MATHEMATICAL MODELLING OF THE TUBERCULOSIS EPIDEMIOLOGY

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KUALA LUMPUR

2020

MATHEMATICAL MODELLING OF THE TUBERCULOSIS EPIDEMIOLOGY

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THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

INSTITUTE OF MATHEMATICAL SCIENCES
FACULTY OF SCIENCE
UNIVERSITI MALAYA
KUALA LUMPUR

2020

UNIVERSITI MALAYA

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Matric No: **SHB160013**

Name of Degree: **DOCTOR OF PHILOSOPHY**

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MATHEMATICAL MODELLING OF THE TUBERCULOSIS EPIDEMIOLOGY

ABSTRACT

This project analyses the tuberculosis (TB) epidemic mathematically using compartmental modelling approach. Three models are presented to discuss drug susceptible and multi-drug resistant TB. The first model presented has 4 compartments; susceptible, exposed, infectious and recovered. The relevance of the exposed class in managing TB is analysed and found to be useful in delaying the eventual onset of the infection. Compared to previous researches, our results significantly show that when efforts are made such that no infected individual bypasses the exposed class and progresses directly to the infectious, the TB epidemic is successfully combatted. Also, the model is used to show that reinfection has no significant relevance to TB incidence. The model is further extended to accommodate vaccination compartment. The vaccination compartment is included to understand the usefulness of a prophylactic vaccine in curbing the growth of TB epidemic. The intrinsic features to be considered in the formulation of the vaccine as well as the effective proportion of people to be vaccinated to achieve herd immunity are presented. A vaccine that would combat the infectivity rate of TB by half displays its potency in drastically reducing the TB incident rate. Placing the patient on good diets also gives a better result as discussed in the optimal control section. Furthermore, a model to analyse the relevance of quarantine in managing the incident rate of multi-drug resistant TB (MDR-TB) is formulated. The quarantine compartment is created to harbour individuals that develop MDR-TB. This shows its efficacy to help; monitor the recovery rate of individuals with MDR-TB, keep the MDR-TB patients under watch regarding their medications, and as well prevent the MDR-TB patients from mingling with susceptible individuals. This model is shown to undergo backward bifurcation which gives a vital information on how to deal with the epidemic.

In general, the equilibria points of all the 3 models are shown to be locally asymptotically stable whenever the basic reproduction number is less than unity ($R_0 < 1$) and also, globally asymptotically stable at the disease free equilibrium (DFE). The global asymptotic stability of the endemic equilibria points (EEP) of the first and last models are established using Lyapunov function while that of the second model is established using Dulac function. These global stabilities are established at special cases.

Keywords: Tuberculosis, mathematical model, vaccination, quarantine, bifurcation, stability

PEMODELAN MATEMATIK EPIDEMIOLOGI TUBERKULOSIS

ABSTRAK

Projek ini menganalisa epidemik tuberkulosis (TB) secara pendekatan matematik melalui permodelan kompartmen. Tiga model dibentangkan untuk membincangkan jangkitan penyakit TB yang mempunyai ketahanan terhadap ubat-ubatan. Model pertama yang dibentangkan mempunyai 4 petak iaitu mudah dijangkiti, terdedah, menular dan pulih. Perkaitan antara petak kelas terdedah menunjukkan pertalian yang baik dan berguna bagi menangguhkan berlakunya jangkitan dalam pengurusan penyakit TB. Selanjutnya, apabila usaha-usaha dibuat bagi memastikan tiada individu yang dijangkiti melangkau proses kelas terdedah daripada terus boleh dijangkiti, epidemik TB boleh dibanteras dengan jayanya. Model ini juga menunjukkan kadar jangkitan semula TB tiada berkaitan boleh berlaku. Model ini diperluaskan lagi untuk menampung petak vaksinasi. Ruang vaksinasi dimasukkan untuk memahami kegunaan vaksin profilaksis dalam membendung pertumbuhan wabak TB. Ciri-ciri intrinsik untuk dipertimbangkan dalam perumusan vaksin serta bahagian berkesan orang yang akan divaksin untuk mencapai kekebalan kawanan dibentangkan. Vaksin yang akan memerang separuh kadar infeksi TB memaparkan potensinya secara drastik mengurangkan kadar insiden TB. Pesakit yang mengamalkan pemakanan yang baik memberikan hasil yang memuaskan seperti yang dibincangkan dalam bahagian kawalan optimum. Tambahan lagi, model untuk menganalisis kaitan kuarantin dalam menguruskan kadar insiden TB (MDR-TB) tahan pelbagai ubat telah dirumuskan. Petak kuarantin yang ditambah untuk melindungi individu yang membangunkan MDR-TB. Ini menunjukkan keberkesanannya untuk membantu memantau kadar pemulihan individu dengan MDR-TB, mengekalkan pesakit MDR-TB di bawah pengawasan mengenai ubat-ubatan mereka, dan juga menghalang pesakit MDR-TB daripada bergaul dengan individu yang mudah terpengaruh. Model ini ditunjukkan dengan menjalani bifokasi mundur yang memberi maklumat penting

mengenai bagaimana menangani epidemik. Secara umum, titik kesamaan dari semua 3 model ditunjukkan secara asimptotik stabil apabila bilangan pembiakan asas adalah kurang daripada perpaduan $(R_0 < 1)$ dan juga secara asimtotiknya stabil di keseimbangan bebas penyakit (DFE). Kestabilan menyeluruh asimptotik titik keseimbangan endemik (EEP) model pertama dan terakhir telah ditubuhkan menggunakan fungsi Lyapunov manakala model kedua ditubuhkan menggunakan fungsi Dulac. Ketidakupayaan global ini ditubuhkan pada kes-kes khas.

Kata Kunci: Tuberkulosis, model matematik, vaksinasi, kuarantin, bifurkasi, kestabilan

ACKNOWLEDGEMENTS

"And you are not given from the knowledge except little" (Q17:85). All praises and adorations are to Allah (SWT) who created man and taught him how to express himself. I give Him all the glory for the successful completion of my program.

A very special appreciation to Associate Professor Dr. Wan Ainun Mior Othman who doubles as my supervisor and the head of the Institute of Mathematical Sciences (ISM) during my candidature. Despite your busy schedule, you have been able to give me necessary guidance, jazaakiLlahu khayran jazaai. To Dr. Kumaresan Nallasamy, thanks for being there. The "Nos" of Encik Abu Omar Awang has actually brought out the better part of me as they would always invoke reasoning, I say thank you. To all the students and staffs of ISM, I say thank you all. And to my colleagues at ISM, especially Mr. Amos, Mr. Habu, Mr. Seun and Miss Nabeelah, thank you all for being there. To the Nigerian Students' Community, University of Malaya (NiSCUM) and faculty of science postgraduate club, thanks for giving me the opportunity to serve as Chairman and representative respectively.

A special thanks to the management and staffs of the University of Ilorin, Nigeria and particularly, the head and staffs of the Department of Mathematics, I am grateful.

This academic pursuit would not have been achievable without the support of my parents; Engr. Musa and Alhaja Khadijat Yeketi, certainly your rewards are with Allah (SWT), and the best I can wish for you both is being admitted to paradise without reckoning. Same is my wish for my in-laws; Mr. and Mrs. Laaro.

To my siblings; Mrs. Halimat, Mrs., Rahmat, Dr. AbdulQaadir, Engr. Nafiu, Mrs. Sherifat and Miss Rofiat among others, jazzakumuLlahu khayran jazaai. And my wonderful set of brothers-in-law and their kids, jazaakumuLlahu khayran jazaai.

To my better half, Haleemah, I wish you the best in this world and the hereafter. Thanks for your support and understanding. Take care of my wonderful boy, Baba.

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LIST OF SYMBOLS AND ABBREVIATIONS

CDC	:	Centers for disease control and prevention
DFE	:	Disease free equilibrium
DR-TB	:	Drug resistant TB
DS-TB	:	Drug susceptible TB
DST	:	Drug susceptible testing
EEP	:	Endemic equilibrium point
LTBI	:	Latent tuberculosis infection
MDR-TB	:	Multidrug resistant TB
TB	:	Tuberculosis
XDR-TB	:	Extensively drug resistant TB
WHO	:	World health organisation

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CHAPTER 1: INTRODUCTION

1.1 Infectious Diseases

Diseases generally can be categorized into two types; infectious (communicable) and non-infectious (non-communicable). Infectious diseases seem to be more dangerous since an infected being may spread the infection to a whole population. An infectious disease is an ailment caused by a specific infectious agent such as; bacteria, viruses, parasites and fungi. It gets spread by the transmission of that infectious agent from an infected carrier to a susceptible individual either directly or indirectly.

For an infection to spread, it needs an agent of spread which are basically the agents of dispersal namely; wind, water and animals. These agents spread infection, depending on its nature. Wind is responsible for the spread of infections whose bacteria are released into the air through coughing, sneezing or even blowing of powdery infected substance such as; dry sputum or mucus. Water spreads an infection from a carrier to an unsuspecting healthy person when he drinks water that is contaminated by the faeces of an infected individual. Animals are another source of spread of infections. Animals in this regard is inclusive of human being (higher animal). Spread of infection through animal is majorly by having contact with the infectious animal. This contact can be through the eating of an infected animal (e.g. bat in the spread of ebola) or the fluid of an infected animal like semen, blood or sputum.

1.2 Bacterial Infection

According to Vidyasagar (2015), “bacteria are microscopic single-celled organisms that thrive in diverse environments”. Bacteria can be classified based on their shapes (morphology), DNA sequencing and biochemistry. This classification gives 28 different bacterial phyla.

The morphological classification is more popular with the list; cocci (spherical), bacilli (rod-like), spirilla (spiral), vibrios (comma) and spirochaetes (corkscrew). An example of a bacillus shaped bacterium is *Mycobacterium tuberculosis (Mtb)*, a bacterium that has human as its primary reservoir.

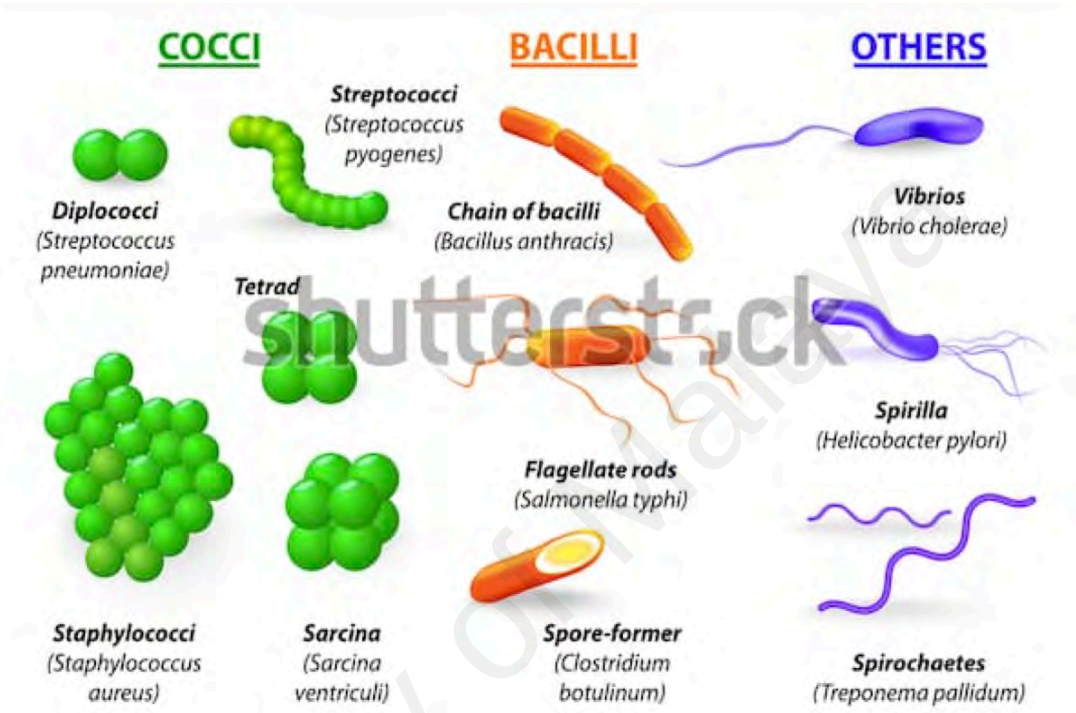

Figure 1.1: Types of bacteria (Adapted from Designua (2019), with permission from Shutterstock)

1.3 *Mycobacterium tuberculosis* complex (MTBC)

"*Mycobacterium tuberculosis* complex (MTBC) is a genetically related group of Mycobacterium species that can cause tuberculosis in humans or animals" (Wikipedia contributors, 2018). It is just a group out of the whole Mycobacterium genus. The Mycobacterium genus presently accommodates 169 different different species with the grouping; *Mycobacterium tuberculosis, Mycobacterium leprae* and nontuberculous mycobacteria (NTM). According to Garcia-Betancur et al. (2012), MTBC consists of six validly published species namely; *Mycobacterium tuberculosis, Mycobacterium africanum, Mycobacterium bovis, Mycobacterium caprae, Mycobacterium microti and Mycobacterium pinnipedii*. Also, there are three not validly published species with the

names; *Mycobacterium canettii, Mycobacterium mungi and Mycobacterium orygis*. From the above list, *Mycobacterium tuberculosis* is the most prominent one.

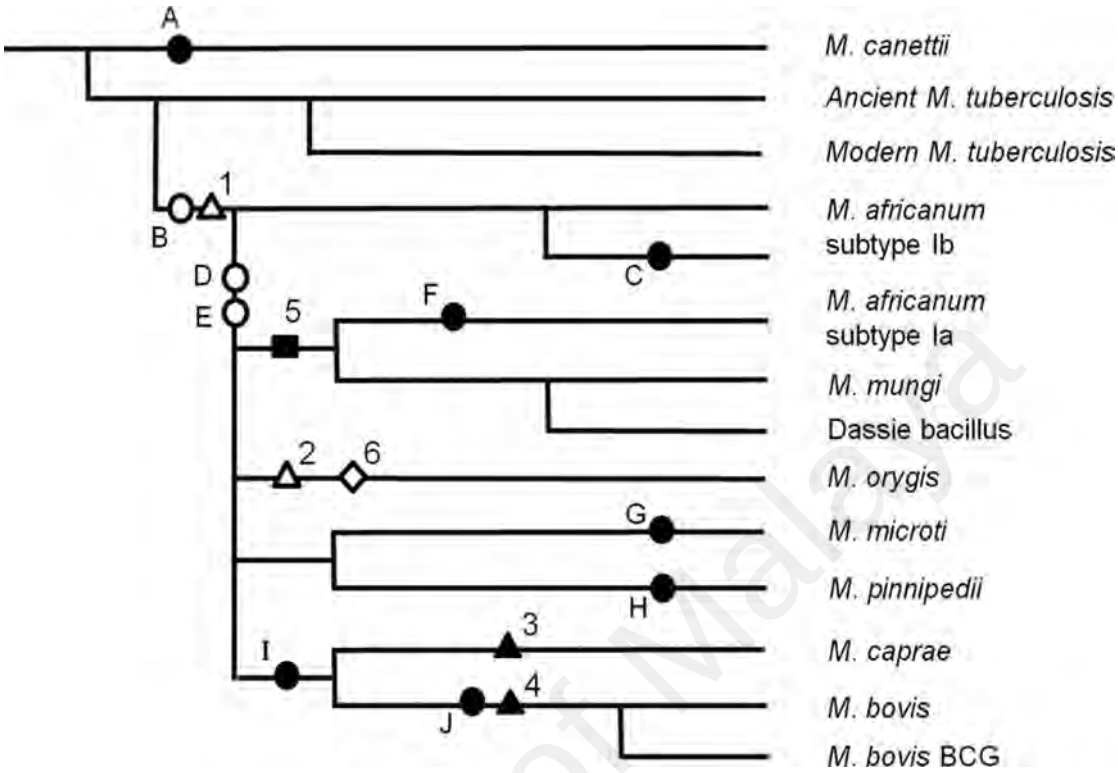

Figure 1.2: *Mycobacterium tuberculosis* complex (MTBC) (Adapted from Dawson et al. (2012), with permission from American Society for Microbiology)

1.4 Tuberculosis Infection

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis (Mtb).* This is an infection that basically affects the lungs, which is referred to as pulmonary TB but also have the ability to affect other parts such as; kidney, brain, spine, bones and joints, which is referred to as extra-pulmonary TB. The major mode of transmission of TB is through air droplets (during sneezing or coughing) and it could also be transmitted through contact with the sputum of an infectious carrier (Charles, 2017). Its major symptoms are; coughing for three or more weeks, coughing up blood, blood stained sputum, chest pain, weight loss, fatigue, fever, night sweats, and loss of appetite. TB is ranked 9th in the hierarchy of killer diseases (WHO, 2017), even ahead of HIV and malaria. This infection was recorded to single handedly be responsible for 1.1 million

deaths globally in the year 2010 (WHO, 2011), 0.9 million in 2011 (WHO, 2012), 1 million in 2012 (WHO, 2013), 1.2 million in 2013 (WHO, 2014) and 1.1 million in 2014 (WHO, 2015). Although, there is 20% reduction in the TB incidence in the year 2016 as compared to 2015 (WHO, 2017) but yet, death totalling 1.4 million (WHO, 2016a), 1.3 million (WHO, 2017) and 1.3 million (WHO, 2018b) were recorded in the years 2015, 2016 and 2017 respectively. Hence intervention strategies on curbing the spread of this infection is highly necessary.

Long latency period is a major characteristic of TB and as such, has important implication for its epidemiology (Blower et al., 1995). At the moment, every one out of four persons is reported to have latent tuberculosis infection (LTBI) globally (WHO, 2018b). This is an improvement as the earlier estimate was one out of every three persons (Houben & Dodd, 2016). Nonetheless, the present estimate of one-quarter is still huge. This huge estimate, coupled with the prolonged latency period puts the world at risk of this deadly infection.

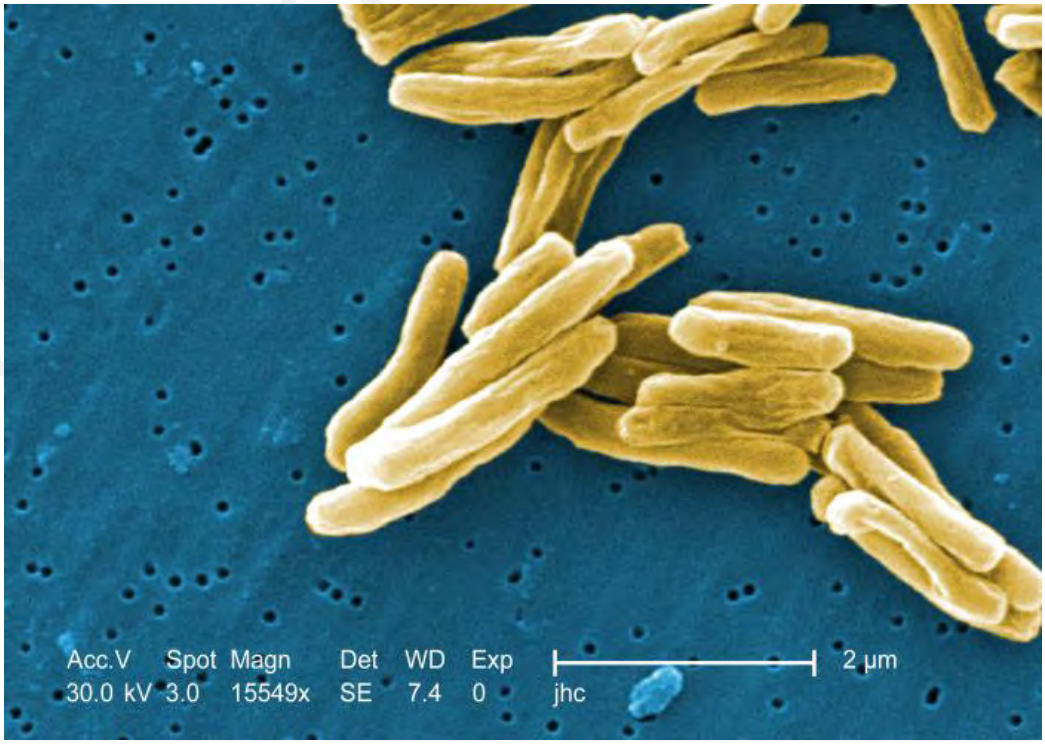

Figure 1.3: *Mycobacterium tuberculosis* (Adapted from Janice et al. (2019), CC0)

In the year 2016, 56% of TB patients in the world were found in five countries; India, Indonesia, China, the Philippines and Pakistan (WHO, 2017). Also, eight countries; India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa accounted for 67% of the global TB cases in the year 2017 (WHO, 2018b). It is observed that its incidence is mostly in densely populated area and also, in under-developed and developing nations. This shows that there is correlation between densely populated environment and the rate of TB incidence, and as such is in consonance with the research of Varughese et al. (2017) for the screening and treatment of immigrants for LTBI. For success to be recorded in the war against TB, attentions should focus on; transmission rate, treatment rate, treatment failure rate and the rate of immunity loss. This is supported by the findings of Ullah et al. (2019).

1.5 History of Tuberculosis

Schachepheth, the Hebrew term for tuberculosis is mentioned in the Biblical books of Deuteronomy (28:22) and Leviticus (26:16) (Daniel & Daniel, 1999). The word shachepheth has been translated as "wasting disease" in English Standard Version bible (ESV) and New International Version bible (NIV) and also translated as "consumption" in 21st century King James version bible (KJ21). There are abundant archeological evidences to establish the presence of tuberculosis around 5500 years ago in Egypt (Cave & Demonstrator, 1939; Morse et al., 1964), which covers the period when the ancient Israelites lived in Egypt (≈3700 to ≈3300 years ago). The biblical verses above further corroborate the existence of TB in that region, since the verses are directed at the Israelites.

Phtisis as it is referred to in Greek (Daniel, 1997), "great white plague" (Jassal & Aldrovandi, 2011), "the captain among these men of death" (Grange et al., 2010),

Consumption (Major, 1945), and Scrofula (Mohajan, 2015) surged in Europe and North America in the 18th and 19th centuries with great casualties. It has afflicted humankind greatly throughout known history (Daniel, 2006).

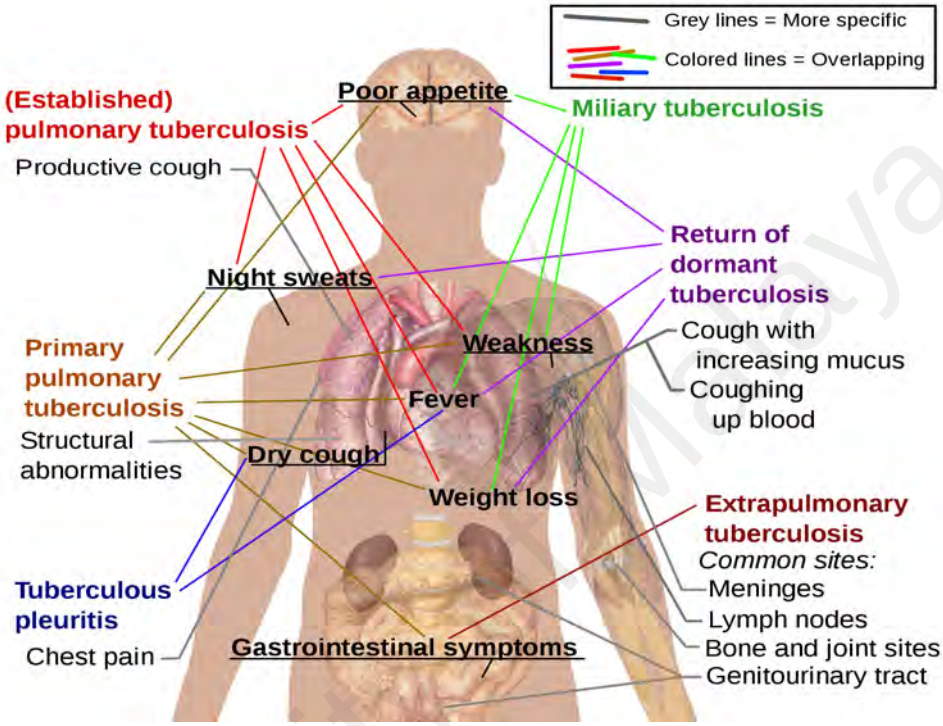

Figure 1.4: Symptoms of tuberculosis (Adapted from Häggström (2014), CC0 1.0)

1.6 Medical Diagnosis and Interventions for Tuberculosis

The expulsion of the bacillus *Mycobacterium tuberculosis* into the air through cough or any other mean increases the likelihood of the spread of TB. Chest x-ray and Symptoms screening; cough, blood stained sputum, lack of appetite, fever, fatigue, weight loss and night sweats, are the two main methods to screen the presence of TB. Chest x-ray is used in querying pulmonary TB. Detection of damage to lungs due to TB is identified by the presence of grey shadows in the lungs region. Normally, air in the lungs is displayed as black, other than black colour (grey or white) indicates problem. Although, this abnormality in the x-ray may indicate another health problem, it is still an indication that the person whose x-ray was taken requires medical attention.

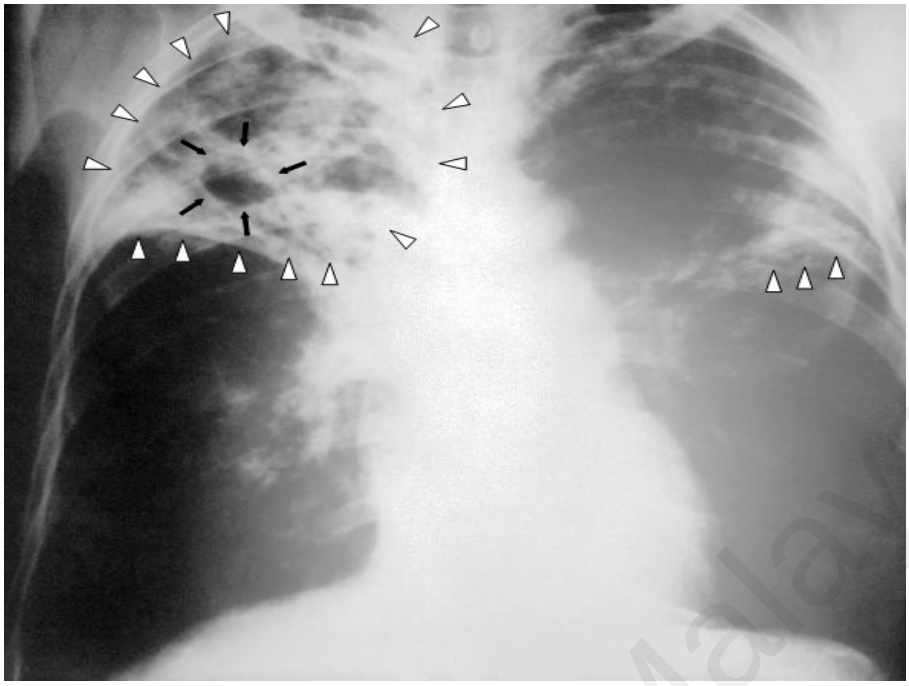

Figure 1.5: An x-ray image portraying tuberculosis (Adapted from Müller (2016), CC BY 3.0)

There are different diagnostic tests for TB such as; sputum smear microscopy, rapid molecular tests and culture-based methods (WHO, 2018b). Sputum smear microscopy is the oldest among them and requires the use of microscope to determine the presence of bacteria in the sputum. This test is cheap, simple and provides result within hours. It requires the application of series of special stains (like; carbol fuchsin, acid alcohol and methylene blue (Wikipedia contributors, 2019)) to the collected specimen (sputum) which is placed on a glass slide. This stained slide is subsequently examined under the microscope for probable existence of signs of the bacillus *Mycobacterium tuberculosis*. Retention of stain by the specimen indicates the presence of the bacillus *Mycobacterium tuberculosis*.

The emergence of resistant TB gave birth to rapid molecular tests and culture based methods. Drug-susceptibility testing (DST) is used in ascertaining the fact that the

individual infected with TB has no resistance to either the first-line or second-line anti tubercular drugs. The first-line anti tubercular drugs are; isoniazid, rifampicin, ethambutol and pyrazinamide (WHO, 2018b) and the second-line anti tubercular drugs are given in Table 1.1 below.

Table 1.1: Second line anti-tubercular drugs (Adapted from Kanabus (2018), CC BY-NC-SA 3.0 IGO)

Group A:	Group B:	Group C:
Levofloxacin (Lfx) or Moxifloxacin (Mfx)	Clofazimine (Cfz)	Ethambutol (E)
Bedaquiline (Bdq)	Cycloserine (Cs) or Terizidone (Trd)	Delamanid (Dlm)
Linezolid (Lzd)		Pyrazinamide (Z)
		Imipenem-cilastatin (lpm-Cln) or Meropenem (Mpm)
		Amikacin (Am) (or Streptomycin)
		Ethionamide (Eto) or Prothionamide (Pto)
		p-aminosalicylic acid (PAS)

DST can be done using the genotypic or phenotypic approach (Suleiman, 2017). The genotypic approach is the rapid molecular based tests while phenotypic approach is the culture based methods. The rapid molecular test is DNA based test for resistance to either first or second-line anti tubercular drugs. According to WHO (2018b), the WHO recommended machines are Xpert MTB/RIF and line probe assay (LPA). Xpert MTB/RIF tests for TB as well as resistance to rifampicin simultaneously. LPA has two types, the one that tests for resistance to rifampicin and isoniazid is called first-line LPA. The other one called second-line LPA tests for resistance to fluoroquinolones and

injectable anti-TB drugs. Another machine recommended by the WHO is loop-mediated isothermal amplification (LAMP), (WHO, 2016a). Although, this does not detect rifampicin resistance but has demonstrated high capacity to detect TB. As such, it has been recommended as a replacement for microscopy test.

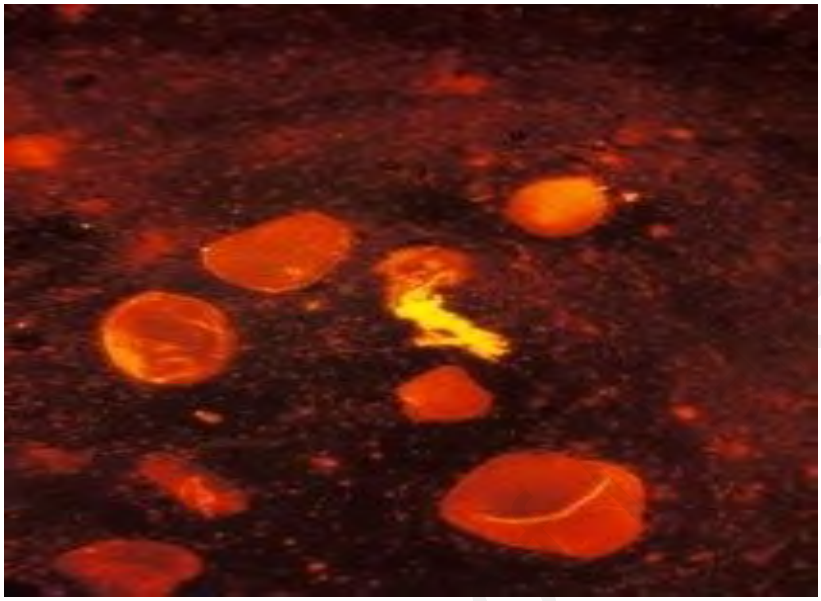

Figure 1.6: A stained sputum smear (Adapted from Ronald and USCDCP (2016), CC0)

Figure 1.7: GeneXpert IV System (Adapted from GDF (2018), with permission from Global Drug Facility)

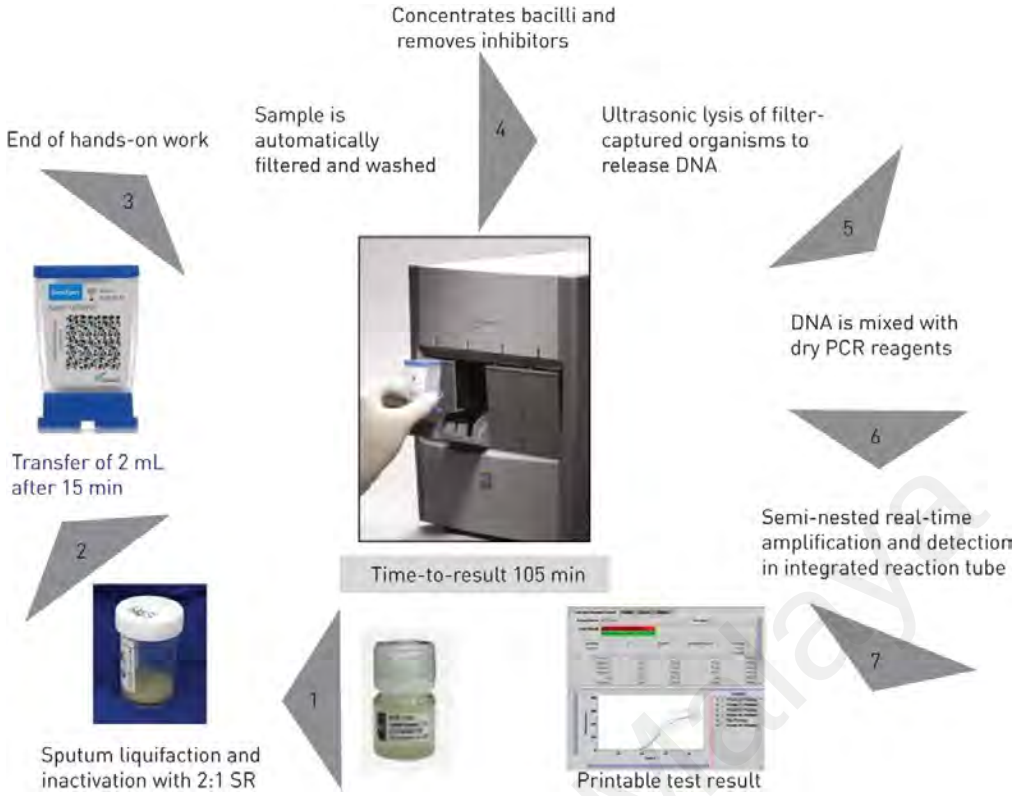

Figure 1.8: Conducting test with Gene Xpert (Adapted from Weyer et al. (2013), with permission from WHO)

The last diagnostic test is the culture based methods. According to Suleiman (2017), "culture means taking sputum or another sample from the body that is thought to contain the TB bug, decontaminating it (to stop the growth of other non-TB organisms) and giving it time to grow on a specific material or medium". The positive growth of the culture implies the presence of TB bacteria. Although, provision of result from the method take weeks, it is the WHO current reference standard to monitor the progress made by a TB patient on therapeutic vaccine (WHO, 2018b). It is also used in detecting drug-resistant TB (DR-TB) and used for monitoring treatment progress for someone with multi-drug resistant TB (MDR-TB), (WHO, 2011).

