UNIVERSITY OF CAPE COAST

MATHEMATICAL MODELLING OF TYPHOID FEVER DISEASE INCORPORATING DELAY CAUSED BY FALSE NEGATIVE DIAGNOSIS

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BY

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Thesis submitted to the Department of Mathematics of the School of Physical Sciences, College of Agriculture and Natural Sciences, University of Cape Coast, in partial fulfilment of the requirements for the award of Master of Philosophy degree in Mathematics

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DECLARATION

Candidate's Declaration

I hereby declare that this thesis is the result of my own original research and that no part of it has been presented for another degree in this university or elsewhere.

Candidate's Signature ..... Date .....

Name: Felix Fiadufe

Supervisor's Declaration

I hereby declare that the preparation and presentation of the thesis were supervised in accordance with the guidelines on supervision of thesis laid down by the University of Cape Coast.

Supervisor's Signature ..... Date .....

Name: Dr. Samuel Mindakifoe Naandam

ABSTRACT

We developed a mathematical model based on a system of ordinary differential equations to explore the dynamics of typhoid fever sickness, taking into account the delay caused by false negative diagnosis. Typhoid fever continues to be a significant public health problem in a number of countries, particularly developing countries. Typhoid fever, for example, has been classified among the top twenty illnesses in Ghana, accounting for approximately 0.92 percent of hospital admissions. An epidemiological model was developed to determine the impact of delay caused by false negative diagnosis in the spread and treatment dynamics of the disease. Protected (P), Susceptible (S), Infected (I), Delayed (D), and Treated (T) classes were established. The next generation technique was used to calculate the basic reproduction number R_0. Additionally, it was demonstrated that for $R_0 < 1$, the disease-free equilibrium points were both locally and globally asymptotically stable, whereas the endemic equilibrium points were locally asymptotically stable. Having done numerical simulations, it was found that the delay caused by false negative diagnosis significantly contributes to the spread dynamics and also has an effect on treatment. As a result, we determined that delays caused by false negative diagnoses should be kept to a minimum in order to minimize disease spread.

KEY WORDS

Basic reproduction number

Disease-free

False negative

False positive

Simulation

Sensitivity analysis

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DEDICATION

To my father, Daniel Korsi Fiadufe, my mother, Dora Deku(deceased) and my uncle, Prof. Prosper Yao Deku(deceased)

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LIST OF ABBREVIATIONS

DFE – Disease Free Equilibrium

EEP – Endemic Equilibrium Point

EE – Endemic Equilibrium

GAS – Globally Asymptotically Stable

LAS – Locally Asymptotically Stable

OPD – Out Patients Department

PSIDT – Protected, Susceptible, Infected, Delayed, Treated

PSIT – Protected, Susceptible, Infected and Treated

QECH – Queen Elizabeth Central Hospital

RDT – Rapid Diagnostic Test

SIR – Susceptible Infected Recovered

SEIR – Susceptible, Exposed, Infected and Recovered

CHAPTER ONE

INTRODUCTION

Typhoid fever disease is a potentially fatal multisystemic illness whose causative agent is a bacterium known scientifically as salmonella typhi. It belongs to the family Enterobacteriaceae. Members of this family are salmonella paratyphi A, salmonella paratyphi B, salmonella choleraesurs and salmonella typhi. The causative agent of typhoid fever is Salmonella typhi and it is associated with the ability of the organism to multiply within mono-nuclear phagocytes (Adetunde, 2008).

A proper treatment of typhoid fever yields a higher cure rate but if left untreated, typhoid fever may progress to delirium which lead to a sudden alteration in the brain that results in mental bewilderment and emotional distress, intestinal obstruction, intestinal hemorrhage, bowel perforation and even death within a month.

Background to the Study

Typhoid fever is a contagious infection that is endemic in many parts of the world. Salmonella typhi is the bacteria that causes it (Khan et al., 2015). Typically, the organism is transferred via contaminated food and water contaminated with feces or urine from an infected person or host. Once swallowed, the organism is taken through the cells to the intestinal lymph nodes, where it is then transferred to the bloodstream. After that, they are distributed to the liver, spleen, and bone marrow. The bacterium then multiplies in the organs' cells and re-enters the bladder and bowel's lymphatic tissue, where it multiplies rapidly. Typhoid fever has an incubation period of eight to fourteen days and the duration of the illness is about four to six weeks, according to Adetunde (2008).

In low- and middle-income nations, the disease is endemic. It is particularly prevalent in the Asian and African continents due to insufficient hygienic systems, i.e. a lack of proper sanitation facilities and safe drinking water in

homes.

Each year, it affects millions of individuals globally, with over 20 million cases reported and roughly 200,000 deaths. For example, it is estimated that 400,000 cases occur annually in Africa, with a prevalence of 50 per 100,000 (Nthiiri, *et al.* 2016).

Ghana's situation is not dissimilar to that of other endemic countries. Typhoid fever has consistently ranked among the top twenty Out Patients Department (OPD) infections in recent years, accounting for 0.92 percent of hospital admissions (Saleh, 2012).

Another study conducted by Fusheini and Gyawu (2020) in the Hohoe municipality in Ghana's Volta Region discovered that typhoid fever was among the top twenty causes of outpatient morbidity in 2015, 2016, and 2017. It accounted for 1.3 percent, 1.7 percent, and 1.2 percent of all hospital cases admissions, respectively.

Typhoid fever is so named due to the fact that its signs and symptoms are similar to those of typhus. Mild to severe fever, abdominal signs, constipation, and headache, lack of appetite, nausea, vomiting, and the appearance of rashes on the belly, sweating, coughing, weakness, dizziness, and muscle pain are all symptoms of infection of typhoid fever. As the fever and abdominal pain become more severe, diarrhea develops (Adetunde, 2008).

Other evaluations show the possibility of problems such as disseminated intravascular coagulation, pneumonia, rheumatoid arthritis, altered mental status, hepatitis, and meningitis.

Due to the perplexing nature of these diseases' symptom manifestations, rigorous procedures are required to identify each disease based on other peculiar symptoms. Combinations of abdominal pain, chills, weariness, and loss of appetite, in addition to headache and possibly fever, are significant indicators of typhoid infection, albeit a number of these symptoms may manifest more prominently in the later stages of illness (Buzğan et al., 2007). Numerous researchers

have discovered that typhoid's primary symptoms include a fever lasting more than 48 hours, followed by an intense headache in approximately 43-90 percent of cases, and then gastrointestinal symptoms such as abdominal pain or cramps, nausea and vomiting, constipation or diarrhoea.

As noted in LaSalle (1976), modeling the transmission dynamics of typhoid disease is an integral and intriguing problem for a large number of computational mathematical scholars.

Statement of the Problem

Typhoid Fever and Malaria are two of the most endemic diseases in the world's poorer countries, posing serious public health challenges in these areas.Additionally, real similarity in the symptoms between Typhoid and malaria is responsible for the incorrect diagnoses due to the similar symptoms and signs leading to false positive results in testing methods, resulting in insufficient controls, are significant obstacles in managing both diseases (Mutua et al., 2015).

Typhoid fever and malaria have many of the same signs and symptoms, including fever, vomiting, headache, and diarrhoea. Due to the similarity of the symptoms, clinicians associate them with the incorrect disease, resulting in a false negative diagnosis. According to Afoakwah et al. (2011), methods of testing, involving the most widely used Widal test, consequently provide false positive results. For instance, in a study by Ekesiobi et al. (2008), the Widal test detected approximately 57% of typhoid positive cases when a more accurate bacteria-culture tests were undertaken. While the bacteria-culture test is more precise, it is less frequently utilized due to its higher cost and longer processing time.

Such erroneous diagnoses result in the mismanagement of numerous typhoid cases, creating a slew of complications in controlling the disease. That is, prescribing malaria medication to someone who genuinely has typhoid fever

may not only aggravate the person's health condition, but may also result in the emergence of future drug resistance. According to WHO (2003), the case mortality rate for typhoid fever is predicted to be 10 – 30 percent without prompt treatment and 1 – 4 percent with adequate management and treatment.

Against this backdrop, this thesis will use mathematical modeling to investigate the influence of false negative diagnosis on the spread and treatment of typhoid fever disease.

Purpose of the Study

The purpose of this study is to inform the local and the global scientific community of the impact false negative and false positive diagnoses have on the spread and treatment of typhoid fever. This research would help the decision makers and health practitioners to put the right measures in place to check, reduce and prevent to the barest minimum the false negative diagnosis by procuring test kits or machines with high percentage of specificity and sensitivity.

Research Objectives

General objectives

The general objective of this thesis is to develop a model similar to an SIR model, incorporating delay caused by false negatives diagnosis of Typhoid fever.

Specific objectives

1. determine the equilibrium points at the disease free and endemic states of the model.
2. determine the basic reproductive number, R_o.
3. perform the stability analysis of the equilibria for both local and global.

4. determine which parameters influence the model dynamics most.

5. perform numerical simulations of the model.

Significance of the Study

Invasive Salmonella infections collectively account for a considerable burden of morbidity and mortality worldwide. Typhoid fever causes an estimated 11–21 million cases and approximately 128000–161000 deaths per year, compared to paratyphoid fever, which causes an estimated 6 million cases and 54000 deaths per year. The majority of instances occur in South and Southeast Asia, as well as Sub – Saharan Africa, according to (WHO, 2007).

Mathematical modeling can assist us in gaining a better knowledge of illness transmission patterns, evaluating the efficacy of various preventive measures and tactics, and ultimately determining how to control it. There exist mathematical models for typhoid fever, but little work has been done on mathematical models for typhoid fever that account for the effect of false negative diagnosis. Thus, by incorporating delay caused by false negative diagnosis into a mathematical model, the worldwide and scientific communities would be informed to build testing systems that minimize false negative diagnosis.

Additionally, this effort would aid our health practitioners and decision makers in evaluating the efficacy of interventions and tactics that can be used in combating the disease.

Delimitations

This research is limited to finding the delay caused by false negative diagnosis of typhoid fever and its impact on spread and treatment. It did not explore all about typhoid fever.

Limitations

The Protected, Susceptible, Infected, Delayed and Treated ($PSIDT$) mathematical model under consideration which incorporates delay caused by false negative diagnosis is a necessary but not sufficient method that can be used to prevent the spread or eradicate the typhoid fever disease. This is because some of the model parameters were assumed whiles other parameters were obtained from literature. The results as presented may not provide the true reflection of what is on the ground in certain jurisdictions.

Definition of Terms

Basic reproduction number (R_0):

It is the average number of secondary cases caused by an infected individual during his/her infectivity period when he/she is introduced to a population of susceptible individuals without any intervention

False negative diagnosis:

It is the erroneous labeling of an infected person of typhoid fever as not having the infection or the condition.

False positive diagnosis:

A false positive diagnosis on the other hand labels an uninfected person as infected with typhoid fever.

Sensitivity:

It signifies the probability of positive test results that are truly positive.

Specificity:

Signifies the probability of correctly diagnosed negative results that are truly negative.

Organization of the Study

This thesis is composed into five chapters. The first chapter introduces typhoid fever and its transmission dynamics. It stated the background of the study, the statement of the problem, the purpose of the problem, the research objectives, the delimitation, limitations and definition of some terms. Chapter Two provided the related literature reviews on the mathematical models on typhoid fever dynamics.

Chapter Three provided the compartmental diagram for typhoid fever which incorporated delay. In this chapter, we also checked the positivity and boundedness of the model solutions. This was followed by the study states, that is, the disease-free and the endemic equilibrium. We also established the local and the global stability in Chapter Three.

The numerical simulations and the sensitivity analysis was discussed in Chapter Four.

The thesis was concluded in Chapter Five with relevant recommendations.

CHAPTER TWO

LITERATURE REVIEW

Introduction

This chapter of the study is concerned with the review of some related relevant literature of our study. It is the part of the study that establishes critically the research work in context of other scholars' stand on typhoid fever, its diagnosis, test procedures and the impact on spread and treatment. Typhoid fever infection is an endemic disease in many parts of the world including Africa and for that matter Ghana. It has become urgent to check its spreading dynamics in the world as a whole. To do this effectively, there is the need to take a look at the models other researchers used and how we can modify them to help eradicate the typhoid fever. Based on review of literature, we have noticed that many researchers, academia and policy makers have used mathematical models to check the behaviour, consequences and effects of typhoid fever infection in the human population over a given period of time with the basic idea of coming out with various interventions, measures and control strategies for this deadly disease. Hence, in this chapter we focus mainly on the review of empirical related literatures on typhoid fever infection with emphasis on false negative diagnosis and its impact on spread and treatment.

Brief History of Infectious Diseases

This section goes over the history of utilizing a mathematical model as a tool for investigating and controlling infectious diseases. If a disease's causal agent, such as a virus, bacterium, protozoa, or toxin, can be transmitted from one host to another by multiple mechanisms of transmission, it is said to be infectious. Physical contact, airborne, water, food, disease vectors, and carrier mother to newborn babies are all means of transmission. (Ma, 2009).

Infectious illness outbreaks have always been a source of concern in the communities where they occur, posing a threat to public health and decision-making bodies. This is because infectious illnesses have wreaked havoc on human cultures over the world, causing major health issues, as well as economic and social woes. For example, the Antonine plague, which lasted from early 165 to early 180 AD, was an ancient pandemic that was carried to the Roman Empire by troops returning from operations in the Near East, possibly via smallpox or measles. These deadly diseases infected the whole Roman Empire, killing two Romans and wreaking havoc on the Roman economy (Ma, 2009).

Smallpox was also spread by Spanish armies commanded by Cortez in areas such as the Caribbean, Mexico, Peru, and Brazil. According to Brauer and Castillo-Chávez (2001), this has reduced the Mexican population from around thirty (30) million to fewer than two (2) million within a 50-year period.

