed, as well as the formula that will be used to calculate for the basic reproductive number.

3.2 Preliminaries

Differential equations have been developed as mathematical models to study the dynamics of disease transmission for many communicable diseases.

When a community identifies people infected with tuberculosis, new individuals get infected by coming in contact with members of the infected population. In epidemics, it is of high interest to know how the disease will spread. Thus, what we really want to know in many cases is how many infected individuals there will be in the next period. In this chapter, a mathematical model will be developed to study the epidemiology of tuberculosis in the central region of Ghana. The specific model to be developed is the Susceptible-Exposed-Infected-Susceptible (SEIS) model.

3.3 Model formulation

3.3.1 Model Assumptions

1. An individual can be infected only by contacting infectious individuals.
2. The death rate is assumed to be the same constant μ for all hosts, and the total deaths is balanced by total recruitment, hence the population is constant.
3. Age, sex social status, and race do not affect the probability of being infected.
4. Individuals of the population have the same interactions with one another to the same degree.
5. It is assumed that, after the initial infection, a host stays in a latent period for some time and either recovers and gets back into the susceptible class or become infectious.
6. An infectious host may die from disease or recover with no acquired immunity to the disease and again become susceptible.
7. We assume that latently infected individuals are not infectious, that is they are not capable of transmitting bacteria.

3.3.2 Description of SEIS Model

The SEIS model is made up of a host population which is grouped into three classes: the susceptible, the exposed (latent/incubation), and infectious, with sizes denoted by S,E,and I respectively. The host total population, N=S+E+I. The dynamical transfer of hosts is described in the following figure;

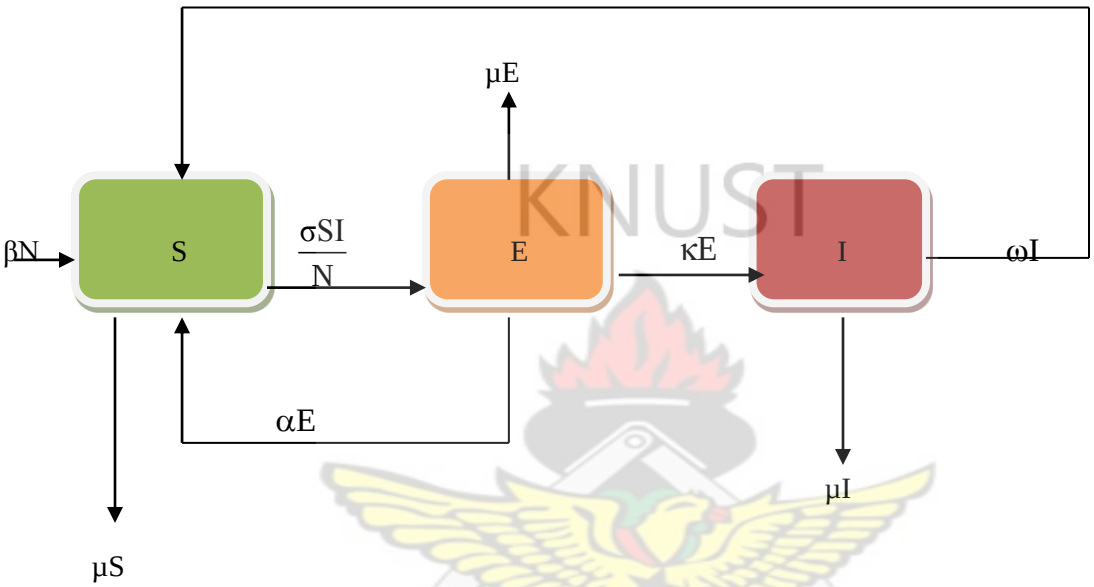

Figure 3.1: Flow chart of SEIS model

Where

β is the constant recruitment rate

σ is the transmission rate

μ is the death rate

κ is the rate at which an individual leaves the latent class by becoming infectious

α is the treatment rate of latent individuals

ω is the treatment rate of infectious individuals

S is the number of susceptible individuals

E is the number of exposed individuals

I is the number of infectious individuals

N is the total population size

The inflow of susceptible comes from three sources, a constant recruitment β, recovered individuals from latency αE, and recovered individuals from the infectious class ωI. The parameters κ, α, and ω denote the transfer rates among the corresponding classes.

3.3.3 Model equations

The population is divided into three classes based on epidemiological status. Individuals are classified as either susceptible, latently infected (exposed), or infectious.

The sizes of these groups are represented by S, E and I, respectively.

In each time unit, a susceptible individual has an average σI contacts that would be sufficient to transmit the disease. Thus, the expression that shows how susceptible individuals are infected is represented as $\frac{\sigma SI}{N}$.

Individuals who die naturally from the susceptible class is expressed as μS and

individuals who recover from the latent class and get back into the susceptible class is also expressed as αE.

Those that recover from the infectious class is expressed as ωI.

The above statements can be put together to form one equation showing the rate of change of the susceptible class. Thus,

$$\frac{dS}{dt} = \beta N - \frac{\sigma SI}{N} - \mu S + \alpha E + \omega I \qquad (3.01)$$

The inflow of the latent class comes from a single source, being those members that move from the susceptible class and this is represented by $\frac{\sigma SI}{N}$.

The population of exposed individuals reduces as a result of the following three factors;

- Death
- Recovery rate of exposed individuals into the susceptible class
- Progression of exposed individuals into the infectious class

The rate of change of the latent class is equal to the difference between exposed members that moved from the susceptible into the latent class and the rate at which exposed individuals die naturally, recover into the susceptible class and also move into the infectious class.

Thus,

$$\frac{dE}{dt} = \frac{\sigma SI}{N} - (\mu + \kappa + \alpha)E \qquad (3.02)$$

From the above equation the number of people leaving the exposed class for the infectious class is denoted by κE. Some of the infectious individuals die naturally while some also die due to the disease, the total death is denoted by μI. Finally some recover and move back into the susceptible class which is denoted by ωI.

From what has just been discussed above, the rate of change of the infected class can be put into an equation form as below,

$$\frac{dI}{dt} = \kappa E - (\mu + \omega)I \qquad (3.03)$$

Putting these equations together, we obtain the following system of differential equations

$$\frac{dS}{dt} = \beta N - \frac{\sigma SI}{N} - \mu S + \alpha E + \omega I \tag{3.01}$$

$$\frac{dE}{dt} = \frac{\sigma SI}{N} - (\mu + \kappa + \alpha)E \tag{3.02}$$

$$\frac{dI}{dt} = \kappa E - (\mu + \omega)I \tag{3.03}$$

which, together yields

$$N = S + E + I \tag{3.04}$$

We scale the above equations by letting

$s = \frac{S}{N}$, $e = \frac{E}{N}$, and $i = \frac{I}{N}$ where s, e and i are the susceptible, exposed and infected proportions of the population respectively. The scaled equations are shown below:

$$\frac{ds}{dt} = \beta - \sigma si - \mu s + \alpha e + \omega i \tag{3.05}$$

$$\frac{de}{dt} = \sigma si - (\mu + \kappa + \alpha)e \tag{3.06}$$

$$\frac{di}{dt} = \kappa e - (\mu + \omega)i \tag{3.07}$$

3.5 Equilibrium Points

Under this, two equilibrium states will be considered, the disease- free equilibrium (where i = 0) and the endemic equilibrium (where $i \neq 0$). We set the right hand side of equations (3.05),(3.06) and (3.07) to zero and solve for the values of s, e and i. That is,

$$\beta - \sigma si - \mu s + \alpha e + \omega i = 0 \quad (3.08)$$

$$\sigma si - (\mu + \kappa + \alpha)e = 0 \quad (3.09)$$

$$\kappa e - (\mu + \omega)i = 0 \quad (3.010)$$

3.5.1 Disease-free Equilibrium Point

At disease-free equilibrium, it is assumed that there is no disease in the system, therefore substituting $i = 0$, into the above equations will yield

$$\beta - \sigma s(0) - \mu s + \alpha(0) + \omega i(0) = 0$$
$$\sigma s(0) - (\mu + \kappa + \alpha)(0) = 0$$
$$\kappa(0) - (\mu + \omega)(0) = 0$$

which reduces to

$$\beta - \mu s = 0$$

$$\Rightarrow \quad s = \frac{\beta}{\mu}$$

So from the evaluations at disease disease-free equilibrium, $(s, e, i) = (\frac{\beta}{\mu}, 0, 0) = (1, 0, 0)$.

3.5.2 Endemic Equilibrium

Endemic equilibrium state indicates that the disease persists in the system.