Figure 1.9: LAMP (Adapted from HUMAN (2018), with permission from HUMAN)

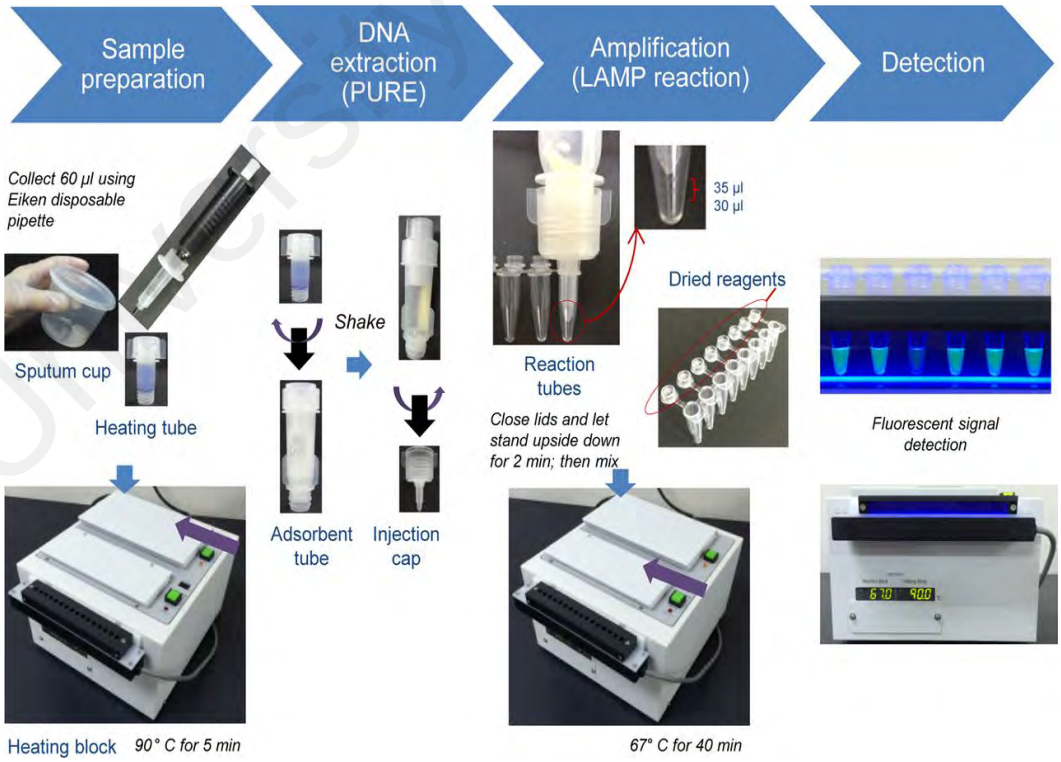

Figure 1.10: Conducting test with LAMP (Adapted from Gray et al. (2016), with permission from American Society for Microbiology)

Breakthrough research on tuberculosis was in the early 19th century with the research of Hermann Heinrich Robert Koch, when he was able to identify a substance from tubercle bacilli which he named tuberculin. This was subsequently followed by the work of Clemens Freiherr von Pirquet in the early 20th century, where he was able to give a measurement of the tuberculin injection to use in testing for latent TB (Daniel, 2005). Positive reaction to the injection indicates the presence of latent TB.

Advancement in the progress of the fight against TB happened in the year 1921 when Albert Calmette and Camille Guérin came up with the famous BCG vaccine. BCG (Bacille Calmette Guérin) is a prophylactic anti tubercular vaccine that is administered on people to prevent TB infection. BCG has done a lot in the prevention of TB, but its ineffectiveness has been a course of discussion in recent time.

Isoniazid is the first oral mycobacterial drug. It was introduced in the year 1952 before being followed by rifamycins (rifampicin, rifapentin and rifabutin) in 1957, which are the two major first-line anti-tubercular drugs (Daniel, 2005). Although, these drugs were predated by streptomycin which happens to be the first antibiotic as well as first effective bactericidal agent against *Mycobacterium tuberculosis*. Table 1.2 below shows the latest anti-TB drugs in pipeline.

Table 1.2: The global clinical development pipeline for new anti-TB drugs and regimens, August 2018 (Adapted from WHO (2018b), CC BY-NC-SA 3.0 IGO)

Phase I[a]	Phase II[a]	Phase III[a]
Contezolid (MRX-1)[b]	Delpazolid (LCB01-0371)	Bedaquiline (TMC-207)[b]
GSK-303656[b]	SQ109	Delamanid (OPC-67683)[b]
Macozinone (PBTZ169)[b]	Sutezolid (PNU-100480)[b]	Pretomanid (PA-824)
OPC-167832	Linezolid dose-ranging	Clofazimine
Q203[b]	Nitazoxanide	High dose rifampicin for treatment of DS-TB
TBA-7371[b]	High dose rifampicin for DS-TB (PANACEA)	Rifapentine for treatment of DS-TB
TBI-166	Bedaquiline and delamanid (ACTG A5343 DELIBERATE trial)	Bedaquiline-Pretomanid-Linezolid (NiX-TB trial)
	Bedaquiline-Pretomanid-Moxifloxacin-Pyrazinamide (BPaMZ) regimen	Bedaquiline-Pretomanid-Linezolid (ZeNix trial)-Linezolid optimization
	Bedaquiline and pretomanid with existing and re-purposed anti-TB drugs for MDR-TB (TB PRACTECAL Phase 2/3 trial) Delamanid, linezolid, levofloxacin, and pyrazinamide for quinolone sensitive MDR-TB (MDR-END trial)	Bedaquiline with two optimised background regimens (oral, 9 months; with oral and injectables, 6 months) (STREAM trial) Bedaquiline-Linezolid-Levofloxacin with OBR[c] for MDR-TB (NExT trial)
	Levofloxacin with OBR[c] for MDR-TB (OPTI-Q)	Bedaquiline and delamanid with various existing regimens for MDR-TB and XDR-TB (endTB trial)
		Pretomanid-Moxifloxacin-Pyrazinamide regimen (STAND
		Rifapentine-Moxifloxacin for treatment of DS-TB (TB Trial Consortium Study 31/A5349) trial)

1.7 Problem Statement, Research Questions, Aim and Objectives

1.7.1 Problem Statement

On the list of the sustainable development goals (SDG), the third goal is "good health and well-being" (WHO, 2018d). This goal is threatened by three main diseases; malaria, HIV/AIDS and tuberculosis. Malaria has a total incidence of 219 million in the year 2017 (WHO, 2018e), HIV/AIDS has 37 million in 2017 (UNAIDS, 2018) and tuberculosis has a total of 10 million incidences in 2017 as well (WHO, 2018b). Of them all, tuberculosis kills more with a record of 1.3 million deaths (WHO, 2018b). This is followed by HIV/AIDS with 900 thousand deaths (UNAIDS, 2018) and malaria with 435 thousand deaths (WHO, 2018e). The total deaths from the three diseases is 2.6 million with malaria being 16%, HIV/AIDS being 36% and tuberculosis being 48%. This shows that the death due to TB is the most and requires utmost attention. This research focuses on addressing the ways by which tuberculosis could be eliminated or perhaps reduce its incidence to a bearable minimum.

1.7.2 Research Questions

1. Can tuberculosis epidemic be eliminated?
2. Under what condition do we have a TB free environment?
3. What are the missing efforts in effectively managing TB?

1.7.3 Research Gap

From the reviewed literatures, it is observed that a lot has been done on the mathematical modelling of tuberculosis. Even with those researches, the disease incidence keeps on persisting and as such gives rise to the research questions in subsection 1.7.2 above. The published researches have failed to exploit the importance and relevance of the latent state of TB in the disease dynamics. Also noted is the fact that the

ineffectiveness of BCG has been discussed in literatures but no definite guide on formulating a better vaccine has been discussed. In the same vein, the incidences of other TB strains are on the rise. As such, there is the need to start giving more focus to these strains as delay may be dangerous.

1.7.4 Aim

The aim of carrying out this research is to come up with analyses on understanding the tuberculosis epidemiology and to subsequently propose solutions to reduce its spread. This is planned to be achieved using the below stated objectives.

1.7.5 Objectives

A critical study of relevant literatures as discussed in Chapter 4 show the vacuum yet to be filled, hence gives direction to our research objectives which are;

1. To formulate a mathematical model to query the relevance of the exposed state in reducing tuberculosis incidence rate.
2. To formulate a mathematical model which gives direction to the formulation of a better vaccine for TB.
3. To formulate a quarantine model to check the rising rate of multi-drug resistant TB (MDR-TB).
4. To determine the equilibrium points and their stabilities alongside the basic reproduction number (R_0) of the formulated models.
5. To find the rate at which the considered parameters (factors) affect the incidence of TB.

1.8 Organization of the Thesis

This thesis consists of six chapters. The chapters are namely; Chapter 1 (Introduction), Chapter 2 (Literature review), Chapter 3 (Analysing tuberculosis), Chapter 4 (Impact of vaccination on tuberculosis), Chapter 5 (The Effect of quarantine in reducing multi-drug resistant TB (MDR-TB)) and Chapter 6 (Summary, conclusion, recommendations and future work).

Chapter 1, gives a general overview about tuberculosis with basic discussion on infectious diseases. Different types of bacteria of which *Mycobacterium tuberculosis (Mtb)* is an example are discussed. Due to the broadness in the species of Mycobacterium genus, the *Mycobacterium tuberculosis* complex (MTBC) is as well discussed briefly. Discussions about tuberculosis infection, its history, medical diagnosis and interventions to address the wilder growth of TB are presented. The definition of some relevant terms are given while presenting the aim and objectives of the research.

Due to the multi-facetted approach to ending the TB infection, Chapter 2, gives literature reviews from three different fields. The fields are; mathematics, medicine and pharmacy. The mathematical point of view describes some of the different models that have been previously formulated to discuss the tuberculosis infection as well as their findings. Researches from the medical field focus majorly on the diagnostics tools for TB. Without proper diagnosis, there is no way a reasonable headway could be achieved in the war to stop TB. Lastly, researches from the pharmaceutical field give focus on the production of effective medicines to combat the tuberculosis infection with much attention given to the identification of the right biomarkers for the production of the drugs.

Chapter 3, presents our first model to address tuberculosis epidemic, it is a four compartment model. The equilibrium points, basic reproduction number (R_0) and

stabilities of the model are discussed to give a proper understanding of the model formulated. This is subsequently followed by the numerical analysis to give pictorial discussions on the model before the presentation of the conclusion.

In Chapter 4, an extension of the model in Chapter 3 is presented. An extra compartment, the vaccination compartment is incorporated to discuss the effect of right vaccine in halting the spread of tuberculosis. Just like in Chapter3, the equilibrium points, basic reproduction number (R_0), stability analysis and the numerical results are presented. The summary of this chapter concludes it.

Another strain of tuberculosis (MDR-TB) is discussed in Chapter 5. This is a strain that is gradually growing wild and not receiving much attention from mathematical modellers. The impact of the use of quarantine in curbing MDR-TB is presented here with the aid of mathematical and graphical analysis.

Chapter 6, summarizes the whole work. The recommendations from the conclusion are presented for further actions in achieving the set goal of sending the tuberculosis epidemic to extinction.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Since time immemorial, man has pre-occupied himself with research, either to aid his survival or to understand his environment better. The discovery of penicillin as a potent drug to fight bacterial infections, identification of differences in finger prints that helps in solving criminal matters and even the knowledge of the sphericity of the earth are among major breakthroughs recorded through research.

The relationship of man with his environment leads him to have contact with different bacteria, which can be harmful and as well useful. *Mycobacterium tuberculosis (Mtb)* is an example of the harmful ones. This bacteria is an intracellular pathogen that lives within phagosomes and also disrupts these organelles to access the cycstol (Schnettger et al., 2017). In the course of research, this bacteria has been identified to be responsible for tuberculosis (TB) and great works have been done by researchers from different fields, charting way forward on how to annihilate its existence or at least reduce its level of incidence. Hence, this literature review dwells on three major fields; mathematical, medical and pharmaceutical researches on tuberculosis.

2.2 Mathematical Modelling of Tuberculosis

Basically, there are two approaches to the mathematical modelling of infectious diseases. These approaches are stochastic and deterministic (compartmental) modelling. Stochastic approach is probabilistic whereby some level of randomness is allowed. See e.g. Wilkinson & Sharkey (2018), Han et al. (2018), Wei et al. (2018), Getz & Dougherty (2018) and Funk et al. (2018). Some earlier researches with the same approach are those of Witbooi (2017), Ming et al. (2016), Pellis et al. (2015), Zhao et al. (2014), Cai et al. (2013), Wang et al. (2012), Nishiura (2011) and Beggs et al. (2010).

On the other hand, the output from a deterministic approach is based on the parameter values and initial conditions provided rather than being a probable result. The efficacy of this approach has been greatly demonstrated by its use in studying different epidemics. Verguet et al. (2015) and Li et al. (2017) are among those that have used it to discuss measles epidemic. It has been useful in discussing HIV epidemic as presented by Ali et al. (2017), Nah et al. (2017), Geetha & Balamuralitharan (2018), Omondi et al. (2018), Wang & Dong (2018), Aldila (2018) and Alshorman et al. (2017). It has also been relevant in the analysis of zika virus infection. This is as presented by Suparit et al. (2018), Goswami et al. (2018), Padmanabhan & Seshaiyer (2017), Tower et al. (2016) and Gao et al. (2016). Aston (2018) also display its efficacy in the analysis of hepatitis C.

Mathematical modelling of infectious diseases could be dated back as far as the 17th century when Bernoulli came up with an inoculation model against smallpox. According to Brauer (2017), first contributions to modern mathematical epidemiology are due to En'ko between 1873 and 1894, before the great works of Ross, Hamer, McKendrick and Kermack between the years 1900 and 1935. This deterministic modelling approach has been used extensively in assessing the tuberculosis epidemic.

Numerous researchers have presented many models to address this epidemic, these models have helped in advancing the approaches to curbing the infection. Okunoghae & Omosigho (2011) came up with a model on what could be done to increase TB case detection. The model was used to test a result gotten from a survey conducted in Benin city, Nigeria. They were able to establish that effective awareness program, active cough identification, associated cost factor for treatment of identified cases and effective treatment are the key factors to be combined in order to achieve effective control of TB, as well as increase the TB case detection rate. The research of Huo &Zou (2016) further corroborate this. They establish that the treatment of TB infected individuals at home

gives different result when compared to those treated in the hospital. This is because the right treatment to any infection is by proper diagnosis. Proper diagnosis can only be achieved at the hospitals. Based on a survey done in Canada, the research of Varughese et al. (2017) identified that screening and treating new immigrants for LTBI has the efficacy of reducing TB incident cases. This is in line with the aforementioned estimate of one-fourth of the world having LTBI, 10% of those with LTBI is expected to develop active TB (WHO, 2015). The work of Chong et al. (2019) also shows the importance of treating LTBI patients. Their model evaluated the impact of treating elderly persons with LTBI as an addition to the established TB control strategies in Hong Kong. Their evaluation shows that the incorporation of treatment for the elderly ones (with LTBI) will reduce the TB incidence by 50%. This 50% reduction is achievable when this measure is merged with the maintenance of treatment completion rate (which stands at 65%) as well as the treatment of a moderate proportion of LTBI patients annually.

Trauer et al. (2014) formulated a ten (10) compartment model to study multi-drug resistant TB (MDR-TB) and drug susceptible TB. They were able to observe that improved treatment of drug susceptible TB does not result in decreased MDR-TB rates. On the other hand, Porco & Blower (1998) advanced the understanding of TB transmission dynamics by the consideration of the non-availability of treatment in their model. Their observation was that the parameters that affect the severity of TB epidemic among the ones considered are; the disease reactivation rate, fraction of infected individuals that progress to active TB soon after infection, the number of persons that an infectious individual infects per year, disease death rate and the population recruitment rate. Arinaminpathy et al. (2019) formulated a mathematical model of TB focusing on Mumbai and Patna; the two major cities in India. The model sought to establish the relevance of private health care service provider in combatting the TB epidemic. The

model reveals that the engagement of the private health care service provider in the treatment of TB could help in capturing 75% TB patients. This would in turn reduce the TB incidence up to 21.3%. This result is reasonable as most health care service seekers would visit a private clinic before public hospitals.

Jia et al. (2008) formulated an eight (8) compartment model to measure the impact of immigration on the tuberculosis epidemiology. They partitioned the total population under consideration to two subpopulations; the immigrants and the locals. These subpopulations were treated individually to establish their respective basic reproduction number. With the denotation of the basic reproduction number numbers of the immigrants' subpopulation and locals' subpopulation (R_{MO}) and (R_{L0}) respectively, they noted that tuberculosis disease cannot die out because $R_{L0} < 1$ and $R_{M0} > 1$. As such, they opined that immigrants have drastic impact on the overall epidemiology of TB. However, the research of Herrera et al. (2013) investigated the spread of tuberculosis in semi-closed communities. A semi-closed community is one with the recruitment of new members and as well departure of some others e.g. prison. In their research, five (5) compartments were considered in which there are two infectious classes. They explained that semi-closed communities should be a major public concern as they promote disease transmission to the outside community.

The research of Bhunu et al. (2008) discusses the effect of incorporating prophylactic measure in curbing TB transmission. They formulated a deterministic model of five (5) compartments to firstly assess the impact of the treatment of infectives and subsequently, the impact of chemoprophylaxis on tuberculosis transmission was assessed. They were able to establish that treating the infectives keep them safe for a certain period of time while the chemoprophylactic approach reduces the eventual number of infectives, which

in turn reduces the TB incident generally. Shrestha et al. (2017) gave a direction on who should be the recipient of vaccine. Their research that focused on the impact of vaccination on a cohort group (a group of miners with high-risk of getting infected with TB) shows a greater efficacy of vaccination on the cohort group when compared to vaccinating the entire population. Hence, they suggest that vaccines should be targeted at those that are at high-risk of getting tuberculosis infection rather than vaccinating the entire community.

In recent time, TB-HIV co-infection has been a major cause of concern. Perspective of Houben et al. (2014) give suggestions on how to address the TB-HIV epidemic. Their suggestions focus on the priorities for future modelling works which are;

1. The difficult diagnosis and high mortality rate of TB-HIV patients.
2. The high risk of disease progression.
3. TB health systems in high HIV prevalent settings.
4. Uncertainty in the natural progression of TB-HIV.
5. Combined interventions for TB-HIV.

The five (5) above suggestions are really valuable to addressing the TB-HIV co-infection because without standard and proper diagnosis of any infection, no reasonable remedy can be offered. It is with the proper diagnosis that the problems of high TB progression rate, proper TB health systems, uncertainty in the natural progression rate of TB-HIV infection and as well as the interventions for TB-HIV could be addressed. As such, the next two sections present the advances made so far in the field of medicine and pharmacy to tame the wild spread of TB.

2.3 Medical Researches on Tuberculosis

At the dawn of any sickness or infection, the first resort is usually medical approach. A medical doctor shall diagnose (examine) the patient and proffer potential solution which could be; administration of drugs, routine checkup or any other necessary action required to be taken. This diagnosis comes in different forms. History taking, physical examination and even diagnostic tests may be required to ascertain the type and cause of a particular infection.

Recovering from an infection or disease at times requires much more than the above stated approach. According to Skiles et al. (2018), provision of social support for TB patient improves their treatment response rate. This was observed from the comparison made among TB infected Ukrainians that received social support in the year 2012 and those that did not receive such in 2011 and 2012. High-risk patients infected of TB who are receiving social support are comparable to low-risk patients in treatment response rate. Also, the importance of having a robust program of public-private relationship of medical practitioners cannot be over emphasised. The result of such program has been demonstrated by Nwe et al. (2017), where they researched on the engagement of public and private medical facilities in tuberculosis care in Myanmar. Since most people would visit a private medical center first due to their proximities, there was a great reportage of TB incidents at the national level, with greater percentage of the reports from private medical practitioners.

It is a well-known fact that ageing comes with a lot of medical challenges which is largely due to the weakened immune system. Lee et al. (2017) researched on TB infection in elderly people. Their approach was to examine the impact of treatment delay in different categories of TB patients. The categories are; those that are less than 65 years

of age (cat 1), 65-79 years (cat 2) and those that are greater than 80 years (cat 3). They reported 6.5%, 18.5% and 34.7% mortality rates respectively for cat 1, cat 2 and cat 3 when there is treatment delay. The delay occurs due to the unawareness of the medical practitioners that these people are TB carriers. As such, querying of TB is encouraged whenever elderly people visit the clinic for a different medical reason, so as to initiate treatment early (if required) and avert fatal consequence.

Incomplete treatment is another critical area to be looked at. Non-completion of TB treatment has given room for the emergence of some other strains. Recently, the study of Dheda et al. (2017a) exposited a strain described as programmatically incurable tuberculosis. This strain is prevalent in South Africa, Russia, India and China (Dheda et al., 2017b). From their cohort study with 273 patients of XDR-TB or resistance beyond XDR-TB in South Africa, they found out that 203 patients representing 74.36% have already developed programmatically incurable TB. More than 50% of this 74.36% got discharged into the community and hence transmit this strain of TB to the unsuspecting community members unknowingly. This finding calls for more attention to be given to ascertain the level of fitness of the patients before being discharged, so as to save the outer world from the spread of TB infections in general. Still on the strains of TB, Dheda et al. (2017b) reviewed the clinical management of adults and children with MDR-TB and XDR-TB, where they remarked that about 20% of all TB strains are resistant to at least one major TB drug. This has major contribution from poorly functioning health care systems, poverty and lack of political will.

Diagnostic methods play vital role on tuberculosis case detection. As discussed in Chapter 1 (1.6), TB laboratory diagnosis are done in different ways. Gupta-Wright et al. (2018) established the relevance of rapid urine-based screening for TB in reducing the

mortality rate in HIV-positive patients. They found out that this test enhances better medical care for these patients as it reveals those that are co-infected with TB. In their research, they considered 1287 patients infected with HIV for HIV treatment alone and considered another 1287 patients for HIV treatment alongside tuberculosis. 21% of the HIV treatment alone group died while 18% of the HIV alongside TB treatment group died. This indicates the importance of testing for TB in a HIV-positive patient. Papaventsis et al. (2017) proposed in their review that whole genome sequencing (WGS) could be considered a better alternative to drug susceptibility testing methods for rifampicin and isoniazid, before having a standardized analytical pipelines. This will help a long way in determining the approach required to combat TB upon detection.

For a continual progress in the fight against tuberculosis, great funds are required to be committed. For instance, 65.6 million was spent between 2003 and 2015 in fast tracking the development of medical interventions for TB, HIV and malaria (Surette et al., 2017). Hence, many collaborators are required in order to finance these researches either on the production of alternative drugs or better machines to help in case and strain detection. This is pertinently important as the funding on TB research is estimated to gulp US $2 billion annually, but the highest funding recorded so far is US $724 million, which was in the year 2016 (WHO, 2018b). Doing this will consolidate on the already recorded successes in combatting TB and as well take the world closer to achieving the sustainable development goals (SDG) and End TB strategy targets set for 2030.

2.4 Pharmaceutical Researches on Tuberculosis

One of the major setbacks recorded in the production of drugs generally is the less reliance of pharmaceutical companies on research and development (R & D) but focusing on how to cut cost to be expended (Casty & Wieman, 2013). Elimination of TB has been

greatly hampered by the existence of XDR-TB. Although, drug resistance could be seen as problem by medical practitioners and their patients but interestingly, it provokes reasoning that could lead to the development of new and even better drugs. To this effect, hands are on deck to find a way out of this set back. Ojima et al. (2017) published their findings on the development of new-generation fluorine containing anti-bacterial agents against TB. Their aim is to use this fluorine in targeting Filamenting temperature-sensitive mutant Z (FtsZ), which is an important protein that aids the division of bacterial cells. It is as well useful in the production of anti-bacterial drugs. They subsequently proposed the inclusion of fluorine in the lead compounds required for the production of anti-tubercular drugs as these lead compounds lack sufficient metabolic and plasma stabilities. This inclusion is expected to produce an improved pharmacological properties. As such, their research led to the development of fluorine benzimidazoles as potential drug candidate.

In China, it is a common practice to prescribe herbs alongside the anti-tubercular drugs. Their belief is that herbs protect liver from damage. However, Liu et al. (2008) countered this belief in their research as they were able to establish that there is no reliable information to support the recommendation of the herbs to be taken in conjunction with the tuberculosis treatment. Zhang et al. (2014) carried out a proteomic analysis to investigate LTBI biomarkers. Biomarkers provide prognostic information about future health status, either for individual patients or cohorts in clinical trials. It is very important in the development of drugs as it serves as a measure of normal biological or pathogenic processes or even pharmacological responses to any therapeutic intervention under consideration (Atkinson et al., 2001). The diagnostic model used by Zhang et al. (2014) was generated using a training set of spectra and they established the accuracy of the model using blind testing. They came up with the result that LTBI diagnosis accuracy

could be stepped up using the proteomic analysis. More researches on biomarkers that are relevant to the production of TB drugs have been presented by different scientists, see e.g. Walis et al., (2009), Walis et al., (2010), Walis et al., (2013), Jayakumar et al., (2015) and Parida & Kaufmann (2010).

Different individuals display different attitudes to drugs taking. Dispensation of multiple drugs to combat a particular illness may not be much effective as the patient may decide not to take the drugs as prescribed due to the much number of drugs given. However, production of the drugs in a single form could help in addressing this. With the exception of isoniazid, all other drugs could be produced as a single dose to reduce the number of drugs to be taken by the patient. This result is discussed in Xu et al. (2013). Jassal & Aldovandi (2011) came up with 6 steps that are to be taken to bring about the possible elimination of "Phtisis". They are; addressing the current issues with TB pharmacotherapy, novel drug formulations, improvement of preclinical testing models, development of strong institutional foundations, direction of focus of clinical drug trials to selected populations that comprises of people with LTBI, diabetes mellitus and TB, HIV and TB co-infection and paediatric TB. Lastly on the list of their proposition is the existence of delivery mechanism for the produced novel drugs.

Since TB is prevalent mostly in poor environments, the investors on the anti-TB drug production record low financial return which in turn hampers the required development of better and new drugs to tackle the infection. In the year 1993, TB was declared a global emergency by WHO due to the established risk of its possible spread with HIV and also the emergence of MDR-TB (Bessa et al., 2017). This gives an insight on why there is the need for the international organisations to step up their supports on the free donation of drugs and vaccines to the concerned nations.

2.5 Conclusion

The aforementioned discussion are the three main approaches to combat the TB epidemic. It should be observed that the researches hover majorly around TB case detection and the production of an effective prophylactic vaccine to prevent TB incident. However, the advantage that could emanate from preventing the direct progression of TB patients from susceptible class to infectious has not been discussed. Also, what should be the focus while producing an effective prophylactic vaccine as well as giving great attention to other strains of TB are not greatly discussed. Hence, this research focuses on taking the advantage of the exposed state (by not progressing directly to the infectious class from susceptible), consideration to be made in the production of an effective vaccine and also, curbing MDR-TB using quarantine.

CHAPTER 3: ANALYSING TUBERCULOSIS

3.1 Introduction

Many researchers have achieved reasonable results with the aid of mathematical models in assessing the dangers that TB infection portends, see e.g. Bhunnu et al. (2012), McCluskey & van den Driessche (2004), Ragonnet et al. (2017), Khajanchi et al. (2018) and Nkamba et al. (2019). Others have proposed intervention strategies see e.g. Okuonghae & Ikhimwin (2016), Murphy et al. (2003), van den Driessche & Watmough (2002), Mushayabasa & Bhunu (2013), Vynnycky et al. (2015) and White & Abubakar (2016). Even with all these efforts, the effect of this infection seems non-subsiding.

Almost all the authors mentioned above did not consider the rate at which recovered individuals move back to the susceptible group. The consideration of this scenario makes the modelling of TB infection mathematically more complete since recovery from bacterial infection confers no permanent immunity against reinfection. As such, it is considered in this model formulation. Also, according to WHO (2017), an estimated 4.1% of new cases of TB and 19% of previously treated cases had MDR-TB or drug susceptible TB globally in the year 2016. Hence, it would be more proper if we initially focus our attentions on understanding the drug susceptible TB (DS-TB) before discussing other strains. This is because most of the other strains emerge from DS-TB.

3.2 Model Formulation

3.2.1 Introduction

There are four groups of human categories considered in the model formulation. They are the susceptible individuals S, latently infected individuals (exposed) E, infected with symptoms (infectious) I and the recovered individuals R. The source of recruitment into

the population is through the susceptible compartment with recruitment rate πN and the total population $N(t)$ at any time t is

$$N(t) = S(t) + E(t) + I(t) + R(t). \tag{3.1}$$

The model allows the individuals from different groups to freely mingle with one another and a susceptible individual is bound to contract TB after an effective contact with an infectious individual at the rate

$$\lambda = \frac{\beta c I}{N}, \tag{3.2}$$

where β is the probability that a susceptible individual would get TB infection and c denotes the average contact rate.

The susceptible individuals move to the latent and infectious classes at the rates $f\lambda$ and $(1-f)\lambda$ respectively while the backward movement of the recovered individuals to the latent and infectious classes occur at the rates $f_1\,\lambda$ and $(1-f_1)\lambda$ respectively. The exogenous reinfection and endogenous reactivation rates are designated as $\delta\lambda$ and k respectively. Natural death of human is assumed to occur at the rate μ and the TB induced death occurs at the rate ε. The natural recovery rate from the infection is designated as ω and the treatment induced recovery is designated as σ. Due to the nature of bacterial infection (non-conferment of immunity against reinfection), it is assumed that a fraction of the recovered class goes back to the susceptible class at the rate α. The diagrammatic representation of the model is given by Figure 3.1 and the parameter values considered in the model formulation are in the interval $(0,1]$ with the exception of the contact rate c.

