KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY

MODELLING HUMAN IMMUNE RESPONSE TO BACTERIA INFECTIOUS DISEASES

BY

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DECLARATION

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

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ABSTRACT

This study is aimed at modeling human immune response to bacteria infectious diseases. The issues of humans' defense against bacterial infections and the reaction of immune system to these infections are the major problems in practical immunology. In addition to antibacterial defense, the human immune system plays a significant role in compatibility reactions such as autoimmune diseases and other allergies.

Two systems of differential equations have been developed, analyzed and the numerical solutions found. These systems have been used to model different stages of the human immune response to bacterial infection. The first set of differential equations describes the behaviour of phagocytes and lymphocytes in the absence of bacteria cells (innate immune response) while the last set of equations describes the behaviour of phagocytes and lymphocytes in the presence of bacteria cells (adaptive immune response) which depicts the final stage of fighting bacterial infections.

Finally the steady states and their stability characteristics for these differential models are deduced. Each of the models permits the existence of two types of stationary states. There is the state of no infection, with no bacteria cells while the other is the state of cohabitation where bacteria cells persist against the background of immune response. An asymptotically stable state implies a state of no infection and an unstable state represents a state of infection. It was found from the study that the state of no infection represents the immune state.

LIST OF FIGURES

CHAPTER ONE

INTRODUCTION

In this chapter, the following aspects of the thesis which include the background, the statement of the problem, the objectives, the methodology, the significance, the scope and finally the organization are presented.

BACKGROUND OF THE STUDY

Infections are prevalent in developing countries, where co-infection is common. The adverse impact of infectious diseases is most severe among poor people, who have limited resources such as inadequate or no access to integrated health care, prevention tools and medications. According to World Health Organization (2011) approximately fifteen million people die each year due to infectious diseases – with one in two deaths in developing countries. Children are particularly vulnerable to infectious diseases. Pneumonia, diarrhea and malaria are leading causes of death among children under age 5; cerebral malaria can cause permanent mental impairment. Infectious diseases are also destructive to the health of adults, causing disability, a diminished quality of life, decreased productivity or death.

Infection of humans ranges from childhood diseases, such as chickenpox, diphtheria and measeals, to faecal–oral infections, such as cholera and rotavirus, vector-borne diseases including malaria and even sexually transmitted such as gonorrhea, syphilis and others. Infectious diseases account for more death and disability worldwide than either non-communicable disease or injury.

Wikipedia encyclopedia (2011), explains that infectious diseases, also known as communicable diseases, contagious diseases or transmissible diseases as clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the

infection, presence and growth of pathogenic biological agents in an individual host organism. In certain cases, infectious diseases may be without obvious symptoms for much or their entire course. Infectious pathogens include some viruses, bacteria, fungi, protozoa, multicellular parasites, and abnormal proteins known as prions. These pathogens are the cause of disease epidemics, in the sense that without the pathogen, no infectious epidemic occurs. These pathogens are able to cause disease in animals and plants.

The frequently occurring infectious diseases throughout the world today include African trypanosomiasis, cholera, hepatitis A, B and C, HIV/AIDS, influenza, common cold, malaria, meningitis, onchocerciasis, tuberculosis and typhoid. Accurate caseload numbers are difficult to determine especially because so many of these diseases are common in developing countries where many people do not have access to reliable medical care.

The World Health Organization (2011), estimates that approximately half of all deaths caused by infectious disease each year can be attributed to just three diseases; tuberculosis, malaria and AIDS. Together, these diseases cause over three hundred million illness and more than five million deaths each year.

A reality of life is that at some point we all get sick. Catching a cold is as common as morning porriage. In an effort to stay healthy, people take vitamin C supplements, get good exercise, and even consume herbal mixtures in an effort to keep their resistance up. However, do they know what their resistance comprises of? It is true that when an individual's resistance is low, one can become sick. But, what is "resistance" and how does it work?

Resistance is well- known as immunity. The immune system is the body's defense mechanism against illness. The immune system includes the organs, tissues, cells and molecules responsible for immunity. The immune response is the collective and coordinated response to the introduction of foreign substances. The system enables the body to know the

difference between self, and non-self. The body sees any illness or outside nuisance such as pollen, as a foreign substance. The body does not like foreign substances because they result in illness, pain, and other physically negative phenomena. That is why the body is set up to battle against what it perceives as an invader.

There are two types of immunity. The first is innate (natural or native or nonspecific) which refers to the basic resistance to disease that an individual is born with. The second one is the specific or acquired or adaptive immunity which requires the activity of a functional immune system involving cells called lymphocytes, phagocytes and their products.

Innate defense mechanisms provide the first line of host defense against invading pathogens until an acquired immune response develops. They are present in all individuals and are effective at birth and function without requiring prior exposure to a microorganism or its antigens. Innate immunity, sometimes referred to as natural immunity, is present from birth, is nonspecific and includes numerous elements. These elements include body surfaces or barriers and internal components. Body surfaces, such as the skin, mucous membranes and the cough reflex, provide effective barriers to many microorganisms. Chemical influences, such as an acid pH and secretion of fatty acids and enzymes, also serve as barriers against invasion by foreign substances.

Acquired or adaptive or specific immunity reflects the presence of a functional immune system that is capable of specifically recognizing and selectively eliminating foreign microorganisms. It is not effective fully at birth and requires time to develop after exposure to the infecting agent or its antigens. Specific immunity may be acquired naturally by infection or artificially by immunization.

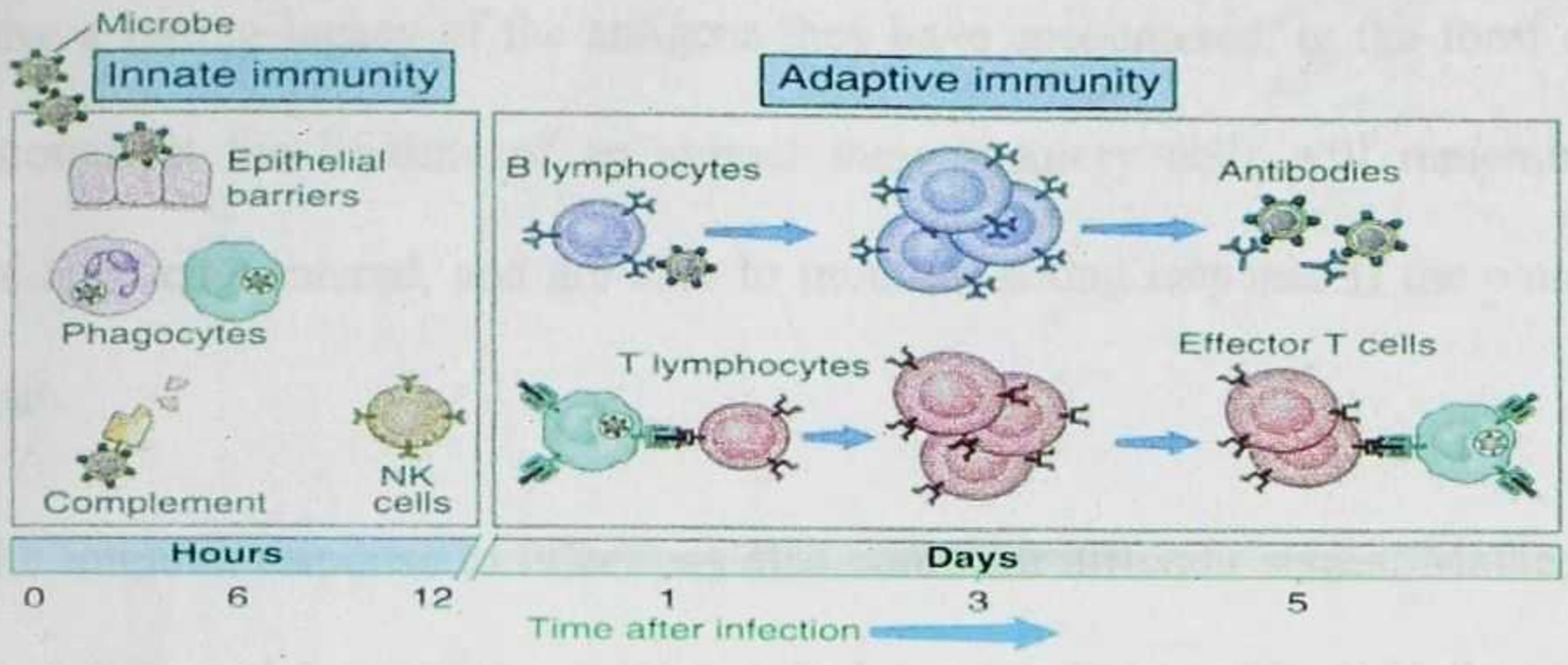


Figure 1.1 illustrates the various components of innate and acquired immunity.

Human immune system is a very complex and dynamic system that involves many different types of cells and immunological pathways. These cells are called lymphocytes which are T cells, B cells and natural killer cells. Natural killer (NK) cells are a part of innate and play a major role in defending the host from both tumors, virally infected cells and other pathogens. NK cells distinguish infected cells and tumors from normal and uninfected cells by recognizing level changes of a surface molecule called MHC (major histocompatibility complex)class I. NK cells are activated in response to a family of cytokines called interferon. Activated NK cells release cytotoxic (cell-killing) granules which then destroy the altered cells.

T cells (Thymus cells) and B cells (bone cells) are the major cellular components of the adaptive immune response. T cells are involved in cell-mediated immunity whereas B cells are primarily responsible for humoral immunity (relating to antibodies). The function of T cells and B cells is to recognize specific "non-self" antigens, during a process known as antigen presentation. Once they have identified an invader, the cells generate specific responses that are tailored to maximally eliminate specific pathogens or pathogen infected cells. B cells respond to pathogens by producing large quantities of antibodies which then neutralize foreign objects like bacteria and viruses. Following activation, B cells and T cells

leave a lasting legacy of the antigens they have encountered, in the form of memory cells. Throughout the lifetime of an animal these memory cells will remember each specific pathogen encountered, and are able to mount a strong response if the pathogen is detected again.

The immune response to infections also comes in different stages. Mathematical modeling using differential equations and dynamical systems has been used in the studies of immune response to various infections, most notably that of the HIV and Measles. The question now is how does the human body develop immunity or immune response to these bacterial infectious diseases? The mathematical biologists (Anderson and May, 1992) proposed a mathematical model to explain this phenomenon.

An infection may be caused by a living organism called bacterium (plural: bacteria) these are a group of microscopic, single-celled prokaryotes—that is, organisms characterized by a lack of a nucleus or any other membrane-bound organelles.

According to Trudy Wassenaar (2009), bacterium is a completely self-contained and self-reproducing unit. When the time is right, a bacterium will split its Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) genetic material into two parts. Separate cell walls will build up around these two new bacteria, and this process will continue until thousands or millions of bacteria have formed. This is how strains of bacteria survive in almost every environment on Earth, including non-living surfaces like rocks or plastic. Although among the most primitive organisms, bacteria reflect many universal features of life, including that they are composed of cells, transmit genetic information via DNA, and need energy from the environment to exist, grow, and reproduce; even sexual reproduction has been exhibited in some species of bacteria. Bacteria are often viewed negatively, given this group's connection to diseases. As prokaryotes, all bacteria have a relatively simple cell structure lacking either a

cell nucleus or membrane-bound organelles such as mitochondria and chloroplasts. The DNA of prokaryotes floats freely inside the cell.

Bacteria are the most abundant of all organisms, they are present in both soil and water and as well as symbionts of other organisms. Many pathogens (disease-causing organisms) are bacteria. Most bacteria are minute, usually only 0.5-5.0μm in their longest dimension, although giant bacteria like *Thiomargarita namibiensis* and *Epulopiscium fishelsoni* may grow past 0.5 mm in size. Bacteria generally have cell walls, like plant and fungal cells, but with a very different composition (peptidoglycans). Many move around using flagella, which are different in structure from the flagella of other groups. Although unicellular, some bacteria form groupings of cells, such as clusters, filaments, or chains, their bodies may be spherical, rod-shaped, or spiral/curved shaped.

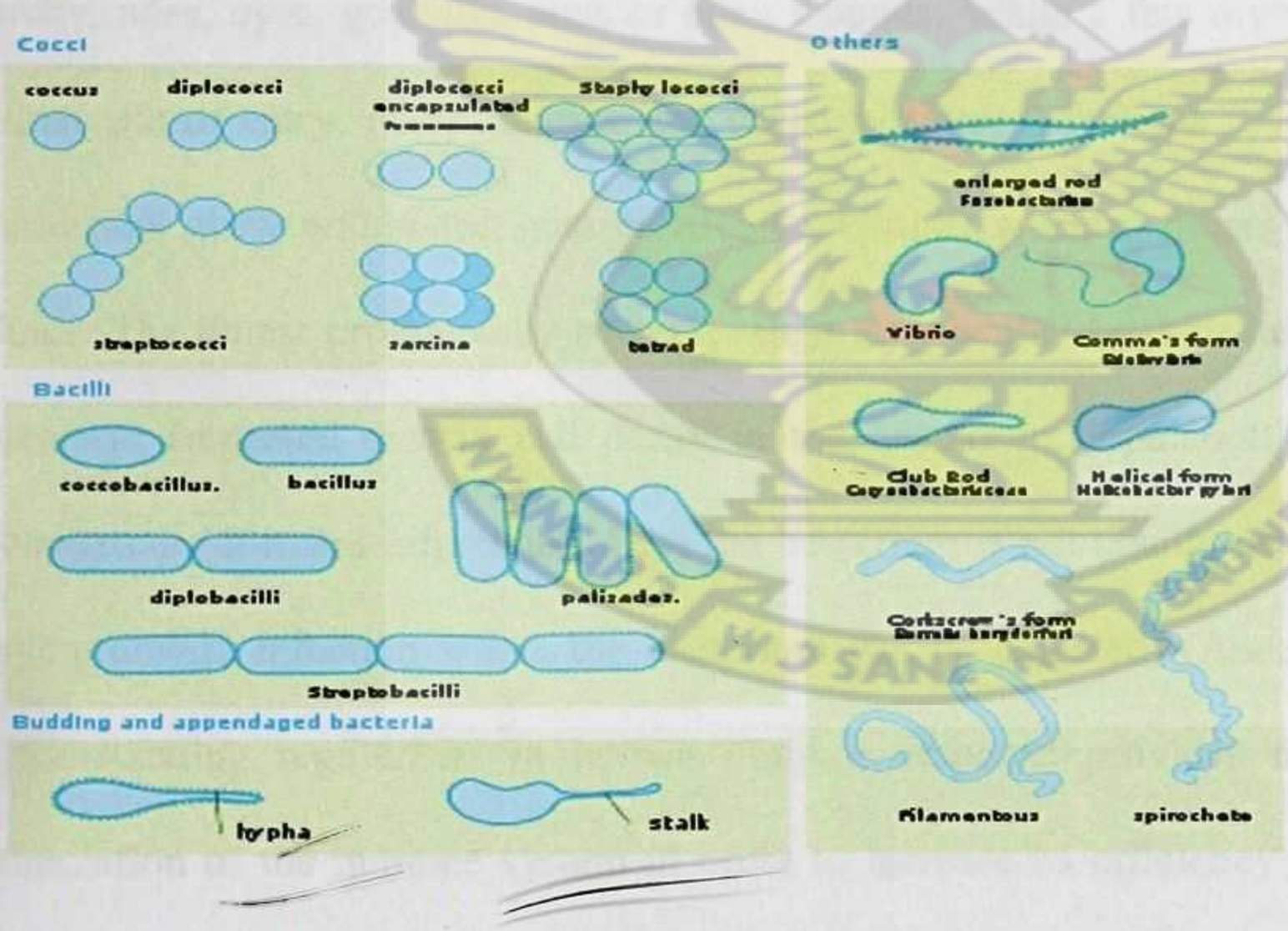


Figure 1.2 shows the various shapes of bacterial bodies.

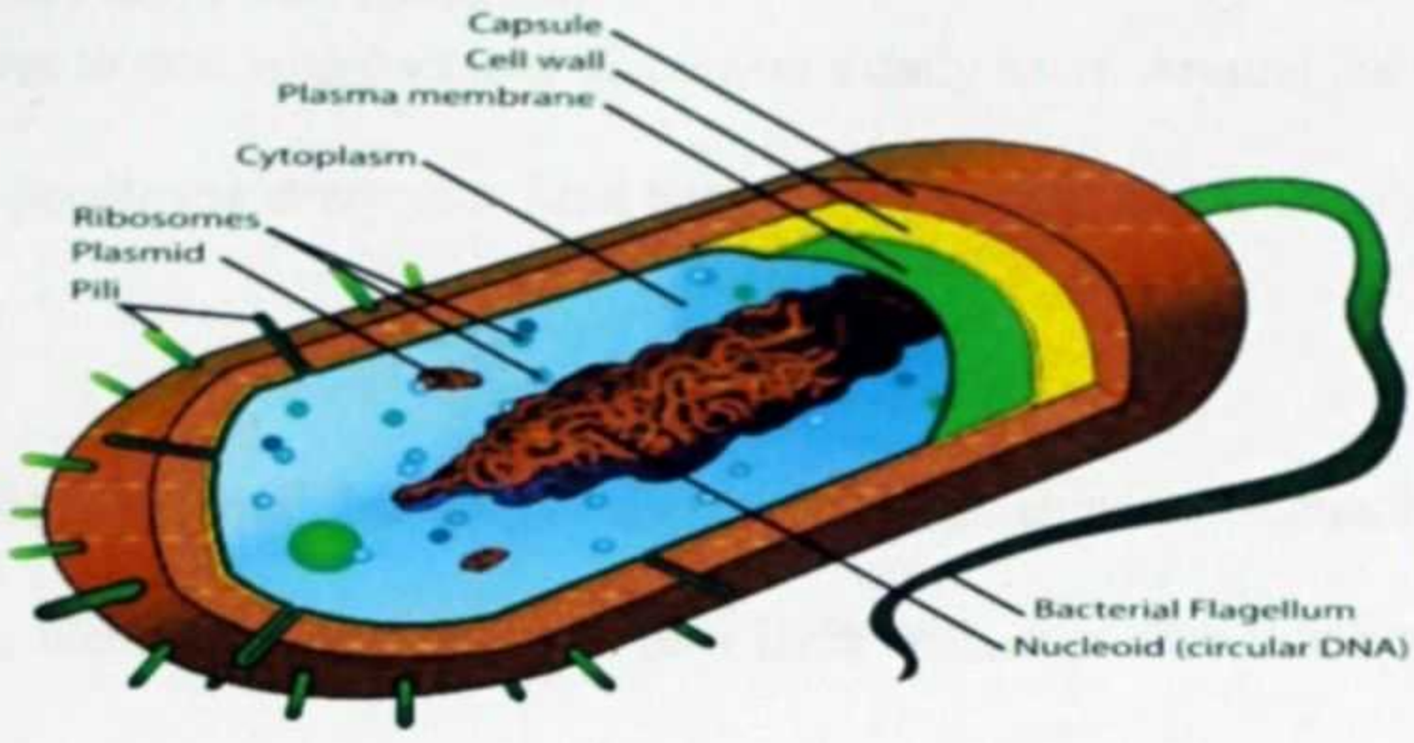


Figure 1.3 shows the parts of a bacterium cell.