The outbreak of corona virus disease in Wuhan, China in 2019 has once again triggered a global pandemic, claiming millions of lives around the world. The fight against these infectious diseases has a lengthy history, and significant progress has been accomplished. This is because the smallpox outbreak has been eradicated thanks to a worldwide vaccination effort (Ma, 2009).

Furthermore, leprosy has been successfully eradicated as a public health hazard since a World Health Assembly resolution was passed in 1991 (Ma, 2009).

Despite significant progress in the prevention and control of infectious illnesses, much more work need to be done to totally eradicate these diseases worldwide. To effectively prevent and manage infectious diseases, it is necessary to first understand the transmission mechanisms and dynamics of their spread, and then to give pragmatic interventions based on mathematical models.

Mathematical Model

Modelling is derived from the Latin term *modellus*, which means human technique of dealing with reality. According to Andrews and McLone (1976), mathematical modeling is the portrayal of real-world problems in mathematical words and techniques in order to gain a better understanding, significance, and attributes of the problems. As a result, mathematical models are built around population dynamics, illness transmission behavior, infectious agent characteristics, and links to other socioeconomic and physiological aspects. Mathematical models provide a clear understanding of how infectious diseases spread from one host to another, discover the factors governing disease transmission dynamics, identify the most significant and sensitive parameters, make reliable predictions, and provide useful prevention and control strategies through the use of analysis such as quantitative, qualitative, sensitivity, and numerical simulations.

Mathematical modeling of infectious diseases dates back to the early 1760s, when Bernoulli utilized mathematical models to examine the smallpox sickness (Bernoulli, 1760). In the twentieth century, researchers studied infectious diseases using deterministic mathematical models. A notable example is a discrete time model developed by Hamer in 1906 to investigate the spread of measles (Hamer, 1906), as cited in (Anderson and May, 1992).

Dr. Ross later proposed a differential equation model in 1910 to analyze the transmission patterns of malaria between humans and mosquitoes. In his model, Dr. Ross was able to set a population size threshold for mosquitos below which malaria spread can be controlled. His second Nobel Prize in medicine was given to him as a result of this (Ross, 1911).

Furthermore, Kermack and McKendrick (1932) developed an SIR (susceptible, infective, recovered) deterministic model to analyze the Black Death epidemic in London between 1665 and 1666, as well as the plague outbreak in Mumbai in 1906. Later, in 1932, they developed the SIS compartmental model

(susceptible, infective, susceptible). The examination and analysis of these two models formally introduced the concept of threshold quantities in mathematical modeling, which govern whether a disease spreads or dies out in a particular population (Kermack & McKendrick,1932). The theory of epidemic dynamics is built on the foundation of ideal thresholds.

After the mid-twentieth century, more intensive studies on epidemic dynamics began, and as a result, several developments and advances in mathematical models to study various infectious diseases such as typhoid fever, malaria, human cancer disease, tuberculosis, cholera, and so on have been made, particularly in the last 20 years.

According to Lindsay et al. (2019), the Coalition Against Typhoid Fever thinks that early detection of typhoid is vital to ensure that sick people get the care they need. They believe that due to the nature of the disease and the limitations of contemporary diagnostic technology, diagnosing typhoid fever offers significant challenges. The symptoms of typhoid are similar to those of a number of other diseases, such as malaria, pneumonia, influenza, and other viral infections. This leads to a high rate of misdiagnosis, emphasizing the urgent need for more precise and rapid diagnostic approaches. The capacity of current typhoid diagnostics to identify the causative bacterium, Salmonella enterica serovar Typhi (Salmonella Typhi), as well as their usefulness in resource-limited and overworked conditions, particularly in third-world nations, are limited.

According to WHO(2003), a conclusive diagnosis of typhoid involves isolation of the Salmonella Typhi bacteria via blood or bone marrow culture. Both of these procedures are regarded as the best practices and standards for diagnosing typhoid fever, albeit both have significant practical limits.

According to Lindsay*et al.* (2019), in the coalition's literature, blood culture is an expensive procedure that requires specialist workers and laboratory facilities. Blood culture facilities are rare in many low-resource countries, and are typically limited to larger hospital facilities in major cities. Because of the

low bacteria numbers in the blood during illness, only around 40% to 60% of typhoid cases are correctly identified when blood cultures are possible. Although testing is most effective in the early stages of sickness, the incubation period indicates that the maximum levels of bacteria in the blood are most likely present before clinical symptoms appear. Blood culture accuracy is also affected by the patient's prior antibiotic treatment and the volume of blood obtained for the sample. Additionally, reports are not available for so many days after blood is obtained, limiting the test's utility in clinical situations where a healthcare provider needs to make a quick treatment decision.

According to the coalition's research as expressed in (Linsay *et al.* 2019), while bone marrow culture is more accurate than blood culture, it is an expensive and technically demanding technique. In low- and middle-income countries, this is not a frequent practice.

Due to these constraints, most low-resource settings diagnose typhoid by clinical criteria, which is highly uncertain given the non-specificity of typhoid symptoms. Additional procedures, such as urine or stool culture, are less time consuming and less expensive to perform but do not provide trustworthy results. Although the Widal test, established in the late 1800s, is straightforward and affordable, it should not be used for diagnosis alone due to cross-reactivity with other pathogenic agents. Additionally, The Coalition Against Typhoid Fever stated in 2018 that numerous diagnostics aimed at overcoming the limitations of current procedures by being cost effective and providing rapid and accurate results are currently in development. Three previously approved serological-based quick diagnostic tests i.e Typhidot, TUBEX, and TEST-It typhoid (KIT) have demonstrated encouraging preliminary findings. However, their specificity and sensitivity are not 100%.

Our model is heavily influenced by the work of (Nthiiri et al., 2016). They developed the $PSIT$ model, which stands for Protected class(P), Susceptible class(S), Infected class(I), and Treated class(T). Their work included typhoid

fever prevention, demonstrating that with effective protection, the infection rate of typhoid fever in the population reduces with time. Additionally, with a poor protection rate, infection becomes prevalent in the community.

Nthiiri *et al.* (2016) investigated the worldwide stability of the typhoid fever equilibrium point, which informed their conclusion that disease transmission may be kept to a bare minimum or managed with protection. However, we believe that reducing false negatives would result in a significant reduction in the rate of typhoid fever infection.

Additionally, (Nthiiri *et al.*2016) based their findings on the assumption that once the typhoid sickness is treated, it cannot be contracted again.

Motivated also by the work of (Nthiiri *et al.*,2016), Karunditu et al. (2019) constructed an $SEIR$ model that included unprotected humans in the spread dynamics of typhoid illness, a feature that they felt was overlooked by (Nthiiri *et al.*,2016).

Their global equilibrium point for global stability was determined utilizing the (Castillo-Chavez et al., 2002) technique, which satisfied their model's global stability criteria. They discovered that unprotected humans had a significant impact on the disease's spread dynamics. Additionally, they determined that if typhoid is to be entirely eradicated from the community, unprotected persons should be viewed among other protective factors.

Their stance strengthened our argument that unprotected populations may also be falsely diagnosed, hence accelerating exponentially the infection dynamics.

Additionally, Wijedoru et al. (2017) recommends growing Salmonella from a person's blood to determine if they have typhoid fever. It does not provide a result for at least 48 hours, and hence cannot assist healthcare practitioners in making a diagnosis the same day a blood sample is obtained.

Although a person may have typhoid fever, a blood sensitivity test may return negative (Wijedoru *et al.* 2017). Additionally, the test requires a labo-

ratory and skilled personnel, which are frequently unavailable in areas where typhoid disease is prevalent. They contended that rapid diagnostic tests (RDTs) are intended to be simple to use and to provide a rapid result without requiring a blood culture laboratory test. A typhoid fever rapid diagnostic test would be substantially less expensive than a blood sensitivity test or blood culture, and would require significantly less training to execute. However, because RDTs generate a high proportion of false negatives and positives, they cannot be relied upon exclusively.

$Sensitivity$ relates to the proportion of patients with a positive test result who are correctly identified with the disease, according to (Wijedoru *et al.* 2017). The fraction of patients who are correctly diagnosed as not having the condition is referred to as $specificity$. TUBEX, an RDT, had a sensitivity of 78 percent and a specificity of 87 percent on average. Typhidot investigations, which included Typhidot, TyphiRapid-Tr02, and Typhidot-M, had an overall sensitivity of 84% and specificity of 79%. When trials with unambiguous reporting of questionable data were included, Typhidot's average sensitivity and specificity were 78 percent and 77 percent, respectively, according to the article. Typhoid Test-It and prototypes (KIT) exhibited a sensitivity of 69% and a specificity of 90% on average. Based on these findings, (Wijedoru *et al.* 2017) claim that in 1000 patients with the infectious diseases, where 30%, that is, 300 patients have typhoid fever, Typhidot tests reporting indeterminate results or tests that do not produce indeterminate results would give an overall score of 66 false negative results, that is, miss the diagnosis in 66 patients with typhoid fever, and TUBEX would give 66 false negatives The average number of people who received an incorrect diagnoses of typhoid fever, that is, a false positive result among the 700 people who did not have typhoid fever would be 161, 91 when using TUBEX, and 70 when using the Test-It Typhoid and prototypes (KIT). There are no statistically significant differences in the proportion of patients who receive false negative and false positive findings from various testing. In

the diagnosis of typhoid fever, the RDTs examined are inadequately accurate to serve as a substitute for blood culture.

Existing diagnostic tests for typhoid fever, according to Mather, Hopkins, and Parry (2019), are insufficiently sensitive and specific to be used reliably at the point-of-care (POC), leading in antibiotic abuse through empiric treatment. They suggested that in order to address the needs of consumers in endemic areas, an improved typhoid diagnostic test must be capable of detecting both S. Paratyphi and S. Typhi, have a sensitivity of at least 90%, a specificity of at least 95%, and a low end user cost.

To make a significant difference in the overusage of antibiotics that has contributed to the emergence of antibiotic resistance in S. Typhi and other bacteria, Mather et al. (2019) suggested that an improved Typhoid POC testing should be done in collaboration with diagnostics for malaria and other acute feverish illnesses as part of a therapy protocol. However, they were unable to build any model to address antibiotic usage as a result of incorrect negative or positive diagnosis.

Edward (2017) established a deterministic compartmental mathematical model for evaluating the effect of education campaigns, vaccination, and treatment on typhoid disease transmission dynamics in the community in their work. The disease-free equilibrium has been calculated and shown to be locally asymptotically stable for $R_e < 1$ and globally asymptotically stable for $R_e > 1$.

Additionally, the effective reproduction number, R_e, was determined and used to examine various management tactics. Their findings indicate that various elements contribute to the management of typhoid dynamics. They believe that unless concerted measures are made, it will be extremely impossible to eradicate or even contain typhoid fever disease. They urged that many sectors, including education, sanitation, and water supply agencies, as well as the health sector, collaborate to contain typhoid outbreaks in the various communities.

It must be stressed that while both direct and indirect education are key

components of typhoid fever control, direct education has a higher and longer-lasting impact on disease management. However, (Edward, 2017) did not stress typhoid fever screening and diagnosis as a means of eradicating the disease in their work.

Additionally, utilizing nonlinear ordinary diffential equations, Aji et al. (2019) built a model for the transmission of typhoid illness. The developed model is a modification of (Mushanyu et al., 2018) prior typhoid fever model.

In comparison to their typhoid fever model, the model we propose takes into account the fact that the population receiving treatment may also exhibit the impact of false negative diagnosis restrictions. After developing their model, they discovered an asymptotically stable disease-free equilibrium point where $R_0 < 1$. Additionally, the model's basic reproduction number was calculated. They discovered that even with $R_0 < 1$, typhoid was still a possibility in the population.

Their numerical simulation suggests that any treatment implementation should take into account the quality of public health resources, such as the availability of in-patient rooms, the number of physicians, and the quality of hospital instruments and services that can minimize false negative diagnoses.

Garba et al. (2020) also developed a simple mathematical model of typhoid fever transmission dynamics with vaccination that included protection against infection. As can be seen, their work was also influenced by the work of (Nthiiri *et at.*, 2016), which included protection against typhoid fever infection. They determined the R_0 by employing a the next generation matrix technique, which also yielded the model's DFE and EEP. The stability of the disease-free population demonstrates that when we strengthen protection, we can significantly reduce disease prevalence in the population.

While it is true that enhanced protection may result in a low prevalence rate, this is not a certainty. Not everyone who is vaccinated is protected against typhoid fever illness. As a result, people who do not receive protection may later

contract the disease and may be misdiagnosed, and thus there should be safeguards in place to account for such circumstances, which is why we conducted our research.

Again, a publication by Pitzer et al. (2015) indicates that true diagnoses of Salmonella Typhi accounted for 2% of typhoid isolates detected by sentinel surveillance at Queen Elizabeth Central Hospital (QECH) Blantyre, Malawi's largest hospital, between 1998 and 2004.

Additionally, the study found that just 105 instances of typhoid fever were diagnosed, reflecting a 2% prevalence. This study by (Pitzer et al., 2015) has reinforced our position that the majority of typhoid cases are misdiagnosed and that mechanisms should be put in place to care for people who diagnosed negative for the disease but are suspected of having it. Thus, integrating delay caused by false negative diagnosis into our model would significantly help reduce fatalities that may occur as a result of delay caused by false negative diagnosis .

According to Pitzer et al. (2015), the basic reproductive number R_0 increased from 1.3% in 1996 to 2.8% in 2015, indicating that those who may have had the infection but were falsely diagnosed, i.e. those in the delayed class, may be infecting other individuals in the susceptible class.