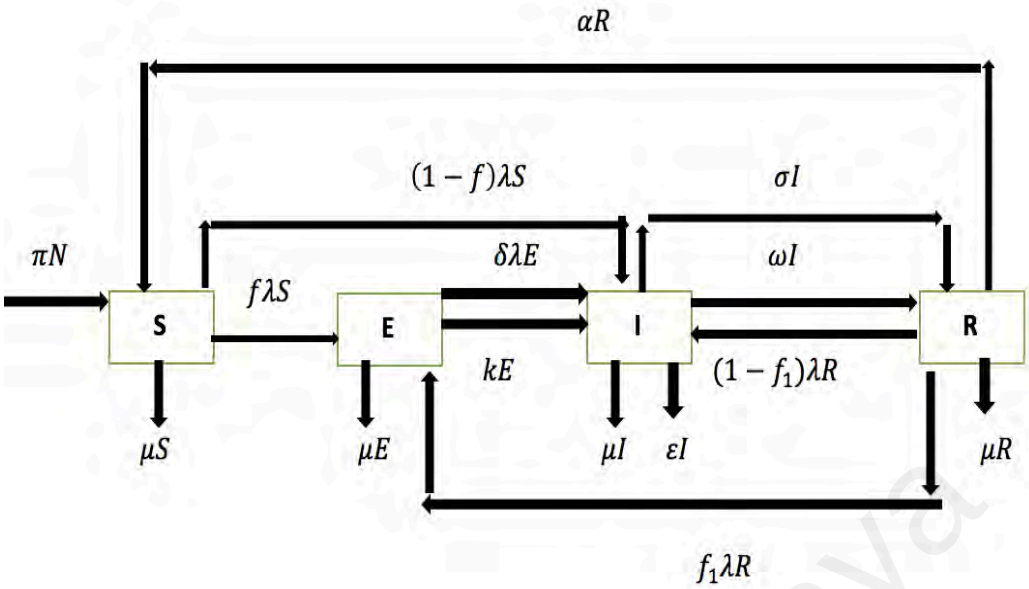

Figure 3.1: Diagrammatic representation of the tuberculosis model

The nonlinear system describing the model is

$$\frac{dS}{dt} = \pi N + \alpha R - (\lambda + \mu)S, \tag{3.3}$$

$$\frac{dE}{dt} = f\lambda S + f_1\lambda R + (\delta\lambda + k + \mu)E, \tag{3.4}$$

$$\frac{dI}{dt} = (1 - f)\lambda S + (1 - f_1)\lambda R + (\delta\lambda + k)E - (\sigma + \omega + \varepsilon + \mu)I, \tag{3.5}$$

and

$$\frac{dR}{dt} = (\sigma + \omega)I - (\lambda + \alpha + \mu)R, \tag{3.6}$$

with the initial conditions:

$$S(0) = S_0 \geq 0, \quad E(0) = E_0 \geq 0, \quad I(0) = I_0 \geq 0, \quad R(0) = R_0 \geq 0.$$

Adding (3.3)-(3.6) yields

$$\frac{dN}{dt} = (\pi - \mu)N - \varepsilon I. \tag{3.7}$$

Normalisation of the nonlinear system (3.3)-(3.6) is achieved by its division throughout by N. If $\frac{S}{N}, \frac{E}{N}, \frac{I}{N}$ and $\frac{R}{N}$ are consecutively denoted by s, e, i and r, then the system becomes

$$\frac{1}{N}\frac{dS}{dt} = \pi + \alpha r - (\beta ci + \mu)s, \tag{3.8}$$

$$\frac{1}{N}\frac{dE}{dt} = f\beta cis + f_1\beta cir - (\delta\beta ci + k + \mu)e, \tag{3.9}$$

$$\frac{1}{N}\frac{dI}{dt} = (1-f)\beta cis + (1-f_1)\beta cir + (\delta\beta ci + k)e - (\sigma + \omega + \varepsilon + \mu)i, \tag{3.10}$$

and

$$\frac{1}{N}\frac{dR}{dt} = (\sigma + \omega)i - (\beta ci + \alpha + \mu)r. \tag{3.11}$$

Since $S = sN$,

$$\Rightarrow \frac{dS}{dt} = N\frac{ds}{dt} + s\frac{dN}{dt}, \tag{3.12}$$

then

$$\frac{1}{N}\frac{dS}{dt} = \frac{ds}{dt} + s[(\pi - \mu) - \varepsilon i]. \tag{3.13}$$

In the same manner,

$$\frac{1}{N}\frac{dE}{dt} = \frac{de}{dt} + e[(\pi - \mu) - \varepsilon i], \tag{3.14}$$

$$\frac{1}{N}\frac{dI}{dt} = \frac{di}{dt} + i[(\pi - \mu) - \varepsilon i] \tag{3.15}$$

and

$$\frac{1}{N}\frac{dR}{dt} = \frac{dr}{dt} + r[(\pi - \mu) - \varepsilon i]. \tag{3.16}$$

The substitution of (3.13)-(3.16) into (3.8)-(3.11) produces

$$\frac{dS}{dt} = \pi + \alpha r - [\pi + (\beta c - \varepsilon)i]s, \tag{3.17}$$

$$\frac{dE}{dt} = f\beta cis + f_1\,\beta cir - [\pi + k + (\delta\beta c - \varepsilon)i]e, \tag{3.18}$$

$$\frac{dI}{dt} = (1-f)\beta cis + (1-f_1)\beta cir + (\delta\beta ci + k)e - [\pi + \sigma + \omega + \varepsilon(1-i)]i \quad (3.19)$$

and

$$\frac{dR}{dt} = (\sigma + \omega)i - [\pi + \alpha + (\beta c - \varepsilon)i]r \quad (3.20)$$

with the initial conditions:

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

such that

$$s + e + i + r = 1$$

3.2.2 Positivity of the Solution

The formulated model shall only be epidemiologically correct if all the considered dependent variables are non-negative at any time t. Hence, the Lemma 3.1 below establishes the positivity of the model.

Lemma 3.1: Given that the initial conditions of nonlinear system ((3.17)-(3.20)) are as given above, then the solutions $s(t), e(t), i(t)$, and $r(t)$ are positive for all $t > 0$.

Proof. Suppose that $t^* = sup\{t > 0: s(t) > 0, e(t) > 0, i(t) > 0, r(t) > 0\} \in [0, t]$, then $t^* > 0$. By the consideration of the first equation in the nonlinear system (3.17)-(3.20), that is

$$\frac{ds}{dt} = \pi + \alpha r - [\pi + (\beta c - \varepsilon)i]s,$$

if $(\beta c - \varepsilon)i = \Lambda_1$, then

$$\frac{ds}{dt} = \pi + \alpha r - [\pi + \Lambda_1]s \geq \pi - [\pi + \Lambda_1]s,$$

$$\frac{d}{dt}\left[s(t)e^{\left(\pi t + \int_0^t \Lambda_1(\xi)d\xi\right)}\right] \geq \pi e^{\left(\pi t + \int_0^t \Lambda_1(\xi)d\xi\right)}$$

$$\Rightarrow s(t_1)e^{\left(\pi t_1 + \int_0^{t_1} \Lambda_1(\xi)d\xi\right)} - s(0) \geq \int_0^{t_1} \pi e^{\left(\pi y + \int_0^y \Lambda_1(\xi)d\xi\right)} dy$$

$$\Rightarrow s(t_1) \geq e^{-\left(\pi t_1 + \int_0^{t_1} \Lambda_1(\xi) d\xi\right)} \left[s(0) + \int_0^{t_1} \pi e^{\left(\pi y + \int_0^{y} \Lambda_1(\xi) d\xi\right)} dy \right] > 0.$$

In similar manner, it can be shown that $e(t), i(t)$ and $r(t)$ are positive.

3.3 Equilibrium Points, Basic Reproduction Number (R_0) and Stability Analysis

3.3.1 Equilibrium Points

At equilibrium, the nonlinear system (3.17)-(3.20) becomes

$$0 = \pi + \alpha r - [\pi + (\beta c - \varepsilon) i] s \tag{3.21}$$

$$0 = f \beta c i s + f_1 \beta c i r - [\pi + k + (\delta \beta c - \varepsilon) i] e \tag{3.22}$$

$$0 = (1 - f) \beta c i s + (1 - f_1) \beta c i r + (\delta \beta c i + k) e - [\pi + \sigma + \omega + \varepsilon(1 - i)] i. \tag{3.23}$$

$$0 = (\sigma + \omega) i - [\pi + \alpha + (\beta c - \varepsilon) i] r. \tag{3.24}$$

From (3.24),

$$r = \frac{(\sigma + \omega) i}{[\pi + \alpha + (\beta c - \varepsilon) i]}, \tag{3.25}$$

if (3.25) is used in (3.21), it gives

$$s = \frac{\pi[\pi + \alpha + (\beta c - \varepsilon) i] + \alpha(\sigma + \omega) i}{[\pi + (\beta c - \varepsilon) i][\pi + \alpha + (\beta c - \varepsilon) i]}, \tag{3.26}$$

whilst the subsequent substitution of (3.25) and (3.26) in (3.22) results to

$$e = \frac{f \beta c i \{\pi[\pi + \alpha + (\beta c - \varepsilon) i] + \alpha(\sigma + \omega) i\} + f_1 \beta c (\sigma + \omega)[\pi + (\beta c - \varepsilon) i] i^2}{[\pi + (\beta c - \varepsilon) i][\pi + \alpha + (\beta c - \varepsilon) i][\pi + k + (\delta \beta c - \varepsilon) i]}. \tag{3.27}$$

When (3.25)-(3.27) are put into (3.23) as functions of i, then

$$A_5 i^5 + A_4 i^4 + A_3 i^3 + A_2 i^2 + A_1 i = 0, \tag{3.28}$$

such that A_1, A_2, A_3, A_4 and A_5 are given in Appendix B.

When (3.28) is solved, five values of $i; i_1, i_2, i_3, i_4, i_5$ are produced. The values are subsequently put in (3.25)-(3.27) to give the corresponding (s, e, r) values in a set of five each i.e., $(s_1, s_2, s_3, s_4, s_5), (e_1, e_2, e_3, e_4, e_5)$ and $(r_1, r_2, r_3, r_4, r_5)$. Two out of the obtained equilibrium points are P_1, which is the disease free equilibrium (DFE) and P_2 which is a member of the endemic equilibrium point (EEP). The other sets of equilibrium points P_3, P_4 and P_5 which are the remaining EEP could not be produced here as they cover almost 2000 pages when solved with Mathematica 10.

$P_1 = (s_1, e_1, i_1, r_1) = (1,0,0,0)$, and $P_2 = (s_2, e_2, i_2, r_2)$, such that

$$P_2 = \left\{ \frac{\pi\beta c + \alpha(\sigma + \omega + \varepsilon)}{\beta c[\alpha\varepsilon + \pi\beta c]}, \frac{\pi f \varepsilon[\pi\beta c + \alpha(\sigma + \omega + \varepsilon)] + \pi^2 f_1 \beta c(\sigma + \omega)}{[\pi\beta c + \alpha\varepsilon][\pi\delta\beta c + k\varepsilon]}, \frac{\pi}{\varepsilon}, \frac{\pi(\sigma + \omega)}{[\alpha\varepsilon + \pi\beta c]} \right\}.$$

By the adopted normalisation approach, it would be expected that the sum of the solution equals to unity at any point in time. Also, four sets of equilibrium solutions would be expected since there are four independent variables. Since five sets of solutions are produced, the validity of the results are tested using the two conditions below;

a. The substitution of the values of i into (3.28) is expected to give its LHS as 0 at all times.

b. The sum of s, e, i and r is expected to be 1 at all times.

All the equilibrium points passed these tests except P_2 which could not pass the second condition. By this failure, P_2 is disregarded as a true solution, and the equilibrium points are reduced to four sets. By inspection, P_1 coincides with the disease free equilibrium (DFE) which can easily be verified by setting $i = 0$ in the nonlinear system

(3.17)-(3.20), ($i = 0$ explains the situation when there is yet to be TB infection in the community under consideration).

3.3.2 Basic Reproduction Number (R_0)

Establishing the Basic Reproduction Number (R_0)

When there is disease outbreak, the number of persons that get the infection from a single carrier is termed as the basic reproduction number (R_0). Simply, basic reproduction number (R_0) is the number of secondary infections from a singly reported one. In establishing the (R_0) of the model under consideration, the use of next generation matrix shall be considered as discussed by van den Driessche & Watmough (2002), where (R_0) is defined as

$$R_0 = \rho(FV^{-\prime}). \tag{3.29}$$

ρ is defined as the spectral radius (dominant eigenvalue) of the matrix FV', where F represents the rate of appearance of new infections in the infected compartments and V represents the inward and outward movements at the infected compartments.

V is defined as

$$V = V_j^- - V_j^+,$$

where

V_j^- = the rate of inward movements of individuals into the infected compartments

and

V_j^+ = the rate of outward movements of individuals from the infected compartments.

From the nonlinear system (3.17)-(3.20), F and V respectively are

$$F = \begin{pmatrix} 0 & f\beta cs + f_1\beta cr \\ \delta\beta ci & (1-f)\beta cs + (1-f_1)\beta cr \end{pmatrix} \tag{3.30}$$

and

$$V = \begin{pmatrix} [\pi + k + (\delta\beta c - \varepsilon)i] & (\delta\beta c - \varepsilon)e \\ -k & [\pi + \sigma + \omega + \varepsilon(1 - i)] \end{pmatrix}. \tag{3.31}$$

When F and V are evaluated at DFE $(1,0,0,0)$, then

$$F = \begin{pmatrix} 0 & f\beta c \\ 0 & (1 - f)\beta c \end{pmatrix} \tag{3.32}$$

and

$$V = \begin{pmatrix} (\pi + k) & 0 \\ -k & (\pi + \sigma + \omega + \varepsilon) \end{pmatrix}. \tag{3.33}$$

$$\Rightarrow V^{-'} = \frac{1}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)} \begin{pmatrix} (\pi + \sigma + \omega + \varepsilon) & 0 \\ k & (\pi + k) \end{pmatrix}. \tag{3.34}$$

From (3.32) and (3.34),

$$FV^{-'} = \frac{1}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)} \begin{pmatrix} 0 & f\beta c \\ 0 & (1 - f)\beta c \end{pmatrix} \begin{pmatrix} (\pi + \sigma + \omega + \varepsilon) & 0 \\ k & (\pi + k) \end{pmatrix} \tag{3.35}$$

$$\Rightarrow FV^{-'} = \begin{pmatrix} \dfrac{f\beta ck}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)} & \dfrac{f\beta c(\pi + k)}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)} \\ \dfrac{(1 - f)\beta ck}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)} & \dfrac{(1 - f)\beta c(\pi + k)}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)} \end{pmatrix}. \tag{3.36}$$

The dominant eigenvalue of (3.36) i.e., $\rho(FV^{-'})$ is

$$\rho\left(FV^{-'}\right) = \frac{\beta c[k + \pi(1 - f)]}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)}.$$

Hence, the basic reproduction number (R_0) is

$$R_0 = \frac{\beta c[k + \pi(1 - f)]}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)}. \tag{3.37}$$

Theorem 3.3.1. Whenever there is no bypassing of the exposed class i.e., $f = 1$ in R_0, the TB infection becomes less rampaging.

Proof. Since $f \leq 1$,

$$0 \leq \pi(1 - f). \tag{3.38}$$

The addition of k to both sides of (3.38) gives

$$k \leq k + \pi(1 - f), \tag{3.39}$$

and the multiplication of (3.39) by βc and subsequent division by $(\pi + k)(\pi + \sigma + \omega + \varepsilon)$ gives

$$\frac{\beta ck}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)} \leq \frac{\beta c[k + \pi(1 - f)]}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)}. \tag{3.40}$$

That is

$$R_{0_1} \leq R_0,$$

where

$$R_{0_1} = \frac{\beta ck}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)}.$$

When $f < 1$

$$\Rightarrow R_{0_1} < R_0 \tag{3.41}$$

and when $f = 1$

$$\Rightarrow R_{0_1} = R_0. \tag{3.42}$$

(3.42) concludes the proof.

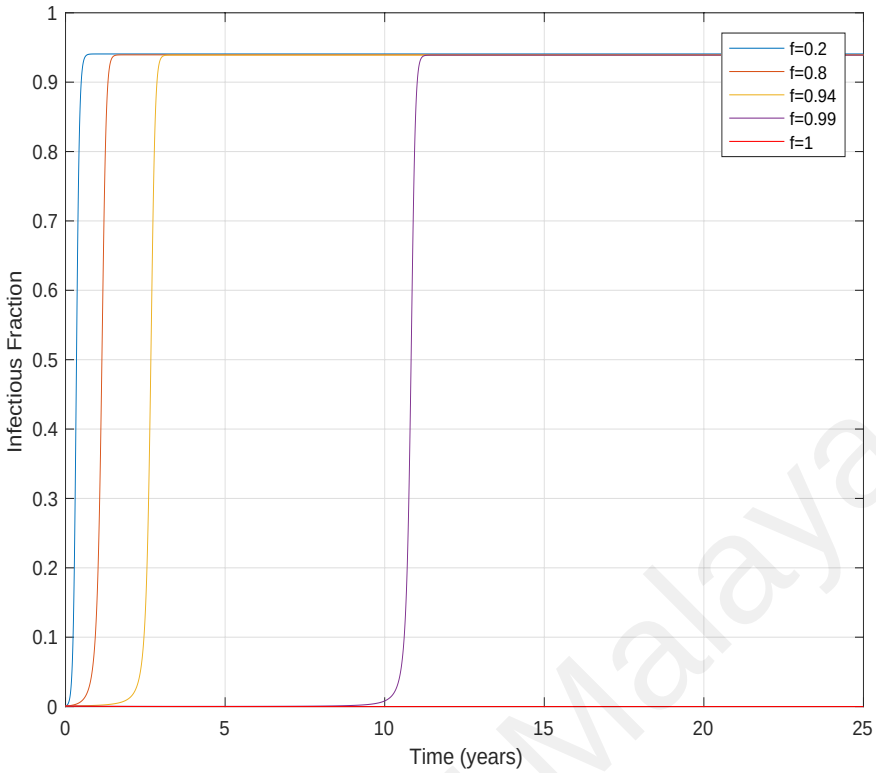

Figure 3.2: Impact of f on the TB infection

The role played by the latent stage of TB is explained by the Theorem 3.3.1 above. The latent stage slows down the infection and in fact, drastically reduces its incidence as displayed in Figure 3.2, when properly utilised. Variation in the value of f from $f = 0.2$ to $f = 0.8$ and subsequently $f = 0.94$ shows early outbreak of the TB infection. Conversely, $f = 0.99$ delays the outbreak while $f = 1$ (no infected individual bypasses the latent stage to move directly to the infectious) almost annihilate the infection.

As discussed at the Dahlem workshop held in 1997, the requisite intervention strategies to combat any infectious disease are in five stages; control, elimination of disease, elimination of infections, eradication and extinction. The list is in the hierarchical order which means, the least expected to be done at the dawn of TB outbreak is control (i.e. reduction of the tuberculosis incidence to an acceptable level in the community where

it has broken out), while the supreme result that could be achieved is the disease going to an extinction (i.e. non-existence of the TB bacteria, *Mycobacterium tuberculosis(Mtb)* naturally or in the laboratory). As such, making sure every carrier of TB passes through the exposed state controls the spread of the infection.

3.3.3 Stability Analysis

The Jacobian matrix of equations (3.17)-(3.20) is expressed as

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial s} & \frac{\partial f_1}{\partial e} & \frac{\partial f_1}{\partial i} & \frac{\partial f_1}{\partial r} \\ \frac{\partial f_2}{\partial s} & \frac{\partial f_2}{\partial e} & \frac{\partial f_2}{\partial i} & \frac{\partial f_2}{\partial r} \\ \frac{\partial f_3}{\partial s} & \frac{\partial f_3}{\partial e} & \frac{\partial f_3}{\partial i} & \frac{\partial f_3}{\partial r} \\ \frac{\partial f_4}{\partial s} & \frac{\partial f_4}{\partial e} & \frac{\partial f_4}{\partial i} & \frac{\partial f_4}{\partial r} \end{pmatrix} \tag{3.43}$$

where

$$f_1 = \pi + \alpha r - [\pi + (\beta c - \varepsilon)i]s,$$

$$f_2 = f\beta cis + f_1\beta cir - [\pi + k + (\delta\beta c - \varepsilon)i]e,$$

$$f_3 = (1-f)\beta cis + (1-f_1)\beta cir + (\delta\beta ci + k)e - [\pi + \sigma + \omega + \varepsilon(1-i)]i,$$

and

$$f_4 = (\sigma + \omega)i - [\pi + \alpha + (\beta c - \varepsilon)i]r.$$

Hence,

$$J = \begin{pmatrix} -[\pi + (\beta c - \varepsilon)i] & 0 & -(\beta c - \varepsilon)s & \alpha \\ f\beta ci & a_{22} & a_{23} & f_1\beta ci \\ (1-f)\beta ci & \delta\beta ci + k & a_{33} & (1-f_1)\beta ci \\ 0 & 0 & (\sigma + \omega) - (\beta c - \varepsilon)r & a_{44} \end{pmatrix}, \tag{3.44}$$

where

$$a_{22} = -[\pi + k + (\delta\beta c - \varepsilon)i],$$

$$a_{23} = f\beta cs + f_1\beta cr - (\delta\beta c - \varepsilon)e,$$

$$a_{33} = (1-f)\beta cs + (1-f_1)\beta cr + \delta\beta ce - (\pi + \sigma + \omega + \varepsilon) + 2\varepsilon i$$

and

$$a_{44} = -[\pi + \alpha + (\beta c - \varepsilon)i].$$

3.3.4 Stability of the DFE

Local Stability

Theorem 3.3.2. The disease free equilibrium (DFE) of the model is locally asymptotically stable whenever $R_0 < 1$ and unstable otherwise.

Proof. The evaluation of (3.44) at the DFE (1,0,0,0) gives

$$J = \begin{pmatrix} -\pi & 0 & -(\beta c - \varepsilon) & \alpha \\ 0 & -(\pi + k) & f\beta c & 0 \\ 0 & k & (1-f)\beta c - (\pi + \sigma + \omega + \varepsilon) & 0 \\ 0 & 0 & (\sigma + \omega) & -(\pi + \alpha) \end{pmatrix}. \qquad (3.45)$$

By denoting the eigenvalue as η, the eigenvalues of (3.45) would be gotten from

$$|J - \eta I| = 0.$$

That is,

$$\begin{vmatrix} -(\pi + \eta) & 0 & -(\beta c - \varepsilon) & \alpha \\ 0 & -(\pi + k + \eta) & f\beta c & 0 \\ 0 & k & (1-f)\beta c - (\pi + \sigma + \omega + \varepsilon + \eta) & 0 \\ 0 & 0 & (\sigma + \omega) & -(\pi + \alpha + \eta) \end{vmatrix} = 0. \qquad (3.46)$$

The first two eigenvalues of (3.46) are

$$\eta_1 = -\pi$$

and

$$\eta_2 = -(\pi + \alpha)$$

after which (3.46) is reduced to

$$\begin{vmatrix} -(\pi + k + \eta) & f\beta c \\ k & (1-f)\beta c - (\pi + \sigma + \omega + \varepsilon + \eta) \end{vmatrix} = 0, \qquad (3.47)$$

hence

$$\eta^2 + \{(\pi + k) + (\pi + \sigma + \omega + \varepsilon) - \beta c(1-f)\}\eta + \{(\pi + k)(\pi + \sigma + \omega + \varepsilon) - \beta c[k + \pi(1-f)]\} = 0. \quad (3.48)$$

If (3.48) is compared with

$$a\eta^2 + b\eta + c = 0$$

such that

$$a = 1,$$

$$b = (\pi + k) + (\pi + \sigma + \omega + \varepsilon) - \beta c(1-f)$$

and

$$c = (\pi + k)(\pi + \sigma + \omega + \varepsilon) - \beta c[k + \pi(1-f)],$$

then the third and fourth eigenvalues, η_3 and η_4 respectively are

$$\eta_3, \eta_4 = \frac{-b \pm \sqrt{b^2 - 4\{(\pi + k)(\pi + \sigma + \omega + \varepsilon) - \beta c[k + \pi(1-f)]\}}}{2} \qquad (3.49)$$

$$= \frac{-b \pm \sqrt{b^2 - 4(\pi + k)(\pi + \sigma + \omega + \varepsilon)\left\{1 - \frac{\beta c[k + \pi(1-f)]}{(\pi+k)(\pi+\sigma+\omega+\varepsilon)}\right\}}}{2}. \quad (3.50)$$

Hence,

$$\eta_3, \eta_4 = \frac{-b \pm \sqrt{b^2 - 4(\pi + k)(\pi + \sigma + \omega + \varepsilon)(1 - R_0)}}{2}. \quad (3.51)$$

Evidently, the eigenvalues of (3.51) depend on R_0. $R_0 < 1 \Rightarrow \eta_3, \eta_4 < 0$ while $R_0 > 1 \Rightarrow \eta_3 > 0$ and $\eta_4 < 0$. Hence, $R_0 < 1$ guarantees the stability and as such completes the proof.

Global Stability

To establish the global stability of the DFE of the nonlinear system (3.17)-(3.20), the use of the global stability theorem discussed by Castillo-Chavez et al. (2002) is employed. This approach has been used by Bhunu et al. (2011), Srivastav & Ghosh (2016) and Goswami et al. (2018) among other researchers.

If the system of equations (3.17)-(3.20) can be written in the form:

$$\frac{dX}{dt} = F(X, Y) \quad and \quad \frac{dY}{dt} = G(X, Y) \quad such \quad that \quad G(X, 0) = 0,$$

where the uninfected and infected compartments are respectively represented as

$X = (s, r)^T$ and $Y = (e, i)^T$, and also, the DFE, P_1 is simply expressed as

$$P_1 = (X_0^*, 0)$$

where

$$X_0^* = (1,0),$$

then the DFE is globally asymptotically stable (GAS) provided $R_0 < 1$ and as well satisfies the conditions H_1 and H_2 given below.

$H_1: \frac{dX}{dt} = F(X_0, 0), X_0^*$ is globally asymptotically stable.

$H_2: G(X, Y) = AY - \hat{G}(X, Y), \hat{G}(X, Y) \geq 0,$

where $A = D_Y G(X_0^*, 0)$ is M-matrix (that is, all the non-diagonal elements of the matrix are non-negative).

Theorem 3.3.3. The DFE, $\mathrm{P}_1 = (\mathrm{X}_0^*, 0)$ of the nonlinear system (3.17)-(3.20) is globally asymptotically stable (GAS) so far it satisfies the conditions H_1 and H_2 above, as well as $\mathrm{R}_0 < 1$.

Proof. From the above, the following are established

$$F(X_0, 0) = \begin{pmatrix} \pi - \pi s \\ 0 \end{pmatrix}$$

and

$$G(X, Y) = AY - \hat{G}(X, Y),$$

where

$$A = \begin{pmatrix} -[\pi + k + (\delta\beta c - \varepsilon)i] & f\beta cs + f_1\beta cr - (\delta\beta c - \varepsilon)e \\ \delta\beta ci + k & A_{22} \end{pmatrix}, \tag{3.52}$$

where A_{22} and $\hat{G}(X, Y)$ are respectively expressed as

$$A_{22} = (1 - f)\beta cs + (1 - f_1)\beta cr + \delta\beta ce - (\pi + \sigma + \omega + \varepsilon) + 2\varepsilon i,$$

$$\hat{G}(X,Y) = \begin{pmatrix} \hat{G}_1(X,Y) \\ \hat{G}_2(X,Y) \end{pmatrix} = \begin{pmatrix} f\beta cis + f_1\beta cir \\ (1-f)\beta cis + (1-f_1)\beta cir + \delta\beta cie \end{pmatrix}. \quad (3.53)$$

Recall that $Y_0 = Y(0) \geq 0 \Rightarrow Y(t) \geq 0$. Since A is an M-matrix, then e^{At} is a positive semigroup. By the variation of constant formula (Wu, 2003; Carrasco & Leiva, 2007) gives

$$0 \leq Y(t) = e^{At}Y_0 - \int_0^t e^{A(t-w)}\hat{G}\big(X(w), Y(w)\big)dw \quad (3.54)$$

$$\leq e^{At}Y_0.$$

It is obvious from (3.51) that A has dominant eigenvalue $m(A) < 0$ for $R_0 < 1$,hence,

$$\lim_{t\to\infty}\left|\left|e^{At}\right|\right| = 0, \quad \Rightarrow \lim_{t\to\infty} Y(t) = 0.$$

X^* is a GAS equilibrium point of $\frac{dX}{dt} = F(X,0)$ which is a limiting system of $F(X(t),Y(t))$.Thus,

$$\lim_{t\to\infty} X(t) = X^*$$

which satisfies condition H_1.Also, evaluating (3.52) and (3.53) at the DFE $(X_0, 0)$ gives

$$A = \begin{pmatrix} -[\pi + k] & f\beta c \\ k & (1-f)\beta c - (\pi + \sigma + \omega + \varepsilon) \end{pmatrix} \quad (3.55)$$

and

$$\hat{G}(X,Y) = 0. \quad (3.56)$$

Apparently, the non-diagonal elements of A are non-negative. Since $f \leq 1$ and $f_1 \leq 1 \Rightarrow \hat{G}(X,Y) \geq 0$, the satisfaction of condition H_2 is thus established. Then, the DFE, P_1 of the nonlinear system (3.17)-(3.20) is GAS.

3.3.5 Stability of the EEP

Local Stability

The establishment of the local stability of the EEP analytically is quite challenging. This is due to the cumbersomeness of the gotten results which was mentioned earlier to be almost 2000 pages long. Hence, phase portrait diagrams are used in demonstrating the local stability of the EEP with five randomly chosen points:

$$\{[s(0) = 0.99175,\quad e(0) = 0.00750,\quad i(0) = 0.00075,\quad r(0) = 0],$$

$$[s(0) = 0.89110, e(0) = 0.09900,\quad i(0) = 0.00990,\quad r(0) = 0],$$

$$[s(0) = 0.80200,\quad e(0) = 0.18000, i(0) = 0.01800,\quad r(0) = 0],$$

$$[s(0) = 0.75250,\quad e(0) = 0.22500,\quad i(0) = 0.02250, r(0) = 0],$$

$[s(0) = 0.60400,\quad e(0) = 0.36000,\quad i(0) = 0.03600,\quad r(0) = 0]\}$ as well as the parameter values given in Table 3.1 below. All the randomly chosen points converge to the same point, which implies the local asymptotic stability of the EEP. The phase portraits are shown in Figures 3.1 - 3.5 below.