A bacterial infection begins when bacterial successfully colonize by entering the body, grow and multiply. Individuals who have a suppressed immune system are particularly susceptible to infections. Entrance to the host generally occurs through the mucosa in orifices like oral cavity, nose, eyes, genitalia, anus or open wounds. While a few organisms can grow at the initial site of entry, many migrate and cause systemic infections in different organs. Some pathogens grow within the host cells (intracellular) whereas others grow freely in bodily fluids. The illness produced by bacteria range from acute (death or recovery from infection), recurrent (repeated growth and decay in the bacterium population within an individual), unapparent (dormant infectious where the bacterium is not readily detectable), or subclinical (symptomless infection where the bacterium can be detected) (Anderson and May, 1992). Understanding regularities in human immune response provides new powerful tool for stimulation of the immune system in order to increase its efficiency in the struggle against bacterial invasion. In view of this, the construction of models of human immune response to bacterial infection seems to be the only right tactics in the cognition of such regularities.

1.2 STATEMENT OF THE PROBLEM

Humans also have to deal with bacterial disease on a daily basis. Around the world, hundreds of thousands of people die every year from bacterial infections, which can invade the body in several ways.

Ghana Web (2011) reported that the last cholera outbreak alone in Ghana, between January and April 2011, claimed more than sixty (60) lives with over five thousand (5,000) cases reported across the country.

The combination of non-communicable with the already massive load of communicable diseases in a third world country like Ghana is heavy enough to impact negatively on national economic efforts, peace and productivity that are pertinent to its development.

According to Cambridge Institute of Medical Research (2010), infectious diseases remain a major cause of mortality and morbidity throughout the world and their occurrence often represents a failure of the immune system to effectively combat the infectious agent. Therefore we need to understand better how microbes interact with their host cells and cause disease and how these interactions often permit microbes to escape from immune control. Immunology itself also impinges on a wide range of other aspects of clinical and basic science and it underpins development of therapeutic approaches to non-infectious diseases, including autoimmune diseases.

1.3 OBJECTIVES OF THE STUDY.

The general objective of this study is to use differential equations model to predict human immune systems' response to bacterial infectious diseases.

The specific objectives are as follows:

I. To investigate the behavior of lymphocytes and phagocytes in the human body in the absence of the pathogenic bacteria.

II. To investigate the behavior of lymphocytes and phagocytes in the human body in the presence of the pathogenic bacteria.

III. To determine and analyze the stability characteristic of the mathematical model.

1.4 METHODOLOGY

Using the alarming rates of infectious diseases in developing countries over time, differential equations model is developed to predict human immune response to bacteria infectious diseases. Equilibrium points and their stability characteristics are analyzed for the set of system of differential equations. Numerical methods through computer Matlab programs are used to determine solutions and investigate their behavior.

1.5 SIGNIFICANCE OF THE STUDY

A good understanding of the dynamics of bacterial infections, modes in which diseases act is gained and an equally important understanding of how humans also respond to these diseases is gained will be helpful so that our natural countermeasures can be augmented with modern medicinal techniques.

All these facts support the need to research into infectious diseases. Even though, most researchers have done research in health related issues, they have not probed into the mechanisms underlying how the human body develops immunity against such infections. It is my hope that the outcome of this study will help to lessen this alarming rate of infectious diseases. The endings of this study will help policy makers and stakeholders in the country to design programs for the control of bacterial infectious diseases. The results and recommendations are likely to create the much needed awareness and attention among

citizens including health workers. The findings will also provide useful information to policy makers, stakeholders and especially educators who usually train greater percentage of the youth who are so vulnerable to such infectious diseases. This study can suggest new avenues for further research that will enhance techniques for effective control interventions.

1.6 THE SCOPE OF THE STUDY

The dynamics of bacterial infectious diseases and their immune response may be quite different. Thousands of types of bacteria are naturally present in our environment. Not all bacteria cause disease in humans. However, a few species of bacteria are pathogenic and cause infectious diseases, such as cholera, syphilis, anthrax, leprosy, and bubonic. The most common fatal bacterial diseases are respiratory infections, with tuberculosis alone killing about two million people yearly, mostly in sub-Saharan Africa.

Some bacteria are used beneficially for example in making cheese and yogurt. Consequently care should be taken when interpreting the results of this study.

1.7 ORGANIZATION OF THE STUDY

The study is organized in five chapters as follows. Chapter one provides general background issues of the study. It also provides the statement of problem and it sets out the objectives of the study, provides the significance of the study as well as the scope of the study.

Chapter two reviews pertinent literature related to the study including some models of epidemiology. Chapter three describes systems of differential equations that model the system. It also looks at the mathematical software (MATLAB) for solving the systems of these differential equations. Chapter three also considers the model, its development, and the

behaviour of phagocytes and lymphocytes. Chapter four discusses the methodology of the study, the empirical results and their interpretation. It also considers the analysis of equilibrium point and their stability characteristics. The final chapter, which is chapter five, summarizes the main findings of the study and provides suggestions and recommendation.

CHAPTER TWO

LITERATURE REVIEW

2.0 INTRODUCTION

Despite improved sanitation, antibiotics and extensive vaccination programs, infectious diseases continue to be major causes of suffering and mortality. This chapter shows the study in the perspective of other studies of mathematical epidemiology. The mathematical theory of infectious diseases initiated by Kermack- McKendrick, Ross, MacDonald, Anderson, May and others has played a vital role in the study of the control and prevention of infectious diseases. In this section, the literature review will be based on the history of infectious diseases; as well as discuss literature on compartmental models; the discussion will be centered on compartments without births and deaths as well as compartments including births and deaths. In addition, mathematical methods that is necessary to analyze and solve the mathematical models such as ordinary differential equations and finally literature on human immune response to bacterial infectious diseases will be discussed. These will lead to a better understanding of the material presented in this thesis.

2.1 HISTORY OF BACTERIAL INFECTIOUS DISEASE

According to Encyclopedia Britannica (2011), there are two basic types of disease: ones that are infectious, or extrinsic, meaning that they are contagious or communicable and can be spread by contact between people, and ones that are intrinsic, or not infectious. Diseases in general and non-infectious diseases in particular are discussed in essays devoted to those subjects. So, too, is infection itself, a subject separate from infectious diseases: a person can get an infection, such as tetanus or salmonella, without necessarily having a disease that can be passed on through contact with others in the same way that colds, malaria, or syphilis is spread.

Bacteria existed long before humans evolved, it is believed that bacteria have been present on earth for 3.5 billion years, and bacterial diseases probably co-evolved with each species which involuntarily hosts them. Many bacterial diseases that we see today have been around for as long as we have, others may have developed later. In either case, for the longest time we were not aware of the cause of infectious diseases. With the beginning of microbiology, bacterial pathogens became apparent.

According to Dr. Alvin Fox, (2012) bacteria are infectious agents that attack the body and break down the immune system. They thrive as large groups of microorganisms that are unicellular in nature, spreading life-threatening diseases such as tetanus, anthrax, cholera, leprosy, buruli ulcer and the bubonic plague etc. Bacteria are very tiny organisms that are typically present in almost every habitat on the planet. Even though they measure just a few micrometers, they prove life-threatening when they infect the respiratory system and deteriorate digestive health. They are omnipresent to soil, radioactive waste, water, biomass and even organic matter. Bacteria inhabit the bodies of life forms, like plants and animals. They are much more in number than the human cells in the human body, and thrive on the skin and within the digestive tract. Bacteria play a very vital role in recycling nutrients. While majority of bacteria in the human body are countered by the immune system, there are a few that are pathogenic in nature. They are also responsible for the spread of respiratory infections like tuberculosis. When certain pathogens enter the food supply, they can cause food-borne illness. Only a few types cause millions of cases of food-borne illness each year. Ironically, most cases of food-borne illness can be prevented. Proper cooking or processing of food destroys bacteria. They can grow in just about any food, but are fond of protein foods, such as meat, poultry, seafood, eggs, and dairy products in particular, as well as high-protein vegetables such as beans and grains.

According to Wassener, T. M, (2009) bacteria are large collections of miniscule unicellular living organisms less than 1 percent of which are harmful to health. These harmful bacteria divide and reproduce rapidly to cause infection and disease. Some even release toxins that injure body tissue. And yet some bacteria are beneficial to health. Surprisingly, bacterial cells outnumber human cells in the body by a ratio of 10:1. Bacteria are concentrated largely in the gastrointestinal tract and on the skin. The human immune system is able to handle most bacteria. The most common types of bacterial infection are in the respiratory tract and account for over two million deaths per annum.

According to Wikipedia (2011), infectious diseases are responsible for one in two deaths in developing countries, where poverty, limited access to health care, drug resistance and a changing environment make populations particularly vulnerable. While bacteria are essential to life on earth, there are some forms of bacteria that wreak havoc on the human body and often lead to disfigurement and death. Many of these diseases have an interesting history, often the cause of wide-spread panic and quarantine until the disease was understood and/or curable.

2.1.1 SOME COMMON BACTERIAL INFECTIOUS DISEASES

According to Encyclopedia Britannica (2011), some bacterial infectious diseases with no specific order include the following:

Tuberculosis is caused by the Koch bacterium (Mycobacterium tuberculosis). It is as old as the humankind is. TBC was found even in mummies coming from the ancient Egypt and Peru. Two million people die annually of tuberculosis and about one hundred and fifty million people are estimated to have died of TBC since 1914. One third of the people carry the Koch bacterium, which spreads through the air and milk from infested cows and affects all the body, especially the lungs. It induces prolonged coughing, fever, shivering, bloody

expectoration, weight loss, sweating, tiredness, and glossy eyes. It infects one third of the world population and each year another new eight million cases appear. Each second a person dies of tuberculosis. It is more aggressive in women and persons between 15 and 45 years old. Mutant strains are resistant to almost all drugs and kill about 50 % of the patients. It is spread worldwide, but its advance is rampant in Bangladesh, China, Indonesia, Philippines, India and Pakistan, with over half of the new cases. TBC has a treatment, but it cannot be eradicated because of the emergence of multi resistant strains and the long and costly treatment, of over 6 months, is often interrupted sooner than it should. The treatment also includes resting, clean air, proper diet, besides medication. 3-5 % of the new cases are co infected with HIV. The vaccine is effective in children, but useless in adults. Current employed drugs are isoniazid, ethambutol and Rifapentin. The BCG decreases the risk of infection, and the pasteurization of the milk, too.

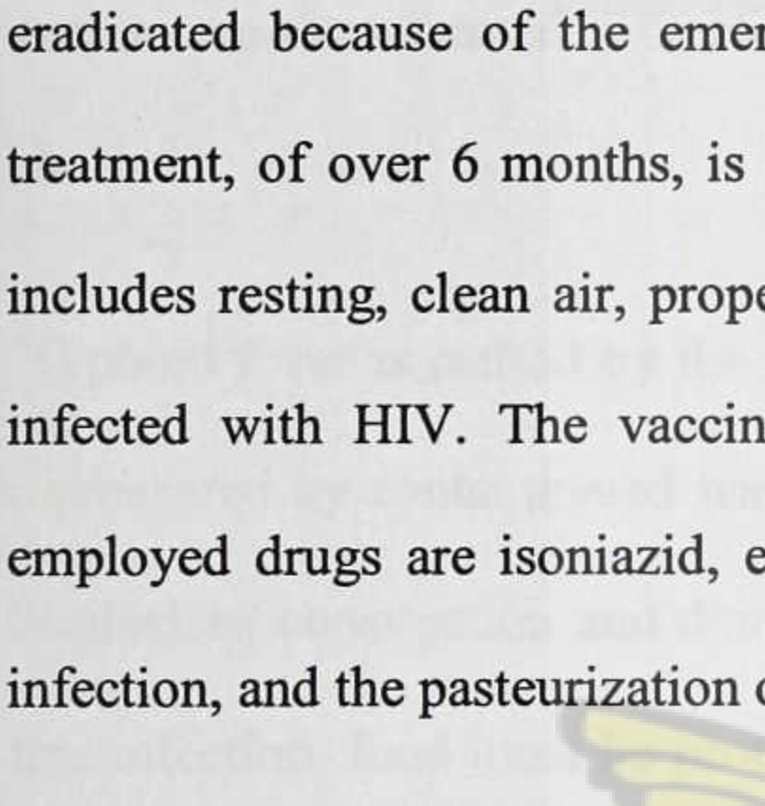


Figure 2.2 shows Chest X-ray of a person with advanced tuberculosis

Cholera is an infection of the small intestine caused by the bacterium Vibrio cholerae. The main symptoms are profuse, watery diarrhea and vomiting. Transmission occurs primarily by drinking water or eating food that has been contaminated by the feces of an infected person, including one with no apparent symptoms. The severity of the diarrhea and vomiting can lead to rapid dehydration and electrolyte imbalance, and death in some cases. The primary

treatment is oral rehydration therapy, typically with oral rehydration solution (ORS), to replace water and electrolytes. If this is not tolerated or does not provide improvement fast enough, intravenous fluids can also be used. Antibacterial drugs are beneficial in those with severe disease to shorten its duration and severity. Worldwide, it affects 3–5 million people and causes 100,000–130,000 deaths a year as of 2010. Cholera was one of the earliest infections to be studied by epidemiological methods. The incubation lasts 1-7 days. The vaccine confers limited protection, that's why hygiene is the main method of controlling cholera.

Typhoid fever is caused by the bacterium Salmonella enterica. The sources of infection are represented by contaminated water and food. The incubation lasts 7 to 14 days, then fever, headaches, constipation and diarrhea install. The treatment consists of antibiotics. To avoid this infection, food must be processed and manipulated in hygienic conditions. The vaccine confers limited immunity. This disease usually accompanies wars. A huge typhus pandemic broke out during the First World War in the Eastern Europe. Since 1914, over twenty million people died of typhus.

Plague is caused by Yersinia pestis. The black plague broke out in Europe in 1347, when a boat coming from Crimea docked at Mesina, Sicily. Besides its load, the ship transported the pest, which soon spread throughout Italy. It was like the end of the days for Europe. In four years, this bacterium killed approximately thirty million Europeans, about one third of the continent's population. Even the remote Iceland was struck. In the Extreme East, China dwindled from one hundred and twenty-three million inhabitants at the beginning of the 13th century to just sixty-five million during the 14th century, because of the pest and hunger. The pest bacterium is transmitted by fleas and, usually, the infection jumps from rats to humans. The incubation lasts 2 to 10 days. The disease causes fever, swelling of the lymphatic

ganglions and skin. Today, antibiotics can treat plague. The vaccine confers limited immunity. This catastrophe has no match in the human history. 25 to 50 % of the inhabitants of Europe, North Africa and certain Asian areas died back then. Knowing the cause of the pandemic helped: in 1907, an outbreak of bubonic plague in San Francisco produced just several victims, as the authorities started a massive campaign for exterminating the rats, while in 1896 an outbreak in India caused ten million deaths in 12 years, as the cause was not known.

Syphilis, caused by the bacterium Treponema pallida, is the most severe sexually transmitted bacterial infection. The first stage has an incubation of 3-12 weeks and it induces ulcered lesions (syphilis chancre) at the entrance of body's aperture organ. After that, it triggers skin eruptions, fever, hair loss, less severe hepatitis and genital condilloma, but if untreated, the lesions extend in several years to the nervous system, leading to death. The treatment consists in extremely powerful antibiotics (ceftriaxone, Cefixime, and others) which are also extremely costly. Antibiotics are most effective in the first stages. People must avoid having sex with probable carriers of the infection; it requires immediate treatment, ceasing sexual contacts until the end of the treatment and informing of the recent sexual contacts, for medical control and treatment.

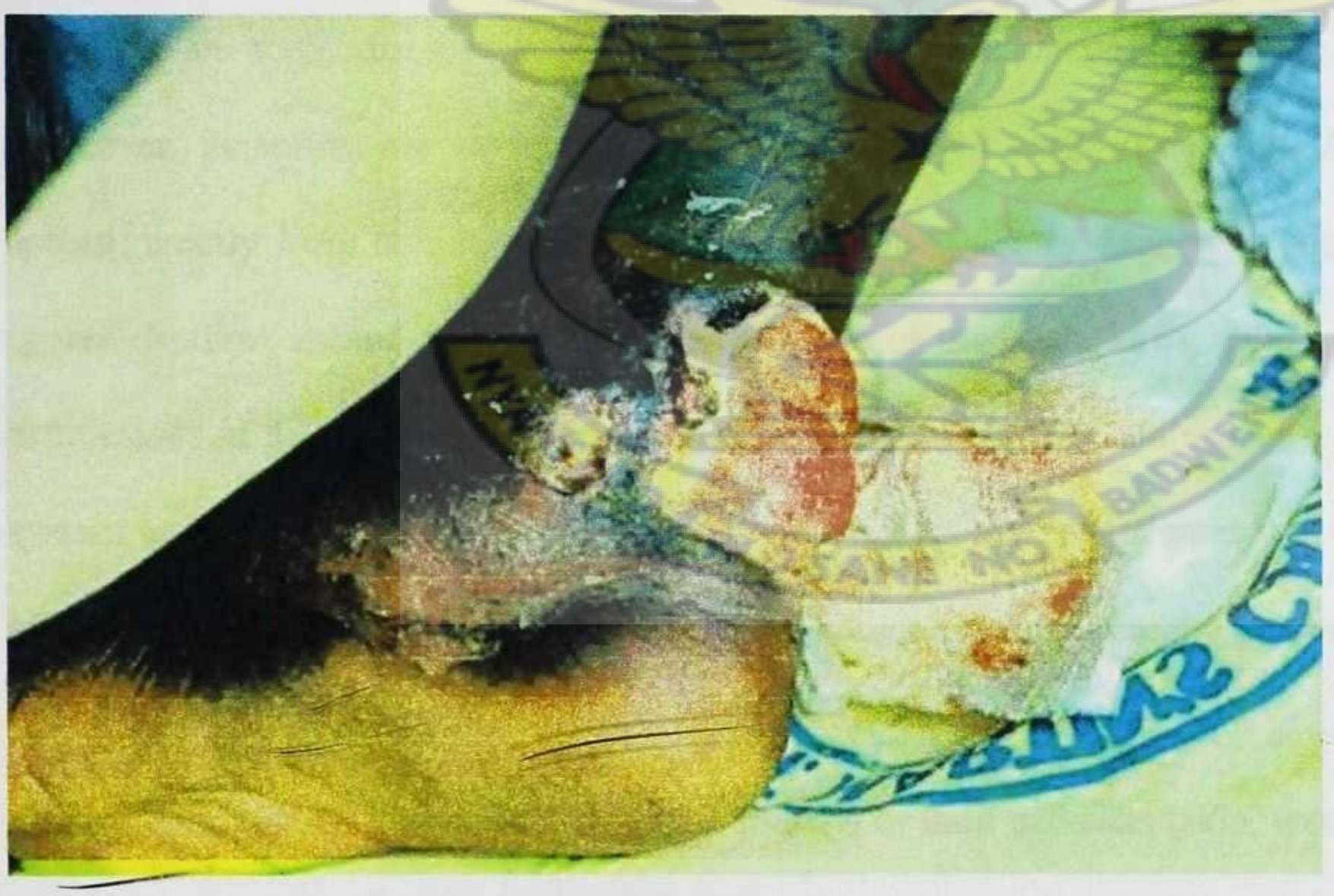
Gonorrhea is triggered by the Neisseria bacteria and it is transmitted sexually. Sixty-two million people, aged mainly 15 to 29, are affected worldwide, especially in urban areas and of low socioeconomic level. The incubation lasts 3 days, and in men, gonorrhea produces urinary incontinence, urethra pain, reddening, penis burning sensation and testicle inflammation. In women, it induces severe pain that reaches the trumps and uterus. The treatment uses antibiotics and prevention is similar to syphilis.