The deficiency in their work in no way compensated for the delayed class. As a result, including it into our work would enable decision makers to make an informed decision on the prevention of future reinfections of the typhoid fever disease.

Chapter Summary

This chapter reviewed the use of differential mathematical models to investigate the transmission dynamics and mechanisms of typhoid fever infections, as well as the critical role of delay in diagnosis in disease control. Ad-

ditionally, the history of using mathematical models to study and control infectious diseases was discussed. The models were developed using characteristics of the transmission dynamics of typhoid fever. While some studies used the standard SIR model to model typhoid transmission dynamics, others used variants of the standard SIR model. The fundamental reproductive number, R_0, was determined in both models and was used to determine whether or not typhoid fever will be endemic in the entire population. Thus, this study examined the transmission dynamics of typhoid fever by developing a deterministic model based on variation and modifying the widely used SIR model developed by (Kermack & McKendrick, 1927). Despite the numerous studies conducted on this typhoid disease, there has been no mathematical modeling of typhoid fever transmission dynamics using the $PSIDT$ model that incorporates delay caused by false negative diagnosis as control strategies to our knowledge. Thus, a combination of this work and the above-mentioned review of mathematical models of typhoid fever transmission dynamics will be beneficial and aid in the eradication of this worldwide disease.

CHAPTER THREE

RESEARCH METHODS

Introduction

Mathematical models can either be a deterministic model or a stochastic model. A deterministic mathematical model is a model in which the model's states are entirely influenced by the model's parameters as well as preceding states. Deterministic models have a finite number of compartment where the mechanisms by which individuals move from one compartment to another are specified through an array of ordinary differential equations.

By contrast, stochastic estimation approximates the probability distributions of possible outcomes by allowing for random change in one or more inputs across time. As a result, stochastic models are dependent on chance fluctuation in risk of exposure, disease, and other disease dynamics.

We would model the impact of false negative diagnosis of typhoid fever using the characteristics of typhoid transmission dynamics. Hence a Protected class, Susceptible class, Infected class, Delayed class and the Treated class (P,S,I,D,T) model will be formulated based on the deterministic approach and we would develop a system of differential equations and expressions for which the equilibrium point, the basic reproductive number and the stability of these equilibrium points would be determined.

The Existing Model

We would formulate our model by reviewing the model by Nthiiri, *et al.* (2016). We would first present their flow chart, parameters and equations and then our assumptions, flow chart, parameters and equations of the incorporated model would follow.

The existing flow chart is presented in the figure below;

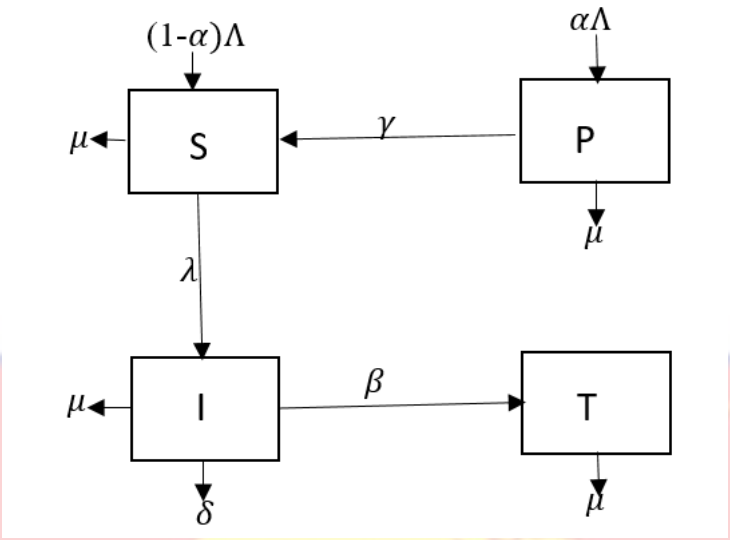

Figure 1: Nthiiri *et al.*(2016) Flow Chart of the Existing Model

Table 1: **Variables and their Descriptions of the Existing Model**

Variable	Description
P	Protected class
S	Susceptible class
I	Infected class
T	Treated class

Source: Nthiiri *et al.*(2016)

Table 2: **Parameters and their Descriptions of the Existing Model**

Parameters	Description
α	the proportion of successful vaccination against typhoid
π	the proportional rate of getting typhoid fever
θ	contact rate of infection
$\alpha\Lambda$	rate of recruitment into the protected class
γ	proportion of the population who failed protection
$(1-\alpha)\Lambda$	recruitment rate into the susceptible class
μ	natural mortality rate
λ	proportion of the susceptible class who are infected
δ	rate of mortality induced by the disease
β	rate at which the infected get treated

Source: Nthiiri *et al.*(2016)

where, $\lambda = \frac{\pi\theta I}{N}$

Equations of the Existing Model

$$\begin{cases} \frac{dP}{dt} = \alpha\Lambda - (\gamma + \mu)P \\ \frac{dS}{dt} = (1-\alpha)\Lambda + \gamma P - (\lambda + \mu)S \\ \frac{dI}{dt} = \lambda S - (\delta + \beta + \mu)I \\ \frac{dT}{dt} = \beta I - \mu T \end{cases} \tag{1}$$

The Extended Model

It is not logical to say that, everybody in the population who is tested against typhoid fever is correctly diagnosed. Hence a proportion of the population may fail the correct diagnosis against the disease. We then provide a mathematical formulation of a compartmental model of typhoid fever which incorporates delay caused by false negative diagnosis. We divide the total population *N(t)* into five compartments. These include, the protected individuals *P(t)*,the susceptible class *S(t)*, the Infected class *I(t)*, the Delayed class *D(t)* and the Treated class *T(t)* and we obtained a system of five differential equations, which would be shown below.

The parameters and the variables of the incorporated model is discussed in the table below.

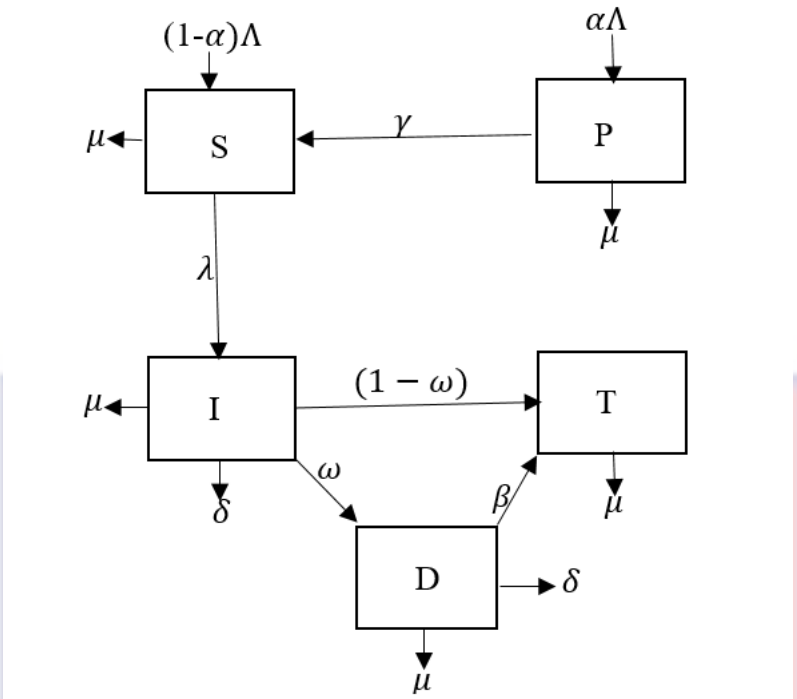

Figure 2: Flow Chart of the Extended Model, Source:Fiadufe (2021)

Table 3: **Variables and their Descriptions of the Extended Model**

Variable	Description
P	Protected class
S	Susceptible class
I	Infected class
D	Delayed class
T	Treated class

Source: Fiadufe (2021)

Table 4: **Parameters and their Descriptions of the Extended Model**

Parameters	Description
$\alpha\Lambda$	recruitment rate into the protected class
γ	proportion of the population who failed protection
$(1-\alpha)\Lambda$	recruitment rate into the susceptible class
μ	natural mortality rate
λ	proportion of the susceptible class who are infected
δ	the disease induced mortality rate
$(1-\omega)$	treatment rate with timely diagnoses
β	treatment rate with delayed diagnoses
ω	rate of false diagnoses

Source: Fiadufe (2021)

Equations of the Extended Model

We obtained a set of five (5) ordinary differential equations from the model diagram in 2 that characterized the dynamics of typhoid illness transmission which incorporates delays caused by false negative diagnosis. We obtained the following systems of non-linear ordinary differential equations:

$\lambda = \frac{\pi}{N}(\theta_1 I + \theta_2 D)$

$$\begin{cases} \frac{dP}{dt} = \alpha\Lambda - (\gamma + \mu)P \\ \frac{dS}{dt} = (1-\alpha)\Lambda + \gamma P - (\lambda + \mu)S \\ \frac{dI}{dt} = \lambda S - (\delta + \mu + 1)I \\ \frac{dD}{dt} = \omega I - (\mu + \delta + \beta)D \\ \frac{dT}{dt} = \beta D + (1-\omega)I - \mu T \end{cases} \tag{2}$$

where $N(t) = P(t) + S(t) + I(t) + D(t) + T(t)$

Basic Model Properties

We demonstrate the positivity of solutions and the boundedness of our model in this section.

Positivity of Solutions

To ensure that the system of equations makes sense and is biologically meaningful, we must establish that all of the model system's specified variables are non-negative. Thus, if the initial condition of the is positive, the model equation's solutions will remain positive. We begin by stating a Lemma.

Lemma 3.1 *Given the system's initial solutions and parameters in (2) are positive, the solutions of* $P(t)$, $S(t)$, $I(t)$, $D(t)$ *and* $T(t)$ *are all non-negative for*

all $t \geq 0$.

Let $\Omega = \left\{ (P(t), S(t), I(t), D(t), T(t)) \in \mathbb{R}_+{}^5; P_0 > 0, S_0 > 0, I_0 > 0, D_0 > 0, T_0 > 0 \right\}$.

then the solution P, S, I, D, T are positive for $t \geq 0$.

Proof:

From the systems of differential equations in (2) above

$\frac{dP}{dt} = \alpha\Lambda - (\gamma + \mu)P$

this implies that

$\frac{dP}{dt} \geq -(\gamma + \mu)P$

by separating the variables we have,

$\frac{dP}{P} \geq -(\gamma + \mu)dt$

by applying the initial conditions and solving, we have

$$P(t) \geq P_0 e^{-(\gamma+\mu)t} \geq 0. \tag{3}$$

Also, taking the second equation of the system equation (2), thus;

$\frac{dS(t)}{dt} = (1 - \alpha)\Lambda + \gamma P - (\mu + \lambda)S$

then, $\frac{dS(t)}{dt} \geq -(\mu + \lambda)S$

$\implies \frac{dS(t)}{S} \geq -(\mu + \lambda)dt.$

Then, by separating variables and applying initial conditions to the solution, we acquired,

$$S(t) \geq S_0 e^{-(\mu+\lambda)t} \geq 0. \tag{4}$$

In the same manner, the third equation of (2) that is;

$\frac{dI}{dt} = \lambda S - (\mu + \delta + 1)I.$

It is true that,

$\frac{dI}{dt} \geq -(\mu + \delta + 1)I$

$\frac{dI}{I} \geq -(\mu + \delta + 1)dt.$

Then, by separating variables and applying initial conditions to the solution, we acquired

$$I(t) \geq I_0 e^{-(\mu+\delta+1)t} \geq 0. \tag{5}$$

Also, by taking the fourth equation of (2),

$\frac{dD(t)}{dt} = \omega I - (\mu + \delta + \beta)D(t).$

It is also true that,

$\frac{dD(t)}{dt} \geq -(\mu + \delta + \beta)D(t)$.

Solving using the techniques of separation of variables and then applying the initial conditions, we acquired the following;

$\frac{dD(t)}{D(t)} \geq -(\mu + \delta + \beta)dt$

this gives,

$$D(t) \geq D_0 e^{-(\mu+\delta+\beta)t} \geq 0. \tag{6}$$

Lastly, we take the fifth equation of the system in equation (2),

$\frac{dT}{dt} = \beta D + (1 - \omega) - \mu T$

then,

$\frac{dT}{dt} \geq -\mu T$

and by separation of variables and integrating, gives;

$\frac{dT}{T} \geq -\mu dt$

and this gives,

$$T(t) \geq T_0 e^{-(\mu t)} \geq 0. \tag{7}$$

The end of the proof of lemma (3.1). Therefore, the solution of the lemma is

positive.

Boundedness of the Invariant Region

We determined the invariant domain of the model in which the solutions are bounded. To accomplish this, we begin by examining the total human population (N) where,

$N = P + S + I + D + T$.

Taking the derivative of N with respect to t, lead to;

$$\frac{dN}{dt} = \frac{dP}{dt} + \frac{dS}{dt} + \frac{dI}{dt} + \frac{dD}{dt} + \frac{dT}{dt} \tag{8}$$

by combining (2) and (8) , gives

$$\frac{dN}{dt} = \Lambda - \mu N - \delta(I + D). \tag{9}$$

When typhoid fever disease is not present in the population, then rate of fatality or mortality, $\delta = 0$ and (9) becomes

$\frac{dN}{dt} \leq \Lambda - \mu N$

and so,

$$\frac{dN}{dt} + \mu N \leq \Lambda. \tag{10}$$

Since equation (10) is a standard form of the first order differential equation, we use the method of integrating factor to solve it. Thus,

$e^{\int \mu dt} = e^{\mu t}$

$e^{\mu t}\frac{dN}{dt} + \mu e^{\mu t} N \leq e^{\mu t}\Lambda$

$\implies \frac{d}{dt}e^{\mu t} N \leq e^{\mu t}\Lambda$

Integrating both sides with respect to t gives,

$e^{\mu t}N \leq N_0 + \frac{\Lambda}{\mu}e^{\mu t} - \frac{\Lambda}{\mu}$

which simplifies into,

$$N(t) \leq \frac{\Lambda}{\mu} + \left[N_0 - \frac{\Lambda}{\mu}\right]e^{-\mu t}. \tag{11}$$

As $t \to \infty$ in equation (11), the population size $N \to \frac{\Lambda}{\mu}$ this signifies that $0 \leq N \leq \frac{\Lambda}{\mu}$.