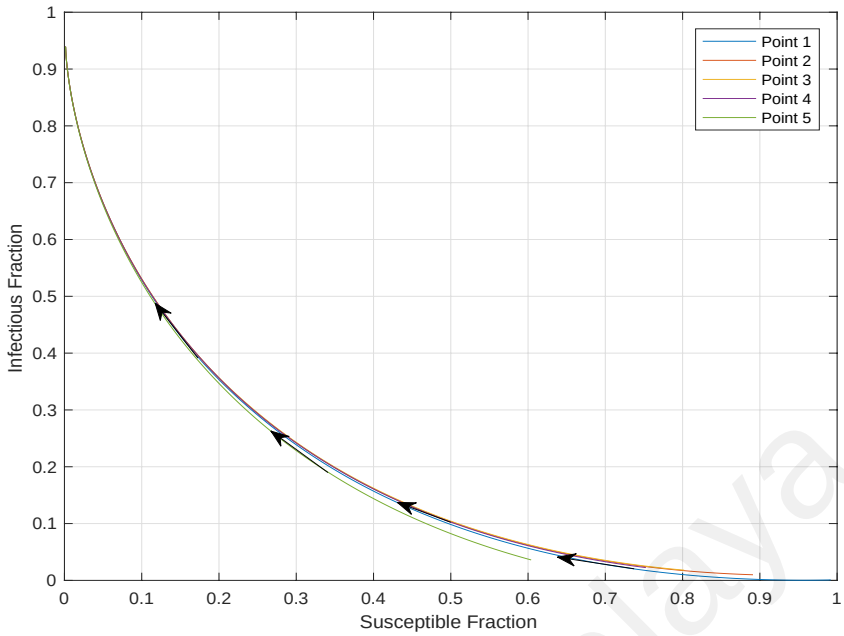

Figure 3.3: Phase portrait of the system (3.17)-(3.20) in s-i Plane

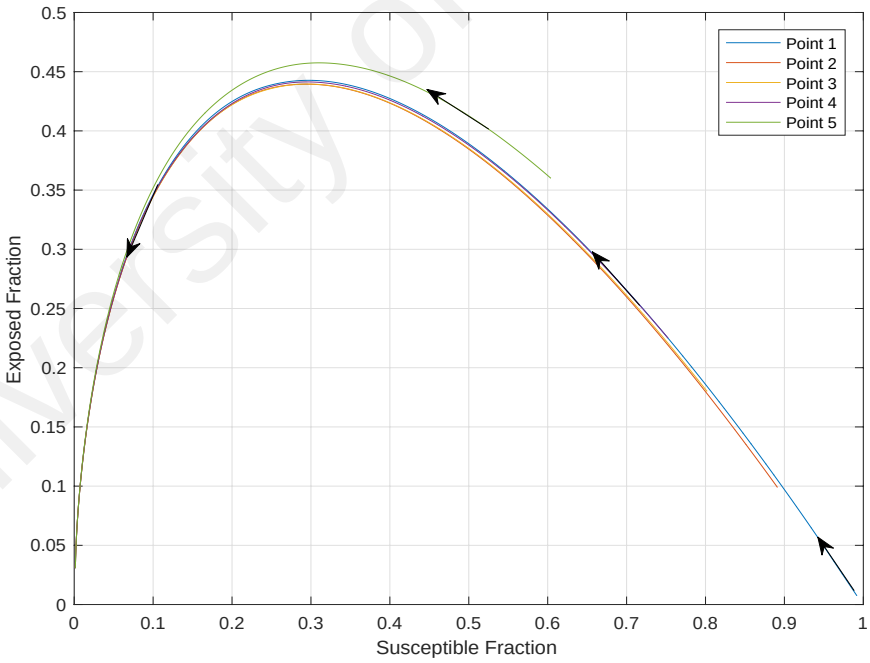

Figure 3.4: Phase portrait of the system (3.17)-(3.20) in s-e Plane

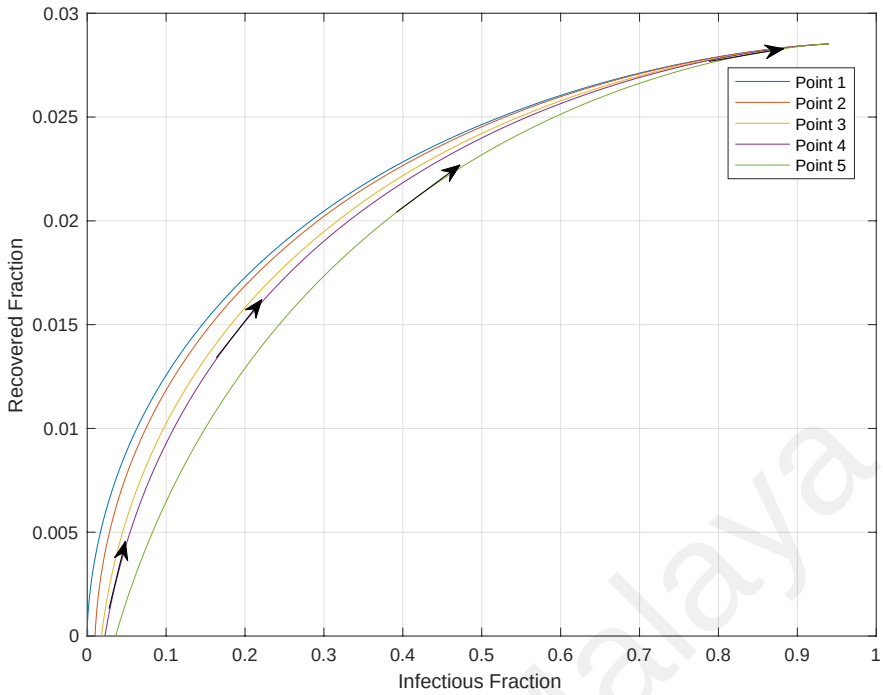

Figure 3.5: Phase portrait of the system (3.17)-(3.20) in i-r Plane

Global Stability

Theorem 3.3.4. The endemic equilibrium point $\{\mathrm{E}_1 = (\mathrm{s}^*, \mathrm{e}^*, \mathrm{i}^*, \mathrm{r}^*) \in \Phi\}$ of the nonlinear system (3.17)-(3.20) is globally asymptotically stable whenever $\mathrm{f} = 1$.

Proof. Consider the Lyapunov function

$$V = K_1\left(s - s^* - s^*\ln\frac{s}{s^*}\right) + K_2\left(e - e^* - e^*\ln\frac{e}{e^*}\right) + K_3\left(i - i^* - i^*\ln\frac{i}{i^*}\right), \quad (3.57)$$

then the time derivative of V is

$$V' = K_1\left(\frac{s - s^*}{s}\right)\frac{ds}{dt} + K_2\left(\frac{e - e^*}{e}\right)\frac{de}{dt} + K_3\left(\frac{i - i^*}{i}\right)\frac{di}{dt}. \quad (3.58)$$

Substituting $\frac{ds}{dt}, \frac{de}{dt}$ and $\frac{di}{dt}$ as expressed in (3.17)-(3.19) in (3.58),

$$V' = K_1\left(\frac{s-s^*}{s}\right)[\pi + \alpha r - [\pi + (\beta c - \varepsilon)i]\mathrm{s}]$$
$$+K_2\left(\frac{e-e^*}{e}\right)[f\beta cis + f_1\beta cir - [\pi + k + (\delta\beta c - \varepsilon)i]\mathrm{e}]$$
$$+K_3\left(\frac{i-i^*}{i}\right)((1-f)\beta cis + (1-f_1)\beta cir + (\delta\beta ci)e + ke$$
$$-(\pi + \sigma + \omega + \varepsilon)i + \varepsilon ii). \tag{3.59}$$

At equilibrium, $\pi = \pi s^* + (\beta c - \varepsilon)i^* s^* - \alpha r^*, (k+\mu) = \frac{f\beta ci^* s^* + f_1\beta cir^* - (\delta\beta c - \varepsilon)i^* e^*}{e^*}$ and$(\pi + \sigma + \omega + \varepsilon) = \frac{(1-f)\beta ci^* s^* + (1-f_1)\beta ci^* r^* + \delta\beta ci^* e^* + ke^* + \varepsilon i^* i^*}{i^*}$ which upon substitution into (3.59) gives

$$V' = K_1\left(\frac{s-s^*}{s}\right)\left[\pi s^* + (\beta c - \varepsilon)i^* s^* - \alpha r^* + \alpha r - \left(\pi + (\beta c - \varepsilon)\right)s\right]$$
$$+K_2\left(\frac{e-e^*}{e}\right)$$
$$\left(f\beta cis + f_1\beta cir - \left[\frac{f\beta ci^* s^* + f_1\beta ci^* r^* - (\delta\beta c - \varepsilon)i^* e^*}{e^*}\right]e - (\delta\beta c - \varepsilon)ie\right)$$
$$+K_3\left(\frac{i-i^*}{i}\right)\left((1-f)\beta cis + (1-f_1)\beta cir + \delta\beta cie + ke - \left(\frac{K_3^*}{i^*}\right)i + \varepsilon ii\right), \tag{3.60}$$

$$K_3^* = (1-f)\beta ci^* s^* + (1-f_1)\beta ci^* r^* + \delta\beta ci^* e^* + ke^* + \varepsilon i^* i^*.$$

From $s + e + i + r = 1$,

$$i = 1 - (s + e + r) \Rightarrow i^* = 1 - (s^* + e^* + r^*). \tag{3.61}$$

Using (3.61) in (3.60) gives

$$V' = \frac{-K_1\pi(s-s^*)^2}{s} + K_1\left(\frac{s-s^*}{s}\right)[(\beta c-\varepsilon)(i^*s^*-is)-\alpha r^*+\alpha r]$$
$$+K_2\left(\frac{e-e^*}{e}\right)$$
$$\left(f\beta cis + f_1\beta cir - \left[\frac{f\beta ci^*s^* + f_1\beta ci^*r^* - (\delta\beta c-\varepsilon)i^*e^*}{e^*}\right]e - (\delta\beta c-\varepsilon)ie\right)$$
$$+K_3\left(\frac{i-i^*}{i}\right)\left((1-f)\beta cis + (1-f_1)\beta cir + \delta\beta cie + ke + \varepsilon i\big(1-(s+e+r)\big)\right)$$
$$-K_3\left(\frac{i-i^*}{i}\right)$$
$$\left(\frac{(1-f)\beta ci^*s^* + (1-f_1)\beta ci^*r^* + \delta\beta ci^*e^* + ke^* + \varepsilon i^*\big(1-(s^*+e^*+r^*)\big)}{i^*}\right)i. \tag{3.62}$$

Let $\frac{s}{s^*} = x_1,\ \frac{e}{e^*} = x_2,\ \frac{i}{i^*} = x_3,\ i^*s^* = a,\ i^*e^* = b,\ i^*r^* = d,\ kE^* = g,\ \varepsilon i^* = m$ and $\alpha r^* = h$, then (3.62) becomes

$$V' = -\frac{-K_1\pi(s-s^*)^2}{s} + K_1\left(1-\frac{1}{x_1}\right)[(\beta c-\varepsilon)(i^*s^*-i^*x_3s^*x_1)-\alpha r^*$$
$$+\alpha r^*x_4] + K_2\left(1-\frac{1}{x_2}\right)(f\beta ci^*x_3s^*x_1 + f_1\beta ci^*x_3r^*x_4 - (f\beta ci^*s^* + f_1\beta ci^*r^*$$
$$-(\delta\beta c-\varepsilon)i^*e^*)x_2 - (\delta\beta c-\varepsilon)i^*x_3e^*x_2) + K_3\left(1-\frac{1}{x_3}\right)((1-f)\beta ci^*x_3s^*x_1$$
$$+(1-f_1)\beta ci^*x_3r^*x_4 + \delta\beta ci^*x_3e^*x_2 + ke^*x_2 - K_3\left(1-\frac{1}{x_3}\right)\left(\frac{K_3^{**}}{i^*}\right)i,$$
$$+\varepsilon i^*x_3(1-(s^*x_1+e^*x_2+r^*x_4))) + \varepsilon i^*x_3(1-(s^*x_1+e^*x_2+r^*x_4)))$$

(3.63)

$$K_3^{**} = (1-f)\beta ci^*s^* + (1-f_1)\beta ci^*r^* + \delta\beta ci^*e^* + ke^* + \varepsilon i^*(1-(s^*+e^*+r^*))$$

$$V' = \frac{-K_1\pi(s-s^*)^2}{s} + K_1\left(1-\frac{1}{x_1}\right)[(\beta c-\varepsilon)(i^*s^*-ax_1x_3)-h+hx_4]$$
$$+K_2\left(1-\frac{1}{x_2}\right)(f\beta cax_1x_3 + f_1\beta cdx_3x_4 - (f\beta ca + f_1\beta cd - (\delta\beta c-\varepsilon)b)x_2$$
$$-(\delta\beta c-\varepsilon)bx_2x_3) + K_3\left(1-\frac{1}{x_3}\right)((1-f)\beta cax_1x_3 + (1-f_1)\beta cdx_3x_4$$
$$+\delta\beta cbx_2x_3 + gx_2 + mx_3 - \varepsilon ax_1x_3 - \varepsilon bx_2x_3 - \varepsilon dx_3x_4))$$
$$-K_3\left(1-\frac{1}{x_3}\right)((1-f)\beta cax_3 - (1-f_1)\beta cdx_3 - \delta\beta cbx_3$$
$$-gx_3 - mx_3 + \varepsilon ax_3 + \varepsilon bx_3 + \varepsilon dx_3).$$

(3.64)

$$V' = \frac{-K_1\pi(s-s^*)^2}{s} + (K_1(\beta c-\varepsilon)a + K_2 f\beta ca + K_3(1-f)\beta ca$$
$$-K_3\varepsilon a)x_1x_3 + (K_3\delta\beta cb - K_2(\delta\beta c-\varepsilon)b - K_3\varepsilon b)x_2x_3 + (K_2f_1\beta cd$$
$$+K_3(1-f_1)\beta cd - K_3\varepsilon d)x_3x_4 + (K_3\varepsilon a - K_3(1-f)\beta ca)x_1$$
$$+(K_2(\delta\beta c-\varepsilon)b - K_2f\beta ca - K_2f_1\beta cd + K_3g - K_3\delta\beta cb + K_3\varepsilon b)x_2$$
$$+(K_1(\beta c-\varepsilon)a + K_2(\delta\beta c-\varepsilon)b - K_3(1-f)\beta ca - K_3(1-f_1)\beta cd$$
$$-K_3\delta\beta cb - K_3g + K_3\varepsilon a + K_3\varepsilon b + K_3\varepsilon d)x_3 + (K_1h - K_3(1-f_1)\beta cd$$
$$+K_3\varepsilon d)x_4 + K_1(\beta c-\varepsilon)a - K_1h - K_1h\frac{x_4}{x_1} + K_1\frac{h}{x_1} - K_1(\beta c-\varepsilon)\frac{a}{x_1}$$
$$-K_2f\beta ca\frac{x_1x_3}{x_2} - K_2f_1\beta cd\frac{x_3x_4}{x_2} + K_2f\beta ca + K_2f_1\beta cd - K_2(\delta\beta c-\varepsilon)b$$
$$-K_3g\frac{x_2}{x_3} + K_3(1-f)\beta ca + K_3(1-f)\beta cd + K_3\delta\beta cb + K_3g - K_3\varepsilon a$$
$$-K_3\varepsilon b - K_3\varepsilon d. \tag{3.65}$$

Equating the coefficients of x_1x_3, x_2x_3, x_3x_4, x_1, x_2, x_3 and x_4 to 0 gives $K_1 = K_2 = K_3$; $g = f\beta ca$; $\varepsilon = (1-f)\beta c, d = h = 0$. Choosing the values of $K_1 = K_2 = K_3 = f = 1$, and substituting the values of g, ε, d and h gives

$$V' = \frac{-\pi(s-s^*)^2}{s} + \beta ca\left(3 - \frac{1}{x_1} - \frac{x_1x_3}{x_2} - \frac{x_2}{x_3}\right). \tag{3.66}$$

Since arithmetic mean (AM) is greater than or equal to geometric mean (GM). $(AM \geq GM)$, then

$$\frac{1}{x_1} + \frac{x_1x_3}{x_2} + \frac{x_2}{x_3} \geq 3.$$

It is clear from (3.66) that $V' \leq 0$ for which the equality holds when $x_1 = x_2 = x_3 = 1$ (which implies $s = s^*$, $e = e^*$ and $i = i^*$). By the LaSalle's invariance principle (LaSalle & Artstein, 1976), the EEP of the system is globally asymptotically stable whenever $f = 1$.

3.4 Numerical Simulation

The simulation of the model is done using $ODE45$ package of MATLAB 2016a. The set of values used are as given in the Table 3.1 below where x^* is used to denote Bhunu et al. (2008) (with permission from Society for Mathematical Biology). The initial populations in terms of fraction for the susceptible, exposed, infectious and recovered are 0.99175, 0.00750, 0.00075 and 0 respectively, while the resulting graphs are as presented below.

3.4.1 Graphical Results

The Simulation

The numerical simulation investigates the interactions between the compartments and also the relevance of some of the factors considered in the model formulation. Figures 3.6 –3.8 show the proportion of each population compartmental-wise while Figures 3.9 and 3.10 respectively display the picture of the infectious compartment when there is an increase in the recruitment rate and when the treatment rate is stepped up.

SEIR Relationship Graphs

Here, the relationship between each compartments are shown. Figures 3.6 – 3.8 reveal the dynamic of the infection by the evolution of time. The proportion of each fractional population under various contact rates *(c)* are shown. In Figure 3.7, 6.25% reduction in the original value of contact rate *c=80* shows a delay in the disease outbreak and in Figure 3.8, the infection tends to disappear when there is 10% reduction in the contact rate.

Sensitivity Analysis Graphs

In the face of any infection, apart from the contact rate investigated above, also of importance are the recruitment and treatment rates. The recruitment is useful in maintaining the constant influx of people into the community while the treatment is useful

in removing the infectious individuals out of the infectious class. Increase in the recruitment rate (Figure 3.9) slightly delays the outbreak of the infection while increment in the treatment rate (Figure 3.10) delays the period of infection in huge proportion with a slight reduction in the infectious population. The result due to treatment is in agreement with the findings of Khan et al. (2019) where increment in the treatment rate and decrement in the transmission and immunity loss rates help in reducing TB epidemic. This delay could be optimised in tackling the spread of the infection, to manage the eventual break out of the epidemic. However, a growth rate of 7% of the population or a treatment rate of 80% for the infectious can lead the infection to extinction as displayed in Figure 3.9 and Figure 3.10 respectively.

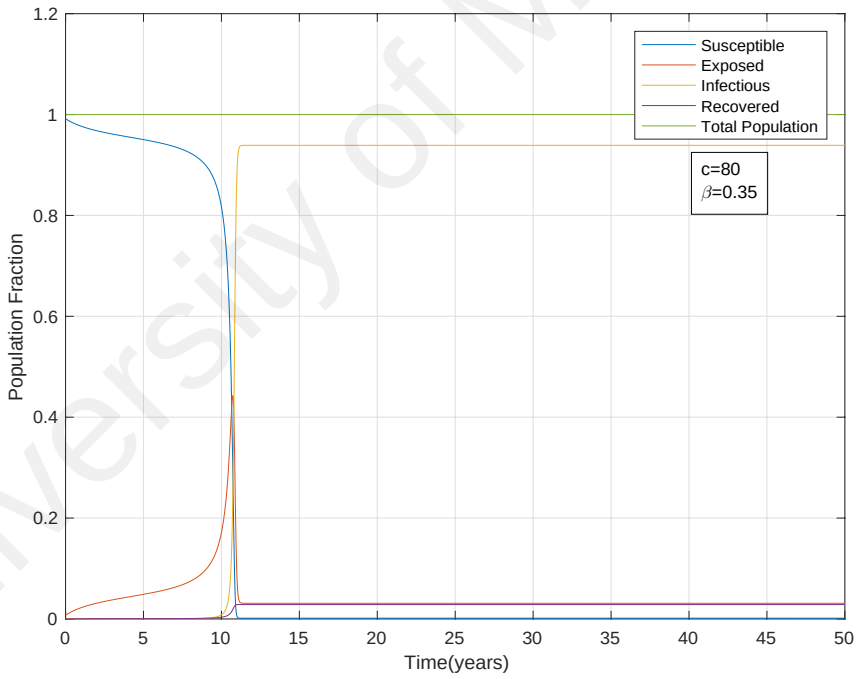

Figure 3.6: SEIR relationship within 50 Years

Table 3.1: Table of values

S/No	Parameter	Meaning	Value (yr^{-1})	Source
1	β	Probability of being infected after effective contact with an infectious being	0.35000	x^*
2	π	Recruitment rate	0.03000	x^*
3	c	Contact rate	80.0000	x^*
4	μ	Natural mortality rate	0.01000	Estimate
5	ε	TB induced death rate	0.30000	x^*
6	k	Endogenous reactivation rate	0.00013	x^*
7	α	Rate of the recovered moving back to susceptible	0.30000	Estimate
8	δ	Exogenous reinfection rate	0.70000	x^*
9	ω	Natural recovery rate	0.20000	x^*
10	σ	Treatment rate	0.60000	Estimate
11	f	Probability that the infected will enter the latent stage of the disease	0.99000	x^*
12	f_1	Probability of the re-infected R moving to E	0.70000	x^*

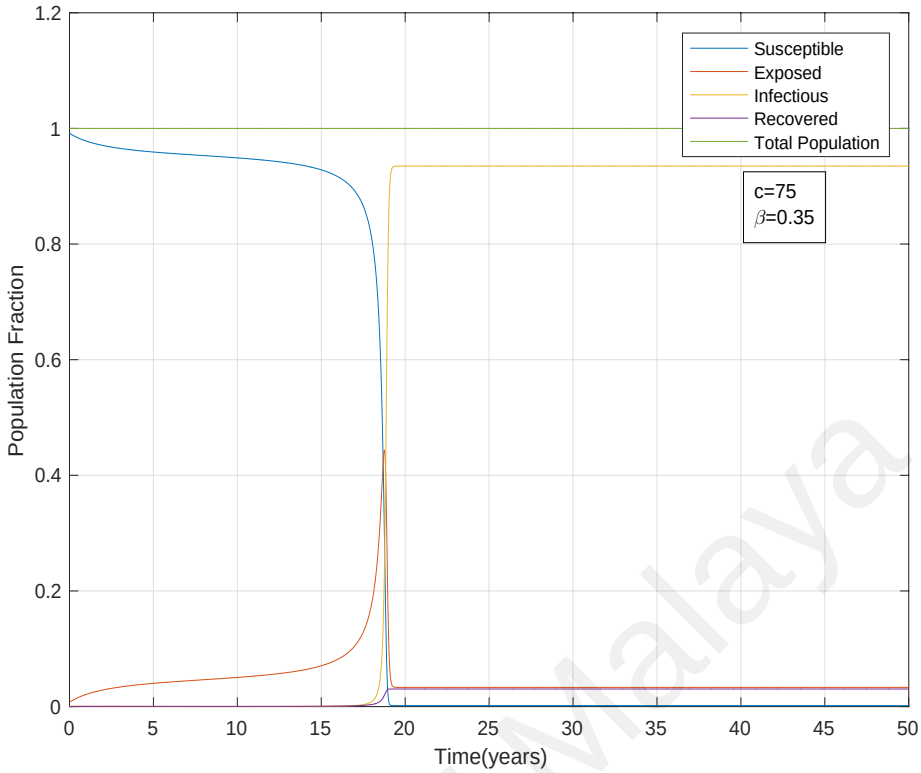

Figure 3.7: Reduction of c by 6.25%

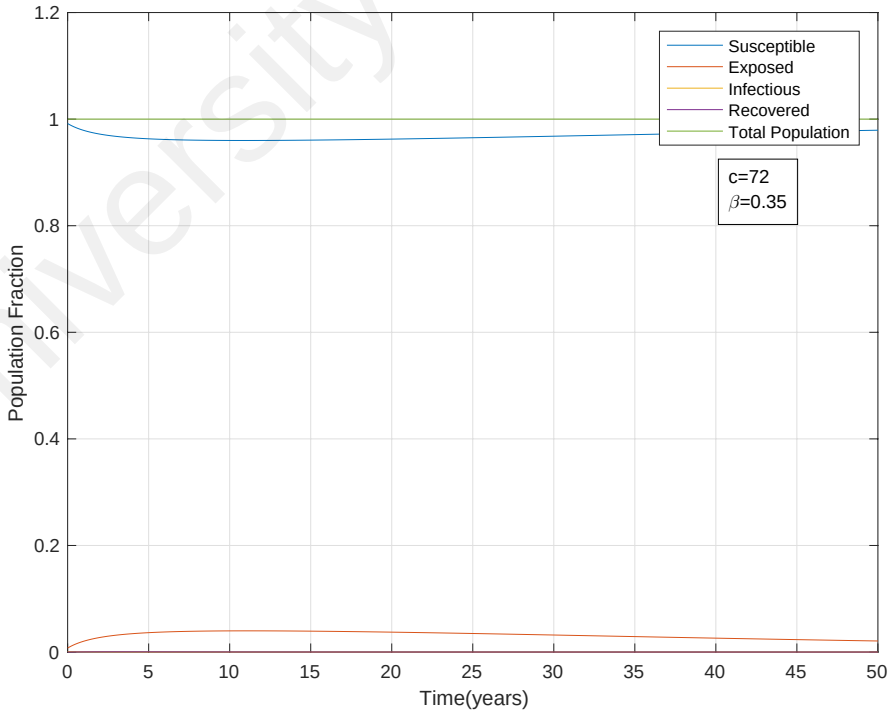

Figure 3.8: Reduction of c by 10%

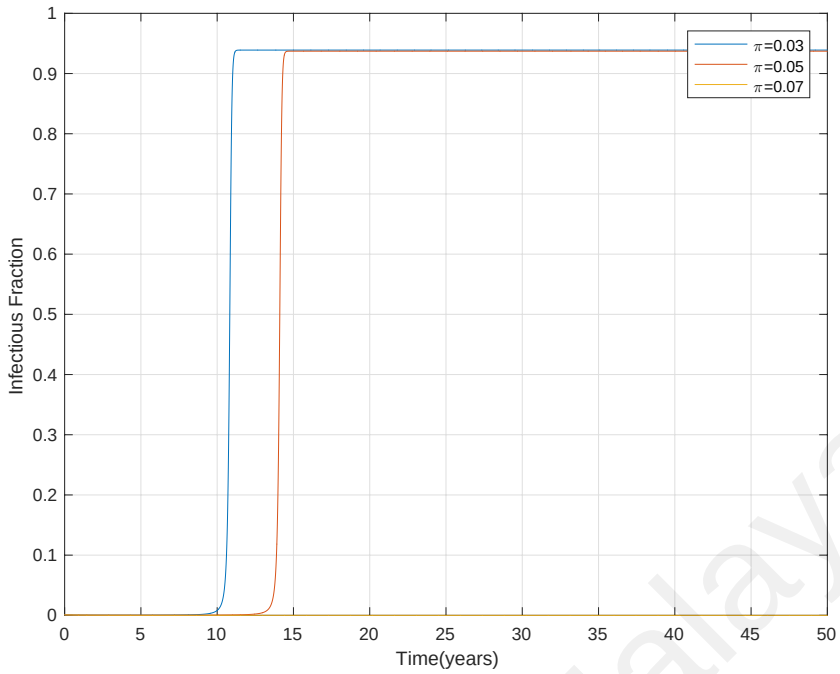

Figure 3.9: Effect of the recruitment rate (π) on the infectious

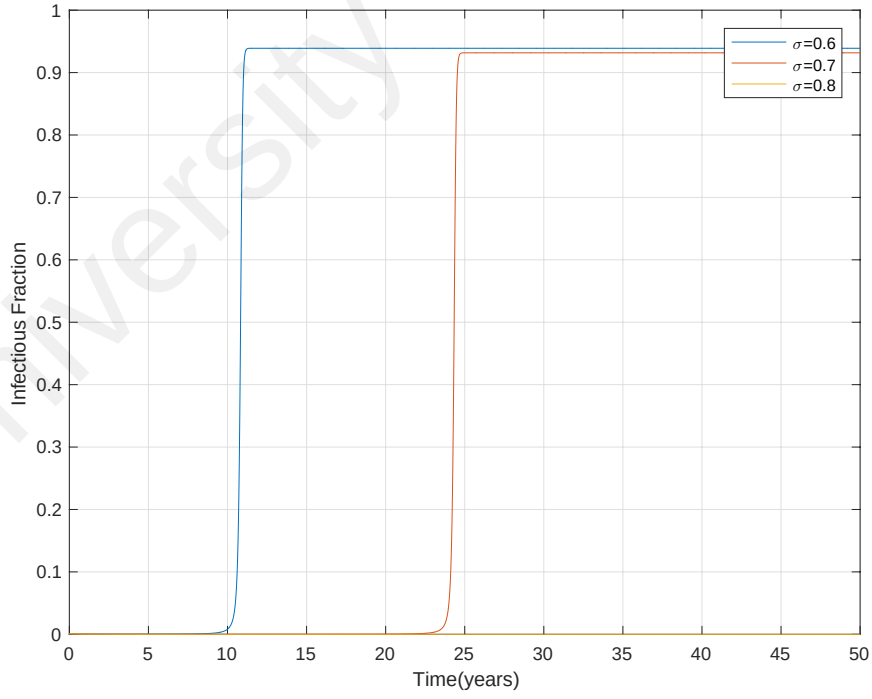

Figure 3.10: Effect of the treatment rate (σ) on the infectious

3.5 Summary

This chapter studies the tuberculosis epidemiology using SEIR compartmental modelling. The disease free equilibrium (DFE) and the endemic equilibrium (EEP) of the model are established and their local and global stabilities are as well shown. Also, normalisation method was used which subsequently helps eliminate the natural death factor (μ), hence allowing the concentration on other factors that can be controlled; recruitment, contact and treatment rates.

The analysis carried out on the basic reproduction number (R_0) (Theorem 3.3.1) reveals the relevance of the exposed class in reducing the incident rate of the TB infection. Non-direct progression of the *Mycobacterium tuberculosis (Mtb)* carriers to the infectious state reduces the eventual number of people with full blown infection due to the fact that R_{0_1} is the same as R_0 whenever $f = 1$, which implies a reduction in the actual value of R_0. The exposed state can be utilised in reducing the incidence of TB infection when measures are put in place to identify *Mtb* carriers at that stage as displayed in Figure 3.2.

The numerical simulation done on the model explains the importance of some of the factors considered in the model formulation. It is shown that the contact rate between the infectious and susceptible individuals play significant role in the rapid spread of the infection. The reduction in the value of the contact rate shows a great improvement in controlling the epidemic. In fact, this result explains part of the reasons why sanatoria used in the 18th century were effective in dealing with the epidemic. Other factors; recruitment and treatment rates have shown how important they are in delaying the infection, and as such, should be optimised in handling the infection before it becomes an epidemic. At 7% growth rate of the population or 80% treatment rate of the infectious,

the infection dies out, as displayed in Figures 3.8 and 3.9. It should be remarked that the recruitment into the population is expected to be constituted by those that are free of *Mtb*.

To win the war against tuberculosis epidemic, listed below are some of the approaches as derived from the model formulated.

i. Normalisation of any formulated model serves as a guide to verify the level of correctness of any result gotten as the equilibrium point must always sum up to 1,
ii. Identifying the exposed individuals and subsequently treating them, drastically reduces the TB incident,
iii. Ascertainment of the medical fitness (TB freeness) of any individual before being allowed to enter any community helps control the infection,
iv. Absolute reduction in the rate of contact between a TB carrier and a susceptible individual should be encouraged and lastly,
v. Provision of vaccine to combat the TB infectivity rate shall transform our environment to a safe haven, free of TB.

It is worthy of note that awareness could also be of great help in reducing the incidence of the infection through e.g., education, social media, local dailies, media houses, etc., as it would help in keeping people informed of the inherent dangers in freely mingling with TB carriers. This is corroborated by the Figures 3.6 – 3.8 in which reasonable control of the epidemic is achieved. This is in agreement with the findings of Xiang et al. (2019) where health education is shown to help in reducing TB burden. These measures are greatly needed in some parts of the developing nations and in most of the under-developed nations as they are the major victims of tuberculosis.

CHAPTER 4: IMPACT OF VACCINATION ON TUBERCULOSIS

4.1 Introduction

When deaths are considered from a single infectious agent, tuberculosis is the topmost cause of death globally (WHO, 2017). Tuberculosis, TB as it is commonly called has greatly claimed the lives of its victims throughout much of known human history. In fact, according to Daniel (2006), *Mycobacterium tuberculosis* which is the bacteria responsible for TB might have killed more people than any other microbe. This simply explains the reason why it was nicknamed "captain among these men of death" in the early 20th century. According to the WHO report stated in section 1.4 of Chapter 1 earlier (WHO, 2016a), TB killed more persons in the year 2015 than HIV and malaria as it was responsible for 1.4 million deaths globally (WHO, 2016a). This portends a great danger which requires urgent attention.

The foundation to understanding the pathogenesis of TB was laid by Théophile Laennec in the early 19th century. This was subsequently expanded by Jean-Antoine Villemin in 1865 and Robert Koch in 1882, where they respectively showed the transmissibility of Mycobacterium infection and identified tubercle bacillus as the etiological agent, (Daniel, 2006). These works led to the discovery of the prophylactic BCG vaccine in the year 1921 whose efficacy was tested in 1930s through field trials (Gomes et al., 2004). BCG is an acronym standing for Bacille Calmette-Guérin coined from the names Albert Calmette and Camille Guérin, the brains behind its invention. BCG did not enjoy much acceptability during this period until after world war II when TB became a major health threat. By the support of the Danish Red Cross Society as well as encouragement by UNICEF, it became more acceptable (Luca & Mihaescu, 2013). Although, there have been discussions about the ineffectiveness of BCG in the prevention of TB lately, whereby some authors (Kernodle, 2010; Moliva et al., 2015; Bhandari, 2016;

Jalan, 2018) have mentioned the likely cause of its ineffectiveness, despite that, many countries have greatly embraced its use (Gerberry, 2009). The perceived ineffectiveness of BCG to prevent adult pulmonary TB has brought about discussions and agitations for its replacement with a more potent vaccine. This new vaccine is required to achieve 95% reduction in the TB induced death as well as decrement by 90% in the incidence of TB worldwide by the year 2035 (WHO, 2018c).

Hawn et al. (2014) discussed about the use of vaccine in the prevention of TB infection. They explained how different researches have discussed about the need to consider preinfection vaccines against TB, which is summarized in five different areas. First on the list is the epidemiology and mathematical modelling studies. Researches in this field show drastic reduction in TB incident when preinfection vaccine is put in place. This is followed by immunology researches that have identified host responses as probably being more effective during acute infection rather than the chronic one. As such, the direction of efforts toward the prevention of infection is promoted.

The natural history studies are the third on the list, and have shown that only paltry proportion of the population have resistance towards TB infection. The fourth are on case control studies of BCG vaccine. The studies give indication that BCG may prevent TB infection. Lastly are the studies on prevention of infection trials. These researches from these five different areas are all pointing at the need to prevent the infection as a good measure to reducing its incidence. They concluded that the prioritization of vaccine products, selection of endpoint assays, endpoint definitions, sample sizes and also the target populations are to be set as the TB vaccine research agenda.

Several models have been presented to understand the dynamics of TB e.g. Aparicio & Castillo-Chavez (2009), Raimundo & Yang (2006), Vynnycky et al. (2015), McCluskey & van den Driessche (2004), Jia et al. (2008), and Trauer et al. (2014) while some have been presented to provide intervention strategies to tame its spread, e.g. Bhunu et al. (2008), Murphy et al. (2003), Ragonnet et al. (2017) and Varughese (2017). The requisite consideration in the formulation of any proposed vaccine have not been discussed by these authors. As such, it is the research focus of this chapter. It is expected to provide guiding frame work for the pharmacists on the intrinsic features expected of any proposed vaccine.