Clostridium tetani, the bacterium causing tetanus, can exist almost anywhere while their spores can remain inactive in soil. When a wound introduces the spores into the deep recesses of the body, the bacteria become active, producing toxins which affect the nerves. The muscles of the body contract sporadically, injuring muscles and bones and causing locking of the jaw. Left untreated, tetanus can cause a mortality rate of about 25 percent in adults, according to the National Institutes of Health. A tetanus vaccine administered to the general population provides protection from the bacteria for approximately 10 years. Physicians may treat a patient diagnosed with tetanus, or lockjaw, with antibiotics, muscle relaxants, antitoxin and surgery, which removes bacteria remaining in the wound.

Legionnaire's disease is caused by Legionella bacteria. The bacteria are taken from air or wet environments. It causes symptoms similar to flue or pneumonia, accompanied by renal failure. The disease requires hospitalization and treatment with antibiotics. As a prevention measure, water and air conditioning installation must be controlled.

Pneumonia affects 1% of the planet's population and can be produced by bacteria (like Aeromonas hydrophilic) or viruses. It produces fever, shiver, sweating, and coughs with expectoration, muscle, head and thoracic pain, appetite loss, weakness. This is the main cause of mortality in the world; it kills 3.5 million people each year. It attacks especially patients with severe immune depression, those who follow chemotherapy, people who are older than 75, asthmatics, smokers, alcoholics, those with renal insufficiency and children under 2 years of age. It affects especially the poor countries. Antibiotics work in the case of the bacteria. Therapy includes oxygen, liquids, and physiotherapy. Patients with a simple pneumonia can cure in 2-3 weeks, but elders or those with debilitating diseases can die of respiratory or cardiorespiratory failure. The vaccine trimetropin sulfamethoxazole is effective against the most frequent complications.

To Wikipedia (2011), Buruli ulcer is a disease caused by infection with Mycobacterium ulcerans, is one of the most neglected but treatable tropical diseases. The causative organism is from the family of bacteria which causes tuberculosis and leprosy but Buruli ulcer has received less attention than these diseases. Infection leads to extensive destruction of skin and soft tissue with the formation of large ulcers usually on the legs or arms. Buruli ulcer often starts as a painless, mobile swelling in the skin called a nodule. The disease can present as a large area of induration or a diffuse swelling of the legs and arms. Strains of Mycobacterium ulcerans isolated from the different clinical forms of the disease in a particular geographical region appear identical, suggesting that host factors may play an important role in determining the different clinical presentations. Patients who are not treated early often suffer long-term functional disability such as restriction of joint movement as well as the obvious cosmetic problem. Early diagnosis and treatment are vital in preventing such disabilities.



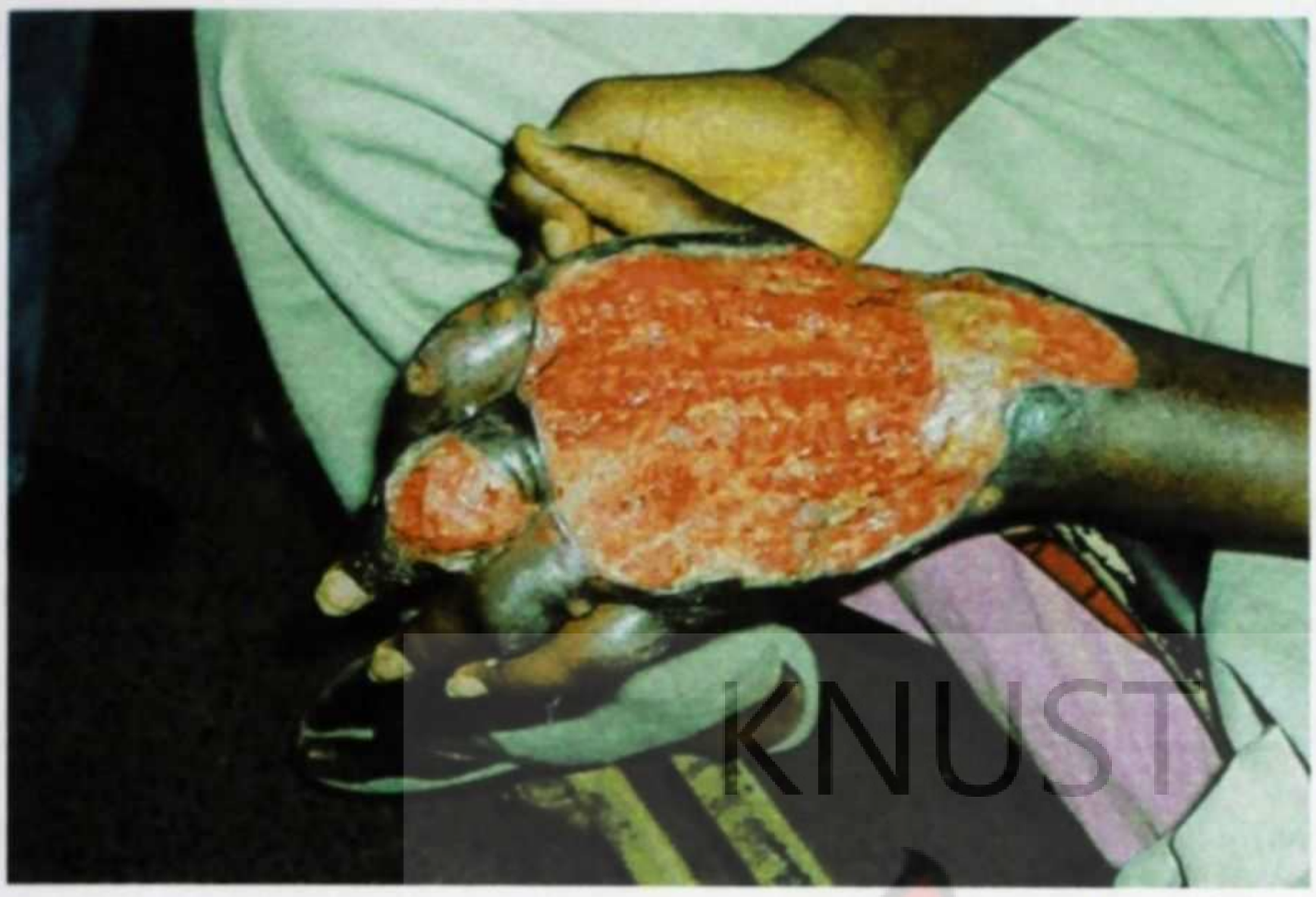


Figure 2.3 shows pictures of a Buruli ulcer patient

Anthrax (Bacillus anthracis) is the most famous bacterium fluttered in the bioterrorism war. It causes an acute disease in humans and animals, and some strains are highly lethal. Moreover, its spores are extremely long-lived, up to 70 years in the soil. Anthrax cannot spread directly from human to human; but corpses are a very dangerous source of anthrax spores. Anthrax means coal in Greek, a reference to the bacterium's ability to cause black skin lesions in its victims. Anthrax is as old as tuberculosis. The anthrax attacks the immune system and releases toxins in the blood stream, which destroys tissues and cause massive inner bleeding, and death. If the antibiotics are administered too late, no matter if the bacteria die, the toxins may kill the person.

The bacterium can be taken from infected animals or their products (skin, wool and meat). It can enter the human body through the intestines (ingestion), lungs (inhalation), or skin (cutaneous).The treatment for anthrax infection and other bacterial infections includes large doses of intravenous and oral antibiotics, such as fluoroquinolones, like ciprofloxacin (cipro),

doxycycline, erythromycin, vancomycin or penicillin. Delays of only a few days may make the disease untreatable.

2.1.2 STAGES OF BACTERIA INFECTION

To Todar ,K (2009), different bacteria worked in different ways. But the reaction of all bacteria is to become intimate with the human cells in the body.

The start of the disease is when the bacterial organisms become aggressive, multiply, grow and begin to attack the human cells.

The second stage is where bacteria secrete damaging toxins into the body where they begin to attach themselves to the cells and send out a signal that triggers a marked alteration in the shape and behavior of the phagocyte cells. For instance common intestinal bacteria like Escherichia coli which causes diarrhea encourages the host cell to shed its filaments called microvilli.

The third stage is to lure the cell to provide a location for the bacteria cells from where it can attack the natural defenses of the phagocyte cells.

The final stage is when bacteria not only come in contact with human cells by pierce and enter them. They trick the cell into allowing them access; the bacteria are equivalent to a Trojan horse.

2.1.3 The Bacterial Growth Curve

According to Todar, K. (2012), under favorable conditions, a growing bacterial population doubles at regular intervals. Growth is by geometric progression: 1, 2, 4, 8, etc. or 2^0, 2^1, 2^2, 2^3.....2^n (where n = the number of generations). This is called exponential growth. In

reality, exponential growth is only part of the bacterial life cycle, and not representative of the normal pattern of growth of bacteria in Nature.

When a fresh medium is inoculated with a given number of cells, and the population growth is monitored over a period of time, plotting the data will yield a typical bacterial growth curve.

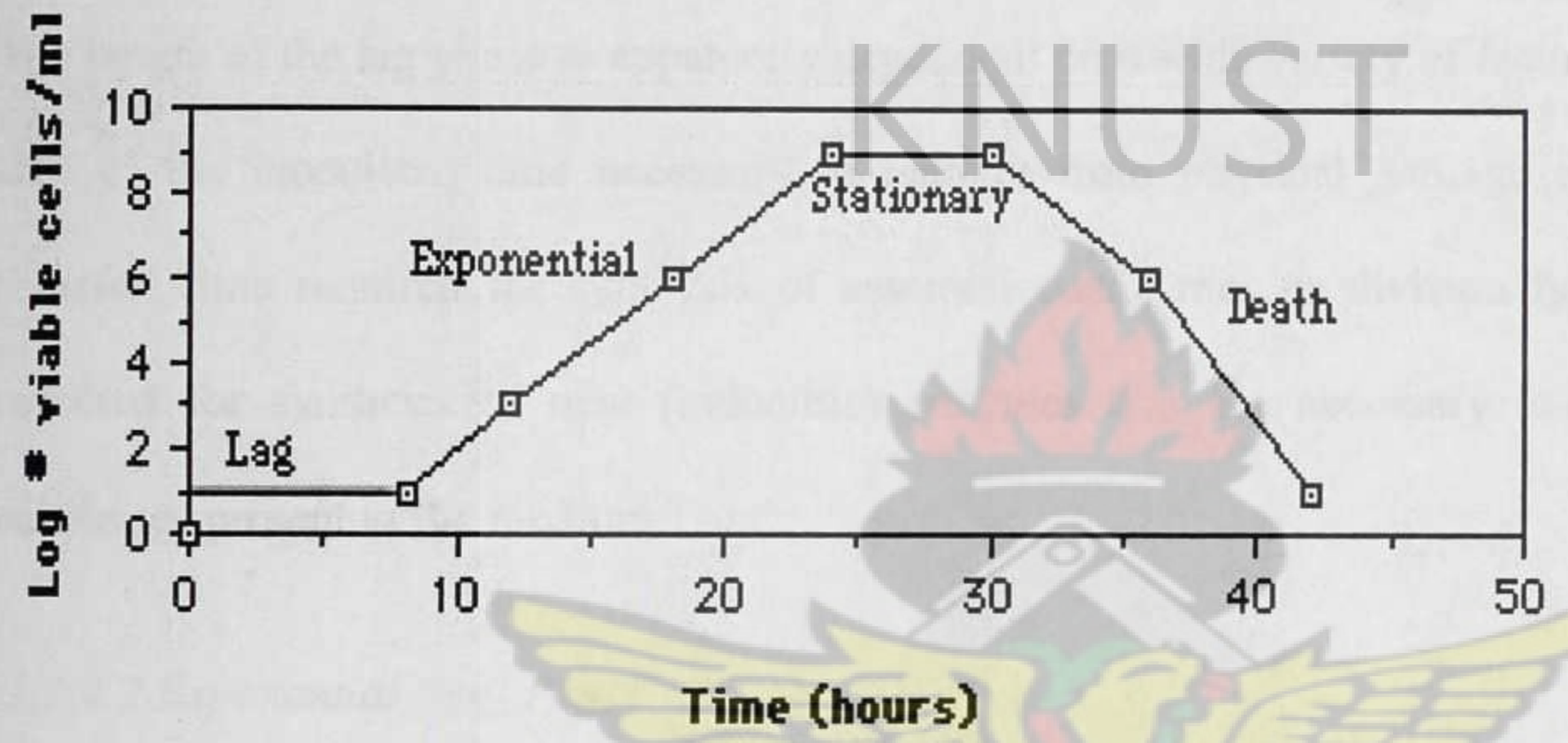


Figure 2.1 illustrates a typical bacterial growth curve.

When bacteria are grown in a closed system (also called a batch culture), like a test tube, the population of cells almost always exhibits these growth dynamics: cells initially adjust to the new medium (lag phase) until they can start dividing regularly by the process of binary fission (exponential phase). When their growth becomes limited, the cells stop dividing (stationary phase), until eventually they show loss of viability (death phase). Note the parameters of the x and y axes. Growth is expressed as change in the number of viable cells verses time. Generation times are calculated during the exponential phase of growth. Time measurements are in hours for bacteria with short generation times.

2.1.4 CHARACTERISTIC OF BACTERIAL GROWTH CYCLE

2.1.4.1 Lag Phase.

Immediately after inoculation of the cells into fresh medium, the population remains temporarily unchanged. Although there is no apparent cell division occurring, the cells may be growing in volume or mass, synthesizing enzymes, proteins, RNA, etc., and increasing in metabolic activity.

The length of the lag phase is apparently dependent on a wide variety of factors including the size of the inoculum; time necessary to recover from physical damage or shock in the transfer; time required for synthesis of essential coenzymes or division factors; and time required for synthesis of new (inducible) enzymes that are necessary to metabolize the substrates present in the medium.

2.1.4.2 Exponential (log) Phase.

The exponential phase of growth is a pattern of balanced growth wherein all the cells are dividing regularly by binary fission, and are growing by geometric progression. The cells divide at a constant rate depending upon the composition of the growth medium and the conditions of incubation. The rate of exponential growth of a bacterial culture is expressed as generation time, also the doubling time of the bacterial population. Generation time (G) is defined as the time (t) per generation (n = number of generations). Hence, G=t/n is the equation from which calculations of generation time (below) derive.

2.1.4.3 Stationary Phase.

Exponential growth cannot be continued forever in a batch culture (e.g. a closed system such as a test tube or flask). Population growth is limited by one of these factors: exhaustion of available nutrients; accumulation of inhibitory metabolites or end products; and exhaustion of space, in this case called a lack of "biological space".

During the stationary phase, if viable cells are being counted, it cannot be determined whether some cells are dying and an equal number of cells are dividing, or the population of cells has simply stopped growing and dividing. The stationary phase, like the lag phase, is not necessarily a period of quiescence. Bacteria that produce secondary metabolites, such as antibiotics, do so during the stationary phase of the growth cycle (Secondary metabolites are defined as metabolites produced after the active stage of growth). It is during the stationary phase that spore-forming bacteria have to induce or unmask the activity of dozens of genes that may be involved in sporulation process.

2.1.4.4 Death Phase.

If incubation continues after the population reaches stationary phase, a death phase follows, in which the viable cell population declines. (Note, if counting by turbid metric measurements or microscopic counts, the death phase cannot be observed.). During the death phase, the number of viable cells decreases geometrically (exponentially), essentially the reverse of growth during the log phase.

2.2 ANTIBIOTICS

According to Bauman, R. (2005) and Park Talaro, K. (2008) bacterial infections are generally treated with antibiotics. These are of two types of antibiotics namely bacteriocidal and bacteriostatic. The former kill's bacteria while the latter simply inhibits their growth. Antibiotics are among the most frequently prescribed medications in modern medicine. Antibiotics cure disease by killing or injuring bacteria. The first antibiotic was penicillin, discovered accidentally from a mold culture. Today, over 100 different antibiotics are available to cure minor, as well as life-threatening infections.

Although antibiotics are useful in a wide variety of infections, it is important to realize that antibiotics only treat bacterial infections. Antibiotics are useless against viral infections (for example, the common cold) and fungal infections (such as ringworm). Your doctor can best determine if an antibiotic is right for your condition.

2.2.1 TYPES OF ANTIBIOTICS

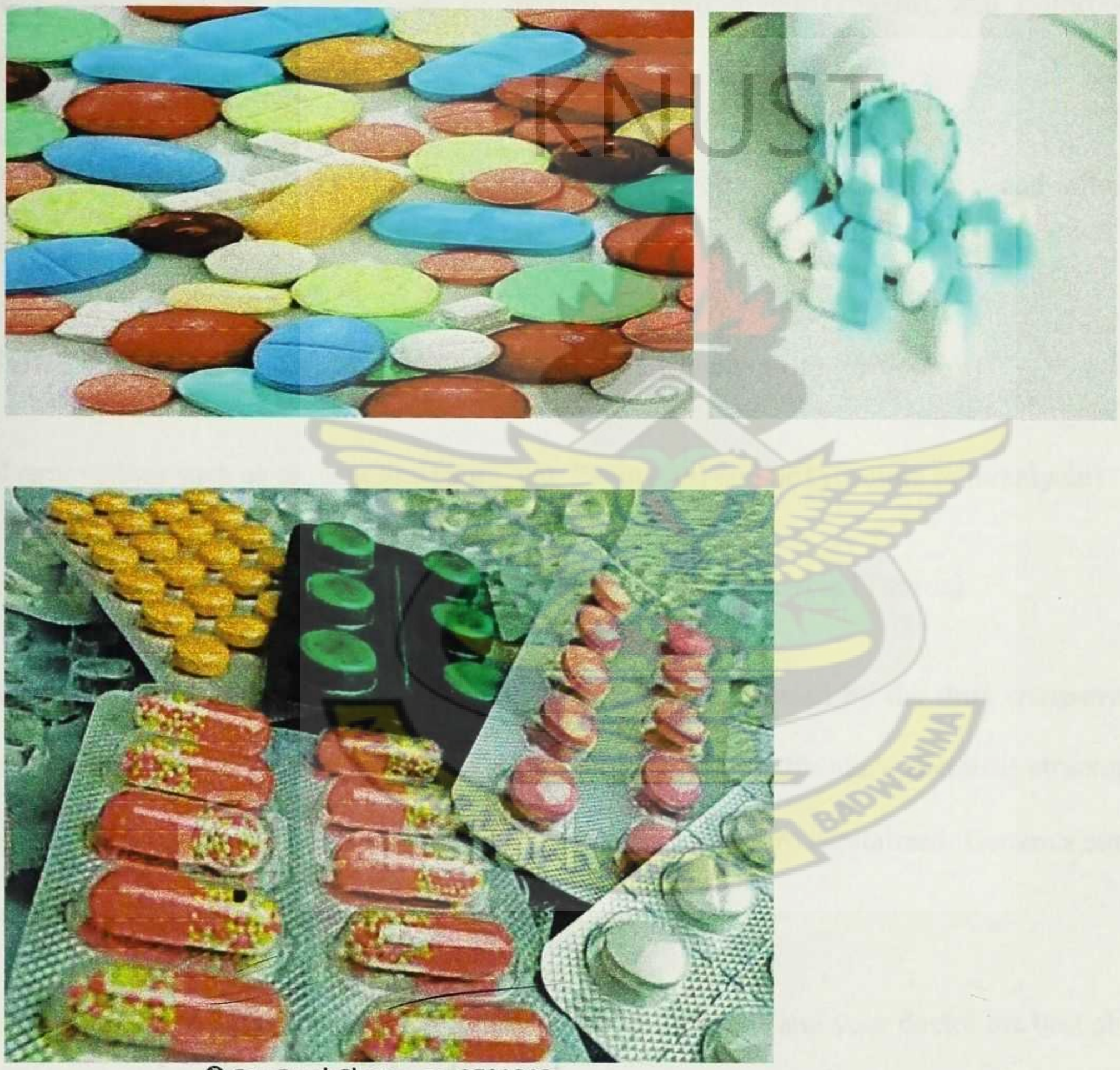


Figure 2.4 illustrates examples of antibiotics.