The model's solutions remain in the feasible region:

$\Omega = \left\{ (S(t), I(t), D(t), T(t)) \in {\mathbb{R}_+}^5; N \leq \frac{\Lambda}{\mu} \right\}$.

As a result, the fundamental model is mathematically well-posed and sufficient condition for studying the fundamental model's dynamics in Ω.

Model Study State

This section examines the model's equilibrium points. Equilibrium points are those points at which the stated variables remain constant over time. The system in (2) has two non-negative equilibrium states represented by E° and $E^\star$, accordingly.(DFE) which is the state at which there no disease in the population, denoted by E°, while the (EE), the state at which the disease is endemic, denoted by $E^\star$. The two steady states have a significant effect on how disease transmission dynamics behave in a community. While there are an infinite number of possible initial infections of typhoid fever in a community, these equilibrium points represent the final reachable states. Using the basic reproduction number, R_0, we also determine the stability of these equilibrium points. Thus, when a system of differential equations is in equilibrium, (2) becomes,

$$\begin{cases} \alpha\Lambda - (\gamma + \mu)P^{\circ} = 0 \\ (1-\alpha)\Lambda + \gamma P^{\circ} - (\mu + \lambda)\, S^{\circ} = 0 \\ \lambda S^{\circ} - (\mu + \delta + 1)\, I^{\circ} = 0 \\ \omega I^{\circ} - (\delta + \mu + \beta)\, D^{\circ} = 0 \\ \beta D^{\circ} + (1-\omega) I^{\circ} - \mu T^{\circ} = 0 \end{cases} \tag{12}$$

where,

$$\lambda = \frac{\pi}{N}(\theta_1 I + \theta_2 D)$$

and let π denote the probability rate of getting typhoid fever disease and θ being the rate of coming into contact with an infected host. Let α also being the probability rate of successfully gaining protection through vaccination against the typhoid fever disease, thus the effective force of infection is

$$\lambda^{p} = \frac{\pi(1-\alpha)}{N}(\theta_1 I + \theta_2 D).$$

Disease-Free Equilibrium (DFE)

At the DFE state, we assume that there is no typhoid bacterium in the population and as a result there is no transmission of the bacteria that will either lead to infection and hence no treatment of individuals in the population is needed.

Computing for the disease free equilibrium (DFE), we set *I=D=T=0* in equation (12).

This now result to,

$$\alpha\Lambda - (\gamma + \mu)P^{\circ} = 0$$

$$(1 - \alpha)\Lambda + \gamma P^{\circ} - (\mu + \lambda)\, S^{\circ} = 0$$

Solving for P° we have;

$$P^{\circ} = \frac{\alpha\Lambda}{\gamma + \mu}$$

Now, solving for S° gives,

$$S^{\circ} = \frac{(\gamma + \mu - \alpha\mu)\Lambda}{(\mu + \lambda)(\gamma + \mu)}$$

but since there is no disease in the population, $\lambda = 0$.

Hence,

$$S^{\circ} = \frac{(\gamma + \mu - \alpha\mu)\Lambda}{(\mu)(\gamma + \mu)}. \tag{13}$$

Hence, the DFE state gives us,

$$E^{\circ}\left(P^{\circ}, S^{\circ}, I^{\circ}, D^{\circ}, T^{\circ}\right) = \left(\frac{\alpha\Lambda}{\gamma + \mu}, \frac{(\gamma + \mu - \alpha\mu)\Lambda}{(\mu)(\gamma + \mu)}, 0, 0, 0\right).$$

Endemic Equilibrium (EE)

The steady state of solutions where the typhoid fever disease is unable to be totally eradicated from the population but remains to invade the total population is called the Endemic Equilibrium State. We determine the endemic equilibrium point by solving the systems of differential equation in equation(14) simultaneously for the state variables $S^{\star}$, $I^{\star}$, $D^{\star}$ and $T^{\star}$.

At the endemic equilibrium, the following equations are satisfied;

$$\begin{cases} \alpha\Lambda - (\gamma+\mu)P^\star = 0 \\ (1-\alpha)\Lambda + \gamma P^\star - (\mu+\lambda)\,S^\star = 0 \\ \lambda S^\star - (\mu+\delta+1)\,I^\star = 0 \\ \omega I^\star - (\delta+\mu+\beta)\,D^\star = 0 \\ \beta D^\star + (1-\omega)I^\star - \mu T^\star = 0 \end{cases} \tag{14}$$

Which means to compute for the (EE), we equate P, S, I, D, T not to be equal to zero.

Solving the above systems of equations simultaneously,

we can solve for $P^\star$ from the first equation of 14 above which gives;

$$P^\star = \frac{\alpha\Lambda}{\mu+\gamma}. \tag{15}$$

Let us take the fourth equation of (14)

i.e

$\omega I - (\delta+\mu+\beta)D^\star = 0$

this implies that;

$$D^\star = \frac{\omega I}{\delta+\mu+\beta}. \tag{16}$$

Now from the third equation of (14)

$\lambda S = (\delta+\mu+1)I^\star$

noting that,

$$\lambda^p = \frac{\pi(1-\alpha)}{N}(\theta_1 I^\star + \theta_2 D^\star).$$

This now becomes,

$$\left(\frac{\pi(1-\alpha)}{N}(\theta_1 I^\star + \theta_2 D^\star)\right) S = (\delta + \mu + 1) I^\star$$

and substituting (16), gives;

$$\left(\frac{\pi(1-\alpha)}{N}(\theta_1 I^\star + \frac{\theta_2 \omega I^\star}{(\delta+\mu+\beta)}\right) S = (\delta + \mu + 1) I^\star$$

$$\left(\frac{\pi(1-\alpha)}{N}(\theta_1 + \frac{\theta_2 \omega}{(\delta+\mu+\beta)}\right) I^\star S^\star = (\delta + \mu + 1) I^\star$$

Let

$$K_1 = \left(\frac{\pi(1-\alpha)}{N}(\theta_1 + \frac{\theta_2 \omega}{(\delta+\mu+\beta)}\right)$$

this implies that;

$$K_1 I^\star S^\star = (\delta + \mu + 1) I^\star$$

therefore,

$$S^\star = \frac{(\delta + \mu + 1)}{K_1}. \tag{17}$$

Also from the second equation of (14), we obtain

$$(1-\alpha)\Lambda + \gamma(\tfrac{\alpha\Lambda}{\gamma+\mu}) = (\mu+\lambda)S^\star$$

which produced,

$$\tfrac{(\gamma+\mu-\mu\alpha)\Lambda}{\gamma+\mu} = \Big(\mu + \tfrac{\pi(1-\alpha)}{N}(\theta_1 I^\star + \theta_2 D^\star)\Big)S^\star.$$

Let also $K_2 = \frac{(\gamma+\mu-\mu\alpha)\Lambda}{\gamma+\mu}$

implies,

$$K_2 = \Big(\mu + \tfrac{\pi(1-\alpha)}{N}(\theta_1 + \tfrac{\theta_2\omega}{(\delta+\mu+\beta)})I^\star\Big)S^\star$$

and so,

$$K_2 = (\mu + K_1 I^\star)S^\star.$$

Now, substitute (17), i.e

$$K_2 = (\mu + K_1 I^\star)(\tfrac{(\delta+\mu+1)}{K_1})$$

hence give,

$$I^\star = \frac{K_1K_2 - \mu(\delta+\mu+1)}{K_1(\delta+\mu+1)}. \tag{18}$$

Again, substitute (18) into (16) and this gives;

$$D^\star = \frac{\omega}{(\delta+\mu+\beta)}\Big(\frac{K_1K_2 - \mu(\delta+\mu+1)}{K_1(\delta+\mu+1)}\Big). \tag{19}$$

And finally we find $T^\star$ by substituting $D^\star$ and $I^\star$ into the fifth equation of (14) and this also gives;

$$T^\star = \beta\left(\frac{\Big(K_1K_2 - \mu(\delta+\mu+1)\Big)\Big((\delta+\mu+\beta)+K_1\omega\Big)}{K_1\mu(\delta+\mu+\beta)(\delta+\mu+1)}\right). \tag{20}$$

Therefore the endemic equilibrium $E^\star = \Big(P^\star, S^\star, I^\star, D^\star, T^\star\Big)$ is given by

$$E^\star = \left(\frac{\alpha\Lambda}{\mu+\gamma}, \frac{(\delta+\mu+1)}{K_1}, \frac{K_1K_2-\mu(\delta+\mu+1)}{K_1(\delta+\mu+1)}, \frac{\omega}{(\delta+\mu+\beta)}\Big(\frac{K_1K_2-\mu(\delta+\mu+1)}{K_1(\delta+\mu+1)}\Big), \beta\left(\frac{\Big(K_1K_2-\mu(\delta+\mu+1)\Big)\Big((\delta+\mu+\beta)+K_1\omega\Big)}{K_1\mu(\delta+\mu+\beta)(\delta+\mu+1)}\right)\right).$$

The Basic Reproduction Number

The system's basic reproduction number, represented by R_0, is a critical metric for studying the behavior of epidemiological models. It can be explained as the mean number of illnesses contracted during an infectious period from an infective individual assuming that the entire community is susceptible. It is a critical criterion for determining whether an outbreak of a disease will spread throughout a population or not.

By studying the infectious compartment of the system in (2), we employed the next generation matrix strategy or technique by Diekmann et al. (1990) and Diekmann and Heesterbeek (2000) to derive the Basic Reproduction Number R_0. The formation of this matrix involves determining two compartments, infected and non – infected, from the model.

Let $F_i(x_0)$ be the rate of emergence of new infections which increase i compartment and $V_i(x_0)$, the rate of transitioning an infected individual from the i compartment to another compartment, given the disease free equilibrium.

Then $F = \left(\frac{\partial F_i(x_0)}{\partial x_j}\right)$ and $V = \left(\frac{\partial V_i(x_0)}{\partial x_j}\right)$ where $i, j = 1, 2$ and x_0 is the disease free equilibrium. The entries of FV^{-1} give the rate at which infected individuals in x_j produce new infections in x_i, times the average length of time an individual spends in a single visit to compartment j. The R_0 is the largest eigenvalue of the next generation matrix $G = \rho(FV^{-1})$ where ρ is the measure of the largest eigenvalue.

$$F_i = \begin{pmatrix} \lambda S \\ 0 \end{pmatrix} \text{ and } V_i = \begin{pmatrix} (\mu + \delta + 1)I \\ -\omega I + (\delta + \mu + \beta)D \end{pmatrix}$$

but $\lambda^p = \frac{\pi(1-\alpha)(\theta_1 I + \theta_2 D)}{N}$

hence $F_i = \begin{pmatrix} \frac{\pi(1-\alpha)(\theta_1 I + \theta_2 D)}{N} S \\ 0 \end{pmatrix}$ but at the disease free equilibrium(DFE), $S = N$.

Therefore,

$$F_i = \begin{pmatrix} \pi(1-\alpha)(\theta_1 I + \theta_2 D) \\ 0 \end{pmatrix}$$

The Jacobian matrices of F_i and V_i at disease free equilibrium E^0 respectively give;

$$F = \begin{pmatrix} \pi\theta_1(1-\alpha) & \pi\theta_2(1-\alpha) \\ 0 & 0 \end{pmatrix} \text{ and.}$$

$$V = \begin{pmatrix} (\mu + \delta + 1) & 0 \\ -\omega & (\delta + \mu + \beta) \end{pmatrix}$$

this implies that,

$$V^{-1} = \frac{1}{(\delta + \mu + \beta)(\mu + \delta + 1)} \begin{pmatrix} (\delta + \mu + \beta) & 0 \\ \omega & (\mu + \delta + 1) \end{pmatrix}$$

$$= \begin{pmatrix} \frac{1}{(\mu+\delta+1)} & 0 \\ \frac{\omega}{(\delta+\mu+\beta)(\mu+\delta+1)} & \frac{1}{(\delta+\mu+\beta)} \end{pmatrix}.$$

We then obtain $\rho(FV^{-1})$, which is defined as the largest eigenvalue of FV^{-1}. Thus the basic reproduction number R_0 for the system is calculated as

$$R_0 = \rho FV^{-1}$$

that is;

$$FV^{-1} = \begin{pmatrix} \pi\theta_1(1-\alpha) & \pi\theta_2(1-\alpha) \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{(\mu+\delta+1)} & 0 \\ \frac{\omega}{(\delta+\mu+\beta)(\mu+\delta+1)} & \frac{1}{(\delta+\mu+\beta)} \end{pmatrix}$$

solving,

$$FV^{-1} = \begin{pmatrix} \frac{\pi(1-\alpha)\left((\delta+\mu+\beta)\theta_1+\omega\theta_2\right)}{(\delta+\mu+\beta)(\delta+\mu+1)} & \frac{\pi\theta_2(1-\alpha)}{(\delta+\mu+\beta)} \\ 0 & 0 \end{pmatrix}.$$

Hence the R_0 is the largest eigenvalue on the principal diagonal, which is;

$$R_0 = \frac{\pi(1-\alpha)\big((\delta+\mu+\beta)\theta_1+\omega\theta_2\big)}{(\delta+\mu+\beta)(\delta+\mu+1)} \tag{21}$$

which measures the severity of an epidemic and one of the most important parameter for the disease to invade a population.