4.2 Model Formulation

4.2.1 Introduction

The model formulated in this chapter is an extension of the model considered in Chapter 5. The extension is the consideration and inclusion of a vaccination compartment to analyse the impact of potent vaccine in managing the TB epidemic. Human population is divided into five group of individuals which are; susceptible (S), vaccinated (V), exposed (E), infectious (I) and the recovered (R) and the total population N(t) at any time t is

$$N(t) = S(t) + V(t) + E(t) + I(t) + R(t). \tag{4.1}$$

There is homogenous mixing of individuals in all compartments and a susceptible individual contracts TB after an effective contact with an infectious person at the rate

$$\lambda = \frac{\beta c I}{N}, \tag{4.2}$$

where β is the probability that a susceptible individual would get infected and c is the average contact rate.

The recruitment into the susceptible class occurs at the rate πN and people progress to the exposed and the infectious classes at the rates $(1-\tau)f\lambda$ and $(1-\tau)(1-f)\lambda$, respectively. $f_1\lambda$ and $(1-f_1)\lambda$, respectively denote the rates at which recovered individuals move back to the exposed and infectious compartments due to loss of immunity. Also, people move from the susceptible compartment to the vaccinated after being vaccinated at the rate τ, from where they can contract TB at the rate θ. The exogenous reinfection and endogenous reactivation rates are designated as $\delta_1\ \lambda$ and k, respectively. After the loss of immunity conferred by the drug, recovered individuals could get re-infected at the rate δ_2. People can die due to nature at the rate μ and rate ε for the TB induced death.

Recovery from TB are basically two ways; the natural inexplicable way or due to treatment. These ways are denoted as ω and γ respectively. Due to the fact that bacterial infections confer no permanent immunity against reinfection, a fraction of the recovered individuals is assumed to go back to the susceptible class at the rate α. Figure 4.1 below presents the pictorial representation of the model which is governed by the nonlinear system (4.3)-(4.7)

$$\frac{dS}{dt} = \pi N + \sigma V + \alpha R - [\tau + (1-\tau)\lambda + \mu]S, \tag{4.3}$$

$$\frac{dV}{dt} = \tau S - (\theta\lambda + \sigma + \mu)V, \tag{4.4}$$

$$\frac{dE}{dt} = (1-\tau)f\lambda S + \theta f\lambda V + f_1\delta_2\ \lambda R - (\delta_1\ \lambda + k + \mu)E, \tag{4.5}$$

$$\frac{dI}{dt} = (1-\tau)(1-f)\lambda S + \theta(1-f)\lambda V + (1-f_1)\delta_2\ \lambda R + (\delta_1\ \lambda + k)E - (\gamma + \omega + \varepsilon + \mu)I \tag{4.6}$$

and

$$\frac{dR}{dt} = (\gamma + \omega)I - (\delta_2\ \lambda + \alpha + \mu)R, \tag{4.7}$$

with initial conditions:

$$S(0) = S_0 \geq 0, V(0) = V_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0.$$

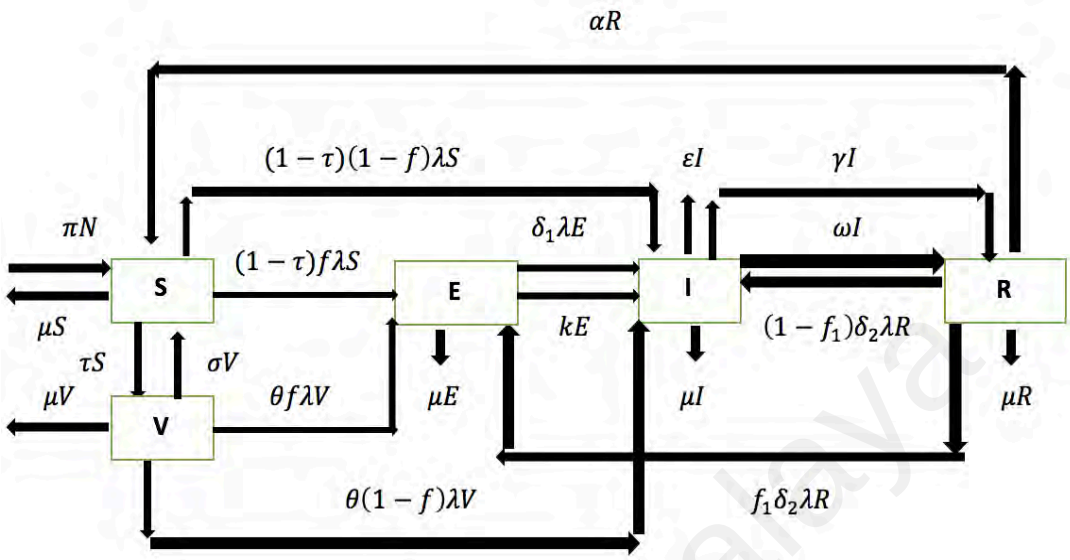

Figure 4.1: Vaccination model for tuberculosis

Adding (4.3)-(4.7) gives

$$\frac{dN}{dt} = (\pi - \mu)N - \varepsilon I. \tag{4.8}$$

Normalisation of the system (4.3)-(4.7) is done by dividing throughout by N. If $\frac{S}{N}, \frac{V}{N}, \frac{E}{N}, \frac{I}{N}$ and $\frac{R}{N}$ are consecutively denoted by s, v, e, i and r, then the system becomes

$$\frac{1}{N}\frac{dS}{dt} = \pi + \sigma v + \alpha r - [\tau + (1 - \tau)\beta ci + \mu]s, \tag{4.9}$$

$$\frac{1}{N}\frac{dV}{dt} = \tau s - (\theta\beta ci + \sigma + \mu)v, \tag{4.10}$$

$$\frac{1}{N}\frac{dE}{dt} = (1 - \tau)f\beta cis + \theta f\beta civ + f_1\delta_2\,\beta cir - (\delta_1\,\beta ci + k + \mu)e, \tag{4.11}$$

$$\frac{1}{N}\frac{dI}{dt} = (1 - \tau)(1 - f)\beta cis + \theta(1 - f)\beta civ + (1 - f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e - (\gamma + \omega + \varepsilon + \mu)i \tag{4.12}$$

and

$$\frac{1}{N}\frac{dR}{dt} = (\gamma + \omega)i - (\delta_2\, \beta ci + \alpha + \mu)r. \tag{4.13}$$

Since $S = sN$, then

$$\frac{1}{N}\frac{dS}{dt} = \frac{ds}{dt} + s[(\pi - \mu) - \varepsilon i]. \tag{4.14}$$

Similarly from $V = vN, E = eN, I = iN$ and $R = rN$, then the appropriate governing nonlinear system becomes

$$\frac{ds}{dt} = \pi + \sigma v + \alpha r - \{\pi + \tau + [(1-\tau)\beta c - \varepsilon]i\}s, \tag{4.15}$$

$$\frac{dv}{dt} = \tau s - [\pi + \sigma + (\theta\beta c - \varepsilon)i]v, \tag{4.16}$$

$$\frac{de}{dt} = (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\, \beta cir - [\pi + k + (\delta_1\, \beta c - \varepsilon)i]e, \tag{4.17}$$

$$\begin{aligned}\frac{di}{dt} = {} & (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\, \beta cir \\ & +(\delta_1\, \beta ci + k)e - [\pi + \gamma + \omega + \varepsilon(1-i)]i,\end{aligned} \tag{4.18}$$

and

$$\frac{dr}{dt} = (\gamma + \omega)i - [\pi + \alpha + (\delta_2\, \beta c - \varepsilon)i]r \tag{4.19}$$

with the initial conditions:

$$s(0) = s_0 \geq 0, \quad v(0) = v_0 \geq 0, \quad e(0) = e_0 \geq 0, \quad i(0) = i_0 \geq 0, \quad r(0) = r_0 \geq 0,$$

where

$$s + v + e + i + r = 1.$$

4.2.2 Positivity of the Solution

The model represented by the system (4.15)-(4.19) shall only be epidemiologically correct if all the dependent variables are non-negative at any time t. As such, the positivity of the model is thus presented.

Lemma 4.1: Given that the initial conditions of nonlinear system ((4.15)-(4.19)) are as given above, then the solutions $s(t)$, v, $e(t)$, $i(t)$, and $r(t)$ are positive for all $t > 0$.

Proof. Suppose that $t^* = \sup\{t > 0: s(t) > 0, v(t) > 0, e(t) > 0, i(t) > 0, r(t) > 0\} \in [0, t]$, then $t^* > 0$. Considering the first equation of system (4.15)-(4.19),

$$\frac{ds}{dt} = \pi + \sigma v + \alpha r - \{\pi + \tau + [(1-\tau)\beta c - \varepsilon]i\}s,$$

let $[(1-\tau)\beta c - \varepsilon]i = \Lambda_2$, then

$$\frac{ds}{dt} = \pi + \sigma v + \alpha r - [\pi + \Lambda_2]s \geq \pi - [\pi + \tau + \Lambda_2]s,$$

$$\frac{d}{dt}\left[s(t)e^{\left((\pi+\tau)t + \int_0^t \Lambda_2(\xi)d\xi\right)}\right] \geq \pi e^{\left((\pi+\tau)t + \int_0^t \Lambda_2(\xi)d\xi\right)}$$

$$\Rightarrow s(t_1)e^{\left((\pi+\tau)t_1 + \int_0^{t_1} \Lambda_2(\xi)d\xi\right)} - s(0) \geq \int_0^{t_1} \pi e^{\left((\pi+\tau)y + \int_0^y \Lambda_2(\xi)d\xi\right)}dy$$

$$\Rightarrow s(t_1) \geq e^{-\left((\pi+\tau)t_1 + \int_0^{t_1} \Lambda_2(\xi)d\xi\right)}\left[s(0) + \int_0^{t_1} \pi e^{\left((\pi+\tau)y + \int_0^y \Lambda_2(\xi)d\xi\right)}dy\right] > 0.$$

Following the same approach, it can as well be shown that $v(t), e(t), i(t)$ and $r(t)$ are positive.

4.3 Equilibrium Points, Basic Reproduction Number (R_0) and Stability Analysis

4.3.1 Equilibrium Points

At equilibrium point, the nonlinear system (4.15)-(4.19) becomes

$$0 = \pi + \sigma v + \alpha r - \{\pi + \tau + [(1-\tau)\beta c - \varepsilon]i\}s, \tag{4.20}$$

$$0 = \tau s - [\pi + \sigma + (\theta\beta c - \varepsilon)i]v, \tag{4.21}$$

$$0 = (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\,\beta cir - [\pi + k + (\delta_1\,\beta c - \varepsilon)i]e, \tag{4.22}$$

$$0 = (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\,\beta cir. \\ +(\delta_1\,\beta ci + k)e - [\pi + \gamma + \omega + \varepsilon(1-i)]i, \tag{4.23}$$

and

$$0 = (\gamma + \omega)i - [\pi + \alpha + (\delta_2\,\beta c - \varepsilon)i]r. \tag{4.24}$$

From (4.24),

$$r = \frac{(\gamma + \omega)i}{[\pi + \alpha + (\delta_2\beta c - \varepsilon)i]}. \tag{4.25}$$

When (4.21) and (4.25) are substituted in (4.20), it produces

$$s = \frac{[\pi + \sigma + (\theta\beta c - \varepsilon)i]\{\pi[\pi + \alpha + (\delta_2\beta c - \varepsilon)i] + \alpha(\gamma + \omega)i\}}{[\pi + \alpha + (\delta_2\beta c - \varepsilon)i]\{[\pi + \sigma + (\theta\beta c - \varepsilon)i][\pi + \tau + [(1-\tau)\beta c - \varepsilon]i] - \sigma\tau\}}, \tag{4.26}$$

whilst substituting (4.26) in (4.21) gives

$$v = \frac{\tau[\pi + \sigma + (\theta\beta c - \varepsilon)i]\{\pi[\pi + \alpha + (\delta_2\beta c - \varepsilon)i] + \alpha(\gamma + \omega)i\}}{[\pi + \sigma + (\theta\beta c - \varepsilon)i][\pi + \alpha + (\delta_2\beta c - \varepsilon)i]K}, \tag{4.27}$$

where

$$K = \{[\pi + \sigma + (\theta\beta c - \varepsilon)i][\pi + \tau + [(1-\tau)\beta c - \varepsilon]i] - \sigma\tau\}$$

and the subsequent insertion of (4.25)-(4.27) in (4.22) gives

$$e = \frac{(1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir}{[\pi + k + (\delta_1\beta c - \varepsilon)i]}. \tag{4.28}$$

When (4.25)-(4.28) are substituted as functions of i in (4.23), it produces

$$A_{11}i^6 + A_{10}i^5 + A_9i^4 + A_8i^3 + A_7i^2 + A_6i = 0, \tag{4.29}$$

where the coefficients $A_6, A_7, A_8, A_9, A_{10}$ and A_{11} are in Appendix B.

Solving (4.29) produces six equilibrium values of i; $i_1, i_2, i_3, i_4, i_5, i_6$. These values are subsequently substituted in (4.25)-(4.28) to establish (s, e, v, r) equilibrium values i.e., $(s_1, s_2, s_3, s_4, s_5, s_6)$, $(v_1, v_2, v_3, v_4, v_5, v_6)$, $(e_1, e_2, e_3, e_4, e_5, e_6)$ and $(r_1, r_2, r_3, r_4, r_5, r_6)$. From the equilibrium points gotten are the disease free equilibrium (DFE),

$$P_1 = \left\{\frac{\pi(\pi+\sigma)}{(\pi+\sigma)(\pi+\tau)-\sigma\tau}, \frac{\pi\tau}{(\pi+\sigma)(\pi+\tau)-\sigma\tau}, 0,0,0\right\} \text{ and } P_2 = \{s_2, v_2, e_2, i_2, r_2\},$$

where

$$s_2 = \frac{\varepsilon\pi\psi\Lambda}{\Gamma\{[\pi\beta c(1-\tau)+\tau\varepsilon]\Lambda-\varepsilon^2\sigma\tau\}}, \quad v_2 = \frac{\varepsilon^2\tau\pi\psi\Lambda}{\Gamma\Lambda\{\Lambda[\pi\beta c(1-\tau)+\tau\varepsilon]-\varepsilon^2\sigma\tau\}},$$

$$e_2 = \frac{(\pi\beta c\delta_1+k\varepsilon)\{\beta cf\pi^2(1-\tau)\Lambda^2\psi+\beta cf\theta\pi^2\varepsilon^2\tau\Lambda\psi\}}{\Gamma\Lambda[(\pi\beta c(1-\tau)+\tau\varepsilon)\Lambda-\varepsilon^2\sigma\tau]} + \frac{\beta c\delta_2 f_1\pi^2(\gamma+\omega)}{\Gamma(\pi\beta c\delta_1+k\varepsilon)}, i_2 = \frac{\pi}{\varepsilon} \text{ and } r_2 = \frac{\pi(\gamma+\omega)}{\Gamma}.$$

such that

$$\psi = \pi\beta c\delta_2 + \alpha(\gamma+\omega+\varepsilon), \ \Lambda = (\pi\beta c\theta + \sigma\varepsilon) \text{ and } \Gamma = (\pi\beta c\delta_2 + \alpha\varepsilon).$$

P_3, P_4, P_5 and P_6 are cumbersome to be presented here. Since the system has been normalised, sum of all the solutions at any point in time shall be unity. As such, the solution P_2 is dropped out of the solutions because its sum could not give unity. This reduces the set of solutions to five which is quite expected as there are five variables in the model.

4.3.2 Basic Reproduction Number (R_0)

Establishing the Basic Reproduction Number (R_0)

Following the method as discussed in subsection 3.3.2,

$$R_0 = \rho\left(FV^{-'}\right). \tag{4.30}$$

ρ is the spectral radius (dominant eigenvalue) of the matrix $FV^{-'}$, where F represents the rate of appearance of new infections in the infected compartments and V represents the inward and outward movement at the infected compartments.

V is defined as

$$V = V_j^- - V_j^+,$$

where

V_j^- = the rate of inward movement of individuals into the infected compartments

and

V_j^+ = the rate of outward movement of individuals from the infected compartments.

From the nonlinear system (4.15)-(4.19) above, F and V are respectively given as

$$F = \begin{pmatrix} 0 & \beta c\{[f(1-\tau)s + \theta v] + f_1\delta_2 r\} \\ \delta_1\beta ci & \beta c[(1-f)s + (1-f_1)\delta_2 r] \end{pmatrix} \tag{4.31}$$

and

$$V = \begin{pmatrix} [\pi + k + (\delta_1\beta c - \varepsilon)i] & (\delta_1\beta c - \varepsilon)e \\ -k & [\pi + \gamma + \omega + \varepsilon(1-i)] \end{pmatrix}. \tag{4.32}$$

Evaluating (4.31) and (4.32) at the DFE $\left\{\frac{\pi(\pi+\sigma)}{(\pi+\sigma)(\pi+\tau)-\sigma\tau}, \frac{\pi\tau}{(\pi+\sigma)(\pi+\tau)-\sigma\tau}, 0,0,0\right\}$ gives

$$F = \begin{pmatrix} 0 & \beta cf[(1-\tau)s + \theta v] \\ 0 & \beta c(1-f)[(1-\tau)s + \theta v] \end{pmatrix} \tag{4.33}$$

and

$$V = \begin{pmatrix} [\pi + k] & 0 \\ -k & [\pi + \gamma + \omega + \varepsilon] \end{pmatrix}, \tag{4.34}$$

$$\Rightarrow V^{-'} = \frac{1}{(\pi + k)(\pi + \gamma + \omega + \varepsilon)} \begin{pmatrix} (\pi + \gamma + \omega + \varepsilon) & 0 \\ k & (\pi + k) \end{pmatrix}. \tag{4.35}$$

From (4.33) and (4.35),

$$FV^{-'} = \begin{pmatrix} \dfrac{\beta cfk[(1-\tau)s + \theta v]}{(\pi + k)(\pi + \gamma + \omega + \varepsilon)} & \dfrac{\beta cf[(1-\tau)s + \theta v]}{(\pi + \gamma + \omega + \varepsilon)} \\ \dfrac{\beta ck(1-f)[(1-\tau)s + \theta v]}{(\pi + k)(\pi + \gamma + \omega + \varepsilon)} & \dfrac{\beta c(1-f)[(1-\tau)s + \theta v]}{(\pi + \gamma + \omega + \varepsilon)} \end{pmatrix} \tag{4.36}$$

After the simplification of (4.36), the dominant eigenvalue $\rho(FV^{-'})$ is established as

$$\rho\left(FV^{-'}\right) = \frac{\beta c\pi(\pi + \sigma)[k + \pi(1-f)][(1-\tau)(\pi + \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \varepsilon)[(\pi + \tau)(\pi + \sigma) - \sigma\tau]}. \tag{4.37}$$

Hence the basic reproduction number, R_0 is

$$R_0 = \frac{\beta c\pi(\pi + \sigma)[k + \pi(1-f)][(1-\tau)(\pi + \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \varepsilon)[(\pi + \tau)(\pi + \sigma) - \sigma\tau]}. \tag{4.38}$$

Theorem 4.3.1. Whenever there is no vaccination program ($\tau = 0$), TB infection shall always be more rampaging.

Proof. Since $0 \leq \tau \leq 1$,

$$1 \geq (1 - \tau). \tag{4.39}$$

When (4.39) is multiplied through by $(\pi + \tau)$ and $\tau\theta$ is subsequently added to both sides, the result is

$$(\pi + \tau) + \tau\theta \geq (\pi + \tau)(1 - \tau) + \tau\theta. \tag{4.40}$$

Multiplication by $\frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}$ gives

$$\frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)][(\pi+\tau)+\tau\theta]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]} \geq \frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)][(\pi+\tau)(1-\tau)+\tau\theta]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}, \tag{4.41}$$

which implies

$$R_{0_1} \geq R_0,$$

where

$$R_{0_1} = \frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)][(\pi+\tau)+\tau\theta]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}$$

and

$$R_0 = \frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)][(\pi+\tau)(1-\tau)+\tau\theta]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}.$$

When $\tau = 0$,

$$\Rightarrow R_{0_1} = R_0 \tag{4.42}$$

which implies there is no intervention strategy put in place, and when $\tau = 1$,

$$\Rightarrow R_{0_1} > R_0, \tag{4.43}$$

which shows the impact of the vaccination intervention and as such concludes the proof.

The need for an effective vaccine to manage the incidence of TB is buttressed by Theorem 4.3.1. From the above, the $\tau = 0$ case explains the implication of not having any vaccination program in place. It shows that nothing would change in the management of TB incidence as the reproduction numbers R_0 and R_{0_1} are the same. On the other hand, when vaccination program is put in place ($\tau = 1$), the disease incidence shall be properly

managed as there shall be reduction in the number of TB cases. This is evident in the reduction of the number of secondary infections as given by $R_0 < R_{0_1}$. Hence, the use of a potent prophylactic TB vaccine should be encouraged.

Theorem 4.3.2. If the TB vaccine is designed to give full immunity against the contraction of TB infection ($\theta = 0$), its incidence shall be drastically reduced.

Proof. Since $0 \leq \theta \leq 1$,

$$\theta \leq 1. \tag{4.44}$$

When both sides of (4.44) are multiplied by τ and $(1-\tau)(\pi+\tau)$ is subsequently added to the resulting equation, (4.45) below is produced

$$(1-\tau)(\pi+\tau) + \tau\theta \leq (1-\tau)(\pi+\tau) + \tau. \tag{4.45}$$

Multiplying this by $\frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}$ gives

$$\begin{gathered}\frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)][(1-\tau)(\pi+\tau)+\tau\theta]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]} \leq \\ \frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)][(1-\tau)(\pi+\tau)+\tau]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}\end{gathered} \tag{4.46}$$

$$\Rightarrow R_0 \leq R_{0_2}$$

such that

$$R_0 = \frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)][(1-\tau)(\pi+\tau)+\tau\theta]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}$$

and

$$R_{0_2} = \frac{\beta c\pi(\pi+\sigma)[k+\pi(1-f)][(1-\tau)(\pi+\tau)+\tau]}{(\pi+\tau)(\pi+k)(\pi+\gamma+\omega+\varepsilon)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}.$$

When $\theta = 0$,

$$\Rightarrow R_0 < R_{0_2}, \tag{4.47}$$

which implies reduction in the number of secondary cases of TB infection, and when $\theta = 1$,

$$\Rightarrow R_0 = R_{0_2}, \tag{4.48}$$

which explains that nothing has been achieved in the management of the infection and hence concludes the proof.

Theorem 4.3.2 targets the intrinsic features to be considered in the vaccine formulation. Since R_0, i.e. (4.38) is the number of secondary infection from a primary one, any value lesser to the established R_0 shall reduce the tuberculosis incidence while a greater value does the opposite. Formulation of a vaccine that provides 100% immunity against TB would reduce the disease incident rate. This is as established in (4.47) where the impact of θ (when it is zero) i.e., $\theta = 0$ is measured, and results to the reduction in the value of R_0. $\theta = 0$ is the scenario where the vaccine provides 100% immunity. Contrastingly, $\theta = 1$ does the opposite. This explains the scenario where the vaccine confers no immunity whatsoever. Equation (4.48) shows that more persons shall contract TB infection due to the non-availability of an effective vaccine.

4.3.3 Stability Analysis

The Jacobian matrix of equations (4.15)-(4.19) is expressed as

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial s} & \frac{\partial f_1}{\partial v} & \frac{\partial f_1}{\partial e} & \frac{\partial f_1}{\partial i} & \frac{\partial f_1}{\partial r} \\ \frac{\partial f_2}{\partial s} & \frac{\partial f_2}{\partial v} & \frac{\partial f_2}{\partial e} & \frac{\partial f_2}{\partial i} & \frac{\partial f_2}{\partial r} \\ \frac{\partial f_3}{\partial s} & \frac{\partial f_3}{\partial v} & \frac{\partial f_3}{\partial e} & \frac{\partial f_3}{\partial i} & \frac{\partial f_3}{\partial r} \\ \frac{\partial f_4}{\partial s} & \frac{\partial f_4}{\partial v} & \frac{\partial f_4}{\partial e} & \frac{\partial f_4}{\partial i} & \frac{\partial f_4}{\partial r} \\ \frac{\partial f_5}{\partial s} & \frac{\partial f_5}{\partial v} & \frac{\partial f_5}{\partial e} & \frac{\partial f_5}{\partial i} & \frac{\partial f_5}{\partial r} \end{pmatrix} \tag{4.49}$$

where

$$f_1 = \pi + \sigma v + \alpha r - \{\pi + \tau + [(1-\tau)\beta c - \varepsilon]i\}s,$$

$$f_2 = \tau s - [\pi + \sigma + (\theta\beta c - \varepsilon)i]v,$$

$$f_3 = (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir - [\pi + k + (\delta_1\beta c - \varepsilon)i]e,$$

$$f_4 = (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e$$

$$-[\pi + \gamma + \omega + \varepsilon(1-i)]i,$$

$$f_5 = (\gamma + \omega)i - [\pi + \alpha + (\delta_2\beta c - \varepsilon)i]r.$$

Then,

$$J = \begin{pmatrix} a_{11} & \sigma & 0 & a_{14} & \alpha \\ \tau & a_{22} & 0 & -(\theta\beta c - \varepsilon)v & 0 \\ (1-\tau)f\beta ci & \theta f\beta ci & a_{33} & a_{34} & f_1\delta_2\beta ci \\ a_{41} & \theta(1-f)\beta ci & (\delta_1\beta ci + k) & a_{44} & a_{45} \\ 0 & 0 & 0 & a_{54} & a_{55} \end{pmatrix}, \tag{4.50}$$

where

$$a_{11} = -\{\pi + \tau + [(1-\tau)\beta c - \varepsilon]i\},$$

$$a_{14} = -[(1-\tau)\beta c - \varepsilon]s$$

$$a_{22} = -[\pi + \sigma + (\theta\beta c - \varepsilon)i]$$

$$a_{33} = -[\pi + k + (\delta_1\beta c - \varepsilon)i],$$

$$a_{34} = (1-\tau)f\beta cs + \theta f\beta cv + f_1\delta_2\beta cr - (\delta_1\beta c - \varepsilon)e,$$

$$a_{41} = (1-\tau)(1-f)\beta ci$$

$$a_{44} = (1-\tau)(1-f)\beta cs + \theta(1-f)\beta cv + (1-f_1)\delta_2\beta cr + \delta_1\beta ce$$

$$-(\pi + \gamma + \omega + \varepsilon - 2\varepsilon i),$$

$$a_{45} = (1-f_1)\delta_2\beta ci,$$

$$a_{54} = (\gamma + \omega) - (\delta_2\beta c - \varepsilon)r,$$

and

$$a_{55} = -[\pi + \alpha + (\delta_2\beta c - \varepsilon)i]$$

4.3.4 Stability of the DFE

Local Stability

Theorem 4.3.3. The disease free equilibrium (DFE) of the model is locally asymptotically stable whenever $R_0 < 1$ and unstable otherwise.

Proof. Evaluation of (4.50) at the DFE $\left\{\frac{\pi(\pi+\sigma)}{(\pi+\tau)(\pi+\sigma)-\sigma\tau}, \frac{\pi\tau(\pi+\sigma)}{(\pi+\tau)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}, 0,0,0\right\}$ gives

$$J=\begin{pmatrix} -(\pi+\tau) & \sigma & 0 & \dfrac{-\pi(\pi+\sigma)[(1-\tau)\beta c-\varepsilon]}{(\pi+\tau)(\pi+\sigma)-\sigma\tau} & \alpha \\ \tau & -(\pi+\sigma) & 0 & \dfrac{-\pi\tau(\pi+\sigma)(\theta\beta c-\varepsilon)}{(\pi+\tau)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]} & 0 \\ 0 & 0 & -(\pi+k) & \vartheta_1 & 0 \\ 0 & 0 & k & \vartheta_2 & 0 \\ 0 & 0 & 0 & (\gamma+\omega) & -(\pi+\alpha) \end{pmatrix}, \tag{4.51}$$

where

$$\vartheta_1=\frac{\pi f\beta c(\pi+\sigma)[(1-\tau)(\pi+\tau)+\tau\theta]}{(\pi+\tau)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}$$

$$\vartheta_2=\frac{\pi\beta c(1-f)(\pi+\sigma)[(1-\tau)(\pi+\tau)+\tau\theta]-\{(\pi+\tau)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]\}(\pi+\gamma+\omega+\varepsilon)}{(\pi+\tau)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}.$$

Denoting the eigenvalue as η, the eigenvalues of (4.51) shall be gotten from

$$|J-\eta I|=0.$$

That is,

$$\begin{vmatrix} -(\pi+\tau+\eta) & \sigma & 0 & a_{14}^{*} & \alpha \\ \tau & -(\pi+\sigma+\eta) & 0 & & 0 \\ 0 & 0 & -(\pi+k+\eta) & \vartheta_1 & 0 \\ 0 & 0 & k & \vartheta_2-\eta & 0 \\ 0 & 0 & 0 & (\gamma+\omega) & -(\pi+\alpha+\eta) \end{vmatrix}=0, \tag{4.52}$$

where $a_{14}^{*}=\frac{-\pi(\pi+\sigma)[(1-\tau)\beta c-\varepsilon]}{(\pi+\tau)(\pi+\sigma)-\sigma\tau}$, $a_{24}^{*}=\frac{-\pi\tau(\pi+\sigma)(\theta\beta c-\varepsilon)}{(\pi+\tau)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}$

The first three eigenvalues of (4.52) are

$$\eta_1=-\pi,$$

$$\eta_2=-(\pi+\alpha)$$

and

$$\eta_3 = -(\pi + \sigma + \tau),$$

and equation (4.52) is subsequently reduced to

$$\begin{vmatrix} -(\pi + k + \eta) & \dfrac{\pi f \beta c(\pi + \sigma)[(1-\tau)(\pi + \tau) + \tau\theta]}{(\pi + \tau)[(\pi + \tau)(\pi + \sigma) - \sigma\tau]} \\ k & \vartheta_2 - \eta \end{vmatrix} = 0. \tag{4.53}$$

Considering the quadratic equation

$$a\eta^2 + b\eta + c = 0, \tag{4.54}$$

where

$$a = 1,$$

$$b = (\pi + k) + (\pi + \gamma + \omega + \varepsilon) - \frac{\beta c\pi(1-f)(\pi+\sigma)[(1-\tau)(\pi+\tau)+\tau\theta]}{(\pi+\tau)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]}$$

and

$$c = (\pi + k)(\pi + \gamma + \omega + \varepsilon) - \frac{\beta c\pi(1-f)(\pi+\sigma)[k+\pi(1-f)]\{(1-\tau)(\pi+\tau)+\tau\theta\}}{(\pi+\tau)[(\pi+\tau)(\pi+\sigma)-\sigma\tau]},$$

the fourth and fifth eigenvalues, η_4 and η_5 respectively are

$$\eta_4, \eta_5 = \frac{-b \pm \sqrt{b^2 - 4(\pi + k)(\pi + \gamma + \omega + \varepsilon)\{1 - R_0\}}}{2}. \tag{4.55}$$

Obviously, the eigenvalues η_4, η_5 from (4.55) depend on R_0. $R_0 < 1 \Rightarrow \eta_4, \eta_5 < 0$ while $R_0 > 1 \Rightarrow \eta_4 > 0$ and $\eta_5 < 0$. Hence, $R_0 < 1$ guarantees the stability and as such completes the proof.

Global Stability

The approach of Castillo-Chavez et al. (2002) as discussed in Chapter 3 is as well adopted to establish the global stability of the DFE of this model.

If the system of equations (4.15)-(4.19) can be written in the form:

$$\frac{dX}{dt} = F(X,Y) \quad and \quad \frac{dY}{dt} = G(X,Y) \ni : \quad G(X,0) = 0,$$

where the uninfected and infected compartments are respectively represented as

$X = (s,v,r)^T$ and $Y = (e,i)^T$, and also, the DFE, P_1 is simply expressed as

$$P_1 = (X_0^*, 0)$$

where

$$X_0^* = \left(\frac{\pi(\pi+\sigma)}{(\pi+\sigma)(\pi+\tau)-\sigma\tau}, \frac{\pi\tau}{(\pi+\sigma)(\pi+\tau)-\sigma\tau}, 0\right),$$

then the DFE is globally asymptotically stable (GAS) provided $R_0 < 1$ and as well satisfies the conditions H_1 and H_2 given below.