To Adams, D. et al (1970) although there are well over 100 antibiotics, the majority come from only a few types of drugs. These are the main classes of antibiotics.

Penicillins such as penicillin and amoxicillin

Cephalosporin such as cephalexin (Keflex)

Macrolides such as erythromycin (E-Mycin), clarithromycin (Biaxin), and azithromycin (Zithromax)

Fluoroquinolones such as ciprofloxacin (Cipro), levofloxacin (Levaquin), and ofloxacin (Floxin)

Sulfonamides such as co-trimoxazole (Bactrim) and trimethoprim (Proloprim)

Tetracyclines such as tetracycline (Sumycin, Panmycin) and doxycycline (Vibramycin)

Aminoglycosides such as gentamicin (Garamycin) and tobramycin (Tobrex)

Most antibiotics have 2 names, the trade or brand name, created by the drug company that manufactures the drug, and a generic name, based on the antibiotic's chemical structure or chemical class. Trade names such as Keflex and Zithromax are capitalized. Generics such as cephalexin and azithromycin are not capitalized.

Each antibiotic is effective only for certain types of infections and your doctor are best able to compare your needs with the available medicines. Also, a person may have allergies that eliminate a class of antibiotic from consideration, such as a penicillin allergy preventing your doctor from prescribing amoxicillin.

In most cases of antibiotic use, a doctor must choose an antibiotic based on the most likely cause of the infection. For example, if you have an earache, the doctor knows what kinds of bacteria cause most ear infections. He or she will choose the antibiotic that best combats those kinds of bacteria. In another example, a few bacteria cause about 90% of pneumonias in previously healthy people. If you are diagnosed with pneumonia, the doctor will choose an antibiotic that will kill these bacteria.

Other factors may be considered when choosing an antibiotic. Medication cost, dosing schedule, and common side effects are often taken into account. Patterns of infection in your community may be considered also.

In some cases, laboratory tests may be used to help a doctor make an antibiotic choice. Special strains of the bacteria such as Gram stains can be used to identify bacteria under the microscope and may help narrow down which species of bacteria is causing infection. Certain bacterial species will take a stain, and others will not. Cultures may also be obtained. In this technique, a bacterial sample from your infection is allowed to grow in a laboratory. The way bacteria grow or what they look like when they grow can help to identify the bacterial species. Cultures may also be tested to determine antibiotic sensitivities. A sensitivity list is the roster of antibiotics that kill a particular bacterial type. This list can be used to double check that you are taking the right antibiotic. Only your doctor can choose the best class and the best antibiotic from that class for your individual needs.

2.3 COMPARTMENTAL MODEL

According to Wikipedia (2011), compartmental model is one for which the individuals in a population are classified into compartment (partitioned) depending on their status with

regards to the infection under study. In view of this to model the progress of an epidemic in a large population, comprising many different individuals in various fields, the population diversity must be reduced to a few key characteristics which are relevant to the infection under consideration. For example, for most common childhood diseases that convene long-lasting immunity it is important to divide the population into those who are susceptible to the disease, those who are infected and those who have recovered and are immune. These partitions of the population are called compartments. Communicable diseases such as cholera, tuberculosis, influenza or measles are a fact of modern life. The transmission of infections is now known for most diseases. Usually , diseases transferred by viral agents, such as influenza, measles, rubella (German measles), and chicken pox, convene immunity against reinfection, while diseases transferred by bacteria, such as tuberculosis, meningitis, and gonorrhea, convene no immunity against reinfection. In view of this, it is important to educate the general public on the need to prevent bacterial infections since prevention is better than cure. Other diseases, such as malaria, are transferred not directly from human to human but by vectors, which are agents (generally insects) who are infected by humans and who then transfer the disease to humans. For sexually transmitted diseases with heterosexual transmissions each sex acts as a vector and disease is transmitted back and forth between the sexes. The researcher's concern will be with both epidemics which are unexpected outbreaks of a disease, and endemic situations, in which a disease is always present.

2.3.1 KERMACK-MCKENDRICK MODEL

According to Weisstein, E.R (2011), Kermack-McKendrick model is an SIR model for the number of people infected with a contagious illness in a closed population over time. It was proposed to explain the rapid rise and fall in the number of infected patients observed in

epidemics such as the plague (London 1665-1666, Bombay 1906) and cholera (London 1865). It assumes that the population size is fixed (i.e., no births, deaths due to disease, or deaths by natural causes), incubation period of the infectious agent is instantaneous, and duration of infectivity is same as length of the disease. It also assumes a completely homogeneous population with no age, spatial, or social structure. The model consists of a system of three coupled nonlinear ordinary differential equations, where S, I and R represent susceptible, infected and recovery respectively.

$$\frac{dS}{dT} = -\beta SI \qquad 2.01$$

$$\frac{dI}{dT} = \beta SI - \gamma I \qquad 2.02$$

$$\frac{dR}{dT} = \gamma I \qquad 2.03$$

where, t is time, S(t) is the number of susceptible people, I(t) is the number of people infected, R(t) is the number of people who have recovered and developed immunity to the infection, beta is the infection rate, and gamma is the recovery rate. The key value governing the time evolution of these equations is the so-called epidemiological threshold,

$$R_0 = \frac{\beta S}{\gamma} \qquad 2.04$$

The Kermack-McKendrick model was brought back to prominence after decades of neglect by Anderson and May (1979). More complicated versions of the Kermack-McKendrick model that better reflect the actual biology of a given disease are often used. Several assumptions were made in the formulation of these equations: First, an individual in the population must be considered as having an equal probability as every other individual of

contracting the disease with a rate of β, which is considered the contact or infection rate of the disease. Therefore, an infected individual makes contact and is able to transmit the disease with βN others per unit time and the fraction of contacts by an infected with a susceptible is S / N. The number of new infections in unit time per infective then is $\beta N(S / N)$, giving the rate of new infections (or those leaving the susceptible category) as $\beta N(S / N)I = \beta SI$ (Brauer & Castillo-Chavez, 2001). For the second and third equations, consider the population leaving the susceptible class as equal to the number entering the infected class. However, a number equal to the fraction (γ which represents the mean recovery rate, or $1 / \gamma$ the mean infective period) of infective are leaving this class per unit time to enter the removed class. These processes which occur simultaneously are referred to as the Law of Mass Action, a widely accepted idea that the rate of contact between two groups in a population is proportional to the size of each of the groups concerned (Daley & Gani, 2005). Finally, it is assumed that the rate of infection and recovery is much faster than the time scale of births and deaths and therefore, these factors are ignored in this model.

2.3.2 The SIR Model with Births and Deaths

Using the case of measles, for example, there is an arrival of new susceptible individuals into the population. For this type of situation births and deaths must be included in the model. The following differential equations represent this model:

$$\frac{dS}{dT} = -\beta SI + \mu(N - S) \qquad 2.05$$

$$\frac{dI}{dT} = \beta SI - \gamma I - \mu I \qquad 2.06$$

$$\frac{dR}{dT} = \gamma I - \mu R \qquad 2.07$$

2.3.3 The SIS Model with Births and Deaths

The SIS model can be easily derived from the SIR model by simply considering that the individuals recover with no immunity to the disease, that is, individuals are immediately susceptible once they have recovered; Removing the equation representing the recovered population from the SIR model and adding those removed from the infected population into the susceptible population gives the following differential equations:

$$\frac{dS}{dT} = -\beta SI + \mu(N - S) + \gamma I \qquad 2.08$$

$$\frac{dI}{dT} = \beta SI - \gamma I - \mu I \qquad 2.09$$

2.3.4 The SIRS Model

This model is simply an extension of the SIR model as we will see from its construction. The only difference is that it allows members of the recovered class to be free of infection and rejoin the susceptible class.

$$\frac{dS}{dT} = -\beta SI + \mu(N - S) + fI \qquad 2.10$$

$$\frac{dI}{dT} = \beta SI - \gamma I - \mu I \qquad 2.11$$

$$\frac{dR}{dT} = \gamma I - \mu R - fR \qquad 2.12$$

2.4 Models with More Compartments

Wikipedia (2011), explains that other models include the SEIS, SEIR, MSEIR and MSEIRS which have various extensions of the SIR model. The SEIS model takes into consideration the exposed or latent period of the disease, giving an additional compartment, E(t).

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

$$\frac{dS}{dT} = B - \beta SI - \mu S + \gamma I \qquad 2.13$$

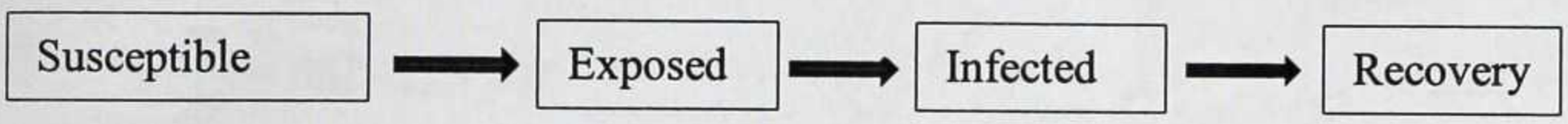
$$\frac{dI}{dT} = \beta SI - \gamma I - \mu I \qquad 2.14$$

$$\frac{dR}{dT} = \gamma I - \mu R - fR \qquad 2.15$$

The SIR model discussed above takes into account only those diseases which cause an individual to be able to infect others immediately upon their infection. Many diseases have

what is termed a latent or exposed phase, during which the individual is said to be infected but not infectious.

2.4.1 THE SEIR MODEL



In this model the host population (N) is broken into four compartments: susceptible, exposed, infectious, and recovered, with the numbers of individuals in a compartment, or their densities denoted respectively by S(t), E(t), I(t), R(t), that is N = S(t) + E(t) + I(t) + R(t)

$$\frac{dS}{dT} = B - \beta SI - \mu S \qquad 2.16$$

$$\frac{dE}{dT} = \beta SI - (\varepsilon + \mu)E \qquad 2.17$$

$$\frac{dI}{dT} = \varepsilon E - (\gamma + \mu)I \qquad 2.18$$

$$\frac{dR}{dT} = \gamma I - \mu R \qquad 2.19$$

2.4.2 THE MSIR MODEL

There are several diseases where an individual is born with a passive immunity from its mother. To indicate this mathematically, an additional compartment is added, M(t), which results in the following differential equations:

$$\frac{dM}{dT} = B - \delta MS - \mu M \qquad 2.20$$

$$\frac{dS}{dT} = \delta MS - \beta SI - \mu S \qquad 2.21$$

$$\frac{dI}{dT} = \beta SI - (\gamma + \mu)I \qquad 2.22$$

$$\frac{dR}{dT} = \gamma I - \mu R \qquad 2.23$$

2.4.3 THE MSEIR MODEL

For the case of a disease, with the factors of passive immunity, and latency period there is the MSEIR model.

$$\frac{dM}{dT} = B - \delta MS - \mu M \qquad 2.24$$

$$\frac{dS}{dT} = \delta MS - \beta SI - \mu S \qquad 2.25$$

$$\frac{dE}{dT} = \beta SI - (\varepsilon + \mu)E \qquad 2.26$$

$$\frac{dI}{dT} = \varepsilon E - (\gamma + \mu)I \qquad 2.27$$

$$\frac{dR}{dT} = \gamma I - \mu R \qquad 2.28$$

2.4.4 THE MSEIRS MODEL

An MSEIRS model is similar to the MSEIR, but the immunity in the R class would be temporary, so that individuals would regain their susceptibility when the temporary immunity ended.

2.4.5 BASIC REPRODUCTION NUMBER

According to Wikipedia (2011), there is a threshold quantity which determines whether an epidemic occurs or the disease simply dies out. This quantity is called the basic reproduction number, denoted by R_0, which can be defined as the number of secondary infections caused by a single infective introduced into a population made up entirely of susceptible individuals ($S(0) \approx N$) over the course of the infection of this single infective. This infective individual makes βN contacts per unit time producing new infections with a mean infectious period of $1/\gamma$. Therefore, the basic reproduction number is

$$R_0 = \frac{\beta N}{\gamma} \qquad 2.29$$

This value quantifies the transmission potential of a disease. If the basic reproduction number falls below one ($R_0 < 1$), i.e. the infective may not pass the infection on during the infectious period, the infection dies out. If $R_0 > 1$ there is an epidemic in the population. In cases where $R_0 = 1$, the disease becomes endemic, meaning the disease remains in the population at a consistent rate, as one infected individual transmits the disease to one susceptible (Trottier & Philippe,2001). In cases of diseases with varying latent periods, the basic reproduction number can be calculated as the sum of the reproduction number for each transition time into

the disease. An example of this is tuberculosis. Blower et al. (1995) calculated from a simple model of TB the following reproduction number:

$$R_0 = R_0^{\text{FAST}} + R_0^{\text{SLOW}}$$

In their model, it is assumed that the infected individuals can develop active TB by either direct progression (the disease develops immediately after infection) considered above as FAST tuberculosis or endogenous reactivation (the disease develops years after the infection) considered above as SLOW tuberculosis.

2.4.6 FRED BRAUER'S MODEL

In addition to Kermack-McKendrick's model, Brauer's et al (2006) also describe and analyze compartmental models for diseases transmission, which they began with models for epidemics showing how to compute the basic reproduction number and the final size of the epidemic. They also studied models with multiple compartments including treatment or isolation of infective. Furthermore they considered models including births and deaths in which there may be an endemic equilibrium and studied the asymptotic stability of equilibrium. In conclusion they studied age infection models which gave a unifying framework for more complicated compartmental models.

Besides, Brauer et al (2006) were concerned with both epidemics which are sudden outbreaks of a disease, and endemic situations, in which a disease is always present. Epidemics such as the 2002 outbreak of SARS, the Ebola virus and avian flu outbreaks are events of concern and interest to many people. The1918 Spanish flu epidemic caused millions of deaths, and a recurrence of a major influenza epidemic is a dangerous possibility. Their aim was to provide

introduction to mathematical epidemiology, including the development of mathematical models for the spread of diseases as well as tools for their analysis.

Moreover they began with an introduction to epidemic models and extended it to incorporate demographic effects into the models to explore endemic states and they finally described models with infectivity depending on the age of infection. The approach used was a qualitative one, which meant that they rather attempted to find explicit solutions of the systems of differential equations which will form their models; they were concerned with the asymptotic behaviour, which is the behavior as $t \longrightarrow \infty$ of solutions.

2.5 MATHEMATICS OF EQUILIBRIUM POINT AND STABILITY OF DYNAMICAL SYSTEMS.

From Wikipedia,(2011): The definitions of equilibrium point and stability are as follows:

Definition: A point Xe is an *equilibrium point* (or stationary point or singular point or critical point or rest point) of the differential equation

$$\frac{dX}{dt} f(t, X)$$

if there exists a finite time t* such that $x \in R^n, t \in R \quad f(t, X) = 0$ for all $t \geq t^*$

Note: In the special case of an autonomous system in which **f** is a function of X only,

i.e., f (t, X) = f(X), then if Xe is an equilibrium point of

$$\frac{dX}{dt} = f(X)$$

at t*, then it is an equilibrium point for all $t \geq t^*$.

2.5.1 SOME BASIC DEFINITIONS

Definition: An equilibrium point $\mathbf{X^*}$ of the scalar differential equation

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

is a point for which $f(x^*) = 0$.

STABLE EQUILIBRIUM

Definition: An equilibrium point Xe of

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

is *stable Lypunov* if for every $\delta > 0$ and any $t_0 \square R^+$ there is $\omega(\delta, t_0) > 0$ such that $|u(t, t0, \gamma) - Xe| < \delta$ for every $t \geq t_0$ whenever $\gamma - Xe < \omega(\delta, t_0)$ where $u(t, t_0, \gamma)$ is a solution of

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

with the initial condition $X(t_0) = \gamma$

Definition: The equilibrium point Xe of

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

is *asymptotically stable* if

1. it is stable and

2. for every $t_0 \geq 0$ there is an $\varepsilon(t_0) > 0$ such that

$$\lim_{t \to \infty} u(t, t_0,) = Xe$$

whenever $|\gamma - Xe| < \varepsilon(t_0)$

Definition: The equilibrium point X= Xe of

$$\frac{dx}{dt} f(t, X)$$

is unstable if it is not stable.

2.5.2 CHARACTERISTICS OF EQUILIBRIUM POINTS

Equilibrium can be classified by looking at the signs of the eigenvalues of the linearization of the equations about the equilibrium. That is to say, by evaluating the Jacobian matrix at each of the equilibrium points of the system, and then finding the resulting eigenvalues, the equilibrium can be categorized. The behavior of the system in the neighborhood of each equilibrium point can be qualitatively determined, (or even quantitatively determined, in some instances, by finding the eigenvector(s) associated with each eigenvalue).

An equilibrium point may be classified as follows:

Asymptotically stable if there is disease free or there is absence of infection in the system or otherwise it is unstable if there is an infection or if pathogens are present in the human system.

Furthermore the equilibrium is said to be

(i) Stable node if it has two negative real part which implies that there are no infections in the individual's system.

(ii) If the eigenvalues are negative or complex with negative real part, then the equilibrium point is a sink (that is all the solutions will dye at the equilibrium point). Note that if the eigenvalues are complex, then the solutions will spiral around the equilibrium point.

(iii) If the eigenvalues are positive or complex with positive real part, then the equilibrium point is a source (that is all the solutions will move away from the equilibrium point). Note that if the eigenvalues are complex, then the solutions will spiral away from the equilibrium point.

(iv) If the eigenvalues are real number with different sign (one positive and one negative), then the equilibrium point is a saddle. In fact, there will be two solutions which approach the equilibrium point as $t \to +\infty$, and two more solutions which approach the equilibrium point as $t \to -\infty$. For the linear system these solutions are lines, but for the nonlinear system they are not in general.

An equilibrium point is *hyperbolic* if none of the eigenvalues have zero real part. If all eigenvalues have negative real part, the equilibrium is a stable point. If at least one has a positive real part, the equilibrium is an unstable. If at least one eigenvalue has negative real part and at least one positive real part, the equilibrium is a saddle point.

2.5.3 LINEARIZATION AND STABILITY ANALYSIS.

According to Weisstein, E W (2011), to determine the stability of equilibrium point of a system of differential equations is not easy but the determination of the asymptotic stability is generally quite easy. The process consists of linearization of the equations about the equilibrium point and then determining the stability of the linearized equations. There are three main methods in solving differential equation namely analytical, qualitative, and numerical.