Here, we will be solving three systems of equations to obtain the values of s, e, and i. However, the endemic equilibrium point will be differentiated from the disease-free equilibrium point by changing (s, e, i) to (s^*, e^*, i^*).

$$\beta - \sigma si - \mu s + \alpha e + \omega i = 0 \tag{3.08}$$

$$\sigma si - (\mu + \kappa + \alpha)e = 0 \tag{3.09}$$

$$\kappa e - (\mu + \omega)i = 0 \tag{3.010}$$

From equation (3.010),

$$i = \frac{\kappa}{(\mu + \omega)}e \tag{3.011}$$

Also from equation (3.09),

$$s = \frac{(\mu+\kappa+\alpha)e}{\sigma i} \tag{3.012}$$

Substituting equation (3.011) into equation (3.012) will give us

$$s = \frac{(\mu + \kappa + \alpha)e}{\sigma} \times \frac{(\mu + \omega)}{\kappa e}$$

$$S^* = \frac{(\mu + \kappa + \alpha)(\mu + \omega)}{\sigma\kappa} \tag{3.013}$$

From equation (3.09), $\sigma si = (\mu + \kappa + \alpha)e$,

substituting the above expression into equation (3.08) will yield

$$\beta - (\mu + \kappa + \alpha)e - \mu s + \alpha e + \omega i = 0$$

Also, from equation (3.011), $i = \frac{\kappa}{(\mu + \omega)}e$, putting this also into the above equation will give us

$$\beta - (\mu + \kappa + \alpha)e - \mu s + \alpha e + \omega\frac{\kappa}{(\mu + \omega)}e$$

We make the above equation linear by multiplying through by $(\mu+\omega)$, thus,

$$\beta(\mu+\alpha)-(\mu+\alpha)(\mu+\kappa+\alpha)e\ -\ \mu s(\mu+\alpha)+\ \alpha e(\mu+\alpha)+\frac{\omega\kappa}{(\mu+\omega)}e(\mu+\alpha)=0$$

Implying that

$$\beta(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)e\ -\mu s(\mu+\omega)+\ \alpha e(\mu+\omega)+\ \omega\kappa e=0$$

From here, we group like terms,

$$\alpha e(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)e\ +\ \omega\kappa e=\ \mu s(\mu+\omega)-\beta(\mu+\omega)$$

factorizing e out gives us

$$e[\alpha(\mu+\omega)-\ (\mu+\omega)(\mu+\kappa+\alpha)\ +\ \omega\kappa]=\ \mu s(\mu+\omega)-\beta(\mu+\omega)$$

But $s=\frac{(\mu+\kappa+\alpha)(\mu+\omega)}{\sigma\kappa}$, therefore, the equation becomes

$$e[\alpha(\mu+\omega)-\ (\mu+\omega)(\mu+\kappa+\alpha)\ +\ \omega\kappa]=\ \mu\frac{(\mu+\kappa+\alpha)(\mu+\omega)(\mu+\omega)}{\sigma\kappa}-\beta(\mu+\omega)$$

We multiply through by $\sigma\kappa$ to make the equation linear,

$$e\sigma\kappa[\alpha(\mu+\omega)-\ (\mu+\omega)(\mu+\kappa+\alpha)\ +\ \omega\kappa]=\ \mu\frac{(\mu+\kappa+\alpha)(\mu+\omega)(\mu+\omega)\sigma\kappa}{\sigma\kappa}-\beta(\mu+\omega)\sigma\kappa$$

Now we divide through by $\sigma\kappa\ [\alpha\ (\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)\ +\ \omega\kappa]$ to get

$$e^*=\frac{\mu(\mu+\kappa+\alpha)(\mu+\omega)^2-\beta(\mu+\omega)\sigma\kappa}{\sigma\kappa[\alpha(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)+\omega\kappa]} \qquad (3.014)$$

Since we now have an expression for e*, it can be substituted into equation 3.011as shown below

$$i = \frac{\kappa}{(\mu+\omega)} e = \frac{\kappa}{(\mu+\omega)} \times \frac{\mu(\mu+\kappa+\alpha)(\mu+\omega)^2 - \beta(\mu+\omega)\sigma\kappa}{\sigma\kappa[\alpha(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)+\omega\kappa]}$$

$(\mu+\omega)$ and κ will cancel out to produce

$$i^* = \frac{\mu(\mu+\kappa+\alpha)(\mu+\omega)-\beta\sigma\kappa}{\sigma[\alpha(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)+\omega\kappa]} \quad (3.015)$$

At the endemic state, the equilibrium point will be

$$(s^*, e^*, i^*) = (\frac{(\mu+\kappa+\alpha)(\mu+\omega)}{\sigma\kappa}, \frac{\mu(\mu+\kappa+\alpha)(\mu+\omega)^2-\beta(\mu+\omega)\sigma\kappa}{\sigma\kappa[\alpha(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)+\omega\kappa]}, \frac{\mu(\mu+\kappa+\alpha)(\mu+\omega)-\beta\sigma\kappa}{\sigma[\alpha(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)+\omega\kappa]})$$

3.6 Stability Analysis of the Equilibrium Points

For the stability analysis of the disease-free and the endemic equilibrium points, we will find the Jacobian matrix of equations (3.05), (3.06) and (3.07). Equilibrium points at disease-free equilibrium and endemic equilibrium will then be substituted into the Jacobian matrix. After this we will solve the matrix equations to obtain an expression for the characteristic equations which will be used in the stability analysis.

Equations (3.05), (3.06) and (3.07) are shown below

$$\frac{ds}{dt} = \beta - \sigma si - \mu s + \alpha e + \omega i \quad (3.05)$$

$$\frac{de}{dt} = \sigma si - (\mu+\kappa+\alpha)e \quad (3.06)$$

$$\frac{di}{dt} = \kappa e - (\mu+\omega)i \quad (3.07)$$

Finding the jacobian matrix of the above equations becomes

$$J(s,e,i)=\begin{bmatrix} \frac{\partial}{\partial s}(\beta-\sigma si-\mu s+\alpha e+\omega i) & \frac{\partial}{\partial e}(\beta-\sigma si-\mu s+\alpha e+\omega i) & \frac{\partial}{\partial i}[\beta-\sigma si-\mu s+\alpha e+\omega i] \\ \frac{\partial}{\partial s}[\sigma si-(\mu+\kappa+\alpha)e] & \frac{\partial}{\partial e}[\sigma si-(\mu+\kappa+\alpha)e] & \frac{\partial}{\partial i}[\sigma si-(\mu+\kappa+\alpha)e] \\ \frac{\partial}{\partial s}[\kappa e-(\mu+\omega)i] & \frac{\partial}{\partial e}[\kappa e-(\mu+\omega)i] & \frac{\partial}{\partial i}[\kappa e-(\mu+\omega)i] \end{bmatrix}$$

$$J(s,e,i)=\begin{bmatrix} -\sigma i-\mu & \alpha & -\sigma s+\omega \\ \sigma i & -(\mu+\kappa+\alpha) & \sigma s \\ 0 & \kappa & -(\mu+\omega) \end{bmatrix}$$

3.6.1 Stability Analysis of the Disease-free Equilibrium

At disease-free equilibrium, $i = 0,\ e = 0$ and $s = \beta/\mu$.

Substituting these values into the jacobian matrix above will produce

$$J\left(\frac{\beta}{\mu},0,0\right) = J_{DFE}=\begin{bmatrix} -\mu & \alpha & -\sigma\frac{\beta}{\mu}+\omega \\ 0 & -(\mu+\kappa+\alpha) & \sigma\frac{\beta}{\mu} \\ 0 & \kappa & -(\mu+\omega) \end{bmatrix}$$

Where J_{DFE} represents Jacobian matrix at disease-free equilibrium

From here, we begin solving the matrix equation.

$J_{DFE} - I\lambda$

$$I\lambda=\lambda\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}=\begin{bmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{bmatrix}$$

Therefore, $J_{DFE} - I\lambda$ implies that

$$\begin{bmatrix} -\mu & \alpha & -\sigma\frac{\beta}{\mu}+\omega \\ 0 & -(\mu+\kappa+\alpha) & \sigma\frac{\beta}{\mu} \\ 0 & \kappa & -(\mu+\omega) \end{bmatrix} - \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{bmatrix} = 0$$

$$J_{DFE} - I\lambda = \begin{bmatrix} -\mu-\lambda & \alpha & -\sigma\frac{\beta}{\mu}+\omega \\ 0 & -(\mu+\kappa+\alpha)-\lambda & \sigma\frac{\beta}{\mu} \\ 0 & \kappa & -(\mu+\omega)-\lambda \end{bmatrix}$$

Finding the characteristic equation, determinant of $J_{DFE} - I\lambda$ is set to zero.

$$\text{Thus, } \det(J_{DFE} - I\lambda) = \begin{bmatrix} -\mu-\lambda & \alpha & -\sigma\frac{\beta}{\mu}+\omega \\ 0 & -(\mu+\kappa+\alpha)-\lambda & \sigma\frac{\beta}{\mu} \\ 0 & \kappa & -(\mu+\omega)-\lambda \end{bmatrix} = 0$$

To find the determinant of the above matrix, we reduce it to three 2×2 matrices and find their determinants.