$H_1: \frac{dX}{dt} = F(X_0, 0), X_0^*$ is globally asymptotically stable.

$$H_2: G(X,Y) = AY - \hat{G}(X,Y), \hat{G}(X,Y) \geq 0,$$

where $A = D_Y G(X_0^*, 0)$ is M-matrix (that is, all the non-diagonal elements of the matrix arenon-negative).

Theorem 4.3.4. The DFE, $\mathrm{P_1} = (\mathrm{X_0^*}, 0)$ of the nonlinear system (4.15)-(4.19) is globally asymptotically stable (GAS) provided it satisfies the conditions $\mathrm{H_1}$ and $\mathrm{H_2}$ above, as well as $\mathrm{R_0} < 1$.

Proof. From the above conditions, the following are established

$$F(X_0, 0) = \begin{pmatrix} \pi + \sigma v - (\pi + \tau)s \\ \tau s - (\pi + \sigma)v \\ 0 \end{pmatrix}$$

and

$$G(X, Y) = AY - \hat{G}(X, Y),$$

where

$$\hat{G}(X, Y) = \begin{pmatrix} \hat{G}_1(X, Y) \\ \hat{G}_2(X, Y) \end{pmatrix}$$

$$= \begin{pmatrix} (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir \\ (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e \end{pmatrix}.$$

Recall that $Y_0 = Y(0) \geq 0 \Rightarrow Y(t) \geq 0$. Since A is an M-matrix, then e^{At} is a positive semigroup. By the variation of constant formula, then

$$0 \leq Y(t) = e^{At}Y_0 - \int_0^t e^{A(t-w)}\hat{G}\big(X(w), Y(w)\big)dw \leq e^{At}Y_0. \tag{4.56}$$

It can be seen from (4.55) that for $R_0 < 1$, $m(A)$ is the dominant eigenvalue of A,hence,

$$\lim_{t\to\infty}\big||e^{At}|\big| = 0, \quad \Rightarrow \lim_{t\to\infty} Y(t) = 0.$$

X^* is GAS equilibrium point of $\frac{dX}{dt} = F(X, 0)$ which is a limiting system of $F(X(t), Y(t))$.

Thus,

$$\lim_{t\to\infty} X(t) = X^*$$

which satisfies condition H_1.

Likewise,

$$\hat{G}(X,Y) = \begin{pmatrix} (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir \\ (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e \end{pmatrix} \tag{4.57}$$

and

$$A = \begin{pmatrix} -[\pi + k + (\delta_1\beta c - \varepsilon)i] & (1-\tau)f\beta cs + \theta f\beta cv + f_1\delta_2\beta cr - (\delta_1\beta c - \varepsilon)e \\ \delta_1\beta ci + k & A_{22}^* \end{pmatrix}, \tag{4.58}$$

$$\begin{aligned} A_{22}^* = {} & (1-\tau)(1-f)\beta cs + \theta(1-f)\beta cv + (1-f_1)\delta_2\beta cr. \\ & +\delta_1\beta ce - (\pi + \gamma + \omega + \varepsilon) + 2\varepsilon i \end{aligned}$$

which at the DFE $(X_0, 0)$ gives

$$A = \begin{pmatrix} -[\pi + k] & (1-\tau)f\beta cs + \theta f\beta cv \\ k & (1-\tau)(1-f)\beta cs + \theta(1-f)\beta cv - (\pi + \gamma + \omega + \varepsilon) \end{pmatrix}. \tag{4.59}$$

It is obvious that the non-diagonal elements of A are non-negative because $\tau < 1$. In line with that, $f \leq 1$ and $f_1 \leq 1 \Rightarrow \hat{G}(X,Y) \geq 0$. Then, the DFE, P_1 of the nonlinear system (4.15)-(4.19) is GAS.

4.3.5 Stability of the EEP

Local Stability

As remarked in Chapter 3, the establishment of the local stability of the system analytically is challenging. This is greatly attached to the fact that gotten equilibrium solutions of the system spans beyond 20000 pages when solved with Mathematica 10. Hence the local stability is shown using the phase portrait diagrams as displayed below. This is done by the consideration of five arbitrary points;

$\{[s(0) = 0.4800, \quad v(0) = 0.3000, \quad e(0) = 0.2000, \quad i(0) = 0.0200, \quad r(0) = 0], [s(0) = 0.6680, \quad v(0) = 0.2000, \quad e(0) = 0.1200, \quad i(0) = 0.0120, \quad r(0) = 0], [s(0) = 0.7200, \quad v(0) = 0.0700, \quad e(0) = 0.1900, \quad i(0) = 0.0190, \quad r(0) = 0], [s(0) = 0.8010, \quad v(0) = 0.1000, \quad e(0) = 0.0900, \quad i(0) = 0.0090, \quad r(0) = 0], [s(0) = 0.8890, \quad v(0) = 0.1000, \quad e(0) = 0.0100, \quad i(0) = 0.0010, \quad r(0) = 0]\}$ as well as the parameter values in Table 4.1. The graphs emanating from the chosen points eventually converge to the same point. The phase portraits are shown in Figures 4.2, 4.3 and 4.4 below.

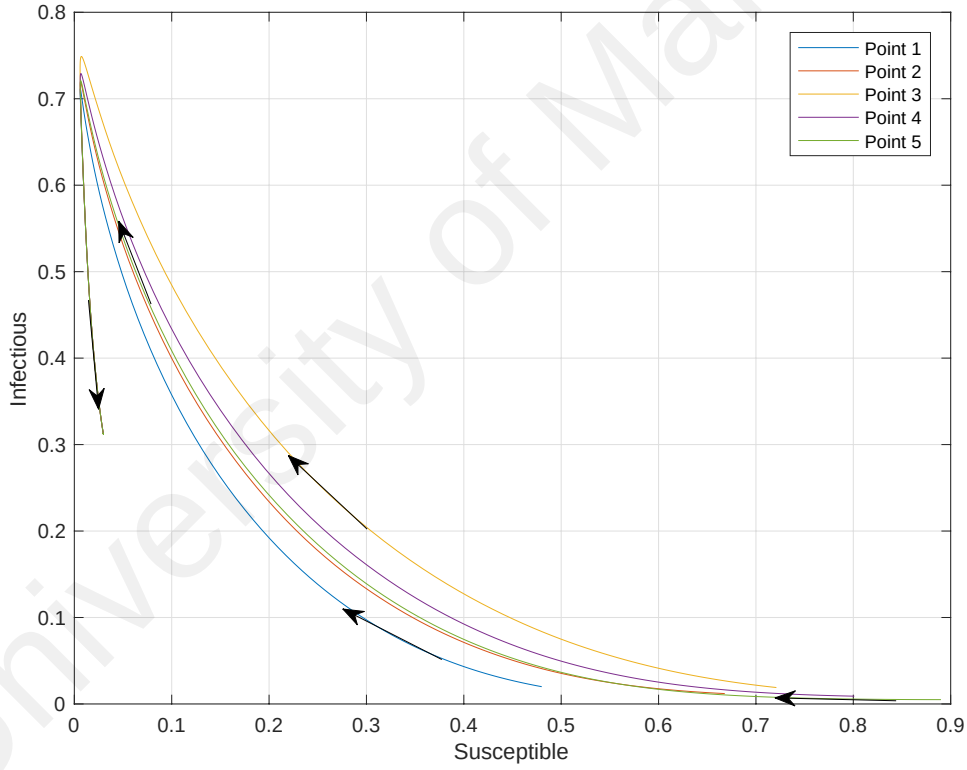

Figure 4.2: Phase portrait of the system (4.15)-(4.19) in s-i Plane

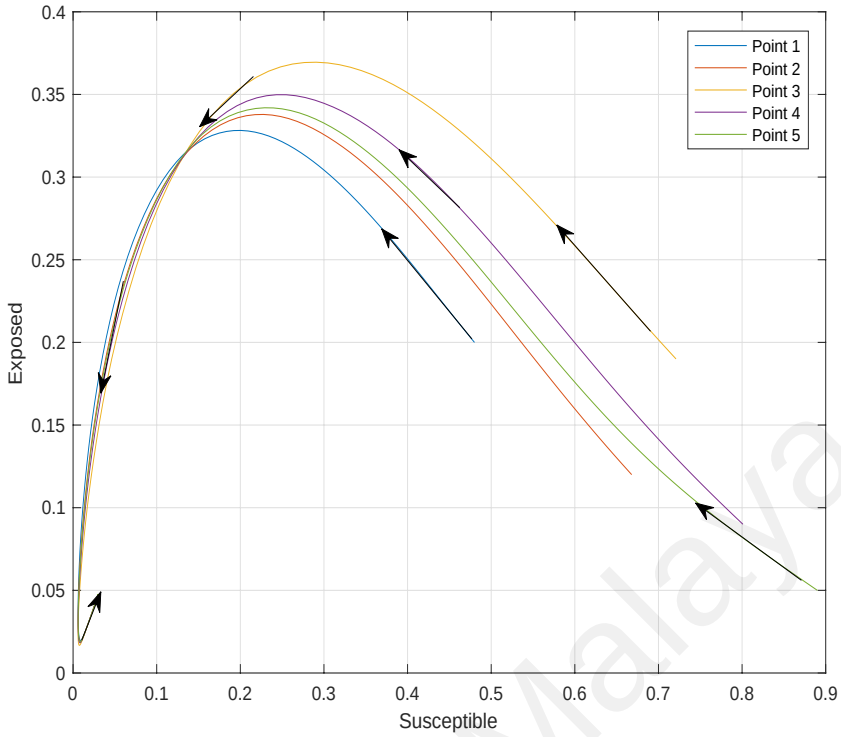

Figure 4.3: Phase portrait of the system (4.15)-(4.19) in s-e Plane

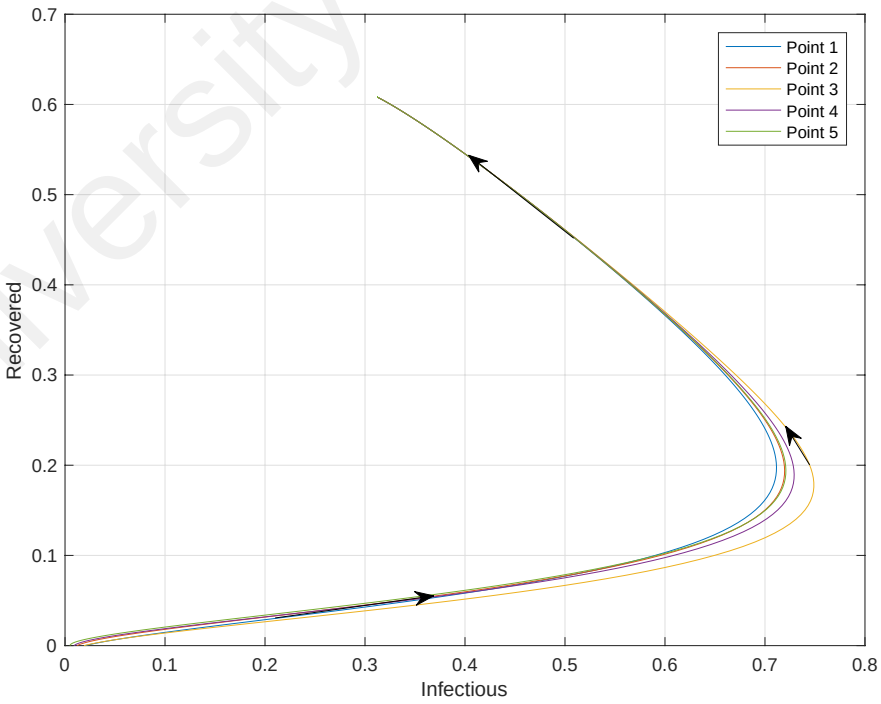

Figure 4.4: Phase portrait of the system (4.15)-(4.19) in i-r Plane

Global Stability

Theorem 4.3.5. The endemic equilibrium point $\{E_1 = (s^*, e^*, i^*, r^*) \in \Phi\}$ of the nonlinear system (4.15)-(4.19) is globally asymptotically stable at the special case $\varepsilon = 0$, whenever $R_0 > 1$.

Proof. From (4.17) and (4.18), when $\varepsilon = 0$

$$\Rightarrow e' = (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir - [\pi + k + \delta_1\beta ci]e \tag{4.60}$$

and

$$i' = (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e - [\pi + \gamma + \omega]i. \tag{4.61}$$

$$\Rightarrow e' = (1-\tau)f\beta ci[1-(v+e+i+r)] + \theta f\beta civ + f_1\delta_2\beta cir - [\pi + k + \delta_1\beta ci]e \tag{4.62}$$

and

$$i' = (1-\tau)(1-f)\beta ci[1-(v+e+i+r)] + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e - [\pi + \gamma + \omega]i. \tag{4.63}$$

Using the Dulac multiplier $\Theta = \frac{1}{ei}$ with the below Dulac function as discussed in Mukandavire et al. (2009) and Omondi et al. (2018)

$$\frac{\partial(\Theta e')}{\partial e} + \frac{\partial(\Theta i')}{\partial i},$$

produces

$$\frac{-\beta c}{e^2}\{f(1-\tau)[1-(v+i+r)] + \theta f v + f_1\delta r\} - \frac{(1-\tau)(1-f)\beta c}{e} - \frac{k}{i^2} \tag{4.64}$$

$$\Rightarrow -\left\{\frac{\beta c}{e^2}\{f(1-\tau)[1-(v+i+r)]+\theta f v+f_1\delta r\}+\frac{(1-\tau)(1-f)\beta c}{e}+\frac{k}{i^2}\right\}<0. \tag{4.65}$$

As such, we can infer by the Dulac's criterion that there are no periodic orbits in Φ. Since Φ is positively invariant and the EEP of the model exists only when $R_0 > 1$, then using Poincaré-Bendixson theorem (Perko, 2001) all solutions of the limiting system emanating in Φ remains in Φ for all t. Also, the uniqueness of the globally asymptotically stable EEP of the special case is established by the absence of the periodic orbits in Φ.

4.4 Numerical Simulation

The model is simulated using $ODE45$ package of MATLAB 2016a. The set of values given in Table 4.1 below are used in the numerical simulation where x^* is Bhunu et al. (2008). The values; 0.6680, 0.2000, 0.1200, 0.0120 and 0 are chosen as the initial fractions of the susceptible, vaccinated, exposed, infectious and recovered populations respectively. Published below are the graphs emanating from the simulation.

4.4.1 Graphical Results

The Simulation

This part discusses the graphical solutions of the model. The nonlinear system (4.15)-(4.19) is solved to produce the Figures 4.5–4.10. Figures 4.5, 4.6 and 4.7 show the behaviour of the infection under various infectivity (β) and contact (c) rates while vaccination is maintained. Figure 4.8 explain the impacts of different vaccination proportions while Figure 4.9 displays the dynamic of the infection when prevention of reinfection is not considered in the drugs formulation. Figure 4.10 explains the scenario when the vaccine is potently designed to confer total immunity against TB.

The Analysis

Combatting epidemics with the aid of drugs are done majorly using two approaches; prophylactic and therapeutic. When the prevention of an infection is desired, prophylactic is the way while therapeutic is used to manage an already contracted infection, this model deals with the prophylactic approach. Figure 4.5 shows the disease dynamics when the standardly declared infectivity (β) and contact (c) rates (from Table 4.1) are maintained. Reduction of the infectivity rate (β) by half gives a reduction in the peak value of the infectious fraction by 30.67% (which is the same when the contact rate is reduced by half itself) as displayed in Figure 4.6. When efforts are made to keep both parameters (factors) at half their values, the infection ultimately dies off the community as there is 98.48% reduction in the peak of the infectious fraction (which is quite significant) as displayed in Figure 4.7 below.

Furthermore, Figure 4.8 gives the impact of varying vaccination rate on the disease management. The variation (in percentage) is from 0 to 100 so as to ascertain the impact of each vaccination proportion. Apart from the observed difference between 0% and 100% vaccination proportions at steady rates, the maximum infectious fraction for the 100% vaccination proportion is 0.5053 whilst that of the 0% vaccination proportion is 0.7451. This is significant reduction by 32.18% in the maximum infectious fraction. The importance of δ_2, the reinfection rate (from the recovered class) is displayed by Figure 4.9. It is observed that its non-consideration in the model formulation i.e. ($\delta_2 = 1$) makes the vaccination non-impactful in reducing the TB incidence. Lastly, Figure 4.10 probes the impact of the vaccination when it confers 100% immunity against tuberculosis infection. When the vaccine confers total immunity, it should also be designed to reduce the infectivity rate of the infection. When this is done, 80% vaccination rate gives herd immunity against TB. The base vaccination proportion considered is 20%, when this is

varied to 40%, 60% and 80% respectively, various degree of reduction (in progressing order) is recorded in the infectious fraction as obviously displayed in Figure 4.10. For the vaccine to have full immunity, it must be designed to have the power of reducing the infectivity rate of *Mycobacterium tuberculosis* by half.

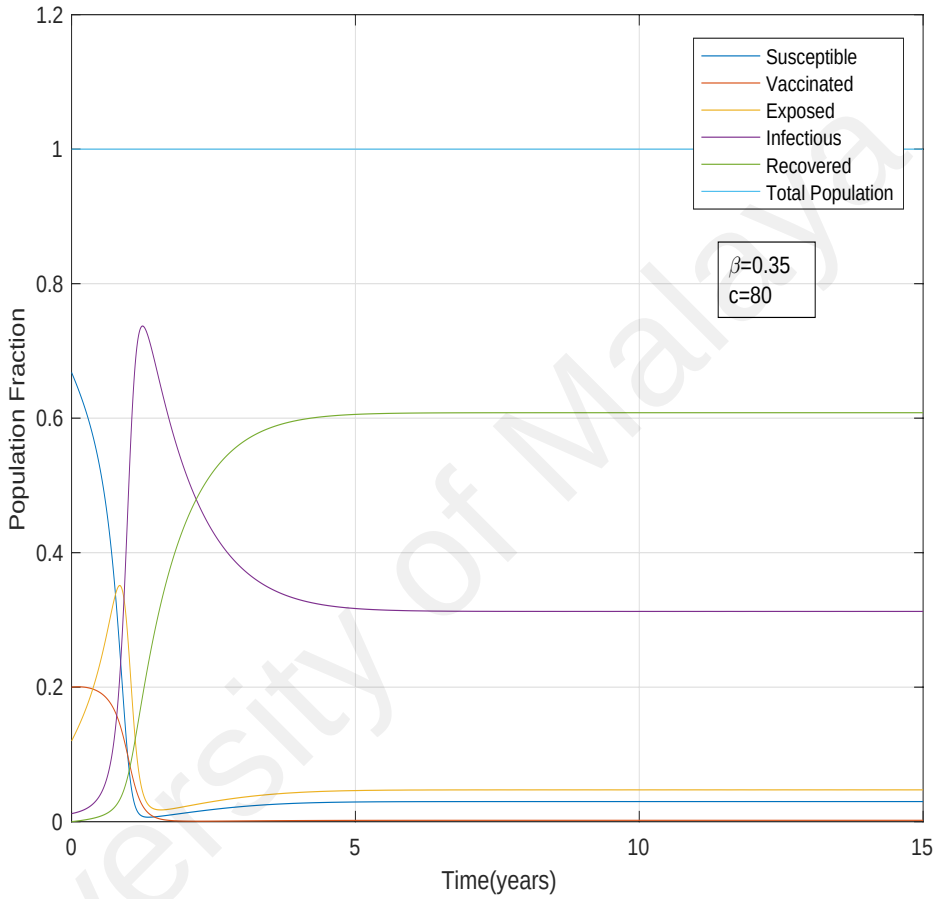

Figure 4.5: SVEIR Relationship within 15 Years

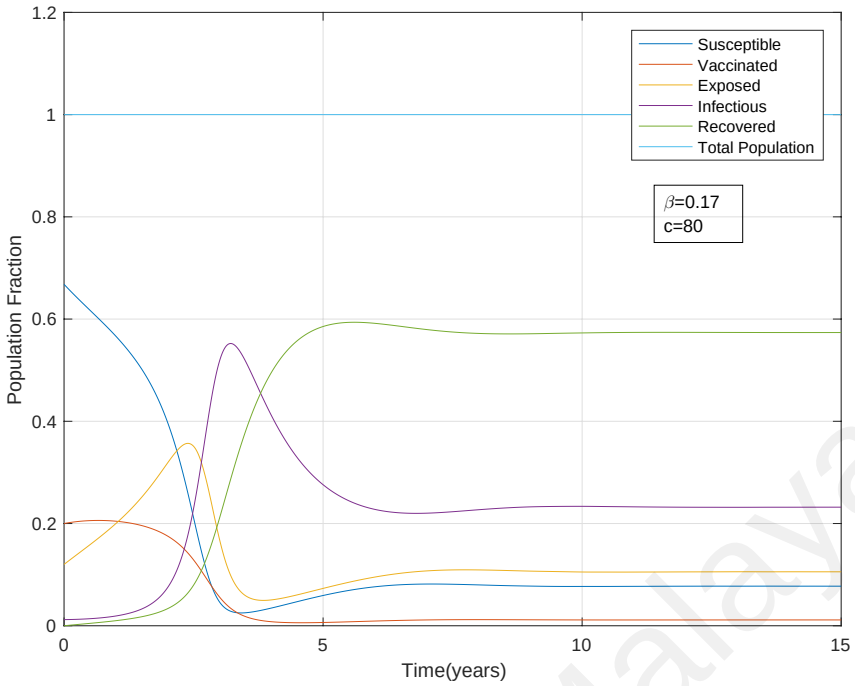

Figure 4.6: SVEIR Relationship within 15 Years

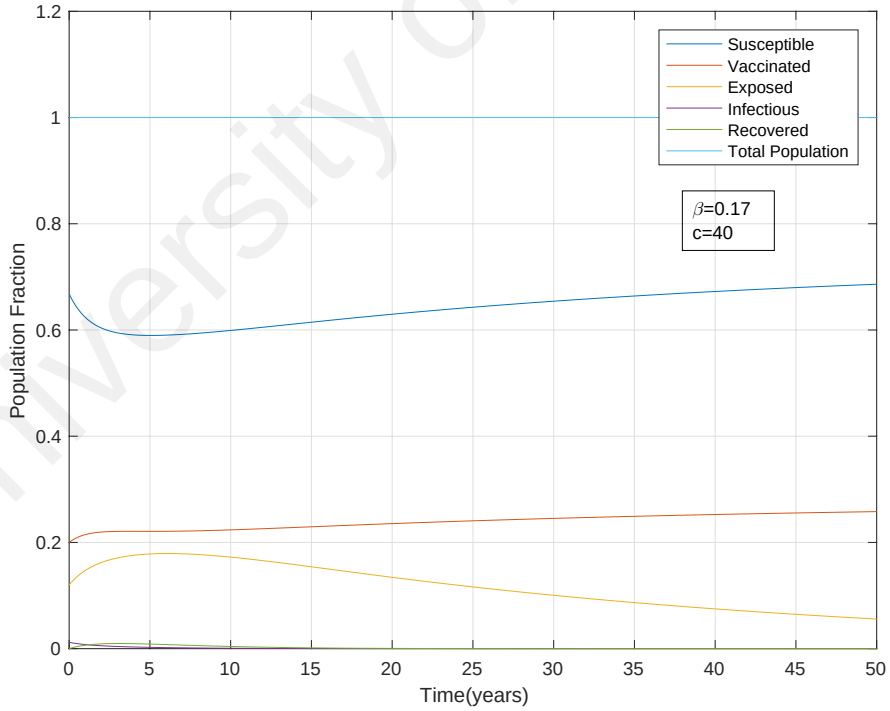

Figure 4.7: SVEIR Relationship within 50 Years

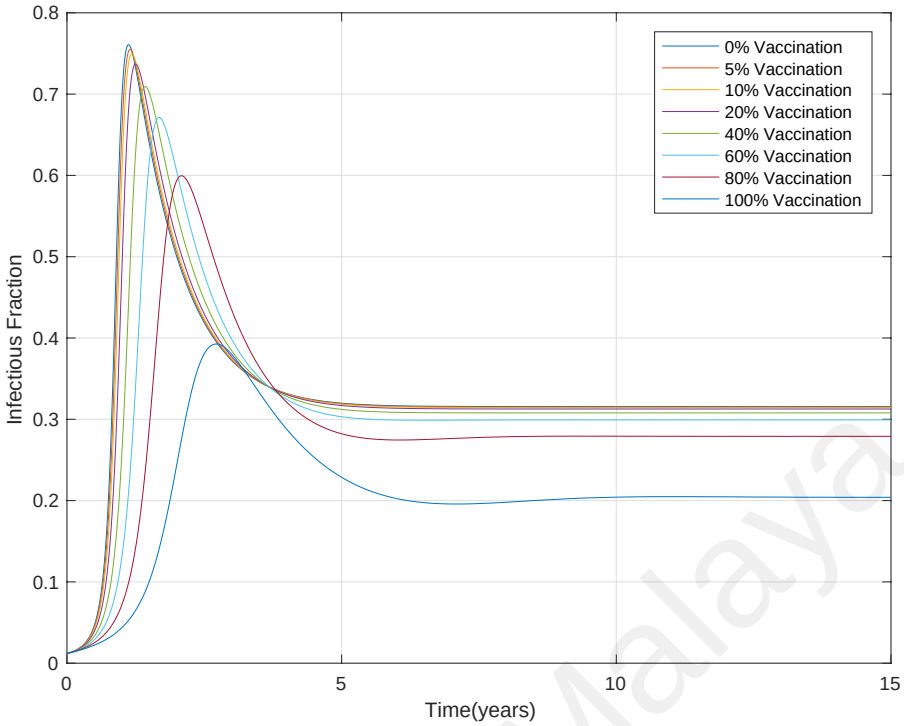

Figure 4.8: Effect of the vaccination rate

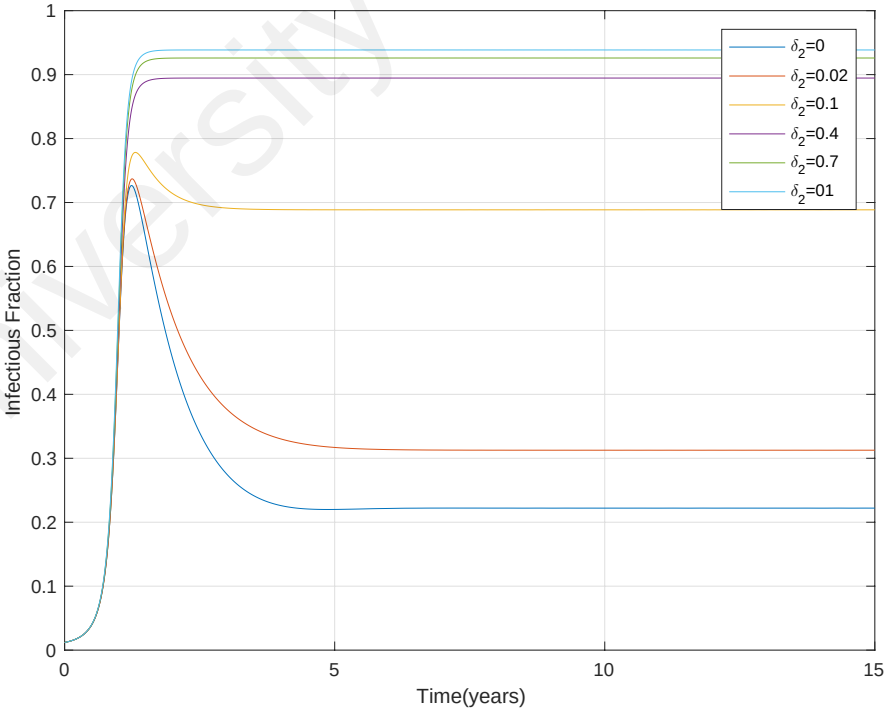

Figure 4.9: Effect of $\boldsymbol{\delta_2}$ (probability of recovered being reinfected) in reducing TB infection

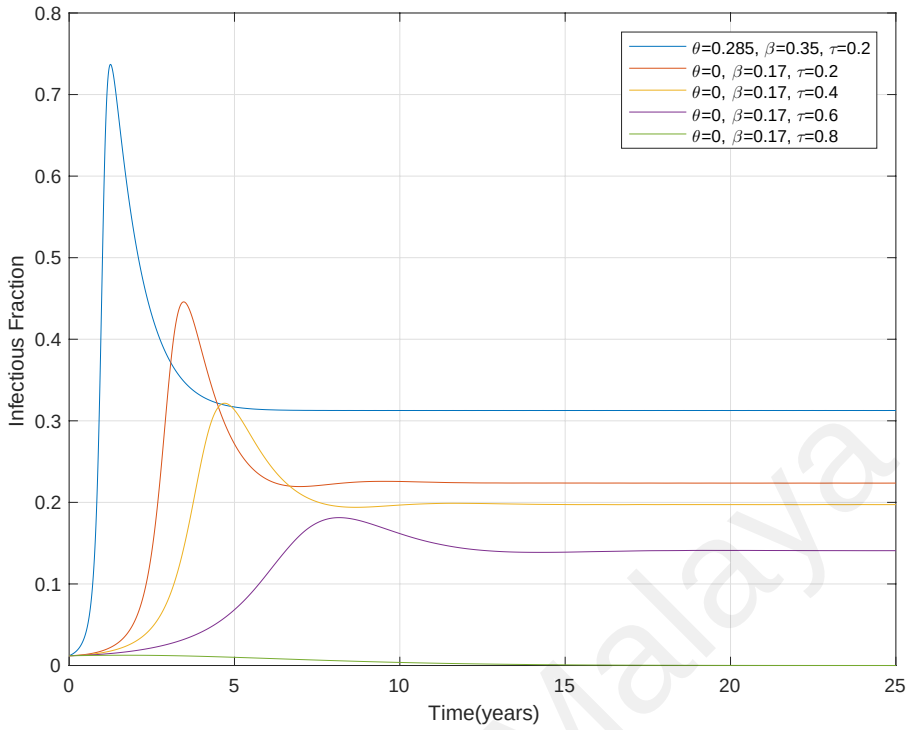

Figure 4.10: Effect of a better vaccine

4.5 The Optimal control

In this section, the analysis on combatting TB is further extended using optimal control. The base objective is to further reduce the TB infection rate while maintaining the associated cost. Choi et al. (2015), Bowong & Alaoui (2013), Gao & Huang (2018) and Moualeu et al. (2015) are among the authors that have presented an optimal control model for tuberculosis.

Controls u_1 and u_2 are introduced such that u_1 is designated as the reduction in the exposure rate of the susceptible individual to the infectious (exposure predates contact) whilst u_2 is the recommendation of healthy meals (by the nutritionists or health practitioners) to boost the immune system of the infectious individuals. Controls $u_1, u_2 \in [0,1]$ as indicated in system (4.66) below.

$$\left.\begin{aligned}
\frac{ds}{dt} &= \pi + \sigma v + \alpha r - \{\pi + \tau + [(1-\tau)(1-u_1)\beta c - \varepsilon]i\}s \\
\frac{dv}{dt} &= \tau s - [\pi + \sigma + (\theta\beta c - \varepsilon)i]v \\
\frac{de}{dt} &= (1-\tau)(1-u_1)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir \\
&\quad -[\pi + k + (\delta_1\beta c - \varepsilon)i]e \\
\frac{di}{dt} &= (1-\tau)(1-u_1)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir \\
&\quad +(\delta_1\beta ci + k)e - \varphi \\
\frac{dr}{dt} &= (\gamma + \omega + u_2)i - [\pi + \alpha + (\delta_2\beta c - \varepsilon)i]r.
\end{aligned}\right\} \quad (4.66)$$

where

$$\varphi = [\pi + \gamma + \omega + u_2 + \varepsilon(1-i)]i.$$

Since the objective is to reduce the infectious (i), the objective functional for the optimal control is

$$J(u_1, u_2) = \int_0^{t_f} \left[Qi + \frac{1}{2}c_1u_1^2 + \frac{1}{2}c_2u_2^2\right]dt \quad (4.67)$$

where $Q \geq 0, c_1 \geq 0, c_2 \geq 0$, represent the weight constants. The control parameters u_1^* and u_2^* are to be established such that $J(u_1^*, u_2^*) = min_{u_1,u_2\in}\ \ J(u_1, u_2)$ such that is the control set defined as $= \{u_1, u_2 : measurable\ \exists : 0 \leq u_1, u_2 \leq 1 \text{for all } t \in [0, t_f]\}$. As expressed in the above objective functional, we have the Lagrangian associated with the problem as

$$L(i, u_1, u_2) = Qi + \frac{1}{2}c_1 u_1^2 + \frac{1}{2}c_2 u_2^2, \tag{4.68}$$

and the Hamiltonian $\mathcal{H}$

$$\mathcal{H} = L(i, u_1, u_2) + \lambda_1^* \frac{ds}{dt} + \lambda_2^* \frac{dv}{dt} + \lambda_3^* \frac{de}{dt} + \lambda_4^* \frac{di}{dt} + \lambda_5^* \frac{dr}{dt}, \tag{4.69}$$

where $\lambda_i^*, i = 1, \ldots, 5$ are the adjoint variables satisfying $\frac{d\lambda_1^*}{dt} = \frac{-\partial \mathcal{H}}{\partial s}, \frac{d\lambda_2^*}{dt} = \frac{-\partial \mathcal{H}}{\partial v}, \frac{d\lambda_3^*}{dt} = \frac{-\partial \mathcal{H}}{\partial e}, \frac{d\lambda_4^*}{dt} = \frac{-\partial \mathcal{H}}{\partial i}, \frac{d\lambda_5^*}{dt} = \frac{-\partial \mathcal{H}}{\partial r}$ and the transversality condition $\lambda_i^*(t_f) = 0, i = 1, \ldots, 5$.