Analytical techniques include linear, separable, and Bernoulli equations whiles Euler's Method demonstrates the use of numerical techniques in solving differential equations.

In qualitative approach, drawing slope field of a differential equation can show how this can be helpful when other techniques fail. When the differential equation is independent, more can be said about the solutions using qualitative techniques.

The numerical calculation of eigenvalues of matrices can now easily be carried out with many mathematical software packages (e.g., Matlab, Maple, Mathematica).

The linearization approach examines the behavior of the system to equilibrium point. The stability of the equilibrium point can be determined by finding the eigenvalues of the system. The linear system in dx/dt = f (t, X), $x' = AX$ has an equilibrium point at x*= 0. In the theory

of equilibrium points of linear systems of the form $x' = J(x,t)X$, it is known that x = 0 is an equilibrium point and that solutions have the time dependence e^λ t, where λ is an eigenvalue of J(x*).Therefore the equilibrium point 0 is asymptotically stable if the real parts of all eigenvalues of J(x*) are negative and not asymptotically stable if the real part of some eigenvalue is greater than zero. A critical value for asymptotic stability is therefore that the real part of some eigenvalue is zero and the real parts of all eigenvalues are less than or equal to zero.

Using the linear results, the linearized test for the equilibrium point of a nonlinear system will be asymptotically stable if the real parts of all eigenvalues of the Jacobian are negative and not asymptotically stable if the real part of some eigenvalues is positive. The test fails if the real part of any eigenvalue is zero. The equilibrium point is a stable node if the eigenvalues are real and negative. It is an unstable node if the eigenvalues are both real and positive. The equilibrium point is unstable saddle point if the eigenvalues are real and opposite in sign. It is a stable focus if the eigenvalues are complex with negative real parts. The equilibrium point is unstable focus if the eigenvalues are complex with positive real parts. The equilibrium point is a center if its eigenvalues are complex with zero real parts.

2.6 WHITE BLOOD CELLS

There are several different types of white blood cells, each with different functions, but they can be put into two main groups: phagocytes and lymphocytes.

2.6 .1 PHAGOCYTES

According to Wikipedia (2011) phagocytes are the white blood cells that protect the body by ingesting (phagocytosing) harmful foreign particles, bacteria, and dead or dying cells. They are essential for fighting infections and for subsequent immunity.

Phagocytes are important throughout the animal kingdom and are highly developed within vertebrates. One litre of human blood contains about six billion phagocytes. Phagocytes occur in many species; some amoebae behave like macrophage phagocytes, which suggests that phagocytes appeared early in the evolution of life.

Phagocytes of humans and other animals are called "professional" or "non-professional" depending on how effective they are at phagocytosis. The professional phagocytes include cells called neutrophils, monocytes, macrophages, dendritic cells, and mast cells. The main difference between professional and non-professional phagocytes is that the professional phagocytes have molecules called receptors on their surfaces that can detect harmful objects, such as bacteria, that are not normally found in the body. Phagocytes are crucial in fighting infections, as well as in maintaining healthy tissues by removing dead and dying cells that have reached the end of their lifespan. During an infection, chemical signals attract phagocytes to places where the pathogen has invaded the body. These chemicals may come from bacteria or from other phagocytes already present. The phagocytes move by a method called chemotaxis. When phagocytes come into contact with bacteria, the receptors on the phagocyte's surface will bind to them. This binding will lead to the engulfing of the bacteria by the phagocyte. Some phagocytes kill the ingested pathogen with oxidants and nitric oxide. After phagocytosis, macrophages and dendritic cells can also participate in antigen presentation, a process in which a phagocyte moves parts of the ingested material back to its surface. This material is then displayed to other cells of the immune system. Some phagocytes then travel to the body's lymph nodes and display the material to white blood cells called lymphocytes. This process is important in building immunity.

2.6.2 DISTRACTION OF BACTERIAL CELLS

The killing of microbes is a critical function of phagocytes that is either performed within the phagocyte (intracellular killing) or outside of the phagocyte (extracellular killing).

2.6.3 Oxygen-dependent intracellular distraction

When a phagocyte ingests bacteria (or any material), its oxygen consumption increases. The increase in oxygen consumption, called a respiratory burst, produces reactive oxygen-containing molecules that are anti-microbial. The oxygen compounds are toxic to both the invader and the cell itself, so they are kept in compartments inside the cell. This method of killing invading microbes by using the reactive oxygen-containing molecules is referred to as oxygen-dependent intracellular killing, of which there are two types.

The first type is the oxygen-dependent production of a superoxide, which is an oxygen-rich bacteria-killing substance. The second type involves the use of the enzyme myeloperoxidase from neutrophil granules.

2.6.4 Oxygen-independent intracellular distraction

Pus under a microscope, there are many white blood cells with lobed nuclei. Inside some of the cells there are hundreds of bacteria that have been engulfed.

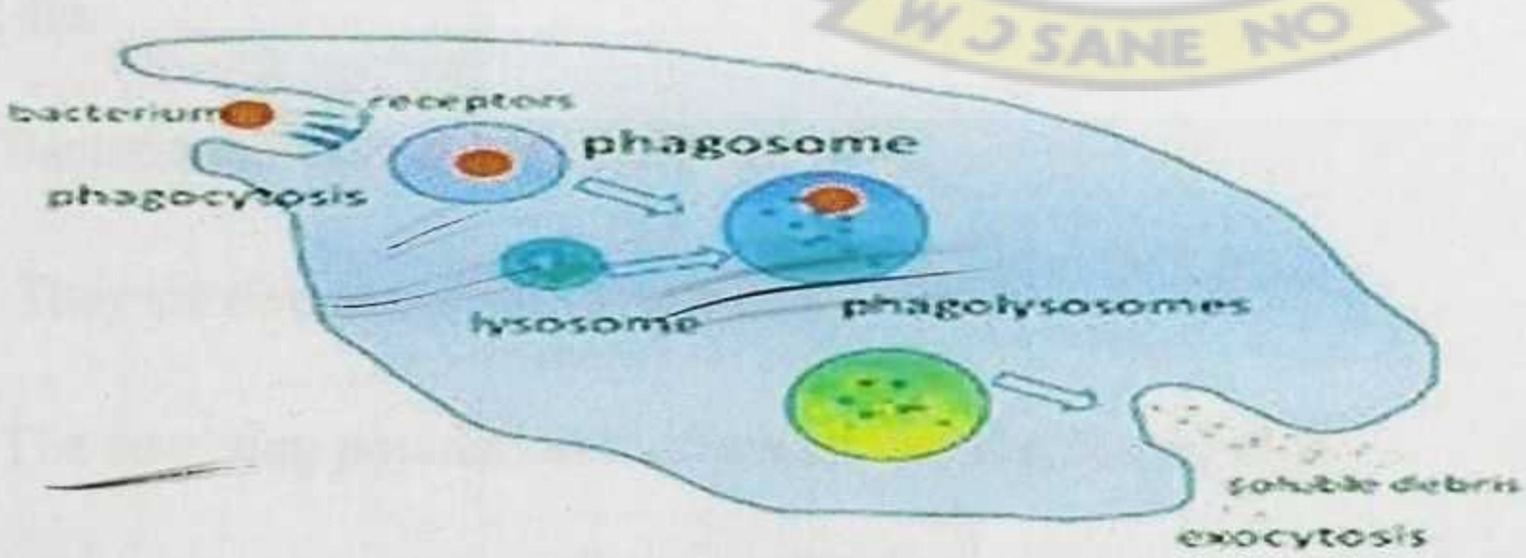


Figure 2.5 illustrates a simplified diagram of the phagocytosis and destruction of a bacterial cell.

Phagocytes can also kill microbes by oxygen-independent methods, but these are not as effective as the oxygen-dependent ones. There are four main types. The first uses electrically charged proteins that damage the bacterium's membrane. The second type uses lysozymes; these enzymes break down the bacterial cell wall. The third type uses lactoferrins, which are present in neutrophil granules and remove essential iron from bacteria. The fourth type uses proteases and hydrolytic enzymes; these enzymes are used to digest the proteins of destroyed bacteria.

2.7 AN SID MODEL ON THE DYNAMICS OF BACTERIA POPULATION AS THEY INVADE THE HUMAN BODY

When bacteria enter the human body, it begins to multiply to increase the population in the body there by reducing the population of phagocytes and lymphocytes which leads to an infection in the human body. It assumed that at a certain time t, N = S that is the initial population is equal to the surviving population of bacteria.

Assumptions of the model:

I N is the initial population of bacteria that enters the human system, I represent the increased in their population, S denotes those that survive as some die and D denotes those that die.

II. Bacteria increase at per capita rate of α.

III They survive at per capita rate of γ.

IV The surviving population increases at per capita rate of β.

V They die at per capita rate of φ.

The assumptions above lead to the following systems of differential equations.

$$N = I + S - D \quad 2.01$$

$$N' = \alpha I + \gamma S - \varphi D \quad 2.02$$

$$I' = \alpha I + N \quad 2.03$$

$$S' = \alpha I + \beta S \quad 2.04$$

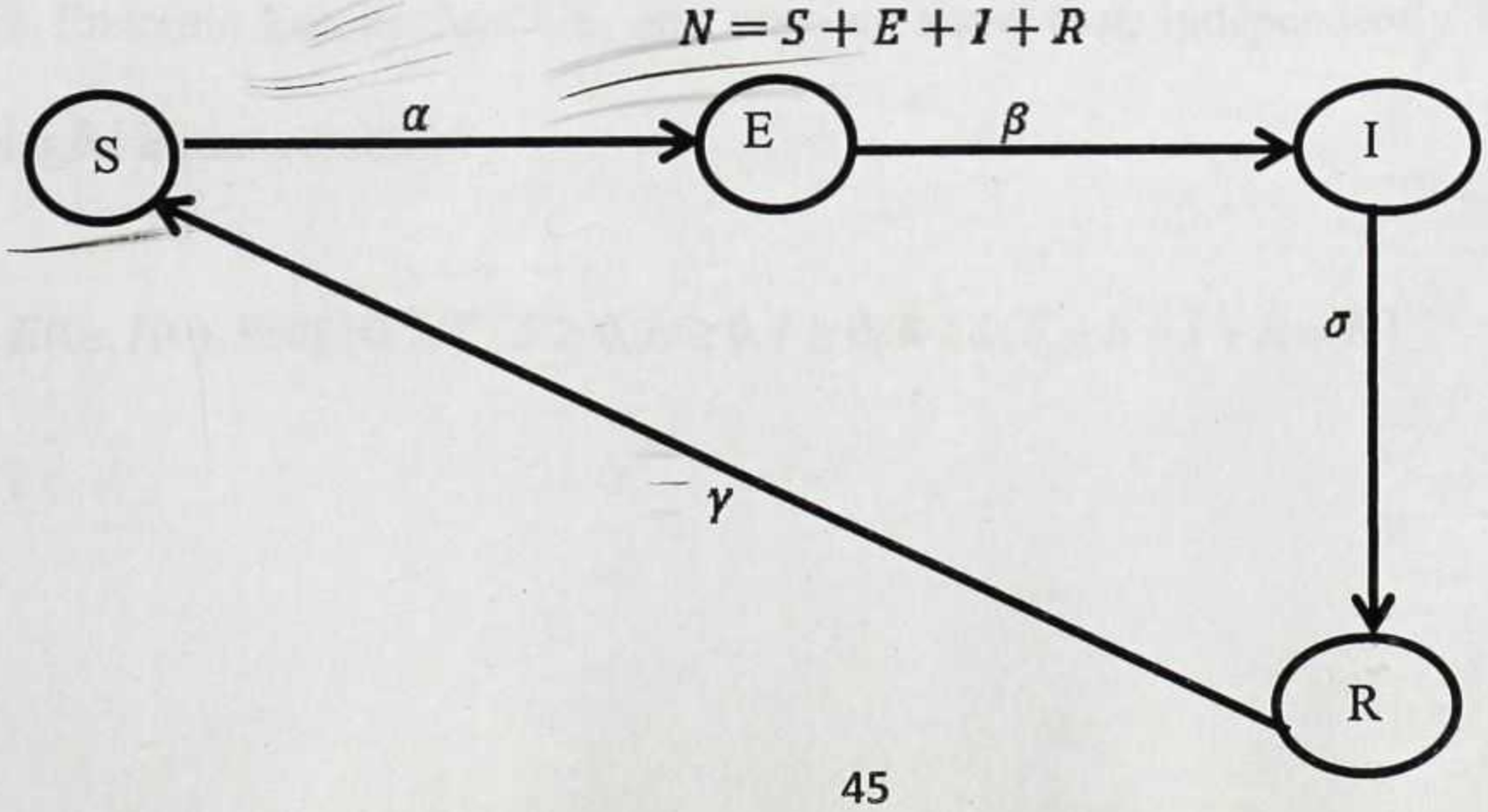
$$D' = \varphi D \quad 2.05$$

2.8 AN SEIR MODELS ON THE DYNAMICS OF HUMAN POPULATION.

The SEIR models the flows of people between four compartments: susceptible (S), exposed (E), infected (I), and resistant (R). Each of those variables represents the number of people in those groups. The parameters alpha and beta partially control how fast people move from being susceptible to exposed (beta), from exposed to infected (sigma), and from infected to resistant (gamma). The SEIR differs from the SIR model in the addition of a latency period. Individuals who are exposed (E) have had contact with an infected person, but are not themselves infectious.

N represent the total population of human in a compartment, E denotes the population of human that would be exposed to the infection, I denotes those who get infected as they are exposed to the infection and R represent those who recover from the infection.

$$N = S + E + I + R$$



Assuming that the period of staying in the latent state is a random variable with exponential distribution with parameter a (i.e. the average latent period is a^{-1}), and also assuming the presence of vital dynamics with birth rate equal to death rate, and also assuming that the disease is fatal, we have the following assumptions of the model as shown below.

I. Some infection does not confer immunity to reinfection. This implies that those who recover can begin the cycle again.

II. The human population are exposed to the infection at per capita rate of α

III. They get infected to the infection at per capita rate of β

IV. They recover from the infection at per capita rate of σ

The assumptions above lead to the following systems of differential equations.

$$S' = B - \alpha SE - \beta I + \sigma R \qquad 2.06$$

$$E' = A + \alpha SE - \beta I \qquad 2.07$$

$$I' = C + \beta EI - \sigma IR \qquad 2.08$$

$$R' = D + \sigma IR - \gamma R \qquad 2.09$$

we have that $S + E + I + R = N$.

For this model, the basic reproduction number

Similarly to the SIR model, also in this case we have a Disease-Free-Equilibrium (N,0,0,0) and an Endemic Equilibrium EE, and one can show that, independently form biologically meaningful initial condition

$$S(0), E(0), I(0), R(0), [0, N]^4, S \geq 0, E \geq 0, I \geq 0, R \geq 0, S + E + I + R = N\}$$

holds that:

$$R_0 \leq 1 \Rightarrow \lim_{t \to +\infty}(S(t), E(t), I(t), R(t) = (N, 0, 0, 0)$$

$$R_0 \geq 1, I(0) > 0 \Rightarrow \lim_{t \to +\infty} S(t), E(t), I(t), R(t) = (S, E, I, R) \neq (N, 0, 0, 0)$$

In case of periodically varying contact rate $\beta(t)$ the condition for the global attractiveness of Differential Equations is that the following linear system with coefficients: $\beta, \nu, \alpha, \sigma$

$$E_1' = \beta I_1(t) - (\nu + \alpha)E_1 \qquad 2.10$$

$$I_1' = \alpha E_1 - (\sigma + \alpha)I_1 \qquad 2.11$$

2.8.1 EXISTENCE OF STEADY STATES ON THE DYNAMICS OF BACTERIA POPULATION

Bacteria multiply to increase their population there by reducing the population of phagocytes and lymphocytes. we obtain steady states by putting derivatives to zero.

$$\alpha I + \gamma S - \varphi D = 0 \qquad 2.12$$

$$\alpha I + N = 0 \qquad 2.13$$

$$\alpha I + \beta S = 0 \qquad 2.14$$

$$\varphi D = 0 \qquad 2.15$$

This leads to (N*, S*,I*) = (0, 0,0) as a trivial steady state of the system. We obtain the characteristics equation of the system.

$$N' = \alpha I + \gamma S - \varphi D = f_1 \qquad 2.16$$

$$S' = \alpha I + N = f_2 \qquad 2.17$$

$$I' = \alpha I + \beta S = f_3 \qquad 2.18$$

In linearizing the systems of equations we obtain

$$J(N,S,I) = \begin{bmatrix} \frac{\partial f_1}{\partial N} & \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial I} \\ \frac{\partial f_2}{\partial N} & \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial I} \\ \frac{\partial f_3}{\partial N} & \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial I} \end{bmatrix} \qquad 2.19$$

Substituting we obtain

$$J(N,S,I) = \begin{bmatrix} 0 & \gamma & \alpha \\ 1 & 0 & \alpha \\ 0 & \beta & 0 \end{bmatrix} \qquad 2.20$$

2.8.2 EXISTENCE OF STEADY STATES ON THE DYNAMICS OF HUMAN POPULATION.

In each compartment the population either increases or decreases depending on the flow rate of each preceding compartment.We obtain steady states by putting derivatives to zero.

$$B - \alpha SE - \beta I + \sigma R = 0 \qquad 2.21$$

$$A + \alpha SE - \beta I = 0 \qquad 2.22$$

$$C + \beta EI - \sigma IR = 0 \qquad 2.23$$

$$D + \sigma IR - \gamma R = 0 \qquad 2.24$$

This leads to (S*,E*,I*,R*) = (0,0,0,0) as a trivial steady state of the system. We obtain the characteristic equation of the systems.

$$S' = B - \alpha SE - \beta I + \sigma R = f_1 \quad 2.25$$

$$E' = A + \alpha SE - \beta I = f_2 \quad 2.26$$

$$I' = C + \beta EI - \sigma IR = f_3 \quad 2.27$$

$$R' = D + \sigma IR - \gamma R = f_4 \quad 2.28$$

In linearizing the equations we obtain

$$J(S,E,I,R) = \begin{bmatrix} \frac{\partial f_1}{\partial S} & \frac{\partial f_1}{\partial E} & \frac{\partial f_1}{\partial I} & \frac{\partial f_1}{\partial R} \\ \frac{\partial f_2}{\partial S} & \frac{\partial f_2}{\partial E} & \frac{\partial f_2}{\partial I} & \frac{\partial f_2}{\partial R} \\ \frac{\partial f_3}{\partial S} & \frac{\partial f_3}{\partial E} & \frac{\partial f_3}{\partial I} & \frac{\partial f_3}{\partial R} \\ \frac{\partial f_4}{\partial S} & \frac{\partial f_4}{\partial E} & \frac{\partial f_4}{\partial I} & \frac{\partial f_4}{\partial R} \end{bmatrix} \quad 2.29$$

Substituting we obtain

$$J(S,E,I,R) = \begin{bmatrix} -\alpha E & -\alpha S & -\beta & \sigma \\ \alpha E & \alpha S & -\beta & 0 \\ 0 & \beta I & \beta E & \sigma I \\ 0 & 0 & \sigma R & \gamma \end{bmatrix} \quad 2.30$$

The Jacobian shown in equations 2.20 and 2.30 are used to analysed the stability characteristics of the equilibrium points of the linear systems

CHAPTER THREE

THE MODEL (METHODOLOGY)

3.0 INTRODUCTION

This chapter emphasis on the various models that will be used to study the human immune response to bacterial infectious diseases. The models are on the dynamics of bacteria population as they are in the human body, human population in various compartment of bacterial infections. The equilibrium points and their stability for the systems of the extended differential equations will be analyzed. The methods for numerical solution of these equations using Matlab will then be discussed.

