ANALYSIS OF TRANSMISSION DYNAMICS OF TUBERCULOSIS (TB) USING DIFFERENTIAL EQUATIONS: A CASE STUDY OF AMANSIE WEST DISTRICT, GHANA.

BY

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DECLARATION

I hereby declare that this submission is my own work towards the Master of Science (MSc.) and that, to my 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.

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ABSTRACT

In this thesis, a Susceptible – Exposed - Infected - Recovered (SEIR) epidemiological model was formulated to determine the transmission of tuberculosis. The equilibrium points of the model were found and their stability was investigated. By analyzing the model, we found a threshold parameter $R_{0,}$ the basic reproductive number. It was noted that when $R_0 < 1$ the disease will fail to spread and when $R_0 > 1$ the disease will persist in the population and become an endemic. The model had two non – negative equilibria namely the disease – free equilibrium and the endemic equilibrium. Using the Routh - Hurwitz stability theorem and computer simulations, it was observed that the number of immunized individuals in the population will increase the level of immunity. The graphical solutions of the differential equations were developed using Matlab as well as the computer simulations. The Appendix contains the Matlab codes used in the computer simulations.

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DEDICATION

I dedicate this work to the Almighty God who is my source of wisdom, knowledge and power.

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CHAPTER 1

INTRODUCTION

1.0 OVERVIEW

1.1 A MATHEMATICAL MODEL

A mathematical model is an abstract model that uses mathematical language to describe the behaviour of a system, designed to aid computations and predictions. Mathematical models are used particularly in the natural sciences and engineering disciplines (such as physics, biology, and electrical engineering) and also in the social sciences (such as economics, sociology and political science); physicists, engineers, computer scientists, and economists use mathematical models most extensively (Science Daily, 2012).

Eykhoff (1974) defined a mathematical model as a representation of the essential aspects of an existing system (or a system to be constructed) which presents knowledge of that system in usable form.

Mathematical modeling and analysis is central to disease epidemiology. The progress of an epidemic through the population is highly amenable to mathematical modelling. In particular, the first attempt to model and hence predict or explain patterns dates back over 100 years, although it was the work of Kermack and McKendrick(1927) that established the basic foundations of the subject.

Once a model that captures the main features of the progression and transmission of a particular disease in a population has been formulated, it can be used to predict the effects of different strategies for disease eradication or control. An example of this successful achievement worldwide is the global eradication of smallpox through the discovery of an effective vaccine, with the last wild case in 1977(WHO, 2007).

1.1.1 HISTORY OF TUBERCULOSIS (TB)

Tuberculosis (TB) describes an infectious disease that has plagued humans since the Neolithic times. Two organisms cause tuberculosis; Mycobacterium tuberculosis and Mycobacterium bovis. Consumption, phthisis, scrofula, Pott's disease, and the White Plague are all terms used to refer to tuberculosis throughout history (Wikipedia/ History of tuberculosis, 2012).

The terms phthisis, consumption first appeared in Greek literature. Around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times, and noted that it was almost always fatal. Due to common phthisis-related fatalities, he wrote something no doctor would dare write today: he warned his colleagues against visiting TB patients in late stages of the disease, because their inevitable deaths might damage the reputations of the attending physicians.

Exact pathological and anatomical descriptions of the disease began to appear in the seventeenth century. In his Opera Medica of 1679, Sylvius was the first to identify actual tubercles as a consistent and characteristic change in the lungs and other areas of consumptive patients. He also described their progression to abscesses and cavities. The earliest references to the infectious nature of the disease appeared in seventeenth century Italian medical literature.

Physicians in ancient Greece called this illness phthisis to reflect its wasting character. During the 17th and 18th centuries, TB caused up to 25% of all deaths in Europe. In more recent times, tuberculosis has been called consumption. It was not clear how TB was transmitted until Robert Koch's brilliant discovery of the tubercle bacillus in 1882 and established TB as an infectious disease. (www.emedicinehealth.com/Tuberculosis, 2012).

In the 19th century, patients were isolated in sanatoria and given treatments such as injecting air into the chest cavity. Attempts were made to decrease lung size by surgery called thoracoplasty. During the first half of the 20th century, no effective treatment was available. Streptomycin, the first antibiotic to fight TB, was introduced in 1946, and isoniazid (Laniazid, Nydrazid) originally an antidepressant medication, became available in 1952(Daniel, 2000).

1.1.2 WHAT IS TUBERCULOSIS (TB)?

Tuberculosis, MTB, or TB (short for tubercle bacillus) is a common, and in many cases lethal, infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis(Kumar *et al*, 2007). Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit their saliva through the air (Konstantinos, 2010). Most infections are asymptomatic and latent, but about one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those infected.

Mycobacterium tuberculosis is a rod-shaped, slow-growing bacterium. Mycobacterium tuberculosis cell wall has high acid content, which makes it hydrophobic, resistant to oral fluids. The cell wall of Mycobacteria absorbs a certain dye used in the preparation of slides for

examination under the microscope and maintains this red color despite attempts of decolourisation, hence the name acid-fast bacilli. (www.emedicinehealth.com/Tuberculosis, 2012).

1.1.3 MODE OF TRANSMISSION OF TUBERCULOSIS

Tuberculosis is caused by mycobacterium, usually Mycobacterium tuberculosis. The bacterium is transmitted from an infected host to a new host through respiratory mist. When people with active pulmonary TB cough, sneeze, speak, sing, or spit, they expel infectious aerosol droplets 0.5 to 5.0 μm in diameter. A single sneeze can release up to 40,000 droplets (Cole and Cook, 1998). Each one of these droplets may transmit the disease since the infectious dose of tuberculosis is very low (the inhalation of fewer than 10 bacteria may cause an infection) (Nicas *et.al*, 2005).

People with prolonged, frequent, or close contact with people with TB are at particularly high risk of becoming infected, with an estimated 22% infection rate (Ahmed and Hasnain, 2011). A person with active but untreated tuberculosis may infect 10–15 (or more) other people per year (TB Fact sheet, WHO, 2011). Transmission occur from people with active TB, those with latent infection are not thought to be contagious (Kumar *et al*, 2007).

The probability of transmission from one person to another depends upon several factors, including the number of infectious droplets expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the Mycobacterium tuberculosis strain, the level of immunity in the uninfected person, and others (CDC, 2007).

The cascade of person-to-person spread can be circumvented by effectively segregating those with active TB and putting them on anti-TB drug regimens. After about two weeks of effective treatment, subjects with nonresistant active infections generally do not remain contagious to others (Ahmed and Hasnain, 2011). If someone does become infected, it typically takes three to four weeks before the newly infected person becomes infectious enough to transmit the disease to others.

1.1.3.1 PATHOGENESIS OF TUBERCULOSIS

Once inhaled, the mycobacteria enter the lungs. When they reach the pulmonary alveoli, they encounter macrophages, which are white blood cells that surround and digest pathogens. Sometimes, the immune system can destroy the mycobacteria, but if not, the mycobacteria begin multiplying within the macrophages. The macrophages are then used as transportation to nearby lymph nodes. Once in the lymph nodes, the mycobacteria can spread throughout the body. (Kumar *et al*, 2007, Herrmann and Lagrange, 2005).

Because mycobacterium tuberculosis is a slow-growing bacterium, the immune system, if not able to destroy it, may be able to keep it from spreading enough to cause symptoms. This is called a latent tuberculosis infection, and it accounts for 90% of TB infections (Skolnik, 2011). While the organism might be present in the body for years, there is only a 10% chance that it will ever progress to an active infection (Arch and Claire, 2009). People with latent infections cannot spread TB to others.

1.1.4 SIGNS AND SYMPTOMS OF TUBERCULOSIS

Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis) (Mandell *et al*, 2010). Extrapulmonary TB occurs when tuberculosis develops outside of the lungs. Extrapulmonary TB may coexist with pulmonary TB as well. General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue, and significant finger clubbing may also occur (Abramson *et al*, 2005). One may not notice any symptoms of illness until the disease is quite advanced. Even the symptoms might be blamed on other disease. The cases of tuberculosis infections are grouped into two forms and are as follows;

1.1.4.1 PULMONARY TUBERCULOSIS

If a tuberculosis infection does become active, it most commonly involves the lungs (in about 90% of cases) (Behera, 2010). Symptoms may include chest pain and a prolonged cough producing sputum. About 25% of people may not have any symptoms (i.e. they remain asymptomatic) (Lawn and Zumla, 2011). Occasionally, people may cough up blood in small amounts, and in very rare cases, the infection may erode into the pulmonary artery, resulting in massive bleeding (Rasmussen's aneurysm).

Tuberculosis may become a chronic illness and cause extensive scarring in the upper lobes of the lungs. The upper lung lobes are more frequently affected by tuberculosis than the lower ones (Mandell *et al*, 2010). The reason for this difference is not entirely clear. It may be due either to better air flow, or to poor lymph drainage within the upper lungs (Kumar *et al*, 2007).

1.1.4.2 EXTRAPULMONARY TB

In 15–20% of active cases, the infection spreads outside the respiratory organs, causing other kinds of TB (Golden and Vikram, 2005). These are collectively denoted as extrapulmonary tuberculosis. Extrapulmonary TB occurs more commonly in immunosuppressed persons and young children. In those with HIV, this occurs in more than 50% of cases (Golden and Vikram, 2005).

Notable Extrapulmonary infection sites include the pleura (in tuberculous pleurisy), the central nervous system (in tuberculous meningitis), the lymphatic system (in scrofula of the neck), the genitourinary system (in urogenital tuberculosis), and the bones and joints (in Pott's disease of the spine), among others. When it spreads to the bones, it is also known as osseous tuberculosis, a form of osteomyelitis (Kumar *et al*, 2007 and Kabra *et al*, 2006).

A potentially more serious, widespread form of TB is called disseminated TB, commonly known as Miliary tuberculosis (Mandell *et al*, 2010). Miliary TB makes up about 10% of extrapulmonary cases (Habermann and Amit, 2008).

1.1.5 RISK FACTORS OF TUBERCULOSIS

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all TB cases are infected by the virus (WHO, 2011). This is a particular problem in sub-Saharan Africa, where rates of HIV are high (WHO, 2006 and Chaisson and Martinson, 2008).

Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty (Lawn and Zumla, 2011). Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather (e.g. prisons and homeless shelters), medically underprivileged and resource-poor communities, high-risk ethnic minorities, children in close contact with high-risk category patients and health care providers serving these clients (Griffith and Kerr, 1996).

Chronic lung disease is another significant risk factor, with silicosis increasing the risk about 30-fold (CDC, 2007). Those who smoke cigarettes have nearly twice the risk of TB than nonsmokers. Other disease states can also increase the risk of developing tuberculosis, including alcoholism and diabetes mellitus (threefold increase) (Restrepo, 2007).

Certain medications, such as corticosteroids and infliximab (an anti-αTNF monoclonal antibody) are becoming increasingly important risk factors, especially in the developed world. There is also a genetic susceptibility for which overall importance is still undefined (Lawn and Zumla, 2011).

1.1.6 DIAGNOSIS OF TUBERCULOSIS

Tuberculosis is diagnosed by finding Mycobacterium tuberculosis bacteria in a clinical specimen taken from the patient. While other investigations may strongly suggest tuberculosis as the diagnosis, they cannot confirm it.

A complete medical evaluation for tuberculosis (TB) must include a medical history, a physical examination, a chest X-ray and microbiological examination (of sputum or some other

appropriate sample). It may also include a tuberculin skin test, other scans and X-rays, surgical biopsy (Kumar *et al*, 2007).

1.1.6.1 LATENT TUBERCULOSIS (TB)

The Mantoux tuberculin skin test is often used to screen people at high risk for TB. Those who have been previously immunized may have a false-positive test result. The test may be falsely negative in those with sarcoidosis, Hodgkin's lymphoma, malnutrition, or most notably, in those who truly do have active tuberculosis. Interferon gamma release assays (IGRAs), on a blood sample, are recommended in those who are positive to the Mantoux test. These are not affected by immunization or most environmental mycobacteria, so they generate fewer false-positive results. However they are affected by Mycobacterium szulgai, Mycobacterium marinum and Mycobacterium kansasii. IGRAs may increase sensitivity when used in addition to the skin test but may be less sensitive than the skin test when used alone (Amicosante *et al*, 2010).

1.1.6.2 ACTIVE TUBERCULOSIS (TB)

Diagnosing active tuberculosis based merely on signs and symptoms is difficult, as is diagnosing the disease in those who are immunosuppressed. A diagnosis of TB should, however, be considered in those with signs of lung disease or constitutional symptoms lasting longer than two weeks. A chest X-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation (Escalante, 2009).

Interferon gamma release assays (IGRAs) and tuberculin skin tests are of little use in the developing world. IGRAs have similar limitations in those with HIV. A definitive diagnosis of TB is made by identifying Mycobacterium tuberculosis in a clinical sample (e.g. sputum, pus, or a tissue biopsy). However, the difficult culture process for this slow-growing organism can take two to six weeks for blood or sputum culture. Thus, treatment is often begun before cultures are confirmed. Nucleic acid amplification tests and adenosine deaminase testing may allow rapid diagnosis of TB. These tests, however, are not routinely recommended, as they rarely alter how a person is treated. Blood tests to detect antibodies are not specific or sensitive, so they are not recommended (Steingart *et al*, 2011).

1.1.7 TREATMENT OF TUBERCULOSIS (TB)

Tuberculosis prevention and control efforts primarily rely on the vaccination of infants and the detection and appropriate treatment of active cases. The World Health Organisation (WHO) has achieved some success with improved treatment regimens, and a small decrease in case numbers (Lawn and Zumla, 2011).

One must note that, everyone infected with TB bacteria becomes sick. As a result, two TB-related conditions exist: latent TB infection and active TB disease. Both latent TB infection and active TB disease can be treated.

1.1.7.1 TREATMENT FOR LATENT TB INFECTION

People with latent TB infection have TB bacteria in their bodies, but they are not sick because the bacteria are not active. People with latent TB infection do not have symptoms, and they cannot spread TB bacteria to others. However, if TB bacteria become active in the body and multiply, the person will go from having latent TB infection to being sick with active TB disease. For this reason, people with latent TB infection are often prescribed treatment to prevent them from developing TB disease. Treatment of latent TB infection is essential for controlling and eliminating TB.