Local Stability at the DFE State

We determine the local stability at the DFE state by calculating the eigenvalues of the linearized Jacobian Matrix at the DFE, in this section.

Theorem 3.2 *The DFE of the system in (2) is LAS if* $R_0 < 1$ *and unstable if* $R_0 > 1$

Proof Let the system of differential equations in (2) be as follows;

$$\begin{cases} F_1 = \alpha\Lambda - (\gamma+\mu)P \\ F_2 = (1-\alpha)\Lambda + \gamma P - \left(\mu + \frac{\pi(1-\alpha)(\theta_1 I+\theta_2 D)}{N}\right)S \\ F_3 = \left(\mu + \frac{\pi(1-\alpha)(\theta_1 I+\theta_2 D)}{N}\right)S - (\mu+\delta+1)I \\ F_4 = \omega I - (\mu+\delta+\beta)D \\ F_5 = \beta D + (1-\omega) - \mu T \end{cases} \tag{22}$$

The variation Jacobian Matrix of the system in (22) is given as;

$$J = \begin{pmatrix} \frac{\partial F_1}{\partial P} & \frac{\partial F_1}{\partial S} & \frac{\partial F_1}{\partial I} & \frac{\partial F_1}{\partial D} & \frac{\partial F_1}{\partial T} \\ \frac{\partial F_2}{\partial P} & \frac{\partial F_2}{\partial S} & \frac{\partial F_2}{\partial I} & \frac{\partial F_2}{\partial D} & \frac{\partial F_2}{\partial T} \\ \frac{\partial F_3}{\partial P} & \frac{\partial F_3}{\partial s} & \frac{\partial F_3}{\partial I} & \frac{\partial F_3}{\partial D} & \frac{\partial F_3}{\partial T} \\ \frac{\partial F_4}{\partial P} & \frac{\partial F_4}{\partial S} & \frac{\partial F_4}{\partial I} & \frac{\partial F_4}{\partial D} & \frac{\partial F_4}{\partial T} \\ \frac{\partial F_5}{\partial P} & \frac{\partial F_5}{\partial S} & \frac{\partial F_5}{\partial I} & \frac{\partial F_5}{\partial D} & \frac{\partial F_5}{\partial T} \end{pmatrix}$$

This implies that,

$$J = \begin{pmatrix} -(\gamma+\mu) & 0 & 0 & 0 & 0 \\ \gamma & -\left(\mu+\frac{\pi(1-\alpha)}{N}(\theta_1 I+\theta_2 D)\right) & -\left(\frac{\pi\theta_1(1-\alpha)}{N}\right)S & -\left(\frac{\pi\theta_2(1-\alpha)}{N}\right)S & 0 \\ 0 & \frac{\pi(1-\alpha)}{N}(\theta_1 I+\theta_2 D) & (\frac{\pi\theta_1(1-\alpha)}{N})S-(\mu+\delta+1) & (\frac{\pi\theta_2(1-\alpha)}{N})S & 0 \\ 0 & 0 & \omega & -(\mu+\delta+\beta) & 0 \\ 0 & 0 & \beta & \beta & -\mu \end{pmatrix}$$

We now compute the Jacobian Matrix at DFE and investigate its stability effect due to the reproduction number R_0. Thus,

$$J_{E^\circ} = \begin{pmatrix} -(\gamma+\mu) & 0 & 0 & 0 & 0 \\ \gamma & -(\mu) & -\pi\theta_1(1-\alpha) & -\pi\theta_2(1-\alpha) & 0 \\ 0 & 0 & \pi\theta_1(1-\alpha)-(\mu+\delta+1) & \pi\theta_2(1-\alpha) & 0 \\ 0 & 0 & \omega & -(\mu+\delta+\beta) & 0 \\ 0 & 0 & \beta & \beta & -\mu \end{pmatrix}$$

The characteristic equation of the matrix above is obtained by $\left|J-\lambda I\right|=0$ this produces,

$$\begin{vmatrix} -(\gamma+\mu)-\lambda & 0 & 0 & 0 & 0 \\ \gamma & -(\mu+\lambda) & -\pi\theta_1(1-\alpha) & -\pi\theta_2(1-\alpha) & 0 \\ 0 & 0 & \Big(\pi\theta_1(1-\alpha)-(\mu+\delta+1)\Big)-\lambda & \pi\theta_2(1-\alpha) & 0 \\ 0 & 0 & \omega & -(\mu+\delta+\beta)-\lambda & 0 \\ 0 & 0 & \beta & \beta & -(\mu+\lambda) \end{vmatrix}=0$$

Solving for the eigenvalues $\lambda_i, i=1,2,3,4,5$, we have

$$\Big(-(\gamma+\mu)-\lambda\Big)\begin{vmatrix} -(\mu+\lambda) & -\pi\theta_1(1-\alpha) & -\pi\theta_2(1-\alpha) & 0 \\ 0 & \Big(\pi\theta_1(1-\alpha)-(\mu+\delta+1)\Big)-\lambda & \pi\theta_2(1-\alpha) & 0 \\ 0 & \omega & -(\mu+\delta+\beta)-\lambda & 0 \\ 0 & \beta & \beta & -(\mu+\lambda) \end{vmatrix}=0$$

$$\Big(-(\gamma+\mu)-\lambda\Big)(-\mu-\lambda)\begin{vmatrix} \Big(\pi\theta_1(1-\alpha)-(\mu+\delta+1)\Big)-\lambda & \pi\theta_2(1-\alpha) & 0 \\ \omega & -(\mu+\delta+\beta)-\lambda & 0 \\ \beta & \beta & -(\mu+\lambda) \end{vmatrix}=0$$

$$\Big(-(\gamma+\mu)-\lambda\Big)(-\mu-\lambda)(-\mu-\lambda)\begin{vmatrix} \Big(\pi\theta_1(1-\alpha)-(\mu+\delta+1)\Big)-\lambda & \pi\theta_2(1-\alpha) \\ \omega & -(\mu+\delta+\beta)-\lambda \end{vmatrix}=0$$

Hence;

$$\Big(-(\gamma+\mu)-\lambda\Big)(-\mu-\lambda)(-\mu-\lambda)[\Big(-(\mu+\delta+\beta)-\lambda\Big)\Big(\pi\theta(1-\alpha)-(\mu+\delta+1)-\lambda\Big)-\omega\pi\theta_2(1-\alpha)]=0$$

This implies that,

$-(\gamma+\mu)-\lambda=0$ or $(-\mu-\lambda)=0$ or $(-\mu-\lambda)=0$ or $(-(\mu+\delta+\beta)-\lambda)=0$ or $[\Big(-(\mu+\delta+\beta)-\lambda\Big)\Big(\pi\theta(1-\alpha)-(\mu+\delta+1)-\lambda\Big)-\omega\pi\theta_2(1-\alpha)]=0$

and therefore;

$\lambda_1=-(\gamma+\mu)<0$

$\lambda_2=-\mu<0$

$\lambda_3=-\mu<0$

and the other two roots λ_4 and λ_5 are the roots of what follows;

$$\lambda^2+z_1\lambda+z_2=0 \tag{23}$$

where

$$z_1=(\mu+\delta+1)+(\mu+\delta+\beta)-\pi\theta_1(1-\alpha),$$

$$z_2=\pi(1-\alpha)[\theta_1(\mu+\delta+\beta)+\omega\theta_2]-(\mu+\delta+\beta)(\mu+\delta+1).$$

Implies that, if $R_0<1$, we would have

$$\pi(1-\alpha)[\theta_1(\mu+\delta+\beta)+\omega\theta_2]<(\mu+\delta+\beta)(\mu+\delta+1).$$

Divide both sides of the inequality by

$$(\mu+\delta+\beta)(\mu+\delta+1)$$

and this gives;

$$\frac{\pi(1-\alpha)[\theta_1(\mu+\delta+\beta)+\omega\theta_2]}{(\mu+\delta+\beta)(\mu+\delta+1)}<1 \tag{24}$$

Now, comparing 21 and 24, implies that;

$R_0 < 1$.

Since $R_0 < 1$, then the system in (2) has a local stability.

This completes the proof.

Global Stability of the DFE

According Castillo-Chavez *et al.*(2002),for a system to be globally asymptotically stable(GAS) at the DFE state, this two conditions as stated below must be met. The system of differential equation in (2) should be represented in the format;

$$\begin{cases} \frac{dr}{dt} = Q(r, I) \\ \frac{dI}{dt} = K(r, I), K(r, 0) = 0 \end{cases} \tag{25}$$

such that $r \in R^m$ representing the number of people or the population not infected by the disease and $I \in R^n$ represent the quantum of the infected population. Also $U_0 = (r, 0)$ represents the disease free equilibrium of the system. The conditions (H1) and (H2) must also be met to guarantee global asymptotic stability.

(H1): $\frac{dr}{dt} = Q(r^*, 0), r^*$ is GAS.

(H2): $K(r, I) = AI - \hat{K}(r, 0) \geq 0$ for $(r, I) \in \Omega$ where $A = D_1 K(r^*, 0)$ is the Metzler matrix, that is, the non-negative off diagonal element of A and Ω is the domain where the model makes biological sense and well-posed. This implies that the fixed point $U_0 = (r^*, 0)$ has a global asymptotic stability equilibrium point of the Typhoid fever model system in (2) provided $R_0 < 1$.

Theorem 3.3 *The model system at the DFE state $E^\circ = (P^\circ, S^\circ, 0, 0, 0)$ is GAS if $R_0 < 1$ and the conditions (H1)and (H2) are satisfied.*

Proof Taking the model system in (2),

$$r \in \mathbb{R}^2 = (P, S)$$

and

$$I \in \mathbb{R}^2 = (I, D)$$

. Therefore for the condition (H1) to be met, we would have;

$$Q(r,0) = \begin{pmatrix} \alpha\Lambda - (\gamma+\mu)P \\ (1-\alpha)\Lambda + \gamma P - (\mu+\lambda)S \end{pmatrix}$$

$$= \begin{pmatrix} \alpha\Lambda - (\gamma+\mu)P \\ (1-\alpha)\Lambda + \gamma P - (\mu + (1-\alpha)\left(\frac{\theta_1 I + \theta_2 D}{N}\right))S \end{pmatrix}.$$

So for the equilibrium $U_0 = (r^*, 0)$, the system now gives,

$$\frac{dr}{dt} = \alpha\Lambda - (\gamma+\mu)P$$

$$\frac{dr}{dt} = (1-\alpha)\Lambda + \gamma P - (\mu + (1-\alpha)\left(\frac{\theta_1 I + \theta_2 D}{N}\right))S$$

Which follows that

$$Q(r,0) = \begin{pmatrix} -(\gamma+\mu) & 0 \\ \gamma & -\mu \end{pmatrix}$$

The characteristic polynomial is given by

$$\lambda^2 - TrA\lambda + detA = 0$$

this implies,

$$\lambda^2 + (2\mu+\gamma)\lambda + \mu(\gamma+\mu) = 0 \tag{26}$$

Since all the characteristic polynomial in (26) are non-negative, using the Routh-Hurwitz criterion, solutions of the characteristic polynomial have negative real parts. Which implies, the eigenvalues have negative real parts. Therefore r^* is concurrently GAS i.e a global asymptotic stability.

Furthermore, $K(r, I) = AI - \hat{K}(r, I)$

$$= \begin{pmatrix} -(\mu+\delta+1) & 0 \\ \omega & -(\mu+\delta+\beta) \end{pmatrix} \begin{pmatrix} I \\ D \end{pmatrix} - \begin{pmatrix} \lambda S \\ 0 \end{pmatrix}.$$

A is a Metzler matrix with non-negative off diagonal elements. It then also follows from equation (10) that, as $t \to \infty, (I, D) \to (0, 0)$. Hence $\hat{K}(r, I) \geq 0$ and the DFE is GAS in Ω.

This completes the proof.

Local Stability of the Endemic Equilibrium

We present a stability analysis of the endemic equilibrium point in this section. As discussed in the previous sections, the R_0 determines the local stability of the equilibria.

Theorem 3.4 *1. Given that $R_0 < 1$, then the DFE is asymptotically stable.*

2. Also if given that $R_0 > 1$, then the DFE is unstable and the EE is asymptotically stable.

Hence we wish to show that the system in (2) is locally asymptotically stable at the endemic state whenever $R_0 > 1$.