3.1 DEVELOPMENT OF THE MODEL

These models have been considered in four phases. The first phase describes the behavior of phagocytes and lymphocytes in the absence of the bacteria. The second part describes the behavior of the phagocytes and lymphocytes in the presence of the bacteria. This third phase describes the dynamics of bacterial population. The final part is the model on human population in various compartments. The first model consist of the interactions between the phagocytes and lymphocytes represented by P(t) and L(t).The second model involves the dynamics on bacterial population at a particular time denoted by B(t).The models on human population in various compartment represented by N(t).

3.1.1 THE BEHAVIOUR OF PHAGOCYTES AND LYMPHOCYTES IN THE ABSENCE OF BACTERIA

In the absence of bacteria, the population of the phagocytes and lymphocytes in the human body are being regulated by their interaction.

Lymphocytes are normally studied in terms of their responsiveness to antigen. However, they bear numerous other receptors that make them aware of events occurring both in their immediate neighborhood and at distant sites. Among these are receptors that detect the presence of infection and receptors that bind cytokines produced by the cell itself or reaching it from elsewhere. When antigen-specific lymphocytes are activated through their antigen receptors in an adaptive immune response, they first undergo blast transformation and begin to increase their numbers exponentially by cell division. This clonal expansion can continue for up to 7 or 8 days, so that lymphocytes specific for the infecting pathogen increase vastly in numbers and can come to predominate in the population.

Phagocytes are usually not bound to any particular organ but move through the body interacting with the other phagocytic and non-phagocytic cells of the immune system. They can communicate with other cells by producing chemicals called cytokines, which recruit other phagocytes to the site of infections or stimulate dormant lymphocytes. Phagocytes form part of the innate immune system, which animals, including humans, are born with. Innate immunity is very effective but non-specific in that it does not discriminate between different sorts of invaders. The adaptive immune system is dependent on lymphocytes, which are not phagocytes but produce protective proteins called antibodies. Phagocytes, in particular dendritic cells and macrophages, stimulate lymphocytes to produce antibodies by an important process called antigen presentation.

Based on the properties of their population the following assumptions are made.

I. Lymphocytes and phagocytes are recruited from the bone marrow at constant rates α_1 and α_2 respectively.

II. Lymphocytes and Phagocytes die at a per capita rate μ_1 and μ_2 respectively.

III. Phagocytes stimulate dormant lymphocytes to produce antibodies by an important process called antigen presentation.

IV. The respective proliferation responses saturate to a maximum net rate which is dependent on the product of their respective densities.

These assumptions lead to the system of equations below, where P represents phagocytes, L denotes lymphocytes, A represents the constant rate at which phagocytes and lymphocytes are produced and μ denotes the rate of self-decay of the lymphocytes and phagocytes.

$$P' = A_1 - \mu_1 P + \frac{\alpha_1 PL}{1+\beta_1 PL} \qquad 3.01$$

$$L' = A_2 - \mu_2 L + \frac{\alpha_2 PL}{1+\beta_2 PL} \qquad 3.02$$

The terms α_1 and β_1 are arbitrary constants that determine the degrees of proliferation arising from cell-cell interaction and the levels at which the net rates of proliferation saturate. The first two terms on the right of each equation correspond to the first two properties or assumptions. The complicated term that follows models the interaction between the phagocytes and lymphocytes. They made us aware that for small values of the product **PL**, this term accounts for a rate of increase that is roughly proportional to the product. It should also be noted that as the product increases, the rate of increase goes no higher than $\frac{\alpha_1}{\beta_1}$.

It is seen that the general form of both equations (3.01) and (3.02) are in the form presented below;

$$P' = A_1 - \mu_1 P + \frac{\alpha_1 PL}{1 + \beta_1 PL}$$

The explanation is that the growth of the lymphocytes and phagocytes population is determined by three factors; the constant rate A_i at which lymphocytes and phagocytes are being produced by bone marrow, the self-decay of the lymphocytes and phagocytes at the rate μ_i and the interaction between the two populations of lymphocytes and phagocytes which saturates that is approaches $\frac{\alpha_1}{\beta_1}$ as **PL** $\longrightarrow \infty$. The system of equations is extremely difficult to solve explicitly. Therefore, the approach used was to gain a general understanding of how solutions to the system behave without finding the solutions outright as presented in chapter four.

Since the system display a high degree of symmetry, we proceeded by finding the equilibrium points, that is, the points at which **P = L = 0.** Setting the equations equal,

3.1.2 THE BEHAVIOUR OF PHAGOCYTES AND LYMPHOCYTES IN THE PRESENCE OF BACTERIA

In the presence of bacteria phagocytes extend portions of their plasma membrane, wrapping the membrane around the particle until it is enveloped and killed and stimulate dormant lymphocytes to produce antibodies to destroy bacteria.

The word 'phagocyte' literally means 'eating cell'. These are immune cells that engulf, i.e. phagocytose, pathogens or particles. To engulf a particle or pathogen, a phagocyte extends portions of its plasma membrane, wrapping the membrane around the particle until it is

enveloped (i.e. the particle is now inside the cell). Once inside the cell, the invading pathogen is contained inside an endosome which merges with a lysosome. The lysosome contains enzymes and acids that kill and digest the particle or organism. Phagocytes generally patrol the body searching for pathogens, but are also able to react to a group of highly specialized molecular signals produced by other cells, called cytokines. Phagocytes can easily pass through blood vessel walls into the surrounding tissue and move towards pathogens or toxins. They then either ingest and absorb the pathogens or toxins and can also release an enzyme to destroy them. Having absorbed a pathogen, the phagocytes may also send out chemical messages that help nearby lymphocytes to identify the type of antibody needed to neutralize them. The phagocytic cells of the immune system include macrophages, neutrophils, and dendritic cells.

Lymphocytes develop in the thymus gland or in the bone marrow. Lymphocytes are called white blood cells. Two types of white blood cells are the T cells and B cells. Lymphocytes in the lymph nodes aid the body in fighting infection by producing antibodies that destroy bacteria. When a lymphocyte with the appropriate antibody meets the antigen, the lymphocyte reproduces quickly, and makes many copies of the antibody that neutralizes the pathogen.

The lymphocyte T cell then engages the help of the lymphocyte B cell which makes a special weapon called an antibody to use against the bacteria. The lymphocyte B cell produces copy after copy of these antibody weapons. When the antibody weapon finds its target, the germ is stunned, wounded and killed. Antibodies neutralize pathogens in a number of ways:

I. they bind to pathogens and damage or destroy them,

II. they coat pathogens, clumping them together so that they are easily ingested by phagocytes,

III. they bind to the pathogens and release chemical signals to attract more phagocytes.

These interactions lead to the following properties:

I. phagocytes are produced in the blood at a growth rate of r

II. phagocytes interact with bacteria at a per capita rate of v

III. phagocytes stimulate the lymphocytes to reduce the bacteria population at a per capita rate of γ

IV. bacteria die at a per capita rate of α .

These assumptions lead to this system of differential equations

$$P' = F_1 - \mu_1 P + vPB \qquad 3.03$$

$$L' = F_2 - \mu_2 L + \beta LB \qquad 3.04$$

$$B' = \alpha B - \gamma PLB \qquad 3.05$$

P L, B, α , γ ,r and v represent population of phagocytes, population of lymphocytes, growth rate of bacterial, growth rate at which phagocytes activate lymphocytes, growth rate of phagocytes and the rate at which bacteria interact with phagocytes respectively.

3.2 MODEL ANALYSIS

The steady states obtained from the various stages of immune system are analyzed with the presentation of Jacobian matrices of the various models.

3.2.1 EXISTENCE OF STEADY STATES IN THE ABSENCE OF BACTERIA

(INNATE IMMUNE RESPONSE)

The procedure used was to achieve a general understanding of how solutions to the various systems behave without finding the solution outright. Steady states are obtained by solving the equations for all time derivatives equal to zero. By system of equations we obtain steady states by putting derivatives to zero.

$$A_1 - \mu_1 P + \frac{\alpha_1 PL}{1+\beta_1 PL} = 0 \qquad 3.09$$

$$A_2 - \mu_2 L + \frac{\alpha_2 PL}{1+\beta_2 PL} = 0 \qquad 3.10$$

This leads to (P*, L*) = (0, 0) as a trivial steady state of the system. We obtain the characteristics equation of the system

$$A_1 - \mu_1 P + \frac{\alpha_1 PL}{1+\beta_1 PL} = A_2 - \mu_2 L + \frac{\alpha_2 PL}{1+\beta_2 PL} \qquad 3.11$$

The two equations are symmetrical therefore at equilibrium equation 3.09 = equation 3.10

$$A - \mu P + \frac{\alpha P^2}{1+\beta P^2} = 0 \qquad 3.12$$

$$A(1+\beta P^2)-\mu P(1+\beta P^2)+\alpha P^2 \qquad 3.13$$

$$A+A\beta P^2-\mu P-\mu\beta P^3+\alpha P^2 \qquad 3.14$$

$$\mu\beta P^3-(A\beta+\alpha)P^2+\mu P-A \qquad 3.15$$

When the system are linearized by finding the Jacobian matrices of first partial derivatives.

$$P' = A_1-\mu_1 P+\frac{\alpha_1 PL}{1+\beta_1 PL}=f_1 \qquad 3.16$$

$$L' = A_2-\mu_2 L+\frac{\alpha_2 PL}{1+\beta_2 PL}=f_2 \qquad 3.17$$

$$\mathrm{J}(f_1,f_2)=\begin{bmatrix}\frac{\partial f_1}{\partial P} & \frac{\partial f_1}{\partial L}\\ \frac{\partial f_2}{\partial P} & \frac{\partial f_2}{\partial L}\end{bmatrix} \qquad 3.18$$

Substituting we obtain

$$J(P,L)=\begin{bmatrix}-\mu_1+\frac{\alpha_1 L}{(1+\beta_1 PL)^2} & \frac{\alpha_1 P}{(1+\beta_1 PL)^2}\\ \frac{\alpha_2 L}{(1+\beta_2 PL)^2} & -\mu_2+\frac{\alpha_2 P}{(1+\beta_2 PL)^2}\end{bmatrix} \qquad 3.19$$

3.2.2 EXISTENCE OF STEADY STATES IN THE PRESENCE OF BACTERIA **(ADAPTIVE IMMUNE RESPONSE)**

In the presence of bacteria cells in the human body, we consider the stages where phagocytes interact with bacteria and when phagocytes stimulate lymphocytes to destroy bacteria.

By system of equations (3.3) – (3.5), we obtain steady states by putting derivatives to zero.

$$F_1 - \mu_1 P + vBP = 0 \qquad 3.20$$

$$F_2 - \mu_2 L + \theta LB = 0 \qquad 3.21$$

$$\alpha B - \gamma PLB = 0 \qquad 3.22$$

This leads to (P*, L*,B*) = (0, 0,0) as a trivial steady state of the system. We obtain the characteristics equation of the system.

$$P' = F_1 - \mu_1 P + vBP = f_1 \qquad 3.23$$

$$L' = F_2 - \mu_2 L + \theta LB = f_2 \qquad 3.24$$

$$B' = \alpha B - \gamma PLB = f_3 \qquad 3.25$$

In linearizing the system of equations we obtain

$$J(P,L,B) = \begin{bmatrix} \frac{\partial f_1}{\partial P} & \frac{\partial f_1}{\partial L} & \frac{\partial f_1}{\partial B} \\ \frac{\partial f_2}{\partial P} & \frac{\partial f_2}{\partial L} & \frac{\partial f_2}{\partial B} \\ \frac{\partial f_3}{\partial P} & \frac{\partial f_3}{\partial L} & \frac{\partial f_3}{\partial B} \end{bmatrix} \qquad 3.26$$

Substituting we obtain

$$J(P,L,B) = \begin{bmatrix} -\mu_1 + vB & 0 & vP \\ 0 & -\mu_2 + \theta B & \theta L \\ -\gamma LB & -\gamma PB & \alpha - \gamma PL \end{bmatrix} \qquad 3.27$$

CHAPTER FOUR

RESULTS, ANALYSIS AND DISCUSSION

4.0 INTRODUCTION

In this chapter, we present the result of the study and use numerical methods to study the mathematical model for bacteria infectious diseases developed in Chapter 3. Numerical solutions of the equations for a range of initial values that appear reasonable for the study will be used. We present the phase portraits of these systems of differential equations and analyze the systems qualitatively. Matlab ordinary differential equation solver 'ode45' is used to compute the numerical solution of the systems of differential equations.

Table 4.1: Parameters Values in the Model

Parameters	Description	Values
A_1	Initial production of Phagocytes	1
A_2	Initial production of Lymphocytes	1
α_1	Rate of recruit of Phagocytes from bone marrow	0.250
α_2	Rate of recruit of Lymphocytes from bone marrow	0.250
β_1	Rate of increase of Phagocytes	0.006
β_2	Rate of increase of Lymphocytes	0.006
μ_1	Death rate of Phagocytes	1.200
μ_2	Death rate of Lymphocytes	1.200

4.1 BEHAVIOUR OF STEADY STATES IN THE ABSENCE OF BACTERIA.

We substitute parameter values into equations (3.09) and (3.10) which yields;

$$7.2P^3 - 256P^2 + 1200P - 1000 = 0 \qquad 4.01$$

The roots of this cubic equation were found using Matlab and the roots of equation 4.01 are;

(30.1868, 4.2984, 1.0704).

It has already been shown that P = L, it then shows that there exits three equilibrium points at

$$\begin{pmatrix} P* \\ L* \end{pmatrix} = \begin{pmatrix} 30.19 \\ 30.19 \end{pmatrix}, \begin{pmatrix} 4.30 \\ 4.30 \end{pmatrix} and \begin{pmatrix} 1.07 \\ 1.07 \end{pmatrix}$$

Substituting the parameter values in Table 4.1, into equation (3.19) becomes;

$$J(P,L) = \begin{bmatrix} -1.2 + \dfrac{0.25L}{(1+0.006PL)^2} & \dfrac{0.25P}{(1+0.006PL)^2} \\ \dfrac{0.25L}{(1+0.006PL)^2} & -1.2 + \dfrac{0.25P}{(1+0.006PL)^2} \end{bmatrix} \qquad 4.02$$

At $J(P^*, L^*) = \begin{bmatrix} 1.07 & 1.07 \end{bmatrix}$ we obtain;

$$J(1.07,1.07) = \begin{bmatrix} -1.2 + \dfrac{0.2676}{1.0138} & \dfrac{0.2676}{1.0138} \\ \dfrac{0.2676}{1.0138} & -1.2 + \dfrac{0.2676}{1.0138} \end{bmatrix} \qquad 4.03$$

$$J(1.07,1.07) = \begin{bmatrix} -0.936 & 0.2640 \\ 0.2640 & -0.936 \end{bmatrix} \qquad 4.04$$

The eigenvalues were obtained to be $\lambda_1 = -1.2$ and $\lambda_2 = -0.672$

At $J(P^*, L^*) = \begin{bmatrix} 4.30 & 4.30 \end{bmatrix}$ we obtain;

$$J(4.30, 4.30) = \begin{bmatrix} -1.2 + \dfrac{1.0746}{1.2340} & \dfrac{1.0746}{1.2340} \\ \dfrac{1.0746}{1.2340} & -1.2 + \dfrac{1.0746}{1.2340} \end{bmatrix} \qquad 4.05$$

$$J(4.30, 4.30) = \begin{bmatrix} -0.3292 & 0.8708 \\ 0.8708 & -0.3292 \end{bmatrix} \qquad 4.06$$

The corresponding eigenvalues were obtained to be $\lambda_1 = -1.2$ and $\lambda_2 = 0.5416$

At $J(P^*, L^*) = \begin{bmatrix} 30.1868 & 30.1868 \end{bmatrix}$ we obtain;

$$J(30.1868, 30.1868) = \begin{bmatrix} -1.2 + \dfrac{7.5467}{41.8280} & \dfrac{7.5467}{41.8280} \\ \dfrac{7.5467}{41.8280} & -1.2 + \dfrac{7.5467}{41.8280} \end{bmatrix} \qquad 4.07$$

$$J(30.1868, 30.1868) = \begin{bmatrix} -1.0196 & 0.1804 \\ 0.1804 & -1.0196 \end{bmatrix} \qquad 4.08$$

The corresponding eigenvalues were obtained to be $\lambda_1 = -1.2$ and $\lambda_2 = -0.8392$

Table 4.2 CLASSIFICATION OF EQUILIBRIUM POINT

EQUILIBRIUM POINT	EIGEN VALUES	CLASSIFICATION
(1.07,1.07)	$\lambda_1 = -1.2$ *and* $\lambda_2 = -0.67$	Asymptotically Stable (Stable Node)
(4.30, 4.30)	$\lambda_1 = -1.2$ *and* $\lambda_2 = 0.54$	Unstable Points- (Saddle)
(30.19, 30.19)	$\lambda_1 = -1.2$ *and* $\lambda_2 = -0.84$	Asymptotically Stable (Stable Node)

4.2 BEHAVIOUR OF STEADY STATES IN THE PRESENCE OF BACTERIA

Table 4.3 Parameter Values in the Model

Parameters	Description	Values
μ	Death rate of Phagocytes and Lymphocytes cells	1.28
α	Intrinsic growth rate of Bacterial	0.20
γ	Rate of interaction between Phagocytes, Lymphocytes and Bacteria.	0.05
θ	Rate of interaction between Lymphocytes and Bacteria	0.04
v	Rate of interaction between Phagocytes and Bacteria	0.008
f_1	Initial number of Phagocytes produced	1
f_2	Initial number of Lymphocytes produced	1

We obtain the equilibrium points of systems (3.25) and (3.27) by substituting the parameter values of table 4.3.

$$1-1.28P+0.008PB=0 \qquad 4.09$$

$$1-1.28L+0.04LB=0 \qquad 4.10$$

$$0.20B-0.05PLB=0 \qquad 4.11$$

The equilibrium points were determined by Matlab. There exists three equilibrium points and

$$\text{these are} \begin{bmatrix} P^* \\ L^* \\ B^* \end{bmatrix} = \begin{bmatrix} 0.153 \\ 0.785 \\ 0.789 \end{bmatrix}, \begin{bmatrix} 31.820 \\ 142.687 \\ 0.892 \end{bmatrix}, \begin{bmatrix} 256.000 \\ -0.112 \\ -9176.720 \end{bmatrix}$$

Substituting the values of the parameters of table 4.3 into (3.27), we obtain

At $J(P^*, L^*, B^*) = \begin{bmatrix} 0.153 & 0.785 & 0.789 \end{bmatrix}$ we obtain

$$J(0.153, 0.785, 0.789) = \begin{bmatrix} -1.28 + 0.006 & 0 & 0.008(0.153) \\ 0 & -1.28 + 0.031 & 0.04(0.785) \\ -0.05(0.619) & -0.05(0.120) & 0.2 - (0.006) \end{bmatrix} \qquad 4.12$$

$$J(0.153, 0.785, 0.789) = \begin{bmatrix} -1.274 & 0 & 0.001 \\ 0 & -1.249 & 0.031 \\ -0.031 & -0.006 & 0.194 \end{bmatrix} \qquad 4.13$$