Because there are less bacteria in a person with latent TB infection, treatment is much easier. Four regimens are approved for the treatment of latent TB infection. The medications used to treat latent TB infection include:

- isoniazid (INH)
- rifampin (RIF)
- rifapentine (RPT)

Certain groups of people (such as people with weakened immune systems) are at very high risk of developing TB disease once infected with TB bacteria. Every effort should be made to begin appropriate treatment and to ensure completion of the entire course of treatment for latent TB infection (CDC, 2007).

1.1.7.2 TREATMENT FOR ACTIVE TB DISEASE

TB bacteria become active (multiplying in the body) if the immune system can't stop them from growing. When TB bacteria are active, this is called TB disease. TB disease will make a person sick. People with TB disease may spread the bacteria to people with whom they spend many hours.

TB disease can be treated by taking several drugs for 6 to 9 months. These drugs are approved by the World Health Organisation's Stop TB Department for treating TB. Of the approved drugs, the first-line anti-TB agents that form the core of treatment regimens include:

- isoniazid (INH)
- rifampin (RIF)
- ethambutol (EMB)
- pyrazinamide (PZA)

Regimens for treating TB disease have an initial phase of 2 months, followed by a choice of several options for the continuation phase of either 4 or 7 months (total of 6 to 9 months for treatment).

It is very important that people who have TB disease finish the medicine, taking the drugs exactly as prescribed. If they stop taking the drugs too soon, they can become sick again; if they do not take the drugs correctly, the TB bacteria that are still alive may become resistant to those drugs. TB that is resistant to drugs is harder and more expensive to treat.

Treatment completion is determined by the number of doses ingested over a given period of time. Although basic TB regimens are broadly applicable, there are modifications that should be made under special circumstances (such as people with HIV infection, drug resistance, pregnancy, or treatment of children).

Surgery on the lungs may be indicated to help cure TB when medication has failed, but in this day and age, surgery for TB is unusual. Treatment with appropriate antibiotics will usually cure the TB. Without treatment, however, tuberculosis can be a lethal infection. Therefore, early diagnosis is important. Those individuals who have been exposed to a person with TB, or suspect that they have been, should be examined by a doctor for signs of TB and screened with a TB skin test (CDC, 2007).

1.1.7.3 TUBERCULOSIS VACCINES

The only currently available vaccine as of 2011 is Bacillus Calmette–Guérin (BCG) which, while it is effective against disseminated disease in childhood, confers inconsistent protection against contracting pulmonary TB (McShane, 2011). Nevertheless, it is the most widely used vaccine worldwide, with more than 90% of all children being vaccinated (Lawn and Zumla, 2011). However, the immunity it induces decreases after about ten years. BCG is only administered to people at high risk. Part of the reasoning arguing against the use of the vaccine is that it makes the tuberculin skin test falsely positive, and therefore, of no use in screening (Teo and Shiggadia, 2006). A number of new vaccines are currently in development (Lawn and Zumla, 2011).

1.2 STATEMENT OF THE PROBLEM

Despite the availability of highly efficacious treatment for decades, TB remains a major global health problem. In 1993, the World Health Organization (WHO) declared TB a global public health emergency, at a time when an estimated 7–8 million cases and 1.3–1.6 million deaths occurred each year (WHO, 1993).

Although TB is currently well-controlled in most countries, recent data indicate that the overall global incidence of TB is rising as a result of resurgence of the disease in Africa and parts of Eastern Europe and Asia (Dye, 2006). In these regions, the emergence of drug-resistant TB and the convergence of the HIV (human immunodeficiency virus) and TB epidemics have created substantial new challenges for disease control.

In 2010, there were an estimated 8.5–9.2 million cases and 1.2–1.5 million deaths (including deaths from TB among HIV-positive people) (WHO, 2011). TB is the second leading cause of death from an infectious disease worldwide (after HIV, which caused an estimated 1.8 million deaths in 2008) (Mandell *et al*, 2010). In 2009 there were 9.4 million new cases of TB and 1.7 million deaths, including 380,000 deaths from TB among people with HIV (WHO, 2011). The vast majority of deaths from TB are in the developing world.

Tuberculosis (TB), a preventable disease linked to poverty, was declared an emergency in Africa in 2005. Each year it claims the lives of half a million Africans, many young and in their most productive years. In the past 15 years, overall rates have doubled in Africa and tripled in high HIV areas. Africa has the highest per capital incidence of TB in the world (28%), with most of

the worst affected countries located in sub-Saharan Africa. Those most at risk include the urban poor, migrants and refugees, who are forced to live in overcrowded conditions (AMREF, 2012).

Africa is also the only continent where TB rates are increasing, with 1,500 TB deaths every day. Tragically and avoidably, 10% of these are children. TB is also a leading killer of HIV-positive people with weakened immune systems. About 200,000 people living with HIV/AIDS die from TB every year, most of them in Africa. Completing a particularly vicious circle, HIV itself has been the single most important factor in the rising incidence of TB in Africa since 1990. Treating co-infected people is hard as the drug therapies for each are hard to safely combine (AMREF, 2012).

One-third of the world's population is currently infected with the TB bacilli with nearly 2 million deaths each year. Of those infected, over 1.5 million cases occur annually in sub-Saharan Africa (WHO, 2005).

Tuberculosis in Ghana started way back in the pre-independence era when the then colonial government recognized the need to combat the disease due to the threat it posed to the larger society. In July 1954, the Ghana Society for the Prevention of Tuberculosis was established to support and supplement government's efforts at combating the disease (GHS – Stop TB Prog., 2012).

Over 46,000 new cases of TB annually are estimated by the World Health Organization (WHO) in Ghana (WHO, 2006). However, in reality, less than a third of the estimated number of cases is officially reported each year by health facilities in the country. For instance, in 2008, only 14,022

TB cases of all forms were reported, the highest cases ever recorded officially in the country (National Tuberculosis Programme Annual Report – GHS / MoH, 2008).

It is believed that many people suffering from the disease do not report to health facilities due to the stigma attached to the disease. Furthermore, some of those who report are misdiagnosed by laboratory personnel due to inaccurate sputum smear examinations. This may lead to a false negative or false positive result which has adverse implications in the community and on the patient.

Prior to this study, Amansie West District was challenged with tuberculosis disease. According to records available at the Amansie West District Health Directorate as well as the St. Martin's Hospital indicates that tuberculosis disease is well established in the district. From 2007 to 2011, there has been an increase in the number of cases recorded. In 2007, 34 cases were diagnosed, 2008 (62 cases), 2009 (59 cases), 2010 (62 cases) and 2011 (70 cases). These records indicate that tuberculosis disease is endemic in the district.

1.3 OBJECTIVES OF THE STUDY

The main objectives of the study are as follows:

1. To find out the mode of transmission of tuberculosis.
2. To formulate a SEIR mathematical epidemiological model for the transmission of tuberculosis and simulate the model.
3. To do mathematical analysis of the model.
4. To interpret the results of the model.

1.4 METHODOLOGY

The mathematical model will be formulated using differential equations based on the epidemiological compartment modelling. The computer software package that will be used to solve the differential equation model numerically is Matrix Laboratory (Matlab R2010a). Analysis and numerical simulations of the model will be conducted. The resources to be used are the Kwame Nkrumah University of Science and Technology School Library and the internet.

1.5 JUSTIFICATION

This thesis will support the efforts of the National Tuberculosis Control Programme to establish and understand the burden of the disease. This is because it will give decision makers and stakeholders a mathematical model to understand the transmission and spread of tuberculosis in order to make precise policy interventions. It will also provide further information on better ways to accelerate progress towards achieving the Millennium Development Goals (MDGs) for Tuberculosis (TB) eradication.

The thesis may also aid mathematicians, research scientist, etc. to further develop suitable models to help public health professionals to make better strategies for controlling the disease.

Lastly, it will also assist to measure the performance of the interventions made by the country as well as the district in controlling and eradicating the disease.

1.6 ORGANISATION OF THE THESIS

The study has been organised into five chapters. Chapter one which is the introduction deals with the historical and biological background to the thesis, statement of the problem, objectives of the thesis, methodology that will be used for the thesis, thesis justification, and organisation of the thesis.

Chapter two discusses the literature related to the thesis. The review involves theoretical and empirical studies i.e. Work done by other researchers in mathematical modelling of tuberculosis and the methods used. The third chapter describes the methodology used in the thesis.

In chapter four, the main focus is the analysis of the model and the discussion of results.

Finally, the conclusions drawn from the model and recommendations are presented in chapter five.

CHAPTER 2

REVIEW OF RELATED LITERATURE

2.0 INTRODUCTION

The outbreak and spread of a disease has been questioned and studied for many years. The ability to make predictions about diseases could enable scientists to evaluate inoculation or isolation plans and may have a significant effect on the mortality rate of a particular epidemic. The modeling of infectious diseases is a tool which has been used to study the mechanisms by which diseases spread, to predict the future course of an outbreak and to evaluate strategies to control an epidemic (Daley and Gani, 2005).

John Graunt was the first scientist who systematically tried to quantify causes of death. In his book "Natural and Political Observations made upon the Bills of Mortality" (1662), the bills he studied were listings of numbers and causes of deaths published weekly. Graunt's analysis of causes of death is considered the beginning of the "theory of competing risks" which according to Daley and Gani (Daley and Gani, 2005) is a theory that is now well established among modern epidemiologists.

The earliest account of mathematical modeling of spread of disease was carried out in 1766 by Daniel Bernoulli. Trained as a physician, Bernoulli created a mathematical model to defend the practice of inoculating against smallpox (Hethcote, 2000). The calculations from his model showed that universal inoculation against smallpox would increase the life expectancy from 26 years 7 months to 29 years 9 months (Bernoulli and Blower, 2004).

Daniel Bernoulli's work, of course, preceded our modern understanding of germ theory, and it was not until the research of Ronald Ross into the spread of malaria, that modern theoretical epidemiology began. This was soon followed by the acclaimed work of A. G. McKendrick and W. O. Kermack, whose paper 'A Contribution to the Mathematical Theory of Epidemics' was published in 1927. A simple deterministic (compartmental) model was formulated in this paper. The model was successful in predicting the behavior of outbreaks very similar to that observed in many recorded epidemics (Brauer and Castillo-Chavez, 2001).

2.1 TUBERCULOSIS (TB) EPIDEMIC MODELS

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.

Stochastic means being or having a random variable. A stochastic model is a tool for estimating probability distributions of potential outcomes by allowing for random variation in one or more inputs over time. Stochastic models depend on the chance variations in risk of exposure, disease and other illness dynamics. They are used when these fluctuations are important, as in small populations (Trottier & Philippe, 2001).

In the 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 (as seen in Figure 2.1).

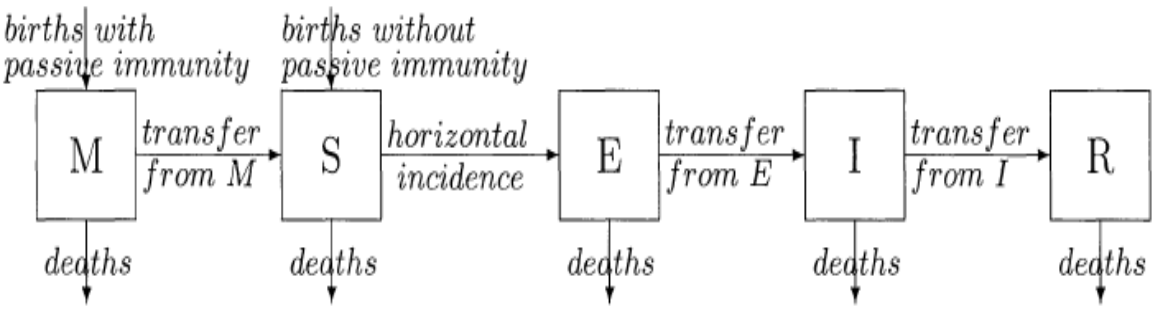

Figure 2.1 General Transfer Diagram for the MSEIR Model.

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. When dealing with large populations, as in the case of tuberculosis, deterministic or compartmental mathematical models are used. In other words, the changes in population of a compartment can be calculated using only the history used to develop the model (Brauer and Castillo-Chavez, 2001).

Mathematical models used for the spread of infectious disease are referred to as dynamic models because they describe change over time. They have a long history in epidemiology and have been used in a wide variety of diseases (Hethcote, 2000), including measles, influenza, rubella and chicken pox (Feng *et al.* 2000).

Most diseases studied using modeling techniques have age-specific transmission rates and exhibit features of reoccurring epidemics. 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 TB.

2.2 TUBERCULOSIS (TB) TRANSMISSION DYNAMICS MODELS

The majority of previous studies on TB models have used deterministic compartment models (Blower 1996, 1998, Murray and Salomon, 1998, Dye *et al*, 1998, Currie *et al*, 2003, 2005, Williams *et al*, 2005, etc.). Deterministic compartmental models are when the population is divided into different epidemiological states and the movements between the states are represented by a system of differential equations.

These previous compartmental models focused on modeling TB at the population level. The studies concentrated on the effect of interventions at a large scale and although many of them addressed the implications of reducing transmission, none of them were able to look at the actual mechanics behind it. These studies have been vital in understanding and quantifying TB disease progression in populations. However it is felt that a discrete event simulation is more appropriate for investigating interventions at the household level and enables the more intricate details of transmission to be understood.

Since the 1960's, simple mathematical models have been used to understand tuberculosis transmission dynamics and to predict the effects of different interventions (Waaler *et al*. 1962). Recently, there has been renewed interest in using mathematical models to study tuberculosis epidemics (Blower *et al*. 1995, Blower *et al*. 1996, Brewer *et al*. 1996).

Blower *et al*. (1995, 1996), in particular, developed a simple analytical framework which they used to calculate threshold levels of preventive therapy and treatment necessary for eradication of tuberculosis. Elaborating the basic model developed by Blower and colleagues to capture some other aspects of the epidemiology of tuberculosis relevant to evaluating the control strategies.