$$(-\mu-\lambda)\begin{vmatrix} -(\mu+\kappa+\alpha)-\lambda & \sigma\frac{\beta}{\mu} \\ \kappa & -(\mu+\omega)-\lambda \end{vmatrix} - \alpha\begin{vmatrix} 0 & \sigma\frac{\beta}{\mu} \\ 0 & -(\mu+\omega)-\lambda \end{vmatrix} + (-\sigma\frac{\beta}{\mu}+\omega)\begin{vmatrix} 0 & -(\mu+\kappa+\alpha)-\lambda \\ 0 & \kappa \end{vmatrix} = 0$$

$$\Rightarrow (-\mu-\lambda)\{[-(\mu+k+\alpha)-\lambda][-(\mu+d+\omega)-\lambda] - \sigma k\frac{\beta}{\mu}\} - 0 + 0 = 0$$

Expanding will give us

$$(-\mu-\lambda)\{[(\mu+\kappa+\alpha)(\mu+\omega)+\lambda(\mu+\kappa+\alpha)+\lambda(\mu+\omega)+\lambda^2]-\sigma\kappa\frac{\beta}{\mu}\}=$$

$$-\mu[(\mu+\kappa+\alpha)(\mu+\omega)+\lambda(\mu+\kappa+\alpha)+\lambda(\mu+\omega)+\lambda^2-\sigma\kappa\frac{\beta}{\mu}]-\lambda[(\mu+\kappa+\alpha)(\mu+\omega)+\lambda(\mu+\kappa+\alpha)$$

$$+\lambda(\mu+\omega)+\lambda^2-\sigma\kappa\frac{\beta}{\mu}]$$

Rearranging yields

$$-\lambda^3-\lambda^2(\mu+\kappa+\alpha)-\lambda^2(\mu+\omega)\text{-}\mu\lambda^2\text{-}\mu\lambda(\mu+\kappa+\alpha)\text{-}\mu\lambda(\mu+\omega)$$

$$-\lambda(\mu+\kappa+\alpha)(\mu+\omega)+\lambda\sigma\kappa\frac{\beta}{\mu}-\mu(\mu+\kappa+\alpha)(\mu+\omega)+\mu\sigma\kappa\frac{\beta}{\mu}=0$$

We then factorize to get

$$-\lambda^3-[(\mu+\kappa+\alpha)+(\mu+\omega)+\mu]\lambda^2\text{-}[\mu(\mu+\kappa+\alpha)+\mu(\mu+\omega)+(\mu+\kappa+\alpha)(\mu+\omega)\text{-}\sigma\kappa\frac{\beta}{\mu}]\lambda$$

$$-[\mu(\mu+\kappa+\alpha)(\mu+\omega)-\mu\sigma\kappa\frac{\beta}{\mu}]=0$$

We multiply through by -1 to get

$$\lambda^3+[(\mu+\kappa+\alpha)+(\mu+\omega)+\mu]\lambda^2+[\mu(\mu+\kappa+\alpha)+\mu(\mu+\omega)+(\mu+\kappa+\alpha)(\mu+\omega)\text{-}\sigma\kappa\frac{\beta}{\mu}]\lambda$$

$$+[\mu(\mu+\kappa+\alpha)(\mu+\omega)-\mu\sigma\kappa\frac{\beta}{\mu}]=0$$

This is a cubic equation and to solve it, we let the coefficients of λ^3, λ^2 and λ be m, p, and q.

That is,

$$m=[(\mu+\kappa+\alpha)+(\mu+\omega)+\mu]$$

$$p=[\mu(\mu+\kappa+\alpha)+\mu(\mu+\omega)+(\mu+\kappa+\alpha)(\mu+\omega)-\sigma\kappa\frac{\beta}{\mu}]$$

$$q = [\mu(\mu+\kappa+\alpha)(\mu+\omega) - \mu\sigma\kappa\frac{\beta}{\mu}]$$

The characteristic equation becomes

$$a\lambda^3 + m\lambda^2 + p\lambda + q = 0 \qquad (3.016)$$

Using Routh-Hurwitz stability criterion, if $m > 0$, $q>0$ and $mp>q$, then the system has negative roots and the roots are all stable, otherwise the roots are unstable.

3.6.2 Stability Analysis of the Endemic Equilibrium

For the stability analysis of the endemic equilibrium point, we will make use of the Jacobian matrix of the model equations

$$\beta - \sigma si - \mu s + \alpha e + \omega i = 0 \qquad (3.08)$$

$$\sigma si - (\mu+\kappa+\alpha)e = 0 \qquad (3.09)$$

$$\kappa e - (\mu+\omega)i = 0 \qquad (3.010)$$

The Jacobian matrix of the above equations is shown below,

$$J(s,e,i) = \lambda^3 + 0.515\lambda^2 + 0.026\lambda - 0.034 = 0$$

In section 3.5.2 ,we proved that, at endemic equilibrium,

$$s^* = \frac{(\mu+\kappa+\alpha)(\mu+\omega)}{\sigma\kappa}$$

$$e^* = \frac{\mu(\mu+\kappa+\alpha)(\mu+\omega)^2 - \beta(\mu+\omega)\sigma\kappa}{\sigma\kappa[\alpha(\mu+\omega) - (\mu+\omega)(\mu+\kappa+\alpha) + \omega\kappa]}$$

$$i^* = \frac{\mu(\mu+\kappa+\alpha)(\mu+\omega) - \beta\sigma\kappa}{\sigma[\alpha(\mu+\omega) - (\mu+\omega)(\mu+\kappa+\alpha) + \omega\kappa]}$$

For simplicity sake, s*, e* and i* will be maintained in the Jacobian matrix to solve for the quadratic equation before their actual values will be substituted.

Thus,

$$J(s^*, e^*, i^*) = J_{EE} = \begin{bmatrix} -\sigma i^* - \mu & \alpha & -\sigma s^* + \omega \\ \sigma i^* & -(\mu + \kappa + \alpha) & \sigma s^* \\ 0 & \kappa & -(\mu + \omega) \end{bmatrix}$$

Now, we find the characteristic equation of the Jacobian matrix

$$J_{EE} - \lambda I = = J_{EE} - \lambda \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} = J_{EE} - \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{bmatrix}$$

$$\Rightarrow \begin{bmatrix} -\sigma i^* - \mu & \alpha & -\sigma s^* + \omega \\ \sigma i^* & -(\mu + \kappa + \alpha) & \sigma s^* \\ 0 & \kappa & -(\mu + \omega) \end{bmatrix} - \begin{bmatrix} \lambda & 0 & 0 \\ 0 & \lambda & 0 \\ 0 & 0 & \lambda \end{bmatrix} = 0$$

$$\begin{bmatrix} (-\sigma i^* - \mu) - \lambda & \alpha & -\sigma s^* + \omega \\ \sigma i^* & -(\mu + \kappa + \alpha) - \lambda & \sigma s^* \\ 0 & \kappa & -(\mu + \omega) - \lambda \end{bmatrix} = 0$$

We will break the above matrix into three 2×2 matrices and find their determinants,

$$[(-\sigma i^* - \mu) - \lambda] \begin{vmatrix} -(\mu + \kappa + \alpha) - \lambda & \sigma s^* \\ \kappa & -(\mu + \omega) - \lambda \end{vmatrix} - \alpha \begin{vmatrix} \sigma i^* & \sigma s^* \\ 0 & -(\mu + \omega) - \lambda \end{vmatrix} +$$

$$(-\sigma s^* + \omega) \begin{vmatrix} \sigma i^* & -(\mu + \kappa + \alpha) \\ 0 & \kappa \end{vmatrix} = 0$$

$$\Rightarrow [(-\sigma i^* - \mu) - \lambda]([-(\mu + \kappa + \alpha) - \lambda][-(\mu + \omega) - \lambda) - k\sigma s^*)$$

$$-\alpha(\sigma i^*[-(\mu + \omega) - \lambda] + (-\sigma s^* + \omega)(\kappa\sigma i^*) = 0$$

$$\Rightarrow [(-\sigma i^* - \mu) - \lambda][(\mu + \kappa + \alpha)(\mu + \omega) + (\mu + \kappa + \alpha)\lambda + (\mu + \omega)\lambda + \lambda^2 - \kappa\sigma s^*]$$
$$-\alpha\sigma i^*(\mu + \omega) - \alpha\sigma i^*\lambda + \kappa\sigma i^*(-\sigma s^* + \omega) = 0$$