The corresponding eigenvalues obtained were $\lambda_1 = 0.1938, \lambda_2 = -1.2740$ and $\lambda_3 = -1.2489$

At $J(P^*, L^*, B^*) = \begin{bmatrix} 31.820 & 142.687 & 0.892 \end{bmatrix}$ we obtain

$$J(31.820, 142.687, 0.892) = \begin{bmatrix} -1.28 + (0.007) & 0 & 0.008(31.820) \\ 0 & -1.28 + (0.036) & 0.04(142.687) \\ -0.05(127.277) & -0.05(28.383) & 0.2 - (227.015) \end{bmatrix} \qquad 4.14$$

$$J(31.820, 142.687, 0.892) = \begin{bmatrix} -1.273 & 0 & 0.255 \\ 0 & -1.244 & 5.707 \\ -6.364 & -1.419 & -226.820 \end{bmatrix} \qquad 4.15$$

The corresponding eigenvalues are obtained

as $\lambda_1 = -226.7769, \lambda_2 = -1.2961$ and $\lambda_3 = -1.2640$

At $J(P^*, L^*, B^*) = \begin{bmatrix} 256.000 & -0.112 & -9176.720 \end{bmatrix}$ we obtain

$$J(256.000,-0.112,-9176.720)=\begin{bmatrix}-1.28+(-73.414) & 0 & 0.008(-9176.720)\\ 0 & -1.28+(-367.069) & 0.04(-0.112)\\ -0.05(1027.793) & -0.05(2349240.320) & 0.2+(1.434)\end{bmatrix} \quad 4.16$$

$$J(256.000,-0.112,-9176.720)=\begin{bmatrix}-74.694 & 0 & -73.414\\ 0 & -368.349 & -0.005\\ -51.390 & 117462.016 & 1.634\end{bmatrix} \quad 4.17$$

The corresponding eigenvalues are obtained to be

$\lambda_1 = 34.6838, \lambda_2 = -109.3512$ and $\lambda_3 = -366.6965$

TABLE 4.4: CLASSIFICATION OF THE EQUILIBRIUM POINTS

EQUILIBRIUM POINTS	EIGENVALUES	CLASSIFICATION
(0.153,0.785,0.789)	$\lambda_1 = 0.1938, \lambda_2 = -1.2740$ and $\lambda_3 = -1.2489$	Unstable Points (Saddle)
(31.820,142.687, 0.892)	$\lambda_1 = -226.7769, \lambda_2 = -1.2961$ and $\lambda_3 = -1.2640$	Asymptotically Stable (Stable Node)
(256 , -0.112, -9176.720)	$\lambda_1 = 34.6838, \lambda_2 = -109.3512$ and $\lambda_3 = -366.6965$	Unstable Points (Saddle)

4.3 RESULTS OF THE STUDY

Figure 4.1 illustrates the behaviour of phagocytes and lymphocytes in the absence of bacteria cells. The curve shows that the population of phagocytes and lymphocytes increase with time when bacterial have not annexed the human body. We notice that these two cells grow at an exponential rate until it reaches it carrying capacity, where it becomes constant. This endorses the logistic growth rate of the population of phagocytes and lymphocytes.

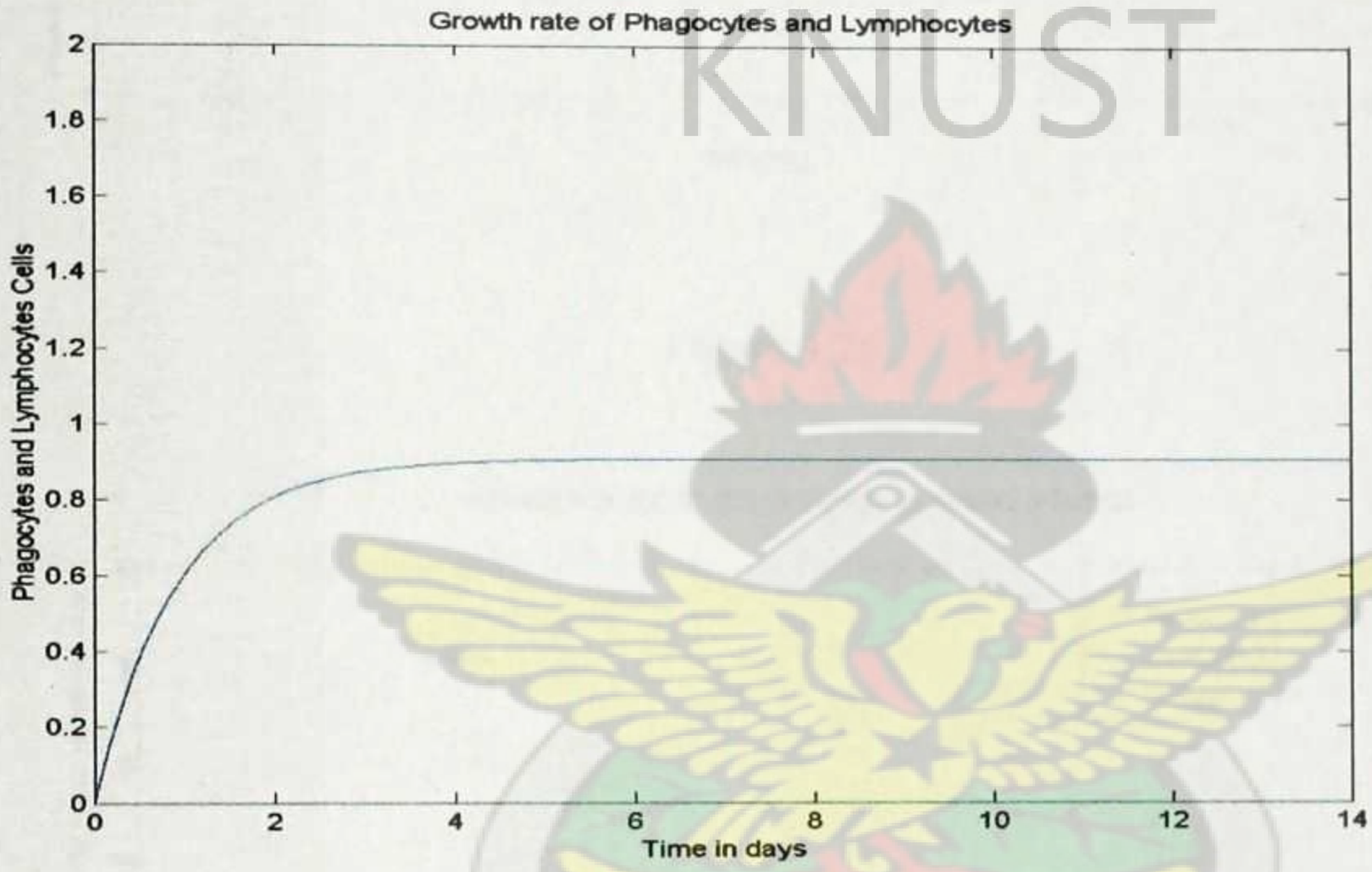


Figure 4.1

Figure 4.1 illustrates the growth rate of phagocytes and lymphocytes cells in the absence of bacteria cells.

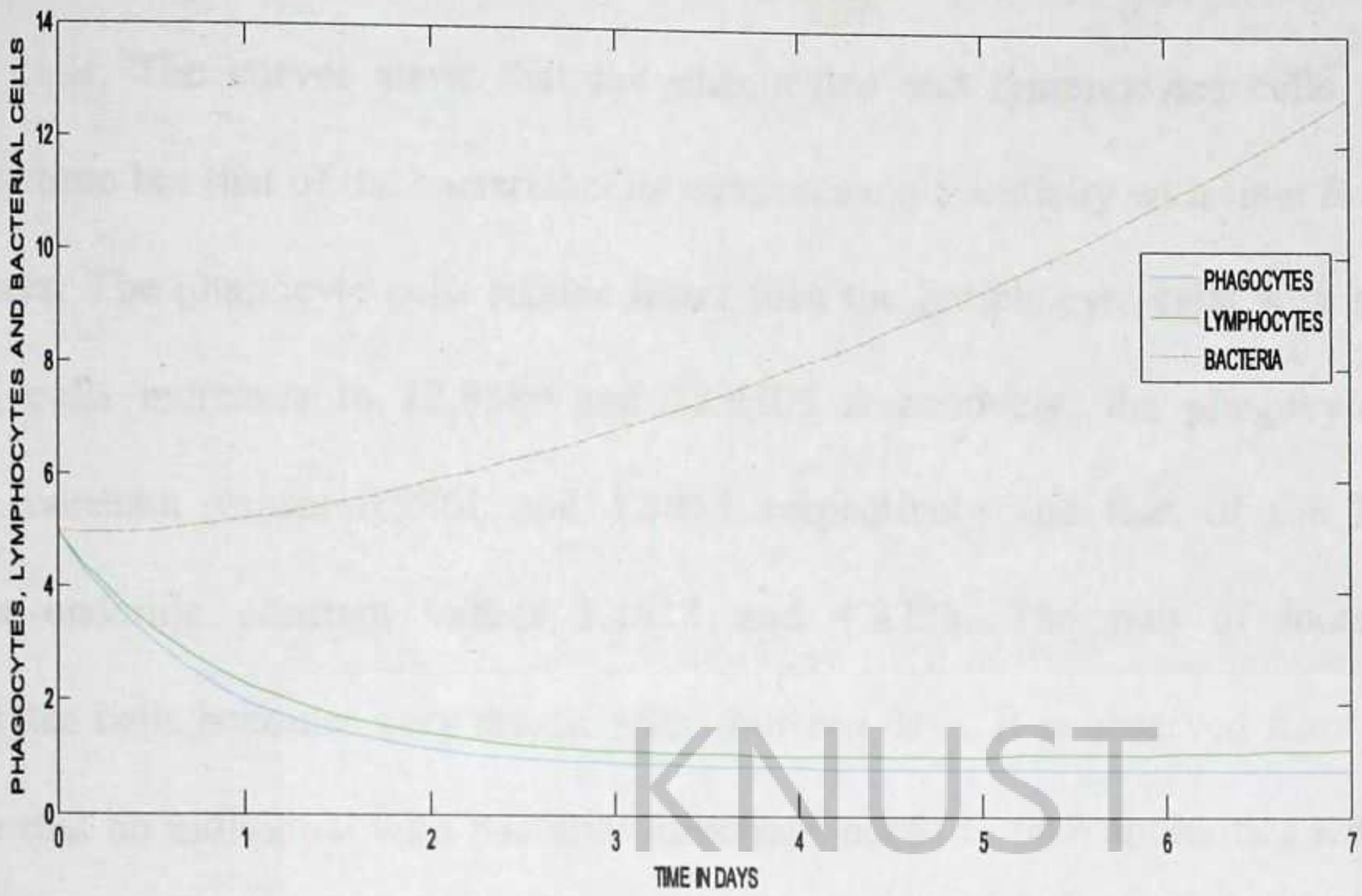


Figure 4.2a

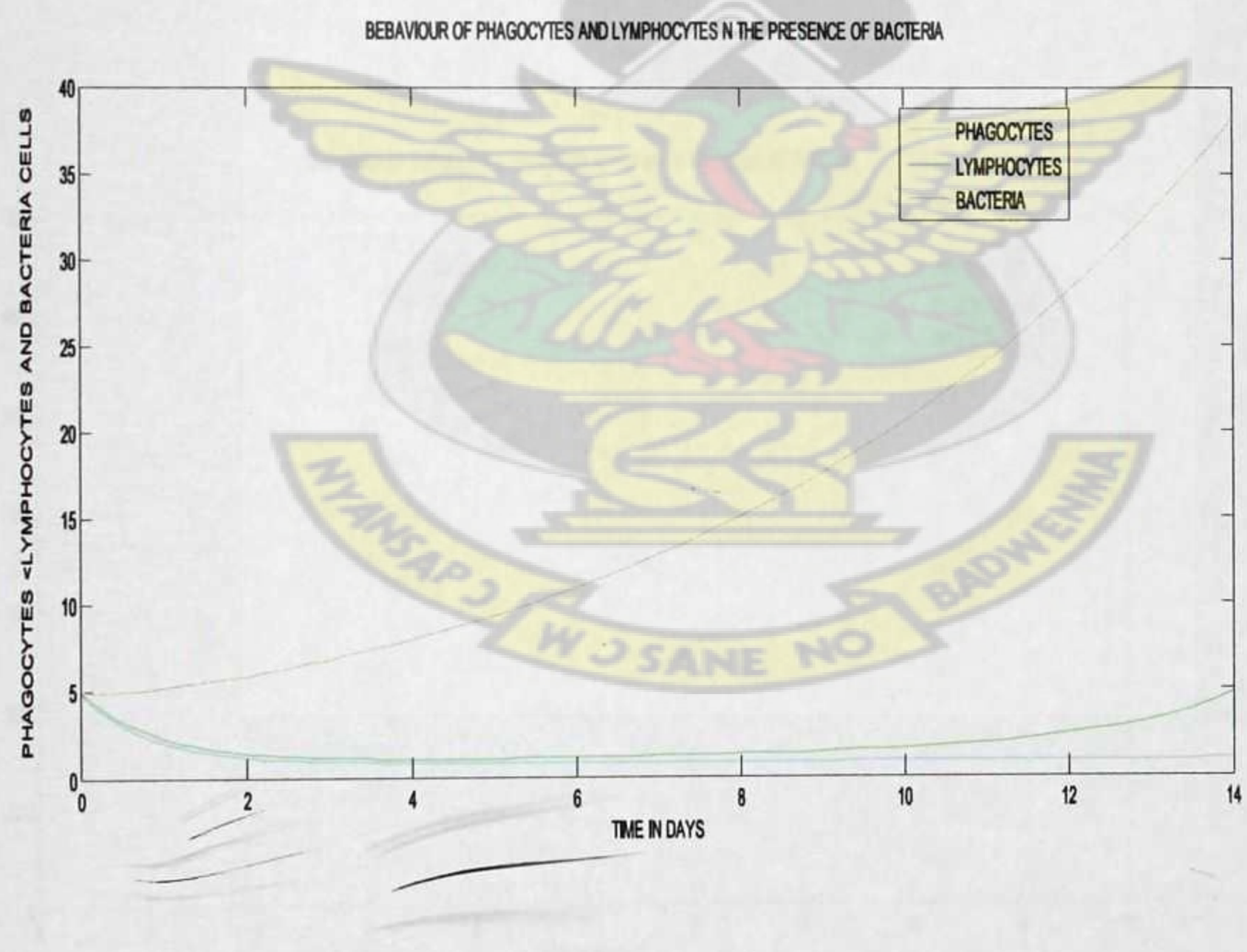


Figure 4.2b

Figures 4.2a and 4.2b shows the behavior of phagocytes and lymphocytes in the presence of bacteria for seven (7) and fourteen (14) days respectively

Figure 4.2a and 4.2b show the behaviour of phagocytes and lymphocytes in the presence of bacteria cells. The curves show that the phagocytes and lymphocytes cells reduce with respect to time but that of the bacterial cells increases exponentially with time for both 7days and 14days. The phagocyte cells reduce faster than the lymphocyte cells with time. As the bacterial cells increases to 12.8580 and 38.0505 respectively, the phagocytes approach endemic constant values 0.9861 and 1.1913 respectively and that of the lymphocytes approach endemic constant values 1.1913 and 4.8228. The rate of increase of the lymphocytes cells becomes very drastic after fourteen days. It is observed from figures 4.2a and 4.2b that an individual with bacterial infections needs to take antibiotics within the first few days to enhance the growth of lymphocytes to combat the bacterial infection in the system.

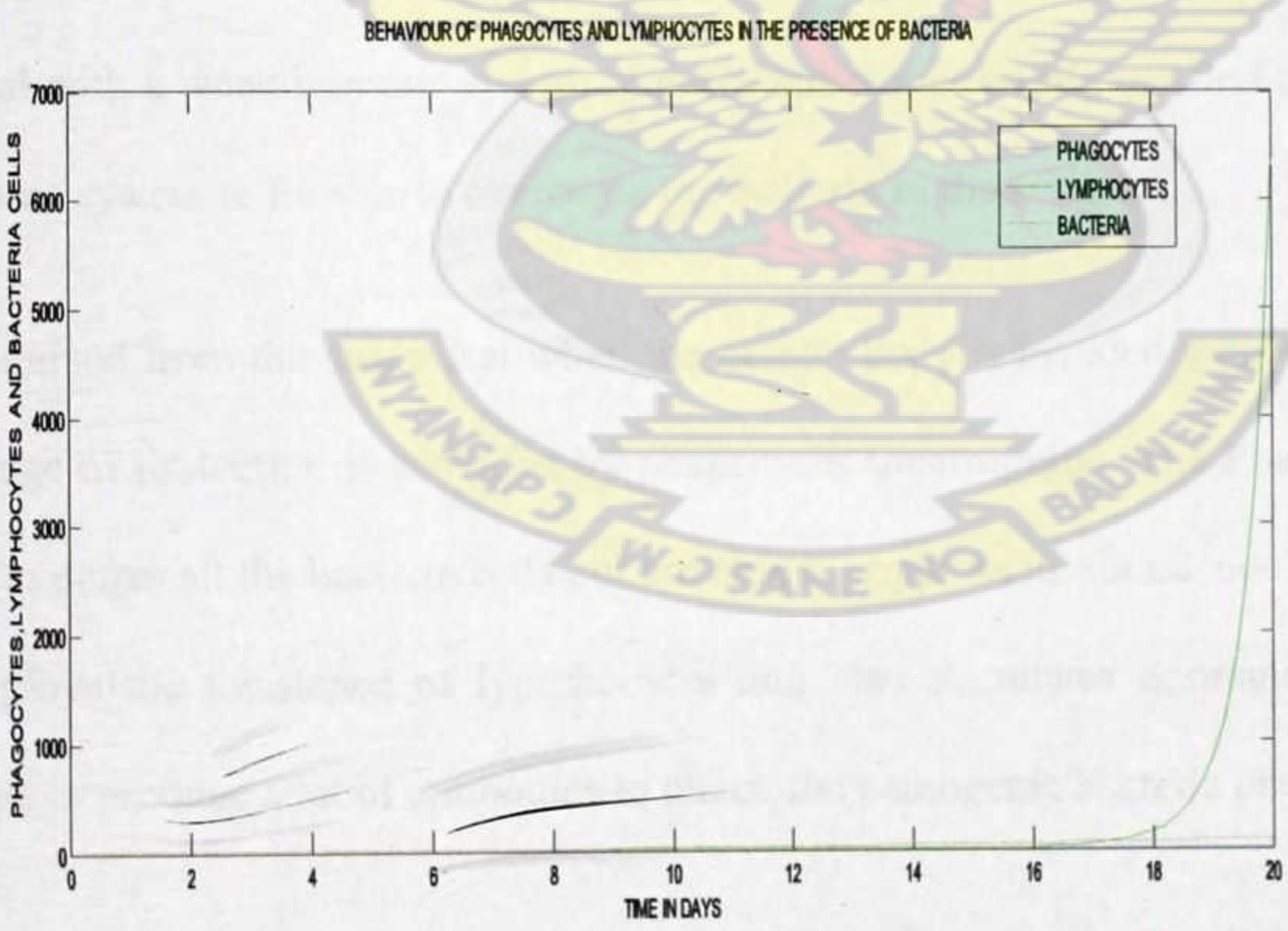


Figure 4.3

Figure 4.3 shows the behavior of phagocytes and lymphocytes in the presence of bacteria.