Mathematical models have played a key role in the formulation of TB control strategies and the establishment of interim goals for intervention programs. Most of these models are of the SEIR framework in which the host population is categorized by infection status as susceptible(*S*), exposed (*E*) (infected but not yet infectious), infectious (*I*) and recovered (*R*). One of the principle attributes of these models is that the force of infection (the rate at which susceptibles leave the susceptible class and move into an infected category, i.e. become infected) is a function of the number of infectious hosts in the population at any time *t* and is thus a nonlinear term. Other transitions, such as the recovery of infectious individuals and death, are modeled as linear terms with constant coefficients.

In many such models, there is a sharp threshold behavior, and the asymptotic dynamics are determined by a parameter R_0, known as the basic reproductive number. When $R_0 < 1$, the disease-free equilibrium is (usually globally) asymptotically stable, and when $R_0 > 1$ there exist a unique endemic equilibrium, which is also (usually globally) stable. R_0 represents the average number of new infectious cases caused by an infectious case in a fully susceptible population, over the course of the entire infectious period.

However, with vaccination, relapse and reinfection, there can be other threshold values and the interpretation of R_0 is not so clear. Sometimes the term "effective reproductive number", usually denoted R, is used in these situations. Not all SEIR-type models have an R_0 threshold (Vynnycky and Fine, 1998 and Heffernan *et al*., 2005).

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 1968 and 1970, Waaler and Piot (1969), and Waaler and Piot (1970). After the 1970's, little work on models of tuberculosis appeared in the literature until the mid - 1990's.

In 1995, Blower *et al.* presented two differential equation models of TB, a simpler model (Equation 2.1) and a more detailed one. Both are SEIR-type models, the detailed model had both infectious and non-infectious active TB as well as recovery.

It is useful to give examples of several models that are proto-typical of models that came later. They used their own (and standard) notation, S for susceptible, L for latent, I for infectious, and R for recovered: The first model of Blower *et al.* (1995) assumed that susceptible people are born into the population at rate λ. Susceptible individuals are infected at rate βIS and move either into the latent class L or directly into the infectious class I (fast progression). Latent individuals progressed to active disease when they are infectious at a constant rate (slow progression). In the infectious state, individuals suffer an increased death rate due to the disease.

$$\dot{S} = \lambda - \beta IS - \mu S$$
$$\acute{L} = (1 - p)\,\beta IS - (v + \mu)\,L \qquad (2.1)$$
$$\dot{I} = p\beta IS + vL - (\mu + \mu\tau)\,I$$

Here β is the transmission parameter, μ is the natural death rate, $\mu\tau$ is the rate of death due to TB, v is the progression rate from latency to active disease and p is the portion of fast progressors.

In their second, more detailed, model, Blower *et al.* (1995) used a similar approach but specified two active TB classes (one infectious and one noninfectious), a recovered class (with entry cI for cure), and relapse into either active class. Note that, as mentioned above, a parameter (in this case p) sets the proportion of new infections that move directly into the infectious class.

In their analysis (Blower *et al.*, 1996), R_0 was decomposed into a sum of R_0 values for each of three routes to disease (fast progression, slow progression and relapse), forming the basis for the authors' subsequent discussion of linked TB epidemics. The model was matched to TB mortality data and R_0 was used to derive a population threshold below which the disease cannot take hold. An interesting aspect of this work was that the authors computed doubling times of TB epidemics (in their initial transient rise as the epidemic invades a population); these are very long (≈100 years) for R_0 near 1, as it has been estimated to be by Salpeter and Salpeter (1998). The authors also compared aspects of young and old TB epidemics, which are different because of the long time scales inherent in the model.

In 1997, Castillo-Chavez and Feng (1997) presented an SEIR model with one form of latency and one class of active TB. In this model, individuals could only move to the infectious class from the latent class, so there was only one progression rate, and there was recovery from latency and active disease back to the susceptible class. They found an R_0 for the model, and showed

global asymptotic stability of the disease-free equilibrium when $R_0 < 1$, and local asymptotic stability of the unique endemic equilibrium for $R_0 > 1$; global asymptotic stability of this was proved in Feng *et al.* (2001). Their first model is analogous to Equation 2.1 and is given by

$$\dot{S} = \lambda - \sigma IS / N + r_1 L + r_2 I - \mu S$$

$$\acute{L} = \sigma IS / N - (\mu + \nu + r_1) L \quad (2.2)$$

$$\dot{I} = \nu L - (\mu + \mu\tau + r_2)$$

Here r_1 and r_2 are cure rates out of latent and active infection, respectively, and N = S + L + I is the population size.

In the same paper, Castillo-Chavez and Feng presented a two-strain model, in which the drug-resistant strain was not treated, and latent, infectious and treated individuals may be re-infected with the drug-resistant strain. Each strain had a different R_0, and there were 3 equilibrium points (no disease, coexistence of both strains, and only the drug-resistant strain). Without acquisition of drug resistance, there was an additional equilibrium with only the drug-sensitive strain. The authors discussed stability of the equilibria and found, interestingly, areas of parameter space of positive measure where coexistence of the strains is possible; they reported that coexistence was rare when drug resistance is mainly primary (resulting from transmission) but almost certain if the resistant strain is the result of acquisition, for example under poor treatment. Neglecting disease-induced death and setting the transmission parameter equal for the two strains, they were able to prove that the disease-free equilibrium is globally asymptotically stable if both R_0's are less than 1. These results were extended by Mena-Lorca *et al*. (1999).

In Blower *et al.* (1996) and Blower and Gerberding (1998), Blower and colleagues discussed two additional models with a focus on chemophrophylactic treatment (which prevents progression

from latency to active disease). These were both like Equation 2.1, in that there was a direct transition from *S* to *I*. The second model contains two strains, drug-sensitive and drug-resistant. The drug-resistant phenotype may be acquired among those treated for drug-sensitive active disease, or directly transmitted to susceptible individuals. This was the first multi-strain model of TB.

In Blower *et al.* (1996), the authors focused on the threshold R_0 and the development of drug resistance. They defined a variable *X* to be the number of drug-resistant cases caused by the treatment of one drug-sensitive case. The authors then used the condition $R_0 < 1$ to compute $r_{max}(X)$, the maximal acceptable probability of treatment failure. They concluded that control programs could become perverse (meaning $X > 1$), though this required a rather high probability of acquisition of drug resistance due to treatment failure (up to 0.5). In countries with a high TB burden, they concluded that the efficacy of treatment combined with the effective overall treatment rates must be kept high in order to control TB. They estimated in model terms the World Health Organization's objectives for the year 2000, and reported that these targets did not satisfy $R_0 < 1$.

Blower and Gerberding (1998) expanded on this work; here the authors focused on trajectories in the two-strain model (rather than threshold conditions with R_0), and simulated specific control policies, numerically in the short term, and using R_0 analyses for long-term consequences. In their model, policies leading to the same long-term equilibrium can have very different transient approaches to that equilibrium, which is relevant in TB because transients can be very long (as the authors pointed out). Furthermore, some transients in their model showed a decline in the

portion of drug-resistant TB over a 10-year period, followed by a slow increase. The authors discussed this qualitatively in terms of TB's inherent fast and slow time scales. In conclusion, they argued for vaccination, and warned about the consequences of focusing control measures only on drug-sensitive TB.

In Blower *et al*. (1999), the authors commented that in their models, while increasing antibiotic use can contribute to the emergence of drug resistance, increasing treatments with higher efficacy can still have an overall beneficial effect. Other papers by Blower and coauthors included, but were not limited to, Sanchez and Blower (1997) and Porco and Blower (1998), in which the authors performed a sensitivity analysis of the three R_0 values from Blower *et al*. (1995) (fast, slow and relapse), and of TB outcomes, respectively. They generally found $1 < R_0 < 9$, and that the most important parameters are the infection rate β, the portion p fast progressors, the reactivation rate ν, and the death rates.

It is not always clear how to define R_0 for a given model. E. Vynnycky argued in Vynnycky and Fine (1998) that the interpretation and application of R_0 is difficult when the rate of transmission of disease changes in time, and when reinfection contributes to disease. Indeed, there are a variety of biological questions that have been asked of TB models that go beyond the threshold behavior in R_0.

Several TB models aimed at investigating optimal treatment strategies. Lietman and Blower (2000) studied pre- and post-exposure vaccines, using models with fast and slow progressors, and vaccines parameterized by their take, degree and duration, permitting various mechanisms

by which these programs may be less than 100% effective. They found 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 appeared to perform best. However the vaccines simulated are theoretical and estimates of the efficacy of the existing vaccine Bacillus Calmette–Guérin (BCG) are highly variable (Colditz *et al*., 1994, 1995).

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

Murray and Salomon (1998) presented a model with 19 different states, which includes fast and slow progression, treatment with chemoprophylaxis (INH), superinfection (e.g. reinfection), three clinical categories of active disease, and "good" and "bad" treatment. The authors calibrated the model to five different regions of the world, and used it (numerically) to quantitatively predict that a major extension to Directly Observed Therapy Short-Course (DOTS) could be quite effective, preventing millions of deaths.

Dye *et al*. (1998) presented a model with explicit fast and slow progression from two latent classes. They studied drug-resistant TB alone, representing treatment failures as potential transmitters of drug-resistant TB. Using Monte Carlo methods to estimate the model's R_0 for drug-resistant TB, they argued that short-course chemotherapy can bring resistant strains under

control, preventing drug-resistant TB from emerging, and that this can probably be done by meeting the WHO targets for case detection and cure. This is in contrast to the conclusion of Blower *et al*. (1996), whose analysis was based on an R_0 threshold in a different model. However, Dye's result depended on the assumption that drug-resistant strains are less transmissible than drug-sensitive strains, and does not explicitly represent the dynamics of drug-sensitive disease.

In a more recent paper, Dye and Williams (2000) used a model that allowed the relative fitness of drug-resistant strains to be as high as 1 (i.e. the same as drug-sensitive strains), and concluded that drug-resistant strains could threaten control of TB. Minimally, they estimated that 70% of drug-resistant cases must be detected and 80% of these must be cured in order to prevent drug-resistant TB outbreaks.

In Espinal *et al*. (2001), however, the authors used data from one molecular epidemiology study and a ceiling of fitness of the drug-resistant strain of 0.7, and concluded that drug-resistant strains were likely to remain a localized problem rather than a problem for global control.

Blower and Chou (2004) introduced a model which allowed amplification of drug resistance. That is, they allowed that strains may become resistant to increasing numbers of drugs if sub-optimal treatment regimens are used. They found, in agreement with results of Dye and Williams (2000) and Cohen and Murray (2004) that individuals with drug-resistant disease must be treated to avoid the further emergence of resistance.

In most of the models discussed thus far, the question of reinfection has not been a central one. However it has been included in various models including Vynnycky and Fine (1997), Dye *et al*. (1998), Gomes *et al*. (2004), Cohen and Murray (2004) and Cohen and Murray (2005).

In Feng *et al.* (2000), the authors added a transition from the latent class to the infectious class of the form $p\beta LI / N$, and showed that this changes the qualitative dynamics of the model, allowing for the existence of multiple endemic equilibria even when $R_0 < 1$, if p is sufficiently large.

Lipsitch and Murray (2003) argued that the required value of p was too large for the result to be meaningful for TB. However, the change in qualitative behavior of the model from the usual R_0-determined dynamics clearly indicated the necessity of establishing the existence of a threshold behavior with respect to R_0 before using basic definitions of R_0 (the average number of new infectious cases from one infectious case in a susceptible population) to derive treatment thresholds.

In Gomes *et al*. (2004), the authors detected a reinfection threshold, which is a value of R_0, larger than one, after which reinfection is the predominant form of disease transmission. Breban and Blower (2005) correctly pointed out that this was not a sharp threshold, in that it does not correspond to a bifurcation point; $R_0 = 1$ is the only bifurcation point.

However, Gomes *et al*. (2005) replied that there was a bifurcation in a submodel of the model of Gomes *et al*. (2004) which gives rise to what resembles threshold behavior.

Because transmission is a function of both contact rate and infectivity, Aparicio *et al.* (2000) formulated a deterministic cluster model to specifically explore the impact of intense and long exposure to individuals with active TB on population level transmission dynamics. In contrast to

Porco and Blower (1998), this model does not assume an average number of individuals infected per year from one infectious case. Specifically, this model differentiates between epidemiologically active clusters (defined as active when one member has active TB infection) and casual infections. Model results indicated that casual infections may be as or more important than cluster-generated secondary infections at a population level. This result was also supported by molecular epidemiological data. The authors recommended the consideration of a lower bound on cluster size required for TB persistence as a new way to consider critical epidemic thresholds.

Though their model is not as detailed as Aparicio *et al.* (2000), Song *et al.* (2002) also modeled TB with fast and slow dynamics by considering the roles of close and casual contacts respectively. Their modeling goal was to try to explicitly understand how population level dynamics emerge from individual behavior without using a microsimulation. This linkage is important if theoretical models are to be translated into health policy recommendations. Song *et al.* incorporated local and individual interactions, assuming that individuals are at risk of infection from both close contacts in generalized households (clusters) as well as from casual (randomly distributed) contacts. Like Porco and Blower (1998), the model does not include reinfection, population structure, or heterogeneous mixing beyond cluster membership. However, unlike Porco and Blower (1998), Song *et al.* (2002) did not include recovery or variable times spent in latently infected state.

Most general TB models are either explicitly or implicitly based on developed nations. Yajnik (2003) noted that such models may not be appropriate for India, because they haven't considered the inclusion of non-allopathic treatments, private health sector efforts, or gender structure. He

therefore attempted to build a deterministic model of TB dynamics in India. Though the model was itself not provided, Yajnik stated that there are 47 subpopulations in the model, within which there are divisions by age and gender. Yajnik raised some important general caveats to TB models: are the populations modeled appropriate to specific human populations? And are the factors described in the model relevant to the situation to which the model is applied?

For many developing nations, or subpopulations within developed and developing nations, current models may not address these concerns.

Several of the authors referred to here, along with others have begun in more recent years to explore the impact of the high prevalence of HIV on TB epidemics. While a full review of this literature is beyond the scope of this paper, this is a topic of increasing importance in Africa where both diseases are at critically high levels and so we will include some examples of these models in the literature.