Expanding the expression will be

$$(-\sigma i^* - \mu)[(\mu + \kappa + \alpha)(\mu + \omega) + (\mu + \kappa + \alpha)\lambda + (\mu + \omega)\lambda + \lambda^2 - \kappa\sigma s^*]$$
$$-\lambda[(\mu + \kappa + \alpha)(\mu + \omega) + (\mu + \kappa + \alpha)\lambda + (\mu + \omega)\lambda + \lambda^2 - \kappa\sigma s^*]$$
$$-\alpha\sigma i^*(\mu + \omega) - \alpha\sigma i^*\lambda + \kappa\sigma i^*(-\sigma s^* + \omega) = 0$$

$$\Rightarrow (-\sigma i^* - \mu)(\mu + \kappa + \alpha)(\mu + \omega) + (\mu + \kappa + \alpha)(-\sigma i^* - \mu)\lambda + (\mu + \omega)(-\sigma i^* - \mu)\lambda$$

$$+(-\sigma i^* - \mu)\lambda^2 - \kappa\sigma s^*(-\sigma i^* - \mu) - (\mu + \kappa + \alpha)(\mu + \omega)\lambda - (\mu + \kappa + \alpha)\lambda^2 - (\mu + \omega)\lambda^2$$

$$-\lambda^3 + \kappa\sigma s^*\lambda - \alpha\sigma i^*(\mu + \omega) - \alpha\sigma i^*\lambda + \kappa\sigma i^*(-\sigma s^* + \omega) = 0$$

Grouping like terms and factorizing λ^2 and λ out will give

$$-\lambda^3 - [(\mu + \kappa + \alpha) + (\mu + \omega) - (-\sigma i^* - \mu)]\lambda^2$$
$$-[-(-\sigma i^* - \mu)(\mu + \kappa + \alpha) + (-\sigma i^* - \mu)(\mu + \omega) + (\mu + \kappa + \alpha)(\mu + \omega) - \kappa\sigma s^* + \alpha\sigma i^*]\lambda$$

$$-[\kappa\sigma s^*(-\sigma i^* - \mu) + \alpha\sigma i^*(\mu + \omega) - (-\sigma i^* - \mu)(\mu + \kappa + \alpha)(\mu + \omega) - \kappa\sigma i^*(-\sigma s^* + \omega)] = 0$$

multiplying through by -1 becomes

$$\lambda^3 + [(\mu + \kappa + \alpha) + (\mu + \omega) - (-\sigma i^* - \mu)]\lambda^2$$

$$+[-(-\sigma i^* - \mu)(\mu + \kappa + \alpha) + (-\sigma i^* - \mu)(\mu + \omega) + (\mu + \kappa + \alpha)(\mu + \omega) - \kappa\sigma s^* + \alpha\sigma i^*]\lambda$$

$$+[\kappa\sigma s^*(-\sigma i^* - \mu) + \alpha\sigma i^*(\mu + \omega) - (-\sigma i^* - \mu)(\mu + \kappa + \alpha)(\mu + \omega) - \kappa\sigma i^*(-\sigma s^* + \omega)] = 0$$

If we let

$$m= (\mu+\kappa+\alpha)+(\mu+\omega)-(-\sigma i^{*}-\mu)$$

$$p=(-\sigma i^{*}-\mu)(\mu+\kappa+\alpha)-(-\sigma i^{*}-\mu)(\mu+\omega)+(\mu+\kappa+\alpha)(\mu+\omega)-\kappa\sigma s^{*}+\alpha\sigma i^{*}$$

$$q= \kappa\sigma s^{*}(-\sigma i^{*}-\mu)+\alpha\sigma i^{*}(\mu+\omega)-(-\sigma i^{*}-\mu)(\mu+\kappa+\alpha)(\mu+\omega)-\kappa\sigma i^{*}(-\sigma s^{*}+\omega),$$

then the expression becomes

$$\lambda^{3}+m\lambda^{2}+p\lambda+q=0 \qquad (3.016)$$

Solving the equation will produce three eigen values (λ_1,λ_2, λ_3).

The equation also has discriminant,

$$\Delta = m^2p^2 - 4p^3 - 4m^3 - 27q^3+18mpq$$

The discriminant has the following characteristics;

If $\Delta=0$, the equation has a multiple root and all its roots are real.

If $\Delta > 0$, then the equation has three distinct real roots.

If $\Delta < 0$, then the equation has one real root and two non real complex conjugate.

3.7 An application of Routh-Hurwitz stability criterion

This stability criterion can also be used to determine whether all roots have negative real parts and establish the stability of the system without solving the characteristic equation itself.

Looking at our developed characteristic equation

$$\lambda^{3}+m\lambda^{2}+p\lambda+q=0,$$

We can apply Routh-Hurwitz stability criterion to test its stability.

According to Routh-hurwitz,

if m>0, q>0 and mp>q, then the system has negative roots and the roots are all stable, otherwise the roots are unstable.

3.8 The Basic Reproduction Number (R_o)

The basic reproductive number, R_o, is defined as the expected number of secondary cases produced by a single infection in a completely susceptible population. The basic reproductive number is dimensionless.

If R_o <1, each individual produces, on average, less than one new infected individual and hence the disease dies out.

If R_o >1, each individual produces more than one new infected individual and hence the disease is able to invade the susceptible population.

This allows us to determine the effectiveness of control measures.

The basic reproductive number, R_o of our model equations is given by the product $\frac{\sigma}{(\mu+\kappa+\alpha)}$, the average number of susceptible infected by one infectious individual during his or her effective infectious period and $\frac{\kappa}{(\mu+\omega)}$, the fraction of the population which survives the latent period(Castillo-Chavez,1997).

$$R_o = \frac{\sigma\kappa}{(\mu+\kappa+\omega)(\mu+\omega)} \qquad (3.017)$$

CHAPTER 4

MODEL APPLICATION

4.1 Introduction

In this chapter, we are going to estimate the parameter values that will be used for the analysis. The values will be substituted into equation (3.017) obtained in chapter three to get the exact value for the basic reproductive number. Besides, parameter values will be substituted into the various equations derived in chapter 3 to get their actual values. Sensitivity analysis will also be carried out on the parameter values to investigate their impact on study results.

The data on tuberculosis for this thesis was obtained from the Central Regional Health Directorate, Cape Coast. This study is based on data on tuberculosis from 2006 to 2010.

4.2 Parameter Estimate

Parameter estimation was based on the data obtained from the Central Regional Health Directorate, and published standard estimates.

$\frac{1}{\text{death rate}}$ = average life expectancy (years) (Gerberry, and Milner, 2012).

According to Gerberry and Milner, the average life expectancy in Ghana is 59.12. Therefore the death rate, μ in Ghana is $\frac{1}{59.12} = 0.017$.

From 2006 to 2010, the number of patients who went for TB test was 7,619 and out of this number of people, 5,766 tested positive while the remaining 1,853 tested negative.

Transmission rate= $\frac{\text{effective contact}}{\text{total contact}}$ (Wikipedia, Transmission risks and rates, 2009)

From the above definition, our transmission rate, $\sigma = \frac{5,766}{7,619} = 0.7568$

Averagely, 10% of latently infected individuals develop active TB (Koo, 2009), hence, the rate at which people leave the latent or exposed class for the infectious class, $\kappa = \frac{10}{100} \times 0.7568 =$ 0.07568

The mean percentage of the exposed class that recovers back into the susceptible group is 60% (Dobler and Marks , 2012).

Averagely, 5 out of every 10 patients recover during the treatment of active TB.

The rate of recovery of the infectious class into the susceptible class, $\omega = 0.07568 \times 0.5 = 0.03784$

From the above illustrations and calculations, the estimated values for the parameters have been summarized in table 4.1.

PARAMETER	DESCRIPTION	VALUE
σ	Transmission rate	0.757
μ	Death rate	0.017
α	Treatment rate of Latent individuals	0.35
ω	Treatment rate of infectious individuals	0.038
κ	The rate at which an individual leaves the latent class by becoming infectious	0.076
β	Constant recruitment rate	0.017

Table 4.1: summary of estimated parameter values

Substituting the above values into the SEIS model equations developed in chapter three, thus, equations (3.05), (3.06) and (3.07), we obtain

$$\frac{ds}{dt} = 0.017 - 0.017s + 0.35e + 0.038i \quad (4.01)$$

$$\frac{de}{dt} = 0.757si - 0.4437e \quad (4.02)$$

$$\frac{di}{dt} = 0.076e - 0.0557i \quad (4.03)$$

4.3 Equilibrium Points

Two equilibrium states were considered.

The equilibrium point was given as (s,e,i) = (1, 0, 0) for the disease free equilibrium.

Also, the endemic equilibrium point,

$$(s^*, e^*, i^*) = \left(\frac{(\mu+\kappa+\alpha)(\mu+\omega)}{\sigma\kappa}, \frac{\mu(\mu+\kappa+\alpha)(\mu+\omega)^2 - \beta(\mu+\omega)\sigma\kappa}{\sigma\kappa[\alpha(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)+\omega\kappa]}, \right.$$

$$\left. \frac{\mu(\mu+\kappa+\alpha)(\mu+\omega)-\beta\sigma\kappa}{\sigma[\alpha(\mu+\omega)-(\mu+\omega)(\mu+\kappa+\alpha)+\omega\kappa]} \right)$$

Thus,

$$(s^*, e^*, i^*) = (\ 0.424,\ 0.242,\ 0.334\ )$$

4.4 Stability Analysis

Here, we are going to investigate the steady states to see which of them will be stable and this will help us confirm whether the disease will die out or persist in the region.

4.4.1 Stability analysis of the Disease-free Equilibrium point

The stability of the characteristic equation would be analysed based on the Routh-Hurwitz stability criterion.