Figure 4.3 shows the behaviour of phagocytes and lymphocytes in the presence of bacteria cells within the first twenty (20) days. It is realized from the curve that as the lymphocytes cells increase to a certain endemic value (6000 +), both the bacteria and phagocytes cells reduce drastically and approach zero. This means that the lymphocytes cells are able to reduce the bacteria load to a very minimal number thereby attaining immunity.

4.4 DISCUSSIONS

The results of the study have confirmed the assumptions of the model. The results of the study are in conformity with Kenneth, Todar's literature on bacteriology (2012). We observed that as time increases, an infected person shows no sign of infection. A decrease of bacterial cells signify that an infected person shows no sign of infection as time increases even though such an individual may have a minimal number of bacterial cells in the system. This happens when the individual's immune system works very well. Alternatively an individual with a weak immune system requires antibiotics within the first few days to boost the immune system to be able to overcome the bacteria in the system.

We recognized from the study that when the human body is invaded with bacteria cells, the initial stage of protection is provided by phagocytes (neutrophils). The Phagocytes cells are not able to defeat all the bacteria cells but are able to suppress its abundance by ingesting it. It then employs the assistance of lymphocytes and also stimulates dormant lymphocytes to proliferate to produce a lot of antibodies to attack the pathogenic bacteria present.

Specific immunity is dependent upon two types of lymphocytes, the B cells and the T cells. B cell lymphocytes are responsible for antibody-mediated immunity (humoral immunity). They produce antibodies, which are proteins that bind with and neutralize specific antigens. Antibodies do not directly kill bacteria, but mark them for destruction. Humoral immunity

works best fighting against target bacteria that are soluble in blood and lymph before the bacteria have entered into cells (extracellular bacteria). Defending the body against intracellular pathogens is the role of T lymphocytes, which carry out cell-mediated immunity (CMI). Macrophages phagocytize invading microbes and present parts of the microbe (antigens) to the T cell lymphocytes. The appropriate T cell is turned on or stimulated. The activated T cell rapidly multiplies into a large homogenous group (clone) of cytotoxic T cells (Tc cells). T cells attack organisms directly and also kill infected cells. At this point the human body is able to attain stability to bring about immune state to this infection.

There Phagocytes cells reduce from the day of the infection. This indicates that the phagocytes (neutrophils) even at high abundance are unable to completely eliminate the bacteria from the human body within the very short time. We observe that following the suppression of bacterial population abundance to a very low level by the Phagocytes cells, it becomes very easy for the T and B cells to achieve stability and attain immunity to bacterial infection. The body achieves stability and corresponding immunity.

In the last phase of immune response, we observed that the body is able to fight against bacterial infection as time increases.

CHAPTER FIVE

CONCLUSION AND RECOMMENDATIONS

5.0 INTRODUCTION

This chapter deals with the conclusion of the study. We also present some recommendations based on the work done for further research.

5.1 CONCLUSION

By numerical simulation analysis, the cells (Phagocytes and Lymphocytes) grow at exponential rate and reach a carrying capacity as time ('t') increases. It is detected that when bacteria enter the human body, within the first seven (7) to fourteen (14) days, these phagocytes stimulate lymphocytes to proliferate to produce a lot of antibodies to attack the bacteria cells. After fourteen days the lymphocytes attack the bacteria cells to attain stability in the immune system. In the final phase of immune response, we observed that the body is able to fight against bacterial infection if these phagocytes and lymphocytes fight against the bacteria cells. Each of the models permits the existence of two types of stationary states. These are the state of no infection, with no bacteria cells while the other is the state of cohabitation where a bacteria cell persists against the background of immune response. It is found from the study that the state of no infection is asymptotically stable and a state of infection is unstable. This state of no infection represents the immune state.

It can be established that an infected person attains immunity if the bacteria cells are reduced to a very minimal number or are completely destroyed in the human body. When an infected person is not able to attain immunity it implies that bacteria cells are not minimal or are not completely destroyed, therefore the infected person requires prescription of specific

antibiotics by their doctors to boost the immune system in order to fight the bacteria cells so as to attain immunity.

5.2 RECOMMENDATIONS FOR FURTHER STUDY

In this thesis no attempt was made to model a specific bacterial infectious disease. Parameter values of any country could be replaced by estimated parameter values in Ghana or elsewhere. Further research can also be done with variations in the parameter values (Bifurcation).

We also recommend that stakeholders use this study to educate people on the need to take precautionary measures on how to keep these phagocytes and lymphocytes strong always to boost their immune system. For example, good nutrition will help to augment strong immune system.

Also they should educate the general public on the need to practice personal hygiene. For instance cooking food properly before eating, cover your mouth when coughing, keeping our surroundings clean and others.

People should desist from self-medication such the use of antibiotics. It is recommended that Antibiotics should be taken within the first few days when an individual suffers bacterial infections, since this will boost the faster rate of proliferation of lymphocytes in producing antibodies to help fight the bacterial infection.

It is also better to use probiotics which are new supplements that promote the growth of healthy and helpful bacteria.

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APPENDIX A

MATLAB PROGRAMMING FOR FINDING THE ROOTS AND EIGENVALUES

M-File to Find the Roots and Eigenvalues

```
eqn1= 1-1.2*y(1)+0.05*y(1)*y(2)/(1+0.006*y(1)*y(2));

[x,y]=solve(eqn1)

p=[7.2 ,- 256 ,1200,-1000];

r=roots(p)

A=[-1.0196,0.1804;0.1804,-1.0196];

lambda= eig(A)

B=[-0.3292,0.8708;0.8708,-0.3292];

lambda=eig(B)

C=[-0.936,0.2640;0.2640,-0.936];

lambda=eig(C)

eqn2='1-1.28*p+0.005*p*b, 1-1.28*l+0.04*l*b, 0.2*b-0.05*p*l';

[P,L,B]=solve(eqn2)

Z=[-1.273,0,0.255;0,-1.244,5.707;-6.364,-1.419,-226.820];

lambda=eig(Z)

X=[-1.274,0,0.001;0,-1.249,0.031;-0.031,-0.006,0.194];

lambda=eig(X)

Y=[-74.69,0,-73.41;0,-368.35,0.01;51.39,117462.02,-1.23];

lambda=eig(Y)

M=[1.996,0,1.256;0,0.358,0.061;-3.138,-32.132,-1.003];

lambda=eig(M)

N=[-1.342,0,2.572;0,-1.311,-6.726;-6.508,1.244,270.514];

lambda=eig(N)
```

K=[-74.649,0,-73.414;0,-368.349,-0.005;-51.390,117462.016,1.634];

lambda=eig(K)

APPENDIX B

NUMERICAL SOLUTION

M-File to Find the Numerical Solutions of the Models

```
function twograph=twograph(t,y)

twograph=zeros(2,1);

twograph(1)=twograph(2);

twograph(1)=1-1.2*y(1)+0.05*y(1)*y(2)/(1+0.006*y(1)*y(2));

%twograph(2)=1-1.2*y(2)+0.05*y(1)*y(2)/(1+0.006*y(1)*y(2));

%twograph=[twograph(1),twograph(2)];

function lap =lap(t,y)

lap(1)=1-1.28*y(1)+0.008*y(1)*y(3);

lap(2)=1-1.28*y(2)+0.04*y(2)*y(3);

lap(3) =0.20*y(3)-0.05*y(1)*y(3);


lap = [lap(1) lap(2) lap(3)]';
```

APPENDIX C

ACTUAL FIGURES OF NUMERICAL SOLUTION

t0=0;

tf=7;

y0=[5;5];

[t,y]=ode45('lap',[t0,tf],y0)

t = 0	0.0010	0.0188
0.0001	0.0012	0.0251
0.0001	0.0025	0.0313
0.0002	0.0037	0.0627
0.0002	0.0050	0.0941
0.0005	0.0062	0.1255
0.0007	0.0125	0.1569
0.2876	2.1308	5.1960
0.4183	2.3643	5.5351
0.5490	2.5979	5.8851
0.6797	2.8314	6.2351
0.8448	3.0649	6.5851
1.0100	3.3433	6.9350
1.1751	3.6218	7.2851
1.3402	3.9003	7.6351
1.5379	4.1788	7.9851
1.7355	4.5178	8.3351
1.9332	4.8569	8.6851

9.0351	11.1351	13.2675
9.3851	11.4851	13.6338
9.7351	11.8351	14.0000
10.0851	12.1851	
10.4351	12.5351	
10.7851	12.9013	

y =

0	2.0000	0.0308	2.0000	0.8213	2.0000
0.0001	2.0000	0.0606	2.0000	0.8411	2.0000
0.0001	2.0000	0.0894	2.0000	0.8564	2.0000
0.0002	2.0000	0.1173	2.0000	0.8681	2.0000
0.0002	2.0000	0.1441	2.0000	0.8771	2.0000
0.0005	2.0000	0.2466	2.0000	0.8854	2.0000
0.0007	2.0000	0.3353	2.0000	0.8915	2.0000
0.0010	2.0000	0.4121	2.0000	0.8958	2.0000
0.0012	2.0000	0.4786	2.0000	0.8990	2.0000
0.0025	2.0000	0.5501	2.0000	0.9020	2.0000
0.0037	2.0000	0.6097	2.0000	0.9040	2.0000
0.0050	2.0000	0.6593	2.0000	0.9052	2.0000
0.0062	2.0000	0.7007	2.0000	0.9061	2.0000
0.0124	2.0000	0.7414	2.0000	0.9068	2.0000
0.0186	2.0000	0.7741	2.0000	0.9073	2.0000
0.0247	2.0000	0.8003	2.0000	0.9075	2.0000

0.9077	2.0000		0.9082	2.0000	0.9082 2.0000
0.9079	2.0000		0.9082	2.0000	0.9082 2.0000
0.9080	2.0000		0.9082	2.0000	0.9082 2.0000
0.9081	2.0000		0.9082	2.0000	0.9082 2.0000
0.9081	2.0000		0.9082	2.0000	0.9082 2.0000
0.9081	2.0000		0.9082	2.0000	0.9082 2.0000
0.9082	2.0000		0.9082	2.0000	0.9082 2.0000


```
t0=0;

tf=7;

y0=[5;5;5];

[t,y]=ode45('lap',[t0,tf],y0)
```

t = 0	1.5409	3.6358
0.0483	1.7147	3.8108
0.0966	1.8884	3.9858
0.1449	2.0621	4.1608
0.1932	2.2358	4.3358
0.3649	2.4108	4.5108
0.5365	2.5858	4.6858
0.7081	2.7608	4.8608
0.8798	2.9358	5.0358
1.0451	3.1108	5.2108
1.2104	3.2858	5.3858
1.3757	3.4608	5.5608

5.7358		6.2608		6.7179	
5.9108		6.4358		6.8590	
6.0858		6.5769		7.0000	

y =

5.0000	5.0000	5.0000	0.9240	1.1460	6.7752
4.7562	4.7929	4.9894	0.9032	1.1216	6.9607
4.5265	4.5962	4.9817	0.8866	1.1025	7.1525
4.3102	4.4094	4.9767	0.8735	1.0878	7.3504
4.1064	4.2321	4.9742	0.8631	1.0769	7.5547
3.4728	3.6718	4.9834	0.8549	1.0691	7.7652
2.9610	3.2069	5.0173	0.8485	1.0640	7.9821
2.5488	2.8220	5.0719	0.8436	1.0612	8.2054
2.2159	2.5032	5.1433	0.8399	1.0604	8.4353
1.9549	2.2478	5.2255	0.8371	1.0613	8.6719
1.7424	2.0351	5.3193	0.8351	1.0637	8.9154
1.5699	1.8583	5.4236	0.8338	1.0675	9.1658
1.4296	1.7111	5.5371	0.8330	1.0724	9.4233
1.3097	1.5830	5.6651	0.8326	1.0785	9.6881
1.2132	1.4776	5.8015	0.8325	1.0855	9.9604
1.1358	1.3912	5.9458	0.8328	1.0935	10.2403
1.0735	1.3205	6.0973	0.8333	1.1024	10.5280
1.0229	1.2622	6.2569	0.8340	1.1121	10.8238
0.9823	1.2148	6.4232	0.8349	1.1227	11.1278
0.9499	1.1766	6.5960	0.8360	1.1341	11.4402
			0.8372	1.1463	11.7613

0.8382 1.1567 12.0265
0.8394 1.1677 12.2976
0.8405 1.1792 12.5748

0.8418 1.1913 12.8580

t = 0 2.7980 8.0772
0.0483 2.9853 8.4272
0.0966 3.1952 8.7772
0.1449 3.4051 9.1272
0.1932 3.6150 9.4772
0.3649 3.8249 9.8272
0.5365 4.0688 10.1772
0.7081 4.3128 10.5272
0.8798 4.5568 10.8772
1.0451 4.8008 11.2272
1.2104 5.0949 11.5772
1.3757 5.3890 11.9272
1.5409 5.6831 12.2772
1.7147 5.9772 12.6272
1.8884 6.3272 12.9772
2.0621 6.6772 13.2329
2.2358 7.0272 13.4886
2.4232 7.3772 13.7443
2.6106 7.7272 14.0000

2.9610 3.2069 5.0173

2.5488 2.8220 5.0719

2.2159 2.5032 5.1433

y =

1.9549 2.2478 5.2255

1.7424 2.0351 5.3193

5.0000 5.0000 5.0000

1.5699 1.8583 5.4236

4.7562 4.7929 4.9894

1.4296 1.7111 5.5371

4.5265 4.5962 4.9817

1.3097 1.5830 5.6651

4.3102 4.4094 4.9767

1.2132 1.4776 5.8015

4.1064 4.2321 4.9742

1.1358 1.3912 5.9458

3.4728 3.6718 4.9834

1.0735 1.3205 6.0973

1.0197 1.2585 6.2684

0.9772 1.2089 6.4472

0.9439 1.1695 6.6335

0.9177 1.1385 6.8271

0.8947 1.1117 7.0524

0.8773 1.0920 7.2867

0.8642 1.0780 7.5300

0.8544 1.0686 7.7823

0.8460 1.0624 8.0872

0.8403 1.0604 8.4047

0.8365 1.0618 8.7352

0.8343 1.0661 9.0791

0.8328 1.0743 9.5118

0.8325 1.0856 9.9653

0.8331 1.0996 10.4405

0.8344 1.1161 10.9381

0.8364 1.1386 11.5609

0.8390 1.1644 12.2188

0.8421 1.1937 12.9134

0.8455 1.2266 13.6467

0.8492 1.2635 14.4208

0.8532 1.3049 15.2378

0.8575 1.3513 16.0999

0.8622 1.4035 17.0094

0.8671 1.4625 17.9687

0.8725 1.5294 18.9805

0.8782 1.6055 20.0473

0.8842 1.6927 21.1719

0.8907 1.7932 22.3571

0.8977 1.9096 23.6059

0.9051 2.0456 24.9213

0.9130 2.2059 26.3065

0.9215 2.3964 27.7646

0.9306 2.6248 29.2991

0.9404 2.9018 30.9133

0.9509 3.2420 32.6107

0.9590 3.5416 33.9053

0.9675 3.8953 35.2475

0.9766 4.3165 36.6388

0.9861 4.8228 38.0805

```
t0=0;
tf=20;
y0=[5;5;5];
[t,y]=ode45('lap',[t0,tf],y)
```

t = 0

0.0483

0.0966

0.1449

0.1932

0.3649

0.5365

0.7081

0.8798	5.3890	15.3836
1.0451	5.6831	15.7216
1.2104	5.9772	16.0596
1.3757	6.3457	16.3975
1.5409	6.7141	16.7355
1.7147	7.0826	16.9925
1.8884	7.4511	17.2495
2.0621	7.9342	17.5065
2.2358	8.4173	17.7635
2.4232	8.9005	17.9688
2.6106	9.3836	18.1741
2.7980	9.8836	18.3793
2.9853	10.3836	18.5846
3.1952	10.8836	18.7899
3.4051	11.3836	18.9952
3.6150	11.8836	19.2005
3.8249	12.3836	19.4058
4.0688	12.8836	19.5543
4.3128	13.3836	19.7029
4.5568	13.8836	19.8514
4.8008	14.3836	20.0000
5.0949	14.8836	

y =

1.0e+003 *

0.0050	0.0050	0.0050	0.0009	0.0011	0.0071
0.0048	0.0048	0.0050	0.0009	0.0011	0.0073
0.0045	0.0046	0.0050	0.0009	0.0011	0.0075
0.0043	0.0044	0.0050	0.0009	0.0011	0.0078
0.0041	0.0042	0.0050	0.0008	0.0011	0.0081
0.0035	0.0037	0.0050	0.0008	0.0011	0.0084
0.0030	0.0032	0.0050	0.0008	0.0011	0.0087
0.0025	0.0028	0.0051	0.0008	0.0011	0.0091
0.0022	0.0025	0.0051	0.0008	0.0011	0.0095
0.0020	0.0022	0.0052	0.0008	0.0011	0.0100
0.0017	0.0020	0.0053	0.0008	0.0011	0.0104
0.0016	0.0019	0.0054	0.0008	0.0011	0.0109
0.0014	0.0017	0.0055	0.0008	0.0011	0.0116
0.0013	0.0016	0.0057	0.0008	0.0012	0.0123
0.0012	0.0015	0.0058	0.0008	0.0012	0.0130
0.0011	0.0014	0.0059	0.0008	0.0012	0.0138
0.0011	0.0013	0.0061	0.0009	0.0013	0.0149
0.0010	0.0013	0.0063	0.0009	0.0013	0.0161
0.0010	0.0012	0.0064	0.0009	0.0014	0.0173
0.0009	0.0012	0.0066	0.0009	0.0015	0.0187
0.0009	0.0011	0.0068	0.0009	0.0016	0.0202
			0.0009	0.0018	0.0219
			0.0009	0.0019	0.0236

0.0009	0.0021	0.0255
0.0009	0.0024	0.0276
0.0009	0.0027	0.0298
0.0009	0.0031	0.0321
0.0010	0.0037	0.0347
0.0010	0.0046	0.0374
0.0010	0.0058	0.0403
0.0010	0.0076	0.0435
0.0010	0.0105	0.0468
0.0011	0.0134	0.0492
0.0011	0.0176	0.0517
0.0011	0.0237	0.0543
0.0011	0.0330	0.0570
0.0011	0.0436	0.0591
0.0012	0.0585	0.0613
0.0012	0.0802	0.0636
0.0012	0.1127	0.0659
0.0012	0.1505	0.0678
0.0012	0.2037	0.0698
0.0013	0.2802	0.0718
0.0013	0.3921	0.0738
0.0013	0.5589	0.0759
0.0013	0.8069	0.0780
0.0014	1.1866	0.0802
0.0014	1.7802	0.0823
0.0014	2.4144	0.0839
0.0014	3.3012	0.0856
0.0015	4.5588	0.0872
0.0015	6.3626	0.0889