Proof We studied the stability of the EE by using the trace(TrJ) and the determinant of the Jacobian matrix at $E^\star$. That is $tr(J_{E^\star}) < 0$ and $det(J_{E^\star}) > 0$. The Jacobian matrix at $E^\star$ is given by

$$J_{E^\star} = \begin{pmatrix} -(\gamma+\mu) & 0 & 0 & 0 & 0 \\ \gamma & -\left(\mu+\frac{\pi(1-\alpha)}{N}(\theta_1 I^\star+\theta_2 D^\star)\right) & -\left(\frac{\pi\theta_1(1-\alpha)}{N}\right)S^\star & -\left(\frac{\pi\theta_2(1-\alpha)}{N}\right)S^\star & 0 \\ 0 & \frac{\pi(1-\alpha)}{N}(\theta_1 I+\theta_2 D^\star) & (\frac{\pi\theta_1(1-\alpha)}{N})S^\star-(\mu+\delta+1) & (\frac{\pi\theta_2(1-\alpha)}{N})S^\star & 0 \\ 0 & 0 & \omega & -(\mu+\delta+\beta) & 0 \\ 0 & 0 & \beta & \beta & -\mu \end{pmatrix}$$

$$= \begin{pmatrix} -(\gamma+\mu) & 0 & 0 & 0 & 0 \\ \gamma & -\left(\mu+\frac{\pi(1-\alpha)}{N}(\theta_1+\frac{\theta_2}{(\mu+\delta+\beta)})\right)I^\star & -\left(\frac{\pi\theta_1(1-\alpha)}{N}\right)S^\star & -\left(\frac{\pi\theta_2(1-\alpha)}{N}\right)S^\star & 0 \\ 0 & \frac{\pi(1-\alpha)}{N}(\theta_1+\frac{\theta_2}{(\mu+\delta+\beta)})I^\star & (\frac{\pi\theta_1(1-\alpha)}{N})S^\star-(\mu+\delta+1) & (\frac{\pi\theta_2(1-\alpha)}{N})S^\star & 0 \\ 0 & 0 & \omega & -(\mu+\delta+\beta) & 0 \\ 0 & 0 & \beta & \beta & -\mu \end{pmatrix}$$

If we let

$$z_1 = I^\star = \frac{K_1K_2-\mu(\delta+\mu+1)}{K_1(\delta+\mu+1)}$$

and

$$z_2 = S^\star = \frac{(\delta+\mu+1)}{K_1}.$$

Then,

$$J_{E^\star} = \begin{pmatrix} -(\gamma+\mu) & 0 & 0 & 0 & 0 \\ \gamma & -\left(\mu+\frac{\pi(1-\alpha)}{N}(\theta_1+\frac{\theta_2}{(\mu+\delta+\beta)})\right)z_1 & -\left(\frac{\pi\theta_1(1-\alpha)}{N}\right)z_2 & -\left(\frac{\pi\theta_2(1-\alpha)}{N}\right)z_2 & 0 \\ 0 & \frac{\pi(1-\alpha)}{N}(\theta_1+\frac{\theta_2}{(\mu+\delta+\beta)})z_1 & (\frac{\pi\theta_1(1-\alpha)}{N})z_2-(\mu+\delta+1) & (\frac{\pi\theta_2(1-\alpha)}{N})z_2 & 0 \\ 0 & 0 & \omega & -(\mu+\delta+\beta) & 0 \\ 0 & 0 & \beta & \beta & -\mu \end{pmatrix}$$

The Trace at $E^\star$ is given by,

$$Tr(J_{E^\star}) = -(\gamma+\mu)-\left(\mu+\frac{\pi(1-\alpha)}{N}(\theta_1+\frac{\theta_2}{(\mu+\delta+\beta)})\right)z_1+(\frac{\pi\theta_1(1-\alpha)}{N})z_2-(\mu+\delta+1)-(\mu+\delta+\beta)-\mu.$$

By substituting z_1 and z_2 and solving, we have

$$Tr(J_{E^\star}) = -(\gamma+\mu)-\mu R_0 \tag{27}$$

For equation (27) to remain negative, then $R_0 \geq 0$

We also determine the $det(J_{E^\star})$ as follows,

For simplicity, we let;

$$h_1 = \Big(\frac{\pi(1-\alpha)}{N}(\theta_1+\frac{\theta_2}{(\mu+\delta+\beta)})\Big)$$
$$h_2 = (\frac{\pi\theta_1(1-\alpha)}{N})$$
$$h_3 = (\frac{\pi\theta_2(1-\alpha)}{N})$$

$$det(J_{E^\star}) = \mu(\gamma+\mu)(\mu+\delta+\beta)\Bigg((\mu+h_1)z_1\big((h_2z_2)-(\mu+\delta+1)\big)+\omega\big(h_1z_1(\mu+\delta+\beta)+(h_1z_1h_3z_2)\big)\Bigg)$$

Upon substituting and simplifying, we obtained

$$= \mu(\gamma+\mu)(\mu+\delta+\beta)\Big((\mu+\delta+1)\mu R_0-\mu(\mu+\delta+1)\Big).$$

Hence,

$$det(J_{E^\star}) = \mu^2(\mu+\gamma)(\mu+\delta+\beta)(\mu+\delta+1)(R_0-1). \tag{28}$$

It is very clear now that, the determinant of the metric is positive provided $R_0 > 1$. Therefore the model has an asymptotically stable endemic equilibrium as $R_0 > 1$.

This completes the proof.

Chapter Summary

We examined the model formulation for typhoid fever transmission dynamics in this chapter by extending the model proposed by Nthiiri *et al.* (2016) to include delay caused by false negative diagnosis. The fundamental model assumptions were detailed, as were the model flow chart and the various state variables, parameters, and their descriptions. Due to the model system's monitoring of the human population, we established that all state variables and their solutions are non-negative at all times t and are constrained above a certain value that the human population cannot exceed. Eq.(2) contains two non-negative equilibrium points: the disease-free equilibrium (DFE) and the endemic equilibrium (EE). The two steady states had an effect on how disease transmission dynamics

behaved in a community. While an infinite number of different initial distributions of typhoid fever disease could exist in a community, these equilibrium points represent the final reachable states. Using the basic reproduction number, R_0, we also determined the stabilities of these equilibrium points. We concluded the chapter with a stability analysis of the model system, which demonstrates that the disease-free equilibrium is both locally and globally asymptotically stable using the Jaccobian matrix and the Routh-Hurwitz criterion approach.

CHAPTER FOUR

RESULTS AND DISCUSSION

Introduction

We considered the numerical simulation of the typhoid fever dynamics which incorporates delay caused by false negative diagnosis and also discussed the results obtained in this chapter.

Our data was obtained from literature which was referenced accordingly and we estimated some parameter values for the delay caused by false negative diagnosis.

The numerical simulation was performed using MATLAB. The aim is to verify analytically the results and also to demonstrate graphically and numerically our model solutions in Chapter Three. This is to equip decision makers in the health sector to know the future trends of typhoid fever especially in the aspect of delay caused by false negative diagnosis.

We also obtained the values of the parameters from literature for the model equations in Eq.(2) for the following parameters; the recruitment rate Λ, probability of success of protection α, the probability of being infected by the disease π, the rate of contact with an infected host θ, the natural mortality rate μ, the disease induced mortality rate δ, and the treatment rate β. Also the proportion of the population who failed protection γ and the proportion of the population that was delayed ω were obtained.

Numerical Analysis

The mathematical analysis of typhoid fever model with non-linear ordinary differential equation is presented. To observe the effects of the parameters used in the model in figure 2 presents several numerical simulations by varying the values of the parameters given in the table below, which resulted in the

varying effect on the R_0 values whereas $R_0 < 1$ and $R_0 > 1$ respectively.

The starting conditions of the state variables are given as;

$P(0) = 1500, S(0) = 3000, I(0) = 10, D(0) = 0$ and $T(0) = 0$, $N(0) = 4510$. The parameters and their values are presented in the table below.

Table 5: **Parameters and their Values**

Parameters	Standard Value	Source
Λ	0.0044	(Nthiiri *et al.*,2016)
γ	0.001	,,
π	0.8	[Assumed]
α	0.000001	[Assumed]
μ	0.018	(Adetunde, 2008)
θ_1	0.1	(Arif et al., 2019)
θ_2	0.5	[Assumed]
δ	0.005	(Nthiiri*et al.*,2016)
β	$0 < \beta < 1$	(Howard *et al.*,1987)
ω	$0 < \omega < 1$	[Assumed]

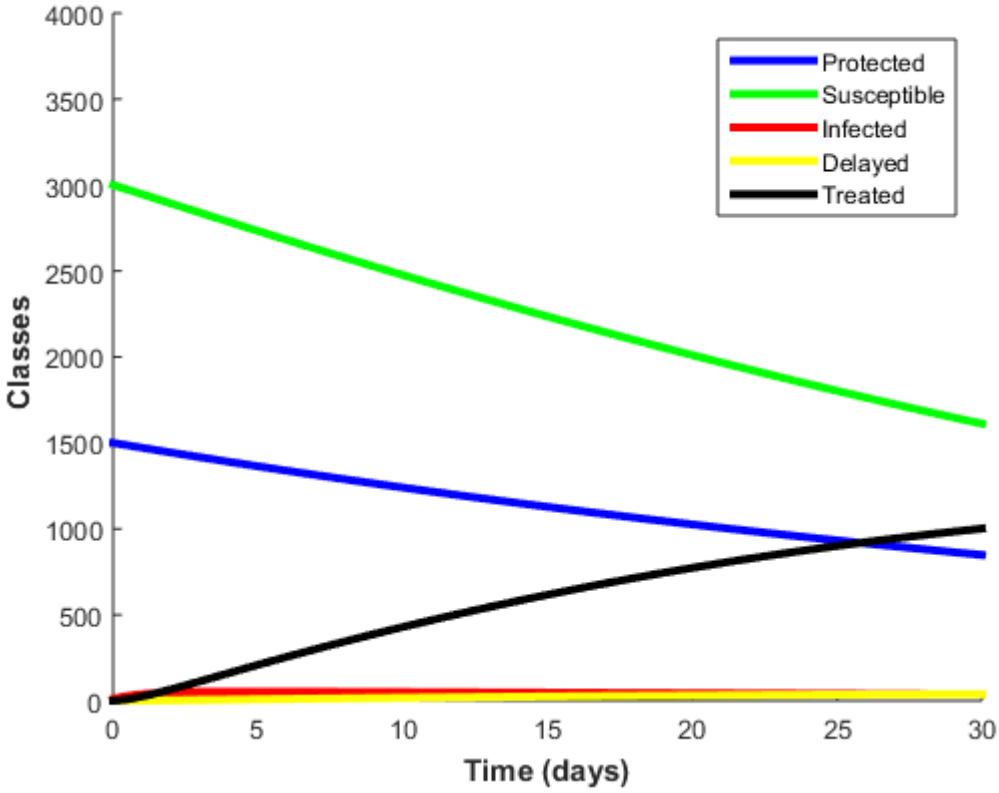

Figure 3: Comparing the Five state Variables at the Disease-Free Equilibrium, $R_0 = 0.7299$

Results

Given the values of the state parameters in Table 5 above, it is observed that the model systems settled at the disease-free equilibrium with $R_0 = 0.7299$ which is less than unity. This result is replicated in Figure 3 above. At the disease-free equilibrium, we expect the state variables; I and D to all go to zero for the fact that, no disease is in the population. Hence from Figure 3, Infected Class and the Delayed Class all tend to zero.

We do not expect the Protected class, Susceptible class and the Treated class to tend to zero given the initial conditions. Because of the constant recruitment of new individuals into the Susceptible class coupled with the movement of some of the individuals from the Protected class who may fail protection, the susceptible compartment shows a slight downward sloping curve which reduced

marginally, attains minimum and continues to increase at a constant rate. This is so because in the absence of an outbreak of a disease, the susceptible compartment becomes the population less the number of natural mortality. Therefore, the susceptible compartment curve may decreases in the long-run but cannot approach zero.

Moreover, we do not expect the Protected class and the Treated Class to tend to zero either. This is because,even if the disease is not present in the population, the vaccinated individuals would exist in the population even at the disease free equilibrium as depicted in Figure 3. More so, the infectious compartments tend to zero and the population of the infectious classes move to the Treated class. As a result, the Treated class continue to increase based on the assumption that, those treated have a permanent immunity against the typhoid fever as depicted in Figure 3. Figure 3 has also confirmed the local stability of typhoid fever model which incorporates delay caused by false negative diagnosis at the disease-free equilibrium state. The biological meaning is that,since R_0 is less than unity, the typhoid fever disease will die out of the population in the short-run if the disease is modeled at the stated parameter rates.

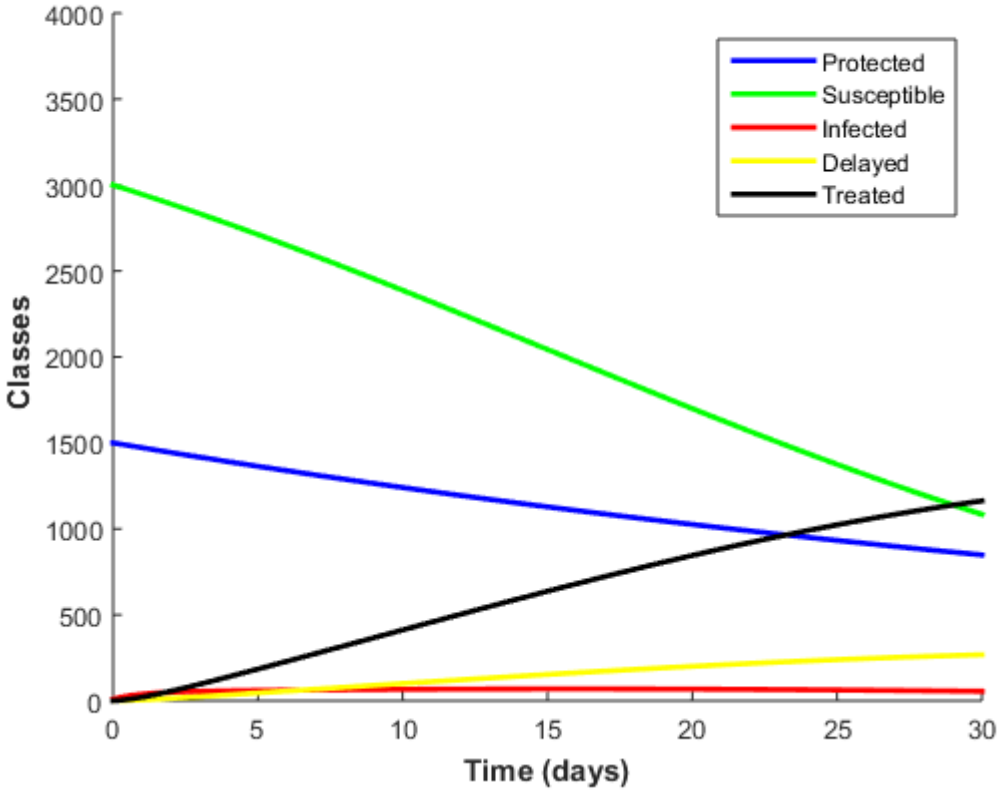

Figure 4: Comparing the Five State Variables at the Endemic Equilibrium State, $R_0 = 1.0068$

We further investigated the evolution of the reproduction number R_0 with transmission probability rate of typhoid π, probability of success of protection α,the contact rate θ and all the other parameters as recorded in table (5) held constant, we varied only (ω) from the initial 0.040 to 0.057, to observe its effects on spread and treatment. The results are shown in Figure (4) above.