The disease free equilibrium is (s,e,i)= (1, 0, 0) and

$$J(1,0,0) = J_{DFE} = \begin{bmatrix} -\mu & \alpha & -\sigma\frac{\beta}{\mu}+\omega \\ 0 & -(\mu+\kappa+\alpha) & \sigma\frac{\beta}{\mu} \\ 0 & \kappa & -(\mu+\omega) \end{bmatrix}$$

$$J_{DFE} - I\lambda = \begin{bmatrix} -\mu-\lambda & \alpha & -\sigma\frac{\beta}{\mu}+\omega \\ 0 & -(\mu+\kappa+\alpha)-\lambda & \sigma\frac{\beta}{\mu} \\ 0 & \kappa & -(\mu+\omega)-\lambda \end{bmatrix} = 0$$

$$\Rightarrow \begin{bmatrix} -0.017-\lambda & 0.35 & -0.719 \\ 0 & -0.443-\lambda & 0.757 \\ 0 & 0.076 & -0.055-\lambda \end{bmatrix} = 0$$

$$\Rightarrow (-0.017-\lambda)\begin{vmatrix} -0.443-\lambda & 0.757 \\ 0.076 & -0.055-\lambda \end{vmatrix} - 0.35\begin{vmatrix} 0 & 0.757 \\ 0 & -0.055-\lambda \end{vmatrix} - 0.719\begin{vmatrix} 0 & -0.443-\lambda \\ 0 & 0.076 \end{vmatrix} = 0$$

Implying that

$$(-0.017-\lambda)\left[(-0.443-\lambda)(-0.055-\lambda)-0.058\right]=0$$

$$\Rightarrow (-0.017-\lambda)\left[0.024+0.443\lambda+0.055\lambda+\lambda^2-0.058\right]=0$$

$$\Rightarrow (-0.017-\lambda)\left[\lambda^2+0.498\lambda-0.034\right]=0$$

$$\Rightarrow -0.017\lambda^2-0.008\lambda+0.0005-\lambda^3-0.498\lambda^2+0.034\lambda=0$$

$$-\lambda^3-0.515\lambda^2-0.026\lambda+0.034=0 \quad = 0$$

Thus,

$$\lambda^3+0.515\lambda^2+0.026\lambda-0.034=0 \qquad (4.04)$$

From Routh-Hurwitz criterion, the characteristic equation for the disease-free equilibrium above has -0.034<0, hence unstable. This means that tuberculosis in Central region will persist.

4.4.2 Stability analysis of the Endemic Equilibrium point

Also, the endemic equilibrium is $(s^*, e^*, i^*) = (0.424,\ 0.242,\ 0.334)$

and the Jacobian matrix for the endemic equilibrium is

$$J(s^*, e^*, i^*) = J_{EE} = \begin{bmatrix} -\sigma i^* - \mu & \alpha & -\sigma s^* + \omega \\ \sigma i^* & -(\mu+\kappa+\alpha) & \sigma s^* \\ 0 & \kappa & -(\mu+\omega) \end{bmatrix}$$

$$\det(J_{EE} - I\lambda) = \begin{bmatrix} (-\sigma i^* - \mu) - \lambda & \alpha & -\sigma s^* + \omega \\ \sigma i^* & -(\mu + \kappa + \alpha) - \lambda & \sigma s^* \\ 0 & \kappa & -(\mu + \omega) - \lambda \end{bmatrix} = 0$$

$$\Rightarrow \begin{bmatrix} -0.270 - \lambda & 0.35 & -0.283 \\ 0.253 & -0.443 - \lambda & 0.321 \\ 0 & 0.076 & -0.055 - \lambda \end{bmatrix} = 0$$

$$\Rightarrow (-0.270 - \lambda)\begin{vmatrix} -0.443 - \lambda & 0.321 \\ 0.076 & -0.055 - \lambda \end{vmatrix} - 0.35\begin{vmatrix} 0.253 & 0.321 \\ 0 & -0.055 - \lambda \end{vmatrix}$$

$$-0.283\begin{vmatrix} 0.253 & -0.443 - \lambda \\ 0 & 0.076 \end{vmatrix} = 0$$

$$\Rightarrow (-0.270 - \lambda)[(-0.443 - \lambda)(-0.055 - \lambda) - 0.24] - 0.35[0.253(-0.055 - \lambda)] - 0.005 = 0$$

$$\Rightarrow (-0.270 - \lambda)[0.024 + 0.443\lambda + 0.055\lambda + \lambda^2 - 0.024] + 0.0049 + 0.089\lambda - 0.005 = 0$$

$$\Rightarrow (-0.270 - \lambda)[0.498\lambda + \lambda^2] + 0.089\lambda - 0.0001 = 0$$

$$\Rightarrow -0.134\lambda - 0.270\lambda^2 - 0.498\lambda^2 - \lambda^3 + 0.089\lambda - 0.0001 = 0$$

$$\Rightarrow -\lambda^3 - 0.768\lambda^2 - 0.045\lambda - 0.0001 = 0$$

$$\lambda^3 + 0.768\lambda^2 + 0.045\lambda + 0.0001 = 0 \qquad (4.05)$$

From Routh-Hurwitz criterion, since 0.768> 0, 0.0001 > 0 and 0.768×0.045 > 0.0001, the characteristic equation above corresponding to the endemic equilibrium is stable.

This means that tuberculosis in Central region will persist.

4.5 Sensitivity Analysis

Sensitivity analysis enables the determination of which parameters of a model are most responsible for generating the variability in the value of the model's outputs over time. In this study, one way sensitivity analysis will be used, thus estimates for each parameter are varied one at a time to investigate the impact on study results.

4.5.1 Sensitivity Analysis Using the Basic Reproduction Number, R_o

From equation 3.017, the basic reproduction number of the SEIS model will be calculated as

$$R_o = \frac{\sigma\kappa}{(\mu+\kappa+\omega)(\mu+\omega)} = 2.361 \cong 2$$

Since $R_o \cong 2$, it implies that on average, each infectious individual transmits bacteria to 2 people; hence, the disease will spread.

In this particular analysis, much concern will be on the changes that will make $R_o < 1$. That is, we are more concern with the parameters that must be well considered in order to control TB in the region.

Four out of the six estimated parameter values were varied using one way sensitivity analysis and σ, κ, ω and α were the parameters varied.

$$R_o = \frac{\sigma\kappa}{(\mu+\kappa+\alpha)(\mu+\omega)} \qquad (4.06)$$

If σ is doubled,

$$R_{o1} = \frac{2\sigma\kappa}{(\mu+\kappa+\alpha)(\mu+\omega)} \tag{4.07}$$

Comparing equations (4.06) and (4.07) above, it can be established that

$$R_{o1} = 2R_o$$

Generally, let $a \in R^+$

Then,

$$R_{o1} = aR_o$$

Which implies that

$$R_{o1} = \frac{a\sigma\kappa}{(\mu+\kappa+\alpha)(\mu+\omega)} \tag{4.08}$$

From what has just been established above, it is clear that increasing σ or κ will increase R_o which will cause the disease to spread and vice versa.

Also, doubling α will yield

$$R_{o1} = \frac{\sigma\kappa}{(\mu+\kappa+2\alpha)(\mu+\omega)} \tag{4.09}$$

and if $a \in R^+$, then

$$R_{o1} = \frac{\sigma\kappa}{(\mu+\kappa+a\alpha)(\mu+\omega)} \tag{4.010}$$

That is, increasing α or ω will reduce R_o.