In Porco *et al.* (2001), the authors used discrete event simulation model to predict HIV's impact on TB epidemiology. They found that HIV can significantly affect levels of TB, but that the system is sensitive to the TB treatment rate. In Currie *et al.* (2003), a different equation model was developed representing both HIV and TB dynamics with simple submodels. The system was fitted to time series data, to compare TB treatment with combined HIV and TB prevention in high-burden areas. Prevention in their model was by reduction of HIV transmission, highly active antiretroviral therapy (HAART), and chemoprophylactic TB treatment (of latent infection). They concluded that prevention was insufficient and treatment of active TB disease should not be replaced with these measures.

Cohen *et al.* (2006) developed a dynamic model of linked TB and HIV epidemics which includes a state of mixed drug-resistant and drug-sensitive TB infection. The inclusion of states of multiple pathogen infection (i.e. TB/HIV co-infection as well as superinfection with multiple strains of TB) reflects recent recognition that individuals may simultaneously harbour several distinct M. tuberculosis strains. Using this model, the authors found that current recommendations for use of single drug preventive therapy to prevent progression from infection to TB disease among those with HIV co-infection may reduce TB prevalence in the short-term but may eventually be counter-productive without directed efforts to improve the diagnosis and treatment of those with drug-resistant TB.

In conclusion, mathematical models associated with the study of tuberculosis (TB) in various countries have existed over the years. In this literature review, researchers sorted to be interested in knowing if the infection will be eradicated or persist in the population through the important parameter R_o. From the view of the public health sector, decision makers will be more concern and interested in knowing if the disease will persist or can be eradicated through interventions. However, mathematical models have not been used to study the spread of the disease in Ghana. The models above are other peoples work and do not apply to Ghana. I therefore want to introduce my model which is not as complex as the ones above and also applies to Amansie West District in Ghana.

CHAPTER 3

METHODOLOGY

3.0 INTRODUCTION

In this chapter, a mathematical model for tuberculosis transmission is formulated in respect of the epidemiological dynamics of the disease in the Amansie West district of Ghana. These models will help in predicting the transmission of the disease and to determine effective ways of controlling it in the Amansie West district. Since we are dealing with a large population, a deterministic or compartmental mathematical model is used. In the deterministic model, individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of the epidemic. The standard Susceptible-Exposed-Infected-Removed (SEIR) epidemiological models are utilized to study and analyse the disease, thus the simple SEIR model is used to explain the spread of tuberculosis in Amansie West district.

The Amansie West District is one of the 27 districts in the Ashanti region of Ghana. It was carved out of the Amansie East District of the Ashanti Region in 1989, as part of the Government's Decentralization Policy. Manso-Nkwanta is the district capital. The district is located in the south-western part of the Ashanti Region. It shares common boundary on its Western part with the Atwima Mponua District. On the northern part can be found the Atwima Nwabiagya and the Bosomtwe – Atwima - Kwanhuma Districts, while a regional boundary separates it from Western and Central Region on its southern part. The predominant occupation is subsistence farming and illegal small scale mining popularly known as Galamsey. Due to the activities of the illegal mining, the district is faced with the problem of immigration making the district exposed to infectious diseases with tuberculosis being prevalent.

Records available at the Ghana Statistical Service indicate that the population as of 2010 was estimated at 134,331. The district covers a total area of 1,141 square kilometers (km^2) making a population density of 112.2 per square kilometers (inhabitants per km^2). The district was chosen for study because records available at the District Health Directorate show that tuberculosis is still prevalent in the district. Below is the map of Ashanti Region with each of it districts including Amansie West district.

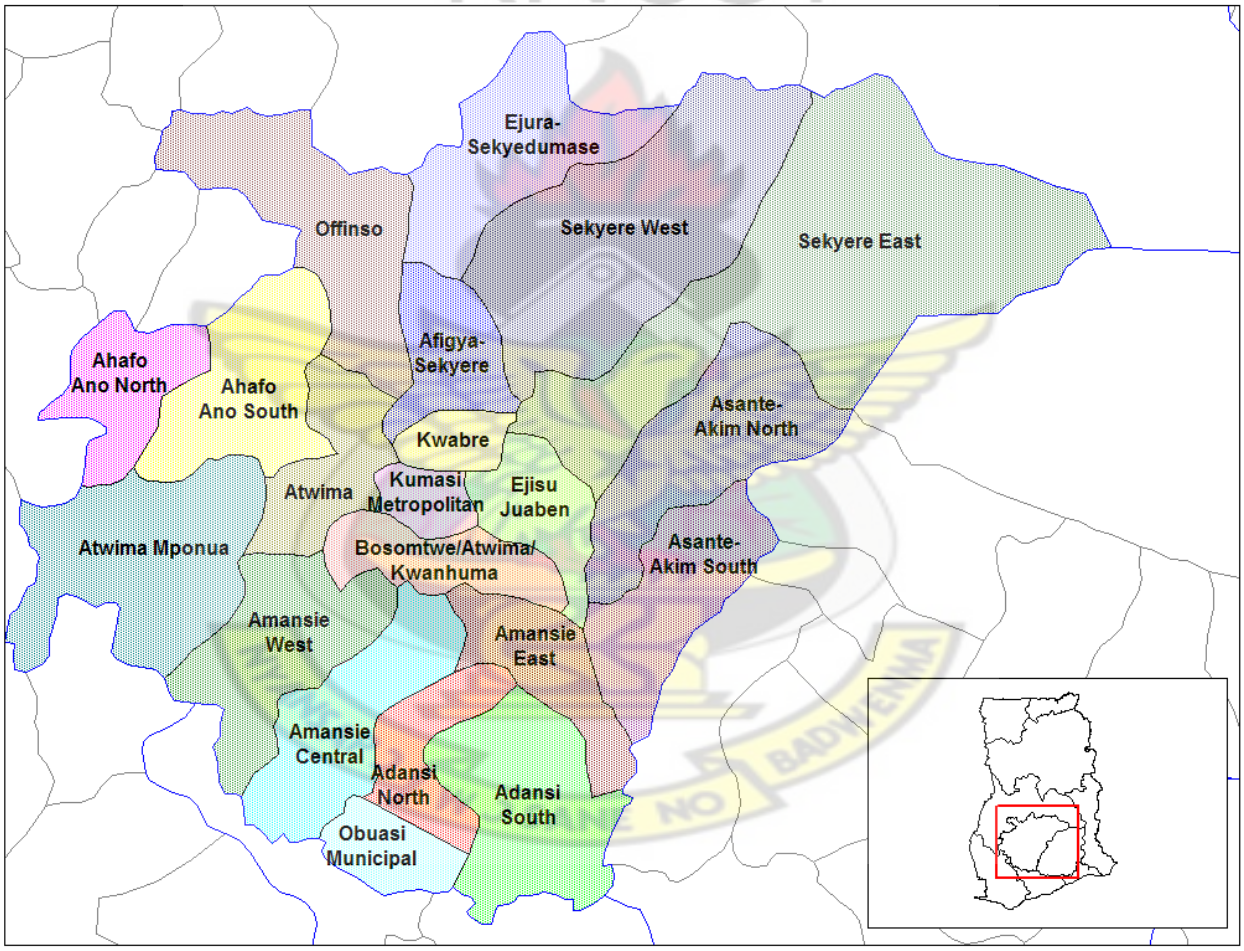

Figure 3.1 Map of Amansie West District within the map of Ashanti Region of Ghana.

Since the district shares common boundary with several other districts and two other regions, the activities of illegal mining has enhanced the free movement of people in the district. This brings about high population density and health risk associated with overcrowding. There is high level of disease incidence, hence there is that need to look into the health condition of the people living in Amansie West district.

3.1 DEFINITIONS

A differential equation is a mathematical equation for an unknown function of one or several variables that relates the values of the function itself and its derivatives of various orders.

$$f\left(y, \frac{dy}{dt}, \frac{d^2y}{dt^2}, ..., \frac{d^ny}{dt^n}, t\right) = 0 \tag{3.01}$$

A differential equation is said to be ordinary if all derivatives are with respect to a single independent variable (ODE).

$$\frac{d^ny}{dt^n} + a_1(t)\frac{d^{n-1}y}{dt^{n-1}} + ... + a_{n-1}(t)\frac{dy}{dt} + a_n(t)y = g(t) \tag{3.02}$$

On the other hand, if there are derivatives with respect to two or more independent variables, then it is a partial differential equation (PDE).

$$F\left(x_1, ..., x_n, u, \frac{\partial u}{\partial x_1}, ..., \frac{\partial u}{\partial x_n}, \frac{\partial^2 u}{\partial x_1 \partial x_2}, ..., \frac{\partial^2 u}{\partial x_1 \partial x_n}, ...\right) = 0 \tag{3.03}$$

The order of a differential equation is defined as the largest positive integer n, for which an nth derivative occurs in the equation. The degree of a differential equation is the power of the highest derivative term.

A differential equation is said to be linear if there are no transcendental functions and multiplications among dependent variables and their derivatives. A differential equation is homogeneous if every single term contains the dependent variables or their derivatives.

There are other types of differential equations such as;

- The Delay differential equation (DDE), which is a differential equation in which the derivative of the unknown function at a certain time is given in terms of the values of the function at previous times.
- The Stochastic differential equation (SDE), which is a differential equation in which one or more of the terms is a stochastic process, thus resulting in a solution which in itself is a stochastic process.
- The Differential algebraic equation (DAE), which is a differential equation comprising differential and algebraic terms, given in implicit form.

3.2 EQUILIBRIUM POINTS / STEADY STATES OF DIFFERENTIAL EQUATIONS

The study states (equilibria, fixed points) of system differential equation of the form $\frac{dx}{dt} = f(x)$ are those values of x that satisfy $f(x) = 0$ .The equilibrium points are the solution the equation $f(x) = 0$.

3.2.1 STABILITY OF THE EQUILIBRIUM POINTS / STEADY STATES

For differential equations of this form, there two approaches to determine the stability of the fixed points: Graphical stability of analysis and Linearization stability analysis. For the purpose of our steady, we are going consider the Linearization stability.

Also, since our study involves the standard SEIR epidemiological model, we are going to have two equilibria. The disease-free equilibrium point and the endemic equilibrium point. The disease free equilibrium point is where there are no infections in the population whiles the endemic equilibrium point is also where the disease will co-exist in all the compartments of the population.

3.2.2 LINEARIZATION STABILITY ANALYSIS

Linearization refers to finding the linear approximation to a function at a given point. In the study of dynamical systems, linearization is a method for assessing the local stability of an equilibrium point of a system of nonlinear differential equations or discrete dynamical systems.

Let $f : R^n \to R^n$ be a map C^1 and suppose that p is a point such that $f(p) = 0$, i.e., p is a fixed point for the differential equation $x`(t) = f(x(t))$. The linear part of f at p, denoted $Df(p)$, is the matrix of partial derivatives at p.

For $x \in R^n$ and $f(x) \in R^n$, we can write: $f(x) = \begin{pmatrix} f_1(x) \\ f_2(x) \\ . \\ . \\ . \\ f_n(x) \end{pmatrix}$ (3.04)

The function f_i are called the component functions of *f*.

We define $Df(p) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(p) & \frac{\partial f_1}{\partial x_2}(p) & \cdots & \frac{\partial f_n}{\partial x_n}(p) \\ \frac{\partial f_2}{\partial x_1}(p) & \frac{\partial f_2}{\partial x_2}(p) & \cdots & \frac{\partial f_n}{\partial x_n}(p) \\ \vdots & \vdots & \cdots & \vdots \\ \frac{\partial f_n}{\partial x_1}(p) & \frac{\partial f_n}{\partial x_2}(p) & \cdots & \frac{\partial f_n}{\partial x_n}(p) \end{pmatrix}$ (3.05)

This is called Jacobian matrix.

Since f is C^1, Taylor's theorem for functions of several variables says that

$f(x) = Df(p)(x-p) + g(x)$, where $f(p) = 0$ and $g(x)$ is a function that is small near p in the view that $\lim_{x \to p} \frac{|g(x)|}{|x-p|} = 0$.

There are several approaches to the study of the stability of the flow of nonlinear systems, but for the purpose of this work, we shall restrict our work to Routh - Hurwitz stability criterion.

3.2.3 ROUTH – HURWITZ STABILITY CRITERION

The Routh – Hurwitz stability criterion is a necessary and sufficient method to establish the stability of a single input, single output, linear time invariant control system. More generally, given a polynomial, some calculations using only the coefficients of that polynomial can lead to the conclusion that it is stable or not. It is an important criterion that gives necessary and

sufficient conditions for all of the roots of the characteristic polynomial (with real coefficients) to lie in the left half of the complex plane (Gantmacher, 1964).

Theorem:

Given the polynomial,

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_{n-1}\lambda + a_n, \tag{3.06}$$

Where the coefficients a_i are real constants, $i = 1, ..., n$, define the *n* Hurwitz matrices using the coefficient a_i of the characteristics polynomial:

$$H_1 = (a_1), H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix} and H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & . & . & . & 0 \\ a_3 & a_2 & a_1 & 1 & . & . & . & 0 \\ a_5 & a_4 & a_3 & a_2 & . & . & . & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ 0 & 0 & 0 & 0 & . & . & . & a_n \end{pmatrix} \tag{3.07}$$

Where $a_j = 0$ if $j > n$. All of the roots of the polynomial $P(\lambda)$ are negative or have negative real part if and only if the determinants of all Hurwitz matrices are positive;

$$\det H_j > 0, \; j = 1, 2, ..., n.$$

When *n = 2*, the Routh – Hurwitz criteria simplify to $H_1 = a_1 > 0$ and $\det H_2 = \det \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix} = a_1 a_2 > 0$ or $a_1 > 0, and, a_2 > 0$.

For polynomials of degree *n = 2, 3, 4* and *5*, the Routh – Hurwitz criteria are summarized below;

$$\left.\begin{array}{l} n=2: a_1>0, and, a_2>0 \\ n=3: a_1>0, a_3>0, and, a_1a_2>a_3 \\ n=4: a_1>0, a_3>0, a_4>0, and, a_1a_2a_3>a_3^2+a_1^2a_4 \\ n=5: a_1>0, i=1,2,3,4,5, a_1a_2a_3>a_3^2+a_1^2a_4, and \\ (a_1a_4-a_5)(a_1a_2a_3-a_3^2-a_1^2a_4)>a_5(a_1a_2-a_3)^2+a_1a_5^2. \end{array}\right\} \quad (3.08)$$

For a proof of the Routh – Hurwitz criteria please see Gantmacher (1964). The theorem is verified in the case *n = 2*.