Figure (4) shows that our model system in (2) attained the endemic equilibrium state with reproduction number $R_0 = 1.0068$.

Given that the 10 infected persons that were introduce into the susceptible population, and given that, $\omega = 0.057$ representing just 5.7% false diagnosis of the 10 infected persons, we can observe clearly that, the false diagnoses has increase the R_0 from 0.7299 which is at disease free state to 1.0068 which is an endemic state of the disease.

We can observe also from Figure (4) that, the susceptible compartment

decreased marginally. This is an indication that, the falsely diagnosed persons are infecting the susceptible class hence the increase in the curve of the delayed class from its initial state as depicted in Figure (4).

Similarly, the infected compartments i.e the Infected Class and Delayed Class increased abruptly from the disease-free equilibrium state in Figure 3 to a point above the initial state as depicted in Figure 4 which is an indication of the presence of typhoid fever in the population.It shows that the disease is endemic in the population.

The graph in Figure 4 has also shown an inverse relationship between the Delayed compartment and the Treated compartment. That is to say that, as more and more of the population is delayed by false negative diagnosis, only few of the infected population get treated.This assertion would be discussed into detail below.

We also analyzed the range of values of ω for which R_0 transitioned from being less than unity to greater than unity, which is from the stable state to an unstable state. The results are presented below;

$\omega = 0.054, R_0 = 0.9580$

$\omega = 0.055, R_0 = 0.9743$

$\omega = 0.056, R_0 = 0.9905$

$\omega = 0.057, R_0 = 1.0068$

Therefore the range of values of ω for which the disease transitions from stability to instability is given as $0.056 \leq \omega \leq 0.057$.

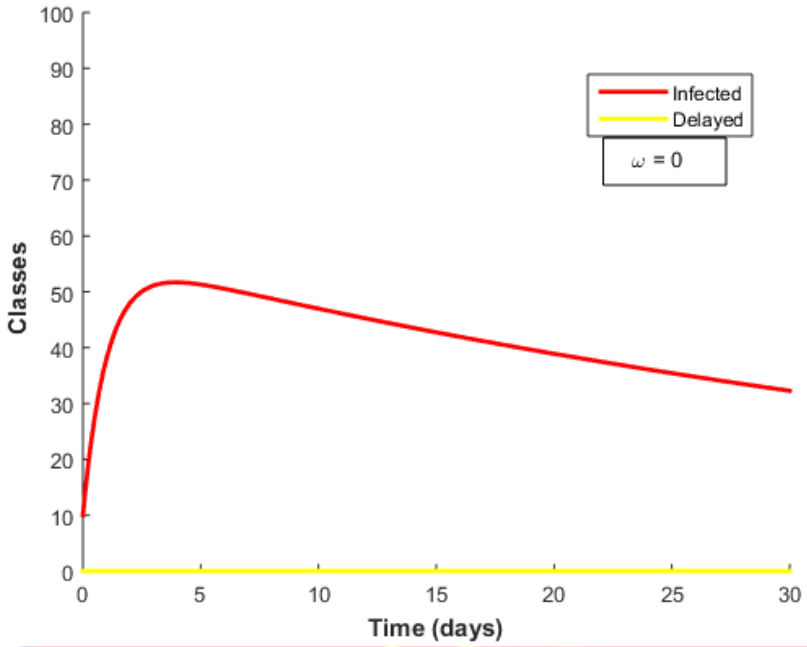

Figure 5: Effect of False Diagnosis on Infections, $R_0 = 0.072$

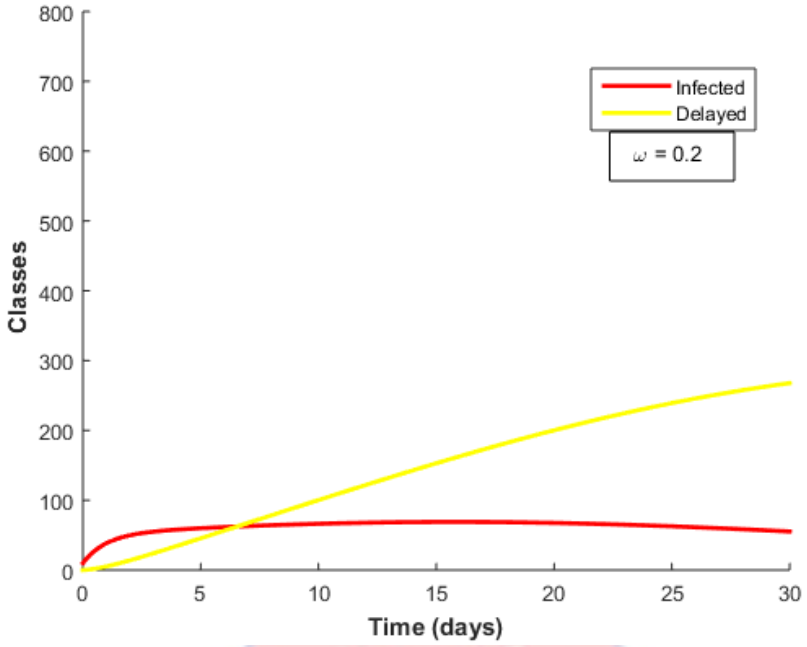

Figure 6: Effect of False Diagnosis on Infection, $R_0 = 3.3366$

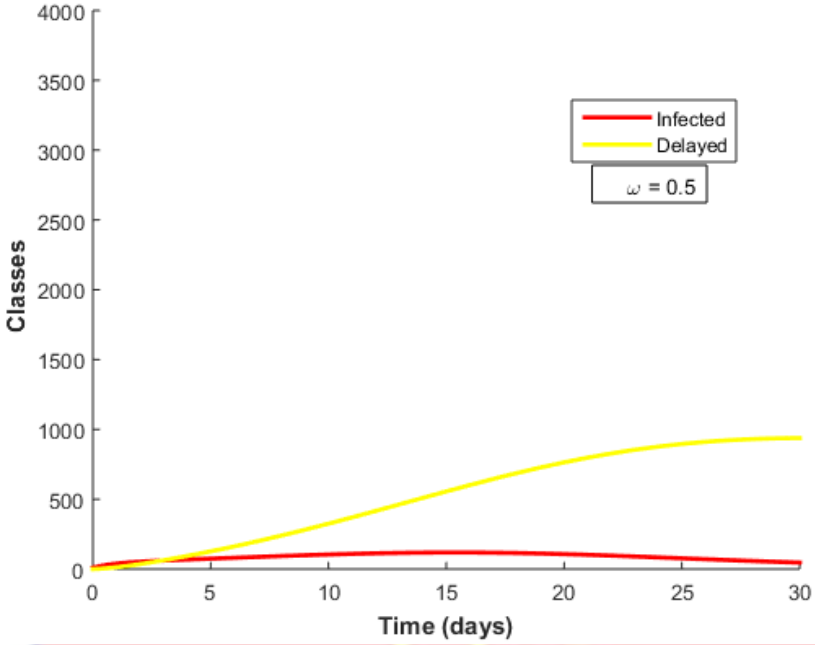

Figure 7: Analyzing the Effect of False Diagnosis on Infection: $R_0 = 8.2242$

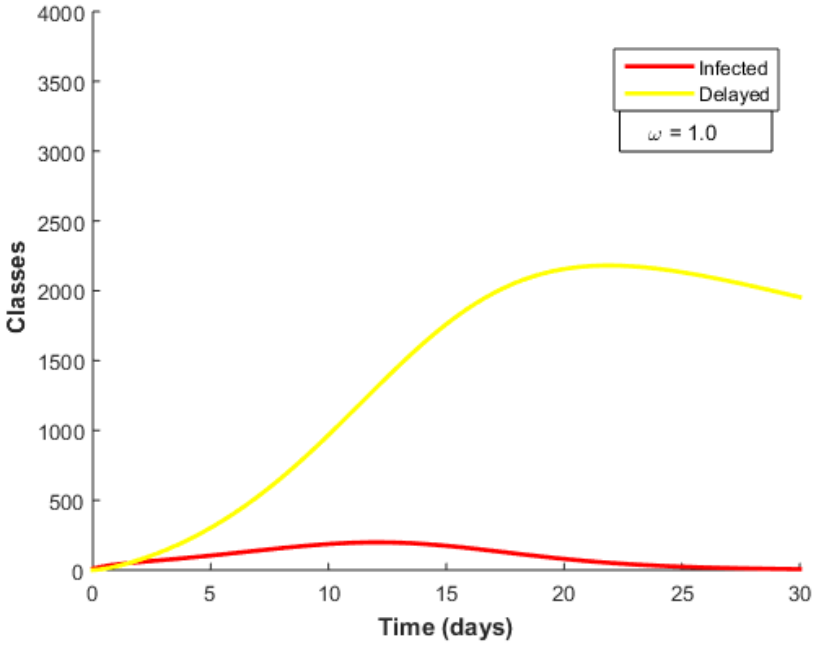

Figure 8: Analyzing the Effect of False Diagnosis on Infection: $R_0 = 16.3701$

Effect of False Diagnosis(Delayed population) on Infected Population

It can be observed from Figure5, Figure6, Figure7 and Figure8 that, as we vary omega(ω), the rate of false diagnosis from [0 - 0.2] the infected compartment declined from its initial position. We further increased ω from [0.2 - 1.0]

and the infected compartment again reduces further as can be seen in Figure7 and 8.

The reduction in the number of infected population as the rate of false diagnosis ω increase means that, as more infected people are falsely diagnose as not having the disease, this depopulates the infected (ith) compartment and giving an erroneous indication that the disease is not in the population or only few people may be having the condition. But on the contrary, the falsely diagnosed individual are the delayed population who are also infectious, who may be transmitting the disease.This is evident, as at this rates of ω, the R_0 continues to increase and greater than unity. This shows that the disease would be endemic in the population. The false diagnosis which reduces the number of the infected population, hinders decision making and planning on the part of health officials and governments as a whole. This may also lead to several numbers of the population being infected and thereby increasing the disease induced mortality.

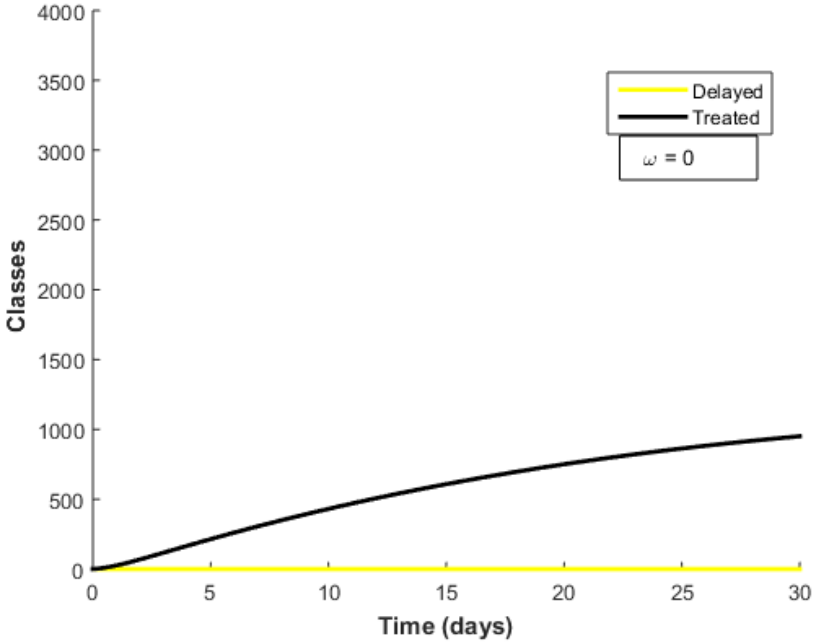

Figure 9: Effect of False Diagnosis on Treatment: $R_0 = 0.0782$

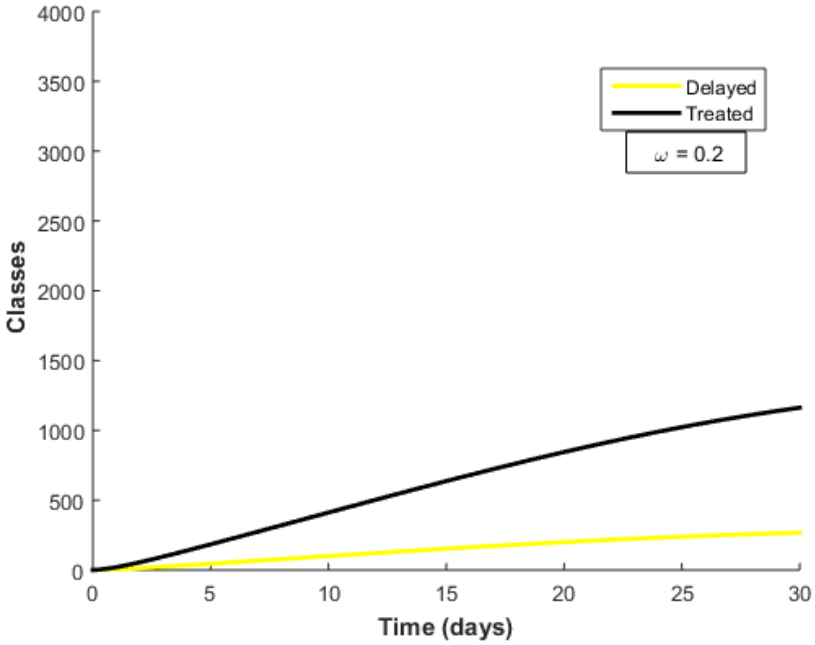

Figure 10: Effect of False Diagnosis on Treatment: $R_0 = 3.3366$

Effect of False Diagnosis on Treatment

From Figure 9, Figure 10, Figure 11and Figure 12 we noticed that, as more people are falsely diagnosed, that is, as we increase ω from [0 - 1.0], the