4.5.2 Sensitivity Analysis of Tuberculosis Transmission by Simulation

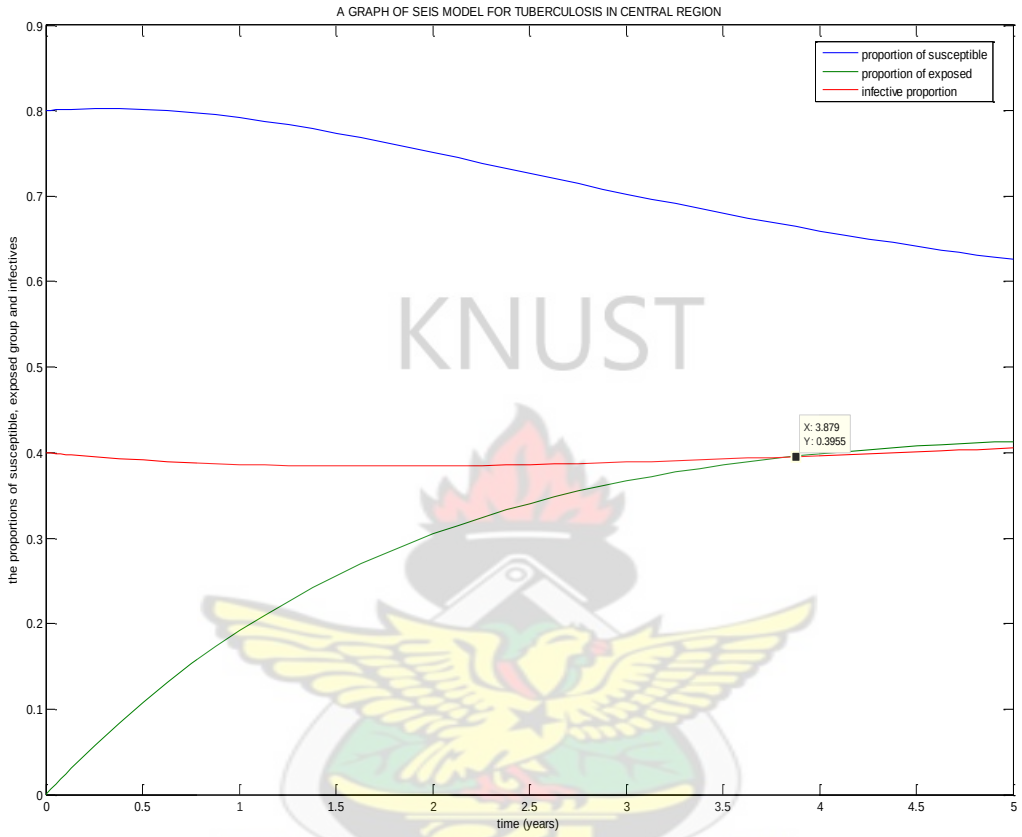

Figure 4.1 : A graph of SEIS Model for Tuberculosis in Central Region

Parameter values					Change in the proportions of (s, e, i)			
σ	α	ω	κ	μ/β	s	e	i	R_o
0.757	0.35	0.038	0.076	0.017	-0.17	+0.42	+0.09	2.361

Table 4.2: Actual parameter values against R_o and changes in the proportions of (s, e, i).

NB: the positive and negative signs represent increase and decrease in proportions.

A graph representing the SEIS Model for tuberculosis in the Central Region of Ghana has been displayed in figure 4.1. The proportion of susceptible was initially 0.8, that of infective begun at

0.4 and the proportion of exposed group was 0. As time progressed, there was an interaction between the infective and the susceptible. Some of the susceptible individuals were latently infected as a result which caused the exposed proportion to increase from 0 to 0.42 while the proportion of susceptible reduced from 0.8 to 0.63 at the end of the 5^{th} year. Considering the proportion of infective, it dropped from 0.4 to 0.390 within the first year and then begun increasing gradually till it was in equilibrium with the exposed class at 0.3955 in the year 3.879. From there, it again increased till it got to 0.409 in the 5^{th} year.

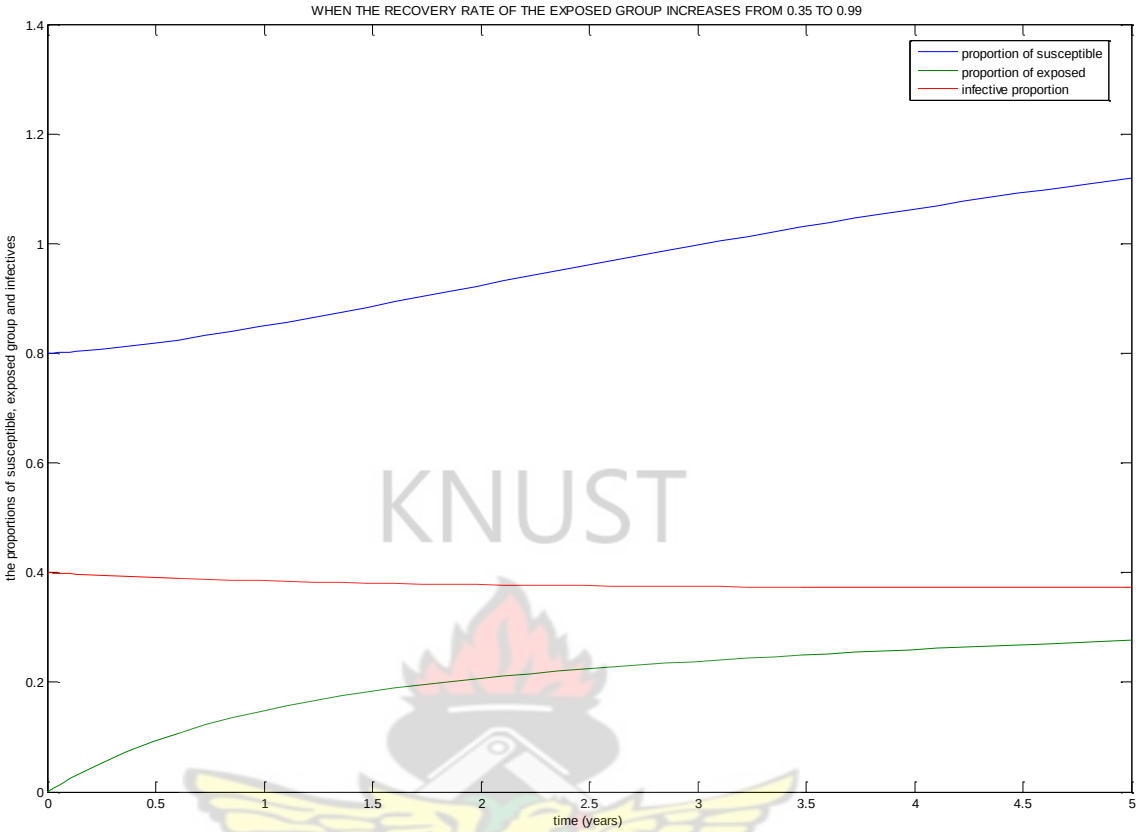

Figure 4.2: the nature of the graph when α is increased from 0.35 to 0.99 with other parameter values maintained.

Parameter values when α increases from 0.35 to 0.99					Change in the proportions of (s, e, i)			R_o
σ	α	ω	κ	μ/β	s	e	i	
0.757	0.99	0.038	0.076	0.017	+0.33	+0.29	-0.03	0.966

Table 4.3: Parameter values against R_o and changes in the proportions of (s, e, i) when α increases from 0.35 to 0.99.

Here, we increase the recovery rate of the exposed group from 0.35 to 0.99 and it is shown in figure 4.2 that the proportion of susceptible increases sharply from 0.8 to 1.13 in the fifth year. The proportion of exposed increased from 0 to 0.29 while that of the infective reduced from 0.4 to 0.37 in the 5^{th} year.

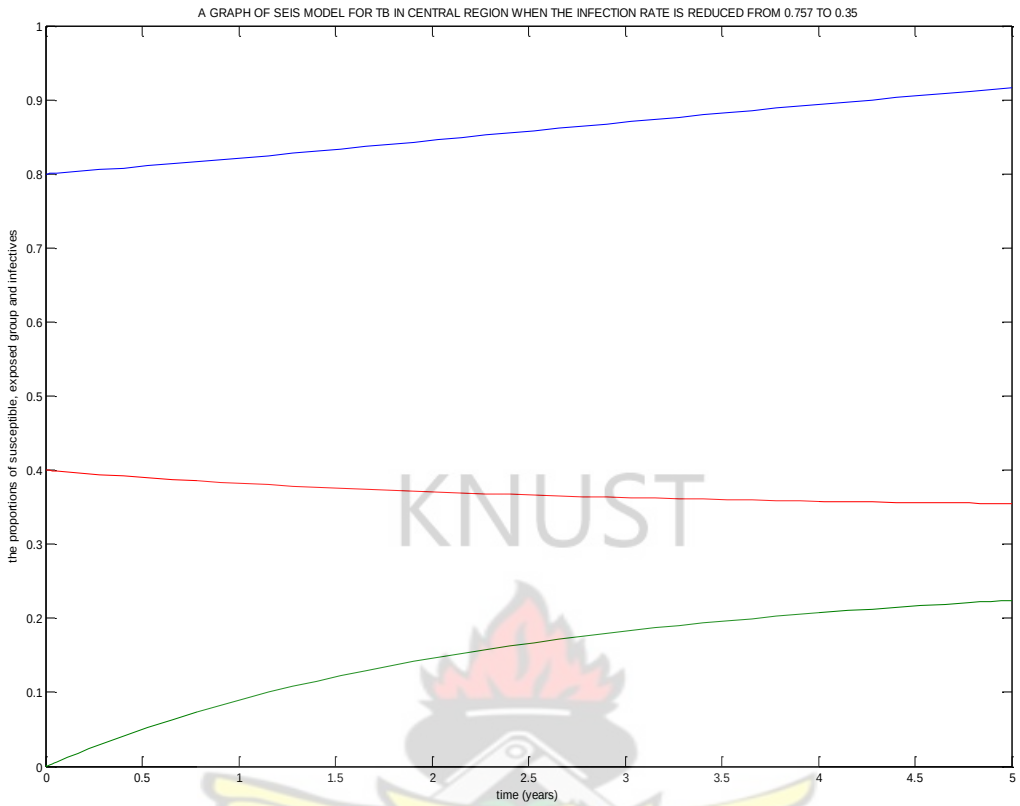

Figure 4.3: the nature of the graph when σ is decreased from 0.757 to 0.35 with other parameter values maintained.