Proof of Theorem

For *n = 2*, the Routh – Hurwitz criteria are just $a_1 > 0$ and $a_2 > 0$. The characteristic polynomial in the case *n = 2* is

$$P(\lambda) = \lambda^2 + a_1\lambda + a_2 = 0 \quad (3.09)$$

The eigenvalues satisfy

$$\lambda_{1,2} = \frac{-a_1 \pm \sqrt{a_1^2 - 4a_2}}{2}. \quad (3.10)$$

Suppose a_1 and a_2 are positive. It is easy to see that if the roots are real, they are both negative, and if they are complex conjugates, they have real part.

Next, to prove the converse, suppose the roots are either negative or have negative real part. Then it follows that $a_1 > 0$. If the roots are complex conjugates, $0 < a_1^2 < 4a_2$, which implies that a_2 is also positive. If the roots are real, then since both of the roots are negative it follows that $a_2 > 0$. Necessary but not sufficient conditions for the roots of the polynomial $P(\lambda)$ to lie in the left half of the complex plane is that the coefficients of $P(\lambda)$ are strictly positive.

3.3 THE MATHEMATICAL MODEL

The compartmental deterministic mathematical model will be used in our model. This is where individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of the epidemic.

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. When dealing with large populations, as in the case of tuberculosis, deterministic or compartmental mathematical models are used. In other words, the changes in population of a compartment can be calculated using only the history used to develop the model.

3.3.1 THE SEIR MODEL FOR TUBERCULOSIS (TB)

For the standard SEIR model, the individuals in the population are divided into four compartments. The susceptibles (S) which refers to the healthy individuals that has not yet come into contact with TB bacterium. The exposed (E) are people who have come into contact with the disease but are not yet infective or infectious. The infective (I) are those who have become infected with TB and are able to transmit the disease and the recovered (R) are individuals who have recovered from TB.

The proportions of the individuals in the compartment of the population, i.e. S, E, I and R, at time t is denoted as S(t), E(t), I(t) and R(t) respectively. Figure 3.2 shows the flow of the compartmental SEIR model.

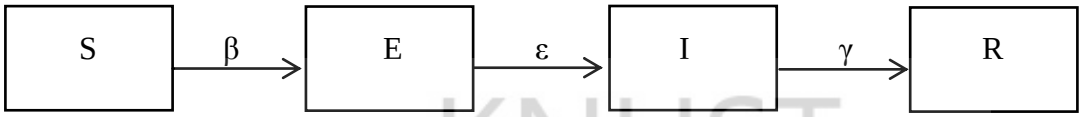

Figure 3.2: Flow chart showing the SEIR model.

3.3.2 MODEL ASSUMPTIONS

1. Age, sex, social status, race coupled with climatic conditions in the district does not affect the probability of an individual being infected.
2. The death rate of all individuals is balanced by a birth rate (birth and deaths occurs at equal rates).
3. We assume that once an individual is infected, he or she become exposed to the environment before becoming infectious.
4. The disease in transmitted in a closed environment. There is no emigration or immigration and there is neither birth nor death in the population. Hence the total population, N of individuals in the district remains constant.

3.3.3 MODEL EQUATIONS

Applying the assumption here, the total population, N is at full capacity (it value is between 0 and N).

Also, the individuals are likely to be infected by the infectious individuals in case of contact except those who are immune. Those who are undetected or late detected infectious are the ones contributing to the disease transmission and spread. Those detected are isolated to the hospital for immediate treatment and education.

Furthermore, those that are recovered become immune and are educated about the transmission of the disease. The transmission of the disease within the sanatorium is neglected.

Lastly, we assume that there is no treatment failure in the sanatorium and therefore a patient will recover or die.

The birth and death rate is μ. Hence μN will be the rate at which individuals are born into the susceptible class without any immunity and μS is the rate at which the leave it through death.

The rate at which the susceptible class changes is equal to the rate at which infections occur. This occurs when the disease is passed from an infective individual to a susceptible one. The number of susceptible – infective contacts is proportional to the product of $S(t)$ and $I(t)$.

Hence the rate of change in the susceptible individuals is

$$\frac{dS}{dt} = \mu N - \mu S - \frac{\beta SI}{N}, \text{ where } \beta SI \text{ is rate of infection.}$$

The term $\frac{\beta SI}{N}$ is negative because the number of susceptible individuals decreases. The rate at which individuals leave the susceptible population is equal to the rate at which they enter the exposed population.

The number of individuals in the exposed class increases since those in the susceptible class becomes exposed to the disease.

Let εE the rate which an exposed individual becomes infectious. Then the rate of change of the exposed population is given by

$$\frac{dE}{dt} = \frac{\beta SI}{N} - (\mu + \varepsilon)E$$

Let γI be the rate at which an infected individual may recover. The rate of change of the infective individuals will be

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

The rate of change of the recovered is given by

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

This leads to the following formulations of the SEIR model from the description, assumptions and compartmental diagram and was given as follows;

$$\frac{dS}{dt} = \mu N - \mu S - \frac{\beta SI}{N} \tag{3.11}$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - (\mu + \varepsilon)E \tag{3.12}$$

$$\frac{dI}{dt} = \varepsilon E - (\mu + \gamma)I \tag{3.13}$$

$$\frac{dR}{dt} = \gamma I - \mu R \tag{3.14}$$

The nonlinear system of differential equations formulated above has initial conditions $S(0) = S_0 > 0, E(0) = E_0 > 0, I(0) = I_0 > 0$ and $R(0) = R_0 > 0$.

Also, the rate of contact, the rate of infection, the recovery rate and the birth and death rate are all non-negative ($\beta > 0, \varepsilon > 0, \gamma > 0 and \mu > 0$ respectively).

Hence $N(t) = S(t) + E + I(t) + R(t)$ and

$$\frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \tag{3.15}$$

Since $\frac{dN}{dt} = 0$ and thus $N = S + E + I + R$ is a constant.

If we let $$\left.\frac{S(T)}{N} = s(t), \frac{E(T)}{N} = e(t), \frac{I(t)}{N} = i(t), and, \frac{R(t)}{N} = r(t)\right\} \tag{3.16}$$

Where $s(t), e(t)$, $i(t)$ and $r(t)$ are the respective fractions of the population for susceptible, exposed, infective and recovered individuals.

Then $$s(t) + e(t) + i(t) + r(t) = 1 \tag{3.17}$$

Variable	Definition
S(t)	The number of Susceptible individuals in the population at time, t
E(t)	The number of Exposed individuals in the population at time, t
I(t)	The number of Infected individuals in the population at time, t
R(t)	The number of Recovered individuals in the population at time, t
N	Total population

Table 3.1: Variables and definitions.

Parameter	Definition
β	The rate of contact. It is defined as the average number of effective contacts with other individuals (susceptible) per infective unit time.
ε	The rate at which the exposed individuals

	become infective or infectious.
γ	The rate at which the infectious individuals recover per unit time.
μ	The birth and death rate

Table 3.2: Parameters and their definitions.

The SEIR model is similar to the SIR endemic model except that it has an additional compartment E or the exposed class. This compartment reflects an inclusion of incubation period. Individuals in this class are infected but not infectious.

We divide equations (3.11) and (3.12) by N and then substitute equation (3.16) into equations (3.11) – (3.14) respectively to obtain

$$\frac{ds}{dt} = \mu - (\mu + \beta i)s \tag{3.18}$$

$$\frac{de}{dt} = \beta si - (\mu + \varepsilon)e \tag{3.19}$$

$$\frac{di}{dt} = \varepsilon e - (\mu + \gamma)i \tag{3.20}$$

$$\frac{dr}{dt} = \gamma i - \mu r \tag{3.21}$$

With initial conditions $s(0) = s_0 \geq 0, e(0) = e_0 \geq 0, i(0) = i_0 \geq 0, r(0) = r_0 \geq 0$

3.4 BASIC REPRODUCTIVE NUMBER, R_0

In epidemiology, the basic reproductive number (sometimes basic reproduction rate or ratio) of an infection is the number of cases one case generates on the average over the course of its infectious period.

This metric is useful because it helps determine whether or not an infectious disease can spread through a population. The roots of the basic reproduction concept can be traced through the work of Alfred Lotka, Ronald Ross, and others, but its first modern application in epidemiology was by George MacDonald in 1952, who constructed population models of the spread of malaria.

The Basic Reproduction number R_0 is the threshold for many epidemiological models. When $R_0 < 1$, the infection dies out in the long run (i.e. each infected individual produces one average less than one new infected individual). One the other hand, if $R_0 > 1$, the infection will be able to spread in a population (i.e. each infected individual produces more than one new infected individual).

For the purpose of our model, we use the approach by Ottar Bjørnstad (2005) to determine the basic reproductive number for this thesis.

From equation (3.19), if we let $\frac{de}{dt} = 0$, it becomes $e(t) = \frac{\beta si}{\mu + \varepsilon}$. Substituting the expression for $e(t)$ into equation (3.20), we have $\frac{di}{dt} = \left(\frac{\beta\varepsilon}{(\mu+\varepsilon)(\mu+\gamma)} s - 1 \right)$. And so $\left(\frac{\beta\varepsilon}{(\mu+\varepsilon)(\mu+\gamma)} \right)$ is the threshold quantity, R_0 (i.e. the basic reproductive number).

The threshold quantity can be interpreted as the product of the contact rate β and average fraction $\frac{\varepsilon}{\mu+\varepsilon}$ surviving the incubation period and average infectious period $\frac{1}{\mu+\gamma}$

Hence

$$R_0 = \frac{\beta\varepsilon}{(\mu+\varepsilon)(\mu+\gamma)} \tag{3.22}$$

(Bjørnstad, 2005).

Also, the number of contacts between susceptible and infective is given by

$$\sigma = \frac{\beta}{\gamma} \tag{3.23}$$

The SEIR model always has at least one solution given by $s = 1$, and $e = i = r = 0$. If the threshold quantity is greater than one then there is a unique endemic equilibrium solution in D where $D = \{e, i, r \mid e \geq 0, i \geq 0, r \geq 0, e + i + r \leq 1\}$, (Hethcote, 2000).

3.5 STEADY STATES OF THE SYSTEM

At the steady state, all the derivatives are equal to zero. That is, the equilibrium points can be obtained by equating the rate of changes to zero;

$$\frac{ds}{dt} = \frac{de}{dt} = \frac{di}{dt} = \frac{dr}{dt} = 0 \tag{3.24}$$

To determine the stability of the model, we need to evaluate the steady state of the system. In solving the equations, we need to consider two states. The disease-free steady state, where $i = 0$ and endemic steady state, where $i \neq 0$.

3.5.1 STEADY STATEOF THE DISEASE FREE – EQUILIBRIUM POINT

From equation (3.17), if we let $r(t) = 1 - s(t) + e(t) + i(t)$, then we have reduced equations (3.18) – (3.21) to a three dimensional system. Studying the global stability of the system of equations (3.18) – (3.20) in the region $s(t) + e(t) + i(t) : 0 \le s(t), e(t), i(t) \le 1, s + e + i \le 1$ is highly nontrivial, because to prove the stability of such a high dimensional system is not usually possible.

That is $\frac{ds}{dt} = 0, \frac{de}{dt} = 0, and \frac{di}{dt} = 0$

$$\Rightarrow \mu - (\mu + \beta i)s = 0 \tag{3.25}$$

$$\beta si - (\mu + \varepsilon)e = 0 \tag{3.26}$$

$$\varepsilon e - (\mu + \gamma)i = 0 \tag{3.27}$$

Solving equations (3.25) – (3.27) at $i = 0$, we get $s = 1$ and $e = 0$.

Hence, the equilibrium point for the disease-free steady state will be

$$s^*, e^*, i^* = 1, 0, 0 \tag{3.28}$$

3.5.2 STEADY STATE OF THE ENDEMIC EQULIBRIUM POINT

The endemic state of the system of equations (3.25) – (3.27) will be determined at $i \neq 0$.

We will let s_e, e_e and i_e represent the endemic equilibrium points for the respective states.

From equation (3.17), we make *e* the subject to get $e = 1 - s - i - r$. Substituting $e = 1 - s - i - r$ into equation (3.27) yields $\varepsilon = (1 - s - i - r) - (\mu + \gamma)i = 0$

$$\Rightarrow \varepsilon(1 - s) - \varepsilon i - \varepsilon r - (\mu + r)i = 0 \tag{3.29}$$

Equating equation (3.21) to zero and substituting the value of *r* in terms of *i* into equation (3.29), we get

$$\varepsilon(1 - s) - \varepsilon i - \frac{\varepsilon\gamma i}{\mu} - (\mu + \gamma)i = 0$$

$$\Rightarrow \varepsilon(1 - s_e) - \frac{i}{\mu}\left[\ \mu + \varepsilon \quad \mu + \gamma\ \right] = 0$$

$$\Rightarrow i_e = \frac{\mu\varepsilon\ \ 1 - s_e}{\mu + \varepsilon \quad \mu + \gamma} \tag{3.30}$$

From equation (3.25), we get

$$s_e = \frac{\mu}{\mu + \beta i_e} \tag{3.31}$$

Substituting the value of i_e from equation (3.30) into equation (3.31), we get

$$s_e = \frac{\mu}{\dfrac{\mu}{\mu + \beta\mu\varepsilon(1 - s_e)}} = \frac{1}{1 + R_0(1 - s_e)}$$

$$\Rightarrow (1 - s_e)(R_0 s_e - 1) = 0$$

$$\Rightarrow \text{Either } s_e = 1 \text{ or } s_e = \frac{1}{R_0}$$

The first solution $s_e = 1$ is trivial. Hence, substituting the second solution ($s_e = \frac{1}{R_0}$) for s_e into equation (3.30), we get

$$i_e = \frac{\mu\varepsilon}{\mu+\varepsilon \quad \mu+\gamma}\left(1-\frac{1}{R_0}\right) \tag{3.32}$$

Substituting the value of i_e from equation (3.32) into equation (3.27), we obtain

$$e_e = \frac{\mu+\gamma \;\; i_e}{\varepsilon} = \frac{\mu+\gamma}{\varepsilon}\frac{\mu\varepsilon}{\mu+\varepsilon \quad \mu+\gamma}\left(1-\frac{1}{R_0}\right) = \frac{\mu}{\mu+\varepsilon}\left(1-\frac{1}{R}\right)$$

Thus, the endemic equilibrium points for the respective states are as follows:

$$s_e, e_e, i_e, = \left(\frac{1}{R_0}, \frac{\mu \;\; R_0 - 1}{(\mu+\varepsilon)R_0}, \frac{\mu \;\; R_0 - 1}{\beta}\right) \tag{3.33}$$

3.6 STABILITY OF THE STEADY STATES / EQUILIBRIUM POINTS

To determine the stability of the system, we will consider linearizing the systems of equations (3.18) – (3.20) about the equilibrium points by taking the Jacobian of them.