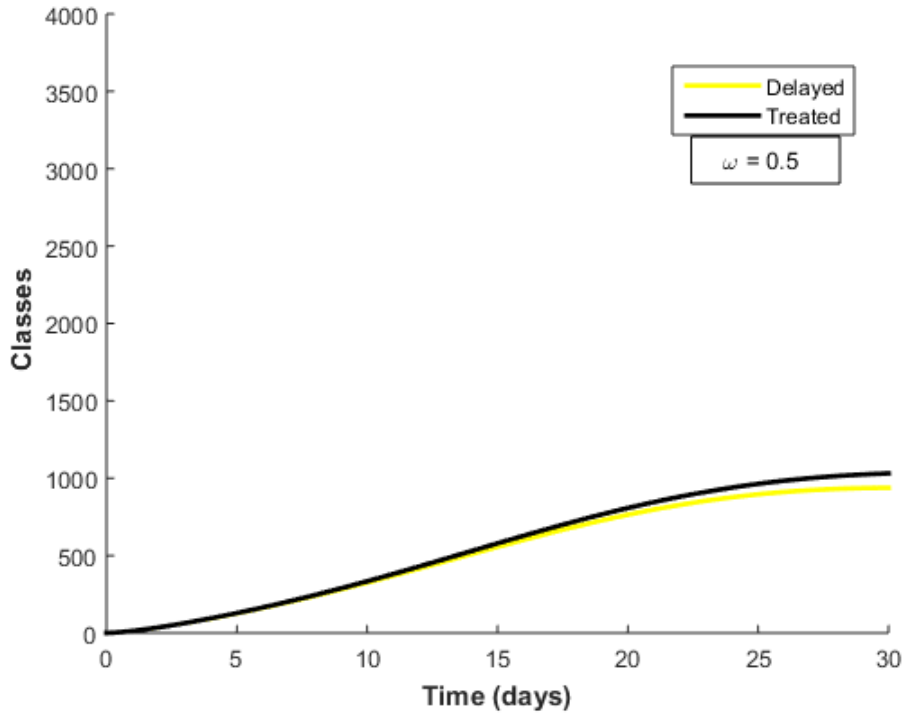

Figure 11: Effect of False Diagnosis on Treatment: $R_0 = 8.2242$

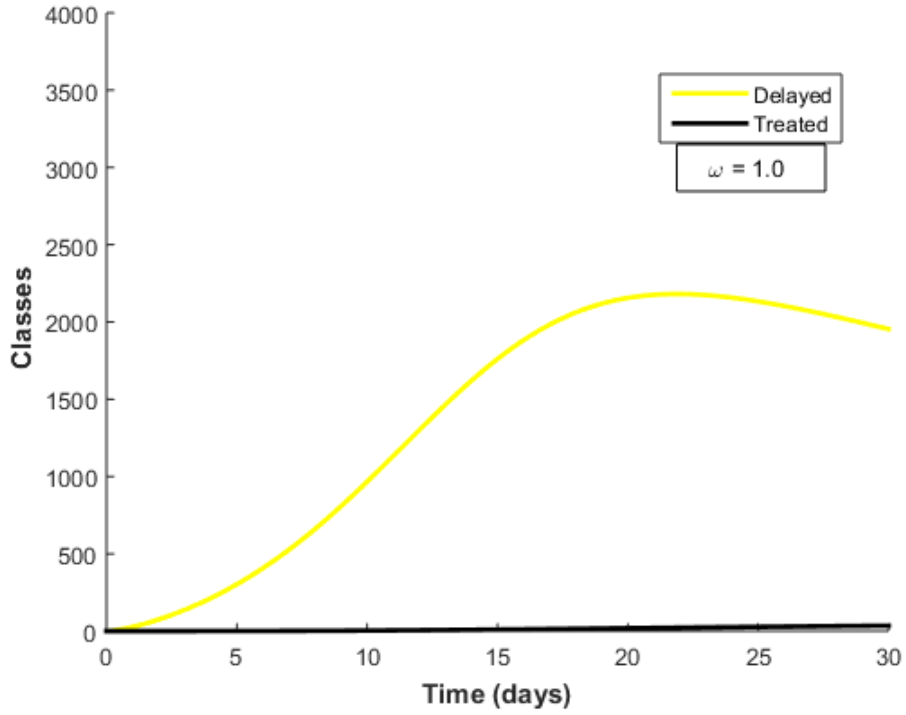

Figure 12: Effect of False Diagnosis on Treatment: $R_0 = 16.3701$

number of people who get treated declines. This is an indication that, if attention is not paid to accurate diagnosis of typhoid fever, only few people may get treated from the disease and the majority of the population who may be falsely diagnosed remains in the susceptible population thereby infecting others and the hosts with the disease. The vice versa is true. Therefore, Figure 9 through to Figure 12 is a confirmation that as infected individuals are falsely diagnosed the disease may be endemic in the population since $R_0 > 1$ and fewer people get treated.

Sensitivity Analysis on the Basic Reproduction Number, R_0

The parameters $\pi, \theta_1, \theta_2, \alpha, \omega, \beta, \delta$, and μ are functions of the Basic Reproduction number. To avoid a disease breakout, we must keep track of the parameter values that make up $R_0 < 1$. This is because these variables are mostly responsible for the disease's transmission. As a result, we're curious about the rate of change of R_0 as the parameter values vary. The rate of change of R_0 for a change in the value of a parameter for example x, can be estimated from a normalized sensitivity index defined as;

$$SI(x) = \frac{\partial R_0}{\partial x} \tag{29}$$

where x represents the parameter. Furthermore, when there is change in the parameter, the relative change in the state variables can be measured using the sensitivity indices. Hence using the normalized sensitivity index in (29) to determine the effect of each parameter on R_0, we obtained the following partial derivatives;

$$\frac{\partial R_0}{\partial \pi} = \frac{(1-\alpha)\Big(\theta_1(\mu+\delta+\beta)+\omega\theta_2\Big)}{(\mu+\delta+\beta)(\mu+\delta+\omega+\beta)} \geq 0$$

$$\frac{\partial R_0}{\partial \omega} = \frac{\pi\theta_2(1-\alpha)}{(\mu+\delta+\beta)(\mu+\delta+\omega+\beta)} \geq 0$$

In similar manner, the rest of the parameters were computed to determine their sensitivity statutes with the Basic Reproduction Number R_0. The results are simplified in the table below;

Table 6: **Parameters and their Relationship with** R_0

Parameter	Relationship
π	+
ω	+
α	-
θ_1	+
θ_2	+
β	-
μ	+
δ	+

From the Table 6 above, we could observe that, $(\pi, \omega, \theta_1, \theta_2, \mu$ and $\delta)$ all have a positive relationship with R_0, whilst the parameters (α, β) have a negative relationship with R_0.

The implication is that, the parameters with positive relationship have a positive effect on R_0, which means they increase R_0, and hence the aim is for these parameters to be reduced in order to eradicate the spread of the disease. Also the parameters with the negative relationship should be increased if the disease were to be eradicated from the population.

Discussions

Typhoid fever, commonly known as enteric fever, is a serious health disease that affects people all over the world. Its control has been a source of concern around the world. As a result, (Nthiiri *et al.*,2016) developed a model that integrates protection against typhoid fever disease infection in order to aid

in the discovery of a solution to the disease's spread.

We extended their analytical approach in this thesis, which includes protection against infection, to include delay induced by false negative diagnosis, in order to study the impact of false negative diagnosis on infection spread and treatment.

A detailed stability and persistent analysis were examined for our model with the control techniques of minimizing false negative diagnosis and also agreeing with Nthiiri *et al.* to boost protection through vaccination.

Parameter values were acquired from standardized published literature and used in numerical simulations. The magnitude of the R_0 is totally defined by the model's modalities, according to the model's analysis. In greater detail, when the $R_0 < 1$ is reached, the endemic status of the typhoid fever disease will naturally settle to a disease-free equilibrium, and the disease will be eradicated from the population. Despite this, the sickness will continue to spread throughout the population.

The analysis revealed that R_0 is an increasing function of the Delay caused by false negative diagnosis parameter, i.e. R_0 rises as the delay induced by false negative diagnosis parameter rises and vice versa. As a result, the time delay created by a false negative diagnosis is extremely important in the control and eradication of typhoid fever. For emphasis if only 5.7% of the infected population is falsely diagnosed, the disease may enter an endemic state. However, we believe that R_0, which constitutes the threshold, is a necessary but insufficient condition for the disease to be entirely eradicated.

The parameters in the basic reproduction number, R_0, were subjected to a sensitivity analysis. The model system was found to settle at a disease-free equilibrium state with low or no false negative diagnosis. Because total eradication of typhoid fever sickness is still a global concern, we propose in this thesis that erroneous negative diagnoses that result in delayed treatment be scrutinized with a keen eye, with the goal of decreasing it to the bare minimum.

Chapter Summary

Numerical simulation using literature values and some derived parameters for the spread and management of typhoid disease was explored in this chapter. The numerical simulation was performed using Matlab.

Also, sensitivity analysis of the model was performed for the model parameters to assess their link with the basic reproduction number R_0.

CHAPTER FIVE

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Overview

A mathematical model for the transmission dynamics of typhoid fever sickness has been presented in this paper. Delay caused by false negative diagnosis has been integrated into an SIR model to assess the impact it has on spread and treatment. The analytical and numerical results of this model was discussed in the preceding chapter. We consequently came out with the idea that, delayed individual induced by false negative diagnosis disseminated the typhoid disease, hence contributing to the spread dynamics of the typhoid fever disease. Therefore, reducing the incorrect diagnosis to the barest minimum will go a long way to restrict the spread and enhance treatment of the typhoid fever sickness.

Summary

A mathematical model of typhoid fever disease which incorporates delay caused by false negative diagnosis and its impact on spread, treatment and control strategies of the disease was investigated. We also used analytical techniques to determine when the disease will die out of the population or remain in the population to invade the entire population. This conclusions were based on the value of the basic reproduction number R_0. That is if $R_0 < 1$, it means an infected individual is reinfecting less than one person in the susceptible population, hence the disease will die out.

On the other hand, if $R_0 > 1$, then an infected individual can reinfect more than one susceptible individual in the population and as a result, the disease remain endemic in the population. Using numerical strategies, we predicted the types of control strategies that should be adopted in order to control the typhoid

fever disease. We concluded on the strategy of combining vaccination of as much as possible the highest number of the susceptible population which was a conclusion drawn by (Nthiiri *et al.*, 2016), and reducing delay caused by false negative diagnosis by procuring effective test kits and using the most effective test methods and personnel. Also treatment of the infected individual timely is highly recommended as a control strategy.

Our results therefore provide a framework which should be taken into consideration by the government, health practitioners and decision making bodies when formulating policies to control the typhoid fever disease.

Conclusions

A mathematical model that integrates protection by Nthiiri *et al.* (2016) was adjusted to incorporate delay caused by false negative diagnosis. The model was generated with the aid of a schematic diagram in Figure 2 and the model parameters are supplied in Table 2. The proposed model solutions were demonstrated to be theoretically well posed and biologically meaningful since all the model solutions were proved to be both positive and bounded. The disease free and the multiple endemic equilibrium state of the model were determined. Delay caused by false negative diagnosis and its impact on spread and treatment was added to know their impact in typhoid fever disease transmission dynamics using the sensitive index of the model parameters. The model was solved numerically using Matlab and findings from the numerical simulations indicates that as more and more people are mistakenly diagnosed, they contribute more to the spread dynamics hence limiting treatment. To be more specific, if the *sensitivity* and the *specificity* of a test kit is less than 94.3% i.e 5.7% false diagnosis, is a recipe for the spread of the disease. Therefore, the limited resources that will be used to manage typhoid fever disease should be focused towards the reduction in delayed population and increasing the protected population. We

further ran a sensitivity analysis on the basic reproduction number with all the model parameters from which we discovered that, the most sensitive parameters are $\alpha, \pi, \theta, \omega, \beta$. These criteria demand attention while evaluating ways to control typhoid fever sickness. Therefore, including delay caused by false negative diagnosis aid to establish an effective control approach to lower the transmission dynamics of the disease.

Recommendations

Based on the findings in this study, we give the following recommendations:

1. The government, stakeholders and the policy makers should consider using both vaccination and effective test systems in diagnosing typhoid fever disease which should reduce as much as possible the false negative diagnosis.

2. The inception of Covid'19 has increased personal hygiene through hand washing. We therefore recommend that, the same attitude be geared towards typhoid fever since infection is mainly through injection of faecal matter.

3. Individuals who show symptoms of typhoid fever disease but having a negative test results should be quarantined or self isolate for at least fourteen days for further and proper management, to avoid the possibility of spreading the disease as a result of false negative diagnosis.

4. Recommended treatments should be carried to the latter.

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