Parameter values when σ reduces from 0.757 to 0.35					Change in the proportions of (s, e, i)			R_o
σ	α	ω	κ	μ/β	s	e	i	
0.35	0.35	0.038	0.076	0.017	+0.12	+0.23	-0.045	1.09

Table4.4: Parameter values against R_o and changes in the proportions of (s, e, i) when σ reduces from 0.757 to 0.35.

From figure 4.3, and table 4.4, decreasing σ from 0.757 to 0.35 increases the susceptible proportion by 0.12, thus, from 0.8 to 0.92, increases the exposed proportion from 0 to 0.23 and reduces that of the infective from 0.4 to 0.355.

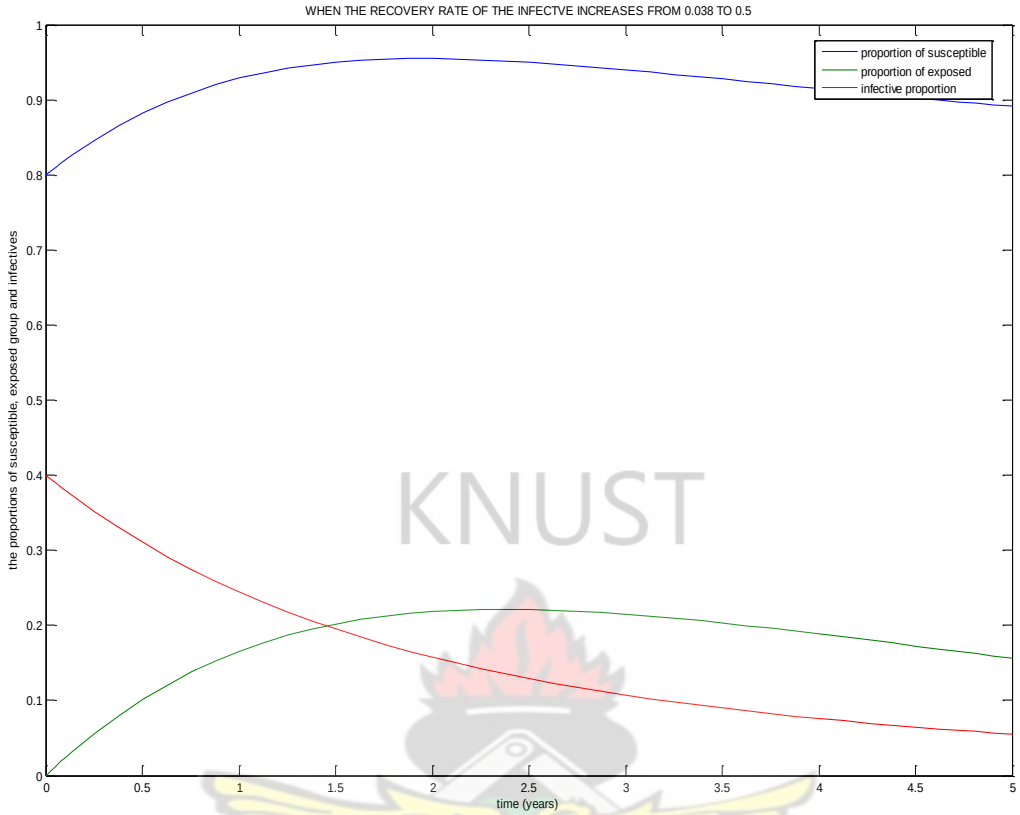

Figure 4.4: nature of the graph when ω is increased from 0.038 to 0.5

Parameter values when ω increases from 0.038 to 0.5					Change in the proportions of (s, e, i)			R_o
σ	α	ω	κ	μ/β	s	e	i	
0.757	0.35	0.5	0.076	0.017	+0.09	+0.16	-0.055	0.251

Table 4.5: Effect of parameter values on R_o and the proportions of (s, e, i) when ω increases from 0.038 to 0.5 .

Considering figure 4.4, when the recovery rate of the infective increases, the proportion of susceptible increases sharply within the first two years and then begins to reduce gradually to 0.89 in the fifth year. The proportion of infective also reduces drastically from 0.4 to 0.051while that of the exposed reduces from 0.42 to 0.154.

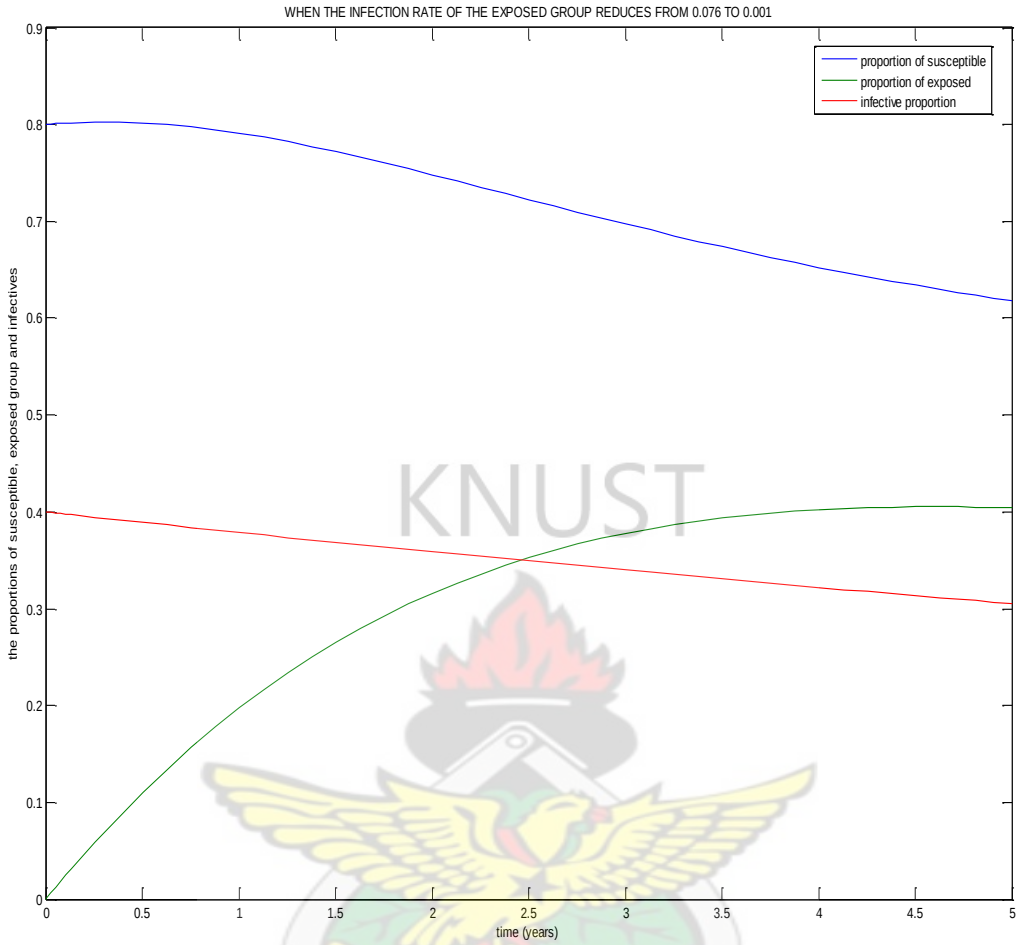

Figure 4.5: the effect of decreasing κ from 0.076 to 0.001while maintaining other parameter values.

Parameter values when κ reduces from 0.076 to 0.001					Change in the proportions of (s, e, i)			R_o
σ	α	ω	κ	μ/β	s	e	i	
0.757	0.35	0.038	0.001	0.017	-0.08	+0.41	0.09	0.0374

Table 4.6: Effect of parameter values on R_o and the proportions of (s, e, i) when κ reduces from 0.076 to 0.001.

When κ was reduced from 0.076 to 0.001 in figure 4.6, the proportion of susceptible reduced from 0.8 to 0.72 and a very small decrease in the exposed proportion, that is, from 0.42 to 0.41 but the proportion of infective dropped from 0.4 to 0.31.

4.6 Discussion

In this thesis, we attempted to modify the SEIS differential equation model developed by Castillo Chavez to predict the spread of tuberculosis in Central region. We discussed the existence and stability of the disease free and disease endemic equilibria of the model and performed sensitivity analysis of the model by varying some of the parameter values. We proceeded to simulate our model using Matlab 7.0.1.24704 (R14) by altering the values of σ, κ,ω and α, and observing the changes that occurred in the model.

Based on the estimated parameter values for our SEIS model, the basic reproductive number, R_o = 2. The value of R_o which is > 1 with a stable unique endemic equilibrium shows that the average number of secondary infections caused by a single infectious individual during their entire infectious lifetime is 2, hence the disease will take hold.