That is

$$\frac{ds}{dt} = \mu - \mu s - \beta si$$

$$\frac{de}{dt} = \beta si - (\mu+\varepsilon)e$$

$$\frac{di}{dt} = \varepsilon e - (\mu+\gamma)i$$

The Jacobian matrix is given by

$$J(s,e,i)=\begin{bmatrix} -\mu-\beta i & 0 & -\beta s \\ \beta i & -\mu-\varepsilon & \beta s \\ 0 & \varepsilon & -\mu-\gamma \end{bmatrix} \tag{3.34}$$

3.6.1 STABILITY OF THE DISEASE-FREE EQUILIBRIUM

For the disease-free equilibrium, we evaluate the Jacobian matrix at the equilibrium points $s^*, e^*, i^* = 1.0.0$ and hence we get

$$J(s^*,e^*,i^*)=\begin{bmatrix} -\mu & 0 & -\beta \\ 0 & -\mu-\varepsilon & \beta \\ 0 & \varepsilon & -\mu-\gamma \end{bmatrix} \tag{3.35}$$

Solving for roots of the characteristic polynomial (with real coefficient) given in the Jacobian matrix leads to the characteristic equation given as:

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{3.36}$$

Where

$$\left.\begin{aligned} a_1 &= 3\mu+\varepsilon+\gamma \\ a_2 &= \begin{bmatrix} \mu+\varepsilon & \mu+\gamma & -\beta\varepsilon+\mu & 2\mu+\varepsilon+\gamma \end{bmatrix} \\ a_3 &= \mu\begin{bmatrix} \mu+\varepsilon & \mu+\gamma & -\beta\varepsilon \end{bmatrix} \end{aligned}\right\} \tag{3.37}$$

Using the Routh – Hurwitz stability criterion analysis we talked about earlier, the conditions $a_1 > 0$, $a_3 > 0$ and $a_1a_2 - a_3 > 0$ must hold. If these conditions are true, then all roots of the characteristic polynomial equation have negative real part, which concludes that there is a stable equilibrium.

3.6.2 STABILITY OF THE ENDEMIC EQULIBRIUM

The endemic steady state has equilibrium point given by

$$s_e, e_e, i_e, = \left(\frac{1}{R_0}, \frac{\mu \ R_0 - 1}{(\mu + \varepsilon) R_0}, \frac{\mu \ R_0 - 1}{\beta} \right) \tag{3.38}$$

The Jacobian matrix of this equilibrium point is evaluated to obtain

$$J(s_e, e_e, i_e) = \begin{bmatrix} -\mu R_0 & 0 & \dfrac{-\ \mu + \varepsilon \quad \mu + \gamma}{\varepsilon} \\ \mu \ R_0 - 1 & -\ \mu + \varepsilon & \dfrac{\mu + \varepsilon \quad \mu + \gamma}{\varepsilon} \\ 0 & \varepsilon & -\ \mu + \gamma \end{bmatrix} \tag{3.39}$$

Solving for the roots of the polynomial in the Jacobian matrix leads to the characteristic equation

$$\lambda^3 + b_1 \lambda^2 + b_2 \lambda + b_3 = 0 \tag{3.40}$$

Where

$$\left.\begin{aligned} b_1 &= \varepsilon + \gamma + \mu \ \ 2 + R_0 \\ b_2 &= \mu R_0 (2\mu + \varepsilon + \gamma) \\ b_3 &= \mu \ \ R_0 - 1 \left[\mu^2 + \mu(\varepsilon + \gamma) + \varepsilon\gamma \right] \end{aligned}\right\} \tag{3.41}$$

From the Routh – Hurwitz stability criterion, we need to determine the stability of the characteristic equation above. From the theorem, if the conditions $b_1 > 0$, $b_3 > 0$ and $b_1 b_2 - b_3 > 0$ are true, then all the roots of the characteristic equation have negative real part, which means a stable equilibrium.

From equation (3.41), the conditions are true for $R_0 > 1$ since $b_1 > 0$, $b_3 > 0$ and $b_1 b_2 - b_3 > 0$ (all non-negative), for all the values of the parameter and $R_0 > 1$, hence it is also true. In conclusion, by the Routh – Hurwitz stability criteria, the endemic steady state is stable when $R_0 > 1$.

3.7 THE HERD IMMUNITY THRESHOLD, H_1

The herd immunity threshold (H_1) is the percentage of the population that needs to be immunized to control the transmission of the disease. The endemicity of a disease depends on the basic reproduction number, R_0. This threshold value can predict whether the disease will approach and spread through the population or not.

Herd immunity (or community immunity) describes a form of immunity that occurs when the vaccination of a significant portion of a population (or herd) provides a measure of protection for individuals who have not developed immunity. Herd immunity theory proposes that, in contagious diseases that are transmitted from individual to individual, chains of infection are likely to be disrupted when large numbers of a population are immune or less susceptible to the disease. The greater the proportion of individuals who are resistant, the smaller the probability that a susceptible individual will come into contact with an infectious individual.

The equation (given by Diekmann and Heesterbeek, 2000) for estimating the herd immunity threshold is given as

$$H_1 = 1 - \frac{1}{R_0} \tag{3.42}$$

CHAPTER 4

MODEL ANALYSIS AND RESULTS

4.0 INTRODUCTION

In this chapter, we look at the epidemiology of tuberculosis using the data obtained. This will deal with the analysis of the models and the discussion of the results obtained.

Analysis of the data shows that tuberculosis is endemic in the district. The district is one of the most deprived and poorest in the Ashanti region of Ghana. As a result of this, the illiteracy rate of also at a very high level. Due to this, many of the inhabitants in the district do not have much idea on the tuberculosis disease. They normally link tuberculosis symptoms to 'African Believes' and superstitions and as a result, they link the infection as curses from gods.

Records obtained from the Amansie West district Health Directorate shows that tuberculosis is an endemic in the district. For instances, from 2007 to 2011, there has been an increase in the number of cases recorded. In 2007, 34 cases were diagnosed, 2008 (62 cases), 2009 (59 cases), 2010 (62 cases) and 2011 (70 cases). Figure 4.1 shows the trend of tuberculosis cases recorded in the district from 2002 – 2011.

We will use Matrix Laboratory (Matlab 7) to solve for the solutions of the differential equations involved in the model. Determination of the equilibrium points of the tuberculosis model will also be accomplished. Sensitivity analysis as well as numerical simulations on the parameter values to determine the effect of these values on the rate of spread on the disease will also be performed.

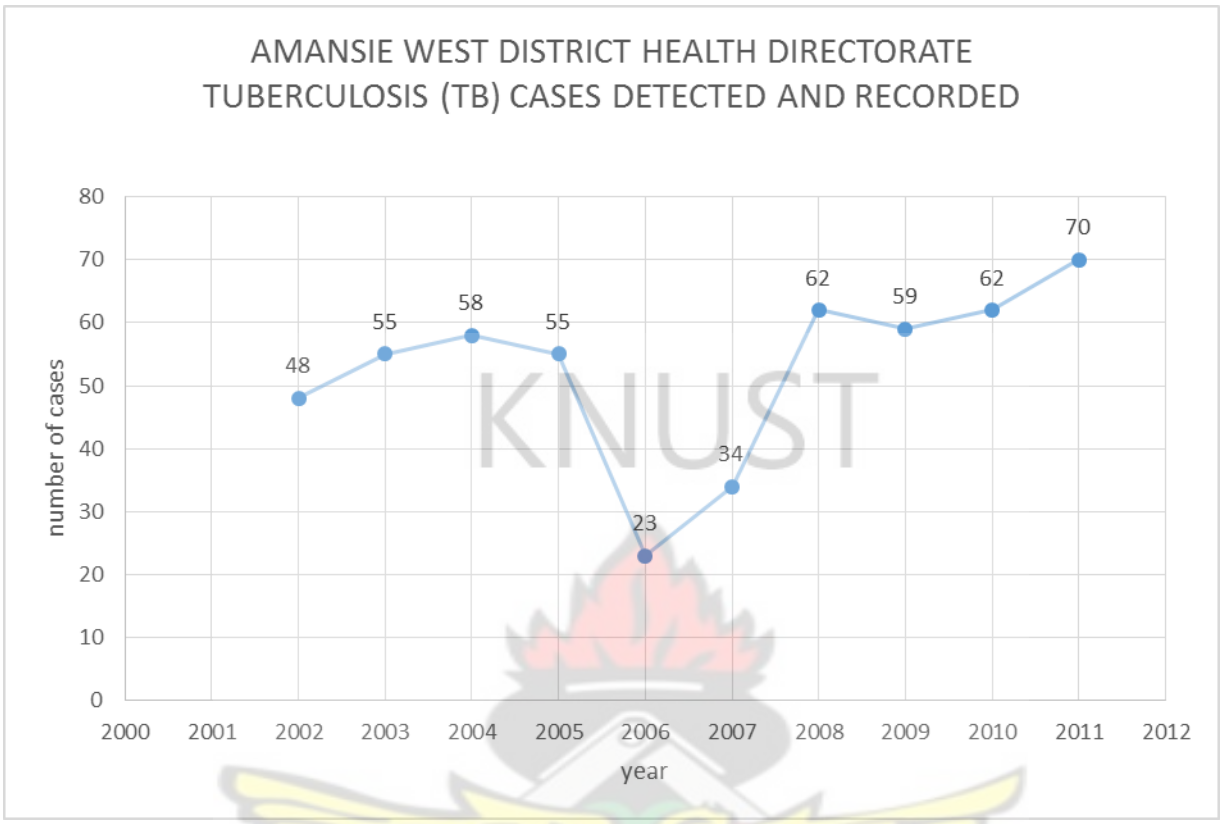

Figure 4.1. Trend of Tuberculosis cases in the Amansie West District from 2002 – 2011.

4.1 ESTIMATION OF PARAMETERS

The parameters are estimated based on the preceding information about the disease. The natural death rate in Ghana ie estimated to be 8.75 deaths per 1000 population or individuals, (INDEX MUNDI, 2012). We therefore have death rate, $\mu = 0.00875$.

For our model, we shall use the year 2002 as the base year. Records available at the district health directorate indicated that a total of 82 individuals were screen for TB infections and of this number, 48 were found to be infected with various strains of mycobacteria (mycobacterium

tuberculosis). We shall use this information to estimate the transmission rate. The transmission rate, $\beta = \frac{\text{effective contacts}}{\text{total contacts}} = \frac{48}{82} = 0.5853$ (Wikipedia, transmission risks and rates)

The incubation or latency period for tuberculosis is approximately within 6 weeks of being exposed. Therefore, the rate of infection, $\varepsilon = \frac{1}{\text{latency period}} = \frac{1}{6} = 0.1666$ per week .

The expected duration of infection is the inverse of the removal rate (Jones, 2007). For tuberculosis, the infectious or contagious period is 2 weeks until on drugs. Hence, the recovery rate, $\gamma = \frac{1}{\text{infectious period}} = \frac{1}{2} = 0.5$ per week .

The table below shows the estimates of the parameters used in the model.

PARAMETER	SYMBOL	VALUE
Death rate	μ	0.00875
Transmission rate	β	0.5853
Infectious rate	ε	0.1666
Recovery rate	γ	0.5000

Table 4.1: Parameters and their estimated values used in the model.

4.1.1 EQUATION OF THE SEIR MODEL WITH THE PARAMETERS

The values of the parameter estimates from Table 4.1 are substituted into equations (3.18) – (3.21) to obtain

$$\frac{ds}{dt} = 0.00875 - (0.00875 + 0.5853i)s \tag{4.01}$$

$$\frac{de}{dt} = 05853i - 0.17535e \tag{4.02}$$

$$\frac{di}{dt} = 0.1666e - 0.50875i \tag{4.03}$$

$$\frac{dr}{dt} = 05i - 0.00875r \tag{4.04}$$

4.1.2 ESTIMATION OF THE BASIC REPRODUCTIVE NUMBER

From equation (3.22), the basic reproduction number for the SEIR model is given by

$$R_0 = \frac{\beta\varepsilon}{\mu+\varepsilon \quad \mu+\gamma} = \frac{0.5853 \times 0.1666}{0.00875+0.1666 \quad 0.00875+0.5} = 1.09305 > 1 \tag{4.05}$$

Since $R_0 > 1$, the prevalence of Tuberculosis will result in an epidemic. This is due to the fact that rate of transmission is greater than the recovery rate.

The number of contacts between susceptible individuals and the infective ones is calculated from equation (3.23) and is given by

$$\sigma = \frac{\beta}{\gamma} = \frac{0.5853}{0.5000} = 1.1706 \tag{4.06}$$

This shows that an average of one tuberculosis patient contacts 1.1706 susceptible individuals during an infectious period.