If $\hat{s}, \hat{v}, \hat{e}, \hat{\imath}, \hat{r}$ are the optimum values of s, v, e, i, r and also, $\hat{\lambda}_1^*, \hat{\lambda}_2^*, \hat{\lambda}_3^*, \hat{\lambda}_4^*, \hat{\lambda}_5^*$ are the solutions of (4.66), then with the aid of Pontryagin's maximum principle, u_1 and u_2 are optimal controls that minimize the function.

Theorem 4.5.1. There are optimal controls $\mathrm{u}_1^*, \mathrm{u}_2^* \ni : \mathrm{J}(\mathrm{u}_1^*, \mathrm{u}_2^*) = \min_{\mathrm{u}_1, \mathrm{u}_2} \mathrm{J}(\mathrm{u}_1, \mathrm{u}_2)$ subject to the optimal control system.

Proof. The approach of the proof is taken from Pontryagin et al. (1962) alongside Lenhart & Workman (2007) as it is obvious that the state variables and the controls are positive. For this minimizing problem, the necessary convexity of the objective functional in (u_1, u_2) is satisfied. Likewise, the control variable set $\ni : u_1, u_2 \in$ is also convex and closed by the definition. The integrand of the functional $Qi + \frac{1}{2}c_1 u_1^2 + \frac{1}{2}c_2 u_2^2$ is convex on the control set and the state variables are bounded.

Pontryagin maximum principle (Pontryagin & Boltyanskii, 1980) is used to minimize the objective functional and also the optimal solution. Consider (x, u) as an optimal solution of an optimal control problem, then there is a non-trivial vector function $\lambda^* = \lambda_1^*, \lambda_2^*, \ldots \lambda_n^*$ that satisfies the following;

Table 4.1: Table of values

S/No	Parameter	Meaning	Value (yr^{-1})	Source
1	β	Probability of being infected after effective contact with an infectious being	0.35000	x^*
2	π	Recruitment rate	0.03000	x^*
3	c	Contact rate	80.0000	x^*
4	μ	Natural mortality rate	0.01000	Estimate
5	ε	TB induced death rate	0.30000	x^*
6	k	Endogenous reactivation rate	0.00013	x^*
7	α	Rate of the recovered moving back to susceptible	0.30000	Estimate
8	δ_1	Exogenous reinfection rate	0.70000	x^*
9	δ_2	Probability of the recovered individuals being re-infected	0.02000	Estimate
10	τ	Vaccination rate	0.20000	Estimate
11	ω	Natural recovery rate	0.20000	x^*
12	σ	Rate of movement to susceptible class after loss of immunity given by vaccine	0.50000	Estimate
13	f	Probability that the infected will enter the latent stage of the disease	0.99000	x^*
14	f_1	Probability of the re-infected R moving to E	0.70000	x^*
15	γ	Treatment rate	0.60000	Estimate
16	θ	Rate of the vaccinated getting infected	0.28500	WHO (2018a)
17	μ_1	Reduction in the exposure rate of the susceptible individuals to the infectious	0.50000	Estimate
18	μ_2	Boosting of the immune system by eating healthy meals	0.20000	Estimate

$$\frac{dx}{dt} = \frac{\partial \mathcal{H}(t, x, u, \lambda^*)}{\partial \lambda^*}$$

$$0 = \frac{\partial \mathcal{H}(t, x, u, \lambda^*)}{\partial \lambda^*}$$

$$\frac{d\lambda}{dt} = \frac{\partial \mathcal{H}(t, x, u, \lambda^*)}{\partial \lambda^*}$$

Theorem 4.5.2. The optimal controls u_1^*, u_2^* that minimize the objective functional J over the region are

$$u_1^* = min\{1, max\{0, \hat{u}_1\}\}$$

and

$$u_2^* = min\{1, max\{0, \hat{u}_2\}\}$$

where

$$\hat{u}_1 = \frac{\beta cis(1-\tau)(\lambda_4^* - \lambda_1^*) + f\beta cis(1-\tau)(\lambda_3^* - \lambda_4^*)}{c_1}$$

and

$$\hat{u}_2 = \frac{i(\lambda_5^* - \lambda_4^*)}{c_2}$$

Proof. From equation (4.69), the below system is established.

$$\left.\begin{aligned}
\frac{d\lambda_1^*}{dt} &= \tau(\lambda_1^* - \lambda_2^*) + \beta ci(1-\tau)(1-u_1)(\lambda_1^* - \lambda_4^*) \\
&\quad + f\beta ci(1-\tau)(1-u_1)(\lambda_4^* - \lambda_3^*) + (\pi - \varepsilon i)\lambda_1^* \\
\frac{d\lambda_2^*}{dt} &= \sigma(\lambda_2^* - \lambda_1^*) + \theta\beta ci(\lambda_2^* - \lambda_4^*) + \theta f\beta ci\lambda_4^* - \lambda_3^* + (\pi - \varepsilon i)\lambda_2^* \\
\frac{d\lambda_3^*}{dt} &= k(\lambda_3^* - \lambda_4^*) + \delta_1\beta ci(\lambda_3^* - \lambda_4^*) + (\pi - \varepsilon i)\lambda_3^* \\
\frac{d\lambda_4^*}{dt} &= -Q + \beta cs(1-\tau)(1-u_1)(\lambda_1^* - \lambda_4^*) + f\beta cs(\lambda_4^* - \lambda_3^*) \\
&\quad + \theta\beta cv(\lambda_2^* - \lambda_4^*) + M \\
\frac{d\lambda_5^*}{dt} &= \alpha(\lambda_5^* - \lambda_1^*) + \delta_2\beta ci(\lambda_5^* - \lambda_4^*) + f_1\delta_2\beta ci(\lambda_4^* - \lambda_3^*) + (\pi - \varepsilon i)\lambda_4^*
\end{aligned}\right\} \quad (4.70)$$

where

$$M = \theta f\beta cv(\lambda_4^* - \lambda_3^*) + \delta_2\beta cr(\lambda_5^* - \lambda_4^*) + f_1\delta_2\beta cr(\lambda_4^* - \lambda_3^*) + \delta_1\beta ce(\lambda_3^* - \lambda_4^*)$$

$$+(\gamma + \omega + u_2)(\lambda_4^* - \lambda_5^*) + \lambda_4^*(\pi + \varepsilon) - \varepsilon(\lambda_1^* s + \lambda_2^* v + \lambda_3^* e + 2\lambda_4^* i + \lambda_5^* r).$$

By the optimality condition $\frac{\partial \mathcal{H}}{\partial u_1} = 0$ and $\frac{\partial \mathcal{H}}{\partial u_2} = 0$,

$$u_1 = \frac{\beta cis(1-\tau)(\lambda_4^* - \lambda_1^*) + f\beta cis(1-\tau)(\lambda_3^* - \lambda_4^*)}{c_1} = \hat{u}_1 \quad (4.71)$$

and

$$u_2 = \frac{i(\lambda_5^* - \lambda_4^*)}{c_2} = \hat{u}_2 \quad (4.72)$$

4.5.1 Numerical Simulation of the Optimal Control Model

The optimal control model (4.66) is solved using the numerical values in Table 4.1 above and the subsequent graphs are the resulting outputs. The impact of the controls u_1, u_2 are tested and are found to be highly relevant in further reducing the incidence of TB. Figure 4.11 queries the relevance of these controls in the model. It is shown that there is significant difference between the infectious fraction of the model with optimal control and that without control. The one with optimal control produces reduction in the infectious fraction. Furthermore, increment in the values of these controls give far better results as shown in Figures 4.12 and 4.13.

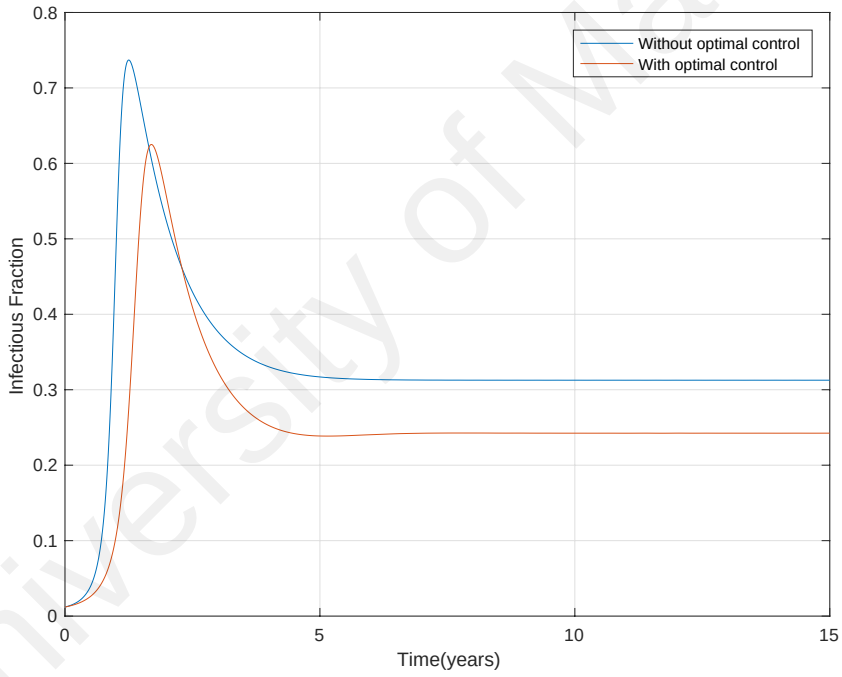

Figure 4.11: Effect of the optimal control on the infectious class

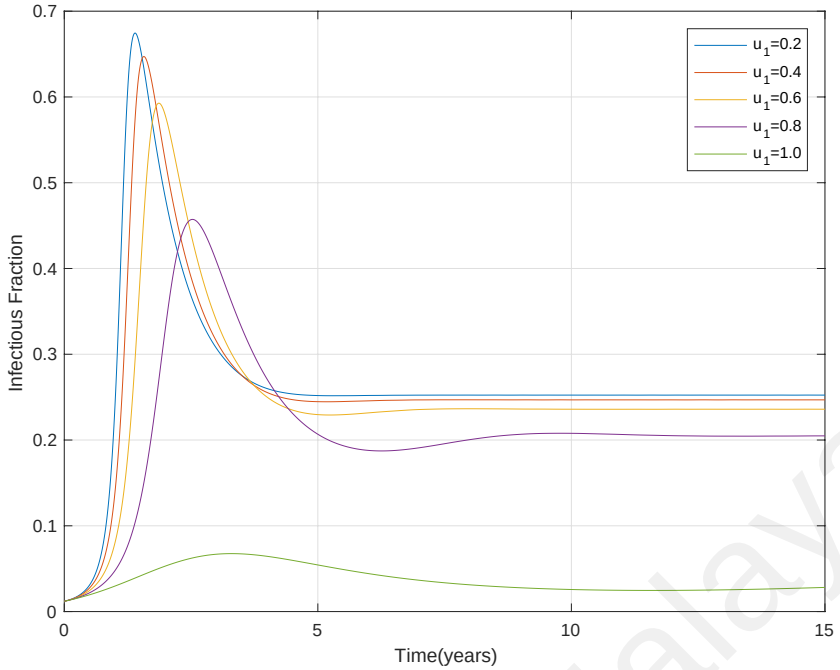

Figure 4.12: Effect of the variations in optimal control u_1

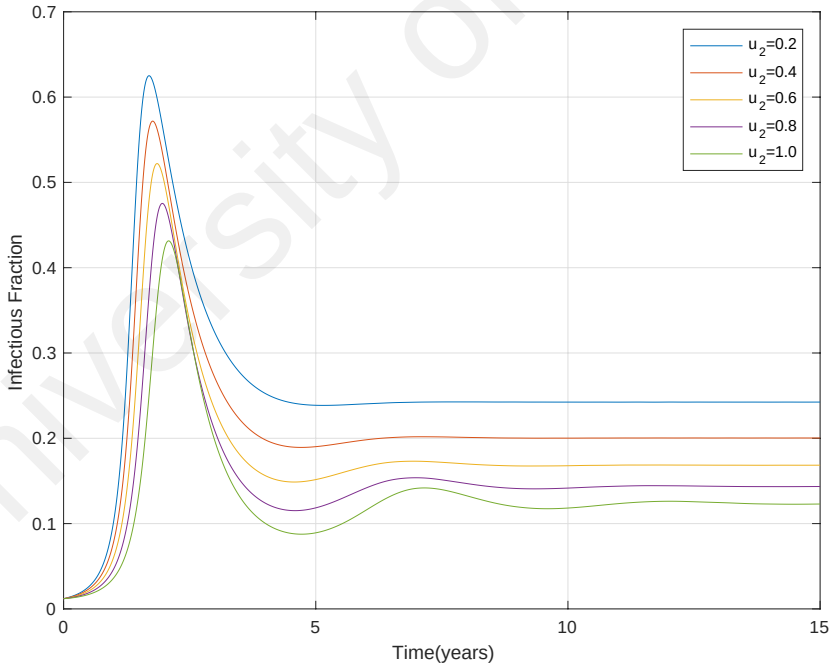

Figure 4.13: Effect of the variations in optimal control u_2

4.6 Summary

A five compartmental model of susceptible (S), vaccinated (V), exposed (E), infectious (I) and recovered (R) was formulated using a nonlinear system of ODE to investigate the relevance of prophylactic vaccine in reducing the rate of TB incident. Since efforts can only be made on the controllable factors like; infectivity rate, contact rate, vaccination rate, reinfection rate, TB induced death rate, e.t.c., the model was normalised in order to eliminate the natural death factor (μ). Subsequently, the basic reproduction number (R_0) was established which was further used to establish the stability of the disease free equilibrium (DFE). It was shown that the DFE is stable whenever $R_0 < 1$. The system is as well shown to be globally asymptotically stable using Theorems 4.3.3 and 4.3.5.

Theorems 4.3.1 and 4.3.2 explain the importance of the vaccination, its potency and immunity conferment power. From Theorem 4.3.1, it is established that vaccination helps a long way in reducing the TB incidence. Similarly, Theorem 4.3.2 explains the reason why the vaccine should be designed in a way that it is potent enough to prevent getting the infection. These Theorems are corroborated by Figure 4.10. In similar manner, if the vaccines and drugs are designed to reduce the infectivity rate coupled with the reduction of contacts between the susceptible and infectious individuals, the tuberculosis incidence would be reduced as shown in Figures 4.5-4.7. Figure 4.8 highlights the fact that variations in the vaccination rate makes much differences in the TB incident rate; as such, it would be reasonable to administer the vaccine on a good proportion of the susceptible class. If the drugs are not designed to prevent reinfection, little or nothing would be achieved in the war against tuberculosis as displayed in Figure 4.9.

As mentioned earlier, any intended vaccine should be designed to combat the infectivity rate of *Mycobacterium tb (Mtb)*. A vaccine that could reduce the infectivity

rate of *Mtb* by half and as well give a permanent immunity against TB infection would drastically reduce the incident of TB. This is as evidently presented by Figure 4.10. Increment in the vaccination rate gives better result as the infection is speedily annihilated.

From the above, it is recommended that any intended vaccine that will replace BCG should target the reduction of the infectivity rate of *Mtb* by at least half. This vaccination would be of great benefit in high TB burden places or regions that are prone to this epidemic, especially developing nations. If the BCG vaccine could be made available to these nations at little or no cost, it would indirectly benefit the wealthy donor nations due to the infectious nature of TB. Also, the drugs designed to treat tuberculosis should be done in way that they prevent reinfection.

In furtherance to the above, an optimal control analysis was done. Controls u_1 and u_2 were introduced. u_1 is the reduction in the exposure rate of the susceptible individuals to the infectious and u_2 is the boosting of the immune system by the intake of healthy meals. The impacts of these two controls were measured as displayed in Figures 4.11-4.13. The inclusion of these controls in the model shows significant reduction in the TB infectious fraction.

When the above measures; design of highly potent vaccine, drugs that prevent reinfection, reduction in the exposure rate of the susceptible persons to infectious and meals that boost the immune system of an infected person are considered, tuberculosis infection would be drastically reduced in our communities.

CHAPTER 5: THE EFFECT OF QUARANTINE IN REDUCING MULTI-DRUG RESISTANT TB (MDR-TB)

5.1 Introduction

The 2018 global tuberculosis report by the WHO has it that one-fourth of the world population is infected with tuberculosis (TB). This estimate is inclusive of different TB strains such as; drug susceptible TB (DS-TB), drug resistant TB (DR-TB), multi-drug resistant TB (MDR-TB), extensively drug resistant TB (XDR-TB) and totally drug resistant TB (TDR-TB). The discovery of MDR-TB took place in 1956 at the Great Britain (Blackman et al., 2013), only to gain prominence in the 90's as a public health threat. This strain of TB has resistance to at least one of the two most powerful anti-tubercular drugs; isoniazid and rifampicin. Its emergence has great attachment to the mismanagement (incomplete treatment course) or misuse (wrong dosage or time length to complete the drugs) (Centers for Disease Control and Prevention (CDC), 2012). It can as well be transmitted from a carrier to a susceptible person.

According to Zignol et al. (2016) the percentages of those diagnosed of MDR-TB in 2011 (Uzbekistan) stands at 62%, 62.3% in 2012 (Moldova), 57.8% in 2013 (Kazakhstan), 55.1% in 2013 (Krygyzstan), 69.1% in 2014 (Belarus), 62.1% in 2014 (Estonia) and 52.2% in 2014 (Tajikistan). Out of the 457,000 cases of MDR-TB reported in 2017 globally, the most concentrations are in India, China and Russian Federation which constitute 47% of the total reported cases. Out of this number, just a paltry 25% got enrolled for treatment in the year (WHO, 2018b). This indicates the existence of a wide gap between the detection and treatment rates of MDR-TB patients. Presently, there are two treatment regimens for MDR-TB, the variation in the regimens is attached to the drugs administration period; the 9-12 months drugs administration period which is termed the shorter treatment regimen (WHO, 2016b) and the 18 months or more drugs

administration period which is termed the longer treatment regimen (WHO, 2016c). Nonetheless, the efficacy of the longer regimen over that of the shorter has been established. The treatment of the multi-drug resistant TB (MDR-TB) as well as the extensively drug resistant TB (XDR-TB) must be maintained alongside measures to prevent drug susceptible TB, vis-á-vis; early detection, completion of treatment and the administration of correct drugs combination among other measures, since wider treatment coverage for MDR-TB decreases MDR-TB incidence (Sharma et al., 2017). In particular, complying with the instructions regarding the TB treatment should be encouraged as stressed by Ronoh et al. (2016). Non-compliance does the opposite by promoting the persistence of TB.

This chapter gives a different look to how MDR-TB is managed. It presents a deterministic model with the consideration of a quarantine class. This class is included to help check the rising rate of the multi-drug resistant TB. This is necessitated due to the fact that the TB menace is now multi-facetted due to the availability of its different strains (DS-TB, DR-TB, MDR-TB, XDR-TB and TDR-TB). This quarantine compartment is included to help monitor drug susceptible patients who may develop multi-drug resistant TB due to the non-compliance with the drugs directives. This approach adopted is to help ensure that no patient is lost due to the absence of follow up. This is in agreement with the discussion in Augusto et al. (2015).

5.2 Model Formulation

5.2.1 Introduction

The model has five human populations namely; susceptible S, infected asymptomatic individuals E (exposed), infected individuals with symptoms I (infectious), individuals

with multi-drug resistant TB Q (quarantine) and the recovered individuals R. The population is assumed to grow at the rate Π and at any time t, the total population $N(t)$ is

$$N(t) = S(t) + E(t) + I(t) + Q(t) + R(t).$$

Susceptible individuals are assumed to freely mix with the infectious individuals at the rate

$$\lambda_1 = \beta c I \tag{5.1}$$

such that β is the probability of a susceptible individual getting infected and c is the average contact rate.

These susceptible individuals have the ability to either move to the exposed state E at the rate $f\lambda_1$ or the infectious state I at the rate $(1-f)\lambda_1$. Exposed individuals are considered to progress in two ways to the I compartment, this is either through endogenous reactivation designated as k or exogenous reinfection designated as $\delta\lambda_1$. The rate of the emergence of MDR-TB from DS-TB state is denoted as ω while treatment relapse back to the quarantine compartment occurs at the rate γ. Successful treatment rates are denoted as σ and α for both the DS-TB and MDR-TB respectively, while death occur due to DS-TB and MDR-TB at the rates ε_1 and ε_2 respectively. It is as well assumed that death due to nature occurs at the rate μ and all parameter values declared are in the interval $(0,1]$ except c. The diagrammatic representation of the model is presented in Figure 5.1 and the model is mathematically described by the system below.

$$\frac{dS}{dt} = \Pi - (\lambda_1 + \mu)S \tag{5.2}$$

$$\frac{dE}{dt} = f\lambda_1 S - (\delta\lambda_1 + k + \mu)E \tag{5.3}$$

$$\frac{dI}{dt} = (1-f)\lambda_1 S + (\delta\lambda_1 + k)E - (\sigma + \omega + \varepsilon_1 + \mu)I \tag{5.4}$$

$$\frac{dQ}{dt} = \omega I + \gamma R - (\alpha + \varepsilon_2 + \mu)Q \tag{5.5}$$

$$\frac{dR}{dt} = \sigma I + \alpha Q - (\gamma + \mu)R, \tag{5.6}$$

having the initial conditions:

$$S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, Q(0) \geq 0, R(0) \geq 0. \tag{5.7}$$

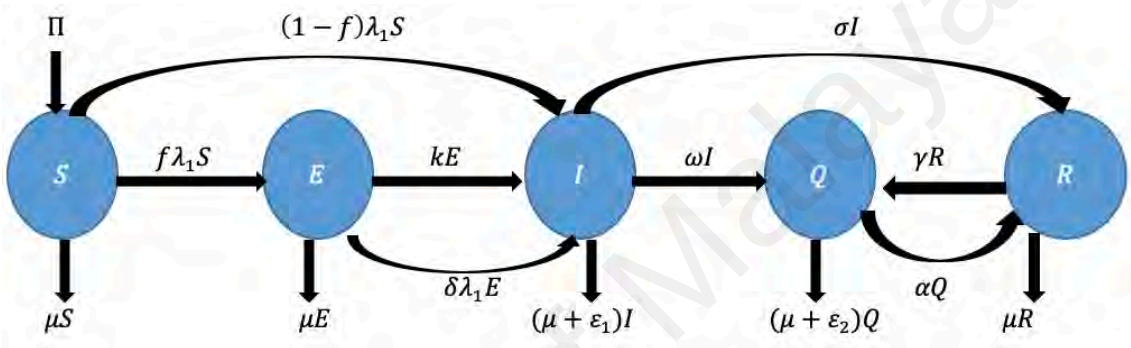

Figure 5.1: A quarantine model for tuberculosis

5.2.2 Positivity of the Solution and Invariant Region

The model represented by the system (5.2)-(5.6) above shall only be epidemiologically correct if all the dependent variables are non-negative at any time t. As such, the positivity of the model as well as its invariant region are thus presented.

Lemma 5.1: Let the initial conditions of system (5.2)-(5.6) be as given in (5.7), then the solutions $S(t), E(t), I(t), Q(t)$ and $R(t)$ are positive for all $t > 0$.

Proof. Suppose that $t^* = \sup\{t > 0: S(t) > 0, E(t) > 0, I(t) > 0, Q(t) > 0, R(t) > 0\} \in [0, t]$, then $t^* > 0$. Considering the first equation of system (5.2)-(5.6),

$$\frac{dS}{dt} = \Pi - (\lambda_1 + \mu)S,$$

then,

$$\frac{d}{dt}\left[S(t)e^{\left(\mu t+\int_0^t \lambda_1(\xi)d\xi\right)}\right] = \Pi e^{\left(\mu t+\int_0^t \lambda_1(\xi)d\xi\right)}$$

$$\Rightarrow S(t_1)e^{\left(\mu t_1+\int_0^{t_1} \lambda_1(\xi)d\xi\right)} - S(0) = \int_0^{t_1} \Pi e^{\left(\mu y+\int_0^{y} \lambda_1(\xi)d\xi\right)}dy$$

$$\Rightarrow S(t_1) = e^{-\left(\mu t_1+\int_0^{t_1} \lambda_1(\xi)d\xi\right)}\left[S(0) + \int_0^{t_1} \Pi e^{\left(\mu t_1+\int_0^{t_1} \lambda_1(\xi)d\xi\right)}dy\right] > 0.$$

Following the same approach, it can as well be shown that $E(t), I(t), Q(t)$ and $R(t)$ are positive.

Lemma 5.2: The biologically feasible region

$$\Omega = \left\{S(t), E(t), I(t), Q(t), R(t) \in \mathbb{R}_+^5 : S(t) + E(t) + I(t) + Q(t) + R(t) \leq \frac{\Pi}{\mu}\right\}$$

is positively invariant.

$$\frac{dN(t)}{dt} = \Pi - \mu N(t) - (\varepsilon_1 I + \varepsilon_2 Q),$$

so that

$$\frac{dN(t)}{dt} \leq \Pi - \mu N(t).$$

Hence, using the standard comparison theorem (Lakshmikantham et al., 1989), $N(t) \leq N(0)e^{-\mu t} + \frac{\Pi}{\mu}(1 - e^{-\mu t})$.

5.3 Stability Analysis

5.3.1 Local Stability of Disease-Free Equilibrium (DFE)

At equilibrium, the DFE of the system (5.2)-(5.6) is given by $E_0 = \left(\frac{\Pi}{\mu}, 0,0,0,0\right)$. As discussed earlier, next generation operator method is adopted to establish the linear stability of E_0. The matrices F (the new infection terms) and V (the transition terms) are respectively given by

$$F = \begin{pmatrix} 0 & f\beta S & 0 \\ 0 & (1-f)\beta S & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{5.8}$$

and

$$V = \begin{pmatrix} k+\mu+\delta\lambda_1 & 0 & 0 \\ -(k+\delta\lambda_1) & (\sigma+\omega+\varepsilon_1+\mu) & 0 \\ 0 & \omega & (\alpha+\varepsilon_2+\mu) \end{pmatrix}. \tag{5.9}$$

When (5.8) and (5.9) are evaluated at the DFE and and subsequently calculating for the spectral radius ρ of $FV^{-\prime}$ i.e. $\rho(FV^{-\prime})$, then

$$\rho\left(FV^{-'}\right) = R_0 = \frac{\beta c\Pi[k+\mu(1-f)]}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)}. \tag{5.10}$$

Basic reproduction number (R_0) is the number of secondary infections from a singly recorded one.

Theorem 5.3.1. The DFE, (E_0), of the system is locally asymptotically stable in if $R_0 < 1$, and unstable otherwise.

Proof. The Jacobian matrix (J_0) of the nonlinear system (5.2)-(5.6) at the DFE $\left(\frac{\Pi}{\mu}, 0,0,0,0\right)$ is given by

$$J_0 = \begin{pmatrix} -\mu & 0 & -\frac{\beta c\Pi}{\mu} & 0 & 0 \\ 0 & -(k+\mu) & \frac{f\beta c\Pi}{\mu} & 0 & 0 \\ 0 & k & J_0^* & 0 & 0 \\ 0 & 0 & \omega & -(\alpha+\varepsilon_2+\mu) & \gamma \\ 0 & 0 & \sigma & \alpha & -(\gamma+\mu) \end{pmatrix}, \tag{5.11}$$

$J_0^* = \frac{(1-f)\beta c\Pi}{\mu} - (\sigma+\omega+\varepsilon_1+\mu).$

Denoting the eigenvalue as η, then the eigenvalues of (5.11) is established from. $|J_0 - I| = 0$,

$$\Rightarrow \begin{vmatrix} -(\mu+\eta) & 0 & -\frac{\beta c \Pi}{\mu} & 0 & 0 \\ 0 & -(k+\mu+\eta) & \frac{f\beta c\Pi}{\mu} & 0 & 0 \\ 0 & k & Z & 0 & 0 \\ 0 & 0 & \omega & -(\alpha+\varepsilon_2+\mu+\eta) & \gamma \\ 0 & 0 & \sigma & \alpha & -(\gamma+\mu+\eta) \end{vmatrix} = 0, \tag{5.12}$$

where

$$Z = \frac{(1-f)\beta c\Pi}{\mu} - (\sigma+\omega+\varepsilon_1+\mu+\eta)$$

(5.12) produces the first eigenvalue, η_1 as $-\mu$, while the other 4 eigenvalues are as expressed in (5.13) and (5.14) below.

$$\eta_{2,3} = \frac{1}{4}\left(-(\alpha+2\varepsilon_2+3\mu) \pm \sqrt{\alpha^2+\alpha(4\varepsilon_2-2\mu)+(2\varepsilon_2+\mu)^2}\right) \tag{5.13}$$

and

$$\eta_{4,5} = \frac{1}{2\mu}\left(-b \pm \sqrt{b^2 - 4\mu^2\eta_*(k+\mu)\left\{1 - \frac{\beta c\Pi[k+\mu(1-f)]}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)}\right\}}\right), \tag{5.14}$$

where

$$b = \mu[(k+\mu)+(\sigma+\omega+\varepsilon_1+\mu)] - \beta c\Pi(1-f).$$

$$\eta_* = (\sigma+\omega+\varepsilon_1+\mu)$$

$\eta_{2,3}$ becomes negative when

$$(\alpha+2\varepsilon_2+3\mu) > \sqrt{\alpha^2+\alpha(4\varepsilon_2-2\mu)+(2\varepsilon_2+\mu)^2}. \tag{5.15}$$

Squaring both sides of (5.15) which after simplification gives

$$\alpha + \varepsilon_2 + \mu > 0,$$

which is always true, and as such, $\eta_{2,3} < 0$.

Also, since

$$R_0 = \frac{\beta c \Pi[k+\mu(1-f)]}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)},$$

then (5.14) implies

$$\frac{-b \pm \sqrt{b^2 - 4\mu^2(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)\{1-R_0\}}}{2\mu}. \tag{5.16}$$

Obviously, the eigenvalues of (5.16) depend on R_0, hence $R_0 < 1 \Rightarrow \eta_{4,5} < 0$ while $R_0 > 1 \Rightarrow \eta_4 > 0$ and $\eta_5 < 0$. As such, the stability of the system is guaranteed by $R_0 < 1$ and thus completes the proof.

5.3.2 Global Stability of Disease-Free Equilibrium (DFE)

Theorem 5.3.2. The disease free equilibrium (DFE), $\mathrm{E}_0 = \{\mathrm{S}^{**}, \mathrm{E}^{**}, \mathrm{I}^{**}, \mathrm{Q}^{**}, \mathrm{R}^{**}\} \in$ of the system (5.2)-(5.6) is globally asymptotically stable.

Proof. Consider the Lyapunov function

$$V = \left(S - S^{**} - S^{**}\ln\frac{S}{S^{**}}\right) + E + I + Q + R, \tag{5.17}$$

$$V' = \frac{(S-S^{**})}{S}S' + E' + I' + Q' + R' \tag{5.18}$$

$$\begin{aligned} \Rightarrow V' = \frac{(S-S^{**})}{S}[\Pi - (\lambda_1+\mu)S] + f\lambda_1 S - (\delta\lambda_1 + k + \mu)E + (1-f)\lambda_1 S \\ +(\delta\lambda_1 + k)E - (\sigma+\omega+\varepsilon_1+\mu)I + \omega I + \gamma R - (\alpha+\varepsilon_2+\mu)Q. \\ +\sigma I + \alpha Q - (\gamma+\mu)R. \end{aligned} \tag{5.19}$$

$$\lambda_1 = 0$$

$$\Rightarrow V' = \frac{(S - S^{**})}{S}[\mu S^* - \mu S] - \mu E - (\varepsilon_1 + \mu)I - (\varepsilon_2 + \mu)Q - \mu R \qquad (5.21)$$

$$\Rightarrow V' = \frac{-\mu(S - S^{**})^2}{S} - \mu E - (\varepsilon_1 + \mu)I - (\varepsilon_2 + \mu)Q - \mu R. \qquad (5.22)$$

From (5.22) $V' \leq 0$ of which the equality holds only when $S = S^{**}$. Using the LaSalle's invariance principle (LaSalle & Artstein, 1976), the DFE of the model is globally asymptotically stable.