The sensitivity analysis revealed that reducing the initial transmission rate and the effective transmission rate or increasing the treatment rate of the latent class will prevent the disease from spreading.

From figure 4.2, the proportion of susceptible reduced from 0.8 to 0.63 because there was an interaction between the proportions of infective introduced into the population and the susceptible. This interaction caused the infective class to transmit bacteria to some of the susceptible individuals and as a result, the proportion of susceptible started decreasing while that of the exposed also began increasing from 0 in the beginning of the first year till it attained a value of 0.42 in the 5^{th} year. The proportion of infective decreased slightly within the first year. The reason for the decrease within the first year is due to the trend of tuberculosis infection. During initial infection, infected individuals are not active, that is, they do not move straight into the infectious class but rather get exposed (latently infected) for a period of time before some of them progress into the infectious class. When this happens, it means the proportion of infective will not increase and since some of the infectious individuals will receive treatment and recover within that period, the proportion of infective will reduce. It has also been observed from figure 4.2 that the proportion of infective began increasing gradually from the 2^{nd} year till the 5^{th} year implying that individuals began to progress from the latent stage into the infectious stage. The

proportion of infective was equal to the proportion of exposed in the latter part of the 3rd year at a point where the exposed curve crossed that of the infective.

After analyzing the graph using the actual estimated values of the parameter, we decided to alter these values and observe their impact on study results.

In figure 4.3, when the recovery rate of the exposed class increased, there was a sharp increase in the proportion of susceptible because more people recover and join the population of susceptible and when this happens, there will be a reduction in exposed group as well as the infective since there will be a small number of people left to progress into active TB.

We observed a similar trend in figure 4.4 when the initial infection rate, σ was decreased. This is also due to the fact that less people get infected and move into the exposed class and since there is a small number of people in the exposed group, there are a few people who are likely to progress into active TB.

When the recovery rate of the infective increased in figure 4.5, there was an increase in the proportion of susceptible and a drastic reduction in the proportion of infective as well as the exposed. The factors that account for these are that, more people will recover from TB infection and there will be less people with active TB in the population to infect the susceptible. Reduced infection of susceptible will mean there will be a small number of exposed individuals likely to progress into active TB. Meanwhile the recovery rate of the infective is so high that there will be a time when the exposed class cannot meet the demand of the infective class and will lead to TB disease disappearing.

Decreasing κ, the infection rate of the exposed into the active class did not have any significant change in the proportion of susceptible and exposed but a reduction was observed in the proportion of infective as in figure 4.6. This normally happens when individuals in the exposed and susceptible group have strong immune system.

A summary of our sensitivity analysis by simulation is shown in table 4.7.

Change in parameter value						Change in proportions			
σ	α	ω	κ	μ/β		s	e	i	R_o
0.757	0.35	0.038	0.076	0.017		-0.17	+0.42	+0.09	2.361
0.35 (-54%)	0.35	0.038	0.076	0.017		+0.12	+0.23	-0.045	1.09
0.757	0.99 (+183%)	0.038	0.076	0.017		+0.33	+0.29	-0.03	0.966
0.757	0.35	0.5 (+1215.8%)	0.076	0.017		+0.09	+0.16	-0.055	0.251
0.757	0.35	0.038	0.001 (-98.7%)	0.017		-0.08	+0.41	-0.09	0.0374
0.757	0.35	0.059 (+54%)	0.076	0.017		+0.01	+0.019	-0.007	5.651
0.757	0.539 (+54%)	0.038	0.076	0.017		0.180	+0.32	-0.055	3.274

Table 4.7: Summary of the effects of parameter value variation on R_o and the proportions of (s, e, i)

NB: the positive and negative signs represent increase and decrease.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

This model focused on tuberculosis transmission in Central region, Ghana through the deterministic approach.

The basic reproductive number, R_o of our SEIS model was calculated to be 2, which implies that on average, each infectious individual transmits bacteria to 2 people. The stability analysis of the endemic equilibrium has been found to be stable; hence, we conclude that the transmission rate of TB in Central region is high and will persist.

The sensitivity analysis that was carried out both R_o and simulation showed that the initial infection rate, σ has a very great influence on the spread of TB in the region than all the other parameters. Varying the value of σ at the same rate as the other parameter values completely decreases the proportions of both the infective and the exposed more effectively than any parameter value. We conclude that TB transmission is primarily as a result of the effective interaction between active TB patients and the susceptible group.

From the analysis and discussions of the model, SEIS epidemiological model is a good model to study the spread of tuberculosis in Ghana.

5.2 Recommendations

It is highly recommended that besides the attempts being made by Ghana Health Service to fight TB in the Central Region, there are other effective measures that can be implemented to reduce drastically the burden of TB on the health of the people in the region.

- More emphasis should be laid on the preventive measures of TB in the region, especially educating the public on how to achieve protective or careful interaction between active TB patients and those with no infection to reduce initial transmission.
- The Regional Health Directorate should sensitize all TB patients in the region (both clinically active and latently infected) for them to understand the nature of the disease and co-operate fully in the treatment programme.
- The public should also be advised to go for early screening whenever they cough for more than a week for early detection in case it is TB infection.

By doing this the TB situation in the Central Region of Ghana can be completely minimized and even eradicated.

- It is again recommended that further studies be done on Tuberculosis by considering how diabetes and HIV influence the rate of TB infection and the rate of TB infection with respect to age.

APPENDIX

Matlab code for the simulation

```
alpha=a;
sigma=d;
beta=b;
mu=g;
kappa=k;
omega=w;
```

Figure 1

```
function dy=sko(t,y)
a=0.35;d=0.757;b=0.017;g=0.017;k=0.076;w=0.038;
dy=zeros(3,1);
dy(1)=b-d*y(1)*y(2)-g*y(1)+a*y(2)+w*y(3);
dy(2)=d*y(1)*y(3)-(g+k+a)*y(2);
dy(3)=k*y(2)-(g+w)*y(3);


[t,y]=ode45('sko',[0 5],[0.8 0 0.4])

plot(t,y(:,1),t,y(:,2),t,y(:,3))

legend('proportion of susceptible','proportion of exposed','infective proportion')

xlabel('time (years)');ylabel('the proportions of susceptible, exposed group and infectives')
```

figure 2

```
function dy=sko(t,y)
a=0.99;d=0.757;b=0.017;g=0.017;k=0.076;w=0.038;
dy=zeros(3,1);
dy(1)=b-d*y(1)*y(2)-g*y(1)+a*y(2)+w*y(3);
dy(2)=d*y(1)*y(3)-(g+k+a)*y(2);
dy(3)=k*y(2)-(g+w)*y(3);


[t,y]=ode45('sko',[0 5],[0.8 0 0.4])

plot(t,y(:,1),t,y(:,2),t,y(:,3))
```

```
legend('proportion of susceptible','proportion of exposed','infective proportion')

xlabel('time (years)');ylabel('the proportions of susceptible, exposed group and infectives')
```

figure 3

```
function dy=sko(t,y)
a=0.35;d=0.35;b=0.017;g=0.017;k=0.076;w=0.038;
dy=zeros(3,1);
dy(1)=b-d*y(1)*y(2)-g*y(1)+a*y(2)+w*y(3);
dy(2)=d*y(1)*y(3)-(g+k+a)*y(2);
dy(3)=k*y(2)-(g+w)*y(3);


[t,y]=ode45('sko',[0 5],[0.8 0 0.4])

plot(t,y(:,1),t,y(:,2),t,y(:,3))

legend('proportion of susceptible','proportion of exposed','infective proportion')

xlabel('time (years)');ylabel('the proportions of susceptible, exposed group and infectives')
```

figure 4

```
function dy=sko(t,y)
a=0.35;d=0.757;b=0.017;g=0.017;k=0.076;w=0.5;
dy=zeros(3,1);
dy(1)=b-d*y(1)*y(2)-g*y(1)+a*y(2)+w*y(3);
dy(2)=d*y(1)*y(3)-(g+k+a)*y(2);
dy(3)=k*y(2)-(g+w)*y(3);


[t,y]=ode45('sko',[0 5],[0.8 0 0.4])

plot(t,y(:,1),t,y(:,2),t,y(:,3))

legend('proportion of susceptible','proportion of exposed','infective proportion')

xlabel('time (years)');ylabel('the proportions of susceptible, exposed group and infectives')
```

figure 5

```
function dy=sko(t,y)
a=0.35;d=0.757;b=0.017;g=0.017;k=0.001;w=0.038;
dy=zeros(3,1);
dy(1)=b-d*y(1)*y(2)-g*y(1)+a*y(2)+w*y(3);
dy(2)=d*y(1)*y(3)-(g+k+a)*y(2);
dy(3)=k*y(2)-(g+w)*y(3);


[t,y]=ode45('sko',[0 5],[0.8 0 0.4])

plot(t,y(:,1),t,y(:,2),t,y(:,3))

legend('proportion of susceptible','proportion of exposed','infective proportion')

xlabel('time (years)');ylabel('the proportions of susceptible, exposed group and infectives')
```

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