4.1.3 ESTIMATION OF THE STEADY STATES

In this thesis, system of equations (3.18) – (3.21) for the SEIR model for tuberculosis has two steady states; the disease – free equilibrium (i = 0) and the endemic equilibrium (i ≠ 0), and they are given as follows:

4.1.3.1 ESTIMATION OF THE DISEASE-FREE EQULIBRIUM POINT

From equation (3.28), the equilibrium point of the disease – free steady state was determined to be

$$s^*, e^*, i^* = 1, 0, 0 \tag{4.07}$$

4.1.3.2 ESTIMATION OF ENDEMIC EQULIBRIUM POINT

The estimates of the endemic steady state equilibrium were determined from equation (3.33) and is given by

$$s_e, e_e, i_e = \left(\frac{1}{R_0}, \frac{\mu(R_0 - 1)}{\mu + \varepsilon \ R_0}, \frac{\mu(R_0 - 1)}{\beta} \right)$$

$$= \left(\frac{1}{1.09305}, \frac{0.00875(1.09305 - 1)}{0.00875 + 0.1666 \ \times 1.09305}, \frac{0.00875(1.09305 - 1)}{0.5853} \right)$$

$$= 0.914871, 0.00042479, 0.00139106 \tag{4.08}$$

4.2 STABILITY ANALYSIS

4.2.1 STABILITY ANALYSIS OF THE DISEASE-FREE EQULIBRIUM

The disease – free equilibrium point for the model was determined as $s^*, e^*, i^* = 1, 0, 0$. We therefore determine the stability of the equilibrium point using the Jacobian matrix from equation (3.35). Hence, we obtain

$$J\ s^*, e^*, i^* = \begin{bmatrix} -0.00875 & 0 & -0.5853 \\ 0 & -0.17535 & 0.5853 \\ 0 & 0.1666 & -0.50875 \end{bmatrix} \tag{4.09}$$

We determine the roots of the character polynomial equation from the equation (3.37), as given in the Jacobian matrix as follows:

$$a_1 = \left[\ 3 \times 0.00875\ + 0.1666 + 0.5 \right] = 0.69285$$

$$a_2 = \left[\ 0.00875 + 0.1666\ \ 0.00875 + 0.5\ -\ 0.5853 \times 0.1666\ + 0.00875\ (2 \times 0.00875) + 0.1666 + 0.5\ \right] = -2.3158 \times 10^{-3}$$

$$a_3 = 0.00875\left[\ 0.00875 + 0.1666\ \ 0.00875 + 0.5\ -\ 0.5853 \times 0.1666\ \right] = -7.2639 \times 10^{-5}$$

Note: $a_1 a_2 - a_3 = \left[\ 0.69285 \times -2.3158 \times 10^{-3}\ -(-7.2639 \times 10^{-5})\ \right] = -1.5318 \times 10^{-3}$

Therefore, the characteristic equation is given by

$$\lambda^3 + 0.69285\lambda^2 - 2.3158 \times 10^{-3}\lambda - 7.2639 \times 10^{-5} = 0 \tag{4.10}$$

The results indicates that $a_1 > 0$, $a_2 < 0$, and $a_1 a_2 - a_3 < 0$. From the Routh – Hurwitz stability criterion, these conditions does not hold. Hence, the disease – free equilibrium is an unstable

steady state. This means that when an individual infected with mycobacterium tuberculosis is present in a susceptible population, it will eventually result in an outbreak of the disease.

4.2.2 STABILITY OF THE ENDEMIC EQULIBRIUM

From equation (4.08), the endemic equilibrium point was given as

$s_e, e_e, i_e = 0.914871, 0.00042479, 0.00139106$. We therefore determine the Jacobian matrix corresponding to the endemic equilibrium point from equation (3.39) and we obtain

$$J\ s_e, e_e, i_e = \begin{bmatrix} 9.56141875\times10^{-3} & 0 & -0.53547 \\ 8.141875\times10^{-4} & -0.17535 & 0.53547 \\ 0 & 0.1666 & -0.50875 \end{bmatrix} \tag{4.11}$$

The roots of the characteristic polynomial equation given in equation (3.41) are obtained as follows

$$b_1 = 0.1666 + 0.5 + 0.00875(2 + 1.09305) = 0.69366$$

$$b_2 = \left[0.00875\times1.09305\ \ 2\times0.00875 + 0.1666 + 0.5 \right] = 6.5429\times10^{-3}$$

$$b_3 = 0.00875\ \ 1.09305 - 1\left[0.00875^2 + 0.00875\ \ 0.1666 + 0.5\ +\ \ 0.1666\times0.5 \right] = 7.2633\times10^{-5}$$

Note: $b_1 b_2 - b_3 = 0.69366\times(6.5429\times10^{-3}) - (7.2633\times10^{-5}) = 4.4660\times10^{-3}$

The characteristic equation is given by

$$\lambda^3 + 0.69366\lambda^2 + 6.5429\times10^{-3}\lambda + 7.2633\times10^{-5} = 0. \tag{4.12}$$

The values of the roots of the characteristic polynomial equation satisfy the Routh – Hurwitz stability criterion. This is because $b_1 > 0, b_2 > 0$, and $b_1 b_2 - b_3 > 0$ .Therefore, the endemic steady state is asymptotically stable.

4.2.3 ESTIMATION OF THE HERD IMMUNITY THRESHOLD, H_1

The herd immunity threshold shows the percentage or proportion of the population that needs to be immunized to control the transmission of the disease when there is an outbreak.

From equation (3.42), the herd immunity threshold is given as

$$H_1 = 1 - \frac{1}{1.09305} = 0.0851 \tag{4.13}$$

Therefore, to control an epidemic, about 8.51% of the population has to be immunized when there is an outbreak.

4.3 SENSITIVITY ANALYSIS

Sensitivity analysis deals with the study of how the uncertainty in the output of a mathematical model or system (numerical or otherwise) can be apportioned to different sources of uncertainty in its inputs (Saltelli *et. al*., 2008). A related practice is uncertainty analysis, which has a greater focus on uncertainty quantification and propagation of uncertainty.

Sensitivity analysis can be useful for the purpose of understanding of the relationships between input and output variables in a system or model. For our model, the input parameters were death rate (μ), transmission rate (β), infectious rate (ε) and recovery rate (γ).We shall analyse how

changes in the transmission rate and the recovery rate affects the endemicity (i.e. the threshold parameter, R_0) of the two non – negative equilibria, namely the disease – free equilibrium and the endemic equilibrium. We used the parameter values given in Table 4.1for the SEIR model equations (3.18) – (3.21).

4.3.1 SENSITIVITY ANALYSIS OF THE DISEASE – FREE EQUILIBRIUM

We analyse the effect on the reproduction number, R_0 and the stability of the disease – free equilibrium. This will be done when the value of the parameter β changes whilst μ, ε and γ remain the same and also, when γ changes whilst μ, β and ε are maintained.

1. If $\beta$is increased and γ is maintained, i.e. $\beta = 0.6853$ and $\gamma = 0.5$,

$$\left.\begin{aligned} &\Rightarrow R_0 = 1.2798 > 1 \\ &a_1 = 0.69285 > 0 \\ &a_2 = -0.018975 < 0 \\ &a_3 = -0.000218 < 0 \\ &a_1 a_2 - a_3 = -0.012928 < 0 \end{aligned}\right\} \quad (4.14)$$

   From these results, the disease-free equilibrium is unstable.

2. If β is reduced and γ is maintained. i.e. $\beta = 0.4853$ and $\gamma = 0.5$,

$$\left.\begin{aligned} &\Rightarrow R_0 = 0.9063 < 1 \\ &a_1 = 0.69285 > 0 \\ &a_2 = 0.014344 > 0 \\ &a_3 = 0.000731 > 0 \\ &a_1 a_2 - a_3 = 0.009207 > 0 \end{aligned}\right\} \quad (4.15)$$

   Hence, we have a stable disease – free equilibrium.

3. If β remains the same and γ is increased. i.e. $\beta = 0.5853$ and $\gamma = 0.6$,

$$\left.\begin{aligned} &\Rightarrow R_0 = 0.9135 < 1 \\ &a_1 = 0.79285 > 0 \\ &a_2 = 0.016094 > 0 \\ &a_3 = 0.0000807 > 0 \\ &a_1 a_2 - a_3 = 0.012679 > 0 \end{aligned}\right\} \quad (4.16)$$

Hence, we have a stable disease – free equilibrium.

4. If β is maintained and γ is reduced. i.e. $\beta = 0.5853$ and $\gamma = 0.4$,

$$\left.\begin{aligned} &\Rightarrow R_0 = 1.3605 > 1 \\ &a_1 = 0.59285 > 0 \\ &a_2 = -0.020725 < 0 \\ &a_3 = -0.000226 < 0 \\ &a_1 a_2 - a_3 = -0.012061 < 0 \end{aligned}\right\} \quad (4.17)$$

Hence, the disease – free equilibrium is unstable.

Conclusion: From the above results, as the transmission rate increases or the recovery rate decreases, $R_0 > 1$ and the disease – free equilibrium is unstable. This indicates that, the disease will spread when there is an outbreak. Apparently, as the transmission rate decreases or the recovery rate increases, $R_0 < 1$and hence the disease – free equilibrium will be stable. This therefore means that the disease will not spread.

4.3.2 SENSITIVITY ANALYSIS OF THE ENDEMIC EQUILIBRIUM

We used the same scenarios as we did for the disease – free equilibrium in section 4.0.7.1.

1. If β increases and γ remains the same. i.e. β = 0.6853 and γ = 0.5,

$$\left.\begin{aligned} &\Rightarrow R_0 = 1.2798 > 1 \\ &b_1 = 0.69529 > 0 \\ &b_2 = 0.00766 > 0 \\ &b_3 = 0.000218 > 0 \\ &b_1 b_2 - b_3 = 0.005108 > 0 \end{aligned}\right\} \quad (4.18)$$

The endemic equilibrium is stable.

2. If the β is reduced and γ remains the same. i.e. β =0.4853 and γ = 0.5,

$$\left.\begin{aligned} &\Rightarrow R_0 = 0.9063 < 1 \\ &b_1 = 0.69203 > 0 \\ &b_2 = 0.005424 > 0 \\ &b_3 = -0.0000755 < 0 \\ &b_1 b_2 - b_3 = 0.00382 > 0 \end{aligned}\right\} \quad (4.19)$$

Hence, the endemic equilibrium is unstable.

3. If β remains the same and γ increases. i.e. β = 0.5853 and γ = 0.6,

$$\left.\begin{aligned} &\Rightarrow R_0 = 0.9135 < 1 \\ &b_1 = 0.79209 > 0 \\ &b_2 = 0.000926 > 0 \\ &b_3 = -0.0000807 < 0 \\ &b_1 b_2 - b_3 = 0.000814 > 0 \end{aligned}\right\} \quad (4.20)$$

Therefore, the endemic equilibrium is unstable.

4. If β remains and γ is reduced. i.e. β = 0.5853 and γ = 0.4,

$$\left.\begin{aligned} &\Rightarrow R_0 = 1.3604 > 1 \\ &b_1 = 0.59600 > 0 \\ &b_2 = 0.00695 > 0 \\ &b_3 = 0.000226 > 0 \\ &b_1 b_2 - b_3 = 0.00392 > 0 \end{aligned}\right\} \tag{4.21}$$

The endemic equilibrium is stable.

In conclusion, when the transmission rate is increases or the recovery rate decreases, $R_0 > 1$and hence the endemic equilibrium is stable. This means that the disease will spread when there is an outbreak. On the other hand, as the transmission rate decreases or the recovery rate increases, $R_0 < 1$, and the endemic equilibrium is in an unstable state. This therefore means that the disease will not spread.

4.4 SENSITIVITY ANALYSIS BY SIMULATION

In this section, we perform numerical simulations on the SEIR model for tuberculosis using the data we have. We simulate our model using Matlab R2010a and the value of the parameters as found in Table 4.1. The Matlab codes are found in appendix 1. We tried to look at the effects and the changes the will occur in the model when the values of each of the compartments of the model are altered .i.e. Susceptible(S), Exposed(E), Infected(I) and the Removed(R). We measured our time in months for a period of one year depending on the period of how tuberculosis prevalence occurs. We made some assumptions and graphing to see the effect of changes in each compartment of the model.

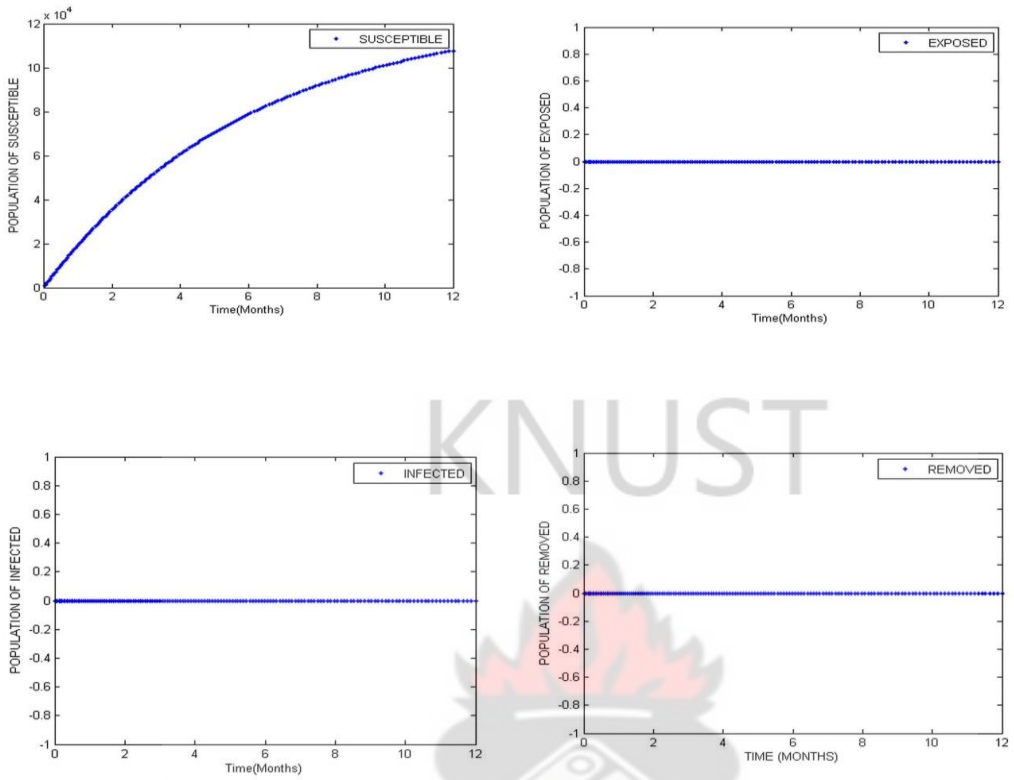

Figure 4.2. S = 500, E = 0, I = 0, R = 0.

We first start with a total population of 500 individuals in which they all belong to the susceptible. This implies that there are no exposed, infected and recovered individuals in the population. The simulation gave the following graphs as shown in Figure 4.2.

It can be noticed from the graph that, the number of susceptibles is constant at 500 throughout the period of time under study whiles the number of exposed, infected and recovered are all at a constant number of zero during the entire period under study. This implies that there will be not be any effect on each compartment when all the population belong to the susceptible.