5.4 Bifurcation Analysis and Global Stability of Endemic Equilibrium Point (EEP)

Bifurcation Analysis

At the equilibrium point, (5.1) becomes

$$\lambda_1^* = \beta c I^* \qquad (5.23)$$

Also,

$$S^* = \frac{\Pi}{\lambda_1^* + \mu}, E^* = \frac{f\lambda_1^*\Pi}{(\lambda_1^* + \mu)(\delta\lambda_1^* + k + \mu)},$$

$$I^* = \frac{(1-f)(\delta\lambda_1^* + k + \mu)\lambda_1^*\Pi + f\lambda_1^*\Pi(\delta\lambda_1^* + k)}{(\lambda_1^* + \mu)(\delta\lambda_1^* + k + \mu)(\sigma + \omega + \varepsilon_1 + \mu)},$$
$$Q^* = \frac{[\omega(\gamma + \mu) + \gamma\sigma][(1-f)(\delta\lambda_1^* + k + \mu) + f(\delta\lambda_1^* + k)]\lambda_1^*\Pi}{(\lambda_1^* + \mu)(\delta\lambda_1^* + k + \mu)(\sigma + \omega + \varepsilon_1 + \mu)[(\gamma + \mu)(\alpha + \varepsilon_2 + \mu) - \gamma\alpha]},$$
$$R^* = \frac{[\alpha(\sigma + \omega) + \sigma(\varepsilon_2 + \mu)][(1-f)(\delta\lambda_1^* + k + \mu) + f(\delta\lambda_1^* + k)]\lambda_1^*\Pi}{(\lambda_1^* + \mu)(\delta\lambda_1^* + k + \mu)(\sigma + \omega + \varepsilon_1 + \mu)[(\gamma + \mu)(\alpha + \varepsilon_2 + \mu) - \gamma\alpha]}. \qquad (5.24)$$

If I^* is substituted into (5.23), then it could be shown that the endemic equilibrium, EEP of the system satisfies the following quadratic equation

$$A(\lambda_1^*)^2 + B\lambda_1^* + C = 0, \qquad (5.25)$$

such that

$$A = \delta(\sigma + \omega + \varepsilon_1 + \mu),$$

$$B = (k + \mu + \mu\delta)(\sigma + \omega + \varepsilon_1 + \mu) - \beta c\delta\Pi,$$

$$C = \mu(k + \mu)(\sigma + \omega + \varepsilon_1 + \mu)(1 - R_0).$$

Hence, the EEP of system (5.2)-(5.6) is obtained when (5.25) is solved for the values of λ_1^* and subsequently substituted in (5.23) to obtain I^*. The coefficient A is always positive and also, C is always positive (negative) when $R_0 < 1$ ($R_0 > 1$). As such, the following is established.

Theorem 5.4.1. The tuberculosis model has

1. a unique endemic equilibrium if $C < 0 \Leftrightarrow R_0 > 1$,
2. a unique endemic equilibrium if $B < 0$ and $C = 0$ or $B^2 - 4AC = 0$,
3. two endemic equilibria if $C > 0, B < 0$ and $B^2 - 4AC > 0$,
4. no endemic equilibrium otherwise.

Obviously, condition shows that the model has a unique endemic equilibrium point. On the other hand, the third case indicates the possibility of backward bifurcation. Backward bifurcation is the scenario when locally asymptotically stable DFE coexists with a locally asymptotically EEP when $R_0 < 1$. The existence of this bifurcation explains that keeping the basic reproduction number less than unity ($R_0 < 1$) is no longer sufficient but required to curb the TB spread. To check this, let the discriminant $B^2 - 4AC$ be zero, which after solving for the critical value of R_0 denoted as R_c gives

$$R_c = 1 - \frac{B^2}{4A\mu(k + \mu)(\sigma + \omega + \varepsilon_1 + \mu)}.$$

Lemma 5.3: The model undergoes backward bifurcation when case (3) of Theorem 5.4.1 holds and $R_c < R_0 < 1$. It is important to note here that the feasibility of the global asymptotic stability property of the DFE established earlier is outside the region of the backward bifurcation.

Global Stability of EEP

Theorem 5.4.2. The endemic equilibrium point (EEP), $\mathrm{E}_1 = \{\mathrm{S}^*, \mathrm{E}^*, \mathrm{I}^*, \mathrm{Q}^*, \mathrm{R}^*\} \in$ of the system (5.2)-(5.6) is globally asymptotically stable.

Proof. Consider the Lyapunov function

$$V_2 = K_1\left(S - S^* - S^*\ln\frac{S}{S^*}\right) + K_2\left(E - E^* - E^*\ln\frac{E}{E^*}\right) + K_3\left(I - I^* - I^*\ln\frac{I}{I^*}\right), \tag{5.26}$$

then the time derivative of V is

$$V_2' = K_1\left(\frac{S-S^*}{S}\right)\frac{dS}{dt} + K_2\left(\frac{E-E^*}{E}\right)\frac{dE}{dt} + K_3\left(\frac{I-I^*}{I}\right)\frac{dI}{dt}. \tag{5.27}$$

The substitution of $\frac{dS}{dt}, \frac{dE}{dt}$ and $\frac{dI}{dt}$ as expressed in (5.2)-(5.4) in (5.27) gives,

$$\begin{aligned} V_2' = {} & K_1\left(\tfrac{S-S^*}{S}\right)[\Pi - (\lambda_1 + \mu)S] \\ & + K_2\left(\tfrac{E-E^*}{E}\right)[f\lambda_1 S - \delta\lambda_1 E - (k+\mu)E] \\ & + K_3\left(\tfrac{I-I^*}{I}\right)[(1-f)\lambda_1 S + (\delta\lambda_1 + k)E - (\sigma + \omega + \varepsilon_1 + \mu)I] \end{aligned} \tag{5.28}$$

At the equilibrium point, $\Pi = \beta c I^* S^* + \mu S^*, (k+\mu) = \frac{f\beta c I^* S^* - \delta\beta c I^* E^*}{E^*}$ and $(\sigma + \omega + \varepsilon_1 + \mu) = \frac{(1-f)\beta c I^* S^* + \delta\beta c I^* E^* + kE^*}{I^*}$ which after substitution into (5.28) produces

$$V_2' = K_1\left(\frac{S-S^*}{S}\right)[\beta cI^*S^* + \mu S^* - (\lambda_1+\mu)S]$$
$$+K_2\left(\frac{E-E^*}{E}\right)\left(f\lambda_1 S - \delta\lambda_1 E - \left[\frac{K_2^*}{E^*}\right]E\right)$$
$$+K_3\left(\frac{I-I^*}{I}\right)\left((1-f)\lambda_1 S + (\delta\lambda_1+k)E - \left[\frac{(1-f)\beta cI^*S^* + \delta\beta cI^*E^* + kE^*}{I^*}\right]I\right). \quad (5.29)$$

where

$$K_2^* = f\beta cI^*S^* - \delta\beta cI^*E^*$$

$$\Rightarrow V_2' = -K_1\mu\frac{(S-S^*)^2}{S} + K_1\left(1-\frac{S^*}{S}\right)[\beta cI^*S^* - \beta cIS]$$
$$+K_2\left(1-\frac{E^*}{E}\right)\left(f\lambda_1 S - \delta\lambda_1 E - \left[\frac{K_2^*}{E^*}\right]E\right)$$
$$+K_3\left(1-\frac{I^*}{I}\right)$$
$$\left((1-f)\lambda_1 S + (\delta\lambda_1+k)E - \left[\frac{(1-f)\beta cI^*S^* + \delta\beta cI^*E^* + kE^*}{I^*}\right]I\right). \quad (5.30)$$

Let $\frac{S}{S^*} = x_1$, $\frac{E}{E^*} = x_2$, $\frac{I}{I^*} = x_3$, $I^*S^* = a$, $I^*E^* = b$ and $kE^* = g$, then the simplification of (5.30) gives

$$V_2' = -K_1\mu\frac{(S-S^*)^2}{S} + K_1\beta ca + [-K_1\beta ca + K_2 f\beta ca + K_3(1-f)\beta ca]x_1x_3$$
$$+[-K_2\delta\beta cb + K_3\delta\beta cb]x_2x_3$$
$$+[K_2\delta\beta cb - K_3(1-f)\beta ca - K_3\delta\beta cb - K_3 g + K_1\beta ca]x_3$$
$$+[-K_2 f\beta ca - K_3\delta\beta cb + K_3 g - K_2\delta\beta cb]x_2 - (1-f)\beta cax_1$$
$$-K_1\frac{1}{x_1} - K_2 f\beta ca\frac{x_1x_3}{x_2} - g\frac{x_2}{x_3} + f\beta ca + (1-f)\beta ca + 2\delta\beta cb + g. \quad (5.31)$$

When the coefficients of x_1x_3, x_2x_3, x_3, x_2 and x_1 are equated to 0, then $K_1 = K_2 = K_3$; $f = 1$; $g = \beta ca$; $\delta = 0$.

Choosing the values of $K_1 = K_2 = K_3 = 1$ and substituting the values of f, g and δ as established above gives

$$V_2' = \frac{-\mu(S-S^*)^2}{S} + \beta ca\left[3 - \frac{1}{x_1} - \frac{x_1 x_3}{x_2} - \frac{x_2}{x_3}\right]. \tag{5.32}$$

Since arithmetic mean (AM) is greater than or equal to geometric mean (GM), $(AM \geq GM)$, then

$$\frac{1}{x_1} + \frac{x_1 x_3}{x_2} + \frac{x_2}{x_3} \geq 3.$$

It is obvious from (5.32) that $V_2' \leq 0$ for which the equality holds when $x_1 = x_2 = x_3 = 1$ (i.e. $S = S^*$, $E = E^*$ and $I = I^*$). By the LaSalle's invariance principle (LaSalle & Artstein, 1976), the EEP of the system is globally asymptotically stable.

5.5 Sensitivity Analysis and Numerical Simulation

5.5.1 Sensitivity Analysis

As earlier defined, the basic reproduction number (R_0) is the number of secondary infection from a singly recorded one, hence the behaviour of an infection can be measured using its R_0. If R_0 is regarded as a function, then the constituent parameters would be designated as its independent variables. When this function (R_0) is partially differentiated with respect to these parameters (independent variables), their effects on the disease incidence could be established. The parameters considered in the model formulation are $\Pi, \beta, c, k, f, \mu, \sigma, \omega$ and ε_1. Positive result after differentiating the function (R_0) partially with respect to each of these variables indicate that parameter promotes the disease incidence while negative result does the opposite.

$$\frac{\partial R_0}{\partial \Pi} = \frac{\Pi\beta c((1-f)\mu + k)}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)}, \frac{\partial R_0}{\partial \beta} = \frac{\Pi c((1-f)\mu + k)}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)},$$

$$\frac{\partial R_0}{\partial c} = \frac{\Pi\beta((1-f)\mu + k)}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)}, \frac{\partial R_0}{\partial k} = \frac{\Pi\beta cf}{(k+\mu)^2(\sigma+\omega+\varepsilon_1+\mu)},$$

$$\frac{\partial R_0}{\partial f} = -\frac{\Pi\beta c}{(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)}, \frac{\partial R_0}{\partial \sigma} = -\frac{\Pi\beta c((1-f)\mu+k)}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)^2},$$

$$\frac{\partial R_0}{\partial \omega} = -\frac{\Pi\beta c((1-f)\mu+k)}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)^2}, \frac{\partial R_0}{\partial \varepsilon_1} = -\frac{\Pi\beta c((1-f)\mu+k)}{\mu(k+\mu)(\sigma+\omega+\varepsilon_1+\mu)^2},$$

$$\frac{\partial R_0}{\partial \mu} = -\frac{\Pi\beta c((1-f)\mu^2(\varepsilon+2\mu+\sigma+\omega)+k\mu(2\varepsilon(4-f)\mu+2(\sigma+\omega))+k^2(\varepsilon+2\mu+\sigma+\omega))}{\mu^2(k+\mu)^2(\varepsilon+\mu+\sigma+\omega)^2}.$$

From the above Π, β, c and k promote the disease incidence while f, σ, ω and ε_1 reduce the incident rate. Π is the recruitment rate into the population, as such it services the population with susceptible individuals which promote the disease spread. Expectedly, β which is the disease incident rate and k which is the endogenous reactivation rate promote the disease incidence as well. Another cogent result is given by c, the contact rate. This explains that the more the TB carrier mingles with unsuspecting individuals, the more the possibility of the spread of the infection. On the other hand, μ and ε_1 representing the death due to nature and disease induced death respectively reduces the spread of the infection. This is because carriers are removed from the population and as such, the number of persons to spread the infection get reduced. In similar manner, σ which represents the successful treatment rate and ω representing the movement to the quarantine compartment after the development of MDR-TB contribute to the reduction in the disease incident rate. The same trend is followed by the differentiation with respect to f which represents the rate at which susceptible individual move to the exposed compartment after infection. This is consonance with the results gotten from the first model considered in this thesis. It is reinstating the fact that proper management of the infected individuals by which no one goes directly to the infectious, I compartment would help curb the TB incidence rate generally.

5.5.2 Numerical Simulation

In this section, the numerical simulation of the model is considered. The simulation is done to query the relevance and importance of the parameters considered in the model formulation. This is to further corroborate the results gotten through the partial differentiation of the basic reproduction, R_0 with respect to the independent variables. The model is simulated using $ODE45$ package of MATLAB 2016a with the hypothetical values; $S = 8000, E = 1000, I = 500, Q = 300, R = 200, \alpha = 0.5, \beta = 0.35, c = 80, \delta = 0.7, \varepsilon_1 = 0.3, \varepsilon_2 = 0.1, f = 0.99, \gamma = 0.1, k = 0.00013, \Pi = 0.03, \sigma = 0.85, \omega = 0.8,$ and $\mu = 0.01$.

The resulting graphs are as presented in Figures 5.2-5.5. As established earlier, Π, β, c and k contribute to the disease persistence while $f, \sigma, \omega, \varepsilon_1$ and μ help in taming the wild spread of the infection.

The impact of the recruitment rate is displayed by the Figure 5.2. This confirms the possibility of greater spread of the infection when more people are admitted into the community. Similar trend is maintained in Figure 5.3 where the impact of the infection rate is queried. When the infectivity rate is drastically reduced, the quarantine class population patients is as well reduced. The quarantine class houses the MDR-TB patients.

Concerted efforts by all concerned in preventing the direct progression of infected individuals from the susceptible class to the infectious is required. This is as displayed in Figure 5.4 where the relevance of f in curbing the spread of the infection is explained. The story is the same when ω (probability of advancement to the MDR-TB stage) is varied. Ordinarily, bigger values of ω would be expected to keep the infection out of control, but it is actually explaining the role of quarantine in curbing the spread of the infection as displayed in Figure 5.5 i.e., the quarantine is effective in the management of

MDR-TB. The Figure shows the greatest value of ω subsiding in little time to be at par with the other values. When patients with MDR-TB are allowed to freely mingle with the general populace, it gives room for the spread of the infection. On the other hand, if they are confined to a designated place, the public would be safe from the havoc that may erupt through mingling with them. Also, the health care givers would be able to monitor them regarding the proper intake of their medications (because of the long administration period of the drugs) as and when due and immediately attend to them in case of any emergency.

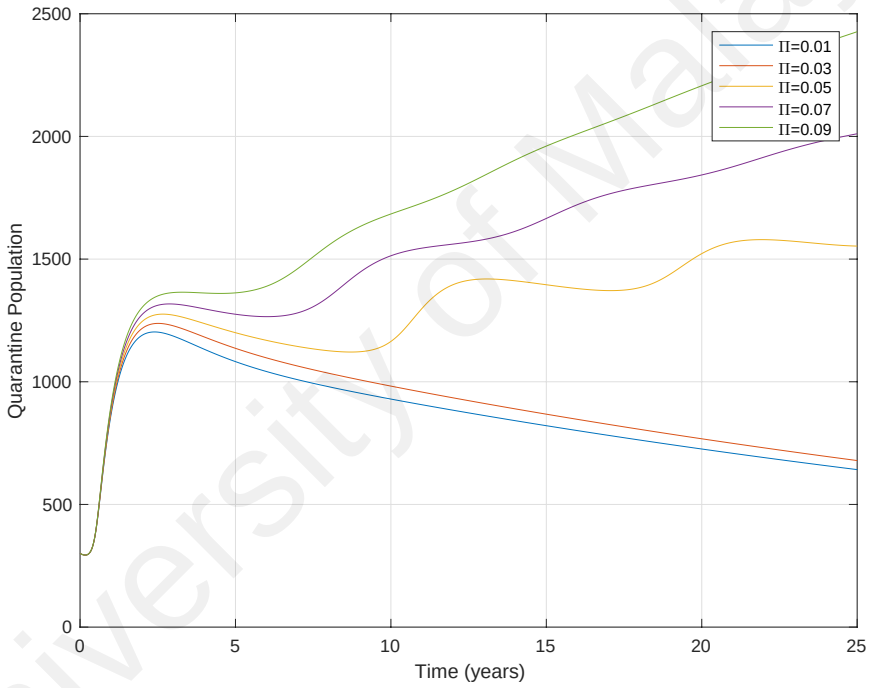

Figure 5.2: Effect of $\boldsymbol{\Pi}$ (recruitment rate) on the quarantine class

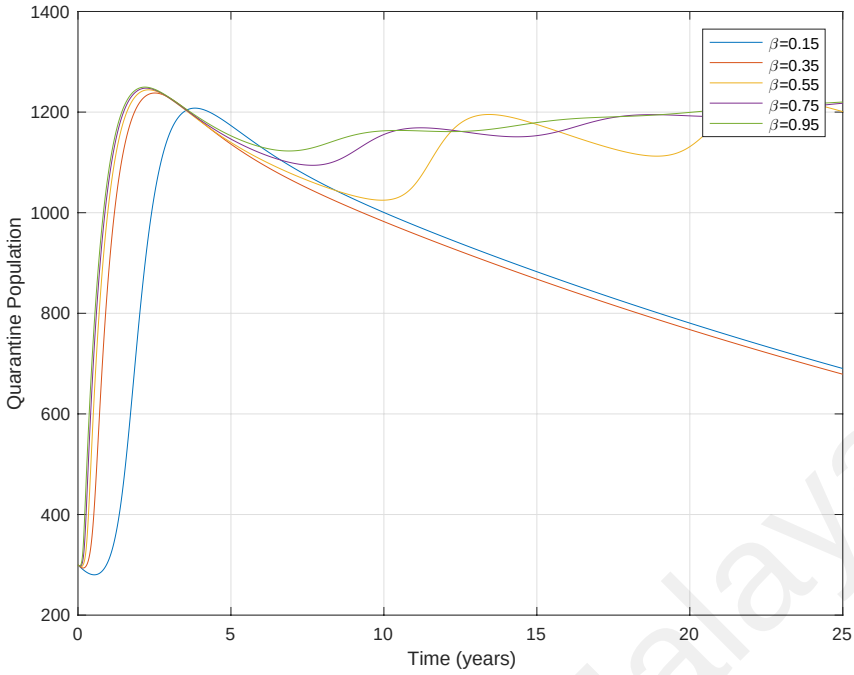

Figure 5.3: Effect of $\boldsymbol{\beta}$ (probability of infectivity) on the quarantine class

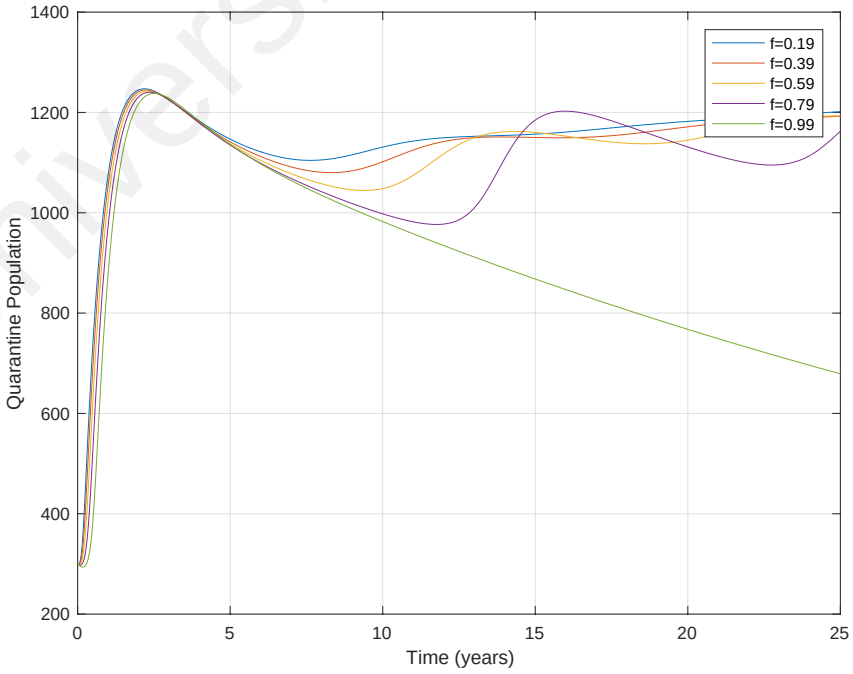

Figure 5.4: Effect of $\boldsymbol{f}$ (progression from $\boldsymbol{S}$ to $\boldsymbol{E}$) on the quarantine class

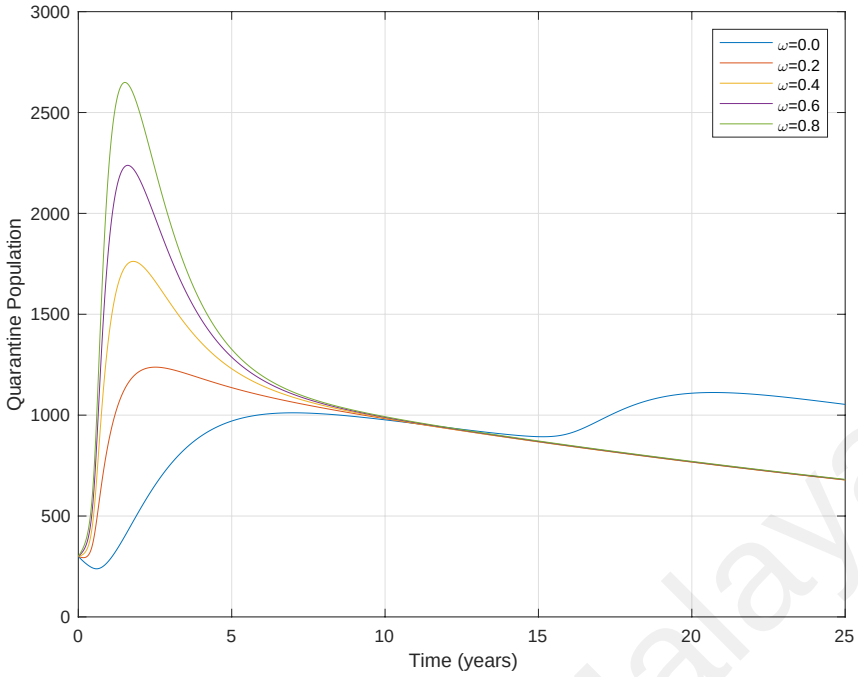

Figure 5.5: Effect of $\boldsymbol{\omega}$ (progression from I to Q) on the quarantine class

5.6 Summary

A five compartmental deterministic model is considered in this chapter to present the relevance of quarantine in the management of multi-drug resistant TB (MDR-TB). The quarantine compartment is positioned after the infectious compartment to harbour those that may develop MDR-TB from the infectious class. The analytical and numerical results presented explain in details the relevance of recruitment, infectivity, contact, treatment, progression, reactivation, reinfection and relapse rates to the disease dynamics. Also established is the need for greater efforts to be put in place in addressing the disease incidence rate as the model shows the existence of backward bifurcation. This implies making sure $R_0 < 1$ is no more sufficient to stall the disease spread.

CHAPTER 6: SUMMARY, CONCLUSION, RECOMMENDATIONS AND FUTURE WORK

6.1 Summary

This research work focuses on mathematical approaches to address tuberculosis epidemic. Basically, there are 6 chapters of the research with Chapters 1, 2, and 6 discussing the introduction, literature review and summary respectively. Chapters 3-5 present different mathematical models to discuss the tuberculosis epidemic.

Chapter 3 presents a model in which the impact of passing through the exposed state is discussed. In that model, there are 4 compartments namely; susceptible, exposed, infectious and recovered. From the mathematical analysis, it is established that when those that have been infected with TB pass through the exposed state without moving directly to the infectious compartment, TB incidence is greatly reduced. Also from the model, the impact of contact, recruitment and treatment rates are established. Expectedly, higher contact rates produce higher TB incident rate. On the other hand, high recruitment and treatment rates delay the eventual onset of the infection which could be used in preventing ultimate breakout of TB infection.

Chapter 4 gives an extension of the model in the third chapter whereby the impact of vaccination is tested. The model was formulated to accommodate vaccination compartment and as such leads to a 5-compartmental model. Two theorems are established in this chapter to discuss the importance of vaccination, its potency and the degree to which it can confer immunity. The results from these theorems are further corroborated by graphical results. From the graphical results gotten, it is safe to say that the more the number of people vaccinated with an effective vaccine, the safer a community would be. The results also show that designing a potent prophylactic vaccine

should focus on how to attack the infectivity rate of *Mycobacterium tuberculosis (Mtb)*. Vaccines that attack the infectivity rate of *Mtb* give better protection against TB.

The model was further extended to take impact of optimal control into consideration. The major highlight of the optimal control approach is the recommendation of healthy meals to TB patients. The healthy meals in this respect are meant to boost the immune system of the TB patient. This consideration also gives good result as there is significant reduction in the number of TB cases. Reduction in the rate of exposure of the susceptible individuals to infectious also reduce the TB incidence. This is established using the second control u_1.

Chapter 5 presents the last model considered. In this model, multi-drug resistant TB (MDR-TB) was considered in the presence of quarantine program. The quarantine class is designed to house drug susceptible individuals that develop MDR-TB. The quarantine program displays its efficacy in reducing the MDR-TB incident cases as the patients are not left to freely mingle with susceptible individuals. This measure also helps in keeping the MDR-TB under watch to ascertain if they are taking their medications as prescribed.

Also established is the fact that the model undergoes backward bifurcation. This indicates the need to put better measures in place as the locally stable DFE coexists with the locally stable EEP. The implication of this behaviour is that, having the basic reproduction number less than unity ($R_0 < 1$) is no longer sufficient to put out the infection.

6.2 Conclusion

Chapters 3 and 4 have their models in fractions of the total population while the model in Chapter 5 is in terms of the total population. From both approaches, it is discovered that the fractional population method helps in ascertaining the correctness of the obtained results as it would be expected that the population fraction sum to 1 at any point in time. However, the mathematical analysis becomes more difficult using this approach. The total population approach on the other hand gives an easier mathematical analysis as compared to the fractional approach, but the correctness of the obtained solution may not be easily ascertained.

The models provide the understanding that tuberculosis epidemic incidence is increasing due to the high contact rates between the susceptible and infectious individuals. Also, the non-availability of an effective prophylactic vaccine in the regions mostly affected keeps the incident rate in an increasing order. Lastly, existence of the backward bifurcation also gives the information why the incident rate is increasing.

The research questions posed in Chapter 1 (1.7.2) are thus answered. The analysis done on the models show that there is the possibility of eliminating TB as shown from the results gotten in the first model when the contact and infectivity rates of the TB are kept at different levels. However, if we are unable to reduce the infectivity rate, reducing the contact rate alone shall help in reducing the rate of incidence. Also, the main condition under which we have a TB free environment is when efforts are made to ensure all TB infected individuals pass through the exposed state before progressing to the infectious class. It is the unavailability of this effort that makes the management of TB ineffective. In overall, awareness, effective vaccination and quarantine should be put in place as an

addition to the stated requirements if any reasonable result is desired to be achieved in reducing the incidence of tuberculosis.

6.3 Recommendations

From our research, a lot of loop holes promoting the incidence of TB are observed and as such, the below recommendations are given;

1. Every TB patient should be made to pass through the exposed state. Passage through the exposed state has been established by one of the models to help reduce the TB incidence drastically. This may not seem easily achievable, but when there is great awareness regarding proper and frequent medical checkup, most unaware TB carriers could be saved from becoming TB infectious patients.

2. Great reduction in the contacts with TB patients should be encouraged. This requires educating people on the basic symptoms of TB such as cough, coughing up blood, night sweats, fatigue, weight loss, fever, etc. When people are aware of these, it will be easy for them to decide who they can freely mix with.

3. Great focus should be on immigrants as they are major contributors to TB incidence. When people are coming from a high TB burden zones, it should be strictly encouraged they undergo TB screening before gaining entrance to the community. This would help ascertain their medical fitness and as well guide on deciding whether the patients are to be placed on some drugs before entering the community. It would be a win-win situation for both parties as the community would be saved from TB and the patient has a good chance of being cured of his infection.

4. Since successes are being recorded in the treatment of TB patients, it would be encouraged that the treatment is stepped up for greater coverage. This is especially required in the under developed nations as most patients there are yet to have access to proper medical care.

5. Another form of awareness should be designed solely to educate the populace on how TB spreads. When people are aware of such, they would be able to make informed decisions when any of the TB symptoms is observed in any individual.

6. It is high time new TB vaccines were produced. This vaccine should be designed to give 100% immunity coverage against TB.

7. The focus of the new vaccine should be on attacking the infectivity rate of *Mycobacterium tuberculosis (Mtb).* Our model has shown that when the vaccine attacks the *Mtb* infectivity rate by half, TB incidence reduces drastically.

8. Enough funds should be earmarked for TB vaccination and campaign. Each nation should be encouraged to set these funds aside from their annual budget to achieve the end TB campaign slated by the WHO for 2035.

9. TB therapeutic drugs should be designed to be potent enough in preventing TB reinfection. When this is done, the recovery trajectory of TB patients can be easily studied for future projections.

10. One of the presented models has shown the importance of good diet. Balanced diet should be recommended for TB patients which would in turn help in boosting the immune system of the TB patients. Perhaps, this may promote the swift recovery of the patient.

11. The production of new TB drugs that lasts less than six months should be encouraged. This would reduce the drug taking burden on the patient and as well give better result in shorter period.

12. A greater focus should be given to drug susceptible TB (DS-TB) strain than other strains. This is because the incidence of most other strains are by the evolution of DS-TB.

13. Decision makers should not only rely on keeping the basic reproduction number less than unity ($R_0 < 1$). This is because the last model considered exhibits backward bifurcation. This is an indication of possible endemicity of TB even when $R_0 < 1$.

14. Isolation option should not be left out. This would also help in containing the spread of other TB strains.

6.4 Future Work

Since our sole aim is to eliminate TB or at least reduce its incidence to minimum, below listed are some of the works considered for the future so as to look at the TB dynamics from a different perspective.

1. Awareness is among the recommendations made, hence we plan to come up with an awareness model of TB with the possibility of TB reinfection.

2. When the awareness model has been done with the understanding of its dynamics, we shall consider extending the model to accommodate vaccination program. This extension is intended to see the impact of the duo in TB management.

3. There is also the plan to extend the vaccination model to accommodate HIV. This extension would be with the assumption that TB vaccine confers permanent immunity against TB infection. This would also give the possible understanding of the dynamics of the TB-HIV co-infection.

4. Also, the TB-HIV co-infection model would be constructed for the other strains of TB. This would give an extensive understanding of the TB dynamics away from the common DS-TB.

5. A model to possibly establish any relationship between TB and malaria is under consideration. This is because in recent news, malaria is said to have resistance to drugs as well.

6. Among the consideration for future work is also the formulation of a fractional order model of TB. This is planned to ascertain which among the fractional and integer order models present better picture of the true dynamics of TB.

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LIST OF PUBLICATIONS AND PAPERS PRESENTED

PUBLICATIONS

1. **Yeketi, A. A.,** Othman, W. A. M., & Awang M. A. O. (2019). The role of vaccination in curbing tuberculosis epidemic. *Modeling Earth Systems and Environment, 5*(4), 1689-1704.
2. **Yeketi, A. A.,** & Othman, W. A. M. (2019). A compartmental model on the effect of quarantine on MDR-TB. *International Journal of Mathematics and Computer Science, 14*(3), 613-629.

PAPERS PRESENTED

1. **Ayinla Ally Yeketi (2019).** A mathematical model of the tuberculosis epidemiology. Colloquium Series, 15th May, 2019, Institute of Mathematical Sciences, University of Malaya.
2. **Ayinla Ally Yeketi (2019).** Ending the great white plague: Mathematical approach. Colloquium Series, 23rd November, 2019, Universiti Tunku Abdul Rahman.