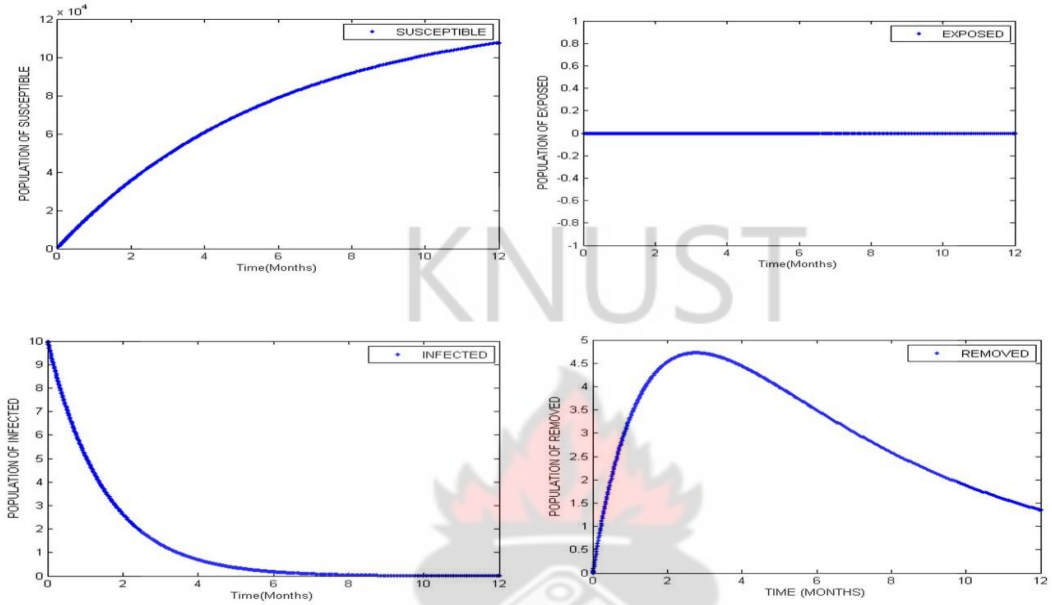

Figure 4.3: S = 490, E = 0, I = 10, R = 0

We make further adjustment of our system and analyse the results by introducing 10 infected, thereby reducing the susceptibles to 490, no exposed and no recovered individuals into the system.

It will be observed from Figure 4.3 that the number of susceptibles increased with time and became constant getting to the end of the period under study. There is also, no effect on the exposed individuals and the 10 infected reduced with time to zero. The 10 infected moves into the recovered compartment and no infection are recorded again. This may be due to early detection and probably seeking immunization. This will eventually cause the disease to die out anyway. By so doing, the recovered individuals begins to increase as the infected recovered and with time, they all move back to the susceptible compartment.

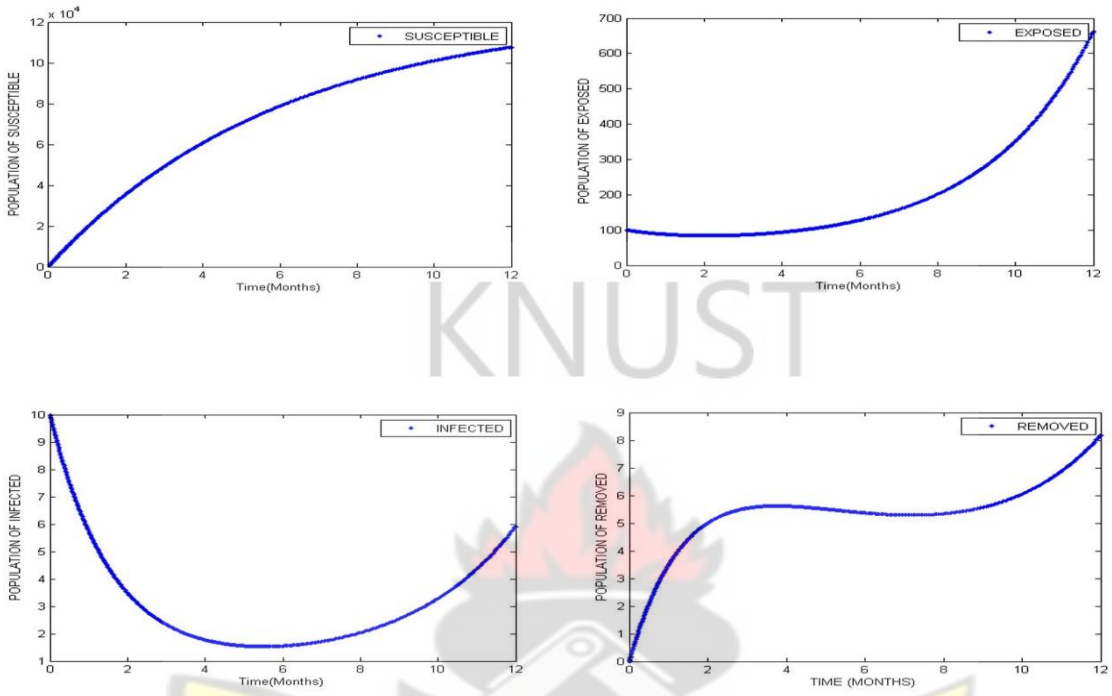

Figure 4.4: S = 390, E = 100, I = 10, R = 0.

The final part of our simulation place emphasis on the exposed class. This will help put the disease under control in the district. With the introduction of some exposed individuals into our system, the number of infected tend to decrease but with time, they increase later. The susceptible class was stable at a point in time within the period of study but increase in number afterwards. When we introduce the infected into our system, with no exposed individuals, the disease failed to spread within some short period of time. The introduction of some exposed individuals will increase the infected after some period of time and hence the disease will spread again.

4.5 DISCUSSION OF RESULTS

In this research, a mathematical model of the prevalence and transmission of tuberculosis in Amansie West district of the Ashanti Region is studied. We attempted to use the standard SEIR differential equation model to predict the transmission and spread of tuberculosis. By analyzing the model, we found a threshold parameter, R_0, which is the basic reproductive number. It is noted that when $R_0 < 1$, then the epidemic will not spread and when $R_0 > 1$, the disease will persist in the population and hence become an endemic. The model has two non-negative equilibria, namely, the disease – free equilibrium and the endemic equilibrium. We discussed the existence and stability of the disease – free and endemic equilibria of the model and sensitivity analysis of the model were performed. The Herd immunity threshold, H_1, which shows the percentage or proportion of the population that needs to be immunized to control the transmission of the disease when there is an outbreak, was also considered.

From the results, the basic reproductive number for the SEIR model was estimated as $R_0 = 1.09305$. As indicated, $R_0 > 1$ and this means that, the disease will spread in case there is an outbreak. Incidentally, an average of one tuberculosis patient contacts 1.1706 susceptible individuals during an infectious period.

The steady states of the two non – negative equilibria were also found and analyzed. The disease – free equilibrium, $(s^*, e^*, i^*) = (1, 0, 0)$, was found to be unstable (saddle point) whiles the endemic equilibrium, $(s_e, e_e, i_e) = (0.914871, 0.00042479, 0.00139106)$, was also found to be asymptotically stable. These equilibrium points and analyses showed that the presence of an infected individual in a susceptible population will result in an outbreak of the disease.

In the sensitivity analysis, we tried to understand the relationship between the inputs and output variables of the model. By doing so, we were looking at how changes in the transmission rate (β) and the recovery rate (γ) affects the endemicity of the disease – free equilibrium and the endemic equilibrium. In this case, we used the basic reproductive number, R_0.

It was seen that, an increase in the transmission rate or a decrease in the recovery rate will make $R_0 > 1$ and the disease – free equilibrium is unstable. This indicates that, the disease will spread when there is an outbreak. Apparently, as the transmission rate decreased or the recovery rate increased, we had $R_0 < 1$and hence the disease – free equilibrium is also asymptotically stable. This therefore means that the disease will not spread.

Also, when the transmission rate was increased or the recovery rate decreased, we had $R_0 > 1$and hence the endemic equilibrium is stable. This means that the disease will spread when there is an outbreak. On the other hand, as the transmission rate decreases or the recovery rate increases, $R_0 < 1$, and the endemic equilibrium is in an unstable state. This therefore means that the disease will not spread.

It was also found in our model that, increasing the number of infective individuals reduces the number of susceptibles whiles the number of exposed individuals also increases. This concludes that, if stakeholders fail to put in place proper measures to control and eradicate the disease, it will spread. Hence, immunization programmes as well as education on tuberculosis must be intensified throughout the communities and the country as a whole so that the disease can be curbed down.

From our thesis, the herd immunity threshold was estimated to be 0.0851. This means that, about 8.51% of the population need to be immunized in order to control the spread of the disease. This is can be effective when early detections are reported at tuberculosis clinics for appropriate

treatments. Children should also be vaccinated with Bacillus Calmette–Guérin (BCG) vaccines. This will help effectively disseminate the disease in them. When the percentage of immune individuals exceeds the herd immunity, the disease will fail to spread. Hence 8.51% shows the minimum percentage of the population that must be screened and immunized on regular basis in order for the disease not to spread in the district.

From the simulations, it was found out that, an increase in the number of immunized individuals in the population will also increase the level of immunity. This is to say that, if immunization are done on regular basis, especially among children will help increase the number of immuned individuals thereby decreasing the spread of tuberculosis within the community. From this, we can conclude that all children must be vaccinated to avoid making them exposed, because every child that is not immunized increases the number of exposed individuals in the system and this puts a threat in the district.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.0 INTRODUCTION

In this chapter, a conclusion and recommendations are made. This will enable stakeholders, the government, public health agencies and health care providers to enable them determine how best to allocate resources for tuberculosis education, prevention and treatment in the country.

5.1 CONCLUSION

In search for the possible way of eradicating tuberculosis, there is the need to address the issue of the mechanism of the transmission and prevalence of the disease.

Many communicable diseases have been modeled using differential equations. The purpose of this thesis was to examine in detail, a mathematical models for the transmission and prevalence of tuberculosis and then to solve them using differential equations. The following assumptions were made before the model was formulated.

We assumed that the population has a constant size N, where birth and death occur at equal rates and that newborns are susceptible (no inherited immunity). Also, there is no restriction of age, mobility or other social factors. We also assumed once infected with tuberculosis bacteria, you become exposed to the environment before becoming infectious.

Based on the assumptions above, which are also consistent with the conditions in Ghana, the tuberculosis model satisfies the SEIR epidemiological model discussed in chapter three, hence we adopted it to study the prevalence of tuberculosis by classifying the population as susceptible (S), exposed (E), infectious (I) and recovered (R). All parameters are as described in chapter four. The model has shown success in attempting to predict the causes of transmission within a population. From the model, it was noticed that the spread of a disease largely depend on the contact rates with infected individuals within a population.

The model gave a basic reproductive number, $R_0 = 1.09305 > 1$. This means that the disease is endemic in the district and this is due to the high level of the transmission rate in the population.

From the model, the herd immunity threshold was found to be 8.51%. It was also realized that if the proportion of the population that is immune exceeds the herd immunity threshold for the disease, then the disease can no longer persist in the population. Thus if this level can be exceeded by mass screening and immunization, then the disease can be eliminated.

The model also pointed out that early detection has a positive impact on the reduction of tuberculosis transmission; that is there is a need to detect new cases as early as possible so as to provide early treatment for the disease. More people should be educated in order to create awareness to the disease transmission so that society will be aware of this deadly disease.

5.2 RECOMMENDATIONS

After carefully analyzing the study, we recommend the following in order to help in controlling and eradicating tuberculosis from Ghana

1. Traditionalist and spiritualist in the community must be involved in TB programmes in their localities for them to be aware of the signs and symptoms of the disease as well as

the consequences of defaulting treatment. This would help them identify cases in their hide – outs and prayer camps and refer for medical attention while they see the spiritual side of the disease.

2. The government should intensify the education on TB in the churches, schools, on durbar grounds, etc. to sensitize the individuals in the communities of its existence, free access to medical care and treatment duration.
3. The government should integrate TB programmes into other existing health services such as outreach, maternal and child welfare programmes among others in order to increase its awareness.
4. Chemical sellers must be enlightened on signs and symptoms of TB for them to detect cases that might be reported at their facility. This will enable individuals to seek the appropriate medical attention and care.
5. TB patients who migrate must be given referral to the clinics in such areas for continuation of treatment.
6. Further research work is also recommended in order to help develop other suitable models to help public health professionals to adopt other strategies to control and eradicate the disease. We therefore suggest SEIR model of tuberculosis in a non – constant population and a model of tuberculosis in a heterogeneous population using SEIR model for further research work.

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APPENDIX

M-File for tuberculosis model

```
function dy=model(t,y,beta,gamma,mu,epsilon)

N= 124507;

dy=zeros(4,1);

dy(1)= mu*N-mu*y(1)-((beta*y(1)*y(3))/N);

dy(2)= ((beta*y(1)*y(2))/N)-(mu+epsilon)*y(2);

dy(3)= epsilon*y(2)-(mu+gamma)*y(3);

dy(4)= gamma*y(3)-mu*y(4);
```

Scripts Used in Calling the M-File for Tuberculosis Model

```
mu = 0.00875;

epsilon = 0.1666;

beta = 0.5853;

gamma = 0.5;

N= 124705;

options = odeset('RelTol',1e-9,'AbsTol',1e-9); [T,Y] = ode45(@emmaseir,[0 12],[390 100 10

0],options,beta,gamma,epsilon,mu);

figure(1)

plot(T,Y(:,1),'.')

legend('SUSCEPTIBLE')

xlabel('Time(Months)');ylabel('POPULATION OF SUSCEPTIBLE');

figure(2)
```

```
plot(T,Y(:,2),'.')
legend('EXPOSED')
xlabel('Time(Months)');ylabel('POPULATION OF EXPOSED');
figure(3)
plot(T,Y(:,3),'.')
legend('INFECTED')
xlabel('Time(Months)');ylabel('POPULATION OF INFECTED');
figure(4)
plot(T,Y(:,4),'.')
legend('REMOVED')
xlabel('TIME (MONTHS)');ylabel('POPULATION OF REMOVED');
```